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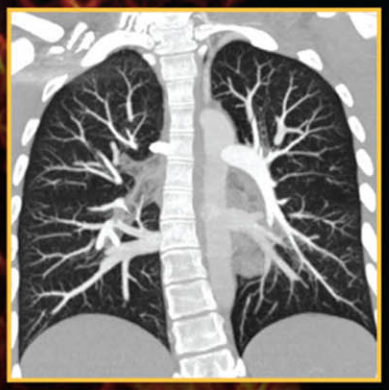
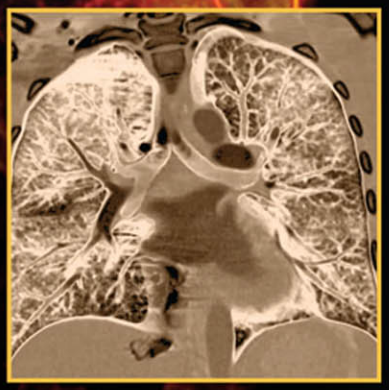
FIFTH EDITION

Fishman's Pulmonary Diseases and Disorders





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ON THE COVER

The background image was obtained using three-dimensional, micro-computed tomography (micro-CT) on a lung specimen from a normal donor. Airways and blood vessels are shown penetrating alveolar ducts and alveoli. Imaging was performed at 8-µm isotropic resolution (McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med.* 2011;365(17):1567–1575. PMCID: PMC3238466). The clinical CT images in the insets are still frames captured from the corresponding online video, which can be accessed by scanning the adjacent QR code. The top image, a maximum-intensity projection of a reformatted coronal section, shows contrast-enhanced pulmonary vasculature. The bottom image, a volume rendering of a similar reformatted coronal section using inverted gray scale, reveals the airways.

The initial portion of the video, comprised of a coronal view from a contrast-enhanced chest CT scan obtained from a normal, 25-year-old woman, shows volume rendering of the bony thorax and pulmonary vasculature. The video transitions to volume rendering of the lungs, trachea, and bronchi. Shown subsequently is a rotating tomographic section of the distal airways. A red box in the section indicates the general location from which a lung specimen was obtained from a separate, normal donor for micro-CT imaging. The last segment of this portion of the video shows rectangular volume rendering of the specimen, which then transitions to a rotating tomographic depiction. Blood vessels *(solid arrow)*, alveolar ducts *(dashed arrow)*, and alveoli *(dotted arrow)* are identified. The second portion of the video demonstrates an unenhanced CT scan from a 63-year-old female lung transplant recipient who had severe COPD. The patient's chest x-ray is shown on the left and axial CT images on the right. The red box indicates the location from which a specimen was obtained from the explanted emphysematous lung for micro-CT imaging. The micro-CT segment in the video includes rectangular volume rendering of the emphysematous lung specimen and, subsequently, a rotating tomographic section of the tissue sample. Loss of alveolar structure is evident. Blood vessels *(solid arrow)*, alveolar ducts *(dashed arrow)*, and alveoli *(dotted arrow)* are noted. In this specimen, blood vessels are filled with residual blood.

Images courtesy of James C. Hogg, MD, PhD, John E. McDonough, PhD (both from the University of British Columbia), Joel D. Cooper, MD, Warren B. Gefter, MD, Michael A. Grippi, MD, Pablo G. Sanchez, MD, Drew A. Torigian, MD, and Alexander C. Wright, PhD (all from the University of Pennsylvania).

Fishman's Pulmonary Diseases and Disorders

NOTICE

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Fishman's Pulmonary Diseases and Disorders

Fifth Edition

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Alfred P. Fishman, MD, 1918–2010

Alfred P. Fishman, MD, was a husband, father, scientist, clinician, author, and consummate editor. The breadth and depth of his intellectual curiosity were great, and his contributions to pulmonary medicine and science of real consequence. He was an exacting task master who set a high bar for all of us, as well as for himself; his commitment to excellence was steadfast. The editors of the fifth edition dedicate this work to Dr. Fishman—the man, the mentor, and the driving force behind the origins of *Pulmonary Diseases and Disorders*.

To Barbara, Kristen, Amy, Emily, Sawyer, Levi, and Kieran
Michael A. Grippi, MD

To Sandy, Lauren, Alma, and Gabby
Jack A. Elias, MD

To Gayle, Aaron, and Brian
Jay A. Fishman, MD

To Debbie, Eric, Brian, and Ethan; and to the memory of Jean and Leon Kotloff
Robert M. Kotloff, MD

To Fran, Alison, Angela, Andrew, and Allan Jr.
Allan I. Pack, MBChB, PhD

To Martha, Jocelyn, Rebecca, Devra, and David
Robert M. Senior, MD

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PREFACE

This, the fifth edition of *Fishman's Pulmonary Diseases and Disorders*, represents a substantial departure in content and style from the previous four editions. Notably, this is the first edition in which the founding editor, Alfred P. Fishman (1918–2010), is no longer at the helm. Dr. Fishman, a legend in pulmonary science and medicine, leaves a legacy based on a long and distinguished career. Incredibly, he served as sole editor of the first two editions of the textbook, which initially appeared in print in 1980. Subsequently, he enlisted a number of coeditors, including several from the current group. Those of us who had the opportunity to work with him on the prior two editions remain grateful for his leadership, editorial style, and unrelenting commitment to excellence. His memory inspired us in preparing the current volume. We can only hope that it measures up to his exacting standards.

While many of the elements of the book have changed, one aspect remains firmly entrenched: The book represents a coupling of the body of knowledge of pulmonary and critical care medicine with the underlying basic and applied science upon which the clinical material is based. The book is designed to appeal both to clinicians and investigators who are interested in the science of medicine, including relevant respiratory biology and underlying cellular and molecular mechanisms. We hope that readers will find it authoritative, well referenced, and a suitable platform from which to launch additional inquiry.

The body of knowledge and level of detail in the fifth edition have evolved substantially since the last edition, published in 2008. In virtually all areas of pulmonary medicine, notable advancements have been made, and each is discussed in detail. For example, tremendous progress has occurred in our understanding of the genetics of respiratory disease; indeed, the era of "personalized medicine" is upon us. A full chapter has been devoted to the genetics of pulmonary disease and another to personalized pulmonary medicine—additions from the previous edition. Similarly, growth in immunology and immunosuppressive management, along with technical advances in lung transplantation, has been amply documented in the literature over the last 5 years and is presented in detail. Advances in the science and treatment of pulmonary hypertension have been noteworthy. This area, which was one of great interest to Dr. Fishman, is discussed in a comprehensive chapter on the subject. In addition, the rapid evolution of cardiovascular and pulmonary imaging techniques has been dramatic, and multiple examples of such advanced imaging populate many of the chapters. Utilization of the technology and its attendant costs constitute the basis for considerable debate and ongoing studies regarding applicability in screening patients for underlying pulmonary disease (e.g., lung cancer screening using low-dose CT scanning in at-risk patients). Finally, as another example of noteworthy progress, developments in interventional bronchoscopic techniques continue to evolve and have become increasingly sophisticated over the last 5 years. They are discussed in two related chapters on diagnostic and interventional bronchoscopy.

Within the realm of critical care medicine, significant advances have been reported in the early diagnosis and management of sepsis, multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), and the newly defined entity of "chronic critical illness." These advances have translated into improved survival of patients with disorders that, at one time, were largely fatal. Patient survival, particularly in the setting of chronic and, sometimes, debilitating, organ dysfunction has generated debate on the appropriateness of application of the technology and affordability of the healthcare thereby engendered. Such considerations inform a discussion of the organization of intensive care units and long-term acute care facilities, topics which have been included in this edition.

Not all of the news has been good. For example, challenges in the medical management of advanced interstitial lung disease, particularly idiopathic pulmonary fibrosis, have remained all too evident. Therapy has been disappointing. Notably, however, several recently completed clinical trials have improved prospects for management.

Those responsible for generating the content of the fifth edition include 278 contributors. They are drawn from among the world's experts in the areas about which they have written. One hundred fifty-nine contributors are new from the last edition, including many from outside the United States, reflecting the vast array of expertise available globally in the areas of pulmonary science and medicine.

Organization and content are not the only metrics that have changed with the fifth edition. Footnoted references are now incorporated extensively. Supplemental content and illustrations are made available by accessing QR codes embedded on the printed pages. Production constraints created by page limitations have been curtailed significantly. Notably, the fifth edition is being made available in an electronic version accessed via the World Wide Web.

An additional technological advance over the prior edition is incorporation of a number of videos designed to complement and, at times, accentuate information contained within the text. Not surprisingly, most of the videos relate to procedures or imaging. They are designed to reflect common or unique findings drawn from "real life" clinical experiences. They, too, are accessible using a QR code reader.

With all of the technological advances in play, at the end of the day, the compilation and synthesis of the information contained within this textbook are a reflection of the commitment, untiring effort, and professionalism of many contributing authors. The editors are enormously grateful for their willingness to "dig deep" and generate authoritative discussions of the complex and expanding fields of pulmonary and critical care medicine.

These same, appreciative editors have, themselves, contributed enormous boluses of time in editing and authoring the chapters that comprise the book. Personally, I found the willingness of my colleagues to step up and orchestrate its preparation extraordinarily gratifying.

Finally, on behalf of all of the editors, I wish to express our thanks for the commitment of key individuals in preparing the fifth edition, including Brian Belval, Executive Editor at McGraw-Hill; Peter Boyle, Sr Project Development Editor; Priscilla Beer, Sr Media Project Manager; and Sarah M. Granlund, Project Manager. Their ability to keep the train on the track was nothing short of exceptional.

Michael A. Grippi, MD

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Fishman's Pulmonary Diseases and Disorders

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PART 1

Perspectives

1 **Milestones in the History of Pulmonary Medicine** 2

CHAPTER 1

Milestones in the History of Pulmonary Medicine*

Michael A. Grippi

The current level of clinical, scientific, and technologic sophistication of medicine has evolved over more than 2000 years. From the inception of medicine, pulmonary medicine has been an integral part of its growth and development. About 300 years ago, progress toward scientific medicine accelerated markedly, and it has continued to gain speed ever since. In the 17th century, research and experimentation began to tilt clinical medicine toward the exact sciences; by the 18th century, pathology had become an integral part of clinical medicine, and clinical–pathologic correlations succeeded empiricism, dogmatism, and metaphysics. The age of the great clinicians dawned in Europe early in the 19th century, when autopsies became legally permissible and socially acceptable, and when physicians who cared for patients actually performed the autopsies.

The road to our current understanding and practice of pulmonary medicine and science has been somewhat convoluted.[1–3] Progress has been punctuated by delays, detours, and reversals. However, it is possible to retrace the scientific trail by examining iconic figures and addressing milestones in drawing the map (Table 1-1). This chapter uses these milestones to trace the course of scientific pulmonary medicine over the last two millennia. By necessity, what follows constitutes a limited overview of *selected* aspects of the history of the field, including alveolar–capillary gas exchange, lung volumes, mechanics of breathing, control of breathing, ventilation–perfusion relationships, and scientific advancements impacting clinical medicine, including chest imaging, lung transplantation, bronchoscopic techniques, and advances in critical care. Indeed, much of the content of the book addresses the many advances in respiratory disorders achieved over the last 50 years.

ALVEOLAR–CAPILLARY GAS EXCHANGE

In reflecting on the history of the science and thinkers largely responsible for our current understanding of the central role of the lungs in gas exchange, the following are considered: the ancient Greeks, William Harvey and the Oxford physiologists, the "phlogiston theory," theories of blood gas diffusion and "secretion" of oxygen, and the physical chemistry of blood gas transport.

■ ANCIENT GREEK MEDICINE

The beginnings of scientific medicine can be traced to ancient Greece in the sixth century BC. At that time, natural philosophers speculated that air, or some essential ingredient in air, was inspired to generate a "vital essence" for distribution throughout the body.

Hippocrates, the "father of medicine," is as much a symbol of the Greek physician of the fifth and fourth centuries BC as the name of a real figure (Fig. 1-1). As an individual, he exemplified the caring physician who kept accurate records, made cautious inferences, and relied more on nature, rest, and diet than on drugs for treatment. His name has been immortalized by affixing it to three major components of Greek medicine, even though none appears to be the work of a single individual.

The first is the *Hippocratic corpus*, a collection of about 70 works that includes case reports, textbooks, lectures, and notebooks. The collection contains a description of Cheyne–Stokes breathing and the use of *Hippocratic succussion* for the diagnosis of fluid and air in the pleural cavity. The second is a collection of aphorisms—a compilation of brief generalizations related to medicine. The third, which is more likely attributable to Pythagoras (c. 530 BC) than Hippocrates (who lived about a century later), is the *Hippocratic oath*, which not only represents the spirit of the physician of ancient Greece, but which has endured to modern times as a reflection of the physician's code of ethics.

Another Greek, Aristotle, not only had an enduring influence on the intellect of humankind in his own time, but also for two millennia, thereafter. Not until the 17th century were Aristotle's doctrine of the four elements (earth, air, fire, and water) and that of Hippocrates (blood, phlegm, yellow bile, and black bile) laid to rest, thereby clearing the way for modern scientific medicine.

Soon after Aristotle, in about 300 BC, an extraordinary medical school was founded at Alexandria in Egypt. One of the first teachers at the school, Erasistratus, postulated that the "pneuma," or spirit essential for life, is generated from interplay between air and blood.

About four centuries after Erasistratus, Galen (Fig. 1-2) drew upon the medical, philosophic, and anatomic knowledge of his day to fashion a remarkable physiologic schema.[3,4] His construct was largely teleologic. Unfortunately, it was so convincing that even though it was ultimately proved to be fanciful, it sufficed to retard scientific progress for a millennium and a half. Galen was a talented individual who was well educated, well read, and well positioned in society to popularize his beliefs. Moreover, his concepts fit well into the tenets of Christianity, which was then in its ascendency; to controvert his authority was tantamount to blasphemy. Among his long-lasting, albeit erroneous, postulates, were the following: invisible pores in the ventricular septum that enabled the bulk of the blood to flow from the right ventricle to the left ventricle, thereby bypassing the lungs; a diminutive pulmonary circulation that served only to nourish the lungs; and two-way traffic in the pulmonary veins that enabled inspired air and "effluent waste vapors" to go their respective ways (Fig. 1-3).

Voices raised in protest to Galen's theories were without lasting effect. In the 13th century, Ibn al-Nafis, writing in his *Canon of Avicenna*, objected that blood does not traverse the ventricular septum from right to left, as Galen had proposed. However, this insight attracted little attention. Three hundred years later, Vesalius voiced similar misgivings. In the 16th century, Michael Servetus, a polymath trained in theology, geography, and anatomy, pictured the pulmonary circulation as the vehicle by which the "inhaled spirit" could be distributed throughout the body. In his theologic treatise, *Christianismi Restitutio*, he pointed out that blood could not traverse the septum between the right and left ventricles, and that the lumen of the pulmonary artery was too large for a nutrient vessel. He became a hunted heretic, wanted for execution by both the Catholic Church and Calvin. He was warned by Calvin to stay out of Geneva. Both Servetus and Calvin then behaved predictably: Servetus showed up at a church where Calvin was preaching and Calvin had him captured and burned at the stake. In 1559, Realdus Columbus of Cremona, a pupil of Vesalius, rediscovered the pulmonary circulation, as did Andreas Caesalpinus in 1571. Despite these challenging observations, Galen's schema was to last for more than another half century—until the physiologic experiments of William Harvey.

■ WILLIAM HARVEY AND THE OXFORD PHYSIOLOGISTS

William Harvey (Fig. 1-4) was led to the discovery of the circulation of the blood[5] by anatomic observations on the valves in systemic

*This chapter constitutes an updated revision of the original chapter written by Alfred P. Fishman.

TABLE 1-1 Landmark Figures in the Evolution of Modern Pulmonary Medicine

Alveolar–Capillary Gas Exchange

Ancient Greek Medicine
- Hippocrates of CoS (c. 460–359 BC)
- Aristotle (384–322 BC)
- Erasistratus of Chios (c. 300–250 BC)
- Galen of Pergamon (AD 129–99)
- Ibn al-Nafis (c. 1210–1288)
- Leonardo da Vinci (1452–1519)
- Miguel Servetus (1511–1553)
- Andreas Vesalius of Brussels (1514–1564)
- Realdus Columbus of Cremona (1516–1559)
- Andreas Caesalpinus of Pisa (1519–1603)

William Harvey and the Oxford Physiologists
- Galileo Galilei (1564–1642)
- William Harvey (1578–1657)
- Giovanni Alfonso Borelli (1608–1679)
- Marcello Malpighi (1628–1694)
- Robert Boyle (1627–1691)
- Richard Lower (1631–1691)
- Robert Hooke (1635–1703)
- John Mayow (1640–1679)

Phlogiston: The Rise and Fall
- Georg Ernst Stahl (1660–1734)
- John Black (1728–1799)
- Joseph Priestley (1733–1804)
- Carl Wilhelm Scheele (1742–1782)

Respiration and Metabolism
- Antoine Laurent Lavoisier (1743–1794)
- John Dalton (1766–1844)
- Julius Robert von Mayer (1814–1878)
- Carl von Voit (1831–1908)
- Nathan Zuntz (1847–1920)

The Blood Gases
- Joseph Black (1728–1799)
- John Dalton (1766–1844)
- Heinrich Gustav Magnus (1802–1870)
- Felix Hoppe-Seyler (1825–1895)
- Paul Bert (1833–1886)
- Christian Bohr (1855–1911)
- John Scott Haldane (1860–1936)
- August Krogh (1874–1949)

Diffusion or Secretion of Oxygen
- Joseph Barcroft (1872–1947)
- Marie Krogh (1874–1943)

The Physical–Chemical Synthesis
- Lawrence J. Henderson (1878–1942)

Mechanics of Breathing
- John Hutchinson (1811–1861)
- Karl Ludwig (1816–1895)
- Franciscus Cornelius Donders (1818–1889)
- Fritz Rohrer (1888–1926)
- Wallace Osgood Fenn (1893–1971)

Control of Breathing

The Central Respiratory Centers
- Thomas Lumsden (1874–1953)
- Hans Winterstein (1878–1963)
- Merkel Henry Jacobs (1884–1970)

The Peripheral Chemoreceptors
- Ewald Hering (1834–1918)
- Joseph Breuer (1842–1925)
- Cornelius Heymans (1892–1968)

Scientific Basis of Clinical Medicine

Pathologic Anatomy
- Gioranni Battista Morgagni (1682–1771)
- Leopold Auenbrugger (1727–1809)
- Jean Nicolas Corvisart (1755–1821)
- René Théophile Hyacinthe Laënnec (1781–1826)

Microbiology
- Robert Koch (1843–1910)

Physiology of the Pulmonary Circulation
- Claude Bernard (1813–1878)
- Auguste Chauveau (1827–1917)
- Étienne Jules Marey (1830–1904)
- Dickinson W. Richards (1895–1973)
- André Frederic Cournand (1895–1988)
- Werner Forssmann (1904–1979)

Thoracic Imaging
- Wilhelm Conrad Roentgen (1845–1923)
- Godfrey N. Hounsfield (1919–2004)

Bronchoscopy
- Gustav Killian (1860–1921)
- Chevalier Jackson (1865–1958)
- Shigeto Ikeda (1925–2001)

Lung Transplantation
- Vladimir P. Demikhov (1916–1998)
- James D. Hardy (1918–2003)
- Joel D. Cooper

veins made by his mentor, Fabricus ab Aquapedente. Harvey's small book, *De Motu Cordis*, published in 1628, not only corrected a self-perpetuating error in Galenical teaching, but also marked the birth of modern physiology. The time, however, was not yet ripe to relate the function of the heart to the physiology of breathing. To his dying day, Harvey clung to the idea that the main function of breathing is to cool the heart. Moreover, since he made no use of the microscope, he could not picture how the pulmonary arteries made connections with the pulmonary veins. Galileo invented the compound microscope in 1610. In 1661, using the compound microscope, Marcello Malpighi reported that alveoli were covered by capillaries and that blood and air were kept separate by the continuous alveolar–capillary barrier.

Figure 1-1 The Hippocrates of Ostia. This damaged bust is believed to represent Hippocrates as perceived in antiquity. It was found in a family tomb in excavations near Ostia. *(Used with permission of Dr. Dickinson W. Richards.)*

Figure 1-2 Galen of Pergamon as depicted in medieval times. No authentic reproduction exists of Galen in ancient times. *(Used with permission of Galen's Therapeutica, published in Venice in 1500.)*

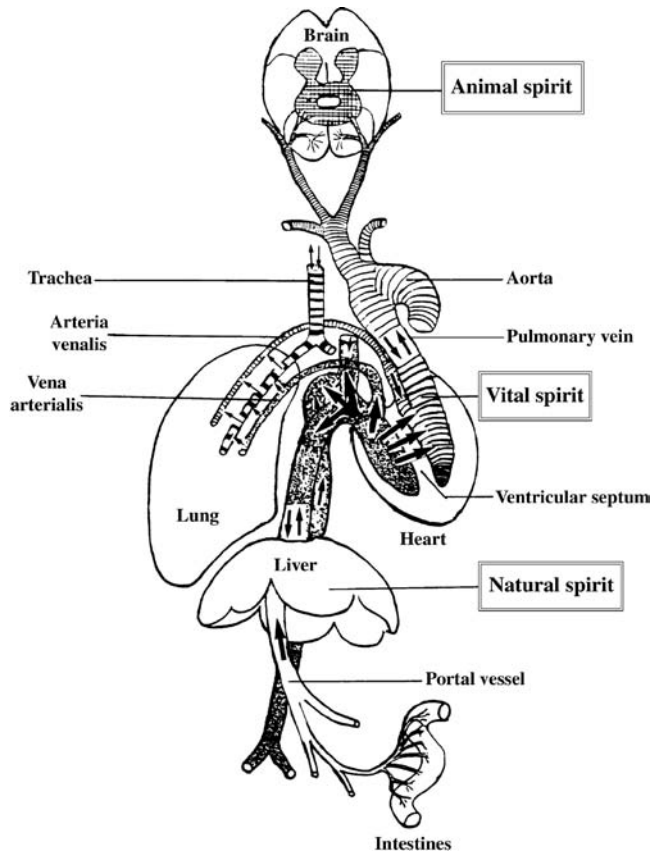

Figure 1-3 Galen's scheme of the circulation. The diagram shows the source and distribution of the three types of spirits. The validity of this scheme depended on invisible pores in the ventricular septum, two-way traffic in the pulmonary vein, and selective permeability of the mitral valve for sooty wastes but not for spirit-containing blood. Vena arterialis, pulmonary vein; arteria venalis, pulmonary artery. *(Modified with permission from Singer C. A Short History of Scientific Ideas to 1900. London: Oxford University Press; 1959.)*

Figure 1-4 William Harvey (1578–1657). This portrait of William Harvey is part of a family group in which William Harvey and his five brothers are gathered around their father, William Harvey.

Figure 1-5 Robert Boyle (1627–1691). This engraving, from an original painting by Johann Kerseboom, hangs in the Royal Society, London. Boyle's invention of a pneumatic air pump and his publications concerning "the spring of air and its effect" stimulated considerable research on the physical properties of air and its role in respiration and combustion. He strongly influenced Hooke, Lower, and Mayow at Oxford.

Harvey's description in 1628 of the circulation of the blood had three major consequences for pulmonary medicine: (1) it oriented pulmonary medicine toward the basic sciences and away from philosophy and empiricism; (2) it demolished the Galenic concept of the movement of the blood; and (3) it set the stage for an upcoming generation of physiologists at Oxford University to explore breathing in chemical and physical terms.

The physiologists working at Oxford in the 1660s were greatly impressed by Harvey's disciplined approach to scientific inquiry. Many were medical practitioners who conducted research as a sideline. Four, in particular, began the systematic study of air and its constituents, thereby laying the foundations for contemporary respiratory physiology and medicine: Robert Boyle (Fig. 1-5), Robert Hooke, Richard Lower, and John Mayow.

In 1660, Robert Boyle proved by means of his air pump that air is necessary for life. In 1667, Robert Hooke showed that insufflation of the lungs with air while breathing movements were arrested could keep an open-chest animal alive, that is, that movement of the lungs was not essential for life. Richard Lower, the first to practice blood transfusion, took advantage of Hooke's continuously inflated lung preparation in the dog to observe that dark venous blood becomes bright red as it traverses lungs insufflated with air. In 1674, Mayow interpreted the change in the color of blood from venous to arterial as due to the uptake of "nitroaerial particles" (later to be called "oxygen") from the air.

PHLOGISTON: THE RISE AND FALL

Unfortunately, the discoveries and insights of the Oxford physiologists went largely unnoticed during the century that followed, overshadowed by the "phlogiston theory" of combustion. The theory, advanced by Stahl, postulated that all combustible materials were composed of two ingredients: phlogiston, a principle that transformed into fire when heated, and an ash that was left behind after the fiery phlogiston escaped. The phlogiston theory was sufficiently malleable to accommodate almost every new discovery that could have overthrown it, including the rediscovery of carbon dioxide in 1754 by John Black, and the independent discoveries of oxygen by Priestley and Scheele. Although the respiratory gases had been discovered by the end of the 18th century and many of their properties characterized, the discoveries were misapplied to support, rather than destroy, the phlogiston theory. The phlogiston theory was finally demolished by the experiments of Lavoisier.

RESPIRATION AND METABOLISM

From the time of Hippocrates until early in the 20th century, debate had continued about the site of heat production in the body. In 1777, Lavoisier suggested that air was composed of one respirable gas (which he later named "oxygine") and another (nitrogen) that remained unchanged in the course of respiration. Between 1782 and 1784, Lavoisier and Laplace concluded, on the basis of calorimetric experiments on guinea pigs, that "respiration is therefore a combustion, admittedly very slow, but otherwise exactly similar to that of charcoal" (Fig. 1-6). The similarity between respiration and combustion had previously been recognized by the Oxford physiologists, especially Mayow.[6] By 1783, Lavoisier was accumulating evidence against the phlogiston theory and began to replace it with an entirely new system of chemistry.

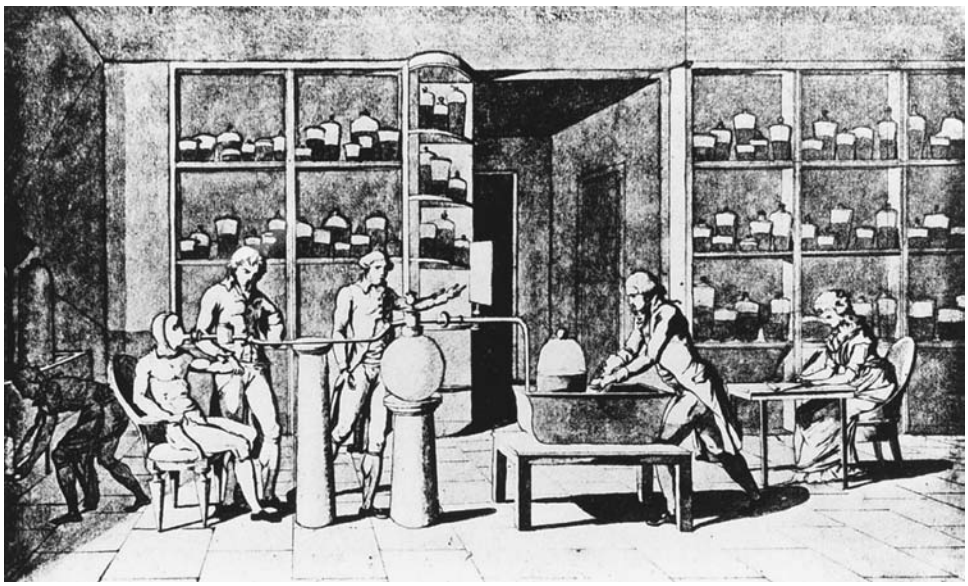

Figure 1-6 Scene from the laboratory of Antoine Laurent Lavoisier (1743–1794). His wife is acting as his assistant, and Sequin is the subject. Studies such as this led to the conclusion that respiration and circulation are similar processes.

As noted previously, the ancients pictured the heart as the heat generator. Lavoisier favored the lungs. Others held that combustion occurred in the blood. Although Spallanzani had shown in the 18th century that isolated tissues take up oxygen and evolve carbon dioxide, the idea that combustion occurred in the tissues was slow to gain acceptance. However, the hypothesis gained strength through the work of Pflüger in 1878. He measured oxygen consumption and carbon dioxide production in dogs and calculated respiratory quotients. His research substantiated a concept that had been enunciated, but not named, by Lavoisier.[7]

Once the idea that oxidation occurred in the tissues had become generally accepted, investigators delved into the processes involved in utilization of foodstuffs by the tissues, energetics, growth, and repair. Carl von Voit and Max von Pettenkofer, using a respiration chamber, drew upon chemical balances and respiratory quotients in humans to distinguish the nature of the foodstuffs being burned and to show that the amounts of fat, protein, and carbohydrate burned varied with the mechanical work done by the subject. Between 1842 and 1845, Julius Robert von Mayer formulated the law of conservation of energy. Subsequently, Max Rubner showed that the law applied to the living body, and Herman von Helmholtz showed that its relevance to metabolism could be demonstrated experimentally. Application of these principles at the bedside was greatly facilitated by the development of a portable metabolic apparatus by Nathan Zuntz. Pioneering bedside studies of metabolic states were conducted by a succession of distinguished investigators, including Magnus-Levy, Graham Lusk, F. G. Benedict, and Eugene F. DuBois.

THE BLOOD GASES

The Oxford physiologists set the stage for the discovery of the blood gases. Using his vacuum pump, Robert Boyle extracted "air" from blood. John Mayow came close to discovering oxygen by showing that only part of air was necessary for life, and that this part, his "nitroaerial spirits," was removed both by respiration and fire (combustion). One of his famous experiments entailed enclosing a mouse and a lighted lamp in an airtight container; the lamp went out first and then the mouse died. However, Mayow did not realize that the "nitroaerial spirits" could be isolated as a gas.[6]

One hundred years after Mayow, Joseph Priestley (Fig. 1-7) exposed a mouse to the gas released from heated mercuric oxide and found that the gas supported life better than air did; he also noticed that a flame burned more vigorously in this gas than in air. Priestley was not alone in his preoccupation with flame. In 1773, about a year before Priestley had obtained oxygen by heating mercuric oxide, Scheele discovered oxygen independently because of his interest in fire, and he designated oxygen as "fire air."

In 1662, Van Helmont, a Capuchin friar and talented chemist, as well as a mystic with a drive to quantify, discovered carbon dioxide, coined the word *gas*, and called carbon dioxide "wild gas" ("gas sylvestre"). In 1755, Joseph Black rediscovered carbon dioxide. He showed that calcium carbonate (limestone) and magnesium carbonate (magnesia alba) lost weight on heating, releasing "fixed air" (CO_2) in the process. This fixed air extinguished both flame and life. Lavoisier knew of the observations of Black and of Priestley and Scheele. He decided in 1778 that the gas obtained from heating

Figure 1-7 Joseph Priestley (1733–1804), the discoverer of oxygen. This figure shows a silver medal struck in his honor in 1783. A Presbyterian minister, he was radical in his religious and political beliefs, inventive in science, and conservative in the interpretation of his findings. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York: Oxford University Press; 1964.)*

Figure 1-8 Christian Bohr (1855–1911). At work in his laboratory, Bohr *(far right)* and his associates systematically explored the interplay between the respiratory gases and hemoglobin that led to the discovery of the "Bohr effect." *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York: Oxford University Press; 1964.)*

mercuric oxide was not "fixed air" or "common air," but "highly respirable air" (oxygen).

The story of hemoglobin, the essential element in the transport of the respiratory gases by the blood, begins with Hoppe-Seyler, who, between 1866 and 1871, crystallized hemoglobin, explored its chemical properties, and assigned it a proper role in the transport of oxygen by the blood. At the turn of the 19th century, Dalton reported his experiments with the respiratory gases, which led to the development of his atomic theory. In 1872, taking advantage of Dalton's law, Paul Bert published the first oxygen dissociation curve, that is, oxygen content at different barometric pressures; he pictured the curve as hyperbolic. Christian Bohr (Fig. 1-8) subsequently identified its s-shaped contour, and in 1904, together with Hasselbach and August Krogh, showed that increasing carbon dioxide tension in blood drives out oxygen, that is, the "Bohr effect." Shortly thereafter, the influence of various factors, for example, temperature and electrolytes, on the affinity of oxygen for hemoglobin (and, consequently, on the position of the oxygen dissociation curve) was explored in detail by Barcroft and associates. In 1914, Christiansen, Douglas, and Haldane reported that an increase in the oxygen tension of the blood drives out carbon dioxide, that is, the "Haldane effect." In 1967, a new dimension was added to the understanding of the position and configuration of the oxygen dissociation curve by the demonstration that diphosphoglycerate, a chemical constituent of red cells, regulates the release of oxygen from oxyhemoglobin.

DIFFUSION OR SECRETION OF OXYGEN

Bohr is a central figure as an investigator and mentor in respiratory physiology.[8] In 1904, he raised a troublesome issue that was not easily resolved, primarily because of limitations in methodology at the time. He postulated that even though diffusion could account for oxygen uptake at rest, it could not suffice during strenuous exercise, particularly at altitude. He held that oxygen *secretion* had to be involved.[9] He held to this misconception during his lifetime, a conviction supported by two major lines of evidence. The first was indirect: Oxygen secretion by the swim bladder of fish showed by extrapolation that active transport of oxygen in the lungs was possible. The second was based on observations made during Bohr's expedition to Pike's Peak in 1912, during which it was erroneously demonstrated that with exercise at altitude, arterial oxygen tension exceeded alveolar oxygen tension.

However, even before the report from high altitude, Bohr's former assistant, August Krogh, and his wife, Marie Krogh (Fig. 1-9) had marshaled new evidence to show that "the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and diffusion alone." The final blow to the secretion theory was delivered by Marie Krogh.[10] Based on the single-breath carbon monoxide method for determining diffusing capacity that she and her husband had developed in 1910,[11] she was able to account for oxygen uptake in the lungs by diffusion alone, even during strenuous exercise under conditions of low oxygen tension. Refinements in the carbon monoxide method by Roughton and others extended

Figure 1-9 August and Marie Krogh in 1922, at the time of their first visit to the United States so that August Krogh could deliver the Silliman Lecture at Yale. They demonstrated that diffusion, without secretion, could account for the transfer of O_2 and CO_2 across the alveolar–capillary membranes of the lungs. *(Used with permission of their daughter, Dr. Bodil Schmidt-Nielsen.)*

Figure 1-10 Two founders of contemporary respiratory physiology in 1936. Sir Joseph Barcroft (1872–1947) *(left)* proved, in experiments on himself, that diffusion was the mechanism for gas exchange in the lungs and pioneered current understanding of the respiratory functions of the blood. Lawrence J. Henderson (1878–1942) *(right)* provided a mathematical analysis of blood as a physiochemical system and stimulated research on the complex interplay involved in respiratory gas exchange during exercise. *(From Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964, with permission.)*

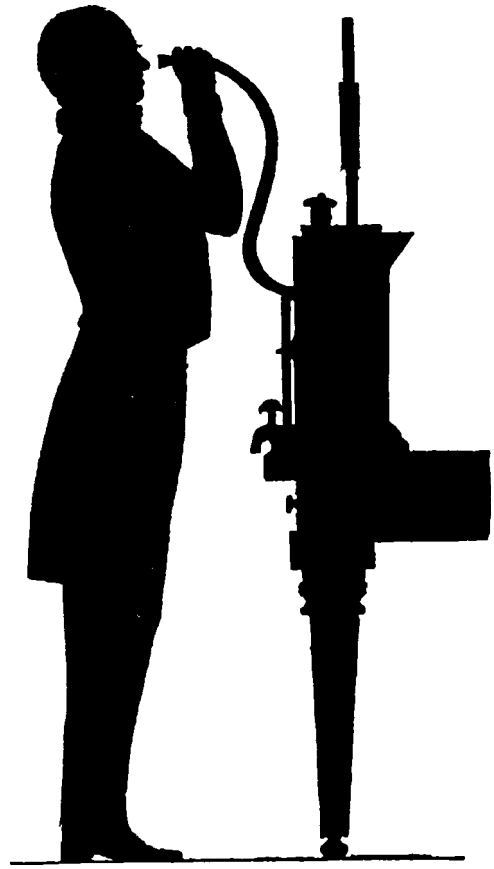

Figure 1-11 John Hutchinson's illustration of a subject about to undergo measurements of lung volumes. *(Reproduced with permission from Hutchinson J: Med Chir Soc (Lond) trans. 1846;29:137.)*

its clinical applicability and provided further evidence against the secretion theory.[12] Despite these observations, Haldane would not let go. Throughout his life, despite mounting evidence to the contrary, he adhered to the idea that oxygen was secreted by the alveolar membrane.

The issue was finally settled by Joseph Barcroft (Fig. 1-10). Using a chamber to reproduce the circumstances of hypoxia and strenuous exercise assessed during the Pike's Peak expedition, he found that under all conditions, the oxygen saturation of arterial blood was less than that of arterial blood exposed to a sample of alveolar gas obtained at the same time. He subsequently confirmed these results by experiments done at high altitude at Cerro de Pasco (1921–1922).

THE PHYSICAL–CHEMICAL SYNTHESIS

Lawrence J. Henderson undertook the herculean task of depicting the reactions of oxygen and carbon dioxide in blood, not as cause and effect, but as interplay among physiochemical variables and functions (Fig. 1-10). His theoretical considerations and practical applications in the Fatigue Laboratory at Harvard University were greatly abetted by close collaboration with Van Slyke, Wu, and McLean at the Rockefeller Institute in New York, who were exploring the exchanges of blood constituents between red cells and plasma. In 1828, Henderson presented his synthesis in the form of a d'Ocagne nomogram that displayed changes in the various elements that entered into the exchange of the respiratory gases between alveolar gas and blood: plasma; the red cell; hemoglobin; and chloride, bicarbonate, and hydrogen ions. He presented nomograms not only for the normal subject at rest and during exercises, but also for individuals with anemia, nephritis, diabetic coma, and other major clinical entities. Henderson dealt with steady-state observations. Roughton and associates enlarged the physiochemical horizons further by discovering carbonic anhydrase in the red cell and addressing transient phenomena related to transport of respiratory gases and carbon monoxide in blood.

LUNG VOLUMES

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800,[13] it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing. He devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age (Fig. 1-11). The many refinements since then are too numerous for mention in this chapter. A big step forward was the invention of the body plethysmograph many years later, which made possible the determination of the thoracic gas volume and airway resistance.

MECHANICS OF BREATHING

The ancients wondered how air moved into and out of the lungs; as far back as the time of Erasistratus, the diaphragm was recognized as involved in breathing. Galen was aware that the lungs fill the chest cavity and are moved by the actions of the thorax, and that the large airways enlarge and lengthen during inspiration. He marveled at the long course of the nerves to the diaphragm and the innervation of the intercostal muscles. After Galen, interest in the mechanics of breathing waned except for sporadic observations and experiments by anatomists, notably Leonardo da Vinci and Andreas Vesalius. Interest in respiratory mechanics resumed in the 16th century, largely as a result of progress in physics and mathematics, as exemplified in the works of Borelli and Galileo.

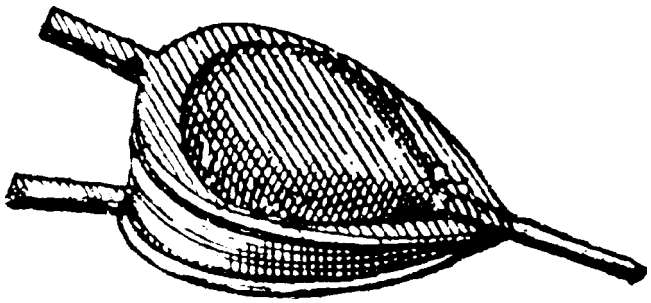

Figure 1-12 Mayow's model of the chest and lungs. The bellows encloses a bladder, the neck of which opens to the outside. A glass window on the upper side makes it possible to observe the bladder during inflation and deflation. *(Reproduced with permission from Mayow J: Medico-Physical Works, Crum A, Brown, Dobbin L (trans). Edinburgh, Alembic Club, Reprints, no 17, 1957. (Translated from Tractatus quinque medico-physics, 1674))*

THE RESPIRATORY MUSCLES

Mayow, one of the Oxford physiologists, drew heavily on the work of colleagues, including Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it (Fig. 1-12). He understood that air moved into the lungs as the chest expanded because of the pressure and elasticity of ambient air; he also appreciated that the chest expands because of the action of the intercostal muscles (internal and external), that the diaphragm is the primary muscle of inspiration, and that normal expiration is passive. After Mayow, little research was done on the role of the respiratory muscles in breathing until the mid-19th century, when Donders distinguished between the respective roles played by the inspiratory muscles and elastic forces.

ELASTIC PROPERTIES OF LUNGS AND CHEST

Until the 20th century, observations on the elastic properties of the lungs and chest cage in humans were fragmentary. Access to the pleural space was the major limiting factor. With few exceptions – notably Neergaard and Wirz, who used pleural pressures to determine elastic recoil in normal human subjects, and Christie, who recorded pleural pressures to demonstrate loss of pulmonary elasticity in emphysematous patients – measurements in humans were largely confined either to therapeutic interventions, for example, induction of a pneumothorax or aspiration of pleural fluid, or experiments done at autopsy. The number of observations on the mechanical properties of the lungs increased dramatically when it was shown by Buytendijk, in 1949, and again by Dornhurst and Leathart, in 1952, that esophageal pressures provided an accurate measure of pleural pressures.

The role of alveolar surface tension in determining the elastic forces in the lungs began to be widely appreciated in the late 1950s, although the stage had been set long before. In 1812, Laplace had published the law of surface tension. The implications of this law for the lungs was appreciated initially in 1929 when Neergaard compared pressure–volume curves of lungs filled with air with those filled with fluid. He concluded that unopposed surface tensions would favor alveolar collapse. Then, between 1954 and 1960, a remarkable outpouring of papers from different laboratories showed that a unique surfactant lined the alveoli, and this material was absent in premature infants with hyaline membrane disease (and alveolar collapse); these papers prompted extensive research on the chemical and physical properties of surfactant and on its sites of formation and removal.

AIRWAY RESISTANCE

A giant step forward occurred in 1916 when Rohrer, as part of his doctoral dissertation, presented a conceptual framework for determining flow and resistance in airways. His equations were based on precise anatomic measurements of airway dimensions in a human cadaver, coupled with aerodynamic principles. During the following decade, he and his coworkers, Neergaard and Wirz, applied Poiseuille's law for laminar flow and his equations to the determination of airway resistance. Use of Fleisch's pneumotachygraph, coupled with periodic interruptions of airflow, permitted measurement of alveolar pressure. Clinically useful measurements of alveolar pressure became available in 1956 with the introduction by DuBois and associates of the whole-body plethysmograph, which they coupled with the application of Boyle's law.

SYNTHESIS OF MECHANICS

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure–volume characteristics of the respiratory system and the work of breathing; they also developed the principle of optimal frequencies of breathing to minimize respiratory work. Together with von Neergaard and Wirz, Rohrer developed and tested, experimentally, concepts involving pressures, flows, and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester, starting in the 1940s. The contributions of W. O. Fenn, H. Rahn, and A. B. Otis to our present understanding of the mechanics of breathing are significant, and there is little doubt that this group shaped much of the contemporary thinking of respiratory physiologists and pulmonary physicians.[14–17]

CONTROL OF BREATHING

The control of breathing is a complex process that depends on the integrity of the entire respiratory system—lungs, airways, circulation, and control systems.[18] Two dominant control systems exist. One is in the central nervous system; the other is outside the brain. Control mechanisms in the central nervous system are influenced by the state of wakefulness or alertness and are subject to voluntary control. These mechanisms are also influenced reflexively by a variety of peripheral receptors.

LOCALIZATION OF THE CENTRAL RESPIRATORY CENTERS

In 1812, Legallois, apparently intrigued by the gasping movements of the head after decapitation, identified an area in the medulla that was essential for life. In 1923, Lumsden systematically explored the effects of serial sectioning of the brain stem on respiration, marking the beginning of the era of contemporary research on rhythmic breathing. He designated an area in the caudal pons responsible for a sustained inspiratory drive as the "apneustic center," and an area in the rostral and lateral portions of the pons that presumably inhibited the apneustic drive as the "pneumotaxic center"; sectioning of the vagi exaggerated the inhibition of the apneustic drive by the pneumotaxic center. Sixteen years later, Pitts et al.[19], using stereotactic stimulation of the cat medulla, identified inspiratory and expiratory centers and proposed a theory that could account for both rhythmic breathing and apneusis.

CHEMICAL STIMULATION OF THE RESPIRATORY CENTERS

The chemical stimuli to breathing have been known for more than a century. In 1885, Miescher-Ruesch showed in humans that ventilation at rest is primarily regulated by carbon dioxide. Between 1887 and 1901, cross-perfusion experiments by Leon Fredericq underscored the role of carbon dioxide. However, it was not until 1905

to 1909 that Haldane, Priestley, and Douglas paved the way to the modern understanding of the role of carbon dioxide under a variety of experimental conditions.[20] In their experiments on humans, they relied heavily on the Haldane gas analyzer and an alveolar gas sampler of their own invention. However, their experiments did not distinguish clearly between CO_2 and H^+ in the stimulation of the respiratory centers. Winterstein, and later Gesell,[21] advanced the idea that the chemical regulation of respiration is determined by the concentration of hydrogen ions within the respiratory centers.

The Winterstein theories[22] provide a good example of the evolution of ideas prompted by new discoveries and inventions. The original theory in 1911 attributed increments in ventilation caused by hypoxic or hypercapnic inspired mixtures to a single mechanism, that is, acidification of arterial blood by either carbonic acid or lactic acid. In 1921, Jacobs' demonstration of the rapid diffusion of carbon dioxide into starfish eggs implicated acidity within the respiratory centers,[23] as well as arterial blood acidity, as the sites of stimulation. To account for the stimulation of breathing by hypoxia (the peripheral chemoreceptors had not yet been discovered), he invoked the release of asphyxiating substances *(Erstickungsstoffen)* within the respiratory centers themselves. A third theory, postulated in 1949, attempted to incorporate the discovery of the peripheral chemoreceptors, and it finally gave way in 1955 to his fourth theory, which explained the effects of acid or hypoxia on both the central and peripheral chemoreceptors.

A major consequence of Winterstein's research was an impetus to subsequent exploration of the chemical control of breathing. These studies led to the identification of central chemoreceptors, distinct from mechanoreceptors, on the ventral surface of the medulla, and clarification of the role of hydrogen ion activity as the central stimulus to breathing. The studies also prompted a search for a unifying theory for the chemical control of breathing.

THE REFLEX REGULATION OF BREATHING

A considerable and diverse number of peripheral receptors can influence breathing reflexively by supplying information to respiratory centers located in the brain. These include pain receptors, stretch receptors in the muscles and distensible thoracic structures, and organs and chemoreceptors in major systemic arteries.

MECHANORECEPTORS

Until the work of Hering and his student, Breuer, little was known about the role of afferent impulses to the central control mechanisms in the control of breathing, other than the fact that electrical stimulation of the vagus nerves influenced respiration.[24] In 1868, Hering and Breuer reported that inflation of the lungs stopped respiration in expiration and promoted expiration, and that, conversely, a decrease in lung volume ended expiration and promoted inspiration. They inferred that inflation mechanically stimulated nerve endings in the lungs and that the resulting impulses ascending the vagi were inhibitory to inspiration.

PERIPHERAL CHEMORECEPTORS

In 1841, Volkmann suggested the existence of chemoreceptors in the systemic circulation that were sensitive to blood-borne stimulants to respiration. In 1927, J. F. Heymans and C. Heymans first showed that the aortic bodies served this function, and in 1930, C. Heymans and Bouckaert demonstrated the peripheral chemoreceptive function of the carotid bodies. These were physiologic observations that tallied well with the observations of F. De Castro, a student, and later a colleague, of Ramón y Cajal, who was sufficiently impressed by the histologic structure, location, and rich innervation of the carotid body to propose that it might be stimulated by blood-borne substances (Fig. 1-13).[25]

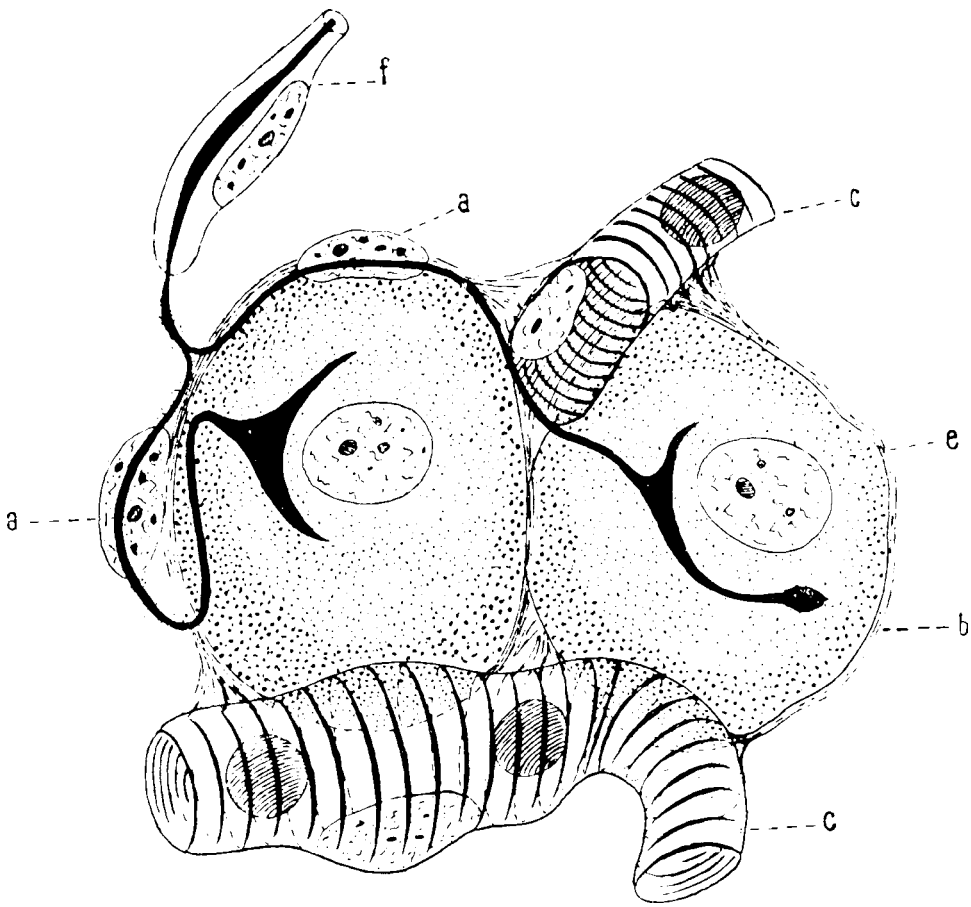

Figure 1-13 Drawing by De Castro showing the structure of the chemoreceptor. The glomus cells (*e*) present an ample cytoplasmic surface for contact with the perfusing blood delivered by the capillary (*c*); sensory nerve fiber (*f*) with sheath of myelin; Schwann cells (*a*) surround the unmyelinated fibers which form the terminal menisci; cell membrane (*b*). *(Reproduced with permission from De Castro F: Sur la structure de la synapse dans les chemocepteurs: leur mécanisme d'Excitation et R™ le dans la circulation sanguine locale. Acta Physiol Scand. 1951;22(1):14–43.)*

Figure 1-14 Giovanni Battista Morgagni (1682–1771). The five volumes of his *De Sedibus* contain the clinical and pathologic descriptions of approximately 700 cases. *(Courtesy of the Library of the College of Physicians of Philadelphia.)*

Figure 1-15 Rene T.H. Laënnec (1781–1826). *(Drawn from life in 1825 by Charles James Blasius Williams (1805–1889) and reproduced in his autobiography, Memoirs of Life and Work, London: Smith, Elder & Co; 1884.)*

VENTILATION–PERFUSION RELATIONSHIPS

In 1946, William Dock attributed the apical localization of tuberculosis to hypoperfusion of well-ventilated alveoli in the lung apices in the upright position.[26] Shortly thereafter, ventilation–blood flow relationships were described in quantitative terms in papers by two separate groups: Rahn and Fenn[27] and Riley and Cournand.[28–30]

SCIENTIFIC BASIS OF CLINICAL PULMONARY MEDICINE

Five remarkable figures serve to illustrate different stages in the evolution of the scientific basis of pulmonary medicine: Morgagni, Laënnec, Koch, Cournand, and Richards. They represent key scientists in the areas of pathologic anatomy, microbiology, and physiology.

■ PATHOLOGIC ANATOMY

Morgagni and Laënnec, almost a century apart, made major contributions to the field of pathologic anatomy. Morgagni (Fig. 1-14), who lived in the 18th century and was a student of Valsalva, veered away from the undisciplined case reports of his predecessors. Instead, he adopted a logical system for relating findings at autopsy to their clinical manifestations. At age 79, he published a compilation of his lifelong experience in his famous work, *De Sedibus et Causis Morborum per Anatomen Indagatis. De Sedibus* includes about 700 cases. The clinical–pathologic correlations in this work benefited greatly from the fact that Morgagni was both a seasoned clinician and a pathologist. One of the compilation's five books is devoted to diseases of the thorax. Among his descriptions were those of a tubercle undergoing liquefaction and the hepatization stage of pneumonia.

René Théophile Laënnec is, perhaps, best known for inventing the stethoscope in 1816 (Fig. 1-15).[31,32] At that time, clinical medicine in Europe, especially in France, was turning from metaphysical concepts and doctrinal systems to pathology as its scientific foundation. Eminent physicians, such as Bichat, Bayle, and Corvisart in France, and William and John Hunter and Baillie in England, were turning to anatomic findings at autopsy to understand the signs and symptoms of their patients. Percussion had been rediscovered by Corvisart. Although Auenbrugger had reported in Latin his "new invention" in 1761, the idea had not caught on until Corvisart – eminent clinician and teacher and personal physician to Napoleon – published a translation in French in 1808. Corvisart's approach to medicine strongly influenced Laënnec. Laënnec applied the stethoscope and Corvisart's "sounding of the chest" to study individual patients with diseases of the lungs and heart throughout their clinical course, along with anatomical examination at autopsy. This was no simple matter. Since there were no pathologists in those days, the physician not only had to provide continuous care during the patient's lifetime, but he also had to arrange for, and perform, the autopsy; he then had to gather all that he had seen and learned and prepare it for publication.

In 1819, two years after the invention of the stethoscope, Laënnec published his famous monograph, *De l'Auscultation médiate*, which drew lessons from carefully documented cases that were studied throughout their clinical course and at autopsy. In this work, Laënnec built upon the monumental tome of Morgagni, who, a generation before, had related the clinical features of the diseases he described to the morbid anatomy, but who had not been able to take the next step of relating the clinical course of individual patients to the anatomic findings after death.

Laënnec's monograph contains descriptions of physical signs, clinical–pathologic correlations for tuberculosis, pneumonia, bronchiectasis, emphysema, and cancer of the lung, and instructions for the treatment of these conditions. The descriptions of tuberculosis were an outstanding contribution to the field and were reported prior to Koch's discovery of the causative agent.

■ MICROBIOLOGY

Tuberculosis provides a remarkably illuminating example of the impact of a novel basic science on clinical medicine.[33–35] The disease

can be traced back to the ancients, who were familiar with the diverse clinical syndromes that we now take for granted as due to tuberculosis; however, they had no way to relate them to a common etiologic agent. A synthesis by Morton in 1685 of all that was then known about tuberculosis focused on cavitary lesions, emaciation ("consumption"), and the tubercle, but it was shrouded in Galenic humors. An understanding of the disease accelerated in the 18th century when clinicians, such as William Cullen, began to sort out the various syndromes relating to phthisis, including hemoptysis, empyema, catarrh, and asthma.

The tempo of discovery increased dramatically in the 19th century after the French Revolution. During the Napoleonic era, distinguished Parisian clinicians, including Bichat, Bayle, Louis, Broussais, and Laënnec, reported clinical–pathologic correlations of tuberculosis (Notably, both Bayle and Laënnec died of tuberculosis.). However, little advance was made in understanding the pathogenesis of tuberculosis until Villemin, who, impressed by the analogy between glanders and syphilis on the one hand, and tuberculosis on the other, and the fact that two of the three diseases had been shown to be infectious in origin, undertook experiments demonstrating that tuberculosis was an infectious disease that could be transmitted from humans to animals, and from animals to animals.

KOCH

In 1876, Koch was a general practitioner in the German township of Wollestein in the province of Posen, where he was responsible for the health care of 4000 inhabitants (Fig. 1-16). Between obstetrical deliveries and satisfying the medical and surgical needs of patients of all ages, he managed to conduct research on the microbial causes of communicable diseases. His laboratory was homemade—based in either the barn or his living room; his major instrument was a microscope used to examine bacteriologic and tissue specimens. In pursuing his research, he kept in mind the dictum of Jacob Henle, one of his teachers in medical school, who counseled that, "before microscopic organisms can be regarded as the cause of contagion in man, they must be found constantly in the contagious material, they must be isolated from it and their strength tested." This lesson was to become the keynote of the future "Koch postulates."

In 1876, Koch, the busy medical practitioner, sent a letter to Professor Ferdinand Cohn, director of the Botanical Institute in Breslau, indicating that he had discovered "the process of development of bacillus anthracis" and requesting permission to present his findings to Professor Cohn, "the foremost authority on bacteria." Koch had discovered the spores of anthrax bacilli. Cohn arranged for him to present his results before a room full of formidable, distinguished scientists, including Julius Cohnheim, Carl Weigert, Moritz Traube, Ludwig Lichtheim, and Leopold Auerbach. Koch's demonstration of the complete life history of the anthrax bacillus, including sporulation, was entirely convincing to these scientists. After the meeting, Cohnheim, upon his return home, announced to his colleagues, "This man has made a splendid discovery which is all the more astonishing because Koch has had no scientific connections and has worked entirely on his own initiative and has produced something absolutely complete. There is nothing more to be done. I consider this the greatest discovery in the field of bacteriology."

During the next 2 years, Koch described novel procedures for the examination, preservation, and photography of bacteria and demonstrated the role of microorganisms in traumatic infections, while continuing his dual existence as a country doctor and an independent investigator. In 1880, Cohn and Cohnheim arranged for him to move to Berlin as a member of the Imperial Sanitary Commission. The move freed more time for research. By 1881, he made another breakthrough—the pour-plate method for isolating pure cultures. The opportunity that this technique afforded to produce transparent solid media, coupled with Koch's invention of new staining methods, paved the way for him to tackle the microbial cause of tuberculosis.

Figure 1-16 Robert Koch (1843–1910), announcing his discovery of the tubercle bacillus as the cause of tuberculosis, Berlin, March 28, 1882. *(Reproduced with permission from Knight D: Robert Koch: Founder of Bacteriology. New York: Franklin Watts, Inc.; 1961:10.)*

Koch's scientific approach, which has been immortalized as "Koch postulates," consisted of four essential steps: (1) To prove that a microbe is the cause of a disease, it must be present in all cases of the disease (Koch showed this for the tubercle bacillus using methylene blue and a counter stain), (2) the microbe must be grown outside of the body in pure culture. (Koch devised blood-serum jelly as a culture medium for the slow-growing tubercle bacillus.), (3) the pure culture must be capable of causing the disease in healthy animals (Koch proved this initially by inoculation and, subsequently, by allowing animals to breathe contaminated air.), (4) the same microbe must then be isolated from the inoculated (infected) animal and grown outside of the body in pure culture.

Koch's discovery of the tubercle bacillus and its modes of transmission revolutionized the treatment of tuberculosis. Before the discovery, tubercular patients were treated in sanitaria, which offered fresh air and altitude. Those who ran the sanitaria did not know that tuberculosis was a contagious disease: Sanitation was unregulated, and neither sterilization nor fumigation was practiced; diagnostic capabilities were limited. Koch's discovery of the tubercle bacillus revolutionized therapy. For the rest of his life, while pursuing the causes of other diseases around the world – rinderpest in South Africa, Texas fever, tropical malaria, blackwater fever, and bubonic plague in Bombay – Koch maintained his interest in tuberculosis.

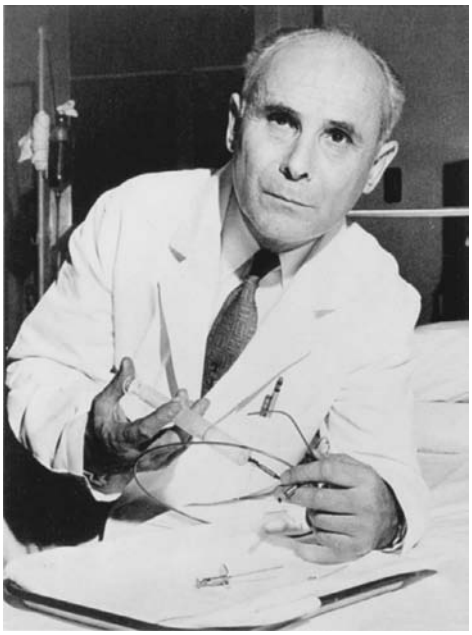

Figure 1-17 André Frederic Cournand (1895–1988) and Dickinson W. Richards (1895–1973). After Forssman's report of the uneventful catheterization of his own right heart, Cournand and Richards pioneered the use of cardiac catheterization for the study of the normal and the abnormal pulmonary circulation and the standardization of pulmonary function tests.

This interest, however, led him into a major mistake—advocacy of tuberculin as a vaccine instead of as a diagnostic test. In 1905, he was awarded the Nobel Prize. On April 7, 1910, the year of his death, he delivered a final address on the epidemiology of tuberculosis before the Berlin Academy of Sciences.

■ PHYSIOLOGY OF THE PULMONARY CIRCULATION

Starting with William Harvey,[5] studies of the pulmonary circulation have gone hand in hand with advances in pulmonary physiology and medicine. For many years, research on the pulmonary circulation was confined to animal experimentation. A giant step forward was made with the introduction of cardiac catheterization in humans.

Accurate measurement of pulmonary blood flow is a sine qua non for assessing pulmonary and cardiac performance in health and disease. The use of nitrous oxide in humans by Krogh and Lindhard was an important beginning in this direction, but not until mixed venous blood could be sampled for application of the Fick principle could reliable determinations of pulmonary blood flow be made.

Claude Bernard in 1846 and Chauveau and Marey in 1861 had catheterized the right side of the heart in animal experiments. Whether this technique could be used safely in humans was not known until 1929, when Werner Forssmann, a young surgeon in Germany, introduced a ureteral catheter into his own right atrium. In the 1940s, Cournand, Richards, and their colleagues resorted to right heart catheterization to obtain mixed venous blood for the determination of cardiac output by application of the Fick principle (Fig. 1-17). The technique opened the way not only to the accurate determination of cardiac output, but also to exploration of the heart and lungs in a wide variety of clinical disorders.

Until 1946, when von Euler and Liljestrand reported the effects of hypoxia and hypercapnia on the pulmonary circulation in an open-chest preparation of an anesthetized cat, (Fig. 1-18)[36] there was little understanding of the regulation of the pulmonary circulation. However, these studies, coupled with the proposition of local control of the pulmonary circulation by local concentrations of the respiratory gases, paved the way to understanding pulmonary hypertension and the behavior of the pulmonary circulation in normal individuals at rest, after birth, during exercise, and at altitude, and in individuals with heart or lung disease.

The interposition of the pulmonary circulation between the right and left sides of the heart is a prerequisite for gas exchange. However, it also serves a variety of other functions, for example, a

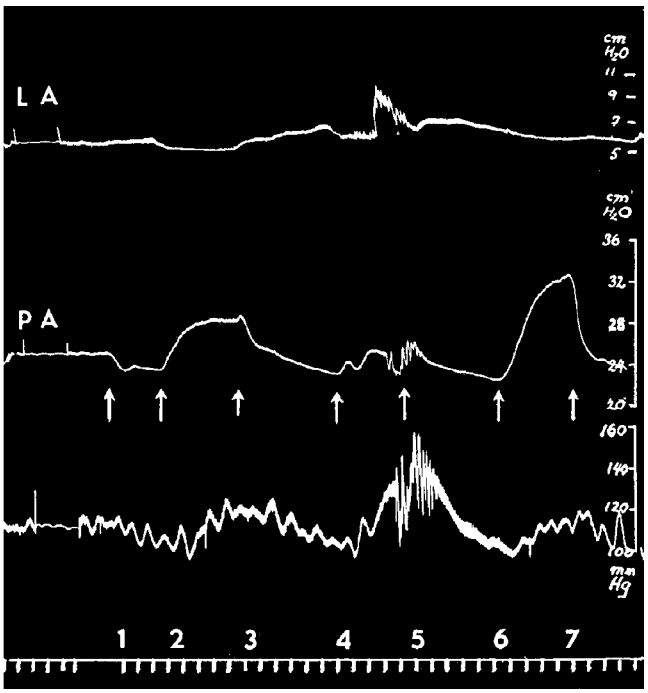

Figure 1-18 Effects of the blood gases on pulmonary arterial pressure in the open-chest cat, artificial respiration. LA, left atrial pressure; PA, pulmonary arterial pressure; lower trace, systemic arterial blood pressure. Numbers along the baseline represent the administration of test gases: 1, O_2 (from air); 2, 6.5% CO_2 in O_2; 3, O_2; 4, 18.7% CO_2 in CO_2; 5, O_2; 6, 10.5% O_2 in N_2; 7, O_2. *(Reproduced with permission from Von Euler, US and Liljestrand, G: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand. 1946;12(4):301–320.)*

mechanical role, as a filter for particulate matter in blood returning to the heart, and a metabolic role, effecting the synthesis, uptake, and breakdown of biologic compounds. Extensive studies have been conducted in recent decades on the nonrespiratory functions of the lungs. From these studies has emerged considerable understanding of the diverse functions served by the branching pulmonary circulation and its components, including the endothelium and smooth muscle and their interplay.

TECHNOLOGIC ADVANCES THROUGH THE EARLY 20TH CENTURY

The road to contemporary pulmonary medicine could be just as easily traced by using technologic advances as landmarks, instead of people and discoveries. For example, the introduction of the manometer for pressure recording, the use of chambers to simulate high altitude, the development of accurate blood gas analyzers, and the application of sophisticated optical systems for viewing the lumens of the airways and the inside of the chest cavity are all notable milestones. However, probably no better example exists than the discovery of radiographs and the application of this discovery to the diagnosis, prevention, and management of pulmonary tuberculosis.

Wilhelm Conrad Roentgen discovered radiographs in 1895 while experimenting with cathode ray tubes in his physics laboratory at the University of Wurzburg. Although others before him had seen radiographs as early as 1890, Roentgen was apparently the first to grasp the full significance of the discovery, and his publication, quite unpretentious, immediately attracted worldwide attention because of its prospects for the study of anatomic structures and pathologic changes.

Within 2 years after Roentgen's discovery, fluoroscopy of the chest had been introduced into clinical practice, and its value in the early detection of tuberculosis and the diagnosis of pleural effusions was appreciated. In 1901, an atlas of chest radiographs was published, and the use of chest radiography increased greatly with each subsequent improvement in hot cathode radiograph tubes and intensifying screens. The radiographic evaluation of tuberculosis was superior to physical examination for diagnosis and characterization of the disease. By 1910, all patients admitted to sanatoriums had a chest radiographic examination, and by 1917 tuberculosis was classified according to radiographic findings.

MAJOR DEVELOPMENTS SINCE THE MID-20TH CENTURY

Many notable developments have occurred over the last 60 years in pulmonary medicine and the related field of critical care. Measured against the metric of having a broad and deep impact on clinical care, several are particularly noteworthy: advances in thoracic imaging, lung transplantation, bronchoscopy and interventional bronchoscopic techniques, and advances in management of the critically ill.

■ ADVANCES IN THORACIC IMAGING

Following Roentgen's discovery of the x-ray at the turn of the 20th century, another major diagnostic leap forward in pulmonary medicine occurred with development of computerized tomography (CT) in the 1960s.[37–39] In 1967, the first experimental CT scan was generated, with computer reconstruction of an image of a mouse taking 9 days to complete. The first human application was a head CT which demonstrated a brain tumor (Fig. 1-19). In 1973, Dr. Godfrey Hounsfield published a description of CT scanning in the British Journal of Medicine. Along with Dr. Allan Cormack, Hounsfield (Fig. 1-20) was awarded a Nobel Prize in 1979.

Application of CT to lung imaging arose in the mid-1970s; high-resolution techniques were developed in the 1980s. Multislice CT scanning now permits rapid acquisition of high-resolution images

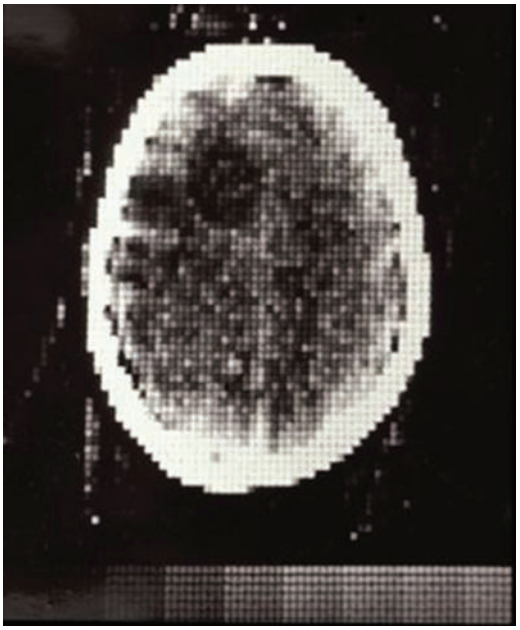

Figure 1-19 The first clinical CT scan, obtained in 1971. The grainy image shows a brain tumor in a frontal lobe (*left side* of image). Advances in image quality over the last four decades have been dramatic. *(Source: impactscan.org.)*

from which multiplanar reconstructions can be derived (Fig. 1-21). Elegant characterization and classification of a variety of interstitial and airway diseases is now possible using CT. In addition, when coupled with intravenous contrast injection (CT angiography), rapid, high-resolution scanners provide for the highly accurate diagnosis

Figure 1-20 Dr. Godfrey Hounsfield, inventor of computerized tomography (CT). Along with Dr. Allan Cormack, Hounsfield was awarded a Nobel Prize in 1979. *(Source: Visible Proofs, National Library of Medicine, National Institutes of Health.)*

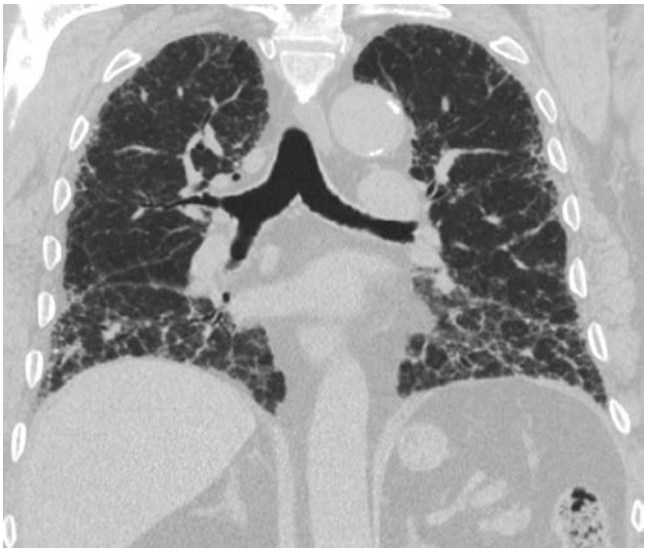

Figure 1-21 A modern day, coronal reconstruction of the chest using CT in a patient with idiopathic pulmonary fibrosis (IPF). Current scanners are capable of rapidly generating high-resolution images from which a variety of computer-generated reconstructions can be derived. *(Used with permission of Dr. Eduardo J. Mortani Barbosa, Jr.)*

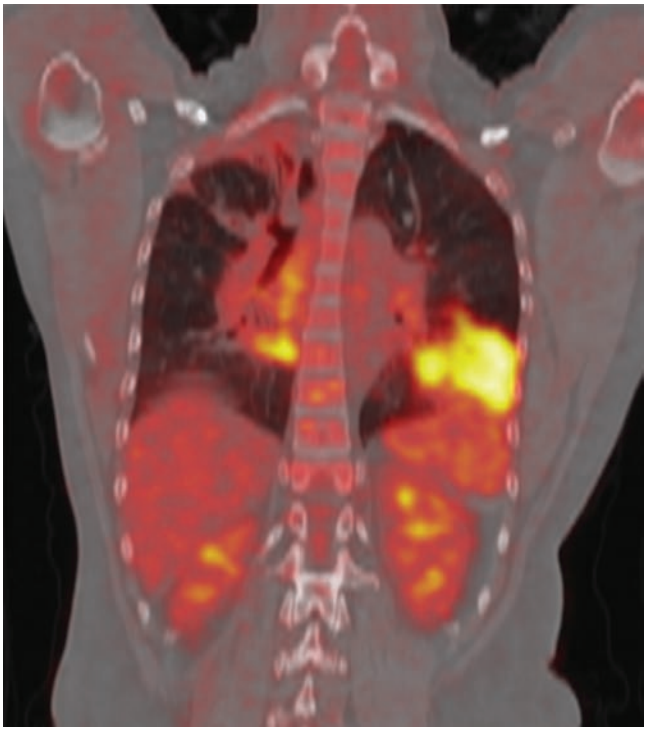

Figure 1-22 A coronal PET/CT image demonstrating metastatic lung cancer, evident as bright areas (in *yellow*) at the left base and the right hilum. The PET and CT images are aligned ("in register") to create precise anatomic localization of the heightened metabolic activity noted in the PET image. *(Used with permission of Dr. Eduardo J. Mortani Barbosa, Jr.)*

of pulmonary embolism[40] and other pulmonary vascular disorders. Advances in multislice techniques (e.g., development of 256-slice or 320-slice scanners) offer the promise of even higher quality imaging.

More recently, aligning the anatomic detail provided by CT with functional images afforded by positron emission tomography (PET) has generated useful information on the staging and clinical assessment of bronchogenic carcinoma, particularly non–small-cell carcinoma.[41–45] Positively charged electrons (positrons), emitted from injected radionuclides are destroyed by electrons and, in the process, produce photons which are detected and imaged by the PET scanner. Malignant cells, by virtue of having increased numbers of cell membrane–based glucose transporters compared with normal cells, accumulate greater levels of the radionuclide,[18] F-fluorodeoxyglucose (F-FDG), which cannot be metabolized further and is trapped within the cells. The tracer-enriched collection of malignant cells stands out against the background of normal tissue. Coupling of the PET-based and CT images provides precise localization of the area of abnormality (Fig. 1-22). PET/CT imaging has been used to evaluate solitary pulmonary nodules, assess local extent of disease (particularly mediastinal and pleural involvement) in lung cancer, and evaluate distant anatomic sites for metastatic disease.

■ LUNG TRANSPLANTATION

Following on the heels of pioneering animal experimentation conducted by Vladimir Demikhov,[46] the first reported human lung transplantation was conducted by Dr. James Hardy and colleagues in 1963.[47,48] However, it was not until the 1980s that clinically meaningful outcomes were achieved by Dr. Joel Cooper and colleagues with single-lung[49] and bilateral-lung[50] transplantation.

Since the advent of lung transplantation, more than 32,000 procedures have been performed worldwide. Survival of recipients has improved from 4.0 years in the late 1980s and early 1990s to 5.7 years in the last decade. Contemporary, overall survival rates are 79% at 1 year, 63% at 3 years, 52% at 5 years, and 29% at 10 years.[51]

Lung transplantation is associated with improvements in lung function, exercise tolerance, and hemodynamic parameters. Currently, the primary diagnoses for which lung transplantation is most commonly conducted include (in descending order of frequency) idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and other disorders, including alpha-1-antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, lymphangioleiomyomatosis (LAM), and primary pulmonary hypertension.[51,52]

Despite tremendous advances in the field, complications of lung transplantation are common and include primary graft dysfunction (noncardiogenic pulmonary edema without other apparent cause occurring in the first 72 hours following transplantation); bronchial stenosis developing at the anastamotic site; a broad array of infectious complications, including CMV infection; acute rejection (occurring in over one-third of recipients); and chronic allograft dysfunction due to bronchiolitis obliterans.[51]

Improved surgical techniques in lung transplantation have been important. However, critical to advances in solid organ transplantation, including lung transplantation, has been development of effective immunosuppressive regimens.The earliest regimens included a limited repertoire of drugs, for example, corticosteroids and azathioprine. Development of calcineurin inhibitors, including cyclosporine in 1977 and tacrolimus in 1983, substantially advanced the field.[53]

While technical and pharmacologic advances in lung transplantation afford many patients with advanced lung disease improved quality of life, a limited supply of suitable donor organs persists. Various approaches have been employed in an attempt to ameliorate the continuous shortage. In addition to obtaining organs from brain-dead donors as the primary source, more recently, many transplant programs have embarked on the somewhat controversial program of donation after cardiac death (DCD) or donation from "non–heart-beating donors," who undergo controlled withdrawal of life support in an operating room. In addition, new technologic developments in organ "reconditioning" offer hope for enlarging the supply of transplantable lungs.[54–56]

Figure 1-23 Gustav Killian (1860–1921), the father of bronchoscopy. *(Used with permission of Klaus D. Peter, Wiehl, Germany. Released to the public domain, via Wikimedia Commons.)*

■ BRONCHOSCOPY AND INTERVENTIONAL BRONCHOSCOPIC TECHNIQUES

Application of bronchoscopic techniques, both rigid and flexible, has revolutionized the field of pulmonary medicine, from both diagnostic and interventional perspectives. Credit for invention of the rigid bronchoscope is given to Gustav Killian (Fig. 1-23) in Germany in the late 19th century;[57] in the United States, the field of rigid bronchoscopy was pioneered by Chevalier Jackson in Philadelphia (Fig. 1-24).[58] The next major wave in bronchoscopy arose with development of the flexible fiberoptic technique by Shigeto Ikeda in Japan.[59,60] Since then, significant advances in optics, digital technology, and a variety of interventional techniques, including those based on the fiberoptic method, have been reported.

Figure 1-24 Chevalier Jackson (1865–1958), a pioneer in American bronchoesophagology. *(Courtesy of Thomas Jefferson University.)*

Figure 1-25 An "iron lung." The patient was placed in the hollow cylinder before the device was sealed, with his or her head protruding from one end. *(Used with permission of CDC/GHO/Mary Hilpertshauser. Photo Credit: Jim Gathany.)*

■ ADVANCES IN CRITICAL CARE

In parallel with the previously noted advances in imaging, transplantation, and bronchoscopy, significant progress in the management of critically ill patients has occurred over the last several decades. One of the most notable is application of mechanical ventilation.[61–63]

The era of the "iron lung," the first widely used negative pressure ventilator, dates back to 1928 (Fig. 1-25).[64–66] Restricted access to the patient was a major limitation to use of the device. The advent of positive pressure ventilators, dramatically evident during the polio epidemic in Copenhagen in 1952, ushered in the "modern" era of mechanical ventilation.[67] Indeed, the clustering of paralyzed patients needing ventilatory support paved the way for development of medical intensive care units. Subsequent invention of the Bennett valve, a result of efforts to establish a means of facilitating high-altitude flight for military purposes, further enhanced clinical use of positive pressure ventilation.[68–71] Many additional refinements in mechanical ventilation, including microprocessor-controlled functions, have evolved over the last quarter century. One noteworthy development in the field deserves special consideration: use of the "low-stretch protocol."

Based on recognition that application of traditionally used tidal volumes of 10 to 15 mL/kg body weight may cause stretch-induced injury in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), a multicenter prospective trial was undertaken to address whether use of smaller tidal volumes (6 mL/kg), that is, a "low-stretch protocol," would improve outcomes. Indeed, in a landmark study published in 2000, an approximate 25% reduction in mortality using a low-stretch protocol was demonstrated.[72] Additional refinements, including use of higher levels of positive end-expiratory pressure (PEEP)[73] and the so-called "lung recruitment maneuvers"[74] have been added to the contemporary ventilator management scheme for these patients.

In addition to advances in mechanical ventilation, other notable recent refinements in critical care include recognition of the value of venous thromboembolism prophylaxis, prophylaxis against gastrointestinal bleeding, semierect patient positioning to minimize aspiration risk, good (but not excessive) glycemic control, application

of spontaneous breathing trials and sedation interruption, and early patient mobilization. However, one particular development warrants special mention: use of early goal-directed therapy (EGDT) in sepsis.

Sepsis is a severe, systemic response to infection and is associated with high mortality. A reflection of the systemic inflammatory response syndrome (SIRS), sepsis may progress to severe sepsis (end-organ dysfunction in the setting of documented or suspected infection) or septic shock (severe sepsis with hypotension unresponsive to intravenous fluid administration). An important study published in 2000 addressed the value of EGDT in the management of septic patients. Such therapy focuses on early and aggressive fluid administration titrated to a goal central venous pressure (CVP), mean arterial blood pressure (MAP), and target central venous oxygen saturation (Scv_{O_2}), and incorporates use of vasoactive agents and transfusion of packed red blood cells as necessary. Application of EGDT has been shown to reduce mortality by as much as one-third[75] and constitutes one of the cornerstones of management of critically ill patients with sepsis, as comprehensively discussed in the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock."[76]

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SECTION 1 Genetic, Cellular, and Structural Basis of Normal Lung Function

CHAPTER 2

Functional Design of the Human Lung for Gas Exchange

Matthias Ochs
Ewald R. Weibel

At the end of a deep breath, about 80% of the lung volume is air, 10% is blood, and only the remaining 10% is tissue. Because this small mass of tissue is spread over an enormous area – nearly the size of a tennis court – the tissue framework of the lung must be extraordinarily delicate. It is indeed remarkable that the substance of the lung manages to maintain its integrity in the face of the multitude of insults that inevitably accompany a lifetime of exposure to ambient air and the complex necessity of keeping air and blood in intimate contact, but separate, for the sake of gas exchange.

Part of this success is undoubtedly attributable to the unique design of the lung, which ensures mechanical stability as well as nearly optimal conditions for the performance of the lung's primary function: to supply the blood with an adequate amount of oxygen even when the body's demands for oxygen are particularly high, as during heavy work.

THE LUNG AS AN ORGAN

At total lung capacity, the lung fills the entire chest cavity and can reach a volume, in the adult human, of some 5 to 6 L, largely depending on body size. Upon expiration, the lung retracts, most conspicuously from the lower parts of the pleural cavity, the posterior bottom edge of the lung moving upward by some 4 to 6 cm. This preferential lifting of the bottom edge is caused by retraction of the tissue throughout the entire lung, the surfaces of which are freely movable within the thoracic cavity.

The structural background for this mobility of a healthy lung is the formation, during morphogenesis, of a serosal space that is lined on the interior of the chest wall and on the lung surface by a serosa, the parietal and visceral pleurae, respectively (Fig. 2-1). However, this serosal space is minimal, since the visceral pleura is closely apposed to the parietal pleura, with only a thin film of serous fluid intercalated as a lubricant between the two surfaces.[1] Both pleural surfaces are lined by a squamous epithelial layer, often called mesothelium (due to its mesodermal origin), whose surface is richly endowed with long microvilli. The apical microvilli increase the surface area available, suggesting that pleural mesothelial cells are capable of participating in active transserosal transport of solutes. The total volume of pleural fluid is about 15 to 20 mL, with approximately 1700 cells/mm^3 (75% macrophages, 23% lymphocytes, 1% mesothelial cells). The volume and composition of the pleural fluid have to be tightly controlled to ensure an efficient mechanical coupling between chest wall and lung. Pleural fluid originates from pleural capillaries through microvascular filtration. Drainage occurs partly via lymphatic stomata in the parietal pleura. Transcytosis through mesothelial cells in both directions represents another mechanism involved in pleural fluid homeostasis.[2–6]

The connective tissue of the visceral pleura consists of three layers. A superficial layer of predominantly elastic fibers follows the mesothelium, thereby forming an elastic "bag" that enwraps each lobe. A deep sheet of fine fibers follows the outline of alveoli and extends into the depth of the lung. Between these sheets lies a bed of loose connective tissue, containing free cells (histiocytes, plasma cells, and mast cells), that is often close to lymphatics and systemic arterial branches from the bronchial arteries.

The lung is maintained in a stable position within the chest by the hilum, where airways and blood vessels enter from the mediastinum, and by the pulmonary ligament, a long, narrow band of attachment between visceral and mediastinal pleura that extends downward from the hilum. Because of these attachments, a pneumothorax causes the lung to retract and form a lump of tissue that is attached to the mediastinal wall of the thoracic cavity.

The shape of the lung is congruent with that of the fully expanded pleural cavity. This shape is preformed in lung tissue and is hence also evident if an excised lung is inflated, revealing its three faces: the convex thoracic face apposed to the rib cage, the concave diaphragmatic face modeled by the diaphragmatic dome, and the mediastinal face, on which the contours of the heart are impressed beneath the hilum.

As the lung retracts during deflation, the acute edges between the thoracic face and the diaphragmatic and (anterior) mediastinal faces of the lung withdraw; the thoracic and diaphragmatic leaflets of the parietal pleura become apposed, thereby forming a costodiaphragmatic recess on each side (Fig. 2-1). Similarly, as the ventral edge of the lung retracts, the costal and mediastinal pleurae form a

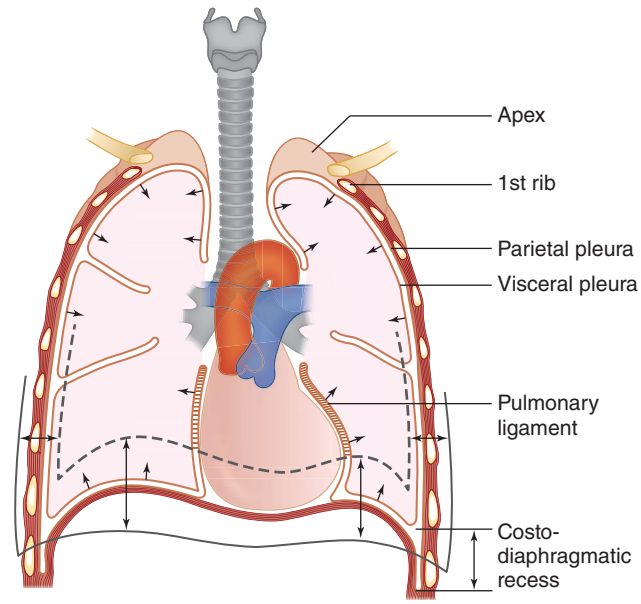


Figure 2-1 Frontal section of chest and lung showing pleural space. *Single arrows* indicate retractive force. *Double arrows* show the excursion of the lung bases and periphery between deep inspiration and expiration.

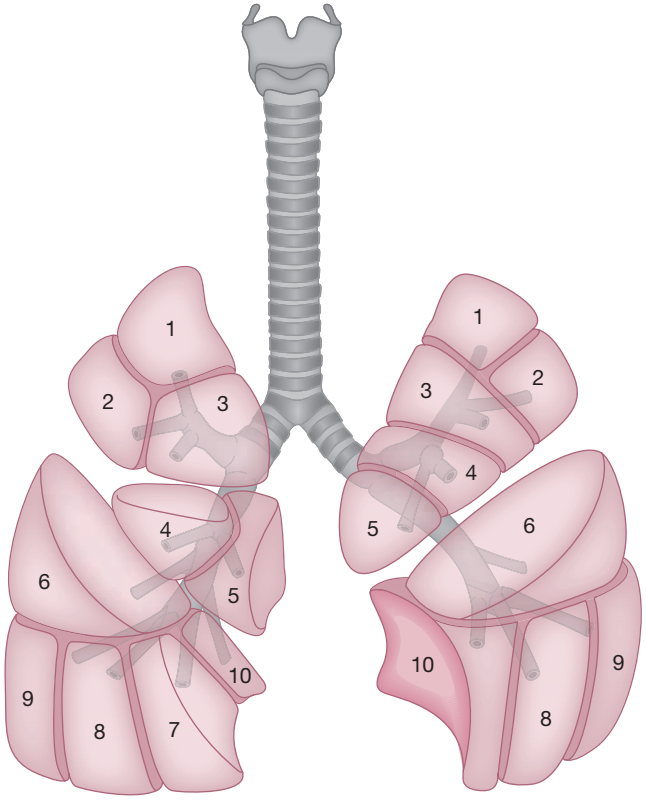


Figure 2-2 Bronchopulmonary segments of human lung. Left and right upper lobes: (1) apical, (2) posterior, (3) anterior, (4) superior lingular, and (5) inferior lingular segments. Right middle lobe: (4) lateral and (5) medial segments. Lower lobes (6): superior (apical), (7) medial–basal, (8) anterior–basal, (9) lateral–basal, and (10) posterior–basal segments. The medial–basal segment (7) is absent in the left lung. (Note: The lungs are represented as turned inward slightly to display part of the lateral face.)

recess on each side, corresponding topographically to the borders of the sternum.

The port through which airways and blood vessels enter the lung is the hilum, that is, the attachment of lung tissue to the mediastinum (Fig. 2-1). The airways reach the two hili by the mainstem, or principal, bronchi (Figs. 2-1 and 2-2). The left mainstem bronchus is longer than the right because it must pass under the aortic arch before it reaches the lung. The two principal bronchi course downward and begin to divide sequentially shortly after entering the lung, first releasing the lobar bronchus to the upper lobe (Fig. 2-2). Since a middle lobe is formed only on the right side, there is no middle lobe bronchus on the left; instead, the corresponding parts form the lingula, which receives its airways from the superior bronchus of the upper lobe (Fig. 2-2). The last branch of the stem bronchus goes to the lower lobe.

The branching pattern of the human bronchial tree and of the pulmonary artery and veins are shown in a resin cast in Figure 2-3. The pulmonary artery joins the bronchi while still in the mediastinum (Fig. 2-4A); its trunk lies to the left of the ascending aorta, and the right pulmonary artery turns dorsally to course between ascending aorta and right principal bronchus. In the hilum, the right pulmonary artery lies anterior to the right principal bronchus; the left pulmonary artery, however, "rides" on the principal bronchus and crosses over the superior lobar bronchus to the posterior side. From there on, the pulmonary artery branches in parallel with the bronchi; characteristically, each bronchus is associated with one closely apposed pulmonary artery branch, and this relationship

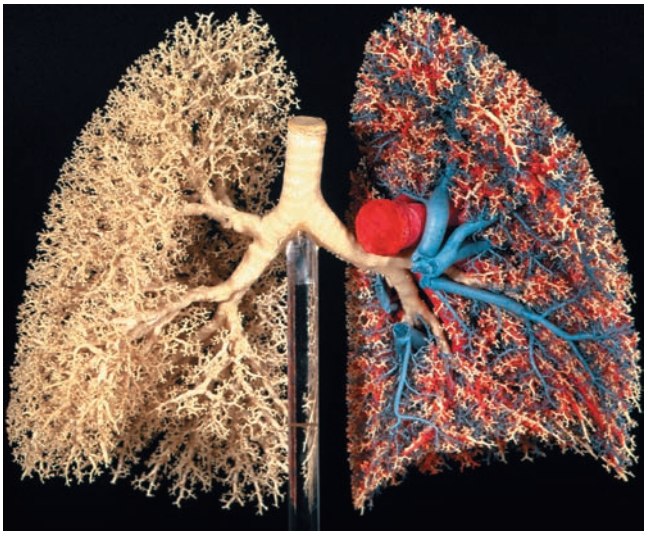


Figure 2-3 A resin cast of the human airway tree shows the dichotomous branching of the bronchi from the trachea and the systematic reduction of airway diameter and length with progressive branching. In the left lung the pulmonary arteries *(red)* and veins *(blue)* are also shown.

is strictly maintained to the periphery, that is to the respiratory bronchioles.

In contrast, the pulmonary veins (Fig. 2-4B) follow a course independent of the bronchial tree; rather, they lie about midway between two pairs of bronchi and arteries; this position is maintained to the periphery of the airway system. In the hilum, these veins are collected into at least two main veins on either side, which lead into the left atrium located at the back of the heart.

The airways systematically branch over an average of 23 generations of dichotomous branching,[7,8] ending eventually in a blind sac (Fig. 2-5). The last nine generations of these airways are connected to tightly packed alveoli, airway chambers in which gas exchange takes place, whereas the central airways serve the function of conducting the air to the gas-exchange parenchyma. In such a system of sequential branching, the unit of lung parenchyma could be defined according to the portion of parenchyma that is supplied by a particular branch of the bronchial tree, and it is possible to conceive of as many types of units as there are generations unless clear definitions for such units are proposed. However, two units appear to be natural:

1. The lobes, which are demarcated by a more or less complete lining of pleura. There are three lobes on the right (superior, middle, and inferior lobes), and two on the left (superior and inferior lobes).
2. The acinus, which is defined as the parenchymal unit in which all airways have alveoli attached to their wall and thus participate in gas exchange. Along the airway tree, the acinus begins with a transitional bronchiole (Fig. 2-5).[9,10]

Since all other units are somewhat arbitrarily defined, it is not surprising that some ambiguity exists in the literature about their meanings. Nonetheless, a certain convention has been adopted with respect to the following:

1. The lung segments, which are considered as the first subdivisions of lobes. Figure 2-2 shows the location and distribution of the segments to the various lobes. The symmetry is imperfect because on the left the two segments corresponding to the right middle lobe are incorporated into the superior lobe as the lingula (segments 4 and 5) and because the medial–basal segment of the lower lobe is generally missing on the left (segment 7).

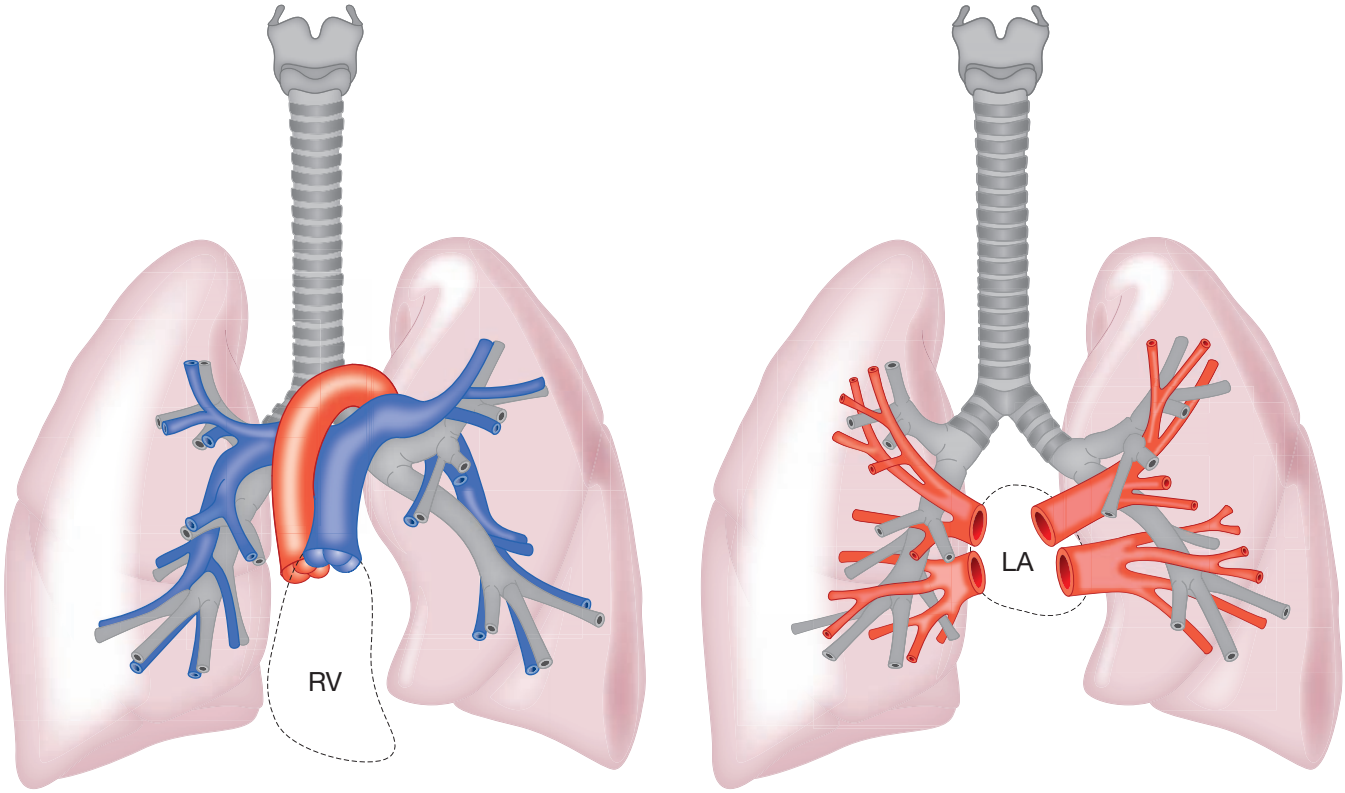


Figure 2-4 Schematic diagrams of the relation of the main branches of pulmonary arteries (**A**) and pulmonary veins (**B**) to the bronchial tree. The arteries follow the airways. Two mainstems of pulmonary vein penetrate independently into the lung on each side. LA, left atrium; RV, right ventricle.

2. The secondary lobule, an old anatomic unit. It was introduced in the 19th century because "lobules" of about 1 cm^3 are visible on the surface of the lung. These lobules are delineated by connective tissue septa that are connected to the pleura. The secondary lobule is difficult to define in terms of the bronchial tree, but it does seem to comprise about a dozen acini. With reference to bronchograms, secondary lobules are supplied by airway branches that are about 1 mm in diameter.

The pulmonary blood vessels show a characteristic relationship to these units (Figs. 2-3 and 2-4). The pulmonary arteries, following the airways, course through the centers of the units and finally fan out into the capillaries located in the delicate alveolar septa of lung parenchyma. In contrast, the veins lie in the boundary between units and collect the blood from at least two or three adjacent units. This arrangement applies to acini and secondary lobules as well as to lung segments.

Therefore, it is evident that the units of lung parenchyma are bronchoarterial units, which share their venous drainage with neighboring units. This architecture has important functional and practical consequences. Except for the lobes, none of the units is separated from each other by complete connective tissue septa.

ORGANIZATION OF LUNG TISSUE

■ BASIC STRUCTURAL ELEMENTS

While looking at the tissue organization of the lung, we must first consider that the airways and the blood vessels each have their own lining by an uninterrupted cell layer. These layers extend all the way out to the gas-exchange region, but they show different properties in conducting as compared with respiratory structures. Likewise, the connective tissue forms a continuum throughout the lung all the way out to the pleura, but it, too, will be differently organized in the different functional zones; whereas it is reduced to a minimum in the alveolar walls, it contributes a number of different ancillary structures to the wall of conducting airways and blood vessels, such as smooth muscle sheaths or cartilage. This connective tissue space also houses the nutritive vessels and nerves as well as the elaborate defense system related to lymphatic vessels. In the gas-exchange region, however, very few of these accessory structures are found.

The complexity of lung structure is also reflected at the cell biologic level. There is no such thing as a standard "lung cell." Instead, we find some 40 different cell types, highly specialized both structurally and functionally, in the lung.[11–13]

A word of caution is also necessary with respect to the extrapolation of structural findings in experimental animals, especially rodents, to the human lung. Noteworthy species differences include the bronchial circulation, the presence of respiratory bronchioles, the ultrastructural composition and distribution of nonciliated bronchiolar epithelial cells and their protein expression pattern, the frequency of certain cell types like alveolar brush cells and lipid-containing interstitial cells (lipofibroblasts), and the ultrastructural organization of lamellar bodies in type II alveolar epithelial cells. All these structural elements have features characteristic of the human lung that are not found in rodents.[14]

■ WALL STRUCTURE OF CONDUCTING AIRWAYS

The wall of conducting airways consists of three major components (Figs. 2-6 and 2-7): (1) a mucosa composed of an epithelial and a connective tissue lamina; (2) a smooth muscle sleeve; and (3) an enveloping connective tissue tube partly provided with cartilage.[15]

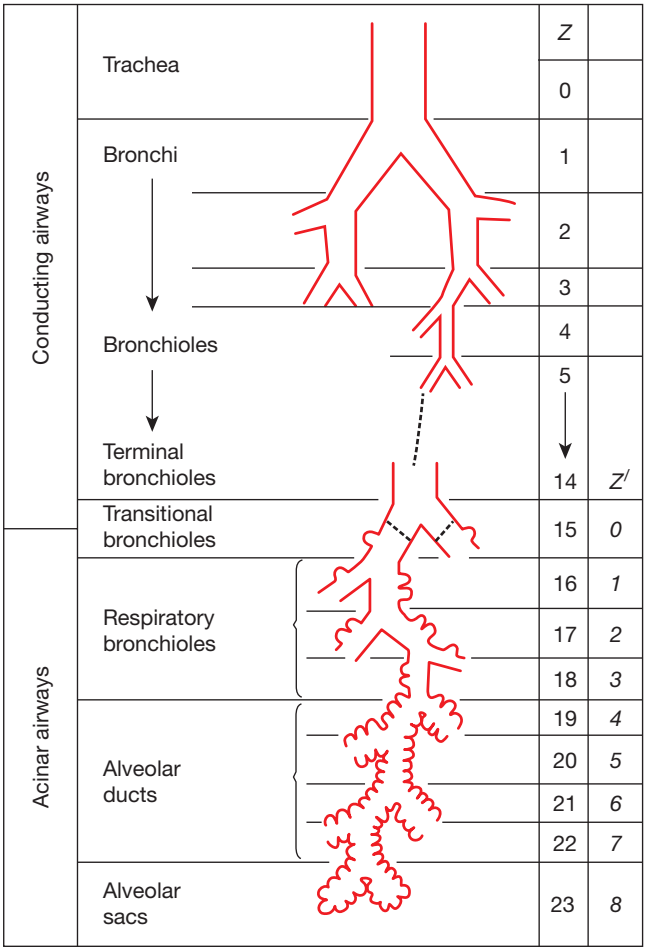


Figure 2-5 Model of airway branching in human lung by regularized dichotomy from trachea (generation z = 0) to alveolar ducts and sacs (generations 19–23). The first 14 generations are purely conducting; transitional airways (generation 15) lead into the acinar airways with alveoli that branch over 8 generations (z′). *(Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963.)*

EPITHELIUM

Although derived from same anlage,[16,17] the airway epithelium modifies its differentiation characteristics as we proceed from large bronchi over bronchioles to the alveolar region (Fig. 2-6). A simple epithelium exists as a lining of smaller bronchioles: As we move upward toward larger bronchi, the epithelium becomes higher and some basal cells appear, making the epithelium pseudostratified. At the point of transition into the gas-exchange region – that is, at the entrance into the complex of alveoli – the epithelium abruptly becomes extremely thin. Figure 2-6 also shows that the epithelium is not made of a uniform cell population but that it is, at each level, rather a mosaic of at least two cell types, in that secretory cells as well as some rarer special cells are interspersed into the complex of lining cells.[15,18]

If we first have a closer look at the epithelium of larger conducting airways, we see that the lining cells are provided with a tuft of kinocilia at their apical cell face, whereas the secretory cells are goblet cells that produce and discharge to the surface a sticky mucus (Figs. 2-7–2-9). This mucus spreads out as a thin blanket on top of the cilia, which are embedded in a periciliary layer containing a dense network of mucins and mucopolysaccharides tethered to the cilia.[19] The mucus layer is capable of trapping dust particles that are still contained in the air entering the lung. Kinocilia (Fig. 2-10) are motile cell extensions that are known to beat rhythmically in a given direction and at a frequency of about 12 to 20 Hz.[20,21] In the airway epithelium, the cilia are oriented in such a fashion that their beat is directed outward. It is interesting that the cilia of airway epithelia develop at their tip fine claws with which they can grasp the mucus blanket in the phase of their forward beat, whereas on their return to the upright position they glide past the mucus blanket. The result of this is that the mucus blanket, together with trapped foreign material, moves outward or "up the airways" in a steady stream, a feature appropriately called the mucociliary escalator. Since the lining by ciliated cells is uninterrupted from the bronchioles, up the bronchi, to the trachea, this mucociliary escalator ends at the larynx, so that the normal fate of bronchial mucus is to be steadily discharged into the pharynx, whence it is swallowed, usually unnoticed. Only when an excessive amount of mucus accumulates in the trachea or in larger bronchi do we have to assist the system by coughing.

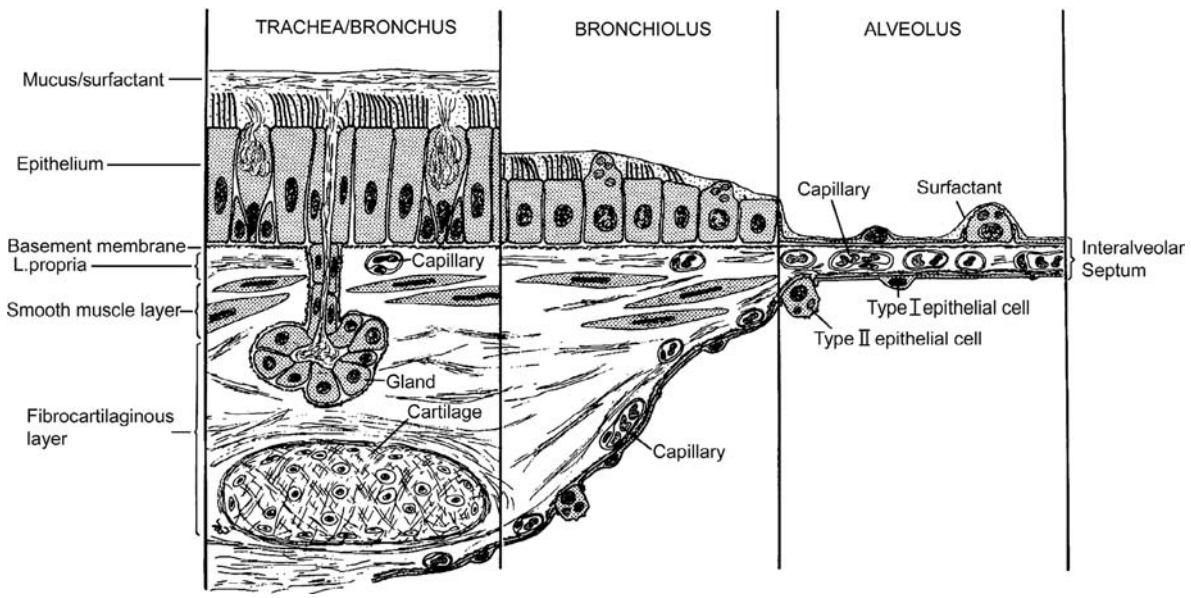


Figure 2-6 Airway wall structure at the three principal levels. The epithelial layer gradually becomes reduced from pseudostratified to cuboidal and then to squamous but retains its organization as a mosaic of lining and secretory cells. The smooth muscle layer disappears in the alveoli. The fibrous layer contains cartilage only in bronchi and gradually becomes thinner as the alveolus is approached.

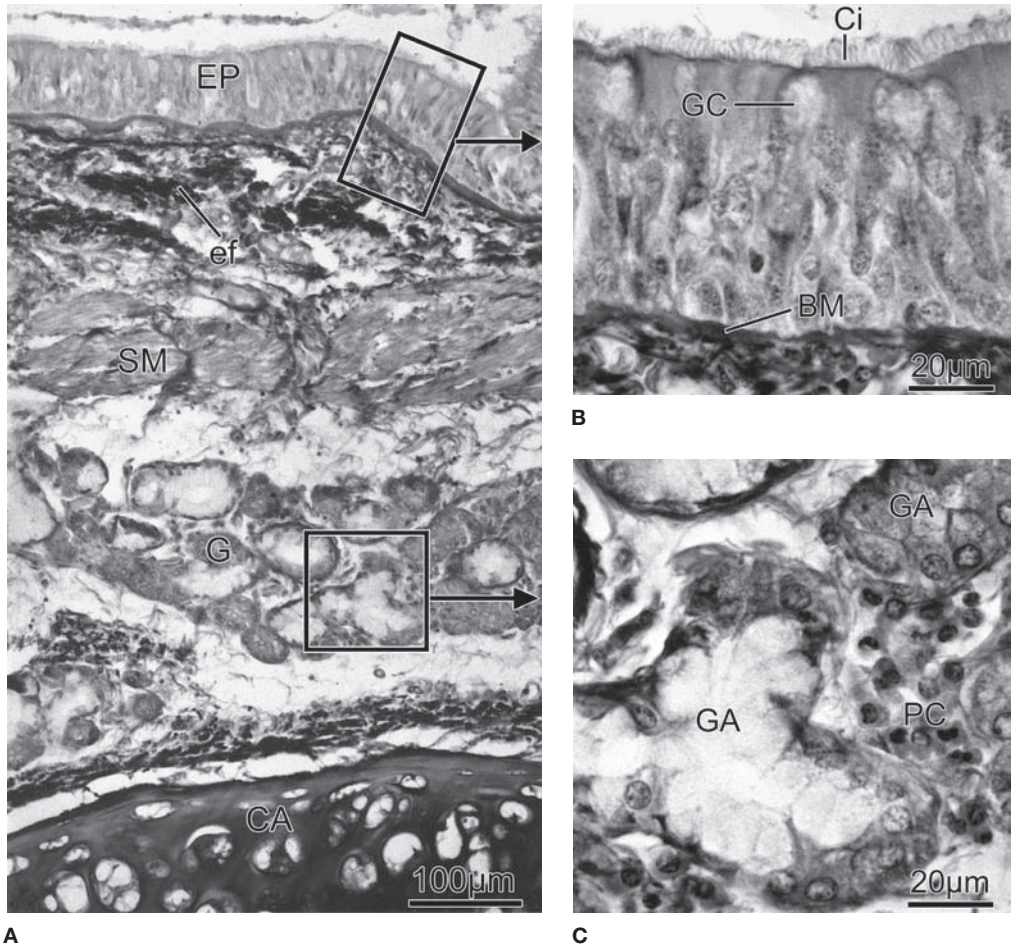


Figure 2-7 Light micrographs of bronchial wall. **A.** The layers from epithelium (EP) to cartilage (CA) with elastic fibers (ef), smooth muscle bundles (SM), and glands (G). **B.** Higher power of pseudostratified epithelium with cilia (Ci). **C.** Details of gland with acini (GA) associated with groups of plasma cells (PC). BM, basement membrane; GC, goblet cell.

The secretory cell population shows a number of specialized features. In the bronchi of all sizes and in larger bronchioles, one finds goblet cells interspersed between the ciliated cells; they form the mucus in their endoplasmic reticulum and Golgi complex, store it as droplets in their apical part, and discharge it in bulk (Figs. 2-8 and 2-9). In larger bronchi, one finds, in addition, small mucus glands located in the connective tissue; they are connected to the bronchial surface by long and narrow ducts (Figs. 2-6 and 2-7). In the normal bronchus, the glandular acini are relatively small and composed of serous and mucus cells; enlargement of the acini and a relative increase of mucus cells are characteristics of chronic bronchitis.

Finally, a special nonciliated secretory cell appears in the smaller bronchioles, the club cell (Clara) (Fig. 2-11).[22,23] This cell population is very heterogeneous, thus displaying both interspecies and intraspecies variations.[24–28] In the human lung, club cells account for about

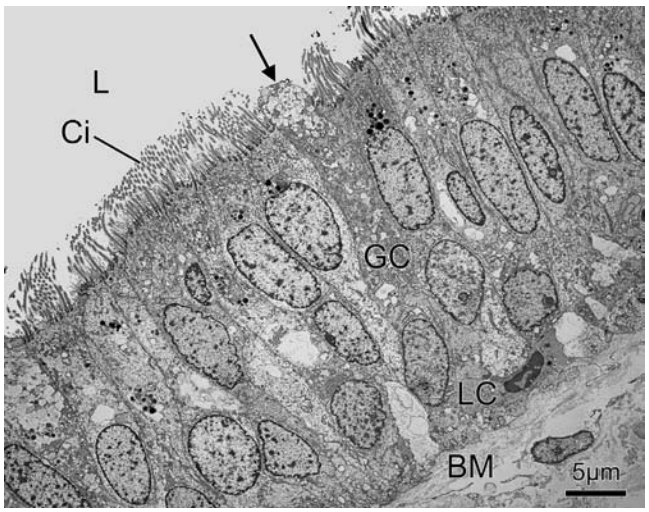


Figure 2-8 Electron micrograph of section across human bronchial epithelium made of high-columnar cells, most of which are ciliated (Ci). A goblet cell (GC) is cut lengthwise; note mucus droplets in process of accumulating at cell apex *(arrow)* and leukocyte (LC) caught in epithelium in process of diapedesis. BM, basement membrane; L, lumen.

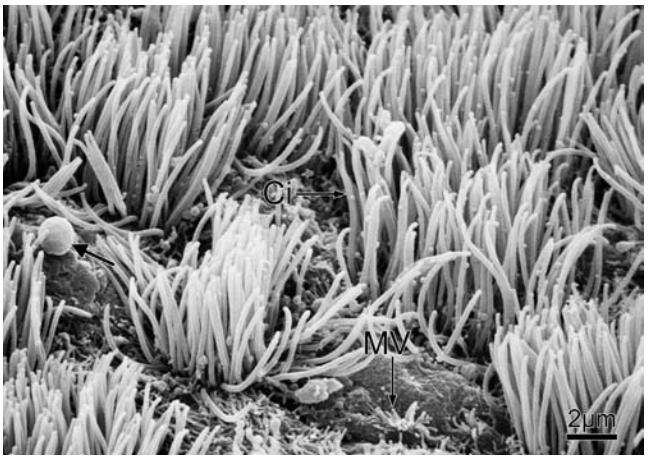


Figure 2-9 Surface view of bronchiolar epithelium shows tufts of cilia (Ci) forming on individual ciliated cells and microvilli (MV) on other cells. Note secretion droplet in process of release from goblet cell *(arrow)*.

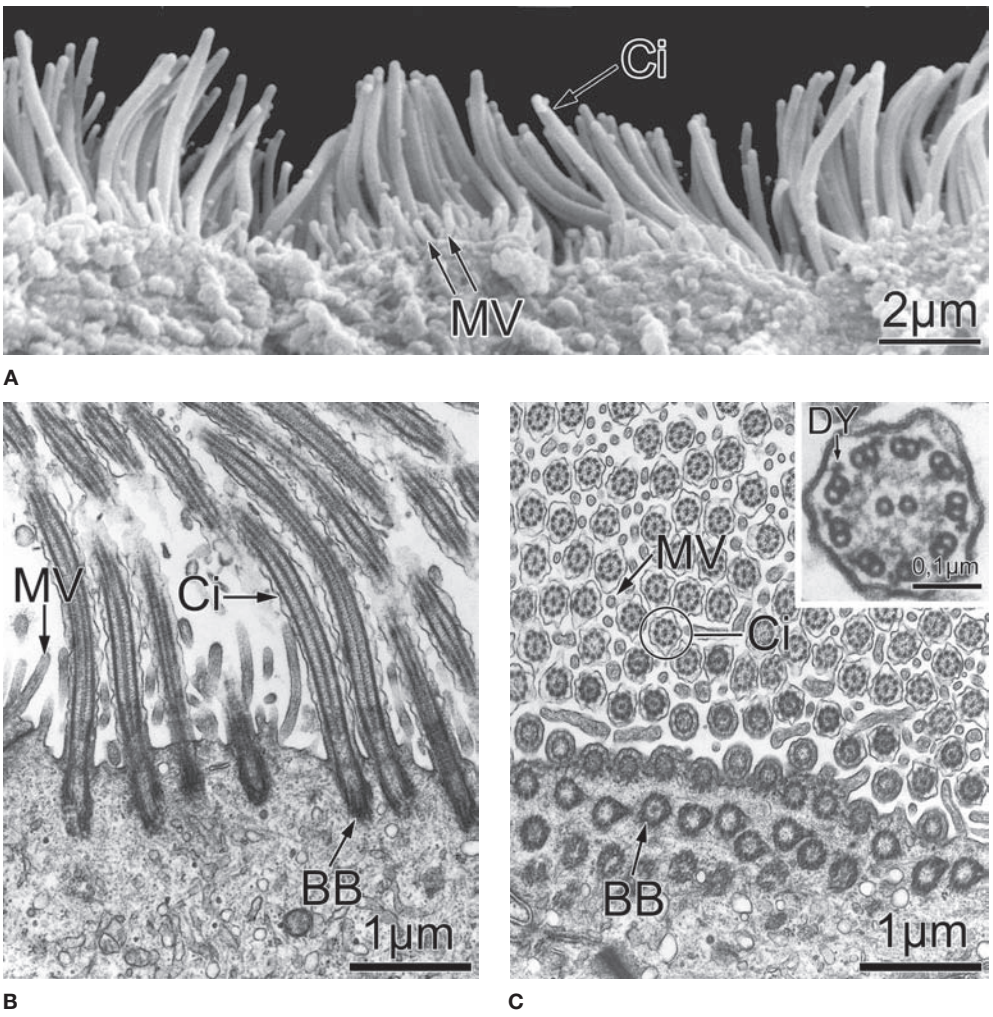


Figure 2-10 Cilia (Ci) from human bronchial epithelium seen on sections of epithelial cells in scanning electron micrograph (**A**), and on thin sections in longitudinal (**B**), and oblique cross section (**C**). They are implanted in the epithelial cell by a basal body (BB). Cross-sectioned cilium at high power (*inset*, **C**) reveals its membrane, which is enveloping a typical set of two axial tubules and nine peripheral duplex tubules with dynein arm (DY) attached. Note abundant short microvilli (MV) interspersed between cilia.

11% and 22% of the total epithelial cell number in terminal and respiratory bronchioles, respectively.[29] Besides the absence of cilia, club cells in conventional preparations are characterized by their dome-shaped apex that protrudes into the airway lumen. In contrast to that in rodents, where this cell is rich in smooth endoplasmic reticulum, club cells in the human lung lack significant amounts of smooth ER. They possess short lateral cytoplasmic extensions while their basal surface that rests on the basement membrane is practically free of infoldings. Membrane-bound electron-dense granules of about 500 to 600 nm diameter are present, which underlines their secretory activity. Our understanding of the functions of club cells is still incomplete. In many aspects, they appear to be functionally related to the secretory cell type of the alveoli, the type II alveolar epithelial cell; ultrastructural features and expression patterns of lung adenocarcinoma cells show characteristics of both club and type II cells. Club cell secretions add to the lining layer of the distal lung. Club cells synthesize and secrete the club cell secretory protein (CCSP),[22] which has been shown to be structurally similar to rabbit uteroglobin. The exact function of CCSP in the human lung still remains to be elucidated. CCSP levels in BAL fluid are decreased in smokers and in patients with COPD or interstitial lung diseases.[30] Animal studies suggest immunomodulatory functions for CCSP.[28] Within the lung, the club cell is the primary site of cytochrome P450 monooxygenase activity. Thus, they are heavily involved in detoxification of xenobiotics. Normal bronchiolar epithelial homeostasis is maintained by proliferation of club cells, whereas a cell population termed "variant Clara cells" or "variant CCSP-expressing cells," which is associated with neuroepithelial bodies or localized at bronchioloalveolar duct junctions, appears to act as progenitor cells for the bronchiolar epithelium under certain pathologic conditions.[28,31]

There are also some additional rarer cells. Neuroendocrine cells are capable of secreting mediators (amines and neuropeptides) into subepithelial capillaries. Prior to secretion, the bioactive substances are stored in dense-cored vesicles (Fig. 2-12). Occasionally, but only rarely in the adult human lung, these cells are organized in extensively innervated groups, and then termed "neuroepithelial bodies." Although it seems clear that neuroepithelial bodies have sensory, most likely oxygen-sensing, properties, their exact physiologic function is still poorly understood.[32–36] Another rare cell type of the airway epithelium is the brush cell. These cells are characterized by the presence of an apical tuft of blunt, broad, and straight microvilli with root-like structures composed of filaments extending into the cytoplasm (Fig. 2-13). Glycogen granules, vesicles, and smooth endoplasmic reticulum are usually present as well. There is species variation in the occurrence of brush cells. While common in rodents (in rats even present in the proximal alveolar epithelium[37]) they are only rarely found in the human lung. Their function is only partly explored. Owing to their ultrastructure and their strategic localization in the airways and at alveolar duct bifurcations, sensory/chemoreceptor as well as sentinel/immune surveillance functions have been proposed.[38,39] Recent evidence suggests that brush cells "taste" the chemical composition of the airway lining fluid.[40,41]

INTERSTITIUM

The layer of connective tissue in the bronchial mucosa consists predominantly of elastic fibers that are oriented longitudinally;

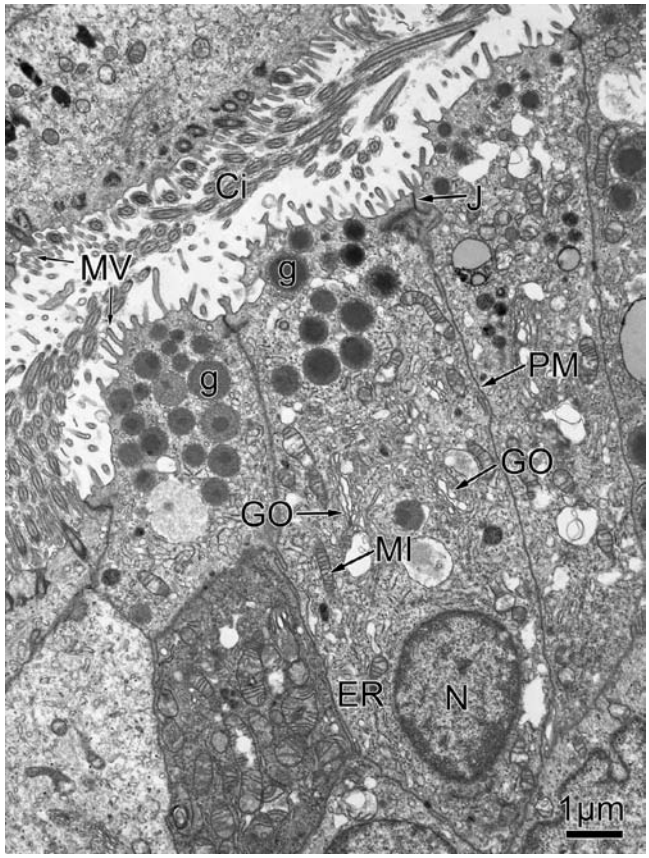


Figure 2-11 Club cells from human bronchiolar epithelium contain dense secretion granules (g) at apex. Note abundant cytoplasmic organelles such as mitochondria (MI), Golgi complex (GO), or endoplasmic reticulum (ER) as well as microvilli (MV) at surface. Cell membranes are closely apposed and form tight junctions (J) at apical edge. Ci, cilia; N, nucleus; PM, plasma membrane.

these fibers serve to maintain a smooth outline of the longitudinal profile of the bronchial lumen no matter how much the bronchi are stretched as the lungs are inflated. In this connective tissue lamina there are foci of lymphoid cells; often they form small lymphoid follicles.[42] However, bronchus-associated lymphoid tissue (BALT) is usually absent in normal adult human lungs and develops only after stimulation when inducible BALT might organize local immune responses.[43–46]

Smooth muscle bundles form a continuous sleeve in the connective tissue underlying the epithelial tube that extends from the major bronchi to the respiratory bronchioles; beyond the respiratory bronchioles, the bundles extend into the wall of alveolar ducts where the muscle fibers lie in the alveolar entrance rings. The bundles have an oblique course and encircle the mucosal tube in a criss-cross pattern; hence, their contraction results primarily in a narrowing of the lumen.

In the small bronchioles there is little else to the airway wall; the smooth muscle layer is ensheathed by a layer of delicate connective tissue that is in direct contact with adjacent alveoli (Fig. 2-6). In the larger bronchioles and even more in the bronchi, the outer connective tissue sheath forms a strong layer of fibers; in the bronchi, rings or plates of cartilage are incorporated into this layer.

The wall structure in the respiratory bronchioles is identical to that of terminal bronchioles except that in some regions the cuboidal epithelium is replaced by an alveolar epithelium of squamous cells (type I cells) closely apposed to capillaries. Very often, these single alveoli constitute outpouchings in these regions; sometimes

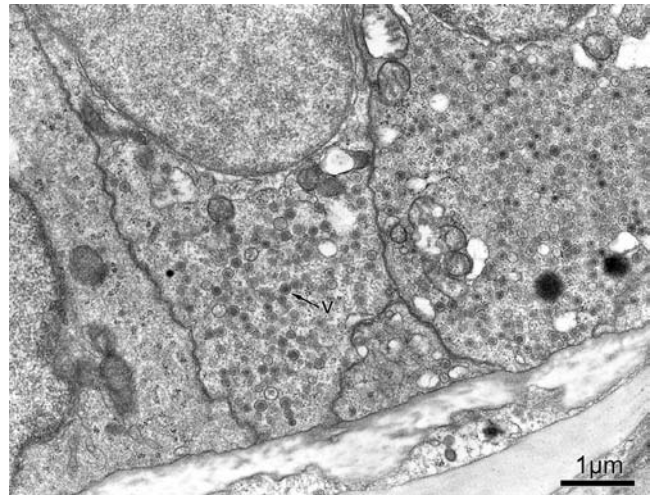


Figure 2-12 Basal part of neuroendocrine cell of human bronchiolar epithelium showing dense-cored vesicles (v). *(Reproduced with permission from Weibel ER. Lung cell biology, in Fishman A, Fisher AB, eds. Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985:47–91.)*

simple "respiratory patches" form in the bronchiolar wall (see below).

■ WALL STRUCTURE OF CONDUCTING BLOOD VESSELS

The endothelial lining of pulmonary arteries and veins differs from that of capillaries by some site-specific structural and functional differences.[47–49] The endothelium of conducting blood vessels is thicker, and parts of its cytoplasm are richly endowed with organelles of various kinds (Fig. 2-14). Clearly, these cells are metabolically more active than those of the capillary endothelium. They are particularly rich in membrane-bound rod-shaped granules termed Weibel–Palade bodies,[50,51] which represent the regulated secretory organelles of endothelial cells (Fig. 2-14). The lumen of

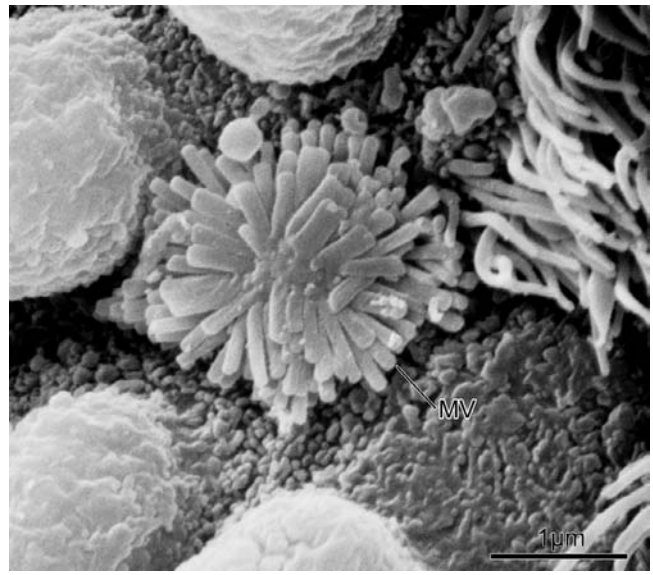


Figure 2-13 Brush cell from small bronchiole of rat lung containing broad microvilli (MV). *(Reproduced with permission from Weibel ER: Lung cell biology, in Fishman A, Fisher AB, eds. Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985:47–91.)*

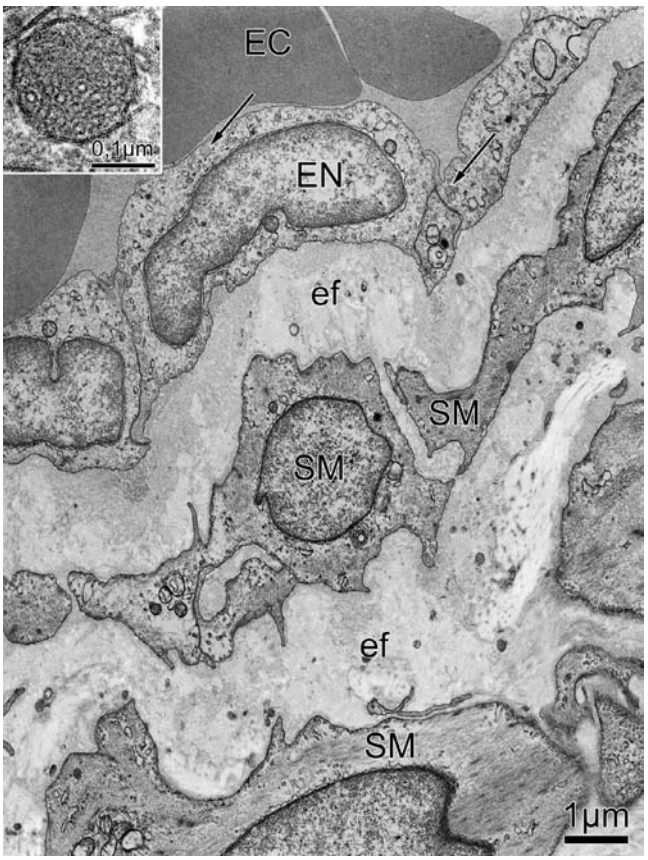


Figure 2-14 Part of wall of pulmonary artery from human lung. Endothelial cells (EN) form thick layer; their cytoplasm is rich in organelles. Specific granules of endothelium *(arrows),* a cross-section of one of which is shown at high power in the inset, are enveloped by a membrane and contain tubules. The arterial wall is of the elastic type, formed of alternating layers of smooth muscle (SM) and elastic fibers (ef). EC, erythrocyte.

Weibel–Palade bodies is filled with longitudinally arranged tubules. These tubules represent von Willebrand factor,[52] packed in a highly organized spiral that allows rapid secretion into the blood. Other components of Weibel–Palade bodies include tissue-type plasminogen activator, endothelin-1, the leukocyte adhesion receptor P-selectin, interleukin-8, the tetraspanin CD63/LAMP-3, and the small GTPase Rab27a. Thus, Weibel–Palade bodies are actively involved in hemostasis as well as in vasoactive and inflammatory responses.[53–56]

Many of the nonrespiratory metabolic functions of the lung – particularly the transformation of certain bioactive substances, such as angiotensin and prostaglandins – are performed in endothelial cells. Caveolae (or plasmalemmal vesicles) have been implicated in these processes.[57,58] Caveolae are plasma membrane invaginations and associated vesicles with an outer diameter of about 50 to 70 nm. Depending on fixation, the shape of these invaginations appears omega- or cup-like.[59] Their structural framework consists of members of the caveolin family of proteins associated with cholesterol and sphingolipids. Caveolae perform transport and signaling functions and are involved in membrane organization. All endocytic activity mediated by caveolae (thereby bypassing the clathrin-coated vesicle pathway) is pooled under the term potocytosis.[60–63]

Accessory structures develop in the wall in accord with the functional properties of the vessels. Thus, the walls of the major pulmonary arteries that are close to the heart, and therefore exposed to the pressure oscillations of large amplitude prevailing in the outflow tract of the right ventricle, are of the elastic type, that is, layers of elastic lamellae are interconnected with smooth muscle cells as in the aorta; the tone of the smooth muscle regulates the elastic modulus of the vessel wall, thereby controlling the shape of the pulse wave. In the pulmonary arterial tree, this pattern prevails out to branches of about 1 mm diameter.

In contrast, branches less than l mm in diameter are of the muscular type, that is, the smooth muscle fibers encircle the vessel lumen; they can modify the vessel's cross-section and can thus regulate blood flow through this vessel. Compared with systemic arteries, the thickness of the pulmonary arterial wall is reduced about in proportion to systolic pressure, that is, by about a factor of 1:5; in pulmonary hypertension, the wall becomes thicker. Although arterioles are a well-defined entity in the systemic vascular bed, where they constitute the major site of arterial resistance, pulmonary arterioles are more difficult to locate and define. A single muscle layer – the histologic definition of an arteriole – does occur in branches about 100 µm in diameter, but the arterial bed continues out to the precapillaries, which consist of vessels 20 to 40 µm in diameter that are enwrapped by an incomplete smooth muscle sheath. This poverty of smooth muscle contributes importantly to the low resistance to blood flow that is normally afforded by the pulmonary arterial tree.

The structure of pulmonary veins is similar to that of systemic veins in the upper half of the organism. Their walls are rich in connective tissue and contain irregular bundles of smooth muscle. Larger veins contain a large amount of elastic tissue. More extensive in rodents, but to a certain degree also in humans, cardiac muscle tissue from the left atrial myocardium forms sleeves in the adventitia of pulmonary veins where they overlap with the smooth muscle of the venous wall. The arrangement of the myocardial sleeves correlates with the distribution of foci of ectopic beats initiating atrial fibrillation.[64–67]

■ NUTRITIVE VESSELS AND NERVES

The tissue of lung parenchyma is very well supplied with blood; the fact that it is venous is of no disadvantage, because O_2 is easily obtained from the air. Thus, nutrient supply from pulmonary arteries combined with O_2 supply from air appears to suffice not only for the parenchyma but also for bronchioles and the smaller pulmonary vessels, whose outer surface is almost directly exposed to air. The thicker-walled bronchi, with their glands and cartilage, require a nutrient blood supply from bronchial arteries.[15,68,69] These derive in part directly from anterior branches of the aorta and partly from the upper intercostal arteries. They course alongside the esophagus and penetrate on both sides into the hilum. The bronchial arteries extend to the most peripheral bronchi but not into the walls of bronchioles. On the other hand, some branches supply large pulmonary vessels as vasa vasorum, whereas others course along larger septa to reach the pleura. Some bronchial arteries form anastomoses with peripheral branches of the pulmonary arteries. There have been long discussions about the role that such anastomoses may play. It seems that in the normal lung their importance has been overrated. However, in certain pathologic conditions, such as bronchiectasis and tumors, the bronchial arteries and perhaps the bronchopulmonary anastomoses appear to play an important role. They also enlarge to form a collateral circulation when branches of the pulmonary artery are obliterated. The peribronchovascular space around larger pulmonary artery branches and bronchi with its capillaries from the bronchial circulation has also been proposed as a unique compartment since it is a preferential site of leukocyte infiltration and edema formation under pathologic conditions.[70] Furthermore, the bronchial circulation attenuates ischemia–reperfusion lung injury. Consequently, interruption of the bronchial circulation without revascularization during lung transplantation often leads to bronchial anastomotic complications.

Except for a few bronchial veins in the hilar region, the bronchial system does not have its own venous drainage into the systemic veins. Instead, the bronchial veins, which begin as a peribronchial venous plexus, drain into pulmonary veins; this drainage seems to constitute one source of normal venous admixture to arterial blood.

The lung is innervated by the autonomic nervous system. The parasympathetic fibers are derived from the vagal nerves and the sympathetic fibers from the upper thoracic and cervical ganglia; together they form the pulmonary nervous plexus in the region of the hilum before entering the lung. The fiber bundles follow the major bronchi and blood vessels, finally penetrating into the acini; some nerves also supply the pleura. In addition, motor nerves influence the smooth muscle tone of airways and blood vessels, and sensory nerves are involved in reflex functions (e.g., cough reflex, Hering–Breuer reflex). Moreover, the secretory function of glands as well as of type II alveolar epithelial cells is at least partly under control of this nervous system. Nerve fibers are easily found in the wall of bronchioles and bronchi, where they often follow the course of bronchial arteries. However, fibers in alveolar septa are small and scarce.

THE CELLS OF THE ALVEOLAR REGION

■ BASIC DESIGN OF THE GAS-EXCHANGE BARRIER

Efficient gas exchange in the lung depends on a very thin barrier of very large surface between air and blood.[16,71] Actually, the barrier is so thin that it cannot be resolved into its constituents by light microscopy. Nevertheless, this barrier must be built of the three minimal tissue layers: an endothelium lining the capillaries, an epithelium lining the airspaces, and an interstitial layer to house the connective tissue fibers. The guiding principle in designing these cells must evidently be to minimize thickness and maximize extent. However, there is definitely a limit to this, set by the need to make the barrier and its constituent cells strong enough to resist the various forces that act on it: capillary blood pressure, tissue tension, and surface tension, in particular. Furthermore, the barrier must remain intact for a lifetime, and this requires continuous repair and turnover of the cells and their components. As a result, about half of the surface of the air–blood barrier is optimized for gas exchange in that the thin epithelial and endothelial cell extensions are only separated by a fused basement membrane. These areas are termed the thin parts of the air–blood barrier. Cell nuclei and connecting tissue fibers are concentrated in the so-called thick parts of the air–blood barrier.

In spite of this delicacy of tissue structure, we find that three-quarters of all the lung cells by volume or weight are contained in the lung parenchyma (Table 2-1). We also note that epithelium and endothelium make up about one-quarter each of the tissue barrier in the alveolar walls, whereas interstitial cells amount to 35%; the interstitial space with the connective tissue fibers makes up no more than 15% of the barrier.[11,72]

■ ALVEOLAR EPITHELIUM

The alveolar epithelium is a mosaic of different cell types. The vast majority of the total surface is lined by a single layer of squamous cells; the remaining fraction – only about 3% (Table 2-2) – is occupied by cuboidal secretory cells; one usually calls the squamous lining cells type I and the secretory cells type II alveolar epithelial cells or pneumocytes. Type I and II cells occur with a numerical frequency of about 1:2. A very rare third cell type, the brush cell, can be found in some specific regions near the entrance of the acinus (see above).

The fine structural details of the different types of alveolar epithelial cells can only be fully visualized by electron microscopy, whereas molecular markers selective for either type I or II cells or some of their constituents can be detected and localized by light microscopy (Fig. 2-15; Table 2-3).

TABLE 2-1 Estimated Cell Volumes in the Human Lung

Cell or Tissue	Volume (mL)	Percent Septal Tissue
Tissue (excl. blood)	284	—
Nonparenchyma	99	—
Alveolar septa	185	—
Cells	213	—
Nonparenchyma	50	—
Alveolar septa	163	—
Parenchymal cells	163	—
Alveolar epithelium type I	23	12.6
Alveolar epithelium type II	18	9.7
Capillary endothelium	49	26.4
Interstitial cells	66	35.8
Alveolar macrophages	7	3.9

Source: Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.

Type I Alveolar Epithelial Cells

At first glance, the squamous type I cells show rather simple design features (Fig. 2-16). Their small, compact nucleus is surrounded by a slim rim of cytoplasm, where one finds a modest basic set of organelles, a few small mitochondria, and some cisternae of endoplasmic reticulum, seemingly the picture of a quiescent cell with no great metabolic activity.[11,73]

At the edge of the perinuclear region, a very attenuated cytoplasmic leaflet emerges (Fig. 2-16) and spreads out broadly over the basal lamina. This leaflet is made essentially of the two plasma membranes forming the apical and basal cell face, respectively, with a very small amount of cytoplasmic ground substance interposed (Fig. 2-17). Here one rarely finds any organelles except for the numerous plasmalemmal vesicles implied in the transcellular transport of molecules. In fact, besides capillary endothelial cells, type I alveolar epithelial cells are among the richest in caveolae.

TABLE 2-2 Morphometric Characteristics of Cell Population in Human Pulmonary Parenchyma

Cell Population	Percent of Total Cell Number[a]	Average Cell Volume (μm^3)	Average Apical Cell Surface (μm^2)
Alveolar epithelium			
Type I	8	1764	5098
Type II	16	889	183
Endothelium	30	632	1353
Interstitial cells	36	637	—
Alveolar macrophages	10	2492	—

[a] *Total cell number in human lung* 230×10^9.

Source: Data from Crapo JD, Barry BE, Gehr P, Bachofen M, Weibel ER: Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis. 1982;125:332–337.

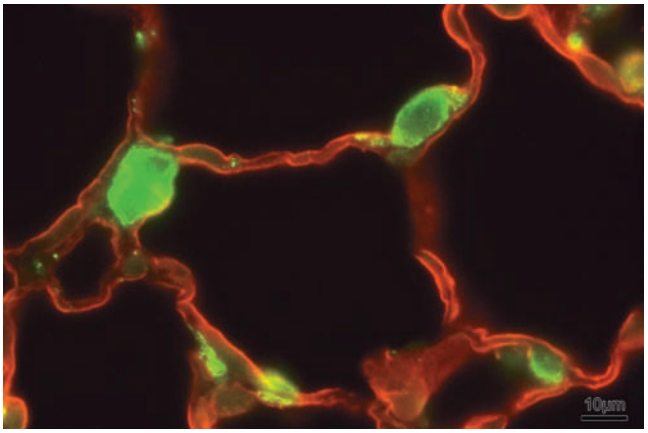


Figure 2-15 Immunofluorescent double labeling of alveolar epithelial cells. Type I cells are stained for Lycopersicon esculentum lectin *(red)*, type II cells are stained for SP-D *(green)*. Compare with Table 2-3. *(Micrograph used with permission of H. Fehrenbach.)*

The surface covered by one type I epithelial cell is about 4000 to 5000 µm^2. In some texts one may find the type I cell called the "small alveolar cell" because of its small nucleus; clearly this is a misnomer, as the type I cell is a rather large cell indeed, with respect to both surface and cell volume (Table 2-2). Terminal bars are formed where the cytoplasmic leaflets of epithelial cells meet (Fig. 2-18). If one looks at the surface of the alveolar epithelium in scanning electron micrographs (Fig. 2-19), one notes that the patches covered by single type I cells are variable in size and that even the largest are much smaller than the 4000 to 5000 µm^2 given earlier, a number derived by dividing the total alveolar surface by the total number of type I cell nuclei. Why is this? There seem to be three to four times as many type I cell domains encircled by terminal bars as there are nuclei. Indeed, this observation was already made some 130 years ago by Albert Kölliker; his interpretation was that part of the alveolar surface was lined by "nonnuclear" cytoplasmic plates rather than by complete cells. It turns out that an alternative explanation is possible. One finds that type I cells are not simple squamous cells but rather branched cells with multiple apical faces, as shown diagrammatically in Figure 2-20. Thus, what appears as nonnucleated plates are cytoplasmic domains connected to the perinuclear region by a stalk, spreading out on one side of the alveolar wall or the other; it is evident that several such domains may share a nucleus.[74]

Although type I cells cover about 97% of the alveolar surface area, they have long been neglected as being "silent," providing solely a barrier function. Although their overall function in the human lung remains to be determined, recent animal and in vitro studies strongly suggest that type I cells are actively involved in alveolar ion and fluid homeostasis.[75–77]

TABLE 2-3 Markers for Alveolar Epithelial Cells

Type I Cell	Type II Cell
HTI-56 (human)	Surfactant proteins:
T1α/RTI-40 (rat, mouse)	SP-A
Aquaporin 5	SP-B
Caveolin 1	SP-C
Receptors for advanced glycation end products	SP-D
(RAGE)	ABCA3
Carboxypeptidase M	HTII-280 (human)
Lectins:	RTII-70 (rat)
Lycopersicon esculentum	MMC4 (rat)
Bauhinia purpurea	Alkaline phosphatase
Ricinus communis 1	CD44
	Lectins:
	Maclura pomifera

These markers allow a selective distinction between type I and type II alveolar epithelial cells and can be visualized at a light microscopic level by immunohistochemistry, enzyme histochemistry, or lectin histochemistry. However, other cell types of the distal bronchiolar and alveolar region, e.g., Club cells, capillary endothelial cells, or alveolar macrophages, might also stain positive for some of these markers. Source: Data from Fehrenbach H. Alveolar epithelial type II cell: defender of the alveolus revisited. Respir Res. 2001;2:33–46; Griffiths MJD, Bonnet D, Janes SM. Stem cells of the alveolar epithelium. Lancet. 2005;366:249–260; Gonzales RF, Allen L, Gonzales L, Ballard PL, Dobbs LG. HTII-280, a biomarker specific to the apical plasma membrane of human lung alveolar type II cells. J Histochem Cytochem. 2010;58:891–901.

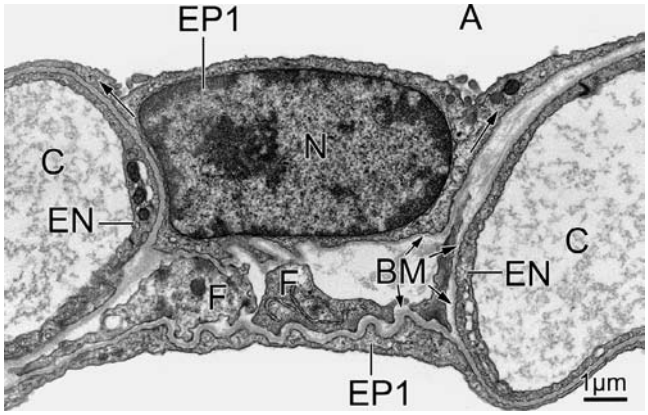


Figure 2-16 A type I alveolar epithelial cell (EP1) from human lung. The nucleus (N) is surrounded by very little cytoplasm, which extends as thin leaflets *(arrows)* to cover the capillaries (C). Note the basement membranes (BM) of the epithelium and endothelium (EN), which become fused in a minimal barrier. Interstitial space contains fibroblast processes (F).

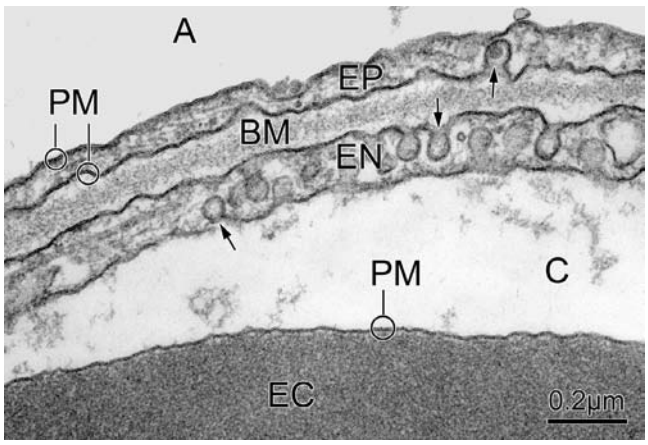


Figure 2-17 Thin, minimal tissue barrier between alveolar air (A) and capillary blood (C) is made of cytoplasmic leaflets of epithelium (EP) and endothelium (EN), joined by fused basement membranes (BM). Note that the epithelial and endothelial leaflets are bounded by plasma membranes (PM), as is the erythrocyte (EC). *Arrows* point to pinocytotic vesicles/caveolae. *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

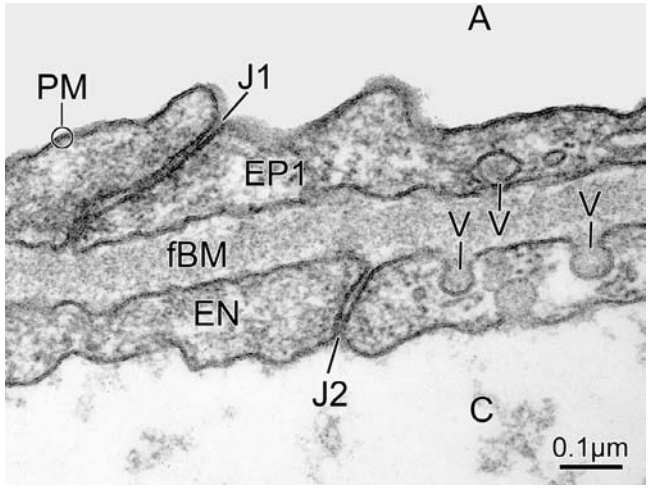


Figure 2-18 Minimal barrier part showing intercellular junctions. Between type I epithelial cells, a "tight" junction (J1) is formed by close apposition of the cell membranes over a comparatively wide band; the junction between endothelial cells (J2) is "leaky" because membranes become apposed over a narrow strip only. Note trilaminar structure of plasma membranes (PM), the occurrence of pinocytotic vesicles/caveolae (V) in both epithelium and endothelium (EN), and the fused basement membranes (fBM). A, alveolus; C, capillary; EP1, type I epithelial cell.

Type I cells are easily damaged, particularly because of their extensive surface area and their complex branching architecture. However, there is an additional problem: one finds that type I cells are not capable of multiplying by mitosis in vivo, neither during lung growth when more cells are needed to coat the expanding alveolar surface nor upon damage in the adult lung when cells need to be replaced. In both instances new type I cells are made by mitotic division and transformation of type II cells, a process that takes about 2 to 5 days.

This seems to work under normal circumstances. There are, however, conditions where this repair mechanism is too slow to cope with excessive damage, so that a syndrome of severe catastrophic

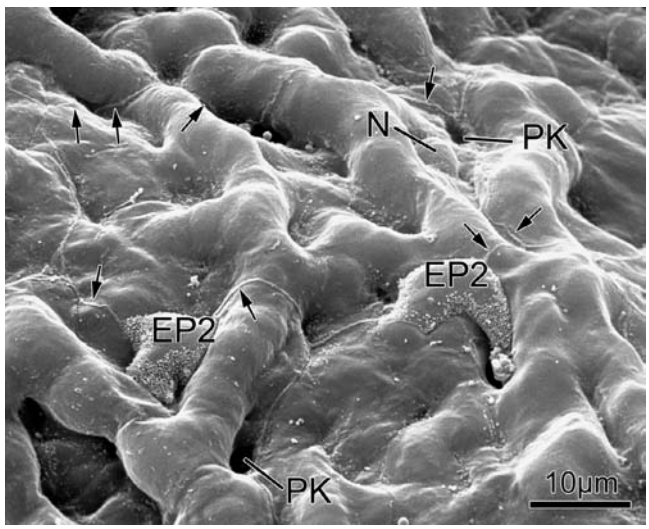


Figure 2-19 Surface of the alveolar wall in the human lung seen by scanning electron microscopy reveals a mosaic of alveolar epithelium made of type I and type II (EP2) cells. *Arrows* indicate boundary of the cytoplasmic leaflet of the type I cell which extends over many capillaries. Note the two interalveolar pores of Kohn (PK). N, nucleus of type I cell.

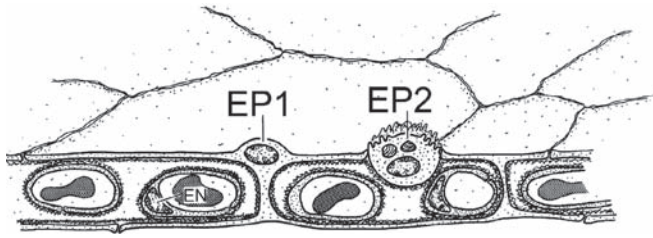


Figure 2-20 Diagram of the alveolar wall showing the complexity of a type I epithelial cell (EP1) and its relation to a type II cell (EP2) and endothelial cell (EN). *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

respiratory failure, acute respiratory distress syndrome (ARDS), develops, which requires intensive care treatment. In such patients one finds large parts of the type I cell lining of the alveolar surface to be destroyed. As a consequence, the barrier has become leaky and the alveoli fill with alveolar edema, so that they can no longer take part in gas exchange.[78,79]

With proper medical care, this alveolar edema can often be resolved within a few days. The alveoli become again filled with air, but in spite of this, gas exchange does not improve. What has happened is that the repair of the severely damaged alveolar epithelium requires a lot of new cells to be made by division of type II cells.[80] These form a rather thick cuboidal lining of the barrier surface, a phenomenon termed cuboidal metaplasia, and this thick barrier offers a high resistance to O_2 flow. It takes several weeks until a thin barrier is restored by transformation of the cuboidal cell lining into delicate type I cells. During this process, the cells go through intermediate stages where they are often positive for both type II and type I cell markers.[81,82]

Type II Alveolar Epithelial Cells

The type II alveolar epithelial cell is a conspicuous but in fact relatively small cell whose mean volume is less than half that of the type I cell (Table 2-2), although it is often called the "large alveolar cell."[11] Its shape is cuboidal, the apical cell surface bulges toward the lumen and is provided, mostly around its periphery, with a tuft of microvilli (Figs. 2-21 and 2-22). Often, type II cells seem to be preferentially located in the corners of alveoli or in

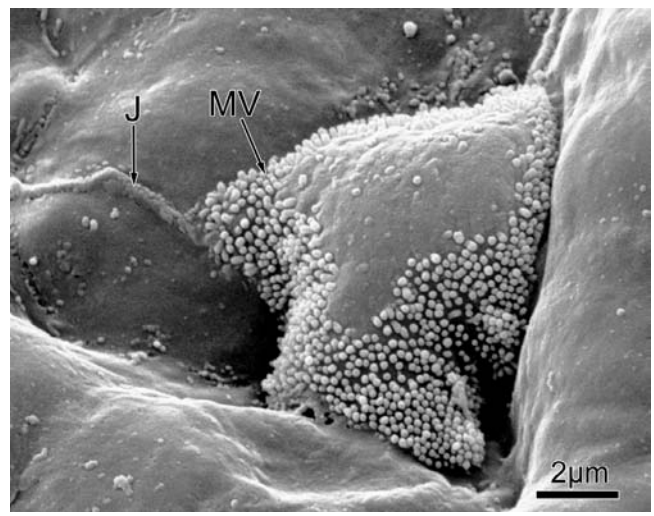


Figure 2-21 Higher magnification of a type II cell reveals a "crown" of short microvilli (MV) and a central "bald patch." Note junction lines of type I cells (J) meeting with the type II cell.

close proximity to interalveolar pores of Kohn. They are usually found as solitary cells; only in cases of alveolar epithelial damage, proliferation of type II cells leads to focal clusters during the repair process. Occasionally, a single type II cell might supply two or even three adjacent alveoli with its apical surface. The basement membrane beneath type II cells is occasionally interrupted. Through these apertures, foot processes of type II cells can extend to the interstitium and come in close proximity to interstitial cells.[83]

Type II cells contain a wealth of cytoplasmic organelles of all kinds (Fig. 2-22): mitochondria, a lot of endoplasmic reticulum with ribosomes, and a well-developed Golgi complex surrounded by a set of small lysosomal granules among which so-called multivesicular bodies – membrane-bounded organelles containing a group of small vesicles – stand out (Fig. 2-23). In addition, one finds the characteristic lamellar bodies, larger membrane-bounded secretory organelles that contain densely packed phospholipid lamellae. There are notable species differences in the ultrastructural organization of lamellar bodies. In rodents, the lamellae are mostly arranged in parallel stacks whereas in humans, concentrically arranged lamellae are mostly found, which are attached to a projection core consisting of randomly arranged short stacks of densely packed membrane segments (Fig. 2-24).[84] The periodicity of the lamellae is in the range of 4 to 6 nm. One human type II cell contains between 200 and 500 lamellar bodies, making up a total volume of about 2 cm^3 in the entire lung. With a diameter of approximately 1 µm, lamellar bodies are among the largest secretory organelles of all cells in the body. Owing to their equipment with lysosomal enzymes (e.g., acid phosphatase, cathepsins) and proteins (e.g., members of the lysosomal membrane protein (LAMP) family and their acidic pH of about 5.5, lamellar bodies are regarded as secretory lysosome-related organelles.[85]

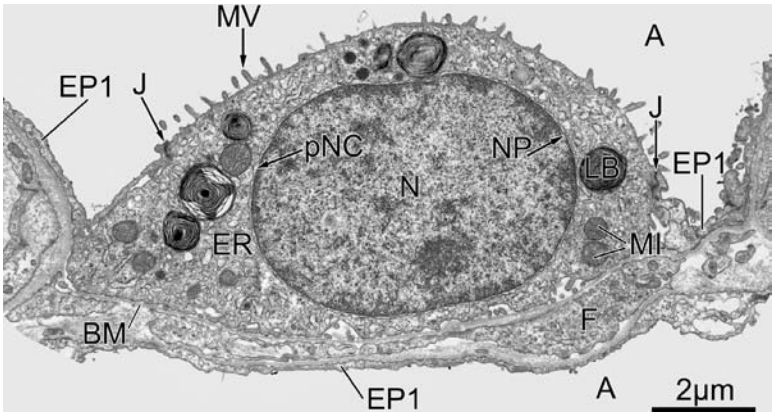


Figure 2-22 A type II epithelial cell from the human lung forms junction (J) with type I epithelial cells (EP1). Its cytoplasm contains osmiophilic lamellar bodies (LB) and a rich complement of organelles: mitochondria (MI), endoplasmic reticulum (ER), and so on. The nucleus (N) is surrounded by a perinuclear cisterna (pNC) which is perforated by nuclear pores (NP). A, alveolus; BM, basement membrane; F, fibroblast; MV, microvilli.

Type II cells have two main functions: they serve as the cellular source of pulmonary surfactant and they contribute to the regeneration of the alveolar epithelium under physiologic and pathologic conditions. These properties form the basis of the concept of the type II cell as the "defender of the alveolus."[86–88]

Surfactant prevents alveolar atelectasis by a surface area–dependent reduction of the alveolar surface tension (see below).[89–92] Another function of surfactant as a result of the reduction of alveolar surface tension is to prevent the formation of intra-alveolar edema.[93] In addition, certain surfactant components have important immunomodulatory functions in the innate host defense system.[94,95] Taken together, the main functions of surfactant might be summarized as to keep alveoli open, dry, and clean. Surfactant is composed of around 90% lipids, mainly saturated phosphatidylcholine, and around 10% proteins, including the surfactant apoproteins termed SP-A, SP-B, SP-C, and SP-D. Besides its biochemical complexity, surfactant is also morphologically very heterogeneous, consisting of different surfactant subtypes with highly organized structure that represent different stages in metabolism (Figs. 2-24–2-26).[84,96]

The alveolar epithelium (including interalveolar pores of Kohn) is lined by a thin but apparently continuous fluid layer inserted between the apical cell membrane and the surface film, thus forming a duplex lining layer.[97,98] Surfactant functions in and on this layer. It is synthesized, stored, secreted, and to a large extent recycled by type II cells.[84,87,99] Therefore, an intracellular surfactant pool present in type II cells and an intra-alveolar surfactant pool present at the surface of the fluid alveolar lining layer as well as within its hypophase can be distinguished. The intracellular storage form of surfactant is represented by lamellar bodies. Prior to storage, the synthesis of surfactant material involves endoplasmic reticulum, (at least partly) Golgi complex, and multivesicular bodies. In type II cells, multivesicular bodies participate in the posttranslational processing of surfactant proteins as well as in endocytosis and subsequent recycling and/or degradation of surfactant material; thus, most probably representing the junction point between the biosynthetic and endocytotic pathway. In addition, transitional forms between multivesicular bodies and lamellar bodies, termed composite bodies, have been described. Surfactant material present in lamellar bodies is secreted into the alveolar lumen via exocytosis (Figs. 2-25 and 2-26).

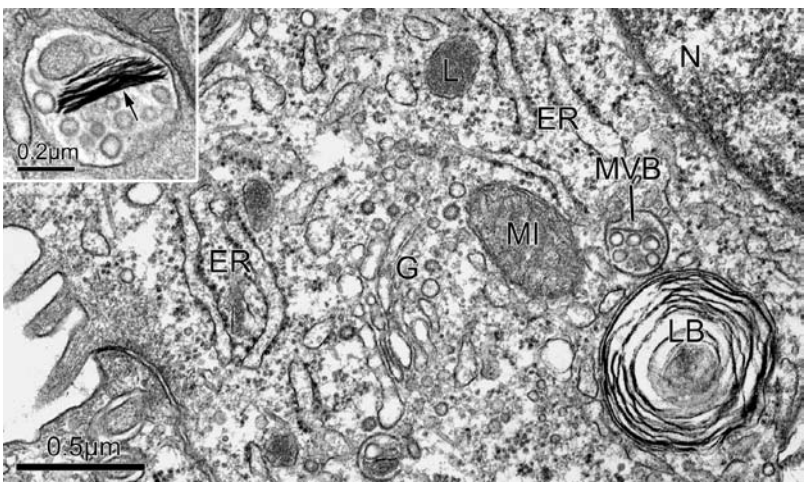
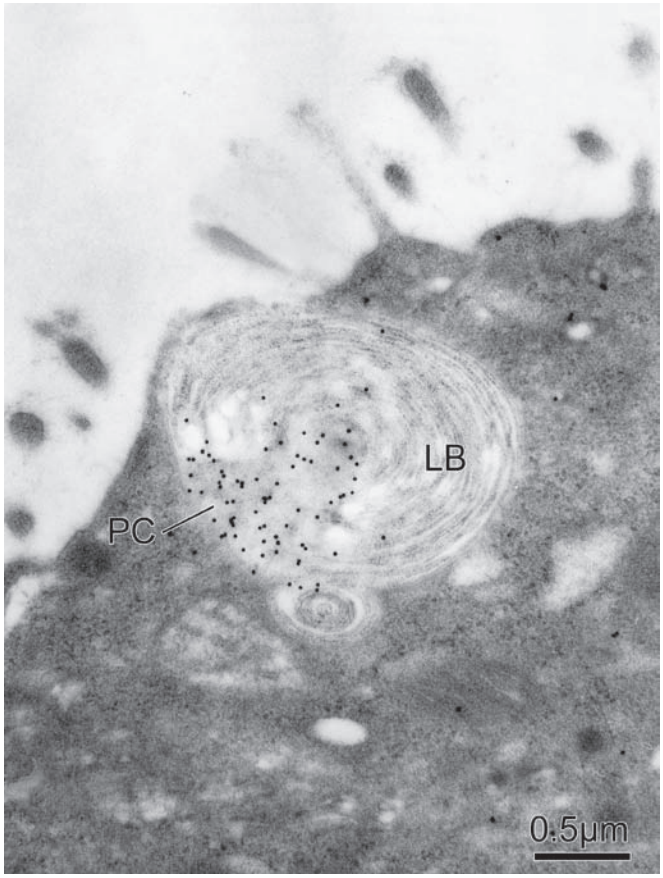
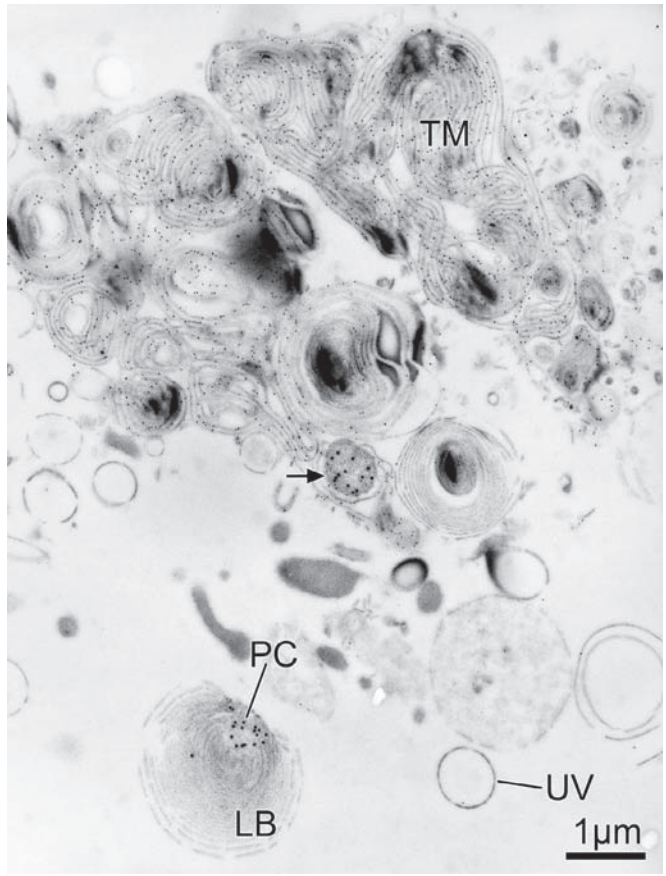


Figure 2-23 Cytoplasmic organelles of the type II cell implicated in the synthesis of surfactant are the endoplasmic reticulum (ER), Golgi complex (G), lysosomes (L), multivesicular bodies (MVB), and finally lamellar bodies (LB). The *inset* shows a large composite body with a stack of phospholipid lamellae *(arrow)*. N, nucleus. *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*



A



B

Figure 2-24 Immunogold labeling for SP-A (5-nm gold particles) and SP-B (15-nm gold particles) in the human lung. **A.** Within type II cells, SP-B is localized in the projection core (PC) of lamellar bodies (LB). **B.** In the alveolar lumen, SP-A is associated with tubular myelin figures (TM) whereas SP-B is found in the projection core (PC) of freshly secreted lamellar bodies (LB) and dense core particles *(arrow)* close to tubular myelin. UV, unilamellar vesicle.

Most surfactant components are assembled in lamellar bodies prior to secretion (Figs. 2-24–2-26)—at least the lipid fraction and the hydrophilic surfactant proteins SP-B and SP-C, whereas the hydrophilic surfactant proteins SP-A and SP-D seem to be secreted independently via a constitutive pathway bypassing the regulated exocytosis of lamellar bodies. Lamellar body secretion starts with the fusion of its limiting membrane with the apical plasma membrane, followed by formation of a fusion pore, and finally the slow release of surfactant material through the pore. The diameter of the pore is considerably smaller than that of the lamellar body. Thus, surfactant seems to be squeezed through the pore.[100] The mechanisms that regulate surfactant secretion in vivo are still not fully elucidated. It seems that, among the various stimuli that can act via several different signaling pathways, mechanical stretch during ventilation – either as a direct effect on type II cells or indirectly via type I cells or capillary endothelial cells which may act as "strain sensors" – is the physiologically most relevant.[87,99,101,102]

Intra-alveolar surfactant consists of several subtypes, namely freshly secreted lamellar body-like forms, tubular myelin, the surface film, and small unilamellar vesicles. After secretion, lamellar body-like forms in the hypophase associate with SP-A, which is separately secreted by type II cells,[103] and undergo a major

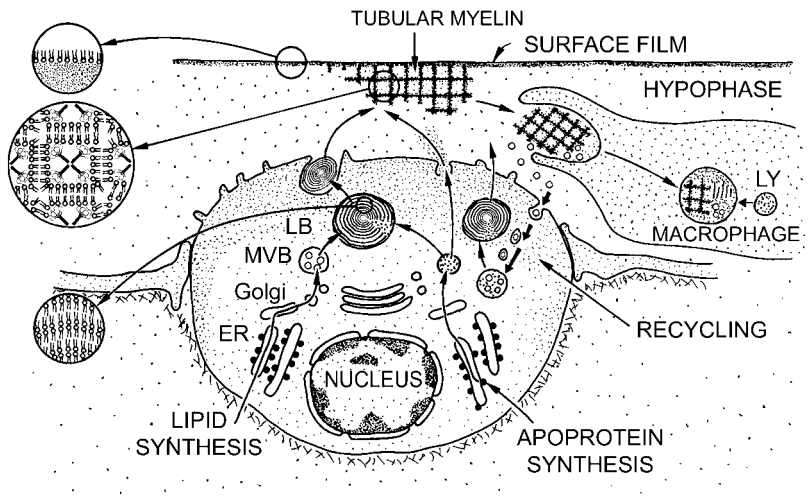


Figure 2-25 Schematic diagram of pathways for synthesis and secretion of surfactant lipids and apoproteins by a type II cell, for their recycling by type II cells, and for their removal by macrophages. Note the arrangement of phospholipids and apoproteins in the lamellar bodies, in tubular myelin, and in the surface film. *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1985.)*

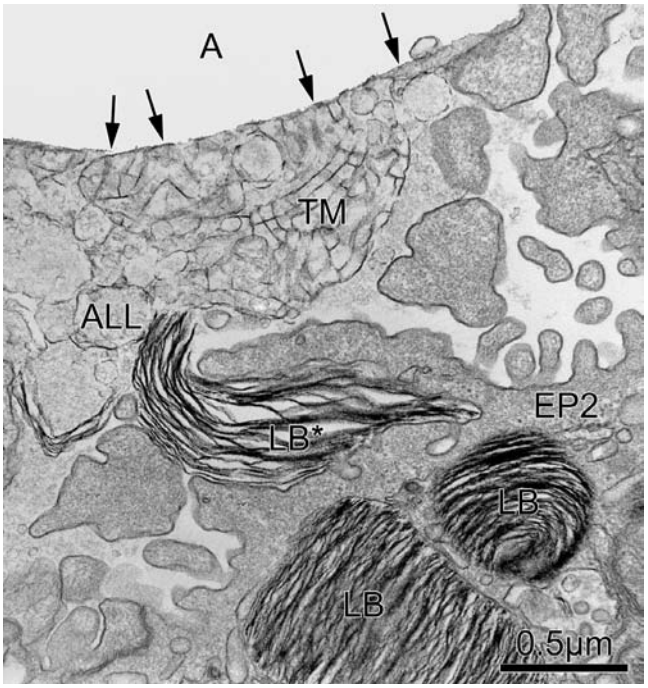


Figure 2-26 Apical part of type II cell (EP2) with lamellar bodies (LB); one of these (LB*) is seen in the process of being secreted into the alveolar surface lining layer (ALL). The free surface of the lining layer is covered by a thin black film of lipids *(arrows)*, which is connected with tubular myelin (TM) in the hypophase. *(Reproduced with permission from Weibel ER, Gil J: Structure-function relationships at the alveolar level, in West JB, ed.: Bioengineering Aspects of the Lung. New York: Springer-Verlag; 1977.)*

structural transformation into tubular myelin figures with a unique lattice-like structure.[104] The precise physiologic function of tubular myelin, however, is still unclear. Tubular myelin is thought to be the immediate precursor of the surface film, although the existence of an additional multilayered surface-associated surfactant reservoir underneath the surface film has been suggested.[96,105] "Spent" surfactant components are found in the hypophase as small unilamellar vesicles. The major route of surfactant clearance is reuptake by type II cells. Within type II cells, surfactant material can either be recycled or degraded. Other routes of surfactant clearance include ingestion and lysosomal degradation by alveolar macrophages and clearance via the airways.

After differential centrifugation of intra-alveolar surfactant material harvested by bronchoalveolar lavage, surface active large aggregates (LA), ultrastructurally largely corresponding to lamellar body-like forms and tubular myelin, and inactive small aggregates (SA), ultrastructurally largely corresponding to unilamellar vesicles, can be distinguished. Thus, the SA/LA ratio can be used to assess the biophysical activity of surfactant.[90,91]

A surfactant film, most likely mainly transported upward from the alveoli, is also present in the airways. Here, surfactant prevents collapse of smaller airways, prevents transepithelial fluid influx, enhances mucociliary transport, and interacts with inhaled pathogens and particles. At least some of the surfactant proteins are also synthesized and secreted by club cells. Club cells express SP-B, but not SP-C, which is exclusively expressed by type II cells. There is some controversy whether club cells express SP-A and SP-D. Although this is obviously the case in rodents, club cells in the normal adult human lung most likely express very low or no SP-A and SP-D.[103,106,107] It seems that club cells are not involved in reuptake or recycling of surfactant components.[108] However, their overall role in surfactant biology is not yet defined.

The surfactant apoproteins as the "smart molecules in the surfactant system"[109] have important functions in surfactant subtype assembly, surfactant biophysics, surfactant homeostasis, and innate immunity.[110–114] The hydrophilic proteins SP-A and SP-D belong to the collectin protein family involved in innate immunity. In addition, SP-A, together with SP-B, is important for tubular myelin formation, thus stabilizing active surfactant forms, whereas the hydrophobic proteins SP-B and SP-C and, in conjunction, SP-A enhance the adsorption of phospholipids into the surface film. SP-A might also inhibit surfactant secretion and stimulate surfactant reuptake by type II cells.

Differences in the ultrastructural organization of intracellular and intra-alveolar surfactant subtypes between humans and rodents are also reflected by a different distribution of surfactant proteins (Fig. 2-24).[84] In the human lung, SP-A within type II cells is mainly found in small vesicles and multivesicular bodies and only rarely at the periphery of lamellar bodies. In the alveolar lumen, SP-A is associated with peripheral membranes of lamellar body-like forms in close proximity to tubular myelin, in the corners of the tubular myelin lattice structure, and partly at the surface film and unilamellar vesicles.[103] SP-B in the human lung is localized in the projection core of lamellar bodies within type II cells and in dense core particles associated with tubular myelin in the alveolar lumen.[115]

The crucial role of the surfactant system for the maintenance of the functional integrity of the lung is clearly demonstrated by surfactant dysfunction disorders, which can be caused either at birth by developmental deficiency (owing to lung immaturity or mutations affecting surfactant synthesis or secretion) or later by acquired dysfunction (owing to damage of type II cells or inhibition/inactivation of intra-alveolar surfactant).[90,91,116] A primary deficiency of surfactant in the immature lungs causes the respiratory distress syndrome of premature neonates (RDS). Surfactant dysfunction mutations causing either acute respiratory failure or chronic lung disease after birth have been identified in the genes encoding for SP-B, SP-C, and the ATP-binding cassette transporter ABCA3, which is present at the limiting membrane of lamellar bodies. Impairment of an originally intact surfactant system is involved in the pathogenesis of a variety of other lung diseases, such as acute lung injury/ARDS as well as obstructive, infectious, and interstitial lung diseases. Mechanisms leading to impaired surfactant activity include apoptotic or necrotic cell death of type II cells, damage of surfactant proteins and lipids by reactive oxygen and nitrogen species, and enzymatic damage by phospholipases or neutrophil elastase. In addition, plasma proteins entering the alveolar space during edema formation are also known to inactivate surfactant.

With a turnover time of about 4 to 10 hours and only a rather small intracellular surfactant reserve available for secretion onto the large alveolar surface, the ability to cope with a lack of active surfactant during lung injury is limited. Hence, there is a rationale to supplement the surfactant material available in cases of surfactant deficiency or damage. One of the major advances in neonatology in our time has been the development of surfactant replacement therapy for the treatment of RDS. The story of the treatment of premature babies with exogenous surfactant is indeed a paradigmatic example in which discoveries from basic research were successfully applied to an important clinical problem.[91,117–119] The indications for surfactant replacement therapy have widened in recent years, with promising results in forms of respiratory failure not caused by a primary deficiency of endogenous surfactant but rather by impairment of an originally intact surfactant system. In these cases, however, the efficacy of exogenous surfactant therapy very much depends on the ability of the surfactant preparation to resist the inhibition/inactivation that caused alterations of the endogenous system.

■ CAPILLARY ENDOTHELIUM

The alveolar septa of the adult lung contain a single capillary network. The capillary endothelium is of the continuous (non-fenestrated) type. Alveolar capillaries are provided with pericytes, but they are rarer and less densely branched than pericytes of the systemic circulation.[120] Pericytes are related to vascular smooth muscle cells in that they both are contractile perivascular cells. Thus, pericytes protect microvessel wall integrity by providing some mechanical support. However, in contrast to vascular smooth muscle cells, pericytes are embedded within the endothelial basement membrane, frequently forming contacts with capillary endothelial cells. They seem to contribute components to the capillary basement membrane and extracellular matrix and secrete vasoactive substances. In addition, pericytes are thought to be involved in the regulation of endothelial cell proliferation and differentiation and to act as progenitor cells for other cell types.[121–124]

Capillary Endothelial Cells

At first glance, capillary endothelial cells resemble type I alveolar epithelial cells, but in contrast to type I cells with their complex branching architecture, capillary endothelial cells form simple sheets (Fig. 2-27).[57] Moreover, compared with the tight occluding junctions between alveolar epithelial cells that constitute a powerful seal of the intercellular cleft, the occluding junctions between capillary endothelial cells are rather leaky, allowing a nearly uninhibited exchange of water, solutes, and even some smaller macromolecules between the blood plasma and the interstitial space (Fig. 2-18). Occluding junctions between capillary endothelial cells are often located at the transition of the thin to the thick part of the air–blood barrier and are often covered by pericytes.

There is another notable and important difference between the two basically similar lining cells on the epithelial and endothelial side of the gas-exchange barrier: their size. Although the capillary surface is some 10% to 20% smaller than the alveolar surface, the capillary endothelial cells are about four times more numerous than type I cells[72]; this means that the surface covered by one type I epithelial cell must be about four times larger, namely 4000 to 5000 μm^2, as compared with about 1000 μm^2 in endothelial cells (Table 2-2).

Numerous caveolae are found in capillary endothelial cells (Figs. 2-17 and 2-18). However, at the bulging part of the capillaries, some parts of the endothelial cell extensions are free of caveolae and are thinned down to a thickness of about 20 to 30 nm, basically consisting of the two plasma membranes with only a minute amount of cytoplasm in between. These areas, rarer in human lungs than in rodents, are termed the avesicular zone of the alveolar capillary endothelium.[11,57] In contrast to the endothelium of conducting vessels, Weibel–Palade bodies are missing in capillary endothelial cells, thereby underscoring the structural and functional differences between alveolar and extra-alveolar endothelial cells.[11,49,125,126]

■ INTERSTITIUM

The interstitium of the alveolar septum is for the most part extremely thin. At the thick parts of the air–blood barrier where epithelial and endothelial basement membranes are separated, one finds elastic fibers and bundles of collagen fibrils in the extracellular matrix as well as interstitial cells, mainly fibroblasts, the cells responsible for production of extracellular matrix components (Figs. 2-28 and 2-29).

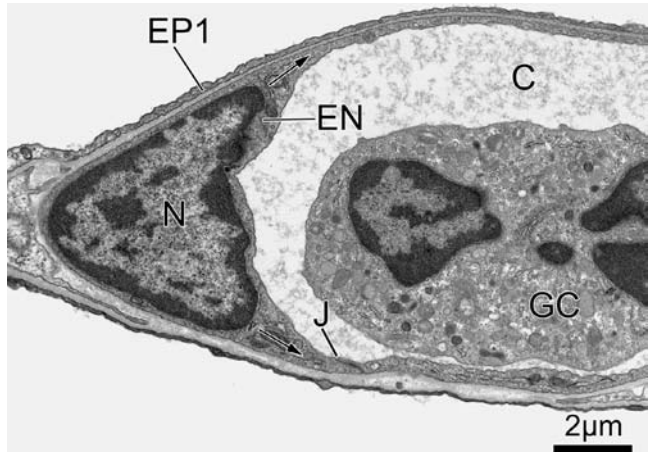


Figure 2-27 An endothelial cell (EN) of capillary (C) is similar in basic structure to a type I epithelial cell (EP1). The nucleus is enwrapped by little cytoplasm but thin leaflets extend as capillary lining *(arrows)*. Note the intercellular junction (J) and a white blood cell/granulocyte (GC), in the capillary. *(Modified with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

The precise arrangement of the connective tissue fibers will be discussed later in relation to the mechanical properties of the lung.

Interstitial Cells

The resident interstitial cells of the alveolar septum comprise fibroblasts and contractile cells (myofibroblasts, lipofibroblasts, smooth muscle cells, and pericytes) (Fig. 2-28). Free interstitial cells are part

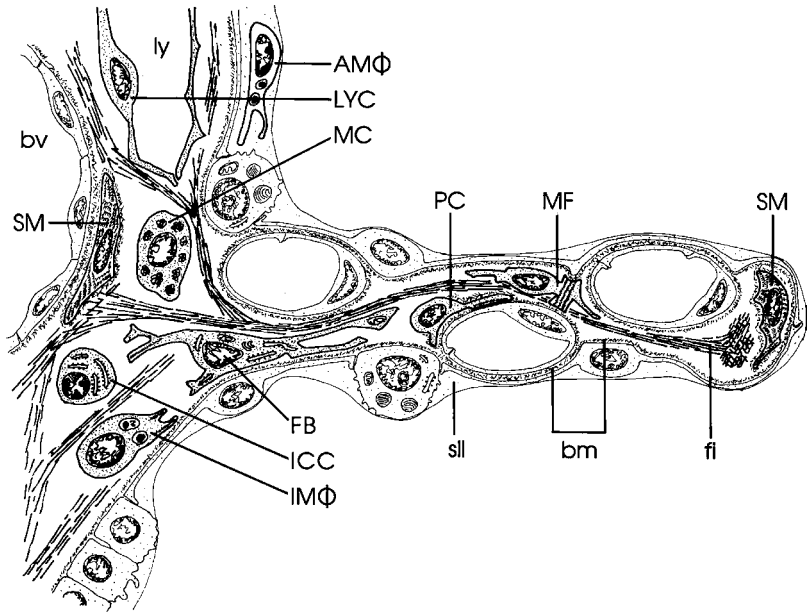


Figure 2-28 Schematic diagram of the structural organization of the alveolar interstitium. The alveolar septum extends between a free edge *(right)* and a perivascular connective tissue sleeve *(left)*, enwrapping a blood vessel (bv). Basement membranes (bm) are associated with epithelium and endothelium, and they bound the interstitial space. Fiber strands (fi) form a continuum. Interstitial cells include: fibroblasts (FB), myofibroblasts (MF), smooth muscle cells (SM), pericytes (PC), various kinds of immune competent cells (ICC), mast cells (MC), lymphatic endothelial cells (LYC), and histiocytes or interstitial macrophages (IMΦ). Alveolar macrophages (AMΦ) are submerged in the alveolar surface lining layer (sll), ly, lymphatic capillary. *(Reproduced with permission from Weibel ER, Crystal RG: Structural organization of the pulmonary interstitium. In: Crystal RG, West JB, Weibel ER, Barmes PJ (eds), The Lung: Scientific Foundations, 2nd ed. New York: Lippincott-Raven; 1997:685–695.)*

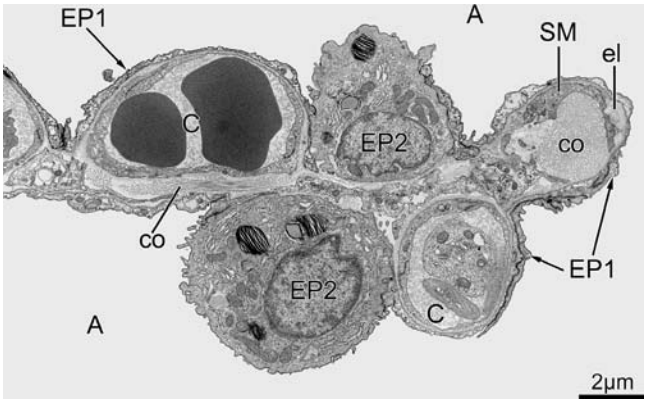


Figure 2-29 Alveolar septum with free edge *(right)* showing reinforced entrance ring with elastic fibers (el), collagen fibrils (co), and smooth muscle cell (SM). The two capillaries (C) are on different sides of the septum, as are the two type II cells (EP2). A, alveolar space; EP1, type I cell. *(Reproduced with permission from Weibel ER, Gil J: Structure-function relationships at the alveolar level, in West JB, ed.: Bioengineering Aspects of the Lung. New York: Springer-Verlag; 1977.)*

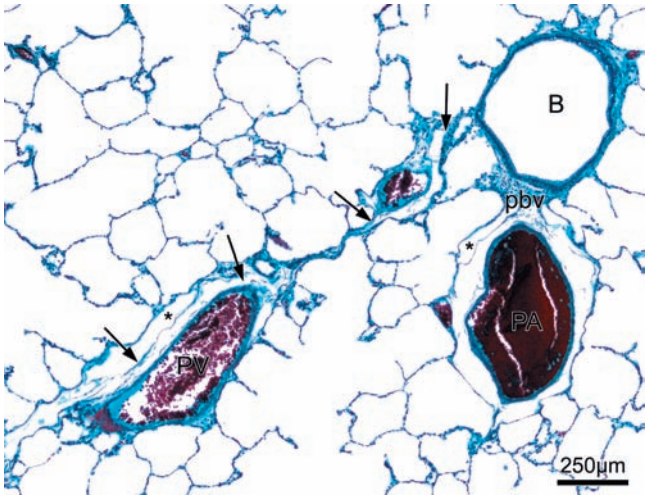


Figure 2-30 Light micrograph of human lung showing connective tissue sleeve *(arrows)* extending from the peribronchovascular space (pbv) around branch of pulmonary artery (PA) and bronchiolus (B) to pulmonary vein branch (PV). Asterisks, lymphatic.

of the defense system usually found in the juxta-alveolar connective tissue sleeves (see below) and include interstitial macrophages (histiocytes), mast cells, and under certain conditions, lymphocytes, plasma cells, and granulocytes.

Fibroblasts are a heterogeneous cell population. Many fibroblasts have notable contractile properties; therefore, they have been termed myofibroblasts. Myofibroblasts contain bundles of microfilaments anchored in patches beneath the plasma membrane. These filament bundles span the entire width of the cell. At the places where the microfilament bundles are connected to the plasma membrane, attachments to the epithelial and/or endothelial basement membrane exist.[11,127,128] Through holes in the basement membranes, myofibroblasts directly link alveolar epithelial and capillary endothelial cells.[83]

Some contractile fibroblasts are equipped with nonmembrane–bound lipid bodies, thus termed lipid interstitial cells or lipofibroblasts.[129,130] These cells are more common in rodent than in human lungs and occur particularly during alveolar development and growth. Lipid bodies consist of an osmiophilic rim of amphipathic phospholipids, glycolipids, sterols and specific proteins, and a hydrophobic core of neutral lipids. In many cell types, lipid bodies represent specialized domains for the synthesis of eicosanoid mediators.[131] Pulmonary lipofibroblasts seem to be related to the lipid-containing perisinusoidal cell (Ito cell) in the liver in that they might serve as a storage depot for retinoids.[130,132] Under certain conditions, lipofibroblasts might provide fatty acid substrates for surfactant synthesis in type II cells.[130]

The occurrence of smooth muscle cells in the alveolar septa is mostly restricted to the free septal edges where they contribute to the network of alveolar entrance rings (Figs. 2-28 and 2-29). Pericytes abut alveolar capillaries (see above).

STRUCTURAL ASPECTS OF THE DEFENSE SYSTEM OF THE LUNG

The large and delicate alveolar surface is constantly challenged by inhaled microorganisms and particulate matter. Thus, normal lung function critically depends on an efficient defense system.[94,113,133–136] At the alveolar level, the primary defense barrier is the alveolar lining layer. Here, alveolar macrophages are the sentinel phagocytic cells of the innate immune system, as we shall discuss later. In addition, protein components of the innate immune system, including the lung collectins SP-A and SP-D as well as a variety of other antimicrobial peptides (e.g., lysozyme, lactoferrin, defensins, cathelicidins), are present in the alveolar lining layer.

Another set of macrophages forms a second defense line just beneath the alveolar epithelium; that is, in the interstitial space of the lung parenchyma. In the normal lung, these interstitial macrophages (histiocytes) are not found in alveolar septa; instead, they occur only in the connective tissue sleeves at the periphery and in the center of acini where the peripheral fiber system connects with the adventitial sheath of bronchioles and pulmonary arteries (Fig. 2-30). Thus, they are found in regions where lymphatics begin their course toward the major airways in the hilar region where lymph nodes are found. In these juxta-alveolar regions of connective tissue, we usually find the common elements of the defense system (Figs. 2-30 and 2-31). These include lymphatic vessels and several mobile cells. Interstitial macrophages are constantly being replenished by blood monocytes migrating into the interstitial space. Sometimes they become permanent residents in the form of storage cells for "indigestible" foreign matter, such as carbon particles and silicates. The relationship

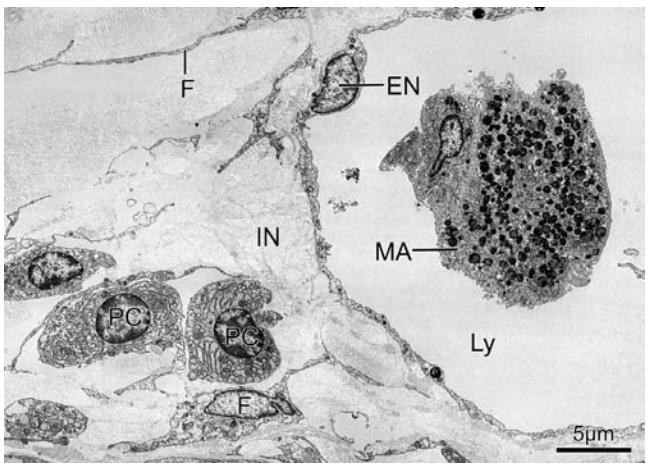


Figure 2-31 Perivascular connective tissue with lymphatic (Ly) containing a macrophage (MA) with heterogeneous population of "lysosomal" granules. Interstitium (IN) contains fibroblasts (F) and plasma cells (PC). EN, lymphatic endothelium.

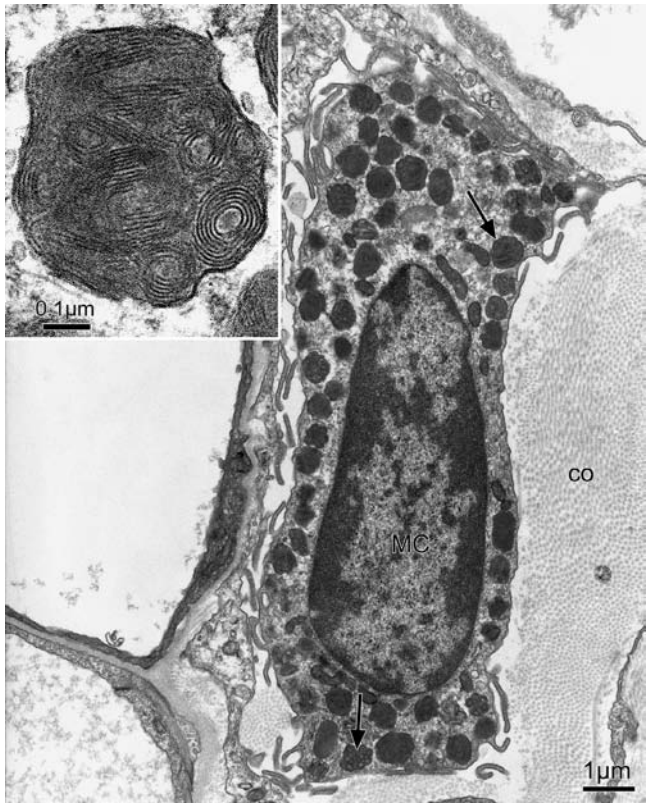


Figure 2-32 Mast cell from human lung containing granules *(arrows)* with scroll-like substructure. *Inset:* Scroll-like substructure of mast cell granule at higher magnification. Co, collagen fibrils. *(Reproduced with permission from Weibel ER: Lung cell biology, in Fishman A, Fisher AB, eds. Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985: 47–91.)*

between interstitial macrophages and dendritic cells (see below) is under discussion.[137,138] Lymphocytes are less common and are mostly present as T cells whereas B cells and natural killer cells are rare in the normal lung. Granulocytes (neutrophils, eosinophils, and basophils) are present in the human lung, but they are also very rare. Mast cells contain granules storing heparin and histamine as well as peptidases such as tryptases and chymases[139] that, in the human, show a characteristic scroll-like substructure (Fig. 2-32) as well as lipid bodies. According to their anatomic location, they show site-specific characteristics, thus displaying considerable heterogeneity.[140] Antigen-presenting dendritic cells possess long branched dendritic cell processes (hence, their name) and an irregular, folded nucleus. Phagolysosomes are absent. Once activated, dendritic cells migrate to lymph nodes where they induce the proliferation of antigen-specific T cells; thus, providing a link between innate and adaptive immunity. In addition to their presence within the lung parenchyma, dendritic cells are found within the tracheal and bronchial epithelium where they seem to form a network comparable to the Langerhans cells in the epidermis. Like Langerhans cells, airway dendritic cells are characterized by pentalaminar plate-like organelles (Birbeck granules).[141–143] In the ciliated epithelium of bronchi and bronchioles diapedesis is seen; that is, lymphocytes and other leukocytes in the process of penetrating the epithelium to reach the mucus blanket. Plasma cells occur in relatively high numbers around the acini of the seromucous glands of bronchi (Fig. 2-7); hence, it is likely that antibodies are being secreted into the mucus blanket by these glands by a process similar to that occurring in the salivary glands or in the glands of the nasal mucosa.

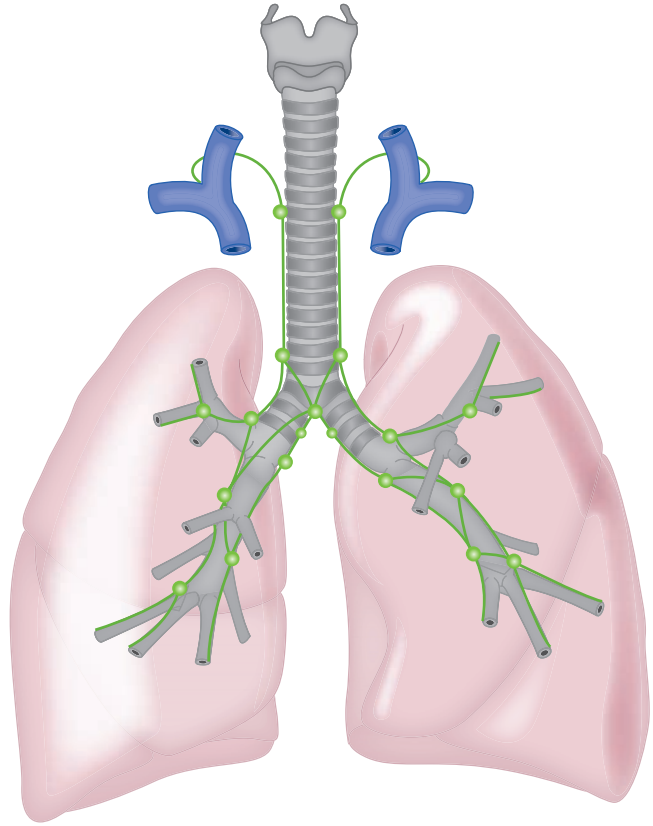


Figure 2-33 Schematic diagram of distribution of lymph nodes and main lymphatic channels along bronchial tree.

The third defense line is constituted by the lymph nodes, which are arranged along the major bronchi and extend to subsegmental bronchi about 5 mm in diameter (Fig. 2-33). The most peripheral lymph nodes are tiny, a mere 1 to 2 mm in diameter, but closer to the hilum they become larger, reaching 5 to 10 mm in diameter in the region of the tracheal bifurcation and along the trachea. The lymph nodes from adult human lungs often appear gray or even black because of deposition in the medullary cords of large numbers of macrophages loaded with carbon pigment. This material entered the lung via the airways, primarily as smoke, soot, or coal dust; depending on the size of the particles, they were either deposited on the surface of conducting airways or reached the alveoli. The further down the deposition, the greater the likelihood that this material cannot be eliminated while in the airways, that is, within the mucus blanket. The only exit from the lung parenchyma then is via the lymphatics, but this exit ultimately leads to the blood, a circumstance that is obviously to be avoided. Filtering the lymph in lymph nodes and providing a depository in the medullary cords protects the blood and hence the entire organism from dissemination of indigestible foreign matter and also, in most instances, of infective agents.

Thus, the lymphatic "circulation" in the lung plays an important defense role.[6,42] It is unidirectional. It begins as interstitial fluid that seeps from the capillaries and is efficiently drained along the connective tissue fibers toward those connective tissue sleeves in the center and at the periphery of acini where lymph capillaries begin. From there, lymphatic vessels, endowed with valves and an irregular smooth muscle wall, course in septal structures, in the pleura, and peribronchial and perivascular sheaths toward the hilar region (Fig. 2-33). Lymph nodes are intercalated in the course of the lymphatics, which lead the lymph toward the tracheal bifurcation and then along the trachea into the right and left mediastinal lymph channels. The right channel drains into the right subclavian vein;

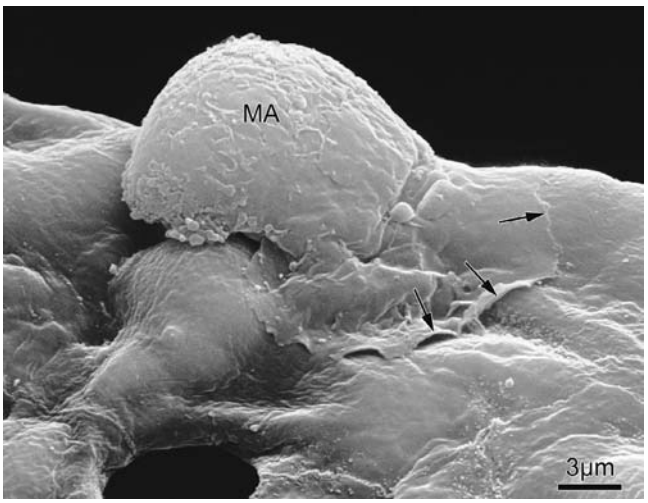


Figure 2-34 Alveolar macrophage (MA) seen sitting on epithelial surface of human lung. Note cytoplasmic lamella *(arrows)* which represents the advancing edge of the cell.

the left, together with the thoracic duct, into the left subclavian vein. Because of the many anastomoses connecting parallel lymphatics, a particular lymph node receives lymph from various lung regions, but the closest regions tend to predominate.

■ ALVEOLAR MACROPHAGES

Lung macrophages can be differentiated into several populations according to the compartment they are found in: intravascular, interstitial, airway, and alveolar macrophages.[144–146] Of these, the alveolar macrophages, the cell population of the surface lining layer, are of particular importance. They are free cells, endowed with a high phagocytic capacity, which are transiently attached to the surface of the alveolar epithelium by pseudopodia and can crawl over this surface by amoeboid movement (Fig. 2-34). Occasionally, alveolar macrophages can be observed during the passage through an interalveolar pore of Kohn. However, they are submerged beneath the surface film of phospholipids (Fig. 2-35) and, therefore, are part of the surface lining layer of alveoli, more specifically of its hypophase. Alveolar macrophages exert their phagocytic activity within the surface lining layer (Fig. 2-25). Hence, it is not surprising that their vacuoles contain large amounts of ingested surfactant material, in part even tubular myelin. The importance of alveolar macrophages for surfactant removal is underscored by the acquired form of pulmonary alveolar proteinosis, where a defect in surfactant catabolism by alveolar macrophages caused by autoantibodies against granulocyte/macrophage colony-stimulating factor (GM-CSF) leads to an accumulation of surfactant material in the alveoli.[147]

Alveolar macrophages are derived from monocytes – indirectly, therefore, from bone marrow cells – and probably reach the alveoli in two steps: first, by settling in the pulmonary interstitial tissue, and second, by migration from the interstitial tissue into the alveoli where they constitute a partly self-reproducing cell population. Their removal seems to involve two different pathways: (1) some of the macrophages undoubtedly move up the bronchial tree in the mucus blanket and eventually appear in the sputum; and (2) others possibly return into the interstitial space. In the normal lung, however, the second path seems to occur exclusively in those alveoli that abut the connective tissue sleeves around larger vessels and conducting airways or on interacinar septa; that is, where the lymphatic capillaries are located. A preferred location appears to be in the respiratory bronchioles at the entrance into the acinus or in the center of the acinus, where one often finds congregations of dust-laden macrophages; this may be at the origin of centroacinar damage observed in smokers, which lead to progressive emphysema. In these places, macrophages either settle as carbon pigment-loaded histiocytes, or they leave the lung parenchyma via lymphatics (Fig. 2-31) to settle in the lymph nodes. The way in which macrophages and/or their ingested material are transferred from the alveolar surface to the interstitial space is still unknown.

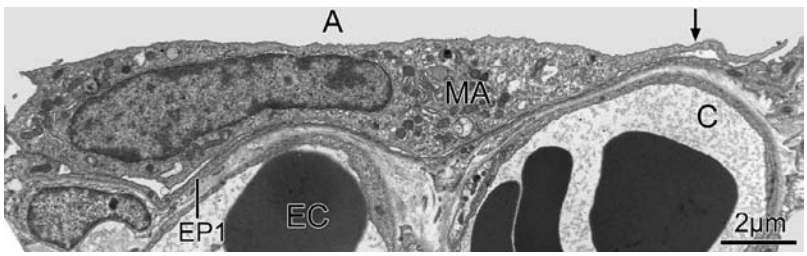


Figure 2-35 Alveolar macrophage (MA) fixed in its natural position of "flat" attachment to the alveolar epithelium. *Arrow* points to advancing cytoplasmic leaflet.

FUNCTIONAL DESIGN OF THE LUNG

From the preceding section it has become apparent that the lung is built of a multitude of cells and tissue elements that all serve specific functions in support of the lung's main function: the exchange of oxygen and carbon dioxide between the air and the blood. But it takes more than cells to make a good lung.[148] The lung's multiple component structures must be integrated to make an efficient and stable gas exchanger, and this demands a blueprint for the integral architecture of the human lung.[7] This must first ensure that the airways and blood vessels are adequately correlated topologically and quantitatively to allow well-matched ventilation and blood flow. It must also realize a complex organization that allows air ventilation, blood perfusion, and gas exchange to function in the most efficient manner. The design principles that govern the architecture of the human lung toward that goal can be characterized as *Complexity, Correlativity, and Connectivity*. Complexity means that the microscopic gas-exchange units are an integral part of the macroscopic airways and vessels; their architectural correlation determines the efficient approximation of air and blood in the gas exchanger; and connecting all the parts into a whole is achieved with a fiber continuum that pervades the entire lung. The implementation of these principles during development is decisive for "making a good lung."

■ DESIGN OF THE BRANCHING AIRWAY TREE

The entrance to the lung's airways is the trachea (Fig. 2-3), a single tube, the gas-exchange elements where air and blood are brought into close contact are contained in several million units. Between entrance and periphery lies a meticulously designed system of branching airways that serve to conduct the inspired air into those peripheral channels that carry alveoli in their walls and can thus contribute to the exchange of gases between air and blood (Fig. 2-5).[8]

In the mammalian and human lung the airways are built as dichotomous trees.[149] This is the result of lung morphogenesis where the end bud of each airway tube gives rise to two daughter branches. In the human lung this goes on for 23 generations, on average, and, since the number of branches doubles with each generation, there are 2^{23} or about 8 million end branches, generally called alveolar sacs.[8] This is an average value; in reality the number of branching generations needed to reach the alveolar sacs is quite

variable, ranging from about 18 to 30. This variability results from the fact that the airways form a space-filling tree (Fig. 2-3) whose endings must be homogeneously distributed in space and reach into every corner and into every gap in the available space, determined by the form of the chest cavity into which the lung develops. Some spaces are filled rapidly and the airways cannot continue to divide, whereas in other places more branches are needed to fill the space.

This branching process is accompanied by growth in length and diameter of the airway segments, the tubes between the branching nodes. The length of the tubes is adjusted to cover the distances needed to fill the space homogeneously with endings, whereas the diameter is, grossly speaking, made proportional to the volume of peripheral lung that is supplied by this branch.

Figure 2-36 shows a portion of a cast of the airway tree from a human lung. It is evident that the airways branch by dichotomy and that the length and the diameter of the tubes become gradually reduced with each generation. At first sight, the airway branching seems quite regular, but there is a certain degree of asymmetry in the sense that the two daughter branches differ in length and diameter; in animal lungs asymmetry is more pronounced than in human lungs.

Despite asymmetric branching some general rules govern the progression of dimensions along the tree. The diameter of daughter branches is smaller than that of the parent in the sense that the diameter reflects the volume of peripheral lung it supplies with air: larger airways serve larger lung units, smaller airways smaller units. The progression of airway diameters follows the law of Hess (1917)[150] and Murray (1926)[151] that, in a dichotomous tree, the diameters of the daughter branches, d_1 and d_2, are related to the parent branch d_0 as:

$$d_0^{\,3} = d_1^{\,3} + d_2^{\,3}$$

a law that predicts optimization of the airway diameters for convective air flow, providing lowest resistance for lowest dead space.

For a symmetric tree in which $d_1 = d_2$ this becomes:

$$d_1 = d_0 \cdot 2^{-1/3}$$

which means that the airway diameter becomes reduced by a factor of cube root of 1/2 or about 0.79 with each generation. Considering the progression of airway dimensions along the tree this law should apply to all successive generations so that we predict the average diameter in generation z to be:

$$d(z) = d_0 \cdot 2^{-z/3}$$

Figure 2-37 shows that this is approximately the case for the first 14 generations of conducting airways.

However, a closer look at the airways of the human lung shows that this is only approximately correct.[152] It appears that the smaller bronchioles (beyond generation 10) are provided with some safety factor in that the diameter is reduced by a factor of 0.83 rather than the physically optimal 0.79. This allows regulation of airway cross-section by contraction of the bronchiolar muscle sleeve without unduly increasing flow resistance which is very low in small airways (Fig. 2-38).[153] Design optimization is limited in favor of physiologic robustness.

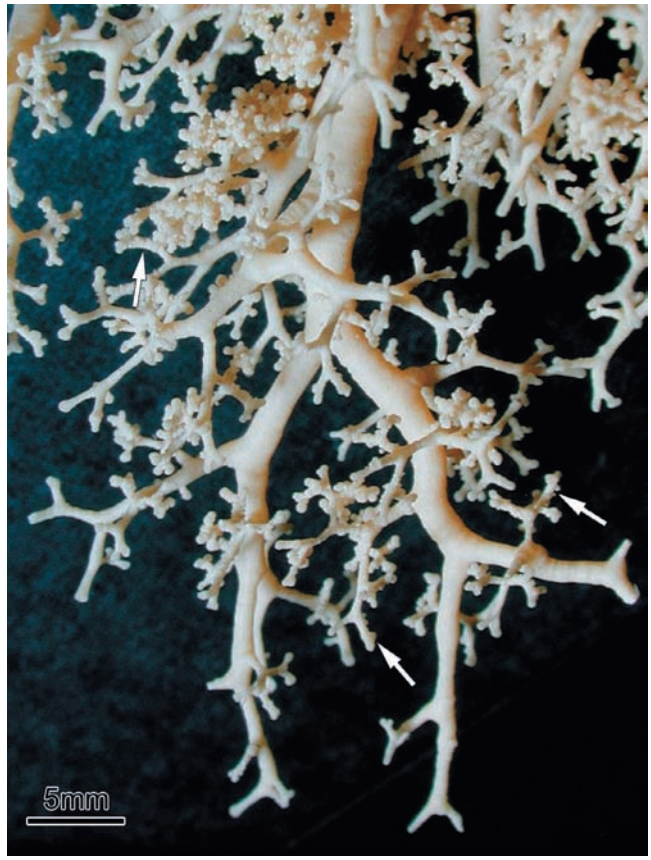


Figure 2-36 Peripheral portion of cast of human airway tree reaching out to the transitional bronchioles and some respiratory bronchioles *(arrows)*.

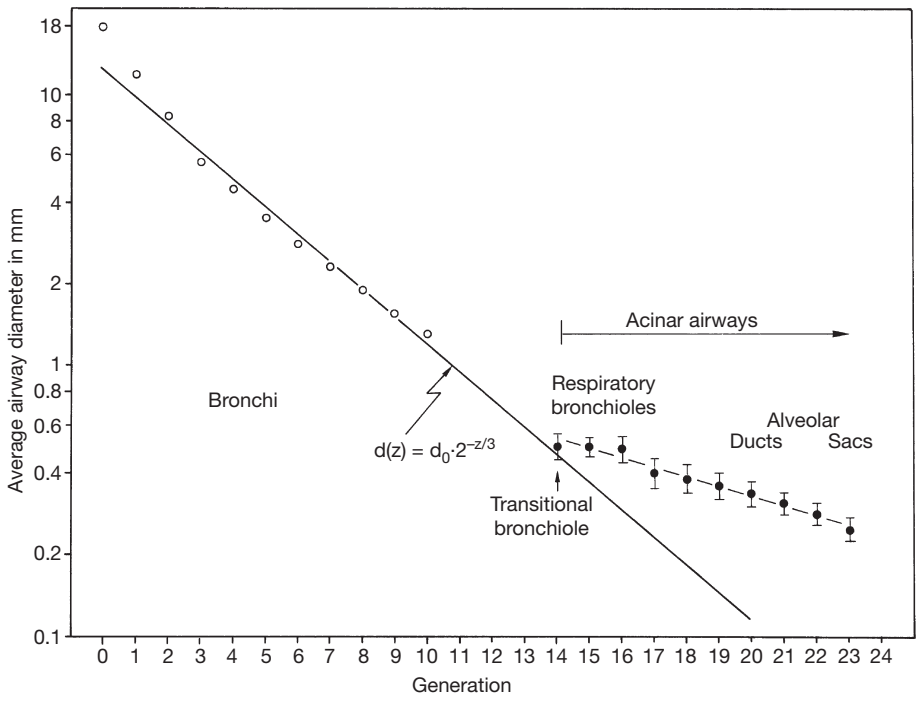


Figure 2-37 Average diameter of airways in human lung plotted by generations of regularized dichotomous branching. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

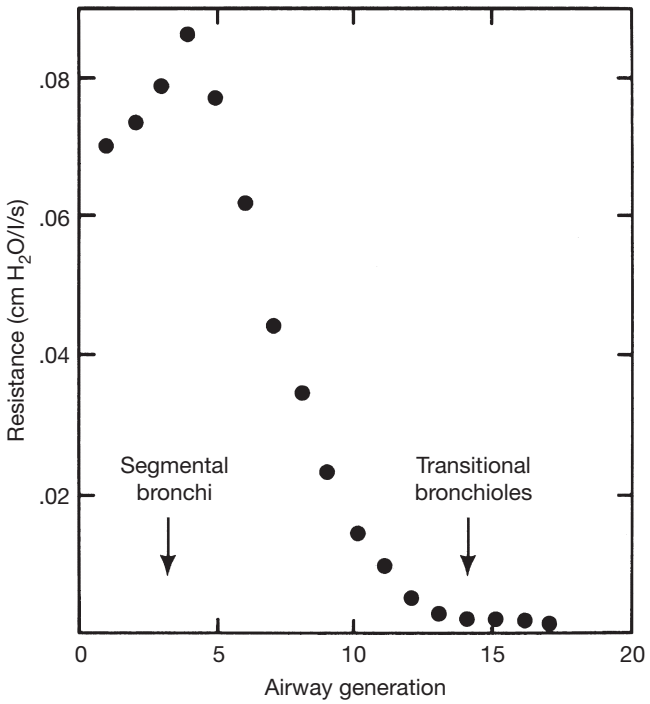


Figure 2-38 Airway resistance to mass air flow is located mostly in the conducting airways and falls rapidly toward the periphery. *(Redrawn with permission from Pedley TJ et al. The prediction of pressure drop and variation of resistance within the human bronchial airways. Respir Physiol. 1970;9(3):387–405.)*

This symmetric airway model reflects the typical pathway along the airway tree. It has been very useful in modeling the basic rules governing the distribution of air flow as well as the deposition of particles entering the lung. However, it disregards the effects of asymmetric branching. It is possible to construct models that take into account irregularities in branching, for example by considering the number of airways of a given diameter, d_u, that exist in each generation, and the length of the bronchial pathway that intervenes between the larynx and particular airways (Fig. 2-39).[8,154]

An alternative approach is to regard the airways as a system of tubes converging from the periphery, the acinus, toward the center, the trachea.[155] By using an ascending ordering system that is employed in analyzing rivers (Strahler system), branches are grouped into orders according to the sequence of convergence, beginning with the smallest most peripheral branches, designated as order l. This ordering pattern is particularly well adapted to a system of irregular dichotomy because the size of branches in one order varies less than with the generations-down model. This approach does not really account for the asymmetry of branching, however; it rather represents an attempt at extracting average data with less variability in each order. The degree of asymmetric branching is reflected in the branching ratio determined as the ratio of the number of branches in order μ to that in order $\mu + 1$. Remarkably, the progression of diameters through the various orders is again roughly proportional to the cube root of the branching ratio. Hence, from a functional point of view both models yield comparable results.

The general conclusion drawn from this type of analysis is that the diameters of the conducting airways are such as to assure optimal conditions for airflow but relaxing physical optimality conditions in the interest of physiologic robustness; the airways of the lung are thus well designed. The total volume of the conducting airways down to generation 14 (the anatomic dead space) is about 150 mL; it is rapidly flushed by simple gas flow in the course of inhaling 500 mL of fresh air during quiet inspiration. Therefore, for the larger airways, optimization for flow and its distribution to peripheral units are essential for good design.

These are the characteristics of the proximal airways built as smooth-walled tubes to distribute convective air flow into the lung. This design ends more or less abruptly when the airways reach lung parenchyma, the complex of alveoli that are arranged around peripheral airways (Fig. 2-40). The airway tree is thus subdivided into two major functional zones (Fig. 2-5): the first about 14 to 16 generations, on average, are designed as conducting airways where air flow is by convection; this is followed by about 8 generations of acinar airways where an axial channel, called alveolar duct, is enwrapped by a sleeve of alveoli with gas-exchange tissue on their surface.

In the human lung the transition is not abrupt. At some point the smooth bronchiolar wall becomes interrupted by one or two alveoli (Fig. 2-41). This so-called transitional bronchiole (Fig. 2-5) marks the entrance into an acinus.[9] It is followed by some three generations of respiratory bronchioles where an increasing fraction of the wall surface is occupied by alveoli, until the alveolar ducts are reached where the central air duct is completely surrounded by alveoli (Fig. 2-42). These acinar airways continue to branch by dichotomy. Their length and diameter decrease with each generation, but the slope does not follow the law of reduction by the cube root of 1/2; the diameters of respiratory bronchioles and alveolar ducts change very little with each generation.[9] Does this arrangement imply less than an optimal design? On the contrary, the cube-root-of-1/2 law relates to optimizing mass flow of a liquid or air. In the most peripheral airways, mass airflow is only part of the means of transporting O_2 toward the air–blood barrier. Since the airways are blind-ending tubes and since a sizable amount of residual air remains in the lung periphery after expiration, O_2 molecules must move into the residual air by diffusion (Fig. 2-43). However, diffusion of O_2 in the gas phase is best served by establishing as large an interface as possible between residual air and the fresh air that flows in from the trachea.[16] In fact, since the airway diameter remains nearly unchanged, the total airway cross section nearly doubles with each generation beyond generation 14.

The dimensions of the airway tree influence the ventilatory flow of air in a number of ways. First of all, airflow velocity falls along the airway tree because the total cross-sectional area of the airways increases with every generation (Fig. 2-44); whereas the cross-sectional area of the trachea is about 2.5 cm^2, that of the 1024 airways in the 10th generation taken together is 13 cm^2, and as we approach the acinar airways, the total cross section reaches 300 cm^2. However, since the same air volume flows through all generations, the flow velocity falls by more than 100-fold from the trachea to the acini: at rest, the mean flow velocity on inspiration is about 1 m s^{-1} in the trachea and less than 1 cm s^{-1} in the first-order respiratory bronchioles. In exercise, the flow velocities are up to 10 times greater, in proportion to the increased ventilation. This is discussed further when considering the relative importance of convection and diffusion in bringing O_2 to the alveolar surface for gas exchange.

The size of airways also determines the resistance to airflow. However, the overall resistance is rather small; it is given by the reciprocal of the ratio of ventilatory airflow to the pressure difference between the mouth and alveoli, which is normally no greater than about 1 cmH_2O (mbar) or less than 1 mm Hg. It is large enough, however, to potentially affect the distribution of ventilation to the many gas-exchange units. Because, in laminar flow, the resistance is inversely proportional to d^4 the distribution of air flow depends on a delicate balance of the size of parallel airway tracts. Even a slight narrowing of one of the two daughter branches at

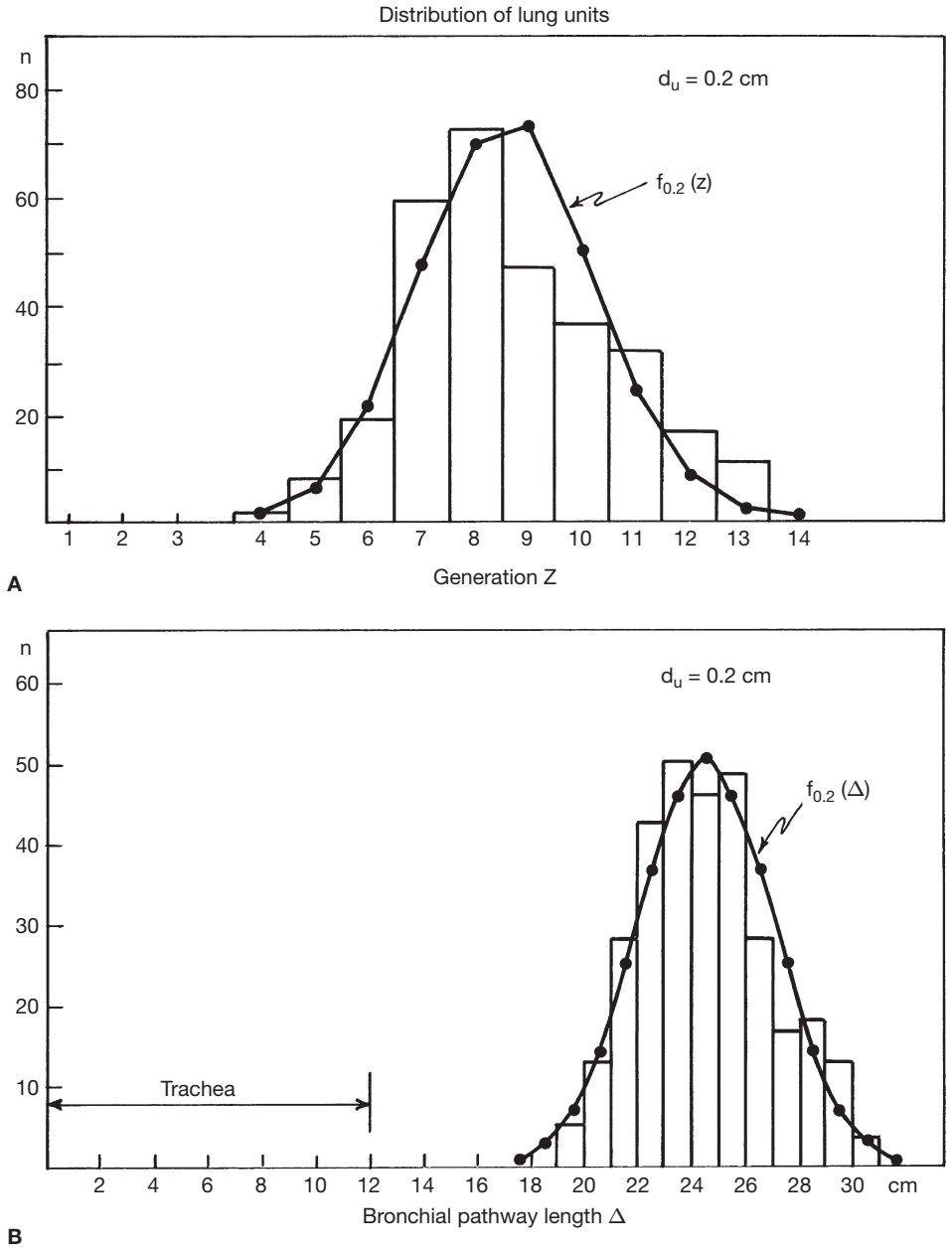


Figure 2-39 Distribution of airways of diameter d_u = 2 mm with respect to (**A**), generations of branching and (**B**), bronchial pathway lengths. *(Reproduced with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963.)*

a branch point will cause disproportionate air flow to the other branch and thus result in ventilation inhomogeneity.

Since the diameter of airways decreases as they branch (Fig. 2-37), one would suspect that their resistance increases toward the periphery. Apparently this is not the case, as the major pressure drop along the airways occurs in medium-sized bronchi; because the airway diameter decreases with a factor larger than the optimal 0.79 resistance becomes very low in the small bronchioles (Fig. 2-38).[153] This is further accentuated by the fact that the thin-walled bronchioles become widened as the lung expands on inspiration because they are subject to the tissue tensions in the coarse fiber system of the lung. Therefore, airway resistance is seen to fall as lung volume increases. When this effect of tissue tension is disturbed, as in emphysema, some small bronchioles may collapse. This causes ventilation of the peripheral lung units to become highly uneven.

This biophysical way of looking at the significance of the progression of airway dimensions has recently been complemented by the alternative notion that the airway and vascular trees could be determined by the laws of fractal geometry.[156] Fractal trees are formed by repeating the branching pattern from one generation to the next. If the proportion between parent and daughter branches remain the same this is called self-similar branching. In a dichotomous tree the diameter is ideally reduced by a factor of $2^{-1/D_f}$ where D_f is the fractal dimension. Since the airway tree is nearly space-filling $D_f \sim 3$, which means that the Hess–Murray law also follows from fractal geometry as a rule of optimal design, but because the reduction factor is somewhat larger than $2^{-1/3}$ it follows that the actual fractal dimension of the airway tree is a bit larger than 3; this is possible because the tree is "cut off" at the entrance to the acini and the "space" becomes filled with alveoli.[157,158]

DESIGN OF THE VASCULAR TREE

In many ways, the course and pattern of dimensional changes in the pulmonary blood vessels resemble those of the airways. Figure 2-3 shows that the pulmonary arteries follow the airways

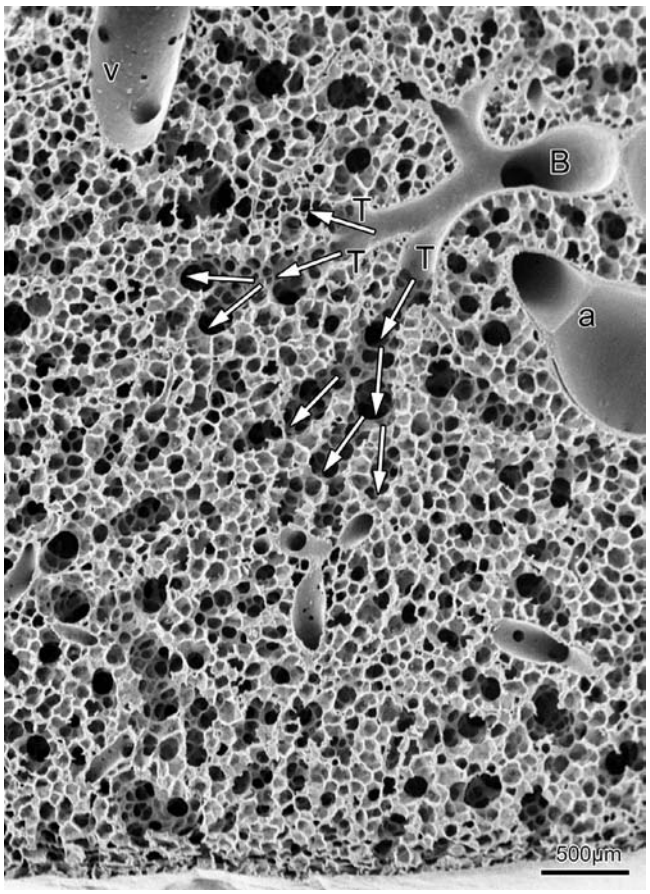


Figure 2-40 Scanning electron micrograph of lung shows branching of small peripheral bronchiole (**B**) into transitional bronchioles (T), from where the airways continue into respiratory bronchioles and alveolar ducts *(arrows)*. Note the location of the pulmonary artery (a) and vein (v) as well as visceral pleura *(bottom)*.

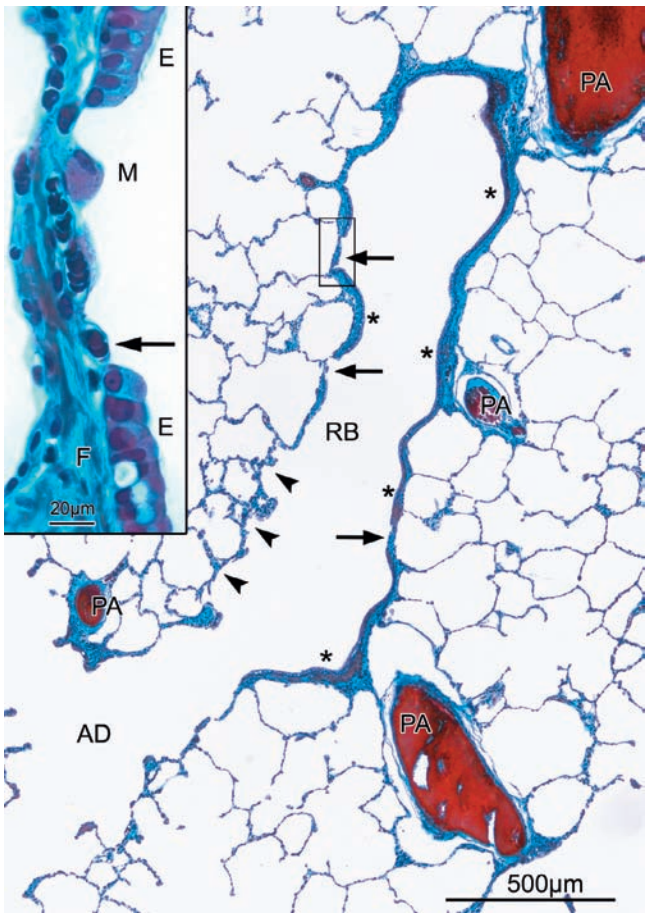


Figure 2-41 Respiratory bronchiole (RB) from human lung cut along its axis toward the transition to alveolar ducts (AD). Note lining by cuboidal airway epithelium *(asterisks)* and the occurrence of respiratory patches *(arrows)* before alveoli proper *(arrowheads)* appear. PA marks branches of pulmonary artery. *Inset:* Higher magnification of one of the respiratory patches in the wall of the respiratory bronchiole with capillaries *(arrow)* and alveolar macrophage (M). The cuboidal epithelium (E) with cilia is replaced by thin squamous epithelium of alveolar type 1 cell. Note thick fibrous layer (F) with smooth muscle cells.

closely, out to the smallest branches; together they form the axis of lung parenchymal units of varying order: acinus, lobule, segment, lobe. As indicated, the veins are differently disposed, lying in the boundary between two or three adjacent units (Figs. 2-30 and 2-45).

The diameter of each pulmonary artery branch also approximates closely that of the accompanying bronchus (Fig. 2-45A). Therefore, it is evident that the diameter law presented earlier for airways must also hold for the first 10 to 16 generations of pulmonary arteries (Fig. 2-37). However, the pulmonary arteries divide more frequently than the airways; very often, small branches leave the artery at right angles and supply blood to the parenchymal units adjacent to the bronchus (Fig. 2-45B). From a count of precapillaries, it seems that the pulmonary arteries divide, on the average, over 28 generations, as compared with 23 for the airways. The diameter of these terminal vessels is about 20 to 50 µm; if this range is plotted onto an extension of the graph of Figure 2-37 to generation 28, it falls on the curve that is obtained by extrapolation from the major branches[8,16]:

$$d(z) = d_0 \cdot 2^{-z/3}$$

This suggests that the pulmonary arteries abide to the cube-root-of-1/2 law from beginning to end. Evidently, the blood is transported to the capillary bed by mass flow only. Therefore, there is no reason to deviate from this fundamental law of design, which minimizes the loss of energy caused by blood flow.

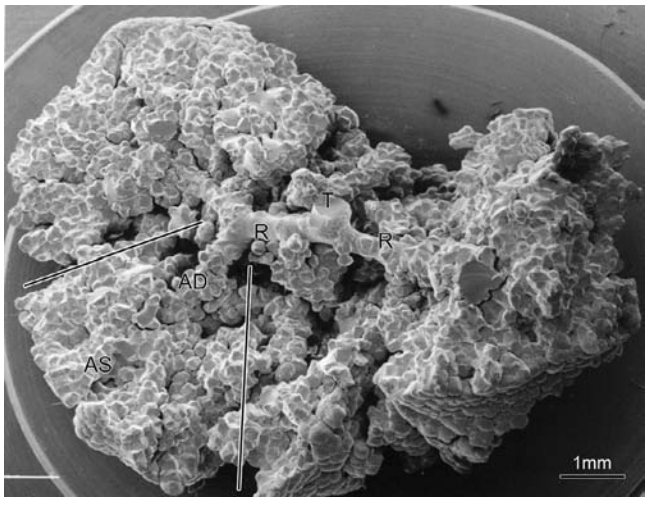


Figure 2-42 Scanning electron micrograph of a complete acinus from a silicon rubber cast of a human lung partly dissected to show transitional (T) and respiratory (R) bronchioles as well as alveolar ducts (AD) and alveolar sacs (AS). Lines mark approximate boundary of 1/8 subacinus. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

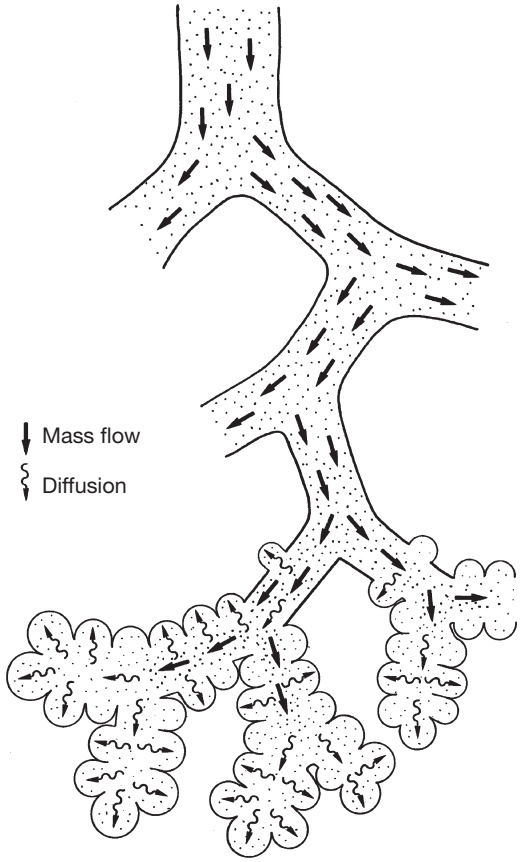


Figure 2-43 Oxygen molecules reach alveoli by combined mass airflow and molecular diffusion, the importance of diffusion increasing toward the periphery.

In a thorough analysis of the pulmonary vascular trees[159] conceived as fractal structures it has been shown that the fractal dimension of both arteries and veins is 2.71, thus somewhat less than 3. The diameter reduction factor is therefore slightly smaller than cube-root-of-1/2, and the diameters follow the regression:

$$d(z) = d_0 \cdot 2^{-z/2.71}$$

Therefore, in contrast to the airways, the resistance to blood flow increases along the pulmonary arteries and is highest in the most peripheral branches or arterioles. The resistance profile of the pulmonary arteries is thus the same as in the systemic circulation.

The alveolar capillary network of the lung is very different from that of the systemic circulation. Whereas in muscle, for example, long capillaries are found to be joined in a loose network, the capillaries of the alveolar walls form dense meshworks made of very short segments (Fig. 2-46).[8,160] The meshes are so dense that some people believe blood flows through the alveolar walls like a sheet rather than through a system of interconnected tubes. In this sheet-flow concept,[161] the sheet is bounded by two flat membranes, the air–blood barrier, connected by numerous "posts." When blood flows through this sheet, it is not channeled in a given direction but has freedom to move in a tortuous way between the posts. Although this concept oversimplifies the actual structural conditions, it does provide a useful description of the pattern of blood flow through the alveolar walls and explains why blood flow is not interrupted when some parts of the capillary bed become squashed flat at high inflation levels (see Fig. 2-58); the capillaries that remain open in the corners are simply some channels of this broad sheet. Furthermore, it is important to note that the capillary network or sheet is continuous through many alveolar walls (Fig. 2-46), probably at least throughout the entire acinus, if not for greater distances.[160] Consequently, it is not possible to isolate microvascular units. One finds, rather, that arterial end branches simply feed into this broad sheet at more or less even distances and that the veins drain these sheets in a similar pattern. However, now we must remember that the arteries reach the acinus along the airways, whereas the veins are in a peripheral location (Fig. 2-45). In principle, therefore, blood flows through the acinar capillary sheet from the center to the periphery of the acinar gas-exchange unit.

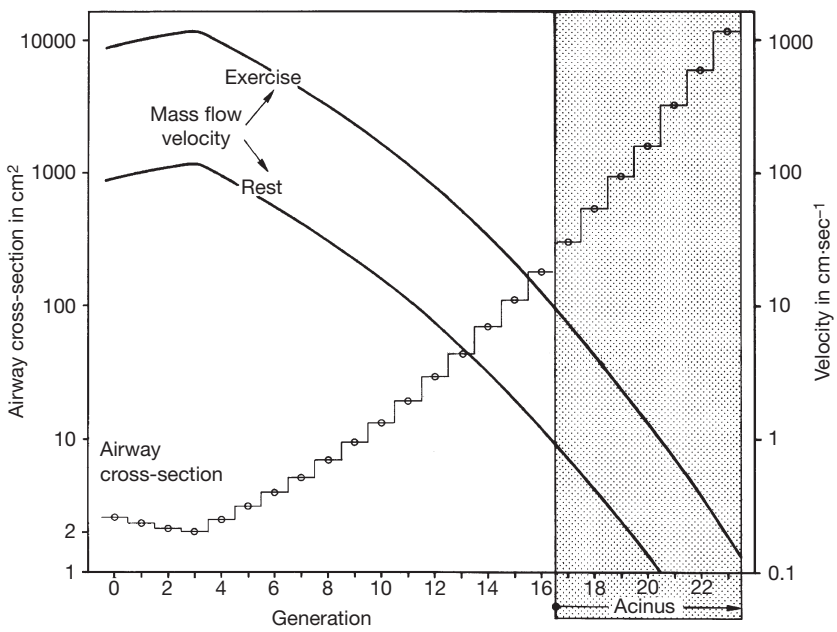


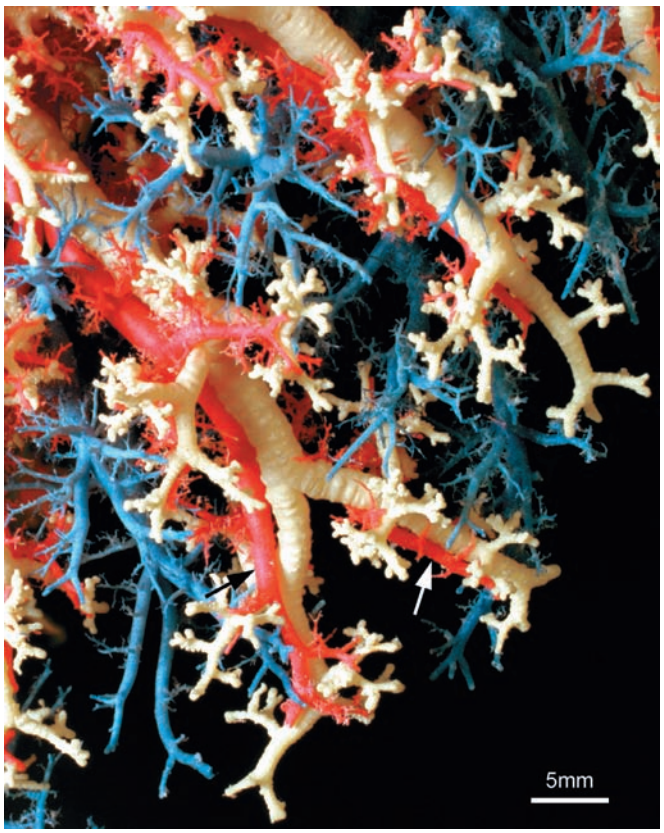
Figure 2-44 As total airway cross-section increases with the generations of airway branching, the mass flow velocity of inspired air decreases rapidly, falling below the molecular velocity of O_2 diffusion in air as we enter the acinus (see Fig. 2-66). *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

DESIGN OF PULMONARY PARENCHYMA

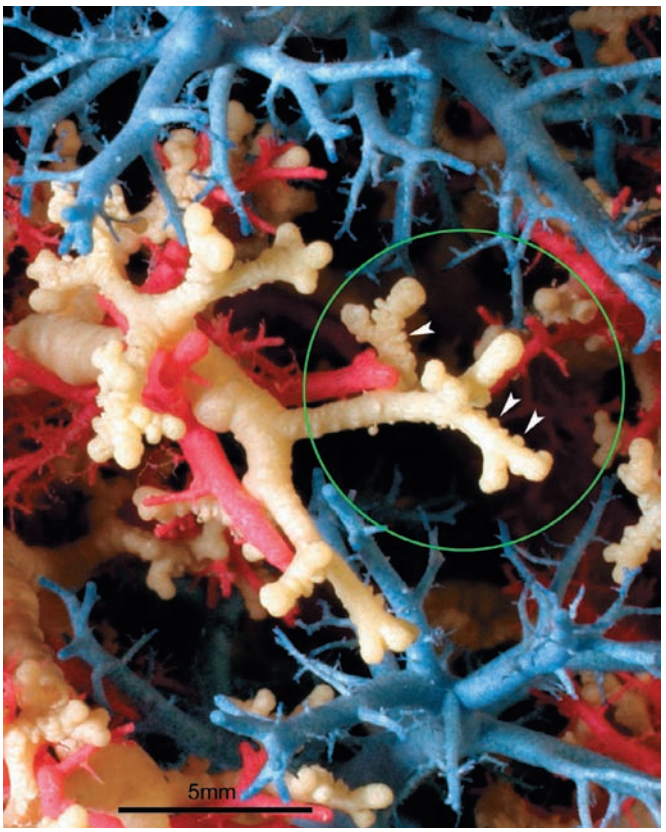
■ ALVEOLI AND CAPILLARIES

The airspaces and blood vessels of lung parenchyma are designed to facilitate gas exchange between air and blood. To this end a very large area of contact between air and blood must be established; for the human lung it is sometimes compared with the area of a tennis court in size. Furthermore, the tissue barrier separating air and blood must be kept as thin as possible—it is found to be about 50 times thinner than a sheet of airmail stationery. This is important, because less than 1 second is available for loading O_2 onto the erythrocytes as they flow through the lung's gas-exchange region.[162]

The first design feature to this end is the formation of alveoli in the walls of all airways within the acinus—that is, in the ventilatory gas-exchange units beginning with a transitional bronchiole (see above) (Fig. 2-40). In the human lung, one estimates that there are about 30,000 acini,[9] and 400 million alveoli[163] so that each of



A



B

Figure 2-45 Casts of airways and blood vessels of human lung. **A.** shows how the pulmonary artery *(red)* closely follows the airways *(yellow)* to the periphery, whereas the pulmonary vein branches *(blue)* lie between the units. Note that the diameter of the pulmonary arteries is similar to that of the accompanying airway, but becomes relatively smaller toward the periphery *(arrow)*; small supernumerary arteries take off at right angles. **B.** Higher power view of group of acini *(circle)*, corresponding about to a secondary lobule, shows how artery penetrates into center of gas-exchange unit with veins collecting the blood around the periphery. *Arrowheads* point to alveolar pouches on transitional and respiratory bronchioles.

the ventilatory gas-exchange units contains some 13,000 alveoli, on average, connected to about seven to nine generations of acinar airways, respiratory bronchioles, and alveolar ducts.[9]

The alveoli are so densely packed that they occupy the entire surface of alveolar ducts; they are separated from each other by delicate alveolar septa that contain the capillary network (Fig. 2-47). About half the space of the septum is taken up by blood, which is thus exposed to the air in two adjacent alveoli (Fig. 2-48A). Although the barrier separating air and blood is extremely thin, we find the capillaries to be provided with a complete endothelial lining, as the alveolar surface of the septum is lined by an epithelium.[11] We have seen earlier that these two cell linings are very much attenuated over the greatest part of the surface.

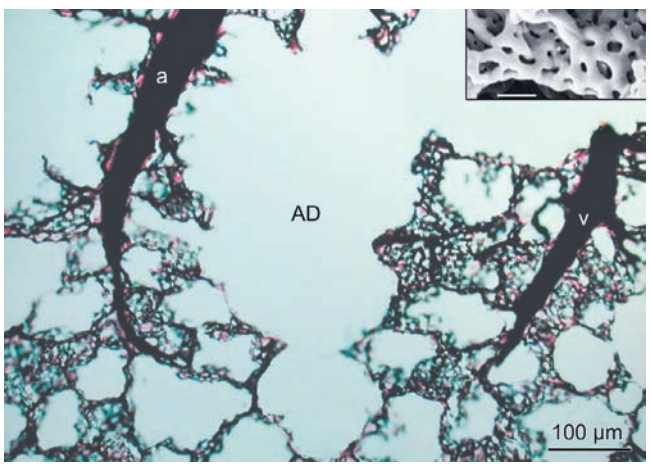


Figure 2-46 Alveolar capillary network demonstrated with gold labeling of blood plasma in a physiologically perfused preparation of a rabbit lung. The dense capillary network spans between end branches of pulmonary artery (a) and vein (v) and extend through many alveolar septa around alveolar duct (AD). *Inset:* Plastic cast shows the dense meshes of the network. Scale bar = 20 µm. *(Inset used with permission of P. Burri.)*

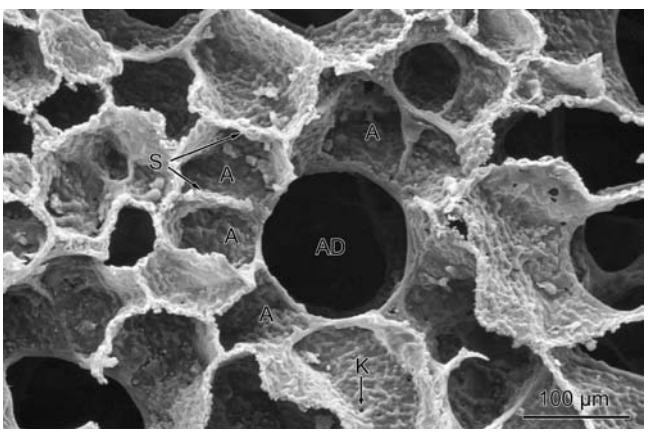
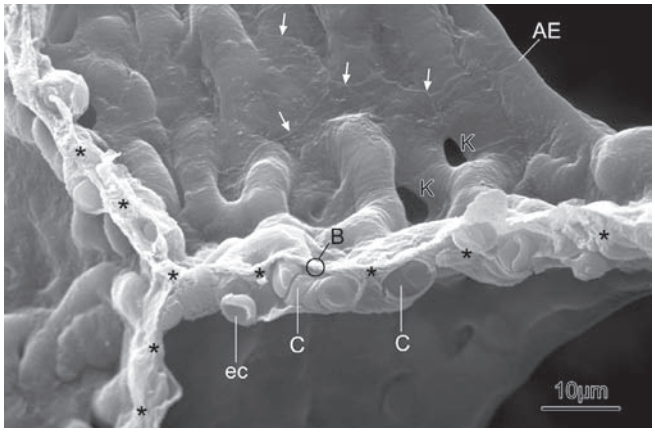
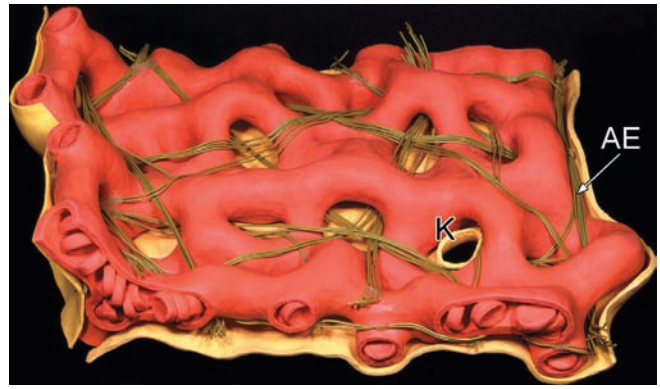


Figure 2-47 Scanning electron micrograph of human lung parenchyma. Alveolar ducts (AD) are surrounded by alveoli (A), which are separated by thin septa (S). K, interalveolar pore of Kohn.



A



B

Figure 2-48 In the alveolar wall, shown in (**A**) in a scanning electron micrograph from a human lung, the capillary blood (C) with its erythrocytes (ec) is separated from the air by a very thin tissue barrier (B). *Short arrows* mark intercellular junctions of alveolar epithelium that course toward interalveolar pores of Kohn (K). The model (**B**) shows the capillary network *(red)* to be interwoven with the meshwork of septal fibers *(green)*, the course of which is marked by asterisks in (**A**). The epithelial lining *(yellow)* that crosses the septum at interalveolar pores (K) is removed on the upper surface of the septum to show the capillary. The septal fibers are anchored on the strong fiber bundle marking the free edge of the septum or the alveolar entrance ring (AE). *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

To make the barrier very thin, the interstitial structures must also be reduced to the minimum required (Fig. 2-49). The septal interstitium contains very few cells, mostly slim fibroblast with long extensions; these contain fine bundles of contractile filaments that serve an as yet unknown mechanical function. The septal interstitium usually does not contain cells of the defense system or lymphatics.

INTERNAL SUPPORT OF PARENCHYMAL STRUCTURES: THE PULMONARY FIBER CONTINUUM

This extraordinary reduction of the tissue mass in the alveolar septa inevitably introduces a number of major problems. How is it possible to secure the mechanical integrity of the system if we consider that several forces act on the septal tissue with a tendency to disrupt it? The thin barrier must not only withstand the distending pressure of the capillary blood due to both hemodynamic forces and gravity, particularly in the lower lung zones, but must also keep the capillary bed expanded over a very large surface—a task that is made difficult because surface forces that act on the complex alveolar surface would tend to collapse alveoli and capillaries (see further below). This requires a very subtle, economical design of the fibrous support system.[164,165]

The problem of supporting the capillaries on connective tissue fibers with as little tissue as possible has been solved ingeniously:

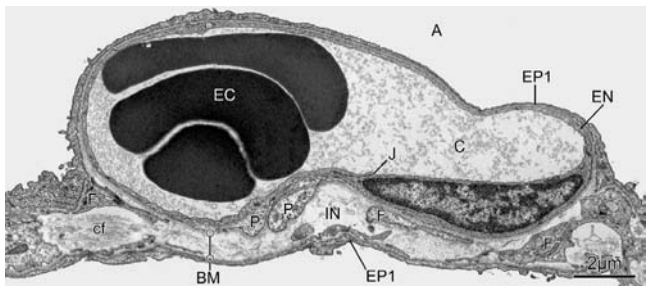


Figure 2-49 Alveolar septum from human lung lined by type I epithelium (EP1) with capillary lined by endothelial cell (EN) that is associated with processes of pericytes (P). Substantial interstitial space (IN) with collagen and elastic fibers (cf) and fibroblasts (F) occurs on one side only, whereas minimal air–blood barrier is formed on other side by fusion of basement membranes (BM) of endothelium and epithelium.

we find that the fiber network is interlaced with the capillary network.[166] Figure 2-48B shows that when the fibers are taut, the capillaries weave from one side of the septum to the other. This arrangement has a threefold advantage: (1) it allows the capillaries to be supported unit by unit directly on the fiber strands without the need of additional "binders"; (2) it causes the capillaries to become spread out on the alveolar surface when the fibers are stretched; and (3) it optimizes gas-exchange conditions by limiting the presence of fibers, which must interfere with O_2 flow, to half the capillary surface. The thin section of a capillary shown in Figure 2-49 reveals that an interstitial space with fibers and fibroblasts exists on only one side of the capillary, whereas on the other the two lining cells, endothelium and epithelium, become closely joined with only a single common basement membrane interposed. Therefore, over half the surface of the capillary blood is separated from the air merely by a minimal tissue barrier made of epithelial and endothelial cytoplasmic sheets with their basement membranes fused leaving no interstitial space that could enlarge with interstitial pulmonary edema (Fig. 2-17).

The principal structural "backbone" of the lung is a continuous system of fibers anchored at the hilum and put under tension by the negative intrapleural pressure that tugs on the visceral pleura.[165] The general construction principle follows from the formation of the mesenchymal sheath of the airway units in the developing lung; as the airway tree grows, its branches remain separated by layers of mesenchyme within which blood vessels form. When fiber networks develop within this mesenchyme, they enwrap all airway units and extend from the hilum right to the visceral pleura. The pulmonary fiber system hence forms a three-dimensional fibrous continuum that is structured by the airway system and is closely related to the blood vessels. By virtue of the design of this fibrous continuum, the lung becomes, in fact, subdivided into millions of little bellows that are connected to the airway tree, as represented schematically in Figure 2-50; these structures expand with expansion of the chest because the tension exerted on the visceral pleura by the negative intrapleural pressure becomes transmitted to the bellows' walls through that fiber system.

To try to put some order into this fiber system, we can first single out two major components that can be identified easily (Fig. 2-50).

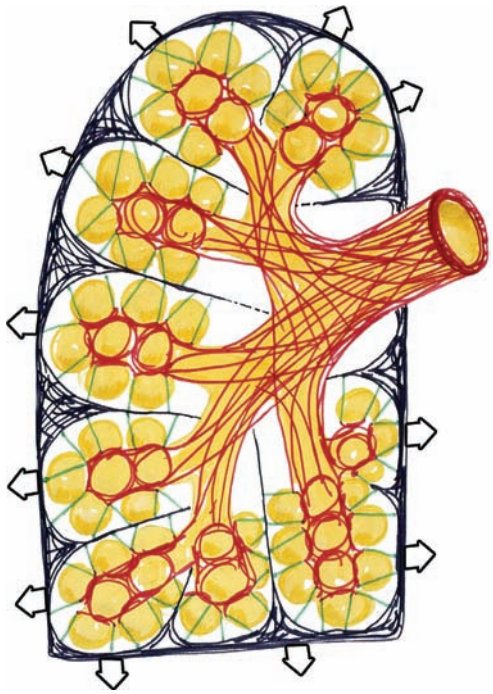


Figure 2-50 The lung's fiber continuum: axial fibers *(red)* extend from airways into the alveolar ducts as a network of entrance rings into alveoli *(yellow)*; peripheral fibers *(black)* extend from the pleura to interlobular septa; the septal fibers *(green)* in the alveolar walls are anchored in peripheral and axial fibers. Arrows indicate the traction on the pleura exerted by thorax and diaphragm. *(Reproduced with permission from Weibel ER: Looking into the lung: What can it tell us? Am J Roentgenol. 1979;133(6):1021–1031.)*

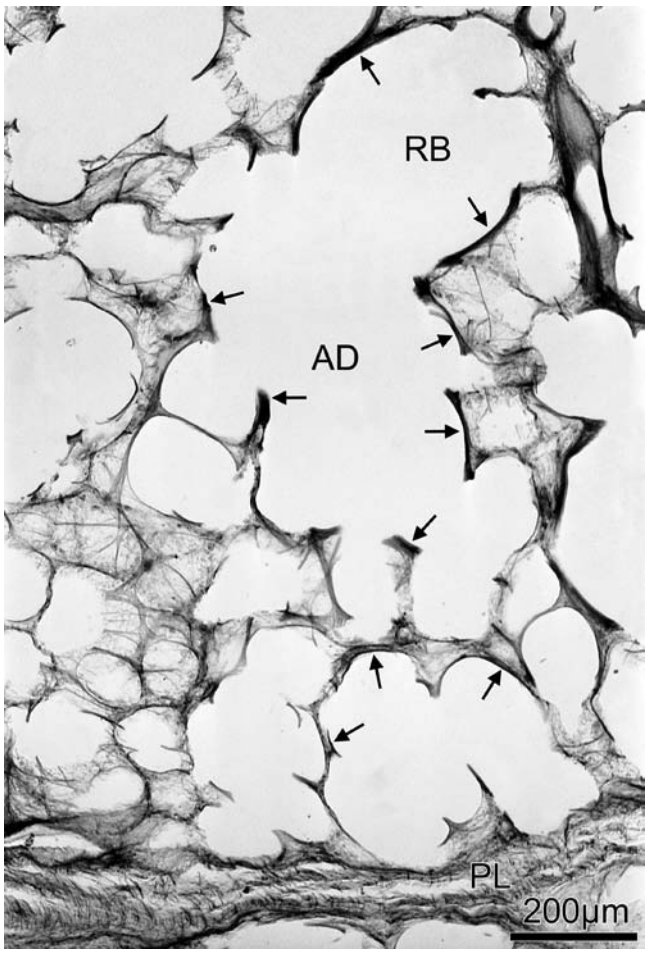


Figure 2-51 Connective tissue stain reveals the strong fiber rings *(arrows)* that demarcate the alveolar ducts (AD) and respiratory bronchioles (RB). Pleura (PL) extends as peripheral fibers into parenchyma. *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

First we find that all airways – from the mainstem bronchus that enters the lung at the hilum out to the terminal bronchioles and beyond – are enwrapped by a strong sheath of fibers. These fibers constitute the axial fiber system; they form the "bark" of the tree whose roots are at the hilum and whose branches penetrate deep into lung parenchyma, following the course of the airways. A second major fiber system is related to the visceral pleura, which is made of strong fiber bags enwrapping all lobes. We then find connective tissue septa penetrating from the visceral pleura into lung parenchyma, separating units of the airway tree. We call these fibers the peripheral fiber system because they mark the boundaries between the units of respiratory lung tissue.

The peripheral fiber system subdivides the lung into a number of units that are not simple to define because they form a continuous hierarchy in accordance with the pattern of airway tree branching. However, as we have seen, two such units appear to be natural: the lobes, which are demarcated by a more or less complete lining by visceral pleura with a serosal cleft interposed (Fig. 2-1); and the acinus, the parenchymal unit in which all airways participate in gas exchange.

The acinus is the functional unit of the pulmonary parenchyma. The airway that leads into the acinus, the transitional bronchiole, continues branching within the acinus for about 6 to 10 additional generations (Figs. 2-5 and 2-40). These intra-acinar airways, called respiratory bronchioles and alveolar ducts, also carry in their wall relatively strong fibers of the axial fiber system, which extend to the end of the duct system. However, since the walls of intra-acinar air ducts are densely settled with alveoli, these fibers are reduced to a kind of delicate network that constitutes the "wall" of the alveolar ducts. The meshes of this network that encircle the alveolar mouths are generally called alveolar entrance rings; it is this fiber network that allows alveoli to be formed as open chambers with free edges of the alveolar septa (Figs. 2-47 and 2-51).[148] These fiber rings are associated with some smooth muscle cells (Fig. 2-29), and they serve as a scaffold for a network of finer fibers that spread within the alveolar septa (Figs. 2-48B and 2-51). However, in a fiber system there may be no loose ends. Accordingly, the septal fiber system must be anchored at both ends—on the network of axial fibers around the alveolar ducts, and on extensions of the peripheral fibers that penetrate into the acinus from interlobular septa. Thus, the fiber system of the lung becomes a continuum that spans the entire space of the lung, from the hilus to the visceral pleura (Fig. 2-50). It is put under varying tension as the pleural bag is expanded by the chest wall and diaphragm. It thus functions as a tensegrity structure where structural integrity is maintained only if the fiber continuum is under tension and undisrupted.[167,168]

The continuous nature of a well-ordered fiber system is an essential design feature of the lung.[148] This becomes evident in emphysema. When some fibers are disrupted, they cannot be kept under tension. They retract and larger airspaces form as the fiber system is rearranged near the damage. Small foci of emphysema form in most lungs in the course of time.

The fiber system serves mainly as a mechanical support for the blood vessels, with which it is intimately associated in an orderly fashion.[148] The pulmonary artery branches in parallel with the airway tree, but it is not related to the axial fiber system. Like the pulmonary veins the pulmonary arteries are associated with those parts of the peripheral fiber system that form an adventitial

sheath on the larger vessels of both types and also form a boundary sheath on the outer surface of bronchi where alveolar complexes touch on the bronchial wall. Therefore, it is justified to characterize the connective tissue surrounding bronchi and pulmonary arteries as a peribronchovascular space, which houses the lymphatics as well as the systemic bronchial arteries and their branches. In fact, this space is continuous with the septal connective tissue that enwraps the pulmonary veins (Fig. 2-30) and is continuous with the visceral pleura. However, whereas the arteries penetrate into the acinus, the veins remain at the periphery and are thus located between the airway units (Fig. 2-45). In the alveolar septa, the capillary network spreads out as a broad sheet of vessels whose paths are continuous throughout the system of interconnected alveolar septa (Fig. 2-46). We have seen that these capillaries are intimately related to the septal fiber system (Fig. 2-48B).

PARENCHYMAL MECHANICS AND TISSUE DESIGN

As in all connective tissue, the fibers of the lung are composed of collagen and elastic fibers.[164] The collagen fibers are bundles of fibrils bound together by proteoglycans; they are practically inextensible (less than 2%) and have a very high tensile strength; they rupture at loads of 50 to 70 dyn/cm^{-2}, which means that a collagen fiber of 1-mm diameter can support a weight of over 500 g. In contrast, elastic fibers have a much lower tensile strength but a high extensibility. They can be stretched to about 130% of their relaxed length before rupturing.

In the fiber system of lung parenchyma, collagen and elastic fibers occur in a volume ratio of about 2.5:1, whereas this ratio is 10:1 for the visceral pleura. In a relaxed state, one finds the collagen fibers to be longer than the accompanying elastic fibers, so that they appear wavy. Because of the association between "rubber-like" elastic and "twine-like" collagen fibers, the connective tissue strands behave like an elastic band. They are easy to stretch up to the point where the collagen fibers are taut, but from there on they resist stretching very strongly.

The elastic properties of the lung's fiber system can be studied by filling the airways with fluid so as to eliminate the effects of surface tension. This reveals that the lung's fiber system has a high compliance until high levels of inflation are reached, and that the retractive or recoil force generated by the fiber system amounts to no more than a few millibars at physiologic inflation levels. The actual recoil force in the air-filled lung, reflected by the negative pressure in the pleural space, is appreciably higher, but this is caused by surface tension rather than the retractive force of the fibers.

Surface tension arises at any gas–liquid interface because the cohesive forces between the molecules of the liquid are much stronger than those between the liquid and gas.[169] As a result, the liquid surface tends to become as small as possible. A curved surface, such as that of a bubble, generates a pressure that is proportional to the curvature and the surface tension coefficient γ. The general formula of Gibbs relates this pressure, P_s, to the mean curvature $\overline{K}$:

$$P_s = 2\gamma \cdot \overline{K}$$

In a sphere, the curvature is simply the reciprocal of the radius r (Laplace's law):

$$P_s = \frac{2\gamma}{r}$$

The most critical effect of surface tension is that it endangers stability of the airspace, because a set of connected "bubbles," the alveoli, is inherently unstable: The small ones should contract and the large ones expand. Since the 400 million alveoli are all connected with each other through the airways, the lung is inherently unstable: Why do the alveoli not all collapse and empty into one large bubble? There are two principal reasons.[16,170]

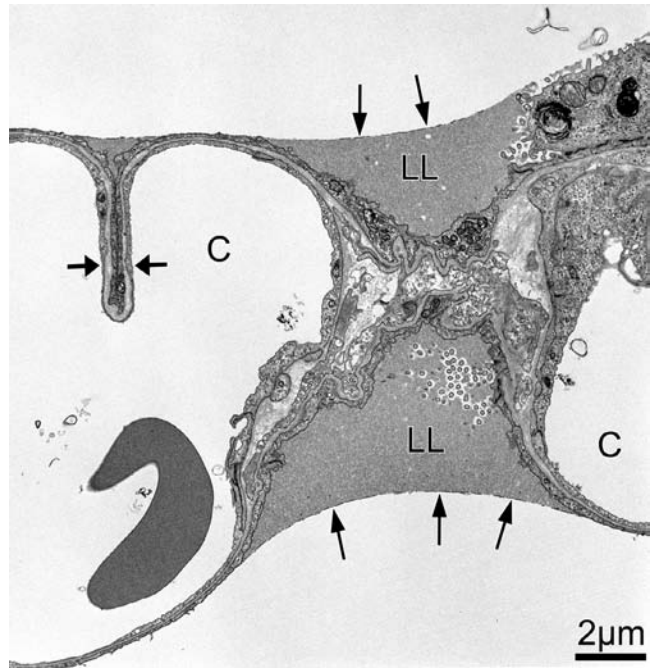


Figure 2-52 Alveolar septum of human lung fixed by perfusion through blood vessels shows alveolar lining layer (LL) in crevices between capillaries (C) topped by surfactant film that appears as a fine black line *(arrows)*. Note the type II cell with lamellar bodies and the fold in thin tissue barrier *(bold arrows)*. *(Used with permission of M. Bachofen and G. Wolff Basel.)*

The first reason is one of tissue structure. The alveoli are not simply soap bubbles in a froth. Rather, their walls contain an intricate fiber system, as we have seen. Thus, when an alveolus tends to shrink, the fibers in the walls of adjoining alveoli are stretched, and this prevents the alveolus from collapsing altogether. It is said that alveoli are mechanically interdependent and this stabilizes them.

The second reason is related to the fact that the alveolar surface is not simply water exposed to air but is lined by surfactant[171] (Figs. 2-25 and 2-52), which has peculiar properties in that its surface tension coefficient γ is variable.[169,172] From a large volume of evidence, it is now established that surface tension falls as the alveolar surface becomes smaller, and that it rises when the surface expands. Because of this feature, which is due to the phospholipoprotein nature of alveolar surfactant (see above), alveoli do not behave like soap bubbles whose surface tension remains constant. When an alveolus begins to shrink, the surface tension of its lining layer falls and the retractive force generated at the surface is reduced or even abolished. Combined with interdependence, this property of surfactant allows the complex of alveoli to remain stable.[170]

Which of the two factors for stabilizing lung structure is now the most important: interdependence or surfactant properties? It turns out that both are essential. If one depletes the lung of its surfactant lining by washing with a detergent, the pressure–volume curve changes dramatically[173] (Fig. 2-53). On deflation, lung volume falls rapidly. If we look at samples from lungs fixed at the same volume (60% total lung capacity) but derived from either normal or detergent-rinsed lungs, we find that surfactant depletion causes the alveoli to collapse. However, this causes the alveolar ducts to enlarge, stretching the strong fiber nets at the mouths of the collapsed alveoli. The ducts do not collapse because of interdependence between adjacent units.

In the normal air-filled lung, surfactant properties and interdependence owing to fiber tension both contribute to stabilizing the

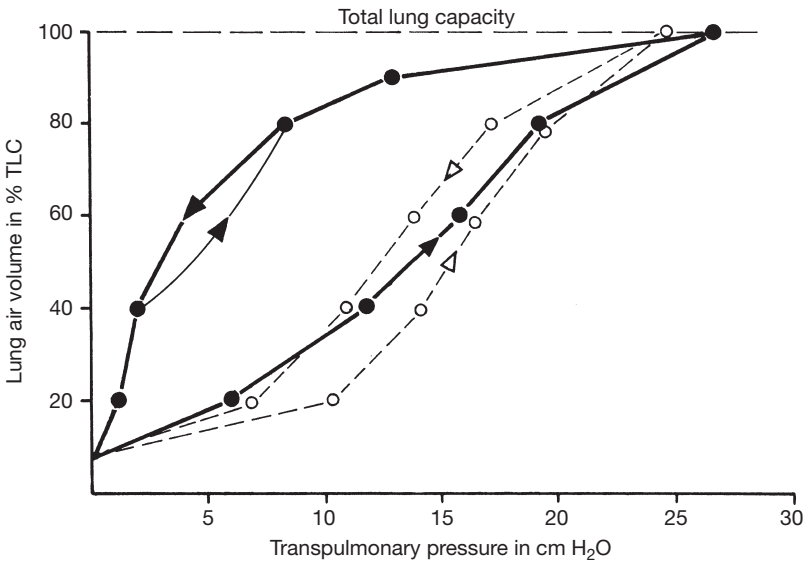


Figure 2-53 Comparison of pressure–volume curve of a normal air-filled rabbit lung *(heavy line)* with that of a surfactant-depleted lung *(broken line)*. The thin line with *paired arrows* represents small hysteresis when breathing between 40% and 80% TLC along the deflation curve.

complex of alveoli and alveolar ducts.[174] To understand this, let us examine Figure 2-54, which shows a highly simplified diagram of a parenchymal unit. Interdependence is established by the continuum of axial, septal, and peripheral fibers. Surface tension exerts an inward pull in the hollow alveoli, where curvature is negative. However, over the free edge of the alveolar septa, along the outline of the duct, the surface tension must push outward because there the curvature is positive.[16] The latter force must be rather strong, because the radius of curvature is very small on the septal edge; but this force is counteracted by the strong fiber strands, usually provided with some smooth muscle cells, that we find in the free edge of the alveolar septum (Figs. 2-29, 2-47, and 2-51). Thus, interdependence is an important factor in preventing the complex hollow of the lung, where negative and positive curvatures coexist, from collapsing. However, its capacity to do so is limited and requires low surface tensions, particularly on deflation when the fibers tend to slack. If surface tension becomes too high, the lung's foam-like structure will partly collapse in spite of fiber interdependence.

This is of considerable physiologic importance. It is sometimes claimed that alveoli pop open when the lung is inflated, collapsing on deflation. That is correct when starting with a deflated lung (Fig. 2-53): collapsed alveoli open up along the inflation curve. But that is not the way we breathe. The normal breathing cycle operates on the deflation slope of the pressure–volume curve (Fig. 2-53) with small hysteresis, a state that is maintained by taking a deep sigh intermittently up to TLC. In this condition the surface tension is kept low because the surfactant lining is spread out[172] and alveoli do not collapse. When we breathe in and out between 80% and 40% of total lung capacity, the range of normal breathing in exercise, alveoli change their size very little. In contrast to the twofold change in air volume the alveolar surface area changes by only about a factor of 1.2.[174] The reason for this is that the main change in air volume does not occur in alveoli, but predominantly in the alveolar ducts as shown in Figure 2-55, and this is very favorable for acinar ventilation. This differential volume change can be explained by the effect of surface forces: at 40% TLC surface tension γ is nearly 0 but it increases to 12 $mN \cdot m^{-1}$ at 80% TLC 2. As the lung inflates this causes the positive surface force to become strong on the free edge of alveolar septa (Fig. 2-54), thus causing the duct cross section to widen, while shrinking when the forces decrease on deflation (Fig. 2-55). In this process the alveolar septa become stretched on inflation by only a small degree, a mere 20% in area. The acinus is thus well ventilated whereas the gas-exchange surface is little affected by varying air volume.[148]

MICROMECHANICS OF THE ALVEOLAR SEPTUM

We must finally consider the mechanical factors that shape the alveolar septum in the air-filled lung. As we have seen, the alveolar septum is made of a single capillary network that is interlaced with fibers (Fig. 2-48). When the fibers are stretched, the capillaries bulge alternatingly to one side or the other, and this causes pits and crevices to occur in the meshes of the capillary network.

This irregular surface is to some extent evened out by the presence of an extracellular layer of lining fluid, which is rather thin over the capillaries but forms little pools in the intercapillary pits (Fig. 2-52).[175] This lining consists of an aqueous layer of variable thickness, called the hypophase, and surfactant, which forms a film on the surface of the hypophase. The hypophase seems to contain considerable amounts of reserve surfactant material, which occurs in a characteristic configuration called tubular myelin (Figs. 2-25 and 2-26).

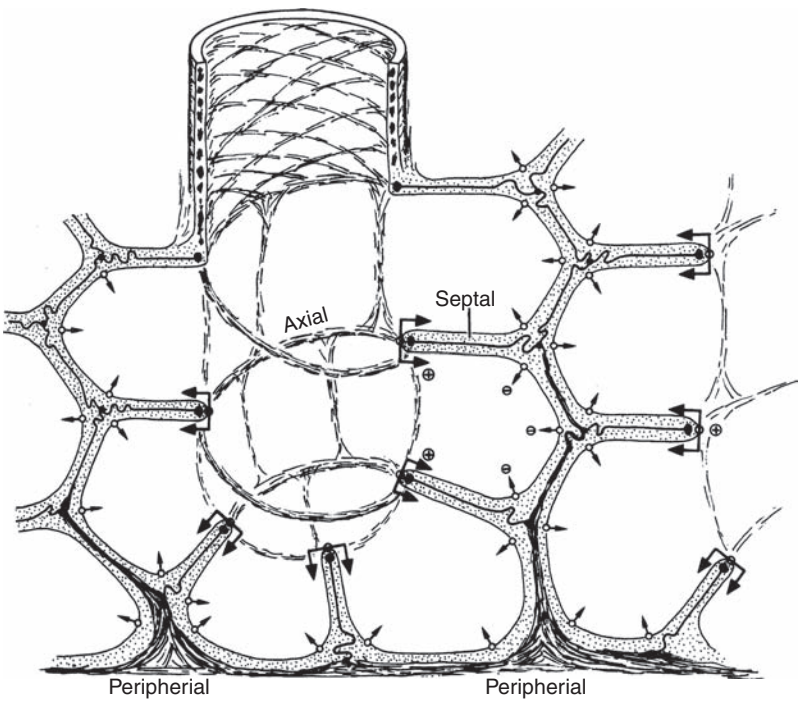


Figure 2-54 Model of the disposition of axial, septal, and peripheral fibers in an acinus showing the effect of surface forces *(arrows). (Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

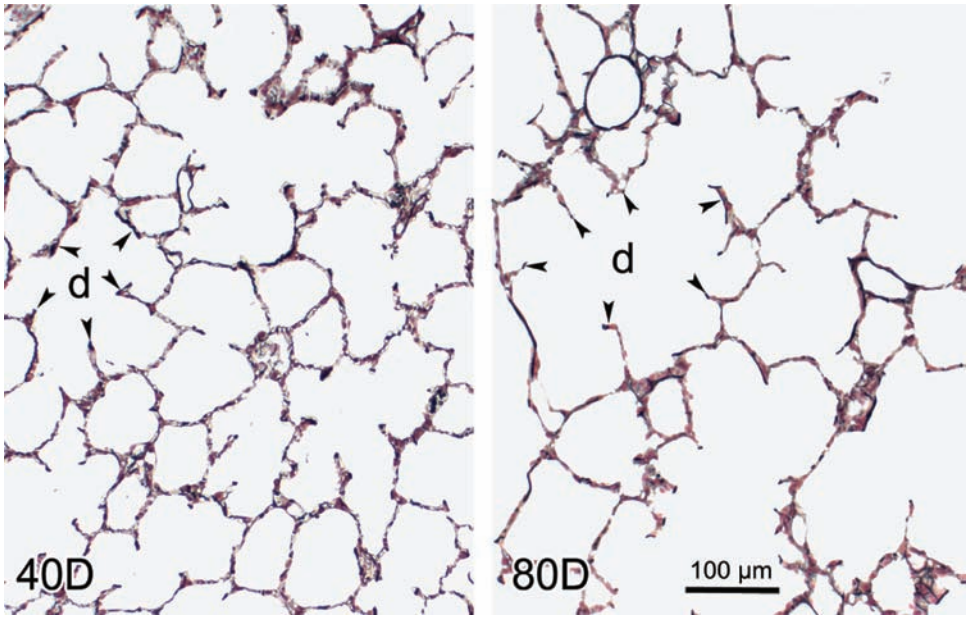


Figure 2-55 Light micrographs of sections of lung parenchyma in rabbit lungs perfusion fixed on deflation to 40% TLC (**A**), and 80% TLC (**B**), respectively (compare Fig. 2-53). Note that the size of the alveolar ducts (d) is markedly enlarged in 80D due to the surface forces acting on the free edges of alveolar septa *(arrow heads)*. *(Preparations used with permission of H. Bachofen, University of Bern.)*

In the alveolar septum, the tissue structures are extremely delicate, as we have seen. Therefore, its configuration is not exclusively determined by structural features but results from the molding effect of various forces that must be kept in balance. Figure 2-56 shows how the three principal mechanical forces – tissue tension, surface tension, and capillary distending pressure – interact in the septum.[16] The fibers of the alveolar septum are under a tension whose magnitude depends on the level of lung inflation. This tends to straighten out the fibers, so that a force (pressure) normal to the fiber axis results, which is responsible for shifting the capillaries to one side of the septum or the other (Figs. 2-48B and 2-56). The walls of the capillaries are exposed to the luminal pressure, which is the result of blood pressure in pulmonary arteries and veins but also depends on gravity, for one finds wider capillaries at the bottom of the lung than at the top. If this distending pressure acts homogeneously over the circumference of the capillary, it will push against the fibers on one side but will cause the thin barrier on the opposite side to bulge outward. This effect is to some extent counteracted by surface tension, which exerts a force normal to the surface (Fig. 2-56). This force depends on two factors. Its direction depends on the orientation of curvature, acting toward the alveolar space over concave regions (negative curvature) and toward the tissue over convexities (positive curvature); and its magnitude depends on the degree of curvature and on the value of the surface tension coefficient γ.

The alveolar septum achieves a stable configuration when all these interacting forces are in balance.[176] Combined forces tend to squash the capillary flat; this happens at high levels of lung inflation when the fibers are under high tension and the surface tension coefficient of surfactant reaches its highest value because of expansion of the surface. On deflation, the fibers are relaxed and surface tension falls drastically. The capillary distending pressure now exceeds both the tissue and the surface forces, with the result that the slack fibers are bent, weaving through the capillary network, whereas the capillaries bulge slightly toward the airspace. Surface tension is apparently so low as to permit a considerable degree of surface "crumpling" to persist (Fig. 2-57).

The importance of the balance between the forces that act on the septum is also shown in Figure 2-58.[177] The specimen of panel B was fixed under zone 3 perfusion conditions, where capillary pressure is larger than alveolar pressure, and all the capillaries are wide, partly bulging toward the airspace, as in Figure 2-57. This is different in panel A, which was fixed under zone 2 conditions where capillary pressure is close to alveolar pressure. In the flat part of the septum, the capillaries are squashed flat, because the surface and tissue forces now exceed the vascular distending pressure. However, it is interesting that the capillaries remain wide in the corners where three septa come together. The distribution of surface forces causes the internal pressure to be lower in the region of these corners, as we can see intuitively from Figure 2-54.

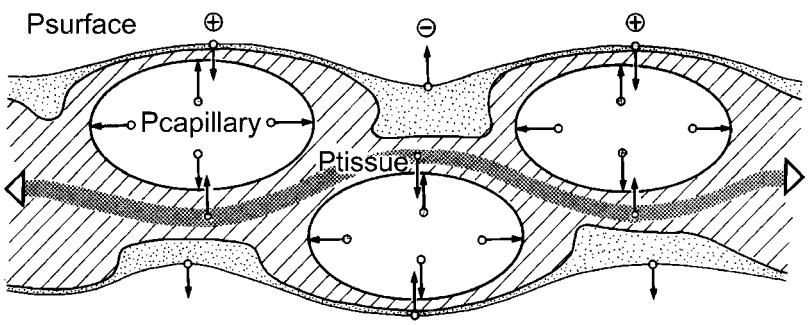


Figure 2-56 Model showing the micromechanical forces of surface tension, tissue tension, and capillary distending pressure that shape the alveolar septum. *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

■ THE LUNG AS GAS EXCHANGER

The structures discussed so far are designed to ultimately serve the lung's main function, gas exchange between air and blood, in relation to the body's varying O_2 needs.[178] These are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells, as will be discussed later. It proceeds along the respiratory system through various steps: into the lung by ventilation, to the blood by diffusion, through the circulation by blood flow, from the blood capillaries by diffusion to the cells and

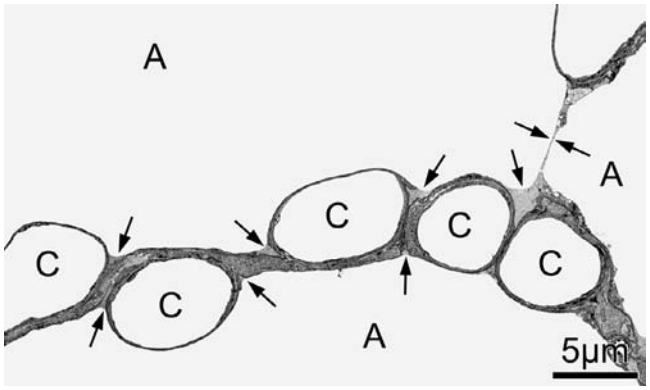


Figure 2-57 Alveolar septum of air-filled rabbit lung perfusion fixed at 60% TLC shows empty capillaries (C), which bulge toward the alveolar airspace (A). Note pools of surface lining layer in the crevices between capillaries *(arrows)* and film spanning across alveolar pore *(double arrows). (Reproduced with permission from Gil J et al. Alveolar volume-surface area relation in air- and saline-filled lungs fixed by vascular perfusion. J Appl Physiol Respir Environ Exerc Physiol. 1979;47(5):990–1001.)*

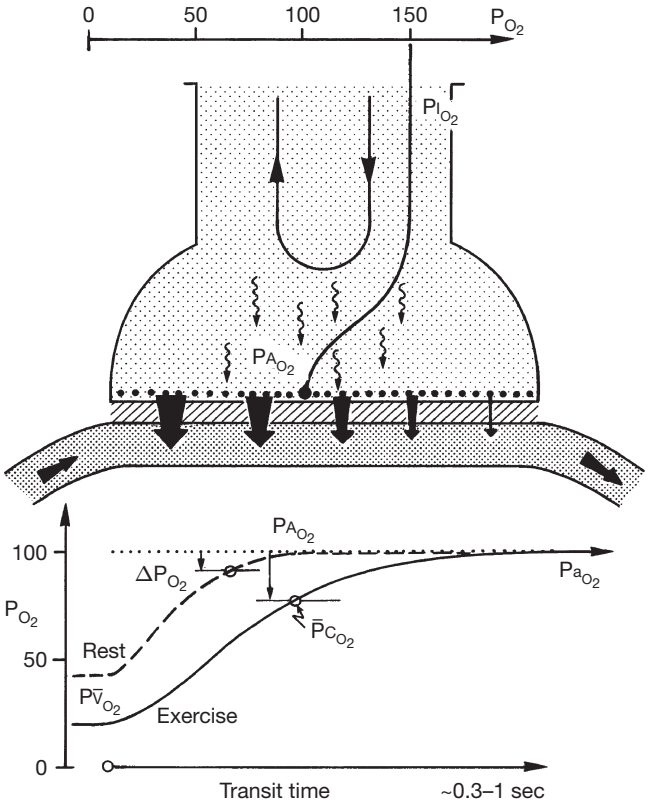


Figure 2-59 Model of gas exchange showing gradual rise of capillary P_{O_2} ($P_{C_{O_2}}$) as blood flows through capillary until it approaches alveolar P_{O_2} ($P_{A_{O_2}}$). *(Reproduced with permission from Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.)*

mitochondria, where it disappears in the process of oxidative phosphorylation.[16] A number of basic features characterize this system[179]: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$ is the same at all levels, that is, O_2 uptake in the lung is equal to O_2 consumption in the tissues; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressure which falls from inspired P_{O_2} down to near zero in the mitochondria; (3) the O_2 flow rate at each step is the product of a partial pressure difference and a conductance which is related to structural and functional properties of the organs participating in O_2 transfer, as will be discussed below in detail.

With respect to gas exchange in the lung (Fig. 2-59), the O_2 flow rate is determined by the Bohr equation:[180]

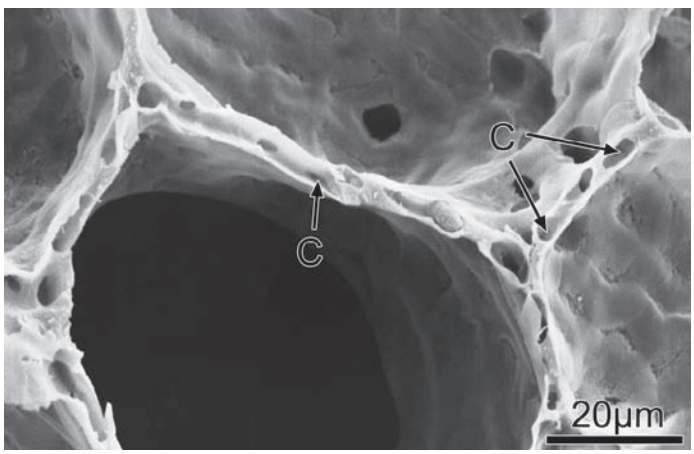
$$\dot{V}_{O_2} = (PA_{O_2} - P\bar{C}_{O_2}) \cdot DL_{O_2}$$

Where

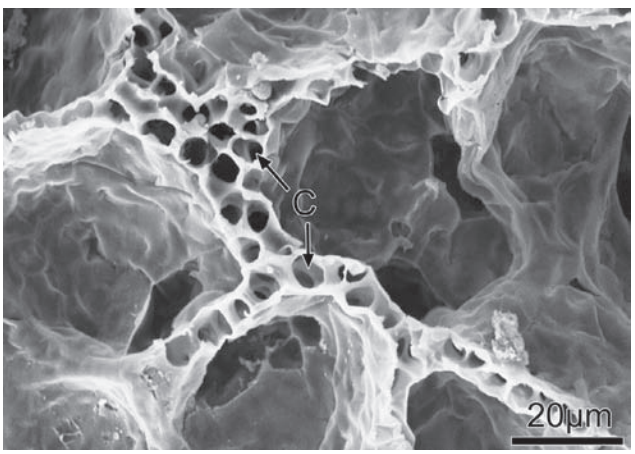
PA_{O_2} = P_{O_2} in alveoli,

$P\bar{C}_{O_2}$ = the mean P_{O_2} in pulmonary capillaries, and

DL_{O_2} = the pulmonary diffusing capacity or the lung's O_2 conductance



A



B

Figure 2-58 Scanning electron micrographs of alveolar walls of rabbit lungs fixed under (**A**), zone 2 and (**B**), zone 3 conditions of perfusion. Note that capillaries (C) are wide in zone 3 and slit-like in zone 2, except for "corner capillaries," which are wide in either case. *(Reproduced with permission from Bachofen H et al: Morphometric estimates of diffusing capacity in lungs fixed under zone II and zone III conditions. Respir Physiol. 1983;52(1):41–52.)*

The important point is now that all parameters to the right of this equation may be significantly affected by design features. We will see that $D_{L_{O_2}}$ is largely determined by the surface area and the thickness of the air–blood barrier. The O_2 partial pressure difference is established by ventilation and perfusion of the gas-exchange units, and this may be affected by the design of the airway and vascular trees, particularly in the acinus.[178]

THE PULMONARY DIFFUSING CAPACITY

In the equation mentioned earlier, $D_{L_{O_2}}$ is the total conductance of the gas exchanger for O_2 diffusion from the alveolar air into the capillary erythrocytes until it is bound to hemoglobin. It can be estimated physiologically if we can measure O_2 uptake $\dot{V}_{O_2}$ and estimate the effective P_{O_2} difference between alveolar air and capillary blood, not a trivial undertaking as the change in capillary P_{O_2} as O_2 is being taken up must be integrated (Fig. 2-59). On the other hand the conductance is a physical characteristic. Therefore, it should be possible to calculate a theoretical value of $D_{L_{O_2}}$ from the physical properties of the gas exchanger, its dimensions and material properties.[181,182] To do that we must consider the geometry of the structures involved, alveoli, tissue barrier, and capillary blood, in setting up a physical model of $D_{L_{O_2}}$. In the first step, we can break the process into two steps (Fig. 2-60):[183] (1) O_2 flow across the barrier or what has been called the membrane conductance $D_{M_{O_2}}$ and (2) O_2 binding to hemoglobin in the red blood cells or the conductance of capillary blood De_{O_2} These two conductances are in series. Accordingly their overall effect on O_2 flow is obtained by adding their resistances or the reciprocal of the conductance:

$$1/D_{L_{O_2}} = 1/D_{M_{O_2}} + 1/De_{O_2}$$

The two conductances $D_{M_{O_2}}$ and De_{O_2} are of very different nature. $D_{M_{O_2}}$ is the conductance of a diffusion barrier that offers "passive" resistance to diffusion and thus depends essentially on the material properties of the barrier, estimated by a diffusion coefficient K, and on the dimensions of the barrier. The larger the surface area S and the thinner the barrier thickness τ the greater $D_{M_{O_2}}$, according to the formula $D_{M_{O_2}} = K \cdot S/\tau$. In contrast, De_{O_2} is related to a more complex process that involves, besides diffusion, the binding of O_2 to hemoglobin, which is a nonlinear process.

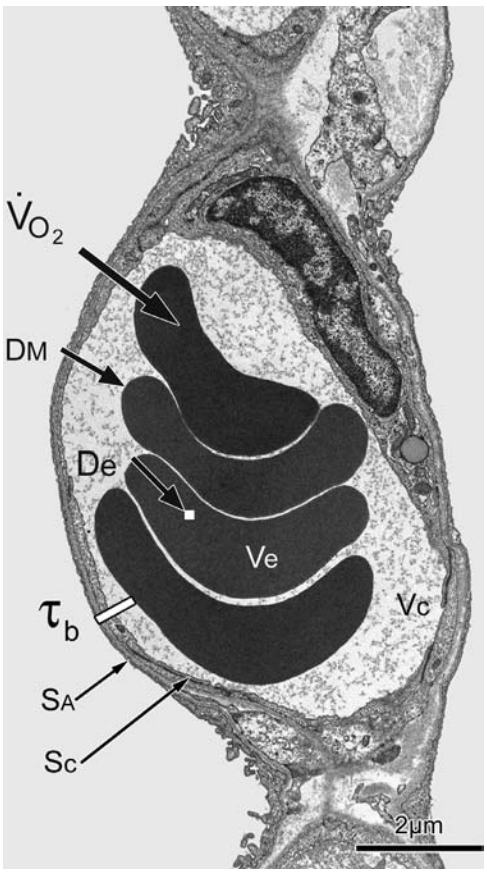


Figure 2-60 Morphometric model for calculating diffusion capacity, DL. Its two components are: (1) the membrane conductance DM, which extends from the alveolar surface (SA) to the nearest erythrocyte membrane traversing the tissue barrier, the capillary surface (Sc), and the plasma layer over the distance τ_b; and (2) the conductance of the erythrocyte interior, De, that depends on the capillary and the erythrocyte volume, Vc and Ve. (See text.)

The Membrane Conductance ($D_{M_{O_2}}$)

The structural characteristics of the membrane conductor are seen in Figure 2-60. It is made of the two layers that separate air in alveoli from the erythrocytes in the capillary: the tissue barrier and the layer of blood plasma. In addition, an alveolar lining layer of varying thickness spreads over the epithelial surface. Even though these layers have distinct characteristics; in effect they act as a single diffusion barrier.[182]

As discussed earlier in this chapter, the tissue barrier is a complex structure. Its two bounding surfaces are formed by independent cell layers, epithelium and endothelium, and they are related to two independent functional spaces, alveoli and capillaries. The two surfaces are not perfectly matched, and the thickness of the barrier varies considerably (Fig. 2-60). Over about half the surface the tissue barrier shows minimal thickness compatible with an intact structure: The thin cytoplasmic leaflets of type I epithelial cells are joined to the thin extensions of endothelial cells by the fused basement membranes leaving no interstitial space. In this region we also find the surface lining layer to be very thin. Over the other half the barrier is thicker because of the occurrence of supporting connective tissue fibers (Fig. 2-49) and the presence of cell bodies of epithelial and endothelial cells as well as fibroblasts, and the lining layer can form deeper pools (Fig. 2-52).

The plasma layer shows even greater variation in its thickness and distribution. Since erythrocytes are of about the same dimension as the capillaries, the plasma layer that separates them from the endothelium can be vanishingly thin where the red cell nearly touches the wall. However, erythrocytes are corpuscular particles and there are "plugs" of plasma of varying size that separate them in the direction of blood flow. Also their distortable disk shape causes the plasma layer between erythrocyte and capillary surface to be quite variable.[184] Furthermore, occasional leukocytes function like plasma plugs in regard to O_2 diffusion to the red cells. Therefore, the diffusion distance from the capillary wall to the red cell membrane can vary from a few nm to several µm.

Strictly speaking, these two layers of the barrier offer O_2 diffusion different resistances so their conductances should be calculated separately. However, this distinction does not appear to be important under normal conditions. Indeed, it is more reasonable to treat them as a single barrier. For one, the flow velocity of the plasma layer is much lower than the diffusion of O_2 so that plasma is quasistatic with respect to diffusion. Furthermore, under normal conditions the surface areas of alveoli, capillaries, and erythrocytes do not differ much, and the diffusion coefficients of tissue and plasma are also quite similar. Therefore, we prefer now to estimate the membrane diffusing capacity by considering O_2 diffusion from the alveolar surface to the erythrocyte membrane as:[182]

$$D_{M_{O_2}} = k_b \cdot S(b)/\tau_{hb} = K_b \cdot (S(A)+S(c))/2 \cdot \tau_{hb}$$

where K_b is Krogh's permeation coefficient estimated at 3.3×10^{-8} $cm^2\ min^{-1}\ mm\ Hg^{-1}$, τ_{hb} is the harmonic mean distance from the

alveolar surface to the nearest erythrocyte membrane, and S(b) is the surface area of the barrier that we estimate as the mean of the alveolar and capillary surface areas, S(A) and S(c), respectively, the two most robust measures of the area of air–blood contact. These parameters can be estimated on sections of properly sampled lung tissue by stereologic methods.[185–187]

We should also mention that the presence of a surface lining layer in the living lung may modify the geometry of the barrier as we see it on electron micrographs with the consequence that both the barrier thickness and the alveolar surface are reduced to a similar degree because some thicker parts of the barrier become shifted beneath the surfactant pools (Fig. 2-52).[177] Therefore, the effect on the estimate of $D_{L_{O_2}}$ is negligible.

Erythrocyte Conductance (De_{O_2})

As mentioned, the erythrocyte conductance is of a different nature in that it involves two coupled events,[183] that is, diffusion of molecular oxygen and oxyhemoglobin within the red blood cell as well as the chemical reaction of O_2 with hemoglobin. A way out of this is to obtain an empirical estimate of the rate at which O_2 is bound to whole blood, θ_{O_2}, and to express the erythrocyte conductance De_{O_2} as:

$$De_{O_2} = \theta_{O_2} Vc$$

where Vc is the total capillary blood volume, which can again be estimated on sections by stereologic methods.

The coefficient θ_{O_2} is estimated in vitro on whole blood, but this is difficult because of the effect of variable unstirred layers around the red cells.[188,189] In addition, θ_{O_2} depends on the hematocrit or hemoglobin concentration, and it is not a constant as it falls with increasing O_2–hemoglobin saturation; recent studies have shown that, as blood moves through alveolar capillaries, θ_{O_2} falls gradually from about 4 to 1 mL O_2 mL^{-1}, $torr^{-1}$ so that the correct value can only be found after Bohr integration of capillary P_{O_2}. For normal human lungs and a hemoglobin content of 15 g/100 mL of blood, a value $\theta_{O_2} = 1.8\ mL\,O_2 \cdot mL^{-1}, torr^{-1}$ is a reasonable estimate, but if the actual hemoglobin concentration [Hb] varies a corrected value can be obtained by multiplying this standard value with a factor c = [Hb]/15.

Morphometry of the Human Lung and Diffusing Capacity

With this model in hand, we can now attempt to estimate the diffusing capacity of the human lung on the basis of morphometric data, as listed in Table 2-4. These data, obtained by electron microscopic morphometry on seven young adults,[190] reveal the alveolar surface area to amount to 130 m^2 and the capillary surface to be about 10% smaller. These values are higher than those most commonly quoted in textbooks derived from light microscopic studies, which did not adequately resolve the alveolar surface texture. The harmonic mean thickness of the tissue barrier is 0.6 μm, whereas the total barrier, from alveolar to red cell surface (Fig. 2-60), measures 1.11 μm.[182] The capillary volume is estimated at about 200 mL. With these data we calculate $D_{L_{O_2}}$ for the adult human lung to be about 150 to 200 mL O_2 min^{-1} mm Hg^{-1}, the variation depending on the choice of θ_{O_2}.

These data also allow us to ask the question how the resistance to O_2 diffusion is distributed between the diffusion barrier and the red cells. Table 2-4 shows that the diffusion conductance of the "membrane" and that of the red cells are very similar, which means that the resistance to O_2 uptake is nearly equally divided between membrane and red cells.

These morphometric estimates of the diffusing capacity are based on model assumptions that are considered reasonable. The test of their validity must be to compare them with physiologic estimates. The standard physiologic value of $D_{L_{O_2}}$ of a healthy adult at rest is about 30 mL O_2 min^{-1} mm Hg^{-1}; thus, considerably less than what we find on the basis of morphometric estimates. However, this is not a valid comparison, because, under resting conditions, we take up only one-tenth the amount of O_2 that our lungs are capable of absorbing under conditions of heavy work. There have been a number of estimates of $D_{L_{O_2}}$ in exercising humans,[191] and these have yielded values of the order of 100 mL O_2 min^{-1} mm Hg^{-1}. This estimate should come closer to the "true capacity" of the lung for O_2 transfer to the blood than the value obtained at rest. The fact that this is only about 50% lower than the morphometric estimate is not disturbing, for we do not know whether the "true diffusing capacity" is completely exploited even in heavy exercise. Inhomogeneities in the distribution of ventilation and perfusion would, for example, limit the degree to which "true" $D_{L_{O_2}}$ can be exploited. One aspect of this type of limitation is discussed in the following when we consider the effect of the acinus design on gas exchange.

To test whether the morphometric estimate of $D_{L_{O_2}}$ is reasonable we performed, some years ago, a combined physiologic and morphometric estimation of pulmonary diffusing capacity on four species of canids ranging from 4 to 30 kg in body mass.[192]

Because it is difficult to estimate mean capillary P_{O_2} reliably, most physiologic measurements of the diffusing capacity use carbon monoxide (CO) as a tracer gas; CO binds to hemoglobin so avidly that, for practical purposes, the Pb_{CO} is zero, so that it suffices to measure CO uptake and alveolar CO concentration. It is also possible to revise the morphometric model of diffusing capacity to estimate the conductance for CO instead of O_2 by appropriately changing the permeability coefficients and the rate of CO binding to erythrocytes, θ_{CO}, whereas the morphometric parameters are not changed. In a study on dogs and on other canids, the calculated morphometric value of $D_{L_{O_2}}$ was found to be larger than the physiologic estimate by less than a factor of 1.5, thus confirming the observation made with respect to human lungs.

Therefore, we conclude that the pulmonary gas exchanger is designed with a certain amount of redundancy or excess capacity, but this is by no means unreasonable from an engineering point of view. Indeed, to design the pulmonary gas exchanger with a certain degree of redundancy may make a lot of sense. The lung forms the interface to the environment and its functional performance will thus depend on environmental conditions, such as the prevailing O_2 partial pressure, which falls as we go

TABLE 2-4 Morphometric Estimate of $D_{L_{O_2}}$ for Young, Healthy Adult Humans of 70-kg Body Weight, Measuring 175 cm in Height

Morphometric data (mean ± 1 SE)			
Total lung volume (60% TLC)	4340	±285	mL
Alveolar surface area	130	±12	m^2
Capillary surface area	115	±12	m^2
Capillary volume	194	±30	mL
Air–blood tissue barrier thickness			
Arithmetic mean	2.2	± 0.2	μm
Harmonic mean	0.62	±0.04	μm
Total barrier harmonic mean thickness	1.11	± 0.1	μm
Diffusing Capacity (mL/min/mm Hg)			
Membrane	$D_{M_{O_2}}$	350	
Total	$D_{L_{O_2}}$	158	

Source: Reproduced with permission from Gehr P, Bachofen M, Weibel ER. The normal human lung: Ultrastructure and morphometric estimation of diffusion capacity. Respir Physiol. 1978;32:121–140 and Weibel ER. Symmorphosis: on form and function in shaping life. Cambridge, MA: Harvard University Press; 2000.

from sea level to higher altitudes. It has been shown that goats, whose $D_{L_{O_2}}$ is about twice as large as seemingly required, can maintain their maximal level of exercise-induced $\dot{V}_{O_2}$ even under hypoxic conditions whereas the dogs that have very small excess $D_{L_{O_2}}$ cannot. It has also been suggested that human athletes exercising at high altitude may fully exploit their $D_{L_{O_2}}$. This suggests that the apparent redundancy in $D_{L_{O_2}}$ may be a safety factor to protect the good functioning of the pulmonary gas exchanger even when environmental conditions are not optimal. Recent studies with partial pneumonectomy in dogs have shown that the lung can achieve 85% of its maximal O_2 uptake even when 40% of lung tissue is removed after left pneumonectomy, making use of some of this reserve capacity; but when right pneumonectomy removes 60% of lung tissue, adequate function can be achieved only after compensatory growth of the residual lung tissue to restore diffusing capacity.[193–196]

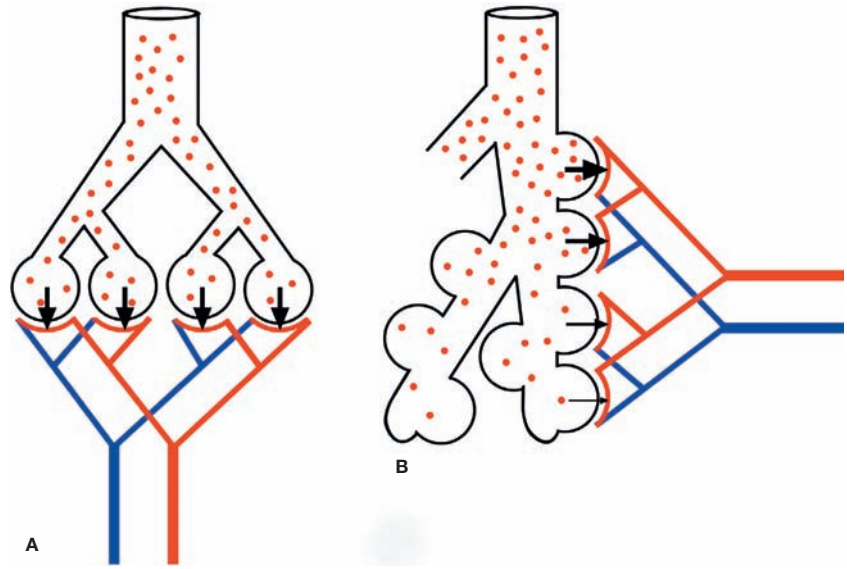


Figure 2-61 Models of ventilation–perfusion relationship in the mammalian pulmonary gas exchanger. **A.** Parallel ventilation/parallel perfusion. **B.** Serial ventilation/parallel perfusion. *(Reproduced with permission from Sapoval B, Filoche M, Weibel ER. Smaller is better, but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proc Natl Acad Sci USA. 2002;99(16):10411–10416. Copyright (2002) National Academy of Sciences, USA.)*

DESIGN OF THE ACINUS AND GAS EXCHANGE

The preceding section considered the overall size of the gas exchanger of the entire lung to compare it with the global performance of this organ. In reality, the surface the size of a tennis court is subdivided into some 400 million gas-exchange units. These are individually perfused with blood because they correspond to the unit capillary network that spans between pulmonary arteriole and venule (Fig. 2-46). The diameter of such a roughly disk-shaped unit is about 500 μm and has a surface area that corresponds approximately to that of an alveolus, even though alveoli and the capillary unit are not congruent as the latter spans over several alveoli and each alveolus is in contact with several capillary units.[162]

These gas-exchange units are arranged along the terminal generations of the airway tree that form the pulmonary acinus (Fig. 2-61B). Note that this arrangement of gas-exchange units to the airway system differs from the common representation of the alveolar–capillary unit as a terminal "bubble" (Fig. 2-61A). This has potential functional consequences because ventilation of alveoli occurs in two steps:[197] (1) upon inspiration oxygen-rich air flows through the airways into the acinus carrying along O_2; (2) in the peripheral airways flow velocity slows down because the airway cross-section increases, and O_2 now moves toward the periphery by diffusion in the air phase, driven by the P_{O_2} gradient that becomes established as O_2 is absorbed at the alveolar surface (Fig. 2-62). Thus, in the peripheral airways diffusion along the airways is combined with diffusive permeation of O_2 into the alveoli and across the tissue barrier to the blood, the actual process of gas exchange. Whereas all capillary network units are individually perfused with venous blood the alveoli are not independent in terms of their O_2 supply, which depends on their location along the airway tree. Therefore, the design of the acinus has significant effects on the gas-exchange conditions.

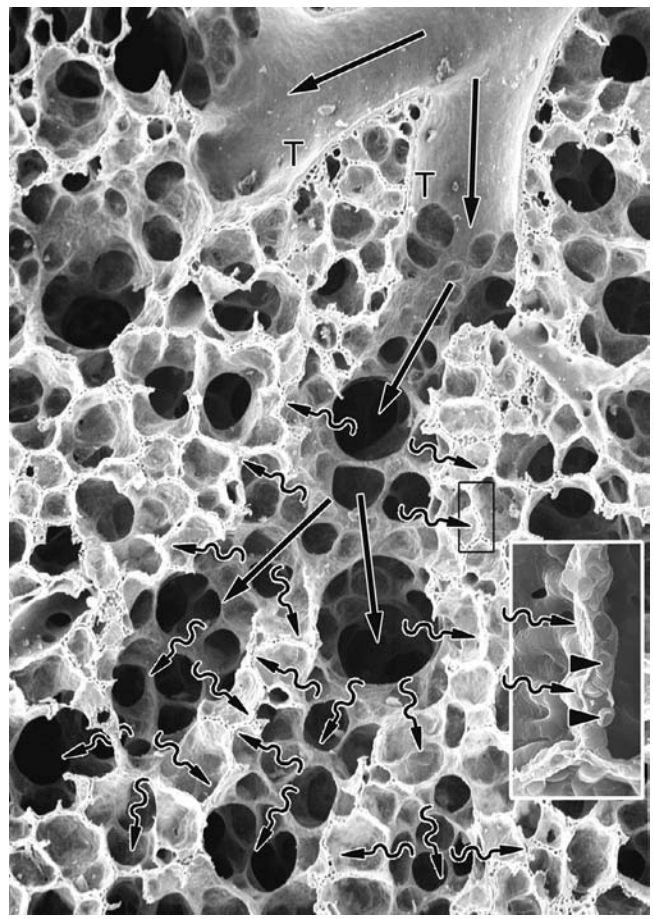


Figure 2-62 Central part of the acinar airways beginning with transitional bronchiole (T) and leading into the branched alveolar ducts. On inspiration air flows in by convection *(straight arrows)*, but as flow velocity falls diffusion of O_2 *(wiggly arrows)* becomes the dominant mechanism for bringing O_2 to the gas-exchange surface. All along acinar airways O_2 is absorbed by the capillary blood in the septa *(inset, arrowheads)*.

THE ACINAR AIRWAY SYSTEM CONNECTED TO THE GAS EXCHANGER

In a systematic study of human lungs[9] the mean volume of acini was found to be 187 mm^3 with a standard deviation of 79 mm^3. The branching pattern for an average size human acinus is shown in Figure 2-63. The segment lengths have been drawn to scale and the terminal clusters of alveoli of the alveolar sacs are marked by a dot. This acinus has been subdivided into eight subacini whose

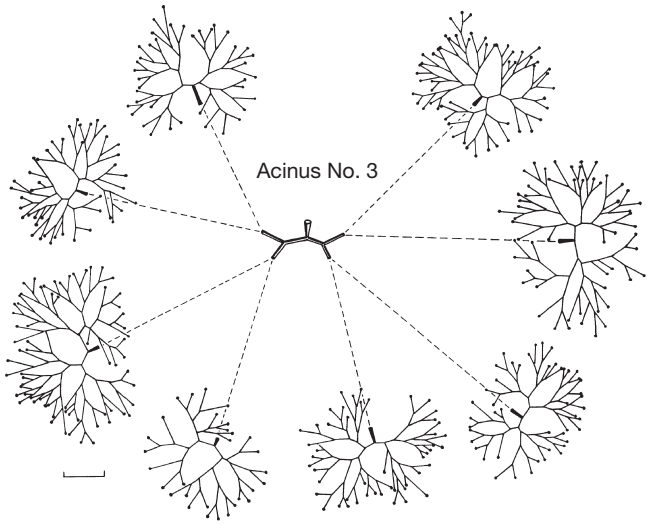


Figure 2-63 Graphic representation of branching pattern of acinar airways in one human acinus of 183 mm^3 volume with the segment lengths drawn to scale. The airways are separated at the third generation thus displaying the branching pattern within each 1/8 subacinus. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

substems are located in the third generation of acinar airways. The first three generations of acinar airways following on the transitional bronchiole are respiratory bronchioles, where there are only a few alveoli. In contrast, the alveolar ducts that follow are completely and densely lined with alveoli (Fig. 2-64). The 1/8 subacinus is a unit

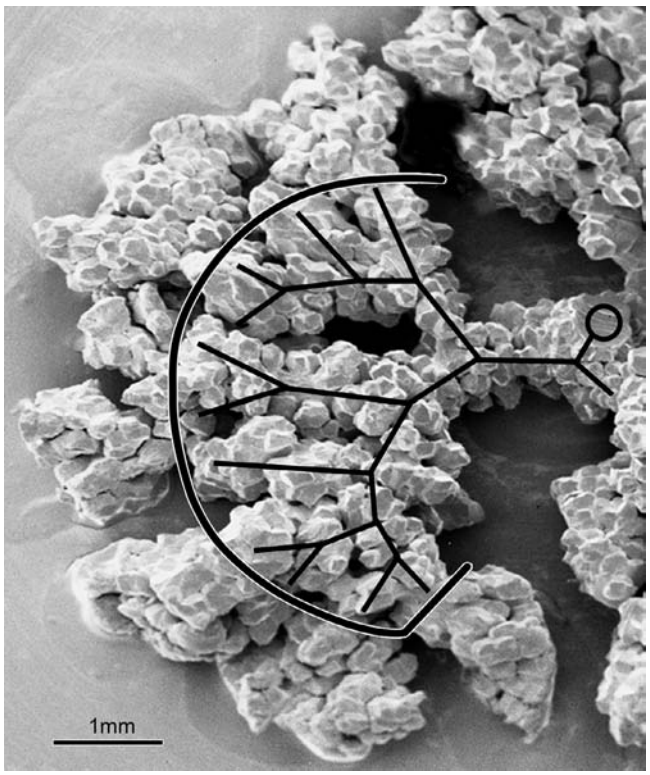


Figure 2-64 Airways of 1/8 subacinus of human lung beginning with generation 18 alveolar duct (circle). The silicon rubber cast has been spread out to show the course of the subsequent branchings. The curved line marks the approximate boundary to the last generation to show that this generation of alveolar sacs (see Fig. 2-5) comprises over half the gas-exchange area of the acinus.

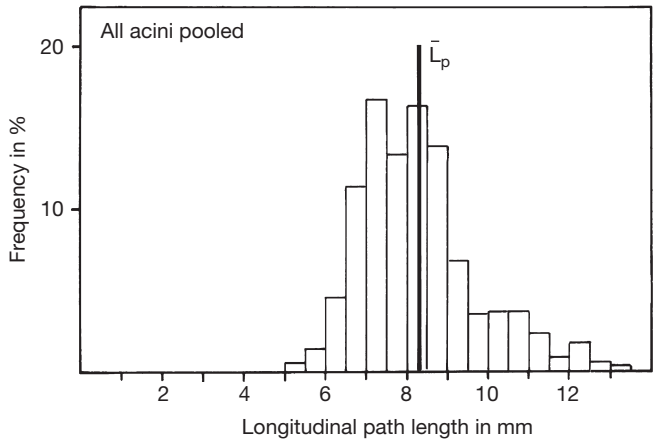


Figure 2-65 Frequency distribution of longitudinal path length from the transitional bronchiole to the alveolar sacs in the human lung. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

of functional significance, as we shall see. The intra-acinar airways branch by irregular dichotomy; terminal sacs are located in generations 6 to 11 so that the intra-acinar airways branch over an average of 8 generations (Fig. 2-5).

The morphometry of the intra-acinar airways of the human lung shows a number of characteristic traits. The inner diameter (d_{in}) that characterizes the cross-section of the duct tube decreases from about 490 μm at the transitional bronchiole to 270 μm in the last generations.[9] When this is plotted onto the graph relating airway diameter to generations of branching (Fig. 2-37), we note that this diameter falls less steeply than the cube-root-of-1/2 law we have observed for conducting airways. This is a significant finding in terms of the ventilation of alveoli by O_2 diffusion.

An important morphometric characteristic of acinar airways is the total path length for O_2 diffusion from the entrance at the transitional bronchiole to the terminal cluster of alveoli at the alveolar sac (Fig. 2-5). This path length is determined by two factors: the number of generations and the segment length. The length of alveolar ducts gradually decreases from 1330 to 640 μm in the peripheral generations, the alveolar sacs being a little bit longer. Since the number of branching generations varies somewhat, we can expect the path length to vary even within one acinus. In the human lung, the average longitudinal path length measures 8.3 ± 1.4 mm (Fig. 2-65).[10] Because of the decreasing length of acinar ducts 3.4 mm of this total path length are for the first three generations of respiratory bronchioles, whereas the path length of alveolar ducts and sacs comprised in the 1/8 subacinus (Fig. 2-64) averages 4.7 ± 0.88 mm.

Typical Path Model of Human Acinus

In view of assessing the effect of these structural features on the functional performance of the pulmonary gas exchanger we can attempt to develop what we may call a typical path model for an average human acinus[9,10]; the relevant morphometric data are given in Table 2-5. Such an acinus has a volume of 187 mm^3. Its airways branch over an average of eight generations to reach the terminal alveolar sacs. With each generation the number of branches doubles to end with some 256 terminal alveolar sacs in an average acinus (Fig. 2-63). Locating the transitional bronchiole ($z' = 0$) in generation 14 (Fig. 2-5) the terminal air sacs are in generation 23 of the typical path airway tree. From the estimates of the lengths and inner diameters of the airway segments we can derive overall parameters of functional significance, such as the total airway cross-section per generation, $A_d(z')$, which is a determinant of air flow velocity (Fig. 2-44). Finally,

TABLE 2-5 Typical Path Model of Human Acinus

Generation		Segments			Dimensions per Generation			Path Length
Airways z	Acinus z′	N(z′)	l mm	d_{in} mm	$A_d(z')$ mm^2	$V_d(z')$ mm^3	$S_{alv}(z')$ mm^2	$L_p(z')$ mm
15	0	1	1.4	0.50	0.20	0.32	7	1.4
16	1	2	1.33	0.50	0.39	0.52	23	2.73
17	2	4	1.12	0.49	0.75	0.84	67	3.85
18	3	8	0.93	0.40	1.00	0.93	129	4.78
19	4	16	0.83	0.38	1.81	1.50	219	5.61
20	5	32	0.70	0.36	3.26	2.28	349	6.31
21	6	64	0.70	0.34	5.81	4.07	661	7.01
22	7	128	0.70	0.31	9.11	6.38	1204	7.71
23	8	256	0.70	0.29	16.9	13.47	2720	8.41

Source: Modified with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.

we can also estimate the distribution of alveolar surface area to the different generations in proportion to the duct surface $S_d(z')$, but adjusting for the fact that only part of this surface is associated with alveoli in the respiratory bronchioles (generations z′ = 1–3). For an estimated alveolar surface of 130 m^2 in the human lung (Table 2-4), there would be about 54 cm^2 of gas-exchange surface per average acinus. It is seen that half this gas-exchange surface is in the last generation (see also Fig. 2-64). A final check of this model is that the path length from the entrance into the transitional bronchiole to the end of the alveolar sacs is 8.4 mm, which agrees well with the mean path length estimated in the human acini (Fig. 2-65).

Implications of Acinar Design for Gas-Exchange Function: The Phenomenon of Diffusion Screening

The gas exchange in the pulmonary acinus involves several physicochemical phenomena that occur within the complex acinar geometry described in the preceding section.[197] As mentioned, in the distal regions of the lung, oxygen is transported toward the alveolar membrane both by convection and molecular diffusion. Oxygen then diffuses through the tissue membrane into the blood, where it is bound by hemoglobin. Several physical parameters govern oxygen uptake at the acinar level, such as air flow velocity, diffusion coefficient of oxygen in air, alveolar membrane permeability, blood hemoglobin content, and its reaction rate with oxygen. Conversely, carbon dioxide is discharged from the blood to the alveolar gas through diffusion across the membrane. It then diffuses backward along the airways to the zone, where convection becomes dominant, and is lastly expelled from the lung. In all these processes, the morphology of the system plays an essential role.

Since oxygen uptake into the blood is driven by the O_2 partial pressure at the alveolar surface we must ask whether this driving force is the same throughout the acinus or whether there could be differences between its central and peripheral parts. Some earlier studies had shown that concentration gradients may exist as a consequence of efficient capture of oxygen by hemoglobin. More recently,[197] we have come to realize that such gradients are strongly influenced by the finite permeability of the membrane that plays a dominant role in the effective properties of the acinus as the ventilatory gas-exchange unit. O_2 molecules entering the unit where diffusion prevails have a larger probability to hit the surface of the alveolar membrane near the entrance than in the more distal regions. If the membrane permeability is large, O_2 molecules are absorbed at the very first hits. As a consequence, O_2 is absorbed into the blood in the first parts of the acinar pathway, a process called *diffusional screening,* so that the gas-exchange units in the deeper part of the acinus would receive less O_2 (Fig. 2-61) or perhaps even not enough for gas exchange to occur. Blood perfusing these regions would not be oxygenated and would thus appear as a shunt. In contrast, if the permeability is small, molecules will be absorbed only after many collisions with the wall. They then have a fair chance to reach the deeper regions and the entire acinar surface can be effective for gas exchange.

To put this into the perspective of structure–function relations this process is related to the balance between two conductances:[197] a diffusion conductance Y_{cross} for O_2 to *cross* the barrier from alveolar air to capillary blood, and a diffusion conductance Y_{reach} for O_2 to *reach* the surface through the airspaces. Both these conductances are determined by the product of: (a) a physical parameter (the permeability coefficient for O_2 in tissue, and the diffusion coefficient for O_2 in air, respectively); and (b) a morphometric parameter (the gas-exchange surface, and the distance along the acinar airways, respectively). The physical coefficients are given quantities, except that the tissue permeability is also affected by the thickness of the tissue barrier, a parameter that varies very little between species. On the other hand, the size and surface of the acinus can be varied during evolution and growth to adjust the two conductances. We can predict that the design of the acinus is optimized if Y_{cross} and Y_{reach} are about equal as this means that both the gas-exchange surface and the acinar air volume, or the diffusion distance, are matched. If Y_{cross} were much smaller than Y_{reach} the low permeability of the gas exchanger would need to be compensated by a larger gas-exchange surface, and this would inevitably entail a larger volume of the acinus to accommodate the surface and by that a longer diffusion distance.

The morphometric study of acini in various mammalian species[9,197,198] revealed that the size of the acini is such that $Y_{cross} \sim Y_{reach}$ so that their morphology seems to be at least partially adapted to minimize the effects of screening. Note that the problem of screening occurs in that part of the acinus where O_2 moves to the surface by diffusion only (Fig. 2-62), in what is called the diffusion cell. The transition between convection and diffusion is determined by the Peclet number (Fig. 2-66), essentially the ratio between air flow and diffusion velocities[197]; diffusion is more effective than convection when the Peclet number is smaller than 1. In the human lung, under resting conditions, this transition occurs in generation 18 and that is the entrance to the 1/8 subacinus (Fig. 2-63); accordingly the diffusion cell corresponds to the 1/8 subacinus. In exercise, where O_2 consumption as well as ventilation is increased, convective transport of O_2 is effective out to generation 21 (Fig. 2-66). So in exercise there are only two to three generations of acinar airways that act as diffusion cell, but that is still highly significant because these generations accommodate 75% of the gas-exchange surface (Fig. 2-64 and Table 2-5).

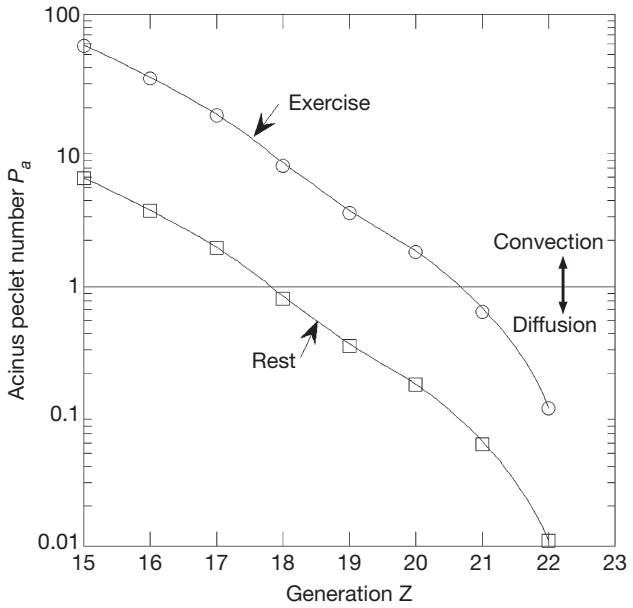


Figure 2-66 In the human acinus the Peclet number, reflecting the relation between convective flow velocity and diffusion velocity of O_2, falls as the airway cross-section increases. Below 1 diffusion becomes the dominant mechanism of alveolar ventilation. This transition point is about in generation 18 at rest and extends out to generation 21 in heavy exercise. *(Reproduced with permission from Sapoval B, Filoche M, Weibel ER. Smaller is better, but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proc Natl Acad Sci USA. 2002;99(16):10411–10416. Copyright (2002) National Academy of Sciences, USA.)*

Note that what has been discussed so far relates essentially to about half the respiratory cycle, namely, inspiration when fresh O_2-rich air is actively brought into the acinus. During expiration things are in a way reversed: CO_2 that has diffused from the blood into the acinar air now dilutes O_2 and the convection–diffusion front is moved toward the bronchi. For this reason, the effective duty cycle of the gas-exchange system is smaller than 1, particularly under the conditions of high O_2 uptake rate in exercise. This must be considered when modeling gas exchange. Recent refined model studies using the same morphometric data together with reasonable assumptions on the physiologic conditions revealed that the size of the human pulmonary acinus is such as to avoid negative effects of diffusional screening.[199]

THE LUNG AS PART OF THE PATHWAY FOR OXYGEN

The lung's main function, gas exchange between air and blood, serves the body's varying O_2 needs as they are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells[16] which proceeds along the respiratory system through various steps from the lung to the blood, by circulatory blood flow to the cells and mitochondria (Fig. 2-67). A number of basic features characterize this system: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$, is the same at all levels; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressures, which fall from inspired P_{O_2} down to near zero around the mitochondria; (3) the O_2 flow rate at each step is the product of an O_2 partial pressure difference and a conductance G, which is related to structural and functional properties of the organs participating in O_2 transfer. In the preceding section we have seen that the principal design features of the lung that determine one of the key conductances, the pulmonary diffusing capacity, are sized to just yield a conductance that allows the O_2 uptake required to satisfy the demands of the whole body cell system at work, with a small margin of safety under normal conditions. Therefore, the lung appears designed to serve the body's needs efficiently and economically. The question we may now ask is whether the other parts of the respiratory system, from the heart to the mitochondria are also designed for economic functional performance.[200]

Let us first look at the overall functional performance of the system. We first note that O_2 consumption is highly variable, increasing by about a factor of 10 between resting conditions and heavy exercise when 90% of the O_2 is consumed in the locomotor muscles. Figure 2-68 shows that the oxygen consumption in muscle is proportional to the energy output,[201] measured for example as running speed, and that it reaches a limit $\dot{V}_{O_2max}$ beyond this the running speed can still be increased, but the additional energy required by the higher speed is then supplied through glycolysis or anaerobic ATP production with the result that lactic acid concentration in the blood gradually increases. It is now interesting to note that $\dot{V}_{O_2max}$ is a characteristic of the work capacity of an individual: well-trained athletes reach their $\dot{V}_{O_2max}$ at a higher running speed and a higher level of oxygen consumption, and lactic acid concentration in the blood also begins to increases at the higher performance levels corresponding to $\dot{V}_{O_2max}$ (Fig. 2-68).

One may now raise the question whether this variable limitation of oxidative metabolism is a result of variable functional constraints affecting the regulation of metabolic rate and circulatory transport, or whether it could be set by variations in design constraints characterizing the structural components of the pathway, one possible candidate being the pulmonary diffusing capacity. The answer to this question depends on an integrated study of structure and function of the respiratory system. For this we need a quantitative model of the oxygen pathway that identifies all the functional variables and the design parameters at the four levels of the system[202]: the lung, circulation of blood with the heart, capillaries, and mitochondria (Table 2-6). This model is a further development of the one shown in Figure 2-67 in the sense that, at each level, the equation describing oxygen flow rate sorts out the parameters of functional

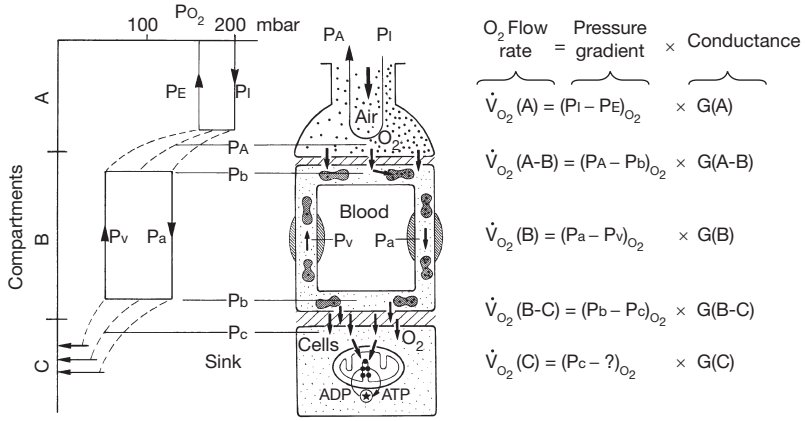


Figure 2-67 Model of the respiratory system from the lung to the cells. Oxygen flow is driven through the system by a cascade of P_{O_2} ranging from inspired $P_{I_{O_2}}$ to near zero at the mitochondria. At each level the flow rate is determined by a partial pressure difference and a conductance. *(Modified with permission from Taylor CR, Weibel ER: Design of the mammalian respiratory system. I. Problem and strategy, Respir Physiol. 1981;44(1):1–10.)*

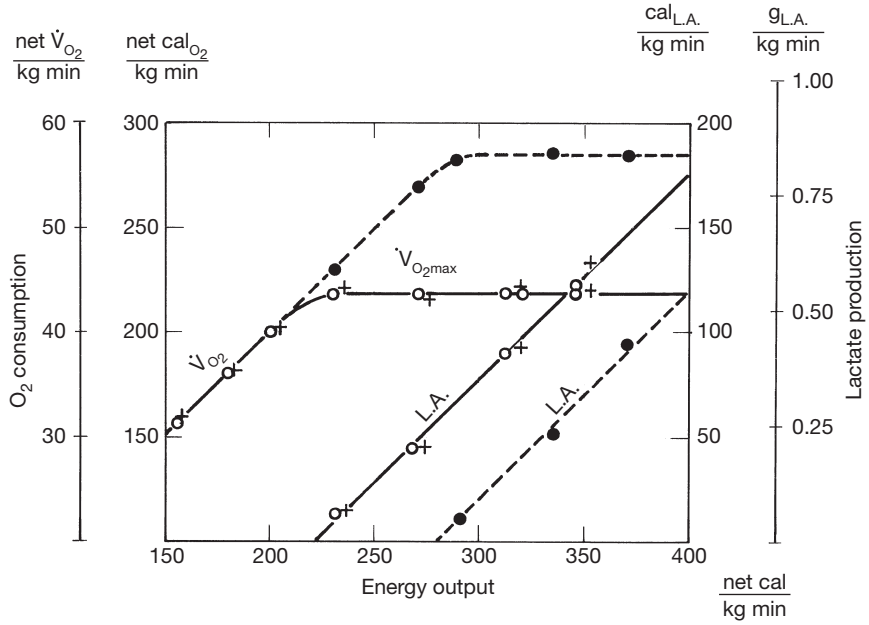


Figure 2-68 Rate of O_2 consumption *(left ordinate)* and lactic acid production *(ordinate at right)* in exercise are plotted as a function of the work intensity and, therefore, of the energy requirement *(abscissa)*. Oxygen consumption increases linearly up to a point corresponding to an energy requirement of 220 cal/kg min^{-1}; if work is pushed beyond that there is no further increase in O_2 consumption ($\dot{V}_{O_2max}$ is reached) but glycolysis now generates the required energy resulting in an increase in lactic acid production. The broken lines refer to athletes (middle- and long-distance runners) whose maximum oxygen consumption is higher; the line of the lactic acid for these subjects is correspondingly shifted to the right. *(Reproduced with permission from Margaria R, Cerretelli P, Diprampero PE, et al. Kinetics and mechanism of oxygen debt contraction in man. J Appl Physiol. 1963;18:371–377.)*

regulation and those of structural design. These are distinguished in the following sense: Functional variables are regulated according to need with short time constants (seconds), whereas structural design parameters are genetically determined static elements that can be adjusted to a certain extent, for example, by training, but with time constants of weeks to months.

Thus, design variables set the capacity of the system because they are determined by structures whose quantitative properties cannot be adjusted at short notice. If the system were designed according to the principle of symmorphosis we would predict that the design variables are adjusted to $\dot{V}_{O_2max}$ at all levels from the lung to the mitochondria.

The experimental test of this hypothesis requires the integrated measurement of $\dot{V}_{O_2max}$ of the relevant functional parameters, and of all the design parameters, which must then be correlated on the basis of the model of Table 2-6. This cannot be easily done in the human so that is where we can learn from studies in comparative physiology. We know that $\dot{V}_{O_2max}$ is highly variable among mammals. Some species such as dogs, horses, or pronghorn antelopes have a much higher level of $\dot{V}_{O_2max}$ than "normal" species of the same size such as goats or cows; this is called adaptive variation.[203] On the other hand body size matters so that small animals have a higher metabolic rate per unit body mass than large species, which is called allometric variation.[200] These are genetically determined variations, the result of evolution and selection by fitness, in contrast to the changes in overall work capacity and $\dot{V}_{O_2max}$ induced by exercise training in human athletes, which are epigenetic variations.[204,205] In all these cases we can ask how and to what extent the structural design parameters are adjusted to meet the different requirements for O_2 to cover the energetic need at the limit of the aerobic work capacity. If there is a bottleneck, then there will be one and only one parameter whose variation is perfectly matched to the variation in the limit of O_2 flow, $\dot{V}_{O_2max}$, whereas all the parameters that are overdesigned would appear in haphazard relations to the flow limit. On the other hand, if the limiting resistances are distributed all steps would have to be matched to the varying $\dot{V}_{O_2max}$. If we take the bold view that the organisms are economically designed we would predict that the structural parameters at all levels should be sized to the maximal total O_2 flow requirement with no unnecessary excess capacity because that would be a waste. We have called this design principle symmorphosis, meaning that there should be no more structure built into the system than required to serve the functional needs.[179]

TABLE 2-6 Model of Structure–Function Relations in Pathway for Oxygen Separating Functional and Structural Parameters in the Equations Defining O_2 Flow Rate Through Four Levels

FUNCTION • DESIGN	
$\dot{V}_{O_2}\ (\text{lung}) = (PA_{O_2} - Pb_{O_2})\{t_c, \theta_{O_2}\} \bullet DL_{O_2}\{S(A), S(c), V(c), \tau_{hb}\}$	(1)
$\dot{V}_{O_2}\ (\text{heart}) = (\sigma_a \cdot Pa_{O_2} - \sigma_{\bar{v}} \cdot P\bar{v}_{O_2}) \cdot f_H \bullet Vs\{V(LV)\} \cdots V_V(ec)$	(2)
$\dot{V}_{O_2}\ (\text{caps}) = (Pb_{O_2} - Pc_{O_2})\{tc\theta_{O_2}\} \bullet DT_{O_2}\{S(c), V(c), V_V(ec), \delta(c, mi)\}$	(3)
$\dot{V}_{O_2}\ (\text{mito}) = \dot{V}_{O_2}\{\dot{m}_{ATP}\} \bullet V(\text{mi})\ \{S_V(im, mi)\}$	(4)

The O_2 flow rate $\dot{V}_{O_2}$ is expressed as the product of functional and design parameters; parameters that affect the factors are shown in italics and placed in braces {.}. The functional parameters include: O_2 partial pressures (P_{O_2}), coefficients of "hematocrit-specific" O_2 capacitance (σ) which depend on O_2-hemoglobin dissociation, O_2 binding rate (θ), heart frequency (f_H), capillary transit time (tc), and mitochondrial O_2 consumption rate as function of ATP flux ($\dot{V}_{O_2}\{\dot{m}_{ATP}\}$). Design parameters include: diffusion conductances (D) of lung and tissue gas exchangers which depend on alveolar and capillary exchange surface areas ($S_{(A)}$, S(c)), capillary volumes (V(c)), hematocrit (V_V(ec)), harmonic mean barrier thickness (τ_{hb}), capillary-mitochondrial diffusion distance (δ(c,mi)), and mitochondrial volume (V(mi)) with inner membrane surface density (S_V(im,mi)).

Source: Data from Weibel ER: Symmorphosis: on form and function in shaping life. Cambridge, MA: Harvard University Press; 2000.

Testing the Hypothesis of Symmorphosis

To test such a hypothesis we can first compare mammals that greatly differ in terms of their maximal O_2 consumption. The first type of this variation is found in comparing normal with athletic species, such as dogs with goats or horses with steers.[203] It has been found that such athletic animals can achieve a $\dot{V}_{O_2max}$ that is about

TABLE 2-7 Comparison of Morphometric and Physiologic Parameters of Muscle Mitochondria and Capillaries, and of Heart, Blood and Lung with Variation of $\dot{V}_{O_2max}$ in Three Pairs of Athletic and Sedentary Species. Data per Unit Body Mass

	Mitochondria		Blood	Capillaries		Heart			Lung
Design Function	$\dot{V}_{O_2max}/M_b$ mL·min^{-1}·kg^{-1}	V(mt)/Mb mL·kg^{-1}	V_V(ec)	V(c)/Mb mL·kg^{-1}	V(ec)/Mb mL·kg^{-1}	fH min^{-1}	Vs/M_b mL·kg^{-1}	$\dot{Q}$(ec)/Mb mL·min^{-1}·kg^{-1}	$D_{L_{O_2}}$/Mb mL·min^{-1}·mmHg^{-1} kg^{-1}
25–30 kg									
Dog	137.4	40.6	0.50	8.2	4.10	274	3.17	434.3	424.8
Goat	57.0	13.8	0.30	4.5	1.35	268	2.07	166.4	288.0
D/G	2.4	2.9	1.68[a]	1.8[a]	3.0	1.02[a]	1.53[a]	2.61	1.48[a]
150 kg									
Pony	88.8	19.5	0.42	5.1	2.14	215	2.50	225.7	284.4
Calf	36.6	9.2	0.31	3.2	0.99	213	1.78	117.5	180.0
P/C	2.4	2.13	1.35[a]	1.6[a]	2.16	1.02[a]	1.40[a]	1.92	1.57[a]
450 kg									
Horse	133.8	30.0	0.55	8.3	4.57	202	3.11	345.5	388.9
Steer	51.0	11.6	0.40	5.3	2.12	216	1.52	131.3	194.4
H/S	2.6	2.6	1.4[a]	0.94[a]	2.16	2.1[a]	2.0[a]	2.63	2.0[a]
Ath/Sed[b]	2.5	2.5	1.5[a]	1.7[a]	2.44	1.0[a]	1.7[a]	2.39	1.7[a]

[a]*These ratios are significantly different from that for $\dot{V}_{O_2max}$.*
[b]*This line presents overall ratios for athletic/sedentary species.*
Source: Data from Taylor, CR, Karas, RH, et al: (1987) Respir. Physiol. 69, 1–127; Jones, JH, Longworth, KE, Lindholm, A et al: (1989) J. Appl. Physiol. 67, 862–870; Constantinopol, M, Jones, JH, Weibel, ER, et al: (1989) J. Appl. Physiol. 67, 871–878; Hoppeler, H, Jones, JH, Lindstedt, SL, et al: (1987) in Equine Exercise Physiology II, eds. Gillespie, JR & Robinson, (Edward Brothers, Ann Arbor, MI), 278–289; Hoppeler, H, Kayar, SR, Claassen, H, et al: (1987) Respir. Physiol. 69, 27–46; Conley JE, Kayar SR, Rosler K, et al: (1987), Respir Physiol 69, 47–64; Karas, RH, Taylor, CR, Rosler, K, et al: (1987) Respir. Physiol. 69, 65–79; Weibel, ER, Marques, LB, Constantinopol, M, et al: (1987) Respir. Physiol. 69, 81–100.

2.5 times higher than that of normal species of the same size. This is much more than what human athletes can achieve. The relevant morphometric data on such species are shown in Table 2-7 for three species pairs.[206] If we go through the respiratory system, beginning at the bottom with the mitochondria, we note that their total volume in the locomotor muscles is also 2.5 times greater in the athletic species with the result that, at $\dot{V}_{O_2max}$ the unit volume of mitochondria consumes the same amount of oxygen in all these six species, namely about 5 mL O_2 per minute and mL mitochondria. In the next level up, the muscle capillaries, we note that the capillary volume is only 1.7 times greater in the athletic species. However we note that in the athletes the hematocrit, that is, the concentration of erythrocytes in the blood, is larger so that as a result the capillary erythrocyte volume, the product of capillary volume with hematocrit, is 2.44 times greater, thus well matched to the mitochondrial O_2 demands. Note that this is what counts because oxygen is delivered exclusively from the capillary red blood cells. When we look at the determinants of total blood flow the heart is the central element. We notice that athletic species have larger hearts resulting in a larger stroke volume Vs, but that the maximal heart frequency is not different between the species pairs so that cardiac output is determined by the stroke volume. This is only 1.7 times greater in the athletic species. However, note that, here again, the hematocrit plays an important role as it determines the amount of O_2 that can be transported to the capillaries. If we calculate the cardiac erythrocyte output $\dot{Q}$ (ec) we find that it is again 2.4 times greater in the athletic species. Thus the design parameters of the internal steps of the O_2 transport cascade are quantitatively adjusted to the needs for O_2 flow under limiting conditions. Thus, it appears that the resistance to O_2 flow is distributed to all levels.

When we then consider the design of the pulmonary gas exchanger we note that the O_2 diffusing capacity of the lung of athletic species is only 1.7 times greater than that of normal species. Considering that we found that the human lung may have some excess capacity by about a factor of 1.5, this may signify that normal sedentary species such as goats or cows have a greater excess capacity than athletic species. Indeed, this can be shown to be the case in two ways:[207] (1) when one calculates the progression of O_2 loading on capillary blood (Bohr integration, Fig. 2-59) one finds that dogs reach saturation just before the blood leaves the capillaries into arterial blood, whereas the goats have some 30% reserve capacity; (2) when goats are run on a treadmill while breathing hypoxic air one finds that they can maintain their $\dot{V}_{O_2max}$ in contrast, dogs cannot run at their established $\dot{V}_{O_2max}$ under such conditions. We concluded from this observation that athletic species have designed a lung to match the requirements for maximal O_2 uptake with no excess capacity while normal sedentary species apparently allow for a certain safety margin which allows them to perform well also under unfavorable hypoxic conditions. If this is now applied to our observations on the human lung this may mean that the excess capacity of the normal lung may just be sufficient to allow athletes to increase their $\dot{V}_{O_2max}$ by training by a factor 1.5, just about what they can achieve (Fig. 2-67).

One has also found that highly trained athletes do not tolerate heavy exercise at very high altitudes as they cannot achieve O_2 saturation of their arterial blood. Thus, it seems that the pulmonary gas exchanger is now the limiting factor for O_2 transfer to the working muscles. The reason for this is that the lung of the adult cannot enlarge its gas-exchange surfaces to match the increased demands of trained muscles. So an athlete must make do with the lung she or he has developed during growth. This contrasts with the changes induced by exercise training in muscle with an increase in mitochondria and capillaries, and in the heart by enlargement of the ventricles, all well matched to the maximal

O_2 demands.[202] Therefore, it is fortunate – and perhaps a sign of good design – that the lung is designed with some excess diffusing capacity to allow the lower, internal, levels of the respiratory system to exploit their capacity to adapt to increased energetic needs.

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CHAPTER 3

The Respiratory Muscles

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Marc Decramer

The respiratory muscles constitute a complex pump system. Several muscles comprise this system, represented schematically in Figure 3-1. Breathing under all circumstances requires a coordinated contraction of different respiratory muscles. The most important inspiratory muscle is the diaphragm. The conditions under which this respiratory muscle system weakens and eventually will fail are addressed in other chapters (see Chapters 83, 85, and 104). This chapter focuses on structural and functional properties of the respiratory muscles, respiratory muscle action, and respiratory muscle interaction.

STRUCTURAL AND FUNCTIONAL PROPERTIES OF RESPIRATORY MUSCLES

The respiratory muscles are skeletal muscles, and, in essence, their structural and functional properties are within the range of other skeletal muscles located in the limbs. Adaptations to their specific function, however, make them distinctly different from other skeletal muscles in a number of respects. First, limb muscles are essentially designed to produce movements, and hence, primarily work against inertial loads. Respiratory muscles mainly have to overcome resistive and elastic loads.

Second, peripheral muscles contract rhythmically during movements, whereas respiratory muscles contract rhythmically and continuously, and they are the only skeletal muscles on which life depends. These vital muscles thus have to be well equipped to sustain continuous rhythmic contraction. These adaptations include high fatigue resistance, high oxidative capacity, greater capillary density, and greater maximal blood flow, and they depend upon structural and functional properties of the muscles.

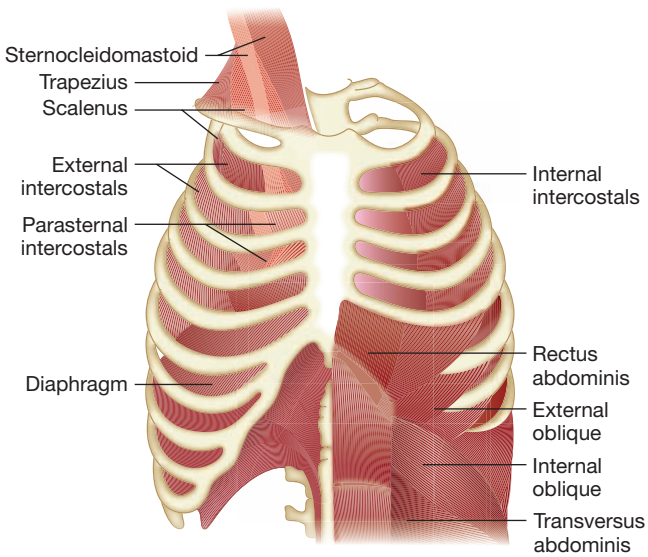

Figure 3-1 Idealized drawing of the respiratory muscles.

STRUCTURAL PROPERTIES

Structural properties of muscles in general, and respiratory muscles in particular, depend upon fiber types present in the muscle, morphological characteristics of the fibers, and motor unit organization.

Fiber Types

Four types of muscle fibers are usually present in skeletal muscles. They are distinguished on the basis of the myofibrillar myosin adenosine triphosphatase (ATPase) activity and its pH dependence and pretreatment with paraformaldehyde.[1,2] Thus, after acid preincubations at pH 4.5, type I fibers are stained dark, type IIa fibers are stained lighter than type IIb and type IIx fibers. In addition, pretreatment with paraformaldehyde after alkaline preincubation at pH 10.4 further allows the distinction between type IIb fibers staining lighter than type IIx fibers. Alternatively, muscle fibers may be distinguished through myosin heavy chain gene expression using electrophoresis and western blotting or via immunostaining.[3] This latter technique has the advantage of revealing the presence of coexpression of different myosin heavy chain isoforms within the same muscle fiber. It has also been revealed that myosin heavy chain 2b is not expressed in human muscle.[4] Type I fibers, or slow oxidative fibers, have a slow contraction profile but are high in endurance and rich in oxidative enzymes.[5] Type II fibers are fast-twitch fibers that develop tension rapidly. They either are fatigue resistant or glycolytic oxidative (IIa), or fatigable or glycolytic (IIb),[5] whereas resistance to fatigue for the type IIx fibers is intermediate between the IIa and IIb fibers. Type II fibers develop greater forces than do type I fibers. Muscles primarily composed of type I fibers have high endurance capacity, whereas those primarily composed of type IIb fibers are designed to develop high forces but have low endurance capacity.[5] Type IIa fibers are intermediate and combine relatively high force development with relatively long endurance.[5] In general, type I fibers have the smallest cross-sectional area, and type IIb fibers tend to have the largest.

The respiratory muscles are mixed muscles containing both fast-twitch and slow-twitch fibers. The human diaphragm contains about 55 ± 5% type I fibers, 21 ± 6% type IIa fibers, and 23 ± 3% type IIx fibers. Other respiratory muscles (i.e., intercostal muscles, abdominal muscles, sternomastoids) contain at least 60% highly oxidative fibers.[6] No data are available on the scalenes. The respiratory muscles thus are generally well equipped to sustain continuous rhythmic contraction.

Morphological Characteristics of the Fibers

The respiratory muscles consist of muscle bundles oriented in a parallel fashion. These bundles consist of hundreds of muscle fibers, each of which in turn consists of hundreds of myofibrils. These myofibrils are made up of hundreds of sarcomeres arranged in series, each sarcomere consisting of a number of myosin (thick filaments) and twice the number of actin (thin) filaments. The capacity of the muscle to produce forces depends upon the number of myofibrils in parallel, since the forces developed by all these myofibrils are additive, whereas the displacement and velocity of shortening depend upon the number of sarcomeres in series. Indeed, the displacements of these sarcomeres arranged in series are additive.

The density of mitochondria in each of the four fiber types tends to be greater than in the same fiber types in limb muscles.[5,7] In addition, in humans, the diaphragm is composed of about 80% oxidative fibers compared with 36% to 46% in the limb muscles of untrained men.[5,7] As a consequence, the volume density of mitochondria in the diaphragm is twofold greater than in the limb muscles.[5,7] Therefore, the oxygen uptake capacity of the diaphragm is considerably greater than that of limb muscles because of the high oxidative fiber content and the greater mitochondrial density.[5,7] Moreover, the maximal blood flow also considerably

exceeds that of limb muscles because of the greater capillary density, which is about twice the capillary density in the limb muscle. The diaphragm is thus well equipped to sustain rhythmic contraction at rest through its type I and IIa fibers: The type IIa fibers permit additional recruitment in power and rate during exercise, and the few type IIx fibers permit high power outputs necessary for sneezing and coughing.

Motor Unit Organization

Muscle fibers are organized by their innervations in motor units that vary in their mechanical and fatigue properties. In adults, all muscle fibers within a motor unit are the same fiber type. The muscle fibers within a given motor unit are broadly dispersed throughout a region of the diaphragm. Dispersion occurs both horizontally across the surface of the diaphragm and vertically with fibers at different depths. The innervation ratio (number of fibers supplied by a single motoneuron) is approximately 400 in rat diaphragm[8] compared with an estimated value of 2500 in humans.[9] There are four types of motor units in the respiratory muscles: a motor unit with slower contraction times and resistance to fatigue (type S) and three types of motor units displaying faster contraction times, with various degrees of fatigue resistance. The type S comprises fibers that express the slow isoform of myosin heavy chain. Fast motor units that are fatigue resistant (type FR) comprise muscle fibers expressing the myosin heavy chain 2a; those that are highly fatigable (type FF) comprise muscle fibers expressing myosin heavy chain 2b; and those that are fatigue intermediate (type FInt) comprise muscle fibers that express the myosin heavy chain 2x. Motor units composed of fast fibers are large and develop forces in the range of 110 millinewton (mN). These, however, are considerably smaller than in limb muscles. Motor units composed of slow fibers are smaller and develop forces in the range of 30 to 60 mN. The recruitment pattern of the diaphragm follows the size principle with the smallest motor units being recruited first.

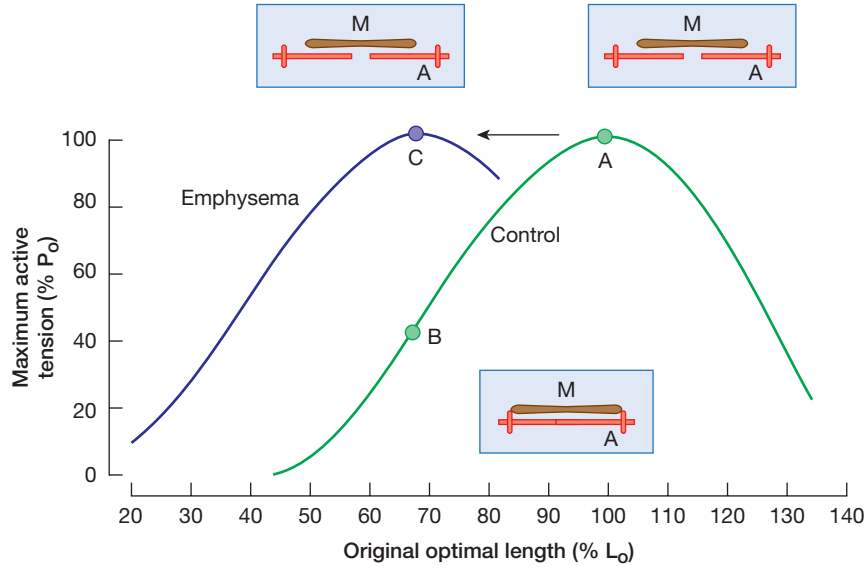

Figure 3-2 Diaphragmatic length–tension curve in normal hamsters and hamsters with elastase-induced emphysema. Tension is expressed as a percentage of maximum tetanic tension, P_o, and length is expressed as a percentage of original optimal length, L_o. The degree of filament overlap among actin (A) and myosin (M) filaments in control (**A**), acute (**B**), and chronic hyperinflation (**C**) is shown. Note that due to sarcomere adaptation in chronic hyperinflation, the degree of filament overlap is the same at a considerably shorter length. *(Reproduced with permission from Farkas G: Functional characteristics of the respiratory muscles. Sem Respir Crit Care Med. 1991;12(4):247–257.)*

■ FUNCTIONAL PROPERTIES

Functional properties of muscles are generally described in terms of force–length relationships, time-dependent characteristics of the twitch, force–frequency, force–velocity, and power–frequency relationships.

The force–length characteristics of the diaphragm are in essence similar to other muscles. Maximal tension is generated at the optimal length. Three aspects of the force–length curve of the diaphragm are potentially relevant to clinical medicine. First, with hyperinflation, the diaphragm shortens and its capacity to generate force is concomitantly reduced.[10] Second, when hyperinflation occurs chronically, adaptation occurs in the muscle. This adaptation consists of drop out of sarcomeres such that muscle shortening is then accommodated by a reduced number of sarcomeres rather than alterations in filament overlap within the sarcomeres.[11] As a consequence, the force-generating capacity is restored, at least in part, at foreshortened length.[10] This adaptation is summarized in Figure 3-2. The consequences of this adaptation to patients with hyperinflation are discussed in the section "Physiological Conditions Affecting Respiratory Muscle Interaction." Third, although less-than-optimal filament overlap is the primary reason for a reduction in force with muscle shortening, calcium deactivation due to T-tubular failure also plays a role.[12] This is potentially significant for treatment, since inotropic agents restore T-tubular function in foreshortened muscle.[13] Accordingly, inotropic agents exert much greater effects on foreshortened diaphragm than on diaphragm placed at its optimal length.[14] This concept opens up new perspectives for respiratory muscle pharmacotherapy in patients with severe hyperinflation. The length–tension curves of other respiratory muscles and their adaptation to hyperinflation have not been systematically studied.

A particularly interesting question is the relationship between the in situ operational length of the respiratory muscles and the optimal length in vitro. For the diaphragm, the length at functional residual capacity (FRC) comes close to the optimal length.[15,16] The length changes undergone by the diaphragm over the vital capacity range are large, 30% to 40%.[17,18] These length changes are considerably smaller for the parasternal intercostals, the scalenes, and the sternocleidomastoids.[19–21] For the parasternal intercostals, the length at FRC is clearly longer than optimal in supine dogs, so that with hyperinflation, the parasternal intercostals move toward their optimal length.[21,22] Subsequent experiments, however, indicate that the fall in pleural pressure caused by stimulation of the parasternal intercostals in dogs is reduced with increasing lung volume.[23] This discrepancy was shown to result from changes in orientation and motion of ribs with hyperinflation. The scalenes and sternocleidomastoids appear to operate on the ascending limb of their length–tension curves in supine dogs.[20] How hyperinflation in patients affects the force-generating capacity of these muscles remains unclear. According to an analysis, the changes in length during passive inflation are proportional to the mechanical advantage of a particular respiratory muscle.[24] In keeping with this analysis, the mechanical advantage of the diaphragm would be considerably greater than the mechanical advantage of other inspiratory muscles (see in the section "Physiological Conditions Affecting Respiratory Muscle Interaction").

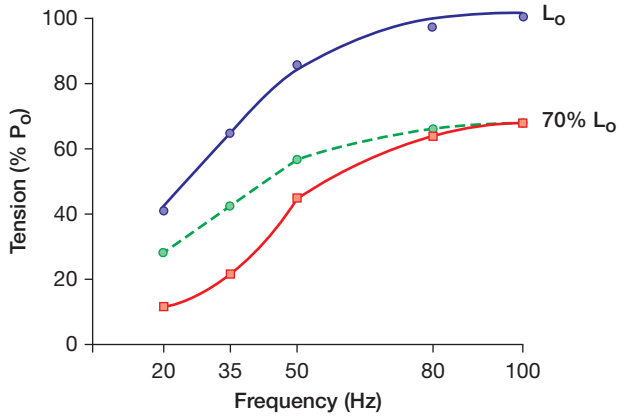

Figure 3-3 Force–frequency curve of human diaphragm at optimal length (L_0) and 70% L_0. Force is expressed as a percentage of maximal tetanic tension, P_0, and frequency is expressed in Hz. *Dashed line* is the predicted line at 70% L_0, whereas the *solid line* is the observed line. The predicted line is based on the assumption that a 30% change in length produces a 35% drop in force at all stimulation frequencies, as is observed for maximal tetanic force. Note that the decrease in force at lower stimulation frequencies is considerably greater than theoretically predicted. *(Reproduced with permission from Farkas G: Functional characteristics of the respiratory muscles. Sem Respir Crit Care Med. 1991;12(4):247–257.)*

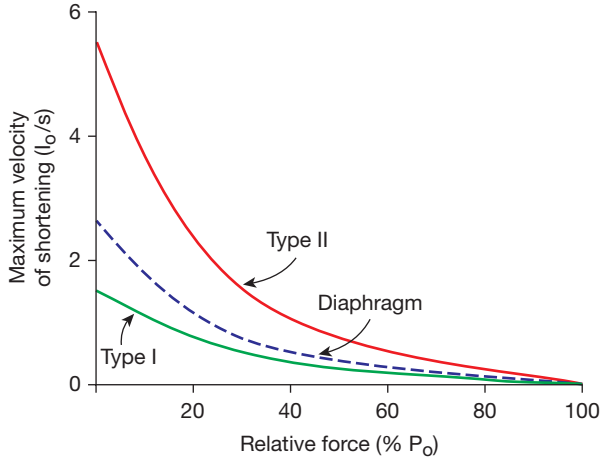

Figure 3-4 Force–velocity curve of human diaphragm *(dashed line)*, which is intermediate between the force–velocity curve of a typical slow muscle (type I) and a typical fast muscle (type II). Maximum velocity is expressed in optimal length (L_0), per second and relative force is expressed as a percentage of maximum tetanic force, P_0.

The force developed by a muscle increases with increasing frequency of stimulation. The increase in force is considerably steeper for a slow muscle in which fusion occurs at lower frequency because of the longer relaxation time than for a fast muscle. The diaphragm is intermediate, so that at in vivo stimulation frequencies (10–30 Hz), a fused tetanic contraction occurs. Particularly interesting is the effect of acute shortening on the force–frequency curve. Since acute shortening is associated with a downward shift of the force–frequency curve, the detrimental effect of acute shortening on the force-generating capacity of the diaphragm appears to be twofold.[10] With muscle shortening there is a clear reduction in maximal tetanic force. However, the decrease in force at submaximal stimulation frequencies is disproportionately greater (Fig. 3-3).

The force–velocity curve of the diaphragm is shown in Figure 3-4. With increasing loads, the velocity of contraction is reduced. The velocity of contraction is a direct function of myosin ATPase activity, and, hence, the force–velocity curve is primarily determined by the muscle fiber composition. The diaphragm is intermediate between the force–velocity curve of a fast and a slow muscle (Fig. 3-4).[6] The production of airflow into the lungs requires power output by the respiratory muscles. Power may be calculated as the product of the values of velocity and force according to the force–velocity relationship (Fig. 3-4). Instantaneous peak power occurs at 30% of maximal force and at 30% of maximal velocity. The frequency–isometric force relationship, frequency–shortening force, and frequency–power relationships show a similar dependency of force and power upon frequency of stimulation.

Fatigue also affects profoundly the force–length, force–frequency, force–velocity, and power–frequency characteristics of the diaphragm. The diaphragm, however, is more resistant to developing fatigue than limb muscles in vivo and in vitro.[25] Of note, the inspiratory muscles recover from fatigue 10 times faster than the elbow flexors performing a similar task.[26] The effects of fatigue on functional properties of the respiratory muscles are discussed in Chapters 84, 85 and 104. The factors determining the development of respiratory muscle fatigue are also discussed in these chapters.

ACTIONS OF RESPIRATORY MUSCLES

THE DIAPHRAGM

The diaphragm is the most important inspiratory muscle. It is innervated by the phrenic nerves supplied by the cervical nerve roots C3 to C5 in humans. It consists of two distinct parts, the costal and crural parts, which have separate actions on the rib cage, separate segmental motor innervations, and a different embryological origin. In respiratory activities, however, the diaphragm frequently operates as a functional unit, and in the following its action is described as such. Diaphragmatic action is schematically represented in Figure 3-5. Diaphragmatic contraction increases chest wall dimensions because of three distinct reasons. First, diaphragmatic descent increases the craniocaudal dimensions of the thorax. Diaphragmatic descent is tightly coupled to outward motion of the free abdominal wall.

Second, diaphragmatic contraction increases the dimensions of the lower rib cage because of the increase in abdominal pressure that it causes. This increase in abdominal pressure acts through the zone of apposition (i.e., the zone in which the diaphragm is immediately apposed to the rib cage) to expand the lower rib cage. This action is the appositional component of diaphragmatic action (Fig. 3-5).[27,28] The magnitude of the appositional component is determined by the magnitude of the zone of apposition, about 25% to 30% of the total internal surface area of the rib cage at FRC in standing humans, and by the magnitude of the increase in abdominal pressure caused by diaphragmatic contraction.[28]

Third, diaphragmatic contraction further increases lower rib cage dimensions because of its insertions into the lower rib cage. The diaphragmatic fibers are oriented axially, and their contraction causes pull on the lower rib cage in an axial direction, leading to cephalad motion and outward rotation of the lower rib and hence, to lower rib cage expansion. This is the *insertional component* of diaphragmatic contraction (Fig. 3-5).[27]

When the diaphragm acts in isolation during diaphragmatic contraction or pacing in high quadriplegics, in whom all inspiratory muscles, except for sternocleidomastoids, are paralyzed,[29,30] it exerts an expiratory effect on the upper rib cage during inspiration.[29,31] These data point out that in normal subjects, quiet inspiration is not accomplished by the diaphragm alone but rather results from the coordinated activity of the diaphragm with the rib cage inspiratory muscles and the abdominal muscles. Indeed, the pattern of chest

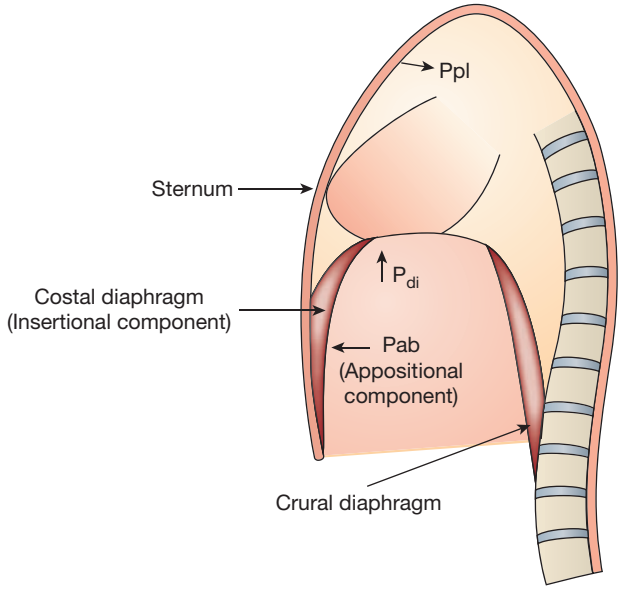

Figure 3-5 Diagram illustrating diaphragmatic action. Lateral view of the thorax. Ppl, pleural pressure; Pab, abdominal pressure; P_{di}, transdiaphragmatic pressure. The costal and the crural diaphragm are shown. See text for further explanation.

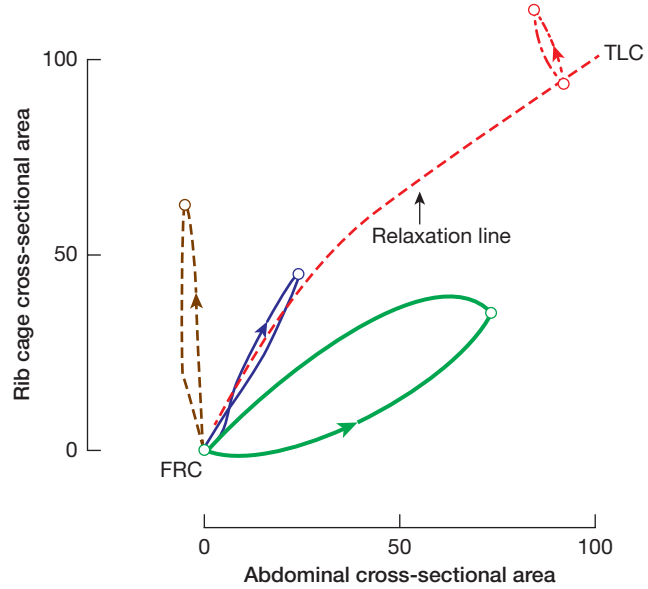

Figure 3-6 Konno–Mead diagram illustrating chest wall motion during quiet breathing *(thin loop)*, diaphragmatic pacing or quiet breathing in tetraplegic patient *(thick loop)*, breathing with diaphragm paralysis *(dash loop)*, and breathing at severely elevated end-expiratory volume *(dash–dot loop)*. Rib cage and abdominal cross-sectional areas are expressed as a percentage of inspiratory capacity. Dashed line is the relaxation line obtained during expiration with muscles relaxed.

wall motion in quadriplegics shown in Figure 3-6 indicates that diaphragmatic contraction alone cannot be responsible for the pattern of chest wall motion observed during quiet breathing (see in the section "Physiological Conditions Affecting Respiratory Muscle Interaction") and hence, that other muscles assist the diaphragm in moving the chest wall during quiet breathing.

■ THE INTERCOSTAL MUSCLES

The functional anatomy of intercostal muscles is schematically represented in Figure 3-7. Between the chondral portions of the ribs only one layer of intercostal muscles, the parasternal intercostals, is present. Between the osseous portions of the ribs, two layers are present. The outermost layer runs obliquely downward and forward and is called the *external intercostal*. The innermost layer runs obliquely downward and backward and is called the *internal intercostal* (Fig. 3-7, left panel). Note that the internal intercostals and parasternal intercostals have the same fiber orientation. Dorsally only an external intercostal is present. Finally, the fusiform muscle running from the lateral border of the transverse processes of the thoracic vertebra and inserting caudally into the rostral border of the rib below is called the levator costae (Fig. 3-7, right panel).

The parasternal portion of the intercostal musculature, the "parasternals," is consistently active during quiet breathing both in animal and human subjects,[19,32] and is the most important inspiratory portion of the intercostal musculature. The parasternal intercostals have the greatest mechanical advantage, and their contraction produces about 60% of the cephalad motion of the rib during inspiration.[33,34] Within the parasternal intercostals, the medial fibers have a greater mechanical advantage and are activated more consistently and before the middle and lateral fibers.[35]

The action as well as the respiratory role of the interosseus intercostals remain the subject of a longstanding debate. The most commonly accepted view on intercostal muscle action is based on a theory of intercostal muscle fiber orientation and rib geometry. This theory states that the external intercostals are inspiratory in action, and the internal intercostals are expiratory in action.[36] Numerous experiments do not fit with this theory, although a finite element analysis largely confirmed these actions.[36] It is commonly believed that the interosseus intercostals constitute a reserve system that may be recruited with increased ventilatory load. The external intercostals are recruited predominantly during inspiration, primarily in the upper interspaces, whereas the internal intercostals are recruited predominantly during expiration primarily in the lower interspaces.[36] Wilson et al.[34] demonstrated

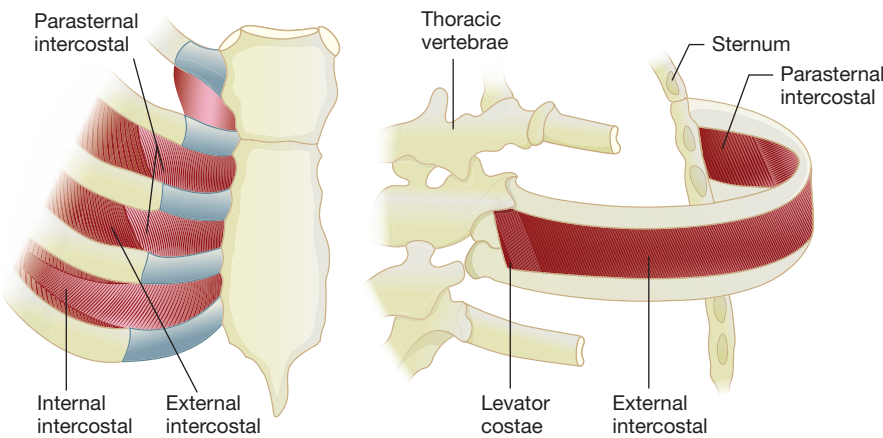

Figure 3-7 Diagram of the functional anatomy of the intercostal muscles, at their anterior *(left)* and posterior *(right)* aspects. Notice the parasternal, internal, and external intercostals, and the levator costae.

by the application of the reciprocity theorem of Maxwell, that the external intercostals in the dorsal portion of the costal interspaces have a large inspiratory mechanical advantage. This advantage decreases in the ventral and caudal directions such that in the ventral portion of the caudal interspaces it is reversed in an expiratory mechanical advantage.[36] Conversely, the internal intercostals in the caudal interspaces have a large expiratory mechanical advantage, but this advantage decreases in the cranial and ventral directions.[36] Because of this pattern of topographic distribution the pattern of neural activation is crucial for the function of these muscles.[36] This pattern was shown to match the pattern of distribution of mechanical advantage, such that the external intercostals have an inspiratory function and the internal intercostals have an expiratory function.[36]

Without question, the levator costae have an inspiratory action on the rib. It is frequently activated even during quiet inspiration in supine dogs.[37] The levator costae's contribution to inspiratory motion of the ribs during quiet breathing, however, appears substantially smaller than that of the parasternal intercostals. This contribution may further increase when the inspiratory motion of the ribs is appreciably increased.

THE SCALENES

The scalenes run between the transverse process of the five lower cervical vertebrae and the upper margin of the first (scalenus anterior) and second (scalenus medius and posterior) ribs. The action of these muscles is to raise the first two ribs. The orientation of their axis in the neck causes upward motion of these ribs ("pump handle" motion). Moreover, the scalenes are consistently active during quiet breathing in normal individuals and contribute to chest wall expansion.[38] They may be very important in the case of spinal cord injury. When the injury is below C4 to C8, the scalenes' function is entirely or partially preserved, and they contribute importantly to upper rib cage motion in these patients.[39]

THE STERNOCLEIDOMASTOIDS

The sternocleidomastoids run between the mastoid processes of the temporal bone and the manubrium sterni and medial portion of the clavicle. The pressure-generating ability of the sternocleidomastoid muscle in normal humans is about the same as that of the scalene muscles. In humans, these muscles are electrically silent during quiet breathing, but they may be recruited with increased ventilatory load. These muscles are particularly important in high quadriplegics in whom they preserve their function because they are innervated by the 11th cranial nerve and spinal nerves C1 to C2.[29,40] Through training the sternocleidomastoids may develop marked hypertrophy and contribute to several hours of ventilator independence in these patients.[40] They also may be recruited in patients with poliomyelitis and diaphragmatic dysfunction. These muscles are thought to be important in moving the upper rib cage in patients with chronic obstructive pulmonary disease (COPD), even though a clinical experimental study failed to demonstrate consistent activity in these muscles in these patients.[41]

THE SHOULDER GIRDLE AND NECK MUSCLES

Several shoulder girdle and neck muscles may contribute to inspiration under particular circumstances. Most of these muscles run from the rib cage to an extrathoracic extension. When the rib cage is fixed in the lean-forward position—a position commonly employed by patients with COPD—these muscles contribute to expansion of the rib cage during inspiration. Muscles that may contribute to inspiration include the trapezius, latissimus dorsi, pectoralis major and minor, erector spinae, teres major, serratus anterior, platysma, mylohyoid, and sternohyoid. Since these muscles commonly contribute to inspiration in patients with severe airflow obstruction, their further use for other activities (e.g., hair combing), may considerably increase dyspnea in these patients.[42]

THE CLAVICULAR HEAD OF PECTORALIS MAJOR

The clavicular head of the pectoralis major runs laterally and caudally from the medial half of the clavicle and manubrium sterni to the humerus. If the arms are fixed and braced, contraction causes downward motion of the ribs and sternum, increase in pleural pressure and, hence, expiration. Simultaneously, the lower rib cage and the abdomen move outward. Tetraplegics use this expiratory action when all other expiratory muscles are paralyzed.[43]

THE TRIANGULARIS STERNI

The triangularis sterni is the most important expiratory muscle of the rib cage.[44] The muscle runs at the inside of the thorax between the inner aspect of the sternum and the inner aspect of the five lower ribs (Fig. 3-8), and its action is to lower the ribs relative to the sternum and thus to cause expiration. The triangularis sterni is electrically silent in humans breathing quietly,[44] but it is recruited during expiration below FRC.[44] Its neural activation is also coupled with that of the abdominal muscles.[44] Its recruitment threshold is low, lower than the recruitment threshold of most other expiratory muscles.

THE ABDOMINAL MUSCLES

The abdominal muscles are composed of four different muscle layers (Fig. 3-1). Ventrally, a muscular sheet running between the lower costal cartilages and the sternum and the pubis, represents the rectus abdominis. This muscle is enclosed in a sheath formed by the aponeuroses of the other three muscles. Laterally, an oblique muscle runs obliquely downward and forward between the lower eight ribs and the iliac crest, inguinal ligament, and linea alba medially, the external oblique. At the inner surface of this muscle lies the internal oblique with a fiber orientation, which is 90 degrees perpendicular to the external oblique. These muscles are homologous to the external and internal intercostals. The innermost layer is the transversus abdominis, a circular muscular sheet surrounding the abdomen, with a fiber orientation that is parallel to the ribs. The transversus abdominis originates from the inner surface of the lower six ribs, where it interdigitates with the costal insertions of the diaphragm. It runs from this origin and the lumbar fascia, iliac crest, and inguinal ligament,

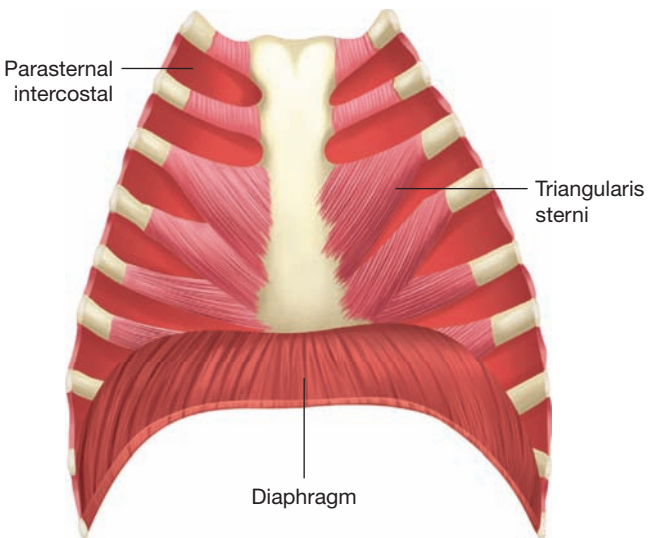

Figure 3-8 Diagram illustrating the functional anatomy of the parasternal intercostal muscles, the triangularis sterni, and the diaphragm.

circumferentially around the abdominal visceral mass to terminate ventrally in the rectus sheet. These muscles all have an expiratory action, by virtue of the inward pull of the abdomen they cause and of the insertions they have in the rib cage. In addition, however, rib cage expansion may occur with contraction of some of these muscles through the increase in abdominal pressure accompanying their contraction.[45]

The abdominal muscles are electrically silent during quiet breathing. Usually, however, tonic activity is present in the abdominal muscles in upright position, particularly in the upper segments.[27] During inspiratory loading, CO_2-induced hyperventilation, exercise, and forced expiration, these muscles are recruited. The transversus abdominis appears to have the lowest recruitment threshold.[46,47]

RESPIRATORY MUSCLE INTERACTION

RESPIRATORY MUSCLE INTERACTION DURING QUIET BREATHING

Respiratory muscle interaction is traditionally studied by means of a Konno–Mead diagram, relating rib cage diameter or cross-sectional area to abdominal diameter or cross-sectional area (Fig. 3-6). First, this relationship is determined in the absence of muscle contraction, during a relaxed expiration, yielding a relaxation line. During quiet breathing in the upright position, the chest wall moves along this relaxation line, which means that proportional expansion of rib cage and abdomen is occurring. In the supine position, abdominal movement is proportionally greater than rib cage movement. Since isolated diaphragmatic contraction in quadriplegics causes abdominal movement without rib cage motion or even inward movement of the upper rib cage (upper rib cage paradox), diaphragmatic contraction alone cannot be responsible for the pattern of motion occurring during quiet breathing (Fig. 3-6). Therefore, this motion requires concomitant contraction of other muscles (i.e., the parasternal intercostals and scalenes). These muscles actively contribute to chest wall motion and cause upper rib cage expansion, whereas diaphragmatic contraction alone would cause upper rib cage paradox. During quiet breathing, the diaphragm probably contributes about 60% to 70% of the tidal volume, and the parasternal intercostals and scalenes contribute the rest.[48]

Posture alters the interaction between the respiratory muscles. For the diaphragm, the resistance of the abdominal contents on diaphragmatic descent is the principal determinant of its action on the rib cage. When changing from a seated to a supine posture in humans, there is a marked increase in abdominal compliance[49] and changes in the diaphragm shape result in less rib expansion. The influence of posture on the lung-expanding action of the diaphragm has been confirmed in patients with upper cervical cord transaction. Indeed, when these patients were supine, the paced diaphragm was able to generate an adequate tidal volume but the latter was progressively and markedly reduced when the patients were gradually tilted head up.[29] The abdominal muscles[50,51] and also the triangularis sterni[44,52,53] are silent in the supine posture in healthy individuals and while the tonic activity of the abdominal muscles in the standing posture is not related to the phases of the respiration, the activity of the triangularis sterni is confined to expiration.[53] Active use of these two sets of expiratory muscles in the standing posture compensates for the adverse effect of this posture on the inspiratory muscles, in particular the diaphragm.

Sleep affects respiratory muscle function negatively but in healthy individuals these physiological changes are not clinically significant. Sleep is associated with a generalized postural muscle hypotonia that is most profound during the phasic events of rapid eye movement (REM) sleep.[54] Therefore, respiratory muscles with a dual respiratory and postural function like the intercostals lose activity during REM sleep whereas the diaphragm, a muscle with only a respiratory function, maintains and even increases its activity to maintain tidal volume during REM sleep.[55] In severe COPD patients where rib cage motion is mainly produced by the inspiratory muscles of the rib cage as the diaphragm is mechanically impaired by hyperinflation, the substantial decrease in the activity of the scalene and sternocleidomastoid muscle during REM sleep is expected to decrease inspiratory pressure development and to lead to hypoventilation.[56]

PHYSIOLOGICAL CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction present during quiet breathing and the chest wall motion resulting from it may be altered in a number of physiological circumstances in which ventilatory load is affected. Indeed, the respiratory muscles participate in tasks that, although not strictly ventilatory in nature, serve important respiratory functions. These tasks of daily life include speech, laughter, swallowing, gagging, vomiting, and coughing. In addition, the interaction of the respiratory muscles is also modified during nonventilatory tasks.

Speech and laughing require the coordination of respiration and structures involved in producing sound features. Spontaneous speech occurs primarily at volume levels below spontaneous end expiration.[57] There is, therefore, a successive recruitment of muscles of expiration to empty the rib cage: first the triangularis sterni muscle[44,57] and the internal intercostal muscles then the external oblique and other muscles of the lateral abdominal wall and finally the rectus abdominis.[46,58,59] At the very end of expiration, the latissimus dorsi is active too.[58,59] Abdominal contraction during speech can optimize the inspiratory function of the diaphragm obliged to contract rapidly between phrases, and will also prevent dissipation of the pressure developed by the rib cage muscles on paradoxical abdominal displacement.[57]

Laughing is a natural maneuver triggered by emotion necessitating the coordination of the laryngeal and respiratory systems to produce a characteristic sound pattern and phasic lung pressure variations superimposed on an active expiratory effort. Laughter generally takes place when lung volume is low, near FRC and is terminated near residual volume.[60] It is characterized by sudden repetitive expiratory efforts leading to a decrease in lung volume due to sudden and sustained increase in gastric and esophageal pressures. The triangularis sterni muscle is recruited during laughing.[44] Higher transdiaphragmatic pressure at the end of the consecutive expiratory efforts indicates that the diaphragm actively prevents part of the increase in abdominal pressure from being transmitted to the chest wall cavity, thereby protecting intrathoracic structures from further mechanical stress and compression.[60] A pilot study suggests that the pattern of diaphragm activation during laughter is different from that induced by coughing or sneezing.[61]

For swallowing, respiration needs to be interrupted. During swallowing, the passive expiration of the diaphragm is interrupted by static activity aimed at preserving respiratory volume for expiration after swallowing.[62] Abdominal activity increases throughout pre- and postswallowing expiration.[62]

Vomiting that is produced by changes in thoracic and abdominal pressures is generated by the coordinated action of the major respiratory muscles. During vomiting, the diaphragm and the external instercostal (inspiratory) muscles cocontract with abdominal (expiratory) muscles in a series of burst of activity that culminates in expulsion while the internal intercostal (expiratory) muscles contract out of phase with these muscles during retching and are inactive during expulsion (see review by Miller[63]). Finally, the portion of the diaphragm surrounding the esophagus relaxes during expulsion, presumably to facilitate rostral movement of the gastric content (see review by Miller[63]).

Coughing, sneezing, and gagging represent complex acts involving both inspiratory and expiratory phases during which most of the respiratory muscles are recruited. Importantly, during those

maneuvers, the maximal diaphragm force is reached.[64,65] Voluntary cough in humans is associated with a coordinated activation of the expiratory and accessory muscles. A graded increase in activity and burst duration proportional to cough flow rates is observed. Low cough flow rates are essentially produced by the activation of the expiratory muscles whereas accessory muscles become involved sequentially and increasingly with the production of higher flow rates.[66] The triangularis sterni muscle is actively recruited during coughing[44,67] and also during sneezing.[67]

Finally, understanding the level of muscle recruitment may be particularly relevant when testing respiratory muscle force to evaluate the degree of impairment in some diseases. Indeed, in untrained normal subjects, maximal inspiratory effort against a closed shutter (Müller maneuver or the maximal inspiratory pressure) mainly activates the intercostal muscle and the diaphragm as well as the sternomastoid.[68] The same holds true for the sniff maneuver through the nose.[68] The combined maneuver consisting in a maximal inspiratory maneuver combined with a maximal expiratory effort activates also the expiratory muscles (rectus abdominis) and produces the highest level of diaphragmatic strength as assessed by measuring transdiaphragmatic pressure.[68] The maximal electrical activity of the diaphragm is reached during the sniff maneuver.[68] These data indicate that the pressure generated by these maneuvers reflects a complex interaction between several groups of muscles.

All the above-mentioned effects pertain to ventilatory aspects of the respiratory muscles but, in addition to their respiratory role, the respiratory muscles also contract during postural tasks. The costal and the crural diaphragm are active with a single rapid movement of the contralateral upper limb in humans.[69] Electromyographic activity of the diaphragm increases prior to the onset of the activity of the muscle responsible for movement. This occurs irrespective of the phase of respiration[69] and is associated with an increase in transdiaphragmatic pressure with an initial reduction in length of the costal diaphragm. Similarly, during trunk rotation external and internal intercostal muscles show increased inspiratory activity superimposed on their postural tone[70,71] as do the parasternal intercostals.[72] During repetitive movement, the diaphragm contracts tonically throughout the respiratory cycle and phasic modulation of diaphragm activity at the frequency of limb movement is superimposed on its respiratory and tonic activation.[73] This was also observed in the transversus abdominis muscle.[73] Modulation of the intra-abdominal pressure that occurs through coordinated activity of the diaphragm, abdominal and pelvic floor muscles, may be important for the control of spinal stability when the limbs move.[69,73] When respiratory demand is increased, the activity of the diaphragm and the transversus abdominis associated with movement of an arm is reduced or even abolished, and the associated changes in gastric pressure are reduced.[74] In humans, the postural role of the diaphragm may also be impaired with specific fatigue of the inspiratory muscles.[75] The human triangularis sterni muscle also contracts during postural maneuvers such as head flexion, trunk rotation, and leg lift.[44]

PATHOLOGICAL CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction is profoundly affected by a number of pathological conditions including hyperinflation, reduced or loss of muscle activity.

Hyperinflation is a functional abnormality of lung diseases in which airflow obstruction or loss of elastic recoil are features. Hyperinflation may be particularly severe in patients with COPD, in whom the FRC often exceeds predicted total lung capacity (TLC). An overwhelming amount of evidence shows that hyperinflation reduces the diaphragmatic effectiveness as a pressure generator and reduces diaphragm contribution to chest wall motion. The contribution of the intercostal muscles and scalenes is likely to be increased, such that chest wall motion becomes exclusively or predominantly rib cage motion (Fig. 3-6). The ineffectiveness of the diaphragm may result from diaphragmatic shortening, geometrical alterations, alterations in diaphragm–rib cage interaction, alteration in mechanical arrangements among the costal and crural parts of the diaphragm, reduction in the zone of apposition.[76] Among these, diaphragmatic shortening appears to be the most important. Indeed, with inflation from FRC to TLC, the diaphragm shortens about 30% to 40%,[17,18] whereas the parasternal and upper external intercostal muscles shorten by only 10%,[19,77] the scalene by 2%,[78] and the sternomastoid muscle by 6%.[78] For the diaphragm, this shortening is expected to reduce significantly its pressure-generating capacity. Several studies indicate that diaphragmatic geometry is not affected significantly by hyperinflation, pointing out that the length–force properties of the diaphragm represents the most important factor for the pressure-generating capacity of this muscle.[79,80] The appositional component of diaphragmatic action is reduced substantially due to a reduction in the zone of apposition.[28] The insertional component is affected so that diaphragmatic contraction causes inward retraction of the lower rib cage. This may be noticed clinically in patients with severe hyperinflation.[81,82] The mechanical arrangement between the costal and crural parts of the diaphragm changes from a parallel arrangement at FRC to a series arrangement at TLC.[17] This is likely to further compromise the pressure-generating capacity of the diaphragm independently of its force–length characteristics.

Hyperinflation also impairs the pressure-generating capacity of the inspiratory intercostal muscles (the parasternals and the external intercostals). This effect is mainly related to the orientation and motion of the ribs.[23] The synergistic interaction between the diaphragm and the inspiratory intercostal muscles becomes prominent at high lung volumes.[23] The force-generating capacity of the neck muscles like the scalene and the sternomastoid muscle is maintained with hyperinflation.[78] In dogs, hyperinflation induces lengthening of the abdominal muscles, particularly the transverse abdominis and internal oblique muscle.[83] Consequently, the rise in abdominal pressure obtained by selective stimulation of the abdominal muscles at TLC is greater than that obtained at FRC.[84] This also happens in normal humans during magnetic stimulation of the abdominal muscles.[83]

It should be emphasized, however, that the above pertains to acute hyperinflation. In chronic hyperinflation, the diaphragm adapts to the chronically foreshortened state by dropping out of sarcomeres.[11] As a consequence, the filament overlap within each sarcomere is restored toward optimal overlap. This adaptation is shown in Figure 3-2. This adaptation, however, only partially restores diaphragmatic function. First, because part of the reduction in force with shortening is due to compression of the T-tubular system, blocking exit-electrolyte flow and impeding excitation–contraction coupling.[12] Whether adaptations in T-tubular function also occur with chronic foreshortening remains to be investigated. Second, sarcomere adaptation adapts only to the loss in diaphragmatic function associated with diaphragmatic shortening and not to the loss in function due to geometrical alterations, alterations in diaphragm–rib cage interaction, changes in mechanical arrangement among different parts of the diaphragm, or loss of zone of apposition. Third, although sarcomere adaptation restores the force-generating capacity of a foreshortened diaphragm, it reduces the number of sarcomeres in series. Consequently, sarcomere adaptation compromises the capacity of the diaphragm to undergo changes in length and, hence, its capacity to produce volume changes, presumably its most important function. The fiber length of the parasternal intercostal muscles[85] and of the scalenus muscle[86] are, however, not affected by chronic hyperinflation in animals.

Interventions aimed at reducing hyperinflation such as lung volume reduction surgery (LVRS) and lung transplantation improve diaphragmatic function. The effects of LVRS are primarily due to an increase in the zone of apposition, lengthening of the diaphragm,

and improved neuromechanical coupling.[87] To what extent complete sarcomere adaptation is present in patients with COPD and extreme hyperinflation is not clear from the clinical studies with LVRS. After lung transplantation the radius of curvature and the zone of apposition of the diaphragm are also restored. This is primarily due to mediastinal displacement toward the graft.

Expiratory muscle recruitment is frequently observed in COPD patients with severe airflow obstruction.[88] The transversus abdominis is frequently recruited. Expiratory muscle recruitment may contribute to the intrinsic positive end-expiratory pressure ($PEEP_i$) that is frequently observed in these patients. $PEEP_i$ is primarily caused by impaired pulmonary mechanics and consequent dynamic hyperinflation. The functional significance of this expiratory muscle activation is poorly understood. Indeed, in severe airflow obstruction, expiratory flow limitation is frequently present. In the presence of expiratory flow limitation, recruitment of expiratory muscles no longer contributes to expiratory flow.

In patients with pulmonary disease in general and COPD in particular, several factors may contribute to generalized muscle weakness, in which the respiratory muscles partake. These include hypoxemia and hypercapnia, malnutrition, cardiac failure, corticosteroid treatment, infection, electrolyte disturbances, and inactivity with consequent disuse atrophy. A recent study demonstrated that COPD exacerbations contribute to the development of this muscle weakness. Of particular importance appears to be treatment with corticosteroids in repetitive bursts, which is often inadvertently administered to COPD patients. Typically this causes a myopathic pattern characterized by scattered necrotic fibers with an increased number of central and subsarcolemmal nuclei, and generalized muscle fiber atrophy as seen on muscle biopsy[89] instead of selective type IIb fiber atrophy as is seen in animal studies.

The continuous patterns of motor activity associated with respiration make the diaphragm the most active muscle in the body. The daily duty cycle (ratio of active to inactive time) of the diaphragm in most species is about 45% compared to 2% for the extensor digitorum muscle (predominantly composed of type IIb fibers) and 14% for the soleus muscle (mainly a type I muscle).[90] Given the diaphragm is highly active, it is expected to be particularly sensitive to inactivity. It is therefore not surprising that serious diaphragm dysfunction develops rapidly during controlled mechanical ventilation, a situation in which the diaphragm is totally inactive.[91–93] Perturbations in respiratory muscle interaction are also marked in patients with cervical spinal cord injuries. In these patients, the intercostal and abdominal muscle contribution to respiratory function is lost. Diaphragm inspiratory capacity is also often compromised when injury is located at the C3 to C5 levels. During quiet breathing, tetraplegic subjects with injuries at C4 to C7 use their scalene[39,94] that becomes hypertrophied.[94] Patients with high tetraplegia use several neck muscles[40] in addition to the sternocleidomastoids and trapezii to breathe.[29] Quadriplegics are also predisposed to the development of inspiratory muscle fatigue because of reduced muscle strength and endurance.[95] Inspiratory muscle training in these patients increases both strength and endurance and protects against fatigue.[95] Diaphragm contracting alone through phrenic nerve pacing in subjects with upper cervical cord transaction or during spontaneous breathing in subjects with traumatic lower cervical cord transaction exerts both an expiratory action on the upper rib cage and an inspiratory action on the lower rib cage.[29,31,39] Finally because abdominal and expiratory rib cage muscles are paralyzed in subjects with tetraplegia, their ability to raise intrathoracic pressure is markedly reduced. Despite active use of the clavicular portion of the pectoralis major to deflate the rib cage during forced expiration,[43,96,97] cough is ineffective and the clearance of airway secretion is markedly impaired. Strength training of the pectoralis major improves expiratory function,[98] an effect that is expected to increase the effectiveness of coughing that might reduce the prevalence of bronchopulmonary infections in these subjects.

CONCLUSIONS

The act of breathing requires the coordinated action of a number of muscle groups. During quiet breathing, chest wall motion results from the action of the diaphragm but also from the other inspiratory muscles such as the parasternal intercostals and the scalenes in addition to the expiratory muscles. Those respiratory muscles are all well equipped to sustain continuous rhythmic contraction. Respiratory muscle interaction is affected by posture and sleep but also in a number of physiological circumstances in which ventilatory load is altered such as during speech, laughter, swallowing, gagging, vomiting, and coughing. In addition to their respiratory role, the respiratory muscles also contract during postural tasks such as limb muscle movement, leg lift, trunk rotation, and head flexion. Finally, several pathological conditions including hyperinflation, reduced or loss of activity caused by undernutrition, medical treatment (in particular corticosteroids), mechanical ventilation, or spinal cord injury may also affect the function and the interaction of the respiratory muscles. Strategies consisting in reducing hyperinflation (e.g., LVRS, lung transplantation), or improving muscle function through muscle training may help to some extent restoring respiratory muscle function.

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CHAPTER 4

Molecular Regulation of Lung Development

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INTRODUCTION

This chapter focuses on the mechanisms that control the development of the respiratory tract from the specification of lung endoderm and tracheal progenitors to the formation of the bronchial tree and the alveolar region. Based essentially on histological criteria lung development can be described in four stages: *(a) Pseudoglandular*: Corresponding to the period of formation of the bronchial tree through branching morphogenesis, the lung exhibits a gland-like morphology with epithelial tubules separated by a thick mesenchymal layer; *(b) Canalicular*: Branching is nearly finished and distinct columnar and cuboidal epithelial cells are seen in proximal (large) and distal (small) airways, respectively. Epithelial tubules are separated by a thinner mesenchyme containing blood vessels; *(c) Saccular*: Primitive saccules are seen at the distal end of bronchial tree with widening of the lumens and the appearance of type I (flat-shaped) and type II (cuboidal, surfactant-producing) cells. The intimate approximation of the type I cell to the vascular structures (primitive alveolar–capillary barrier) allows gas exchange during the immediate postnatal period; *(d) Alveolar:* Primitive saccules undergo septation to form numerous smaller mature alveolar structures to increase gas exchange surface.[1,2]

The development of the respiratory system encompasses prenatal and postnatal life, although timing and duration of specific events vary among species. Lung development starts much earlier in humans than in mice and rats; alveolar formation initiates in the human lung by late gestation in contrast to the murine lung, in which alveolization is a postnatal process (see comparison in Fig. 4-1).

HOW RESPIRATORY PROGENITORS ARISE

The lung originates from the anterior portion of the gut tube (foregut), which also gives rise to organs, such as the thyroid, stomach, liver, and pancreas. Respiratory progenitors of the lung and trachea arise from the ventral foregut endoderm in mice at around embryonic day 9 (E9.0, midgestation) and in humans around the 3rd week of gestation. Studies in mice show that these cells can be readily recognized even before a lung primordial bud forms by the expression of Nkx2–1 (Ttf1, thyroid transcription factor 1); this gene, however, is not lung specific and also labels progenitor cells of the thyroid seen in more anterior (cranial) regions of the foregut (Fig. 4-2A).[3] Nkx2–1 is essential for lung cell fate as disruption of this gene in mice results in severe inhibition of branching and no evidence of epithelial cells expressing surfactant protein or other differentiation marker genes typically found in the lung.[3] Questions remain whether in these mutants lung progenitors are never specified or just cannot be maintained in the absence of Nkx2–1. How are these progenitors specified? There is strong evidence that Fgf and Wnt signaling play a key role in this process. Studies in organ culture suggest that Fgf2 at high concentrations is able to induce lung cell fate in the early foregut endoderm.[4] High levels of Fgf1 and 2 are found in the cardiac mesoderm immediately adjacent to the ventral foregut endoderm (Fig. 4-2A). These observations suggest a model in which high levels of Fgfs diffusing from the developing heart induces Nkx2–1-expressing lung progenitor cells.[4] Interestingly, canonical Wnt pathway is also required for lung specification. Both Wnt2 and Wnt2b are present in the foregut mesoderm at the prospective site of lung formation. Loss of canonical Wnt or their ligands prevents the appearance of Nkx2–1-expressing cells.[5,6] Moreover, there is a role for Bmp signaling in the maintenance or expansion of Nkx2–1-expressing lung progenitors.[7]

FORMATION OF THE LUNG AND TRACHEAL PRIMORDIA

Once the Nkx2–1-expressing progenitor cells are specified in the prospective lung region of the foregut, they are subsequently expanded to generate the tracheal and the lung primordia. The primordial lung is identified in human embryos at the beginning of gestation (around the 4th week), much earlier compared to mice (midgestation at E9.5). The two primordial lung buds arise as lateral outgrowths of the ventral foregut endoderm and fuse at the midline, the site where tracheal primordium also starts to form (Fig. 4-2B–D). From then on, the trachea and the digestive tube separate through a mechanism still poorly understood that involves formation of a tracheoesophageal septum.[8,9] Primary lung bud formation is crucially dependent on the local expression of Fgf10 (fibroblast growth factor 10) in the foregut mesoderm.[10,11] Fgf10 diffuses to the nearby endoderm at the prospective lung region and activates Fgfr2b signaling in Nkx2–1-expressing progenitor cells leading to epithelial proliferation and migration toward the Fgf10 source.[12,13] Fgf10-null mice die at birth and have multiple defects. Strikingly, lungs do not form but tracheal development occurs.[10,11] This raises the possibility that tracheal and lung progenitors, although originating from a population of Nkx2–1-expressing endodermal cells, are different at least in their requirement for Fgf10 signaling for expansion or survival.

How is the expression of Fgf10 controlled? How is positioning of the lung primordium along the anteroposterior (AP) axis of the foregut determined? There is accumulated evidence that signaling

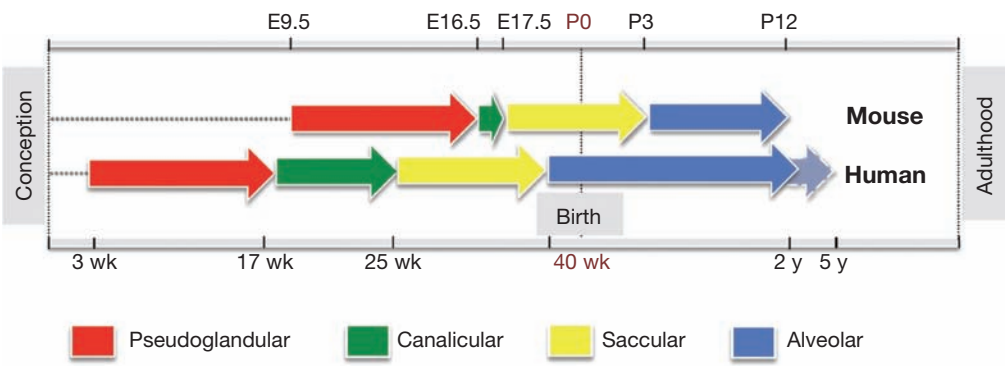

Figure 4-1 Timeline for the developmental stages of mouse and human lungs. Mouse (E, embryonic; P, postnatal days); humans (wk, gestation week; y, year).

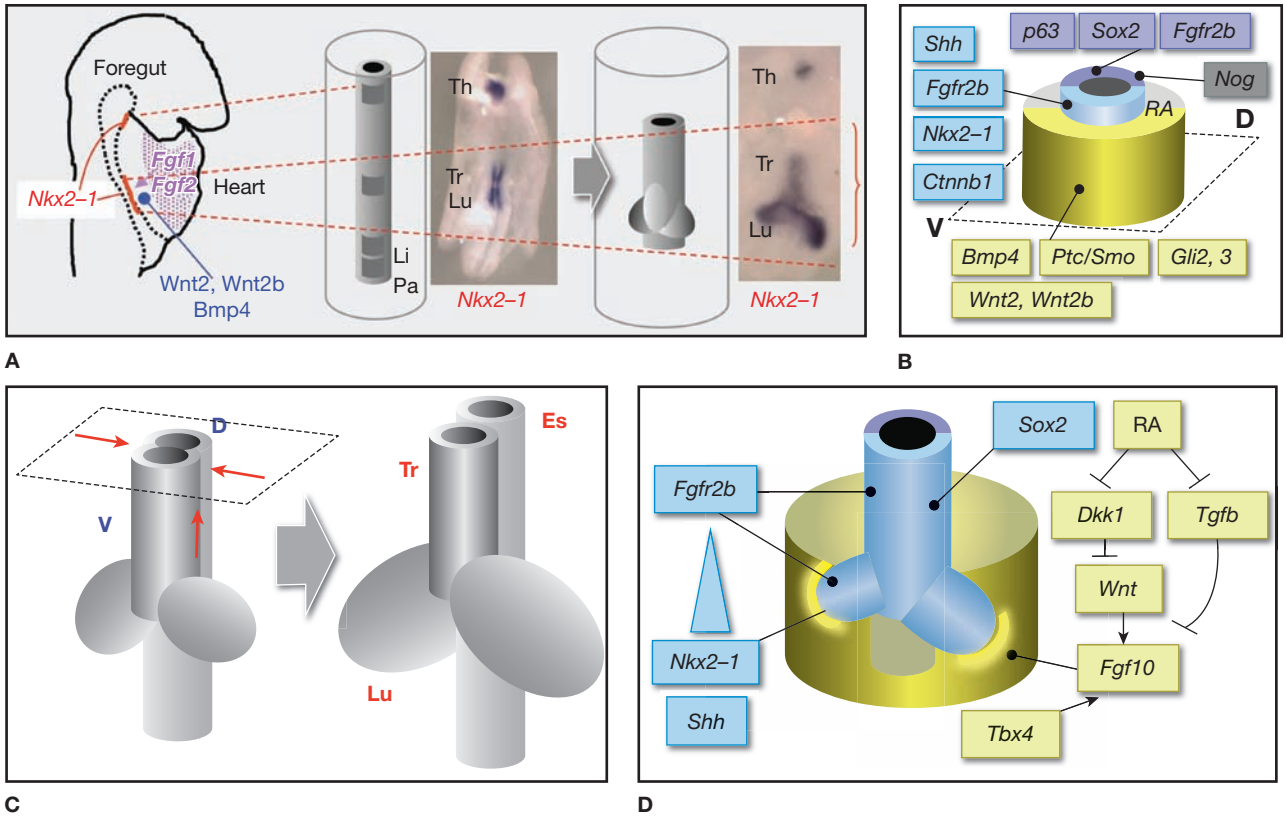

Figure 4-2 Regulation of early lung and tracheal development. **A.** Specification of respiratory progenitors in the foregut by Fgfs *(purple)* from the heart (*red*, Nkx2–1-expressing endoderm) and Wnt2, 2b from foregut mesoderm; expansion of these progenitors initially by Bmp4 signaling. Nkx2–1 ISH labeling respiratory progenitors (Tr, Lu) in the mid foregut endoderm and in the thyroid (Th) primordium of mouse embryos at E9.0 (no signal in the Li, liver and Pa, pancreatic fields). At E9.5, these Nkx2–1-positive cells give rise to the tracheal primordium and primary lung buds. **B.** Ventral–dorsal (V–D) differences in gene expression in the foregut at the onset of lung development. **C.** V–D foregut patterning and tracheoesophageal separation (Es, esophagus). **D.** Regulation of primary lung bud formation in the foregut: Gene network in the mesenchyme *(yellow)* and epithelium (*blue*; highest levels of Nkx2–1 and Shh in the distal bud).

by the vitamin A–derivative retinoic acid (RA) is a major regulator of Fgf10 expression at the onset of lung development.[14] RA synthesis and RA receptor (RAR) activity is prominent in the E8.5–9.5 mouse foregut.[15] Disruption of RA signaling by vitamin A deficiency, or genetic disruption of key components of the RA pathway, or RA antagonists in organ cultures leads to multiple developmental abnormalities, including lung agenesis.[14,16–18] RA integrates multiple pathways in the foregut to regulate primary lung bud morphogenesis. RA signaling in the foregut mesoderm allows activation of the Wnt pathway by suppressing expression of the Wnt inhibitor Dkk1 (Dickkopf-1)[19]; RA also inhibits Tgfβ signaling.[20] The balanced activity of Wnt and Tgfβ leads to proper mesodermal Fgf10 expression required for formation of the lung primordium (Fig. 4-2D). Thus, the disruption of Wnt/Tgfβ/Fgf10 interactions is likely to represent the molecular basis for the failure to form the lung classically reported in vitamin A deficiency. The role of Wnt in the expression of Fgf10 is further supported by the lack of Fgf10 expression in the lung field mesenchyme of foregut in Wnt2a/Wnt2b double null mice.[5]

Other essential regulators of early events associated with the lung primordium are T-box (Tbx) and Gli transcription factors (Fig. 4-2B–D). Multiple T-box genes are expressed in the foregut and particularly Tbx2–Tbx5 have been reported in the developing lung mesenchyme.[21] Studies in chick embryo show that Tbx4 is expressed in the foregut mesoderm at the domain where Fgf10 induces lung bud formation; Tbx4-Fgf10 appear to regulate the posterior boundary of Nkx2–1-expressing lung progenitors.[22] Genetic studies in mice showed a dose-dependent activity of Tbx4 and Tbx5 in regulating primary bud formation, likely through regulation of Fgf10 and Wnt.[23] Gli 1, 2, 3 are known transcriptional effectors of the sonic hedgehog (Shh) signaling detected early in the foregut mesoderm and subsequently in the lung mesenchyme.[24] Disruption of both Gli2 and Gli3 in mice results in dramatic abnormalities that include abrogation of both tracheal and lung primordium.[25] This intriguing phenotype is more severe than that observed in Shh-null mice and thus may represent a disruption of additional Gli-dependent pathways critical for the primary lung buds.[26]

VENTRAL–DORSAL (V–D) PATTERNING AND TRACHEOESOPHAGEAL SEPARATION

Differences in V–D cell fate are already obvious in the prospective lung region of the foregut (Fig. 4-2B) as the ventral endoderm expresses Nkx2–1 (respiratory progenitors) while the dorsal region (prospective esophagus) expresses Sox2 (SRY-box containing gene 2) and the p63.[3,27,28] Epithelial disruption of Sox2 leads to ectopic dorsal expansion of the Nkx2–1 domain and respiratory fate in the esophagus.[27] The Bmp (Bone Morphogenetic Protein) pathway is also important for V–D patterning. Bmp4 is expressed in the ventral foregut mesenchyme prior to and during the emergence of primary buds while its antagonist Noggin is localized to the dorsal endoderm.[7] Conditional deletion of both Bmpr1a and Bmpr1b

receptors leads to expansion of a dorsal cell population marked by Sox2 at the cost of the ventral population of Nkx2–1 positive cells. Interestingly this results in tracheal agenesis and formation of lung buds ectopically.[7] Noggin has been proposed to protect the dorsal endoderm from the ventralizing effects of Bmp4.[29]

As the lung and tracheal primordia form, a tracheoesophageal septum extends from the posterior to the anterior region of the foregut and ultimately separates the respiratory from the digestive tracts (Fig. 4-2C). Alternative mechanisms initiating this process have been proposed, including the fusion of endodermal ridges in the midline.[8] Failure to separate these compartments results in tracheoesophageal fistula, a condition of high morbidity relatively frequent in neonatal settings. This defect has been observed as part of the phenotype of several mouse mutants, including the $Shh^{-/-}$, $Nkx2\text{–}1^{-/-}$, Sox2 conditional mutant, $Gli2^{-/-}$; $Gli3^{+/-}$, and the $RAR\alpha^{-/-}$; $RAR\beta^{-/-}$ null-mice.[3,25–27,30]

BRANCHING MORPHOGENESIS: FORMATION OF THE BRONCHIAL TREE AND PATTERNING

The bronchial tree forms through a reiterative process of growth and budding of the epithelial tubules collectively termed as branching morphogenesis. This process initiates right after secondary buds form from the lung primordium, in mice at E10.5. Interestingly, at this time the pattern of lobation of the right and left lungs is also established. The lungs are asymmetric in respect to their right and left axis and their number of lobes varies according to the species. For example, mouse lungs have one left lobe and four right lobes. It is thought that this asymmetry is regulated by left–right (L–R) determinants as part of an early global program of axis specification. Among the signals involved in this process are several Tgfβ-related molecules, such as activin receptor II, Lefty1 and 2, growth differentiation factor 1 (Gdf1), and paired-like homeodomain transcription factor 2 (Pitx2).[31–35] Loss of left–right asymmetry resulting in equal number of lobes in both sides is called pulmonary isomerism and is found in several human conditions.[36,37]

Analysis of the three-dimensional branching pattern of embryonic mouse lungs suggests that the bronchial tree is generated by three geometric branching modes: Domain branching, planar bifurcation, and orthogonal bifurcation, following three sequential orders (Fig. 4-3).[38] All modes are used concurrently during development of the bronchial tree. More than one mode is often used in the individual founder branches to generate the next generation of buds. Domain branching is first used to form founder or parent (secondary) branches. This is followed by permanently switching to an orthogonal bifurcation mode or by a combination of the three modes in a defined sequential order. Results from these analyses

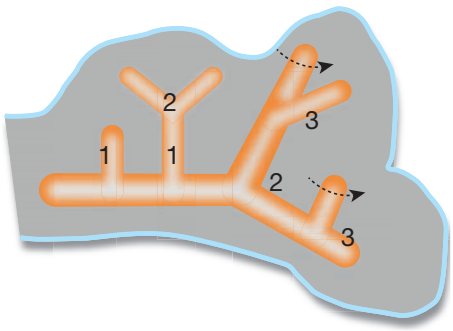

Figure 4-3 Diagram representing the three branching modes: Domain branching (1), planar bifurcation (2), and orthogonal bifurcation (3) (for details see Ref. 38).

strongly suggested that distinct genetically encoded pathways control each branching model. It is likely that these subroutines are also used in the developing human lungs, but this has not been yet demonstrated.

The mechanism generating new buds during branching morphogenesis is similar to that of primary bud morphogenesis and relies on local epithelial activation of Fgfr2b signaling by mesenchymal Fgf10 at the sites of budding.[12,13] Perturbations in levels or distribution of Fgf10 have a major impact in airway morphogenesis and result in smaller than normal hypoplastic lungs. Reduced number of branches among other abnormalities of patterning is found in Fgf10 hypomorphic mice ($Fgf10^{lacZ/-}$).[39] Interestingly, during branching morphogenesis Fgf9 expressed from the pleura and transiently from the distal epithelium serves to expand a population of distal mesenchymal progenitors that expresses Fgf10 (Fig. 4-4A). Mice deficient in Fgf9, have reduced mesenchymal cell population and Fgf10 expression; this leads to disruption of branching morphogenesis and hypoplastic lungs.[40]

How is bud formation controlled during branching morphogenesis? The size and shape of the growing buds is controlled dynamically by exchange of signals between the tip bud epithelium and the immediately adjacent mesenchyme. Shh is a member of the hedgehog family of proteins (sonic, desert, and Indian hedgehog) expressed in the lung predominantly at the tip bud epithelium. Shh signaling is activated in a paracrine fashion in the lung mesenchyme via patched (Ptc)/smoothened (Smo) and its transcriptional effectors Gli (1, 2, 3) proteins where it acts as a critical survival factor for mesenchymal cells.[41–43]

There is accumulated evidence both in vitro and in vivo that Shh has a key role in the developing airways as negative regulator of Fgf10 expression.[41,44] The idea is that during branching, Shh at the tip of growing buds progressively downregulates Fgf10 in distal mesenchymal cells, inhibiting bud outgrowth (Fig. 4-4A). In Shh-null mice there is widespread expression of Fgf10 transcripts and generalized activation of Fgfr2b in lung endoderm that results in severely disrupted branching morphogenesis and cyst-like lungs.[26] A mechanism proposed to maintain the proper balance of Fgf10 levels and prevent excessive Shh signaling is through the Hedgehog interacting protein, Hhip1. Hhip1 is induced by Shh in the mesenchyme adjacent to the distal bud, where it binds to and sequesters Shh ligand preventing it from activating signaling and repressing Fgf10 locally. Indeed Shh activity is aberrantly increased in Hhip-null mice leading to a repression of Fgf10 expression and branching in the developing lung.[45]

The balance of Fgf10 activity in the emerging bud can be regulated by the Sprouty **(Spry)**, a highly conserved family of cysteine-rich proteins (Fig. 4-4A). Spry2 and Spry4 are expressed in the distal lung in the epithelium and mesenchyme, respectively.[46,47] Spry2 negatively regulates the Fgf-mediated activation of receptor tyrosine kinase signaling in the epithelial bud and thus, inhibits bud growth, as demonstrated by functional studies in Drosophila and mice.[48–51] Moreover, Fgf10 protein distribution and receptor binding can be modulated by interactions with heparan sulfate (HS) proteoglycans at sites of budding. Disrupting endogenous gradients of HS or altering HS sulfation in lung culture systems prevents Fgf10 from inducing local responses and can markedly alter lung pattern formation.[52,53]

Another mechanism contributing to airway branching is cleft formation. Here extracellular matrix (ECM) is deposited at branch points, accumulating in the epithelial–mesenchymal interface and preventing local expansion of the epithelium. Clefting has been classically associated with local activity of Tgfβ signaling in the mesenchyme, which suppresses Fgf10 expression and induces synthesis of ECM components (Fig. 4-4B,C). Members of the Tgfβ subfamily Tgfβ1, 2, and 3, their receptors (Tgfβr1 and Tgfβr2)

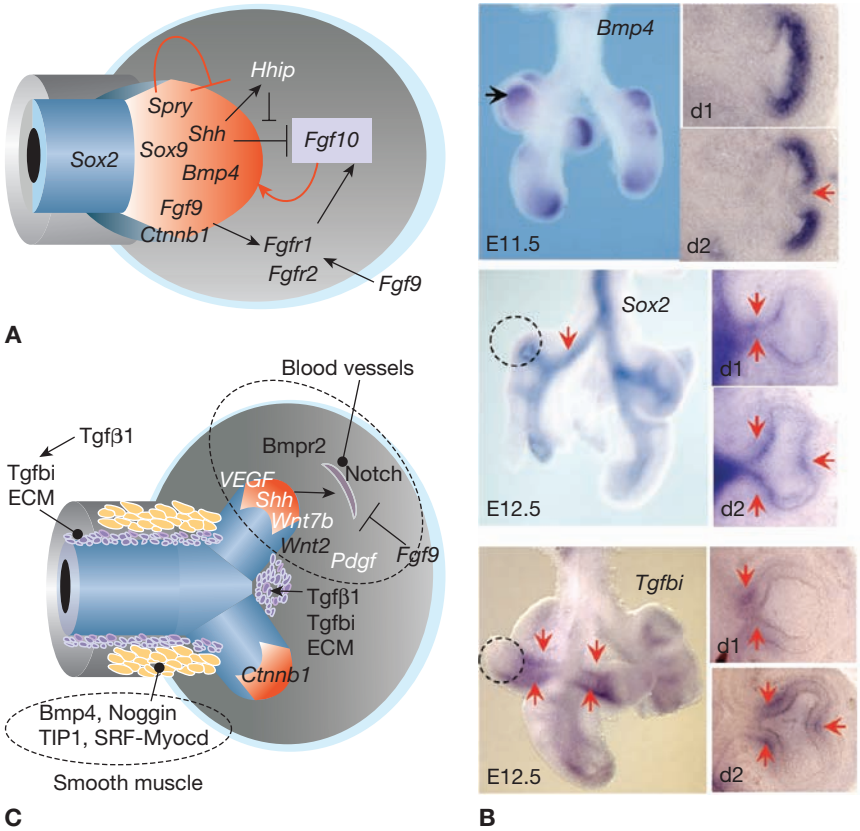

Figure 4-4 Regulation of lung branching morphogenesis, proximal–distal (P–D) patterning and differentiation. **A.** Gene network regulating lung bud elongation. Bud outgrowth is restricted by Fgf10 induction of Bmp4 and Spry2; Spry2 inhibits epithelial Fgf signaling; Bmp4 inhibits epithelial proliferation; Shh inhibits Fgf10 expression through activation of Ptc/Smo signaling. Shh signaling is inhibited by Hhip through a feedback loop. Fgf9 expressed by both mesothelial or distal epithelial cells activate Fgfr1/2 signaling in mesenchyme promoting Fgf10 expression. **B.** ISH of Bmp4, Sox2, and Tgfbi during branching (E11.5–12 in vivo and in E11.5 lungs cultured for 1 and 2 days). Bmp4 labels distal epithelial buds while Sox2 marks the epithelium in stalk and nonbranching proximal regions; Tgfbi labels newly-formed stalks and proximal mesenchyme. **C.** Airway branching and differentiation of mesenchymal components. Localized Tgfβ activity promotes local ECM deposition and cleft formation. Airway and vascular SM requires the input of Shh, Wnt, VEGF, Pdgf notch, and Fgf.

and transducing proteins, Smad 2 and 3 are expressed in different compartments and in a complex pattern during branching morphogenesis. Tgfβ1 transcripts are distributed throughout the lung mesenchyme; however Tgfβ1 protein accumulates in regions between buds and along proximal airways, where ECM components collagen I, III, and fibronectin are abundant.[54] The dynamic activity of Tgfβ during branching is best visualized by expression of its target Tgfbi (Tgfβ-induced or BigH3) in the stalk region of growing buds (Fig. 4-4B,C).[55] Treatment of embryonic lungs in culture with recombinant Tgfβ1 dramatically inhibits branching morphogenesis.[44,56,57] This is likely due to the negative effects on growth and differentiation by epithelial activation Tgfβ signaling, but also from the Tgfβ effects in the mesenchyme. Studies in NIH3T3 fibroblasts, lung and prostate organ cultures demonstrate that Tgfβ1 signaling in mesenchymal cells markedly inhibits Fgf10 expression.[44,58,59] Interestingly Tgfβ1-null mice do not show these defects, presumably due to rescue by maternal transfer of Tgfβ1.[60] Tgfβ2 and Tgfβ3 are expressed in lung epithelium; Tgfβ3 is also found in the developing lung mesenchyme and pleura.[61] Both the Tgfβ2- and Tgfβ3-deficient mice do not have major morphological defects in the lungs at E18.5 but show collapsed lungs postnatally.[62,63]

There is increasing evidence that small noncoding regulatory RNAs are part of the regulatory networks controlling lung development. MicroRNAs (miRNA) are endogenous small noncoding RNAs that regulate target gene expression posttranscriptionally and play important roles in diverse biological processes.[64–67] Individual miRNAs may target multiple message RNAs (mRNAs); conversely, individual mRNAs may contain sequences complementary to multiple miRNA family members.[68] The importance of the miRNA pathway in lung development was demonstrated by the epithelial deletion of Dicer, the key enzyme that processes microRNA precursors into mature miRNAs. Loss of Dicer in the mouse lung epithelium results in drastic arrest of branching morphogenesis and increased epithelial cell death.[69] The increased levels of Fgf10, Bmp4, and Spry-2 in these mutant lungs suggested that the miRNA pathway represses expression of these genes during epithelial–mesenchymal interactions.[69] Interestingly, in humans, DICER mutation has been linked to pleuropulmonary blastoma, a rare pediatric tumor that arises during fetal lung development.[70] It is speculated that loss of DICER in developing lung epithelium alters miRNA-dependent regulation of diffusible growth factors that promote proliferation of both epithelial and mesenchymal cells.

ESTABLISHMENT OF PROXIMAL–DISTAL (P–D) CELL FATE

During lung development, the appearance of distinct fates in epithelial progenitors along the P–D axis is tightly coupled with the branching process. Morphological changes that occur in the epithelial tubules during branching are accompanied by highly dynamic changes in P–D differentiation. For example, the high levels of Bmp4 and Sox9 typically found in the newly formed distal buds are markedly downregulated in the stalks and more proximal regions of the epithelial tubules, which then express Sox2 (Fig. 4-4A,C). Canonical Wnt and Bmp signaling have been implicated as major regulators of P–D cell fate in the lung epithelium.

Wnt ligands, receptors (frizzled), and β-catenin are widely expressed in the developing lung but show distinctive pattern in both epithelium and mesenchyme.[71–73] High activity of Wnt signaling reporter (TOPGAL), nuclear-localized β-catenin, TCF/LEF transcripts, are found in the distal lung buds undergoing branching.[74,75] Targeted disruption of β-catenin, or overexpression of Wnt inhibitor D (Dkk1) in the distal lung epithelium prevents distal bud formation and proximalizes the lung, a phenotype characterized by proximal epithelial phenotypes extending to distal sites. Conversely, activation of canonical Wnt signaling throughout the lung epithelium inhibits Sox2 expression and leads to the appearance of distal fates in proximal airways.[76,77] Thus canonical Wnt plays a key role in the establishment and or maintenance of distal cell fates.

Bmp4 is expressed in lung epithelial progenitors at the tip of growing buds and has been implicated in distal cell fate, potentially through an autocrine activation of Bmpr-Smad signaling.[78] In the lung Bmp4-mediated responses are regulated at

multiple levels, for example by Fgf10-Fgfr2b activation in distal buds, which induces Bmp4 expression, or by known Bmp antagonists present in the lung, such as Noggin, Chordin, Gremlin, and the Cerberus-related factor, Cer1.[42,79–82] Bmp4 protein levels in distal epithelium are potentially under the control of the cysteine protease Cathepsin H, which is significantly induced by Fgfr2b signaling.[83] Transgenic mice expressing Bmpr antagonists in lung epithelial progenitors fail to properly form a distal lung and show proximalization.[84] Using a similar genetic approach Bmp4 overexpression results in small lungs containing distal flat cells that are reminiscent of the distal alveolar type I cells.[78] In lung organ cultures Bmp4 antagonizes the proliferative effects of Fgf10 in the distal epithelium; this could presumably foster distal differentiation.[85] Histone deacetylases 1 and 2 (Hdac1/2), enzymes involved in epigenetic modifications, have been recently shown to regulate P–D patterning through controlling expression of Bmp4 and the tumor suppressor Rb1.[86]

miRNAs also play a significant role in lung P–D patterning. For example, the miR-17-92 cluster is expressed during early lung development; gain of function selectively in the developing lung epithelium of transgenic mice results in increased cell proliferation.[87] Conversely, miR-17-92 cluster knockout mice have hypoplastic lungs.[88] In an independent study, miR-17 family members were shown to modulate Fgf10-Fgfr2b downstream signaling by targeting Stat3 and Mapk14.[89] miR-302/367, a direct target of Gata6 transcription factor, coordinates the balance between proliferation and differentiation of lung epithelium and also regulates apical–basal polarity.[90]

FORMATION OF THE VASCULAR AND OTHER MESENCHYMAL COMPONENTS OF THE LUNG

Besides playing a crucial role in epithelial development, the lung mesenchyme gives rise to the vascular, cartilage, and other stromal components of the lung. In turn, expansion and differentiation of mesenchymal progenitors into these different components require diffusible signals from the epithelial and mesothelial (pleural) layers.

The vasculature develops through sprouting angiogenesis from arterial vessels of the aortic arches migrating to the developing lung and formation of a capillary plexus around the distal bud.[91–93] Pulmonary veins arise from the neighbor atrium. Vascular endothelial growth factor (VEGF) signaling plays a major role in vascular development by promoting endothelial cell differentiation (Fig. 4-4B).[94] VEGF-A is found predominantly in the distal lung epithelium but also in the mesenchyme at early stages and signals through VEGFR2 (Flk1) and VEGFR1 (Flt1) in the mesenchyme.[95–97] Among the several VEGF isoforms, VEGF164 is the most active in the lung.[98] Development of lymphatic vessels is still poorly understood. Studies in mice show that VEGF-C and -D acting through their receptor VEGFR-3 promote lymphoangiogenesis.[99,100] VEGFR-3–null mice fail to develop proper lymphatic vessels.[101]

Smooth muscle (SM) is an integral component of vascular and airway epithelium of the lung (Fig. 4-4B). Vascular SM develops by contribution from mesenchymal precursors through signals derived from the epithelium but also from pleural cells migrating to the vascular structures during blood vessel assembly.[102] Significantly reduced mesenchymal cell proliferation and SM differentiation were observed in Shh-null lungs.[43] Interestingly, a signaling cascade involving Shh, miR-206, and Bdnf (brain-derived nerve growth factor) coordinates innervation and formation of the airway SM layer.[103] Wnt7b, acting through Fzd1, Fzd10, and LRP5, is an important epithelial signal required for vascular SM development and the integrity of blood vessels.[104] Wnt7b-null mice show hemorrhagic lungs resulting from rupture of the blood vessels due to SM structural defects.[105] Assembly of the pulmonary arterial wall occurs through controlled migration of SM cells from the inner to the outer layers in a process mediated mostly by PDGFβ.[106] In addition, vascular SM formation depends on Bmp and Notch signaling.[107,108] Bmp4 and Bmpr2 are expressed in SM precursors and disruption of Bmp signaling is associated with increased SM cell proliferation. This phenotype is reminiscent of the excessive SM growth reported in pulmonary hypertension patients with mutations in the Bmpr2 gene.[109–111] Disruption of canonical Notch signaling interferes with specification of arterial SM cells.[107] Notch3 dysregulation is associated with structural changes in the pulmonary artery postnatally and has been implicated in the pathogenesis of adult pulmonary hypertension.[112] The importance of having a precisely matched airway–vascular development is well illustrated by the role of Foxm1, a transcription factor present in the lung mesenchyme. Foxm1-null mice show pulmonary hemorrhage and perinatal death due to misalignment of epithelial and vascular structures.[113] This phenotype closely reminds the abnormalities seen in human congenital alveolar dysplasia.

Airway SM originates from mesenchymal cells of the developing lung when the initial airway start to branch, preceding the appearance of the lung vascular SM. Evidence from a Fgf10-lacZ reporter mouse, which labels Fgf10-derived lineage cells,[114] suggests that a myogenic program of cell fate in developing airways initiates in the distal lung mesenchyme and progresses as these cells are relocated to the bud stalks and more proximal regions.[114,115] This myogenic program is likely to be triggered by high levels of Bmp4 and Shh present at the bud tips (Fig. 4-4C).[41,78] Canonical Wnt signaling is required for the expansion of the SM progenitors in developing airways.[116] Proper differentiation of the airway SM requires input from pathways, including Fgf, TGFβ, as well as physical stretch transduced by tension-induced proteins, such as Tip1.[117–120] Fgf9-Fgfr1/2 signaling suppresses airway SM differentiation through inhibition of myocardin expression.[42,121,122]

During development, SM is responsible for phasic contractility of airways and growth factor production, contributing to maintain normal lung growth. Airway peristalsis influences branching and epithelial differentiation.[123,124] Interfering with process can result in lung hypoplasia.

Cartilage rings present in trachea and proximal airways develop from the precursors in ventral mesenchyme. Proper formation and patterning of cartilage primordia requires signaling by RA (particularly RAR gamma mediated), Foxf1, Shh, Nkx2–1, among others.[125,126]

AIRWAY DIFFERENTIATION

As the epithelial tubules form and branch, they initiate a program of cell fate choice and differentiation that ultimately gives rise to the various airway epithelial cell types. The initial stage is marked by expression of Sox2 throughout the P–D axis of these tubules from trachea to the most distal airways (Fig. 4-4B).[127]

By the middle of the pseudoglandular period, epithelial cells in proximal airways start to express markers of cell commitment to secretory Clara (the secretoglobin Scgb3a2) ciliated (Foxj1) and neuroendocrine (the bltb transcription factor Ascl1) lineages (Fig. 4-5).[128–133] These committed epithelial progenitors then initiate specific programs of differentiation. Foxj1-expressing cells undergo a dramatic organization of their apical compartment and by the end of the canalicular period form multiciliated cells marked by β-tubulin staining.[134] Concomitantly Scgb3a2-expressing cells acquire expression of the Clara cell marker CC10 (Scgb1a1).[135,136] While in humans mucin-secreting goblet cells are seen throughout the respiratory tract epithelium, in mice, they are relatively rare occurring mostly postnatally in trachea and proximal airways. Their presence is largely increased in exposure to environmental agent or infection.[137]

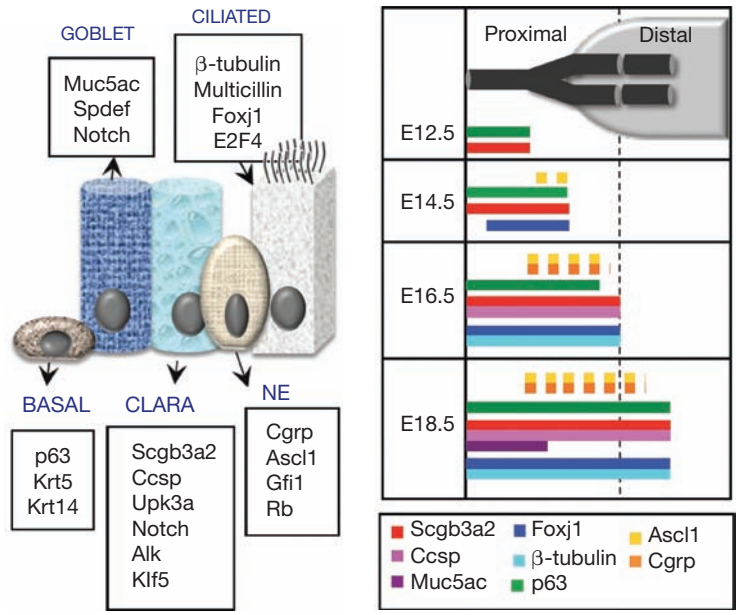

Figure 4-5 Epithelial differentiation in conducting airways. **A.** Cell types and markers associated with or required for the differentiation of specific cells. **B.** Time course of appearance of gene markers associated with different cell lineages in proximal and distal airways of the developing mouse lung.

Ascl1-expressing cells are found in clusters initially in proximal regions and generate neuroendocrine bodies (NEB) and isolated neuroendocrine (NE) cells; they express neural markers such as Cgrp and Pgp9.5. Mice deficient in Ascl1 do not form NE cells or NEB.[130]

Both Clara and basal cells are considered to be progenitor cells of the lung for their ability to self-renew and generate Clara and ciliated cells. Basal cells are recognized by the expression of the transcription factor p63, and also keratins 5 and 14. p63 mutant mice do not form basal cells in the lung or in other regions, such as skin.[138,139] Although p63/Keratin 5-labeled cells can be identified in the embryonic lung, there is no evidence that prenatally they function as lung progenitor cells.

Notch signaling is critical to generate Clara cells and to maintain the balance of the different cell types in the airways.[132] Disruption of Notch signaling in mice results in loss of Clara cells and airways overpopulated by ciliated and NE cells.[107,132,140–141] Conversely, constitutive activation of Notch in the embryonic lung epithelium leads to a decrease in number of ciliated cells and increase in secretory goblet cells.[142] During postnatal life Notch is required to maintain the Clara cell phenotype and prevent them from undergoing goblet cell (mucus) metaplasia.[143] Downregulation of Notch pathway components has been identified in patients with chronic pulmonary obstructive disease (COPD), a condition in which one of the hallmark features is mucus metaplasia.[144] Goblet cell differentiation is also controlled by transcription factors, such as SAM pointed domain-containing ETS transcription factor (Spdef) and Foxa2.[145–147]

Formation of multiciliated cells in the airways depends on expression of the E2F family member E2F4, as well as Foxj1 and multicilin.[148,149] Loss or gain of function of Foxj1 in genetically altered mice leads to absence or ectopic formation of multiciliated cells, respectively.[150,151] miR-449 has been shown to promote the differentiation of ciliated cells by targeting NOTCH1 and the ligand DLL1 in human airway epithelial cells.[152]

FORMATION OF THE GAS EXCHANGE REGION OF THE LUNG

Once branching morphogenesis is completed, distal epithelial buds undergo sacculation. During this morphogenetic process, the lumen of epithelial tubules enlarges at their distal ends to form primitive saccules. Some of the epithelial cells become flattened and very thin, differentiating into type I cells, while the others remain cuboidal and differentiate into surfactant-producing type II cells (Fig. 4-6). Type I cells cover a large area of these saccules and, as the mesenchyme becomes thinner, they come into intimate contact with the capillary network of the primitive saccules to form the primitive alveolar–capillary barrier.[153] Multiple gene knockout mice show defects in sacculation. Among these are T1 alpha,[154] Nfib (nuclear factor I/B),[155] Erk3 (extracellular signal-regulated kinase 3), and Foxm1.[156]

Finally, by late gestation in humans or postnatally in mice the primitive saccules subdivide into smaller units to form the mature alveoli. Alveolization involves formation of secondary septa, which greatly increases the surface area for gas exchange (Fig. 4-6). Alveolar formation is dependent on interstitial myofibroblasts and appear to require tight control of elastin levels. Signaling by Pdgf is necessary to form lung myofibroblasts[157]; Fgfr3 and 4 are required to control proper levels of elastin gene expression.[158] VEGF signaling has also been implicated in maintaining the alveolar structure.[159] Flt1 inhibition leads to immature lungs with decreased alveolar septation. Although there is evidence from some animal models that RA fosters alveolization, some controversies exist and further studies are required to clarify this issue.[160,161] Transcription factors, such as Foxn4 also influence alveolization.[162] Unilateral pneumonectomy (PNX) in mouse stimulates pulmonary capillary endothelial cells (PCECs) to produce angiocrine growth factors that induce

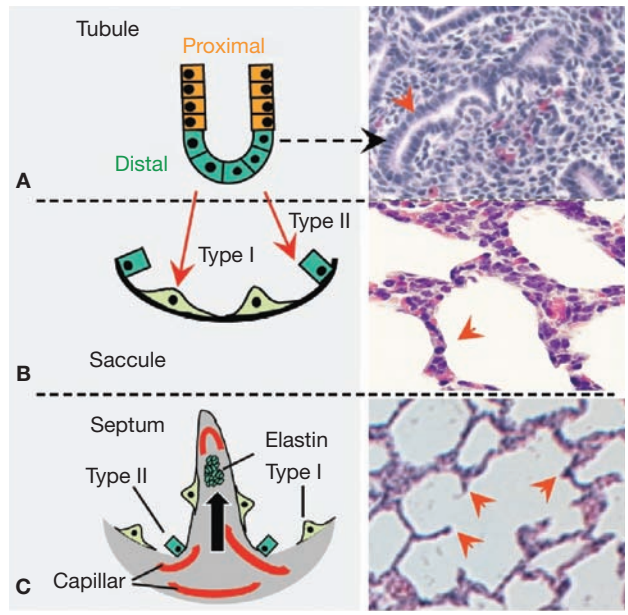

Figure 4-6 Sacculation and alveolar formation, H&E. **A, B.** Distal epithelial tubules expand their lumens and form primitive saccules lined by type I and type II cells. **C.** Septation subdivides saccules into smaller units to form the definitive alveoli.

proliferation of epithelial progenitor cells promoting regenerative alveolization.[163]

FINAL REMARKS

A wealth of information has been generated over the past decades on how growth factors, transcription factors, and matrix components influence lung development. Many of these studies suggest that alterations in developmental pathways reported in animal models are relevant to understand the pathogenesis of human lung conditions. There is also increasing evidence that developmental regulators are recruited in different contexts to mediate normal and aberrant injury–repair responses in the adult lung. Further understanding of these issues will be invaluable in discovery of different therapeutic targets and for the new field of lung regenerative medicine.

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CHAPTER 5

Pulmonary Surfactant and Disorders of Surfactant Homeostasis

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INTRODUCTION

Pulmonary surfactant is a complex mixture of phospholipids and proteins that creates a unique interface separating alveolar gas and liquids at the alveolar cell surface, reducing surface tension, and maintaining lung volumes at end expiration. Reduction of the surface tension at the air–liquid interface is a requirement for respiratory function following birth. Deficiency of pulmonary surfactant causes respiratory failure in premature infants, or infantile respiratory distress syndrome (IRDS). The adequacy of pulmonary surfactant is maintained by unique and highly regulated systems mediating the synthesis, secretion, reutilization, and catabolism of surfactant. Loss or inactivation of pulmonary surfactant later in life occurs in the adult respiratory distress syndrome (ARDS), a significant cause of morbidity and mortality following infection, shock, or trauma. Mutations in genes regulating surfactant homeostasis, including SFTPA, SFTPB, SFTPC, ABCA3, TITF1, and CSF2RA cause acute and/or chronic lung disease in newborn infants, children, and adults. Disorders of GM-CSF signaling inhibit surfactant lipid and protein catabolism by alveolar macrophage causing pulmonary alveolar proteinosis (PAP). This chapter reviews the biology of the surfactant system and its implications for the pathogenesis, diagnosis, and treatment of respiratory disease in premature infants and adults. Suggested reviews of these topics are provided in the References section.[1–5]

PHYSICAL FORCES AT THE AIR–LIQUID INTERFACE

In 1929, Van Neergard recognized the critical role of surface tension as a "retractile force" in the lung, observing the marked difference in inflation pressures required to inflate the air- versus water-filled lung. Avery and Mead associated the lack of a lipid-rich material in the lungs of infants dying from idiopathic respiratory distress syndrome with alveolar collapse and respiratory failure.[6] In the absence of pulmonary surfactant, molecular forces at the air–liquid interface create a region of high surface tension because intermolecular forces between water molecules are unopposed at the air–liquid interface, and an area of high retractile force at the surface is created. Forces of 70 dynes/cm^2 are generated at the air–water interface; if unopposed in the alveolus, such forces lead to alveolar collapse and respiratory failure. A surface film composed of multilayered sheets of phospholipids creates a distinct phase separating air and liquid, reducing surface tension to nearly zero and maintaining residual lung volume at end expiration. Complex interactions between surfactant phospholipids and proteins are required to maintain surfactant film throughout life. Pulmonary surfactant lipids and proteins are synthesized and secreted by alveolar type II epithelial cells into the alveoli, where they form multilayered lipid-rich films that reduce surface tension to maintain ventilation (Figs. 5-1 and 5-2).

COMPOSITION OF PULMONARY SURFACTANT

Pulmonary surfactant isolated by lung lavage consists of highly heterogeneous forms of phospholipid–protein aggregates of distinct sizes, structural characteristics, and composition. Tubular myelin is the most abundant form of alveolar phospholipid and consists of large, relatively dense aggregates (termed large aggregate surfactant) composed of phospholipids and surfactant proteins (SPs). Tubular myelin is a highly organized form of surfactant phospholipid, forming square tubular arrays. Tubular myelin represents an extracellular pool of surfactant lipids that rapidly moves to the air–liquid interface and reorganizes to form multilayered sheets that reduce surface tension in the alveolus (Fig. 5-2). Large lamellated structures, with lipid composition similar to that of tubular myelin, are seen within the alveolus and likely represent newly secreted lamellar bodies that unravel to form tubular myelin in the alveoli. The phospholipid composition of lamellar bodies, the intracellular storage form of surfactant, tubular myelin, and lamellated forms present in the alveolus are virtually identical. Smaller, less dense particles (small aggregate surfactant) are also present within the alveolar space, representing remnants or catabolic forms of surfactant that have relatively poor surface activity. Small aggregate surfactant is destined for uptake, reutilization, or catabolism by type II epithelial cells and catabolism by alveolar macrophages.[2,3]

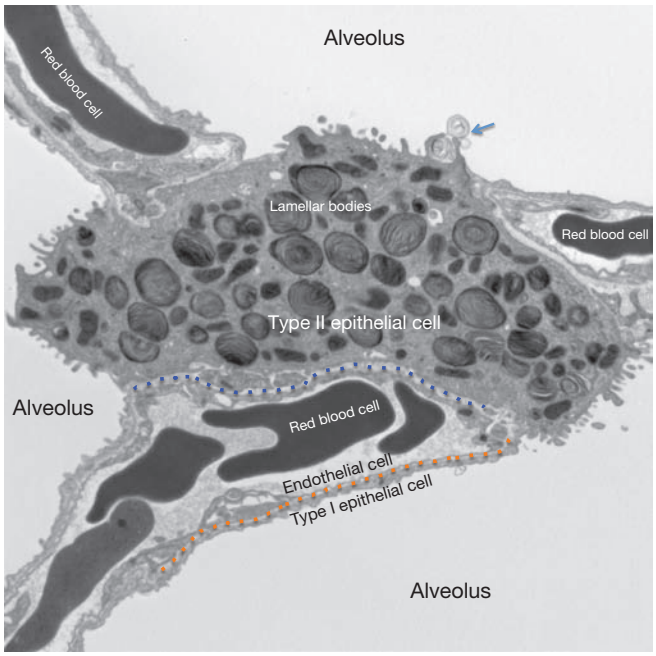

Figure 5-1 Pulmonary alveolar ultrastructure. The air–blood barrier is comprised of the capillary endothelium (above *the dotted orange line*) and the closely apposed type I epithelial cell (below *the dotted orange line*). The dotted blue line delineates the interstitial space between endothelial cells and type II epithelial cells with their specialized secretory lipid organelles (lamellar bodies). Type II cells form tight junctions with type I cells and serve as alveolar progenitor cells. Surfactant lipids and proteins are secreted as lamellar membranes *(arrow)* into the alveolar space forming tubular myelin and lipid membrane multilayers that reduce surface tension, preventing alveolar collapse.

SURFACTANT PHOSPHOLIPIDS AND PROTEINS

The composition of surfactant lipids is similar in all of the structural forms of surfactant isolated from mammalian lungs, with phospholipids generally representing 80% to 90% of the mass of pulmonary surfactant.[3] In the adult lung, phosphatidylcholine (PC) and phosphatidylglycerol (PG) are the most abundant phospholipids, representing approximately 70% to 80% and 5% to 10%, respectively, of the lipid mass. Dipalmitoyl phosphatidylcholine (DPPC) is the most abundant species of PC. Lesser amounts of phosphatidylserine, phosphatidylethanolamine, sphingomyelin, neutral lipids (mostly cholesterol), and glycolipids are also present in surfactant. The lung content of surfactant phospholipids increases markedly with advancing gestation, regulated by a complex signaling and transcriptional network that controls type II alveolar cell differentiation, lipid synthesis, and SP gene expression. Lamellar bodies are secreted into the fetal amniotic fluid. PC, lamellar body counts, DPPC content, and increased lecithin (PC) to sphingomyelin (L/S) ratio, correlate with postnatal respiratory function. These tests are used to predict pulmonary maturity prior to the birth of preterm infants. Lung maturation and synthesis of surfactant components are induced by maternal administration of glucocorticoids, used clinically to prevent respiratory distress prior to premature birth.[7] Proteins represent approximately 5% to 15% of the mass of pulmonary surfactant and include serum proteins and proteins that are synthesized and secreted by type II alveolar epithelial cells. In addition to its specific interaction with SP-B, the anionic phospholipid PG may also play an important role in innate defense. PG constitutes 10 mole% of surfactant lipid, with palmitoyl-oleoyl-PG (PoPG) being the most common species in human surfactant. PoPG specifically suppresses LPS-induced inflammatory responses and prevents infection of epithelial cells by binding RSV or influenza A virus.[8] Thus the unique enrichment of PoPG in the distal airspaces may be an important component of host defense against inhaled pathogens. Four surfactant proteins (SPs), SP-A, SP-B, SP-C, and SP-D, are produced by respiratory epithelial cells, each playing specific roles in surfactant homeostasis and innate host defense.[2,3,9,10]

Surfactant is uniquely enriched in disaturated DPPC. The saturated C16 acyl chains pack densely at an air–liquid interface, reducing tension at the surface. However, dense and stable packing of DPPC occurs at a phase transition of 41°C, far above physiologic temperatures. Thus, at 37°C, pure DPPC maintains a semicrystalline or gel phase that is incapable of moving rapidly with the expansion and compression of the alveoli during the respiratory cycle. The capability of DPPC pulmonary surfactant to move rapidly to the alveolar interface at 37°C and to maintain low surface tension during dynamic compression is conferred by the surfactant-associated

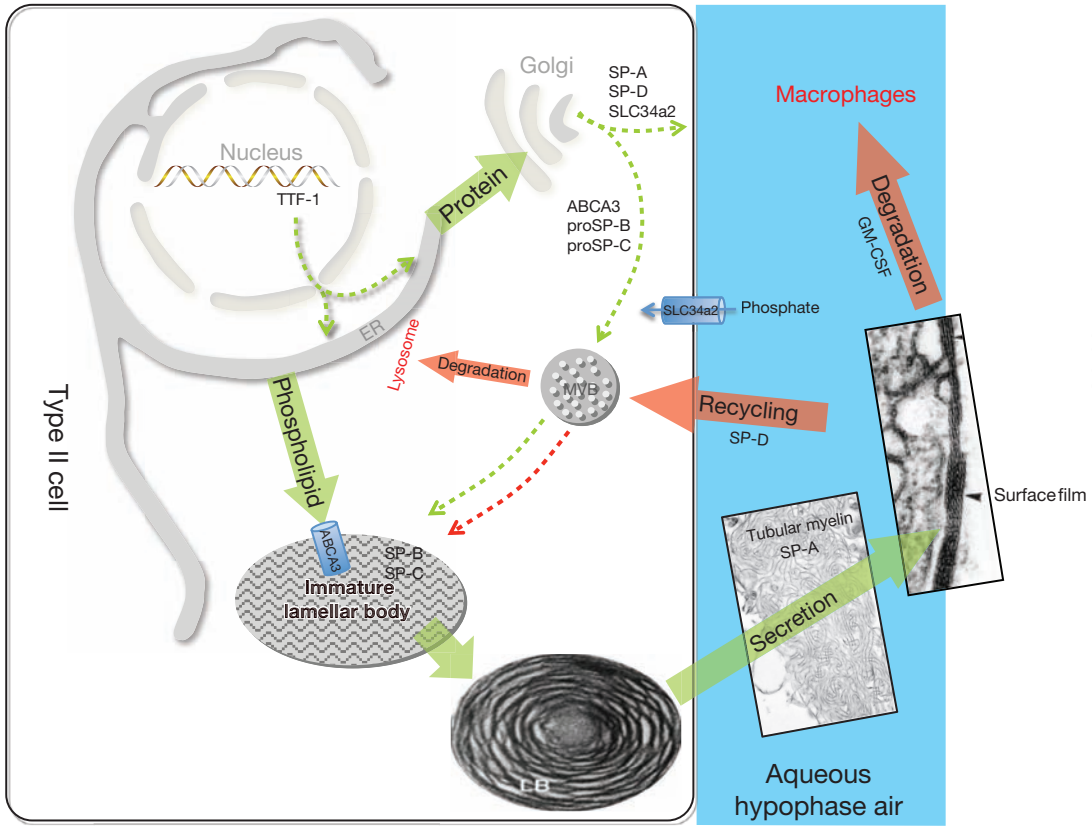

Figure 5-2 Surfactant metabolism. Newly translated surfactant proteins (proSP-B and proSP-C) and lamellar body (ABCA3) proteins traffic from the endoplasmic reticulum (ER) to the Golgi and subsequently to the multivesicular body (MVB). Fusion of the MVB with the lamellar body (LB) is accompanied by proteolytic processing of SP-B and SP-C proproteins to their mature peptides. Surfactant phospholipids (DPPC, PG) are likely transported directly from the ER to the LB by lipid transfer proteins. The contents of the LB are secreted into the alveolar space where they interact with SP-A to form tubular myelin and, ultimately, a phospholipid-rich film (surfactant) at the air–liquid interface. Alveolar surfactant lipids and proteins are cleared through a GM-CSF dependent pathway that regulates alveolar macrophage differentiation and function. Surfactant remnants are also taken up by the type II epithelial cell and recycled to the LB, via the MVB, for resecretion, while a portion is degraded in lysosomes. SP-D plays an important role in regulating alveolar surfactant pool size likely by enhancing its reuptake by type II epithelial cells. The MVB serves to integrate surfactant synthesis, secretion, recycling, and degradation pathways in the type II cell. TTF-1 is a transcription factor critical for differentiation of type II epithelial cells and regulation of expression of Abca3, Slc34a2, and the surfactant proteins. Synthetic pathways are shown in green and catabolic pathways are shown in red.

proteins SP-B and SP-C. PC synthesis in the lung is controlled by genes encoding choline phosphate cytidylyltransferase (PCYTLA) and choline kinase (CHKA), which are required for surfactant lipid synthesis and lung function at birth. DPPC is synthesized in type II alveolar cells via both a de novo pathway and remodeling of lysoPC. The enzyme lysoPC acetyltransferase (LPCAT1) mediates reacylation during surfactant lipid biosynthesis. Surfactant lipids, synthesized in the endoplasmic reticulum (ER) are transferred via a Golgi-independent pathway to lamellar bodies, the major intracellular storage site of surfactant (Fig. 5-2). Transfer of lipids occurs via nonvesicular transport and uptake into lamellar bodies requires the ABCA3 transporter, which selectively transports PC and PG. In contrast, surfactant proteins SP-B and SP-C traffic from the ER to the Golgi and subsequently to multivesicular bodies where proteolytic processing is initiated. Ultimately, multivesicular bodies are incorporated into lamellar bodies with surfactant lipids prior to secretion from type II alveolar cells.[3]

■ STRUCTURE AND FUNCTION OF SURFACTANT PROTEINS

Four distinct surfactant-associated proteins have been isolated from surfactant obtained by lung lavage. Their cDNAs, genes, and structures have been identified and are well characterized (Table 5-1).[9,10] The SPs are expressed in a relatively lung epithelial cell–selective manner and are secreted into the airspaces, where they influence the structure, metabolism, and function of surfactant. Two classes of proteins have been distinguished on the basis of their structures. SP-A and SP-D are relatively abundant, hydrophilic, structurally related proteins and are members of the calcium-dependent lectin family of proteins that have similar amino-terminal collagenous and C-terminal lectin domains.[11] SP-A and SP-D have little "surfactant"-like qualities but are able to bind complex carbohydrates, lipids, and glycolipids, including those on the surface of cells, bacteria, viruses, fungi, and other lung pathogens. SP-A and SP-D influence the structural forms and metabolism of surfactant lipids in the alveolus. They act as opsonins, activate alveolar macrophages, and play important roles in innate host defense in the lung. In contrast, SP-B and SP-C are small, hydrophobic proteins that play critical roles in enhancing the rate of spreading and stability of surfactant phospholipids needed to optimally reduce surface tension.[10] SP-B and SP-C are the sole protein components of the animal-derived surfactant replacement preparations used for the treatment of IRDS at present.[10]

TABLE 5-1 Regulation of Surfactant Homeostasis

Genes/locus	Functions	Inheritance	Presentation	Age at Presentation
ABCA3 16p13.3	Lipid transport Surfactant packaging/function	AR	RDS ILD	Newborns Children
SFTPB 2p12	Surfactant packaging/function	AR	RDS	Newborns
SFTPC 8p21	Surfactant function	AD	ILD > RDS	Infants, children, adults
SFTPA 10q22.2	Tubular myelin, host defense	AD	ILD/lung cancer	Adults
TITF1 14q13	Lung, thyroid, CN morphogenesis, surfactant regulation	AR haploinsufficiency	Thyroid/lung/CNS malformations ILD	Newborns Infants
GM-CSFRα 22.32	Alveolar macrophage function	AR	PAP	Children
GM-CSF 15q31	Alveolar macrophage function	Autoimmune	PAP	Adults

AR, autosomal recessive; RDS, respiratory distress syndrome; ILD, interstitial lung disease; AD, autosomal dominant; PAP, pulmonary alveolar proteinosis.

Surfactant Protein B (SP-B)

SP-B is a hydrophobic, amphipathic 8.8-kDa protein produced from a single gene (SFTPB, OMIM 178640) located on human chromosome 2. The SP-B mRNA is expressed in nonciliated bronchiolar cells and type II alveolar cells and is translated to produce a 40- to 42-kDa precursor that is proteolytically processed in the secretory pathway of type II epithelial cells to form the active 79-amino acid peptide found in alveolar surfactant. In combination with lipids, SP-B can reconstitute most of the surface activity of natural lung surfactant. SP-B contains two regions, (Trp_9-Pro_{23}) and (Ile_{56}-Pro_{67}), predicted to form amphipathic α-helices that interact with the surface of lipid films. Almost 50% of the protein is in an α-helical conformation; the amphipathic domains of SP-B interact with surfactant lipids, and PG in particular, to promote lipid incorporation into and stabilization of the surface film. SP-B contains three intramolecular disulfide bonds that confine the amphipathic helices of SP-B in an antiparallel configuration. Intermolecular disulfide bonds stabilize SP-B dimers. Dimers and higher multimers of SP-B, which are probably stabilized by noncovalent interactions, are readily identified in pulmonary surfactant.

ProSP-B is synthesized in the ER and proteolytically processed in multivesicular and lamellar bodies by cathepsins and other intracellular proteases. The active SP-B peptide is packaged with SP-C and surfactant lipids in lamellar bodies prior to secretion into the alveolus. In the alveoli, the positively charged amino acid residues of SP-B selectively interact with the negatively charged phospholipid DPPG. In a mixed DPPC/DPPG monolayer, SP-B is believed to purify the DPPC monolayer by removal of DPPG. SP-B increases order in the lipid head groups with little effect on order on acyl chains in the lipid membrane interior. The ability to order the lipid head group region is located in the amino- and carboxy-terminal regions of SP-B (1–20) and (53–78), which contain the predicted amphipathic helices. Synthetic peptides that contain these two regions have surface-tension–lowering activity similar to that of native SP-B and peptide mimics have been developed for therapy of respiratory distress in infants. SP-B enhances the insertion (fusion) of phospholipid vesicles into a preformed DPPC/DPPG monolayer, particularly in the presence of divalent cations. SP-B causes lipids in solution to form discoid particles often appearing as stacks or sheets. Together with SP-A, lipids, and Ca^{2+}, SP-B reconstitutes the characteristic ultrastructural features of tubular myelin, producing multilamellar aggregates and square lattice configurations.

SP-B is Required for Survival After Birth Mutations in the gene encoding SP-B (SFTPB, OMIM 265120) cause acute respiratory failure at birth related to surfactant dysfunction.[12,13] Similarly, deletion of Sftpb in the developing lung or its conditional deletion in adult mice causes acute respiratory distress associated with alveolar capillary leak and surfactant deficiency.[14] Pathologic findings of patients with lung disease related to SFTPB mutations are similar to those in mice in which the Sftpb gene is deleted.[14,15] SP-B deficiency is associated with failure to form lamellar bodies, accumulation of abnormal multivesicular bodies within the type II cells, and failure to form tubular myelin or functional surfactant films after secretion into the alveoli.

Hereditary SP-B Deficiency Causes Respiratory Failure at Birth SP-B deficiency is inherited in an autosomal recessive pattern, affected infants developing respiratory failure shortly after birth. While lung morphogenesis proceeds normally in utero, the lack of SP-B results in acute atelectasis and respiratory distress, usually presenting as full-term infants with signs and symptoms of diffuse alveolar collapse after birth. More than 40 distinct SFTPB mutations in patients with SP-B deficiency have been identified.[13,15] The disorder is refractory to surfactant replacement therapy and most patients die from respiratory failure within several months after birth, requiring oxygen and ventilatory support throughout their clinical course. Lung transplantation has been offered to some patients. SP-B deficiency disrupts the formation of lamellar bodies and tubular myelin, and interferes with the processing of proSP-C to the active peptide. Thus, most SP-B–deficient patients lack both SP-B and SP-C peptides in the alveolus. In patients with SFTPB-related disease, proSP-C accumulates in the airspaces, contributing to an alveolar proteinosis–like syndrome. Pathologic diagnoses include desquamative interstitial pneumonitis (DIP), chronic pneumonitis of infancy (CPI) or infantile alveolar proteinosis, histologic changes being influenced by age, and supportive therapies (Fig. 5-3).[16] The definitive diagnosis is made by identification of SFTPB gene mutations, enabling prenatal diagnosis and genetic counseling. While various missense, nonsense, frameshift, and splice variants have been identified, 121ins2 mutation in exon 4 is the most common

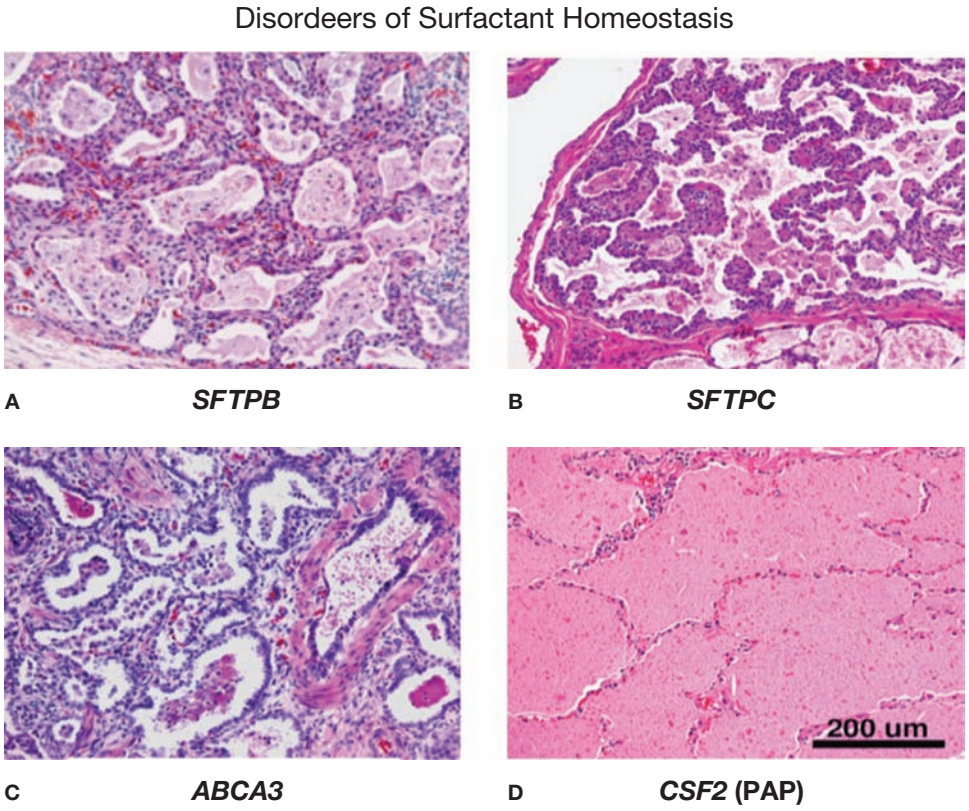

Figure 5-3 Pulmonary histopathology associated with disorders of surfactant homeostasis. Pathologic findings in eonates with mutations in SFTPB (**A**), SFTPC (**B**), and ABCA3 (**C**) are consistent with varying pathologic diagnoses, for example, childhood interstitial pneumonitis (CIP), nonspecific interstitial pneumonitis (NSIP), desquamating interstitial pneumonitis (DIP) or pulmonary alveolar proteinosis (PAP) (**D**). Severe alveolar remodeling, alveolar loss, macrophage infiltration, varying degrees of alveolar proteinosis, and stromal thickening are observed. In contrast, auto-antibodies against GM-CSF or mutations in the GM-CSF receptor (CSFR2A) are associated with pulmonary alveolar proteinosis in which surfactant lipids and proteins accumulate in the alveolus. Alveolar structure is generally well maintained in PAP. *(Reproduced with permission from Whitsett JA, Wert SE, Trapnell BC: Genetic disorders influencing lung formation and function at birth. Hum. Mol. Genet. 2004;13:R207–R215.)*

mutation.[12] In most affected infants, SP-B is lacking in bronchoalveolar lavage fluid and the abnormal proSP-C peptide accumulates in the alveoli, findings that can be verified by immunohistochemistry. Patients with SP-B deficiency do not respond to surfactant replacement and generally succumb from chronic respiratory failure early in infancy in spite of intensive care.

Surfactant Protein C (SP-C) In humans, SP-C is encoded by a single gene (SFTPC, OMIM 178620), located on human chromosome 8.[2,10] SP-C mRNA is expressed exclusively in type II epithelial cells in the lung and is translated to produce a 22-kDa precursor that is palmitoylated and proteolytically processed during intracellular transport to form the active, hydrophobic peptide of 35 amino acids stored in lamellar bodies.[2,3] After secretion, SP-C enhances the surface-active properties of lipid mixtures, lowering surface tension during compression, and enhancing adsorption rate of lipid films at the air–water interface. Both SP-C and SP-B enhance the speed of formation and stability of lipid films. A mixture of surfactant lipids and proteins SP-B and SP-C improves lung inflation and compliance and is useful for treatment of respiratory distress syndrome (RDS) in newborn infants. SP-C is palmitoylated on cysteine residues near the NH_2 terminus. The surface activity of depalmitoylated SP-C is somewhat less than that of palmitoylated SP-C, likely related to reduced stability of the α-helical domain that anchors the peptide within the lipid bilayer. Although the orientation of the palmitoyl groups in a lipid environment is not currently known with certainty, the lipid moiety on SP-C enhances the hydrophobicity of the amino-terminal region enabling its close contact with multilayered lipid films and likely serves to stabilize the α-helical, hydrophobic domain of SP-C. SP-C enhances the uptake of lipids by type II alveolar cells and plays an important role in lipid homeostasis in the alveoli.

In a lipid bilayer, the orientation of the α-helical segment of SP-C is closely parallel with the lipid acyl chains, implying a transbilayer orientation. In a surface monolayer, SP-C has a preferential orientation parallel to the interface, as observed by circular dichroism of monolayer films. The positive charges near the NH_2 terminus of SP-C may promote binding of phospholipid vesicles to the monolayer, a step required for insertion of phospholipids into the monolayer. SP-C forms well-defined domains within DPPC/DPPG films below the phase transition temperature of the bulk lipid. SP-C alters the size and shape of lipid vesicles, disrupting vesicular structures, causing the formation of larger vesicles and discoid particles.

Surfactant lipid films fold as a consequence of dynamic compression during the respiratory cycle in a process enhanced by SP-C and SP-B, each interacting with lipids in distinct ways. SP-B serves to stabilize the membrane-to-membrane interactions between the folded lipid layers to create multilayers.[3]

Role of SP-C in the Pathogenesis of Pulmonary Disease Deletion of Sftpc in transgenic mice perturbed surfactant function and caused severe interstitial lung disease (ILD) with advancing age.[17] While $Sftpc^{-/-}$ mice survive after birth, the mice develop emphysema, pulmonary inflammation, and abnormal lipid accumulations in alveolar macrophages, epithelial, vascular, and stromal cells. Surfactant lipid spreading and stability are only modestly perturbed in the absence of SP-C in vivo. The severity of pulmonary disorder related to SP-C deficiency in mice is strongly influenced by genetic strain, age, and other injuries, indicating that both genetic and environmental factors influence lung structure and function in the absence of SP-C. SP-C binds bacterial endotoxin, supporting a role in innate host defense in the lung. SP-C–deficient mice are susceptible to viral and bacterial pathogens and develop severe pulmonary injury in mouse models of pulmonary fibrosis. The finding that $Sftpc^{-/-}$ mice develop an interstitial pulmonary disorder is consistent with findings in humans, wherein SFTPC mutations cause both acute and chronic lung disease.

Mutations in SFTPC Cause Severe Interstitial Lung Disease in Humans Mutations in SFTPC represent a rare cause of acute and

chronic lung disease in humans.[18,19] SFTPC mutations are generally inherited as an autosomal dominant gene that has been causally linked to acute respiratory disease in newborn infants and more commonly, to chronic ILD in infants, children, and adults. De novo mutations in the SFTPC gene have been reported. The diagnosis of SFTPC-related lung disease (OMIM 610913) is usually made during infancy, but can present later in life, the severity of disease varying in a single extended family.[19] Most mutations occur in the C-terminal BRICHOS domain of proSP-C that serves as an intramolecular chaperone for the metastable membrane-spanning helical domain.[20] The mutant proSP-C protein is misfolded and/or misrouted resulting in intracellular accumulation. Most mutations result in the lack of synthesis of the active SP-C peptide that may influence the pathogenesis of lung disease. Various forms of ILD have been associated with the disease, including acute RDS in newborns, CPI, nonspecific interstitial pneumonitis (NSIP), and other forms of idiopathic pulmonary fibrosis (IPF) (Fig. 5-3).[16] Lung histopathology associated with SFTPC mutations is likely influenced by age, duration and severity of the disease, treatment, and both genetic and environmental factors. Infants with SFTPC mutations often present with severe respiratory signs and symptoms following viral infections. Definitive diagnosis is made by identification of mutations in the SFTPC gene. The onset and severity of pulmonary disease in humans is highly variable, even in the same kindreds, indicating that genetic and environmental factors strongly influence the disorder. At present, there is no effective therapy for SP-C–related disease. Lung transplantation has been offered for treatment of hereditary SFTPC deficiency in patients with respiratory failure. Mutations in SFTPC are a rare cause of acute and chronic ILD. More than 50 distinct mutations in SFTPC have been associated with clinical lung disease and include missense, frameshift, splice, insertions, and deletions that generally disrupt the structure of the C-terminal BRICHOS domain. The most common mutation, I73T, is found in more than one-third of patients.

ABCA3 Mutations Cause Respiratory Failure at Birth ABCA3 is a large, membrane-spanning transport protein that is present in the limiting membrane of lamellar bodies in type II epithelial cells (Fig. 5-2). More than 140 different mutations associated with severe lung disease in newborn infants have been identified, ABCA3 mutations (OMIM 610921) representing the most common genetic cause of neonatal respiratory failure.[1,4,21,22] While expressed in many tissues, patients with mutations in ABCA3 present with isolated lung disease, and abnormalities in other organ structures or functions have not been observed. Pathologic findings in newborn infants with respiratory failure are similar to those in mice wherein ABCA3 has been genetically deleted. ABCA3-related lung disease is generally inherited as an autosomal recessive disorder (Table 5-1). Affected infants present with severe respiratory failure characteristic of surfactant deficiency within the first days of life. Their lung disease is refractory to conventional therapies, resulting in respiratory failure and death within the first months of life. Pathologic findings are similar to those in SFTPB-related disease, and include alveolar proteinosis, lipoid pneumonia, cuboidal epithelial cell hyperplasia, interstitial thickening, loss of normal alveolar structures, and features of DIP (Fig. 5-3).[16] Older children present with features of NSIP. In newborn infants, respiratory failure is not responsive to surfactant replacement. Lung transplantation has been offered to some patients. ABCA3 is a member of the ATP-dependent, Walker domain–containing proteins that comprise a family of membrane-associated transport proteins that includes the cystic fibrosis transmembrane conductance regulator (CFTR). ABCA3 mediates PC and PG transport into lamellar bodies. The diagnosis of ABCA3-related lung disease is confirmed by nucleotide sequencing of the gene in infants and children with refractory pulmonary disease. While most mutations cause respiratory failure in infancy, the E292V mutation is associated with less severe lung disease, these patients often presenting with ILD later in childhood. Ultrastructural analysis of lung tissue from patients with ABCA3 mutations usually demonstrates the presence of small, atypical lamellar bodies in type II epithelial cells and the absence of tubular myelin in the airways, indicating an abnormality in both intracellular and extracellular lipid homeostasis. The processing of proSP-B is disrupted in some patients with ABCA3-related lung disease.[13]

Role of TITF1 in Surfactant Homeostasis TITF1, encoding the homeodomain-containing nuclear transcription factor, thyroid transcription factor-1 (TTF-1), plays a critical role in lung morphogenesis and the expression of SPs.[23,24] TTF-1 is expressed in the central nervous system, thyroid, and lung and is required for lung formation during embryonic development.[24] TTF-1 regulates the SP genes (SFTPA, B, C, and D), ABCA3, SLC34a2, all expressed in alveolar type II epithelial cells.[23] SLC34a2, is a phosphate transporter associated with the disease pulmonary alveolar microlithiasis.[25] Mutations in TITF1 have been linked to disorders of the central nervous system, thyroid, and lung (OMIM 600635), and more than 150 patients have been reported to date.[26,27] TTF-1–related lung disorders are generally inherited as heterozygous mutations resulting in lung dysfunction of varying severity, ranging from disordered alveolar morphogenesis, surfactant deficiency with respiratory failure in neonates and infants, and ILD in older patients. The majority of patients with TITF1 mutations present with severe lung disease, approximately half of which have a spectrum of brain, thyroid, and lung disease. Histologic findings vary greatly with severe abnormalities in the alveoli, and variable loss of SPs and lipids. Pulmonary disease associated with TITF1 mutations is frequently accompanied by congenital hypothyroidism. The severity of TITF1-related CNS, thyroid, and pulmonary disease varies widely in patients with TITF1 mutations. Diagnosis is made by identification of mutations in the TITF1 gene.

THE PULMONARY COLLECTIONS (SP-A AND SP-D)

SURFACTANT PROTEIN A (SP-A)

SP-A is an abundant hydrophilic 26-kDa (monomer) glycoprotein that functions in the host defense, and regulation of extracellular surfactant lipid structure. SP-A mRNA is expressed in nonciliated bronchiolar and alveolar type II epithelial cells in the lung, being translated from two genes (SFTPA1 and 2) located on chromosome 10 in the human.[2,9,11] SP-A in combination with SP-B and SP-C enhances formation of a surface lipid film in the presence of divalent ions, but is not critical for surfactant activity in the alveoli. The amino-terminal third of SP-A is arranged in a collagen-like triple helix, while a carboxy-terminal region has structural similarity to mammalian lectins including SP-D, serum mannose-binding lectin (MBL), and C1q. Protein–protein interactions among SP-A molecules are mediated by the collagen-like domains via intermolecular disulfide bonds that are necessary for SP-A–mediated aggregation of lipids and formation of tubular myelin. Binding and uptake of SP-A by type II alveolar cells and alveolar macrophages are mediated by specific, saturable cell surface receptors; however, the precise nature of the SP-A receptors and their intracellular functions remain unclear.[28] Both collagenous and noncollagenous domains of SP-A bind to isolated type II alveolar cells and immune cells. SP-A increases the association of lipids with type II cells but does not appear to increase internalization of lipid. Deletion of the SP-A gene (Sftpa) in mice does not alter survival or lung function after birth. While tubular myelin is absent, surfactant function, uptake, and secretion are not strongly influenced by deletion of Sftpa in mice.[29] Nevertheless, $Sftpa^{-/-}$ mice are highly susceptible to lung infections by bacterial, viral, and fungal pathogens, indicating that SP-A plays an important role in innate host defense of the lung.[2,9,11]

Usual Interstitial Pulmonary Disease Caused by Mutations in SFTPA2

Missense mutations in the gene encoding SP-A (SFTPA2) have been linked to pulmonary fibrosis pathologically diagnosed as usual interstitial pneumonitis (UIP) (OMIM 178642), generally presenting as ILD in the 4th and 5th decades of life.[30,31] Increased risk of pulmonary adenocarcinoma was observed at more advanced ages. This rare disorder is inherited as an autosomal dominant mutation in which the oligomerization and intracellular trafficking of SP-A(2) is disturbed, resulting in the unfolded protein response and chronic alveolar cell injury.

■ SURFACTANT PROTEIN D (SP-D)

SP-D is a collagenous Ca^{2+}-dependent carbohydrate-binding protein that is structurally related to SP-A and other C-type lectins.[11] SP-D is encoded by a single gene (SFTPD) located near the SFTPA genes on human chromosome 10.[2,9,11] SP-D is synthesized by alveolar type II epithelial cells and nonciliated bronchiolar cells in the lung, but it is also expressed in many other tissues. SP-D forms large oligomers that bind carbohydrates and glycolipids on the surface of bacteria, fungi, and viruses. The interaction of SP-D with microbial pathogens is Ca^{2+}- and carbohydrate-dependent.[11] In contrast to other SPs (SP-A, SP-B, and SP-C), SP-D is not strongly associated with surfactant lipids in the alveolus but plays an important role in determining surfactant structure and homeostasis.

Functions of SP-D In Vivo

Deletion of Sftpd in mice has provided insight into its important role in surfactant and alveolar homeostasis. $Sftpd^{-/-}$ mice survive after birth, but develop severe pulmonary disease associated with macrophage activation, airspace enlargement, and marked accumulation of surfactant lipids in the alveoli.[32,33] SP-D regulates alveolar pools of large and small aggregate surfactant, influencing surfactant particle size and its uptake by type II epithelial cells. Addition of SP-D to surfactant lipid extracts enhances surfactant stability in vitro and protects the preterm lung from endotoxin-induced injury. Infiltration with lipid-laden macrophages, and the induction of synthesis of metalloproteinases 2, 9, and 12 by alveolar macrophages, may contribute to the spontaneous airspace remodeling seen in the $Sftpd^{-/-}$ mice. $Sftpd^{-/-}$ mice are highly susceptible to pulmonary infections and inflammation associated with viral (respiratory syncytial and influenza virus), bacterial, and endotoxin or fungal exposures, indicating that SP-D plays a critical role in innate host defense of the lung.[2,9,11] SP-D binds bacterial, fungal, and viral pathogens, enhancing their opsonization and their killing by alveolar macrophages. Levels of SP-D are low in preterm infants and in infants and older patients with chronic lung disease. SP-D influences immunologic responses to allergens, interacting with alveolar macrophages and lymphocytes in the innate immune system. Thus, SP-D plays an important role in the regulation of surfactant lipid homeostasis, innate host defense of the lung, and prevention of inflammation and alveolar remodeling. Susceptibility to influenza A viral infections has been linked to specific SFTPD alleles, but to date, mutations in SFTPD have not been directly linked to acute or chronic lung disease.

■ RECYCLING AND CATABOLISM OF SURFACTANT LIPIDS AND PROTEINS

Pulmonary surfactant is taken up rapidly in the lung, and much of the lipid is reutilized (Fig. 5-2). After intratracheal administration, labeled lipid appears in type II cells and alveolar macrophages, but is not found in type I cells, indicating that the type II cells actively take up surfactant lipids from the alveolus for recycling or catabolism. Isolated epithelial type II alveolar cells internalize[3] H-PC and resecrete the internalized material or degrade it with reincorporation into other lipids. Isolated type II cells endocytose SP-C and SP-B. SP-A also binds to type II epithelial cells and is endocytosed by a receptor-mediated mechanism. While a number of candidate SP-A and SP-D receptors and binding proteins have been identified, whether the proteins are efficiently recycled and mechanisms by which they signal to influence surfactant homeostasis remain unclear.

Pulmonary surfactant as isolated from lavage fluid exists in several forms that can be fractionated based on density. In vivo labeling indicates that phospholipid is initially secreted in the heaviest forms, followed by conversion into distinct heavy and light forms. The most dense or ultraheavy form contains lamellar bodies and tubular myelin. Small aggregate forms are comprised of small unilamellar vesicles. While their lipid composition is similar to that of large aggregates, small aggregates are depleted of SP-A, SP-B, and SP-C, and lack surfactant function. SP-A and SP-D play important roles in the maintenance of the large aggregate surfactant structures. Cycling surfactant by expansion and contraction of a surface film in vitro converts lipids from large to small aggregates that are likely remnants destined for catabolism or recycling. See Perez-Gil and Weaver[3] for review.

REGULATION OF SURFACTANT PRODUCTION

The synthesis of pulmonary surfactant is subject to precise regulatory controls both during development and postnatally.[34] Surfactant phospholipid synthesis increases markedly in late gestation and is enhanced by a variety of hormones, including glucocorticoids in the fetal lung. Lung phospholipid content increases in the latter two-thirds of gestation in preparation for respiratory adaptation at birth. Prenatal glucocorticoids are routinely used to induce lung maturation and surfactant synthesis in infants at risk for preterm delivery.[7] Glucocorticoids reduce the risk of IRDS and enhance the efficacy of surfactant replacement therapy after birth. Like surfactant phospholipids, the SPs are highly regulated, increasing in the latter two-thirds of gestation in the mammalian species studied. Expression of SPs is regulated in complex ways by a variety of hormonal agents. The levels of SP mRNA increase in the perinatal period in association with increased surfactant synthesis and secretion required for postnatal respiratory adaptation. Expression of the SPs is regulated at both transcriptional and posttranscriptional levels, maintaining steady-state protein concentrations within tight constraints in the adult lung. Surfactant production is, in general, enhanced by glucocorticoids, epidermal growth factor (EGF), and cyclic adenosine monophosphate (cAMP) but inhibited by tumor necrosis factor-α (TNF-α), transforming growth factor-β(TGF-β), and insulin, depending on experimental conditions. Transcriptional control of the surfactant genes is modulated by a number of nuclear transcription factors, for example, TTF-1, cyclic AMP-responsive binding protein (CREBPα), members of the forkhead family transcription factors (FOXA2), retinoic acid receptors (RARs), sterol-responsive element-binding protein (SREBP), GATA-binding proteins, Krüppel-like factor 5 (KLF-5), NFATC3, and coactivators associated with these transcription factors.[35] In the lung, surfactant proteins A, B, and D are expressed in nonciliated bronchiolar and type II alveolar cells, while SP-C is expressed exclusively in type II alveolar cells. Transcriptional, epigenetic, and posttranscriptional mechanisms influence the synthesis of SPs and lipids, regulating surfactant concentrations in the airspace during development and repair.

■ SURFACTANT SECRETION

Lamellar bodies containing SPs SP-B and SP-C and lipids are secreted into the alveoli in a process mediated by activation of β-adrenergic receptors and P2×7R purinergic receptors that regulate intracellular cAMP and calcium homeostasis to influence cytoskeletal organization and secretion.[36] Recent studies support a role

for the orphan receptor (GPRC116) in the regulation of surfactant secretion, loss of GPRC116 resulting in increased purinoreceptor activity, increased surfactant secretion, and increased alveolar surfactant pool sizes.[37] While secretion of surfactant lipids SP-B and SP-C occurs via lamellar bodies, secretion of surfactant-associated proteins SP-A and SP-D occurs via a distinct, vesicular secretory pathway (Fig. 5-2). Interactions of SP-A and SP-D with lipids occur after their secretion into the alveoli.

GM-CSF Signaling Regulates Surfactant Clearance

Mutations in the genes encoding the GM-CSF receptor (CSFR2A, OMIM 13899) and autoantibodies against CSF2 (GM-CSF) have been associated with early-onset PAP in children and in adults, respectively.[5,38] While less than 10% to 15% of surfactant lipids is cleared by catabolism in alveolar macrophages, this pathway is critical in controlling steady-state surfactant concentrations in vivo. Granulocyte macrophage colony–stimulating factor (GM-CSF or CSF2) and GM-CSF receptors are required for normal surfactant catabolism. See Suzuki et al.[5] and Trapnell et al.[39] for review. SP and lipid clearance are decreased in Csf2 and Csfr2a gene–deleted mice causing PAP in which SPs and phospholipids accumulate in the lung. Findings in the mouse models led to the discovery that GM-CSF signaling abnormalities cause idiopathic PAP.[5,40] Clinical studies demonstrate that idiopathic PAP in adults is usually caused by autoantibodies against GM-CSF.[38] Similar abnormalities in surfactant homeostasis, alveolar macrophage morphology, and function are observed in patients with PAP, whether caused by mutations in GM-CSF receptors or by neutralization of GM-CSF by autoantibodies. Lung lavage and GM-CSF, given systemically or by aerosol, have been successfully used to treat adults with PAP (see Chapter 70).

SURFACTANT HOMEOSTASIS AND REPLACEMENT IN INFANTILE RESPIRATORY DISTRESS SYNDROME

IRDS is associated with prematurity, the risk increasing as gestational age decreases. In addition to the morphologic immaturity of the respiratory tract, lung phospholipid content and surfactant secretion are decreased in preterm infants. While functional surfactant can be isolated from infants with IRDS, surfactant pool sizes are markedly decreased in the preterm compared to the term infant and the surface activity of surfactant from infants with IRDS is decreased. Alveolar–capillary leak of blood or serum proteins inactivate surfactant function. Decreased alveolar surfactant activity associated with pulmonary immaturity causes atelectasis, alveolar collapse, pulmonary hemorrhage, and hypoxemia in preterm infants. A schematic representing factors influencing the pathogenesis of IRDS is provided by Figure 5-4.[41]

Supplemental oxygen and mechanical or assisted ventilation is routinely used to treat IRDS. During the last two decades, widespread use of exogenous surfactant has markedly ameliorated the morbidity and mortality associated with IRDS in preterm infants. Exogenous surfactants – in the form of synthetic mixtures of phospholipids and extracts of lung or surfactant containing bovine or porcine SPs B, C, and phospholipids – have been used extensively for prevention and therapy of RDS in newborn infants.[42] Surfactant replacements with preparations containing SPs B and C act rapidly, increasing lung volumes, and compliance and decreasing the requirements for positive-pressure ventilation and oxygen. Morbidity and mortality from IRDS have been markedly reduced since the application of surfactant replacement for preterm neonates, decreasing barotrauma, pneumothorax, and mortality. Surfactant replacement is given intratracheally resulting in improved lung function and oxygenation. Synthetic surfactants lacking SPs improve lung function in a delayed manner, and treatment with both synthetic and protein-containing surfactants were effective in decreasing morbidity and mortality from IRDS in clinical studies. Animal-based surfactant preparations containing SP-B and SP-C are now standard treatment for IRDS. The effectiveness of surfactant therapy is likely related to the immediate surface tension–reducing properties and to the reuptake and reutilization of the exogenous surfactant lipids by the respiratory epithelium. Following preterm birth, production of endogenous surfactant lipids and proteins by the respiratory epithelium is rapidly induced; therefore, surfactant replacement is primarily utilized in the first few days following birth. Surfactant replacement has been used successfully in the treatment of meconium aspiration and pneumonia in neonates.

SURFACTANT HOMEOSTASIS IN ADULT RESPIRATORY DISTRESS SYNDROME

ARDS occurs in association with trauma, sepsis, long bone fractures, thermal burns, and injury to the lung from aspiration of gastric contents, pneumonia, inhalation of toxic gases, and infection (see Chapter 141). In ARDS, increased permeability of the microvasculature permits leakage of protein and fluid into the lung, inactivating surfactant. Epithelial cell injury may also contribute to surfactant deficiency in ARDS. Various non-SPs and lipids present in elevated concentrations in the lung in ARDS have been implicated in reducing surface activity of pulmonary surfactant; these include immunoglobulins, albumin, fibrinogen, fatty acids, lysophosphatidylcholine, and C-reactive protein. The mechanisms causing the decrease in surfactant activity in ARDS include competition of the proteins for the air–liquid interface, sequestration and dilution of surfactant in non–surface-active particles, and inhibition of SP and lipid synthesis and secretion. Alterations in surfactant composition occur during ARDS and may precede the development of respiratory failure.[43] Phospholipid, SP-A, and SP-B concentrations are decreased, and the minimum surface tension of surfactant tested in vitro is increased

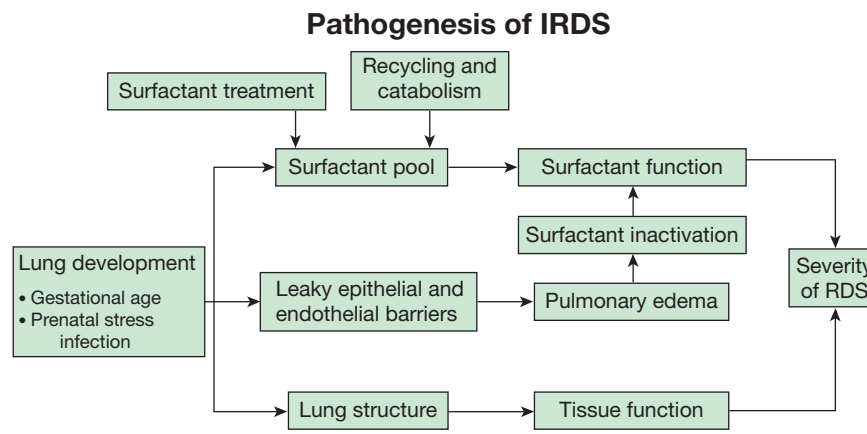

Figure 5-4 Factors influencing the pathogenesis of idiopathic respiratory distress syndrome. The pathogenesis of idiopathic RDS is multifactorial. Immaturity of the alveolar type II cells results in decreased surfactant pools. Lung collapse and injury are caused by surfactant deficiency. Alveolar damage causes leakage of serum proteins and edema that inactivate surfactant, increasing the severity of respiratory distress. Surfactant treatment reduces surface tension, restores phospholipid pool sizes, and improves alveolar–capillary leak to maintain surfactant function. *(Used with permission of Dr. Alan Jobe.)*

in patients at risk for ARDS. In ARDS, total phospholipid, PC, PG, and surfactant proteins SP-A and SP-B are decreased and the ratio of small to large aggregates is significantly increased compared to that in non-ARDS patients. Thus, ARDS leads to both a deficiency in pulmonary surfactant constituents and inhibition of the activity of the remaining surfactant. While surfactant has been effective in ARDS syndromes in laboratory experiments, to date, clinical studies have not supported the routine use of surfactant replacement for RDS in adult patients. In contrast, application of careful ventilatory support has improved outcomes in ARDS.

INHIBITION OF SURFACTANT ACTIVITY DURING LUNG INJURY

Phospholipases A_2 and C and their products, fatty acids, lysoPC, and dipalmitin inhibit surface activity in vitro. These molecules may be released or produced during lung injury. Inhibitory effects of oleic acid may be related to its miscibility with phospholipids, disrupting the interfacial surfactant film, rather than by competition for the interface. The inhibition by PAF, lysoPC, and oleic acid is not reversible, suggesting that their direct interaction with surfactant lipids disrupts lipid organization needed to form stable films. In contrast, palmitic acid improves surfactant function of preparations used for therapy of IRDS. The surface activity of pulmonary surfactant is readily destroyed by phospholipase A_2 or phospholipase C. Oxygen therapy, used routinely for ARDS and IRDS, may influence surfactant homeostasis and function in the alveolus. The rate of synthesis of surfactant lipids and clearance of radiolabeled surfactant extracts decreased in rabbits exposed to 100% O_2 for 64 h. In contrast, exposure of adult rats to 85% O_2 increased expression of surfactant proteins SP-A, SP-B, and SP-C and phospholipids. Oxidants are also released locally in the lung by activated immune cells. Activated alveolar macrophages secrete NO and superoxide, which can then react to form peroxynitrite that can oxidize and inactivate proteins and lipids.[44] Peroxynitrite inhibited the surface activity of surfactant, damaging both lipids and SPs.[42]

PLASMA PROTEINS INACTIVATE PULMONARY SURFACTANT

Edema fluid leaks into the airspace in both ARDS and IRDS. Edema fluid obtained from hyperoxia-exposed rabbits contains serum proteins capable of inhibiting surface activity of surfactant extracts, as evaluated in the pulsating bubble apparatus. Thus edema fluid may interfere with surfactant therapy, although the concentration dependence of the inhibition suggests that increased doses of surfactant may aid in overcoming the inhibitory effects of edema fluid. Serum albumin, globulin, and fibrinogen reduce the rate of adsorption, increase the minimum surface tension of the surfactant film, and reduce the hysteresis area between compression and expansion curves in vitro. The mechanism by which plasma proteins inhibit the activity of pulmonary surfactant is likely to be one of competition for the interface, because higher surfactant lipid concentrations overcome albumin inhibition even at high albumin concentrations. Inhibition by C-reactive protein, fibrinogen, and other plasma proteins is reversible. Addition of SP-A and organic surfactant extracts reverses inhibition caused by soluble proteins but not by lysoPC. Both SP-C and SP-B increase the ability of a phospholipid mixture to resist inhibition of surface activity by plasma proteins. SP-B is more effective than SP-C at resisting inhibition by fibrinogen. Optimal resistance to surfactant inhibition by serum protein was observed when both SP-C and SP-B were present.

REDUCTION OF SURFACTANT SYNTHESIS IN ARDS

In addition to the inactivation of pulmonary surfactant by proteins and lipids in edema fluid, a reduction of synthesis of surfactant may contribute to the decreased surfactant activity in ARDS. *Escherichia coli* endotoxin inhibited surfactant synthesis in lung organ cultures. Synthesis of SPs is also influenced by inflammatory responses following lung injury or infection. TNF-α decreased de novo synthesis of SP-A, SP-B, and SP-C mRNA and caused respiratory distress when administered intratracheally to the mouse. TGF-β1, produced during lung injury, decreased the expression of SP-A and SP-C in vitro. Thus, sepsis or lung injury may reduce both the synthesis and functions of surfactant lipids and proteins.

SUMMARY

Pulmonary surfactant is required for airbreathing after birth and for protection of the lung from microbial pathogens and toxicants. Surfactant homeostasis requires the integrated functions of SPs and lipids to reduce surface tension in the alveolus. Decreased production or inactivation of pulmonary surfactant has been associated with both IRDS and ARDS. Mutations in genes mediating surfactant synthesis (ABCA3, SFTPA, SFTPB, SFTPC, TITF1, and CSFR2A receptors) are rare genetic causes of acute or chronic lung diseases.[1–5,15,45] Identification of the genes and proteins mediating alveolar homeostasis provides the knowledge and tools to diagnose and treat rare lung diseases caused by disorders of surfactant homeostasis.

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CHAPTER 6

Mucociliary Clearance

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Mucus forms an essential barrier that protects the lungs from inhaled particles, pathogens, and toxicants. However, excessive mucus accumulation contributes to the pathogenesis of all the common diseases of the airways. Therefore, understanding airway mucus function and dysfunction is important for pulmonary medicine. The airway mucus barrier is mobile, continually propelled in a proximal direction by ciliary beating. Ciliary dysfunction causes disease both because of the failure to clear xenobiotics from the lungs and because it results in mucus accumulation. Mucus and ciliary biology will be considered together in this chapter as they interact to achieve, or fail to achieve, airway clearance.

MUCOCILIARY CLEARANCE IN HEALTH

AIRWAY SURFACE LIQUID

Liquid in the airway lumen is distributed between two distinct layers—a mobile mucus layer and a stationary periciliary layer (Fig. 6-1). Secreted polymeric mucins are the principal macromolecular components of the mucus layer, whereas membrane-tethered mucins and nonmucin glycoconjugates are the principal macromolecular components of the periciliary layer.

Mucus Layer

Normal mucus has physical characteristics on the border between a viscous fluid and a soft and elastic solid. Its physical state can vary with the extent of hydration and other conditions as described below in Mucociliary Dysfunction in Disease. Mucus is formed by a network of mucin polymers in water, with water accounting for ~98% of the mass, mucins 0.7%, and salts and nonmucin macromolecules the remainder. Mucins are exceedingly large glycoproteins (monomeric masses up to 3×10^6 Da) that link up to form long chains and branched networks. MUC5AC and MUC5B are the major secreted mucins in the airways.[1–3] They exhibit similar molecular weights and primary structure (Fig. 6-2A), but differ in function (see Secretory Cells) and polymer structure. Whereas MUC5B forms end-to-end polymers (Fig. 6-2B), emerging data suggest that MUC5AC forms branched covalent networks. They have characteristic regions rich in serine and threonine residues linked by their hydroxyl side groups to sugar chains (*O*-glycosylation) that account for 50% to 90% of the mass of mucins.

Mucins are packaged dehydrated in secretory granules. After secretion, they rapidly adsorb several hundred fold their mass of water, so it is critical there be sufficient airway surface liquid.[4] Insufficient liquid results in formation of a gel that is too viscoelastic to be readily cleared by ciliary motion or cough. Once immobile mucus plaques are formed, they swell only very slowly if subsequently exposed to additional liquid because of the high degree of entanglement of the mucin polymers. Besides the need for sufficient surface liquid, adequate bicarbonate must be present in the liquid to allow proper mucus maturation by chelating calcium. In secretory granules, calcium organizes the folding of mucin polymers, and must dissociate to allow mucus expansion.[5–7] Chloride and bicarbonate are both secreted into

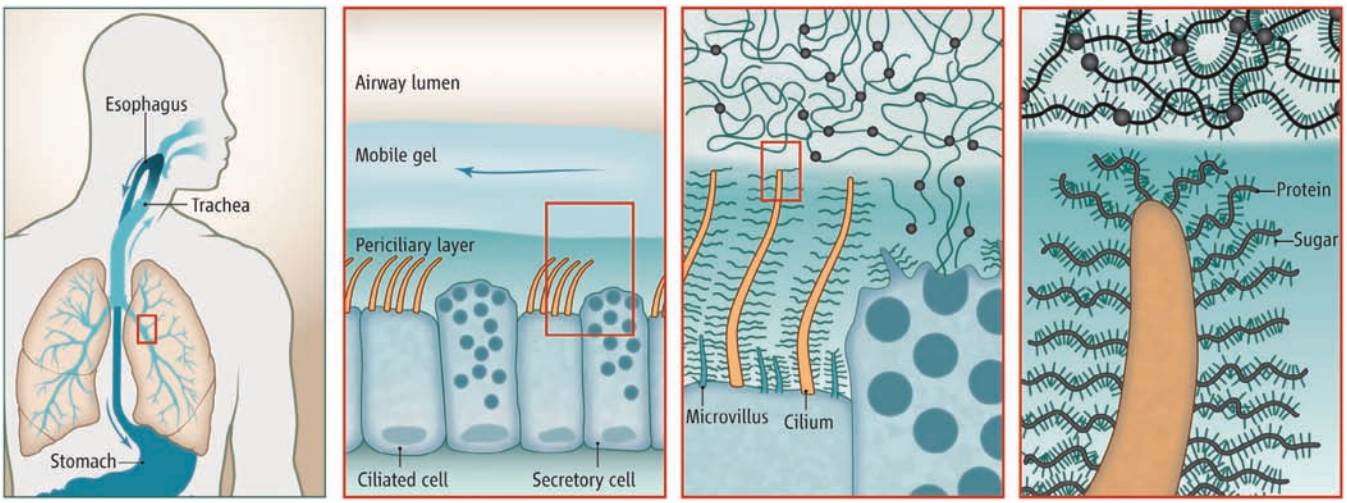

Figure 6-1 Airway surface liquid layers. **A.** Mucus is continuously produced in the conducting airways of the lungs, and swept by ciliary action from distal to proximal airways. After passing through the larynx, mucus is swallowed. **B.** The mobile mucus layer *(light blue)* glides over a periciliary layer of higher osmotic modulus *(dark blue)*. **C.** Airway secretory cells synthesize and secrete mucin polymers that interact with water to form the mobile mucus layer. Ciliated cells are covered by a dense glycocalyx containing glycosaminoglycans, membrane-tethered mucins, and other glycoconjugates that give the periciliary layer its high osmotic modulus. **D.** Mucin polymers are illustrated in the mucus layer with the protein core shown in *black*, sugar side chains in *blue*, and sites of end-to-end polymerization as *black circles*. Membrane-tethered mucins are shown densely coating cilia, while other glycoconjugates are not illustrated. *(Reproduced with permission from Dickey BF: Biochemistry. Walking on solid ground, Science. 2012;337(6097):924–925.)*

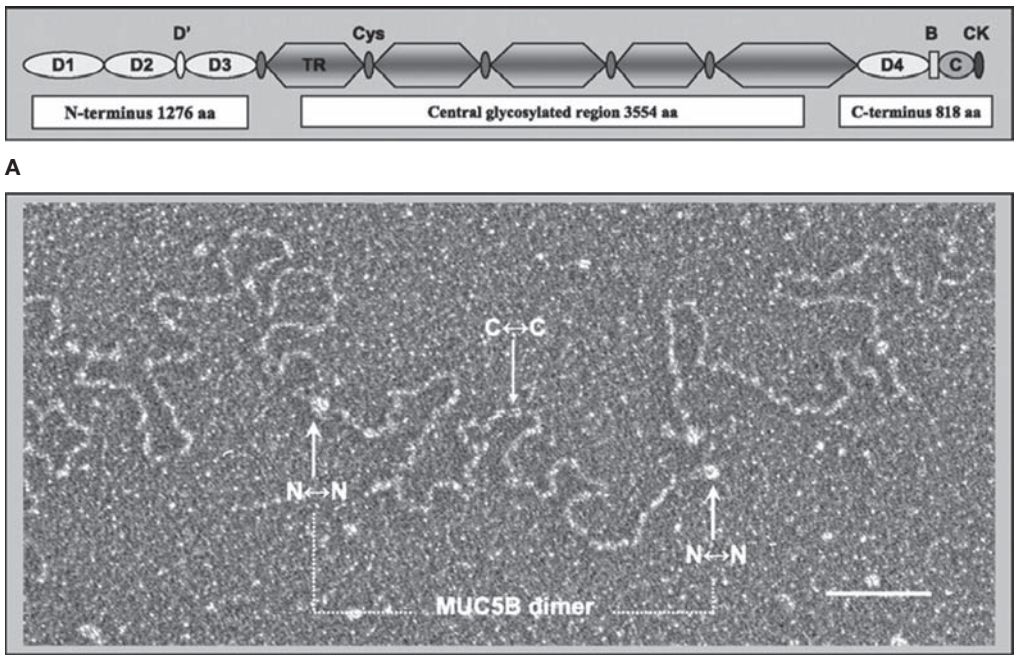

Figure 6-2 The structure of MUC5B. **A.** Structural domain representation of the MUC5B monomer. MUC5B has Von Willebrand factor (VWF)-like domains at NH_2- and COOH-terminal regions (D, B, C, and CK domains). The central region contains five heavily glycosylated, tandem repeat (TR), mucin domains and five small cysteine-rich (cys) regions. **B.** Electron microscopy image of a conformationally relaxed, linear MUC5B molecule. The MUC5B intact molecule in mucus is assembled from disulfide bond-mediated interactions between COOH-terminal domains of monomers to form dimers, and subsequent interactions between NH_2-terminal domains to form higher polymer oligomers. The assignment of the structure as a dimer (dotted bar) is made on the basis of the length (850 nm), which is greater than that obtainable by a single MUC5B monomer. The N↔N terminal region and C↔C terminal region can be identified by their size. Scale bar, 100 nm. *(Reproduced with permission from Kesimer M1, Makhov AM, Griffith JD, et al. Unpacking a gel-forming mucin: a view of MUC5B organization after granular release. Am J Physiol Lung Cell Mol Physiol. 2010;298(1):L15-L22.)*

the airway lumen by the cystic fibrosis transmembrane regulator (CFTR). Since the airway epithelium is quite water-permeable, water follows chloride and bicarbonate into the airway lumen.[8] Additional hydration can be provided by other chloride channels as described below in "Mucociliary Dysfunction Disease the sections "Secretory Cells" and "Asthma."

Mucus is produced throughout the conducting airways down to the level of the smallest bronchi and the larger bronchioles, but not in terminal or respiratory bronchioles (Fig. 6-3A). Bronchioles lack submucosal glands, and overall it is estimated that two-thirds of airway mucus is produced by surface epithelial cells and one-third by submucosal glands in primates (Fig. 6-3B).[9] In the most distal airways, the mucus layer is vanishingly thin, but it becomes increasingly thick as it travels proximally, both because additional production adds to its bulk and because the total cross-sectional area of the airways progressively narrows. In the trachea, the mucus gel layer is ~50 μm thick. Besides mucus acting as a simple physical barrier, the mucin sugar side chains act as a combinatorial library to bind particles and pathogens, and a thicker mucus layer has been shown to protect against infection.[10]

Periciliary Layer

It was widely believed until recently that cilia beat in a watery layer of lower density than the overlying mucus layer. However, recent data indicate that the periciliary layer has a higher density than the mucus layer due to a high concentration of membrane-tethered mucins (MUC 1, 4, and 16) and mucopolysaccharides (also called glycosaminoglycans).[11–13] This finding has several important implications for airway function.[14] First, it helps to explain how distinct layers form because dense packing of the grafted glycoconjugates of the periciliary layer tends to exclude the unattached polymeric mucins of the mucus layer (Fig. 6-1C). Second, charged polymers are highly effective lubricants in an aqueous environment, allowing low friction ciliary beating despite the high density of grafted glycoconjugates, and low friction between the periciliary and gel layers. Third, spatial impingement by grafted glycoconjugates may physically couple neighboring cilia to coordinate their beating (Fig. 6-1C). Fourth, glycoconjugates are grafted with increasing density from the top of the periciliary layer to the bottom, which should propel exogenous particles and pathogens out of the periciliary layer for removal by the mobile mucus layer. Fifth, the higher density of water-avid glycoconjugates in the periciliary layer and their grafting to the cell surface results in a nearly constant amount of liquid in this layer except under conditions of severe underhydration. In conditions of overhydration, liquid is transferred to the mucus layer, which is generally well tolerated.

■ AIRWAY EPITHELIAL CELLS

The surface airway epithelium forms a mosaic of two major cell types—secretory and ciliated (Figs. 6-1, 6-4, and 6-5). In addition, basal cells that do not contact the airway lumen serve as progenitors in the proximal airways, and neuroendocrine cells that secrete basolaterally toward sensory neurons are scattered throughout the airways. Secretory and ciliated cells are multilayered and have a tall columnar shape in proximal airways but become single layered and progressively shorter in distal airways until they have a cuboidal shape in bronchioles. Ciliated cells are more abundant than secretory cells in proximal airways, whereas secretory cells are more abundant in distal airways.

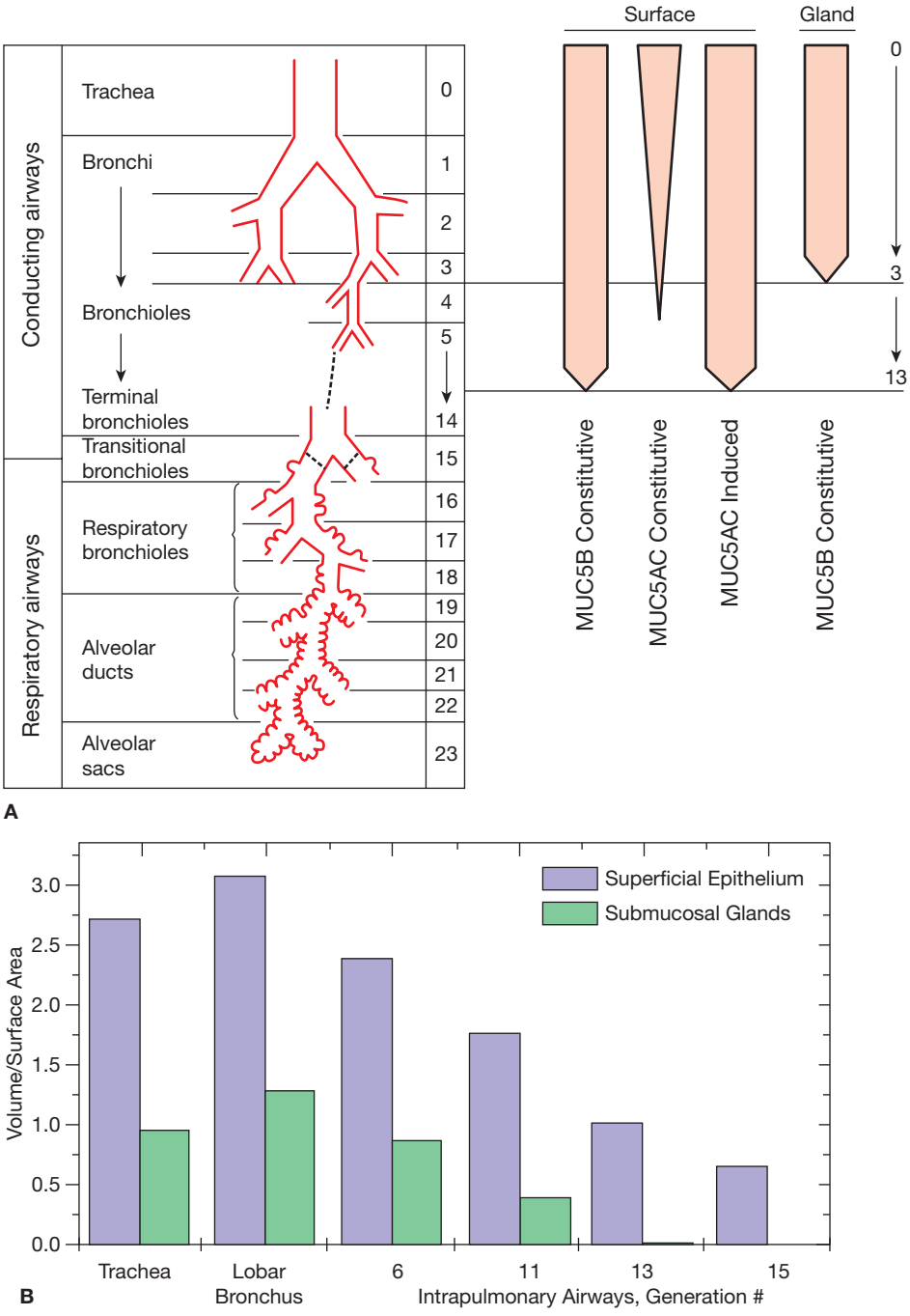

Figure 6-3 Mucin production in conducting airways. **A.** MUC5B is produced constitutively by surface epithelium down to the level of bronchioles proximal to terminal bronchioles, and by submucosal glands present in the trachea and bronchi but not bronchioles. MUC5AC is produced constitutively by surface epithelial cells with a goblet morphology in more proximal airways, and its production can be induced in nongoblet secretory cells that produce MUC5B down to the level of terminal bronchioles. Airway generation is listed numerically in the third column. **B.** The relative amount of mucin produced by surface epithelium and submucosal glands has been estimated by morphometric analysis of the airways of rhesus monkeys stained with Alcian blue/PAS, expressed as the ratio of volume of stained material ($mm^3 \times 10^{-3}$) per unit area of basal lamina (mm^2). *(A: Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963; B: Reproduced with permission from Plopper CG1, Heidsiek JG, Weir AJ, et al. Tracheobronchial epithelium in the adult rhesus monkey: a quantitative histochemical and ultrastructural study, Am J Anat. 1989;184(1):31–40.)*

Secretory Cells

Subsets of airway secretory cells have been given different names based upon differences in their microscopic appearances, including goblet and club (Clara) cells. However, molecular techniques reveal overlap between these subsets, such as the presence of CCSP (SCGB1A1) in cells with a goblet morphology that express mucin, and the presence of MUC5B in cells with a club morphology.[15–17] Secretory cells are unified by the stable expression of an apical-regulated exocytic machinery,[18,19] whereas the presence of secretory products such as mucins and secretoglobins varies with exposure to extracellular signals that acutely regulate their expression and secretion (Fig. 6-5). Therefore, it is simplest to refer to these cells generically as airway secretory cells, while further specifying their appearance, airway level, and gene expression as appropriate.

Secretory cells in bronchi and proximal bronchioles constitutively express MUC5B (Figs. 6-3 and 6-5), whereas secretory cells in terminal and distal bronchioles do not express MUC5B either constitutively or inducibly.[1,15,20] The same bronchial and proximal bronchiolar secretory cells that express MUC5B can also express MUC5AC, with MUC5AC expressed constitutively in proximal airways but only inducibly in distal airways (Figs. 6-3 and 6-5). Mice with deletion of Muc5b die postnatally from upper and lower respiratory tract inflammation and infection.[21] In contrast, mice with deletion of Muc5ac are healthy at baseline but fail to clear parasitic worms from their guts,[22] and induced expression of Muc5ac in rat lungs prevents worms from transiting the lungs.[23] Thus, Muc5b/MUC5B appears to be the principal mucin functioning in baseline clearance of the airways, while Muc5ac/MUC5AC appears to function principally in parasite defense.

The effector function of Muc5ac in parasite defense dovetails well with the central role of IL-13 in parasite defense and the ability of IL-13 to strongly induce expression of Muc5ac/MUC5AC (>100-fold

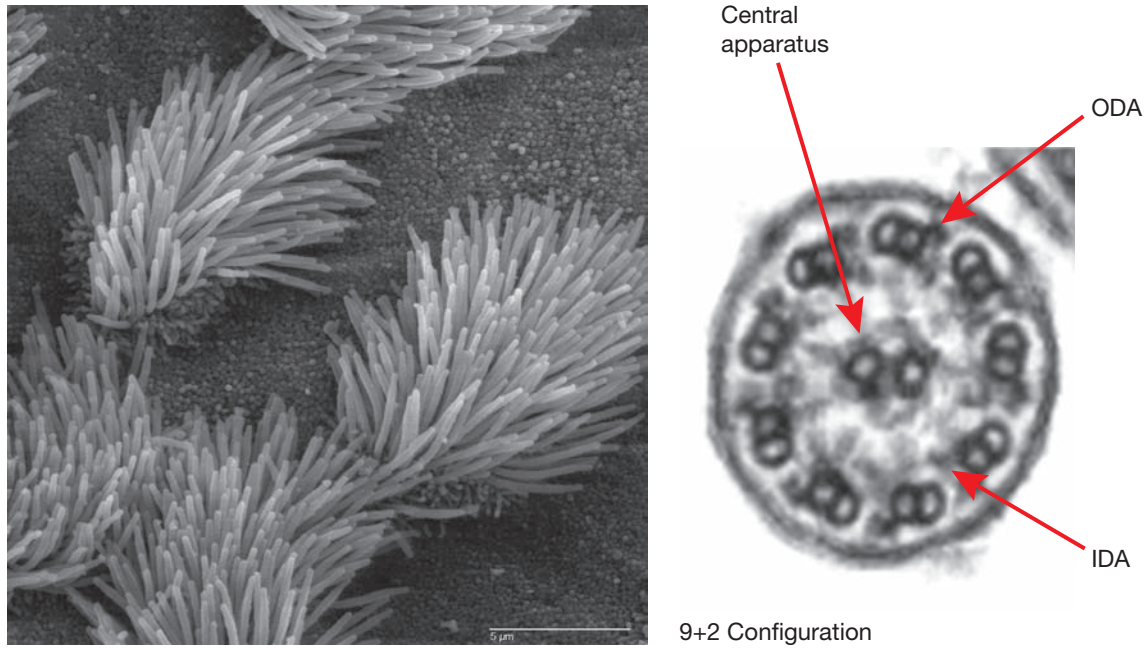

Figure 6-4 Cilia structure. **A.** Scanning electron micrograph of mouse tracheal epithelium showing both ciliated and nonciliated cells. Note the difference in size between the microvilli (on nonciliated cell surfaces) and the cilia. Scale bar, 5 µm. **B.** Transmission electron micrograph of an airway cilium in cross section showing the 9+2 configuration of the microtubules. Arrows point to the central pair of microtubules, and to the outer dynein arms (ODA) and inner dynein arms (IDA) that are critical for ciliary movement and common sites of mutation in PCD. *(A: Photograph used with permission of Charles Daghlian, Dartmouth Electron Microscope Facility. Released to the public domain, via Wikimedia Commons.)*

in cultured human airway cells and 40-fold in mice in vivo).[24–26] Other cytokines that promote mucin gene expression include IL-1β, 4, 6, 9, 23, and 25, but whether they do this directly or by amplifying the intensity of IL-13 signaling is not yet clear.[1] Complement protein C3a, epinephrine, and γ-aminobutyric acid signaling interact with IL-13 signaling to augment Muc5ac expression.[1] ClCa1 is a secreted protein that signals in an autocrine and paracrine fashion in response to IL-13 to increase Muc5ac/MUC5AC expression.[24] A network of transcription factors has been identified that regulates Muc5ac/MUC5AC expression, including STAT6, SPDEF, Foxa2, Foxa3, Notch, β-catenin and XBP-1. While some components of the signaling pathways connecting extracellular ligands with transcriptional regulation are known, such as the key roles of STAT6 downstream of IL-13 and MAPK13 downstream of ClCa1,[24,27] many details remain to be elucidated. The pathways and transcription factors regulating Muc5b/MUC5B expression have been less studied, probably reflecting the fact that expression of this mucin is relatively stable compared to Muc5ac/MUC5AC.[28] However knowledge of the regulation of MUC5B expression during development is likely to give important insight into cell fate specification in the airway, and the recent discovery of aberrant MUC5B expression in interstitial lung diseases highlights its clinical importance (see the section "Interstitial Lung Diseases"). Along with production of the polymeric mucins themselves, specialized enzymes required for glycosylation (e.g., GalNAc-T),[29] folding and polymerization (e.g., AGR2),[30] and other aspects of mucin processing are produced by airway secretory cells.

Mucins are secreted into the airway lumen at a low basal rate and a high stimulated rate. A regulated exocytic mechanism mediates both rates as indicated by abnormal phenotypes in both basal and stimulated secretion when Munc13-2, a sensor of second messengers, is deleted in mice.[16] Additional molecular components of the exocytic mechanism have been identified and their function studied (Fig. 6-6).[18,19,31,32] The rate of mucin secretion is regulated by the second messengers calcium and diacylglycerol, which are generated by a signaling cascade downstream of G-protein–coupled receptors that include the $P2Y_2$ purinergic and A3 adenosine receptors.[18,33,34] ATP is released in autocrine and paracrine fashion and activates $P2Y_2$ receptors and is metabolized to adenosine. It is possible that additional ligands such as histamine and acetylcholine may serve as secretagogues in inflammation, though they may act indirectly by causing smooth muscle contraction and nucleotide release.

As secreted mucins must adsorb large volumes of water to yield mucus of normal viscoelasticity, it is important that adequate airway lumenal water be available. The autocrine/paracrine ligands ATP, adenosine, and ClCa1 regulate the expression and/or activity of CFTR, the calcium-activated chloride channel (CaCC) TMEM16 A, and solute carrier family 26, member 9 (SLC26A9) to control chloride secretion.[24,33,35] As these same ligands regulate mucin production and/or secretion as described earlier, mucin release is thus coordinately regulated with water translocation.

Besides their role in mucin production and secretion, airway secretory cells serve as progenitors of both secretory and ciliated cells.[36] They also express components of the cytochrome P450 system that inactivates toxic inhaled organic compounds by oxidation.[37] They secrete antimicrobial peptides and reactive oxygen species constitutively, and they are capable of sensing pathogens and responding by augmenting their antimicrobial defenses and signaling to leukocytes.[38]

Ciliated Cells

Motile cilia are the defining structural and functional feature of airway ciliated cells (Fig. 6-4) (Video 6-1 Normal). They are evolutionary conserved and share homologous features with flagella of unicellular eukaryotes and mammalian sperm tails. Respiratory cilia have the "9+2" microtubular axonemal structure, which comprises nine peripheral doublets plus a central pair.[39,40] The outer doublets are linked together by proteins that form the dynein regulatory

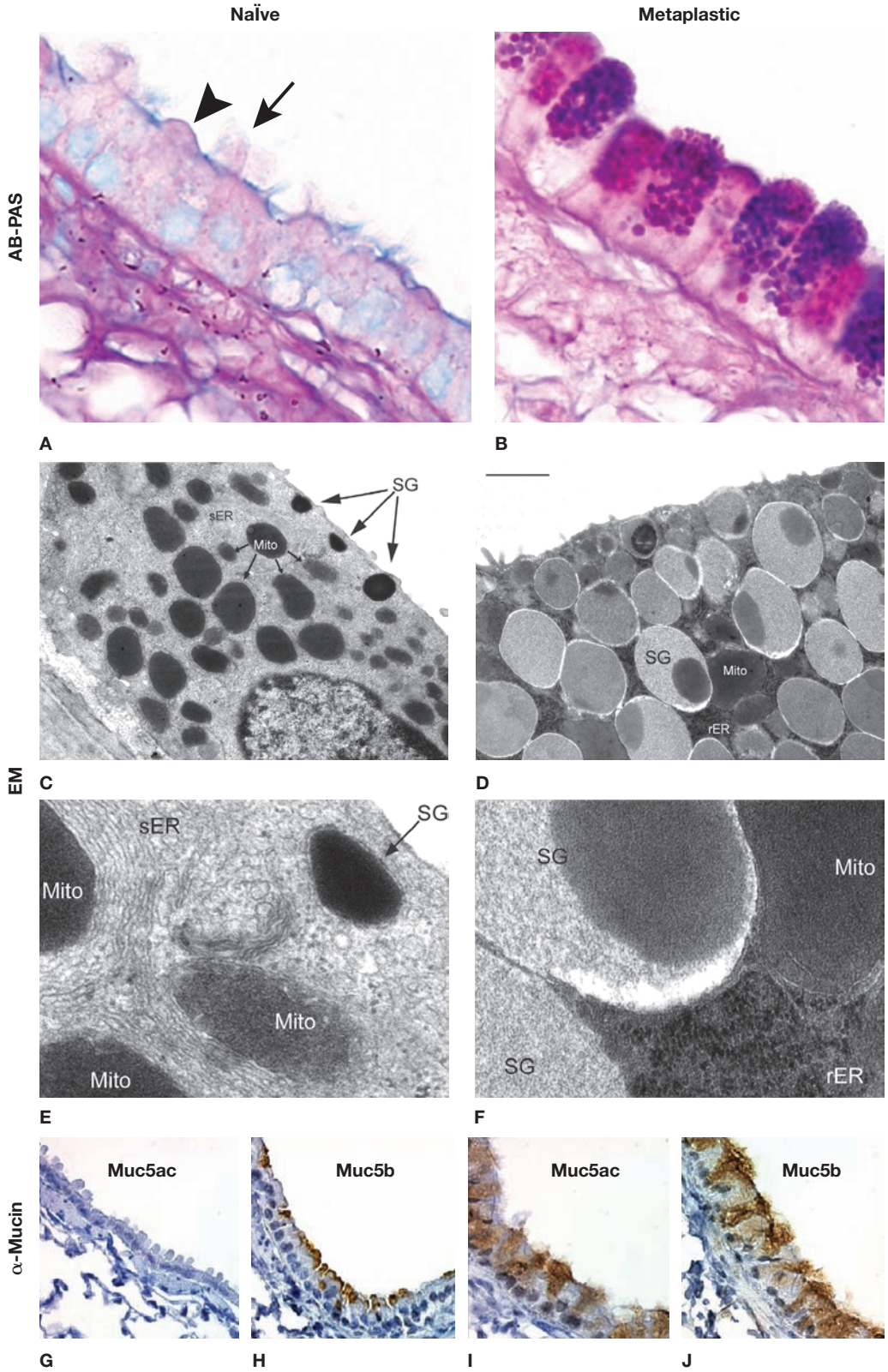

Figure 6-5 Airway epithelial mucus metaplasia. Light micrographs with AB-PAS staining (**A, B**), electron micrographs (EM) (**C–F**; low and high magnification), and immunohistochemical images using mucin-specific antibodies (**G–J**). On the left are images from the airway of a healthy mouse without airway inflammation (naïve), and on the right are images from the airway of a mouse with mucus metaplasia 3 days after the onset of allergic inflammation, as described by Evans et al.[15] Cells in the top row on the left show alternating ciliated *(arrow)* and domed secretory *(arrowhead)* cells, and on the right show prominent mucin granules in secretory cells. Cells in the EM images on the left show small numbers of electron-dense secretory granules (SG) near the apical membrane, numerous mitochondria (Mito), and abundant smooth endoplasmic reticulum (sER). Cells in the EM images on the right show numerous electron-lucent SG containing mucins and an electron-dense core, and abundant rough ER (rER). Images in the bottom row show that Muc5b is present in naïve airways even though it is not apparent by insensitive AB-PAS staining, and that both Muc5ac and Muc5b are present in the thickened metaplastic epithelium. Scale bar in the right middle panel is 10 μm for top row, 1 μm for second row, 150 nm for third row, and 30 μm for bottom row.

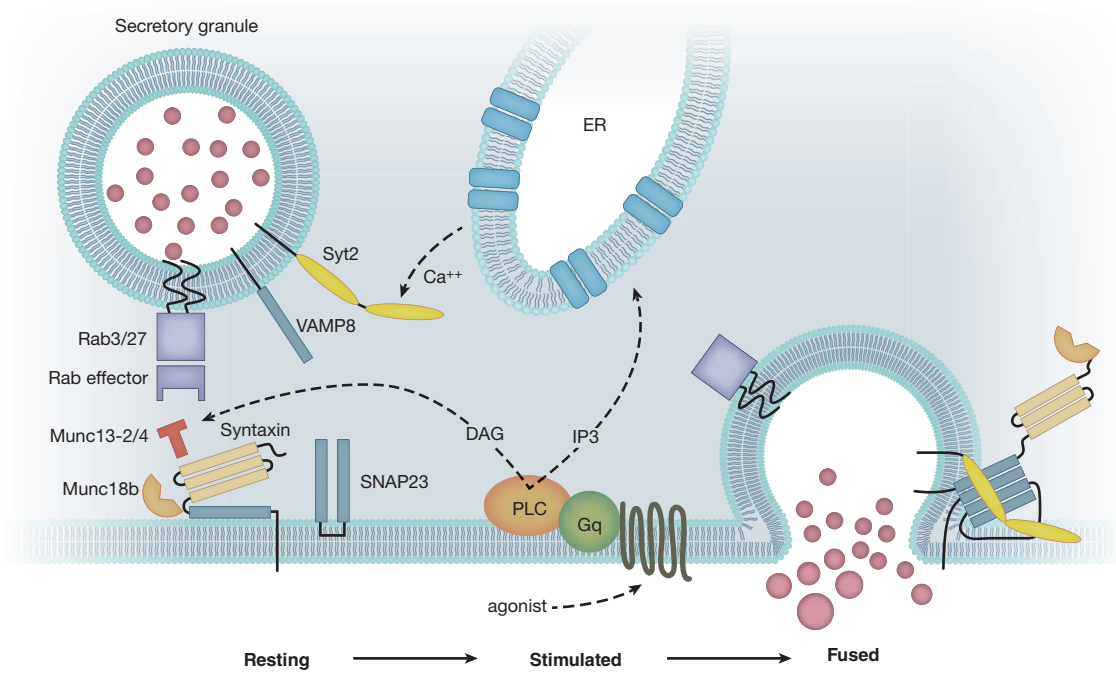

Figure 6-6 Airway mucin secretion. Initially, mucin granules become tethered to the plasma membrane by Rab proteins and their effectors in the vicinity of the exocytic SNARE proteins (VAMP8, SNAP23, and an unknown Syntaxin, shown as black bars) *(Left)*. Activation of heptahelical receptors such as those for ATP ($P2Y_2$) and adenosine (A3R) leads to activation of the trimeric G-protein, Gq, and phospholipase C (PLC), resulting in generation of the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP_3). Diacylglycerol activates the priming protein Munc13-2, and IP_3 induces the release of calcium from apical ER to activate Synaptotagmin-2 (Syt2) *(Center)*. Activation of the regulatory Munc13 and Syt proteins leads to full coiling of the SNARE proteins to induce fusion of the granule and plasma membranes. The interactions of the SNARE proteins take place on a scaffold provided by Munc18b *(Right)*. *(Adapted with permission from Davis CW1, Dickey BF: Regulated airway goblet cell mucin secretion, Annu Rev Physiol. 2008;70:487–512.)*

complex (previously known as "nexin link"), and radial spokes extend from the doublets to the central pair. Taken together, these axonemal components provide the framework for generation of a complex ciliary waveform. The key components for driving ciliary movement are the inner and outer dynein arms, which are present at repetitive multiple units of 96 nm along the length of the peripheral microtubules (doublets) and contain enzymes for ATP hydrolysis to generate force for dynein arm movement. Each cilium contains >300 different proteins and is rooted in the airway epithelial plasma membrane by a basal body, which is a modified centriole. Mutations in genes encoding any part of the axonemal structure or functional components of motile cilia, or components necessary for the biogenesis of cilia, including cytoplasmic proteins, can result in primary ciliary dyskinesia (PCD), as described below in Mucociliary Dysfunction in Disease.

The function of normal motile cilia is to provide mucociliary clearance in the conducting airways, an important innate defense mechanism of the lungs.[41] Cilia provide the coordinated motive force for mechanically clearing mucus containing infectious agents, particles, and toxic substances from the conducting airways. ATP hydrolysis in the dynein arms produces sliding of adjacent axonemal structures and generates the complex ciliary waveform that occurs in human airways.[39,40] Approximately 200 cilia per cell beat in a coordinated fashion on and across cells (Video 6-1). This coordinated vectorial synchrony results from the planar orientation that occurs during ciliogenesis, as well as refinement by cilia-driven fluid flow and the tight packing of cilia due to the negatively charged glycoproteins that coat the ciliary shaft.[11,42] The ciliary forward (power) stroke is more rapid and extends a bit more into the mucus layer than the recovery stroke.[42] Cilia beat at ~6 to 12 Hz, and propel mucus proximally at ~1 mm/min. The regulation of ciliary beat frequency involves a variety of signaling molecules and multiple feedback mechanisms.[39,43] In brief, ciliary beat frequency and mucociliary clearance do not operate at full capacity under basal conditions, but can be stimulated by several intracellular signaling mechanisms including cyclic adenosine monophosphate (cAMP)– and cyclic guanosine monophosphate (cGMP)–dependent phosphorylation of axonemal components, as well as changes in intracellular calcium and pH. In contrast, protein kinase C downregulates ciliary beat frequency.

Besides their role in moving the mucus layer, ciliated cells play additional crucial roles in airway homeostasis. They have a major function in ion transport across the airway luminal surface since both the epithelial Na^+ channel (ENaC) and CFTR are expressed predominantly in ciliated cells. Ciliated cells autoregulate airway surface hydration by sensing both macroscopic (e.g., airflow) and microscopic stresses (e.g., interaction of cilia with the mucus layer) and transmitting these signals into extracellular ATP release. Extracellular ATP regulates the balance between ENaC (inhibits) and CFTR (activates) to constantly adjust airway surface hydration.[44] In addition, ciliated cells are capable of flattening to cover epithelial gaps when secretory cells are injured.[45]

Video 6-1 Lateral view of normal ciliary activity, using high-speed videomicroscopy. Note the full range of motion (forward and backward) and coordination of ciliary beating within and across ciliated cells. *Access at www.fishmansonline.com*

SUBMUCOSAL GLANDS

In bronchial airways, submucosal glands contribute to the secretion of mucins and liquid. Each gland is connected to the airway lumen

by a superficial ciliated duct that propels secretions outward and a deeper nonciliated collecting duct.[46] The body of the gland is located between the spiral bands of smooth muscle and the cartilage plates in the airway wall. Mucus cells constitute ~60% of the gland volume, and serous cells, located distal to the mucus cells, make up the remaining ~40%. Glandular mucus cells express MUC5B almost exclusively with very little expression of MUC5AC.[1] The serous cells secrete anions, proteoglycans, and numerous antimicrobial proteins. The rate of submucosal gland secretion can be greatly increased by cholinergic, adrenergic, and peptidergic stimulation. In pathologic states such as COPD and cystic fibrosis (CF), the volume of submucosal glands can increase several fold while maintaining a normal ratio of mucus and serous cells.[47,48]

MUCOCILIARY CLEARANCE

Mucus rises up the trachea by ciliary beating, then leaves the lungs by passing through the vocal cords to enter the pharynx to be swallowed (Fig. 6-1A). The vocal cords are covered by squamous epithelium that cannot provide a propulsive surface, but the posterior commissure is covered by mucociliary epithelium and is ideally situated adjacent to the esophagus. Approximately 30 mL of respiratory mucus is propelled out of the lungs daily, carrying inhaled particles and pathogens that are excreted in the gastrointestinal tract.[49]

The rate of mucociliary clearance can be measured in human subjects by a variety of techniques, including direct bronchoscopic observation of the movement of instilled particles and external imaging of the movement of radiolabeled particles. From a practical standpoint, the only commonly used technique is the inhalation of small radiolabeled particles, such as sulfur colloid labeled with technicium-99m, followed by serial imaging with a planar gamma camera.[49,50] The movement of labeled particles from peripheral to central lung regions over the course of several hours is then measured. This technique is used for the evaluation of both disease pathophysiology and the efficacy of therapeutic interventions.[50] Mucus velocity is highest in the trachea and decreases in successive airway generations.[49] Different techniques yield different velocities, but these center around a mucus velocity of 10 mm/min in the trachea of a healthy young adult. Cough clearance provides an important backup mechanism when mucociliary clearance is impaired, and its rate can also be measured using standardized protocols of controlled coughs with imaging of the clearance of inhaled radiolabeled particles.[50]

Mucociliary clearance depends upon a mucus layer of appropriate viscoelasticity, a periciliary layer of appropriate depth, and effective ciliary beating. When these components are interacting optimally, particles and pathogens suspended in the 10,000 L of air that are inspired daily are cleared from the lungs with minimal impact on the underlying epithelium. However failure of any of these components can lead to cascading dysfunction that causes symptoms and contributes to disease pathogenesis.

MUCOCILIARY DYSFUNCTION IN DISEASE

The principal symptoms of mucociliary dysfunction are dyspnea and cough. Dyspnea is caused by reduction of the total cross-sectional area of the conducting airways from mucus occlusion. This occurs most commonly from diffuse plugging of small airways, but may also occur when a central airway becomes plugged by mucus due to an underlying anatomical abnormality. Cough is caused by the stimulation of vagal afferents in the intrapulmonary airways or larynx and pharynx. Patients often infer that laryngopharyngeal stimulation, described as "a tickle in the throat," results from postnasal drip because they recognize that mucus descends from the nasopharynx by gravity but are unaware it also ascends from the lungs by ciliary action. Physical signs of impaired mucus clearance include cough, bronchial breath sounds, rhonchi, and wheezes. Radiographically, retained mucus may appear as localized atelectasis or linear and branched opacities. It is important to recognize the role of retained mucus in disease presentation so that symptoms can be relieved and its contribution to disease progression addressed.

Asthma

The central role of diffuse airway obstruction by lumenal mucus in fatal asthma (Fig. 6-7) has been recognized by pathologists for more than 100 years and confirmed in multiple subsequent autopsy case series.[51,52] Mucus occlusion is particularly dangerous

A B C

Figure 6-7 Airway obstruction by mucus in asthma. **A.** Lungs removed at autopsy from a patient who died from asthma. The lungs did not spontaneously collapse as they normally do because the airways were obstructed by lumenal mucus and bronchoconstriction. **B.** Cut surface of the lungs from the same patient showing mucus plugs *(arrows)* filling the large airways. **C.** Light microscopic image of a small airway from another patient who died from asthma showing infiltration of the airway wall and the lumenal mucus by inflammatory cells. *(**A, B:** Used with permission of James C. Hogg, University of British Columbia; (**C**) Used with permission of Martha L. Warnock, University of California, San Francisco.)*

in asthma because smooth muscle contraction around the lumenal plugs further constricts airflow. The principal underlying cause of mucus dysfunction in asthma is mucin overproduction. This is usually driven by allergic inflammation mediated by IL-13,[53] though IL-17 can also cause mucin overproduction and airway hyperresponsiveness.[54–56] IL-13 can increase the production of MUC5AC in human airway epithelial cells in vitro more than 100-fold,[24,25] and the production of Muc5ac in the lungs of mice in vivo more than 40-fold.[26] In contrast, the production of Muc5b/MUC5B increases minimally or may even decrease at the level of transcripts.[26,57] Mucus plugs in asthma often have a rubbery quality, suggesting that the large quantities of mucins that are produced overwhelm the available airway surface liquid when they are suddenly secreted in response to inflammatory stimuli. This abnormality can occur despite the additional hydration provided by SLC26A9 and ClCa1-dependent CaCC activity that are coordinately upregulated with MUC5AC production by IL-13.[24,35] Additional contributors to abnormal rheologic properties of asthmatic mucus are a high concentration of plasma proteins resulting from increased microvessel density and permeability in the airway wall,[58,59] and the presence of granule and cytoplasmic macromolecules from eosinophils and other leukocytes. The therapeutic focus in addressing mucus dysfunction in asthma should be reducing mucin overproduction and plasma extravasation through the use of anti-inflammatory drugs. Corticosteroids have been the mainstay of treatment, but immunotherapies directed at IgE, IL-13, and IL-5 play increasing roles, and deeper understanding of pathways that control MUC5AC expression may lead to targeted therapies.

Cystic Fibrosis

Complications from the impaired clearance of airway mucus dominate the clinical course of patients with CF. Mutation of the anion channel CFTR causes an imbalance between salt and water absorption mediated by ENaC and secretion mediated by CFTR that results in insufficient airway surface liquid.[60] Defective CFTR function also produces deficient bicarbonate transport that results in impaired mucin unfolding.[5,7] Together these deficiencies lead to the formation of mucus with an abnormally high mucin concentration and viscoelasticity that is poorly cleared by ciliary motion. This problem is compounded when the insufficiency of airway surface liquid becomes so severe that the periciliary layer loses height such that cilia cannot beat and the dehydrated mucus layer adheres to periciliary glycoconjugates.[11,14] Retained lumenal mucus is apparent pathologically in small airways and glandular ducts early in life.[61] Eventually, the failure of mucociliary clearance results in airway colonization with bacteria and fungi, and paradoxically, the mucus gel layer that evolved to protect the lungs from infection instead provides a protected environment for microbial growth. Besides the mechanical problems of mucus clearance in CF, there are likely additional defects in host defenses. For example, the deficiency of bicarbonate secretion results in acidification of airway surface liquid which impairs antimicrobial protein function,[62] and CFTR normally transports thiocyanate that is oxidized by lactoperoxidase to form isothiocyanate, an antimicrobial effector of the innate immune system that is variably reduced in CF.[63] Microbial infection leads to inflammation, and cellular debris such as DNA and actin from necrotic leukocytes further impairs the biophysical properties of mucus. Hydration therapy with aerosolized hypertonic saline solution has become a mainstay of the therapy of CF, together with aerosolized DNase and aerosolized antibiotics. Further discussion of the pathogenesis and therapy of CF is found in Chapter 50.

Video 6-2 Lateral view of defective ciliary function in Primary Ciliary Dyskinesia (PCD) associated with defective outer dynein arms (ODAs). Note the very limited range of motion, which gives the appearance of the cilia being "stiff." *Access at www.fishmansonline.com*

Primary Ciliary Dyskinesia

PCD is a genetically heterogeneous recessive disorder of motile cilia with an estimated incidence of 1 per 10 to 20,000 births.[64] However, due to the inadequacies of diagnostic methods that involve studies of ciliary ultrastructure and/or function, there are only ~1000 patients in the United States with a well-established diagnosis of PCD. Clinical disease reflects defective function of motile cilia in the conducting airways, paranasal sinuses, middle ear (eustachian tube), and the reproductive tract (Video 6-2, ODA defect). Respiratory distress occurs in >80% of full-term neonates with PCD, and infants and children have daily nasal congestion and year-round wet cough occurring soon after birth.[65] Chronic otitis media and recurrent sinus infections are also common. Cough clearance is preserved in PCD compared to CF, which may partially compensate for defective mucociliary clearance; however, recurrent bacterial infections occur in the lower airways, and ~65% of older pediatric patients and all adults have bronchiectasis with predilection for the middle lobe, lingula, and basal segments. Abnormal lung function develops early in life in PCD infants and young children, and spirometry worsens with increasing age.[65] Respiratory microbiology is similar to CF, though chronic *Pseudomonas aeruginosa* infection occurs at an older age in PCD. The prevalence of nontuberculous mycobacterial infection also parallels that seen in CF, with ~15% of adults and a lower percentage of children infected.

The diagnosis of PCD is challenging, because current diagnostic techniques are not standardized or readily available. Identification of PCD requires recognition of key phenotypic features, which include neonatal respiratory distress and situs inversus or ambiguous.[64,65] Identification of ciliary ultrastructural defects by electron microscopy can no longer be the sole "gold standard" for diagnosis because of technical limitations in its routine performance and the fact that at least 30% of PCD patients have normal ultrastructure.[66] The majority of electron microscopic abnormalities involve defective outer dynein arms or combined defects in outer and inner arms. Isolated inner dynein arm defects account for <5% of electron microscopic defects, and false-positive diagnoses commonly occur. Assessment of ciliary motility has been used to confirm a diagnosis of PCD, but technical limitations also preclude this as the sole diagnostic method. Mutations have been described in 21 genes that cover ~65% of PCD patients, and there is strong correlation between mutations in specific genes and defects in ciliary ultrastructure and function. Diagnostic capabilities have recently benefited greatly from measurement of nasal nitric oxide (nNO), which is low in PCD (10%–20% of normal, or <77 nL/min) regardless of the mutated gene.

There are no validated PCD-specific therapies, and treatment for PCD lung disease is extrapolated from other diseases with abnormal mucociliary clearance, particularly CF. Airway clearance therapies, inhaled antibiotics, oral macrolides, and inhaled hypertonic saline solution are useful in CF; thus, these therapies are being used in PCD. Otolaryngologic complications of middle ear disease and sinusitis are managed by standard approaches.

COPD

A role for mucus dysfunction in COPD has long been recognized in the syndrome of chronic bronchitis, defined as a persistent cough

that produces sputum for at least 3 months per year in 2 consecutive years. The productive cough probably results from mucus overproduction in proximal airways due to surface epithelial mucus metaplasia and submucosal gland expansion, combined with ciliary dysfunction.[1,67] More recently a second role for mucus dysfunction in COPD has been recognized in the widespread obstruction of small airways identified in pathologic analysis of resected surgical specimens.[68,69] The extent of small airway mucus occlusion correlates with the degree of airflow obstruction, occurs even in patients with an emphysematous phenotype, and predicts longevity. These two mucus phenotypes in COPD – productive cough and airflow obstruction – correlate only weakly.[67] These findings suggest that individuals have differential susceptibility to the effects of cigarette smoke on different aspects of mucociliary clearance, as well as reflecting the independent roles of emphysema and small airway fibrosis in airflow obstruction in COPD.

Mucus overproduction and ciliary dysfunction both result from exposure to toxic products in cigarette smoke and environmental pollutants. Among these products, acrolein is a particularly potent inducer of MUC5AC production.[70] In ciliated cells, cigarette smoke causes both structural and functional changes.[71] Besides these effects, cigarette smoke also decreases airway surface liquid by reducing CFTR function and increasing ENaC function.[72] As is the case in CF, impaired mucociliary clearance results in persistent airway infection, particularly with unencapsulated *Haemophilus influenzae*. Further discussion of the pathogenesis and therapy of COPD is found in Chapters 40 and 42.

Interstitial Lung Diseases

A link between mucus dysfunction and interstitial lung disease was not suspected until a genome-wide association study in 2011 found genetic linkage between a polymorphism in the MUC5B promoter and both familial interstitial pneumonia (FIP) and idiopathic pulmonary fibrosis (IPF). The promoter variant is present in 50% to 60% of individuals with FIP or IPF compared to 19% of unaffected individuals, and increases the risk of disease 7-fold in heterozygotes and 21-fold in homozygotes.[73] Subsequent studies have extended the association to other idiopathic interstitial pneumonitides[74] and subclinical radiographic interstitial abnormalities.[75] The presence of the promoter variant is associated with improved survival in patients with IPF.[76] The promoter variant causes overexpression of MUC5B, but whether disease ensues because of mucus dysfunction in the airway lumen, an epithelial stress response induced the demands of synthesizing such a large and complex molecule, or some other mechanism is not yet known. Further discussion of the pathogenesis and therapy of IPF is found in Chapters 28 and 56.

Other Diseases

Acquired bronchiectasis may be due to a variety of causes including an unrecognized genetic disorder, a respiratory infection early in life, or immunodeficiency. Similar to CF, retained mucus and airway infection dominate the clinical course. Aerosolized 7% hypertonic saline solution treatment has been shown to improve lung function and quality of life.[77]

Viral respiratory infections commonly lead to mucociliary dysfunction, both because of increased mucin production and injury to ciliated cells. In subjects with underlying asthma, viral respiratory infections are a common cause of exacerbation.[78]

Allergic bronchopulmonary aspergillosis (ABPA) can present with symptoms and clinical findings that range from mild to severe. Florid overproduction of MUC5AC resulting from allergic inflammation induced by the persistent fungal infection can lead to atelectasis and mucus impaction of small or large airways. ABPA is addressed in greater detail in Chapter 48

Panbronchiolitis is a syndrome of small airway inflammation and mucus obstruction that occurs predominantly in Asian subjects, and was reported to be associated with a polymorphism in the MUC5B promoter.[79] A molecular mechanism of mucin gene dysfunction has not been identified, nor is it yet known whether there is a relationship between promoter dysfunction in panbronchiolitis and in the interstitial lung diseases.

Localized anatomic abnormalities of the airways, such as the presence of a stricture, a surgical anastomosis, or a therapeutic stent, can result in localized mucus accumulation that can lead to infection or airway closure. It may be possible to remove the localized mucus accumulation by flexible or rigid bronchoscopy, and instillation of sodium bicarbonate solution may partially dissolve the mucus.

Retained mucus is a common problem in intubated patients and those in whom lung mechanics are disrupted as a result of paralysis, immobilization, or surgery; atelectasis and pneumonia are frequent complications in such patients.[1]

Treatment

Therapies for mucus dysfunction can be divided into those that treat mucin production, mucin secretion, mucus clearance, or airway infection.[1] Mucin overproduction has been effectively treated in asthma with the use of corticosteroids and newer drugs that target allergic inflammation, though these agents have not been very effective in neutrophilic airway inflammation as occurs in COPD and CF. Despite evidence of a general role of the EGF receptor in mucin production, an inhibitor did not show benefit in COPD patients.[80] In view of the generally pathologic role of MUC5AC and generally homeostatic role of MUC5B, strategies that selectively target MUC5AC production are attractive. Inhibiting mucin secretion may seem to be an obvious strategy to treat combined overproduction and secretion (mucus hypersecretion), and is being pursued using modified botulinum toxins and MARCKS inhibitors.[1] However it may be difficult to precisely titrate mucin secretion to preserve baseline homeostatic function while inhibiting pathologic secretion, and clinical trials have not so far shown evidence of benefit.

Treatments that promote mucus clearance include physical measures to remove retained secretions and pharmacologic agents to improve mucus rheology.[1] Among physical measures, mechanical insufflation–exsufflation has been shown to effectively clear mucus in patients with weak cough, there is evidence of moderate benefit from multiple measures to increase expectoration in CF, and there is anecdotal evidence of benefit in non-CF bronchiectasis.[81,82] Drugs that effectively improve mucus rheology in specific settings include inhaled dornase alfa, inhaled hypertonic saline solution, and ivacaftor in CF. Inhaled hypertonic saline solution has also shown benefit in non-CF bronchiectasis,[77] and is under investigation in COPD. In contrast, dornase alfa did not show benefit in non-CF bronchiectasis, asthma, or COPD. For the treatment of infected airway mucus, a variety of inhaled, oral and intravenous antibiotic regimens have been shown to have utility in specific situations, particularly in CF and COPD.[1]

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CHAPTER 7

The Genetic Basis of Respiratory Disorders

Micheala A. Aldred

The field of genetics and genomics is advancing at an incredible pace. The completion of the Human Genome Project was just the beginning. Now, thanks to rapid advances in sequencing technology and bioinformatics, we have made significant progress toward sequencing 1000 genomes from around the world, uncovering great genetic diversity and challenging us to understand the biologic relevance. Sequencing the exome (the protein-coding parts of the genome) of a patient with an undiagnosed condition is already a reality. Even beyond human genetics, genomic technologies are making an impact on pulmonary disease, enabling characterization of new respiratory pathogen genomes, such as the SARS virus and pandemic H1N1 influenza, with unprecedented speed. Against this backdrop, a chapter on the genetics of lung diseases could easily be out of date before it is even in print. Thus it does not seek to be encyclopedic, but to give the reader a grounding in the principles of human genetics, an overview of current knowledge in Mendelian lung diseases and a summary of recent progress in understanding genetic factors contributing to common lung conditions. It outlines some of the emerging roles of epigenetic modifications and aims to give a vision of where the field is moving, concluding with current and future prospects for genetically targeted therapies.

PRINCIPLES OF HUMAN GENETICS

GENOME ORGANIZATION

The term "genome" refers to the genetic make-up of an organism (Table 7-1). Mammalian genomes are composed of deoxyribonucleic acid (DNA) and can be subdivided into a nuclear genome – DNA within the nucleus of each cell – and a separate circular genome housed within each mitochondrion. DNA has a double-helix structure, each strand comprises four constituent bases – adenine (A), cytosine (C), guanine (G), and thymine (T) – that pair together, A with T and G with C. DNA needs to be replicated each time a cell divides. This strict base pairing ensures accurate copying of the DNA code.

The human genome is approximately 3.3 billion base pairs in size. This large amount of DNA is wound around proteins known as histones, then packaged into higher-order structures called chromosomes that can be visualized under a light microscope. Most cells of the body contain two copies of each chromosome; one inherited from each parent, and are termed "diploid." Diploid cells contain 23 pairs of chromosomes. During meiosis, these pairs of chromosomes are separated, giving rise to oocytes and sperm that contain a single copy of each chromosome (termed "haploid"). Thus fusion of two haploid gametes gives rise to a new diploid organism, preserving the correct copy number of DNA through the generations. Gender is determined by a pair of sex chromosomes, X and Y; females have two copies of the X-chromosome, whereas males have one each of X and Y. The other 22 pairs of chromosomes are known as the autosomes. Genetic diseases are mainly caused by mutations in autosomal or X-chromosome genes; the Y-chromosome harbors only a few genes and these are mainly involved in determining male characteristics.

GENE STRUCTURE

Only about 1% to 2% of the human genome actually encodes for proteins. The noncoding portion was originally considered to be junk DNA, but it is now increasingly clear that some of it has important regulatory functions. The protein-coding units are called genes. The DNA within a gene is first transcribed into ribonucleic acid (RNA). RNA has a similar base structure to DNA, but is single stranded, has a slightly different sugar backbone and thymine (T) is replaced by uracil (U). Genes are typically divided into coding exons and intervening noncoding introns. The intronic sequences are spliced out of the initial RNA transcript to produce the mature messenger RNA (mRNA) molecule. Some genes have alternative splicing patterns that can give rise to slightly different variants ("isoforms") of the protein. The mRNA is then translated into protein by ribosomes. Ribosomes read the RNA code as a triplet of bases or "codon" and add the corresponding amino acid to the growing protein chain. There is some redundancy in the genetic code and amino acids may be encoded by several different codons. Four codons have a special function: AUG encodes methionine and always marks the initiation site for protein translation, while UGA, UAG, and UAA are stop signals that lead to termination of translation. The DNA flanking the coding region of a gene is not translated but contains important regulatory elements, including the promoter region that regulates transcriptional activity.

CLASSES OF MUTATION

Alterations in the DNA sequence occur when there is an error in DNA replication prior to cell division or DNA damage occurs through environmental exposures such as UV radiation or tobacco smoke. Such mutations may affect a single base (known as a point mutation) or may involve the insertion or deletion of multiple bases. Cells have an extensive DNA repair mechanism that will correct most of these mutations, but any that escape may lead to a permanent change in the sequence that is propagated to daughter cells. Mutations in noncoding regions of the genome often have no detrimental effect and over time, they may become quite common in the population. Variants that are present at a frequency of greater than 1% are known as polymorphisms and have been widely used in genetic mapping studies. Thus the two copies of a gene in any individual are subtly different at the DNA sequence level. These variant forms are known as "alleles." However, mutations that occur in the introns of genes may lead to disease, especially if they disrupt the highly conserved splicing signals immediately flanking an exon. Within the coding region of a gene, the consequence of a point mutation depends on whether it alters the genetic code (Fig. 7-1). Most redundancy lies in the third base of the codon, so for example, a change from GGG to any of GGA, GGC, or GGU still encodes glycine and would not change the sequence of the protein. Such changes are usually silent and may become common polymorphisms. Mutations that lead to an amino acid substitution, for example UGU (cysteine) to UAU (tyrosine), are known as missense mutations. Their effect on protein function depends much on the specific structure and function of that protein. In general, missense mutations in regions that are functionally critical, such as the catalytic domain of an enzyme, will be highly deleterious. These regions are often highly conserved across species, indicating that mutations have not been tolerated during evolution. Missense mutations that affect residues important in secondary structure and protein folding are also likely to have adverse effects, whereas mutations in linker regions may be less critical. Thus interpreting the consequences of genetic changes requires an in-depth knowledge of the protein concerned.

TABLE 7-1 Glossary of Genetic Terms

Genome	The complete genetic makeup of an organism, including all coding and noncoding DNA
Gene	A discrete protein-coding unit within the genome. Genes are typically subdivided into exons (blocks of protein-coding DNA), introns (intervening noncoding DNA), and flanking regulatory regions
Exome	The entire sequence of all exons within the genome
Somatic	Relating to any cell of the body other than the germ cells. Mutations in somatic cells cannot be passed on to the next generation
Chromosome	A higher order structure into which DNA is packaged. Humans have 23 pairs of chromosomes, 22 autosomes, and a pair of sex chromosome, X and Y, that determine gender
Telomere	The cap at the ends of each chromosome, composed of hundreds of copies of the repeat sequence TTAGGG
Diploid	Containing a full complement of 23 chromosome pairs. All normal somatic cells are diploid
Haploid	Having only a single copy of each chromosome. Mature gametes are haploid, ensuring that a new zygote has the correct chromosome complement
Aneuploid	Cells that have a nondiploid number of chromosomes due to gain or loss of one or more chromosomes during cell division. Aneuploidy commonly occurs in cancer cells, which may become highly abnormal as the tumor progresses
Mutation	Strictly, any change that occurs in the DNA sequence, however in relation to genetic diseases, the term is mainly used to refer to changes that have a deleterious clinical effect
Polymorphism	A genetic variant present at a frequency of at least 1% in a given population, often used synonymously with mutations that have no adverse effect
SNP	Single nucleotide polymorphism: a polymorphism resulting from a single DNA base substitution
Allele	Referring to a specific version of a gene, often used to distinguish between the copies inherited from each parent, or between wild-type and mutant copies
Heterozygote	An individual with one wild-type allele and one variant
Homozygous	An individual with two copies of the same variant allele. In autosomal recessive diseases where an individual inherits two different mutations, one from each parent, the term "compound heterozygote" is used
Genotype	The genetic sequence of the two alleles at a particular gene location
Phenotype	The clinical manifestation of genetic change
Dominant	A mutation that exerts a phenotypic effect in heterozygous form
Recessive	A mutation that is masked by the wild-type allele in a heterozygote and only results in a phenotype when wild-type function is lost
Penetrance	The likelihood that an individual with a mutation will develop clinical disease
Heterogeneity, allelic	The presence of different pathogenic mutations in same gene across different individuals. Most genetic diseases show allelic heterogeneity, unless they are caused by gain of an abnormal function that is only conferred by one specific mutation (e.g., sickle cell disease)
Heterogeneity, genetic	Diseases for which a mutation in one of several different genes can lead to the same clinical phenotype
Heritability	The proportion of trait variance that can be attributed to genetic factors versus the environment
Haplotype/ Haplogroup	A specific combination of SNPs on a contiguous piece of DNA. Haplotype is used when defining the arrangement of SNPs on an individual chromosome; haplogroup refers to groups of ancestrally related variants in mitochondrial genome
Genetic anticipation	A phenomenon in which the age of onset of an autosomal dominant disease becomes earlier with each successive generation. It is most often observed in a group of neuromuscular diseases caused by a unique class of DNA-repeat mutations, but also occurs in familial pulmonary fibrosis associated with telomerase mutations
Imprinting	Epigenetic silencing of an allele based on its parental origin. Relatively few genes are imprinted, but those that are give rise to unusual patterns of inheritance, as the mutation is masked when present on the silenced allele

Mutations that lead to premature truncation of a protein are highly likely to be pathogenic and are a major cause of inherited diseases. Several different types of mutation can lead to premature protein truncation. Nonsense mutations result from a single base change that introduces a stop codon earlier than the natural translation end-point, for example, AGA (arginine) to UGA (stop). Small insertions and deletions can also introduce premature stop codons because if the number of bases added or lost is not a multiple of three, the reading frame for the triplet codon is offset and it is read incorrectly. This is known as a frameshift mutation (Fig. 7-1). Splice-site mutations can lead to retention of an intron, which does not normally code for a protein and, therefore, often contains a stop codon. Alternatively splice-site mutations can lead to exon skipping and again, if the size of the missing exon is not a multiple of three bases, this leads to a downstream frameshift, in addition to losing a whole exon of sequence. The presence of a premature stop codon often triggers a process known as nonsense-mediated mRNA decay (NMD), which leads to degradation of the nonsense-containing mRNA transcript, preventing translation of a truncated protein. This protects the cell from potentially adverse effects of an abnormal protein product. The mechanisms underlying NMD are not fully understood and some transcripts are degraded more efficiently than others. Nonsense mutations in the last exon of a gene do not trigger NMD, due to their proximity

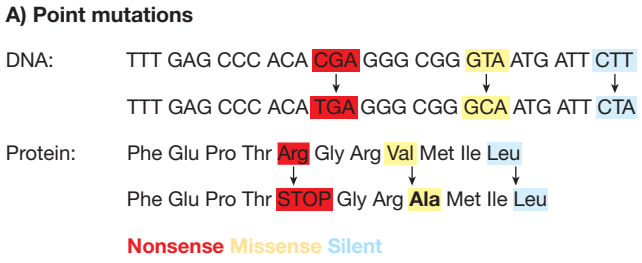

Figure 7-1 Classes of genetic mutations. **A.** Single base changes within an exon may lead to premature protein truncation (nonsense mutation, shaded in red), an amino acid substitution (missense mutation, yellow), or there may be no change due to redundancy in the genetic code (silent, blue); **B.** Insertions or deletions lead to frameshift mutations if the number of bases involved is not divisible by three. This almost invariably leads to premature protein truncation downstream of the mutation site.

to the natural stop codon, whereas mutations in first exon, close to the translation initiation codon, may lead to reinitiation at a downstream ATG site.

The last major class of mutation is gene rearrangements, large deletions, or duplications that affect one or more exons. These mutations can be missed by sequence-based methods of DNA analysis and require specialized methods that measure the copy number of DNA across the gene. They typically lead to major disruption of the gene structure and any protein that may be produced is likely to be nonfunctional.

MODES OF INHERITANCE

The pattern of inheritance of a genetic disease within a family is determined by the location of the mutation – on an autosome, the X-chromosome, or in the mitochondrial genome – and whether or not a clinical effect (phenotype) is evident when only one copy of the gene is mutated. When mutation of a single allele is sufficient to cause disease, it is known as dominant because the mutation is sufficient to overcome the positive effect of the remaining wild-type allele. Genes that are affected by dominant mutations are typically very sensitive to the 50% reduction in gene dosage that results from inactivating one allele. Alternatively the mutation may cause an abnormal gain of function, or create an abnormal protein that in turn interferes with the function of the wild-type protein, an effect known as dominant negative. In contrast, recessive mutations have no detrimental effect when only one allele is mutated. The remaining wild-type allele is sufficient to maintain normal gene function and a clinical phenotype is only apparent when both alleles are inactivated and the gene function is completely lost. Individuals with a personal or family history of genetic disease should be offered genetic counseling to help them understand their risks and options, and to facilitate appropriate genetic testing.

AUTOSOMAL DOMINANT

Autosomal dominant mutations result in a strong pattern of disease in each generation of a family (Fig. 7-2A). An individual with such a mutation has a 50% chance of passing the disease on to each of their children. The hallmarks of autosomal dominant inheritance are approximately equal proportions of males and females affected by the disease and the presence of male-to-male transmission. However, several factors can complicate this model. Some dominant diseases may skip a generation, due to reduced penetrance (Fig. 7-2B). The penetrance of a mutation is defined as the likelihood that someone with the mutation actually develops the disease. If the penetrance is less than 100%, then an individual who inherits the mutation may escape the disease themselves, while still being at 50% risk of passing it on to their children. Independently, the gender ratio may skewed by environmental and/or genetic modifying factors. The most extreme example is inherited diseases affecting sex-specific organs. For example, ovarian cancer can be inherited in an autosomal dominant manner but only females with the mutation actually develop the disease.

AUTOSOMAL RECESSIVE

The pattern of inheritance of autosomal recessive diseases is quite different. Individuals with a single copy of the mutation are known as carriers or heterozygotes. Since there is no clinical effect, such individuals are usually unaware of their status. However, when both parents are carriers, each has a 50% chance of passing on the mutation, meaning there is a 25% chance that a child will inherit two copies of the mutation and be affected by the disease. Consequently, autosomal recessive diseases often appear "out of the blue" in a family with no previous history of the condition (Fig. 7-2C). The incidence of recessive diseases largely depends on the heterozygote frequency in the population, but the risk increases in consanguineous families.

X-LINKED INHERITANCE

X-linked diseases are caused by mutations in genes on the X-chromosome. Most are recessive, but the different sex-chromosome constitution between females and males, XX versus XY, leads to a unique pattern of inheritance. Males who inherit an X-linked mutation have no wild-type allele on the Y-chromosome to mask its effect, and consequently they develop the disease. Female carriers are generally unaffected, as for autosomal recessive diseases. Thus X-linked diseases are passed through the female line and typically affect only males (Fig. 7-2D). A female carrier has a 50% chance of an affected son. Importantly, males cannot pass the mutation to their sons, so an evidence of male-to-male transmission rules out X-linked inheritance, but all of their daughters will be carriers. In reality, females only have a single X-chromosome active in any given cell, due to a process of X-inactivation in early embryonic development that adjusts the dosage of X-linked genes to be the same as in males. If X-inactivation is random, approximately half of cells in a carrier will express the wild-type allele and half express the mutation, meaning that female carriers usually have no phenotype or are only mildly affected. However, if X-inactivation is highly skewed toward expression of the mutant allele, then female carriers may be as severely affected as males. Rarely, X-linked mutations may be dominant, meaning that all females who inherit the mutation will be affected. Such mutations are often lethal in males. Examples of X-linked recessive conditions that affect the lung include X-linked agammaglobulinemia, an immunodeficiency that can lead to chronic lung disease, and X-linked severe combined immunodeficiency caused by mutations in the *IL2RG* gene that encodes a subunit of the receptor for multiple interleukins.

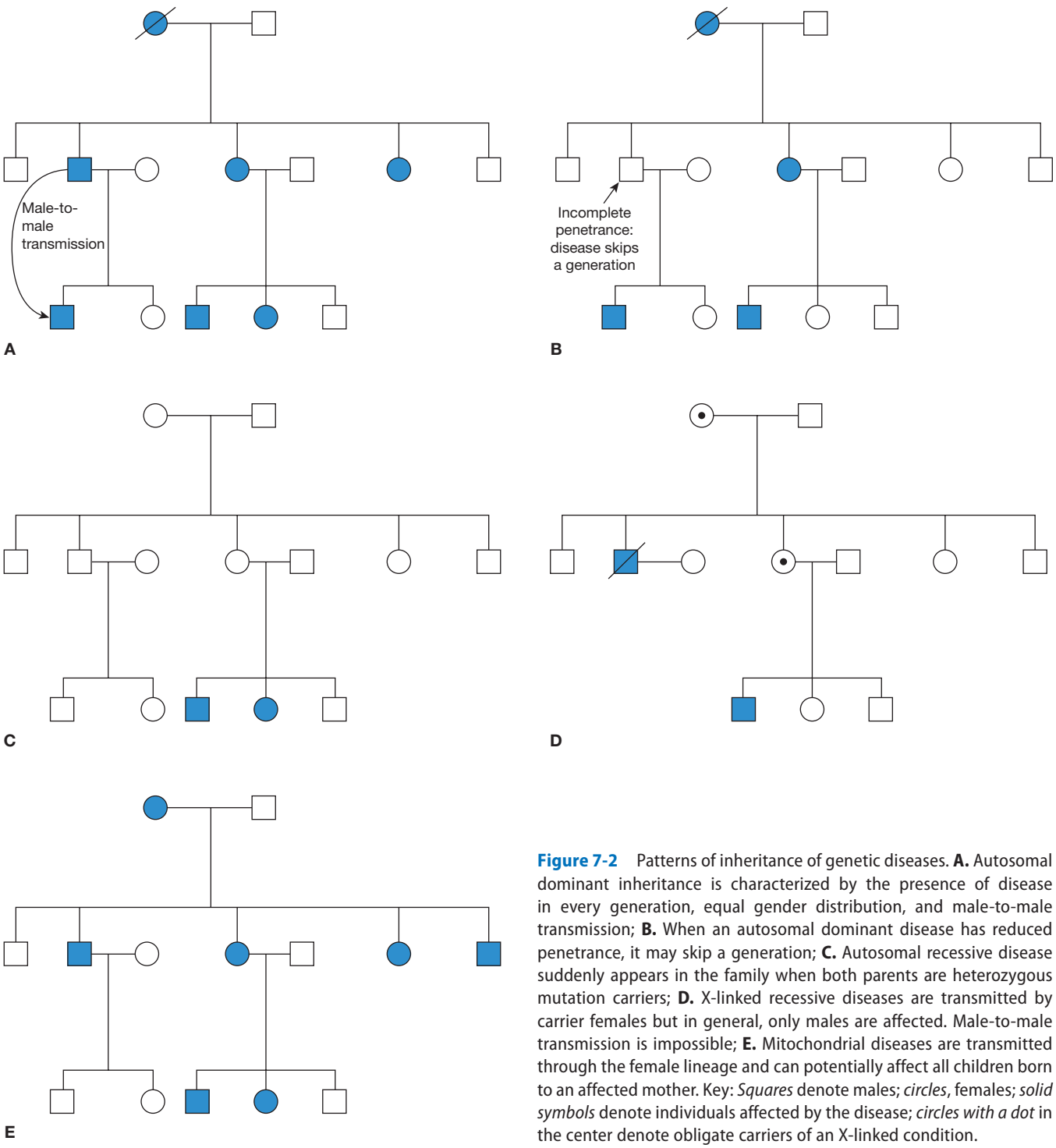

Figure 7-2 Patterns of inheritance of genetic diseases. **A.** Autosomal dominant inheritance is characterized by the presence of disease in every generation, equal gender distribution, and male-to-male transmission; **B.** When an autosomal dominant disease has reduced penetrance, it may skip a generation; **C.** Autosomal recessive disease suddenly appears in the family when both parents are heterozygous mutation carriers; **D.** X-linked recessive diseases are transmitted by carrier females but in general, only males are affected. Male-to-male transmission is impossible; **E.** Mitochondrial diseases are transmitted through the female lineage and can potentially affect all children born to an affected mother. Key: *Squares* denote males; *circles*, females; *solid symbols* denote individuals affected by the disease; *circles with a dot* in the center denote obligate carriers of an X-linked condition.

■ MITOCHONDRIAL MUTATIONS

The mitochondrial genome is a small circular molecule, approximately 16,500 bases long. It encodes some of the proteins required for oxidative phosphorylation and electron transport, together with multiple transfer RNAs and ribosomal RNAs. Mutations in mitochondrial genes adversely affect energy production and thus the clinical consequences are greatest in tissues with high-energy requirements, such as heart, brain, and skeletal muscle. Two characteristics make the inheritance of mitochondrial gene mutations unique. First, mitochondria are almost exclusively transmitted through the maternal lineage; sperm only have mitochondria in the tail for motility and do not enter the oocyte at fertilization. Thus, the pattern of inheritance within a family is similar to X-linked inheritance, with no male-to-male transmission, but differs in that females and males are equally likely to be affected (Fig. 7-2E). In theory, all children born to an affected mother would inherit the mutation and develop the disease. In reality, however, there are many copies of the mitochondrial genome per cell and each cell has a mixture of wild-type and mutant mitochondria (heteroplasmy). The segregation of these mitochondria during cell division is random, so by chance, an oocyte may have a

high or low number of mitochondria carrying the mutation. This random drift continues throughout embryonic development and beyond, generating considerable variability in the severity of disease and the tissues that are affected, even among individuals in the same family. Pulmonary involvement is not a major feature of most mitochondrial diseases, but several case reports link pulmonary hypertension with mutation in mitochondrial genes or a nuclear-encoded mitochondrial protein.[1–8] Pulmonary complications of mitochondrial disease are most likely to present as part of a multiorgan syndrome that may also include cardiac and/or skeletal myopathy, neuropathy, retinopathy, renal problems, or metabolic abnormalities.

Another fascinating property of the mitochondrial genome is its high degree of polymorphic variation. Clusters of variants, or "haplogroups," have been used to plot early human migration patterns across the globe. As new variants arose, they were propagated to offspring in the immediate geographic area, but were not present in other populations that had already migrated to different regions. Some of these variants confer subtle functional differences and may have been selectively enriched by helping adaptation to a new environment. They may also modulate risk of disease, particularly for conditions where there is oxidative stress. Data concerning lung diseases are currently limited, but associations with different haplogroups have been reported for atopy and asthma, chronic obstructive pulmonary disease (COPD), high-altitude pulmonary edema, and lung cancer risk.[9–13]

SOMATIC MUTATIONS AND CANCER

Not all of the genetic changes that contribute to disease are inherited. This is particularly true in cancer where, although there may be an inherited predisposition, most genetic changes are somatic and confined to the tumor itself. A later chapter is devoted to the molecular basis of lung cancer, so here we will briefly review the types of somatic changes observed in cancer cells and their relevance to benign lung conditions.

Two major classes of genes may be mutated in cancer: oncogenes and tumor suppressor genes. Oncogenes promote tumorigenesis when they are expressed at an abnormally high level or are inappropriately expressed in tissues where the gene should normally be silent. This may occur due to amplification (extra copies) of the gene, overactivation by upstream transcription factors, a chromosome rearrangement that brings the gene under the control of a strong promoter, or loss of DNA methylation as described in the following section on epigenetics. Alternatively the gene may be mutated in a way that gives the protein a novel gain of function. For example, mutation of a ligand-dependent receptor such that, once activated, it cannot be switched off and continues to signal in the absence of the ligand. These types of oncogenic mutations are usually dominant missense mutations at specific amino acid sites within the protein.

Tumor suppressor genes (TSGs) are like the brakes on the cell; they control cell growth, differentiation, and apoptosis. When their function is lost, the cell proliferates uncontrollably or evades programmed cell death. TSGs are predominantly inactivated by nonsense and frameshift mutations, large gene deletions, or loss of an entire chromosome. They may also be silenced by hypermethylation of their promoter, as described in the next section. In contrast to oncogenes, TSG mutations are often recessive at the cellular level and both copies of the gene must be inactivated before the full cancer-promoting effect is seen. Both mutations may occur as somatic changes in the cell that initiates the cancer, or the first mutation may be inherited, predisposing the individual to the risk of cancer, a model that was first proposed by Alfred Knudson.[14]

As tumors proliferate, their genome may become highly disorganized. Abnormal segregation of the chromosomes during mitosis can lead to aneuploidy, with gains and/or losses of entire chromosomes. There may also be translocations, where segments of different chromosomes are inappropriately joined together, and localized deletions or duplications of large segments of DNA. Such large rearrangements will clearly affect many different genes and can contribute to the activation of oncogenes and/or loss of TSG function.

The study of somatic mutations requires tissue from the affected area, ideally with a comparison to normal tissue from the same patient and also normal tissue from unrelated controls. Due to the difficulty of obtaining such tissues for benign lung diseases, somatic changes have mainly been studied in the context of cancer, but the same approach has recently been applied to pulmonary arterial hypertension (PAH). In addition, somatic epigenetic changes described below are common both in cancer and in several chronic lung diseases, emphasizing the importance of acquiring tissue from the site of disease when this is ethically possible.

EPIGENETICS

DNA AND HISTONE MODIFICATIONS

The term epigenetics refers to factors that influence gene expression without altering the underlying base sequence. Both DNA and histones, the proteins around which DNA is wound, may be epigenetically modified. These changes are usually reversible and play important roles in regulating gene expression and genome stability. The most common DNA modification is methylation of cytosine residues. The promoters of many genes contain a CpG island, a region with a high density of CG dinucleotides. Methylation of CpG sites in these islands leads to a closed chromatin conformation that makes the DNA inaccessible to transcription factors, turning off expression of the gene. Conversely, when most of the cytosines are unmethylated, the DNA is open and actively transcribed. DNA methylation, therefore, plays a critical role in regulating tissue-specific patterns of gene expression. Patterns of DNA methylation are controlled by DNA methyltransferases (DNMTs). DNMT3A and 3B are responsible for de novo methylation of residues that were previously unmethylated. Established patterns of methylation are then maintained by DNMT1. Further fine tuning of gene regulation comes through methylation and acetylation of histones. Acetylation mainly occurs on lysine residues and relaxes the interaction between histone and DNA, leading to increased gene transcription. Deacetylation reverses this and leads to a more tightly closed chromatin conformation. Histone acetylation patterns are controlled by histone acetyltransferases (HATs) and deacetylases (HDACs).

Within noncoding regions of the genome, DNA methylation and chromatin condensation act to suppress repetitive elements that could otherwise recombine and cause structural alterations. In cancer, there is often a global loss of methylation, which can lead to activation of mobile and repetitive elements, predisposing to the genomic instability that is the hallmark of many cancers. Loss of methylation at gene promoters can also activate oncogenes that in turn accelerate the growth of the tumor. At the same time, there may be hypermethylation of specific gene promoters, causing loss of expression of TSGs. It is increasingly clear that more subtle epigenetic changes likely contribute many other diseases, including lung conditions such as idiopathic pulmonary fibrosis (IPF) and COPD.[15,16] Unlike the DNA sequence, epigenetic modifications can change dynamically with age and are influenced by dietary factors such as folate intake. There is also mounting evidence that airborne pollutants such as small diesel particulates and tobacco smoke can directly mediate epigenetic changes.[17,18] Thus the lung may be particularly susceptible to epigenetic changes caused by repeated exposure to these environmental modulators. Importantly, though, some adverse epigenetic changes are reversible with time, for example, smoking-induced changes in DNA methylation gradually revert after quitting.[19] Also, the anti-inflammatory action of

corticosteroids is in part epigenetic, recruiting HDAC2 to the site of acetylated (activated) inflammatory genes.[20] Characterizing the role of epigenetics in lung disease is challenging because it requires access to affected and control lung tissues. It may also be difficult to distinguish which changes are causative of disease and not just a reaction to the disease state. However, considerable progress has already been made under the auspices of the NIH Roadmap Epigenomics Consortium and other focused research initiatives.

NONCODING RNAs

Noncoding RNAs can directly regulate gene expression at the RNA level without being translated into a protein product. The best characterized family is the microRNAs (miRs), first studied in plants but now also recognized to be important throughout the animal kingdom. Primary miR transcripts are transcribed in the same manner as regular protein-coding genes. In some cases the miR gene may be within an intron of a protein-coding gene and is controlled by the promoter of the "parent" gene. In other cases, miRs may be encoded as separate genes, individually or in a cluster, with their own promoter. The primary miR transcript is then processed into a pre-miR, about 70 to 80 nucleotides in length (Fig. 7-3). The ends of the pre-miR are highly homologous, causing the molecule to loop back on itself in a hairpin-like conformation. This double-stranded RNA structure is then exported from the nucleus into the cytosol, where it is cleaved by the enzyme Dicer into a mature single-stranded miR, approximately 18 to 22 nucleotides long (Fig. 7-3). The mature miR negatively regulates gene expression by binding to the 3′-untranslated region of its target mRNA, which either leads to degradation of the mRNA or inhibits protein synthesis. The seed sequence that initiates binding between the miR and its mRNA target is very short, typically around seven nucleotides, and does not require perfect base pairing. As a consequence, a single miR can potentially target tens or even hundreds of genes.

miRs have been widely studied in cancer and several, such as miR-21, have been dubbed "oncomiRs" because their overexpression promotes tumorigenesis by downregulating tumor suppressor pathways.[21–24] In comparison, relatively little is known about the role of miRs in benign lung diseases. However, it is now an intense area of research and recent data highlight important roles in IPF and PAH, as detailed in the disease-specific sections that follow. The miR pathway is often considered to be an epigenetic mechanism, yet it can be influenced by changes in DNA sequence, either through mutation affecting the miR gene itself, or mutations and polymorphisms that alter the seed sequence in the mRNA target.

Another major class of noncoding RNAs is the long noncoding (lnc) RNAs, greater than 200 bases long. lncRNA transcripts can be thousands of bases in length and, unlike miRs, they may be encoded by large multiexon genes that undergo splicing in the same manner as most protein-coding genes. Well-known examples of lncRNAs are *XIST*, which coats the inactive X-chromosome in female cells, and *TERC*, part of the telomerase complex that maintains the ends of the chromosomes (telomeres). As yet, very little is known about the role of lncRNAs in human disease, the notable exception being *TERC* mutations, one of several causes of IPF described below.

INHERITED LUNG DISEASES

This section provides an overview of the genetic basis of inherited conditions that include lung disease as a major component (Table 7-2). These brief summaries cannot provide exhaustive

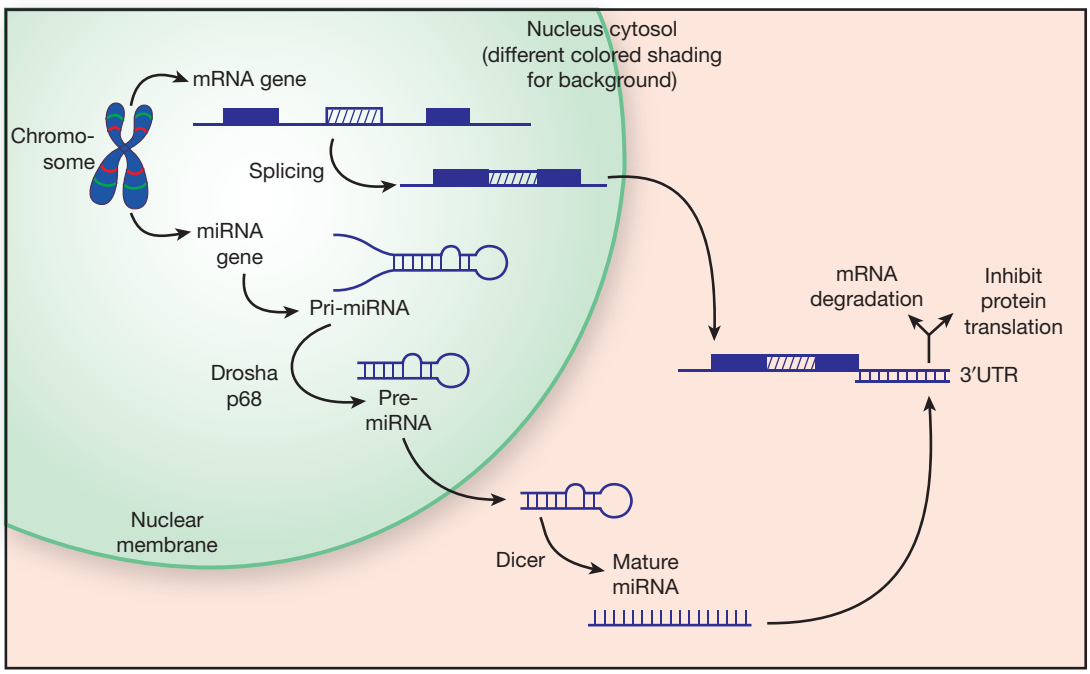

Figure 7-3 microRNA biogenesis. microRNAs that are encoded by independent genes are transcribed by RNA polymerases (mainly RNA pol II) into a primary miRNA transcript with a 5′-cap and 3′-polyadenylation. The primary miRNA molecule is cleaved by a protein complex, including Drosha and p68, into a double-strand hairpin RNA known as the pre-miRNA. For a subset of microRNAs, recruitment to the p68-Drosha complex is stimulated by activation of the bone morphogenetic protein and transforming growth factor-beta pathways,[67,68] a process that is disrupted by some mutations that cause pulmonary arterial hypertension.[58] Alternatively, some miRNA genes are embedded within the introns of mRNA genes, in which case they are transcribed along with the host gene and the pre-miRNA is generated during mRNA splicing. The pre-miRNA is then exported to the cytosol, where the Dicer complex converts it to the mature single-stranded miRNA molecule. Mature microRNAs negatively regulate expression of their target genes by binding to the 3′-untranslated region of the mRNAs, which either leads to degradation of the mRNA or blocks protein translation.

TABLE 7-2 Mendelian Inherited Lung Diseases

Disease	OMIM	Mode of Inheritance	Gene(s)	Chromosome	Comments
Cystic fibrosis	219700	Autosomal recessive	*CFTR*	7	ΔF508 accounts for ~75% of mutations; many other mutations described at a frequency of 5% or less
Alpha-1 antitrypsin deficiency	613490	Autosomal recessive	*SERPINA1*	14	Z allele (E342K) associated with severe disease, S allele (E264V) is intermediate
Sickle cell disease	603903	Autosomal recessive	*HBB*	11	Predominantly caused by a single mutation, E6V, which leads to an abnormal hemoglobin molecule (HbS)
Pulmonary arterial hypertension	178600	Autosomal dominant, reduced penetrance	*BMPR2* *SMAD9* *ACVRL1* *ENG* *CAV1*	2 13 12 9 7	6–10% of patients have a family history and an additional 15–20% of patients with sporadic idiopathic disease carry a mutation in one of these genes. *BMPR2* mutations account for about 80% of all families and over 200 different mutations have been described
Idiopathic/Familial Pulmonary fibrosis	614742 614743 178500 610913	Autosomal dominant, variable penetrance	*TERT* *TERC* *SFTPA2* *SFTPC*	5 3 10 8	Mutations in *TERT* or *TERC* lead to shortened telomeres. The severity of disease is inversely correlated with telomere length and the age of onset decreases with each succeeding generation (genetic anticipation)
Surfactant metabolism dysfunction	265120 610921 614370 300770	Autosomal recessive X-linked	*SFTPB* *ABCA3* *CSF2RB* *CSF2RA*	2 16 22 X	Disease presentation can range from severe respiratory distress in neonates, through childhood or adult-onset interstitial lung disease. *SFTPC* mutations, listed above under IPF, can also lead to neonatal or childhood surfactant metabolism dysfunction
Alveolar capillary dysplasia	265380	Usually de novo	*FOXF1*	16	Caused by de novo heterozygous mutations or deletions of maternal origin; gene is imprinted; occasionally transmitted as a dominant trait by an unaffected mother
Primary ciliary dyskinesia	Multiple	Autosomal recessive	Multiple	Multiple	Highly heterogeneous disorder with at least 15 different genetic loci
Agammaglobulinemia	300300	X-linked	*BTK*	X	Rare B-cell disorder; recurrent respiratory tract infections
Severe combined immunodeficiency	300400	X-linked	*IL2RG*	X	Rare, affects at least two immune cell types; more severe than agammaglobulinemia; also several autosomal recessive forms

OMIM, Online Mendelian Inheritance in Man; http://omim.org/

reviews of current knowledge, but we refer the reader to entries in Online Mendelian Inheritance in Man (OMIM) and other web resources listed at the end of this chapter, for in-depth information.

CYSTIC FIBROSIS

Cystic fibrosis (CF; OMIM 219700) is the most common autosomal recessive disorder in Northern European Caucasians, with a carrier frequency of 1 in 20 to 1 in 25. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7, which encodes a transmembrane channel protein important for chloride transport.[25] The most common mutation in Northern Europeans, accounting for about 75% of all CFTR mutations, is a deletion of three base pairs of DNA encoding phenylalanine at codon 508, denoted ΔF508. The frequencies of other mutations are all much lower, each accounting for less than 5% of the total. Thus approximately 56% of individuals with CF will be homozygous for ΔF508 and the majority of others will be compound heterozygotes for two different mutations. In Southern Europeans, ΔF508 is somewhat less common and the mutation spectrum is markedly different in the Ashkenazi Jewish population. Many countries now perform newborn screening for the most common CF mutations, enabling early diagnosis and treatment.

CF mutations can be subdivided into several categories, based on their molecular consequences.[26] Class I mutations, including most nonsense, frameshift, and splice-site mutations and large gene deletions, result in loss of CFTR protein. Class II mutations encode stable proteins that are abnormally processed, leading to retention of the mutant protein in the endoplasmic reticulum. ΔF508 is an example of a Class II mutation. Class III and IV mutations localize correctly to the membrane but they either fail to activate or are inefficient at transporting chloride ions. Class V mutations reduce the rate of CFTR synthesis. Some of these mutations retain a degree of residual function and can mitigate the severity of clinical phenotype.[26,27] Understanding the molecular consequences of these different mutations has been instrumental to developing new therapeutic approaches that seek to correct these defects, as described in the concluding section of this chapter.

Most genetic diseases show variability in the extent and severity of clinical disease, even for individuals with identical mutations. Just as common SNPs may confer risk or protection for common disease, they may also act as genetic modifiers in Mendelian traits. CF is a multisystem disease and with a large enough cohort of patients, it has been possible to identify polymorphisms that modify different aspect of the disease, including pulmonary function (FEV1), bacterial colonization, meconium ileus, and diabetes.[28,29] One particularly interesting polymorphism involves a run of thymine residues in intron 8 of CFTR, commonly present as 9T, 7T, or 5T alleles. These bases are just upstream of exon 9 of the genes and are part of an important signal to regulate mRNA splicing. The shorter alleles splice less efficiently and, in particular, the 5T allele can lead to abnormal splicing that excludes exon 9 from a proportion of the transcripts. Since some full-length CFTR is still made, this is not a severe CF mutation. However, it can lead to a partial phenotype in combination with other mutations and is, therefore, an intragenic modifier. Embryonic development of the vas deferens in males is especially sensitive to the amount of CFTR protein and the 5T allele

can contribute to congenital bilateral absence of the vas deferens, even in individuals with little or no lung disease.[30]

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin deficiency (AATD; OMIM 613490) is an autosomal recessive disease caused by mutations in the *SERPINA1* gene on chromosome 14, which encodes the protease inhibitor alpha-1 antitrypsin (AAT). AATD was one of the earliest genetic diseases to be understood at the molecular level, since the variant alleles could be identified by protein gel electrophoresis (isoelectric focusing) before the advent of DNA-based genetic testing. Consequently, the alleles are denoted by letters assigned for their relative position on the gel. The wild-type allele is designated M. The most common deficiency allele is Z, a missense mutation that changes glutamic acid to lysine at codon 342 (E342K). Its frequency is highest in Northern European populations. AATD is likely underdiagnosed and the true prevalence may be higher than CF in some countries.[31–33] ZZ homozygotes have low plasma AAT concentrations and are at highest risk for developing lung disease. Accumulation of the mutant protein in the liver can also lead to liver damage. The other most common allele, denoted S (amino acid change E264V), is intermediate in respect to both the level of AAT and disease risk. It is highly prevalent in Southern European populations, with frequencies of 15% to 20% in Spain and Portugal.[33] Clinically, the S allele is of greatest concern in SZ compound heterozygotes, but the severity of lung disease is generally less than for ZZ homozygotes. Individuals with the MZ, MS, or SS genotypes may have slightly impaired lung or liver function. Thus, while overt AATD is considered a recessive condition, the alleles are codominant in their influence on AAT levels and associated risk of disease. There is also a strong gene–environment interaction with tobacco smoking, which can inactivate AAT, further decreasing the level of active protein and greatly increases the risk of lung disease in susceptible genotypes.

Testing for the S and Z alleles may be performed by isoelectric focusing or DNA-based testing. Isoelectric focusing has the advantage that it will pick up other rare alleles that lead to altered protein mobility, whereas the DNA-based tests target only the two known mutations. However, both methods fail to detect rare null mutations that lead to complete loss of protein and, therefore, it is also important to measure the level of AAT in the plasma. This may be followed up with sequencing of the entire *SERPINA1* gene if rare alleles are suspected. Recommendations for genetic testing have been developed by a joint task force of the American Thoracic Society and European Respiratory Society.[34]

PULMONARY ARTERIAL HYPERTENSION

PAH (OMIM 178600) may be idiopathic (IPAH) or associated with an underlying condition such as connective tissue disease, congenital heart defect, or HIV infection (APAH). About 6% of IPAH patients have a family history. PAH is inherited as an autosomal dominant trait with reduced penetrance; on average, only about 27% of mutation carriers will actually develop symptomatic disease. It is more common in females than males and the gender-specific penetrances were recently estimated to be 42% and 14%, respectively.[35] Initial suggestions of genetic anticipation have now been disproved.[35]

Mutations in the bone morphogenetic protein receptor type-II (*BMPR2*) gene account for approximately 80% of familial PAH.[36,37] These are predominantly nonsense, frameshift, or splice-site mutations that lead to premature protein truncation or NMD.[38] Larger gene rearrangements are also frequent.[39,40] Mutations triggering NMD may cause less severe disease than missense mutations resulting in a stable dominant-negative protein, but data from different centers are conflicting.[41,42] *BMPR2* mutations are also found in 11% to 40% of IPAH patients without a family history.[43–45] The revised classification of PAH agreed at the fourth World Symposium created a new category – heritable PAH (HPAH) – that encompasses all patients with a detectable mutation, irrespective of family history.[46,47] *BMPR2* mutations have also been identified in patients with pulmonary veno-occlusive disease[48,39] and in PAH associated with anorexigen exposure,[49,50] congenital heart disease[51] but not in connective tissue disease.

Other genes within the bone morphogenetic protein pathway can also predispose to PAH. Mutations in the type-I receptor ALK1 and its accessory protein endoglin (*ENG*) predominantly cause hereditary hemorrhagic telangiectasia (HHT). However, PAH has been reported in a number of families and may precede the onset of signs or symptoms of HHT.[52–56] Patients with HHT may also develop pulmonary arteriovenous malformations. Several mutations have also recently been identified in the *SMAD9* gene, which encodes Smad8, a downstream mediator of bone morphogenetic protein signaling.[57–59] About 20% of PAH families remain without an identified genetic mutation. Exome sequencing is now being used to determine the cause of PAH in these families and has already led to the identification of two new loci, caveolin-1 (*CAV1*)[60] and a potassium channel gene, *KCNK3*.[61] Whereas *CAV1* mutations were only found in one family and one sporadic case,[60] *KCNK3* mutations were found in three families and 3 of 230 patients with idiopathic PAH.[61] One exciting aspect of this gene discovery is that some mutations could be corrected in vitro by the phospholipase inhibitor ONO-RS-082, raising the possibility of targeted therapeutic intervention for patients carrying a *KCNK3* mutation.[61]

The low penetrance of PAH mutations suggests that additional genetic and/or environmental factors also play a role. The proliferative vascular changes share many features with cancer[62–64] and analysis of affected lung tissues provides molecular support for this hypothesis, with evidence of somatic mutations, microsatellite instability, and aneuploidy.[65,66] miRs likely play an important role in PAH pathogenesis. The bone morphogenetic protein pathway regulates expression of a subset of miRs by promoting processing of the primary miR transcripts.[67,68] This pathway is lost in patients with *BMPR2* or *SMAD9* mutations,[59] whereas several other miRs have also been implicated in PAH, independent of mutation status.[69–74] Overall, despite the progress in understanding HPAH, relatively little is known about the genetic factors that may influence other forms of PAH, particularly APAH, and the heterogeneous nature of the disease remains a challenge.

IDIOPATHIC PULMONARY FIBROSIS

The genetics of IPF (OMIM 178500, 614742, 614743) parallels that of PAH in many respects. A small proportion of cases are familial and the only significant difference in clinical presentation is an earlier age of onset. The pattern of inheritance is autosomal dominant with variable penetrance. Familial pulmonary fibrosis (FPF) is genetically heterogeneous, but unlike PAH, the genes involved do not all fall in a common pathway. Around 3% of families have mutations in either surfactant protein A2 (*SFTPA2*) or surfactant protein C (*SFTPC*) genes, but a much larger proportion of families have mutations affecting telomerase.[75–77] Telomeres are like protective caps on the ends of chromosomes, important in maintaining genome stability. Their DNA sequence comprises many hundreds of copies of the repeat TTAGGG. Due to its position at the end of the chromosome, this sequence cannot be fully replicated and over time the number of repeats gets progressively shorter. Indeed, telomere shortening is believed to be one of the major molecular factors underlying aging. To counteract this, proliferative cells express telomerase, which catalyzes the addition of telomeric DNA. It is especially important in stem cells and germ cells, but is turned off in most differentiated cells. Cancer cells frequently reactivate telomerase. Telomerase is a heteromeric complex composed of a protein with reverse transcriptase activity, encoded by the gene *TERT*, and

an lncRNA (*TERC*) that provides the template for synthesizing new telomeric DNA.

The link between IPF and telomerase first came from the identification of genes causing dyskeratosis congenita, a rare multisystem genetic disorder. Patients with dyskeratosis congenita have shortened telomeres and a high incidence of pulmonary fibrosis, prompting analysis of telomere-related genes in FPF.[78] About 18% of families have now been identified with heterozygous mutations in *TERT* and about 1% with *TERC* mutations.[76,77] The average length of the telomeres modifies disease severity and, since the telomeres become progressively shorter with each generation, families with these mutations demonstrate increasingly earlier onset of disease in successive generations, a phenomenon known as "genetic anticipation." Patients with very short telomeres are also at risk for developing aplastic anemia or dyskeratosis congenita.[77] An additional 20% of FPF families have evidence of shortened telomeres but the genetic mutation has not yet been identified. In the remaining 60% of families, the cause of their disease remains unknown.[76]

For patients with IPF (i.e., without a family history), approximately 3% have a *TERT* mutation and less than 1% surfactant protein mutations. However, 25% have a telomere length below the 10th percentile in the general population, suggesting that shortened telomere length is a major risk factor for pulmonary fibrosis, even in the absence of an identifiable mutation.[79] Genomic studies of IPF lung tissue have already yielded considerable insight into the genetic changes contributing to lung fibrosis,[80] including distinct changes in gene expression,[81–83] DNA methylation patterns,[84–86] and miR expression,[87–90] though these have not as yet been translated in new therapeutic approaches.

SURFACTANT METABOLISM DYSFUNCTION

Genetic disorders of surfactant metabolism (OMIM 265120, 300770, 610913, 610921, 614370) range from severe neonatal respiratory distress and congenital pulmonary alveolar proteinosis to interstitial lung disease presenting in childhood or adulthood. It is important to note that acquired pulmonary alveolar proteinosis is a distinct autoimmune disorder. Autosomal recessive forms of surfactant metabolism dysfunction are caused by mutations in surfactant protein B gene (*SFTPB*)[91] or the transporter gene *ABCA3*.[92–94] Both lead to severe neonatal respiratory distress. Recessive forms of pulmonary alveolar proteinosis can also be caused by mutations in the granulocyte-macrophage colony-stimulating factor receptor subunits *CSF2RA,* which is X-linked recessive, or *CSF2RB,* autosomal recessive. *SFTPC* mutations are inherited as an autosomal dominant trait with variable penetrance. The phenotype may range from severe neonatal or childhood-onset interstitial lung disease to adult-onset pulmonary fibrosis.[95,96]

ALVEOLAR CAPILLARY DYSPLASIA

Alveolar capillary dysplasia (ACD; OMIM 265380) with misalignment of the pulmonary veins is a rare condition caused by heterozygous mutation or deletion of the *FOXF1* gene on chromosome 16.[97] It is usually lethal in infancy and, therefore, mutations are not inherited from an affected parent, rather they occur de novo in the oocyte or sperm, or in the very early embryo. However, one family has been described very recently in which the mother had five affected children and was found to carry a missense mutation in *FOXF1,* despite being unaffected herself.[98] The mutation had arisen de novo on her paternally derived chromosome 16. The authors proposed that *FOXF1* is imprinted on the paternal allele, meaning that it is only expressed from the maternal allele. Thus when the mutation first arose on the paternal allele, its effect was masked because only the normal maternally derived allele was expressed. However, when the mother passed the mutation on to her children, it was now on a maternally derived chromosome and was expressed, leading to ACD and multiple congenital anomalies.

PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia (PCD; numerous OMIM numbers) is an autosomal recessive disorder in which abnormalities of the cilia lead to frequent respiratory infections and chronic lung disease. Other manifestations of the condition may include situs inversus and infertility. PCD is genetically very heterogeneous; mutations in at least 15 different genes have so far been identified. Several of these encode components of axonemal dynein, a critical structural component of cilia. Approximately 40% of cases have no identifiable mutation and thus it is expected that many more genes may be identified. This very high level of genetic heterogeneity represents a significant challenge, but the ability to sequence the entire exome of affected individuals holds promise for identifying additional genes.[99–101]

SICKLE CELL DISEASE

Sickle cell disease (OMIM 603903) is the most common autosomal recessive disease in Africans and African Americans. Although primarily a blood disorder, it can give rise to significant pulmonary complications, including acute chest syndrome, emboli, and pulmonary hypertension. It is caused by a single A>T mutation in the beta-globin gene that leads to substitution of valine in place of glutamic acid at codon 6. The resulting hemoglobin molecule has reduced solubility compared to the wild-type protein, an example of a mutation that causes gain of an abnormal function. Heterozygous carriers of the mutation have increased resistance to malaria, which is believed to account for the high frequency of the mutation in regions where malaria is or was previously endemic.

GENETIC BASIS OF COMMON LUNG DISEASES

Common lung diseases such as asthma and COPD are not inherited as strong Mendelian traits. However, they may show evidence of familial clustering, suggesting that there is a genetic component to their etiology. The proportion of variation that is estimated to come from genetic factors is termed the "heritability" of the trait, high heritability indicating a strong genetic component. Since common complex diseases do not show clear segregation patterns within families, traditional model-based (parametric) mapping studies cannot be used. Instead, nonparametric methods have been employed across large collections of small family groupings, such as affected sib pairs. Early studies used a candidate gene approach. More recently genome-wide association studies (GWAS) have been used in very large case–control cohorts. Both types of study utilize some of the millions of polymorphic genetic variants throughout the genome and look for a statistically significant association between these genetic markers and the trait of interest. Single nucleotide polymorphisms (SNPs) are now the most commonly used genetic variants, as microarray technology enables simultaneous analysis of more than one million SNPs on a single array. Correlations can also be tested with clinical parameters and biomarkers such as exhaled nitric oxide, serum IgE, and FEV1. Analyzing so many variants across thousands of samples raises the problem of multiple testing, whereby the large number of comparisons between cases and controls greatly increases the likelihood that differences will be identified just by chance. To reduce the number of false-positive results, stringent correction for multiple testing is required. Also, cases and controls must be carefully matched to ensure there is no hidden population stratification that might distort allele frequencies. It is important to note that many of these SNPs are in noncoding regions of the genome and do not directly affect gene regulation or protein function. Rather, they are markers that tag a nearby sequence that may modulate disease risk. In comparison to Mendelian diseases, where mutations confer a high risk of developing the condition, the relative risks for loci identified in GWAS are generally quite small. They have little or no predictive value and so in this respect their

clinical utility is limited; the value of these studies is in identifying new pathways and targets for therapeutic intervention.[102] Large amounts of money have been invested in GWAS in a wide range of diseases and the challenge now is to identify the functional variants and fully realize the translational potential of this research. A new and powerful approach is systems biology, which aims to integrate multiple types of "omics" data, such as GWAS, genome-wide expression data, miRs, and epigenomics into networks that identify new pathways and biologic connections.

The literature on GWAS in common lung diseases is large and continues to expand rapidly. In this brief space, it is not possible to discuss these studies in any detail, especially given the complexities of racial and ethnic differences in SNP frequencies and the many subphenotypes that have been studied. We will, therefore, briefly overview some of the major candidate loci and refer the reader to reviews that can be used as a starting point for in-depth reading.

■ ASTHMA

Asthma has a high heritability and has, therefore, been a good candidate for GWAS. Some of the strongest loci identified thus far include HLA-DQ, Orosomucoid-like 3 (*ORMDL3*), and several interleukins and interleukin receptors.[103,104] *ORMDL3* is inducible in the bronchial epithelium and in mice, has been shown to regulate metallloproteinases and several cytokines.[105] SNPs in the same region also modulate expression of a neighboring gene, gasdermin-B (*GSDMB*), part of a family of genes implicated in regulating epithelial cell apoptosis. Through increasingly large studies and meta-analyses, it has been possible to start dissecting the genetic factors associated with specific subgroups, such as childhood asthma, severe asthma, and atopy.[106] Several genes are also associated with response to bronchodilators.[107] Hispanic and African American populations have a higher incidence of severe asthma but are understudied in comparison to Caucasians and represent an important research priority.

Environmental factors such as air pollution and smoking are known to be important modulators of asthma risk. This may be mediated, at least in part, through epigenetic changes affecting DNA methylation, histone acetylation, and miR expression.[16] Changes in DNA methylation directly regulate the arginase–nitric oxide pathway[18,107] and distinct methylation profiles have been identified in asthmatic children compared to controls.[108]

■ CHRONIC OBSTRUCTIVE PULMONARY DISEASE

As described previously, the strongest genetic risk factor for COPD is a mutation in the *SERPINA1* gene that encodes AAT, a risk that is further heightened by tobacco smoke exposure. More common variants with smaller effect size include the nicotine receptors *CHRNA3* and *CHRNA5*, hedgehog-interacting protein (*HHIP*), and *FAM13A*.[109] Smoking is a major risk factor for COPD and as mentioned previously, induces many epigenetic changes in the lung. Altered DNA methylation patterns have been identified in COPD patients in comparison with controls[110] and histone deactylase activity is decreased.[111] Importantly, methylation changes associated with cigarette smoking are reversible with time after quitting[19] and epigenetic changes offer promising targets for drug therapy.[20]

■ SARCOIDOSIS

Relatively little is known about genetic susceptibility to sarcoidosis and despite its prevalence in African Americans, early studies were mainly conducted in cohorts of European ancestry.[112,113] Surprisingly, emerging data suggest common risk loci across multiple different ethnic groups,[114–116] a marked contrast from the heterogeneity in GWAS data for some other diseases. Key loci identified from these studies include the *ANXA11* gene and several HLA subtypes.

TARGETED THERAPIES FOR GENETIC DISEASE

The completion of the human genome project led to high expectations (and in some cases, hype) of a new era of personalized medicine. The first arena in which this has been realized is in the treatment of cancer. Drugs such as imatinib (for chronic myeloid leukemia) and Herceptin (in breast cancer) target specific gene rearrangements or amplifications occurring in these cancers. Several drugs are approved to target epidermal growth factor receptor (EGFR) in non–small-cell lung cancer. Targeted lung cancer therapies are discussed in detail in a later chapter. Progress in other fields has been slower, but some recent advances show great promise, especially for CF.

Initial hopes for gene replacement therapy in CF failed to live up to expectations, but detailed characterization of the types of mutations and their functional consequences are now translating into new therapies. One approach is to promote read-through of nonsense mutations with a small molecule called Ataluren (PTC124).[117] This reduces the recognition of a premature stop codon and allows the ribosome to translate a full-length protein. The same approach has been tried previously with aminoglycoside antibiotics, but Ataluren is more potent and has fewer adverse effects.[118] In theory it should work for any nonsense mutation, but in practice some mutant transcripts are rapidly degraded by nonsense-mediated decay. Logically, therefore, the approach has proven to be most effective for mutations that are relatively stable and not subject to NMD.[119] After positive results in mouse models of CF and Duchenne muscular dystrophy, Ataluren was given orphan drug designation by the FDA and has shown very promising results in phase-II CF clinical trials.[120]

Where a full-length protein is made but it either mislocalizes (class II) or is an inefficient chloride transporter (classes III and IV), drugs are being tested that could improve trafficking to the membrane and improve transporter function. Ivacaftor (VX-770) was found to be effective in rescuing function of the G551D mutation,[121] a class III mutation with a frequency of 3% to 5%. A randomized placebo-controlled trial of Ivacaftor produced exciting results, with highly significant improvements in FEV1, sweat chloride levels, weight, and quality of life scores.[122] Therapies to help the majority of CF patients who are homozygous for ΔF508 are still awaited, but these successes build hope that the vision of personalized medicine, therapies tailored to an individual's personal genetic profile, may become a reality.

Other lung diseases are lagging behind compared with CF, although many do not have the benefit of more than two decades of research on a single gene. However, new therapeutic targets are starting to emerge from some of the research summarized earlier, particularly at the epigenetic level. Several approaches to improving BMPR2 signaling in HPAH are being studied.[123–125] At the epigenetic level, histone deacetylase inhibitors have been proposed as a possible therapy in PAH,[126] whereas corticosteroid-resistant COPD may benefit from increasing HDAC2 activity.[20] As our understanding of the effect of specific genetic mutations and epigenetic modifications increases, the future for targeted therapeutic intervention is bright.

WEB RESOURCES

Online Mendelian Inheritance in Man (OMIM): http://omim.org/
GeneReviews (current expert-authored disease descriptions of inherited diseases): http://www.ncbi.nlm.nih.gov/books/NBK1116/
Genetic Testing Registry: http://www.ncbi.nlm.nih.gov/gtr/
NIH Epigenomics Roadmap Consortium: http://www.roadmapepigenomics.org/
Mitochondrial genome database: http://www.mitomap.org/MITOMAP

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CHAPTER 8

Stem Cells and Respiratory Disease: Prospects for the Future

Darrell N. Kotton*

INTRODUCTION

Advances in stem cell research offer unprecedented opportunities to develop new treatments, disease models, and drug screens for previously untreatable conditions. These discoveries have captivated the imagination of the lay press and have inspired hope in patients, clinicians, and scientists. Inevitably, in an emerging new field, there are false starts that accompany promising discoveries. If rigorous researchers in the field have difficulty discerning hype from hope, what is a busy clinician to do when confronted with basic questions, such as: "Is stem cell therapy available for my lung disease?" or "Shall I bank my baby's cord blood in case he/she develops cystic fibrosis or emphysema?". This chapter is designed to describe the quickening pace of stem cell and regenerative medicine research related to lung disease and to place the latest discoveries in a historical context, before discussing future prospects.

Stem cells have been found in an increasing number of tissues whose biology is characterized by rapid turnover of differentiated cells. In these tissues, for example, blood, skin, and intestine, a stem cell hierarchy has been described where rare stem cells proliferate occasionally, giving rise to stem cell daughters or to progenitors that can proliferate rapidly, and differentiate into mature cells required for the function of that tissue. These properties of self-renewal and differentiation are the classic hallmarks of stem cells, and their importance in homeostatic maintenance of the blood, skin, and intestine, are well accepted.[1–3] These features also make stem cells attractive vehicles for clinical applications such as the reconstitution of injured or diseased tissues. Several decades of research focused on animals and humans, including the seminal bone marrow transplantation work of Till and McCullough[4] has rigorously proven, for example, that the hematopoietic stem cell, a cell that comprises 1 in 10,000 bone marrow cells, can be delivered to a recipient by simple intravenous infusion, reconstituting all cells of the bone marrow and circulating blood for the life-time of the recipient.[1]

Given the virtually unlimited self-renewing capacity and blood differentiation repertoire of hematopoietic stem cells, most pulmonologists are surprised to learn that cells of similar capacity have not been reproducibly proven to exist in the lung and may not be necessary for the homeostasis of an organ with a quiescent epithelium that contrasts with the rapidly self-renewing epithelia of intestine and skin.

LUNG EPITHELIAL RESPONSES TO INJURY

Because the unperturbed adult lung epithelium displays remarkably slow cell turnover, the post-injury or disease responses of human or animal lung have been studied to elucidate both the proliferation potential and differentiation repertoire of various lung cell types. These injury models have been used to search for potential specialized lung cells that might exhibit stem cell properties, such as self-renewal and multipotent differentiation (reviewed by Rawlins and Hogan).[5] Beginning in the 1970s, morphologic studies of human and animal lungs defined subsets of lung epithelia with proliferative capacity, revealing basal, secretory, and club cells (previously called Clara cells) of the proximal airway, and type 2 alveolar cells of the distal lung parenchyma all had the capacity to enter cell

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cycle in response to lung injury.[6–14] More recently, thymidine-labeling techniques have been replaced by newer methods of identifying proliferating cells or tracking their progeny. These studies have emphasized that most lung epithelial cells, except for airway ciliated cells or type 1 alveolar cells, can proliferate after injury in a remarkably resilient organ where many differentiated epithelial subtypes contribute to tissue repair.[5,15–18]

Beyond assessing the proliferation of cells in the adult lung, the classic developmental biologist's method of "lineage tagging" cells has allowed investigators to follow the origin of lung epithelial cells during development, and to assess where they go upon ageing or after injury.[15,19–21] It is now well established that the many types of epithelial cells in the adult lung arise during development from a few progenitor cells in the embryonic foregut endoderm.[22] The concept has become generally accepted that a limited number of lung epithelial cell types are specified during embryonic development and sustain their committed differentiated state throughout life.[21] In the nascent field of stem cell research, most investigators agree that multipotent, bona fide lung epithelial progenitors exist, if only fleetingly early in embryonic development.[22,23] It remains unclear, however, whether any specialized progenitors or stem cells similar to these embryonic endodermal precursors remain in the lung postnatally or are rederived after injury.

EVOLVING STUDIES IN THE SEARCH FOR LUNG STEM CELLS

With so many proliferation-competent epithelial cells in the adult lung able to participate in post-injury repair, perhaps equally, some investigators have begun to wonder whether some cells are "more equal" than others. The search for specialized reparative lung cells in recent years has been propelled by the emergence of specific and sensitive molecular biology tools and laboratory instruments that can refine our previous understanding of lung biology (Fig. 8-1). New studies suggest that a much greater diversity exists within the previously identified broad classifications of lung airway and alveolar epithelial cells.[24] For example, the response of mouse lung to recover from naphthalene exposure, an injury that depletes the lung of most club cells (identified by the marker club cell secretory protein [CCSP; also known as Scgb1a1 or CC10]), revealed a small subset of airway progenitors, called "variant club cells" (previously variant Clara cells).[25,26] These cells expressed CCSP, but were resistant to naphthalene injury and rapidly reconstituted both secretory and ciliated populations of the injured airway. Most intriguing was the observation that, this rare subset of CCSP+ cells appeared to reside in two specialized microanatomical locations or niches: adjacent to neuroepithelial bodies of the airways and at bronchoalveolar duct junctions. This observation remains one of the most convincing examples to date, suggesting the lung contains progenitor niches, or microanatomical cell compartments with specialized stem or progenitor cells.

One remarkable and controversial study by Kim et al. has proposed that some of these rare CCSP+ progenitors located at the bronchoalveolar duct junction may possess the capacity to reconstitute both airway and alveolar epithelia, suggesting the lung contains rare, multipotent, "bronchoalveolar stem cells" (BASCs).[27] However, the existence of BASCs has been contested in later work by Hogan et al.[19] who employed lineage tagging to trace the progeny of club or variant club cells expressing the CCSP marker which would presumably include the putative BASC population. These investigators found that these cells, either following an injury or during normal fetal lung development, gave rise only to conducting airway but not alveolar epithelia. In later work, Hogan et al. found that under some circumstances, such as following bleomycin-induced lung injury in mice, CCSP+ lineage tagged cells could give rise to alveolar epithelial cells. This confusing literature continues to cause controversy and uncertainty in the field and has dampened enthusiasm for the concept of a lung stem cell

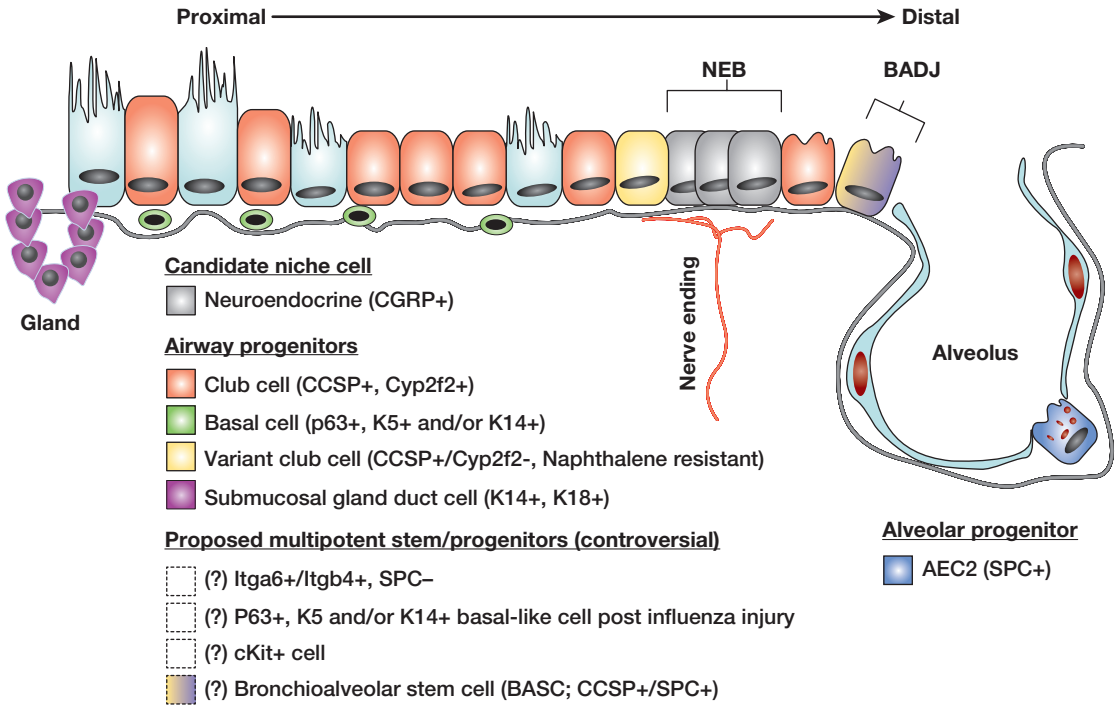

Figure 8-1 Lung epithelial stem and progenitor cell candidates. Schematic of proposed lung epithelial candidate stem or progenitor cells and their niches in the proximal conducting airways and distal alveoli. Cells whose localization or existence is not yet clear or accepted are indicated with dashed boxes and/or question marks. NEB, neuroepithelial body; BADJ, bronchoalveolar duct junction; Gland, submucosal gland duct; AEC2, type 2 alveolar epithelial cell; Marker abbreviations used for each cell subtype include the following: Itg, integrin; K, cytokeratin; CCSP, club cell secretory protein; SPC, surfactant protein-C. *(Modified with permission from Kotton DN: Next-generation regeneration: the hope and hype of lung stem cell research. Am J Respir Crit Care Med. 2012;185(12):1255–1260.)*

hierarchy that might follow the classical paradigm of hematopoietic stem cells of the blood-forming bone marrow.

In the more proximal airways, such as the mouse trachea or human bronchi, investigators have also found remarkable subsets of basal cells that contain extensive proliferative potential and a multipotent differentiation repertoire consisting of the capacity to give rise to basal, secretory, and ciliated lung epithelial cells.[28,29] With the advent of modern flow cytometry, these cells can now be sorted to purity, allowing the cataloging of protein markers (such as p63, NGFR, CK5, or CK14) that identify these cells as well as the delineation of their global transcriptome by microarray analysis.[28,30] The capacity to purify, expand in culture, and differentiate basal cells has resulted in a number of publications in recent years with important implications for those searching for lung cells with stem or progenitor potential.[28,30,31] First, these studies have confirmed that heterogeneity and diversity within the previously limited subsets of lung epithelial cells is indeed much greater than that appreciated a decade ago.[24,32] Second, the studies have revealed the impressive proliferative potential and differentiation repertoire of some subtypes of single lung epithelial cells (such as basal cells), which can expand almost indefinitely in vitro, similar to classically studied stem cells of the skin.[28,31] Taken together, this body of work supports the concept that basal cells can function as tissue-specific stem cells of the proximal conducting airway epithelium.

While there is a quickly growing list of stem/progenitor candidate cells able to reconstitute the conducting airway epithelium, the type 2 alveolar epithelial cell to date remains the best accepted progenitor of the lung alveolus.[33] Basic scientists are on the trail of new candidate alveolar progenitors, however, as evidenced by a notable new study demonstrating the clonal expansion in culture of cells from human or mouse lungs that express basal cell markers yet possess both airway and alveolar differentiation potential in vitro.[31] The authors who described these cells have proposed them as candidate alveolar stem cells, and other labs are working on reproducing these findings before their differentiation repertoire or nomenclature can be established. Most importantly, the p63+ or CK5/14+ lung stem cells described in this exciting study appeared to emerge during recovery from influenza-induced injury in regions of distal lung alveoli, an area of the lung that does not normally harbor cells expressing the basal cell markers p63 or CK5. Other recent studies have utilized flow cytometry to isolate new candidate lung progenitors, identified by coexpression of alpha6 and beta4 integrins.[34] This population appeared to proliferate in response to lung injury, and after purification from mouse lungs displayed remarkable potential for multipotent airway and alveolar differentiation.

While the therapeutic application of these progenitor populations remains years away, it is already clear that the lessons learned from studying the biology of progenitor cells in both mouse models and humans with lung disease can be applied to clinical settings. For example, many publications now demonstrate that communications between some of the best studied lung epithelial progenitors and their neighbors, either in the epithelium or surrounding lung mesenchyme, helps to regulate the fine balance between progenitor self-renewal and differentiation.[17,32,35] Perturbations in these communications, controlled by familiar developmental signaling molecules (such as Wnt, Notch, FGF, retinoic acid, and TGFβ) disturb the balance of lung epithelial homeostasis[36] and contributes to the disordered histopathology and physiology of many lung diseases, including cystic fibrosis, emphysema, idiopathic pulmonary fibrosis, and asthma.[32,37,38] The increased understanding provided by studying the basic biology of lung progenitors and epithelial–mesenchymal interactions has thus allowed a more complete understanding of clinical disease.[37,39] and already is being applied for the development of new pharmaceuticals designed to modulate the above signaling pathways. The long-term goal of achieving sophisticated drug therapies for a variety of lung diseases is likely to ultimately involve activation of endogenous lung progenitors or mature epithelia to accomplish reparative reepithelialization to avoid pathologic lung remodeling.[40]

Common to most of the aforementioned studies evaluating the differentiation repertoire of purified lung progenitor candidates is the suggestion that if an effective technique for grafting these cells into injured lungs were available, these progenitors might be used to regenerate injured epithelia in patients. The prospect of engineering entirely new bioartificial lungs from these cells has also been proposed to meet the needs of growing numbers of patients with end-stage lung diseases who require lung transplantation. Pioneering studies in tissue engineering[41,42] have attempted to develop methods for preparing lung scaffolds or bioartificial lungs that might surmount this highest hurdle in our field: a method for delivering candidate progenitors or lung reparative cells in vivo for engineered lung regeneration. For example, the laboratories of Harald Ott and Laura Niklasson in 2010, both published a technique of engineering bioartificial lungs through the method of detergent-based decellularization of rodent lungs. This method leaves the 3D architecture of the lung matrix intact while stripping away rodent cells. This matrix then served as a scaffold upon which rodent or human cells were adhered to generate "recellularized" lung tissue able to carry out gas exchange in vitro or even in vivo after transplantation.[41,42]

CONTROVERSIAL CLAIMS OF PARADIGM SHIFTING STEM CELL RESEARCH DISCOVERIES

This aforementioned studies of lung epithelial injury, proliferation, and regeneration are slowly defining and refining our understanding of candidate lung epithelial progenitors, but there are occasional studies that challenge earlier paradigms of lung development and repair after injury. For example, the laboratory of Anversa et al. in 2011 reported the discovery of a rare cKit+ lung stem cell that they claim can be purified from human lung tissue, can be expanded indefinitely in simple culture media supplemented with serum alone, can be differentiated into multiple lung epithelia by adding dexamethasone, and most importantly, can be injected into injured mouse lungs giving rise to essentially all lung tissues, including mesodermally derived vasculature and endodermally derived airway and alveolar epithelia.[43] This property of naturally occurring pluripotency, defined as the capacity to give rise to multiple cell types across multiple germ layers, is without proven precedent in any adult tissue outside the germline and contradicts many decades of developmental biology research, according to some leaders in this field.[44]

Perhaps it is easiest to understand this new work when placed in the historical context of other prior studies that also initially proposed to shift paradigms in lung biology, including the work of this writer[45] who found that advances in techniques and methods often reveal established paradigms to be correct, and data suggesting paradigm shifts often have simple, alternative explanations that are not obvious at first glance.[46] In the 1990s and early 2000s, for example, a wave of publications claimed that, cells within the bone marrow, such as marrow stromal cells (also known as mesenchymal stem cells [MSCs]) or hematopoietic stem cells, could circulate to the lung and give rise to almost any type of differentiated lung epithelial or vascular endothelial cell. Similar findings were reported when examining injured hearts, brains, livers, and other organs, creating understandable excitement (reviewed by Weiss et al. and Wagers and Weissman[32,47]). Clinical trials were rapidly planned to expose patients to injections of bone marrow–derived cells in the hope of reconstituting degenerative or injured tissues. The opportunity for financial profit inspired companies to promote the banking of cord blood from babies, with glossy pamphlets suggesting to expectant parents that umbilical cord blood containing "stem cells" (now more appropriately called HSCs and MSCs) had the potential to treat diabetes, cystic fibrosis, Parkinson's disease, strokes, or a myriad of

other diseases. These diseases might be treated with banked cord blood, if indeed, circulating blood or bone marrow–derived cells could form reconstituting cells for each relevant organ. In hindsight, the launch of some clinical trials and the promotion of cord blood as a panacea was premature as it was based on a first wave of controversially published literature. Advances in laboratory instruments and follow-up laboratory studies begun in 2000, slowly revealed that artifacts, such as autofluorescence, nonspecific antibody labeling, and the fusion of marrow-derived myeloid cells with recipient tissues were actually responsible for the bulk of initial observations and misinterpretations of bone marrow–stem cell engraftment.[46,47]

Clinicians understand that results from an initial, controversial clinical trial require repeating and reproduction of findings before treatment approaches, or established conventions should be radically altered. Likewise, the 2011 published work by Anversa et al. will need to be repeated and reproduced by other scientists before a paradigm shift is warranted. The historical context and false starts of our "lung stem cell field" should make this requirement for reproducibility particularly apparent.

ONE CELL TO RULE THEM ALL: PLURIPOTENT STEM CELLS

Because it remains controversial as to whether an endogenous lung cell possesses broad multipotency or the capacity to produce any type of lung cell, some investigators have chosen to focus their research on the de novo derivation of lung lineages in vitro from pluripotent stem cells, such as embryonic stem (ES) cells, which have well-established potential to generate all cell types in the body,[48] including all lung cells (at least after injection into mouse embryos). The controversy over human ES cell research, unlike other stem cell fields, is not focused on the differentiation potential of the cells, but rather on the ethical debate over whether it is permissible to utilize cells for research that are derived from a pre-implantation human blastocyst embryo (typically those unused from fertility clinics). Despite this ethical controversy, rapid progress is being made in recent years, and ES cells can now be grown indefinitely in culture and then differentiated into lung epithelial lineages upon exposure to defined growth factors.[49–51]

The key advance that has enabled the derivation of lung progenitors from ES cells came with the discovery by Keller et al. that the soluble growth factor, Activin A (hereafter Activin) induced the differentiation of these pluripotent stem cells into the germ layer, definitive endoderm.[52] Since the lung develops from this germ layer, emerging from the anterior foregut endoderm by budding and then branching, the derivation of definitive endoderm from ES cells is a key milestone on the way to generating lung epithelial cells from ES cells.[54] Keller's discovery was based on a careful study of how the embryo develops in vivo. Secreted nodal protein from the node of the embryo is known to differentiate embryonic cells of the epiblast into primitive streak and then into definitive endodermal progenitors within the anterior region of this primitive streak. Since Activin binds similar receptors to nodal protein, Keller et al. found that ES cell cultures exposed to Activin differentiated efficiently into definitive endoderm. Subsequently, investigators in the laboratories of Snoeck,[49] and later Kotton,[50] and Rajagopal[51] found that ES cell–derived endoderm could be patterned into anterior foregut-like precursors that were competent to respond to activated BMP, FGF, and Wnt signaling, differentiating further into primordial lung epithelial progenitors, identified by expression of the transcription factor Nkx2–1 (also known as thyroid transcription factor-1 [TTF1 or Titf1]). Again, these discoveries of how to differentiate stem cells into lung progenitors through activating a sequence of developmental milestones was made possible by mimicking the published inductive signals known to be active during in vivo embryonic endoderm and lung development.[53,54] Once primordial Nkx2–1-expressing primordial lung progenitors have been derived from ES cells (or from induced pluripotent stem [iPS] cells) the cells can be further differentiated into cells expressing a variety of markers of airway and alveolar lineages, including markers of basal cells (p63), ciliated cells (Foxj1 and Cftr), secretory cells (CCSP or mucins), and type 2 or type 1 alveolar epithelia (SPC, SPB, or T1 a), respectively.[50,51] Most intriguing is the finding that ES cell–derived lung epithelia can be used to reconstitute 3D lung tissue scaffolds with cells reminiscent of the morphologic and molecular phenotypes of primary alveolar epithelia.[50]

REPROGRAMMING APPROACHES FOR THE DERIVATION OF LUNG DISEASE-SPECIFIC OR PATIENT-SPECIFIC "INDUCED PLURIPOTENT STEM (iPS) CELLS"

Despite the accepted scientific promise of ES cell research discoveries, there has been a continuing public debate and uncertainty regarding whether it is ethically acceptable to allow public funding of research that uses cells derived through a process that previously involved the destruction of human embryos. The political and ethical concerns that have limited funding or progress in the ES cell research fortunately have found one potential solution in the remarkable discovery of reprogramming technology by Dr. Shinya Yamanaka in 2006. Yamanaka's work revealed that four transcription factors (Oct4, Klf4, Sox2, and cMyc) transferred into cells could reset the epigenetic state of somatic cells, such as skin fibroblasts, into an embryonic like state virtually indistinguishable from ES cells.[55] Reproduction and refinement of this discovery established reprogramming as an accepted technique to engineer iPS cells from dermal fibroblasts or from peripheral blood cells, such as those obtained from simple skin punch biopsies, or banked blood (reviewed by Stadtfeld and Hochedlinger[56]). Like ES cells, the broad differentiation repertoire of iPS cells suggests their potential to form any desired somatic cell type, including lung epithelium.[49] In contrast to ES cells, iPS cells are genetically identical to the individual from whom they are derived, raising the prospect of utilizing iPS cells for autologous cell-based therapies without risk of rejection. Yamanaka, together with his predecessor, Sir Jon Gurdon, who discovered reprogramming approaches in tadpoles 50 years earlier, were awarded the 2012 Nobel Prize in Physiology or Medicine for their paradigm shifting discoveries.[57]

To establish clinically relevant pluripotent stem cell platforms for lung disease research, some investigators have developed new reprogramming technologies able to derive "clinical grade" iPS cells from human skin or blood.[56] and have successfully applied these technologies to generate banks of "lung-disease specific" iPS cell lines from patients with a variety of end-stage lung diseases.[58] In one example of how these cells are being applied to model disease, Rossant et al. generated iPS cells from patients with cystic fibrosis and differentiated these cells in air–liquid interface cultures into cells expressing the Cftr gene responsible for cystic fibrosis, thus modeling Cftr dysfunction using cells of the patients' own genetic background and studying the effects of a pharmaceutical product designed to correct Cftr chloride ion flux.[59] Many other groups are now focused on utilizing patient-specific iPS cell lines (and ES cells) to model lung diseases in vitro, to screen drugs and gene therapy approaches, and to derive de novo replacement lung epithelia and endothelial cells that may one day be transplanted back into the patients from whom they have been derived (Fig. 8-2). The lessons learned from the failed attempts to deliver bone marrow–derived cells to the injured lung epithelium have taught us that delivery of iPS cell–derived lung cells (or any other lung cell) in vivo will not be easy or straightforward. Still, precedent has already been set in rat models of Parkinson's disease and mouse models of sickle cell disease, for example, where iPS-derived replacement neurons and hematopoietic stem cells, respectively, can result in clinical improvementwhen technology for effective differentiation and transplantation of these cells is carefully developed (reviewed in Stadtfeld and Hochedlinger[56]).

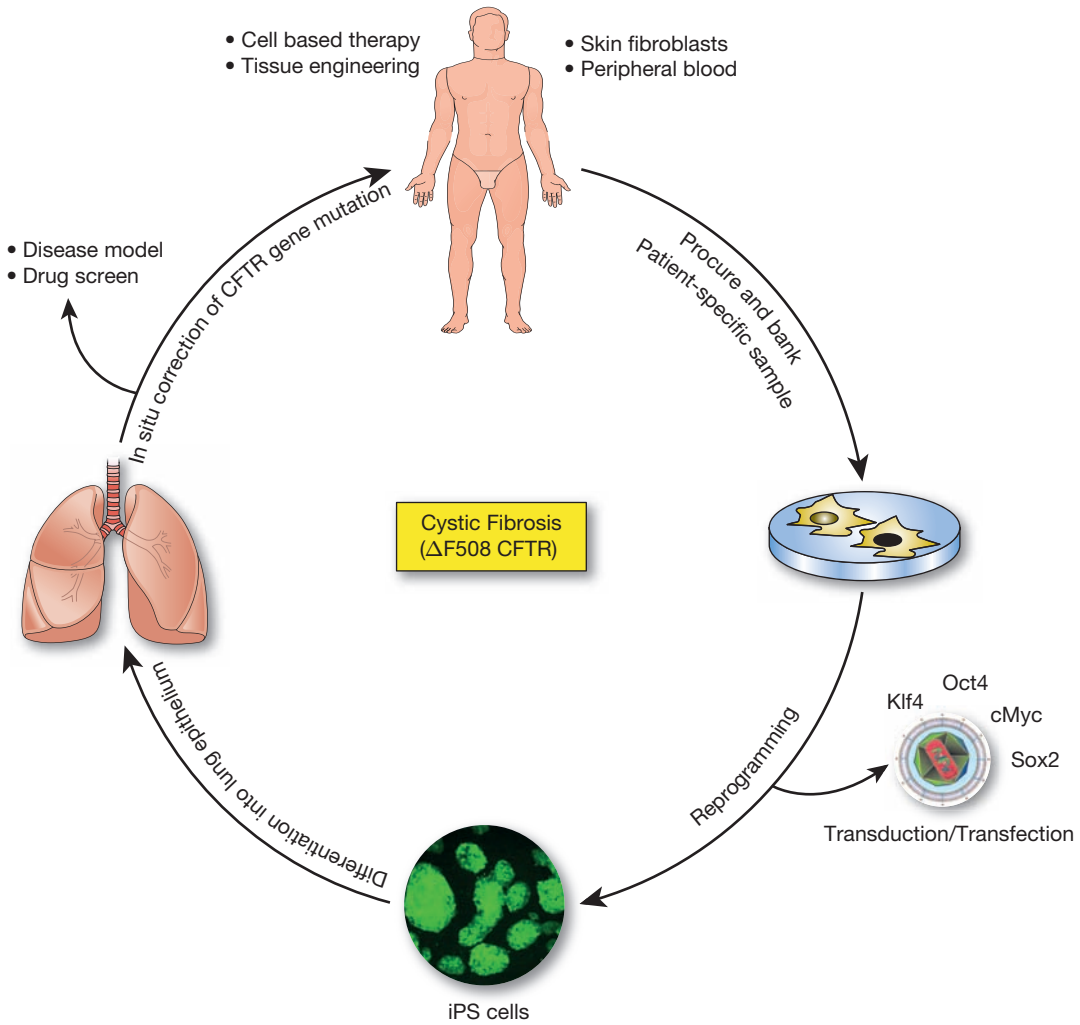

Figure 8-2 Schematic indicating approach for generating patient-specific or disease-specific induced pluripotent stem (iPS) cells from humans with lung disease. Peripheral blood cells or skin fibroblast cells harvested from a patient with lung disease, exemplified by cystic fibrosis, are reprogrammed into iPS cells using defined transcription factors. The resulting iPS cells undergo in vitro "directed differentiation" into lung epithelial or other lung lineages. These lineages can be employed for in vitro studies of disease pathogenesis modeling or high-throughput screening of drugs to predict efficacy. The cells may also undergo correction of any disease-causing gene mutations (such as ΔF508 CFTR) *via* zinc finger nuclease–mediated gene repair. Correction may be performed in the undifferentiated state, or (as shown) following directed differentiation into lung lineages. For future studies, corrected cells may be employed to tissue engineering bioartificial lungs or to develop cell-based therapy by transplantation back into the patient from whom they have been derived. Alternatively, drugs passing in vitro screening can be administered to the patient as personalized medicine.

In almost any field of research where cells reminiscent of the early embryo are employed, such as iPS cells or ES cells, recapitulating the milestones of early development of that tissue lineage has proven to be the most effective and most efficient way to derive desired differentiated lineages in vitro.[48] Unfortunately, little is known about many stages of embryonic lung development, a deficit that limits progress in deriving de novo mature lung epithelia from pluripotent stem cells (be they ES or iPS cells) in vitro and hampers our ability to properly understand and modulate repair after lung injury.

FUTURE PROSPECTS FOCUSED ON THE CLINICAL APPLICATIONS OF STEM CELLS

Given that safe clinical applications of most of the aforementioned exciting stem cell advances remain years away, how is a pulmonologist able to answer questions and respond to the pleas of patients desperate for stem cell therapies? One resource designed to help both physicians and patients access reliable information is the International Society for Stem Cell Research (ISSCR) webpage, which features a downloadable free "Patient Handbook" designed to educate the public about the promise and perils of stem cell research (www.closerlookatstemcells.org). The American Thoracic Society webpage equivalent also helps to objectively caution patients that most stem cell trials charging fees for claimed "treatments" have not been reviewed or substantiated by experts (http://patients.thoracic.org/materials/stem-cells.php).

At the time of publication of this chapter, a number of clinical trials are listed at clinicaltrials.gov for evaluating various cell-based therapies for several lung diseases (reviewed by Weiss et al.[32]). Infusions of MSCs to treat patients suffering from COPD, bronchopulmonary dysplasia, bronchiolitis obliterans, asthma, or acute lung injury, are either planned or underway. Additional trials are listed to test treatments for pulmonary hypertension (employing infusions of endothelial progenitor cells (EPCs) or bone marrow progenitors) and to assess treating pulmonary silicosis utilizing intrabronchial instillations of bone marrow cells.[32] Clinical

investigations in Europe, not listed on this website, have also targeted idiopathic pulmonary fibrosis with cell-based therapy.

It is still too early to determine whether any of these trials will prove efficacious, but accumulating data from >100 MSC clinical trials (mostly phase I or II) registered on clinicaltrials.gov for treating diseases affecting other organs suggests that, at least for MSCs, there appears to be little safety risk to participants. That said, there is also little reason to believe that these trials will result in regeneration of lung tissue for participants, as the bulk of basic mechanistic studies in animals suggest the infused cells work mostly via paracrine or immunomodulatory effects on recipient lung tissue.[32] Thus, these trials might be viewed as evaluations of cell-based immunomodulatory drug delivery rather than attempts to regenerate lung tissue.[60] Infused EPCs also appear to have paracrine and perhaps angiogenic effects on recipient tissue,[32] but their capacity to directly form replacement endothelial cells in the lung remains in doubt. When viewed with these results in mind, the term "stem or progenitor cell" – used to refer to the cells being infused in the trials to date – risks misleading clinicians and participants attracted by the promise that these terms imply. The dream of delivering truly regenerative or reconstituting cells to the lung, such as endogenous lung progenitors, ES cells, or iPS cells, will need to be appropriately delayed while these cell populations are fully evaluated in laboratory animals. The impressive differentiation and proliferation potential of the newly described pluripotent stem cell populations also makes them potentially risky and teratogenic in human trials, if deployed before their biology is more fully understood.

All indicators suggest that we are at the onset of realizing the promise of lung regenerative medicine propelled by the quickening pace of stem cell research. Endogenous lung stem or progenitor cell populations, such as basal cells, are just beginning to reveal the mechanisms that control their biology in careful studies at the lab bench.[30,35] New bioartificial lungs generated in the laboratory have already been successfully transplanted into rat recipients,[41,42] and human iPS cells generated from patients with alpha-1 antitrypsin (AAT) deficiency have undergone successful gene correction in vitro followed by hepatic transplantation into rodents.[61] This latter study by Vallier et al. is a conceptual advance for research related to preventing the progression of emphysema caused by AAT deficiency. These researchers demonstrated the full proof of concept of how gene edited iPS cells might be used as a clinical therapy since the research team derived iPS cells from a patient with AAT deficiency, performed gene editing with zinc finger nuclease technology to change the iPS cells from mutant (PiZZ) genotyped cells into gene-corrected (PiMZ or PiMM) cells. The gene-corrected cells were then differentiated into hepatocytes in vitro and then were engrafted in a rodent liver in vivo and secreted human AAT protein. If this approach were applied successfully to humans with AAT deficiency, it would be expected to replace current weekly augmentation therapy treatments and might potentially prevent the progression of emphysema through modulating protease–antiprotease imbalance.

How will the emerging studies focused on lung stem cells impact future clinical care of patients with lung disease? Treatment approaches are likely to involve one or more of several approaches based on the growing literature on endogenous lung progenitors and the newly described lung lineages just now being developed from exogenous pluripotent stem cell sources, such as iPS cells. First, an improved understanding of the pathways that regulate endogenous lung progenitors and control their cell fate decisions to self-renew or differentiate is likely to result in pharmaceutical approaches designed to regulate the behavior of these cell populations during disease pathogenesis. For example, if syndromes such as bronchiolitis obliterans result from an inability to maintain bronchiolar epithelial homeostasis, then an improved understanding of the biology of progenitors of the airways should with time lead to drug approaches for regulating the behavior of these cells toward improved maintenance of homeostasis, epithelial–mesenchymal cross talk, or epithelial barrier integrity. Second, gene therapies aimed at correcting monogenic lung diseases, such as cystic fibrosis or alpha-1 antitrypsin deficiency, likely will involve gene editing[61] or gene correction of lung progenitors or stem cells. A key hurdle limiting progress in lung gene therapy has been the inability to accomplish gene transfer into enough cell numbers. Stem cells provide a potential solution to this problem, since correction of just one stem cell may be sufficient if that cell can self-renew (either in vitro or after engraftment in vivo) extensively enough to reconstitute large numbers of lung epithelial cells via their progeny. Hence, methods for the delivery or engraftment of stem cells into human lung tissue remain a key hurdle still to be solved in order for this hope to come to fruition.

iPS cells are likely to impact lung disease treatments in several ways in the future. First, personalized therapeutic drug regimens can be screened in vitro using lung lineages derived from each patient's iPS cells, potentially predicting effective individualized drug regimens for each individual, rather than the globalized approach currently used to treat disease, where treatments for disease targets are chosen based on trial data from heterogeneous cohorts of patients. If approaches for engrafting or reconstituting lung tissue with exogenously delivered cells are ever successfully developed, iPS-derived cells are one potential source of autologous cell derivatives for potential reconstituting therapies. A particularly attractive, yet far-off goal of some stem cell researchers is the engineering of tissues from stem cells, including the tissue engineering of a whole, functioning, transplantable lung.[41,42] Several groups are working to optimize this approach using iPS cells to derive lung lineages for recellularizing these grafts to optimize tissue engineering of bioartificial lungs for transplantation in future.

While some prospects for employing stem cell–based therapies will take many years to come to fruition, this exciting field of research raises many potential avenues for achieving the long sought-after goal of lung regenerative therapies. Perhaps at this, the most optimistic time in a century of basic science research, we would be most wise to re-emphasize that many of the miraculous advances being made in this field are based on basic science research discoveries realized by investigators who originally had no practical clinical translation in mind. Those who simply wondered what made the Drosophila fly's wing notched, or made the jellyfish glow green, for example, paved the way for today's stem cell discoveries. In 1976, Comroe and Dripps found that the top 10 clinical advances in cardiac and pulmonary medicine derived from 529 key articles, 61.7% of which were classified as "basic science research" and 42% were not clinically oriented at the time the work was done, leading the authors to conclude that "basic science research" pays off in terms of key discoveries.[62] Their report from 38 years ago potentially provides a guide for realizing the full promise of lung-related stem cell research in the years ahead.

SUMMARY

Research discoveries in the fields of stem cell biology and regenerative medicine are beginning to advance and refine an understanding of lung injury and repair. While these emerging studies offer unprecedented opportunities to develop novel therapies for a variety of lung diseases, realization of these therapies will take time and clinical application remains predominantly a future prospect rather than a clinical trial-ready treatment. Given the increasing number of questions from patients about how stem cell research will impact their care, this chapter provides an overview for the clinician or clinician-researcher of the latest advances in lung-related stem cell research and places the new discoveries in a historical context. Established, lineage-restricted, epithelial progenitors of the conducting airways and gas-exchanging alveoli are briefly reviewed,

and controversial, newly proposed, tissue-specific candidate lung stem/progenitor cells with broader differentiation repertoire are introduced. Exogenous derivation of lung epithelia from ES cells or iPS cells is also presented as an alternative method for engineering lung tissue de novo in culture.

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CHAPTER 9

Personalized Pulmonary Medicine

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INTRODUCTION

Since the first draft sequences of the human genome were completed in 2001,[1,2] medical research has increasingly focused on the utilization of genetic and genomic profiling in the prediction of disease susceptibility and natural history, as well as drug response and drug development. Personalized medicine can be defined as an approach to medicine in which medical decisions are tailored to the individual patient. In theory, personalized medicine will avoid costly and prolonged trial and error approaches resulting in unwanted therapeutic side effects or diminished treatment efficacy. Diagnostically, personalized medicine uses molecular tracking to signal risk of disease on a genetic level, which may identify disease presence before clinical indications and symptoms appear. Thus, personalized medicine enhances the focus on preventive medicine at the primary, secondary, and tertiary levels. Fully realized, personalized medicine has the potential to facilitate early diagnosis and/or prevention of disease and selection of optimal therapeutic choices with minimal attendant side effects for established disease states. The potential savings, from both a financial and quality-of-life perspective, are enormous.

Much of the efforts to adopt personalized medicine into clinical practice have centered on genetic approaches, as sequence changes in deoxyribonucleic acid (DNA) have been closely associated with a wide range of disease susceptibilities and therapeutic responses. However, the "omics" era includes enhanced focus on cellular and metabolic changes downstream of DNA sequence variation including genomics or transcriptomics (the analysis of gene expression), proteomics (the analysis of protein changes), and metabolomics (the analysis of end products of cellular metabolism). Adding to genomic complexity are the so-called epigenetic changes, the study of changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence, such as DNA methylation, post-translational modification of gene expression, and microRNA (see further in Chapter 7). Each of these genomic study types has the potential to serve as a biomarker in a personalized medicine context.

In this chapter, the foundations of personalized pulmonary medicine will be reviewed and current approaches designed to facilitate a personalized approach to the diagnosis and treatment of pulmonary disorders will be discussed, including specific examples of personalized approaches currently being implemented in clinical practice. We provide overviews of human genetics, personalized pulmonary diagnostic testing, pharmacogenomics, biomarkers, and future implementation as they relate to personalized respiratory medicine.

DETERMINANTS OF THE CLINICAL UTILITY OF A GENETIC TEST

The predictive power of a genetic test is a function of four interdependent estimable parameters: (1) the *heritability* of the trait; (2) the *penetrance* of the tested genetic variant; (3) *allelic heterogeneity*; and (4) the variant *allele frequency*.

Heritability can be defined as the proportion of disease risk that is explained by genetic determinants. Heritability is highest (~100%) among monogenic diseases like cystic fibrosis (CF), while common diseases such as asthma or obstructive sleep apnea have more modest estimates (30%–60%), with a substantial proportion of disease risk is due to environmental factors. The heritability for many of the commonly measured pulmonary traits is modest (Table 9-1).

Penetrance is defined as the likelihood of the disease among individuals who carry the risk genotype (Fig. 9-1). Penetrance is highest for variants implicated in rare monogenic disorders, approaching 100% for the ΔF508 mutation in CF, and is lowest for more frequent genetic variants associated with common diseases. Wide ranges of intermediate penetrance have also been reported in pulmonary disease, from 90% for FLCN mutations in Birt–Hogg–Dubé syndrome (BHD)[3] to 20% to 50% for *BMPR2* mutations in familial pulmonary hypertension[4] and the *MUC5B* promoter polymorphism in familial pulmonary fibrosis.[5] Penetrance is phenotype-dependent. For example, in BHD, although ~90% of patients with *FLCN* mutations have radiographic evidence of cystic lung disease, dermatologic findings are seen in only ~60%, and spontaneous pneumothorax is observed in only 38% of patients.[3] Similarly, though virtually all PiZ homozygotes have markedly reduced circulating levels of alpha 1-antitrypsin levels, only a subset of these individuals manifests symptomatic emphysema.[6]

TABLE 9-1 Heritability Estimates in Pulmonary Medicine

Trait	Heritability Estimates
Pulmonary diseases	
Cystic fibrosis	1.0
Asthma	0.36–0.72
COPD	0.40–0.77
Sarcoidosis	0.60–0.70
Obstructive sleep apnea	0.33–0.52
Quantitative traits	
FEV_1	0.38–0.77
FVC	0.54–0.91
FEV_1/FVC	0.44–0.46
Airways responsiveness	0.30–0.66
D_{LCO}	0.39–0.46
IgE levels	0.40–0.60

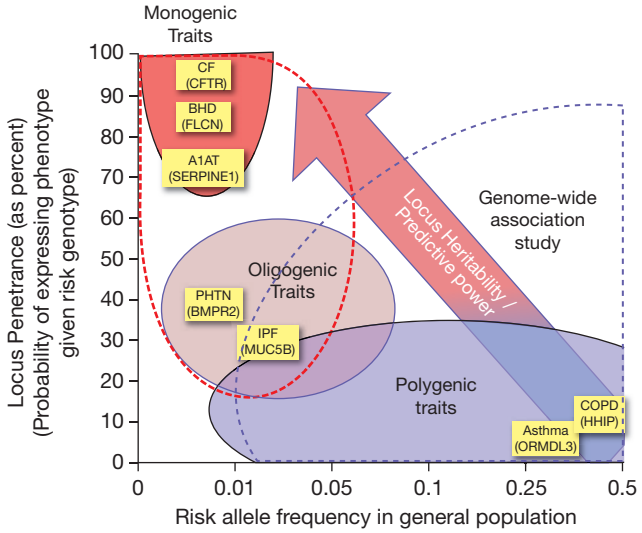

Figure 9-1 The relationship between allele frequency, locus heritability, predictive power, and genetic mapping strategies: Monogenic diseases, such as cystic fibrosis (CF), Birt–Hogg–Dubé syndrome (BHD), and alpha 1-antitrypsin deficiency (A1AT) are caused by highly penetrant, deleterious causal mutations that can be detected by parametric linkage analysis. Polygenic, complex traits, such as asthma and COPD, are caused by numerous genes (dozens to hundreds) harboring variants of much weaker genetic effect. Genome-wide association studies can identify the subset of these variants, but their individual predictive value is low. Oligogenic traits, like familial forms of pulmonary hypertension (PHTN) and idiopathic pulmonary fibrosis (IPF), are caused by variants in a handful of genes with both intermediate frequencies and intermediate penetrance functions.

Allelic heterogeneity refers to the existence of more than one causal allele present in the reference population. Though one variant often predominates as the most prevalent disease allele (e.g., the Z allele in 85% in alpha 1-antitrypsin deficiency), numerous pathogenic variants are typically described, including more than 20 *SERPINE1* mutations in alpha 1-antitrypsin, 50 *FLCN* mutations in BHD, and more than 1800 pathogenic *CFTR* variants in CF. *Locus heterogeneity* is a situation where the same phenotype can manifest through mutations in different genes. For example, familial bronchiectasis resulting from primary ciliary dysfunction has been mapped to no fewer than 18 genes that code for distinct proteins of the ciliary apparatus. There are numerous reports of confirmed primary ciliary dyskinesia where only one of two pathogenic mutations is identified in any one gene,[7,8] suggesting the potential for digenic inheritance, where the combination of two mutations in different genes is sufficient to cause disease.

The influence of variant *allele frequency* on the predictive power of a genetic test is complex, and depends largely on the strength of the genetic effect conferred (the locus heritability) and the disease prevalence. Rare monogenic lung diseases typically result from highly penetrant, low frequency (<1%) variants situated in highly conserved protein-coding sequences. Most common disease susceptibility variants reported are of high frequency (>5% in the general population) but individually are of weak effect. In many instances, the population risk allele frequency exceeds the population disease prevalence (such as the asthma-associated *ORMDL3/GSDMB* risk haplotype, frequency of 62% in asthmatics). In these cases, the specificity of the variant is quite weak. In contrast, rare variants of high penetrance implicated in common disease will have high specificity, yet their low population prevalence diminishes their clinical predictive value, as sensitivity and negative predictive values will be poor.

GENETIC TESTING

All of the major classes of genetic variation – including single nucleotide substitutions, insertions and deletions, copy number variants, and larger, more complex structural variants – have been described in pulmonary disease (Table 9-2), and no single technology has been developed that can reliably survey all these forms simultaneously, though next-generation sequencing (NGS) technologies are emerging as one possible solution. The rapid pace of technological advancement and the vast number of technologies in current use preclude comprehensive survey of all aspects of DNA technologies here. Instead, we emphasize NGS technology as a current and future direction for use in clinical practice.

Whole-genome sequencing. NGS platforms enable DNA sequencing in a highly paralleled fashion, without the need for predefined sequence-dependent hybridization. These methods generate short sequence reads (30–135 bases in length), sampled randomly from the target sample. With these methods, whole-genome sequencing of nearly all genomic regions is now feasible, and is being widely implemented for both research and clinical purposes. The massive parallel nature of these techniques, and their lack of reliance on Sanger chemistries, have resulted in dramatic reductions in cost (now $1500–$2000) for whole-genome sequence, favorably raising the prospects for comprehensive genomic testing and personalized medicine.

The major technical challenge, and primary determinant of cost, is achieving sufficient base-calling accuracy. Given the very large numbers of both the bases being called (billions) and polymorphisms per genome (~3–4 million), accuracies of >99.9% are needed to limit the number of spurious findings (both false positive and false negative). Such accuracy can be achieved by ensuring high read depth—the number of times a given base is sequenced. For clinical purposes, minimum average read depths of 30 to 40 times provide reasonable accuracies. For whole genomes, such coverage can only be achieved by performing multiple sequencing runs, increasing costs considerably. More expensive are the downstream costs related to the involved analytical processes of quality assessment, sequence annotation, and variant classification (see below). Additional costs are incurred from the current clinical guidelines that mandate independent technical validation of all actionable (clinically relevant, reportable) variants by Sanger sequencing. Thus, while the technical cost continues to fall, current total charges (often exceeding $10,000 per clinical genome) preclude widespread adoption of whole genome sequencing at present.

TABLE 9-2 Types of Genetic Variation and their Relative Contribution to Disease Phenotype

Genetic Variation	Definition	Phenotypic Variation %[a]	Example	Pulmonary Manifestation
Chromosomal abnormalities				
Numerical abnormalities	Variations in chromosome number			
Polyploidy	Additional genome copies		69 XXY	Fetal loss
Aneuploidy	Variable number of single chromosome	<1%	Trisomy 21: Down syndrome	Obstructive sleep apnea and pulmonary hypertension
		<1%	Monosomy XO: Turner syndrome	No common pulmonary phenotype
Structural abnormalities	Variations in chromosome structure			
Gross rearrangements	Visible by karyotype/FISH	1%	del(4)(q12): FIP1L1-PDGFRA gene fusion	
Translocations	Aberrant exchange of DNA sequence between two different chromosomes		T(9;22) – Philadelphia chromosome of chronic myelogenous leukemia	Somatic translocations commonly seen in lung cancer tumors
Inversions	Altered sequence orientation		900-kb inversion on 17q21	Glucocorticoid pharmacogenetic response
Copy number variants	Gains or losses of DNA sequence spanning 500 bp or more	9%	GSTM1 null variant	Smoking-related lung function decline
Sequence variants				
Single nucleotide polymorphism	Single base pair substitutions			
Nonsense/Missense	Variant introduces stop codon/ amino acid substitution	55%	FLCN R4496X: Birt–Hogg–Dubé	Spontaneous pneumothorax
			SERPINE1 Glu366Lys (Z) allele	alpha 1-antitrypsin deficiency, emphysema
Splicing	Variant alters normal intron splicing pattern	9.20%	DNAI1 IVS1+3insT: Primary ciliary dyskinesia	Bronchiectasis
Regulatory	Variant alters mRNA transcription or protein translation	2%	17q21 rs12936231 variant alters ORMDL3/GSDMB expression	Asthma
Insertion/Deletion (Indel)	Gain or loss of one or more nucleotides	23%	CFTR ΔF508	Cystic fibrosis
Short tandem repeat	Repetitive element that varies in copy number	0.30%	PHOX2B exon 3 polyalanine repeat expansion	Primary central hypoventilation syndrome

[a]*Percent of total variation listed in Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php, accessed May 30, 2013).*

Targeted sequencing panels. While use of whole-genome sequencing in clinical practice remains modest, there is increasing utility in highly focused, targeted NGS of selected genes or gene regions, which is achieved by "pulling-down" DNA segments of interest using oligonucleotide filters (i.e., probe sets that bind complementary sequence). These filters can be customized to target specific sequences, ranging from a handful of genes to all gene-coding regions (i.e., whole exome filters). This approach markedly reduces the size of targeted sequence length (e.g., an exome sequence is only 3% of the total genome sequence), with numerous advantages for clinical implementation. The marked reduction in target size accommodates clinically reliable read depths in one sequence run, reduces analytic costs (as there is less sequence to annotate), and reduces follow-up validation costs.

Pulmonary-specific sequencing panels. Targeted sequencing of selected genes implicated in pulmonary disease is available commercially through several companies and clinical laboratories. The services provided differ from each other primarily in the gene content of the tests, which are frequently organized in discrete gene panels. Most panels are designed to assess selected gene sets implicated in disorders typified by a particular clinical or radiographic manifestation (i.e., a pulmonary fibrosis panel) or a shared molecular defect (i.e., ciliopathy panel). The largest panels available are those for workup of pulmonary fibrosis and bronchiectasis. Due to technical limitations and the constant pace of novel disease-gene discovery, few panels can be considered fully comprehensive. Yet, most offer coverage of the most commonly implicated genes being considered clinically. Panels of 5 to 20 genes typically cost $2500 to $6000, in comparison to the cost of clinical resequencing of individual genes (on average $1500–$2000). Thus, when more than one gene is clinically suspected, or for diseases with known locus heterogeneity, diagnostic panels offer greater cost efficiency over single gene resequencing.

More broad sequencing panels may have particular value in the evaluation of patients with more complex presentations (e.g., patients presenting with a combination of bronchiectatic and fibrotic features, or with parenchymal lung disease disproportionate to the degree of concomitant pulmonary hypertension). When a genetic basis is suspected, massively paralleled sequencing across panels of genes may help narrow the differential diagnosis to one or two disorders. Currently, only one laboratory – the Laboratory for Molecular Medicine at the Partners HealthCare Center for Personalized Genetic Medicine – offers combination panel testing, at incremental cost over one panel. Though possibly more cost-effective over current diagnostic strategies, the value of such an approach to the workup of patients with complex presentations remains unclear.

We emphasized that, before ordering more expansive tests, patients must be made aware that surveys of larger panels of genes increase the likelihood of identifying variants of unknown clinical significance (so-called VUS). Patients must be counseled pretest regarding the uncertainty these findings may impart. Genetic test results classify variants according to their likelihood as disease-causing variants. Variants classified as "pathogenic" are those firmly implicated as disease causing due to their demonstrated functional impact, their localization to a highly conserved functional genomic sequence, their presence in affected individuals only, and their strong segregation with disease. So-called "likely pathogenic" variants have many, but not all, of these features. "Benign" variants are those that are common among healthy controls, have no demonstrable function, and do not segregate with disease in families. Counseling of patients regarding these three classes of variants is often unambiguous. In contrast, VUS variants fall into a grey zone, in that they do have features that suggest functional impact but are either observed in unaffected subjects or segregate imperfectly in affected pedigrees (features that suggest incomplete penetrance). Patients must understand the possibility of such findings, and their implications on subsequent workup and management.

Clinical indications for genetic testing. Table 9-3 lists the most common uses of genetic information in clinical practice, both for the patient and at-risk family members. Diagnostic genetic testing is of greatest value when knowledge of the specific gene or mutation will directly impact clinical management. In these cases, genetic testing should be offered to patients in whom the possibility of defining an actionable variant is high, including those with specific disease presentations compatible with the diagnosis of interest, at-risk family members of patients with confirmed molecular diagnoses, and subjects with strong family histories. Some examples are as follows:

- Confirmation of alpha 1-antitrypsin deficiency in patients with emphysema and lung function decline identifies a small subset of COPD patients who may benefit from replacement therapy.
- Identification of Class III CFTR genotypes (particularly the G551R variant) in patients with CF. These patients are candidates for mutation-specific CFTR potentiating therapy with ivacaftor.[9]

TABLE 9-3 Utility of Genetic Information in Clinical Practice

Activity	Paradigmatic Example	Current/*Potential* Utility in Pulmonary Medicine
Preimplantation screening	Tay–Sachs disease	*Primary ciliary dyskinesia*
In utero diagnosis	Trisomy 21	*Congenital diaphragmatic hernia*
Newborn screening	Phenylketonuria	Cystic fibrosis
Diagnostics		LAM vs. Birt–Hogg–Dubé syndrome
Prognostics	Expansion length and age of onset in Huntington's disease	*MUC5B as positive prognostic in IPF*
Presymptomatic interventions	BRCA1 and prophylactic mastectomy/oophorectomy	*BMPR2 and vasodilator therapy*
Surveillance strategies	APC mutations and familial adenomatous polyposis	FLCN mutations and renal cancer screening in Birt–Hogg–Dubé syndrome
Replacement therapies	Gaucher's disease	Alpha 1-antitrypsin deficiency
Mutation-directed therapies	Tyrosine-kinase inhibition in EGFR+ tumors	Ivacaftor in G551R positive cystic fibrosis
Pharmacogenetics	Warfarin dosing	*Polygenic model of inhaled corticosteroid response in asthma*
Gene replacement therapy	X-linked severe combined immunodeficiency	*Surfactant gene replacement in infantile pulmonary fibrosis*

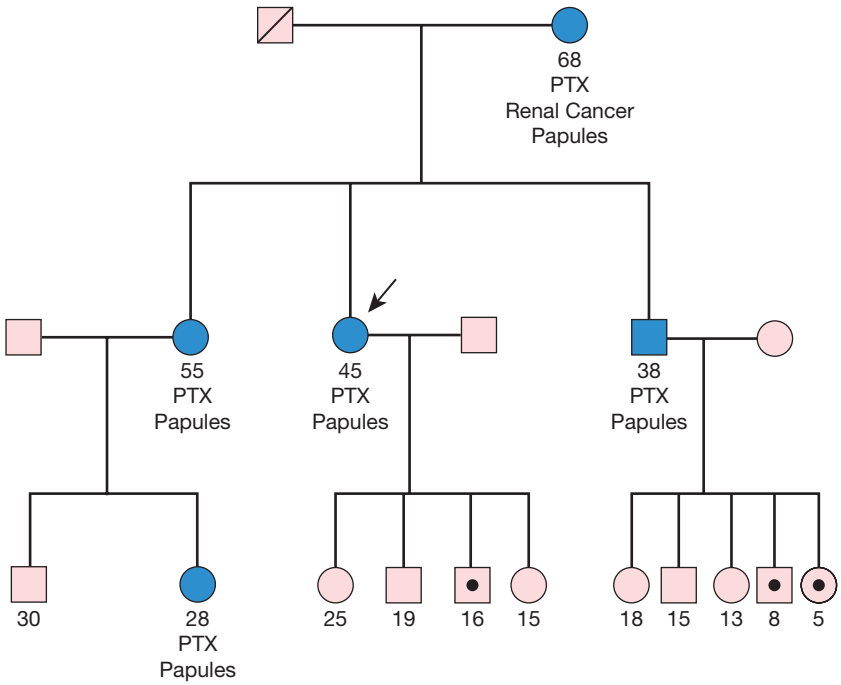

Figure 9-2 Birt–Hogg–Dubé (BHD) syndrome: Index patient *(arrow)* confirmed to harbor a pathogenic FLCN gene mutation. The maternal history of renal cancer places other mutation carriers in this family at risk of both renal and other malignancies. In this pedigree, the large number of reportedly unaffected offspring of two carriers is unusual, given a 50% probability of transmission from carrier to offspring. More likely, the mutation was passed on (hypothetically denoted by *dot*), but these carriers have not yet developed clinical manifestations, possibly due to their younger age. Such individuals would be at risk of eventually developing BHD, including malignancy. Therefore, confirmation of carrier status among at-risk, but seemingly unaffected, family members is warranted.

- Differentiating molecular forms of familial idiopathic pulmonary fibrosis: (1) Patients with *SFTPC* mutations may benefit from hydroxychloroquine treatment[10]; (2) TERC and TERT mutations help identify patients with short telomere syndrome (STS) at risk of marrow and liver failure, including during the post-lung transplant period; (3) Hermansky–Pudlak syndrome (HPS) can often be overlooked clinically due to subtle neurologic (nystagmus) and dermatologic (albinism) features, though these patients are at risk for a potentially severe, but treatable (with DDAVP), bleeding diathesis.

For highly penetrant monogenic diseases, the implications of a positive test result are often profound, even in instances where gene- or mutation-specific therapies are not yet available. Examples include preclinical identification of patients at risk for malignancy (e.g., in BHD or LAM), accelerated lung function decline (in LAM, familial fibrosis), or pulmonary hypertension, who can be more closely followed enabling earlier intervention, and who can be more vigorously counseled regarding the benefits of tobacco smoke avoidance. An illustrative example is provided in Figure 9-2, depicting the value of testing in a family pedigree with BHD. For autosomal dominant diseases of variable penetrance, and for recessive disease, genetic testing offers the ability to identify at-risk carriers prior to the onset of symptoms, providing opportunities for early diagnosis. Negative test results are also of value, providing reassurance to relatives that they are not at risk of developing an illness they may have witnessed afflicting their relatives.

Genetic counseling in pulmonary medicine. The inherently predictive, personal, and irreversible nature of an individual's genetic code distinguishes genetic from other forms of clinical testing. The psychological impact of genetic test results, whether positive or negative, cannot be underestimated. Feelings of inadequacy or imperfection, a sense of inevitable doom and therapeutic nihilism due to a genetic "fate" are not uncommon with a confirmed genetic diagnosis. Conversely, negative results can lead to a false sense of invincibility, leading to unhealthy behaviors (e.g., continuing to smoke). Inherently, the potential impact of genetic testing extends beyond the patient, implicating all blood relatives. Moreover, test results can impact family dynamics and the way in which individual family members react to their test results. For example, though most at-risk family members will be relieved by a negative test result, some experience a deep sense of guilt (so-called "survivors guilt") in relation to their affected family members. Finally, despite legislation at state and federal levels protecting patients from genetic discrimination in the workplace and in access to health care insurance, patients must be informed regarding this risk in other contexts (e.g., the impact on eligibility for life insurance policies).

For all these reasons, it is advised that genetic testing be offered only by, or in consultation with, experienced providers familiar with these issues, including certified genetic counselors, who can adequately address the medical, psychological, and familial implications of test results. We recommend initiating these discussions before testing, so that patients are empowered to provide truly informed consent. Patients should be made aware of the medical implications of both positive and negative results, and should be advised regarding the impact these results may have on them and their family members. Genetic pretest counseling should also address the potential identification of variants of unclear significance.

MUTATION-SPECIFIC THERAPIES IN MONOGENIC LUNG DISEASE

One of the primary goals of genetic classification of disease is the development of mutation-specific therapies. Such activities have traditionally focused on the development of replacement therapies for loss-of-function recessive diseases (i.e., recombinant human alpha 1-proteinase inhibitor replacement therapies). Newer pharmacologic approaches, including small molecule screens and others informed by the functional impact of specific mutations are emerging.

TYROSINE-KINASE INHIBITION FOR HYPEREOSINOPHILIC SYNDROME

Imatinib was identified as a therapy for chronic myelogenous leukemia (CML). However, once the functional mechanisms underlying its therapeutic effects were elucidated, other therapeutic uses were identified. The treatment of hypereosinophilic syndrome (HES) is one such example. Subsets of HES patients harbor a chromosome 4q interstitial deletion that results in the creation of a fusion of the *FIP1L1* and *PDGFRA* genes. The resultant fusion protein has tyrosine-kinase activity similar to that of BCR-ABL, the target site in CML and HES patients positive for the *FIP1L1-PDGFRA* rearrangement respond positively to imatinib therapy.[11,12] *FIP1L1-PDGFRA*-negative HES patients do not. Similar to CML,

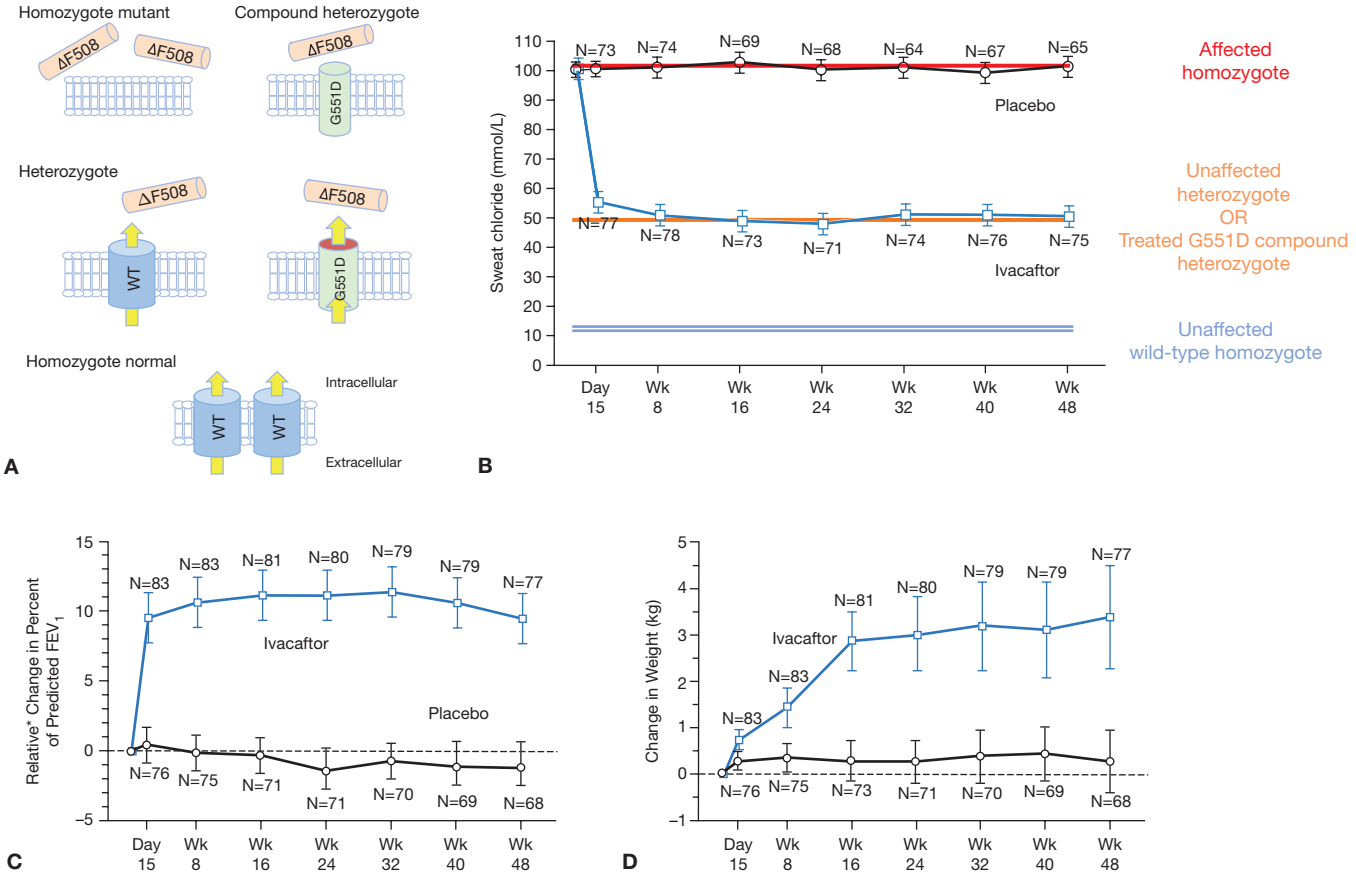

Figure 9-3 Mutation-specific therapeutic action of ivacaftor in cystic fibrosis: **A, B.** The additive effect of CFTR mutations on epithelial chloride efflux and sweat chloride levels, and the effect of ivacaftor. Individuals with two normal alleles have normal chloride efflux *(yellow arrows)*, and a corresponding normal sweat chloride test *(blue double line)*. Individuals with two mutated alleles demonstrate markedly reduced chloride efflux and elevated sweat chloride *(red line)*. Heterozygotes with ~50% normal functional chloride channels on epithelial cell surfaces manifest intermediate reductions in both chloride efflux and sweat chloride responses *(orange line)*. G551D compound heterozygotes treated with ivacaftor *(red disc)* demonstrate sweat chloride levels similar to heterozygote carriers. **C, D.** Therapeutic efficacy of ivacaftor: Patients randomized to ivacaftor demonstrated improvements in relative change in percent of predicted FEV_1 (**C**) and weight (**D**) over 48 weeks, in addition to improvements in symptoms and in quality of life scores (not shown). *Original report erroneously labeled figure as Absolute (not relative) change in percent of predicted FEV_1. (***B–D.*** *Reproduced with permission from Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365(18):1663–1672.)*

mutations of the tyrosine-kinase binding site have been reported upon HES relapse.

■ MUTATION-SPECIFIC THERAPIES FOR CYSTIC FIBROSIS

In 2011, positive results of a randomized clinical trial of a novel therapy for G551D-positive CF were reported (Fig. 9-3).[9] In a 48-week, randomized, double-blind, placebo-controlled trial, 167 patients received either placebo or ivacaftor—an oral agent that "potentiates" CFTR activity by prolonging channel opening times and augmenting transmembrane chloride transportation. Compared to patients receiving placebo, patients treated with ivacaftor demonstrated significant improvements in FEV_1, fewer respiratory exacerbations, improved quality of life, and a positive weight gain. The ~50% reduction in sweat chloride levels to those approaching those observed in asymptomatic *CFTR* mutation carriers (i.e., heterozygotes) serves as an elegant molecular–clinical correlate, suggesting selective effect on the G551D+ channel, but not ΔF508+ channels. While G551D and other variants likely to benefit via ivacaftor are observed in only ~6% of patients, their identification opens new therapeutic options for this subset of CF patients. The advent of this novel treatment strategy provides motivation for the development of additional agents that target other *CFTR* mutation classes (including the most common *CFTR* mutation—ΔF508), and the application of similar strategies for the treatment of other genetic diseases.

BIOMARKERS IN PULMONARY MEDICINE

Biomarkers have been defined as "biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention".[13] Ideal biomarker characteristics have been espoused (Table 9-4).[14] There are two major types of biomarkers applicable to clinical medicine: (1) biomarkers of exposure, which are used in risk prediction; and (2) biomarkers of disease, which are used in the screening, diagnosis, and monitoring of disease progression, as well as response to therapy. Thus, biomarkers have the potential to support clinical decisions, from diagnosis to treatment planning; to improve tailored treatment strategies; to avoid over- or undertreatment and adverse side effects; and to enhance prognosis and cost-effectiveness.

While a number of biomarkers have been evaluated in a wide range of pulmonary conditions, including MMP-7, ICAM-1, and IL-8 for interstitial lung disease,[15] procalcitonin for community acquired pneumonia,[16,17] exhaled nitric oxide for asthma and other inflammatory lung disease,[18,19] and RAGE, ICAM-1, and SP-D for ARDS,[20] few are

TABLE 9-4 Ideal Biomarker Characteristics

Easy to measure
Safe to measure
Low cost to measure
Consistent across gender, age, race
Cost of follow-up tests is reasonable
Proven therapy to modify biomarker
Modification of biomarker is proven to protect against disease or outcome

recommended for routine clinical use. This stems largely from their relatively weak predictive power. For instance, at a 5% false-positive rate (specificity 95%), a relative odds of 3.0 between the first and fifth quartiles of a biomarker gives only a 20% detection rate.[21] As such, most current biomarkers cannot substitute other clinical parameters in clinical evaluation, but are used as adjuncts to support clinical judgment.

An example of a biomarker in prominent routine use in pulmonary medicine is the D-dimer and its role in the diagnosis of acute pulmonary embolism (Fig. 9-4). The quantitative rapid enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 95%. In patients with low pretest clinical probability (i.e., 4%–15%), a normal D-dimer rapid ELISA substantially reduces the posttest probability of pulmonary embolism to 0.7% to 2%.[22] Therefore, these patients can safely be excluded from further evaluation.[22–25] Notably, the D-dimer is still used adjunctively to clinical judgment, as both the predictive ability falls in patients with intermediate to high pretest clinical likelihood of pulmonary embolism and the relatively poor specificity (of about 27%)[26] of the D-dimer limit its usefulness outside of low probability cases. There is, however, evolving evidence that may support the use of the D-dimer in the exclusion of pulmonary embolism, even with intermediate levels of clinical probability.[27–29]

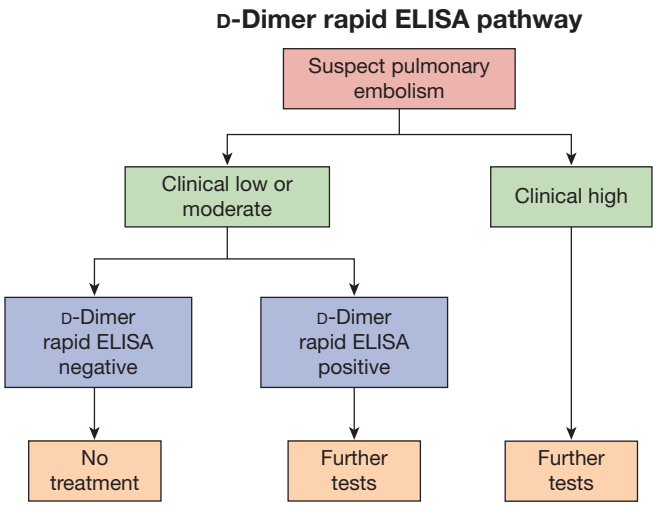

Figure 9-4 Use of D-dimer as a biomarker in the exclusion of pulmonary embolism. The quantitative rapid enzyme-linked immunosorbent assay (ELISA), with a sensitivity of 95%, showed the most clinically useful values among the various D-dimer assays. When used in combination with a low probability objective clinical assessment, which ranges from 4% to 15%, the post-test probability of pulmonary embolism ranges from 0.7% to 2% with a normal D-dimer rapid ELISA. No further testing is required if D-dimer is normal in a patient with a low probability clinical assessment. *(Reproduced with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. 2006;119(12):1048–1055.)*

The integration of biomarkers in drug development and their use as a companion diagnostic in clinical practice has been encouraged by regulatory authorities.[30,31] One example of this in clinical practice has been the development of periostin as a biomarker for treatment with lebrikizumab (anti-IL-13). In a study of 42 asthmatic patients and 28 healthy controls, conducted by Woodruff et al.,[32] a three-gene airway epithelial cell expression signature composed of periostin (*POSTN*), chloride-channel regulator 1 (*CLCA1*), and serpin peptidase inhibitor clade B, member 2 (*SERPINB2*), was used as a surrogate marker of T_H2 inflammation. Multivariate cluster analysis defined groups of patients: a T_H2-high cluster (asthmatic patients with high expression of T_H2 cytokine-induced gene expression) and a T_H2-low cluster (asthmatic subjects whose expression analysis was the same as healthy controls). The T_H2-high cluster phenotype was characterized by increased serum IgE levels, allergic inflammation, airways hyperresponsiveness, and increased responsiveness to inhaled corticosteroids.[32]

In a study of lebrikizumab, an IL-13 monoclonal antibody, in 219 adults who had poorly controlled asthma despite inhaled glucocorticoid therapy,[33] high serum periostin levels at baseline predicted a positive treatment response (improvement in FEV_1). Nevertheless, the performance of periostin expression as a clinical predictor has yet to be independently confirmed. Indeed, in a clinical trial of asthmatic subjects not taking inhaled corticosteroids, lebrikizumab did not show any significant improvement in lung function regardless of baseline periostin status.[34]

PHARMACOGENETICS

The response to pharmacologic agents varies tremendously between individuals. For instance, the plasma level of a given medication can vary more than 1000-fold between two individuals having the same weight when treated with the same drug dosage.[35] On average for a given drug, 30% of patients show beneficial effects, 30% fail to improve, 10% only experience side effects, and 30% are noncompliant (which may be related to either lack of efficacy or side effects).[36] Therefore, as many as 70% of all patients are unnecessarily exposed to the potential to develop adverse drug reactions (ADRs).[37–39] In the United States, over 2 million hospitalizations due to serious ADRs and over 100,000 fatal ADRs were noted in 1994, ranking ADRs between the fourth and the sixth leading cause of death.[40] Worldwide, the prevalence of hospitalizations due to ADRs was recently estimated at a median of 5.3% (interquartile range [IQR] 2.7%–9.0%), as based on prospective cohort studies of over 100,000 admissions.[41] Overall, the cost of drug-related morbidity and mortality in the United States exceeded $177.4 billion in 2000,[42] a figure more than double the estimate from 1995.[43] As enormous as these figures are, the burden due to lack of therapeutic response to drug therapy is likely to be much greater.[44]

Pharmacogenetics is the study of variability in drug response due to heredity. Pharmacogenetic variability in drug absorption, drug metabolism, and drug action at the receptor level is well-known. Overall, it is estimated that genetics can account for 20% to 95% of variability in drug disposition and effects.[45] Ideally, pharmacogenetics will allow for "individualized therapy" based upon an individual's genetic makeup that will maximize the potential for therapeutic benefit, while minimizing the risk of adverse effects. The potential for cost savings and for decreasing morbidity and mortality is immense.

PHARMACOGENETIC RESPONSE CATEGORIES

The heritability of many therapeutic agents has been formally established via genetic studies, including the twin studies of Vessel and Page.[46–50] Barring formal genetic studies, the response distribution can also strongly suggest a heritable response. The interindividual response

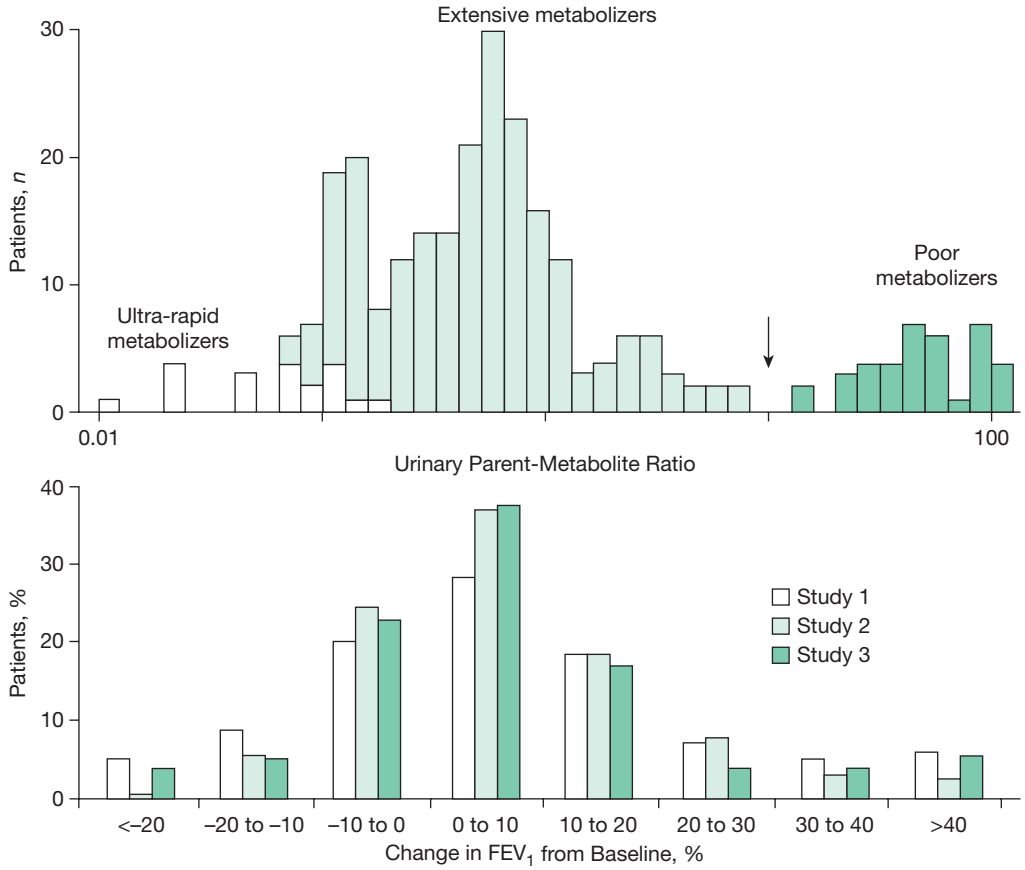

Figure 9-5 Patterns of variation in drug response. *Top.* Multimodal response common to many drug metabolizing enzymes. *Bottom.* Unimodal, yet highly variable, response noted in complex trait drug response. In this case, Studies 1 to 3 refer to three independent clinical trials that measured inhaled corticosteroid response over time. *(Reproduced with permission from Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: challenges and opportunities. Ann Int Med. 2006;145(10):749–757.)*

distribution may be either multimodal or unimodal (Fig. 9-5). A multimodal distribution suggests distinct population subgroups of response, thereby directly supporting a pharmacogenetic basis for response. A unimodal drug response distribution still supports the concept of interindividual variation, with subjects demonstrating both "good" and "poor" responses. The combination of wide interindividual response with high repeatability (the likelihood of a subsequent beneficial/poor response to a drug given a prior response) supports the plausibility of a pharmacogenetic effect.[51]

Pharmacogenetics has traditionally been divided into four categories based upon the effects of genetic variability on the pharmacologic properties of a drug. For instance, one genetic variant can alter the rapidity of drug metabolism (thereby altering bioavailability), whereas another genetic variant can affect binding to a drug receptor (thereby decreasing therapeutic efficacy). The four categories include variation related to pharmacokinetics, pharmacodynamics, idiosyncratic reactions, and disease pathogenesis (Fig. 9-6).[52] Each of these categories will be discussed below, followed by a known example or examples pertinent to pulmonary medicine. Clinical implementation guidelines for several of these examples have been developed.[53–57] Additional examples likely to be encountered by the respiratory practitioner and labeled by the US Food and Drug Administration (FDA) are listed in Table 9-5.

Pharmacokinetics studies the effect of the body upon an administered drug, including the absorption, distribution, tissue localization, biotransformation, and excretion of drugs.[58] Common drug metabolizing enzymes implicated in pharmacogenetics and their estimated effect on drug dosing are shown in Figure 9-7. The cytochrome p450 enzymes (*CYP*s) encode for ~60% to 70% of all phase I (i.e., structural transformation) dependent metabolism and have been the classic examples of drug metabolizing enzymes. The clinically most important *CYP*s are *CYP2C9, CYP2D6,* and *CYP3A4*, with *CYP2C9* discussed in the context of warfarin administration later in this chapter. *CYP* genotypes generally result in three metabolic phenotypes, ultra-rapid metabolizers, extensive (normal) metabolizers, and poor metabolizers (Fig. 9-5).

An example of polymorphic phase II (i.e., drug conjugation) drug metabolizing enzymes is the metabolism of azathioprine by thiopurine-*S*-methyltransferase (*TPMT*).[59] Azathioprine, which is commonly used in the therapy of interstitial lung disease and pulmonary vasculitides, is converted to the active 6-mercaptopurine, which is then metabolized by *TPMT* or converted into 6-thioguanine nucleotides. Decreased *TPMT* activity, as mediated through genetic variation, occurs in about 10% of individuals at intermediate levels, while ~0.3% (1 in 300) have low to absent activity. Clinically, this results in drug-related myelosuppression in 5%, severe leukopenia in 1.2%, and is fatal in 0.3% of subjects taking azathioprine.[60] Both clinical phenotyping (predrug assessment of *TPMT* activity) and genotyping assays are available. Such testing has been noted to be cost-effective

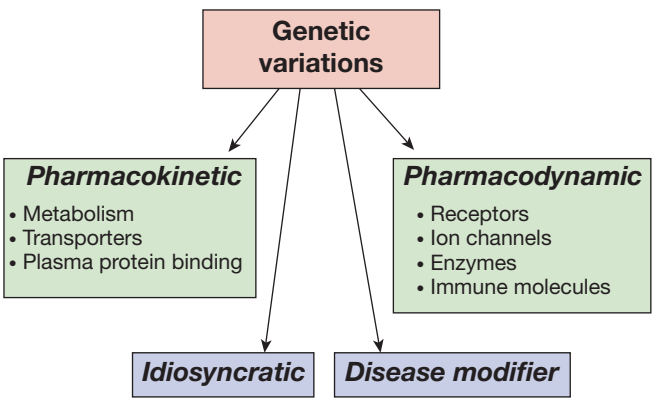

Figure 9-6 Categories of pharmacogenetic response, based upon site of activity of the genetic variant of interest.

TABLE 9-5 Common Pulmonary Medications FDA Labeled for Pharmacogenomic Effects

Drug	Therapeutic Area	Genotype	Variant Genotype Effect
Azathioprine	Interstitial lung disease	*TPMT*	Increased potential for bone marrow suppression
Cisplatin	Oncology	*TPMT*	Children with variants may have an increased risk of ototoxicity
Codeine	Analgesics, cough suppression	*CYP2D6*	Decreased pain relief in poor metabolizers
Dapsone	Anti-infective	*G6PD*	Hemolytic anemia
Erlotinib	Oncology	*EGFR*	EGFR-TK mutation is biomarker of erlotinib efficacy in lung cancer
Gefitinib	Oncology	*EGFR*	EGFR-TK mutation is biomarker of gefitinib efficacy in lung cancer
Imatinib	Pulmonary hypertension	*CYP3A4*	Decreased efficacy in rapid metabolizers, increased toxicity in poor metabolizers
Irinotecan	Oncology	*UGT1A1*	Increased potential for severe diarrhea and fatal neutropenia
Ivacaftor	Pulmonary	*CFTR (G551D)*	G551D genotype is one benefitting from actions of ivacaftor
Lansoprazole	Gastroenterology	*CYP2C19*	Increased efficacy (higher intragastric pH) vs. extensive (normal) metabolizers
Mercaptopurine	Oncology	*TPMT*	Increased potential for bone marrow suppression
Mycophenolic acid	Transplantation	*HGPRT*	Should be avoided in patients with hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) such as Lesch–Nyhan or Kelley–Seegmiller syndrome
Omeprazole	Gastroenterology	*CYP2C19*	Increased efficacy (higher intragastric pH) vs. extensive (normal) metabolizers
Isoniazid	Anti-infective	*NAT1; NAT2*	Increased risk of peripheral neuropathy with *NAT1* variation; attenuated with pyridoxine administration; *NAT2* influences drug level
Voriconazole	Antifungals	*CYP2C19*	Possible risk of subtherapeutic voriconazole concentrations, and subsequently of treatment failure
Warfarin	Hematology	*CYP2C9; VKORC1*	Higher warfarin levels and increased potential for adverse effects

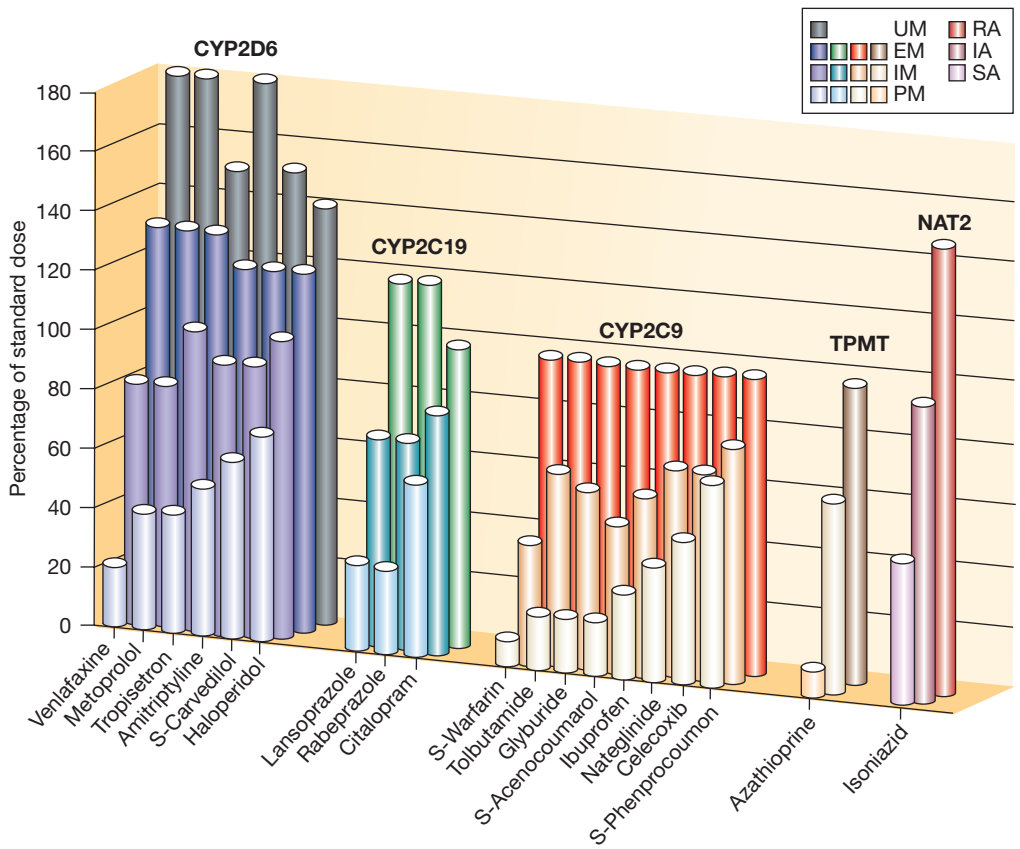

Figure 9-7 Common drug metabolizing enzymes and their standardized effect on drug dosing, according to the difference in pharmacokinetic parameters from clinical studies. Substantial adjustments need to be made to drug dose to achieve the same level of drug exposure in individuals with different genotypes. EM, extensive metabolizer; IA, intermediate acetylator; IM, intermediate metabolizer; PM, poor metabolizer; RA, rapid acetylator; SA, slow acetylator; UM, ultra-rapid metabolizer. *(Reproduced with permission from Kirchheiner J, Fuhr U, Brockmoller J. Pharmacogenetics-based therapeutic recommendations–ready for clinical practice? Nat Rev Drug Discov. 2005;4(8):639–647.)*

in a variety of diseases,[61–63] including recent modeling of azathioprine use in interstitial pulmonary fibrosis.[64] Clinical pharmacogenomic implementation guidelines have been published.[53,56]

Genetics can also influence drug transporters affecting drug absorption, distribution, and excretion. As an example, the solute carrier organic anion transporter family member 2B1 (*SLCO2B1)* mediates the Na(+)-independent transport of organic anions such as leukotriene C4. A nonsynonymous *SLCO2B1* polymorphism (rs12422149) has been associated with significantly reduced plasma concentration of differential response to therapy with montelukast as assessed by change in baseline Asthma Symptom Utility Index scores.[65]

Pharmacodynamics is the study of the biochemical and physiological consequences of the administration of a drug and its mechanism of action,[58] that is, the effect of a drug at its therapeutic target. Genetic variation may lead to response differences despite appropriate concentrations of a drug at its intended target. This category is especially pertinent to pulmonary medicine, since many conditions are treated with inhaled medications which bypass first-pass metabolism by the liver, thereby limiting the effect of pharmacokinetic variants.

Warfarin is the most commonly prescribed anticoagulant medication worldwide and in respiratory medicine is commonly used for the treatment of pulmonary embolism. For warfarin, cytochrome p450 2C9 (*CYP2C9*) is the primary enzyme involved in its metabolism, while vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) is its primary therapeutic target, responsible for the conversion of vitamin K-epoxide to vitamin K. FDA labeling of warfarin includes consideration for testing of variants involved in both pharmacokinetics and pharmacodynamics. "High" and "low" dose risk variants of the *VKORC1* gene, as well as variants of the *CYP2C9* gene have been identified.[66] Overall, *VKORC1* variants account for ~25% of variability in warfarin dosing, with *CYP2C9* adding an additional 6% to 10%.

Multiple early studies supported the ability to predict initial warfarin dosing using a genotype stratified approach.[66–70] Initial guidelines for the clinical implementation of warfarin pharmacogenetics have been detailed.[55,71] However, in two[72,73] of three recently published clinical trials comparing use of a pharmacogenetic algorithm to a clinical dosing strategy, no significant benefit was noted in terms of percentage of time spent within the therapeutic international normalized ratio (INR) range, with the third[74] demonstrating only a modest (67.4%–60.3%) benefit to pharmacogenetics. While disappointing from a pharmacogenetic dosing standpoint, these studies were not powered to address the more important issue of bleeding and thrombotic complications. One study comparing a current genotyped cohort with historical controls demonstrated 31% fewer hospitalizations overall (adjusted hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.58–0.82) and 28% fewer hospitalizations for bleeding or thromboembolism (HR: 0.72, 95% CI: 0.53–0.97) based upon pharmacogenetic dosing.[75] Further study in this area is warranted.

Pharmacogenetic tests aimed at combining multiple genetic predictors will likely continue to be a focus going forward. For instance, variants in *CRHR1* and *GLCCI1* have been associated with lung function response to inhaled corticosteroids in multiple asthmatic populations.[76,77] However, these account for just a small proportion of the variability in response to these medications. Nonetheless, combining two variants in the *CRHR1* and *GLCCI1* genes significantly improves the ability to predict response in a replicable fashion.[78]

The **idiosyncratic** category of pharmacogenetic response to drugs includes the individuals that experience an ADR to a therapeutic agent that could not be anticipated based upon the known drug target. Examples of the idiosyncratic category include some compounds that are metabolized by arylamine-*N*-acetyltransferase 2 (*NAT2*). Genetic differences in *NAT2* have been associated with predisposition to the development of peripheral neuropathy in certain individuals taking isoniazid[79] and hypersensitivity reactions to trimethoprim/sulfamethoxazole (including rash, granulocytopenia, and abnormal liver function tests).[79,80] Interestingly, the *NAT2* acetylator phenotype (based upon metabolized level of drugs) may correlate poorly with *NAT2* genotype,[81,82] suggesting that factors other than drug level may explain these idiosyncratic reactions associated with genetic variation.

The final pharmacogenetic category is that of genetic factors influencing **disease pathogenesis**. By modifying the underlying biology/severity of the disease, these genetic factors can also influence which therapies will work or how effective a given medication might be. As a brief example, in CF, the *CFTR* ΔF508 variant has been associated with earlier colonization with *Pseudomonas aeruginosa*,[83] whereas the G551D mutation has a milder clinical phenotype with later *P. aeruginosa* colonization.[84] Therefore, *CFTR* genotype would affect both severity of disease and frequency of antibiotic dosing.

PERSONALIZED PULMONARY MEDICINE: THE CHALLENGE

Despite the availability of personalized diagnostic panels, labeling changes implemented by regulatory agencies (e.g., FDA), and an ever-increasing compilation of genetic, biomarker, and pharmacogenetic studies in the literature, actual translation of personalized pulmonary testing to the bedside has been slower than expected. There are several of reasons for this delay. In the preceding sections, we have outlined how low heritability, variable penetrance, and the need for large effect sizes may affect test performance. Other implementation issues include (1) limitations in the design of published studies, (2) regulatory and ethical concerns, (3) lack of cost-effectiveness analyses, and (4) need to educate both patients and providers.

Study design limitations. Despite the availability of numerous reported genetic and pharmacogenetic associations in the literature, many have not been reproduced in subsequent studies.[85,86] False-positive initial associations may be due to the fact that many pharmacogenetic studies are "spin-offs" from clinical trials or for improperly designed case-control studies and, thus, are underpowered for genetic association. The nature of clinical trials (for pharmacogenetics) and of individualized cohorts (for genetic association) may also result in multiple distinct clinical phenotypes, which vary from study to study. This "phenotypic heterogeneity" combined with "genotypic heterogeneity" (interrogating disparate markers within the same gene) may also contribute to failure to replicate initial findings. These issues were detailed in an evaluation of the pharmacogenetic associations of the β_2-adrenergic receptor (*ADRB2*) gene[87] with β_2-agonist response in asthma. Overall, in 21 studies that focused on the two most common *ADRB2* coding variants (Arg16Gly and Gln27Glu), there were large differences in study design for both genotype definition (e.g., single variant vs. haplotype) and phenotypic outcome. Of a total of 487 interrogated associations, only 2 associations were probed in at least 5 of the studies, for the same endpoint, time of assessment, type of intervention, and genetic group. Not surprisingly, no definitive conclusions have been made regarding the utility of *ADRB2* variants to guide asthma therapy. Clearly, a continued focus on appropriate phenotypes and more precise replication of existing data are needed.

While beyond the scope of this chapter, two additional topics related to study design should be mentioned. The first relates to systems biology and personalized medicine. Given that multiple genetic and environmental factors impact the majority of respiratory disease susceptibility and treatment response, systems approaches seek to integrate data both at the level of data type (e.g., epistasis or gene–gene interactions) and across data types (e.g., integration of biomarker, gene expression, and SNP data) to formulate predictive models.[88–92] While young, this approach is promising with regard to complex trait test development. The second additional point is the ongoing controversy regarding study design and whether prospective, genotype-stratified trials are necessary prior to implementation of pharmacogenetic testing. One perspective is that dosing and administration of drug changes warrant such trials, while the other

perspective argues that genotypes are invariant (since people are born with them) and therefore precede even retrospective studies. A potential compromise might be in the use of adaptive clinical trials, with pharmacogenomics included as part of the main trial adaptations.[93]

Regulatory and ethical concerns. As noted earlier the FDA has been proactive in terms of pharmacogenetics, with pharmacogenetic information included on about 10% of labels for drugs approved by the FDA. Nevertheless, questions regarding the regulation of genotyping tests and the extent to which pharmacogenetic analyses should be incorporated into new drug development before or after large clinical trials, remain.[94] While beyond our current scope, one detailed perspective on how pharmacogenetic testing might be included in each phase of clinical drug development has been recently published.[95] Another potential boon to genetic test development is the recent ruling by the US Supreme Court that genes cannot be patented.[96,97]

From an ethics perspective, the longstanding concern has been whether genetic variants could result in stigmatization (e.g., denied insurance).[94] A major step in the protection of individuals' rights came with the passage of H.R. 493, the Genetic Information Nondiscrimination Act of 2008. This law protects Americans against discrimination based on their genetic information in matters related to health insurance and employment and should translate into increased acceptance of personalized testing by the public in the future.

Lack of cost-effectiveness analyses. Despite the multitude of pharmacogenetic association studies in the literature, relatively few cost-effective analyses have been performed. These studies will be crucial prior to the availability of widespread reimbursement for routine personalized pulmonary testing. Circumstances that favor cost-effectiveness of a genetic test include the following: a high prevalence of the genetic variant of interest in the target population, good correlation between phenotype and genotype, satisfactory diagnostic test criteria, disease associated with significant morbidity or mortality if left untreated or undiagnosed, and, for pharmacogenetic variants, significant reduction in ADRs resulting from testing.[98]

Need to educate both patients and providers. Pharmacogenetics and the promise of personalized medicine have been frequently mentioned in the popular lay press. It is therefore incumbent upon both the developers of a given test, as well as healthcare professionals responsible for ordering the test, to be cognizant of the test characteristics and interpretation and to be able to effectively disseminate that information to patients. In turn, in the era of personalized medicine, the need for educating health care providers in both the broad array of potential predictive tools (in addition to genetic variants, genomic, proteomic, and other molecular biomarkers will be increasingly available), as well as the strengths and weakness of each of these approaches, will be needed. The context for these educational efforts is not yet clear. Given available tests, providers will potentially need a diagnostic step to determine which drug is best suited to each patient. Of paramount importance, providers will need to be reassured and cognizant that these tests will not and cannot replace sound clinical judgment.

CONCLUSION

Variation in the susceptibility to disease and response to drugs within pulmonary medicine has a significant heritable component. Although many challenges remain, testing of personalized pulmonary medicine, biomarkers, and pharmacogenetics has begun in earnest. Given the rapidity of new genetic knowledge, we are making progress toward the goal of individualized medicine.

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CHAPTER 10 Pulmonary Mechanics

Murray D. Altose

For venous blood to be properly arterialized, the distribution of air and blood within the lung is automatically matched to ensure effective gas exchange across alveolar–capillary membranes. Arterialization comprises a series of interrelated processes that begin with the mechanical performance of the ventilatory apparatus—that is, the lungs and the chest wall, including the rib cage, diaphragm, and abdominal wall. The ventilatory apparatus is critical for replenishing fresh air to the lungs for gas exchange. Although the function of each component of the lung and of the chest bellows can be deranged by injury or disease, the design of the ventilatory apparatus provides for considerable reserve. As a result, mechanical derangements are usually quite severe by the time clinical symptoms appear or arterial blood-gas levels become abnormal.

Depending on the nature of the underlying disorder, assessment of the mechanical properties of the ventilatory apparatus provides several different types of information. In some instances, characterization of the mechanical abnormality provides insight into pathogenesis and affords a quantitative measure of severity. In others, once the nature of the mechanical disorder is understood, the mystery surrounding a life-threatening disorder in gas exchange may be dispelled. Finally, certain breathing patterns make sense only if the mechanical performance of the chest bellows is taken into account.

During breathing, the lungs and chest wall operate in unison. The lungs fill the chest cavity so that the visceral pleura are in contact with the parietal pleura of the chest wall. The two pleural surfaces are separated by only a thin liquid film, which provides the bond holding the lungs and chest wall together.

At the end of a normal exhalation when the respiratory muscles are at rest, the ventilatory apparatus is in a state of mechanical equilibrium. The pressure along the entire tracheobronchial tree from the airway opening to the alveoli is equal to atmospheric pressure. The tendency of the lung is to deflate, however, and lung elastic recoil is directed centripetally. This is counterbalanced by the elastic recoil of the chest wall, which is directed centrifugally to favor an increase in volume. These opposing forces generate a subatmospheric pleural pressure of about −5 cmH_2O (Fig. 10-1A). The tendency for the lung to recoil inward and for the chest wall to recoil outward is illustrated by the observation that when the chest is opened at autopsy, the lungs collapse to a nearly airless state and the thorax expands.

Although it is conventional to consider pleural pressure as a single, mean value that reflects mechanical events within the entire ventilatory apparatus, this is clearly an oversimplification on several accounts: (1) pleural pressure is not directly determinable because normally there is only a potential space between the visceral and parietal pleura; (2) on conceptual grounds, distinctions exist between surface and liquid pleural pressures; (3) pleural pressures are not uniform over the surface of the lungs, being strongly affected by gravity; and (4) transmission of pleural pressures at the surface to alveoli located at different depths and loci with the lungs depends on the structural interplay among supporting structures in the alveolar walls (interdependence), which resists any inclination of individual alveoli or even a lobule to collapse.[1] Nonetheless, the concept of mean pleural pressure, as generally used in considerations of respiratory system mechanics, has proved to be of great practical value.[2]

The contraction of the muscles of inspiration produces the forces that permit the flow of gas along the tracheobronchial tree and the expansion of the lungs and chest. The movement of air into the lungs requires a pressure difference between the airway opening and the alveoli sufficient to overcome the resistance to airflow of the tracheobronchial tree. Also, a pressure difference across the alveolar walls (between the alveoli and pleural space) must be generated to overcome elastic recoil and inflate the lungs. During spontaneous breathing, the action of the inspiratory muscles causes an increased outward pull on the chest wall.[3] As a result, the pleural pressure becomes more subatmospheric. This pressure change is transmitted to the interior of the lungs, so alveolar pressure also becomes subatmospheric (Fig. 10-1B). In contrast, during artificial ventilation with a positive-pressure ventilator, a supra-atmospheric pressure applied at the inlet to the airways creates the proper pressure gradient between the airway opening and alveoli for airflow.

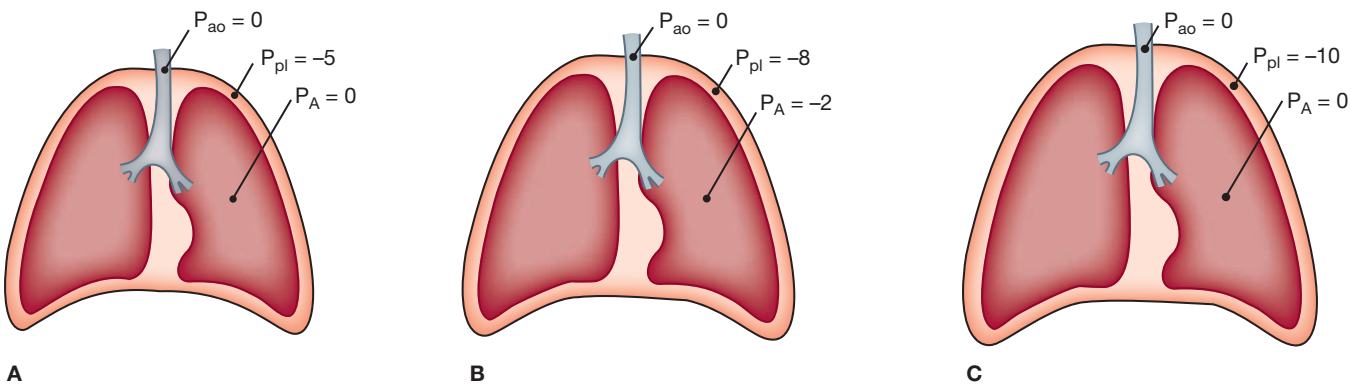

Figure 10-1 Respiratory pressures during a breathing cycle. **A.** End expiration. **B.** During inspiration. **C.** End inspiration. P_{pl}, pleural pressure; P_A, pressure in the alveoli; P_{ao}, pressure at the airway opening.

TABLE 10-1 Lung Volumes and Subdivisions

The *functional residual capacity* (FRC) is the volume of air that remains in the lungs at the end of a normal expiration.
The *tidal volume* (TV) is the volume of air that is drawn into the lungs during inspiration from the end-expiratory position (and also leaves the lungs passively during expiration) in the course of quiet breathing.
The *expiratory reserve volume* (ERV) is the maximum volume of air that can be forcibly exhaled after a quiet expiration has been completed (i.e., from the end-expiratory position).
The *residual volume* (RV) is the volume of air that remains in the lungs after a maximal expiratory effort.
The *inspiratory capacity* (IC) is the maximum volume of air that can be inhaled from the end-expiratory position. It consists of two subdivisions: tidal volume and the *inspiratory reserve volume* (IRV).
The *total lung capacity* (TLC) is the total volume of air contained in the lungs at the end of a maximum inspiration.
The *vital capacity* (VC) is the volume of air that is exhaled by a maximum expiration after a maximum inspiration.

Expansion of alveoli depends on the achievement of an appropriate distending pressure across alveolar walls. This distending pressure or transpulmonary pressure is the difference between alveolar (P_A) and pleural (P_{pl}) pressures. As shown in Figure 10-1A, the transpulmonary pressure at end expiration ($P_A - P_{pl}$) is 5 cmH_2O. At the end of inspiration (Fig. 10-1C), the lungs contain more air and the distending pressure which also represents the recoil pressure is greater.

The energy used during inspiration to overcome the elastic resistance of the lungs is stored. Expiration occurs when these forces are released. When the inspiratory muscles relax, the recoil of the lungs causes the alveolar pressure to exceed the pressure at the mouth, and air flows out of the lungs. Although expiration during quiet breathing is passive, the expiratory muscles are engaged at high levels of ventilation to assist the movement of air out of the lungs.

LUNG VOLUMES

The lung volumes and capacities (Table 10-1) are also considered elsewhere in this book (see Appendix B). The end-expiratory position of the lungs, functional residual capacity (FRC), is the major reference point for the subdivisions of lung volume. This position is set by the opposing recoil forces of the lung and chest wall when the respiratory muscles are at rest.

Total lung capacity (TLC), the total volume of air contained in the lungs after a maximal inhalation, is determined by the balance between the force-generating capacity of the inspiratory muscles and the opposing elastic recoil forces of the lung and chest wall.[4] Weakness of the muscles of inspiration or increased stiffness of the lung reduces TLC. Loss of retractive forces exerted by the lung, as in emphysema, enlarges TLC.

Residual volume (RV), the volume of air remaining in the lungs after a complete exhalation, is set by the balance between the actions of the expiratory muscle and the recoil forces of the lung, which act to decrease lung volume, and the outward recoil forces of the chest wall, which favor lung expansion. In middle-aged and older individuals, closure of airways at low lung volumes, with air trapping in the lung, is an important determinant of RV.[5]

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

To assess the elastic properties of the ventilatory apparatus, it is expedient to evaluate the elastic properties of the lungs and chest separately. Elastic properties are conventionally assessed over a fixed range of volumes during periods of arrested airflow.

ELASTIC PROPERTIES OF THE LUNGS (PULMONARY COMPLIANCE)

The change in transpulmonary pressure required to effect a given change in the volume of air in the lungs is a measure of the distensibility, or compliance, of the lungs. Pulmonary compliance is calculated as the ratio of the change in lung volume to the change in transpulmonary pressure—that is,

$$C = \frac{\Delta V_L}{\Delta(P_A - P_{pl})}$$

where

C = lung compliance
$\Delta(P_A - P_{pl})$ = change in transpulmonary pressure
P_A = alveolar pressure and P_{pl} = pleural pressure
ΔV_L = change in lung volume

Compliance denotes distensibility, the ease of stretch or inflation. The inverse of compliance (i.e., elastance) refers to the stiffness or the tendency to resist distortion and to return to the original configuration when the distorting force is removed.

In practice, pulmonary compliance is determined by relating the changes in transpulmonary pressures to the changes in lung volume during interruptions in the course of an expiration after a maximal inspiration (i.e., starting from TLC).

The pressure–volume characteristics of the lung are nonlinear. As lung volume increases, the elastic elements approach their limits of distensibility, and a given change in transpulmonary pressure produces smaller and smaller increases in lung volume.[6,7] Thus, the compliance of the lung is least at high lung volumes and greatest as RV is approached (Fig. 10-2). Elastic recoil forces favoring collapse of the lung can be demonstrated throughout the range of the vital capacity, even at low lung volumes approaching the RV. If the

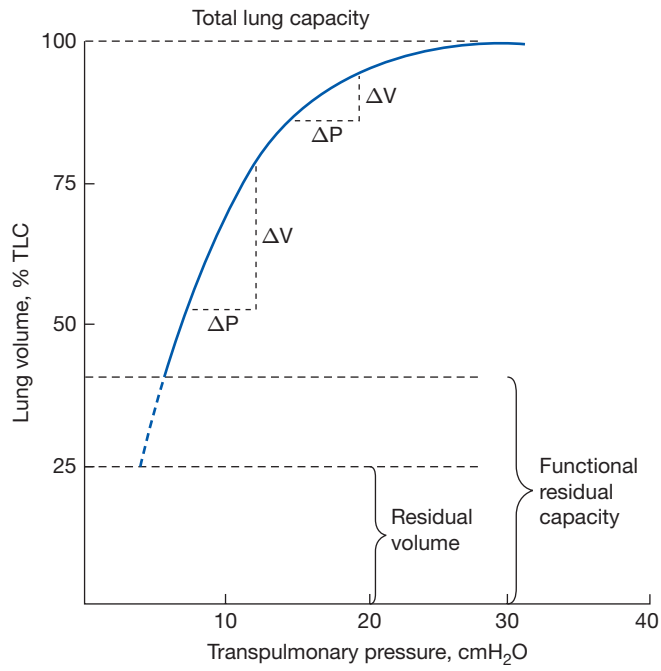

Figure 10-2 Pressure–volume curve of the lung. The static elastic recoil pressure of the lung is approximately 5 cmH_2O at FRC and 30 cmH_2O at TLC. The compliance of the lung ($\Delta V/\Delta P$) is greater at low lung volumes than at high lung volumes.

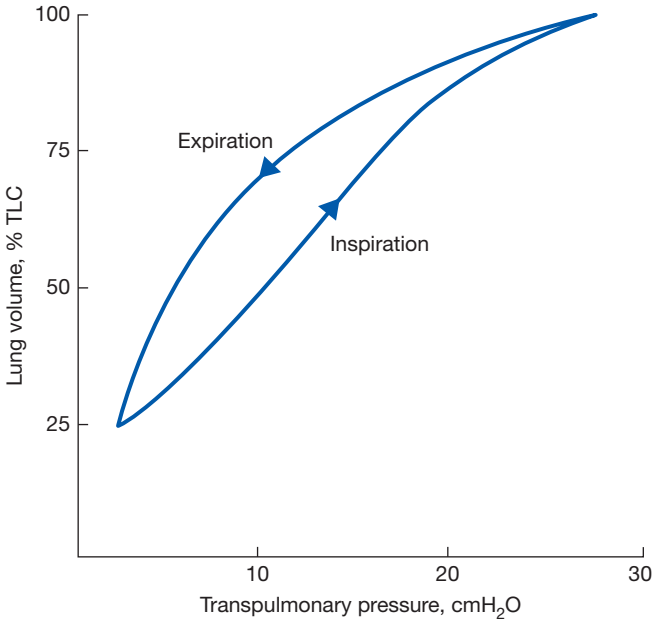

Figure 10-3 Pressure–volume curves of the lung during inspiration and expiration.

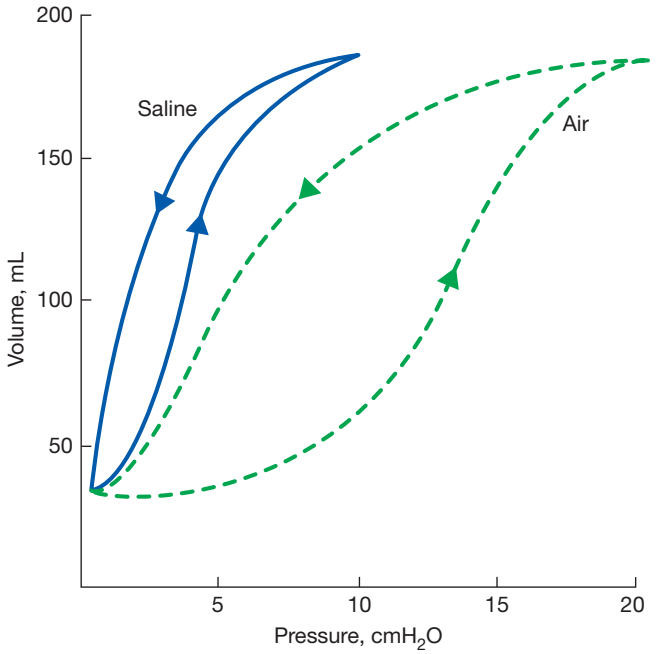

Figure 10-4 Comparison of pressure–volume relationships of air- and saline-filled excised lungs. *Arrows* directed upward indicate inflation; those directed downward indicate deflation. Since saline eliminates surface forces at the liquid–air interface without affecting tissue elasticity, the difference in pressure between the two curves, at any lung volume, is that required to overcome surface forces. To maintain a small lung volume, a large proportion of the pressure is used to overcome surface forces. In contrast, at high lung volumes a greater fraction of the pressure is used to overcome tissue elasticity.

opposing forces of the chest wall on the lungs are eliminated – for instance, by removing the lungs from the thorax or by opening the chest – the lung collapses to a near-airless state. A minimal volume of air does remain in the lungs because of closure of small airways resulting in the trapping of air in more distal airspaces.

If static measurements of transpulmonary pressure are made during lung inflation rather than deflation, the pressure–volume curve has a different configuration (Fig. 10-3). This indicates that the elastic recoil of the lung depends not only on the lung volume at which the determination is made but also on the "volume history" of the lung.[8]

■ HYSTERESIS

Differences in the pathways of the static pressure–volume curve during inspiration (when force is applied) and expiration (when force is withdrawn) are designated as hysteresis, which is a property of all elastic structures. In the lungs, it is due to the surface forces and the properties of the surface material lining the alveolar walls and also to the elastic properties of the tissues. The tissues of the lung are also subject to stress adaptation whereby over time, the pressure required to maintain a given lung volume will decline.[9] An additional factor relates to the closure of small airways at low lung volumes. Once these airways close, the lung units that they serve will not expand during inspiration until a critical opening pressure has been exceeded; only then will the closed units inflate. Recruitment of additional lung units as increasing transpulmonary pressure expands the lungs from low lung volume contributes to the hysteresis of the pressure–volume curve.

The elastic behavior of the lung depends on two factors: the physical properties of the lung tissue, per se, and the surface tension of the film lining of the alveolar walls.

■ SURFACE FORCES

The interior surfaces of the alveoli are lined by a thin liquid layer of osmophilic material. The surface tension at the air–liquid interface of the alveoli, in addition to the elastic properties of the parenchyma, contributes importantly to the elastic recoil of the lungs and acts to decrease lung compliance.[10] The cohesive forces between the molecules of the liquid lining of the alveoli are stronger than those between the film and alveolar gas, thereby causing the film to shrink to its smallest surface area. The behavior of this surface film has been examined in experimental animals by comparison of pressure–volume relationships of air-filled lungs with those of saline-filled lungs; saline eliminates the liquid–air interface without affecting elastic properties of the tissue. A lung distended with saline requires a lower transpulmonary pressure to maintain a given lung volume than a lung that is inflated with air.[11] Also, hysteresis is less in the saline-filled lung. The greater hysteresis in the air-filled lung is explained by the surface tension of the film lining the alveoli, which is higher during inflation as the film expands than it is during deflation as the film is compressed (Fig. 10-4).

By considering the alveolus to be a sphere, Laplace's law can be applied. Laplace's law states that the pressure inside a spherical structure—for example, the alveolus—is directly proportional to the tension in the wall and inversely proportional to the radius of curvature:

$$\text{Alveolar pressure} = \frac{2T}{r}$$

where

T = tension (dyn/cm)
r = radius

Abolition of the liquid–air interface by the instillation of saline into the alveolar spaces eliminates surface forces, thereby reducing the transpulmonary pressure required to maintain a given lung volume.

The surface film lining the alveoli of the lung is termed surfactant.[12] The superficial layer of the film facing the alveolar air is made up of surface-active phospholipids, notably dipalmitoyl lecithin. The deeper layer termed the hypophase consists of surface-active phospholipids linked to protein. Surfactant is generated by type

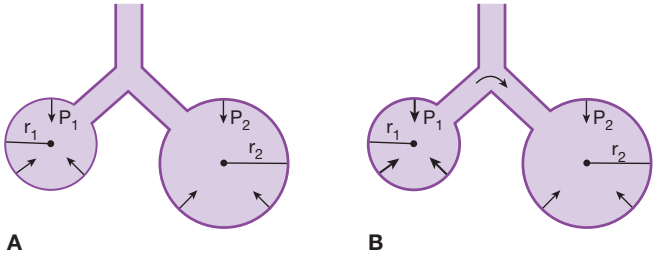

Figure 10-5 The effects of surfactant in maintaining alveolar stability. **A.** Surfactant lowers the tension of the alveolar walls at low lung volumes. Consequently, the transpulmonary pressure (P) of large and small communicating airspaces is the same. $r_1 < r_2, T_1 < T_2, P_1 \leftarrow P_2$. **B.** Without surfactant, the surface tension remains constant as lung volume changes, and the recoil pressure of small airspaces exceeds that of larger ones. As a result, small alveoli tend to empty into larger ones. $r_1 < r_2, T_1 = T_2, P_1 > P_2$.

II alveolar cells and undergoes a continuous cycle of formation, removal, and replenishment.[13]

Surfactant serves several important functions. The surface tension of surfactant is inherently low and decreases even further at low lung volumes when the surface area of the film is reduced. The minimization of surface forces, particularly at low lung volumes, minimizes the adherence of the walls of distal airways that tend to close at low lung volumes and increases the compliance of the lung and decreases the work required to inflate the lungs during the next breath. The automatic adjustment of surface tension as lung volume changes also promotes stability of alveoli at low lung volumes; if the surface tension were to remain constant instead of changing with lung volume, the transpulmonary pressure required to keep an alveolus open would increase as the radius of curvature diminished with decreasing lung volume. Therefore, small alveoli would empty into the larger ones with which they communicate, and atelectasis would be a regular occurrence (Fig. 10-5). Surfactant dysfunction as occurs with acute lung injury results in marked increases in surface tension causing stiffening and instability of alveoli and leads to alveolar collapse.

INTERDEPENDENCE AND COLLATERAL VENTILATION

The low surface tension of surfactant is not the most important determinant of alveolar stability. In reality, the alveoli form a froth rather than individual bubbles.[14] The walls of each alveolus are shared in common with those of adjacent alveoli so that contiguous airspaces attached by their connective tissue framework are tethered to one another and are not free to move independently. The tendency of any one alveolus to collapse is opposed by the traction exerted by the surrounding alveoli. This mechanical interdependence of adjacent airspaces resists the collapse of individual alveoli and serves as a stabilizing influence and ensures uniform inflation.[15] Even when a distal airway is completely obstructed, the alveoli served by the airway can still be ventilated through collateral channels between alveoli (pores of Kohn) and from bronchioles to alveoli (canals of Lambert). This collateral ventilation also prevents alveolar collapse and enhances the uniformity of ventilation, particularly in patients with lung disease.[16]

PHYSICAL PROPERTIES OF LUNG TISSUE

A number of different tissue components contribute to lung elasticity. The pleura, the intralobular septa, peripheral airway smooth muscle tone, and pulmonary vasomotor tone, as well as the tissues of the alveolar walls, play a role in shaping lung elastic recoil.

The major connective-tissue elements of the alveolar walls are the collagen and elastin fibers.[17] Elastin fibers in the alveolar walls and surrounding the bronchioles and pulmonary capillaries have a low tensile strength but can be stretched to over twice their resting length. Elastin fibers are thought to bear most of the stress in the lung at low volumes. Collagen fibers have high tensile strength but are poorly extensible and probably act to limit expansion at high lung volumes.[18] Like a stretched nylon stocking, expansion of the lungs appears to entail an unfolding and geometric rearrangement of the fibers and only slight elongation of individual fibers.

As a result of alterations in the elastin and collagen fibers in the lung, the distensibility of the lungs (measured as compliance) increases with age.[7] This is part of the normal aging process. Pulmonary compliance is also increased by the destruction of alveolar walls and the enlargement of alveolar spaces that characterize pulmonary emphysema. In contrast, the distensibility of the lungs is reduced by pulmonary fibrosis, which stiffens its interstitial tissues.[6]

ELASTIC PROPERTIES OF THE THORAX

The elastic recoil of the chest wall is such that if it were unopposed by the lungs, the chest would enlarge to approximately 70% of TLC. This position represents its equilibrium or resting position.[19] In this position (when the respiratory muscles are completely relaxed), the pressure difference across the chest wall – that is, the difference between pleural pressure and the pressure at the surface of the chest – is zero. If the chest were forced to enlarge beyond its equilibrium position by an increasingly positive pleural pressure or by the application of subatmospheric pressure at the body surface, it would, like the lung, recoil inward, resisting expansion and favoring return to its equilibrium position. Conversely, at volumes less than 70% of TLC, the recoil of the chest is opposite that of the lung and is directed outward (Fig. 10-6).[20] The chest wall can also be

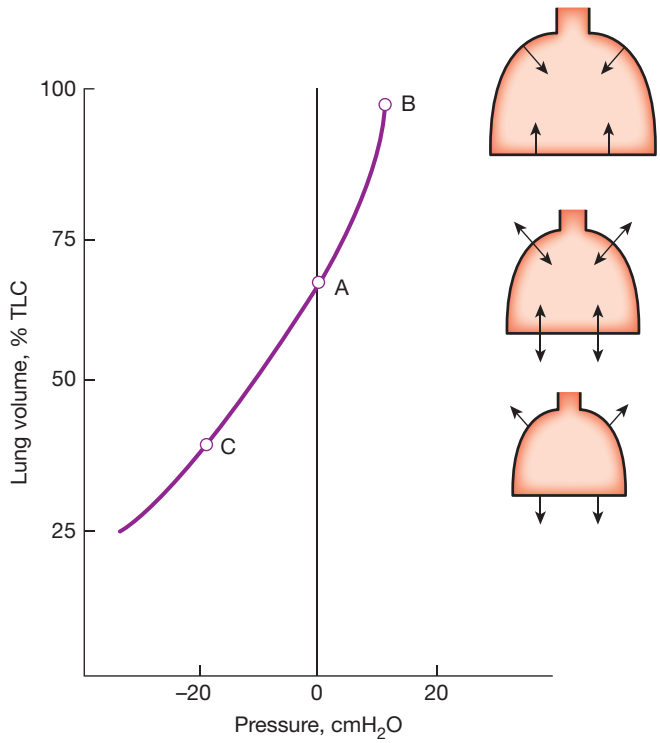

Figure 10-6 Pressure–volume relationships of the isolated chest wall. The direction of the recoil forces across the chest wall is represented by the *arrows*. The equilibrium position of the chest wall at point A, unopposed by the lungs, is approximately 70% of the total lung capacity. In this position, the pressure difference across the chest wall is zero. At larger volumes (B), there is inward recoil of the chest wall; at volumes below the equilibrium position (C), the recoil of the chest wall is directed outward, favoring expansion.

represented as a two-compartment system consisting of the rib cage and the abdomen, and volume changes can be partitioned between the two compartments.[21] Changing from the upright to the supine position at a constant overall lung volume produces a shift in volume from the abdominal to the rib cage compartment. The compliance of the rib cage is similar in the supine and upright positions, but the compliance of the abdominal compartment – particularly at high volumes – is greater in the supine position.[22]

The elastic recoil properties of the chest wall play an important role in determining the subdivisions of lung volume. They may be seriously deranged by disorders affecting the chest wall, such as marked obesity, kyphoscoliosis, and ankylosing spondylitis.

■ ELASTIC PROPERTIES OF THE RESPIRATORY SYSTEM AS A WHOLE

During breathing the lung and the chest wall move together and operate mechanically in series. At any given lung volume the elastic recoil pressure of the total respiratory system (P_{rs}) can be calculated as the algebraic sum of the pressures exerted by the elastic recoil of the lung (transpulmonary pressure) and the elastic recoil of the chest wall.[23]

Since the elastic recoil of the lung is determined (under static conditions of arrested airflow) as the difference between alveolar pressure (P_A) and pleural pressure (P_{pl}) – that is, $P_A - P_{pl}$ – and the elastic recoil of the chest wall is determined (while the respiratory muscles are completely at rest) as the difference between pleural pressure and the pressure at the external surface of the chest (P_{bs})—that is, $P_{pl} - P_{bs}$, the elastic recoil of the entire respiratory system can be expressed as the sum of the two:

$$P_{rs} = (P_A - P_{pl}) + (P_{pl} - P_{bs}) = P_A - P_{bs}$$

Thus, a measure of the elastic recoil of the respiratory system is supplied by the alveolar pressure, provided that the respiratory muscles are completely at rest and the pressure of the body surface is at atmospheric levels. In the absence of airflow into or out of the lung and when the glottis is open, alveolar pressure corresponds to the pressure at the mouth.

Relaxation Pressure–Volume Curve

The elastic properties of the entire respiratory system can be determined from the relaxation pressure–volume curve (Fig. 10-7). FRC represents the equilibrium position of the lung–chest wall system while the respiratory muscles are relaxed. At this point, the opposing recoils of the lung and chest wall are of equal magnitude, and the recoil pressure of the entire respiratory system is zero. With increases in lung volume above FRC, the recoil pressure of the entire system becomes positive, owing to the combination of an increase in centripetal elastic recoil of the lungs and a decrease in the centrifugal recoil of the chest wall. The net effect favors a decrease in lung volume, and lung volume can be maintained with the airway open to the atmosphere only by the action of the inspiratory muscles. As lung volume exceeds 75% of TLC, the recoil of the chest wall also becomes centripetal and the recoil pressure of the chest wall adds to the inward forces acting to diminish lung volume. TLC represents the lung volume at which the inward passive elastic recoil pressure of the respiratory system reaches the maximum force that can be generated by the inspiratory muscles.

At lung volumes below FRC, when the centrifugal recoil of the chest wall exceeds the reduced centripetal recoil of the lungs, the relaxation pressure is negative and this net effect favors an increase in lung volume. Lung volumes below FRC are achieved and maintained by the muscles of expiration.

A switch from the sitting to the supine position decreases FRC because of the effects of gravity. In the upright position, gravity pulls the abdominal contents away from the chest wall. In contrast, in the supine position, the push of the abdominal contents against the diaphragm decreases the centrifugal recoil of the chest wall. The chest wall pressure–volume curve – and, consequently, the pressure–volume curve of the entire respiratory system – is displaced to the right.

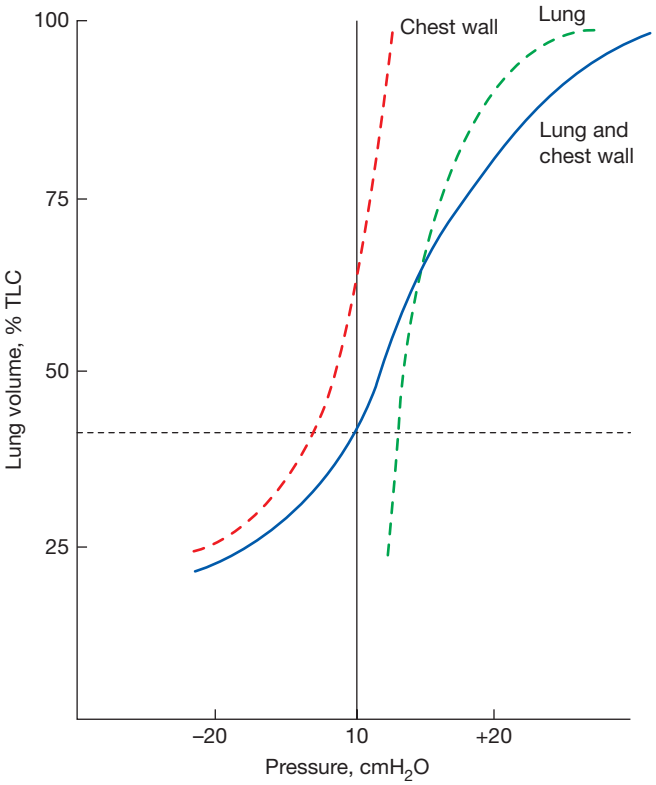

Figure 10-7 Relaxation pressure–volume curves. The lungs and the chest wall function mechanically in series so that the elastic recoil pressures of the total respiratory system, represented by the *solid line*, is the algebraic sum of the separate recoil pressures of the lung and chest wall. At the volume represented by the horizontal *dashed line*, the recoil pressures of the lung and chest wall are equal but in opposite directions. Consequently the net recoil pressure is zero, and the respiratory system is in a position of equilibrium.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The total nonelastic resistance of the lungs consists of the resistance of the airways to airflow (airway resistance), defined in terms of the driving pressure and the resulting rate of airflow, and the frictional resistance of the lung tissues to displacement during breathing (tissue resistance). Normally, tissue resistance makes up only 10% to 20% of the total pulmonary nonelastic resistance, but in diseases of the pulmonary parenchyma, it may increase considerably.

■ AIRWAY RESISTANCE

A large fraction of the resistance to airflow is in the upper respiratory tract, including the nose, mouth, pharynx, larynx, and trachea. During nasal breathing, the nose constitutes up to 50% of total airway resistance. During quiet mouth breathing, the mouth, pharynx, larynx, and trachea constitute 20% to 30% of the airway resistance; but they account for up to 50% of the total airway resistance when minute ventilation increases—during vigorous exercise, for example. Most of the remainder of airway resistance is in medium-sized lobar, segmental, and subsegmental bronchi up to about the seventh generation of airways.[24,25] Additional branching distally causes a progressive increase in the number of airways in

any generation. While the caliber of individual airways in daughter branches compared to the parent branch is reduced, the total cross-sectional area of all of the airways in a given generation increases tremendously with successive generations along the tracheobronchial tree. Consequently, in the normal lung, the small peripheral airways, particularly those less than 2 mm in diameter, constitute only about 10% to 20% of the total airway resistance.[26]

Airway Caliber

The airways, like the pulmonary parenchyma, exhibit elasticity and can be compressed or distended. Therefore, the diameter of an airway varies with the transmural pressure applied to that airway—that is, the difference between the pressure within the airway and the pressure surrounding the airway. The pressure surrounding intrathoracic airways approximates pleural pressure, since these airways are tethered to the parenchymal tissue and are exposed to the expansive forces that are active in overcoming the elastic recoil of the lung.[1]

Airway resistance varies inversely with lung volume. As the lung volume increases, the elastic recoil forces of the lung increase; the traction applied to the walls of the intrathoracic airways also increases, widening the airways and decreasing their resistance to airflow. Conversely, at low lung volumes, the transmural airway pressure is lower and airway resistance increases.[27,28] If the elastic recoil of the lung is reduced – by destruction of alveolar walls in pulmonary emphysema, for instance – the transmural airway pressure at any given lung volume decreases correspondingly; the airways are narrower and airway resistance is greater even though there is no disease of the airways per se.

The effects of a change in transmural pressure on airway caliber depend on the compliance of the airways—which, in turn, is determined by their structural support. The trachea, for example, is almost completely surrounded by cartilaginous rings, which tend to prevent complete collapse even when the transmural pressure is negative. The bronchi are less well supported by incomplete cartilaginous rings and plates, whereas the bronchioles lack cartilaginous support. All airways can be stiffened, albeit to different degrees, by contraction of smooth muscle in their walls.

In patients with airway disease, mucosal edema, hypertrophy and hyperplasia of mucus glands, increased elaboration of mucus, and hypertrophy of smooth muscle further compromise airway caliber and increase airway resistance.

Neural pathways and humoral mechanisms are also important in controlling airway smooth muscle tone and regulating airway caliber. Cholinergic parasympathomimetic stimulation originating from the vagus nerve and mediated through the release of acetylcholine causes airway smooth muscle contraction and airway narrowing. Noncholinergic parasympathetic activity may play a role in airway smooth muscle relaxation through the release of vasoactive intestinal peptide and the subsequent production of nitric oxide.[29] Beta-adrenergic receptors in bronchial smooth muscle activated by various sympathomimetic agents promote airway smooth muscle relaxation and airway dilatation.[30]

Pressure–Flow Relationships: Theoretical Considerations

In the lungs, pressure–flow relationships are extremely complicated because the airways consist of a system of irregular branching tubes that are neither rigid nor perfectly circular. For purposes of simplification, pressure–flow relationships in rigid tubes are generally regarded as a model for those in the airways.

The driving pressure that produces flow of air into and out of the lung must suffice to overcome friction and to accelerate the air. Acceleration in the lungs is of two types: local (i.e., changes in the rate of airflow with time when flow is initiated) and convective (i.e., acceleration of molecules of air over distance while flow is constant). The driving pressure required for convective acceleration

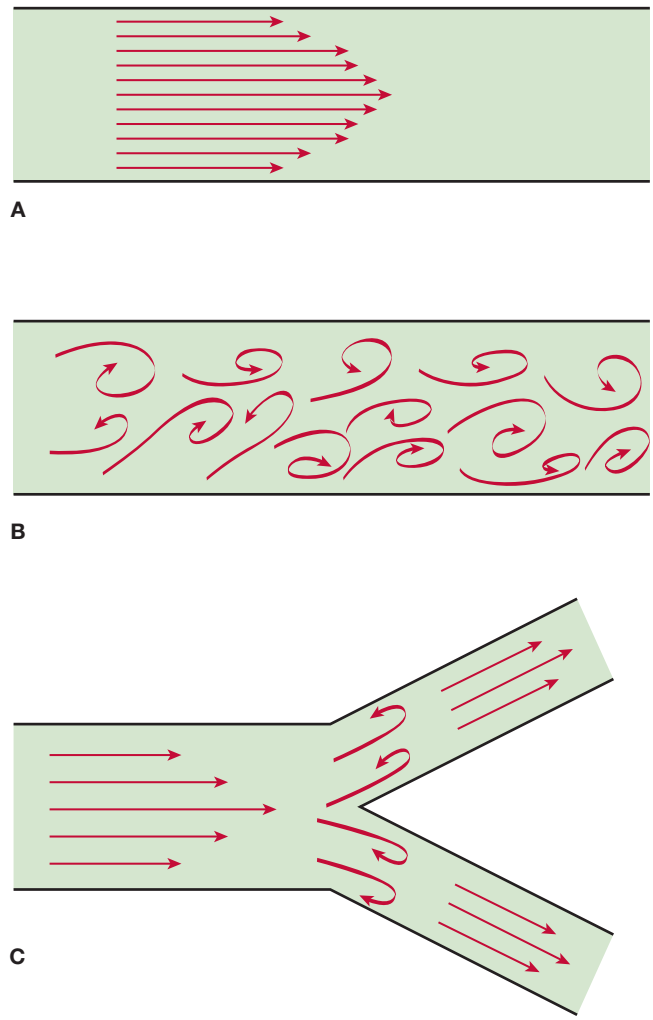

Figure 10-8 Patterns of airflow. **A.** Laminar flow. **B.** Turbulent flow. **C.** Transition flow that occurs at bifurcations.

is proportional to the gas density and to the square of the flow rate. It is important during expiration because, as air moves downstream from the alveoli toward the airway opening, the total cross-sectional airway diameter decreases; therefore, molecules of air must accelerate through the converging channels even though the overall flow rate remains unchanged. Also, the driving pressure that produces high expiratory flow rates at large lung volume serves for convective acceleration rather than for overcoming friction.[31,32]

The driving pressure required to overcome friction depends on the rate and the pattern of airflow. Two major patterns of airflow warrant special consideration: laminar and turbulent. Laminar flow is characterized by streamlines that parallel the sides of the tube and are capable of sliding over one another. Also, because the streamlines at the center of the tube move faster than those closest to the walls, the flow profile is parabolic (Fig. 10-8). The pressure–flow characteristics of laminar flow depend on the length (l) and the radius (r) of the tube and the viscosity of the gas (η) according to Poiseuille's equation:

$$\Delta P = \frac{\dot{V} 8 \eta l}{\pi r^4}$$

where

ΔP = the driving pressure (pressure drop between the beginning and the end of the tube)
$\dot{V}$ = the flow rate that the driving pressure produces
r = the radius of the tube

The critical importance of tube radius in determining the driving pressure for a given flow is apparent in the previously mentioned equation. If the radius of the tube is halved, the pressure that is required to maintain a given flow rate must be increased 16-fold. Laminar flow patterns occur only in small peripheral airways, where, because of the enormous overall cross-sectional area, flow through the individual airways is exceedingly slow.

Turbulent flow occurs at high flow rates and is characterized by a complete disorganization of streamlines, so that the molecules of gas move laterally, collide with each other, and change velocities. Under these circumstances, pressure–flow relationships change. In contrast to laminar flow, the rate of turbulent airflow is no longer proportional to the driving pressure. Instead, the driving pressure to produce a given rate of airflow is proportional to the square of flow and is dependent on gas density. Turbulent flow occurs regularly in the trachea.

At lower flow rates during expiration – particularly at branches in the tracheobronchial tree, where flow in two separate tubes comes together into a single channel – the parabolic profile of laminar flow becomes blunted, the streamlines separate from the walls of the tube, and minor eddy formation develops. This is referred to as a mixed, or transitional, flow pattern. In a mixed pattern of airflow, the driving pressure for a given flow depends on both the viscosity and the density of the gas.

Whether airflow is laminar or turbulent is predictable from the Reynolds number (Re), a dimensionless number that depends on the average velocity ($\overline{v}$), the density of the gas (ρ), the viscosity of the gas (η), and the diameter of the tube (D), so that

$$\mathrm{Re} = \frac{\overline{v} D \rho}{\eta}$$

In straight, smooth, rigid tubes, turbulence occurs when the Reynolds number exceeds 2000. Therefore, turbulence is most apt to occur when the average velocity is high, gas density is high, gas viscosity is low, and the tube diameter is large. Since most of the resistance to airflow in the normal lung is in large airways, where airflow is largely turbulent and where resistance is density dependent, breathing a mixture of 80% helium and 20% oxygen (a mixture that is 64% less dense than air) reduces the Reynolds number favoring a conversion from turbulent to laminar flow. Consequently airflow increases at a given driving pressure and airway resistance falls.[24]

Calculation of Airflow Resistance

The driving pressure along the tracheobronchial tree – that is, the difference between alveolar pressure and the pressure at the airway opening (mouth) that is required to produce a given rate of airflow into the lungs – provides a measure of the flow resistance of the airways, according to the equation

$$R_{aw} = \frac{P_A - P_{ao}}{\dot{V}}$$

where

$\dot{V}$ = airflow (L/s)
P_A = alveolar pressure (cmH_2O)
P_{ao} = airway-opening pressure (cmH_2O)
R_{aw} = airway resistance (cmH_2O/L/s)

Flow–Volume Relationships

Considerable insight into the flow-resistive properties of the airways can be obtained from the relationship between airflow and lung volume during maximal expiratory and inspiratory maneuvers.[33] In practice, a person inhales maximally to TLC; then exhales as forcefully, rapidly, and completely as possible to RV; and then returns to TLC by a rapid, forceful inhalation (Fig. 10-9). During the maximal

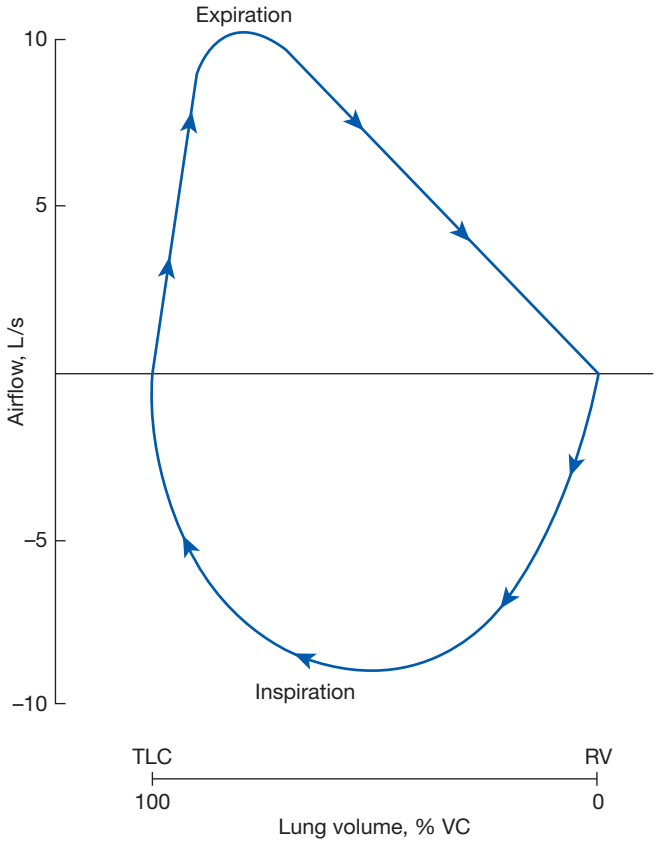

Figure 10-9 Maximal expiratory and inspiratory flow–volume loop.

expiration, the rate of airflow peaks at a lung volume that is close to the TLC; as the lung volume decreases and intrathoracic airways narrow, airway resistance increases, and the rate of airflow decreases progressively.

During maximal inspiration, the pattern of airflow is different. Because of the markedly negative pleural pressure and large transmural airway pressure, the bronchi are wide, and their calibers increase further as lung volume increases. Consequently, inspiratory flow becomes high while the lung volume is still low and remains high over much of the vital capacity, even though the force generated by the inspiratory muscles decreases as they shorten.

A family of flow–volume loops is produced by repeating full expiratory and inspiratory maneuvers over the entire range of the vital capacity using different levels of effort (Fig. 10-10). The greater the effort exerted during inspiration, the greater is the rate of airflow over the entire range—that is, from RV to TLC. Similarly, during expiration, the rate of airflow increases progressively with increasing effort at large lung volumes close to TLC. At intermediate and low lung volumes, the rate of expiratory airflow reaches a maximum while the effort expended is only moderate; thereafter, airflow does not increase further despite increasing expiratory efforts.

■ ISOVOLUME PRESSURE–FLOW CURVES

Separation of the effects of increasing effort from those of changes in lung volume on the rate of airflow during expiration can be accomplished by using isovolume pressure–flow curves (Fig. 10-11). During repeated expiratory maneuvers performed with varying degrees of effort, simultaneous measurements are made of airflow rate, lung volumes, and pleural pressure. For each lung volume the rate of airflow is plotted against the pleural pressure, as an index of the degree of effort.[34]

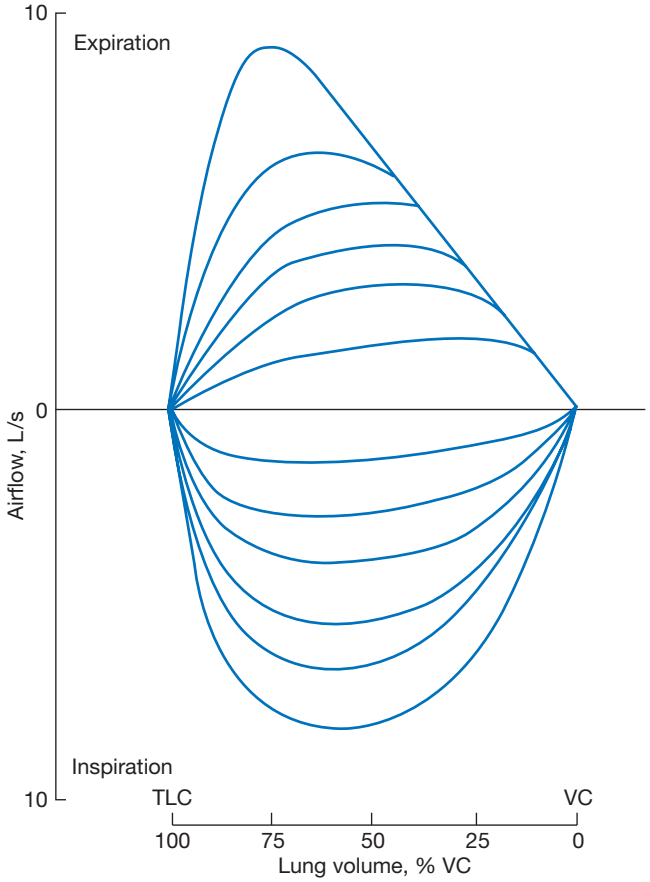

Figure 10-10 Series of flow–volume loops constructed from complete inspiratory and expiratory maneuvers repeated at different levels of effort.

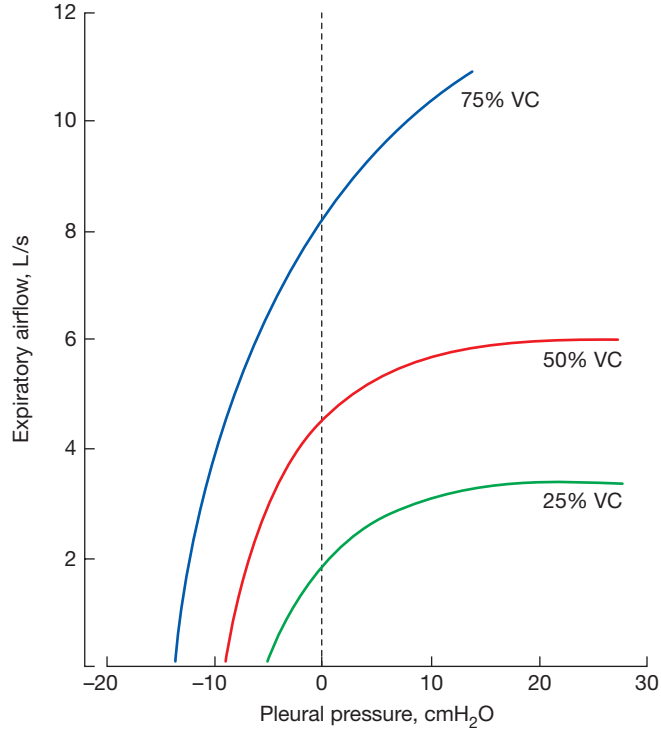

Figure 10-11 Isovolumetric pressure–flow curves. At lung volumes greater than 75% of the vital capacity, airflow is effort dependent; that is, airflow increases progressively with increasing effort. At lower lung volumes, airflow is effort independent; that is, airflow becomes fixed at a maximum level and does not increase despite further increases in effort.

As expiratory effort is increased at any given lung volume, the pleural pressure increases toward, and then exceeds, atmospheric pressure; correspondingly, the rate of airflow increases. At lung volumes above 75% of the vital capacity, airflow increases progressively as pleural pressure increases; it is considered to be effort dependent. In contrast, at lung volumes below 75% of the vital capacity, the rate of airflow levels off as the pleural pressure exceeds atmospheric pressure and becomes fixed at a maximum level. Thereafter, further increases in effort, and in pleural pressure, effect no further increase in the rate of airflow; at these lower lung volumes, airflow is considered to be effort independent. Since the rate of airflow remains constant despite increasing driving pressure, it follows that the resistance to airflow must be increasing in direct proportion to the increase in driving pressure. This increase in resistance is attributed to compression and narrowing of large intrathoracic airways.

EQUAL PRESSURE POINT THEORY: DYNAMIC COMPRESSION OF AIRWAYS

To illustrate the mechanisms that normally limit airflow during a maximal expiratory maneuver, it is useful to consider a model of the lung where the alveoli are represented by an elastic sac and the intrathoracic airways by a compressible tube, both enclosed within a pleural space (Fig. 10-12).[35]

At a given lung volume, when there is no airflow (as during breath holding with the glottis open), pleural pressure is subatmospheric, counterbalancing the elastic recoil pressure of the lung. The alveolar pressure (P_A), which is the sum of the recoil pressure of the lung and pleural pressure (P_{pl}), is zero (Fig. 10-12A). Since airflow has ceased, the pressure along the entire airway is also atmospheric.

At the same lung volume during a quiet expiration, pleural pressure is less subatmospheric. Since lung volume and the elastic recoil pressure of the lung are unchanged, alveolar pressure is now positive with respect to atmospheric pressure; airflow occurs. The alveolar pressure is gradually dissipated along the airway in overcoming resistance so that the pressure at the airway opening (P_{ao}) is zero. All along the airway, however, the airway pressure exceeds pleural pressure and the transmural pressure is positive; the airways remain open, and flow continues (Fig. 10-12B).

A forceful expiration raises pleural pressure above atmospheric pressure and further increases alveolar pressure (Fig. 10-12C). Airway pressure again falls progressively from the alveolus toward the airway opening. But at some point along the airway – the equal pressure point – the drop in airway pressure is equal to the recoil pressure of the lung; intraluminal pressure and the pressure surrounding the airways are equal and the same as pleural pressure. Downstream (i.e., toward the airway opening) the transmural pressure is negative, because the intraluminal airway pressure is less than pleural pressure; the airways are subjected to dynamic compression.

The equal pressure point divides the airways into two components arranged in series: an upstream segment, from the alveoli to the equal pressure point, and a downstream segment, from the equal pressure point to the airway opening. With increasing expiratory effort as the pleural pressure becomes more and more positive with respect to atmospheric pressure, the equal pressure point moves upstream. Once maximum expiratory flow is achieved, the position of the equal pressure point becomes fixed in the region of the lobar or segmental bronchi. Further increase in pleural pressure by increasing expiratory force simply produces more compression of the downstream segment without affecting airflow through the upstream segment.

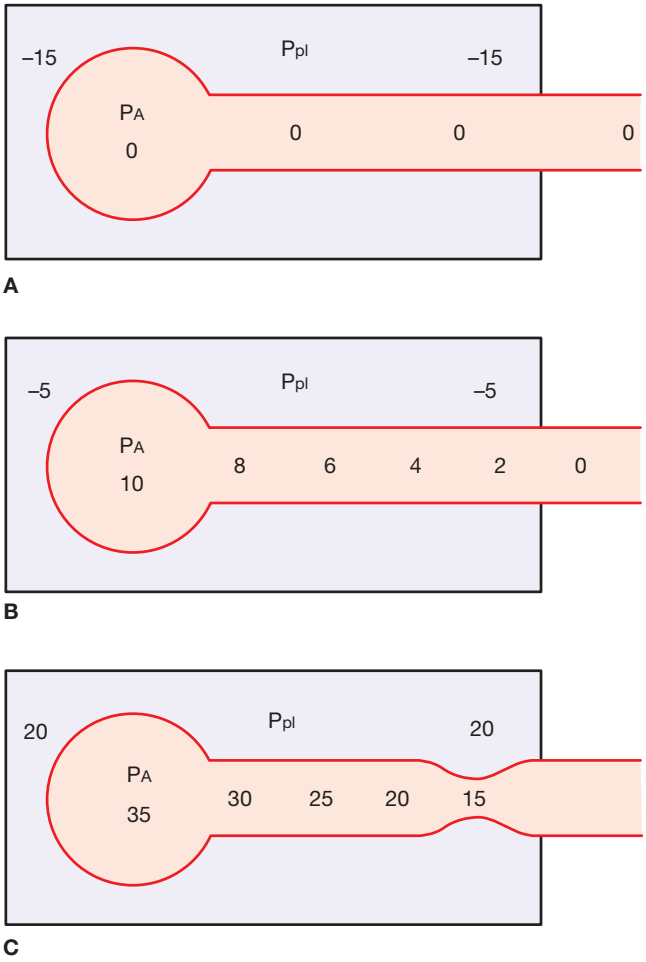

Figure 10-12 Schema of the distribution of pleural, alveolar, and airway pressures at rest and during expiration, illustrating the equal pressure point concept. **A.** End expiration. **B.** Quiet expiration. **C.** Forced expiration.

The driving pressure of the upstream segment – that is, the pressure drop along the airways of that segment – is equal to the elastic recoil of the lung. The maximum rate of airflow during forced expiration ($\dot{V}_{max}$) can be expressed in terms of the elastic recoil pressure of the lung (P_L) and the resistance of the upstream segment (R_{us}), as follows:

$$\dot{V}_{max} = \frac{P_L}{R_{us}}$$

Measurements of the rate of airflow during force expiration form the basis of many tests used to assess the flow-resistive properties of the lung. It is evident, however, that the maximum rate of expiratory airflow depends on many factors: The lung volume at which airflow is determined; the force of expiration (particularly at high lung volumes [i.e., above 75% of vital capacity]); the elastic recoil pressure of the lung; the cross-sectional area of large airways; the collapsibility of large intrathoracic airways; and the resistance of small peripheral airways.

WAVE SPEED LIMITATION THEORY

An alternative explanation for airflow limitation during forced expiration is based on principles of wave speed theory.[36] The wave speed theory proposes that flow is limited by the velocity of propagation of pressure waves along the wall of the tube. The velocity of propagation (v) varies proportionally with the cross-sectional area of the tube (A) and with airway stiffness. At a site where the linear velocity of gas molecules equals the velocity of propagation of pressure waves that is, wave speed, a choke point develops, preventing further increases in flow rate. The flow rate at wave speed is a function of the cross-sectional area of the tube at the choke point (A) and the stiffness of the choke segment (dP/dA), where P is the transmural airway pressure. Where choke points occur in the tracheobronchial tree depends on the lung volume: at large lung volumes, a choke point is situated in the vicinity of the lower trachea; at lower lung volumes, choke points develop more upstream along the bronchial tree. Extension of the neck exerts longitudinal tension and stiffens the trachea, increases wave velocity, and increases maximum expiratory flow rates at large lung volumes.[37]

MECHANICAL DETERMINANTS OF REGIONAL VENTILATION

The lung is not homogeneous, and the mechanical properties of all airways in a given generation and of all alveoli are not the same. This results in important nonuniformities of regional ventilation.

Pleural pressure in the upright person is more subatmospheric at the apex than at the base of the lung, because of the effects of gravity and the weight of the lung.[38] Pleural pressure topography and regional lung expansion are also determined by the shape of the chest wall and by the forces required for the lung to conform to the thoracic cavity shape[9].[39] The rate of increase in pleural pressure from top to bottom is approximately 0.25 cmH_2O per centimeter of vertical distance. Consequently, the transpulmonary pressure – that is, alveolar pressure minus pleural pressure – is greater at the top than at the bottom of the lung. Therefore, at most lung volumes, the alveoli at the lung apexes are larger (more expanded) than those at the lung bases (Fig. 10-13).

Because of regional variations in lung compliance, ventilation is not uniform, even in the normal lung. With the use of external scanners after the inhalation of a radioactive gas, such as ^{133}Xenon, it has been demonstrated that within the range of normal tidal volume, lung units are better ventilated, and ventilation per alveolus is greater, at the bottom than at the top of the lung.[40] This is because alveoli near the top of the lung are positioned on the upper, flatter part of the pressure–volume curve and are less compliant than alveoli at the lung bases positioned on the lower, steeper portion of their pressure–volume curves.

At low lung volumes (i.e., near the RV), pleural pressure at the bottom of the lung actually exceeds airway pressure and leads to closure of peripheral airways (Fig. 10-13). During a breath taken from RV, air that enters the lungs first is preferentially distributed to the lung apexes.

The distribution of ventilation within the lungs and the volume at which airways at the lung bases begin to close can be assessed by the single-breath N_2 washout test.[41] This test requires a maximum expiration into an N_2 meter after a maximal inspiration of pure O_2 from RV; the changing concentration of nitrogen is plotted against expired lung volume (Fig. 10-14). Because the inspiration starts at the RV,

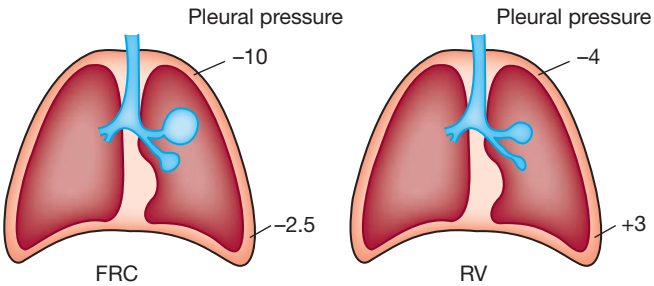

Figure 10-13 Pleural pressure gradients in the upright lung at FRC (left) and at RV (right). The effect of the gradient on alveolar volumes is shown schematically for each case.

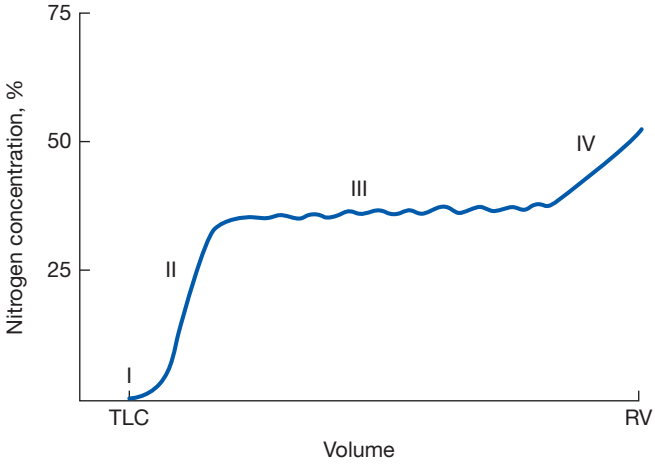

Figure 10-14 Tracing of expired nitrogen concentration during a slow expiration from TLC to RV after a full inspiration of pure O_2. The four phases are indicated. For further details, see text.

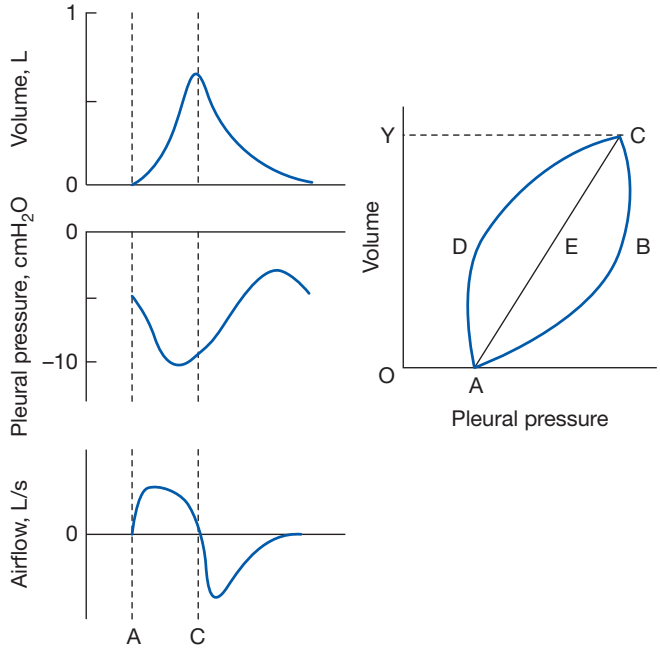

Figure 10-15 Individual tracings of tidal volume, pleural pressure, and airflow, taken simultaneously during a single complete breath, are shown on the left. The relationship between volume and pleural pressure is illustrated by the dynamic pressure–volume loop on the right. Dynamic compliance is determined as the slope of the line AEC. The work of breathing during inspiration to overcome the elastic forces of the lung is represented by the area of the trapezoid OAECY, and the work required to overcome nonelastic forces is represented by the area of the loop ABCEA. The loop AECDE represents the work required to overcome airflow resistance during expiration.

the initial portion of the breath containing dead-space gas, rich in nitrogen, is distributed to alveoli in the upper lung zones. The rest of the breath, which contains only O_2, goes preferentially to lower lung zones. Consequently, the concentration of nitrogen is lower in the alveoli at the lung bases than in the alveoli at the apexes of the lungs.

During expiration, the initial portion of the breath consists of O_2 remaining in the large airways; it contains no N_2 (phase I). As alveolar gas containing N_2 begins to be washed out, the concentration of N_2 in the expired air rises to reach a plateau. The portion of the curve where the concentration of N_2 rises steeply is phase II. The plateau is phase III. Phase III depends on the uniformity of the distribution of ventilation in the lung. If gas enters and leaves alveoli throughout the lung synchronously and equally, phase III is flat. But when the distribution of ventilation is nonuniform, so that gases coming from different alveoli have different N_2 concentration, phase III slopes upward.

At low lung volumes, airways at the lung bases close; only alveoli at the top of the lung continue to empty. Since the concentration of N_2 in the alveoli of upper lung zones is higher than in the alveoli at the lung bases, the slope of the N_2–volume curve increases abruptly, marking the start of phase IV. The volume, above RV, at which phase IV begins is termed the closing volume.[42]

The closing volume increases with advancing age. With diseases of the peripheral airways closing volume may rise to levels above FRC. This results in lung units that are perfused but poorly ventilated leading to reductions in arterial oxygenation.[43,44]

■ DYNAMIC COMPLIANCE OF THE LUNGS

The relationship between changes in volume and changes in pleural pressure during a normal breathing cycle is shown in Figure 10-15. Airflow momentarily ceases at the end of expiration (A) and at the end of inspiration (C); the change in pleural pressure between these two points reflects the increasing elastic recoil of the lung as the volume of air in the lungs increases. The slope of the line connecting the end-expiratory and end-inspiratory points (AEC in the figure) on a pressure–volume loop provides a measure of the dynamic compliance of the lungs.

In normal persons, dynamic compliance closely approximates inspiratory static lung compliance and remains essentially unchanged even when breathing frequency is increased up to 60 breaths per minute. This indicates that lung units that are parallel with each other normally fill and empty uniformly and synchronously, even when airflow is high and the change in lung volume is rapid. The rate of filling and emptying of a lung unit depends on its time constant—that is, the product of its resistance and compliance. Lung units with high resistance and high compliance take longer to fill and empty more slowly compared to units with low resistance and low compliance. In order for the distribution of ventilation in parallel lung units to be independent of the rate of airflow, the resistance and compliance of these units must be matched so that the time constants of individual units throughout the lungs are approximately the same. The time constants of lung units distal to airways 2 mm in diameter are approximately 0.01 second, and fourfold differences in time constants are necessary to cause dynamic compliance to become frequency dependent.[26]

Patchy narrowing of small peripheral airways produces regional differences in time constants. At low breathing frequencies, when the rate of airflow is low, ventilation is fairly evenly distributed. As the breathing frequency increases, however, ventilation tends to be distributed to areas that offer the least resistance to airflow. Therefore, lung units fed by narrowed airways receive proportionally less ventilation than do areas of the lung where the airways remain normal; the change in pleural pressure required to effect the same change in overall lung volume increases. As a result, the dynamic compliance falls.

Measurements of frequency dependence of dynamic compliance are time-consuming and technically difficult, but this test has proved useful in the diagnosis of obstruction in small peripheral airways when results of other conventional tests of lung mechanics are still within normal limits.[45]

WORK OF BREATHING

During breathing, the respiratory muscles work to overcome the elastic, flow-resistive, and inertial forces of the lungs and chest

wall.[46] The elastic work of breathing is done to overcome the elastic recoil of the lungs and chest wall; the resistive work is done in overcoming the resistance of airways and tissues. The mechanical work of breathing can be determined by relating the pressure exerted across the respiratory system to the resulting change in volume, since the product of pressure (P) and volume (V) has the dimension of work, according to the equation

$$\text{work} = \int P \, dV$$

Recordings of pleural pressure and lung volume changes during spontaneous breathing can be used to measure the work of breathing; the work of breathing performed on the lungs can be determined from the area of the dynamic pressure–volume loop (Fig. 10-15) and fractionated into its elastic and resistive components. During inspiration, the work done to overcome the elastic forces of the lung is determined from the area of the trapezoid OAECY (Fig. 10-15). The area of the loop ABCEA is the work in overcoming nonelastic forces during inspiration, and the area of the loop OABCY is the total work of breathing during inspiration.

Expiration during quiet breathing is passive, since the elastic recoil of the lung suffices to overcome the expiratory airflow resistance. Some of the stored elastic energy is also used to overcome inspiratory muscle activity that persists into the expiratory phase of breathing. At high levels of ventilation and when airway resistance is increased, additional mechanical work during expiration is required to overcome nonelastic forces. Under these circumstances, the pleural pressure exceeds atmospheric pressure, and the loop AECDA extends beyond the confines of the trapezoid OAECY (Fig. 10-15).

The work of breathing at any given level of ventilation depends on the pattern of breathing. Large tidal volumes increase the elastic work of breathing, whereas rapid breathing frequencies increase the work against flow-resistive forces. During quiet breathing and during exercise, people tend to adjust tidal volume and breathing frequency to values that minimize the force and the work of breathing.[47] Similar adjustments are also seen in patients with pulmonary disorders. Patients with pulmonary fibrosis, which is characterized by an increased elastic work of breathing, tend to breathe shallowly and rapidly; those with airway obstruction and increased nonelastic work of breathing usually breathe more deeply and slowly.

The work done on the chest wall during breathing is calculated by subtracting the work performed on the lung from the total mechanical work of breathing. The total mechanical work of breathing cannot be readily measured during spontaneous breathing because the respiratory muscles that perform the work also make up part of the resistance offered by the chest wall. But the total mechanical work can be determined during artificial ventilation by using either intermittent positive airway pressure or negative pressure applied to the chest, provided that the respiratory muscles are completely at rest. For this determination, the change in lung volume is related to the pressure difference across the respiratory system—that is, differential pressure between the mouth and the body surface. Disturbances of the chest wall, such as kyphoscoliosis and obesity, increase the work of breathing severalfold.

■ OXYGEN COST OF BREATHING

In order to perform their work, the respiratory muscles require O_2. The O_2 cost of breathing, which reflects the energy requirements of the respiratory muscles, provides an indirect measure of the work of breathing.[48,49] The O_2 cost of breathing is assessed by determining the total O_2 consumption of the body at rest and at an increased level of ventilation produced by voluntary hyperventilation or CO_2 breathing. Provided there are no other factors acting to increase O_2 consumption, the added O_2 uptake is attributed to the increased metabolism of the respiratory muscles.

The O_2 cost of breathing in normal subjects is approximately 1 mL/L of ventilation and constitutes less than 5% of the total O_2 consumption. At high levels of ventilation, however, the O_2 cost of breathing becomes progressively greater. There is a dramatic increase in the O_2 cost of breathing at high levels of ventilation in some diseases of the lung, such as pneumonia, pulmonary fibrosis, and emphysema, and in disorders of the chest wall, such as obesity and kyphoscoliosis. The increase in the energy requirement of the respiratory muscles during increased ventilation, concomitant with a decrease in O_2 supply secondary to arterial hypoxemia, contributes to muscle fatigue, thereby limiting the amount of exertion that these patients can sustain.[3]

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CHAPTER 11
Control of Ventilation

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INTRODUCTION

Breathing is a rhythmic motor act, which is under both conscious and automatic control. This system maintains numerous controlled variables within their homeostatic ranges, but is also responsible for rapidly changing ventilation in response to often unpredictable stimuli. We will discuss the anatomy and physiology of the ventilatory control system, then address integrated responses and illustrative examples of adaptation and dysfunction in the setting of selected disease states.

ANATOMY AND PHYSIOLOGY

The respiratory control system, broadly speaking, comprises a controller, sensors, and a plant (Fig. 11-1). This hierarchical structure, in which there is central processing of afferent input, is important for coordinating respiratory movements with behaviors such as eating, speaking, and moving.[1] The controller is a neuronal network within the central nervous system (CNS), which is responsible for generating and modulating individual breaths and the overall breathing pattern. Often referred to as the respiratory central pattern generator (rCPG), the controller comprises reciprocally connected neuronal populations in the medulla and pons.[2,3] Neural output from the rCPG drives the activity of various motor neuron pools. Motor

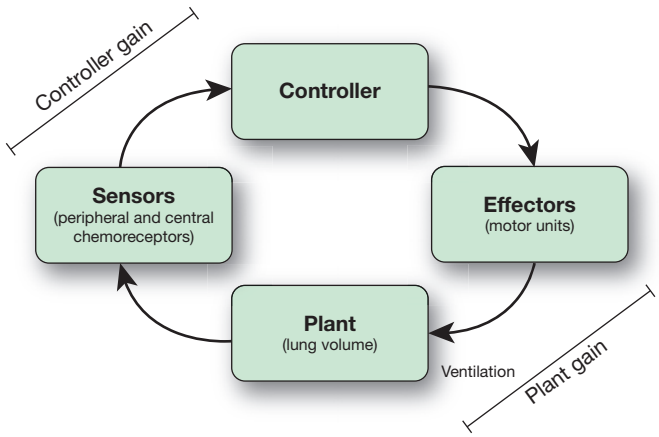

Figure 11-1 Block diagram of the respiratory control system.

neurons in the spinal cord (e.g., phrenic and intercostal) innervate the respiratory pump muscles, while brain stem motor neurons innervate upper airway muscles. The so-called "plant" includes the CO_2 stores, which are made up of lung stores and circulating blood volume including hemoglobin, and is an important component of breathing control. Closed loop feedback to the controller is supplied by chemoreceptors and mechanoreceptors.

The consistent cycling of the ventilatory pattern is generated spontaneously from the spatial and functional architecture of the rCPG. Intrinsic membrane properties of rhythmically active neurons within the rCPG are capable of producing automatic periodicity.[4] In addition, reciprocal (excitatory and inhibitory) synaptic connections between neuronal populations in the medulla and pons are believed to be critical for the automatic generation of the respiratory rhythm.[2,3]

The neural respiratory cycle comprises three phases (Fig. 11-2).[5] Inspiration (T_I) involves ramp-like increases in inspiratory motor neuron firing, which drive phrenic nerve activity throughout this phase. The first phase of expiration (T_{E1}) is often called post-inspiration, because inspiratory motor neurons are still active. Persistent inspiratory motor activity during T_{E1}, which declines throughout this phase, acts to slow the exit of air from the lungs. Finally, during the second phase of expiration (T_{E2}), expiratory muscles are typically electrically silent. During this phase of passive relaxation, gas is expelled as the lungs and chest wall return to their equilibrium state (i.e., functional residual capacity). However, under conditions where respiratory drive is increased, expiratory muscles including the internal intercostal and abdominal muscles become active during T_{E2}. This notion is an example of how the central controller, influenced by sensory feedback, modulates and alters the integrated motor response of the system.

BRAIN STEM

Within the medulla and pons, interconnected neuronal populations constitute a network, which is considered necessary for the generation of the respiratory rhythm (Fig. 11-3).[2,3,6] This bilateral pontomedullary respiratory network, which is also responsible for control of the ventilatory pattern, contains the ventral respiratory column (VRC) and the pontine respiratory group (PRG). Afferent signals from lung mechanoreceptors and peripheral chemoreceptors enter the pontomedullary network via the nucleus of the solitary tract (nTS) in the dorsal respiratory group (DRG). The nTS has projections to both pontine and ventral medullary components of the central respiratory network. Taken together, the VRC, DRG, and PRG comprise the brain stem rCPG. The rhythmic output of the rCPG drives the activity of spinal phrenic, intercostal, and lumbar motor neuron pools that innervate the muscles of respiration. Other brain stem motor neurons exhibit respiratory modulation and control muscles of the upper airway. Finally, the rCPG is influenced by higher CNS structures, which allows for conscious control of the ventilatory pattern.

Several regions of rhythmically active neurons in the VRC represent the core circuitry of the rCPG. The pre-Bötzinger complex (pre-BötC) within the VRC is believed to be the main source of rhythmic excitation driving inspiratory premotor neurons and other brain stem circuits. Furthermore, the pre-BötC has been shown to manifest intrinsic rhythmic activity.[4] However, the mechanisms responsible for rhythmic inspiratory pattern generation are complex given the large number of modulatory inputs that converge on the pre-BötC compartment, and are likely to manifest as the result of

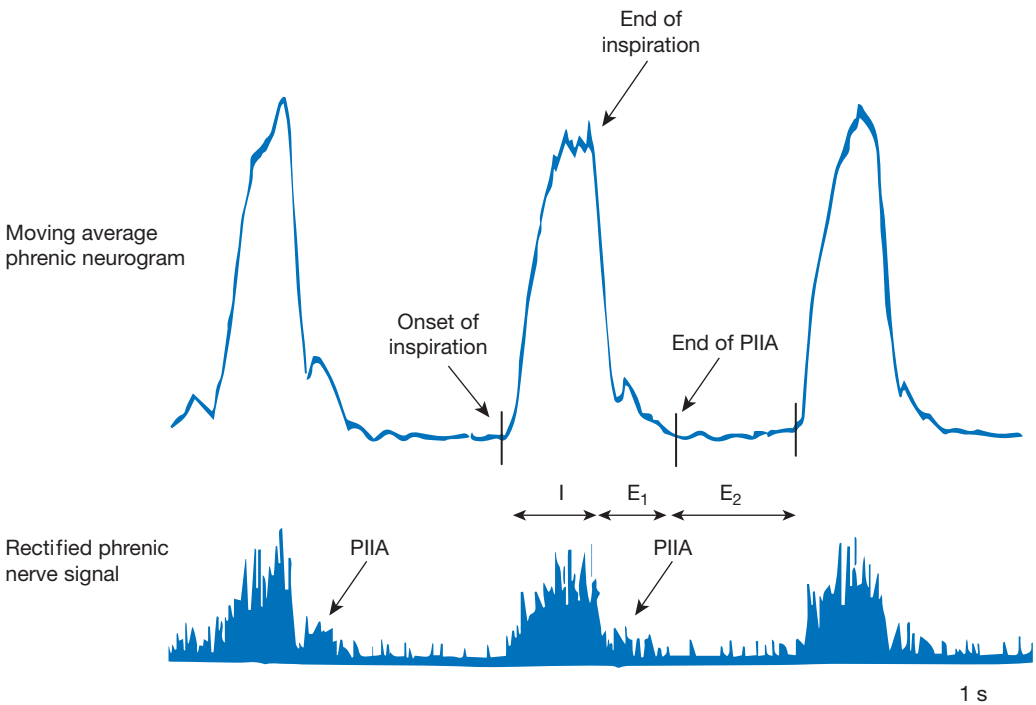

Figure 11-2 Recording of phrenic nerve activity (below) and its moving average (above), which highlights the three phases of the respiratory cycle: (1) Inspiration (I), (2) post-inspiratory activity (expiration, phase 1, E_1), and (3) late expiration (expiration, phase 2, E_2). PIIA, post-inspiratory inspiratory activity.

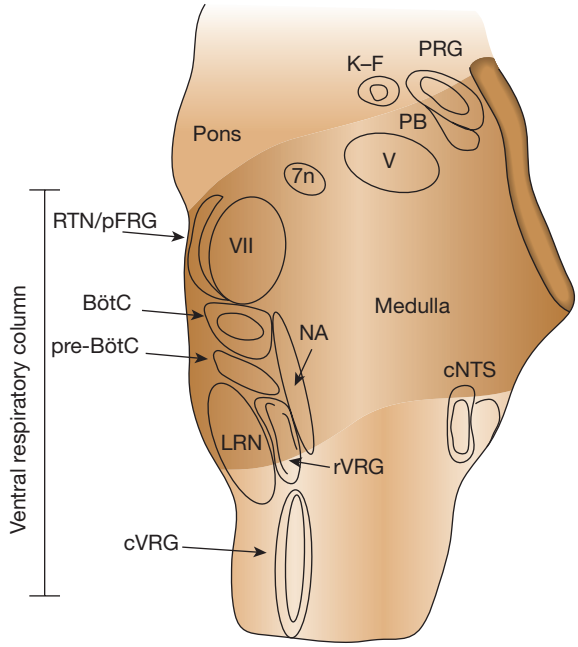

Figure 11-3 Overview of the respiratory central pattern generator (rCPG) within the brainstem. The ventral respiratory column (VRC) is orientated in the rostral-to-caudal direction. The VRC extends from the retrotrapezoid nucleus (RTN) adjacent to the rostral facial nucleus (VII) superiorly, to the caudal ventral respiratory group (cVRG) near the spinomedullary junction inferiorly. The main areas of rhythmically active VRC respiratory neurons are in the Bötzinger complex (BötC), pre-Bötzinger complex (pre-BötC), rostral ventral respiratory group (rVRG), and cVRG. The parafacial respiratory group (pFRG) overlaps anatomically with the RTN, and together these regions include intrinsically bursting neurons which may contribute to rhythm generation. Peripheral chemo- and mechanosensory inputs are transmitted to the nucleus of the solitary tract (nTS) in the dorsal respiratory group (DRG). The pontine respiratory group (PRG) includes the Kölliker–Fuse (K–F) and the parabrachial (PB) nuclei which contain respiratory-modulated neurons. See text for additional details.

network properties. Neuronal populations in the Bötzinger complex (BötC) are the major source of expiratory network activity during normal breathing. Thus, BötC neurons are important for control of the transition between inspiratory and expiratory activities in the rCPG and maintenance of the rhythmicity of normal breathing.

Neurons within the PRG are critical for formation of normal resting breathing patterns. Functional connections between the pons and the rest of the rCPG modulate phase switching (onset and termination of inspiration). For example, the dorsolateral pons (dlPons) is a region within the PRG with respiratory-modulated neurons whose activity varies depending on the presence of vagal afferent feedback. In particular, eupneic breathing patterns are dependent on excitatory drive from pontine neurons to the VRC, emphasizing the importance of the spatial and functional architecture of the brainstem respiratory network. Medullary raphé nuclei likely represent a system of intermediate relays for signaling between the PRG and the VRC. Transmission of an efference copy of ventilatory drive from the VRC is an example of one of these reciprocal connections. These medullary circuits may serve to maintain an overall level of rCPG activity. In addition, certain (particularly rostral) regions within the medullary raphé are chemosensitive, responding to local changes in carbon dioxide or pH, as well as exhibiting altered activity with stimulation of peripheral chemoreceptors.

The rostral ventral respiratory group (rVRG) region within the VRC comprises excitatory neurons that drive spinal phrenic and intercostal inspiratory motor neurons. This group of neurons is inhibited by the BötC during expiration and excited by the pre-BötC during inspiration. These rhythmically alternating influences, along with modulatory inputs from other areas of the pontomedullary network, are responsible for shaping and controlling the pattern of inspiratory rVRG activity. In contrast, the cVRG is thought to be the expiratory counterpart to rVRG activity.

Peripheral chemo- and mechanosensory inputs are transmitted to the nTS, which contains second-order neurons critical for reflex respiratory responses. For example, carotid body chemoreceptor and baroreceptor afferents terminate in the medial and lateral subnuclei of the nTS. Lung mechanoreceptors have projections to "pump cells" in the nTS, resulting in rhythmic activity of these cells which is modulated by lung inflation. The retrotrapezoid nucleus (RTN) is a site of central chemoreception. Chemoresponsive neurons within this region project to other areas of the rCPG and provide excitatory drive to the VRC and PRG. These sensory afferents, and the way in which they modulate breathing, will be discussed in subsequent sections. As part of the respiratory neural network, the nTS modulates breathing via projections to both pontine and ventral medullary components of the central respiratory network. In addition, neurons within the nTS receive inspiratory drive from the VRC and reciprocal pontine projections gate neuronal activity in the nTS.

CHEMORECEPTORS

The carotid and aortic bodies are bilateral sensory organs that detect changes in arterial oxygen. Although very small in size, the reflexes initiated by these tissues (particularly the carotid bodies) are critical for evoking stimulation of breathing during hypoxemia.[7] Stimulation of the carotid body by hypoxia (O_2 sensing) involves stimulus transduction and afferent nerve activation. Carotid bodies are composed of two cell types: type I and type II. Type I cells (also referred to as glomus cells) are of neural crest origin and are considered the putative oxygen-sensing cells. Glomus cells express a variety of neurotransmitters that play critical roles in sensory transmission of hypoxemia. Afferent nerve endings, whose cell bodies lie in the petrosal ganglion, form synaptic contacts with glomus cells and are responsible for afferent signaling to the CNS. The type II cells (also referred to as sustentacular cells) resemble glial cells and they are thought to act primarily as supporting cells.

There are two main pathways by which the carotid body senses hypoxia, although which mechanism is primary remains an area of debate.[8–10] The first main pathway for oxygen sensing involves heme-containing proteins in the glomus cell (metabolic hypothesis). First proposed by Mills and Jobsis, and later supported by studies using exogenous carbon monoxide (CO), there is evidence that mitochondrial cytochrome(s) may act as potential O_2 sensors. Further, several nonmitochondrial heme proteins that are expressed in glomus cells, including NADPH oxidases and heme oxygenase-2 (HO-2), have been proposed as potential oxygen sensors. Finally it has been suggested that hypoxia leads to the formation of iron-containing compounds via chelation as part of the transduction process, although the putative proteins and downstream signaling pathways responsible for afferent nerve activation are not well defined.

The second general mechanism by which hypoxia leads to depolarization of glomus cells is via inhibition of an O_2-sensitive, membrane-bound K^+ channel. This pathway for sensory transduction is based on the neuronal phenotype of the glomus cells and is referred to as the membrane hypothesis. Glomus cells express a variety of O_2-sensitive K^+ channels including outward rectifiers, Ca^{2+}-activated K^+ channels, human-ether-a-go-go (hERG), and twin pore-acid–sensitive K^+ (TASK) channels.[11] There is published evidence supporting and refuting aspects of both the metabolic and

membrane hypotheses. Most likely, both pathways complement each other and work in concert to facilitate oxygen sensing by glomus cells. For example, it has been proposed that with increasing severity of hypoxemia, additional pathways are activated, allowing the carotid body to respond to a wide range of arterial oxygen levels.

Regardless of the mechanism(s) involved, hypoxic sensing ultimately leads to a Ca^{2+}-dependent release of neurotransmitters from glomus cells. These signaling molecules activate nerve endings in the carotid sinus nerve leading to an increase in afferent nerve activity (sensory transmission). The carotid body expresses several classes of neurotransmitters, including (1) biogenic amines (acetylcholine [Ach], dopamine, norepinephrine, and 5-hydroxytryptamine), (2) neuropeptides (enkephalins, substance P, and endothelins), (3) adenosine triphosphate (ATP), (4) amino acids (e.g., GABA), and (5) gas transmitters (CO and nitric oxide, NO). Some of the transmitters (e.g., ACh, substance P, ATP) stimulate whereas others (e.g., dopamine, enkephalins) inhibit carotid sinus nerve activity. Identifying which transmitters are primarily responsible for hypoxia-induced afferent nerve activation under physiological conditions remains an area of active research, and it is possible that corelease of multiple molecules, acting in concert, may ultimately be responsible for sensory excitation by hypoxia. While the carotid body is the primary peripheral chemoreceptor responsible for oxygen sensing, carbon dioxide also stimulates the carotid body, but the mechanisms are not fully understood. Finally, the interaction of the central and peripheral chemoreceptors is still debated, but recent evidence supports a hyperadditive model whereby the gain of one group of chemoreceptors can increase the responsiveness of the other (e.g., carotid body stimulation increases the gain of the central chemoreceptors).[12]

MECHANORECEPTORS

The lung, chest wall, and respiratory muscles all contain mechanoreceptors, which provide closed-loop feedback to the rCPG. This afferent input regulates minute ventilation independent from chemical drive. In addition, mechanoreceptor reflexes modulate the respiratory pattern on a breath-by-breath basis by enhancing or terminating inspiration. Afferent axons from lung mechanoreceptors are contained within the vagus nerve, but the importance of these receptors to control of respiration in awake, adult humans is likely small. Additional mechanoreceptors in the respiratory muscles and chest wall have central projections which travel in spinal nerves and the spinal cord. These receptors are important to coordinating the breathing pattern during trunk twisting and during movement between the upright and supine positions.

Several broad categories of mechanoreceptors have been identified which are relevant to ventilatory control:

1. Lung stretch receptors are present in the airway smooth muscle of the distal airways. These slowly adapting receptors are stimulated by lung inflation. Afferent signaling following activation of these receptors tends to terminate inspiration without altering the slope of the inspiratory ramp, as well as to promote expiratory activity. Slowly adapting receptors in the lung are the afferent fibers responsible for the Hering–Breuer reflex, which describes the termination of inspiration (promotion of inspiratory-to-expiratory phase switching) that occurs as a result of lung inflation. In addition, expiratory prolongation and occasional apneas which occur with large and sustained inflation of the lung are a manifestation of this reflex.
2. Rapidly adapting receptors respond to changes in airway mechanical properties that accompany lung inflation and deflation, and become more active as the rate of airflow increases. These receptors are also activated by stimuli that induce bronchospasm, edema, or mucus secretion. For example, they produce cough and laryngeal narrowing in response to stimulation by dust, ammonia, histamine, and other agents, as well as in response to increases in inspiratory airflow. These lung mechanoreceptors are primarily located in the epithelial and submucosal layers of the larger airways, accounting for their sensitivity to inhaled agents. Finally, rapidly adapting receptors lead to increased respiratory frequencies at low lung volumes, due to afferent signaling which increases inspiratory neural activity during lung deflation.
3. Bronchial J receptors are named for their juxtacapillary location. These lung mechanoreceptors project centrally through unmyelinated (in contrast to the first two types) fibers, and respond to pulmonary vascular congestion associated with increases in pulmonary artery and capillary pressure. Stimulation contributes to the increase in respiratory frequency and a decrease in tidal volume in response to pulmonary edema.
4. Bronchial C receptors are named for their sensitivity to capsaicin, and are located in the airway wall. Similar to type J receptors, these lung receptors project centrally through unmyelinated fibers. Activation of C fibers with capsaicin or bradykinin produces cough and a rapid, shallow breathing pattern. Unlike other lung receptors described here, bronchial C receptors are relatively insensitive to mechanical stimulation and changes in lung volume.
5. Muscle spindles transduce muscle length. The diaphragm has few if any muscle spindles, but these mechanoreceptors are plentiful in the intercostal muscles. Muscle spindles tend to augment breathing when activated.
6. Muscle tendon organs are located in series with muscle fibers in the tendon and are activated as muscle fibers generate force. Thus, these mechanoreceptors sense the efficiency of force generation and inhibit breathing when activated. The central tendon of the diaphragm contains tendon organs, as do the tendons of accessory muscles of respiration.
7. The rib cage joints and upper airways (larynx, pharynx, and nasal cavity) also contain receptors that impact control of ventilation. For example, cold air stimulation of the pharynx initiates the cough reflex, and can reduce the ventilatory response to carbon dioxide.

UPPER AIRWAY AND PUMP MUSCLES

The upper airway muscles are described more completely elsewhere but are addressed briefly here for completeness. The pharyngeal dilator muscles can be broadly classified into those with phasic activity (burst with inspiration) and tonic activity (constant activity throughout the respiratory cycle). The genioglossus is a frequently studied muscle as it is a representative phasic muscle which is readily accessible for intramuscular recordings and is controlled by the hypoglossal motor nucleus. The genioglossus is a major dilator muscle, which serves to protrude the tongue and protect pharyngeal patency in the face of collapsing perturbations. The tensor palatini, in contrast, is a representative tonic muscle controlled by trigeminal motor branches. Recent insights from recordings of single motor units have defined the complexity of these various muscles and provided insights into brainstem control in humans.[13] Although robust activity of the pharyngeal dilator muscles have been observed in obstructive sleep apnea patients during wakefulness, the fall in activity of these muscles at sleep onset likely contributes to a propensity to upper airway collapse in susceptible individuals. Some data also support evidence of structural neural remodeling and reinnervation of genioglossus muscle fibers suggesting neural injury may also be present in people with sleep apnea.[14] Given the recent realization that sleep apnea has multiple underlying mechanisms, there is likely a subset of OSA patients who have dysfunction in upper airway muscles as a major pathogenic factor. Various approaches are being considered to augment upper airway dilator muscle activity, including the possibility of pharmacological manipulation of hypoglossal output or electrical stimulation of the hypoglossal nerve. Pharmacological targets

are being defined through careful studies of premotor inputs to the hypoglossal motor nucleus, although as yet no human trials have shown clear augmentation of genioglossus activity with pharmacotherapy. While the role of hypoglossal nerve stimulation in treating sleep apnea remains incompletely defined, recent work highlights the clinical promise of this approach.[15]

STABILITY OF VENTILATORY CONTROL: LOOP GAIN

Loop gain is an engineering term that is used to define the stability or instability of a negative feedback control system. Overall loop gain can be thought of as the integration of controller and plant factors and is thus the product of controller gain and plant gain (Fig. 11-1). A system with a high loop gain is prone to instability whereas a system with low loop gain is one which is intrinsically stable. The concept of loop gain can be considered in the context of the thermostat analogy, which is a common example of a negative feedback control system designed to regulate room temperature. Situations that lead to oscillations in room temperature can be considered analogous to situations in humans in which CO_2 levels fluctuate. For example, a highly sensitive thermostat is one that responds to trivial fluctuations in room temperature with major changes in output from the air conditioner or furnace; thus, a very sensitive thermostat will lead to marked fluctuations in room temperature. By analogy, exquisite sensitivity of chemoreceptors will contribute to marked fluctuations in CO_2 levels. Another example is a furnace, which is too powerful such that a minor drop in room temperature leads to major elevations in room temperature as a result of the output of the furnace. By analogy, if a minor increase in Pa_{CO_2} led to major increases in ventilation yielding marked reductions in Pa_{CO_2}, the system would be considered unstable, that is, elevated loop gain. Thus, situations, which lead to fluctuations in room temperature, can be considered to understand the factors underlying CO_2 fluctuations in the human.

In the case of ventilation, the propensity for CO_2 fluctuations is a function of an individual's loop gain. That is, an individual with a high loop gain is prone to developing periodic breathing or Cheyne–Stokes breathing, even with minimal perturbation. On the other hand, an individual with low loop gain will maintain relatively stable breathing patterns even with major perturbations. The mechanism underlying a high loop gain can be highly varied, but can generally be considered due to either an elevation of controller gain or plant gain. Controller gain is also known as chemoresponsiveness, which includes chemosensitivity (i.e., how much chemoreceptors fire with a given CO_2 stimulus) in addition to the actual change in ventilation for a given CO_2 stimulus (e.g.,which includes upper airway patency). In addition, plant gain describes the efficiency of CO_2 excretion, that is, how much the CO_2 actually changes for a given change in ventilation. Individuals with congestive heart failure are at risk of Cheyne–Stokes respiration (CSR) likely due to elevated chemoreflex gain as well as elevated plant gain compared to matched controls.

The delay in the circulation, sometimes defined by a mixing gain, is also an important factor in determining breathing pattern. The ability for the human ventilatory control system to develop instabilities is a result of chemoreceptors being located in the brainstem and carotid bodies rather than in the lung. Circulatory delay can also contribute to an unstable breathing pattern, although most studies suggest that marked prolongation of circulatory delay is not present in CSR patients with congestive heart failure compared to heart failure patients without CSR. In classic Guyton experiments, several minute delays were occasionally required to induce periodic breathing in dogs; such circulatory delays are beyond the range of what occurs in humans even in pathological states (e.g., end-stage congestive heart failure). Thus, circulatory delay is considered necessary but not sufficient to induce periodic breathing or CSR. Some interventional studies suggest improvements in sleep apnea with reduction in circulatory delay, emphasizing the importance of this variable in some individuals.[16]

The measurement of loop gain is cumbersome currently as it requires overnight experimental measurements and considerable expertise. However, the concepts are useful in a qualitative manner even if quantitative data are not available. In addition, efforts are ongoing to simplify the loop gain measurement to determine expeditiously which patients may respond to particular interventions.[17] The importance of loop gain is receiving increasing attention given the recognition of its importance in obstructive sleep apnea,[18] central sleep apnea,[19] periodic breathing at high altitude and other conditions. Indeed, manipulation of loop gain using interventions such as oxygen or acetazolamide can lead to improvements in sleep apnea in small physiological studies.[20,21] Thus, further work on ventilatory loop gain is required to define the optimal diagnostic and therapeutic approaches.

CONTROL OF VENTILATION IN HEALTH AND DISEASE: ILLUSTRATIVE EXAMPLES

The afferent, efferent, and central neural systems described earlier, respond to a variety of challenges that affect both normal individuals and patients with respiratory disease. These pathophysiological changes will affect the level of ventilation, the respiratory rhythm, or both. The impact of ventilatory control on specific disease states is addressed as appropriate in relevant sections elsewhere in this text. Following are illustrative examples which are considered to highlight how the respiratory control system adapts in clinically important conditions.

VENTILATORY ACCLIMATIZATION TO OXYGEN DISTURBANCES

There are many pathophysiological mechanisms that cause hypoxemia, and it has been well known for more than a century that hypoxia stimulates the respiratory and cardiovascular systems.[22] Heymans et al., among others, demonstrated the importance of carotid body chemoreceptors for the hypoxic ventilatory response.[23,24] Comroe and Mortimer[6] established the idea that arterial chemoreceptors are the dominant O_2-sensitive chemoreceptors for cardiopulmonary control. Elimination of the carotid and aortic body chemoreceptors elicits hypoventilation and essentially obliterates the acute ventilatory response to hypoxemia.[25] Therefore, it has been assumed that central O_2 sensitivity may not play a major role in this response.[26] In fact, chronic hypoxia reportedly has a depressive effect on the brain, limiting its response to further hypoxia. This hypoxic depression spreads rostral caudally in the brain; and may be the result of slowed removal of inhibitory neurotransmitters like GABA during hypoxia due to the buildup of lactic acid in the brain. However, in some experimental preparations, hypoxia continues to stimulate ventilation and the cardiovascular system in the absence of carotid body chemoreceptors, suggesting that other arterial chemoreceptors or sites in the CNS must be sensitive to hypoxia.[6] Focal hypoxia produced by cyanide in the medulla excites sympathoexcitatory neurons,[27] and experimental evidence supports central O_2 sensitivity in the C1 sympathoexcitatory region of the rostral ventrolateral medulla, the posterior hypothalamus, the pre-BötC, and the nucleus tractus solitarius.[25]

Hypoxic Ventilatory Response: The hypoxic ventilatory response is characterized by discrete, time-dependent mechanisms that depend on the severity, duration, and pattern of hypoxic exposure. A reduction in the partial pressure of oxygen produces an immediate increase in ventilation mediated through the peripheral chemoreceptors.[28] While the ventilatory response to hypoxia is independent of the source of hypoxemia, the brain has multiple time domains of O_2 sensitivity that can elicit different ventilatory responses to acute versus chronic hypoxia. Furthermore, this ventilatory response has several unique forms of respiratory plasticity.[29]

Acute and chronic exposure to high altitude: The hypoxic and hypobaric environment encountered at high altitude results in a reduction

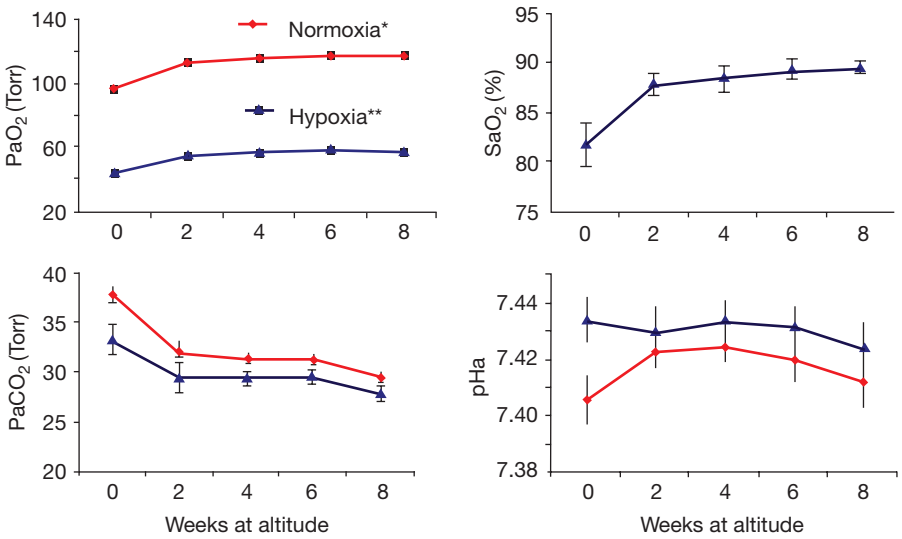

Figure 11-4 Arterial oxygenation increases and arterial CO_2 decreases during time at altitude. These changes persist in normoxia, indicating hyperventilation. pHa is partially compensated during acclimatization. *(Data from Hupperets MD, Hopkins SR, Pronk MG, et al. Increased hypoxic ventilatory response during 8 weeks at 3800 m altitude. Respiratory physiology & neurobiology. 2004;142(2–3):145–152.)* *Normoxia is from data collected breathing at sea level. **Hypoxia is from data collected breathing at 3800-m altitude.

in the available inspired oxygen (inspiratory partial pressure of O_2 [$P_{I_{O_2}}$]). Acute exposure to altitude results in hypoxemia, which produces an immediate increase in minute ventilation mediated through the peripheral chemoreceptors and characterized by an increase in frequency (respiratory rate) and amplitude (tidal volume). With ongoing exposure, ventilation continues to increase for several days resulting in a sustained gradual decrease in arterial P_{O_2}. Chronic exposure to high altitude, lasting from several hours to months, results in acclimatization. This adaptation to high altitude is characterized by a gradual rise in minute ventilation with a time course depending on the altitude. In humans, at very high altitudes (~8000 m), this process may take at least 30 days. At less extreme altitudes, complete adaptation may be achieved in less than 10 days. However, in one study, ventilation and arterial oxygenation were noted to be greater than during the initial ascent to 3800 m after 8 weeks.[30] In addition, there is an increase in CO_2 sensitivity with exposure to altitude. In people living in high altitude for long periods of time the P_{CO_2} falls to the lower level of normal or even less (Fig. 11-4).[30]

A number of physiological mechanisms of ventilatory acclimatization to hypoxia have been identified. They include (a) plasticity in O_2 sensitivity of the carotid body chemoreceptors, (b) the CNS integration of peripheral O_2-sensitive reflexes (e.g., carotid body chemoreflex), (c) plasticity of CNS mechanisms of acute O_2 sensing, and (d) the CNS integration of other nonchemoreflex ventilatory control pathways such as reflexes from pulmonary vagal chemoreceptors or respiratory rhythm generators.[25,31,32] For example, hypoxia-inducible factor-1 (HIF-1) is a key regulator of O_2-sensitive gene expression in the brain, and increases in HIF-1 have been identified in respiratory nuclei of the CNS as soon as 1 hour after hypoxemia. Hence, O_2 sensing by HIF-1α could be involved in the ventilatory acclimatization to high altitude by increasing the expression of genes with products known to modulate the hypoxic ventilatory response.[33]

OXYGEN-INDUCED HYPERCAPNIA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In severe chronic obstructive pulmonary disease (COPD), transient falls in ventilation and respiratory acidosis have been reported with breathing 100% oxygen for 20 minutes.[34–36] Initially CO_2 retention with oxygen treatment was thought to result from the suppression of the hypoxic drive mediated by carotid chemoreceptors.[37] Subsequently, additional mechanisms have been shown to contribute to oxygen-induced hypercapnia in COPD as follows:

(1) The increase in oxygen tension in lung units with low ventilation/perfusion (V/Q) ratios can blunt hypoxic pulmonary vasoconstriction in these low V/Q lung units, thus diverting perfusion away from high V/Q lung units yielding higher dead space; (2) the Haldane effect, which refers to the reduction in hemoglobin affinity for CO_2 with the binding of oxygen to hemoglobin. With increased blood oxygen levels, the Haldane effect promotes dissociation of carbon dioxide from hemoglobin and leads to a small increase in Pa_{CO_2}; (3) suppression of hypoxic drive as mentioned earlier. Data on P_{CO_2} recruitment threshold in intubated COPD patients support a change in sensitivity of the CNS to CO_2 during hyperoxia; (4) some patients with acute exacerbations of COPD are susceptible to the development of severe hypercapnia due to sleep deprivation that is common in acute illness; patients with associated obstructive sleep apnea might be susceptible since they have high sleep drive and are likely to lose the wakefulness drive to breathe at sleep onset upon initiation of therapy. For example, patients during acute exacerbations of COPD will commonly be sleep deprived and will typically fall asleep once they receive the anxiolytic and antidyspnea effects of oxygen therapy[36,38]; and (5) increases in Fi_{O_2} which occur with noninvasively delivered oxygen as minute ventilation falls. Actual delivered Fi_{O_2} is a function of inspiratory flow demand and room air entrainment; thus, higher oxygen tensions result as ventilatory drive falls for any reason. Occasionally vicious cycles can occur whereby supplemental oxygen leads to a rise in CO_2 level, which contributes to a further increase in oxygen level due to a resultant decrease in inspiratory flow with reductions in room air entrainment.

Understanding these mechanisms has clinical implications, as maintaining the arterial oxygen saturation between 87% and 92% may be a safer approach in patients with a history of respiratory disease, and is unlikely to compromise tissue oxygen delivery.

RESPONSES TO EXTERNAL MECHANICAL LOADS AND BRONCHOCONSTRICTION

In response to external mechanical loads, several compensatory factors act to maintain ventilation[39]: (1) *Responses intrinsic to the respiratory muscles.* The force that the muscle develops for a fixed electrical input depends on the length of the muscle (the force–length relationship). As the muscle shortens, less force is developed. The generated force also decreases as the velocity of shortening increases (force–velocity relationship). With external mechanical impediments (loading), both the magnitude and the velocity of shortening tend to decrease. (2) *Reflex effects.* At the spinal level, less shortening of the inspiratory muscles increases the signal from muscle spindles that, in turn, augments contraction of these muscles. During loading, afferent information from pulmonary mechanoreceptors also

changes. Since tidal volume is depressed, inspiratory duration tends to be prolonged (Hering–Breuer inspiratory terminating reflex), but this mechanism is of little importance in humans. (3) *Conscious responses.* Loads increase neuromuscular output even in the face of a constant chemical drive. The magnitude of the increase is related to the severity of the mechanical load. This aspect of load compensation is abolished by anesthesia. Furthermore, the intensity of this load-compensating mechanism is variable, and it is reduced in some chronic lung disease like COPD.

While external loading is used experimentally, major differences exist between the neural responses to bronchoconstriction and external loading. In particular, inspiratory muscle activity increases during bronchoconstriction, even in anesthetized animals. Bronchoconstriction increases breathing frequency via reflex changes in respiratory timing. Expiratory duration (especially the second phase of expiration) shortens more than inspiratory duration. In asthma-induced bronchoconstriction, rapidly adapting receptors are stimulated by mechanical changes in the airways and by substances such as histamine and bradykinin.

■ RESPONSE TO EXERCISE

The exercise ventilatory response is the most frequently engaged ventilatory response in everyday life.[29] Despite the increase in CO_2 production and O_2 utilization during exercise, ventilatory control mechanisms normally keep arterial P_{CO_2} and $[H^+]$ remarkably constant over a wide range of metabolic rates.[40] This pattern is achieved by graded increases in minute ventilation (V_E) as the rate of CO_2 production increases, and acts to minimize acidosis that would impair cellular function. This response is tightly controlled; respiratory alkalosis does not typically develop during moderate exercise in normal subjects, although it occasionally occurs in pathophysiological states. With increased intensity of exercise, oxygen demand outstrips oxygen supply, anaerobic pathways start to operate and blood lactate levels increase. With exertion above this anaerobic threshold, the exercise-induced metabolic acidosis becomes more marked due to a net increase in lactic acid production. As a result, high-level exercise results in a large increase in ventilation to enhance carbon dioxide excretion and minimize acidemia.

The minute ventilation required to maintain acid–base equilibrium during exercise is defined by (1) the amount of carbon dioxide produced as a result of metabolism (V_{CO_2}); (2) physiological dead space, and (3) the set point at which P_{CO_2} is regulated by the respiratory control system. There is an incomplete understanding of the reflexes responsible for controlling how pulmonary ventilation matches the increases in metabolic demand during exercise without appreciable changes in arterial blood gas composition. The magnitude of oscillations in ventilation is directly related to metabolic CO_2 production. Thus, it has been proposed that a blood-borne signal helps in the coupling of metabolic production of CO_2 and ventilation. Neurally mediated signals from exercising muscles and from higher brain centers are also likely important in the ventilatory response. Finally, this response is responsible for meeting the increased need for oxygen consumption by exercising limb and respiratory muscles.

The initial phase of the exercise response is a rapid increase in ventilation. Proposed sources include signals arising from the cortex (so-called feedforward control), temperature increases, afferent signals arising as a result of muscle contraction (locomotor muscle afferents and respiratory muscle metaboreflex), accumulation of catecholamines, and increases in potassium in the venous blood.[41] There is also evidence that the abrupt initial increase in ventilation at the onset of exercise is a learned response. That is, the primary drive to breathe at the start of exercise will augment respiration in anticipation of impending metabolic needs based on past exercise experiences.[42] Chemoreceptor feedback may act in concert with the feedforward stimulus to minimize disruptions in homeostasis as the intensity of exercise increases. In addition, there is capacity for modulation and plasticity of the mechanisms controlling breathing during exercise. For example, serotonergic modulation of descending drive is a mechanism for long-term modulation of exercise hyperpnea, which may be important in individuals with underlying cardiorespiratory disease.[43]

■ DISTURBANCES OF RESPIRATORY RHYTHM

Congenital central hypoventilation syndrome (CCHS), occasionally referred to as Ondine's curse, is a rare neurological disorder characterized by inadequate breathing during sleep and, in more severely affected individuals, also during waking periods. Patients congenitally lack or have poor chemosensitivity to both hypercapnia and hypoxia, and suffer from inadequate ventilation. Over 90% of patients with CCHS have an increased polyalanine repeat expansion mutation (PARM) in the paired-like homobox 2B (PHOX2B) gene. Other cases of CCHS are the result of non-PARM mutations of the PHOX2B gene. Most cases are the result of a *de novo* mutation, although patients may have a family history of the disorder. There is a correlation with the number of polyalanine repeat expansion genotype and the need for continuous ventilatory support. The disease typically presents in childhood, but rare adult-onset cases have been reported.[44] A number of conditions are associated with CCHS and reflect the autonomic nervous system dysregulation, including Hirschsprung disease (about 20% of cases) and tumors of neural crest origin (neuroblastomas). While PHOX2B is considered to be the disease-defining gene in CCHS, these patients may have other protein-altering mutations including mutations in the receptor tyrosine kinase, the RET gene, brain derived neurotrophic factor (BDNF), and endothelin1 and 3 genes. Rett syndrome is a neurodevelopmental disorder that occurs almost exclusively in females. After a period of initially normal development, affected patients experience loss of speech and purposeful hand use, stereotypic hand movements, gait abnormalities, and breathing abnormalities among others. Most cases result from mutations in the gene encoding methyl-CpG-binding protein 2 (Mecp2). Loss of Mecp2 function is associated with an irregular breathing pattern. The implicated mechanism has not been established, but may be related to widespread hyperexcitability in respiratory-related regions in the brainstem. Apnea that occurs during wakefulness is typically central, although it may be obstructive. These events may be isolated, or precede or follow hyperventilation. During apneic episodes, the child may stare quietly ahead or smile and appear happy with no evidence of distress, despite severe cyanosis.

Cheyne–Stokes Breathing is one form of periodic breathing characterized by a cyclic rise and fall in ventilation with recurrent periods of apnea or near apnea (Fig. 11-5). It was first observed in patients with cardiac or CNS disease, but it has since been reported in seemingly normal humans. The appearance of Cheyne–Stokes breathing can occur during wakefulness although often masked by behavioral influences, but is more common during nonrapid eye movement (NREM) sleep. The period of the oscillations in ventilation in Cheyne–Stokes breathing often averages 60 to 90 seconds. Cycle length is related to the circulation time measured from the lung to a systemic artery, and increases when circulation time is prolonged. Arousal tends to occur during the hyperpneic phase of the respiratory pattern, a finding which is often associated with paroxysmal nocturnal dyspnea in patients with heart failure.

Cheyne–Stokes breathing has not been consistently produced in animals by lesions in the CNS, but it has been shown to follow manipulations that are likely to produce unstable feedback control of breathing. Cheyne–Stokes breathing is seen in chronic heart failure, as well as in stroke and traumatic brain injury. A similar breathing pattern with a shorter cycle time (~15–30 seconds), often referred to

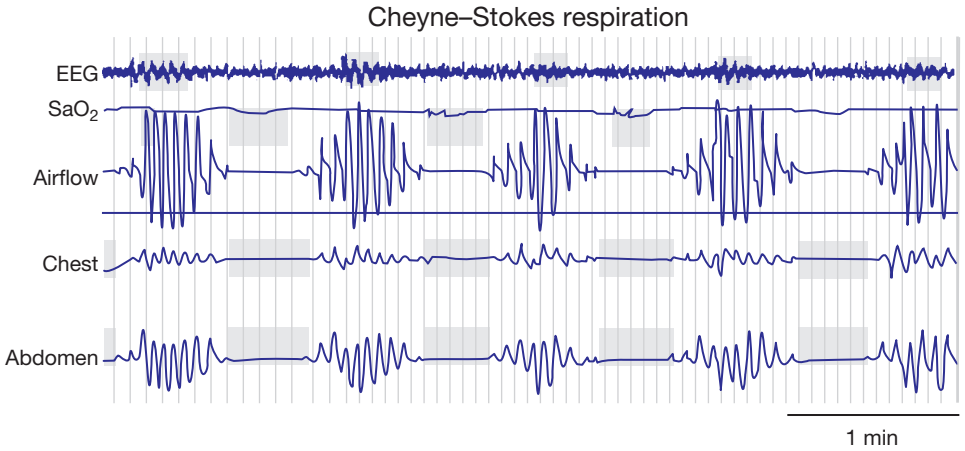

Figure 11-5 An example respiration in a patient with Cheyne–Stokes breathing. Note the characteristic crescendo/decrescendo pattern of breathing, long circulation time (each oxygen desaturation corresponds to the previous apnea), and arousal occurring at the peak of respiratory effort.

as periodic breathing at high altitude, can occur in otherwise healthy individuals at high altitude during the acclimatization period.

Sleep-related abnormalities of ventilatory control: Abnormal ventilatory patterns that can emerge during sleep are increasingly appreciated, including their associations with adverse neurocognitive and cardiovascular consequences. Ventilatory control instability may contribute to both central and obstructive sleep apnea. Indeed, sleep promotes breathing instability because it unmasks a highly sensitive dependence of the respiratory control system on chemoreceptor input. For example, the CO_2 reserve (i.e., the difference between the eupneic Pa_{CO_2} and that required to induce apnea) is labile during sleep and is reduced by hypoventilation, predisposing patients to the development of apneas.[45] Transient cortical arousals promote ventilatory overshoots, upper airway dilator muscle tone is reduced and airway collapsibility is enhanced.[46] In addition, depending on the prevailing pharyngeal mechanics, anatomical factors may cause or contribute to sleep-related disorders. Thus, both basic and clinical investigators have focused on mechanisms that influence upper airway patency during wakefulness and sleep, along with ventilatory control stability during sleep.

There are a number of changes in ventilatory control that occur during sleep; however, most of the same basic mechanisms active during wakefulness are also relevant during sleep. During sleep, there is an elevation of the CO_2 set point (~45 mm Hg as opposed to 40 mm Hg during wakefulness), associated with reduced alveolar ventilation during sleep. In all stages of sleep, there is decreased ability to respond to increments in resistance–load and the work of breathing. Thus, narrowing of the upper airway during sleep is a factor contributing to the rise in Pa_{CO_2}.

Other ventilatory control mechanisms are also affected. Sleep apnea results in recurrent episodes of hypoxemia, which alter the hypoxic ventilatory response resulting in respiratory long-term facilitation (LTF).[47] LTF is a form of neuronal plasticity that is induced by exposure to intermittent hypoxia and causes a persistent increase in ventilation even when normoxia is restored.[29,48] Phrenic (innervating the diaphragm) and hypoglossal (innervating upper airway muscles) nerve activities are both increased. Whereas the impact of LTF on ventilatory stability remains uncertain in the context of sleep apnea at this time, experiments in preclinical animal models suggest that LTF has the potential for both stabilizing and destabilizing influences on breathing that warrant further investigation.[20,49,50]

Apnea is a cessation of airflow for at least 10 seconds, and is probably the most common respiratory rhythm abnormality. Apneas occur often in premature infants and occasionally during sleep in healthy humans. Central apneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep (Fig. 11-6). In contrast to obstructive apneas, in which inspiratory efforts are made against the occluded upper airway, no respiratory effort is generated during central apneas due to cessation of respiratory drive. Thus central apneas are distinguished from obstructive apneas by the absence of respiratory effort, which can be detected by routine monitoring techniques such as respiratory inductive plethysmography combined with assessment of nasal pressure.[19] Mechanisms which can produce central apneas include (1) reduced excitation of chemoreceptors as a consequence of hypocapnia and hyperoxia; (2) functional or actual structural medullary damage which may result in a pattern of grossly irregular ataxic breathing; (3) loss of nonspecific respiratory excitatory stimulation (noise, light, tactile stimuli) in the absence of adequate chemical drive; and (4) active suppression of breathing by respiratory inhibitory reflexes, which is observed in a number of clinical situations including pharmacological therapy with methadone and other opiate medications. Reflex inhibition may arise from the cardiovascular system, from the lung and chest wall, or from somatic and visceral afferents. For example, excitation of receptors located in the upper airway can, via the superior laryngeal nerve, trigger an apnea. Stimulation of J receptors in the lungs by inhaled irritants may produce temporary apnea.

Complex sleep apnea syndrome describes the appearance and persistence of central apneas or hypopneas in patients with obstructive sleep apnea upon successful restoration of airway patency. Patients with complex sleep apnea syndrome present with features of obstructive sleep apnea syndrome. However, when instability of upper airway tone is treated with positive airway pressure therapy, these patients exhibit unstable, chemosensitive ventilatory control leading to repetitive central apneas or periodic breathing during sleep.[51] Adaptive servo-ventilation, which provides both a minimum pressure to hold the airway open as well as a ventilatory assist to minimize persistent cycles of hypo- and hyperventilation, has emerged as an effective treatment. Noninvasive ventilation using bi-level positive airway pressure in the spontaneous-timed mode may also normalize ventilation in some patients.[52]

Central apneas may also occur in critically ill patients as a result of artificial ventilatory support. Application of positive pressure mechanical ventilation may result in a loss of respiratory drive and associated apneas both during and after periods of ventilatory support. This may occur despite normocapnic conditions, and is more frequent during NREM sleep.[52] It is unclear whether these inhibitory effects are dependent on increases in tidal volume (i.e., Hering–Breuer mechanism) or are caused by a resetting of the inherent respiratory rhythm by the externally imposed ventilator frequency.[53,54] In addition, hypocapnia, oversedation, and the presence of CNS disease will also impact the prevalence of apneas during mechanical ventilation.

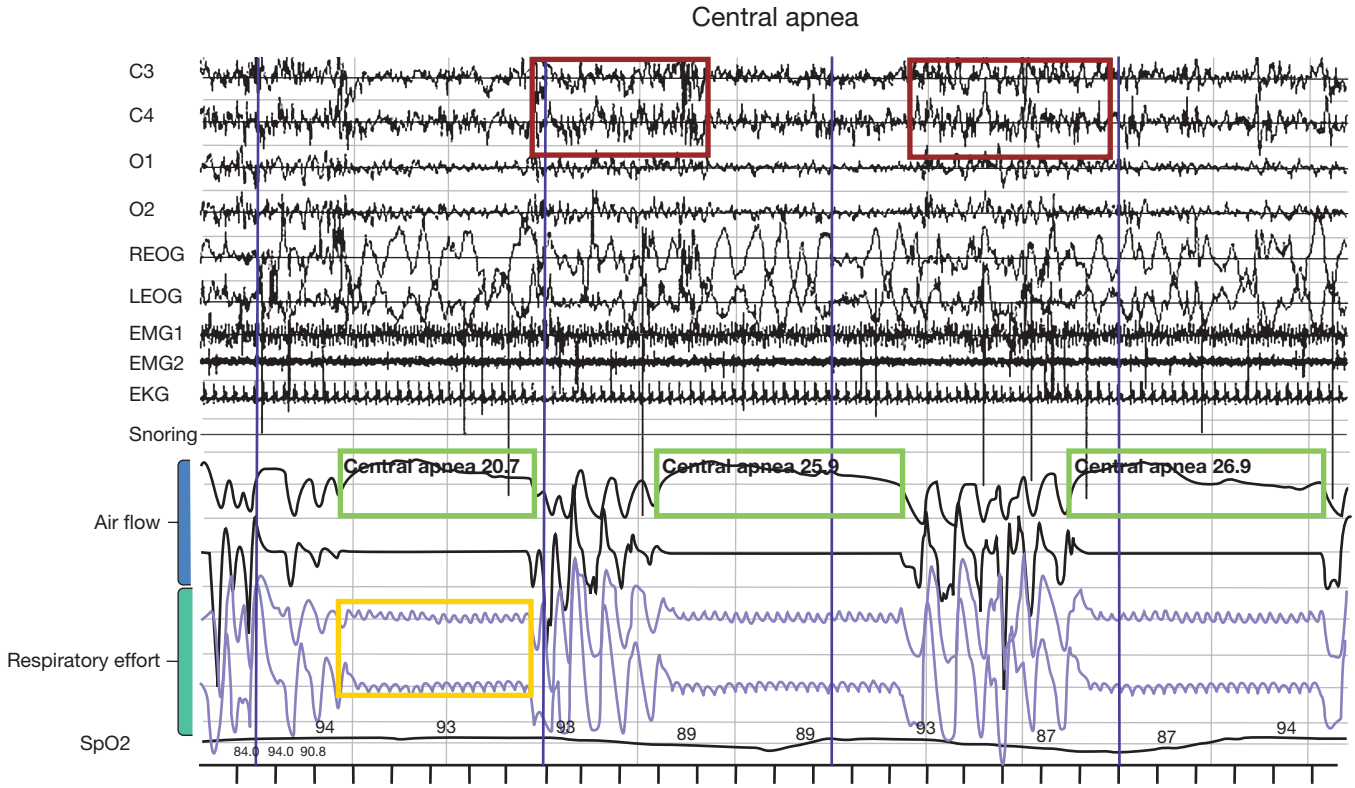

Figure 11-6 An example of respiratory pattern in a patient with central apneas. Note the typical characteristics of central apneas including absence of air flow by both nasal cannula pressure transducer and nasal–oral thermistor (durations in seconds), absence of respiratory effort measured with piezoelectric bands of the thorax and abdomen (orange box), associated oxygen desaturation corresponding to the previous apnea measured by pulse oximeter, and EEG arousal (red box) occurring after an apneic event. EEG channels (C3, C4, O1, O2); electrooculogram channels (REOG, LEOG), chin electromyogram (EMG1), bilateral tibialis anterior EMG2, EKG, snoring microphone.

■ DYSPNEA AND BREATHLESSNESS

Dyspnea is defined as a subjective sensation of difficulty breathing, frequently termed "shortness of breath." Under normal conditions, breathing is not noticeable. However, with increased demands (e.g., during exercise or with progressive cardiopulmonary disease), respiratory movements and forces become more perceptible. When sufficiently intense, respiratory efforts result in symptoms of dyspnea, and patients with lung disease may complain of dyspnea even at rest. The development of dyspnea is a warning signal, which likely serves to protect the body from harm; but since dyspnea itself can become an incapacitating symptom, considerable attention has been given to its etiology.[55–60] Experiments using breath-holding techniques showed that hypercapnia and hypoxia decrease breath-holding times, supporting the idea that increased levels of chemical drive promote dyspnea. In contrast, increased lung volume (increased oxygen stores) lengthened breath-holding time. Other investigations identified that combined blockade of the phrenic and vagus nerves extends the time apnea can be voluntarily maintained, suggesting that signals from respiratory muscles contribute to the sense of dyspnea. Dyspnea also seems to be related to the effort (as a percentage of maximal capacity) required during breathing. In particular, dyspnea increases as the pressures required for tidal breathing grow greater or the maximal inspiratory pressure decreases (e.g., respiratory muscle paresis or fatigue). Taken together, these data suggest dyspnea may manifest as a sense of air hunger (breath holding) and/or as a sense of excessive effort (breathing against a resistance); and it has been proposed that the two types of dyspnea are produced by different mechanisms with different anatomical pathways. In addition, cognitive and affective factors which determine the relative pleasantness and intensity of sensations may affect the level of dyspnea. A corollary discharge hypothesis has emerged whereby dyspnea is related to a mismatch between the central respiratory output and the actual achieved ventilation. During exercise, dyspnea is not profound since elevations in respiratory drive are associated with increases in the achieved minute ventilation. However, in situations where respiratory mechanics are impaired, for example, airway obstruction, dyspnea can be profound since high drive does not translate into high minute ventilation.

SUMMARY

Considerable progress has occurred in the area of control of breathing both in terms of the basic underlying mechanisms as well as the clinical implications of the applied physiology. Given the ubiquitous nature of the associated diseases and conditions, further efforts into the basic and clinical aspects of this field will likely allow new therapeutic strategies to emerge.

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CHAPTER 12
Circadian Rhythms and Sleep Biology

Allan I. Pack

Sleep and circadian rhythm are highly coupled processes. In the original formulation they were considered independent but interacting. Borbely et al.[1–4] posited that the circadian process (Process C) had a 24-hour rhythm that interacted with the sleep drive system (Process S) (Fig. 12-1). Process S is envisaged to be like an old-fashioned egg timer. The drive for sleep is at a very low level following the major sleep bout and increases progressively as wakefulness proceeds, that is, the drive to sleep is related to the duration of prior wakefulness.

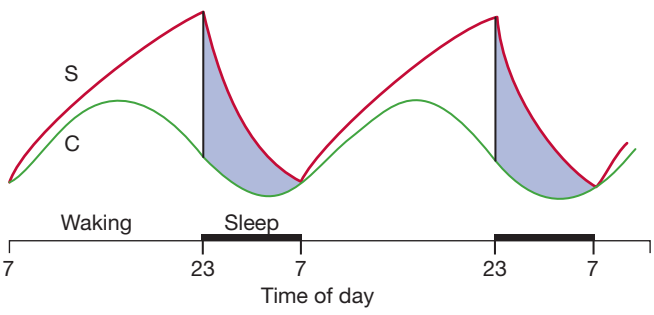

Figure 12-1 Two process model of sleep/wake control. Behavioral state is controlled by the interaction between two processes: (a) Process C, the biological clock and (b) process S, the sleep homeostatic drive. The dark bar below from 23:00 to 07:00 hours is the lights-off period. For further details, see text. *(Reproduced with permission from Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine, 5th ed. Philadelphia, PA: Elsevier; 2011.)*

Humans are programmed to sustain wakefulness for 16 hours but beyond this develop progressive performance impairments. During the day the drive to sleep is counteracted by an alertness signal from the clock. When this alertness signal declines later in the evening, the sleep drive is unopposed and sleep ensues. During sleep the drive to sleep progressively declines, that is, the egg timer is flipped and the sands recover (Fig. 12-1). The situation is actually more complex than this since sleepiness occurs twice a day, that is, siesta time in early afternoon and late in the evening. While these processes were initially considered independent, they are not at a molecular level.[5,6] Core clock molecules increase their expression in brain when sleep is deprived.[7] Moreover, mutations of a clock-associated gene – DEC2, now called BHLEH41 – result in short sleep in humans (<6 hours) without evidence of daytime performance impairment.[8,9]

In this chapter we describe the basis of the clock and make the point that the lung itself has a clock. We then describe sleep and review recent evidence that sleep alters gene transcription in the lung. The reader will get a background in sleep that will facilitate understanding the cardiopulmonary changes during sleep (see Chapter 101) and sleep-disordered breathing (see Chapter 99).

MOLECULAR MECHANISMS OF THE CLOCK

The fundamental principles of how the clock ticks are conserved across species, although the specific details, that is, genes involved, vary between species (for reviews, see[10,11]).

The original concept that the clock involves a distinct molecular mechanism came from identification of mutant fruit flies (Drosophila) with long circadian periods, short circadian periods, and flies with no circadian rhythm.[12] Subsequently it was determined that these different flies all had different mutations in the same gene which was given the name period (PER), that is, the first clock molecule identified.[13] Later forward genetic studies identified another clock molecule in Drosophila, that is, timeless.[14] The first mammalian clock gene was also identified by forward genetic studies, that is, studying mice that had received a chemical mutagen – ENU – and had an abnormal circadian period.[15] This clock molecule is Clock and is a transcription factor.

In both Drosophila and rodents the major mechanism of oscillation is a negative feedback loop (for mammalian model, Fig. 12-2). There

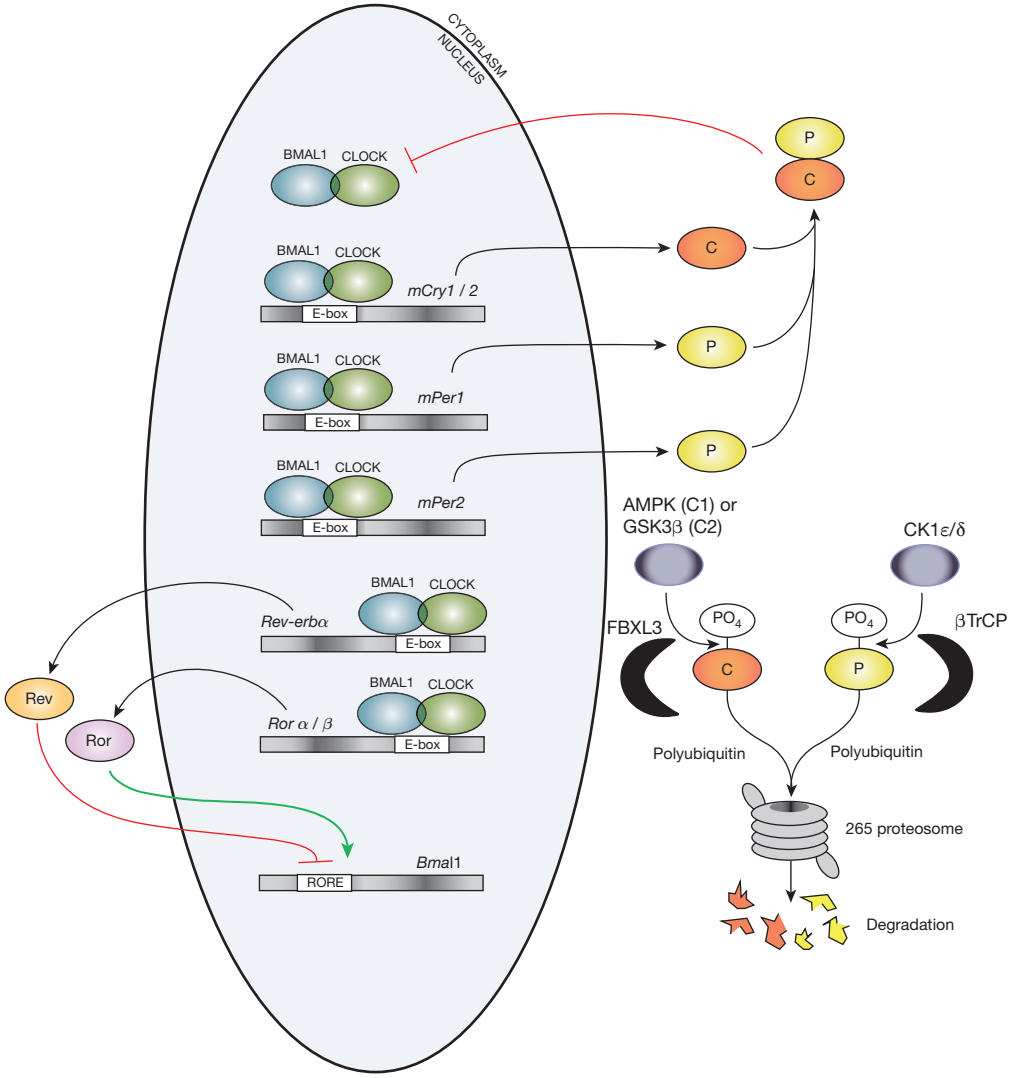

Figure 12-2 The major mechanisms that result in diurnal oscillation of clock genes. For further details, see text. *(Reproduced with permission from Buhr ED, Takahashi JS. Molecular components of the mammalian circadian clock. Handb Exp Pharmacol. 2013;(217):3–27.)*

are also positive feedback loops. In mammals the main clock proteins are the three-period proteins (PER1, PER2, and PER3) and the two cytochrome proteins (CRY1 and CRY2). These proteins form a complex in the cytoplasm that enters the nucleus where they inhibit their own transcription that is controlled by the CLOCK/BMAL1 complex (Fig. 12-2). The degradation of the PER and CRY proteins is important in setting the period of the clock. The PER proteins are phosphorylated by enzymes such as casein kinase 1e and CKII. Once phosphorylated, the PER proteins are targeted for ubiquitination and degradation. In humans mutations in PER2, in the site in which it is phosphorylated[16] and also in CK1 delta,[17] lead to familial phase advance syndrome (for reviews, see[18]). Individuals with this have marked phase advance going to sleep at 7:30 PM and waking up at 4:00 AM.

The other core feedback loop involves the orphan nuclear-receptor genes—REV-ERBα/β and RORα/β. RORs activate BMAL1 while REV-ERBs repress BMAL1 and CLOCK RORs and REV-ERBs are themselves targets of CLOCK-BMAL1 and are negatively regulated by the repressors CRY1 and 2 and PER, particularly PER2.

Thus, the clock is a cell autonomous process and individual cells show circadian oscillation and clock mechanisms can be studied in vitro with cells in culture.

SUPRACHIASMATIC NUCLEUS—THE MASTER CLOCK

The master clock is in the suprachiasmatic nucleus (SCN) of the hypothalamus (for review, see[19]). It contains ~20,000 neurons. Destruction of this nucleus by lesioning results in the animal becoming arrhythmic, that is, with no obvious circadian period.[20,21] The intrinsic period of the clock is not exactly 24 hours and the clock is entrained each day to 24 hours by environmental cues. For the SCN, the main entrainment is by light/dark signals. There is a direct track from the retina to the SCN—the retinohypothalamic tract. Moreover, there is a separate light-sensing mechanism in the eye for entrainment of the clock. This was identified in knockout mice that lacked rods and cones in the retina. While they were blind, there was normal entrainment of the circadian system to light/dark.[22,23] Subsequently, the basis of this light-sensing mechanism was identified (for reviews, see[24,25]). It is the pigment, melanopsin, that is in retinal ganglion cells scattered across the retina.[26–28] This pigment is particularly sensitive to light in the blue color range.[29] This has led to development of blue light boxes, blue light glasses, and glasses that filter out blue light to manipulate the light input to the clock. Following time zone change the output of the master clock is entrained to the new time zone by altered light/dark input. However, this reentrainment is relatively slow with the clock adjusting only about 1 h/d.

PERIPHERAL CLOCKS

Once clock molecules were identified, the surprising result was that they were expressed in all tissues (for review, see[11,30]). It is now realized that there are functioning clocks in all tissues. These peripheral clocks are synchronized with signals from the master clock in the SCN. These peripheral clocks result in rhythmic expression of genes in each tissue and of the order of 3% to 10% of all mRNAs show rhythmic expression in different issues.[31] (The precise number of

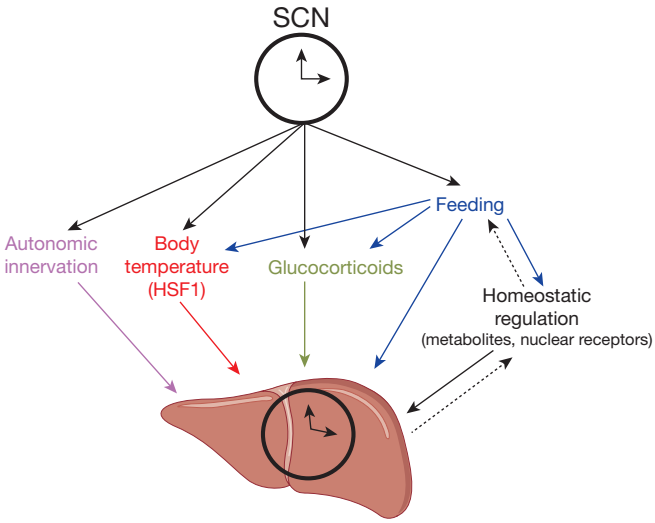

Figure 12-3 There are peripheral clocks in all organs. This diagram is for liver, but there are also clocks in the lung (see text). The "master" clock is in the suprachiasmatic nucleus (SCN) of the hypothalamus. It sends signals to peripheral clocks to synchronize them. There is also local control of clocks by metabolites, etc. *(Reproduced with permission from Mohawk JA, Green CB, Takahashi JS11. Central and peripheral circadian clocks in mammals. Annu. Rev. Neurosci. 2012;35:445–462.)*

genes oscillating depends on the mathematical definition of oscillation such that some estimates of the number of mRNAs oscillating are higher than this.) Thus, there are substantial changes in the molecular functions of different organs at different times of day. The lung is no exception in this regard (see further below).

Peripheral clocks are not only controlled by signals from the master clock but also by signals that occur locally in the particular tissue (Fig. 12-3). Important signals include changes in autonomic nerve activity, body temperature, glucocorticoids, and feeding pattern (Fig. 12-3). Phase shifting of peripheral clocks occurs much more rapidly than for the SCN. Altering the feeding pattern of mice can produce large phase shifts in liver clocks without any effect on the rhythmic expression in genes in the SCN.[32,33]

There is also a molecular clock, not surprisingly, in the lung (for review, see[34]). There is a clock in the Clara cells of the mouse bronchial epithelium.[35] As in other organs, there are a large number of genes that show diurnal changes in expression including genes involved in extracellular matrix, cell cycle, and apoptosis.[36] Genes encoding inflammatory molecules such as chemokine ligands also show diurnal oscillation.[36] The immune response, which is such a critical function of the lung, is under circadian control.[37] Circadian rhythm of other functions of the lung are known to occur, including in FEV_1.[38] Circadian variation also occurs in asthma symptoms[38] as do changes in the cellular content of bronchoalveolar lavage fluids in patients with mild asthma.[39]

Although a new area of inquiry, there are already data that pathological processes may interfere with the normal clock mechanism in the lung. In rats ventilator-induced lung injury results in reduction of REV-ERBα mRNA and protein in lung.[40] The role of REV-ERBα in clock mechanisms at the mRNA and protein level is increased in hyperoxic lung injury.[41] The role of REV-ERBα in clock mechanisms was described briefly earlier. It is likely that in the future the role of clock genes and mechanisms in pathogenesis of lung disease will be further elucidated.

CLOCK GENES AND PHARMACOLOGY

Given that a large part of the genome is regulated by clocks, it is not surprising that clock mechanisms can affect actions of drugs (for reviews, see[42,43]). The absorption of many commonly used drugs show time of day effects as does drug metabolism and drug excretion.[42,43] For example, there is a circadian variation in gene expression of several members of the cytochrome P450 system, the main system for drug oxidation, in liver.[31] Protein levels of cytochrome P450 also oscillate across the day[44] and there is a circadian rhythm of the activity of all cytochrome P450 enzymes.[45]

Thus, efficacy of specific drugs can vary with time of day. The anticoagulant effect of heparin, for example, varies with time of day.[46] When heparin is administered by constant intravenous infusion, the anticoagulant effect varies at different times of day.[46]

The concept of chronopharmacology is most developed for cancer therapy. Levels of plasma 5-fluorouracil vary across the day when the drug is delivered at the same rate.[47–49] There is a circadian variation of the pharmacokinetics of 5-fluorouracil.[50] Clinical trials show that treatment efficacy and toxicity of a chemotherapeutic regimen for metastatic colorectal cancer are enhanced using appropriate chronotherapy compared to constant infusion.[51]

Thus, time of day circadian effects need to be considered in pharmacology. It is likely that there will be a developing interest in this aspect when considering optimal drug regimens.

SLEEP AND ITS STAGES

It is now realized that sleep is universal. While definitions of sleep in mammalian species are based on the electroencephalogram, behavioral criteria[52,53] have led to identification of sleep in many species. In particular, a sleep state has now been identified in Drosophila,[54] zebra fish,[55,56] and most recently in the worm, *Caenorhabditis elegans*.[57] Thus, all model systems are available to study sleep. There are already data that molecular mechanisms regulating sleep are conserved across species.[58]

While there is a suggestion that there are different stages of sleep in Drosophila,[59] rapid eye movement (REM) sleep has only been recognized in mammals and birds. In mammals sleep is divided into two major types—nonrapid eye movement (NREM) sleep and REM sleep (for review, see[60]). REM sleep is a stage with the following: the brain is quite active with flurries of activity resulting in REMs; individuals waking from REM sleep recall their dreams; there is active paralysis of muscles apart from the diaphragm such that normal individuals do not live out their dreams. Individuals with REM behavior disorder do enact their dreams since the atonia of REM sleep is no longer in place. This is a synucleinopathy and a high percentage of individuals with REM behavior disorder go on to develop Parkinson disease (for review, see[61]). Also in REM autonomic instability with variations in heart rate and breathing pattern (for further details, see Chapter 101). NREM sleep is divided into stages based on the electroencephalogram (Fig. 12-4). Originally four stages of NREM sleep were identified but recently stage 3 and stage 4 NREM sleep have been collapsed into one stage—N3. In this stage there is synchronized oscillatory firing of cortical neurons that generate large slow waves which are detected on the electroencephalogram (Fig. 12-4). In all mammalian species there is distinct cycling of the different sleep stages, although the periods of these cycles vary between species. In humans the cycles have approximately a 90-minute duration with episodes of REM sleep occurring every 90 minutes (Fig. 12-5). In the first part of the night individuals cycle down into stage 3 sleep; slow-wave sleep occurs early in the sleep period. Episodes of REM sleep get longer and indeed more phasic, that is, more eye movements etc., as the night progresses. Thus, typically humans are waking up out of REM sleep in the morning. There are major differences in the behavior of the cardiopulmonary system in these different sleep stages. These are discussed in Chapter 101.

MECHANISMS CONTROLLING SLEEP

Sleep is a circuit property, that is, there is no evidence that single neurons sleep, although the intensity of "sleep" may vary across the

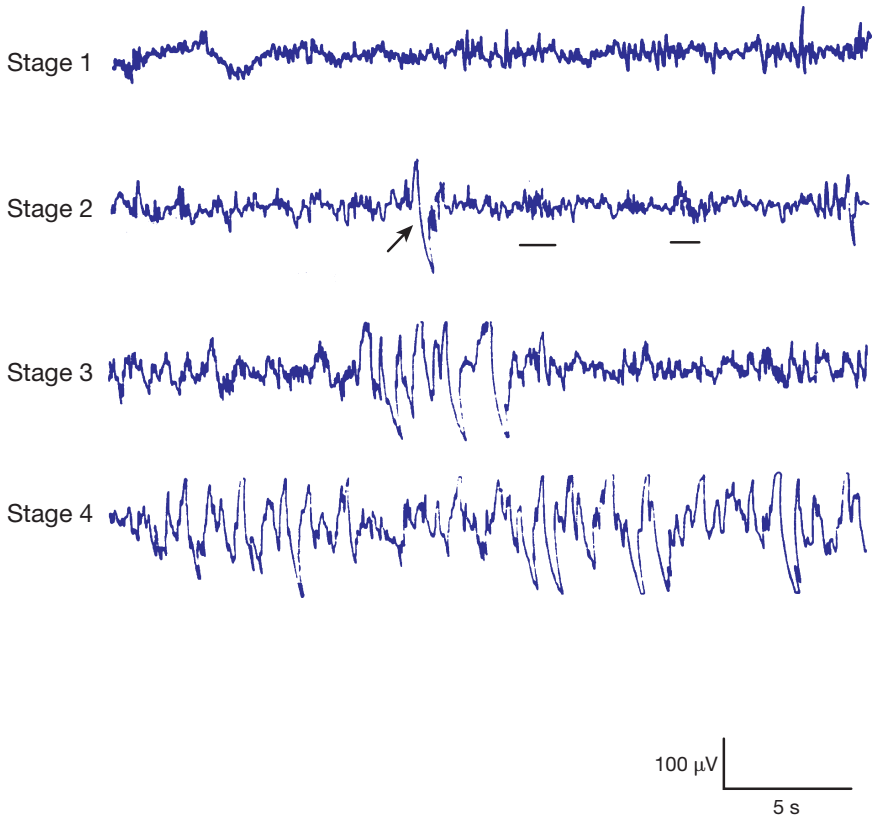

Figure 12-4 Electroencephalographic tracings recorded from a normal young adult demonstrating the four stages of NREM sleep. In the stage 2 recording, the *arrow* points to a characteristic K complex and the underlining to sleep spindles.

brain, that is, local sleep slow waves in NREM sleep are particularly marked over brain regions that have been very active during wakefulness as a result of their involvement in specific tasks.[62,63] Much work over the last two to three decades has identified the neuronal basis for sleep/wake control (for reviews, see[60,64]). Many neuronal groups have increased firing during wakefulness, reduced firing during NREM sleep, and virtually absent firing during REM sleep. These include the following: Cholinergic cells in basal forebrain; orexin (hypocretin) cells in lateral hypothalamus; histamine cells in posterior hypothalamus; dopamine cells in periaqueductal gray; noradrenaline cells in locus coeruleus; and serotonin cells in brain stem raphe nuclei. While these neurons are all more active in waking, they are likely to have different functions during wakefulness. For example, it has been shown that orexin (hypocretin) neurons respond to emotions, for example, positive emotions that result in pleasure increase the level of hypocretin.[65]

While all of these neurons show similar differences in firing between wake and sleep states, there is a different pattern for cholinergic neurons in the pedunculopontine tegmentum (PPT) and lateral–dorsal tegmentum (LDT) in the brain stem. These neurons have reduced firing in NREM sleep compared to wakefulness but higher firing in REM sleep.[60] Thus, REM sleep is thought of as a time with higher cholinergic activity.[60]

While many neurons show increased firing during wakefulness, there are very limited numbers of neurons that increase their activity during sleep. These neurons are in the ventrolateral preoptic (VLPO)[66] and medial preoptic (MPO)[67] area of the hypothalamus. The VLPO has been called the sleep switch.[66] Neurons active during sleep contain the inhibitory neurotransmitter GABA and the neuropeptide galanin.

Since control of wake, sleep and its stage is a circuit property, it has been proposed that behavioral state is controlled by a flip-flop (Fig. 12-6) (for review, see[64]). It is posited that wake-active neurons inhibit sleep-active cells during wakefulness but there are state-dependent changes such that a flip occurs and now sleep cells inhibit wake neurons during sleep. There is a secondary flip-flop that controls oscillation between NREM and REM sleep.[68]

In this proposed mechanism orexin cells play a critical role in stabilizing the flip-flop, that is, preventing too many state transitions. Orexin cells play an important role in narcolepsy. Following the description of this new neuropeptide by two groups – one of which called the neuropeptide, hypocretin[69] while the other called it orexin[70] – it was quickly recognized that it played a key role in narcolepsy. Dogs with a mendelian recessive genetic form of narcolepsy had mutations in the orexin-2 receptor that made it nonfunctional[71] while mice with orexin knockout showed key features of human narcolepsy.[72] Postmortem studies have shown that patients with narcolepsy and cataplexy have loss of orexin (hypocretin) neurons.[73] Thus, narcolepsy is likely an autoimmune disorder in which the main pathogenetic mechanism is destruction of orexin neurons.[74]

Functions of Sleep

Although much effort has been made to understand the neuronal basis of sleep, an equally if not important question is what the

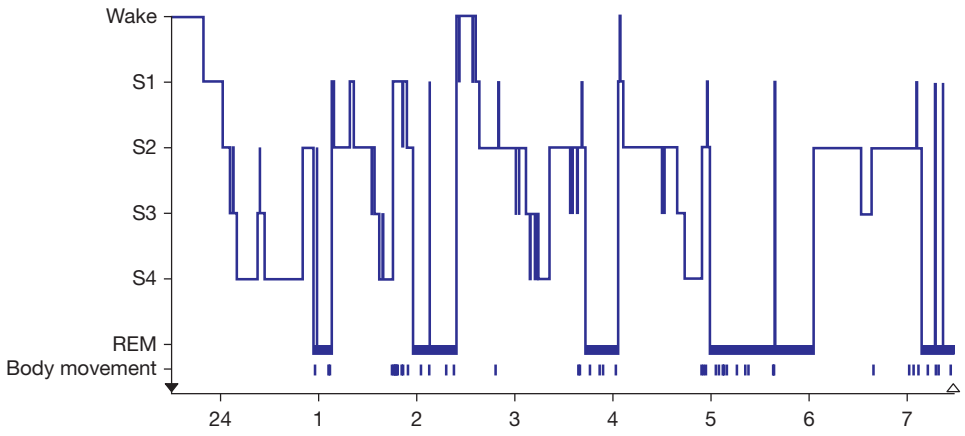

Figure 12-5 The progression of sleep stages across a single night's sleep of a normal young adult. The histogram was drawn on the basis of continuous recordings scored in 30-s epochs.

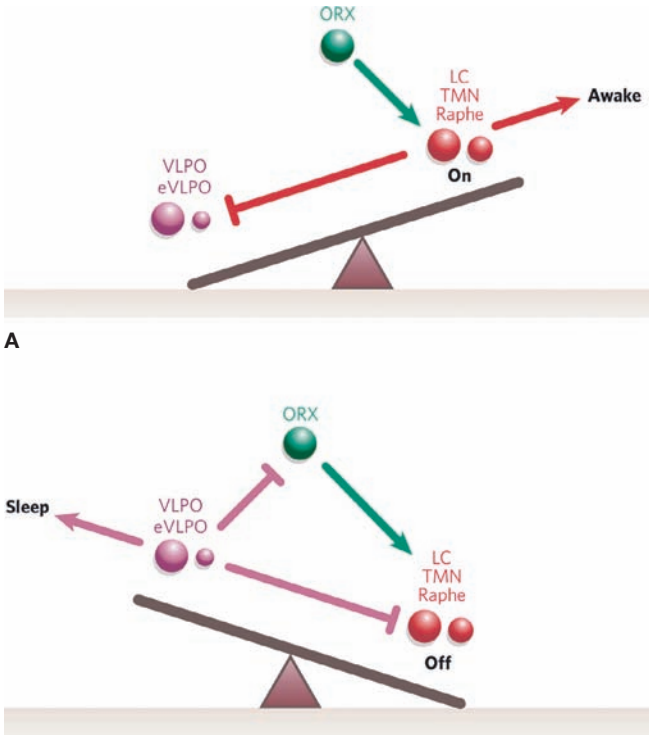

Figure 12-6 A schematic diagram of the flip-flop switch model. During wakefulness (**A**), the monoaminergic nuclei inhibit the ventrolateral preoptic nucleus (VLPO), thereby relieving the inhibition of the monoaminergic cells, and that of the orexin (ORX) neurons, and the cholinergic pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT). Because the VLPO neurons do not have orexin receptors, the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. During sleep (**B**), the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. The direct mutual inhibition between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state, but is relatively unstable. The addition of the orexin neurons stabilizes the switch. eVLPO, extended ventrolateral preoptic nucleus.

functions of sleep are. We spend about one-third of our lives sleeping. The question is what benefit do we obtain? Is benefit just for the brain or do other organs, such as the lung, also obtain benefit?

While theories as to the functions of sleep have been proposed for decades, the concepts that have been articulated recently have in large part, although not exclusively, come from microarray studies comparing gene expression between sleeping and wake animals (often enforced with sleep deprivation) sacrificed at the same time of day. The major focus, not surprisingly, has been on the functions of sleep for the brain.

The following functions of sleep for the brain have been proposed.

ENERGY RESTORATION HYPOTHESIS

One of the concepts that has been proposed is the Benington–Heller hypothesis (for review, see[75,76]). It posits that energy stores in brain – primarily glycogen in glia – are depleted during wakefulness and are restored during sleep. There are some data to support this.[77] However, the situation is more complex (for review, see[76]). There is upregulation of key components of the electron transport chain during wakefulness.[78] This is presumably to make ATP to provide increased energy utilization during wakefulness with higher neuronal firing rates.

SYNAPTIC HOMEOSTASIS THEORY

Expression of genes involved in synaptic upscaling such as BDNF and ARC are upregulated during wakefulness and downregulated during sleep.[80] This has led to the concept that there is synaptic upscaling during wakefulness and downscaling during sleep (for review, see[79]). There are data to support this hypothesis. In Drosophila there are increased amounts of synaptic proteins detected during wakefulness and less during sleep.[81]

There is, however, contradictory evidence. In developing animals there is evidence that synaptic plasticity is enhanced during sleep (not wakefulness).[82] It is conceivable, of course, that this phenomenon is specific to the developmental period. Sleep is a critical period for brain development.[83] It is also conceivable that changes in synaptic plasticity with sleep/wake are different in different brain regions (for debate on this, see[84]). Thus, much remains to be determined and it is likely that the situation is more complex than simply strengthening of synapses during wakefulness and downscaling during sleep.

MACROMOLECULAR BIOSYNTHESIS

Microarray studies also suggest that sleep is a stage of macromolecular biosynthesis (for review, see[85]). Among classes of genes whose expression is increased in cerebral cortex and hypothalamus during sleep compared to wakefulness are genes involved in macromolecular biosynthesis.[86] These gene classes are very overrepresented among genes whose expression is increased during sleep.[86] This involves pathways for multiple molecules, for example, all genes in the cholesterol synthesis pathway, six of seven genes in heme synthesis pathway, and genes involved in protein synthesis. Thus, sleep and wake may be part of a metabolic cycle (for concept, see[87]). Energy resources during wakefulness are used for neural activity, that is, ion pumps etc., but during sleep they are used for macromolecular biosynthesis. Thus, sleep is a stage where new molecules are made to restore membranes, vesicles, etc., that is, to prepare for subsequent wakefulness.

RECOVERY FROM ENDOPLASMIC RETICULUM (ER) STRESS

Another concept that arose from microarray studies is that prolonged wakefulness leads to ER stress with protein misfolding.[88,89] This was suggested by the observation that the molecular chaperone, BiP, the master regulator of the unfolded protein response (for review, see[90,91]) is upregulated in multiple brain regions in multiple species with sleep loss.[88,89] The unfolded protein response is a ubiquitous protective mechanism that is activated when ER stress occurs in the ER with misfolding of proteins.[90,91] The UPR results in helping misfolded proteins to fold properly, chaperoning those not folded out for degradation and inhibition of protein translation to reduce protein production (see[90,91]). All components of the unfolded protein response are activated in mouse cerebral cortex following 6 hours of sleep loss.[92] Inhibiting protein translation by administration of the drug salubrinal that is a modulator of the ER stress response, enhances slow-wave sleep and activates sleep promoting neurons in the MPO area.[93]

CLEARANCE OF COMPOUNDS FROM BRAIN

The brain is unique among organs in that it has no lymphatic system (see[94]). Thus, the question is how are compounds cleared from the brain? This has led to the intriguing concept of glia-lymph, that is, glial cells in brain are responsible for clearance of compounds. Recent data show that compounds are much more rapidly cleared during sleep than during wakefulness.[94] Studies with fluorescent-labeled compounds show that there is substantially more convective flux across the brain in sleeping as compared to waking animals.[94] The precise mechanism that allows this increased transport to occur during sleep is unknown, although it seems to be a result of lower levels of the neurotransmitter, noradrenaline during sleep.[94] A compound that is cleared more rapidly during sleep is beta-amyloid that

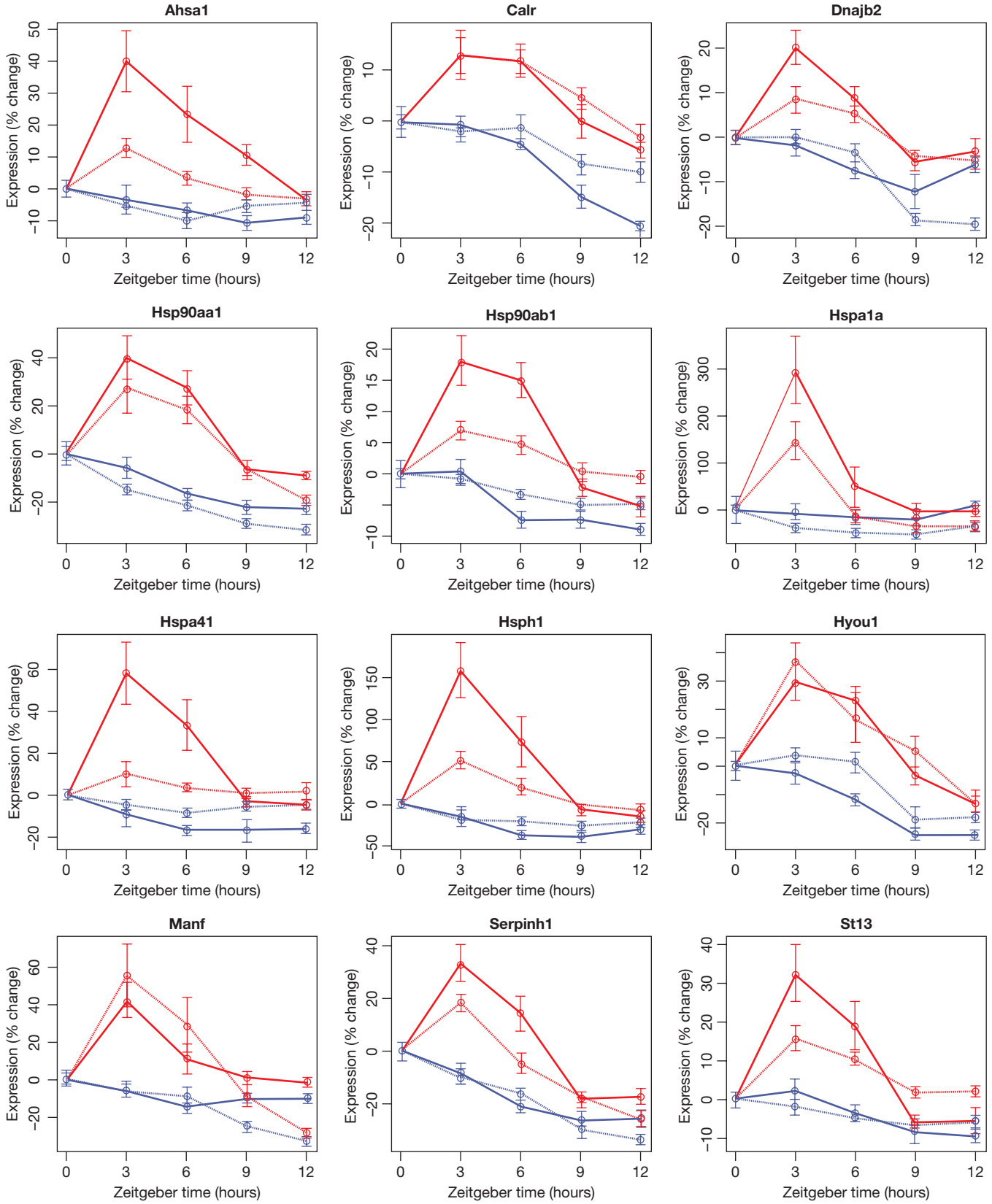

Figure 12-7 Transcript profiles of sleep-repressed genes involved in the unfolded protein response. Temporal profiles of expression for select sleep-responsive genes with annotations relating to protein processing and endoplasmic reticulum (ER) stress. Changes in gene expression from the baseline condition (lights on) are plotted as a percent of baseline expression levels. Maroon curves show data from experimentally sleep-deprived animals and blue curves show data from spontaneously sleeping animals. Data from heart tissue is connected with dashed lines. Data from lung tissue is connected by uninterrupted lines. All genes shown here met statistical criteria for sleep-specific repression in both tissues. Data shown represents mean ± standard error for eight or nine biological replicates. *(Reproduced with permission from Anafi RC, Pellegrino R, Shockley KR, Romer M, Tufik S, Pack AI102. Sleep is not just for the brain: transcriptional responses to sleep in peripheral tissues. BMC Genomics. 2013;362.)*

plays a key role in the pathogenesis of Alzheimer disease. Thus, disturbances of sleep might accelerate Alzheimer's pathology. This has been shown experimentally in mice since sleep loss over many days accelerates plaque development in a mouse model of the disease.[95] Moreover, sleep apnea is now recognized as an independent risk factor for mild cognitive impairment and dementia.[96]

MEMORY CONSOLIDATION

All of the functions described earlier indicate that at a molecular level sleep is an active state with several specific functions (for reviews, see[97,98]). It is not only an active state at a molecular level but also with respect to cognition and memory consolidation. Performance or tasks that require identification of a "hidden rule" are enhanced following sleep, that is, sleep allows the brain to continue to process information and enhances insight.[99] Memory tasks are enhanced after sleep. This is not simply a matter of time since repeating the task several hours later during wakefulness does not result in this enhancement. Enhancement of performance in some tasks is correlated with the amount of slow-wave sleep while for other tasks the correlation is with the amount of REM sleep.[97,98] It has been proposed that REM sleep enhances procedural and emotional memories, while slow-wave sleep enhances declarative memories.[98] Sleep enhancement of memory is reduced with aging.[100]

Thus, sleep seems to have many functions for brain rather than simply one. This is not surprising since it seems logical to ensure maximal benefit from "downtime." The discussion of functions of sleep largely treats sleep as a single entity. We know, however, as described above, that there are specific stages of sleep. Thus, it is conceivable that slow-wave sleep and REM sleep have different functions (see discussion above about memory consolidation). One of the challenges to elucidating function of different stages of sleep is that in mouse models REM sleep episodes are extremely short—of the order of minutes. They are so short that if REM sleep has particular functions they cannot be at the transcriptional level but are likely to be related to posttranslational modifications. It is of interest to consider what the impact of fragmented sleep such as occurs in obstructive sleep apnea (see Chapter 99) will have on the functions described. This has not, however, been studied and is an area of research need and opportunity.

Does the Lung Sleep?

One of the fundamental tenants of sleep biology is that sleep is by the brain and for the brain—a title of a provocative article in *Nature*.[101]

Again, data from microarrays challenge this tenant. Comparing gene expression between sleeping and awake animals sacrificed at the same time of day shows that there are common pathways downregulated in both lung and heart during sleep. As in brain, these pathways are those involved in ER stress, molecular chaperones, and heat shock molecules.[102] There is remarkable similarity in the changes in gene expression in both organs with sleep and sleep deprivation in key genes in these pathways (Fig. 12-7). This suggests that there must be a common signaling mechanism that leads to these dynamic changes in expression of these genes in different tissues in a coordinated way. The nature of this mechanism is unknown. While there are common gene pathways downregulated in sleep in lung and heart, upregulated pathways with sleep are different between organs. In the lung there is upregulation of certain genes for antioxidant enzymes. Thus, is sleep a time for clearing the free radicals produced in the lung during the day? There is a need for more in-depth exploration of the changes in the lung during sleep. These recent data would lead to the conclusion, however, that the lung does indeed sleep.

CONCLUSION

Sleep and circadian biology are dynamic areas of research. New concepts are emerging and some of the fundamental mechanisms are being elucidated. From the point of view of the pulmonologist, there are two major issues. First, both circadian rhythm and sleep have direct effects on molecular mechanisms in the lung. Second, disturbances of sleep like these produced by sleep-disordered breathing will have adverse consequences at a molecular level on the functions of sleep, including potentially in the lung itself.

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CHAPTER 13
Pulmonary Circulation

Robert Naeije

INTRODUCTION: HISTORY AND EVOLUTION

The discovery of the pulmonary circulation was reported in the 13th century by Ibn al-Nafis (1213–1288) in the "Commentary on Anatomy in Avicenna's Canon" and, probably independently, in the 16th century by Michael Servetus (1511–1553) in the "The Restoration of Christianity."[1] However, it has only been recently realized that the pulmonary circulation as a separate high-flow low-pressure system is the end result of an evolutionary process aimed at the optimization of gas exchange of endothermic birds and mammals.[2] Evolution from ancestors of fishes to amphibians, reptiles, and finally birds and mammals has led to progressively greater oxygen consumption requiring thinner pulmonary blood–gas barrier. The alveolocapillary membrane in mammals is a vulnerable structure only 0.3 μm thick. Preservation of the integrity of this barrier has been made possible by the complete separation of the pulmonary circulation from the systemic circulation. This evolution has been accompanied by a progressive unloading and reshaping of the right ventricle (RV) as a thin-walled flow generator.

The extreme potential physiological stresses on the pulmonary circulation are exercise and hypoxia. Exercise increases oxygen uptake and carbon dioxide output up to some 20-fold above resting values, and increases cardiac output up to some sixfold. Strenuous exercise may eventually alter gas exchange because of excessive capillary filtration and stress failure, or expose the RV to excessive loading resulting in a limitation of maximum cardiac output. Hypoxia adds the burden of further increase in pulmonary vascular pressures due to hypoxic pulmonary vasoconstriction.

PULMONARY VASCULAR PRESSURES AND RESISTANCE

LIMITS OF NORMAL

The pulmonary circulation is characterized by an inflow pressure or pulmonary artery pressure (Ppa), an outflow pressure or left atrial pressure (Pla), and a pulmonary blood flow (Q) approximately equal to systemic cardiac output. Pulmonary vascular pressures and flows are pulsatile. However, a simple and clinically useful description of the functional state of the pulmonary circulation may be provided by a calculation of pulmonary vascular resistance (PVR) from mean values of Ppa (mPpa), Pla, and Q.

$$PVR = (mPpa - Pla)/Q$$

Measurements of pulmonary vascular pressures and cardiac output are usually performed during a catheterization of the right heart with a fluid-filled balloon-tipped thermodilution catheter (Fig. 13-1). This procedure allows for the estimation of Pla from a balloon-occluded (Ppao) or wedged (Ppw) Ppa and Q by thermodilution.

METHODOLOGICAL ASPECTS

The frequency response of fluid-filled catheters is considered to be sufficient for meaningful measurements of systolic and diastolic Ppa (sPpa and dPpa), and derived calculation of mPpa. However, errors may be caused by overdamping or underdamping of signals related to the insufficient or excessive flushing or excessive length of tubing systems.[3] A comparison of pulse pressure (PP, or sPpa − dPpa) measured with fluid-filled catheters compared to gold standard high fidelity micromanometer-tipped catheters in eight dogs with pulmonary hypertension induced either by ensnarement of the pulmonary arteries or injection of microbeads is illustrated in Figure 13-2.[4] Measurements of PP were highly correlated, with an analysis according to Bland and Altman[5] showing almost no bias, indicating excellent accuracy. However, the limits of agreement reached ± 8 mm Hg, which may be insufficiently precise in certain clinical circumstances.

Estimations of Pla by Ppw are generally believed to be accurate based on earlier reports of high levels of correlations.[6] This was recently revisited in a large quality-control study in almost 4000 patients with pulmonary hypertension who underwent measurements of Ppw during a right heart catheterization and Pla estimated by left ventricular (LV) end-diastolic pressure during a left heart catheterization.[7] The results showed a bias of −3 mm Hg, corresponding to an expected pressure gradient from small pulmonary veins to the left ventricle at end diastole, thus indicating excellent accuracy, but limits of agreement ranged from −15 to +9 mm Hg, indicating insufficient precision for cut off number-derived individual diagnosis.

Thermodilution Q compared to gold standard direct Fick measurements has been reported to present with little bias, ±0.1 L/min, and thus excellent accuracy, even in patients with severe pulmonary hypertension and tricuspid regurgitation (TR). The limits of agreement were ±1 L/min, which is relatively large but probably often of minor clinical relevance.[8]

Fluid-filled catheters measure vascular pressures with a zero-leveled external manometer. The best reference is the hydrostatic indifference point, at the level of the tricuspid valve, where pressure is independent of body position.[9] This is midchest or 5 cm below the Louis angle in the supine position, with midaxillary intersection at the two inferior fourths of the rib cage to consider when measurements are in the upright position. Zero leveling at the catheterization table is associated with an overestimation of Ppa and Ppw.

Measurements are generally performed at end expiration, when the lungs are at functional residual capacity (FRC). Lung volumes below or above FRC are associated with increased PVR, because of predominant increased alveolar vessel resistance at high lung volumes, and increased extra-alveolar vessel resistance at lower lung volumes.[10] Thus patients with obstructed airways as a cause of increased FRC may present with an increased PVR. Furthermore, these patients have important intrathoracic pressure swings, which are predominantly positive during expiration.[11] This is illustrated in Figure 13-3. Measurements at end expiration may then overestimate Ppa and Ppw.

Sometimes a measurement of Pla or Ppao cannot be obtained, and a *total* PVR (TPVR) is calculated as:

$$TPVR = mPpa/Q$$

Since Pla is not negligible with respect to Ppa, TPVR is larger than PVR and this difference may be flow dependent. Thus TPVR is not a correct characterization of the flow-resistive properties of the pulmonary circulation when Pla is increased. On the other hand, TPVR may be a more realistic estimate of RV afterload. The RV is exposed to Ppa and not to the difference between Ppa and Pla.

PULMONARY CAPILLARY PRESSURE

While wedged or occluded Ppa measurements (Ppw) are acceptable estimates of Pla, micropuncture studies have shown that pulmonary

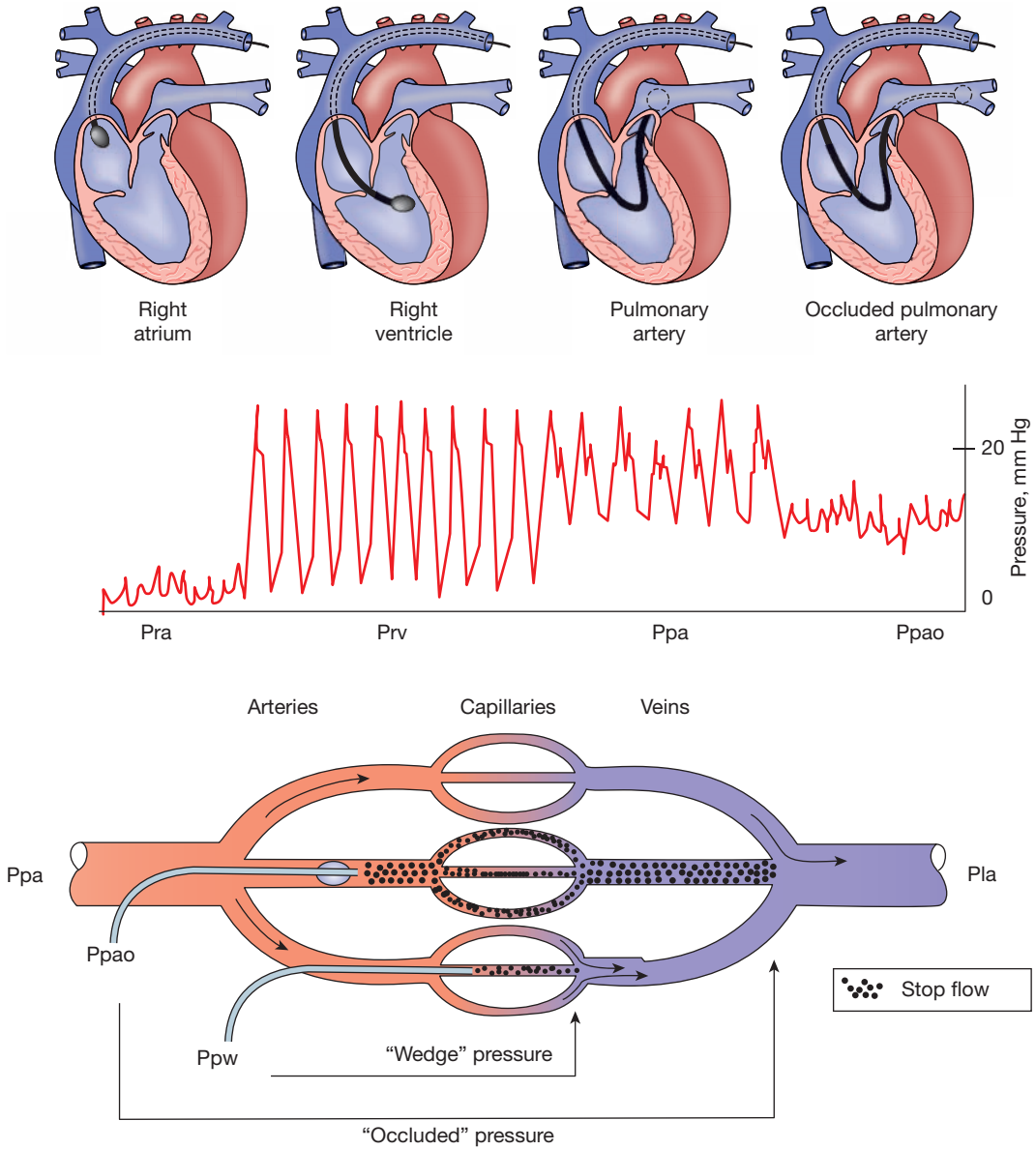

Figure 13-1 Right heart catheterization with flow-directed balloon-tipped catheter with successive measurements of right atrial pressure (Pra), right ventricular pressure (Prv), pulmonary artery pressure (Ppa), and occluded Ppa (Ppao). Because of the fractal structure of the arterial and venous branching of the pulmonary vascular tree, occluded or wedged Ppa prolongs the fluid column of the catheter until same diameter pulmonary vein, which is a satisfactory estimate of left atrial pressure or left ventricular end-diastolic pressure.

capillary pressure (Ppc) is higher than Ppw, about halfway between arterial and venous pressures.[12] Thus wedged or occluded Ppa should not be called "capillary" or "capillary-wedge" pressure. Estimates of Ppc can be obtained from the analysis of Ppa decay curves after arterial occlusion (Fig. 13-4).[13] The limits of normal of Ppc measured in healthy volunteers at rest using single arterial occlusion[14] are shown in Table 13-1. Based on measured distribution of resistances in perfused normal lungs, with 60% arterial resistance and 40% capillary plus venous resistance, Ppc can be estimated from the equation:

$$Ppc = Pla + 0.4 \times (mPpa - Pla)^{15}$$

THE CALCULATION OF PVR

A vascular resistance calculation derives from the physical law that governs laminar flows of newtonian fluids through nondistensible, straight cylindric tubes, originally proposed by the French physician Poiseuille and later put in mathematical equation by the German physicist Hagen. Poiseuille showed experimentally that flow was inversely related to the fourth power of the internal radius, and confirmed previous demonstrations that arterial pressure remains high in arteries down to 2 mm in diameter while venous pressure is low in animals. The Hagen–Poiseuille law states that resistance R to flow of a single tube is equal to the product of the length l of the tube and viscosity η and a constant 8 divided by the product of π and the fourth power of the internal radius r. More generally R can be calculated as a pressure drop ΔP to flow Q ratio:

$$R = l\eta 8/\pi r^4 = \Delta P/Q$$

The ratio of pressure drop to flow through an entire vascular bed accounts for the resistances in series and in parallel of the individual vessels. The fact that *r* in the equation is to the fourth power explains why *R* is exquisitely sensitive to small changes in caliber of these

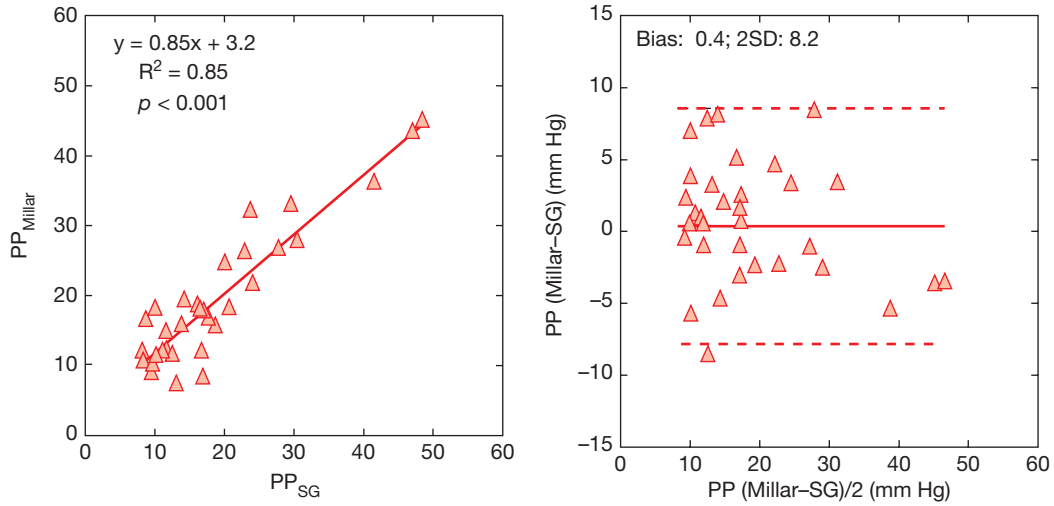

Figure 13-2 Correlation between pulmonary arterial pulse pressure (PP) measured using fluid-filled Swan–Ganz (SG) versus high-fidelity micromanometer-tipped Millar catheters and same measurements presented as Bland and Altman plots. The bias was negligible, indicating accuracy of fluid-filled catheter measurements, but the limits of agreement were of ± 8 mm Hg, indicating limited precision. *(Data from Pagnamenta A, Vanderpool R, Brimioulle S, Naeije R. Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload. J Appl Physiol. 2013;114:1586–1592.)*

small vessels (a 10% change in radius results in almost 50% change in resistance). Accordingly, PVR is a good indicator of the state of constriction or dilatation of pulmonary-resistive vessels and is useful for detecting changes in arteriolar vessel caliber due to changes in tone and/or structure.

■ EFFECTS OF AGE, SEX, AND BODY POSITION

The limits of normal of resting pulmonary vascular pressures and flows as derived from invasive measurements in 60 resting supine young adult healthy volunteers[14,16–18] are shown in Table 13-1. In that study population, cardiac output was lower in women, who are smaller than men, and thus PVR in women was higher. However, there were no sex differences in pulmonary hemodynamics after correction for body dimensions. These data have been confirmed by a recent review of invasive measurements reported in 47 studies on a total of 1187 individuals, of whom 225 were identified as women and 717 as men.[19]

Aging is associated with an increase in PVR. This is due to a slight increase in mPpa and a more important decrease in cardiac output leading to a doubling of PVR over a period of five decades.[20,21]

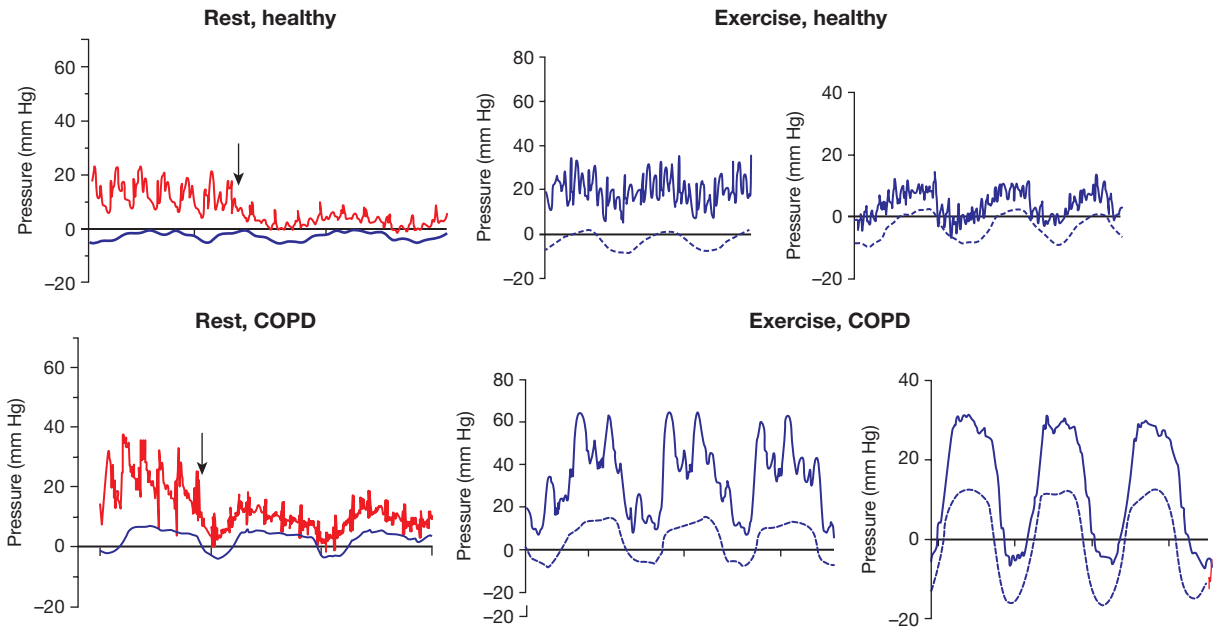

Figure 13-3 Simultaneous pressure recordings of pulmonary artery pressure (Ppa) and wedged Ppa (Ppw) with esophageal pressure (Pes) in a healthy subject and a patient with chronic obstructive pulmonary disease (COPD), at rest and at exercise. The *arrows* represent the moment of balloon inflation. Note the large influence of intrathoracic pressure on the Ppa and Ppw during exercise in COPD. *(Reproduced with permission from Robert Naeije and Bart G. Boerrigter. Pulmonary hypertension at exercise in COPD: does it matter? Eur Respir J. 2013;41:1002–1004.)*

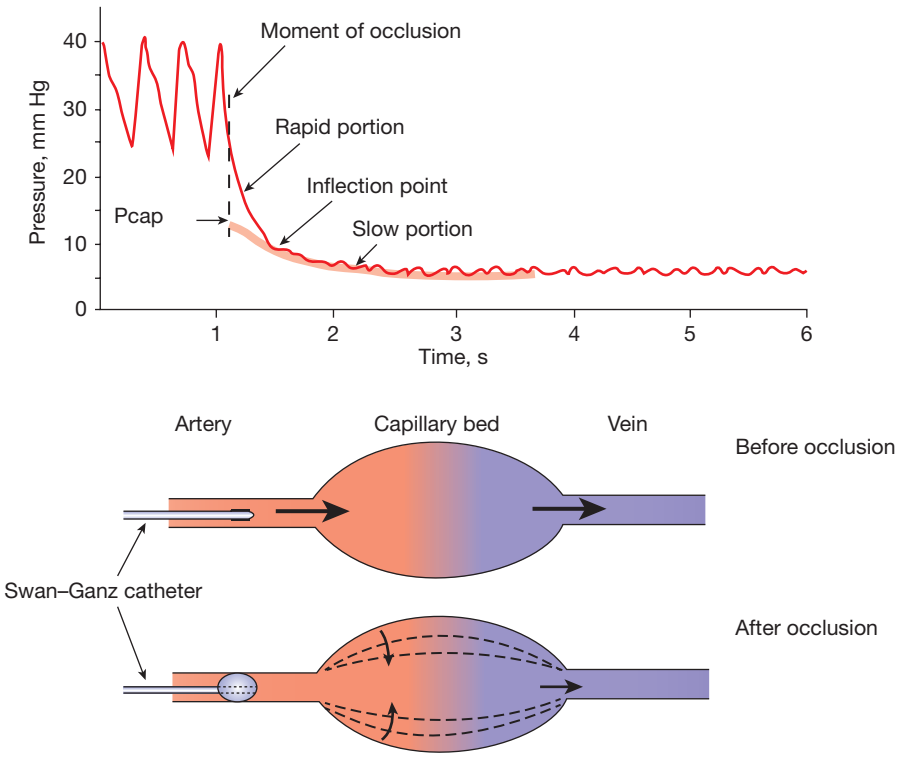

Figure 13-4 Analysis of the pressure transient after pulmonary arterial occlusion for the estimation of pulmonary capillary pressure (Pcap) either by the intersection of the fast and the slow components of the pressure decay curve, or by the extrapolation of the exponential fitting of the slow component of the pressure decay curve to the moment of occlusion.

EFFECTS OF PULMONARY BLOOD FLOW

The inherent assumption in a PVR calculation is that the mPpa–flow relationship is constant and crosses the pressure axis at a value equal to Pla (such that when flow is zero, theoretically, mPpa = Pla). Then, PVR is constant, independent of the absolute pressure or flow.

The relationship between (mPpa–Pla) and Q has been shown to be reasonably well described by a linear approximation over a limited "physiological" range of flows, with a zero extrapolated pressure intercept in well-oxygenated lungs in supine resting intact animals including man, suggesting complete recruitment and minimal distension of the normal well-oxygenated pulmonary circulation. However, hypoxia and a number of cardiac and respiratory diseases increase both the slope and the extrapolated intercepts of multipoint mPpa–Q plots.[23]

While an increase in the slope of mPpa–Q is easily understood as being caused by a decreased cross-sectional area of pulmonary-resistive vessels, the nonzero and typically positive extrapolated pressure intercept has inspired various explanatory models.

However, measurements in healthy elderly individuals are few, so that the exact limits of normal of the pulmonary circulation as a function of age are not exactly known.

Body position affects PVR through associated changes in systemic venous return. In the upright position, Pla, right atrial pressure (Pra), and cardiac output are lower in the supine position. Because of pulmonary vascular derecruitment, mPpa remains essentially the same. Accordingly, PVR is higher upright. This difference in upright versus supine PVR is important to keep in mind when examining PVR changes during exercise performed upright as compared to supine (Fig. 13-5).[22]

TABLE 13-1 Limits of Normal of Pulmonary Vascular Pressures and Pulmonary Blood Flow at Rest

Variables	Mean	Limits of Normal
Q L/min	6.4	4.5–8.5
Heart rate, bpm	67	40–100
Ppa systolic, mm Hg	19	13–26
Ppa diastolic, mm Hg	10	6–16
Ppa, mean, mm Hg	13	8–20
Ppw, mm Hg	9	5–12
Ppc, mm Hg	10	8–12
Pra, mm Hg	5	1–8
PVR, dyne·s·cm^{-5}	55	12–100

Q, pulmonary blood flow; Ppa, pulmonary artery pressure; Ppw, wedged pulmonary artery pressure; Ppc, pulmonary capillary pressure; Pra, right atrial pressure; PVR, pulmonary vascular resistance.

THE STARLING RESISTOR MODEL OF THE PULMONARY CIRCULATION

To explain the nonzero and positive pressure intercept, Permutt et al.[24] conceived a vascular "waterfall" or "Starling resistor" model made of parallel collapsible vessels with a distribution of nonzero and positive closing pressures. The waterfall analogy refers to the fact that the flow rate (Q) over a waterfall is independent of

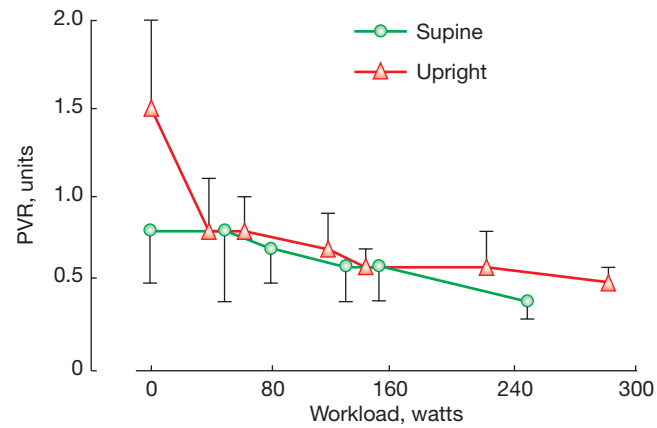

Figure 13-5 Pulmonary vascular resistance (PVR) at rest and during progressively increased workload in healthy volunteers in the upright *(triangles)* versus the supine position *(circles)*. Resting PVR was higher in the upright position. As soon as at moderate workload, upright and supine PVR converge, with mild further decline with increasing levels of exercise. Vertical bars indicate SDs. *(Data from Reeves JT, Dempsey JA and Grover RF. Pulmonary circulation during exercise. In: Pulmonary Vascular Physiology and Physiopathology. Edited by Weir EK and Reeves JT. New York: Marcel Dekker; 1989:107–133.)*

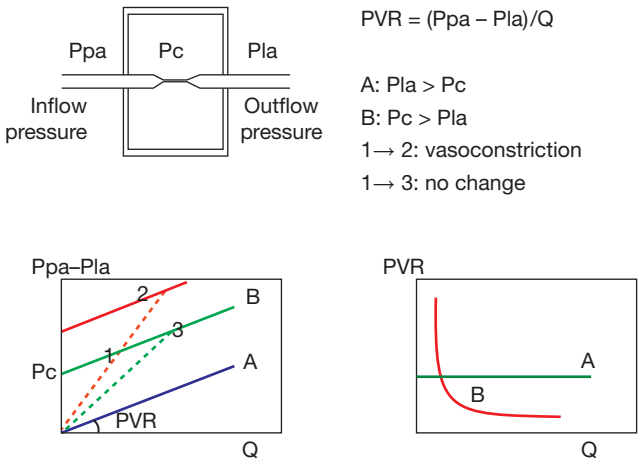

Figure 13-6 Starling resistor model to explain the concept of closing pressure within a circulatory system. Flow (Q) is determined by the gradient between an inflow pressure or mean pulmonary artery pressure (Ppa), and an outflow pressure which is either closing pressure (Pc) or left atrial pressure (Pla). When Pla > Pc, the (Ppa — Pla)/Q relationship crosses the origin (A curve) and PVR is constant. When Pc > Pla, the (Ppa — Pla)/Q relationship has a positive pressure intercept (B curve), and PVR decreases curvilinearly with increasing Q. The B curve is curvilinear a low flow representing recruitment. Also shown are possible misleading PVR calculations: PVR, the slope of (Ppa — Pla)/Q may remain unchanged in the presence of a vasoconstriction (from 1 to 2) or decrease (from 1 to 3) with no change in the functional state of the pulmonary circulation (unchanged pressure/flow line). *(Adapted with permission from Naeije R. Pulmonary vascular resistance: a meaningless variable? Intens Care Med. 2003;29:526–529.)*

its height (the pressure difference between upstream and downstream). Instead, an "external" factor (in the case of a waterfall, fluid momentum) controls the flow rate. The Starling resistor itself was actually a device: A collapsible tube inside of a closed chamber that could be pressurized, thus providing an "external" control over the flow rate through the collapsible tube. Starling used this device in the circuit of his heart–lung preparation to control blood pressure. Permutt postulated that in the pulmonary circulation, as flow decreased, arteries would be progressively derecruited, accounting for a low-flow mPpa–Q curve that is concave to the flow axis, and intercepts the pressure axis at the lowest closing pressure needed to be overcome to generate a flow. At higher flows, complete vessel recruitment and negligible distension account for a linear mPpa–Q curve with an extrapolated pressure intercept representing a weighted mean of closing pressures. In this model, the mean closing pressure is the effective outflow pressure of the pulmonary circulation. At higher flows, Pla is equal to the mean closing pressure. However, at lower flows, Pla is less than the mean closing pressure and becomes irrelevant to flow, analogous to the height of water below a waterfall (Fig. 13-6).

A characteristic typical of a vascular system made up of collapsible vessels is the functional dissociation between inflow pressures, outflow pressures, and flow rate when the closing pressure is higher than the (apparent) outflow pressure (Fig. 13-7). The functional dissociation of inflow and outflow pressures is a feature of derecruited upright upper lung zone 1 described by West et al.[25] It has been reported in pulmonary hypertension associated with acute lung injury[26,27] and in patients who have undergone a cardiac transplantation.[28]

Thu Starling resistor model of the pulmonary circulation appears adequate to explain pressure–flow relationships in derecruited lung regions in healthy states and possibly in certain pathological states associated with an increased surrounding pressure of the small pulmonary-resistive arterioles, such as in lung edema. However, the model has failed to predict correctly mPpa–Q relationships in embolic pulmonary hypertension or after changes in hematocrit.[29] Therefore distensibility models at variable hematocrit have been developed.

DISTENSIBLE MODELS OF THE PULMONARY CIRCULATION

Zhuang modeled the feline pulmonary circulation taking into account not only morphometry but also mechanics (i.e., distensibility) of the pulmonary vascular tree and rheological properties of each of its branched segments.[30] The authors predicted mPpa–Q curves with a slight curvilinearity concave to the flow axis over physiological ranges of flow that was progressively enhanced at decreasing flow. This curvilinearity was generated via arterial, capillary, and venous distensibility based on experimental data with no need to invoke a closing pressure. The distensible or compliant model of Zhuang has been shown to predict parallel shifts of Ppa–Q plots to higher pressures, induced by various interventions such as embolism, changes in lung volume, and hypoxia, and even a functional dissociation between Ppa and Pla at constant Q.[30–32] The model was effective in accurate predictions of mPpa–Q curves at various levels of angiographically determined embolic pulmonary vascular obstruction[33] (Fig. 13-8).

Linehan reasoned that previously reported compliant models were too complex, requiring a large number of parameters not identifiable from pressure and flow measurements alone.[29] Accordingly, he developed a simpler distensibility model and showed its adequacy to describe mPpa–Q relationships at variable hematocrits in

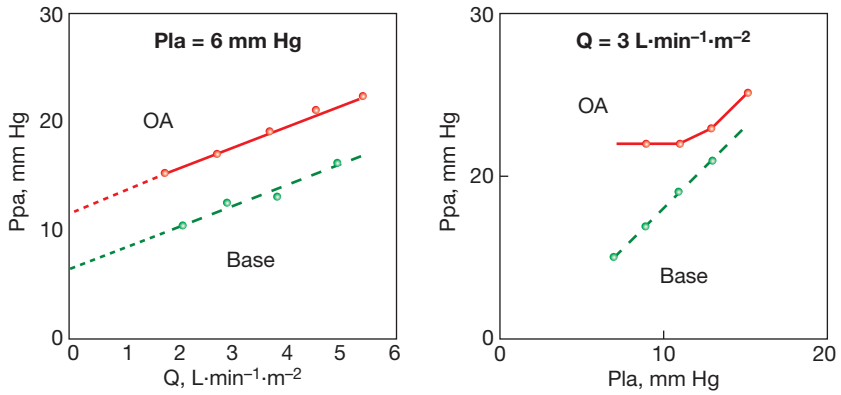

Figure 13-7 Mean pulmonary artery pressure (Ppa) as a function of cardiac output (Q) at constant left atrial pressure (Pla), *left panel*, and Ppa as a function of Pla at constant Q in an anesthetized dog before *(stippled line)* and after *(full line)* injection of oleic acid (OA) to produce an acute lung injury. Lung injury was associated with a shift of linear Ppa–Q relationship to higher pressures, with increased extrapolated pressure intercept *(small stipple line)*. Pla was transmitted to Ppa in a close to 1/1 relationship before oleic acid, but only at a pressure equal to the extrapolated pressure intercept of Ppa–Q after oleic acid, which is compatible with an increased closing pressure becoming the effective downstream pressure of the pulmonary circulation. *(Reproduced with permission from Leeman M, Lejeune P, Closset J, Vachiéry JL, Mélot C and Naeije R. Nature of pulmonary hypertension in canine oleic acid pulmonary edema. J Appl Physiol. 1990;69:293–298.)*

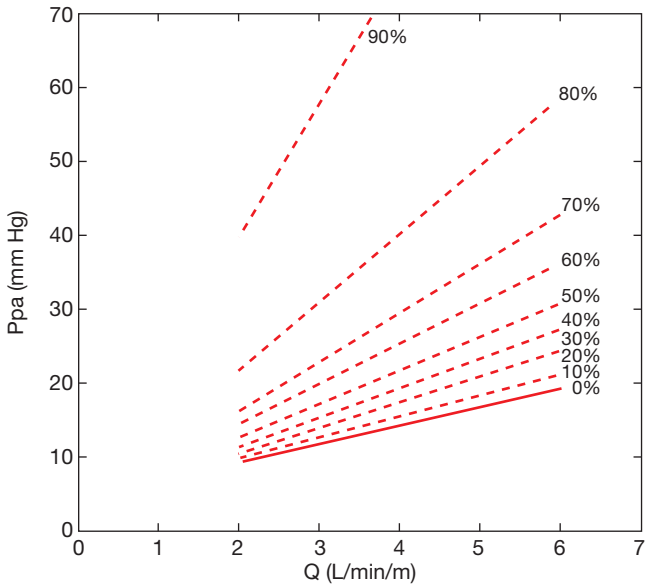

Figure 13-8 Mean pulmonary artery pressure (Ppa)–cardiac output (Q) relationships predicted by the viscoelastic model of Zhuang at increasing levels of angiographically determined embolic obstruction. An increase in mean Ppa above 25 mm Hg corresponding to the definition of pulmonary hypertension occurs after approximately 50% obstruction of the pulmonary vascular bed. A mean Ppa of 50 mm Hg as seen in severe pulmonary hypertension corresponds to 80% obstruction. These estimates are for a Q of 5 L/min, the Ppa–obstruction relationship is flow dependent. *(Data from Mélot C, Delcroix M, Lejeune P, Leeman M and Naeije R. Starling resistor versus viscoelastic models for embolic pulmonary hypertension. Am J Physiol. 1995;267 (Heart Circ Physiol 36):H817–H827.)*

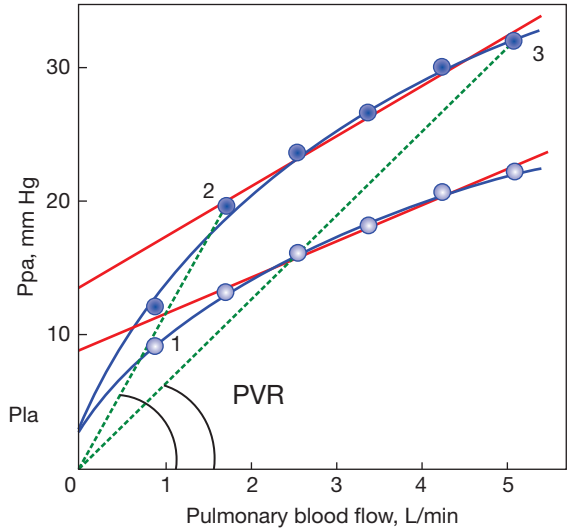

Figure 13-9 Pulmonary artery pressure (Ppa) as a function of blood flow (Q) in normoxia *(empty circles)* and in hypoxia *(full circles)*. Left atrial pressure was 6 mm Hg. Pressure–flow relationships show a slight curvilinearity. Linear adjustment of data points is a cause of positive extrapolated pressure intercepts, and misleading pulmonary vascular resistance (PVR) calculations. Hypoxia-induced increase in Ppa because of hypoxic vasoconstriction is accompanied by unchanged PVR (from 1 to 2) or decreased PVR (from 1 to 3) depending on increased flow. *(Data from Nelin LD, Krenz GS, Rickaby DA, Linehan JH and Dawson CA. A distensible vessel model applied to hypoxic pulmonary vasoconstriction in the neonatal pig. J Appl Physiol. 1992;73:987–994.)*

perfused dog lung lobes. In this model, PVR is calculated with the introduction of a pulmonary-resistive vessel distensibility factor α:

$$PVR = [(1+\alpha Ppa)^5 - (1+\alpha Pla)^5]/5\alpha Q$$

The distensibility factor α corresponds to the % increase in diameter D_0 per mm Hg increase in pressure:

$$D = D_0 + \alpha P$$

This model allows for prediction of mPpa at given levels of resistance Pla, Q, hematocrit, and distensibility.[34]

Multipoint mPpa–Q plots disclose a slight curvilinearity, which is explained by the natural distensibility of resistive vessels (Fig. 13-9). When generated over a limited physiological range of flows, such curves can still be described by a linear approximation. It is then possible to calculate slope for the estimation of average resistance and an extrapolated pressure intercept to suggest a closing pressure. The slope of multipoint mPpa–Q plots offers a refined definition of the resistive properties of the pulmonary circulation, superior to isolated PVR calculations.[23] Extrapolated pressure intercepts are of unclear significance and would overestimate any possible pulmonary closing pressure in proportion to increased distensibility (Fig. 13-9).

Alternatively, from a given set of values of resistance, Ppa_m, Pla, and Q and at rest and during exercise, the Linehan equation permits recalculation of the distensibility coefficient α. Reeves et al.[35] used reported pulmonary hemodynamic data obtained by right heart catheterization at rest and during exercise in healthy volunteers, and were able to recalculate a value of α equal to 2 ± 0.2%/mm Hg in normoxia. This value was remarkably identical on average to the 2%/mm Hg measured on isolated vessels from a variety of various mammalian species.[36] Reeves also showed that α tends to decrease with aging, and with chronic but not acute hypoxic exposure.[35] Similar values of α were calculated by Argiento et al.[37] from Doppler echocardiographic measurements of pulmonary vascular pressures and flows in normal volunteers. In that study, α was lower in men compared to premenopausal women and decreased with age. The same noninvasive approach revealed a decreased α with chronic hypoxic exposure.[38]

VISCOSITY

Chronic hypoxic exposure is associated with an increased expression of erythropoietin, resulting in increased red blood cell mass, hematocrit, and hemoglobin levels. The upper limits of normal of hemoglobin in healthy subjects chronically exposed to hypobaric hypoxia at high-altitude dwellers has been estimated to be at 21 g/dL in men and 19 g/dL in women.[39] In the Poiseuille–Hagen equation, resistance is directly proportional to viscosity.

The most often used reference equation describing a linear relationship between resistance and hematocrit was reported by Whittaker and Winton based on studies on hind limb vessels[40]:

$$R_0(45\%) = R_0(\mathrm{HCT})\frac{1-\varphi^{1/3}}{0.234}$$

where R_0 is PVR at a hematocrit (HCT) of 45% and φ the measured hematocrit.

Linehan et al.[29] reported an exponential relationship to explain the effect of hematocrit on mPpa–Q relationships in isolated dog lung experiments,

$$R_0(45\%) = R_0(HCT)\frac{1}{\exp(2(\varphi-0.45))}$$

The effect of altered hematocrit on representative mPpa–Q relationships in healthy sea level and high-altitude dwellers[38] is

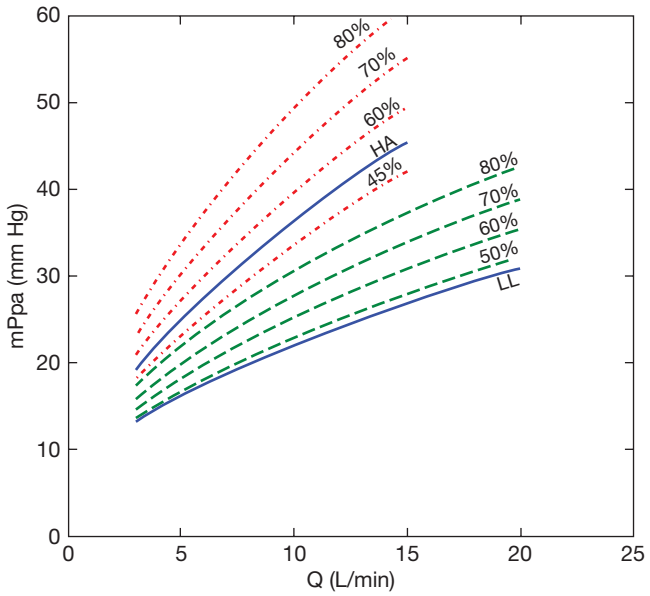

Figure 13-10 Averaged mean pulmonary artery pressure (mPpa)–flow (Q) relationships measured at high altitude in 15 high altitude dwellers (HA) and in 15 lowlander sojourners (LL), *full lines* at the hematocrit of 45% for LL and 52% for HH. The mPpa–Q curves where shifted to higher pressures due to increased hematocrits up to 80%, as modeled from measurements at increasing levels of exercise[37] adjusted with the distensible model of Linehan and associated corrections for hematocrit.[28] Increased hematocrit may be a cause of marked pulmonary hypertension at high altitudes.

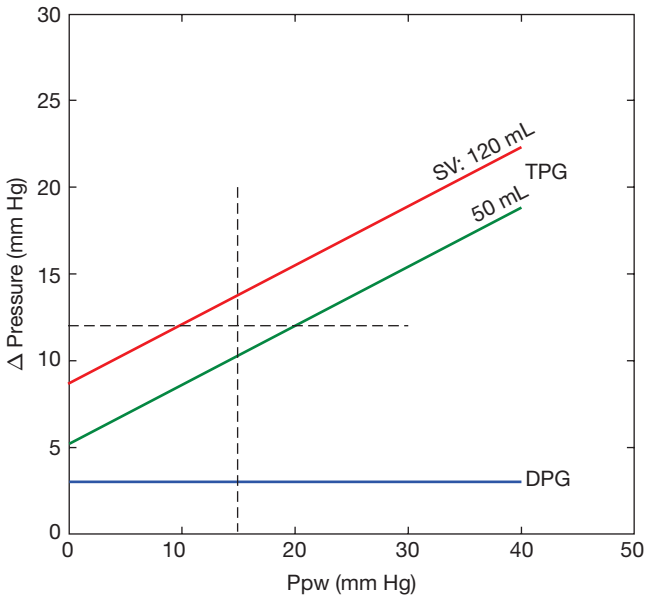

Figure 13-11 Effects of increased pulmonary artery wedge pressure (Ppw) on systolic, diastolic, and mean pulmonary artery pressures (sPpa, dPpa, mPpa) showing progressive increase of the transpulmonary pressure gradient mPpa — Ppw (TPG) with almost unchanged diastolic pressure gradient dPpa — Ppw (DPG). *(Data from Naeije R, Vachiery J, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013;41:217–223.)*

shown in Figure 13-10. Hematocrit was increased from 45% to 80% in both groups. There was a proportionally more important contribution of increased hematocrit to slope of mPpa–Q in the high-altitude dwellers due to their less distensible pulmonary circulation. Thus the impact of hematocrit on mPpa is enhanced in less distensible pulmonary circulations, for example, typically in old and chronically hypoxic subjects.

LEFT ATRIAL PRESSURE AND THE TRANSPULMONARY PRESSURE GRADIENT

An increase in Pla is transmitted upstream to mPpa. The PVR equation assumes that this is in a 1/1 ratio at any given level of Q. Chronic increase in Pla may induce pulmonary vascular remodeling, and therefore lead to an "out of proportion" increase in mPpa.[41] For this reason, clinicians like to reason in terms of a transpulmonary pressure gradient (TPG) for the differential diagnosis of purely passive increase in mPpa and increased mPpa resulting from pulmonary vascular disease.[42] The TPG is equal to the difference between mPpa and Pla.

$$TPG = mPpa - Pla$$

The upper limit of normal of the TPG is usually assumed to be 12 mm Hg.[42] This corresponds to a PVR of 1.5 Wood units at a cardiac output at the upper limit of normal of 8 L/min. However, it has been recently realized that the TPG is often higher than 12 mm Hg in patients with left heart failure in whom purely passive upstream transmission could be demonstrated by observing an acute return of the TPG to <12 mm Hg after active diuresis or after a cardiac transplantation.[28] In steady-flow conditions, an increase in Pla is transmitted upstream in a less than 1:1 ratio because the pulmonary-resistive vessels are distensible.[43] In pulsatile flow conditions, an increased Pla increases pulse pressure (PP, or sPpa — dPpa) because of a decreased pulmonary arterial compliance.[44] The latter effect is largely predominant.[43] Furthermore, the TPG increases with Q because at any increase in flow mPpa increases more than Pla.[43] These problems are limited or even avoided by using the gradient between dPpa and Pla, or the diastolic pressure gradient (DPG) instead.[43] The upper limit of normal of the DPG is ~5 mm Hg. The effects of increased Ppw on the TPG versus the DPG are modeled in Figure 13-11. Assuming an unchanged dPpa as a function of Ppw, which is reasonable, it can be seen that high Ppw is associated with a passive increase in TPG to more than 12 mm Hg because of a proportionally greater increase in mPpa.[43]

GRAVITY

Pulmonary blood flow increases almost linearly from nondependent to dependent lung regions. This inequality of pulmonary perfusion is best demonstrated in an upright lung.[25] The vertical height of a lung is on average about 30 cm. The difference in pressure between the extremities of a vertical column of blood of the same size amounts to 23 mm Hg, which is large compared to the mean perfusion pressure of the pulmonary circulation. Accordingly, the physiological inequality of the distribution of perfusion of a normal lung can be explained by a gravity-dependent interplay between arterial, venous, and alveolar pressures. At the top of the lung, alveolar pressure (P_A) is higher than mPpa and pulmonary venous pressure (Ppv). In this *zone 1*, flow may be present only during systole, or not at all. Zone 1 is extended in clinical situations of low flow, such as hypovolemic shock, or increased alveolar pressure such as during ventilation with a positive end-expiratory pressure. Further down the lung there is a *zone 2* where Ppa > P_A > Ppv. In this zone 2, alveolar pressure is an effective closing pressure, and the driving pressure for flow is the gradient between mean mPpa and P_A. As mentioned before, such a flow condition can be likened to a waterfall since Ppv, the apparent outflow pressure, is irrelevant to

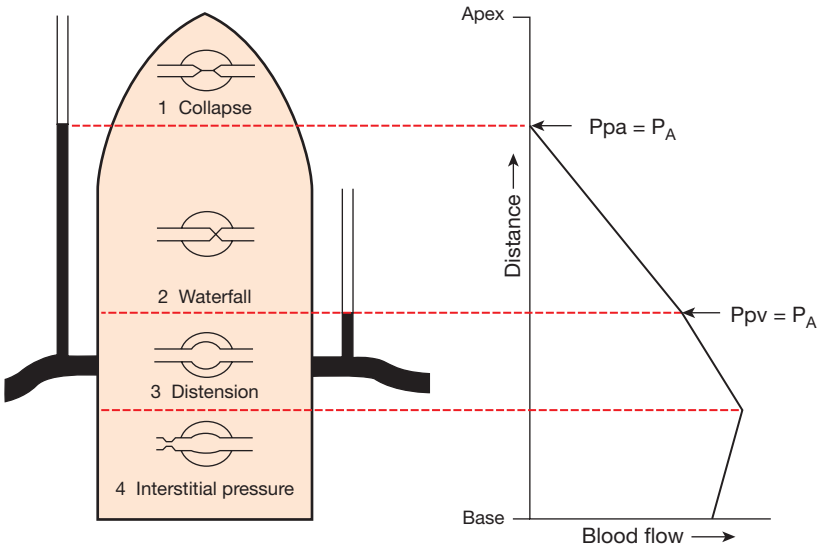

Figure 13-12 Zonal distribution of pulmonary perfusion in an upright lung as determined by the interrelationships between arterial (Part), alveolar (Palv), and venous pressures (Pv), explaining a gravity-determined progressive increase in perfusion from zones 1 and 2 to 3. There is a zone 4 of decreased perfusion at the most dependent part of the lung. *(Adapted with permission from Hughes JM, Glazier JB, Maloney JR, West JB. Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol. 1968;4:58–72.)*

flow as is the height of a waterfall. In *zone 3*, Ppv is higher than P_A, so that the driving pressure for flow is mPpa − Ppv. West's zones are illustrated in Figure 13-12.

At the most dependent regions of upright lung, there is an additional region where flow decreases.[45] This *zone 4* has been attributed to an increase in the resistance of extra-alveolar vessels, because this zone expands when lung volume is reduced or in the presence of lung edema. Active tone may be an additional explanation for zone 4 as it is also reduced by the administration of vasodilators.

The vertical height of lung tissue in a supine human subject is of course reduced compared to the upright position, and accordingly, the lung is then normally almost completely in zone 3. There is however a still measurable increase in flow from nondependent to dependent lung regions (Fig. 13-13).

Three-dimensional reconstructions using single photon emission computed tomography have shown that there is also a decrease in blood flow from the center of the lung to the periphery.[46] High-resolution methods and fractal modeling of the pulmonary circulation have actually led to the notion of a nongravity-dependent distribution of pulmonary blood flow.[47] Subtle differences in arterial branching ratios may indeed influence flow distribution with increased heterogeneity as the scale of the inquiry narrows.[48] However, the overwhelming evidence remains in favor of the thesis that gravity is the single most important determinant of pulmonary blood flow distribution.[48] Vascular geometry-related small unit heterogeneity of pulmonary blood flow distribution has not been shown to be relevant to gas exchange.

HYPOXIA

There is an active intrapulmonary control mechanism able to some extent to correct the passive gravity-dependent distribution of pulmonary blood flow: A decrease in P_{O_2} increases pulmonary vascular tone. Hypoxic pulmonary vasoconstriction was first demonstrated on isolated cat lungs by von Euler and Liljestrand,[49] who proposed a functional interpretation that can still be considered valid. In lung tissue, P_{O_2} is determined by a ratio between O_2 carried to the lung by alveolar ventilation (V_A) and O_2 carried away from the lung by blood flow (Q):

$$P_{O_2} = V_A / Q$$

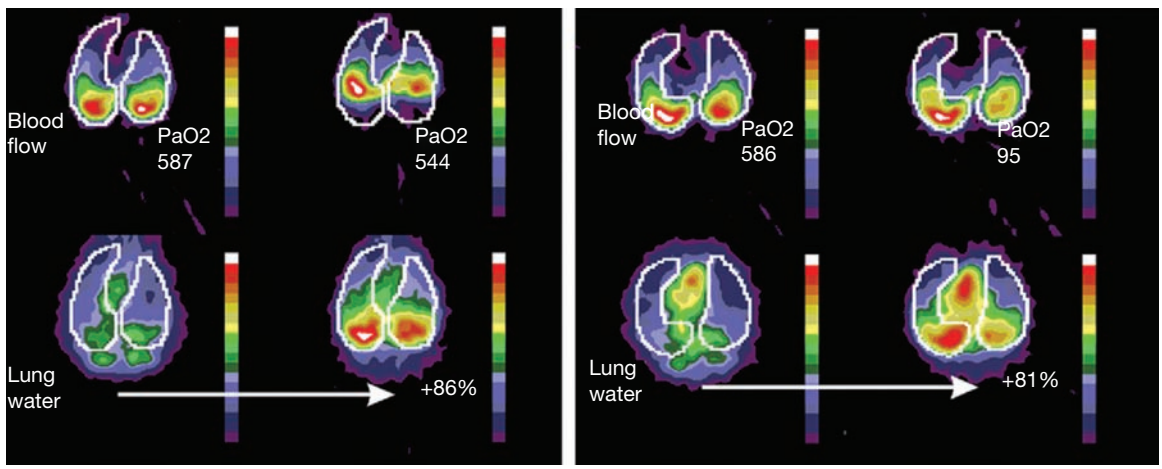

Figure 13-13 PET scan measurements of blood flow and lung water in a supine dog before and after induction of acute lung injury, with preserved hypoxic vasoconstriction (**A**) or without hypoxic vasoconstriction (**B**). In the normal lung, blood flow and water increase to the most dependent lung regions (from *blue* to *red*). Acute lung injury approximately doubles lung water, but arterial P_{O_2} (Pa_{O_2}) is preserved because of a hypoxic vasoconstriction redirecting flow to better aerated lung regions. Prevention of hypoxic vasoconstriction increases flow to the dependent edematous lung regions, and this is associated with a marked decrease in Pa_{O_2}. *(Reproduced with permission from Gust R, Kozlowski J, Stephenson AH, et al. Synergistic hemodynamic effects of low-dose endotoxin and acute lung injury. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1919–1926.)*

In contrast, in systemic tissue, local P_{O_2} is accordingly determined by a ratio of O_2 carried to the tissues by blood flow (Q) and local O_2 consumption (V_{O_2})

$$P_{O_2} = Q/V_{O_2}$$

The attributes of hypoxic pulmonary vasoconstriction have been recently extensively reviewed.[50] The hypoxic pulmonary pressor response is universal in mammals and in birds, but with considerable interspecies and interindividual variability. It is intense in pig, horse, and cow, moderate in rodents and humans, and very low in dog, guinea pig, yak, and llama. Chronic hypoxia induces pulmonary hypertension, in proportion to initial vasoconstriction. Initial hypoxic vasoconstriction is a quasi-immediate response with subsequent modulation depending on the experimental model or preparation. Hypoxic vasoconstriction strengthens during the first few hours of hypoxic exposure in humans. The temporal sequence of hypoxia-induced remodeling is less well known. After 6 hours of hypoxic exposure, reoxygenation immediately decreases PVR, without however a complete return to normal.[51] The reversibility of increased PVR with reoxygenation is largely lost after 24 to 48 hours exposure to hypoxia.[14]

Hypoxic vasoconstriction is observed in lungs devoid of nervous connections, and indeed also in isolated pulmonary arterial smooth muscle cells.[50] The response is enhanced by acidosis, a decrease in mixed venous P_{O_2}, repeated hypoxic exposure (in some experimental models), perinatal hypoxia, decreased lung segment size, cyclooxygenase inhibition, nitric oxide inhibition, and certain drugs or mediators that include almitrine and low-dose serotonin. The response is inhibited by alkalosis, hypercapnia, an increase in pulmonary vascular or alveolar pressures, vasodilating prostaglandins, nitric oxide, complement activation, low-dose endotoxin, calcium channel blockers, β_2-stimulants, nitroprusside, and, paradoxically, by peripheral chemoreceptor stimulation. The hypoxic pressor response is biphasic, with a progressive increase as P_{O_2} is progressively decreased to approximately 35 to 40 mm Hg, followed by a decrease ("hypoxic vasodilatation") with more profound hypoxia.

The hypoxia-induced increase in PVR is mainly caused by a constriction of precapillary small arterioles.[50] Small pulmonary veins also constrict in response to hypoxia, but this should not normally contribute to more than 20% to 30% of the total change in PVR.[52]

While hypoxic pulmonary vasoconstriction has been shown to be an only moderately efficient feedback mechanism,[18,53] it may still produce substantial improvements in arterial oxygenation of patients with inhomogenous lungs such as in chronic obstructive pulmonary disease (hypoxemia mainly explained by low V_A/Q ratios) or in the acute respiratory distress syndrome (hypoxemia mainly explained by V_A/Q ratios equal to zero, or shunt).[54]

Topographical blood flow distribution measured by PET scan and arterial P_{O_2} can be shown to conform to the expected functional effects of hypoxic pulmonary vasoconstriction in experimental acute lung injury models, as an inhibition of the response prevents redistribution of blood flow to nondependent lung regions and markedly aggravates shunt and arterial hypoxemia.[55] This is illustrated in Figure 13-13, in an experiment which also shows the predominant effects of gravity on the distribution of pulmonary blood flow and its relevance to gas exchange.

The biochemical mechanism of hypoxic pulmonary vasoconstriction remains incompletely understood.[50] Current thought is that a decrease in P_{O_2} inhibits smooth muscle cell voltage-gated potassium channels, resulting in membrane depolarization, influx of calcium, and cell shortening. However, the nature of the low P_{O_2}-sensing mechanism remains elusive. Mitochondria and nicotinamide adenine dinucleotide phosphate oxidases are discussed as oxygen sensors. Reactive oxygen species, redox couples, and adenosine monophosphate-activated kinases are candidate mediators. The reversal of hypoxic vasoconstriction by profound hypoxia, in the range of 25 to 30 mm Hg and lower, is due to an activation of ATP-dependent potassium channels.

MAINTENANCE OF VASCULAR TONE

Normal as well as abnormal pulmonary vascular tone is modulated by a series of endothelium-derived and circulating mediators.[50] Endothelium-derived relaxing factors include nitric oxide, prostacyclin, and the endothelium-derived hyperpolarizing factor. The major endothelium-derived contracting factor is endothelin. These observations have been on the basis of efficient treatments of pulmonary arterial hypertension with prostacyclin derivatives, phosphodiesterase-5 inhibitors to enhance nitric oxide signaling, and endothelin receptor blockers.

The pulmonary circulation is richly innerved by the autonomic nervous system, which includes adrenergic, cholinergic, and nonadrenergic noncholinergic signaling systems.[56] However, the role played by the autonomic nervous system in the control of pulmonary vascular tone appears to be minor. Sympathetic innervation of the pulmonary arterial tree is predominantly proximal and plays a role in the modulation of proximal compliance.

EXERCISE

PULMONARY ARTERY PRESSURE

Exercise stresses the pulmonary circulation by an increase in cardiac output and in left atrial pressure.[22] In 1989, Reeves et al.[57] reviewed the published data on invasive pulmonary hemodynamic measurements during supine or upright exercise in a total of nearly 100 normal subjects. This analysis established that supine exercise is associated with a slight decrease in PVR, which is explained by pulmonary vascular distension of fully recruited lungs in West's zone 3 conditions. In the upright position, the resting PVR was found to be higher, which is explained by pulmonary vascular derecruitment caused by a lower cardiac output (via decreased venous return). A higher resting PVR accounts for the more marked and hyperbolic decrease of PVR with exercise reported in upright subjects (Fig. 13-5).

Reeves et al. were able to find measurements at rest and at least two levels of exercise in 63 subjects (including 21 women), so that they could calculate linear regressions relating mPpa to Q in each of them. On average, each liter per minute of increase in cardiac output was accompanied by 1 mm Hg increase in mPpa in young adult men and women. Advanced age (60–80 years) was found to be associated with a more than doubling of the slope of mPpa–Q relationships, to an average of 2.5 mm Hg/L/min. However, there was large interindividual variation, with standard deviations on the order of the means, which makes it difficult to estimate the limits of normal.

A more recent review of the literature of invasive pulmonary hemodynamic data in normal subjects confirmed this data.[58] Invasive measurements of PVR were found in only 13 subjects aged more than 50 years. The review otherwise confirmed an only moderate decrease in PVR with exercise, which was, however, less important or absent in older subjects; and slopes of mPAP–Q of ~1 mm Hg/L/min in subjects of less than 50 years.[58]

The pulmonary circulation during exercise has been more recently reevaluated, using Doppler echocardiography in a total of 177 healthy subjects[37,38,59,60] and a right heart catheterization in 24 other healthy volunteers.[61] In these studies at least four mPpa–Q coordinates were measured at increasing levels of workload. There was a perfect agreement between invasive and noninvasive measurements The results confirmed that the linear adjustment of multipoint mPpa–Q relationships should not exceed 3 mm Hg/L/min, which corresponds to an mPpa at a Q <10 L/min, or a maximum exercise TPVR <3 Wood units. Fitting the data using

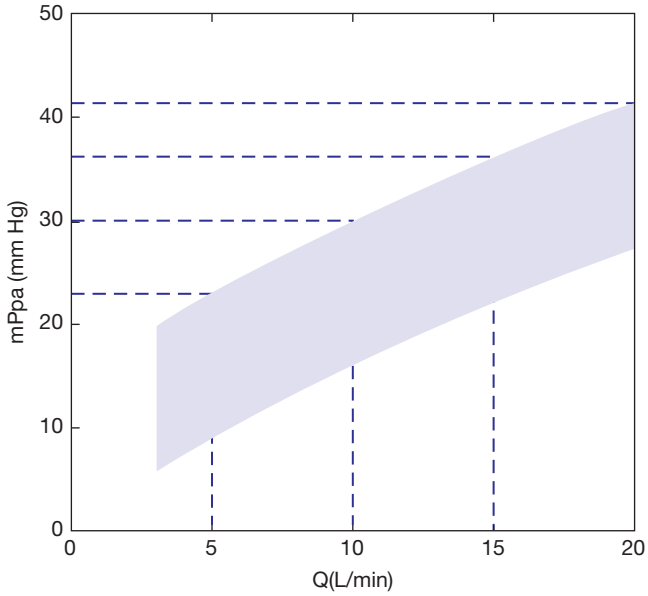

Figure 13-14 Limits of normal of mean pulmonary artery pressure (mPpa) as a function of increasing flow (Q) with exercise in healthy young adults, constructed from noninvasive and invasive data reported.[60] *Stippled lines* indicate upper limits of mPpa increasing from 25 mm Hg at a Q of 5 L/min to 45 mm Hg at Q of 20 L/min. *(Data from Bossone E, D'Andrea A, D'Alto M, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr. 2013;26(1):1–14.)*

Linehan's distensible model of the pulmonary circulation allowed for the calculation of normal α values <2%/mm Hg, decreasing at increasing levels of exercise.[37,38,59,60] These results have also been recently confirmed by invasive measurements,[61] allowing for a definition of the limits of normal of mPpa as a function of Q at exercise (Fig. 13-14).

After exercise, mPpa and Q rapidly return to resting values. Measurements within 5 minutes after a maximum exercise test in normal subjects are nearly back to resting normal.[59] Rapid return to normal of pulmonary vascular pressures and flows decreases the relevance of postexercise measurements as a reflection of exercise-induced changes. On the other hand, the workload–Q relationship is quite variable.[37] It is therefore preferable to express mPpa at exercise as a function of cardiac output rather than of workload to define the functional state of the pulmonary circulation.[61]

■ LEFT ATRIAL PRESSURE

Left atrial pressure increases with exercise. Strenuous exercise may be associated with very high Pla, up to 20 to 30 mm Hg in athletes.[20,21,62,63] At levels of exercise corresponding to increases in Q to less than 15 L/min, Pla remains more or less within the limits of normal or slightly above.[22] Increased Pla at very high levels of exercise is explained by progressive decrease in LV diastolic compliance in part related to competition for space with the RV within a nonacutely distensible pericardium.[64]

■ SHUNTING OF AGITATED CONTRAST

In 2004, Eldridge and Stickland independently reported on the occurrence of exercise-induced shunting demonstrated by agitated saline contrast echocardiography in subjects with otherwise no evidence of intrapulmonary or intracardiac shunt at rest.[65,66] In these studies, exercise-induced pulmonary shunting of bubbles was shown to be correlated with cardiac output, mPpa, and alveolar-to-arterial P_{O_2} gradient at exercise, suggesting an impact on gas exchange.[66] Agitated saline or gelatine contrast echocardiography is standard practice for the detection of cardiac right-to-left shunts. The contrast bubbles are of 10 to 35 μm in size, and do not normally traverse the pulmonary circulation. In the case of a cardiac right-to-left shunt, the appearance of contrast in the left heart chambers is immediate. In the case of pulmonary shunt, the appearance of contrast in the left heart chambers is delayed by 3 to 5 beats. The most likely explanation for positive pulmonary transit of agitated contrast is pulmonary capillary distension.[60,67]

In addition to variable LV diastolic compliance resulting in variable increase in Pla transmitted upstream to Ppa, much of the variability of the mPpa and PVR responses is related to pulmonary-resistive vessel distensibility. Data are emerging supporting the notion that low PVR at high levels of exercise is associated with an increased pulmonary vascular reserve defined by a combination of high α and lung diffusing capacity and positive pulmonary transit of agitated saline at Doppler echocardiography.[60,67]

PULSATILE FLOW PULMONARY HEMODYNAMICS

The study of the pulmonary circulation as a steady-flow system is a simplification. Pulmonary pulse pressure, or the difference between sPpa and dPpa, is proportionally much higher than systemic pulse pressure. Instantaneous pulmonary blood flow varies from a maximum at midsystole to around zero in diastole.

The morphology of pulmonary pressure and flow waves changes with the development of pulmonary hypertension. In patients with severe pulmonary hypertension, the RV pressure wave is characterized by a sharp initial upstroke, followed by a short plateau, and by a late systolic peaking, and the Ppa pressure wave is characterized by a huge pulse pressure and a late systolic peaking as well,[68] while the pulmonary flow wave presents with a shortened acceleration time and late or midsystolic deceleration.[69] In the most severe forms of pulmonary hypertension the pulmonary artery pressure wave looks "ventricularized."[68] These morphological aspects are entirely explained by the combined effects of decreased compliance[70] and wave reflection.[71]

■ PULMONARY VASCULAR IMPEDANCE

A complete evaluation of pulmonary vascular function relies on the calculation of the relationship between pulsatile pressure and flow or pulmonary vascular impedance (PVZ) instead of the relationship between mean pressure and flow (PVR). PVZ is calculated from a spectral analysis of the pulmonary arterial pressure and flow waves.[72] This analysis is possible because the pulmonary circulation behaves nearly linearly. This means that a purely sinusoidal flow oscillation produces a purely sinusoidal pressure oscillation of the same frequency. The sinusoidal pressure and flow waves can be related by the ratio of their amplitudes (modulus) and the difference in their phases (phase angle). A typical PVZ spectrum in a dog is illustrated in Figure 13-15.

Pulmonary arterial impedance at zero Hz, Z_0, (the ratio of mean pressure to mean flow, mPpa/Q) corresponds to TPVR. This parameter is mainly determined by the small resistance vessels as well as Pla. As frequency increases, the impedance is affected by more proximal elements of the arterial tree. The modulus of the impedance decreases from Z_0 rapidly to a first minimum at 2 to 3 times the heart rate and then oscillates about a constant value. The impedance phase increases from a negative value at low frequencies, indicating that flow leads pressure to zero at higher frequencies. The precipitous fall in modulus and the negative phase of the impedance are a measure of the total arterial compliance. At high frequencies the rather constant modulus and nearly zero phase angle are a measure of the proximal arterial compliance.

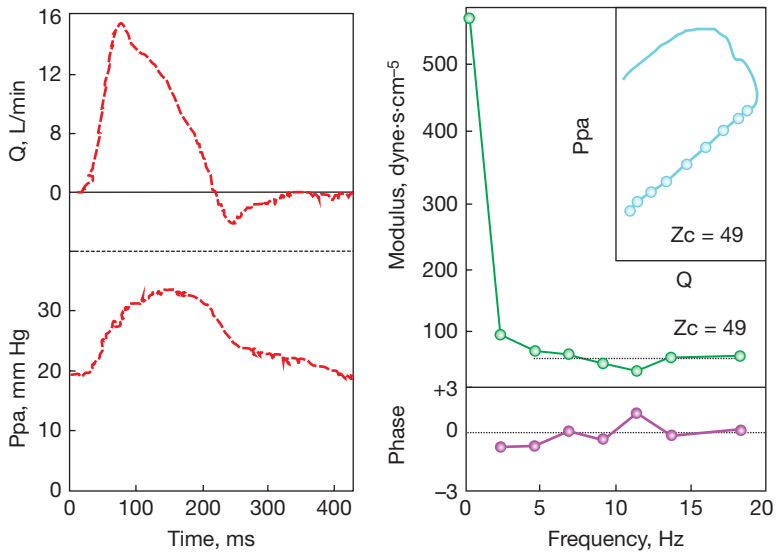

Figure 13-15 Pulmonary artery flow (Q) and pressure (Ppa) waves and pulmonary arterial input impedance spectrum. At 0 Hz the total PVR is obtained (mean pressure over mean flow). Between 0 and 4 Hz the impedance is mainly determined by total arterial compliance. The averaged input impedance for high frequencies, usually taken between 4 and 8 Hz, equals the characteristic impedance (Zc). The oscillation of the impedance about the characteristic impedance results from wave reflection. Zc is also the slope of early-systolic Ppa–Q relationship.

The impedance modulus at high frequencies, when impedance phase is nearly zero and therefore wave reflections can be ignored, is the characteristic impedance Zc. It is typically measured as the average modulus at higher frequencies (usually 10–20 times the heart rate). It can also be measured as the slope of the early systolic pulmonary artery pressure–flow relationship in the time domain (Fig. 13-15).[73]

The oscillations of the impedance modulus about its mean value result from distinct wave reflections. Increased magnitude of these oscillations implies increased reflections. A shift of the first minimum of modulus to higher frequencies indicates an increased wave velocity or a decreased distance to the dominant reflection site.

Characteristic impedance depends on the ratio of inertia to compliance of the proximal pulmonary circulation, and can be approximated by the equation:

$$Zc = [(\rho/\pi r^4)/(\Delta\pi r^2/\Delta P)]$$

where ρ is the density of blood, r the mean internal radius, $\rho/\pi r^4$ the inertance, and $\Delta\pi r^2/\Delta P$ the compliance of the pulmonary arterial tree.

The human PVZ spectrum has the same pattern as reported in canine studies, but with lower Z_0 and Zc values due to greater body size and thus relatively higher pulmonary blood flow.

Distal small vessel obstruction such as caused by microembolism, hypoxia, or pulmonary arterial hypertension increases Z_0 but have limited effects on the PVZ spectrum, with some shift of first minimum and maximum of Ppa/Q to higher frequencies, but unchanged or sometimes even a decrease in Zc.[71,74] Proximal vessel disease such as by experimental proximal ensnarement of the pulmonary arteries or clinical chronic thromboembolic pulmonary hypertension shifts the entire PVZ spectrum to higher ratios of pressure and flow moduli.[71,74] Very high Ppa due to major peripheral small vessel obstruction may also increase Zc because of extreme stiffening of the pulmonary arteries and increased reflected wave speed.[75,76]

Exercise has been reported in an animal study to decrease PVR but to shift the PVZ spectrum to higher pressure and flow moduli at all frequencies with an increase in Zc, a shift of the first minimum of the ratio of pressure and flow moduli to higher frequencies and more negative phase angle.[77] The authors explained the increase in Zc by a decreased area compliance of the proximal pulmonary arterial tree because of increased distending pressure related to increased flow, with possibly a contribution of exercise-associated sympathetic nervous system activation. It had indeed already been shown experimentally that sympathetic nervous system activation may increase Zc without significantly changing PVR.[78] However, the authors could not exclude a spurious increase in Zc caused by too tight fitting of the electromagnetic flow probe placed around the main pulmonary artery.[77]

There has been one small study on the effects of exercise on pulmonary arterial compliance (Ca), Zc, and PVR in eight normal subjects.[79] Exercise was associated with a 50% decrease in PVR and a 30% increase in pulmonary arterial compliance (Ca), while Zc did not change (Fig. 13-16). The apparent discrepancy between changes in Zc and Ca is explained by the sensitivity of Zc to proximal stiffness and dimensions, while Ca integrates the distensibility of the entire pulmonary circulation. Thus unchanged Zc would be explained by the balanced effects of proximal stiffening and increased cross-sectional area.

THE TIME CONSTANT OF THE PULMONARY CIRCULATION

A few decades ago, Reuben[80] had noted an inverse relationship between PVR and Ca in the normal or diseased pulmonary circulation. This was recently revisited in a series of studies that showed that the product of PVR and Ca, or the time constant (RC-time) of the pulmonary circulation remains constant over a wide range of severities, etiologies, and treatments of pulmonary hypertension (Fig. 13-17).[81–83] This remarkable property of the pulmonary circulation has two consequences. The first is that Ca becomes a more important determinant of RV afterload than PVR when mPpa and

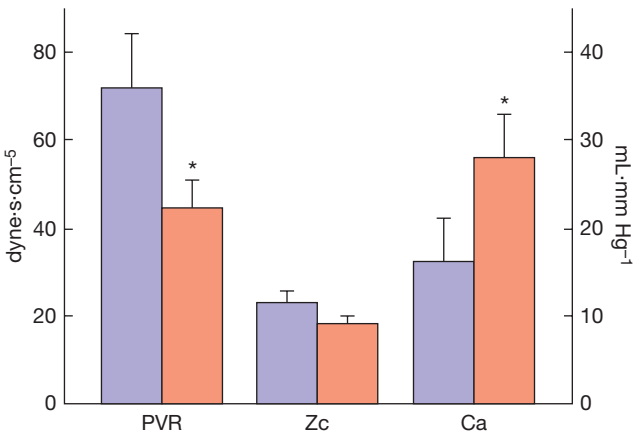

Figure 13-16 Effects of exercise on pulmonary vascular resistance (PVR), characteristic impedance (Zc), and arterial compliance (Ca) in healthy human subjects. Compared to resting state (blue bars), exercise (red bars) decreased PVR and increased Ca, while there was no significant (*) change in Zc. *(Data from Slife DM, Latham RD, Sipkema P and Westerhof N. Pulmonary arterial compliance at res and at exercise in normal humans. Am J Physiol. 1990;258 (Heart Circ Physiol 27): H1823–H1828.)*

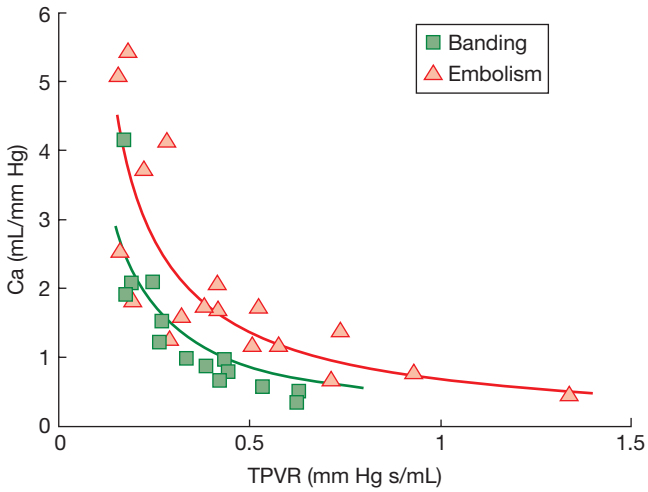

Figure 13-17 Pulmonary arterial compliance (Ca) as a function of total pulmonary vascular resistance (TPVR) in dogs with pulmonary hypertension induced either by an ensnarement of the pulmonary arteries (banding, proximal obstruction) or the injection of microbeads (embolism, distal obstruction). The time constant Ca × TPVR is shorter with proximal obstruction.

PVR are only modestly elevated.[84] The second is that RV oscillatory power (Wosc) remains a constant fraction of total power (Wtot) irrespective of Ppa.[80,85]

The only noticeable exception to the constancy of RC-time is pulmonary hypertension secondary to LV failure.[86] In these patients, RC-time is decreased because of a stiffer pulmonary arterial tree caused by increased pulmonary venous pressure.[43] One would expect proximal obstruction of the pulmonary circulation, like in patients with proximal chronic thromboembolic pulmonary hypertension, to be a cause of shorter RC-time as well (Fig. 13-17). A slight but significant decrease in RC-time has indeed recently been reported in such patients[87] like in experimental pulmonary hypertension on proximal pulmonary arterial banding.[4] It must however be underscored that a constancy or near constancy of RC-time in the pulmonary circulation contrasts with the absence of relationship between resistance and compliance in the systemic circulation.

The stability of the time constant of the pulmonary circulation explains the reported tight correlation between systolic, diastolic, and mean Ppa in normal subjects and in patients with pulmonary hypertension of all possible etiologies.[88] Accordingly, mPpa can be calculated from sPpa using a simple formula:

$$\text{mPpa} = 0.6 \times \text{sPpa} + 2$$

This notion is of practical relevance as noninvasive evaluations of the pulmonary circulation in clinical practice often rely on the measurement of a maximum velocity of TR to calculate a sPpa using the simplified form of the Bernoulli equation and a measurement or estimate of Pra[89]:

$$\text{sPpa} = (\text{TR}^2 + 4) + \text{Pra}$$

RIGHT VENTRICULAR FUNCTION

The RV is functionally coupled to the pulmonary circulation.[90] Because of the normally low pulmonary vascular pressures taking the entire cardiac output, the RV acts as a thin-walled flow generator. The structural and functional characteristics of the RV allow for the accommodation of large increases in flow, less so small increases in afterload. However, the basic laws of the heart remain applicable, that is rapid beat-to-beat heterometric adaptations (Starling law of the heart) and otherwise progressive structural and inotropic homeometric adaptations (Anrep's law of the heart) to changes in loading conditions.[91] Thus the RV adaptation to pulmonary hypertension is homeometric with increased contractility, eventual hypertrophy, and preserved dimensions. Failure of this mechanism depends on rate of onset and magnitude of increase in Ppa and results in heterometric adaptation, with increased RV dimensions and systemic congestion.[88,89]

RIGHT VENTRICULAR HYDRAULIC LOAD

Increased Ppa requires increased RV hydraulic power to sustain adequate forward flow. Hydraulic power is made of two components: The energy per unit time (power) to produce steady flow, which is the product of mPpa and Q, and the power to produce the pulsatile component of Ppa and Q. The latter can be calculated from the difference between the product of the integrations of instantaneous Ppa and Q waves and the product of mPpa and Q. Since mean flow determines oxygen transport, mean power may be considered useful whereas oscillatory power is "wasted." As a consequence, the ratio of oscillatory to mean power, or oscillatory to total (mean plus oscillatory) power, should preferably be small.[92]

Because of the proportional relationship between systolic, diastolic, and mPpa, one would expect the ratio of oscillatory to total RV power to remain constant. This was indeed recently reported in a study of 49 patients with pulmonary hypertensions of variable severities.[85] Total power increased with severity of pulmonary hypertension, but the ratio of oscillatory to total power remained reasonably constant, at 23%. Accordingly, the authors proposed that the total power of the RV should be equal to 1.3 times mean power in all circumstances. As the proportionality of pulmonary artery pressures appears to be maintained at exercise[93] the calculation of total RV power as 1.3 times mean power is probably transposable, but this will require confirmation by further studies. On the other hand, situations of shortened RC-time like heart failure[87] or purely proximal pulmonary arterial obstruction[4,87] are associated with an increased oscillatory component of total RV power.

RIGHT VENTRICULOARTERIAL COUPLING

The calculation of power includes a measurement of cardiac output, and thus depends not only on the mechanical properties of the pulmonary circulation, but also on ventricular function. It has been suggested that power transfer and ventricular efficiency are near maximal in normal subjects. A simplified approach to test this has been given by Sunagawa et al.[94] These authors proposed a graphical analysis based on the right ventricular pressure–volume diagram[91,95] and a characterization of the arterial system by means of its arterial elastance (Fig. 13-18).

The diagram allows for the determination of maximal ventricular elastance (Emax), which is the best possible load-independent measurement of contractility, and of arterial elastance, Ea, as a measurement of afterload as it is "seen" by the ventricle, and the calculation of an Emax/Ea ratio as a measurement of the coupling of ventricular to arterial function.

Mathematical modeling shows that the optimal matching of systolic ventricular and arterial elastances occurs at an Emax/Ea ratio around 1.5. Isolated increase in Ea, or decrease in Emax, decreases the Emax/Ea ratio, indicating uncoupling of the ventricle from its arterial system. Everything else being the same, a decrease in Emax/Ea is necessarily accompanied by a decrease in stroke volume. On the other hand, an isolated increase in preload is associated with an increase in stroke volume with unaltered ventriculoarterial coupling.[91]

However, the complex geometry of the RV makes functional evaluations with measurement of instantaneous volume changes

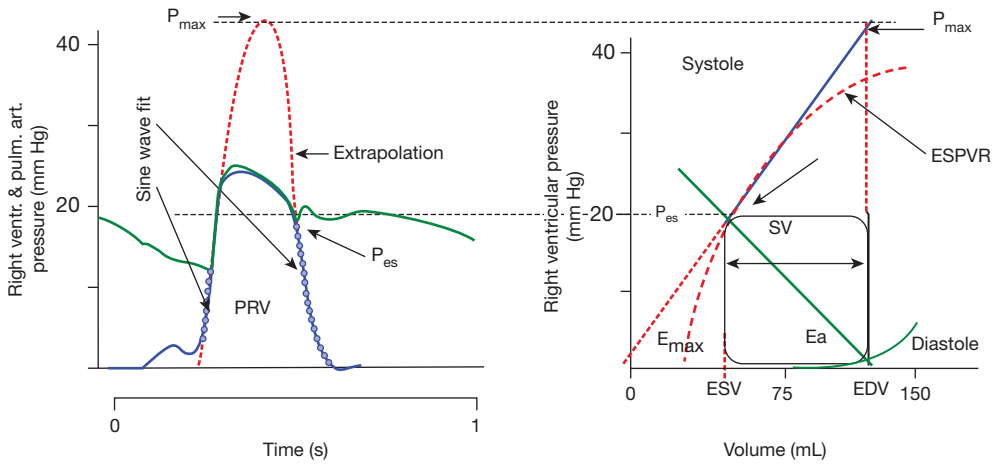

Figure 13-18 Single-beat method to measure right ventriculoarterial coupling. A maximum pressure (*P*max) is calculated from nonlinear extrapolation of early and late isovolumic portions of the right ventricular pressure curve. A *straight line* is drawn from *P*max and the end-diastolic volume (EDV) to *P*es and the end-systolic volume (ESV), thus *E*max = (*P*max — *P*es)/SV, where SV is the stroke volume. The arterial elastance *E*a is defined by the ratio *P*es/SV. ESPVR, end-systolic pressure-volume relationship.

technically difficult, and the determination of Emax may be unreliable because of the particular shape of the RV pressure–volume loop and noncoincidence of end-ejection and end-systole. This problem can be overcome by measuring pressure–volume loops at several levels of preload,[96] but bedside manipulations of venous return are too invasive to be ethically acceptable. In addition, when applied to intact beings, changes in venous return are associated with reflex sympathetic nervous system activation, which affects the ventricular function that is measured.

These concerns have been addressed by a single-beat method allowing for a direct quantification of the coupling of the RV to the pulmonary circulation.[97] The approach had been initially proposed for the left ventricle.[98] In its principle, the method avoids absolute volume measurements and related technical complexities, to calculate Emax and Ea from instantaneous RV pressure and flow output measurements. As shown in Figure 13-18, a Pmax is estimated from a nonlinear extrapolation of the early- and late-systolic isovolumic portions of the right ventricular pressure curve. This estimated Pmax has been shown to be tightly correlated with Pmax directly measured during a nonejecting beat.[97] A straight line drawn from Pmax to the RV pressure versus relative change in volume curve allows for the determination of Emax. A straight line drawn from the Emax point to the end-diastolic relative volume point determines Ea.

The Emax/Ea ratio as determined by the single-beat method has been shown to be decreased by propranolol and increased by dobutamine, and maintained in the presence of increased Ea due to hypoxic pulmonary vasoconstriction.[97] In fact, Emax increases adaptively to increased Ea in hypoxia, even in the presence of adrenergic blockade, which is compatible with the notion of homeometric adaptation of right ventricular contractility. The method has been used to show that acutely administered prostacyclin does not have a positive inotropic effect as the explanation for the increased cardiac output associated with its use.[99]

Kuehne et al.[100] used magnetic resonance imaging (MRI) together with RV pressure measurements with Pmax calculations to generate pressure–volume loops and Emax and Ea determinations in patients with pulmonary arterial hypertension. As compared to controls, Emax was almost doubled, but Emax/Ea was decreased, indicating insufficient homeometric adaptation and pending RV failure. The importance of RV systolic function adaptation for the preservation of RV–arterial coupling in patients with severe pulmonary hypertension PAH has been confirmed by a study that used conductance catheter measurements of pressure and volume, and the Valsalva maneuver to decrease venous return and generate a family of pressure–volume loops.[101]

Since Emax/Ea can be simplified to a ratio of volumes, Sanz et al. reported on the estimation of RV–arterial coupling estimated by the ratio of stroke volume to end-systolic volume measured by MRI in 139 patients referred for pulmonary hypertension. The resulting "Emax/Ea" was shown to decrease progressively with increasing severity of pulmonary hypertension.[102]

An alternative approach was developed by Elzinga and Westerhof in 1978.[103] The authors described RV pump function curves by plotting mean RV pressure as a function of stroke volume. As shown in Figure 13-19, the pump function curve is built from measurements of mean RV pressure and stroke volume, a calculated maximum pressure at zero stroke volume, and a parabolic extrapolation to a zero pressure stroke volume. In this representation, an increase in preload shifts the curve to greater stroke volumes with no shape change, while an increased contractility leads to a higher maximum pressure with no change in maximum stroke volume. This analysis has been used to explain the more severe RV failure in pulmonary arterial hypertension associated with systemic sclerosis,[104] in agreement with pressure–volume loop-derived estimations of RV–arterial coupling.[101] A derived simplified measure of the adequacy of RV systolic function adaptation to afterload is contractile reserve, defined by the increase in RV systolic pressure during an exercise stress. RV

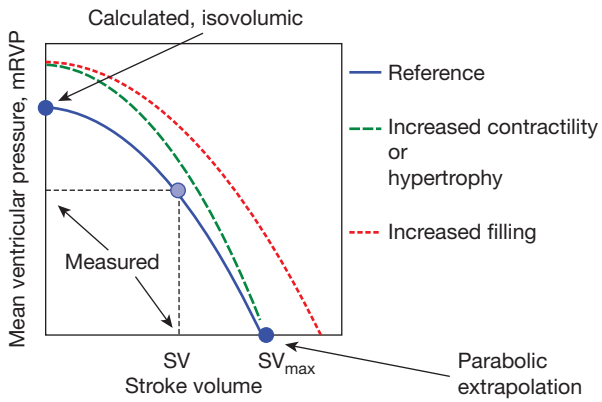

Figure 13-19 Pump function curve defined by mean right ventricular pressure as a function of stroke volume. The zero stroke volume point is calculated from a maximum pressure determination (see Fig. 13-18). The zero pressure point results from a parabolic extrapolation, from measured and zero stroke volume points. *(Data from Elzinga G, Westerhof N. The effect of an increase in inotropic state and end-diastolic volume on the pumping ability of the feline left heart Circ Res. 1978;42:620–628.)*

contractile reserve has been reported to be an important predictor of survival in patients with severe pulmonary hypertension.[105]

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CHAPTER 14

Ventilation, Pulmonary Blood Flow, and Ventilation–Perfusion Relationships

Peter D. Wagner

This chapter and the two succeeding it together share responsibility for presenting the physiological basis of normal pulmonary gas exchange. Gas exchange occurs by an integrated series of gas transport steps between the environmental air we breathe and the Hb molecule of the red cells passing through the pulmonary capillaries. These transport steps are of two types—diffusive and convective, and a number of conceptually separate diffusive as well as convective processes interact to accomplish the gas exchange mission. This is true both for gases that are taken up from the environment into the blood (i.e., O_2 and occasional toxic gases or volatile anesthetics) and for gases that are eliminated from the body (i.e., CO_2 and volatile anesthetic agents).

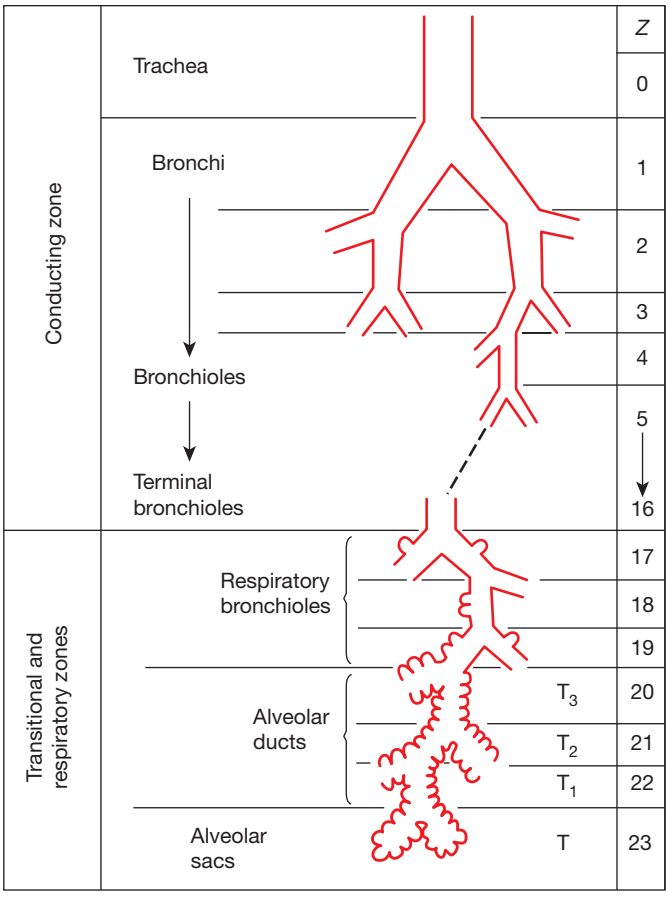
This chapter deals principally with the convective processes and Chapter 16 with those involving diffusion. However, since the two types of process occur simultaneously they are closely linked.

BASIC OUTLINE OF THE GAS EXCHANGE PATHWAY

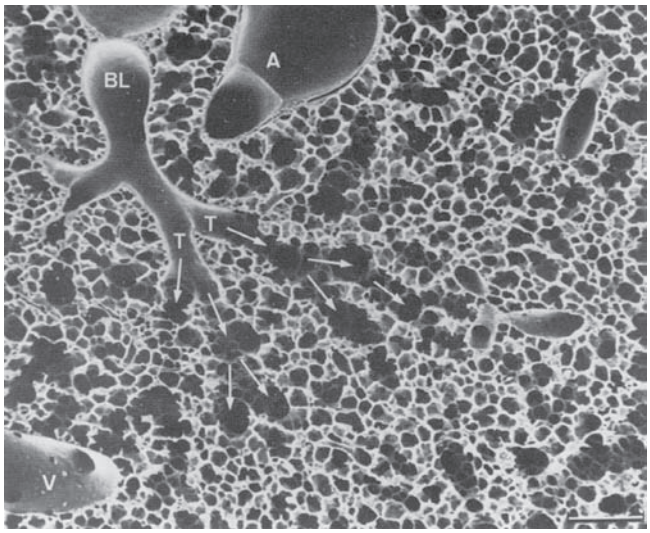
This section dwells on O_2, being the gas of principal physiological interest. However, the pathway components are of course identical for all gases and furthermore do not depend on whether the gas is being taken up (O_2) or eliminated (CO_2). On the other hand, distinct quantitative differences in the uptake or elimination patterns of different gases exist, but those are readily explained by differences in their fundamental physical or chemical properties, and not by transport pathway differences.

To understand the gas transport pathway one must first appreciate the anatomy of the lungs, laid out in detail in Chapter 2. The salient functional features are presented in Figure 14-1.

The chest wall (rib cage and diaphragm) contains muscles that on contraction expand the volume of the chest cavity and thus reduce the hydrostatic pressure of the pleural space, expanding the



A



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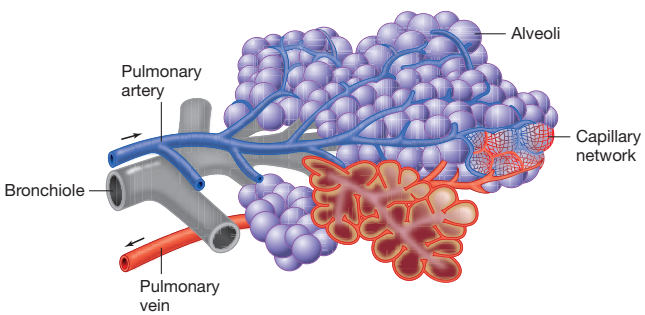
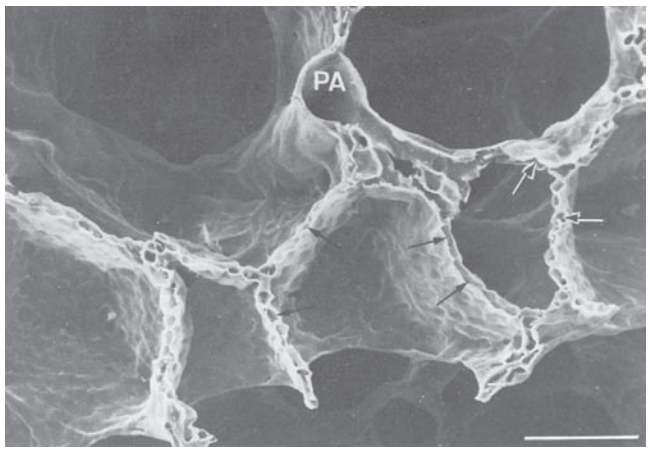
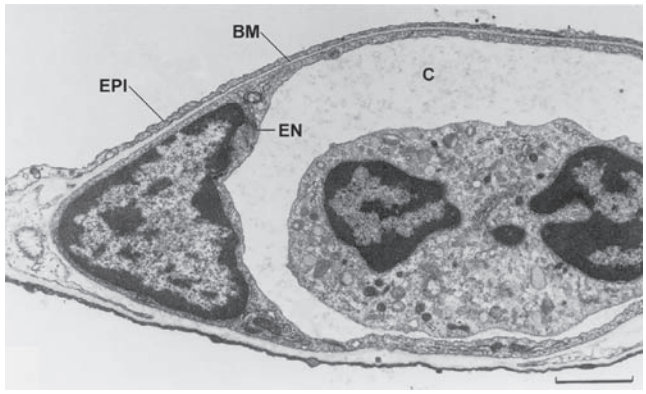


C

Figure 14-1 Principal anatomical features of the lung related to gas exchange. **A** shows the organization of branching airways, mirrored by a photograph of a lung slice showing terminal and respiratory bronchioles and the alveolar parenchyma (see also **B**) (***A.*** *Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg, Springer-Verlag; 1963).* **C** shows how the capillaries are wrapped around alveoli and **D** is a scanning electron micrograph indicating the rich capillary networks in the alveolar walls (PA, pulmonary artery). **E** is a transmission electron micrograph showing the capillaries (C) and the three layers of the blood–gas barrier (EN, endothelium; BM, basement membrane; and EPI, epithelium). (***B, D,*** *and* ***E.*** *Reproduced with permission from Weibel ER. The Pathway for Oxygen. Cambridge, MA: Harvard University Press; 1984.) (continued)*



D



E

Figure 14-1 *(Continued)*

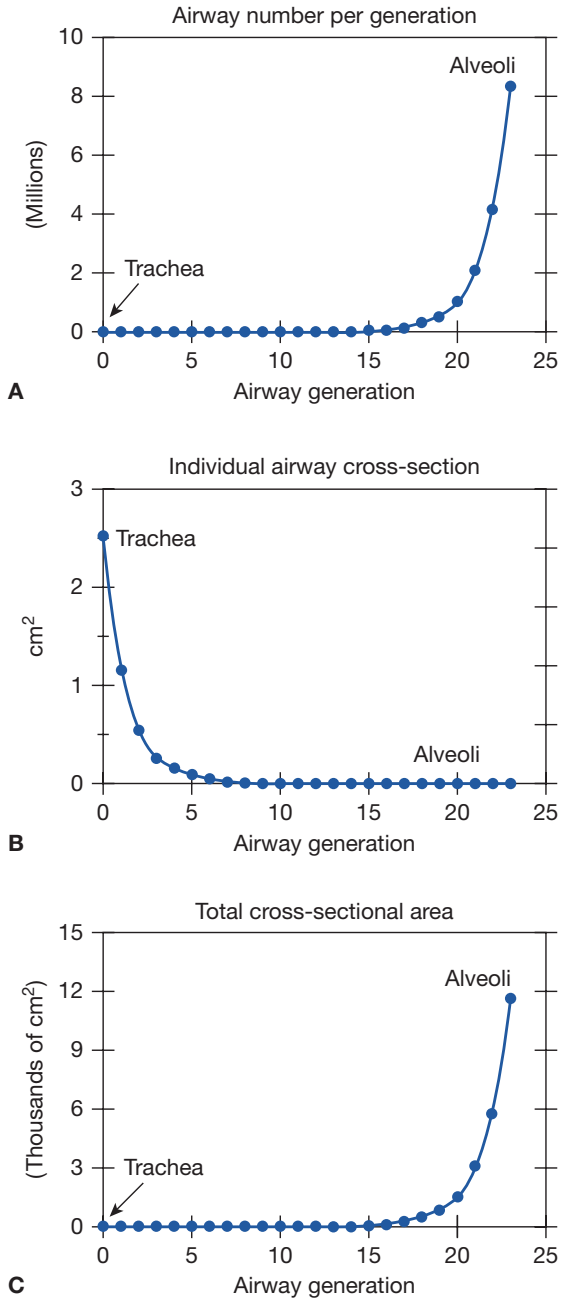


Figure 14-2 Relationship between number (**A**) and cross-sectional area (**B**) of the airways at a given generation. Note that total airway cross-sectional area (**C**) increases extremely rapidly beyond airway generation 15 or so, the beginning of the respiratory zone for gas exchange.

lungs with air drawn in via the mouth and nose. Although there is but a single air passage in the neck (i.e., the trachea), this soon branches into right and left main bronchi. These also divide many times, essentially dichotomously. There are some 16 such orders of branching of these bronchi, resulting in a structure that resembles an inverted deciduous tree without its leaves in winter.[1] With each successive branch the airways become shorter and narrower, but ever greater in number, usually doubling at each branching. Thus, although the cross-sectional area of any one airway becomes smaller with each branching, the greater number of airways more than makes up for loss of individual cross-sectional area such that the sum of cross-sectional areas of all airways of a given generation rises essentially exponentially with each branching (Fig. 14-2). The total volume of gas in these 16 conducting airway generations is called the anatomic or conducting airway dead space, and approximates 1 mL per pound of body weight. After these 16 or so successive branches, the tubular, purely conducting airways begin to show alveolar units in their wall (generations 17–19 or so) and these finally give way to fully alveolated structures (in succession: alveolar ducts, alveolar sacs, and alveoli). There are some 300 million alveoli, each about 300 μm in diameter. They are blind structures so that ventilation has to be accomplished by a tidal, in-and-out process (rather than a flow-through process as for pulmonary blood flow). The alveoli can be seen in Figure 14-1, from a different perspective. For gas exchange to occur, O_2 must be moved from the mouth all the way to the alveoli—it is only within alveoli that gas exchange occurs.

Each alveolus is densely covered in a capillary network, seen from various perspectives in Figure 14-1. This network is closely applied to the alveolar gas space as Figure 14-1 shows, with on average only about 1/2 μm of cellular and interstitial tissue between the blood inside the capillary and the alveolar gas outside.[2] The capillary network is fed by the pulmonary arterial tree which branches alongside the airways in a very similar pattern as the airways. The capillaries then drain into venules that join to form larger and larger vessels, eventually becoming the pulmonary veins that drain oxygenated blood into the left atrium. This coalescence of venous vessels forms a similar branching tree to the pulmonary arteries and airways, but in reverse. The right ventricle is responsible for unidirectional pumping of blood through this vascular system.

The gas exchange pathway from the lips to the left atrium is therefore highly complex structurally, and understanding how gases pass along the pathway requires following the events an O_2 molecule must participate in between the lips and the left atrium.

1. The first step is inspiration of air into the trachea via mouth and nose. Accomplished by inspiratory chest wall muscle contraction which reduces intrathoracic pressure, this step is convective (like water flowing from a region of high to low pressure along a garden hose). All the respired air must pass the trachea but at the first branch point some air goes to the right lung, the rest to the left. At each successive branch point, similar mass-conserving distribution of air must occur between the daughter branches of each parent pathway. Remembering that there are some 23 total branchings from the mouth to the 300 million alveoli, there is a very real risk of quite uneven distribution of that inspired air amongst those alveoli.[3] The principal determinants of how air is distributed at branch points (i.e., between daughter branches) are the mechanical properties of the respiratory system: the compliance (elastic properties), the resistance, and the inertial properties. These concepts are more fully treated in Chapter 10.
2. During normal resting inspiration, flow is laminar in most of the airways. Thus inspired gas develops a parabolic profile due to higher molecular velocities in the center than periphery of the airway (Fig. 14-3). The parabolic "tongue" of inspired gas in Figure 14-3 moves down an airway, while around the tongue is gas remaining from the previous expiration. The tongue therefore has O_2 at a concentration of 21% and essentially no CO_2. The gas around the tongue, having undergone gas exchange during the preceding breath, has about 14% O_2 and 5% CO_2. Consequently, during forward motion of this tongue toward the alveoli, O_2 will diffuse from the tongue to its surrounding gas while CO_2 will diffuse in the opposite direction. This is called Taylor dispersion,[4] and it reduces the forward transport of O_2 produced by the onward convective movement of the tongue. This effect however is considered quite small and is generally not of significance to overall gas exchange.

   Note that if inspiration occurs at high rates as in exercise, such laminar flow may not occur in the larger airways—it may be turbulent and then Taylor dispersion is essentially noncontributory, as the turbulent mixing evens gas concentrations across the airway lumen.
3. Figure 14-2 shows the exponential increase in airway cross-sectional surface area as one proceeds deeper and deeper into the lungs. The significance of this curve is that since the mass flow rate of inspired gas is the same at every generation (because the airways are simply a conducting system), the forward velocity of O_2 molecules falls (since flow rate is the product of velocity and cross-sectional area). As it happens, by about generations 17 to 19, where the alveoli are just beginning to appear, this forward velocity has become so low that passage of O_2 from here on out to the alveoli is heavily dependent on simple gaseous diffusion, not just on continuing convective flow.
4. If alveoli are not equally ventilated with gas (and equally perfused with blood), their alveolar O_2 concentration will differ, as explained later in this chapter. Because adjacent alveoli are so physically close, there can be considerable diffusion of O_2 between such alveoli when their O_2 levels are different. This passive process tends to reduce concentration differences between these alveoli. However, although it can be detected experimentally, it is of probably minor clinical significance. Step 3 (and to some extent Step 4) are responsible for most of the alveolar gas mixing that must occur for gas exchange to take place—that is, the mixing of each breath of newly inspired gas with alveolar gas still present from prior breaths.
5. The heart acts as a massaging pump to further enhance gas mixing into the alveolar gas spaces. Alternate filling and emptying of the cardiac chambers respectively facilitates exhaling and inhaling of airway gas into those alveoli physically close to the heart,[5] but has little effect on more distant alveoli. Although a well-known and easily demonstrated phenomenon, this so-called cardiogenic mixing is probably also of minimal physiological impact for gas exchange.
6. Once the dominant convective and diffusive gas transport steps have brought O_2 from the lips to the alveolar gas spaces, O_2 physically dissolves in the tissues separating alveolar gas from capillary blood, the blood–gas barrier (Fig. 14-1). O_2 then moves by diffusion through the blood–gas barrier and into the plasma. Over 98% of these O_2 molecules diffuse further, that is, into the red cell interior, and then bind rapidly to hemoglobin. The remaining 2% or so remain physically dissolved in the plasma and red cell water.

   This transport process from alveolar gas to hemoglobin is accomplished passively by simple diffusion: No convective forces or active transport processes are involved. The diffusion process is discussed more fully in Chapter 16. In normal lungs at rest, this process is very rapid and causes no O_2 transport limitation.
7. Finally, the red cells are transported convectively by cardiac pumping action out of the pulmonary capillaries and into the pulmonary veins and then to the left atrium, and left ventricle, finally reaching the various body tissues.

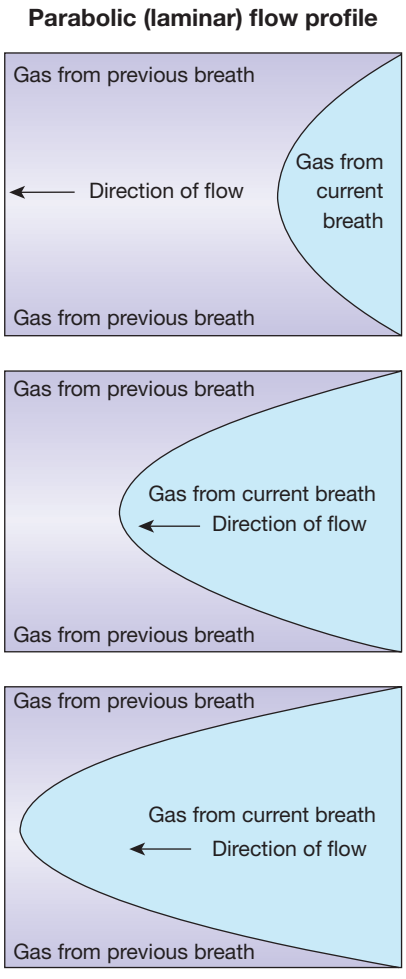


Figure 14-3 The parabolic profile of laminar flow. The three panels indicate sequential points in time during a single inspiration proceeding from right to left. Because the gas remaining from the previous breath has a low oxygen concentration and high CO_2 concentration relative to that of the inspired gas in the current breath, there will be diffusive exchange between the parabolic tongue and the surrounding gas (Taylor dispersion).

POTENTIAL DISRUPTIONS OF THE GAS TRANSPORT PATHWAY

If all the above elements of the transport pathway mentioned previously were functionally perfect, the partial pressure of O_2 (and other gases) would be identical in the gas of all 300 million alveoli and equal to that in systemic arterial blood. The system comes close to perfection in health,[6] but there is never complete equivalence of alveolar and arterial pressures, even in healthy young, normal people. Aging further leads to a progressive impairment of the pathway with arterial P_{O_2} falling from 95 to 100 mm Hg at age 20 to 75 to 80 mm Hg at age 80 or thereabouts.[7] However, alveolar P_{O_2} tends to be invariant with age. Thus, the difference between alveolar and arterial P_{O_2} steadily increases from about 5 to 10 mm Hg to about 20 to 25 mm Hg over this age range. Pulmonary diseases such as asthma, emphysema and bronchitis, fibrosis, pneumonia, and many others can greatly disrupt gas transport to the point of causing death from insufficient tissue O_2 supply.

Consequently, it is essential to have a good understanding of the O_2 transport pathway and what may affect it even in health, in order to appreciate the problems seen in pulmonary diseases.

A traditional view of how to consider abnormalities of the transport pathway has evolved over the years and is very useful as a framework for discussion. It is based upon the end result of gas exchange – the arterial P_{O_2} – and there are different reasons why this variable can fall below normal values.

Four principal potential mechanisms of failure of the O_2 transport pathway can lead to a reduced arterial P_{O_2} (i.e., to arterial hypoxemia):

1. Hypoventilation
2. Diffusion limitation
3. Shunt
4. Ventilation–perfusion ($\dot{V}_A/\dot{Q}$) inequality.

These are the so-called "intrapulmonary" factors that directly cause hypoxemia. Modulating "extrapulmonary" factors are also important. These include changes in inspired O_2 concentration, in total cardiac output, in overall metabolic rate, and in Hb concentration.

The four "intrapulmonary" factors are now defined and discussed.

HYPOVENTILATION

Normal levels of ventilation produce a tightly regulated arterial P_{CO_2} at 40 ± 2 mm Hg in normal subjects with several control systems in place to ensure this (for details, see Chapter 11). However, if overall ventilation is reduced for any reason, alveolar P_{CO_2} ($P_{A_{CO_2}}$), and therefore arterial P_{CO_2}, must rise to maintain constant the elimination of metabolically produced CO_2. Reciprocally, alveolar P_{O_2} ($P_{A_{O_2}}$), and hence arterial P_{O_2}, will fall (and by relatively similar amounts as P_{CO_2} will rise). The alveolar gas equation[8] quantitatively relates $P_{A_{O_2}}$ and $P_{A_{CO_2}}$, and is used to calculate how much $P_{A_{O_2}}$ will change for a change in $P_{A_{CO_2}}$:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{Pa_{CO_2}}{R} + P_{A_{CO_2}} \cdot F_{I_{O_2}} \cdot \frac{(1-R)}{R} \qquad (1)$$

$P_{I_{O_2}}$ and $F_{I_{O_2}}$ are inspired O_2 partial pressure and fractional concentration, respectively, and R is the respiratory exchange ratio, normally 0.8.

Hypoventilation represents a failure of step 1 of the gas transport pathway (see above) and can occur for several reasons: (1) the control centers in the nervous system that regulate ventilation could malfunction due to trauma, diseases, drugs, or anesthetics; (2) there could be neuronal or neuromuscular dysfunction of the nerves supplying the chest wall muscles of respiration; (3) the chest wall muscles could be fatigued, damaged, or paralyzed; or (4) the airways or chest wall could be disrupted from trauma or other mechanical derangement such as compression, or in the case of airways, obstruction.

Conceptually this type of problem is usually thought of as a whole-lung issue, usually with obvious causes, and can be reversed by recognizing the cause and taking appropriate reparative and/or ventilatory supportive steps.

DIFFUSION LIMITATION

Whereas diffusive transport plays a recognizable, if small, role within the airways and alveolar gas (see above), the concept of diffusive limitation affecting arterial P_{O_2} is more usually associated with transport step 6 – diffusion of O_2 from alveolar gas into the capillary and red cell.

This topic is specifically the focus of Chapter 16 and is not dealt with here. Indeed, the ensuing discussion of other factors sets aside diffusion limitation of O_2 transport for the sake of simplicity and assumes that the diffusive exchange of O_2 (and CO_2) between alveolar gas and capillary blood proceeds to completion within a single red cell's passage through the pulmonary microcirculation. This is reasonable under most conditions. Diffusion limitation in health is seen at sea level in some but not all athletes[9] but only at or near maximal exercise. It is universally seen in normal subjects exercising at altitude.[10,11]

SHUNT

A shunt is a blood pathway that does not allow any contact between alveolar gas and red cells, so that no gas exchange occurs in the affected region. Consequently, blood passes through a shunt maintaining a mixed venous blood composition. When this blood reaches pulmonary veins, the left atrium and eventually arterial blood, it mixes with other blood that has undergone alveolar gas exchange. The result is a fall in arterial P_{O_2} and potentially an increase in arterial P_{CO_2} (arterial P_{CO_2} may not increase if the patient raises his or her level of ventilation, but hypoxemia will persist).

Classical pathophysiological scenarios giving rise to shunts are: (1) pulmonary edema, which fills alveoli with fluid, thereby abolishing their ventilation and any gas exchange; (2) alveolar filling with cellular and micro-organismal debris as in pneumonia, with the same result as in edema; (3) collapse of a region of lung due to pneumothorax, gas absorption distal to a fully obstructed airway, or to external compression; (4) rarely, the presence of abnormal arteriovenous vascular channels in the lungs, that can occur in, for example, hepatic cirrhosis; and (5) direct right-to-left vascular communications at the level of the heart or great (extrapulmonary) blood vessels.

VENTILATION–PERFUSION ($\dot{V}_A/\dot{Q}$) INEQUALITY

The exquisite and complex branching architecture of the airways and of the blood vessels makes the lungs very susceptible to the potential problem of nonuniform distribution of alveolar ventilation and of pulmonary blood flow. Whenever alveoli are ventilated at less than average rates, for example if their feeding airways become partially obstructed for any reason, the ratio of ventilation to blood flow ($\dot{V}_A/\dot{Q}$ ratio) will fall (assuming their blood flow does not fall similarly). In certain other conditions, lung regions may suffer a reduction in local blood flow rather than ventilation, so that the $\dot{V}_A/\dot{Q}$ ratio rises above the average value in those areas.

Whenever there is a range of $\dot{V}_A/\dot{Q}$ ratios in a lung such that the $\dot{V}_A/\dot{Q}$ ratio is not identical everywhere, it is said that $\dot{V}_A/\dot{Q}$ inequality exists. The pathological cause of $\dot{V}_A/\dot{Q}$ inequality does not matter in this definition, nor whether the problem originates in the airways or blood vessels. The principal concept is that, compared to a lung having the same total alveolar ventilation and blood flow, a lung that has $\dot{V}_A/\dot{Q}$ inequality will exchange (all) gases in an inefficient manner.[12] The result is hypoxemia and, potentially, hypercapnia (raised arterial P_{CO_2}). A large section of this chapter presents the physiological reasons for this effect of $\dot{V}_A/\dot{Q}$ inequality.

Understanding of $\dot{V}_A/\dot{Q}$ inequality can be demanding, but no matter what its pathologic origins, the concepts are similar. $\dot{V}_A/\dot{Q}$

inequality can occur at many different scales. Not uncommonly, it can be manifest on a large scale as differences between the right and left lungs. Classical examples of this include unilateral atelectasis, pneumothorax, pulmonary embolus, or pneumonia. All these are relatively common phenomena that can lead to severe gas exchange disturbances. At the other end of the scale, there can be $\dot{V}_A/\dot{Q}$ ratio differences between essentially adjacent alveoli. However, research has shown that small groups of contiguous alveoli can maintain functional homogeneity of $\dot{V}_A/\dot{Q}$ ratios via rapid gas diffusion rates, possibly augmented by collateral ventilation and/or blood flow.[13] It is likely that all alveoli distal to individual respiratory (or perhaps terminal) bronchioles can retain functional homogeneity for gas exchange through these mechanisms.[14]

In between these two extremes of scale, vascular or airway obstruction at all levels will produce $\dot{V}_A/\dot{Q}$ inequality that, depending on how widespread it is, causes hypoxemia and potentially hypercapnia.

Even the young normal lung usually contains $\dot{V}_A/\dot{Q}$ inequality, which explains the 5 to 10 mm Hg P_{O_2} difference between alveolar gas and arterial blood generally observed in healthy young subjects.[15] There are several mechanisms for the existence of such $\dot{V}_A/\dot{Q}$ inequality.

Gravity-Based Inequality

Ventilation, and, even more so, blood flow are unevenly distributed in a manner systematically influenced by gravity.[6,16] This is due respectively to the weight of the lungs and of the blood in the blood vessels. Thus, dependent lung regions receive far more blood flow than nondependent regions, a finding that is in concept independent of body position. It turns out that the gravitational gradient in blood flow considerably exceeds that of ventilation. As a result, the nondependent lung regions are of higher than average $\dot{V}_A/\dot{Q}$ ratio, and the dependent regions are of lower than average $\dot{V}_A/\dot{Q}$ ratio.[6] Average $\dot{V}_A/\dot{Q}$ ratio is about 1.0, because total alveolar ventilation and blood flow are similar. At the apex of the upright human lung, the $\dot{V}_A/\dot{Q}$ ratio is about 3; at the base it is about 0.6, 5-fold lower. There is a smooth gradation between the two extremes as depicted in Figure 14-4. This large-scale

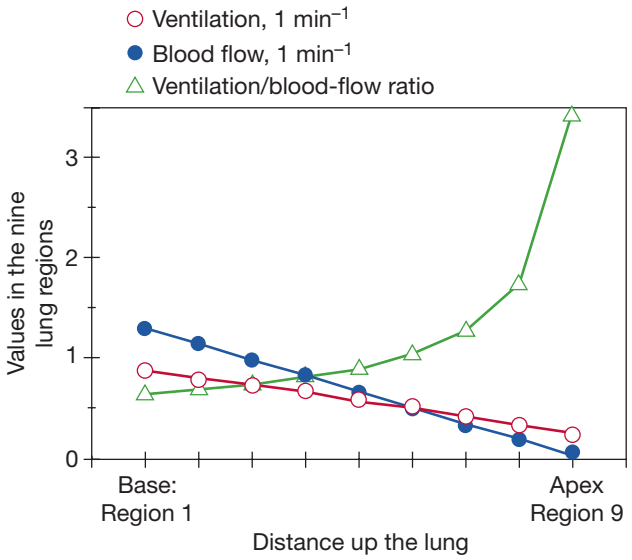


Figure 14-4 Topographical relationships between ventilation and blood flow as a function of distance up and down the upright lung (divided into nine contiguous regions). Although both ventilation and blood flow are higher at the base than at the apex, the ventilation–perfusion ratio ($\dot{V}_A/\dot{Q}$) rises exponentially from the bottom to the top of the lung. *(Adapted with permission from West JB. Ventilation/blood flow and gas exchange, 5th ed. Chicago, IL. Blackwell Scientific Publications; 1990.)*

apex-to-base gradient in $\dot{V}_A/\dot{Q}$ ratios does not produce more than about a 4 mm Hg drop in arterial P_{O_2} (compared to expectations in the absence of this phenomenon), and thus a 4 mm Hg alveolar–arterial P_{O_2} difference.[6]

Fractally Based $\dot{V}_A/\dot{Q}$ Inequality

The branching airway and blood vessel structure of the lung constitutes a fractal system that is innately susceptible to $\dot{V}_A/\dot{Q}$ inequality independent of gravity.[17] A fractal system is one in which the geometric pattern (e.g., of airway branching) is repeated at ever smaller scales. In the case of the airway tree it means in essence that the division of an airway into two "daughter" branches is a repeating feature from the large to the small airways. With some 23 sequential orders of branching, very small random inequalities in gas or blood flow distribution repeated at each branch point of the system can rapidly escalate into very significant degrees of nonuniform ventilation or blood flow. To illustrate, consider a branching system of just 16 dichotomous sequences—at each of the 16 branch points, air is not precisely split 50/50 between each daughter pair. Rather, suppose a 49%/51% split—a nonuniform effect of trivial proportions at any one airway branch. The most poorly ventilated regions (receiving 49% of the split at every one of the 16 branchings) end up with only about half as much ventilation as the best ventilated regions that receive 51% of the split at each branch.

Unless the fractal structure somehow distributes both ventilation and blood flow in a correlated manner to preserve $\dot{V}_A/\dot{Q}$ ratios (even as $\dot{V}_A$ or $\dot{Q}$ individually vary), significant hypoxemia could result. Understanding the consequences of the fractal nature of the lung is a topic of much current interest. It appears that there must be correlation of $\dot{V}_A$ with $\dot{Q}$ since the large potential for fractally based hypoxemia is not generally realized.

Longitudinally Based Inequality

As airways and blood vessels progressively narrow with each branch point, resistance to gas and blood flow increases. Not all alveoli receive gas or blood from airways that have gone through the exact same number of branchings. Hence, some alveoli will be more and some will be less distant from the mouth. Such simple principles suggest the possibility of reduced $\dot{V}_A$ and/or $\dot{Q}$ of those alveoli further from the mouth compared to more proximal alveoli, and therefore the chance of a central to peripheral, or longitudinal, gradient in ventilation and blood flow. Although not universally observed, there is a fair amount of evidence that such inequality exists,[18] but its contribution to gas exchange is hard to establish. To the extent that similar physical principles apply to both gas and blood flow in the present context, one can theorize that more distant alveoli have both less ventilation and blood flow, so that again there is a natural tendency to preserve the $\dot{V}_A/\dot{Q}$ ratio between central and peripheral regions.

Anatomically Based Inequality

Another potential reason for nonuniform gas or blood flow distribution is intrinsic anatomical differences between lung regions. Perhaps the best example is in the dog and horse where, independent of body position in relation to gravity, the dorsal regions of the lower lobes often can be shown to have an unduly high share of total pulmonary perfusion. This tendency, presumably based on the overall branching architectural differences between lobes or within lobes, becomes important in concept when patients are moved from one body position to another, in order to best understand consequent changes in gas exchange.[19]

Collateral Ventilation and Blood Flow

To this point, a picture has been painted of a branching architecture that has no lateral connections between either adjacent airways or

blood vessels at any level of branching. Such lateral connections can exist at several airway levels from large airways down to alveoli.[13,20] This is a species-dependent phenomenon, so that while the pig has little or no such collateral pathway structures, the dog has extensive collateral ventilatory channels. Humans are somewhere between these extremes.

Whatever the evolutionary pressure for collateral channel development, the ability to move gas around obstructions in airways by the use of collateral channels appears to be a useful property of human lungs. This is because total airway obstruction in the absence of collateral channels often leads to rapid alveolar gas absorption into the blood from the alveoli distal to the obstructed airway, and this in turn leads to atelectasis and therefore vascular shunts and hypoxemia. Remarkably, chronic human lung diseases typified by airway obstruction – chronic obstructive pulmonary disease (COPD), asthma – produce $\dot{V}_A/\dot{Q}$ inequality due to presence of poorly ventilated areas, but only uncommonly lead to true shunts.[21,22] The likely explanation for the paucity of shunts in COPD and asthma is the existence of collateral ventilation.

Collateral ventilation in man therefore appears to be a naturally occurring structural phenomenon that can to some extent counteract the gas exchange consequences of diseases.

Collateral perfusion must also occur in the alveolar capillary network. This is deduced simply from the richly interconnecting microvascular network that has the potential to allow blood to flow easily around microvascular obstructions into adjacent vessels. Just how much collateral blood flow potential exists at a larger scale is not clear, being difficult to study. However, well-documented connections occur between the bronchial and pulmonary circulations,[23] creating a different kind of collateral circulatory network. The importance of this connection is evident when the pulmonary artery is either absent or embolized. Then, the bronchial circulation expands considerably and can support function of the affected lung regions long term.

Reactive Vasoconstriction and Bronchoconstriction

The distribution of ventilation or blood flow in the lung can be modified by vasoreactive or bronchoreactive functional changes that appear triggered by changes in alveolar gas composition. The most well-documented phenomenon is that of hypoxic pulmonary vasoconstriction.[24,25] Here, in response to local alveolar hypoxia produced by locally reduced ventilation, local pulmonary arterial constriction reduces blood flow in the hypoxic region. Whether this system developed to counteract disease or to cope with intrauterine life and the abrupt transition to air-breathing is arguable, although most people favor the latter explanation.

Irrespective of the reasons, the effect of hypoxic vasoconstriction is to help return the local ratio of ventilation to blood flow towards normal. This automatic effect (mediated by O_2-sensitive potassium channels in pulmonary arterial smooth muscle cells) is rarely able to fully restore $\dot{V}_A/\dot{Q}$ ratios to normal, but even partial improvements in $\dot{V}_A/\dot{Q}$ ratio facilitate gas exchange significantly. The negative aspect of hypoxic vasoconstriction is a rise in pulmonary vascular resistance. If this is substantial and protracted over time, pulmonary arterial hypertension can develop, eventually leading to right heart failure. However, factors other than hypoxic vasoconstriction are then also generally present – microvascular destruction and alveolar distortion – and these may be more important to heart failure than hypoxia per se. However, hypoxic vasoconstriction has provided a rationale for enriched O_2 therapy in patients with chronic disease to reduce the severity, or to delay the progression, of pulmonary hypertension.

To a much less obvious extent, a counterpart to hypoxic vasoconstriction occurs in the airways: hypocapnic bronchoconstriction.[26] Here, especially when pulmonary embolism occurs, the $\dot{V}_A/\dot{Q}$ ratio in the embolized area rises due to loss of blood flow from vascular obstruction. This increase in $\dot{V}_A/\dot{Q}$ ratio leads to a lower local P_{CO_2} (see below), which causes bronchoconstriction in the local area. This reduces local ventilation and thus tends to normalize the local $\dot{V}_A/\dot{Q}$ ratio. Radioactive tracer ventilation scans may show evidence of this as a modest reduction in the ventilation of embolized regions.

THE $\dot{V}_A/\dot{Q}$ RATIO AND GAS EXCHANGE

To this point, much space has been given to the concepts underlying the distribution of ventilation ($\dot{V}_A$), blood flow ($\dot{Q}$), and hence their ratio, $\dot{V}_A/\dot{Q}$. The reason for this lies in the importance of $\dot{V}_A/\dot{Q}$ ratios to the basic function of the lung—to exchange O_2 and CO_2 between the blood and the air. $\dot{V}_A/\dot{Q}$ inequality, no matter what its physiological basis or pathological cause, interferes with gas exchange and causes hypoxemia and sometimes hypercapnia.

The following section will explain the relationship of $\dot{V}_A/\dot{Q}$ inequality to gas exchange. The subject is complex and must be considered at several "concentric" levels. To start, we will consider how the $\dot{V}_A/\dot{Q}$ ratio in a small local lung region controls local P_{O_2}, P_{CO_2}, and therefore how much O_2 and CO_2 are exchanged in that region. This isolated approach requires at first some key assumptions. Removing the restrictions of these assumptions is the next "concentric" step in understanding $\dot{V}_A/\dot{Q}$ relationships. A final outer shell of modifying factors that can further affect gas exchange forms a third level of the analysis.

THE $\dot{V}_A/\dot{Q}$ RATIO OF A SMALL HOMOGENEOUS UNIT OF LUNG AND GAS EXCHANGE

How the $\dot{V}_A/\dot{Q}$ ratio determines gas exchange is best explained by considering the flux of O_2 from the environment into and out of the alveolus with each breath as well as from the alveolar gas into the capillary blood. Equations that describe these processes and follow the fundamental principle of mass conservation must be used. Original descriptions of these appeared more than 50 years ago.[8,27–30] Figure 14-5 provides a model of the lung and specifies the total ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$) of this model together with the key locations of the relevant O_2 levels. It can be used to consider a small homogeneous unit of lung.

Convention has long considered ventilation over a period of time as a constant in spite of the tidal nature of breathing. This is in fact a very reasonable approximation that has stood the test of

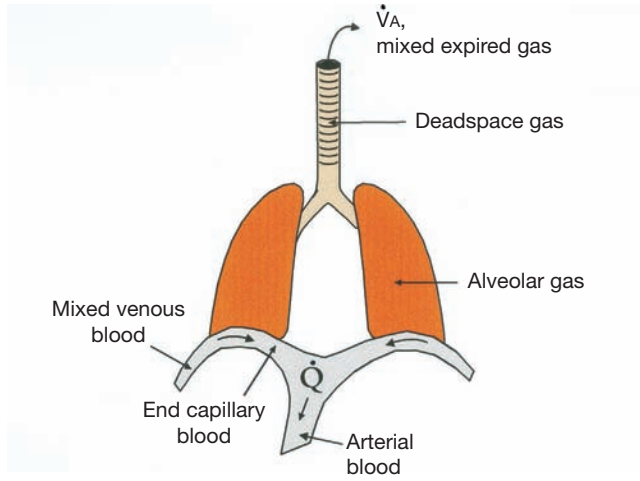


Figure 14-5 Conceptual model of the lungs indicating main sites in which oxygen and carbon dioxide partial pressures are different, together with the principal convective processes accomplishing gas exchange, ventilation ($\dot{V}_A$), and blood flow ($\dot{Q}$).

time. Similarly, blood flow is considered constant, and this too has proved reasonable. If $\dot{V}_A$ and $\dot{Q}$ are therefore considered as alveolar minute ventilation and blood flow of a small homogeneous unit respectively, the following simple mass conservation equations can be written for O_2:

$$\dot{V}_{O_2} = \dot{V}_I \cdot F_{I_{O_2}} - \dot{V}_A \cdot F_{A_{O_2}} \quad (2)$$

and

$$\dot{V}_{O_2} = Q \cdot Cc'_{O_2} - \dot{Q} \cdot C\bar{v}_{O_2} \quad (3)$$

In these equations, $\dot{V}_{O_2}$ is amount of O_2 transferred from the environment into the blood per unit time and, given the assumption of steady state conditions, this, when summed over all such units in the lungs, equals metabolic rate. $\dot{V}_I$ and $\dot{V}_A$ are, respectively, the inspired and expired volumes of gas respired per minute, less than the amount remaining in the conducting airways. As anticipated, $\dot{V}_I$ and $\dot{V}_A$ are close to being identical, otherwise the lungs would blow up or collapse in a short period of time. However, $\dot{V}_I$ does not generally equal $\dot{V}_A$ because slightly more O_2 is consumed per minute than is CO_2 produced (i.e., the respiratory quotient is in general not 1.0). Thus, $\dot{V}_A = \dot{V}_I - \dot{V}_{O_2} + \dot{V}_{CO_2}$. Mostly, the inequality of $\dot{V}_I$ and $\dot{V}_A$ can be ignored because the difference is only about 1%—if $\dot{V}_I$ is 6 L/min and $\dot{V}_{O_2}$ is 300 mL/min with $\dot{V}_{CO_2}$ at 240 mL/min, $\dot{V}_A$ = 5.94 L/min. Although this small difference is not ignored in research applications, it can be for the present purposes, so that $\dot{V}_I$ is replaced by $\dot{V}_A$ in Equation (1), simplifying the analysis. In Equation (1), $F_{I_{O_2}}$ and $F_{A_{O_2}}$ are the fractional concentrations (F) of O_2 in inspired (I) and exhaled alveolar (A) gas, respectively, from a small unit in Figure 14-5. In Equation (2), Cc'_{O_2} and $C\bar{v}_{O_2}$ are the O_2 concentrations (C) in the oxygenated end capillary blood leaving (c′) and the deoxygenated blood entering ($\bar{v}$) the vasculature respectively. The abbreviation c′ stands for end capillary blood; $\bar{v}$ for mixed venous (pulmonary arterial) blood.

Since Equations (1) and (2) both describe the same O_2 flux rate ($\dot{V}_{O_2}$) they may be set equal to each other:

$$\dot{V}_A [F_{I_{O_2}} - F_{A_{O_2}}] = \dot{Q} [Cc'_{O_2} - C\bar{v}_{O_2}] \quad (4)$$

and rearranged so that:

$$\dot{V}_A/\dot{Q} = [Cc'_{O_2} - C\bar{v}_{O_2}]/[F_{I_{O_2}} - A_{O_2}] \quad (5)$$

It should further be noted that because diffusion equilibration of O_2 transfer across the alveolar–capillary membrane is assumed to be complete, alveolar P_{O_2} and end capillary P_{O_2} are identical. Hence, the relationship between $F_{A_{O_2}}$ and Cc'_{O_2} is uniquely dictated by the O_2-Hb dissociation curve such that knowing $F_{A_{O_2}}$ allows us to determine directly Cc'_{O_2} (or vice versa).

Equation (5) is very revealing and explains directly the role of the $\dot{V}_A/\dot{Q}$ ratio in governing alveolar gas exchange. This equation states that for a given set of what may be called boundary conditions (i.e., composition of inspired gas and mixed venous blood, represented here by $F_{I_{O_2}}$ and $C\bar{v}_{O_2}$, respectively) and for a known O_2–Hb dissociation curve, alveolar (and thus end capillary) P_{O_2} is uniquely determined by the ratio of alveolar ventilation ($\dot{V}_A$) to blood flow ($\dot{Q}$).

Under the given assumptions, summarized as (1) continuous and constant ventilation and blood flow; (2) steady state conditions; (3) diffusion equilibration of alveolar–capillary exchange; and (4) equality of inspired and expired ventilation, equations identical in construct to Equation (5) can be written for any gas being exchanged by the lung.

For CO_2, this produces Equation (6):

$$\dot{V}_A/\dot{Q} = [C\bar{v}_{CO_2} - Cc'_{CO_2}]/[F_{A_{CO_2}} - F_{I_{CO_2}}] \quad (6)$$

The order of bracketed terms on the right is reversed to maintain positive numbers, since CO_2 is being eliminated from the blood. Of course, $F_{I_{CO_2}}$ is essentially zero and thus drops out of the equation.

Unfortunately, neither Equation (5) nor (6) is amenable to simple quantitative solutions, because of the complexity of the O_2 and CO_2 dissociation curves. The equations are however readily explored by appropriate computerized numerical analyses.[31–35] Using such programs, one can explore the relationship between $\dot{V}_A/\dot{Q}$ ratio and alveolar P_{O_2} and P_{CO_2}, and this is done in Figure 14-6. These relationships are important because they indicate what degrees of $\dot{V}_A/\dot{Q}$ abnormality are required to affect gas exchange for both O_2 and CO_2. The four panels of Figure 14-6 show alveolar P_{O_2} and P_{CO_2} as well as end capillary O_2 and CO_2 concentrations. The latter better reflect total gas exchange as a function of $\dot{V}_A/\dot{Q}$ ratio. Specific conditions for Figure 14-6 are that mixed venous blood P_{O_2} is 40 mm Hg and P_{CO_2} 45 mm Hg, normal resting values. Also, inspired gas is room air, and [Hb] is 15 g/dL. In each panel, the three solid circles are positioned at the normal $\dot{V}_A/\dot{Q}$ ratio (of about 1.0) and at $\dot{V}_A/\dot{Q}$ ratios 10 times greater and less. All four relationships are highly non-linear. Focusing on the two lower panels, it is evident for O_2 that a 10-fold reduction in $\dot{V}_A/\dot{Q}$ greatly reduces local O_2 transport, whereas a 10-fold increase barely improves it. Furthermore, as $\dot{V}_A/\dot{Q}$ falls even lower than 0.1, there is little further loss in O_2 transport. There is however little protection against a fall in $\dot{V}_A/\dot{Q}$ below 1.0, because the curve is very steep below a $\dot{V}_A/\dot{Q}$ of 1.0, as the lower left panel shows. For CO_2, the curves are opposite in slope (P_{CO_2} falls as $\dot{V}_A/\dot{Q}$ increases).

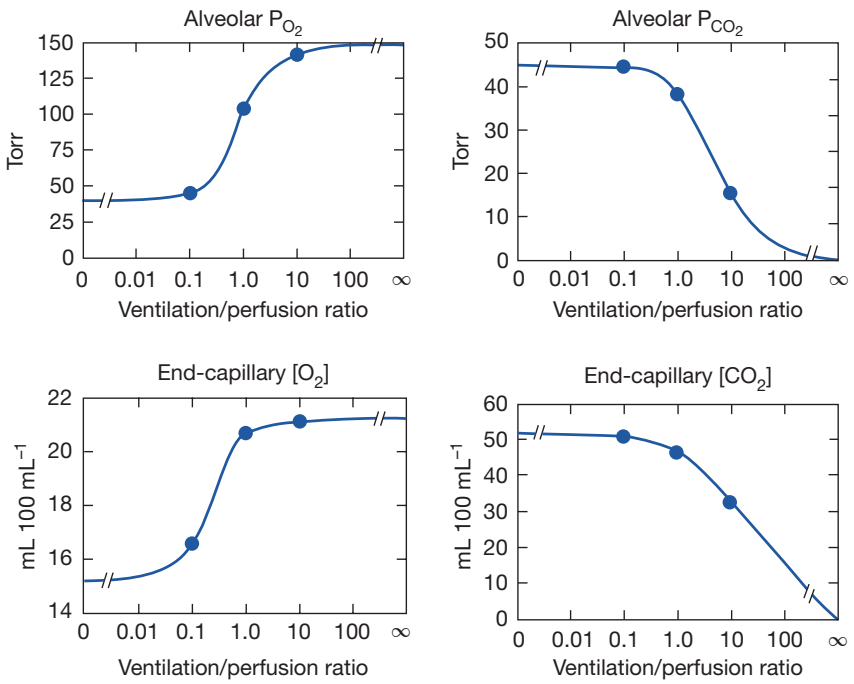


Figure 14-6 Calculated relationships between alveolar P_{O_2} and P_{CO_2} and the ventilation–perfusion ratio *(top panels)* and their corresponding end-capillary blood concentrations *(lower panels)*. The three solid circles in each case represent values for ventilation–perfusion ratios of 0.1, 1.0, and 10. (See text for further details.)

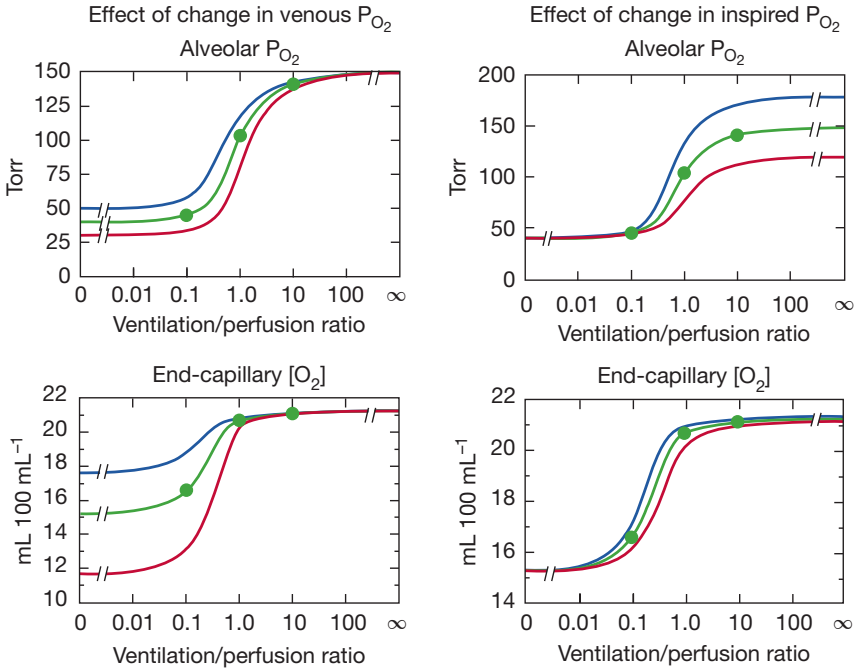


Figure 14-7 Effects of changes in mixed venous P_{O_2} *(left panels)* or inspired P_{O_2} *(right panels)* on alveolar P_{O_2} and associated end-capillary oxygen concentrations. Note that changes in venous P_{O_2} mostly affect values associated with low ventilation–perfusion ratios, whereas changes in inspired P_{O_2} affect units throughout the $\dot{V}_A/\dot{Q}$ range, especially those with medium to high $\dot{V}_A/\dot{Q}$ ratios.

However, unlike the case for O_2, there is little difference between a $\dot{V}_A/\dot{Q}$ of 1.0 and a 10-fold reduction, whereas an increase in $\dot{V}_A/\dot{Q}$ considerably reduces alveolar P_{CO_2} and end capillary CO_2 concentration. The reason for the differences between O_2 and CO_2 lies mainly in the slopes of their dissociation curves: that for CO_2 is about 10-fold greater than that for O_2. It has been shown that the higher the slope of the dissociation curve (or equivalently for an anesthetic gas, its solubility) the more it is sensitive to areas of high $\dot{V}_A/\dot{Q}$. The lower the slope or solubility, the more the gas is affected by areas of low $\dot{V}_A/\dot{Q}$. Consequently, areas of low $\dot{V}_A/\dot{Q}$ predictably cause more reduction in arterial P_{O_2} than increase in arterial P_{CO_2}. Although Figure 14-6 is true strictly only for the stated "boundary" conditions (i.e., mixed venous blood and inspired gas composition), the principles hold even for different such conditions, as shown in Figure 14-7 for O_2. The left panels illustrate how changes in mixed venous P_{O_2} alone will affect alveolar P_{O_2} and end capillary $[O_2]$ via Equation (4). The right panels correspondingly show how change in inspired P_{O_2} affects O_2. Venous P_{O_2} is selected at 30, 40, and 50 mm Hg, and inspired P_{O_2} is chosen to be 120, 150, and 180 mm Hg. Changes in venous P_{O_2} dramatically affect P_{O_2} and $[O_2]$ in unventilated and poorly ventilated regions as well as regions approaching normal, but have no real effect on high $\dot{V}_A/\dot{Q}$ alveoli. Altering inspired P_{O_2} (but not venous) has the converse effect if P_{O_2} is examined (top right panel), but, due to the nonlinear shape of the O_2–Hb dissociation curve, effects on $[O_2]$ are minimal in high $\dot{V}_A/\dot{Q}$ areas, small in very low $\dot{V}_A/\dot{Q}$ areas, and more significant between $\dot{V}_A/\dot{Q}$ ratios of 0.1 and 1.0 (bottom right panel). This figure shows how the inspired and mixed venous "boundary conditions" alter the magnitude (but not basic patterns) of alveolar gas exchange.

If one returns to the normal boundary conditions ($P\bar{v}_{O_2}$ = 40 mm Hg, $P_{I_{O_2}}$ = 150 mm Hg), one can explore the consequences of $\dot{V}_A/\dot{Q}$ inequality on gas exchange. In reality, the complex structure of the lungs defies a simple analysis but conceptually even a two-compartment model is an invaluable aid to understanding this conceptually difficult area.

Figure 14-8 shows such a simple two-compartment model in three configurations: (1) each compartment equally ventilated and perfused such that there is no $\dot{V}_A/\dot{Q}$ inequality; (2) the left compartment hypoventilated due to airway obstruction, causing $\dot{V}_A/\dot{Q}$ inequality; and (3) the left compartment hypoperfused from vascular obstruction. Table 14-1 shows the corresponding O_2 and CO_2 calculations for each compartment. Specific assumptions common to all three models are (1) the mixed venous P_{O_2} remains at 40 mm Hg; inspired P_{O_2} is constant at 150 mm Hg; total alveolar ventilation summed over both compartments is constant as is total blood flow, both taken to be 6 L/min; [Hb] is constant at 15 g/dL. Further, airways obstruction reduces L-hand compartmental ventilation from 3.0 to 0.3 L/min, redistributing the balance to the R-hand compartment. Vascular obstruction is of the same order as the right panel of the figure shows. Note that for both obstructive models, one compartment has developed a $\dot{V}_A/\dot{Q}$ ratio less than average and the other a $\dot{V}_A/\dot{Q}$ ratio greater than average, irrespective of the location of the obstruction.

Using the curves of Figure 14-6, for $P\bar{v}_{O_2}$ = 40 mm Hg and $P_{I_{O_2}}$ = 150 mm Hg, $P\bar{v}_{CO_2}$ = 45 mm Hg and $P_{I_{CO_2}}$ = 0 mm Hg, alveolar P_{O_2} and P_{CO_2} are listed for each compartment of Figure 14-8 in Table 14-1.

In Table 14-1, alveolar diffusion equilibration is assumed to be complete such that alveolar P_{O_2} ($P_{A_{O_2}}$) equals end capillary P_{O_2} (Pc'_{O_2}); the same holds for P_{CO_2}. In each obstructive model, the low $\dot{V}_A/\dot{Q}$ compartment has a lower-than-average P_{O_2} and higher-than-average P_{CO_2} as Figure 14-6 dictates. The converse is seen for the compartment of high $\dot{V}_A/\dot{Q}$ ratio. Corresponding end capillary O_2 and CO_2 concentrations are also listed in Table 14-1.

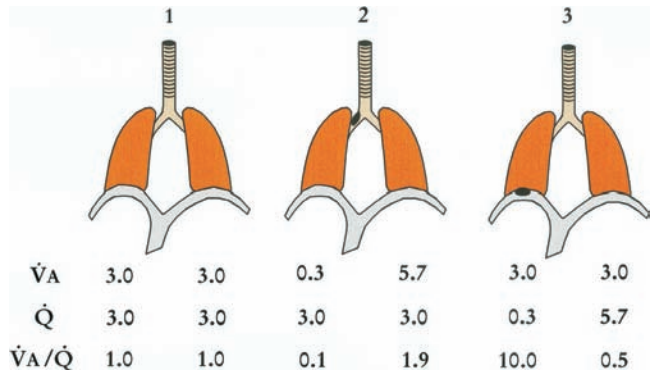


Figure 14-8 Three two-compartment models of ventilation–perfusion relationships. *Model 1* represents an ideal lung without ventilation–perfusion mismatch. *Model 2* represents a lung in which one compartment has a 90% reduction in its alveolar ventilation due to airway obstruction, and *Model 3* is a lung in which one compartment has a 90% reduction in capillary blood flow due to vascular obstruction. Ventilation, blood flow, and ventilation–perfusion ratio of each compartment are indicated. Total ventilation and total blood flow remain the same among the three models. (See text for further details.)

TABLE 14-1 O_2 and CO_2 Calculations for the Models of Figure 14-8

	Normal		Airway Obstruction Model		Vascular Obstruction Model	
	Left	Right	Left	Right	Left	Right
$P_{A_{O_2}}$, Pc'_{O_2}, mm Hg	103.0	103.0	45.0	120.0	142.0	77.0
$P_{A_{CO_2}}$, Pc'_{CO_2}, mm Hg	38.8	38.8	44.9	32.5	15.5	42.7
Cc'_{O_2}, mL·dL^{-1}	20.7	20.7	16.7	20.9	21.1	20.1
Cc'_{CO_2}, mL·dL^{-1}	46.9	46.9	50.8	43.9	32.5	48.8
Ca_{O_2}, mL·dL^{-1}	20.7		18.8		20.1	
Ca_{CO_2}, mL·dL^{-1}	46.9		47.5		48.0	
Pa_{O_2}, mm Hg	103.0		55.0		77.0	
Pa_{CO_2}, mm Hg	38.8		39.0		40.9	
$P\bar{A}_{O_2}$, mm Hg	103.0		118.0		110.0	
$P\bar{A}_{CO_2}$, mm Hg	38.8		33.7		29.2	
Total O_2 exchange, mL·min^{-1}	328.0		212 (65%)		294 (90%)	
Total CO_2 exchange, mL·min^{-1}	270.0		234 (87%)		203 (75%)	
$P\bar{A}_{O_2}$—$P_{A_{O_2}}$, mm Hg	0.0		63.0		33.0	
$P_{A_{CO_2}}$—$P\bar{A}_{CO_2}$, mm Hg	0.0		5.0		11.7	

The question is what will the mixed arterial blood and mixed expired gas O_2 and CO_2 levels change to as a result of obstruction of one compartment, and how will this affect the ability of the total system to exchange O_2 and CO_2? To answer these questions one applies simple mixing questions to the two individual compartments [left (L) and right (R)]:

For O_2 :

$$P\bar{A}_{O_2} = (P_{AO_{2L}} \cdot \dot{V}_{A_L} + P_{AO_{2R}} \cdot \dot{V}_{A_R})/(\dot{V}_{A_L} + V_{A_R})$$

$$Ca_{O_2} = (Cc'_{O_{2L}} \cdot \dot{Q}_L + Cc'_{O_{2R}} \cdot \dot{Q}_R)/(\dot{Q}_L + \dot{Q}_R) \quad (7)$$

For CO_2, identical equations apply. These mixing equations conserve mass and use the principle that the two gas or blood streams combine in a manner proportional to their relative ventilation and blood flow, respectively. Table 14-1 lists the results of these calculations, giving mixed alveolar partial pressure ($P\bar{A}_{O_2}$, $P\bar{A}_{CO_2}$) and mixed arterial concentrations (Ca_{O_2}, Ca_{CO_2}). From the blood–gas concentration, corresponding arterial partial pressures (Pa_{O_2}, Pa_{CO_2}) are read directly off the O_2 and CO_2 dissociation curves. Finally, whole-lung computations of O_2 and CO_2 exchange rates (mL/min) are determined using either Equations (1) or (2) and the mixed alveolar or arterial data respectively, and the mixed alveolar to arterial partial pressure differences expressed for each gas.

The results are very instructive. Both obstructive models result in hypoxemia and slight hypercapnia, but the effects on arterial P_{O_2} and on the alveolar–arterial P_{O_2} difference greatly exceed those for CO_2 due to both shape and slope differences between the dissociation curves of the two gases. Airways obstruction produces more hypoxemia but *less* hypercapnia than the identical degree of vascular obstruction. This reflects the 10-fold greater dissociation curve slope of CO_2 compared to O_2, rendering O_2 relatively more susceptible to the lower $\dot{V}_A/\dot{Q}$ areas seen in the airway obstruction model (0.1 vs. 0.5) (Fig. 14-8) and CO_2 relatively more susceptible to the higher $\dot{V}_A/\dot{Q}$ areas of vascular obstruction (10.0 vs. 1.9) (Fig. 14-8) as Figure 14-6 would predict.

Both models have impaired overall O_2 and CO_2 exchange (recall that venous blood, inspired gas, total ventilation, and blood flow were all considered fixed and identical for all three models) as a result of the development of $\dot{V}_A/\dot{Q}$ mismatch. In keeping with the differential sensitivity of O_2 and CO_2 to regions of low and high $\dot{V}_A/\dot{Q}$ discussed earlier, total O_2 transport is diminished to a greater extent in the airway obstruction model than in the vascular obstruction model (Table 14-1). The converse is true for CO_2, also shown in Table 14-1.

The principal effects of $\dot{V}_A/\dot{Q}$ inequality as they apply to O_2 and CO_2 exchange may thus be listed.

$\dot{V}_A/\dot{Q}$ inequality:

a. Affects both gases, no matter what the pathological basis of the inequality.
b. Causes arterial hypoxemia and hypercapnia.
c. Causes usually more severe hypoxemia than hypercapnia.
d. Affects O_2 more than CO_2 when very low $\dot{V}_A/\dot{Q}$ regions develop.
e. Affects CO_2 more than O_2 when very high $\dot{V}_A/\dot{Q}$ regions develop.
f. Impairs total O_2 and CO_2 exchange by the lung.
g. Creates alveolar–arterial differences for both gases.

COMPENSATION FOR THE EFFECTS OF $\dot{V}_A/\dot{Q}$ MISMATCH

The preceding analysis shows that if no changes in total ventilation, blood flow, mixed venous blood, or inspired gas composition occur, O_2 and CO_2 transfer across the lung is compromised. This is not viable in the steady state: the lungs must find a way to restore total O_2 and CO_2 transfer to levels equal to metabolic use of O_2 and production of CO_2. This leads to the next concentric level of consideration of $\dot{V}_A/\dot{Q}$ inequality referred to at the start of this section.

Here we ask what compensatory mechanisms exist to achieve restoration of O_2 and CO_2 transfer assuming that the initial pathophysiological insults have persisted unchanged. The same models as in Figure 14-8 and Table 14-1 will be used.

CHANGES IN MIXED VENOUS BLOOD

The only possible short-term compensatory changes are in mixed venous blood, total ventilation, and cardiac output. (Hb change in response to tissue hypoxia requires days to weeks to develop and then is by no means always observed; changing inspired P_{O_2} is not usually an option until the patient seeks medical attention.) To reduce complexity, changes in venous blood alone are first addressed.

TABLE 14-2 Gas Exchange Effects of Passive Changes in Mixed Venous Blood—Gas Values Required to Restore $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to Normal in the Models of Figure 14-8

	Airway Obstruction Model		Vascular Obstruction Model	
	Before Change	After Change	Before Change	After Change
$P\bar{v}_{O_2}$, mm Hg	40.0	30.4	40.0	39.5
$P\bar{v}_{CO_2}$, mm Hg	45.0	50.7	45.0	62.4
Pa_{O_2}, mm Hg	55	46	77	67
Pa_{CO_2}, mm Hg	39.0	44.5	40.9	55.6
$\dot{V}_{O_2}$, mL·min^{-1}	212.0	328 (normal)	294.0	328.0 (normal)
$\dot{V}_{CO_2}$, mL·min^{-1}	234.0	270 (normal)	203.0	270.0 (normal)

If it is assumed that there is no limit to how much O_2 can be extracted from the arterial blood by the peripheral tissues, it is evident that $\dot{V}_A/\dot{Q}$ inequality will passively lead to a reduced venous P_{O_2} and increased venous P_{CO_2}. This is deduced simply from the hypoxemia and hypercapnia initially produced by the $\dot{V}_A/\dot{Q}$ insult, together with the need to extract the same amount of O_2 from (and add CO_2 to) each mL of blood perfusing the tissues as before the $\dot{V}_A/\dot{Q}$ insult developed.

If venous P_{O_2} falls (and P_{CO_2} rises), Figure 14-7 indicates that alveolar P_{O_2} will fall in each $\dot{V}_A/\dot{Q}$ compartment (as will P_{CO_2} rise). Thus a circle of events is set up such that if a single red cell were followed around the circulation, at each passage through the lungs and then tissues, P_{O_2} would fall progressively with each circuit of the body.

Although not intuitively obvious, this reduction in both arterial and venous P_{O_2} will not "bottom out" at zero (or in the case of CO_2 rise toward infinity) unless the $\dot{V}_A/\dot{Q}$ insult was fatally overwhelming in the first place. Both arterial and venous P_{O_2} will restabilize at new lower values (P_{CO_2} values will be higher) than were present immediately after the $\dot{V}_A/\dot{Q}$ insult developed. In so doing, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ will have been restored to normal values.

To explore this quantitatively, we will continue on with the models of Figure 14-8 and Table 14-1 to show just what changes in venous and arterial P_{O_2} and P_{CO_2} must occur as a result of this process in order to restore pulmonary O_2 and CO_2 exchange to normal. The values are shown in Table 14-2. For the airways obstruction model, the passive blood gas changes are greater for O_2 than CO_2, consonant with the greater initial decrement in O_2 exchange caused by airways obstruction in the first place. For the vascular obstruction model, the effects are more marked for CO_2, for corresponding reasons. To restore $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the airways obstruction model, hypoxemia is now more severe, but hypercapnia is mild. However, with vascular obstruction, hypoxemia remains mild while hypercapnia is severe. In both cases, the lung is meeting the original healthy requirement of transferring 328 and 270 mL/min of O_2 and CO_2, respectively.

The speed of passive venous blood composition changes is very rapid, taking place in seconds to minutes as the blood moves continuously around the vascular system between lungs and tissues. The principal effects of the changes can be summarized as follows:

a. Following development of $\dot{V}_A/\dot{Q}$ mismatch, and a fall in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at the lungs, mixed venous P_{O_2} will fall and mixed venous P_{CO_2} will rise to restore pulmonary $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to equal the original metabolic requirements for O_2 and CO_2 transport.

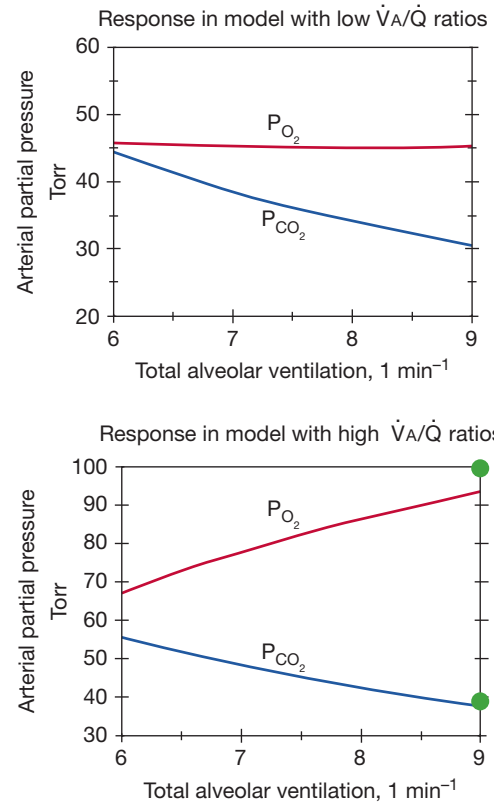


Figure 14-9 Effect of increasing alveolar ventilation on arterial P_{O_2} and P_{CO_2} in the two models with ventilation–perfusion inequalities in Figure 14-8. *Top panel* is that for Model 2 and *bottom panel* is that for Model 3. Increasing ventilation is ineffective in restoring arterial P_{O_2} in the low $\dot{V}_A/\dot{Q}$ Model 2, but much more effective in the high $\dot{V}_A/\dot{Q}$ Model 3. Both models respond in terms of P_{CO_2}.

b. As a result, there will always be a further fall in arterial P_{O_2} and rise in arterial P_{CO_2}, compared to conditions prior to mixed venous blood changes.
c. When the $\dot{V}_A/\dot{Q}$ insult primarily involves development of extremely low $\dot{V}_A/\dot{Q}$ areas, those effects are more marked for O_2 than for CO_2.
d. When the $\dot{V}_A/\dot{Q}$ insult primarily consists of high $\dot{V}_A/\dot{Q}$ areas, CO_2 is affected more than O_2.

■ CHANGES IN TOTAL VENTILATION

When either low or high $\dot{V}_A/\dot{Q}$ areas develop and the mixed venous and arterial adjustments occur as described earlier, there is hypoxemia and hypercapnia. Either or both may well stimulate an immediate increase in total ventilation,[36] which will alleviate to some extent both the hypoxemia and hypercapnia. Figure 14-9 shows for the same two examples used earlier how increases in alveolar ventilation (distributed in the same proportions as in each of the two $\dot{V}_A/\dot{Q}$ models of Fig. 14-8) variably improves arterial P_{O_2} and P_{CO_2}. In the low $\dot{V}_A/\dot{Q}$ (airways obstruction) model, a 50% increase in total alveolar ventilation from the normal value of 6 to 9 L/min drops arterial P_{CO_2} to almost 30 mm Hg, well below the normal standard value of 40 mm Hg. Arterial P_{O_2}, however, is not affected at all. This is because even a 50% increase in ventilation of the very poorly ventilated unit fails to significantly increase end capillary P_{O_2} of that unit (Fig. 14-6), whereas in the better ventilated unit of that model, Hb in the end capillary blood was already virtually fully saturated before the increase in ventilation.

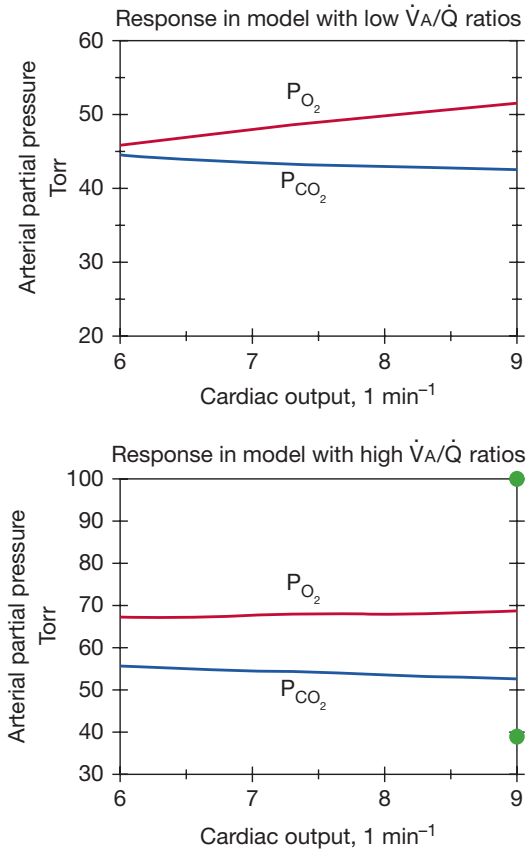


Figure 14-10 Effects of increases in cardiac output on arterial P_{O_2} and P_{CO_2} in Models 2 and 3 of Figure 14-8. Cardiac output produces a significant rise in P_{O_2} in the presence of regions of very low ventilation–perfusion ratio *(top panel)* but has little influence in the presence of higher ventilation–perfusion ratios *(bottom panel)*. P_{CO_2} is affected only minimally in either case.

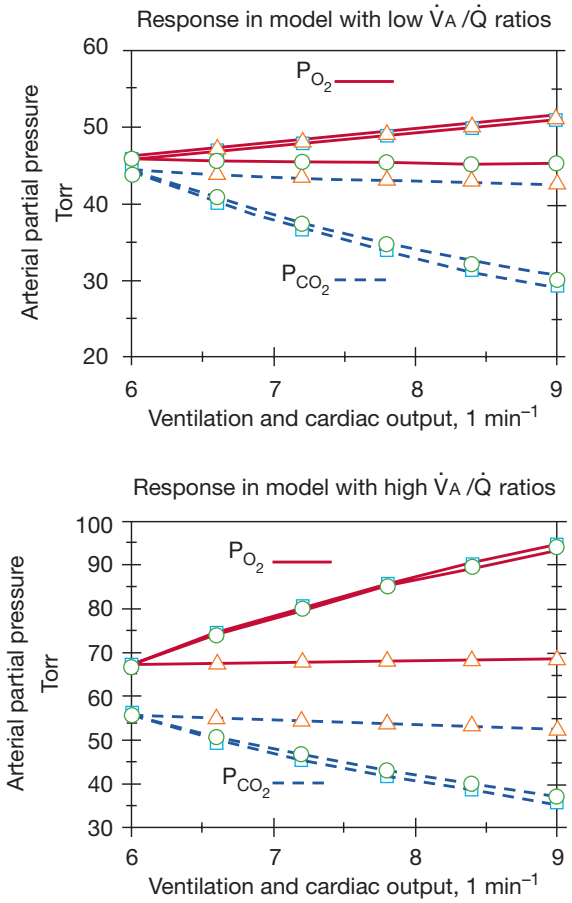


Figure 14-11 Responses to simultaneous increases in ventilation and cardiac output (compared to responses to individual increases as shown in Figs. 14-9 and 14-10). Simultaneous increases do not provide for significantly more improvement than with either alone. o-o, response to increased ventilation only; Δ-Δ, response to increased cardiac output only; □-□, response to simultaneously increased ventilation and cardiac output.

For the model with vascular obstruction, a 50% increase in alveolar ventilation returns both P_{O_2} and P_{CO_2} to near-normal values (Fig. 14-9, lower panel). The difference in the two model responses to ventilation reflects the original $\dot{V}_A/\dot{Q}$ ratios of the two compartments—that is, where they lie on the curves of Figure 14-6.

■ CHANGES IN CARDIAC OUTPUT

One final compensatory adjustment is possible—an increase in cardiac output. Adrenergic stimulation by arterial hypoxemia can raise cardiac output by 50% or more, and this will also tend to improve arterial blood gases by raising mixed venous P_{O_2} (and lowering mixed venous P_{CO_2}). Figure 14-10 shows the effects on arterial P_{O_2} and P_{CO_2} of such increases, as was done for ventilation in Figure 14-9, again assuming that the relative distribution of blood flow remains unaltered between the two compartments as total blood flow is increased. For a lung with airways obstruction causing very low $\dot{V}_A/\dot{Q}$ regions (upper panel), an increase in cardiac output significantly improves arterial oxygenation—more so than does the same relative increase in ventilation. However, arterial P_{CO_2} is only slightly improved. In stark contrast, increases in cardiac output barely alter arterial P_{O_2} and P_{CO_2} in the high $\dot{V}_A/\dot{Q}$ ratio model, especially when it is recalled (Fig. 14-9) how effective an increase in ventilation is in restoring arterial P_{O_2} and P_{CO_2}.

When both ventilation and cardiac output are simultaneously increased, there is no real synergistic effect (Fig. 14-11): P_{O_2} and P_{CO_2} are improved as predicted from the individual changes (i.e., as shown in Figs. 14-9 and 14-10).

In all the calculations depicted in Figures 14-9 to 14-11, the two-compartment models are exchanging the necessary amounts of O_2 and CO_2 to sustain normal metabolism. Depending on (a) the ventilatory and cardiovascular responses to the original insult causing $\dot{V}_A/\dot{Q}$ mismatch and (b) the fundamental pattern of $\dot{V}_A/\dot{Q}$ mismatch (i.e., the preponderance of low and/or high $\dot{V}_A/\dot{Q}$ areas), it is possible to observe hypercapnia, normocapnia, or hypocapnia. However, it is very uncommon for arterial P_{O_2} to be fully normalized by the compensatory mechanisms, and the observed degree of hypoxemia can be extremely variable. As an important clinical corollary, it becomes difficult to establish the severity of the $\dot{V}_A/\dot{Q}$ insult per se when the extent of compensating mechanisms cannot be easily established, since these two aspects are so intertwined in their resulting effect on gas exchange.

ASSESSMENT OF VENTILATION–PERFUSION INEQUALITY

Whereas the preceding discussion highlights the complexity of how $\dot{V}_A/\dot{Q}$ inequality impairs gas exchange, there is a need for methods to assess the extent of such mismatch in the clinical setting. The multiple inert gas elimination technique was developed expressly for this purpose.[37,38] Although the technique provides the necessary

descriptions of the extent and pattern of inequality, it remains a complex technique that is not well suited to routine clinical use. Several traditional quantifying indices of $\dot{V}A/\dot{Q}$ mismatch remain useful on a daily basis. They all make use of O_2 and CO_2 as indicator gases:

1. The first is the alveolar–arterial P_{O_2} difference, $P_{A_{O_2}} - Pa_{O_2}$. This is the difference between alveolar P_{O_2} ($P_{A_{O_2}}$, calculated from the alveolar gas equation presented subsequently) and the measured arterial P_{O_2} (Pa_{O_2}). The $P_{A_{O_2}} - Pa_{O_2}$ is therefore given by

$$PI_{O_2} - Pa_{CO_2}/R + Pa_{CO_2} \cdot FI_{O_2} \cdot (1-R)/R - Pa_{O_2} \quad (8)$$

   Use of this equation requires knowledge of inspired P_{O_2} and $[O_2]$, the respiratory exchange ratio R, and the ideal alveolar P_{CO_2}, which is the P_{CO_2} that would be observed in alveolar gas of a homogeneous lung having the R value of the patient's actual lung at the time. Three problems arise with the application of this equation: First, the result is very dependent on PI_{O_2} even when the amount of $\dot{V}A/\dot{Q}$ inequality does not change as PI_{O_2} is varied. Second, the value of R is generally not known and must be assumed. Suppose $P_{CO_2} = 40$ mm Hg and $Pa_{O_2} = 90$ mm Hg for a subject breathing sea level air. If R were 0.7, $P_{A_{O_2}} - Pa_{O_2}$ would be 7 mm Hg (Equation 8). But if R were 1.0, $P_{A_{O_2}} - Pa_{O_2}$ would be 20 mm Hg, a quite different value. Third, in some cases, the usual substitution for the ideal alveolar P_{CO_2}, the measured arterial P_{CO_2}, leads to a systematic error because arterial P_{CO_2} can be significantly higher than the ideal alveolar value. However, $P_{A_{O_2}} - Pa_{O_2}$ remains a very useful index of $\dot{V}A/\dot{Q}$ inequality providing these limitations are kept in mind.
2. The second index is simply the ratio of arterial P_{O_2} to FI_{O_2} which in a perfectly normal lung is virtually insensitive to PI_{O_2}, a major advantage. However, even that is an over-simplification, because this ratio may not be as constant as hoped for depending on the pattern of $\dot{V}A/\dot{Q}$ inequality present.
3. A third index is venous admixture (QsQT) or, equivalently, physiological shunt. This is a parameter that expresses what magnitude shunt would have to be present in a particular case to explain a patient's arterial P_{O_2} if that shunt were the sole cause of hypoxemia. The formula is:

$$\%\ QsQT = 100 \cdot [Cc'_{O_2} - Ca_{O_2}]/[Cc'_{O_2} - C\bar{v}_{O_2}] \quad (9)$$

   where Cc'_{O_2} is the calculated end capillary $[O_2]$ of blood perfusing a hypothetical alveolus exchanging gas at the overall respiratory exchange ratio of the patient's actual lungs. Ca_{O_2} is arterial and $C\bar{v}_{O_2}$ mixed venous $[O_2]$, respectively. This parameter, working in the O_2 concentration domain (rather than the partial pressure domain of the $P_{A_{O_2}} - Pa_{O_2}$), better reflects the degree of the gas exchange defect but requires knowledge of the ideal alveolar conditions to calculate Cc'_{O_2}, as well as [Hb]. It also is sensitive to PI_{O_2} in that when $\dot{V}A/\dot{Q}$ inequality is present, its contribution to QsQT diminishes progressively as PI_{O_2} is raised. The most limiting aspect of this parameter however is the need to know the value of $C\bar{v}_{O_2}$, reflecting mixed venous blood. If this must be assumed rather than measured, the value of QsQT will be only as good as the assumption, which may be extremely misleading if changes in $C\bar{v}_{O_2}$ in fact occur but are not accounted for in the QsQT calculation.
4. Finally, as a fourth index, using the arterial and mixed expired partial pressures of CO_2 (Pa_{CO_2}, $P\bar{E}_{CO_2}$, respectively), a very similar calculation to QsQT can be performed to compute the percentage of total ventilation that is wasted on nongas exchanging ("deadspace") areas of the lungs. As for QsQT, the calculation determines the magnitude of the deadspace that would have to be present to dilute the alveolar P_{CO_2} down to the mixed expired level if that deadspace were the only abnormality in ventilation. Expressed as deadspace (VD)/tidal volume (VT) percentage,

$$\%\ VD/VT = 100 \cdot [Pa_{CO_2} - P\bar{E}_{CO_2}]/[Pa_{CO_2}] \quad (10)$$

This parameter is independent of PI_{O_2}, but is weakened by the fact that the normal airway conducting volume is included in the computed result. Thus it may be difficult to separate how much the VD/VT value represents this normal anatomic deadspace as opposed to reflecting $\dot{V}A/\dot{Q}$ inequality amongst the alveoli. This problem is amplified because even normally VD/VT is very dependent on the size of the tidal volume even if the deadspace volume itself is essentially constant. Thus, for a deadspace volume of 150 mL and a tidal volume of 500 mL, VD/VT is 30%, but if tidal volume were to drop to 400 mL, VD/VT now becomes 38%—not because $\dot{V}A/\dot{Q}$ inequality has developed, but simply because smaller breaths are being taken.

In summary, no index of $\dot{V}A/\dot{Q}$ inequality is without potentially significant limitations, both quantitative and qualitative. However, if these limitations are recognized and the data interpreted accordingly, they still remain very useful indices of clinical gas exchange function.

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CHAPTER 15
Blood-Gas Transport

Adrian Shifren
Robert A. Klocke

OXYGEN TRANSPORT

Oxygen is relatively insoluble in aqueous solutions like blood. Dissolved oxygen alone is insufficient to meet the demands of tissue metabolism. Therefore, an alternate means of transporting oxygen is essential. Oxygen binds reversibly to hemoglobin, enhancing the effective solubility of O_2 in blood, and enabling the transport of significant amounts of oxygen—approximately 20 mL/100 mL of blood at a hemoglobin concentration of 150 g/L.

■ OXYGEN DISSOCIATION CURVE

The oxygen dissociation curve represents the relationship between the oxygen content of blood and the partial pressure of oxygen to which it is exposed (Fig. 15-1).[1] Oxygen content is expressed as the volume of oxygen contained in 100 mL of blood, but may also be expressed as either volumes % or mL/dL. The standard oxygen dissociation curve (Fig. 15-1) demonstrates the effects of oxygen–hemoglobin interaction at standard pH (7.40), temperature (37°C), and atmospheric pressure (760 mm Hg). The blue line at the bottom of the graph in Figure 15-1 shows the amount of oxygen dissolved in blood, and the red line shows the total amount of oxygen in blood at any given oxygen tension. Almost the entire quantity of oxygen transported in blood is bound to hemoglobin. However, the role of dissolved oxygen cannot be ignored. Oxygen diffuses across the alveolar–capillary membrane, enters the plasma, traverses the red cell membrane, and enters the erythrocyte interior—all while dissolved in aqueous solutions. It then combines with hemoglobin enabling the transport of large amounts of oxygen to the metabolizing tissues. Dissolved oxygen, although present in very low concentration in blood, is a critical component of the process of O_2 exchange.

Changes in the quaternary structure of hemoglobin that accompany oxygen binding result in a sigmoid, rather than hyperbolic, oxygen dissociation curve. The S-shaped dissociation curve is the result of changes in oxygen affinity of unbound heme groups following the binding of oxygen to another heme group in the same

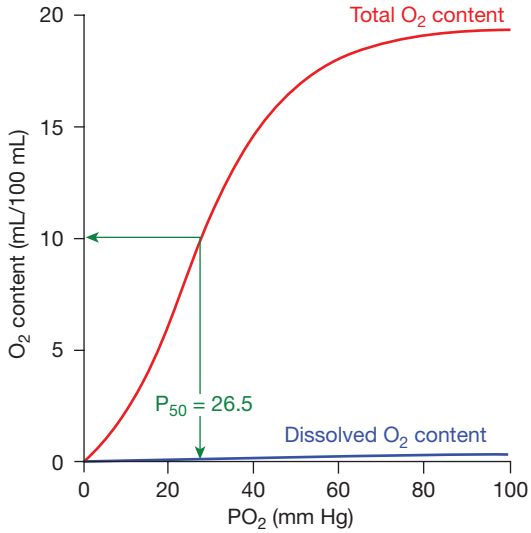

Figure 15-1 Oxygen dissociation curve. Relationship between oxygen content and pressure in normal human blood. The total oxygen content of blood as a function of the partial pressure of oxygen is indicated by the *red line*. The *blue line* indicates the content of dissolved oxygen resulting from changes in P_{O_2}. The partial pressure of oxygen (P_{50}) necessary to saturate one-half of hemoglobin in blood is indicated in *green*.

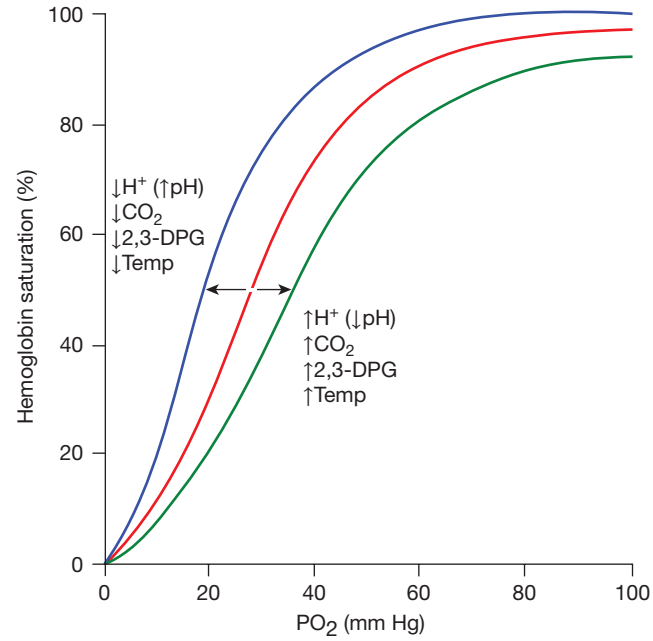

Figure 15-2 Oxygen dissociation curve. The ordinate is % saturation, the percentage of the maximum possible oxygen content. The normal oxygen dissociation curve is shown in *red*. The *blue curve* is shifted to the left of the normal curve (increased oxygen affinity of hemoglobin) as a result of decreased blood hydrogen ion, decreased carbon dioxide, and 2,3-DPG concentrations or decreased temperature. The *green curve* is shifted to the right (decreased oxygen affinity) of the normal curve caused by increases of these factors.

hemoglobin molecule. As illustrated in Figure 15-1, once the partial pressure of oxygen reaches 90 to 100 mm Hg, hemoglobin is almost completely saturated with bound oxygen. There is little additional oxygen binding even at higher oxygen tensions. The flatness of the curve in the arterial oxygen tension range is an advantage because reductions in arterial P_{O_2} (as might be caused by lung disease) will still allow for a relatively normal arterial O_2 content as long as arterial P_{O_2} remains ≥60 mm Hg. The normal partial pressure of oxygen in mixed venous blood at rest is ~40 mm Hg with an oxygen content of ~75% of maximum oxygen capacity. Thus, at rest only one-quarter of the oxygen delivered to body tissues is extracted from blood. However, oxygen extraction varies widely in different tissues. In addition, oxygen utilization changes appreciably during states of increased metabolism. In the tissues, the steep slope of the oxygen dissociation curve between 20 and 60 mm Hg facilitates the release of large amounts of oxygen with relatively moderate decrease in oxygen tension. This permits maintenance of blood oxygen tensions that promote diffusion of oxygen from the capillary blood into metabolizing tissues.

The maximum quantity of oxygen transported in blood is dependent upon hemoglobin concentration, which varies moderately in normal circumstances and substantially in disease states. To facilitate comparison of oxygen dissociation curves with different hemoglobin concentrations, the ordinate of the curve can be normalized by expressing oxygen content at any given pressure as a percentage of the maximum possible oxygen content. This approach substitutes % saturation of hemoglobin for oxygen content, as illustrated in Figure 15-2. Using this format, all normal oxygen dissociation curves are superimposable, regardless of differing hemoglobin concentrations.

■ ALTERATIONS OF OXYGEN AFFINITY

The relationship between oxygen content and pressure can be affected by several factors. Increases in temperature, carbon dioxide pressure, hydrogen ions (decreased pH), and 2,3-diphosphoglycerate (2,3-DPG) all shift the oxygen dissociation curve to the right.[1] This results in a decrease in the affinity of hemoglobin for oxygen, that is, a greater oxygen tension is required to bind the same amount of oxygen to hemoglobin (Fig. 15-2). Conversely, decreases in temperature, carbon dioxide tension, hydrogen ion (increased pH), and 2,3-DPG shift the curve to the left, that is, increase the affinity of hemoglobin for oxygen.[1] The degree of shift of the oxygen dissociation curve is described by the P_{50}, the partial pressure of oxygen required to achieve 50% oxygen saturation of hemoglobin. The normal P_{50} for human blood is 26.5 mm Hg (Fig. 15-1). The basic sigmoid nature of the relation between oxygen and hemoglobin does not change with alterations in the P_{50}. Rather, the curve is uniformly either stretched or compressed along the P_{O_2} axis.

The human erythrocyte contains large quantities of 2,3-DPG, an organic phosphate that binds to hemoglobin and affects O_2 affinity. The normal concentration of 2,3-DPG in erythrocytes is approximately 5 mM. However, this concentration can change significantly, markedly altering the P_{50}. There is a substantial change in the configuration of the hemoglobin molecule between the oxygenated and deoxygenated states. Oxygen and 2,3-DPG bind at different sites on the hemoglobin molecule, and binding of both molecules changes the overall configuration of hemoglobin, but in different ways. The β-chains are more widely separated in the deoxygenated state than in the oxygenated state, and have positive charges surrounding the central cavity of the hemoglobin tetramer. The widened gap between the β-chains of the deoxygenated molecule enables the highly negatively charged 2,3-DPG molecule to enter the cavity between the β-chains and bind electrostatically to positively charged amino acids of the hemoglobin molecule. This tends to stabilize the hemoglobin molecule in the deoxygenated configuration. Higher pressures of oxygen are thus required to force the change in molecular configuration to the oxygenated form, resulting in a shift of the dissociation curve to the right along the P_{O_2} axis.

The Donnan effect results from the presence of charged macromolecules on one side of a semipermeable membrane failing to distribute

evenly across the membrane. This leads to an uneven distribution of charge across the membrane that, in turn, affects the distribution of small, permeable ions across the same membrane. At body pH 2,3-DPG has four negative charges and reduces intraerythrocytic pH by the Donnan effect since 2,3-DPG does not cross the cell membrane. The reduction in intracellular pH resulting from the presence of intracellular 2,3-DPG causes a decrease in oxygen affinity of hemoglobin through the Bohr effect (see below Carbon Dioxide).

Most abnormal hemoglobins have normal oxygen equilibrium curves despite differences in amino acid sequences. Although some hemoglobinopathies are accompanied by changes in oxygen affinity, this usually is due to other factors, such as altered DPG concentration or mean corpuscular hemoglobin concentration. Some relatively rare mutant hemoglobins are exceptions to this rule and exhibit increased O_2 affinity that is accompanied by erythrocytosis. Previously, measurements of P_{50} were advocated to investigate erythrocytosis, but identification of mutant hemoglobins with current molecular techniques is far more likely to identify this rare cause of erythrocytosis.

Large quantities of carbon monoxide (CO) bound to hemoglobin can increase the affinity for oxygen of the remaining unbound sites on hemoglobin. The adverse effects of CO poisoning are twofold: (1) Binding of CO to hemoglobin interferes with oxygen binding and produces a functional anemia; and (2) binding of CO to hemoglobin also increases the affinity of hemoglobin for oxygen, thereby shifting the oxygen equilibrium curve to the left. This increased affinity hinders the release of oxygen in the tissues, but is not as important as the functional anemia caused by CO binding.

BOHR EFFECT

The shift of the oxygen dissociation curve produced by changes in P_{CO_2} and pH is known as the Bohr effect, after the individual who first described this phenomenon. Similar to 2,3-DPG, both hydrogen ions and carbon dioxide bind at sites on the hemoglobin molecule that differ from the oxygen-binding sites.[2] However, binding of these two moieties at different sites alters the oxygen affinity of hemoglobin through their effects on the configuration of the hemoglobin molecule.[3]

It has been speculated that the increased carbon dioxide tension and hydrogen ion content in blood perfusing metabolizing tissues facilitate the release of oxygen bound to hemoglobin at a higher P_{O_2} by shifting the oxygen dissociation curve to the right.[4] However, quantitative analysis indicates that this mechanism results in minimal augmentation of oxygen release in tissues at rest (2%–3%) because of the minute difference in pH between arterial and venous blood (0.03–0.05 pH units).[5] This effect does become significant during exercise, with the addition of lactic acid, from muscle to venous blood.[6] This is an adaptive response for improving oxygen delivery at high levels of exercise. However, the main benefit of the Bohr effect is the increased buffering capacity of hemoglobin that accompanies deoxygenation of the molecule.[2,4] Figure 15-3 illustrates the buffering curves of normal arterial and venous blood. Both exhibit effective, but parallel, buffering curves. As hemoglobin is deoxygenated, its buffering curve shifts upward and significant amounts of hydrogen ion can be buffered with a smaller change in pH.[2] Approximately half of the hydrogen ions released in aerobic metabolism are buffered in this manner (see section Haldane Effect).

CARBON DIOXIDE TRANSPORT

Carbon dioxide (CO_2) is primarily the by-product of aerobic metabolism. It is also generated through the buffering of hydrogen ions (H^+) from organic acids, such as lactic acid and ketoacids. This buffering occurs through chemical reaction of H^+ ions with intracellular and extracellular bicarbonate ions (HCO_3^-). The CO_2 produced by these reactions diffuses into capillary blood and is carried

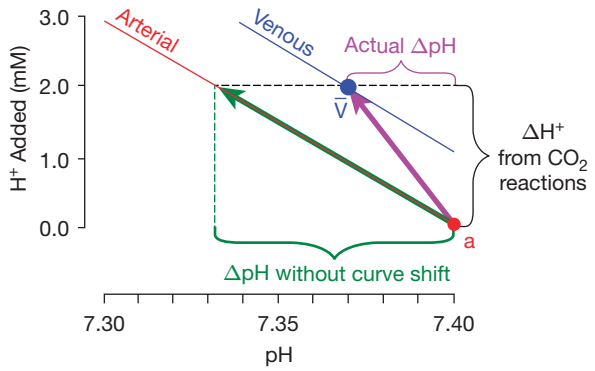

Figure 15-3 Buffer curves (change in pH produced by binding of hydrogen ions) of normal arterial (a) and mixed venous ($\bar{V}$) blood. With release of oxygen bound to hemoglobin in tissues, buffering sites on the hemoglobin molecule increase their affinity for hydrogen ions, thereby shifting the buffer curve upward. The quantity of hydrogen ions (ΔH^+) added to blood by production of CO_2 in normal metabolizing tissues at rest is indicated by the *black bracket*. The figure shows the change in pH *(green bracket)* that would occur if buffering occurred only along the arterial buffer curve *(green arrow)*. The actual, much smaller change in pH *(purple bracket)* that accompanies buffering *(purple arrow)* is due to the upward shift of the arterial buffering curve to the venous relationship that accompanies release of oxygen in the tissues. *(Reproduced with permission from Klocke RA: Encyclopedia of Respiratory Medicine. Philadelphia: Elsevier; 2007.)*

in both chemical combination and physical solution to the lungs, where it is eliminated through expired ventilation (see Chapter 16, p. 200). Similar to O_2 transport, most CO_2 in blood is not carried as gas, but rather in chemical forms directly or indirectly dependent on hemoglobin.

THE CARBON DIOXIDE DISSOCIATION CURVE

Carbon dioxide is transported in three forms in blood: Dissolved CO_2, bicarbonate ions, and carbamate compounds. The relationship between the blood content and partial pressure of CO_2 differs noticeably from that of O_2. The total quantity of CO_2 contained in arterial blood is more than twice that of O_2 despite the lower partial pressures of CO_2. The CO_2 dissociation curve is very steep (Fig. 15-4). As a result, the difference in partial pressures of CO_2 between arterial and venous blood is small when compared to the large arterial–venous differences in blood P_{O_2}.[7] The total content of blood CO_2, that is, the vertical axis of the CO_2 dissociation curve, is the sum of all three forms of CO_2 (dissolved CO_2, bicarbonate, and carbamate).

DISSOLVED CO_2

Carbon dioxide is 20 times more soluble in aqueous solution than oxygen.[8] However, this increased solubility is insufficient to facilitate transport of all the CO_2 produced by metabolism. Approximately 5% of total CO_2 content in blood exists as dissolved CO_2 in plasma and red cell water. Despite this, dissolved CO_2 has a critical role in gas exchange since only dissolved CO_2 crosses the alveolar–capillary membrane. Therefore, regardless of how CO_2 is transported in blood, each molecule must be converted into the dissolved form for excretion through ventilation. The quantity of dissolved CO_2 is directly proportional to the partial pressure of carbon dioxide in blood, that is, the P_{CO_2}.

BICARBONATE

Carbon dioxide combines with water to form carbonic acid, which dissociates into hydrogen and bicarbonate ions. At normal blood

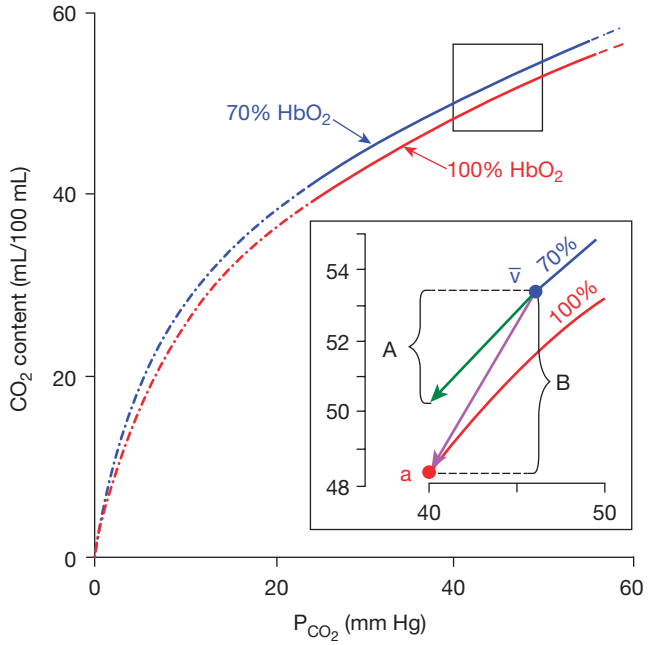

Figure 15-4 The Haldane effect showing the carbon dioxide dissociation curves of blood with 70% *(blue)* and 100% *(red)* oxygen saturations. The portions of the curves most commonly involved in gas exchange are drawn with *solid lines*. The P_{CO_2} and CO_2 contents of mixed venous ($\bar{v}$) and arterial blood (a) normally present at rest are shown in the enlarged inset. If there were no change in the CO_2 dissociation curve with oxygenation in the lung, the decrease in P_{CO_2} would take place along the venous curve *(green arrow)*. This would produce a decrease in blood CO_2 content indicated by the vertical bracket A. The course of CO_2 exchange between arterial and mixed venous points is shown by the *magenta arrow*. The enhanced CO_2 exchange produced by the Haldane effect is indicated by the greater vertical height of bracket B.

pH, carbonic acid dissociates into hydrogen ions and bicarbonate ions.

$$CO_2 + H_2O \xleftrightarrow{CA} H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (1)$$

The pKa for reaction (1), including hydration and dissociation, is 6.1.[8] The natural rate of formation of carbonic acid from CO_2 and water is slow and takes seconds to minutes to reach completion in simple aqueous solutions. Under the influence of the carbonic anhydrase (CA) enzyme in the cytosol of erythrocytes, this reaction is increased by a factor of approximately 15,000.[7] CA occurs as two isoenzymes: CA I is present in high concentrations in erythrocytes, but its activity is inhibited by intracellular chloride ions. CA II is present at one-sixth the concentration of CA I within red cells, but is not inhibited by chloride ion and has a sevenfold greater intrinsic activity than CA I. CA II is therefore responsible for almost all the CO_2–bicarbonate catalysis in vivo.[7]

CARBAMATE

Carbon dioxide is also transported as carbamate compounds. Less than 10% of all CO_2 binds to hemoglobin as carbamate, which are salts of carbamic acid formed by the reaction of CO_2 with amino groups on proteins. CO_2 combines with uncharged terminal amino groups on the α and β chains of hemoglobin.

$$R\text{-}NH_3^+ \rightarrow H^+ + R\text{-}NH_2 \quad (2)$$

$$R\text{-}NH_2 + CO_2 \rightarrow R\text{-}NHCOOH \rightarrow R\text{-}NHCOO^- + H^+ \quad (3)$$

where R represents either an α or β chain of hemoglobin.[7] While any NH_2 group on hemoglobin can potentially bind CO_2 as a carbamate compound, only the terminal amino groups of the α and β chains participate in carbamate generation. At the pH present inside red cells, carbamic acid (R-NHCOOH) dissociates completely into a carbamate ion and a hydrogen ion. These H^+ ions, like those liberated by the formation of bicarbonate ions, are buffered principally by hemoglobin (see section Haldane Effect).

Changes in the quaternary structure of hemoglobin accompanying binding and release of oxygen affect the pK's of reactions (2) and (3), altering the equilibrium between the NH_2 and NH_3^+ forms of the terminal amino groups. Because deoxygenated hemoglobin binds more CO_2 than oxygenated hemoglobin, more CO_2 can be carried in venous blood at any given P_{CO_2} than in oxygenated (arterial) blood. The change in CO_2 binding between oxygenated and deoxygenated hemoglobin accounts for approximately one-eighth of the difference between the arterial and venous CO_2 contents during normal gas exchange. The physiological importance of this process would be twice as great but is reduced by interactions between DPG and hemoglobin that limit carbamate formation.[7] Binding of the highly negatively charged DPG molecule to hemoglobin induces change of the amino-NH_2 moieties to the positively charged amino-NH_3^+ forms that do not bind CO_2 as carbamate.

HALDANE EFFECT

Oxygenated blood at any partial pressure of CO_2 contains less total CO_2 content than deoxygenated blood at the same partial pressure (Fig. 15-4). This is known as the *Haldane effect*, after one of the investigators who first described the phenomenon.

Transport of CO_2 in blood as bicarbonate or carbamate is altered by blood oxygenation. These changes are described as "oxylabile" since they are dependent upon the state of hemoglobin oxygenation.[7] Changes in configuration of the hemoglobin molecule accompanying the release of oxygen facilitate binding of CO_2 to hemoglobin as carbamate, that is, *oxylabile carbamate formation*. This increases the total CO_2 content in deoxygenated blood compared with oxygenated blood.[9]

Formation of both bicarbonate ions and carbamate compounds releases large quantities of hydrogen ions. It is essential to buffer these hydrogen ions effectively to promote CO_2 transport. Deoxygenation of hemoglobin also results in a shift of the buffering curve of hemoglobin since deoxygenated hemoglobin is a stronger base than oxyhemoglobin. This shift permits binding of a greater number of hydrogen ions (Fig. 15-3). This *oxylabile buffering*, in turn, facilitates formation of larger quantities of carbamate and bicarbonate.[9]

The synergistic effects of oxygen and carbon dioxide transport result in a change in the carbon dioxide dissociation curve as oxygen is bound and released.[10] Approximately equal changes in bicarbonate and carbamate concentrations are responsible for the Haldane effect. Quantitatively, the Haldane effect has a far greater physiological effect on gas transport than does the Bohr effect. Without the change between the oxygenated and partially reduced CO_2 dissociation curves (the Haldane effect), the difference between arterial and venous CO_2 tensions would be approximately twice the normal value, thereby increasing tissue P_{CO_2}. Model calculations and in vitro data suggest that the Haldane effect accounts for 40% to 50% of total CO_2 exchange in the lung under normal conditions.[7–9]

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CHAPTER 16

Diffusion, Chemical Reactions, and Diffusing Capacity

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Uptake of oxygen and excretion of carbon dioxide require rapid, efficient exchange in the lung. The quantities of exchanged gases are staggering. For example, a 1800-calorie diet requires absorption of 375 L of oxygen per day, as well as excretion of a slightly smaller volume of carbon dioxide. Because blood remains in the pulmonary capillary bed for a limited time, the process of exchange must be accomplished in less than 0.75 second at rest and 0.5 second during exercise. This rapid, high-volume exchange occurs efficiently despite numerous interacting processes of diffusion and chemical reaction that occur in the lung. The rates of these processes are not only affected by intrinsic characteristics of blood but also determined by a host of other factors, including inspired oxygen fraction, alveolar gas tensions, cardiac output, and metabolic activity. The ease of exchange of respiratory gases belies the complexity of the overall process.

DIFFUSION

The concentration (C) of a gas dissolved in fluid depends upon its partial pressure (P) and solubility (α)

$$C = \alpha P \quad (1)$$

Gases diffuse from a higher to a lower partial pressure, not necessarily from a higher to a lower concentration. This fact is especially pertinent when a gas diffuses between two phases, as occurs when O_2 and CO_2 are exchanged between alveolar gas and blood. For example, dissolved CO_2 diffuses down a partial pressure gradient from blood (46 mm Hg) into the alveolus (40 mm Hg), even though its actual concentration (millimoles of molecular CO_2 per liter of gas or blood) is greater in alveolar gas (2.5) than it is in venous blood (1.4).

INFLUENCE OF PHYSICAL PROPERTIES

The rate of a gas diffusing through an aqueous membrane such as that separating alveolar gas and capillary blood is influenced by five factors. The rate is directly proportional to the surface area of the membrane, but inversely proportional to the thickness of the membrane. The rate increases in direct proportion to the difference in gas pressure between alveolar gas and capillary blood, and the diffusion and solubility coefficients of the gas in the membrane.

The diffusion coefficient of a gas in the alveolar–capillary membrane is largely a function of the size of the gas molecule, which is inversely proportional to the square root of its molecular weight (MW). Oxygen (MW 32) has a slightly greater diffusion coefficient than carbon dioxide (MW 44) in the alveolar membrane. However, the solubility of CO_2 in water, the major component of tissue composing the membrane, is much greater than the solubility of O_2. This difference far outweighs the effect of the slightly smaller size of the oxygen molecule. Thus, the rate of CO_2 transfer across the alveolar membrane is approximately 20 times greater than that of O_2 when both gases diffuse under the same partial pressure gradient. As a result, a much greater P_{O_2} gradient across the membrane is required to maintain O_2 transfer equal to that of CO_2.

On the other hand, the rate of carbon monoxide (CO) transfer is very similar to that of oxygen when both gases diffuse across the alveolar–capillary membrane under the same partial pressure gradient. CO (MW 28) is a slightly smaller molecule than oxygen so its diffusion coefficient is slightly greater. This diffusive advantage is offset by a slightly lower aqueous solubility of CO compared to oxygen. As a result, CO and O_2 transfer across the membrane have approximately equal rates at the same transmembrane partial pressure gradient.

The rate of diffusion is affected by the viscosity of the medium through which the diffusion occurs. Diffusion of a gas in air occurs at a rate that is four orders of magnitude greater than diffusion in water. Diffusion coefficients in tissues are only moderately less than those in water, since most tissues are composed primarily of water. The interior of the erythrocyte is an exception to this general rule. As a consequence of the high concentration of hemoglobin inside the red cell, the viscosity of the cell contents is substantially greater than that of water. This greater viscosity reduces the diffusion coefficient for oxygen to one-third of its aqueous coefficient. The combination of increased viscosity and the large size of the hemoglobin molecule decreases the diffusion coefficient of hemoglobin within the red cell to less than 10% of its diffusion coefficient in a dilute aqueous solution. As a result, significant diffusion gradients are thought to exist within the red cell even though the distance between the cell membrane and the innermost portion of the cell is only a few microns.

EFFECT OF DIFFERENT CAPACITANCES

The alveolar–capillary membrane provides a barrier to diffusion of gases between the alveoli and the capillaries. The rate of approach to diffusion equilibrium of a gas in the lung is dependent on the

capacitances of the gas in the alveoli and blood relative to its solubility in the alveolar–capillary membrane. Normal ventilation of alveoli results in a large reservoir of oxygen with a pressure of ~100 mm Hg to promote diffusive transfer across the alveolar–capillary membrane. The ability of hemoglobin to bind O_2 increases the oxygen capacity of blood by two orders of magnitude compared with that of the alveolar–capillary membrane. This large capacitance for oxygen in blood requires substantial oxygen transfer across the membrane to reach diffusion equilibrium. Because the solubility of oxygen in the membrane is small relative to the large capacitances in alveolar gas and blood, oxygen exchange across the membrane requires 0.2 to 0.4 second to reach equilibrium.[1] Fortunately, this delay in reaching equilibrium is less than the average of 0.75 second that blood remains in the pulmonary capillary bed. These same conditions are present during carbon monoxide transfer. The large capacitance and the low aqueous solubility of CO lead to similar impediments in gas exchange.

In contrast to oxygen and carbon monoxide, the solubility of carbon dioxide in the membrane is sufficiently great compared to the capacitances of CO_2 in blood and alveoli to permit rapid equilibration of CO_2 across the alveolar–capillary membrane. As discussed (see below Carbon Dioxide) CO_2 exchange requires a finite time for completion, but this delay is the result of the time needed to complete chemical and transport processes in blood, and is not the result of slow diffusive transport across the alveolar–capillary membrane.

Gases transported in blood only in dissolved form are exchanged almost instantaneously across the alveolar–capillary membrane. As long as gas solubilities in the membrane and blood are similar, diffusion equilibrium between alveolar contents and blood is reached within 0.01 second because the normal alveolar–capillary membrane is extremely thin (median thickness of 0.3 μm). Only gases such as oxygen and carbon monoxide that have large alveolar and blood capacitances and reduced solubility in the alveolar–capillary membrane will require a finite time to reach diffusive equilibrium.

CHEMICAL REACTIONS OF GASES

Transport of respiratory gases entails numerous chemical reactions with components of the blood. Like diffusive transport of oxygen, these chemical reactions are not instantaneous and require finite periods of time to reach completion. It is commonly thought that diffusion provides the greatest time-dependent impediment to gas exchange, but in actuality, chemical processes, especially those occurring in combination with diffusion or other chemical reactions, are more likely to slow rates of exchange.

OXYGEN AND CARBON MONOXIDE

From a stoichiometric viewpoint, the successive binding of O_2 to the heme moieties of hemoglobin is described by successive steps, each with separate association and dissociation rate constants. If the heme rings acted independently, these constants would be the same for each heme ring and the resulting dissociation curve would have a hyperbolic shape. However, binding of oxygen to one of the heme rings affects the affinity for O_2 of the remaining heme moieties of the molecule, leading to the familiar sigmoid shape of the oxygen dissociation curve.

Reactions of oxygen and hemoglobin during capillary transit are further complicated by the rate of oxygen diffusion through the viscous interior of the red cell. The chemical reactions of oxygen and hemoglobin occur quite rapidly in dilute hemoglobin solutions but proceed more slowly in red cell suspensions. Because of the large size of the hemoglobin molecule and increased viscosity of the red cell contents, hemoglobin remains relatively immobile. As the red cell enters the pulmonary capillary, oxygen molecules bind to reduced hemoglobin molecules just inside the erythrocyte membrane. As these hemoglobin molecules become saturated, subsequent oxygen molecules entering the red cell must diffuse more deeply into the interior of the cell to reach reduced hemoglobin molecules. This combination of diffusion and chemical reaction causes oxygen uptake to occur as an "advancing front" that proceeds at a rate that is an order of magnitude slower than O_2 uptake in well-mixed, dilute hemoglobin solution. This combined process is complex and not easily described from a theoretical standpoint. As a result, the rate of oxygen uptake by hemoglobin contained in red cells is described by a single overall descriptive parameter, θ_{O_2}, which incorporates all the processes into a single phenomenological value. θ_{O_2} varies with oxygen saturation, pH, and hemoglobin type. The same approach is used to describe carbon monoxide uptake in blood. The rate at which CO replaces bound O_2 in blood with a normal hemoglobin concentration is described by θ_{CO}.

The rates of O_2 and CO uptake by erythrocyte suspensions are determined in vitro and assumed to be representative of the rates of gas exchange in vivo. However, measurements of these rate constants in red cell suspensions in vitro may be affected adversely by methodological artifacts. The actual rates of combination of O_2 and CO with red cells in vivo have not been measured and this lack of data leads to uncertainties in our understanding of exchange of the two gases in the lung.

CARBON DIOXIDE

CO_2 is transported in blood as dissolved molecular CO_2, bicarbonate ion, and carbamate ion.[2] The latter is a salt of a carbamic acid formed by reaction of CO_2 with terminal amino groups of the four chains comprising the hemoglobin molecule. The relation between the partial pressure of CO_2 and the total content of CO_2 in all forms is described by the CO_2 dissociation curve of blood (see Chapter 15, Fig. 15-4). Because CO_2 is more soluble than O_2 in the alveolar–capillary membrane, it often is assumed that CO_2 exchange occurs much more rapidly than O_2 exchange. However, only dissolved CO_2 can cross the alveolar–capillary membrane, and conversion of bicarbonate and carbamate to dissolved CO_2 limits the rate of CO_2 exchange. As indicated in Figure 16-1, *Upper Panel*, when a bolus of dissolved CO_2 is injected into an isolated lung perfused with saline buffer, CO_2 is rapidly exchanged similar to the inert gas acetylene.[3] In contrast, when a bicarbonate bolus is injected into the same preparation (Fig. 16-1, *Lower Panel*), CO_2 exchange lags behind acetylene excretion because a finite period of time is required to convert bicarbonate into dissolved CO_2 that can cross the alveolar–capillary membrane.

As blood enters the pulmonary capillary bed, dissolved CO_2 immediately diffuses into the alveoli and capillary blood P_{CO_2} falls to the level present in the alveolar gas. The majority (>85%) of the CO_2 content in blood entering the capillary bed exists as bicarbonate ion.[2,4] The rapid decrease in capillary P_{CO_2} disturbs the equilibrium between bicarbonate ion and dissolved CO_2 in both the plasma and the red cell. Bicarbonate ion combines with hydrogen ion extremely rapidly to form carbonic acid (H_2CO_3). The natural rate of dehydration of carbonic acid to CO_2 and water is a slow process, requiring 60 to 90 seconds to reach completion. However, the reaction is catalyzed inside the red cell by a factor of ~15,000 by the large concentration of carbonic anhydrase (CA) in red cells.

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \xrightarrow{CA} CO_2 + H_2O \qquad (2)$$

The substantial buffering capacity of hemoglobin inside the erythrocyte, augmented by the simultaneous conversion of reduced to oxygenated hemoglobin, provides the hydrogen ions required for this reaction.[4] The dissolved CO_2 formed by this reaction inside the red cell immediately leaves the blood and enters the alveoli.

There is a minimal amount of CA attached to the interior surface of the pulmonary capillaries, but its activity is <1% of the erythrocytic enzyme. As a result, little or no conversion of bicarbonate to dissolved CO_2 occurs in the plasma during the short

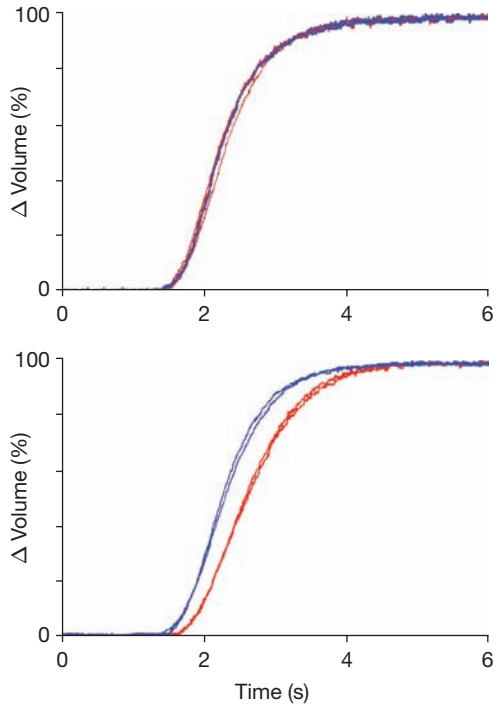

Figure 16-1 Rates of acetylene *(blue curves)* and CO_2 *(red curves)* excretion after two pairs of injections into the pulmonary artery of a single isolated lung preparation perfused with buffer. Volume changes are normalized to facilitate comparison. *Upper Panel*: The excretion of both acetylene and CO_2 proceed at the same rate after injections of buffer containing either dissolved CO_2 or acetylene. Differences in mean transit times for CO_2 and acetylene were −0.027 second for first pair and +0.022 second for second pair of injections. Thus, CO_2 crosses the alveolar–capillary membrane at the same rapid rate as the inert gas acetylene. *Lower Panel*: The excretion of CO_2 generated from injections of bicarbonate *(red curves)* lags behind the excretion of dissolved acetylene (*blue curves*) by +0.301 second in the first set of paired injections of acetylene and bicarbonate and 0.312 second in the second set of paired injections. This slower excretion of CO_2 is caused by the time required to convert bicarbonate to CO_2 with catalysis in this experiment provided by carbonic anhydrase localized to the capillary endothelium. *(Reproduced with permission from Schunemann HJ, Klocke RA: Influence of CO_2 kinetics on pulmonary carbon dioxide exchange. J Appl Physiol. 1993;74:715.)*

pulmonary capillary transit time (0.75 second at rest, 0.5 second during exercise). Inside the red cell, the catalyzed formation of dissolved CO_2 rapidly (~0.1 second) depletes the concentration of intracellular bicarbonate and the production of CO_2 slows substantially[1,5] However, as the intracellular concentration of bicarbonate decreases, plasma bicarbonate enters the cell in exchange for intracellular chloride. Bicarbonate–chloride movement across the erythrocyte membrane occurs in an electrically neutral, one-for-one exchange that is facilitated by an anion exchange protein present in the erythrocyte membrane.[2] Despite the presence of approximately one million anion exchangers with an extremely rapid turnover (50,000 ions per second) in each red cell membrane, bicarbonate–chloride exchange requires 0.3 to 0.4 second to reach completion.[1]

Besides exchange of dissolved CO_2 and bicarbonate, a modest amount of CO_2 excretion (13%) results from release of CO_2 bound to hemoglobin as carbamate.[2] The release of CO_2 bound as carbamate is caused by the alteration of the molecular conformation of hemoglobin that accompanies oxygenation. The carbamate reaction is complete in 0.2 to 0.3 second, but cannot occur until hemoglobin is first oxygenated. The process of oxygenation further delays conversion of carbamate to dissolved CO_2.

Thus, exchange of CO_2 in the lung is thought to require at least ~0.4 to 0.5 second because of the series of processes that are necessary to convert CO_2 carried as bicarbonate and carbamate to dissolved CO_2.[1,5] In fact, computational models of CO_2 exchange suggest that in some circumstances exchange is not quite completed prior to blood leaving the pulmonary capillary.[1,5] Even in the worst case, the degree of disequilibrium is small and a minimal increase in ventilation can easily compensate for a slight impairment of CO_2 exchange.

SOURCES OF CO_2 EXCRETED IN THE LUNGS

Bicarbonate accounts for the majority (>85%) of the total CO_2 content transported in arterial and venous blood. Dissolved CO_2 (~5%–6%) and carbamate (<10%) contribute substantially less to the total CO_2 content of blood. The quantity of bicarbonate transported in plasma is much greater than that carried within the red cells for three reasons. First, plasma volume constitutes 55% and erythrocytes only 45% of the total blood volume. Second, bicarbonate is present only in the volume of water in each component; plasma water content (95%) is substantially greater than erythrocyte water content (72%). Third, because of the Donnan distribution of anions across the erythrocyte membrane, bicarbonate concentration inside the red cell is only 63% of the plasma concentration.

The relative contributions of each form of CO_2 content to the quantity of CO_2 excreted during gas exchange in the lung are not exactly proportional to their blood contents. Analysis of the differences between arterial and venous blood CO_2 contents can be used to calculate the amounts of each form of carbon dioxide content excreted in expired ventilation.[2,6,7] This analysis of differences between arterial and venous blood CO_2 contents is shown in Figure 16-2. The vast majority of expired CO_2 enters the lung as bicarbonate and is converted into CO_2 during capillary transit. The contribution of plasma bicarbonate (49%) is greater than the erythrocytic bicarbonate (30%) that is converted into CO_2 and excreted in expired ventilation. Essentially all the CO_2 derived from bicarbonate, whether in plasma or erythrocytes, has to be exposed to CA within the red cells to allow for reaction catalysis during the

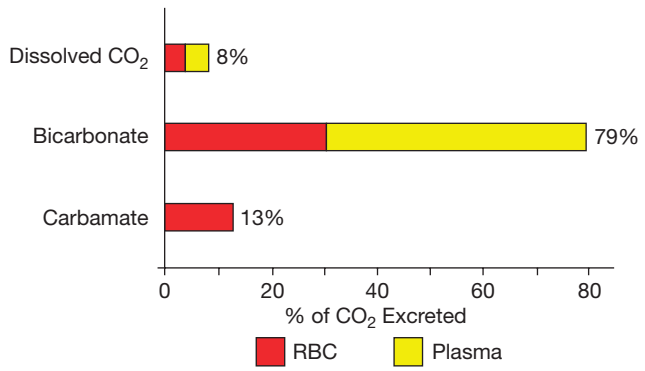

Figure 16-2 Sources of carbon dioxide excreted during passage of blood through the lungs in resting humans. The bars indicate the quantities of the different sources of CO_2 leaving blood from red cells *(red)* and plasma *(yellow)*. Bicarbonate contributes the overwhelming majority of CO_2 to the expired ventilation. As indicated in the figure, the majority of excreted bicarbonate enters the lung in plasma and is exchanged for chloride to reach carbonic anhydrase and hemoglobin buffering capacity within the red cell. *(Data from Klocke RA. Carbon Dioxide Transport, in Handbook of Physiology. Section 3, The Respiratory System, vol 4, edited by LE Farhi, SM Tenney SM. Bethesda: American Physiological Society; 1987.)*

brief capillary transit. This emphasizes the importance of anion exchange across the erythrocyte membrane in the process of carbon dioxide excretion.

The contributions of dissolved CO_2 and carbamate to the quantity of CO_2 in expired ventilation are modest, but are slightly greater than their relative concentrations in blood. Slightly more dissolved CO_2 originates in the plasma than in the red cells because of the greater amount of water in plasma. All excreted CO_2 derived from carbamate entered the lung bound to hemoglobin inside the erythrocytes.

DIFFUSING CAPACITY

The pulmonary diffusing capacity (D_L) of a gas provides an estimate of its rate of transfer from the alveoli into capillary blood. Initially investigators thought that only diffusion of gas across the membrane limited exchange. This is the case for inert gases and, as noted earlier, equilibrium of these gases is achieved rapidly even in disease. However, transfer of gases that combine with hemoglobin are limited both by diffusion across the alveolar membrane and by the rate of reactions inside red blood cells.[8] The only gases that have measurable diffusing capacities are those with low solubility in the pulmonary membrane and high capacitance in blood as a result of binding to hemoglobin. These gases include oxygen (O_2), carbon monoxide (CO), and nitric oxide (NO).

DIFFUSING CAPACITY OF OXYGEN ($D_{L_{O_2}}$)

The diffusing capacity is calculated as the volume of gas absorbed by pulmonary blood per unit time ($\dot{V}$) divided by the pressure gradient between alveolar gas (P_A) and pulmonary capillary blood (Pcap).

For oxygen,

$$D_{L_{O_2}} = \frac{\dot{V}_{O_2}}{PA_{O_2} - Pcap_{O_2}} \quad (3)$$

Measurement of $D_{L_{O_2}}$ is difficult because, in addition to diffusion, O_2 transfer may be limited by other mechanisms, such as ventilation–perfusion mismatching and shunting. The measurement is further complicated by a changing capillary P_{O_2} during capillary transit that cannot be accurately determined. These difficulties have led investigators to abandon attempts to measure the diffusing capacity of oxygen.

DIFFUSING CAPACITY OF CARBON MONOXIDE ($D_{L_{CO}}$)

Carbon monoxide provides an excellent alternative to measuring diffusing capacity because CO normally is present in minimal amounts in blood and binds to hemoglobin similar to O_2. Because capillary P_{CO} is extremely low in usual circumstances, it can be assumed to be negligible and $D_{L_{CO}}$ is calculated by dividing CO uptake ($\dot{V}_{CO}$) by alveolar P_{CO}. However, like oxygen, CO uptake is limited both by diffusion across the alveolar–capillary membrane and by chemical reaction of CO with intracellular hemoglobin. As described by Roughton and Forster,[8] $D_{L_{CO}}$ comprises two elements:

$$\frac{1}{D_{L_{CO}}} = \frac{1}{Dm_{CO}} + \frac{1}{\theta_{CO} V_c} \quad (4)$$

where

Dm_{CO} = the diffusing capacity of the alveolar–capillary membrane for CO

θ_{CO} = the rate of displacement of O_2 from intracellular hemoglobin by CO

V_c = the volume of blood in the pulmonary capillary bed

Because O_2 and CO compete for binding sites on hemoglobin, CO binding is inhibited by increases in P_{O_2}. Thus, $D_{L_{CO}}$ and θ_{CO} vary inversely with P_{O_2}. Using known in vitro values of θ_{CO} and two measurements of $D_{L_{CO}}$ at normal and elevated inspired O_2 concentrations, Eq. (4) can be solved to provide values of both Dm_{CO} and V_c. Calculation of the diffusing capacity is based on the assumption that the lung is homogeneous, that is, all portions of the lung have the same relative ventilation, perfusion, alveolar volume, and diffusing capacity.

DIFFUSING CAPACITY OF NITRIC OXIDE ($D_{L_{NO}}$)

Nitric oxide binds to hemoglobin at the same sites as O_2 and CO, but the rate of NO binding is much more rapid. Since NO binds to hemoglobin in solution two orders of magnitude faster than the rate of CO binding, it has been postulated that θ_{NO} is much greater than θ_{CO} and approaches a value of infinity. If this is the case, then the term $1/\theta_{NO}V_c$ (analogous to Eq. (4) for CO) approaches zero and the diffusing capacity measured with NO should reflect only the resistance to gas transfer provided by the alveolar–capillary membrane, that is, the Dm_{CO} component of the CO diffusing capacity. If NO binds to intracellular hemoglobin instantaneously, D_L (and hence Dm) measured with NO should be 1.97 times Dm measured with CO because NO has a greater aqueous solubility and a minimally larger diffusion coefficient than CO. Phansalkar et al.[9] performed simultaneous measurements of $D_{L_{NO}}$ and the components of $D_{L_{CO}}$ in both normal individuals and patients with sarcoidosis at varying levels of exercise intensity. The ratio of $D_{L_{NO}}/Dm_{CO}$ did not differ in the two groups and averaged 2.42, moderately greater than the theoretical value of 1.97 (Fig. 16-3, *Lower Panel*). The ratio of

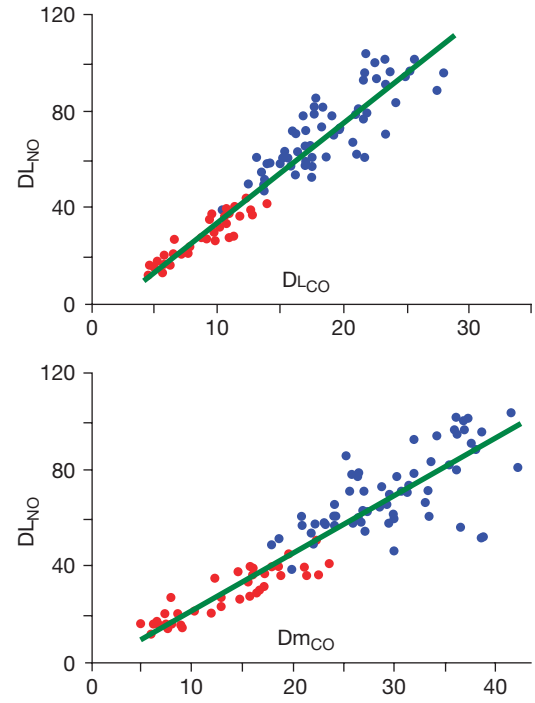

Figure 16-3 Relationships between simultaneous measurements of *(Upper Panel)* $D_{L_{NO}}$ and $D_{L_{CO}}$ and *(Lower Panel)* $D_{L_{NO}}$ and Dm_{CO} in patients with sarcoidosis *(red circles)* and normal subjects *(blue circles)*. The units of all parameters in the figure are mL/min/mm Hg/m^2. $D_{L_{CO}}$ was expressed under standardized conditions of hemoglobin concentration (14.6 mg/dL) and alveolar O_2 tension ($P_{A_{CO_2}}$ 120 mm Hg). Regression lines through the pooled data are *(Upper Panel)* $D_{L_{NO}} = 4.16D_{L_{CO}} - 6.82$, $r^2 = 0.918$ and *(Lower Panel)* $D_{L_{NO}} = 2.42\ Dm_{CO} - 1.87$, $r^2 = 0.865$. *(Reproduced with permission from Phansalkar AR, Hanson CM, Shakir AR, et al. Nitric oxide diffusing capacity and alveolar microvascular recruitment in sarcoidosis. Am J Respir Crit Care Med. 2004;169(9):1034–1040.)*

$D_{L_{NO}}/D_{L_{CO}}$ in both groups did not differ and averaged 4.16 (Fig. 16-3, *Upper Panel*).

More recent work challenges the postulate that θ_{NO} has a value of infinity and $D_{L_{NO}}$ can be used to calculate Dm_{CO}. Borland et al.[10] have shown that $D_{L_{NO}}$ increases progressively as red blood cells are replaced with hemolyzed blood or cell-free heme-based blood substitute, an observation that should not occur if θ_{NO} truly has a value of infinity. As a result, it is premature to speculate on the potential clinical value of measurements of $D_{L_{NO}}$ until the underlying physiology of the measurement of $D_{L_{NO}}$ is clarified. The technique of the measurement itself varies among laboratories. In addition, it requires sophisticated equipment and technical expertise that only are present in research settings.

METHODS FOR MEASURING THE DIFFUSING CAPACITY

Several different techniques are used to measure the carbon monoxide diffusing capacity. In clinical settings the single breath method is utilized almost exclusively. The steady-state and rebreathing methods of determining $D_{L_{CO}}$ are employed primarily in research. The steady-state method usually is performed in subjects who are exercising, thereby limiting its clinical application in patients with restricted ability to exercise. The rebreathing methodology requires rapid-responding gas analyzers and has technical requirements that are not available in most clinical laboratories.

Single Breath Method

With the single breath technique the subject exhales to residual volume, inhales a maximal breath of 0.3% CO, a tracer gas (usually 10% helium), 21% oxygen, and balance nitrogen. The breath is held for approximately 10 seconds followed by a maximal exhalation. After sufficient expiration to clear the dead space, a gas sample is collected to estimate final alveolar CO and helium fractions. After inspiration, the alveolar partial pressure of CO falls exponentially as CO enters the capillary blood. The volume of CO absorbed in the lungs can be calculated from the alveolar volume and the initial and final concentrations of CO in alveolar gas. The rate of CO uptake during the breath-hold is a function of the alveolar $P_{A_{CO}}$, which falls exponentially during the breath-hold. Capillary CO pressure is assumed to be equal to zero. The single-breath diffusing capacity is calculated by:

$$D_{L_{CO}} = \frac{60 V_A}{t_{bh}(P_B - 47)} \ln \frac{F_{A_{CO\ initial}}}{F_{A_{CO\ final}}} \quad (5)$$

where

- 60 = the number of seconds per minute
- V_A = the alveolar volume of gas (mL_{STPD}) present in the lung at the start of the breath-hold
- t_{bh} = the duration of the breath-hold (seconds)
- P_B = the barometric pressure (mm Hg)
- $F_{A_{CO}}$ = the alveolar fraction of carbon monoxide at the initial and final times of the breath-holding period

The insoluble inert gas (usually helium) included in the inspired volume is not absorbed in capillary blood and is diluted in the residual volume present at the start of the maximal inspiration. V_A is calculated from the dilution of the helium and the inspired volume (V_I):

$$V_A = V_I \frac{F_{I_{He}}}{F_{A_{He}}} \quad (6)$$

where

$F_{I_{He}}$ and $F_{A_{He}}$ = the inspired and alveolar helium concentrations

The alveolar fraction of He and the final alveolar CO fraction are obtained by measuring CO and He concentrations in the expired alveolar gas sample. The initial alveolar CO fraction is calculated from the dilution of the inspired CO in the volume of gas present in the lung during the breath-hold,

$$F_{A_{CO}} = F_{I_{CO}} \frac{V_I}{V_A} \quad (7)$$

where

$F_{I_{CO}}$ = the inspired CO fraction

The single breath method requires some degree of patient cooperation to perform the necessary respiratory maneuvers. A patient with an extremely reduced lung volume may not have a vital capacity large enough to clear the dead space and provide a sufficient sample for analysis of alveolar gas concentrations. The ability to hold the breath for 10 seconds also limits applicability to some patients. Finally, this method can be employed only in the resting state since few patients can hold their breath during exercise. Despite these limitations, the single breath $D_{L_{CO}}$ is the most practical and widely used method for measuring $D_{L_{CO}}$. The technical aspects of the test have been standardized so that the same methodology is utilized in most laboratories.[11]

MEASUREMENT OF Dm AND V_c

Using values of θ_{CO} measured in vitro and values of $D_{L_{CO}}$ determined with different inspired O_2 concentrations, Eq. (4) can be solved for the membrane diffusing capacity (Dm_{CO}) and capillary blood volume (V_c).[8] However, there is considerable uncertainty regarding values of θ, the rate of red cell uptake of gases that bind to hemoglobin. Most in vitro measurements of θ have utilized rapid reaction techniques that may be flawed due to unstirred layers of fluid surrounding the red cells in the experimental apparatus. This artifact is greater the more rapidly that the gas reacts with hemoglobin ($NO > O_2 > CO$). Furthermore, the rate of gas uptake by erythrocytes may be influenced by the ability of the red cells to be deformed during passage through the pulmonary capillaries, a factor not present during in vitro measurements of θ. Mathematical models suggest that the rate of uptake of gases also depends on erythrocyte orientation and spacing within capillaries. Since the characteristics of erythrocyte transit in the capillary bed have not been defined, extrapolation of in vitro measurements to the in vivo situation introduces elements of uncertainty. Despite these reservations, solution of Eq. (4) using values of θ_{CO} determined in vitro yields values of Dm_{CO} and V_c that agree with independent estimates of these variables using alternate techniques.

Calculation of pulmonary capillary blood volume (V_c) from measurements of $D_{L_{CO}}$ is dependent upon the value of θ_{CO} chosen for the computation. Using in vitro data for θ_{CO} yields values at rest of 75 to 100 mL for men and slightly less for women. V_c measured by the CO method is dependent upon the quantity of hemoglobin present in the capillary bed in addition to the actual capillary volume. Calculation of V_c assumes a normal hemoglobin concentration in capillary blood and variation in this parameter affects the $\theta_{CO}V_c$ component of $D_{L_{CO}}$.

Dm and V_c have been estimated from morphometric data obtained from excised, fixed canine lungs.[12] Calculations of $D_{L_{CO}}$ using these postmortem morphometric values and in vitro values of θ_{CO} have yielded estimates of $D_{L_{CO}}$ that are much greater than measurements of $D_{L_{CO}}$ under resting conditions in the same intact animal. This discrepancy arises because morphometric measurements are obtained in maximally inflated lungs. The morphometric estimates reflect a fully recruited alveolar surface area and V_C, a circumstance seen during maximal oxygen uptake during exercise. When $D_{L_{CO}}$ calculated from morphometric data is compared to $D_{L_{CO}}$ measured in intact animals under conditions of maximum exercise, there is good agreement between the two estimates.

FACTORS INFLUENCING DIFFUSING CAPACITY

The CO diffusing capacity originally was thought to reflect the resistance of the alveolar–capillary membrane to transfer of CO from

the alveoli to capillary blood. The classic work of Roughton and Forster[8] elucidated the influence of chemical reactions on transfer of CO. D_{LCO} may be a measure of decreased gas transfer caused by abnormal diffusion, but also can reflect reduction in hemoglobin concentration, nonuniform distribution of physiological properties throughout the lung, loss of lung tissue, or artifacts in measurement. Because multiple factors in addition to diffusion can affect D_{LCO}, in Europe this test is often termed the CO transfer factor, rather than the CO diffusing capacity.

Hemoglobin Concentration

Capillary blood volume (V_c) is a prime variable in the diffusing capacity; its importance is due to the quantity of hemoglobin available to combine with CO within the capillary bed. The calculated value of V_c can be reduced directly by diseases that decrease capillary volume, but also can vary with the concentration of hemoglobin in blood. For this reason, the predicted D_{LCO} can be corrected for alterations in hemoglobin concentration.[11] For adult males and adolescents:

$$\text{Predicted } D_{LCO} \text{ (Corrected)} = \text{Predicted } D_{LCO} \, (1.7 \, Hb/(10.22 + Hb)) \quad (8)$$

where

Hb = hemoglobin concentration expressed in g/dL

For adult women and children less than age 15, the factor of 10.22 in Eq. (8) is replaced by a factor of 9.38. However, most clinical laboratories do not correct the predicted value of D_{LCO} for abnormal hemoglobin values.

Partial Pressure of Alveolar Oxygen

As indicated previously, θ_{CO} depends on P_{O_2}. Increased alveolar P_{O_2} will reduce measured D_{LCO}. Therefore, D_{LCO} will be lowered if patients receive supplemental oxygen during the measurement. Conversely, reduced alveolar P_{O_2} will lead to an increment in measured D_{LCO}. This has led to the suggestion to apply a correction to D_{LCO} if the measurement was made with an altered inspired oxygen fraction or at altitude. Even when alveolar P_{O_2} is kept at a sea level value during the measurement, lifelong residents of a community located 10,000 ft above sea level have demonstrated moderately greater diffusing capacities than sea-level residents.[13] Short-term residence (6 weeks) at altitude does not cause an increase in D_{LCO}. Beagles raised at altitude, even after reacclimation to sea level, still have moderately greater diffusing capacities than beagles raised at sea level. However, adult dogs taken to altitude for 3 years do not exhibit an increased D_{LCO}, suggesting that residence at altitude during growth is the basis for the increased D_{LCO}.

Body Position

D_{LCO} is 5% to 15% greater in the supine position than in the erect position. Blood volume shifts from the lower trunk and legs to the lungs when in the supine position. Most of the increase in D_{LCO} appears to be due to a 13% to 27% increase in V_c accompanying the fluid shift. However, there is also a minimal increase in Dm_{CO} in the supine position, possibly the result of recruitment of capillaries by the increased intravascular volume. The effect of posture on D_{LCO} decreases with age, but the reasons underlying this observation remain unknown.

Exercise

D_{LCO} can increase as much as twofold during exercise. This increase is attributed to proportionally equal increases in both Dm and V_c. Both alveolar–capillary surface area and capillary volume are recruited by the increase in cardiac output that accompanies exercise. The transit time through the capillary bed decreases, but not to the same degree as would be predicted in a vascular bed with fixed resistance. The potential reduction in transit time is partially offset by recruitment and distention of the pulmonary capillary bed.

Theoretically, D_{LCO} must have a maximum that cannot be exceeded when the entire pulmonary capillary bed and alveolar surface have been recruited. This should lead to a plateau in measured D_{LCO} even though the level of exercise continues to increase. This has never been observed in humans. Using a unique animal model of conscious greyhounds exercising on a treadmill, Carlin et al.[12] could not demonstrate a plateau in D_{LCO} with increasing exercise even though oxygen uptake reached a level of approximately 120 mL/kg/min. This level of O_2 uptake is almost twice that is seen in highly trained humans. Thus, it seems unlikely that the diffusing capacity in humans reaches a plateau during maximal exercise, but this does not rule out the possibility that gas exchange is limited by diffusion in this circumstance. Disequilibrium may occur before maximum recruitment of the diffusing capacity because capillary transit time may be less than the time required for O_2 exchange to be completed. Evidence in humans suggests that blood may leave the capillary bed without attaining complete equilibrium between alveolar P_{O_2} and capillary P_{O_2} at sea level in some patients with lung disease during exercise and in some highly trained athletes during maximal exercise. This also can occur in normal individuals at extremely high altitude with a marked reduction in the inspired P_{O_2}.

Alveolar Volume

D_{LCO} decreases with reduction in alveolar volume due to accompanying decreases in Dm_{CO} and V_c. This occurs with an inadequate inspiration to total lung capacity in persons with normal lungs, or with maximal inspiration in patients whose total lung capacities have been reduced by disease. In an effort to correct for alterations in alveolar volume rather than a true loss of diffusing capacity, some clinicians and investigators normalize D_{LCO} by dividing the observed D_{LCO} by the alveolar volume present during the measurement. This ratio of D_{LCO}/V_A will be a useful index only if two assumptions are valid. First, there must be an approximately linear relation between D_{LCO} and V_A. This assumption is reasonable at lung volumes greater than 50% of total lung capacity, but not at lower lung volumes. Second, the relation between D_{LCO} and V_A must be directly proportional (i.e., a graph of D_{LCO} vs. V_A must pass through the origin of the graph). This clearly is not the case. D_{LCO}/V_A is not constant in normal persons and varies as alveolar volume changes.[14] Although frequently used, the D_{LCO}/V_A ratio alone does not provide a valid index of the effect of changes in alveolar volume.[14,15]

Nonuniform Distribution of Physiological Properties

Calculation of D_{LCO}, regardless of the method used to make the measurement, implicitly assumes that the lung is completely uniform with regard to ventilation, alveolar volume, perfusion, and diffusive properties. This requires that each gas exchange unit possesses the same relationship between all these physiological properties, an assumption that is not completely valid even in normal, healthy persons. The most important factor determining CO uptake is the relationship of local diffusing capacity to local blood flow, the ratio of D_{LCO}/Q. Nonuniform distribution of important physiological variables throughout the lung produces a decrease in diffusing capacity and, by analogy, a reduced ability to transfer oxygen from the inspired air to capillary blood. Transfer is further complicated by the nonlinear nature of the processes involved. For example, the oxygen dissociation curve of hemoglobin has a sigmoid shape and a change in alveolar P_{O_2} may have a large or a minimal effect on the quantity of O_2 exchanged depending on the absolute value of the P_{O_2}. Disruptions of these complex relationships among physiological parameters have variable effects on O_2 transfer. The contributions of individual pathophysiological deviations cannot be assessed

by a global measurement such as the diffusing capacity. Thus, D_{LCO} provides a means of assessing overall oxygen exchange but does not indicate specific defects in gas exchange.

■ TECHNICAL CONSIDERATIONS

Measurements of D_{LCO} have greater variation than spirometric observations such as the forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV_1). Criteria for acceptable measurements of D_{LCO} have been based upon relative or absolute differences between repeated measurements. The American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement[11] recommends reporting the average of two measurements, both of which agree within 3.0 mL/min/mm Hg or within 10% of the higher measured value. Punjabi et al.[16] reported that an absolute difference of 2.5 mL/min/mm Hg between duplicate measurements could be achieved in 96% of patients. This criterion was deemed more reasonable than a percentage variation because it remained constant over a wide range of measured values in contrast to a changing percentage criterion. The strength of this study is in its size (over 6000 patients) and its performance during routine pulmonary testing in a single clinical setting. A drawback to its universal application is that three or more determinations of D_{LCO} were required in one-half of patients to meet criteria of acceptability. It is important to note that some clinical laboratories will perform only a single diffusing capacity measurement and report this value rather than reporting the mean of at least two acceptable determinations. This obviously increases the variability of reported values and lessens the ability to compare measurements over a period of time.

There is considerable variation in measurements of D_{LCO} among different clinical laboratories. These differences can be overcome by following strict technical protocols. In a carefully controlled multicenter (33 sites) clinical trial, Wise et al.[17] reported that 75% and 95% of the differences between duplicate D_{LCO} determinations with acceptable subject efforts (4797 pairs) were within <1 and <2 mL/min/mm Hg, respectively (Fig. 16-4). Acceptable criteria included inspired volume >90% of the FVC and a breath-hold time between 9 and 11 seconds.

The time of the breath-holding maneuver in the single breath method requires patient cooperation. Because of nonuniform distribution of physiological variables, CO uptake does not occur in a strictly exponential fashion even in healthy persons. As a result, measured D_{LCO} decreases slightly with prolonged breath-hold in normal subjects. This decrement can be substantially greater in patients with lung disease. The empirical breath-holding time of 10 seconds was chosen as a practical compromise to permit measurable CO uptake but still be feasible for patients to perform. Many laboratories set a breath-hold range of 9 to 11 seconds as acceptable, although the ATS/ERS consensus report[11] accepts a range of 8 to 12 seconds. Patients with lung disease often cannot perform rapid respiratory maneuvers mandated by the single breath D_{LCO} measurement. Slower flow rates prolong the time required for inspiration and expiration. As a result, instantaneous, uniform mixing of alveolar contents assumed in the calculation of D_{LCO} is not achieved. This may lead to a decrement in the reported measurement.

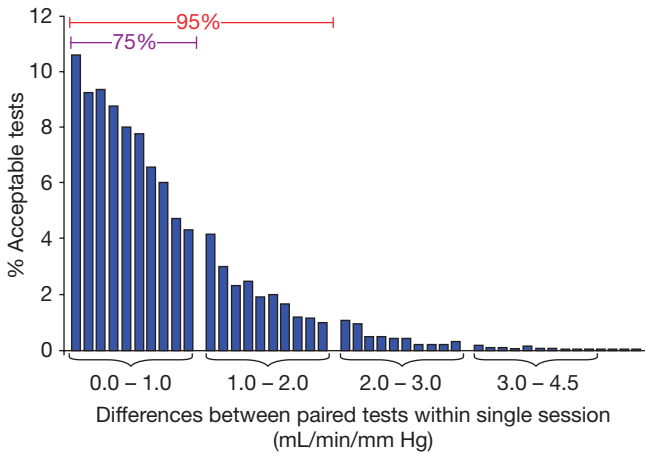

Figure 16-4 Differences between pairs of D_{LCO} measured within a single session in 4732 patients who had acceptable D_{LCO} efforts. The bars in the figure include differences in 75% of paired measurements *(purple)* and the differences in 95% of paired measurements *(red). (Data from Wise RA, Teeter JG, Jensen RL, et al. Standardization of the single breath diffusing capacity in a multicenter clinical trial. Chest. 2007;132:1191.)*

Most laboratories request that patients refrain from smoking for variable periods of time prior to measurement of D_{LCO} to avoid accumulation of CO in blood. Significant elevation of carboxyhemoglobin reduces measured D_{LCO} in two ways. First, the presence of carboxyhemoglobin produces a functional anemia, lessening the capacity of hemoglobin to bind O_2 or CO. This reduces the $\theta_{CO}V_c$ component of D_{LCO}. Second, calculation of D_{LCO} assumes that the back pressure of CO in the capillary is zero, and the gradient for CO transfer is equal to $P_{A_{CO}}$. The presence of carboxyhemoglobin in blood produces an actual alveolar–capillary PCO gradient less than that assumed in the calculation, thereby leading to a lower calculated value of D_{LCO}. Graham et al.[18] measured the effect of experimental elevation of carboxyhemoglobin in normal individuals. Values of D_{LCO} obtained with the usual single breath calculation decreased approximately 1.5% from the true value for each 1.0% elevation of blood carboxyhemoglobin. Although algorithms are available to correct observed D_{LCO} for carboxyhemoglobin effects, it is preferable to make the measurement without a significant elevation of carboxyhemoglobin. At a minimum, 12 hours of abstinence from smoking is advisable in patients who smoke extensively because carboxyhemoglobin levels as great as 6% to 12% are observed immediately following tobacco usage.

■ CONTROVERSIES IN INTERPRETATION OF D_{LCO}

As noted previously, D_{LCO} is affected by a number of circumstances. Alveolar P_{O_2} and body position do not present significant problems since a standard inspired P_{O_2} and the sitting position are utilized during measurements in most clinical laboratories. Equations to correct for alterations of alveolar P_{O_2} are available if needed. Empirical equations also can adjust the predicted value of D_{LCO} to compensate for anemia or polycythemia.

Variability in cardiac output and the alveolar volume present during the measurement provides more significant problems. The increases in D_{LCO} observed during exercise are the result of large increases in cardiac output. Increasing cardiac output together with enlargement of the capillary bed increases not only V_c, but also increases Dm because capillary volume and surface area of the alveolar–capillary membrane are related variables. Clinical measurements of D_{LCO} are accomplished under resting conditions, minimizing but not obviating, variability in cardiac output. In addition, disease can alter the distribution of blood flow in the lung in patterns that do not match the distribution of diffusive properties. Unfortunately, measurements of pulmonary blood flow and its distribution are not conveniently measured in clinical laboratories. As a result, the effect of cardiac output on D_{LCO} may not be appreciated in routine determinations. The only practical alternative is to minimize conditions that might alter pulmonary blood flow.

Reduction in alveolar volume by disease is the largest potential source of error in interpreting D_{LCO}. Correction for the effect of altered alveolar volume has been attempted by reporting the ratio of D_{LCO}/V_A. However, this attempt to normalize measurements by

alveolar volume leads to errors because D_{LCO}/VA does not remain constant as alveolar volume changes. Stam et al.[14] reported values of D_{LCO} and D_{LCO}/VA obtained at several alveolar volumes in normal subjects. They recommend using predicted values of D_{LCO} or D_{LCO}/VA for patients with reduced alveolar volumes equal to values in normal subjects measured at the same reduced alveolar volume. This assumes that disease processes that reduce alveolar volume in patients produce the same changes in D_{LCO} as voluntary reduction in alveolar volume in normal subjects. In a subsequent report,[19] they demonstrated this to be the case in patients with normal lung function tested before, during, and after undergoing treatment with bleomycin for malignancies. In these patients, the linear relationship of D_{LCO}/VA measured at different alveolar volumes shifted downward in parallel fashion as bleomycin produced lung injury. This finding supports the adjustment of predicted values on the basis of reduced alveolar volumes in normal subjects since the slope of the D_{LCO}/VA ratio in relation to VA was the same before and after lung injury. These data were obtained by measuring D_{LCO} at a variety of alveolar volumes prior to and after the pulmonary insult, a situation that is rarely possible in clinical practice. Data obtained in patients with sarcoidosis also support the concept of using predicted values obtained at lower lung volumes in normal subjects.[9] However, other reports in different clinical conditions suggest that some diseases may not affect D_{LCO} in the same manner as voluntary changes in normal subjects. These uncertainties have led to substantial controversy regarding the value of the ratio D_{LCO}/VA.[15,20] Final judgment will require collection of extensive data in a variety of disease states. Regardless of the outcome of this controversy, it is apparent that if D_{LCO}/VA is used in the interpretation of measurements of D_{LCO}, there must be some adjustment of predicted values of D_{LCO}/VA to reflect reductions in alveolar volume. D_{LCO}/VA, whether expressed as a ratio of these two linked measurements or as a rate constant for CO uptake (K_{CO}), is basically the same. The value of using either expression for clinical use is uncertain.

Measurements of Dm_{CO} and V_c can be useful in a carefully controlled, research setting, but there is little or no value of using isolated measurements of these two parameters to aid in diagnosis and clinical management.[21] Calculation of Dm_{CO} and V_c involves both a number of assumptions and extrapolations of data in the literature to a specific clinical setting. Even more cogent is the lack of sufficient data to validate the use of these measurements in clinical practice.

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CHAPTER 17

Acid–Base Balance

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Kumar Sharma

Regulation of $[H^+]$ is of crucial importance for maintenance of normal cellular functions. The normal $[H^+]$ is maintained at about 40 nEq/L. When there is even a small change in the $[H^+]$, intracellular proteins gain or lose H^+ ions resulting in alterations in charge distribution which may affect molecular structure and protein function. The hydrogen ion concentration in bodily fluids is largely regulated by the ratio of the concentrations of carbon dioxide and bicarbonate. This is predicated upon the relationship demonstrated in the Henderson–Hasselbalch equation:

$$pH = pKa + \frac{[HCO_3^-]}{0.03P_{CO_2}} \quad (1)$$

where $pH = -\log[H^+]$ (the H^+ concentration measured in moles per liter) and $pKa = 6.10$. The lungs are responsible for modulating arterial P_{CO_2}, whereas the kidneys are primarily responsible for modulating the concentration of bicarbonate in plasma. In concert, these organs maintain a stable extracellular acid–base milieu that is readily assessed by measuring arterial pH.

The normal internal environment is maintained within narrow limits: The arterial blood pH is kept remarkably close to 7.40, the bicarbonate concentration is maintained around 24.5 mEq/L, and the P_{CO_2} is maintained at about 40 mm Hg. Deviations of the pH with accompanying changes in the P_{CO_2} and $[HCO_3^-]$ result in the four major categories denoted in Table 17-1. Metabolic acidosis is characterized by acidemia ($pH < 7.35$) that is due to reduced plasma $[HCO_3^-]$. Metabolic alkalosis is characterized by an alkalemia ($pH > 7.45$) that results from an elevation in the plasma $[HCO_3^-]$. Respiratory acidosis is due to hypoventilation resulting in a net increase in P_{CO_2} (hypercapnia) and a concomitant fall in pH. Respiratory alkalosis is due to primary hyperventilation leading to a fall in P_{CO_2} (hypocapnia) and a rise in pH.

TABLE 17-1 Patterns of P_{CO_2} and HCO_3 Changes in Acid–Base Disorders

Primary Disturbance	Initial Abnormality	Compensatory Response	Expected Compensation
Metabolic acidosis	Decreased pH, decreased $[HCO_3^-]$	Decreased P_{CO_2}	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$ (Winter's formula)
Metabolic alkalosis	Increased pH, increased $[HCO_3^-]$	Increased P_{CO_2}	P_{CO_2} increases 0.6 mm Hg per mEq/L rise in $[HCO_3^-]$
Respiratory acidosis	Decreased pH, increased P_{CO_2}	Increased $[HCO_3^-]$	Acute: $[HCO_3^-]$ increases 1 mEq/L per 10 mm Hg rise in P_{CO_2} Chronic: $[HCO_3^-]$ increases 3.5 mEq/L per 10 mm Hg rise in P_{CO_2}
Respiratory alkalosis	Increased pH, increased P_{CO_2}	Decreased $[HCO_3^-]$	Acute: $[HCO_3^-]$ falls 2 mEq/L per 10 mm Hg fall in P_{CO_2} Chronic: $[HCO_3^-]$ falls 5 mEq/L per 10 mm Hg fall in P_{CO_2}

In this chapter, we first review the basic physiologic roles that the kidneys and lungs play in maintaining acid–base balance and then discuss their adaptation in primary acid–base disorders. The following section then focuses on clinical application of physiologic concepts in analyzing acid–base problems as encountered by the clinician.

BASIC PHYSIOLOGY OF THE ROLE OF THE KIDNEY IN ACID–BASE BALANCE

Normal metabolism generates large quantities of volatile acid (CO_2) and nonvolatile acid daily. The complete metabolism of carbohydrates and fats generates 15,000 mmol of CO_2 daily. This leads to acid generation as the CO_2 combines with H_2O to form carbonic acid (H_2CO_3). As the volatile fraction is excreted by the lungs during respiration, acid accumulation does not occur. The nonvolatile or "fixed" fraction is produced at a rate of 1 mEq/kg per day. The major source of the nonvolatile acid fraction is the oxidation of sulfur-containing proteins from the diet to sulfuric acid. If this amount of nonvolatile acid is not excreted, life-threatening metabolic acidosis ensues; therefore, for a normal individual to maintain acid–base balance, 50 to 100 mEq of nonvolatile acid must be excreted daily by the kidneys.

The addition of 50 to 100 mEq of acid requires initial buffering before it can be excreted. Whole-body buffering capacity is composed of interacting buffer systems: the bicarbonate and nonbicarbonate buffers (Buf^-), consisting primarily of hemoglobin, proteins, and phosphates. The sum of the buffer anions $[HCO_3^-]$ and $[Buf^-]$ is the total buffer base and defines total-body buffering capacity. Since all body buffer systems are in equilibrium, a change in the serum $[HCO_3^-]$ reflects concurrent changes in the other body buffer systems. The importance of bicarbonate in buffering is due to its relationship with CO_2. As H^+ ions are buffered by HCO_3^-, there is a decrease in the $[HCO_3^-]$ and a concurrent increase in the dissolved $[CO_2]$. As the $[CO_2]$ can be excreted by the lungs to maintain a constant $[CO_2]$, this substantially increases the buffering capacity of bicarbonate. Since the kidney plays a major role in controlling the $[HCO_3^-]$ and $[HCO_3^-]$ is easily measured in serum, the HCO_3^- anion is a useful parameter to evaluate the renal response to an acid load.

The H^+ ions released from the dissociation of sulfuric acid are titrated by blood bicarbonate and nonbicarbonate buffers.

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2H_2O + CO_2 \quad (2)$$

Although the added H^+ is excreted via CO_2 elimination by the lungs, this occurs at the cost of depletion of $[HCO_3^-]$. To *replenish* the consumed base, bicarbonate is reabsorbed by the kidneys and returned to the blood. This process does not accomplish the replacement of consumed base, since continuous metabolic production of acid will ultimately decrease the available base present. The process of renal *regeneration* of base requires the urinary excretion of acid or H^+ ions in the absence of any urinary bicarbonate. For every H^+ ion excreted, a bicarbonate is returned to the body. If there is any bicarbonate in the urine, there will be a net gain of H^+. Therefore the kidney has two major functions in this context: (1) reabsorption of all the filtered bicarbonate—this takes place primarily in the proximal tubule and (2) the base consumed by metabolism must be generated in the process of urinary acid excretion. This takes place

in the distal portions of the nephron, the distal collecting tubule, and the collecting ducts.

BICARBONATE RECLAMATION

The proximal tubule is responsible for reclaiming 70% to 90% of the filtered bicarbonate. This may occur either by direct bicarbonate absorption at the proximal tubule or via proton secretion into the lumen of the tubule. The latter mechanism appears to be the predominant pathway.[1] Acid excretion across the apical membrane of the proximal tubule occurs by an Na^+/H^+ antiporter (NHE3)[2] and to a lesser extent by a proton pump. The secreted proton enters the tubular fluid and combines with filtered bicarbonate ions leading to carbonic acid formation. Under the influence of carbonic anhydrase, carbonic acid is then split into CO_2 and H_2O. The CO_2 diffuses into the cell where it is rehydrated to carbonic acid and then again split into protons and bicarbonate. The bicarbonate ion exits from the cell through the basolateral membrane into the interstitium via a $3HCO_3/Na$ (NBCe1) symporter, while the proton is secreted into the lumen. The basolateral membrane Na^+/K^+ ATPase antiporter, maintaining a low intracellular sodium concentration, further enhances the NHE3 activity.

In summary, reabsorption of bicarbonate is a cyclic phenomenon and requires carbonic anhydrase and is strictly associated to sodium reabsorption.

Biochemical studies show that total NHE3 and NBCe1 protein abundance are upregulated by chronic respiratory acidosis.[3] However, the main mechanism responsible for the elevation in serum bicarbonate is the increased excretion of titratable acid and ammonium which are stimulated by persistently elevated P_{CO_2} (see Fig. 17-1).[4] It is important to understand that this process reclaims filtered bicarbonate but does not result in a net gain of bicarbonate. At the end of the proximal tubule there is a lowering of the luminal pH from 7.26 to 6.70, and the bicarbonate concentration is lowered from 24 mEq/L to 8 mEq/L.[5] The fluid delivered to the distal tubule is essentially the same with respect to pH and bicarbonate concentration as that which leaves the proximal tubule. The reclamation of the remaining bicarbonate occurs in the thick ascending limb and in the outer medullary collecting tubule. At the collecting tubule, H^+ secretion occurs primarily by an H^+ ATPase pump at the luminal membrane and bicarbonate entry to the blood is via a Cl^-/HCO_3^- exchanger at the basolateral membrane.[6]

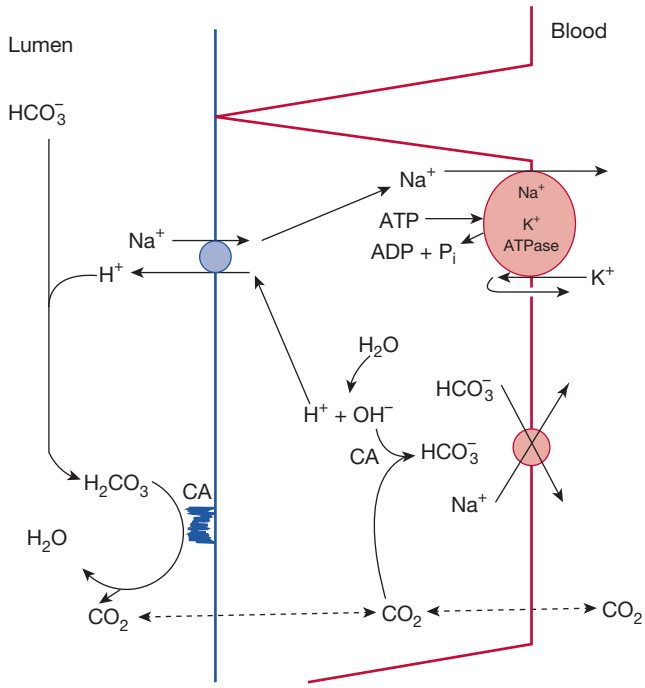

Figure 17-1 Schematic representation of proximal tubular reclamation of filtered bicarbonate. In the lumen, filtered bicarbonate reacts with secreted H^+, generating carbonic acid, which is dehydrated by carbonic anhydrase, CA, located on the brush border. The cell secretes H^+ by a process that exchanges H^+ for filtered Na^+. The source of secreted H^+ is water, which in turn generates OH^- and subsequently bicarbonate because of the presence of intracellular CA. Bicarbonate exits the basolateral side of the cell linked in some fashion with Na^+; sodium is also actively pumped out of the cell.

The crucial role of carbonic anhydrase is demonstrated by the fact that carbonic anhydrase inhibitors, that is, acetazolamide, result in bicarbonate wasting and the generation and maintenance of metabolic acidosis. The most physiologically important regulators of reclamation of bicarbonate are the pH, the P_{CO_2}, and the extracellular volume status of the patient. In states of acidosis, there is enhanced luminal Na^+/H^+ exchange that may be mediated by an increase in intracellular H^+ ions and by increasing the number of new exchangers and increased activity of the Na^+/HCO_3^- cotransporter at the basolateral membrane. Elevation of the P_{CO_2} will promote higher proximal tubular concentration of CO_2 and lead to intracellular acidosis, giving rise to further secretion of H^+ ions and reclamation of bicarbonate. If there is volume depletion, there will be avid Na^+ reabsorption at the proximal tubule in exchange for H^+ and thus greater reabsorption of bicarbonate. Other factors that are important include the luminal bicarbonate concentration, the tubular flow rate, and the serum potassium.

NET RENAL ACID EXCRETION

Net excretion of acid occurs primarily in the distal nephron and is largely mediated by the active secretory pumps, H^+-K^+ ATPase and H^+ ATPase. The latter appears to be linked in some way to Cl^- reabsorption to preserve electroneutrality. By definition, to produce net H^+ excretion the secreted H^+ will have to be excreted in processes that do not consume bicarbonate.

To achieve net secretion of protons in the luminal fluid of the distal nephron requires association of the protons with urinary buffers other than bicarbonate. Although secreted protons lower the urinary pH to 4.5 resulting in a 3 pH unit differential from arterial pH (a 1000-fold increase in H^+ concentration), the quantity of acid excreted as free H^+ is trivial. For example, daily excretion of 2 L of urine with a pH of 5 would result in excretion of only 0.02 mEq of dissociated H^+ ions in contrast to the 50 to 100 mEq of H^+ generated each day from dietary sources. The nonbicarbonate buffers present in the urine that carry out the role of net acid excretion are the titratable buffers, primarily phosphate, which accounts for 40% of net acid excretion, and ammonia, which accounts for the remainder.

The ability of phosphate to act as proton acceptor in the urine is based on its pKa of 6.8. As the urine pH is lowered below the pKa of 6.8, there is conversion of HPO_4^- to H_2PO_4. This transfer continues until the urine pH reaches 5.5, at which point almost all the phosphate present is in the associated form, H_2PO_4. Other components of this system are uric acid (pKa = 5.75) and creatinine (pKa = 4.97). Although the titratable buffers account for a sizable fraction of net basal acid excretion, they cannot increase in amount to enhance acid excretion in settings of acid loading since phosphate excretion depends on phosphate intake and not on synthesis as is the case for ammonia excretion.

The rate of ammonium (NH_4^+) production and excretion can, however, be varied according to physiologic needs. Ammonia (NH_3) combines with H^+ to form ammonium, which is trapped in the collecting tubule lumen and excreted in the urine. The pKa for this reaction is 9.0. The majority of ammonia is synthesized in the proximal tubular cell by the enzymatic breakdown of glutamine.

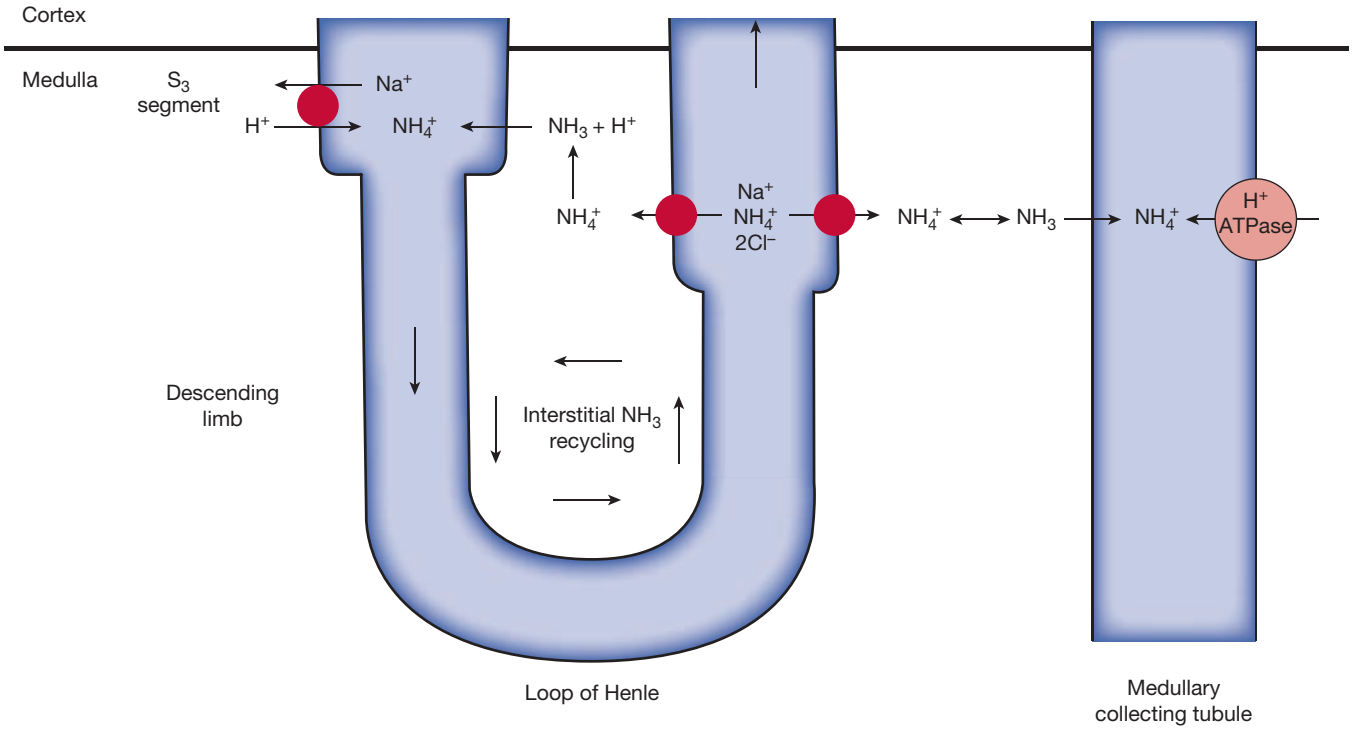

Figure 17-2 Schematic representation of ammonia recycling within the renal medulla. Although NH_4^+ production occurs predominantly in the proximal tubule, most of the NH_4^+ is then reabsorbed in the thick ascending limb, apparently by substitution for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Partial dissociation into NH_3 and H^+ then occurs in the less acid tubular cell. The NH_3 diffuses into the medullary interstitium, where it reaches relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: the S_3 segment of the late proximal tubule and, more important, the medullary collecting tubule, where the secreted NH_3 is trapped as NH_4^+ and then excreted. *(Reproduced with permission from Rose B. Clinical Physiology of Acid-Base and Electrolyte Disorders, 4th ed. New York: McGraw-Hill; 1994.)*

Glutamine is actively taken up by the proximal tubule at the apical and basolateral membranes and transported to mitochondria.[1] Deamidation by glutaminase forms ammonium and glutamate. The latter is further metabolized by glutamate dehydrogenase to form ammonium and α-ketoglutarate. Metabolism of α-ketoglutarate to bicarbonate in the liver leads to return of bicarbonate to the systemic circulation (Fig. 17-2).

The ammonium that is formed is transported into the proximal tubular lumen via the Na^+-H^+ antiporter, working in this case as an Na^+–NH_4^+ antiporter. The ammonium is then reabsorbed in the thick ascending limb by substitution of NH_4^+ for K^+ on the Na^+–K^+–$2Cl^-$ carrier. The intracellular ammonium in the thick ascending limb cell is then dissociated into ammonia and H^+. The ammonia accumulates in the medullary interstitium and is finally secreted into the lumen of the medullary collecting tubule. At this site, due to the low lumen pH (4.5–5) the ammonia accepts an H^+ and is trapped in the lumen and excreted in the urine as NH_4Cl.

The importance of the ammonia system is that it can be regulated by the systemic acid–base state. An acid load initially leads to an increase in ammonium excretion within 2 hours due to formation of a more acidic urine which enhances ammonia diffusion into the lumen at the collecting duct. After 5 to 6 days there is maximal NH_4^+ excretion due to increased glutamine uptake and enhanced activity of phosphate-dependent glutaminase and glutamate dehydrogenase to produce more ammonium in the proximal tubule.[6] This is presumably mediated by intracellular acidosis of the proximal tubular cell. The net effect is that NH_4^+ excretion can increase from about 30 mEq per day to as much as 300 mEq/d in severe metabolic acidosis. The plasma potassium is an important regulator of ammonia synthesis as hyperkalemia will result in a transcellular influx of K^+ in exchange for H^+ resulting in lowering of the intracellular H^+ concentration, thus causing an intracellular alkalosis with consequent inhibition of ammonia synthesis. Hypokalemia would have the opposite effect. Urinary acidification is also very important, since an inability to lower urinary pH will result in a reduction in NH_3 trapping in the collecting duct lumen and a subsequent inhibition of the degree of ammonium formation. Inadequate acidification of the urine will also inhibit H_2PO_4 formation.

RESPIRATORY CONTRIBUTION TO ACID–BASE BALANCE

The major roles of the lungs in acid–base balance are to excrete the CO_2 produced daily by aerobic metabolism and to compensate for primary metabolic acid–base disturbances by altering the rate and depth of ventilation. The CO_2 generated by the tissues diffuses into the plasma, at the peripheral capillaries, and is present in the blood in three compartments. Part of the CO_2 remains in the gas phase, but the amount is limited by the solubility coefficient of CO_2 (0.03 mM/mm Hg). CO_2 may also react with amino groups of proteins and form carbamino compounds. The majority of the CO_2 is carried within red blood cells.[7] The red cells contain carbonic anhydrase, which hydrates the CO_2 and thus forms carbonic acid, which dissociates to H^+ and HCO_3^-. The protons are buffered by hemoglobin which has an increased affinity for H^+ at the low oxygen tension present in the peripheral capillaries and venous blood. The bicarbonate produced in the red cell leaves the cell in exchange for chloride. This chloride shift is a characteristic response to elevation of CO_2 in the blood resulting in an acute elevation of bicarbonate in exchange for a drop in serum chloride. When the blood enters the pulmonary circulation, the enhanced oxygenation of hemoglobin promotes release of bound H^+. The H^+ and HCO_3^-, via carbonic

anhydrase, combine to reform CO_2, which passively diffuses from the blood into the pulmonary interstitium where the CO_2 tension is very low. Subsequently, CO_2 is lost into the alveolar space.

The rate of minute ventilation is controlled by two sets of chemoreceptors: Those in the respiratory center in the brain stem and those in the carotid and aortic bodies located at the bifurcation of the carotid arteries and in the aortic arch, respectively. The central chemoreceptors are stimulated by an increase in the P_{CO_2} or by metabolic acidosis, both of which appear to be sensed by a fall in the pH of the surrounding cerebral interstitial fluid. The peripheral chemoreceptors are primarily stimulated by hypoxemia, although they may also respond to acidemia. The level of alveolar or effective ventilation varies in accord with the total minute ventilation. Level of total ventilation changes as a function of metabolic demand. Under normal circumstances, P_{CO_2} is well controlled between 38 and 42 mm Hg according to the relationship:

$$P_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \quad (3)$$

where $\dot{V}_{CO_2}$ is CO_2 production (reflecting metabolic rate) and $\dot{V}_A$ is alveolar ventilation (reflecting CO_2 clearance).

Under basal conditions the volatile acid production or CO_2 that is metabolically generated is completely eliminated by the lungs. The mechanism of the central stimulation of respiration in response to an elevated CO_2 is a topic of intense debate and will not be focused upon in this section (see further details in Chapter 11). However, intracranial adjustments to pH have been consistently observed and have interesting parallels to the effects of acidosis on the proximal tubular cell in the kidney. Increased concentrations of CO_2 in the cerebrospinal fluid (CSF) result in intracellular acidosis, an increase in CSF bicarbonate concentration, and an equimolar reduction in CSF chloride concentration.[7] As brain cells increase their bicarbonate concentration, there is increased buffering, and intracellular brain pH is returned toward normal. The major group of cells within the central nervous system (CNS) responsible for acid–base regulation are the glial cells and the cells of the choroid plexus.[7,8] These cells contain carbonic anhydrase[9] which converts intracellular CO_2H_2O to H^+ and HCO_3^-. The H^+ is exchanged for Na^+ on the blood side, allowing the intracellular pH to increase. The administration of acetazolamide into the cerebral ventricles blocks the expected increase in CSF bicarbonate in response to hypercapnia.[8] In addition to changes in bicarbonate concentration in the CSF in response to hypercapnia, there are also changes in the levels of ammonia.[10] Brain and CSF ammonia increase in hypercapnia; ammonia acts to enhance H^+ buffering thereby preventing a fall in the bicarbonate concentration.

ACUTE AND CHRONIC ADAPTATION TO RESPIRATORY ACIDOSIS

Figure 17-3 depicts the acute steady-state relationships among P_{CO_2}, plasma bicarbonate concentration, and plasma hydrogen concentration during graded degrees of acute hypercapnia.[11,12] These observations were obtained by sequentially exposing unanesthetized normal human volunteers to increasing concentrations of inspired carbon dioxide in a large environmental chamber. Increasing degrees of hypercapnia are associated with a curvilinear rise in plasma bicarbonate concentration, with higher levels of P_{CO_2} resulting in lesser incremental changes in bicarbonate concentration. This acute rise in bicarbonate is largely due to the chloride shift as described earlier. As a result of the modest increment in bicarbonate, the average rise in plasma $[H^+]$ is limited to 0.75 nEq/L per mm Hg rise in P_{CO_2} rather than the 1 nEq/mm Hg rise that would have occurred if the plasma bicarbonate concentration did not change.[13]

The quantitative aspects of the adaptive response to acute hypercapnia are influenced markedly by the baseline acid–base

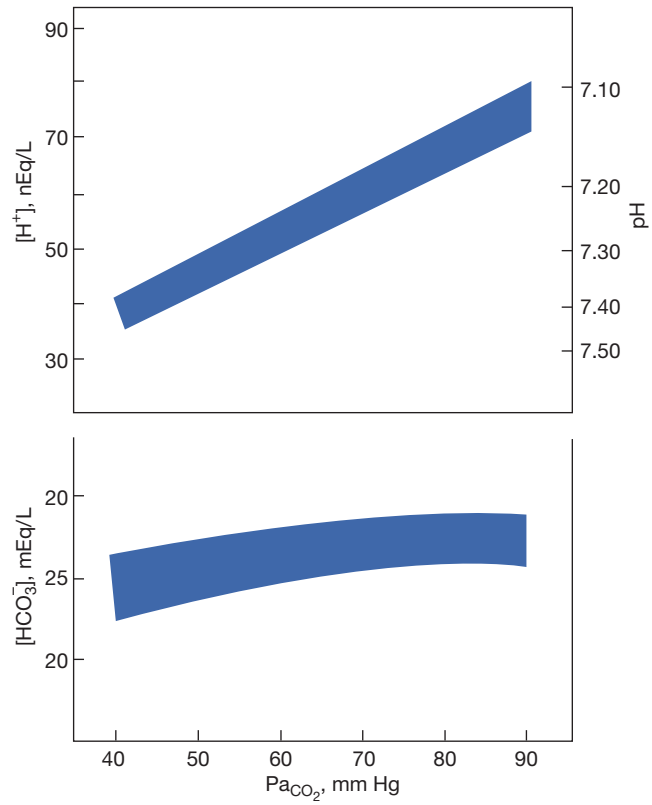

Figure 17-3 Ninety-five percent confidence bands for plasma hydrogen ion and bicarbonate concentrations during acute hypercapnia in normal humans. *(Adapted with permission from Brackett NC Jr, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man: effect of increasing degrees of acute hypercapnia on acid-base equilibrium. New Engl J Med. 1965;272:6–12.)*

status. Acute hypercapnia induces a larger increment in both plasma bicarbonate and H^+ ion concentrations in animals with pre-existing hypobicarbonatemia (whether from metabolic acidosis or from chronic respiratory alkalosis) than in animals with pre-existing hyperbicarbonatemia (whether from metabolic alkalosis or from chronic respiratory acidosis).[14] This points out that the factor controlling the amount of bicarbonate generated from an acute rise in P_{CO_2} is not only the initial pH but also the initial bicarbonate concentration. Although the rise in bicarbonate in response to hypercapnia limits the fall in pH acutely, to excrete the gain of H^+ produced from the rise in P_{CO_2} requires renal compensatory mechanisms.

During the initial period of respiratory acidosis, renal compensation takes about 3 to 5 days, during which time there is enhanced reabsorption of proximal tubular bicarbonate, enhanced secretion of H^+, and increased ammonia production.[15]

These processes will lead to an increase of the serum bicarbonate concentration and a rise in the systemic pH toward normal. However, when a steady state is achieved and a stable P_{CO_2} is present, there is no longer an increase in ammonia production. As filtered bicarbonate is increased, there is enhanced proximal secretion of H^+ and a normalization of intracellular pH removing the stimulus for ammonia synthesis.[15]

RENAL ADAPTATION TO RESPIRATORY ALKALOSIS

The adaptive responses to respiratory alkalosis occur in two distinct steps, in close analogy with respiratory acidosis. Hypocapnia reduces the carbonic acid concentration and causes a prompt fall

in H^+.[16] Acutely, this alkalemia is ameliorated by a secondary, adaptive reduction in plasma bicarbonate concentration that stems principally from titration of nonbicarbonate body buffers.[17] During protracted hypocapnia, renal adaptive mechanisms yield a further and larger secondary reduction in plasma bicarbonate that results in still greater amelioration of the alkalemia.[17]

In acute uncomplicated respiratory alkalosis the plasma bicarbonate concentration falls by approximately 0.2 mEq/L for each mm Hg reduction in P_{CO_2}. Thus, a reduction in plasma bicarbonate of 3 to 4 mEq/L occurs within minutes after P_{CO_2} is lowered to 20 to 25 mm Hg. The resulting change in plasma H^+ concentration is approximately 0.75 mEq/L for each mm Hg fall in P_{CO_2}, similar to the relationship between P_{CO_2} and H^+ in acute hypercapnia.

When hypocapnia persists beyond the acute phase, the additional decrement in plasma bicarbonate concentration is a consequence of renal adaptive responses and reflects a dampening of hydrogen ion secretion by the renal tubule.[5] As a result, a transient suppression of net acid excretion occurs, largely manifested by a fall in ammonium excretion and by an increase in net bicarbonate excretion. These changes lead, in turn, to a positive hydrogen ion balance and a reduction in the body's bicarbonate stores. Persistence of the resulting hypobicarbonatemia is explained by the continued inhibition of tubular hydrogen ion secretion and suppression of bicarbonate reabsorption.

The adaptive retention of acid during chronic hypocapnia is normally accompanied by a loss of sodium into the urine; the resultant decrease in the extracellular volume promotes chloride retention and the typical hyperchloremia of chronic respiratory alkalosis.[18] Upon reaching a new steady state, the net excretion of acid returns to control levels, and the altered anionic concentration of the extracellular fluid (ECF), namely hypobicarbonatemia and hyperchloremia, is maintained by a reduced bicarbonate reabsorption and enhanced chloride reabsorption. On average, the combined effect of cell buffers and renal compensation results in a new steady state in which the plasma HCO_3^- concentration falls approximately 4 mEq/L for each 10 mm Hg reduction in the P_{CO_2}.[19] The renal adaptation to persistent hypocapnia appears to be mediated by some direct effect of P_{CO_2} itself, not the systemic pH. In animals in which plasma bicarbonate was reduced by HCl loading prior to adaptation to sustained hypocapnia, the renal response to a primary reduction in P_{CO_2} was the same as in normal individuals, even though the net effect of this adaptation was an overt fall in pH.

RESPIRATORY ADJUSTMENT TO METABOLIC ACIDOSIS

Metabolic acidosis stimulates both central and peripheral chemoreceptors to increase alveolar ventilation and decrease P_{CO_2} to limit the fall in pH. Although peripheral chemoreceptors appear to play a small role, in animal experiments the same degree of respiratory compensation occurs with intact and with ablated peripheral chemoreceptors. The increase in ventilation begins within 1 to 2 hours and reaches its maximal level at 12 to 24 hours. The stereotype is Kussmaul's breathing in acute diabetic ketoacidosis, in which tidal volume is characteristically large with minute ventilation increasing by as much as 35 L. On average, studies in otherwise normal patients with metabolic acidosis reveal that the P_{CO_2} will fall 1.2 mm Hg for every 1.0 mEq/L reduction in plasma HCO_3^- down to a minimum P_{CO_2} of 10 to 15 mm Hg.[20]

On the other hand, failure to mount the expected ventilatory response to metabolic acidosis is an important indicator of respiratory decompensation. Daniel et al.[21] in 140 critically ill trauma patients with metabolic acidosis applied the traditional formula derived from patients with chronic metabolic acidosis. Those whose Pa_{CO_2} exceeded the predicted Pa_{CO_2} by 2 mm Hg or more were 4.2 times more likely to be intubated and compensation status was an independent predictor of intubation as early as 60 minutes after episodes of significant hypotension.

RESPIRATORY ADJUSTMENT TO METABOLIC ALKALOSIS

The development of metabolic alkalosis is sensed by the respiratory chemoreceptors resulting in a decline in alveolar ventilation and an elevation of the P_{CO_2}. On average, the P_{CO_2} rises 0.7 mm Hg for every 1.0 mEq/L increment in the plasma HCO_3^- concentration.[18] Values significantly different from the predicted value represent superimposed respiratory acidosis or alkalosis. However, it is unclear whether this response significantly protects the pH from rising. In experimental animals, the rise in P_{CO_2} in metabolic alkalosis increases net H^+ excretion leading to an increase in the HCO_3^- concentration. The effect after several days is that the arterial pH is the same as it would have been if there had been no respiratory compensation.[6,18]

Ventilation may be strongly affected by influences other than acid–base balance. Among these influences are body temperature, increases in circulating catecholamines, changes in cerebral blood flow, changes in systemic blood pressure, and changes in metabolic activities of different organs (e.g., liver), as well as the physiologic state of the lung itself. Perhaps for teleologic reasons, the defense of chronic metabolic acid–base imbalances by ventilatory compensation is not of major importance.

ALTERNATIVE CONCEPTS OF ACID–BASE BALANCE

The preceding discussion has tacitly assumed that the systemic pH is the final control that affects the renal and respiratory response to an acid–base disorder; however, this issue is certainly not settled. The proximal tubular cell of the kidney can often have effects that are more predictably based on the P_{CO_2} rather than the arterial pH. If P_{CO_2} is elevated, the proximal tubular cells act to secrete protons and reabsorb bicarbonate whether or not there is systemic alkalosis or acidosis. This may be explained if an elevation in P_{CO_2} results in intracellular acidosis and the cell is responding appropriately to its internal milieu.[6,18] Similarly, in the central control of respiration, it is controversial as to whether it is CSF pH, interstitial pH, P_{CO_2}, or the bicarbonate concentration that stimulates compensatory changes in ventilation.[7]

In addition to the previously mentioned observations, it is also known that changes in salt and water balance may affect acid–base status. For example, Schwartz's group[18] found that a low dietary sodium chloride intake in dogs with a stable amount of water intake results in hypoventilation, increased P_{CO_2}, and increased HCO_3^- concentration. Studies in dogs have demonstrated that increasing dietary NaCl with a fixed water intake increases the acidity of body fluids, whereas decreasing the NaCl in diet with a fixed water intake decreases the acidity of body fluids.[22]

An alternative view to understanding acid–base disorders and the regulatory response of the lungs and kidneys is offered by the theories initially proposed by Stewart.[23,24] Based on physicochemistry, Stewart emphasized the important principle that H^+ and HCO_3^- as well as the acidic and anionic forms of weak acids are actually dependent variables in a solution. The three independent variables, P_{CO_2}, the strong ion difference (SID), and the total weak anion concentration, can be manipulated externally and serve to determine the concentration of the dependent variables, H^+ and HCO_3^-. The major components of the weak anions in plasma are the albumin and inorganic phosphate concentrations. The SID is the difference between the sums of all strong cations and all strong anions:

$$[SID] = [Na^+] + [K^+] + [Ca^{2+}] + [MG^{2+}] - [CL^-] - [\text{Other Strong Anions}] \quad (4)$$

This equation is based on the principles of: (1) electroneutrality, (2) dissociation equilibria of all incompletely dissociated substances, and (3) conservation of mass. This concept appears to better explain the basis for renal and ventilatory response in a variety of states

which also affects acid–base balance. Practically, it is observed that the plasma SID is primarily regulated by the kidneys, whereas the P_{CO_2} is regulated by alveolar ventilation. The weak anion concentration is generally not regulated and may often be assumed to be stable.

This concept has primarily been used by investigators in relation to the study of central regulation of ventilation.[7] As albumin and other proteins are not present in the CSF, it is the SID and P_{CO_2} that determine the concentration of weakly dissociating electrolytes, H^+, OH^-, and HCO_3^-. In analyzing various acid–base disturbances, it appears that the change in CSF SID can predict the concentration of CSF bicarbonate.[7]

In evaluating acid–base balance in many species, there is a consistent inverse relationship between the pH and body temperature, whereas the CO_2 content remains stable.[4,25] To explain this relationship Reeves and his coworkers provided evidence that the imidazole ring structure of histidine is responsible for the pH–temperature relationship.[26] This is because imidazole has a pKa in the physiologic range (7.00), is relatively ubiquitous, and has total energy of ionization (7 kcal/mol). To integrate acid–base regulation with receptor function and control of respiration, Reeves and Rahn[4] have proposed the hypothesis that it is not the arterial or intracellular pH that is being regulated per se but rather the constancy of the fractional dissociation of the imidazole moiety of histidine contained in proteins throughout the body.

α-Imidazole is defined as the ratio of the absolute amount of unprotonated imidazole (Im) to total imidazole (HIm + Im):

$$\alpha\text{-Imidazole} = \frac{\text{Im}}{\text{HIm} + \text{Im}} \quad (5)$$

α-Imidazole regulation (alphastat regulation) would have the effect of maintaining cellular protein charge states and enzymatic functions constant. It would also maintain the OH^-/H^+ ratio constant in all compartments. There is also evidence that alphastat regulation directly influences ventilatory status. For example, application of an imidazole blocker to the chemosensitive area of the medulla in cats blocked increases in ventilation caused by local application of acid.[27] Thus, changes in P_{CO_2}, reflecting alveolar ventilation, may be determined by alphastat regulation, which maintains the OH^-/H^+ ratio constant in membranes of the cells in the chemosensitive areas of the medulla.

The difficulty with using these concepts lies in the practical measurement of the relevant molecules. For example, although the imidazole moiety of histidine is considered the most important of the intracellular buffers,[26] its pKa and total energy of ionization may vary widely due to the influence of the local configuration of molecules into which they are incorporated. Thus, even in lower animals such as fish under different temperatures, calculations based on the alphastat model do not accurately predict the acid–base disturbance, since the pKa and enthalpy of ionization vary with temperature and are difficult to measure.

Similarly, measurement of the plasma SID is problematic and is often replaced by the "SID effective," which is roughly equal to the bicarbonate concentration plus albumin and inorganic phosphate.[23] Calculation of the anion gap (AG) – $[Na^+] - [Cl^-] - [HCO_3^-]$ – accounts for the roles of the strong ions Na^+ and Cl^- as well as bicarbonate but does not account for the role of inorganic phosphate or plasma proteins. Although the bicarbonate concentration may not be, strictly speaking, an independent variable, the AG calculation does indicate the quantity of unmeasured anions and hence is an indirect measure of the SID. If one considers the impact of serum proteins and inorganic phosphate in the unmeasured anion pool, the AG gives a very useful parameter in evaluating acid–base disturbances. Many studies have compared the utility of SID versus corrected AG (corrected for the level of serum albumin) and found that it was no more accurate in making a diagnosis. One study of patients in an intensive care unit, reported that Stewart's method diagnosed underlying metabolic acidosis in 22 patients (of the total of 152 patients in the study) with normal plasma bicarbonate level. However, when the AG was corrected for hypoalbuminemia, it was elevated in all of the samples with normal bicarbonate showing the effectiveness of the traditional approach.[28] In another study of 935 ICU patients, the Stewart method detected metabolic acidosis in 14% patients with normal bicarbonate levels, whereas the traditional method made a similar diagnosis in 13% of patients.[29] A recent study in patients with septic shock and liver transplantation found an excellent correlation between SID and corrected AG.[30]

Thus, as will be described in more detail in the following section, the use of the AG is still the most clinically useful tool to determine the contribution of different metabolic etiologies of metabolic acidosis.

APPROACH TO PATIENTS WITH AN ACID–BASE DISTURBANCE

In this section, we examine the diagnostic approach to disorders of acid–base balance with a particular emphasis on the ventilatory response and its role in mitigating or exacerbating acid–base disorders. We will also review the approach to the patient with complex acid–base disorders.

■ ANALYSIS OF CLINICAL INFORMATION

Table 17-1 summarizes the pattern of abnormality of arterial blood acid–base parameters in the four classic acid–base disorders. It also indicates the physiologic or compensatory response induced in pulmonary or renal function in response to the initial disturbance.

Base Excess and Base Deficit Notations

Base excess and *base deficit* are terms applied to an analytic method for determination of the appropriateness of responses to disorders of acid–base metabolism.[31] The base excess or deficit is determined by measuring blood pH against ambient P_{CO_2} and against a P_{CO_2} of 40 mm Hg. If the calculated HCO_3^- is below 25 when the P_{CO_2} is 40 mm Hg and the original pH is low, a base deficit is indicated. The magnitude of the deficit is expressed as the number of mEq of bicarbonate needed to restore the serum bicarbonate to 25 mEq/L at a P_{CO_2} of 40 mm Hg compared to that at the ambient P_{CO_2}. The use of notations for base excess and deficit has been debated in the medical literature. This notation is favored in the evaluation of acid–base status in the operating room because acute changes in P_{CO_2} and in HCO_3^- can be simply evaluated by this approach. However, this notation can be misleading in chronic respiratory alkalosis or acidosis, since the patient with chronic respiratory alkalosis will be categorized as suffering from a base deficit because of the low serum bicarbonate induced as compensation for the reduced P_{CO_2}. In fact, a "base deficit" is a normal physiologic response to the chronic reduction in P_{CO_2}. Unfortunately, lack of familiarity with the complete analytical paradigm used for this analysis of acid–base disorders has led some to focus on the designations "base deficit" and "base excess" as guides to bicarbonate or acid therapy in chronic respiratory disorders. In addition, discrepancies between the buffering characteristics of plasma, blood, and whole body have also been cited as potential weaknesses in a system for assessing acid–base disorders which relies on in vitro CO_2 titration methods. We, therefore, recommend that the physiologic evaluation of the patient be the mode of analysis of acid–base disorders rather than an emphasis on derived formulae.

Use of Nomograms

As indicated earlier, the body buffers and the kidneys respond in a predictable fashion to a change in P_{CO_2} whereas ventilatory

response to changes in $[HCO_3^-]$ is also predictable. Also, the resulting changes in bicarbonate and pH are time dependent so that a larger change occurs in several days than in the first hours. The confidence bands for changes in P_{CO_2} or HCO_3^- in response to primary disturbances are shown in Figure 17-4.[7] Any deviation can be interpreted as a reflection of processes other than a compensatory response. For example, in a patient with chronic obstructive airways disease, other factors affecting the acid–base status are the concentration of potassium in the plasma, the size of ECF volume, chloride depletion, diuretics, renal hypoperfusion, and coexisting renal disease. The special case of posthypercapnic alkalosis is discussed in the next section.

In evaluating an acid–base disorder, the history and physical examination are invaluable in focusing attention on potential pathologic processes.[32] The composition of blood, with respect to serum electrolytes and blood gases, is then examined for consistency with clinical impressions. However, in using the acid–base map (Fig. 17-4), remember that the map is based on data from individuals who had a single disorder. Therefore, the map does not take into account the possibility of multiple disorders. For example, in a patient with chronic obstructive airways disease whose sputum has turned purulent and who develops nausea and vomiting, the possibility arises of coexistent metabolic alkalosis and acute respiratory acidosis. However, ill-advised application of the arterial blood-gas values from this patient (e.g., pH = 7.25 and P_{CO_2} = 75 mm Hg) to the acid–base map would lead to the erroneous conclusion that a chronic respiratory acidosis is present. Thus, the clinician needs to integrate laboratory data with clinical assessments to properly analyze clinical disorders of acid–base balance.

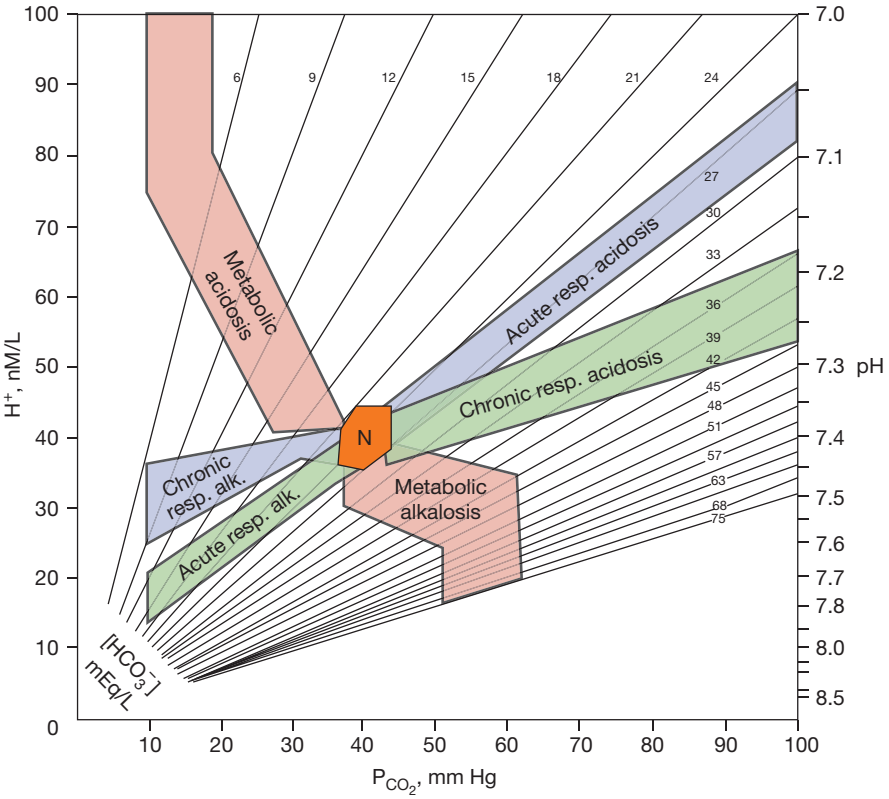

Figure 17-4 Acid–base map showing the normal range (N) and the confidence bands for acute or chronic respiratory and metabolic acid–base disturbances. The ordinates are the partial pressure of CO_2 and the hydrogen-ion activity given in nmol/L and pH units. Isopleths for bicarbonate concentration, in mEq/L, are also shown. *(Reproduced with permission from Goldberg M, Green SB, Moss ML, et al. Computer-based instruction and diagnosis of acid-base disorders. A systematic approach. JAMA. 1973;223(3):269–278.)*

■ APPROACH TO THE PATIENT WITH METABOLIC ACIDOSIS

An increase in the H^+ concentration of the ECF will result in a series of predictable responses which allow the clinician to ascertain the appropriateness of organized homeostatic responses to the perturbation.[20] The pathophysiologic basis for the initiation of metabolic acidosis and homeostatic responses in the defense of systemic pH have been defined earlier in descriptions of the buffering of newly introduced acid [see Eq. (1)] and in the demonstration of the normal confidence band for the ventilatory response to metabolic acidosis as detailed in the acid–base nomogram (Fig. 17-4).

A key clinical distinction in the pathogenesis of metabolic acidosis is whether the production of the acidosis is rapid or slow. If the etiology of the metabolic acidosis is merely the continued ingestion of a diet which generates a variety of fixed acids such as H_2SO_4 [see Eq. (2)] from the metabolism of methionine residues, then the serum HCO_3^- will fall slowly as only that fraction of the 50 to 100 mEq of H^+ generated from diet that is not excreted would be added to the body fluids each day. However, if the addition occurs because of an acute increase in the acid load such as may occur with lactic acidosis, the kidney capacity can be rapidly overwhelmed, and serum bicarbonate may fall precipitously. See Table 17-2 for the common causes of metabolic acidosis.

Utility of the AG

As seen in Eq. (6), the buffering of mineral acids will result in the production of the salt of the acid, NaA.

$$NaHCO_3 + HA \rightarrow NaA + H_2CO_3^- + H^+ \rightarrow CO_2 + H_2O + NaA \quad (6)$$

TABLE 17-2 Causes of Metabolic Acidosis (Common)

Failure to generate new bicarbonate to replace that consumed in buffering dietary acid load
Diminished NH_4^+ production and excretion
Reduced renal mass
Chronic hyperkalemia
Chronic aldosterone deficiency
Decreased H^+ ion secretion (primary)
Distal renal tubular acidosis
Increased H^+ ion production
Lactic acidosis
Ketoacidosis
Toxic ingestion
Bicarbonate or equivalent losses from body fluids
Renal–proximal RTA, carbonic anhydrase inhibitors
GI-diarrhea, villous adenoma, fistula

If the kidney is able to excrete this salt or, in the case of the production of the salts of organic acids such as lactic acid, if the liver can metabolize the anion to HCO_3^-, then there will be no accumulation of the anion in the ECF. Typically, anions associated with strong organic acids are not measured with routine electrolyte determinations and contribute to the so-called anion gap (AG). Determination of the plasma AG is primarily used in the differential diagnosis of metabolic acidosis. However, the AG also changes in other conditions, a finding that may be of diagnostic importance.

The plasma AG is calculated from the following formula based on routine laboratory determination[33]:

$$AG = (\text{cations}) - (\text{anions})$$

Since Na^+ is the primary measured cation and Cl^- and HCO_3^- are the primary measured anions:

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \quad (7)$$

The normal value is 12 ± 2 mEq/L.

An increase in the AG can be produced by an increase in unmeasured anions or by a reduction in unmeasured cations. Hypokalemia, hypocalcemia, or hypomagnesemia can only raise the AG by a few mEq/L, since these ions can only deviate from normal by a mEq/L or less and maintain a physiologic condition. The predominant extracellular unmeasured anion is actually albumin with many negative charge sites per molecule. Hence, a mild elevation in the AG can occur in conditions in which the albumin concentration or the charge characteristics of albumin are altered, for example, in metabolic alkalosis. In that instance, a number of factors may contribute to the increment, including a rise in the plasma albumin concentration due to extracellular volume depletion and contraction of plasma constituents, an increase in the number of negative charges per albumin molecule induced by the rise in extracellular pH titrating protons off the albumin molecule, and a tendency for systemic alkalemia to induce an increase in lactate production. This latter response serves a homeostatically beneficial function.

In forms of metabolic acidosis in which there is buffering of excess hydrochloric acid by extracellular bicarbonate, then

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \quad (8)$$

Bicarbonate is replaced on an equimolar basis by chloride, and there is no change in the AG; this disorder is also called a *hyperchloremic acidosis* because of the rise in the plasma chloride concentration. Both diarrhea and type 2 (proximal) renal tubular acidosis can lead to the loss of $NaHCO_3$. The kidneys compensate by retaining NaCl in an attempt to preserve volume, with the net effect being a mEq-for-mEq exchange of chloride for bicarbonate.

If the retained acid is not HCl but an organic acid whose anion is not routinely measured such as lactic acid, then the increase in the unmeasured lactate anion will raise the AG. It is important to emphasize that the acidosis is due to the retained proton; the anion is irrelevant to the change in acid–base status or systemic pH but is important as a diagnostic tool. The major causes of a high AG metabolic acidosis include those listed in Table 17-2 under disorders of increased H^+ production. Although renal failure produces an acidosis because of failure of H^+ excretion and bicarbonate production, most patients with severe renal failure retain both hydrogen and anions, such as sulfate, phosphate, and urate, and hence demonstrate a high AG.

The diagnostic utility of a high AG is greatest when the AG is above 20 mEq/L; in this setting, renal failure, lactic acidosis, or evidence of a toxic ingestion will almost always be present. When the AG is less than 20 mEq/L, identifying the anions which contribute to the mild elevation[33] is often impossible.

Urine AG

Estimation of the urinary ammonia content may be a useful clue to the etiology of metabolic acidosis as the value will increase in diseases in which kidney function affecting acid–base balance is completely intact but in which bicarbonate is lost from the body fluids.[13] The calculation of the urinary AG is shown in Eq. (9):

$$\text{Urine AG} = (\text{Urine } [Na^+] + \text{Urine } [K^+]) - \text{Urine } [Cl^-] \quad (9)$$

The usual value will be negative, between −25 and −50 mEq/L, as the ammonium content of the urine is typically in this range, and ammonium accounts for the apparent discrepancy between the level of cations and anions in the urine. In states of metabolic acidosis due to diarrhea or to chronic acid ingestion, the value will be >50 mEq/L as ammonium production is stimulated.

In some conditions, the urine AG will be very low or even positive in the face of metabolic acidosis. In all forms of renal insufficiency, ammonia production by the kidney will be deficient and significantly contribute to a reduced urinary AG and to metabolic acidosis. In type I distal RTA, inability to maintain a steep gradient for protons in the distal tubular lumen and in the collecting duct results in a deficiency in ammonia trapping in the luminal fluid and therefore a decreased excretory rate for ammonia. This in turn leads to metabolic acidosis, a low ammonia excretion, and an abnormally low urinary AG. Finally, type IV RTA, a condition in which hyperkalemia and mild renal insufficiency are found, hyperkalemia suppresses renal ammonia production, and a low urinary AG is found.

In any condition associated with hypokalemia, increased intracellular proton accumulation (which results from the exchange of cellular potassium for extracellular protons) will lead to an exaggerated ammonia production in the kidney. Hence, the use of the AG in the urine will be particularly useful to differentiate classic type I RTA from hypokalemia and acidosis due to diarrhea. The former will show a very low urine AG. Typically, a careful history will elicit the crucial information, and measurement of the urine AG will be confirmatory.

Clinical Assessment of Metabolic Acidosis

In approaching a patient with metabolic acidosis, the clinician should first assess the history and clinical circumstances. For example, patients with renal failure or with uncontrolled diabetes may be presumed to have a metabolic acidosis until disproved by laboratory analysis. The next step is to evaluate the serum electrolytes to determine the level of the serum HCO_3^- and the presence of an AG of greater than 12 ± 2 mEq/L. If both are present, then one must consider the possibility of a metabolic acidosis secondary to increased acid production as listed in Table 17-2. If the HCO_3^- is reduced but the serum AG is normal, then one is dealing with either a respiratory alkalosis or a metabolic acidosis due to reduced renal capacity to generate replacement HCO_3^- to compensate for that lost as a result of decreased acid excretion or increased HCO_3^- loss.

At this point arterial blood gases should be assessed to determine the pH and the ventilatory response. Finding a low pH establishes the diagnosis of metabolic acidosis. Reference to the acid–base nomogram (Fig. 17-4) will verify whether the clinical response is consistent with a simple metabolic acidosis with a normal ventilatory response or whether some other disturbance in ventilation is present.

■ APPROACH TO THE PATIENT WITH METABOLIC ALKALOSIS

Two separate processes are involved in metabolic alkalosis: an excess load of base that is generated either endogenously or exogenously (see Table 17-3) and maintenance of an abnormally high

TABLE 17-3 Causes of Metabolic Alkalosis

Gastrointestinal hydrogen loss
Removal of gastric secretions
Renal hydrogen loss
Primary mineralocorticoid excess
Loop or thiazide diuretics
Posthypercapnic alkalosis
Intracellular shift of hydrogen
Hypokalemia
Alkali administration
Contraction alkalosis

concentration of bicarbonate in the plasma.[5] During hypercapnia, the load of base is the result of renal compensation and *de novo* bicarbonate generation; in posthypercapnic alkalosis, the key abnormality is maintaining the bicarbonate level in plasma at inordinately high levels, as will be discussed below.

Generation of Metabolic Alkalosis

Causes of metabolic alkalosis are predominantly events that remove H^+ ions from the body but also include circumstances in which excess base is added to the body fluids. Hydrogen loss can occur from the gastrointestinal tract or in the urine. Each mEq of hydrogen lost generates 1 mEq of bicarbonate, as the source of hydrogen ions in cells which produce and secrete protons is:

$$H_2O \rightarrow H^+ + OH^- + OH^- + CO_2 \rightarrow HCO_3^- \qquad (10)$$

When vomiting or tube drainage prevents stomach acid from reaching the duodenum and combining with HCO_3^- released from pancreatic secretions, the net balance of bicarbonate in body fluids becomes positive, and serum HCO_3^- begins to rise.

Increased renal acid losses may result from enhanced distal hydrogen secretion. Aldosterone acts both by directly stimulating the secretory H^+ ATPase pump and, via the stimulation of sodium reabsorption, by making the lumen more electronegative, thereby favoring hydrogen ion secretion. Increased distal nephron delivery and reabsorption of sodium further stimulates hydrogen ion secretion as the accompanying anion is less avidly reabsorbed than is sodium, and the lumen of the distal nephron becomes more negatively charged. Excess secretion of mineralocorticoids can lead to metabolic alkalosis by this pathway. In patients treated with loop-active or thiazide diuretics, enhanced distal delivery of sodium and increased secretion of aldosterone are usually present, thereby enhancing renal bicarbonate production as a result of enhanced hydrogen ion secretion. This pattern commonly leads to the development of metabolic alkalosis.

Chronic respiratory acidosis leads to a secondary increase in renal hydrogen secretion, as the subsequent rise in the plasma bicarbonate concentration will restore the pH toward normal as a compensatory response. If the patient undergoes a therapeutic maneuver such as rapid lowering of the P_{CO_2} by mechanical ventilation, a posthypercapnic form of metabolic alkalosis will ensue as the patient is left with an elevated plasma bicarbonate concentration.

Hypokalemia is a frequent finding in patients with metabolic alkalosis and may not only be the consequence of some of the disorders which lead to the initiation of metabolic alkalosis but may also actually induce an alkalotic tendency. Gastric drainage, diuretics, and mineralocorticoid excess, all induce potassium as well as hydrogen losses through the GI tract and kidney, respectively. Hypokalemia also induces a transcellular shift in which potassium is exchanged in an electroneutral fashion for hydrogen ions in the ECF. This exchange directly raises the extracellular pH, lowers the intracellular pH, and mitigates the hypokalemia. Intracellular acidosis in renal tubular cells promotes hydrogen secretion and therefore bicarbonate reabsorption (see Section Bicarbonate Reclamation p. 208).

Administering large amounts of alkali does not maintain metabolic alkalosis in normal individuals because of rapid urinary excretion, but it may induce the initiation stage of metabolic alkalosis if factors are active to sustain a high rate of renal HCO_3^- reabsorption. A form of metabolic alkalosis termed *contraction alkalosis* occurs when there is loss of relatively large volumes of bicarbonate-free fluid. Administration of a loop diuretic to induce rapid fluid removal in a markedly edematous patient is the most common cause of a contraction alkalosis. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate. The degree to which this occurs is in part minimized by intracellular buffering, as the release of hydrogen ions from cell buffers lowers the plasma bicarbonate concentration toward the baseline value. Even this form of alkalosis is probably critically dependent on increases in renal bicarbonate production for its manifestation, since the diuretics promote excess renal hydrogen ion secretion as noted earlier.

Maintenance Phase of Metabolic Alkalosis

Maintenance of metabolic alkalosis requires an increase in the reabsorption of bicarbonate by the renal tubule.[27] Four factors are known to be important in the maintenance phase of metabolic alkalosis: extracellular volume depletion, chloride depletion, hypokalemia, and mineralocorticoid excess.[34]

A reduction in ECF volume and possibly a fall in the glomerular filtration rate (GFR) secondary to extracellular volume depletion are major stimuli for increasing the proximal reabsorption of bicarbonate. The enhanced proximal tubular bicarbonate reabsorption is likely the most important factor. This reabsorption is stimulated by extracellular volume depletion which is a frequent accompaniment of metabolic alkalosis. Enhanced proximal tubular reabsorption of sodium ions is a major factor in the enhanced rate of proton secretion, a key factor in the proximal tubular reabsorptive pathway for bicarbonate. Enhanced activity of the sodium–proton exchanger in the luminal membrane of the proximal tubule is an important component of the transport system.

In addition, an important role is played by the distal nephron in maintaining metabolic alkalosis by way of the secondary phenomena of chloride depletion, extracellular volume depletion, and hypokalemia.[35] Cells of the cortical collecting tubule can either reabsorb or secrete bicarbonate depending on homeostatic requirements. For example, during excess bicarbonate ingestion, the secretory process predominates, and excess bicarbonate is lost into the urine. Chloride depletion enhances the bicarbonate reabsorptive pathway by reducing chloride availability at an anion exchange site on the luminal membrane of the type A intercalated cell. This exchange process normally allows bicarbonate entry into the urine in exchange for chloride absorption. Chloride depletion thus blocks bicarbonate loss.

Hypokalemia acts to stimulate bicarbonate reabsorption through several mechanisms. First, loss of potassium from the ECF leads to a shift of protons into the cell as potassium leaves the cell. Hence, intracellular pH falls, driving enhanced tubular bicarbonate reabsorption. Also, severe potassium depletion produces a defect in tubular fluid chloride reabsorption thus mimicking a chloride depletion state. Finally, excess mineralocorticoid hormone, either as a result of primary overproduction or due to a variety of secondary hyperreninemic states, stimulates H^+ secretion in the cortical

collecting tubule and thereby stimulates increased renal tubular bicarbonate production and helps maintain metabolic alkalosis.

Typically, all four components coexist in patients with metabolic alkalosis secondary to vomiting or gastric drainage following gastric intubation. If any of the factors is present in a patient with metabolic alkalosis, therapy will be only partially successful until all the factors have been eliminated.

Depression of ventilation in metabolic alkalosis is a normal physiologic response to the elevation in serum bicarbonate but is difficult to assess clinically and may not be found in many patients as detailed earlier.[36]

Posthypercapnic Metabolic Alkalosis

In response to sustained hypercapnia, the increased excretion of hydrogen ion in the urine and the increased bicarbonate generated by the acid secretory process increase the concentration of bicarbonate in the plasma as described earlier. During this process, the total sodium content of the body remains stable as does the ECF volume (unless there is a separate reason for a volume abnormality, e.g., right ventricular failure and the use of diuretics). If correction of hypercapnia occurs, for example, through the use of mechanical ventilation without simultaneous replacement of sodium chloride, the urinary loss of sodium bicarbonate may lag for several hours or days. This is particularly true if there is concomitant depletion of the ECF volume. This leads to an increase in the reabsorption of solute, including sodium bicarbonate, by the proximal tubule, sustaining the high bicarbonate concentration in blood. This process is similar to the maintenance phase of metabolic alkalosis described earlier; the other processes outlined also could pertain to this posthypercapnic state and produce a persistent metabolic alkalosis following correction of hypercapnia.[37]

APPROACH TO THE PATIENT WITH A MIXED ACID–BASE DISORDER

The approach to patients with mixed acid–base disorders, that is, more than one disturbance in acid–base metabolism, is particularly challenging because no nomogram, calculation of base excess or deficit, or other formula can allow the clinician to parse the pathophysiologic disorders and allow a rational therapeutic plan.[18] Rather, it is the combination of clinical assessment, application of expected compensatory responses, assessment of the AG, and application of principles of physiology that together allow a successful analysis.

To determine the presence of a mixed or complex acid–base disorder, the clinician must follow a rigorous approach that integrates clinical observation with assessment of a variety of laboratory parameters. No single nomogram or other shortcut device will suffice. The initial step is to perform a history and physical examination to seek processes which could contribute to acid–base disorders. For example, any patient who has vomited has the potential for developing a metabolic alkalosis, and any patient with chronic renal failure surely has metabolic acidosis as an ongoing process for which compensation will be necessary. Moreover, many clinical conditions are typically characterized by the presence of more than one concurrent disorder. Patients with severe liver failure will usually experience respiratory alkalosis as a consequence of hepatic encephalopathy so that any other conditions associated with abnormalities of acid–base balance which may develop in these patients will result in mixed acid–base disorders. Septic shock is associated with the mixed disorders of respiratory alkalosis and metabolic acidosis due to lactic acid production. Immediately, following cardiac arrest, patients will have both a respiratory and a metabolic acidosis. Patients with renal failure who undergo gastric drainage will manifest both metabolic alkalosis and metabolic acidosis as a result of the underlying conditions. The clinician must consider these expected abnormalities in acid–base balance when addressing laboratory results.

The second step in the process is to evaluate a venous blood sample for determination of the electrolytes, blood urea nitrogen (BUN), creatinine, and other parameters indicative of liver function. Here, the evaluation of the $[HCO_3^-]$ and analysis of the AG is invaluable. Decrements or elevations of $[HCO_3^-]$ will point toward a disturbance in the body's buffering system. The AG measurement, if elevated, will clarify whether a metabolic acidosis is present, as described earlier. Also, analyzing the AG together with the venous $[HCO_3^-]$ can provide important information. Because the anions which accumulate in most forms of organic acidosis (lactic acidosis, ketoacidosis, many toxic ingestions) can be metabolized in the liver to bicarbonate through the Kreb's cycle, adding the unmeasured anion concentration to the current plasma HCO_3^- concentration indicates the level of $[HCO_3^-]$ prior to the onset of the metabolic acidosis.

ILLUSTRATIVE CASES

The following cases illustrate the clinical approach to the patient with acid–base disturbances.

METABOLIC ACIDOSIS

A 75-year-old patient presented with a 7-day history of intermittent diarrhea and a 5-lb weight loss. The rest of the history was unrevealing. Physical examination only revealed signs of volume depletion. Laboratory values were as follows:

$$[BUN] = 18 \text{ mg/dL}$$
$$[Na^+] = 138 \text{ mEq/L}$$
$$[K^+] = 3.0 \text{ mEq/L}$$
$$[Cl^-] = 110 \text{ mEq/L}$$
$$[HCO_3^-] = 13 \text{ mEq/L}$$

At this point, the lack of an elevated AG (12 mEq/L) and the reduced bicarbonate concentration together suggest the possibility of either respiratory alkalosis or metabolic acidosis of the non–AG variety, that is, in which the chloride concentration has risen as bicarbonate has been utilized in buffering reactions or has been lost from body fluids. The history of diarrhea strongly suggests that a metabolic acidosis is the culprit in the disorder. The relatively low BUN supports the theory that diarrhea, and not renal insufficiency, is the main etiologic factor.

Arterial blood gases are then obtained:

$$pH = 7.24$$
$$P_{CO_2} = 27 \text{ mm Hg}$$
$$P_{O_2} = 100 \text{ mm Hg}$$
$$[HCO_3^-] = 13 \text{ mEq/L}$$

The low serum bicarbonate in association with a low arterial blood pH indicates that the patient has a metabolic acidosis. Finding that the rate of ventilation produces a P_{CO_2} of 27 is consistent with the expected P_{CO_2} of 27.5 ± 2 mm Hg calculated from Winter's formula (see Table 17-1). Reference to the acid–base nomogram (see Fig. 17-4) reveals the graphical equivalent of this calculation as the values for pH, P_{CO_2}, and $[HCO_3^-]$ fall in the confidence band for metabolic acidosis. Other possible etiologies for this form of non–AG metabolic acidosis would include mild renal insufficiency, wherein the decline of GFR has not reached a level where the unmeasured anions such as SO_4^{2-} would begin to accumulate in plasma, and the ingestion of salts such as ammonium chloride which are metabolized in the liver to urea and hydrochloric acid. Urinary electrolyte analysis confirms the diagnosis:

$$[Na^+] = 50 \text{ mEq/L}$$
$$[K^+] = 20 \text{ mEq/L}$$
$$[Cl^-] = 140 \text{ mEq/L}$$
$$\text{Urine volume} = 2 \text{ L}$$
$$\text{Urinary AG} = -70 \text{ mEq/L}$$

The discrepancy between the sum of urine cations and anions in the negative range indicates that an unmeasured cation, in this case

ammonium, is being excreted into the urine.[13] It is the excretion of protons in association with ammonia that allows the renal excretion of the accumulated acid load and the attempted regeneration of body HCO_3^- stores. If this value was not greater than −20 to −50 mEq/L, a defect in ammonia production or excretion such as could be found in renal insufficiency or in renal tubular acidosis could be present. In this case, the large urinary cation gap suggests that diarrhea is the culprit.

METABOLIC ALKALOSIS

A 65-year-old patient experienced severe and unremitting vomiting for 4 days. He has had a history of peptic ulcer disease, but he decided to medicate himself with an antacid, which he could not keep from vomiting. There was no other significant past medical history. Physical examination showed a moderate degree of orthostatic hypotension as blood pressure fell from 100/70 mm Hg supine to 90/60 mm Hg when seated. The rest of the examination was not remarkable except for some abdominal tenderness.

Laboratory results revealed the following:

$$[BUN] = 28 \text{ mg/dL}$$
$$[Na^+] = 43 \text{ mEq/L}$$
$$[K^+] = 3.0 \text{ mEq/L}$$
$$[Cl^-] = 85 \text{ mEq/L}$$
$$[HCO_3^-] = 39 \text{ mEq/L}$$

The elevation in HCO_3^- content is consistent with either metabolic alkalosis or with chronic respiratory acidosis with renal compensation. The clinical circumstances strongly imply that metabolic alkalosis will be found, since the patient has been vomiting and has therefore been generating new alkali in the body fluids as gastric hydrochloric acid is lost. Also, the vomiting-induced deficit in ECF volume and in body fluid chloride content will likely act to help sustain the metabolic alkalosis by stimulating a high rate of renal bicarbonate transport by the proximal tubule and inhibiting distal nephron bicarbonate secretion.

Arterial blood gases are then obtained:

$$pH = 7.52$$
$$P_{CO_2} = 46 \text{ mm Hg}$$
$$[HCO_3^-] = 36 \text{ mEq/L}$$

These confirm the diagnosis. Note that the hypoventilatory response is modest, probably because of the degree of hypokalemia which tends to acidify the intracellular fluid and stimulate ventilation. Correction of this abnormality will require both replacement of fluid with sodium and chloride and adequate intake of potassium to fully restore acid–base balance to normal.

MIXED ACID–BASE DISTURBANCE

An insulin-dependent diabetic patient with several days of vomiting developed diabetic ketoacidosis. The following set of electrolytes is obtained:

$$[Na^+] = 140 \text{ mEq/L}$$
$$[K^+] = 5 \text{ mEq/L}$$
$$[Cl^-] = 90 \text{ mEq/L}$$
$$[HCO_3^-] = 15 \text{ mEq/L}$$
$$\text{Anion gap (AG)} = 35 \text{ mEq/L}$$

Since the normal AG is 12 ± 2 mEq/L, this individual has utilized 23 mEq/L of HCO_3^- to buffer the ketoacids. If the production of ketoacids ceases and hepatic metabolism is restored through insulin administration, then 23 mEq/L of HCO_3^- could be added to body fluids. The new set of electrolytes would be:

$$[Na^+] = 140 \text{ mEq/L}$$
$$[K^+] = 5 \text{ mEq/L}$$
$$[Cl^-] = 90 \text{ mEq/L}$$
$$[HCO_3^-] = 38 \text{ mEq/L}$$
$$\text{Anion gap (AG)} = 12 \text{ mEq/L}$$

By assessing the value – (AG increment above 12 mEq/L) + (serum $[HCO_3^-]$) – and finding a value greater than 30, one can infer that some process has previously raised the bicarbonate content above normal even if the ambient total CO_2 level is subnormal at the current moment. Hence either metabolic alkalosis or respiratory acidosis is a component process of the acid–base disorder. Conversely, finding a value less than 20 suggests that the patient had a pre-existent metabolic acidosis or a respiratory alkalosis prior to the onset of the organic acidosis. Finally, the clinician may assess the alveolar–arteriolar O_2 gradient to determine the effectiveness of oxygenation as an initial assessment of respiratory gas exchange efficiency.

At this point the clinician is able to ascertain a tentative diagnosis and perform an arterial blood gas determination to conclude the process. Measurement of the blood gas will show whether the respiratory response to a metabolic disturbance (metabolic alkalosis or metabolic acidosis) or the metabolic (renal) response to a respiratory disturbance is as expected. The acid–base disorder could still be labeled a simple disturbance if the initial assessment of the clinical condition and the AG support that conclusion. Consulting the acid–base map (see Fig. 17-4) will provide the expected compensatory response to each disturbance. In the previously mentioned case of a patient with diabetic ketoacidosis and an initially increased (AG + total CO_2) concentration, the following arterial blood gases were obtained:

$$pH = 7.18$$
$$P_{CO_2} = 38 \text{ mm Hg}$$
$$[HCO_3^-] = 15 \text{ mEq/L}$$

In pure metabolic acidosis the ventilatory response to an $[HCO_3^-]$ lowered to 15 mEq/L would be a P_{CO_2} of 25 mm Hg (see Table 17-1 and Fig. 17-4). In this example, the patient shows a P_{CO_2} that is higher than the expected value of 25 for a patient with pure metabolic acidosis and a depressed HCO_3^- value of 15 mEq/L. Hence this patient demonstrates a so-called triple disturbance, metabolic acidosis (low HCO_3^-, high AG), a metabolic alkalosis ([HCO_3^- + AG increment above 12] >30 mEq/L) and a respiratory acidosis (P_{CO_2} higher than expected value given the lowering of HCO_3^- level as determined from the acid–base nomogram or the formula for expected compensation). Therapy for this patient will require awareness of these various processes, since removal of one of multiple disturbances can induce a more severe expression of the still-present abnormality.

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CHAPTER 18

Respiratory System Response to Exercise in Health

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The increases in muscular oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) accompanying whole-body exercise present a greater challenge to the maintenance of pulmonary gas exchange than any other physiologic stressor. This chapter discusses the responses of the healthy respiratory system to exercise with an emphasis on the following problems: What neurochemical mechanisms regulate the ventilatory response to exercise and what are the consequences of this hyperpnea to the work and to the fatigue of the respiratory muscles? What mechanisms underlie the widening of the alveolar to arterial partial pressure of oxygen (P_{O_2}) difference during exercise? How do the unique characteristics of the pulmonary circulation determine its response to exercise? How does respiration impact the cardiovascular response to exercise? Under what circumstances might the respiratory system provide a limitation to O_2 transport and/or exercise performance? We consider these problems primarily in the healthy, young, normally fit adult, with reference to special cases of the highly trained athlete and to the effects of healthy aging, high altitude hypoxia, and physical training.

EXERCISE HYPERPNEA

In healthy humans, breathing in all physiological states is remarkably well controlled. Accordingly, the partial pressures of oxygen and carbon dioxide, in systemic arterial blood along with its acidity, are regulated precisely throughout mild to moderate exercise.[1–4]

These relationships are shown in the following alveolar gas equations, where alveolar gas partial pressures are approximately equal to the ratio of the metabolic requirement to alveolar ventilation.

$$P_{A_{CO_2}} = [\dot{V}_{CO_2} \div \dot{V}_A] \cdot K \quad (1)$$

$$P_{A_{O_2}} = P_{I_{O_2}} - [\dot{V}_{O_2} \div \dot{V}_A] \cdot K \quad (2)$$

where:

$P_{A_{CO_2}}$ and $P_{A_{O_2}}$ = alveolar carbon dioxide and oxygen partial pressures (it is assumed $P_{A_{CO_2}} \approx$ arterial P_{CO_2})

$\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ = volumes of carbon dioxide produced and oxygen consumed

$\dot{V}_A$ = alveolar ventilation

$P_{I_{O_2}}$ = inspired partial pressure of oxygen

K = constant (0.863). This constant allows alveolar gases to be calculated from these equations if $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are expressed in mL/min and $\dot{V}_A$ in L/min.

Table 18-1 illustrates the interrelation of these variables, as one goes from rest to exercise. With exercise, there is an increased metabolic rate, with alveolar ventilation increasing to regulate arterial blood gases near resting levels. In health, dead space (V_D) increases slightly as intrathoracic airways stretch and dilate with increased tidal volume (V_T) – but V_T rises out of proportion; thus, V_D/V_T falls to about one-half its resting value during exercise. In order that $P_{A_{CO_2}}$ be precisely controlled, overall minute ventilation ($\dot{V}_E$) during exercise must be regulated in such a fashion so as to compensate both for the increasing CO_2 production as well as a reduced V_D/V_T. Accordingly, the ratio of $\dot{V}_E$ to $\dot{V}_{CO_2}$ falls from rest to moderate exercise, whereas the $\dot{V}_A$:$\dot{V}_{CO_2}$ ratio and arterial P_{CO_2} are maintained constant until heavy exercise intensities, during which both ratios rise and $P_{A_{CO_2}}$ is reduced. Note the impressive magnitude of ventilatory response required to maintain arterial P_{CO_2} homeostasis during exercise, amounting to a 20-fold increase above resting in the untrained at $\dot{V}_{O_{2\,max}}$ and 30-fold in the highly trained.

REGULATION OF EXERCISE HYPERPNEA

More than a century of highly innovative research on this question has left us with three major stimuli as the primary regulators of exercise hyperpnea. The schematic diagram shown in Figure 18-1 includes these three potential stimuli in a ventilatory control system which features three components, namely a central rhythm generator/integrator in the medulla, mechanical and chemical feedback and feedforward inputs to this integrator, and control of the distribution of efferent output to muscles of both the upper airway and chest and abdominal wall.

CO_2 FLOW

The primary suspects for mediation of the exercise hyperpnea include **humoral stimuli** in the form of CO_2 flow to the lung or the product of blood flow and mixed venous CO_2 content. While still controversial (and mysterious) there is compelling evidence in support of a significant fundamental role for this feedback mechanism. When extracorporeal perfusion is used to increase (or reduce) CO_2 flow to the lung in a resting animal, alveolar ventilation is changed in proportion to $\dot{V}_{CO_2}$ and an isocapnic hyperpnea (or reduced ventilation) is achieved.[5] In human quadriplegic patients, increasing locomotor muscle CO_2 production via electrical stimulation of muscle contraction, increases ventilation. Similarly, increasing $\dot{V}_{CO_2}$ and the respiratory quotient with bicarbonate ingestion in resting humans will increase $\dot{V}_A$ in an isocapnic fashion. Furthermore, when sinusoidal exercise regimens are employed at changing frequencies, the ventilatory response follows the change in $\dot{V}_{CO_2}$ rather than the change in work rate, per se. The case against this purely humoral feedback stimulus in the mediation of exercise hyperpnea is that it has only been tested over a very narrow range of $\dot{V}_{CO_2}$ near resting levels and the exact nature of the stimulus or its site of action has not been identified. Recently, c-fiber receptors in the lung interstitium have been implicated, responding to an increased transport of plasma water into the lung interstitium, secondary to the effects of both increased venous CO_2 content on the osmotic state of blood plasma and increased blood flow on pulmonary capillary pressure.[6] We suspect that $\dot{V}_{CO_2}$ plays an important modulatory role in the control of breathing near resting levels, but it is unlikely to provide sufficient drive to be considered as a primary drive to hyperpnea during exercise.[7]

CENTRAL COMMAND

A purely feedforward input to medullary respiratory controller neurons originates from supramedullary regions of the motor cortex and hypothalamus and operates along synaptic pathways in parallel with

TABLE 18-1 Group Mean Values of Healthy Untrained and Trained Subjects Cardiorespiratory Responses to Steady-State Exercise

	Untrained									
	Relative Exercise Intensity (% Maximal Oxygen Uptake)								Trained A	Trained B
	Rest	**15**	**30**	**45**	**60**	**75**	**90**	**100**	**100**	**100**
$\dot{V}_{O_2}$ (L/min)	0.24	0.45	0.9	1.35	1.8	2.25	2.7	3	5.25	5.25
$\dot{V}_{CO_2}$ (L/min)	0.19	0.4	0.77	1.21	1.71	2.31	3	3.3	6.04	6.04
$\dot{V}_E$ (L/min)	6	14	22	35	51	75	100	115	183	168
$\dot{V}_A$ (L/min)	4	9	18	28	41	60	81	94	150	138
V_T (L)	0.6	0.9	1.2	1.6	2.2	2.5	2.6	2.6	3.1	2.9
fR (breaths·min^{-1})	10	15	18	22	23	30	38	44	59	58
V_D/V_T	0.35	0.28	0.21	0.2	0.19	0.18	0.18	0.18	0.18	0.18
EELV (% TLC)	0.5	0.49	0.46	0.45	0.44	0.43	0.42	0.42	0.48	0.48
Gas exchange										
Pa_{O_2} (mm Hg)	95	95	93	93	92	94	94	94	90	70
$P_{A_{O_2}}$ (mm Hg)	101	101	101	101	107	112	114	117	117	112
Pa_{CO_2} (mm Hg)	41	41	41	41	39	35	33	31	31	38
A-aDO_2 (mm Hg)	6	6	8	8	15	18	20	23	27	42
pH	7.40	7.40	7.38	7.36	7.34	7.30	7.29	7.28	7.25	7.25
Sa_{O_2} (%)	97	97	97	97	96	96	95	95	93	86
$\dot{V}_A/\dot{Q}$	0.8	1.3	2	2.5	2.9	3.5	4.1	4.5	4.7	4.3
Pulmonary circulation										
$\dot{Q}$ (L·min^{-1})	5	7	9	11	14	17	20	21	32	32
PCBV (mL)	83	95	107	119	137	155	173	180	180	180
Transit time (s)	1	0.81	0.71	0.65	0.59	0.55	0.52	0.51	0.33	0.33
PAP (mm Hg)	13	15	17	20	23	27	29	32	30	35
PAWP (mm Hg)	8	9	10	12	13	15	17	21	14	18
PVR (mm Hg·min^{-1}·s^{-1})	60	51.4	46.7	43.7	42.8	42.4	36	31.4	30	33

$\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{CO_2}$, expired carbon dioxide; $\dot{V}_E$, minute ventilation; $\dot{V}_A$, alveolar ventilation; V_T, tidal volume; fb, breathing frequency; V_D/V_T, dead space to tidal volume ratio; EELV, end-expiratory lung volume as a percentage of total lung capacity; Pa_{O_2}, arterial P_{O_2}; $P_{A_{O_2}}$, alveolar P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; A-aDO_2, alveolar to arterial oxygen partial pressure difference; Sa_{O_2}, arterial oxyhemoglobin saturation; $\dot{V}_A/\dot{Q}$, global ventilation to perfusion ratio; $\dot{Q}$, cardiac output; PCBV, pulmonary capillary blood volume; transit time, mean pulmonary capillary transit time; PAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance. Two columns of values for highly trained subjects are shown, both with equal $\dot{V}_{O_{2max}}$ values. Group A experiences little arterial hypoxemia while Group B experiences substantial hypoxemia in heavy intensity exercise.

the motor control of locomotor muscles. Animal models using electrical or pharmacological stimulation of these supramedullary sites show powerful cardioventilatory responses even in the face of paralyzed locomotor muscles, that is, in the absence of neural feedback.[8] Further, in hypnotized humans even the "suggestion" of exercise – while still at rest – elicits exercise-like cardioventilatory responses with coincident PET imaging studies showing an increased blood flow to motor control regions of the cortex.[9] On the other hand, the "exercise-like" ventilatory response to electrical stimulation of the limbs shows that feedforward central command is not obligatory to the hyperpnea and a normal ventilatory response to exercise is also observed in decorticate animals, that is, in the absence of key hypothalamic regions of purported cardioventilatory central command.

MUSCLE AFFERENT FEEDBACK

Lightly and unmyelinated afferents from locomotor muscle sensitive to the metabolic milieu, mechanical deformation, and even vascular distension in the muscle, project via the dorsal horn of the spinal cord and then via the nucleus of the solitary tract to the medullary cardiorespiratory controller neurons. When their effect on ventilation is studied in isolation, using electrical stimulation of muscle, a proportionate increase in $\dot{V}_E$ occurs. However, evidence against a role for muscle afferents in the intact human include the failure of imposed vascular occlusion causing accumulation of muscle metabolites to augment ventilation during recovery from exercise, the failure of spinal cord lesioning to alter the ventilatory response to muscle stimulation, or of epidural anesthesia to reduce the cardioventilatory response to rhythmic exercise. On the other hand, if afferent blockade techniques are employed – such as intrathecal fentanyl which blocks only muscle afferents and leaves efferent motor pathways intact, hypoventilation occurs throughout mild and moderate exercise – uncovering a significant obligatory role for muscle afferents in the steady-state exercise hyperpnea (see Fig. 18-2).[10,11] This inhibitory effect of muscle afferent blockade on exercise hyperpnea has also been shown in patients with COPD and CHF.[12,13] Interestingly, in COPD patients muscle afferent blockade during exercise reduced primarily V_D ventilation, suppressed dyspneic sensations, and substantially improved exercise performance.[12]

In summary, the dilemma of exercise hyperpnea is that findings using isolation of each of these three stimuli support a significant contributory role for each of these mechanisms to the isocapnic hyperpnea of moderate intensity exercise—but there is contradictory evidence against an obligatory major role for any of them. Accordingly, most models emphasize the powerful redundancy of the hyperpnea mechanisms operating under steady-state conditions of exercise or emphasize the importance of compensatory feedback

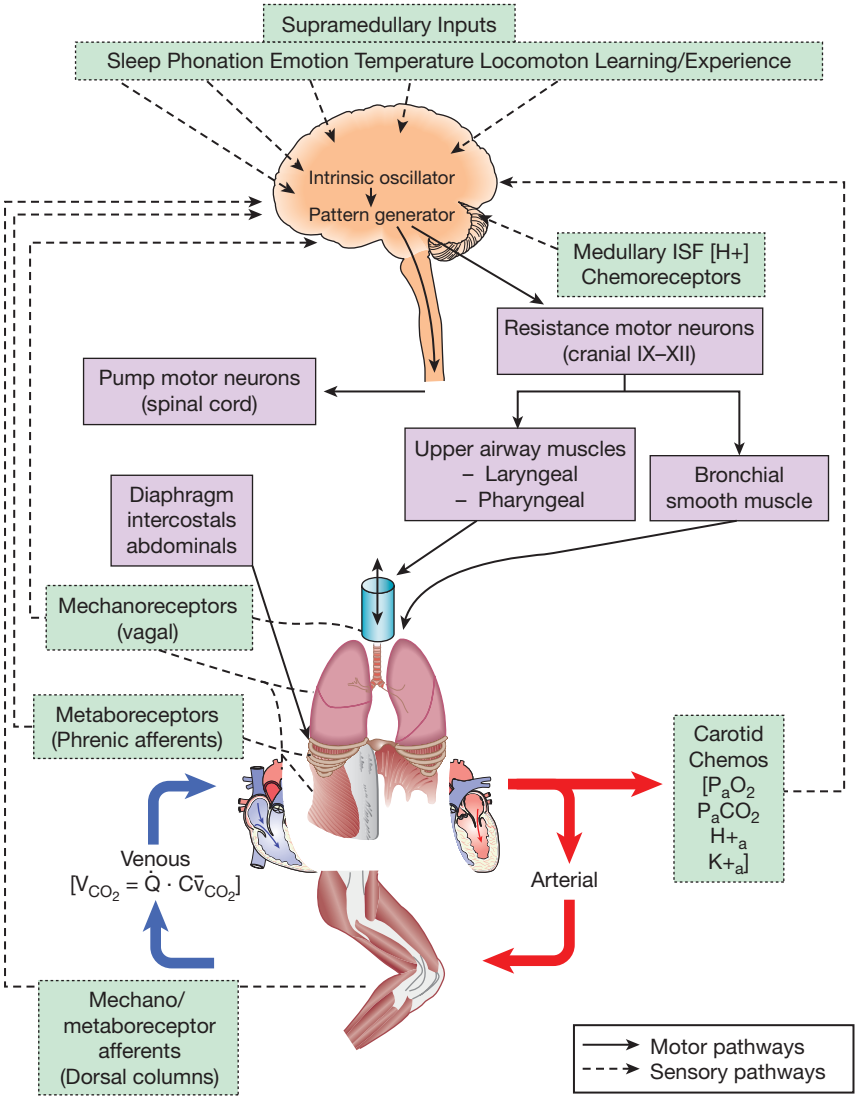

Figure 18-1 Schematic depicting multiple structures contributing to the control of breathing. It is hypothesized that respiratory rhythm originates within a brain stem oscillator which activates brain stem pattern generating neurons that provide for the proper sequential activation of respiratory pump (diaphragm, intercostal, and abdominal) and airway (laryngeal and pharyngeal) muscles. These brain stem neurons receive excitatory and inhibitory input from multiple sources during exercise, including supramedullary central command and mechano/metaboreceptor-initiated spinal afferents from limb and respiratory skeletal muscles. In addition, the brain stem controller neurons receive carotid and intracranial chemoreceptor (RTN, retrotrapezoid nucleus) and vagal mechanoreceptor input critical to meet the appropriate ventilatory and breathing pattern responses to exercise. *(Reproduced with permission from Taylor N. Physiological Bases of Human Performance during work and exercise. New York: Churchill Livinstone; 2008.)*

from carotid and central chemoreceptors if blockade of any of these primary mechanisms was sufficient to cause transient CO_2 retention. There are also suggestions that feedback mechanisms are likely of little consequence; rather, the ventilatory response to exercise depends critically on a "stored memory" of the appropriate ventilatory response by the motor cortex as a result of repetitive trial and error during maturation.[14] We hypothesize – with limited direct evidence – that each of these three mechanisms have an important obligatory role, with CO_2 flow to the lung providing the essential underpinning to ventilatory control in all physiologic states and the interaction of feedforward (central command) and feedback (from muscle afferents) mechanisms providing the primary "exercise" stimulus. The proof for this awaits the appropriate experimental tools – such as was done with the use of opiate receptor agonists (see Fig. 18-2) – to test a specific mechanism without altering the remaining elements of the control system.

Finally, we need to emphasize that this hypothesis applies only to the isocapnic hyperpnea achieved in mild to moderate steady-state levels of exercise. For the hyperventilatory response to heavier intensity exercise we need to add additional mechanisms: an important input from carotid chemoreceptors responding to the changing hydrogen ion, potassium, norepinephrine, temperature, etc. of the arterial blood induced by heavy intensity exercise; the additional powerful inputs from central command responding to the need to recruit more motor units in the presence of fatiguing locomotor muscles; and muscle afferents responding to accumulating ionic changes in the muscle interstitium. Even an obligatory role for carotid chemoreceptors and the hyperventilatory response to heavy exercise has been challenged by the fact that preventing the blood-borne acidity during heavy exercise (via depleting muscle glycogen and preventing acid production) did not prevent the hyperventilatory response.[7] Again multiple, redundant mechanisms are apparently at play. This hyperventilatory response is extremely important in partially compensating for the metabolic acidosis incurred with increasing lactic acid levels in heavy exercise and also for raising alveolar P_{O_2} to maintain arterial P_{O_2} in the face of a widening alveolar to arterial P_{O_2} difference.[15]

■ BREATHING PATTERN DURING EXERCISE

During low to moderate intensity exercise both V_T and breathing frequency (fb) increase roughly in proportion to intensity, while at higher intensities V_T attains a plateau and further increases in $\dot{V}_E$ are accomplished by increases in fb alone (see Fig. 18-3). The increase in fb is accomplished by decreases in both inspiratory time (T_I) and expiratory time (T_E). However the ratio of T_I to total breath cycle duration (T_{TOT}), known as the duty cycle (T_I/T_{TOT}), increases only slightly during exercise (~0.40 at rest to ~0.50 during high-intensity exercise). The fact that the duty cycle remains low is important and beneficial, because prolonged diaphragmatic contractions hinder blood flow to this muscle and may precipitate excessive diaphragmatic fatigue.[16]

The increase in V_T at the onset of exercise is accomplished by both an increase in end-inspiratory lung volume (EILV) and a decrease in end-expiratory lung volume (EELV). However, as exercise intensity increases, EILV does not normally increase beyond 85% to 90% TLC. Beyond this point lung compliance decreases markedly and the respiratory pressure production required for a given change in volume is very large. This inefficiency at high operating lung volumes leads to neuromechanical uncoupling in that a mismatch develops between the required "effort" to inspire and the actual volume of air inhaled. This hyperinflation (secondary to expiratory flow limitation) underlies much of exertional dyspnea, that is, "unsatisfied inspiratory effort" in COPD patients.[17] In health, EELV decreases at the onset of all levels

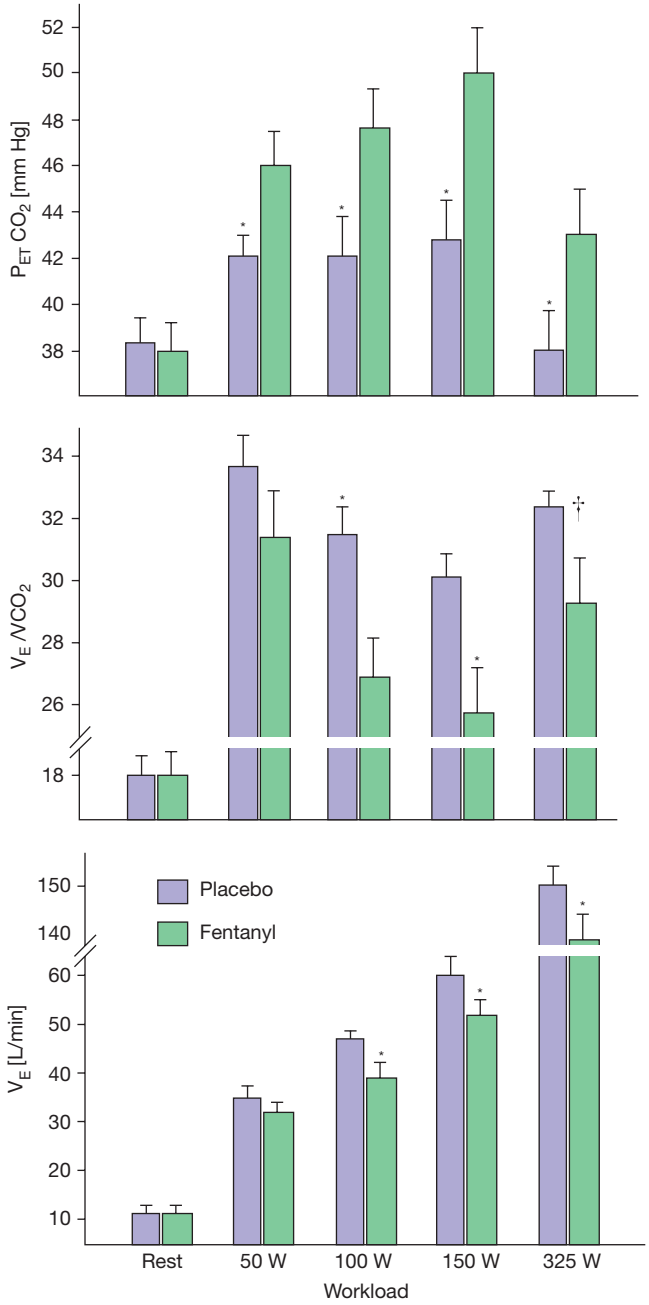

Figure 18-2 Effect of blockage of μ-opioid sensitive type III–IV muscle afferents via intrathecal fentanyl on the steady-state ventilatory response to 3 minutes of cycling exercise at each of four work rates. (*$p < 0.05$, †$p < 0.08$). The fentanyl-induced hypoventilation was due to a reduced breathing frequency. Heart rate, mean arterial blood pressure, and $\dot{V}_E$ were significantly reduced at each work rate. Taking into account the reduced exercise $\dot{V}_E$ with fentanyl plus the ventilatory equivalent of the concomitant rise in $P_{ET_{CO_2}}$, it is estimated that the partial blockage of muscle afferents accounted for 47%, 45%, and 15% of the total exercise hyperpnea at 100, 150, and 325 W, respectively. *(Modified with permission from Amann M, Blain GM, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA. Group III and IV muscle afferents contribute to ventilatory and cardiovascular response to rhythmic exercise in humans. J Appl Physiol. 2010;109(4):966–976.)*

of exercise due to active recruitment of the expiratory muscles, and its decrease is roughly proportional to exercise intensity.[18] The drop in EELV maintains operating lung volumes within the linear portion of the pressure–volume relationship, which minimizes the reduction in respiratory system compliance and associated dyspnea that develops at high lung volumes. The reduced EELV also serves to lengthen the diaphragm and place it in a more optimal range of its length–tension relationship. Thus the maximum dynamic capacity of the inspiratory muscles for force production is improved during tidal breathing and they are required to produce only about one-half of their capacity for force production at maximum exercise in the untrained subject (see Fig. 18-3).[19] A reduced EELV also reduces inspiratory muscle work during the ensuing inspiration due to outward recoil of the rib cage at the onset of inspiration.

Tidal exercise flow–volume loops plotted within the maximal volitional flow–volume envelope provide a simple and useful method to analyze alterations in flow rates, V_T, and operating lung volumes during exercise (Fig. 18-4). In normal, healthy untrained young adult humans the maximal attainable flow rates at any given lung volume are usually much greater than the spontaneous tidal flow rates reached during exercise of all intensities. Thus, as shown in Figure 18-4 (at $\dot{V}_{E\,max}$ in the 100–120 L/min range) there is usually a large reserve for increasing $\dot{V}_E$ even at maximal exercise.

CONTROL OF AIRWAY CALIBER DURING EXERCISE

UPPER AIRWAY CALIBER

The upper airway comprises the nose, mouth, pharynx, and larynx, and provides the majority of resistance to airflow at rest and during exercise. In addition, each region of the upper airway has the potential to independently contribute to any alterations in airway resistance during exercise. The work required to produce the large increases in airflow during exercise would become excessive during even low-intensity exercise if several mechanisms were not in place to reduce resistance to airflow in the upper airway during exercise.

First, the route of airflow switches from predominately nasal to oronasal breathing when $\dot{V}_E$ reaches approximately 30 L/min.[20] Second, nasal resistance decreases during exercise in an intensity- and duration-dependent manner secondary to sympathetically mediated vasoconstriction of the nasal mucosal vasculature.[21] Third, the nasal dilator muscles and presumably the skeletal muscles of the pharyngeal and laryngeal regions contract in phase with, but slightly preceding, inspiratory pump muscle recruitment, and this drive to the upper airway muscles is increased at increasing $\dot{V}_E$, resulting in decreased resistance and a larger diameter, stiffer, less collapsible upper airway.[22] Finally, the glottic narrowing that normally occurs during expiration is attenuated during exercise due to laryngeal abductor muscle activation, in addition to a widened mean glottic aperture throughout the respiratory cycle.[23] Thus, the work required to produce the increased airflow that occurs during whole-body exercise is minimized by a variety of adjustments that occur in the upper airway, all of which act to decrease resistance to airflow.

BRONCHIAL CALIBER

Bronchial dilation in response to exercise has been well documented in healthy humans.[24] Furthermore, this bronchodilator influence occurs at exercise onset and is very powerful, as evidenced by the prevention of an increase in pulmonary resistance during exercise after histamine inhalation in asthmatic subjects who exhibited large increases in resistance during histamine inhalation at rest.[25] In addition, forced expiratory volume in 1 second (FEV_1) and the maximum volitional flow:volume envelope increase immediately after exercise in both normal[26] and asthmatic subjects.[27] There are several potential mechanisms contributing to the bronchodilator effect of exercise, including neural, mechanical, and locally released mediator mechanisms.

A primary component of the exercise-induced increase in airway caliber is withdrawal of vagal parasympathetic tone to the airways that occurs at the immediate onset of exercise, resulting in bronchial smooth muscle relaxation.[24] The withdrawal of cholinergic tone is thought to be mediated in part by the stimulation of muscle mechano- and chemosensitive afferents (i.e., the same muscle afferents

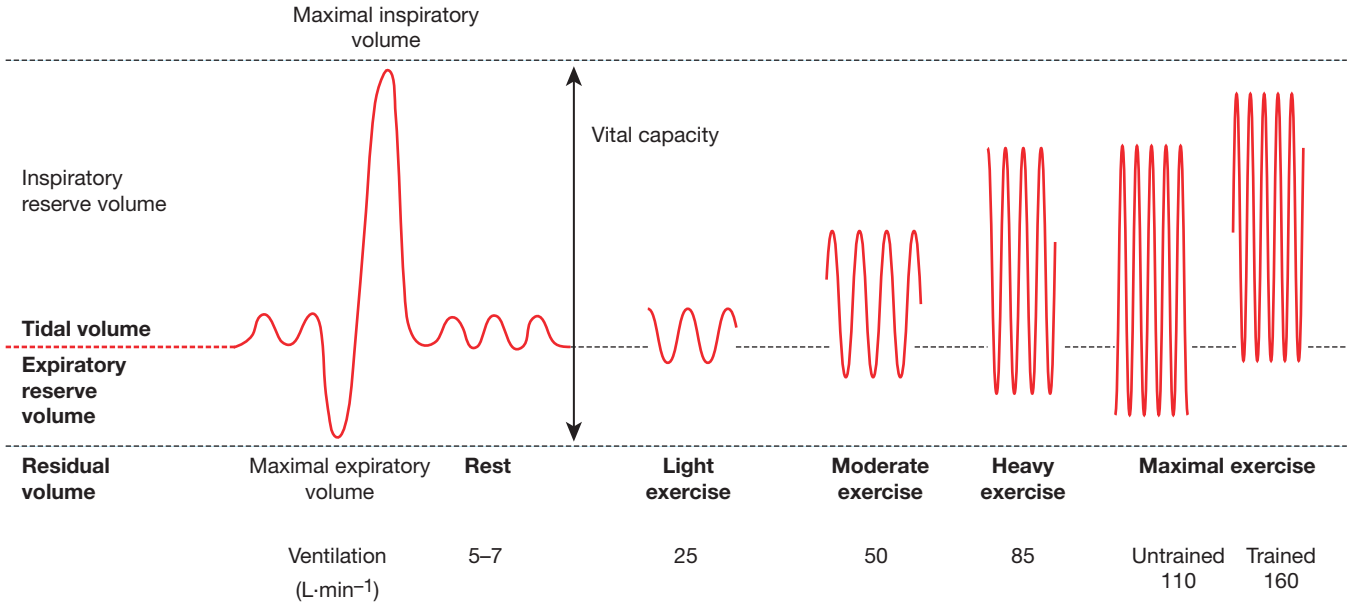

Figure 18-3 Changes in breathing pattern during exercise. The spirograph on the left is from a resting subject showing normal tidal volume, maximum expiration to residual lung volume, then maximal inspiration to total lung capacity. With light to heavy exercise (in both untrained and highly trained subjects) the increase in ventilation is achieved by increasing breathing frequency and tidal volume. Tidal volume increases by encroaching on the expiratory and inspiratory reserve volumes. The reduced end-expiratory lung volume is maintained at maximal exercise in the normally fit subject (maximal oxygen uptake [$\dot{V}_{O_2\,max}$] 45 mL kg^{-1} L min^{-1}). In the trained subject ($\dot{V}_{O_2\,max}$ = 75 mL kg^{-1} L min^{-1}), ventilation, breathing frequency, and tidal volume are all higher and maximal exercise end-expiratory lung volume is increased to near resting values due to expiratory flow limitations. *(Reproduced with permission from Farrell PA, Joyner MJ, Caiozxo VJ. ACSM's Advanced Exercise Physiology, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.)*

believed to be involved in the pressor and ventilatory responses to exercise) (see Fig. 18-2).[28] Increased lung stretch and activation of slowly adapting pulmonary stretch receptors (that occurs as EILV is increased during exercise) may contribute to this withdrawal of vagal tone.

Mechanical influences may also play a substantial role in increasing airway caliber during exercise. The airways are tethered open by the lung parenchyma, and the increase in EILV and operating lung volumes during exercise will enlarge airway diameter simply as a result of this airway–parenchymal interdependence. Further, the

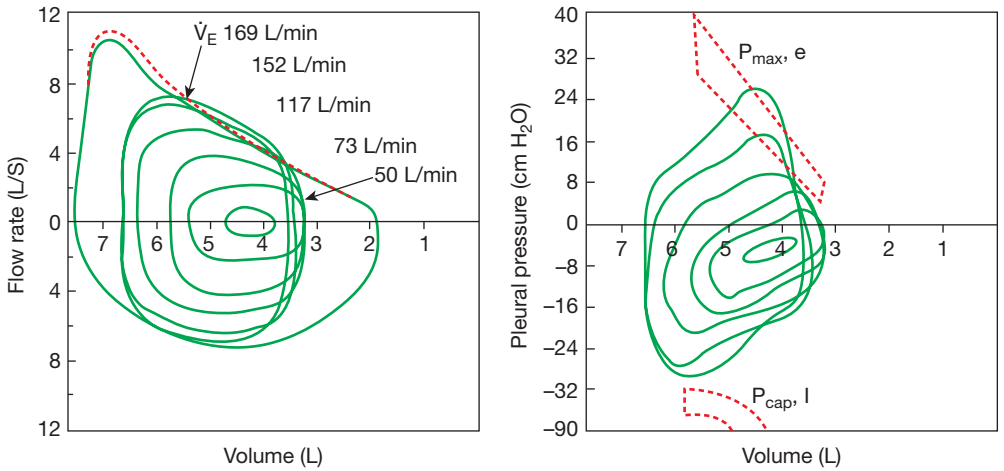

Figure 18-4 Flow–volume and pressure–volume relationships in a young healthy adult, at rest and during exercise. The maximal (outer envelope) flow–volume relationship is obtained via maximal volitional inspiratory and expiratory efforts, before *(solid line)* and immediately following exercise *(broken line)*. For the pressure–volume relationships, only tidal breaths from rest through to maximal exercise are shown. In addition, the maximum inspiratory pleural pressures (P_{cap}, I) are shown at the specific peak volume and flows achieved during tidal breathing in heavy exercise. For minute ventilations up to 115 L min^{-1}, approximating peak exercise in an untrained adult, the inspiratory muscles are activated to only ~40% to 50% of capacity. The more highly trained subject is shown achieving ventilations >150 L min^{-1} at higher metabolic rates. Under these conditions, the tidal flow–volume loop often encroaches on the maximum flow–volume envelope, end-expiratory lung volume rises, and the inspiratory muscles approach 90% of their dynamic capacity for force output and shortening velocity. The broken area on the expiratory side indicates expiratory pressures for any given lung volume (P_{max}, e), beyond which extraexpiratory muscle effort will not produce a higher flow. In almost all instances up to ventilations of ~150 L min^{-1}, this critical expiratory pressure is not exceeded but it is exceeded slightly in the highly trained athlete at maximum exercise. *(Modified with permission from Johnson BD, Saupe KW, Dempsey JA. Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol. 1992;73(3):874–886.)*

increased outward radial force exerted by the parenchyma on the airways during exercise may induce bronchodilation by a separate mechanism operating at the level of the crossbridges of bronchial smooth muscle.[29] Airway stretch modulates bronchial smooth muscle crossbridge formation, resulting in decreased bronchial smooth muscle force and stiffness and relaxation of airway smooth muscle. Finally, airway mast cells, macrophages, neutrophils, eosinophils, epithelial cells, and smooth muscle cells all have the potential to release a variety of chemical mediators that may alter airway caliber.

WORK, METABOLIC AND CIRCULATORY COST OF BREATHING

During exercise the inspiratory and expiratory muscles perform work on the lung, the abdominal wall, and the rib cage. The work on the lung is composed of elastic work – a function of both the V_T and lung compliance and flow resistive work – a function of airway caliber and flow rate. As the diaphragm descends during inspiration, work is performed on the abdominal wall—a function of abdominal wall compliance. This work maximally contributes about 25% to the total work of breathing during exercise—but in the presence of expiratory flow limitation abdominal muscle tension will persist well into the inspiration which will markedly increase work done by the diaphragm on the abdominal compartment. As shown in Figure 18-5 the total work of breathing rises linearly with the isocapnic hyperpnea of mild and moderate intensity exercise and then rises alinearly with the hyperventilation of heavy intensity exercise.

This severalfold increase in respiratory muscle work requires increases in respiratory muscle $\dot{V}_{O_2}$ and blood flow. Thus, at maximal $\dot{V}_{O_2}$ (~45 mL/kg/min) and cardiac output (~20 L/min) and $\dot{V}_E$ (100–120 L/min), about 8% to 10% of $\dot{V}_{O_2}$ and cardiac output are devoted to breathing in the untrained human and up to 14% to 16% of $\dot{V}_{O_2}$ and cardiac output in the highly trained ($\dot{V}_{O_{2max}}$ ~65 mL/kg, $\dot{V}_E$ >150 L/min, and CO ~30 L/min—see Table 18-1). Respiratory muscle blood flow, was determined directly by using distribution of infused microspheres in exercising animals[30] and indirectly in humans by the reduction in total cardiac output and increased blood flow to the exercising limb muscles measured when respiratory muscle work was reduced during maximal exercise using a mechanical ventilator (see Fig. 18-6).[31,32]

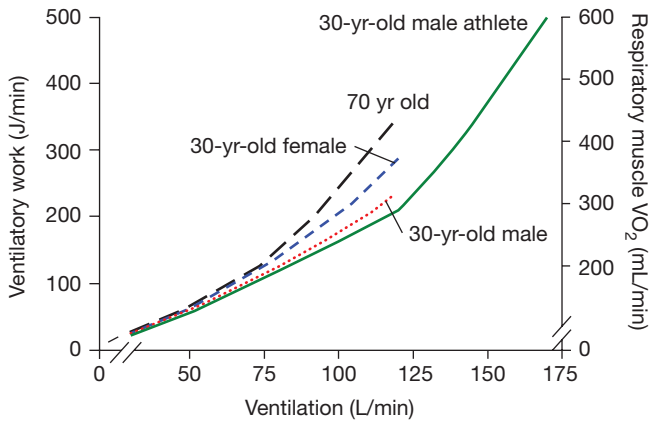

Figure 18-5 Ventilatory work and respiratory muscle $\dot{V}_{O_2}$ during exercise of increasing intensity plotted as a function of $\dot{V}_E$ for sedentary men, active young females, and trained young and older men. In young adult males the O_2 cost of exercise hyperpnea was determined by having subjects mimic the pressure–volume loop, breathing frequency, duty cycle, and ventilation they experienced during submaximal and maximal exercise and measuring the change in $\dot{V}_{O_2}$ from resting eupnea.[108,109] *(Reproduced with permission from Harms CA, Dempsey JA. Cardiovascular consequences of exercise hyperpnea. Exerc Sport Sci Rev. 1999;27:37–62.)*

Several lines of evidence are available in support of the concept that during heavy intensity exercise a metaboreflex is triggered from the diaphragm which travels in phrenic nerve afferent fibers to increase efferent vasoconstrictor outflow from sympathetic neurons in the medulla. For example, studies in healthy humans using muscle microneurography and Doppler blood flow measurements of limb muscle blood flow demonstrated increases in muscle sympathetic nerve activity together with reduced limb vascular conductance and blood flow in the face of inspiratory or expiratory muscle fatigue induced by volitional hyperpnea against increased airway resistive loads.[33] In animals specific acidification of the diaphragm or pharmacologic stimulation of diaphragm afferents caused vasoconstriction in limb muscle and these effects were prevented via ganglionic blockade.[34,35] The finding that vasoconstriction occurs under these conditions of heightened sympathetic outflow in the locomotor muscle vasculature and not in the diaphragm is supported by in situ studies which show feed arteries in the diaphragm to undergo substantially less norepinephrine-induced vasoconstriction than that which occurs in vessels isolated from limb muscle.[36] Apparently these reflex mechanisms and vascular response characteristics combine to protect blood flow to the respiratory muscles during intense exercise.

EXERCISE-INDUCED RESPIRATORY MUSCLE FATIGUE

The structural and functional properties of the respiratory muscles appear to be well suited to the substantial ventilatory requirements of exercise. For example, the human at rest can voluntarily sustain up to 6 to 8 times the resting diaphragmatic pressure production for 10 to 15 minutes without inducing significant fatigue or task failure of the diaphragm.[37] Furthermore, pressures and velocities of shortening sustained by the diaphragm that are 1.5 to 2 times greater than those reached during exhaustive exercise are required to cause diaphragm fatigue when the subject is in the resting state and increases ventilation voluntarily.[37] Nevertheless, significant 15% to 50% reductions in the transdiaphragmatic pressure response to bilateral super maximal phrenic nerve stimulation, across a wide range of stimulation frequencies (1–100 Hz) and lung volumes (residual volume to TLC), have been observed following constant-load, whole-body endurance exercise at >85% $\dot{V}_{O_{2max}}$ to exhaustion.[38–41] Recent studies using phrenic nerve stimulation at multiple time points during high-intensity exercise shows that significant diaphragm fatigue actually begins to occur fairly early in the time course of the exercise.[42] The magnitude of exercise-induced diaphragm fatigue is determined in part by the amount of diaphragm work contributing to the exercise hyperpnea. Thus, substantially reducing the pressures produced by the diaphragm during endurance exercise using a proportional assist ventilator prevented diaphragm fatigue.[40] Whole-body exercise itself appears to lower the threshold of force output by the diaphragm required for its fatigue, likely because a finite blood flow must be distributed to both locomotor and respiratory muscles.[32] Such a disparity between O_2 supply and demand to the diaphragm appears to occur in subjects of varying fitness levels, but only at workloads exceeding 85% of $\dot{V}_{O_{2max}}$,[41] or when arterial O_2 saturation is decreased.[43]

CARDIOVASCULAR EFFECTS OF INTRATHORACIC PRESSURE

Respiration has important and complex effects on stroke volume and cardiac output during exercise through changes in intrathoracic and transventricular pressures. This has been demonstrated in human and animal studies by manipulating inspiratory and expiratory pressures during exercise. During inspiration the negative pressure generated in the intrathoracic space widens the pressure gradient across the walls of the right heart thereby augmenting ventricular filling of venous return from the limbs by lowering the pressures within the heart's chambers and augmenting cardiac preload. Conversely, during expiration ventricular filling is impeded by

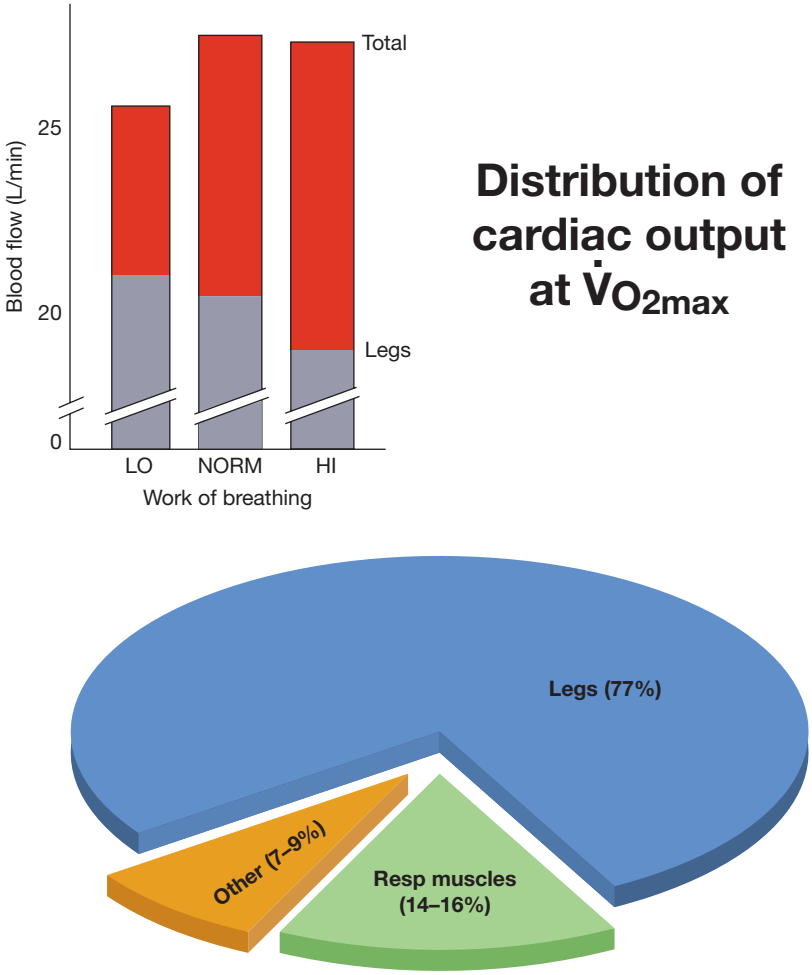

Figure 18-6 Effects of respiratory muscle work during exercise on cardiac output and its distribution in highly fit adult male subjects cycling at $\dot{V}_{O_{2\,max}}$ ($\dot{V}_{O_2}$ = 65 mL/kg/min, cardiac output = 28 L/min), "LO, NORM, HI" refer to the relative level of the work of breathing present during heavy intensity exercise under normal physiologic conditions, with added resistive loads ("HI") and during unloading of the respiratory muscles via mechanical ventilation ("LO"). The top of each bar indicates the total cardiac output and each bar is divided into blood flow to the limbs and to the rest of the body. The estimated distribution of blood flow to the limb locomotor and to the respiratory muscles is shown in the pie chart. These estimates come from three sources: 1. The oxygen cost of breathing at maximum exercise[108]; 2. Measurements based on microsphere distribution to the respiratory muscles during maximum exercise in the equine[110]; and 3. The change in cardiac output and in limb muscle blood flow determined in response to unloading of the respiratory muscles during maximum exercise.[31,32] These effects of respiratory muscle unloading at maximum exercise on limb blood flow and on total cardiac output are shown in the insert. Note that with reduced respiratory muscle work, that is, unloading, the total cardiac output falls and the limb muscle blood flow (and vascular conductance) rises; whereas with respiratory muscle loading and increased work of breathing at maximum exercise the maximum cardiac output remains unchanged whereas the limb blood flow (and vascular conductance) is reduced. *(Reproduced with permission from Farrell PA, Joyner MJ, Caiozzo VJ. ACSM's Advanced Exercise Physiology, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.)*

a narrowing of the transmural pressure gradient across the ventricle due to a positive shift in intrathoracic pressure (ITP) which reduces the pressure gradient for venous return. In the steady state these modulatory effects of ITP will be limited by intrinsic "autoregulatory" cardiac mechanisms termed ventricular interdependence, by which the filling of one ventricle shifts the common wall – the IV septum – toward the opposite ventricle which in turn limits its filling. Nevertheless, during exercise – especially in heavy intensity exercise with huge negative shifts in ITP, if positive pressure mechanical ventilation is introduced, stroke volume and cardiac output are reduced – likely due to a less negative inspiratory ITP limiting cardiac preload, that is, reducing ventricular transmural pressure during diastole.[32] Alternatively, with active expiration in heavy exercise – especially in the presence of excessive positive expiratory pressures accompanying expiratory flow limitation – transventricular wall pressures are reduced, diastolic filling is impaired, and stoke volume and cardiac output are compromised.[44,45]

PULMONARY CIRCULATION AND GAS EXCHANGE

The lungs are unique in that they are the only organ that receives all the blood pumped from the heart and thus, the lungs must accommodate the entire increase in cardiac output during exercise. The pulmonary circulation is under limited adrenergic[46] or endothelial[46–51] control during exercise and therefore, because of its unique in-series relationship, the pulmonary circulation is tightly coupled to left (downstream) ventricular function. At the same time, the pulmonary microcirculation has been engineered to maximize gas-exchange efficiency and as a result, vessel walls are very thin, strong, and distensible. Correspondingly, pulmonary vascular resistance and perfusion pressures are about one-fifth of those observed in the systemic circulation at rest.

With upright exercise, there is an increase in venous return to the heart, causing a central shift of blood volume into the thorax.[52] This increases both right and left ventricular filling pressures,[53] helping to maintain, or increase, both end-diastolic volume and stroke volume, despite reductions in filling time secondary to exercise-induced tachycardia. The dominant determinant of pulmonary artery pressure during exercise is left ventricular filling pressure.[54]

The rise in both pulmonary arterial and pulmonary capillary wedge pressures with exercise recruits previously unperfused and distended pulmonary capillaries, increasing capillary blood volume and reducing pulmonary vascular resistance. This increases the surface area for gas diffusion[55] and helps to maintain the red blood cell capillary transit time necessary for complete gas exchange (>0.25 seconds). (Mean pulmonary capillary transit time [seconds] is equal to the ratio of pulmonary capillary blood volume and blood flow [cardiac output].) At peak exercise in untrained subjects, despite the fourfold increase in pulmonary flow (cardiac output) from rest, capillary transit time at maximum exercise is reduced to only about one-half that at rest, due to a doubling of the pulmonary capillary blood volume (see Table 18-1).

It is important for the lung to remain relatively dry for gas exchange. At rest, there is a small outward flow of plasma fluid (~10–20 mL h^{-1}) from the capillaries into the interstitial space of the alveolar wall. The fluid passes into the perivascular and peribronchiolar spaces of the lung, with the lymphatic system transporting this fluid to the hilar lymph nodes. With exercise, thoracic lymph flow increases substantially, due to augmented pulmonary capillary pressures and capillary surface area.[56] In addition, the augmented ventilation with exercise increases lymph flow, acting

as a safety mechanism to oppose edema formation in the alveoli or interstitial space.[57] Thus, the lymphatic system is vitally important in preventing exudation of fluid into the alveoli during exercise.

The efficiency of gas exchange for O_2 within the lung is defined and quantified as the difference in P_{O_2} between the alveolar gas and the arterial blood, and is known as the alveolar to arterial P_{O_2} difference ($A\text{-}aDO_2$). If gas exchange within the lung were perfect, the $A\text{-}aDO_2$ would be equal to zero. However, the $A\text{-}aDO_2$ normally amounts to 5 to 10 mm Hg at rest in young, healthy subject.[58] During exercise, the efficiency of gas exchange worsens in an intensity-dependent manner, and the $A\text{-}aDO_2$ increases to values of 15 to 25 mm Hg or more at maximal exercise (see Table 18-1). In contrast, fixed workload endurance exercise does not result in a time-dependent worsening of gas exchange when compared to the first minute of exercise,[59] indicating that the magnitude of the $A\text{-}aDO_2$ is determined primarily by metabolic rate as opposed to exercise duration.

The $A\text{-}aDO_2$ is a complex physiologic variable and as such is determined by a variety of mechanisms during rest and exercise. The worsening of gas-exchange efficiency during exercise is primarily due to an exaggeration of mechanisms present at rest. The principle contributor to the $A\text{-}aDO_2$ during both rest and exercise is the imperfect matching of the distributions of alveolar ventilation ($\dot{V}_A$) and pulmonary blood flow ($\dot{Q}$), otherwise known as the $\dot{V}_A/\dot{Q}$ ratio (see full discussion on $\dot{V}_A/\dot{Q}$ in Chapter 14). The ratio of $\dot{V}_A$ to $\dot{Q}$ can be partitioned into that occurring *among* lung regions (i.e., interregional, primarily dependent on gravity) and to that *within* an isogravitational plane of the lung (i.e., intraregional, or independent of the effects of gravity). The distributions for $\dot{V}_A$ and $\dot{Q}$ were once thought to be dominated by gravity, however, recent studies have resulted in the realization that there is also a great deal of pulmonary blood flow heterogeneity within an isogravitational plane of the lung.[60] Presumably, much intraregional heterogeneity exists for alveolar ventilation as well. These intraregional inhomogeneities are likely due simply to the normal anatomical heterogeneity of vessel and airway diameters, compliances, and resistances within specific lung regions.

During exercise, overall $\dot{V}_A/\dot{Q}$ nonuniformity increases slightly as measured by the multiple inert gas elimination technique (a technique that is not able to partition the $\dot{V}_A/\dot{Q}$ into separate inter- and intraregional distributions).[61,62] Despite this increasing nonuniformity, both $\dot{V}_A$ and $\dot{Q}$ become more uniform from lung apex to base resulting in a more uniform interregional $\dot{V}_A/\dot{Q}$ distribution.[63] Thus, the increased overall $\dot{V}_A/\dot{Q}$ nonuniformity observed during exercise can be attributed almost entirely to a more maldistributed intraregional $\dot{V}_A/\dot{Q}$, which contributes to the decreased efficiency of gas exchange (i.e., widening of $A\text{-}aDO_2$) at increasing exercise intensities. Counteracting the greater nonuniformity of the $\dot{V}_A/\dot{Q}$ distribution during exercise is the fact that overall $\dot{V}_A$ increases out of proportion to $\dot{Q}$ at increasing exercise intensities (see Table 18-1).[62] Thus, even though the distribution of $\dot{V}_A/\dot{Q}$ becomes more nonuniform, the higher overall $\dot{V}_A/\dot{Q}$ assures that little if any of the lung will be markedly underventilated (i.e., $\dot{V}_A/\dot{Q} < 0.8$). Alveolar P_{O_2} is therefore maintained high throughout the lung and this assures maintenance of end-capillary P_{O_2} near resting levels, even in the face of a progressive reduction in mixed venous O_2 content.

A second contributing factor to the $A\text{-}aDO_2$ is the mixing of shunted blood (i.e., venous blood that does not pass a ventilated alveolus) with arterial blood. There are two types of shunt that may contribute to the $A\text{-}aDO_2$ in health. The first type is known as an extrapulmonary shunt, and – in health – primarily consists of Thebesian venous drainage from the coronary circulation, which drains deoxygenated blood directly into the left ventricle.[64] Extrapulmonary shunts as small as 1% to 2% of the cardiac output have been calculated to account for about half of the $A\text{-}aDO_2$ during moderate intensity exercise.[62] Importantly, these shunts would be expected to increase total venous admixture during exercise of increasing intensity due to both a decreased O_2 content of Thebesian effluent (as a result of increased myocardial O_2 extraction)[65] as well as increased total Thebesian flow.

A second type of shunt that may contribute to the $A\text{-}aDO_2$ is commonly referred to as an intrapulmonary shunt, and is the result of direct anatomic connections between pulmonary arterial and venous vessels. These arteriovenous connections have been shown to exist in isolated, perfused whole human lungs.[66,67] and would be expected to have a greater influence on Pa_{O_2} during exercise of increasing intensity as $P\overline{v}_{O_2}$ falls. To date only indirect methods – using a delayed echo-Doppler visualization of intravenous infused microbubbles in the left atrium – support the concept that the intrapulmonary shunt pathway opens during exercise in healthy humans.[68] While the distensibility of this shunt pathway may modify the rise in pulmonary artery pressure during exercise, there is no evidence to indicate that it influences pulmonary O_2 exchange.[69]

SUMMARY: THE OVERBUILT HEALTHY RESPIRATORY SYSTEM

Based on our discussion to date of the respiratory system response to exercise in the untrained healthy adult there appears to be few exceptions to the conclusion that the respiratory system is substantially "overbuilt" and precisely regulated in meeting metabolic requirements of up to 10 to 12 times the resting levels. Key lines of supportive evidence include the following:

- At least three primary and redundant interrelated feedforward and feedback mechanisms combine – along with carotid chemoreceptors involvement with heavy exercise – to ensure near proportional ventilatory responses up to 10- to 12-fold increases in metabolic CO_2 production, that is, a highly precise isocapnic and mechanically efficient "just right" ventilatory response.
- Exercise-induced bronchodilation minimizes the increase in flow resistance respiratory muscle work and precise regulation of increases in V_T and f and reductions in EELV minimize increases in elastic work and V_D ventilation.
- A 20-fold increase in $\dot{V}_E$ is accomplished using less than 50% of the dynamic capacity of inspiratory muscles for force generation and requiring less than 10% of maximum $\dot{V}_{O_2}$ and cardiac output and with tidal flows and volumes which are well within the healthy airways maximal flow:volume envelope.
- Slight increases in overall $\dot{V}_A$:$\dot{Q}$ maldistribution and a small shunt of desaturated mixed venous blood results in a widened alveolar to arterial P_{O_2} difference signifying some degree of inefficiency in pulmonary gas exchange during exercise. However, high overall $\dot{V}_A$:$\dot{Q}$ raises alveolar P_{O_2} sufficiently to avoid severely low $\dot{V}_A$:$\dot{Q}$ regions and prevent arterial hypoxemia.
- The thin-walled and extensive capillary network and "passive" regulation of the pulmonary circulation during exercise, combined with a high capacity thoracic lymphatic "sump pump" in the lung interstitium, means that up to a fourfold increase in cardiac output and pulmonary blood flow do not result in critical reductions in mean red cell transit time or in accumulation of edematous fluid in the alveoli.

The result of these special structural characteristics and neuroregulation in the healthy lung parenchyma, airways, vasculature, and respiratory muscles is that the respiratory system contributes little to the limitation of O_2 transport to working locomotor muscles or to the symptoms of effort perception accompanying exercise and therefore to the limitation of either $\dot{V}_{O_{2max}}$ or endurance exercise performance.

EXCEPTIONS TO THE RULE—RESPIRATORY SYSTEM LIMITATIONS

There are a growing number of instances being reported in which the healthy respiratory system response to acute exercise appears to be less than "adequate" or inefficient, thereby contributing to exercise

limitation and that repeated bouts of high-intensity exercise experienced in the elite endurance-trained athlete may even be maladaptive.

- In a significant number of highly trained endurance athletes exercise-induced arterial hypoxemia (EIAH) occurs (SaO_2 rest to exercise, ~–5 to –10%) secondary primarily to an excessively widened alveolar to arterial O_2 difference and often in combination with a limited hyperventilatory response (see Fig. 18-7 and Table 18-1).[58,70] Preventing this hypoxemia (via increased FI_{O_2}) raises $\dot{V}_{O_{2max}}$ (up to 15%) or with longer endurance-type performances reduces the rate of development of limb locomotor muscle fatigue and improves performance time.[71,72] Accumulation of edematous fluid and red cells in the alveoli has also been reported at these high work rates – suggesting a disruption in the alveolar–capillary barrier because of excessive pulmonary capillary hydrostatic pressures.[73] There are a number of continuing mysteries surrounding EIAH including, why the excessive A-aDO_2, that is, diffusion, shunt and/or $\dot{V}A$:$\dot{Q}$ nonuniformity? …why does the hypoxemia first appear in submaximal exercise? … and why is there such marked heterogeneity in its occurrence among subjects of equal high fitness levels[15,74]?
- Heavy exercise-induced expiratory flow limitation with some degree of hyperinflation occurs at high ventilations in many young trained athletes and even at not so high ventilations in healthy fit elderly and in female athletes (see examples below under "Healthy Aging").This incurs a limitation to expiratory flow and to ventilation, causes high rates of inspiratory and expiratory muscle force generation (see Fig. 18-4, right) and high levels of expiratory ITP which compromises stroke volume and cardiac output. Increasing the maximal flow–volume loop via breathing low-density gases such as $He:O_2$ prevents this expiratory flow limitation and increases the ventilatory response to heavy exercise.[75]
- When cardiac output exceeds 25 L/min during exercise in endurance athletes mean pulmonary arterial pressures will often exceed 35 to 40 mm Hg because of the limited capability of the pulmonary vasculature (relative to the systemic vasculature) to reduce its vascular resistance.[69,76] Accordingly, a substantial stress is placed on the right ventricle wall which greatly exceeds that on the left ventricle.[77] With prolonged heavy intensity exercise this substantial vascular load results in reduced RV (but preserved LV) function as reported following a marathon or triathlon.[78]
- If the exercise is of very high intensity and sustained, significant fatigue occurs in the diaphragm and expiratory muscles thereby promoting increases in sympathetic vasoconstrictor activity and a reduction in limb vascular conductance and blood flow. Use of positive pressure mechanical ventilation during exercise to prevent respiratory muscle fatigue, also reduces the rate of limb muscle fatigue development and improves endurance performance.[79,80]

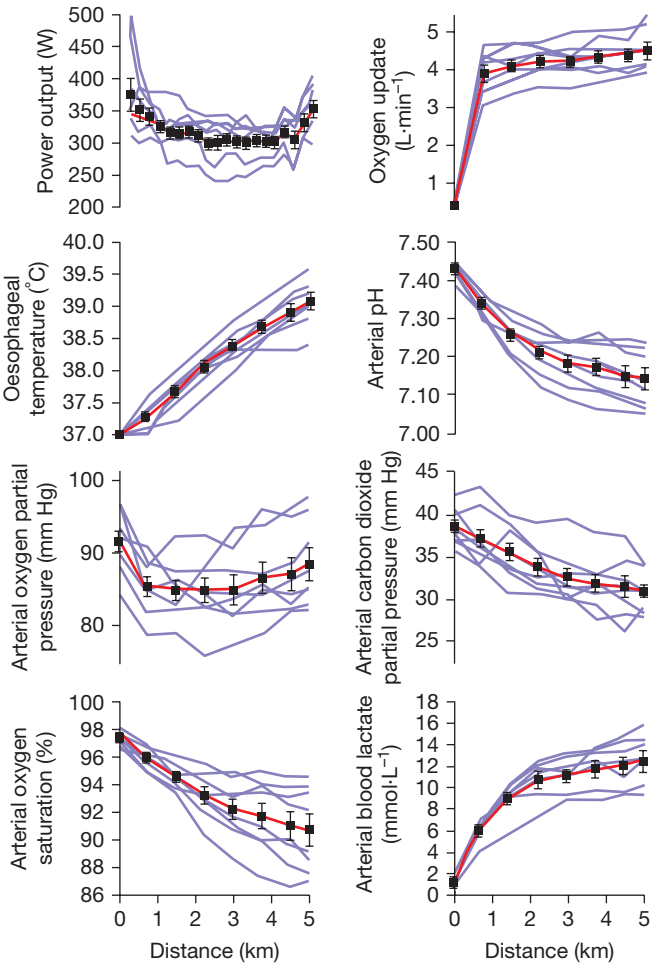

Figure 18-7 Effects of a 5-km time trial (cycle ergometer) in a normoxic environment on the physiological responses of trained cyclists. Thin lines are individual data ($n = 8$), with thick lines showing mean responses. Mean performance time was 483.4 ± 7.5 seconds (range, 437.5–478.4 seconds). Hemoglobin concentration was 14.4 ± 0.5 g L^{-1} and arterial oxygen content was 19.8 ± 0.8 mL O_2 100 mL^{-1} at rest and 16.4 ± 0.7 mL O_2 100 mL^{-1}/20.9 ± 1.0 mL O_2 100 mL^{-1} at 5 km. Note the progressive reduction in arterial hemoglobin O_2 saturation, due to a reduced Pa_{O_2} in the early stage of exercise, and thereafter to a progressive metabolic acidosis and increasing blood temperature. Also note the marked heterogeneity among subjects in their regulation of arterial P_{O_2}, Sa_{O_2}, and P_{CO_2}. (*Modified with permission from Amann M, Eldridge MW, Lovering AT, Stickland MK, Pegelow DF, Dempsey JA. Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. J Physiol. 2006;575(Pt 3):937–952.)*

SPECIAL CASES OF RESPIRATORY SYSTEM LIMITATION TO EXERCISE PERFORMANCE

Healthy aging. Beginning in the second decade of life the healthy nonsmoking lung begins to lose elastic recoil (see Fig. 18-8A). This leads, during exercise, to expiratory flow limitation—with sequelae as described earlier such as ventilatory limitation, maldistribution of inspired ventilation, compromised stroke volume, and a significant prevalence of arterial hypoxemia (see Fig. 18-8B).[81] As mentioned earlier, expiratory flow limitation and its sequelae also occur during heavy/maximum exercise in the young highly trained athlete but with aging this occurs at much lower metabolic rates and ventilations than in the young (see Fig. 18-8B and contrast to Fig. 18-4 in younger athletes). Loss of elastic recoil also influences ventilation distribution in the lung resulting in a high V_D/V_T in the elderly. The V_D/V_T undergoes the normal decline during exercise but at a higher absolute V_D/V_T. This means that the healthy elderly must increase their $\dot{V}_E$ not only in proportion to the rising $\dot{V}_{CO_2}$ but also to accommodate the raised V_D. Remarkably this "extra" hyperpnea does indeed occur and Pa_{CO_2} is regulated at resting levels, but this homeostatic regulation also means greater ventilatory work and higher flow rates thereby increasing the probability of flow limitation—especially in the highly fit older subject during heavy intensity exercise.

Gender differences. Exercise-induced expiratory flow limitation is more prevalent in young healthy females versus males and occurs at lower levels of metabolic and ventilatory demand.[82] The explanation for this gender difference appears – as based on CT scan evidence – to be one of airway structure limitation, that is, the so-called airway dysanapsis wherein the diameter of intralobar airways is narrowed for any given lung volume in the female.[83] This gender difference blunts the ventilatory response to heavy exercise[82] and may also lead to maldistribution of inspired ventilation which may explain at least

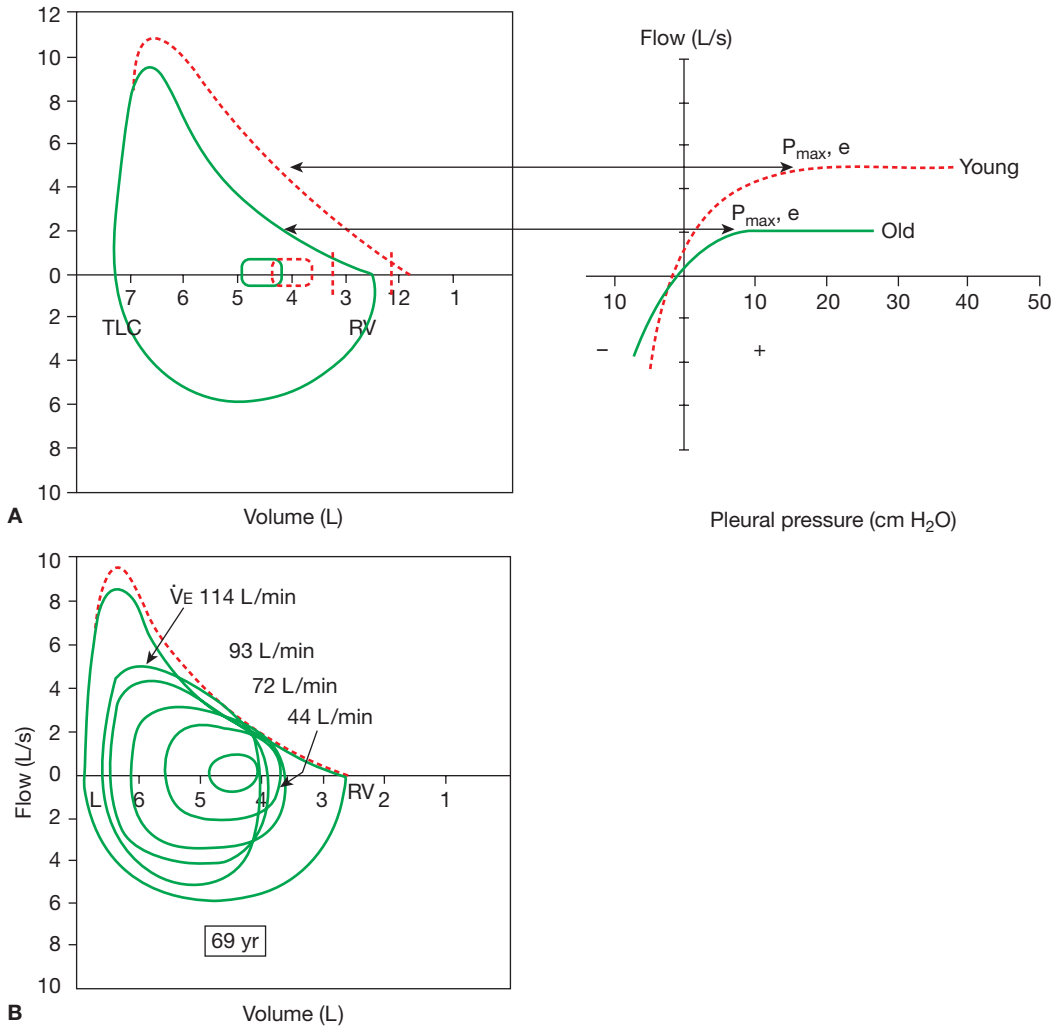

Figure 18-8 **A.** Maximum flow:volume loops and the isovolume pressure:flow relationships in the 30-year-old *(dashed line)* and 70-year-old nonsmoking male *(solid line)*. Note in the older subject the "scooping" in the expiratory limb of the maximum flow:volume loop indicating that airways are narrowing thereby reducing flow rate at any given lung volume during most of a forced expiration. The diagram on the right hand side shows that expiratory flow increases with increasing expiratory effort up to the critical closing pressure (P_{max}, e), at which point, despite additional expiratory effort, airways narrow and close and no increase in flow rate is achieved. Note the much lower P_{max}, e in the older subjects. Also note in the left hand figure that the end-expiratory lung volume is higher in the aged as is the airway closing volume *(solid line)*. These changes in the flow:volume loop and in airway closing volume and in the critical closing airway pressure occur with aging because of reduced lung elastic recoil. **B.** Flow:volume relationships at increasing levels of ventilation during steady-state exercise in the highly fit 69-year-old person. Contrast these with Figure 18-4 in the younger subject. The largest flow:volume envelope shown is that achieved via maximum volitional effort at rest, preexercise *(solid line)* and postexercise *(dashed line)* and the flow:volume loops within this maximal loop are from tidal breaths at rest and during increasing exercise intensities. In older subjects significant expiratory flow limitation begins at exercise ventilations (70 L/min or less) that are much lower than in the younger subject (>100 L/min.) Also note in the older subject that with the onset of the intersection of the tidal with the maximum expiratory flow–volume loop, end-expiratory lung volume increases back to and even in excess of resting levels. *(Reproduced with permission from Johnson BD, Reddan WG, Seow KC, Dempsey JA. Mechanical constraints on exercise hyperpnea in a fit aging population. Am Rev Respir Dis. 1991;143(5 Pt 1):968–977.)*

some of the occurrence of the widened A-aDO_2 and hypoxemia at lower work rates in female- versus male-trained athletes.

Athletic species differences. The thoroughbred horse with a $\dot{V}_{O_2max}$ >160 mL/kg/min or more than twice that of the highest fit humans are the epitome of respiratory system limitations as shown by substantial arterial hypoxemia and CO_2 retention, pulmonary hypertension, and alveolar–capillary barrier disruption developed by these equine athletes during exercise.[84] Thus the lung appears to be truly "under built" in these amazing athletes in terms of its capability for accepting the very high cardiac outputs and ventilations required by their large cardiovascular and locomotor muscle driven metabolic requirements. This respiratory system limitation to exercise contrasts sharply with other highly aerobic animals such as the prong-horned antelope whose $\dot{V}_{O_2max}$ is almost double that of the thoroughbred horse but has substantial upregulation of its lung alveolar–capillary surface area that is capable of accommodating their high metabolic requirements.[85]

Extrathoracic, upper airway flow limitation. A growing number of reports demonstrate that some athletes undergo sudden onset, paradoxical narrowing of the glottic aperture (vocal cord dysfunction or VCD) during exercise of severe intensity demanding high rates of airflow. This event immediately precipitates flow limitation, CO_2 retention, hypoxemia, and dyspnea. Evidence is accumulating to suggest that a highly significant portion of these VCD cases are wrongly diagnosed as asthma and therefore improperly treated—often with high doses of inhaled corticosteroids over many years.[86–88] Exercise-induced VCD seems to be especially prevalent in the highly competitive young adult or adolescent endurance athlete of both sexes. In a

large group of elite endurance athletes about 5% experienced symptoms of inspiratory stridor during heavy exercise and about one-half of these cases showed both VCD and exercise-induced asthma.[89]

The key to detecting exercise-induced VCD is to understand that this problem involves extrathoracic airway narrowing in both inspiration and expiration and that it most commonly occurs only *during* heavy intensity exercise with sudden onset when flow rates are high. Immediately following cessation of exercise, as air flow rate falls precipitously, the extrathoracic airway diameter is usually no longer compromised. Therefore, an appropriate (noninvasive) test to detect VCD is to examine the characteristics of the breath-by-breath, tidal flow:volume envelope *during* exercise—because the usual means of examining forced maximum expiratory maneuvers, pre- and/or postexercise, will most often miss the event.[88] Accompanying sudden increases in end-tidal P_{CO_2} and reductions in Sa_{O_2} are also helpful markers of VCD. For diagnostic purposes, it is especially important that heavy intensity exercise demanding high flow rates be employed.

Perhaps the starting point here is for the clinician to recognize that not all symptoms of exercise-induced shortness of breath in the competitive athlete are attributable to the intrathoracic airway. Furthermore, the failure of routine spirometry or acute bronchodilator or airway provocation tests to detect significant asthma may not just be due solely to the high intra and inter individual variability in these tests. Please consider the upper airway.

Training effects on the respiratory system – an enigma. The examples of the respiratory system limitations in the equine and human athletes cited earlier raise the question of why the respiratory system has not – apparently – adapted to meet the increased maximum metabolic requirements in the highly trained. After all, there is ample evidence of alveolar and capillary growth in response to chronic hypoxia in the maturing human and canine lung.[90,91] Even caloric restriction with refeeding and partial pneumonectomy elicit substantial compensatory growth in the lung's diffusion surface of rodents.[92] In contrast, there is substantial evidence that chronic physical training does not enhance structure or function of the lungs airways, diffusion surface, or pulmonary vasculature.[93–95] Even the normal age-dependent loss of lung elastic recoil and diffusion capacity and the occurrence of exercise-induced expiratory flow limitation were unaltered by chronic habitual physical training, as demonstrated via longitudinal study of long-distance runners in their sixth and seventh decades of life.[96] To the contrary, evidence is now accumulating to show that reactive, asthmatic airways are highly prevalent in elite endurance-trained athletes. Further, longitudinal training studies – including the use of repeated airway biopsies in elite cross-country skiers – revealed that much of this hypersensitivity may result from hyperpnea-induced epithelial airway injury and subsequent airway repair and remodeling (see Fig. 18-9). Airway dehydration and shear stress along with increased transmural pressure gradients occurring repeatedly with sustained heavy exercise may be the cause of epithelial injury.[97–99] These negative effects on the airway of high-intensity physical training stand in contrast to evidence showing an alleviation of airway hyperresponsiveness in mildly asthmatic children achieved via moderate intensity level training.[100] One potential mechanism accounting for these training-induced reductions in airway responsiveness may be a reduced tone of airway smooth muscle secondary to hyperpnea-induced repeated stretching of the airway. This positive training effect on the airways has also been observed in nonasthmatic sedentary children.[101]

In contrast to the lung, the inspiratory muscles of the chest wall do undergo substantial changes in strength and aerobic capacity with intense training as induced by either whole-body training or specific respiratory muscle training.[102] This training effect on the respiratory muscles might improve exercise performance in health and disease.[103,104] One such mechanism for this improvement

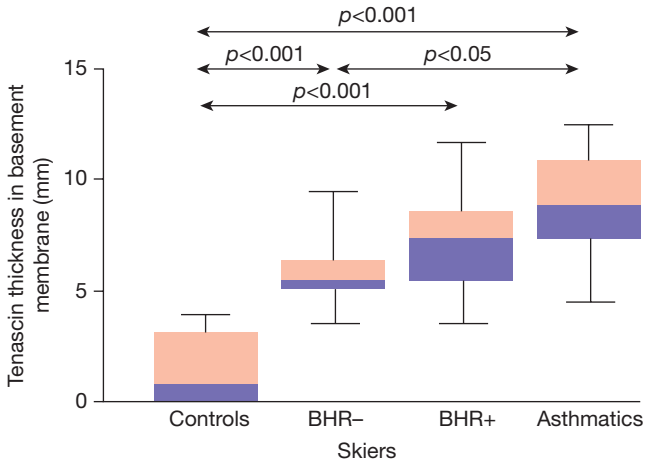

Figure 18-9 Thickness of tenascin immunoreactive band in subepithelial basement membrane zone in controls, in cross-country skiers with (+) and without (–) bronchial hyperresponsiveness (BHR), and in asthmatic subjects. Horizontal bar = median value. The basement membrane thickness is increased in all skiers relative to control subjects, indicating airway remodeling from chronic exercise training. In addition, skiers with asthma-like airway hyperresponsiveness tended to have a greater degree of remodeling. *(Reproduced with permission from Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjermer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. Am J Respir Crit Care Med. 2000;161:2086–2091.)*

may involve a delay in diaphragm fatigue during prolonged heavy exercise, which would be expected to reduce metaboreflex effects on sympathetic, vasoconstrictor outflow and prevent reductions in blood flow and oxygen transport to limb locomotor muscles. This hypothesis has not yet been tested during whole-body exercise.

Hypoxic environments. Even mild elevations in altitude, that is, to only 1000 m or so have significant detrimental effects on $\dot{V}_{O_{2max}}$ and endurance performance. This is especially true in the highly trained athlete who may experience or be very close to significant arterial O_2 desaturation even at sea level and will undergo diffusion limitation and severe O_2 desaturation during exercise at even mild elevations in altitude (see Fig. 18-10).[58] Three major factors come into play as limiting factors to exercise performance at altitude in both acute and long-term hypoxic exposures. First, exercise-induced arterial O_2 desaturation and reduced O_2 transport will exacerbate fatigue of limb locomotor muscles, which in turn feeds back via limb afferents to inhibit cortical motor output, that is, "peripheral" leading to "central" fatigue.[105] Second, the marked hyperventilatory response to exercise in hypoxia is critically important to minimizing arterial O_2 desaturation – but at the same time comes at the cost of increasing respiratory muscle work. This increased respiratory muscle work hastens the onset of diaphragm fatigue, activation of the respiratory muscle metaboreflex triggering sympathetically mediated vasoconstriction of the locomotor muscle vasculature. Thus, a greater share of the cardiac output will be devoted to respiratory locomotor muscle blood flow and limb fatigue is exacerbated.[106] Third, CNS hypoxia, per se, depresses brain neurotransmitter turnover and inhibits motor output to locomotor muscles, that is, the so-called "central fatigue."[107]

Thus, in hypoxic environments both exercise-induced arterial O_2 desaturation and excessive blood flow requirements of the respiratory muscles would contribute significantly to exercise performance limitations by compromising O_2 transport to locomotor muscle ("peripheral" fatigue) and to the brain ("central" fatigue). CNS hypoxia, per se, appears to increase its relative contributions to exercise limitation as the severity of hypoxemia intensifies.

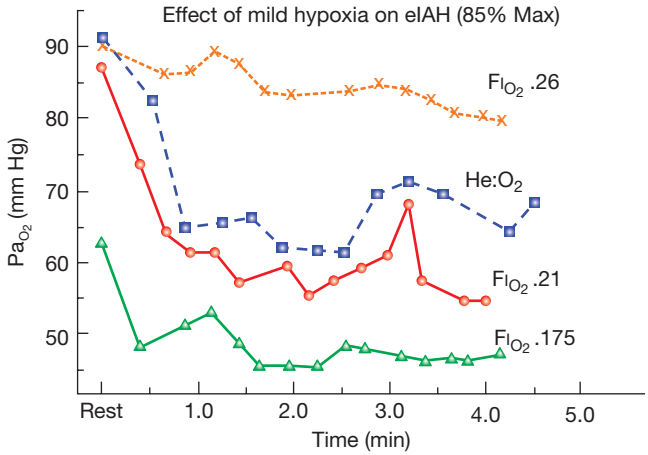

Figure 18-10 Effects of varying $F_{I_{O_2}}$ and of normoxic helium breathing on Pa_{O_2} during constant treadmill running at 15 mph (0% grade) i.e., 4 min. mile pace, in one fit subject ($\dot{V}_{O_2}$ = 4.54 L/min, or 97% $\dot{V}_{O_{2\,max}}$) ×, 0.26 O_2:N_2; o, 0.209 O_2:N_2; Δ, 0.175 O_2:N_2; □, 0.21 O_2:He; (b) the increase in Pa_{O_2} with He:O_2 breathing (vs. air) reflects the higher ventilation because the low air density gas decreased airway resistance and expanded the maximum flow:volume envelope, thereby reducing expiratory flow limitation during exercise; and (c) the prevention of arterial hypoxemia during exercise with mild inspired hyperoxia (0.26 $F_{I_{O_2}}$), indicating that the hypoxemia was not secondary to an extrapulmonary shunt. Note the marked arterial hypoxemia during exercise which accompanied the exposure to mild acute hypoxia (0.175 $F_{I_{O_2}}$). *(Modified with permission from Dempsey JA, Hanson PG, Henderson KS. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. J Physiol. 1984;355:161–175.)*

SUMMARY

With few exceptions it is safe to generalize that the healthy respiratory system – especially in youth and at sea level – is truly "overbuilt" to efficiently meet the considerable gas transport demands imposed by exercise. The key responses of the respiratory system insuring this homeostatic response include prevention of arterial O_2 desaturation and minimizing the work and therefore metabolic and circulatory costs of breathing. In turn these appropriate respiratory responses are insured by both the very special anatomical structure of the airways, lung parenchyma, pulmonary vasculature, and respiratory musculature as well as the precision with which ventilation is matched to metabolic requirements by the multifaceted autonomic control system. Among highly trained endurance athletes with near-normal respiratory system capacities but supernormal cardiovascular and locomotor capacities, the high demands for systemic O_2 transport do – in rare instances – exceed the lung's gas-exchange capabilities. More often in the highly trained, the high ventilatory requirements demand excessive respiratory muscle work and blood flow. So in these instances, the respiratory system will contribute significantly to exercise limitation. However, even in these cases cardiovascular system limitations remain the major "weak link" in O_2 delivery. Finally, there are instances where inadequacies within the healthy respiratory system impose more significant limitations to locomotor muscle O_2 transport and to exercise performance, including normal aging and gender effects on lung elastic recoil and/or airway resistance and upper airway patency during heavy intensity exercise. Again, the highly trained are more susceptible to these severe respiratory limitations because of their high demand for O_2 transport. Finally, the hypoxic environment through its effects on pulmonary diffusion limitation and ventilatory requirements greatly enhances the contribution of the respiratory system to O_2 transport and exercise performance limitations.

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CHAPTER 19

Aging of the Respiratory System

Edward J. Campbell

The fastest growing segment of the US population consists of individuals of age 65 and older. In the 2010 census, this segment comprised 16% of the population. Since the 1950s, the median age of the US population has increased by 20 years.

The largest decrements in age-adjusted death rates have been occurring in older patients. With the increasing longevity of human population, it is necessary to understand the effects of aging on the respiratory system in healthy people. Perhaps more importantly, because the age-related decrements in respiratory system function can be unmasked by disease, it is critically important to point out that the aged: (1) have an enhanced predisposition to lung disease; (2) have a decreasing reserve of respiratory system function that decreases their ability to cope with the stresses of illness, injury, and surgery; and (3) may have differing responses to therapy when compared with their younger counterparts.

Even in individuals who enjoy apparently good health, there are measurable decrements in function of the respiratory system with age. These changes occur progressively as a healthy individual grows older and are most marked beyond 60 years of age. Cross-sectional studies show clear differences between elderly and young persons with regard to the structure and function of the components of the respiratory system (Table 19-1). As we will see, however, caution must be exercised in ascribing observed changes to age alone. It is also necessary to be aware that longitudinal studies of "healthy" individuals followed to old age are essentially not available. Where appropriate, methodologic problems in the available cross-sectional studies are described.

Although age-associated changes can be measured easily by objective testing, it is important to note that the routine activities of healthy elderly persons are not limited by the decreasing respiratory system function. However, whereas youthful persons have a marked excess of functional capacity over the amount required to meet metabolic needs at rest or with stress (physiologic reserve), the respiratory system draws on this reserve as its function declines with age. Thus, the physiologic reserve, especially for alveolar gas exchange, is reduced with aging. This leaves elderly individuals vulnerable to stresses, diseases, and injuries that are weathered much more easily in the young.

ARE CHANGES IN THE RESPIRATORY SYSTEM CAUSED BY AGING OR RELATED TO AGE IN OTHER WAYS?

For decades, the phenomena explained purely by aging have been required to satisfy specific principles. Roughly according to Hayflick,[1] the changes must be (1) intrinsic (as opposed to environmentally mediated); (2) universal; (3) progressive; and (4) usually detrimental to the organism. Developing an understanding of changes to the lung over time is complicated by the fact that the lung is an open system that is exposed to environment. As such, it is assaulted by respiratory infections and by a constant barrage of particulates and other air pollutants. In addition, the lungs are commonly exposed to tobacco smoke, to occupational dusts and fumes, and to effects of aspiration. At times, environmental influences are inextricably involved in the changes that are observed in the respiratory system over time. However, it is important to draw a distinction between alterations

TABLE 19-1 Respiratory System: Functional Divisions and Changes with Aging

Functional Division	Components	Function	Change(s) with Aging
Conducting airways	All airways not involved in gas exchange (mouth to terminal bronchioles)	Gas movement between environment and alveolar space	Slight changes in size; calcification; glandular hypertrophy
Lung parenchyma	Gas-exchanging airways and vessels; connective tissue framework	Gas exchange between alveolar space and capillary blood	Enlarged terminal airspaces; ventilation/perfusion mismatching
Bellows apparatus	Chest wall and muscles of respiration	Provide mechanical forces for ventilation	Increased rigidity of chest wall; decreased respiratory muscle strength
Ventilatory control	Respiratory control center (pons and medulla); carotid and aortic bodies	Maintaining homeostasis by altering ventilation to match metabolic needs	Markedly decreased responses to hypercapnia and hypoxemia
Cardiovascular system	Heart and systemic vasculature	Blood transport and tissue exchange of respiratory gases	Decreased maximal heart rate and cardiac output; decreased responsiveness to hypoxemia

purely related to aging and those associated with older individuals. Purely age-related changes are biologic phenomena and irreversible. Other alterations associated with increasing age have the potential to be preventable, treatable, and/or reversible.

CHANGES IN THE UPPER AIRWAY

There is a clearly increased risk of aspiration in the elderly that is thought to be a consequence of a number of age-related factors, including comorbid illnesses and debility, medications, and the aging process itself. With regard to purely age-related changes, attention has been focused upon the cough and swallowing reflexes, both of which are protective against aspiration. In the past, these reflexes have been thought to be controlled primarily by the brainstem, but there is now evidence that cortical and subcortical structures play critical roles in their control.[2] By their nature, reflexive cough and swallowing activate both sensory and motor areas in the cortex. The sensory component, including the sensory cortex in reflexive circuits, seems to be more vulnerable to aging than the motor component, including the motor cortex. Therefore, strategies to restore effective cough and swallowing reflexes should be focused upon compensations of sensory components.

Variable amounts of aspiration of both oropharyngeal contents (food particles, saliva, and oropharyngeal organisms), and also gastric contents (food particles and gastric secretions including gastric acid), are increasingly common with aging. Aspiration is particularly common in the very old. Because of the sensory alterations discussed earlier, aspiration in elderly individuals can be associated with few, or no, symptoms.[3]

A potentially important contributor to aspiration is gastroesophageal reflux. In accordance with the earlier discussion of sensory impairments, reflux esophagitis severity increases with age while heartburn severity decreases with age.[4] Consequences of gastroesophageal reflux may be exacerbated by esophageal motor abnormalities associated with aging. Recurrent aspiration of gastric contents in the elderly can lead to airway inflammation, bronchiectasis, and pneumonia.

STRUCTURAL CHANGES IN THE LUNG

Studies of the aging lung have shown changes in shape, with increase in anteroposterior diameter that lead to a "rounding" shape of the lung. These changes are presumably secondary to changes in the shape of the surrounding thoracic cage that are very common after the age of 75. In a study of 100 chest radiographs from individuals ranging in age from 75 to 93 years, 25% had severe kyphosis (>50 degrees) and 43% had moderate kyphosis (35–50 degrees) from vertebral fractures.[5]

CONDUCTING AIRWAYS

The conducting airways consist of the air passages from mouth to the level of respiratory bronchioles. Their volume comprises the anatomic dead space, and their geometry is a primary determinant of airway resistance. The larger cartilaginous airways show a modest increase in size with age, resulting in slight but probably functionally insignificant increase in anatomic dead space. Although calcification of cartilage in the walls of the central airways and hypertrophy of bronchial mucus glands is seen in advanced age, these changes in the extraparenchymal conducting airways appear to have little or no physiologic significance.

Ciliary motility is significantly decreased in subjects over the age of 60, which likely further increases the risk of lower respiratory infection and inflammation.[6]

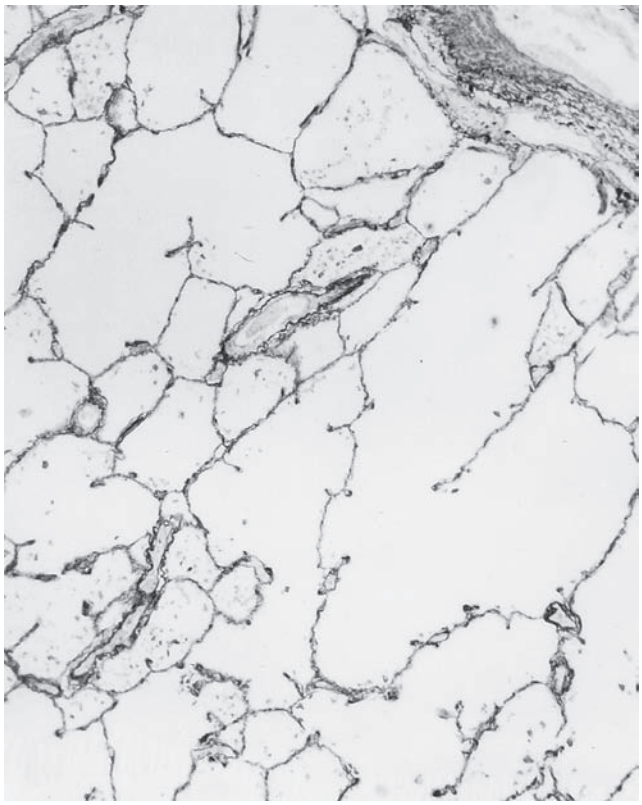
LUNG PARENCHYMA

After the age of 30 or 40, the respiratory bronchioles and alveolar ducts undergo progressive enlargement (Fig. 19-1). This change has been termed "ductectasia" because of the prominent finding of enlargement of alveolar ducts.[7] The proportion of the lung made up of alveolar ducts increases, and alveolar septa become shortened, leading to a "flattened" appearance of the alveoli. With the change in geometry, the distance between alveolar walls (known to morphologists as the mean linear intercept, or MLI) increases, while the surface-to-volume ratio of the lung decreases.[8] The age-related enlargement of the terminal respiratory units also produces a decrease in the percentage of parenchymal air contained within the alveoli.[9] The net result of these structural changes is that the alveolar surface area decreases by approximately 15% by age 70.

Pulmonary emphysema is also characterized by an increase in the size of terminal airspaces, an increase in MLI, and a decrease in surface area; however, destruction of alveolar septa with fusion of terminal airspaces is a defining characteristic of emphysema. There have been some reports of emphysematous lesions in aged lungs, but it is not certain that smokers were excluded from these studies. Since the fate of individual alveolar septa during the aging process has been somewhat controversial, some have referred to the histologic changes in aged lungs as "senile emphysema." A National Heart, Lung, and Blood Institute Workshop on the definition of emphysema[10] weighed the available evidence, and decided not to include age-related changes in the lung parenchyma under the definition of *emphysema*. To simplify terms and avoid confusion, they recommended use of the term *aging lung* to apply to the uniform airspace enlargement that develops with increasing age. Despite the continued use of "senile emphysema," this term should be avoided.

Computed tomography of the chest in individuals over 75 years of age has shown a surprising prevalence (60%) of a subpleural

A



B

Figure 19-1 Histologic changes in the aging lung. **A.** Normal lung of a 36-year-old woman. **B.** Lung of a 93-year-old woman. In (**B**), the alveolar ducts are dilated, and shortening of inter-alveolar septa is observed. *(Used with permission of the Mayo Foundation; photomicrographs used with permission of Charles Kuhn III, MD.)*

basilar reticular pattern that was absent from images from a control population that was less than 55 years old. Lung cysts were seen in 25% of the elderly subjects, but none of the controls.[11] These findings are usually associated with interstitial lung disease, but in the elderly they seem not to reflect a clinically relevant disease process. Caution must be exercised to avoid overreacting to similar image findings in older patients.

CHANGES IN MECHANICAL PROPERTIES OF THE LUNGS

Both the Lungs and chest wall are elastic. The resting volume of excised lungs is smaller than that contained within an intact thoracic cage, because the lungs are held at an increased volume by the outward recoil forces of the chest wall. Thus, in the intact thoracic cage, the lungs exert an inward recoil force. The retractile force of the lungs, or the "elastic recoil," can be measured during life by estimating the pleural pressure with an esophageal balloon at progressively decreasing lung volumes from total lung capacity to functional residual capacity (FRC), when the airways are open and there is no air flow. The negative pleural pressure is generated by the lungs' elastic recoil forces.

The pressure measurements may be displayed on a pressure–volume diagram (Fig. 19-2). Figure 19-2 compares, at the same volume, the elastic recoil pressures of a young man, a normal elderly adult, and a patient with emphysema. The normal elderly individual and the patient with emphysema, both have a greater decrease in elastic recoil pressure than does a young person.[12] This is reflected in the leftward shift of their pressure–volume curves.[13–16] This loss of elastic recoil is the physiologic hallmark of emphysema. However, emphysema is characterized by a much greater loss of elastic recoil than is caused by aging alone.

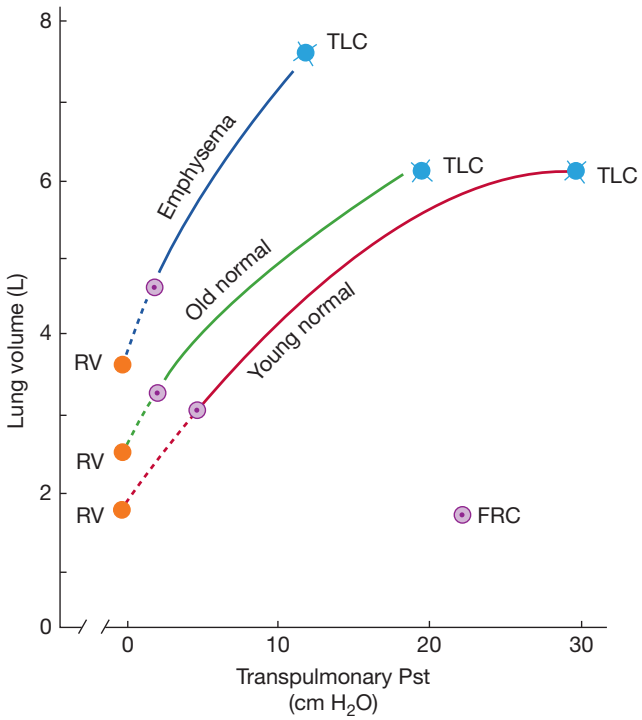


Figure 19-2 Static pressure–volume curves of the lungs. Static recoil pressure, expressed as transpulmonary pressure measured at various lung volumes, is plotted against lung volume on the ordinate. Note that at any lung volume, the recoil pressure is less in the aged individual than in the young, normal control, resulting in a pressure–volume curve that is shifted upward and to the left. For comparison, a curve for a patient with emphysema is shown. In emphysema, recoil pressures are reduced much more, and lung compliance (the slope of the pressure–volume relationship) is clearly abnormal. *(Reproduced with permission from Pride NB. Pulmonary distensibility in age and disease. Bull Physiopathol Respir. 1974;10(1):103–108.)*

There has been some disagreement regarding the effects of aging on lung compliance (Δ volume/Δ pressure; that is , the slope of the pressure–volume relationship Fig. 19-2). The question is whether there is a parallel leftward shift of the pressure–volume curve with aging (no change in compliance), or, instead, a steeper slope in addition to a shift (indicating an increase in compliance), as seen in emphysema. In aged individuals, the static pressure–volume curve is slightly steeper and is more concave in relation to the pressure axis. However, there is a general agreement that changes in lung compliance with aging are not physiologically significant.

Two forces in the lung parenchyma are responsible for producing the elastic recoil of the lungs. The greatest part of the elastic recoil forces is provided by the surface tension at the curved air–fluid interface of the small airways and alveoli. The second retractive force is that produced when the fibrous skeleton of the lung (primarily the elastic fibers) is stretched.

CHANGES IN SURFACE FORCES

Most of the loss in lung recoil with age is likely to be related to the decrease in lung surface area with age The loss of surface area that accompanies aging can be expected to reduce the area of gas–liquid interface, resulting in a decrease in the surface tension forces and, ultimately, a decrease in the total elastic recoil of the lung. Whether it is due to loss of air–liquid interface or to changes in lung structural macromolecules the reduced elastic recoil has important consequences for the function of the intraparenchymal airways and, ultimately, on alveolar gas exchange and forced expiratory flow (see "Pulmonary Function Tests").

CHANGES IN STRUCTURAL MACROMOLECULES

Weibel has produced elegant studies of the "integral fiber continuum" that extends from the hila to the pleura. This consists of axial fibers extending to the alveolar septae, and septal fibers extending to the pleura.[17] Although most proteins in the lung turn over relatively rapidly, the structural proteins, elastin and collagen, in the lung fibrous network provide a very stable, long-lived skeletal structure for the lung.

Elastic fibers consist in large part of an extremely hydrophobic, highly cross-linked, and very elastic macromolecule (elastin). These fibers are thought to contribute substantially to lung elasticity. Analysis of whole lungs has revealed that the elastin content actually increases (rather than decreases) with age. More recent evidence indicates that the increase in lung elastin with age is accounted for by an increase in pleural elastin; parenchymal elastin does not change.

Careful studies of the elastic fibers in the lung parenchyma have shown that they are remarkably stable following postnatal lung growth. Certain biochemical changes in very long-lived proteins (change of amino acids into their mirror-image structures, or racemization) provide a type of "biological clock" that permits an estimate of the time that has elapsed since the proteins were synthesized. Because of the constraints of the protein synthetic mechanisms, only L-amino acids are incorporated into newly synthesized proteins. With the passage of years at body temperature, however, there is a readily measurable accumulation of D-aspartic acid. When all of the lung proteins are examined together, minimal D-aspartic acid is found. In purified lung elastin, however, there is an age-related accumulation of D-aspartic acid,[18] indicating that lung elastin is turning over very slowly if at all (Fig. 19-3). It has also been possible to estimate lung elastin turnover by measurement of the incorporation into elastic fibers of carbon 14 (^{14}C) from atmospheric nuclear weapons testing. For example, individuals who completed their postnatal lung growth prior to the nuclear age show no excess ^{14}C in their lung elastin, indicating absence of new elastin synthesis. In contrast, an appropriate excess of ^{14}C is found in the lung elastin of individuals whose lungs were growing in the post–weapons testing era. Modeling of the radiocarbon data indicates that the "mean carbon residence time" in elastin is 74 years.[18]

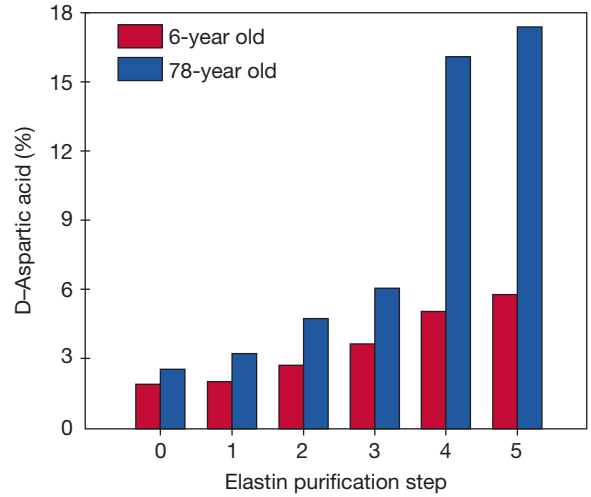


Figure 19-3 Longevity of human lung parenchymal elastin, as evidenced by in vivo racemization of aspartic acid. Each pair of bars shows results from two individuals with greatly differing ages at time of death. Step 0 of elastin purification represents whole lung parenchyma, while step 5 is purified elastin. D-aspartic acid detected in the 6-year-old specimen can be attributed to racemization that occurs during the analytical procedures, whereas, the difference in prevalence of D-aspartic acid between the young and old individual has resulted from racemization in vivo. Note that results from whole-lung hydrolysates (step 0) are similar for both specimens, reflecting their composition of proteins, having predominantly rapid turnover. However, purified elastin from the oldest specimen has racemized extensively in vivo, indicating that it was synthesized many decades before death. These data for elastin agree well with results for other very long–lived proteins. *(Reproduced with permission from Shapiro SD, Endicott SK, Province MA, et al. Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons–related radiocarbon. J Clin Invest. 1991;87(5):1828–1834.)*

Taken together, the amino acid racemization and radiocarbon data indicate that lung parenchymal elastin is stable over the human life span, and it appears that the elastin content of the lung parenchyma not only does not change with age, but the individual fibers persist for at least many decades.

Other studies of lung elastic fibers have shown changes in the location and orientation of individual fibers with age as well as changes in the cross-linking of elastin. Thus, some authors have suggested that remodeling of the lung architecture may occur without replacement of elastic fibers. In any case, at the present time, the age-related changes in connective tissue do not provide a sufficient explanation for the decrease in elastic recoil forces observed in the elderly.

Studies of collagen in alveolar walls of humans, as measured by hydroxyproline, have failed to show a consistent change in its quantity during aging.[19] Although human studies have not been done, studies in rodents and birds suggest that lung collagen fibers, like elastic fibers, are very long-lived.[20] Finally, although some qualitative changes in collagen during aging have been described (decreases in solubility and increases in intermolecular cross-links), these appear to have no relationship to changes in lung elastic recoil.

Although convincing evidence for very slow compensatory human lung growth (over many years) has been provided following pneumonectomy,[21] under more ordinary circumstances it appears that the lung adapts to changing dimensions of thorax by realignment of its fibrous skeleton rather than by molecular remodeling.

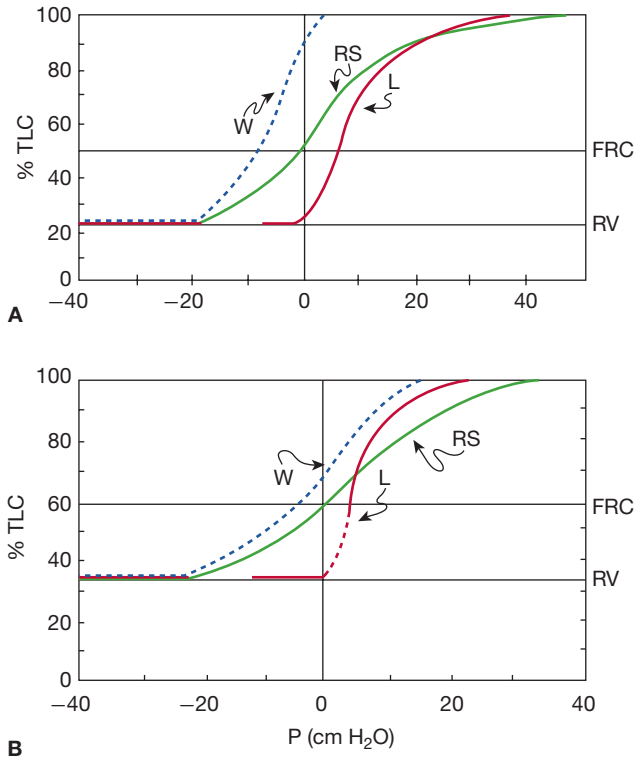


Figure 19-4 Static compliance relationships of the components of the respiratory system. (L, lungs; W, chest wall; RS, total respiratory system.) **A.** A 20-year-old man. **B.** A 60-year-old man. Note that the static compliance of the chest wall is substantially decreased (reduced slope) in the older individual, while functional residual capacity (the resting volume of the respiratory system, or the point at which the pressure gradient across the respiratory system is zero) increases. As in Figure 18-2, it is also apparent that the static recoil pressure of the lungs is reduced in the older subject. *(Data from Mittman C, Edelman NH, Norris AH, et al. Relationship between chest wall and pulmonary compliance and age. J Appl Physiol. 1965;20:1211–1216; and Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. J Appl Physiol. 1968;25:664–671.)*

■ CHANGES IN CHEST WALL

There is good evidence that the chest wall becomes more rigid with advancing age.[22] As may be seen in Figure 19-4, the static pressure–volume curve of the chest wall is shifted to the right and is less steep with increasing age. The articulations of the ribs with the sternum and the spinal column may become calcified, and the compliance of the rib articulations decreases. The changes in rib articulations may be compounded by the development of kyphosis due to osteoporosis. The decreasing compliance of the chest wall demands greater work from the respiratory muscles. For example, in a 70-year-old person, approximately 70% of the total elastic work of breathing is expended on the chest wall, whereas this value is 40% in a 20-year-old person.

Figure 19-4 also demonstrates that the compliance of the total respiratory system decreases with age because the decrease in lung elastic recoil is outweighed by the changes in the mechanical properties of the chest wall.

CHANGES IN MUSCLES OF RESPIRATION

Age-related changes in nonrespiratory skeletal muscle include decreased work capacity due to alterations in the efficiency of muscle energy, metabolism, atrophy of motor units, and electromyographic abnormalities. Based upon lessons learned with other skeletal muscles, it appeared likely that age-related abnormalities in respiratory muscles also would be found.

An early study by Black and Hyatt appeared to confirm age-related decrements in respiratory muscle function by measuring maximal inspiratory pressure ($P_{I_{max}}$) and maximal expiratory pressure ($P_{E_{max}}$) in 120 normal individuals (both smokers and nonsmokers) between the ages of 20 and 70.[23] Maximal respiratory pressures in females were 65% to 70% of those in males. No significant age-related changes were observed in individuals under the age of 55. Trends toward reduced maximal respiratory pressures with age were seen in both genders and with both $P_{I_{max}}$ and $P_{E_{max}}$. With the number of males studied, the change with age in $P_{I_{max}}$ was not statistically significant for male gender.

More recently, McElvaney and coworkers came to a different conclusion in a similar study of 104 healthy individuals over the age of 55.[24] They found a large variation in maximal respiratory pressures from individual to individual (as by Black and Hyatt), but no significant correlation with age. In contrast, in a third population of 160 healthy individuals who ranged in age from 16 to 75 years, Chen and Kuo found significant gender differences in maximal respiratory pressures as well as trends toward decrements with age for $P_{I_{max}}$ and $P_{E_{max}}$ in both genders. The age-related change in $P_{E_{max}}$ in males was not statistically significant with the sample size studied. When the 40 individuals of both genders in the youngest age group (16–30 years) were compared with the 40 individuals in the oldest group (61–75 years), the decrement in $P_{I_{max}}$ was 32% to 36%, while the decrement in $P_{E_{max}}$ was 13% to 23%.[25] Representative findings for maximal respiratory pressures in women are illustrated in Figure 19-5.

Chen and Kuo also measured inspiratory muscle endurance against a resistive load, and found significant decrements with age. Physically active men had greater inspiratory muscle endurance than sedentary men.

In summary, it appears that when populations of healthy individuals of widely differing ages are studied, moderate age-related decrements in respiratory muscle strength and endurance can be

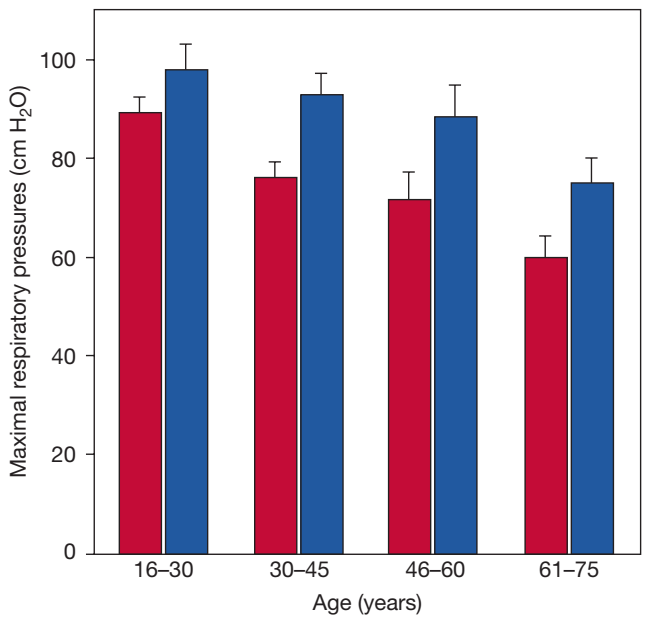


Figure 19-5 Representative variations in maximal respiratory pressures with age among women. Inspiratory and expiratory measurements were made at residual volume and total lung capacity, respectively. Maximal inspiratory pressure *(open bars)* and maximal expiratory pressure *(hatched bars)*. Error bars are standard errors of the mean. Although quantitatively moderate, variations with age were statistically significant for both measurements. *(Data from Chen H-S, Kuo C-S. Relationship between respiratory muscle function and age, sex, and other factors. J Appl Physiol. 1989;66(2):943–948.)*

found. These studies usually define *healthy* only by the absence of disease and do not control for physical activity. They are complicated by marked interindividual variability, and longitudinal studies have not been reported. Continuous respiratory muscle activity may have a training effect that leads to better preservation of respiratory muscle function when compared with other skeletal muscles. Finally, physical activity may have an additional training effect that enhances inspiratory muscle endurance in all age groups.

CONTROL OF BREATHING

In young individuals, minute ventilation is matched with metabolic demands. As a result, arterial blood gas values remain stable throughout a wide range of activities from rest to strenuous exertion, while oxygen consumption and carbon dioxide production are varying widely. Similarly, when the efficiency of gas exchange is diminished by lung disease or congestive heart failure, appropriate increases in minute ventilation minimize the resulting hypercapnia and/or hypoxemia in healthy young individuals. The ventilatory control system is described in detail in Chapter 11.

Ventilatory control mechanisms are typically tested by stressing the respiratory system, by inducing either hypoxemia or hypercapnia while monitoring ventilatory parameters (and often cardiac parameters as well). Such tests have shown striking differences between young and elderly individuals in both ventilatory and cardiac responses.

DIMINISHED VENTILATORY RESPONSE TO HYPERCAPNIA

Kronenberg and Drage compared the ventilatory responses to hypercapnia in eight young (mean age, 25.6 years) and eight elderly (mean age, 69.6 years) individuals.[26] During the tests, the subjects were asked to rebreathe 5% CO_2, while their $P_{A_{O_2}}$ was held above 200 mm Hg by supplemental oxygen to eliminate hypoxic ventilatory drive. Measurements were made while $P_{A_{C_2}}$ was allowed to rise to 65 mm Hg. Although there was considerable individual variation and some overlap between the groups, the elderly individuals had a significantly diminished ventilatory response to hypercapnia, measured as the slope of the relationship between ventilation and $P_{A_{C_2}}$.

DIMINISHED VENTILATORY RESPONSE TO HYPOXIA

When Kronenberg and Drage measured the ventilatory response to hypoxia at constant CO_2, they found even more striking differences between the young and elderly subjects (Fig. 19-6). For example, the ventilatory response to a $P_{A_{O_2}}$ of 40 mm Hg was uniformly smaller in the older subjects, and there was no overlapping between the groups.[26] The mean minute ventilation at a $P_{A_{O_2}}$ of 40 mm Hg was 40.1 and 10.2 L/min in the young and old groups, respectively.

DIMINISHED OCCLUSION PRESSURE RESPONSES

Peterson et al. confirmed the previously discussed observations and have shown that the differences in responses of elderly subjects to both hypercapnia and hypoxia are due to a lesser increase in tidal volume while the ventilatory rate increases normally. Since this observation could be caused by differences in respiratory muscle strength or increases in chest wall stiffness, the authors also measured airway occlusion pressures, which are valuable indices of respiratory drive that are not affected by respiratory muscle strength or respiratory mechanics.[27] The measurement (P_{100}) is the negative pressure at the mouth, measured 100 ms after the start of inspiration against an occluded airway. The occlusion pressure responses to both hypoxia and hypercapnia (Fig. 19-7) were significantly reduced in the 10 elderly subjects studied by Peterson (mean age, 73.3 years) when compared to nine young control subjects (mean age, 24.4 years). Although the elderly individuals had reduced respiratory muscle strength (mean, 24% lower maximal static inspiratory pressure), the differences in occlusion pressure persisted when normalized for these differences.

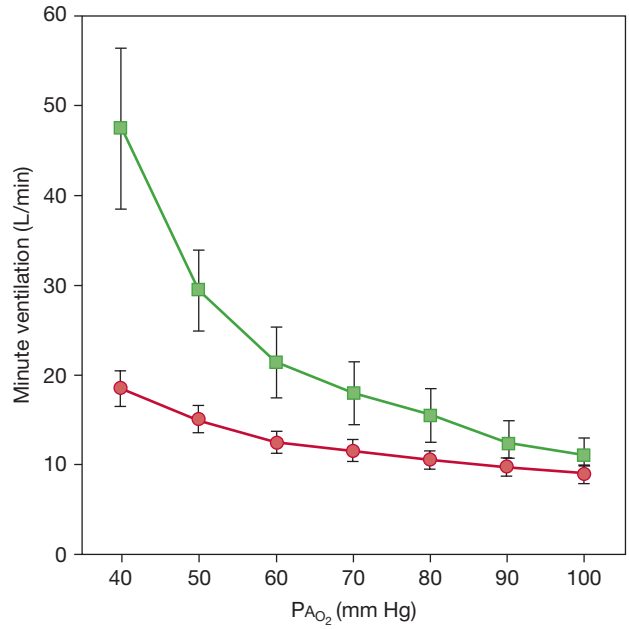


Figure 19-6 Variations with age in ventilatory responses to hypoxia. Eight normal men aged 64 to 73 *(circles)* and eight controls aged 22 to 30 *(squares)* were subjected to isocapnic progressive hypoxia by a rebreathing method. Data values are means, with standard errors of the mean shown by the error bars. Note that the ventilatory responses differ strikingly between the elderly individuals and the controls. *(Reproduced with permission from Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest. 1973;52(8):1812–1819.)*

The previously mentioned seminal studies of ventilatory control have been discussed in some detail out of respect for their groundbreaking conceptual importance. Subsequent studies have created some confusion that appears likely to be due to methodologic differences, ages of subjects, and small sample sizes. However, in 14 of 16

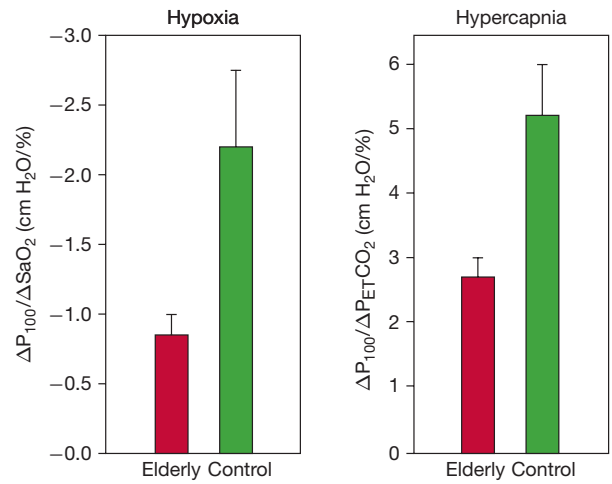


Figure 19-7 Variations with age in occlusion pressure responses to hypoxia and hypercapnia. Data shown are slopes of relationships between occlusion pressure responses and either Sa_{O_2} or end-tidal P_{CO_2}; error bars are standard errors of the mean. Elderly individuals had significantly diminished occlusion pressures in response to both hypoxia and hypercapnia. Both differences were significant, with $p < 0.01$. *(Reproduced with permission from Peterson DD, Pack AI, Silage DA, et al. Effects of aging on the ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am Rev Respir Dis. 1981;124(4):387–391.)*

studies reviewed by Lalley, ventilatory responses in the elderly were found to be abnormal.[28]

In summary, the reduced responsiveness in tidal volume to either hypoxemia or hypercapnia with age is apparently due to a reduced responsiveness of ventilatory drive or neural output from the respiratory center. It has not been determined whether the diminished ventilatory drive results from altered chemoreceptor function or from altered function of the respiratory center. Kronenberg and Drage favored altered receptor function based on their observation that elderly subjects responded to an alveolar oxygen tension of 40 torr with only an 11% increase in heart rate, whereas the young subjects responded with a 34% increase.

■ RESPIRATORY LOAD COMPENSATION AND DYSPNEA

Reflex compensation for a change in respiratory mechanical load (as in lung disease, changes in posture, and mouth versus nose breathing) normally serves to maintain ventilation constant during the change. Akiyama et al. measured responses to inspiratory flow-resistive loading in young and elderly individuals and found significant differences.[29] In the young control group, inspiratory loading resulted in an increase in P_{100} at each level of induced hypercapnia, such that inspiratory loading did not change the ventilatory response to hypercapnia when compared with unloaded responses. In marked contrast, the P_{100} in the elderly group did not change when an inspiratory load was applied. In the absence of a compensatory change in ventilatory drive, ventilatory responses to hypercapnia were reduced during inspiratory loading in the elderly group.

At each level of P_{CO_2}, the intensity of perceived dyspnea in response to inspiratory loading was greater in the elderly than in the control group. Thus, the sensation of dyspnea was intact or enhanced in the elderly subjects, while their compensatory responses were reduced. This suggests the possibility that, elderly individuals may complain of a greater dyspnea than younger individuals with similar pathophysiologic deterioration.

■ SENSITIVITY TO RESPIRATORY DEPRESSION BY OPIOIDS AND SEDATIVES

Older individuals are substantially more sensitive to respiratory depression by opioids and sedatives. This phenomenon demands extra vigilance when these medications are prescribed in nonintubated elderly patients. The enhanced drug effect has been shown to be multifactorial, and the various mechanisms involved are beyond the scope of this chapter.[30–32] However, the dangers associated with higher levels and more prolonged effects of these drugs are real and potentially catastrophic.

PULMONARY CIRCULATION

Invasive physiologic studies of pulmonary artery catheterization have typically been biased by including only subsets of patients whose signs and symptoms led to referral for heart catheterization and who, therefore, may not be representative of a "healthy" cohort. Further, age-related changes in the pulmonary circulation are difficult or impossible to separate from changes due to heart disease or age-related changes in cardiac function.

Ehrsam et al. reported a retrospective analysis of right heart catheterization studies performed in 125 asymptomatic subjects who ranged from 14 to 68 years of age.[33] Small increases in right atrial, pulmonary artery, and pulmonary artery wedge pressures observed in the highest age group disappeared when values were adjusted for sex, weight, and height. No significant age-related changes were found in cardiac output, stroke volume, or oxygen uptake. Age explained 10% or less of the total variation in the hemodynamic and pressure variables when assessed by multiple regressions. During supine exercise with a bicycle ergometer, however, pulmonary artery and wedge pressures increased with age, particularly in subjects over the age of 45. The changes were highly significant with age accounting for 12% to 30% of the total variation when assessed by multiple regressions. Finally, pulmonary artery resistance showed a highly significant increase with age, whether measured at rest or during exercise, with age contributing 12% to 27% to the total variation in pulmonary artery resistance. Although the cohort studied were all asymptomatic and ambulatory, it is possible that silent coronary artery disease was present in some of the subjects, and the prevalence of coronary artery disease can be expected to increase with age. Moreover, younger patients tended to be referred for evaluation of a heart murmur, whereas the older patients were referred for "pulmonary investigation" that included coin lesions, hilar lymphadenopathy, "previous pulmonary infiltrates," and smoke inhalation. Cigarette smoking history was not discussed. Thus, it is not certain that the younger and older patients were strictly comparable.

More recently, Davidson and Fee reported the results of right-heart catheterization at rest in 47 normal subjects who were free of coronary disease and had normal left ventricular systolic function.[34] Smokers were included. The investigators found highly significant but quantitatively modest age-related increases in mean pulmonary artery pressure, pulmonary vascular resistance, and pulmonary/systemic vascular resistance ratio, but they found no age-related differences in pulmonary artery wedge pressure. The authors felt that the most likely explanation for the age-related changes in pulmonary artery pressure and pulmonary vascular resistance was a primary abnormality of the pulmonary vascular bed, but they could not exclude the effects of subtle abnormalities in left ventricular function.

In summary, studies of pulmonary hemodynamics with aging are limited by retrospective design, bias in patient selection, and potential effects of smoking. Minor increases in pulmonary vascular resistance and age-related increases in pulmonary artery wedge pressure during exercise have been reported. These age-related changes may not be physiologically significant.

PULMONARY FUNCTION TESTS

Lung function and exercise capacity decline with age in concert with numerous other physiologic, morphologic, and biochemical changes. Descriptions of "normal" age-related changes are confounded by an increasing prevalence of disease, chronic illness, medication use, and an increasingly sedentary lifestyle. Further, chronologic age only approximates physiologic age; the two often differ significantly. Chronologic age is, therefore, an imperfect measure for indexing changes with senescence. While it would be desirable to isolate the effects of biologic aging (aging in the absence of disease), it is essentially impossible to do so. The best studies to do so are longitudinal, tracing change with time, because they avoid the obvious biases of cross-sectional studies. Longitudinal studies, however, have methodologic problems and biases of their own, the most obvious being that the healthy elderly represent a healthy survival population. If, as a group, they have better than average lung function, they would not represent the general population of elderly people well.

■ LUNG VOLUMES

Figure 19-8 illustrates typical lung volume changes with aging based on cross-sectional studies. With the exception of vital capacity, the effect of aging on lung volumes is based on cross-sectional rather than longitudinal data because there are almost no longitudinal studies of static lung volumes. Total lung capacity (TLC), the volume of air in the lungs at the end of a maximal inspiration, is marked by the point at which the recoil pressure exerted by the respiratory system is exactly counterbalanced by the maximal inspiratory pressure generated by the respiratory muscles. Since both the compliance of respiratory system (lung and chest wall combined) and maximum inspiratory pressure fall with aging, TLC might also be expected to fall. However, in seven cross-sectional studies of TLC summarized

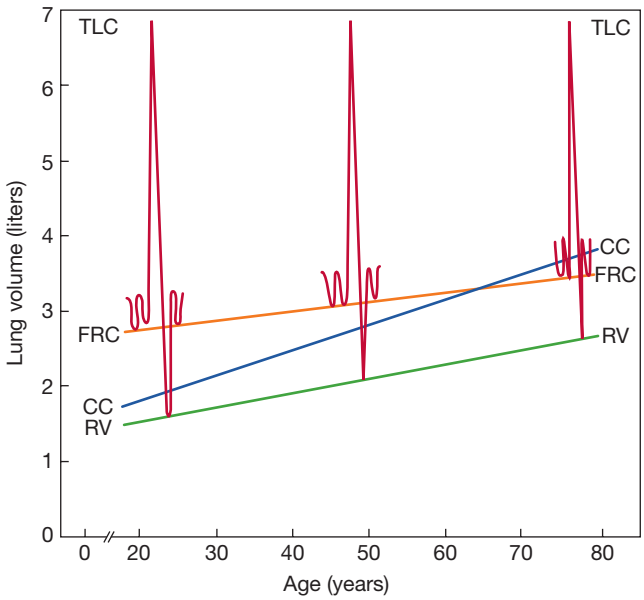


Figure 19-8 Schematic illustration of lung volume changes with age based on cross-sectional studies in seated individuals. (TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; CC, closing capacity.) Although not labeled, vital capacity (VC) is TLC minus RV. The most consistent changes are an increase in RV and a decrease in VC. *(Reproduced with permission from Peterson DD, Fish-man AP. Aging of the respiratory system, in Fishman AP (ed). Update: Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1992, pp 1–17.)*

by the European Coal and Steel Community, four of the studies in men and three of those in women did not find a significant age coefficient.[35] The remaining studies found only small declines in TLC with age, on the order of −8 to −19 mL/yr. When these study results were combined into average equations, no significant age coefficients were reported for either men or women. McClaran et al. measured lung volumes twice in 18 healthy, fit men.[36] The first measurement was at a mean age of 67 and the second was 6 years later. Although average TLC fell 25 mL/yr, the change was not statistically significant. The study was small and the interval was short.

In summary, current cross-sectional studies suggest that TLC either does not decline with age or declines very slowly. It is interesting to speculate on the possibility that cross-sectional studies of TLC might be confounded because they typically index TLC to both age and height. Height declines with aging, and maximum height during a life span appears to increase with successive generations. The author believes that longitudinal studies of TLC with age are likely to show small but significant declines with age.

Both slow and forced vital capacity (FVC) decline with age, more rapidly in men than women. Average decrements in vital capacity per year vary considerably; in cross-sectional studies, declines range from 21 to 33 mL/yr in men and 18 to 29 mL/yr in women. Theoretically, longitudinal studies should provide better estimates of the effect of aging on lung function. Ware et al., in a study containing both longitudinal and cross-sectional computations, found cross-sectional falls in FVC for men and women to be −34 and −27.8 mL/yr, respectively.[37] The longitudinal estimates were −40 mL and −31.3 mL/yr, respectively. This study contradicts the generally held concept that longitudinal studies show smaller declines in FVC than cross-sectional studies. Currently, it is not certain whether longitudinal studies are all that much different from cross-sectional studies in describing declines in FVC and forced expiratory volume in 1s (FEV_1). Longitudinal studies tend to show an acceleration in the rate of loss in FVC and FEV_1 as age advances.

Cross-sectional studies of residual volume (RV) and the RV/TLC ratio consistently show increases with age. In the young, RV, the volume of air in the lungs at the end of a maximal expiration, is the volume at which the outward static recoil pressure of the respiratory system is counterbalanced by the maximal pressure exerted by the expiratory muscles. In older subjects, expiratory flow never completely reaches zero and the determination of RV is made partly by the length of time an individual can maintain expiratory effort.[38] Other factors leading to an increased RV with aging include loss of lung recoil, decreased chest wall compliance, decreased expiratory muscle force, and increased small airway closure (air trapping) in dependent lung zones. Time of exhalation and increase in air trapping are probably more important than changes in lung and chest wall compliance in explaining the increase in RV with aging.

FRC is also determined by the balance of the elastic recoil forces of the lung and chest wall; but, in this instance, the equilibrium occurs at the end of a quiet (unforced) exhalation. Since lung recoil falls and the chest wall stiffens with age, one would expect FRC to increase. Cross-sectional studies, however, show inconsistent results, with most showing no change in FRC with aging. Studies that find an increase in FRC with aging show a small positive age coefficient on the order of 7 to 16 mL/yr. McClaran's longitudinal study found FRC to increase 40 mL/yr, but again, the change was not significant.[36] Despite the conflicting data, it is generally believed that FRC increases with aging.

Loss of lung recoil also changes the volume at which airway closure occurs. When adults exhale fully, small airways close in the region of the terminal bronchioles in dependent lung zones. The lung volume at which this closure begins is measured as closing volume or, if it is added to RV, closing capacity. Closing volume increases linearly with age from about 5% to 10% of TLC at age 20 to about 30% of TLC at age 70.[39] The loss of lung elastic recoil, a possible decrease in the recoil of the intrapulmonic airways, and decreases in small airway diameter probably explain most of the changes in CV.

Closing volume encroaches on tidal volume by about age 44 when subjects are supine and about age 65 when they are seated (Fig. 19-8). Airway closure during tidal breathing explains most of the decrease in arterial oxygen tension (PA_{O_2}) observed with aging[40,41] and may contribute to an aging-related increased frequency dependency of compliance.

AIRFLOW

While essentially all expiratory flows measured during a maximum expiratory maneuver decrease with age, the declines are most evident at lower lung volumes (Fig. 19-9). Nunn and Gregg, in a study of 225 male and 228 healthy female nonsmokers,[42] reported a modest, nonlinear decrease in peak expiratory flow (PEF) with aging (Fig. 19-10), which reached a high point at age 30 to 35; a decline became evident at about age 45. After age 50, the average decline was about 4 L/min per year in men, about 2.5 L/min per year in women.

Figure 19-11, from Paoletti et al.,[43] illustrates changes in FEV_1 during growth, maturation, and senescence. Changes in FVC are similar. In one model of aging, FVC and FEV_1 increase progressively during the growth phase until about age 12. In the maturation phase (during adolescence), there is an acceleration of these increases. Increases in FVC and FEV_1 are seen up to about 20 years in women and about 25 years in men; increases in lung volumes occur even after somatic growth ceases. There appears to be a plateau phase where there is little or no change in FVC or FEV_1 prior to the onset of a decline. However, Robbins et al. demonstrated that, while the plateau correctly represents average data, lung function is often increasing or decreasing in individuals (Fig. 19-12). Their study confirms the suspicion that the "plateau" phase represents the merging of slower maturation-related increases in FVC and FEV_1 in some subjects, with subtle decreases in others.[44] In the decline phase, there appears to be acceleration in the rate of loss of FVC and FEV_1 as age progresses.

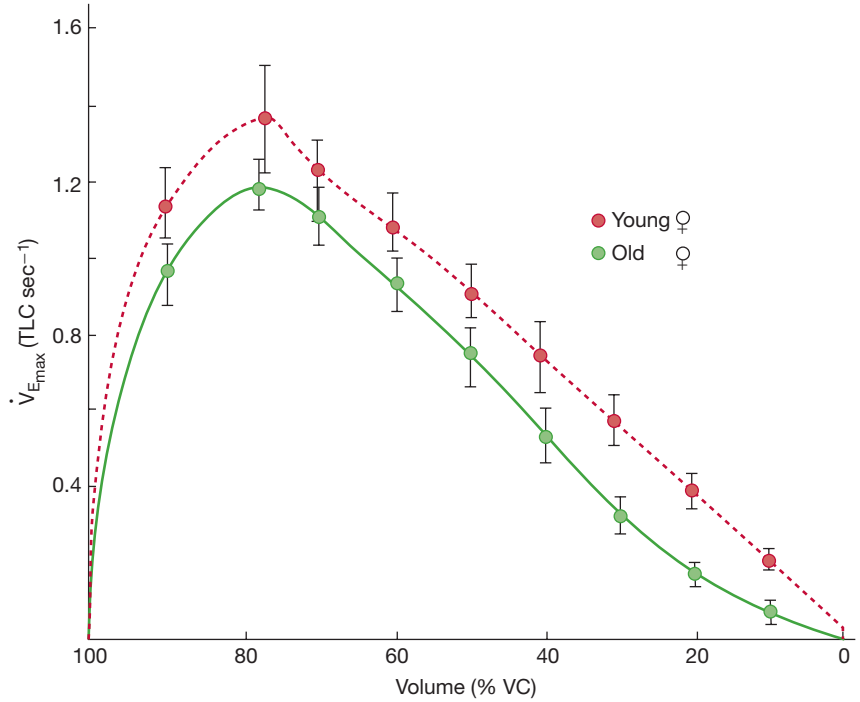


Figure 19-9 Illustrative maximal flow–volume curves for healthy "elderly" women (mean age, 63 years) and healthy young women (mean age, 25 years). Although all flows tend to be reduced with aging, the reduction in flow is most evident at lower lung volumes, where the flow–volume curve is clearly concave to the volume axis. *(Reproduced with permission from Peterson DD, Fish-man AP. Aging of the respiratory system, in Fishman AP (ed). Update: Pulmonary Diseases and Disorders. New York, McGraw-Hill; 1992:1–18.)*

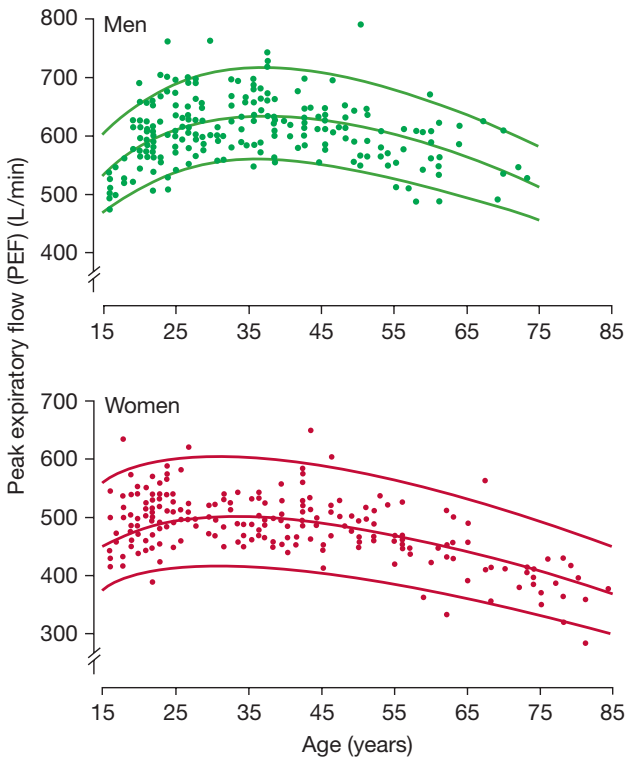


Figure 19-10 Changes in peak expiratory flow in 225 males and 228 females who were healthy nonsmokers. The *center line* is a regression curve representing mean data and the boundaries are 90% confidence intervals. *(Reproduced with permission from Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. Br Med J. 1989;298(6680):1068–1070.)*

An accelerated rate loss at older ages is, however, not found in all studies. The rate of decline in FVC and FEV_1 with age tends to be greater: (1) in men; (2) in taller individuals; (3) in individuals with larger baseline values; and (4) in individuals with increased airway reactivity.

AIRWAYS RESISTANCE

Total airway resistance measured at FRC does not change with aging. Since upper airways increase and smaller airways decrease in size with aging, it is likely that peripheral airway resistance increases and central airway resistance decreases. That total airway resistance does not change with aging may be a function of the counterbalancing of these two opposite changes. However, since about 90% of total airway resistance resides in the upper airways, significant changes in peripheral airway resistance might not be readily reflected in total airway resistance. Significant increases in peripheral airway resistance with age also would be consistent with the more dramatic decreases in maximum flow observed at low lung volumes.

GAS EXCHANGE

The carbon monoxide diffusing capacity (D_{LCO}), also known as transfer factor (T_{LCO}), declines with age. Earlier cross-sectional studies report a linear decline in D_{LCO} of about −0.2 mL CO/min per mm Hg per year for men and −0.15 mL CO/min per mm Hg per year for women. These declines are roughly 0.5% per year. In a large representative sample of US adult men, Neas and Schwartz found an almost linear fall in D_{LCO}.[45] In women, however, they found a nonlinear, quadratic decline in D_{LCO} with age. After age 47, the nonlinear component was not significant and the decline in D_{LCO} was identical to that in the earlier studies. The decline in D_{LCO} with age did not vary with race.

The decline in D_{LCO} with age is not explained by increased nonhomogeneity of gas distribution. Measured D_{LCO} falls as alveolar P_{O_2} increases, and venous hemoglobin concentration falls. Neither alveolar P_{O_2} nor hemoglobin concentration varies enough with age to explain the aging decline in D_{LCO}. The magnitude of the decline in D_{LCO} corresponds fairly well to the magnitude of the known aging-related decrease in the internal surface area of the lung.

The components of D_{LCO} are membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc). Both Dm and Vc decrease with age. In a cross-sectional reference value study of 54 male and 36 female healthy nonsmokers, the decline in Dm and Vc with age were found to be linear.[46] Membrane diffusing capacity fell at about 0.6% per year in both men and women. Pulmonary capillary blood volume fell at about 0.3% per year.

Although alveolar oxygen pressure ($P_{A_{O_2}}$) remains constant with age, arterial P_{O_2} (Pa_{O_2}) decreases and the alveolar–arterial oxygen tension gradient ($P_A - a_{O_2}$ increases with aging (Fig. 19-13).[47] The decline in Pa_{O_2} with aging is more pronounced when subjects are studied in a recumbent as contrasted with an upright position. The most likely explanation for the decline in Pa_{O_2} with aging is increased mismatching of ventilation to blood flow ($\dot{V}_E/\dot{Q}$) as airway closure begins to occur during tidal breathing. Increased ($\dot{V}_E/\dot{Q}$) mismatching with aging is also associated with an increase in physiologic dead space.[48,49] Hypoventilation does not contribute to the age-related fall in Pa_{O_2}, since Pa_{CO_2} and pH do not change with age (Fig. 19-13).

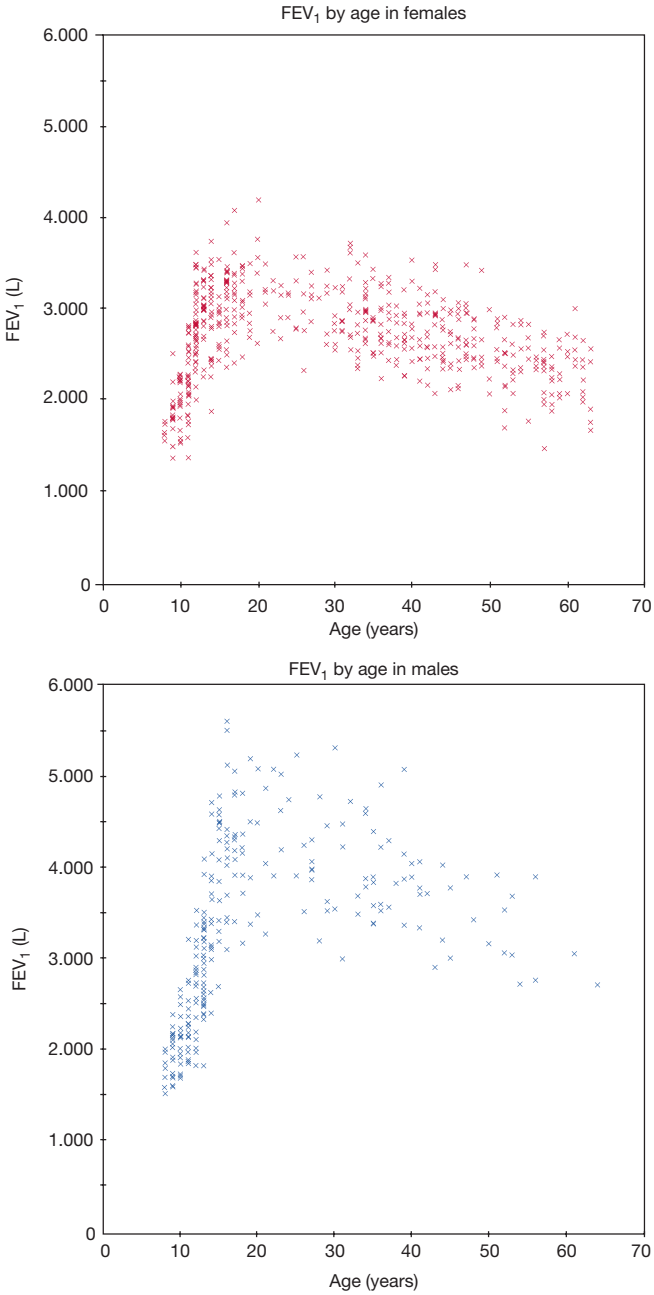


Figure 19-11 Change in FEV_1 with age from a cross-sectional study of 538 females and 263 males selected as "normal" from a larger study of 3289 subjects. Changes in FVC are similar. *(Reproduced with permission from Paoletti P, Pistelli G, Fazzi P, et al. Reference values for vital capacity and flow-volume curves from a general population study. Bull Eur Physiopathol Respir. 1986;22(5):451–459.)*

EXERCISE CAPACITY

Peak $\dot{V}_{O_2}$ ($\dot{V}_{O_2\,peak}$) and maximum work capacity decrease with aging in both sedentary and active individuals.[50] $\dot{V}_{O_2\,peak}$ (L/min) increases until about age 20. Declines are evident at about age 25 in both men and women and continue at about 1% per year (Fig. 19-14). If one expresses $\dot{V}_{O_2\,peak}$ as a function of body weight (L/kg per min), the decline is evident much earlier, perhaps in the first decade of life. The magnitude of the decline in $\dot{V}_{O_2\,peak}$ tends to be greater in longitudinal than in cross-sectional studies and occurs roughly twice as fast in sedentary than in physically active persons. Most, but not all, studies report linear declines in $\dot{V}_{O_2\,peak}$ with age, even though a nonlinear decline would be expected based on the number and type of variables that affect exercise capacity.

The decline in exercise capacity with age occurs as a result of normal aging but is accelerated by lifestyle issues. Aging is associated with significant changes in body configuration. Specifically, there is an increase in total body weight, primarily representing an increase in fat mass, since fat-free mass (mostly muscle mass) decreases with aging. The changes are most pronounced in sedentary persons. Muscle mass decreases, with a preferential atrophy of type II muscle fibers, and is associated with a decrease in muscle capillarization and oxidative activity. Muscle strength decreases on the order of 2%/yr from ages 20 to 70. Variables associated with loss of exercise capacity with aging are listed in Table 19-2.

While exercise capacity declines with aging, it is also clear that the ability to respond to exercise conditioning is well maintained even at very advanced ages. Elderly individuals respond to both endurance and resistive training with improvements similar in magnitude to those seen in the young.[50–52] There are equivalent increases in $\dot{V}_{O_2\,peak}$, muscle mass, capillarization of muscle tissue, muscle oxidative activity, and general muscle strength.

LUNG AND AIRWAY INFLAMMATION

In recent years, there has been considerable interest in the presence and control of lung inflammation in elderly individuals, and this has become a confusing subject. A variety of quantitative abnormalities in mediators of inflammation have been described in elderly individuals that have mostly been in the direction of increased lung parenchymal and airway inflammation. However, these differences from younger subjects must be viewed in the context that elderly individuals have impaired cough, increased evidence of gastroesophageal reflux, and decreased effectiveness of the ciliary escalator. All of these abnormalities can be expected to lead to an increased load of particulates and microorganisms in the lower respiratory tract, and/or recurrent episodes of aspiration. As a striking example of studies of airway inflammation, the mean quantity and percentage of neutrophils in broncho-alveolar lavage fluid have been found to be increased in elderly individuals, but many of the studied elderly subjects were indistinguishable from young normals.[53] The increased mean values in the elderly were strongly influenced by outlying high values in a subpopulation, and thus presumably did not result from a direct effect of aging.

SLEEP

Sleep complaints from elderly patients present a difficult problem for the clinician, who must determine whether the complaints are related to the normal aging process, sleep hygiene issues, or the presence of pathology.[54,55] Problems with sleep are widespread among elderly persons, with 25% to 40% complaining about sleep difficulties. There is no evidence to confirm the widely held belief that the need for sleep declines with age. However, sleep quality decreases, and the frequency of various primary sleep disorders increases. The most common age-related change in sleep pattern is a striking increase in the number of nocturnal awakenings, resulting in lower total sleep time and lower sleep efficiency (total sleep time/time in bed). Whether or not sleep latency changes with aging is equivocal. The amount of time spent in stage 1 nonrapid eye movement (NREM or light) sleep tends to increase with age. The decrease in total sleep time at night is associated with an increase in unwanted daytime naps. Disrupted sleep in the elderly is, in large part, explained by medical and psychological issues and the lack of structured physical and social activity during the day. Chronic illnesses, nocturia, medication and alcohol use, periodic leg movements, bereavement, and depression also play a role. Not surprisingly, the elderly are more likely to use sedatives or hypnotics; their use is more frequent in elderly women than in elderly men. While

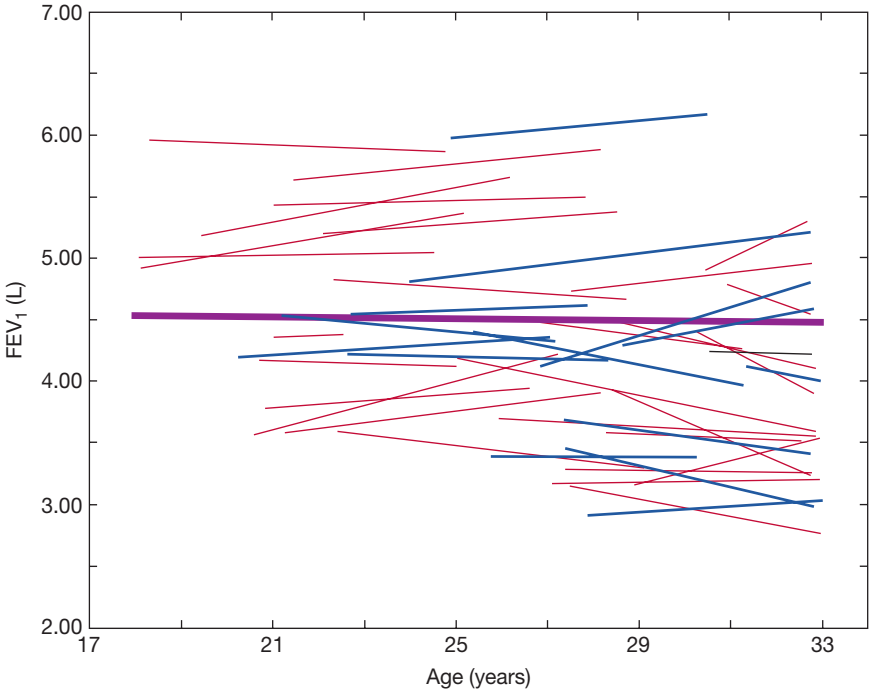


Figure 19-12 Predicted FEV_1 trajectories from 44 men based on linear regressions of longitudinal data. Nonsmokers *(fine lines)* and smokers *(dashed lines)*. The heavy line is based on the entire group's data. While the group's data show no change with age, data for individuals show both increases and declines with age during this time period, when a plateau in lung function was theorized to occur. *(Reproduced with permission from Robbins DR, Enright PL, Sherrill DL. Lung function development in young adults: Is there a plateau phase? Eur Respir J. 1995;8(5):768–772.)*

hypnotics and sedatives are occasionally necessary, their chronic use may contribute to sleep disruption and aggravate certain sleep disturbances, such as sleep apnea. Increased autonomic activity, increased sensitivity to external stimuli (which may increase arousals as a result of environmental factors), decreased exposure to outdoor light, inactivity, and daytime napping also play a role in sleep disruptions in the elderly. Alterations in endogenous circadian rhythms for variables like temperature and cortisol or thyroid-stimulating hormone (TSH) levels may also contribute to sleep disruption in the elderly.

The neural system that regulates sleep is, like most other systems, subject to the aging process, and sleep disruption occurs in the elderly in the absence of any pathologic process. The amount of stages 3 and 4 sleep (slow- or delta-wave sleep) declines with aging, although some argue that the aging decline is mostly a technical issue related to how delta-wave amplitude is defined. Changes in slow-wave sleep appear to be evident early, perhaps by 20 years of age. Arguments have been made both for and against declines in the amount of REM sleep with age. The persistent controversy about REM sleep and aging suggests that if REM sleep does change with aging, the magnitude of decline is so small that it does not overwhelm the confounding factors in studies.

Sleep disorders such as sleep apnea and restless limb syndrome, with periodic limb movements, appear to be more prevalent in older persons, and they are also marked more among nursing home residents than the independent elderly. For example, using an apnea index of five per hour as a threshold, one study found evidence of sleep apnea in 42% of elderly nursing home residents, in contrast to 24% of the independent elderly. A community-based study of individuals aged 71 to 87, showed a 55% prevalence of sleep-disordered breathing that was documented by polysomnography, including 38% obstructive sleep apnea and 17% central sleep apnea.[56] However, longitudinal follow-up of these individuals did not show an independent correlation with either cardiovascular disease or mortality.

INTERPRETING PULMONARY FUNCTION TESTS IN THE ELDERLY

Several issues complicate the interpretation of lung function tests in the elderly, as reviewed by Vaz Fragoso and Gill.[57] The elderly are not well represented in most reference value reports; the number of subjects usually falls off significantly after age 60. The number of

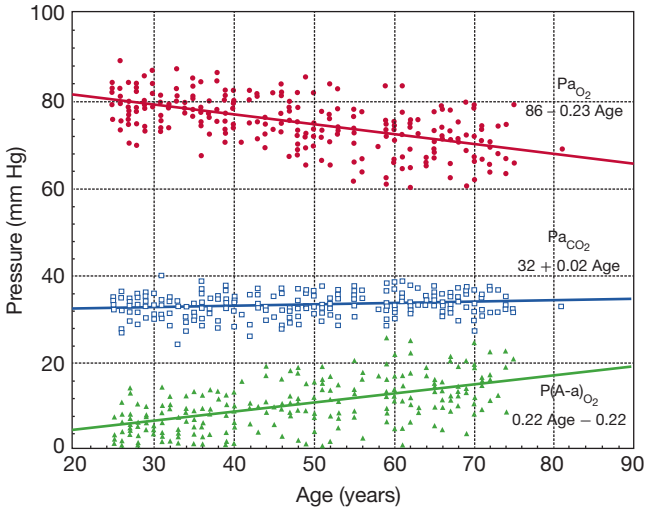


Figure 19-13 Change in Pa_{O_2}, Pa_{CO_2} and A-a gradient $P(A\text{-}a)_{O_2}$ with age. Data were obtained from 200 healthy men and women living in Salt Lake City, UT (altitude = 1400 m). Sea-level data would be similar, with a small upward shift in Pa_{O_2} and Pa_{CO_2}.

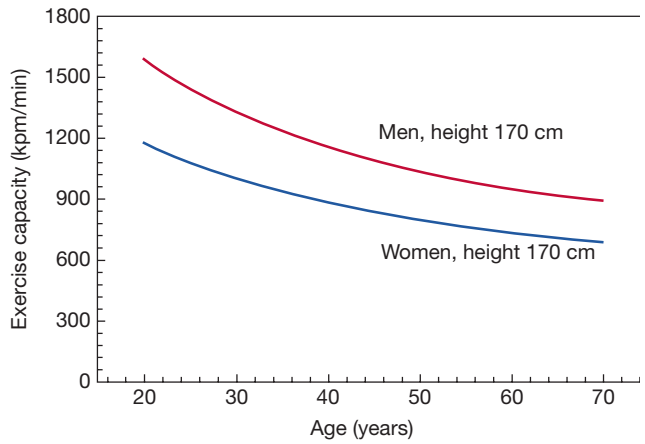


Figure 19-14 Decline in maximum exercise capacity with age. Exercise capacity declines nonlinearly with age. Maximum work capacity correlates strongly with peak oxygen uptake. *(Reproduced with permission from Jones NL, Summers E, Killian KG. Influence of age and stature on exercise capacity during incremental cycle ergometry in men and women. Am Rev Respir Dis. 1989;140(5):1373–1380.)*

TABLE 19-2 Variables Associated with a Decline in Exercise Capacity with Age

Variable	Comment
Decreased muscle mass	These changes especially affect $\dot{V}_{O_2}$ calculated per kg of body weight
Increased fat mass	
Decreased tissue oxygen delivery Decreased maximal heart rate Decreased stroke volume Decreased maximal $C(a-\bar{v})_{O_2}$ difference	As a result of the decreased cardiac output and maximal $C(a-\bar{v})_{O_2}$, delivery and extraction are reduced; decreased cardiac output is a major contributor to the age–related decline in exercise capacity
Maximum voluntary ventilation	
Increased ventilation at each workload	At each workload, older individuals breathe more and work harder for each breath than younger persons; however, the effect is small and contributes little to the decline in exercise capacity with aging
Increased oxygen cost of breathing	
Sedentary lifestyle	Lifestyle issues play a large role in the rate at which exercise capacity is lost with age; the good news is that, like other deconditioned groups, the elderly respond very well to exercise training
Decreased training intensity in active persons	
Decreased willingness to work to maximal level during tests	

subjects over age 80 is usually so small that mean values calculated from regression equations are essentially an extrapolation of the data for younger persons. This means that the average or "predicted" value may not be as representative for the elderly as it is for middle-aged persons. The fall in sample size with aging likely reflects the reduced total number of candidates for participation and the larger number of individuals who fail screening criteria. In reference value studies, individuals are screened so as to be free of symptoms and illnesses that alter lung function. These selection criteria may eliminate more older than younger candidates because of their increased prevalence of illness. Also, test quality is carefully standardized. Cognitive impairment may compromise test quality. As a result, older individuals may have more difficulty meeting test quality criteria, increasing their likelihood of exclusion and potentially increasing the variability of reference data for the elderly. In summary, the selection processes may make the older individuals who participate in reference studies less representative of the individuals who present for clinical lung function testing.

These same issues also affect the limits applied to determine whether a tested individual is within the "normal" range. Limits are often defined assuming that the distribution of data is Gaussian. Although tests of this assumption are sparse, there is reason to suspect that it is more likely to fail in the elderly. Even when the "normal" range is defined using methods that avoid assumptions about data distribution, data from the elderly are often lumped with those of the younger subjects. The result may be an erroneous "normal" range. All these reference value issues suggest that increased caution should be used in interpreting lung function tests in the elderly. This caution is especially important for those over age 80 and in any elderly person whose data lie near the limits of a "normal" range.

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CHAPTER 20

Innate and Adaptive Immunity in the Lung

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The lung is constantly exposed to foreign agents. As a result it is faced with the challenge of distinguishing nonpathogenic moieties in ambient air from potentially pathogenic antigens derived from microorganisms. Here, we use the term "pathogens" to refer to infectious agents, allergens, toxins, and other inhaled antigens unless stated otherwise. The lung protects itself using local tissue structures such as the mucus layer, ciliary ladder, and smooth muscles. It also employs complex immune defenses that are both innate and adaptive.[1,2] The immune responses need to be able to recognize and to react to a wide variety of stimuli. They must be able to recognize and to eliminate unwanted pathogens to keep pulmonary structures free of infection. On the other hand, they must not overreact to inhaled stimuli to avoid potential excessive inflammation and lung injury. This need to control the intensity and duration of such responses is required to preserve normal lung structure, especially the highly vascularized and fragile alveolar epithelial surface that is required for gas exchange. Alterations of these lung protective mechanisms lead to many of the pulmonary diseases physicians face in their patients. Therefore, understanding the innate and adaptive immune responses in the lung is important in our attempts to understand the pathophysiology and to improve the management of many pulmonary diseases. The anatomic and immune defenses will be reviewed in this chapter.

ANATOMIC MECHANISMS

Given the lungs' large surface area, it is exposed to many inhaled environmental challenges, because the air we breathe contains infectious agents, toxic gases, and fine particulate matter (Fig. 20-1). The alveolar and capillary membrane barriers are important for gas exchange, and need to be defended from the injurious effects of incoming toxic and infectious pathogens. If the consequences of these exposures are not controlled, this can lead to excessive inflammation, lung edema, as well as propagation of infectious agents. This can, in turn, lead to alveolar destruction, abnormal fibrotic repair, and compromised gas exchange. Air is inhaled through the nose or the mouth into the extrathoracic portion of the trachea before it enters the thorax. The nose filters and conditions the inhaled air for humidity and body temperature as it flows through the nasal turbinates. Nasal hairs also provide a barrier that traps larger particulates. The nasal secretions lining the airway mucosa contain many substances such as lysozyme, immunoglobulins (such as secretory immunoglobulin A [sIgA]), and antimicrobial peptides that bind to, and inactivate invading microbes. For example, sIgA accounts for 15% of the total protein in upper airway secretions and plays a significant role in neutralizing and preventing epithelial attachment of invading viruses and bacteria.[3] The conducting airway mucosa is also coated with acidic viscous fluid and mucus secreted by Clara cells, goblet cells, and bronchial glands (Fig. 20-1). This fluid makes up an important airway surface lining that coats the bronchial epithelium and forms a barrier between the outside world and the lung parenchyma.

INNATE IMMUNITY IN THE LUNG

The innate immune response is an evolutionarily conserved system of host defense evident in all multicellular organisms. In the constant battle between host and pathogens, the purpose of the innate immune system is to provide a rapid response, in contrast to the adaptive immune system, which provides a more specific response but takes longer to respond (see Section "Adaptive Immune Responses in the Lung"). Because humans breathe approximately 10 L of air per day (12 to 15 breaths/min × 500 mL tidal volume), we are constantly exposed to pathogens (e.g., viruses, bacteria, and fungi), allergens (e.g., house dust mites, dander), and toxins (e.g., cigarette smoke and pollutants). The innate immune system allows humans to respond to these stimuli even if they have not been exposed to them previously.

Because of the constant exposure to the environment, similar to other mucosal surfaces (e.g., gut and skin), the innate immune system must maintain a balanced response. Ideally, this should include (1) pathogen recognition, (2) initiation of an appropriate response, which is typically manifested by inflammation, and (3) resolution of inflammation. An inappropriately regulated innate response contributes to the pathogenesis of lung diseases as diverse as asthma, emphysema, and interstitial lung disease.

The most important property of the innate immune system is its response to pathogens regardless if there has been a prior exposure. Thus, an acquired immunologic memory against the pathogen is not required. The anatomic and antimicrobial structures that prevent infection and injury noted earlier can be thought of as part of the innate response. Therefore, one of the most important roles of the lung innate immune system is its function as a barrier to inhaled pathogens.[4] The epithelial surface of the lung creates a barrier with tight junctions between neighboring cells that prevent pathogen entry (Fig. 20-1). In addition to this barrier function, the epithelium has a coordinated system for the removal of inhaled pathogens. Goblet cells and secretory glands produce mucus that engulfs pathogens. A coordinated system of ciliated cells moves mucus up the mucociliary "ladder" to be expectorated during coughing. A disturbance in this essential function leads to significant pathology. In primary ciliary dyskinesia (PCD), cilia function is impaired and individuals develop bronchiectasis with recurrent bacterial infection.[5] In cystic fibrosis (CF), an abnormality in epithelial chloride channel function causes changes in the airway surface liquid that prevents effective mucus clearance, which also leads to chronic inflammation, bronchiectasis, and recurrent bacterial infections.[6,7] The mucociliary "ladder" is particularly effective for large molecules, but smaller molecules (<5 μM) are able to directly descend to the distal alveolar epithelium. Here, instead of mucociliary clearance, particles encounter secreted surfactant proteins (specifically SP-A and SP-D; also known as pulmonary collectins) that act as opsonins, and assist resident macrophage in phagocytosis.[8] Finally, the epithelium also produces a variety of innate immune antimicrobial molecules that activate alveolar macrophages (AMs) to kill pathogens.[9]

PATHOGEN RECOGNITION

The innate immune response allows the host to respond to a wide array of pathogens. However, the mechanism(s) that the host uses to recognize these pathogens was poorly understood until the 1980s. At that time, a seminal advance in our understanding of the immune system occurred when it was proposed that the host detects, and responds to these

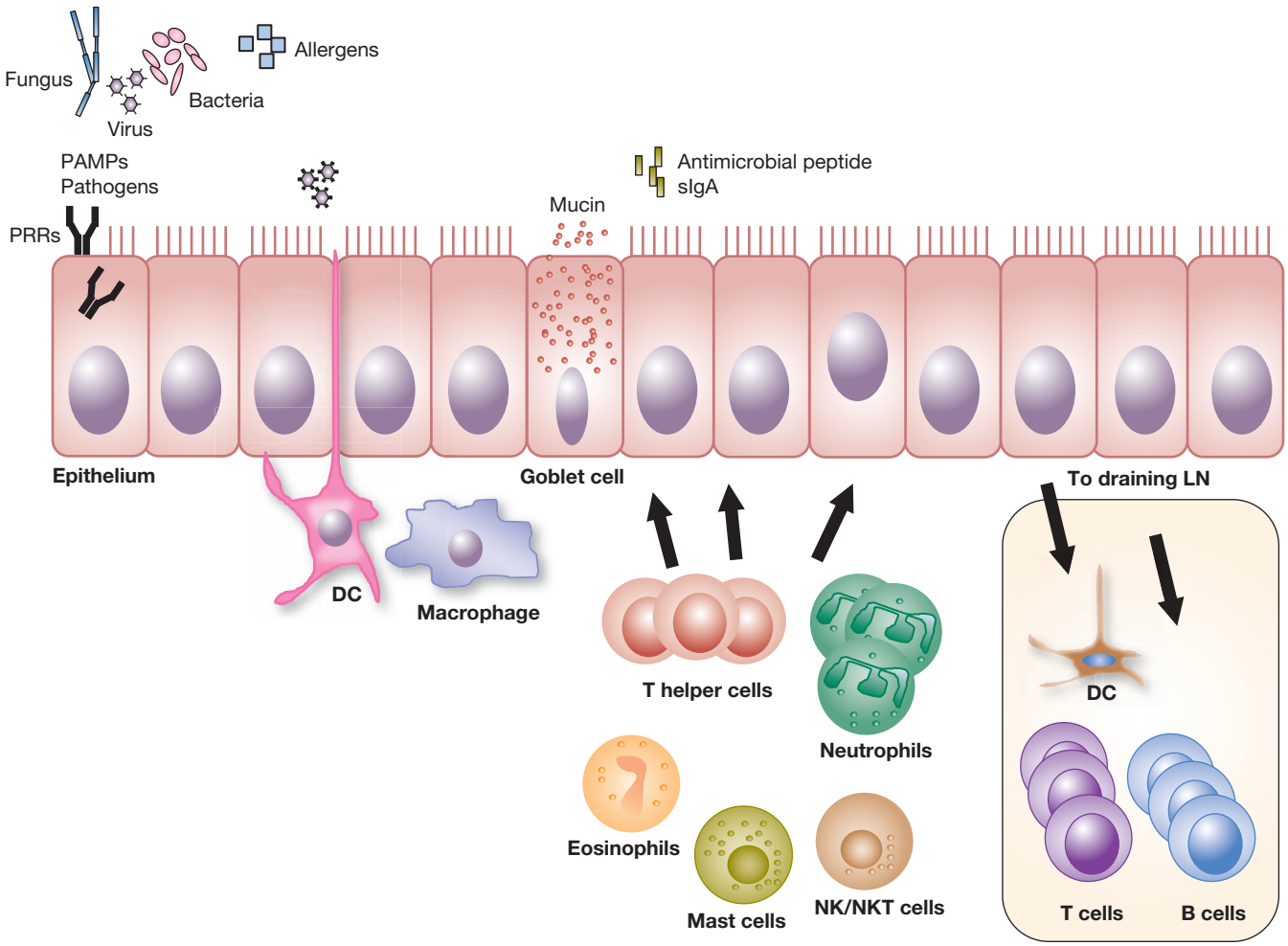

Figure 20-1 Innate recognition of pathogen or PAMPs on airway epithelium. Pathogens such as fungus, virus, or bacteria (or their associated pattern-associated molecular proteins [PAMPs]) and environmental allergens are first detected by membrane bound, cytosolic and/or endosomal innate sensors or pattern recognition receptors (PRRs). The respiratory epithelial cells provide a physical barrier between the airway luminal antigens and the underlying respiratory tissues in their control of immune defense and tolerance. Specialized epithelial cells can have cilia, produce a mucus layer and secrete antimicrobial proteins and secretory IgA (sIgA) that limit pathogen exposure to the epithelial cells. Dendritic cells (DCs) interdigitating between and lying near the epithelium, as well as tissue macrophages, are well positioned to sample and ingest incoming antigen. Recognition of the antigen by the innate immune receptors leads to production of pro-inflammatory cytokines and chemokines which recruits immune cells such as neutrophils, T cells, NK cells, NKT cells, eosinophils, or mast cells. Activated DCs that have taken up the inhaled antigen migrate to nearby draining lymph nodes. In the lymph nodes, the DCs help integrate the signals from the inhaled substance and the innate immune response into signals that direct cells of the adaptive immune system. The DCs encounter appropriate naïve $CD4^+$ T cells where factors such as the phenotype of the antigen-presenting cells (APCs) and cytokine milieu modulate differentiation of $CD4^+$ T cell subsets with their characteristic cytokine and functional profiles. These immune cell functions and cytokine production determine whether an activating or a tolerant response will develop.

pathogens via a cadre of receptors that recognize conserved sequences called pathogen-associated molecular patterns (PAMPs), which exist in pathogens, and are not present in the host (Fig. 20-2).[10,11] Experiments in *Drosophila* (fruit flies) in 1996 identified pattern recognition receptors (PRRs) that recognized PAMPs and supported the concept of innate receptors.[12] Subsequently, PRRs were identified in humans,[13] and more recently, additional PRRs have been shown to recognize endogenous molecules released from damaged cells, which are referred to as damage-associated molecular patterns (DAMPs).[14,15] The major types of PRRs are described in sections "Toll-Like Receptors", "RIG-I-Like Receptors", "Nod-Like Receptors" and "C-Type Lectin Receptors".

Toll-Like Receptors

The mammalian Toll-like receptor (TLR) family received its name from the *Drosophila* Toll gene. Early studies that involved the genetic manipulation of Toll resulted in dramatic defects in innate immune responses (Table 20-1; Fig. 20-2).[12,16] Since this discovery, the TLRs are appreciated to be the prototypical PRR molecules.[13,17] It is now known that some TLRs are present on the cell surface, and others are in endosomes (intracellular vesicles). As a group, they are characterized by N-terminal leucine-rich repeats that recognize pathogens, a transmembrane region, and a cytoplasmic domain that is highly homologous to the interleukin (IL)-1 receptor and the IL-18 receptor.[18] To date, 11 TLRs have been identified in humans, with different TLRs recognizing distinct PAMPs.[19] In general terms, TLR recognition of PAMPs is based upon cellular compartmentalization. Recognition of viral RNA and DNA occurs in endosomes by TLR3, TLR7, and TLR9, while TLR2 and TLR4 have been shown to recognize viral proteins. The remaining TLRs recognize bacteria, parasite, and host

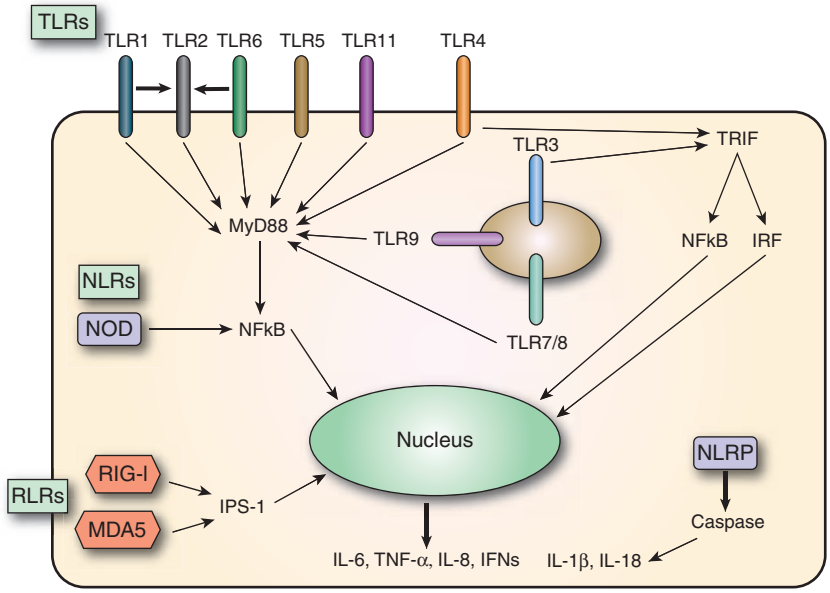

Figure 20-2 Pattern recognition receptors (PRRs). Classes of PRRs include Toll-like receptors (TLRs), retinoic acid–inducible gene-I–like receptors (RLRs) and nucleotide oligomerization domain–like receptors (NLRs). Not shown are C-type lectin receptors (CLRs). TLRs, RLRs (e.g., RIG-I, MDA5, and other sensors), and NLRs (e.g., NOD1, NOD2, NLRP3, etc.) are innate immune sensors that recognize danger signals derived from pathogens (PAMPs), damaged cells (DAMPs), or associated nucleic acids at the cell surface, in endolysosomes or in the cytoplasm. Signaling by these sensors promotes, either the activation and nuclear translocation of transcription factors (IRFs, NFκB and AP-1) that drive expression of cytokines (IFN-α/β, TNF, and pro-IL-1β), or the assembly of the caspase-1 inflammasome and subsequent maturation of IL-1β from pro-IL-1β. IFN, interferon; IL, interleukin; IRFs, interferon regulatory factors; MDA5, melanoma differentiation–associated gene-5; NFκB, nuclear factor κB; NLRP, NLR with a pyrin domain; NOD, nucleotide oligomerization domain; RIG-I, retinoic acid–inducible gene-I; TNF, tumor necrosis factor; TRIF, TIR-domain–containing adapter-inducing interferon-β.

proteins (e.g., DAMPs), while TLR7 and TLR9 recognize DNA from bacteria or protozoa.

TLR Signaling Pathways

TLR recognition of PAMPs stimulates signaling pathways that ultimately lead to activation of gene transcription and protein production. The responses that are elicited can be cell type specific. They also utilize two distinct pathways based on which of two adaptor molecules they employ: (1) myeloid differentiation primary response gene 88 (MyD88) and (2) TIR-domain–containing adapter-inducing interferon-β (TRIF). With the exception of TLR3, and one of the pathways downstream from TLR4, MyD88 is required for the downstream signaling of TLRs. MyD88 interacts with the IL-1R–associated kinase (IRAK)-4, and other IRAK family members, before they dissociate from MyD88 and interact with TNFR-associated factor 6 (TRAF6). IκB kinase (IKK)-β and MAP kinases are activated, leading to another complex of IKK molecules that are degraded and release nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB is a critical transcription factor for TLR-induced genes in inflammation. In addition, activation of the MAP kinase cascade leads to another transcription factor, AP-1, which is associated with activation of cytokines. TRIF-dependent signaling was found to be responsible for TLR3 signaling and, more recently, TRIF was implicated in TLR4 signaling.[20] TRIF interacts with TRAF3 and TRAF6, and leads to TNF receptor (R)-associated death domain protein (TRADD), ultimately leading to activation of NF-κB. Interestingly, TLR4 was found to activate MyD88 at the surface of the plasma membrane, while TRIF activation occurred when TLR4 was in endosomes.[20] Downstream from TRIF is activation of interferon regulatory factors (IRFs), which lead to interferon production and activation of interferon-dependent genes.

TABLE 20-1 Toll-Like Receptors

TLRs	PAMP	Cellular Location
TLR1	Lipoprotein (bacteria)	Plasma membrane
TLR2	Lipoprotein (e.g., bacteria, viruses, parasites, host damage)	Plasma membrane
TLR3	dsRNA	Endosome
TLR4	LPS (bacteria, virus, host damage)	Plasma membrane
TLR5	Flagellin (bacteria)	Plasma membrane
TLR6	Lipoprotein (bacteria, virus)	Plasma membrane
TLR7 (human TLR8)	ssRNA (virus, bacteria, host damage)	Endosome
TLR9	CpG-DNA (virus, bacteria, protozoa, host damage)	Endosome
TLR10	Unknown	Endosome
TLR11	Profilin-like molecule (protozoa)	Plasma membrane

RIG-I–Like Receptors

The RIG-I–like receptor (RLR) family presently includes three members: retinoic acid–inducible gene-I (RIG-I), melanoma differentiation–associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) (Table 20-2).[21] RLRs are expressed at a basal level by all nucleated cells, suggesting a central role in innate immune recognition and response to viral infection. A measure of their importance can be seen in the evolution of viral mechanisms to evade or suppress RLRs.[22] In the 1950s, interferons were discovered to be a critical antiviral innate immune response to viral infection produced by infected cells, and important in the recruitment and activation of natural killer (NK) cells and lymphocytes that recognize and kill virus-infected cells.[23] While the presence of an intracellular TLR receptor for dsRNA was hypothesized in 1969,[24] and subsequently identified, the discovery of RLRs introduced a second family of PRRs that are cytoplasmic sensors of viral nucleic acids that contribute to antiviral host defense by inducing interferon production. RIG-I was initially discovered in 1997 as a gene induced in acute promyelocytic leukemia cells after stimulation

TABLE 20-2 RIG-I-Like Receptors

RLRs	PAMP	Cellular Location
RIG-I	Short dsRNA	Cytoplasm
MDA5	Long dsRNA	Cytoplasm
LGP2	Unknown	Cytoplasm

with retinoic acid.[25,26] Several years later, RIG-I was found to be activated by interferon.[27] Similarly, MDA5 was identified in 1999,[28] and was later found to be induced by interferon.[29] LGP2 was suggested to function as a RIG-I inhibitor, exerting a regulatory role on antiviral innate immune responses,[30] but recent experiments suggest that LGP2 may modify viral RNA to assist RIG-I and MDA5 recognition of dsRNA.[19] Three genes encode RLRs in mice and humans, and all share a conserved helicase domain. Briefly, RIG-I and MDA5 are composed of two N-terminal caspase recruitment domains (CARDs), a central DEAD box helicase/ATPase domain, and a C-terminal regulatory domain.[31] LGP2 retains the helicase domain but lacks the CARD domain.[31] Their cytoplasmic location allows for recognition of dsRNA viruses and dsRNA intermediates generated during ssRNA viral replication. In addition, there is evidence that ssRNA is detected from viruses that do not produce significant amounts of dsRNA.[19] Importantly, eukaryotic cells avoid self-activation of RLRs by RNA in mitochondria, and RNA released into the cytosol is packaged to avoid RLR recognition.[22]

In the human lung, RLRs have been found to respond to a range of respiratory viruses, from rhinovirus (common cold virus) to influenza virus. In response to viruses, activation of intracellular signaling ultimately leads to interferon production and the activation of interferon-dependent genes. RLR signaling is dependent on CARDs, which interact with the interferon-β–promoter stimulator 1 (IPS-1, also known as MAVS, CARDIF, or VISA). IPS-1 is localized on the mitochondrial membrane. IPS-1 activates TRAF3 and TRADD, which are common molecules for IFN-inducible gene expression.[19] In addition, NF-κB signaling has been implicated.[32]

NOD-Like Receptors

Nucleotide oligomerization domain (NOD)-like receptors (NLRs) are another family of cytoplasmic pathogen sensors that were discovered in the 1990s (Table 20-3).[33] Briefly, the molecular structure of NLRs includes a central nucleotide-binding domain and C-terminal leucine-rich repeats. The N-terminal portions of most NLRs contain protein-binding motifs (e.g., CARDs, a pyrin domain, and a baculovirus inhibitor of apoptosis protein repeat [BIR] domain).[19] NLRs activate important signaling pathways mediated by NF-κB and MAP kinases, and activate caspases. The result is activation of diverse signaling pathways that induce innate immune responses.[34]

NOD1 and NOD2 identify bacterial PAMPs by recognition of peptidoglycan from gram-negative bacteria, gram-positive bacteria, and mycobacteria. The importance of NLRs was highlighted by the evidence that NOD polymorphisms are associated with increased severity of atopy, eczema, and asthma,[35] as well as other inflammatory diseases (e.g., Crohn disease,[36] tuberculosis,[37] and lung cancer[38]). This suggests that a defect in bacterial clearance may influence the host microbiome and subsequent pathophysiology of disease. Distinct from NOD1 and NOD2 are a group of NLRs that activate caspases, such as caspase-1. Caspase-1 is the prototypical caspase that has been shown to be required for cleavage and processing of inflammatory cytokines (IL-1β, IL-18) into their active forms. This signaling pathway is now commonly referred to as the "inflammasome," and has been shown to be critical for effective innate immune responses against a wide range of microbial pathogens, cancer, and inflammatory, metabolic, and autoimmune diseases.[39] Specific to the lung, the inflammasome is critical for responses to important pathogens such as influenza A virus,[40,41] *Streptococcus,*[42,43] *Pseudomonas aeruginosa,*[44] and *Mycobacterium tuberculosis.*[45] In addition, activation of the inflammasome has been suggested to contribute to the pathogenesis of asthma,[46] chronic obstructive pulmonary disease (COPD),[47] and pulmonary fibrosis.[48]

TABLE 20-3 NOD-Like Receptors

NLRs	PAMP	Cellular Location
NOD1	Gram-negative > Gram-positive bacteria	Cytoplasm
NOD2	Gram-negative, Gram-positive bacteria, mycobacteria	Cytoplasm
NLRP 1–14	Viruses, bacteria, mycobacteria	Cytoplasm

C-Type Lectin Receptors

The C-type lectin receptors (CLRs) were identified in the early 1900s, and represent a diverse family that includes over one thousand members.[49] The CLRs were initially characterized as Ca^{2+}-dependent (C-type) carbohydrate-binding (lectin) proteins[49] but, subsequently, some CLRs were found to not bind carbohydrate ligands or require Ca^{2+}-dependent signaling.[50] Currently, CLRs have been classified into 17 groups.[50] Structurally, CLRs are characterized by a carbohydrate-recognition domain (CRD) that is highly conserved.[49] Despite this conserved CRD structure, CLRs are involved in cell functions as diverse as adhesion, repair, endocytosis, and phagocytosis, as well as innate immune pathogen recognition. CLRs recognize carbohydrates on a wide variety of pathogens including viruses, bacteria, and fungi. Several of the canonical CLRs include dectins, mannose-binding lectin (MBL) receptors, and surfactant protein (SP). Dectin-1 and Dectin-2 are important PRRs for recognition of fungi.[51] Upon recognition of fungal PAMPs, intracellular signaling pathways involve activation of NF-κB and MAP kinases.[52] MBL receptors function as PRRs by recognition of carbohydrate motifs on pathogens, which leads to complement activation.[18] MBL recognizes diverse pathogens that include gram-positive and gram-negative bacteria, yeast, parasites, mycobacteria, and viruses.[53] SP was first identified as a critical phospholipid for maintaining alveolar compliance to prevent atelectasis.[54] However, in the 1980s after the discovery of MBLs, sequencing of SP revealed significant structural similarities.[55] In accord with these similarities, SP-A and SP-D, secreted by alveolar epithelium, have been shown to function as agglutinins, opsonins, and inflammatory modulators[8] in response to viruses, bacteria, mycobacteria, and fungi.[56]

PATHOGEN-INDUCED INNATE IMMUNE RESPONSES

Inhaled pathogens may circumvent the mucociliary "ladder" on airway epithelium, which is typically the first responder to pathogens by virtue of its location and distribution. Antigen-presenting cells (APCs) such as dendritic cells (DCs) provide a critical role for pathogen recognition by extending projections into the airway between epithelial cells to sample the environment. On both airway epithelium and DCs, there is a wide repertoire of PRRs that recognize pathogens.[57] Upon recognition of PAMPs, PRRs activate signaling pathways that lead to subsequent inflammatory responses. An important component of this inflammatory response is the production of chemokines to recruit hematopoietic cells (e.g., neutrophils, eosinophils, macrophages, and lymphocytes including NK, and NKT cells) that are critical effector cells for the initiation and resolution of inflammation. In addition to chemokine production, PRR activation stimulates the production of a variety of cytokines (e.g., tumor necrosis factor (TNF)-α, IL-1β, IL-6, TGF-β, IL-10) that activate effector cells and contribute to the regulation of innate and adaptive responses in the lung.[57] PRR activation influences the balance of oxidation and proteases present in the lung. Importantly, dysregulation of oxidation has been shown to contribute to the pathogenesis of COPD,[58] while defective antiproteases, best exemplified by α1-antitrypsin deficiency, is a significant risk factor for the development of asthma, bronchiectasis, and emphysema.[59] Antimicrobial peptides are also produced by epithelial cells, as well as recruited hematopoietic cells, in response to PRR activation

(Fig. 20-1).[60] In humans, two significant groups of antimicrobial peptides are the cathelicidins[61] and defensins.[60] These small cationic peptides have antimicrobial activity against gram-negative and gram-positive bacteria, fungi, parasites, and viruses.[62] Epithelial and hematopoietic cells (e.g., neutrophils) produce both cathelicidins and defensins, and in addition to their antimicrobial properties, these peptides have been implicated in the induction of inflammation, influencing adaptive immune responses and wound repair.[61,62] Therefore, antimicrobial peptides are an excellent example of an innate immune response, initiated by PRR recognition of pathogens or PAMPs, which results in a protective response, regulates inflammation, and bridges innate and adaptive immunity. Recently a group of innate immune cells, known as innate lymphoid cells (ILCs), have been identified that lack specific antigen receptors but can produce an array of effector cytokines.[63,64] These ILCs have morphologic characteristics of lymphoid cells and can respond to a variety of signals and play an important role in immunity against microorganisms, tissue homeostasis, and repair of damaged tissues. Currently, there are three subsets of ILCs identified: ILC1s include IL-15–dependent NK cells; ILC2s are characterized by their production of T helper (Th) 2 cytokines (IL-5 and IL-13); and ILC3s express the nuclear hormone receptor retinoic acid receptor–related receptor (ROR)γt and produce cytokines IL-17 and IL-22.[63,65] These cells are important in innate immunity and very likely will be discovered to contribute to the development of effective adaptive responses.

CELLULAR RESPONSES IN THE LUNG

When pathogens bypass the initial lung mucosal barriers, the host's immune system responds in an orchestrated defense that involves a number of specialized cells that target the threat, neutralize it, and cleanup remnants to prevent the tissue injury. Macrophages function as phagocytes to engulf pathogens (viable and nonviable microorganisms), as well as apoptotic and necrotic cells that have undergone physiologic and pathologic cell death.[66] Ultimately, the lung must perform these tasks in a selective manner to avoid unnecessary inflammation that can cause continued tissue destruction. The innate immune system, as described earlier, is made up of a humoral arm (lactoferrins, lysozyme, sIgA, SPs, MBLs, and defensins) as well as a cellular arm (AMs, DCs, neutrophils, ILCs, etc.) that express numerous PRRs and or phagocytic receptors important for their diverse functions.

MACROPHAGES

Macrophages, initially described in the 1880s, are large mononuclear phagocytic cells. They play an important role in host defense based on their ability to phagocytize inhaled moieties, maintain tissue homeostasis, and function as APCs which are important in adaptive humoral and cell-mediated responses.[67] Macrophage precursors arise from committed hematopoietic stem cells in the bone marrow and are released into the circulation as monocytes before they differentiate into macrophages and DCs as they migrate into the lung. Tissue-resident macrophages form a specialized population based on their local anatomic location. Once called dust cells for their ability to engulf particulates, AMs, named for their presence in the pulmonary alveolus, frequently contain granules of various exogenous materials.[68] One example is particulate matter such as the black carbonaceous granules seen in lungs from smokers and long-term city dwellers. Routine bronchoalveolar lavage will identify these resident airway and AMs. However, pulmonary interstitial macrophages from lung tissue can only be collected by tissue dispersion techniques.[69] Of note, AMs are inferior APCs when compared to DCs.[70]

AMs secrete numerous products (e.g., cytokines, chemokines, and peptides) and directly interact with other cells and molecules through the expression of a variety of surface receptors.[71] AMs have multiple functions that include phagocytosis of cells undergoing apoptosis and necrosis, clearance of ingested pathogens or particulates, routine clearance of surfactant, and suppressing inappropriate inflammation and immune responses to harmless inhaled antigens. Macrophages ingest and phagocytose microbial or environmental particulate matter, which is then enclosed in intracellular vesicular phagosomes that undergo fusion with primary or secondary lysosomes to form phagolysosomes. In these AMs vacuoles, intracellular killing takes place through mechanisms that include antimicrobial proteins, degradative enzymes, oxidation, reactive oxygen intermediate generation, and "respiratory burst" known as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase degradation. Macrophages facilitate many innate recognition functions because they express diverse PRRs (e.g., TLRs, NLRs, and CLRs) to assist host defense in combating invading pathogens. The recognition and clearance of invading pathogens can also occur via opsonin-mediated phagocytosis through the Fcγ receptors. These receptors allow macrophages to be selective in their response to phagocytosed antigen, minimize damaging effects on normal cells, and limit responses to harmless moieties that can be frequently encountered in the airway.

While AMs have greater respiratory burst capacity than other phagocytes,[72] there are certain organisms that have evolved to evade AMs to improve their growth and survival. For example, mycobacteria prevent the fusion of phagosomes and lysosomes, escaping the harmful effects of the lysosomal hydrolases, and thus are resistant to the effects of macrophages. Some inhaled pathogens such as *M. tuberculosis* and environmental particulates such as silica are resistant to AM function and remain in intracellular lysosomal vacuoles for the duration of the macrophage life span. Macrophages also produce inflammatory cytokines and chemokines to recruit other specialized cells to assist in PRR recognition and host defense, in turn, helping to shape the adaptive immune response that follows.

Lung resident AMs are continuously encountering inhaled substances because of their unique position in the alveolar lumen (Fig. 20-1). Because of this location and the potential to cause harm to surrounding delicate and sensitive lung structures (e.g., alveolar epithelium), AMs are normally kept in a quiescent state to limit unnecessary inflammation and injury to nearby structural type I and surfactant producing type II pneumocytes when they encounter harmless antigens. Compared to AMs, DCs are less capable phagocytes with lower levels of expression of phagocytic receptors such as CD11b. In contrast, AMs produce lower levels of pro-inflammatory cytokines and suppress adaptive immune responses through their effects on neighboring DCs and T cells. It has been shown that depletion of AMs can lead to exuberant lung inflammation in response to otherwise innocuous antigens.[73] These AMs, when mixed with DCs in vitro, can suppress T cell function through the release of factors such as nitric oxide, IL-10, TGF-β, and various prostaglandins.[74]

DENDRITIC CELLS

If the relatively nonspecific mechanisms of the innate immune system fail, there is a highly developed network of DCs that is responsible for mobilizing the adaptive immune response, especially against invading pathogens and unwanted antigens.[70,75] DCs are also important phagocytic cells and, in general, are better APC than macrophages.[70] DCs are critical at bridging innate and adaptive immunity because of their extensive interdigitating physical extensions that reach between cells to provide a tight surveillance network within intraepithelial and subepithelial structures of the respiratory tract. Via this network, DCs continuously sample what the lung encounters. Because of their distribution, they are ideally positioned to participate in determining whether an inhaled moiety results in pulmonary immunity or tolerance. DCs express MHC and accessory molecules such as CD80, CD86, and CD40 making them excellent professional APCs to incoming naïve T cells.[76,77]

They also express a number of innate immune receptors including TLRs, NLRs, and CLRs for the recognition of various patterned motifs from inhaled antigen and pathogens. Lung DCs also express prostaglandin receptors that affect migratory behavior and cell maturation. They also express inflammatory receptors that detect DAMP proteins such as uric acid, ATP, and high-mobility group box (HMGB)-1. Their ability to sense, take up, process incoming molecules, and migrate to nearby draining lymph nodes for antigen presentation, allows DCs to bridge innate and adaptive immunity in the lung. In the lymph nodes, DCs present MHC peptide antigen complexes to T cell receptors (TCRs) on naïve T cells and in the appropriate context of costimulatory molecules on their cell surface and cytokines in the local microenvironment, naïve T cells are activated and proliferate. In the absence of appropriate costimulation or cytokines, DC and T cell interaction can lead to tolerance to an antigen, a mechanism that likely helps to avoid harmful immunologic response to harmless inhaled antigens.

DCs have been divided into several subsets based on their cell surface protein expression, origin, location, and specialized function.[78] In mice, three major subsets of DCs have been described: resident conventional DCs (cDCs), plasmacytoid DCs (pDCs), and inflammatory DCs. The resident cDCs expresses CD11c markers and have been divided into those that express CD11b, and those that are CD11b negative. At baseline, cDCs expressing MHC and CD11c line the conducting airways and are able to extend their dendrites into the airway lumen between tight junctions. In murine models, these cDCs can also express langerin and the mucosal integrin CD103. cDCs have good antigen presentation function. A migratory cDCs subset migrates to nearby lymph nodes after capturing inhaled antigen in the airway lumen, while lymphoid tissue resident cDCs reside in the lymph nodes and spleen and respond to antigen delivered via the draining lymphatics. pDCs are characterized by the expression of the surface marker Siglec-H (a bone marrow stromal antigen-1) and abundance of endosomal innate receptors TLR7 and TLR9, which make pDCs particularly important antiviral effectors because of their type I interferon production in response to viruses and bacterial DNA. Residing in the alveolar space are alveolar DCs, which classically express MHC class II and CD11c, and can have CD103 subsets. These alveolar DCs have been described to resemble human Langerhans cells.[79]

In response to innate and inflammatory stimuli, DCs are able to increase their numbers with rapid recruitment. These DCs have similar abilities to undergo antigen processing, to migrate to draining lymph nodes, and to modulate naïve T cells for either activation or tolerance. The inflammatory cDCs are normally not present in the lung. However, in the setting of inflammation and/or infection, circulating monocyte–derived $CD11b^+$ DCs upregulate CD11c, retain Ly6C, and can rapidly be recruited to the lung as inflammatory cDCs to respond to the stimulus. Comparable subsets of DCs in human lungs have been described such as myeloid type of DC that express both blood dendritic cell antigen (BDCA)1 or BDCA3 and HLA-DR and pDCs that express BDCA2 and CD123.[80–82]

Overall, DCs rely on neighboring structural cells, such as the airway epithelial cells, to influence the type of antigen-specific immune response. This epithelial–DC interaction in the lung plays an important role in immune homeostasis as well as the initiation and transition of innate immunity toward antigen-specific adaptive immunity. Some have proposed that extracellular matrix surrounding epithelial cells and DCs produces certain chemokines that allow for the activation properties of DCs.[83] Antigen presentation by APCs such as AMs and DCs is a required priming event for T cell activation to occur.

NEUTROPHILS

Neutrophils are derived from the bone marrow and require granulocyte colony–stimulating factor (G-CSF) for their proliferation and differentiation into their mature form. In times of stress or infection, neutrophils are mobilized from the bone marrow into the blood stream and eventually to sites of inflammation such as the lungs.[84] During this process, neutrophils become activated, generate free radicals, release granule contents, and participate in phagocytosis and degradation of invading microbes. Neutrophils are one of the first phagocytes recruited to sites of acute lung diseases, but they have a limited life span after their release from the bone marrow and within hours they are cleared with the resolution of the inflammation or disease process. However, in chronic lung diseases, neutrophils can be persistently recruited to the lung. Recruited tissue neutrophils are thought to live substantially longer, up to several days, than circulating neutrophils.[85] These neutrophils, which are modulated by the local microenvironment, are important for antipathogen responses, but they can cause significant lung tissue damage when they accumulate over longer time periods and release granule contents that can be toxic when released in an uncontrolled manner.[86,87] Neutrophils are able to respond to a number of particulate and soluble stimuli. They also have the ability to be primed prior to exposure to stimuli.[88] For example, neutrophils can be primed, or pre-activated, by stimuli such as IL-8, granulocyte macrophage colony–stimulating factor, platelet activating factor, and reactive oxygen species. This process helps prepare neutrophils for subsequent contact with pathogens by extending their life span, upregulating cell surface integrins (such as CD11b), optimizing NADPH oxidase assembly, and prolonging neutrophil functional longevity.[89,90] Neutrophils play an important role in innate immune response to infection, as these phagocytic cells also possess an impressive array of microbicidal weapons against invading pathogens that include toxic oxygen radical species and proteolytic enzymes. Local infiltration and tissue accumulation of neutrophils are mediated by chemokines that are produced by inflamed tissues. At sites of inflammation, mediators such as IL-1 or TNF-α induce or augment the expression of adhesion molecules on endothelial cells and circulating granulocytes. Intravascular circulating neutrophils slow down, roll along, and then anchor on the endothelium allowing entry to the lung interstitium and subsequently the alveolar space. Ultimately, inflammation will cease and, with successful containment of pathogens, resolution of inflammation often follows. This resolution of inflammation requires wound healing and restoration of the lung's normal structure and function. Mechanisms for resolution of tissue inflammation are not as well established, but include substances such as sphingosine-1-phosphate for restoring endothelial barrier and vascular permeability after endotoxin injury or natural mediators derived from essential fatty acids such as ω-3 fatty acids with their anti-inflammatory and pro-resolving properties.[91] Cytokines such as IL-10, TGF-β, and IL-1 receptor antagonist have also been implicated as important mediators of inflammatory resolution. An inability to resolve inflammation can lead to chronic inflammation in the lung as seen in a number of pulmonary diseases.

ADAPTIVE IMMUNE RESPONSES IN THE LUNG

An essential prerequisite for a successful host immune response is the ability to discriminate between self and nonself.[92,93] Adaptive immune responses, which can also be described as acquired, refer to antigen-specific immunity that often takes several days to mature and to develop a targeted response to a specific antigen. Ultimately, the goal of this adaptive response is to react with, and subsequently remove, a specific antigen. This type of immunity is one that develops throughout life and is the premise behind vaccination for pulmonary infections caused by pathogens such as influenza virus and *Streptococcus pneumoniae*.[94,95] From an immunologic standpoint, an antigen is defined to be a substance that reacts to antibody molecules or antigen receptors on lymphocytes. For example, B cells recognize antigen through specific B cell receptor (BCR) (and in this case immunoglobulin [Ig]), while T cells recognize antigen through specific TCR.

This recognition is through specific epitopes on the antigen being recognized. For T cells to recognize antigenic epitopes through TCR, cells recognize peptide epitopes from antigen only when presented by APCs (e.g., DCs and macrophages) in the context of appropriate MHC molecules. Adaptive immune responses are often divided into two major branches: humoral immunity and cell-mediated immune responses. Humoral immune responses rely on the production of antibodies in response to encountered antigens and are mediated by B lymphocytes. Cell-mediated immune responses involve various immune cells such as T lymphocytes, cytotoxic T lymphocytes, activated macrophages, and/or activated NK cells. Activated macrophages and NK cells destroy intracellular pathogens and stimulate nearby structural cells to secrete cytokines that influence other cells of the immune system. Cytotoxic T lymphocytes (often $CD8^+$ cells) are capable of destroying host cells that display foreign antigens on the cell surface, such as cells infected with viruses or intracellular bacteria, or cancer cells that display tumor antigens.

The adaptive arm of the immune response relies on specific recognition of antigens by B and T lymphocytes. These cells are highly equipped to be specific because of their receptors, thus the immune system is capable of recognizing a large number of antigens. The functionality of adaptive immunity is based on specific gene rearrangement that results in the generation of over 10^{11} different species of antigen receptors on the cell surface of T and B cells.[96–98] In addition to adaptive immune responses, this defense system targets pathogens that have evolved mechanisms to evade or to counteract innate immune responses. Therefore, the adaptive immune response builds upon, is shaped by, and itself shapes innate immune responses resulting in a strong interplay between the innate and adaptive arms of our immune system.[99] Adaptive immunity helps protect the lungs not only against a range of pathogens, but environmental inhalants, such as cigarette smoke, dusts, as well as allergens. The adaptive immune response is quite versatile, relies on exquisite specificity, and takes advantage of robust memory. This is especially evident when it comes to countering airborne antigens. It is estimated that our human body has the ability to recognize 10^7 or more different epitopes and can make up to 10^9 different antibodies, each with different specificity. These epitopes are antigenic determinants that are part of the antigen that is recognized by the antibodies generated by B cells, or by receptors on B and T cells. To recognize the immense number of different epitopes, the human body produces 10^7 or more distinct clones of both B and T lymphocytes, each with their unique BCR or TCR, respectively.[85,100] Among the large variety of BCRs and TCRs, there is bound to be at least one that has the epitope-binding site capable to recognize any antigen the immune system eventually encounters. Thus, the body is able to recognize any conceivable antigen it may eventually encounter, allowing for an adaptive immune response. However, only a few B and or T cells can recognize any one epitope, and these cells require an appropriate stimulus to allow for rapid proliferation. This process typically takes several days to occur. During this time, to achieve an effective and mature adaptive immunity, the invading pathogen could cause considerable damage, which is why innate immune responses are important at the early stage of infection, unless the host has already encountered the antigen before and has developed a specific adaptive immune response against the antigen. In this situation, during a repeated encounter with an antigen, adaptive immunity, which already has an established memory response, will take a shorter period of time to mobilize the adaptive effector cells to counter the invading antigen.

A majority of T cells express TCR with αβ variable chains, which permits them to recognize short peptide epitope of an antigen. Typically, precursor αβ T cells are recruited out of the bone marrow to the thymus. In the thymus, they undergo the process of positive, then negative selection to assure that the resultant T cells appropriately respond to peptide in the context of self-MHC, but not strong enough to cause potentially damaging autoreactivity. It is also during this thymic maturation that the T cells acquire the expression of either CD4 (allowing it to recognize peptide in the context of class II MHC) or CD8 (allowing it to recognize peptide in the context of class I MHC). Of note, only a small fraction, <5% of all precursor T cells, complete this process of thymic education and maturation. These cells become naïve T cells that circulate throughout the host to encounter their specific antigen for antigenic stimulation. Thymus-independent T cells do exist and have been identified in the gut, but are less well understood in the lung. However, these cells are limited in their diversity and recirculatory capacity and cannot compensate for the lack of thymus-dependent T cells.[101]

T cell development occurs in the thymus where bone marrow–derived premature naïve T cell precursors congregate.[102–104] These T cells start off as double negative cells (CD4 and CD8 negative). Upon acquisition of successful rearrangement of α- and β-TCRs, as well as expression of both CD4 and CD8 (making them double positive cells), these developing T cells undergo positive and negative selection. Since TCRs recognize antigen only in the context of MHC molecules, T cells must be "educated" to first recognize host MHC. During positive selection, double positive T cells that can recognize self-MHCs are selected for proliferation, and those T cells that do not recognize self-MHCs are removed through apoptotic cell death pathways. Positive selection also assures that the appropriate TCR selection will associate with the appropriate CD4 or CD8. For example, TCRs specific for MHC class II need to retain CD4, and lose CD8. If the reverse occurs, they will die via apoptosis. The same is true for T cells that are specific for MHC class I, which need to retain CD8 and lose CD4. Single positive thymocytes (either $CD4^+$ or $CD8^+$) undergo negative selection to remove potential autoreactive cells. Those T cells that have high affinity for binding self-proteins presented on self-MHCs are induced to upregulate genes that drive apoptosis, eliminating them in the thymus. However, if they escape this elimination process, they may subsequently react against self-antigens, which can result in autoimmunity. Positive selection identifies T cells that react with self-MHC and self-antigen.[105] Negative selection eliminates those that react strongly with self-MHC and self-antigen. Therefore, a successful T cell differentiation selects for MHC restricted TCRs with low affinity for self-antigens.

The underlying premise of the adaptive immune response that allows the system to recognize an unlimited scope of antigens that the host ultimately can encounter is the generation of antigen receptor diversity through gene translocation and recombination processes.[106] This process helps shape each receptor (either TCRs on T cells or BCRs, or the Igs on B cells). The TCRs have α- and β-chains, where there are many different V and J genes that can make up the TCR α-chain, and many V, D, and J genes that can recombine to form the variable TCR β-chain. Similarly, BCR undergoes similar gene recombination, including junctional diversity and somatic hypermutation that help generate a wide scope of BCR diversity. In the end, each T or B cell will exhibit a unique receptor capable of recognizing its unique antigen. For B cells, the BCR (Ig) recognizes specific epitopes of the antigen. For T cells, $CD8^+$ or $CD4^+$ T cells will express unique cognate complementary shaped peptide that is bound to either MHC class I or MHC class II molecules, respectively.

GENERATION OF AN IMMUNE RESPONSE

Upon cognate recognition of T cells with antigen/peptide presented on MHC molecules on APCs, the activated lymphocytes rapidly proliferate to produce large clonal populations (Fig. 20-3). Circulating memory T cells have the capacity to persist in the host for a long time and become mobilized and reactivated during a repeat encounter with the same antigen. This subsequent exposure of antigen leads to a more rapid and persistent production of effector cells in a process called clonal expansion. This allows the limited

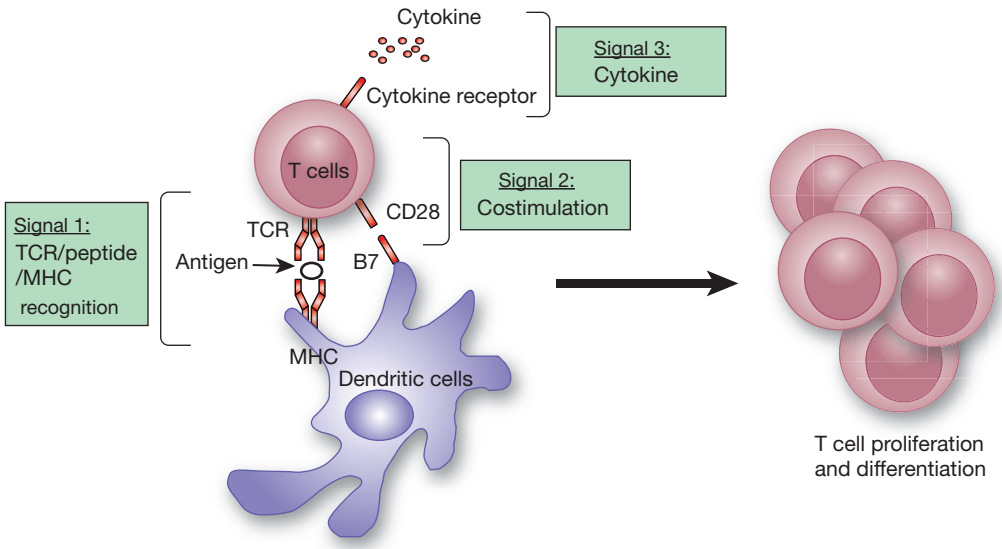

Figure 20-3 Generation of an immune response. Dendritic cells (DCs) and other antigen-presenting cells (such as macrophages) link the innate and adaptive immune response. DCs from the innate immune system present their antigen to naïve T cells at local draining lymph nodes; in the case of the respiratory tract, these are the mediastinal draining lymph nodes. T cell receptor (TCR) ligation to MHC molecules associated with peptides processed from antigen (e.g., pathogen, allergen, toxin) by DCs provide "signal 1." The binding of costimulatory molecule CD28 on lymphocyte to CD80 and CD86 expressed by DCs ("signal 2") leads to T cell activation and cell lineage differentiation. "Signal 3" is provided by the polarizing cytokine signals from nearby innate immune cells and local tissue environment. Depending on the type of antigen that is presented and the nature of cytokines in the microenvironment, innate DC cells direct the development of various T helper lymphocyte lineages that play crucial role in adaptive immune system.

T cell number, with the appropriate antigen recognition and specificity, to expand and proliferate when necessary. During adaptive immunity, pathogens encountered in the mucosal surfaces and, in the lung, the airway mucosa, are transported to draining lymphoid organs where antigen is recognized by naïve B and T lymphocytes, which leads to cell activation. These activated B and T cells proliferate and differentiate into effector cells.

Naïve T cells undergo development and maturation in the thymus and circulate out of the thymus to mucosal surfaces and lymph nodes to encounter antigens.[107,108] APCs, such as macrophages and DCs from the innate immune system, present endocytosed foreign antigen to naïve T cells at local draining lymph nodes. APCs present MHC class II–associated peptides processed from pathogens to $CD4^+$ T cells that express specific TCR against the particular antigen peptide/MHC complex. The TCR–CD3 complex binds to the antigen peptide MHC complex on APC, and this interaction triggers intracellular signaling pathways that provide the first signal, "signal 1," of T cell activation. Upon a subsequent encounter with the same antigen, memory T cells are reactivated using these same TCR pathways.[107] A second signal, "signal 2," is required to ensure that naïve T cells are responding to foreign antigen. This process involves binding of CD28 on lymphocytes to costimulatory molecules CD80 and CD86 that are expressed only by activated APCs. "Signal 2" leads to T cell lineage differentiation. Without "signal 2," during the initial antigen exposure, T cells become anergic and are unable to respond to subsequent antigen encounters, a process that avoids or minimizes production of autoreactive cells, and thus autoimmunity against self-antigens. Once T cells are activated by the two signals, only "signal 1" is required for subsequent future activation; an example of this is seen with memory T cells providing a faster immune response. After two-signal activation, Th cells proliferate and produce multiple cytokines, and this includes IL-2 production for autocrine activation by upregulation of the IL-2 receptor, CD25. "Signal 3" involves polarizing cytokine signaling from innate immune cells that allow for the development of specific types of immune responses.[109] Inflammatory cytokines such as IL-12 can act directly on naïve T cells to provide a third signal, along with antigen and IL-2, to optimally activate differentiation and clonal expansion. $CD4^+$ Th cells play an important role in mediating various types of immune responses through their cytokine release. There are also other CD4-expressing T cells that are not Th cells; these include some cytotoxic T cells, NKT cells, and regulatory T (Treg) cells.

■ ACTIVATION OF NAÏVE HELPER T CELLS

$CD4^+$ T cells play an important role in adaptive immune responses. Proliferating Th cells that develop into effector T cells can differentiate into one of several lineages (Fig. 20-4).[110] Depending on the type of antigen that is presented, the strength of the TCR signal, and the nature of cytokines in the microenvironment, innate APCs (typically DCs) direct the development of various Th lymphocyte lineages. The differentiation of each $CD4^+$ T cell subset is associated with the expression of specific transcription factors that lead to production of an array of cytokines that help orchestrate a specific host response. $CD4^+$ Th cells, based on their cytokine production, help dictate this type of response. The most studied and established Th subset is the dichotomy between type 1 and type 2 responses, often called T helper 1 (Th1) and T helper 2 (Th2) responses.

Th1 cells promote cell-mediated immune responses and are required for host defense against viral and intracellular bacterial pathogens. Th1 responses can be characterized by the secretion of IFN-γ, IL-12, IL-10, and TNF-α/β, and stimulation of classically activating macrophages to tackle intracellular pathogens.[111] These cytokines promote macrophage activation, nitric oxide production, and cytotoxic T lymphocyte proliferation, leading to phagocytosis and destruction of microbial pathogens. Th1 responses in the lung are important because AMs encounter antigens to activate these specific effector responses. IL-27 signaling in naïve $CD4^+$ T cells induces STAT1-dependent expression of the Th1-specific transcription factor, T-bet, which promotes expression of IFN-γ and IL-12 receptors. Subsequent activation stimulates STAT4-dependent

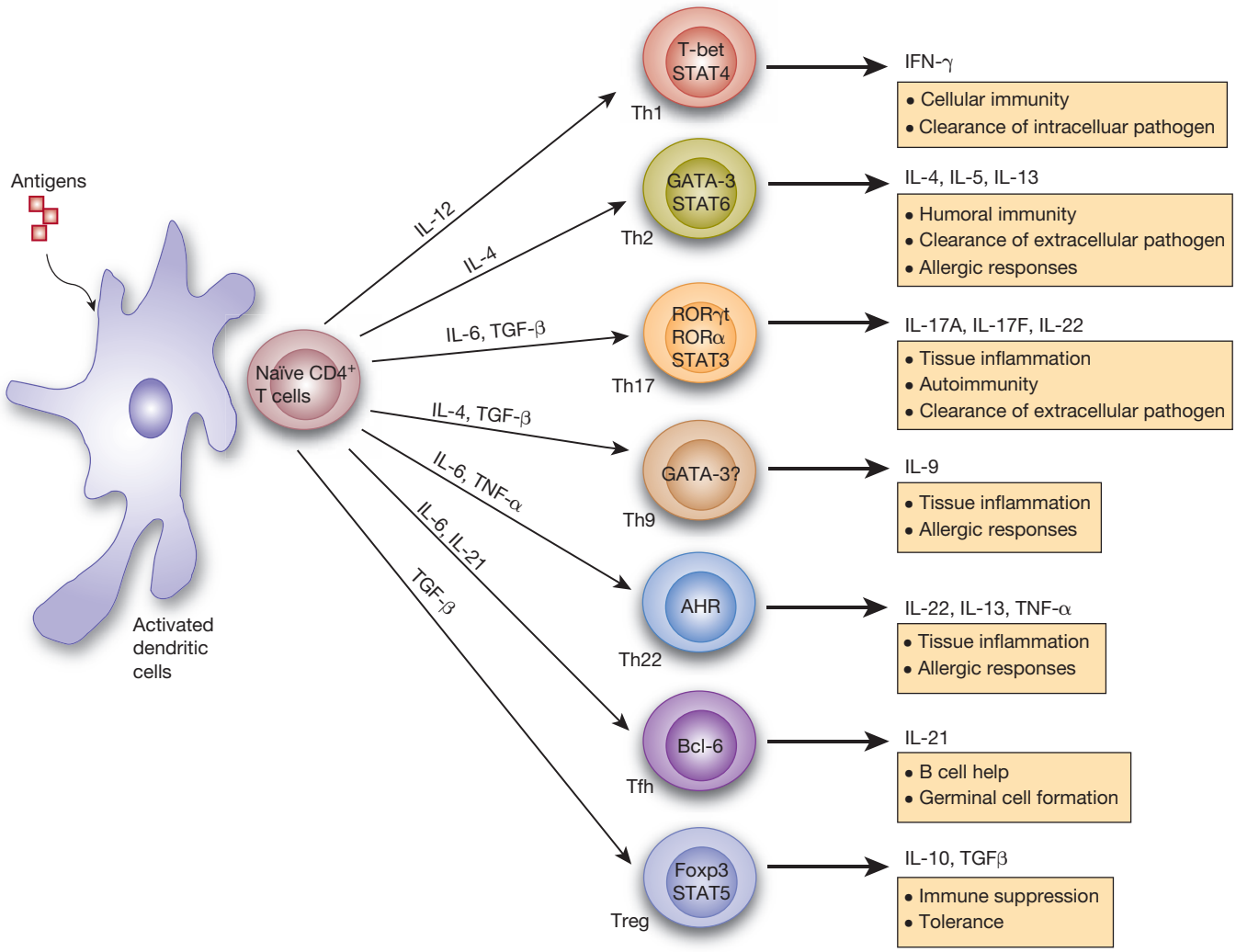

Figure 20-4 T cell differentiation. Naïve CD4$^+$ T cells differentiate into one of several T helper (Th) cell lineage based on signals from innate immune cells induced by antigenic and inflammatory stimuli as presented by activated DCs. The resultant products of differentiated T cells subsequently help tailor the immune response to various encountered antigen scenario. Th cell differentiation is classically regarded as a dichotomy between two main cell types, termed Th1 and Th2. Th1 cells produce IFN-γ as the signature cytokine and are predominantly involved in cell-mediated immunity against intracellular pathogens. In contrast, Th2 cells do not produce IFN-γ and instead produce IL-4, IL-5, and IL-13. Th2 cells are effective activators of B cell proliferation and antibody production, mediating humoral immunity essential for the eradication of extracellular pathogens as well as mediating allergic type of inflammation. Th17 cells have been described as a distinct Th subset characterized by the production of IL-17A, IL-17F, and IL-22, contributing to host defence against extracellular pathogens particularly on mucosal surfaces, as well as in the pathogenesis of autoimmune diseases. Recently, more Th cell subsets have been described such as Th9 and Th22 cells that participate in allergic type of immune responses. Other stimuli cause CD4$^+$ T cells to become regulatory T (Treg) cells that help dampen immune responses. Other stimuli allow CD4$^+$ T cells to reside in lymph nodes, differentiate into follicular helper T (Tfh) cells and provide help to B cells. The various Th subsets require activation of specific master regulator transcription factors such as T-bet, GATA-3, RORγt, Bcl-6, and Foxp3 as well as various STAT molecules for their differentiation as indicated in the diagram. Bcl-6, B cell lymphoma-6; Foxp3, forkhead box p3; ROR, retinoid-related orphan receptor; AHR, aryl hydrocarbon receptor; STAT, signal transducer and activation of transcription.

IFN-γ production and Th1 differentiation. While Th1 cells are critical for the clearance of intracellular pathogens, exaggerated Th1 responses can result in lung pathology (e.g., autoimmune disease, interstitial lung disease, and COPD). Th2 responses are characterized by production of IL-4, IL-5, IL-9, IL-13, and IL-25, and these cytokines favor antibody production and class switching to IgE and IgG. Th2 cells are required for humoral immunity and play an important role in coordinating immune responses to extracellular pathogens.[112] Th2 differentiation occurs in the presence of IL-4 and either IL-2, IL-7, or thymic stromal lymphopoietin (TSLP). IL-4 stimulates naïve CD4$^+$ T cells to induce STAT6-dependent expression of GATA-3, the transcriptional regulator of Th2 cells, which promotes IL-5 and IL-13 expression, and stimulates the expansion of Th2 cells, while suppressing the differentiation of other T cell subtypes. In addition to IL-4–induced activation of GATA-3, IL-2, IL-7, or TSLP is required during Th2 differentiation to activate STAT5, which cooperates with GATA-3 to promote T cell production of IL-4. IL-4 regulates clonal expansion of Th2 cells and, along with IL-13, promotes B cell production of IgE and alternative macrophage activation. Th2 cells also produce IL-5 to stimulate eosinophil activation and survival, or IL-9 to promote mast cell activation. Th2 responses are typically important host immune responses to

extracellular pathogens such as parasites or helminths. However, excessive Th2 signaling has been implicated in the development of chronic allergic inflammation and asthma.

T helper 17 (Th17) cells are involved in the immune response against specific fungi and extracellular bacteria.[113] Th17 cells develop from naïve $CD4^+$ T cells in the presence of TGF-β and IL-6, cytokines that induce STAT3-dependent expression of IL-21 and the transcription factor RORγt. IL-21 and IL-23 help establish, regulate, and develop (via clonal expansion) Th17 cells. RORγt-induced gene expression leads to the secretion of IL-17A, IL-17F, and IL-22. Cytokines secreted by Th17 cells stimulate chemokine secretion by resident cells, leading to the recruitment of neutrophils and macrophages to sites of inflammation. These cells produce additional cytokines and proteases that further augment immune responses. For human Th17 differentiation, Th17 polarization requires IL-1β, IL-6, IL-21, and IL-23, and is less dependent upon TGF-β. While Th17 cells play a central role in eliminating harmful microbes, persistent secretion of Th17 cytokines can promote chronic inflammation and has been implicated in lung diseases such as COPD, sarcoidosis, and granulomatous diseases. The role of cytokine polarization in lung diseases has been studied in transgenic animal modeling systems where specific cytokines are over-expressed, or cytokine receptors or transcriptional factors such as GATA-3 and T-bet are modified. These studies have helped to elucidate the effector function of individual cytokines and their pathophysiologic consequences in the lung.[114]

T helper 9 (Th9) cells secrete high levels of IL-9, CCL17, CCL22, and in mouse, IL-10. Th9 cell differentiation requires the presence of TGF-β and IL-4, which induce transcription factors PU.1/Spi-1 and IRF 4 that regulate IL-9.[115] Cytokines such as IL-1β, IL-6, IL-21, and type I interferons all enhance Th9 differentiation, and IL-2 and IL-25 promote IL-9 secretion. Different from Th2 cells, Th9 cells do not express IL-4, IL-5, or IL-13. Th9 cells are important for host defense against parasitic and helminthic infections, but they are also associated with the development of chronic allergic inflammation, airway remodeling, and autoimmune diseases.[115,116] T helper 22 (Th22) cells primarily secrete IL-22, IL-13, and TNF-α. Similar to Th17 cells, Th22 cells express IL-22, but in contrast, they express several fibroblast growth factors (FGFs) and do not express IL-17, IL-4 (Th2 marker), or IFN-γ (Th1 marker).[117] Th22 cells differentiate in the presence of IL-6 and TNF-α, and their differentiation is inhibited by TGF-β.[118] Th22 cells can be regulated by the aryl hydrocarbon receptor (AHR) transcription factor. IL-22 secreted by Th22 cells primarily affects epithelial and stromal cells rather than other hematopoietic cells, which lack a functional IL-22 receptor. Th22 cells contribute to allergic inflammation in the lung, but their role in skin immunity is better established.

Another subset of $CD4^+$ T helper cells are follicular helper T cells (Tfh) which regulate the development of antigen-specific B cell immunity.[119,120] These Tfh cells help B cells generate antibody-producing plasma cells and long-lived memory B cells. Tfh cells are identified by Bcl-6 (a transcriptional repressor) expression and IL-21 secretion. IL-6 and autocrine IL-21 signaling induce Th cells to express Bcl-6, which controls Tfh cell differentiation and suppresses differentiation of Th1, Th2, and Th17 cells. These Tfh cells have been implicated in several autoimmune diseases, including systemic lupus erythematosus and Sjögren syndrome. The actions of Th cells are balanced by Treg cells, a subpopulation of CD4-expressing cells that specializes in suppression of T cell–mediated immune responses.[121,122] Treg cells are identified by their expression of CD25 and the transcription factor Foxp3. Treg cells are capable of regulating and suppressing immune responses. They produce cytokines such as TGF-β and IL-10 that have immune suppressive activities. Of note, failure to activate an appropriate T cell response can lead to chronic infection, while exaggerated T cell responses can cause excessive tissue damage and are associated with inflammatory and autoimmune diseases. During lung infections, Th1 may mediate lung damage in response to infection. Thus, downregulation of such Th1 responses may help preserve lung integrity. Th2 responses are known to be important during the wound healing process, but if this response is prolonged and uncontrolled, it can worsen the injury and contribute to fibrosis.

Considering the diverse and important roles Th cells play in the immune system, it is not surprising that these cells influence the immune response in many pulmonary diseases. Th cells can make occasional mistakes or generate responses that would be considered harmful. In the worst-case scenario, Th cell responses may be disastrous and prove fatal to the host. Fortunately, this is a very rare occurrence. The adaptive immune system must achieve a balance of sensitivity to respond appropriately to foreign antigens, without responding to host antigens and damaging self. When the immune system responds to very low antigen levels that it should not respond to, a hypersensitivity response, such as seen in airway allergies and autoimmune lung diseases, ensues. There are four general types of hypersensitivity reactions that have been described: Type 1 reactions, such as in asthma and allergic lung diseases, involve IgE antibodies and a Th2 response; Type 2 and Type 3 hypersensitivity responses involve the role of autoimmune and low affinity antibodies (and, in some instances, it is felt that Th2 cytokines promote such disorders); and Type 4 reactions, also known as delayed-type hypersensitivity, are the result of chronic inflammation and activation of lymphocytes and macrophages, typically a Th1 cytokine response. Another T cell subtype more recently discovered and less well studied is the γδ T cell subset.[123,124] These T cells have TCR with γδ-chains, rather than the conventional TCR chains. They represent 1% to 5% of circulating lymphocytes and are often found in mucosal surfaces, such as the airways. γδ TCRs have more limited repertoire diversity, and are considered, at times, invariant because they are only able to recognize limited types of antigens. These γδ T cells have been shown to be important in maintaining normal airway responsiveness or tone, as well as in their immunoregulatory role in numerous infectious and noninfectious diseases in the lung.[123,125]

CONCLUSIONS

The lung is a vast organ composed of conducting airways, alveoli, and tissue parenchyma that is highly specialized to sample the diverse antigens that we breathe in. The lung is equipped with a well-orchestrated immune system to clear particulate debris and to eliminate inhaled pathogens and toxins to protect the delicate capillary–alveolar barrier system that is critical for gas exchange. The immune system in the lung has evolved complex and diverse innate and adaptive immune responses to accomplish these critical functions of host defense.

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CHAPTER 21

Lymphocyte- and Macrophage-Mediated Inflammation in the Lung

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INTRODUCTION

The lung receives a continual flow of foreign infectious and noninfectious antigens during respiration. Like the gut, genitourinary tract, and skin the lung is one of the interfaces of the sterile body with the environment. The lung's immune defense system and inflammatory mechanisms are poised to deal with this role. In this chapter we will consider the inflammatory and immune roles of two key cells of hematopoietic origin: the lung lymphocyte and the lung macrophage.

While these two cell types interact extensively and might even be considered co-dependent in many situations, they represent two very different arms of the inflammatory response. The macrophage, as a phagocytic cell, is of ancient phylogenetic lineage. It is a sentinel of the innate immune system. As such, it is not antigen specific but it is triggered by many inflammatory stimuli through both specific and pattern recognition receptors. Lymphocytes are present only in vertebrates and represent a significant refinement in the inflammatory response by the ability to recognize and adapt to specific antigens and discriminate between self and nonself. The functional distinction between these two arms of the immune system is blurring with the recent discovery of innate lymphoid-derived immune cells and the appreciation of multiple functions of macrophages in the inflammatory response.

Macrophages or dendritic cells (DCs) are required for optimal presentation of antigens to lymphocytes, and for optimal lymphocyte activation and cytokine production. Conversely macrophage microbicidal function and release of arachidonate and oxygen metabolites is influenced by cytokines produced by activated T lymphocytes and phagocytosis is markedly enhanced by antibodies produced by B lymphocytes. The cooperation between these two cell types represents a cornerstone of lung defense against noninfectious antigen challenge or microbial infection. Another chapter will deal with acute lung inflammation mediated by neutrophilic leukocytes. In this chapter we will present a brief overview of the macrophage and lymphocytes in the human lung, their function and interactions, and a synthesis of their role in lung inflammation and disease.

We will assume a basic knowledge of immunology. However, an explanation of the terminology used in this chapter is appropriate. Many surface receptors expressed by immunologic cells have had multiple names based on different functions. In the past 30 years these terms have been grouped together in a series of standardized "clusters of differentiation" (CD) for the purpose of standard nomenclature. A list of the CD markers referred to in this chapter, other names used for them, and their putative functions are included in Table 21-1.

TABLE 21-1 Cluster of Differentiation Antigens and Surface Molecules Discussed in this Chapter

Name/CD Designation	Function
CD1	Accessory molecule for antigen presentation on APCs
Sheep RBC receptor/CD2	Accessory molecule for T lymphocyte activation, adhesion receptor (ligand LFA-3)
CD3	Signaling subunit of TCR
αβ TCR	T-cell receptor for antigen
γδ TCR	Alternate form of the T-cell receptor for antigen
CD4	T-cell coreceptor (ligand MHC Class II); marker for helper/inducer cells
CD8	T-cell coreceptor (ligand MHC Class I); marker for cytotoxic cells
CD11a,b,c	α chains of the β2 integrin/CD18; CD11a (LFA-1); CD11b (Mac-1/CR3); CD11c (CR4)
CD14	Macrophage receptor for lipopolysaccharide
CD18	β2 integrin chain
CD25	p55 IL-2 receptor; T-cell activation antigen (TAC)
HLA-DR	Class II MHC; expressed on APCs; activation antigen for T cells
CD28	Stimulatory accessory molecule for T lymphocyte activation (ligands B7–1/CD80, B7–2/CD86)
CTLA-4/ CD152	Inhibitory accessory molecule for T lymphocyte activation (ligands B7–1/CD80, B7–2/CD86)
CD29	Common β chain of the β1 integrins
VLA-1–6/ CD49a–f	Adhesion molecules; α chains of the β1 integrins (ligands ECM proteins)
VLA-4/α4β1 integrin	Adhesion molecule (ligand VCAM-1 expressed on endothelium, fibronectin)
α4β7 integrin	Adhesion molecule (ligand VCAM-1, fibronectin)
HML-1/αEβ7 integrin	Adhesion molecule (ligand epithelial cell carbohydrate antigen)
ICAM-1/CD54	Cell adhesion molecule for cell–cell interaction (ligand LFA-1/CD11a/CD18)
B7–1/CD80, B7–2/CD86	Accessory molecules for T-cell activation; ligands CD28 (enhances) CTLA-4 (inhibits)
CD95/Fas	Receptor for Fas ligand, induction of apoptosis
VCAM-1/ CD106	Adhesion molecule expressed on activated endothelium (ligand α4 integrins)
CCR3	Chemokine receptor (CKR) for CCL11/eotaxin
CCR4	CKR for CCL17/TARC (thymus and activation-regulated chemokine)
CCR5	CKR for CCL4
CCR7	CKR for CCL21/SLC (secondary lymphoid-tissue chemokine)/TCA-4 (T-cell activation-4)

CD, cluster of differentiation; RBC, red blood cell; TCR, T-cell receptor; VLA, very late activation antigen; LFA, lymphocyte function–associated antigen; APC, antigen-presenting cells; MHC, major histocompatibility complex antigen; CR, complement receptor; ECM, extracellular matrix; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; CCR, chemokine CC type receptor; CCL, chemokine CC type ligand.

LYMPHOCYTES IN THE LUNG

Lymphocytes are much more abundant in the lung than previously documented. Recent estimates from CD3+ stained cells in histologic sections of normal human lung approximate the resident T-cell pool to be 10 billion T cells, which is comparable to the number of T cells in human blood.[1] These resident T cells have been examined in detail (see[2]) and are primarily memory T cells with a resident effector phenotype (rTem). In the normal lung these lymphocytes are distributed in one of four compartments (Fig. 21-1). The compartments include lymphocytes at the epithelial surface (LES) including those in the bronchoalveolar space; lymphocytes associated with the epithelium in lymphoid aggregates (also known as bronchus-associated lymphoid tissue [BALT]); interstitial and intraepithelial lymphocytes (IELs); and an intravascular pool. Although the presence of BALT in normal human lung is controversial, it is clear that BALT is present in the setting of infection and possibly with chronic airway inflammation.[3,4] Each compartment has a distinct phenotypic and functional repertoire. It is not yet clear whether there is a sequential influx of lymphocytes from the blood/intravascular pool to interstitium or BALT and finally to the epithelial surface, or whether lymphocytes are destined to reside in one or another of these pools from the time of maturation and/or activation. The absence of afferent lymphatics to the lung dictates that the intravascular pool is the original source of lymphocytes destined to one of the pulmonary compartments. The exact nature of influx and turnover of normal lung lymphocyte populations is not clear. However, the identification of organ- and lung-specific homing chemotactic cytokines (chemokines) with selective distribution of their cognate receptors raises the possibility that the origins of the populations of each compartment are distinct and for intercompartmental trafficking to occur, there must be site-specific signals that alter the chemotactic receptor repertoire in situ.

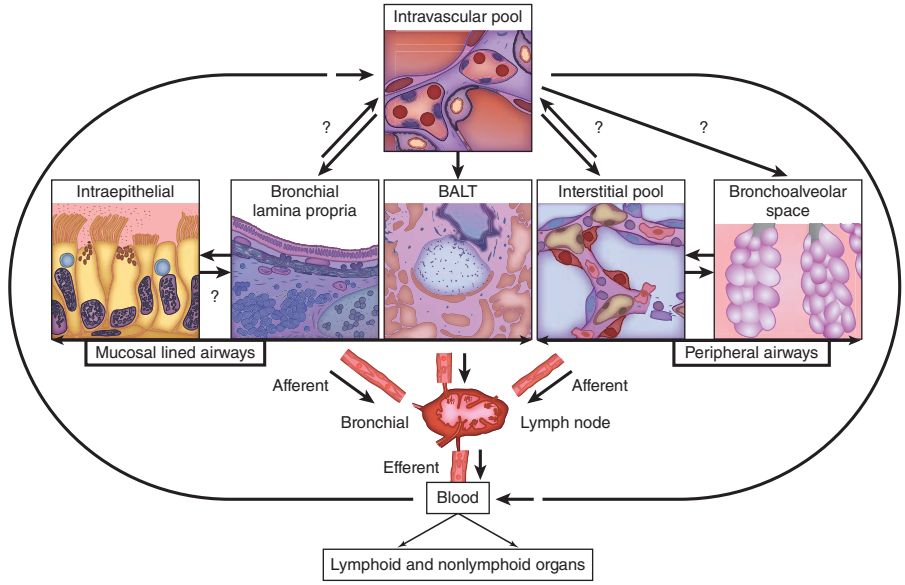

Figure 21-1 Lymphocytes are found in the lung in distinct sites. These include LES (including those at the bronchoalveolar surface); the interstitial and intraepithelial lymphocytes (IELs), bronchus-associated lymphoid tissue (BALT) which are centers of airway antibody production; and an intravascular pool. Lymphocytes travel from lymph nodes to blood and into lung via interaction with lung endothelial cells. Arrows indicate hypothesized trafficking from one pulmonary compartment to another. Some lymphocytes from these various compartments may be able to exit the lung back to lymph nodes, and others become effete and die. For further explanation see text. *(Reproduced with permission from Pabst R. IS BALAT a major component of the human lung immune system? Immunology Today. 1992;13(4):119–122.)*

LYMPHOCYTES AT THE EPITHELIAL SURFACE (LES)

LES and IELs are best studied as lymphocytes from the bronchoalveolar space, are easily recovered from the lung using bronchoalveolar lavage (BAL). Although in normal nonsmoking individuals lymphocytes make up only about 5% to 15% of the 10^5 cells found per milliliter of BAL fluid, lymphocyte numbers may increase dramatically during an inflammatory response.[5–7] LES differ markedly from blood lymphocytes suggesting either a selection bias or organ-specific maturation process that occurs between the blood and lung (Table 21-2). Approximately 70% of LES are T cells; the CD4/CD8 ratio of T cells is approximately the same as in the blood, though with a larger scatter among individuals.[8] Over 70% of BAL T cells are of the previously activated memory type as determined by expression of a low–molecular-weight form of the leukocyte common antigen CD45 (CD45RO),[9,10] and many have been chronically activated as shown by expression of the $\alpha 1\beta 1$ integrin. The balance of BAL T cells are naive, based on their expression of one of the chemokine receptors CCR7,[11] which primarily identifies T cells that have not come into contact with their cognate antigen. It is unclear what the T-cell representation in BAL is of IEL compared to LES. LES are more likely than blood T cells to express the activation antigen HLA-DR, and CD8+ (cytotoxic/suppressor) and LES are more likely to express markers associated with cytotoxic cell function.[5] An unusual population of memory cytotoxic cells which lack the accessory molecule CD28 has also been described in normal LES.[12] In the neonatal rodent lung the majority of T cells express the gamma-delta T-cell receptor, and account for about 20% of resident (whole lung) pulmonary T cells in adult mice—a percentage that is markedly upregulated with infection.[13] By contrast, the vast majority of human T cells at the epithelial surface are alpha-beta+. The function of the small population of gamma-delta LES T cells in humans remains unknown, but functional similarities to homologous mouse cells suggest that their primary role is to regulate the primary immune response.[14] There are a variable number of natural killer (NK) (including NK-T) cells in this compartment as might be expected in an area of microbial and antigen assault. However, the bulk of NK activity in the lung is found in the interstitial population.[15,16] B cells are also present in the LES population derived by BAL. They have been documented to produce antibodies of all types, with their primary role being to provide mucosal immunity through the secretion of IgA.[5] It is unknown whether there are selected B cell populations among LES.

The source and fate of these T and B cells are unknown. It seems reasonable to hypothesize that epithelial surface T cells (and other lung T cells) emerge from the circulation, perhaps proliferate locally and differentiate further while in the lung, and then die or recirculate.[17] The appearance of labeled blood T cells in LES have been found in the circulation. The predominant memory phenotype of epithelial surface and interstitial T cells strongly suggests that such differentiation occurs before entry into the lung. Once in the epithelial compartment it

TABLE 21-2 Characteristics of Lung Lymphocytes[a]

Location	Number	Cell Type	Comments
Epithelial surface	10^4/mL BAL; approx 10^8 total	CD4/CD8 ratio = blood 70% T cells >90% memory cells 40% express $\alpha_E\beta7$ integrin (70% of CD8+) Memory CTL NK phenotype present, decreased function	Specialized for interaction with epithelial cells. First line of defense?
BALT	? If present in normal (i.e., uninflamed) human lung	B cells in center T cells scattered in center and surrounding follicle	Local antigen sampling and antibody production
Interstitium	10^7/g lung tissue; approx 6×10^9 total	CD4/CD8 ratio < blood >90% memory T cells Bulk of NK activity	With intravascular, equal to total blood lymphocyte pool.
Intravascular	? Characteristics in human	?	Possible mobilizeable cells poised for lung entry

BAL, bronchoalveolar lavage; CD, cluster of differentiation; CTL, cytotoxic T lymphocyte; BALT, bronchus-associated lymphoid tissue.
[a]For a review, see Reference.[15]

appears that bronchial IEL T cells can be long lived potentially surviving within the epithelium for several months, in contrast to the short life span of lymphocytes in the lamina propria.[18,19]

Many LES adhere to and interact with airway epithelial cells through the expression of a unique adhesion molecule (HML-1/αeβ7 integrin).[20,21] This integrin is expressed on 40% of LES (60% of CD8+ cells are HML-1+ while fewer CD4+ cells express it) and on intestinal lymphocytes, but only rarely on blood or lung interstitial lymphocytes. It is likely that local influences, such as epithelial-derived cytokines like transforming growth factor beta-1 (TGFβ1), result in the expression of this molecule on LES.[22–24] Epithelial cells are directly stimulated by bacteria to release specific chemokines and cytokines (e.g., interleukin (IL)-8, MIP2α (CXCL2), MIP3α (CCL20), IL-7, IL-15) depending on the organism and pathogenicity.[25] These ligands can bind surface chemokine and cytokine receptors on adjacent LES, suggesting that these cells are not necessarily effete or dying cells, which are present in the airway only to be cleared by the mucociliary escalator and expectorated. Rather, they include a specialized lymphocyte population involved in the surveillance of the airway and interaction with epithelial cells. The possibility that LES re-enter the interstitium and lymphoid tissue has been confirmed experimentally in rats.[26] In addition to their interaction with airway epithelial cells, LES directly interact with mucosal DCs, whose phenotype directs further T-cell phenotype evolution (see Lymphocyte Activation in the Lung, below)

LES can be stimulated to proliferate, produce cytokines and antibodies, and to perform cytolytic functions. However, they are in general hyporeactive in proliferative or antibody responses to antigen or mitogens when compared to blood T cells or even when compared to memory T cells in lung interstitium. The reason for this is not known, but may relate to immunosuppressive influences in the airways, including alveolar macrophages (AMs),[27] local production of TGFβ1,[28] the immunosuppressive activity of pulmonary surfactant lipids or proteins,[29] and the possible presence of other immunomodulatory cytokines like IL-10 and IL-16.

■ BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT)

BALT is the term applied to localized subepithelial collections of lymphocytes in the airways, and is a secondary lymphoid tissue analogous to other types of mucosa-associated lymphoid tissue (reviewed by Berman et al.,[6] in-depth review by Randall[30]). BALT is present in normal rodent airway and increases in amount with age. Current evidence suggests these structures are uncommon or absent in adult humans but are present in childhood and may appear and proliferate later in life in response to infection or chronic inflammation.[3,30–35] These data suggest that inflammation or infection induces the development of these lymphoid aggregates in humans, and are termed inducible BALT (iBALT) to distinguish them from the classically defined BALT observed in rodents, which is believed to be formed independent of antigen.[36]

Classically defined BALT is similar to gut-associated lymphoid tissue (GALT; e.g., Peyer's patches) in appearance, association with epithelium and a blood vessel, presence of specialized cuboidal or high endothelial venules characteristic of lymphoid tissues, and a specialized thinned overlying epithelium facilitating antigen entry from the bronchial lumen and exit of lymphocytes and lymphocyte products. Immunohistochemistry has revealed a preponderance of B cells staining with IgM, IgG, and IgA, with a scattering (approximately 20%) of T cells, especially CD4+ helper cells within and surrounding the aggregate. BALT lacks organized germinal centers found in other secondary lymphoid tissue. The resemblance of BALT to GALT, as well as the similarity of lymphocyte recirculation patterns from lung- and gut-associated lymphoid tissue has suggested to some authors that these structures represent a common mucosal immune system. In this paradigm, recirculating blood lymphocytes exit into these structures which provide an efficient exposure to antigens sampled from the environment. Activated memory cells are then a source of local antibody production, and they may disperse through the circulation to other mucosal sites to provide dissemination of immunologic memory.

Despite these observations that have been made in rodents, several issues continued to limit what we can infer about BALT function in humans. They include its near absence in normal human airways and limited presence in experimental animals which are primarily observed in pathogen-free colonies. In fact, the infrequent appearance of BALT in humans and mice has led some to doubt whether BALT is an important secondary lymphoid organ.[31] However, there is accumulating evidence that iBALT plays a role in the adaptive immune response to infection.[36] In this new paradigm, infection and inflammation trigger the development of these localized lymphoid tissues through recruitment and priming of naive lymphocytes thereby generating antigen-specific lymphocytes in situ. At the same time, infection and inflammation activate local antigen-presenting

cells, which migrate to conventional secondary lymphoid organs (i.e., lymph nodes) for priming and activation of effector cells. Thus, these local lymphoid tissues are capable of not only expanding effector cells that were primed in conventional secondary lymphoid organs but also initiating primary immune responses in situ. In support of this paradigm, splenectomized lymphotoxin-α-null mice that lack the ability to form any secondary lymphoid tissues are still able to develop iBALT[36] in response to infection suggesting distinct mechanisms govern over these lymphoid tissues.

The uniqueness of iBALT in humans and mice is highlighted by the structural difference compared to constitutive BALT in rodents. The iBALT can vary in organization from small clusters of B cells, T cells, and DCs to well-developed follicular aggregates and unlike constitutive BALT, which is found in the upper airway of rodents, iBALT is found in perivascular, peribronchial, and even interstitial areas in the lower airways of the lung.[36] In humans, the specialized overlying epithelium has not been characterized.[37] B-cell follicles, which are seen in iBALT, are centered around CD21-expressing follicular dendritic cells (FDCs)[36] and separated by interfollicular regions containing resident CD11c+ DCs and both CD4+ and CD8+ T cells.[38] The lymphocyte homing chemokines CXCL13 and CCL21 are required for recruitment of naive lymphocytes at HEVs, but unlike conventional lymphoid organs their secretion appears to be independent of LTα.[36] IL-17–producing T cells[33] and CCR7-dependent Tregs[39] have been shown to be important for development of iBALT.

Knowledge of the role of iBALT in the lung is still evolving. BALT development appears to be part of the normal immune response to infectious antigens. The role of BALT expansion in a wide variety of chronic lung diseases such as hypersensitivity pneumonitis, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis is less clear.[40]

INTERSTITIAL LYMPHOCYTES

Lymphocytes are rarely seen in histologic sections of normal human lung, and there are no established techniques to study these cells as an exclusive, pure population. However, several investigators have prepared lymphocytes from human lungs extensively washed to remove airway surface cells using minced tissue and enzymatic digestion. The resulting population of pulmonary infiltrating lymphocytes in normal humans appears to be distinct from lymphocytes recovered from normal BAL.[41,42] Specifically, approximately 20×10^6 mononuclear cells were found per gram of wet lung tissue; of these 70% were lymphocytes, of which 90% were CD2+ T lymphocytes. There was enrichment for memory T cells similar to that seen in LES, but the CD4/CD8 ratio among IL T cells was lower than that seen in blood or LES. Memory T lymphocytes from the interstitial compartment can be stimulated to produce cytokines, and to proliferate in response to IL-2 despite a decreased proliferative response to mitogens.[43] Most, if not all NK activity in the lung has been localized to the interstitial compartment.[44] The exact origin, fate, and function of interstitial lymphocytes are not known.

INTRAVASCULAR LYMPHOCYTES

The presence of this lymphocyte pool has been convincingly shown in animals, especially the pig.[32] Experimental data includes lung perfusion studies showing the continued slow elution of lymphocytes from lung following elimination of red blood cells. The presence of an intravascular lymphocyte pool in humans has not been directly confirmed. However, labeled lymphocytes injected into humans are "held up" in the lung whether injected intravenously or intra-arterially (reviewed by Berman et al.[6]). These data confirm the more recently detected presence of homing receptors on the surface of lymphocytes that match cognate organ-specific chemokine expression.[45] Therefore, this phenomenon likely represents margination of lymphocytes in capillaries due to adhesion molecule interactions. Complete phenotypic characterization of this pool in the human is unknown, as is the size and role of this pool in populating interstitial or epithelial lymphocytes.

LYMPHOCYTE RECRUITMENT TO THE LUNG

Lymphocytes are recruited to extravascular sites through a complex process involving adhesion to endothelial cells (ECs), release from adhesion, transendothelial migration, interaction with cellular matrix, and response to locally produced chemoattractants.[6,46,47] This sequential process is characterized by an initial capture step that is mediated by selectins and integrins, followed by arrest/activation mediated by chemokine and cytokine receptors and other integrins.[45,48] The role of chemokines has emerged as central to the regulation of tissue-specific lymphocyte homing and retention. These are low–molecular-weight proteins that share a cysteine repeat motif (e.g., C-C or C-X-C), near the N-terminus. As a class, these proteins have cationic charge, and therefore bind heparin.[49] Chemokine function is mediated through cognate seven transmembrane-spanning receptors. There is significant promiscuity between chemokine receptors and their ligands, such that any specific chemokine may have several ligands and vice versa. Because of their physicochemical properties, the chemokines may bind to heparin-like regions of EC membrane receptors, preventing dilution of locally produced chemoattractant signal by blood flow and facilitating concentration gradients, a phenomenon known as haptotaxis. Chemokines have been shown to enhance both adhesion to ECs and endothelial transmigration of multiple leukocyte types including T-cell subsets and monocytes. Recently, chemokines have also been found to act as accessory growth factors for T-lymphocytes.[50] While CXCL15 (lungkine) appears to be selectively expressed in mouse lung, there does not appear to be a unique human lung–specific lymphocyte directed chemokine profile. However, certain chemokines (see below) are preferentially expressed in TH2 and TH1 type immune responses in the lung.

The interaction of adhesion molecules expressed on blood T cells with complementary adhesion molecules on EC is the critical first step to T-cell emigration from the blood. This step is closely regulated at the level of expression of adhesion molecules by T cells at different stages of development, and by transiently increased adhesion molecule function following T-cell activation. Similarly, expression of adhesion molecules by EC may be increased markedly by organ site and location, or by proinflammatory cytokines, especially tumor necrosis factor (TNF)-α, IL-1, and interferon-γ (IFN).[51–54] Treatment of EC with these cytokines markedly alters the adhesiveness of EC for leukocytes, including certain subsets of T cells. The result of such EC activation by local production of cytokines or other factors is that the exit of T cells from the blood is not random, but rather is restricted to sites such as lymphoid tissues, mucosal sites, or tissue sites of inflammation.

The specific events involved in T-cell transendothelial migration have been dissected at the cellular level, while their characterization in human lung is incomplete. T lymphocytes first appear to "roll" along the endothelium, an interaction which requires loose adhesion via T-cell α4β1 integrin/endothelial VCAM-1 and P-selectin/PSGL-1.[15] A signal is required to produce formal "capture" via other integrin molecules, particularly lymphocyte LFA-1 (αLβ2 integrin) interaction with ICAM-1 or other ligands on endothelium. This latter signal enhances the avidity of integrins for ligand, strengthening adhesion. Other interactions, including decay of integrin affinity, homotypic interaction of T cell and endothelial PECAM (CD31) at EC junctions, and release of matrix degrading enzymes, permit release of firm adhesion and T-cell migration into matrix.[47] Preliminary evidence in TH2-cell migration suggests that this step is mediated by T-cell CCR3/endothelial CCL11 and CCR4/CCL17, respectively.[16,55,56]

T cells are constantly recirculating from blood to tissue and back, with an average half-life in the blood of only about 18 hours.[57] In addition, the sites of migration in vivo appear to be quite different for naive/virgin cells, as opposed to previously activated memory cells. Due to a high level of CCR7 expression, naive cells preferentially traffic to lymphoid tissue where they are likely to encounter antigen,[58] while memory cells traffic to nonlymphoid tissues such as skin or lung.[53,59]

The normal lung vasculature may have unique properties that facilitate the retention of circulating lymphocytes. Whether injected intravenously or intra-arterially, labeled lymphocytes are held up in the lung disproportionately in comparison to other organs. Thus, this is not just a "first-pass" clearance effect from capillary passage.[6] Several investigators have found that antibodies to adhesion molecules, particularly lymphocyte function–associated antigen (LFA)-1, decrease lymphocyte retention in the lung. However, capillary size may determine trapping of activated cells since cytoskeletal changes occurring coincident with activation reduce cellular deformability; this has been shown to be a significant force in the lung trapping of activated neutrophils and monocytes. Lymphocytes also become larger, and lose deformability with activation, but the role of this process in lung retention of lymphocytes is not yet defined.

Lymphocyte chemoattractants represent another step in the regulation of the exit of adherent or trapped T cells from the capillary circulation. As noted earlier, varied T-cell chemoattractants have been described which are relevant to the lung, many of which also alter the growth and activation of T cells (reviewed in References[6,49,50,60]). A partial listing of known chemoattractants may be found in Table 21-3. In lung diseases multiple T-cell chemoattractants have been found in BAL or in tissue specimens, including the chemotactic growth factors IL-2,[29,61] IL-16,[62] IL-33,[63,64] insulin-like growth factor I[13], the C-X-C chemokine IL-8 (CXCL8), and the C-C chemokines macrophage chemotactic protein (MCP)-1 (CCL2), RANTES (CCL5), and macrophage inflammatory protein (MIP)-1α (CCL3).[62,65,66] These chemokines have multiple cellular origins, including macrophages, ECs, and epithelial cells. IL-2 is presumed to be of lymphocyte origin while IGF-1 and IL-16 have multiple potential cellular sources including T cells, eosinophils, and epithelial cells.[67,68] IL-33 is an epithelial-derived alarmin which in addition to being a chemoattractant to TH2 cells via ST2/IL1RAcP receptor also attracts ILC2, eosinophils, and mast cells. Its central role in TH2 immune deviation in asthma in response to epithelial cell necrosis to a variety of injuries is becoming increasingly appreciated.[69–72] It has also been noted that CXCL9, 10, and 11 appear to be important in TH1 responses in the lung, but their expression may relate more to induction by interferon-γ rather than a lung-related phenomena.

Recruitment of lymphocytes to the lung along chemotactic gradients is a complex phenomena involving multiple chemotactic factors, gradients, and responding cell receptors. The final complexion of the lymphocyte population in any compartment is therefore the sum of the responsiveness of each phenotype sequentially responding to and then releasing from chemotactic gradients to respond again. The hierarchy of responses involves regulation of expression of receptors and responsiveness, a phenomena termed chemotactic factor receptor cross desensitization. This can explain retention of T cells (lack of responsive chemotactic receptors) and relocation (sequential responsiveness to induced or constitutive chemotactic gradients). Examples of these modulatory steps are present in human[74–76] and mouse T cells of all phenotypes and likely this is one of the prime factors for accumulation of T cells in organized lymphoid tissues in the thorax and lung (e.g., lymphadenopathy) during infection and inflammation. Moreover, chemotactic gradients and receptor desensitization can be induced by exogenous chemotactic factors of infectious origin, which can in turn regulate responses to endogenous chemotactic factors. For example, HIV-1 gp120 can downregulate the responsiveness of thoracic lymph node lymphocytes to sphingosine-1-phosphate, resulting in lack of normal egress.[74,75,77]

TABLE 21-3 Lymphocyte Chemoattractants[a]

Interleukins	Activation Stimuli
IL-1	Antibody to T-cell receptor (T cells)
IL-2	Antisurface immunoglobulin (B cells)
IL-6	Phorbol esters
IL-10	
IL-15	
IL-16	
IL-33	
Chemokine Chemoattractants	**Growth Factors**
CXCL8/IL-8	Insulin
CCL5/RANTES	IGF-1
CCL3/MIP1-α, CCL4/MIP-1β	TGFβ1
CCL2/MCP-1, CCL8/MCP-2, CCL7/MCP-3	
CXCL10/IP-10	
CL11/eotaxin	
Matrix Proteins	**Miscellaneous Chemoattractants**
Laminin	Lysophosphatidylcholine
Fibronectin	fMLP, mycobacterial lipoarabinomannan
Amyloid protein AA	Casein/denatured protein
Sphingosine 1 phosphate	

[a]*Not a complete listing.*
IL-, interleukin; RANTES, regulated activated normal T cells expressed, secreted; MIP, macrophage inflammatory protein; MCP, monocyte chemotactic peptide; IGF, insulin-like growth factor; TGF, transforming growth factor. For reviews, see References.[11,52,73]

LYMPHOCYTE FUNCTION IN THE LUNG

Lymphocytes in the lung serve four major functions: (1) antibody production; (2) cytotoxic activity including lysis of virally infected cells, cells that have bound antibody, and tumor cells; (3) cytokine production; (4) immune tolerance. These functions are summarized in Table 21-4 and in a number of references cited.[5,49,78]

Antibody production in the lung by B lymphocytes serves to bind antigen and facilitate inactivation of bioactive material and phagocytosis by macrophages. Mucosal IgA is of particular interest in its active transepithelial transport to the bronchial lumen. Antibody production by lung B cells has been extensively studied in mouse lung. Following challenge, antigen is removed to regional lymph nodes by motile phagocytic cells (macrophages and DCs) where optimal activation of T and B cells occurs. Activated cells relocate into the circulation and migrate into the lung at areas of inflammation, and local antibody production results. Rechallenge with antigen results in a more rapid local response derived from resident memory cells.[5,6,79] While the duration of pulmonary memory lymphocytes is unknown, systemic B lymphocytes can persist for over 100 days in the absence of antigen,[80] as is the case with memory CD4+ and CD8+ T cells.[81]

The lung contains multiple types of cytotoxic cells, including NK cells (not antigen restricted), antigen-restricted cytotoxic cells, and cells exhibiting antibody-dependent cytotoxicity. One unusual aspect of lung cytotoxic cells is the pre-eminence of CD3+ cytotoxic T cells

TABLE 21-4 Function of Lung Lymphocyte Subpopulations[a]

Cell Type	Function	Secreted Products
TH1 cell	Intracellular microbes, (i.e., intracellular bacteria, antiviral and antifungal defense) granuloma formation, graft rejection	IL-2, IFN-γ, IL-3, IL-6, IL-12, IL-16, GM-CSF, TGFβ1
TH2 cell	Allergic inflammation, antiparasite (e.g., helmiths) defense	IL-2, IL-4, IL-5, IL-9, IL-10, IL-3, IL-13 IL-16, GM-CSF, TGFβ1
TH17 cell	Extracellular bacteria and certain fungi. Neutrophilic inflammation	IL-17 A(IL-17), IL-17 F, IL-21, IL-22, TNFα GMCSF, IL-26 (human TH17)
TCTL (CD8 cell)	Antigen-restricted lysis of viral- or mycobacteria-infected macrophages or epithelia; lysis of fungi, tumor cells	TH1 cytokines, perforin, IL-4
T REG cell	Peripheral tolerance (various phenotypes). Maintenance of immature DC	IL-10, TGF-β1, IL-35
NK cell	Nonantigen-restricted lysis of virally infected and tumor cells	Perforin, granzymes, α-defensins, IFNγ, TNFα/β, CCL3, CCL4, CCL5, also IL-17A, IL-22
NKT cell	Restricted αβTCR interacting With cells presenting glycolipids associated to CD1d	IFN-γ, IL-4, IL-13, IL-2
B cell	Antibody production	IgM, IgG subtypes 1–4, IgE, IgA, IL-10

[a]Not a complete listing. Listed are cytokines or other products produced under in vitro conditions or documented in lung disease.
TH1, T helper type 1; TH2, T helper type 2; CTL, cytotoxic T lymphocyte; NK, natural killer cell; IL-, interleukin-; CMI, cell-mediated immunity; GM-CSF, granulocyte macrophage colony–stimulating factor; TGFb1, transforming growth factor beta 1; DC, dendritic cell.
For reviews, see References.[15,55]

with NK activity (nonantigen-receptor–mediated killing of tumor cell targets). This is in contradistinction to the blood, where the majority of cells expressing NK activity are CD3–.[5] These natural killer T cells (NKT cells) make up less than 0.2% of human peripheral blood T cells and, contrary to an earlier report,[82] are low in number in bronchial tissue and BAL in health and disease. In asthmatics, it is approximated they account for, at most, 1.7% and 0.2% in bronchial tissue and BAL, respectively.[83] They have an invariant TCRα–receptor chain receptor (variable [V] and joining chain [J] Vα14 Jα18 in mice and Vα24 Jα18 in humans) combined with a limited, but not invariant TCRβ-chain repertoire (Vβ8.2, Vβ7, or Vβ2 in mice and Vβ11 in humans), and conventionally are referred to as iNKT or type 1 NKT cells. They recognize foreign and self-glycolipid antigens presented by MHC-class-I-like CD1d antigen-presenting molecule (reviewed by Godfrey, Stankovic, and Baxter[84]). While a role for iNKT cells in host defense to a variety of infectious antigens (e.g., Cryptococcus neoformans)[85] and in modulating the inflammatory response in asthma[86] has been suggested, details of their function have to be elucidated.

NK activity is found in the interstitial compartment of lung T cells and NK cells are present among LES accounting for approximately 10% of tissue lymphocytes. The majority (80%) are phenotypically the cytotoxic subset (CD56dimCD16high) in humans and resting pulmonary NK cells have been found to be functionally impotent.[44,87–89] The impairment of cytotoxic capacity of resting pulmonary NK cells in BAL and lung tissue is believed to be due to the suppressive effects of cytokines such as TGFβ and other mediators such as prostaglandins from AMs, pulmonary surfactant[90] and respiratory epithelial products such as IL-15.[91] The importance of this regulation of NK cells in the lung is exemplified in certain genetic deficiencies which result in either chronic activation of NK cells leading to granulomatous inflammation or recurrent viral and bacterial infections that can involve the upper and lower respiratory tract.[92–94]

Cytokine production by lung T helper cells (TH) has emerged as a major focus of investigation in lung inflammation. In contrast to antibody production by B cells, T cells produce cytokines. Broad ranges of cytokines have been documented to be produced by lung T cells in inflammatory disease (Table 21-4). In general, the complexion of the inflammatory response correlates with the cytokines produced by T cells, suggesting that T cells orchestrate many inflammatory responses.

Activated T-helper (TH) cells produce a distinct spectrum of cytokines.[95–97] The repertoire of a single T cell to produce cytokines appears to be limited and stereotyped, depending on the circumstances of activation. According to data accumulated in mice, naive T cells produce mainly IL-2 in response to activation. After proliferation and switch to memory cell phenotype, T cells differentiate and produce one of four major clusters of effector cytokines, the best characterized being TH1 (interferon-γ, IL-2), TH2 (IL-4, IL-5, IL-10, IL-13), TH17 (IL-17, 23, 25), and Treg (TGFβ, IL-10, PGE). These TH phenotypes share mutually exclusive transcriptional programs, regulated by the transcription factors T-bet (TH1) and GATA-3 (TH2), RORγ/STAT3 (TH17), and FoxP3 (Treg), respectively.[98–100]

Historically, the division between TH1 and TH2 phenotypes was derived by exclusion of the alternate type and led to confusion in the distinction between these phenotypes particularly in humans where the distinction is not as predictable as in the mouse.[95] These two major phenotypes roughly conform to polarized expressions of cell-mediated immune responses: granuloma formation with activation of mononuclear phagocytes and production of opsonizing IgG2 antibody (TH1); or optimal antibody response including IgE formation, often with associated eosinophilia (TH2).

Certain immune responses in the lung are dominated by either a TH1 or TH2 response, while others are mixed. For example, in human asthma T cells producing TH2 cytokines predominate,[101] but IFN-γ producing cells are found in the airways suggesting a mixed response.[102] In contrast, granulomas at sites of tuberculin reactions in skin show evidence for production of IFN-γ and IL-2 but not IL-4.[103] In leprosy or leishmaniasis an ineffective host reaction is associated with a TH2 response, and an effective granulomatous response is associated with a TH1 response. In addition, treatment of ineffective responses to leishmania with IFN-γ have been reported to increase the efficacy of chemotherapy.[96] In sarcoidosis, airway and granuloma cells, particularly activated CD4+ (HLA-DR+) T cells, have been found to produce both IL-2 and IFN-γ, suggesting the predominance of a TH1 response. There is considerable cross-regulation of TH1 and TH2 subsets even after commitment to production of these cytokines, leading to the general concept that the character of an immune response as well as its termination may depend on the sequential predominance of TH1 or TH2 responses. Indeed, the functional distinction between TH1 and TH2 cells is less distinct in humans as it is in the mouse. As a result of these earlier studies, it is now clear that other T-cell phenotypes participate in all these inflammatory events in the lung beyond traditional TH1 and TH2 dichotomy.

First, there is an important role of T cells (and T-regulatory cells in particular) in mediating mucosal tolerance and immune homeostasis.[104,105] This function in the mucosa is directly related to their interaction with mucosal DCs.[78,106,107] While the phenotypic classification of these cells is evolving, the peripheral pool of regulatory T cells (Tregs) is a mixture of natural thymus–derived Tregs (nTregs) and induced Tregs (iTregs), which originate from naive CD4+ T cells under conditions of low antigenic stimulation or by cytokines primarily transforming growth factor beta (TGFβ). While the relative contribution of each type of Treg to immune suppression and homeostasis is not clear, the fact that their TCR repertoire is different suggests a nonredundant complementary role.[108] There appear to be multiple phenotypes within the Treg population with overlapping mechanisms of action. However, the transcriptional factor forkhead box protein 3(Foxp3) appears essential for the suppressive function of this T-cell subset. Deletion of Foxp3 in mice (Scurfy) and humans (IPEX syndrome) results in a lethal condition of autoimmunity and inflammation emphasizing the critical role of Tregs in immune homeostasis and IL-2 in the growth and expansion of Treg. The majority of studies examining the regulatory potential of T cells in inflammatory lung disease, however, have been in *ex vivo* manipulation, depletion, and adoptive transfer experiments in the mouse.[109,110] The evidence for intraparenchymal (i.e., mucosal or interstitial) human Treg cells is not direct, but the requirement for maintenance of peripheral tolerance in the lung and systemic inducibility of tolerance to inhaled antigen[111] provides the basis for their speculated presence in the epithelium. In addition, intratracheal treatment of mice with the immunomodulatory cytokine IL-16[112,113] elicits an expansion of lung CD4+CD25+ T cells.[114]

TGFβ is required for the development of iTregs, but dual stimulation of TGFβ with either IL-4 or IL-6 (IL1β in humans) can alter the cytokine profile of peripheral T cells from suppressive Tregs to proinflammatory TH9 or TH17 cells, respectively. Similar to TH1 and TH2 development, TH9/TH17 and Treg cell development is cross-regulated at the transcription factor level, an important mechanism for maintaining immune homeostasis in the periphery.[115] At the functional level, this requirement of TGF-β for the induction of both Foxp3+ Tregs and TH17 cells provides a system for efficient balance between tolerance and immunity. In the steady state, TGFβ induces Foxp3 and Tregs, inhibits inflammation, and maintains self-tolerance, but once IL-6 is produced by innate immune cells in response to microbial triggers, Treg generation is prevented and the function of nTregs is suppressed while TH17 cells are induced to produce a strong proinflammatory response characterized by neutrophilia.[115]

While a distinct functional role of predominantly IL-9 secreting TH9 cells in the lung is unknown, the TH17 cell cytokine cluster (IL-17A, IL-17 F, IL-22, and IL-21) is understood to help protect the lung against extracellular bacteria and fungi.[116] However, the observed elevations of IL-17A and IL-17F in sputum and blood/BAL in asthma[117,118] indicate that TH17 cells contribute to chronic inflammatory disease as well. TH17 cells, like TH1 and TH2 cells, accomplish some of their role by recruiting cells of the granulocytic–monocytic lineage: TH1 cells recruit monocytes/macrophage, TH2 cells recruit eosinophils, basophils, and mast cells, and importantly TH17 cells recruit neutrophils. Given that up to 50% of asthmatics are nonatopic[116] and IL-17 mediates neutrophilic inflammation, there has been interest in understanding TH17 role in difficult to treat asthma. Interestingly, in vitro experiments have shown that the neutrophilic airway inflammation and bronchial hyperresponsiveness caused by TH17 cells was steroid resistant, consistent with the clinical phenotype.[119] While sarcoidosis is classically thought of as a TH1 disease, IL-17–producing cells are also elevated in peripheral blood and bronchoalveolar lung fluid of these patients.[120] Moreover, both single IL-17A+ and double IL-17/IFNγ+ cells have been reported in sarcoid granulomatous tissue.[121] Thus TH17 cytokine cluster helps understand the heterogeneity in classical TH1 and TH2 disease in the lung.

However, T cells are not the only source of IL-17, innate lymphoid cells (ILCs) such as NKT cells, NK cells and γδ T cells produce IL-17.[115] There is great interest in understanding the contribution of ILCs to immune homeostasis and pathology in the lung. Three features define ILCs: the absence of recombination-activating gene (RAG)-dependent rearranged antigen receptors; a lack of myeloid cell and DC phenotypic markers; and their lymphoid morphology. While the prototypical ILC population is NK cells (see previous section), several other distinct ILC populations have recently been described, all of which appear to originate from a common lymphoid (Id2+) progenitor cell and all, like conventional T cells, produce cytokines.

A particular source of confusion is the number of different names that have been used to characterize these different ILC populations. For example, ILCs that produce TH2-cell–associated cytokines have been variously called natural helper cells,[122] nuocytes,[123] and innate helper 2 (Ih2) cells[124] without clear evidence of uniqueness. A functional nomenclature system based on cytokines produced[125] has recently been proposed: Group 1 ILCs produce IFNγ, Group 2 produce type 2 cytokines (including IL-5 and IL-13), and Group 3 ILCs produce IL-17 and IL-22. ILCs are changing our view of how lymphocytes function in lung inflammation. For example, ILC2 have been shown to contribute IL-13 not IL-4 production in ovalbumin-induced lung inflammation mouse models[126,127] and in IL-13 –/– mice, which are resistant to allergic lung inflammation and virus-induced airway hyperresponsiveness transfer of IL-13 expressing ILC2 s was sufficient to restore airway hyperresponsiveness in both models[126,128] A human equivalent of ILCs have been found in patients with chronic rhinosinusitis.[129]

B-lymphocyte biology has also significantly advanced in recent years and now B cells are known to be comprised of different populations and proven to be pleiotropic in function (Ref.[130] summarizes the current understanding of B-cell lineages in the lung.) Briefly, in mice the majority of B cells are B2 B cells, which originate from the adult bone marrow precursor, traffic through peripheral lymphoid tissue, interact with cognate antigen, and after activation develop into either memory B cells or antibody-secreting plasma cells. In the human lung, the majority of B cells are these mature naive B2 B cells and they reside in BALT (see previous section) or draining lymph nodes. In mice, there is a family of innate-like B cells: marginal zone B cells, B1α and B1β B cells that contribute to rapid immune responses against pathogens and other stimuli. B1 B cells are a small self-renewing subset of B cells that originate from the fetal liver and secrete most, if not all, natural antibodies (IgM and IgA isotype) in the apparent absence of antigenic challenge. Natural antibodies are often polyreactive and bind to foreign antigens as well as to self-components (ex rheumatoid factor) and are important for early pathogen recognition and maintenance of tissue homeostasis.[131] B1 B cells constitute a minor fraction of the spleen and secondary lymphoid tissues but are enriched in the pleural and peritoneal cavities. It is not known whether B1 B cells residing in the pleural cavity migrate into the lung. Human B1 B cells do exist and are found to have marker profile of CD20+CD27+CD43+CD70– and could either be CD5+ or CD5–.[132]

The central role of B cells is the production of immunoglobulins, both within the parenchyma and for export to the mucosal surface of the airway, in the case of polymeric IgA and IgM. In addition, B cells are now known to function as antigen-presenting cells and producers of both inflammatory and regulatory cytokines (i.e., IL-10–producing B-regulatory cells [B-regs]). Very little is known about either of these functions in the lung by B cells. Much of disease

immunopathology in the lung is based on T-cell biology, but there is an expanding appreciation of B-cell contribution to diseases such as hypersensitivity pneumonitis, COPD, autoimmune connective tissue diseases, and idiopathic pulmonary fibrosis (see the review by Kato et al.[130] for details). But overall, all these diseases illustrate the potential for the lung to generate an exuberant B-cell response to antigen, either inhaled or self-antigen.

LYMPHOCYTE ACTIVATION IN THE LUNG

T lymphocytes are designed to require specific (antigenic) signals for activation, restricting their involvement in inflammation to situations where antigen overwhelms the mucociliary escalator and macrophage and neutrophil defenses. Lymphocytes are activated following engagement of an antigen receptor of remarkably fine specificity. This receptor is unique to a given lymphocyte clone, and is generated by recombination of gene segments in the antibody (for B cells) or T-cell–receptor genes. B-cell receptors consist of single membrane–spanning antibody molecules of the same specificity as the B cell, while T-cell receptors consist of a heterodimeric receptor (dimers of alpha and beta or gamma and delta chains). The T-cell receptor is highly antigen specific and has structural homology to the immunoglobulin molecule. Lymphocytes are activated by cross-linking of membrane antibody by antigen (B cells) or by engagement of the antigen receptor by antigen bound to major histocompatibility complex (MHC) molecules on the surface of so-called antigen presenting cells (APCs), also known as accessory cells. APCs provide many "accessories" for T-cell activation including: (1) a source of MHC molecules to which antigen can bind; (2) internalization and "processing" of antigen including protease digestion into antigenic fragments; (3) multiple cell adhesion molecules which bind to complementary adhesion molecules on T cells and serve to strengthen T-cell–accessory cell interactions and transduce activation signals required for optimal lymphocyte activation; and (4) production of cytokines that amplify activation including IL-1 (reviewed by Cruikshank et al.[112]).

APCs in the lung include pulmonary macrophages of all varieties, however, DCs and Langerhans cells are most efficient in this function (see below). These cells express important "accessory" cell adhesion molecules important to accessory cell function, including ICAM-1, LFA-2, LFA-3, and the CD28 ligands B7–1, B7–2, and CTLA-4.[68,133,134] Other cells, which may be induced to express Class II MHC molecules, may also act as weak accessory cells. Such cells include local B cells, epithelial cells, smooth muscle cells, and fibroblasts. Uncommitted naive T cells require intense accessory cell interaction to be activated by antigen, while previously activated (memory) T cells require less accessory cell input and might be influenced by interaction with such weak accessory cells. Due to naive CCR7+ T cells' inability to cross postcapillary venules, as mentioned earlier most lung T cells are memory cells, which suggests that the relatively weak lung accessory cells may indeed play a role in T-cell activation in the lung inflammatory response (Table 21-5).

As discussed earlier, the lung has proved to contain major immunosuppressive elements, which may serve to prevent inappropriate or excessive T-cell activation in an area of the body, characterized by constant antigen bombardment. These influences include surfactant lipids which have been shown to inhibit T-cell activation, proliferation, and cytokine production[136]; basal production (perhaps by epithelial cells) of the potent immunosuppressive cytokine TGF-β1[28]; and an inhibitory effect of AMs.[27] These inhibitory effects may be moderated, reduced, or increased in various disease states.[137] The role of DC phenotype and degree of maturation in directing activation versus tolerance in T cells is emerging as a key determining step in pulmonary T-cell differentiation. DCs can be broadly described as activating or tolerogenic, and this distinction appears to be related to the maturity of the DC and functionally to the presence of costimulatory molecules on the cell surface (e.g., CD80, CD86, CD40).[106,107] Typically, DCs process inhaled antigen and migrate to draining lymph nodes to present antigen to naive T cells. (The role of BALT in this process is unknown, see earlier discussion.) Thereafter, the nature and concentration of processed antigen determines the fate of cognate T cells: TH1, TH2, TH17, or Treg.[138,139] Presumably, TH cells that have encountered Ag in secondary lymphoid tissue acquire cell surface markers that direct homing and permit postcapillary emigration to lung interstitium and epithelium, either as regulatory or effector cells. There is evidence that the communication between DC and T cells is not exclusively toward T cells; differentiated T cells communicate with local DC via cytokines and cell surface markers to alter DC phenotype. This phenomenon has been described in a mouse diabetes model,[140] and proposed in murine allergic airway inflammation.[141] In light of the emerging central role of DCs in immunologic lung disease and growing knowledge of their plasticity, future directions will likely approach modulating DC phenotype and function as targets for therapy.

LYMPHOCYTE CLEARANCE AND DEATH IN THE LUNG

The means by which lymphocytes exit the lung or are cleared during homeostasis or following an inflammatory response is largely unknown. Certainly apoptosis and autophagy play a role in clearing of senescent cells, but signals unique to lung diseases in activating these pathways are less clear. It is not known how long memory T or B cells reside in the lung in any of the compartments, nor is the extent of lymphocyte exit from the lung via lymph to nodes or to the circulation. However, it is clear from studies in the mouse that programmed cell death, or apoptosis, is involved in the termination of antigen-induced inflammatory responses. In lymphocytes, this energy-requiring form of cell death leading to the fragmentation of the nucleus and DNA may result from one of three events: (1) "neglect" or absence of stimulation; (2) stimulation out of context, or without the appropriate second signals (such as CD28 or matrix interactions); or (3) signaling via Fas (CD95) engagement with Fas ligand. Such regulation of cell death appears to be critically important for the termination of an immune response once

TABLE 21-5 Function of Lung Macrophage Populations

Cell Type	Phagocytosis	Microbial Killing	AG Presentation	Cytokine Production
Alveolar macrophage	++++	++++	+/– (suppression)	++++
Interstitial macrophage	++	++	++	++
Dendritic cell	+	+	++++	++
Langerhans cell	++	+	++++	++
Blood monocyte	++	++	+++	+++

Source: Data from Erle DJ, Brown T, Christian D, Aris R. Lung epithelial lining fluid T cell subsets defined by distinct patterns of beta 7 and beta 1 integrin expression. Am J Respir Cell Mol Biol. 1994;10:237–244; Ford WL, Simmonds SJ. The tempo of lymphocyte recirculation from blood to lymph in the rat. Cell Tissue Kinet. 1972;5:175–189; Johnston RB, Jr. Current concepts: immunology. Monocytes and macrophages. N Engl J Med. 1988;318:747–752.

antigen has been cleared, preventing the accumulation of activated lymphocytes.[142]

MACROPHAGES IN THE LUNG

Macrophages reside in many organs. However, they are especially prominent in the lung and perform many functions. Macrophages ingest inhaled particles or antigens and are then removed on the mucociliary escalator. They also serve as "professional" APCs, traveling to regional lymph nodes where they sensitize T and B lymphocytes. Lung macrophages release a variety of cytokines and biologically active arachidonate metabolites, which influence the function of nearby cells including T cells, B cells, ECs, and fibroblasts. Finally, macrophages ingest microorganisms and, when stimulated, kill them using a variety of means including toxic oxygen metabolites and nitric oxide.

Macrophages or macrophage-like cells are found in several lung compartments including the epithelial lining fluid, interstitium, epithelium, and intravascular compartment. These cells have varying functional repertoires and are typically categorized as AMs, interstitial macrophages (IMs), DCs, Langerhans cells, blood monocytes, or blood macrophages, respectively. Each of these cell types, their recruitment, and their activation will be discussed.

MACROPHAGE TYPES

Alveolar Macrophages (AMs)

Derivation of AMs from blood monocytes was initially suggested by an experiment in which the quantity of AM declined 20 to 30 days after bone marrow ablation despite in situ proliferation and increased cell stability.[143] Conversely, similar experiments, but with shielding of the chest during bone marrow ablation, have now found that even by 8 months bone marrow monocytes contribute little to the alveolar macrophage compartment during steady-state conditions.[144,145] It is now appreciated in mice at least that lung macrophages have a chimeric origin being derived from the fetal yolk sac and bone marrow–derived blood monocytes and certain subtypes may persist for the mouse lifetime.[146,147] The differentiation of AM derived from blood monocytes is regulated by the tissue microenvironment.[21,135,148,149] However, the molecular details of this differentiation remain largely unknown.[150]

If quantity implies importance, then one would surmise that AMs play an essential role in the lung's defense against foreign invaders. Found in air spaces throughout the lung, it is estimated that macrophages make up 90% of cells found in the alveolar spaces of both smokers and nonsmokers. The absolute quantity of AM, however, is approximately four-fold greater in smokers than nonsmokers.[148] The increased quantity of AMs in smokers is likely due to both recruitment of blood monocytes from the bone marrow and their differentiation into AMs. In one study, AMs were exposed to ambient particles and their supernatant collected. The supernatant promoted transit of monocytes through the bone marrow and their release into the circulation. Analysis of the supernatant revealed large amounts of inflammatory mediators including granulocyte macrophage colony–stimulating factor (GM-CSF), macrophage colony–stimulating factor (M-CSF), macrophage inflammatory protein (MIP)-1beta (CCL4), monocyte chemotactic protein (MCP)-1 (CCL2), IL-6, and ICAM-1.[151] Many of these mediators are known to increase monocyte turnover in the bone marrow and to enhance their recruitment into peripheral tissues.

AMs have a diverse repertoire of functions. Importantly, AMs are the first line of defense against inhaled antigens and pathogens. As such, they have well-developed phagocytic activity that is enhanced when activated by opsonization or inflammatory signals (e.g., IFN-γ).[6,51,152] Activated AMs release more inflammatory mediators and have superior microbial killing than their unstimulated counterparts.[143,150,151] It is impossible to accurately assess the phagocytic and microbicidal capabilities of AM compared to other lung macrophages because many of the accessible AMs may have been depleted of a portion of their functional capabilities due to previous activation. In general, smaller AMs are more efficient at phagocytosis and microbial killing than larger AMs. The smaller AM may represent younger, recently emigrated phagocytes and the larger AM may represent previously activated AM.[143]

TABLE 21-6 Cytokines and other Bioactive Substances Released from Lung Macrophages[a]

Arachidonate Metabolites	Cytokines	
Thromboxane A_2	IL-1[b]	IL-10[υ]
PGE_2, D_2, $F_{2\alpha}$	IL-1RA	IL-12[b]
LTB_4	IL-6[b]	IL-15
5-HETE	TNF-α[b]	IL-23[b]
IFN-α/β	MIF Ym1,2[υ]	TGF-β[υ]
Reactive Oxygen Metabolites[b]	**Nitric Oxide[b]**	
Superoxide anion (O_2^-)	Constitutive	
H_2O_2	Inducible?	
hydroxyl radical (OH–)		
Chemokines		
Enzymes[b]	CCL3,4,5[b]	
Metalloproteases	IL-8(CXCL8)[b]	
Elastase	IP-10 (CXCL10)[b]	
Procoagulant activity	CCL17, 18, 22[υ]	

[a]*Not a complete listing.*
PG, prostaglandin; LT, leukotriene; IL-, interleukin; HETE, hydroxy tetraenoic acid; TNF, tumor necrosis factor; ; IFN, interferon; MIF, macrophage migration inhibitory factor; TGF, transforming growth factor; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (CXC-motif) ligand; IP-10, Interferon gamma-induced protein 10 kd; Ym1, Chitinase 3-like protein 3; Ym2, Chitinase 3-like protein 4.
[b]*Bioactive substances associated with classically activated macrophages υ bioactive substances associated with alternatively activated macrophages. See References.*[79,135,136,154]

AMs release a variety of inflammatory mediators including arachidonate products, cytokines, and enzymes (see Table 21-6). These mediators impact extracellular matrix, fibrin deposition, and the function of leukocytes and lung cells at sites of inflammation.[21,143,153] Many also play key roles in the pathogenesis of lung diseases. As an example, IFN-γ–inducible protein 10 (IP-10; CXCL10), monokine induced by IFN-γ (MIG; CXCL9), and IFN-inducible T-cell α chemoattractant (I-TAC; CXCL11) are released by AMs and stimulate the release of matrix metalloproteinases-9 and -12 in emphysema.[73]

A wide array of receptors are expressed by AMs, of which most mediate AM activation, migration, or phagocytosis. Perhaps most important are the toll-like receptors (TLRs) which are pattern recognition receptors for microbial cell wall lipids, DNA repeats, and other components of infectious agents. They provide the recognition function of the innate immune system that links to CD14 and subsequent inflammatory cytokine release (e.g., IL-1, IL-6, TNFα) secretion reviewed by Basu and Fenton[155]). These cytokines are essential in controlling infection with intracellular organisms like *Mycobacterium tuberculosis*. For example, AMs express TLR-2 which, when activated, induces killing of intracellular *Mycobacterium tuberculosis*.[156] MARCO is a scavenger receptor

TABLE 21-7 Ligands Recognized by Alveolar Macrophage Receptors[a]

Immunoglobulins (Fc Receptors)	Complement Receptors for:
IgG1, IgG2a (murine)	C3b, iC3b, C4b, C3d, C5a
IgG2b, IgG3 (murine)	
IgG1, IgG3 monomers (human)	
IgE, IgA (murine, human)	
Protein, Cytokine, and Matrix Receptors	**Lipoprotein Receptors for:**
Fibronectin R	Low-density lipoprotein
Fibrin R	Beta–very-low-density lipoprotein
Lactoferrin R, transferrin R	
GM-CSF R	
IFN-γR, IL-2R, IL-4R, IL-1R, IL-1RA	
Insulin	
Chemotactic factor receptors	
Other Receptors and Adhesion Molecules	**Lectin Receptors for:**
Class II MHC (HLA-DR, -DP, -DQ)	α-linked galactose residues
CD4	N-acetyl galactosamine residues
β2 Integrins (CD18; CD11a, b, c)	N-acetyl galactosamine residues
β1 Integrins (CD29; CD49a, b, c, e, f)	α-Linked fucose residues
CD54 (ICAM-1)	N-acetyl neuraminic acid residues
CD14 (Lipopolysaccharide receptor)	Mannose residues (mannose receptor)

[a]*Not a complete listing.*
Fc, complement binding fragment of immunoglobulin; Ig, immunoglobulin; R, receptor; GM-CSF, granulocyte macrophage colony–stimulating factor; IFN, interferon; IL, interleukin; RA receptor antagonist; MHC, major histocompatibility complex antigen; CD, cluster of differentiation.
Source: Data from Hunninghake GW, Bedell GN, Zavala DC, Monick M, Brady M. Role of interleukin-2 release by lung T-cells in active pulmonary sarcoidosis. Am Rev Respir Dis. 1983;128:634–638; Palecanda A, Paulauskis J, Al-Mutairi E, et al. Role of the scavenger receptor MARCO in alveolar macrophage binding of unopsonized environmental particles. J Exp Med. 1999;189:1497–1506.

expressed by AMs that facilitates phagocytosis of unopsonized particles.[157] In the absence of MARCO, pulmonary infection and inflammation is markedly increased.[158] Other receptors expressed by AMs include chemokine receptors, cytokine receptors, Fc receptors that recognize opsonizing antibodies, complement receptors that facilitate phagocytosis, lectin receptors, bacterial endotoxin (CD14) receptors, and mannose receptors (see Table 21-7).

Under certain circumstances, AMs function as APCs and facilitate memory T lymphocyte activation. This ability is enhanced in disease states such as HIV, transplant graft rejection, and sarcoidosis. In alternative situations, AM may impact the immunologic synapse to suppress T lymphocyte activation. This supposition is corroborated by one animal model in which AM depletion enhanced lymphocyte activation, suggesting that AMs can suppress T lymphocyte activation in normal lung homeostasis.[27]

Interstitial Macrophages (IMs)

IMs are a population of macrophages found in the interstitium of the lung instead of the airway lumen. They may be precursors of AMs in transit from the vasculature to the air spaces.[143] Little is known about human IMs because they are not readily accessible for study. In murine models, IMs have been shown to be functionally different from AMs and suggest IMs have a unique role in immune homeostasis in the lung by protecting against aberrant immune responses to nonpathogenic environmental antigens, even in the presence of proinflammatory stimuli.[159] To this end, IMs have been shown to be more immunoregulatory than microbiocidal in comparison with AMs and one mechanism postulated is by inhibition of maturation and migration of DCs.[159,160] Conversely, IMs can exert a supportive influence on pulmonary DC immune function by preprocessing particulate antigen into smaller peptides that are then loaded on the surface of neighboring DCs.[161]

DCs and Langerhans Cells

DCs are potent APCs that reside within airway epithelium and lung parenchyma. Like AMs, they likely originate in the bone marrow, travel via the blood (0.5% of blood mononuclear cells are DCs), then translocate into tissue. Although chemokines and other factors like IL-16 that are chemotactic for DCs have been identified, the precise stimulus for translocation of lung DCs is unknown.[143] DCs are most numerous in large airway epithelium and decrease in quantity as the airways become smaller.[133] Histologic sections along the long axis of airways have revealed a meshwork of DC processes ideal for antigen sampling and interaction with T cells. A similar meshwork is found in BALT in the mouse.[162] It is unknown whether DCs proliferate in the lung.

DCs are highly mobile and travel from the airway to regional lymph nodes where they interact with lymphocytes.[162] DCs are 10- to 100-fold more potent than monocytes at presenting antigens to naive T lymphocytes. DCs express cell surface proteins that are essential for antigen presentation and lymphocyte activation including MHC, cell–cell adhesion molecules (e.g., ICAM/CD54, LFA-3/CD58, β1 and β2 integrins), CD4, and the CD28 ligands.[134,162] Specialized DCs with distinctive invaginations of the plasma membrane called Langerhans cells also exist in the lung, especially those of smokers. Like DCs, Langerhans cells are potent APCs but are less efficient at phagocytosis, microbial killing, and cytokine secretion compared to macrophages.[133] In mouse lungs, it has been shown that langerin+ DCs are able to sample the content of the airway lumen while keeping the epithelium barrier function intact through expression of tight-junction proteins claudin-1, claudin-7, and zonula-2, which form tight junctions with the airway epithelial cells.[163]

The importance of DCs to the pathogenesis of lung diseases was highlighted by a murine model in which CD11c+ DC depletion during an allergen trial resulted in abrogation of the characteristics of an asthmatic response eosinophilic inflammation, goblet cell hyperplasia, and bronchial reactivity.[164] Their role with T-cell education in the lung is discussed earlier. For the interested reader, one is directed to a state-of-the-art review on DCs in the lung.[161]

Blood Monocytes and Intravascular Macrophages

As discussed earlier, blood monocytes are likely the precursors of both lung macrophages (alveolar and interstitial) and intravascular macrophages with differentiation being directed by the microenvironment. This is supported by the observation that blood monocytes can be induced in vitro to express receptors characteristic of AM over a period of days if cultured in the correct microenvironment. The average monocyte spends 1 to 3 days in the circulation and then exits the circulation to differentiate into a macrophage. During inflammation, translocation from blood to tissue increases.[165]

Intravascular macrophages are found within the vasculature of the lung. They are located in postcapillary venules, strongly adherent, and face the flow of blood. Like IMs, these cells are not readily accessible and, therefore, are difficult to study.[166] They are presumed to act as intravascular inflammatory sentinels, ingesting antigens in the form of microbes, erythrocytes, fibrin, cellular debris and immune cells,[167] and releasing mediators in response to inflammatory stimuli which reach the lung via the blood.[168]

RECRUITMENT OF MONOCYTES AND MACROPHAGES

Monocytes are motile cells that adhere to ECs and then migrate with extraordinary efficiency. Monocyte adherence to ECs is promoted by the monocyte "rolling" along vascular walls to increase the likelihood that its β2 integrins (αLβ2, αMβ2, and 4β1) will bind the EC selectins.[43,51,169] Following adhesion, translocation into the lung parenchyma occurs. Once the monocytes have entered the tissue, they differentiate into IMs and continue to migrate via their β1 integrins. Both differentiation and migration are influenced by local tissue-specific factors including chemokines, cytokines, matrix components, complement fragments, antigens, and interactions with other cells.[43,143,149,165]

Monocytes respond to a variety of chemotactic influences including complement fragments (e.g., C5 a), bacterial peptide f-MLP, leukotriene B4, and the chemokines CCL2, CCL3, CCL4, and CXCL8 ((IL-8).[143] The importance of chemokines for monocyte migration is illustrated by a study that investigated the impact of CCR2 (the receptor for CCL2; MCP-1) deletion in a murine model of pulmonary granulomatous inflammation.[170] Following deletion, there was marked decrease in granuloma size and a dramatic decrease in the level of interferon-γ in draining lymph nodes. These findings suggest that CCL2 is vital for monocyte/macrophage migration to sites of inflammation.

Motility of AMs and DCs has also been studied. When labeled DCs and AMs are introduced into the airways, DCs but not AMs are readily found in draining lymph nodes, suggesting that DCs are far more motile than AMs.[133,162] DC migration is likely chemokine mediated. In one set of experiments, IL-13 and IFNγ were administered intranasally, resulting in increased numbers of DCs accumulating in draining lymph nodes, similar to the experiment previously described.[171] Compared to untreated mice, the treated mice had more expression of chemokines including CCL5, CCL2, and CCL7 (MCP-3). In addition, chemokine receptor expression was increased including CCR2, CCR5, and CCR10.

ACTIVATION OF LUNG MACROPHAGES

A major feature of tissue macrophages is the ability to be "activated."[21,143,150] Activation of macrophages is a key event in the inflammatory cascade in the lung and defines a functional state characterized by extrusion of pseudopodia and an increase in cell size and membrane ruffling. Examples of stimuli that interact with receptors on the macrophage's surface to induce activation include antigen–antibody complexes (via the macrophage's Fc receptors), complement fragments (via the macrophage's complement receptors), and cytokines (e.g., interferon-γ) and TLR ligands (e.g., LPS lipopolysaccharide) When activated, macrophage phagocytosis, receptor expression, and production of toxic oxygen metabolites are markedly enhanced. The activated macrophage is a secretory cell, releasing cytokines, toxic oxygen metabolites, and enzymes. Finally, antigen presentation is optimized in activated macrophages but increased expression of Class II MHC.[150]

Using several surface markers ([154]), activated macrophages can be further characterized as exhibiting an M1 phenotype (classically activated macrophages, i.e., induced typically by IFNγ) or an M2 phenotype (alternatively activated macrophages, i.e., induced by IL-4/IL-13). M1 macrophages are generally associated with TH1 (and TH17) immune responses, the production of reactive oxygen intermediates, proinflammatory cytokines, and robust antimicrobial activity. M2 macrophages are associated with TH2 immune response, immune response to helminthes, tissue healing, collagen production, and fibrosis (see Table 21-6). However, this binary view of macrophage activation and its functional alignment with TH1 and TH2 lineages is an oversimplification; a third class of macrophages called "regulatory macrophages" has also been described. These macrophages can be activated by TLR agonists in the presence of immunoglobulin G (IgG) immune complexes, apoptotic cells, and prostaglandins, and are defined by production of the immunosuppressive cytokines IL-10 and TGF-β1.[172] These cells are poor antigen-presenting cells and have a propensity to induce TH2 and some believe T regulatory cell responses. Rather than discrete stable subpopulations, many studies have documented flexibility in macrophage programming, with macrophages readily switching from one functional phenotype to another in response to new microenvironmental signals.[172]

These signals result in activated macrophages playing a prominent role in many lung diseases. While it is unclear whether macrophage activation is a cause or result of lung disease, it is probably both. As an example, in emphysema, macrophage activation is initiated by cigarette smoke exposure and results in the release of inflammatory mediators and byproducts that are toxic to lung parenchyma. These inflammatory mediators, in turn, activate additional macrophages, establishing a vicious cycle of macrophage activation and parenchymal lung destruction.

LYMPHOCYTE–MACROPHAGE INTERACTIONS IN THE LUNG

The interactions between lymphocytes and macrophages, and their effects on lung inflammatory cells and on lung inflammation are summarized in Figure 21-2. Lung macrophages and lymphocytes each perform important functions and influence the differentiation and function of a large variety of cells. Lung macrophages and lymphocytes also interact via direct cell–cell contact during T-cell activation and are greatly codependent. The interaction between bronchial DCs, which are highly effective APCs and typically more effective at antigen presentation than macrophages, is not detailed herein as DC's primary action in regulating pulmonary inflammation, as noted earlier, is following migration to regional lymph nodes.

AM and related cells are the initial sentinels of the innate immune response, phagocytizing and eliminating invading antigens and microbes. After interaction with microbial invaders, and especially in conditions of overwhelming invasion, lung macrophage activation via TLRs and CD14 and other receptors (see Table 21-6) results in the release of inflammatory mediators which activate adhesion molecule expression on ECs, and promote the migration and activation of blood leukocytes including polymorphonuclear leukocytes (PMNs), monocytes, lymphocytes, and eosinophils (*left half* of Fig. 21-2). Rapid induction of selectin molecules stored in Weibel–Palade bodies of endothelium results in the rolling adhesion of neutrophils and monocytes. Migration of these leukocytes may be rapidly modulated by rapid release of arachidonate products such as LTB4, bacterial products themselves like the peptide f-MLP, complement fragments, and chemokines. More time is required for optimal expression of adhesion molecules, which enhance lymphocyte entry, especially VCAM and expression of the chemokine chemoattractant cytokines. One exception is the release within hours of IL-16 from epithelium or resident T cells in response to mast cell–derived histamine.[62]

Interaction of resident or infiltrating T cells with APCs (mainly DC, Langerhans cells and monocytes) results in optimal T-cell activation with resultant production of cytokines, which act upon a variety of cytokine-receptor bearing cells (*right half* of Fig. 21-2). This results in the activation of endothelium, optimal B-cell production of antibody, generation of cytotoxic effector T cells, and depending on the nature of the cytokines produced a delayed-type hypersensitivity or granulomatous (type 1 cytokines), allergic (type 2 cytokines), or other T-cell immune response including neutrophilic TH17 inflammation. Fibrosis or repair may also be influenced by the production of neutral proteases by AM,[151,173] or by the elaboration of the fibrogenic cytokine TGFβ1 by T cells or other

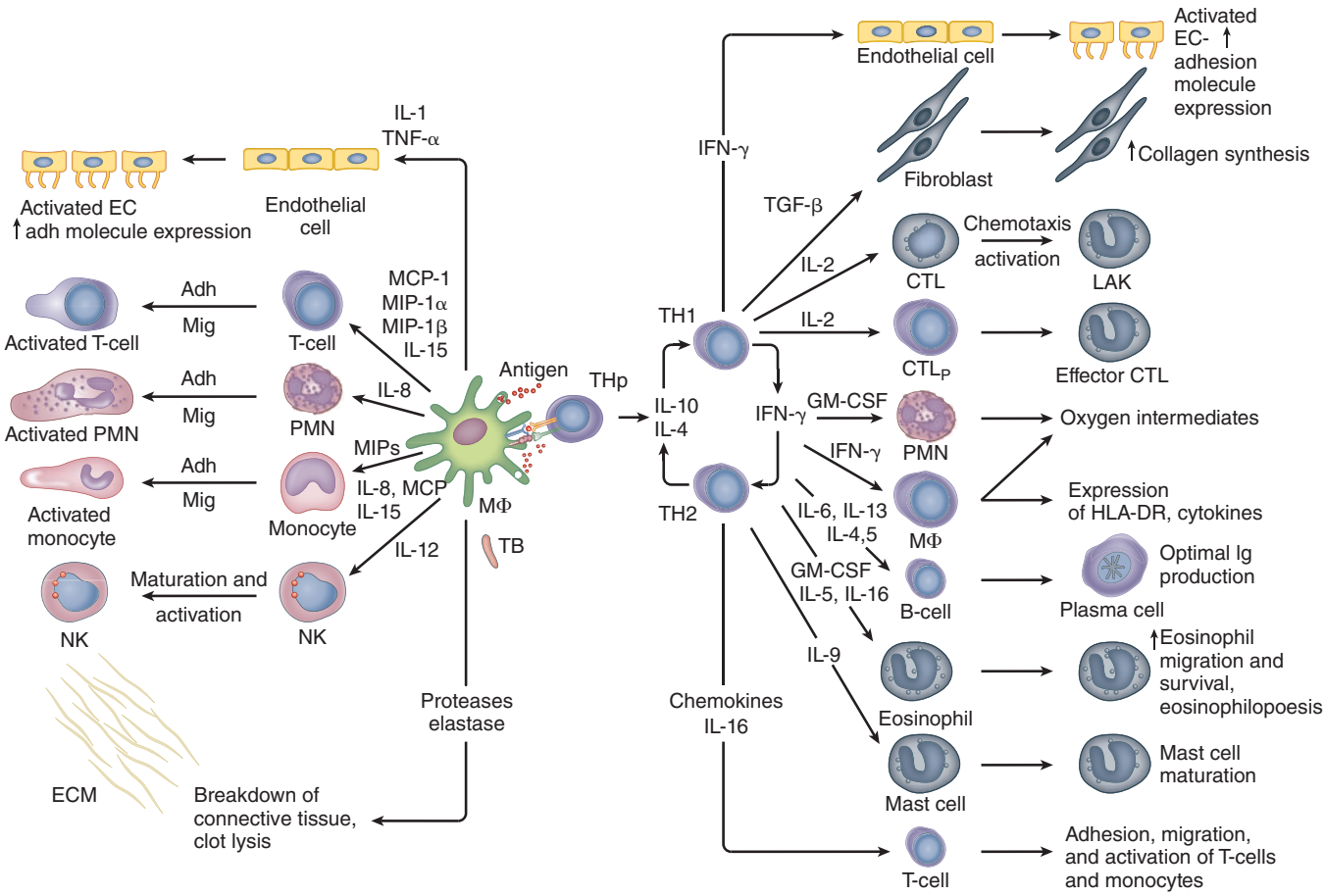

Figure 21-2 Lymphocyte and macrophage interactions in lung inflammation. Lymphocytes and macrophages interact directly and indirectly to influence lung inflammation. These interactions are complex, as illustrated in this diagram, which contains a necessarily incomplete sampling of these processes. Lymphocytes and macrophages interact directly in the process of lymphocyte activation; macrophages also are immunosuppressive in some circumstances. Activated T lymphocytes express a broad range of cytokines, which interact with a variety of effector cells; B lymphocytes produce antibodies. T lymphocytes also may interact with infected epithelial or phagocytic cells or with tumor cells to effect cell lysis. Macrophages similarly produce a large number of cytokines, which alter the functions of a variety of cells. Macrophages also release arachidonate metabolites, reactive oxygen species, nitric oxides, and a large number of proteases, which alter the function of surrounding cells, kill invading microorganisms and degrade matrix proteins. See text for further explanation. *(Adapted with permission from Agostini C, Chilosi M, Zambello R, Trentin L, Semenzato G. Pulmonary immune cells in health and disease: lymphocytes. Eur Respir J. 1993; 6(9):1378–1401.)*

cells depending upon the TH skewing. Of particular interest for the future are the ways the lung macrophage–lymphocyte inflammatory access is "turned off." The networks responsible for control and/or resolution of inflammation to prevent lung damage are likely to be as complex as those that initiate the inflammatory responses in infectious and noninfectious lung diseases.

Overall, the mammalian lung is uniquely poised to protect the environment of the lower respiratory tract and its essential gas exchange units though the presence of a complex network of monocyte/macrophage and lymphocytes selectively sequestered in various anatomical compartments. Together, they coordinate early innate responses to microbial infection and subsequent specific acquired immune responses (e.g., to viruses) that have evolved to protect the organ. Of particular interest in certain noninfectious or autoimmune lung diseases is the similarity of inflammatory responses to those in response to infections where the consequences are deleterious rather than beneficial. Thus, understanding ways to control lung innate and acquired immune responses will be essential in developing appropriate therapies for inflammatory lung diseases. Unfortunately, the converse is also true. Individuals treated with antibodies to TNFα to control the inflammation of rheumatoid arthritis or inflammatory bowel disease are at risk for reactivating latent *Mycobacterium tuberculosis* infections, an infectious disease clearly controlled by early innate and late acquired immunity. More detailed understanding of these processes, how to regulate them quantitatively and how to replace essential elements, is clearly needed to adjust the balance in individuals whose immune systems are compromised or in those whose immune systems are overwhelmed by infection or self-antigens.

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CHAPTER 22

Mast Cells and Eosinophils

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INTRODUCTION

For more than a century physicians have noted a clear connection between mast cell (MC) activation and the subsequent appearance of eosinophils both within the circulation and in tissues. Only recently, however, have basic insights been gained into the mechanisms of this cellular collusion. In keeping with this association, human MCs and eosinophils are considered together in this chapter.

MCs and eosinophils were discovered in the 1870s by the same observer, Paul Ehrlich. He noted that some cells stained in a peculiar fashion when incubated with standard aniline dyes such as toluidine blue and alcian blue. He used the term metachromasie or metachromasia to describe the peculiar color modifications that occurred and the term Mastzellen, meaning "well fed" or "fattened" in German, to describe what we now call MC. Interestingly, this latter term is now known to be a misnomer, since MC cytoplasmic granules are not phagocytosized but rather synthesized during cell growth and again during regranulation. Ehrlich also noted that some cells stained intensely when incubated with the acidic dye eosin. As a result, these cells were called eosinophils. Studies of these two cell types, over the ensuing years, have provided great insight into their roles in biology. They have also highlighted the differences that exist in these cells among different species and their heterogeneity even within a single species and even within single organs.

MAST CELLS

The capacity of strategically localized human MC to rapidly release a panoply of powerful chemical mediators makes this cell a unique member of the body's immune response network. Although most frequently discussed in the context of hypersensitivity immune responses, MCs are also known to participate in normal physiological processes including gastric acid secretion,[1] angiogenesis,[2,3] and lipid clearance.[4–8] Increasing evidence supports a role in the innate immune response, especially serving bacterial defense.[9] MCs also participate in nonallergic pathophysiological processes such as inflammatory bowel disease,[10,11] arthritis,[12] scleroderma,[13,14] tumors, interstitial pulmonary fibrosis,[15–18] envenomation,[3,19–22] and atherosclerosis.[4,5,23,24] Over the years, basophils have been confused with MC in a number of contexts.[25] This confusion is due, in part, to a number of similarities between the cells, including the shared expression of FcRI (high-affinity receptor for Fc fragment of IgE), release of preformed histamine, and metachromatic staining. However, MCs are mononuclear cells and are almost exclusively localized to tissues. In contrast, basophils are circulating polymorphonuclear cells that are found occasionally in tissue reactions, including the late-phase allergic response. In addition, significant differences in the two-cell populations exist in cell lineage, ultrastructure, mediator release biochemistry, mediator profiles, pharmacology, and surface antigenicity.

ANATOMIC LOCALIZATION

MCs are present in all organs but are particularly abundant in the nose, skin, gastrointestinal tract, and lung. They reside primarily near blood vessels, within the adventitia of arteries, and also near lymph vessels and nerves.[26–28] Estimated concentrations of human lung MCs (HLMCs) range from 500 to 4000 mm^{-3}. In nonasthmatics, HLMCs localize to submucosal connective tissues and not epithelium or smooth muscle. Though data in asthmatics are conflicting as to whether numbers are increased versus nonasthmatics, MCs localize to three critical sites: bronchial epithelium,[29] airway mucus glands,[30] and within smooth muscle.[31–34] Mediator release from the small numbers of HLMCs within the epithelium may subserve initial antigen recognition and also be strategically placed to respond to nonantigenic signals, including hyperosmolarity,[35] as well as "endogenous" mediators, including extracellular adenosine and adenosine 5′ monophosphate (ATP).[36–38] In the case of aeroallergens, permeabilization resulting from epithelial MC mediators enhances further antigen penetration to deeper airway smooth muscles and mucus glands, which in turn, promotes bronchoconstriction and mucus secretion, respectively. The finding of HLMC within the smooth muscle layer appears to be a common and critical finding in asthmatics. It is an uncommon finding in nonasthmatics and in patients with eosinophilic bronchitis. Other than MC localization to ASM, the latter condition has virtually identical

structural remodeling changes to asthma but is not associated with obstruction or airway hyperresponsiveness (AHR).[31,39] In the lung periphery, abundant MCs reside within small airways and in the alveolar septa, within a few microns of the alveolar lumen.[37] The small numbers of MC in bronchoalveolar lavage (BAL) fluid (≤0.1% of all cells) likely result from epithelial shedding.[27,40]

■ ORIGINS OF MAST CELLS

MCs are believed to be derived from pleuripotent hematopoietic stem cells.[41] Tryptase-negative MC-colony–forming cells leave the marrow and circulate with a surface phenotype that is CD (cluster of differentiation) 34+, c-kit (CD117)+, LY–, CD14–, and CD17–. The progenitors home in a tissue-specific manner where they undergo differentiation, maturation, and synthesis of granule proteases in response to microenvironmental factors, including the matrix and chemokines from fibroblasts, endothelial cells, airway smooth muscle cells, and possibly T cells. The microenvironmental factor most critical in chemotaxis, differentiation, adhesion, proliferation, maturation and survival is stem cell factor (SCF or c-kit ligand), the ligand for the c-kit tyrosine kinase receptor. This receptor is expressed on the MC surface throughout its life span.[42,43]

■ MAST CELL HETEROGENEITY

Striking differences in the morphology, T cell dependence, resident proteoglycans, and responsiveness to secretagogues and drugs have been described in human MC.[44–51] The ontogeny of this heterogeneity, as well as the differing roles these MC play in physiology and disease remain speculative.

The most commonly recognized system for classifying human MC is based on the expression of protease profiles as determined by immunohistochemical staining using monoclonal antibodies. According to this system, the serine proteinase tryptase (T) is expressed in virtually all human MC, and a subset, predominantly in the submucosa of the gut and in the skin and within asthmatic airway smooth muscle also express chymase (C) and multiple other proteases including carboxypeptidase A and cathepsin G. Those that express tryptase alone are classified as the MC_T type, and those with additional proteases, as the MC_{TC} type.[52–54] Because significant numbers of both types can be found in the same organ (e.g., lung), tissue location alone cannot dictate the protease type. In the lung, only 8% to 35% of MCs are MC_{TC}, 1% is MC_C, and the remainder are MC_T. The protease system does follow some rules of distribution and function. MC_T are preferentially localized in bronchi, bronchioles, at mucosal surfaces, alveolar parenchyma, lamnia propia, in areas of T-cell infiltration and are reduced in immunodeficiency syndromes. The MC_{TC} phenotype does not appear immune related and more prevalent in pulmonary vessels and pleura. As detected by immunohistochemical staining, the subtype more selectively expresses interleukin (IL)-4 (85% MC_{TC} vs. 15% MC_{TC}). IL-5 and IL-6 are almost exclusively restricted to the MC_T subtype. Within human lung different compartments appear to show site-specific expression of FcεRIα, IL-9 receptor, histidine decarboxylase (higher in MC_T of bronchi than MC_T of alveoli), 5-lipoxygenase, leukotriene C_4 (LTC_4) synthase, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF)[55] and renin.

HLMC diameters vary between 8 and 18 μm with the majority being 12 to 15 μm. Histamine contents of 2.5 to 10.0 pg/MC vary directly with cell diameter. HLMC densities vary from 1.053 to 1.123 g/mL with the majority (67%) between 1.077 g/mL and 1.088 g/mL. These diameter and density-based subtypes also are distinct with respect to mediator content and function. MC location also subserves function: Airway and parenchymal MC differ in their releasibility. At the ultrastructural level, marked heterogeneity has been described (see Morphology below). Finally, at least two types of proteoglycans are present in HLMC: chondroitin sulfates, predominantly chondroitin sulfate E, and heparin. HLMCs are both positive and negative for the heparin-sensitive dye berberine sulfate, whereas stomach MCs synthesize exclusively chondroitin sulfate E and not heparin.[56,57]

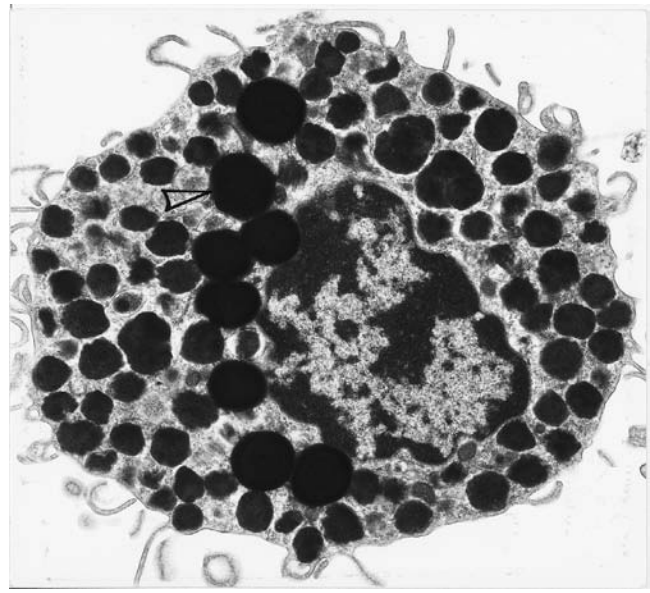

Figure 22-1 Ultrastructure of the human lung mast cell after purification. The mast cell is a mononuclear cell packed with multiple dense cytoplasmic granules that vary in size and shape. Eight electron-dense lipid bodies *(open arrow)* are bunched near the nucleus (×15,000). *(Reproduced with permission from Dvorak AM. Recovery of human lung mast cells from anaphylactic degranulation utilizes a mixture of conservation and synthetic mechanisms, in Galli SJ, Austen KF (eds). Mast Cell and Basophil Differentiation and Function in Health and Disease. New York: Raven; 1989.)*

■ MORPHOLOGY

All MCs are mononuclear cells with heterogeneous cytoplasmic granules (Fig. 22-1). A variety of granule-filling patterns occur within individual cells: scrolls, crystals, particles (the least seen in pure form), and combinations (mixed). The appearance of individual patterns can be influenced by cross section. Granules are outlined by a perigranular membrane. Cell membranes are outlined by short, narrow surface folds.[58–62]

■ MORPHOLOGY OF DEGRANULATION AND REGRANULATION

Following IgE-mediated (anaphylactic) activation of HLMC, granules swell and their perigranular membranes fuse to form canaliculi that open through multiple pores to the cell exterior. Within 20 minutes of activation, granular matrix materials solubilize within these intracytoplasmic channels and empty. In HLMC, only rarely is extrusion of nonsolubilized granules observed. Lipid bodies, which are electron-dense nonmembrane-bound organelles,[63–66] remain adjacent to these channels. They appear to serve as repositories of arachidonic acid and occasionally release lipid into the degranulation channels. In vivo, a process termed "piecemeal degranulation" is more frequently observed than anaphylactic degranulation.[67] This process involves the budding of small vesicles from granule membranes and their movement to the cell surface. Piecemeal degranulation may be more typical of the ongoing MC release observed in chronic asthma.

Depending on the extent to which an individual cell has degranulated, one of two predominant types of regranulation are observed individually or in combination. In partially degranulated cells, the channel (formerly perigranular) membranes are reutilized, and regranulation events resemble degranulation in reverse. In cells with

more complete degranulation, the channel membranes are placed in continuity with the plasma membrane and externalized. This results in the appearance of elongated, activated cell surface folds. These excessive folds can be internalized or shed. Shedding results in cells that are initially small (7 μm), but then enter a rapidly expanding recovery cycle to produce a fully mature cell.[62]

■ ACTIVATION

Immunological activation of MC is the mechanism most studied.[68] It results from antigen cross-linking of antigen-specific cell surface IgE molecules and subsequent aggregation of the high-affinity receptors (FcεRI) to which they are attached.[69,70] Receptor dimerization is the minimum cross-linkage requirement for IgE-mediated activation. In vitro, immunological activation can be achieved using antibodies directed against human IgE or the FcεRI-receptor itself. The mechanism(s) involved in chronic HLMC activation characteristic of asthma are not known but likely may reflect low-level allergen activation. Recent evidence contends that monomeric IgE alone, in the absence of antigen, can also induce prolonged mediator release, a mechanism that may be operative within the asthmatic airway.[71]

Non–IgE-mediated release triggers of MC are also well characterized. In general, the profile of agents that degranulate MC from human intestine and synovium is similar to that of HLMC but different from skin MC.[62,72,73] These non–IgE-mediated secretagogues include ionophores, hyperosmolar stimuli, and "histamine-releasing activities" derived from human alveolar macrophages and other cells.[74–77] The purified anaphylatoxin C5a, an active trigger of human basophils and dermal MC, is generally inactive in HLMC,[78,79] although CD88, the receptor for C5, has been reported in the MC_{TC}.[80] Consistent degranulators of dermal but not HLMC include substance P, morphine, polyamines such as 48/80, and SCF. Even within lung compartments, responsiveness to triggers may vary. Compound 48/80 is reported to degranulate BAL MC, whereas those from lung parenchyma are minimally responsive. To date, neuropeptides have been shown to be inactive in degranulating HLMC. Bee venom phospholipase (PL) A_2 and antigens from dust mites, cockroaches, pollens and fungal spores contain phospholipases and proteases, which can lead to MC release through the protease-activated receptor (PAR) 2.[81,82] Finally, expression in both mouse MC and human progenitor–derived MC of several innate pattern recognition receptors, including the Toll-like receptor-2 (TLR-2) and TLR-4, has been reported.[83,84] The expression of TLR and effects on activation of HLMC are as yet poorly defined. Human peripheral blood–derived cultured MCs are reported to produce type I IFNs following exposure to double-stranded RNA and/or virus, the former implicating TLR-3 expression.[83]

■ MODULATORS OF ACTIVATION

Although not acting as direct release triggers, a number of endogenous chemicals in the MC microenvironment can influence activation. Extracellular ATP and its breakdown product, adenosine, are potent modulators of HLMC degranulation, although neither directly activates HLMC in vitro.[36–38,85] In asthmatics, aerosolized adenosine induces bronchoconstriction, an effect not observed in other groups of pulmonary patients or normals.[86] The ability of antihistamines to inhibit this response has directly implicated activation of allergically primed airway MC by adenosine.[87,88] Components of the local connective tissue matrix such as fibronectin also modulate MC reactivity.[89]

■ BIOCHEMICAL ANALYSIS OF HLMC ACTIVATION

Elegant studies defining the biochemical events following IgE-mediated activation have been performed in rodent MCs or cell lines.[90,91] Evaluations of similarities and differences in HLMC activation await future investigations. Two receptors for IgE have been identified. The high-affinity IgE receptor (FcεRI) on MC and basophils is expressed in a tetrameric form ($\alpha\beta\gamma2$) and on antigen-presenting cells is present in a trimeric form ($\alpha\gamma2$). The Fc fragment of IgE binds to the α-chain of FcεRI. Expression of the β-chain amplifies signaling. A low-affinity IgE receptor (FcεRII; CD23) is present on B cells but not on MC or basophils.[92] Serum IgE levels correlate with basophil expression of FcεRI, likely indicating a role for IgE in stabilizing the FcεRI on the cell surface. As noted earlier, receptor dimerization is the minimum cross-linkage requirement for antigen-mediated allergen activation through the FcεRI. Following receptor aggregation, multiple signal transduction pathways are activated. Since FcεRI possesses no inherent tyrosine kinase activity, critical to the sequential activation are two tyrosine kinases, lyn which is associated with the β chain and syk. Lyn binds to the β-chain–associated immunoreceptor tyrosine-based activation motifs (ITAMs), which are phosphorylated after FcεRI aggregation. For degranulation to proceed, syk then binds to the γ-chain–linked ITAM, which are also phosphorylated after receptor aggregation. The lynsyk-driven pathway directly or indirectly stimulates tyrosine phosphorylation of several adapter proteins, including the transmembrane adaptor molecule linker for activation of T cells (LAT) among others. These events lead to the generation of inositol triphosphate (IP_3) which induces Ca^{2+} mobilization from intracellular rough endoplasmic reticulum (RER) stores. Also activated are phospholipase C-γ1 and PLC-γ2.[93–101] In this context, at 2 minutes following FcεRI aggregation, extracellular calcium influx occurs through CRACM channels (Ca^{2+} release–activated Ca^{2+} [CRAC] modulator 1),[102,103] which is a prerequisite for degranulation to proceed over the next 5 to 20 minutes. Other "early-phase" granule-associated and lipid mediators (e.g., arachidonate metabolites) are also released over 20 minutes. Over the ensuing 1 to 24 hours, mRNAs for select cytokines are generated followed by their protein synthesis and release.

■ CHEMICAL MEDIATORS

The clinical expression of MC-mediated responses may reflect the individual mediators or in certain instances, the interplay of the multiple mediators these cells release (Table 22-1). The temporal sequence of their release appears critical to the development of both the early- and late-phase responses after antigen challenge (Fig. 22-2). Certain mediators are virtually unique to MC (e.g., tryptase, chymase, heparin), and others are shared with one or more other cells (e.g., histamine, LTC_4, and IL-5).

Mediators released within minutes after activation are divided into preformed, or secretory, granule-associated mediators (e.g., histamine) and nonpreformed, or newly synthesized mediators (e.g., lipids). It is now known that tumor necrosis factor alpha (TNFα) may be both preformed and newly synthesized. Other cytokine mediators, including IL-5 and IL-13, are only detected over hours and may be critical to the evolution of the "late-phase" response.

■ PREFORMED MEDIATORS

Mast cells contain a number of preformed mediators. Each is discussed below.

Histamine

Histamine measurements have served as a classic marker of MC-mediated events. The pleiotrophic effects of histamine are mediated through the differential expression, regulation, and distinct intracellular signals evoked by four distinct receptors, H1, H2, H3, and H4. The actual role of histamine in asthma remains less clear, although levels in BAL fluid are many-fold higher in asthmatics, and plasma levels rise three- to fivefold following airway antigen challenge. Most histamine-induced allergic respiratory reactions are mediated via the H1 histamine receptor subclass, producing enhancement of vascular permeability, mucus production, initiation of neurogenic reflexes, and bronchial smooth muscle contraction. The reasons for the marginal value of the H1 receptor-blocking drugs in asthma may be due to high local tissue concentrations of histamine that exceed the inhibitory

TABLE 22-1 Human Mast Cell and Eosinophil Mediators

	Mast Cells	Eosinophils
Granule-associated (preformed) mediators	Histamine	MBP
	Heparin	ECP
	Chondroitin-sulfate E	EDN
	TNFα	EPO
		CLC protein
Enzymes	Tryptase	EPO
	Chymase	ECP, EDN
	Cathepsin G	Collagenase
	Elastase	MMP-9
	Carboxypeptidase-A	Indoleamine 2,3-dioxygenase
Acid hydrolases	β-hexosaminidase	β-glucuronidase
	β-glucuronidase	Arylsulfatase B
	Arylsulfatase	
Lipid mediators (nonpreformed)	PGD_2	LTC_4
	LTC_4	15-HETE
	LTB_4	5-oxo-ETE
	PAF	PAF
	Thromboxane-A_2	
Cytokines	IL-4, IL-5, IL-13	IL-1α, IL-2, IL-3
	IL-6, IL-8	IL-4, IL-5, IL-6, IL-8
	TNFα	IL-10, IL-12, IL-13
	TGFβ	IL-16, IL-17
	bFGF	GM-CSF
		TNFα
		TGFα
		TGFβ
		SCF
		NGF
		PDGF
		VEGF
Chemokines		CCL3
		CCL5
		CCL13
		CCL11
Reactive oxygen products	None detected	O_2^-, H_2O_2, OH
		HOBr, HOCl

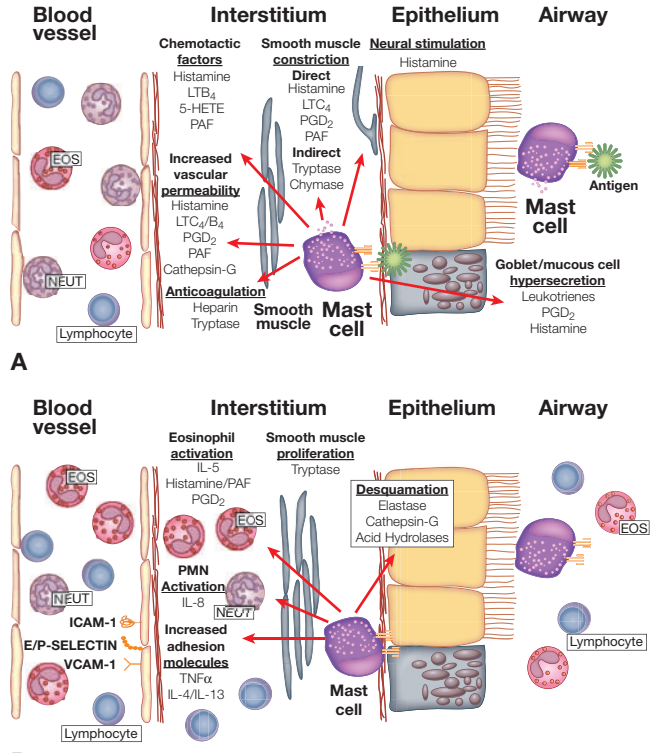

Figure 22-2 Effects of mast cell mediators in the early- and late-phase responses following airway allergen challenge. **A.** Early phase: Mediators are released within minutes following antigen cross-linking of allergen-specific IgE on the cell surface. Mechanisms of the initial airflow obstruction that persists for 30 to 60 minutes include smooth muscle constriction, edema formation due to increased vascular permeability, nerve stimulation, and mucus hypersecretion from both goblet cells and submucosal glands. **B.** Late phase. Within hours, the effects of newly synthesized and released cytokine mediators along with delayed effects of early-phase mediators produce recurrent airway obstruction. Mast cell mediators and cytokines can increase the expression of adhesion molecules on endothelial cells, both recruit and activate leukocytes (particularly eosinophils), contribute to epithelial desquamation, and stimulate smooth muscle proliferation.

capacity of these agents and/or the redundancy of histamine actions with the multiple other mediators that are released.

Proteoglycans

MC proteoglycans serve as the major determinant for the metachromatic tinctorial properties of the cell and form the granule backbone to which other preformed mediators, including histamine and neutral proteases, are bound. HLMCs synthesize heparin and chondroitin sulfate E proteoglycans in roughly a 2:1 ratio.[56] In humans, heparin appears to be unique to MC. In addition to anticoagulant activity, heparin possesses both anti-inflammatory and immunoregulatory properties.[104–106] Heparin may limit allergic responses in the skin, nose and lung and exert protective effects on exercise-induced asthma (EIA). The inhibitory effects may be related to the extracellular binding and inhibition of multiple mediators, including histamine and cytokines.

Chemotactic Factors

Within hours of MC activation, airway inflammation (the late-phase response) at the tissue level is characterized by the infiltration of leukocytes. This response is principally eosinophilic but also contains neutrophils and, over time, lymphocytes. Chemotactic mediators may be derived directly from MC and/or other cells through secondary stimulation. Early-phase MC-derived eosinophilic chemotactic activities include leukotriene B_4 (LTB_4), platelet-activating factor (PAF), and histamine.[107] HLMCs robustly express IL-8, which along with LTB_4, attracts neutrophils. MCs are responsive to chemokines released from other cells. Airway smooth muscle secretes a number of chemotactic factors including CXCL8, -10, -11, and -12. It appears that the CXCR3/CXCL10 axis predominately mediates the HLMC migration into the airway smooth muscle observed in asthmatic airways.[108,109]

Proteases

Large quantities of neutral proteases are contained within MC and constitute the predominant protein component of the secretory

granule. The proteases include tryptase, chymase, cathepsin G, carboxypeptidase A, and elastase.[52–54,110]

Tryptase is the predominant neutral protease of the MC granule. It is a tetramer that is stabilized by its association with proteoglycan. The concentration of tryptase in pulmonary MC is 11 pg/MC. Since the concentrations of tryptase in circulating basophils (α tryptase, see below) are negligible, responses characterized by the presence of histamine but not tryptase at the reaction site or in the circulation implicate mediation by basophils and not MC. Two forms of tryptase (α and β) have been identified. The α tryptase is constitutively secreted in an inactive form and reflects systemic MC burden. The active β form is packaged in the secretory granule and acutely rises in anaphylactic reactions. Postulated roles for tryptase in pathophysiology remain to be established. Described actions include the degradation of the neuropeptide vasoactive intestinal peptide (VIP), mitogenic effects on smooth muscle and epithelial cells, and inactivation of procoagulant proteins.

Chymase is associated with heparin in a manner similar to tryptase. The role of chymase in asthma and other disorders is not clearly defined. Chymase may play a role in tissue remodeling. Substrates include angiotensin I, converting it to the angiotensin II, VIP (inactivates), substance P, bradykinin, and kallidin (inactivates). Other activities include activation of matrix metalloprotease and stimulation of tissue neutrophilia and eosinophilia.

Cathepsin G is a neutral protease with chymotryptic specificities. The concentration of cathepsin G in HLMC is roughly 100 to 700 ng/10^6 cells. An elastase released from HLMC appears to be identical to human neutrophil elastase. A measurement of 40 to 170 ng/10^6 cells assumes all HLMCs contain this enzyme, although it may be localized to an HLMC subset. Among carboxypeptidases, the MC carboxypeptidase A, a metalloexopeptidase, is unique. Granule-associated acid hydrolases include β-hexosaminidase, β-glucuronidase, and arylsulfatase.

NONPREFORMED MEDIATORS

Arachidonic acid metabolites are generated within minutes of MC activation and play a crucial role in the early phases of the asthmatic response. Cyclooxygenase metabolism in MC generates large quantities of prostaglandin (PG) D_2 and a small quantity of thromboxane A_2.[37,111] PGD_2 is the most potent bronchoconstrictor of the cyclooxygenase metabolites. Additional actions of PGD_2 include induction of chemotaxis in eosinophils, basophils, and Th2 cells; increase in capillary permeability and vasodilation. Although all tissue MCs generate PGD_2, not all generate significant quantities of 5-lipoxygenase products (e.g., lung > skin). The major 5-lipoxygenase pathway products of HLMC are LTC_4, and LTB_4, with lesser quantities of 5-HETE. In IgE-mediated human lung challenges, MCs constitute the major source of released LTC_4.[112]

PAF is an early-phase phospholipid bronchoconstrictor that consists of a family of molecules. In contrast to the other lipid mediators, MCs appear to retain PAF intracellularly or demonstrate rapid reuptake of any that may be released.

HLMCs synthesize and release TH2-type cytokines, including IL-5, and -13, which are felt to be central to the evolution of the late-phase response.[113,114] Additional multifunctional cytokines, including IL-3, -6, -8, transforming growth factor beta (TGFβ), basic fibroblast growth factor (bFGF) and TNFα, are also synthesized by HLMC. In general, cytokine protein products are released over a 1- to 24-hour period following allergic activation. IL-4, a cytokine that virtually defines Th2 immunity, is immunolocalized to HLMC, which are rich in surface IL-4 receptors. However, generation of IL-4 mRNA and protein release has been reported by some, but not all, investigators.[113,115] TNFα, stored preformed within MC granules is in a unique position to exert diverse host defense effects in allergy and innate immunity.[116] Recent studies suggest that increased expression of TNFα within HLMC may play a role in asthmatic airway inflammation and correlates with asthma severity.[117,118]

Amphiregulin, a member of the epidermal growth factor family, is secreted following FcεRI-mediated activation. Its effects include increasing mucin gene expression, which may contribute to the epithelial cell metaplasia and mucus hypersecretion of asthma.[119]

PHARMACOLOGIC MODULATION OF MAST CELL FUNCTION

Only a limited number of pharmacologic agents have been tested in vitro on HLMC activation–secretion. In general, these agents have been tested on human parenchymal MC rather than those in bronchi or resident in BAL.[36,37,120] Moreover, inhibitory potency has been evaluated with anaphylactic degranulation rather than piecemeal degranulation, the latter being more characteristic of asthma.[121,122] Several receptors that inhibit MC activation contain immunoreceptor tyrosine-based inhibition motifs (ITIMs). Following inhibitory receptor activation these regions are phosphorylated, and then recruit phosphatases that dephosphorylate key-signaling molecules.[123] The common classes of antiallergic and/or antiasthmatic drugs used in clinical practice have received most evaluation. To date, the β-agonist pharmacologic agents, as typified by fenoterol and salmeterol, are reported to be among the most potent global inhibitors of HLMC mediator release with concentrations that inhibit histamine release by 50% (IC_{50}) of $\leq 10^{-8}$ M. Less effective inhibitors include the theophylline-like phosphodiesterase inhibitor isobutylmethylxanthine (IC_{50} = 0.5 mM) and PGE_2 ($IC_{50} = 10^{-5}$ M). Although widely touted as "MC stabilizers," disodium cromoglycate and nedocromil sodium, which recently have been shown as agonists at G-protein–coupled receptor 35 (GPR35)[124] poorly inhibit purified HLMC histamine release.[47,125] Inhibition of BAL MC activation by these agents is reportedly more striking.[126]

The effects of glucocorticosteroids on MC are diverse, including both stimulatory and inhibitory effects on the transcription of select genes. Release of early-phase mediators (e.g., histamine, LTC_4) in vitro and acute airway responses in vivo are unaffected by short pretreatment (up to 24 hours) with these drugs. In contrast, IgE-mediated generation of TH2-type late-phase cytokine mRNA and protein (e.g., IL-5, -13) are suppressed ($IC_{50} = 10^{-8}$–10^{-9} M).[127]

FK-506, a macrolide that binds to a specific binding protein, inhibits HLMC mediator release at low concentrations (0.1–300 nM). Cyclosporin A, which binds to cyclophilin, and auranofin, an orally absorbable gold compound, both inhibit HLMC mediator release.

Specific inhibitors of leukotriene generation include direct 5-lipoxygenase enzyme inhibitors, such as A-60477 (Zileuton), and indirect inhibitors, such as MK-886, which bind to a protein termed 5-lipoxygenase–activating protein (FLAP). Interestingly, PGD_2 release is markedly enhanced by FLAP inhibiton. This phenomenon has been termed a reverse shunt effect. Generally, 5-lipoxygenase pathway inhibitors do not affect HLMC histamine release. Cyclooxygenase-1 inhibition plays a critical role in a certain subset of "aspirin-sensitive" asthmatic patients (see below). Agents such as indomethacin potently inhibit HLMC PGD_2 generation ($IC_{50} = 5.5 \times 10^{-10}$ M) while producing significant enhancement of LTC_4 release.

MAST CELLS IN PULMONARY DISEASE

MCs have been implicated in a variety of pulmonary disorders based, to a great extent, on their presence in increased numbers and/or percentages in diseased tissues and the recovery of increased concentrations of MC-derived mediators, particularly histamine, in BAL fluid. Implicated pulmonary disorders include asthma, idiopathic pulmonary fibrosis, sarcoidosis, extrinsic allergic alveolitis, and chronic bronchitis.[51,128–131]

Asthma

MCs within airway epithelium are in an ideal sentinel position to be exposed to inhaled inciting stimuli. Intraepithelial MCs (IEMCs) express tryptase but seldom chymase except in severe asthma[27,29] and were traditionally thought to represent the classic MC_T phenotype. Recent reports assert that intraepithelial MC_T in "Th2-high" asthma also expresses carboxypepeptidase A3 (CPA3), which had previously been identified only in association with MC_{TC}. At baseline, even very mild asthmatics show evidence of continuous MC degranulation in bronchial mucosa and increased histamine content in BAL. Analysis of BAL in allergen-challenged atopic subjects and asthmatics demonstrates increased release of histamine, tryptase, and PGD_2. Increased numbers of lumenal MC are also noted and correlate with mediator content, airflow obstruction, eosinophil numbers, and bronchial hyperresponsiveness. In general, asthmatic MCs exhibit ultrastructural evidence of degranulation. In nonfatal asthma, there is a significant increase of MC within airway smooth muscle and mucosal gland stroma.[30] Multiple redundant MC mediators likely contribute to increased mucus gland secretion and smooth muscle constriction. Following chronic corticosteroid treatment, allergic reactions are diminished in association with depletion of MC in both the epithelium and submucosa.

Although much attention has been given to IgE-mediated mechanisms of asthmatic airway activation, it is likely that multiple other MC-triggering mechanisms operate under a variety of immunologic, occupational, and environmental conditions. One mechanism proposed for EIA relates to airway cooling and the generation of hyperosmolarity on the dried airway surface leading to MC degranulation.

Up to 10% of asthmatics are intolerant of aspirin and other nonstructurally related nonsteroidal anti-inflammatory drugs (NSAIDs). In vitro pretreatment of human airway tissues with indomethacin results in increased LTC_4 generation following IgE-mediated stimulation. MCs are the principal cells expressing LTC_4 synthase in the airways of aspirin-exacerbated asthmatics[132] and these patients have increased Cox-2 expressing bronchial MC numbers.[133]

Fibrosis

The cellular composition of diffuse fibrotic reactions includes striking increases in MC numbers. MCs synthesize and release important mediators of fibrosis, including TGFβ and hFGF.[15–18,134] The hypothesis that MCs and their mediators are critical to the development of fibrotic reactions is supported by animal models in which MC hyperplasia has been a constant finding in pulmonary fibrosis induced by bleomycin, ionizing radiation, and asbestos. Bronchial remodeling with subepithelial fibrosis is also a prominent feature of the asthmatic airway. It is not clear whether MC proliferation and activation drive and/or are secondary to the fibrotic process. The latter mechanism could be effected through fibroblast generation of SCF, producing MC proliferation, chemotaxis, and inhibition of apoptosis.

EOSINOPHILS

While eosinophils are considered leukocytes, like MC, they in fact reside primarily in the tissues. Indeed, the ratio of tissue to blood eosinophils is estimated to be 100:1 or greater. Under normal circumstances, the major resident population of eosinophils is in the lamina propria of the gastrointestinal tract. Eosinophils are also present in the thymus, as well as the uterus and developing mammary gland in females. In the absence of disease, very few eosinophils are found in the lung. On the other hand, large numbers of eosinophils traffic to the lungs and other tissues in the setting of allergic diseases, helminthic parasite infections and certain other pathological states.

■ EOSINOPHIL DEVELOPMENT

Eosinophils develop in the bone marrow from hematopoietic stem cell precursors. The immediate eosinophil precursor is a common eosinophil–basophil progenitor. Specific differentiation to the eosinophil lineage involves coordinated expression of the transcription factors, GATA-1, PU.1, and C/EBP. Among these, GATA-1 plays a central role, since mice with deletion of a high-affinity GATA-binding site in the GATA-1 promoter (ΔdblGATA1 mice) completely lack eosinophils, without loss of other hematopoietic lineages.[135] The cytokines, IL-3, granulocyte-macrophage/colony-stimulating factor (GM-CSF) and IL-5 stimulate growth and differentiation of eosinophils in the bone marrow. IL-5, the only one of these that is eosinophil specific, plays an essential role in stimulating bone marrow production of eosinophils and triggering their release into the circulation.[136] IL-5 is produced by lymphocytes and endothelial cells in the bone marrow, as well as by lymphocytes and parenchymal cells in the lung and other tissues. The importance of IL-5 in eosinophil production is demonstrated by the fact that transgenic mice overexpressing IL-5 develop profound blood and tissue eosinophilia.[137] On the other hand, IL-5 knockout mice have markedly reduced numbers of eosinophils at baseline, and fail to develop eosinophilia in response to allergen sensitization and challenge.[138] These and other findings have provided the impetus for development of IL-5 and IL-5 receptor–targeted monoclonal antibodies, which are under study for therapy of asthma and other eosinophilic diseases, as discussed below.

■ MORPHOLOGY AND STRUCTURE

The mature human eosinophil has a diameter of 12 to 17 μm, slightly larger than the neutrophil. The nucleus is usually bilobed, and the cytoplasm contains characteristic granules that stain yellow-pink with eosin. The distinctive features of eosinophil granules can be seen clearly by electron microscopy (Fig. 22-3). Primary granules, which appear during the promyelocytic stage of development, are round, membrane-limited structures that contain Charcot–Leyden crystal (CLC) protein.[139] Secondary (also termed specific or cytoplasmic crystalloid) granules appear later during eosinophil differentiation.[140] These are more numerous and appear as oval or elongated membrane-bound structures with a dense crystalline core and less dense matrix. The secondary granule core contains major basic protein (MBP), while other granule proteins are in the matrix. Lipid bodies are non-membrane-bound, lipid-rich organelles that localize arachidonic acid-metabolizing enzymes and serve as sites of eicosanoid synthesis.[141]

■ GRANULE PROTEINS

Eosinophils contain a number of cationic granule proteins that have toxic effects on parasitic helminths and RNA viruses, as well as on host cells. In addition, a variety of other proteins, including enzymes and cytokines, are stored in and released from eosinophil granules. MBP, a highly basic protein that accounts for more than half of eosinophil granule protein mass, is found in the crystalline core of specific granules.[142] MBP is synthesized as a preproprotein, which is cleaved to a 13.8-kD highly cationic molecule during eosinophil maturation. The pro-peptide, which is anionic, is thought to protect the developing eosinophil from the toxic effects of the highly cationic mature MBP. Low levels of MBP are expressed in basophils, consistent with their close lineage relationship to eosinophils. MBP is directly toxic to larvae of Schistosoma mansoni, Trichinella spiralis, and other helminths, supporting a role in host defense against parasites.[143] Several lines of evidence have suggested that MBP could be an important mediator of asthma. MBP inhibits ciliary function and is toxic to respiratory epithelial cells.[144,145] When administered to the airways of monkeys, MBP caused transient bronchoconstriction followed by persistent bronchial hyperresponsiveness.[146] In addition, MBP was shown to bind to and inhibit M2 muscarinic receptors, increasing vagally mediated bronchoconstriction in guinea pigs.[147] On the other hand, mice deficient in MPB showed no attenuation of airway histopathological changes or airway hyperreactivity in an allergen-induced asthma model,[148] suggesting that

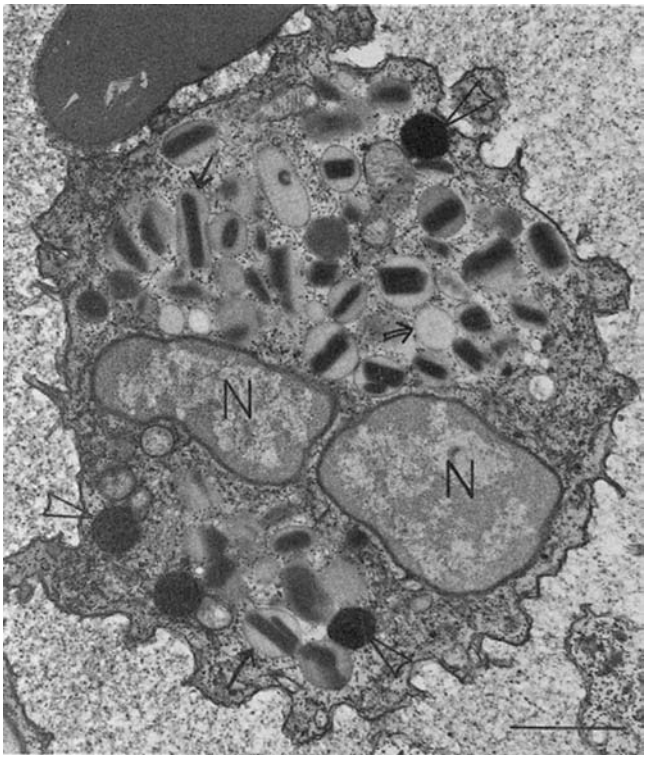

Figure 22-3 Ultrastructure of a mature human blood eosinophil. The bilobed nucleus (N), specific granules *(closed arrows)*, primary granules *(open arrow)*, lipid bodies *(open arrowheads)*, mitochondria, and irregular surface processes are seen. Dark cytoplasmic particles represent glycogen. *(Reproduced with permission from Dvorak AM, Ackerman SJ, Weller PF. Subcellular morphology and biochemistry of eosinophils, in Harris JR (ed). Megakaryocytes, Platelets, Macrophages, and Eosinophils, vol 2. New York: Plenum Press; 1991.)*

MBP does not play an essential role in allergic airway disease, at least in the mouse.

Eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) are both highly basic proteins found in the matrix of specific granules. ECP and EDN are homologous proteins (67% amino acid sequence identity), the result of gene duplication, that are also similar to human pancreatic ribonuclease (RNase) A.[143] Indeed, both ECP and EDN are active RNases, with the ability to inactivate RNA viruses, such as respiratory syncytial virus (RSV).[143] EDN was initially described as a neurotoxin that causes severe damage to myelinated neurons, a property possessed by ECP, as well. This activity may account for the neurological abnormalities seen in patients with hypereosinophilic syndrome (HES) and CSF eosinophilia. Like MBP, ECP and EDN are both helminthotoxic.[143] Levels of ECP are elevated in blood, BAL fluid, and sputum in patients with asthma, and have been found to correlate with disease activity.[149] For this reason, ECP levels in blood or sputum are often monitored in asthma clinical trials as a means of assessing response to treatment.

Eosinophil peroxidase (EPO) is another highly basic protein found in the matrix of specific granules. EPO is a unique peroxidase, expressed only in eosinophils. In the presence of H_2O_2, EPO oxidizes halide ions to form highly reactive hypohalous acids. Bromide is the preferred substrate, leading to hypobromous acid (HOBr), an extremely potent oxidant that damages DNA and other critical cellular targets. EPO plus H_2O_2 and halide ions can kill multiple parasites, bacteria, mycobacteria, and also MC and tumor cells.[150] The potential role of EPO in allergic airway disease has been explored in mice with targeted deletion of the EPO gene. In this study, despite a marked reduction in bromo-oxidation of lung proteins, EPO deficiency did not result in any attenuation of allergen-induced airway inflammation or bronchial hyperresponsiveness,[151] indicating that EPO is not essential for development of allergic pulmonary pathology in the mouse.

CLC protein localizes to the primary eosinophil granule, and is also expressed in basophils. The protein readily crystalizes to form bipyramidal CLCs, often seen in affected tissues and considered a hallmark of eosinophil-associated diseases. Previously thought to possess lysophospholipase activity, CLC protein has been shown to belong to the galactose-binding lectin family (galectins) and to avidly bind the sugar mannose.[152] Despite the long-recognized association of CLCs with eosinophil infiltration of tissues, the role of CLC protein in eosinophil-related pathology is unknown.

Eosinophils also contain within their granules various other enzymes, including β-glucuronidase, arylsulfatase B, and matrix metalloproteinase-9 (MMP-9), as well as preformed cytokines and chemokines, which can be released in regulated fashion, as discussed further below.

CHEMICAL MEDIATORS

Eosinophils may produce a number of important chemical mediators, each of which is discussed below.

Lipid Mediators

Upon stimulation, eosinophils produce large quantities of the 5-lipoxygenase–derived eicosanoid, LTC_4. Synthesis of LTC_4 in eosinophils occurs at the nuclear membrane.[153,154] and in cytoplasmic lipid bodies.[155] Following secretion, LTC_4 is converted extracellularly to LTD_4 and LTE_4. These cysteinyl leukotrienes act through $cysLT_1$ and $cysLT_2$ receptors to cause bronchoconstriction, stimulate mucus secretion, promote synthesis of Th2 cytokines, and contribute to airway remodeling.[156] The ability to block these effects underlies the beneficial actions of cysLT receptor antagonists and leukotriene synthesis inhibitors in asthma. Other biologically active lipids produced in substantial quantities by eosinophils include 15-HETE, 5-oxo-ETE, and PAF. However, the roles of these products in asthma and other eosinophil-associated diseases remain unclear.

Cytokines and Chemokines

Classically, eosinophils were considered terminal effector cells of inflammatory responses, acting by secretion of granule proteins and the acute release of other mediators. However, it is now recognized that eosinophils synthesize a wide array of cytokines and chemokines, equipping them to participate in the regulation of immune and inflammatory responses. The major cytokines and chemokines expressed in eosinophils are listed in Table 22-1. Interestingly, a number of these factors have autocrine or paracrine effects on eosinophils themselves. Most notably, IL-3, GM-CSF, and IL-5, which are produced by activated T lymphocytes and other cells, including MCs and eosinophils themselves, enhance eosinophil survival and activate eosinophil function in vitro and in vivo.[154,157–164] In another example, IL-16, a product of eosinophils and other cells, triggers rapid eosinophil release of CCL5 (RANTES), which generates autocrine signals that augment release of LTC_4 and IL-4.[165] A number of cytokines and chemokines synthesized by eosinophils are stored within granules. When cells are stimulated, these preformed cytokines are released by a regulated process involving piecemeal degranulation, which is described further below.

Eosinophil-derived cytokines likely contribute to regulation of inflammatory responses in eosinophil-associated diseases and drive specific pathophysiological responses. For example, elaboration of Th2 cytokines amplifies allergic responses, and is likely important in host defense against parasites and in pulmonary fibrosis. TGFα released by eosinophils is a potent stimulus for synthesis of mucins by airway epithelial cells,[166] which contributes to asthma and other eosinophilic airway diseases. Also, accumulating evidence implicates eosinophil-derived TGFβ as a driver of airway remodeling in asthma,[167] and suggests a link to pulmonary fibrosis, as well.[168] A clearer understanding

of the roles of eosinophil cytokines in human diseases will emerge as therapeutic agents designed to target specific cytokines, their receptors and downstream signaling pathways are tested in clinical trials.

Reactive Oxygen Metabolites

Like neutrophils, eosinophils synthesize superoxide anion ($\bullet O_2^-$) and H_2O_2 through the action of NADPH oxidase. Notably, NADPH oxidase components are more highly expressed and more readily activated in eosinophils than neutrophils, endowing stimulated eosinophils with a greater capacity to produce $\bullet O_2^-$ and H_2O_2.[169] As discussed previously, eosinophils produce HOBr through the action of EPO on bromide and H_2O_2.[150] In a reaction involving HOCl and $\bullet O_2^-$, EPO also catalyzes formation of hydroxyl radical (•OH), the most reactive of all oxygen metabolites. As noted, EPO-derived oxidants kill parasites and other microorganisms, and thus may be important for host defense. By contrast, EPO appears not to play a key role in allergic airway disease in mice.[148,151] The importance of eosinophil-derived oxidants in human health and disease is at present uncertain, and requires further study.

Eosinophil Recruitment

Current knowledge about the mechanisms of eosinophil recruitment into tissues is based largely on studies of asthma and allergic diseases, but these mechanisms may operate in other eosinophilic disorders as well. The initial step in eosinophil recruitment involves priming, which converts the resting cell to an adhesive, migratory and activation-sensitive phenotype. Priming likely results from exposure to IL-3, IL-5, GM-CSF and chemokines such as CCL11 (eotaxin-1), particularly in allergic individuals, in whom these factors are elevated in the circulation.[170–173] TNFα, leukotrienes, and other inflammatory mediators may prime eosinophils as well. Once primed, eosinophils make contact with the blood vessel wall and undergo rolling, mediated by E- and P-selectins on endothelial cells, which can be upregulated by IL-1 and TNFα, and L-selectin that is constitutively expressed on the eosinophil.[174–177] Rolling activates eosinophil integrins, which mediate tight adhesion through high-affinity binding to endothelial cell adhesion molecules. The eosinophil integrins, VLA-4 (α4β1 or CD49d/CD29) and CD11b/CD18, and their respective endothelial counterligands VCAM-1 and ICAM-1, comprise the most important binding pairs responsible for firm adhesion to the vessel wall. IL-4 and IL-13 increase VCAM-1 expression on endothelial cells.[178,179] Because VLA-4, the binding partner for VCAM-1, is highly expressed on eosinophils, but not neutrophils, this represents a mechanism for selective eosinophil recruitment to sites of allergic inflammation.[175,180] Integrin-mediated firm adhesion is followed by diapedesis, or transmigration across the endothelium. Eosinophils are further activated by endothelial transmigration, which also increases their ability to survive.[181] Based on in vitro studies, eosinophils can probably survive in tissues for 2 weeks or longer.

Upon entering tissue, eosinophils shift from β_1- to β_2-integrin–dominated interactions under the influence of chemokines such as CCL24 (eotaxin-2),[182] and migrate along chemoattractant gradients. Multiple factors are known to be chemotactic for eosinophils, including PAF, LTB_4, complement factors C3a and C5a, GM-CSF, IL-3, IL-5, IL-16, and the chemokines CCL3 (MIP-1α), CCL5, CCL7 (MCP-3), CCL11, CCL24, CCL26 (eotaxin-3), and CXCL8 (IL-8). Among these, IL-5 and the eotaxins (CCL11, CCL24, and CCL26) are the most highly selective for eosinophils, making them attractive as potential therapeutic targets. Indeed, clinical trials of agents directed against IL-5, CCL11, and their receptors in patients with asthma have recently been reported or are underway. The results of some of these studies are discussed at the end of this chapter.

Eosinophil Activation and Degranulation

The priming process required for eosinophil recruitment also represents the initial phase of eosinophil activation. IL-5 is the most important cytokine for priming of eosinophils in vivo.[170,171,183] IL-5 binds to heterodimeric receptors on the eosinophil surface, consisting of a ligand-specific α chain and common β chain that is also used in the receptors for IL-3 and GM-CSF. Binding of IL-5 to its receptor triggers a variety of intracellular signaling cascades, which enhance multiple eosinophil functions, including the response to chemotactic factors, integrin-mediated adhesion, agonist-stimulated LTC_4 and superoxide generation, phagocytosis, and helminthotoxic activity.[154,158,160,171,173,184] IL-3 and GM-CSF are capable of enhancing these functions, as well. As noted earlier, IL-5, IL-3, and GM-CSF also enhance eosinophil survival. The effects of all three cytokines are antagonized by glucocorticoids, which also induce eosinophil apoptosis.[185,186]

Priming of eosinophils in the circulation is enhanced in patients with asthma and hypereosinophilic states, resulting in greater functional responses when blood eosinophils from such individuals are studied in vitro, in comparison to cells from normal controls.[171] In vivo priming has also been demonstrated in eosinophils obtained by BAL following antigen instillation into the lungs of allergic subjects (segmental allergen challenge).[164]

Eosinophils express a panoply of surface receptors that can mediate cell activation. These include receptors for immunoglobulins (IgA, IgG, and IgE), complement components (C3a and C5a), eicosanoids (LTB_4, cysteinyl leukotrienes, and PGD_2) and PAF, and numerous cytokines and chemokines. Priming can upregulate cell surface expression and/or activation of specific receptors,[187] and may induce new expression of receptors not normally present on resting eosinophils, such as the high-affinity IgE receptor FcεRI.[188] Ligand binding to many of these receptors triggers responses that include degranulation, lipid mediator synthesis, and generation of reactive oxygen species. Various ligands activate distinct signaling cascades within the cell, resulting in stimulus-specific differential activation of eosinophil effector functions.

As in MC, the principal mode by which granule-associated proteins are released from human eosinophils is piecemeal degranulation.[140,189–191] This process involves secretion of specific granule contents in discrete packets, without granule-to-granule or granule-to-plasma membrane fusion. An eosinophil undergoing piecemeal degranulation in vitro is illustrated in Figure 22-4. Electron microscopic studies reveal that piecemeal degranulation is associated with the development of complex vesiculotubular networks within emptying granules.[190,191] Interestingly, it has been shown that intracellular cytokine receptors within granules and secretory vesicles play a key role in transporting and guiding selective secretion of their cognate cytokines, allowing for stimulus-specific, selective and sequential release of cationic granule proteins and stored cytokines and chemokines.[192] In addition, receptors for cysteinyl leukotrienes have been demonstrated on eosinophil granule membranes, where they may mediate secretion of granule contents from intact cells in response to endogenously generated LTC_4 or secretion from cell-free granules triggered by extracellular LTD_4.[193]

Besides piecemeal degranulation, the secretion of whole granules, referred to as compound exocytosis, has been described, although this process is not usually observed in vivo. Compound exocytosis involves SNARE family transport docking and vesicle fusion proteins.[194] Finally, cytolytic degranulation is a term used to account for the presence of cell-free eosinophil granules seen in tissue in certain eosinophilic diseases.[140] Whether this is a regulated process or the result of eosinophil necrosis at sites of inflammation is not known.

■ MAST CELL–EOSINOPHIL INTERACTIONS

Since shortly after their discovery, it has been recognized that MC and eosinophils home to many of the same tissues, particularly in the setting of allergic and other inflammatory conditions. Not surprisingly, therefore, researchers have identified a variety of cooperative interactions between the two cell types. For example, the eosinophil granule proteins MBP and ECP can trigger histamine, PGD_2, and cytokine

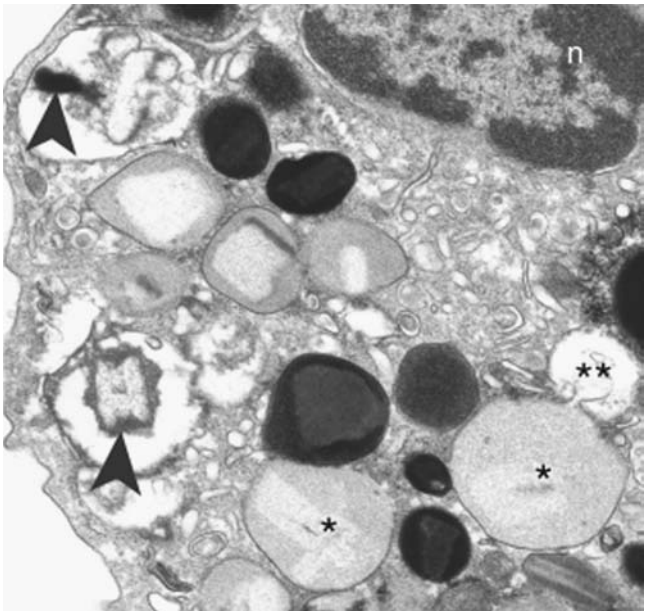

Figure 22-4 Ultrastructure of a human blood eosinophil activated in vitro with CCL11 (eotaxin). Specific granules undergoing piecemeal degranulation exhibit lucent areas in their cores, matrices, or both. Granules with residual cores *(arrowheads)*, reduced internal electron density (*) and membrane empty chambers (**) are shown. *(Reproduced with permission from Melo RCN, Perez SAC, Spencer LA, et al. Intragranular vesiculotubular compartments are involved in piecemeal degranulation by activated human eosinophils. Traffic. 2005;6(10):866–879.)*

release from human MC.[195,196] Eosinophils also produce important MC survival and activation factors, such as SCF and nerve growth factor (NGF).[197] Conversely, MC-derived TNFα induces eosinophil GM-CSF release and autocrine survival enhancement,[198] and MC tryptase induces eosinophil IL-6 and IL-8 secretion.[199] Also, the MC mediators histamine and PGD_2 have been shown to augment synthesis of LTC_4 in human eosinophils.[200] In addition, MC chymase suppresses eosinophil apoptosis and increases adhesion molecule expression, chemokinesis, and cytokine and chemokine release by human eosinophils.[201] Not all MC–eosinophil interactions are proinflammatory, however, as it has been shown that MC tryptase can cleave and inactivate the eosinophil chemokines CCL5 and CCL11.[202] Thus, MCs and eosinophils communicate bidirectionally in complex ways that may amplify or potentially modulate the inflammatory response.

EOSINOPHILS AND HOST DEFENSE

Many years ago, histopathological evidence of eosinophils surrounding dying helminths in tissue biopsy specimens led to the hypothesis that eosinophils play a role in the immune response to multicellular parasites. Subsequently, it was demonstrated that, in the presence of antibodies or complement, eosinophils can kill parasites in vitro, as can purified eosinophil granule proteins.[203] Further support of a role for eosinophils in host defense against helminths came from epidemiological studies that correlated high eosinophil counts with resistance to posttreatment reinfection with Schistosoma spp. in humans.[204] Moreover, studies of experimental helminth infections in mice depleted of eosinophils by IL-5 neutralization or gene targeting have indicated that IL-5 and eosinophils are important for protective innate immunity against a variety of parasites,[205–207] although the results are not all consistent.[208] Other studies of mice deficient in CCL11 or treated with a monoclonal antibody targeting CCR3 (the receptor for CCL11 and other eosinophil-active chemokines) have also demonstrated that eosinophils are important for clearance of parasites in vivo.[209,210] A recent study using mice made eosinophil-deficient by expressing the diphtheria toxin A gene under control of the EPO promoter (*PHIL* mice),[211] as well as mice lacking either MBP or EPO, showed that eosinophils kill parasite larvae during primary *Strongyloides stercoralis* infection by a mechanism dependent on MBP.[212] A consistent finding in a number of these studies is that eosinophils play an important role in host defense during primary parasite infection, whereas they appear not to be essential for adaptive responses leading to protective secondary immunity.[207,209,210,212] Interestingly, other recent studies showed that survival of *Trichinella spiralis* was actually reduced in mice genetically ablated of eosinophils, and that parasite growth and survival were restored when the mutant mice were reconstituted with eosinophils by intravenous transfer; in this model, eosinophils enhanced parasite survival by promoting accumulation of Th2 lymphocytes and preventing induction of inducible NO synthase in macrophages and neutrophils at sites of disease.[213,214] Thus, while substantial evidence indicates that eosinophils are protective in the innate immune response to many parasites, the roles they play in helminthic infections are complex and depend on interactions with other immune cells.

As noted earlier, human ECP and EDN are both RNases, and can inactivate RSV in vitro.[143] Mouse eosinophils express a diverse array of eosinophil-associated RNases (EARs) with the ability to inactivate pneumonia virus of mice (PVM),[215] a major pathogen in rodents that is closely related to RSV. More recently, it has been demonstrated that hypereosinophilic IL-5 transgenic mice exhibit enhanced virus clearance when infected with RSV,[216] and that activated eosinophils recruited to the lung in a model of allergen-induced airway disease are profoundly antiviral and promote survival in an otherwise lethal PVM infection.[217] Thus, while they contribute to the pathophysiology of allergic airway disease in the mouse, in the same context activated eosinophils have the capacity to mediate effective antiviral host defense. Further studies are needed to define the role of eosinophils in the immune response to viral infection in humans.

Human MBP and ECP also possess bacteriocidal activity, and various bacteria can induce degranulation of human eosinophils in vitro.[143] In addition, human eosinophils are able to kill *Escherichia coli* in vitro by a mechanism involving NADPH oxidase- and EPO-generated oxidants.[143] Despite these observations, few data exist to implicate a role for eosinophils in host defense against bacterial infections in vivo.

IMMUNOREGULATORY CAPACITY OF EOSINOPHILS

Recent investigations have demonstrated that human and mouse eosinophils can process antigen, express major histocompatibility complex II (MHC-II) and co-stimulatory molecules, and function as "professional" antigen-presenting cells.[218,219] In mice, eosinophils within the airway lumen can migrate to regional lymph nodes where they stimulate antigen-specific T-cell proliferation.[220] In addition, eosinophils synthesize, store, and secrete Th2 cytokines and chemokines, endowing them with the capacity to initiate Th2 differentiation of CD4+ T cells as well as recruit Th2 cells to sites of infection or allergen deposition, as demonstrated in several mouse models of allergen-induced airway disease and parasitic infection.[221] Thus, there is now substantial evidence, largely from murine models, that eosinophils play a central role in directing the Th2 immune response. These findings emphasize that, beyond their cytotoxic and destructive potential, eosinophils contribute in complex ways to host defense and the pathophystiology of allergic disease.

EOSINOPHIL–DISEASE ASSOCIATIONS

Peripheral blood eosinophilia and eosinophilic lung inflammation are common in a variety of pulmonary conditions, including those listed in Table 22-2. The clinical manifestations and treatment of these disorders are discussed in detail elsewhere in this textbook.

TABLE 22-2 Eosinophilic Lung Diseases

Asthma
Allergic bronchopulmonary aspergillosis/mycosis
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Helminthic infections
Drug hypersensitivity reactions
Hypereosinophilic syndrome

Among eosinophilic lung diseases, asthma is by far the most common and most well studied. Over the years, much evidence has accumulated supporting a key role for eosinophils in the pathogenesis of asthma. Among the numerous animal studies addressing this question, most compelling are those involving genetically eosinophil-deficient (ΔdblGATA1 and *PHIL*) mice, which are protected against allergen-induced airway hyperresponsiveness, allergic airway inflammation, mucus hypersecretion, and peribronchiolar collagen deposition.[135,211,222,223] In humans with asthma, eosinophils and their specific products (e.g., ECP) increase in the airway lumen and airway wall during spontaneous exacerbations and following experimental allergen challenge.[149,224,225] Sputum eosinophil numbers and ECP levels also correlate with asthma severity.[149] When asthma improves, either spontaneously or in response to treatment, eosinophils and their products decline.[226,227] Corticosteroids, the most effective therapy for asthma, have potent anti-eosinophil effects.[228] Also, an inhaled corticosteroid treatment strategy directed specifically at reducing sputum eosinophils resulted in significantly better asthma control than treatment based on standard asthma guidelines.[229] Finally, as discussed in the next section, specific eosinophil-targeted therapy with an IL-5–neutralizing monoclonal antibody has been shown to reduce exacerbations and facilitate steroid tapering in patients with severe, oral corticosteroid-dependent asthma with high eosinophils.[230,231]

HES is a rare disorder characterized by persistent marked blood eosinophilia (>1500/μL) or prominent tissue eosinophilia and eosinophil-induced organ damage or dysfunction, in which secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drugs, and hypoadrenalism have been excluded.[232] Pulmonary involvement is seen in 50% of cases. HES is classified as either myeloproliferative or lymphocytic, based on pathophysiology. The myeloproliferative form, exemplified by patients bearing the FIP1L1-PGDFRA fusion gene, which produces a constitutively active tyrosine kinase that drives eosinophil hyperproliferation, represents a type of myeloproliferative neoplasm. The tyrosine kinase inhibitor, imatinib mesylate, is useful in treatment of these patients. In lymphocytic HES, eosinophil proliferation is driven by T-cell overproduction of IL-5 and/or other eosinophil hematopoietins. Corticosteroids are the first line of treatment for these patients. The anti–IL-5 monoclonal antibody, mepolizumab, has also been shown to be effective in steroid-requiring lymphocytic HES.[233]

In addition to the disorders listed in Table 22-2, eosinophils may play a role in the pathogenesis of several pulmonary diseases not normally thought of as eosinophilic in origin. Among these is idiopathic pulmonary fibrosis, in which elevated numbers of eosinophils in BAL fluid have in some studies been associated with a poor prognosis.[234] This is consistent with in vitro and animal data demonstrating the ability of eosinophils to promote tissue fibrosis. Another example is cystic fibrosis, in which increased levels of cationic eosinophil granule proteins correlate with worse pulmonary function, presumably due to toxic effects of these proteins on lung cells.[235]

PHARMACOLOGIC MODULATION OF EOSINOPHILS

Corticosteroids have been the mainstay of pharmacotherapy for eosinophilic disorders for many years. Corticosteroids induce apoptosis of eosinophils, both directly and by inhibiting formation of the prosurvival cytokines, IL-5, IL-3, and GM-CSF.[185,186,228] This leads to rapid reductions of circulating and tissue eosinophils and clinical improvement in the majority of treated patients. Leukotriene receptor antagonists and the anti-IgE monoclonal antibody omalizumab are two other classes of drugs used to treat asthma and allergic diseases that have been shown to reduce circulating eosinophil counts and cause eosinophil apoptosis.[226,236] Of course, these classes of drugs are not specific for eosinophils, so the degree to which their anti-eosinophil activities contribute to their beneficial effects is uncertain.

More recently, highly selective anti-eosinophil therapeutics have been developed and tested in clinical trials. To date, the best studied of these new agents has been the anti–IL-5 monoclonal antibody, mepolizumab, which is highly effective in reducing circulating eosinophil levels in asthma. Although it did not improve clinical endpoints in mild to moderate asthma,[237] mepolizumab has been shown to reduce exacerbation rates, facilitate corticosteroid tapering and improve asthma-related quality of life in patients with severe, oral steroid-dependent asthma and increased sputum eosinophils.[230,231,238] As noted earlier, mepolizumab also led to clinical improvement and facilitated steroid tapering in a randomized trial of patients lymphocytic HES.[233] Similar benefits were seen in an open-label trial of mepolizumab in eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome).[239] Other eosinophil-selective therapies in earlier phases of clinical development include monoclonal antibodies, antisense oligonucleotides or small molecule inhibitors targeting the IL-5 receptor, CCL11, CCR3, IL-13, and the IL-4 receptor α chain.[240] An intriguing anti-eosinophil strategy in preclinical development involves targeting Siglec-8, a sialic acid–binding immunoglobulin-like lectin expressed on the surface of human eosinophils and MCs. Engagement of Siglec-8 with cross-linking antibody or glycan ligands triggers selective apoptosis of eosinophils and inhibits inflammatory mediator synthesis and release by MCs (without affecting their survival), suggesting the possibility that activators of Siglec-8 signaling might be particularly effective therapeutic agents by virtue of their ability to target two major cell types that drive allergic respiratory disease.[241]

Ongoing and future investigations involving the novel eosinophil–targeted therapies listed earlier, as well as others yet to be devised, will hopefully lead to safe, new treatments for eosinophilic respiratory disorders. Such studies will also almost certainly yield new and unexpected insights into the complex roles eosinophils play in human health and disease.

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CHAPTER 23

Leukocyte Accumulation in Pulmonary Disease

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INTRODUCTION

Mediators produced during inflammatory/immune responses dictate the severity and intensity of pulmonary disease. The profile of inflammatory leukocyte populations accumulating in inflamed tissues is initiated by cytokine-induced expression of adhesion molecules on the vascular endothelium. Endothelial adhesion molecules include intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), as well as E- and P-selectins that initiate, and in some cases, mediate the migration of leukocytes into tissues. Subsequently, leukocyte adherence to the endothelium is followed by leukocyte migration into the inflamed tissue, directed by chemotactic molecules at the site of the inflammatory/immune response. Upregulation of these early response mediators is crucial for the initiation of early events that regulate the inciting agent, whether it is infectious or noninfectious in nature. However, the continuous over-production of these mediators can lead to destructive, pathologic consequences due to the continued recruitment and activation of disease-specific leukocyte populations. In human lung, inflammation-induced damage can be observed in numerous inflammatory diseases, including both acute and chronic disease settings. In this chapter, we will examine the mediators that promote inflammatory diseases in lung and outline how specific leukocyte populations can contribute to pulmonary pathology.

LEUKOCYTE ADHESION AND MIGRATION INTO THE LUNG

Important considerations in the biology of leukocyte adhesion and migration into the lung are discussed below.

SELECTIN AND ADHESION MOLECULES IN LUNG INFLAMMATION

The release of early response mediators leads to the upregulation of selectins (E and P) and other adhesion molecules (ICAM-1, VCAM-1, etc.) on surfaces of vascular endothelial cells within the site of inflammation.[1–7] Initially, selectin molecules (P and E) are quickly upregulated on the vascular endothelium and initiate "rolling" of leukocytes on activated endothelium through Ca^{2+}-dependent recognition of cell surface carbohydrates of the *sialyl Lewis X* family and related oligosaccharides. Initial and rapid expression of selectin molecules results in a slowing of leukocyte velocities in the circulatory flow, allowing additional interactions to proceed.[8–11] However, such interactions are required to ultimately allow firm adhesion of leukocytes to endothelial cells. Once the leukocytes have begun the selectin-mediated rolling process, they must next go through a series of activation events to allow them to firmly adhere to other adhesion molecules. Leukocytes ultimately bind firmly to the vascular endothelium via β-integrin receptors on leukocyte surfaces, resulting in a very rapid increase in binding affinity, and engagement of other molecules that are upregulated during inflammatory responses on the vascular endothelium. A number of β-integrin adhesion molecules play a role in the migration process, and they are differentially expressed on subsets of leukocytes.[12–14] The β1α4 integrins (VLA-4), expressed primarily on mononuclear cells and eosinophils, have been shown to bind to vascular cell adhesion molecule-1 (VCAM-1), while β2-integrins (CD11/CD18) are expressed on all leukocytes and bind varyingly to intracellular adhesion molecules-1,2,3 (ICAM-1,2,3), the first of which is highly expressed on endothelial cells. These families of adhesion molecules are able to facilitate leukocyte binding to the activated endothelium and can further dictate the type of leukocytes that bind and extravasate into the inflamed tissue. For example, while neutrophils rely on CD11/CD18 binding to ICAM-1, eosinophils depend upon VLA-4/VCAM-1 interactions to firmly adhere to the endothelial cell surface. Once firmly adherent, leukocytes then enter the tissue following chemotactic gradients through a series of detachment/readherence events typified by the polar expression of integrins specific for the adhesion molecules contained on surfaces of mesenchymal-derived cells.

Cell-to-cell communication during inflammatory events is mediated by cytokines that initiate, maintain, and regulate the inflammatory responses, dictating the intensity of the inflammatory response. The early response cytokines, IL-1 and TNF appear to play a pivotal role in the induction of inflammatory responses through the initiation of cytokine cascades.[15–19] The exuberant production of IL-1 and TNF may lead to multisystem injury and systemic complications, as exemplified in septic shock syndromes. As indicated earlier, IL-1 and TNF initially upregulate selectin (E-selectin) and other adhesion molecules (ICAM-1, VCAM-1) needed for the first step of leukocyte extravasation into tissues. In addition, IL-1 and TNF upregulate other inflammatory cytokines (e.g., IL-6) involved in the chemotactic responses of leukocytes into inflamed tissues. Interestingly, the type of cytokine expressed can dictate the nature of the inflammatory response based upon the adhesion molecule that it induces. For example, while TNF and IL-1 are critical for upregulation of ICAM-1 that facilitates neutrophil and monocyte adhesion, IL-4 produced during allergic responses preferentially upregulates VCAM-1. This adhesion molecule mediates eosinophil adhesion. Thus, the inflammatory/immune cytokine environment in lung can tailor the initiation and adhesion interactions for a particular leukocyte recruitment profile. The production of one of a number of classes of chemotactic factors is required for the movement of leukocytes from the vascular compartment to the extravascular compartment of the lung. We will next describe and characterize the function of chemotactic mediators that are expressed in the lung during specific disease conditions.

CHEMOKINES AND GPCR SIGNALING IN LEUKOCYTE ADHESION

The rapid change in affinity of the β-integrins rely on two events: (1) Initial binding to selectin molecules that activates Syk and MAPK, allowing β-integrin to reach an intermediate affinity state; and (2) activation of leukocyte expressed G-protein coupled receptors (GPCR) on the surface of leukocytes.[20–27] The GPCR ligands, usually chemokines bound to the endothelium via glycosaminoglycans (GAGs), initiate rapid Ca^{2+}-dependent β-integrin activation.[28,29] The β-integrin activation results in a conformational change in its extracellular domain, allowing the active binding site for the putative adhesion molecule to be accessible. If the adhesion molecule is also upregulated and expressed on the activated vascular endothelium, the leukocyte rapidly and firmly adheres and spreads along the endothelial surface due to additional actin polymerization, which is also induced during chemokine-GPCR activation events. Thus, the leukocyte very rapidly transitions from a rolling leukocyte to a cell that is firmly adherent, resulting subsequently in transmigration into the tissue. In addition to the GPCR signal, it also appears that the shear stress experienced by leukocytes also plays a role in development in firm adhesion events. These interactions are described in Figure 23-1.

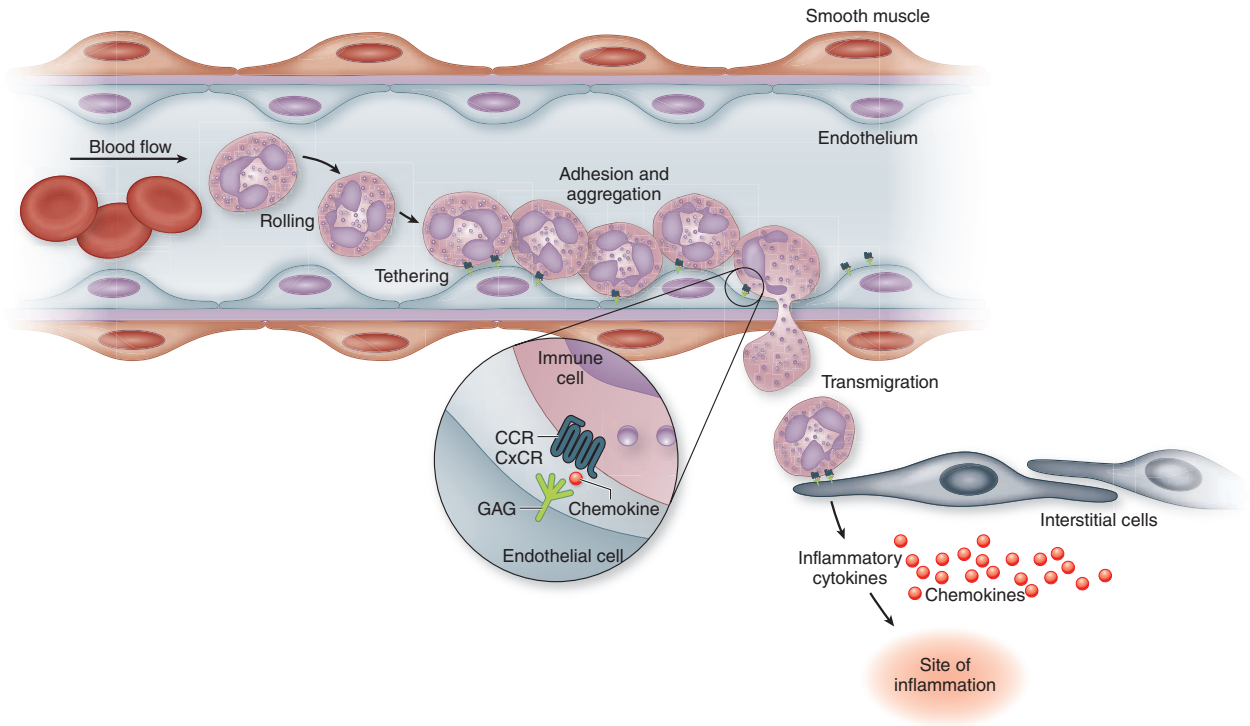

Figure 23-1 Leukocyte migration requires coordinated interactions between adhesion molecules and chemotactic molecules.

A significant amount of research has occurred in recent years, defining critical signaling events that occur during the early stages of leukocyte migration, including selectin-mediated rolling, GPCR-mediated integrin binding, actin polymerization, and leukocyte polarization. One of the most critical events in the transition of leukocytes from rolling to firm adhesion and extravasation is engagement of endothelial bound chemokine ligands with appropriate GPCRs. Chemokine binding activates the Gi-coupled protein-mediated phospholipase C (PLC), which results in inositol-1,4,5 triphosphate (IP_3) formation as well as diacylglycerol (DAG), triggering intracellular Ca^{2+} increases due to translocation from the ER.[30–32] This signaling cascade initiates the activation of Rho GTPases, Rap-1 and Talin1, subsequently mediating integrin affinity increase for their adhesion molecule ligands and allowing clustering following binding. Blockade of events at any stage along this activation pathway can inhibit the β-integrin–mediated adhesion, and interrupting firm adhesion to the activated endothelium.

■ CHEMOATTRACTANTS AND MIGRATION INTO THE LUNG

Below is discussed the role of various chemoattractants in the immune response against pathogens, including complement, arachidonic acid and its derivatives, and chemokines.

Complement

The complement activation cascade plays a significant role in the innate immune response against pathogens, but continual or excessive activation during inflammatory or infectious responses can lead to severe tissue injury. The initiation of the complement cascade can be accomplished via multiple mechanisms, including antibody–antigen complexes, bacterial products, toxins, and lectins (Fig. 23-2). Of the complement activation products, fragments from C3 and C5 have the most profound effects on the inflammatory response. The split products of C3, C3a and C3b, are generated by C3 convertase (other products of C3 cleavage [iC3b, C3d, C3g]) have significant activating roles in the inflammatory pathway. C3a is an anaphylatoxin that induces the activation of mast cells/basophils resulting in mediator release, all of which appear to have direct and indirect effects on vascular permeability.[33–35] C3b acts as a potent opsonizing component, binding to bacteria and allowing accelerated phagocytosis and clearance of pathogens via the C3b receptor on neutrophils and macrophages (Mac-1 [CD11b/CD18]). The split products of C5, C5a and C5b, can subsequently be induced through the sequential participation of C3b and C5 convertase. Similar to C3a, but much more potent, C5a is an anaphylatoxin that interacts with its two receptors (C5aR, C5L2), causing mast cell and basophil degranulation and activation of neutrophils, which collectively induces immediate changes in vascular permeability.[34,36–40] In addition, C5a stimulates vascular smooth muscle contraction and has neutrophil chemotactic and activating characteristics that promote directed migration of these leukocytes toward a concentration gradient.[41,42] C5a can also stimulate neutrophil oxidative metabolism, granule discharge, adhesiveness to vascular endothelium, and assembly on the neutrophil surface of NADPH oxidase (NOX2). C5a can directly stimulate endothelial cells in a G-protein receptor-dependent fashion to cause signal transduction events resulting in increased intracellular Ca^{2+}, induction of superoxide (O_2^-), and expression of P-selectin.[43–45] C3a lacks these activities. Altogether, the functions of C3 and C5 split products indicate that they are potent inflammatory mediators.

Elevated complement component levels in plasma have been described with several pulmonary diseases, including sarcoidosis, idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD).[46,47] Not only can complement initiate GPCR-mediated leukocyte migration but it appears complement activation products can direct the development of immune responses. This can be accomplished via several pathways during initiation of immune responses by regulating IL-12 production.[48] Specifically, C3a appears to drive IL-12 production that then favors type 1 immune responses,[49] while C5a downregulates IL-12 and allows IL-4–mediated type 2 immune responses to be induced.[50] Interestingly, recent studies in $C3^{-/-}$ mice have shown that Th17 responses are also regulated by complement.[51] In contrast, another study suggested that, when C5aR was blocked, there was an exacerbated allergic response that

Leukocyte population	Chemokine receptor
Neutrophil	CxCR1 (human only) CxCR2 CCR1
Monocyte	CxCR2 (inflammatory) Cx3CR1 (homeostatic) CCR1 CCR5
Dendritic cell	CCR1 CCR2 CCR6 (resting) CCR7 (activated/mature) CxCR4
Basophil	CCR2 CCR3
Eosinophil	CCR1 CCR3
Th1 cell	CCR1 CCR5 CxCR3
Th2 cell	CCR3 CCR4 CCR8
Th17 cell	CCR6
Treg cell	CCR4 CCR8

Figure 23-2 Preferential expression of chemokine receptors on leukocyte subsets can lead to preferential recruitment during pulmonary disease.

also was dependent upon increased IL-17,[52,53] suggesting that the previous study with $C3^{-/-}$ mice was due to inhibition of downstream C5a activation. Thus, while early complement-induced response is critical for containment of infectious organisms, it may be especially important during sensitization to various antigens in determining the phenotype of the pulmonary immune response that will govern the severity of disease outcomes.

The receptors for C3a and C5a have been a source of intense research over the past several years and have led to the resurgence of interest in potentially blocking specific responses during pulmonary disease. The distribution of these receptors depicts their broad role in innate and acquired immune responses. Both C3aR and C5aR are present on alveolar macrophages, DCs, and mast cells, and are also present on sentinel cell populations in the lung that provide important cues for the immediate and prolonged determination of effective immune responses.[54] In particular, activation of these cell populations have been assessed for the differential activation consequences of C3a and C5a. At the same time the expression of C5aR on neutrophils allows an immediate and efficient migration into the lung and activation at the site of inflammation. C5aR is also displayed on cells involved in chronic immune responses, such eosinophils recruited during allergic responses. Thus, activation of the complement system can have potent effects on both acute inflammatory responses as well as chronic inflammation, both of which can lead to long-term pulmonary dysfunction. Interestingly, a second C5a receptor, C5L2, binds C5a and C5a *des arg* extremely efficiently, but C5L2 has no linkage to G proteins.[55] Research examining the possible implications of this second receptor for modulating C5a-mediated responses by competitively binding up C5a during inflammatory responses is the subject of focus from several laboratories. While the function of this second C5a receptor has been controversial, C5L2 appears to mediate several pathologic events, including events in sepsis and perhaps diabetes.[56–60]

Role of Arachidonic Acid and its Products in Lung Responses

The production of arachidonic acid (AA) followed by its enzymatic processing produces a number of lipid mediators that have long been known to be associated with acute and chronic inflammatory responses in the lung.[61–63] Phospholipase A2 degradation of AA leads to its breakdown into platelet activation factor (PAF) that can be immediately processed by 5-LO into 5-HPETE and further processed by 5-LO into leukotriene A4 (Fig. 23-3). 5-HPETE can alternatively be processed into 5-HETE by peroxidases. Leukotriene A4 can be further processed into LTB4 by LTA4 hydrolase or LTC4 by LTC4 hydrolase, followed by continued processing of LTC4 into LTD4, and finally, LTE4. These latter metabolites, C4, D4, and E4 are known as the cysteinyl leukotrienes that are best known to cause airway contractility, causing decreased lung function during large airways disease, such as asthma. Targeting the cysteinyl leukotrienes for blockade has provided significant relief to particular subsets of asthmatic patients.[64]

Of the AA metabolites, PAF and LTB4 have been characterized for their chemotactic activity, promoting migration of leukocytes into sites of inflammation. These mediators were originally identified as potent neutrophil chemoattractants and were associated with acute inflammation-induced airway damage. PAF has a broad range of specificity in its ability to induce leukocyte chemotaxis, since it induces the recruitment of not only neutrophils, but also of monocytes, lymphocytes, and eosinophils.[65,66] During allergic diseases, PAF may have a role in augmentation of eosinophil responses.[67] The actions of PAF on endothelial cells indicate that PAF has a direct role in upregulation of selectin and adhesion molecules and can induce the release of superoxide anion (O_2^-). Instillation of PAF into human, monkey, or guinea pig airways induced an immediate LTC4-independent

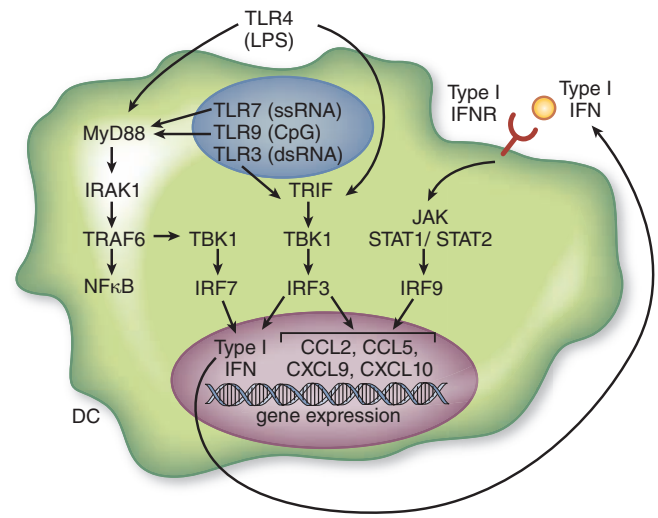

Figure 23-3 Inflammatory gene activation by TLR and type I IFN leads to enhanced leukocyte recruitment.

bronchoconstrictor response, suggesting a possible role in development of pathophysiology in asthmatic responses. Overall, these studies indicate that the signals provided by PAF are not only chemotactic but can also participate in the augmentation of immune/inflammatory pathways in lung. However, over the years several PAF specific inhibitors have been developed, but they have failed to demonstrate effective blocking or attenuating inflammatory responses in human lung.

While leukotrienes in general have broad effects on inflammatory responses, LTB4 is one of the most potent neutrophil chemotactic molecules known and induces O_2^- production. LTB4 can also act to recruit other leukocyte populations, such as monocytes and eosinophils.[68,69] In eosinophil chemotactic assays, LTB4 is more potent than PAF in the activation and degranulation of eosinophils. LTB4 has been found in many disease states, including psoriasis, bacterial peritonitis, inflammatory bowel disease and asthma.[70] LTB4 is rapidly expressed by phagocytic cells (PMNs and macrophages) following stimulation with bacterial LPS or fMLP. More recently, the LTB4 receptor, BLT1, has been implicated in preferential recruitment of Th2 type T lymphocytes during allergic pulmonary responses.[71–73] This receptor has also been implicated in recruitment of T lymphocytes that mediate lung allograft rejection and development of obliterative bronchiolitis in lung allographs in rodents.[74] Thus, LTB4 and BLT1 are now being considered as targets for therapy in chronic immune responses in the lung, in contrast to their traditional roles as potent neutrophil and mononuclear cell chemoattractant in acute lung injury.

Chemokines and Immune Cell Migration

Chemokines (discussed in chapter 26) have been divided into two main families based upon their sequence homology and the position of the first two cysteine residues, C-x-C (alpha) and C-C (beta).[75,76] There are two minor families described each with a single member, the C and Cx3C families. Much of our understanding of chemokines has centered upon their role in mediating leukocyte recruitment to the site of inflammation in lung or specifically directing recirculation of leukocytes during homeostasis. Interestingly, results have indicated that many of these family members also have diverse roles in the activation and differentiation of various immune and nonimmune cell populations. While the chemokine family members' function is diverse, the promiscuous binding relationship between multiple members with a single receptor as well as a specific receptor being able to bind multiple chemokines underscores our relative lack of understanding of the biology of the chemokine family. In particular, it is often difficult to understand how such a vast number of chemotactic molecules, several being produced simultaneously, could coordinate inflammatory responses. Recent studies demonstrate that it may be the overall profile of chemokines being produced that dictates the inflammatory cell response resulting in leukocyte accumulates at a site of injury or infection. This latter aspect can be best displayed during acute inflammatory responses, such as in bacterial infections, when the cellular infiltrate is primarily neutrophilic.[77] Chemokines that bind to CxCR1 and CxCR2 mediates this process. Likewise, when more insidious pathogens are present and acute inflammatory mechanisms cannot effectively control the infectious process, immune cytokines, such as IFN and IL-4, tend to drive the production of chemokines that allow the mononuclear cells, macrophages, and lymphocytes to accumulate at sites of infection, resulting in a more effective immune response for enhanced clearance of the pathogen. Thus, although there are numerous chemokines being produced during any single inflammatory response, the overall profile of the response may be directed to recruitment of cells that are most appropriate to deal with particular stimuli. These "fine tuned" responses mediated by chemokines also depend upon the chemokine receptor profile of the transmigrating leukocyte (Fig. 23-2). For example, while many leukocytes such as PMNs and macrophages tend to have a fairly fixed chemokine receptor expression (CxCR2 for PMNS and CCR2 for inflammatory macrophages),[78–80] T cell subsets (Th1, Th2, Th17, Treg cells) express a differential profile of chemokine receptors that may preferentially allow recruitment to specific types of inflammatory/immune responses.[81–84] Those aspects will be discussed in later sections.

LEUKOCYTE ACCUMULATION AND LUNG PATHOLOGY

A variety of leukocytes may accumulate with the lung. Each is discussed below.

■ NEUTROPHILS

The accumulation of neutrophils (PMNs) in the lung is the first line of defense against infectious organisms. There are significant numbers of PMNs circulating normally, and they can be quickly mobilized from the bone marrow during inflammatory responses or during acute lung injury. Once activated at the site of inflammation, PMNs preform phagocytic and bacterial/fungal killing functions that promote clearance of bacterial and fungal pathogens. They also can quickly release a number of enzymes, (proteases, etc.), that can have detrimental effects on the local lung tissue and cause physiologic dysfunction and severe damage if not tightly regulated. Individuals with one of many abnormalities in PMN formation, recruitment, or activation defects often develop recurrent, severe infections, both bacterial and fungal.[85,86] As described earlier, PMNs enter the lung via an initial adhesion event that progresses via a selectin-mediated rolling and subsequently through a β_2-integrin (CD11b/CD18)/ICAM-1–induced firm adhesion. While controversial evidence using animals exists, it appears that entry into the lung via the alveolar vasculature may not require the entire adhesion progression since there is low shear stress, allowing leukocytes to migrate into the airspace with less resistance.[87–90] This is because the diameter of the neutrophil and the capillary is nearly the same, which would not allow rolling. Nevertheless, in the alveolar vasculature the adhesion molecules described in section II are still present, functional, and are required for ultimate PMN transmigration. Not surprisingly, numerous chemotactic factors can quickly mobilize and mediate PMN migration into inflamed tissues. These factors include bacterial products such as fMLP, an N-formylated 3 amino acid peptide that is produced by numerous bacteria. fMLP binds to a GPCR (fMLPR). Other chemotactic factors expressed by the host early during pathogen responses include C3a and C5a, as well as the primary lipid mediator, LTB4, all interacting with specific GPCR signaling on the surface of PMNs. Usually, the early migration of PMNs to the lung is likely due to the latter mediators that are quickly cleaved or stored in cells (such as in mast cell granules) and are readily activated or released upon pathogenic or injurious stimuli. Subsequently, the prolonged activation of the pulmonary environment beyond immediate responses (>4 hours) results in cytokine cascades leading to additional and numerous more efficient chemokine protein mediators of migration, including CxCL1 (GROα), CxCL5 (ENA-78), and CxCL8 (IL-8). The CxC family chemokines are produced by both immune and nonimmune cell populations and provide relative specificity for PMN accumulation during lung inflammatory disease via their cognate receptors, CxCR1 and CxCR2, predominantly found on PMNs. Increased numbers of PMNs are often found in severe inflammatory diseases of the lung and likely provide nonspecific damage that may result in lung dysfunction. Several strategies for blocking adhesion as well as chemotactic receptors are currently under development by numerous pharmaceutical companies.

■ EOSINOPHILS

The role of eosinophils evolutionarily has been linked to chronic parasitic diseases, in which they perform a protective killing response linked to parasite clearance.[91,92] However, as the parasitic burden in humans has been greatly reduced, the immune responses, especially at mucosal surfaces, have led to detrimental chronic responses to

inert parasitic antigens. This has led to a number of allergic inflammatory diseases, especially allergic asthma in the lung. Eosinophils are derived in the bone marrow, primarily in the presence of a Th2 type response that provides systemic IL-5 levels that feedback to the bone marrow, directing the maturation and release of eosinophils into circulation. The migration of eosinophils into the lung and other tissues rely on a different subset of adhesion and chemotactic factors for entry into the tissue compartments.[93–99] While the migratory adhesion pathway has not been as thoroughly defined, it appears that it also relies on an initial combination of selectin and β-integrin–mediated adhesion events prior to responding to chemotactic mediators in the lung. While eosinophils are able to utilize CD11b/CD18-ICAM-1–mediated migration pathways, it appears that more efficient and preferential migration is VLA-4 β-integrin–mediated VCAM-1 adhesion. Since VCAM-1 is highly upregulated in the lung during Th2 cytokine–mediated responses, as in asthma, such responses may relate to the inflammatory cytokine environment that stimulates maturation of eosinophils in the bone marrow (IL-5 mediated). Subsequent to adhesion of eosinophils to endothelial cells, eosinophil migration and accumulation in lung can also be regulated by the chemotactic factors that appear to preferentially recruit eosinophils. While C5a and the lipid mediators, LTB4 and PAF, can each provide a stimulus for such migration, it appears that chemokines are the primary stimuli for migration of eosinophils. In particular, CCR3 ligands are the most potent, including CCL5 (RANTES), CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3). CCR3 is the characteristic chemokine receptor expressed on eosinophils and although they also appear to express CCR1, it appears to have only a minor role in the recruitment during chronic disease. Similar to the PMN, eosinophils can induce local damage in lung after their degranulation and release of proteases and enzymes. In addition, eosinophils have been implicated in progression of remodeling diseases, linked to their interaction with fibroblasts.[100,101] Eosinophils have the ability to transform normal fibroblasts into matrix-producing myofibroblasts. Eosinophils have been identified as a significant source of TGFβ, FGF, as well as other pro-fibrotic factors and have been implicated in severe remodeling in chronic allergic and inflammatory diseases.[102,103] Thus, significant effort continues to be made to target eosinophil migration during chronic pulmonary diseases, especially asthma.

MONOCYTES/MACROPHAGES

Resident macrophage populations play an important role in the lung, providing initial protection against pathogenic and noxious damage. The alveolar and interstitial macrophages that reside in and around airways appear to be ideally suited, having optimal ability to phagocytize and kill microorganisms as well as producing regulated levels of inflammatory cytokines. Macrophages also function for uptake of inhaled particles. Phagocytosis requires an intact cytoskeleton and is most efficient when phagocytosis is mediated by Fc receptors. Complement and scavenger receptors such as MARCO are also important mechanisms for mediating clearance of microorganisms.[104–107] During responses to infectious and inflammatory stimuli, the migration of monocytes from the blood can also play an important role in the clearance of the inciting agents. In humans, there appear to be two distinct subsets of circulating monocytes, CD14+ monocytes with high CCR1, CCR2 and CxCR2 expression, and low Cx3CR1 expression as well as a distinct CD16+ population of monocytes with high levels of Cx3CR1 and low levels of CCR2 expression.[108–110] Similar subsets exist in mice and, while not exact, this allows characterization of their different roles in disease once recruited to the site of inflammation allowing extrapolation to human disease. Mice lacking inflammatory, CCR2+ monocytes are highly susceptible to *Listeria monocytogenes* and *Mycobacterium tuberculosis* infections, demonstrating that infiltrating monocytes are important effector cells for the clearance of intracellular bacteria.[111,112] In a similar fashion the inhibition of inflammatory macrophage infiltration into the lung during *Aspergillus fumigatus* and *Cryptococcus* infections can lead to prolonged and detrimental infection by these organisms.[113,114]

The circulating CCR2+ monocyte population also appears to be the progenitor to inflammatory dendritic cells (DC), which express CD11b/CD11c. DC have a different developmental program and upregulate CCR6 on their surfaces for localization to airway epithelium where its ligand, CCL20, is expressed. This distinct subset of DC appears to be crucial for proper T cell activation to infections pathogens mediating Th1 type responses (IFNg producing) for the clearance of *M. tuberculosis*, *Toxoplasmosis gondii*, and *Cryptococcus neoformans* infections in animal models. In contrast, however, inflammatory DC recruitment to the lung (via CCR2) during chronic allergic disease may result in development of Th2 cytokine associated disease. Thus, the role of the inflammatory monocyte accumulation may depend on whether the inciting agent is an intracellular pathogen or a noninfectious stimulus that should optimally be ignored (immunologically tolerated), such as an allergen. Thus, attempts to regulate chronic inflammatory disease by targeting CCR2, its ligands or inflammatory monocytes themselves may cause deviations in lung inflammatory responses that are harmful.

INNATE LYMPHOID CELLS

A new classification of cytokine-producing cells has recently been named for their ability to respond to an inflamed environment in the absence of an antigenic specific stimulus. Innate lymphoid cells (ILC) have been further classified into three types, ILC1 (IFNγ-producing cells), ILC2 (IL-5/IL-13–producing Nuocytes), and ILC3 (IL-17/IL-22–producing cells).[115–117] These subsets are present in relatively low numbers in the lung and respond to innate cytokine signals and information of their accumulation during disease is only now beginning to be explored. ILC1 respond directly to IL-12 and express t-bet, similar to NK and Th1 cells, and have been recently shown to reside at much higher numbers in inflamed intestines of Crohn's disease patients. ILC1 cells appear to be distinct from NK cells, since they do not express granzyme B and other NK cell markers.

ILC2 (a.k.a. Nuocytes) or innate helper cells, respond to epithelial-cell–derived IL-33 and IL-25, express the GATA3 transcription factor, and contain Sca1+, c-kit+, Lin–, and ST2+ (IL-33R) surface markers.[118,119] ILC2 have been clearly implicated in parasite clearance in the intestine, but more recently have been identified in playing a role in models of asthma and influenza-induced disease.[120,121] The ILC2 have been the most extensively characterized and, although there appears to be only a few thousand residing in the mouse lung at baseline, they can produce high levels of Th2 type cytokines, (IL-5 and IL-13), in response to cytokine stimuli, especially IL-33.[122,123] Recent data has suggested that circulatory pools of ILC2 exist in human asthma patients, but further studies need to be explored to determine their relevance in human pulmonary diseases. Early studies suggested that ILC2 (nuocytes) express CCR2 and CCR3, but further study will be required to determine if these receptors mediate accumulation of the cells in the lung.

CD4+ T LYMPHOCYTE SUBSETS

The severity and chronicity of lung disease is dictated by multiple factors including the persistence of stimuli, pathogen or antigenic challenge, as well as the phenotype of the immune response. As discussed earlier and in other chapters, the mediators produced during pulmonary disease may be the most critical in determining the type of inflammation that develops. The discovery of several subsets of CD4+ lymphocytes that are defined by the profile of cytokines produced is critical for selectively responding to various infectious organisms and/or different phase of immune responses.[124,125]

The trafficking of naive lymphocytes from the blood to lymph nodes is pivotal to the maintenance of effective immune surveillance.

However, deciphering the mechanisms involved in lymphocyte recruitment during inflammation may be more pharmaceutically attractive in order to therapeutically regulate chronic debilitating inflammatory diseases. Functional diversity of T cells has been demonstrated by the observation that naive T lymphocytes are activated and differentiate into Th0 type cells that produce different combinations of cytokines. Subsequently, these cells can further differentiate into either Th1 type cells (IL-2 and IFN), Th2 type cells (IL-4, IL-5, and IL-13), Th17 cells (IL-17 and IL-22), or Th9 cells (IL-9) depending upon the cytokine environment that the Th0 cells are exposed. It has become clear that certain diseases are characterized by the Th cytokine phenotype that is produced. For example, allergy and asthma responses have been identified as a largely Th2 type disease, with IL-4, IL-5, and IL-13 promoting the pathogenic phenotype. However, these traditional points of view have begun to break down as we begin to understand that, when we look at an exacerbated disease phenotype, such as a virus or bacterial infection, there appears to be a complex mix of Th cytokine phenotypes.[126–131] In particular, both bacterial- and viral-induced exacerbations appear to enhance the pathology by promoting IL-17 production that, while responding to the pathogenic assault, can also create chronic disease, examples of which are remodeling and mucus hypersecretion responses.[132,133]

Although numerous chemotactic mediators have been implicated in lymphocyte migration, the chemokine mediators appear to preferentially attract specific lymphocyte subsets, both based upon differential receptor display as well as chemokine ligands that are produced in the lung during a particular disease.[125,134,135] For example, IFN and TNF that are produced during Th1 type responses induce CCL3 and CCL5 that bind to CCR1 and CCR5 that are found on Th1 type cells. Other Th1 associated chemokines CxCL9, 10, and 11 all bind specifically to CxCR3 that is also highly expressed on Th1 type cells along with expression on $CD8^+$ cytotoxic T cells. Thus, these profiles of chemokine production are most appropriate for viral and intracellular bacterial infections. Likewise, there are CC chemokines that are preferentially upregulated by Th2 cytokines (IL-4 and IL-13), but not Th1 type cytokines including CCL1, CCL11, CCL17, and CCL22. These chemokine mediators bind to CCRs preferentially found on Th2 cells, including CCR8, CCR3, and CCR4, respectively. Thus, the cytokine environment can reinforce itself by recruiting additional T cells capable of producing chemokines associated with the allergic/asthmatic responses.[136–139] Recent data has also identified other chemokine receptor phenotypes, including CCR6/CCL20 receptor system that appears to be associated with Th17 cell migration.[140,141] Interestingly, CCL20 (LARC) is produced at significant levels by bronchial epithelial cells and attract both inflammatory DC and Th17 type cells that have increased expression of CCR6. Thus, effort continues to be made to identify compounds that might inhibit specific chemokine receptor GPCRs that can be used in specific chronic disease responses.

BACTERIAL INFECTION AND SEPSIS

The early response to infectious organisms is most important when dealing with bacterial infections that can be reversed by preventing colonization and by quickly eliminating the inciting agents. Bacteria, once established, can proliferate at an exponential rate that outpaces the ability to clear bacteria. These events can quickly overwhelm the local sentinel defenses provided by lung macrophage populations. A critical step in early bacterial clearance is the efficient and early recruitment of phagocytic cells (PMNs and monocytes) from the blood. The first response initiated in this case is activation of the complement system quickly resulting in the generation of C3a and C5a.[142] This initiates an early wave of infiltrating leukocytes that may be sufficient for removal of the invading pathogens. In a parallel process of de novo synthesis, continued persistence of the bacteria quickly leads to release of LTB4 from granulocytes, mast cell degranulation, and production of LTB4 from macrophages. LTB4 release effectively maintains the inflammatory influx of PMNs to cope with the presence of bacteria.[143] Subsequently, macrophage populations produce activating cytokines, (IL-1 and TNF), that mediate both adhesion molecule expression on endothelial cells and chemokine production, such as IL-8 and MCP-1, that promote continued influx of phagocytic cells.[144–146] A critical mechanism associated with bacteria-induced inflammatory responses has been shown to be inflammasome activation that induces a caspase-mediated process that cleaves pro-IL-1 to active IL-1 and activates NFkB pathways leading to induction of chemotactic responses that exacerbates inflammation.[147–149] Targeting inflammasome activation and especially IL-1 can significantly attenuate inflammatory diseases.[150–152] Recent evidence suggests that these activation pathways are central to the numerous inflammatory diseases, such as IBD,[153] with recent evidence indicating that pulmonary diseases may also be affected by inflammasome activation.[154–156] Thus, a well-coordinated and multifaceted series of chemoattractants are produced to promote acute inflammatory responses to control the bacterial infection. In addition to bringing about leukocyte migration, these chemoattractants activate PMNs and macrophages to promote enhanced phagocytosis and killing.

One of the harmful consequences of a vigorous and sustained recruitment of PMNs and macrophages, however, is the release of substances that cause tissue damage and necrosis of epithelial cells. Phagocytic cells, in response to the bacterial stimuli and phagocytic action, release proteolytic enzymes, reactive oxygen metabolites, and additional activating cytokines that cause injury to vascular and stromal cells in small and large airways. In particular, elastase release from PMNs may have a devastating effect on tissue.[157] Reports have suggested that the level of PMN-derived elastase in the airway reflects the intensity of PMN accumulation and correlates to the incidence of ARDS development.[158,159] There are numerous causes of PMN activation, including trauma, hemorrhage, burn, etc., all of which can lead to the development of life-threatening ARDS.

ARDS is a common disorder encountered in the ICU and involving septic patients, whether related to bacterial-induced disease or "sterile" inflammatory syndromes. Bacterial infections release danger associated molecules patterns (DAMPs), such as lipopolysaccharide or lipoteichoic acid, which interact with TLRs.[160] Sterile inflammation is a situation in which there is no bacterial inciting agent. This response leads to release of a variety of endogenous products generically referred to as "alarmins." These products interact with NOD receptors the result sometimes being a cytokine storm, multiorgan failure, and death.[160,161] ARDS is an overwhelming inflammatory response ("cytokine storm"), control of which is not possible at this time. These uncontrollable hyperinflammatory responses have been linked to PMN-associated inflammation. Thus, much of the current therapeutic effort has been focused upon attempts to reduce the ongoing influx and activation of PMNs. A number of investigations have examined the potential role of blocking PMN accumulation by blocking CD18 (Mac-1) with antibodies. These studies were largely unsuccessful, emphasizing our inadequate knowledge of lung inflammatory responses.

Given the lack of requirement in some models for adhesion molecule-dependent PMN accumulation, the role of chemotactic molecules has been more widely studied. In animal models of acute lung injury, blockade of C5a and/or its receptor, C5aR, attenuates lung injury, preserving vital lung function.[33,89,162,163] There has been interest in developing new therapies around blocking complement activation cascades as well as development of therapeutic antibodies designed to inhibit the acute inflammatory response. However, since complement and LTB4 mediators are primarily thought to be involved during the initial stages of inflammation and may only constitute a portion of the chemotactic environment, other more stable mediators have been targeted, especially the chemokines. A

large body of literature has characterized the significant levels of PMN-associated chemokines, in the CxC family.[164] They have been identified in the airways of ALI and ARDS patients, with the mediators' presence correlating with the severity of the inflammatory response. Numerous animal model studies have demonstrated that, by targeting the CxCR2 or its ligands, or using functionally inert CxCL8 (IL-8) homologs, a reduction in inflammation severity can be achieved. This has led to numerous pharmaceutical attempts for development of efficacious and safe compounds and biologics directed against chemokine ligands and their receptor, CxCR2. The CxCR2 antagonists may not only be useful in ALI or ARDS but in numerous other pulmonary diseases that appear to have PMN infiltration, including COPD, severe asthma, and even cystic fibrosis. Thus, controlling PMN infiltration and activation may be at the core of preserving lung function.

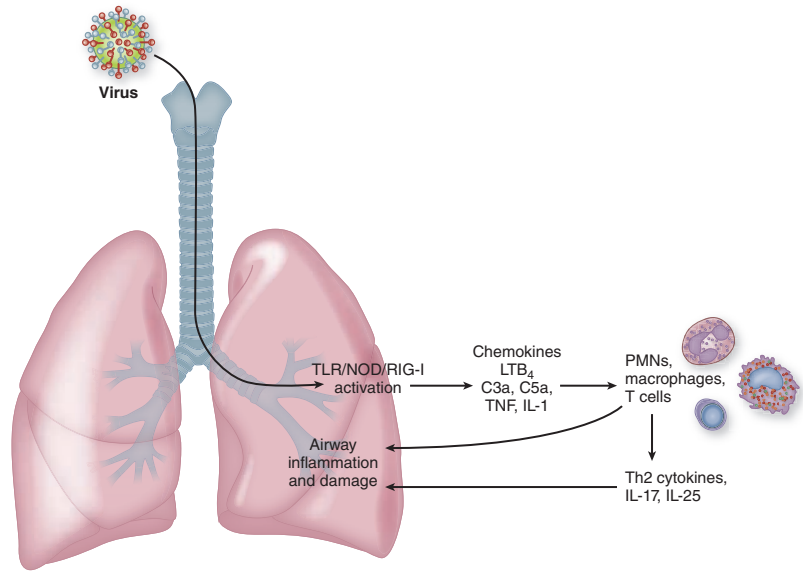

Figure 23-4 Viral exacerbation in pulmonary disease enhances chemotactic and inflammatory cytokine production leading to increased disease severity.

VIRAL EXACERBATION OF LUNG DISEASE

Many causes have been identified to explain exacerbation in patients with underlying lung disease, especially asthma and COPD. Viral infections appear to be the most common cause, such as with influenza, rhinovirus (RV), adenovirus, and respiratory syncytial virus (RSV). While there may be common pathways involved in the exacerbation of pulmonary diseases, activation of chemokines by viral pathogens may be the most prevalent mechanism.[165–168]

Approximately 10% of adults and up to 30% of children are affected by asthmatic disease, making it the most prevalent chronic respiratory disease, whereas COPD is an induced disease most clearly associated with smoking and occurs predominantly in older adults. The mechanism for viral exacerbation of the chronic lung response is unclear, but evidence points to a key role for increased leukocyte recruitment, inflammatory cell activation, and T cell differentiation. The asthmatic condition includes increases in mucus production and epithelial damage along with possible increases in airway remodeling and smooth muscle cell hyperplasia. While many viruses may be causative of asthma and COPD exacerbations, the most common viruses, RV, RSV, and influenza, all appear to function through many common pathways.[169–172] During infections, the upregulation of CxCL8 is significantly increased in sputum samples. CxCL8 is the mediator most frequently associated with exacerbation. Its presence correlates with the number of neutrophils and is productive of the severity of the exacerbation. PMN accumulation and activation lead to the local release of a number of proteases and MPO, with elastase having a significant effect on potentiating mucus production in the airway. In addition, other inflammatory mediators have also been detected during viral-induced exacerbations, including IL-6, LTB4, LTC4/D4, and histamine. Other chemokines that appear include CCL11 (eotaxin) and CCL5 (RANTES). Both have the ability to recruit eosinophils, further intensifying the inflammatory environment in lung.

The commonality of responses between these different RNA viruses likely stems from activation of Toll-like receptors (TLRs).[173,174] Virus-infected epithelial cells and innate immune cells quickly respond to the viral nucleic acid by TLR3 and TLR7/8 activation via dsRNA and ssRNA, respectively.[175,176] The activation of these TLR pathways activate several important mediator pathways including the TRIF adapter pathway leading to IRF3 and MyD88 adapter pathways that lead to NFkB for TLR3 and TLR7 (Fig. 23-3). The NFkB pathway mediates the production of a number of activating and chemotactic proteins, whereas the TRIF pathway primarily upregulates type I IFN and associated chemokine such as RANTES. Interestingly, however, there are differences in the ability of the different viruses to induce different levels of mediators, especially type I IFN. Influenza virus is known to promote high levels of type I IFN, described in animal models, often accompanied by secondary bacterial infection.[177,178] In contrast, RSV promotes comparatively low type I IFN due to specific inhibition of the activation pathways by nonstructural (NS) proteins produced by the virus.[179–182] Since type I IFN can induce additional chemokines together with the lytic nature of influenza, this may explain the intensity of the inflammatory responses that accompany influenza versus RV and RSV infections. Other pathogen recognition pathways, including the helicase (RIG-I) and NOD/inflammasome pathways have also been identified in these responses and contribute significantly to the inflammatory outcome of the responses.[183,184]

In addition to increased chemokines, it appears that other important mediators may also be preferentially expressed during viral exacerbation of asthma and COPD. Both IL-17 A and/or IL-25 (IL-17E) are induced during viral infections. The addition of these two IL-17 family members, both of which share a common receptor chain (IL-17RA), may contribute significantly to the pathogenic environment. Both types of infection induce a steroid-resistant response.[185,186] In the case of IL-17, a neutrophilic inflammation is induced through activation of CxC family chemokines, whereas IL-25 appears to induce an eosinophil accumulation and Th2 cytokine responses that on its own promotes a mucus-rich pathogenic environment. Thus, the addition of these two cytokines may be very important targets during these chronic airway responses where patients often develop steroid resistance in the most severe cases. As depicted in Figure 23-4, the ability of viruses to exacerbate pulmonary disease severity is a consequence of increasing the overall inflammatory response through the activation of several chemotactic mediators via PAMP-mediated pathways, as well as the activation of additional cytokine responses. Similar responses are operative during bacterial-induced disease exacerbation. While this section has outlined several of the critical mediators, other pathways are also important for the overall disease phenotype.

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CHAPTER 24

Antibody-Mediated Lung Defenses and Humoral Immunodeficiency

Homer L. Twigg III

Antibody-mediated, or humoral, immunity is essential for host defense against respiratory pathogens. Defects in humoral immunity are common and frequently underappreciated. From a respiratory perspective, patients with impaired humoral immunity are susceptible to recurrent bacterial sinopulmonary infections and bronchiectasis. Antibody responses are also the principal mechanism behind the efficacy of vaccination against respiratory pathogens. This chapter focuses on our understanding of the normal B cell environment in the lung, generation of appropriate antibody responses after antigenic challenge, disease states associated with impaired lung humoral immunity, and the pulmonary response to vaccination.

OVERVIEW OF B CELL DEVELOPMENT (ONTOGENY)

The primary cell responsible for generating humoral immunity is the B lymphocyte. There are two phases in the development of antibody responses. The first phase is antigen independent and is called lymphopoiesis. As with the generation of other immune cells, the process begins with a multipotent stem cell in the bone marrow, which undergoes multiple maturation steps leading to mature but antigen naïve B lymphocytes (Fig. 24-1), which express IgM and IgD on the cell surface.[1] This process occurs entirely within the bone marrow (or liver during fetal development). Important cytokines in this process include interleukin (IL)-7,[2] *ckit*-ligand (stem cell factor),[3] and IL-11.[4] Mature B cells express the surface receptors CD19, CD20, CD21, and CD72.[5,6] CD20 is especially relevant as it is the target of the monoclonal antibody rituximab, which is used to deplete B lymphocytes in B cell lymphoproliferative disorders[7] and autoimmune disorders characterized by the production of pathogenic autoantibodies.[8]

At the completion of lymphopoiesis IgM expressing B cells traffic to various lymphoid organs, including lymph nodes in the lung, to await antigenic challenge and enter immunopoiesis.[9,10] Thus, unlike

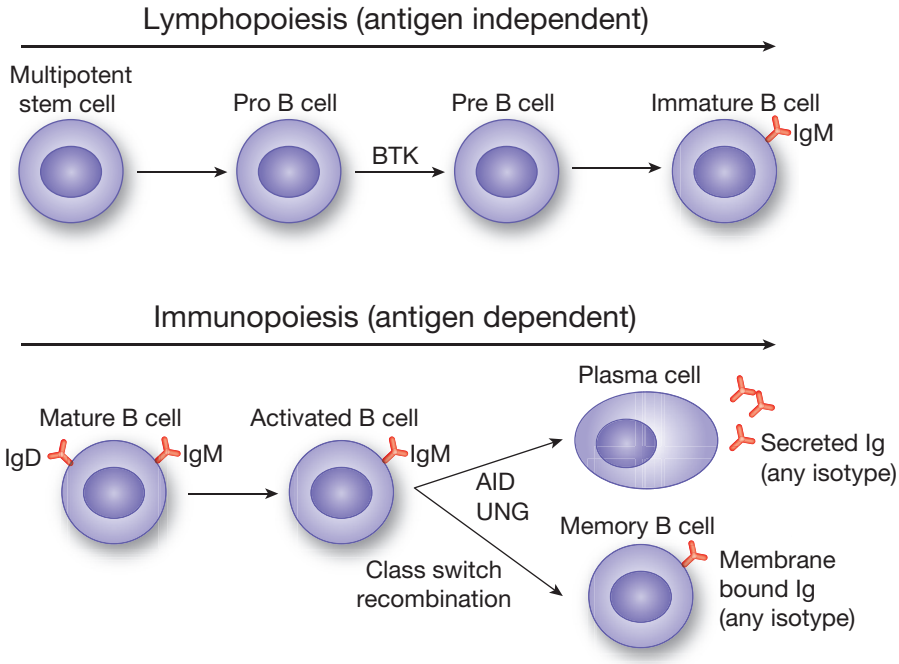


Figure 24-1 Overview of B cell ontogeny. Lymphopoiesis, which occurs in the bone marrow or fetal liver, is an antigen independent process, which begins with a multipotent stem cell and ends with an IgM expressing immature B cell, which will migrate to lymphoid tissues. Immunopoiesis begins with antigen stimulation (hence antigen dependent) and results in antibody secreting plasma cells and antibody expressing memory B cells. Class switch recombination leads to the generation of different immunoglobulin subtypes (IgG, IgA, IgE) from activated IgM expressing B cells. BTK, Bruton's tyrosine kinase, AID, activation-induced cytidine deaminase, UNG, uracil-N-glycosylase.

lymphopoiesis, immunopoiesis is antigen-dependent. The end result of immunopoiesis is the generation of antibody secreting plasma cells[1] and long lived memory B cells, which secrete immunoglobulin only upon re-exposure to antigen.[11] During immunopoiesis class switch recombination and somatic hypermutation occur resulting in the generation of IgA and IgG secreting cells out of IgM precursors and will be discussed in detail below. Immunopoiesis is most efficient in the presence of antigen activated T cells that provide "help" to B cells in the form of cytokines and cell surface activation signals. The most critical latter signal is the interaction between CD40 on B cells and CD40L on activated T cells. In the absence of such signaling (i.e., due to genetic mutations in CD40 or CD40L) class switching fails to occur, resulting in the accumulation of IgM secreting cells and the hyperimmunoglobulin M syndromes, discussed later in this chapter.

IMMUNOGLOBULIN DEVELOPMENT AND STRUCTURE

Below are discussed the basic structure of immunoglobulins and important characteristics of those immunoglobulins found in the lung.

BASIC STRUCTURE

Immunoglobulin (Ig) molecules are made up of two identical protein heavy chains and two identical kappa (κ) or lambda (λ) light chains.[12] Immunoglobulin heavy-chain genes reside on chromosome 14 and immunoglobulin light chains are derived from either the Igκ locus on chromosome 2 or the Igλ locus on chromosome 22. Immunoglobulin heavy chains contain both a variable region that will ultimately contribute to antigen binding and a constant region that binds to cell Fc receptors and complement. Mature immunoglobulin light chains also contain variable and constant regions. Within each variable region, there are hypervariable regions that represent the actual antigen binding site and less variable regions which make up the *framework region*.

The variable domain of the heavy chain is encoded by three sets of genes, the variable (V), diversity (D), and junctional (J) genes, which must be physically rearranged to result in expression of immunoglobulin heavy-chain protein.[13] Similarly, the variable region of the immunoglobulin light-chain protein is encoded by two sets of genes, the V and J genes, which are likewise rearranged to allow transcription of functional protein.[13] The rearrangement of DNA to join V, D, and J heavy-chain genes and V and J light-chain genes also results in elimination of unused V, D, and J sequences and noncoding stretches of DNA or introns. The many possible variable regions resulting from these random rearrangements confer a broad range of potential antigen specificities to the mature immunoglobulin molecules.

CLASS SWITCHING

Once immunopoiesis is initiated B cells alter the isotype of antibody that is produced via *isotype switching*.[13,14] This occurs in *switch regions* on immunoglobulin heavy chains through a process called *class switch recombination*. By translocation of the IgM variable region to *switch regions* adjacent to one of the constant regions coding for IgG, IgA, or IgE, the B cell is able to maintain antigen specificity and at the same time generate different immunoglobulin subtypes with different functional capabilities. Class switch recombination requires an enzyme called activation-induced cytidine deaminase (AID). AID also is critical for *somatic hypermutation*, a process where rapidly proliferating activated B cells have a high rate of point mutations in genes encoding the variable region leading to production of antibodies with different antigen binding affinities.[15] This results in a greatly expanded repertoire of B cells expressing surface IgG of different affinities for the triggering antigen. B cells expressing high affinity antibody on their surface (and thus bind greater amount of antigen) have a survival benefit over B cells coated with weaker affinity to antigen, where less signaling through antigen recognition results in B cell apoptosis. In this way the antibody response moves toward production of higher affinity and more specific immunoglobulin. The importance of AID is reflected in the development of one of the hyperimmunoglobulin M syndromes in patients with defects in this enzyme.[16] The structure of the various immunoglobulin classes is shown in Figure 24-2.

LUNG IMMUNOGLOBULINS

In the lung immunoglobulins comprise the second largest class of proteins present in bronchoalveolar lavage (BAL) fluid after albumin.[17] IgG is the major immunoglobulin in the lower respiratory tract[18] In contrast, IgA is the most abundant immunoglobulin in secretions from the upper respiratory tract, exceeding the concentration of IgG by a ratio of 2.5:1. Smaller amounts of IgE are consistently found in the BAL fluid of normal subjects.[17]

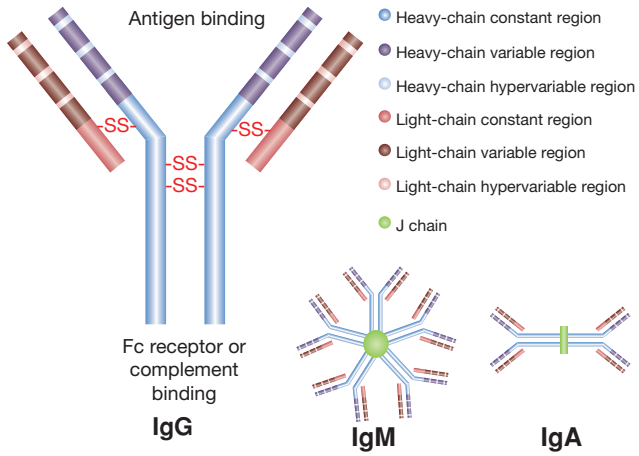


Figure 24-2 Basic immunoglobulin structure. Immunoglobulin molecules consist of two identical protein heavy chains and two identical light chains joined by disulfide bonds. Both heavy and light chains contain a constant and a variable region. Within each variable region there are hypervariable regions that represent actual antigen binding sites. IgM typically exists as a pentamer and IgA as a dimer.

IgG

IgG is the major circulating immunoglobulin found in the vascular compartment. In normal subjects, the amount of IgG measured in BAL (usually expressed as an immunoglobulin/albumin ratio) is in the same proportion as serum, suggesting that under resting conditions most IgG in the lung represents transudation from the vascular compartment.[17,19] This is further supported by the relatively small size of IgG (150,000 D). There are four IgG subclasses found in BAL fluid in approximately the same proportions as found in serum. IgG1 represents approximately 60% to 70% of the IgG present in BAL fluid, IgG2 20% to 25%, and IgG3 and IgG4 are present only in small amounts (<5%).[18] Responses to protein antigens predominantly reside in the IgG1 and IgG3 subclasses while polysaccharide antigens predominantly give rise to IgG2 antibodies.[20,21]

The major function of IgG is to opsonize pathogens and target them for clearance either through uptake by phagocytic cells or by fixing complement. In this regard IgG1 and IgG3 fix complement more avidly than IgG2.[22] Antibody also binds to Fc receptors on phagocytic cells to facilitate uptake. The three primary Fc receptors are FcRI, FcRII, and FcRIII. IgG1 and IgG3 bind FcRIII receptors on phagocytic cells equally well and more potently than IgG2.[23] IgG1 binds to the other Fc receptors more avidly than the other IgG subclasses. Binding of antigen–antibody complexes to Fc receptors is potentially a double-edged sword. On the one hand, not only is uptake of opsonized pathogens through Fc receptors more efficient, so is the intracellular digestion of organisms in phagolysosomes. For example, uptake of opsonized Mycobacterium tuberculosis through the Fc receptor results in intracellular killing of the organism, while uptake through other receptors (i.e., the mannose receptor) allows the organism to escape digestion.[24] On the other hand, uptake of opsonized pathogens through Fc receptors represents an "inflammatory clearance" mechanism that is associated with release of potentially harmful inflammatory mediators into the lung environment.[25]

IgA

In contrast to IgG, IgA is likely locally produced based on an elevated IgA/albumin ratio in BAL compared to serum.[26] IgA can exist as monomeric and polymeric proteins. The latter is usually found as dimeric IgA, characterized by two monomers connected by a J chain.[27] Most IgA in the lung is in dimeric form, with features of secretory IgA (sIgA) characterized by the presence of a J chain and secretory component (SC).[28] The large size of dimeric IgA (385,000 D) also argues against simple transudation of IgA from the vascular compartment into the lung. Finally, the presence of secretory component in BAL is another argument for the local production of IgA in the lung.[29]

IgA has two subclasses: IgA1 and IgA2.[27] IgA1 comprises nearly 80% of serum IgA. In contrast, IgA2 appears to be important in mucosal immunity and nearly half of the IgA present in secretions is IgA2. IgA exerts its protective effect through three mechanisms.[30] First, it serves as an immunologic barrier, inhibiting binding of organisms to mucosal surfaces. Second, the normal movement of IgA from the basilar to apical region of epithelial cells suggests that it may be effective in neutralizing intracellular pathogens. Finally, pathogens bound to IgA may be taken up by airway macrophages through the phagocytic process.

IgM

IgM is present only in very low amounts in respiratory secretions from normal subjects.[17] It exists as a pentamer and the resulting very large size (900,000 D) limit transudation into the lung under normal conditions. Nevertheless, IgM in BAL is greater than would be expected for simple diffusion suggesting some local production.[31] Furthermore, in some disorders characterized by lower respiratory tract inflammation IgM can be detected. However, in this setting it is almost certainly largely derived from serum transudation as part of the inflammatory process.

IgE

Under normal conditions the amount of IgE in BAL is lower than IgG, IgA, or IgM.[31] When present the IgE/albumin ratio suggests local production.[31] IgE–antigen complexes bind the high affinity receptor for IgE (FcRI) on mast cells, basophils, and eosinophils leading to immediate hypersensitivity responses.[32,33] IgE is important for host defense against parasites mediated by eosinophils.[34] However, in developed countries the main role of IgE in pulmonary immunity is in the pathogenesis of allergic and asthmatic disease.[35,36] The severity of disease is correlated with serum IgE in asthma and allergic patients. The importance of this molecule in the pathogenesis of asthma has led to the development of anti-IgE antibodies for patients with resistant IgE-mediated disease.[37] Interestingly, when IgE binds to the low affinity FcRII receptor it inhibits IgE synthesis and reduces inflammation.[38] Thus IgE may also have a role in downregulating the immune response.

CELLULAR INTERACTIONS LEADING TO ANTIBODY SECRETING CELLS

A number of important cellular interactions take place that eventuate in antibody secretion by cells.

B1 AND B2 CELLS

B lymphocytes comprise 1% to 10% of the lung lymphocyte population and can be separated into two main classes. Plasma cells constitutively secrete IgG and other immunoglobulin subclasses.[1,11] In contrast, memory B cells produce immunoglobulin only in response to re-exposure to particular antigens.[11] B cells can be further classified into B1 and B2 cells. B1 cells were first described in the gastrointestinal tract. These cells are IgM+, CD5+ cells that do not require T cell help for development.[39] In the lamina propria B1 cells undergo class switching to an IgA secretory cell. B1 cells home to peritoneal and pleural cavities, respond to common bacterial antigens, and are felt to be very important in the production of IgM and IgA against bacterial pathogens at mucosal sites.[40] As such, they are thought to be important in innate immunity against conserved bacterial antigens. Because of their autonomous ability to secrete antibody, they are also felt to contribute to autoimmune diseases. These cells are difficult to demonstrate in normal lung. As stated earlier, T cells are not necessary for B1 cells to produce antibody, though the presence of T cells appears to augment the immune response.[40–44]

In contrast to B1 cells, B2 cells require T cell help, mainly through secretion of the cytokines interleukin IL-4, IL-5, IL-6, and IL-10, as well as ligation between CD40 on B cells and CD40L on T cells.[45] T cell dependent antibody responses begin with uptake of antigen by accessory cells (AC) and presentation to T cells. AC function can be carried out by mononuclear phagocytes (monocytes, macrophages) or dendritic cells. Submucosal dendritic cells are likely the principal accessory cell in the lung.[46] B cells themselves can also serve as the accessory cell leading to T cell activation.[47] B cells in the lung express surface IgG and IgM. Crosslinking of surface IgG or IgM by antigen results in partial activation of B cells leading to expression of IL-2 receptors and MHC class II molecules,[1] which allows them to serve as accessory cells in T cell activation. With appropriate T cell help activated B cells eventually differentiate into short lived antibody producing plasma cells or memory B cells, the latter characterized by the coexpression of CD20 and CD27.[48] Other surface markers indicating B cell activation and differentiation include CD69, CD80, and CD86.[1] The latter two interact with CD28 and CTLA4 on T cells, respectively, thereby enhancing proliferation of helper T cells. Activation results in production of CD38+ CD138+ plasma cells that secrete IgM (primary response) or other immunoglobulin isotypes (secondary immune responses).[49]

COGNATE VERSUS NONCOGNATE RESPONSES

Activated T cells can provide cognate and noncognate B cell help. Cognate B cell help is antigen and MHC restricted and occurs after helper T cells have been activated through T cell receptor (TCR)–MHC class II/antigen complex mechanisms. It was initially thought that B cells were the obligate accessory cells for cognate responses since B cell–T cell contact was occurring through MHC class II/antigen complexes on activated B cells and the TCR on T cells. In contrast, when T cells are stimulated by accessory cells other than B cells or activated in an accessory cell independent manner (i.e., with immobilized anti-CD3), T cells can induce immunoglobulin production in many B cells in a non-MHC or antigen (noncognate) restricted manner. This latter phenomenon results in stimulation of both antigen specific as well as "bystander" B cells leading to a polyclonal antibody response. Subsequent work has shown that this bystander response is only important when the T cells providing B cell help are highly activated and/or differentiated, such as after exposure to IL-4 and IL-6.[49] This latter observation may explain the link between increased IL-6 secretion and nonspecific hypergammaglobulinemia in diseases such as HIV infection.[50] Additional work has shown that this bystander effect is mediated through LFA-1 (CD11a/CD18) on B cells and ICAM-1 (CD54) on activated T cells.[51,52]

CYTOKINE SECRETION

Resting T cells provide poor B cell help. T cells that have been stimulated by antigen can be loosely divided into Th1 and Th2 cells based on the cytokine profile they secrete.[53] Th1 cells secrete predominantly interferon-γ (IFN-γ) and interleukin (IL)-2 and are involved primarily in cellular immunity. Th2 cells secrete IL-4, IL-5, and IL-10 and drive humoral immunity. Th2 cells that provide B cell help are called "effector" cells. Signals from T cells to B cells are in two forms: direct cell to cell contact and cytokine secretion. While direct B cell–T cell contact is required for induction of antibody production, both Th1 and Th2 cell membranes can provide this signal.[54] What differentiates these two T cell populations is the cytokine profile they secrete. In particular, IL-4 seems to be an early competence factor that increases the number of B cells responsive to T cell help.[54,55] In contrast, IL-6 is a late factor[55] that promotes continued B cell proliferation and immunoglobulin secretion. IFN-γ downregulates most immunoglobulin secretion.[56] Thus Th2 cells secrete a more favorable cytokine pattern for immunoglobulin production. The one exception is IgG2, which is dependent on IFN-γ secretion.[56]

SPECIFIC B CELL AND T CELL RECEPTOR INTERACTIONS AND DOWNREGULATION OF B CELL RESPONSES

Tight regulation of antibody production and secretion is necessary to turn off the response when it is no longer needed and to prevent production of unwanted autoantibodies (Fig. 24-3). This control is mediated through a combination of signaling pathways between T cells and B cells. CD40L is an activation-induced molecule on CD4 T cells that delivers signals to B cells through its counterreceptor CD40, which is constitutively expressed on B cells. Highly activated T cells express increased CD40L. CD40 on B cells in turn downregulates CD40L on activated T cells.[57] These cells are subsequently unable to stimulate resting B cells. Thus this may represent an attempt to downregulate noncognate immunoglobulin production. However, CD40 ligation is still critically important for cognate interactions. Crosslinking of surface immunoglobulin on B cells results in apoptosis of the B cell unless simultaneous binding of CD40 by CD40L occurs.[58] Interestingly, CD40 binding alone induces Fas expression on B cells, an effect that is not inhibited even in the presence of B cell tropic factors such as IL-2, IL-4, and IL-10.[59] Thus ligation of CD40 acts to costimulate B cells that have been activated by binding of specific antigen while simultaneously increasing sensitivity to apoptosis in B cells not crosslinked by antigen. This drives an antigen-specific antibody response.[58]

The role of Fas/FasL interactions in modulating immune responses is well established. Activation of T cells upregulates expression of both Fas and FasL. This is seen as a mechanism to control chronic T cell activation.[60] Fas/FasL interactions are also important in modulating B cell responses.[61] As stated earlier, B cells stimulated through CD40 increase expression of Fas. Thus, these cells are susceptible to apoptosis mediated by FasL expressed by activated T cells. B cell apoptosis induced by FasL is blocked if there is simultaneous crosslinking of surface immunoglobulin by antigen, thereby preserving secretion of protective antibody in the presence of persistent pathogen exposure.

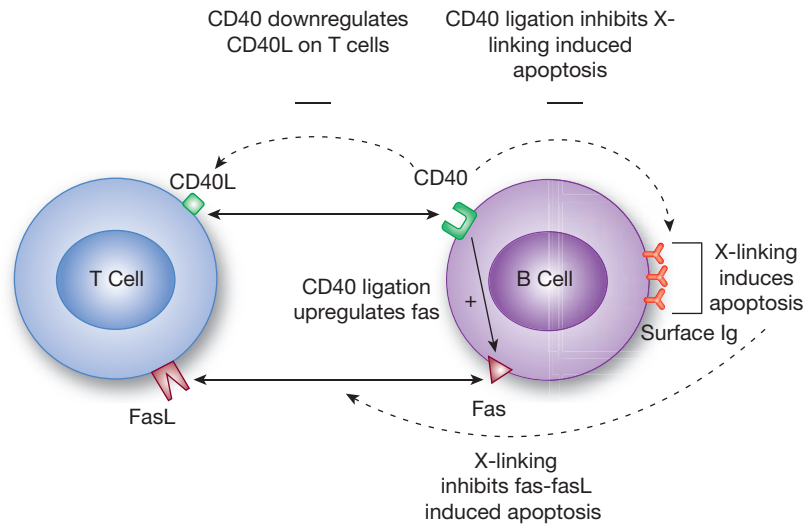


Figure 24-3 Interaction between T cells and B cells during the generation of a humoral response. Multiple signals occur between T cells and B cells. Depending on the presence or absence of crosslinking of surface immunoglobulin on B cells, T cells can either promote B cell growth or induce apoptosis.

PULMONARY ANTIBODY PRODUCTION IN RESPONSE TO ANTIGEN EXPOSURE

Pulmonary immunity to pathogens can be divided into innate and acquired responses. Most pathogens gaining access to the alveolar space are handled by phagocytosis by alveolar macrophages, the principal form of innate immunity. If phagocytosis of pathogens occurs in the absence of opsonizing antibody this usually results in "noninflammatory clearance," with minimal release of inflammatory mediators and preservation of lung structure and function.[62] If phagocytosis is overwhelmed, a specific acquired immune response occurs. This involves the interaction of B and T lymphocytes to produce an antigen-specific cellular and humoral immune response. In the lung, the acquired response has three distinct phases (Fig. 24-4)—afferent antigen processing and transport to regional lymph nodes,[63] presentation to naïve lymphocytes, and efferent migration of activated T lymphocytes and mature B cells back to the site of initial antigen challenge in the lung.[64] This results in the presence of antigen-specific immunoglobulin in the lung lining fluid and consequent increased effectiveness of professional phagocytes such as alveolar macrophages and neutrophils.[65]

This general pathway is similar for IgG and IgA production, though the length of the "circuit" is likely much less for IgA. Rather than having antigen travel to regional lymph nodes, in mucosal immunity IgA can be generated in specialized lymphoid tissue just beneath the mucosal surface, called mucosal-associated lymphoid tissue (MALT), suggesting that IgA secreting plasma cells are produced locally and IgA can readily diffuse back into the airspaces. Such submucosal lymphoid tissue in the upper airway, called nasal-associated lymphoid tissue (NALT), is seen in most animal species, including humans.[66] In contrast, in the lower respiratory tract bronchus-associated lymphoid tissue, or BALT, is readily demonstrable in mice[66] but has been more difficult to find in normal human airways.[67] Prior studies claiming that humans have BALT have generally been in subjects with an inflammatory pulmonary process.[68] Recent investigations may be shedding some light on this controversy, introducing the concept of inducible bronchus-associated lymphoid tissue, or iBALT. In mice lacking secondary lymphoid tissues (spleen, lymph nodes) a robust protective primary pulmonary B and T cell response was demonstrated after influenza infection.[69] This response was associated with induction of B cell follicles centered around follicular dendritic cells in submucosal tissues. Thus collections of antigen presenting cells, B cells, and T cells in the submucosa, which are thought to collectively represent BALT, may only be readily detectable during times of antigenic challenge.

Once antibody producing B cells are formed in secondary lymphoid tissue or MALT, they must traffic back to the original point of entry of the pathogen. This trafficking of lymphocytes back to mucosal sites has been intensely studied, giving rise to a four-step model. The first step is tethering. L-selectin on lymphocytes interacts with addressins on endothelial cells to slow down the movement of lymphocytes through capillaries. In NALT, the responsible endothelial receptor is PNAd[70] while in the lung adhesion is mediated by ICAM-1.[71] Tethering leads to lymphocyte activation mediated by chemokines and their receptors and subsequent firm adhesion to the endothelium. The latter is mediated by LFA-1 binding to ICAM-1 and $\alpha_4\beta_7$ integrin binding to MADCAM-1.[72] Finally, diapedesis through the mucosa occurs, a process that probably involves all the above receptor–counterreceptor interactions.

The end result of this process is the accumulation of antibody secreting plasma cells at the site of initial challenge. Once the invading pathogen has been cleared, plasma cells disappear and are replaced by memory B cells. The great majority of B cells in the normal lung are mature memory B cells. This mirrors the predominance of memory T cells in the lung,[73] suggesting that the lung is primed to respond quickly to antigenic challenges. IgG-, IgM-, and IgA-secreting B cells are present in normal subjects; however, poor correlations exist between the numbers of Ig producing BAL cells and the levels of Ig in BAL fluids.[17,74] In BAL fluid from nonsmokers IgG is present in the same proportion as in serum, leading to speculation that most IgG enters via transudation from the plasma compartments.[17,19] These two observations fit in well with the primary presence of memory B cells in the lung, suggesting that under resting conditions very little local antibody is made. Only after antigenic challenge is local production increased. In support of this is the finding of increased ratios of specific to total antibody in BAL fluid after pneumococcal infection suggesting that local antibody production can be increased after relevant exposures.[75]

DISORDERS OF HUMORAL IMMUNITY AND LUNG DISEASE

Either quantitative or qualitative defects may be associated with disorders of humoral immunity and resultant lung disease. In addition, lung disease has been noted in conjunction with development of autoantibodies. These topics are presented below.

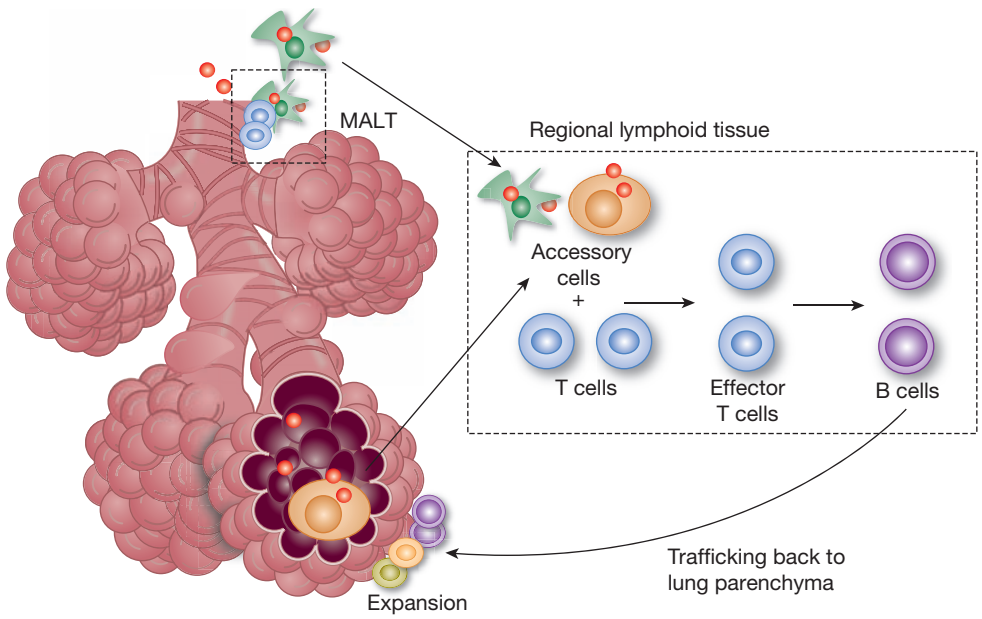


Figure 24-4 Pathway for generation of antigen-specific immune responses in the lung. Foreign antigen is taken up by antigen presenting cells and transported to regional lymph nodes where the primary cellular and humoral immune response is generated. Effector cells then traffic back to the lung to the site of initial antigen challenge. B cells will become antibody secreting plasma cells while others will become memory B cells. This circuit is significantly shorter in the presence of mucosal-associated lymphoid tissue (MALT).

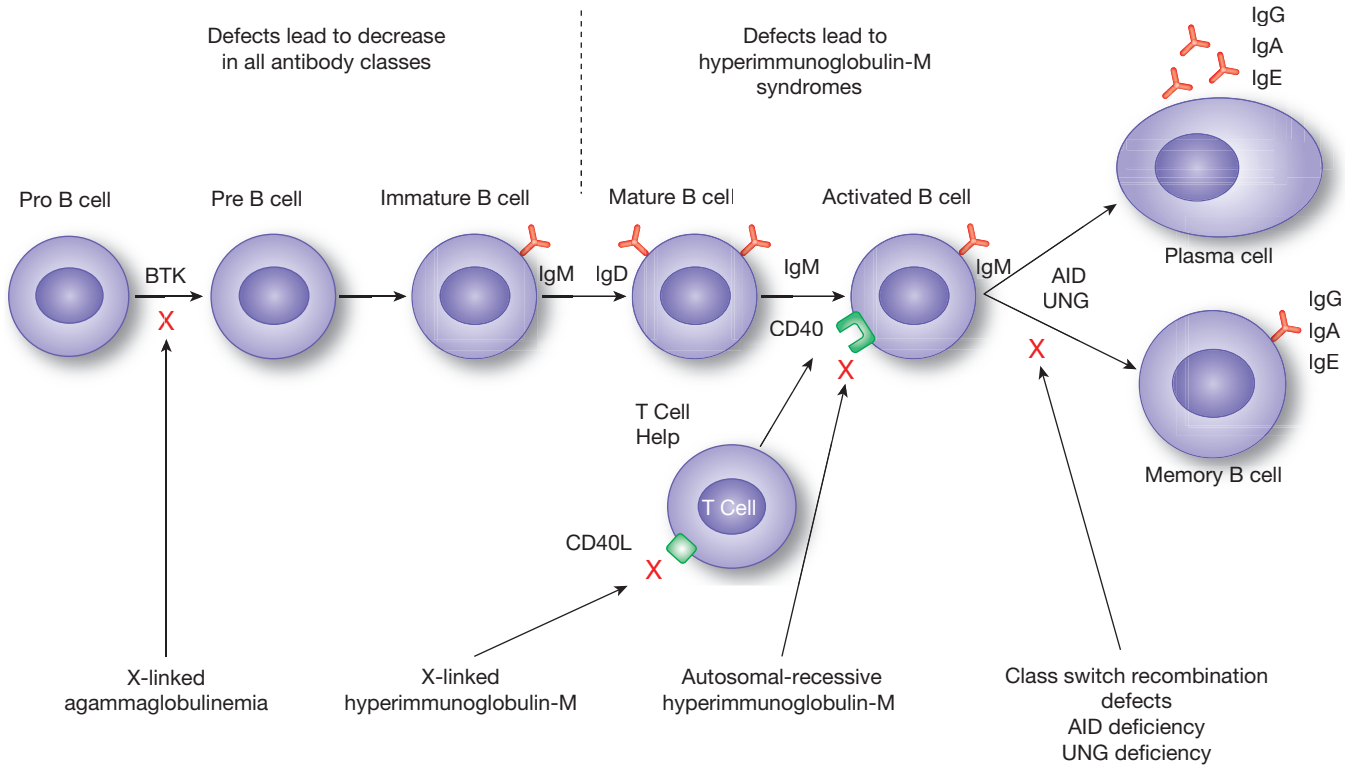


Figure 24-5 Known sites of molecular defects leading to immunoglobulin deficiency. Note defects that occur past the mature B cell stage tend to lead to hyperimmunoglobulin-M syndromes while defects prior to this stage lead to loss of all immunoglobulin classes. BTK, Bruton's tyrosine kinase, AID, activation-induced cytidine deaminase, UNG, uracil-N-glycosylase.

INTRODUCTION

In general, defects in humoral immunity result in an increased susceptibility to bacterial infections, including recurrent sinusitis, bronchitis, pneumonia, otitis media, and even meningitis. In particular, the patients are susceptible to infection with encapsulated organisms such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Neisseria* species. Chronic diseases such as bronchiectasis and obstructive lung disease can occur as a result of recurrent infection. Antibody defects can be either quantitative (an absolute decrease or loss of antibody) or qualitative (poor antigenic specificity and/or poor opsonic function). In addition, the presence of antibodies against host antigens can lead to autoimmune lung disease. Figure 24-5 shows some of the known molecular defects causing immunoglobulin deficiency. The cause of most of the selective immunoglobulin deficiencies described below is unknown.

QUANTITATIVE DEFECTS

Isolated *IgA deficiency* is the most common primary immunodeficiency in humans, occurring in roughly 1 in 500 individuals.[76] The presence of IgA deficiency is defined by a serum IgA level of less than 5 mg/dL and normal levels of other immunoglobulins. Asthma, IgE-mediated allergic disease, and autoimmune diseases are more common in patients with IgA deficiency.[77] Only about a third of patients with IgA deficiency develop recurrent sinus, pulmonary, and gastrointestinal tract infections, usually with encapsulated bacteria. In the absence of an associated IgG subclass deficiency the development of structural lung disease is rare. These patients almost never require immunoglobulin replacement therapy. However, the coexistence of IgA and IgG subclass deficiency is extremely important to document since the latter may require immunoglobulin infusions. IgA deficient patients are at increased risk for anaphylactic reactions after blood product infusions, including immunoglobulin preparations, because of the presence of IgG anti-IgA antibodies in up to 60% of individuals.[78,79] As such, when the decision is made to give immunoglobulin infusions to an IgG deficient patient with a coexisting low IgA level, immunoglobulin preparations low in IgA must be used.

In contrast to IgA deficiency, patients with *IgG subclass deficiencies* frequently exhibit recurrent sinus and respiratory tract infections with encapsulated organisms regardless of whether it is associated with IgA deficiency.[80] IgG1 deficiency is the most common and it is frequently linked with deficiency of IgG2 and IgG3 as well. Unlike patients with IgA deficiency, the recurrent infections in IgG subclass deficiency can lead to chronic bronchiectasis, and assessment of immunoglobulin deficiency should be part of the standard evaluation of patients with unexplained recurrent infections with destructive lung disease. Patients with IgG2 subclass deficiency have an impaired ability to respond to polysaccharides.[20] As such, their response to the standard polysaccharide pneumococcal vaccine is poor. When IgG subclass deficiency is combined with IgA deficiency the resultant lung disease is more severe than with either deficiency alone.

More severe disease occurs when there are multiple immunoglobulin defects. Perhaps the most common immunodeficiency in this group is *common variable immunodeficiency (CVID)*. Present in 1 in 25,000 individuals, this disease is characterized by hypogammaglobulinemia, decreased antigen-specific antibody responses, and recurrent sinopulmonary infections, frequently leading to chronic lung disease.[81] IgG levels are usually below 300 mg/dL and are accompanied by low IgA and IgM levels as well. Specific antibody responses to common antigens such as tetanus toxoid and pneumococcus are usually very low. Cellular immune defects, primarily lymphopenia with a normal or decreased CD4:CD8 ratio, may also be present. Thus, patients may present with infections typically associated with T cell defects (fungi, mycobacteria) in addition to infections caused

by encapsulated bacteria. Proliferation of B cells and T cells in response to strong mitogens is impaired as well. Thus CVID is felt to result from a failure of B cells to terminally differentiate, either due to poor T cell help or an intrinsic B cell defect. The impairment in immunity and immunosurveillance probably contributes to the increased incidence of autoimmune disease, malignancies, and gastrointestinal malabsorption in patients with CVID.[82–84]

Patients with *X-linked agammaglobulinemia (Bruton's agammaglobulinemia)* demonstrate a generalized defect in the ability to make all immunoglobulin classes. This is due to a deficiency of Bruton's tyrosine kinase (BTK), which is essential for early lymphopoiesis.[85] These individuals present in early childhood with recurrent middle ear, sinus, pulmonary, joint, bone, and CNS infections. They almost always develop chronic lung disease, including bronchiectasis, pulmonary fibrosis, and pulmonary hypertension.[86–88] IgG levels are below 200 mg/dL and the other Ig subclasses may be absent. In contrast to patients with CVID, lymphoid tissue is hypoplastic in these patients.

Hyperimmunoglobulin M syndrome refers to several diseases characterized by low concentrations of IgG, IgA, and IgE and a normal or elevated IgM level. As might be expected based on our understanding of normal B cell development, these syndromes result from failure of IgM secreting B cells to undergo class switching. The most common disorder is X-linked hyperimmunoglobulin M syndrome, which arises from a deficiency in the important T cell costimulatory molecule CD40L.[89] Deficiency in the B cell CD40 molecule has also been described, though this is rare.[90] Patients with either of these disorders have severely impaired T cell dependent antibody production. Other hyperimmunoglobulin M disorders are caused by genetic mutations in the enzymes required for class switching, such as AID[91] and uracil nucleoside glycosylase.[92]

Immunoglobulin replacement therapy can prevent recurrent infection and ameliorate some of the long term sequelae of IgG deficiency.[93,94] However, it is important to base treatment decisions on the inability to make specific antibody, not just on an isolated low IgG (or IgG subclass) level. Typically when immunoglobulin deficiency is suspected total IgG, IgA, IgM, and IgG subclass concentrations are checked. A lymphocyte phenotype panel should also be obtained to look for low T and B cell numbers. If low antibody titers are detected, then one should measure common specific antibody titers. Usually tetanus toxoid and pneumococcal antibody titers are assessed because this assesses both the ability to respond to protein (tetanus) and polysaccharide (pneumococcal) antigens. If specific antibody titers are low the patient should be given the tetanus or pneumococcal vaccine and repeat antibody titers obtained 4 weeks later. Failure to increase antibody titers into a "protective" range is indicative of immunoglobulin deficiency and warrants consideration of immunoglobulin replacement therapy. There are several immunoglobulin preparations available. As mentioned earlier, if IgA deficiency is present, a preparation that contains very low IgA should be used to minimize the risk of anaphylaxis.[78] A typical dose of immunoglobulin is 400 mg/kg given once a month, with a goal trough serum immunoglobulin level immediately before the next infusion of 500 mg/dL.

■ QUALITATIVE DEFECTS

Once antibody is produced in the lung, it must be effective in promoting clearance of the offending pathogen. Just having a vigorous antibody response is insufficient. There are several diseases characterized by poor functioning antibody.

Selective antibody deficiency with normal immunoglobulins (SADNI) was first recognized in the 1980s. The disease is characterized by poor antibody responses to polysaccharide antigens despite normal IgG, IgG subclass, IgM, and IgA concentrations.[95] While many of the primary immunodeficiency diseases described earlier are associated with poor responses to polysaccharide antigens, SADNI should be reserved for patients with only this specific defect. SADNI is one of the most common immunodeficiencies occurring in 5% to 10% of older children and adults presenting with recurrent sinopulmonary infections.[96,97] As with other immunoglobulin deficiencies, these patients also have an increased incidence of atopic disease. Since SADNI is a diagnosis of exclusion, normal IgG, IgG subclass, IgM, and IgA levels must be demonstrated. To demonstrate polysaccharide unresponsiveness, baseline pneumococcal titers are measured and then the 23-valent polysaccharide pneumococcal vaccine is administered.[98] Four weeks later pneumococcal titers are repeated. An appropriate response is indicated by an antibody titer of 1.3 μg/mL or greater in 70% of the serotypes tested.[98] Some patients have an appropriate response to vaccination, but this is followed by a rapid loss of antibody titers over 6 months. These patients fall within the spectrum of patients with SADNI. One of the main reasons for establishing the diagnosis of SADNI versus other immunodeficiencies is the differences in treatment. Patients with SADNI should be administered the 13-valent conjugated pneumococcal vaccine, which is more immunogenic due to the presence of a protein carrier attached to polysaccharide antigens that acts as a hapten.[99] Unlike in more severe humoral immunodeficiencies, immunoglobulin replacement therapy is needed only in a minority of patients with SADNI.

While *HIV infection* is most notably characterized by profound defects in cell-mediated immunity, antibody defects are also present. In fact, the occurrence of two bacterial pneumonias in a year is an AIDS defining illness.[100] HIV infection is characterized by an increased amount of total and pneumococcal-specific antibody in the alveolar space,[75,101] yet invasive pneumococcal disease is prevalent in this population. For example, in HIV-infected Malawians, a population with a high incidence of invasive pneumococcal infection, BAL contains four times the amount of pneumococcal-specific IgG compared to non-HIV-infected subjects. Capsule-specific IgG levels were highest in a group of HIV-infected patients with recent invasive pneumococcal disease, suggesting that despite polyclonal IgG responses in HIV-infected adults, appropriate responses to infection were also present.[75] However, the ability of highly purified BAL IgG from HIV-infected subjects to bind pneumococci is impaired compared to BAL IgG from non-HIV-infected subjects.[102] This parallels the work of other investigators who have demonstrated impaired immunoglobulin opsonic function in HIV-infected subjects, including activity against pneumococcus.[103,104] Thus HIV-infected subjects appear to have dysfunctional pneumococcal antibody in the alveolar space. The reasons for this observation are not known, but could include structural abnormalities in HIV IgG or the lack of a diverse antigenic response (i.e., antibody produced against only a few pneumococcal antigens in HIV-infection compared to a more diverse response in non-HIV-infected subjects).[105] These findings highlight the fact that better correlates are needed for assessing the host response to natural infection or vaccination besides simple measurement of antibody concentrations.[106]

■ PULMONARY DISEASE ASSOCIATED WITH AUTOANTIBODIES

There are many well-described lung diseases associated with the presence of autoantibodies. Classically these have been described in patients with vasculitic processes such as Goodpasteur's syndrome or granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), and various connective tissue diseases. A discussion of these disorders is beyond the scope of this chapter. However, a great deal of interest is now turning toward the potential role of autoantibodies in some of the more commonly encountered lung diseases.

Chronic obstructive lung disease (COPD) is increasingly being thought of as an autoimmune disease.[107] Patients with COPD

have increased lung titers of autoantibodies against elastin,[108] cytokeratin[109] and against epithelial and endothelial antigens.[110,111] Furthermore, lymphoid follicles consisting of B cells and follicular dendritic cells with adjacent T cells are present in the parenchyma and in bronchial walls of patients with emphysema suggesting that at least some these antibodies may be locally produced.[112] This is further supported by detailed studies demonstrating that the B cells in these aggregates have a limited (oligoclonal) repertoire.[113] That these autoantibodies may be pathogenic is suggested by the presence of immune complex and C3 deposition in the lungs of patients with emphysema.[110] In animal models smoking is able to induce autoantibodies against extracellular matrix proteins in mice,[114] and adoptive transfer of anti-endothelial antibodies can cause emphysema in rats.[115] This discussion would suggest that immunosuppressive medications may be effective in COPD. Indeed, systemic and inhaled corticosteroids result in decreased lymphoid aggregates in the lungs of humans with COPD.[116] Whether reduction in lung B cell immunity is helpful or harmful will depend on whether the B cells are secreting destructive autoantibodies or protective antibodies against microbes that have colonized the airway of these patients.

Another lung disease in which autoantibodies may contribute to pathogenesis is *pulmonary fibrosis*. The current paradigm for the pathogenesis of pulmonary fibrosis starts with lung epithelial and/or microvascular injury leading to an exaggerated inflammatory and fibrotic response. While extensive literature exists on the inflammatory and fibrotic response, much less is known about the inciting event. In pulmonary fibrosis associated with connective tissue disease numerous autoantibodies have been described, including anti-SSA, anti-RNP, and anti-Jo-1.[117–119] Whether similar potential pathogenic roles can be ascribed to autoantibodies in idiopathic pulmonary fibrosis (IPF) is not known. Early on an increase in lung IgG was described in patients with IPF.[120] Up to 30% of patients with IPF have positive antinuclear antibody or rheumatoid factor without other overt signs of autoimmune disease.[121] Anti-phospholipid and anti-endothelial cell antibodies are found in a significant number of patients with IPF.[122] In another study anti-collagen antibodies were found in 81% of patients with IPF.[123] Anti-cytokeratin antibodies are also frequently found in the serum of patients with IPF.[124] Finally, antibodies to heat shock protein 70 identified a group of patients with IPF with a poor prognosis.[125] Thus there is evidence to support a contribution of unchecked humoral immunity in the pathogenesis of fibrotic lung diseases.

Dysregulated humoral immunity also plays a role in lu*ng transplant rejection.* Rejection is associated with upregulation of IgG2 production resulting in an IgG2/IgG1 ratio of greater than 1 in BAL fluid. Since the ratio was normal in serum this strongly argues for local production of IgG2 in the lungs of patients undergoing rejection.[126] In support of this, B cells are a prominent finding in areas of the lung demonstrating obliterative bronchiolitis, the pathologic hallmark of lung rejection,[127] and these cells preferentially produce IgG2.[128] Subsequent work in animal models[129] and humans[130,131] has shown that the major antigens driving this response are collagen V and k-α tubulin. In fact, the presence of circulating anti-collagen V antibody predicts primary graft dysfunction after transplant.[129] That these antibodies may have a pathogenic role in lung transplant rejection is further supported by observations that rituximab or intravenous immunoglobulin therapy reduces the concentration of the autoantibody and reduces the severity of bronchiolitis obliterans syndrome.[130] The current paradigm for lung transplant rejection holds that ischemic injury during the transplant process "uncovers" normally hidden collagen V epitopes that elicit an autoimmune response.[132] This is strongly supported by recent work showing increased collagen V expression in obliterative bronchiolitis lesions and the presence of collagen V antibodies in the lungs of patients who had lung transplant rejection.[133]

PULMONARY ANTIBODY RESPONSES TO VACCINATION

The pulmonary antibody response to vaccination against common pathogens is an important consideration in disease prevention and is discussed below.

SYSTEMIC VERSUS MUCOSAL VACCINATION

Vaccination against pulmonary pathogens is a common and effective practice against many diseases. However, the mechanisms behind their effectiveness are not always clear. In theory, both IgA and IgG have a role in protection after vaccination. The presence of pathogen-specific IgA should decrease colonization of the respiratory tract by limiting attachment to respiratory epithelium. Since airway colonization is usually the first step in the development of bacterial pneumonia, decreased colonization should lead to a decreased incidence of pneumonia. When pathogens manage to reach the alveolar space, IgG should take on a greater role as an opsonin in the phagocytosis of organisms. Thus the most effective immunity against bacterial infections should involve both an IgG and IgA response. That being said, the vaccine delivery mechanism impacts the type of immune response generated. In general, systemic administration of a protein antigen results in the generation of circulating IgG, some of which will diffuse into the epithelial lining fluid. In contrast, mucosal antigenic challenge results in a more vigorous IgA response locally at the site of challenge.

Despite the recognition that local antibody may be important in pulmonary host defense, there is little information on humoral responses in the respiratory tract after systemic immunization, the standard approach to vaccine strategies. Much of what we know about mucosal immunity comes from animal models. In a mouse model of mucosal immunity against *Mycoplasma pulmonis*, it has been demonstrated that the site of antigen deposition greatly influences the antibody response and subsequent protective immunity.[134] Intranasal challenge resulted in an increase in IgA antibody forming cells in the nasal submucosa and an increase in mycoplasma-specific IgA in nasal washes. Low numbers of IgA antibody forming cells and IgA concentrations were seen in the lung after isolated nasal challenge, but were increased significantly if animals received both nasal and pulmonary immunization. Both nasal and nasal-pulmonary vaccine exposures resulted in equivalent antigen-specific IgA and IgG in the systemic circulation. Both forms of immunization also significantly reduced the ability of mycoplasma to colonize the nasal passages after experimental exposure to a mycoplasma inoculum. However, animals receiving nasal-pulmonary immunization had significantly fewer organisms in the lungs compared to animals that only received nasal immunization. Since serum mycoplasma-specific IgA and IgG were similar after both types of immunization, this suggests that circulating antibody is less effective in protection against pulmonary pathogens compared to locally produced antibody.

In another animal immunization model against a different pulmonary pathogen, *Moraxella catarrhalis,* the site of specific antibody production and protection after intranasal and subcutaneous challenge was examined.[135] Intranasal administration of *M. catarrhalis* surface proteins resulted in antigen-specific IgA and IgG in both nasal washes and BAL. IgA concentrations far exceeded IgG concentrations in both sites. IgA was significantly higher in BAL and nasal washes than in serum, whereas IgG was higher in serum than both mucosal sites. Immunization was associated with a marked increase in bacterial clearance after intranasal challenge with live *M. catarrhalis* organisms. As might be predicted, subcutaneous administration of the same vaccine resulted in production of far greater antigen-specific IgG compared to IgA, especially in the lung, where moraxella-specific IgG in BAL was nearly 20 times greater than that found in nasal washes. Subcutaneous vaccination induced a marked

systemic IgG response, but virtually no antigen-specific IgA in serum, BAL, or nasal washes. Interestingly, despite the brisk systemic and pulmonary IgG response after subcutaneous immunization, intranasal immunization promoted significantly greater bacterial clearance after intranasal challenge with the organisms. These data further support the general premise that while systemic vaccination results in system antigen-specific IgG that may passively diffuse into the epithelial lining fluid in the lung, significant protection will only be afforded if local IgA immune responses are also induced.

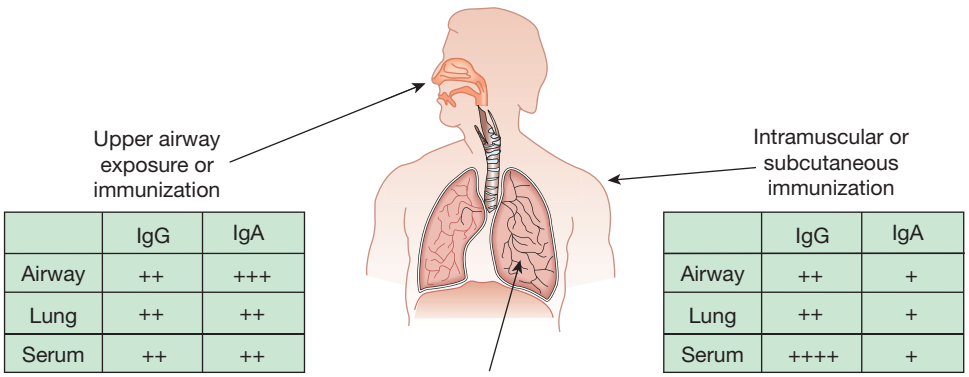
The effect of the intranasal and intramuscular polysaccharide pneumococcal vaccine has also been studied in a mouse model.[136] Intranasal vaccination, when accompanied by IL-12 administration (which increases IF-γ production), resulted in increased serum IgG2a anti-pneumococcal antibody, consistent with the known stimulatory effect of IF-γ on IgG2a production.[56] This regimen also resulted in increased pneumococcal-specific IgA in BAL fluid. The serum antibody response was functional in opsonophagocytosis assays. Interestingly, intramuscular vaccination afforded more protection against subsequent intraperitoneal pneumococcal challenge compared to intranasal vaccination. In contrast, intranasal vaccination was more effective in reducing nasopharyngeal colonization after nasal challenge of the organism compared to intramuscular vaccination, despite the higher serum IgG response after the latter. Finally, using IgA knockout mice, these investigators demonstrated that IgA was responsible for reducing pneumococcal colonization after vaccination and intranasal challenge.[136] These results again highlight the general principal that systemic immunization is more effective in providing protection against systemic challenges, while mucosal immunization is more protective against mucosal challenges.

There are significantly fewer studies on the pulmonary response to vaccines in humans. One study compared oral and nasal administration of a cholera toxin B subunit vaccine.[137] Nasal immunization resulted in a fivefold increase in the levels of specific IgA antibodies in BAL fluid. No significant specific IgA responses were seen after oral immunization. Specific IgG antibody concentrations increased eightfold in BAL fluid in the nasally vaccinated subjects, though this was felt to be from transudation from serum rather than local production. Several studies have examined systemic and salivary pneumococcal-specific antibody titers after systemic vaccination in children. Infants given the 7-valent conjugated pneumococcal vaccine at 2, 4, 6, and 15 months had significant plasma IgG responses at 7 months.[138] However, salivary pneumococcal-specific IgG and IgA concentrations were minimal at this time and did not appear till a booster vaccine was given at 15 months. Further studies suggested the salivary IgG was derived from serum while the salivary IgA was locally produced. This same group demonstrated that by age 4 to 5 years, anti-pneumococcal IgA, especially IgA1, was still present in saliva.[139] Interestingly, there was no difference in pneumococcal-specific antibody titers between vaccinated and unvaccinated children at age 4 to 5 years, suggesting that natural environmental exposure also resulted in mucosal immunity. Finally, immunization with the pneumococcal polysaccharide vaccine has been shown to lead to an increase in salivary pneumococcal-specific IgG and IgA in adults as well.[140] In other studies, despite the lack of immunologic correlation, systemic pneumococcal vaccination appears to decrease the incidence of nasopharyngeal carriage of vaccine-specific serotypes.[141]

In total, these studies suggest that in general systemic vaccination induces primarily an IgG response whereas mucosal vaccination induces primarily an IgA response (Fig. 24-6). While it is clear that systemic immunization can result in some local lung IgA production, the strongest mucosal immunity is induced when antigen is introduced directly into the respiratory tract. Intranasal and inhaled vaccines offer advantages in addition to the potential for improved local immunity, including the ability to immunize large populations at less cost.[142] In safety trials of intranasal vaccination against influenza using a virosome formulated inactivated virus the vaccine was associated with high serum concentrations of influenza-specific IgG and the presence of specific IgA in nasal lavage fluid.[143] Similarly, an inhaled measles vaccine has been shown to be immunogenic (as determined by serum measurement of measles-specific IgG) in a large children population.[144]

VACCINATION AGAINST PNEUMOCOCCAL DISEASE

There are currently two active vaccines against pneumococcal disease: the 23-valent pneumococcal polysaccharide vaccine (23-PPV) and the 13-valent pneumococcal conjugate vaccine. Because the conjugated vaccine contains protein linked to various polysaccharides, it is theoretically more immunogenic by virtue of its ability to induce T cell help for antibody secretion. The 23-PPV comprises capsular polysaccharide from 23 of the 90 serotypes of *S. pneumoniae*. Cross-reactivity between serogroups and the epidemiology of disease[145,146] suggest that if adequately immunogenic, this vaccine



	IgG	IgA
Airway	++	+++
Lung	++	++
Serum	++	++

	IgG	IgA
Airway	++	+
Lung	++	+
Serum	++++	+

	IgG	IgA
Airway	++	+++
Lung	+++	+++
Serum	+++	++

Figure 24-6 Summary of IgG and IgA concentrations at various sites after upper airway, lower airway, or systemic exposure to bacteria, either as a pathogen or in a vaccine.

should be effective against more than 90% of disease episodes worldwide.[147]

In humans the pneumococcal vaccine is clearly effective in reducing the morbidity and mortality of invasive pneumococcal disease.[148,149] However, studies describing the effect of vaccination on respiratory tract antibody concentrations are lacking. Most studies assessing the immune response to the pneumococcal vaccine focus on serum and salivary antibody titers. Only a few studies have tried to analyse the pulmonary response after vaccination. One study found no difference in the opsonic function of BAL IgG against pneumococcus 1 and 6 months after systemic immunization with the conjugate pneumococcal vaccine.[150] In another study the effect of intramuscular administration of the 23-valent vaccine was compared to inhalation of the same preparation.[151] BAL was performed one month after vaccination. Intramuscular administration resulted in significant increases in serum and BAL pneumococcal-specific IgG titers. Pneumococcal-specific IgA1 titers increased in serum, but not in BAL. This observation supports the concept that mucosal exposure is needed to get a local IgA response. However, no change was seen in any serum or BAL measurement in subjects who inhaled the vaccine. This contrasts with two other studies that found a mild systemic IgG response to inhaled pneumococcal vaccine.[152,153] Lung specific measurements were not assessed in these latter two studies. Thus the conclusion from currently available data suggests effective immunization against pneumococcus still requires systemic (intramuscular) immunization.

VACCINATION AGAINST INFLUENZA

Like the pneumococcal vaccine, vaccination against influenza is highly effective in preventing morbidity and mortality.[154,155] There are two currently available routes for influenza vaccination in humans. The more commonly administered trivalent vaccine consists of neuraminidase and hemagglutinin antigens from three viral strains and is usually given as an intramuscular injection. A second formulation consists of a live attenuated influenza vaccine and is given intranasally. Because it is a live vaccine it is not given to individuals with underdeveloped or impaired immunity. Thus candidates for the nasal vaccine are individuals between the age of 2 and 49 and no existing potentially immunosuppressive condition, including pregnancy.[156]

Because there are systemic and mucosal vaccination options for influenza, more is known about the pulmonary immune response to these vaccines.[157] In one study comparison of inactivated intramuscular and live intranasal influenza vaccines in young children undergoing primary immunization demonstrated that the intranasal preparation induced longer lasting protective antibody concentrations.[158] Nasal secretory IgA developed almost exclusively in nasally vaccinated individuals, whereas nasal IgG was detected in both nasal and intramuscular vaccine recipients. In general, studies show that the trivalent vaccine administered systemically induces a strong IgG response but minimal mucosal influenza-specific IgA. In contrast, the nasal live attenuated vaccine gives a stronger mucosal IgA response. Furthermore, because it results in low level infection, intranasal formulation also induces a specific cellular (cytotoxic T cell) response. Despite these differences, both appear to have similar efficacy in reducing morbidity and mortality from influenza.

Newer vaccine strategies are being developed to enhance population vaccination strategies and improve immunogenicity in individuals with poor antibody responses. In a controlled clinical trial, high dose trivalent influenza vaccination was more immunogenic than standard dose vaccination in subjects over 65, a population known to have a poorer vaccine response.[159] Adjuvants are also being developed to augment the immune response. In humans, using the adjuvant MF59 improves the immune response to the trivalent vaccine.[160] Another innovative approach is to target more conserved influenza antigens, which would obviate the need for yearly vaccination.[161,162] However, many conserved epitopes are poorly immunogenic, indicating that novel delivery methods will be necessary to elicit broad immune responses. In an animal study nucleocapsid and matrix proteins, which are not immunogenic, were able to induce protective antibody responses when administered with nanoparticles coated with papaya mosaic virus as an adjuvant.[163] Very recent animal models are exploring the use of adenovirus vectors to immunize with conserved influenza vaccines.[164] Thus recent advances in vaccine strategies offer hope that newer influenza vaccines will generate broader antigenic coverage, induce both humoral and cellular immunity, and provide longer lasting and better protection against this worldwide pathogen.

CONCLUSION

The humoral immune response is essential for host defense against bacteria. After exposure to potential pathogens, antibody responses in the respiratory tract can occur either quickly through activation of resident memory B cells if there has been prior bacterial exposure, or more slowly through the induction of both systemic and local mucosal immunity if the host is naïve to the organism. The resulting production of antigen-specific IgG and IgA act in concert to help clear the invading pathogen and reduce subsequent colonization of respiratory epithelium. The type and concentration of antibody produced is dependent on the site of exposure. Upper airway exposure results in primarily an IgA response. Organisms that reach the lung after passing through the upper airway induce a more systemic response, including increased production of pathogen-specific IgG. The importance of an effective pulmonary antibody response is highlighted by the significant morbidity associated with diseases characterized by deficient or defective antibody production. Increasing evidence is also pointing toward a key role of autoantibodies in many common lung diseases. Finally, vaccination against respiratory pathogens is dependent on an intact humoral immune system. Systemic vaccination against respiratory pathogens, while effective in generating systemic IgG responses and some mucosal IgA responses, may be less effective than vaccination through mucosal surfaces, which induce a brisk IgA and IgG response both locally and systemically depending on the site of vaccine deposition. Future studies should provide further insight on the pulmonary humoral host response to bacterial challenge and optimal vaccine regimens to minimize the burden of respiratory disease caused by pathogenic bacteria.

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CHAPTER 25

T Lymphocytes in the Lung

Lauren E. Cohn

The lung is a major site of exposure to the outside world in air-breathing species. Lung immunity has developed to recognize pathogens and activate appropriate responses, to temper inflammation in response to nonpathogenic exposures and turn off immune responses when danger signals have been eliminated. T lymphocytes play a major role in lung immunity predominantly through the induction of CD4 and CD8 T cells in adaptive immunity. A number of smaller subsets of T lymphocytes also play critical roles in early immune responses to pathogens and stimulating adaptive immune responses. Long-lived memory CD4 and CD8 T cells are crucial for host protection from pathogens, but also may drive chronic disease states, such as asthma. In this chapter the basic biology of T lymphocytes and their relevance in the lung in health and disease will be reviewed.

T LYMPHOCYTE SUBSETS

Lymphocytes make up approximately 10% of leukocytes in the blood and nearly 70% of leukocytes in the normal human lung.[1] In both sites, a majority of lymphocytes are T lymphocytes. Lymphocytes include T and B cells and are small, mononuclear cells with a characteristic large nucleus-to-cytoplasm ratio in the resting state. T lymphocytes have their origin in the thymus. T lymphocytes are essential for adaptive immune responses, the type of immunity that develops over a period of days to weeks that fine-tunes an immune response to limit a specific pathogen or insult. The majority of T lymphocytes express alpha-beta (α/β) T cell antigen receptors (TCRs) on the cell surface. The α/β TCR consists of two polypeptide chains with a variable region that binds to antigen, a constant region, and an anchor to the cell membrane. During development in the thymus, T cells undergo TCR gene rearrangement to generate a receptor that has an antigen-binding structure. Each mature T cell bears only this TCR with its unique specificity for antigen binding. Approximately 10^6 different TCRs develop in an individual, thus allowing the individual to respond to an extraordinary range of antigens throughout life. After exposure to a new antigen, TCRs expressed on T lymphocytes develop even finer antigen-binding capabilities through a process called affinity maturation.

The subsets of T lymphocytes that express receptors with less diversity and ability to recognize antigens include natural killer T (NKT) and mucosal-associated invariant T (MAIT) cells that also express an α/β TCR, and gamma-delta (γ/δ) TCR-expressing cells. These subsets of T lymphocytes are more prominent at sites of pathogen exposure, such as the mucosal surfaces. They express preformed receptors that bind to common pathogen components. This preset ability to bind and react to pathogens allows them to respond quickly, leading to early release of cytokines. NKT, MAIT, and γ/δ T cells are part of the innate immune response to pathogens and other insults that provide signals to initiate and direct CD4 and CD8 T cell activation in the adaptive immune response.

In addition to the α/β TCR, T lymphocytes express coreceptors CD4 or CD8. CD4+ T cells are called T helper (Th) cells because of their ability, through production of cytokines, to stimulate other immune cells. Another subset, CD4 regulatory T cells (Treg), downregulate immune responses. CD8 T cells, traditionally called cytotoxic T cells (Tc), release preformed effector molecules that destroy infected cells. They also produce cytokines that aid in local immunity. TCRs on CD4 T cells recognize peptide antigens that bind to domains on MHC Class II molecules that are present on the surface of antigen-presenting cells (APCs). CD8 T cells recognize endogenously derived antigens bound to MHC Class I molecules. MHC Class I molecules are present on the surface of all nucleated cells, whereas MHC Class II molecules are only present on APCs, including dendritic cells (DCs), B cells, and macrophages. Exogenous protein antigens, such as extracellular pathogens and environmental substances, are taken up by APCs and processed into peptides in endocytic vesicles, which are presented on the cell surface bound to MHC II molecules. Endogenous antigens, such as those of intracellular pathogens, including viruses, are processed and presented by Class I MHC molecules.

CD4+ T CELLS

CD4+ T Cell Activation

Mature, naive CD4+ T cells are released from the thymus into the circulation and enter the lymph node through specialized blood vessels, the high endothelial venules (HEVs). Expression of L-selectin (CD62L) on the naive CD4 T cell along with chemokine signals produced by stromal cells within lymphoid tissues permits attachment and transit through the HEVs into the lymph node.[2,3] In the lung, this occurs in the lymph nodes that drain the trachea, bronchi, and lung parenchyma.

Antigens or pathogens that enter the lung are taken up by APCs in the airways and alveoli. DCs are the major APC of the mucosal surfaces. DC in the airway walls and alveoli form a dense network just beneath the epithelium with processes that extend to the airspaces, designed to catch foreign antigens.[4] Macrophages in the airways and lungs also engulf large particles and pathogens through phagocytosis, but they are typically poor stimulators of adaptive immune responses, and likely eliminate antigens or induce regulatory responses, rather than activate immunity. After antigen uptake, APCs break down antigens into peptide fragments in endocytic vesicles, where the peptides are loaded onto Class II MHC proteins and transported to the cell surface. Concurrent with antigen presentation, the APC increases expression of costimulatory molecules and migrates to the lung-draining lymph nodes.

In the T cell area of the lymph node, naive CD4+ T cells move past antigen-expressing APCs, permitting the interaction of TCR and MHC Class II peptide. When the TCR on a CD4+ T cell interacts with its specific antigen on an APC, it ceases to migrate further. T cell activation is initiated upon (1) TCR recognition of MHC class II peptide (signal 1) and (2) costimulatory signaling from the APC (signal 2) (Fig. 25-1). The principal costimulatory molecules expressed on the surface of APCs are CD80 (B7-1) and CD86 (B7-2), which both interact with CD28 on the T cell.[5] If both signal 1 and signal 2 are received, the T cell goes into G1 phase of the cell cycle, begins to produce interleukin-2 (IL-2) and undergoes clonal expansion. This gives rise to a population of effector cells with the identical TCR specificity to the parental cell.

CD4 Helper T Cell Differentiation

Primary Immune Response Antigen-activated CD4+ T cells differentiate into effector cells of different types. CD4 T cell subsets are defined by the cytokines they secrete, and that pattern of cytokines confers its functional properties (Table 25-1). *T helper type 1* (Th1) cells are a subset of CD4+ T cells that secrete the macrophage activating factor, interferon gamma (IFN-γ), and lymphotoxin (LT or TNF-β). *T helper type 2* (Th2) cells produce interleukin-4 (IL-4), IL-5, and IL-13. *T helper type 17* (Th17) cells produce IL-17A, IL-17F, and IL-22. IL-10, an anti-inflammatory cytokine, was originally defined as a Th2 cytokine, but it is now recognized that it can be synthesized by all Th cell subsets upon appropriate activation.[6] Treg produce IL-10 and/or TGF-β1. Since Treg suppress T cell differentiation and APC activation, they are not considered effector cells. Th1 cells stimulate strong cell-mediated immune responses, particularly against intracellular pathogens. Th2 cells, through the production of IL-4 and IL-13, are potent activators of B cell antibody production, particularly immunoglobulin E (IgE). IL-5 secretion by Th2 cells is critical for eosinophil differentiation and maturation. Th2 cells are elicited in immune responses that require a strong humoral component and in antiparasitic responses. Th17 cells stimulate neutrophil mobilization and recruitment, release of antimicrobial peptides, and serve critical host defense functions at mucosal surfaces. An effective immune response to a pathogen commonly results in the induction of a balance of Th1, Th2, and Th17 cells to provide strong cellular and humoral immunity.

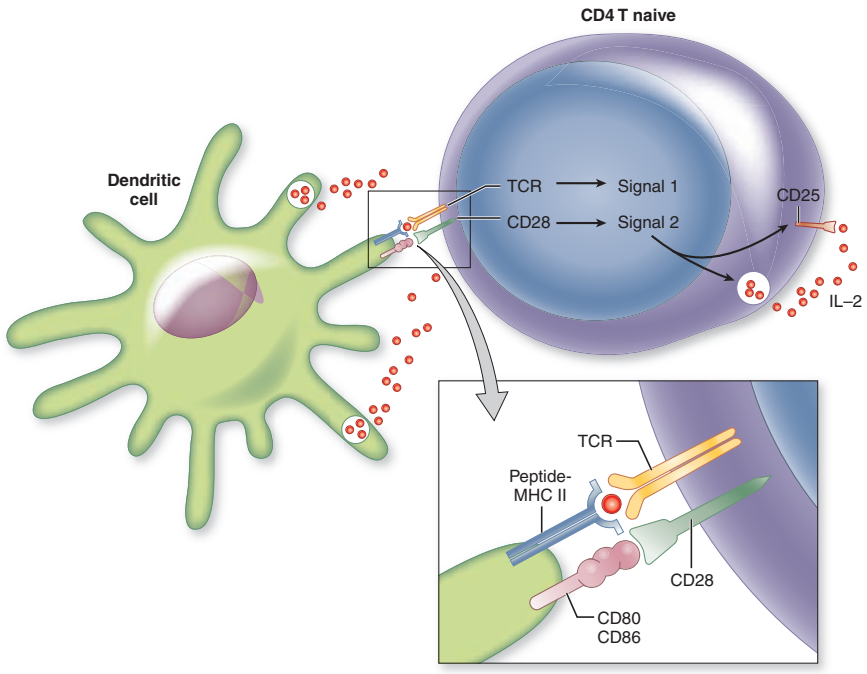

Figure 25-1 Two-signal mechanism of CD4 T cell activation. Antigen-presenting cell (APC) takes up a protein antigen and processes it into peptide fragments that are presented by class II major histocompatibility complex (MHC) molecules. Signal 1 required for CD4 T cell activation is recognized by the T cell antigen receptor (TCR) and engagement of class II MHC-peptide complex. Signal 2 is an interaction of CD28 on the T cell with CD80 or CD86 on the APC, termed costimulation. These signals stimulate interleukin-2 (IL-2) production, IL-2 receptor (IL-2R) expression and induce CD4 T cell proliferation.

CD4+ Treg comprise subsets of cells generated in the thymus (natural Treg) or induced in the secondary lymphoid tissues (inducible (i) Treg) that produce IL-10 and/or TGF-β1 and express the transcription factor Foxp3. They are often identified by their high expression of CD25 and Foxp3.[7] CD4 Treg inhibit the development

TABLE 25-1 T Lymphocyte Subsets and Their Functions

T Lymphocyte		Signals to Activate/Differentiate: Cytokine	Signals to Activate/Differentiate: Transcription Factor	Cytokines and Mediators Produced	Major Functions
CD4 Activated by peptide–MHC Class II	Th1	IFN-γ, IL-12	T-bet	IFN-γ, lymphotoxin	Anti-viral and -mycobacterial effects, activation of macrophages to kill intracellular pathogens
	Th2	IL-4	GATA-3	IL-4, IL-5, IL-13	Antiparasitic responses Stimulation of IgE and other antibody production, increases mucus production, promotes eosinophilia
	Th17	IL-6, TGF-β1, IL-1β (human)	RORγt	IL-17A, IL-17F, IL-22	Antibacterial and anti-fungal effects, recruitment and activation of PMNs
	Treg	TGF-β1, IL-10	Foxp3	TGF-β1, IL-10	Suppression of T cell activation, inhibition of APC function
CD8		Peptide–MHC Class I		IFN-γ, TNF-α Granzyme perforin	Cytotoxicity of cells infected with virus or bacteria
NKT		Glycolipids		Extensive range of preformed cytokines that are rapidly released	Shaping adaptive immunity against pathogens
MAIT		Vitamin B metabolites		IFN-γ, TNF-α, IL-17, granzyme	Antimicrobial responses
γ/δ		Mycobacterial lipids, heat-shock proteins		Extensive range of preformed cytokines that are rapidly released	Antimicrobial responses, immune surveillance

of Th1, Th2, and Th17 subsets through actions on both APCs, naive T cells, and effector T cells.[8] Treg exert their suppressive effects by secreting cytokines, including TGF-β1 and/or IL-10, by cell contact leading to cytotoxicity or metabolic disruption or by suppression of APCs.[9]

Molecular Mechanisms of CD4 Th Differentiation

Differentiation of naive CD4 T cell into Th1, Th2, Th17, or Treg requires the coordinate action of multiple molecular signals induced by stimulation of the TCR, costimulatory molecules, and cytokine receptors (Fig. 25-2). Major factors in these processes are critical lineage-determining molecules important for stimulation of T cell differentiation, simultaneous inhibition of the opposing phenotypes, T cell proliferation, epigenetic remodeling to modify the chromatin structure and cytosine methylation, and expression of key transcription factors.

T-bet is one of the lineage-determining molecules required for Th1 differentiation. It belongs to the T-box family of transcription factors that regulate multiple developmental processes. T-bet is upregulated in Th1 cells, through effects of IL-12 and activation of STAT4, and IFN-γ and activation of STAT1.[10] Induced expression of T-bet in vitro and in vivo led to IFN-γ production.[11] Thus T-bet drives Th1 development. T-bet also promotes Th1 induction through negative regulation of GATA-3.[12]

The transcription factor GATA-3 is an essential regulator of Th2 differentiation.[13,14] Whereas, GATA-3 is expressed at low levels in naive CD4+ T cells,[13] it is markedly upregulated in cells differentiating along the Th2 lineage and is downregulated in cells differentiating along the Th1 pathway.[13] The differentiation of a naive CD4+ T cell along the Th1 or Th2 pathway is accompanied by extensive reorganization of chromatin structure around the IFN-γ or IL-4/IL-5/IL-13 loci, respectively.[15] GATA-3 appears to be the critical downstream regulator of chromatin remodeling around the IL-4 locus.

The orphan nuclear receptor RORγt induces differentiation of naive CD4+ T cells into Th17 cells.[16] RORγt is required for the expression of IL-17 and the related gene IL-17F in response to IL-6 and TGF-β in mice or IL-1β in humans.

Cytokines, by stimulating production of critical lineage-determining molecules, are the primary factors that affect CD4 Th generation.[17,18] Cytokines produced in innate immune responses modulate how the adaptive immune response will develop. IFN-γ and IL-12 cause induction of Th1 cells. IL-4 and IL-13 drive Th2 cell generation. IL-10 enhances Th2 cell development by inhibiting Th1 cell induction. IL-6, IL-1β, IL-23, and TGF-β1 promote Th17 development.

Other factors that influence CD4 differentiation into Th subsets affect the quality of the signal through the TCR. The dose and structure of the antigen affects the APC–TCR interaction and has been shown to drive Th differentiation along distinct pathways.[19] If peptide–MHC Class II complex on the APC has a high-affinity interaction with the TCR, then a Th1-predominant response results, whereas a weaker-affinity interaction leads to a Th2-like response. Very low doses of soluble protein antigen tend to stimulate Th2-predominant responses, and at higher antigen doses, Th1 responses, suggest that the antigen dose affects the APC–T cell interaction. This may have important implications in atopy, since it has been estimated that exposure to common allergens is so small that it does not exceed 1 μg per year. Another line of investigation suggests that high-affinity interactions lead to preferential generation of Th2 cells.[20] More recent studies show that the fate of Th differentiation is an effect of both antigen dose and TCR–MHC Class II binding.[21]

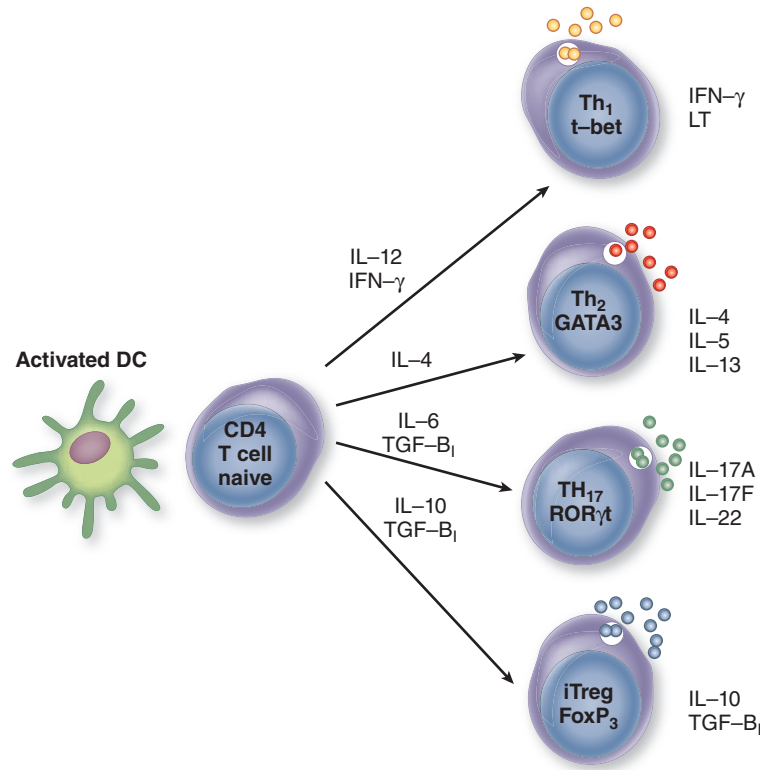

Figure 25-2 Generation of T helper types 1, 2, and 17 (Th1, Th2, Th17) and regulatory T cells (Treg) from a naive CD4+ T cell. A naive CD4+ T cell secretes very low levels of cytokines. Differentiation along the Th1, Th2, Th17, and Treg pathways is triggered when antigen is presented to the T cell receptor in the context of the major histocompatibility complex (MHC) by the appropriate antigen-presenting cell and a second signal imparted by ligation of costimulatory molecules CD80/CD86 and CD28. Dendritic cells (DCs) represent the key APCs for naive T cells. Cytokines produced in innate immune responses activate DC to produce cytokines that direct differentiation of Th subsets leading to induction of critical lineage–determining molecules, T-bet for Th1 cells, GATA-3 for Th2 cells, RORγt for Th17 cells, and Foxp3 for inducible (i)Treg. The cytokines produced by each subset of CD4 T cells are depicted.

Ultimately, the quality of the signals delivered to the T cell through the TCR influences which Th subsets are activated.

Effector/Memory CD4 T Lymphocytes

It takes 4 to 5 days of proliferation in the lymph node for a naive CD4 T cell to differentiate into an effector cell. Associated with differentiation is a change in expression of cell surface of selectins, integrins, and chemoattractant receptors that permit exit from the lymph node and recruitment to sites of inflammation. With differentiation there is loss of expression of the lymph node homing receptor CD62L and gain of function of tissue homing receptors. Whereas skin and gut effector CD4 T cells each have specific ligands that confer their localization to that tissue through binding to vascular endothelial cells (skin, cutaneous lymphocyte-associated antigen [CLA], small intestine, integrin α4β7), such a lung-specific surface marker has not yet been identified. Human lung effector CD4 T cells are enriched for expression of CCR5, CCR6, chemokine (C-X-C motif) receptor 3 (CXCR3) and the integrins VLA1 (α1β1), CD103 (αEβ7), and VLA4 (α4β1).[22] In addition to expression of receptors that respond to specific signals that direct them to the tissue, subsets of effector CD4 Th cells express different panels of chemokine receptors so they can be called to perform specific duties. The type of injury or invading pathogen leads to release of mediators that recruit appropriate, effective populations of CD4 Th cells to manage the specific problem. Th1 cells typically express CCR5 and CXCR3, Th17 cells express

CCR6, and Th2 cells express CCR4 and CCR8, and the prostaglandin D2 chemoattractant receptor DP_2 (CRTH2) in humans.[22]

Effector cells that were activated in the lymph node arrive at an inflammatory site in the lung where they proliferate and produce cytokines. The major function of CD4 T cells is to produce cytokines to recruit other inflammatory cells and modulate local host-protective responses. Following this robust response, most activated effector CD4+ T cells die, either by a process of apoptosis or necrosis. A small population of CD4+ cells persists as memory cells for the life of the host.

CD4 memory T cells, upon reexposure to specific antigen, respond quickly with a strong response of longer duration. Subsets of CD4 memory T cells have been identified based on tissue localization and circulation patterns, cell surface markers, and functional differences. Effector memory cells (T_{EM}) are found in blood and in nonlymphoid tissues, such as liver and lung. Central memory T cells (T_{CM}) circulate through secondary lymphoid organs, lymphatics and blood, produce higher levels of IL-2 and proliferate more than T_{EM}.[23] The third CD4 memory subset, tissue-resident memory T cells make up large pools of cells in the skin and mucosal tissues, including the lung. T_{RM} remain in the tissue compartment to which they were initially called and do not recirculate. T_{RM} are responsible for barrier protection, exhibit the activation marker CD69 and can be activated locally in the tissue, without trafficking to the lymph node, to provide expedient control of infection.[23]

CD4 Regulatory T Cells

CD4 Treg comprise subsets of cells generated in the thymus (natural Treg) or induced in the secondary lymphoid tissues (inducible (i) Treg) that produce IL-10 and/or TGF-β1 and exhibit high expression of CD25 and the transcription factor Foxp3. They make up 5% to 10% of the peripheral CD4 T cell population. Cytokines produced by CD4 Treg inhibit the development of Th1, Th2, and Th17 subsets through actions on APCs, naive and effector T cells.[8] CD4 Treg are critical for suppressing primary immune responses to self, as indicated by mice and humans deficient in a functional Foxp3 protein that develop autoimmune diseases.[24,25] Treg exhibit additional diverse mechanisms to achieve immune suppression in different inflammatory milieu.[26]

■ CD8 T CELLS

Pathogens that enter the lung activate tissue-resident DCs and migrate to lymph nodes where they activate naive CD8 T cells. CD8 T cells are activated to differentiate into effector cells through interactions with DCs and the provision of two required activation signals, antigenic peptide presented by MHC Class I molecules and costimulatory signals. Viruses and intracellular bacteria are classical activators of CD8 T cells. Cytokines secreted by DC drive the proliferation and differentiation of CD8 T cells to acquire the ability to become effector CD8 T cells that most commonly secrete IFN-γ and TNF-α and have cytotoxic capabilities through production of granzyme B and perforin.[27] Effector CD8 T cells may also differentiate into subsets of Tc2 cells that secrete IL-4, IL-5, and IL-13 and Tc17 cells that produce IL-17.[28] CD8 memory cells develop from a small subpopulation of cells activated in a primary immune response. Memory CD8, like CD4, T cells include subsets of T_{CM}, T_{EM}, and T_{RM}. While CD8 and CD4 memory T cells may exhibit different homing patterns, memory functions and surface markers appear to mirror observations in CD4 T cells that were described earlier. For example, CD8 $T_{RM,}$ like CD4 T_{RM}, do not recirculate and confer rapid tissue-specific recall responses in the lung.[23,29]

■ T LYMPHOCYTES WITH RESTRICTED TCR DIVERSITY

T lymphocytes with less diverse arrays of TCRs accumulate in the lung. They respond to different antigens than traditional α/β CD4 and CD8 T cells. Their numbers in tissues are low, but because many respond to the same antigen, they can be activated quickly without further differentiation. Therefore, they participate in innate immunity and some subsets can expand and adapt to exposures. Thus, these T lymphocyte subsets bridge innate and adaptive immunity. There are two small populations of α/β T cells, iNKT cells and MAIT cells that have semi-invariant α chains. Thus, they have undergone somatic mutation in the thymus to generate a TCR, but they have limited diversity due to fewer possible TCR combinations. Both iNKT and MAIT cells are found in high frequencies in mucosal tissues.

Natural Killer T Cells

Type I or invariant (i)NKT cells are a small subpopulation of α/β T cells that express a narrow repertoire of TCRs due to invariant expression of the TCR variable (V)α chain and limited TCR Vβ chains. In humans Vα24-Jα18 pairs almost exclusively with Vβ11, whereas in mice Vα14-Jα18 pair with a limited number of Vβ chains. iNKT cells respond to glycolipid antigens presented on the MHC-like molecule CD-1d, which is a member of a family of nonpolymorphic proteins that bind to lipids, rather than peptide antigens, and is expressed on populations of DCs, B cells, and macrophages.[30]

iNKT cells leave the thymus upon maturation and migrate into tissues. In mice, iNKT cells are enriched in the liver and spleen. In humans iNKT cells are highly enriched in the omentum but have not been well characterized in all tissues.[31] In the bronchoalveolar lavage (BAL) of normal control subjects iNKT cells constituted less than 1% of the lymphocyte population.[32] In mouse, iNKT cells may be 5% to 10% of the lung lymphocytes.[33] Murine studies show that iNKT cells are resident in the lung and, for the most part, do not recirculate to other organs.[34] iNKT cells also reside in the lung microvasculature in the resting state and upon exposure to inhaled lipids, become activated and extravasate into the lung parenchyma where they contribute to lung inflammation.

A hallmark of iNKT cell activation is the rapid elaboration of an extensive array of cytokines and chemokines including IFN-γ, TNF-α, TGF-β, GM-CSF, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IL-21, RANTES, eotaxin/CCL11, MIP-1α/CCL3, and MIP-1β/CCL4.[30] The early activation of iNKT cells in tissues by specific pathogens is believed to be important in shaping the appropriate adaptive immune response.

MAIT Cells

MAIT cells are another small subpopulation of α/β T lymphocytes that express TCRs with limited diversity. MAIT cells express a semi-invariant α chain, Vα7.2-Jα33, that pairs with a limited number of Vβ chains. MAIT cells are present in humans in the peripheral blood, lamina propria of the intestine, and in the lung.[35] MAIT cell activation requires interaction with the nonpolymorphic MHC I–like molecule MR-1. MR-1 binding of vitamin B metabolites, specifically a precursor of riboflavin synthesis, activates MAIT cells. Since only certain bacteria, fungi, and yeast synthesize this B vitamin, MAIT cells are activated early after exposure to pathogens capable of producing riboflavin.[36,37] Activation of MAIT cells leads to release of cytokines, including IFN-γ, TNF-α, IL-17, granule exocytosis leading to apoptosis, and delivery of antimicrobial peptides.[38,39] MAIT cells help to stimulate effective antipathogen CD4 and CD8 adaptive immune responses. MAIT cells are enriched in the lung in infections, such as tuberculosis, where a fivefold increased frequency, compared to the blood, has been observed.[35]

γ/δ T Cells

Gamma/delta (γ/δ) cells are a subset of T cells that have a TCR composed of γ and δ chains. The γ/δ TCR is generated by VDJ recombination, but unlike the α/β TCR, γ- and δ-chain recombination results in a less diverse repertoire of TCRs. Upon release from the thymus, γ/δ T cells migrate to tissues including lung, skin, intestine, and uterus. γ/δ T cells, like α/β T cells, are found in blood, LN,

and spleen. Within specific tissue compartments all γ/δ T cells may express a monoclonal TCR. γ/δ T cells engage a different group of antigens than α/β T cells. γ/δ TCRs respond to a diverse array of antigens including moieties large and small, self and foreign, and peptide and nonpeptide. This includes mycobacterial lipids and heat-shock proteins.[40] γ/δ T cells do not recognize antigens in the context of class I or II MHC; rather, they may recognize their target antigens directly. The full scope of γ/δ TCR-binding antigens remains unknown.[41] γ/δ T cells secrete a range of cytokines and chemokines, many of which are preformed and quickly produced, to recruit inflammatory cells. Their narrow TCR diversity in a tissue compartment, and ability to respond to their stimuli quickly allows for rapid clonal activation without the need for expansion. This suggests that γ/δ T cells play a role in surveillance and protection from infection, and serve as a bridge between innate and adaptive immune responses.

T LYMPHOCYTES IN THE LUNG

T LYMPHOCYTE DISTRIBUTION IN THE LUNG

In the normal human lung, T lymphocytes are found in the airways and alveolar spaces, in the lung parenchyma/interstitium, the pulmonary intravascular spaces, and in lymph nodes, and their numbers differ in each of these compartments. In adult humans, lymphocytes in the lung are not typically organized into lymphoid structures, such as bronchus-associated lymphoid tissue (BALT), whereas BALT is more common in healthy children, in smokers and those with chronic infections and inflammatory diseases, and in normal animals such as rabbits and rats.[42,43] Recent studies show that lymphocytes are not randomly distributed in each lung compartment, but appear to be organized at sites of pathogen entry.[44] T lymphocytes likely have a multidimensional organization in the lung, including close associations with dendritic, epithelial, and mast cells, but these detailed interactions and their structure is not yet well defined. Until recently, analyses of lung lymphocytes have assessed collections of cells from BAL, which includes cells from the airways and alveolar spaces, or in digested lung tissue. Histopathologic assessments afforded, at best, little more than a two-dimensional analysis. Future studies will define the three-dimensional organization of T lymphocytes in the lung, their detailed interactions with both structural cells, including epithelial, endothelial and neuronal, and hematopoietic cells. Kinetic studies will define how lymphocytes transit between compartments in the lung, to secondary lymphoid and other tissues.

Lymphocytes, including T and B cells, make up about 7% of leukocytes isolated from the human lung. It has been estimated that between 2 and 4 × 10^8 lymphocytes reside in the airways and alveolar spaces. Twentyfold more are estimated to make up the pool of lymphocytes in the lung parenchyma in the normal human lung.[45,46] Lymphocytes isolated from the lung parenchyma consist of large populations within the interstitium and the intravascular space.[47]

In the lung parenchyma, T lymphocytes are the predominant lymphocyte population, a majority of which are CD4 T cells (T:B ratio 15:1, CD4:CD8 2:1).[48] Memory CD4 T cells make up a majority of CD4 T cells in the lung and at other mucosal sites. CD8 memory cells make up half of the CD8 T cell population in the lung. With age, the number of lymphocytes and the proportion of lymphocytes with a memory phenotype increase. In the BAL, CD4 T cells comprise about 4% of leukocytes in young adults and 20% in older adults.[49–51] In lung parenchyma, memory CD4 T cells were 65% in young adults and almost 80% in older adults.[48] Thus, the proportion of antigen-experienced CD4 T cells increases in the lung and likely reflects an individual's accumulated respiratory exposure over time.

T LYMPHOCYTES IN LUNG INFECTION

T lymphocytes play critical roles in host defense against bacteria, viruses, and fungi that enter the host through the respiratory tract. This essential function of T lymphocytes is illustrated in HIV infection, in which individuals lack functional T cell subsets leading to susceptibility to pulmonary infection with bacteria, including *Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenzae*, and mycobacterial species, viruses such as influenza, and fungi such as histoplasmosis and *Cryptococcus neoformans* and pneumocystis jiroveci pneumonia (PJP).[52]

The immunocompetent individual responds to pathogen invasion through activation of NKT, MAIT, and γ/δ T cells along with other first responders, including macrophages, neutrophils, and epithelial cells. These innate immune cells are rapidly activated to secrete cytokines to help contain the pathogen, and to provide signals to activate CD4 and CD8 T cells. The range of cytokines produced by innate immune cells after activation shape the patterns of CD4 and CD8 T cell subsets induced to differentiate to control the invading pathogen. In a primary response to a pathogen, antigen-specific CD4 and CD8 effector T cells begin to arrive from the secondary lymphoid organs in the lung days after the initial infection.

In lung infection, the primary function of CD4 T lymphocytes is to produce cytokines that ultimately lead to elimination of pathogens. CD8 T cells have the additional capacity to kill infected cells. A primary infection results in the development and recruitment of a range of pathogen-specific T cell subsets, including CD4 Th1, Th2, and Th17, and CD8 T cells. Each subset serves a specific purpose in the complex antimicrobial immune response. Yet, in some infections, one subset is essential for antipathogen immunity. Th1 cells are absolutely required for elimination of a number of pathogens, and this reflects Th1 production of IFN-γ. IFN-γ is essential for immunity to respiratory infections because of its myriad antimicrobial functions including macrophage activation, stimulation of microbicidal effectors, and stimulation of antiviral enzymes.[53] Th1 cells are essential for host defense against all mycobacterial species, other intracellular pathogens such as *Chlamydia pneumonia* and *Francisella tularensis*, virus infections including influenza and RSV, gram-negative bacterial infections with *Klebsiella pneumonia*, and fungal infections including coccidiodes, cryptococcosis, and histoplasma.[54] Th2 cells are required for immunity to helminth parasites, and Th17 cells are essential to eliminate the gram-negative bacteria *K. pneumonia* and *Pseudomonas aeruginosa*, chlamydia, *and Mycoplasma pneumonia* and for immunity to various fungal infections including candida.

After a primary infection, pathogen-specific memory CD4 and CD8 T cells develop. Some are retained in the lung as T_{RM} and are presumed to persist there through the life of an individual. Animal studies show that maintenance of the memory CD4 T cell population in the lung in the first year after primary infection required recruitment of new cells from the circulating pool.[44,55] It remains unknown if memory cells continue to be replaced at this rate further out from infection, but it is likely that a dynamic process sustains the population of memory T cells in the lung long after infection.

The population of memory T_{RM} appears to be retained in the lung by surface expression of tissue-specific homing molecules.[56,57] Animal studies show that in different species memory CD4 and CD8 isolated from the lung returned to the lung when reinjected systemically into another animal. One such localization signal is CD103, which is expressed on antigen-specific T cells.[23,58] In both mice and humans, CD69 expression characterized CD4 and CD8 memory T cells that were retained in the lung, rather than those that recirculated.[44] Influenza-specific CD4 and CD8 T_{RM} were compartmentalized in bronchovascular bundles surrounding the airways.[44] Thus, CD4 T_{RM} may be retained adjacent to the tight web of DCs just below the epithelial surface where they can be quickly activated by specific antigen.[59] Virus-specific memory CD8 T cells were observed in or near capillaries in the lung by chemokines secreted by epithelial cells.[55,60] After reexposure to a pathogen in the lung, CD4 and CD8 T_{RM} are activated locally, rather than recirculating to local lymph nodes.[23,44] In humans, T_{RM} produced IFN-γ and

IL-2 upon activation,[48] thus insuring both antimicrobial and proliferation signals at the site of infection. Therefore, T_{RM} in the lung reside in compartments near key sites of exposure that insure rapid recruitment, reactivation, and proliferation upon pathogen reexposure, and they may be skewed toward a memory type 1 phenotype.

■ T LYMPHOCYTES IN CHRONIC LUNG DISEASES

T lymphocytes serve essential functions in host defense as they respond to specific antigens and are retained in the lung as memory cells, but they may also drive chronic disease when immune responses are generated against nonpathogens such as allergens or self-antigens. The development of immunity against nonpathogenic aeroallergens in allergic asthma is an example of immune dysregulation. While asthma is the most extensively studied T lymphocyte–driven lung disease, many other chronic pulmonary diseases may be caused and/or perpetuated by T lymphocytes, including sarcoidosis, hypersensitivity pneumonitis, autoimmune lung diseases, idiopathic pulmonary fibrosis, pulmonary hypertension and lung cancer, and others.

T Lymphocytes in Allergic Asthma

Long-lived antipathogen responses are protective and reflect useful host immunity. In allergic asthma, the long-lived memory lymphocytes that respond to allergens are deleterious and may remain capable of reactivation throughout the life of the individual. T lymphocytes appear to drive this chronic disease state in the airways. Many T lymphocyte subsets have been implicated in initiating and sustaining asthma.

CD4 T Helper Type 2 Cells in Asthma CD4+ T cells are the predominant lymphocyte population infiltrating the airways and they express markers of activation in asthmatic subjects. CD4+ T cells producing IL-4, IL-5, and IL-13 have been identified in BAL and airway biopsies and are secreted in the airways of patients with mild or asymptomatic asthma.[61] GATA-3 expression was increased in airways of asthmatic patients compared with those in control subjects, indicating the presence of Th2 cells.[62] Antigen challenge in allergic asthmatic patients led to an increase in Th2 lymphocytes in the airways.[63] In asthmatic patients, airway hyperreactivity (AHR) and airway eosinophilia correlated with airway CD4 T cells that produced IL-4 or IL-5 or expressed GATA-3.[62] In conjunction with known effects of IL-4, IL-5, and IL-13, these studies support the hypothesis that Th2 cells drive the characteristic inflammatory response that results in asthma.

Animal studies show that activation of CD4 Th2 cells in the airways leads to pathophysiologic manifestations of asthma. Eosinophilic airway inflammation and AHR have both been shown to be dependent on CD4+ T cells.[64] Studies that employed adoptive transfer of CD4+ T cells from animals with antigen-induced AHR resulted in airway inflammation and hyperresponsiveness in recipient mice, indicating that CD4+ T cells can control many aspects of the disease. CD4+ Th2 cells induced airway eosinophilia, mucus hypersecretion, and AHR, whereas Th1 cells caused a neutrophil-predominant inflammatory response without any of these features of asthma.[64]

Gene association studies also support a role for Th2 cells in asthma. Strong linkages have been identified to flanking markers of the human cytokine gene cluster on chromosomes 5q31 and 16p12, which include genes for IL-4, IL-13, and IL-4Rα.[65] Variants in the IL-4 promoter region are associated with atopy, as are polymorphisms of IL-4Rα, a component of both the IL-4 and IL-13 receptors, and a variant IL-13R.[66] Thus, modifications of IL-4 and/or IL-13 or their signaling, increasing Th2 cell functions, are associated with atopy and asthma.

CD4 T Helper Type 1 Cells in Asthma Th1 cells are also present in the airways of asthmatic patients, but it is still not clear if they serve a protective or pathologic function in asthma. IFN-γ was elevated in the airways of some severe asthmatics, and it was reduced in subsets of other asthmatics[67,68] Some studies show that Th1 cell activation inhibits allergic airway inflammation, whereas other studies suggest that Th1 cells potentiate the inflammatory response in asthma due to the proinflammatory effects of Th1 cytokines.[64]

Human and animal studies suggest that enhancing Th1 cytokines in the lung before or early in the generation of a Th2 response may protect against the development of asthma. IFN-γ–dominated immune responses to viral or mycobacterial infection in childhood are associated with a reduced incidence of asthma.[69] Attendance at day care and exposure to other siblings was protective against wheezing in childhood, which is hypothesized to be from beneficial exposures to respiratory infections. Also, mice immunized in the presence of a Th1-stimulating environment exhibited a reduction in antigen-induced eosinophilic airway inflammation and AHR.[70] Thus, reducing the generation of Th2 cells appears to decrease allergic inflammation. However it is also apparent that a high frequency of virally induced wheezing in early life is a strong predictor for the subsequent development of asthma in children,[71] thus suggesting that timing and nature of infections in early life may be crucial.

Th1 cells can also inhibit the effects of ongoing Th2 cell responses. Th1 cells, through the production of IFN-γ, have been shown to inhibit Th2 cell cytokine production and Th2 cell proliferation in vitro.[72] In mice the Th1 cytokine IFN-γ has inhibitory effects on Th2-induced airway eosinophilia and AHR. When administered before inhaled antigen challenge, IFN-γ reduced the number of CD4+ T cells in the respiratory tract or reduced Th2 cytokine secretion.[73] These effects may result from inhibition of Th2 cell recruitment by IFN-γ. Once Th2 cells are present in the respiratory tract, IFN-γ promotes the resolution of airway eosinophilia and suppresses Th2 cytokine production.[74] Th1 cells, through the production of IFN-γ, can inhibit airway eosinophilia, mucus production, and AHR without an increase in airway inflammation.[75] Although many studies support Th1 cells and IFN-γ as inhibitors of Th2-type responses, other studies show that Th1 cells enhance inflammation and do not ameliorate disease.[76] The proinflammatory effects of Th1 cells are supported by the association of viral respiratory infections, which tend to induce Th1 responses, and exacerbation of symptoms in asthmatic patients. Ultimately, the influence of Th1 cells on allergic airway inflammation may depend on the timing of Th1 relative to Th2 cell activation and the subphenotype of the asthmatic.

CD4 T Helper Type 17 Cells in Asthma Th17 cells, IL-17A and IL-17F are increased in the airways, sputum, and blood of subjects with asthma.[77] Given the heterogeneity of asthmatic airway inflammation and the effects of IL-17A and IL-17F on neutrophil recruitment, it was hypothesized that Th17 cells would be pathogenic in neutrophilic, nonatopic asthma. Yet, there was a positive association of IL-17 and IL-5, and IL-17 with atopic, not with nonatopic asthma.[78] As expected, IL-17A levels were associated with sputum neutrophils and not eosinophils,[79] suggesting that Th17 cells may drive disease in a subset of neutrophilic asthmatics.[80]

Studies to determine the function of Th17 cells have not established a definitive role of Th17 and IL-17A in animal models of asthma. A number of laboratories have shown that Th17 cells, IL-17A and IL-17 receptors are critical for optimal Th2 cell function, AHR, and eosinophilic inflammation. Furthermore, IL-17A was a major determinant in the development of AHR in mice with susceptibility compared to mice with resistance to develop AHR.[81] Yet, other investigators showed neutralization of IL-17 leads to worse disease.[25,82] The complex interplay of Th17 and Th2 cells is highlighted by studies showing that IL-13 inhibits IL-17A production and IL-17A production inhibits IL-25 that drives Th2 function. These studies suggest that disease pathogenesis in asthma may result

from a disruption in a critical balance of cytokines that includes IL-17.

Regulatory T Cells in Asthma Foxp3+ Treg likely determine early sensitization to allergen, as suggested by studies of the rare, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), which is caused by mutations in the *Foxp3* gene on the X chromosome. This results in markedly reduced or absent Foxp3+ Treg. Young boys with this condition suffer from both severe autoimmune and allergic symptoms.[24] T cells from these patients show skewing toward a Th2 phenotype. Mice with a mutation in the Foxp3 gene also demonstrate intense multiorgan inflammation, including allergic airway disease, high levels of IgE, eosinophilia, and dysregulated Th1 and Th2 cytokine responses, but they do not exhibit Th2 skewing, as observed in humans with IPEX.[83]

Studies to assess the numbers of CD4+CD25+ T cells in the peripheral blood of healthy, compared to allergic, subjects have not consistently shown differences[8,84] However, some of the methodology used to detect Treg make interpretation of some of these earlier data limited due to the methodologies used to detect Treg. There are data, though, that show impaired $CD4+CD25^{high}$ Foxp3 Treg in allergic disease. In asthmatic children there were reduced numbers of $CD4+CD25^{high}$ T cells in BAL, but not blood, as compared to control children with chronic cough.[85] A lower level of Foxp3 mRNA was reported in asthmatic children. $CD4+CD25^{high}$ T cells in the airways of the asthmatic children correlated with clinical parameters such as lung function, and were restored following corticosteroid treatment. A similar increase in Foxp3 mRNA was reported in the peripheral blood of adult asthma patients following inhaled corticosteroid treatment.[86] Foxp3-expressing Treg are also important negative regulators of asthma and allergic disease in animal models. Treg expressing either IL-10, TGF-β1, or both were required to limit airway inflammation in numerous models of tolerance induction.[87–90] Overall, it appears that impaired Treg responses may contribute to the development of asthma and allergic diseases.

CD8 T Cells in Asthma In atopic asthmatics there were increased CD8 T cells in airway biopsies when compared to biopsies in non-asthmatic, atopic, and normal subjects.[91] Furthermore, the number of CD8 T cells in airway biopsies of atopic asthmatics was associated with a decline in FEV1.[92] During asthma exacerbations and in death from status asthmaticus, there were increased CD8+ T cells in the respiratory tract.[93] These observations suggest that CD8 T cells are detrimental in asthma. Animal studies both support these observations and show that CD8 T cells inhibit allergic airway disease through the production of IFN-γ and induction of IL-12 production. Most likely, CD8 T cells have varying effects in different individuals and under different circumstances.

CD8 T cells recognize endogenous antigens, like viral peptides, rather than allergens. Since asthma exacerbations are most commonly caused by viral respiratory infections, then virus-specific CD8 T cells will be recruited and retained in the lung. Thus, the presence of CD8 T cells in asthmatic lungs may reflect recent infections.

CD8 T cells, like CD4 T cells, can be polarized into subsets. Cytotoxic T cell–type 1 (Tc1) cells are activated in viral infections and generally produce IFN-γ and lymphotoxin. These are classical CD8 T cells. Smaller subsets of CD8 T cells can make other panels of cytokines. For example, when activated in the presence of IL-4, CD8 T cytotoxic–type 2 (Tc2) cells can be induced to produce IL-4, IL-5, and IL-13. Animal studies show that Tc2 cells retain their cytotoxic function, stimulate recruitment of eosinophils, provide B cell help for IgE production, and promote airway hyperresponsiveness.[93] It has been theorized that some respiratory infections may stimulate CD8 Tc2 responses, thus initiating or exacerbating local allergic responses.

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CHAPTER 26

Chemokines, Adipokines, and Growth Factors in the Lung

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Normal development of organ systems, including the lungs, in utero, during subsequent maturation into adulthood, and in health throughout life, requires intricate signals to be exchanged among various tissues, capable of permitting diversity and adaptation in differing cellular and extracellular contexts, while being robust to onslaughts from ever-changing environmental stimuli. Among the mediators involved in such complex cellular signaling, and relevant in the setting of many pulmonary disorders, are chemokines and growth factors. There has been further complexity added with increasing recognition of adipose tissue as a source of systemic bioactive mediators called adipokines, that impact on lung health. While some of these mediators are implicated in the development of disease states, they are more often than not also critical to tissue homeostasis, and are challenging target systems for therapeutic manipulation. Nonetheless, we are now in an era of exciting developments in targeted biologic therapies that offer the potential for substantial progress in the fight against difficult-to-treat pulmonary disorders characterized by pathogenic processes including acute and chronic inflammation, fibrosis, vascular remodeling, and neoplasia.

CHEMOTACTIC CYTOKINES AND THE INFLAMMATORY RESPONSE

The salient feature of inflammation is leukocyte infiltration. These recruited leukocytes contribute to the pathogenesis of chronic inflammation and promote fibrosis via the elaboration of a variety of cytokines. Maintenance of leukocyte recruitment during inflammation requires the expression of cell surface adhesion molecules, and the production of chemotactic molecules, such as chemokines.[1] The chemokines can be divided into four families—CXC, CC, C, and CXXXC—which behave as potent chemotactic factors for neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells, NK cells, and T and B lymphocytes (Table 26-1). There is approximately 20% to 40% homology between the members of the four chemokine families.[2] Chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T and B lymphocytes, NK cells, and various structural cells, including keratinocytes, mesangial cells, epithelial cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells. Production of chemokines by both immune and nonimmune cells supports the contention that these cytokines may play a pivotal role in orchestrating chronic inflammation.[3]

CXC CHEMOKINES

CXC chemokines can be further divided into two groups on the basis of a structure/function domain consisting of the presence or absence of three amino acid residues (Glu-LeuArg; ELR motif) that precede the first cysteine amino acid residue in the primary structure of these cytokines. ELR+CXC chemokines are chemoattractants for neutrophils and act as potent angiogenic factors. In contrast, ELR−CXC chemokines are highly induced by interferons, are chemoattractants for mononuclear cells, and are potent inhibitors of angiogenesis (Table 26-2).[4]

Chemokine activities are mediated through G-protein–coupled receptors. Seven CXC chemokine receptors have been identified (Table 26-3). The ELR+ chemokines bind to CXCR1 and CXCR2 receptors, which are found on neutrophils, T lymphocytes, monocytes/macrophages, eosinophils, basophils, keratinocytes and mast cells, and endothelial cells.[5] CXCR3 is the receptor for CXCL9, CXCL10, and CXCL11, and is expressed on activated T lymphocytes. CXCR3 is also expressed on human umbilical vein endothelial cells (HUMVECs) in a cell cycle–dependent fashion. CXCR4 is the specific receptor for CXCL12 and is the cofactor for lymphotropic HIV-1. In contrast to CXCR3, CXCR4 appears to be expressed on resting T lymphocytes.[5] Two other chemokine receptors have been identified that bind chemokines without a subsequent signal-coupling event. The DARC receptor is similar to other chemokine receptors and it binds both CXC and CC chemokines without apparent signal coupling. This receptor was originally found on human erythrocytes and was thought to represent a "sink" for chemokines.[6] The second nonsignaling chemokine receptor is the D6 receptor, which binds several CC chemokines with high affinity, including CCL2, CCL4, CCL5, and CCL7.[7]

CXC Chemokines in Pulmonary Inflammation

CXC chemokines play a significant role in mediating neutrophil infiltration in the lung parenchyma and pleural space in response to endotoxin and bacterial challenge. CXCL8 is in the bronchoalveolar lavage of patients with community-acquired pneumonia and nosocomial pneumonia and a variety of animal models of pneumonia. In a model of *Aspergillus fumigatus* pneumonia, neutralization of TNF resulted in marked attenuation of the expression of CXCL1 and CXCL2/3 that was paralleled by a reduction in the infiltration of neutrophils and associated with increased mortality.[8] Administration of a TNF agonist peptide to animals that had been intratracheally inoculated with *Klebsiella pneumoniae* led to markedly elevated levels of CXCL2/3 associated with increased neutrophil infiltration.[9] Studies have shown that ventilator-induced lung injury is secondary to stretch-induced chemokine release with a subsequent inflammatory response and neutrophil recruitment.[10] CXCR2 −/− mice are also protected from hyperoxia-induced lung injury. In other studies, the production of CXCL5 in the lung was correlated with the presence of neutrophil-dependent lung injury, and passive immunization with neutralizing CXCL5 antibodies resulted in significant attenuation of lung injury.[11]

Several studies have demonstrated that CXCL8 levels correlate with the development and mortality of ARDS. Early increases in CXCL8 in bronchoalveolar lavage fluid correlated with an increased risk of subsequent development of ARDS, and also demonstrated that alveolar macrophages were an important source of CXCL8 prior to neutrophil influx.[10] Furthermore, there is an imbalance in the expression of ELR+ (CXCL1, CXCL5, CXCL8) as compared with ELR−CXC (CXCL10, CXCL11) chemokines from bronchoalveolar lavage fluid (BALF) of patients with ARDS as compared with controls. This imbalance correlated with angiogenic activity and both procollagen I and procollagen III levels in BALF.[12] These findings suggest that CXC chemokines have an important role in the fibroproliferative phase of ARDS via the regulation of angiogenesis.

TABLE 26-1 The Human C, CC, CXC, and CXXXC Chemokine Families of Chemotactic Cytokines

Systemic Name	Human Ligand Name
C Chemokines	
XCL1	Lymphotactin
XCL2	SCM-1β
CC Chemokines	
CCL1	I-309
CCL2	Monocyte chemotactic protein-1 (MCP-1)
CCL3	Macrophage inflammatory protein-1 alpha (MIP-1α)
CCL4	Macrophage inflammatory protein-1 beta (MIP-1β)
CCL5	Regulated on activation normal T-cell expressed and secreted (RANTES)
CCL7	Monocyte chemotactic protein-3 (MCP-3)
CCL8	Monocyte chemotactic protein-2 (MCP-2)
CCL9	Macrophage inflammatory protein-1 delta (MIP-1δ)
CCL11	Eotaxin
CCL13	Monocyte chemotactic protein-4 (MCP-4)
CCL14	HCC-1
CCL15	HCC-2
CCL16	HCC-4
CCL17	Thymus and activation-regulated chemokine (TARC)
CCL18	DC-CK-1
CCL19	Macrophage inflammatory protein-3 beta (MIP-3β)
CCL20	Macrophage inflammatory protein-3 alpha (MIP-3α)
CCL21	6Ckine
CCL22	MDC
CCL23	MPIF-1
CCL24	MPIF-2
CCL25	TECK
CCL26	Eotaxin-3
CCL27	CTACK
CCL28	MEC
CXC Chemokines	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL4	Platelet factor-4 (PF4)
CXCL5	Epithelial neutrophil–activating protein-78 (ENA-78)
CXCL6	Granulocyte chemotactic protein-2 (GCP-2)
CXCL7	Neutrophil-activating protein-2 (NAP-2)
CXCL8	Interleukin-8 (IL-8)
CXCL9	Monokine induced by interferon-γ (MIG)
CXCL10	Interferon-γ-inducible protein (IP-10)
CXCL11	Interferon-inducible T cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor-1 (SDF-1)
CXCL13	B-cell–attracting chemokine-1 (BCA-1)
CXCL14	BRAK/Bolekine
CXCL16	
CXXXC Chemokine	
CXC3CL1	Fractalkine

TABLE 26-2 The CXC Chemokines that Display Disparate Angiogenic Activity

CXC Chemokines that contain the ELR motif	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL5	Epithelial neutrophil–activating protein-78 (ENA-78)
CXCL6	Granulocyte chemotactic protein-2 (GCP-2)
CXCL7	Neutrophil-activating protein-2 (NAP-2)
CXCL8	Interleukin-8 (IL-8)
CXC Chemokines that lack the ELR motif	
CXCL4	Platelet factor-4 (PF4)
CXCL9	Monokine induced by interferon-γ (MIG)
CXCL10	Interferon-γ-inducible protein (IP-10)
CXCL11	Interferon-inducible T-cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor-1 (SDF-1)

The Role of CXC Chemokines in Pulmonary Fibrosis

IPF is characterized by the progressive deposition of collagen within the interstitium and subsequent destruction of lung tissue.[13,14] The mechanisms of cellular injury and the role of classic inflammatory cells remain unclear. CXCL8 is significantly elevated in IPF, as compared with either normal or sarcoidosis patients, and correlates with BALF presence of neutrophils. The alveolar macrophage is an important cellular source of CXCL8 in IPF.[15] In addition, BALF levels of CXCL8 in IPF may correlate with a worse prognosis.[16]

Vascular Remodeling in Pulmonary Fibrosis: The Role of CXC Chemokines

The existence of neovascularization in IPF was originally identified in 1963 by Turner-Warwick, who demonstrated that within areas of pulmonary fibrosis there was extensive neovascularization with anastomoses between the systemic and pulmonary microvasculature.[17] Further evidence of neovascularization during the pathogenesis of pulmonary fibrosis has been demonstrated in a rat model of bleomycin-induced pulmonary fibrosis.[18] An imbalance in the levels of angiogenic chemokines (CXCL5, CXCL8), as compared with angiostatic chemokines (CXCL9, CXCL10, CXCL11), favoring net angiogenesis has been demonstrated in both animal models and tissue specimens from patients with IPF (Fig. 26-1).[19] Renzoni[20] has demonstrated vascular remodeling in both IPF and fibrosing alveolitis associated with systemic sclerosis. Cosgrove et al.[21] provided further support for the concept of vascular remodeling in IPF when they demonstrated a relative absence of vessels in the fibroblastic foci of IPF. This appeared to correlate with increased expression of pigment epithelium–derived factor in the fibroblastic foci. Interestingly, they also noted significant vascularity in the areas of fibrosis around the fibroblastic foci, with numerous abnormal vessels in the regions of severe architectural distortion. These findings are similar to those of Renzoni and support the concept of regional heterogeneity of vascularity in IPF. This heterogeneity is not surprising, as usual interstitial pneumonia, which is the pathologic description of IPF, is defined by its regional and temporal heterogeneity.[14]

TABLE 26-3 The CXC Chemokine Receptors

Receptor	Ligand
CXCR1	CXCL6, CXCL7, CXCL8
CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8
CXCR3A	CXCL9, CXCL10, CXCL11
CXCR3B	CXCL4, CXCL9, CXCL10, CXCL11
CXCR4	CXCL12
CXCR5	CXCL13
CXCR6	CXCL16
CXCR7	CXCL11, CXCL12

CXC Chemokines in Pulmonary Hypertension

The potential role of the CXCL12/CXCR4/CXCR7 axis in pulmonary hypertension was first suspected when it was reported that CXCR7 expression increased in the lungs of hypoxic hypertensive mice and in the lungs of patients with idiopathic pulmonary arterial hypertension (IPAH).[22] Subsequently, CXCL12 was found to be elevated in the peripheral plasma of patients with pulmonary artery hypertension (PAH), although in a separate study this increase was not observed.[23,24] Increased expression of CXCL12 in remodeled vessels and particularly in the plexiform lesions in explanted IPAH lungs has also been shown.[25]

CXR7 was most prominently expressed in the endothelium of the explanted lungs of hypertensive subjects and, in addition to its well-established role in leukocyte chemotaxis, was shown to play a central role in stimulating endothelial proliferation, whereas CXCR4 was required for endothelial cell chemotaxis.[23] Recruitment of progenitor cells to the remodeled pulmonary vessels is a prominent feature in PAH lungs.[25,26] In vivo blockade of CXCR4 in hypoxic mice reduced the recruitment of progenitor cells to the remodeled vasculature of hypertensive lungs, whereas blockade of CXCR7 did not affect this behavior.[24,26,27]

In rodent models inhibition of CXCL12 action using function-blocking antibodies, or separate selective inhibition of CXCR4 signaling or CXCR7 signaling, attenuates the development of hypoxic pulmonary hypertension.[24,27,28] Taken together these data suggest an important role of CXCL12 signaling, requiring both its cognate receptors, in the pathogenesis of pulmonary hypertension.

■ CHEMOKINES AND THE TRAFFICKING OF FIBROCYTES TO THE LUNG

Fibrocytes present in the peripheral circulation were first identified in 1994, comprise a minor component of the circulating pool of leukocytes (less than 1%), and express a characteristic pattern of markers, including collagen (Col) I and CD45.[29] Subsequent studies have revealed that circulating fibrocytes express chemokine receptors such as CXCR4 and CCR7 and extracellular matrix (ECM) proteins, such as procollagen I and procollagen III. Fibrocytes migrate in response to CXCL12 and traffic to the lungs in a model of bleomycin-induced pulmonary fibrosis. Treatment of bleomycin-exposed animals with specific neutralizing anti-CXCL12 antibodies inhibits intrapulmonary recruitment of fibrocytes and attenuated lung fibrosis.[30] Levels of circulating CD45+ Col1+ cells are elevated in stable IPF patients versus controls, are transiently higher during an exacerbation and predicted survival.[31] These findings challenge the dogma that fibroblasts and myofibroblasts arise from an intrapulmonary pool of tissue fibroblasts.[32]

■ THE CC CHEMOKINES

CC chemokines (Table 26-1) are chemoattractants for monocyte, T and B lymphocytes, NK cells, dendritic cells, basophils, mast cells, and eosinophils.[33] The CC chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T cells, B cells, and NK cells, as well as structural cells such as keratinocytes, mesangial cells, epithelial

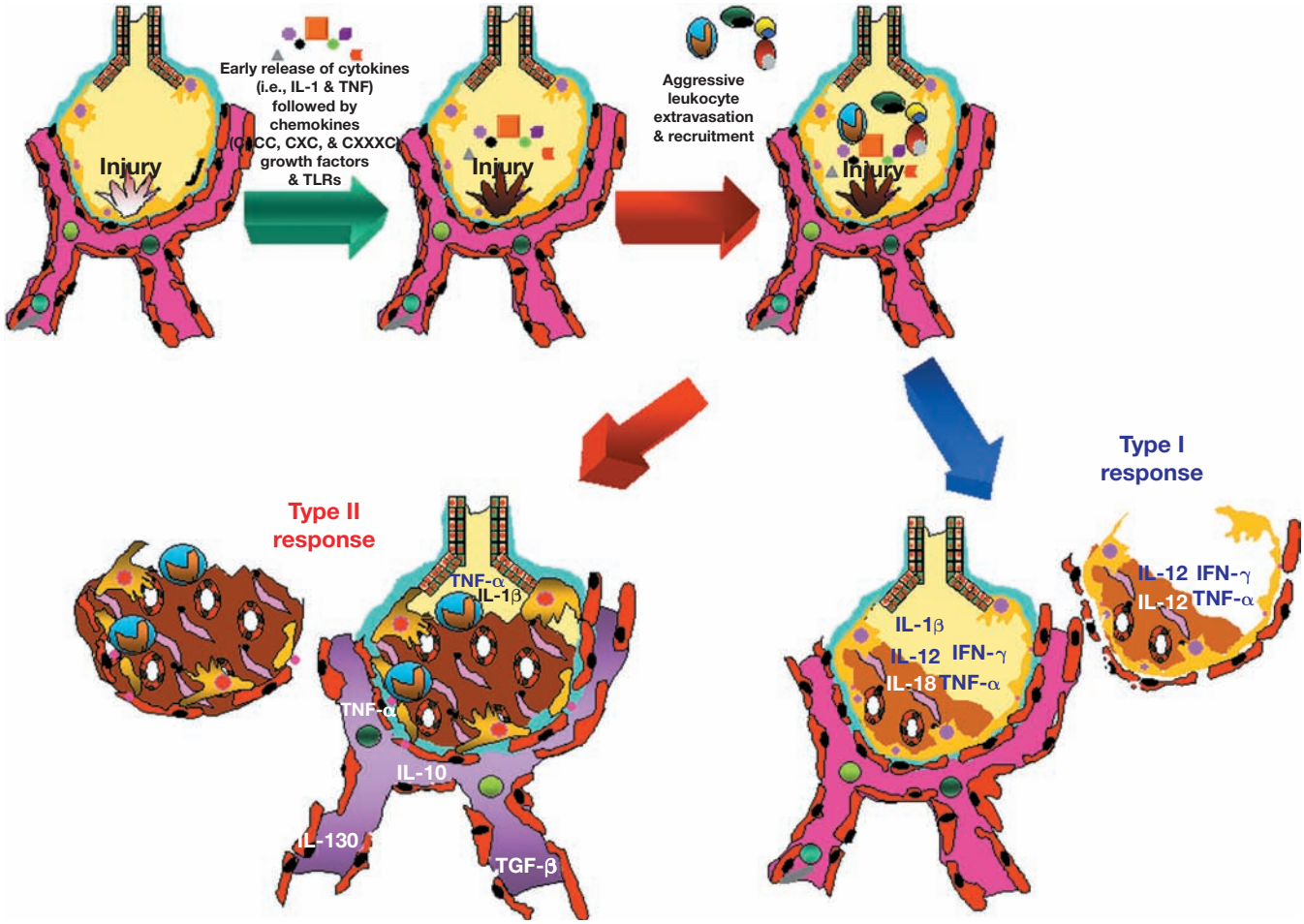

Figure 26-1 The inflammatory response to lung injury. The cytokine profile that is secreted by inflammatory cells during lung injury determines the ultimate outcome following injury. Polarization of the inflammatory response toward a type I response is associated with resolution of lung injury or infection. In contrast chronic infections (e.g., tuberculosis) and chronic inflammatory diseases (e.g., idiopathic pulmonary fibrosis) are associated with a type II profile.

cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells.[34]

CC Chemokine Receptors

CC chemokine receptors are structurally homologous and have been identified to have specific ligand-binding profiles (Table 26-4).[34] Naïve T cells express CXCR4 and CCR7 and migrate in response to CXCL12 and CCL19. CXCR3, CXCR6, and CCR5 are expressed at higher levels on type I cells than type II, whereas CCR3, CCR4, and CCR8 are more characteristic of type II cells.[35]

CC Chemokines in Pulmonary Inflammation

The CC chemokines, CCL2, CCL3, CCL4, CCL5 have been implicated in mediating the innate host defense in animal models of pulmonary infection.[36,37] These studies have demonstrated that CC chemokine ligand/receptor biology plays a critical role in innate host defense and development of pulmonary inflammation that is important in eradication of microorganisms.

Mehrad et al. have shown that CCL3 and the recruitment of mononuclear cells play an important role in the eradication of invasive pulmonary aspergillosis. They demonstrated that in both immunocompetent and neutropenic mice CCL3 is induced in the lungs in response to intratracheal inoculation of *A. fumigatus*.[38] These studies indicate that CCL3 and elicitation of mononuclear cells are crucial in mediating host defense against *A. fumigatus* in the setting of neutropenia.[39]

CC Chemokines in Pulmonary Fibrosis

Animal models, such as bleomycin-induced pulmonary fibrosis, have demonstrated the presence and contribution of CC chemokines to the pathogenesis of fibrosis. CCL2 is an important cofactor for the stimulation of fibroblast collagen production and induction of the expression of TGF-β_1. Inhibition of CCL2 or CCL3 resulted in

TABLE 26-4 The CC Chemokine Receptors

Receptor	Ligand
CCR1	CCL2, CCL3, CCL3LI, CCL4, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL16, CCL23
CCR2	CCL2, CCL7, CCL8, CCL13, CCL16
CCR3	CCL5, CCL7, CCL8, CCL11, CCL13, CCL15, CCL16, CCL24, CCL26, CCL28
CCR4	CCL17, CCL22
CCR5	CCL3, CCL3LI, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL16
CCR6	CCL20
CCR7	CCL19, CCL21
CCR8	CCL1
CCR9	CCL25
CCR10	CCL27, CCL28

a reduction of infiltrating cells into the lungs of bleomycin-treated animals.[40,41]

Furthermore, it has been shown that CCL2 can stimulate interleukin-4 (IL-4) production, indicating that it might be involved in type II polarization.[42] IL-13 promotes bleomycin-induced fibrosis through the elaboration of CCL6.[43] Both CCL17 and CCL22 and their receptor, CCR4, are significantly elevated in the bleomycin model and neutralization of CCL17 attenuates pulmonary fibrosis.[44] Thus, chemokines may have an important role in the switch toward a profibrotic type II phenotype.

Both CCR1 and CCR2 have been shown to play an important role in the pathogenesis in the mouse model of bleomycin-induced pulmonary fibrosis. Treatment with antibodies to CCR1 leads to a reduction in both inflammatory cell infiltrates and the development of fibrosis.[45] Similarly, CCR2 −/− mice are protected from pulmonary fibrosis in response to bleomycin.[46] Furthermore, alveolar epithelial cells from CCR2 −/− mice suppress fibroblast proliferation more than AECs from wild-type mice.[47] CCL2 and CCR2 have an important role in suppression of PGE2, thereby promoting fibroproliferation. Similarly, an important role for CCR2 has been seen in murine model of obliterative bronchiolitis, in which the fibrotic response associated with this disorder was attenuated in CCR2 −/− mice.[48] Similarly, CCL2 and CCL3 are elevated in BALF and lung tissue of ILD patients.[49,50] Accordingly, targeting chemokine receptors may be an efficient way to inhibit pulmonary fibrosis.

Choi et al.[51] described enhanced expression of the chemokines CCL7 and CCL22, in lung tissue of patients with IPF as compared with nonspecific interstitial pneumonia, and nonidiopathic interstitial pneumonia. Furthermore, they describe increased expression of CCL5 in nonspecific interstitial pneumonia as compared with usual interstitial pneumonia. Interestingly, CCL5 protein was identified in nonspecific interstitial pneumonia more prominently than usual interstitial pneumonia. This is all the more interesting as CCL5 is a major stimulus for the production of CCL7 through its interactions with CCR5. These findings raise the possibility that there is a continuum from nonspecific interstitial pneumonia to usual interstitial pneumonia with higher levels of CCL5 in nonspecific interstitial pneumonia leading to subsequent increased CCL7 expression as the disease progresses to usual interstitial pneumonia. There is considerable controversy as to whether nonspecific interstitial pneumonia is an earlier lesion of usual interstitial pneumonia.[52] Several studies have demonstrated the presence of usual interstitial pneumonia and nonspecific interstitial pneumonia patterns in the same patients, which suggests that these are overlapping processes.[52–54] The findings of Choi suggest a transition from a predominance of CCL5 to CCL7 and further support this notion. Of further interest is the previous description that CCL7 can act as a natural antagonist at the CCR5 receptor, which raises the possibility that CCL7 may play a role in regulating its own production.[55]

ADIPOKINES AND PULMONARY INFLAMMATION

With the emergence, in the 20th century, of obesity as a major epidemic linked to systemic metabolic dysfunction, concerted efforts have been made to gain a fuller understanding of the varied functions of adipose tissue, beyond that of being an energy storage organ, and leading to the discovery of various factors that are secreted by adipocytes.[56] These mainly proteinaceous endocrine factors were initially termed adipocytokines, and later, adipokines,[57] and possess pro- and anti-inflammatory activities, potentially of relevance in the context of pulmonary disorders associated with body mass index, including asthma, obstructive sleep apnea syndrome, chronic obstructive pulmonary disease (COPD), PAH, various pulmonary infections, and lung cancer.[58] While the main source of adipocytes in the body is from deposits of subcutaneous and visceral adipose tissue, the development of obesity can give rise to collections of adipose tissue in other locations including the heart, kidneys, bone marrow, the adventitia of major blood vessels, and within the lungs. There is evidence that differential adipokine secretion and functional outcomes can occur at different sites of adiposity within the body, following the stimulus of dietary modification.[59] White adipose tissue, the major form in humans, is predominantly composed of lipid-laden adipocytes, but also adipocyte precursor cells, fibroblasts that generate ECM scaffolding, vascular (smooth muscle and endothelial) cells that provide systemic access for secreted adipokines, and macrophages and T cells that influence the immune phenotype.[60] The cellular composition of adipose tissue can vary in conditions of altered body mass, and macrophages in particular, seem to traffic in larger numbers to adipose tissue under conditions of increased obesity with associated capillary rarefaction and adipose tissue hypoxia.[61]

PROINFLAMMATORY ADIPOKINES

Beyond the "pure" effects of uncomplicated obesity upon respiratory mechanics, pulmonary gas exchange, ventilatory drive, and work of breathing, there is increasing evidence of an association among obesity, adipokines, and pulmonary disease states that are characterized by inflammation.[58] Most of the adipokines identified to date are proinflammatory in their effects (Table 26-5). Some important adipokines that are better known for their other roles, such as TNF-α, IL-6, CCL2, and CXCL5, will not be discussed here.

Leptin

Leptin, coded for by the *ob* gene on chromosome 17, is a 16 KDa protein hormone, mainly secreted by adipocytes,[62] and regulated principally by food intake, whereby fasting reduces leptin levels,

TABLE 26-5 Adipokines Linked to Pulmonary Disease States

Adipokine	Pulmonary Source	Receptor	Lung Disease State
Proinflammatory Adipokines			
Leptin	Alveolar type II pneumocytes, alveolar macrophages, bronchial epithelial cells, lung endothelial cells	Leptin receptor	OSAHS, OHS, COPD, asthma, NSCLC, PAH
Apelin	Lung endothelial cells	Apelin receptor	PAH
Nampt	Lung endothelial cells	Unknown	ALI
Resistin	Unknown	Unknown	Asthma
Anti-inflammatory Adipokines			
Adiponectin	Bronchial epithelial cells	Adiponectin receptors 1 and 2, T-cadherin	COPD, asthma, ALI, PAH

OSAHS, obstructive sleep apnea-hypopnea syndrome; OHS, obesity hypoventilation syndrome; COPD, chronic obstructive pulmonary disease; NSCLC, non–small-cell lung cancer; PAH, pulmonary arterial hypertension; ALI, acute lung injury.

and food consumption transiently increases *ob* gene expression, with leptin being initially regarded as a satiety hormone.[63,64] It is also expressed in human peripheral lung tissue, including alveolar type II pneumocytes, alveolar macrophages, and bronchial epithelial cells,[65,66] and is known to be modulated by gender, sepsis, catecholamines, glucocorticoids, and insulin.[67,68] It is now clear that leptin has pleiotropic effects, which include stimulating TNF and IL-6 production by monocytes, stimulating production of CCL3–5 by macrophages, and stimulating reactive oxygen species production, cell proliferation, and migration. In addition, leptin may have a role in lung development,[56] as it is differentially expressed by fetal rat lung fibroblasts during the time of alveolar differentiation,[69] and capable of stimulating fetal rat surfactant protein synthesis in vitro,[70] although contradictory in vivo findings were observed in fetal sheep and mice lungs.[71]

There have been extensive efforts to relate leptin to respiratory disorders, most notably with obstructive sleep apnea-hypopnea syndrome (OSAHS), COPD, asthma, pneumonia, and other pulmonary infections. Some data suggest leptin has a stimulatory effect on ventilation; for example, the mutant *ob/ob* mouse, which lacks functional leptin and has a phenotype of obesity, hyperphagia, and a low-resting metabolic rate, displays an elevated arterial Pa_{CO_2} independent of obesity onset, which is acutely reversible through exogenous leptin replacement.[72] It has been speculated that OSAHS is a leptin-resistant state, but progress in this field has been hampered by conflicting results of leptin and leptin receptor candidate gene association studies[73,74] and trials of nasal continuous positive airway pressure.[75,76]

In COPD, it has been hypothesized that the known link between the cachexia of COPD and increased mortality, might somehow be related to leptin function. There appears to be an absence of the usual circadian rhythm of circulating leptin in cachectic COPD patients, as opposed to normal weight COPD patients, with associated heart rate variability changes that raise the possibility of a role for leptin in the pathophysiology of COPD cachexia,[77] although further data are needed. The reproducible finding of elevated serum leptin levels during acute exacerbations of COPD, that track markers of the systemic inflammatory response, points to disturbance of the normal leptin feedback loop regulating food intake and energy balance, due to the influence of the acute inflammatory response and systemically administered glucocorticoids, as a possible contributing mechanism to cachexia in COPD.[78] Wild-type mice exposed chronically to cigarette smoke have increased leptin expression in bronchial epithelial cells and pneumocytes versus air-exposed controls. *Ob/ob* mice (lacking functional leptin) that are then exposed acutely or chronically to cigarette smoke exhibit higher neutrophils, CD4+, CD8+, and dendritic cells in BAL and lung tissue than smoke-exposed wild-type mice, compatible with modulation of innate and adaptive immune cell recruitment by leptin in response to smoke.[79] Within human airways, leptin expression is increased in bronchial epithelial cells and alveolar macrophages of ex-smokers with or without severe COPD compared to never smokers, and leptin can induce phosphorylation of the transcription factor STAT3 in lung epithelial cells, supporting the notion of a functioning leptin signaling pathway in these cells.[65]

Obesity is believed to be a risk factor for asthma, but some controversy still surrounds whether or not obesity is a central cause or a confounding comorbidity of asthma.[80,81] Notably, unbiased clustering approaches in severe asthma subjects have identified an obesity-related clinical asthma phenotype typified by obese, female patients with late-onset asthma, and lacking in eosinophilic Th2-mediated inflammation.[82] Ob/ob mice, a model of loss of leptin function, appear to have elevated pulmonary resistance, and increased responses to ozone and methacholine, though this could be mechanical bias from the low lung size of these mutant mice.[68] Interestingly, when a cohort of obese asthmatic women and obese female controls were studied in the setting of bariatric surgery, leptin expression and macrophage inflammation were both increased in visceral adipose tissue of asthmatics independent of BMI, and correlated with airway reactivity, but there was no association with airway inflammation measurements even though the airway epithelial cells expressed receptors for leptin, suggesting that leptin exerts a direct effect on airway epithelium (and not indirectly via enhancing airway inflammation) that is important in the pathogenesis of asthma in obesity.[83] These observations run counter to the hypothesis that leptin is merely a marker for airway inflammation in poorly controlled asthma.[84]

Nampt (PBEF/visfatin)

The gene Nampt codes for a cytokine called pre–B cell colony-enhancing factor (PBEF), also known as visfatin. It is now known to be produced by various cell types including adipocytes, and especially by visceral as opposed to subcutaneous fat, and has gained greater interest by the rediscovery of PBEF as Nampt, the rate-limiting enzyme in the biosynthesis of the essential redox cofactor, NAD. Nampt is inducible in neutrophils and lung microvascular endothelial cells by endotoxin, TNF-α and IL-1β, and in monocytes, it induces production of IL-1β, TNF-α, and IL-6, and the surface expression of costimulatory molecules CD54, CD40, and CD80.[85,86] Against this background of catalyzing the respiratory burst, and its proinflammatory and immunomodulatory capabilities, Nampt has been demonstrated to be found at higher concentrations in serum and BAL fluid from patients with acute lung injury.[87] There have also been a number of independent candidate gene association studies that support a role for Nampt promoter genetic variants in ALI pathogenesis.[87–89]

■ ANTI-INFLAMMATORY ADIPOKINES

Adiponectin

The most intensely studied of the anti-inflammatory adipokines, and with notable evidence of a role in inflammatory lung disorders, is adiponectin, which shares some structural similarity with complement factor C1q, and forms trimers that can go on to form stable hexamers or a high molecular weight form, all of which are detectable in blood.[60] Circulating adiponectin levels are decreased in obesity, particularly in visceral obesity, nonalcoholic fatty liver disease, and type 2 diabetes, being inversely related to insulin resistance. The adipokine is inhibited by proinflammatory factors such as TNF, IL-6, hypoxia, and oxidative stress.[56] There has been considerable interest concerning the involvement of adiponectin in pulmonary disease states. Three described adiponectin receptors (AdipoR1, AdipoR2, and T-cadherin) are expressed in the lungs, with AdipoR1 expressed by lung epithelial cells, and importantly, the baseline phenotype of mice following targeted disruption of the adiponectin gene shows evidence of emphysema-like dilated air spaces and activation of alveolar macrophages.[90,91] These same adiponectin-deficient mice develop pulmonary hypertension with evidence of perivascular inflammation,[92] and an exaggerated form of LPS-inducible acute lung injury that is abrogated by adiponectin.[93]

As further evidence of anti-inflammatory functionality, adiponectin can bind to apoptotic cells and facilitate their phagocytosis by macrophages, analogous to other members of the collectin family, such as C1q and surfactant proteins A and D.[94] In keeping with this intuitive role in airways disease pathobiology, a number of groups have reported increased levels of circulating adiponectin in COPD.[91,95] Adiponectin was found to be elevated in BALF of COPD patients, being highly expressed in their airway epithelium, and the adiponectin receptor AdipoR1 on lung epithelial cells was shown to be functional, releasing IL-8 in the presence of adiponectin.[91] Animal and human data suggest that short-term exposure to cigarette smoke downregulates adiponectin whereas the COPD

disease state elevates its expression.[91] In contrast, AdipoR2 is more highly expressed in the airway epithelium of obese asthma patients versus obese control subjects, and the opposite to what is observed for T-cadherin expression.[83] In mice, allergen challenge appears to decrease the pulmonary expression of all three adiponectin receptor types, and T-cadherin may play a role in transporting adiponectin into the lungs.[96] The exact role of adiponectin signaling in asthma will require further study.

■ ADIPOKINES AND PULMONARY HYPERTENSION

The high prevalence of pulmonary hypertension in obese subjects has previously been attributed to hypoxemia resulting from associated obstructive sleep apnea or obesity hypoventilation syndrome.[97–99] However, more recently evidence has been presented that alterations in three specific adipokines (adiponectin, apelin, and leptin) may directly contribute to pulmonary vascular dysfunction.

Adiponectin concentrations are paradoxically reduced in the plasma of obese subjects despite the expansion of adipose tissue.[100] Mice in which adiponectin has been deleted spontaneously develop elevated pulmonary arterial pressure, vascular remodeling, and perivascular inflammation as they grow older.[92] Conversely constitutive overexpression of adiponectin in mice protects against the development of both hypoxia-induced and inflammation-induced (ovalbumin challenge) pulmonary hypertension.[101] These suggest that reduced adiponectin concentrations contribute directly to the development of pulmonary vascular dysfunction in obesity due to a loss of its normal vascular homeostatic action.

Apelin is produced and secreted by adipocytes and acts by binding to the apelin receptor.[102] It is also expressed by a wide variety of other tissues including the pulmonary vasculature.[102] Plasma apelin concentrations are increased in obese individuals.[103] Apelin null mice develop more severe hypoxic pulmonary hypertension than wild-type mice, which is associated with endothelial dysfunction.[104] Leptin concentrations are elevated in patients with both idiopathic PAH and scleroderma-associated PAH and in the pulmonary endothelium from these patients.[105,106] However, the exact role of apelin and leptin in the pulmonary circulation in obese humans remains to be determined.

GROWTH FACTORS

■ TRANSFORMING GROWTH FACTOR-BETA

Mammalian transforming growth factor-beta (TGF-β) belongs to a superfamily of genes and exists as three closely homologous (72%–80%) dimeric isoforms: TGF-β_1, TGF-β_2, and TGF-β_3. Although the three isoforms of TGF-β appear to have overlapping biologic activity, the predominant isoform of TGF-β is TGF-β_1. There are three TGF-β receptors and signal transduction to the nucleus is via the Smad group of proteins. Smad 1, 2, 3, 4, 5, 8, and 9 are activating signals, whereas Smad 6 and 7 are inhibitory signals of TGF-β_1 signaling.[107]

TGF-β is produced by a variety of cells, including platelets, neutrophils, eosinophils, mononuclear leukocytes, fibroblasts, and endothelial cells.[108,109] TGF-β is a pleiotropic cytokine that can modulate inflammatory and immune responses, and orchestrate fibrosis and tissue repair.[110] TGF-β is a potent immunosuppressive agent that inhibits IL-1–dependent lymphocyte proliferation.

TGF-β is chemotactic for fibroblasts and can indirectly induce their proliferation via the expression and autocrine and paracrine activity of PDGF-B. TGF-β is perhaps the most potent and efficacious promoter of ECM production–inducing gene expression and protein production of many of the constituents of ECM. Furthermore, it inhibits the generation of metalloproteinases and augments the expression of tissue inhibitors of metalloproteinases (TIMP).[108,111]

Transient overexpression of active TGF-β_1 results in prolonged and severe interstitial and pleural fibrosis.[112] Transfer of TNF-α or granulocyte macrophage colony–stimulating factor (GM-CSF) to rat lung induces pulmonary fibrosis, due in part to induction of TGF-β_1.[113] Furthermore, transient expression of IL-1β using an adenoviral vector can lead to progressive fibrosis that is associated with a sustained increase in levels of TGF-β_1.[114] Smad 3 −/− mice developed less fibrosis in response to bleomycin compared with wild-type controls.[115] In contrast, IL-7 downregulates TGF-β production and inhibits bleomycin-induced pulmonary fibrosis, and this is mediated via Smad 7 signaling.[116]

In IPF, increased expression of TGF-β has been found in bronchiolar epithelial cells, epithelial cells of honeycomb cysts, and hyperplastic type II pneumocytes. BALF from patients with IPF induces apoptosis in cultured bronchiolar epithelial cells, and this effect is attenuated using anti–TGF-β_1 antibodies.[117] In the bleomycin model, in vivo administration of TGF-β_1 enhanced Fas-mediated epithelial cell apoptosis and lung injury.[117] These studies support the contention that TGF-β is an important mediator of human pulmonary fibrosis.

TGF-beta Superfamily Members and Pulmonary Hypertension

Disturbance of signaling by members of the TGF-β superfamily plays a key role in pulmonary hypertension.[118–121] The bone morphogenetic proteins (BMPs) and their receptors form part of the TGF-β superfamily, whose activities include important proangiogenic and vascular remodeling effects in endothelial and vascular smooth muscle cells.[22,122] The BMPs, like all ligands of the TGF-β superfamily, bind to transmembrane cell surface receptors formed from heterodimerization of a type 1 and type 2 receptor, many of which are expressed in the normal lung and can form a large number of different heteromeric receptor combinations binding with particular BMP ligands. BMP signaling is further modulated by a family of secreted extracellular glycoproteins, accessory proteins that bind directly to BMPs and prevent or enhance their interactions with BMPRs.[123,124]

The requirement for normal BMP function to maintain a healthy pulmonary circulation was first demonstrated by the identification of heterozygote inheritance of mutations in BMPR2 gene as the underlying cause in the rare heritable form of pulmonary arterial hypertension (HPAH) and in a significant proportion (10%–40%) of patients with IPAH without a previous family history.[125–127] These mutations cause attenuation of the normal cellular responses to the BMPs in the lung, where BMP2 and BMP4 signaling through BMP type 1 receptor (BMPR1) and BMPR2 heterodimers play particularly important roles in normal vascular homeostasis, and result in pulmonary hypertension.[121,128–132] Experimentally induced loss of function BMPR2 mutations in mice, or expression of dominant negative BMPR2 constructs, were sufficient to cause the development of pulmonary hypertension alone or increased susceptibility to other well-known causes of PH.[130,132–134] Conversely, overexpression of BMPR2 in the endothelium protected mice against the development of hypoxic pulmonary hypertension.[135] These data show that reduced BMP signaling in the lung either causes pulmonary hypertension or increases susceptibility to other causes of PH.

Later studies reported that reduced BMP signaling was found in many of the common forms of pulmonary hypertension, including hypoxic pulmonary hypertension,[121,131,136] although it was not clear what mechanisms cause reduced BMP signaling in these conditions. More recent work has shown that the glycoprotein BMP antagonist gremlin is markedly and selectively increased in the hypoxic mouse lung and in human lungs with PAH.[22] Genetically manipulated mice with reduced gremlin expression (haplodeficient) are partially protected against the development of hypoxic pulmonary hypertension, suggesting that upregulation of gremlin with a consequent

reduction in BMP signaling is an important contributor to the pathogenesis of pulmonary hypertension.[123,137] Furthermore the basal normoxic expression of gremlin is higher in the lung than in any other organ, potentially rendering it more vulnerable to any loss of BMP signaling and may help to explain why the vascular abnormality in hereditary PAH is restricted to the pulmonary circulation even though the expression of mutant BMPR2 is ubiquitous in all vascular beds.[138]

TGF-β are also expressed in the lung as are their type 1 receptors (TGF-βR1) ALK1 and ALK5, and TGF-β receptor type 2 (TGF-βR2) and increased TGF-β signaling has been observed in some forms of pulmonary hypertension.[118–121] Furthermore, PAH develops in a subset of hereditary hemorrhagic telangiectasia patients who have heterozygous mutations in one of the TGF-β type 1 receptors, the ALK1 (activin receptor-like kinase 1).[139,140] Heterozygous mutations in the endoglin (ENG) gene, which codes for a TGF-β coreceptor, are also associated with the spontaneous development of PAH.[139] $ENG^{+/-}$ mice developed pulmonary hypertension associated with loss of peripheral vasculature in adulthood but not in early postnatal life.[141] Taken together these data indicate a requirement for normal TGF-β signaling to prevent the development of pulmonary hypertension.

EPIDERMAL GROWTH FACTOR

Epidermal growth factor (EGF) is the prototype member of a family of polypeptide ligands that interact with the ERBB family of four tyrosine kinase receptors (ERBB1–4, also known as human epidermal growth factor receptor, HER1–4).[142,143] All 13 of the EGF extracellular ligands described to date, which include transforming growth factor-α (TGF-α), heparin-binding(HB)-EGF, amphiregulin, epiregulin, and betacellulin among others, contain a conserved EGF domain and are made as a transmembrane protein that is then cleaved by cell surface proteases (ectodomain shedding) to release mature growth factors that bind ERBB, such as the case with EGF which binds to HER1/EGFR.[144] EGF motifs are also found in unrelated proteins including ECM and cell adhesion proteins, blood coagulation factors, and immune response proteins.[145] Control of ERBB family signaling occurs at many levels, including specific cellular patterns of ligand and receptor expression, subcellular segregation of ligands and receptors, and the diversity of intracellular receptor binding proteins that can amplify or attenuate receptor signaling and transcription factor activation, leading to varying cellular outputs of cell proliferation, adhesion, migration, differentiation, or apoptosis.[142] Dysfunctional EGF–ERBB signaling in the lung has consequently been implicated in lung tumorigenesis and lung injury.[146]

EGFR (ERBB1/HER1) is overexpressed in a large number of non–small-cell lung cancers (NSCLCs), and its expression has been correlated with a poor prognosis.[147] NSCLCs will also often express EGFR cognate ligands EGF and TGF-α, leading to receptor hyperactivity in an autocrine fashion.[148] The tyrosine kinase inhibitors gefitinib and erlotinib target the EGF–ERBB complex by acting as competitive inhibitors of ATP binding at the active site of the kinase. It became apparent that drug-responsive cases were enriched for somatic activating mutations in the EGFR kinase domain, with these mutations occurring at a greater frequency in nonsmokers, women, those of Asian genetic ancestry, and in adenocarcinoma.[149]

There is overlap between the signaling events that orchestrate the proliferation, migration, and differentiation of the developing lung epithelia, and those events that are active during lung injury and repair. The importance of EGF motif signaling in lung development is apparent from the HB-EGF(−/−) mouse hypoplastic lung phenotype, characterized by fewer alveoli and less surfactant. Similarly, the EGFR knockout mice display alveolar collapse, reduced alveolarization and loss of surfactant expression, resulting in a phenotype similar to the neonatal respiratory distress syndrome,[150] and exogenous EGF can rescue EGFR(−/−) fetal lambs from such a phenotype.[151] Later in life, there is evidence implicating EGFR signaling in an in vitro model of alveolar epithelial wound repair.[152] and bronchial epithelial repair in asthma.[153] A body of evidence has also implicated EGFR signaling in the pathogenesis of pulmonary fibrosis: For example, TGF-α (−/−) mice are protected from bleomycin-induced fibrosis,[154] as are wild-type mice exposed to bleomycin but administered gefitinib.[155] Given that ERBB tyrosine kinase inhibitors can also cause interstitial lung disease in clinical use,[156] it remains to be seen how best the complex ERBB signaling pathways can be therapeutically manipulated in the lung fibrosis arena.

VASCULAR ENDOTHELIAL GROWTH FACTOR

Initially described as a growth factor for endothelial cells, vascular endothelial growth factor (VEGF) is highly expressed in many different lung cell types, and has important roles in lung development and maintenance of lung tissue integrity, through its angiogenic, lymphangiogenic, and hematopoietic roles.[157] VEGF is produced by endothelial cells, fibroblasts, neutrophils, peripheral blood mononuclear cells (PBMCs), and macrophages, and exists as any of five family members, VEGF A, B, C, D, and placenta growth factor (PLGF) and further diversity in biologic activity arises from various alternatively spliced isoforms of family members,[158] including VEGFA121, VEGFA145, VEGFA165, VEGFA189, and VEGFA206, named after the number of coded amino acids. Transcription of VEGF is induced by hypoxia, IL-1β, and by many growth factors including platelet-derived growth factor, TGF-α and -β, insulin growth factor 1, fibrocyte growth factor, and FGF7 (keratinocyte growth factor [KGF]). The VEGF family members have three different VEGF receptors, with VEGFA binding to VEGFR1 and VEGFR2. VEGFR2 −/− mice have lethal defects in vasculogenesis and angiogenesis.[159] The role of VEGF in lung development is complex and can be highlighted by a number of observations. When embryonic murine lungs are cultured, VEGF expression, initially diffuse, is restricted over time and space to subepithelial matrix in the branching tips of the developing airways.[160] Furthermore, aberrant lung morphology has been shown to arise from targeted overexpression or underexpression of VEGF.[161,162] In bronchopulmonary dysplasia, the disease of prematurity and its attending interventions including hyperoxia, there was a demonstrable reduction in lung expression of VEGF, VEGFR1, and Tie-2 associated with disrupted pulmonary vasculature.[163]

There is some evidence to suggest that VEGF may play a protective role in emphysema. Partial and transient inactivation of VEGF gene in murine lungs using an adeno-associated *cre* recombinase virus and conditional VEGF knockout mice, VEGF*loxP*, resulted in apoptosis of alveolar and bronchial cells with ensuing air space enlargement and reduced elastic recoil, reminiscent of emphysema.[164] The low levels of VEGF expressed in human emphysematous lung[165] may be due to upstream factors that cause a reduction in expression of the major controller of VEGF expression, hypoxia-inducible factor (HIF)-1α in COPD lungs.[166]

VEGF and Pulmonary Hypertension

VEGF levels have been variably reported as increased, reduced, or unchanged in pulmonary hypertension with no consistent pattern emerging. However, studies directly examining the effect of inhibiting or stimulating VEGF receptors have produced a coherent picture. Blockade of VEGFR2 using small molecule inhibitors in rats aggravated hypoxic pulmonary hypertension, reduced pulmonary VEGFR2 expression, and increased endothelial cell apoptosis suggesting that VEGFR2 was essential for maintaining and expanding the vascular bed in the hypoxic lung.[167] Moreover, even following return to normoxia and withdrawal of VEGFR2 blockade the pulmonary hypertension was progressive and ultimately fatal. After

extended time periods in this model complex plexiform-like lesions similar to those found in human PAH are observed.[168] Mice also show aggravation of hypoxic pulmonary hypertension in the presence of VEGFR2 blockade.[169] Interestingly, pulmonary hypertension has occasionally been reported in patients receiving VEGF inhibitors as part of a cancer chemotherapy treatment program.[170]

Overexpression of VEGFA in the rat lung using adenoviral vectors protected against the development of pulmonary hypertension although no analysis of the capillaries and small intra-acinar vessels (<50 μm) was carried out so it is not possible to know if this protection was accompanied by angiogenesis.[171] Louzier et al.[172] found that overexpression of VEGFB in the hypoxic rat lung using an adenoviral vector strategy protected against the development of hypertension and increased vessel density within the lung. Thus, it is clear that the balanced actions of agonist and inhibitory members of the VEGF family are essential for normal adaptation of the pulmonary circulation to hypoxia although the precise role of the VEGF pathway in human pulmonary hypertension is at present unclear.

FIBROBLAST GROWTH FACTOR

The fibroblast growth factor (FGF) family consists of 18 secreted polypeptide ligands that bind to one of four target cell surface FGF receptors (FGFR), that are tyrosine kinase receptors (FGFR1–4), and have many isoforms as a result of exon skipping and alternative splicing, the latter being generally tissue specific.[173] FGF subfamilies are grouped for their shared sequence homology and phylogeny. FGFs regulate diverse biologic processes including angiogenesis and organogenesis including proliferation, cell migration, and paracrine effects on tissue patterning. Two of the FGF ligands have particular relevance to the lung, both within the FGF7 subfamily including FGF7 (KGF) and FGF10.[173,174]

FGF7 is expressed specifically by mesenchymal cells including fibroblasts and vascular smooth muscle cells, and binds exclusively to an epithelial receptor FGFR2-IIIb, suggesting a paracrine loop effect in its epithelial–mesenchymal interactions. Using a dominant-negative mutant to inhibit FGFR2-IIIb results in an absence of branching morphogenesis within the developing murine lung,[175] and FGF7 overexpression results in enlarged bronchial air spaces and papillary cystadenomas.[176] A variety of experimental data have indicated that FGF7 expression increases following acute lung injury and that FGF7 is protective, principally when used as a pretreatment, in the face of injury caused by varied insults including hyperoxia, radiation, graft versus host disease following allogeneic bone marrow transplant, acid, and bleomycin,[174,177–179] but FGF7 may also partially prevent loss of barrier function in airway epithelium when given after an inciting exposure, potentially making FGF7 a more attractive therapeutic intervention were it so.[180,181] Notably, recombinant FGF7 (palifermin) which improves wound healing through cellular proliferation, is FDA approved for the treatment of chemoradiation-induced oral mucositis.[182] In addition to FGF7, FGF10 plays a critical role in lung development, given that FGF10(−/−) mice have defects in branching morphogenesis in lungs and other organs.[183] FGF10 overexpression attenuates bleomycin-induced pulmonary fibrosis in mice.[184] Interestingly, the triple angiokinase inhibitor nintedanib (BIBF 1120), inhibits VEGFR(1–3), platelet-derived growth factor receptors α and β, as well as FGFR1–3, and in a recent phase II clinical trial in patients with idiopathic pulmonary fibrosis, produced clinically meaningful reductions in the decline in forced vital capacity.[185]

GRANULOCYTE MACROPHAGE COLONY–STIMULATING FACTOR

GM-CSF is a glycosylated secreted protein produced by a variety of cells including macrophages, endothelial cells, T cells, natural killer cells, mast cells, and fibroblasts. It is defined by its ability to expand in vitro bone marrow precursor cells, via proliferation and differentiation, into colonies of mature myeloid cells, and act as a proinflammatory cytokine.[186–188] Interest from the pulmonary field grew with the initial observation that mice lacking GM-CSF had no major perturbation of hematopoiesis, but had an unexpected finding of compromised maturation of alveolar macrophages resulting in a phenotype of pulmonary alveolar proteinosis (PAP), with defective clearing of surfactant by alveolar macrophages.[189] The major form of human PAP is classified as autoimmune (or primary) PAP, accounting for about 90% of all PAP cases.[190] Autoimmune PAP is characterized by abnormally elevated levels of GM-CSF IgG autoantibodies, that bind GM-CSF with high affinity and neutralize GM-CSF functionality, and results in persistence of dysfunctional alveolar macrophages that are less efficient, with associated neutrophil dysfunction leading to opportunistic infections.[191] While whole lung lavage remains the cornerstone of therapy for PAP, targeted interventions to address the neutralization of GM-CSF are under active study using either (subcutaneous or inhaled) recombinant GM-CSF therapy, rituximab, or plasmapheresis, all with varying success to date.[192]

CONNECTIVE TISSUE GROWTH FACTOR

Connective tissue growth factor (CTGF) is a member of the structurally related CCN (ctgf/cyr61/nov) gene family, which contains six genes: ctgf, cyr61, nov, elm1, cop1, and WISP-3.[193] CTGF is produced by vascular smooth muscle cells, fibroblasts, endothelial cells, and epithelial cells, and is activated by a number of factors, particularly TGF-β.[193] CTGF has in vitro activities that include fibroblast proliferation, fibroplasia, and ECM production.[193–195] Furthermore, its presence has been documented in skin lesions of systemic sclerosis, keloids, scar tissue, and eosinophilic fasciitis and in BALF from patients with IPF and sarcoidosis, and it induces ECM in asthmatic airway smooth muscle.[193–196] Transient overexpression of CTGF in a rat model leads to a moderate but reversible pulmonary fibrosis that is associated with increased levels of TIMP-1.[197] Overexpression of TGF-β leads to a concomitant increase in CTGF and TIMP-1, suggesting that CTGF may be a cofactor for the development of fibrosis.[197] CTGF may be responsible for some of the downstream actions of TGF-β and is a potential therapeutic target for the treatment of interstitial lung disease.

CONCLUSIONS

Chemokines, adipokines, and growth factors are now recognized to play fundamental roles in lung development, the lifelong maintenance of lung health, and the development of pulmonary disorders characterized by inflammation and/or fibrosis, some of which are modulated by body mass. The generation of complex, overlapping signaling networks is necessary for both the pathogenesis and resolution of a variety of acute and chronic lung diseases, as these mediators are fundamental to the initiation, maintenance, and final resolution of the inflammatory response. Studies that illuminate the mechanistic role of chemokines, adipokines, and growth factors in mediating lung inflammation are beginning to lead to novel targeted forms of therapies, which will significantly aid in treating enigmatic lung disease.

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CHAPTER 27

Redox Signaling and Oxidative Stress in Lung Diseases

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INTRODUCTION

Molecular oxygen is a prerequisite to life of all aerobic organisms. The human lung with its large surface area and extensive blood supply is engineered for its primary function in gas exchange. While oxygen is essential for its many roles in human physiology, high concentrations of oxygen or its metabolites, commonly referred to as reactive oxygen species (ROS), have the potential to cause cellular injury and contribute to disease pathogenesis. The most damaging forms of ROS are free radicals. A free radical, by definition, refers to any chemical species containing one or more unpaired electrons in their atomic or molecular orbitals. These unpaired electron(s) give considerable reactivity to free radical species, which can trigger chemical reactions that damage cellular constituents of living organisms. Molecular oxygen (dioxygen) is itself, a radical based on the presence of unpaired electrons in its outermost orbital; however, their parallel spin retrains its reactivity. O_2 can form the superoxide anion radical ($O_2^{\bullet -}$) upon addition of an electron; thus, overcoming this restraint and making $O_2^{\bullet -}$ a highly reactive species.[1,2] The photodynamic activation of oxygen can result in the formation of singlet oxygen, and its reductive activation results in the formation of hydrogen peroxide (H_2O_2) or the highly reactive hydroxyl radical ($^{\bullet}OH$).[3,4] When two free radicals share their unpaired electrons, nonradical species of lower reactivity are generated. Thus, ROS constitute both free radicals and nonradicals.

Nitric oxide ($NO^{\bullet}$) is another small gaseous molecule that serves as an important signaling molecule in diverse physiological processes, including vasorelaxation and immune regulation during chronic inflammation in the lung.[5,6] The regulated production of $NO^{\bullet}$ by lung cells is critical for homeostasis of the lung. However, in some contexts, the reaction of $NO^{\bullet}$ with $O_2^{\bullet -}$ to form reactive nitrogen species (RNS), such as peroxynitrite ($ONOO^-$), may contribute to the pathophysiology of chronic lung diseases.[7–9]

ROS and RNS together play important roles in regulation of cell proliferation, differentiation, and survival.[10–12] ROS/RNS can inactivate enzymes including antiproteases, induce apoptosis, regulate cell proliferation, and modulate the immune-inflammatory system in the lungs and other tissues.[13–16] ROS/RNS have been implicated in initiating inflammatory responses in the lungs through the activation of transcription factors, protein kinase pathways, chromatin remodeling, and gene expression of proinflammatory mediators.[13–16] Under normal physiological conditions, the balance between generation and elimination of ROS/RNS maintains the functional integrity of redox-sensitive signaling cascades regulating cellular phenotypes. In this context, it is important to differentiate the roles of ROS/RNS in "oxidative stress" from "redox signaling." Paradoxically, it appears that nature has co-opted the chemical reactivities of ROS/RNS to function as signaling molecules in homeostasis and normal cellular physiology.

Redox homeostasis of cells/tissues is maintained by the regulated balance of oxidant production and antioxidant systems, both enzymatic and nonenzymatic. However, an increase in oxidant generation in excess of the capacity of cells/tissues to detoxify or scavenge reactive species leads to oxidative stress.[10,17,18] Oxidative stress typically causes damage to cellular components in an indiscriminant manner. Such states are accelerated in the presence of transition metals, such as iron and copper, and/or specific monooxygenases or oxidases.[13,15,16] It is also important to recognize that aberrations in redox signaling or oxidative stress may contribute to the pathogenesis of lung diseases. In this chapter, we review the physiology of ROS and RNS; cellular antioxidant systems; and the role of oxidative stress and redox signaling in the development and progression of selected acute and chronic lung diseases.

METABOLISM OF REACTIVE OXYGEN/NITROGEN SPECIES

ENZYMATIC AND NONENZYMATIC SOURCES OF ROS

The primary ROS include superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$), which can be generated from both enzymatic and nonenzymatic sources. The human lung is constantly exposed to ambient air, which may contain environmental toxins capable of inducing ROS generation.[13,19] ROS may also be generated by electron transfer reactions in the mitochondria and endoplasmic reticulum (ER), from xenobiotics, and a range of metabolic enzymes that catalyze oxidation reactions.[19] The major endogenous ROS/RNS and the primary mechanisms for their generation are summarized in Table 27-1.

The highly reactive $O_2^{\bullet -}$ formed by the addition of an electron to molecular oxygen is unstable with a half-life of milliseconds. The major site for producing $O_2^{\bullet -}$ is the mitochondria, which is also the primary site for ATP generation in any cell. During mitochondrial

TABLE 27-1 Key Reactive Oxygen and Nitrogen Species

Reactive Species	Formula	Chemical Reaction		
Superoxide	$O_2^{\bullet -}$	$NADPH + 2O_2$	$\longleftrightarrow$	$NADP+ + 2O_2^{\bullet -} + H^+$
		$2O_2^{\bullet -} + H+$	$\longrightarrow$	$O_2 + H_2O_2$
Hydrogen peroxide	H_2O_2	$Hypoxanthine + H_2O + O_2$	$\rightleftharpoons$	$Xanthine + H_2O_2$
		$Xanthine + H_2O + O_2$	$\rightleftharpoons$	$Uric\ acid + H_2O_2$
Hydroxyl radical	$^{\bullet}OH$	$Fe^2 + H_2O_2$		$Fe^{3+} + OH^- + {}^{\bullet}OH$
Hypochlorous acid	HOCl	$H_2O_2 + Cl^-$	$\longrightarrow$	$HOCl + H_2O$
Peroxyl radicals	$ROO^{\bullet}$	$R^{\bullet} + O_2$	$\longrightarrow$	$ROO^{\bullet}$
Peroxynitrite	$ONOO^-$	$O_2^{\bullet} + NO$	$\longrightarrow$	$ONOO^-$
		$H_2O_2 + NO_2^-$	$\longrightarrow$	$ONOO^- + H_2O$

electron transport, there is an estimated leak of 1% to 3% of electrons to oxygen resulting in the formation of $O_2^{\bullet -}$.[16] $O_2^{\bullet -}$ generated in the mitochondria, due to its negative charge, does not cross membranes and is released into the mitochondrial matrix where it targets proteins with heme moieties or iron–sulfur clusters to cause loss of protein or enzymatic function.[20] The steady-state levels of intramitochondrial $O_2^{\bullet -}$ concentrations are maintained at very low levels by detoxifying enzymes. ER is another intracellular compartment in which enzymes that detoxify lipid-soluble drugs and other toxic metabolites, reduce molecular O_2 to produce $O_2^{\bullet -}$ and/or H_2O_2, while oxidizing unsaturated fatty acids and xenobiotics.[19,20]

The NADPH oxidase (NOX) gene family encompasses enzymes, the primary function of which is the regulated generation of ROS. NOX enzymes form a membrane-bound multicomponent complex that is present in phagocytes and nonphagocytic cells in the lung.[15,16,18] NOX enzymes play crucial roles in host defense, signal transduction, and hormone synthesis in eukaryotes. There are seven mammalian NOX homologs comprising NOX1 to 5 and the DUOX1 and 2.[21–24] The best characterized NOX isoform is NOX2, which is essential for microbicidal-killing activity of phagocytes. NOX2, upon activation, generates ROS by coordinated assembly and activation of the NOX2 enzymatic complex, which comprises the membrane-associated flavocytochrome b558 ($gp91^{phox}$), $p22^{phox}$, and the various cytosolic cofactors ($p47^{phox}$, $p67^{phox}$, and $p40^{phox}$, and the GTPase, Rac1). This complex then mediates the transmembrane electron transfer from the major electron donor, NADPH, to reduce molecular O_2 to $O_2^{\bullet -}$ and H_2O_2.[15,16,18]

Similar to NOX2, activation of NOX1 and NOX3 also requires association with $p22^{phox}$, and assembly with Rac1 and cytosolic cofactors ($p47^{phox}$ and $p67^{phox}$ or their homologs, NOX organizer 1 (NOXO1) and NOX activator 1 (NOXA1). NOX4 also requires $p22^{phox}$, but is constitutively active and functions independently of activation of other cofactors.[16,21–24] Expression of NOX1 and NOX4 in nonphagocytic fibroblasts results in increased levels of both $O_2^{\bullet -}$ and H_2O_2, implying that these, unlike the phagocytic NOX2, possess intrinsic basal activity. NOX5 and DUOX1/2 differ from the other NOX homologs and contain additional intracellular Ca^{2+}-binding EF-hand domain regions, and are regulated by Ca^{2+} signaling, independent of $p22^{phox}$ or other cytosolic factors.[16,21–24] The dual oxidases, DUOXs, are composed of the NOX-like region at the C-terminal half, two EF-hands, a membrane-spanning region, and a peroxidase-like domain at the N-terminus. DUOXs do not require cytosolic regulatory components for their activity.[16,21–24] However, transmembrane maturation factors, DUOXA1 and DUOXA2, are essential for ER-to-Golgi transition, maturation, and targeting DUOXs to the plasma membrane as functional complexes. Although initially identified in the thyroid gland, DUOX1 and DUOX2 are the primary sources of H_2O_2 production in the airway epithelium.[25] The NOX/DUOX isoforms are expressed widely in the lung extending from the proximal trachea and large airways to terminal bronchioles and alveoli (Table 27-2).[16,21–25]

In biological systems, dismutation reaction of $O_2^{\bullet -}$ generates H_2O_2, either spontaneously or by enzymatic catalysis by superoxide

TABLE 27-2 Enzymatic Sources for ROS and RNS

Enzyme	Distribution in Lung	Lung Cell Types
DUOX1, DUOX2, NOX2, NOX4	Trachea and upper airways	Airway epithelial cells
NOX1, NOX2, NOX4	Pulmonary vasculature	Pulmonary artery endothelial cells
NOX4	Pulmonary vasculature	Pulmonary artery smooth muscle cells
DUOX1, DUOX2, NOX2, NOX4	Lower airways/ alveolus	Airway epithelial cells
NOX3	Airway alveolus	Endothelial cells
NOX4	Airway alveolus	Myofibroblasts
NOX2, NOX4	Alveolar space/ blood	Monocytes, Macrophages, Neutrophils, Eosinophils
NOS1 (neuronal)	Trachea, bronchus, airways	Airway epithelial cells Neutrophils Neurons
NOS2 (inducible)	Airways, alveolus, alveolar space/ blood	Airway and vascular smooth muscle cells Type II pneumocytes Fibroblasts Macrophages Monocytes Neutrophils Eosinophils Mast cells
NOS3 (endothelial)	Airways, pulmonary vasculature	Airway epithelial cells Type II pneumocytes Pulmonary artery Smooth muscle cells Endothelial cells Macrophages

dismutases (SODs). $O_2^{\bullet-}$ can be generated by molybdenum hydroxylase reactions involving xanthine, sulfite, and aldehyde oxidases, dihydroorotate and flavoprotein dehydrogenases, tryptophan dioxygenases as well as arachidonic acid metabolism.[26,27] Certain oxidases such as monoamine and amino acid oxidases can generate H_2O_2 directly without the intermediate formation of $O_2^{\bullet-}$.[17] During chronic inflammation in the lung, H_2O_2 is produced by both resident and inflammatory cells of the lung.[26,27] The oxidizing potential of H_2O_2 is amplified by inflammatory cell peroxidases such as myeloperoxidase (MPO) and/or eosinophil peroxidase (EPO).[28–32] The hydroxyl radical, $^{\bullet}OH$, is the neutral form of the hydroxide ion that is highly reactive toward cellular constituents, more so than $O_2^{\bullet-}$ or H_2O_2. This radical contributes to most of the reactivity by $O_2^{\bullet-}$ and H_2O_2 in a series of reactions that are catalyzed by transition metal ions. Excess $O_2^{\bullet-}$ targets Fe–S cluster-containing enzymes and catalyzes production of $^{\bullet}OH$ from H_2O_2 by reducing free iron (Fe^{3+} to Fe^{2+}) for Fenton chemistry (see Table 27-1). MPO and EPO enzymes represent an alternate pathway for $^{\bullet}OH$ formation *in vivo*. MPO uses Cl^- as substrate to generate hypochlorous acid, whereas EPO uses Br^- to generate brominating species. The hypohalous acids then generate $^{\bullet}OH$ by reaction with $O_2^{\bullet-}$.[33–38] Both these enzymes can accelerate oxidative modifications of proteins, in particular bromination and chlorination.

■ ENZYMATIC AND NONENZYMATIC SOURCES OF RNS

An important RNS in the lung is $NO^{\bullet}$, which is endogenously generated by specific nitric oxide synthases (NOSs). These NOS enzymes metabolize L-arginine to $NO^{\bullet}$ and L-citrulline via a five electron oxidation reaction.[6,39–48] This reaction requires a dimeric enzyme, oxygen, NADPH and the cofactors, flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), tetrahydrobiopterin (BH_4), calmodulin, and iron protoporphyrin. Active NOS enzymes exist in the dimeric form with each monomer consisting of an N-terminal oxygenase domain that binds heme, BH_4, and substrate L-arginine. The cofactors FAD, FMN, and NADPH bind the C-terminal end of the NOS monomer. There are three different NOS forms, all of which are expressed in the lung, the inducible form iNOS or NOS2, neuronal NOS or NOS1, and the endothelial NOS enzyme NOS3 (Table 27-2). The NOS1 and NOS3 enzymes are calcium dependent and produce picomolar levels of NO, while nanomolar levels are generated by the calcium-independent iNOS. $NO^{\bullet}$ synthesis by iNOS is regulated by the availability of the substrate L-arginine and cofactor BH_4. Transfer of electrons occur from the carboxyreductase domain to the heme iron of the oxygenase domain, which then binds oxygen and oxidizes L-arginine to generate the end products, $NO^{\bullet}$ and citrulline.[6,39–48] Uncoupling of NOS enzymes can contribute to the formation of the $O_2^{\bullet-}$. In a low arginine condition, NADPH is oxidized by the enzyme to generate $O_2^{\bullet-}$. Arginase, an enzyme that competes with the NOSs for L-arginine decreases the arginine availability for NOS. Arginase is a critical enzyme in the urea cycle and converts arginine to ornithine, and then to urea; it can promote uncoupling of NOSs to generate $O_2^{\bullet-}$.[49,50] About 40% of the highly reactive and highly diffusible $NO^{\bullet}$ is consumed in chemical reactions and, when metabolized, give rise to reactive intermediates. $NO^{\bullet}$ reacts with O_2 yielding nitrite (NO_2^-) and recycling of nitrite causes regeneration of bioactive $NO^{\bullet}$. NO_2^- is also a substrate for the heme peroxidases, MPO and EPO, which oxidize nitrite to nitrogen dioxide radical ($NO_2^{\bullet}$). $NO^{\bullet}$ is also oxidized to methemoglobin and NO_3^- by reaction with oxyhemoglobin. $NO^{\bullet}$ reacts with $O_2^{\bullet-}$ to form peroxynitrite ($ONOO^-$), which can mediate tyrosine nitration that may result in either the loss or gain of function of proteins.[7–9,51] In acidic environments, the protonation of $ONOO^-$ results in the formation of ONOOH (peroxynitrous acid), which is then decomposed to both NO_3^- via intermediate $^{\bullet}OH$ and NO_2.[52] ONOOH can also react with thiol residues to form S-nitrosothiols (SNOs) and the reaction is referred to as S-nitrosation or S-nitrosylation. A wide variety of proteins including kinases, channels, and transcription factors are susceptible to S-nitrosylation. SNOs are important molecules in the signaling of $NO^{\bullet}$ bioactivity in the respiratory system.[53–57] SNOs are present in the airway epithelial lining fluid in μmol concentrations, can influence airway tone, and possess substantially greater half-lives than $NO^{\bullet}$ in the lung. It has also been reported that iNOS can specifically bind to cyclooxgenase-2 (COX-2) and S-nitrosylate COX-2, upregulate its catalytic activity and enhance prostaglandin E2 production. Thus, S-nitrosylation represents an important signaling pathway for $NO^{\bullet}$.[53–57] Under physiological conditions, interaction with metal centers of enzymes and S-nitrosylation are the major mechanisms for biological actions of $NO^{\bullet}$. In biological systems, the levels of $O_2^{\bullet-}$ are 10^{-11} to 10^{-10} M while that of NO is 10^{-9} to 10^{-7} M. Under these conditions, $ONOO^-$ is formed at a low rate by the reaction of $NO^{\bullet}$ with $O_2^{\bullet-}$ with a 1:1 stoichiometry.[7–9,51,53–57] However, under pathophysiological conditions, $ONOO^-$ and its derivatives are formed at high levels and may cause irreversible damage to the respiratory chain, inhibit ATP synthesis, and induce cytochrome c release and caspase-dependent apoptosis. RNS may also mediate lipid peroxidation, protein oxidation and nitration, enzyme inactivation, or even cell necrosis.[7–9,51,53–57]

MECHANISMS TO DETOXIFY ROS/RNS

ROS/RNS play a key role in the initiation, amplification, and persistence of inflammation associated with chronic lung diseases.[15–18,58,59] Similar to the formation of ROS/RNS, the removal or detoxification of these species may involve enzymatic and nonenzymatic mechanisms. Nonenzymatic systems constitute the first line of defense against ROS/RNS. The low–molecular-weight nonenzymatic antioxidants in the lung include glutathione, vitamins C and E, β-carotene, uric acid, thiols, and taurine. The larger–molecular-weight antioxidants include lactoferrin, albumin, ceruloplasmin, and transferrin; these molecules mediate their antioxidant function by binding heavy metals, making them unavailable for participation in the Fenton reaction to produce free radicals such as hydroxyl radical.[15,18,26,59,60] Nonenzymatic antioxidant activities range from the hydrophilic quenching of free radicals, protection of critical sulfhydryl groups on proteins to inhibition of lipid peroxidation.

Although nonenzymatic antioxidants are the first line of defense against different ROS, several enzymatic antioxidants work in concert with nonenzymatic antioxidants to form a tightly regulated antioxidant network. The major components of the pulmonary enzymatic antioxidant defense systems are SODs, catalase, and glutathione peroxidases. Peroxiredoxins (PRXs), thioredoxins (TRXs), glutaredoxins, heme oxygenases, and reductases are also involved in cellular adaptation and protection against oxidative stress in the lung. The enzymatic reactions that catalyze the elimination of ROS/RNS are summarized in Figure 27-1.

Superoxide Dismutases: The $O_2^{\bullet-}$ radical is a primary oxidant in chronic lung inflammation.[15,17,61] It participates in the generation of other reactive metabolites, H_2O_2, $^{\bullet}OH$, and $ONOO^-$. SODs represent a key defense against reactive species generated during normal metabolism or inflammatory states. SODs are ubiquitous enzymes that catalyze the dismutation of $O_2^{\bullet-}$ radical to the weaker oxidant, H_2O_2 (see Fig. 27-1). The function of SOD extends beyond its catalysis of $O_2^{\bullet-}$ dismutation to its participation in the regulation of normal cellular homeostasis. H_2O_2 formed from the SOD-catalyzed reaction may function as a signaling molecule at low concentrations. By reducing steady-state concentrations of $O_2^{\bullet-}$, which reacts with $NO^{\bullet}$ to form $ONOO^-$, SOD may serve to promote vasoreactivity and reduce inflammation.[15,61]

There are three mammalian SOD isozymes: the intracellular copper-zinc SOD (CuZn-SOD), the mitochondrial manganese SOD

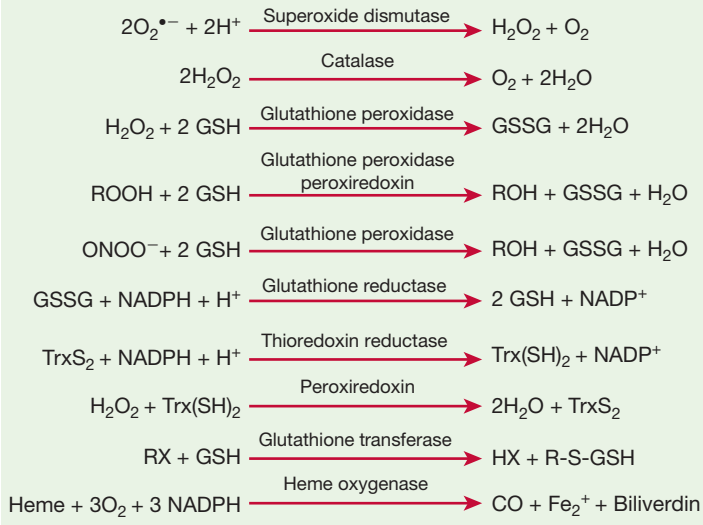

Figure 27-1 Enzymatic mechanisms to detoxify reactive oxygen and nitrogen species.

(Mn-SOD), and extracellular SOD (EC-SOD).[61] The structural and catalytic characteristics of these SOD isozymes are highlighted in Table 27-3.[62–65] Given the complexity of the human lung with its plethora of different cell types, it is conceivable that these isozymes are expressed differentially in specific lung cells with subcellular compartmentalization, as summarized in Table 27-4.[66–79]

Aside from dismutating $O_2^{\bullet-}$ radical by the cyclic oxidation–reduction of its metal ion Cu^{2+}, CuZn-SOD exhibits peroxidase activity.[65] At high levels, H_2O_2 may reduce the Cu^{2+} to either Cu^+-O or Cu^{2+}-OH that may oxidize the histidine residue in the monomer and inactivate or oxidize lung proteins.[80–82] CuZn-SOD also nitrates tyrosine residues in proteins via peroxynitrite,[83–87] and catalyzes the release of NO from nitrosothiols.[88] Although Mn-SOD has similar dismutase activity, it does not elicit peroxidation or nitration, and is inactivated by tyrosine nitration, but not by hydrogen peroxide or cyanide.

EC-SOD is the primary extracellular SOD in the lung[72] containing Cu and Zn ions.[89,90] The EC-SOD has an active site inhibitable by H_2O_2 and cyanide, similar to CuZn-SOD.[74–76] EC-SOD has an arginine- and lysine-rich heparin/matrix-binding domain at its C-terminal region.[91–94] Its extracellular localization is maintained by the interaction of this domain with heparin and heparin sulfate proteoglycans on diverse lung cell types and in the extracellular matrix (ECM) of the lung. This heparin/matrix-binding polybasic region is sensitive to proteolysis, leading to reduced affinity of EC-SOD for ECM and increased release of EC-SOD in plasma.[72,91–97] EC-SOD is abundant in the lung both at the mRNA and protein levels.[91–94] As indicated in Table 27-4, the wide cellular distribution of EC-SOD is consistent with robust EC-SOD activity in the human lung (eightfold > liver, sixfold > brain, two- to threefold > heart, and one- to twofold > kidney)[61]; in comparison, CuZn-SOD and Mn-SOD activities are much lower. The lower activities of CuZn-SOD and Mn-SOD in the lung suggest that cytoplasmic production of $O_2^{\bullet-}$ is lower in lung cells, compared with the metabolically more active cells of the liver and kidney. The dense airway and vascular network in the lung and the higher potential for extracellular inflammatory events resulting from direct exposure of the lung to the external environment may account for high EC-SOD levels in the lung. Even with its high lung localization, EC-SOD is not present at sufficient concentrations to justify its role as the sole scavenger of $O_2^{\bullet-}$ across the entire extracellular space. While CuZn-SOD and Mn-SOD function mainly as bulk scavengers of the $O_2^{\bullet-}$ radicals, the relatively high levels of EC-SOD in the lung and its binding specificity to the ECM components provide protection for the lung matrix.[14,98]

Lack of abnormalities in CuZn-SOD–deficient mice suggest that pathological consequences of mutations are perhaps due to gain of compensatory functions of the enzyme including its peroxidase or nitration reactions and not associated just with the complete loss of SOD activity.[97,99] EC-SOD–overexpressing mice were only partially protected from hyperoxia-induced lung injury, influenza, bleomycin, and hemorrhagic shock,[14,61,98] suggesting that EC-SOD may not be sufficient to attenuate oxidative stress in pathological states in which the EC-SOD system is overwhelmed. Under hyperoxia, mice lacking EC-SOD show shortened survival and extensive lung damage.[14,61,98] Thus, although other antioxidant enzymes may compensate for the loss of EC-SOD under homeostatic conditions, during inflammatory stress, EC-SOD is essential for protecting the lung and limiting injury. Over 90 genetic polymorphisms have been identified in CuZn-SOD, several in association with neurodegenerative diseases.[62] The Arg 213-gly polymorphism in EC-SOD (R213G) is found in 4% to 6% of the human population and influences chronic obstructive pulmonary disease[100,101] and acute lung injury.[102]

Catalase: H_2O_2 is reduced to water by catalase (CAT) and the glutathione peroxidases (see Fig. 27-1). CAT is a metalloprotein oxidoreductase enzyme widely expressed in lung cells (see Table 27-4).[62,103–106] In the presence of excess H_2O_2, CAT undergoes alternate divalent oxidation and reduction at its heme-containing active site. Catalase degrades H_2O_2 to O_2 and water.[62,103–106] Although catalase is the principal scavenger of H_2O_2, it is unable to metabolize large molecular peroxides including lipid peroxides. The gene for catalase is not induced by oxidant stress. However, posttranslational tyrosine phosphorylation of CAT upregulates its activity[107]; whereas, oxidation of tyrosine residues inhibits CAT activity.[8]

Glutathione peroxidases: Glutathione peroxidases (GSH-Pxs) are selenocysteine-containing tetrameric enzymes that utilize reduced glutathione (GSH), a low–molecular-weight tripeptide, as an electron donor and catalyze the biotransformation of various organic and inorganic peroxides, including H_2O_2 and lipid peroxides, to their corresponding alcohols. The detoxification of peroxides by GSH-Pxs occurs via bidirectional second-order kinetics and is a saturation-limited process.[26,108] GSH-Px1, GSH-Px2, GSH-Px3, and GSH-Px4 are the four glutathione peroxidases.[26,108] GSH-Px1 is a ubiquitous intracellular form and is the predominant isoform

TABLE 27-3 Characteristics of Superoxide Dismutases

SOD	Structure	Metal Ions	Type of Enzymatic Activity	Intracellular SOD activity (%)
Mn-SOD	Homotetramer	Mn and Zn	$O_2^{\bullet-}$ Dismutation	10
CuZn-SOD	Homodimer	Cu and Zn	$O_2^{\bullet-}$ Dismutation Peroxidation Nitration	90
EC-SOD	Homotetramer	Cu and Zn	$O_2^{\bullet-}$ Dismutation Peroxidation	0

TABLE 27-4 Enzymatic Mechanisms to Detoxify or Remove ROS/RNS

Antioxidant Enzymes	Acronym	Expression of Antioxidant Enzymes in Lung Cell Types	Cellular Distribution
Superoxide dismutase	SOD		
Mn-SOD		Alveolar type II epithelial cells, septal tip of the alveolar duct, arterioles near the airways, alveolar macrophages	Mitochondria
EC-SOD		Bronchial epithelium, alveolar epithelium, epithelial cells lining intrapulmonary airways, ECM, endothelial cells lining arteries and veins, alveolar macrophages	Plasma membrane
CuZn-SOD		Bronchial epithelium, alveolar epithelium, mesenchymal cells, fibroblasts, arterioles, capillary endothelial cells	Cytosol, nucleus, lysosome, peroxisomes
Catalase	CAT	Airway and alveolar epithelial cells, type II pneumocytes, alveolar macrophages	Peroxisomes, mitochondria
Glutathione peroxidase-1	GSH-Px	Airway epithelial cells, bronchial epithelial cells, alveolar macrophages	Cytosol, mitochondria
Thioredoxin	TRX1 and 2	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, mitochondria
Thioredoxin peroxidase	TRXPrx	Bronchial epithelial cells, type II pneumocytes, macrophages	Cytosol
Thioredoxin reductase	TRR	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, mitochondria
Glutaredoxin	Glrx	Bronchial epithelium, alveolar macrophages	Plasma membrane, cytoplasmic vacuoles, nucleus
Glutathione S Transferase	GST	Bronchiolar Clara and alveolar type II cells, bronchial epithelial cells	Plasma membrane, cytosol, microsomes, mitochondria
Peroxiredoxin	PRX	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, nuclear matrix, peroxisomes, mitochondria
Heme oxygenase	HO	Alveolar type II cells, lung fibroblasts, monocytes, alveolar macrophages	Microsomes, mitochondria, endoplasmic reticulum

that catalyzes the removal of inorganic peroxides, lipid peroxides and hydroperoxides.[26,108–111] GSH-Px2 is localized to the gastrointestinal epithelia with substrate specificities similar to that of GSH-Px1. GSH-Px3 is a secreted form able to reduce lipid hydroperoxides.[110,111] This extracellular isoform accounts for 57% of the GSH-Px activity in the epithelial lining fluid, and GSH-Px1 contributes to 40% activity.[110,111] The fourth isoform, GSH-Px4, is an intracellular peroxidase that preferentially catalyzes the peroxidation of phospholipid hydroperoxides.[109]

Thioredoxins: Thioredoxins (TRXs), which contain an active site cysteine, serve as redox sensors while also reducing H_2O_2.[112,113] H_2O_2 oxidizes the reduced dithiol group (-SH HS-) in TRX to a disulfide bridge (-S-S-). TRXs can reduce protein disulfides (-SH) and protein sulfenic acid intermediates (-SO_3H) by cysteine thiol–disulfide exchanges.[10,11] Two human TRXs are expressed widely in various lung cell types (see Table 27-4). In addition to its direct antioxidant function, TRX, in cooperation with PRXs, augments gene expression of other antioxidant enzymes, including SOD.[114–118] TRXs also participate in refolding of oxidized proteins and activate transcription factors by reducing cysteines present in the DNA-binding site.[119] TRX can be activated by hypoxia, lipopolysaccharide, H_2O_2, microbial infections, and photochemicals. Thus, TRXs are powerful redox modulators, protects cells against oxidative stress, and participates in cell proliferation and survival.[114–118]

Glutaredoxins: Glutaredoxins (GRXs) are thiol–disulfide oxidoreductases with antioxidant capacity in human lung (see Table 27-4).[18,120–123] GRX regulates cellular redox state and redox-dependent signaling pathways via modulation of protein glutathionylation; it regulates the intracellular and extracellular homeostases of glutathionylated proteins and GSH.[18,120–124] These enzymes use glutathione as a cofactor and catalyze the reversible exchange of glutathione with protein thiol groups (see chemical reactions in Fig. 27-1). GRX enzymes are dependent on GSH/GSSG concentrations.[125]

Glutathione-S-Transferases: Glutathione-S-transferases (GSTs) are detoxification enzymes that require intracellular GSH for their catalytic activity. These antioxidant enzymes inactivate secondary metabolites, such as unsaturated aldehydes, epoxides, and hydroperoxides.[126] Three major families of GSTs have been described; the cytosolic GST, mitochondrial GST, and membrane-associated microsomal GST (see Table 27-4).[60] GSTs regulate eicosanoid and glutathione metabolism.[60,127] Under conditions of oxidative stress, cytosolic GST interacts with PRXs.[126] GST family enzymes are expressed in normal lung, mainly in the airways. They protect cells against a number of oxidizing species. GSTs have high genetic variability, and are implicated in the development of smoking-related nonmalignant and malignant diseases.[60,128–131]

Peroxiredoxins: Peroxiredoxins (PRXs) are broad-spectrum peroxidases that detoxify or reduce H_2O_2, peroxynitrite, and organic hydroperoxides (ROOH).[132,133] These are nonseleno-peroxidases whose antioxidant properties are dependent on redox-active cysteines.[133] Six different PRXs have been found in human lung (see Table 27-4).[134,135] These PRXs differ widely in their specificities for H_2O_2, lipid and phospholipid hydroperoxides.[134–138] PRX V and VI function as peroxynitrite reductases, and are protective in ROS/RNS-mediated lung injury.[134–136,139,140] PRXs also regulate peroxide-mediated signaling cascades related to cell proliferation, differentiation, and apoptosis by modulating cytokine-mediated induction of H_2O_2.[18,133,137,138]

Heme oxygenases: Heme oxygenase (HO) catalyzes the breakdown of pro-oxidant heme to generate equimolar amounts of carbon monoxide, ferrous iron, and biliverdin (Fig. 27-1). Biliverdin is then converted by biliverdin reductase to bilirubin, the antioxidant endproduct of the HO reaction.[141–144] CO transported to the lung has vasodilatory and antiapoptotic properties.[145–150] Iron is used for heme synthesis in the cells required for heme-containing proteins or transported to the bone marrow and other tissues.[18,141,144,151,152] There are three isoforms of HO, the inducible HO-1, and the constitutive forms, HO-2 and HO-3. During oxidative stress, transcriptional activation results in rapid induction of HO-1.[141,144,145] This adaptive response of HO-1 confers protection during inflammation and oxidative stress. HO-1 is expressed widely in the lung (see Table 27-4). Consistent with the antioxidant properties of HO-1, mice deficient in HO-1 are more susceptible to oxidative stress.[153,154] Overexpression

or induction of HO-1 suppresses inflammation in several models of chronic lung disease.[18,141,144,151,152]

CELLULAR SOURCES AND REGULATION OF ROS/RNS

IMMUNE CELLS

Inflammation is an adaptive response to infectious and noninfectious tissue injury. Recruited inflammatory cells emigrate from the pulmonary microcirculation into the airspaces where they become activated to generate ROS/RNS.

$NO^{\bullet}$ participates in pathogen killing by macrophages.[155] $NO^{\bullet}$ also delays fusion of phagosomes with lysosomes to form a functional phagolysosome, which enhances antigen processing/presentation of macrophages. Macrophages scavenge endogenous dying cells. Phagocytosis of dying cells requires the secretion of alarmins by dying cells to attract and preactivate phagocytes; these signals by dying cells ensures specific recognition and phagocytosis/efferocytosis, all of which involve redox regulation.[156,157]

Beyond the chemical interactions of $NO^{\bullet}$ and ROS that cooperatively eradicate pathogens, these redox-active biomolecules regulate cellular metabolism, inflammation, and tissue-repair functions. Cellular supply of substrates/cofactors for iNOS activity, including arginine, is required for $NO^{\bullet}$ production. However, in the absence of arginine or BH_4, uncoupled NOS becomes an $O_2^{\bullet-}/H_2O_2$ generator. The flavin-binding sites of the reductase domain of iNOS, eNOS, and nNOS are a source of $O_2^{\bullet-}$ generation in the absence of arginine.[155,158–161] Therefore, metabolic pathways that control arginine and BH_4 play a role in determining $NO^{\bullet}$–$O_2^{\bullet-}$ balance. Cellular arginine levels are dependent on uptake and transport mechanisms and the activation of NOS-arginase enzymatic systems that use arginine. Arginase activation produces ornithine, a starting metabolite for the production of polyamines that are critical molecules supporting DNA stabilization, ion channel transport, and cell proliferation.[155,158–161] Arginase is regulated by NOS and NOX activities; N-hydroxyarginine, a product of NOS, inhibits arginase, while $O_2^{\bullet-}$ increases arginase activity.[155,158–161] High arginase activity is associated with elevated ROS and low $NO^{\bullet}$ fluxes. $NO^{\bullet}$ antagonizes NOX2 assembly through the activation of PPARγ which, in turn, inhibits expression of the p47 subunit required for NOX2 activation.[155,158–161] Thus, $O_2^{\bullet-}$ production is suppressed when NOS activity and $NO^{\bullet}$ levels are high. $NO^{\bullet}$ also inhibits COX2 activity, reducing COX2-dependent ROS production.[162] Thus, as $NO^{\bullet}$ levels decline, ROS generation may increase via multiple mechanisms.

The balance between $NO^{\bullet}$ and ROS may play a key role in the orchestration and resolution of inflammation. RNS and ROS actively control innate and adaptive immune signaling. This aspect of redox function is evident in cells of myeloid lineage, such as monocytes, macrophages, and neutrophils. RNS and ROS produced by these cells participate in induction, maintenance, and/or termination of proinflammatory and anti-inflammatory signaling. Similar to the effect of $NO^{\bullet}$ on pathogen eradication, the temporal and spatial concentration profiles of $NO^{\bullet}$ are key determinants of immune-mediated processes.[155,158–161] A relationship between increasing steady-state levels of $NO^{\bullet}$ has been linked to regulation of expression of tumor suppressor gene p53 and apoptosis in murine and human macrophage cell lines.[163,164] Concentration- and time-dependent changes in the functional profiles of $NO^{\bullet}$ are evident from NO-mediated regulation of cell survival protein signaling cascade[165–169]

Macrophages rely primarily on the NOX2 complex to produce ROS,[5,17,157,168] although the oxidative burst of macrophages is less intense than that of neutrophils. Induction of the proinflammatory phase of an innate immune response is an early response in the immune activation process. This is defined as "classical activation" in macrophages (also called M1 macrophages), and is associated with the production and release of proinflammatory cytokines, proteases including MMP-9, transcription factors such as NF-κB as well as RNS and ROS, including $NO^{\bullet}$ and $O_2^{\bullet-}$. In addition to a role in pathogen eradication, the localized levels of ROS/RNS may dictate integrated signaling and the type of immune activation and determination of cellular phenotypes; ROS/RNS may also regulate crosstalk between proinflammatory and resolution pathways. Classical (proinflammatory) activation of macrophages is followed by an anti-inflammatory healing/tissue-repair phase, which is the ideal outcome of a successful innate immune response. These phases of the innate immune response are initiated by the pathogens or tissue injury, but are rapidly reenforced by the actions of anti-inflammatory cytokines released from macrophages that function in an autocrine manner.[157,158,170–172] These cytokines initiate downregulation of the proinflammatory phase and induction of the repair or tissue remodeling phase.

$NO^{\bullet}$ also affects function of T lymphocytes.[155,173–176] Low $NO^{\bullet}$ concentrations promote differentiation of IFN-γ producing Th1 (T helper 1) in mice and humans, mediated by cGMP activation.[177] During the immune repair/restoration phase, the collective activity of IL-4, IL-13, IL-10, and TGF-β suppress iNOS expression, thereby decreasing $NO^{\bullet}$ and shifting in favor of ROS.[155,173–177] An $NO^{\bullet}$-independent role for arginase has been identified in the differentiation of alternatively activated macrophages. Although arginase expression in macrophages is prominently associated with Th2 responses, part of its function is to sequester arginine away from effector T cells resulting in a reduced Th2 response; reconstitution with exogenous arginine blocks this reduced Th2 response. In general, low $NO^{\bullet}$ favors Th2 responses, and high $NO^{\bullet}$ augments Th1 responses, suggesting that a $NO^{\bullet}$/ROS balance may be a critical determinant of immune polarity.[155,178,179] Naïve lymphocytes exposed to high μmol concentrations of $NO^{\bullet}$, however, regulate the expansion and proliferation of regulatory T cells within lymphoid tissue.[155]

This concentration-dependent regulation by $NO^{\bullet}$ is seen in immunosuppression by heterogeneous immature myeloid cells called myeloid-derived suppressor cells (MDSCs).[180,181] Free radical producing subsets of these MDSCs are critical regulators of allergic airway inflammation.[182,183] $NO^{\bullet}$-producing cells suppress T cell proliferation and airway hyperresponsiveness (AHR), while $O_2^{\bullet-}$ enhance T cell proliferation and exacerbate AHR.[182,183] Immunosuppression by MDSCs also occurs in the tumor microenvironment in which $NO^{\bullet}$-mediated increase in cGMP activation, facilitates their binding to cytotoxic lymphocytes to reduce their proliferation.[184,185] Peroxynitrite and H_2O_2 are produced by the combined and cooperative activities of NADPH oxidase, arginase, and iNOS in different MDSC subsets. These drive several molecular blocks in T cells, ranging from the loss of TCRζ-chain expression, interference with IL-2 receptor–mediated signaling and nitration, and subsequent desensitization of the TCR.[184,185] Signal transducer and activator of transcription 3 (STAT3) is a critical regulator of MDSCs. STAT3-mediated upregulation of the NADPH oxidase and ROS levels enhances the suppressive potential of MDSCs.[155,184,185]

Inflammasome activation is an innate immune response to pathogens, but also accompanies the development of autoimmune and chronic inflammatory diseases. Inflammasomes are multicomponent platforms that sense a variety of danger signals, including bacteria, viruses, pathogenic crystals; aggregates through a family of nod-like receptors and consists of caspase-1 to process proinflammatory cytokines for activation.[186–188] Inflammasome activation starts with a priming signal followed by an activation signal. Studies with ROS scavengers suggest a role of ROS in inflammasome activation.[186–190]

EPITHELIAL CELLS

The epithelium of the airways and the alveoli is exposed to high levels of oxygen and to other environmental oxidizing species. Although inflammatory cells are major producers of RNS/ROS, resident lung cells such as epithelial cells, possess enzymatic systems for regulated production of RNS and ROS. DUOX enzymes are the primary

contributors of H_2O_2 in the airway epithelium.[25,191] DUOXs are expressed in ciliated surface cells, but not in nonciliated cells or basal cells of the upper airway. The levels of expression of DUOX1 and DUOX2 are selectively regulated by cytokines, with Th1 cytokines regulating DUOX2 and Th2 cytokines regulating DUOX1.[19,21,192,193] The highly inducible DUOX2 mediates host responses to infection and inflammation, while DUOX1 is constitutively expressed in noninflamed airways; DUOX2 plays a role in innate immunity, cell signaling, and mucus production.[19,21,193,194] The airway epithelium participates in innate immune response through the secretion of immune effectors such as mucin, antimicrobial peptides, and ROS to entrap or kill invading microbes. Epithelial cells use microbial pattern recognition receptors for innate immune system recognition to discriminate self from nonself.[19,21,192,193] The release of cytokines/chemokines by the epithelium induces neutrophil recruitment and the activation of transcription factors augmenting the inflammatory response. Lactoperoxidase (LPO) a heme-containing peroxidase in concert with DUOX-generated H_2O_2 generates hypohalous acids that kill pathogens.[25,194] A functional difference between the airway DUOX/LPO system and the phagocytic NOX2/MPO system is that the phagocytic system is active only during the respiratory burst, whereas DUOX generates H_2O_2 continuously.[19,21,192,193]

ENDOTHELIAL CELLS

Endothelial cells (ECs) also participate in innate immunity and crosstalk with immune cells. The importance of ECs in inflammation-induced vascular dysfunction is dependent on their ability to produce and respond to ROS and RNS. Inflammation may alter the balance between $NO^{\bullet}$ and $O_2^{\bullet-}$ within (and surrounding) ECs, which is necessary for normal vascular function. ROS produced by the endothelium play an important role in vascular pathology.[195,196] ROS can quench $NO^{\bullet}$ and mediate proinflammatory signaling. Targeting ROS-quenching enzymes catalase and SOD in ECs alleviates toxic effects of excessive ROS and suppresses proinflammatory mechanisms, including endothelial cytokine activation and barrier disruption.[197–199] Pulmonary EC-derived ROS play a pivotal role in EC activation and function. Alterations in EC phenotype contribute to vascular tone, permeability, and inflammatory responses and, thus, have been implicated in lung diseases, including pulmonary hypertension, ischemia-reperfusion (IR) injury, and adult respiratory distress syndrome.[200–202] Contrasting effects of NOS isoforms occur during IR injury, where eNOS appears to be protective and iNOS detrimental. Under homeostatic conditions, the low NO flux generated by eNOS prevents leukocyte recruitment and associated tissue damage through scavenging of ROS. However, when iNOS expression increases, $NO^{\bullet}$ levels rise and induce tissue injury.[200–202] Thus, the beneficial effects of specific NOS isoforms depend on the type of primary damaging event.

FIBROBLASTS

Fibroblasts and fibroblast-like mesenchymal cells participate in innate immunity and in tissue repair. Such cells are typically resident within the adult human lung[203]; however, studies have reported fibroblasts derived from bone marrow cells[204] or epithelial cells, the latter in a process known as epithelial-to-mesenchymal transition (EMT).[205] EMT is a process regulating cell plasticity, which allows epithelial cells to lose their polarity and specialized junctional structures, to undergo cytoskeletal reorganization, and to acquire morphological and functional features of mesenchymal-like cells. Myofibroblasts are the primary "effector" cells in tissue remodeling and pulmonary fibrosis.[206–208] Activation of the NADPH oxidase isoform, NOX4, mediates generation of H_2O_2, myofibroblast differentiation, contractility, and ECM production in response to TGF-β1.[209] In addition, NOX4 may play a profibrotic role by inducing apoptosis of lung epithelial cells, while myofibroblasts themselves acquire an apoptosis-resistant phenotype. Epithelial cell death may also be mediated indirectly by the paracrine secretion of H_2O_2 by activated myofibroblasts, supporting the concept that NOX4 may be responsible for both myofibroblast activation and epithelial cell disrepair.[210]

OXIDATIVE STRESS IN VARIOUS LUNG DISORDERS

Oxidative stress is implicated in the pathogenesis of both acute and chronic inflammatory and fibrotic lung diseases, some of which are discussed here (Fig. 27-2).

ASTHMA

Asthma is a chronic inflammatory airway disease.[211,212] ROS and RNS have been implicated in the pathogenesis of asthma.[20,213–216] Dysregulation in pathways that lead to oxidative stress or its defense may contribute to the initiation and severity of asthma.[8,20,213–218] Recruitment of inflammatory cells and ROS production have been documented in the airways of asthmatic subjects.[20,112,214,219–222] $O_2^{\bullet-}$ generation was observed highest in airspace cells at the sites of antigen challenge.[213] Leukocyte activation with induction of NADPH oxidase and production of $O_2^{\bullet-}$ and H_2O_2 correlate negatively with FEV_1 in asthmatic subjects.[222] Besides airway macrophages and eosinophils, blood eosinophils and monocytes are also major sources of ROS in asthmatic patients.[213,218,223]

Airway inflammation-associated oxidative stress in asthma may induce oxidative modifications of proteins or lipids.[89,90,224] Increased numbers of eosinophils and neutrophils in association with higher

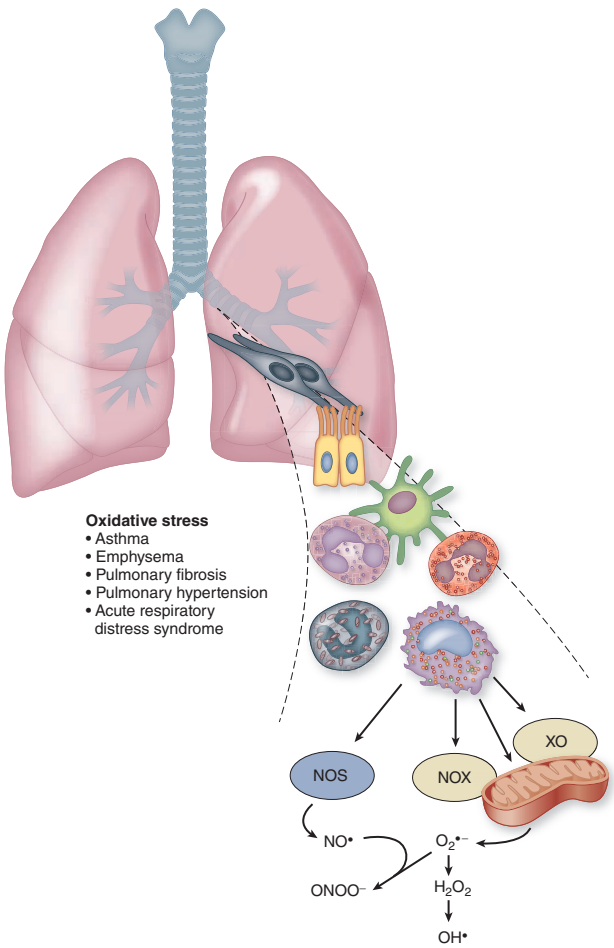

Figure 27-2 Oxidants initiate a number of pathological processes with a multitude of complex mechanisms that contribute to pathogenesis of both acute and chronic inflammatory diseases of the lung. Resident lung cells and recruited inflammatory cells together orchestrate these multilevel processes by regulating enzymatic pathways to balance the generation and metabolism of oxidants.

expression of peroxidases and other markers of eosinophil activation are found in bronchoalveolar lavage fluid (BAL) and bronchial tissues of asthmatics.[225,226] Oxidant products of neutrophil/eosinophil activation, 3-bromotyrosine, and MPO-mediated oxidants, such as chlorotyrosine are increased in asthmatics compared to control subjects; these have been implicated in the pathophysiology of severe asthma.[227,228] Other reactive products including malondialdehyde, thiobarbituric acid-reactive products, and 8-isoprostane, a biomarker of lipid peroxidation are also elevated in exhaled breath condensates of adults and children with asthma.[229–234] The precise mechanisms by which ROS exacerbate asthma is not known, but may involve effects on airway smooth muscle, mucin secretion, and T cell responses.[59,235] ROS can decrease β-adrenergic function in lungs and sensitize airway smooth muscle to acetylcholine-induced contraction.[103,236] H_2O_2 activates mitogen-activated kinases in tracheal myocytes and stimulates contraction of tracheal smooth muscle cells.[235] ROS also stimulates mucin secretion,[103,236] contributes to Th2 cell differentiation,[179] and promotes T cell proliferation via arginase and NADPH oxidase pathways.[182,183] Proinflammatory cytokines are elevated during airway inflammation, which activate oxidases leading to increases in ROS, the targets of which include receptor kinases, phosphatases, phospholipids, or nonreceptor tyrosine kinases.[16,237,238]

Another target of ROS is NO•. NO• metabolism appears to be dysregulated in asthma. Exhaled NO• is increased in asthmatics and is associated with airway inflammation.[54,55,239] Despite the expression and distribution of all three NOS enzymes in the airway, it is primarily iNOS that contributes to exhaled NO•. Induction of iNOS is observed at both transcriptional and translational levels principally in steroid-naïve patients.[41–43] In mild asthmatics, NO•, nitrate, and SNOs are enhanced in the lower airways.[54] Following antigen challenge, levels of NO• decrease, while nitrate increases without perturbing levels of nitrite and SNO.[54] Decreasing NO• levels correlates with increased nitrotyrosine formation from reaction of NO• with $O_2^{\bullet-}$.[54] Peroxynitrite, thus formed during inflammation, is toxic to microbes; however, it can also cause AHR. Nitrate can be generated from peroxidase-mediated RNS production.[54,240] SNOs are primarily formed during the late asthmatic response.[54,240] Thus, persistent increases in ROS and NO• lead to RNS formation and subsequent oxidation and nitration of proteins, which contributes to the dysregulation of airway inflammation in asthma.[15] NO• synthesis can reduce airway resistance mediated by increased production of the bronchodilator S-nitrosoglutathione (GSNO).[241–245] Two mechanisms to co-opt beneficial effects of NO• signaling are (1) shifting NO• to a more stable species, such as GSNO; or (2) reducing the local concentrations of ROS, potentially by augmenting the concentration of antioxidant enzymes in the extracellular space. Elevated NO• has also been attributed to the greater catabolic breakdown of the storage pools of GSNO during changes in the redox state of the lungs.[241–243] GSNOR, a glutathione-dependent formaldehyde dehydrogenase reduces GSNO to hydroxylamine, which is converted to NO by catalase.[245–247] GSNOR-deficient mice are protected from methacholine hyperreactivity following allergen sensitization and challenge, implicating GSNO in controlling airway hyperreactivity.[245–247]

High levels of ROS may overwhelm antioxidant defenses, causing significant loss of antioxidant activity in asthma.[8,67,70,213,217] Global loss of SOD activity, due to SOD deficiency, loss of circulating SOD activity, or inactivation of SOD via oxidative modification reflects the increased oxidative stress in asthmatic patients.[8,67,70,213,217] Oxidative modification-mediated reduction of catalase activity is also observed in asthmatics.[8] Although airway glutathione is increased in asthmatic patients, the ratio of oxidized to reduced glutathione is elevated reflecting an oxidizing microenvironment. Inhalation of exogenous ROS and RNS from exposures to environmental pollutants including ozone, diesel exhaust particles, and oxidant components of tobacco smoke, all contribute to additive oxidative stress, airway hyperreactivity, and inflammation in asthma.

EMPHYSEMA

Emphysema is a dominant phenotype of chronic obstructive pulmonary disease,[248–251] defined pathologically by airspace enlargement and destruction of alveolar septae.[248–251] Important contributing factors to the pathobiology of emphysema include inflammation, alveolar epithelial cell injury/apoptosis, protease–antiprotease and oxidant–antioxidant imbalances.[250–255] Inflammatory cells are recruited to the alveolar environment where they release elastases, cytokines, and oxidants that may then perpetuate the cycle of epithelial injury and inflammation.[250–255] In addition to inflammation, oxidative stress caused by cigarette smoke inhalation contributes to the pathogenesis of emphysema. Cigarette smoke contains $O_2^{\bullet-}$, •OH, and H_2O_2.[256] ROS are also generated by the chronic inflammation, characteristic of emphysema and that persists even after smoking cessation. Activated macrophages and neutrophils present in high numbers in the emphysematous lung are major producers of ROS.[257–262] Oxidative stress originating from constituents of cigarette smoke or products of inflammatory cells can overcome the antioxidative capacity of lung tissues and diminish antiprotease defenses.[263,264] A major consequence of oxidative stress is the activation of the transcription factor nuclear factor-κB (NF-κB), which activates transcription of proinflammatory cytokines.[251,263–265] Cigarette smoke also inhibits histone deacetylase, further promoting the release of proinflammatory cytokines.[266] Therefore, oxidant injury and lung inflammation act in concert to increase alveolar destruction or compromise maintenance and repair of alveolar structure. Antioxidant defenses are determinants of susceptibility to emphysema. A protective role for Nrf2, a transcription factor that regulates multiple critical antioxidant enzymes, has been identified in pulmonary emphysema.[267–270] SOD mimetics abrogate alveolar cell apoptosis and emphysema in mouse models.[271] This blockade of apoptosis prevents oxidative stress and emphysema further supporting the link between oxidative stress and apoptosis.[272,273]

PULMONARY FIBROSIS

Pulmonary fibrosis may result from a number of infectious and noninfectious injuries; by far, the most lethal form is idiopathic pulmonary fibrosis (IPF). IPF is characterized by exuberant ECM deposition, tissue contraction, and apoptosis resistance of (myo) fibroblasts, alongside apoptosis-prone and aberrantly differentiated alveolar type 2 cells.[18,274] This loss of epithelial–mesenchymal homeostasis and communication is central to the pathogenesis of IPF.[206,208] Myofibroblasts are key effector cells in tissue remodeling and fibrosis, typically contained in fibroblastic foci, which are a pathological hallmark of IPF. Chronic inflammation, aberrant wound healing, and degenerative aging processes have all been proposed as contributing to the pathogenesis of IPF.[275] Oxidative stress is common to these processes and is implicated in IPF pathogenesis.[276–278] Lung tissues and bronchoalveolar lavage fluid from IPF patients demonstrate a signature profile of oxidatively damaged proteins.[279–282]

NOX enzymes are a major source of ROS production in pulmonary fibrosis.[207,283–286] Several NOX isoforms, including NOX1,[287–289] NOX2,[290–293] and NOX4[209,285,294] have been implicated in tissue fibrosis. In addition to NOX enzymes, another potential source of ROS implicated in fibrosis is the mitochondria.[295,296] Epithelial cell death is a prominent feature in the IPF lung.[285,297,298] During acute lung injury in mice, NOX1-mediated ROS generation by endothelial and epithelial cells induces cell death.[299,300] NOX4 is expressed in hyperplastic alveolar type II cells in the lungs of IPF patients[294] and may mediate fibrogenic effects by promoting alveolar epithelial cell death.[214] NOX4-deficient mice are protected from bleomycin-induced pulmonary fibrosis through modulation of epithelial cell apoptosis *in vivo*.[214] EMT has been proposed to contribute to the accumulation of myofibroblasts in lung fibrosis.[301,302] ROS has also been shown to promote EMT.[303,304] A role for NOX4 in mediating

myofibroblast differentiation and lung fibrosis has been identified.[227] NOX4 mRNA expression is induced by the profibrotic cytokine, transforming growth factor-β1 (TGF-β1), while other NOX/DUOX isoforms were unaffected. NOX4-dependent generation of ROS, specifically H_2O_2, is required for TGF-β1–induced myofibroblast differentiation, ECM generation, and contractility of lung myofibroblasts.[209] Genetic or pharmacological targeting of NOX4 attenuates lung fibrogenesis in murine models of lung injury. Myofibroblasts from IPF patients also produce high levels of H_2O_2 in response to TGF-β1.[210] NOX4 may also contribute to pulmonary vascular remodeling associated with IPF.[305]

ROS generation from alveolar inflammatory cells, primarily neutrophils, and macrophages, may promote alveolar epithelial cell injury in IPF.[276,306] Mice deficient in NOX2 are protected from bleomycin-induced lung injury and fibrosis suggesting a role for inflammatory injury in this model.[307] The protection in $p47^{phox-/-}$ mice was accompanied by enhanced neutrophilic inflammation and MMP-9 activity.[307] Interestingly, airway neutrophils isolated from IPF patients exhibit elevated expression of $p47^{phox}$ and $p67^{phox}$,[308] supporting roles for the NOX2 isoform and neutrophilic inflammation in IPF. MMPs and tissue inhibitors of matrix metalloproteinases play a role in homeostasis and turnover of the ECM. In IPF, oxidation of the cysteine switch of MMPs by ROS activates the latent forms of MMPs.[210,276,309] ROS also regulates MMPs at the transcriptional level.[210,276,309] Thus, oxidative stress, from exogenous sources and multiple endogenous enzymatic sources, contributes to altered cellular homeostasis, including resident cells, recruited inflammatory cells, and their activated products.

PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) is a disorder of the pulmonary circulation characterized by endothelial dysfunction, intimal and smooth muscle proliferation.[310,311] Increased expression of ROS-generating enzymes, uncoupling of NOS enzymes, and mitochondrial dysfunction all contribute to the oxidative stress in PAH.[310,311] Upstream dysregulation of ROS/$NO^{\bullet}$ redox homeostasis impairs vascular tone, which then triggers the activation of antiapoptotic and mitogenic pathways, leading to cell proliferation and obliteration of the vasculature.[310,311]

ROS derived from the NOX2 and NOX4 isoforms contribute to the long-term responses of the pulmonary vasculature to hypoxia.[312–315] Increased NOX4 expression in pulmonary artery smooth muscle cells (PASMC) has been linked to hypoxia-dependent PAH in mice.[315] Levels of the NOX1 and 2 regulatory proteins, $p47^{phox}$, and Rac1 are increased in both the endothelial and SMC layers of pulmonary arteries[316–318] accompanied by an increase in NOX-derived $O_2^{\bullet-}$.[316–318] NOX-derived ROS is associated with medial thickening, disordered proliferation and migration, impaired angiogenesis, and disturbed fibrinolysis.[316–320] Another source of vascular ROS is xanthine oxidoreductases (XORs), including xanthine dehydrogenase (XD) and xanthine oxidase (XO). In PAH, XO activity dominates over XD activity and is a significant source of ROS production. XO is increased in idiopathic PAH patients compared with healthy controls.[320] In a rat model of chronic hypoxia-induced PAH, lung XO activity was enhanced and inhibition of XO activity with allopurinol reduced the right ventricular hypertrophy and the pulmonary vascular thickening.[316–319,321] Clinical studies have also demonstrated alterations of TGF-β1 expression in adult PAH patients.[322] In hypoxia-dependent PAH in mice, hypoxia increases the expression of TGF-β1 and NOX4 expression.[314,315] TGF-β–induced NOX4 expression and NOX4-mediated ROS production have been implicated in PASMC proliferation.[323,324] TGF-β1 also induces proangiogenic effects by upregulating VEGF.[325] In PASMCs, cyclic stretch induces VEGF expression, both at the mRNA and protein levels[326]; this is preceded by both an increased expression and secretion of TGF-β1 and an increase in ROS generation by the activation of NOX enzymes.[323,324] In models of spontaneously developing PAH, mitochondrial dysfunction and hyperpolarization is associated with reduction in ROS production.[327,328] Decreases in ROS inhibit a $O_2^{\bullet-}$ sensitive K^+ channel leading to pulmonary vascular constriction.[327–329]

Nitrosative stress with increased nitrated eNOS is an early contributor to the development of PAH.[316,330–333] The vasodilatory effects of cGMP are mediated through protein kinase G (PKG).[316,330–333] However, nitration of PKG, attenuates the kinetic activity of PKG, impairs vasodilation, and increases smooth muscle proliferation.[334] This nitration-dependent reduction in PKG activity is observed in lungs of patients with PAH.[334] Nitration of carnitine acetyltransferase, an enzyme that maintains normal mitochondrial function is another indicator of early nitrosative stress in PAH.[335]

Alterations in arginine metabolism have also been noted in models of PAH,[317] where the activity of arginase that catalyzes the hydrolysis of L-arginine to L-ornithine and urea is increased,[158,317,336,337] and the activity of the caveolar enzymes involved in the recycling of L-citrulline and other L-arginine byproducts back to L-arginine are attenuated.[158,317,336,337] Further, increased arginase activity is associated with formation of polyamines and L-proline, which promote smooth muscle cell growth and collagen synthesis. In addition, uncoupling of NOS enzymes occur when L-arginine becomes limited resulting in the production of ROS.[318,338–340] Therefore, high arginase activity may promote aberrant pulmonary vascular remodeling and neointima formation in PAH.[158,336,337]

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury and a syndrome of acute pulmonary inflammation.[341,342] ARDS is characterized by sudden onset, impaired gas exchange, and an increase in pulmonary capillary permeability.[341–343] Oxidative damage by ROS and RNS has been implicated in the pulmonary vascular endothelial damage that characterizes ARD. Several factors contribute to the intracellular and extracellular oxidant stress in ARDS patients.[341–343] The high inspiratory concentrations of oxygen required to achieve adequate arterial oxygenation, infection, or extrapulmonary inflammation lead to increased ROS production. This, combined with decreased antioxidant capacity of tissues resulting from consumption of the natural antioxidants leads to cellular damage and loss of vasomotor control.[341–343] Measurements of antioxidant concentrations have revealed an oxidant–antioxidant imbalance in ARDS patients. The production of toxic levels of ROS and RNS not only leads to damage of key molecules in cells but can signal changes in cellular responses such as proliferation, apoptosis, and necrosis.[341–343] H_2O_2 has been detected in the exhaled breath, while MPO and oxidized α1-antitrypsin have been detected in BAL of ARDS patients.[341–343] Nitration and oxidation of alveolar space proteins including the surfactants have been identified *ex vivo* in patient samples with ARDS.[341–343] Overabundance of ROS also induces adhesion molecules and cytokines that contribute to endothelial injury.

CONCLUSION

The lungs are exposed to exogenous oxidants from the environment, in addition to endogenous generation of ROS/RNS from resident and recruited inflammatory cells. Several measures of oxidative stress have been used to estimate oxidative stress within the lungs; however, current approaches do not adequately differentiate between different oxidative mechanisms and are used as biomarkers of oxidative damage. Further investigations are needed to discover biomarkers that correlate and differentiate between various types of oxidative injury. While progress has been made to delineate mechanisms through which oxidants initiate and propagate cell and tissue damage, specific signaling pathways and mechanisms of

activation are not well understood. Elucidation of these mechanisms may provide strategies for intervention to prevent or protect from disease pathogenesis or progression. A better understanding of factors that influence individual susceptibility will also be useful in risk stratification of patients. Investigations on how early life exposures to oxidants impact airway morphology, immune function, and the airway epigenome may also aid in determining susceptibility, disease expression, and progression.

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CHAPTER 28

Fibroblasts in Lung Homeostasis and Disease

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INTRODUCTION

Fibroblasts are the primary cellular source responsible for synthesis and remodeling of the extracellular matrix (ECM). These cells are in communication with the surrounding microenvironment and play a key role in lung homoeostasis. Following lung injury, fibroblasts are activated and undergo myofibroblast differentiation. Myofibroblasts are key effector cells for lung repair following injury. In addition to fibroblasts, perivascular pericytes and mesenchymal stem cells (MSCs) of bone marrow (BM) origins contribute to myofibroblast population. There is evidence that type II alveolar epithelial cells can differentiate into myofibroblasts in vitro through a process known as epithelial–mesenchymal transition (EMT); however, the role of EMT in fibrogenesis in vivo remains controversial. Myofibroblasts express α-smooth muscle actin (α-SMA), develop robust actin filaments (stress fibers), and acquire contractile activity. The function and behavior of myofibroblasts are regulated by both biochemical and physical cues in the surrounding microenvironment. The fate of myofibroblasts is a key determinant of whether an injury–repair response will resolve or progress into fibrosis. Destruction and aberrant remodeling of the ECM is a common feature of many lung diseases, including pulmonary fibrosis, asthma, chronic obstructive pulmonary disease (COPD), and lung cancer. Targeting myofibroblasts and tissue remodeling may provide a novel and effective strategy for treating a number of chronic lung diseases.

FIBROBLAST BASICS

WHAT ARE FIBROBLASTS?

Fibroblasts were described as early as in the late 19th century, based on their location and their microscopic appearance.[1] These are elongated cells that display a spindle-shaped morphology with extended cell processes.[2] Fibroblasts are ubiquitous in tissues and organs throughout the body and communicate with other cells such as epithelial cells (Fig. 28-1). Despite its discovery over a century, a reliable and specific molecular marker that identifies the fibroblast is currently lacking. Many indicators of fibroblast phenotype have been suggested in the previous studies (e.g., fibroblast-specific protein 1, vimentin, prolyl 4-hydroxylase, procollagen-Iα2, etc.).[3] However, none of them are specific to fibroblasts and/or are present in all fibroblasts. Currently, fibroblasts are identified by their ability to adhere to plastic, and their lack of markers that indicate other cell lineages. Clearly, better cellular markers with absolute specificity for fibroblasts will aid in the study of sources, differentiation, and phenotypic plasticity of fibroblasts.

Tissue-Specific Fibroblasts and Fibroblast Heterogeneity

Fibroblasts isolated from different tissues display a considerable degree of heterogeneity in phenotype and activity.[4] Such diversity is evident by divergent and specific gene expression patterns among fibroblasts isolated from distinct anatomical locations.[5] For example, fetal skin fibroblasts express high levels of collagen types I and V, whereas fetal lung fibroblasts lack collagen I and V expression.[5] Instead, fetal lung fibroblasts exclusively express lung-specific forkhead family transcription factors FOXF1 and FOXP1.[5] Tissue-specific fibroblasts may provide location-specific signaling for a given anatomic origin as well as important positional cues for wound healing and tissue regeneration. Besides the differences in fibroblasts from different anatomical sites, fibroblasts derived from a single tissue are often composed of subsets of different fibroblasts.[6] For example, fibroblast subpopulations isolated from lung differ in expression of surface markers such as Thy-1, cytoskeletal composition, lipid content, and cytokine profile.[7,8] Fibroblasts isolated from lungs with active fibrotic disease such as in the fibroblastic foci of human idiopathic pulmonary fibrosis (IPF) are morphologically and functionally distinct from fibroblasts isolated from normal lungs,[9] suggesting that selective

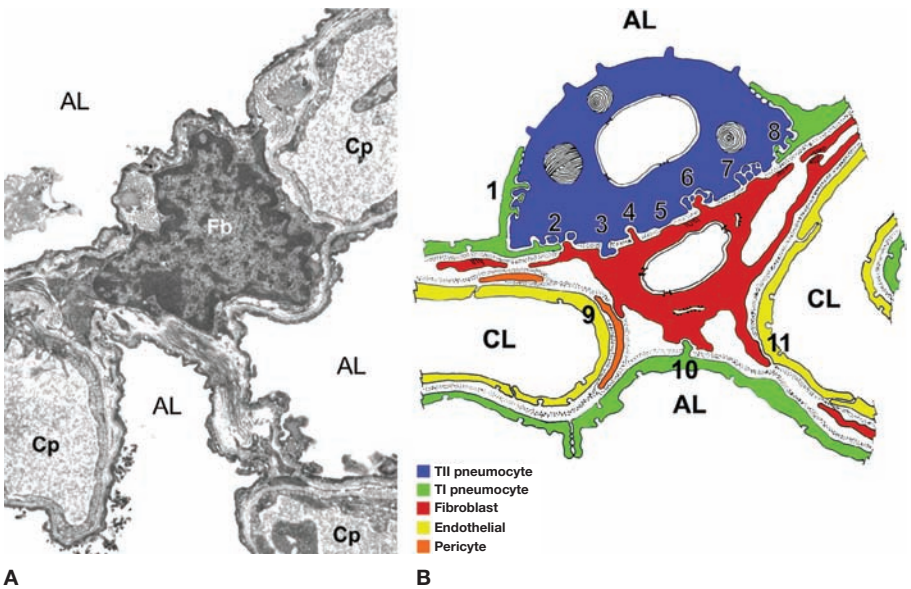

Figure 28-1 An interstitial fibroblast in the alveolar wall. **A.** A transmission electron microscopic image showing the structural organization of the alveolar wall in canine lung. Fb, fibroblast; Cp, capillary; AL, alveolar lumen; (**B**) summary of fibroblast *(red)* relationships with type I *(green)* and type II *(purple)* alveolar epithelial cells, capillary endothelial cells *(yellow)*, and pericytes *(orange)* in human and rabbit alveolar walls. *(Reproduced with permission from Burns AR, Smith CW, Walker DC. Unique structural features that influence neutrophil emigration into the lung. Physiol Rev. 2003;83(2):309–336.)*

expansion of specific fibroblast subsets is associated with the pathogenesis of this disease.

■ FIBROBLAST FUNCTIONS

The important functions of fibroblasts include deposition of ECM, regulation of inflammation, and wound healing.[10] Fibroblasts produce ECM-degrading proteases such as matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), supporting their crucial roles in regulating ECM turnover and homeostasis.[11]

ECM Production

One of the major functions of fibroblasts is the production of ECM. The ECM in the lung provides an essential scaffold on which cells can proliferate and differentiate. It also provides the lung with tensile strength and elasticity that are essential for ventilation. Lung ECM is composed of fibrillar proteins, glycoproteins, proteoglycans (PGs), and polysaccharides, each of which has distinct biochemical and biomechanical properties; these include collagens, elastin, fibronectin, PGs, hyaluronan (HA), laminin, vitronectin, and thrombospondin.[12] Type I and type III collagens are the most abundant collagens in the lung interstitium (ratio 3–6:1). Collagen IV is mainly localized to basement membranes. A fibroblast is estimated to synthesize approximately 3.5 million procollagen molecules/cell/day.[13,14] Depending on tissue type and age, 10% to 90% of synthesized procollagens are intracellularly degraded by lysosomal enzymes (e.g., cathepsins B, D, and L). It is postulated that regulation of procollagen-degrading rate may provide an important mechanism for rapid secretion of collagen in response to injury without de novo synthesis of new proteins.

Secretion of Proteolytic Enzymes and Inhibitors

The ECM is a dynamic structure that undergoes constant remodeling. Remodeling of the ECM is regulated by complex mechanisms including stimulatory and inhibitory mediators derived from resident cells in the local environment.[14] Fibroblasts synthesize a variety of proteolytic enzymes and inhibitors that enable them to control the assembly and turnover of the ECM. MMPs are either secreted by fibroblasts as inactive zymogens or anchored to the cell surface. Activation of MMPs occurs by disruption of interactions between the prodomain and the catalytic domain through either the proteolytic cleavage or the conformational change of the proenzymes.[15] MMPs function as proteinases that degrade most ECM proteins. Proteolysis of the ECM macromolecules by MMPs results in the release of cryptic fragments and neoepitopes that promote angiogenesis and cellular migration.[16,17] MMPs also have critical roles in the posttranslational regulation of other proteins including latent growth factors stored within the ECM, membrane receptors, and other proteases.[18] Hence, MMPs impact cell behavior both through modulation of cell–matrix interactions and through regulation of other signaling molecules. MMPs themselves are regulated by their endogenous inhibitors, TIMPs. TIMPs block MMP activity by noncovalently binding to the MMP active site. A tight balance between MMP proteolysis and TIMP expression is required for maintaining lung homeostasis.[19]

Innate Immune Function

Fibroblasts are capable of synthesizing many inflammatory cytokines that are initially thought to be exclusively produced by inflammatory cells.[20] Fibroblast-derived cytokines play an important role in the amplification and perpetuation of the immune response. Fibroblasts generate constitutive and cytokine-induced C-C and C-X-C chemokines that recruit inflammatory and immune cells to the injured cites.[21] Lung fibroblast–derived granulocyte macrophage colony–stimulating factor promotes the survival of eosinophils, which contributes to the fibrotic response in the lung.[22,23] Direct contacts between fibroblasts and T cells promote the production of adhesion molecules and cytokines by the T cells.[24] Interactions between fibroblasts and mast cells facilitate de novo production of eotaxin, a potent eosinophil chemoattractant.[25] The impact of interactions between fibroblasts and inflammatory cells are bidirectional. Th2 cells produce IL-4 that recognizes specific receptors on fibroblasts and modulates fibroblast proliferation and biosynthetic capacity.[26] Eosinophils release mitogens that augment fibroblast proliferation and collagen production.[27,28] Fibroblasts are the main producers of ECM proteins. Since ECM components affect multiple functions and properties of inflammatory and immune cells,[29,30] it suggests a further regulatory role of fibroblasts in innate immune response by the effects on the ECM.

Regulation of Tissue Interstitial Fluid Pressure and Microhemodynamics

Fibroblasts regulate tissue interstitial fluid volume, pressure, and microcirculation hemodynamics by generation of actomyosin-derived forces and transmission of the forces to the ECM via transmembrane integrins.[31] Such mechanical interactions between fibroblasts and matrix are subjected to modulation by soluble factors, such as PDGF that results in increased interstitial fluid pressure, and TNF-α that leads to decreased interstitial fluid pressure.[32,33] Fibroblasts express ecto-5′-nucleotidase (CD73) and soluble guanylyl cyclase (cGC) that affect hemodynamics,[34] suggesting a role of fibroblasts in the regulation of the microcirculation.

MYOFIBROBLASTS: EFFECTOR CELLS IN TISSUE REPAIR

■ HISTORICAL CONTEXT

Myofibroblasts were first identified as fibroblastic cells with a strong muscle cell–like contractile filamentous apparatus in the granulation tissue of healing wounds.[35] These cells are present in organs with increased remodeling, such as in development, inflammation, fibrosis, cancer invasion, and metastasis.[36] Myofibroblasts display prominent cytoplasmic actin microfilaments (stress fibers) (Fig. 28-2). They are connected to one another with adherens and gap junctions as well as to the ECM with focal adhesion (FA) complexes.[37] Myofibroblasts may be further classified into subtypes based on the presence or absence of vimentin, desmin, and/or α-SMA in cytoskeletal filaments. Expression of these proteins varies upon tissue types and is subjected to the regulation by environmental factors.[38] Alternatively, myofibroblasts can be simply classified into two subpopulations, proto-myofibroblasts and mature myofibroblasts.[39]

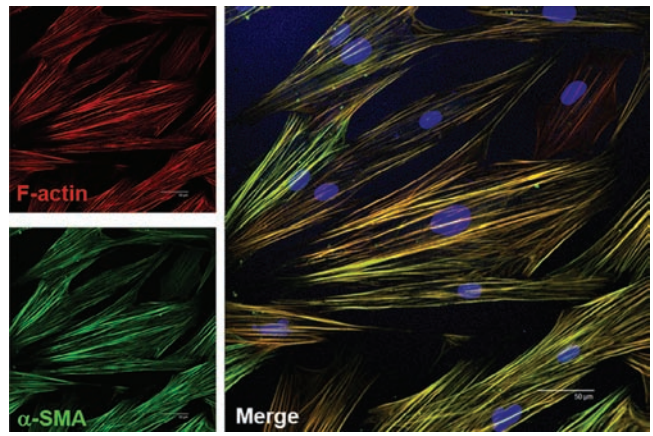

Figure 28-2 Myofibroblasts are characterized by de novo synthesis of α-SMA and incorporation of α-SMA into filamentous actin stress fibers. Scale bar: 50 μm.

TABLE 28-1 Myofibroblast Markers

Marker	Cellular Overlap
Cytoskeletal component	
α-SMA[40]	Smooth muscle cells
Desmin[41]	Hepatic stellate cells, cardiomyocytes
Cofilin[42]	Smooth muscle cells
GB 42-antigen[43]	Smooth muscle cells
Paladin 4Ig[44]	Smooth muscle cells
Tropomyosin-1[45]	Cardiomyocytes
Cell membrane receptor	
Angiotensin II type 1 receptor (AT1R)[46]	Cardiomyocytes, smooth muscle cells
Integrin $a_{11}b_1$[47]	Musculoskeletal cells
Thy-1[48]	Lipofibroblasts
Endosialin[49]	Cardiomyocytes, smooth muscle cells, adipocytes
Cadherin-11[50]	Tenocytes, endothelial cells, mesenchymal cells
Frizzled-2[51]	Smooth muscle cells
Extracellular protein	
Collagen I, III, IV, V, VI[52]	Various cells
Tenascin C[53]	Smooth muscle cells
Fibronectin ED-A[54]	Smooth muscle cells
Osteopontin[55]	Osteoblasts, osteocytes, chondrocytes
Periostin[56]	Preosteoblasts, cardiomyocytes

Proto-myofibroblasts are partly differentiated myofibroblasts that contain α-SMA–negative actin stress fibers, whereas mature myofibroblasts possess extensive network of α-SMA–positive stress fibers and large FAs (termed supermature FAs). α-SMA is the most widely used marker for identification of myofibroblasts (Fig. 28-2). In addition, studies have identified several other markers and modulators of myofibroblasts (Table 28-1). However, a specific and universal myofibroblast marker remains to be identified.

■ ORIGIN OF MYOFIBROBLASTS

The precise origin of myofibroblasts remains unsolved at present. Studies have suggested that local fibroblasts, perivascular pericytes, BM-derived MSCs, tissue MSCs, and epithelial/endothelial cells (through epithelial/endothelial–mesenchymal transition) are among potential cellular sources for myofibroblast population.

Resident Fibroblasts—Mesenchymal Stem Cells

Fibroblasts are the most widely accepted origin for myofibroblasts.[57,58] Fibroblasts influx into injured sites from the surrounding tissue and differentiate into myofibroblasts in response to extracellular stimuli including biochemical and physical cues.[59] These stimuli induce intrinsic changes in gene expression and stress fiber formation that characterizes myofibroblast differentiation.

MSCs that reside in tissues lack hematopoietic and leukocyte markers, but may express α-SMA.[60] Tissue MSCs have been described in the dermal sheath that surrounds the hair follicle facing epithelial stem cells.[61] These MSCs are involved in papilla regeneration and differentiate into myofibroblasts in response to environmental insults. It has been reported that MSCs from subcutaneous fat are responsible for collagen accumulation in scars.[62] Following lung injury, myofibroblasts were found to originate from perivascular and peribronchial sources.[63] It is likely that there are tissue MSCs in the human adult lung,[64] which become activated and undergo myofibroblast differentiation in response to lung injury. In support of this notion, a previous study has provided evidence for isolation of postnatal MSCs from different organs including liver, kidney, and lung.[65]

Pericytes

Pericytes are perivascular cells located on the abluminal side of endothelial cells in microvasculature.[66] These cells share developmental origins with fibroblasts, but differ from fibroblasts by the fact that pericytes anatomically connect with endothelial cells through cell processes within capillary basement membrane, whereas fibroblasts do not directly interact with endothelial cells.[67] The normal function of pericytes includes the regulation of vascular tone and blood flow through expression of contractile microfilaments (actin, myosin) and intermediate filaments (desmin, vimentin).[68] Microvascular pericytes differentiate into myofibroblasts in diffuse cutaneous systemic sclerosis, providing a link between microvascular damage and skin fibrosis.[69] Recent studies using the genetic fate-mapping approach have clearly demonstrated that pericytes are a major cellular source of myofibroblasts in animal models of acute injury to muscle, dermis, and kidney.[70,71] In addition, HSCs, pericyte-like cells in the liver, are the primary myofibroblast progenitors in mouse models of alcoholic and toxic liver fibrosis.[72]

Bone Marrow–Derived Mesenchymal Cells

BM-derived MSCs are self-renewable, multipotent progenitor cells with the capacity to differentiate into lineage-specific cells that form bone, cartilage, fat, tendon, and muscle.[73] Compared with hematopoietic stem cells, MSCs are more radio-resistant and reside mostly in BM stroma. BM-derived MSCs do not express hematopoietic markers and can be isolated as Lin-CD45-CD31-CD34-CD133-Sca-1+Vitamin A-cells.[74] In vitro evidence for a BM origin of myofibroblasts was first presented more than four decades ago. By plating BM cells on culture dishes, colonies consisting of cells exhibiting elongated or polygonal cytoplasm and clear nuclei were formed.[75] Transplantation studies using Y chromosome or green fluorescent protein (GFP) as a marker of donor cells provide in vivo evidence that (myo)fibroblasts in wounded skin, lung fibrosis, and intestinal fibrosis may derive from the BM.[76] There is evidence that monocytes may represent the major BM-derived cell population that contributes to myofibroblasts in fibrotic lesions, at least in some contexts.[77]

Circulating fibrocytes express markers of hematopoietic cells (CD34), leukocytes (CD11b, CD13, and CD45), and fibroblast products (collagens I, III, and fibronectin). These cells are distinguished from monocytes/macrophages, dendritic cells, and B cells by their lack of expression of specific markers for these cell lineages. Circulating fibrocytes migrate into injured tissues and have been identified in a number of fibrotic conditions.[78] Studies have identified the potential for fibrocytes to participate in wound healing and pathological scarring.[78,79] However, the direct contribution of fibrocytes to myofibroblast population during wound healing and fibrosis remains controversial. Evidence for and against fibrocyte-to-myofibroblast differentiation exists.[76,80] It is likely that instead of direct differentiation into myofibroblasts, circulating fibrocytes contribute to fibrosis by production of profibrogenic paracrine mediators that target resident cells.

Epithelial–Mesenchymal Transition

EMT refers to as a process through which fully differentiated epithelial cells lose their epithelial characteristics (e.g., apico-basal polarity, polygonal cell shape, and tight and adherens junctions) and acquire properties of mesenchymal cells (e.g., elongated cell shape, increased motility, and contractility). Epithelial cells undergoing EMT are characterized by downregulation of epithelial markers

(e.g., E-cadherin and ZO-1) and concomitant upregulation of mesenchymal markers (e.g., FSP1 and α-SMA) in the injured epithelium.[81] There is overwhelming evidence that primary epithelial cells cultured in vitro undergo EMT in response to a stimulatory input of soluble growth factors (e.g., TGF-β, EGF, and HGF) and/or ECM components (e.g., collagen).[82] However, the concept of in vivo fibrogenic EMT has been challenged by new epithelial lineage tracking studies in a variety of models of kidney, lung, and liver fibrosis in animals.[83]

FACTORS REGULATING FIBROBLAST ACTIVATION AND MYOFIBROBLAST DIFFERENTIATION

Fibroblasts isolated from the site of a healing wound or from fibrotic tissue secrete higher levels of ECM constituents and proliferate more than their normal counterparts isolated from healthy organs.[84] Such an increased activity is referred to as "fibroblast activation." Activated fibroblasts express α-SMA, leading to the term "myofibroblasts." Fibroblast activation and differentiation into myofibroblasts are regulated by various stimuli, including biochemical factors, biophysical cues from the ECM, and epigenetic modifications.

Growth Factor and Cytokine-Mediated Activation

Fibroblasts become activated by stimulation with cytokines such as TGF-β1, PDGF, and FGF2, which are released from injured epithelial cells, infiltrating mononuclear cells such as monocytes and macrophages as well as the ECM.[85–88] TGF-β1 is a pluripotent cytokine that plays a central role in the development of fibrosis. TGF-β1 is sequestered in a latent form (termed latent TGF-β1) in the ECM.[89] Latent TGF-β1 becomes activated in a spatially and temporally regulated fashion in response to injury.[89] Active TGF-β1 binds to its membrane receptors (TGF-βRI and TGF-βRII) and signals through both Smad-dependent canonical pathway and Smad-independent noncanonical pathway that promote fibrotic gene expression.[39] Active TGF-β1 also increases the assembly of stress fibers and FAs that are required for the development of cellular contractility.[39] In addition, prototypic cytokines produced by CD4+ T cells such as IL-13/IL-4 and IL-17 exert profibrotic effects on fibroblasts and play a crucial role in the development of fibrosis.[90,91]

Components of Vascular/Coagulation System

Coagulation proteases such as factor Xa and thrombin activate fibroblasts through receptor-mediated effects elicited by high-affinity thrombin receptor, proteinase-activated receptor (PAR)-1.[92] PAR-1 signaling promotes fibroblast proliferation via the autocrine production of PDGF and CTGF, and drives fibroblast differentiation into myofibroblasts via αvβ5-dependent TGF-β activation.[93,94] Thrombin upregulates expression of the fibrinolysis inhibitor, plasminogen activator inhibitor (PAI)-1, resulting in increased fibrin matrix.[95] Fibrin matrix inhibits surfactant function and contributes to alveolar collapse and traction of remaining airspaces (honeycombing).[92] Lysophosphatidic acid (LPA), a platelet-derived molecule during blood coagulation, promotes fibroblast activation and pulmonary fibrosis by activation of latent TGF-β1 through LPA receptor.[96] Endothelin-1 (ET-1), an activator of extrinsic coagulation cascade, exerts potent mitogenic and profibrotic effects on fibroblasts.[97] Transgenic mice expressing human ET-1 transgene have been shown to develop progressive pulmonary fibrosis.[97]

Reactive Oxygen Species

Accumulating evidence indicates that oxidative stress and reactive oxygen species (ROS) production, mainly in the form of superoxide and hydrogen peroxide, play a significant role in myofibroblast differentiation.[98] The NAD(P)H oxidases of the Nox family have been identified as the enzyme system that is primarily responsible for ROS generation by fibroblasts in response to injury and are recognized as key mediators of myofibroblast differentiation and matrix accumulation in lung fibrosis.[99] Nox4, the most abundant Nox isoform in the lung, has been characterized as a "constitutively active" enzyme, meaning that the enzymatic activity of Nox4 is primarily regulated at the level of gene expression. TGF-β1 increases Nox4 expression and ROS production in lung fibroblasts, which mediates TGF-β1–dependent myofibroblast differentiation.[99] A similar mechanism for myofibroblast differentiation has been demonstrated in cardiac fibroblasts, renal fibroblasts, and mesangial cells.[100,101] Nox4 is also associated with TGF-β1–induced cellular contractility in lung myofibroblasts and cytoskeletal remodeling in vascular smooth muscle cells as well as endothelial cells.[99,102,103] Together, these results indicate that Nox-derived ROS regulate fibroblast morphology, contractility, and differentiation.

Mechanical Stress

Fibroblasts respond to mechanical cues, including externally applied forces, interstitial fluid flow, and matrix rigidity sensed through internally generated forces. Externally applied forces such as stretch provoke diverse fibroblast signaling responses, including activation of mitogen-activated protein (MAP) kinases, [104]Akt,[105] and focal adhesion kinase (FAK). It has been shown that stretch augments TGF-β release and signaling, and promotes the myofibroblast phenotype.[106,107] The continuous interactions between cell-generated forces and the resistance of matrix to cellular forces strengthen cell–matrix contacts and develop α-SMA–positive stress fibers characterizing myofibroblast differentiation.[39,108] Normal lung fibroblasts grown on polyacrylamide gels with a stiffness grade similar to fibrotic lungs undergo myofibroblast differentiation.[109] The effects of matrix stiffening on myofibroblast differentiation may occur through TGF-β–dependent intrinsic and/or TGF-β–independent extrinsic mechanotransduction (see Section "Mechanotransduction in Myofibroblastsinsser").[109,110] Interstitial fluid flow induces fibroblast proliferation, collagen alignment, and fibroblast-to-myofibroblast differentiation in the absence of exogenous mediators.[111,112] $\alpha_1\beta_1$ integrin appears to play an important role in the specific response to interstitial fluid flow.[111] Taken together, these results suggest that fibroblasts are mechanosensitive and are programmed for matrix production, contraction, and differentiation in the presence of mechanical stimuli.

Epigenetic Regulation

The findings that specific signatures of gene profile in myofibroblasts are "memorized" over passages suggest that epigenetic modifications may be involved in the regulation of myofibroblast differentiation.[113] Epigenetic regulation of myofibroblastic phenotype involves DNA methylation, histone modification, and sequence-specific microRNAs (miRNAs). DNA methylation at CpG islands is associated with expression of myofibroblast marker α-SMA in lung cells. Type II alveolar epithelial cells that do not express α-SMA exhibit high levels of methylation at the three CpG islands in the regulatory regions of ACTA2 gene encoding α-SMA protein, whereas lung (myo)fibroblasts exhibit significantly low levels of DNA methylation at these sites.[114] Inhibition of DNA methyltransferase (DNMT) induces α-SMA expression, whereas overexpression of DNMT suppresses α-SMA expression in lung fibroblasts.[114] Inhibition of DNA methylation activates PPARγ and NF-κB, transcription factors known to suppress ACTA2 gene expression,[115] suggesting that modifications of DNA methylation may also indirectly regulate α-SMA expression by inactivation of PPARγ and NF-κB. Histone acetylation has been shown to regulate myofibroblast differentiation. It has been shown that histone deacetylase (HDAC)4 is an essential epigenetic regulator of TGF-β1–induced skin fibroblast-to-myofibroblast differentiation.[116] HDAC8 binds to α-SMA and the binding is likely to regulate actin cytoskeleton–derived cellular contractility.[117]

miRNAs are single-stranded RNA molecules that target multiple mRNAs and induce silencing of multiple transcripts. It has been shown that miR-21 mediates TGF-β1–induced lung myofibroblast differentiation by targeting Smad7, a major inhibitor of TGF-β signaling.[118] In contrast, downregulation of miRNA let-7d expression by TGF-β results in increased mesenchymal gene expression (e.g., ACTA2) in multiple epithelial cell lines, indicative of EMT.[119] miR-132 inhibits MeCP2 and PPARγ expression, resulting in enhanced α-SMA expression in lung fibroblasts.[115]

Other Factors

Wnt ligands induce fibroblast activation and collagen synthesis.[120] β-catenin, a transcription factor and a downstream signal transducer of Wnt signaling, was found to accumulate in the nuclei of cells located in the fibroblastic foci of IPF lungs.[121] Selective inhibition of β-catenin–mediated transcription attenuates lung fibrosis in bleomycin-induced mouse model.[122] These studies suggest a crucial role of the Wnt/β-catenin signal in fibroblast activation and lung fibrosis. Integrins have been implicated in the differentiation of proto-myofibroblasts into mature myofibroblasts.[123] Integrin $\alpha_5\beta_1$ is associated with α-SMA expression in differentiating myofibroblasts.[123] Large clusters of $\alpha_5\beta_1$ are present in the FAs of mature myofibroblasts.[123]In addition, environmental stimuli including hypoxia and hyperglycemia as well as direct contacts between fibroblasts and leukocytes have been reported to be associated with fibroblast activation.[124,125]

■ MECHANICAL ASPECTS OF MYOFIBROBLASTS

Myofibroblast Contractility

Acquisition of contractility similar to smooth muscle cells is a defining feature of myofibroblasts. Myofibroblasts generate intracellular contractile forces by ATP-powered sliding of actin–myosin filaments.[126] Compared with Ca^{2+}-regulated rapid and reversible contraction in smooth muscle cells, myofibroblast contraction is relatively slow, sustained, and nonreversible.[127] Myofibroblast contractility is primarily regulated by the Rho family of small GTPases (Rho, Rac, and Cdc42) and their downstream targets, primarily myosin light-chain kinase (MLCK) and myosin light-chain phosphatase (MLCP).[39] α-SMA expression and incorporation of α-SMA into stress fibers contribute to myofibroblast contractility.[128] However, the mechanism by which α-SMA regulates myofibroblast contractile force formation is not clear. Myofibroblast contractility facilitates a normal wound healing process by limiting and closing the exposed surface area of the wound. Myofibroblasts disappear from the wound site when a normal repair process is successfully completed. The persistence of myofibroblasts is associated with aberrant wound repair and leads to tissue fibrosis/scarring. Increasing evidence suggests that myofibroblast contractility may provide a feed-forward mechanism (known as mechanotransduction; see Section "Mechanotransduction in Myofibroblasts") that sustains fibrosis. Inhibiting myofibroblast contractility by targeting Rho/Rho kinase (ROCK)/actin cytoskeleton signal pathway selectively activates mitochondria-dependent intrinsic apoptotic pathway in myofibroblasts and ameliorates bleomycin-induced mouse lung fibrosis.[129]

Sensing Matrix Stiffness

The ECM in healthy organs has well-defined mechanical properties that fall within a physiological range.[130] Changes in matrix stiffness that occur in pathological states, such as fibrosis and cancer, have profound effects on cell morphology, proliferation, migration, and gene expression.[130] Characterization of the mechanical properties of normal and fibrotic lung matrix demonstrates increased matrix rigidity in both human IPF and experimental models of lung fibrosis.[131,132] It is believed that protein cross-linking enzymes such as lysyl oxidase (LOXL2) and tissue transglutaminase (TG2) and/or matrix-degrading enzymes such as MMPs regulate the stiffness of ECM, although the precise mechanisms remain to be determined. Fibroblasts sense changes in matrix stiffness by cell–matrix adhesions.[133] Transmembrane integrins at FAs act as direct mechanosensors on the cell membrane by providing a physical link between intracellular actin cytoskeleton and the ECM. The cytoplasmic domain of integrins interacts with signaling molecules at the FA sites (e.g., FAK and c-Src). Thus, integrins also act as indirect mechanosensors to regulate cell function and behavior by modulating FA signals.[134] Matrix stiffness sensing depends largely on cellular contractility and actin cytoskeleton integrity. Fibroblast contractility generates cytoskeletal tension that serves to transmit mechanical information from the ECM. Disruption of actin cytoskeleton–mediated contractility blocks matrix stiffening–induced myofibroblast differentiation.[109]

Mechanotransduction in Myofibroblasts

Mechanotransduction is a process in which cells sense mechanical stimuli and convert mechanical signals into biochemical signals. Recent studies suggest that mechanotransduction in myofibroblasts with prolonged survival/resistance to apoptosis may provide a feed-forward mechanism for progression of fibrosis, as in IPF. It has been reported that lung myofibroblast contraction promotes latent TGF-β activation, the most potent fibrogenic cytokine characterized to date, in the extracellular compartment (Fig. 28-3).[110,135] In this process, the actomyosin apparatus in myofibroblasts generates contractile forces that are transmitted across the cell membrane to the ECM. The force transmission results in a conformational change of the ECM-bound latent TGF-β1 complex, resulting in the release/exposure of active TGF-β1 from the latent complex. The finding suggests an extrinsic mechanotransduction pathway in which mechanical forces derived from intracellular stress fibers are transduced to the ECM and converted into TGF-β1 fibrogenic signal capable of regulating fibrosis.

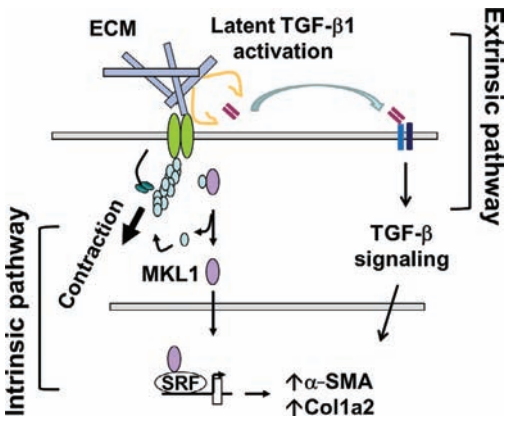

Figure 28-3 Contractile forces promote myofibroblast differentiation via intrinsic and extrinsic mechanotransduction pathways. In the intrinsic mechanotransduction pathway, mechanical stimuli from stiff/fibrotic ECM promote G-actin polymerization into F-actin. This results in the release of MKL1 and its nuclear translocation. MKL1 binds to serum response factor (SRF) in the nucleus to form a transactivation complex and activates fibrotic gene expression that specifies myofibroblast differentiation. In the extrinsic mechanotransduction pathway, actomyosin-generated contractile forces pull against stiff/fibrotic ECM. This results in a conformational change of latent TGF-β1 complex, which releases active TGF-β1 from the latent molecule. Active TGF-β1 then binds to its receptors on the cell membrane and initiates TGF-β signaling that promotes fibrotic gene expression.

In contrast to TGF-β–mediated extrinsic mechanotransduction pathway, an intrinsic mechanotransduction pathway in which the myofibroblast contractile signal is converted into a nuclear signal by transcription factor coactivator megakaryocytic leukemia protein (MKL)1 (also known as MAL/MRTF-A) has also been identified (Fig. 28-3).[109] MKL1 is a serum response factor (SRF) coactivator that constitutively binds to monomeric G-actin in the cytoplasm.[136] In response to matrix stiffening, normal lung fibroblasts undergo extensive actin cytoskeletal remodeling and develop contractile forces. This changes actin cytoskeletal dynamics that favors G-actin polymerization into F-actin. Polymerization of G-actin into F-actin results in the release of MKL1 from G-actin. The liberated MKL1 enters into nucleus, where it binds to SRF and targets to the CArG sequence in the promoter region of ACTA2 gene and col1a2 gene, leading to gene activation.[137] TGF-β neutralizing antibody does not block MKL1-mediated α-SMA expression,[109] suggesting that MKL1-mediated intrinsic mechanotransduction is independent of TGF-β–dependent extrinsic mechanotransduction. In addition to sensing mechanical stimuli, integrins are important mechanotransducers that allow bidirectional transduction and conversion of external forces into intracellular response (outside-in signaling) and internal forces (e.g., stress fiber-derived contractile forces) into extracellular and/or FA signals (inside-out signaling).[39,138] Besides integrins, stretch-activated ion channels, receptor tyrosine kinases (RTKs), CD44, and syndecan-4 are potential mediators of mechanotransduction as well.[139–142] However, mechanical stress may also regulate gene expression in fibroblasts through mechanotransduction-independent mechanisms. It has been shown that cyclic strain increases the mRNA level of tenascin-C within 1 hour in cultured fibroblasts[143] and this induction does not require synthesis of new proteins.[144]

Myofibroblasts in Tissue Homeostasis and Wound Repair

Myofibroblasts play a role in the regulation of differentiation and homeostasis of adjacent epithelia. Such mesenchymal–epithelial interactions are crucial for morphogenesis and organogenesis.[145] Myofibroblasts regulate epithelia by secretion of soluble growth factors and production of basement membrane molecules.[146]

Myofibroblasts play important roles in both normal and aberrant wound repair. As mentioned earlier, myofibroblast contractility facilitates wound closure. During the resolution phase, myofibroblasts produce MMPs and TIMPs that change the local microenvironment from a balance favoring ECM deposition to matrix degradation.[147] Interconnected gap junctions of myofibroblasts allow the electrical signals created by cyclic ion movements to be transmitted through the syncytium and the length of the resident organ.[148] Myofibroblasts sustain their activated state in fibrosis/hypertrophic scarring even when the initial insults have regressed. Myofibroblasts in such a sustained state of activation continue to secrete ECM constituents, growth factors, and cytokines. These result in a self-perpetuating autocrine loop that further stimulates myofibroblast differentiation and prevents normal resolution of tissue injury. In addition to fibrosis/hypertrophic scars, diseases associated with myofibroblastic phenotype include inflammatory pseudotumors, cancer metastasis, and neoplastic transformation of the myofibroblasts themselves.

■ THE FATE OF MYOFIBROBLASTS

The fate of myofibroblasts is a key determinant between normal repair and fibrosis. In normal wound healing, myofibroblasts gradually disappear after wounds are closed. Persistent myofibroblast differentiation is associated with pathological wound healing and fibrosis. Understanding of the physiological clearance of activated fibroblasts is particularly important for developing therapeutic strategies for persistent/progressive fibrosis such as IPF.

Apoptosis

Apoptosis has been suggested as an intriguing possibility for the elimination of myofibroblasts from healing wounds and reversible fibrosis.[149] An earlier study has observed that myofibroblasts undergo apoptosis in granulation tissue on which a vascularized skin flap is grafted.[150] Reduced growth factor and increased MMP expression appear to link to myofibroblast cell death.[151] In addition, disruption of cell–matrix interactions using RGD peptides or soluble fibronectin promotes myofibroblast anoikis, a type of apoptosis that is induced by inadequate or inappropriate cell–matrix interactions.[152] In reversible liver fibrosis, HSC-derived myofibroblasts undergo apoptosis in parallel to the reduction of the total number of HSCs in the recovery phase.[153] Hepatic myofibroblast apoptosis appears to occur by a Fas ligand (APO-1/CD95)–mediated extrinsic pathway.[153] Pharmacological inhibition of ROCK inhibits actin polymerization, downregulates the constitutive expression of antiapoptotic protein, Bcl-2, in IPF lung myofibroblasts; this results in release of cytochrome *c* from mitochondria, triggering mitochondria-dependent intrinsic apoptosis pathway. Furthermore, Fasudil-induced myofibroblast apoptosis ameliorates bleomycin-induced lung fibrosis in mice.[129] This study indicates that targeting mechanosensitive signaling in myofibroblasts may offer an effective approach for treatment of fibrotic disorders (Fig. 28-4).

Dedifferentiation

A recent study showed that HSC-derived myofibroblasts regress to a more quiescent state upon the removal of the fibrogenic stimuli in a carbon tetrachloride–induced mouse model of liver fibrosis.[72] The finding suggests that reversion of myofibroblasts to a more quiescent phenotype may be a second possibility for the clearance of these cells. However, such quiescent HSCs are reactivated more rapidly (in comparison to native HSCs) by subsequent insults, and result in more robust liver fibrosis,[72] suggesting that myofibroblast regression may be an intermediate step toward the resolution of fibrosis. Although regression to an inactive precursor cell may limit the activity of myofibroblasts, this does not appear to completely eliminate the potential for reactivation.

Senescence

Cellular senescence is associated with the loss of the ability of cells to replicate their genome and enter permanent growth arrest in the G1/G0 cell-cycle phase.[154] Although senescent fibroblasts do not respond to mitogens, they remain metabolically active and are resistant to apoptosis. Cellular senescence often occurs by telomere shortening and subsequent activation of p53 and p21 and/or inactivation of pRB and activation of p16.[154] Senescence may also be triggered by other forms of cellular damage, including oxidative stress, DNA damage, and oncogene activation.[154] Myofibroblast senescence has been proposed as an antifibrotic mechanism by limiting the proliferative capacity of fibrogenic fibroblasts and/or by modulating the cellular microenvironment.[155,156] However, this basic assertion is inconsistent with the clinical observation of an increased risk of fibrotic disease with advancing age. This highlights the complexities of cellular senescence in tissue injury repair processes, and supports the concept that the plasticity and fate of senescent cells may be altered with aging which, ultimately, determines the outcome of the tissue repair response.

MYOFIBROBLASTS IN LUNG DEVELOPMENT AND DISEASE

■ ALVEOLOGENESIS

Lung development is a complex process involving reciprocal interactions between mesoderm-derived mesenchyme and endoderm-derived epithelium. Alveolar myofibroblasts are present during alveologenesis, but absent in the adult lung.[157] Myofibroblasts surround

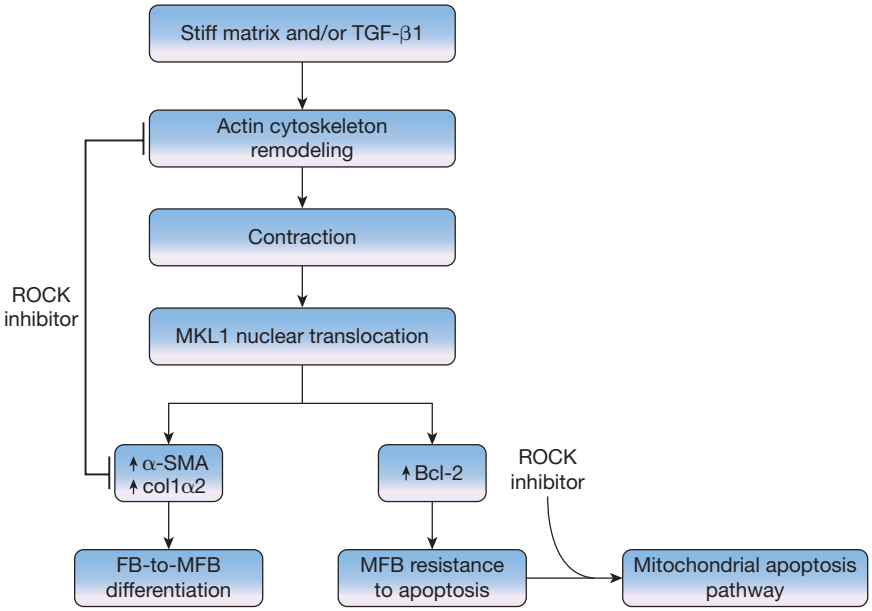

Figure 28-4 Mechanosensitive signaling in myofibroblasts as a target for antifibrotic therapy. In response to extracellular biomechanical and biochemical stimuli, such as matrix stiffness and active TGF-β1, lung fibroblasts undergo actin cytoskeleton remodeling and activation of the actomyosin contractile system, which result in MKL1 translocation from cytoplasm to the nucleus, where it activates fibrogenic genes that specify myofibroblast differentiation. Inhibition of ROCK blocks actin cytoskeletal reorganization, fibroblast acquisition of contractile activity, and MKL1 nuclear translocation, preventing fibroblast-to-myofibroblast differentiation. Inhibition of ROCK activity disrupts the actin cytoskeleton required for myofibroblast contractility. This deactivates constitutively activated MKL1 signaling in myofibroblasts, resulting in downregulation of the antiapoptotic protein, Bcl-2, and activation of the intrinsic apoptotic pathway.

the distal lung epithelial tubules and buds in the pseudoglandular stage of lung development. The absence of alveolar myofibroblasts is associated with deficient secondary septation and the failure of alveolar development.[158] Although alveolar myofibroblasts play an essential role in the morphogenesis of pulmonary alveolar septa, mechanisms involved in the regulation of alveolar myofibroblast survival and clearance in the process of alveologenesis are poorly understood and need further investigation.

■ PULMONARY FIBROSIS

Pulmonary fibrosis is characterized by excessive synthesis and deposition of ECM proteins in the lung parenchyma, resulting in deficient gas exchange. IPF is the most common and lethal diffuse fibrosing lung disease, with a mortality rate that exceeds that of many cancers. Currently, there is no FDA-approved pharmacological therapy for patients with IPF. The pathogenesis of IPF remains elusive. The current paradigm posits that repeated alveolar epithelial injury and persistent myofibroblast activation are central to the progression of IPF.[159] Regardless of the origins, myofibroblasts isolated from IPF lungs have increased migratory activity, ability to deposit ECM, and prolonged survival/resistance to apoptosis compared to their normal counterparts.[159] Abnormal myofibroblast survival is a key determinant of whether fibrosis will progress or resolve.[160] The survival of IPF myofibroblasts has been found to be regulated by multiple antiapoptotic signals.[48] These include enhanced responsiveness to growth factors and fibrotic cytokines; impaired cyclooxygenase-2 expression and consequential reduction in prostaglandin E2 production; decreased caveolin 1 (CAV1) and PTEN expression; and increased antiapoptotic protein expression as well as signals from the extracellular microenvironment. Myofibroblasts isolated from fibrotic lungs induce cytotoxic effects on epithelial cells. Coculturing of myofibroblasts with lung epithelial cells results in epithelial cell apoptosis by FAS–Fas ligand (FAS–FasL)-dependent and -independent mechanisms.[161,162] Epithelial cell apoptosis can cause further lung injury that augments lung fibrosis. Myofibroblasts produce cytokines and growth factors that signal to the epithelium, resulting in damage to the alveolar basement membrane that prevents reepithelialization.[163] Myofibroblast-produced chemokines promote the recruitment of immune cells and fibrocytes that actively participate in fibrotic progression.[164,165]

■ ASTHMA

Airway remodeling in patients with asthma encompasses the structural alterations that lead to persistent airflow limitation. Both smooth muscle cells and (myo)fibroblasts have been implicated in the pathogenesis of airway remodeling in asthmatic airways. In asthmatic patients, susceptibility to injury and aberrant repair responses result in fibroblast activation and myofibroblast differentiation, leading to subepithelial fibrosis.[166] Reduced airway remodeling in antileukotriene therapy is due, in part, to diminished myofibroblasts in asthmatic airways.[167] Viral infections are major triggers of acute asthma exacerbations.[168] The susceptibility to viral infections in asthmatic patients is not limited to epithelial cells. Rhinoviruses have been detected in subepithelial cells including fibroblasts, likely due to the disrupted and inflamed epithelium.[169] Fibroblasts from asthmatic patients have enhanced abilities for replication of rhinoviruses and subsequent production of IL-6 and IL-8, resulting in vigorous proinflammatory responses.[170] TGF-β augments rhinovirus replication in fibroblasts isolated from asthmatic patients.[171]

■ EMPHYSEMA

Emphysema is characterized by the progressive destruction of pulmonary alveoli. A vast majority of cases of pulmonary emphysema is associated with chronic lung injury induced by cigarette smoke. Chronic smoke exposure induces inflammation, protease/antiprotease imbalance, oxidative stress, and death of bronchiolar and alveolar epithelial and endothelial cells.[172] Cigarette smoke reduces lung fibroblast proliferation and migration, and induces fibroblast apoptosis.[173,174] In addition to the cytotoxic effects, cigarette smoke inhibits elastin synthesis and cross-linking in fetal lung fibroblasts.[175,176] Interactions between fibroblasts and alveolar epithelial cells are greatly reduced in the emphysematous lung,[177] suggesting that the repair and regeneration function of fibroblasts are impaired. Emphysema fibroblasts display features of myofibroblast differentiation and senescent phenotype characterized by enlarged morphology and cell-cycle arrest.[178,179]

■ NON–SMALL-CELL LUNG CANCER

Carcinoma-associated fibroblasts (CAFs) constitute a major portion of reactive tumor stroma. CAFs express α-SMA and high levels of collagens and ED-A FN, indicating that these cells are of myofibroblast characteristics.[180] CAFs are responsible for dense ECM deposition around tumors and thus have been considered as a defense mechanism for tumor growth. In established tumors,

CAFs synthesize cytokines/growth factors (e.g., TGF-β1) and ECM-degrading proteases (e.g., MMPs) that promote angiogenesis, recruitment of inflammatory cells, cancer cell proliferation, invasion, and metastasis.[3] CAF-associated prognostic factors have been identified in non–small-cell lung cancer (NSCLC). In adenocarcinomas, carbonic anhydrase IX expression has been found a better prognostic predictor in CAFs than in cancer cells.[181] Expression of podoplanin, a lymphatic endothelial cell marker, in CAFs is associated with shorter survival in patients with NSCLC.[182] In squamous cell carcinomas, MMP-2 expression in CAFs is found to be a significant unfavorable prognostic factor.[183] While expression of PDGF-B, PDGF-C, and PDGFR-α in cancer cells is associated with a negative prognosis, expression of PDGF-A, PDGF-B, PDGF-D, and PDGFR-α in CAFs is favorable prognostic indicators.[184] In addition, it has been found that stromal expression of PDGF-B, PDGF-D, and PDGFR-α is associated with less nodal metastasis.[185] Clinical prognostic values of TGF-β and FGF in NSCLC have been evaluated in the previous studies.[186–189] Due to the conflicting results, the prognostic roles of TGF-β and FGF2 in NSCLC remain uncertain.

TARGETING MYOFIBROBLASTS AND MATRIX REMODELING FOR LUNG DISEASE THERAPIES

Tissue remodeling in response to injury is a common pathological feature observed in many lung diseases including IPF. Dysregulation of fibroblast function and matrix metabolism are crucial to the aberrant injury repair in IPF lungs. Currently, there are no treatments that specifically target myofibroblast-associated pathologies in IPF.

Pirfenidone inhibits fibroblast proliferation and collagen synthesis and attenuates bleomycin-induced lung fibrosis in mice.[190,191] Two randomized, double-blinded placebo-controlled trials for pirfenidone in patients with IPF (CAPACITY) have been recently completed.[192] In one trial, pirfenidone showed a significant reduction in FVC decline at all study timepoints in patients with IPF compared to the placebo control. In the other trial, an apparent pirfenidone effect on predicted FVC change in IPF patients was observed until week 48. However, the difference between groups was not significant at week 72. These data suggest that pirfenidone has a favorable benefit risk profile and represents a potentially effective treatment for IPF.

PDGF is a potent mitogen and chemoattractant for fibroblasts and induces procollagen production by fibroblasts in vitro. Targeting PDGF receptor with imatinib mesylate, a tyrosine kinase inhibitor, has been shown to prevent bleomycin-induced mouse lung fibrosis.[193] However, a randomized, placebo-controlled trial showed that imatinib does not improve survival or lung function in patients with mild to moderate IPF.[194]

TGF-β1 is the most potent inducer of fibroblast ECM production characterized to date and promotes fibroblast to myofibroblast differentiation. Several types of pharmacotherapy to block TGF-β have been developed including antibodies, soluble receptors, intracellular signaling pathway inhibitors and agents that target the cell surface receptors for TGF-β (TGF-βRI/II).[195,196] A phase I clinical trial with TGF-β–neutralizing antibody (Genzyme) has begun in patients with IPF. Orally active TGF-βRI kinase inhibitors have been shown to attenuate bleomycin-induced mouse lung fibrosis.[197] Since TGF-β has important homeostatic functions in the regulation of immune response and tumor suppression, therapeutic strategies that directly blocks TGF-β may yield undesirable side effects. Alternatively, targeting latent TGF-β activation has become a more favorable approach for the antifibrotic therapy. Integrins are important mediators for in vivo activation of latent TGF-β.[198] $\alpha_v\beta_6$ integrin plays the primary role in regulating epithelial latent TGF-β1 activation.[199] Mouse studies have shown that inhibition of $\alpha_v\beta_6$ integrin blocks bleomycin- and radiation-induced lung fibrosis and this integrin is also abnormally regulated in human fibrotic diseases.[199] Stromedix, a humanized monoclonal antibody to integrin $\alpha_v\beta_6$, is currently in phase II clinical trial in IPF. $\alpha_v\beta_5$ integrin regulates mechanical tension–induced latent TGF-β1 activation in lung (myo)fibroblasts.[110] This integrin is coexpressed with α-SMA–positive myofibroblasts, but absent on hyperplastic epithelial cells in the fibroblastic foci in IPF.[200] The GPI-linked Thy-1 blocks mechanical tension–induced latent TGF-β1 activation, presumably by disruption of the binding of latent TGF-β1 with $\alpha_v\beta_5$ integrin.[135]

Inhibition of excess ECM generation, deposition, and stabilization, and increasing matrix degradation has become important targets for pharmacological therapy. Cytokines including CTGF, PDGF, ET-1, and IGF can induce fibroblast/myofibroblast activation and regulate matrix production. Inhibition of all of these cytokines can inhibit pulmonary fibrosis in a variety of in vivo models of fibrosis.[90,201–203] MMPs including MMP-1, 3, 7 among others have been implicated in the pathogenesis of pulmonary fibrosis,[204] although the exact role of the MMPs in the pathogenesis of pulmonary fibrosis remains not known. Matrix cross-linking enzymes are responsible for the regulation of ECM stabilization. Cross-linking makes matrix potentially more resistant to degradation and may favor fibrosis progression. TG2 induces the cross-linking of collagen and fibronectin, resulting in stabilization of the matrix.[205] TG2 is elevated in many forms of human and murine pulmonary fibrosis.[205] Inhibition of the extracellular cross-linking function of TG2 results in inhibition of ECM generation and cross-linking in the lung.[205] Irreversible inhibitors of TG2 have been developed and are available from several commercial sources. LOXL2, another matrix cross-linking protein, catalyzes the first step in the formation of cross-links in collagens and elastin.[206] LOXL2 cross-links fibrillar collagen, making it more resistant to homeostatic turnover. LOXL2 is induced by TGF-β and is upregulated in IPF.[207,208] Administration of a monoclonal anti-LOXL2 antibody (AB0023) in either a prophylactic manner or a therapeutic manner significantly attenuates bleomycin-induced fibrosis in mice.[208] Phase II clinical studies utilizing the LOXL2 inhibitor GS-6624 are currently carrying out for patients with primary sclerosing cholangitis, nonalcoholic steatohepatitis, and cirrhosis secondary to hepatitis C and/or HIV.

CONCLUSION AND PERSPECTIVES

The understanding of the physiology and pathophysiology of fibroblasts has greatly advanced in the past few decades. It has become increasingly clear that fibroblasts and myofibroblasts play important roles in human health and disease. Despite this, many fundamental questions remain to be answered. The origins of myofibroblasts remain to be clarified. It is not known whether myofibroblasts of various origins exhibit different characteristics and functions in the injury and repair process. Identification of specific markers for fibroblasts will allow their specific isolation and more precise characterization, both in vitro and in vivo. In addition, specific markers could facilitate genetic animal studies allowing the specific targeting of these cells. The independent and interactive roles of cytokines, ECM, and mechanical forces in the regulation of the structure and function of fibroblasts and myofibroblasts need to be characterized.

The identification of myofibroblasts as key cells and potential targets in fibrotic diseases such as IPF has led to the concept that targeting these cells may be a promising approach for disease therapy. Interesting approaches that target myofibroblasts and the ECM include termination of myofibroblast persistence by inducing their apoptosis or their reversion to nonfibrogenic cell phenotypes, interference with collagen cross-linking and ECM stiffening by controlling the activities of protein cross-linking enzymes (e.g., LOXL2 and TG2), and the use of miRNAs as potential therapeutic targets. We believe that these novel approaches will eventually lead to more effective treatments for patients with fibrotic lung diseases.

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PART 3

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CHAPTER 29

Approach to the Patient with Respiratory Symptoms

Michael A. Grippi
Robert M. Senior
Jeffrey P. Callen

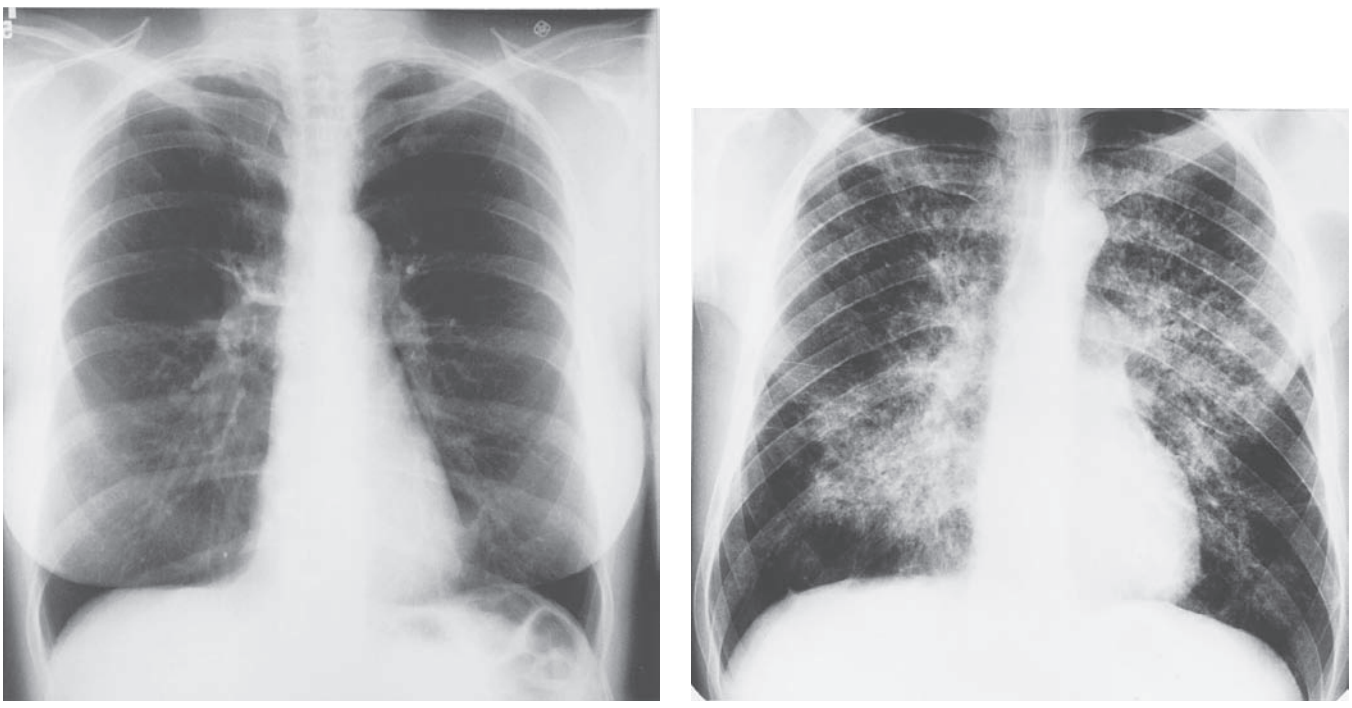
The most common respiratory complaints prompting medical evaluation are shortness of breath and cough. Less frequent are hemoptysis and thoracic pain. As in any medical assessment, a detailed history and thorough physical examination are of paramount importance. Use of plain chest radiography for routine screening, once popular in the hope of uncovering silent disease amenable to therapy, is not routinely employed, as it has not been proven to decrease mortality or to be cost effective. Chest radiography is now usually reserved for patients who have clinical manifestations of thoracic disease; serial chest radiographs often provide invaluable clues regarding the underlying problem. More sophisticated imaging techniques, including computed tomography (CT),[1,2] along with tests of lung function, help complete the clinical picture.

HISTORY

Although seasoned clinicians may be adept at quickly spotting telltale diagnostic clues, a comprehensive medical history is central to patient evaluation. The history should include a detailed inventory of exposure to air-borne substances that may result in lung injury. One of the most common offenders is cigarette smoke. An attempt should be made to quantify the exposure.

Often, the workplace is the site where toxic air is inhaled. An almost forgotten exposure to a toxic inhalant 20 years ago may explain certain types of pulmonary or pleural diseases. Symptoms that appear to improve during weekends or other periods away from work may be a clue to an occupational exposure that causes a respiratory ailment. A newly installed home humidifier or an air conditioning system that incorporates stagnant pools of water can point the way to resolving a mysterious illness. Brief residence in an area where either cryptococcosis (southwestern United States) or histoplasmosis (southern and midwestern United States) is endemic may help clarify the nature of an illness that mimics tuberculosis. A recent visit to a South or Central American country may bring into focus a more remote possibility (e.g., South American blastomycosis) (Fig. 29-1).

The history should include a thorough evaluation of prior and current medical problems. Rheumatologic disorders, such as systemic sclerosis (scleroderma), may be associated with interstitial lung disease, aspiration pneumonia due to esophageal involvement, or pulmonary vascular disease. Certain malignancies often metastasize to the lung (e.g., breast or colon carcinoma), or predispose to development of venous thromboembolism (e.g., pancreatic carcinoma). Infection with the human immunodeficiency virus (HIV) should not be overlooked, since pulmonary complications are often



A B

Figure 29-1 Exposure in an endemic area. **A.** Clear lung fields. **B.** South American blastomycosis. *(Used with permission of Dr. Nelson Porto.)*

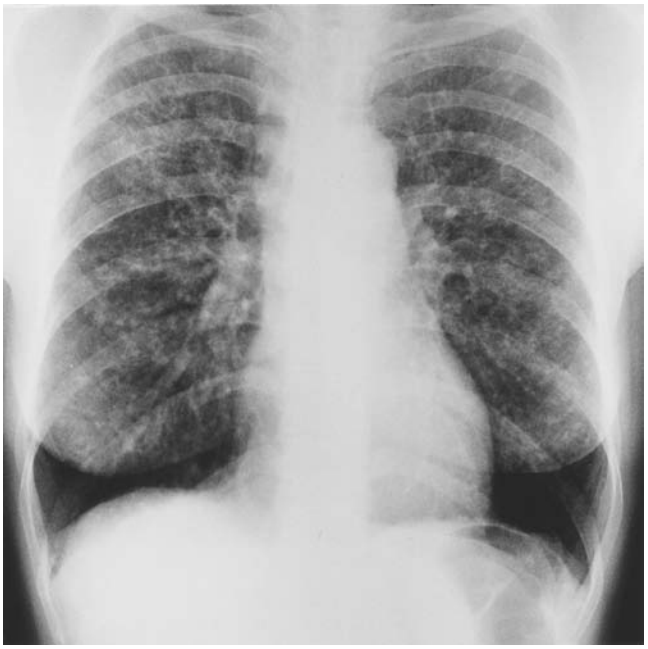


Figure 29-2 Nitrofurantoin hypersensitivity pneumonitis. The ingestion of nitrofurantoin was accompanied by the appearance of patchy interstitial and alveolar changes throughout both lungs.

the initial presentation of acquired immunodeficiency syndrome (AIDS). Other causes of immunodeficiency, such as hematologic malignancy, or prior administration of chemotherapeutic agents, should heighten suspicion of infection as the cause of respiratory symptoms, as well as potential pulmonary drug toxicity.

Indeed, many pharmacologic agents, including chemotherapeutic and nonchemotherapeutic agents, have a propensity for inflicting lung damage (see Chapters 65 and 66). Classic examples include bleomycin, nitrofurantoin, and methotrexate (Fig. 29-2). Beta blockers, administered as part of a cardiac regimen, may evoke bronchoconstriction. Even a common medication, such as aspirin, may, on rare occasion, cause a severe pulmonary disorder (e.g., pulmonary edema).

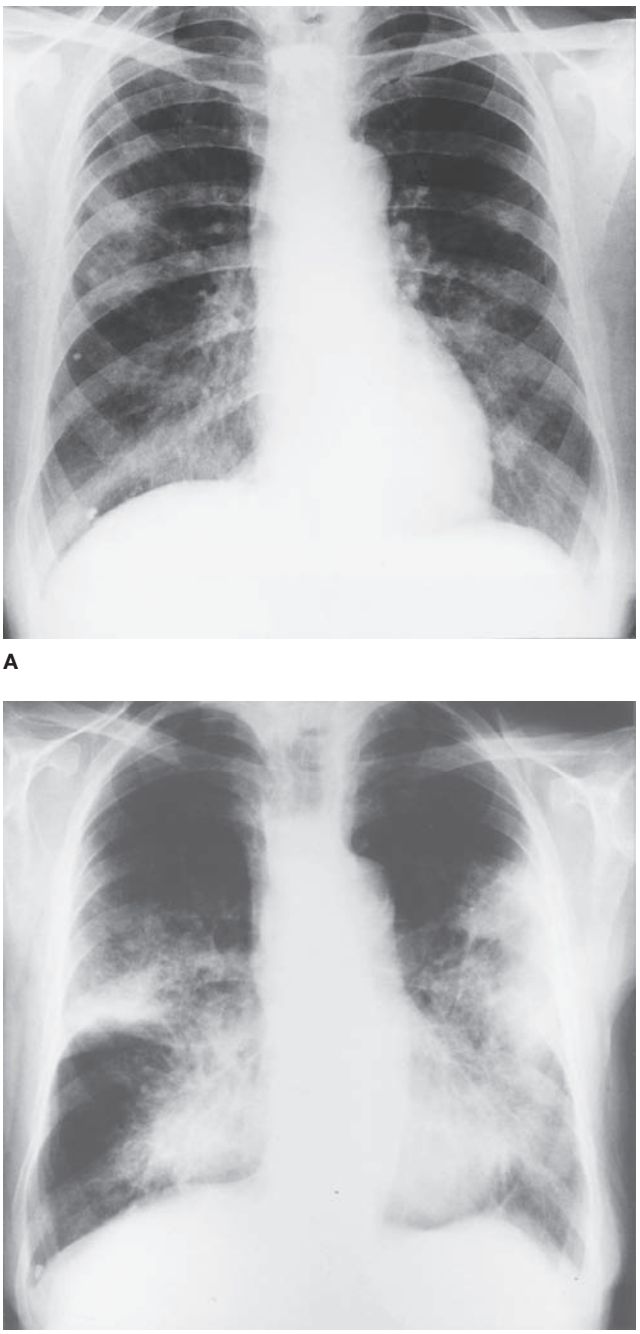
Finally, the family history is an essential ingredient of the medical inventory. This history can uncover a heritable disease of the lungs (e.g., cystic fibrosis [CF], α_1-antitrypsin deficiency, alveolar microlithiasis, and hereditary telangiectasia).

PHYSICAL EXAMINATION

Before the widespread use of chest radiography, physical examination, along with the history, played a pivotal role in the diagnosis of pulmonary disease. The advent of chest radiography and chest CT imaging has de-emphasized the value of the physical examination. Nonetheless, the physical examination remains a valuable diagnostic measure in the appraisal of chest disease.[3,4]

GENERAL ASPECTS

Important clues are often available before examination of the chest. For example, neglected pyorrheal teeth raise the prospect of necrotizing aspiration pneumonia. A lacerated tongue suggests that a convulsive episode may have led to aspiration (Fig. 29-3). Pursing of the lips during expiration ("pursed-lip breathing") may be seen in patients with chronic obstructive pulmonary disease (COPD). Subtle changes in consciousness or coordination may signal that metastasis has occurred to the brain from a primary carcinoma of the lung. In the patient with COPD, a clouded sensorium or a disturbed personality can signify acute elevation in arterial P_{CO_2}.



A

B

Figure 29-3 Chronic aspiration pneumonia. **A.** Chronic aspiration pneumonia in a 72-year-old man hospitalized for repair of hernia. Patchy infiltrates bilaterally. No pulmonary symptoms. Initiating cause was achalasia of esophagus. **B.** Eighteen months later. Persistent cough and breathlessness.

Inspection of the skin often provides clues to diseases of the chest; a more detailed discussion of notable cutaneous manifestations in respiratory disorders is provided later in this chapter. Evidence to support the diagnosis of pulmonary sarcoidosis may be found in the eyes and skin. Petechiae, purpura, necrosis, and/or ulceration of the skin may reflect a systemic vasculitis. The skin lesions of neurofibromatosis type 1 (von Recklinghausen disease) may signify that a solitary pulmonary nodule in the paraspinal region may be a neurofibroma. A minute skin abscess may turn out to be the source of multiple lung abscesses. Distinctive scars over the antecubital veins of a drug addict can help to clarify the etiology of old lesions

TABLE 29-1 Clinical Disorders Commonly Associated with Clubbing of Digits

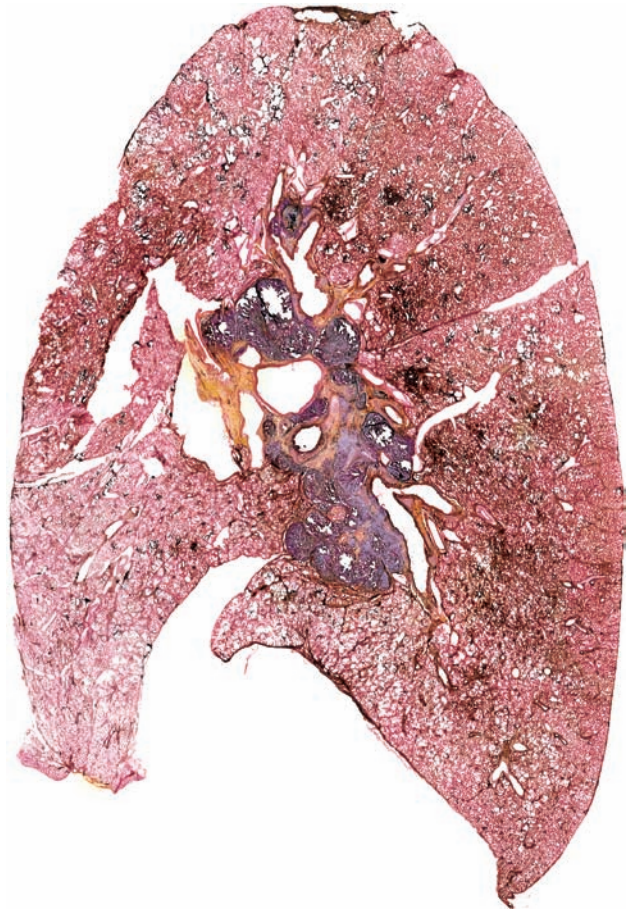
Pulmonary and thoracic
Primary lung cancer
Bronchiectasis
Cystic fibrosis
Lung abscess
Pulmonary fibrosis
Pulmonary arteriovenous malformations
Empyema
Mesothelioma
Neurogenic diaphragmatic tumors
Cardiac
Congenital
Subacute bacterial endocarditis
Gastrointestinal and hepatic
Hepatic cirrhosis
Chronic ulcerative colitis
Regional enteritis (Crohn's disease)

in the lungs, as well as of a newly discovered lung abscess. Erythema nodosum (EN) is frequently due to sarcoidosis, but may also occur in patients with tuberculosis, histoplasmosis, or coccidioidomycosis. Skin papules in Birt–Hogg–Dube syndrome (see Pulmonary-Cutaneous Syndromes, below) may antedate the pulmonary manifestations of cystic lung lesions and pneumothorax by decades.[5]

A variety of endocrine syndromes may accompany carcinoma of the lung. An altered mental status may be due to hyponatremia caused by the syndrome of inappropriate antidiuretic hormone (SIADH). Clubbing of the digits may accompany various clinical disorders, including idiopathic pulmonary fibrosis, bronchiectasis, and certain carcinomas of the lung (Table 29-1).[6] A puffy face, neck, and eyelids, coupled with dilated veins of the neck, shoulder, thorax, and upper arm (i.e., superior vena cava syndrome) may constitute the first clinical evidence of obstruction of the superior vena cava by a neoplasm of the lung. Although the causes of superior vena cava syndrome are many and diverse, at least 80% are attributable to a primary carcinoma of the lung (Fig. 29-4). In the patient in whom a neoplasm has evoked acute signs and symptoms of increased systemic venous pressure that progresses rapidly (e.g., to laryngeal edema), early diagnosis and prompt treatment of the neoplasm can be lifesaving. The presence of Horner syndrome – unilateral ptosis, miosis, and anhidrosis – in a patient with a carcinoma of the lung suggests a pulmonary sulcus tumor with involvement of the ipsilateral sympathetic pathway within the thorax (Fig. 29-5).

■ INSPECTION OF THE CHEST

Observation of the chest from the foot of the bed can be informative: a visible lag in expansion of one side of the thorax localizes a pleural effusion, pulmonary infection, or paralyzed diaphragm. The respiratory pattern may be informative: patients with severe airflow obstruction often take slow, deep breaths, whereas rapid and shallow breaths are often seen with restrictive processes, such as interstitial lung disease or kyphoscoliosis. Inspection of the chest and abdomen in the supine position may reveal paradoxical inward movement of the abdomen, indicative of respiratory muscle weakness.[7]



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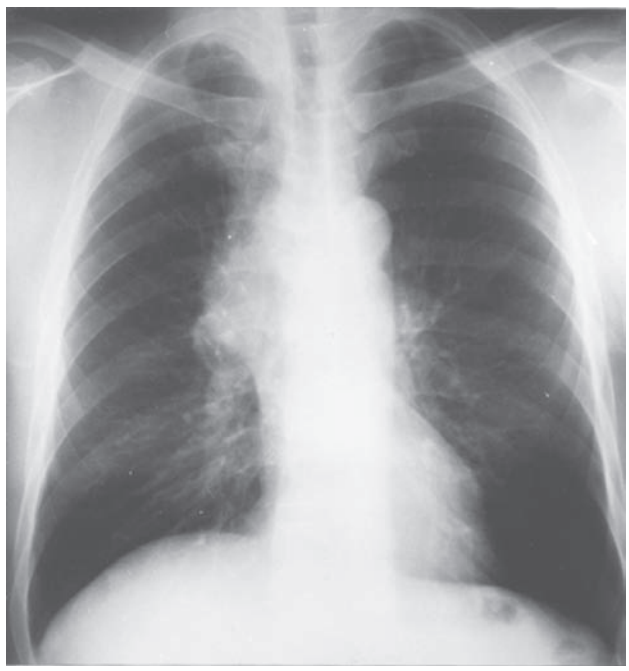
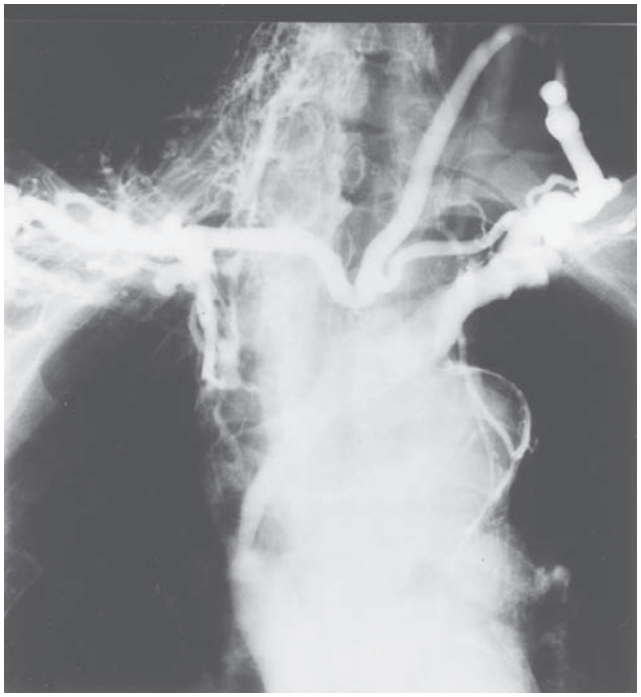


B

Figure 29-4 Local invasiveness of carcinoma of the lung. **A.** Sagittal section of the lung illustrating a carcinoma *(blue)* of the lung in the vicinity of the hilus. **B.** Chest radiograph showing right hilar mass.



C

Figure 29-4 *(Continued)* **C.** Angiogram showing obstruction and extensive collateral circulation.

PALPATION OF THE CHEST

Over the years, the role of palpation in examination of the chest has been considerably devalued. Nonetheless, palpation may provide helpful diagnostic clues as well as confirmatory evidence for other physical signs. For example, the position of the trachea determined by palpation in the suprasternal notch may be helpful in detecting a lateral displacement of the upper mediastinum. Displacement of the apical impulse and of cardiac dullness may be useful indices in detecting shift of the lower mediastinum.

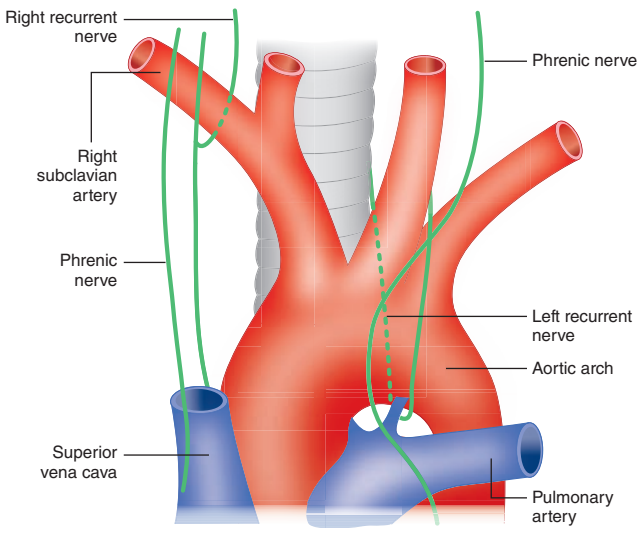


Figure 29-5 Courses of the recurrent laryngeal nerves. Invasion or compression of a nerve by a carcinoma of the lung causes paralysis of the vocal cord.

Tenderness over a rib may reflect a fracture, metastasis, or underlying pleuritis. Enlargement of the right ventricle can be readily detected by palpation in the subxiphoid region. *Hoover sign* may be useful in disclosing a unilateral lag in motion of one side of the chest due to pleuritis or a pleural effusion. The sign is elicited by comparing the displacement from the midline during a patient's deep inspiration of the examiner's hands, each placed lightly over one hemithorax, with thumbs touching beneath the xiphoid at the start of the breath.

An abnormal mass or fullness palpated in the supraclavicular space may be a clue to a neoplasm or an involved lymph node and suggests a convenient location to obtain a biopsy for diagnosis.

Consolidation of the lung, which causes increased transmission of sound, can be detected as fremitus (i.e., as a palpable vibration) over the affected area while the patient repeatedly vocalizes the traditional "one, two, three" as the examiner moves his or her palms systematically over the two hemithoraces. Conversely, impairment of sound transmission, as by a pleural effusion, diminishes vocal fremitus. In some instances, a pleural friction rub is palpable.

PERCUSSION OF THE CHEST

Percussion as part of the physical examination follows Auenbrugger sounding of beer barrels to determine their fluid levels. The response to percussion is impaired whenever something other than air-filled lung lies directly beneath the chest wall. Common causes of dullness to percussion are consolidation or atelectasis of the lung, fluid in the pleural space, pleural thickening, and a large mass at the surface of the lung. Widespread hyperresonance may be elicited in emphysema, and circumscribed hyperresonance over a pneumothorax or large bulla.

AUSCULTATION OF LUNGS

Ever since the time of Laennec, physicians have applied a stethoscope to the chest in search of sounds of disease.[8] Attention is focused on the intensity and quality of the sounds, as well as on the presence of abnormal (often called "adventitious") lung sounds.[9] Other devices have been used to assess sounds generated by breathing.[10,11] Web sites providing access to audio files demonstrating normal and adventitious breath sounds are available (e.g., www.easyauscultation.com/lung-sounds.aspx).[12]

Changes in the Intensity and Duration of Lung Sounds

The generation of lung sounds requires an ability to move air through patent airways. A global decrease in the intensity of breath sounds over the thorax or a hemithorax may be due to a variety of abnormalities: impaired movement of air due to airways disease (e.g., in emphysema), paralysis of a diaphragm, or complete obstruction of a bronchus. A decrease in audible breath sounds may also occur when the transmission of sounds to the chest wall is impaired (e.g., by a pleural effusion, pleural thickening, or a pneumothorax). A bulla gives rise to a more circumscribed diminution in breath sounds. In a patient with COPD, regional variations in breath sounds correspond to the distribution of ventilation. With adequate pressure of the diaphragm of the stethoscope, it is possible to auscultate the lungs as effectively through thin clothing as over bare skin; of course this approach hinders inspection and percussion.[13]

An abnormal increase in intensity of breath sounds is accompanied by a change in their character (the sounds become either harsh or bronchial). The abnormal sounds are heard over consolidated, atelectatic, or compressed lung as long as the airway to the affected portion of the lung remains patent. Consolidated lung is presumed to act as an acoustic conducting medium that, unlike normal lung, does not attenuate transmission of tracheal sounds to the periphery.

Noting the duration of the inspiratory and expiratory phases of breathing may be useful. Inspiration is normally audible for a longer period, with little, if any, expiratory noise. A prolongation of expiration, often longer than inspiration, is found with obstructed airways.

Changes in the Transmission of Lung Sounds

Changes in voice sounds are often easier to appreciate than changes in breath sounds. Large pleural effusions, pneumothorax, and bronchial occlusion produce distant or inaudible breath sounds. Transmission of voice sounds is enhanced by consolidation, infarction, atelectasis, or compressions of lung tissue. Accompanying the increased transmission is a change in the character of the voice sounds that causes them to be higher pitched and less muffled than normal *(bronchophony)*. When bronchophony is extreme, spoken words assume a nasal or bleating quality *(egophony)* and the sound "ee" is heard through the stethoscope as "ay."[14] Egophony is most common when consolidated lung and pleural fluid coexist; sometimes it is heard over an uncomplicated lobar pneumonia or pulmonary infarction. Transmission of whispered voice sounds with abnormal clarity *(whispered pectoriloquy)* has the same significance as bronchophony.

Changes in the Quality of Lung Sounds

Normal breath sounds have a smooth, soft quality and are described as *vesicular*. Abnormal, or adventitious, lung sounds have traditionally been resistant to meaningful clinical classification. However, a rational, clinically useful set of definitions based on acoustic analysis of tape recordings and the nomenclature introduced by Forgacs is commonly employed (Table 29-2). Using this approach, lung sounds are categorized as continuous (*wheezes*, *rhonchi*, or *stridor*) or discontinuous *(crackles)*.

Wheezes, rhonchi, and stridor are musical adventitious sounds. Wheezes originate in airways narrowed by spasm, thickening of the mucosa, or luminal obstruction. Although wheezes are more apt to occur during forced expiration (which further narrows airways), they may occur during both inspiration and expiration in asthma. Wheezes presumably originate through a combination of limitation to airflow and vibrations in the walls of the airways. Rhonchi are due to the presence of liquid or mucus in the airways; the quality and location may be readily changed by asking the patient to cough, thus moving the secretions. Stridor is predominantly inspiratory and best heard over the neck. Common causes of stridor are a foreign body in the upper intrathoracic airway or esophagus, an acquired lesion of the airway (e.g., carcinoma in adults), or a congenital lesion in children.

Crackles are generally attributed to a rapid succession of explosive openings of small airways that closed prematurely during the previous expiration.[15] Crackles have been subdivided according to their timing during inspiration (early or late) and by differences in their quality ("wet" or "dry"); at times they have been termed "*rales*." Noting differences in timing has been advocated as a way of distinguishing between possible causes (e.g., "dry" crackles in the fibrosis of interstitial lung disease vs. "wet" crackles in pulmonary edema).[16] Unfortunately, wide variation in the interpretation of these sounds generally renders such attempts at classification of little value and often a cause of confusion. Crackles may accompany alterations in the elastic recoil of airways (emphysema), the presence of secretions (bronchitis or pneumonia), inflammation or fibrosis (interstitial lung disease), or fluid (pulmonary edema). Crackles may also be due to atelectasis, as noted in bedridden patients, and may clear with sequential deep breaths.

TABLE 29-2 Classification of Common Lung Sounds

Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Discontinuous, interrupted explosive sounds; loud, low in pitch	Coarse crackle	Coarse rale
Discontinuous, interrupted explosive sounds; less loud than above and of shorter duration; higher in pitch than coarse crackles or rales	Fine crackle	Fine rale, crepitation
Continuous sounds longer than 250 ms, high-pitched; dominant frequency of 400 Hz or more, hissing sound	Wheeze	Sibilant rhonchus
Continuous sounds longer than 250 ms, low-pitched; dominant frequency about 200 Hz or less, snoring sound	Rhonchus	Sonorous rhonchus

Source: Adapted with permission from Loudon R, Murphy RLH. Lung sounds. Am Rev Respir Dis. 1984;130(4):663–673.

Pleural Rub

A pleural friction rub is a coarse, grating, or leathery sound that is usually heard late in inspiration and early in expiration; most often a pleural friction rub is audible low in the axilla or over the lung base posteriorly. The rub sounds close to the ear and usually is not altered by coughing.

DYSPNEA

Dyspnea is the medical term for breathlessness or shortness of breath.[17] The American Thoracic Society has published a comprehensive discussion of the topic.[18] For the patient, dyspnea involves an experience of discomfort in breathing. It is alarming to most and may arouse great concern about a potential dire cause, making it one of the most frequent complaints prompting patients to seek medical evaluation.

In the extensive medical, physiologic, and psychological literature, dyspnea is used variously to designate a variety of sensations, ranging from awareness of breathing on the one hand to respiratory distress on the other. The wide range of meanings is understandable on several counts: (1) dyspnea is a subjective complaint without consistency in objective signs such as tachypnea; (2) few physicians have experienced the respiratory discomfort associated with chest disease, so that most interpretations of the complaint represent extrapolations from normal breathlessness (e.g., after strenuous exercise); (3) most experimental observations relating to dyspnea are based on the study of normal subjects or animals under artificial circumstances; and (4) most physicians apply the term loosely, based on their experience with the predominant patient population that they serve (e.g., patients with COPD or asthma). Despite this variability, in clinical medicine, the complaint of dyspnea almost invariably implies respiratory discomfort.

Because of its subjective nature, the sensation of dyspnea is an amalgam of two components. The first is the sensory input to the cerebral cortex, which consists of information from specialized receptors, predominantly mechanoreceptors, at various sites in the respiratory apparatus (predominantly the upper airways) and face (Fig. 29-6). The different sites of stimulation may contribute to disparities in the sensation. Furthermore, no specific area in the central nervous system (CNS) has been identified as the sensory locus for dyspnea. The input – from airways, lungs (via the vagus nerves), respiratory muscles, chest wall, and chemoreceptors – is processed at consecutive levels of the nervous system (i.e., spinal cord and supraspinal regions en route to the sensorimotor cortex). Additional sensory input, triggered by inadequate oxygen delivery or utilization, is poorly understood. The second component is the perception

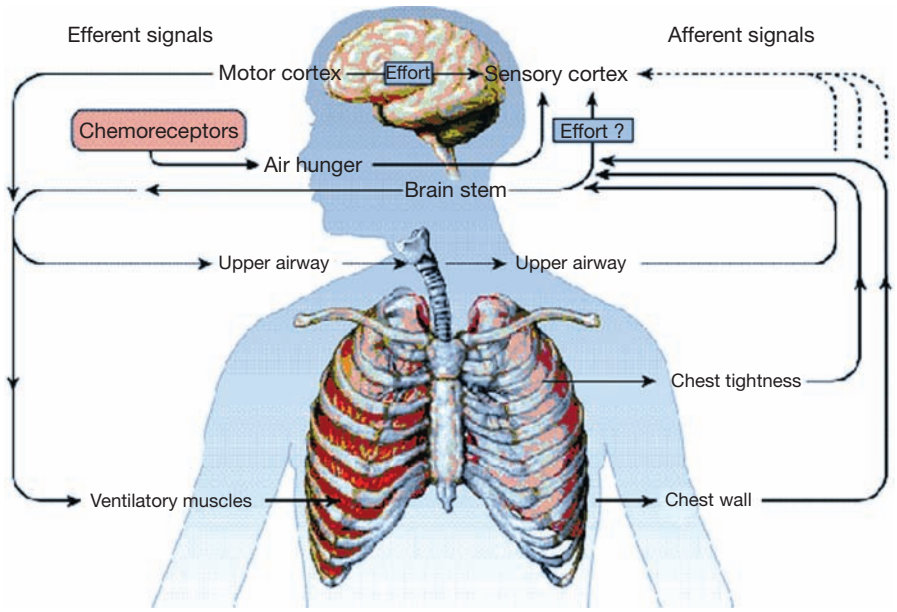


Figure 29-6 Pathways to the sensation of breathlessness. Respiratory effort is believed to originate as a signal transmitted from the motor cortex simultaneously to the sensory cortex and to the motor command to ventilatory muscles. The brain stem may also contribute to the sense of effort. The perception of air hunger is believed to arise, in part, from increased respiratory activity within the brain stem, whereas the sensation of chest tightness probably results from stimulation of vagal irritant receptors. Although afferent information from airway, lung, and chest-wall receptors most likely passes through the brain stem before reaching the sensory cortex, the *dashed lines* indicate uncertainty about whether some afferents bypass the brain stem and project directly to the sensory cortex. *(Reproduced with permission from Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med. 1995;333(23):1547–1553.)*

of the sensation, which rests heavily on the interpretation of information arriving at the sensorimotor cortex. The interpretation depends greatly on the psychological makeup of the person.

A variety of influences may modify the psychological component of dyspnea. During "Kussmaul breathing" (see below), "air hunger" may seem obvious to the observer, even though the patient does not feel short of breath. In contrast, patients with congestive heart failure or COPD frequently volunteer the complaint of "air hunger." Blunting of the sensorium, as by narcotics or by acute hypercapnia, can eliminate the sensation of breathlessness, even though the abnormal breathing pattern remains. Anxiety may heighten the sense of breathlessness. Indeed, anxiety may be responsible for the clinical syndrome of psychogenic dyspnea, in which the patient experiences "breathing discomfort" that eludes explanation on the basis of a somatic cause. Ill-defined sensations may accompany a full-blown hyperventilation syndrome, consisting of lightheadedness, tingling of the hands and feet, tachycardia, inversion of T waves on the electrocardiogram, and even syncope. Breathing discomfort at rest that decreases with activity is often seen when anxiety or other psychological issues are the cause and is a distinctly unusual pattern for dyspnea due to a cardiopulmonary abnormality.

The quality of dyspnea can vary greatly. In normal persons, as well as in those with chest disease, dyspnea may simply signify the transition from an effortless process that is ordinarily conducted at a subconscious level to the awareness that muscular effort is being expended in breathing.[19] The healthy athlete completing a sprint experiences breathlessness that can be exhilarating, rather than uncomfortable. The asthmatic often interprets breathlessness in terms of "tightness in the chest." The patient with COPD often complains of less severe breathlessness than would be expected from the degree of airway obstruction, possibly reflecting adaptation, either to the chronic obstructive airway disease or to CO_2 retention.

Patients may use different terms to describe breathing discomfort due to various causes.[20–25] In some instances these descriptors may be useful in establishing a differential diagnosis and in assessing the response to therapy.[26] Patients with asthma or myocardial ischemia often refer to "chest tightness."[27] Patients with pulmonary edema may suffer a sensation of "air hunger" or "suffocation."[28] Patients with COPD and hyperinflation of the chest often note an inability to take a deep, satisfying breath. Individuals who are deconditioned may complain of "heavy breathing." Unfortunately, no descriptor has sufficient sensitivity or specificity to be used alone in establishing the cause of a patient's dyspnea. Ethnic and gender differences in the descriptors and perceptions related to dyspnea have been reported.[29,30]

CLINICAL PRESENTATIONS

Dyspnea may be acute, chronic, or paroxysmal (Table 29-3).

TABLE 29-3 Common Causes of Acute and Chronic Dyspnea[a]

Acute
Pulmonary edema
Asthma
Injury to chest wall and intrathoracic structures
Spontaneous pneumothorax
Pulmonary embolism
Pneumonia
Adult respiratory distress syndrome
Pleural effusion
Pulmonary hemorrhage
Foreign body aspiration
Vocal cord dysfunction
Chronic, progressive
Chronic obstructive pulmonary disease
Left ventricular failure
Diffuse interstitial fibrosis
Asthma
Pleural effusions
Pulmonary thromboembolic disease
Pulmonary vascular disease
Psychogenic dyspnea
Anemia, severe
Postintubation tracheal stenosis
Hypersensitivity disorders

[a]Many chronic processes (e.g., left ventricular failure, asthma, and COPD) may have acute exacerbations.

Acute Dyspnea

The usual causes of acute dyspnea in children differ from those in adults. In children, upper airway infection (e.g., epiglottis, laryngitis, or acute laryngotracheobronchitis) is a common cause. In adults, the causes of acute dyspnea are much more varied (Table 29-3). Among the most common are acute left ventricular failure, pulmonary thromboembolism, pneumonia, and spontaneous pneumothorax. Less common, but not unusual, is massive collapse of one lung due to inability to clear the airways of thick, tenacious secretions (e.g., in chronic bronchitis or asthma) or the first attack of asthma.

Chronic Dyspnea

Chronic dyspnea is almost invariably progressive. As a rule, this type of dyspnea begins with breathlessness on exertion—which, in time, progresses to dyspnea at rest. Pulmonologists encounter dyspnea in patients who have COPD; cardiologists more often deal with dyspnea in patients who are in chronic congestive heart failure. Especially in older patients, distinction between the heart and lungs in the etiology of dyspnea, or the relative contributions of each, can be difficult to establish.

Asthma is a common cause of recurrent bouts of dyspnea, which are usually accompanied by cough and wheezing. Cardiac dysfunction is another cause of acute bouts of bronchospasm, especially in middle-aged or elderly persons.

■ PHYSIOLOGIC CORRELATES OF DYSPNEA

Historically, attempts to understand the physiologic bases of dyspnea have evolved along four separate lines: ventilatory performance, the mechanics of breathing, chemoreception, and exercise testing. Exercise testing is presented in Chapter 34.

Ventilatory Performance

Early investigations related the sensation of dyspnea to the level of minute ventilation. Dyspnea was found to correlate with excessive minute ventilation relative to the level of oxygen uptake. Most of the increase in ventilation was accounted for by an increase in respiratory rate, especially in patients with stiff lungs. In patients who continued to ventilate excessively for the level of oxygen uptake (e.g., those with chronic left ventricular failure), the sensation of breathlessness gradually diminished, suggesting adaptation to the continued stimulus.

A second ventilatory measurement that proved to correlate well with dyspnea is the maximum voluntary ventilation (MVV). MVV is decreased by diseases of the lungs, airways, or chest wall. The smaller the MVV, the more likely is dyspnea to occur.

A third time-honored approach to measurement is the "breathing reserve." This value is determined as the difference between the MVV and the actual minute ventilation. In principle, the sensation of breathlessness during the performance of any ventilatory task may be related to the fraction of the maximum breathing capacity (i.e., the MVV) that is used for force generation by the respiratory apparatus. Thus, the closer the minute ventilation is to the maximum breathing capacity, the more likely is the subject to complain of breathlessness. Indeed, when the actual level of ventilation reaches 30% to 40% of the maximum breathing capacity, dyspnea is inevitable. Unfortunately, the breathing reserve correlates better with the dyspnea of normal subjects during exertion than with the dyspnea of chronic bronchitis and COPD or of left ventricular failure. Thus, in COPD the minute ventilation may be a very large fraction of the MVV (>50%) without eliciting dyspnea. In contrast, in acute left ventricular failure, a mild increase in ventilation and a nearly normal MVV may be associated with considerable breathlessness.

Mechanics of Breathing

One teleologic way to regard dyspnea is as a sensation that prompts an unconscious effort to minimize the work, energy cost, or force of breathing. In this light, dyspnea protects the respiratory apparatus from overwork and inefficient operation. This approach has led to exploration of the relationships between dyspnea and the work or oxygen cost of breathing.

Work, Oxygen Cost, and Efficiency of Breathing

It has not been possible to identify a critical level for the work of breathing at which dyspnea will occur. However, a breakdown of the work of breathing into its elastic, resistive, and inertial components has helped to relate physiologic disturbances to particular diseases. For example, in chronic mitral stenosis with pulmonary congestion, the elastic work is greatly increased (Fig. 29-7), whereas in obstructive airway disease, resistive work predominates. Moreover, such observations have reinforced the concept that patterns of breathing are automatically adjusted to minimize the work done by the respiratory muscles in breathing.

The relationship between ventilation and O_2 consumed by the respiratory muscles is curvilinear (Fig. 29-8). This O_2 cost of breathing may increase extraordinarily in patients with COPD or with abnormalities of the chest wall. Indeed, in patients with COPD, the quantity of O_2 delivered to the respiratory muscles during the large ventilatory effort may fail to satisfy their aerobic needs, leading to anaerobic metabolism and lactic acidosis. Although the greater the O_2 cost of breathing the greater the likelihood of dyspnea, the determination of O_2 cost provides no more useful insight into the mechanism of dyspnea than does the work of breathing. Calculation of the efficiency of breathing (i.e., the work of breathing related to energy cost) provides no further clarification.

Length–Tension Inappropriateness

The concept of "length–tension inappropriateness" explains dyspnea as a mismatch between the central motor command to the respiratory muscles (i.e., the motor signal emitted from the brain) and the suboptimal ("inappropriate") shortening of the respiratory muscles elicited by this command (e.g., suboptimal thoracic expansion for any level of central motor command).[31] In essence, this concept pictures a decrease, instead of an increase, in the pressure-generating capacity of the respiratory muscles in the face of the increased need arising from the heightened respiratory drive.

Chemoreception

Chemoreceptors in the medulla respond to changes in pH and Pa_{CO_2} (see Chapter 11). Peripheral receptors in the aortic arch and carotid body also respond to alterations in Pa_{O_2}. Acute hypoxia, hypercapnia, and acidosis are the traditional stimuli for ventilation. For example, upon ascent to altitude, acute hypoxia can stimulate ventilation to the level of awareness that may progress to discomfort during exertion. The effects of these stimuli on breathing decrease if they continue unabated. In addition, side effects, such as blunting of the sensorium during chronic CO_2 retention, diminish the likelihood of dyspnea, even if the level of ventilation is increased. In patients with abnormal pulmonary mechanics, the onset of abnormalities in blood gas composition, as during exercise, may aggravate or contribute to dyspnea. In general, acute hypercapnia is a stronger stimulus for dyspnea than is acute hypoxia.

■ SCALING

A variety of scaling methods have been devised to quantify dyspnea during exercise and various experimental settings. Some, such as the Borg Category Scale (Table 29-4), use numbers and descriptive terms to depict a change in the intensity of the stimulus ("threshold stimulus detection methods"). Others rely on visual analog scales, which are straight lines, usually 10 cm long, that extend from "not breathless" at one end to "extremely breathless" at the other. The

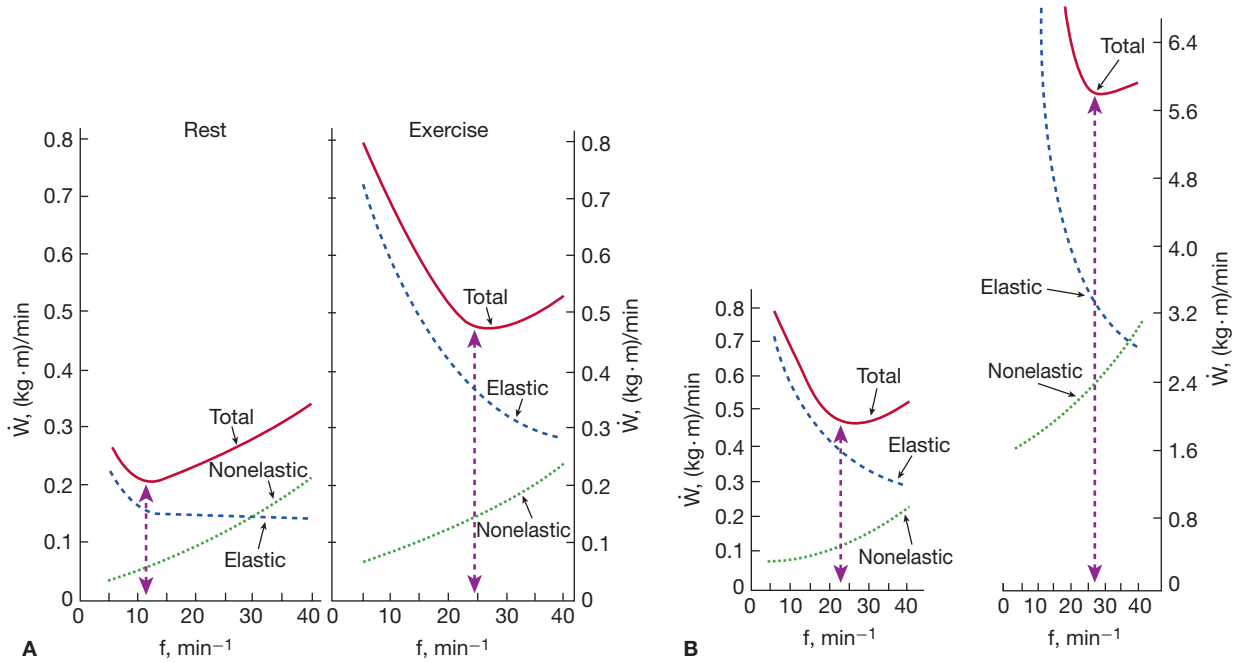


Figure 29-7 Partition of the work of breathing in pulmonary congestion and edema at rest and during exercise. **A.** Normal. The minimal work of breathing at rest was at a respiratory frequency of 12 breaths/min; during exercise, the minimal work was done at a higher frequency (25 breaths/min). **B.** Mitral stenosis. At rest, the frequency for least respiratory work was abnormally high (22 breaths/min); during exercise it increased further (to 28 breaths/min). The *dashed vertical line* (capped by *arrowheads*) in each frame indicates the respiratory frequency at which respiratory work was minimal. f, respiratory frequency. *(Reproduced with permission from Christie RV. Dyspnea in relation to the visco-elastic properties of the lung. Proc R Soc Med. 1953;46(5):381–386.)*

patient marks on the line the intensity of respiratory discomfort elicited by external stimuli, such as resistive loads or exercise testing. The score is measured as the length of the line between "not breathless" and the mark made by the patient. The Shortness of Breath Scale issued by the American Thoracic Society (Table 29-5) has also been used in one form or another, particularly in epidemiologic studies. A recent method of quantifying dyspnea severity that utilizes patient descriptors appears to be applicable and reproducible in a variety of disorders.[32]

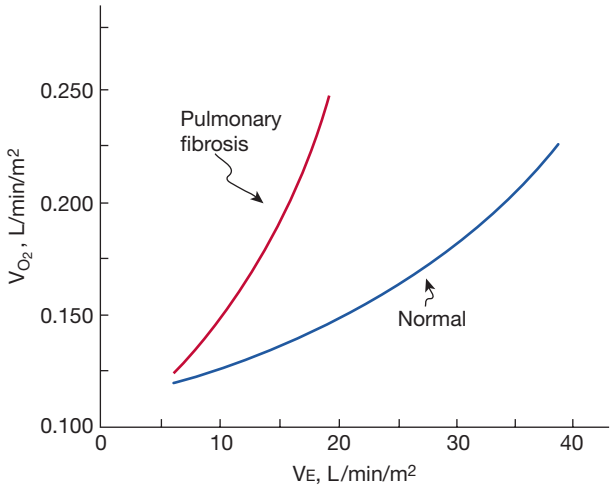


Figure 29-8 Oxygen cost of breathing in restrictive lung disease. Relationship between ventilation and O_2 consumption in pulmonary fibrosis. At each level of ventilation, the patient with pulmonary fibrosis does more work and expends more energy in breathing than does the normal subject.

DYSPNEA IN OBSTRUCTIVE AND RESTRICTIVE PULMONARY DISORDERS

Two common pathophysiologic categories of pulmonary disease in which dyspnea features prominently are chronic obstructive airway disease and restrictive pulmonary disorders.

CHRONIC OBSTRUCTIVE AIRWAY DISEASES

Several chronic obstructive airway diseases associated with dyspnea are well recognized, including COPD and asthma.

COPD

COPD refers to a spectrum of airway diseases in which obstruction to airflow is the common denominator (Chapters 39 and 40).

TABLE 29-4 Modified Borg Category Scale

Rating	Intensity of Sensation
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

TABLE 29-5 American Thoracic Society Shortness of Breath Scale

Descriptions	Grade	Degree
Not troubled by shortness of breath when hurrying on the level or walking up a slight hill	0	None
Troubled by shortness of breath when hurrying on the level or walking up a slight hill	1	Mild
Walks more slowly than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level	2	Moderate
Stops for breath after walking about 100 yards or after a few minutes on the level	3	Severe
Too breathless to leave the house; breathless on dressing or undressing	4	Very severe

Cigarette smoking is the leading cause of COPD (Chapter 41). The outer limits of the spectrum are marked by chronic bronchitis at one end and emphysema at the other. Most patients with COPD fall into categories between those limits (i.e., they manifest mixtures of chronic bronchitis and emphysema, which vary in degrees) (Fig. 29-9).

Patients with COPD suffer from disturbances in the mechanics of breathing, abnormal lung volumes, and derangements in gas exchange. The minute ventilation, which may be only slightly increased at rest, constitutes an abnormally large fraction of the maximum breathing capacity (i.e., the "breathing reserve" is low).

Abnormalities in the mechanics of breathing dominate the scene: resistance to airflow is high; the thorax assumes a hyperinflated position, placing the inspiratory muscles at mechanical disadvantage; the work of breathing is greatly increased. The O_2 cost of breathing is correspondingly high. Derangements in dead space ventilation and in alveolar–capillary gas exchange add to the afferent stimuli. As a result of the disturbances in mechanics and gas exchange, swings in pleural pressure (a measure of force applied to the lungs) are large, and a considerable muscular effort is expended in breathing; instead of the normal increase of about 1 mL of O_2 uptake per liter of ventilation per minute, the O_2 uptake increases enormously (up to 25 mL/min). Should O_2 delivery to the overworked respiratory muscles be insufficient, fatigue and exhaustion may send nervous and chemical signals of their own to the brain. Finally, if the patient accumulates excess water in the lungs, the juxtacapillary ("J") receptors provide additional sensory input to the central integrating mechanism. As noted above (see "Length–Tension Inappropriateness"), the convergence of these diverse stimuli upon the sensorimotor cortex may generate an inordinate motor command to the respiratory muscles, which cannot mobilize the thorax sufficiently to generate the pleural pressures needed for adequate ventilation.

One enigma is why patients with COPD maintain different levels of ventilation despite equal abnormalities in conventional pulmonary function tests. The "CO_2 retainer," with respiratory acidosis and arterial hypoxemia, often breathes less than does the non–CO_2 retainer in whom blood gas levels are near normal. One teleologic explanation is that the lower ventilation in the CO_2 retainer causes less dyspnea. However, this explanation affords no insight into the physiologic mechanism.

Treatment of the patient with COPD is directed at diminishing airways resistance and restoring arterial blood gases toward normal. Unfortunately, bronchodilators generally have only modest effects, and the basic abnormalities in the mechanics of the lungs and airways remain. Consequently, the load on the respiratory muscles is not readily alleviated by medical management. Management strategies also include consideration of ways in which the performance of the respiratory muscles can be improved. These have generally taken the form of training exercises to facilitate adaptive changes and to increase both muscle strength and endurance. Exercise reconditioning in patients with COPD has been shown to diminish breathlessness, possibly owing to three interactive mechanisms: (1) increased mechanical efficiency of the exercising muscles, which decrease ventilatory requirements; (2) improved function of the respiratory muscles; and (3) increased tolerance of the "dyspneagenic" sensory input to the brain. Attempts to rest the respiratory muscles have no lasting effect on dyspnea.

Asthma

Asthma constitutes a different entity, not only in its clinical expressions but also because it is usually episodic and is often related to allergic manifestations, and generally affects younger individuals (Chapters 45 to 47).

The mechanisms described previously for COPD apply as well to asthma. However, these mechanisms do not account for the sensation of "tightness in the chest" or the inordinate sense of labored breathing that accompanies the breathlessness in asthma.

■ RESTRICTIVE VENTILATORY DEFECTS

Restrictive ventilatory defects are due to a variety of causes, ranging from lung disorders to diseases that affect the pleural space, as well as neuromuscular diseases that affect the function of the thorax (Table 29-6). Diffuse interstitial disease has many different etiologies and may be either acute or chronic (Table 29-7). Characteristically, in widespread interstitial disease the diffusing capacity is low and is accompanied by a considerable decrease in total lung capacity and in vital capacity, as well as lesser decrements in functional residual capacity and residual volume (see Chapter 33). Similar findings occur in severe kyphoscoliosis or encasement of the lung by pleural thickening (Fig. 29-10). In contrast, in pulmonary vascular disease, such as idiopathic pulmonary arterial hypertension, a low diffusing capacity may be accompanied by normal lung volumes. Neuromuscular disease that affects the inspiratory muscles sufficiently to diminish maximum inspiratory pressures may decrease vital capacity and total lung capacity, leaving functional residual capacity and residual volume increased.

Patients with widespread pulmonary fibrosis breathe faster and maintain a higher minute ventilation than do normal subjects, both at rest and during exercise. The work and oxygen cost of ventilating

TABLE 29-6 Common Causes of Restrictive Ventilatory Defects

Cause	Example
Interstitium	
Interstitial fibrosis and/or infiltration	Usual interstitial pneumonitis/ idiopathic pulmonary fibrosis
Pulmonary edema	Left ventricular failure
Pleura	
Pleural disease	Fibrothorax
Thoracic cage and abdomen	
Neuromuscular disease	Poliomyelitis
Skeletal abnormalities	Severe kyphoscoliosis
Marked obesity	Grossly overweight

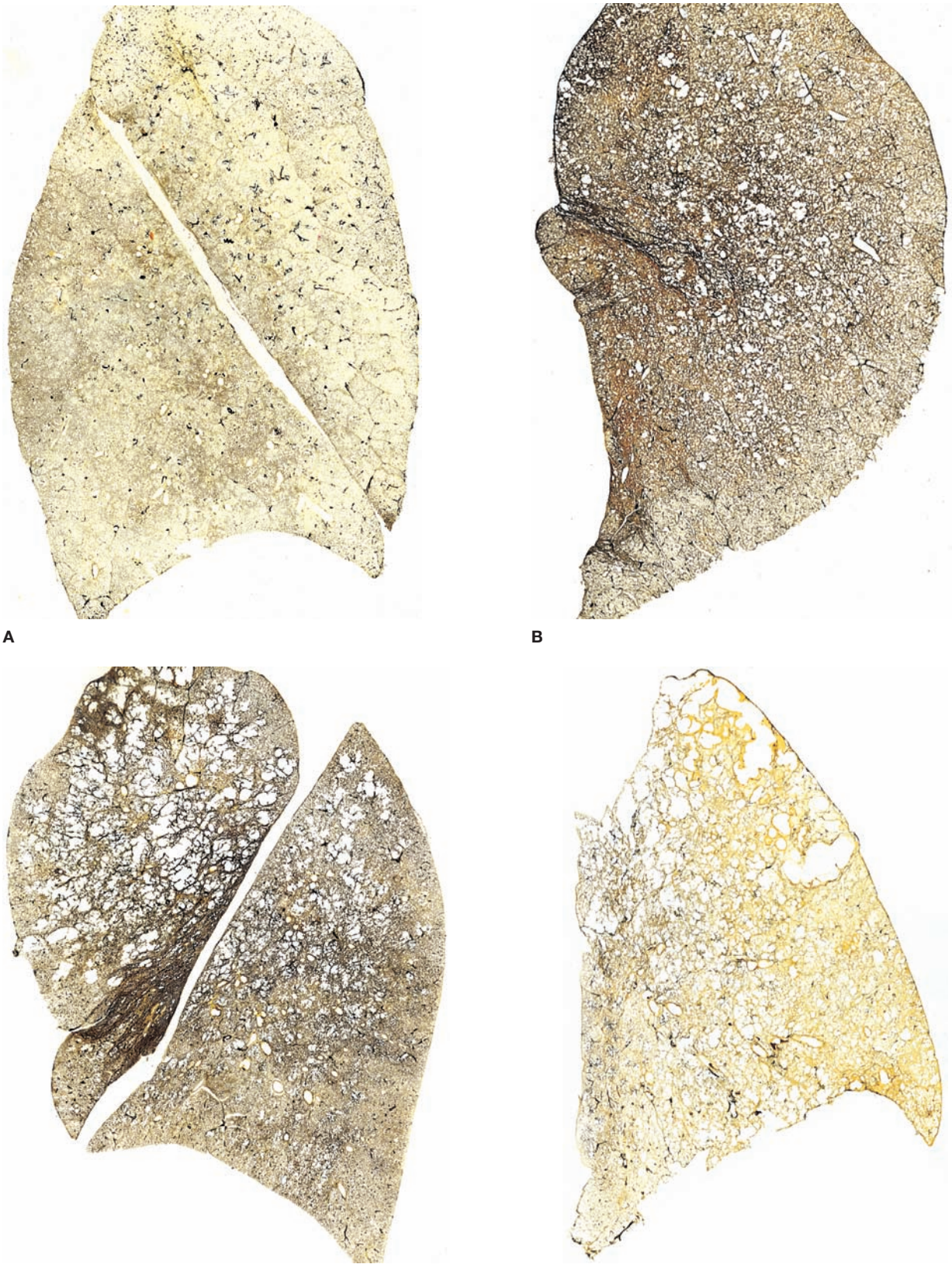
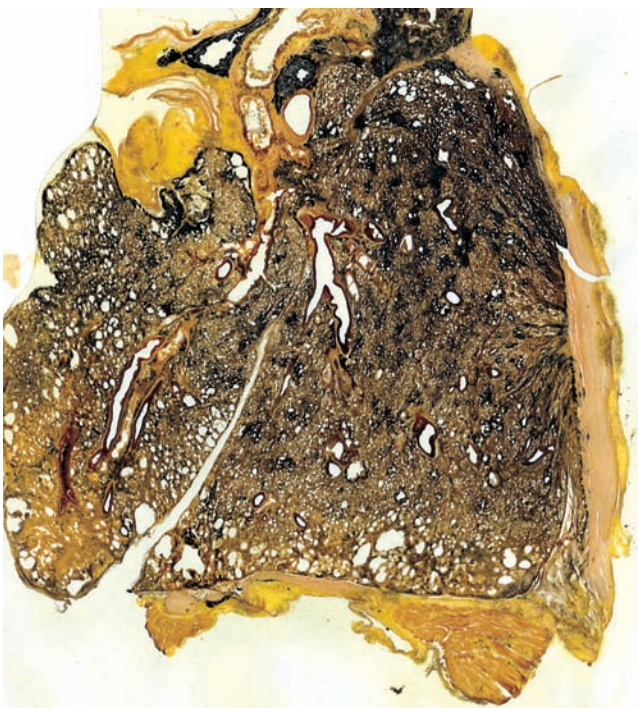


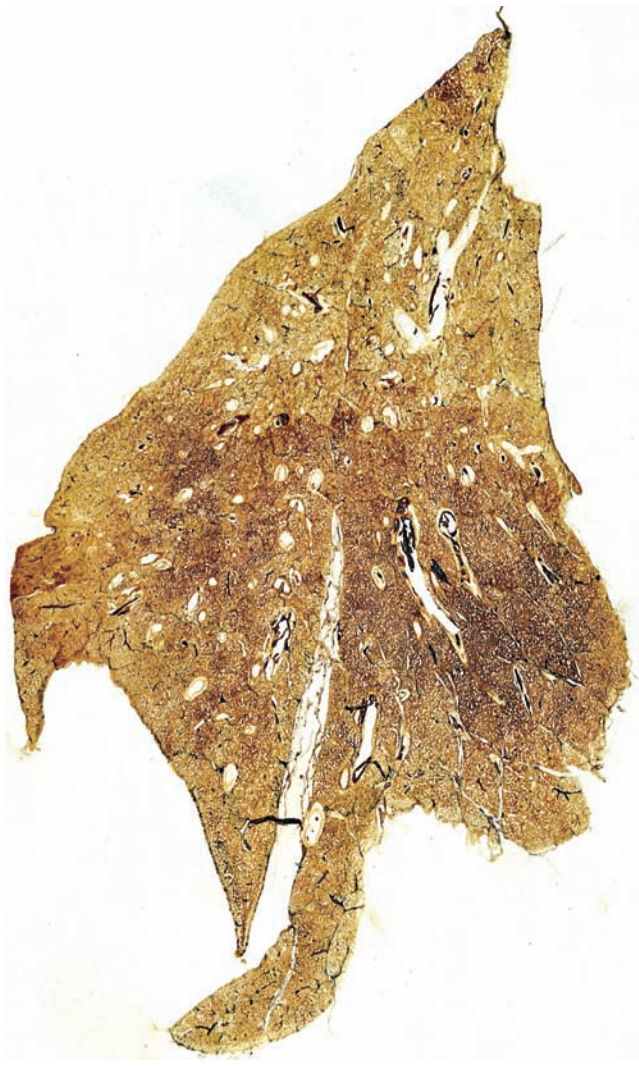
Figure 29-9 Chronic obstructive pulmonary disease (COPD). Sagittal sections showing patterns of emphysema. **A.** Normal lung from a patient who died of unrelated causes. **B.** Predominantly centrilobular emphysema. **C.** Predominantly centrilobular and panlobular emphysema. **D.** Predominantly panlobular emphysema. Centrilobular emphysema is less marked. The three patients with emphysema (**B, C, D**) also had clinical manifestations of chronic bronchitis confirmed by histologic sections.

TABLE 29-7 Some Types of Diffuse Interstitial Diseases

Etiology	Example	Common Features
	Acute	
Infections	Miliary tuberculosis, histoplasmosis	Opportunity for exposure to organism
	Pneumocystis, cytomegalic inclusion virus, fungi	Immunosuppression
Pulmonary edema	Narcotic overdosage, nitrogen dioxide (silo-filler's disease), uremia	Distinctive history
Inhalation	Byssinosis	Monday morning asthma and fever
Aspiration	After loss of consciousness	History of alcoholism or epilepsy
Immunologic	Goodpasture syndrome	Renal and pulmonary involvement
Carcinoma of lung	Adenocarcinoma in situ or minimally invasive adenocarcinoma (previously known as alveolar cell carcinoma)	
	Chronic	
Inhalation	Pneumoconioses	History of exposure to inorganic dust
Radiation therapy	After mastectomy	Gradual evolution after treatment
Lymphangitic spread	Carcinoma of breast, lung, stomach, pancreas	Evidence of primary carcinoma
Medications	Bleomycin, busulfan, cyclophosphamide	History, suggestive chest radiograph
Systemic disorders	Sarcoidosis, connective tissue disorders, eosinophilic granuloma, amyloidosis, tuberous sclerosis	Multiorgan involvement; biopsy
Idiopathic	Idiopathic pulmonary fibrosis	Exclusion of known causes



A



B

Figure 29-10 Restrictive ventilatory disorders. **A.** Asbestosis with markedly thickened pleura that encases and compresses the lungs. In addition, the lungs were afflicted with diffuse interstitial fibrosis. **B.** Compressed, distorted lung in patient with kyphoscoliosis. The lungs were otherwise normal, so that in this instance restriction was imposed by the chest wall rather than by intrapulmonary or pleural disease.

the stiff lungs are increased. Dyspnea is attributable to the considerable effort by the respiratory muscles in ventilating the stiff lungs and in sustaining the high ventilatory rate. During exercise, dyspnea may become intolerable.

DYSPNEA IN CHRONIC CARDIAC DISEASE

The mechanisms responsible for dyspnea in cardiac disease vary with the extent to which the lungs are stiffened.

Dyspnea occurs in many forms of heart disease that are not associated with congestion of the lungs. Uncomplicated pulmonic stenosis is an excellent example. The symptom is probably related to an inadequate cardiac output during exercise. In Tetralogy of Fallot, dyspnea is sometimes severe and often relieved by assuming a squatting position. In this and other forms of cyanotic heart disease, both dyspnea and fatigue appear during exertion when the arterial oxyhemoglobin saturation decreases appreciably below the resting level.

Cardiac dyspnea is associated with an increase in blood and water content of the lungs. It is a common occurrence in left ventricular failure and mitral stenosis, both of which are accompanied by increases in pulmonary venous and capillary pressures. The engorged pulmonary circulatory bed, coupled with interstitial and alveolar edema, stiffens the lungs (i.e., decreases their compliance) and stimulates the ventilation via "J" receptors. In chronic left ventricular failure, pulmonary fibrosis, consequent to long-standing interstitial edema, contributes to the stiff lungs. Edema of the tracheobronchial mucosa increases airway resistance.

As a result of the stiff lungs and increased airway resistance, swings in pleural pressure during the respiratory cycle are large and the work and energy cost of breathing are increased. Arterial hypoxemia, generally mild, may add to the ventilatory drive. Exercise exaggerates the pulmonary congestion and edema, promotes arterial and mixed venous hypoxemia, and increases the dyspnea.

In patients with pulmonary congestion and edema, tachypnea is a regular feature at rest and increases during exercise. Although tachypnea is consistent, its degree is generally modest and probably not entirely responsible for the dyspnea. Fatigue is a common concomitant of low cardiac output and may stem from diminished O_2 delivery to the respiratory muscles, contributing to respiratory discomfort.

■ ORTHOPNEA AND OTHER POSITIONAL FORMS OF BREATHLESSNESS

Orthopnea signifies dyspnea in the recumbent, but not in the upright or semiupright, position; it is usually relieved by two or three pillows under the head and back. *Platypnea* signifies dyspnea induced by assuming the upright position and relieved by recumbency.[33]

Platypnea may be seen when, due to gravity, increased blood flow worsens right to left shunting of blood through arteriovenous malformations at the lung bases; it may be accompanied by *orthodeoxia*—desaturation of arterial blood when the patient is upright.

Orthopnea is a hallmark of pulmonary congestion that stiffens the lungs (i.e., decreases their compliance). The decrease in compliance on lying flat is attributable to the fact that more of the lung is located at or below the level of the heart. During recumbency, the swings in pleural pressure, the work of breathing, and the respiratory frequency increase. The increase in respiratory frequency appears to be automatically adjusted to minimize the work of ventilating the more rigid lungs.

Some patients with chronic lung disease or asthma are also intolerant of lying flat. Their discomfort is attributed to the greater difficulty of performing vigorous movements of the chest bellows in the recumbent position.

Finally, patients with asymmetric lung disease may experience *trepopnea*—dyspnea when the affected side of the chest is in the dependent position, thereby promoting ventilation–perfusion mismatch (Chapter 14) and resultant hypoxemia.

■ PAROXYSMAL NOCTURNAL DYSPNEA

In an episode of paroxysmal nocturnal dyspnea (PND), the patient is aroused from sleep, gasping for air, and must sit up or stand to catch his or her breath; sweating may be profuse. Sometimes the patient opens a room window in an attempt to relieve the oppressive sensation of suffocation. The chest tends to become fixed in the position of forced inspiration. Both inspiratory and expiratory wheezes, often simulating typical asthma, are heard. In some instances, overt pulmonary edema occurs, accompanied by inspiratory crackles. Attacks occasionally recur several times a night, forcing the patient to sleep upright in a chair.

An episode of PND represents precipitous failure of the left ventricle caused by the factors that produce orthopnea (see above), abetted by pulmonary hypervolemia caused by a surge in systemic venous return. Mobilization of peripheral edema from the periphery as the extremities are elevated from the dependent position may contribute to the increase in systemic venous return. The acute increase in pulmonary blood volume increases pulmonary capillary pressures, thereby promoting pulmonary edema, while the surge in venous return imposes an additional burden on the left ventricle.

A variety of factors may trigger an episode of PND: coughing, abdominal distention, the hypercapnic phase of Cheyne–Stokes respiration (see below), a startling noise, or anything that causes a rise in heart rate and further increases the pulmonary capillary and venous pressures. Usually the attack is terminated by assumption of the erect position and a few deep breaths. Cough, an important manifestation of pulmonary congestion, frequently occurs during the attack.

■ CARDIAC ASTHMA

Asthmatic wheezes, often audible in patients with pulmonary congestion, have given rise to the term *cardiac asthma.* The wheezes are a manifestation of tracheobronchial edema and often are accompanied by overt signs of pulmonary edema. In addition to the reduction in the lumen of the airways and thickening of bronchial walls by edema, the high intrathoracic pressures, which are required to overcome the obstruction during expiration, tend to narrow the airways even further. The resistance to airflow is increased during both inspiration and expiration, and the compliance of the lungs is greatly reduced, reaching values as low as one-tenth of normal. Upon recovery from the acute episode of pulmonary edema, airway resistance and pulmonary compliance return toward normal unless previous episodes have left a residue of pulmonary fibrosis.

DYSPNEA IN ANEMIA

Shortness of breath during exercise or excitement is a common complaint in severe anemia (e.g., hemoglobin concentration under 6–7 g/dL). It is more common in acute than in chronic anemia. Often the dyspnea is associated with dizziness or faintness, and invariably the patient manifests signs of a high cardiac output and low peripheral resistance (i.e., bounding pulse, warm skin, and systolic cardiac murmurs). Although the pathogenesis of the dyspnea is not clear, inadequate oxygen delivery to the respiratory muscles has been proposed.

METABOLIC ABNORMALITIES AND DRUGS

Increases in CO_2 production demand a concomitant rise in ventilation to dispose of the metabolic load and, hence, may result in dyspnea. To prevent acidemia, patients with diabetic ketoacidosis may require an enormous increase in minute ventilation in order to reduce Pa_{CO_2}. Thyrotoxicosis, fever, infection, and pregnancy can also cause an increased minute ventilation, as can drugs, such as aspirin and progesterone.

MISCELLANEOUS DISORDERS

Breathlessness is not uncommon in patients with musculoskeletal disorders. The usual explanation is the heightened motor drive that is needed to activate the weakened respiratory muscles. In the intensive care unit, inadequate ventilator settings for flow and tidal volume may fail to satisfy the intrinsic ventilatory drive of the patient, generating the sensation of breathlessness.

ABNORMAL BREATHING PATTERNS

An important clue to the nature of a clinical problem in pulmonary disease is sometimes provided by bedside observation of a patient's breathing pattern. The pertinent features are the rate, regularity, depth, and apparent effort being expended in breathing. A normal person at rest breathes about 12 to 15 times per minute, with a tidal volume of 400 to 800 mL. As a result, minute ventilation is normally greater than 5 L/min. The pattern is quite regular except for an occasional slow, deep breath, and the respiratory movements appear effortless.

Severe skeletal deformity, as well as massive obesity, can limit chest excursions to cause alveolar hypoventilation (Chapter 83). Neuromuscular weakness, as in myasthenia gravis or Guillain–Barré syndrome, may do the same, not only by diminishing ventilatory excursions as a result of generalized weakness of the respiratory muscles, but also by causing overload of respiratory muscles (e.g., residual effects of poliomyelitis) (Chapters 83 and 84). Unilateral involvement of one pleural space by pneumothorax, effusion, or fibrothorax limits excursions on the affected side. Massive chest trauma may cause flail chest.

In COPD, a slow respiratory rate and large tidal volumes are characteristic. This pattern presumably serves to minimize the work of breathing. Pursed-lip breathing, a self-induced type of positive-pressure breathing, is often part of the picture. In contrast, persons with restrictive ventilator disorders adopt a breathing pattern that is characterized by small tidal volumes and a rapid respiratory rate, often with little apparent effort. This pattern is seen in patients with a decrease in the distensibility of the lung or chest wall or with reduction of the vital capacity from any other cause. During exercise, minute ventilation increases inordinately with respect to the level of O_2 uptake, and respiratory frequency increases more than tidal volume.

Fatigue of the diaphragm and intercostal muscles, sufficient to disturb their coordinated contractions, may give rise to paradoxical breathing, which heralds the onset of respiratory failure.

■ CHEYNE–STOKES RESPIRATION

In the fourth century BC, in a preterminally ill person with fever, sweats, and black urine, Hippocrates described a pattern of breathing in which "the respiration throughout [was] like that of a man correcting himself, and rare and large." Presumably he had observed Cheyne–Stokes breathing, which was described more graphically by William Stokes two millennia later (in 1854) as follows:

"The symptom in question (previously described by Dr. Cheyne) consists in the occurrence of a series of inspirating, increasing to a maximum, and then declining in force and length, until a state of apparent apnea is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and descending series of inspirations."

Cheyne–Stokes breathing is characterized by alternating periods of hypoventilation and hyperventilation (Fig. 29-11). In its typical form, an apneic phase, which lasts for 15 to 60 seconds, is followed by a phase during which tidal volume increases with each successive breath to a peak level and then decreases in a progressive fashion to the apneic phase. At the onset of apnea, CO_2 tension in brachial or femoral arterial blood is at its lowest. As apnea persists, CO_2 tension gradually increases, and respiration is stimulated. CO_2 tension continues to increase until maximum hyperventilation is attained, after which ventilation decreases until apnea again occurs. The arterial oxyhemoglobin saturation varies in an inverse manner, being highest at the onset of apnea and lower during midhyperpnea. During the cycle, CO_2 tension varies by as much as 14 mm Hg and oxyhemoglobin saturation by as much as 18%.

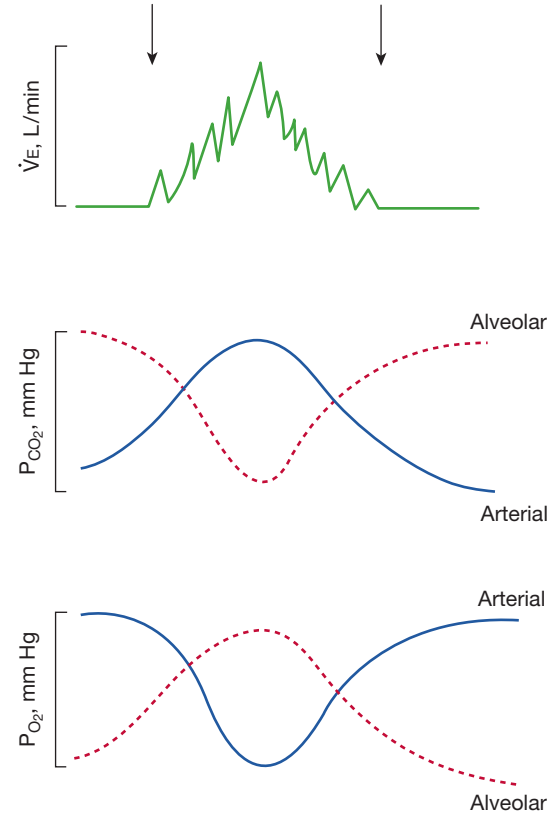


Figure 29-11 Cheyne–Stokes breathing, illustrating the relationship between the ventilation and the blood and alveolar gas tensions during the periods of apnea and hyperpnea. *(Reproduced with permission from Cherniack NS, Fishman AP. Abnormal breathing patterns. Dis Mon. 1975:1–45.)*

In patients with congestive heart failure, the respiratory oscillations are attributable to slowing of the circulation so that the blood gases reaching the respiratory centers in the brain are 180 degrees out of phase with those in pulmonary capillary blood. This mechanism has been verified experimentally by eliciting Cheyne–Stokes breathing in dogs by prolonging the circulation time from heart to brain by way of an extracorporeal circuit.

Fluctuations in mental state and electroencephalographic patterns, and evidence of nervous system dysfunction, may occur during Cheyne–Stokes breathing because of swings in cerebral blood flow. In neurologic disorders, Cheyne–Stokes breathing may be due to supramedullary dysfunction, particularly in patients who have destructive lesions in the tegmentum of the pons.

Less common than in heart failure or neurologic disorders is the occurrence of Cheyne–Stokes respiration in normal infants, in healthy elderly persons, and in normal persons at high altitude. It is also seen occasionally after the administration of respiratory depressants (e.g., morphine), often accompanied by an increase in intracranial pressure, uremia, or coma. At one time, the respiratory center was believed to be depressed in Cheyne–Stokes respiration. This hypothesis has been proved to be in error, since it has been shown that the respiratory response to inhalation of CO_2 is greater than normal in individuals with Cheyne–Stokes respiration. Respiratory alkalosis is common and the arterial P_{CO_2} remains subnormal in both the apneic and hyperpneic phases.

KUSSMAUL BREATHING

In 1874, Kussmaul described three patients with diabetic ketoacidosis who manifested "air hunger": they were breathing with large tidal volumes and so rapidly that there was virtually no pause between breaths. In essence, they were breathing at rest as though they were exercising; breathing was accomplished with little apparent effort. Since then, this pattern of breathing has been observed in other types of severe metabolic acidoses (e.g., alcoholic ketoacidosis). The usual sequence leading to this type of breathing is renal failure with a progressive decrease in plasma bicarbonate and resultant acidosis. The "compensatory" increase in ventilation that Kussmaul described mitigates the fall in systemic pH caused by the fall in plasma bicarbonate (see Chapter 17).

OTHER ABNORMAL PATTERNS

Gasping respirations are characteristic of severe cerebral hypoxia. The pattern consists of irregular, quick inspirations associated with extensions of the neck and followed by a long expiratory pause. It is commonly seen in shock or in other conditions associated with severe reduction in cardiac output.

Hyperventilation is commonly seen in anxious patients without structural disease of the lungs. In some of these patients, striking deep sighs dominate the ventilatory pattern.

DIAGNOSTIC TESTING IN THE EVALUATION OF DYSPNEA

Attention to the history and physical examination findings, as described in the preceding sections, will help to focus the initial approach to diagnosis.[34] In most cases, the initial diagnostic impression can be confirmed or excluded with only a few tests, and appropriate therapy instituted or the hunt for a cause continued (Table 29-8).

A plain chest radiograph is useful in demonstrating changes suggestive of COPD (chest hyperinflation, bullous changes). Vascular engorgement, an enlarged cardiac silhouette, increased interstitial markings, and pleural effusions may indicate left heart failure.

Spirometry is useful in identifying airways obstruction; improvement in values may be noted following administration of a bronchodilator. The measurement of lung volumes or the diffusing capacity may be reserved for when there is suspicion of an interstitial process or other cause of restriction (e.g., muscle weakness). Measurement of arterial oxyhemoglobin saturation both at rest and with exertion is important. While oxyhemoglobin desaturation will not indicate the etiology of the problem, its presence is always an important indicator of the severity of the disease. An echocardiogram can be used to assess ventricular or valvular cardiac function and to estimate pulmonary arterial pressures.

A complete blood count may reveal anemia or suggest an infection. Measurement of serum electrolytes may indicate the presence of an acidosis or renal dysfunction. Measurement of brain natriuretic peptide (BNP) has been useful in helping to exclude heart failure as an acute cause of dyspnea.[35]

Additional testing is usually not required unless the cause of dyspnea remains unclear following basic studies. Further tests often include CT of the chest, which may rarely reveal changes of emphysema or an interstitial process not suggested by plain radiographs or lung function testing. The CT may additionally help to better

TABLE 29-8 Common Tests in the Evaluation of Dyspnea

Test	Some Possible Abnormalities	Some Possible Diagnoses
Plain chest radiograph	Cardiac enlargement	Congestive heart failure
	Vascular enlargement	Pulmonary hypertension
	Abnormal interstitial markings	Pulmonary fibrosis
	Pleural effusions	Malignant pleural effusion
	Hyperinflation	COPD
	Nodules/masses	Neoplastic process
Pulmonary function tests		
Spirometry	Obstructive ventilation defect (decreased FEV_1/FVC, %)	Asthma
		COPD
	Restrictive ventilatory defect	Interstitial lung disease
Diffusing capacity	Decreased	Interstitial lung disease
		Pulmonary vascular disease
	Increased	Alveolar hemorrhage
Inspiratory and expiratory pressures	Decreased values	Respiratory muscle weakness
Computed tomography	Abnormal interstitial markings	Interstitial lung disease
	Cystic changes	Bullous lung disease
	Lymphadenopathy	Sarcoidosis
	Vascular filling defects	Pulmonary embolism
	Ground-glass opacities	Neoplastic disease
Blood tests	Elevated white blood cell count	Infection
	Anemia	Anemia
	BNP	Heart failure
	Cr	Renal failure
		Respiratory or metabolic acidosis
	ABG	Acidoses or alkaloses (respiratory or metabolic)

COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity; BNP, brain natriuretic peptide; Cr, creatine; ABG, arterial blood gas.

characterize an interstitial process identified on plain radiographs. Cardiopulmonary exercise testing (Chapter 34) may be helpful in differentiating between cardiac and respiratory causes of dyspnea, or in excluding a significant abnormality of either system and suggesting deconditioning as the culprit. Arterial blood gas measurements may be necessary to characterize the level of blood oxygenation or to identify hyperventilation or hypercapnia. More invasive testing, including cardiac catheterization or lung biopsy (by either bronchoscopy or surgery), is reserved for situations when the diagnosis remains unsettled and the results will be helpful in guiding therapy or discussions of prognosis.

COUGH

Cough is one of the most frequent causes of visits to the doctor's office.[36,37] Patients are frequently anxious about the possibility of a serious underlying cause. They may also be troubled by the complications of cough, including chest pain from intercostal muscle strain or even a fractured rib. They may be embarrassed by cough-induced urinary or fecal incontinence. Social isolation may also arise from the frequent fear of others that the patient's cough is infectious and communicable.

A cough is an explosive expiration that protects the lungs against aspiration and promotes the movement of secretions and other airway constituents upward toward the mouth. It is a critical element in the self-clearing and protective mechanisms of the lungs—a reflex act that usually, but not invariably, arises from stimulation of the bronchial mucosa somewhere between the larynx and the second-order bronchi. On rare occasions the cause is remote: impacted cerumen in the external auditory canal[38] or an inflammatory process of the pleura (see "Mechanism" below) (Fig. 29-12). The stimuli that may elicit a cough are diverse: inhaled particles, mucus that has been elaborated by the lining of the airways, inflammatory exudate in airways or parenchyma, a new growth or foreign body in an airway, or pressure on the external wall of the bronchus.

A cough may be voluntary, involuntary, or a combination of the two if the subject attempts to control an involuntary cough. Three categories of stimuli are commonly at work in producing an involuntary cough: mechanical, inflammatory, and psychogenic. Mechanical and chemical causes range from inhalation of irritants, such as smoke or dust, to distortions of the airways produced by pulmonary fibrosis or atelectasis. Most often, cough is due to tracheobronchial inflammation. The cigarette smoker is particularly vulnerable to exacerbation of cough by inhaled particles and fumes because of underlying chronic pharyngitis, laryngitis, and tracheobronchitis. As a rule, cough represents organic disease. But on occasion, psychogenic influences are responsible for a dry cough that is related to anxiety. Psychogenic stress can aggravate cough due to organic causes.[39]

The site of origin and significance of a cough may sometimes be ascertained from telltale signs and symptoms (Table 29-9). For example, the cough of acute tracheitis is often associated with retrosternal "burning." Acute laryngitis is usually associated with hoarseness and sore throat, as well as cough. Tuberculosis of the larynx is associated not only with painful swallowing but also with unequivocal evidence of pulmonary tuberculosis. In asthma, cough is part of a constellation of airway obstruction.

Interpretation of the significance of a cough depends on the clinical features with which it is associated. It has to be viewed in context: Is it acute or chronic? Is it productive or nonproductive? How long has it lasted? What is the general condition of the patient, and what comorbidities are present? For example, the acute onset of a hacking, nonproductive cough accompanied by coryza, sore throat, malaise, sweating, and fever generally heralds a viral upper respiratory infection. An episode of asthma may begin with cough and wheezing. In contrast, a persistent cough, even if virtually ignored by the patient, may be a harbinger of serious disease (e.g., carcinoma of the lung). In a cigarette smoker, a change in the nature of the cough from nonproductive to productive may signify the onset of a serious tracheobronchial infection or pneumonia.

A cough that is productive of purulent sputum is generally a reliable indication of infection in the tracheobronchial tree or lungs. When this symptom is associated with an acute illness, the characteristics of the sputum can be of considerable diagnostic help. Rust-colored sputum, which has a distinctive coloration from the even dispersion of blood in yellow, purulent sputum, was previously seen often in pneumococcal pneumonia; it is less commonly seen today due to the widespread use of antibiotics. The classic description of sputum in *Klebsiella* pneumonia is a resemblance to currant jelly; it also contains blood, but it is bright red and more translucent and viscid than the sputum of pneumococcal pneumonia. Purulent sputum with a foul odor usually indicates an anaerobic infection, commonly due to streptococci or *Bacteroides* in a lung abscess. A persistent cough that is productive of purulent sputum occurs in chronic bronchitis, bronchiectasis, and a variety of other suppurative disorders. Sputum that is mucoid may be a consequence of any long-standing bronchial irritant. Copious sputum production *(bronchorrhea)* may be a sign of adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), previously known as bronchoalveolar carcinoma.

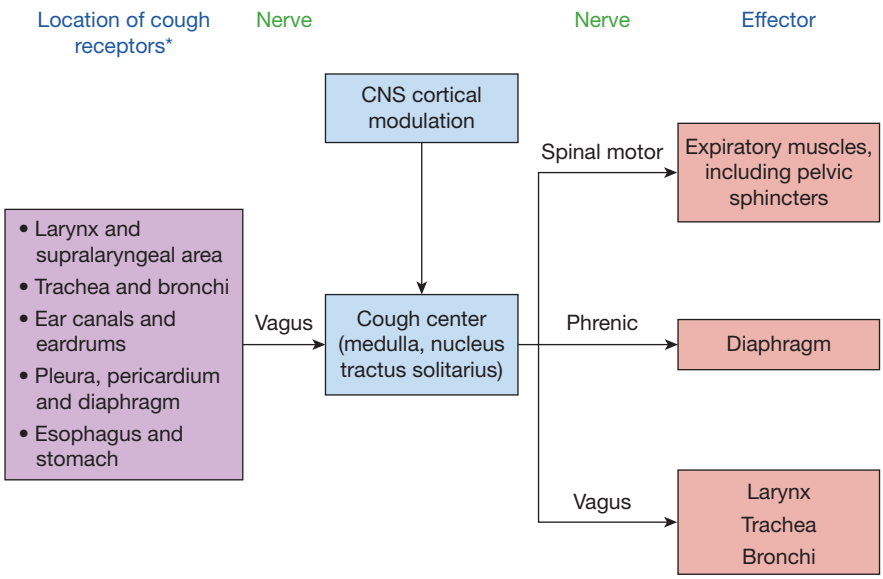


Figure 29-12 Signaling pathways in the development of cough. CN, cranial nerve. *(Reproduced with permission from Silvestri RC, Weinberger SE. Evaluation of subacute and chronic cough in adults. In: UpToDate, Post TW (Ed). UpToDate, Waltham, MA. In: UpToDate, Post TW (Ed). UpToDate, Waltham, MA. (Accessed on November 18, 2014) Copyright © 2014 UpToDate, Inc. For more information visit www.uptodate.com.)*

TABLE 29-9 Some Causes and Characteristics of Cough

Cause	Characteristics
Sinusitis or nasopharyngitis	Cough following an upper respiratory syndrome or sinus symptoms; sensation of a need to clear the throat; postnasal drip
Acute infections of lungs	
Tracheobronchitis	Cough associated with sore throat, running nose, and eyes
Lobar pneumonia	Cough often preceded by symptoms of upper respiratory infection; cough dry, painful at first; later becomes productive
Bronchopneumonia	Cough dry or productive, usually begins as acute bronchitis
Mycoplasma and viral pneumonia	Paroxysmal cough, productive of mucoid or blood-stained sputum associated with flulike syndrome
Exacerbation of chronic bronchitis	Cough productive of mucoid sputum becomes purulent
Chronic infections of lungs	
Bronchitis	Cough productive of sputum on most days for more than 3 consecutive months and for more than 2 y Sputum mucoid until acute exacerbation, when it becomes mucopurulent
Bronchiectasis	Cough copious, foul, purulent, often since childhood; forms layers upon standing
Tuberculosis or fungus	Persistent cough for weeks to months, often with blood-tinged sputum
Parenchymal inflammatory processes	
Interstitial fibrosis and infiltrations	Cough nonproductive, persistent, depends on origin
Smoking and inhalation of irritants	Cough usually associated with injected pharynx; persistent, most marked in morning, usually only slightly productive unless succeeded by chronic bronchitis
Tumors	
Bronchogenic carcinoma	Cough nonproductive to productive for weeks to months; recurrent small hemoptysis common
Adenocarcinoma *in situ* or minimally invasive adenocarcinoma	Cough similar to that with bronchogenic carcinoma except in occasional instances, when large quantities of watery, mucoid sputum are produced
Benign tumors in airways	Cough nonproductive; occasionally hemoptysis
Mediastinal tumors	Cough, often with breathlessness, caused by compression of trachea and bronchi
Aortic aneurysm	Brassy cough
Gastrointestinal	
Gastroesophageal reflux disease (GERD)	Nonproductive cough often following meals or with recumbency; may (or may not) be accompanied by other symptoms of GERD (e.g., heartburn, a bitter oral taste, belching)
Foreign body	
Immediate, while still in upper airway	Cough associated with progressive evidence of asphyxiation
Later, when lodged in lower airway	Nonproductive cough, persistent, associated with localizing wheeze
Cardiovascular	
Left ventricular failure	Cough intensifies while supine, along with aggravation of dyspnea
Pulmonary infarction	Cough associated with hemoptysis, usually with pleural effusion
Medication-induced	
Angiotensin-converting enzyme (ACE) inhibitors	Nonproductive cough, more common in women, may occur at any time (following soon after drug initiation or with years of use)

MECHANISM

A cough begins with a rapid inspiration, followed, in rapid sequence, by closure of the glottis, contraction of the abdominal and thoracic expiratory muscles, abrupt increase in pleural and intrapulmonary pressures, sudden opening of the glottis, and expulsion of a burst of air from the mouth (Fig. 29-13). The high intrathoracic pressures, which often exceed 100 to 200 mm Hg, increase the velocity of airflow through the airways, hastening the propulsion of the offending particles and producing the sound of a cough by setting into vibration airway secretions, the tracheobronchial walls, and the adjacent parenchyma (Fig. 29-14).

Afferent stimuli for a cough originate in irritant receptors and are conveyed centrally by the vagus, glossopharyngeal, trigeminal, and phrenic nerves (Fig. 29-12). In subjects with an idiopathic, persistent, nonproductive cough, increased sensitivity of the afferent nerves of the airways due to neuropeptides stored in them has been proposed.

The vagus nerve carries impulses not only from the larynx, trachea, and bronchi, but also from the pleura and stomach. Receptors in the airways are most concentrated in the larynx, diminish in density in the conducting airways, and are absent from the distal airways, enabling the pooling of secretions in the periphery. The glossopharyngeal nerve carries stimuli from the pharynx; the trigeminal nerve, from the nose and paranasal sinuses; the phrenic nerve, from the pericardium and diaphragm. The motor pathways are even more extensive, comprising not only the cranial and phrenic nerves but also the nerves to the muscles of the rib cage and the accessory muscles. Additional impulses from chemoreceptors are located in the esophagus and carried by the phrenic nerve.

The effectiveness of a cough is strongly influenced by the lung volume at which it occurs. As indicated elsewhere in this volume, cough only removes particles toward the mouth ("downstream"

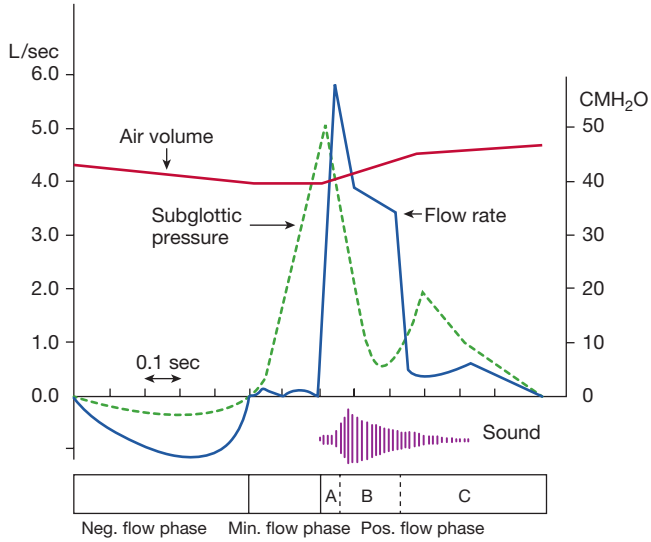
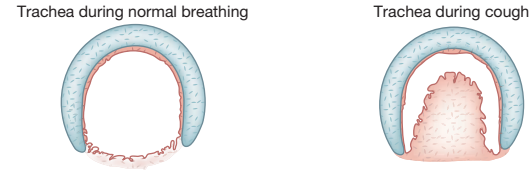


Figure 29-13 Sequence of events during a cough. Simultaneous recordings obtained during a single explosive cough by a normal subject. The three phases of a cough are identified by the boxes at the bottom of the figure. They correspond to (1) a deep initial inspiration, (2) compression of air in the lungs and airways by forceful contraction of the expiratory muscles coupled with tight closure of the glottis and opening of the larynx, and (3) sudden explosive expiration followed by narrowing of the glottis and return of the larynx to its normal inspiratory position. *(Reproduced with permission from Yanagihara N, Von Leden H, Werner-Kukuk E. The physical parameters of cough: the larynx in a normal single cough. Acta Otolaryngol. 1966;61(6):495–510.)*



Intrathoracic pressure, cm H_2O	− 4	+ 150
Cross-sectional area, cm^2	1.5	0.25
Volume flow, L/sec	1	7
Linear velocity, cm/sec	667	28,000

Figure 29-14 Effects of tracheal narrowing during a cough. The forced expiratory effort during coughing causes invagination of the noncartilaginous part of the intrathoracic trachea by the high intrathoracic pressure. Air rushing with a high linear velocity through the exceedingly narrow trachea dislodges the material to be dispelled and propels it into the throat. *(Reproduced with permission from Comroe. Physiology of Respiration. St. Louis. Mosby-Year Book; 1965.)*

from the "equal pressure points"). In healthy persons at high lung volumes, the equal pressure points are located in the larger airways; they move toward the alveoli ("upstream") as lung volume decreases. A series of coughs without any intervening inspiration moves the equal pressure points even closer to the small airways, helping to clear the depths of the lungs.

The cough reflex may be impaired by interrupting or blunting any step in the sequence. Irritant receptors can be damaged by a local destructive process (e.g., bronchiectasis), or their sensitivity can be diminished by narcotics or anesthetics.

The reflex pathways may be damaged as part of a neurologic disease. Tracheostomy, which eliminates glottic closure, decreases peak intrapulmonary pressures. Contraction of the respiratory muscles may be impaired by weakness due to illness, age, or neuromuscular disease. In general, as long as the patient can achieve maximum expiratory pressures greater than about 60 cm H_2O, the peak flow will suffice to produce effective coughs.

CIRCULATORY CONSEQUENCES

The increase in intrathoracic pressure that is part of the cough mechanism exerts considerable circulatory effects. However, because the increase in intrathoracic pressure is accompanied by an equal rise in vascular (and cerebrospinal fluid) pressures, distending pressures on the vessels of the heart, lungs, and other vital organs are unaltered, so they are normally spared the ill consequences of marked swings in transmural pressures.

The increase in intrathoracic pressure is accompanied by reflex vasodilation of systemic arteries and veins. Both of these effects contribute to a decrease in cardiac output. In patients with cor pulmonale and right heart failure, cough impedes systemic venous return and may result in syncope.

POSTTUSSIVE SYNCOPE

Over 100 years ago, Charcot recognized the syndrome of posttussive syncope in individuals without underlying cardiopulmonary disease. Originally conceived of as a form of epilepsy or a consequence of a laryngeal reflex, it is now attributed to the same circulatory consequences of raised intrathoracic pressures that coughing evokes in a normal person. However, the patient with cough syncope probably coughs more forcefully and longer than does a normal person.

The syncope usually develops within a few seconds after the onset of a paroxysm of coughing and ends quickly once the coughing has stopped. Return to consciousness is without sequelae unless the subject falls and is injured during the faint. Posttussive syncope nearly always occurs in men, probably because they generate a higher intrathoracic pressure and much more profound decrease in cardiac output than do women. It is not clear why this type of fainting occurs in the supine, as well as the upright, position; this occurrence suggests that the reduction in cerebral blood flow during posttussive syncope reflects more than interference with cardiac output. The extent to which intense reflex vasodilation contributes to posttussive syncope is unclear. It is important to distinguish cough syncope from epilepsy and cataplexy.

ETIOLOGY

The most common causes of chronic cough and sputum (defined as lasting longer than 8 weeks) are postnasal drip, gastroesophageal reflux disease (GERD), and asthma. In one series of 71 patients, the cause was determined in 97%, with one cause noted in 38%, two causes in 36%, and three causes in 26%. The spectrum of conditions included postnasal drip in 40%, asthma in 24%, GERD in 15%, and bronchitis in 11%.[40]

In patients treated with angiotensin-converting enzyme (ACE) inhibitors, the drug is very often the cause of a chronic cough (even one developing after years of uncomplicated use). The association of cough and ACE inhibitors may be different among various ethnic groups.[41]

A deliberate evaluation can identify the cause of cough in the vast majority of patients. Usually, the diagnosis is established only by the resolution of the cough following a specific intervention (Fig. 29-15). For example, cough that disappears after antihistamines and inhaled nasal corticosteroid treatment for allergic rhinitis can logically be attributed to postnasal drip. Similarly, cough may disappear after interventions for GERD (e.g., use of H_2-blockers) or asthma (use of

inhaled bronchodilators and steroids). A cough that resolves after discontinuation of an ACE inhibitor was presumably caused by the drug. Although the causes of chronic cough are usually benign, a chest radiograph is warranted at the beginning of the evaluation of a chronic cough to assess for serious causes.

HEMOPTYSIS

The coughing up of blood is termed *hemoptysis.*[42] The material and amount produced varies from mere blood streaking of expectorated sputum to massive volumes of pure blood. Massive hemoptysis has been variably defined according to the volume, but its presence

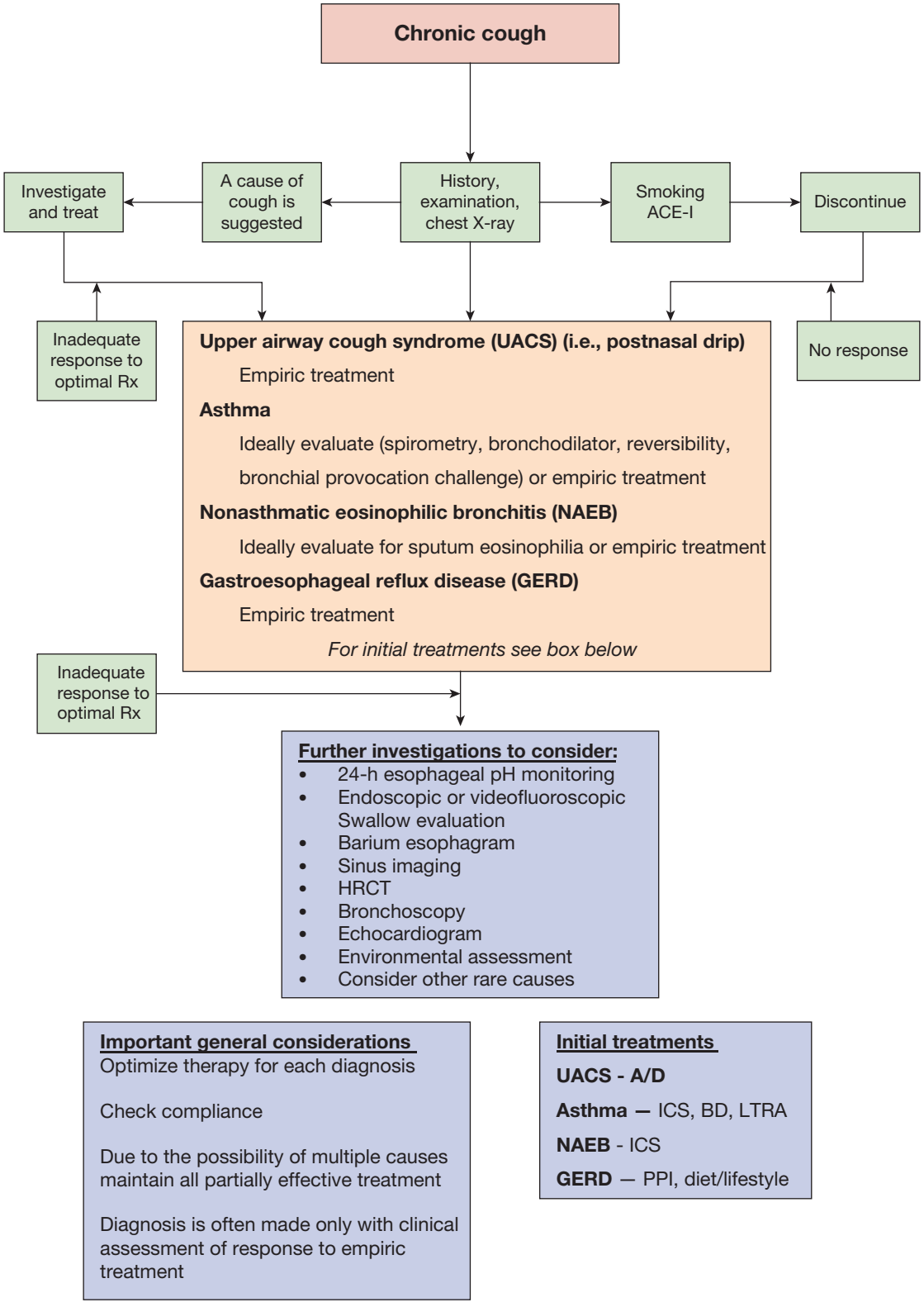


Figure 29-15 Algorithm for the evaluation of chronic cough lasting 8 weeks in adults. ACE-I, ACE inhibitor; BD, bronchodilator; LTRA, leukotrienes receptor antagonist; PPI, proton pump inhibitor; ICS, inhaled corticosteroid; A/D, antihistamine/decongestant; HRCT, high-resolution computed tomography. *(Reproduced with permission from Irwin RS, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129 (1 Suppl):1S–23S.)*

implies a potentially life-threatening process requiring immediate evaluation and treatment.

An initial decision faced by the physician who is told that blood has been coughed up is whether to conclude that the blood is coming from the respiratory tract. Any portion of the respiratory tract can be the source of bleeding including a main bronchus, the lungs, or the nose or throat. On occasion, blood from the nose and throat is inhaled and then expectorated. As long as this possibility is kept in mind, bleeding that originates in the nose, throat, or larynx is not apt to be overlooked.

An additional consideration is distinguishing hemoptysis from hematemesis (vomited blood). Even if the blood is aspirated and then coughed up, the patient can usually tell if the blood originated in the respiratory or alimentary tract. The appearance of the bloody material also helps to distinguish between hemoptysis and hematemesis: blood that originates in the airways is usually bright red, is mixed with frothy sputum, has an alkaline pH, and contains alveolar macrophages that are laden with hemosiderin; in contrast, blood from the stomach usually is dark, has an acid pH, contains food particles, and often occurs in patients with a long history of gastric disease.

Blood arising from the bronchial arteries is more often the source of massive hemoptysis, owing to its higher perfusion pressure, than blood from the pulmonary circulation. The bronchial circulation may be the source of life-threatening bleeding, for example, in patients with bronchiectasis in whom the vessels frequently become distorted and easily ruptured. Dieulafoy's disease of the bronchus, in which there is a submucosal fistula between bronchial and pulmonary arteries, is a rare cause of massive hemoptysis.[43]

The differential diagnosis of hemoptysis includes disorders arising within the airways and the pulmonary parenchyma. Inflammatory processes (e.g., bronchitis and bronchiectasis) and neoplasms are the most common causes of blood arising within the airways. Within the pulmonary parenchyma, common causes are infections, such as tuberculosis, pneumonia, *Aspergillus*, or lung abscess. Inflammatory processes that involve the lung, such as granulomatosis with polyangiitis (formerly known as Wegner's granulomatosis) or Goodpasture syndrome, are also important causes of hemoptysis (Fig. 29-16). Bleeding may be iatrogenic, as for example, after a lung biopsy or when chemotherapy for bone marrow transplantation evokes diffuse alveolar hemorrhage. Vascular disorders, including pulmonary embolism, arteriovenous malfunctions, and mitral stenosis are also to be considered in the differential diagnosis. Unexplained hemoptysis occurs in COPD and usually is not recurrent.[44]

The causes of hemoptysis are numerous and diverse (Table 29-10). The clinical setting is usually helpful in identifying the cause. Hemoptysis before middle age usually brings to mind infections; after 40 to 45 years of age, or if there is a history of smoking, bronchogenic carcinoma heads the list. In patients left with a pulmonary cavity after pulmonary disease that has healed (e.g., tuberculosis), and in regions of the country where pulmonary fungal diseases are prevalent, a bout of hemoptysis is occasionally the first sign of the disease. In patients who have a predisposing cause, such as oral contraceptives or chronic heart failure, pulmonary embolism must be considered.

The evaluation of hemoptysis involves a careful history, physical examination, and a chest radiograph. Initial studies also include a complete blood count. The degree of anemia may influence the rapidity of further testing, and thrombocytopenia may be a contributing factor to hemoptysis. Rapid correction of anemia, thrombocytopenia, or coagulopathy with the transfusion of appropriate blood products may be required promptly depending upon the clinical status and degree of abnormality. Similarly, measurement of coagulation parameters is important. Studies of renal function and a urinalysis may be indicated when a systemic process, which causes a pulmonary-renal syndrome is a possibility. Sputum should be collected and, depending on the circumstance, microbiologic cultures and stains or cytologic examination should be performed. Depending on whether a cause is identified, and the risk factors for a serious cause of bleeding, the evaluation next involves additional studies to search for a source.

TABLE 29-10 Some Causes of Hemoptysis

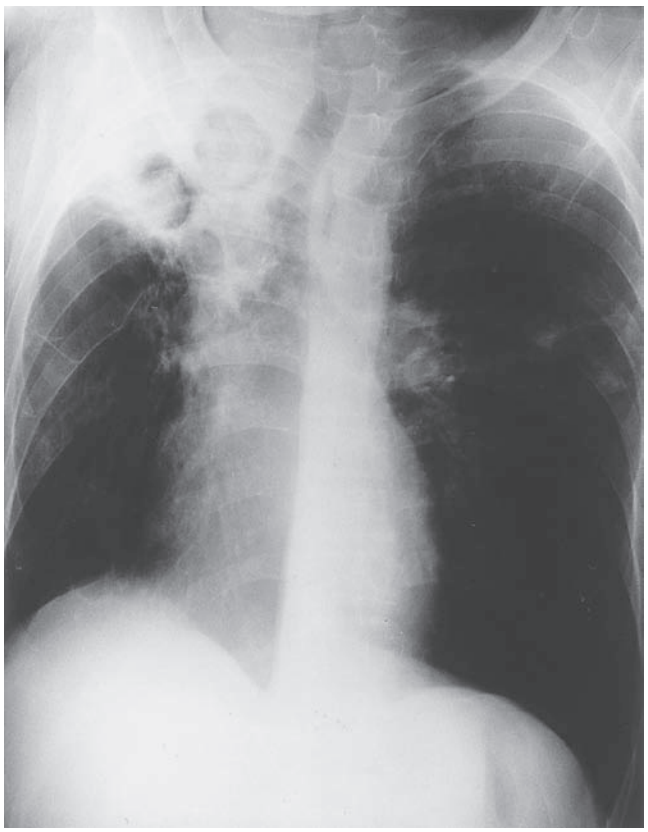
Infections
Bronchitis
Tuberculosis
Fungal infections
Pneumonia
Lung abscess
Bronchiectasis
Neoplasms
Bronchogenic carcinoma
Bronchial adenoma
Cardiovascular disorders
Pulmonary infarction from thromboembolism
Mitral stenosis
Trauma
Foreign body
Hematologic/immunologic
Disorders of hemostasis
Goodpasture syndrome

Because hunting for the cause and the source of bleeding is generally uncomfortable for the patient and often expensive, the intensity of the search depends on the circumstances. For example, rarely is a search for the bleeding site needed in a patient with acute bronchitis, pneumonia, or bronchopulmonary suppuration. But as a rule, unless the cause is evident, a full-scale investigation is mandatory.

Patients with hemoptysis and a history of tobacco smoking, individuals who are more than 40 years of age, or those who experience hemoptysis that lasts for more than 1 week are at greater risk for a worrisome cause and warrant additional studies. A high-resolution computed tomography (HRCT) of the chest is usually the next step if the patient has no history of tobacco use or if the plain chest radiograph suggests a parenchymal abnormality, such as bronchiectasis or arteriovenous malformation. Patients with a history of tobacco use or other risk factors for a malignancy warrant fiberoptic bronchoscopy (Chapter 35). In practice, HRCT and bronchoscopy are often complementary for visualizing abnormalities that are not apparent on plain chest radiographs. Patients with chronic bronchitis and who are at low risk for malignancy, or in whom the chest radiograph is normal or identifies the cause of hemoptysis (e.g., pneumonia) can usually be treated initially for bronchitis with follow-up appraisals to show prompt resolution of hemoptysis. However, should hemoptysis recur, further evaluation is required.

■ NEOPLASMS

Nonmassive hemoptysis (<500 cc/24 h) is common in bronchogenic carcinoma; less frequently carcinoma is the cause of massive hemoptysis. The likelihood of a neoplastic cause of hemoptysis is greatly increased in a cigarette smoker. Usually a troublesome cough and vague chest pain precede and accompany the hemoptysis. For hemoptysis to occur, the lesion must communicate with the airways. Most often the bleeding is a consequence of ulceration caused by an expanding tumor; sometimes it is due to a pneumonic process or to an abscess in the lung behind an obstructive lesion. Hemoptysis



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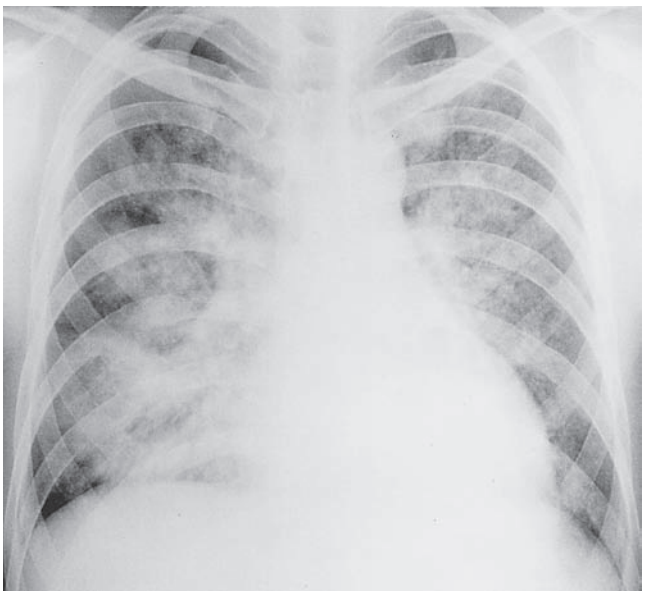

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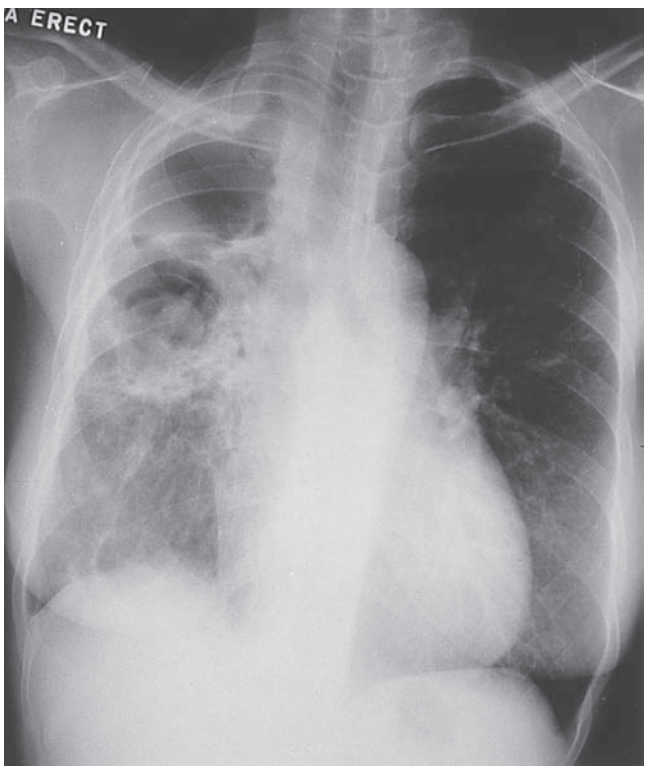


C

D

Figure 29-16 Causes of hemoptysis. **A.** Old tuberculosis cavities in right apex. They were removed surgically to control hemoptysis. **B.** Goodpasture syndrome. **C.** Fungus ball in coal miner's pneumoconiosis. *(Used with permission of J. Gough.)* **D.** Sagittal section of lung. Fungus ball due to aspergillosis in old tuberculosis cavity. Recurrent hemoptysis was treated with surgical removal of right upper lobe.

rarely complicates metastatic tumors of the lungs (primarily renal and colon carcinomas).

Not only malignant, but also benign, tumors of the lung cause bleeding. The classic example is bronchial carcinoid.

Hemoptysis may accompany a severe infection occurring anywhere from the top to the bottom of the respiratory tract. It is uncommon in the usual viral or bacterial pneumonia. Conversely, it is not uncommon in the pneumonia that complicates bronchogenic carcinoma or in the pneumonia that is caused by staphylococci, influenza virus, or *Klebsiella*.

The infecting organism determines the appearance and composition of the material that is expectorated with the blood. As indicated previously, in pneumococcal lobar pneumonia, the sputum at the onset is characteristically rusty-looking, but sometimes it is faintly or grossly bloody. In staphylococcal pneumonia, the blood is mixed with pus. In *Klebsiella* pneumonia, the bloody sputum may resemble currant jelly. Brisk bleeding is common in lung abscess; the blood is mixed with copious amounts of foul-smelling pus. In lung gangrene, blood is associated with necrotic lung tissue.

Bleeding is common in bronchiectasis. Because it usually originates in a bronchial artery, bleeding is often brisk. While most episodes stop spontaneously, the hemoptysis tends to recur and may be life-threatening.

Fungal infections of the lungs may cause hemoptysis (Fig. 29-16). As in tuberculosis, hemoptysis is generally a consequence of a continuing necrotizing and ulcerating inflammatory process or of bronchiectasis. The most common fungal disorder associated with hemoptysis is a "fungus ball" that resides either in a healed tuberculous or bronchiectatic area or in a cystic residue of sarcoidosis. *Aspergillus* is the usual fungal agent; less often another fungus (e.g., *Mucor*) is the cause.

At one time, the most common source of hemoptysis was an active tuberculosis cavity. Despite the increasing frequency of tuberculosis, hemoptysis is uncommon because of effective antituberculous therapy. If tuberculosis is allowed to progress to the point of extensive fibrosis and cavitation, or becomes complicated by bronchiectasis, hemoptysis can be troublesome and persistent. Hemoptysis may arise from a *Rasmussen aneurysm*, which is an erosion of a small- or medium-sized pulmonary artery into an adjacent tuberculosis cavity.

The "right middle lobe syndrome" is frequently associated with hemoptysis. It is due to a partial or complete obstruction of the right middle lobe bronchus, resulting in atelectasis or pneumonitis in the right middle lobe. The obstruction is more often caused by scarring or inflammation than by physical compression of the lumen by an enlarged lymph node. The cause is usually infectious; the infection may be tuberculosis.

In parts of the world where amebiasis is endemic, hemoptysis follows perforation into the airways of an amebic lung abscess. The sputum resembles anchovy sauce.

CARDIOVASCULAR DISORDERS

Pulmonary congestion and alveolar edema sometimes produce blood-tinged sputum. In chronic pulmonary congestion secondary to left ventricular failure or to mitral valve disease, alveolar macrophages in the sputum are often laden with hemosiderin ("heart failure cells"). In severe congestion and edema, the sputum is often pink and frothy. Usually there is no difficulty in recognizing that inadequate performance of the left ventricle is the cause of the bloody sputum.

Pulmonary thromboembolism may produce hemoptysis when associated with infarction (Fig. 29-17). The hemoptysis of pulmonary infarction is usually associated with pleuritic pain and, often, with a small pleural effusion because of the peripheral location of the infarct.

Tight mitral stenosis is sometimes first manifested by a bout of brisk, bright-red hemoptysis that is difficult to control. The source of the bleeding is the submucosal bronchial veins, which proliferate considerably in this disorder. Massive hemoptysis due to mitral stenosis is a medical emergency and is an indication for surgical intervention to relieve the obstruction at the mitral valve.

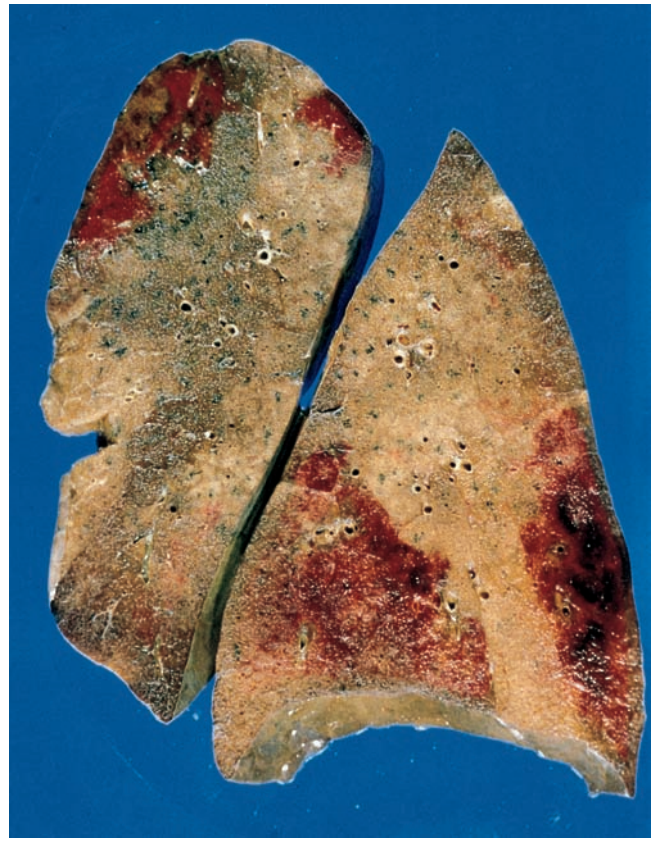


Figure 29-17 Hemorrhagic pulmonary infarcts. Several subpleural areas of infarction are clearly demarcated.

Hemoptysis from other circulatory disorders is much less common. Occasionally, an aortic aneurysm penetrates into the tracheobronchial tree, causing death by exsanguination and asphyxiation. An extraordinary event is the communication of an arteriovenous fistula with a small airway, causing bleeding that is exceedingly difficult to arrest.

TRAUMA

Hemoptysis follows a variety of chest injuries: puncture of a lung by a fractured rib, contusions of a lung by severe blunt trauma to the chest, and necrosis of the lining of the tracheobronchial tree by inhaled fumes or smoke. Blunt trauma from the steering wheel during an automobile collision sometimes lacerates or fractures the tracheobronchial tree. Stab or gunshot wounds often tear the lungs or airways. On occasion, mucosal lacerations in the course of severe coughing evoke hemoptysis.

After lobectomy, or now, less commonly, pneumonectomy, a large hemothorax occasionally empties into the airways. This is an alarming and ominous event. Its imminent occurrence is often heralded by the expectoration of blood-stained sputum after a paroxysm of coughing. The hemothorax must be promptly evacuated and the bronchus surgically repaired. Hemoptysis within a few weeks to months after lung resection has different implications: recurrence of tumor, granulation tissue, or bronchial sutures. Prompt bronchoscopy is necessary for accurate appraisal of the situation.

MISCELLANEOUS

Other causes of hemoptysis are listed in Table 29-10. They vary greatly in severity, urgency, and prognosis. Sometimes the cause is obscure, as in the occasional instance of hemoptysis that

accompanies menstruation (*catamenial hemoptysis*). An aspirated foreign body produces bleeding by damaging the mucosa on impact; if allowed to remain in place, it sometimes causes bronchiectasis, which, in turn, may cause bleeding. Pulmonary calcific foci, either in the pulmonary parenchyma or in lymph nodes, sometimes cause hemoptysis by ulcerating into a bronchus.

Thrombocytopenic purpura and hemophilia and the therapeutic use of anticoagulants are occasional causes of hemoptysis.

Hemoptysis in Goodpasture syndrome (Fig. 29-16) or in idiopathic hemosiderosis is life-threatening.

■ MANAGEMENT OF MASSIVE HEMOPTYSIS

The first priority in the care of a patient with life-threatening hemoptysis is to protect the airway and prevent asphyxiation.[45] Intubation should be contemplated and consideration given to selective intubation of one lung in order to protect it from spillage of blood from the other. When the site of bleeding is known, one simple, initial bedside maneuver is to place the involved side in a dependent position in order to protect the uninvolved lung. Bronchoscopy should be performed promptly in order to identify the source (Chapters 35 and 36). This may also allow bronchoscopic interventions, such as the placement of a balloon catheter to isolate the involved segment, lavage with iced saline, or the application of topical epinephrine (1:20,000). Bronchoscopic localization may help to guide attempts at arresting the bleeding by angiographic embolization. If these modalities fail to stop the bleeding, surgical exploration may be required. Not surprisingly, emergency procedures are accompanied by a high mortality. None of the approaches has been rigorously studied, and the choice is frequently dictated by the urgency, local experience, and availability of bronchoscopy.

CYANOSIS

Cyanosis refers to a bluish discoloration of the skin that is caused by increased amounts of reduced hemoglobin in the subcapillary venous plexus. The discoloration is most apparent in the lobes of the ears, the cutaneous surfaces of the lips, and the nail beds. In patients with dark skin, the mucus membranes and the retina are important sites to examine for cyanosis. Unless flow through the skin is slowed, as in heart failure, cyanosis implies arterial hypoxemia. Cyanosis does not appear in carbon monoxide poisoning or in severe anemia, even though arterial O_2 content is extremely low. This is because there is an insufficient amount of reduced hemoglobin present for the cyanotic discoloration to be visible. The presence of abnormal pigments in blood, such as methemoglobin or bilirubin, complicates the detection of cyanosis.

■ CAPILLARY O_2 CONTENT

An increase in the amount of reduced hemoglobin in the capillaries of the skin, as elsewhere, results from inadequate oxygenation of arterial blood, excessive removal of O_2 from capillary blood (as when the circulation through a region is slowed by vasoconstriction or a very low cardiac output), or from a combination of the two. The concentration of reduced hemoglobin in the skin capillaries must reach about 5 g/dL before cyanosis becomes discernible. Thus, in severe anemia, when hemoglobin concentrations are exceedingly low (on the order of 3–4 g/dL), although virtually all the hemoglobin can be reduced in traversing the skin capillaries, an insufficient amount of reduced hemoglobin remains to produce a visible discoloration. On the other hand, the polycythemic patient develops cyanosis at a higher arterial O_2 saturation than does the normal individual.

■ CAUSES OF CYANOSIS

Several types of cyanosis are usually identified according to the underlying mechanism. They include peripheral cyanosis, cyanosis arising from pulmonary disease, cyanosis from venous admixture, and cyanosis due to abnormal pigments in the blood.

Peripheral Cyanosis

This type of cyanosis is secondary to abnormally large extraction of O_2 from blood flowing through peripheral capillaries. The most common cause is a diminished cardiac output associated with peripheral vasoconstriction. Not only the hands and feet but also the tip of the nose become blue in severe heart failure. Indeed, in patients with intractable heart failure, necrosis occasionally develops at the tip of the nose.

Peripheral vasoconstriction per se, as in Raynaud's disease, also produces cyanosis of the nail beds.

Cyanosis in Pulmonary Disease

Patients with chronic bronchitis and emphysema characteristically manifest derangements in ventilation–perfusion relationships. In some, arterial hypoxemia results. In patients with diffuse interstitial fibrosis, normal arterial oxygenation at rest is succeeded by arterial hypoxemia, and sometimes, by cyanosis, during exercise. Another cause of arterial hypoxemia is the syndrome of alveolar hypoventilation in patients with normal lungs. In any of these situations, cyanosis is intensified if heart failure supervenes and slows blood flow through the skin (i.e., is associated with decreased O_2 delivery).

Cyanosis Due to Venous Admixture

In patients with intracardiac right-to-left shunts, cyanosis arises from a mixture of venous and arterial blood. The effect of venous admixture is particularly striking if the O_2 content of mixed venous blood is inordinately low, as in some types of congenital heart disease and in severe heart failure. Often, secondary polycythemia contributes to the cyanosis. On occasion, regional cyanosis is diagnostic. For example, in patent ductus arteriosus with reversal of blood flow, the lower extremities are deeply cyanotic, whereas the upper extremities are virtually normal in color.

Cyanosis Due to Abnormal Pigments in Blood

Methemoglobinemia is an occasional cause of cyanosis. Methemoglobinemic blood is chocolate brown, and spectrophotometric examination of blood reveals the characteristic pigment. Arterial blood examination discloses a normal P_{O_2}.

The cause of methemoglobinemia may be hereditary (i.e., due to the presence of hemoglobin M or a deficiency in methemoglobin reductase) or, more often, acquired (e.g., by exposure to chemical agents such as aniline dyes, chlorates, nitrates, and nitrites); methemoglobinemia may also result from drugs, such as dapsone, nitroglycerin, phenacetin, or primaquine. Nitrates are a common cause of methemoglobinemia. Nitrates are reduced to nitrites by bacteria in the intestinal tract. Excessive use of nitroglycerin, an organic nitrate, leads to methemoglobinemia.

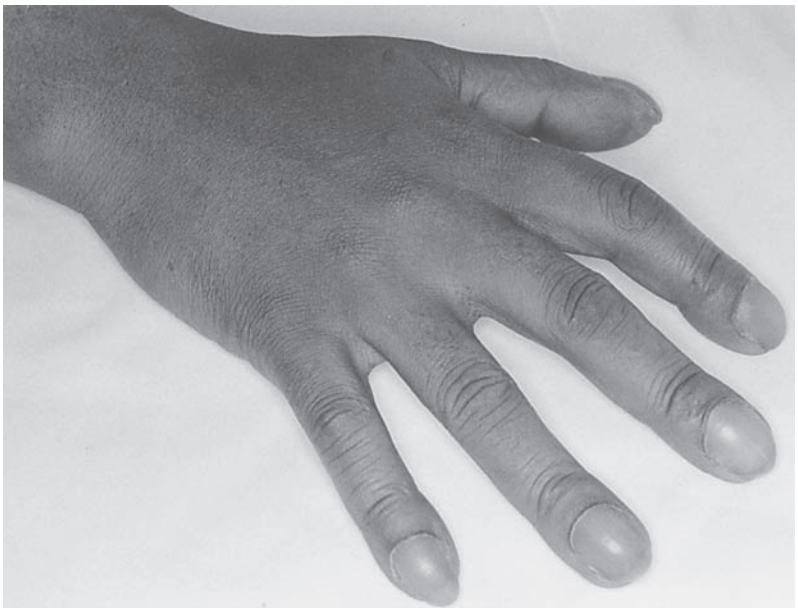
In methemoglobinemia, the ferrous iron is oxidized to ferric iron, rendering the hemoglobin molecule incapable of binding O_2 or CO_2. Methemoglobin is formed continuously in the normal erythrocyte, but its level within the cell is kept low (<2%) by intracellular reductive mechanisms. High levels of methemoglobin result from hereditary abnormalities (e.g., a deficiency in methemoglobin reductase) or from exposure to drugs or chemicals that increase the rate of oxidation beyond the reductive capacity of the erythrocytes. Clinical manifestations of methemoglobinemia vary with the blood levels. Concentrations of methemoglobin between 10% and 25% usually cause asymptomatic cyanosis. When these levels are exceeded, dizziness, fatigue, and headache appear.

CLUBBING

Clubbing of the digits is a classic finding in medicine that dates back to Hippocrates' awareness of the association between characteristic

changes in the fingertips and empyema. Occasionally, it constitutes a valuable clue to clinically inapparent disease of the lungs and pleura. Clubbing of the fingers designates the selective bulbous enlargement of the distal segments of the digits due to an increase in soft tissue (Fig. 29-18). Although most often it is painless, clubbing remains an important finding, as its presence should signal an evaluation for potential serious causes.

When full-blown, clubbing is easy to recognize: (1) the nails, particularly the index finger, become abnormally curved in the longitudinal and coronal planes; (2) the hyponychial angle, viewed



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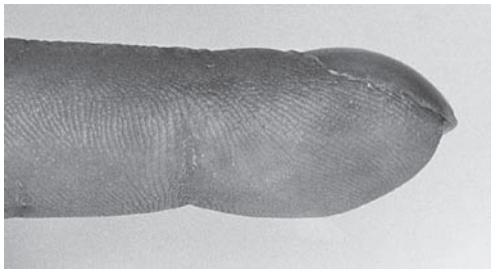

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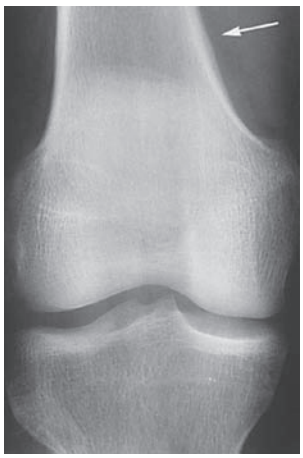

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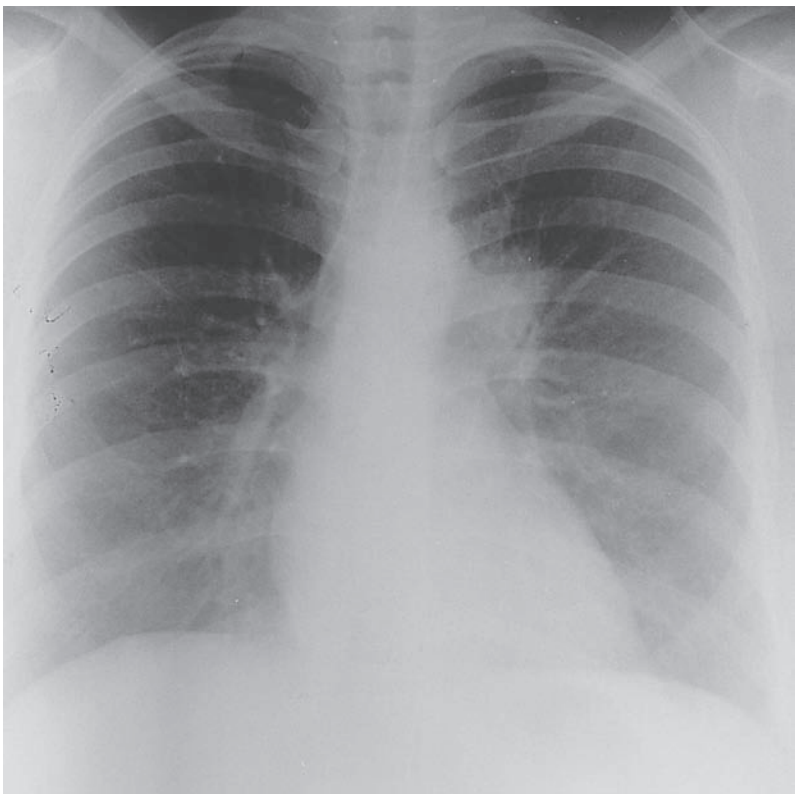

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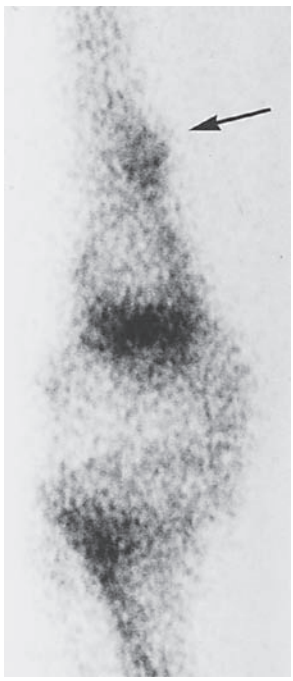


E

Figure 29-18 Clubbing of the digits and hypertrophic osteoarthropathy. A 40-year-old woman developed swelling and tingling of the fingertips in association with painful swelling of both knees. She was a heavy smoker (36 pack-years) and had an 8-month history of a dry cough. **A.** Clubbing of all fingers. **B.** Index finger. **C.** Left hilar mass that proved to be a primary adenocarcinoma of the lung. **D.** Subperiosteal formation of new bone on the medial aspect of the diaphysis of the femur. **E.** Bone scan, using ^{99m}Tc methylene diphosphonate. An abnormal accumulation of isotope is seen in the area of new bone *(arrow)*.

in profile, becomes blunted, often in conjunction with softening and sponginess of the base of the nail; and (3) the undersurface of the terminal digit becomes large and bulbous. Early stages of clubbing are subtle and generally difficult to diagnose. Clubbing often has to be distinguished from simple curvature of the nails and, occasionally, from chronic paronychia and Heberden nodes. A variety of methods have been proposed for quantifying clubbing (e.g., measuring casts of the fingertips), but none has become popular.

Clubbing is generally acquired, but it may be hereditary. Acquired clubbing is seen in a wide variety of disorders, both extrathoracic and thoracic (Table 29-1).

It is important to recognize that clubbing is not caused by all forms of chronic lung disease. COPD, for example, does not cause clubbing. The presence of clubbing in a patient with COPD should alert the clinician to the possibility of a second process, commonly lung cancer. As a rule, clubbing is bilaterally symmetrical, affecting hands and feet; on occasion, local factors, such as injury of a finger or of the median nerve, may cause clubbing that is confined to a single finger. Rarely, clubbing may be confined to the digits of one hand (e.g., in an ipsilateral pulmonary sulcus tumor that has invaded the brachial plexus or following hemiplegia). In certain types of congenital heart disease, a telltale distribution of clubbing is of considerable diagnostic value. For example, in patent ductus arteriosus associated with reversal of shunt through the ductus, clubbing affects only the toes.

■ PATHOGENESIS

The pathogenesis of clubbing is unknown, and no suitable animal model of clubbed fingers has yet been developed, largely because so few species other than primates have fingers. A common denominator in the pathogenesis of clubbing appears to be vasodilation of vessels in the fingertip, including formation of the arteriovenous connections. As a result, hydrostatic pressures increase in the capillaries and venules, promoting the transduction of fluid into the interstitium. The reason for this preferential vasodilation is unclear. A popular notion is that a humoral substance escapes normal deactivation by pulmonary capillaries. This theory could account for clubbing in cyanotic congenital heart disease, in various pulmonary diseases in which proliferation of the bronchial circulation occurs, and in hepatic cirrhosis in which pulmonary arteriovenous anastomoses and right-to-left shunts are common. However, it is difficult to relate this theory to the high incidence of clubbing in subacute bacterial endocarditis.

At present, a single hypothesis that would account for the clubbing that occurs in such diverse disorders as subacute bacterial endocarditis, carcinoma of the lung, hemiplegia, chronic mountain sickness, and purgative abuse is not possible. Indeed, it seems likely that clubbing of the digits is a stereotyped consequence of diverse influences that have in common the capacity to induce marked digital vasodilation and interstitial edema of the soft tissue.

HYPERTROPHIC OSTEOARTHROPATHY

Occasionally, clubbing of the digits is accompanied by hypertrophic osteoarthropathy (HOA), a separate clinical and radiographic entity. Clinically, HOA is manifested by pain and swelling of the soft tissues over the distal ends of the long and tubular bones. Radiographically, the distinctive feature of HOA is the formation of new bone beneath the periosteum of the distal diaphyses of the long bones of the extremities (Fig. 29-18).

The most common disorder associated with HOA is carcinoma of the lung. The incidence is about 5% and is unrelated to the cell type of the cancer, except that small cell carcinoma is rarely implicated; a peripheral carcinoma of the lung is slightly more common than a central one. Joint symptoms precede the local signs of tumor in about one-third of the cases; the interval is sometimes as long as 2 years. Pulmonary metastases rarely cause HOA. Pulmonary tuberculosis is seldom, if ever, associated with HOA. CF and idiopathic pulmonary fibrosis may be accompanied by HOA. Pregnancy may rarely be a cause of HOA, with symptoms resolving promptly with delivery.

As in the case of clubbing of the digits, theories about pathogenesis tend to focus on humoral factors generated elsewhere. However, a neurogenic theory has also been advanced on the basis of two types of observations: (1) in a few patients, vagotomy has relieved the symptoms of inoperable carcinoma of the lung and led to regression of the bony lesions; and (2) in keeping with the observations on the few patients, vagotomy in dogs is usually followed by a decrease in blood flow to the limbs.

In contrast to clubbing of the digits, which is rarely painful, HOA associated with carcinoma of the lung often causes severe rheumatic symptoms. These symptoms vanish after resection of the carcinoma, even though clubbing usually remains. In patients who are treated with radiotherapy for unresectable carcinoma, pain in the vicinity of the joints usually decreases greatly and usually does not recur even if metastases develop in the lungs or elsewhere.

CHEST PAIN

Pain in the chest is a common clinical problem. It may arise from within the thorax (the heart, pericardium, lungs, pleura, chest wall) or be referred from elsewhere (e.g., from below the diaphragm). Characteristic patterns and associations may help to clarify the source of the pain.

First thoughts about chest pain almost invariably turn to the pain of myocardial ischemia. However, cardiac pain is often distinguishable from other types of chest pain because of its viselike nature; its characteristic radiation to the left arm, shoulder, or neck; and its lack of relation to breathing. Extracardiac painful sensations can arise from various sites within the thorax, most often from the pleura, the lungs, or the chest wall. Pain may also be referred to the thorax as a result of GERD.[46–48] In the primary care setting, in stable patients it is usually possible to exclude as the basis for pain cardiac, gastrointestinal, or pulmonary diseases.[49,50]

■ PLEURITIC PAIN

The most characteristic pain associated with the respiratory apparatus is pleural pain. It originates in the parietal pleura and endothoracic fascia; the visceral pleura is insensitive to pain. In contrast to the deep, oppressive substernal pain of myocardial infarction, pleuritic pain is identified by the patient as being close to the thoracic cage. It is predominantly an inspiratory pain, reflecting the stretching of inflamed parietal pleura during movement of the thorax; coughing or laughing is distressing; the patient often clutches the chest to minimize its excursion. The pain is usually local, but sometimes it spreads along the course of the intercostal nerves that supply the affected area. Irritation of the diaphragmatic pleura by an inflammatory process either below or above the diaphragm often causes ipsilateral shoulder pain when the central portion of the diaphragm is involved; sometimes the pain is referred to the abdomen when the outer diaphragmatic pleura is irritated.

As a rule, pleural pain is part of a syndrome of pleural inflammation that includes malaise and fever; an important exception to this generalization is the pleural pain of pulmonary infarction, which is often unassociated with any premonitory signs. In addition to inflammation and malignant etiologies, pleuritic pain occurs with pneumothorax.

■ PULMONARY PAIN

A second distinctive type of respiratory chest pain accompanies a tracheitis or tracheobronchitis. The pain is searing and is most pronounced after cough. Invariably, this central chest pain is associated with evidence of upper respiratory infection. It is aggravated by cough. Cold air may be intolerable.

An uncommon type of chest pain is associated with pulmonary hypertension. It is usually absent at rest and appears during exertion.

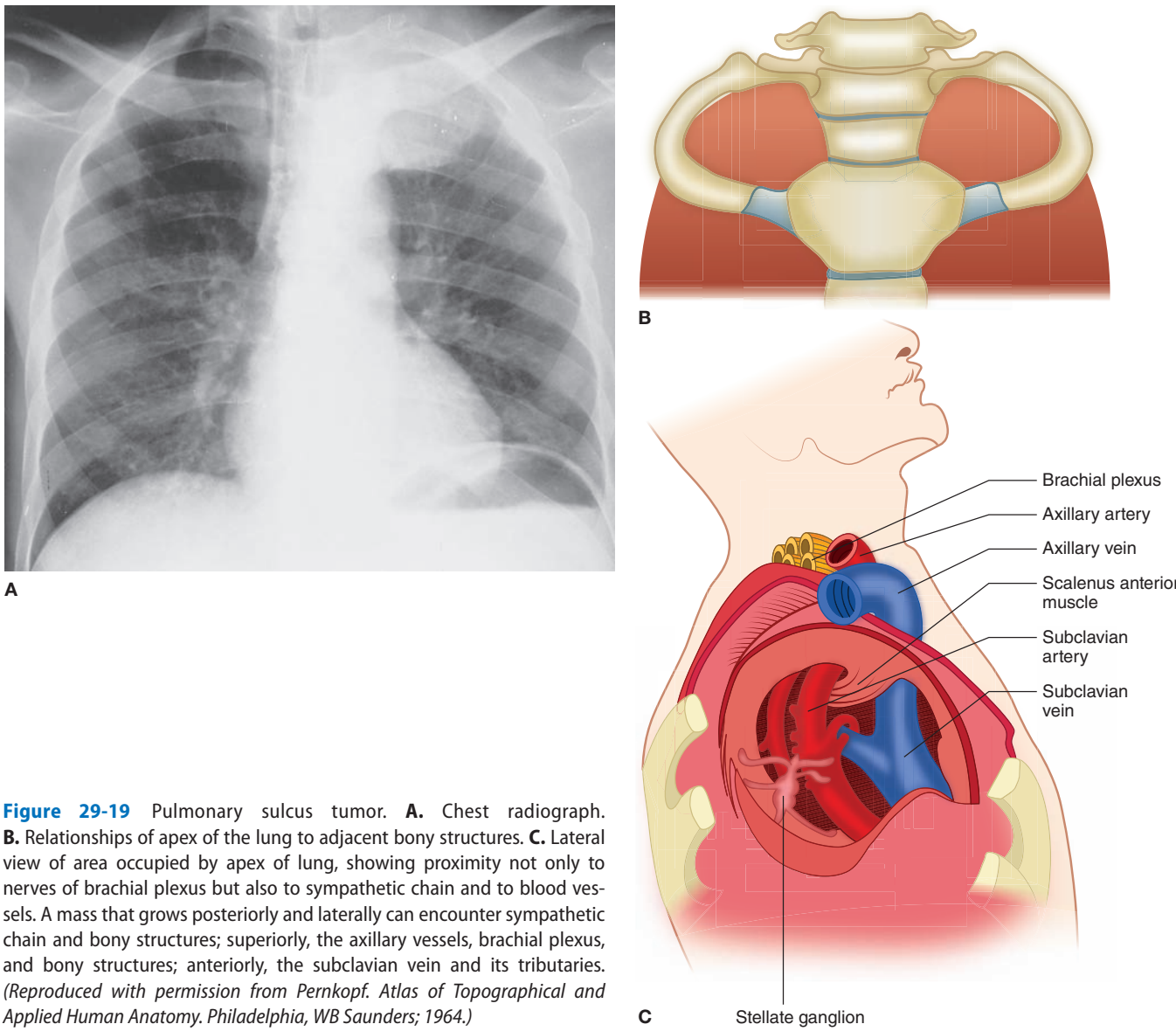


Figure 29-19 Pulmonary sulcus tumor. **A.** Chest radiograph. **B.** Relationships of apex of the lung to adjacent bony structures. **C.** Lateral view of area occupied by apex of lung, showing proximity not only to nerves of brachial plexus but also to sympathetic chain and to blood vessels. A mass that grows posteriorly and laterally can encounter sympathetic chain and bony structures; superiorly, the axillary vessels, brachial plexus, and bony structures; anteriorly, the subclavian vein and its tributaries. *(Reproduced with permission from Pernkopf. Atlas of Topographical and Applied Human Anatomy. Philadelphia, WB Saunders; 1964.)*

The pain is substernal and is associated with dyspnea; it subsides promptly when exercise stops. It is often mistaken for classic angina until the presence of pulmonary hypertension is uncovered. It may be due to right ventricular strain and ischemia.

■ CHEST-WALL PAIN

Musculoskeletal pain arising in the chest that is also aggravated by breathing may be confused with pleuritic pain. It is rarely severe and incapacitating, is often bilateral, and generally is intensified by changes in body position or flexing the thorax. The affected muscles are often tender to gentle pressure. A fractured rib is often identified as the source of pain by a history of a fall, injury, or trauma. Additional clues are point tenderness and crepitus of the affected area, reproduction of the pain upon manual compression of the chest, or radiographic evidence of a broken rib.

The pain of a pulmonary sulcus tumor, or "Pancoast tumor," (Fig. 29-19) is quite distinctive. This unusual location of a carcinoma of the lung was originally described by Pancoast in 1932. Pain due to the tumor occurs along the distribution of the eighth cervical and first and second thoracic nerves. In addition, Horner syndrome, local destruction of bone by the tumor, and atrophy of hand muscles may be observed. The chest radiograph is distinctive in showing a small, sharply defined shadow at one apex. Destruction of one or more of the upper three ribs posteriorly and of their adjacent transverse processes may also be seen.

■ CARDIAC PAIN

Attention was called above to the pain of myocardial ischemia. Another type of cardiac pain is that of pericarditis. Pericardial pain is often aggravated by deep breathing and, almost invariably, is accompanied by a telltale rub that is synchronous with the heartbeat. The discomfort may be relieved by leaning forward.

The *postcommissurotomy* or *postpericardiotomy syndrome* is characterized by chest pain that develops within a few days to weeks after cardiac surgery or pericardiotomy. The pain is usually sudden in onset and substernal, with radiation to the left side of the neck; often it is aggravated by deep breathing. Low-grade fever and a high erythrocyte sedimentation rate are regular concomitants.

Chest pain may also be troublesome in patients who have undergone cardiac transplantation. The diagnosis is usually self-evident when account is taken of the antecedent history of cardiac surgery. Indeed, confusion is more apt to arise with the pain of myocardial infarction than with respiratory causes of chest pain.

MISCELLANEOUS CAUSES OF PAIN

Other structures in the mediastinum may be the source of chest pain. Noteworthy are the types of pain arising from the esophagus (peptic esophagitis) and dissection of the aorta. Their patterns and intensity help to distinguish them from respiratory pain. Esophageal disease is typically accompanied by a burning pain, frequently after eating. Acid reflux may worsen with recumbency. Aortic dissection is often described with a sharp, tearing sensation of acute onset, with radiation to the shoulder; these are often signs of impending cardiovascular collapse.

Arthritis of the cervical spine is a common cause of thoracic pain. Usually the cause is quite clear because of the characteristic distribution of the pain. Cervical spondylosis occasionally causes severe pain in the chest and arms, but it is more apt to mimic myocardial infarction than is respiratory pain. A metastatic tumor to the thoracic spine often causes bilateral symmetric pain; there is often discomfort to palpation over the affected area. Unilateral pain, along the distribution of an intercostal nerve, is characteristic of herpes zoster before the appearance of the skin eruption and is often described as an intense burning sensation.

Anxiety may produce or intensify chest pain. Usually, pain related to anxiety is accompanied by dyspnea and hyperventilation. Manifestations of vasomotor instability, such as excessive palmar sweating, flushing, and tachycardia, may accompany the complaint of chest pain due to anxiety. Rarely does the pain conform to a characteristic or consistent pattern. Anxiety also interferes with the quantification of pain originating in a somatic lesion and with its management.

FEVER

In the patient with lung disease, fever usually, but not invariably, signifies infection. When the lung disease is chronic, as in bronchitis and emphysema, a bout of acute bronchitis usually elicits only a modest fever, even though the sputum turns purulent. In contrast, an acute pneumonia or lung abscess may be associated with high fever.

The possibility that fever is due to infection lends urgency to the situation. The wide range of pulmonary infections is considered elsewhere in this book. Often overlooked at the outset is miliary tuberculosis, which occasionally escapes detection on the initial chest radiograph. Favoring this diagnosis is a history of recent contact with a patient with active tuberculosis, general malaise, easy fatigability, and anorexia during the previous few weeks. This insidious onset differs strikingly from the more sudden onset of acute pneumonia.

Neoplasms are also associated with fever. In certain neoplasms, such as carcinoma within a bronchus, the fever is generally a secondary effect attributable to infection distal to obstruction; necrosis within the tumor is a less common cause. In others, such as hypernephroma, fever and chills are striking, even though evidence of infection is absent. A mesothelioma of the pleura is often associated with fever. Presumably, in patients with neoplasms who have no evidence of infection, necrosis within the tumor leads to the elaboration of fever-producing factors within and around the tumor.

Acute hypersensitivity pneumonitis (extrinsic allergic alveolitis) is sometimes accompanied by fever.

In contrast to the pulmonary disorders in which fever is a characteristic feature, pulmonary sarcoidosis is uncommonly associated with fever unless there is extrapulmonary involvement, such as lymphadenopathy or EN. Nor is pneumoconiosis associated with fever unless complicated by necrosis in the midst of conglomerate fibrosis or by superimposed tuberculosis. Among the other many disorders of the lungs that cause no fever (and few systemic complaints) are idiopathic pulmonary fibrosis, lymphangitic carcinomatosis, multiple pulmonary metastases, alveolar proteinosis, idiopathic pulmonary hemosiderosis, and alveolar microlithiasis.

PULMONARY-CUTANEOUS SYNDROMES

Examination of the skin may provide important clues in the diagnosis and treatment of patients with pulmonary disease. Some skin lesions either accompany pulmonary disease or complicate its treatment; occasionally, systemic diseases that affect both skin and lung first manifest themselves in the skin.

This section focuses on processes in which there is prominence of cutaneous manifestations that might impact the care of the patient with pulmonary disease. The diagnosis and development of a differential diagnosis of cutaneous lesions is beyond the scope of this chapter and can be found in general dermatology textbooks.[51–53]

ATOPIC DERMATITIS

Atopy refers to a group of disorders, including asthma, allergic rhinitis, and atopic dermatitis, in which immune and pharmacologic responses are abnormal. The atopic person usually has a family history of one or more of these disorders. Atopic dermatitis is a common disorder, affecting 1% to 3% of the population in the United States. In 85% of affected subjects, the skin lesions appear before 5 years of age.[54] The dermatitis may resolve as the patient reaches adulthood; in the adult, either the skin lesions or respiratory systems may predominate although there is a wide range of individual variability.

In infants, the skin lesions often begin as dry, erythematous plaques on the cheeks; excoriations and scaling may be prominent. In older children, the lesions localize in flexures; lichenification and excoriated papules are prominent features (Fig. 29-20). In adults, the lesions favor the hands and extremities. Atopic subjects also manifest prominent folds of the lower eyelids, periorbital hyperpigmentation with facial pallor, generalized dry skin, and white dermatographism. At any age, pruritus may be prominent, leading to secondary bacterial infection (bacterial impetigo) within the lesions.

The cause of atopic dermatitis is unknown. In all likelihood, the pathogenesis is multifactorial, probably including disordered immune regulation as a causative factor. Patients with atopic dermatitis often have elevated levels of IgE; may have abnormalities of CD30, macrophage-derived chemoattractant, interleukins (IL)-12, -16, -18, and -31, and thymus and activation-regulated chemokine; and have mutations of the filaggrin gene. The use of any of these biomarkers has not yet been demonstrated to be diagnostic or of prognostic value.[54] In persons with atopic dermatitis, abnormalities in cell-mediated immunity and lymphocyte function increase the risk of disseminated viral disease, particularly herpes simplex. The role of food or environmental antigenic challenge in flares of atopic dermatitis is unsettled, but it is known that asthma can be precipitated by such challenges.

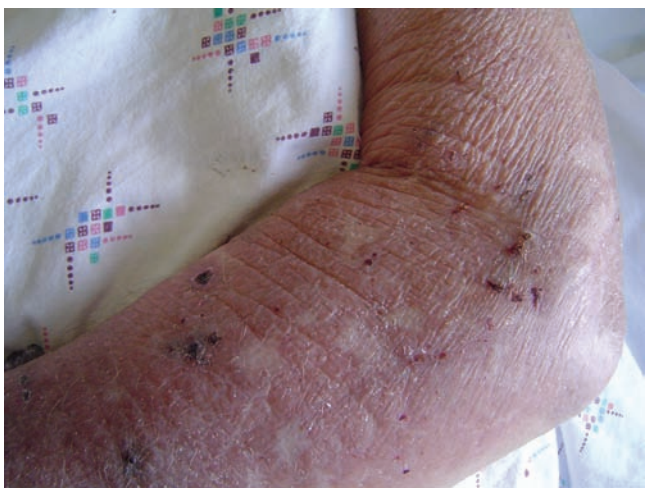


Figure 29-20 Atopic dermatitis is characterized by lichenification, excoriations, and slight scale.

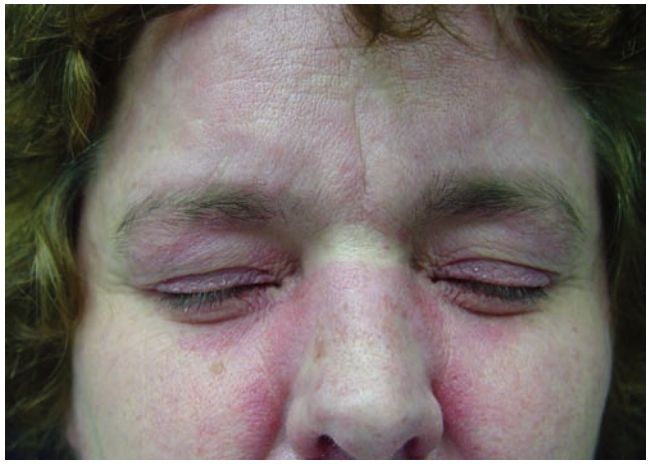


Figure 29-21 Heliotrope eruption of dermatomyositis.

The relationship between atopic dermatitis and lung disease is imperfect. Although hyposensitization is useful for asthma, it is either not helpful or is detrimental in atopic dermatitis. In addition, the use of omalizumab, while beneficial for asthma, has demonstrated mixed results for patients with atopic dermatitis. Recent evidence suggests that the use of dupilumab, an IL-4, IL-13 antagonist might be useful for atopic dermatitis, as well as for the associated asthma[55]

COLLAGEN VASCULAR DISORDERS

Common collagen vascular disorders warrant discussion in relation to possible coexisting pulmonary manifestations, especially dermatomyositis (DM) and scleroderma.

DERMATOMYOSITIS

DM is an idiopathic inflammatory myopathy characterized by proximal, symmetrical, slowly progressive muscle weakness, and characteristic cutaneous lesions.[56,57] The pathognomonic skin lesions include a heliotrope eruption, which consists of erythematous-to-violaceous periorbital changes that may be accompanied by edema (Fig. 29-21), and Gottron papules, which consist of erythematous papules over the bony prominences on the dorsal hands (Fig. 29-22). Patients may also manifest a photodistributed poikiloderma (Fig. 29-23), nail-fold changes, and an erythematous-to-violaceous scaly alopecia. Patients with DM frequently complain of marked itching.

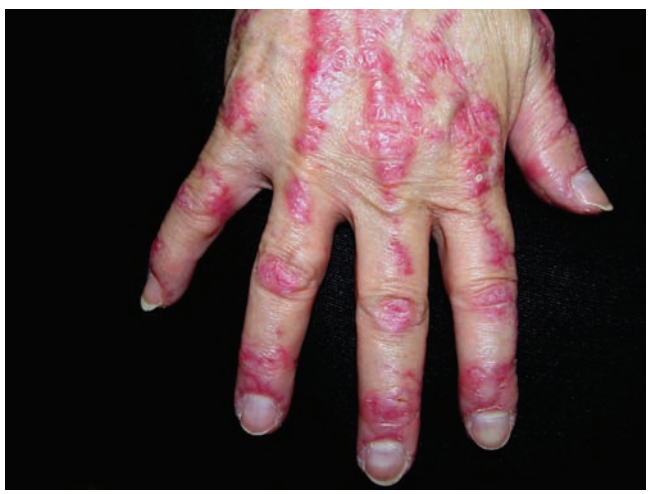


Figure 29-22 Gottron papules in dermatomyositis: Erythematous to violaceous lesions are most prominent over the joints. In addition, this patient demonstrates cuticular and periungual changes that are frequent in dermatomyositis.

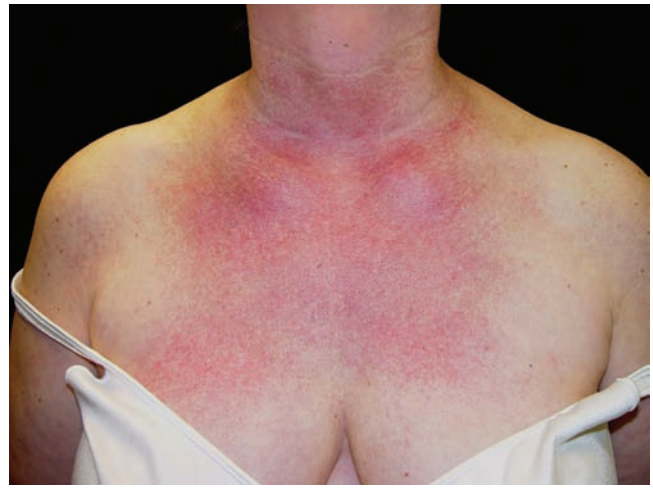


Figure 29-23 Photodistributed poikiloderma in a patient with dermatomyositis.

Patients with DM may also have other systemic manifestations, including arthritis, esophageal disease, and cardiopulmonary disease; some have a malignancy. Others with the characteristic cutaneous lesions of DM are not weak and do not have an increase in muscle-derived enzymes. These patients are said to have amyopathic dermatomyositis if they have skin lesions with normal strength, and normal muscle-derived enzyme assessments for a period of 2 or more years without having been treated with systemic immunosuppressives or corticosteroids for more than a month.

Pulmonary disease occurs in classic dermatomyositis and in amyopathic dermatomyositis in approximately 15% to 65% of patients. Interstitial pneumonitis is a primary process in DM/polymyositis. Interstitial lung disease also occurs in patients with amyopathic dermatomyositis; in this subset of patients, survival is poor.

Pulmonary involvement is more frequent in patients with esophageal dysfunction. Lung disease may also occur as a direct complication of the muscle disease, for example, hypoventilation or aspiration in patients with dysphagia, or may be a result of treatment, such as opportunistic infections or drug-induced hypersensitivity pneumonitis.

Pulmonary disease appears to be more prominent in patients in southeast Asia, China, and Japan; however, there are many reports of patients in the United States with varying ethnicities who have developed pulmonary disease, particularly interstitial fibrosis, as well as rapidly progressive and, at times, fatal disease.[58] Patients with polymyositis and lung disease tend to have antisynthetase antibodies, particularly the Jo-1 antibody. However, Jo-1 is rarely found in patients with dermatomyositis. Recently, the anti-melanoma-differentiation gene 5 antibodies appeare to be associated with an increased risk of pulmonary disease.

Treatment of interstitial lung disease in patients with dermatomyositis is often difficult. Several recent studies have suggested that Mycophenolate mofetil is useful for these patients.[59,60]

SCLERODERMA

Scleroderma refers to hard skin. This process may be localized to the skin or may be part of a systemic disease.[61,62] Localized cutaneous scleroderma may occur as limited plaques of morphea, generalized morphea, deep morphea, or linear scleroderma. Interstitial pneumonitis is a rare complication of morphea or linear scleroderma.

Two principal forms of progressive systemic sclerosis (PSS) have been described: limited scleroderma (acrosclerosis) and diffuse scleroderma. Acrosclerosis is the more common of the two and is characterized by sclerosis of the skin of the fingers (sclerodactyly) (Fig. 29-24) and Raynaud's phenomenon (Fig. 29-25).

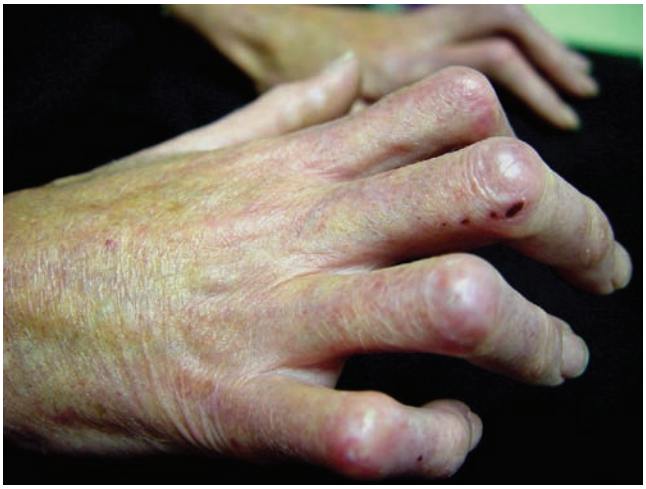


Figure 29-24 Acrosclerosis characterized by marked contractures and sclerodactyly.

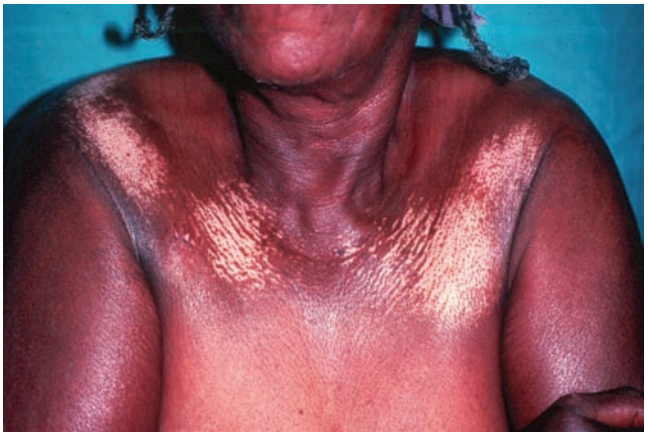


Figure 29-26 Vitiligo-like dyspigmentation associated with progressive systemic sclerosis.

A variant (CREST syndrome) includes calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia.

In contrast, patients with diffuse scleroderma have widespread sclerosis beyond the acral areas of sclerodactyly. The prognosis for diffuse scleroderma is much worse than for acrosclerosis. Both types of scleroderma are often preceded by Raynaud's phenomenon, diffuse arthralgias, or arthritis. The skin manifestations begin with transient, recurrent swelling of the hands, and progress to tapered fingers with shiny, hidebound skin (sclerodactyly). The feet, chest, face, and scalp are often involved in the sclerotic process. In time, the skin becomes taut, leading to contractures of the large and small joints that culminate in a claw-like deformity of the hand.

A variety of pigmentary disturbances may occur in scleroderma, including generalized hyperpigmentation that resembles adrenal insufficiency, focal hyperpigmentation or hypopigmentation, and areas of perifollicular pigmentation that resemble vitiligo (Fig. 29-26). Raynaud's phenomenon leads to small pitted scars at the fingertips or frank ulceration, with or without gangrene of the fingertips, toes, knuckles, and ankles, especially the malleoli.

The face often undergoes distinctive changes, leading to a fixed stare and inability to wrinkle the forehead. As the facial tissues shrink, the nose becomes pinched, the cheeks sunken, the mouth narrowed, and the lips thinned. In diffuse scleroderma, cutaneous sclerosis, accompanied by a yellowish-brown hue, spreads from the chest to the head and extremities. Sharply delineated, broad telangiectatic macules appear on the face, buccal mucosa, lips, and hands.

PSS is associated with interstitial pneumonitis. This is more common in patients with diffuse disease than in patients with limited disease. Pulmonary hypertension has been reported to occur in patients with CREST syndrome (see Chapter 72).

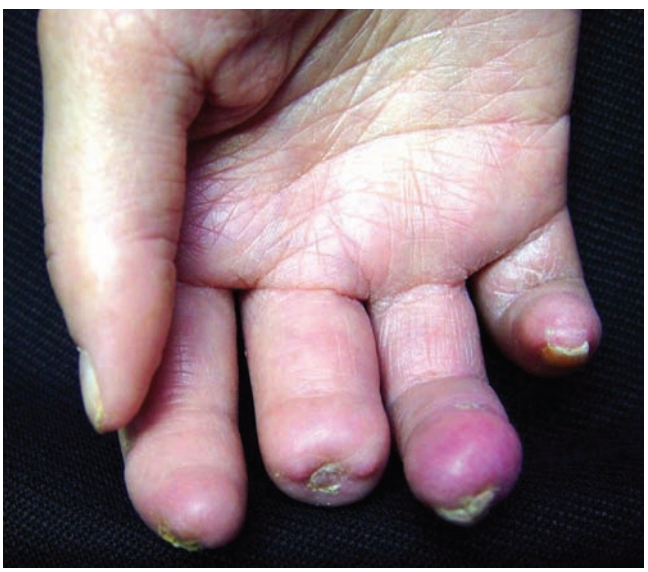


Figure 29-25 Raynaud's phenomenon in this patient was so severe that autoamputation of the distal digits occurred.

■ INFECTIONS

A variety of infections involving the lungs may have cutaneous involvement.[63] Prototypical examples are described below.

Blastomycosis

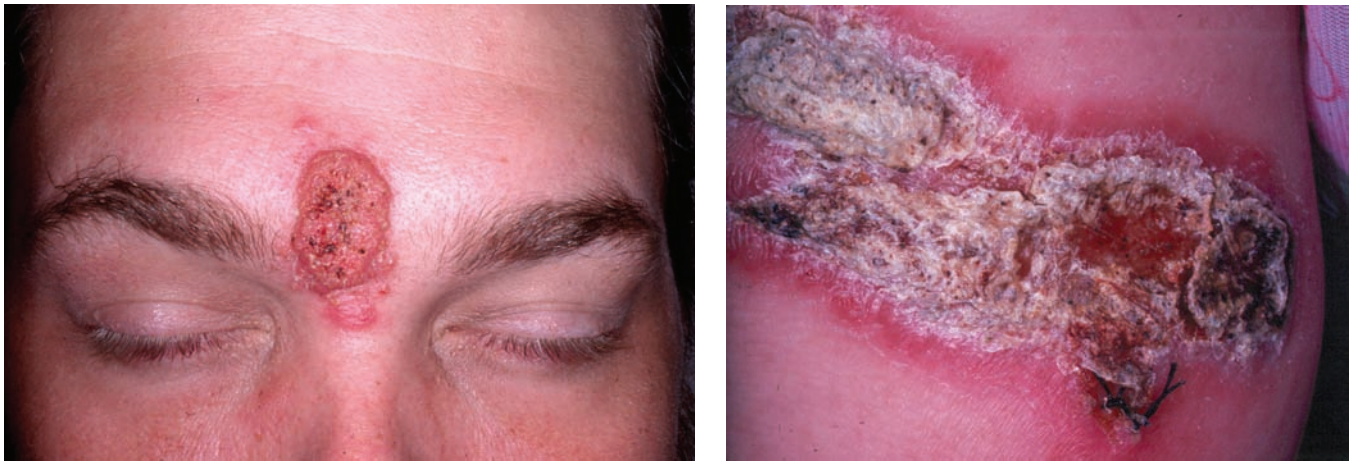
Skin lesions are as common as pulmonary lesions in patients with blastomycosis. Cutaneous disease usually represents dissemination from a pulmonary focus that is often small and may be inapparent. The typical presentation is as a solitary nodule or multiple papules or nodules on the face, wrists, hands, or feet, which subsequently ulcerate and discharge pus (Fig. 29-27). The lesions grow eccentrically at the periphery and atrophy centrally over a period of months, eventually forming an arciform or serpiginous contour with sharply elevated and verrucous borders. Miliary abscesses occur along the borders of the lesions. In addition to the cutaneous involvement, osteolytic lesions may occur.

Coccidioidomycosis

Coccidioidomycosis is usually manifest as a pulmonary infection. In its acute form, it is often associated with cutaneous symptoms; roughly 20% of patients develop erythema nodosum (EN). EN is often accompanied by fever, arthritis, and eosinophilia. In patients with progressive pulmonary disease and eventual disseminated disease, the skin may be affected; subcutaneous granulomatous eruptions form and undergo necrosis and ulceration. After several months, the lesions tend to become verrucous. A third form is primary cutaneous disease, which occurs in farmers and laboratory workers as a chancriform lesion with sporotrichotic spread. This variant is extremely rare.

Actinomycosis

The thoracic form of this disease presents as a pulmonary parenchymal process that sometimes forms multiple draining sinus tracts.[64] Diagnosis is often difficult, but identification of sulfur granules in the draining exudates is helpful.



A B

Figure 29-27 **A, B.** Blastomycosis: verrucous lesions on the face (**A**) and trunk (**B**).

Tuberculosis

Cutaneous involvement results from direct inoculation with the tubercle bacillus via either the skin or mucus membranes, or as a consequence of widespread organ involvement that begins in the respiratory tract.

When the tubercle is introduced via the skin or mucus membranes by a contaminated syringe or a wound in a previously unexposed host, a nodule usually develops at the site of injury. Within several weeks, the nodule evolves into a chancre, a well-circumscribed ulcer. Particularly if host defenses are impaired, these chancriform lesions, which are typically located on the extremities, develop associated regional lymphadenitis, followed by systemic dissemination of the organism.

A person who was previously infected with *Mycobacterium tuberculosis* is apt to develop *tuberculosis verrucosa cutis* after receiving a cutaneous inoculation. The characteristic lesion in a sensitized person is a papule or a pustule, which becomes verrucous. On occasion, this disorder produces plaque-like lesions of the extremities, consisting of verrucoid–indurated papules surrounded by an erythematous halo.

Lupus vulgaris is the most common form of cutaneous postprimary tuberculosis that follows inoculation or lymphatic or hematogenous spread of *M. tuberculosis.*[65] Patients with this disorder typically present with reddish-brown plaques surrounded peripherally by yellowish nodules, especially on the neck or extremities. The skin lesions tend to spread centrifugally as the center becomes atrophic. Papillary growths also occur in the nasal, buccal, and conjunctival mucosa. Histologically, lupus vulgaris generally shows epithelioid tubercles with caseation necrosis. Chronic cutaneous eruptions tend to involute, leaving considerable scarring. Treatment with antituberculosis drugs is effective in treating these skin manifestations.

Disseminated miliary tuberculosis may result in macules, papules, or vesicles. In children, especially those who are debilitated, subcutaneous nodules or gummas appear, ulcerate, and eventually develop draining sinus tracts, especially in the extremities and trunk. *Scrofuloderma,* which occurs following the necrosis of cervical nodules, is associated with fistula and sinus tract formation in the overlying cutaneous tissues.

Tuberculids are skin lesions that are considered to represent either a hypersensitivity reaction to *M. tuberculosis* or an embolic response to atypical *Mycobacteria.* EN also occurs in association with primary tuberculosis.

HIV Infection

Early in the epidemic of HIV infection, the incidence of Kaposi's sarcoma (KS) increased. However, since the advent of HAART therapy, KS has become less common.[66,67] KS can occur in any immune-suppressed individual, whether the immune dysfunction is due to HIV infection, age, or iatrogenic immunosuppression in transplant recipients.

Human herpesvirus-8 (HHV-8) has been identified and linked to all forms of KS. In addition, HHV-8 viremia is associated with progression on KS in both classic and endemic forms. In the elderly population, KS has an indolent course and occurs primarily on the lower extremities. At the outset, the lesions are dark-blue, purplish, or reddish papules, macules, and nodules (Fig. 29-28). After months to years, plaques evolve in association with thickening of the skin from midtibia to ankle and lymphedema. In patients with immune dysfunction, including AIDS, KS is more aggressive and is often widespread in its cutaneous manifestations.

The respiratory tract is second only to the gastrointestinal tract in frequency of systemic involvement. Tumors may involve the larynx, trachea, bronchi, pulmonary parenchyma, and pleura. Accordingly, local manifestations of respiratory tract involvement range from hoarseness, signs of airway obstruction, cough, and hemoptysis, to dyspnea. When the parenchyma of the lung is affected, chest radiographs usually show many small nodules; occasionally, parenchymal infiltration of the lung is massive. On bronchoscopic examination, bronchial and tracheal lesions appear as small bluish nodules. Bloody pleural effusions are rare.

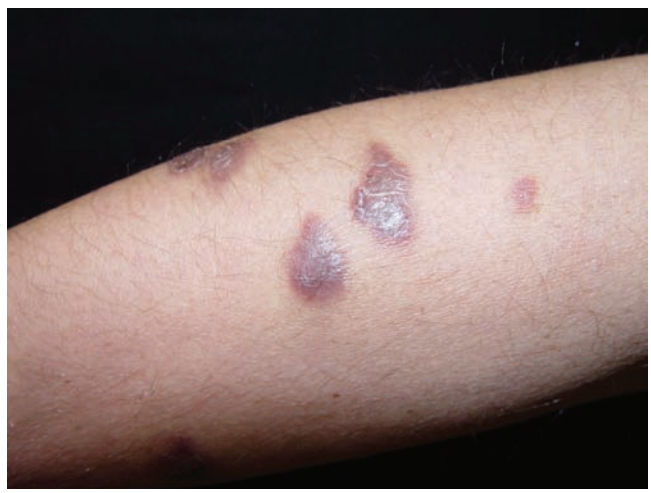


Figure 29-28 Kaposi's sarcoma in an HIV-positive patient.

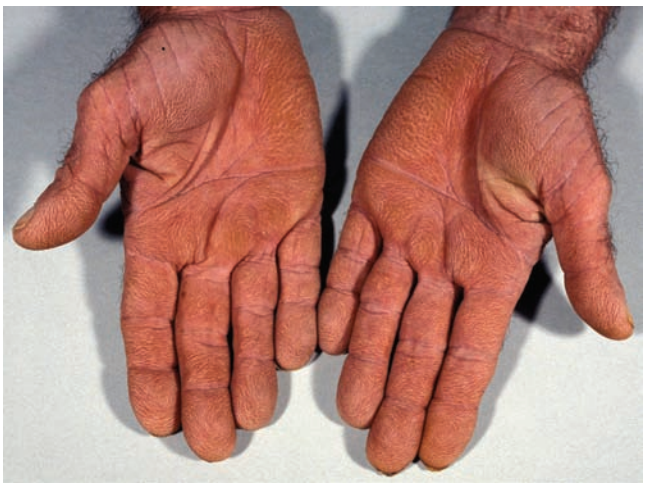


Figure 29-29 Tripe palms. *(Used with permission of Dr. Jon Dyer.)*

LUNG CANCER

Several paraneoplastic syndromes may occur in patients with lung cancer.[68] In most instances the dermatosis is not specific for lung cancer; other sites may be involved. The following are some of the more ominous manifestations of potential pulmonary malignancy.

Tripe palms is a paraneoplastic condition that is manifest as rugose thickening of the palms and, occasionally, the soles (Fig. 29-29).[69] Patients often have coexistent acanthosis nigricans (AN). Patients with tripe palms and AN usually have adenocarcinomas of the gastrointestinal tract; however, when tripe palms occur in the absence of AN, patients often have squamous cell carcinoma of the lung.

Patients with *Bazex syndrome (acrokeratosis paraneoplastica)* develop an erythematous-to-violaceous psoriasiform eruption primarily on acral surfaces.[70] (Fig. 29-30). The ears, nose, cheeks, hands, feet, and knees are most often affected, but the nails may become dystrophic, and the palms and soles may develop a keratoderma in later stages of the disease. The disorder may develop in stages, and is associated primarily with carcinomas of the upper respiratory and digestive tracts (larynx, pharynx, trachea, bronchus, and/or upper esophagus); the malignancy is often detected concurrently. If the tumor is effectively treated the eruption may resolve, but it may return with tumor recurrence.

Ectopic ACTH-producing tumors cause many of the typical signs and symptoms of Cushing syndrome. Intense hyperpigmentation, present in only 6% to 10% of patients with Cushing disease, is especially common in association with ectopic ACTH production and should alert the clinician to the possibility of a hormone-secreting tumor. Although the cause of the hyperpigmentation is unclear, it may be related to tumor production of the peptide β-lipotropin, which contains within its sequence of 91 amino acids the 22–amino acid sequence of β-MSH. A myasthenia gravis–like syndrome, including profound proximal muscle weakness, may be a striking clinical feature and may reflect either underlying hypokalemia or polymyositis. Small cell carcinoma of the lung is the tumor most often associated with ectopic ACTH production, although other malignancies have been reported.

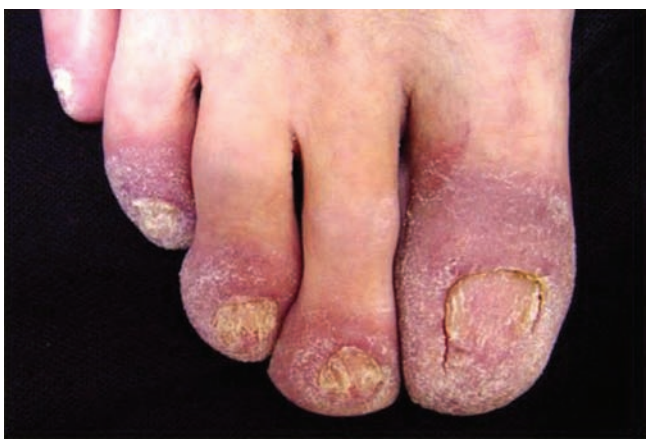


Figure 29-30 Acrokeratosis paraneoplastica (Bazex syndrome). This patient was thought to have psoriasis prior to the diagnosis of a squamous cell carcinoma of the tonsillar pillar.

The *carcinoid syndrome* is another example of a hormonal syndrome associated with a nonendocrine tumor. The disorder is probably most often caused by the release of the enzyme kallikrein from tumor cells, with subsequent conversion of kininogen to vasoactive kinin peptides, including bradykinin; in addition, increased blood levels of histamine may be important in the rare metastatic gastric carcinoid. The most striking cutaneous manifestations are episodes of flushing, initially lasting 10 to 30 minutes and involving only the upper half of the body; as the flush resolves, gyrate and serpiginous patterns may be noted. With successive attacks more extensive areas may be affected and the redness takes on a cyanotic quality, eventually leading to a more permanent facial cyanotic flush with associated telangiectasia, resembling rosacea. Persistent edema and erythema of the face may result in leonine facies. A pellagra-like picture, which has been noted in some patients, may be due to abnormal tryptophan metabolism. Systemic symptoms associated with the cutaneous flushing include abdominal pain with explosive watery diarrhea, shortness of breath, and hypertension.

Carcinoid tumors are usually found in the appendix or small intestine; extraintestinal carcinoid tumors may arise in the bile ducts, pancreas, stomach, ovaries, or bronchi.[71] The carcinoid syndrome occurs primarily when an intestinal carcinoid tumor metastasizes to the liver or with extraintestinal tumors; flushing attacks can be provoked by palpation of hepatic or abdominal metastases or by alcohol ingestion, enemas, emotional stress, or sudden changes in body temperature. When the syndrome is associated with bronchial adenomas of the carcinoid variety, the flushing is more prolonged and often associated with fever, marked anxiety, disorientation, sweating, salivation, and lacrimation.

Migratory superficial thrombophlebitis and multiple deep venous thromboses have been noted in patients with cancer, especially those with tumors arising in the pancreas, lung, stomach, prostate, or hematopoietic system. The neck, chest, abdominal wall, pelvis, and limbs are most frequently affected.

LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis is classified as a B cell lymphoproliferative disorder of uncertain malignant potential. It has been associated with Epstein–Barr Virus infection and may occur more frequently in patients with immunologic diseases undergoing therapy with immunosuppressive agents, particularly thiopurines and methotrexate. The skin is the most commonly affected extrapulmonary site, occurring in 40% to 50% of patients.[72]

In 10% to 25% of patients, the skin lesions are the first clinical evidence of the disorder; the skin lesions precede involvement of the lungs by 2 weeks to 9 years. Because of the frequent occurrence of skin lesions, ease of performing a skin biopsy, and characteristic histology of the disease, careful dermatologic examination should be carried out in patients suspected of having lymphomatoid granulomatosis.

The characteristic cutaneous lesions are 1- to 4-cm erythematous-to-purplish dermal papules, or subcutaneous nodules, with or without ulceration.[73]

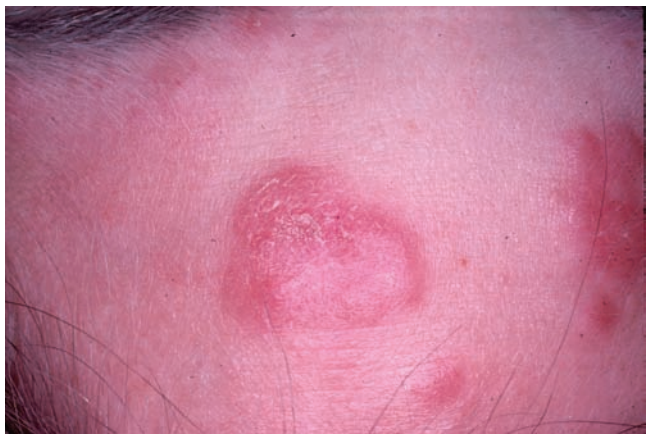


Figure 29-31 Lymphomatoid granulomatosis. This young woman developed the acute onset of multiple erythematous plaques on her face, accompanied by dyspnea and fever. She died within a month from pulmonary disease.

The lesions generally occur over the buttocks, thighs, and lower extremities (Fig. 29-31), but they may occur anywhere. Healing is often accompanied by scarring and hyperpigmentation.

The skin histopathology is similar to that observed in the lungs and is characterized by a marked angiocentric and angiodestructive lymphohistiocytic infiltrate composed predominantly of CD4-positive T cells. EBV-positive B cells are often present.

■ REACTIVE DERMATOSES

Two disorders in this category warrant mention: pachydermoperiostosis and EN.

Pachydermoperiostosis is a syndrome in which HOA is associated with cutaneous changes of the face and extremities that are similar to those that occur in patients with acromegaly. Although this disorder is generally benign, it is occasionally associated with bronchogenic carcinoma.

EN is a relatively common process and is usually acute and self-limited.[74] The typical clinical presentation is the sudden onset of one or more, tender, erythematous nodules on the anterior legs, which are more easily palpated than visualized (Fig. 29-32). The eruption is often preceded by a prodrome of fever, malaise, or arthralgias. As the lesions age, they may develop an ecchymotic appearance. They heal over a 4- to 6-week period, usually without scar formation. Ulceration of the primary process is rare. Although EN is usually acute, patients with chronic or recurrent disease have been described using such terms as "chronic EN," "EN migrans," "subacute nodular migratory panniculitis" (Vilanova's disease), or "septal granulomatous panniculitis." Chronic or recurrent EN most commonly occurs in middle-aged women. The disease is often present for several years and is most common on the legs.

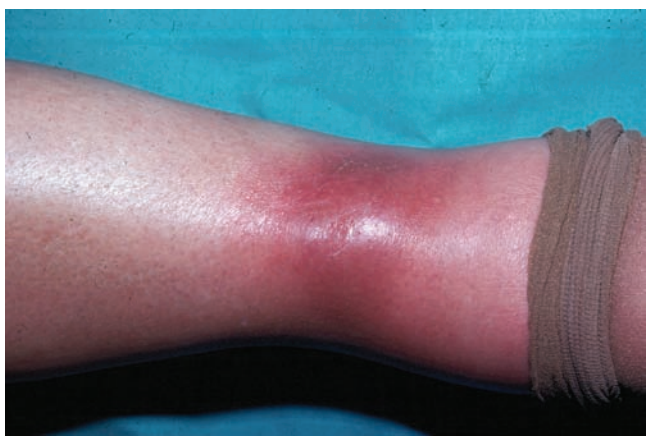


Figure 29-32 Erythema nodosum. Red tender subcutaneous nodule on the leg.

Etiologic or associated conditions are present in about 50% of patients with EN. The associated conditions can be divided into three broad categories: infections, drugs, or systemic diseases (usually inflammatory disorders). The infectious agents associated with EN tend to primarily affect the respiratory or gastrointestinal tract and are most often bacterial or fungal in origin. The most common drugs are antibiotics and oral contraceptives. Pregnancy, particularly in its second trimester, is a known association, and the EN will recur with subsequent pregnancies or with the administration of oral contraceptives. EN-like lesions may occur in Behçet disease and are accompanied by oral and genital ulcerations, pathergy, uveitis, or CNS disease or other systemic manifestations.

A specific variant of sarcoidosis associated with EN is known as Löfgren syndrome.[75] This is an acute, self-resolving process in which EN occurs with bilateral hilar lymphadenopathy, arthritis, and anterior uveitis. Granulomatous colitis (Crohn disease), regional enteritis, and ulcerative colitis have been associated with EN. In patients with inflammatory bowel disease, it appears that the EN parallels the activity of the bowel disease. At least half of the cases of EN are not found to have an associated or underlying process.

■ NEUTROPHILIC DERMATOSES: SWEET SYNDROME AND PYODERMA GANGRENOSUM

Sweet syndrome (Fig. 29-33) and pyoderma gangrenosum (Fig. 29-34) are distinct dermatoses, but they share common associations and are often managed using similar therapies.[76,77] In addition, a condition known as neutrophilic dermatosis of the dorsal hands (Fig. 29-35) often has characteristics that overlap between a superficial variant of pyoderma gangrenosum (also termed atypical pyoderma gangrenosum) and Sweet syndrome.[77] The associated diseases include inflammatory bowel disease, rheumatoid arthritis, and myelogenous malignancy and premalignancy. Extracutaneous neutrophilic inflammation has been reported in multiple organs, but the lungs are most frequently involved. The inflammatory reaction may cause pulmonary infiltrates, including cavitary disease. It is critical that infectious diseases be excluded with appropriate cultures before initiating therapy with corticosteroids or other immunosuppressive therapy.

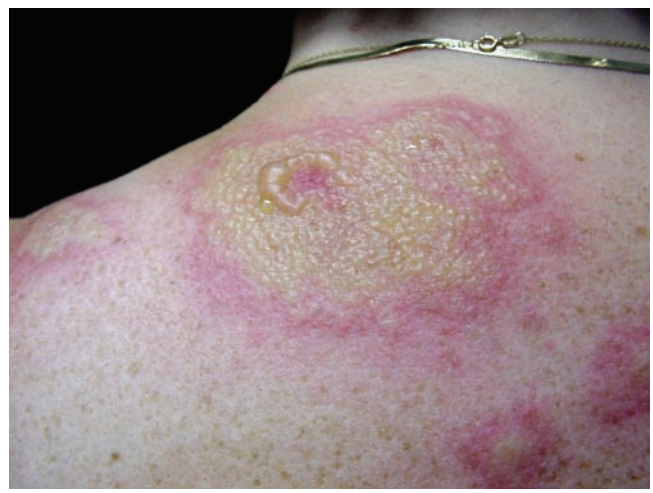


Figure 29-33 Acute febrile neutrophilic dermatosis (Sweet syndrome): erythematous plaque with what appears to be vesiculation on the surface.

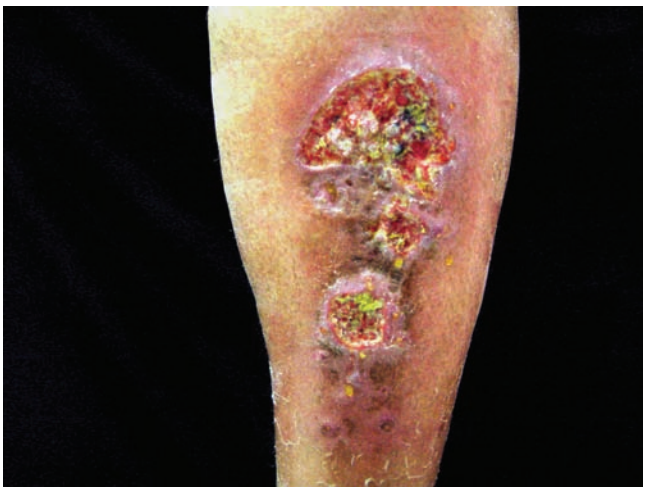


Figure 29-34 Pyoderma gangrenosum: large ulceration on the leg with a violaceous, undermined border. This patient had active Crohn's disease.

■ PRURITUS

Pruritus is a symptom that accompanies many dermatoses, but it may also accompany systemic diseases.[78] Patients without an obvious cause for their itching require a systemic evaluation, which usually includes a chest x-ray. Causes for pruritus are not commonly found, but Hodgkin disease and other malignancies might be uncovered during the evaluation. Effective treatment of an underlying malignancy will result in a disappearance of the pruritus.

■ URTICARIA

Urticaria is a reactive cutaneous disease manifested by transient urticarial skin lesions. Acute urticaria is almost always due to the ingestion of a food or medication and usually subsides within several days. The presence of chronic urticaria requires a thorough evaluation and, at times, pulmonary evaluation may reveal an infectious, inflammatory, or neoplastic cause (<25% of patients).

■ VASCULITIC SYNDROMES

Important vasculitic syndromes with cutaneous and pulmonary (Chapter 60) involvement are discussed below: Churg–Strauss syndrome, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), polyarteritis nodosa, and urticarial vasculitis.

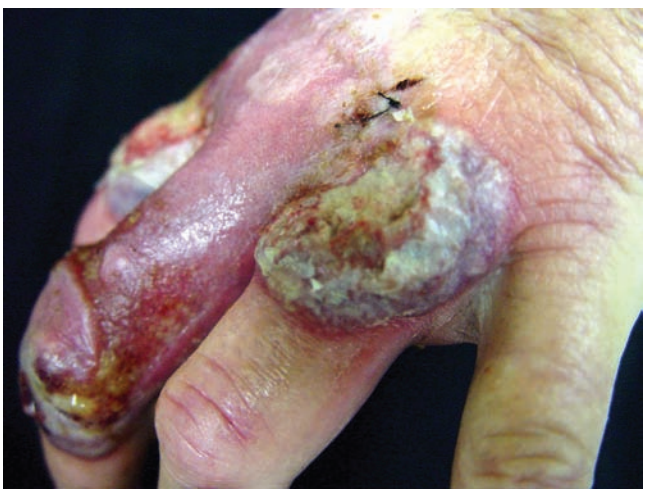


Figure 29-35 Neutrophilic dermatosis of the dorsal hands (also known as atypical pyoderma gangrenosum). Such patients often have a hematologic malignancy or premalignant process.

Churg–Strauss Syndrome

The clinical picture of allergic rhinitis, asthma, peripheral eosinophilia, and pulmonary infiltrates occurring with systemic vasculitis has been designated the Churg–Strauss syndrome.[79] However, the histologic finding of necrotizing granulomas and tissue eosinophilia is not unique to this clinical syndrome. Indeed, the same histologic appearance may be seen in a wide variety of systemic diseases, including allergic granulomatosis, granulomatosis with polyangiitis (see below), rheumatoid arthritis, and lymphoproliferative disease.

One or more types of skin lesions develop in 70% of patients with Churg–Strauss syndrome. Most common is palpable purpura of the extremities; histologically, the lesions show necrotizing vasculitis without granuloma formation. In one-third of patients, the cutaneous lesions are nonspecific—that is, erythematous and urticarial. In another one-third, however, the skin lesions are distinctive—that is, tender, red-to-violaceous, indurated nodules, measuring 0.5 to 2 cm, which develop central crusting or become infarcted. These nodules occur most often over the scalp or symmetrically over the extensor surfaces of the extremities. These nodules are the ones most likely to have the histologic picture of necrotizing granulomatous vasculitis and eosinophilic infiltration; immunofluorescence staining may show vascular deposition of fibrin and complement.

Granulomatosis with Polyangiitis

About 45% of patients with granulomatosis with polyangiitis have cutaneous manifestations, most often small vessel vasculitis.[80] Occasionally, biopsy of the skin lesions reveals a granulomatous vasculitis. In addition, the presence of cutaneous disease is usually indicative of active systemic involvement; therefore, such patients should be carefully evaluated and aggressively treated.

Polyarteritis Nodosa

Patients with polyarteritis nodosa frequently have cutaneous lesions. The skin disease may represent small vessel vasculitis as in granulomatosis with polyangiitis or may represent medium-sized vessel involvement. In the latter case, the manifestation is livedo reticularis or ulceration.

Urticarial Vasculitis

Urticarial lesions may occur in patients as a manifestation of small vessel vasculitis. Urticarial vasculitis was first described in four patients with recurrent attacks of erythematous urticarial and hemorrhagic skin lesions associated with synovitis and, sometimes, abdominal distress. The patients did not have systemic lupus erythematosus or paraproteinemia, but they did have hypocomplementemia; two had nephritis.

Urticarial lesions may also be an early clinical manifestation of lesions that become typical palpable purpura. The spectrum of urticarial vasculitis has also grown in recent years to include the presence of lung disease, characterized by asthma or obstructive lung disease. Patients with hypocomplementemic urticarial vasculitis often have or develop obstructive pulmonary disease, whereas most patients with normal complement levels, chronic urticarial, and vasculitis have little or no systemic involvement.[81]

Patients are often treated with corticosteroids or other immunosuppressive drugs. Although these agents are useful in controlling the cutaneous lesions, they do not appear to have any impact on progression of the pulmonary disease.

■ TOXIC EPIDERMAL NECROLYSIS

Toxic epidermal necrolysis (TEN) is one of the true dermatologic emergencies.[82] This disorder is most often due to drug administration and develops acutely. Patients often have a prodrome followed shortly by widespread skin involvement with a superficial blistering

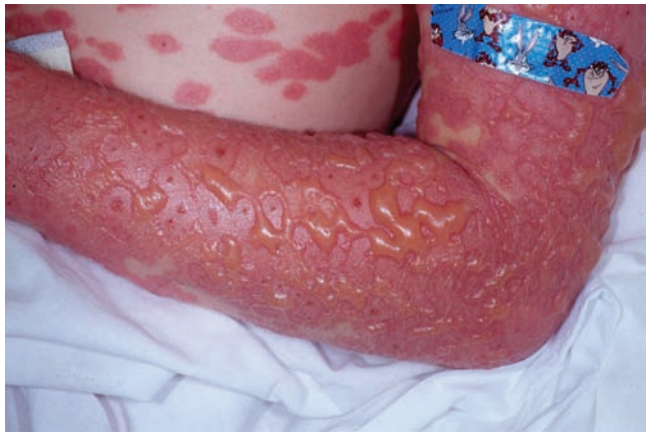


Figure 29-36 Stevens–Johnson syndrome/toxic epidermal necrolysis.

(Fig. 29-36). Multiple mucosal surfaces are affected (Fig. 29-37). Prognosis is dependent upon the extent of the blistering, age, and the presence of comorbid diseases.

Lung involvement in TEN is unusual, but affected patients often are treated in an intensive care unit or burn unit and frequently become ventilator-dependent. Infections, particularly pneumonia, are a frequent complication and may result in death.

■ YELLOW NAIL SYNDROME

Thick, yellow discoloration of all 20 nails occurs in the yellow nail syndrome[83] (Fig. 29-38). The nails are thick, but there is no onycholysis and no subungual debris, allowing clinical differentiation from onychomycosis. The nails are not clubbed, and there are no underlying bony abnormalities. This disorder is almost always associated with pulmonary abnormalities, including pleural effusions, lymphoma, and sleep apnea. There is no known therapy for the nail changes in this disorder, but improvement of the associated pulmonary disease may result in improvement of the nails.

■ MISCELLANEOUS DISORDERS

Pulmonary-cutaneous syndromes include a number of inherited congenital and developmental disorders.

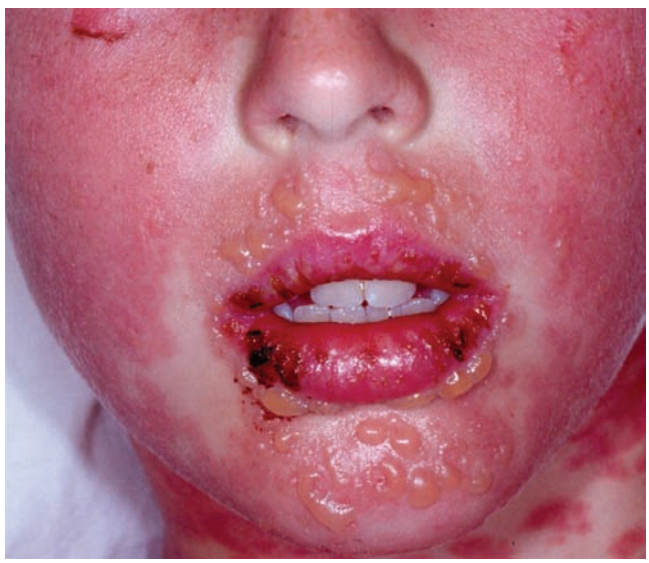


Figure 29-37 Mucosal lesions of Stevens–Johnson syndrome/toxic epidermal necrolysis.

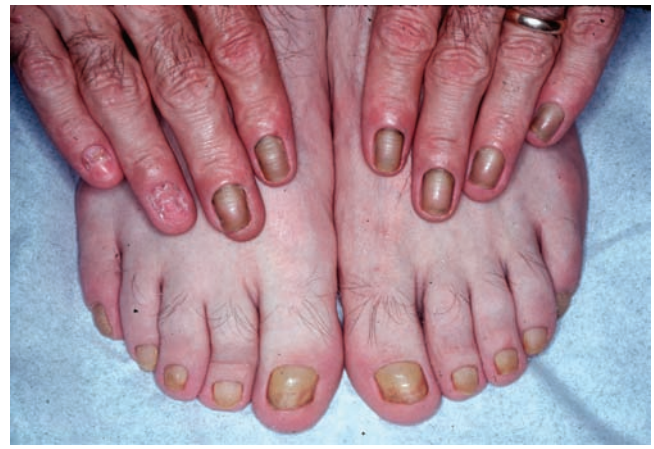


Figure 29-38 Yellow nail syndrome. All 20 nails were affected in this patient.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is regularly associated with pulmonary (Chapters 39 and 40) or hepatic disease. Cutaneous manifestations may also occur in some patients with this inherited disorder and most commonly manifest as panniculitis or, rarely, as a cutaneous vasculitis.[84,85] Although the panniculitis is a lobular panniculitis, in contrast to the septal panniculitis that is found in EN, the clinical disease is similar except that these patients' lesions may ulcerate.

Cutis Laxa

Cutis laxa is caused by a disorder in the formation of elastin that is transmitted as a dominant hereditary trait.[86] In children with this disorder, skinfolds of the abdomen and face are large and pendulous. The pulmonary manifestations of cutis laxa include emphysema and pulmonary artery stenosis.

Cystic Fibrosis and the Skin

CF is an inherited disorder that frequently affects the lungs and results in premature death (Chapter 50). Some patients with CF have skin disease.[87] Specifically, cutaneous vasculitis seems to be more frequent in CF patients, probably due to the frequent formation of circulating immune complexes.

Ehlers–Danlos Syndrome

The most important disorder of collagen affecting the skin and lungs is Ehlers–Danlos syndrome (cutis hyperelastica), a hereditary disorder of collagen in which the skin and blood vessels are unduly elastic and fragile and the joints are hyperextensible. The skin is smooth, rubbery, and bruisable; the joints are hypermobile. Associated systemic abnormalities include megaesophagus, megacolon, dissecting aortic aneurysm, and diaphragmatic and inguinal hernias. Among the pulmonary disorders are spontaneous pneumothorax, arteriovenous fistulas, megatrachea, and bronchial ectasia.[88]

Birt–Hogg–Dubé Syndrome

Birt, Hogg, and Dubé described an autosomal dominant condition that is manifested by multiple facial flesh-colored papules characterized histologically as trichodiscomas.[89] BHD is due to heterozygous mutations in the folliculin (FLCN) gene located on chromosome 17, which encodes a highly conserved tumor suppressor protein. (Fig. 29-39) Affected patients frequently develop renal cell carcinomas, particularly oncocytomas. In addition, multiple lung cysts and development of spontaneous pneumothorax at a young age are common. Although there is no known therapy, recognition of affected patients may lead to discovery of renal tumors prior to metastasis and assessment of family members.

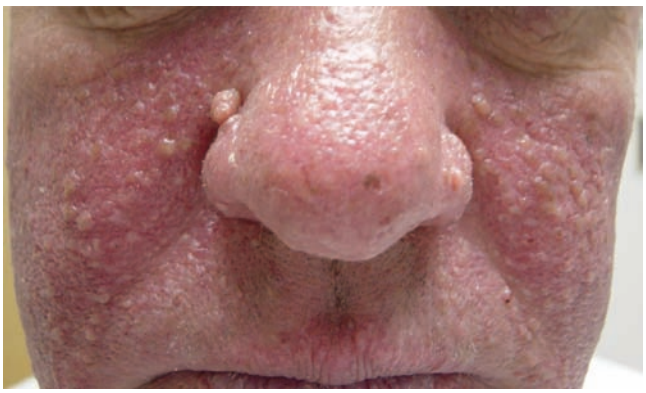


Figure 29-39 Flesh-colored central facial papules in a patient with Birt–Hogg–Dubé syndrome.

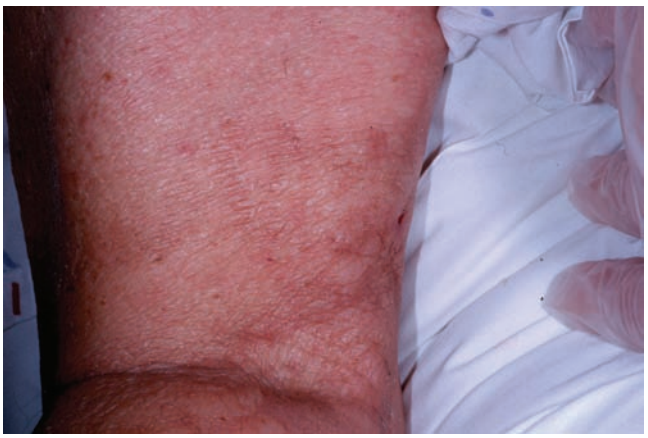


Figure 29-41 Peau 'd orange changes in a patient with nephrogenic systemic fibrosis.

Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Rendu–Weber syndrome, is an autosomal dominant disorder that is manifested by vascular ectasia in various organs, including the skin and mucus membranes (Fig. 29-40). HHT often is first manifested as nosebleeds. Eventually lesions affect the lips, tongue, nasal mucosa, palate, and palms. Patients with HHT may have arteriovenous malformations in the lungs or CNS. Epistaxis, melena, and hemoptysis are common in adults.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a disorder of the skin in which a rapid onset of skin hardening (Fig. 29-41) occurs in patients with some form of renal disease.[90] Often the onset of the fibrosis is preceded by anasarca. The disease has been linked to gadolinium deposition in tissue following its use for MRI or MRA. Initial descriptions of the disease focused on the cutaneous findings, but it has become evident that patients may also have systemic fibrosis, including pulmonary fibrosis. There is no known effective therapy for these patients, but with time the fibrosis does seem to lessen.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is a severe mucocutaneous disease with a specific pattern of immunofluorescence. It is a rare vesiculobullous disorder. Patients with PNP often present with severe oral erosions and polymorphous cutaneous lesions, including targetoid lesions, bullae, and erosions (Fig. 29-42). Patients with PNP often have a lymphoproliferative disorder with a high prevalence of Castleman disease. In addition to the mucocutaneous disease, these patients frequently have bronchiolitis obliterans.[68]

Sarcoidosis

Sarcoidosis is a multisystem disorder with protean manifestations (Chapter 55). Skin lesions occur in about 25% of patients and may be "histopathologically specific" or "nonspecific." The most common nonspecific manifestation is EN. Histopathologically specific lesions are manifestations of granulomatous inflammation in the skin. Although associated with chronic disease in the past, it now appears that there are many patients with self-limiting granulomatous disease of the skin. Skin lesions are most commonly papules, plaques, or nodules. Rarely is there a great deal of surface change, and ulceration is uncommon.

Several clinical variants are worth noting. Papular lesions on the knees (Fig. 29-43) are commonly associated with EN and are self-limiting. Lesions on the nasal ala (Fig. 29-44) are frequently associated with sarcoidosis of the upper respiratory tract (SURT), and a thorough otolaryngologic evaluation is indicated. Erythematous-to-violaceous plaques on the face are known as lupus pernio (Fig. 29-45); residual scarring in this disorder is possible. In addition, patients tend to have accompanying chronic disease in the lungs. Finally, lesions of sarcoidosis frequently occur within scars or tattoos (Fig. 29-46). In this circumstance it may be difficult to distinguish sarcoidosis from foreign body granulomas.

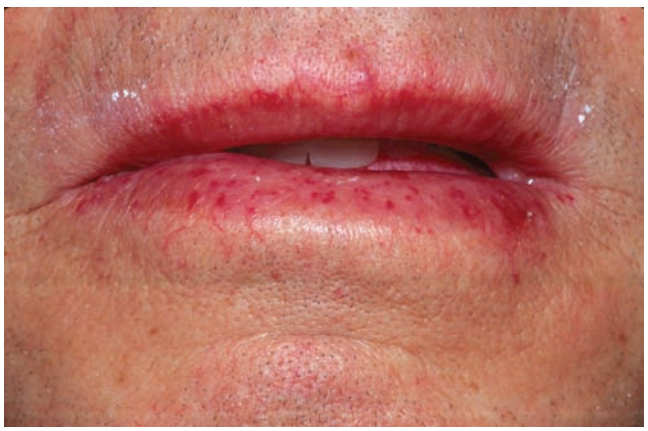


Figure 29-40 Mucosal telangiectasia in a patient with hereditary hemorrhagic telangiectasia.

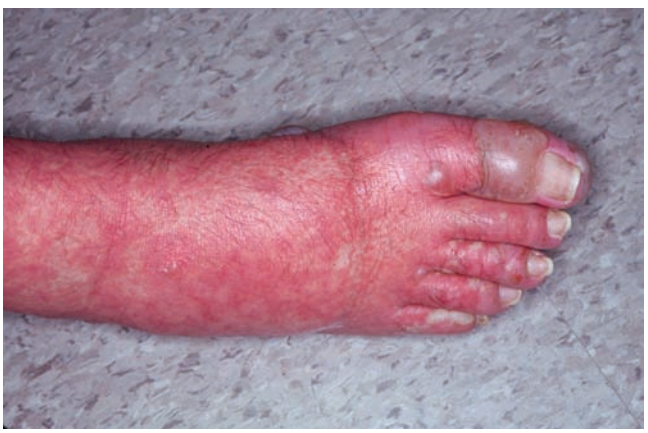
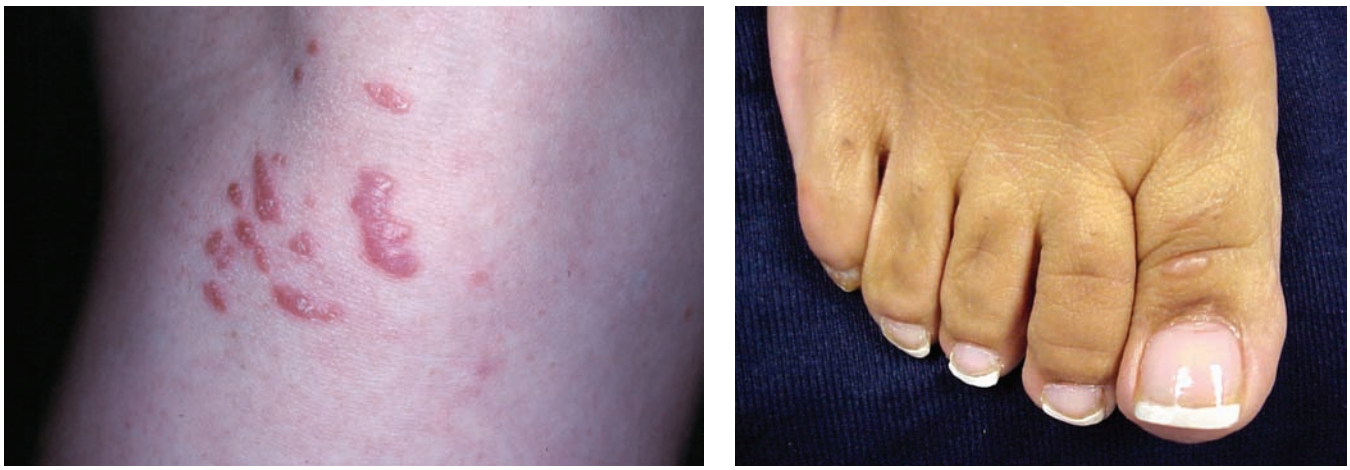


Figure 29-42 Paraneoplastic pemphigus.



A B

Figure 29-43 **A, B.** Sarcoidosis: acute onset of papular lesions (**A**) on the knees and feet (**B**) were associated with a self-limited course in these patients.

Tuberous Sclerosis

Tuberous sclerosis is a hereditary disorder characterized by mental retardation, epilepsy, and skin lesions, including adenoma sebaceum, Shagreen patches, and ash leaf macules. Also seen as part of this disorder are retinal phakomas, calcification of basal ganglia, and ungual fibromas. Approximately 9% of patients with visceral tuberous sclerosis have pulmonary manifestations; some of the pulmonary lesions are cystic and may be associated with recurrent spontaneous pneumothorax and hamartomas. Certain poorly understood diseases, such as fibrocystic pulmonary dysplasia, may represent a forme fruste of tuberous sclerosis.

MEDICATION TOXICITY

Cutaneous toxicity may arise from therapy given for pulmonary disease. In addition, pulmonary toxicity may develop in the setting of treatment of dermatologic disorders.

■ DERMATOLOGIC TOXICITY FROM AGENTS USED TO TREAT PULMONARY DISEASE

Two examples of dermatologic injury from agents used to treat lung disease are described below: epidermal growth factor receptor inhibitors and immunosuppressive agents.

Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor inhibitors are now being used for the treatment of solid tumors, including lung cancers. These agents are regularly associated with development of an acneiform eruption on the face.[91] The presence and severity of the eruption appear to correlate with survival.

Immunosuppressive Therapy in Lung Transplant Recipients

Patients who are organ recipients are regularly treated with corticosteroids in combination with various immunosuppressive agents. Therapy with corticosteroids has well-known dermatologic consequences, including striae, steroid-acne, or folliculitis, and an increased risk of superficial fungal infections. The intensity of the immunosuppression and duration of therapy are associated with increasing risk of cutaneous malignancy, specifically nonmelanoma skin cancer (NMSC) and KS. Squamous cell carcinoma is overrepresented in comparison to basal cell carcinoma; in addition, the tumors appear to be more aggressive in the presence of immunosuppressive therapy. Therefore, in patients who develop multiple squamous cell carcinomas immunosuppressive therapy should be less intense, if possible, or substitution of cyclosporin and azathioprine by other "less" toxic agents should be considered.

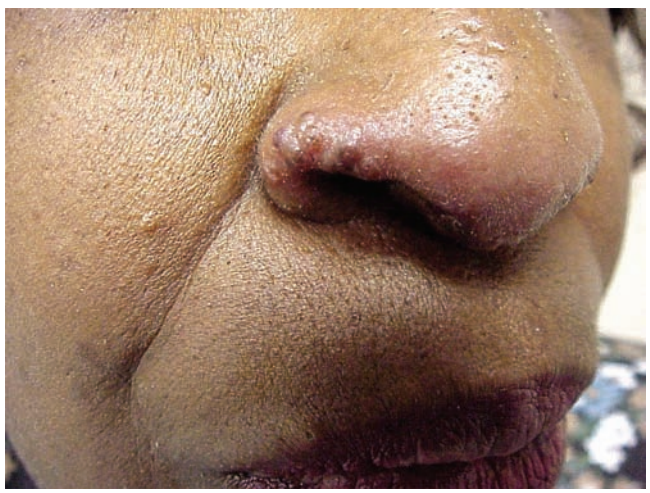


Figure 29-44 Sarcoidosis affecting the nasal ala is regularly associated with granulomatous disease in the upper respiratory tract (SURT).

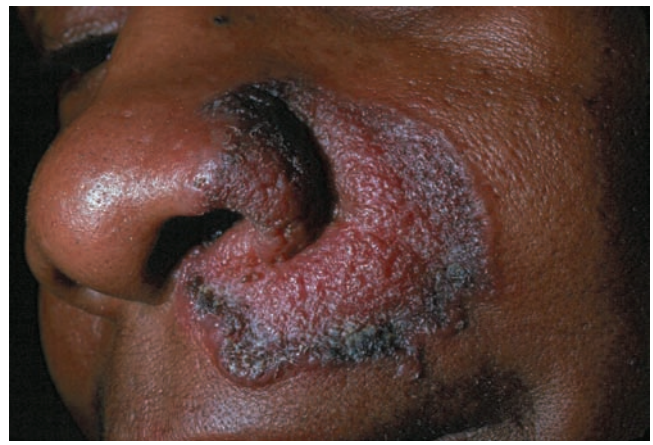


Figure 29-45 Lupus pernio (sarcoidosis).

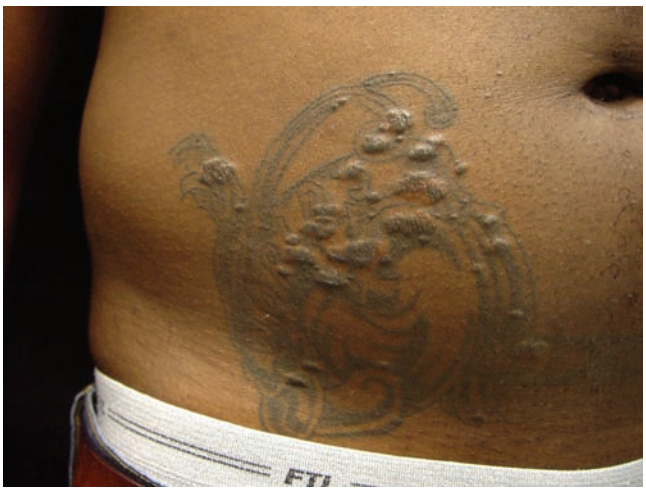


Figure 29-46 Sarcoidosis within tattoos.

■ PULMONARY TOXICITY FROM DERMATOLOGIC THERAPIES

Two examples of pulmonary toxicity arising from agents used to treat dermatologic disorders are described below: methotrexate and tumor necrosis factor-α inhibitors.

Methotrexate

Methotrexate is a common systemic therapy for patients with psoriasis. In addition, it is regularly used for cutaneous dermatomyositis, cutaneous sarcoidosis, and cutaneous lymphomas. Pulmonary toxicity is not common and is believed to be idiosyncratic. Most of the dermatologic use is for psoriasis vulgaris and psoriatic arthritis; fortunately, pulmonary disease appears to be quite rare in these patients. No specific monitoring is recommended.

Tumor Necrosis Factor-α Inhibitors

A growing number of tumor necrosis factor (TNF) antagonists are available, including infliximab, etanercept, and adalimumab. These therapies have revolutionized our approach to psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis. All have been associated with an increased risk of infection, particularly pneumonia and tuberculosis.

SUMMARY

The diagnostic approach to a patient with suspected pulmonary disease begins with a thorough history and physical examination. Elements of the family history, along with determination of work and other environmental exposures, are important components of the history. Many times, characteristic cutaneous findings shed light on an underlying pulmonary diagnosis. The clinical examination is complemented by radiographic studies, assessment of pulmonary and cardiac function, and routine and specialized laboratory studies, as warranted.

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CHAPTER 30

Modern Approach to Thoracic Imaging Diagnosis

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Warren B. Gefter

INTRODUCTION

This chapter is not intended to provide a comprehensive review of the entire scope of thoracic imaging; dedicated textbooks in radiology serve this purpose well. Moreover, the chapter does not provide a comprehensive guide to the interpretation of thoracic imaging studies. Rather, the focus is on what modern thoracic imaging can provide to empower clinicians to diagnose and manage common clinical scenarios in the second decade of the 21st century. The goal is to present a strategic approach to thoracic imaging, which starts with broad clinical categories of disease and addresses the following central clinical questions: What is the differential diagnosis and how can a specific diagnosis be confirmed? What is the prognosis and how can disease progression and therapeutic effectiveness best be monitored?

In each subsection, organized initially by imaging technique, and subsequently, by broad diagnostic categories, the authors aim to answer these questions by providing a practical, logical, and evidence-based approach that emphasizes which imaging tests to order and what to expect from each test. Oftentimes, imaging findings are either pathognomonic or highly characteristic of a diagnosis in the appropriate clinical context and, therefore, will suffice for clinical diagnosis and management. However, when this is not the case, tissue sampling or additional laboratory tests may be required for diagnostic confirmation; these scenarios are outlined and options discussed for tissue sampling, including image-guided percutaneous biopsy, bronchoscopy, and surgical biopsy. In addition, the ways in which modern functional and quantitative radiographic techniques may impact the field of thoracic imaging in the near future will be considered, and validated clinical applications differentiated from promising research applications that may evolve into useful clinical tools in the next several decades.

Finally, since radiology and, in particular, thoracic imaging, play such a major and central role in modern medicine, our ultimate goal is to enable the practicing pulmonologist to use imaging resources consistently, wisely, efficiently, and effectively.

SUMMARY OF TECHNIQUES: DIAGNOSTIC AND INTERVENTIONAL

The inception of the field of radiology dates back to 1895 with Wilhelm Röentgen's serendipitous discovery of x-rays and subsequent production of the first radiograph. Within only a few years, radiology became established as a new medical field. Chest radiography, although one of the first clinical applications and currently over 100 years old, is still the most frequently performed imaging test worldwide and the cornerstone of initial imaging assessment of most patients with thoracic diseases. Nonetheless, over the last four decades we have witnessed an explosion of technical innovation and developments, with the introduction of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MR), positron emission tomography (PET), and hybrid scanners (PET/CT and PET/MR), which have greatly expanded the ability of modern imaging to accurately diagnose even the smallest or earliest disease processes and revolutionized the practice of medicine.

More recently, the widespread impact that computers have made on the acquisition, distribution, visualization, and postacquisition processing of medical images have consolidated the central role of radiology. In the future, we hypothesize that major trends will include quantitative imaging, functional imaging, molecular diagnosis, and value assessment with regard to generating better patient outcomes. In the following sections we present current clinical applications, advantages, and disadvantages of each modality, as well as appropriateness criteria for ordering each test, according to the clinical scenario.

CHEST RADIOGRAPHY

Two basic types of chest radiographic examinations are available—bedside portable AP (anteroposterior) and the combination of PA (posteroanterior) and lateral projections. Supplementary views include oblique, lordotic, lateral decubitus, and expiratory radiographs. For most clinical scenarios, the evaluation should begin with a chest radiograph, as this study remains the most cost-effective imaging test for diagnosing a variety of common clinical conditions. Moreover, chest radiographs are universally available and can be obtained even in patients who cannot be moved to an advanced scanner (e.g., patients in the ICU setting). Nonetheless, in many clinical scenarios, additional advanced imaging will be required to clarify radiographic findings or obtain more accurate characterization of disease pattern and severity (Figs. 30-1–30-4).

Whereas the basic physical principles of radiography have not changed in over a century, the quality and clinical availability of chest radiographs have been greatly enhanced in recent decades due to the transition from analog to digital technology. Digital imaging provides better image contrast, reduces the number of suboptimal or nondiagnostic examinations, and permits more immediate examination availability using image transfer and display software.

Currently, two standards for digital radiography exist: computed radiography (CR) and digital radiography (DR), which differ in the process of imaging acquisition. CR utilizes a photostimulable phosphor cassette, just as does the film-screen analog technique; however, the latent image is read by a laser and converted from an analog to digital signal, rather than being transferred to film. DR bypasses this step and utilizes flat panel detectors that directly transform the x-ray signal to a digital image via integrated, thin-film, transistor readout systems. From a practical perspective, DR images are often sharper, with better spatial resolution and, consequently, better visualization of detail. In addition, DR streamlines workflow for routine images and offers the possibility of tailoring the radiation dose.

Most modern facilities use a combination of CR and DR units, due to cost considerations. The principal benefit of CR and DR technology is the ability to process the acquired images to emphasize specific anatomical areas (e.g., lung parenchyma, soft tissues, bones), thereby greatly reducing the need to repeat examinations due to over- or underpenetration by the x-ray beam.[1] Digital methods to "remove" the ribs from the image are now available using either postprocessing bone-suppression software or dual-energy

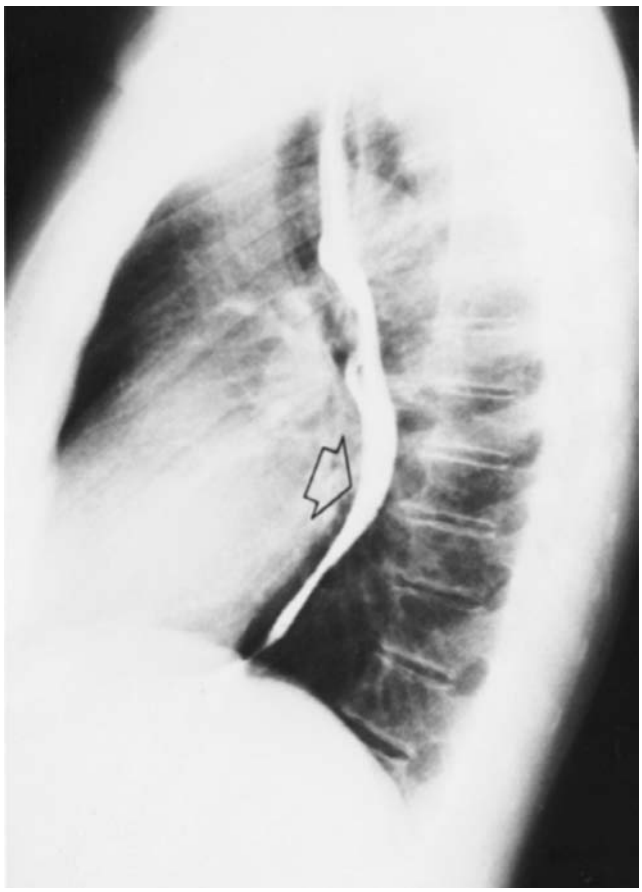


Figure 30-1 Lateral chest radiograph following barium contrast swallow. Not only is this technique very useful for evaluating the esophagus, it is also able to demonstrate left atrial enlargement, with consequent posterior displacement of the contrast column *(arrow)*.

acquisition techniques. These approaches can provide an unobstructed view of the lungs for improved detection of nodules and other pulmonary findings. In addition, computer-aided diagnostic techniques may now assist the radiologist in the detection of subtle lung lesions.

The PA view obtained in the erect position is the standard radiographic examination and demonstrates the anatomy and most thoracic pathologic processes. In particular, the PA view allows evaluation of pulmonary masses and consolidation, diffuse lung disease, pleural effusion, pneumothorax, mediastinal abnormalities, and disorders of the rib cage and scapular girdle.

The lateral view provides additional information by better depicting the posterior diaphragms and posterior lung bases, retrocardiac left lung base, anterior mediastinum, and thoracic spine.

The AP view provides similar information to the PA view, but it is limited by lower spatial and contrast resolution and by magnification of the mediastinal structures. In addition, it is less sensitive for detection of small pneumothoraces and pleural effusions. The AP view is often performed in the supine position in bedridden patients, particularly those who are postoperative or in the ICU. AP portable chest radiographs can be very helpful in assessing the position of support lines, tubes, and medical devices. Medical devices can also be enhanced using newer digital image-processing algorithms.

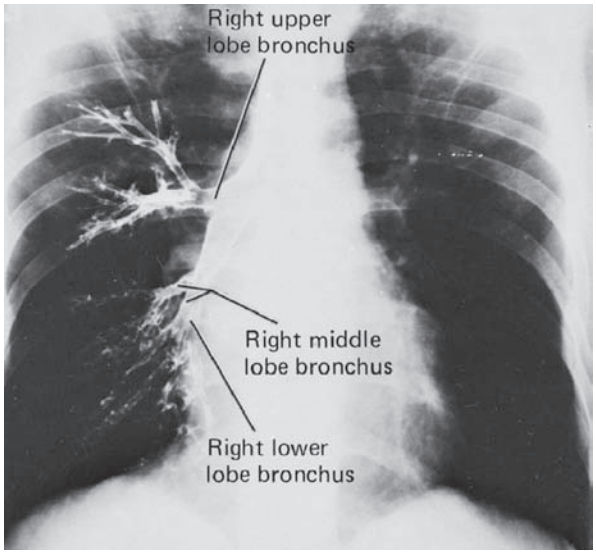
Supplementary views are not routinely performed, unless there is a specific clinical question. In the past, lordotic views were obtained to better visualize the lung apices by displacing the clavicle and first rib shadows superiorly. However, their role has been largely replaced by CT. Expiratory views may be more sensitive in detecting small pneumothoraces, particularly in the setting of recent lung interventional procedures. Lateral decubitus views, although used less frequently than in the past, may be helpful in determining if a pleural opacity seen on standard views is a freely mobile effusion or a loculated effusion or pleural mass. When the patient is imaged with the pleural opacity on the dependent side, a freely mobile pleural effusion conforms to the most dependent region of the hemithorax and a sharp horizontal level demonstrated due to gravity. If a nondependent lucency is seen in the chest or abdomen, in conjunction with a sharp horizontal level delineating it from normal anatomical structures, the diagnosis of a small pneumothorax or pneumoperitoneum may be made. Finally, oblique views are helpful in determining if a questionable radiographic abnormality seen on the frontal view is real or artifactual, as well as in determining its location in the thorax. Performed properly, supplementary views can increase the diagnostic accuracy and clinical utility of chest radiography, sometimes obviating the need for chest CT with its attendant higher cost and radiation exposure.

Many radiographic techniques that were widely used in the past (e.g., laminography, bronchography, air contrast studies, and fluoroscopy) have been made obsolete by other techniques and are of historical interest only. The exception is focused fluoroscopy for evaluation of diaphragmatic motion ("sniff test"), in which the patient is imaged during quiet breathing, deep breathing, and forceful inspiration ("sniff"). A paralyzed hemidiaphragm moves paradoxically upward with forceful inspiration. Fluoroscopy in conjunction with barium swallow may also be used to assess esophageal diseases.

CHEST CT

CT is the current cornerstone of advanced thoracic imaging. It is a digital cross-sectional imaging technique that utilizes a rotating x-ray source around the patient, coupled to diametrically positioned sodium iodide detectors in a circular configuration. As the scanner gantry rotates, multiple projections are generated at different angles with different x-ray beam attenuations, depending on which part of the patient's anatomy was traversed. Following scan acquisition, through a mathematical procedure (filtered back projection or, more recently, iterative reconstruction), the sum of projections is transformed into an image in which the relative density of each small volume of the patient's anatomy (voxel) is proportional to its x-ray absorption coefficient, and normalized from a scale of −1000 to > +1000 HU (Hounsfield units, zero representing the absorption coefficient of water, −1000 of air). Because it eliminates the main drawback of radiographic techniques, that is, the projection of a three-dimensional (3D) structure into a two-dimensional image, CT allows very accurate localization of pathologic processes. Moreover, the superior contrast resolution of CT allows detailed evaluation of mediastinal and chest wall soft tissue attenuation structures, which are poorly assessed radiographically. CT is also superior to chest radiographs for detection of small pulmonary lesions, as well as for their characterization (Figs. 30-5 and 30-6).

Early CT scanners had a single row of detectors and a single x-ray source, acquiring one axial image at a time before the scanner table was moved to acquire the next image. This process could take more than 30 minutes for a single thoracic CT examination. Most modern scanners have between 64 and 320 rows of detectors, one or two x-ray tubes, extremely fast and continuous gantry rotation, and simultaneous table translation, resulting in helical image acquisition and the ability to scan the entire chest in less than 1 second. Modern CT scanners are able to produce high-quality, submillimeter, isotropic resolution images that can be reconstructed in any arbitrary plane without loss of detail. Postprocessing techniques utilizing computational algorithms also allow 3D reconstructions,



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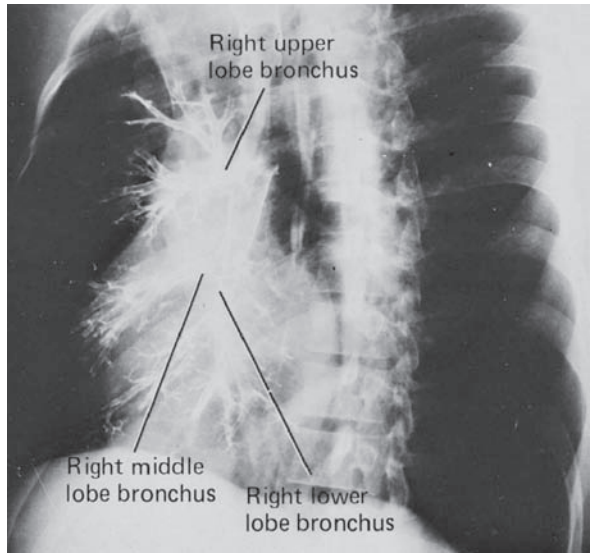

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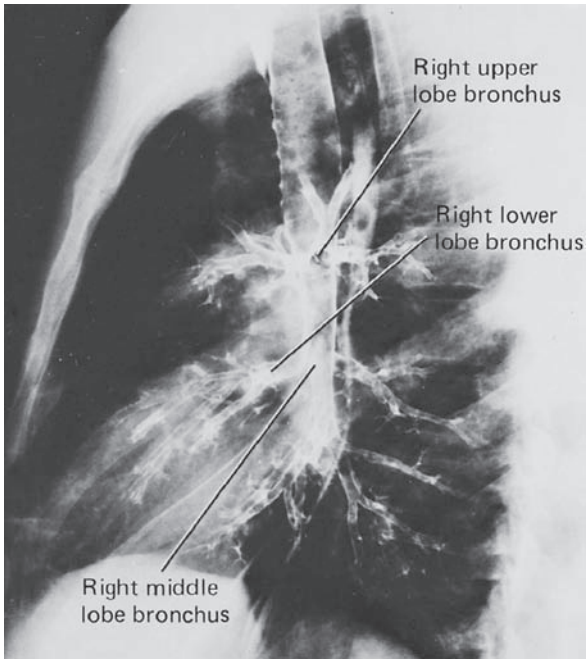

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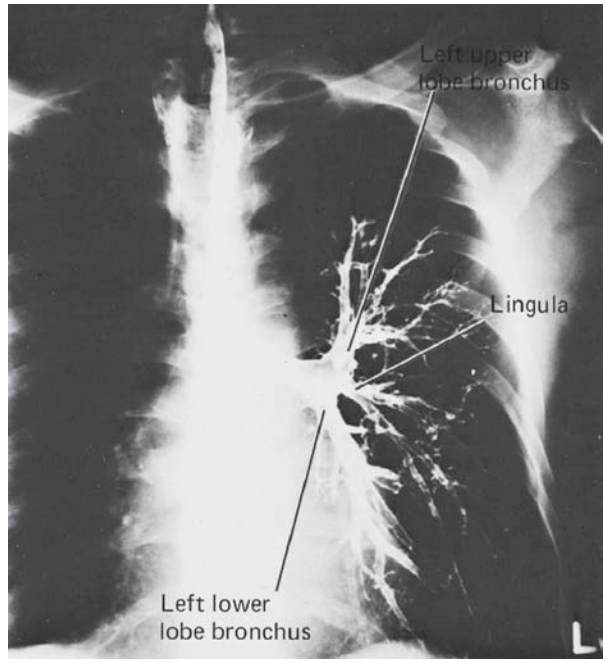

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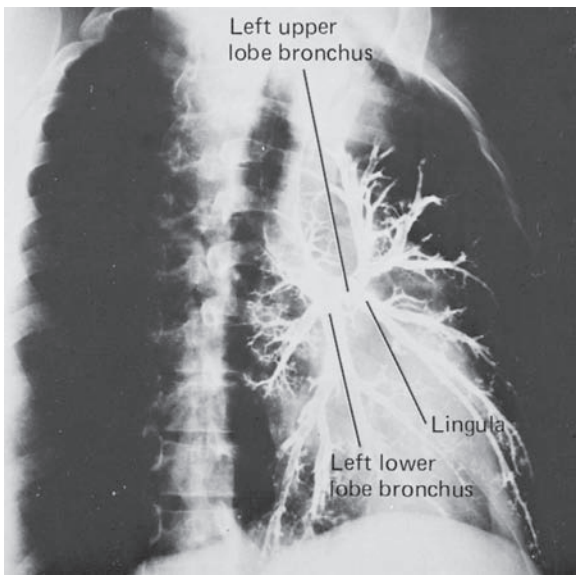

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Figure 30-2 Normal bronchogram. The normal bronchial anatomy of the right lung is shown in the PA (**A**), oblique (**B**), and lateral (**C**) projections. The corresponding anatomy of the left lung is demonstrated in the PA (**D**) and oblique (**E**) projections; the latter also illustrates bronchiectasis. Although valuable to demonstrate bronchial anatomy and pathology, the bronchogram is an obsolete examination, having been replaced by CT and airway reconstruction techniques.

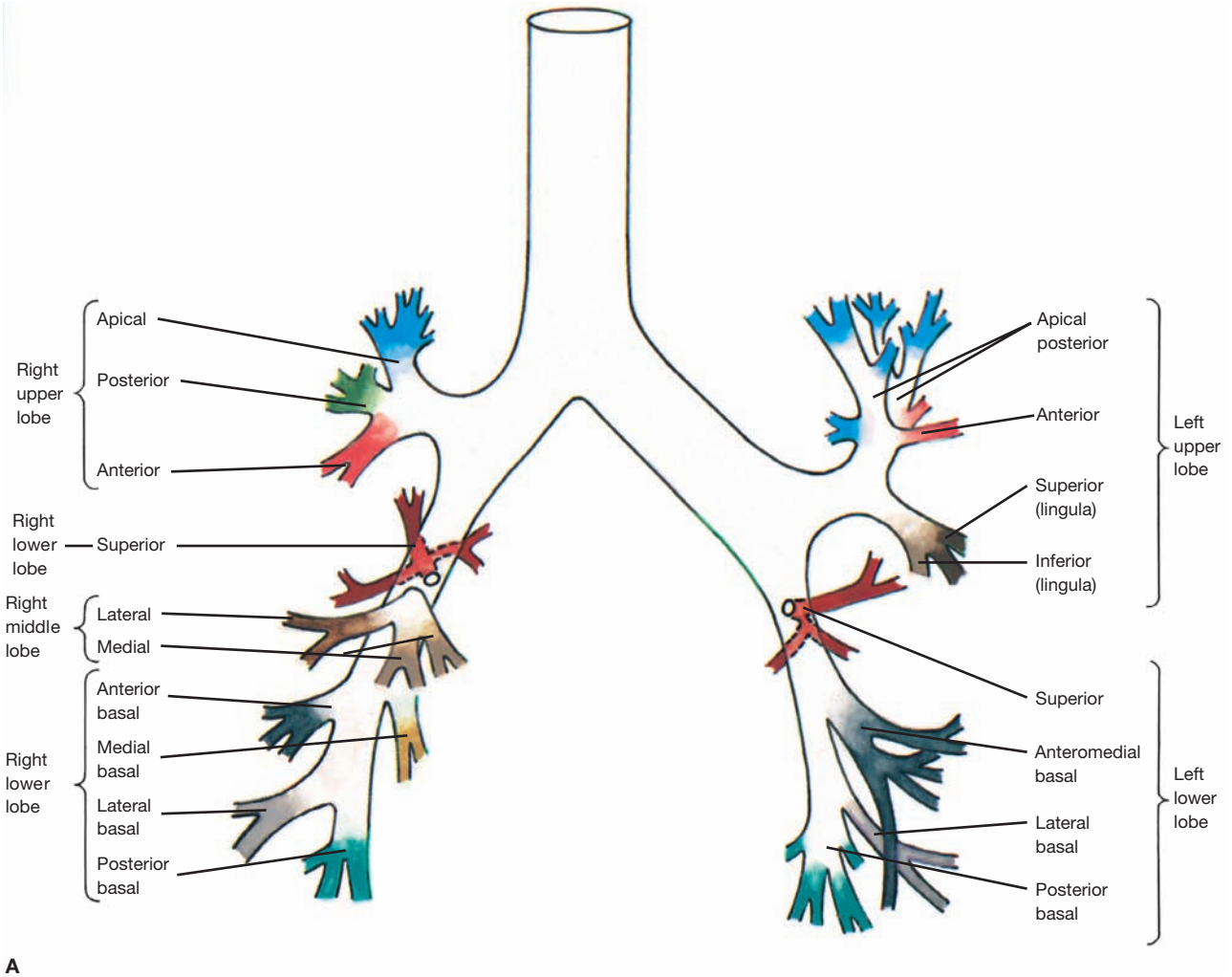


Figure 30-3 Topographic anatomy of the tracheobronchial tree and respective pulmonary subsegments. **A.** Tracheobronchial tree. **B.** Right lung segments. **C.** Left lung segments. Currently, CT is the best modality for accurate anatomical delineation of pulmonary airway segmentation. RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

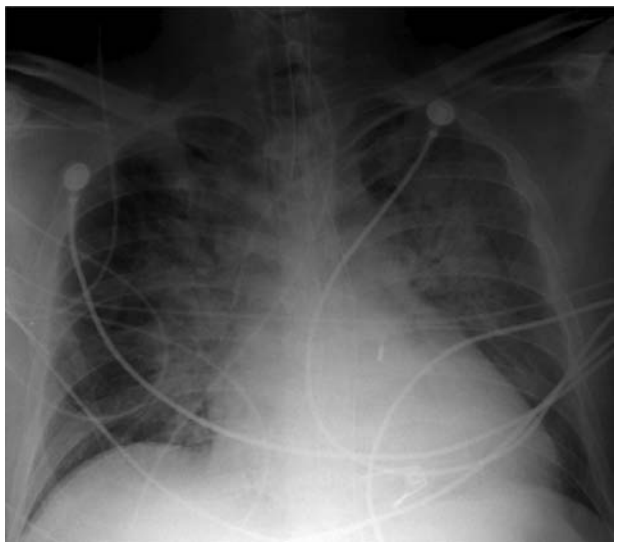


Figure 30-4 Portable AP (anteroposterior) projection chest radiograph, in a patient in the ICU, demonstrating multiple support tubes and lines and the typical configuration of cardiogenic pulmonary edema, with symmetrical bilateral consolidations with perihilar predominance.

such as volume rendering and maximal intensity projection images, which can be utilized to demonstrate complex 3D vascular or airway anatomy and pathology.

An important concept is that of high-resolution CT ("HRCT") of the thorax. Historically, when early CT scanners were limited to the acquisition of relatively thick axial slices (7 to 10 mm) in the thorax, the only way to adequately assess lung parenchymal detail was to acquire serial thin (1 mm) anatomic images utilizing an axial, rather than helical mode; this required noncontiguous (i.e., slices with an interslice gap, typically 20 mm wide), rather than contiguous, slices. These images were also reconstructed using a high spatial frequency algorithm, sharpening edges and allowing improved visualization of fine detail. The result was a set of higher spatial resolution, thin-section images that sampled the lung parenchyma and provided excellent insight into certain pulmonary disorders. This was termed "high-resolution CT" or "HRCT" of the chest, differentiating it from the "standard" chest CT scan, in which thicker sections were acquired through the entire chest in a contiguous helical mode (i.e., without interslice gaps). Generally, a choice had to be made as to which of these two types of scans to perform, since both studies could not be performed simultaneously. Standard CTs were ordered for a general assessment of larger pulmonary lesions, as well as mediastinal, bone, and chest

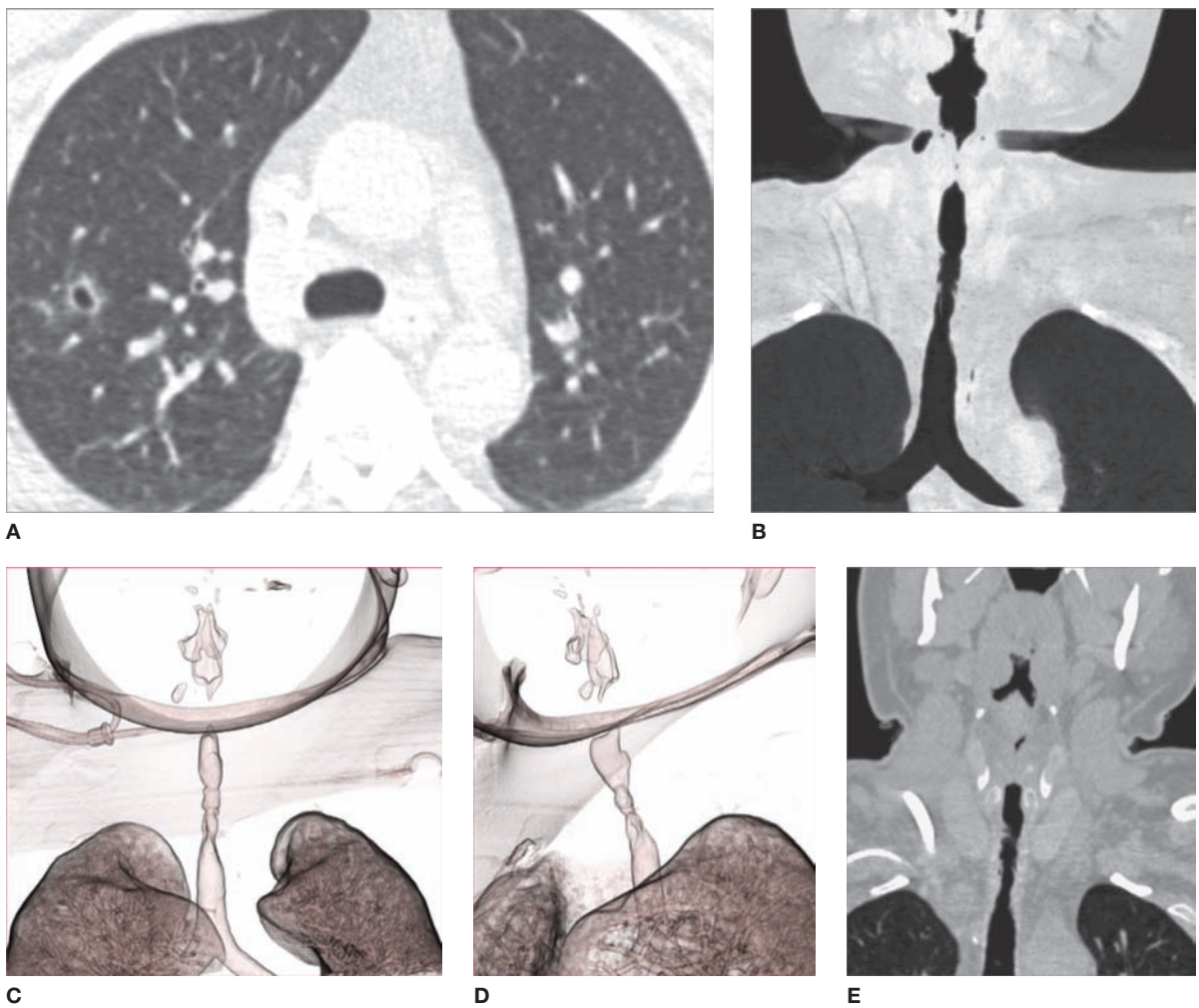
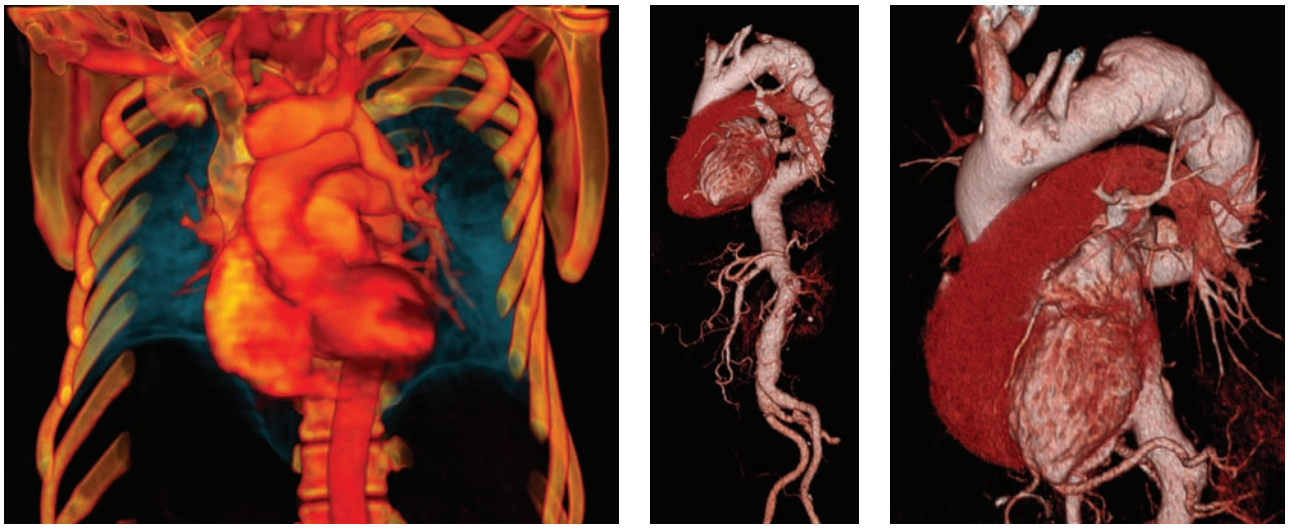


Figure 30-5 CT offers the best imaging evaluation of the pulmonary parenchyma and airways, and advanced postprocessing techniques can provide exquisite views of disease distribution and extension. Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) affecting the lung and airways. **A.** Cavitary nodule in the right upper lobe; (**B**) minimum intensity projection image demonstrating irregular, long segment narrowing of the upper and middle trachea; (**C**) and (**D**) two different projections of a 3D volume rendering airway reconstruction demonstrating the complex configuration of the stenotic tracheal segment; (**E**) coronal reformatted image depicting tracheal wall thickening associated with stenosis.



A B C

Figure 30-6 CT allows acquisition of isotropic volumetric images, in which advanced 3D postprocessing can be performed to demonstrate complex disease processes with a high level of detail. **A.** VR (volume rendering) reconstruction demonstrating partial anomalous pulmonary venous connection of the left upper lobe to the left brachiocephalic vein; (**B**) and (**C**) VR reconstructions at different degrees of rotation, demonstrating the complex configuration of a thoracic aortic aneurysm. These images are invaluable for treatment planning.

wall pathology. High-resolution chest CTs were ordered to assess pulmonary parenchymal disease, such as bronchiectasis, interstitial diseases, and micronodular diseases.

With advances in CT technology, however, it is currently feasible to acquire volumetric, isotropic thin-section (1 mm) images throughout the entire thorax in a single breath-hold, and to reconstruct them in any arbitrary plane (typically axial, sagittal, and coronal) using soft tissue and high-resolution algorithms. Consequently, every chest CT is now effectively both a standard, as well as a high-resolution CT, combining the advantages of each in a single study. This simplifies the ordering process for clinicians. Currently, when ordering a chest CT, there are only two decisions that the clinician needs to make: (1) whether to include expiratory imaging; and (2) whether to perform the study with or without intravenous contrast (these are discussed in detail below).

The first important decision is whether to perform expiratory images, noting that normally, a chest CT is acquired in full inspiration. The reason to avoid performing expiratory images for every patient is to decrease medically unnecessary radiation exposure. Typically, an expiratory CT is ordered if there is a clinical concern for an obstructive lung disease (e.g., asthma, COPD, or small airway disease) or if there is a risk of developing bronchiolitis obliterans (e.g., related to lung or bone marrow transplantation) (Video 30-1A,B). Expiratory CT may also be ordered to assess for large airway diseases, such as tracheobronchomalacia. Expiratory CT is currently the best imaging test to demonstrate small airway air trapping and, therefore, it is a very useful tool to evaluate potential causes of a "mosaic attenuation pattern" on CT (as discussed in detail in the following sections addressing specific diseases).

The second important decision is whether to perform the study with or without intravenous contrast administration. For the sake of decreasing medically unnecessary radiation exposure, there are very few indications for combined chest CT (i.e., with and without intravenous contrast); these are discussed below. The vast majority of chest CT is performed either with or without intravenous contrast. Generally, to assess the lung parenchyma and airways, no intravenous contrast is required. Assessment of bone lesions also usually does not benefit from intravenous contrast administration. On the other hand, vascular and cardiac assessment is greatly enhanced by intravenous contrast. Moreover, mediastinal and hilar pathology (including lymphadenopathy) and cervical and chest wall masses are more conspicuous and better evaluated using intravenous contrast. For certain thoracic neoplasms, the enhancement pattern adds information to their diagnostic characterization. Finally, assessment of pleural diseases also is enhanced using intravenous contrast administration.

It is important to emphasize that since iodinated CT intravenous contrast is excreted primarily by the kidneys, substantially impaired renal function may preclude intravenous contrast administration and may increase the risk of nephrotoxicity. Additional risks associated with intravenous contrast administration include local effects related to contrast extravasation at the injection site and anaphylactoid reactions, ranging from clinically insignificant symptoms to life-threatening airway or cardiovascular collapse; the latter is very rare with the low osmolar contrast material currently utilized.

When performing chest CT with intravenous contrast, it is important to inform the radiologist of the clinical indication. Broadly, three different basic protocols can be utilized: (1) standard contrast-enhanced CT; (2) CT angiography (CTA) for visualization of the aorta or coronary arteries; and (3) CTA for visualization of the pulmonary arteries ("pulmonary embolism [PE] protocol").

Video 30-1 **A.** Axial cine images using lung window and inspiratory acquisition. This CT airway examination demonstrates bronchiectasis, mosaic attenuation, and faint peribronchial opacities, compatible with a diagnosis of bronchiolitis obliterans. Inspiratory acquisitions should ideally reflect the lung appearance at TLC (total lung capacity). **B.** Same patient as in Video 30.1A. Axial cine images on lung window/level, expiratory acquisition, in this CT airway examination, demonstrating same findings earlier, plus dynamic partial collapse of the trachea and central bronchi, compatible with tracheobronchomalacia superimposed on bronchiolitis obliterans. Note the value of expiratory imaging to establish the diagnosis of tracheobronchomalacia and to increase the conspicuity of the mosaic attenuation pattern reflecting small airway disease. Expiratory acquisitions should ideally reflect residual volume (RV). *Access at www.fishmansonline.com*


Video 30-2 **A.** Axial cine images using soft tissue window, demonstrating a massive saddle embolus straddling the bifurcation of the main pulmonary artery. Note that the clot extends to the bilateral lower lobes; oligemia of the right lower lobe is demonstrated. Also note right ventricular enlargement and leftward deviation of the interventricular septum, findings compatible with right ventricular strain. **B.** Same patient as in Video 30.2A. Full-color, coronal, 3D VR (volume rendering) thick slab cine (anterior to posterior), emphasizing cardiovascular structures. This type of reconstruction provides exquisite detail of vascular anatomy and extent of massive pulmonary embolism. *Access at www.fishmansonline.com*


Video 30-3 Full-color, coronal 3D VR (volume rendering) with 360 degrees of rotation about the long axis of the trachea, emphasizing central airways. **A.** Lower magnification with vertical and horizontal axis for spatial orientation. **B.** Higher magnification without axis. The images demonstrate an irregular, long region of segmental stenosis involving the upper trachea. The patient also presented with multiple pulmonary nodules, at least one of which was cavitary. A diagnosis of granulomatosis with polyangiitis or GPA (previously known as Wegener granulomatosis) was established on tracheal biopsy. *Access at www.fishmansonline.com*

For a standard contrast-enhanced CT, the injection rate and imaging acquisition relative to the contrast injection are tailored for maximum enhancement of parenchymal organs and soft tissues; consequently the images are acquired during the venous or equilibrium phase of contrast distribution. This is the standard approach for routine, contrast-enhanced chest CT.

CTA of the aorta and CTA of the coronary arteries are dedicated examinations that are tailored for maximum enhancement of these systemic vessels and are not covered further in this chapter. In particular, cardiac CTA is a thriving application that is usually performed in conjunction with ECG gating to compensate for cardiac motion. CTA of the pulmonary arteries is a well-established application and the current reference standard for the diagnosis of PE (Video 30-2A,B). With this CT technique, contrast injection and imaging acquisition are optimized for maximum enhancement of the pulmonary arteries. This requires a high rate of injection (4–6 mL/s, as opposed to 2 mL/s for regular contrast-enhanced CT) through a large-caliber peripheral IV access (ideally larger than 20G) and very fast volumetric imaging acquisition, usually using contrast bolus tracking to maximize the probability of scanning the patient at the peak of opacification of the pulmonary arteries. When optimally performed, this study allows confident diagnosis of PE in even small subsegmental vessels via direct visualization of vascular filling defects. It also allows accurate assessment of pulmonary vascular caliber and distribution to diagnose pulmonary hypertension, chronic thromboembolic disease, and vasculitides.

CTA of the pulmonary arteries has supplanted conventional pulmonary angiography (except for therapeutic applications) and largely supplanted ventilation–perfusion scanning, although the latter still has an important role in specific clinical settings, such as pregnancy, young patients with normal chest radiographs, or in patients with renal insufficiency. This advanced CTA technique not only allows the diagnosis of PE and possible complications, such as pulmonary infarcts, but also accurately reflects the overall clot burden and signs of right ventricular strain, both important prognostic indicators.[2]

An additional, specific advanced application of CT in the chest is the evaluation of the airways. The imaging protocol for CT of the airways utilizes thin-section (1 mm), volumetric, isotropic images, both in full inspiration and end expiration. The images are acquired from the base of the tongue to the basilar segmental bronchi to include the entire tracheobronchial tree and larynx. Postprocessing 3D techniques are routinely utilized—that is, volume rendering, minimal intensity projections, and virtual bronchoscopy (Video 30-3A,B). The result is accurate depiction of global, regional, and local large airway disorders, including tracheobronchomalacia, airway stenoses, infiltrative and obstructive neoplasms, and inflammatory conditions.

An important consideration recently receiving much attention is the issue of medical radiation exposure in CT. CT, as any imaging modality that utilizes x-rays, exposes the patient to ionizing radiation, which is a known carcinogen due to stochastic effects and which, at very high doses, can have deterministic detrimental effects. To understand the true magnitude of the risks associated with radiation exposure related to diagnostic chest CT, it is critical to have a basic understanding of the ways in which radiation dose is measured, as well as how to quantitatively estimate risk based on best available evidence.

Ionizing radiation dose equivalent (which takes into account energy absorbed (J/kg) and the biologic effects of the specific type of radiation) is measured in Sieverts (Sv). Every human is exposed to approximately 3 mSv/yr of background radiation from natural and man-made sources. In contrast, a chest radiograph delivers 0.1 to 0.2 mSv, whereas a chest CT performed using standard protocols delivers between 5 to 20 mSv. Deterministic effects are extremely rare below 2000 mSv of acute exposure. Although it is difficult to quantify the magnitude of stochastic effects, the International Commission of Radiological Protection (ICRP) estimates the risk coefficient (additional cancers due to radiation exposure) as 0.00005 per mSv of exposure (i.e., ~5% per 1000 mSv). In summary, CT delivers a low, but nonnegligible, radiation dose that is unlikely to cause detrimental biologic effects if used in a prudent and medically justifiable manner.

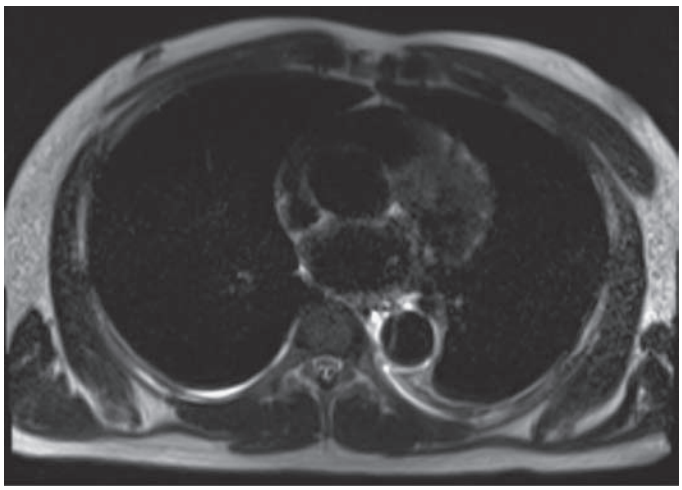
Notwithstanding the relative small risks, radiologists, engineers, and physicists have made substantial strides to develop reconstruction algorithms and protocol optimization techniques that decrease the radiation dose of thoracic CT to the lowest attainable level and that allows diagnostic-quality images. Among the recent dose-reduction methods that have become widely available are iterative reconstruction techniques, combined with tube current and voltage modulation. The combined effects can generate markedly reduced radiation dose, down to sub-mSv (<1 mSv) levels. This is particularly useful for low-dose screening CT, which is discussed in detail later (see Lung Cancer Evaluation).[3,4]

Finally, CT has a major role for guidance of thoracic interventional procedures, which is described in detail below.

CHEST MR

MR is another advanced cross-sectional technique utilized in thoracic imaging. The physics behind MR is complex and beyond the scope of this chapter. Fundamentally, MR uses a very strong static magnetic field (main field) generated by superconducting coils in combination with a radiofrequency radiation pulse sequence and variable magnetic field (gradients) to cause oscillation of hydrogen proton nuclear spins. The result is generation of a radiofrequency signal, which is detected and measured. The signal can be also spatially localized to generate an image that can be obtained in any arbitrary plane. Image contrast with MR depends on the physical properties of the tissue being imaged, as well as on the specific pulse sequence utilized (Fig. 30-7).

MR has advantages and disadvantages with respect to CT. The main advantage of MR is the lack of ionizing radiation. CT utilizes high-energy x-rays, whereas MR utilizes low-energy radiofrequency



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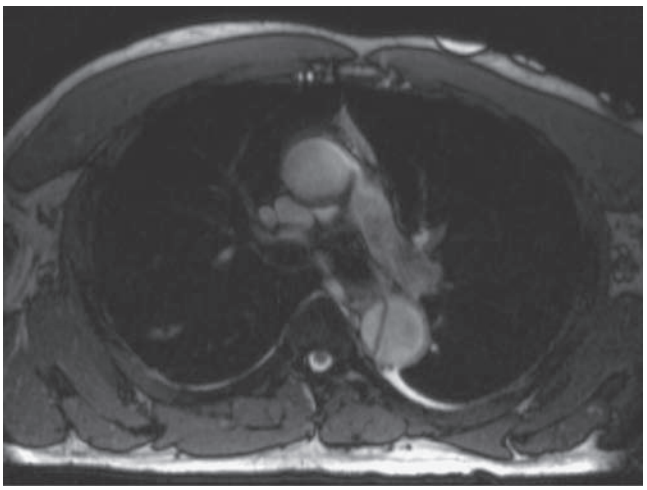

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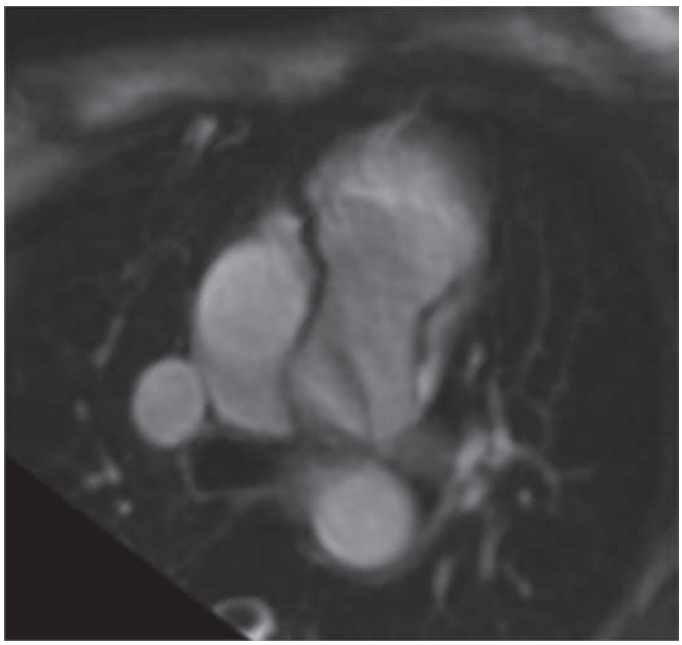


C

Figure 30-7 MR offers lower spatial resolution than CT; however, it allows better contrast resolution and tissue characterization through utilization of varied pulse sequences that emphasize specific aspects of tissue composition. For example, (**A**) and (**B**) demonstrate a dissection of the descending thoracic aorta. **A.** The blood pool appears black and this is, therefore, termed a "black blood" sequence (typically, spin echo sequence). In contrast (**B**) demonstrates the blood pool to be bright and is, therefore, termed a "bright blood" sequence (typically, steady-state free precession gradient echo sequence). **C.** Different patient with a patent ductus arteriosus (PDA), which causes a linear flow artifact (dark band from the aorta to the left PA).

radiation which has minimal biologic effects and no ionization potential. MR also has better contrast resolution than CT and is exquisitely sensitive in the detection of water and fat. MR thus provides a greater degree of soft tissue characterization than is possible with CT. Examples of this greater resolution of soft tissue densities include identification of proteinaceous fluid in bronchogenic cysts, which can appear solid on CT, and the presence of fat in confirming thymic hyperplasia as a cause for an anterior mediastinal mass, thereby enabling differentiation from lymphoma. Another advantage of MR over CT is that iodinated contrast material is not used, obviating the potential problem of CT contrast allergy. In the past, MR also had the advantage of intrinsic multiplanar imaging, but modern multidetector-based CT now demonstrates similar capability.

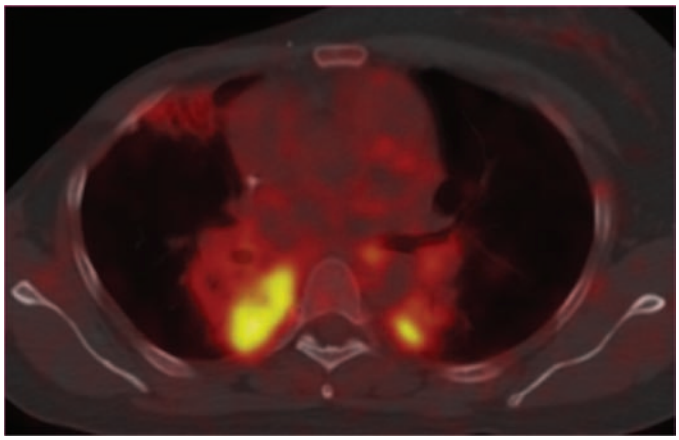
The disadvantages of MR include longer examination time, greater susceptibility to artifacts, lower spatial resolution, and generally very low signal-to-noise ratio in the lung parenchyma, making it unsuitable for optimal pulmonary parenchymal evaluation. However, it should be noted that recently developed fast-proton MR sequences appear promising for the evaluation of patients who need to undergo multiple serial imaging studies and in whom cumulative radiation exposure is of particular concern, such as in young patients with cystic fibrosis.

From a clinical perspective, MR is not the first-line advanced modality for assessment of pulmonary diseases, but it is a very valuable technique for evaluation of the heart and great vessels, for tissue characterization of mediastinal and chest wall masses, and for dynamic assessment of thoracic wall and diaphragmatic motion. Current applications of MR, in addition to those mentioned earlier, include evaluation of the brachial plexus, local staging of superior sulcus tumors, evaluation of neurogenic tumors and lesions involving the thoracic spine, and cardiac or paracardiac masses.[5,6]

Recently considerable interest has arisen in the use of hyperpolarized gases, including helium-3 and xenon-129, for MR imaging of the lungs. Hyperpolarized gas MR can provide detailed images of pulmonary ventilation, as well as information on lung microstructure, beyond the resolution of CT. The latter includes measurements of alveolar size and alveolar–capillary membrane thickness. Nonetheless, to date, hyperpolarized gas MR remains investigational.

PET, PET/CT, AND PET/MR

PET is a nuclear medicine emission tomographic technique (see Chapter 32), in which an intravenously administered radionuclide that decays via positron emission (most often ^{18}F coupled



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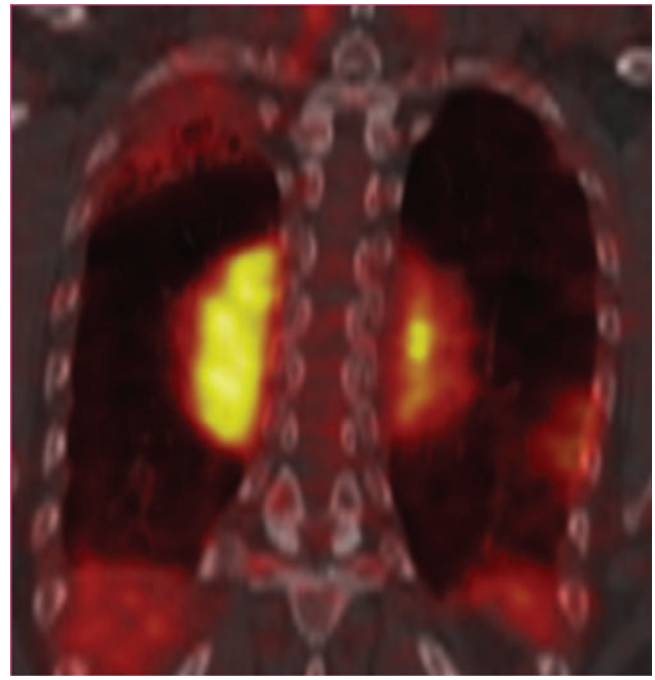


B

Figure 30-8 Fusion images combining CT and PET data in a patient with multifocal MALT pulmonary lymphoma. (**A**) Axial and (**B**) coronal images demonstrate that the areas of consolidation in the posterior medial lungs also demonstrate high FDG uptake, thus appearing bright yellow in this color scheme, a typical feature of metabolically active lymphomas.

to deoxyglucose [FDG]), generates an annihilation event (when a positron collides with an electron and two antiparallel 511-keV photons are simultaneously generated). The event is registered by coincidence detectors, allowing localization of the origin inside the body. Because FDG is very similar to glucose in biodistribution and pharmacokinetics, it effectively concentrates in tissues that have a high metabolic rate and therefore increased glucose uptake—namely, the brain, heart (in the nonfasting state), and many neoplasms; in addition, FDG is concentrated where it is metabolized and excreted: the liver, kidneys, and urinary collecting system. FDG-PET images essentially map the biodistribution of glucose in the body. CT and MR may be performed almost simultaneously with PET in dedicated hybrid scanners (PET/CT and, more recently, PET/MR). The higher spatial resolution of these modalities is helpful for localization of the abnormal PET signals in fused imaging analysis (Fig. 30-8).

It is a common misconception that PET/CT is specific for cancer diagnosis. In reality, it is not. Many normal tissues and inflammatory or infectious processes have a high metabolic rate and high glucose uptake and, therefore, are also bright on PET images. Moreover, many cancers are not highly metabolically active or are not FDG avid, and these may not be detectable by PET imaging. A typical example in the chest is an indolent adenocarcinoma in situ (AIS), formerly called bronchioloalveolar cell carcinoma (BAC).

The strength of PET/CT relies on its ability to accurately stage malignancy if the primary neoplasm is FDG avid. In this context, it is superior to CT or MR because it may demonstrate small metastases in normal-sized structures, particularly lymph nodes, which would not be detectable by CT or MR. PET/CT is, therefore, routinely employed for staging of malignancies such as lung cancer, lymphoma, head and neck carcinoma, and esophageal carcinoma.[7]

ULTRASOUND

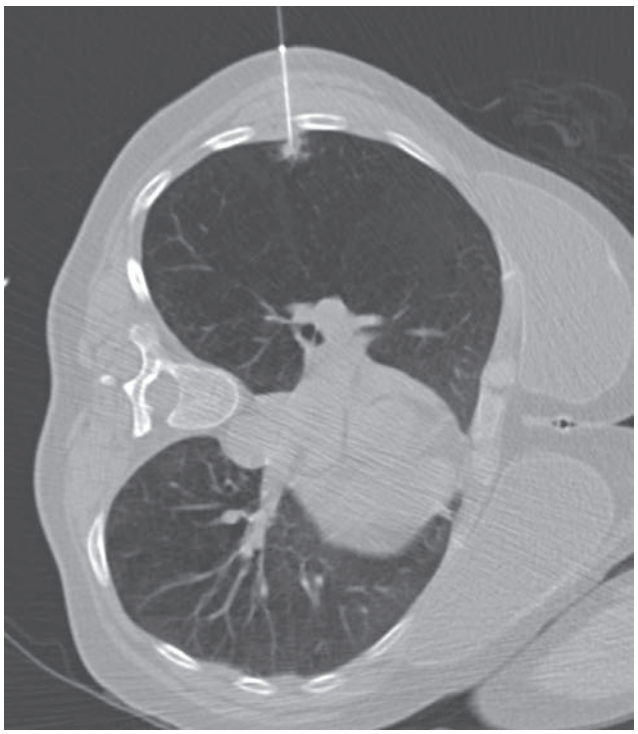
US has a more limited application to thoracic imaging. The primary reason is that both the thoracic cage and the lungs act as reflecting interfaces that block penetration of the US mechanical wave. However, US has been shown to be useful for specific applications, such as detection of pneumothorax or pneumonia, as well as in evaluation of pleural effusions and chest wall pathology. In addition, it is useful in guiding imaging interventions. Thoracic US is discussed in detail in Chapter 31.

IMAGE-GUIDED INTERVENTIONS

Image-guided interventions have dramatically changed the diagnosis of thoracic diseases that require tissue sampling for pathologic confirmation. They have also impacted the treatment of many benign and malignant diseases. Increasingly, image-guided biopsy procedures are being performed for tumor genotyping to guide more targeted, personalized therapies. Half a century ago, surgical procedures were necessary to obtain tissue from the lungs, mediastinum, or chest wall. Surgical biopsies may require hospitalization, are costlier, and carry small, but measurable rates of morbidity and mortality. Currently, most diagnostic procedures can be performed percutaneously or via bronchoscopy in a minimally invasive fashion. Bronchoscopy and endobronchial interventions are described in Chapters 35 and 36 (Fig. 30-9).

Percutaneous transthoracic biopsies (PTBs) may be performed via a variety of imaging guidance systems, most commonly CT, but also fluoroscopy or US (Videos 30-4 and 30-5A,B). Different needle types, lengths, and calibers may be chosen according to the clinical question and lesion characteristics. As a general rule,

Video 30-4 4D cine using custom window. The images are acquired sequentially at the same level and used for guidance in performing a transthoracic fine-needle aspiration (TTNA). The needle was advanced to perfectly engage a small RUL nodule (9 × 7 mm). Final diagnosis was primary adenocarcinoma. *Access at www.fishmansonline.com*



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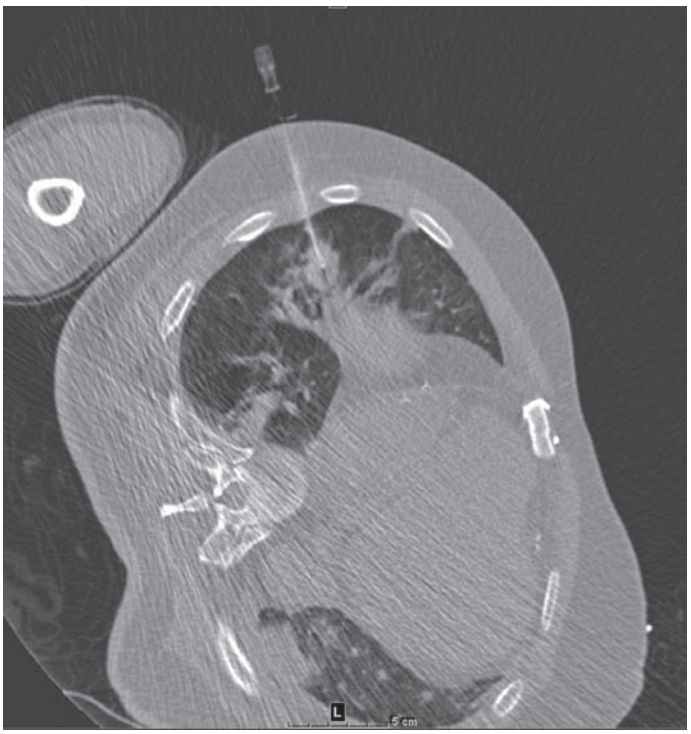

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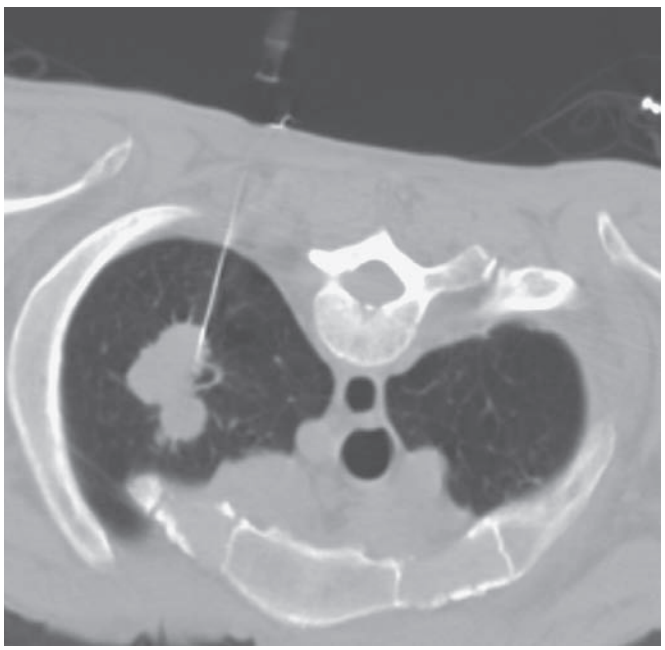

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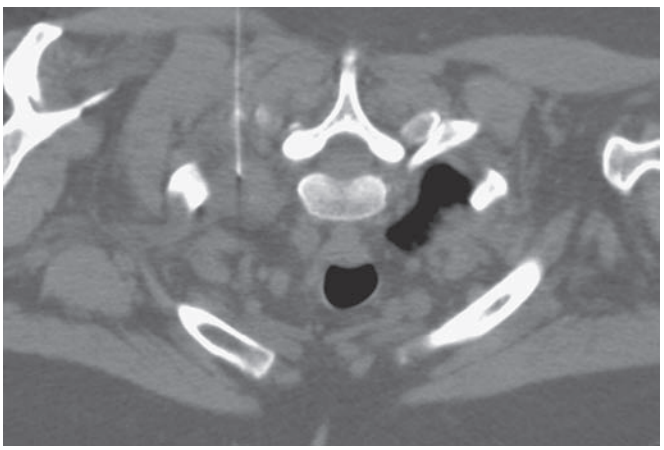


D

Figure 30-9 CT offers accurate, near–real-time localization of lesions for image-guided percutaneous small-needle biopsy. **A.** CT-guided biopsy of a small (0.8 cm) RUL spiculated nodule, a biopsy-proved adenocarcinoma; (**B**) CT-guided biopsy of a larger (1.8 × 2.2 cm) RML nodule, biopsy-proved small cell carcinoma; (**C**) CT-guided biopsy of a lobulated LUL mass (3.0 × 4.2 cm), biopsy-proved adenocarcinoma; (**D**) CT-guided biopsy of a soft tissue mass in the left superior sulcus, biopsy-proved malignant neurogenic neoplasm.

Video 30-5 4D cine using custom window. **A.** Lung window. **B.** Reversed lung window. The images are acquired sequentially at the same level and used for guidance in performing a transthoracic fine-needle aspiration (TTNA). The needle was advanced to perfectly engage a 14- × 13-mm LUL nodule. Final diagnosis was metastasis from RCC (renal cell carcinoma). *Access at www.fishmansonline.com*

superficial chest wall lesions can be accessed via US or CT; pleural, pulmonary, and anterior mediastinal lesions are accessed via CT; central hilar lesions and deep mediastinal masses are not accessible via PTB.

There are two basic types of PTB: fine-needle aspiration (FNA) and automated core needle biopsies (CNBs). In FNA, a small-caliber needle (25–22G) is inserted through the chest wall into the lesion via CT guidance. The tip of the needle is positioned inside the lesion. Negative pressure (suction) is applied via a syringe, and fluid

or clusters of cells are aspirated. The material obtained via FNA is processed using cytopathology techniques, and specific stains and molecular tests can be performed.

In contradistinction, CNB uses a larger coaxial system in which a 19G introducer (outer core) hollow needle is advanced to the pleura or close to the edge of the lesion, followed by introduction of a 20G automated inner core biopsy needle, which is advanced to the lesion. An automated mechanism is then activated, rapidly moving the needle forward and filling the needle trough, or shallow receptacle, with cylindrical "cores" of tissue. The outer sheath instantly moves forward to cut the tissue and keep it in the trough. This process is repeated several times as multiple tissue cores are obtained. The material obtained via CNB is processed using surgical pathology techniques. Both FNA and CNB provide material for microbiology studies, including stains and cultures.

From a diagnostic perspective, FNA is almost equally accurate to CNB for diagnosis of malignant diseases, although CNB is superior for diagnosis of benign diseases. FNA sensitivity for diagnosis of lung cancer is 80% to 95%, and the rate is higher if onsite cytopathology is available and the procedure is approved and performed by experienced radiologists. Limitations of FNA include diagnosis of indolent or low-grade malignancies (for which more tissue or histoarchitecture is required for confident pathologic diagnosis) and inflammatory or infectious diseases—scenarios in which CNB is superior. The advantage of FNA over CNB is a lower complication rate and the capacity to engage and sample very small lesions that would otherwise be inaccessible.

Lesion location, lesion size, and patient body habitus are major determinants utilized by the radiologist in deciding the optimal biopsy technique. All other factors being equal, large pulmonary masses (>3 cm), pleural masses, chest wall masses, and large anterior mediastinal masses are best sampled via CNB. On the other hand, small pulmonary nodules (as small as 0.8 cm), pulmonary nodules in highly mobile regions (posterior or anterior lung bases), and small lymph nodes are best approached using FNA.

Complications related to PTB are relatively infrequent, but occasionally they can be life-threatening. For mediastinal, chest wall, and pleural biopsies, the major risk is hemorrhage, with infection and postprocedural pain following in incidence. Major vascular injury is rare, but it has been reported following biopsies of mediastinal masses. For lung biopsies, the major risk is pneumothorax, followed by hemorrhage, infection, and, rarely, air embolism. While air embolism is the rarest complication, with reported frequency of 0.05% to 0.10%, it is potentially the most life-threatening, due to its unpredictable nature and difficult treatment. Pneumothorax rate varies widely according to institution, and estimates from 5% to 50% have been reported. Most postprocedural pneumothoraces are small and not clinically significant; however, in up to 5% to 10% of patients, a large or symptomatic pneumothorax requires chest tube placement.

The following precautions are advised to minimize the risks associated with PTB: (1) critical appraisal of the clinical need for biopsy and whether PTB is the best approach; (2) thorough preprocedural laboratory assessment to ensure normal platelet count and function and normal coagulation profile. Anticoagulants and antiplatelet medications should be discontinued after conferring with the referring physician; (3) performance or supervision of the procedure by an experienced radiologist; (4) careful preprocedural planning, choosing a patient position and needle trajectory that minimizes the risk of vascular injury and decreases the distance to the lesion; (5) proper biopsy technique with purposeful, fast, accurate needle motion, confirming with imaging the needle location, depth, and relationship to the lesion prior to, and after, each needle movement; and (6) minimization of the effects of patient motion by tracking chest wall movement and advancing the needle in a consistent phase of the respiratory cycle.[8,9]

Therapeutic, percutaneous, image-guided techniques have also been increasingly accepted and utilized. These range from percutaneous chest tube or drain placement to ablation of neoplasms utilizing microwave or cryoablation techniques. The same principles of imaging guidance described for PTB apply for percutaneous therapeutic interventions. Given their complexity and the availability of alternative treatment options (such as surgery or radiation therapy), their use is best reserved for selected patients following discussion with multidisciplinary healthcare teams.

OBSTRUCTIVE LUNG DISEASES, WITH EMPHASIS ON COPD

Pulmonary ventilation, as is the case for pulmonary perfusion, is not homogeneous; it is affected by gravity, airway caliber, and chest wall mechanics. Ventilation is greater at the bases in the erect position due to greater regional changes in lung volume with inspiration, but the apical–basal ventilation gradient is smaller than the perfusion gradient (noting that perfusion is also greater at the bases). Therefore, the ventilation–perfusion ratio (V/Q) is greater at the apices in the erect patient. A similar pattern occurs in the supine patient between the dependent posterior and the nondependent anterior lungs, albeit to a lesser extent. Changes in relative ventilation affect the relative volume and average density of the lung parenchyma and, therefore, can be depicted by imaging.

Chronic obstructive pulmonary disease (COPD) is a complex group of disorders characterized by chronic, progressive airflow limitation that is not fully reversible and is associated with a range of pathologic changes in the lungs (Chapters 39 and 40). In addition, significant extrapulmonary effects caused by chronic inflammation and structural changes are observed. The chronic airflow limitation is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). In addition, large airway inflammation, with increased sputum production and cough, is the hallmark of chronic bronchitis, part of the spectrum of COPD. The relative contributions of these components vary substantially from patient to patient. The presence and extent of each component has the potential to affect clinical presentation, disease severity, prognosis, and therapeutic response. COPD is strongly related to smoking. It has emerged as the third leading cause of death in the United States.

Another clinically prevalent obstructive lung disease is asthma, which is an inflammatory condition affecting mainly small airways, with increased mucus production, airway wall inflammation, and reduced luminal caliber (Chapters 44–46). Asthma differs from COPD from an imaging standpoint in that the clinical manifestations are usually intermittent and reversible, and the degree of hyperinflation tends to be mild, except in severe, longstanding disease.[10,11]

Chest radiographs are not particularly useful in diagnosing obstructive lung disease. In early disease, these are generally normal, as is the case with most asthmatic patients. In more severe or advanced disease, hyperinflation ensues and can be detected radiographically. The classic radiographic appearance of hyperinflation is manifested by increased radiolucency of the lungs; low, flat diaphragms; exaggerated verticality of the heart; increased AP diameter of the chest; and widening of the retrosternal lucent space. Of all these criteria, diaphragmatic flattening is probably the most reliable in supporting a diagnosis of COPD, as it is likely associated with severe emphysema. Care must be taken in making a diagnosis, however, as hyperinflation can be simulated radiographically when a healthy person exerts a maximal inspiratory effort. The lungs also appear hyperinflated in very slender persons. Therefore, it is unwise to make the diagnosis of emphysema solely on the basis of the radiographic finding of hyperinflation (Figs. 30-10 and 30-11).

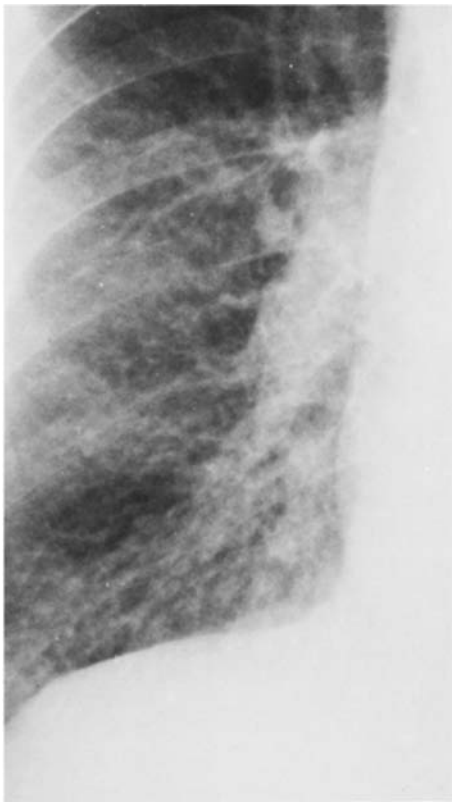


Figure 30-10 Detail view of the lung parenchyma in a PA radiograph, demonstrating increased bronchovascular markings, which are particularly prominent throughout the central lung fields. The patient has COPD with predominant chronic bronchitis. Hyperaeration is minimal.

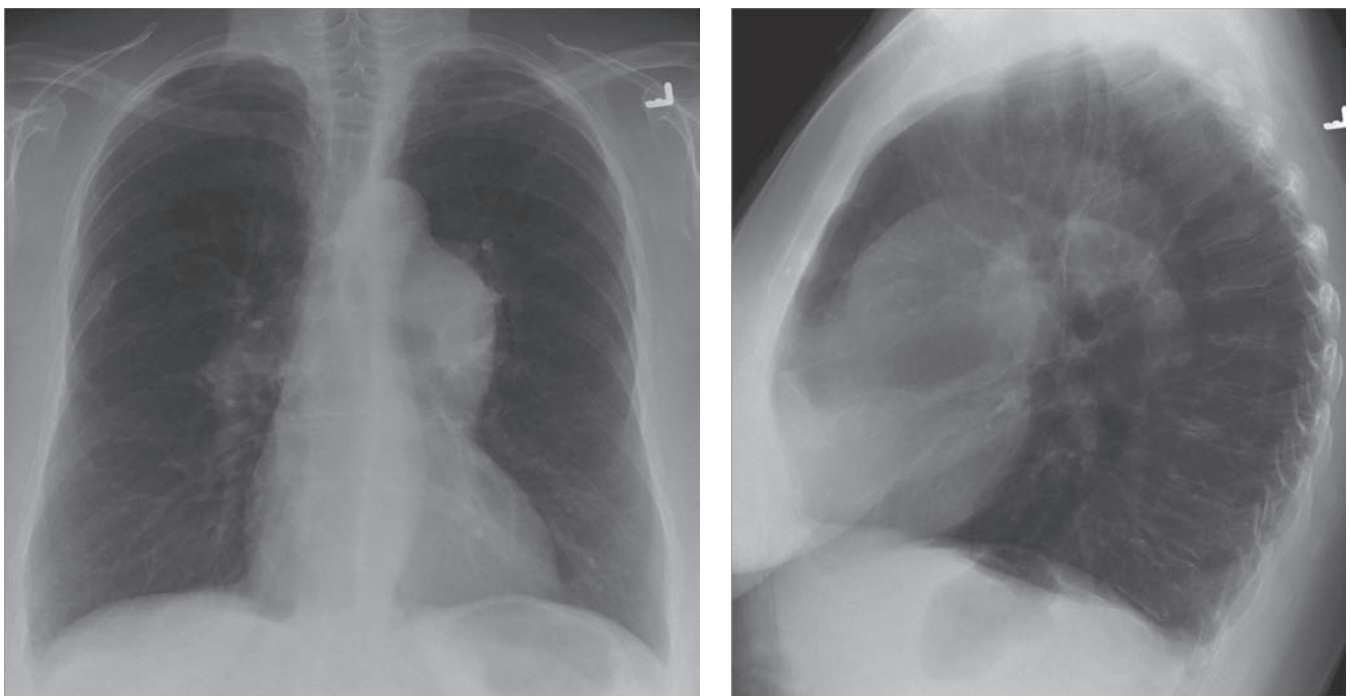
Radiographic evaluation of the pulmonary vessels may also support a diagnosis of emphysema. Two distinctly different vascular patterns have been identified in patients with chronic bronchitis and emphysema: arterial deficiency and increased lung markings. Patients who show the arterial deficiency pattern often have panlobular emphysema and manifest the clinical syndrome of the "pink puffer." Those who have the pattern of increased lung markings often have centrilobular emphysema and manifest the "blue bloater" syndrome. Notably, these radiographic findings occur relatively late in the clinical course of emphysema. Moreover, these findings are not specific and must be considered in the clinical context provided.

Similarly, the diagnosis of chronic bronchitis is a clinical one, based upon a history of chronic cough and sputum production and supplemented by characteristic abnormalities in pulmonary function tests. The radiograph rarely provides substantive help. Vascular markings throughout the lung fields are sometimes prominent, but this finding is nonspecific.

CT, on the other hand, is capable of demonstrating the pathologic changes associated with COPD, including large and small airway inflammation and parenchymal destruction (emphysema). Three basic types of emphysema can be detected by CT—centrilobular, paraseptal, and panlobular.

Centrilobular emphysema is characterized by focal areas of lucency within the centers of secondary pulmonary lobules and without perceptible walls. The lobular arteries and bronchi are maintained, appearing as small dots within the involved secondary lobules. These features help to differentiate the holes of centrilobular emphysema from the cysts of cystic lung disease, as the latter have thin walls and are devoid of internal structure.

Paraseptal emphysema occurs peripherally, adjacent to the visceral pleura, and adjacent to the bronchovascular interstitium. Centrilobular and paraseptal emphysema are both associated with



A **B**

Figure 30-11 (**A**) PA and (**B**) lateral of a patient with severe emphysema-predominant COPD. Salient features are hyperinflation (denoted by flattening of the diaphragms and increased craniocaudal and anteroposterior diameters of the chest) and hyperlucency of the parenchyma. Also note prominence of the central pulmonary arteries, compatible with pulmonary hypertension.

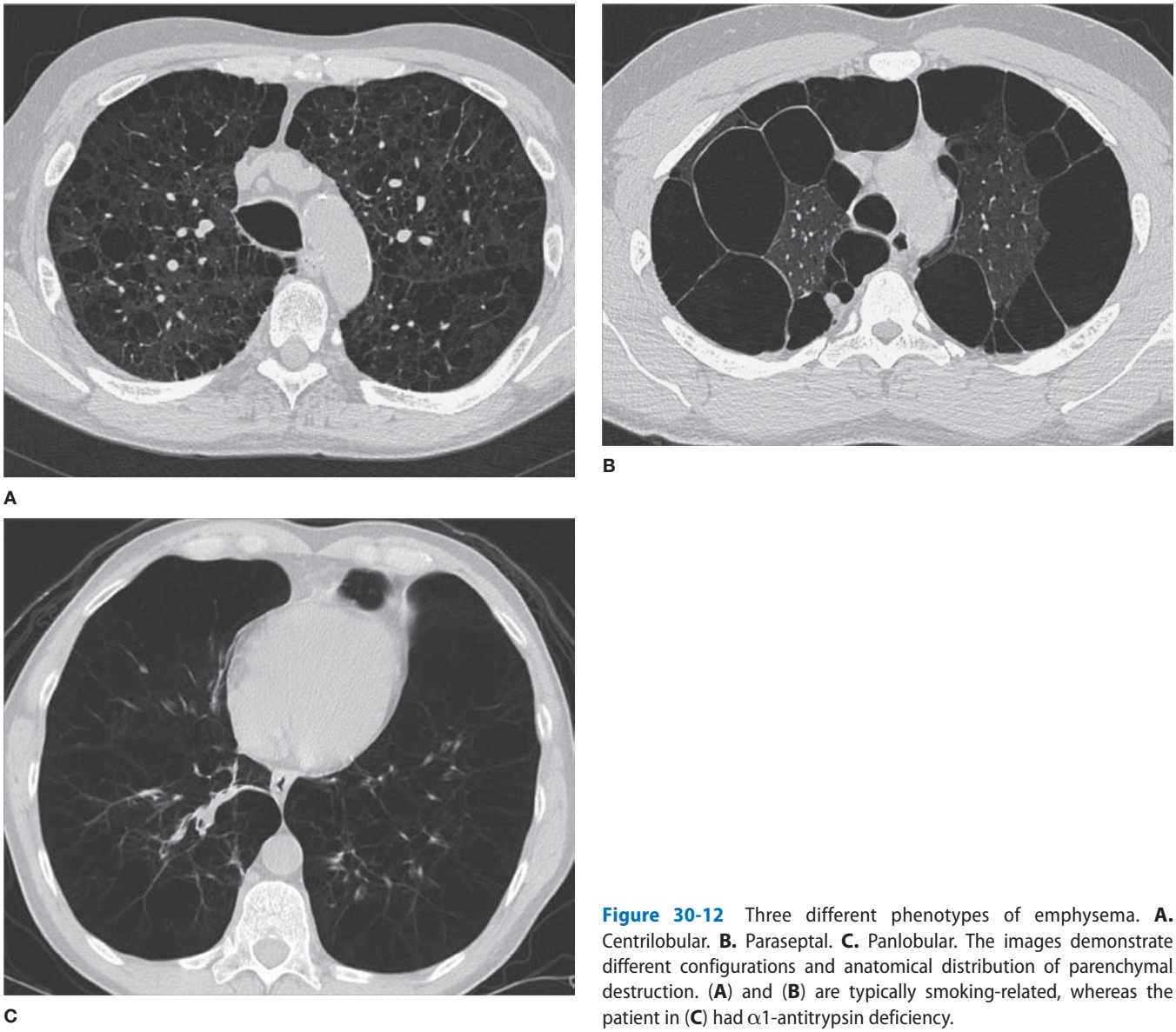


Figure 30-12 Three different phenotypes of emphysema. **A.** Centrilobular. **B.** Paraseptal. **C.** Panlobular. The images demonstrate different configurations and anatomical distribution of parenchymal destruction. (**A**) and (**B**) are typically smoking-related, whereas the patient in (**C**) had α1-antitrypsin deficiency.

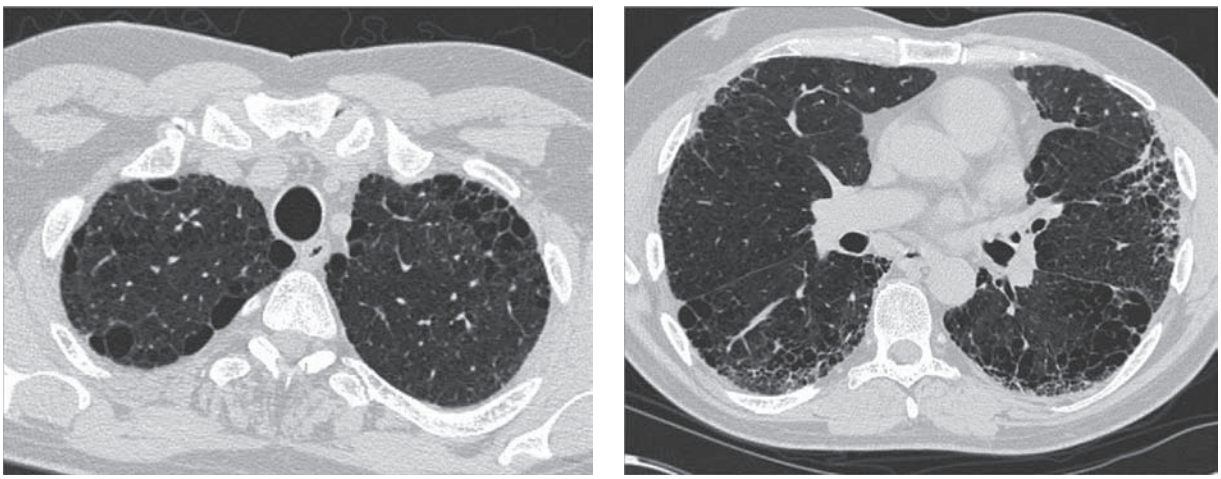
smoking and, therefore, tend to coexist, although the contribution of each form for the total amount of emphysema varies substantially. There is generally upper lung predominance, except in very severe disease. The extreme form of paraseptal emphysema is evident as bullous disease, in which the cystic spaces may become large enough to compromise lung mechanics due to their mass effect.

Finally, panlobular emphysema is a distinct entity in which there is diffuse hyperlucency, hypovascularity, and a paucity of interstitial markings, often with a basilar predominance. These important findings can be overlooked even in patients with marked panlobular emphysema, since there are no discrete holes, as is the case in centrilobular emphysema. This form of emphysema is less likely associated with smoking, and more likely associated with α1-antitrypsin deficiency, a genetic condition that can be exacerbated by smoking (Figs. 30-12 and 30-13).[12–14]

Large airway inflammation as a manifestation of chronic bronchitis may be suggested by the presence of airway wall thickening, the diagnosis of which is somewhat subjective, although several studies have described computer-assisted quantitative measurement methods. Mucoid impaction is a reliable indicator of airway inflammation, but it is not specific for COPD, as it can be seen in the setting of asthma, acute bronchitis, or bronchopneumonia.

Small airway inflammation was previously the most difficult component of COPD to diagnose by imaging. While it is still not possible to directly image inflammation of the very distal airways, expiratory CT now provides the best technique to indirectly diagnose small airway disease. The presence of small airway disease may be inferred by the presence of expiratory air trapping. Normally, the average CT attenuation of aerated lung parenchyma increases in expiration due to volume averaging of voxels that contain less air. In contrast, with air trapping, the increased lung attenuation with expiration is not observed. Thus, in the presence of small airway disease a "mosaic attenuation pattern" is demonstrated on CT images obtained in end expiration, with the darker (lower attenuation) areas corresponding to areas of regional air trapping. Up to 25% of the lung may show air trapping in healthy subjects (typically at the lung bases); higher degrees of air trapping correlate with decreases in functional parameters assessed with pulmonary function testing, such as residual volume (RV) or functional residual capacity (FRC) (Figs. 30-14 and 30-15).

The major future trend in the imaging of COPD is the development of computer-assisted quantification techniques for disease phenotyping, namely, detecting and measuring the severity and



A B

Figure 30-13 Severe emphysema and pulmonary fibrosis in a long-term smoker. **A.** Paraseptal and centrilobular emphysema involving the upper lung fields; (**B**) Additional presence of traction bronchiectasis, peripheral reticulation and honeycombing—features of fibrosis. Smoking-related pulmonary fibrosis is associated with COPD and resembles UIP from an imaging standpoint.

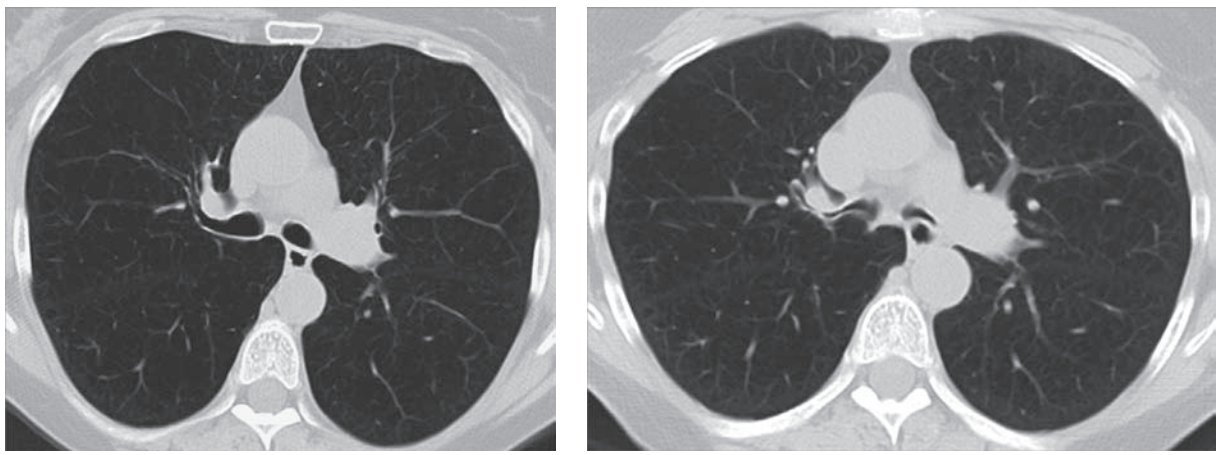


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Figure 30-14 (**A**) Inspiratory and (**B**) expiratory CT images at the level of the mainstem bronchi, demonstrating dynamic expiratory collapse of the central airways, indicative of bronchomalacia, a common association with COPD.

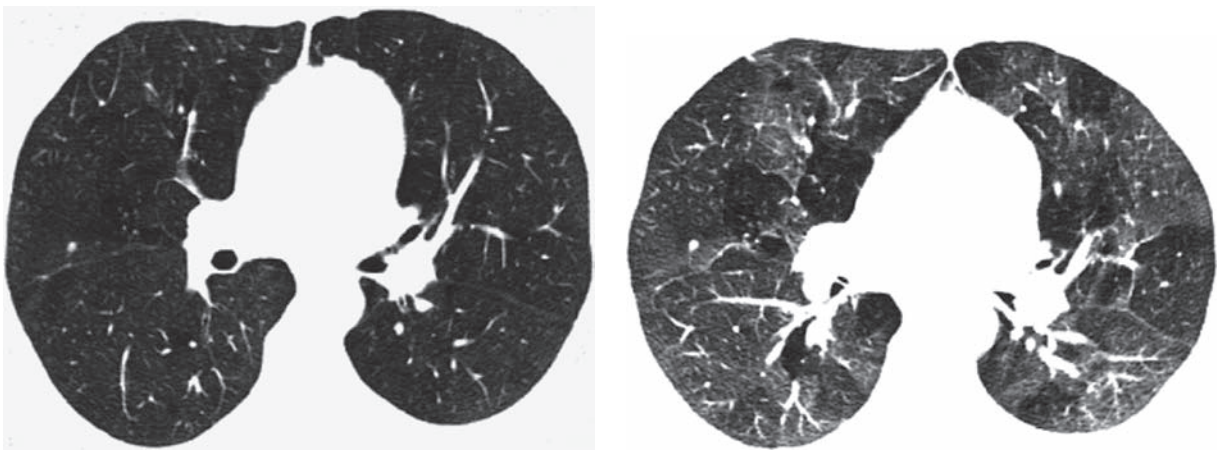

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Figure 30-15 (**A**) Inspiratory and (**B**) expiratory CT images demonstrate the presence of mosaic attenuation (i.e., geographic areas of low parenchymal attenuation interspersed within normal, higher-attenuation areas in expiration), characteristic of air trapping. This patient had a diagnosis of bronchiolitis obliterans.

relative contributions of emphysema and large and small airway diseases to the overall clinical presentation and functional status. Many studies have been published on this subject in the last decade. For quantitative imaging, strict standardization of the scanning technique is required. Sophisticated computer algorithms are also required to accurately separate the lung parenchyma, central airways, central vasculature, mediastinum, and chest wall structures based upon attenuation characteristics and geometric constraints using thin-section, isotropic volumetric data sets primarily obtained using CT. A variety of computational methods can then be applied to detect several disease patterns and characterize their extent and distribution, for both diagnosis and disease quantification as a means of better assessing prognosis and response to therapies.[15,16]

It has been established that "attenuation masks" that separate all low attenuation voxels in the segmented lung parenchyma (e.g., areas of <–950 HU), not including central airways, can accurately quantify the volume of emphysema compared with the reference standard of pathologic assessment. Such CT measures of emphysema demonstrate strong correlation with functional metrics that denote obstruction (e.g., FEV1/FVC,%). Moreover, it is possible to measure the thickness of the central airways (to the fifth or sixth generation) as a quantitative metric in chronic bronchitis. In addition, small airway disease can be indirectly measured using quantification of expiratory air trapping, which can be accomplished via several different techniques. The simplest method uses attenuation masks in expiration. Voxels measuring less than –856 HU on expiratory CT are considered areas of air trapping. This attenuation threshold has been validated in multiple publications. More sophisticated techniques take into account how much each voxel varies in attenuation between full inspiration and end expiration (at FRC). The latter approach requires mathematical, nonrigid registration techniques that track individual voxel motion and regional volume changes between data acquired at two different time points, allowing for a one-on-one correspondence between lung voxels in inspiration and expiration.[17,18]

While these sophisticated quantitative applications are still largely investigational, they will likely reach the clinical realm within this decade. Studies continue to validate the superiority of quantitative imaging over standard qualitative assessment of thoracic imaging studies, demonstrating improved correlations with disease severity and functional impairment. Such quantitative imaging will ultimately provide better tools to estimate prognosis and monitor the efficacy of therapy.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) is a broad and complex topic, with many distinct and unrelated clinical entities potentially contributing to a single imaging pattern. Their detailed pathophysiology is described elsewhere. The focus of this discussion is the contribution of imaging to the differential diagnosis of ILD, emphasizing the most common and clinically relevant diseases.

The chest radiographic pattern of interstitial disease differs from the pattern of alveolar disease in that with interstitial disease the imaging pattern tends to be discrete and sharp, rather than fluffy and irregular; the lesions tend to be diffused, rather than localized. In addition, coalescence is not a typical feature in ILD, and the small opacities are characteristically nodular, reticular, or linear. Large masses or consolidations are not characteristic of the interstitial pattern (Fig. 30-16).

In and of itself, the recognition of an interstitial pattern on chest radiographs is not specific for a particular diagnosis. Most often a CT is necessary for further characterization. However, two observations that may provide useful insight into the likely diagnosis are the temporal course and distribution of disease.

Most interstitial diseases have a chronic, progressive course. Therefore, recognition of an acute interstitial pattern, that is, development and rapid evolution over hours or a few days, is strongly suggestive of interstitial pulmonary edema. This is even more likely if ancillary findings indicative of congestive heart failure or volume overload are present, such as cardiomegaly, pleural effusions, and widening of the vascular pedicle in the mediastinum. Occasionally, a rapidly changing interstitial pattern represents atypical pneumonia due to *Pneumocystis jiroveci*, cytomegalovirus, or mycoplasma. The acute interstitial disorders typically cause a radiographic linear or reticular pattern, which is characterized by prominent Kerley lines throughout the lungs.

In his original description in 1951, Kerley associated thin, radiographic parenchymal opacities with left ventricular failure. Initially, Kerley lines were thought to represent swollen pulmonary lymphatics. It is now recognized that Kerley lines usually represent edematous septae within the pulmonary interstitium. Three patterns exist. Kerley type B lines are the most familiar and are particularly prominent at the lung bases, where they appear as straight, thin, peripheral lines approximately 1 cm long and oriented parallel to the diaphragm. Kerley type A lines represent septae deep within the substance of the lungs; they radiate from the hili, but they are thinner than central vessels. Kerley type C lines probably represent coalescence of A and B lines and are difficult to recognize.

Chronic ILDs may be caused by a wide variety of diseases, including idiopathic interstitial pneumonias, connective tissue diseases, pneumoconiosis, sarcoidosis, lymphangitic spread of malignancy, infections, Langerhans cell histiocytosis (LCH), and lymphangioleiomyomatosis (LAM). Of note, LCH and LAM are not interstitial diseases per se, but rather cystic lung diseases that can present as an interstitial pattern on chest radiography; they are better characterized as cystic diseases on CT.

Characterization of the pattern of interstitial disease as nodular, reticular, or linear on chest radiograph may help in differential diagnosis, since many of the ILDs have a predilection for one of these three patterns. However, beyond that, the radiographic findings are not sufficient for a specific diagnosis. Nonetheless, separation of the distribution of disease into two broad categories can be helpful—upper lung predominant versus basilar predominant.

Upper lung–predominant distribution favors airway-related pathology, with inhalational diseases such as infections, LCH, and pneumoconiosis predominating in this group. Moreover, sarcoidosis is also typically upper lung predominant, a finding compatible with the hypothesis that the disease is triggered by an inhaled agent, although its exact cause remains elusive. On the other hand, basilar-predominant distribution favors idiopathic interstitial pneumonias and connective tissue diseases, in which increased blood flow and greater regional volume changes may play a role in explaining the lower lung predominance. Following such radiographic assessment, CT is generally the next diagnostic step.[19,20]

CT has been validated as the optimal imaging technique for evaluating chronic ILDs. CT can often identify interstitial disease that is not seen on chest radiography, and it provides better disease pattern characterization to enable identification of the underlying etiology, as well as better qualitative or quantitative assessment of severity. CT patterns of ILD follow, to some degree, the patterns seen on the chest radiograph; however, CT allows distinction of reticular, linear, and nodular patterns much more confidently. In addition, it permits evaluation of ancillary findings, such as honeycombing, traction bronchiectasis, ground-glass opacities, and cystic changes, all of which may be very challenging or impossible

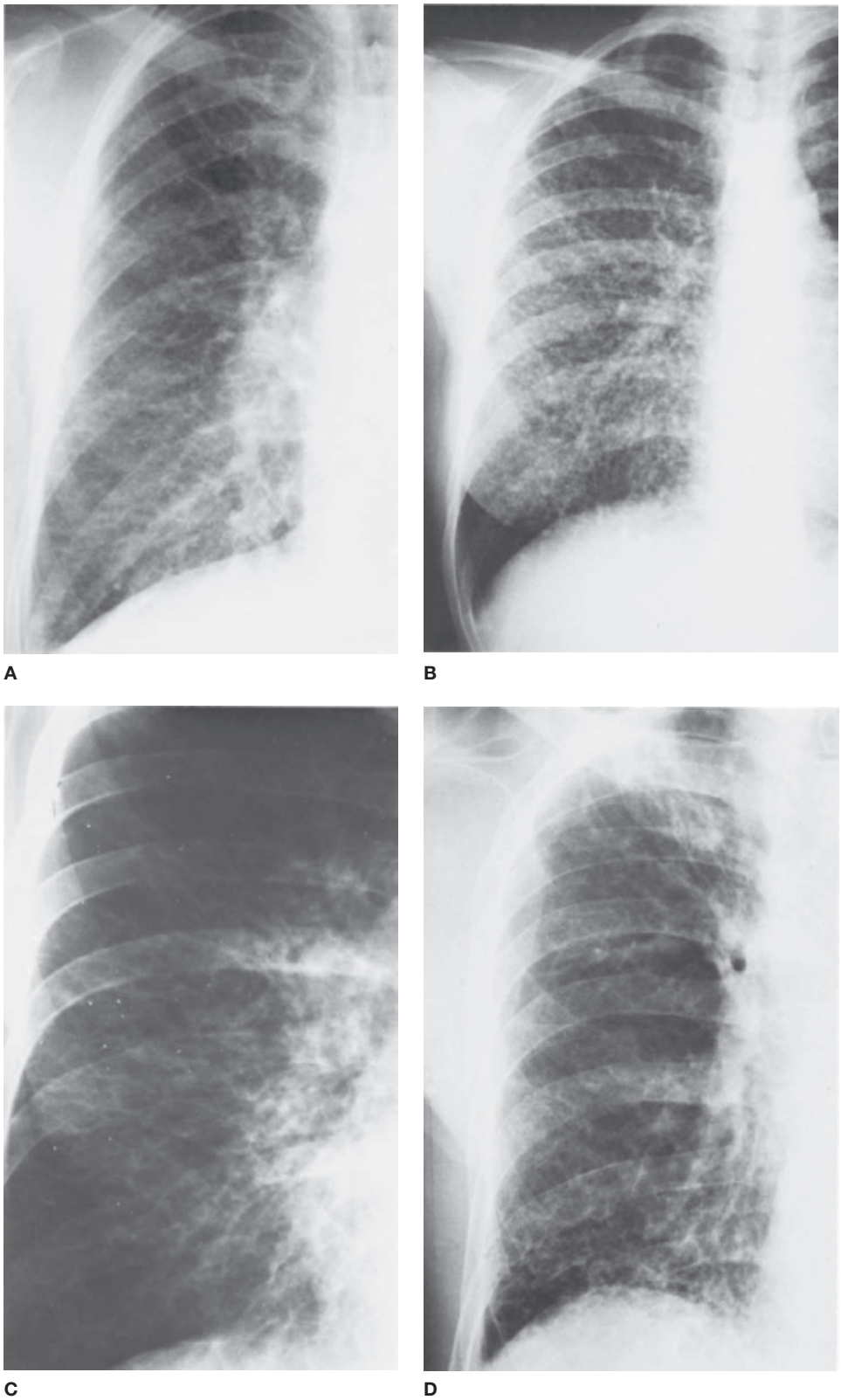


Figure 30-16 Radiographic patterns of interstitial disease. **A.** Linear interstitial pattern produced by interstitial pulmonary edema. The pattern is caused by fluid in the axial and septal interstitial spaces of the lungs, particularly in interlobar septae. **B.** Nodular interstitial pattern due to sarcoidosis. Multiple small, discrete nodules involve both lung fields diffusely. Adenopathy is absent. **C.** Lymphangitic spread of neoplasm. The linear interstitial pattern was caused by metastatic carcinoma of the pancreas. **D.** Reticular interstitial lung pattern. The pattern is most marked at the bases and is characteristic of idiopathic pulmonary fibrosis or collagen vascular disease, particularly scleroderma (as in this patient).

to recognize on chest radiographs. Important to emphasize is that, as previously discussed, every chest CT performed using current protocols on modern scanners may serve as a high-resolution examination. Therefore, the distinction between standard and high-resolution chest CT is obsolete, and detailed interstitial disease characterization can be performed on all current chest CT studies.[21]

Careful analysis of the CT in evaluating ILD can be described as comprising three steps.

The first step in the diagnostic approach of ILD on CT is to exclude interstitial pulmonary edema as the cause. An acute course and ancillary findings of cardiomegaly, bilateral pleural effusions, and central vascular engorgement strongly suggest interstitial pulmonary edema. CT findings include symmetric

Video 30-6 Axial cine images using lung window, demonstrating a typical usual interstitial pneumonia (UIP) pattern of fibrosing interstitial lung disease—in this case, idiopathic (and, therefore, classified as IPF, or idiopathic pulmonary fibrosis). *Access at www.fishmansonline.com*

Video 30-7 Axial cine images using lung window, demonstrating mild interstitial lung disease characterized by basilar-predominant ground-glass opacities without overt fibrotic features, likely reflecting cellular nonspecific interstitial pneumonia (NSIP). In this case, the findings were attributed to connective tissue disease (likely due to scleroderma). *Access at www.fishmansonline.com*

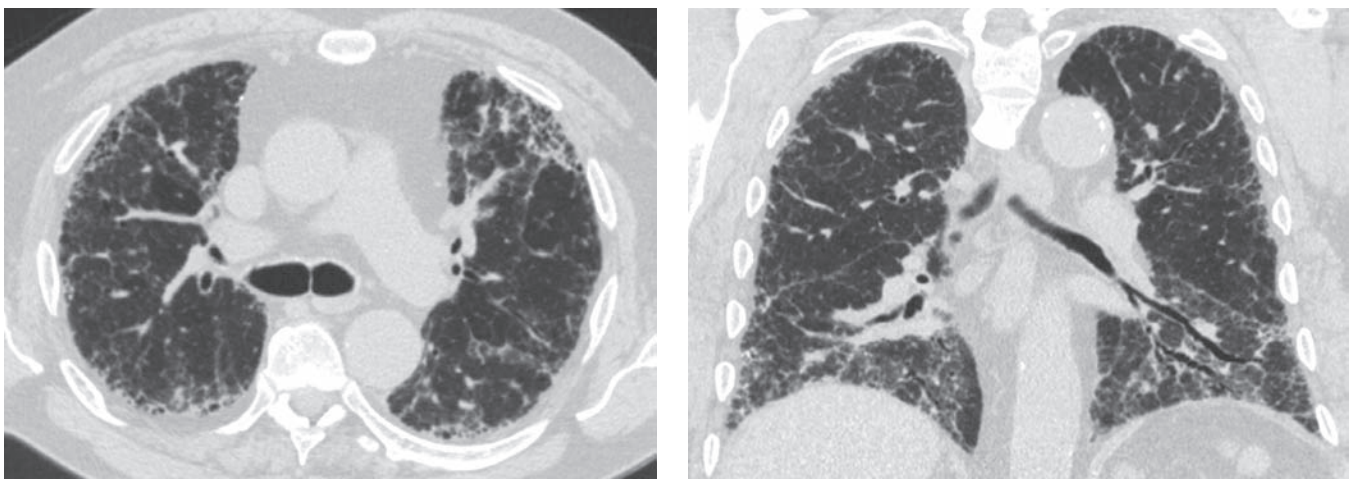
bilateral axial (peribronchovascular) and interlobular septal thickening, with central and basilar predominance. Ground-glass opacities may be present, denoting concomitant alveolar edema. It is important to remember that lymphangitic spread of neoplasm may present with a similar CT pattern; however, the temporal course is not acute and the findings are often asymmetric and more nodular, with additional features of malignancy present, such as pulmonary masses and hilar or mediastinal lymphadenopathy.[22,23]

The second step is to decide whether usual interstitial pneumonia (UIP) is the most likely cause of the pattern. UIP is the pathologic correlate of idiopathic pulmonary fibrosis, although it may also be associated with connective tissue disorders and asbestosis, as well. The latter should be considered if other findings that correlate with asbestos exposure, such as pleural plaques, are present. It is important to recognize UIP because it generally has a much worse prognosis than other causes of ILD and because typical CT features may be sufficient for diagnosis and obviate the need for surgical lung biopsy. CT imaging findings of UIP include symmetric, basilar-predominant reticular opacities, peripheral stacked layers of small cysts (honeycombing), and traction bronchiectasis (Video 30-6). Honeycombing, in particular, is the imaging finding most suggestive of, and specific for, UIP. If this constellation of findings is present, the pattern can be confidently diagnosed as typical UIP and a surgical biopsy avoided.[22]

The third step is to ascertain whether there are features that suggest fibrosis but which are not typical of UIP. In the absence of honeycombing, the combination of reticulation, architectural distortion, and traction bronchiectasis indicates the presence of fibrosis. If fibrosis is present, the differential diagnosis is relatively limited, including atypical UIP, fibrotic nonspecific interstitial pneumonia (NSIP), end-stage sarcoidosis, and chronic hypersensitivity pneumonitis (CHP). Fibrotic NSIP is favored over atypical UIP if there is central, rather than peripheral, predominance, and honeycombing and associated ground-glass opacities are absent. Moreover, the early phase of NSIP may manifest as multifocal bilaterally symmetric ground-glass opacities without fibrotic features or consolidation, denoting early inflammatory changes (cellular NSIP) (Video 30-7). Untreated cellular NSIP generally progresses to fibrotic NSIP, though cellular NSIP tends to respond to anti-inflammatory drugs such as steroids. Nonetheless, significant overlap occurs between fibrotic NSIP and atypical UIP. Both may be idiopathic or associated with connective tissue disorders. Clinical correlation and laboratory tests usually are required to exclude a connective tissue disorder. Of note, the presence of a patulous esophagus may be a clue to the diagnosis of CREST syndrome or systemic sclerosis (Figs. 30-17 and 30-18).[24]

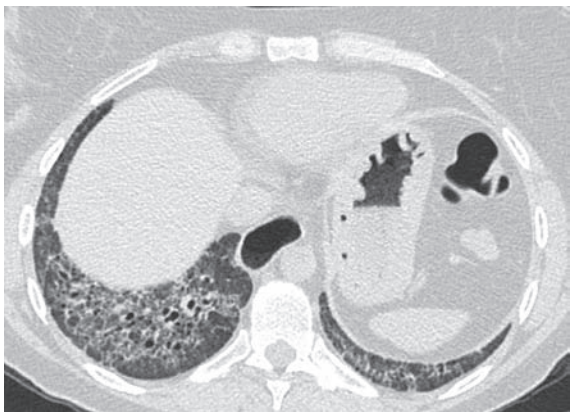
Sarcoidosis is suspected when there is a combination of upper lung–predominant disease that is bilaterally symmetric, axial and interlobular septal interstitial thickening, multiple diminutive nodules with perilymphatic distribution (see section on Pulmonary Nodules and Lung Cancer, below), and associated mediastinal and hilar lymphadenopathy. Mosaic air trapping may also be present. The presence of fibrotic features denotes end-stage disease (radiographic Stage IV). The differential diagnosis includes interstitial pulmonary edema and lymphangitic spread of neoplasm, with interlobular septal thickening as the unifying theme for these three entities.[25]

CHP frequently is associated with a mosaic attenuation pattern that is accentuated on expiratory imaging, denoting heterogeneous small airway air trapping. In addition, CHP tends to show upper zone predominance and may cause multiple tiny nodules. The presence of air trapping is somewhat specific for CHP in the setting of pulmonary fibrosis that does not conform to typical UIP or show features of sarcoidosis, unless the patient has superimposed asthma or COPD (Figs. 30-19–30-21).[26]



A B

Figure 30-17 (**A**) Axial and (**B**) coronal CT images demonstrate a classic usual interstitial pneumonia (UIP) pattern, depicting symmetric, basilar- and peripheral-predominant reticulation, traction bronchiectasis and honeycombing. A UIP pattern confers the worst prognosis among interstitial diseases and is associated with the clinical diagnosis of idiopathic pulmonary fibrosis (IPF).



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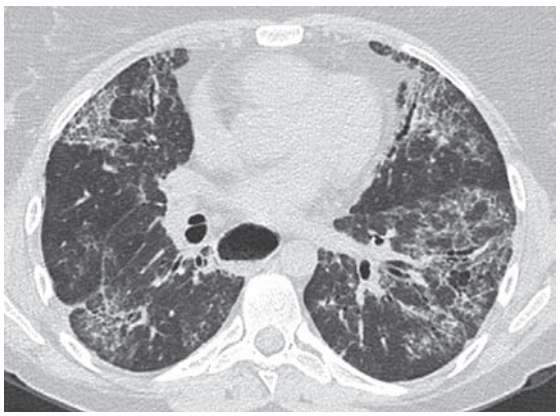
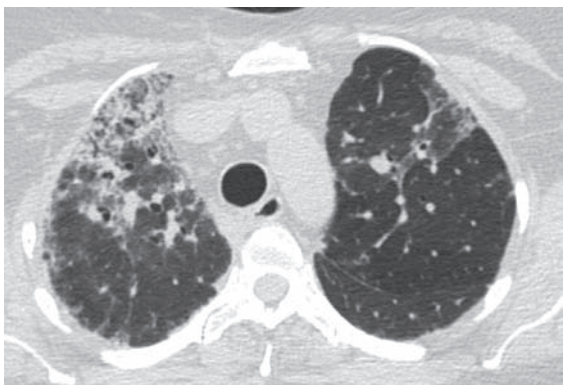


B

Figure 30-18 (**A**) Axial basilar and (**B**) axial midlung CT images in a patient with nonspecific interstitial pneumonia (NSIP) pattern. This pattern is distinguished from UIP by the absence of honeycombing and the more central (or peribronchovascular) distribution of reticulation denoting fibrosis. Traction bronchiectasis is also noted. The patient had a clinical diagnosis of scleroderma.



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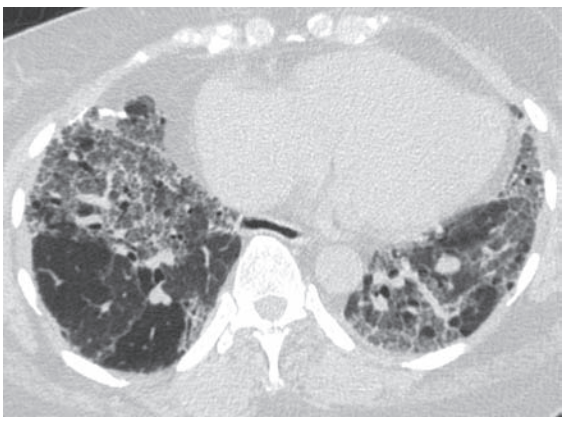

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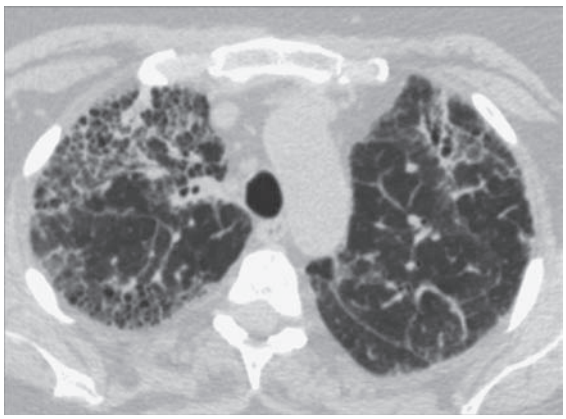

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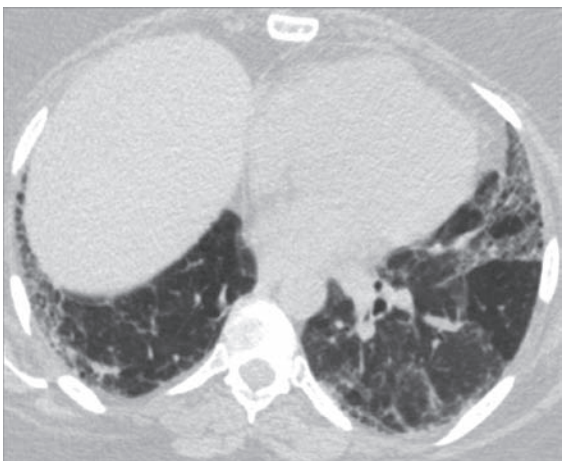

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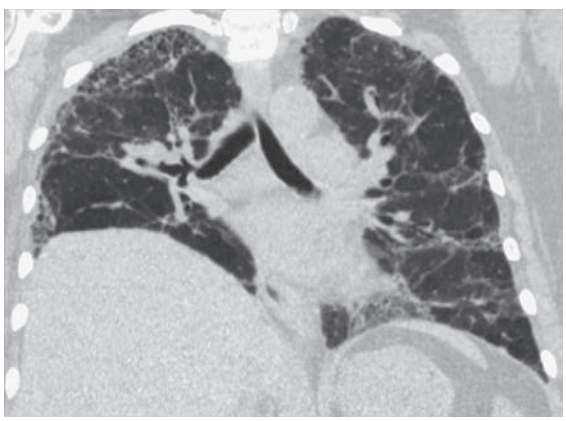


E

Figure 30-19 (**A**) and (**B**) are axial apical and axial basilar CT images in a patient with biopsy-proved CHP (chronic hypersensitivity pneumonitis); (**C**), (**D**), and (**E**) are axial apical, axial basilar, and coronal CT images in another patient with the same diagnosis, but with a more severe presentation. CHP is a differential diagnosis of fibrosing interstitial disease. It differs from UIP and NSIP by the upper lung predominance, patchy (or nonhomogeneous) distribution, and presence of air trapping (noting mosaic attenuation).

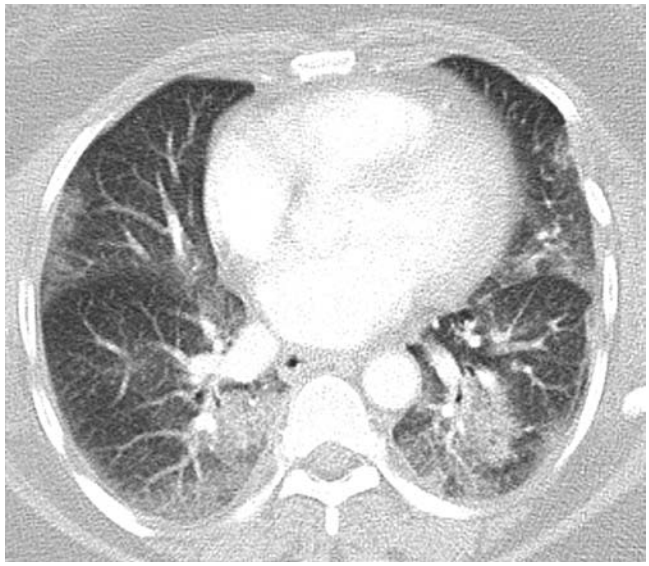


Figure 30-20 Multifocal airspace consolidation and ground-glass opacities in a patient with cryptogenic organizing pneumonia (COP). Infection is the most common differential diagnosis.

Pneumoconioses, particularly silicosis and berylliosis, may present with interstitial interlobular septal and axial thickening, as well as with perilymphatic nodules—a pattern that can be indistinguishable from sarcoidosis. The presence of calcified nodules and mediastinal or hilar lymph nodes support the diagnosis of pneumoconiosis, but these findings may also be seen with sarcoidosis. Specific environmental exposure history is, of course, central in suggesting the diagnosis of pneumoconioses.

Currently, severity of ILD is assessed routinely via subjective analysis of disease extent on CT, along with evaluation of the degree of restriction on pulmonary function testing. Ongoing research has shown the promise of computational quantitative imaging techniques, which allow not only accurate diagnosis based upon pattern, but also quantification of the individual contributions of each pattern feature (e.g., ground-glass opacities and septal thickening) to the overall disease extent. This approach offers the potential for better tools for monitoring disease progression, predicting prognosis, and development of quantitative, surrogate imaging biomarkers for future medication trials.[27]

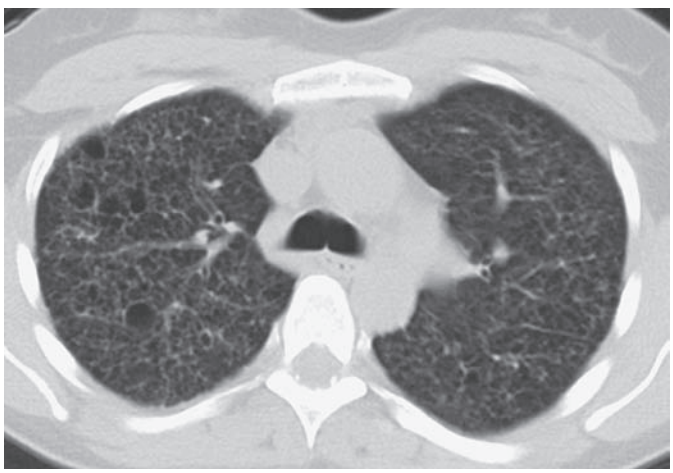
PULMONARY NODULES AND LUNG CANCER

Pulmonary nodules are exceedingly common and may be noted in up to 50% of CT examinations performed in hospital settings. Furthermore, the differential diagnosis is extremely broad and the imaging findings often nonspecific. Therefore, management of pulmonary nodules can be very challenging. We aim here to present a practical, evidence-based approach that is centered on answering four key questions: (1) Is the nodule likely malignant? If so, what is the best approach to tissue sampling? (2) If not, does the nodule need to be followed? If so, how often and for how long? (3) If it is not likely malignant, is the nodule likely to be manifestation of an infectious or inflammatory process that requires pathologic confirmation for proper management? (4) Does the nodule have any features that allow either a specific diagnosis or a confident diagnosis of benignity? The reader is also referred to Chapter 110 for further discussion.

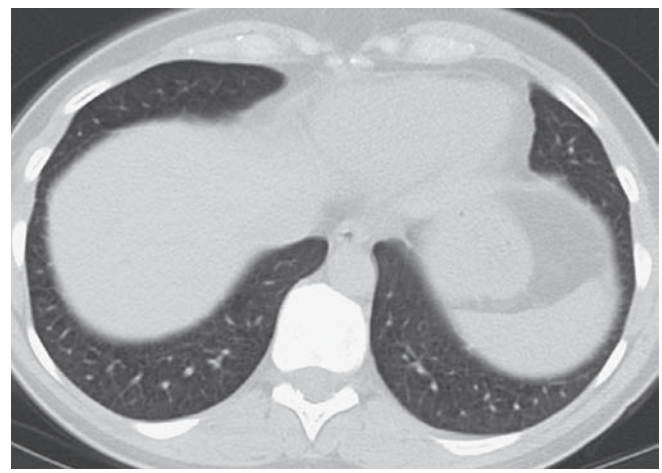
The discussion of pulmonary nodules starts with their definition, which is not always straightforward. While there is no question that well-circumscribed round or ovoid opacities should be characterized as nodules, the distinction of nodules from focal consolidations and interstitial opacities can sometimes be cloudy, particularly when ill-defined or ground-glass nodules are taken into account. As a general rule, any opacity that has mostly convex borders and a shape that can be described as round or ovoid should be classified as a nodule. This has implications for differential diagnosis (Figs. 30-22 and 30-23).

From an imaging perspective, the following descriptors are important in assigning a nodule to a particular differential diagnostic category: number (solitary versus multiple), size, border, CT attenuation, and distribution (if multiple). Below each category is described and a strategic approach to diagnosis and management discussed, emphasizing a combination of clinical and CT findings.[28,29]

To answer the first question, that is, the nodule likely to be malignant, one must be cognizant of the pretest clinical probability. Age is important; the older the patient, the more likely that a lung nodule is malignant. Smoking history and COPD are major risk factors for lung cancer and should be taken into account. A known diagnosis

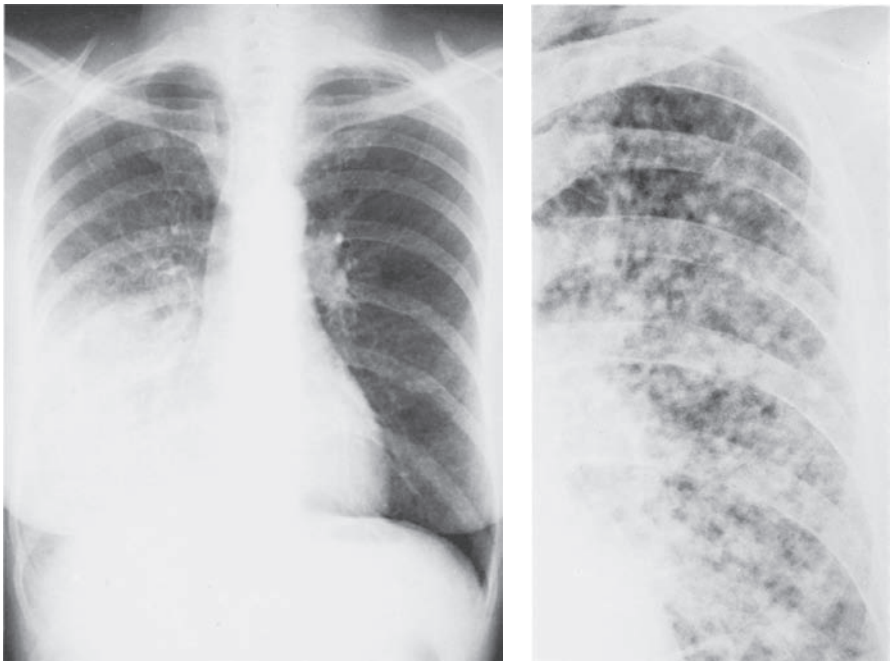


A



B

Figure 30-21 (**A**) and (**B**) are axial apical and axial basilar CT images in a patient with Langerhans cell histiocytosis (LCH). Although LCH is not considered an interstitial lung disease proper (instead, it is classified as a cystic lung disease), this disease does cause an interstitial pattern on chest radiographs. Key features are cysts with upper lung predominance, occasional nodules, and associated hyperinflation. A strong smoking history is often elicited.



A B

Figure 30-22 Radiographic patterns of adenocarcinoma. **A.** Large area of consolidation in the right lower lobe. The alveolar pattern suggests pneumonia, but it failed to improve with antibiotic treatment and was discovered to be an adenocarcinoma. **B.** Multiple ill-defined nodules. The nodules have irregular or fuzzy margins that are characteristic of alveolar, rather than interstitial, nodulation, in this patient with metastatic adenocarcinoma.

of malignancy also places the patient at a higher risk of pulmonary metastases.

Nodule features on CT are of considerable importance in suggesting malignancy. For a solitary nodule, the larger its size, the more likely it is malignant and represents a primary bronchogenic carcinoma. Ill-defined borders are also more highly associated with primary bronchogenic carcinoma than benign etiologies, although infectious processes, such as fungal pneumonia, also have to be considered in the proper clinical setting. Mixed attenuation nodules, that is, subsolid nodules with coexistence of solid and ground-glass components, are highly associated with a diagnosis of primary bronchogenic carcinoma. Multiple nodules that are well circumscribed, vary in size, and are basilar predominant are strongly suggestive of metastatic disease (Figs. 30-24–30-32).

The best evidence-based guidelines for management of solid pulmonary nodules are those published by the Fleischner Society.[30] Although originally described only for solitary nodules, the guidelines are oftentimes applied to multiple nodules.

The Fleischner Society guidelines stratify the risk of malignancy and recommend imaging follow-up intervals according to nodule size and clinical risk factors (Table 30-1). Nodules measuring <4 mm in a low-risk patient do not require follow-up, whereas larger nodules in higher-risk patients require follow-up at progressively shorter intervals (between a maximum of 12 months and a minimum of 3 months). Most nodules measuring more than 8 mm and lacking definitive benign imaging characteristics or confirmation of temporal stability are potentially malignant and, therefore, require more aggressive evaluation. Evaluation may include short-term interval CT follow-up, PET imaging, and often tissue sampling, which can be accomplished via minimally invasive transthoracic CT-guided or bronchoscopic techniques, or rarely, via surgical biopsy. As a general rule, peripheral and smaller nodules are more accurately sampled using transthoracic CT-guided techniques, whereas central or larger masses are more safely approached via bronchoscopic techniques.

It has been shown that only two CT features generally allow confident diagnosis of benignity for solid nodules: a benign pattern of calcification and absence of growth for at least 2 years.

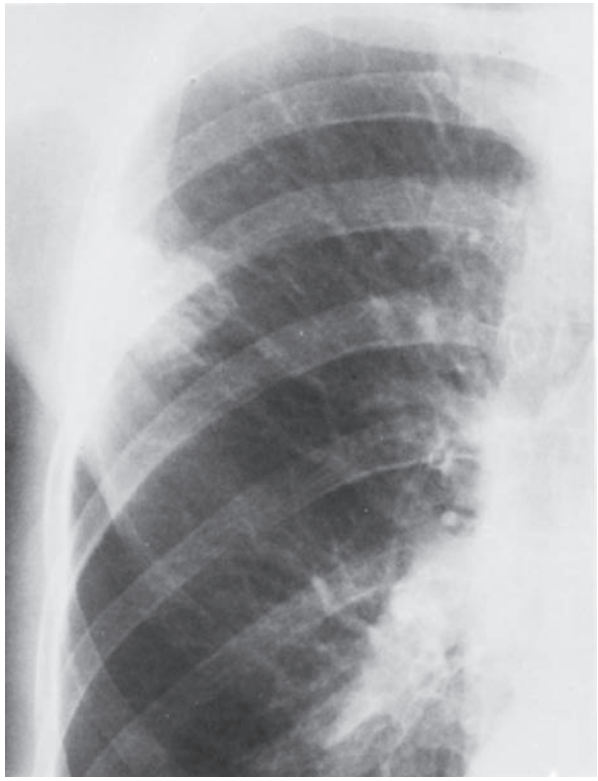
A benign pattern of calcification includes any of the following: central, concentric, diffuse, or coarse ("popcorn" calcification). On the other hand, punctuate or eccentric calcifications are considered indeterminate, as both benign and malignant nodules may demonstrate these findings. Recognition of a benign pattern of calcification is, therefore, very important, as it may obviate the need for imaging follow-up or intervention, alleviating patient and clinician anxiety.

As noted, the second benign feature is interval stability for 2 years as measured by CT, following the Fleischner Society guidelines. The feature is based on the concept of doubling time, which is the time required for a nodule to double in volume. Very fast doubling time (<1 month) is most characteristic of inflammatory or infectious nodules. Extremely slow doubling time (>24 months) is more typical of benign processes, such as granulomas, hamartomas, intraparenchymal lymph nodes, or pulmonary arteriovenous malformations. Intermediate doubling times (>1 month but <24 months) are observed with most malignancies, as well as some indolent infections. In this indeterminate range of growth rate, tissue sampling should be strongly considered to exclude primary or metastatic malignancy.[31]

A CT finding of low-attenuation areas compatible with macroscopic fat in an otherwise well-circumscribed pulmonary nodule is strongly suggestive of a benign pulmonary hamartoma and can obviate the need for more aggressive workup. Care must be taken, however, in differentiating true fat from noise on thin-section CT performed with high-resolution ("HRCT") reconstruction kernels. The use of soft tissue kernels may help in making a more confident diagnosis of fat.

Cavitation is a useful finding in narrowing the differential diagnosis, although it is not specific for malignancy. A cavitary nodule suggests a necrotizing malignancy, particularly primary or metastatic squamous cell carcinoma. However, a number of benign entities may present with cavitary nodules, most typically septic emboli if multiple, granulomatous infections (including mycobacterial and fungal), bacterial abscesses, and granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis).

Ancillary findings on chest CT that support a diagnosis of malignancy include hilar and mediastinal lymphadenopathy, unilateral



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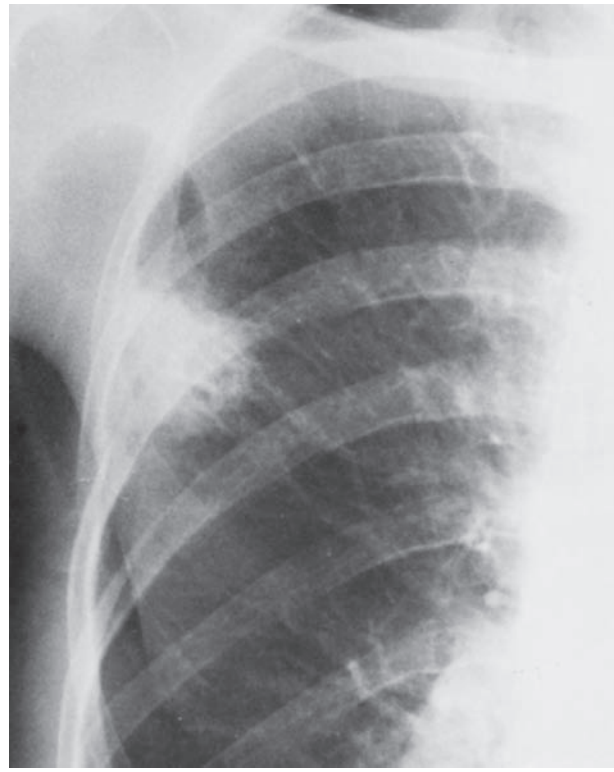

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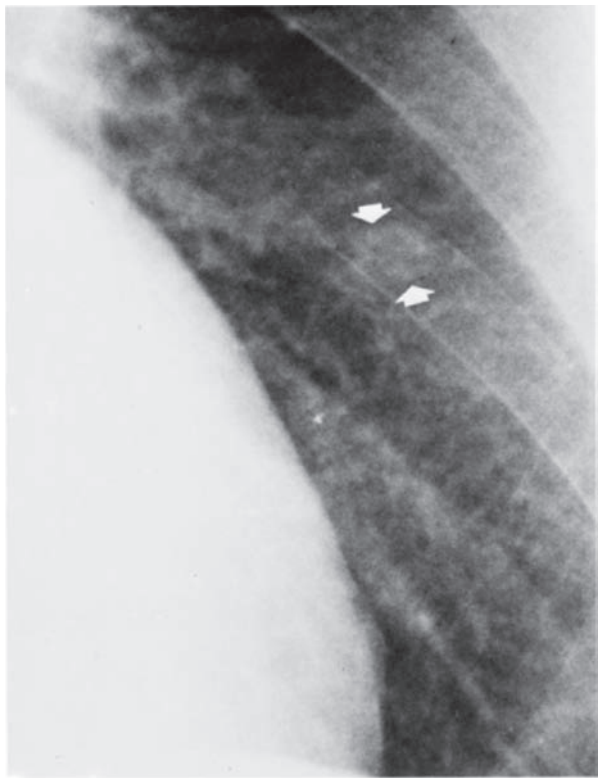

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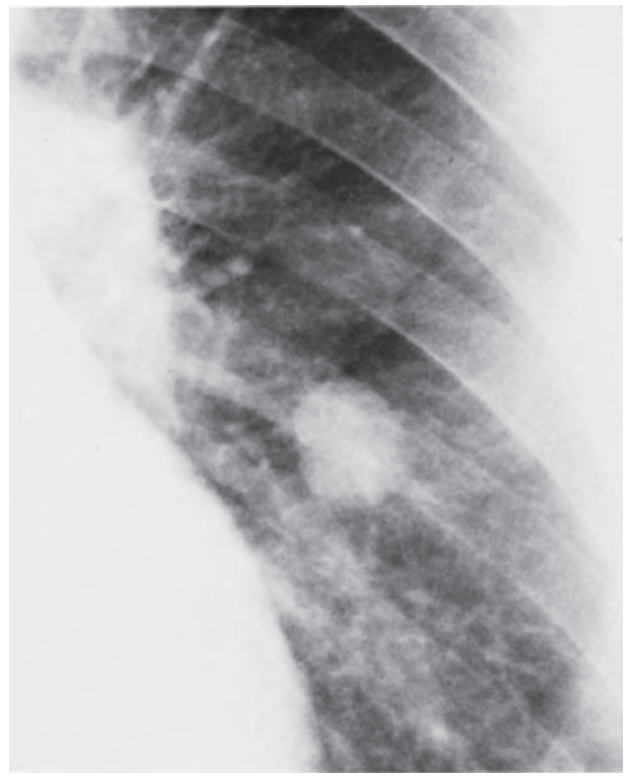
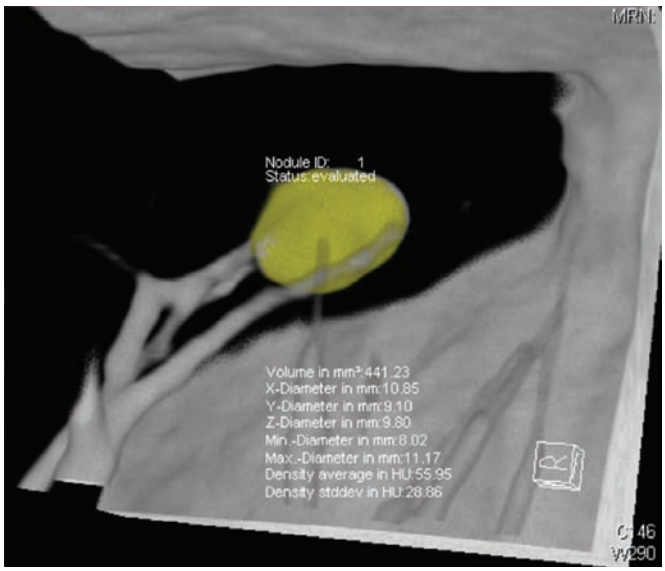
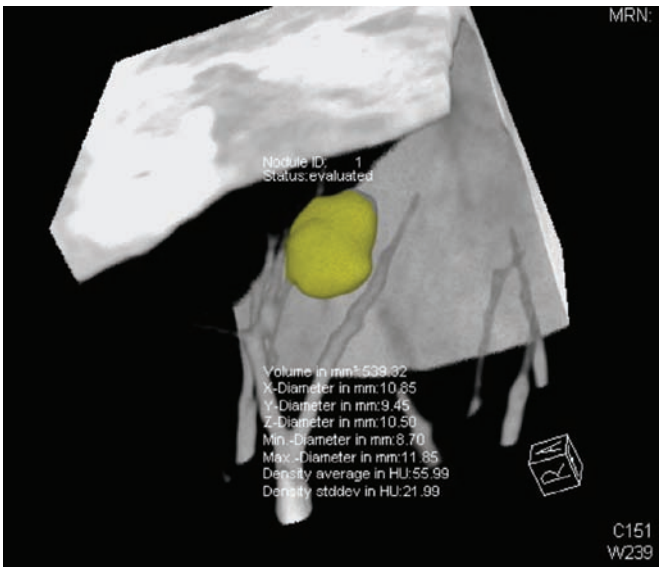


D

Figure 30-23 *Top:* Carcinoma of the lung with a long doubling time. An interval of 18 months elapsed between (**A**) and (**B**). The right upper lobe lesion, which enlarged minimally during that time, proved to be primary squamous cell. *Bottom:* Carcinoma of the lung with a short doubling time. An interval of 4 months elapsed between (**C**) and (**D**). The nodule was not detected on the first radiograph (**C**). It proved to be a primary small cell carcinoma.

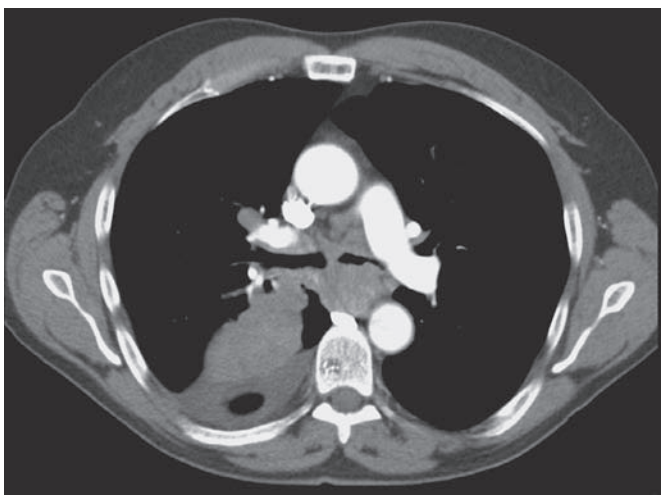


A



B

Figure 30-24 CT allows accurate volumetric measurement, which is not possible with chest radiographs, with the use of postprocessing software for nodule segmentation and volume calculation. This nodule grew from 441 mm^3 (**A**) to 539 mm^3 (**B**) in 7 months, an increase of 19%; it was later confirmed as metastasis from colon cancer.



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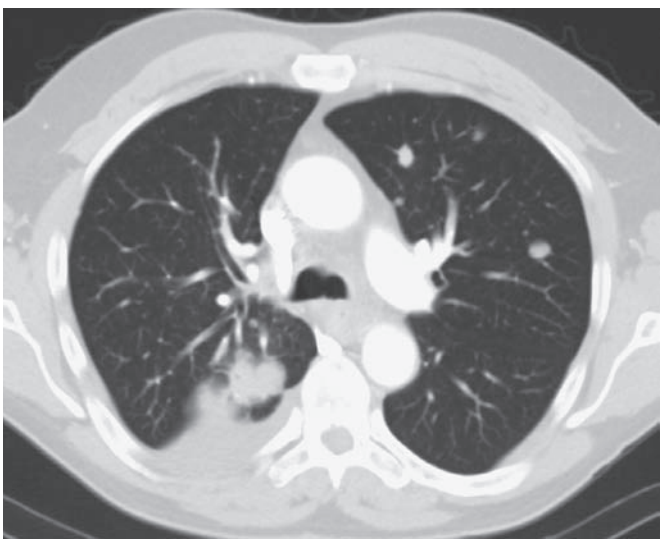

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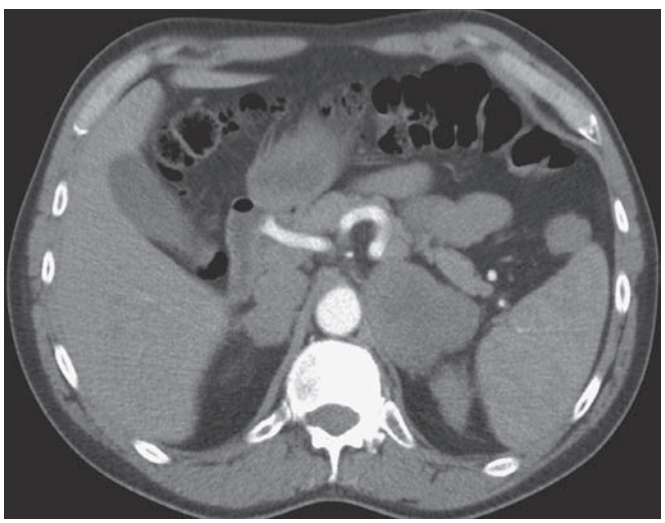
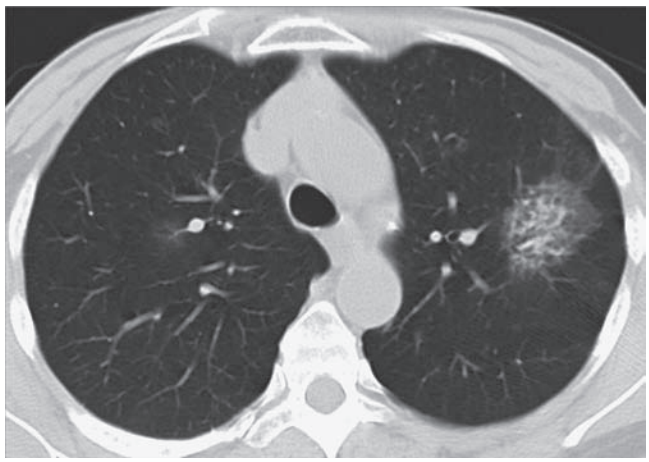


C

Figure 30-25 Advanced-stage lung cancer. The right lower lobe mass was proved to represent a small cell carcinoma. **A.** Axial CT on soft tissue window demonstrates the primary RLL mass, a malignant right pleural effusion, and mediastinal lymphadenopathy. **B.** Axial CT on lung window demonstrates multiple metastatic nodules in the left lung. **C.** Axial CT on soft tissue window demonstrates bilateral adrenal metastasis. The constellation of findings indicates Stage IV disease.



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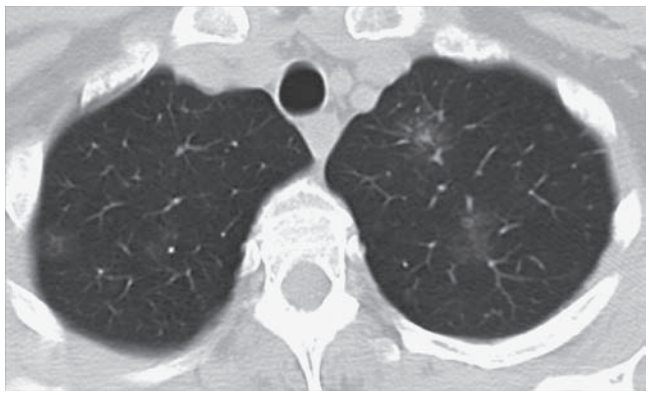


B

Figure 30-26 Spectrum of pulmonary adenocarcinoma. **A.** Axial CT image demonstrates a dominant, mixed-attenuation left upper lobe nodule, with solid and ground-glass components, which was resected and characterized as an adenocarcinoma. **B.** Axial CT image at a higher level demonstrates multiple smaller nodules, some of them mixed, most of purely ground-glass attenuation, which are compatible with multiple lesions in the spectrum of atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA). In the past, all of these lesions would have been classified as BACs (bronchoalveolar carcinomas), a terminology that should no longer be utilized, as discussed in the text.

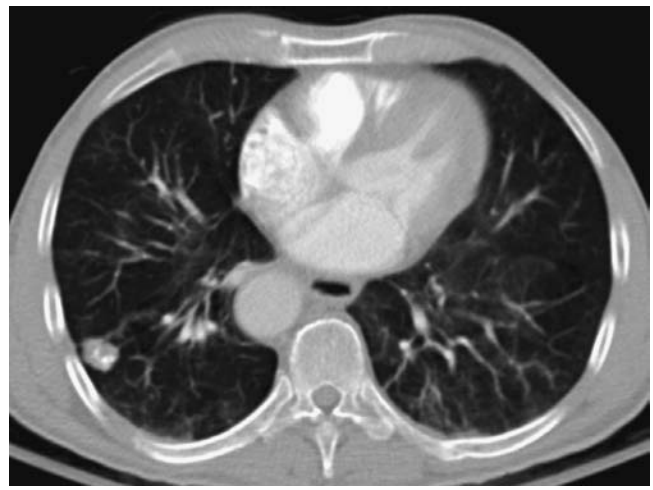


Figure 30-28 Right lower lobe nodule with coarse calcification, typical of a benign pulmonary hamartoma. Incidentally noted is a right-sided descending thoracic aorta.

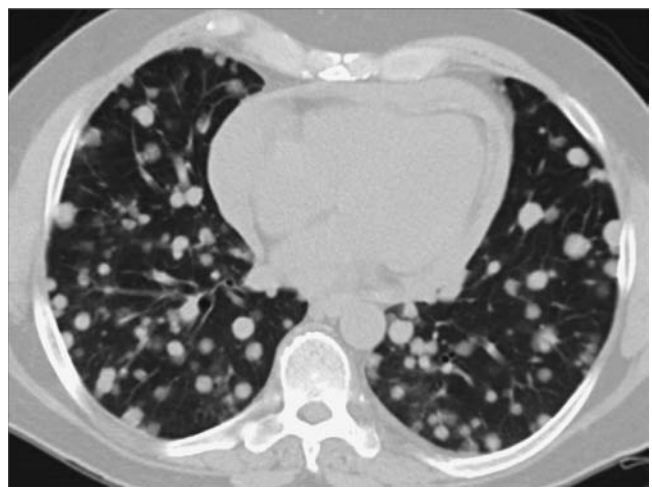
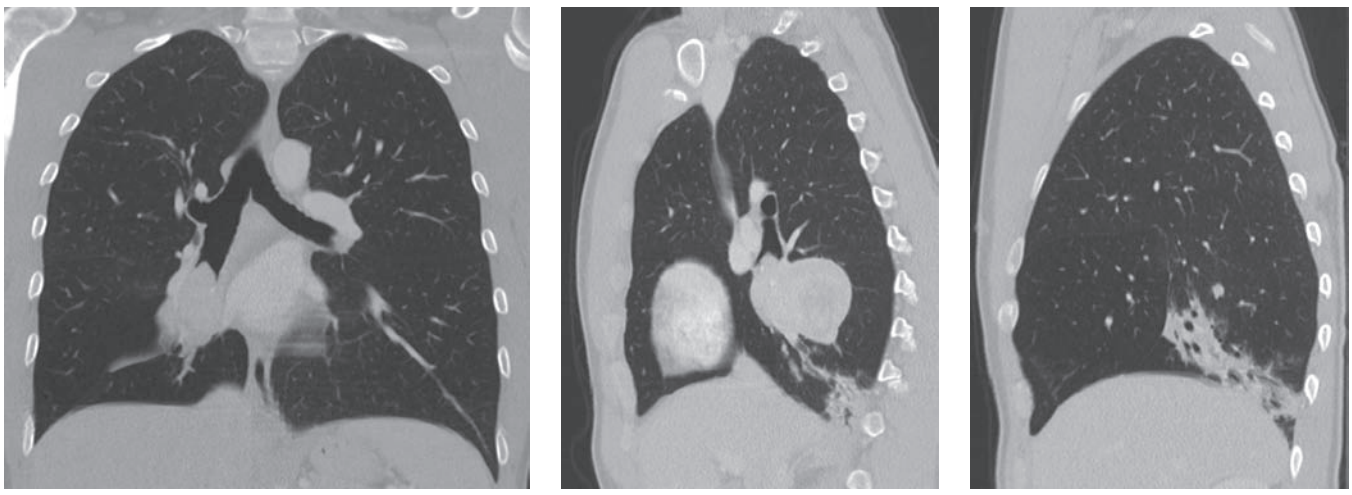


Figure 30-29 Differential diagnosis of multiple pulmonary nodules: axial CT image showing multiple well-circumscribed nodules, of varying size, characteristic of pulmonary metastases, in this case from renal cell carcinoma.



A B C

Figure 30-27 Coronal (**A**) and two sagittal CT images (**B**) and (**C**) showing a large endobronchial mass obstructing the RLL and growing concentrically into the lung parenchyma, with well-circumscribed borders. Note the associated atelectasis of the RLL basilar posterior segment. This mass was a carcinoid neoplasm.

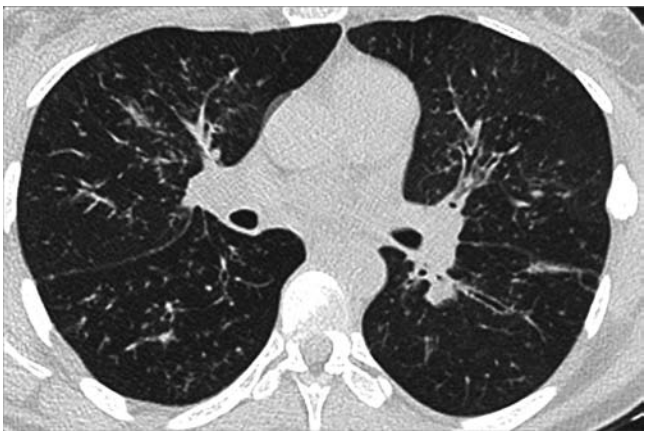


Figure 30-30 Differential diagnosis of multiple pulmonary nodules: axial CT image demonstrating very numerous, very small (1–2 mm) pulmonary nodules with a perilymphatic distribution (along the septal and axial interstitial compartments), typical of sarcoidosis—the diagnosis in this patient. This pattern can also be seen in lymphangitic carcinomatosis.

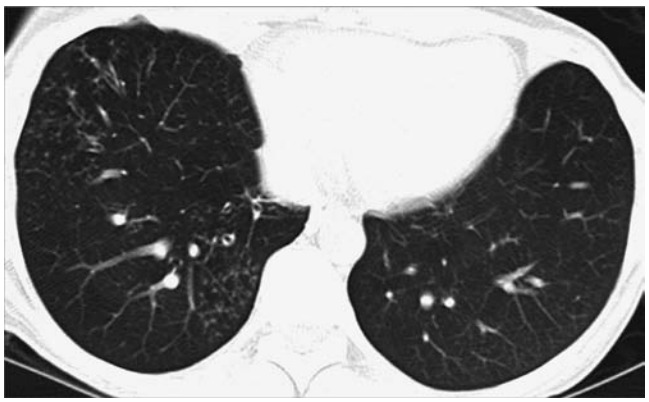


Figure 30-31 Differential diagnosis of multiple pulmonary nodules: axial CT images demonstrating multiple clusters of small nodules (measuring <2–3 mm each) in the RLL and RML, with centrilobular distribution and tree-in-bud configuration. This pattern is typical of infection and usually represents bronchiolitis. In this case, it was due to nontuberculous mycobacterial infection.

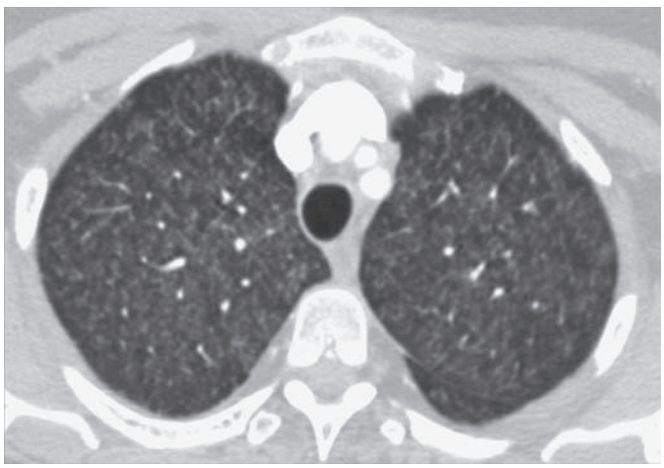
pleural effusion, pleural nodules, and hepatic, osseous, or adrenal metastases.

MULTIPLE PULMONARY NODULES

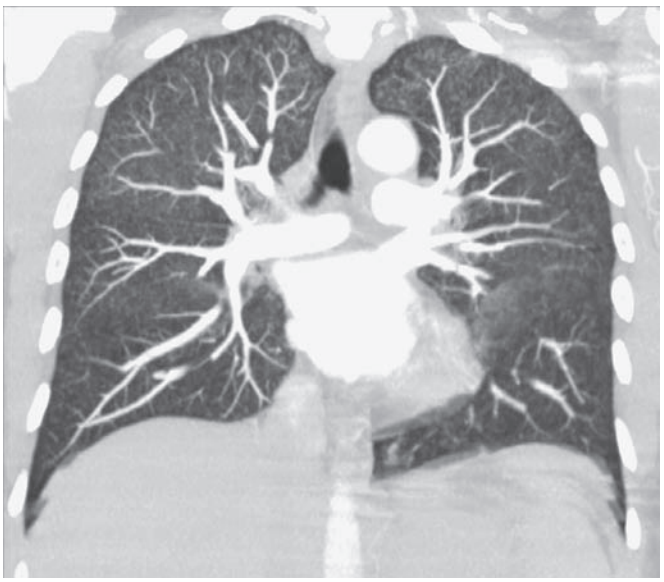
Most of the previously mentioned discussion applies to solitary or few pulmonary nodules, which should be approached similarly. In the setting of numerous, usually small (subcentimeter) pulmonary nodules, a different diagnostic approach must be utilized, emphasizing the distribution of the nodules. Two characteristics of the spatial distribution are relevant: (1) upper lung–predominant versus basilar predominant versus widespread; and (2) centrilobular versus perilymphatic versus random. The otherwise very long list of differential diagnoses can be substantially narrowed by correctly recognizing the distribution.

As discussed previously, an upper lung–predominant distribution suggests inflammatory or infectious etiologies, in which the inciting factor is inhaled; the exception is primary bronchogenic carcinomas that are more likely in the upper lungs, but uncommonly multiple. A lower lung–predominant distribution suggests hematogenously disseminated processes, such as hematogenous metastasis or hematogenous infectious processes. Diffuse distribution comprises a combination of both differential diagnoses and is the least specific.

The centrilobular distribution implies that the majority of nodules are in or near the center of the secondary pulmonary lobule. Such a distribution suggests small airway and acinar disease, indicative of endobronchial spread. This distribution can be further subclassified into two groups: (1) centrilobular nodules in which



A



B

Figure 30-32 Differential diagnosis of multiple pulmonary nodules: (**A**) axial and (**B**) coronal MIP (maximum intensity projection) images demonstrate very numerous, very small (1–2 mm) pulmonary nodules with centrilobular distribution, low attenuation, and indistinct contours. Also noted is symmetric upper lung field predominance. The diagnosis is acute hypersensitivity pneumonitis. In a smoker, the differential diagnosis includes respiratory bronchiolitis.

TABLE 30-1 Fleischner Society Recommendations for Follow-Up and Management of Nodules Smaller than 8 mm Detected Incidentally at Nonscreening CT

Nodule Size (mm)	Low-Risk Patient	High-Risk Patient
≤4	No follow-up needed	Follow up CT at 12 mo; if stable, stop
>4–6	Follow up CT at 12 mo; if stable, stop	Initial follow-up at 6–12 mo, then at 18–24 mo if stable
>6–8	Initial follow-up at 6–12 mo, then at 18–24 mo if stable	Initial follow-up at 3–6 mo, then at 9–12 mo and at 24 mo if stable
>8	Follow-up at around 3, 9, and 24 mo, CT, PET/CT, and/or biopsy[a]	Same as for low risk[a]

Notes:
These recommendations apply for solid, noncalcified nodules—see Table 30-2 for ground-glass nodules.
Size is measured as an average of length and width (axial), for nonspherical nodules.
High-risk patient has a more than minimal history of smoking, and/or other risk factors such as prior or known malignancy, and/or increased risk for metastatic disease. A low-risk patient does not have any known risk factors for primary or metastatic lung cancer.
The higher the risk and the bigger the nodule, the shorter the follow-up interval is and the longer the period of follow-up is, up to 24 months if there is continued stability.
[a]Nodules measuring >8 mm generally require tissue diagnosis via CT-guided percutaneous biopsy, bronchoscopy, or surgical resection, depending on clinical and technical considerations.
Source: Adapted with permission from MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society, Radiology. 2005;237(2):395–400.

the nodules are fuzzy, ill-defined, and often of ground-glass attenuation—findings indicative of small airway inflammatory diseases, as can be seen with respiratory bronchiolitis–interstitial lung disease (RB-ILD) and subacute hypersensitivity pneumonitis; and (2) centrilobular nodules in which the nodules are sharp, well defined, and measure less than 2 mm—findings associated with distal bronchiolar filling, a pattern referred to as, "tree-in-bud." A tree-in-bud pattern strongly suggests infectious bronchiolitis of bacterial, viral, or mycobacterial etiology. Least commonly, the centrilobular distribution may indicate small vessel disease, such as pulmonary vasculitides or capillary hemangiomatosis. Among the vasculitides, Churg–Strauss syndrome and microscopic polyangiitis are primary considerations.

The perilymphatic distribution implies that the majority of nodules are within the septal and bronchovascular interstitial compartments. A perilymphatic distribution is associated with diseases with lymphatic system involvement. Such a distribution suggests a narrow differential diagnosis, including pulmonary interstitial edema, sarcoidosis, or lymphangitic spread of neoplasm ("lymphangitic carcinomatosis"). The latter two diagnoses are more likely if there is nodular interstitial thickening.

A random distribution usually implies hematogenous dissemination of metastases or infection. The archetypal infectious process with numerous random nodules is miliary tuberculosis, although miliary fungal infections can be indistinguishable. Patients with miliary infectious are often immunocompromised and may present with bacteremia or fungemia.

GROUND-GLASS PULMONARY NODULES

Ground-glass nodules deserve separate consideration, as their pathophysiology, differential diagnosis, biologic behavior, and management strategies differ considerably from solid pulmonary nodules.

Ground-glass attenuation is defined as increased attenuation of the lung parenchyma, although the attenuation is not as high as soft tissue attenuation and, therefore, is insufficient to obscure adjacent pulmonary vessels. From a pathology perspective, ground-glass attenuation implies partial filling of the distal airspaces (acini) at a scale below the spatial resolution of CT, causing volume averaging of gas, acinar structures, and material partially filling the alveoli. It is often associated with the lepidic growth pattern, that is, cellular proliferation along the walls of the alveoli, rather than the more common hilic (radial) growth pattern characteristic of most neoplasms.

Multiple ground-glass nodules were described previously, and the rationale for their imaging assessment is included in the description of multiple pulmonary nodules.

Solitary or few ground-glass attenuation nodules carry a different implication from solid nodules. The differential diagnosis is essentially limited to nonspecific infectious or inflammatory processes versus indolent primary bronchogenic adenocarcinoma or premalignant lesions. Therefore, these lesions must be followed to assess their persistence and chronicity. Most nonspecific infectious or inflammatory processes resolve spontaneously within 3 months. Therefore, lesions that persist on a 3-month follow-up chest CT are suspicious for malignancy.

Ground-glass nodules include a spectrum of premalignant to low-grade malignant diseases, which correlate pathologically with the diagnoses of atypical adenomatous hyperplasia (AAH) (a premalignant precursor to adenocarcinomas), AIS, and minimally invasive adenocarcinoma (MIA). These specific diagnoses cannot be differentiated accurately by CT imaging findings or by small biopsies; surgical biopsy is generally necessary. Nonetheless, CT features suggest a specific diagnosis. Namely, smaller lesions (particularly those ≤5 mm) with pure ground-glass attenuation are more likely AAH, whereas the larger the lesion and the more complex its structure (particularly if solid or cystic areas are noted), the more likely it represents AIS (formerly called bronchioloalveolar carcinoma, BAC) or MIA. Large (≥5 mm) or progressive solid components are strongly associated with invasive adenocarcinomas.

The Fleischner Society has published a statement with evidence-based recommendations for management of ground-glass (subsolid) nodules.[32] The statement is mostly based on the revised classification of pulmonary adenocarcinoma proposed in 2011 by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS).[33] In the same spirit as the original recommendations for solid nodules, subsolid nodules are stratified according to size, and different follow-up intervals are proposed. However, unlike the guidelines for solid nodules, those for ground-glass nodules do not differentiate between low- and high-risk

TABLE 30-2 Fleischner Society Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT

Nodule Size (mm)	Management Recommendations	Additional Remarks
Solitary pure GGNs		
≤5 mm	No CT follow-up required	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN
>5 mm	Initial follow-up CT at 3 mo to confirm persistence, then annual surveillance CT for a minimum of 3 yr	FDG PET is of limited value, potentially misleading, and therefore not recommended
Solitary part-solid nodules	Initial follow-up CT at 3 mo to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 yr. If persistent and solid component ≥5 mm, then biopsy or surgical resection[a]	Consider PET/CT for part-solid nodules >10 mm
Multiple subsolid nodules		
Pure GGNs ≤5 mm	Obtain follow-up CT at 2 and 4 yr	Consider alternate causes for multiple GGNs ≤5 mm
Pure GGNs >5 mm without dominant lesions	Initial follow-up CT at 3 mo to confirm persistence and then annual surveillance CT for a minimum of 3 yr	FDG PET is of limited value, potentially misleading, and therefore not recommended
Dominant nodule(s) with part-solid or solid component	Initial follow-up CT at 3 mo to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5-mm solid component[a]	Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer

Notes:
These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.
[a]Small biopsies (CT-guided percutaneous biopsy vs. transbronchial biopsies) may be limited to establish a diagnosis of adenocarcinoma in situ or minimally invasive adenocarcinoma. Consider surgical resection for a complete pathologic analysis of the lesion.
Source: Reproduced with permission from Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology. 2013;266(1):304–317.

groups because of the incidence of subsolid lesions in younger and nonsmoking patients.

The algorithm for subsolid lesions is more involved, also accounting for multiplicity of nodules and the fact that many subsolid nodules are inflammatory (Table 30-2). For example, a subsolid nodule measuring <5 mm does not need any follow-up. If it is >5 mm, then an initial follow-up chest CT should be obtained at 3 months to determine persistence. If persistent, then yearly surveillance is recommended for a minimum of 3 years (Many institutions, including our own, pursue longer surveillance.). If a subsolid nodule >5 mm demonstrates a solid component measuring more than 5 mm and is persistent after 3 months, then tissue sampling and/or resection is emphasized, as these nodules have a very high probability of representing AIS or MIA. The size of the solid component correlates with the likelihood of an invasive component being present.

For multiple ground-glass opacities, the algorithm is similar and the management dictated by the CT characteristics of the most suspicious nodule; the only difference is that if all nodules measure <5 mm, a longer initial follow-up interval (2–4 years) is suggested, as infectious or inflammatory etiologies become far more likely in that setting. Important caveats are the limited usefulness of PET/CT for evaluation of subsolid nodules, since most are not substantially metabolically active (therefore, a negative PET/CT can be misleading), the need to obtain clinical correlation, and the requirement for a meticulous evaluation protocol that includes thin-section (1 mm) volumetric images and consistent use of low radiation dose CT technique.[32]

A comprehensive management algorithm for both solid and subsolid pulmonary nodules was recently published by the American College of Chest Physicians.[34] The algorithm commences with identification of a new nodule on chest CT and proceeds with follow-up recommendations according to size, risk factors for malignancy, and surgical risk. The recommendations emphasize the need for tissue sampling for most nodules larger than 8 mm and compare the advantages and disadvantages of surgical biopsy, CT-guided percutaneous biopsy, and bronchoscopy with biopsy. The specific recommendations for nodules measuring <8 mm are in line with the Fleischner Society guidelines.

LUNG CANCER

The classification, pathophysiology, epidemiology, and management of lung cancer are described elsewhere (Chapters 112–118). This chapter focuses on the contributions of imaging to lung cancer screening, initial diagnosis, and staging.

Lung cancers are typically initially identified on chest radiography or are noted incidentally on chest CT performed for another clinical indication (except in the context of lung cancer screening). Most lung cancers present as pulmonary nodules or masses. Hilar or mediastinal lymphadenopathy and overt signs of metastatic disease are indicative of more advanced stages of disease. Central masses may cause obstructive atelectasis or consolidation.

At initial presentation, the clinical aim is to confirm the diagnosis pathologically, for which tissue sampling is required. In the past, surgical biopsies were the only available options, but in the last two decades, minimally invasive biopsies performed either percutaneously using CT guidance, or transbronchially with bronchoscopic techniques, have been strongly favored for their better risk/benefit ratio, lower complication rate, faster patient recovery, and good diagnostic accuracy. As a general rule, most peripheral lesions (i.e., within 3 cm of a costal pleural surface) are better accessed percutaneously using CT guidance, whereas central lesions, particularly if

an airway visible on CT leads to the lesion, are better accessed via bronchoscopy.[33,35]

Once the diagnosis of lung cancer is pathologically confirmed and fully characterized, staging is of paramount importance to determine the extent of disease and, therefore, the management approach. The most current staging system for lung cancer is the seventh edition of the TNM classification, which was published in 2010. Several references depict visual maps of the T, N, and M criteria and tables with the detailed revised classification.[36,37] In summary, the most important aspects of staging are the size and location of the primary tumor (T), the presence of abnormally enlarged lymph nodes and their location and distribution (N), and the presence of distant metastasis (M). By combining the T, N and M scores, a specific stage from I to IV is obtained, and management strategies are tailored for the type of cancer (histology and genotypic profile) and the staging classification. It cannot be overemphasized that imaging, particularly CT, plays an overarching role not only in tumor detection, but also in tumor staging. It is the primary method for obtaining TNM staging information. PET/CT is also valuable, particularly for nodal staging and identification of distant metastasis. Finally, nodal metastasis may be evaluated using endobronchial US combined with transbronchial biopsies of suspicious lymph nodes.

LUNG CANCER SCREENING

A discussion of the role of modern imaging in the diagnosis of lung cancer would not be complete without mention of the current status of lung cancer CT screening.

Several major prospective multicenter trials using low-dose CT to screen for lung cancer are currently underway. The two largest trials are the National Lung Screening Trial (NLST) in the United States and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) in the Netherlands and Belgium. Many additional smaller prospective trials (including the DANTE trial in Italy and Danish Randomized Lung Cancer CT Screening Trial in Denmark) are also ongoing.

The NLST, launched in 2002, has published promising initial results. This trial compared the performance of low-dose chest CT versus single, frontal view chest radiographs. In the low-dose CT arm there was a statistically significant lung cancer–specific mortality reduction of 20.0% (95% CI: 3.8–26.7), far greater than that expected by chance. A lower, but still statistically significant decrease in all-cause mortality of 6.7% was also observed in the low-dose CT cohort.[38,39]

The NELSON trial, launched in 2003, compared low-dose CT against no screening. In addition, NELSON differed from the NLST in many important aspects, including serial imaging protocol and patient selection criteria. Final results are not available at the time of this writing, but partial results from the NELSON and other European trials did not demonstrate a significant difference in lung cancer mortality (RR 1.37, 95% CI: 0.63–2.97) or all-cause mortality (1.46, 95% CI: 0.99–2.15); these results are from the Danish trial, which is coordinated with the NELSON trial. The reasons for the discrepant results between the North American and European trials are being actively investigated and may be at least partially related to patient selection criteria and management protocols.[40,41]

In summary, while the NLST provides compelling evidence of the mortality benefit from low-dose CT screening in high-risk patients and demonstrates its superiority to radiographic screening, many important questions remain regarding cost-effectiveness of screening, as well as optimal management of false-positive results. Modeling studies are currently underway and recommendations based on cost-effective analysis are expected in the future.

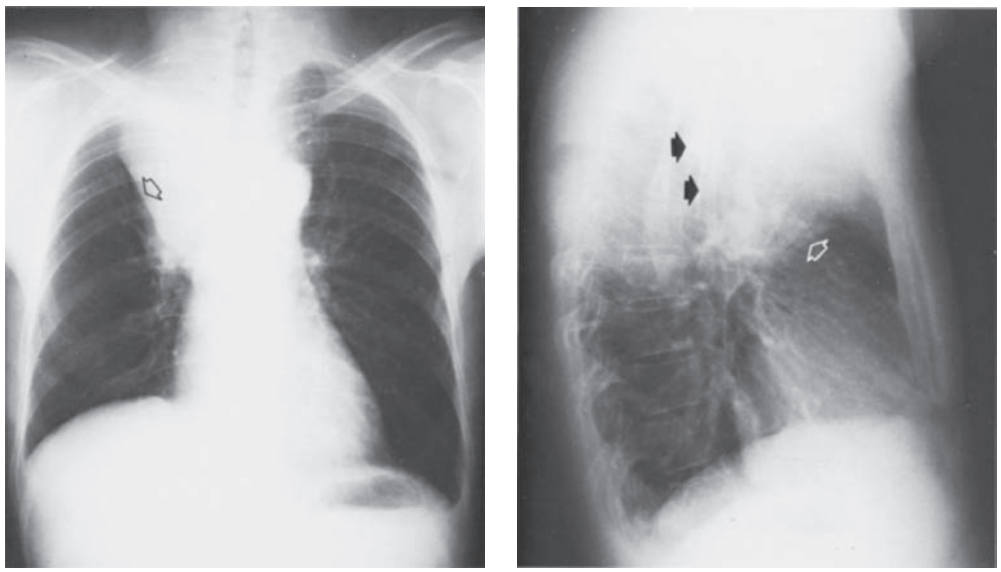
PULMONARY INFECTIONS

Pulmonary infections comprise a very broad group of diseases caused by a wide variety of viruses, bacteria, and fungi. The imaging findings are helpful to establish a diagnosis of pneumonia, but they are virtually never specific as to etiology. Therefore, most patients with suspected pulmonary infections are treated empirically, based upon epidemiologic considerations. Subgroups of vulnerable patients (particularly very ill or immunocompromised patients) may require etiologic confirmation, which can be obtained by sampling the abnormalities via percutaneous or bronchoscopic techniques and requesting microbiologic testing of the material.

The imaging approach to a suspected pulmonary infection involves identifying the imaging patterns that are more likely associated with an infectious etiology, as well as recognizing the more likely associations with a specific pattern. The most typical pattern of pneumonia is focal or multifocal consolidation, denoted by dense, conspicuous alveolar opacities that obscure vascular contours on CT and which may or may not be associated with air bronchograms. Other patterns include focal or multifocal ground-glass opacities (which can be difficult to recognize on chest radiographs and require CT for adequate evaluation); peribronchovascular patchy opacities (bronchopneumonia pattern); centrilobular nodules with tree-in-bud configuration (bronchiolitis pattern); multiple nodules or masses (cavitary or not); solitary cavitary nodule or mass; and nodules or masses associated with calcifications or ground-glass halo. None of these patterns is specific for infection; they are even less specific for a particular infectious etiology. Nonetheless, some imaging patterns allow a narrower differential diagnosis in the proper clinical setting and are worth recognizing.[42–49]

Notable radiographic patterns include: (1) focal or multifocal consolidation, which favors typical bacterial infection (e.g., *Streptococcus pneumoniae*). A bronchopneumonia pattern can be seen in a variety of bacterial and viral infections. (2) Focal or multifocal ground-glass opacities favor atypical infections, including *Pneumocystis jiroveci* and hematogenously disseminated bacterial and viral infections (e.g., CMV pneumonitis).[50,51] (3) A bronchiolitis pattern may be seen in community-acquired viral infections, including influenza, parainfluenza, and adenovirus. If associated with air trapping, respiratory syncytial virus (RSV) should be considered. (4) Multiple cavitary nodules or masses suggest septic emboli or virulent infections, such as those due to *Staphylococcus aureus*. (5) A solitary cavitary mass suggests a pulmonary abscess; anaerobic infections related to aspiration are primary considerations, although if in the upper lobes, reactivation tuberculosis must be excluded.[52] (6) Calcified nodules or masses suggest granulomatous infectious, typically chronic, and favor mycobacterial (tuberculous and nontuberculous) or fungal etiologies.[53,54] (7) Nodules or masses with ground-glass halo are suggestive of opportunistic fungal infection, particularly invasive aspergillosis, in the setting of immunocompromised hosts who are neutropenic.

With regard to localized alveolar disease, the very important distinction between atelectasis and consolidation needs to be clarified. Patchy opacification of airspaces without a decrease in the volume of the affected area suggests consolidation, while opacification of airspaces associated with a decrease in the volume of the affected area suggests atelectasis. The differential diagnosis depends largely on the extent to which lung volume is decreased. However, assessment of the magnitude of volume loss is not always useful. For example, while pneumonia usually is associated with minimal or no volume loss, occasionally, volume loss is considerable. On the other hand, atelectasis usually has moderate or severe loss of volume, but in some instances, there may be little volume loss (Figs. 30-33–30-37).



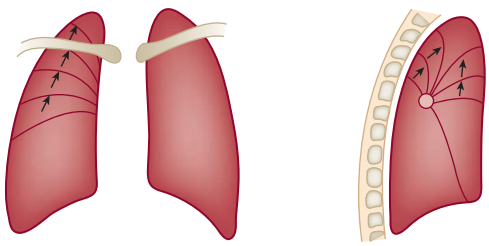
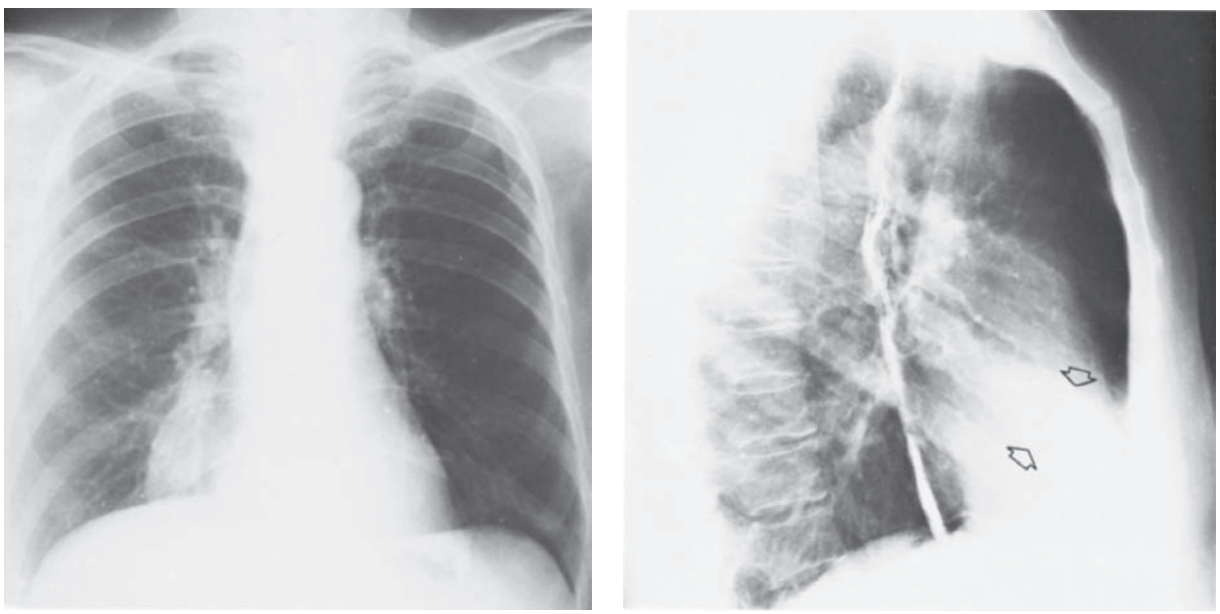


Figure 30-33 Right upper lobe atelectasis secondary to bronchogenic carcinoma. **A.** PA view. The minor fissure is elevated *(arrow)*. **B.** Lateral view. The minor fissure is displaced upward *(open arrow)*, and the major fissure is displaced anteriorly *(closed arrows)*. **C.** Schematic representation of atelectasis of the right upper lobe.



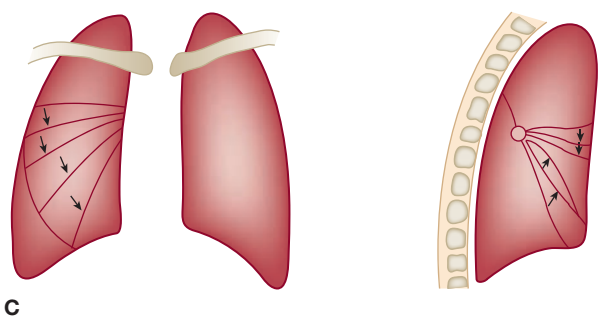
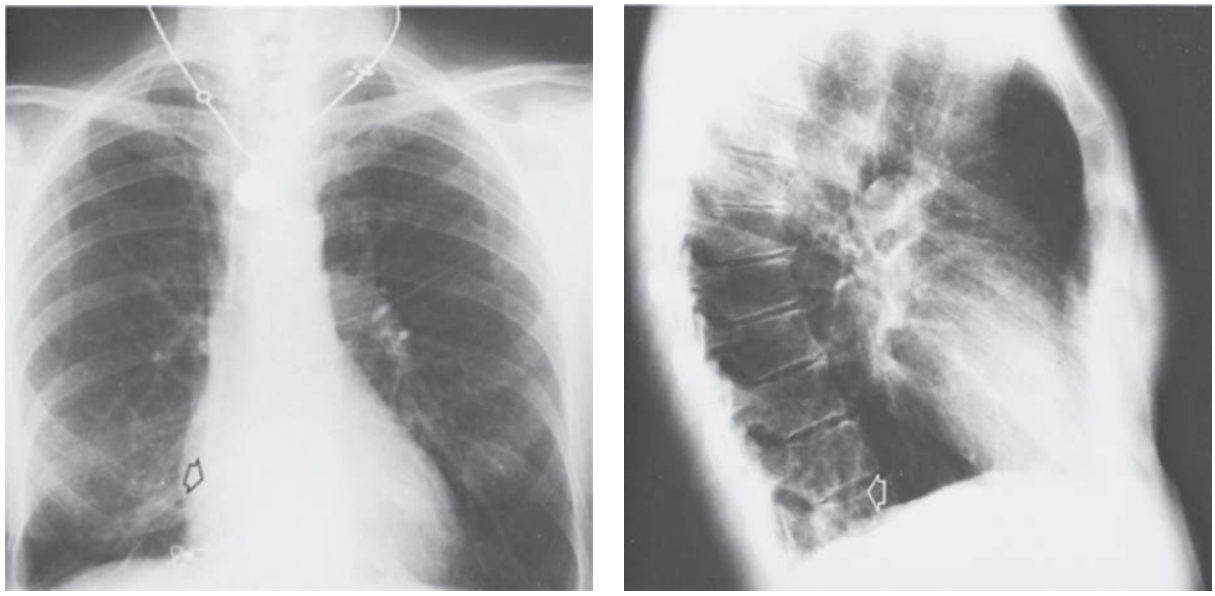
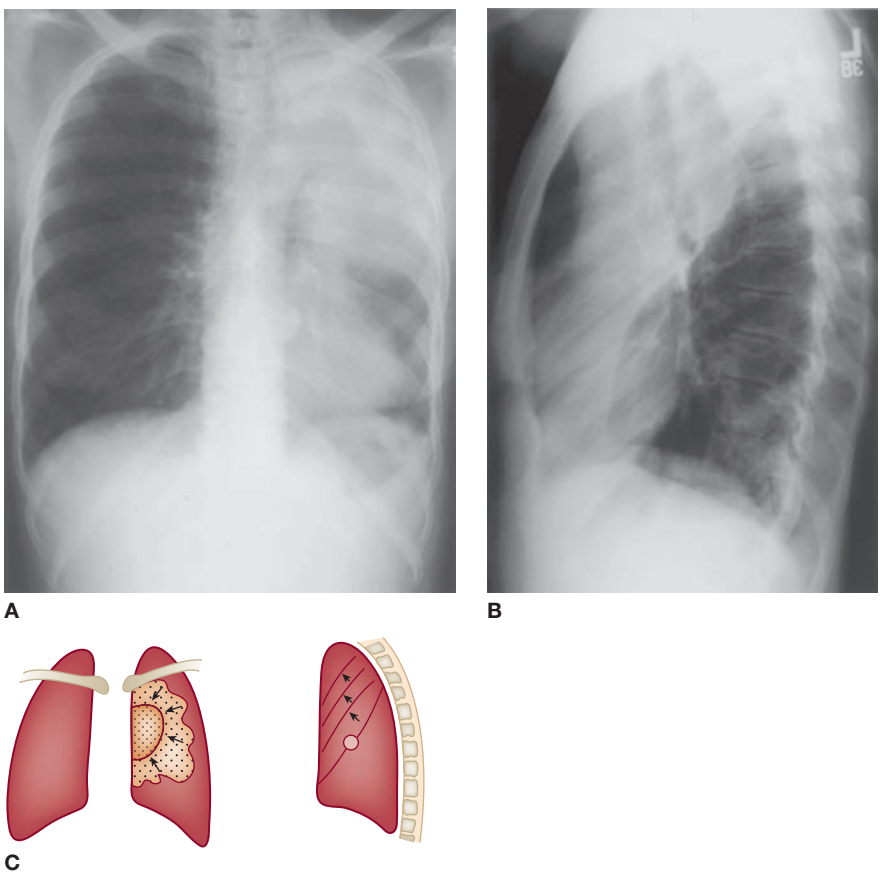


Figure 30-34 Right middle lobe atelectasis secondary to right middle lobe syndrome. **A.** PA view. The middle lobe is collapsed against the right side of the heart. **B.** Lateral view. The major and minor fissures are drawn together *(arrows)*, creating an opacity that overlies the cardiac shadow. **C.** Schematic representation of right middle lobe atelectasis.



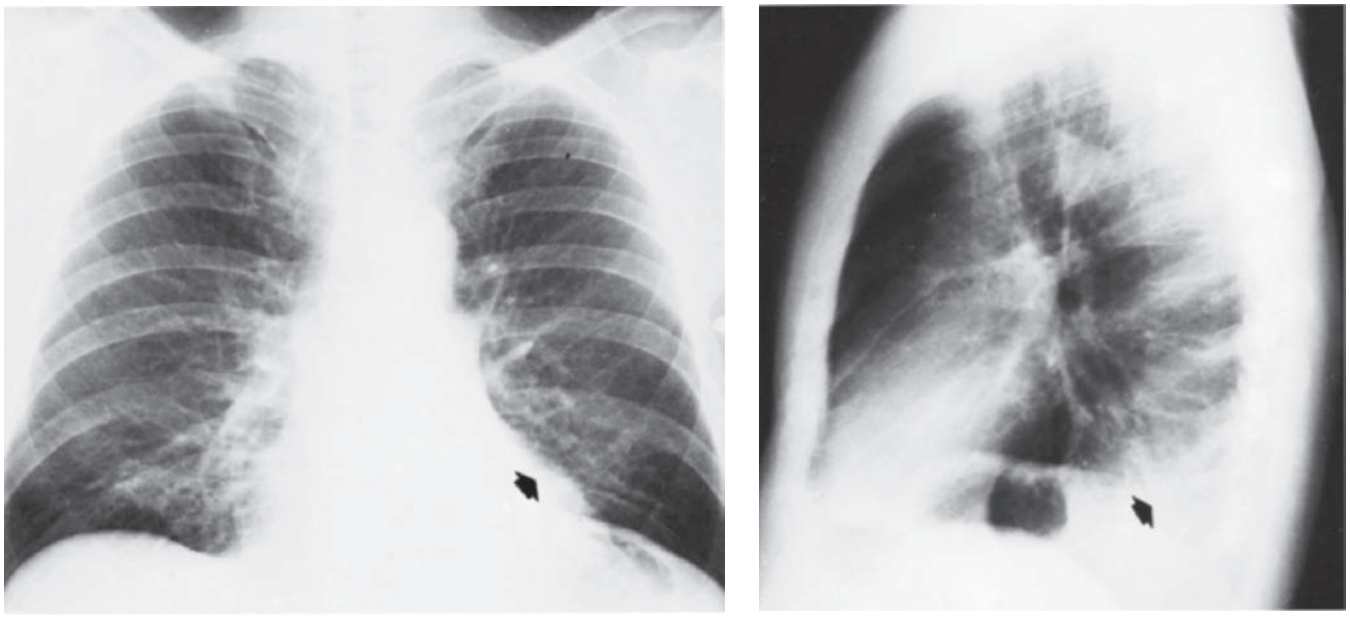
A B C

Figure 30-35 Atelectasis (severe) of the right lower lobe due to chronic inflammatory disease. **A.** PA view. Secondary signs of atelectasis are present in the right lung: small hemithorax, stretching of the pulmonary vessels, hyperlucent lung, and small hilus. In this instance, these secondary signs are important in suspecting atelectasis. In addition, there is downward displacement of the right hilus, and the collapsed lower lobe can be seen (poorly) through the right heart border *(arrow)*. **B.** Lateral view. The entire right lower lobe appears only as a diffuse opacity overlying the spine *(arrow)*. The posterior portion of the right hemidiaphragm cannot be identified (silhouette sign). **C.** Schematic representation of collapse of right lower lobe.



A B C

Figure 30-36 Left upper lobe atelectasis secondary to bronchogenic. **A.** PA view. The left superior mediastinum and left side of the heart are indistinct, due to collapse of the left upper lobe medially. **B.** Lateral view. The collapsed lung is seen as an opacity anterior to the major fissure, which is displaced anteriorly. **C.** Schematic representation of collapse of left upper lobe.



A B C

Figure 30-37 Left lower lobe atelectasis (postoperative). **A.** PA view. The collapsed left lower lobe is seen as a straight line *(arrow)* behind the left heart border. No vasculature can be seen through the heart shadow, and the medial border of the left hemidiaphragm is obscured by the collapsed left lower lobe *(arrow)*. **B.** Lateral view. Opacity over the spine and absence of left posterior diaphragm. This is difficult to differentiate from a pleural effusion. **C.** Schematic representation of collapsed left lower lobe.

Consolidations are statistically likely to represent pneumonias, especially in the acute setting, whereas atelectasis indicates airway obstruction (obstructive atelectasis), adjacent mass effect (compressive atelectasis), or, more rarely, surfactant deficiency or scarring (adhesive atelectasis). For practical purposes, focal airspace opacities, particularly if lobar, are considered consolidations if the degree of volume loss is negligible or mild, and atelectasis if the degree of volume loss is substantial. The various patterns of lobar atelectasis are important to recognize, since this radiographic finding is a very common manifestation of carcinoma of the lung or, occasionally, some other endobronchial neoplasm.

Atelectasis is also common in the postoperative patient (the so-called, "dependent atelectasis"), presumably because of hypoventilation of dependent parts of the lungs and inadequate clearing of respiratory secretions. In this instance, loss of volume may be mild or absent. Atelectasis may also occur as a consequence of inflammatory disease of the airways or aspiration of a foreign body. Atelectasis also invariably accompanies pleural effusions and pneumothorax. With pleural effusions, atelectasis is greatest in the vicinity of the pleural effusion. Rounded atelectasis is a subtype characterized by ovoid peripheral opacity, associated with underlying chronic pleural disease (manifested by loculated effusion or pleural thickening). There is architectural distortion and convergence of the bronchovascular structures supplying the area of rounded atelectasis ("comet tail sign"). It is important to recognize the typical features of rounded atelectasis, as it can be confused with pulmonary neoplasms.

In nonimmunocompromised hosts, most acute consolidations reflect bacterial pneumonias and should improve to complete resolution with treatment, generally within 4 to 6 weeks; radiographic clearance lags a few weeks behind clinical improvement. Therefore, in adult patients it is important to obtain chest radiographs at the end of this time frame to demonstrate complete resolution of the consolidation. Any consolidation that persists (>1 month) in spite of optimal empirical treatment should be considered potentially neoplastic; the differential diagnosis includes pulmonary mucinous adenocarcinoma (formerly classified as BAC), pulmonary lymphoma (of the MALT type, denoting low-grade extranodal lymphomas), or hemorrhagic metastasis (such as from breast, renal cell carcinoma, or melanoma primaries). In addition, atypical infectious processes (such as fungal or mycobacterial infection) may present as persistent consolidations, as well as several noninfectious or inflammatory processes, such as cryptogenic organizing pneumonia (COP), eosinophilic pneumonia, and granulomatous vasculitides (e.g., granulomatosis with polyangiitis). Most chronic consolidations ultimately require chest CT and tissue sampling (via transthoracic or bronchoscopic approaches) for final diagnosis (Figs. 30-38–30-43).

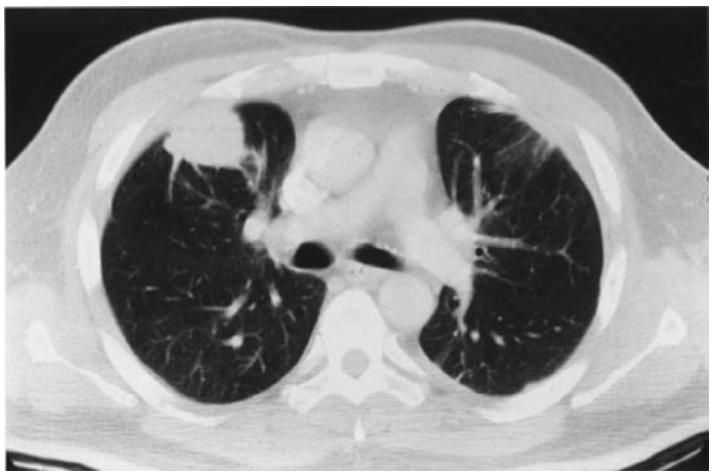
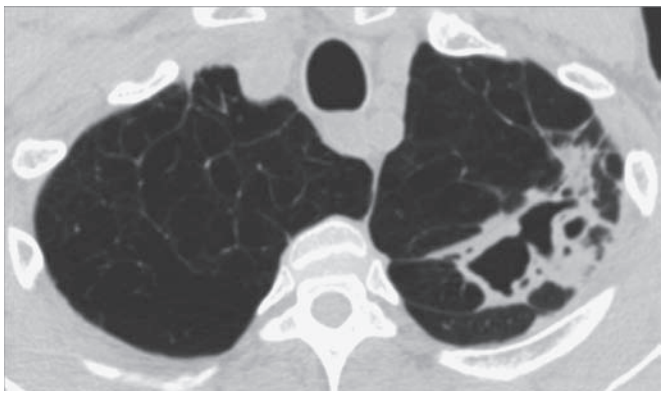


Figure 30-38 Axial CT image showing rounded atelectasis. A mass with a "tail" can be seen in the anterior segment of the right upper lobe. Pleural thickening is seen on the left side, with transpulmonary bands extending into the left upper lobe. The mass on the right represents rounded atelectasis, a finding usually associated with asbestos exposure or chronic pleural disease. The changes on the left probably represent an early stage in the development of rounded atelectasis.



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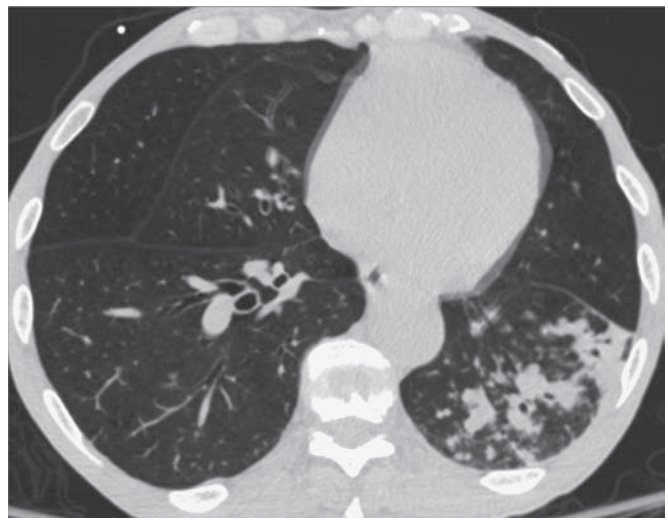

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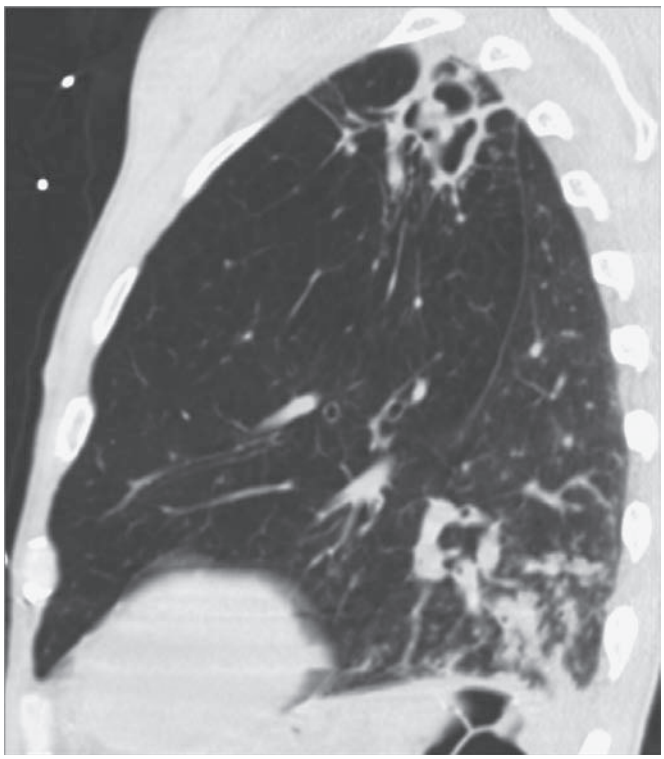
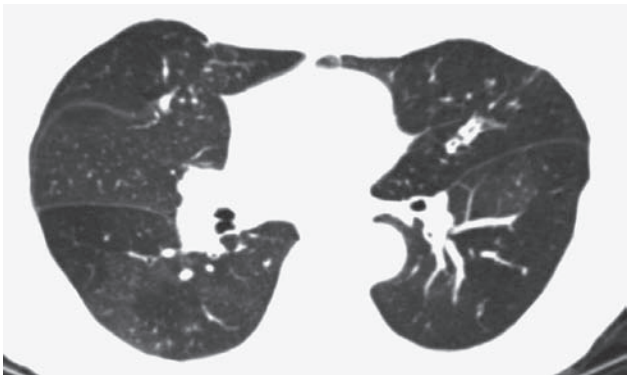


C

Figure 30-39 **A.** Axial CT image shows an irregular cavity in the left upper lobe, with architectural distortion of the surrounding parenchyma. **B.** Axial CT at a lower level demonstrates bronchiectasis, mucoid impaction and peribronchial consolidations in the left lower lobe, as well as a few centrilobular nodules. **C.** Sagittal CT at the median left lung demonstrates both disease processes. This constellation of findings is very characteristic of reactivation tuberculosis and is highly suggestive of the diagnosis, which was confirmed in this case. The left lower lobe opacities reflect endobronchial spread of the mycobacteria from the left upper lobe cavity.



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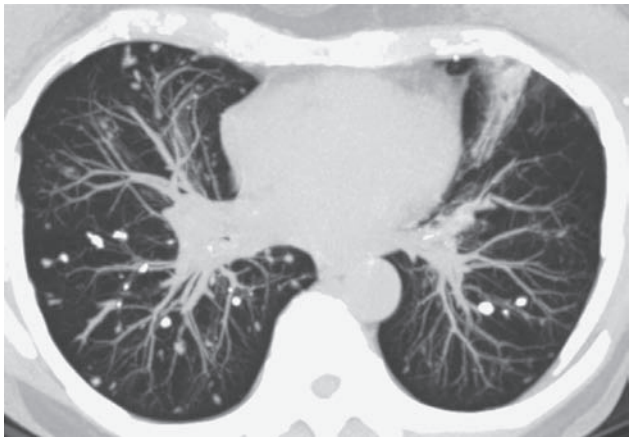

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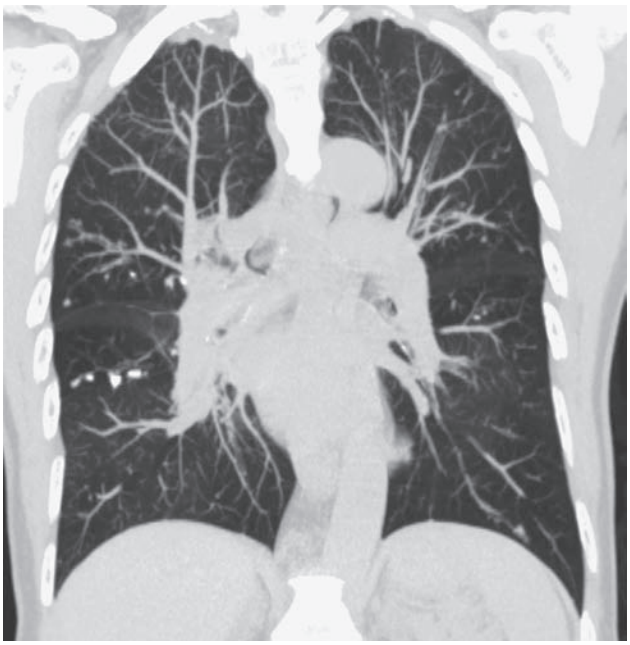

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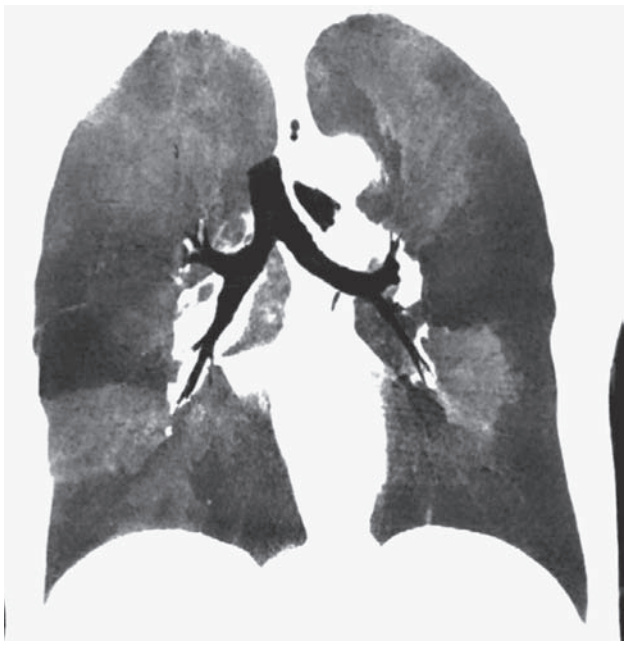

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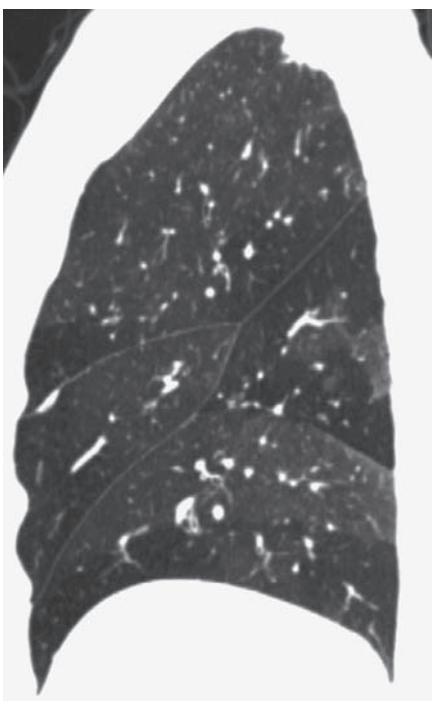
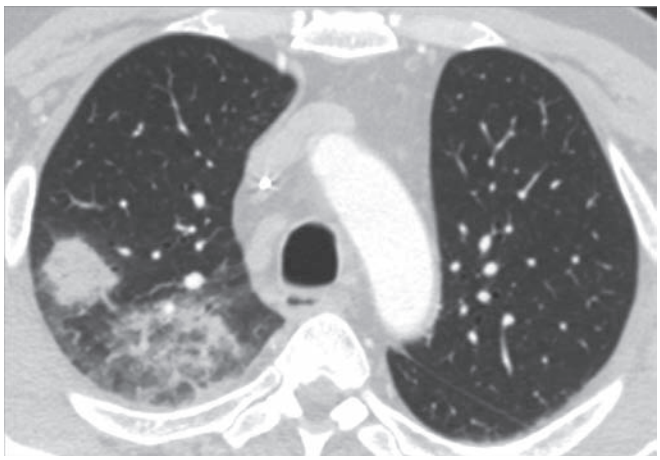


E

Figure 30-40 **A.** Axial CT image showing left upper lobe bronchiectasis with wall thickening, as well as a striking mosaic attenuation pattern suggestive of air trapping. **B.** Axial CT MIP (maximum intensity projection) reconstruction and (**C**) coronal CT MIP reconstruction demonstrate multiple calcified and noncalcified small nodules. **D.** Coronal CT MinIP (minimum intensity projection) reconstruction clearly shows the mosaic attenuation pattern, which is also notable in (**E**), a sagittal image. This constellation of findings was due to nontuberculous mycobacterial infection, specifically MAI *(Mycobacterium avium-intracellulare)*.



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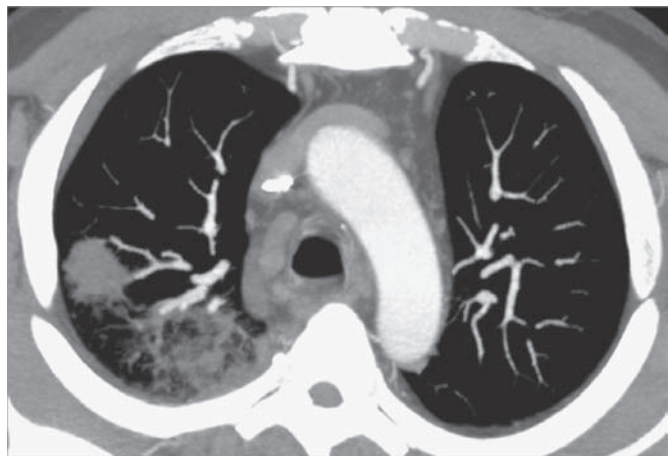

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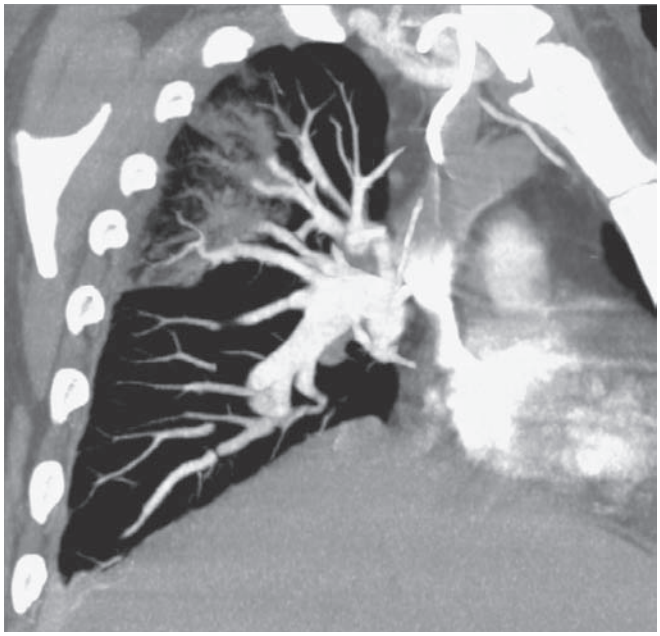
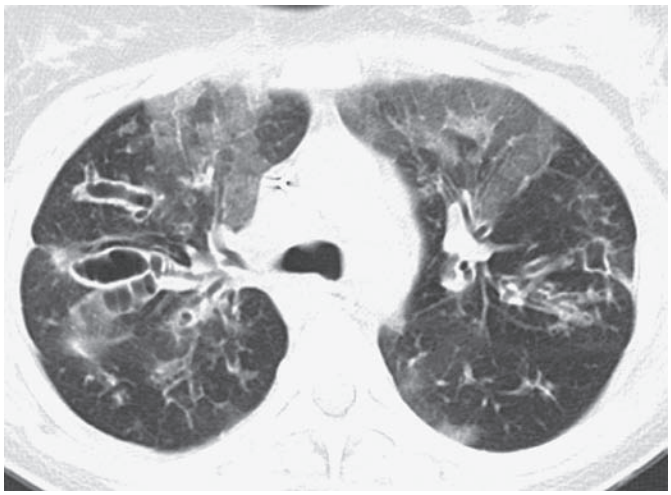


C

Figure 30-41 Immunocompromised patient (post-bone marrow transplant) with neutropenia and fever. **A.** Axial CT shows consolidation and ground-glass opacity in the RUL. (**B**) Axial MIP reconstruction and (**C**) curved MIP reconstruction, contrast-enhanced CT, demonstrate that several right upper lobe arteries are "amputated" at the areas of consolidation in the RUL, a finding that is indicative of angioinvasive aspergillosis, given the clinical setting.



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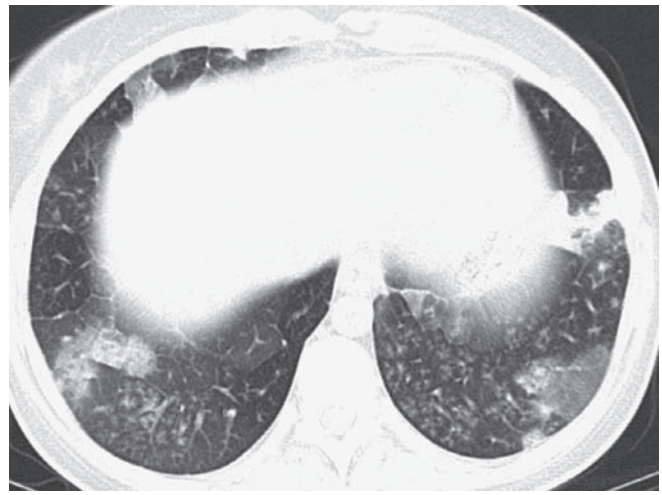
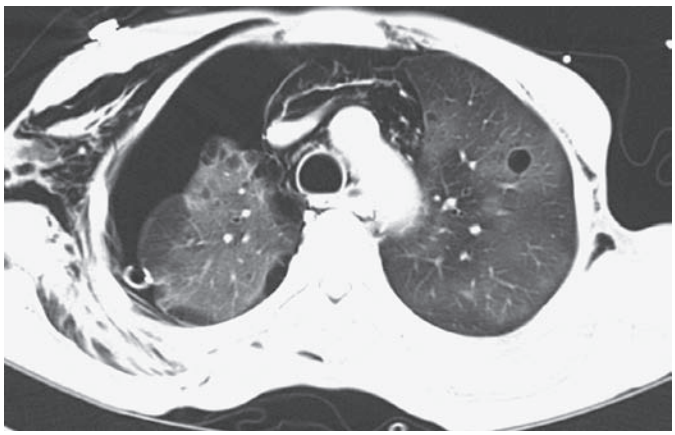


B

Figure 30-42 **A.** Axial CT through the level of the carina demonstrates extensive bronchiectasis. **B.** Axial CT at a lower level demonstrates multiple areas of consolidation and numerous centrilobular nodules. This patient had a diagnosis of cystic fibrosis, complicated by superinfection by *Pseudomonas aeruginosa*.



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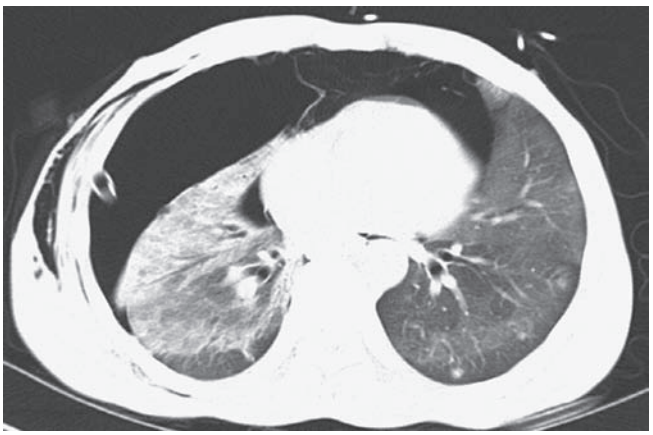


B

Figure 30-43 **A.** Axial CT through the upper lung fields demonstrates a large right-side pneumothorax with a chest tube partially visualized. The lung parenchyma demonstrates diffuse, but nonhomogeneous, ground-glass opacities, as well as scattered cysts. **B.** Axial CT at a lower level demonstrates diffuse ground-glass opacities, small nodules, and patchy areas of consolidation. This patient had AIDS complicated by *Pneumocystis jiroveci* pneumonia. Spontaneous pneumothorax is a known complication of this disease.

PULMONARY EDEMA: CARDIOGENIC AND NONCARDIOGENIC

Imaging offers a comprehensive display of the anatomy of the cardiopulmonary system and its function. Chest radiographs can demonstrate the heart size and configuration, the width of the vascular pedicle, as well as the caliber and distribution of the pulmonary arteries and veins. Pulmonary arteries and veins can generally be distinguished on chest radiographs by their anatomical location, with the pulmonary veins more horizontal, more inferior, and more lateral to the pulmonary arteries in relationship to the hila. The distinction is, nonetheless, seldom useful radiographically and, therefore, the generic terms *pulmonary vessels* and *pulmonary vasculature* are used. CT and MRI more readily depict the pulmonary arteries and veins. The pulmonary arteries arise from the main pulmonary artery trunk, while the pulmonary veins enter the left atrium and are readily distinguished on cross-sectional imaging even without intravenous contrast. Moreover, CT and MRI can accurately evaluate cardiac structure and function, particularly cardiac MRI, providing quantitative metrics to assess ventricular and valvular function.

Congestive heart failure is a common clinical condition characterized by systolic and/or diastolic dysfunction of the left ventricle, leading to increasing diastolic filling pressure, increasing left atrial pressure, and fluid retention. Ultimately, left ventricular failure leads to right ventricular failure. The heart is almost invariably enlarged, and the central pulmonary vasculature appears prominent and indistinct. These changes are easier to recognize on PA and lateral views than on portable chest radiographs.

A rational progression of chest radiographic findings in congestive heart failure can be fully appreciated on PA, erect radiographs and is strongly correlated with increases in pulmonary capillary wedge pressure (PCWP, reflecting left atrial pressure), indicating progressive pulmonary venous congestion.

The first stage is correlated with a PCWP of 13 to 18 mm Hg and is characterized by increased width of the vascular pedicle and vascular redistribution in the erect patient; the caliber of the upper lung vessels is increased relative to the lower lung vessels (cephalization), and cardiomegaly is present.

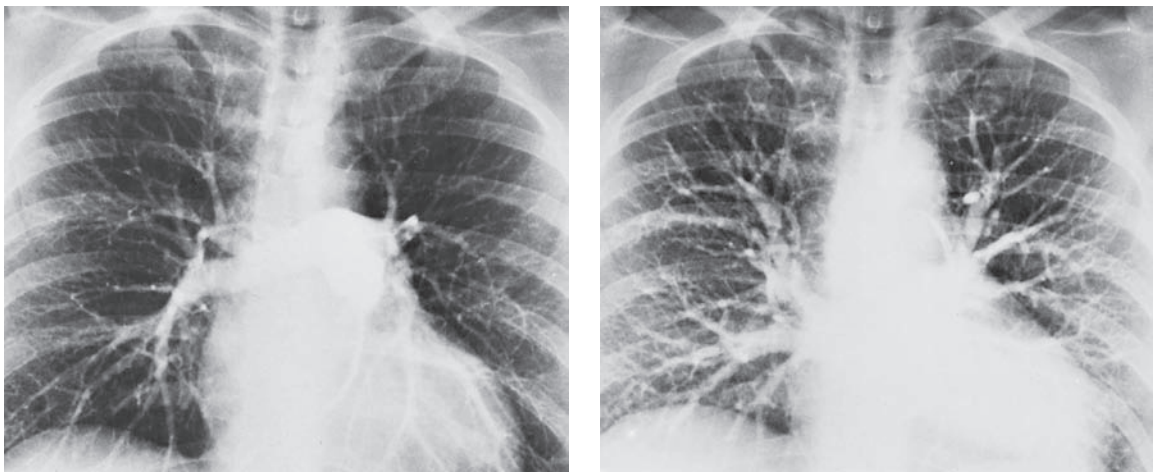
The second stage is correlated with PCWP of 18 to 25 mm Hg and is characterized additionally by the presence of pulmonary interstitial edema—which is manifested on chest radiography as Kerley lines, thickened fissures, and peribronchial cuffing with indistinct contour of the central vessels. Kerley B lines, as previously described, represent small (1–2 cm), thin, linear opacities that are seen peripherally perpendicular to a pleural surface, reflecting edema involving interlobular septae.

Finally, the third stage is correlated with PCWP >25 mm Hg and is characterized by the additional presence of alveolar edema, manifested as fluffy (cotton-wool appearance), symmetric airspace consolidation with mid and lower lung field predominance. Pleural effusions are often present in stages II or III and may be present earlier if there is a substantial component of right ventricular dysfunction or central volume overload, such as in patients with pulmonary hypertension or superimposed chronic renal or liver disease.

Pleural effusions often accompany biventricular heart failure. However, while the pulmonary congestion usually clears rapidly in response to therapy, the pleural effusions often remain after the pulmonary vessels have returned to normal size and require a longer time to resolve. Pleural effusions in congestive heart failure may be unilateral or bilateral, although they are most often bilateral. The effusions are nearly always transudates. Therefore, the presence of a unilateral effusion, particularly an isolated left effusion, should prompt consideration of a diagnostic thoracentesis. If the effusion is an exudate, an alternate cause, such as malignancy or infection, should be considered (Figs. 30-44 and 30-45).

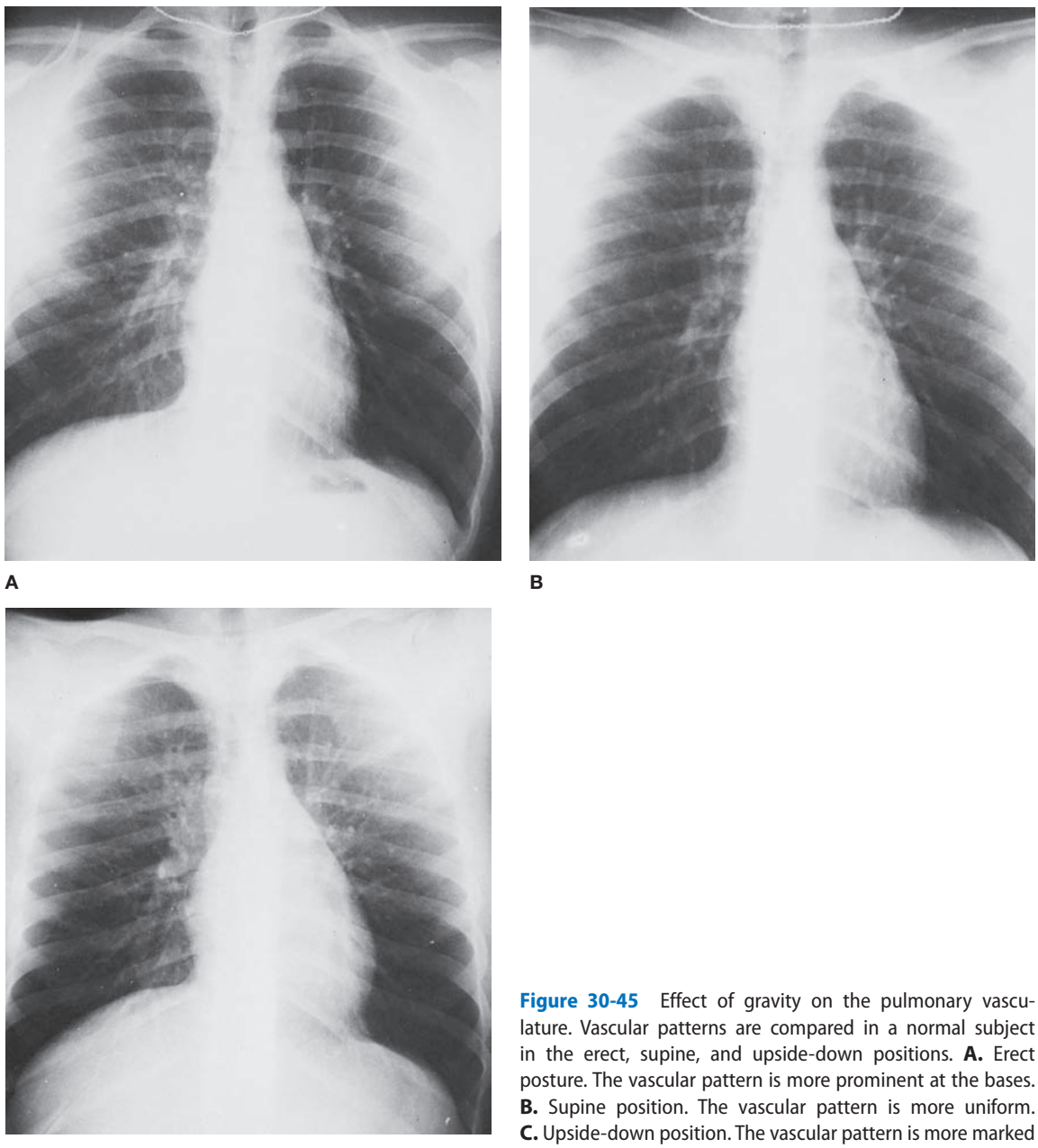
CT may demonstrate the same findings and the same pattern of progression according to the degree of left heart dysfunction and PCWP increase. Nonetheless, it allows better assessment of cardiac chamber size, vascular caliber, and presence of pulmonary interstitial or alveolar edema. Nonetheless, because the combination of clinical, laboratory, and radiographic findings generally suffices for the diagnosis of congestive heart failure, CT is not routinely obtained in patients in this setting, although it is not uncommon to establish the diagnosis on CT studies performed for other reasons.

As previously discussed, pulmonary interstitial edema presents on CT as axial (peribronchovascular) and septal interstitial thickening (interlobular and intralobular); the findings are usually symmetric, smooth, and lower lung field predominant. The differential diagnosis, especially if the pattern of interstitial thickening is nodular, upper lung predominant, or asymmetric, includes sarcoidosis and lymphangitic spread of neoplasm. Pulmonary



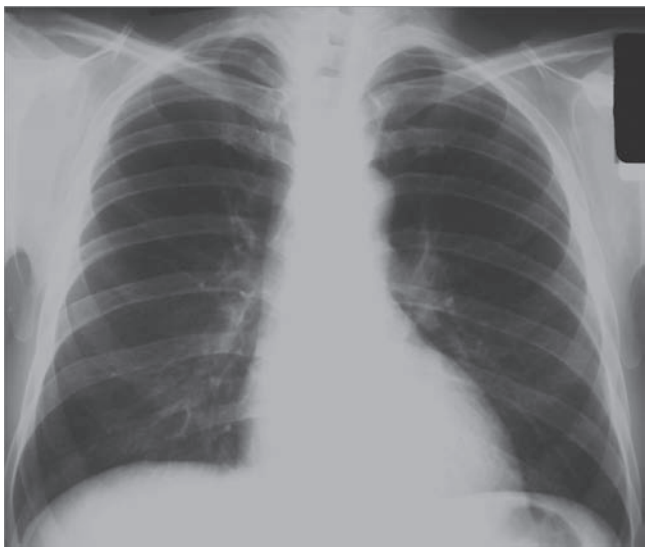
A B

Figure 30-44 Pulmonary arteries and veins: **A.** The early phase of the pulmonary angiogram depicts the normal course and caliber of the pulmonary arteries. **B.** The late phase shows the normal course and caliber of the pulmonary veins. The veins have a more horizontal course than the arteries and enter the hila below the arteries.

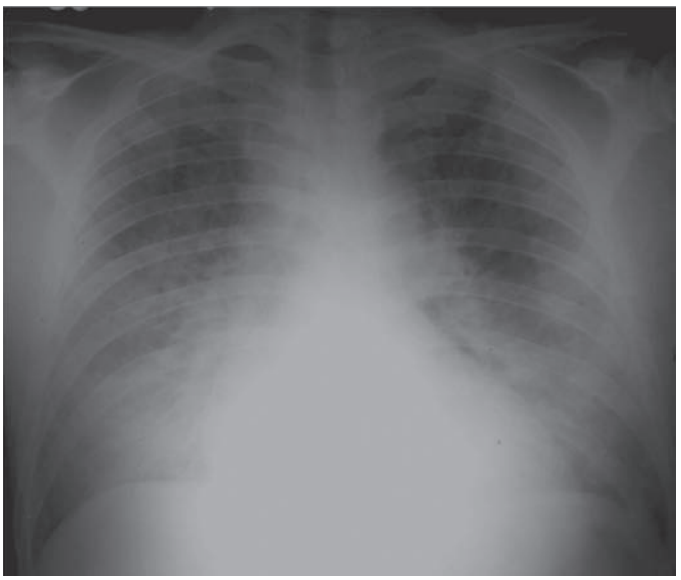


A B C

Figure 30-45 Effect of gravity on the pulmonary vasculature. Vascular patterns are compared in a normal subject in the erect, supine, and upside-down positions. **A.** Erect posture. The vascular pattern is more prominent at the bases. **B.** Supine position. The vascular pattern is more uniform. **C.** Upside-down position. The vascular pattern is more marked at the apices.



A



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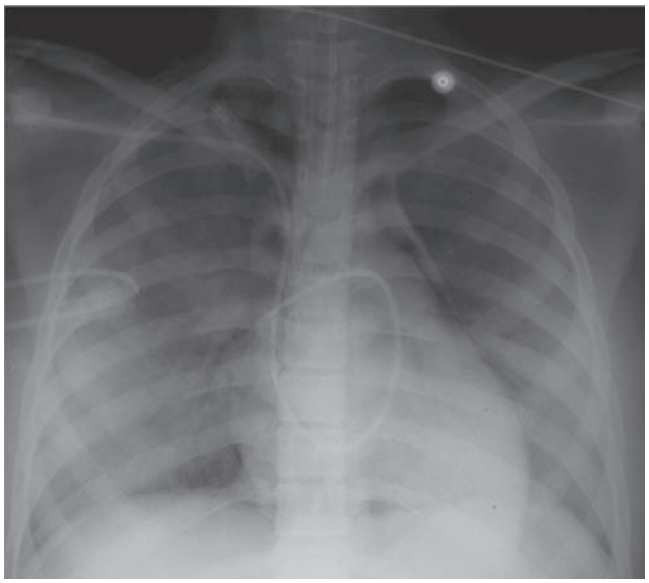

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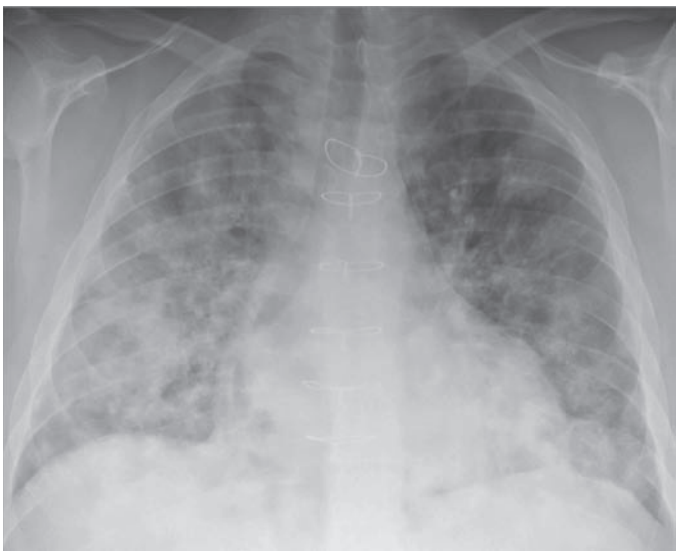
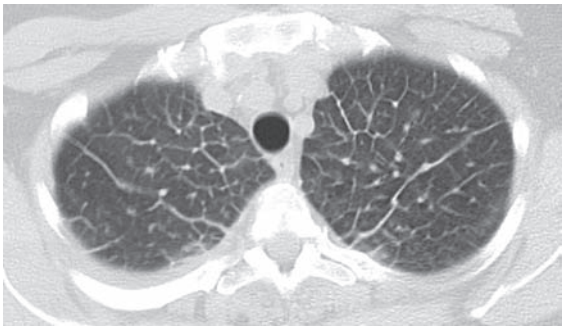


D

Figure 30-46 Patterns of diffuse alveolar disease. **A.** Normal PA chest radiograph, for comparison. **B.** Cardiogenic edema, with severe, symmetric, basilar-predominant airspace opacities, associated with cardiomegaly and likely small effusions. **C.** Noncardiogenic edema, with severe, symmetric, more diffuse airspace opacities; however, the cardiac size is normal and no pleural effusions are present. This patient has ARDS. **D.** Diffuse alveolar hemorrhage (DAH)—patchy, but fairly diffuse, airspace opacities are noted, with borderline heart size. This patient had systemic lupus erythematosus. Note that this pattern can be difficult to distinguish from diffuse pneumonia or pulmonary edema – clinical correlation is often needed.

alveolar edema is demonstrated as airspace opacities (ground-glass or consolidation), with fluid-filled acinar structures; the opacities are symmetric, ill-defined, confluent, and central and lower lung field predominant. Findings of pulmonary alveolar edema often coexist with pulmonary interstitial edema, but not vice versa. The exception is flash pulmonary edema, in which alveolar edema develops so rapidly that there is not enough time for interstitial edema to manifest. Flash pulmonary edema may occur with sudden changes in intravascular volume, such as following resuscitation in trauma patients or with sudden changes in cardiac function, as occurring with cardiac arrhythmias or myocardial infarction.

Pulmonary edema is the prototype of diffuse lung disease. Etiologically, it can be broadly separated into cardiogenic and noncardiogenic causes. Cardiogenic edema is caused by congestive heart failure.[55,56] Noncardiogenic edema is a manifestation of increased permeability of the pulmonary capillaries in which cardiac function is relatively preserved. Major differential diagnoses include acute hypersensitivity reactions, inhaled toxins, near-drowning, sepsis, and several processes that lead to the pathologic diagnosis of diffuse alveolar damage (DAD), most notably acute respiratory distress syndrome (ARDS).[57–61] From an imaging perspective, cardiogenic edema is more likely associated with cardiomegaly and functional impairment of the ventricles and tends to clear rapidly following administration of diuretics and drugs that optimize cardiovascular status. Noncardiogenic edema tends to resolve slowly and often requires clinical and laboratory correlation for etiologic characterization (Figs. 30-46–30-48).



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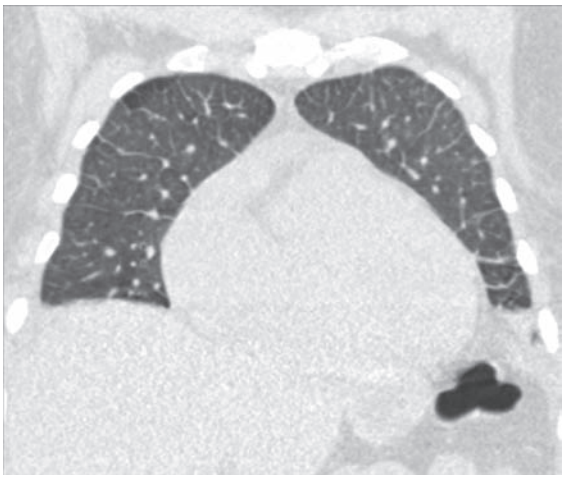

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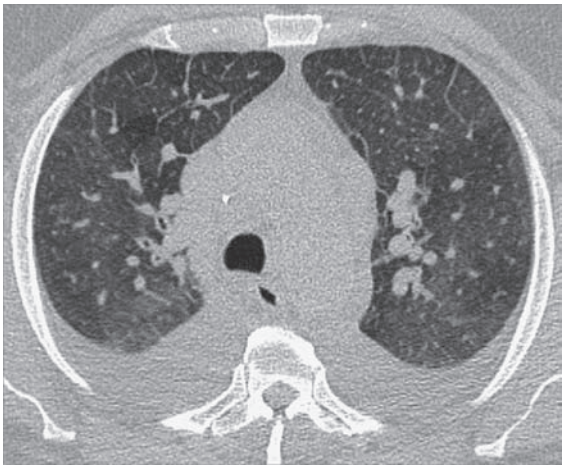
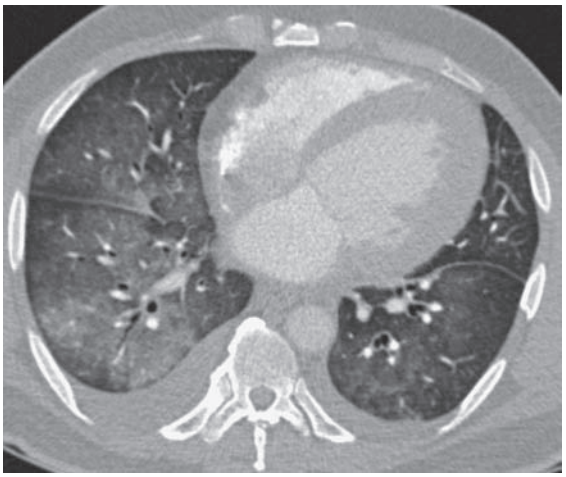


B

Figure 30-47 CT findings of pulmonary interstitial edema. **A.** Axial CT at the lung apices demonstrates classic smooth interlobular septal thickening, the hallmark of interstitial edema. **B.** Axial CT at the level of the carina demonstrates additional axial (peribronchial) interstitial thickening and vascular engorgement, indicating interstitial edema. Also note bilateral pleural effusions, in keeping with cardiogenic failure and volume overload. **C.** Coronal CT clearly demonstrates smooth interlobular septal thickening, which is diffuse, due to interstitial edema.



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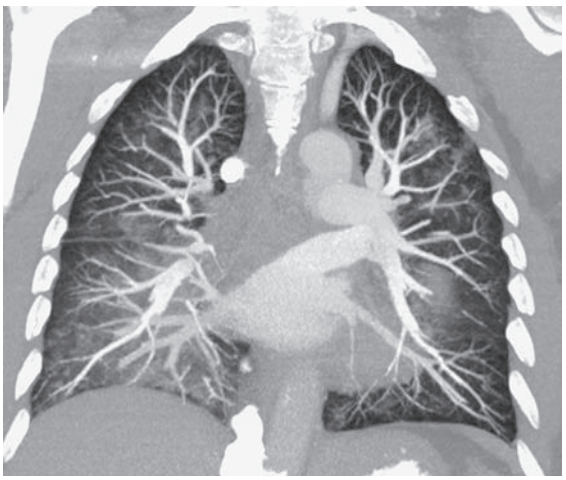

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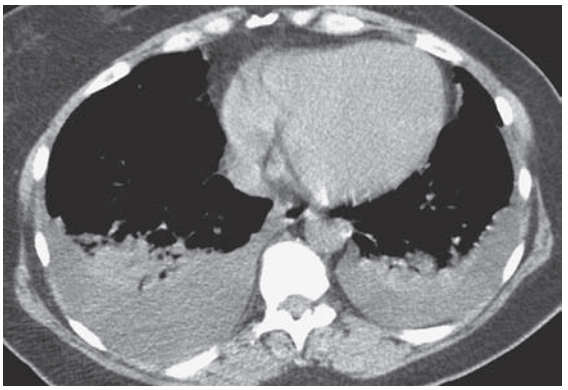
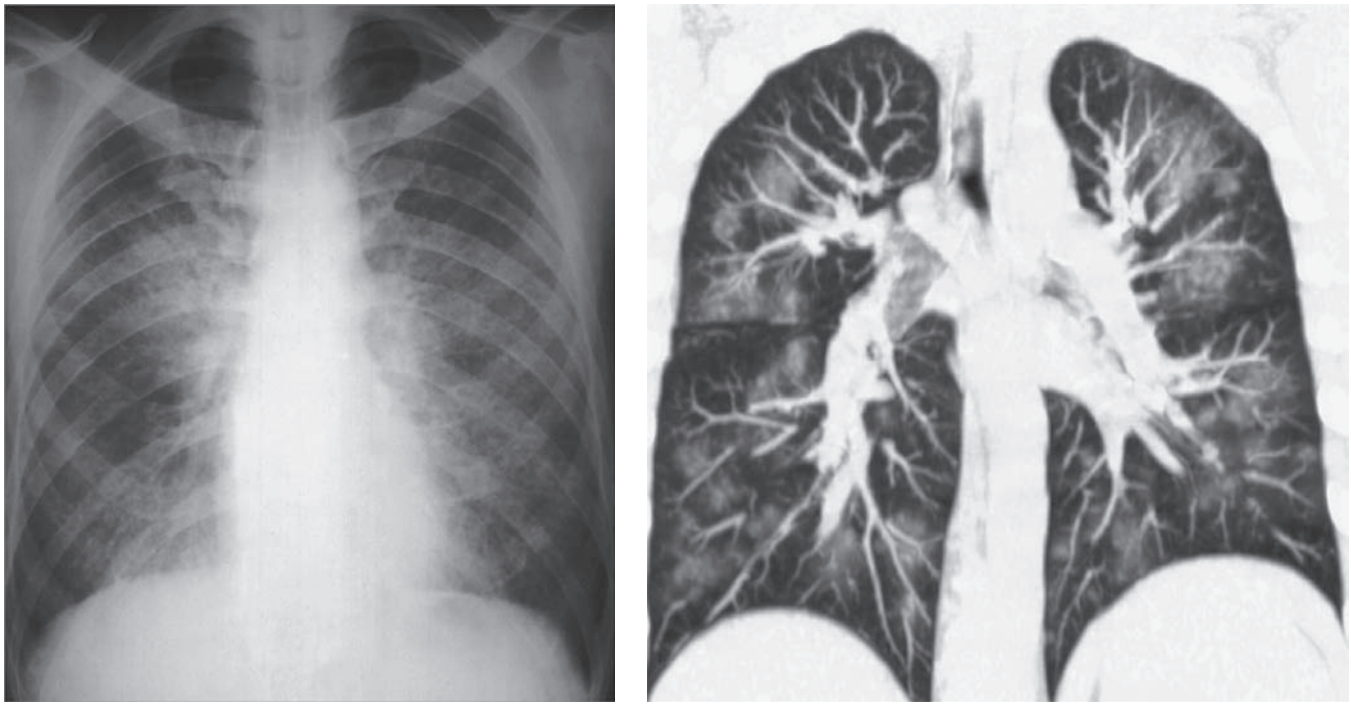


B

Figure 30-48 CT findings of pulmonary alveolar edema. **A.** Axial CT at the lung bases demonstrates diffuse ground-glass opacities, reflecting alveolar edema. Note left ventricular dilatation. **B.** Axial CT at the same level on mediastinal window demonstrates bilateral pleural effusions, in keeping with cardiogenic failure. **C.** Coronal MIP CT reconstruction clearly demonstrates diffuse ground-glass opacities more prominent along the bronchovascular bundles, characteristic of alveolar edema.



A B

Figure 30-49 CT findings of diffuse alveolar hemorrhage (DAH). **A.** PA chest radiograph demonstrates patchy, but predominantly perihilar, alveolar opacities. **B.** Coronal MIP CT reconstruction better demonstrates the patchy, but widespread, ground-glass opacities, more prominent along the bronchovascular bundles. This patient had a diagnosis of DAH due to Goodpasture syndrome. This pattern can be indistinguishable from pulmonary edema or diffuse infection. Clinical correlation is often needed to narrow the differential diagnosis.

In the proper clinical setting, diffuse alveolar opacities represent pulmonary edema until proved otherwise. If standard therapy for congestive heart failure fails to clear the opacities, and if clinical and laboratory findings exclude noncardiogenic pulmonary edema, other diagnostic entities must be considered. The most important is a diffuse pneumonia, which can be caused by several bacterial and viral agents, including, most notably, influenza. Other differential diagnostic considerations for diffuse lung disease include diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, extensive multifocal mucinous adenocarcinoma, acute hypersensitivity pneumonitis, for example, that due to drug toxicity,[62] sarcoidosis, NSIP, and desquamative interstitial pneumonia (DIP). These entities are described elsewhere in Chapters 54–66 (Fig. 30-49).

PULMONARY EMBOLISM AND PULMONARY HYPERTENSION

Two critically important clinical entities involving the pulmonary vasculature can be assessed using CT: PE and pulmonary hypertension. Each is discussed subsequently.

■ PULMONARY EMBOLISM

Contrast-enhanced, multidetector chest CT provides a powerful and readily available technique for the evaluation of PE and has become the current reference standard for the diagnosis of acute and chronic pulmonary thromboembolic disease. Not only does CT enable direct visualization of clots, it also can provide alternative diagnoses to explain symptoms in the many patients who do not prove to have PE. Moreover, CT may facilitate diagnosis of associated right heart strain when present, a finding of prognostic importance. While CT may be limited in detecting small, peripheral, subsegmental clots, particularly if the study is not of optimal quality, it has a very high negative predictive value for PE. CT may also be combined with CT venography of the pelvis and lower extremities in selected cases, when clinically indicated.

The major disadvantage of CT relative to ventilation–perfusion scanning is the breast radiation dose, which is of concern in young women and pregnant patients. The problem is further heightened by the current overutilization of CT PE studies, manifested by a yield of positive cases that is generally under 10%. Technical methods to reduce the CT radiation dose continue to be introduced. However, the best approach to radiation dose reduction is to improve the appropriate utilization of CT. Better clinical pretest assessment of risk factors for PE is required. Such assessment using the Wells, Simplified Geneva, and PERC scores are frequently not used. Other more objective and easily implemented scoring systems have been advocated.

D-dimer measurement is a very useful screening test that carries a high negative predictive value for PE; measurement is particularly useful in the emergency room setting. A negative D-dimer in combination with a low or intermediate clinical suspicion for PE may obviate the need for CT in approximately 50% of outpatients and 20% of inpatients.

Young patients with normal chest radiographs (and without a history of asthma or COPD) can undergo radionuclide perfusion scans as an alternative to CT; the diagnostic yield of perfusion scans in this setting is high and the breast dose significantly lower than with CT. Patients with coexisting symptoms and/or signs of DVT should have Doppler US of their lower extremities as the initial test.[63–65]

The imaging workup of suspected PE in pregnancy presents several unique challenges, as both fetal and maternal breast radiation doses must be considered. Moreover, D-dimer is generally positive in pregnancy and, thus, not of value. In addition, there

Video 30-8 **A.** Full-color, coronal 3D VR (volume rendering) thick slab cine (anterior to posterior) emphasizing cardiovascular and pulmonary parenchymal structures and demonstrating marked ectasia of the central pulmonary arteries, compatible with pulmonary hypertension (in this patient, mean pulmonary artery pressure was 100 mm Hg). Also note asymmetry of arterial caliber, with relative oligemia of the left lower lobe and ectatic right upper lobe arteries, attributed to chronic thromboembolic pulmonary hypertension. **B.** Same patient as in Video 30.8A. Coronal, minimum intensity projection (minIP) thick slab cine (anterior to posterior). This type of reconstruction provides excellent assessment of mosaic attenuation, which, in this case is due to mosaic perfusion secondary to chronic thromboembolic pulmonary hypertension. The brighter areas of the lung parenchyma are relatively hyperperfused, whereas the darker areas are oligemic, and correlate with areas of diminished regional vascular caliber. *Access at www.fishmansonline.com*

are no useful pretest clinical risk assessment scoring systems for pregnancy. Recently published national guidelines recommend the use of ventilation–perfusion scans in pregnant women with normal chest radiographs (and without COPD or recently active asthma) and CT in the setting of chest radiographic abnormalities that do not provide an alternative diagnosis to PE.[66]

Acute and chronic pulmonary thromboembolic disease can be distinguished on CT imaging by the morphology of the pulmonary arterial filling defects. Acute emboli are usually more centrally located within the vessel lumen and may be occlusive. The nonopacified pulmonary arterial branches tend to be dilated in the setting of acute thromboembolic disease. In contrast, chronic clots are more likely eccentric along the vessel wall, nonocclusive, and sometimes calcified (if long-standing). The involved vessels tend to be smaller than normal. Moreover, chronic thromboembolic disease tends to present with associated dilated central pulmonary arteries, indicating pulmonary hypertension, whereas acute emboli generally present with normal caliber central pulmonary arteries, unless there is pre-existing pulmonary hypertension (Video 30-8A). Other findings suggesting chronic thromboembolic disease include a mosaic perfusion pattern and the presence of dilated bronchial or other systemic collateral vessels (Video 30-8B).

Given the immense functional reserve of the normal pulmonary vasculature, it is uncommon for acute PE to cause pulmonary hypertension and right ventricular dysfunction. Nonetheless, in the setting of large embolic burden, as measured by an obstruction index of the pulmonary arterial circulation of 40% or higher on helical chest CT, poor clinical outcomes are associated with right ventricular dysfunction. This situation generally only occurs with massive saddle emboli in the large proximal pulmonary arteries, or with a large number of relatively smaller emboli occluding the more distal segmental or subsegmental arteries. Chronic pulmonary thromboembolism, on the other hand, is far more prone to be associated with pulmonary hypertension, even in the absence of a substantial thromboembolic burden, due to molecular adaptation mechanisms that lead to remodeling of the pulmonary vasculature, including medial hypertrophy and in situ small vessel thrombosis.[67–69]

More recently, dual-energy CT has been proposed as a method for the combined assessment of acute and chronic emboli, pulmonary vascular anatomy, pulmonary parenchymal abnormalities, and pulmonary perfusion. Pulmonary perfusion, in particular, is obtained via dual-energy CT's ability to derive iodine maps. Identification of pulmonary perfusion defects can increase the sensitivity and specificity of CT for clot detection. Dual-energy CT has also been used for quantitative perfusion in chronic thromboembolic PE, given the strong correlation of dual-energy CT derived perfusion parameters with subjective assessment of a mosaic attenuation pattern. Consequently, contrast-enhanced chest CT is the most useful

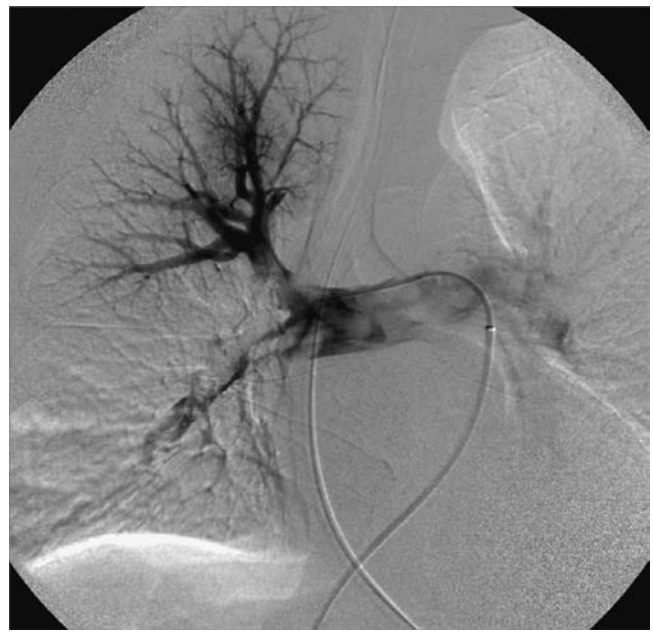


Figure 30-50 Pulmonary angiogram, arterial phase. Note normal caliber of the pulmonary arteries, with multiple filling defects in the right main, right interlobar, and proximal right upper lobar arteries, diagnostic of acute pulmonary embolism.

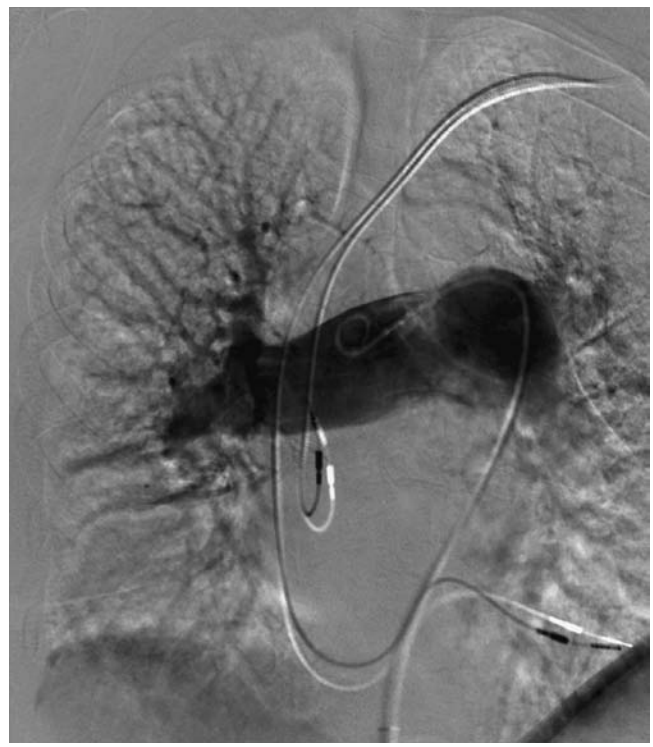
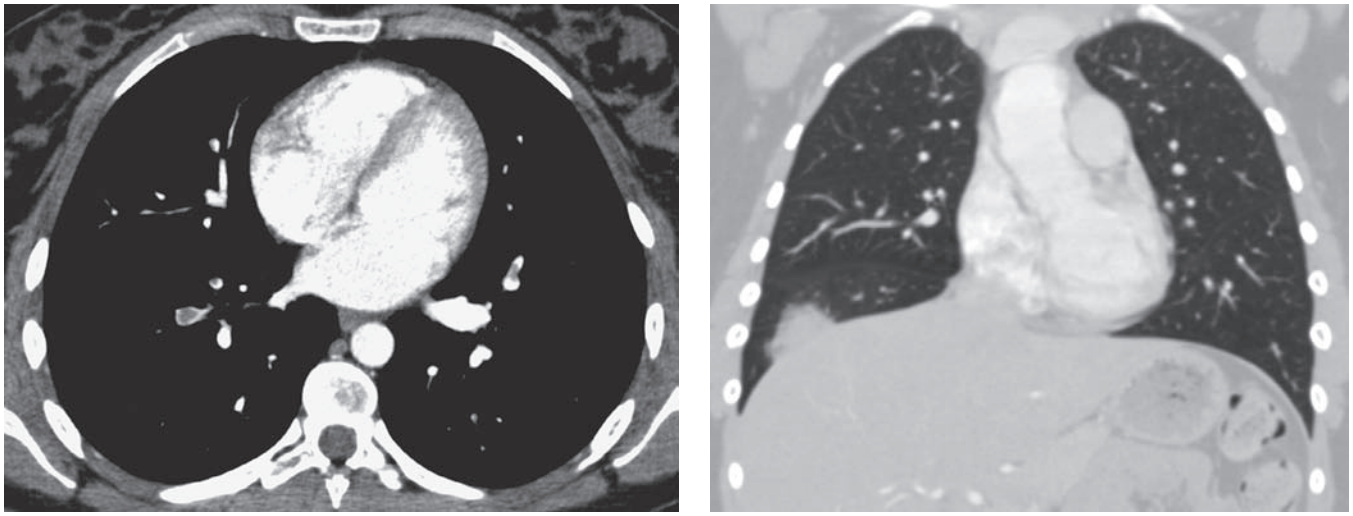


Figure 30-51 Pulmonary angiogram, arterial phase. Note marked dilatation of the pulmonary arteries, without occlusive filling defects, but with overall poor delineation of the arteries, suggesting semiocclusive defects and increased contrast transit time. The constellation of findings indicates chronic thromboembolic pulmonary hypertension (CTEPH).



A B

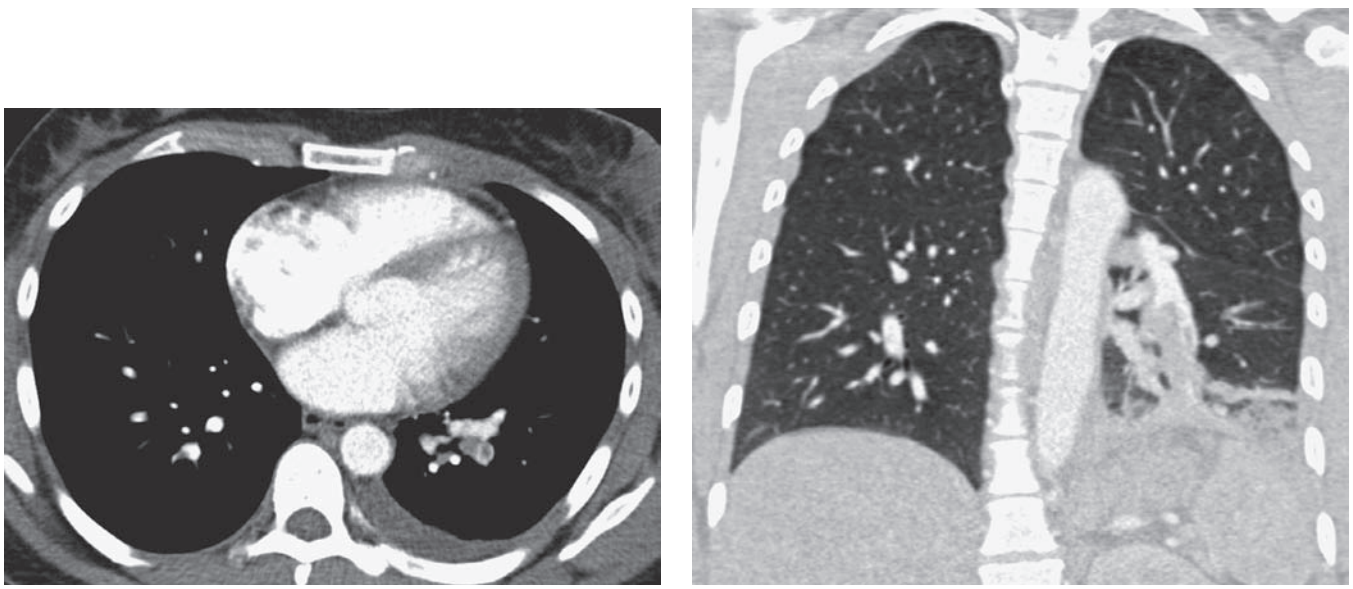
Figure 30-52 Acute pulmonary embolism. **A.** Axial CT at the lung bases demonstrates filling defects in the right lower lobe segmental arteries and left lower lobe anterior segmental artery, compatible with acute PE. **B.** Coronal CT image demonstrates a peripheral RLL consolidation, compatible with pulmonary infarct.

diagnostic modality for diagnosing chronic thromboembolic pulmonary hypertension (Figs. 30-50–30-53).[70–72]

■ PULMONARY HYPERTENSION

Because of its dual vascular supply (systemic and pulmonary, in series), the lungs effectively receive slightly greater than 100% of the cardiac output (100% via the pulmonary circulation and 1%–2% via the systemic bronchial circulation arising from the aorta), far more than the brain, heart, liver, or kidneys (which comprise the group of highly perfused organs). In addition, the pulmonary circulation is a low-pressure, low-impedance, high-flow system that demonstrates some remarkable physiologic adaptations, such as vasoconstriction whenever there is tissue hypoxia (the opposite response of arteries elsewhere in the body, which normally vasodilate in response to hypoxia), and the ability to adapt to major changes in flow with minimal changes in pressure. Inasmuch as the caliber and distribution of pulmonary vessels provide insight into the pathophysiology of the cardiopulmonary system, imaging methods can be used to study pulmonary vascular diseases.

Pulmonary blood flow is not uniform in the normal, upright human. Moreover, the blood flow pattern shifts with changes in posture, during exercise, and in a variety of heart and lung diseases. In the normal pulmonary circulation, gravity and distance from the heart are the predominant determinants of the pattern of



A B

Figure 30-53 Acute pulmonary embolism. **A.** Axial CT at the lung bases demonstrates filling defects in the left lower lobe segmental arteries, compatible with acute PE. Note small left pleural effusion. **B.** Coronal CT image demonstrates a peripheral LLL consolidation, compatible with pulmonary infarct.

blood flow, given that pulmonary vascular impedance is relatively uniform throughout the lungs (1/10 of average systemic vascular impedance). Assuming a normal average pulmonary arterial pressure of 15 mm Hg, in an adult patient in the erect position a gradient of 22 to 23 mm Hg exists between the apex (2–3 mm Hg) and the bases (25 mm Hg). Given that vascular impedance in the lungs is uniformly low, flow to the bases is approximately 10 times greater than flow to the apices. These differences are greatly reduced in supine position, in which there is a much smaller pressure gradient between the posterior and anterior lungs; consequently, flow is far more uniform in the supine position. In the healthy patient, exercise may increase cardiac output and pulmonary blood flow fivefold, with minimal changes in pressure due to decreased pulmonary vascular impedance. The decline in pulmonary vascular impedance is secondary to capillary recruitment and increased vascular distension.

In pathologic conditions in which pulmonary arterial or venous pressures are increased, or in which alveolar pressure is elevated, the importance of gravity as the major determinant of pulmonary flow is diminished. Furthermore, impaired gas exchange and ventilation may cause alveolar hypoxia that further interferes with pulmonary blood flow via hypoxic vasoconstriction of small arterioles.

The concept of lung "perfusion zones" is based on functional compartmentalization of the lung into three zones according to the relationships among pulmonary arterial, pulmonary venous, and alveolar pressures. In Zone 1, average alveolar pressure > arterial pressure > venous pressure, such that perfusion is minimal. In Zone 2, average arterial pressure > alveolar pressure > venous pressure, such that perfusion is pulsatile. In Zone 3, average arterial pressure > venous pressure > alveolar pressure, such that perfusion is continuous. Normal healthy subjects do not manifest Zone 1 physiology; however, patients on mechanical ventilation with high positive end-expiratory pressure (PEEP) or patients with COPD and air trapping may develop large areas of Zone 1 physiology. Moreover, heart diseases characterized by left ventricular dysfunction demonstrate increased left atrial and, consequently, increased pulmonary venous pressure. In the short term, this may cause vascular redistribution (with cephalization of the pulmonary vasculature) or pulmonary edema (if acute and more severe). In the long term, adaptation mechanisms of the pulmonary arterial circulation and right ventricle, including increased vascular impedance and right ventricular hypertrophy and dilatation, ultimately result in increased pulmonary arterial pressure; pulmonary hypertension ensues. Understanding the underlying pathophysiology is important for interpreting the imaging findings of pulmonary hypertension.

In its broadest sense, pulmonary hypertension is a pathophysiologic condition in which pulmonary hemodynamics are altered, including an increase in pulmonary vascular impedance and a consequent increase in mean pulmonary arterial pressure above 25 mm Hg (current diagnostic criteria). The pathophysiology, current WHO classification, and treatment of pulmonary hypertension are described in Chapter 72.

The reference standard for diagnosis of pulmonary hypertension is right heart catheterization, an invasive diagnostic modality which allows direct measurement of right ventricular pressure and pulmonary arterial pressure, as well as indirect measurement of pulmonary venous pressure throughout the cardiac cycle. Noninvasive imaging tests cannot measure pressure directly, although echocardiography can be used to estimate pulmonary arterial pressure via Doppler techniques that measure the velocity of the regurgitant jet through the tricuspid valve during systole. The right atrial pressure is usually assumed to be 7 to 8 mm Hg plus the central venous pressure, as estimated by physical evaluation of neck veins distention. These pressures cannot be directly measured by Doppler ultrasonography.

From a diagnostic standpoint, imaging tests may, nonetheless, provide important insight into the possible presence and potential etiology of pulmonary hypertension. The hemodynamic distinction between precapillary pulmonary hypertension (defined by mean pulmonary arterial pressure >25 mm Hg and PCWP <15 mm Hg) and postcapillary pulmonary hypertension (defined by mean pulmonary arterial pressure >25 mm Hg and PCWP >15 mm Hg) can generally be made by advanced imaging. Precapillary pulmonary hypertension includes pulmonary arterial hypertension, pulmonary hypertension due to lung parenchymal diseases, chronic thromboembolic pulmonary hypertension, and miscellaneous causes (WHO Classes I, III, IV, and V). Postcapillary pulmonary hypertension includes pulmonary venous hypertension associated with left heart disease (WHO Class II).

Imaging studies are important in separating pulmonary arterial hypertension from pulmonary hypertension related to pulmonary parenchymal diseases, left ventricular failure, and chronic thromboembolic pulmonary disease, since the management of these entities differs substantially.

Chest radiographs are helpful in the initial assessment of suspected pulmonary hypertension, although they are not sensitive for early diagnosis. Given their low cost and universal availability, chest radiographs can provide an assessment of cardiac size and pulmonary vasculature caliber and distribution, as well as suggest findings of congestive heart failure or diffuse lung parenchymal disease. Published studies suggest that on erect PA examinations, if PCWP is greater 13 but less than 18 mm Hg, there is usually vascular redistribution with relative hypervascularity of the upper lung fields; if between 18 and 25 mm Hg, there is also interstitial pulmonary edema; if greater than 25 mm Hg, there is usually alveolar edema and often pleural effusions. If pulmonary hypertension is present in these clinical settings, strong consideration should be given to left ventricular failure as a causal factor.

Chest CT and, increasingly, MRI have been proposed as diagnostic tests that can provide pertinent detailed information regarding the pulmonary parenchyma, cardiac anatomy and function, and the status of the pulmonary vasculature, with minimum patient risk.

Chest CT has a major role in evaluating patients with suspected pulmonary hypertension. It is the best imaging test to demonstrate lung parenchymal disease. A normal appearance of the lung parenchyma on chest CT in the setting of pulmonary hypertension effectively eliminates the possibility of COPD or ILD significantly contributing to the pulmonary hypertension and should prompt search for alternative etiologies.

Furthermore, chest CT is also useful for direct assessment of the pulmonary arteries in the setting of suspected pulmonary arterial hypertension. It has been reported that a main pulmonary artery caliber >29 mm, when measured 2 cm from the pulmonary valve, has a sensitivity of 84%, a specificity of 75%, and a positive predictive value of 97% for the presence of pulmonary arterial hypertension, as confirmed by invasive imaging. Moreover, if the main pulmonary artery has a maximum transverse diameter greater than that of the proximal ascending thoracic aorta, there is a sensitivity of 70%, specificity of 92%, and positive predictive value of 96% for the presence of pulmonary arterial hypertension. One should be mindful to first determine that the ascending aorta is not aneurysmal when performing these measurements.

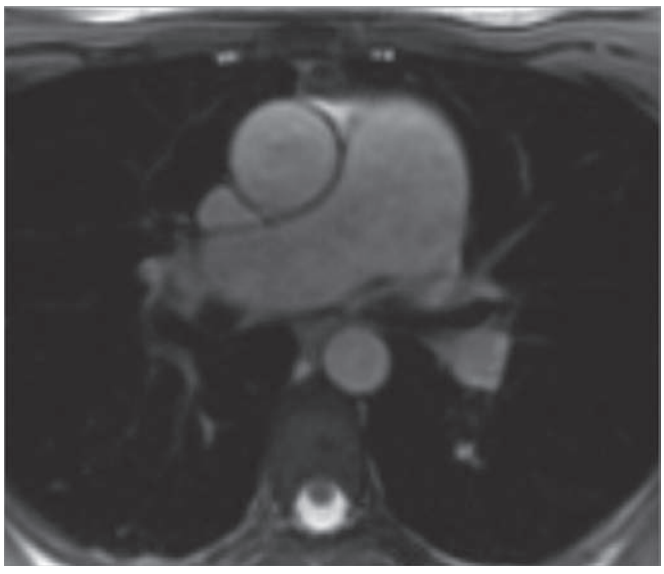
An additional chest CT finding suggesting pulmonary arterial hypertension is enlargement of the segmental arteries greater than 1.25 times the caliber of the adjacent bronchus. A combination of positive findings increases diagnostic confidence. For instance,

the presence of enlarged main pulmonary artery (>29 mm) and concomitant enlargement of three out of four segmental arteries (arterial/bronchial diameter > 1.25) provides a very high specificity (100%) for the diagnosis of pulmonary arterial hypertension. However, if pulmonary fibrosis or emphysema is present, the correlation between pulmonary artery dimension and severity of pulmonary hypertension is substantially weaker. In these clinical settings, a combination of findings is warranted to suggest the diagnosis.

A prospective study comparing right heart catheterization and chest CT demonstrated that CT-derived measurement of the main pulmonary artery diameter (MPAD) correlates more strongly with the presence of pulmonary hypertension in patients without ILD (MPAD >31.6 mm associated with a PPV of 90.0% and a NPV of 58.3%) than in patients with ILD (MPAD >25 mm associated with a PPV of 46.3% and a NPV of 83.8%), although in both groups the MPAD was significantly greater in patients with pulmonary hypertension than in those without. One conclusion is that pulmonary hypertension is more likely to be present even with normal caliber pulmonary arteries if the underlying diagnosis is ILD. The presence of bronchial artery hypertrophy >1.5 mm has also been implicated in pulmonary arterial hypertension, although this sign is probably far more common in chronic pulmonary thromboembolic disease.

Several pulmonary parenchymal findings are associated with pulmonary arterial hypertension, although they are not individually sensitive or specific enough to warrant the diagnosis. The first is mosaic attenuation, which is more commonly seen in the setting of pulmonary hypertension due to chronic pulmonary thromboembolic disease, but which can also be seen in the presence of small airway disease without pulmonary hypertension, among other possibilities. Widespread tiny centrilobular ground-glass nodules may also be present, similar to those observed in hypersensitivity pneumonitis, but pathologically deemed to represent cholesterol granulomas or large plexogenic arterial lesions, which have been described in 7% to 47% of patients with pulmonary arterial hypertension.[73–75]

MRI is currently the reference standard for assessment of congenital heart diseases, as it accurately delineates structural changes, cardiac situs, intracardiac shunts, atrial–ventricular and ventriculoarterial relationships, and vascular dimensions, along with wall motion and valvular abnormalities. It is the most useful modality for assessing right ventricular anatomy and function, which is a critical prognostic determinant in pulmonary hypertension. Furthermore, contrast-enhanced MRI, through demonstration of delayed enhancement, uniquely enables detection of the presence and extent of myocardial scarring related to prior infarction, myocarditis, or infiltrative disease in the myocardium—findings that may be associated with left ventricular dysfunction and pulmonary venous hypertension. MRI, similar to Doppler echocardiography, can be used to quantitatively measure flow velocity using phase contrast imaging, allowing for estimation of arterial and intracardiac pressures. However, a major strength of MRI when compared with echocardiography is that arbitrary planes can be set without limitation by available acoustic windows, providing for greater accuracy and reproducibility. Further developments in MRI techniques will increase the clinical usefulness of this modality. In the future, it is conceivable that the combination of advanced CT and MRI techniques will be able to provide a thorough anatomical and functional assessment of the heart–lung unit in patients with suspected pulmonary hypertension, obviating the need for invasive right heart catheterization in selected patients (Figs. 30-54–30-56).[76–78]



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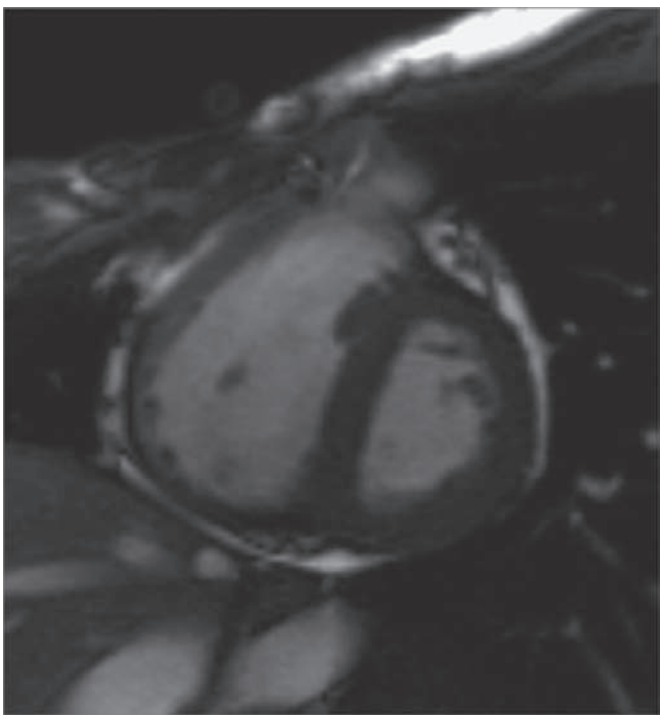
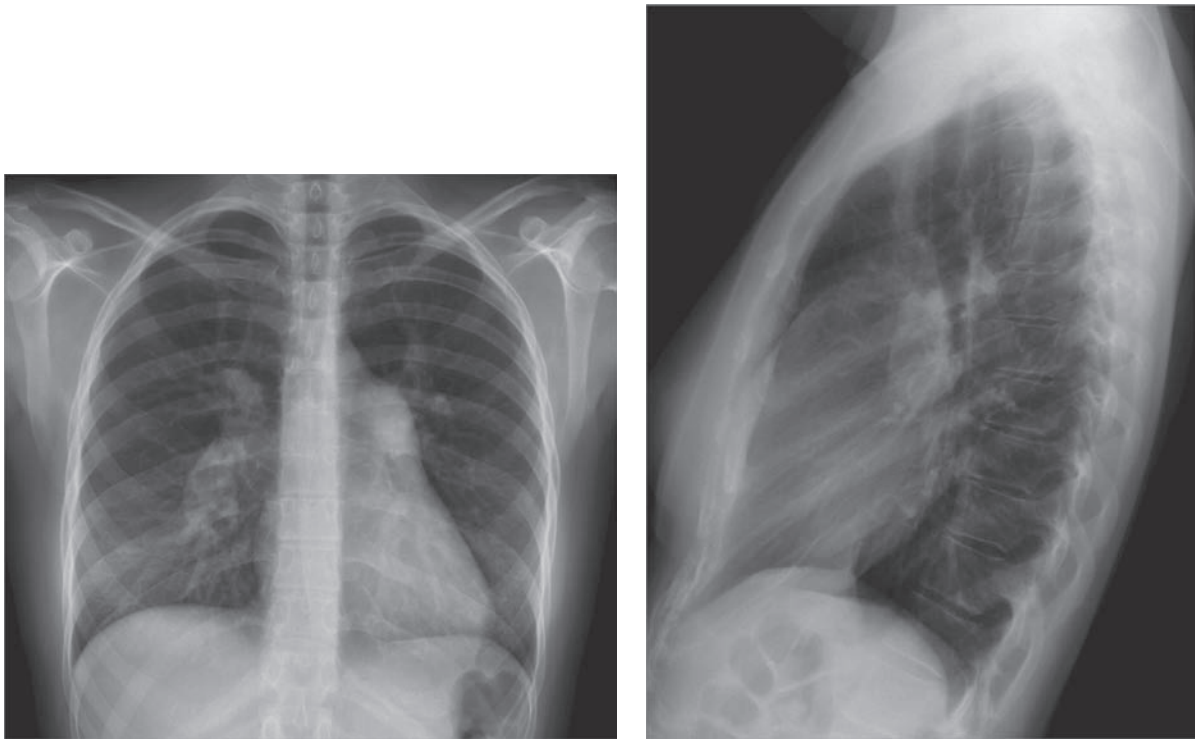


B

Figure 30-54 Pulmonary hypertension and right ventricular strain. **A.** Steady-state, free precession axial (SSFP) MR image ("bright blood") demonstrates dilatation of the central pulmonary arteries, with the main PA larger than the ascending aorta, compatible with pulmonary arterial hypertension. **B.** SSFP MR image, short axis of the heart, demonstrates right ventricular dilatation and straightening of the interventricular septum, indicative of right ventricular strain. The septum is normally convex toward the RV, due to normally higher LV pressure.



A B

Figure 30-55 Pulmonary hypertension due to cardiac shunt. (**A**) PA, (**B**) lateral chest radiographs demonstrate moderate dilatation of the central pulmonary arteries, secondary to a long-standing uncorrected atrial septal defect (ASD).

PLEURAL, DIAPHRAGMATIC, AND CHEST WALL DISEASES

Radiographic imaging of the pleural space, diaphragm, and chest wall plays an important role in the diagnosis and evaluation of common, clinically important disorders involving these structures.

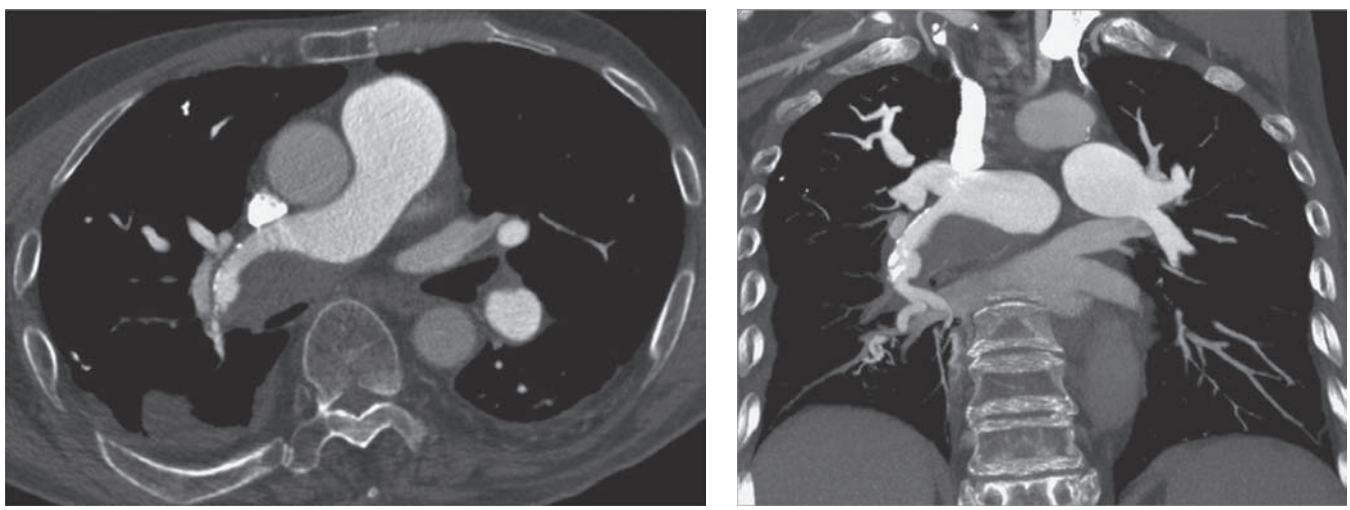
■ PLEURAL DISEASES

Pleural pathology can be broadly classified, for imaging purposes, into three major categories: pneumothoraces; pleural effusions; and pleural thickening, nodules, or masses. These are described in the subsections that follow.

Pneumothorax

Even though generally placed within the subgroup of pleural pathology, pneumothorax, characterized as the presence of gas within the pleural cavity separating the parietal from the visceral pleura, is rarely related to a disease process of the pleura itself (see also Chapter 31). Rather, it is associated with pulmonary or chest wall lesions. Nonetheless, pneumothorax is a very important clinical diagnosis, since it can lead to substantial morbidity or mortality if undetected or not properly treated.

Imaging is generally extremely accurate in the diagnosis of pneumothorax. The only exception is a portable chest radiograph obtained



A B

Figure 30-56 Chronic thromboembolic pulmonary hypertension (CTEPH): (**A**) axial CT image and (**B**) coronal MIP CT image demonstrating marked dilatation of the central pulmonary arteries, partially occlusive filling defect in the right main pulmonary artery, and tortuosity of the pulmonary arteries, with asymmetric vascular caliber. The constellation of findings reflects CTEPH.

in a supine position, which is relatively insensitive for detection of small pneumothoraces. In this scenario a pneumothorax should be suspected if there is increased lucency in the least dependent portion of the hemithorax (the anterolateral costophrenic angle in supine position), known as the "deep sulcus sign." This finding should prompt a lateral decubitus film, with the patient positioned with the suspected pneumothorax in the nondependent side; findings include a sharply marginated lucency along the lateral nondependent hemithorax.

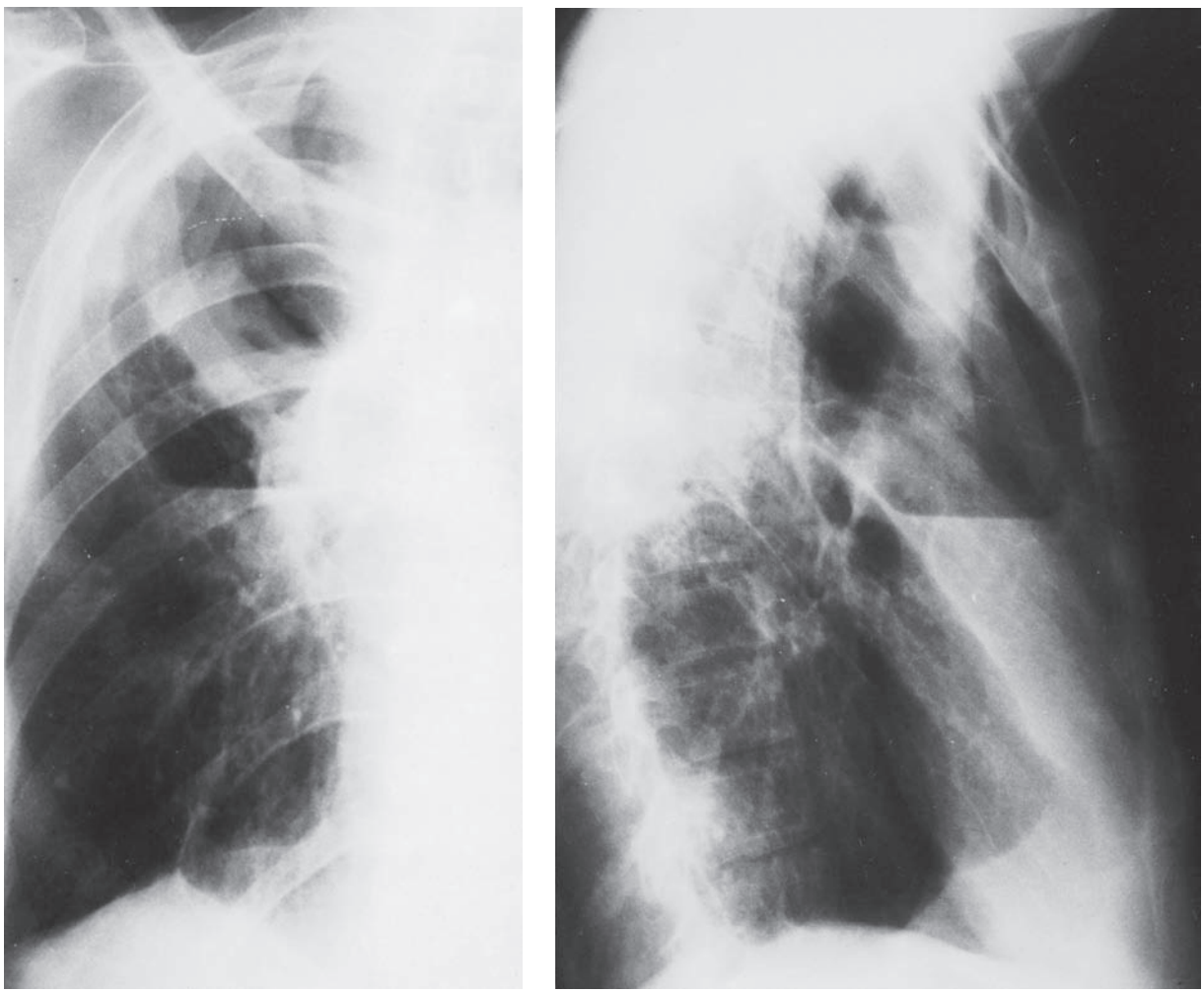
On the other hand, erect PA radiographs are very sensitive and can detect even very small pneumothoraces, which are identified as crescentic-shaped lucencies lateral and superior to the apex of the lung and delineated from the lung parenchyma by a thin visceral pleural line. If there is doubt regarding the presence of a very small pneumothorax, an expiratory view may help by increasing the conspicuity of the pneumothorax, as the lung volumes will be reduced while the pneumothorax volume remains constant, resulting in an increase in the percent volume of the hemithorax occupied by the pneumothorax. In addition, lung parenchymal attenuation will be slightly increased relative to the pneumothorax.

Finally, CT is the most accurate modality for detecting pneumothorax and can demonstrate even minuscule pneumothoraces (<1%) that cannot be detected by standard radiographic techniques.

Special cases include tension and loculated pneumothoraces. Tension pneumothorax is a critical diagnosis that requires emergent treatment. A tension pneumothorax manifests on imaging as substantial lung collapse, contralateral mediastinal shift, and downward ipsilateral diaphragmatic displacement. It is generally associated with respiratory and cardiovascular compromise and requires prompt decompression. Loculated pneumothorax occurs when there are inflammatory or neoplastic adhesions between the parietal and visceral pleura, causing gas to accumulate in the pleural space in unusual locations and geometric configurations that do not respect gravitational gradients.

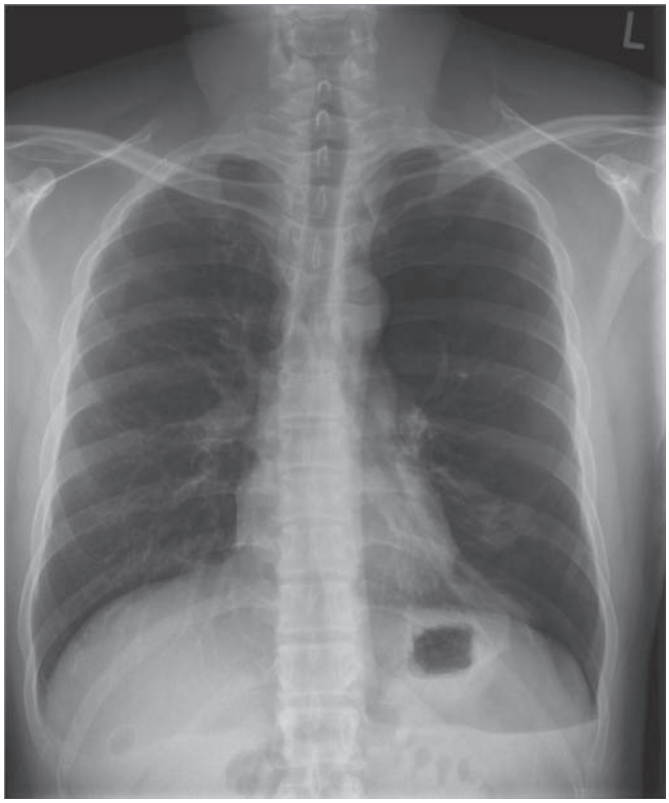
Imaging can also be performed to monitor a pneumothorax, for example, to decide if and when to place a chest tube, and also to investigate the etiology. Most pneumothoraces are either traumatic (in the setting of rib fractures or pulmonary lacerations) or iatrogenic (in the setting of pulmonary, mediastinal, or chest wall interventional procedures, which may be percutaneous, bronchoscopic, or surgical). CT is the best imaging modality to demonstrate rib fractures and pulmonary lacerations. Occasionally, a patient presents with a spontaneous pneumothorax. Most often these are related to rupture of pulmonary blebs or bullae, which may occur in patients with COPD or cystic lung diseases; in some cases, no specific cause can be demonstrated.[79]

A chronic pneumothorax usually occurs in association with pleural effusion, resulting in a hydropneumothorax. Hydropneumothoraces are generally associated with surgical procedures, malignancy, or severe infections, such as empyema. A chronic pneumothorax strongly suggests the presence of a bronchopleural fistula, as gas-forming infection in the pleural space is rare (Figs. 30-57 and 30-58).[80]



A B

Figure 30-57 Hydropneumothorax. **A.** PA view. A distinct air–fluid level is seen overlying the right hilus. **B.** Lateral view. The fluid and air are anterior to the hilus. The findings are difficult to differentiate from a lung cavity, but the very thin edge suggests localization in the pleural space. This was a hydropneumothorax and was secondary to a postoperative bronchopleural fistula.



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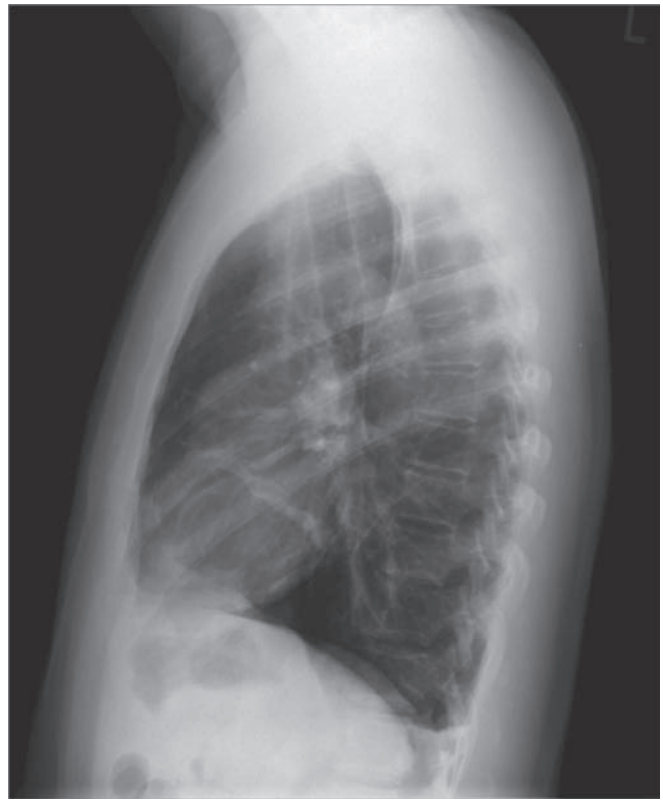

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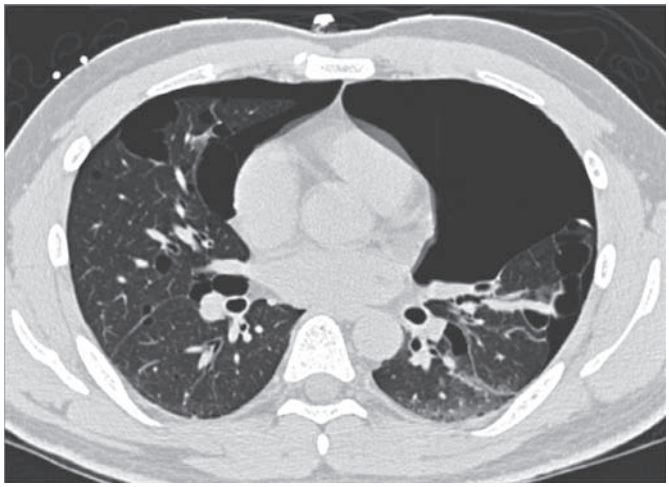


C

Figure 30-58 Bilateral pneumothoraces. (**A**) PA and (**B**) lateral chest radiographs demonstrate bilateral pneumothoraces, approximately 20% on the right and 40% on the left. The patient presented with spontaneous pneumothoraces. **C.** Axial CT at the lung bases confirms bilateral pneumothoraces and also indicates the etiology, demonstrating multiple pulmonary cysts. The patient was found to have Birt–Hogg–Dubé syndrome, a genetic disease that causes pulmonary cysts and predisposes the patient to recurrent spontaneous pneumothorax.

Pleural Effusions

Fluid in the pleural cavity appears radiographically as a homogeneous opacity that generally occupies a dependent position. A small pleural effusion that is barely perceptible or is overlooked on the PA view is often readily apparent on the lateral radiograph as blunting of the posterior costophrenic sulcus. The best non-CT radiographic study for demonstrating small quantities of pleural fluid is the lateral decubitus view, with the suspected pleural effusion on the dependent side. Using this technique, as little as 25 mL of fluid can be detected. Larger pleural effusions usually blunt the lateral costophrenic sulcus on the PA radiograph as well.

Occasionally, pleural fluid remains between the diaphragm and the lung, that is, infrapulmonary or subpulmonic, displacing the lung upward so that the lateral costophrenic angle remains sharp. The presence of a subpulmonic accumulation of fluid should be suspected if the diaphragm appears elevated, particularly along its lateral aspect on the frontal radiograph; if the costophrenic sulcus is blunted posteriorly; or if the gastric gas bubble is separated from the dome of the apparent left hemidiaphragm by more than a few millimeters (The last finding is frequently normal, however). CT is especially sensitive in identifying even the smallest of pleural effusions, which may be undetectable on chest radiographs. In the intensive care unit, where many portable radiographs are obtained in supine patients, CT imaging is particularly helpful in the diagnosis of pleural effusions, often revealing sizable effusions that are unsuspected.

Pleural effusions can be classified into two major categories: transudates and exudates. Transudates are characterized by low protein concentration relative to the plasma, and very low cellularity; exudates are characterized by higher protein concentration and cellularity, as discussed in detail elsewhere (Chapters 76 and 77). Transudative pleural effusions are commonly caused by congestive

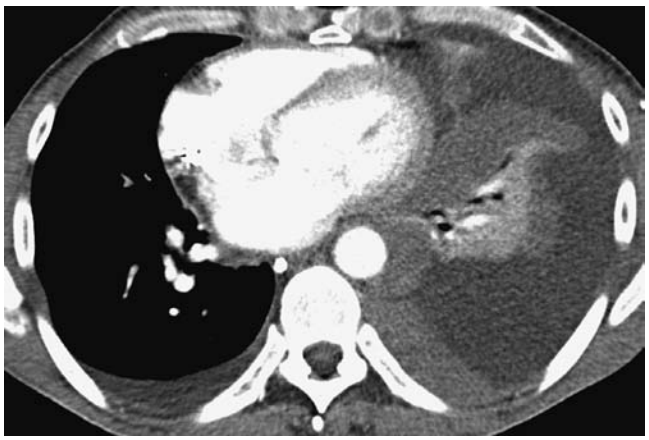


Figure 30-59 Malignant pleural effusion. Axial CT image demonstrates bilateral pleural effusions. The left effusion is associated with enhancing pleural masses, better visualized at the posterior medial costophrenic angle and adjacent to the descending thoracic aorta. This is characteristic of a malignant effusion. The patient was later diagnosed with mesothelioma.

heart failure, volume overload in the setting of renal dysfunction, or ascites in the setting of hepatic failure. Rarely, they are due to connective tissue disease or metastatic neoplasm. Broad causes of exudative effusions include parapneumonic collections, pulmonary infarction, malignancy (metastatic or due to primary pleural neoplasms), connective tissue disorders, subdiaphragmatic inflammatory processes, and infections (including empyema). Obtaining a specific diagnosis usually requires extensive evaluation that includes CT or MR, thoracentesis, and, possibly, pleural biopsy (Fig. 30-59).

Imaging modalities, particularly CT, may suggest, but not confirm, that an effusion is more likely a transudate or an exudate, thereby guiding patient management. Most transudates are bilateral, simple, nonloculated effusions occurring in dependent locations. Many exudates are unilateral, loculated effusions. A loculated effusion usually conforms to an unusual shape, commonly ovoid or with geometric edges, and sometimes along the fissures. Loculated effusions may resemble pulmonary masses on chest radiographs, although the pleural location can be readily ascertained on CT. The differential diagnosis of pleural effusions is one scenario in which US can be used to provide additional information beyond CT. For example, US may demonstrate internal septations within an effusion, a finding that can be difficult to demonstrate using CT and which is highly associated with exudative effusions. Furthermore, US can be used therapeutically to provide real-time guidance for thoracentesis and chest tube placement.[81–83] Conversely, US may occasionally fail to detect exudative pleural effusions, including empyemas, which are echogenic and which are readily detected by CT.

Pleural Thickening, Nodules, and Masses

Pleural diseases that cause diffuse thickening or localized nodularity may be separated into three broad etiologic categories: inflammatory, infectious, and neoplastic (both benign and malignant). Specific subgroups that are commonly encountered, but rarely clinically relevant, include apical pleural thickening (apical capping), which is usually bilateral and age-related and usually idiopathic (attributed to age-related ischemic changes); however, apical capping may potentially be associated with sequelae of granulomatous infections, particularly if accompanied by apical parenchymal scarring. Blunting of the lateral costophrenic angle on the PA view with sparing the posterior costophrenic angle on the lateral may be attributed to postinflammatory pleural thickening. Radiographic follow-up is helpful in excluding a focal mass. Multifocal pleural plaques, which are smoothly marginated, localized areas of pleural thickening, and which are often associated with calcifications, are common late manifestations of prior asbestos exposure. Frequently, they are the sole imaging manifestation of past asbestos exposure. CT is the optimal modality for their detection and characterization.

Diffuse pleural thickening involving both hemithoraces is more likely of inflammatory etiology, although bilateral pleural metastases can definitely occur and should be considered. Unilateral, extensive pleural thickening is more suspicious for a malignant etiology, either pleural metastases or primary malignancy, such as pleural mesothelioma. Nodular thickening of the mediastinal pleura and involvement of the interlobar fissures are particularly correlated with a malignant etiology; as a rule, the more nodular the pleural thickening appears, the more likely a malignant process is its cause. The differential diagnosis includes empyema, particularly tuberculous empyema, which may be indistinguishable from mesothelioma based on imaging appearance. Imaging cannot distinguish mesothelioma, pleural metastases, and tuberculous empyema; tissue sampling and correlation with other clinical and laboratory findings is required.[84–86]

A special case to consider is extensive pleural thickening associated with calcifications and diminished volume of the adjacent lung parenchyma—a fibrothorax. Most fibrothoraces reflect sequelae of prior substantial pleural inflammation caused by empyema or hemothorax, and their clinical significance is due to their potential to impair chest wall mechanics and restrict lung expansion.

A localized pleural nodule suggests a benign pleural neoplasm, such as a solitary fibrous tumor of the pleura or lipoma. The nodule may be difficult to distinguish from a localized area of pleural thickening, but generally it is larger and more symmetric in contour. On CT, these nodules usually have a characteristic appearance: Their shape is ovoid with their largest diameter parallel to the chest wall, and their edges are flat and tapering. The appearance is similar to the extrapleural sign on chest radiographs, which is defined as a shadow that has smooth margins, tapering edges with obtuse angles with the chest wall, and is generally seen well in only one of the two standard views of the chest. Occasionally, a peripheral nerve sheath tumor (e.g., schwannoma or neurofibroma) arising from an intercostal nerve may mimic a pleural nodule. These lesions, however, tend to cause indentation of adjacent ribs due to long standing mass effect, helping to suggest the diagnosis.

Rarely, solitary or multiple pleural nodules without associated effusion may represent a malignant process; the classic example is the so-called "drop" metastases from thymic neoplasms.

DIAPHRAGMATIC DISEASES

Diaphragmatic evaluation can be performed initially via chest radiographs, ideally PA and lateral views. The normal hemidiaphragm has smooth contours and gentle curvature, with its dome near its center and no focal protrusions, with the left hemidiaphragm slightly lower than the right. The most common diaphragmatic abnormality is an eventration, in which there is focal weakness of the muscle, correlated with focal protrusion or bulge. Diaphragmatic paralysis should be suspected when an entire hemidiaphragm is elevated, typically more than 2 cm in comparison to the normal side. To confirm diaphragmatic paralysis, the standard test is a fluoroscopic dynamic evaluation ("sniff test"), in which the patient is imaged during shallow breathing, deep breathing, and forceful inspiration ("sniff"). The normal hemidiaphragm moves downward with the sniff maneuver, while a paralyzed hemidiaphragm will demonstrate paradoxical upward motion.

Diaphragmatic hernias can be classified into three broad categories: hiatal, congenital, and traumatic. Hiatal hernias occurring

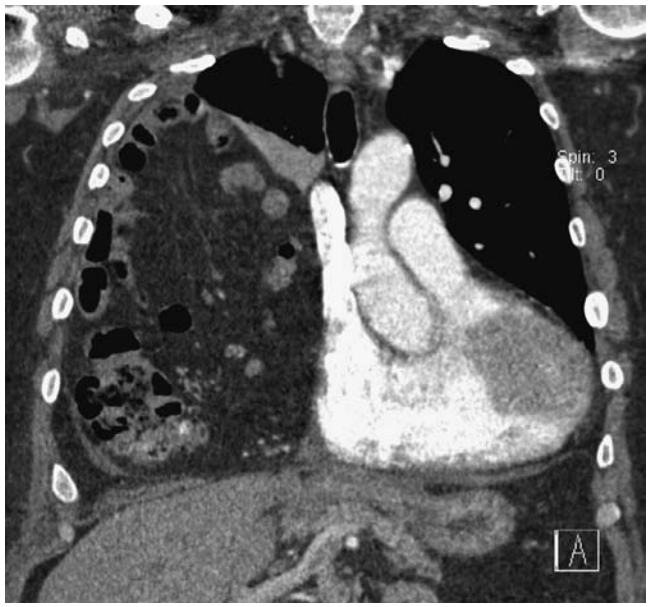


Figure 30-60 Diaphragmatic hernia. Coronal CT image demonstrates a wide defect in the right hemidiaphragm. The right lung is nearly completely collapsed, and the right hemithorax is nearly completely occupied by small and large bowel loops with associated mesenteric fat. This is diagnostic of diaphragmatic hernia, in this case due to blunt trauma to the abdomen.

through the centrally placed esophageal hiatus are the most common, and usually contain a portion of the stomach, although very large hernias can contain small or large bowel loops as well. Congenital hernias are usually through the paired foramina of Morgagni (anterior and medial) or the paired foramina of Bochdalek (posterior and central). The latter are more frequent and are usually small, incidental hernias containing fat. When large, these congenital hernias can contain viscera, either bowel loops (Morgagni) or retroperitoneal structures such as the kidney (Bochdalek), but these are virtually always diagnosed in infancy. Traumatic hernias should be suspected in patients who had blunt trauma and present with a newly elevated hemidiaphragm. These are more common on the left, as the liver usually prevents herniation on the right except in very large defects. Traumatic diaphragmatic ruptures may occur in the setting of trauma without detectable herniation, and the actual herniation of abdominal viscera into the thorax may occur days, months, or even years later. Inquiry regarding a history of remote trauma is thus important in the evaluation of diaphragmatic hernias. Multiplanar coronal and sagittal CT or MR images allow accurate assessment of diaphragmatic contour abnormalities, and are the reference standard for the diagnosis of diaphragmatic rupture. MR offers the additional advantage of functional assessment with fast gradient echo cine sequences (Figs. 30-60 and 30-61).[87–89]

CHEST WALL MASSES

Chest wall masses may extend into the pleura and cause pleural nodularity or masses. These are very difficult to detect radiographically unless causing bone destruction or substantial mass effect. CT or MR associated with tissue sampling is generally necessary for accurate diagnosis. The differential diagnosis of chest wall masses includes soft tissue infection (cellulitis, phlegmon, abscess), which is generally associated with trauma and surgical procedures; hematoma, also often associated with trauma or surgical procedures; extension of infection arising from the lung, with the prototype

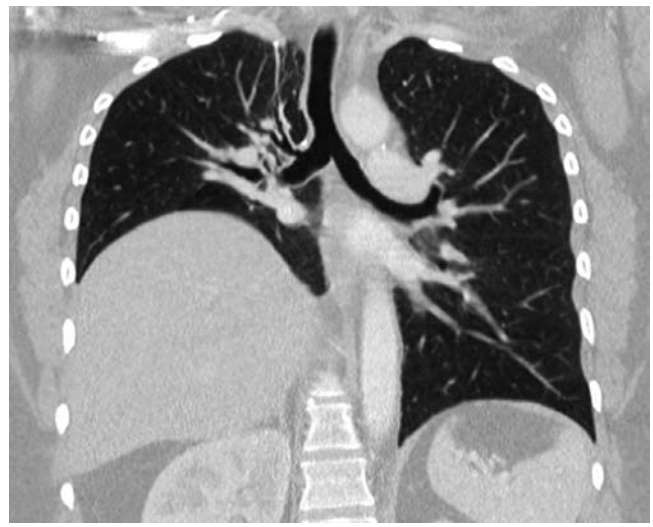


Figure 30-61 Diaphragmatic paralysis. Coronal CT image shows marked elevation of the right hemidiaphragm. Fluoroscopic examination confirmed a paralyzed right hemidiaphragm.

disease being actinomycosis; and rarely neoplasms, such as soft tissue sarcomas, metastatic disease, and malignant nerve sheath tumors.

MEDIASTINAL DISEASES

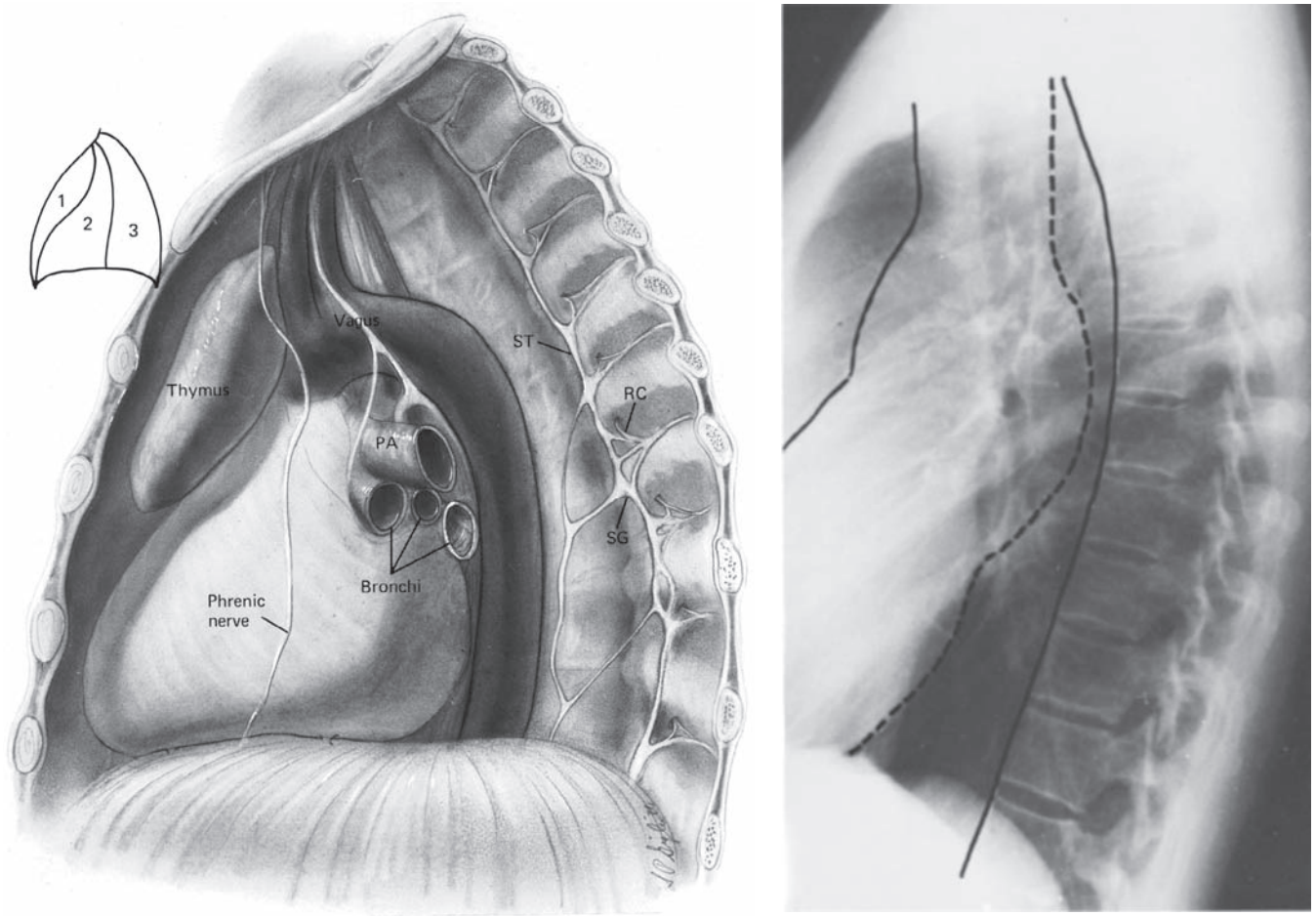
Mediastinal diseases encompass multiple systems, organs, and a vast array of differential diagnoses. Before discussing mediastinal diseases, it is necessary to define the contents of the mediastinum and its boundaries.

The anatomic delineations of "compartments" of the mediastinum are not defined consistently throughout the medical literature. For radiographic diagnosis, a simple classification has been employed: (1) The *anterior compartment*, which extends from the sternum anteriorly to the heart, aorta, and brachiocephalic vessels posteriorly, comprises only the thymus, fat tissue, and a few lymph nodes. (2) The *middle* or *visceral compartment* contains the heart, great vessels, trachea and its branches, esophagus, and descending aorta. It extends from the posterior border of the anterior compartment to the anterior border of the vertebral column. These boundaries differ from the anatomist's classification, which relegates portions of the esophagus and the descending aorta to the posterior mediastinum. (3) The *posterior compartment* contains the vertebrae and paravertebral sulci.

Application of this classification to the lateral chest radiograph facilitates generation of a relevant differential diagnosis. However, with modern modalities such as CT or MR, one is able to accurately categorize mediastinal masses according to their exact location within the mediastinum, obviating the need for compartmental localization. For example, instead of categorizing a mass as in the posterior mediastinum, CT or MR often allows accurate differentiation among different etiologies, such as paraspinal masses, neurogenic neoplasms, vascular lesions, and esophageal masses (Figs. 30-62 and 30-63).[90]

This section focuses on diseases of the lymph nodes and thymus. Cardiac and systemic vascular diseases are beyond the scope of this textbook and will be mentioned only briefly. Pulmonary vascular diseases have been described previously. Esophageal diseases and spinal or paraspinal diseases are discussed briefly (Fig. 30-64).

Before a discussion on mediastinal neoplasms, it is important to emphasize the role of CT for evaluation of suspected mediastinal infections in the postoperative patient.



A B

Figure 30-62 Compartments of the mediastinum: **A.** Anatomic view of the compartments of the mediastinum. The subdivisions (1, anterior; 2, middle; 3, posterior) in the small schematic *(top left)* correspond to those designated by the *solid black lines* in **B.** PA, pulmonary artery; ST; sympathetic trunk; SG, sympathetic ganglion; RC, ramus communicans. **B.** Radiographic division of the mediastinum. The *closed lines* delineate the anterior, middle, and posterior compartments. The *dashed line* represents the division of the middle and posterior mediastinum that is conventionally used by anatomists. *(**A:** Reproduced with permission from Jones KW, Pietra GG, Sabiston DC. Primary Neoplasms and Cysts of the Mediastinum, in Fishman AP (ed). Pulmonary Diseases and Disorders. New York: McGraw-Hill; 1980:1490–1521.)*

Mediastinitis is a catastrophic complication of multiple types of cardiothoracic surgeries and, if unrecognized and not treated aggressively, it often leads to a fatal outcome. In the immediate postoperative period in a patient status, post cardiac, central vascular, major pulmonary, or esophageal surgery, the presence of a small amount of gas and fluid in the mediastinum is an expected occurrence. The findings tend to subside within hours or a few days. While there is no absolute rule to apply to the time frame over which a pneumomediastinum or mediastinal fluid collection becomes clearly pathologic, some general guidelines are helpful in guiding management decisions: (1) It is expected that any postoperative fluid or gas collection will decrease in size over time, and any increase in size is suspicious for an evolving mediastinitis. (2) Large fluid and gas collections (those measuring >2 cm in the smallest diameter) are almost always pathologic. (3) Any persistent mediastinal fluid or gas collection more than 1 week following surgery is suspicious, and the index of suspicion rises if the patient is clinically worsening, if there are laboratory signs to support infection (e.g., leukocytosis with a left shift), and if there are CT features suggesting active inflammation, such as rim enhancement in the boundaries of the collection. Any of these findings should prompt aggressive management with percutaneous or surgical drainage of the collection and institution of broad-spectrum antibiotics.

A spontaneous pneumomediastinum has different clinical implications, as it may be a sign of an ominous condition, such as esophageal perforation (which warrants urgent surgical treatment), or a relatively benign condition when associated with barotrauma and tear of the distal airways or acini. Clinical correlation and careful clinical observation are very important to distinguish these etiologies (Fig. 30-65).[91,92]

The classical differential diagnosis of masses in the anterior compartment includes enlarged lymph nodes, substernal goiter or thyroid neoplasm, thymic hyperplasia and thymic neoplasms, and germ cell neoplasms. Distinction among these can be made on the basis of the patient's age and clinical presentation, their position within the anterior mediastinum, and the appearance on CT or MR.

Thyroid masses invariably lie high in the anterior mediastinum and often displace or compress the trachea and esophagus. On CT, the thyroid has characteristic high attenuation on unenhanced images due to its iodine content, and multinodular goiter often presents with a very heterogeneous texture containing cystic and calcified opacities within a background of dense thyroid parenchyma. Ultimately, any high anterior mediastinal mass with these imaging characteristics and unequivocal contiguity with the thyroid gland on CT or MR is deemed to represent a thyroid neoplasm or multinodular goiter, until proved otherwise.[93]

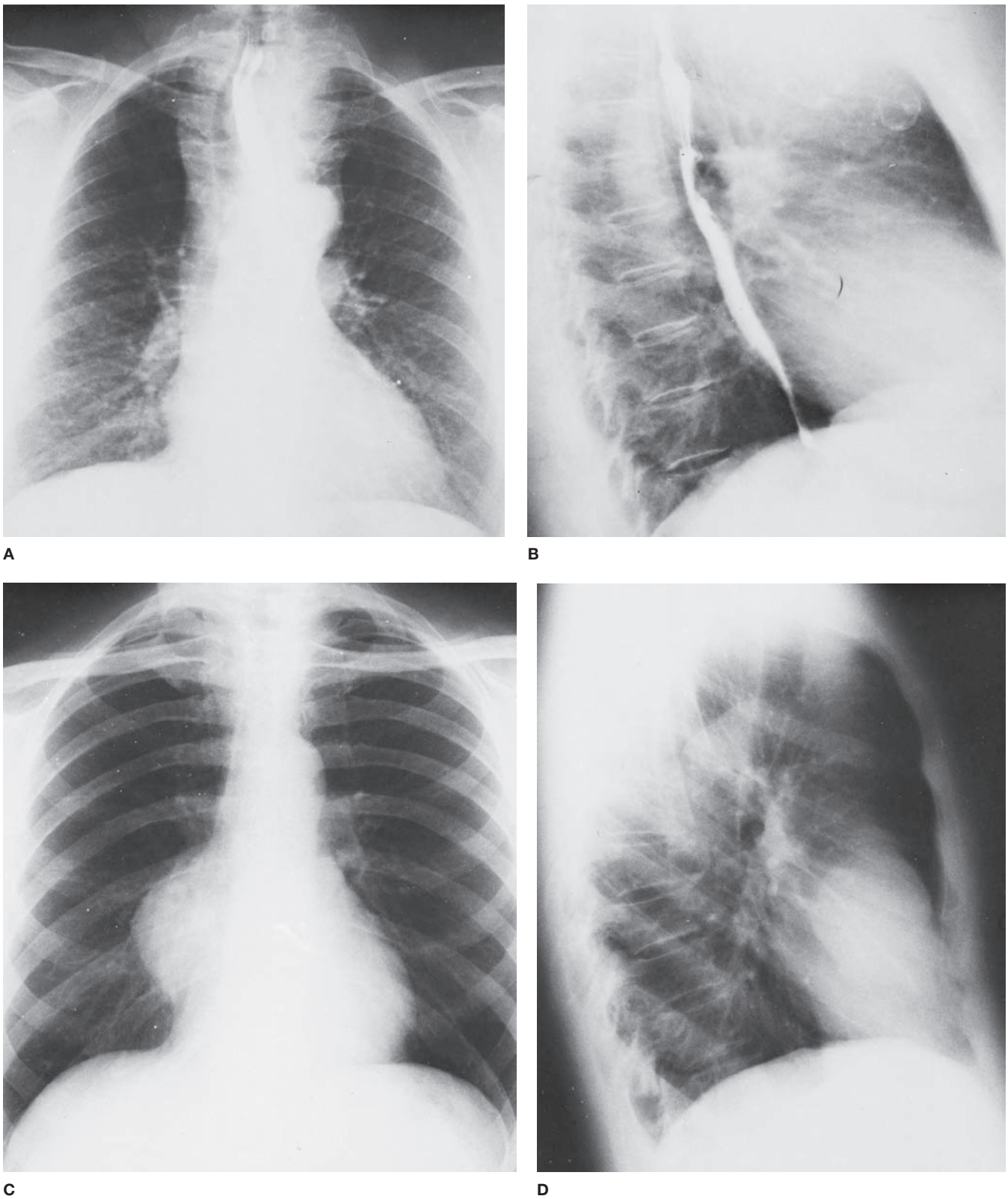
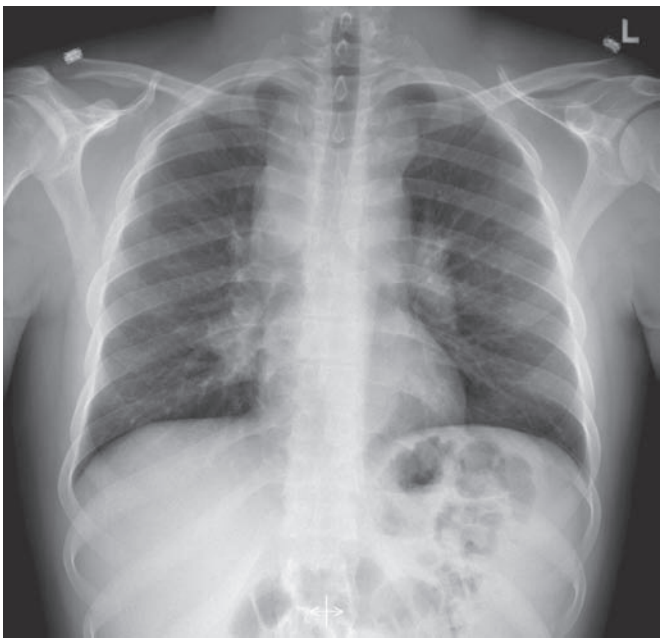


Figure 30-63 Radiographic spectrum of mediastinal masses: Substernal thyroid. **A.** PA view. A large mass in the neck extends below the clavicle. The trachea and esophagus are displaced to the right. **B.** Lateral view. The trachea and esophagus are also displaced posteriorly. Several calcifications are present within the mass. **C.** PA view. A discrete mass (thymoma) lies along the right heart border. **D.** Lateral view. The mass also overlies the anterior portion of the cardiac shadow. Despite being radiographically well circumscribed, the mass may be either invasive or noninvasive thymoma. CT is required for further characterization.



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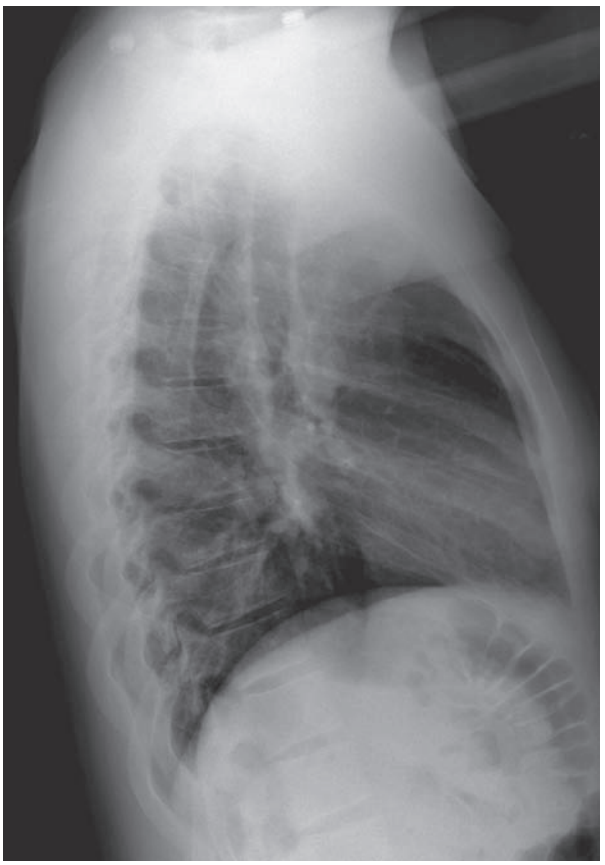

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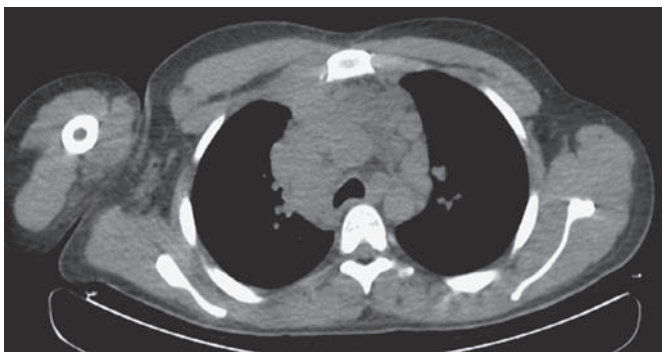

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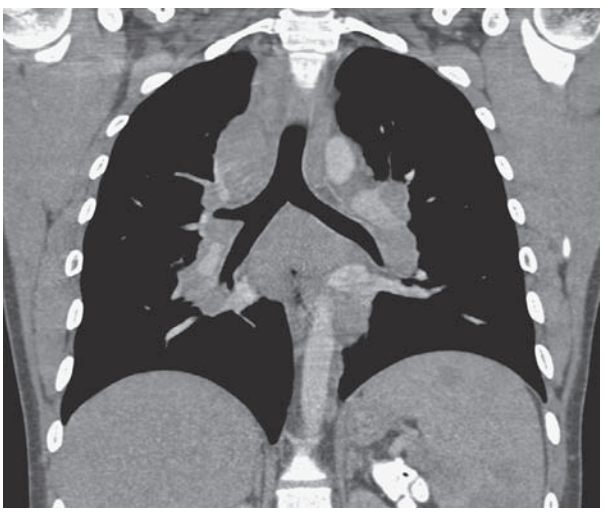

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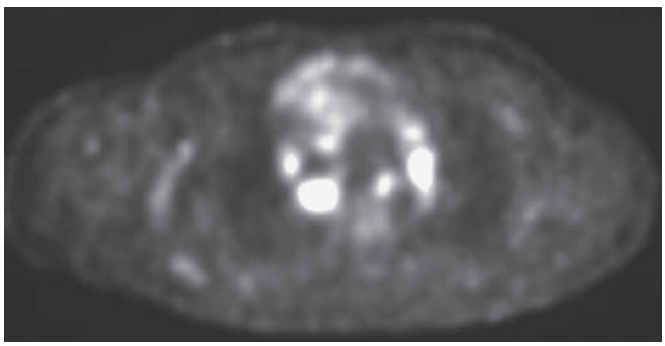
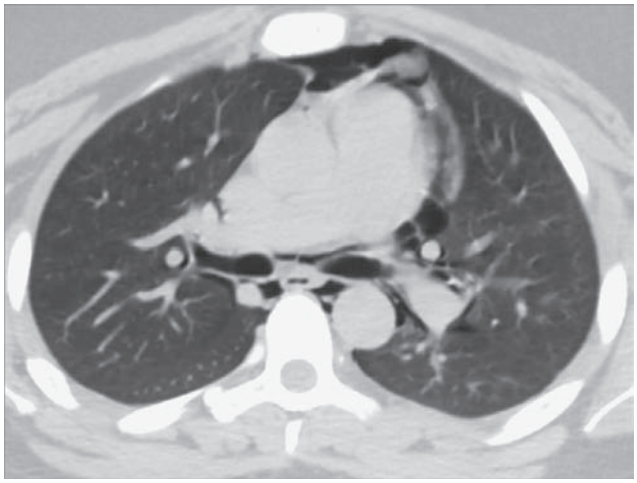


E

Figure 30-64 Lymphadenopathy: (**A**) PA and (**B**) lateral chest radiographs demonstrate marked widening of the bilateral paratracheal stripes and mild prominence of the bilateral pulmonary hila, compatible with mediastinal and hilar lymphadenopathy. (**C**) Axial noncontrast CT and (**D**) Coronal contrast-enhanced CT better demonstrate the extent of mediastinal and hilar lymphadenopathy. Pathology confirmed a large B-cell lymphoma. **E.** Axial FDG-PET at the level of the upper lung fields demonstrates increased glucose uptake within the enlarged mediastinal lymph nodes, indicative of increased metabolic activity. This study can be performed to monitor treatment response.

If an anterior mediastinal mass does not arise from the thyroid, the differential diagnosis of germ cell neoplasm, thymoma, and lymphoma can be challenging using imaging; tissue sampling is almost always necessary. Nonetheless, some clinical and imaging features may suggest a specific diagnosis. For example, germ cell neoplasms tend to occur in younger patients and are often heterogeneous—in particular, CT demonstration of fat and calcification within an anterior mediastinal mass is diagnostic of a teratoma.[94] Teratomas may also contain cystic components. Thymic hyperplasia or neoplasms tend to conform to the triangular shape of the thymus (particularly benign thymomas, although invasive thymomas and thymic carcinomas may have a more irregular configuration). Thymomas tend to occur in older patients and may be associated with the diagnosis of myasthenia gravis. Because of the presence of intracellular



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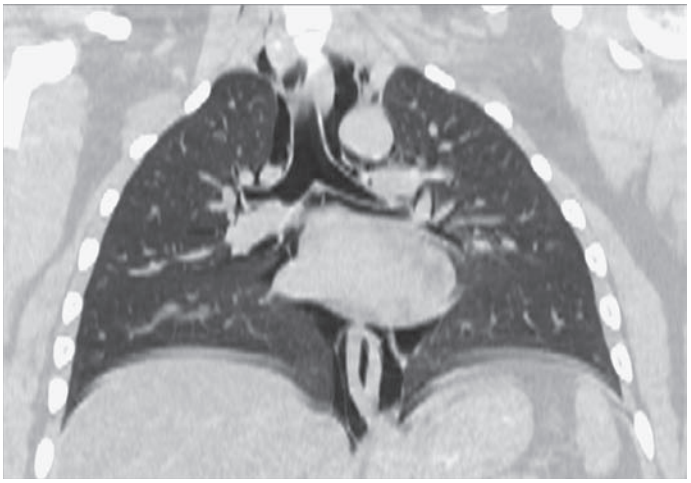
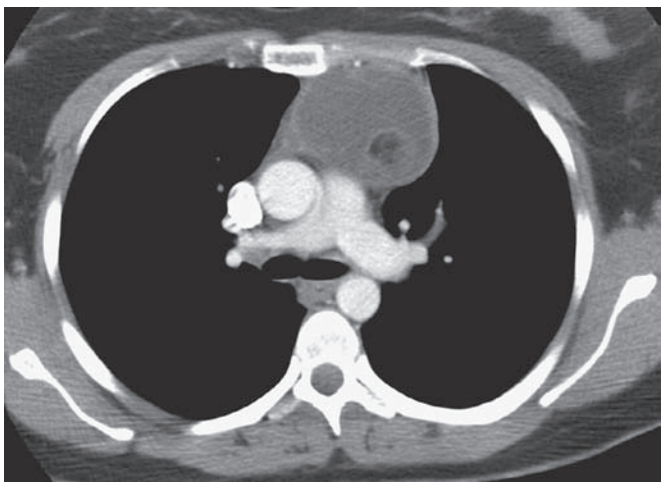


B

Figure 30-65 Pneumomediastinum. **A.** Axial CT at the level of the mainstem bronchi demonstrates gas within the anterior, middle, and posterior mediastinal compartments, compatible with pneumomediastinum. **B.** Coronal CT demonstrates the full extent of the pneumomediastinum. Note absence of pneumothorax. There is also subtle pulmonary interstitial emphysema, denoted by linear lucencies parallel to the proximal airways. This patient had barotrauma related to a severe asthma exacerbation.

lipids in the normal thymus, thymic hyperplasia can be distinguished from thymomas and infiltration by lymphoma using proton chemical shift MR; signal loss is noted in out-of-phase sequences. Finally, lymphomas occur over a wide age range (with Hodgkin disease having a bimodal distribution) and are generally homogeneous on CT and MR, unless treated (Figs. 30-66 and 30-67).[95]

Lymphadenopathy in the thorax has an extremely broad differential diagnosis, and it is best assessed using CT or MR. Anatomically, the largest lymph nodal chains in the thorax can be divided in axillary, supraclavicular (which includes lower cervical chains), mediastinal, and bilateral hilar. Smaller chains include internal thoracic (mammary), anterior cardiophrenic (or paracardiac), and



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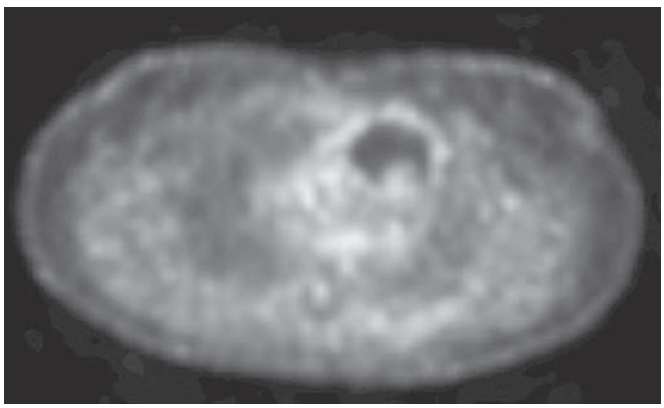

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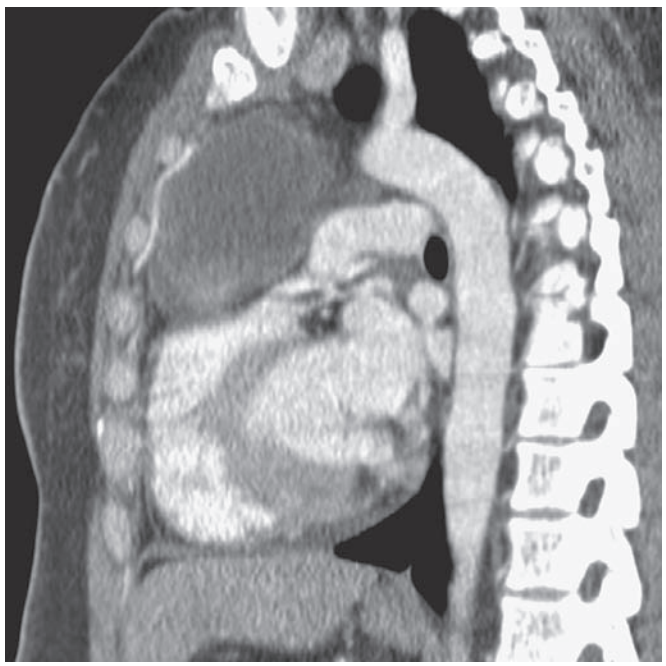


B

Figure 30-66 Anterior mediastinal mass. (**A**) Axial contrast-enhanced CT and (**B**) Sagittal contrast-enhanced CT show a heterogeneous, well-circumscribed anterior mediastinal mass. The mass is mostly cystic, with a nodular component that measures fat attenuation. Enhancing components are also noted. **C.** Axial FDG-PET through the mass demonstrates lack of glucose uptake. The constellation of findings is diagnostic of a mature teratoma, a benign germ cell neoplasm.

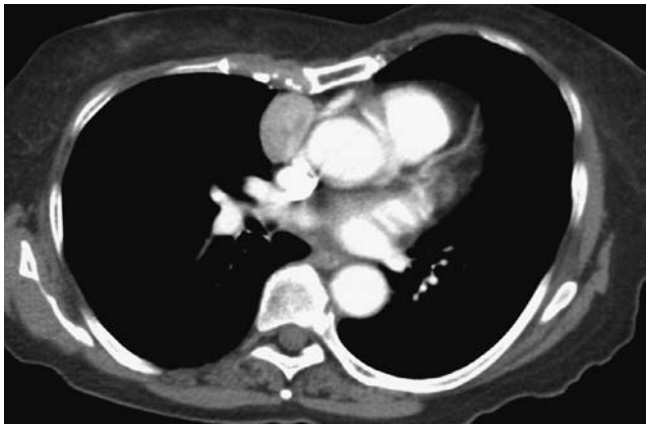


Figure 30-67 Anterior mediastinal mass. Axial contrast-enhanced CT demonstrates a homogeneous, enhancing, well-circumscribed anterior mediastinal mass along the anterior right heart border. Pathology confirmed a thymoma.

retrocrural. Mediastinal lymph node stations are further subdivided into prevascular, paratracheal (upper and lower, right and left), subaortic (or AP window), subcarinal, para-aortic, and paraesophageal.

A normal lymph node on CT or MR has an ovoid, reniform shape ("kidney shape") and a fatty hilum and measures less than 1 cm in its smallest diameter. An abnormal lymph node is frequently rounded, loses the delineation of the hilum, and measures more than 1 cm in its smallest diameter. It is important to emphasize that early neoplastic or infectious disease may be associated with "normal" lymph nodes on CT or MR, but "abnormal" lymph nodes on CT or MR are virtually never normal from a pathologic standpoint, even if the diagnosis is not clinically significant.

From an imaging perspective, establishing the etiology of mediastinal lymphadenopathy implies assessing the size, configuration, number, and location of the enlarged lymph nodes. Enhancement patterns on CT or MR have a limited role, although FDG uptake on PET/CT may be helpful. The presence of calcification is also an important sign in narrowing the differential diagnosis.

The following guidelines should be utilized in the general assessment of mediastinal and thoracic lymphadenopathy.[96–98]

Very large (measuring >2–3 cm), confluent, conglomerate lymphadenopathy is malignant until proven otherwise. Considerations include nodal metastasis and lymphoma, particularly high-grade, large B-cell lymphomas or Hodgkin disease. An anterior mediastinal, prevascular location favors lymphoma. Distribution of disease may help elucidate the origin of the primary neoplasm, in case the diagnosis is not obvious or previously established if one is cognizant of the typical lymphatic drainage pathways. For example, lung carcinomas present more frequently with ipsilateral hilar, subcarinal, and paratracheal lymphadenopathy; head and neck squamous cell carcinomas more often involve supraclavicular lymph nodes; breast carcinomas frequently involve ipsilateral axillary and internal thoracic lymph nodes; hepatocellular carcinomas usually involve anterior cardiophrenic lymph nodes (paracardiac nodes).

An increased number of nodes in disseminated lymphadenopathy, symmetric distribution involving multiple nodal stations, and moderately or substantially enlarged nodes suggest a low-grade lymphoproliferative disease, particularly chronic lymphocytic leukemia/small lymphocytic lymphomas (CLL/SLL). Note that early disease may present with only mildly enlarged lymph nodes.

Mild or moderately enlarged lymph nodes with a bilateral hilar and lower paratracheal distribution suggests the diagnosis of sarcoidosis.

Mild, bilateral, predominantly axillary lymphadenopathy can be seen in the setting of connective tissue diseases, such as systemic lupus erythematosus.

Mild disseminated lymphadenopathy can be seen in systemic infections, particularly "mono-like" syndromes caused by mononucleosis, CMV, and related infections.

Necrotizing lymphadenopathy may be seen in the setting of infectious lymphadenitis (particularly mycobacterial), but is also commonly seen in nodal metastasis.

Coarsely calcified lymph nodes, particularly mediastinal and hilar, suggest sequelae of granulomatous inflammation, including sarcoidosis and mycobacterial or fungal infection; however, treated malignancy and pneumoconiosis should also be considered in the differential diagnosis in the proper clinical setting.

Mild lymphadenopathy can be ascribed to a "reactive" etiology, including prior infections, congestive heart failure, or ILDs. Reactive lymphadenopathy is a diagnosis of exclusion.

Additional structures of the middle mediastinal compartment are the heart and central vessels. Aortic or aortic branch aneurysms can be suggested on chest radiographs by the presence of mediastinal widening and prominence of the aortic contours. Diagnostic confirmation and full characterization require CT or MR, typically with intravenous contrast. Duplication cysts of the foregut may arise from the esophagus or tracheobronchial tree and are also common in the middle compartment. These localized masses are smooth and well circumscribed; generally, they do not contain air, and their attenuation is low on CT (generally of simple fluid density) without contrast enhancement. However, duplication cysts containing highly proteinaceous fluid may have CT densities comparable to soft tissue, thus mimicking solid masses. As indicated earlier, MRI is useful in characterizing proteinaceous fluid and, thus, may be diagnostic in these cases. Bronchogenic cysts commonly occur at the tracheal carina or paratracheal region, whereas esophageal duplication cysts are characteristically located near the distal esophagus. However, esophageal and bronchogenic cysts may occur anywhere within the middle compartment.

A dilated (patulous) esophagus is sometimes seen on the chest radiograph as a long tubular mass in the middle compartment and is readily identified by CT. The significance of a patulous esophagus is its association with dysmotility disorders, such as achalasia, CREST syndrome, and presbyesophagus. Neoplasms of the esophagus or trachea may also present as more localized mediastinal masses by chest radiograph; usually, CT is required for recognition. Early esophageal neoplasms may involve primarily the mucosa and may not be well seen on the CT, even if clearly demonstrated on a barium swallow study or endoscopy. Hiatal hernias are readily diagnosed using CT. The presence of esophageal wall thickening is usually clinically relevant. Smooth and concentric wall thickening favors esophagitis, particularly reflux esophagitis; irregular and eccentric wall thickening is concerning for esophageal carcinoma.[99]

In the posterior (paraspinal) compartment, the most common radiographic abnormalities are neurogenic neoplasms. However, neoplasms or infections of the vertebral column may also present as masses in the posterior compartment. CT or MR usually distinguishes between a neurogenic neoplasm, which is unilateral and paraspinal in location, and lesions which erode or destroy the vertebrae and are generally present on both sides of the vertebral column. MR is the best modality to diagnose a neurogenic neoplasm (Figs. 30-68 and 30-69).[100,101] Other considerations in the posterior compartment include paraspinal hematoma in the setting of trauma, and rarely, extramedullary hematopoiesis in patients with hemoglobinopathies, myeloproliferative disorders, or bone marrow infiltration.

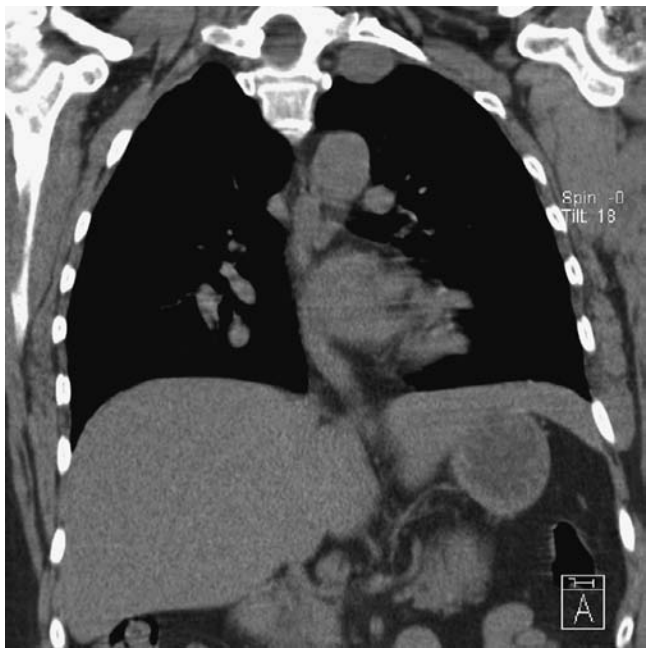


Figure 30-68 Posterior mediastinal mass. Coronal noncontrast CT shows a homogeneous, well-circumscribed posterior mediastinal mass in the left superior sulcus medially. Note absence of aggressive features by CT. Pathology confirmed a neurogenic neoplasm (schwannoma).

OUTLOOK FOR THE FUTURE

This chapter provides a modern, evidence-based overview of the wide scope and central role imaging plays in the diagnosis and management of thoracic diseases. Currently, it is inconceivable to imagine practicing thoracic medicine and surgery without the constant support of radiologist consultants and their armamentarium of basic and advanced imaging modalities.

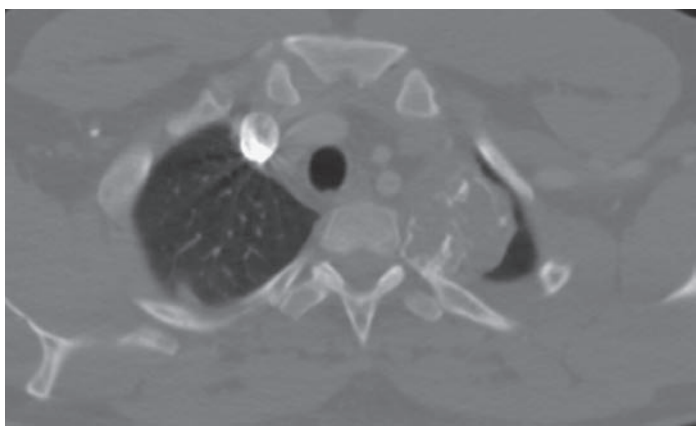
Predicting the long-term future is most often a futile endeavor. However, there are clear trends that allow us to attempt to forecast likely innovations and changes in the field of thoracic imaging over the next decade.

The most important trend is demonstrating that imaging-based diagnostic and therapeutic approaches are beneficial to patient care, improving morbidity and mortality, and decreasing the overall cost of care. This trend is imposed by the current global economic environment and the mandate to increase the efficiency of healthcare systems by diminishing waste and redundancy and eliminating procedures that do not positively impact patient outcomes. Future clinical trials will emphasize what imaging can offer to empower practitioners to diagnose thoracic diseases earlier, faster, and in a less invasive manner. In addition, studies will address delivery of therapeutic approaches that will be more effective and less costly and contribute to better patient outcomes and quality of life.

Another important trend is combining functional and anatomical information within a single imaging modality. PET/CT already offers this capability by coupling anatomic and metabolic imaging. MR and CT, when performed with 4D cine sequences, may provide insight into chest wall, central airway, and lung mechanics, as well as detect air trapping related to small airway disease. MR performed with specific pulse sequences may provide surrogates of tissue characterization. Thoracic oncology will greatly benefit from new molecular imaging agents that target important cellular and subcellular biochemical pathways associated with carcinogenesis. Furthermore, molecular imaging will allow in vivo real-time assessment of the genetic and epigenetic processes underlying a number of pathologic conditions in the heart, lungs, and mediastinum, leading to more targeted, individualized, and, ultimately, more effective therapeutics.

Quantitative imaging will be another trend, which will aim to provide a much better assessment of disease severity, particularly for diffuse lung diseases, such as COPD and ILD. Instead of simply reporting the presence of a specific disease and, at most, subjectively classifying the severity of the disease, radiologists will utilize computational image analysis tools to provide accurate disease quantification that reflects, and highly correlates with, physiologic metrics. Quantitative imaging utilizing computer-assisted detection and quantification of disease-specific imaging patterns on CT, MR, and PET/CT will, therefore, allow development of biomarkers that will reflect disease prognosis and response to therapies far more accurately and earlier then currently possible. Future drug trials will particularly benefit from this approach.

More distant on the horizon is computer-assisted diagnosis utilizing pattern recognition and classification. Its development will allow radiologists and clinicians to improve diagnostic accuracy, particularly in complex diffuse diseases or in the setting of coexisting diseases.



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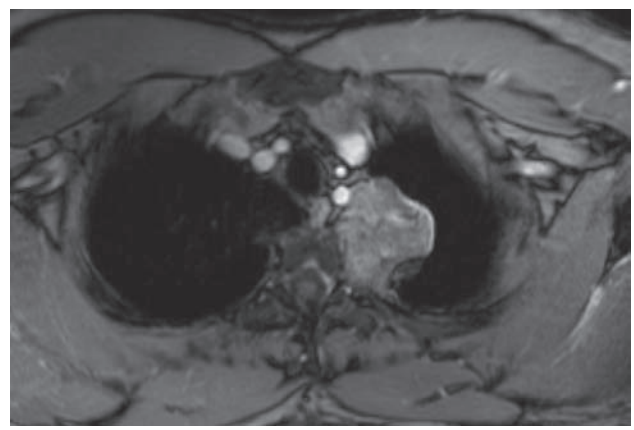

B

Figure 30-69 Posterior mediastinal mass. **A.** Axial noncontrast CT demonstrates a large left posterior mediastinal mass that appears to arise from the left posterior second rib, which demonstrates expansion and cortical destruction. Note irregular calcifications within the mass. **B.** Axial T1-weighted postcontrast MR shows moderate enhancement throughout the lesion. The constellation of findings suggests a primary bone neoplasm with chondroid differentiation. Pathology confirmed a chondrosarcoma.

Finally, it is of interest to consider what role plain chest radiography will play in the future, if any. Practical and economic considerations imply that chest radiographs will not disappear soon, given their low cost, very low radiation dose, universal availability, portability, and capacity to address basic clinical questions. Nevertheless, we hypothesize that this century-old technique will not last another century; rather, it will be replaced in the next decades by newer generations of CT scanners that will offer similar qualities of portability and ultralow radiation dose, along with vastly improved diagnostic accuracy and 4D capabilities.

Irrespective of the many uncertainties, challenges, and exciting prospects for the future, it is undeniable that thoracic imaging will continue to be an indispensable companion to the practicing physician caring for patients with thoracic disorders and a central component of modern pulmonary medicine.

ACKNOWLEDGMENT

The authors dedicate this chapter to the memory of the late Wallace Miller, Sr., MD, who authored the previous version. Dr. Miller was an enlightening presence and a major source of inspiration to generations of thoracic radiologists and pulmonologists.

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CHAPTER 31

Thoracic Ultrasonography

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Paul H. Mayo

INTRODUCTION

Thoracic ultrasonography is a readily available, noninvasive imaging method that has proved particularly useful for pulmonary and critical care specialists. The technique is easy to learn and engenders multiple applications related to lung and pleural disease. The ease of use and portability of ultrasonography allows physicians to perform point-of-care imaging and reduce dependence on traditional thoracic imaging techniques, such as chest computerized tomography (CT) and standard radiography (CXR).

This chapter focuses on use of ultrasonography for diagnosis and management of pleural and lung diseases and emphasizes those areas that are of particular interest to the pulmonary specialist. Many elements of thoracic ultrasonography that have utility for the pulmonary consultant are also germane to critical care medicine. However, this chapter focuses on the broad context of pulmonary medicine, rather than the elements of thoracic ultrasonography that are specific to critical care. Furthermore, the chapter is written with the assumption that the pulmonary consultant will personally perform image acquisition, interpret the image, and apply results at the bedside—a paradigm that is different from the standard one of thoracic imaging requiring reliance on a radiologist's acquisition and interpretation of the image. While this approach is advantageous with regard to cost and clinical efficiency, it requires technical and cognitive skills. An additional advantage of clinician-performed, point-of-care thoracic ultrasonography is that it couples imaging results with the clinician's overall knowledge of the case. Indeed, thoracic ultrasonography is not performed in vacuo, rather, it is always combined with other key elements of clinical evaluation, such as the history, physical examination, and laboratory analysis. Ultrasonography is an *additional* tool in the diagnosis and management of pleuropulmonary disease.

TRAINING IN THORACIC ULTRASONOGRAPHY

The goal of training in thoracic ultrasonography is, of course, to enable clinical competence in performing the procedure. "Competence" must be defined to facilitate development of specific learning objectives as the goals of training. One pragmatic approach is to establish a reasonable minimum standard for competence. The Statement of Critical Care Ultrasonography provides a well-defined description of training goals in pleural and lung ultrasonography.[1] The statement is a good starting point for pulmonary specialists who seek training in the field, and the competencies outlined should constitute the initial learning objectives.

No definitive literature is available to guide the optimal duration of training or the minimal number of studies to be performed and interpreted. No widely accepted course of study for the cognitive elements of the field exists, and, at present there is no formal certification process.

Despite these limitations, many clinicians are competent in thoracic ultrasonography. Compared with the training required in the complex fields of cardiac and abdominal ultrasonography, training in thoracic ultrasonography is straightforward. The authors have considerable experience in training many fellows and attending physicians in thoracic ultrasonography and have found that a motivated learner will achieve skill in the basic elements of pleural and lung ultrasonography within several hours of formal teaching. Training should include practicing image acquisition, initially on normal human models and then on patients at the bedside. In addition, training should include a review of a comprehensive image set of normal and abnormal findings, enabling the learner to recognize a wide range of findings during their initial encounter at the bedside. The cognitive elements of the field may be learned through reading chapters or review articles.[2–4] For more advanced training, comprehensive textbooks are available.[5,6] Formal courses on thoracic ultrasonography are offered. In addition, the learner may choose to develop a local training resource, which requires identification of a local expert who is able to help with bedside training.

EQUIPMENT NEEDS

Thoracic ultrasonography may be performed using a wide variety of ultrasound machines. Virtually any machine that is used for or cardiac or abdominal ultrasonography will generally yield adequate image quality. A probe designed for cardiac ultrasonography, employing a frequency range of 3.5 to 5.0 MHz works well, as the small footprint of the probe allows for easy placement between rib interspaces; frequency selection allows for adequate penetration to enable imaging the deeper structures of the thorax. A larger, curvilinear abdominal probe gives serviceable images as well. A linear vascular probe using a frequency range of 7.5 to 10.0 MHz is required for detailed imaging of the pleural surface; the higher frequency improves the resolution, but at the sacrifice of signal penetration.

Every machine has its own design characteristics, so that the operator must adapt machine setup to optimize image quality. What works well using one machine may not translate into the same effectiveness when using another. Some machines have presets for thoracic ultrasonography, but they may not necessarily be the optimal setup for thoracic imaging. Consequently, the operator must be prepared to alter machine settings from standard cardiac, abdominal, or thoracic presets. Machines from the 1990s that lack extensive postimage processing often give excellent results. Modern, high-end cardiac echocardiography machines give excellent cardiac image quality, but they often yield poor near-field images. Many modern portable machines have acceptable thoracic imaging capability and provide the additional advantage that they are designed specifically for point-of-care scanning.

SCANNING TECHNIQUE

For the pulmonary specialist, thoracic ultrasonography may be performed with the patient in a seated position. The supine scanning position is more typical for the critically ill patient, but it has the disadvantage that it is difficult to scan the posterior chest. The standard transducer orientation is the transducer indicator oriented in a cephalad position, defining the primary scanning plane in a longitudinal axis. With the screen indicator placed to the left of the screen, images on the left side of the screen represent cephalad structures.

Machine control is integral to good quality image acquisition; hence, total, near, and far field gains must be adjusted for optimization. Depth should be set to place the target structure in the middle of the screen, and the focal point should be adjusted for optimal image quality of the target structure. Using adequate ultrasound coupling gel and application of firm pressure, the transducer is applied perpendicular to the chest wall and adjusted

to examine the rib interspace. Adjacent interspaces are examined by sliding the transducer to the next interspace. In this way, the examiner performs a scan line while the transducer is moved over the chest wall. In an orderly fashion, multiple adjacent scan lines are performed so that the entire chest wall can be imaged. Using this approach, the examiner obtains multiple, two-dimensional, tomographic ultrasound planes of the thorax, in effect, developing a three-dimensional model. If a focal abnormality is identified, the examiner may then perform a more detailed ultrasonographic examination of the area.

Aerated lung blocks ultrasound, whereas the liver and spleen do not. Consequently, to visualize the peridiaphragmatic area, the transducer may be angled such that the scanning plane passes through the liver or spleen to obtain an adequate image window. In addition, bone also blocks ultrasound. So, when an abnormality lies deep to a rib, the transducer may need to be angled to look over or under the rib. Conversely, pleural effusion and consolidated lung each transmit ultrasound. Their presence may yield a window for examination of the heart, mediastinum, or, in the case of pleural effusion, the lung. While the standard scanning plane is longitudinal, a transverse plane may be utilized on occasion. This may be required when examining for a "lung point" or to establish an optimal angle for needle insertion for access to a lung mass. Most thoracic ultrasonography is performed using a cardiac or abdominal transducer. A vascular transducer is preferred if detailed examination of pleural anatomy is required.

PLEURAL ULTRASONOGRAPHY

Ultrasonography is particularly effective for identifying pleural fluid, since fluid is either anechoic or hypoechoic relative to adjacent soft tissue. While physical examination is neither specific nor sensitive for detection of pleural effusion,[7] a pleural effusion as small as 5 cc may be identified with ultrasonography.[8] Pleural ultrasonography is superior to standard chest radiography in identifying pleural effusions and in differentiating a pleural effusion from pleural thickening or atelectasis.[7,9] Compared with chest CT, pleural ultrasound demonstrates 93% sensitivity and specificity for identification of pleural effusion.[10] When a patient has complete hemithoracic opacification on CXR, ultrasound has 95% sensitivity for identification of pleural effusion.[9]

IDENTIFICATION OF PLEURAL FLUID

The pulmonary specialist will generally examine the patient in the seated position. Pleural fluid, unless loculated, distributes by gravitational effect to the most dependent part of the thorax. Therefore, the ultrasonography examination focuses on the lower, dependent area of the posterior thorax.

The examiner seeks to identify three characteristic findings indicating the presence of a pleural effusion: (1) An anechoic or hypoechoic space that is surrounded by typical anatomic boundaries. This space represents the pleural effusion. Diagnosis requires definitive identification of a relatively echo-free space surrounded by the typical anatomic boundaries (Fig. 31-1; Video 31-1). (2) Typical anatomic boundaries. This element requires definitive identification of the chest wall, lung surface, and diaphragm. The heart may form an anatomic boundary on the left side. Recognition of the diaphragm requires definitive identification of the subdiaphragmatic organs (including liver, spleen, and kidneys) (Fig. 31-2; Video 31-2). (3) Dynamic changes typical of a pleural effusion, as described later) (Video 31-3).

Usually, pleural fluid is hypoechoic relative to the liver or spleen. However, complex pleural effusions may demonstrate echogenicity similar to these organs. The chest wall, as a "stationary" structure, does not show dynamic changes with respiration. Lung that is adjacent to, or surrounded by, pleural fluid is compressed by the pleural effusion and, consequently, is airless. The atelectatic lung, which is of tissue density and presents a pattern of alveolar consolidation on ultrasonography examination, is visualized as "floating" in the pleural fluid. It moves in both cardiac- and respiratory-phasic fashion—one of the typical dynamic changes required for identification of pleural effusion. Other typical dynamic changes include those of swirling debris or fibrin strands agitated by respiratory

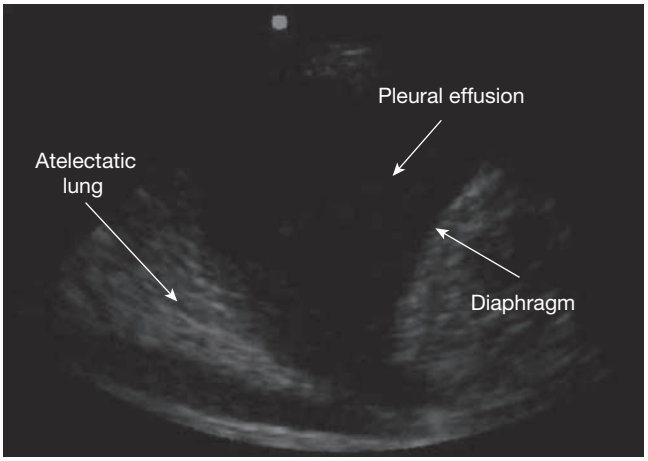

Figure 31-1 Typical anatomic boundaries that surround a hypoechoic pleural effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the seventh intercostal space in the right midaxillary line.

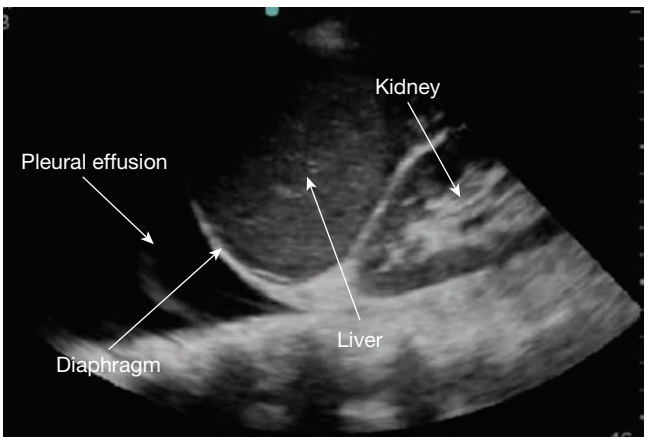

Figure 31-2 Pleural effusion above the diaphragm, liver, hepatorenal space, and kidney. These structures must be positively identified before thoracentesis to avoid inadvertent subdiaphragmatic device insertion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the eighth intercostal space in the right midaxillary line.

Video 31-1 Typical anatomic boundaries that surround a hypoechoic pleural effusion: chest wall, surface of lung, and diaphragm. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the seventh intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

Video 31-2 Pleural effusion above the diaphragm, liver, hepatorenal space, and kidney. These structures must be positively identified before thoracentesis to avoid inadvertent subdiaphragmatic device insertion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the eighth intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

or cardiac motion. On occasion, a highly cellular pleural effusion forms a layer because of gravitational effects if the patient is immobile for a period of time; patient movement disrupts the fluid-to-cell interface.

Identification of the diaphragm is imperative for localizing a pleural effusion and enabling safe performance of thoracentesis. Subdiaphragmatic device insertion is a serious complication of thoracentesis.

The diaphragm is a curvilinear structure lying above the spleen and liver, which demonstrates respirophasic movement. The inexperienced operator may mistake the hepatorenal or splenorenal space for the diaphragm, as they appear as curvilinear structures that resemble the diaphragm. The overlying spleen or liver may then be mistaken for an echo-dense pleural effusion. This may result in inadvertent subdiaphragmatic device insertion while attempting a thoracentesis with potentially catastrophic consequence to the patient (Fig. 31-2; Video 31-2). It is helpful to identify the kidney when scanning below the diaphragm to avoid this dangerous pitfall. Identification of the chest wall allows measurement of the depth required for needle penetration when planning thoracentesis. Identification of the underlying lung allows the operator to limit the depth of needle insertion to avoid visceral pleural laceration.

■ CHARACTERIZATION OF THE PLEURAL EFFUSION

Ultrasound examination can be helpful in distinguishing transudative from exudative effusions. Transudates lack constituents that are ultrasound reflectors and are, therefore, echo-free (anechoic) (Fig. 31-3; Video 31-4). An anechoic pleural effusion is very likely to be transudative, although some may have a complex, nonseptated pattern.[11] Slow flowing movement of ill-defined heterogeneous elements within a hypoechoic effusion, referred to as swirling, may be observed with a transudate, but its presence suggests an exudative cellular effusion, such as that associated with malignancy.[12]

A heterogeneously echogenic pattern, with swirling echoes, septations, fronds, or strands is typically observed with exudates. However, very cellular exudates, such as empyema or hemothorax, may demonstrate homogeneous echogenicity (Fig. 31-4; Video 31-5).[13] Exudates are usually echogenic, but are occasionally anechoic. The presence of strands, debris, or septations is characteristic of a parapneumonic effusion or empyema.[14]

The presence of a septated effusion on ultrasonography suggests the need for fibrinolytic therapy or surgical intervention, prolonged chest tube drainage, and longer hospital stay when compared with

Video 31-3 Dynamic findings typical of a pleural effusion, including movement of atelectatic lung, movement of the diaphragm, and movement of echogenic elements within the effusion (plankton sign). The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

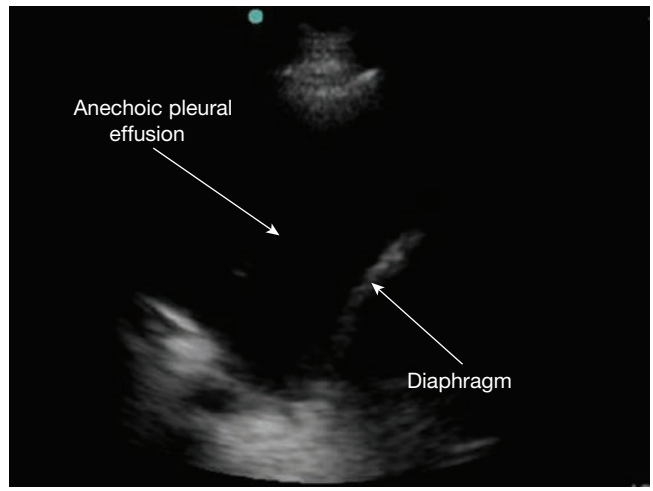

Figure 31-3 Anechoic pleural effusion, likely a transudate. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

effusions lacking ultrasound complexity (Fig. 31-5; Video 31-6).[15] Pleural ultrasound is superior to CT scanning in detecting pleural fluid complexity.[16]

By making a number of defined measurements, the volume of a pleural effusion may be reasonably estimated using ultrasonography.[17] For clinical purposes, it generally suffices to characterize the effusion as small, moderate, or large. Finally, pleural effusions may become loculated collections, which characteristically develop in nondependent positions and fail to move with changes in body position. The loculum may be thick-walled and often has internal hyperechoic complexity.

■ PERFORMANCE OF THORACENTESIS

Pleural ultrasonography facilitates performance of thoracentesis. When compared with physical examination combined with standard chest radiography, ultrasonography is superior in identifying a safe site for needle insertion.[7] A meta-analysis supports the use of ultrasonography to guide thoracentesis to reduce the risk of pneumothorax.[18] As needle insertion is required not only for simple thoracentesis, but also for a wide variety of pleural procedures requiring use of guidewires and device placement, pleural ultrasonography is an essential component of interventional practice.

Thoracic ultrasonography allows for identification of a safe site, depth, and angle for needle insertion. Using the technique of scan lines described previously, the operator identifies the pleural effusion and establishes the best site and trajectory for needle insertion and, hopefully, avoiding any injury to structures that surround the fluid collection. The site is marked by indenting the skin with a needle cap. Just prior to sterile skin preparation, the operator rescans to confirm site selection, depth of needle penetration required,

Video 31-4 Anechoic pleural effusion, likely a transudate. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

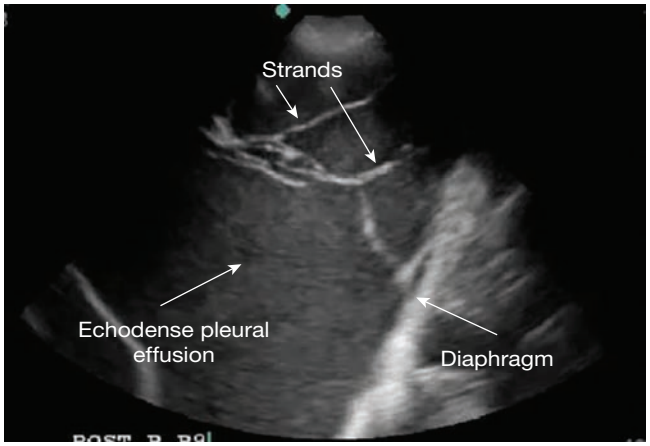

Figure 31-4 Pleural effusion with a homogeneously echogenic pattern and mobile strands suggestive of an exudate. Thoracentesis showed a hemothorax. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

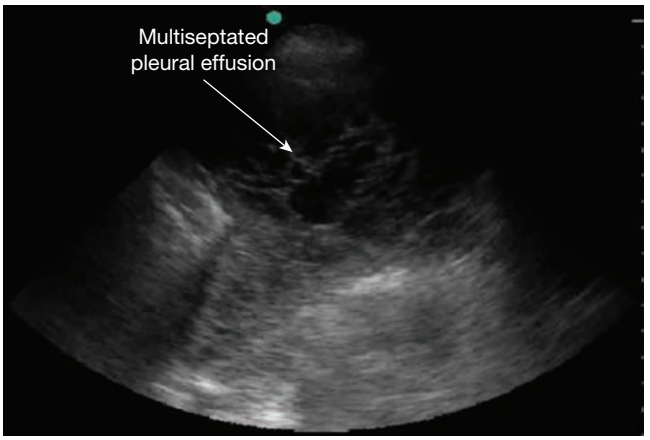

Figure 31-5 Multiseptated pleural effusion. The pattern is consistent with a complex parapneumonic effusion or empyema that will likely require fibrinolytic treatment or surgical drainage. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fourth intercostal space in the left midaxillary line.

and the angle of insertion. The procedure is then performed using an angle of insertion of the needle and syringe assembly that duplicates the angle of the transducer employed at the time of the final scan. No patient movement is permitted between the final scan and needle insertion, as this may cause movement of the fluid within the thorax.

For the pulmonary specialist, thoracentesis is usually performed with the patient in the seated position. For more complex procedures requiring tunneling of a catheter or chest tube insertion, the patient may be supine or in lateral decubitus position. Using the same scan line technique as utilized for the upright patient, the operator identifies the pleural effusion based on the previously described ultrasound criteria; once again, the site, angle, and depth for safe needle insertion are determined. Immediately before final skin preparation, the operator rescans to confirm that it is a safe site for device insertion and, without patient movement, proceeds with device insertion.

While ultrasonography facilitates pleural access, pitfalls exist. Although pneumothorax is a rare occurrence with ultrasound-assisted thoracentesis, the operator should always check for pneumothorax before and after the procedure by examining the anterior chest for lung sliding (see Lung Ultrasonography). The presence of sliding lung rules out pneumothorax. The most common cause of pneumothorax following ultrasound-assisted thoracentesis is the presence of nonexpandable lung, rather than visceral pleural laceration.[19]

In selecting a site, the operator needs to be aware that the lung may move in a respirophasic fashion. Safe site selection is predicated on the absence of intermittent respirophasic movement of lung into the needle path. When such movement is observed, constituting the so-called "curtain sign," needle insertion is contraindicated at that point.

In performing ultrasound-assisted thoracentesis, several causes may account for failure of fluid return, despite good site selection.

In edematous or obese patients, the operator may press the probe into the skin surface with some force, causing a compression artifact. As the measurement for depth of needle penetration is made when the skin is indented by the probe, if the skin has rebounded, the distance of needle penetration required may be greater than that predicted during initial measurement.

In performing the procedure in patients who lack subcutaneous tissue, the operator may place tension on the skin at the time of mark placement, displacing the skin from the underlying soft tissue. When the tension is released, the mark may rebound to a new position on the chest wall that is not optimal for needle insertion.

While it is not necessary to use real-time needle guidance in performing ultrasound-assisted thoracentesis, failure of needle insertion to yield fluid may warrant rescanning to confirm appropriate site selection. Occasionally, a "dry" tap results from tissue impaction in the needle during insertion or as a result of septations occluding the needle.

PLEURAL PATHOLOGY

In addition to identification of pleural fluid, ultrasonography allows visualization of a variety of pleural pathologies.

A number of pleural diseases cause echogenic abnormalities within the pleural space. Some of these solid pleural abnormalities may coexist with pleural effusions. For example, metastatic pleural disease often occurs with a coexisting pleural effusion, such that the pleural effusion acts as an acoustic window that allows ready observation of the metastatic disease. Metastatic tumors are usually hyperechoic and are often multiple (Fig. 31-6; Video 31-7). They may demonstrate a variety of different sizes and shapes, such as nodular, hemispheric, or circular. The tumors may be broad-based

Video 31-5 Pleural effusion with homogeneous echogenic pattern and mobile strands, suggestive of an exudate. Thoracentesis showed a hemothorax. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

Video 31-6 Multiseptated pleural effusion. This pattern is consistent with a complex parapneumonic effusion or empyema that will likely require fibrinolytic treatment or surgical drainage. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fourth intercostal space in the left midaxillary line. *Access at www.fishmansonline.com*

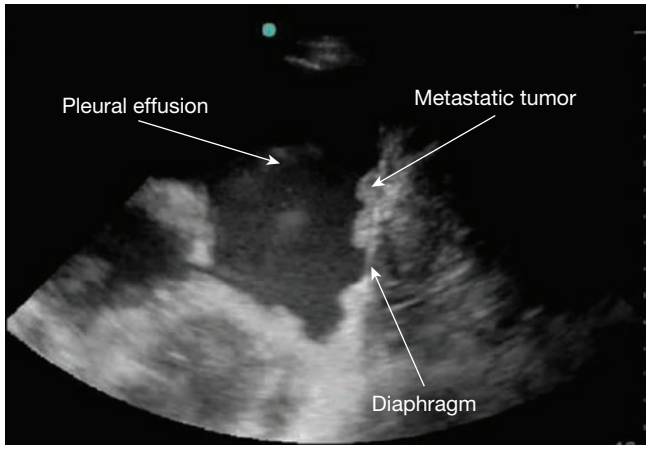

Figure 31-6 Pleural effusion with pleural masses on the diaphragm caused by metastatic breast cancer in the pleural space. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the left midaxillary line.

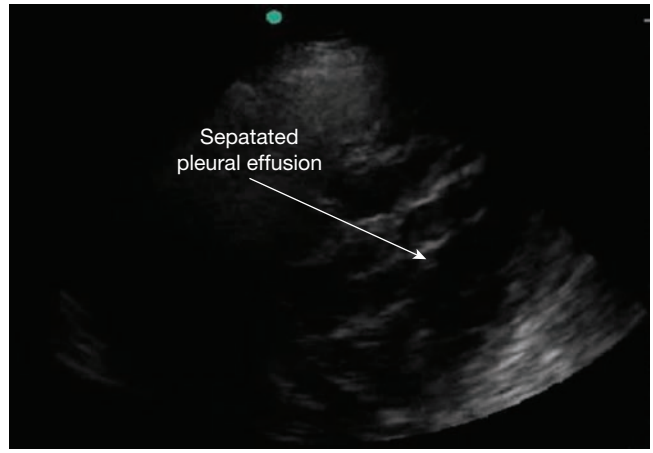

Figure 31-7 Complex, multiloculated pleural effusion with thick septations caused by an empyema. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

or have frond-like protrusions. Chest wall or diaphragmatic invasion may cause disruption of normal tissue interfaces and direct extension of tumor into adjacent structures, each of which is visible with ultrasonography. Ultrasonography is superior to chest CT for the diagnosis of transpleural chest wall invasion.[20]

Benign pleural tumors, such as benign mesothelioma, chondroma, lipoma, or thoracic sclerosis are very uncommonly found during pleural ultrasonography. They are usually hyperechoic, have a distinct capsule, and do not demonstrate invasion through adjacent tissue planes. Ultrasonographic morphology is not sufficiently diagnostic, but the technique may be used to guide biopsy.

Primary pleural malignancy, such as malignant mesothelioma, has ultrasonographic features that include pleural thickening with unclear and irregular borders, nodularity, and evidence of chest wall or diaphragmatic invasion.

Inflammatory diseases that involve the pleural space are characteristically caused by infection. Both parietal and visceral pleurae are thickened and hyperechoic, while the underlying lung may demonstrate an alveolar consolidation pattern. Within the pleural fluid collection, linear mobile echogenic elements float freely. Over time, the elements may thicken and divide the effusion into multiple fluid-filled cavities that have variable echogenicity. Eventually, the infected space becomes a multiseptated conglomerate of thick-walled cavities (Fig. 31-7; Video 31-8). A homogeneously echogenic empyema may be so dense that no dynamic findings are discernible within the pleural collection. This makes differentiation from the underlying liver or spleen difficult and may even complicate delineation of the diaphragm, which is a key element in identifying a safe site for device insertion.

Pleural fibrosis shows variable echogenicity, so it may be difficult to differentiate fibrosis from an adjacent pleural effusion. Color-flow Doppler is helpful in distinguishing between the two.[21] Color-flow Doppler signals are generally absent from areas of fibrosis but are present in pleural effusions due to small ultrasound reflectors moving within the fluid.

LUNG ULTRASONOGRAPHY

Lung ultrasonography is performed using the same equipment and scanning techniques as used for pleural ultrasonography. As with pleural ultrasonography, the results are immediately available for integration into the standard tools of patient evaluation, including the history, physical examination, and laboratory analysis. Lung ultrasonography is designed to be used in a goal-directed fashion at the point of care.

In a series of landmark articles, Daniel Lichtenstein described and validated the important elements of the field of lung ultrasonography, the clinical utility of which is now supported by a growing literature. The following discussion is based on Lichtenstein's terminology.[5]

■ BASIC FINDINGS OF LUNG ULTRASONOGRAPHY

Several basic findings are central to the diagnostic application of ultrasonography to lung diseases. These include lung sliding, lung pulse, A lines, B lines, and consolidation. Each is discussed in subsequent sections.

Lung Sliding

When the transducer is placed perpendicular to the chest wall and orientated to enable imaging through rib interspaces, the pleural line is visualized approximately 5 mm deep to the rib periosteum. Normally, examination of the pleural line demonstrates a shimmering to-and-fro movement that is respirophasic—the so called "lung sliding," which is caused by movement of the visceral pleura against the parietal pleura during breathing (Fig. 31-8; Video 31-9).

The presence of lung sliding indicates that, at that point of examination, no pneumothorax is present; that is, the lung is fully

Video 31-7 Pleural effusion with pleural masses on the diaphragm. The patient had metastatic breast cancer in the pleural space. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left midaxillary line. *Access at www.fishmansonline.com*

Video 31-8 Complex multiloculated pleural effusion with thick septations caused by an empyema. The transducer was in longitudinal orientation and placed perpendicular to the chest wall. The examiner moved the transducer over several intercostal spaces to show the extent of the fluid collection. The scan line is in right midaxillary line. *Access at www.fishmansonline.com*

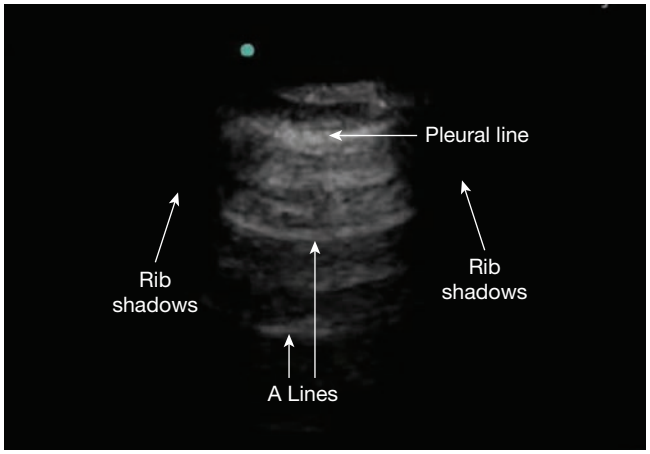

Figure 31-8 Pleural line, A lines, and adjacent rib shadows. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line.

inflated against the inside of the chest wall.[22] Lung sliding can be detected rapidly over the anterior upper chest by moving the probe over multiple interspaces. Since a loculated pneumothorax is very uncommon, in the supine or upright patient, examination of several anterior interspaces suffices to rule out pneumothorax. Free air in the pleural space rises to the nondependent part of the thorax, unlike fluid, which gravitates to the dependent position. Lung sliding is generally more prominent at the base of the lung as a result of the effect of diaphragmatic movement on lung inflation; lung sliding may be more difficult to detect at the lung apex. To optimize visualization of lung sliding, the ultrasound machine gain should be decreased and depth adjusted to place the pleural line in center of the screen.

A finding related to lung sliding is lung pulse. If a normal subject suspends respiration, lung sliding is temporarily absent; however, cardiophasic movement of the pleural line continues due to the lung movement that derives from transmission of cardiac contraction. The finding of lung pulse has the same implication as lung sliding; when noted, there is no pneumothorax at the site of the examination.

While lung sliding and lung pulse, when present, rule out pneumothorax, their absence is less helpful (Video 31-10). The absence of lung sliding indicates the *possibility* of pneumothorax. Other causes for absence of lung sliding include pleurodesis, apnea, mainstem bronchial obstruction, giant lung bullae, and severe parenchymal lung disease. The absence of lung sliding should be correlated with the clinical context. For example, if a patient demonstrates lung sliding before an ipsilateral thoracentesis or central-line insertion, the absence of lung sliding following the procedure suggests a very high probability of a procedure-related pneumothorax. On the other hand, the patient who has had prior chemical pleurodesis will lack lung sliding upon initial ultrasonographic evaluation.

While the absence of lung sliding is only indicative of the possibility of pneumothorax, it is still feasible to diagnose the disorder using lung ultrasonography, based on identification of a so-called "lung point."[23]

Most pneumothoraces result in only partial collapse of the affected lung; hence, the partially deflated lung is, at some point, still apposed to the chest wall. Under these circumstances, when the transducer is placed into an anterior interspace, no lung sliding will be noted, as the lung is not inflated against the inside of the chest wall. More laterally, lung sliding may become apparent if there is partial collapse of the lung. At the interface between the aerated lung and the pneumothorax space, the lung will be seen to enter the scanning plane in respirophasic manner (Video 31-11). This interface is called the *lung point*. Identification of a lung point is diagnostic of pneumothorax and allows for an estimate of pneumothorax size. While a lung point is 100% specific for pneumothorax, its sensitivity depends on the skill of the examiner; furthermore, a very large pneumothorax will not have a lung point. High-frequency vascular probes are useful in examining for lung point.

A Lines

Once the pleural line has been examined, the depth setting on the machine is increased to examine deeper structures within the thorax. The normal lung reveals *A lines,* which are one or more horizontally orientated lines visible deep to the pleural line (Fig. 31-8; Video 31-9). When multiple, they are equidistant; their separation distance corresponds to the distance between the chest wall and pleural line. A lines are reverberations of the pleural line caused by echoes reflecting off the air just deep to the pleural line, which then reflect off of the probe face. When this reflection returns to the probe, it appears on the screen as an ultrasound interface similar to the pleural line, but twice as far away. A lines may be single or multiple, but they are always separated by the same distance. In the presence of sliding lung, A lines indicate normally aerated lung. When present without lung sliding, they suggest the possibility of a pneumothorax. A lines correlate with a normal aeration pattern seen on a CT scan.[24]

B Lines

Using standard scanning technique and a depth set to visualize deeper structures, B lines may be observed instead of A lines. B lines have several distinct characteristics: (1) They are vertical in orientation; (2) one or more per field may be seen; (3) they extend to bottom of the device screen; (4) they originate at the pleural interface; (5) they move with the pleural interface (if it is mobile); and (6) they efface A lines where A lines and B lines intersect (Fig. 31-9; Video 31-12). The presence of B lines correlates with an interstitial

Video 31-9 This video demonstrates the presence of lung sliding. The image is obtained using a 7.5-MHz vascular transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line. The resolution of the 7.5-MHz transducer is superior to that of the 3.5-MHz transducer at the expense of reduced penetration (See also Video 78-1). *Access at www.fishmansonline.com*

Video 31-10 Absence of lung sliding. The image was obtained using a 7.5-MHz vascular transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line. The resolution of the 7.5-MHz transducer is superior to that of the 3.5-MHz transducer, although depth of penetration is reduced (See also Video 78-2). *Access at www.fishmansonline.com*

Video 31-11 Lung point. A pneumothorax has caused partial deflation of the lung. Respirophasic movement of the partially deflated lung into the pneumothorax space is seen. The image was obtained using a 7.5-MHz vascular transducer. The transducer was in transverse orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the right anterior axillary line (See also Video 78-4). *Access at www.fishmansonline.com*

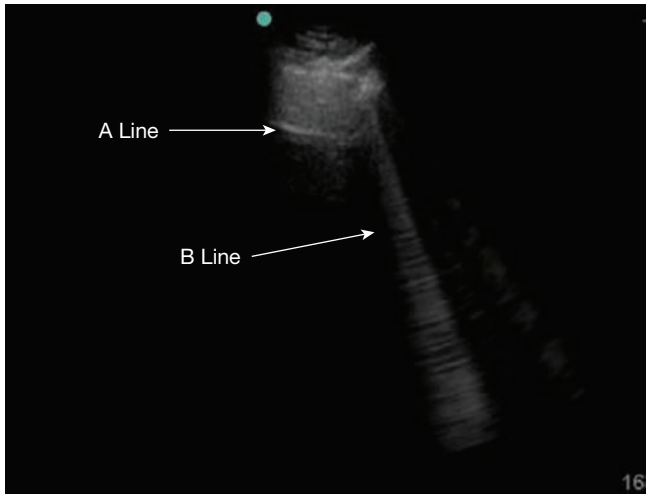

Figure 31-9 B lines. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line.

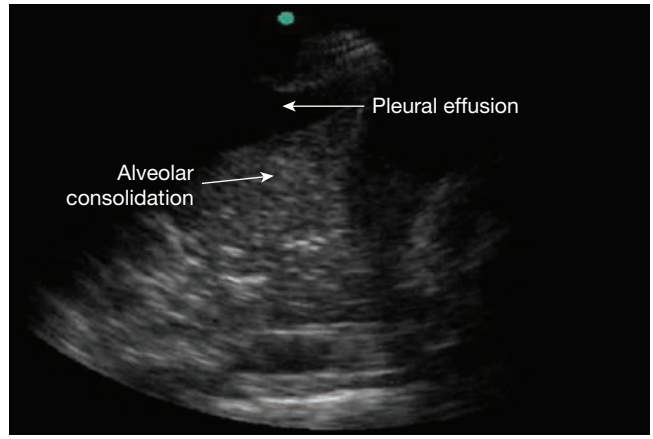

Figure 31-10 Alveolar consolidation of the left lower lobe and pleural effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left posterior axillary line.

pattern or alveolar abnormalities noted on CT scanning (reticular pattern or ground glass abnormality).[25]

B lines result from of any interstitial infiltrative process, such as inflammation, neoplasm, fibrosis, or edema.[26–30] B lines may be focal, scattered, or profuse in distribution, based on the underlying disease process. Disorders associated with a granular pattern on standard chest radiography or with ground glass opacification on chest CT are associated with B lines.

As with any radiographic abnormality, clinical correlation is required to determine the cause of B lines. For example, normal individuals often have one or two inconsequential B lines on examination of the lateral lower rib interspaces. More than two B lines in a single field is considered significant. Pneumonia may be manifest with focal B lines detected over the involved lobe or segment. Pulmonary fibrosis results in scattered B lines, whereas cardiogenic pulmonary edema yields profuse bilateral B lines. Pleural morphology may be useful in distinguishing B lines related to elevation of left atrial pressure from those caused by a primary lung process. Typically, the B lines noted in cardiogenic pulmonary edema are associated with a smooth pleural surface, while those seen in primary lung injury manifest an irregular pleural surface.[30] As B lines originate from the area of the visceral pleura, their presence rules out pneumothorax.

Consolidation

Consolidated lung is manifest as tissue density on ultrasound.[31] Its echogenicity is similar to that of the liver (sonographic hepatization of lung) (Fig. 31-10; Video 31-13). Consolidation may be localized to a specific lobe or segment of the lung and may also be observed in the lung periphery as a subpleural consolidation pattern. Within the consolidated lung, punctate, hyperechoic foci are often visible. These foci represent air retained within the bronchi. If they move in respirophasic manner, the finding indicates patency of the bronchus supplying that portion of the lung (Video 31-14).[32] Demonstration of consolidation on lung ultrasonography correlates strongly with results of chest CT scanning.[25]

As with chest radiography and CT scanning, the finding of alveolar consolidation on lung ultrasonography is not diagnostic. While pneumonia may result in alveolar consolidation, so will atelectasis (compressive, resorptive, or cicatricial). Severe pulmonary edema, with complete filling of the alveolar compartment, and infiltrative processes, such as tumor, may result in the ultrasonographic finding of lung consolidation. While lung ultrasonography identifies consolidation, the pulmonary specialist determines its cause.

■ ADVANCED LUNG ULTRASONOGRAPHY

A wide variety of additional lung ultrasound findings have been described. Mastery of the basic findings is the first step of training for the pulmonary specialist. The reader is referred to standard texts for a complete review of the subject.[5]

■ LIMITATIONS OF LUNG ULTRASONOGRAPHY

Any disease process resulting in focal abnormality surrounded by aerated lung, for example, a solitary pulmonary nodule with normal surrounding lung, will not be visible with ultrasonography. Similarly, mediastinal structures are not visible using surface ultrasonography unless there is a convenient acoustic window related to lung consolidation or pleural effusion.

Documentation of the results of lung ultrasonography is challenging compared with CXR and chest CT scanning, in which results can be stored indefinitely in a durable format and serial studies compared. While a written report of lung ultrasonography is important and can be generated in a durable format, comparison of serial studies is difficult.

Video 31-12 B lines. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line (See also Video 78-5). *Access at www.fishmansonline.com*

Video 31-13 Alveolar consolidation of the left lower lobe and pleural effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left posterior axillary line. *Access at www.fishmansonline.com*

Video 31-14 Mobile air bronchograms in an area of alveolar consolidation. The gain was turned down to bring out the punctate hyperechoic mobile foci that have respirophasic movement. The foci represent air within the bronchi surrounded by alveolar consolidation. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Access at www.fishmansonline.com*

CLINICAL APPLICATIONS

With development of high-quality, portable ultrasound machines, it is now feasible to integrate lung ultrasonography into both hospital- and office-based pulmonary practice. Ultrasonography will never completely replace CXR or chest CT, and it should be viewed as a complementary imaging modality. Its utility has been well characterized for critical care applications, and it is being increasingly utilized in pulmonary medicine.

PROCEDURES

In addition to its utility in performing pleural procedures, ultrasonography may be used to guide other transthoracic interventions. For example, thoracic ultrasonography is useful in localizing masses abutting the pleural surface. As noted previously, although a lung mass that is entirely surrounded by aerated lung is not visible with ultrasonography, if part of the mass abuts the pleural surface, it may be visualized, and its size and pattern of echogenicity characterized (Fig. 31-11; Video 31-15). While lung ultrasonography has limited utility in establishing etiology of masses, localization of the abnormality and delineation of a safe path for needle insertion may be helpful. Furthermore, ultrasonography may be used as an alternative to CT to guide transthoracic needle insertion.[33]

Pneumothorax is a complication of a variety of pulmonary procedures, including bronchoscopy, thoracentesis, and transthoracic needle insertion. Ultrasonography is superior to CXR in the detection of pneumothorax and can be used in place of radiography for postprocedure evaluation.[34,35]

Following pleural drain insertion, ultrasound may be useful in determining whether the lung is expanded. In addition, ultrasound may assist in determination of when to remove the chest drain following tube clamping and may be used to rapidly ascertain whether there is continued leakage of air into the pleural space.[36]

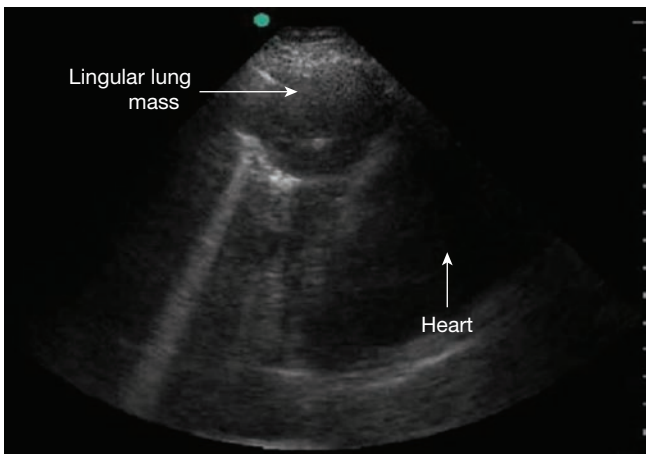

Figure 31-11 Lingular lung mass adjacent to the chest wall and heart. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the left anterior axillary line.

Video 31-15 Lingular lung mass adjacent to the chest wall and heart. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the left anterior axillary line. *Access at www.fishmansonline.com*

ASSESSMENT OF DIAPHRAGMATIC FUNCTION

Thoracic ultrasonography is useful in assessing diaphragmatic function.[37] The diaphragm is easy to identify with ultrasonography, and characteristics of diaphragmatic function, such as velocity, force, and amplitude of contraction can be readily assessed.

DIAGNOSIS OF SPECIFIC DISEASES

Lung ultrasonography is useful for the diagnosis and follow-up of community-acquired pneumonia.[38] It also has utility in the diagnosis of pulmonary embolism.[39,40] Thoracic ultrasonography may be useful in the evaluation of dyspnea in the critical care setting and may be helpful in assessing dyspnea in less acute settings.[30,41]

REDUCTION IN USE OF CHEST RADIOGRAPHY AND CHEST CT SCANNING

Thoracic ultrasonography has been compared with both CXR and chest CT scanning. For many indications, it is superior to CXR and similar to chest CT.[24,42,43]

CONCLUSION

Thoracic ultrasonography is a useful imaging modality for the pulmonary consultant. Thoracic ultrasonography is easy to learn and has multiple applications as a point-of-care tool. The technique may allow the pulmonary consultant to reduce the use of CXR and chest CT while providing information of immediate clinical relevance.

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CHAPTER 32

Physiologic and Metabolic Study of Pulmonary Disorders Using Conventional Imaging Techniques and Positron Emission Tomography

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INTRODUCTION

Since the mid-1950s, the use of radiopharmaceuticals has made it possible to assess a variety of pulmonary disorders. In 1955, ^{133}Xe was introduced for the study of regional pulmonary ventilation.[1] Shortly thereafter, it became possible to evaluate regional pulmonary blood flow using inhaled carbon dioxide containing radioactive $^{15}O_2$ or intravenous injection of ^{133}Xe dissolved in saline solution.[3] In 1964, intravenous injection of ^{131}I-macroaggregated albumin made it feasible to obtain perfusion scans of the lungs.[4] Although these techniques rapidly gained wide acceptance as tests of regional abnormalities in ventilation and pulmonary blood flow, the main practical application has been in the diagnostic evaluation of patients with suspected pulmonary embolism (PE). Increasingly, the role of nuclear medicine in respiratory medicine has been expanded to include disorders such as preoperative assessment of lung function, inflammatory lung disease, and lung cancer. The more widespread availability of positron emission tomography (PET) and integrated PET/CT (computed tomography) has provided powerful tools to aid in the diagnosis, staging, and management of patients with lung cancer.

RADIOPHARMACEUTICALS AND TECHNIQUES IN VENTILATION–PERFUSION LUNG SCANNING

Radiopharmaceuticals commonly utilized in both perfusion and ventilation studies, as well as the techniques employed are discussed in subsequent sections.

PERFUSION AGENTS AND TECHNIQUES

Clinical application of perfusion lung scanning was first described in 1964, when iodine 131–labeled macroaggregates of albumin was utilized in the evaluation of pulmonary perfusion.[4] Currently, the two agents used for pulmonary perfusion imaging are technetium 99m–labeled human albumin microspheres (^{99m}Tc HAM) and macroaggregated albumin (^{99m}Tc MAA). ^{99m}Tc MAA particles range in size from 10 to 150 μm; more than 90% of injected particles measure between 10 and 90 μm. ^{99m}Tc HAM particles are relatively uniform in size and range between 35 and 60 μm. However, ^{99m}Tc MAA is considered the agent of choice for routine perfusion lung scanning because of its availability, short residence time in the lungs, and relatively low cost.

Radiolabeled particles are injected intravenously while the patient is in the supine position, thereby limiting the effect of gravity on regional pulmonary arterial blood flow. Following the administration of ^{99m}Tc MAA, particles mix uniformly with venous blood flowing to the heart; the particles lodge in precapillary arterioles of the lungs, obstructing approximately 0.1% of their total number. The usual administered dose of radioactivity is between 74 and 185 MBq (2–5 mCi) (typically, 200,000 to 500,000 particles are injected during clinical perfusion scan). The usual pediatric-administered activity is 0.5 to 2.0 MBq/kg (20–80 mCi/kg), with a minimum of 7 to 8 MBq (approximately 200 mCi).

The blockage of pulmonary precapillary arterioles by ^{99m}Tc MAA is transient; the biologic half-life in the lung ranges between 2 and 8 hours. The physical half-life of ^{99m}Tc is 6 hours. The MAA particles are cleared by enzymatic hydrolysis, forming smaller particles that are phagocytized by reticuloendothelial cells. In pediatric patients and patients with suspected or known right-to-left shunts, severe pulmonary hypertension, poor respiratory function, pregnancy, prior pneumonectomy, or a single lung transplant, the number of particles injected should be reduced. In infants and children, the use of low number of particles can be calculated based on weight.[5] The distribution of particles in the lungs is proportional to regional pulmonary blood flow at the time of injection.[6] A routine perfusion scan should include at least six views of the lungs: Anterior, posterior, right and left lateral, and right and left posterior oblique views, using large field of view high-resolution gamma camera. Right and left anterior oblique views may be helpful in selected cases. In spite of imaging in multiple projections, the perfusion scan may underestimate perfusion abnormalities. A solitary segmental perfusion defect within the medial basal segment of the right lower lobe is completely surrounded by normal lung. Consequently, a perfusion defect in this segment will not be detected on planar perfusion imaging.

Perfusion lung scans are routinely utilized to examine patients with suspected PE. Unfortunately, perfusion imaging is sensitive, but not specific, for diagnosing PE. Virtually all lung diseases (including tumors, infections, asthma, and chronic obstructive pulmonary disease [COPD]) may cause decreased pulmonary arterial blood flow in the affected lung zones. Therefore, combined use of perfusion and ventilation studies improves the diagnostic specificity of lung scanning for PE (Fig. 32-1). PE almost always causes abnormal perfusion, while ventilation is preserved (mismatched defects) (Fig. 32-2). In contrast, in parenchymal pulmonary disorders, decreased ventilation and perfusion are noted in the same lung region (matched defects). Conditions in which the ventilation abnormality may appear larger than the perfusion abnormality (reverse mismatch), indicating a functional right-to-left shunt, include airway obstruction, mucus plug, atelectasis, and pneumonia.[7] Reverse mismatch may be exacerbated in patients on positive end-expiratory pressure (PEEP)[8] as PEEP is less efficiently transmitted to obstructed, well-perfused areas, in patients with metabolic alkalosis,[9] or in patients treated with inhaled albuterol.

VENTILATION AGENTS AND TECHNIQUES

Historically, ^{133}Xe has been the agent used to determine regional ventilation.[1,10] ^{133}Xe has a physical half-life of 5.24 days and a low gamma energy emission of 81 keV compared to 140 keV for ^{99m}Tc. The examination is somewhat laborious and encompasses three phases. Thus, other tracers, such as ^{81m}Kr, and, the ^{99m}Tc-labeled aerosols – Technegas and Pertechnegas – are now replacing it.

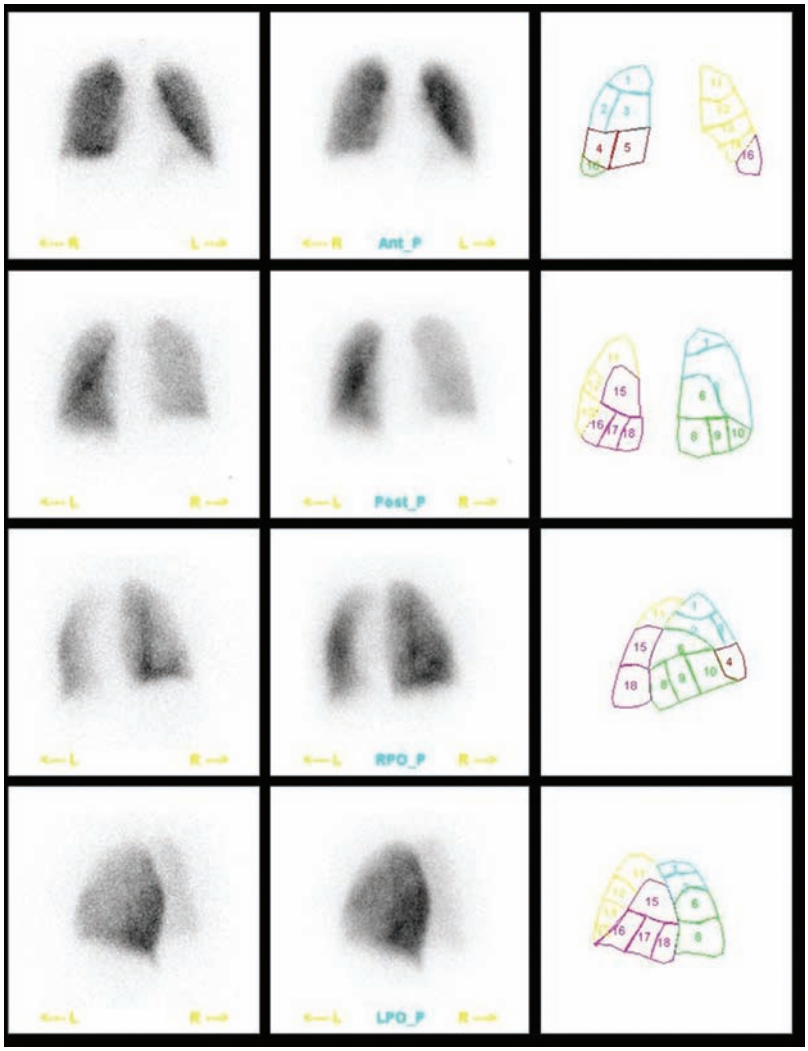


Figure 32-1 Normal ventilation–perfusion lung scanning. Ventilation scan using ^{99m}Tc Technegas® aerosol *(left column)*: Uniform distribution of the aerosol throughout both lungs. Perfusion scan using ^{99m}Tc MAA *(middle column)*: Uniform distribution of particles throughout both lungs.

^{81m}Kr is a noble gas that has a very short physical half-life (13 seconds). Therefore, images acquired using this agent reveal ventilation to major airway systems only. However, the short physical half-life of ^{81m}Kr allows generation of lung images in multiple projections that can be matched with perfusion images. ^{81m}Kr is produced from a rubidium-81 generator. The parent radionuclide has a physical half-life of 4.7 hours, which limits the useful lifetime of the generator to only 1 day. Imaging with ^{81m}Kr is generally performed following the perfusion scan due to its higher energy than ^{99m}Tc.

A radioaerosol is produced by nebulizing the radiopharmaceutical into a fine mist, which is subsequently inhaled. ^{99m}Tc-labeled aerosol studies can be performed following the inhalation of several preparations; ^{99m}Tc DTPA (diethylene triamine penta-acetic acid) is the most popular and commonly used worldwide. The advantages of ^{99m}Tc aerosols are that they are widely available, inexpensive, and have a 140-keV energy photopeak, which is ideal for gamma camera imaging. One limitation of this agent is its relatively rapid absorption across the pulmonary capillaries into the blood in the presence of inflammation, including that caused by smoking (typical ^{99m}Tc DTPA aerosol biologic half-life is about 80 minutes compared to ~20 to 30 minutes in smokers).[11,12] Since ^{99m}Tc DTPA aerosol is cleared from the alveoli by transepithelial diffusion, the clearance rate may be used as an index of alveolar–epithelial membrane integrity.[11]

^{99m}Tc-labeled radioaerosols have particles between 0.5 and 2 μm in size and are produced by utilizing commercially available nebulizers.[13] The patient generally breathes from the nebulizer (with oxygen at 8 to 10 L/min) for 3 to 5 minutes or until 37 MBq (1 mCi) of radioactivity is deposited in the lungs. Only 2% to 10% of administered radioactivity goes to the lungs. The regional distribution of radioactivity in the lungs is proportional to local ventilation. ^{99m}Tc-labeled radioaerosol studies are generally performed before perfusion imaging. Although less preferred, the ventilation study can be performed following the perfusion scan, but the dose placed in the nebulizer should be increased to at least 1665 MBq (45 mCi), instead of the usually used 1110 MBq (30 mCi) to overwhelm the activity present in the lungs from ^{99m}Tc MAA.

The lungs are imaged in multiple projections, which correspond to those obtained during the subsequent perfusion study. Ventilation studies using ^{99m}Tc-labeled radioaerosols require minimal patient cooperation and can be performed at the bedside and on patients who are on ventilators. Disadvantages of ^{99m}Tc-labeled radioaerosols include the central deposition of radioactivity in patients on PEEP, patients with COPD or airway obstruction, and the need to dispose of the substantial unused amount of radioactivity that is deposited in the nebulizer. Indeed, the central deposition of ^{99m}Tc-labeled radioaerosol in patients with COPD is a major drawback to the use of aerosol agents, and newer agents have been developed to overcome this deficiency, including ^{99m}Tc Technegas and ^{99m}Tc Pertechnegas.[14]

LUNG SCANNING IN THE DIAGNOSIS OF ACUTE PULMONARY EMBOLISM

PE is a common and potentially fatal disorder for which treatment is highly effective in decreasing mortality and morbidity if initiated soon after the event.[15] The accurate and expeditious diagnosis of acute PE can be difficult because of the nonspecificity of clinical, laboratory, and radiographic findings. Despite diagnostic advances, delays in diagnosis of PE are still common and represent an important clinical issue.[16]

Venous thromboembolism (VTE) and PE are no longer considered a one-time only event, as they have a high recurrence and mortality rate.[17] Although the incidence of PE has not significantly changed over the past three decades,[18] the overall mortality rate from PE has decreased substantially (by roughly 30% from 1998 to 2009),[19] which has been attributed to better detection and treatment of deep venous thrombosis (DVT), risk factor modification, and improvement in PE diagnostic tests.[19–21] Although prompt anticoagulation therapy remains the cornerstone of PE treatment, as it is effective and reduces mortality, it is not without risks, including hemorrhagic complications.[22] Therefore, accurate diagnosis of PE is essential, not only to prevent death from recurrent embolism but also to avoid complications related to unnecessary anticoagulant therapy.

Ventilation–perfusion (V/Q) lung imaging has been shown to be a safe, noninvasive technique in evaluating regional pulmonary function undertaken for a variety of purposes. The technique has been widely used in the assessment of patients with suspected PE.

The first major study that utilized perfusion lung scanning as a screening test for the diagnosis of PE was the Urokinase Pulmonary Embolism Trial (UPET).[23] In more than 90% of patients enrolled in the trial, perfusion lung scanning was performed following intravenous administration of ^{131}I-labeled MAA. Lung imaging was

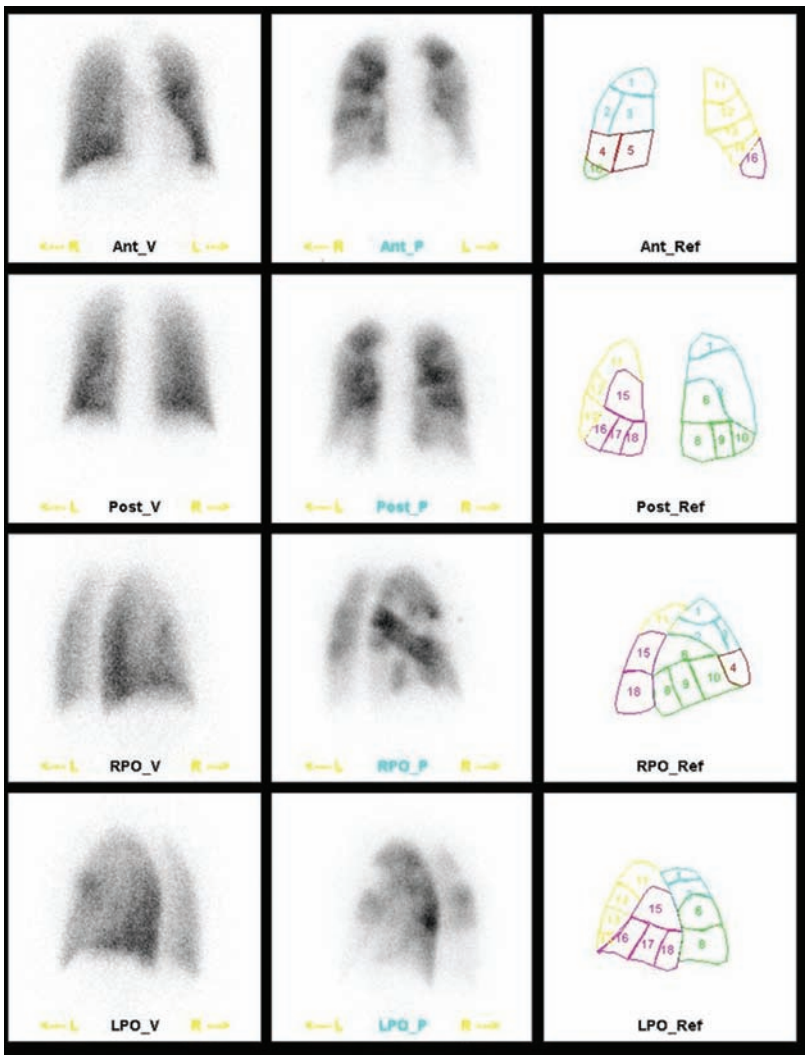


Figure 32-2 High probability scan for pulmonary embolism. Ventilation scan using ^{99m}Tc Technegas® aerosol *(left column)* is within normal limits. Perfusion scan using ^{99m}Tc MAA *(middle column)* shows large segmental defects in both lungs. This combination of findings (mismatch) is consistent with pulmonary embolism.

carried out using rectilinear scanners; ventilation studies were not performed. Despite utilizing a suboptimal radiopharmaceutical and imaging equipment, the UPET study established perfusion lung scanning as an effective technique in both screening for PE and assessing restoration of pulmonary blood flow following an embolic event. Approximately 75% to 80% of perfusion defects resolved by 3 months; those that did not, persisted after 1 year, indicating that most patients with acute PE either completely lyse the thrombi or partially recanalize the pulmonary artery.

Data from prospective, large, outcome-based studies have reported on the important diagnostic information provided by V/Q scanning in patients suspected of having acute PE when coupled with clinical assessment and noninvasive leg testing.[24,25] In patients with suspected PE who had a non–high probability or nondiagnostic V/Q scan, normal cardiorespiratory reserve, and negative serial noninvasive leg tests for proximal venous thrombosis (as determined by serial impedance plethysmography [IPG]), PE at 3 months of follow-up occurred in only 0.6% of cases while the patients were not on anticoagulation.[24] Among patients with suspected PE, but who had a low probability clinical assessment and negative serial noninvasive leg tests, as well as a nondiagnostic V/Q scan, PE at 3 months follow-up occurred in 0.5% of patients.[25] When the probability for clinical assessment was intermediate, PE occurred in only 0.4% of patients.[25]

These studies demonstrated that anticoagulation could be safely withheld in patients with adequate cardiorespiratory reserve who did not have high probability V/Q scans or proximal venous thrombosis, since the incidence of recurrent PE is very low. Unfortunately, the criteria used in the studies to categorize the probability of PE ("normal," "nondiagnostic," or "high") were different than those used in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), and direct comparison is not possible. In the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED),[26] which utilized perfusion scanning alone in conjunction with the chest radiograph, the sensitivity and specificity of scintigraphy were 92% and 87%, respectively. The prevalence of PE was high (39%). When considered in conjunction with clinical assessment of the likelihood of PE ("very likely," "possible," or "unlikely"), the positive predictive value (PPV) of a perfusion scan was 99%; the combination of a near-normal or abnormal perfusion scan without segmental defects and low clinical likelihood of PE had a negative predictive value (NPV) of 97%. Using standardized clinical assessment and perfusion lung scanning, the authors were able to accurately diagnose or exclude PE (PPV, 96%; NPV, 98%). CT angiography (CTA) was required in only a minority of cases having discordant clinical and scintigraphic findings.

PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS STUDY

To date, the most comprehensive prospective investigation addressing the role of V/Q scanning in the diagnosis of PE has been the PIOPED study. This multi-institutional study was designed to evaluate the efficacy of various conventional methods for diagnosing acute PE. In particular, PIOPED focused on the sensitivity and specificity of lung scans in the diagnosis of acute PE. Although the clinical diagnosis of PE is not definitive, results from PIOPED emphasize the importance of incorporating clinical assessment in evaluating patients suspected of having acute PE. As expected, combining clinical assessment with lung scan interpretation improves diagnostic accuracy of the imaging technique.

Ninety-two percent of patients with PE in PIOPED had at least one of the following risk factors: Immobilization and recent surgery (two most common risks), underlying malignancy, history of DVT or PE, estrogen use, or pre-existing cardiac disease. Of patients diagnosed with PE in PIOPED, >90% had dyspnea, tachycardia, or pleuritic chest pain. Similarly, although chest radiographic findings alone are not sensitive or specific for PE, they are essential for diagnosing conditions that can mimic PE clinically. The most common radiographic findings in patients with PE were atelectasis or parenchymal opacity. Furthermore, chest radiographic findings heavily influence the criteria utilized for estimating the probability of PE based on lung scan patterns. For example, in patients with COPD, the sensitivity of a high probability V/Q scan is significantly lower than in patients with no cardiopulmonary disease. The more severe the underlying cardiopulmonary disease, the higher the likelihood of the scan will be of intermediate probability. Intermediate probability occurred in 60% of patients with COPD in PIOPED, compared with only 13% of patients with a normal chest x-ray.[27]

The sensitivity, specificity, and PPV from PIOPED of V/Q lung scans in detecting acute PE are presented in Table 32-1.

TABLE 32-1 Sensitivity, Specificity, and Positive Predictive Value of Lung Scans in Detecting Pulmonary Embolism in Patients Enrolled in PIOPED

Lung Scan Interpretation (Probability)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)
High[a]	40	98	87
High, intermediate[b]	82	64	49
High, intermediate, low[c]	98	12	32

[a]*Only high-probability scans considered indicative of PE; all other classifications considered negative for PE.*
[b]*High- and intermediate- probability scans considered indicative of PE; all other classifications considered negative for PE.*
[c]*High-, intermediate-, and low- probability scans considered indicative of PE; normal or near-normal scans considered negative for PE.*

All patients enrolled in PIOPED were to undergo a V/Q scan and pulmonary arteriogram. However, a large number of patients with low probability or normal V/Q scans did not undergo pulmonary arteriography to avoid additional risks. Therefore, there was a selection bias toward patients with intermediate or high probability scans, leading to an overestimation of the sensitivity, but underestimation of the specificity of V/Q scanning. In an analysis of the angiography results in PIOPED, PE occurred more frequently on the right than on the left, and more commonly in the lower lung zones. One of the limitations of V/Q scanning in PIOPED was the interobserver variability in scan interpretation. As expected, agreement among readers was excellent for normal, high, and very low probability V/Q scans (92%–95%). However, it was not as good for intermediate and low probability studies.[27]

Use of anatomic lung segment reference charts has been shown to reduce interobserver disagreement when interpreting scans. Other interpretative pitfalls include false-negative and -positive readings. False-negative interpretations (i.e., low probability read with PE present) do occur, and patients who have a recent history of immobilization (bed rest for 3 days), recent surgery, trauma to the lower extremities, or central venous instrumentation are particularly at risk. In patients with low or very low probability scans who have none of the aforementioned risk factors, the prevalence of PE is only 4.5%. Conversely, in patients with low or very low probability scans and one or more of the risk factors, the prevalence of PE is 12% and 21%, respectively (Table 32-2).

TABLE 32-2 Risk Factors and Prevalence of Pulmonary Embolism in Patients with Low Probability and Very Low Probability Lung Scans Enrolled in PIOPED

	Patients with 0 Risk Factor[a]	Patients with 1 Risk Factor[a]	Patients with ≥2 Risk Factors[a]	Total
PE positive	14 (2.2%)	19 (2.9%)	37 (5.7%)	70
PE negative	301 (46.4%)	136 (21.0%)	142 (21.9%)	579
Prevalence of PE	4.5%	12.2%	20.7%	10.8%

[a]*Risk factors include immobilization, trauma to lower extremities, surgery, and central venous instrumentation within 3 months of enrollment.*

Patients with false-negative lung scans tend to have nonocclusive subsegmental thrombi and a low pulmonary clot burden. The prognostic value of a low probability scan is excellent, particularly in patients with a low clinical pretest likelihood of disease or negative lower leg ultrasound.[28] The most common cause of V/Q mismatch in patients who do not have acute PE is chronic or unresolved PE. Other causes include compression of the pulmonary vasculature (e.g., from mass lesions, lymphadenopathy, or mediastinal fibrosis), vessel wall abnormalities (e.g., pulmonary artery tumors or vasculitis), nonthromboembolic intraluminal obstruction (e.g., tumor emboli or foreign body emboli), and congenital vascular abnormalities (e.g., pulmonary artery agenesis or hypoplasia).

In patients who have unilateral V/Q mismatch (hypoperfusion or absent perfusion) within an entire lung or in multiple contiguous segments and normal perfusion in the contralateral lung, extrinsic compression of the pulmonary vasculature, congenital abnormalities, or proximal PE should be considered. Patients with a suspected false-positive scan or unilateral V/Q mismatch often require further imaging using CTA, even though emboli are frequently multiple (in 90%) and bilateral (in 85% of cases), and unilateral decreased or absent perfusion to one lung is uncommonly the result of PE.

Shortly after the PIOPED study, helical CTA was introduced.[29] This led to PIOPED II, which is the largest multicentered, prospective, outcome-based study to date designed to assess the accuracy of CTAin evaluation of acute PE in comparison to the composite reference standard.[30]

In PIOPED II, CTA had a sensitivity, specificity, PPV, and NPV of 83%, 96%, 86%, and 95%, respectively, in detecting acute PE.[30] Study results suggested that the predictive value of CTA is highly concordant with the pretest clinical probability of PE using Wells' criteria.[25] The PPV of PE with a positive CTA was 97% for a main or lobar artery, 68% for a segmental vessel, and 25% for a subsegmental branch. The probability of a false-negative chest CTA is minimal in large PE, but false-negative findings may occur in the small group of patients with clot limited to subsegmental arteries. The PPV of PE in patients with positive CTA and high, intermediate, or low clinical probability was 96%, 92%, 58%, respectively. NPV of PE in patients with negative CTA and low, intermediate, or high clinical probability was 96%, 89%, and 60%, respectively.

The limitations of the study included use of 4- to 16-slice multidetector CT (mostly 4-detector) and use of noninvasive diagnostic test in the reference standard. In contrast to original PIOPED population, of whom 68% were inpatients, PIOPED II included only 11% inpatients. Inpatients are more likely to have abnormalities on chest radiographs, which would potentially interfere with optimal V/Q scan reading.[31] Also, the accuracy of CTA would be lower if patients with inconclusive interpretations of CT (51 patients or 6%) were included, giving an overall sensitivity and specificity of 78% and 90%, respectively. The overall PPV of 86% and NPV of 95% are comparable to V/Q performance parameters. The combination of CT venography and CTA increased the sensitivity from 83% to 90% when using CTA alone. CT venography, however, showed similar results in diagnosing or excluding DVT as compression ultrasound.[32]

Finally, PIOPED III, a multicenter collaborative investigative trial was designed to determine the diagnostic accuracy of gadolinium-enhanced magnetic resonance angiography (Gd-MRA) of the pulmonary arteries in combination with magnetic resonance venography (MRV) of the veins of the thighs in patients with clinically suspected acute PE. In PIOPED III, most centers had difficulty in obtaining MR pulmonary angiograms of adequate quality; indeed, studies were deemed inadequate in 25% of patients.[33] Adequacy of the studies varied between 11% and 52% among centers. Adequate quality images were obtained in assessing the main or lobar pulmonary arteries in 91% of patients, segmental pulmonary arteries in 87%, and subsegmental branches in 73%. A technically adequate

MRA had a sensitivity of 78% and specificity of 99%. These findings led the PIOPED III investigators to conclude that MRA should only be considered at centers that routinely perform it well, and for patients who have contraindications to other standard tests.

V/Q SCAN INTERPRETATION AND MODIFICATIONS TO ORIGINAL PIOPED CRITERIA

Several diagnostic schemes have been suggested for interpretation of V/Q scans. The original PIOPED criteria were developed to interpret scans generated from the study based upon experience gathered over the preceding decade. A PE is characterized by V/Q mismatch, which is an area of normal ventilation corresponding to a segmental, wedge-shaped area of decreased or absent perfusion extending to the pleural surface. The segmental defect should correspond to vascular anatomy. Due to the high proportion (44%) of intermediate probability V/Q scans in PIOPED[34] and interobserver disagreements, several revisions and modifications have been made to the original criteria.

One nuance in V/Q scan interpretation is the so-called "gestalt interpretation," which is based on an experienced nuclear medicine physician's subjective estimate of the likelihood of PE (without using specific interpretation criteria). This interpretation takes into account various published lung image interpretation algorithms, clinical data, ancillary findings, and pathophysiologic features of PE, which are integrated with the individual case presentation. The gestalt interpretation has been shown to correlate well with the fraction of patients with angiographic evidence of PE in the PIOPED study, with good-to-excellent intra- and interobserver variability.[35,36] Thus, experienced readers (such as the PIOPED investigators) can provide an accurate estimate of the probability of PE based on clinical, radiographic, and scintigraphic findings.

Another nuance is the "triple match," which is a reference to matching perfusion, ventilation, and chest radiographic abnormality. Based on the PIOPED data, in the presence of a triple match, the prevalence of PE varies depending on the location of the abnormality. A triple match in the upper (prevalence of PE, 11%) or middle lung (prevalence of PE, 12%) zones is considered low probability for PE, but a triple match in the lower lung zones should be interpreted as intermediate probability (prevalence of PE, 33%).[37]

Yet another nuance is the "stripe sign," which describes a rim of perfused lung tissue between the perfusion defect and adjacent pleural surface.[38] In PIOPED, this sign excluded the diagnosis of PE within the affected zone in 93% of cases. Hence, in the absence of other perfusion abnormalities, a V/Q scan with a stripe sign should be considered very low probability for PE. A single, moderate-sized V/Q mismatch was found to harbor PE in 36% of cases in PIOPED[39]; if present, the V/Q scan should be described as intermediate probability for PE. A single matched V/Q defect (of any size) was found to correspond to PE in 26% of cases in PIOPED; such a finding should be classified as intermediate probability.[39]

The limitations in original PIOPED led the investigators to revise the original interpretation criteria for easier application and better integration of clinical pretest probability of PE. Modifications to the original PIOPED interpretation criteria were used in the PIOPED II trial (Table 32-3),[40] which decreased the number of intermediate scan readings (73.5% of patients had V/Q scans with definitive interpretation) and provided a more accurate assessment of angiographically proven PE than the original criteria (sensitivity increased to 83%; specificity essentially unchanged at 96%).

On the other hand, the PISA-PED[26] criteria (Table 32-4) for interpretation of perfusion lung scans were based on diagnosing PE when there was one or more wedge-shaped perfusion defects. PE was considered absent when there was normal or near-normal perfusion or a nonsegmental, non–wedge-shaped perfusion defect.[41] All other scans were called nondiagnostic.

TABLE 32-3 Revised PIOPED Criteria for Interpretation of Lung Scans[a]

High probability (≥80%)
≥2 Large segmental perfusion defects (>75% of a segment) without corresponding ventilation or radiographic abnormalities
One large segmental perfusion defect and ≥2 moderate segmental perfusion defects (25–75% of a segment) without corresponding ventilation or radiographic abnormalities
≥4 Moderate segmental perfusion defects without corresponding ventilation or radiographic abnormalities
Intermediate probability (20–79%)
One moderate to <2 large segmental perfusion defects without corresponding ventilation or radiographic abnormalities
Corresponding ventilation–perfusion defects and radiographic parenchymal opacity in lower lung zone
Single, moderate, matched ventilation–perfusion defects with normal radiographic findings
Corresponding ventilation–perfusion defects and small pleural effusion
Difficult to categorize as normal, low, or high probability
Low probability (<19%)
Multiple matched ventilation–perfusion defects, regardless of size, with normal radiographic findings
Corresponding ventilation–perfusion defects and radiographic parenchymal opacity in upper or middle lung zone
Corresponding ventilation–perfusion defects and large pleural effusion
Any perfusion defects with substantially larger radiographic abnormality
Defects surrounded by normally perfused lung (stripe sign)
>3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
Nonsegmental perfusion defects (cardiomegaly, aortic impression, enlarged hilum)
Very low probability
≥3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
Normal scan
No perfusion defects; perfusion outlines the shape of the lung seen on the radiograph

[a]*Criteria generated after completion of prospective study.*

According to modified PIOPED II criteria (Table 32-4) established in 2008, PE was diagnosed when there were equivalent of two large, segmental perfusion scan–chest radiograph mismatches (which may include one large and two moderate segmental mismatches, or four moderate segmental mismatches).[41] PE was considered absent when there was normal perfusion. PE was deemed very low probability when there was a nonsegmental perfusion defect smaller than the corresponding radiographic lesion, one to three small segmental defects, a solitary matched chest x-ray abnormality and perfusion defect in the mid or upper lung zones, a stripe sign, or a pleural effusion ≥1/3 of the pleural cavity with no other perfusion defect in either lung. The scan was considered nondiagnostic with all other findings.

When perfusion scans obtained in PIOPED II were reinterpreted using a composite reference standard (all PIOPED II patients were eligible for this study if they had a diagnosis based on CTA or digital subtraction angiography [DSA], an interpretable perfusion scan and chest radiograph, and a positive Wells' score), investigators

TABLE 32-4 Modified PIOPED II and PISA-PED Criteria for Interpretation of Perfusion Scans

	Modified PIOPED II	PISA-PED
PE present	• High probability (≥2 segments of perfusion scan—chest radiograph mismatch. May be ≥2 large segmental mismatches, or 1 large and 2 moderate mismatches, or 4 moderate segmental mismatches)	• ≥1wedge-shaped perfusion defects

PE absent	• Normal perfusion
	• Very low probability
	  • Nonsegmental lesion (eg, prominent hilum, cardiomegaly, elevated diaphragm, linear atelectasis, costophrenic angle effusion with no other perfusion defect in either lung)
	  • Perfusion defect smaller than radiographic lesion
	  • 1–3 small segmental defects
	  • Solitary CXR-Q matched defect in the mid or upper lung zone confined to a single segment
	  • Stripe sign present around the perfusion defect (best tangential view)
	  • Pleural effusion ≥1/3rd the pleural cavity with no other perfusion defect in either lung
		• Normal perfusion
		• Near normal
		  • Contour defect (caused by enlarged heart, mediastinum, or diaphragm)
		• Perfusion defect, not wedge-shaped

Not diagnostic	• All other findings	• Cannot classify as PE-positive or PE-negative

Source: Data from Miniati, M, Pistolesi, M, Marini, C, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med. 1996;154(5):1387–1393; and Sostman, HD, Miniati, M, Gottschalk, A, et al. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med. 2008;49(11):741–748.

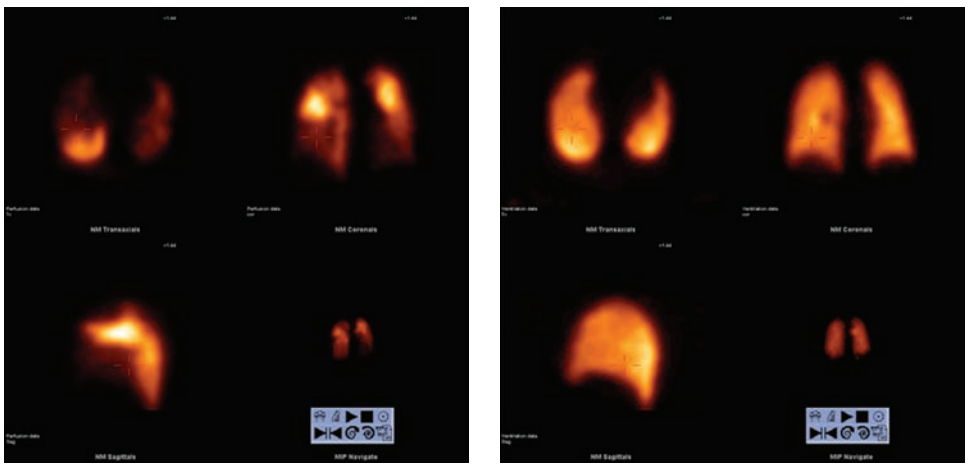
found only 21% of patients with nondiagnostic results using revised PIOPED II criteria.[41] Only 11% patients had nondiagnostic perfusion scans among the 72% of patients with normal or near-normal chest radiographs. The prevalence of PE in the sample was 19%. Using the modified PIOPED II criteria, and after excluding nondiagnostic perfusion scans, the sensitivity of "PE present" reached 85%, and the specificity of "PE absent" reached 93%. When using PISA-PED criteria, none had nondiagnostic perfusion scans; the sensitivity of a "PE present" scan was 80% and the specificity of "PE absent" scan was 97%. Based on these findings, it was postulated that perfusion scintigraphy combined with chest radiography can provide diagnostic accuracy similar to CTA at a lower cost and, most importantly, with a lower radiation dose.[41]

SPECT V/Q IMAGING FOR THE EVALUATION OF PULMONARY EMBOLISM

Single-photon emission tomography (SPECT) V/Q imaging has several advantages over planar imaging, including higher contrast resolution and avoidance of overlapping small perfusion defects by normal tissue, particularly at the lung bases.[42] In the last two decades, technologic advances have been made with SPECT and new radiopharmaceuticals developed for SPECT ventilation studies, such as ^{99m}Tc Technegas.[43] Due to the availability of Technegas outside the United States, most SPECT V/Q scanning is performed in Australia and Europe (Figs. 32-3 and 32-4).

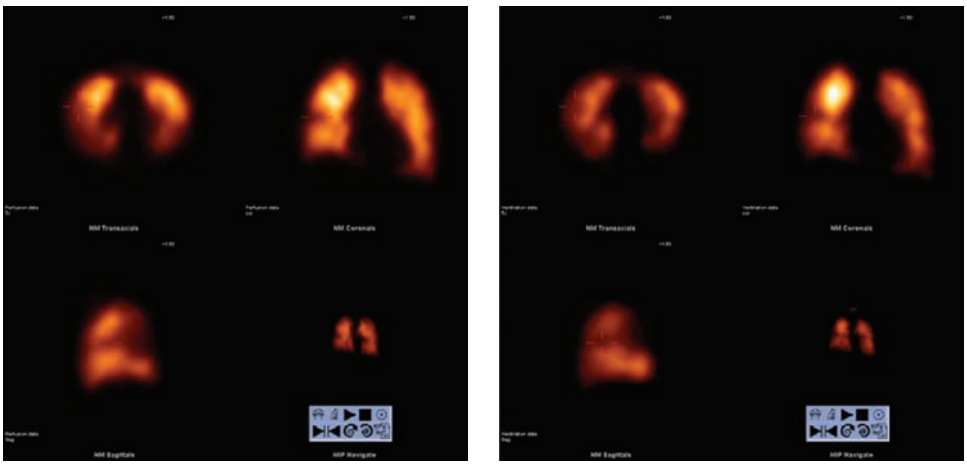
Total acquisition time for the SPECT V/Q examination is between 20 and 30 minutes for a dual-headed camera.[44] The advantages of SPECT over planar imaging in the evaluation for PE have been reported in several studies.[45–48] Importantly, SPECT V/Q scans have been reported by most investigators to be ≤3% nondiagnostic.[44] When compared to planar V/Q scans, SPECT V/Q scans show more and better delineated mismatched defects, better quantification, and less interobserver variation.[46]

In most studies, sensitivity (80%–100%) of SPECT V/Q scanning is higher than planar V/Q scan, but the specificity (93%–100%) is not always higher.[44] Some investigators have also suggested the



A B

Figure 32-3 High probability V/Q SPECT scan for pulmonary embolism. Perfusion scan using ^{99m}Tc MAA in transaxial, coronal, and sagittal views (**A**) shows large segmental defects in both lungs. Ventilation scan using ^{99m}Tc Technegas® aerosol in transaxial, coronal, and sagittal views (**B**) is within normal limits. This combination of findings (mismatch) is consistent with pulmonary embolism.



A B

Figure 32-4 V/Q SPECT scan for pulmonary embolism. Perfusion scan using ^{99m}Tc MAA in transaxial, coronal, and sagittal views (**A**) and ventilation scan using ^{99m}Tc Technegas® aerosol in transaxial, coronal, and sagittal views (**B**) show matched defects.

use of combined SPECT V/Q scan and low-dose CT scanning to improve accuracy in diagnosing PE.[49] The interpretation criteria, however, for SPECT V/Q scanning are not yet clearly defined or universal (i.e., it remains unclear whether modified PIOPED or PISA-PED criteria can be simply transposed from planar to SPECT V/Q scanning). Despite the many advantages of SPECT, substitution of planar V/Q by SPECT V/Q scan in patients with suspected PE remains controversial.[31,50,51]

There is a growing interest in "positive" imaging based on the use of antibody fragments and radiolabeled peptides directed against components of thromboemboli and glycoprotein IIb/IIIa receptors on the surface of activated platelets. ^{99m}Tc-labeled apcitide is a synthetic peptide that binds with high affinity and specificity to the glycoprotein IIb/IIIa receptor on the membrane of activated platelets.[52] The main advantage of the agent is its ability to distinguish between acute and chronic DVT.

Several ^{99m}Tc-labeled peptides directed against activated platelets are currently under investigation in the evaluation of patients with suspected PE. Radiolabeled peptide imaging has the potential to serve as a single, comprehensive modality in the evaluation of patients with VTE.

Finally, another agent under investigation is ^{99m}Tc-labeled anti–D-dimer (DI-80 B3) monoclonal antibody Fab′ fragment that binds specifically to thromboemboli. In a recent prospective, multicenter study to investigate the sensitivity and specificity of ^{99m}Tc DI-80 B3/SPECT in patients with suspected acute PE, ^{99m}Tc-DI-80 B3/SPECT had a sensitivity of 76.2% and a specificity of 90.5%.[53] At the current time, further studies and development of newer radiopharmaceuticals are required to fully realize this potential.

RECOMMENDATIONS FOR THE USE OF V/Q SCANNING AND CT ANGIOGRAPHY IN SUSPECTED PULMONARY EMBOLISM

Over the past decade, significant technical improvements have occurred in both CTA and V/Q scanning. However, use of CTA of the chest in patients with suspected PE has increased significantly and has markedly surpassed use of V/Q scanning.[54] Although studies show equivalent outcome-based results, the ready availability of CTA, particularly after hours, and the bias toward anatomic, rather than functional imaging, has made CTA the favored diagnostic test for PE.[55]

In a recent large prospective randomized study with high pretest probability and/or positive D-dimer levels, the false-negative rates for V/Q scan and CTA were very close at 1% and 0.4%, respectively.[56] Despite the fact that CTA can detect more small emboli than V/Q scan,[56] the risk of recurrent PE and death have not decreased during the CTA era.[57] In fact the ability of sophisticated new multidetector CT scans to detect emboli in subsegmental branches of the pulmonary arteries has created a healthcare challenge, pushing clinicians to now treat patients who have incidental, asymptomatic pulmonary emboli, whose natural history and optimal management are currently unknown (except in cancer patients in whom these emboli carry a poor prognosis).[58,59] These scans are usually ordered in the emergency department with no particular pretest diagnosis. The same logic will probably be true with SPECT V/Q scan, as it is not yet clear whether treating small, peripheral PE will confer a benefit unless the patients have significant clot burden and limited cardiovascular reserve.[34]

In patients with a normal chest radiograph, the V/Q lung scan is an effective, noninvasive initial study. However, in patients with significant chest radiographic abnormalities, CTA is more likely to provide a definitive diagnosis of PE or an alternative diagnosis, as well as a risk assessment of PE based on the evaluation of right ventricular size and function.[60,61] Furthermore, the combination of CTA and CT venography has the potential to provide a single, comprehensive evaluation of patients with suspected VTE, albeit with increased radiation exposure. V/Q scan remains an important alternative to CT in patients with contrast allergy or renal failure.

V/Q scan may be the modality of choice to evaluate patients with chronic thromboembolic disease and in providing follow-up of PE after therapy.[31] There is concern regarding the high radiation exposure, particularly to the female breast, associated with chest CTA.[62,63] CTA delivers a minimum radiation dose of 20 mGy (2.0 rad) to the breasts of an average-sized woman,[64] whereas breast irradiation with V/Q scan is approximately 0.28 to 0.9 mGy.[65] Furthermore, concern exists that increasing use of CTA may result in an increased incidence of radiation-related cancer in the future.[62] The potential latent carcinogenic effects of such radiation exposure at this time remain unknown.

As part of the American Board of Internal Medicine's *Choosing Wisely* campaign, which focused on potentially unnecessary or harmful medical tests and procedures, the Society of Nuclear Medicine recommended avoiding CTA to diagnose PE in young women with a normal chest radiograph, and consideration of a V/Q study instead.[66] Considerable debate exists regarding fetal radiation doses from pulmonary CTA versus V/Q scanning.[67] During pregnancy, when only a perfusion scan with 50 MBq of ^{99m}Tc MAA is used, the fetal absorbed dose is 0.1 to 0.2 mGy. It is estimated that a 16-slice MDCT scan gives an absorbed fetal dose of 0.24 to 0.66 mGy during the first trimester.[68] A comparison between CTA and V/Q scan for the evaluation of PE is summarized in Table 32-5.

In summary, based upon results from prospective and outcome-based studies, the following conclusions can be drawn regarding the use of V/Q scan and CTA in evaluating patients with suspected PE:

TABLE 32-5 Comparison of CTA and V/Q Scan in the Evaluation of PE

	Advantages	Disadvantages
CTA	– Accuracy – Interobserver agreement – Provides alternative diagnosis, and risk assessment based on the evaluation of right ventricular size and function – After hours availability – High speed in image acquisition – Suitable for unstable patients – Binary reports ("PE" or "no PE")	– Radiation exposure – Contrast allergy – Nephrotoxicity – Relative cost – Potential overdiagnosis of nonclinically relevant peripheral PE
V/Q scan	– High NPV in low pretest probability – High PPV in high pretest probability – Low radiation – Relative cost – Serial follow-up	– Low overall specificity – Low interobserver agreement – After hours availability – Slower speed in image acquisition – Unsuitable for unstable patients – Limited in providing alternative diagnosis – Unpopular probabilistic reports

Source: Data from Reid, JH, Coche, EE, Inoue, T, et al. Is the lung scan alive and well? Facts and controversies in defining the role of lung scintigraphy for the diagnosis of pulmonary embolism in the era of MDCT. Eur J Nucl Med Mol Imaging. 2009;36(3):505–521.

1. Proper pretest clinical probability scoring is important irrespective of the modality used. When imaging results for either V/Q scan or CTA are discordant with the pretest probability, the alternative test should be recommended.
2. A normal V/Q scan excludes the diagnosis of clinically significant PE.
3. Patients with very low or low probability scans and a low clinical likelihood of PE have a low (<5%) prevalence of PE and generally do not require pulmonary angiography or anticoagulation.
4. Patients with very low or low probability scans, intermediate or high clinical likelihood of PE, and negative serial noninvasive venous studies of the lower extremities generally do not require anticoagulation. In selected cases, CTA is helpful in excluding PE and providing an alternative diagnosis.
5. Clinically stable patients with intermediate probability scans require noninvasive venous studies of the legs; if negative, CTA is required for definite diagnosis of PE.
6. A clinically stable patient with a high probability scan and high clinical likelihood of PE, or a patient suspected of having a false-positive scan, requires treatment; no further diagnostic tests are required to confirm the diagnosis.
7. Clinically stable patients with high probability scans and a low clinical likelihood of PE require noninvasive venous studies of the legs; if negative, CTA may be required for definitive diagnosis.
8. V/Q scintigraphy has a high NPV and should be used particularly where low radiation dose is desirable, such as in young female with normal chest radiograph, in an outpatient with low clinical probability plus normal chest radiograph, a patient with high clinical probability plus normal chest radiograph, a patient with prior contrast anaphylaxis and strong allergic history, and a patient with renal failure or multiple myeloma. Since, in most patients, PE can be excluded on the basis of a normal perfusion pattern, to minimize radiation to the fetus in a pregnant patient, a 1- to 2-day protocol is suggested. Perfusion-only scans should be performed on day 1, using a reduced dose of ^{99m}Tc MAA.
9. V/Q scan is preferred over pulmonary CTA for follow-up of PE and investigation of the etiology of pulmonary hypertension.
10. If after-hours imaging is not available and a patient has a high clinical suspicion of PE, a reasonable approach includes administering a single dose of low–molecular-weight heparin and imaging the patient the next morning. This strategy may be particularly advisable for performing V/Q scintigraphy in young women to avoid the excessive breast radiation exposure associated with CTA.
11. If there is a contraindication to V/Q scan or CTA, MRA of the pulmonary artery may be performed in centers that perform it well. There is always concern about nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy, which occurs rarely in patients with poor renal function who receive gadolinium-containing contrast material.[69,70]
12. Whenever possible V/Q scintigraphy should be interpreted as either "positive for PE," "nondiagnostic," or "no evidence of PE."

EVALUATION OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as the persistence of pulmonary hypertension (defined as a mean pulmonary artery pressure >25 mm Hg) after a single or recurrent PE (see Chapter 73). CTEPH is a serious, underdiagnosed disease and the only cause of pulmonary hypertension that can be potentially cured by pulmonary endarterectomy (PEA). Estimates are that between 0.5% and 3.8% of patients eventually develop CTEPH after an acute PE; CTEPH may develop in up to 10% of those with a history of recurrent PE.[71,72]

It is not entirely clear why some patients with a history of acute PE go on to develop CTEPH. The risk of developing CTEPH increases in patients with a history of prior PE, presentation at a younger age, larger perfusion defects, and idiopathic PE at presentation.[71] Diagnosis is the key to survival in CTEPH, as without appropriate treatment long-term prognosis is poor. There is positive correlation between increased mean pulmonary artery pressure and mortality.[73] Unfortunately, the clinical features, laboratory studies, chest radiograph, electrocardiogram, and echocardiogram are often unreliable in distinguishing CTEPH from primary and nonthromboembolic secondary pulmonary hypertension.

In most centers, conventional pulmonary angiography remains the gold standard imaging study to confirm the diagnosis of CTEPH and determine whether surgical intervention is indicated; chest CTA and MRA provide complementary information, if needed.

V/Q lung scanning is a safe, noninvasive technique that facilitates selection of patients with pulmonary hypertension for pulmonary angiography to confirm the diagnosis of chronic PE. V/Q scanning remains one of the most important diagnostic tests to help distinguish CTEPH from other forms of pulmonary hypertension. In a retrospective analysis, V/Q scanning had a sensitivity of 97.4% for detection of chronic thromboembolic disease, while that for CTA was only 51%.[74]

Patients with CTEPH usually have at least one, and often several, segmental or larger, mismatched perfusion defects.[75] To prevent potential adverse hemodynamic effects when performing V/Q scans in patients with pulmonary hypertension, the number of ^{99m}Tc MAA particles administered should be reduced. V/Q scanning may underestimate the magnitude of central vascular occlusion by

chronic emboli, as determined at conventional pulmonary angiography or thromboendarterectomy.[76]

Most patients with primary or secondary nonthromboembolic pulmonary hypertension have low probability scans. The distribution of ^{99m}Tc MAA particles within the lungs is diffuse and nonhomogenous. Patients with CTEPH rarely, if ever, have normal or very low probability scans. Thus, a low probability V/Q scan effectively excludes chronic thromboembolism as the cause of pulmonary hypertension. In patients with primary pulmonary hypertension, areas of reverse mismatch on the V/Q scan have been shown to correlate with areas of mosaic-increased attenuation on high-resolution CT scans.[77] In a small study of 55 patients suspected of having CTEPH, the detection rates for central emboli with CTA were similar to conventional pulmonary angiography, although detection of segmental disease was superior with conventional pulmonary angiography.[78]

Even though SPECT is more sensitive than planar perfusion lung scanning for identifying obstructed segments in CTEPH, the technique still underrepresents the true extent of the vascular occlusions in CTEPH.[79] Although CTA and MRA may provide complementary information, they often miss the eccentric lesions of CTEPH. Accordingly, the V/Q scan remains the screening study of choice for CTEPH. Any patient with unexplained pulmonary hypertension should be evaluated for the presence of CTEPH; a V/Q scan is recommended as screening method of choice.[80]

QUANTITATIVE VENTILATION–PERFUSION LUNG SCANNING

In patients undergoing pulmonary resection, bronchoscopic lung volume reduction, or lung transplantation, quantitative V/Q lung scanning is a useful method for determining regional lung function and, thus, predicting postoperative pulmonary function (see Chapter 103).[81–83]

Currently, the presurgical assessment to predict response to lung volume reduction surgery (LVRS) in patients with emphysema is mainly performed using chest CT scanning,[84] which provides an anatomic diagnosis of emphysema, delineates its extent and distribution, and detects any other incidental findings that may represent a contraindication to the procedure. A V/Q scan can provide additional information concerning the heterogeneity and distribution of the functional disruption caused by emphysema.[84] Patients with advanced, upper lobe–predominant emphysema derive the most benefit from LVRS,[85] and perfusion scintigraphy is a commonly available test for assessing the distribution of emphysema by reflecting regional lung function.[86] Rectangular regions of interest over the anterior and posterior scintigraphic images of each lung are divided into upper, middle, and lower zones of equal craniocaudal height, and the geometric mean for a given zone is obtained and presented as the percent perfusion to that zone.[87]

In patients being considered for lung cancer surgical resection, a V/Q scan can predict postoperative pulmonary function and enable assessment of the risk of surgery for patients with borderline pulmonary function.[88] The predicted postoperative forced expiratory volume in 1 second (ppo FEV_1) is calculated by multiplying the preoperative value by the ratio of the counts in the remaining lung to total lung activity (Fig. 32-5).[89,90]

Lung perfusion scintigraphy can be used to quantify the degree of right-to-left shunting due to patent foramen ovale, atrial septal defect, elevated right heart pressures, or hepatopulmonary syndrome (HPS).[91,92] The number of injected ^{99m}Tc MAA particles should be reduced in patients with suspected right-to-left shunt. Normally, <5% of ^{99m}Tc MAA is taken up in the brain, but in HPS, fewer MAA particles are entrapped in pulmonary vasculature and are able to enter the systemic circulation and lodge in different organs (thyroid, spleen, liver, kidneys, and brain), leading to >6% uptake in the brain (Fig. 32-6). The major disadvantage of perfusion scintigraphy is that it cannot distinguish intracardiac from intrapulmonary right-to-left shunt. Estimation of the right-to-left shunt fraction is calculated using the following equation: 100 × (TBC − TLC)/(TBC), where TBC is total body count and TLC is total lung count. A less precise alternative method of right-to-left shunt quantification derives an estimate of total body counts from the measurement of renal and/or cerebral activity.

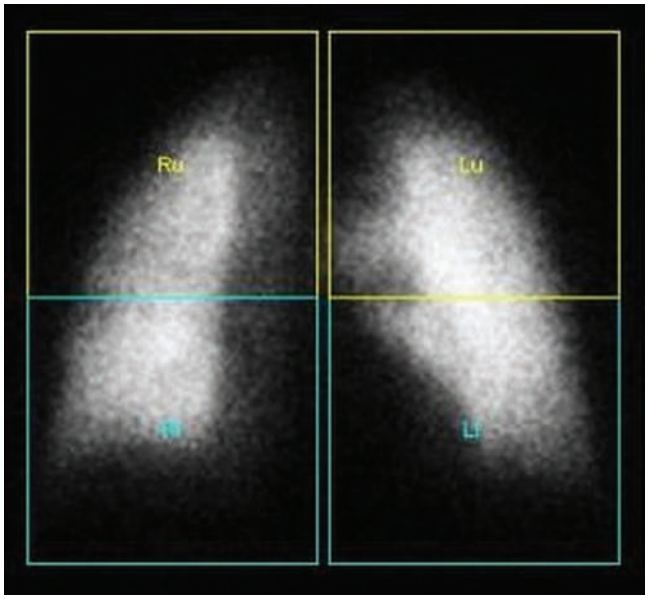


Figure 32-5 Quantitative perfusion lung scan. Regional perfusion can be quantified by outlining regular or irregular regions of interest and generating ratios that correspond to percent of total pulmonary function. Images shown were analyzed by dividing each lung into two equal rectangles.

ASSESSMENT OF ALVEOLAR–CAPILLARY MEMBRANE PERMEABILITY AND MUCOCILIARY CLEARANCE

The clearance rate of inhaled ^{99m}Tc DTPA aerosol from the lungs can be measured using a gamma camera and provides an index of lung epithelial permeability.[11] Aerosols of relatively small aerodynamic diameter (e.g., ^{99m}Tc DTPA) are deposited largely within the small airways and alveoli; the normal half time of ^{99m}Tc DTPA wash out from the lungs is about 80 minutes.[12] In the presence of epithelial

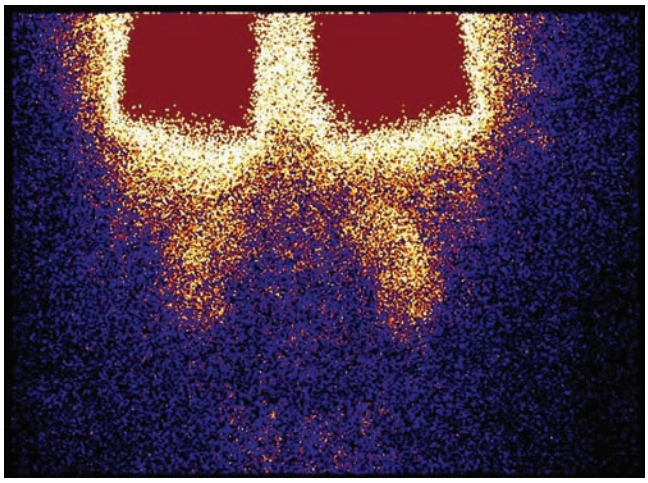


Figure 32-6 Right-to-left shunt in a patient with hepatopulmonary syndrome. Perfusion scan using ^{99m}Tc MAA is showing particles in the systemic circulation lodged in the kidneys.

alveolar damage, the clearance of ^{99m}Tc DTPA is accelerated.[11] Examples of such injuries include amiodarone toxicity, inhalation damage in fire victims, pneumoconiosis, idiopathic pulmonary fibrosis, collagen vascular diseases, sarcoidosis, acute respiratory distress syndrome, and pneumocystis pneumonia.[11,93] Cigarette smoking or physiologic factors, such as posture and exercise, also influence epithelial lung clearance.[11,94] Since increased alveolar–capillary membrane permeability is relatively nonspecific, ^{99m}Tc DTPA aerosol clearance studies have been utilized only to assess the effects of therapy in patients with known pulmonary diseases.

Mucociliary clearance is a primary physiologic defense mechanism, protecting the lungs from damage caused by inhaled particles and microorganisms. Determination of mucociliary clearance may be obtained after the inhalation of relatively large aerosolized particles, followed by measurement of the rate of clearance using a gamma camera. The rate of mucociliary clearance depends on several factors, including ciliary activity and mucus production. Inhaled particles, such as ^{99m}Tc MAA or ^{99m}Tc sulfur colloid, tend to be deposited within the proximal airways.[95] The normal mucociliary clearance half time is approximately 24 hours. Delayed mucociliary clearance is seen in patients with airway inflammation (e.g., cystic fibrosis, COPD, asthma, or viral respiratory tract infections), following bronchial surgery, or after irradiation.

Scintigraphic assessment of alveolar–capillary membrane integrity and mucociliary clearance has not gained wide clinical use,[93] but it is employed in the development of orally inhaled drugs that are administered by inhalation by assessing their deposition patterns, extent of delivery, and depth of penetration into the lungs.[96] In addition, the technique is applicable in quantification of the impact of new drugs on the rate of mucociliary clearance—a key biomarker for products in development for the treatment of respiratory diseases.[97]

POSITRON EMISSION TOMOGRAPHY

PET is used in assessing nonmalignant thoracic disease, as well as pulmonary nodules and known or suspected malignancy. Following are considered basic principles and the role of PET in evaluating inflammatory lung diseases in the overall population, and infections in immunocompromised hosts. Comparison is made with other diagnostic tests, including ^{67}Ga-citrate scanning. The role of PET in assessment of lung nodules and cancer is discussed in a separate section (see Role of Positron Emission Tomography in the Assessment of the Solitary Pulmonary Nodule and Lung Cancer).

BASIC PRINCIPLES

PET is a nuclear medicine imaging modality that provides a 3D image of molecular processes in the body. A PET scan detects gamma rays emitted by positron-emitting tracers. The most commonly used radiopharmaceutical in clinical PET is 2-[^{18}F] fluorodeoxy-D-glucose (FDG), a fluorine-labeled glucose analog with a favorable, 110-minute half-life. FDG competes with glucose for transport into cells and for enzymatic phosphorylation by hexokinase. Unlike glucose, once phosphorylated to FDG-6-phosphate, FDG does not undergo further metabolism; rather, it is trapped inside the cell, and its net accumulation allows for detection by PET.[98]

FDG uptake is proportional to the metabolic activity of the cells that have undergone malignant transformation and, as such, have increased glucose transport and metabolism and increased hexokinase activity. FDG accumulation also depends on various factors, including cellular mitotic rates, level of hypoxia (hypoxia-inducible factor-1-alpha upregulates glucose transport receptors), and degree of cell differentiation (well-differentiated tumors have low FDG uptake).[99] In addition, inflammatory cells share many of the same features as malignant cells; therefore, FDG-PET imaging can be employed to assess infectious and inflammatory processes and diseases. FDG-PET imaging is performed in the fasting state to minimize competitive inhibition of FDG uptake by circulating glucose in the plasma (hyperglycemia may result in decreased FDG accumulation in either malignant or inflammatory cells).

A key advantage of PET over conventional imaging techniques is the possibility of accurate quantification of the ongoing metabolic activities in normal or diseased states. The most common means used for this purpose is measurement of the standardized uptake value (SUV), a semiquantitative expression of the intensity of FDG accumulation in a region of interest (ROI) assigned on the PET scan. SUV normalizes the amount of FDG accumulation in an ROI to the total injected dose and the patient's body weight. It is calculated by dividing the mean activity within a selected region (or volume) of interest (in mCi/mL) by the injected dose (in mCi/kg). SUVmax is derived from the single voxel showing the highest uptake within a defined ROI, which typically represents the most metabolically active part of a tumor or inflammatory process.[100,101] However, it is important to note that several factors can impact SUV, including extravasation of the compound administered, hyperglycemia, respiratory motion, time from injection, and size of ROI.

Today, the mainstay for PET imaging is integrated PET/CT scanners, which allow combining metabolic and structural imaging modalities into a single device. Based on existing data from the past decade, PET/CT scans have been shown to be superior to images generated from separate PET and CT studies for assessing a multitude of disorders.[102] The newest generation of PET/CT scanners contain a state-of-the-art multidetector CT machine that provides up to 128 slices, and time-of-flight PET technologies that reconstruct high-quality images using low FDG doses and short scan times, especially in large patients.[103] PET/CT has some limitations related to attenuation artifacts, leading to false-positive results on corrected images. In addition, motion and misregistration between PET and CT images can also result in major artifacts in regions adjacent to the heart and diaphragm.[104] Combined PET/MRI systems are now commercially available, but their added potential clinical benefit has not yet been validated.[105] This is particularly true in thoracic disorders.

ROLE OF POSITRON EMISSION TOMOGRAPHY IN PULMONARY INFLAMMATION AND INFECTION

FDG-PET has been used in the evaluation of patients with a variety of inflammatory disorders, including venous thromboembolic disease, infections in immunocompromised hosts, and other noninfectious inflammatory conditions. Each of these entities is discussed in subsequent sections.

Potential Role for FDG-PET in Evaluating Suspected Venous Thromboembolism

In recent years, FDG-PET/CT has been explored in many inflammatory conditions. Activated inflammatory cells demonstrate increased FDG uptake due to increased numbers of cell surface glucose transporters following cellular stimulation by various cytokines.[106] Similar biochemical changes are also seen with VTE.

Based on our own experience and that reported in the literature,[107] the potential value of PET in assessing VTE is clear for several reasons. Current imaging techniques, which are based on structural detection of thrombi, are limited; DVT and PE are only two manifestations of VTE, which may occur in parts of the venous system (e.g., within the pelvis) that are not easily accessible by conventional methods. This limitation also applies to the detection of occult disease (e.g., cancer), which is often a key factor in developing VTE (Fig. 32-7). Furthermore, structural imaging techniques cannot differentiate among different phases of thrombus formation, which may hold therapeutic implications.

We believe that many of these shortcomings will be overcome by using FDG-PET/CT. Several case reports have addressed the incidental detection of VTE with FDG-PET/CT in patients with

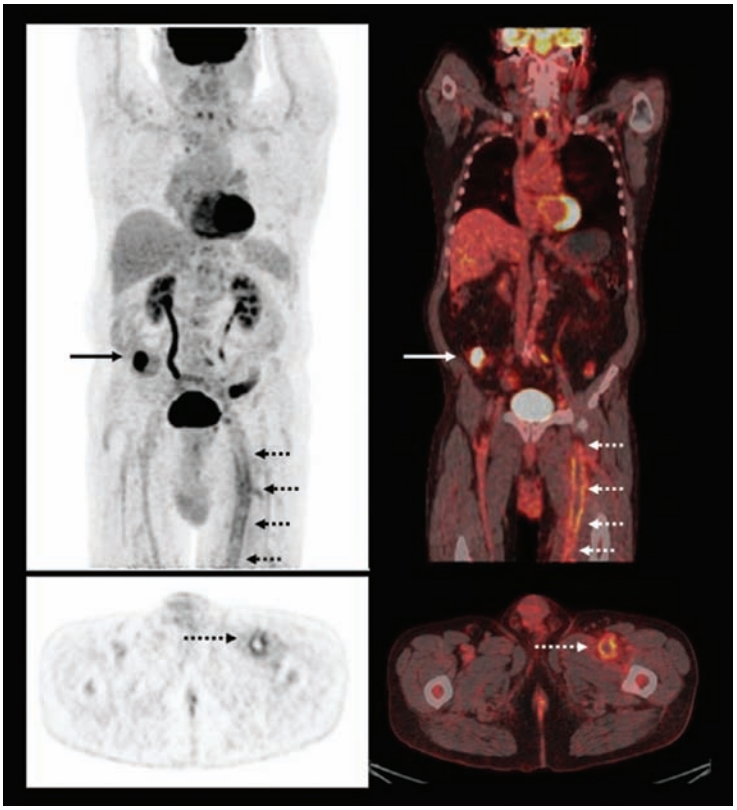


Figure 32-7 Left femoral thrombosis on FDG-PET/CT scan. Maximum intensity projection PET scan (**top left**), transaxial PET scan (**bottom left**), fused coronal PET/CT scan (**top right**), and fused transaxial PET/CT scan (**bottom right**) in a patient with venous thromboembolism having a FDG-PET/CT in search of underlying malignancy. Increased FDG uptake is seen along the acutely thrombosed vein *(interrupted arrows)*, and focally increased FDG uptake is seen in the cecum *(solid arrows)* corresponding to a biopsy-proven colon cancer.

cancer or bacteremia.[108,109] Inflammatory processes also play a key role in nonmalignant, noninfectious VTE, that is, local vessel wall inflammation and inflammatory components, including activated leukocytes in the thrombus itself.

In a small, prospective, proof-of-concept series,[110] both DVT and PE were shown to be visible on FDG-PET/CT. All patients with proved acute lower extremity DVT had marked FDG uptake along the venous wall at the site of thrombus. Diagnosis was established by positive compression ultrasound in patients with symptoms less than a week; no history of cancer, infection, or prior DVT; and a high clinical probability by Wells' DVT score. Conversely, none of the control patients with suspected, but disproved, DVT had FDG uptake in any part of the venous vasculature. The diagnosis was disproved by negative compression ultrasound in patients with symptoms less than a week; no history of cancer, infection, or prior DVT; and a low clinical probability by Wells' DVT score. Results were more equivocal in PE with some patients with high probability V/Q scans showing no FDG uptake in the pulmonary arteries. However, this may be attributed to significantly longer symptom duration (i.e., months) in some patients. It may, in fact, be that FDG-PET/CT was truly negative for active thrombi, since recent data suggest a significant decrease in FDG avidity over time.

In a pivotal study of 12 patients with confirmed proximal thrombosis in the lower extremity, the authors not only found a specificity of 87.5% to 100% and sensitivity of 87.5% to 100% (depending on SUVmax threshold used), but also a steady decrease in SUVmax and possible complete normalization within 3 months.[111] These findings are in accordance with VTE pathophysiology: The thrombus may be classified as acute when inflammatory cells and mediators are abundant, subacute with subsiding inflammation and increasing fibrosis, and finally, chronic with recanalization and loss of inflammation. This pathophysiology will have significant clinical implications, since active thrombi need therapy, while unresolved old clots require no treatment. However, a substantial fraction of patients with VTE experience symptoms of recurrence, and in as many as half the morphologic features suggestive of the diagnosis remain for years after the first event.[107] FDG-PET/CT likely will differentiate new, active clots from old, inactive ones and facilitate an individualized therapeutic approach.

Although the literature is still sparse, the role of FDG-PET/CT imaging appears to be very promising in VTE and may contribute significantly by detecting clots at any location throughout the body, by early diagnosis of underlying malignancy, and by differentiating acute from chronic thrombi.

Imaging of the Thorax in the Immunocompromised Host

In the last three decades, ^{67}Ga-citrate and white blood cells labeled with ^{111}In or ^{99m}Tc were considered as appropriate agents for imaging pulmonary infection and inflammation. However, due to poor image quality, laborious labeling techniques, and the requirement for imaging several days after injection, imaging with either ^{67}Ga-citrate or radiolabeled white blood cells is now considered obsolete. In recent years these methods have been largely replaced by FDG-PET/CT in the evaluation of suspected infection or inflammation in many anatomic locations. This is also the case in the lungs, where FDG-PET/CT is employed for evaluating suspected pulmonary infections, fever of unknown origin in the immunocompromised host (Fig. 32-8), opportunistic infections in patients infected with

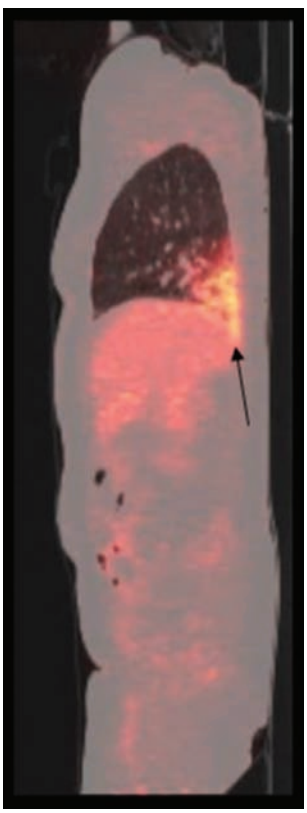


Figure 32-8 Fever of unknown origin in an immunocompromised patient with a kidney transplant. Conventional chest x-ray was normal. Fused sagittal FDG-PET/CT image shows characteristically increased FDG uptake in the right lower lung *(arrow)* consistent with lobar pneumonia.

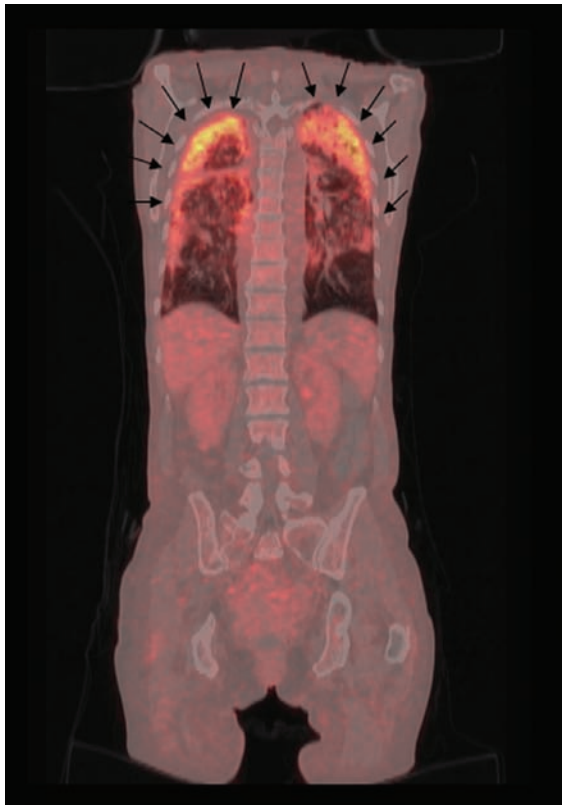


Figure 32-9 *Pneumocystis jirovecii* pneumonia. Diffuse, markedly increased FDG lung uptake bilaterally *(arrows)* in a patient with human immunodeficiency virus.

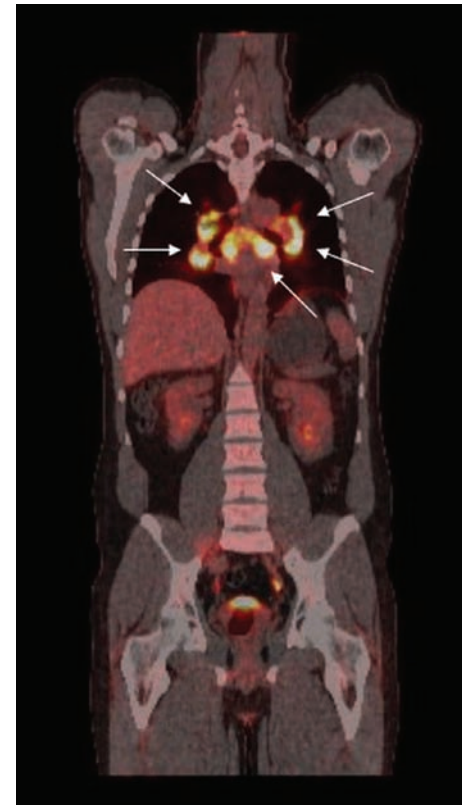


Figure 32-10 Sarcoidosis. Typical presentation of sarcoidosis on FDG-PET/CT with markedly increased FDG uptake in mediastinal and hilar lymph nodes *(arrows)*. Similar patterns are seen in patients with lymphoma.

HIV (Fig. 32-9), and a multitude of inflammatory disorders.[112] In spite of limited data, an early pilot study also suggested that FDG-PET might be helpful in determining treatment response in patients with tuberculosis.[113]

Noninfectious Inflammatory Lung Disease

^{67}Ga-citrate lung imaging has been used to quantify the degree of alveolitis in various interstitial lung diseases, particularly sarcoidosis and idiopathic pulmonary fibrosis. Unfortunately, pulmonary accumulation of ^{67}Ga in idiopathic pulmonary fibrosis was found not to be reliable in predicting the response to treatment or prognosis.[114] Also, in these settings, FDG-PET/CT appears to be substantially superior to ^{67}Ga. A novel potential indication is the assessment of inflammatory disease activity in COPD using FDG-PET/CT. Even with sparse reports in the literature, the evidence points toward a correlation between the distribution and severity of emphysema and the degree of FDG uptake, which may have significant implications for managing patients with this serious disorder.

Sarcoidosis is a multisystem inflammatory granulomatous disease, which involves the lungs in 90% of patients; it may affect any organ in the body. Scintigraphy with ^{67}Ga-citrate has been advocated for assessment of disease activity, but in recent years, this technique has been overshadowed by FDG-PET, which has several technical advantages, including lower radiation exposure, shorter time interval between injection and imaging, and higher quality images. Hilar and mediastinal lymph nodes (as well as any other soft tissues) harboring active granulomas due to sarcoidosis accumulate FDG (Fig. 32-10). Although FDG-PET cannot distinguish sarcoidosis from other diseases, such as Hodgkin or non-Hodgkin lymphomas, the technique is quite effective in assessing the extent of disease after an initial diagnosis, thereby selecting the appropriate site for a successful biopsy. FDG-PET can also provide a means for assessing response to treatment (Fig. 32-11).

FDG-PET has been found to be more sensitive (97%) than ^{67}Ga-citrate scintigraphy (88%) in detecting active sarcoidosis.[115] Comparative studies have shown that FDG-PET can detect more intra- and extrathoracic lesions than ^{67}Ga scintigraphy, with better interobserver agreement.[115–118] High FDG uptake in the involved lung parenchyma correlates with disease severity as revealed by bronchoalveolar lavage.[119] FDG-PET will likely have an increasing role in evaluating the efficacy of therapeutic interventions in this serious disease.[118] In a recent study of 90 patients with chronic sarcoidosis and persistent symptoms, FDG-PET/CT proved helpful in detecting active inflammatory sites, especially in patients with normal ACE levels, thereby influencing adjustment of therapy.[120]

Pneumoconioses may be progressive, even after dust exposure has ceased. The inhaled particles activate pulmonary macrophages that secrete cytokines that mediate an inflammatory reaction, inducing fibroblast proliferation and collagen deposition. FDG is taken up by both fibroblasts and alveolar inflammatory cells. The intensity of pulmonary FDG uptake in pneumoconioses depends on whether active inflammation (increased uptake) or end-stage fibrosis (reduced uptake) predominates at the time of the scan.[121] In addition, progressive massive fibrosis has been shown to be associated with increased FDG accumulation.[122] The findings from FDG-PET have direct clinical implications, as therapeutic interventions are ineffective in end-stage fibrosis.

Interstitial lung disease may also be FDG-avid, but there is limited data on the use of FDG-PET in this setting (Fig. 32-12). In a small prospective study of 21 patients, FDG-PET did not allow differentiation of idiopathic from nonidiopathic pulmonary fibrosis.[123] However, dual–time point FDG-PET imaging holds promise in differential diagnosis and prediction of disease progression in patients with idiopathic interstitial pneumonia.[124]

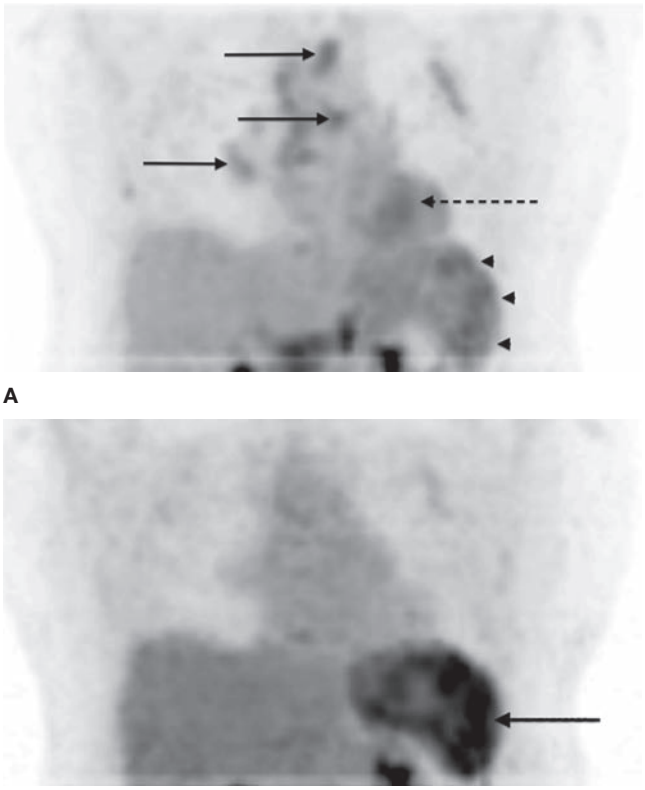


Figure 32-11 **A.** FDG-PET/CT images of the thorax and upper abdomen reveal significant disease activity in mediastinal and hilar lymph nodes *(solid arrows)*, the myocardium *(interrupted arrow)*, and the spleen *(arrow heads)*. **B.** Following successful treatment, there is substantial response in the affected site in the heart and the lymph nodes. However, there is significantly increased uptake of FDG in the splenic lesions *(solid arrow)*, which demonstrates the complexity of the biologic behavior of sarcoidosis in various organs during the course of the disease.

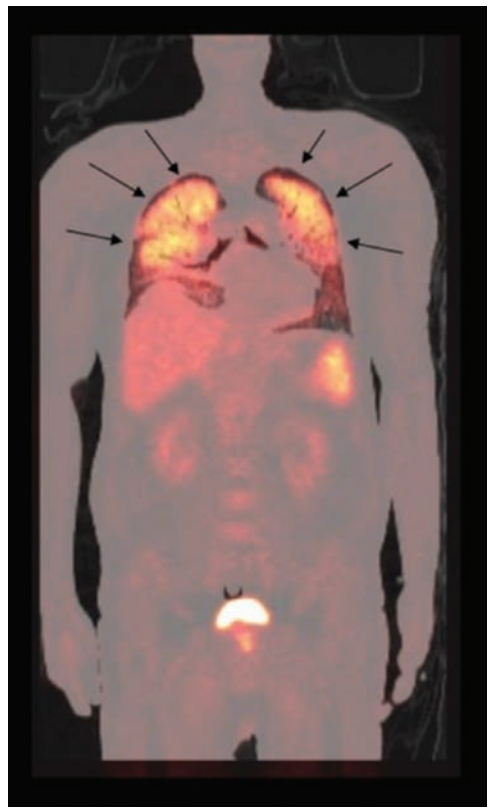


Figure 32-12 Interstitial lung disease. The patient presented with dyspnea and intermittent fever and the PET/CT showed diffusely increased FDG uptake in both lungs *(arrows)*.

ROLE OF POSITRON EMISSION TOMOGRAPHY IN ASSESSMENT OF THE SOLITARY PULMONARY NODULE AND LUNG CANCER

Current clinical indications for FDG-PET imaging in malignant lung disease include evaluation of the solitary pulmonary nodule (SPN), staging of lung cancer (nonsmall cell, small cell, mesothelioma), and planning and monitoring the response to therapy.

EVALUATION OF THE SOLITARY PULMONARY NODULE

An SPN is defined as a round or oval radiographic opacity in the lung parenchyma that measures up to 3 cm in size and is not associated with mediastinal adenopathy or atelectasis (see Chapter 110).[125] An SPN is commonly identified on chest radiographs or CT scans. In the United States, approximately 150,000 new SPNs are diagnosed per year; 30% to 50% of such lesions are malignant and may represent a potentially curable stage of bronchogenic carcinoma.[126] Therefore, early and accurate diagnosis is essential for timely intervention, as lung cancer remains, by far, the leading cause of cancer death among both men and women in the world. Importantly, survival depends on the stage of the cancer when diagnosed.[127]

The most common type of lung cancer is nonsmall cell lung cancer (NSCLC) (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma), which accounts for about 85% of lung cancers.[127] About 10% to 15% of lung cancers are small cell carcinoma, which tend to spread quickly; fewer than 5% of lung cancers are neuroendocrine (carcinoid) tumors, which tend to grow slowly and rarely spread.[127] Most malignant SPNs are adenocarcinoma (47%), followed by squamous cell carcinoma (22%), and small cell lung cancer.[126] Of benign SPNs, about 80% are caused by infectious granulomas.[125]

While a number of benign etiologies for SPNs may have a characteristic appearance on CT, many cannot be characterized accurately using CT and often require further invasive assessment for accurate diagnosis. Certain factors, including smoking history, characteristics of the nodule (size, edge irregularity, and spiculation, pure ground-glass opacity, and absence of calcification), and the age when such lesions are detected are features that determine the probability of malignancy. Despite application of radiographic and other clinical criteria employed for distinguishing benign from malignant lesions, considerable overlap exists.[128] CXRs and CT scans are not accurate in differentiating benign from malignant noncalcified pulmonary nodules that range from 1 to 3 cm in diameter. However, benign patterns of calcification and morphologic stability over 2 years are the most reliable signs of benignity.[128] Bayesian analysis can be used to stratify risk (based on clinical information and imaging characteristics) and guide management of SPN.[129]

FDG-PET provides an accurate, noninvasive diagnostic assessment of SPNs, without the morbidity and costs associated with invasive tissue sampling.[130] In a prospective multicenter trial designed to determine the utility of FDG-PET in discriminating between benign and malignant pulmonary nodules, the sensitivity and specificity of FDG-PET ranged from 92% to 98% and 69% to 100%, respectively (Table 32-6).[130] False-positive studies are seen with active granulomas due to aspergillosis, tuberculosis, or sarcoidosis.[106] False-positive findings may also be related to injection technique (Fig. 32-13). False-negative results are noted with hyperglycemia, malignancies that have a low metabolic activity (e.g., adenocarcinoma *in situ*, previously known as bronchoalveolar cell carncinoma, or carcinoid tumors),[131] and nodules that are <8 mm in diameter.

TABLE 32-6 FDG-PET in Evaluation of Solitary Pulmonary Nodules

Nodule Size (cm)	Type of Analysis	Sensitivity %	Sensitivity 95% Confidence Interval	Specificity %	Specificity 95% Confidence Interval	Accuracy (%)
≤1.5	SUV	80	60–100	95	85–100	88
	Visual	100	100–100	74	55–93	
>1.5	SUV	96	90–100	80	55–100	93
	Visual	98	94–100	60	45–74	91
≤3	SUV	90	82–98	92	85–99	91
	Visual	98	94–100	69	56–82	88
All sizes	SUV	92	82–100	90	79–100	91
	Visual	98	82–100	69	57–81	89

Source: Adapted with permission from Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol. 1998;16(3):1075–1084.

In one meta-analysis of 40 studies that included 1474 pulmonary lesions evaluated using FDG-PET (including dedicated and gamma camera-based PET), the technique had an average sensitivity of 97% and specificity of 78%.[132]

In general, SUVmax >2.5 has been shown to be very sensitive and specific for differentiating malignant lesions from benign ones.[133] Several studies have shown that no significant differences are noted between results using a semiquantitative analysis of FDG uptake with SUV and those based on qualitative visual assessment.[132,134,135] FDG uptake greater than that in the liver or mediastinum (which typically have an SUV of about 2.0) is considered indicative of malignancy.[130] Visual analysis may be more sensitive for nodules that are smaller than 1.5 cm in diameter, but it carries a lower specificity.[130] Lesions that have no visually detectable FDG uptake have a very low probability for malignancy.[136]

The low accuracy of FDG-PET in assessing nodules having a "ground-glass" or "mixed" appearance on CT scanning is likely related to the cell types that predominate in these lesions, including pure adenocarcinoma *in situ* (bronchioloalveolar cell cancer) or adenocarcinomas with bronchioloalveolar features.[137] In a study of 344 patients in whom a definitive diagnosis was known (prevalence of malignancy: 53%, average size of nodule: 16 mm), FDG-PET had a sensitivity of 92% compared with 96% for CT, but the specificity of PET was markedly better than that of CT, at 82% versus 41%.[138]

As noted previously, the sensitivity of FDG-PET is a function of lesion size and the degree of respiratory motion. In one study addressing the issue of size, the technique's sensitivity in detecting malignancy was 69% for nodules ranging from 5 to 10 mm in diameter and 95% for nodules >10 mm in diameter.[139] The lower limit of spatial resolution of PET, which is about 5 to 6 mm, is lower than

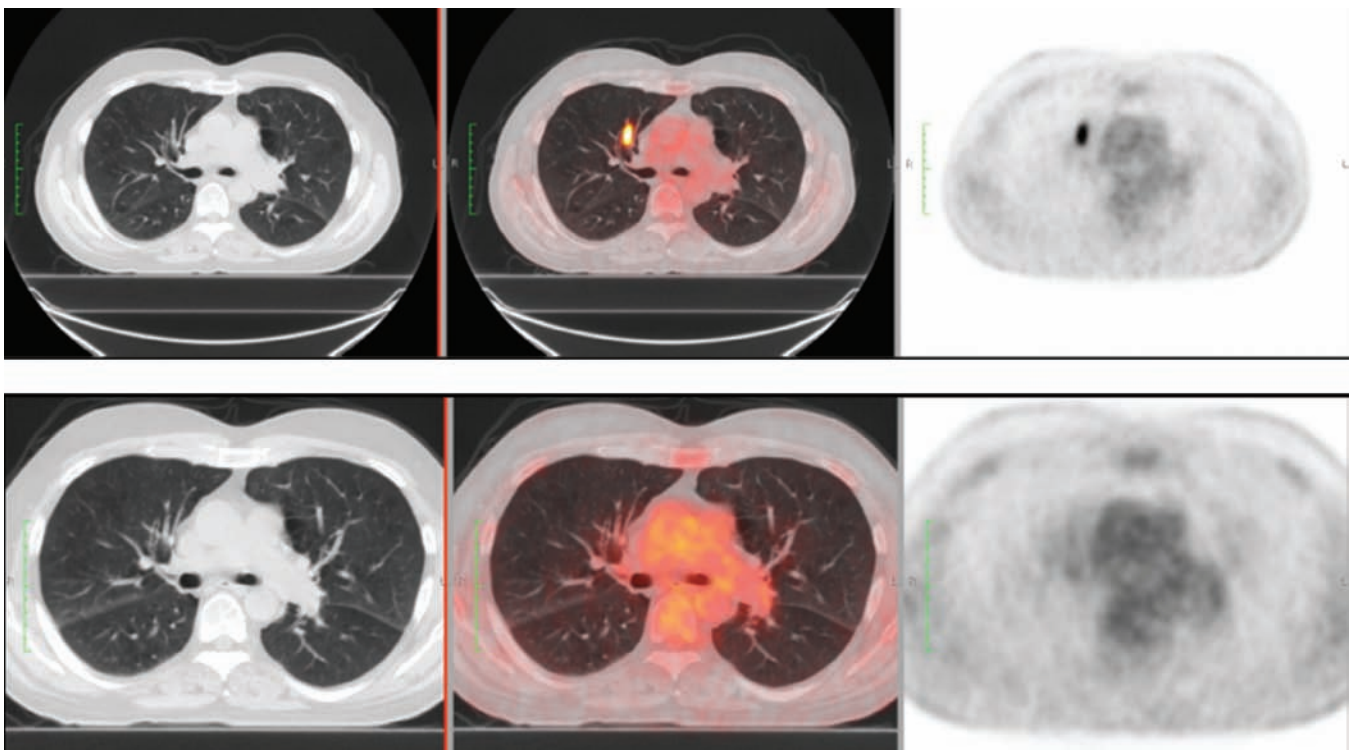


Figure 32-13 A patient referred for characterization of the right upper lobe pulmonary nodule. Transaxial CT, fused PET/CT, and PET images at baseline (**top row**) show solitary, intense focal uptake in the right upper lope. The intense focal uptake was not present in a repeat scan one week later (**bottom row**). This is an example of a false positive finding related to injection technique.

that of CT or MRI. Therefore, PET is not recommended for SPN <8 mm.[140] One method aimed at compensating for this limitation is based on using lesion size measured on CT imaging to correct the underestimated SUV with conventional measurements.

Lung cancers have a wide range of FDG uptake. Furthermore, while most infectious or inflammatory pulmonary disorders generally have a lower FDG uptake than malignancies, overlap exists. An SUV threshold of 2.5, measured at a single point in time, has been proposed to separate malignant (higher SUV) from benign (lower SUV) disorders. Based on the observation in animal and human studies that FDG uptake by malignant tumors increases over time, while that of inflammatory tissue decreases, dual–time point FDG-PET scanning has been proposed as a potentially useful means of improving discrimination between benign and malignant diseases.

Using dual–time point FDG-PET scanning, images are obtained 1 hour and a later time point after administration of FDG. In one study in which an SUV cutoff value of 2.5 and a 10% increase in SUV were used to indicate malignancy, the sensitivity and specificity of FDG-PET were 80% and 94%, respectively, for the single–time point method, and 100% and 89%, respectively, for the dual–time point technique.[141] Recent meta-analysis comparing diagnostic performance of integrated PET/CT scanners showed that dual–time point FDG-PET/CT is more specific than single–time point FDG-PET/CT.[142] Dual time imaging is not required in lesions with a baseline SUV of <1.0, since these lesions have a very high likelihood of being benign, and dual time imaging may result in false-positive examinations.[141] Even for nodules with SUVmax of <2.5, dual time imaging technique may not discriminate accurately between benign and malignant lesions, particularly in areas with a high incidence of granulomatous disease, since false-positive examinations have been reported in association with granulomatous inflammation.[143]

In a study comparing the accuracy of integrated FDG-PET/CT scanning with dynamic CT scanning for pulmonary nodule characterization, FDG-PET/CT scanning was found to be more sensitive and accurate than dynamic CT scanning. The sensitivity, specificity, and accuracy for malignancy with dynamic CT scanning were 81%, 93%, and 85%, respectively, whereas the values for PET/CT scanning were 96%, 88%, and 93%, respectively.[144] Assessment of multiple pulmonary nodules using FDG-PET is limited because of false-positive findings in instances of active granulomatous disease, such as tuberculosis, fungal disease, sarcoidosis, or rheumatoid lesions. In this setting, pattern recognition on CT, in combination with FDG-PET, may improve characterization of the lesions.

Guidelines from the American College of Chest Physicians (ACCP) recommend use of FDG-PET in patients where the probability of cancer is low or moderate (5%–60%) and an indeterminate nodule measures at least 8 to 10 mm.[140] Current National Comprehensive Cancer Network (NCCN) guidelines version 4.2014 recommend FDG-PET for the diagnosis of suspected NSCLC in solid, noncalcified pulmonary nodules >8 mm in diameter.[145] PET/CT scan is not recommended as a screening tool for healthy individuals, since the likelihood of finding cancer is extremely low and the risk increased with detecting harmless findings that may lead to more tests or invasive procedures.[66]

We wish to point out that the data in the literature are based on assigning standard ROIs to the lesions visualized by FDG-PET. Unfortunately, because of the limited spatial resolution of PET imaging, along with respiratory motion of pulmonary lesions, the SUVs generated by this approach result in substantial underestimation of values; the degree of underestimation is proportional to the size of the lesion and the degree of respiratory motion. The physical factors described are known as the "partial volume effect" and, as such, introduce substantial errors to the quantitative data from PET studies, particularly those performed in the evaluation of pulmonary nodules.[146] Therefore, methodologies that can correct for partial volume effects should be employed for accurate measurement of metabolic activity of the lesions assessed. By adopting this approach, significant changes will be noted in the SUVs in most clinical settings. Therefore, total reliance on what has been described in the literature will result in significant mismanagement of patients with SPNs.[147] In particular, adopting an SUV of 2.5 as a threshold for separating malignant and benign lesions is fraught with error and should be abandoned. Many lesions that are smaller than 3 or 4 cm will be prone to such errors.

USE OF POSITRON EMISSION TOMOGRAPHY IN LUNG CANCER

The application of FDG-PET in assessing NSCLC is considered later, followed by a discussion of FDG-PET in small cell lung cancer.

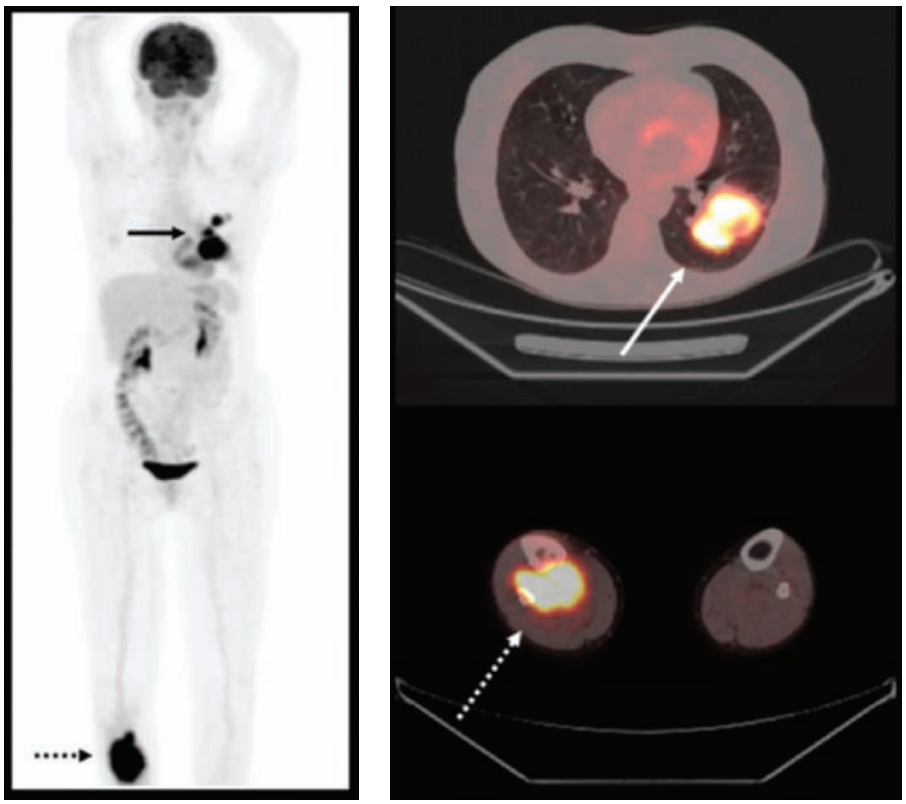
Nonsmall Cell Lung Carcinoma

A major role of FDG-PET is in the staging of NSCLC. Correct lung cancer staging is important because treatment options and prognosis vary significantly by stage. FDG-PET imaging may have a significant impact on patient management by identifying unsuspected sites of disease and by guiding selection of a biopsy site (Fig. 32-14). Similarly, a negative PET scan indicates a low likelihood for malignancy and supports use of conservative management and follow-up (Fig. 32-15). Patients with stage I or II NSCLC are typically referred for surgical resection, while those with stage III or stage IV disease are almost never surgical candidates; in these advanced stages, chemotherapy, radiation therapy, or both may be offered.

The basis for staging NSCLC is the TNM system. For T (tumor) staging, CT and MRI remain the best imaging modalities to demonstrate the local extent of the tumor and its relationship to adjacent organs and vessels. FDG-PET is limited for T staging due to its inability to accurately define the tumor limits. However, FDG-PET/CT has demonstrated a clear advantage in T staging of certain cases, especially in areas of postobstructive atelectasis[148] or low CT density variation and may in the future replace CT and MRI alone for this purpose.[149,150]

In a prospective study of 50 patients with NSCLC, integrated FDG-PET/CT provided additional diagnostic information in 41% of patients and was significantly more accurate in TNM disease staging than either PET or CT alone.[151] Integrated PET/CT provides important clinical information by virtue of accurate localization of known disease and identification of lesions that do not consistently accumulate FDG, such as carcinoid tumors and adenocarcinoma *in situ* (bronchioloalveolar cell carcinoma).[151] PET/CT without contrast-enhanced CT is unable to distinguish confined, centrally located tumors from those producing direct invasion of mediastinal structures. Therefore, clinicians may still rely on contrast-enhanced CT scans to help define mediastinal vascular invasion. From a prognostic point of view, FDG uptake in NSCLC has been correlated with tumor growth rate, aggressiveness, and proliferation capacity, and it has been found to be an independent prognostic factor correlated with survival in patients with NSCLC, especially early-stage disease.[152]

Mediastinal nodal staging most often determines appropriateness for surgical resection. Mediastinal staging using CT scanning is based primarily on assessment of lymph node size; nodes <1 cm in their short axis are considered benign, while those >1 cm are considered potentially malignant. Unfortunately, up to 21% of nodes <1 cm are malignant, and up to 40% of nodes >1 cm are benign.[153,154] A systematic review of the medical literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer showed a sensitivity and specificity of 51% and 86%, respectively.[155] A large meta-analysis reported the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes as 61% and 79%, respectively.[156] These results were similar to an earlier meta-analysis that reported an average sensitivity and specificity of 60% and 77% for CT scanning, respectively (using a transaxial short axis >1.0 cm).[157] In that same meta-analysis of 14 studies (514 patients) for FDG-PET and 29 studies (2,226 patients) for FDG-PET/CT, sensitivity and

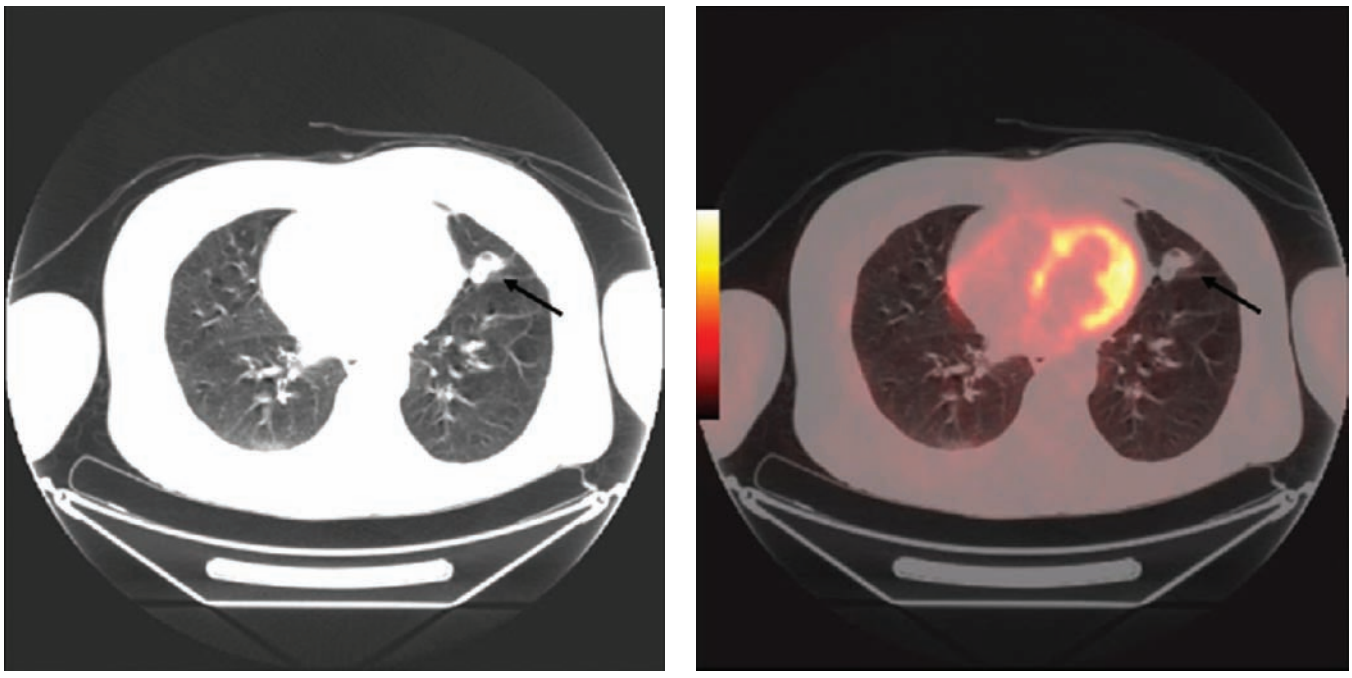


A B

Figure 32-14 Lung cancer. Preoperative evaluation of a patient with a lung cancer in the left lower lobe intended for curative surgery. Whole-body maximum intensity projection PET (**A**) and fused transaxial PET/CT (**B**) show increased FDG uptake in the lung tumor *(solid arrows)*, and unexpected focal FDG uptake in a soft tissue mass in the left proximal tibia *(interrupted arrows)*. Biopsy showed metastasis from the lung cancer obviating surgery.

specificity were higher for determining nodal status in patients with NSCLC (sensitivity and specificity of 79% and 91%, respectively).[157]

The accuracy of FDG-PET in the evaluation of mediastinal lymph nodes depends on the size of the nodes. As reported in a large meta-analysis of 39 studies, the sensitivity and specificity of FDG-PET was 100% and 78%, respectively, in patients with enlarged mediastinal lymph nodes.[156] Sensitivity and specificity were 82% and 93%, respectively, for normal-sized nodes.[156] Positive PET findings in this situation should be confirmed by directed biopsy, as inflammatory or infectious processes can lead to false-positive results. Absence of tissue diagnosis could result in patients with surgically resectable disease being denied curative surgery.



A B

Figure 32-15 Suspected lung cancer. CT scan (**A**) shows a mass suspected of malignancy *(arrow)*. Transaxial fused PET/CT (**B**) shows no abnormal FDG uptake in the mass *(arrow)* consistent with benign process. There is slight misalignment between CT and PET images, but this had no bearing on the interpretation.

Exact classification as N1 or N2 disease is somewhat difficult using FDG-PET alone; anatomic information provided by a CT scan as part of combined FDG-PET/CT imaging is important for this purpose. Integrated PET/CT scanners combine the advantages of both studies, but there are as yet few studies addressing the accuracy of this modality. In one study, the accuracy of mediastinal lymph node staging increased from 89% with FDG-PET alone to 93% with FDG-PET/CT, compared to 63% with CT; a change in the planned treatment was noted in up to 15% of patients.[154] In another study, FDG-PET/CT was significantly better than CT alone for nodal staging: Sensitivity rose from 70% for CT to 85% for FDG-PET/CT; specificity rose from 69% to 84%; and accuracy rose from 69% to 84%.[158] FDG-PET is the best modality to detect tumor in normal-size lymph nodes.

Using an SUVmax of 2.5 is a reasonable threshold for distinguishing between benignity and malignancy, but SUV may be falsely low in lymph node <1 cm due to partial volume effect, and visual assessment is generally accurate.[159] Lymph nodes containing calcification are more likely to be benign, even if they accumulate FDG.[160] Interestingly, studies have shown that FDG-PET/CT has a lower specificity and accuracy for nodes >1 cm compared with those <1 cm, but it still performs better for large lymph nodes than does CT alone.[161,162] The incidence of false-positive nodes is generally larger than that of true-negative nodes as staged by FDG-PET.[162] For patients with stage II or III disease, the incidence of false-negative results is higher with PET than with mediastinoscopy (11.7% and 3%, respectively).[163] These studies illustrate an important limitation of FDG-PET. Therefore, this modality is not currently considered the "gold standard" for confirmation or exclusion of N2/N3 disease in patients with NSCLC.

The variability in false-positive examinations suggests that FDG-PET results should not replace histologic confirmation for suspected mediastinal nodal metastases.[164] FDG-PET–positive lymph nodes still require pathologic confirmation, usually by mediastinoscopy. Other choices of nodal sampling include transbronchial, transthoracic, or transesophageal needle aspiration, or more extensive surgery. These invasive procedures may be guided by the PET findings, as mediastinoscopy is limited to the anterior mediastinum; in addition, approximately 15% of patients may still be found to have N2 disease at thoracotomy.[165] The use of intraoperative FDG-sensitive gamma probes to guide lymph node sampling following the injection of FDG may be helpful.[166]

While studies have demonstrated that patients with metastases detected at mediastinoscopy have a worse prognosis than patients in whom N2 disease is found only at surgery,[167,168] no prospective studies have yet been conducted to determine whether patients with negative mediastinal nodes on preoperative FDG-PET have a similar prognosis to those in whom N2 disease is found at thoracotomy following a negative mediastinoscopy. Therefore, mediastinoscopy still remains part of the standard protocol for mediastinal staging.[163] Guidelines from the ACCP recommend the use of FDG-PET to evaluate for mediastinal and extrathoracic disease in the staging of patients with clinical IA, IB to IIIB lung cancer being treated with curative intent.[140] Patients with abnormal FDG-PET scan need sampling of abnormal lymph nodes prior to surgical resection of the primary tumor.[140]

In addition to being the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer, whole-body FDG-PET imaging is useful in evaluating extrathoracic sites for possible metastatic disease. FDG-PET is superior to conventional imaging in detecting distant metastases. In one prospective study, FDG-PET showed a high sensitivity and specificity in the detection of distant metastases alone (92% and 83%, respectively); 11% of patients had distant metastases detected by FDG-PET that other modalities had failed to detect.[164] Detection of unsuspected extrathoracic metastases may be identified in 6% to 24% of patients (mean frequency of about 13%), and the likelihood for detecting unsuspected metastases increases with the patient's stage.[163] This is particularly important in patients with locally advanced stage III lung cancer.[169] In one multicenter trial, addition of FDG-PET to the conventional workup prevented unnecessary surgery in one out of five patients with suspected NSCLC, with a 50% decrease in futile thoracotomy in comparison to a conventional workup.[170] The likelihood for occult metastatic disease at presentation can be found in up to 30% of patients with adenocarcinoma or large cell carcinoma, but is less common with squamous cell carcinoma (under 15% of patients).[163]

The two most common sites for NSCLC metastases are the adrenal glands and bone marrow. Studies have shown that FDG-PET has a sensitivity of 93% to 100% for the characterization of metastatic adrenal lesions in patients with bronchogenic carcinoma (specificity, 80%–100% and accuracy, 92%–100%).[171–173] Necrotic or hemorrhagic adrenal metastases and small lesions can lead to false-negative FDG-PET.[173] Despite the fact that benign adrenal adenomas generally demonstrate mild FDG uptake that is less than the liver, false-positive studies may still occur.[172] FDG-PET/CT can improve characterization of adrenal masses by improving the specificity based on the combination of SUV and CT attenuation.[174] A Hounsfield Unit (HU) measurement of <10 is indicative of a benign adrenal lesion, even if the SUV measurement is >3.1.[174]

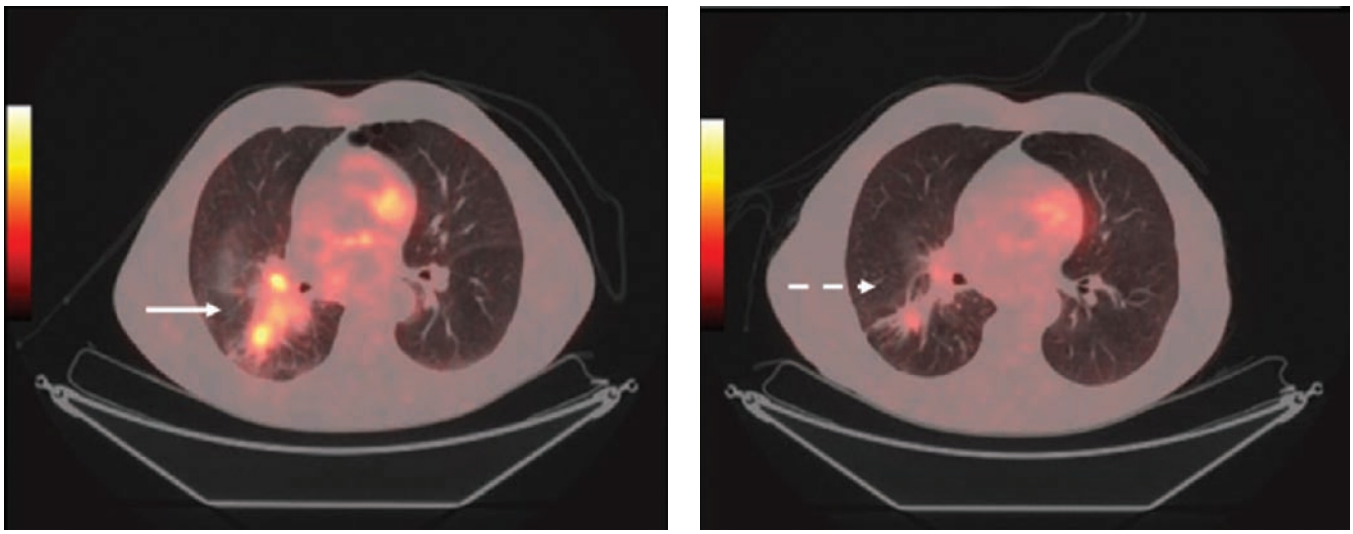
In detecting bone marrow metastases, a comparison of ^{99m}Tc methylene diphosphonate (^{99m}Tc MDP) standard bone scintigraphy to FDG-PET showed a higher accuracy with FDG-PET, (96% vs. 66%).[175] FDG-PET may detect bone marrow metastases before reactive bone formation takes place or prior to development of gross anatomic abnormalities. In a comparison of FDG-PET/CT to ^{99m}Tc MDP and ^{18}F-fluorine PET (F-PET), FDG-PET/CT had a lower sensitivity than F-PET, but was superior to ^{99m}Tc MDP. However, FDG-PET/CT had a higher specificity.[176]

Numerous benign skeletal conditions (including trauma, infection, and physiologic variants) may cause a false-positive FDG-PET. A recent meta-analysis of 17 studies addressed this issue comparing FDG-PET/CT, FDG-PET, MRI, and ^{99m}Tc MDP. The pooled sensitivity of each modality in the detection of bone marrow metastases was 92%, 87%, 77%, and 86%; the specificity was 98%, 94%, 92%, and 88%, respectively.[177]

In the initial evaluation for brain metastases in patients with NSCLC, FDG-PET brain imaging does not provide additional clinical information.[178] Current ACCP recommendations for patients with clinical stage IIIA and IIIB NSCLC are to obtain routine imaging for extrathoracic metastases, including a head CT scan or MRI, plus either whole-body FDG-PET or bone scan plus abdominal imaging.[140]

Until recently, radiation therapy planning has been based on CT imaging because of its excellent delineation of structures in attaining precise assignments of the radiation portals. However, a number of studies have demonstrated the added benefit of PET in defining and refining radiation treatment volumes, thereby reducing (or increasing) the radiation portal and allowing an increase in dose delivery to target tissues, as well as eliminating exposure to normal tissues to avoid toxicity from this therapy.[179] PET/CT is particularly helpful in planning radiation therapy for patients with lung cancer associated with atelectasis. In a prospective study of 76 patients, 34% of patients eligible for radical radiation therapy after conventional staging received palliative therapies instead because of FDG-PET/CT-based detection of advanced disease.[180] FDG-PET/CT frequently changed the planning target volume, which was associated with excellent survival.[180]

FDG-PET imaging may allow for better evaluation of the response to treatment than anatomic imaging, and it may also provide prognostic information that correlates strongly with survival rate following initiation of therapy (Fig. 32-16).[181] Assessment of prognosis can be improved with early FDG-PET imaging, as a 50% decrease in SUV between scans performed at 1 and 3 weeks following initiation of chemotherapy was shown to predict a favorable response.[182]



A B

Figure 32-16 Treatment response in lung cancer. Fused transaxial PET/CT scan at baseline (**A**) showed marked FDG uptake in a tumor in the right lung hilum and mediastinal lymph nodes *(solid arrow)*. Repeat scan (**B**) after three cycles of chemotherapy reveals marked response to treatment *(interrupted arrow)*.

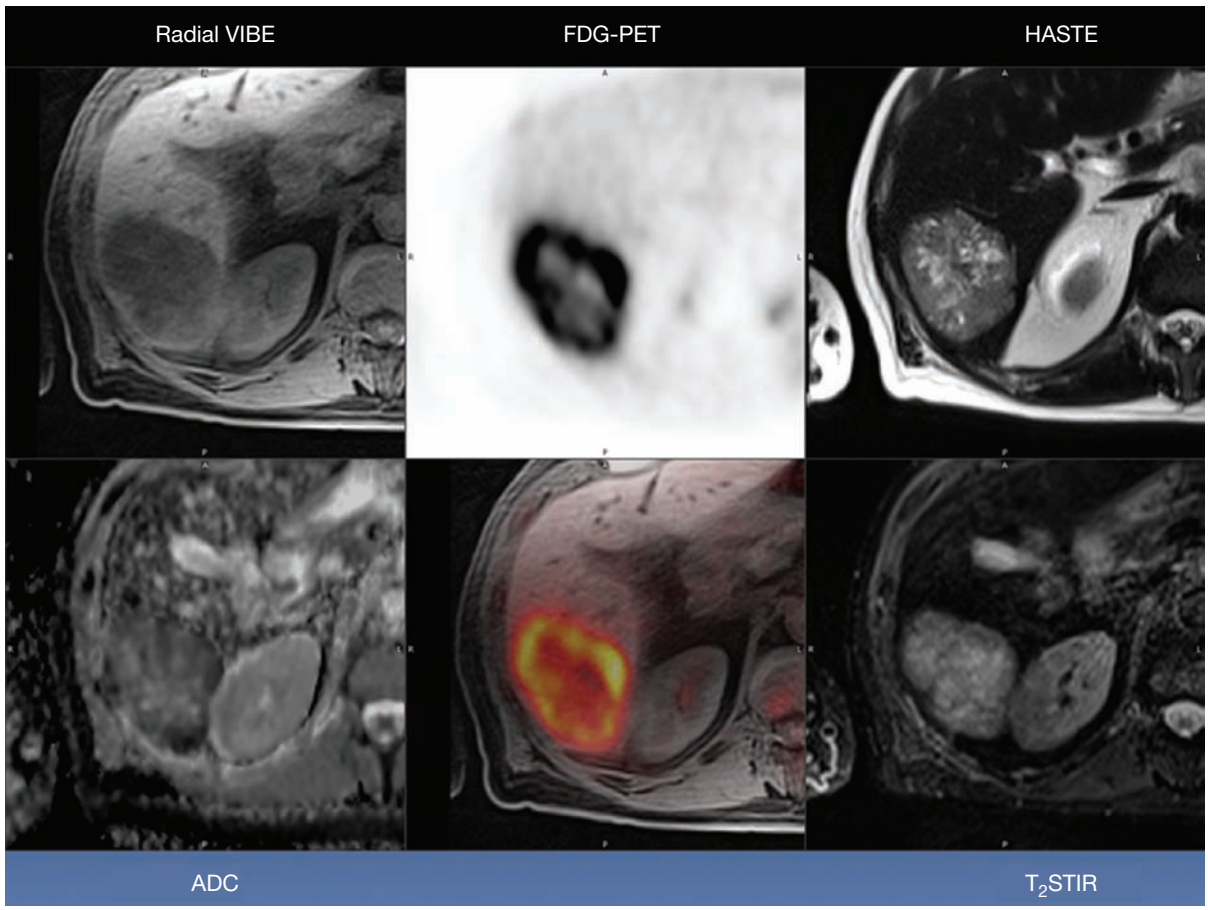


Figure 32-17 A 72-year-old male with lung cancer and liver metastases. Multisequence PET/MR of the liver demonstrates excellent co-registration of PET and multiple MRI sequences. Simultaneous acquisition maximizes accuracy of image registration and facilitates voxel-to-voxel correlations to support quantitative imaging. *(Used with permission of Dr. Kent Friedman. Department of Radiology. Nuclear Medicine Section. New York University School of Medicine, New York, USA.)*

In patients with residual parenchymal abnormalities following radiotherapy for lung cancer, FDG-PET scanning can be used to distinguish between persistent or recurrent cancer and radiation fibrosis.[183] In a study evaluating changes in FDG uptake following definitive radiation therapy, the higher the residual SUVmax in the primary tumor (cutoff, 3.7) or lymph nodes (cutoff, 3.1), the worse was the prognosis.[183] FDG-PET is also useful in assessing response to percutaneous radiofrequency ablation of NSCLC.[184] The novel hybrid method PET/MRI is emerging and shows great potential in lung cancer management (Fig. 32-17).

Small Cell Lung Carcinoma

Small cell lung carcinoma (SCLC) accounts for 18% to 25% of cases of lung cancer. SCLC has a high proliferation rate that results in avid FDG uptake.[185] At presentation, patients are either considered to have limited disease (LD), in which tumor is confined to unilateral chest, or extensive disease (ED), in which tumor has spread to contralateral chest or distant sites. Approximately 60% to 70% of patients present with ED, while 30% to 40% of patients have LD. Except in rare cases of surgically operable, limited-stage SCLC, patients with LD receive chemotherapy and radiation; those with ED are treated with chemotherapy alone. The role of FDG-PET in the staging of SCLC remains controversial, but it may change management in up to 37% of patients for initial staging, and in up to 15% of patients for restaging.[185] Complete metabolic response on posttherapeutic FDG-PET/CT in patients with SCLC is an important prognostic factor, as overall survival is significantly longer compared with that for patients who do not have a complete response.[186]

Mesothelioma

Benign fibrous mesothelioma is a rare, nonmalignant, localized tumor of the pleura that is unrelated to asbestos exposure. The tumor can be cured by excisional surgery. In contrast, malignant pleural mesothelioma (MPM), which is a rare cancer, is the most common primary pleural neoplasm. Affected patients have a median survival of 12 to 18 months. Thus, it is important to differentiate between benign pleural lesions and MPM. The radiologic appearances of benign and malignant pleural diseases are very similar. More than 50% of patients have a pleural effusion at the time of diagnosis; however, pleural fluid cytology is positive in only approximately 25%.[187] Reverse bevel needle biopsy and CT-guided percutaneous needle biopsy of the pleura have low sensitivities of about 21% to 43% and 25% to 60%, respectively.[187] Distinction based on histopathologic criteria is also difficult.

Currently, definitive diagnosis is based on video-assisted thoracoscopic surgery (VATS) (sensitivity, 90%), which, for MPM, carries the risk of tumor seeding along the operative tract. Therefore, radiation therapy is performed to all entry ports following the procedure. CT scan and MRI cannot always differentiate between benign and malignant pleural processes and are of limited value in staging of MPM.[188] Findings from CT and MRI studies can be used in tandem with those from FDG-PET in managing these difficult patients (Fig. 32-18).

Use of FDG-PET in mesothelioma in the mid-90s provided a paradigm shift in the management of patients with this serious cancer.[189] Because of the rarity of this disease, only limited studies have been performed, but FDG-PET has shown promising results in differentiating MPM from benign pleural disease. FDG uptake in MPM is significantly greater in benign pleural disease.[190] For the first time, this approach allowed separating malignant transformations from those that were purely related to inflammatory reactions. This significantly improved the clinician's ability to determine the sites of biopsy in this population. The degree of metabolic activity

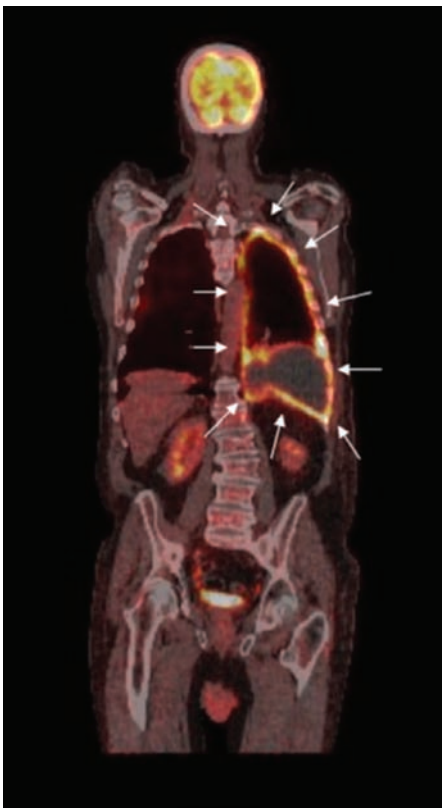


Figure 32-18 Transaxial coronal view of FDG-PET/CT scan demonstrating diffusely increased FDG activity throughout the diaphragmatic, mediastinal, and lateral left pleura, consistent with malignant mesothelioma.

of the lesion has been shown to correlate with survival[191]; higher FDG uptake in MPM is associated with significantly shorter survival.[188] Using the single SUV cutoff technique, however, may not be the optimal approach. Dual–time point imaging and SUVmax on FDG-PET/CT in the delayed phase (120 minutes) have been found to be more reliable, diagnostic, and prognostic factors than that in the early phase (60 minutes)[192]; dual–time point imaging enhances the role of FDG-PET in this population.[193] This approach allows separation of malignant from inflammatory lesions. While malignant lesions show increasing activity over time, inflammatory lesions show a decline. In recent years, global disease assessment has become feasible using modern quantitative techniques. In general, it provides a single number expressing the disease activity in the entire body as one summed score, "the global disease burden," instead of assessing the parameters independently on a per-lesion basis.[194] The so-called "image segmentation methodologies" permit better definition of the boundaries of malignant lesions based on PET images and determination of lesional and whole-body metabolic burden.[194]

In addition to differentiating benign from malignant pleural disease and facilitating assessment of prognosis in MPM, FDG-PET has shown good results in staging, planning of radiotherapy, evaluation of therapy response, and posttreatment surveillance.[194] In a study of 15 patients, FDG-PET upstaged 13% of patients, downstaged 27% of patients, and changed management in 20% of cases.[195] In another study of 29 patients, FDG-PET/CT had a major impact on increasing the accuracy of MPM-TNM staging and determining appropriate therapy.[196]

Finally, FDG-PET is useful in identifying the extent of disease locally and in the mediastinum. In addition, it is helpful in

evaluating abnormal findings in the contralateral lung, and in detecting occult extrathoracic metastases. The metabolic response after neoadjuvant chemotherapy, as determined by FDG-PET, was found to be an independent prognostic factor for patients with resectable MPM, thereby helping to determine which patients are good candidates for extrapleural pneumonectomy.[197]

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CHAPTER 33

Pulmonary Function Testing

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INTRODUCTION

The assessment of human pulmonary function dates back to the seventeenth century, when the earliest measurements of tidal volume were noted. In 1800, Humphry Davy employed a hydrogen dilution technique to measure his own residual volume (RV).[1] Subsequently, John Hutchinson, in his treatise, *On the Capacity of the Lungs and on Respiratory Functions,* defined the functional subdivisions of lung volume and reported the results of vital capacity measurements performed in more than 1800 subjects. He related these measurements to the subjects' height, age, and weight, thereby establishing a basis for determining normal values.[2,3]

Progress in development of techniques for pulmonary function testing progressed slowly over the next century. However, in the 1950s, pulmonary physiologists made use of the tools provided by the evolving fields of electronics and computer science. Currently, many techniques exist for assessing both the integrated performance of the cardiovascular and respiratory systems and their individual components. This chapter focuses on commonly used tests of pulmonary function.[4] Detailed assessment of integrated pulmonary and cardiovascular function is described in Chapter 34. Additional tests that have not yet been validated or are not routinely available for clinical purposes[5] are not included in the discussion.

LUNG VOLUMES AND SUBDIVISIONS

Important quantitative aspects of respiratory function are the changes in lung volume with inspiration and expiration and the absolute volume of air that the lungs hold at various times during the respiratory cycle. These volumes and changes in volume are described in subsequent sections.

DEFINITIONS AND ASSESSMENT

For purposes of quantification and comparison, the total volume of gas in the lungs is conventionally subdivided into compartments (volumes) and combinations of two or more volumes (capacities). For many of these subdivisions, the end-expiratory volume – the volume of gas remaining in the lungs at the end of normal expiration – is the point of reference. Lung volumes and capacities are defined in Table 33-1 and are depicted schematically in the tracing shown in Figure 33-1, which was obtained using a device called a spirometer. The relationships between the volumes recorded directly by the spirometer and the other lung volumes and capacities – including total lung capacity (TLC), functional residual capacity (FRC), RV, and inspiratory capacity (IC) – are highlighted in the figure.

Spirometers that measure volume or change in volume versus time have been used extensively in pulmonary function laboratories. Previously, through manual calculations, or, in modern times, through application of microprocessors, the relationships among volume, flow, and time are generated to provide a measure of the respiratory system's ability to move air. Two examples of volume-type spirometers of historical note are shown in Figure 33-2. They are discussed briefly to highlight the ingenuity behind their use in determining clinically important physiologic measurements.

In the water-sealed spirometer (Fig. 33-2A), a mouthpiece is attached to a tube through which air passes into a lightweight bell that is inverted over a water bath. Air movement through the mouthpiece into the bell during expiration causes the bell to rise; conversely, as air is withdrawn from the system during inspiration, the bell falls. The change in volume with time can be recorded on a calibrated rotating drum or digitally noted by a computer and displayed on a screen in both graphic and numeric formats.

In the dry, rolling-seal spirometer (Fig. 33-2B), a cylinder with a rolling plastic seal is substituted for the spirometer bell and its water seal. Movement of air through the mouthpiece effects a change in the position of the piston, which is attached to a variable resistor. The resistor, in turn, generates voltage signals proportional to volume changes reflected in displacement of the piston. These signals are processed by a computer to generate graphic and numeric outputs similar to those of the water-sealed spirometer.

Currently, most pulmonary function laboratories utilize flow-type spirometers using pneumotachographs or rotating turbines to determine airflow. Two types of pneumotachographs are in general use: hot wire and flow resistive. In the hot-wire type, air flowing past

TABLE 33-1 Glossary for Static Lung Volumes and Capacities

Term	Symbol	Definition
Volumes		
Residual volume	RV	Volume of air remaining in the lungs after maximal expiration
Expiratory reserve volume	ERV	Maximal volume of air expired from the resting end-expiratory level
Tidal volume	TV[a]	Volume of air inspired or expired with each breath during quiet breathing
Inspiratory reserve volume	IRV	Maximal volume of air inspired from the resting end-inspiratory level
Capacities		
Inspiratory capacity	IC	Maximal volume of air inspired from the end-expiratory level (the sum of IRV and TV)
Vital capacity	VC	Maximal volume of air expired form the maximal inspiratory level
Inspiratory vital capacity	IVC	Maximal volume of air inspired form the maximal expiratory level
Functional residual capacity	FRC	Volume of air remaining in the lungs at the end-expiratory level (the sum of RV and ERV)
Total lung capacity	TLC	Volume of air in the lungs after maximal inspiration (the sum of all volume compartments)

[a]*The symbol TV is traditionally used for tidal volume to indicate a subdivision of static lung volumes. However, the symbol V_T is used for tidal volume in formulas for gas exchange.*

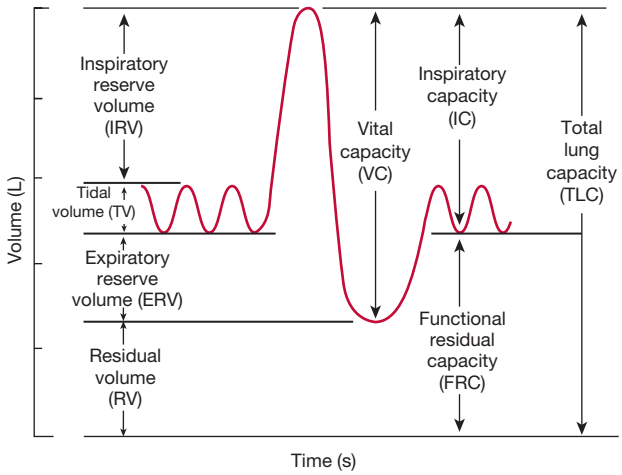

Figure 33-1 The subdivisions of lung volume as recorded by a spirometer. The record is generated on paper calibrated for volume in the vertical direction and time in the horizontal. The term *capacity* is applied to a subdivision composed of two or more *volumes*. The definitions of these subdivisions are found in Table 33-1.

a heated wire cools the wire, thereby altering its resistance in proportion to changes in airflow. Flow-resistive pneumotachographs contain a resistive element composed of parallel tubes (Fig. 33-3), a wire mesh, or a fibrous, paperlike element. Airflow through the resistive element results in a pressure gradient across the device, which can be measured by a very sensitive differential pressure gauge. In the model depicted in Figure 33-3, the array of parallel,

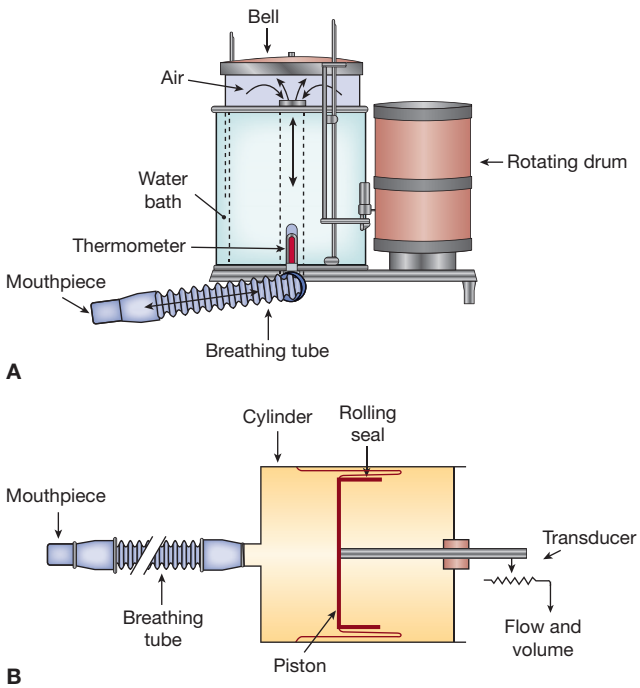

Figure 33-2 Two types of spirometers: water sealed (**A**) and dry rolling seal (**B**). Movement of air through the breathing tube results in movement of the bell (**A**) or piston (**B**). The output signal is either mechanical (pen on rotating drum) or electrical (flow and volume as voltage changes). The primary design criteria for these instruments are that inertia and resistance to airflow must be held to negligible levels, and the calibration must be accurate and stable.

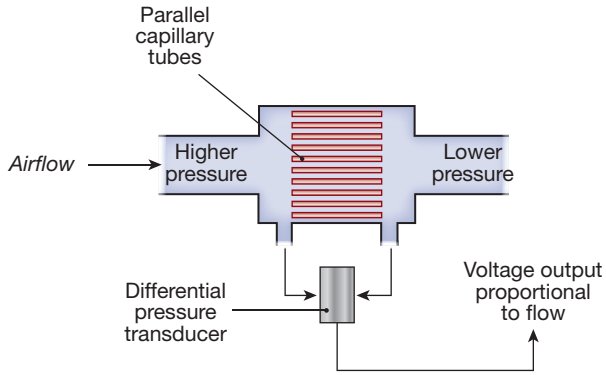

Figure 33-3 Principle of pneumotachography. During unidirectional airflow, a pressure drop is created across a resistive element made up of an array of parallel capillary tubes. The magnitude of the pressure drop is related to airflow, as described by Poiseuille's law for a laminar flow system. The pressure drop is transduced to a proportional voltage output, which can be recorded. A heating element (not shown) maintains the temperature of the expired gas near body temperature.

small-bore tubes maintains a laminar gas flow pattern through the pneumotachograph. As a result, the pressure–flow characteristics of the system can be described by Poiseuille's law:

$$\Delta P = \dot{V}\frac{8\eta l}{\pi r^4}$$

where

ΔP = pressure drop across the resistive element, dyn/cm^2
$\dot{V}$ = gas flow, cm^3/s
η = viscosity of gas, dyn s/cm^2
l = length of resistive element, cm
r = radius of resistive element, cm

Hence, under laminar flow conditions, the flow of gas in each tube is proportional to the pressure drop across the tube. The calculation for the overall pressure drop across the entire resistive element is based on the parallel arrangement of the array of tubes. The pressure drop across the resistive element is sensed by a pressure transducer and converted to a voltage output that is proportional to flow. The flow signal can be integrated electronically to yield volume. The output signals for flow and volume are displayed on a monitor and recorded. Minimal standards have been established by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (Table 33-2) for spirometers used either for diagnostic purposes or patient monitoring.[6–8]

In a diagnostic setting, spirometers are used to (1) evaluate symptoms, signs, or abnormal laboratory tests; (2) measure the effect of disease on pulmonary function; (3) screen persons at risk of having pulmonary disease; (4) assess preoperative risk; (5) assess prognosis; and (6) assess health status before enrollment in strenuous physical activity programs.

On the other hand, spirometers used for patient monitoring are used to (1) assess therapeutic interventions, including bronchodilator therapy, management of congestive heart failure, etc.; (2) characterize the course of diseases affecting lung function (e.g., obstructive or interstitial lung diseases, congestive heart failure, or neuromuscular diseases); (3) track pulmonary function in persons working in occupations or receiving medications known to affect the lung; (4) evaluate large numbers of people in disability assessments; and (5) provide data as part of epidemiologic surveys.[8]

In general, the diagnostic spirometer is used to assess a patient's lung function for purposes of comparison with values expected in a

TABLE 33-2 Minimal Recommendations for Diagnostic Spirometry

Test	Range/Accuracy (BTPS)	Flow Range (L/s)	Time(s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	30		3-L cal syringe
FVC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	15	<1.5 $cmH_2O/L/s$	24 standard waveforms 3-L cal syringe
FEV_1	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	1	<1.5 $cmH_2O/L/s$	24 standard waveforms
Time zero	The time point from which all FEV_t measurements are taken			Back extrapolation	
PEF	Accuracy: ± 10% of reading or ± 0.30 L/s, whichever is greater Precision: ± 5% of reading or ± 0.15 L/s, whichever is greater	0–14		Mean resistance at 200, 400, 600 L/s must be <2.5 $cmH_2O/L/s$	26 flow standard waveforms
$FEF_{25–75\%}$	7.0 L/s ± 5% of reading or ± 0.200 L/s, whichever is even greater	±14	15	Same as FEV_1	24 standard waveforms
Instantaneous flows	±5% of reading or 0.200 L/s, whichever is greater	0–14		<1.5 $cmH_2O/L/s$	Proof from manufacturer
MVV	250 L/min at TV of 2 L within ± 10% of reading or ± 15 L/min, whichever is greater	±14 ± 3%	12–15	<1.5 $cmH_2O/L/s$	Sine wave pump

Note: BTPS, body temperature and pressure, saturated with water vapor; VC, vital capacity; FVC, forced expiratory vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; $FEF_{25–75\%}$, forced expiratory flow, 25–75%; MVV, maximal voluntary ventilation; TV, tidal volume.
Source: Reproduced with permission of Miller MR1, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338.

normal population. The monitoring spirometer, which is less expensive and more portable, is used to evaluate a patient's performance over time and to study large numbers of people for epidemiologic or other purposes.

THE VITAL CAPACITY AND ITS SUBDIVISIONS

Two methods of performing a vital capacity maneuver can be used: closed-circuit and open-circuit methods. In the closed-circuit method, the seated patient, with nose clip in place, breathes quietly into the apparatus. After several breaths to establish the resting end-expiratory level, which serves as a point of reference for all subsequent measurements, the patient is urged to inspire fully and then, after reaching a plateau at maximal inspiration, to expire maximally. This expiration must be performed slowly and evenly; attempts by the patient with obstructive pulmonary disease to maximize flow often reduce expiratory volumes because of dynamic compression of the airways caused by high positive pleural pressures (see Chapter 10). Figure 33-1 illustrates schematically this relaxed or "slow" vital capacity maneuver. From the record, tidal volume, inspiratory reserve volume, expiratory reserve volume (ERV), vital capacity, and IC are calculated. A similar maneuver in which the subject breathes out as rapidly and forcefully as possible after a maximal inspiration provides a measure of the forced vital capacity (FVC). Other timed measurements of expiratory airflow (e.g., the forced expiratory volume in 1 second, or FEV_1) are also determined from this type of record (see Dynamic Mechanical Properties of the Respiratory System).

In the open-circuit method of determining vital capacity, the patient inspires maximally, inserts the mouthpiece, and then exhales with a slow, constant effort to the point of maximal expiration. With this technique, the resting end-expiratory position is not recorded. Thus, only the vital capacity, not its component volumes, can be measured. The open-circuit technique offers some advantages. Since the patient inspires from room air before expiring into the apparatus, concern over acquisition of infection from contaminated inspired air is minimized. In addition, the open-circuit method is generally completed in a shorter time, providing a major advantage when epidemiologic studies are being performed on large numbers of subjects.

FUNCTIONAL RESIDUAL CAPACITY AND RESIDUAL VOLUME

One compartment of the TLC that cannot be measured by spirometry is RV, the volume of air remaining in the lungs at the end of a maximal expiration. RV is determined indirectly in three steps: (1) FRC is typically measured using one of the three techniques: closed-circuit helium, open-circuit nitrogen, or total-body plethysmograph. (2) ERV is determined spirometrically. (3) RV is calculated as the difference between FRC and ERV. In principle, it is possible to determine the RV using a dilution technique or body plethysmography after maximal expiration. In practice, however, the resting end-expiratory level is a more reproducible starting point for determining FRC than is the maximal end-expiratory level for determining RV.

Closed-Circuit Helium Method

The closed-circuit helium dilution method for determining FRC is a variation of the hydrogen dilution method first used in the early 19th century. Both methods take advantage of the virtual insolubility of the test gas in body tissues and the law of conservation of mass. The development and simplification of this test were accomplished over a 20-year span in the mid-20th century. Schematic depictions of the principle upon which the technique is based and the apparatus used are shown in Figure 33-4.

When a fully manual device is used for measuring FRC, the system is prepared by the addition of about 2 L of air and sufficient helium to achieve an initial helium concentration of approximately 10% in the apparatus. The patient, with nose clip in place, then breathes room air through the mouthpiece (Fig. 33-4A). After a preliminary period of quiet breathing to familiarize the patient with the mouthpiece, apparatus, and environment, and after the baseline resting end-expiratory level is established, the test begins.

At the end of a normal expiration, the valve at the mouthpiece is turned to connect the patient to the spirometer system

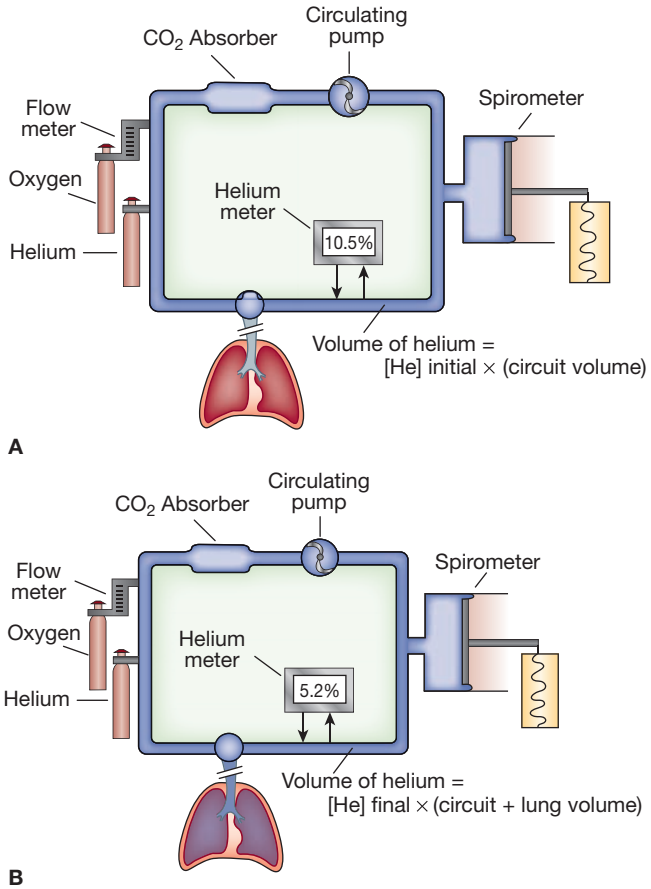

Figure 33-4 Closed-circuit helium dilution method for measurement of FRC. **A.** Spirometer and tubing system with helium before subject begins breathing through the circuit. At the end of an expiration, the mouthpiece valve is turned and the patient rebreathes through the circuit. Expired CO_2 is "scrubbed" out of the system, and O_2 is added to compensate for continued O_2 uptake in the lungs. **B.** During equilibration, the measured helium concentration falls, reflecting a dilutional effect of the additional volume (FRC) on the spirometer circuit.

(Fig. 33-4B). As the patient rebreathes from the closed circuit, the blower circulates the gas mixture. The CO_2 is absorbed by soda lime (CO_2 absorber), while O_2 is added through a valve and flowmeter at a rate corresponding to the subject's O_2 consumption. As the helium, which was at first contained entirely within the apparatus, mixes with air contained in the lungs, its concentration, as monitored by the helium analyzer, falls. Stabilization of the helium concentration, indicated by a rate of change in concentration of less than 0.02% over a 30-second interval, signals the point at which the helium concentration has equilibrated throughout the lung-breathing circuit system; equilibration, the end-point of the test, occurs within 7 minutes in normal persons. However, in patients in whom the distribution of ventilation is abnormal – for example, those with chronic obstructive pulmonary disease (COPD)– equilibration may take much longer. Upon equilibration, the following equation, based on the law of conservation of mass, is applied:

$$F_{0He} \times V_0 = F_{F_{He}} \times V_F$$

where

F_{0He} = initial concentration of helium
V_0 = initial volume of system, L
$F_{F_{He}}$ = final concentration of helium
V_F = final volume of system, L

The initial volume of the system is the volume of the spirometer and circuit tubing, whereas the final volume consists of the initial volume plus FRC. The latter value is the only unknown in the preceding equation. Corrections are usually made for the small amount of helium dissolved in body tissues during the test and for slight volume changes caused by a respiratory exchange ratio that is not equal to 1.0.[9] Although the method described here is based on a manually operated device, the same principles hold when all the mechanical and computational steps are accomplished with a computer-controlled system.

Nitrogen Washout Method

Conceptually, the nitrogen washout method is similar to the helium dilution method described previously; however, it relies on an open circuit rather than the closed circuit used in the helium dilution method. The open-circuit nitrogen washout method for determining FRC.[10] requires that the subject breathe 100% O_2 for 7 minutes; during this period, the concentration of N_2 in expired gas is monitored. When the expired N_2 concentration falls to zero, all the N_2 present in the lungs at the start of O_2 breathing has been "washed out." The total volume of gas expired and the concentration of N_2 in the expired gas are measured.

The calculation of FRC is based on the reasonable assumption that the volume of N_2 in the lungs at the start of the test (i.e., the product of lung volume and the concentration of N_2 in the lungs) is the same as the total volume of N_2 expired and collected during the period of the test – that is, the product of the total volume of gas expired and the concentration of N_2 in the expired gas:

$$F_{0_{N_2}} \times V_0 = F_{E_{N_2}} \times V_E$$

where

$F_{0_{N_2}}$ = concentration of N_2 in the lungs
V_0 = volume of gas in the lungs, L
$F_{E_{N_2}}$ = concentration of N_2 in the expired gas
V_E = volume of expired gas, L

Since the test is started at the end of a quiet expiration, the volume of gas in the lungs is FRC. This volume is calculated by substituting into the above equation the initial concentration of N_2 in the lungs, estimated at 0.81 in fasting and 0.79 to 0.80 in nonfasting subjects, and the measured values for volume and N_2 concentration of expired gas.

Body Plethysmography

The word plethysmography is derived from the Greek plethysmos, meaning "enlargement." Although the concept of measuring FRC by recording changes in the volume of the body during "enlargement" of the chest was described in 1882, not until 1956 did DuBois and coworkers introduce a practical plethysmographic technique, based on Boyle's law, for determining thoracic gas volume (TGV).[11]

Any of three types of body plethysmographs can be used: (1) the *pressure plethysmograph,* in which pressure during breathing varies while volume remains constant; (2) the *volume plethysmograph,* in which volume varies during breathing while pressure remains constant; and (3) the *pressure-corrected flow plethysmograph,* which couples the pressure plethysmograph's fidelity of response to high-speed events with the volume plethysmograph's ability to follow large changes in volume. Since the conceptual basis for all three devices is similar, only the most popular one – the pressure plethysmograph – will be described.

The pressure plethysmograph (Fig. 33-5) contains a pneumotachograph and transducer for measuring flow and volume, and two strain-gauge transducers, one for sensing pressure at the mouth (Pm) and the other for sensing pressure in the box (Pbx). A solenoid-operated shutter mechanism is situated between the mouthpiece and the pneumotachograph. The three transducers are connected to

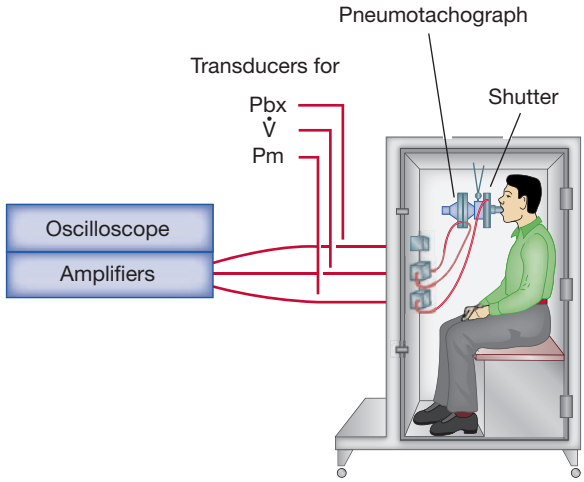

Figure 33-5 Constant-volume, variable-pressure plethysmograph used for measuring functional residual capacity and airway resistance. The device has a fixed volume. Thoracic gas volume changes associated with changes in alveolar pressure are reflected as changes in pressure within the plethysmograph.

an amplifying and monitoring system so that box pressure (or lung volume) and mouth pressure are displayed simultaneously on the X and Y axes, respectively, of an oscilloscope (Fig. 33-6).

In order to determine FRC, the patient, seated comfortably within the box with nose clip in place, is asked to breathe quietly through the mouthpiece. At the end of a quiet expiration, the shutter is closed and the patient is instructed to pant gently against it. The panting movements cause both mouth pressure and box pressure to change. With each inspiratory effort, as mouth pressure falls and gas in the lungs is rarefied, lung volume increases. Because the plethysmograph is a closed box, the increase in lung volume produces a corresponding increase in box pressure. With each expiratory effort, as lung volume decreases, box pressure falls. Because the shutter is closed while the measurements are made, mouth pressure equals alveolar pressure (P_A). These oscillations in mouth pressure and box pressure or lung volume appear on the oscilloscope as a closed loop (Fig. 33-6). Measurement of the slope of this loop is used to determine the volume of gas in the lungs at the time of shutter closure – that is, TGV or V_{TG}. When the occlusion occurs at resting, end-expiratory lung volume, the measurement yields FRC (see below).

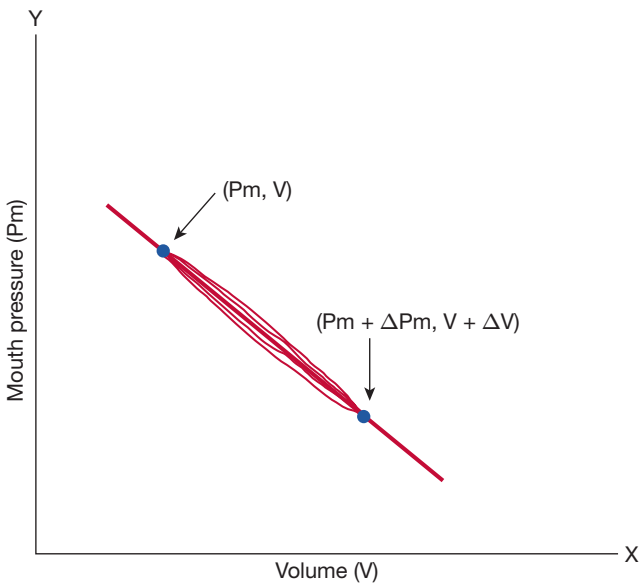

Figure 33-6 Pressure–volume loop obtained from a person seated in a body plethysmograph. Pressure at the mouth represents alveolar pressure; pressure in the box represents thoracic gas volume. After the shutter has closed at end-expiration (Pm, V), the subject attempts to inspire. Pm falls, and the pressure in the box increases. This increase in box pressure is calibrated in terms of an equivalent volume change. The new position of the trace at the end of the inspiratory effort is (Pm + ΔPm, V + ΔV). The slope of the loop depends on the volume of gas in the lungs when the shutter is closed (FRC).

Applying Boyle's law to the plethysmographic determination of lung volume,

$$PV = (P + \Delta P)(V + \Delta V)$$

where

P = pressure in the lungs at end-expiration (atmospheric pressure), cmH_2O
ΔP = change in pulmonary pressure produced by respiratory efforts, cmH_2O
V = volume of gas in the lungs at end expiration (FRC), L
ΔV = change in gas volume in the lungs produced by compression (during expiration) and rarefaction (during inspiration) secondary to respiratory efforts, L

In the pressure plethysmograph, ΔV is sensed as a change in pressure within the box, and ΔP is determined from the change in mouth pressure during breathing efforts against the closed shutter.

Rearranging the above equation and solving for V yield

$$V = \frac{\Delta V}{\Delta P}(P + \Delta P)$$

However, since ΔP is small compared to P (atmospheric pressure), it may be disregarded. The equation then becomes

$$V = P \times \frac{\Delta V}{\Delta P}$$

where

V = functional residual capacity, L
P = atmospheric pressure, cmH_2O
$\Delta V/\Delta P$ = inverse of slope of the loop on the oscilloscope

Therefore, the only unknown in this equation is V, which can be calculated by incorporating values for barometric pressure and the inverse of the slope of the plot of mouth pressure versus box pressure ($\Delta P/\Delta V$).

Two methods for measuring static lung volumes using plethysmography have been standardized by the ATS and ERS. One entails shutter closure at FRC, followed by expiration to RV, and then an IC maneuver to TLC; the other method is shutter closure at FRC, followed by an IC maneuver to TLC, and then an expiratory vital capacity maneuver to RV.[12] Application of each method may yield different calculations of lung volumes.[13]

Comparison of Methods

Compared to the dilution and washout techniques, body plethysmography is, by far, the fastest method available for determining FRC. Indeed, it enables several determinations to be made per minute. Although the equipment required for body plethysmography is more expensive than that required for the other methods, in a busy laboratory this technique generally proves to be more economical because of the time saved and the additional uses to which the equipment can be put (e.g., measurement of airway resistance; see Airway Resistance). Technically, the test is only slightly more difficult than the inert gas dilution method.

Sources of error inherent in the use of body plethysmography and discrepancies between results obtained by body plethysmography and the inert gas techniques should be noted. In patients with COPD[14] or asthma,[15] values for FRC obtained by body plethysmography may be artifactually high because of pressure differences between the mouth and alveoli generated during panting across narrowed airways. Consequently, pressures recorded at the mouth during shutter occlusion of the airway underestimate changes in alveolar pressure. Overestimation of TLC using body plethysmography appears to be greatest in patients whose FEV_1 (see below) is less than 30% predicted.[16]

The inert gas dilution and washout methods are similar both in principle and in results. The values for FRC with these techniques match those from the body plethysmograph except in persons in whom considerable areas of the lungs are poorly ventilated, usually due to obstructive airway disease. In these individuals, complete mixing or washout of the indicator gas is very slow, at times requiring 45 minutes or longer. Because of the slow equilibration of gas concentrations in the poorly ventilated areas, the usual time allotted for the test is inadequate, resulting in a lower value for FRC by the washout methods than by body plethysmography. One strategy commonly used to deal with this problem is to prolong the washout time. The primary advantage of these techniques over body plethysmography is that they can be used in persons for whom the plethysmograph is impractical – for example, those with marked obesity, skeletal abnormalities, or claustrophobia.

TEMPERATURE CORRECTION FACTORS

By convention, all lung volumes described above and airflows (see below) are expressed in terms of body temperature and pressure, saturated with water vapor (BTPS). This practice enables direct comparison of pulmonary function data from laboratories operating at different ambient temperatures and altitudes. To convert the volume of gas collected in a volume-type spirometer under ambient conditions (i.e., ambient temperature and pressure, saturated with water vapor, or ATPS) to BTPS, a conversion factor is applied (Table 33-3). Previously, it was presupposed that air entering a spirometer was cooled *immediately* to ambient temperature and remained saturated with water vapor (ATPS). Under this assumption, only ambient temperature was considered in determining the appropriate correction factor. However, studies have addressed the assumption that expired gas is immediately cooled,[17,18] as well as the practical consequences of temperature correction errors. The ATS recommends temperature correction of results from volume-type spirometers based on *measured* gas temperature at the time of testing.

TABLE 33-3 Factors for Converting Volumes from ATPS to BTPS at Barometric Pressure of 760 mm Hg[a]

Ambient Temperature (°C)	Multiplier to Convert Volumes to BTPS[b]
20	1.101
21	1.096
22	1.091
23	1.085
24	1.080
25	1.074
26	1.069
27	1.062

[a] *Based on Boyle's, Charles's, and Dalton's laws.*
[b] *Volume at ATPS × multiplier = volume at BTPS.*
Note: ATPS, ambient temperature and pressure, saturated with water vapor; BTPS, body temperature and pressure, saturated with water vapor.

RADIOGRAPHIC ASSESSMENT OF LUNG VOLUME

Although initial reports describing use of radiographic techniques to measure lung volumes date back over 40 years, these methods have not found widespread use in adult populations. More sophisticated computerized tomographic (CT) applications have demonstrated good correlation with plethysmographic and gas dilution techniques in normals. However, significant differences may be observed in patients with COPD,[19] in whom TLC determinations using plethysmography may be up to 2 L greater than TLC assessed with CT scanning.[20]

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Exploration of the elastic properties of the respiratory system and their effect on lung volumes and work of breathing began in earnest during the earlier part of the 20th century. Although the groundwork had been laid centuries before (by Robert Hooke's *The Theory of Springs* in 1678), between 1923 and 1956 investigators provided a wealth of information about the elastic properties of the respiratory system and its components and the work done in overcoming these elastic forces during breathing.

STATIC COMPLIANCE OF THE LUNGS

The elastic properties of the lungs are determined by relating the change in the volume of air contained in the lungs to the corresponding change in the recoil force of the lungs. Change in lung volume is most easily measured by determining the volume of gas inspired or expired at the mouth. Although expedient, this approach to determining the elastic properties of the lungs can underestimate the change in lung volume when incorporated into techniques (see below) that require the subject to expire gently against a closed shutter, a maneuver that compresses thoracic gas. However, the problem can be circumvented by placing the subject in a volume plethysmograph that uses a spirometer attached to the plethysmograph to record changes in TGV due to gas compression.

The recoil force of the lungs, measured as the transpulmonary pressure (Fig. 33-7), is the difference between the alveolar and pleural pressures (P_A and Ppl, respectively). Alveolar pressure is determined as the pressure at the airway opening (Pao) – that is, the mouth – when airflow is arrested and the glottis is open. The pleural pressure is determined indirectly by measuring the pressure in the esophagus using an esophageal balloon catheter. This technique, first introduced in 1949, has been improved over the years and provides accurate reflections of changes in pleural pressure at all lung volumes except those below FRC.[21]

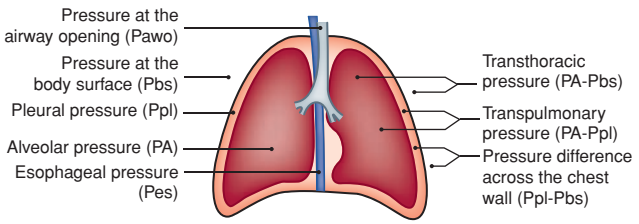

Figure 33-7 Schematic representation of the chest depicting pressure terms and gradients used in analysis of the mechanics of breathing. The expressions for individual pressure measurements on the left are relative to atmospheric pressure. Pleural pressure (Ppl) is not routinely measured directly but is approximated by esophageal pressure (Pes) measured with a balloon catheter.

A thin rubber balloon, about 10 cm long, is placed over a small-diameter polyethylene catheter. Several holes in the terminal portion of the catheter allow pressure to be transmitted from the balloon, through the catheter, to a transducer. The balloon is positioned in the lower third of the esophagus, where esophageal pressure and, therefore, balloon pressure accurately reflect the pressure acting on the lung surface (pleural pressure). Use of an elongated balloon of low volume helps to minimize changes in pressure due to esophageal contractions. By conveying mouth pressure and esophageal pressure to opposite sides of a differential pressure transducer, an output signal is generated that is proportional to the difference between these two pressures – that is, the transpulmonary pressure ($P_A - P_{pl}$).

To determine the elastic properties of the lungs, the patient, with esophageal balloon in place, is seated in a closed body plethysmograph. The patient then breathes ambient air through a tube to the outside until the volume trace, inscribed by the plethysmograph spirometer, indicates that the end-expiratory level is stable. At this juncture, the patient is instructed to first inspire slowly to TLC and then to expire slowly to the resting end-expiratory level (FRC). This maneuver is then repeated; during the second expiration, the shutter is activated to occlude the airway intermittently. Since each closure of the shutter interrupts the expiration briefly, the recorded trace of expiratory volume versus time displays a staircase pattern (Fig. 33-8A). The plateau resulting from each closure of the shutter marks a finite period of zero change in lung volume as the lungs empty during expiration. Associated with each plateau is a corresponding plateau in transpulmonary pressure.

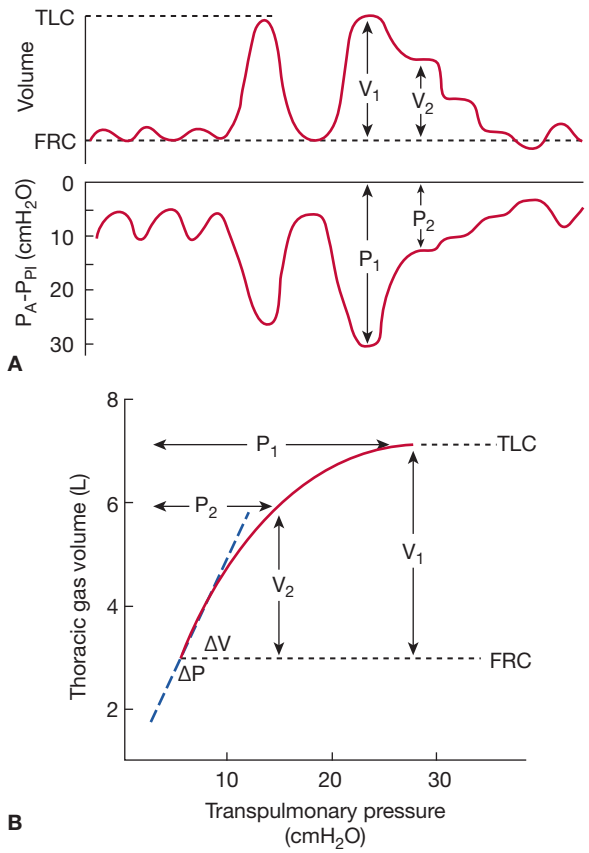

Figure 33-8 Measurement of the elastic properties of the lungs. **A.** Recordings of changes in lung volume and transpulmonary pressure ($P_A - P_{pl}$) using the esophageal balloon technique described in the text. Simultaneous measurements of volume and pressure are obtained during periods of arrested airflow at lung volumes ranging from TLC to just below FRC. **B.** Thoracic gas volume is plotted on the ordinate and transpulmonary pressure on the abscissa. The curve formed by the plot using values from **A** describes the elastic properties of the lungs. The slope of the line, $\Delta V/\Delta P$, over the range of the tidal volume is the static compliance of the lungs.

The relationship between the change in volume and the change in pressure is a measure of the *recoil force* of the lungs at each of the lung volumes that are registered (Fig. 33-8B). The resulting curve provides several useful indices of the elastic behavior of the lungs. The slope of the curve over the range corresponding to the tidal volume is the *static lung compliance.* The transpulmonary pressure attained at TLC is the *maximal static recoil pressure.* The ratio of the maximal static recoil pressure to the corresponding maximal lung volume is the *coefficient of retraction.* However, since these values are derived from only small segments of the curve, inspection of the total static pressure–volume curve remains the most comprehensive means of assessing the elastic properties of the lungs.

STATIC COMPLIANCE OF THE CHEST WALL

Functionally, the chest wall includes the bony thorax, intercostal muscles, overlying soft tissue, pleura, and diaphragm. The chest wall is distensible and has its own distinctive elastic properties. In the normal, end-expiratory, resting position of the respiratory system (FRC), the inward recoil of the lung is balanced by the outward recoil of the chest wall (Fig. 33-9B). As the volume of the thoracic cavity enlarges progressively during inspiration from FRC to TLC, the outward recoil pressure of the chest wall lessens, becoming zero at approximately 70% of TLC; beyond this point, the chest wall begins to recoil inwardly (Fig. 33-9C). Conversely, as the chest wall is compressed below FRC by the action of the expiratory muscles, the natural outward recoil tendency is increased (Fig. 33-9A).

In practice, assessment of the elastic properties of the chest wall is accomplished by first determining the compliance curve of the respiratory system as a whole and then subtracting the contribution of the lungs. For a given lung volume, the pressure across the chest wall, Ppl – Pbs (Fig. 33-7), is simply the difference between the transthoracic ($P_A - P_{bs}$) and transpulmonary ($P_A - P_{pl}$) pressures. As indicated above, Ppl is determined using an esophageal balloon catheter.

ELASTIC PROPERTIES OF THE RESPIRATORY SYSTEM AS A WHOLE

The elasticity of the respiratory system as a whole is determined by measuring the change in volume resulting from a change in pressure applied to the system – that is, the transthoracic pressure ($P_A - P_{bs}$) – *while the respiratory muscles are completely relaxed.*

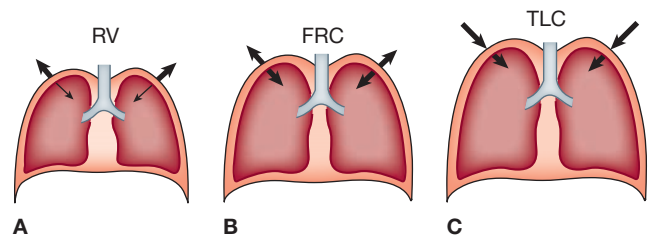

Figure 33-9 Schematic depiction of elastic recoil vectors across the lung and chest wall as determined by the level of inflation. **A.** At RV, the outwardly directed recoil pressure of the chest wall is large and the inwardly directed recoil pressure of the lung is small. **B.** At FRC, the recoil pressures of the lung and chest wall are equal and in opposite directions. **C.** At TLC, both recoil pressures are directed inward, and each contributes substantially to the overall recoil pressure of the respiratory system.

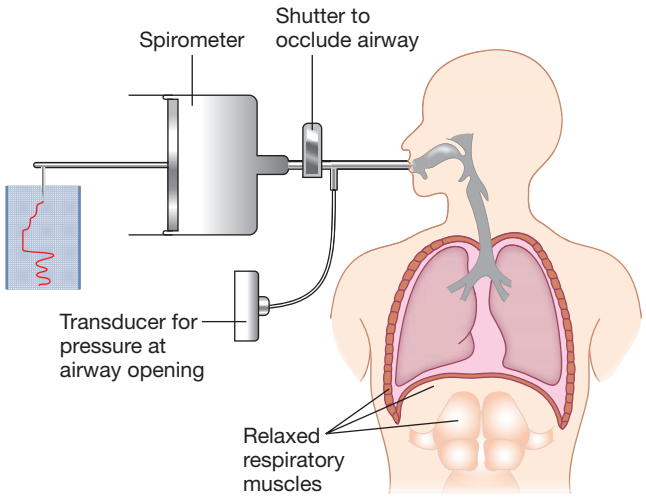

Figure 33-10 Relaxation technique for measurement of elastic recoil pressure of the respiratory system. After a period of normal tidal volume breathing, the subject inspires to TLC. A shutter in the airway is closed, and the subject relaxes his or her respiratory muscles. The shutter is periodically opened, permitting exhalation of a small volume of air measured by the spirometer. Airway pressures are recorded at times of shutter closure (i.e., during no airflow, when mouth pressure equals alveolar pressure). A pressure–volume curve is then constructed from the simultaneously recorded values for pressure and volume.

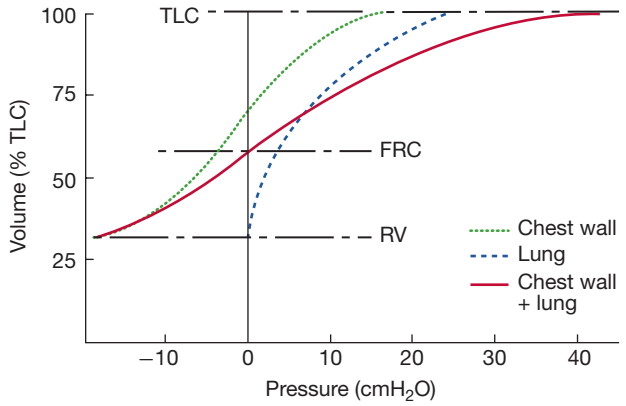

Figure 33-11 The pressure–volume curves of the respiratory system and its components. The elastic recoil pressures of the total respiratory system *(solid line)* over the vital capacity range are the sum of the recoil pressures of the lung *(dashed line)* and chest wall *(dotted line)*. At FRC, the chest wall recoil pressure is counterbalanced by the lung recoil pressure. The net result is a total system recoil pressure of 0. The total system recoil pressure is obtained by relaxation pressure or continuous positive-pressure breathing techniques. The chest wall recoil pressure is calculated as the difference between the recoil pressure of the entire respiratory system and the recoil pressure of the lungs.

The first method used for this evaluation employed the relaxation technique described by Rahn and associates.[22] The subject breathes quietly into an apparatus consisting of a spirometer, a shutter, and a pressure transducer connected to the subject's side of the shutter (Fig. 33-10). After a period of quiet breathing, the subject is instructed to inspire maximally; the shutter is closed at peak inspiration, and the subject is then asked to relax the respiratory muscles completely while keeping the glottis open. Periodically, the shutter is opened, allowing a small volume of air to move from the subject into the spirometer; the shutter is then closed again. This maneuver is repeated until FRC is reached. During the periods of arrested airflow, pressure at the mouth (Pao) is equal to the pressure in the alveoli (P_A). Provided the pressure at the body surface is atmospheric and the respiratory muscles are completely at rest, this value represents transthoracic pressure. In practice, however, full relaxation of the respiratory muscles is difficult, and a contribution by them to the pressure at the airway opening is frequently unavoidable.

A more practical technique entails the application of continuous positive pressure to the airways during spontaneous breathing. The subject breathes quietly into a water-sealed spirometer until a constant end-tidal level is achieved. A weight is then placed on the spirometer bell to increase the pressure in the respiratory system and, thereby, to raise the resting end-expiratory lung volume. This procedure is repeated using several different weights so that a pressure–volume curve of the total respiratory system can be constructed.

The individual pressure–volume curves for the lungs and chest wall and the composite curve for the intact respiratory system are shown in Figure 33-11. As illustrated, the elastic recoil of the chest wall alone is determined by subtracting the recoil pressure of the lung from that of the total respiratory system. Chest wall elasticity is an important determinant of the subdivisions of lung volume and the overall compliance of the respiratory system; the latter is, in turn, an important determinant of the work of breathing.

Several features of the pressure–volume relationships shown in Figure 33-11 are worth emphasizing. As lung volume approaches RV, the elastic recoil pressure of the respiratory system is largely due to the outwardly directed recoil pressure of the chest wall. At RV, the contribution of the lung to the recoil pressure of the respiratory system is minimal. At the other extreme of lung volume, TLC, elastic recoil pressure is high and directed inwardly, due to the combined elastic recoils of the lung and chest wall. At FRC, the outwardly directed recoil of the chest wall balances the inwardly directed recoil of the lung, and the transthoracic pressure is zero (i.e., $P_A - P_{bs} = 0$). Indeed, the system "comes to rest" at FRC because of the counterbalancing of these forces at that volume. Since alveolar pressure at FRC is zero, no pressure gradient exists for airflow. Therefore, the system remains stationary until acted upon by the muscles of inspiration or expiration.

ELASTIC PROPERTIES OF THE RESPIRATORY SYSTEM IN HEALTH AND DISEASE

The elastic properties of the respiratory system are altered by a wide variety of diseases that can affect the lung parenchyma or chest wall, either selectively or in concert. Most instances of clinically significant reductions in static compliance are due to abnormalities in the lung. The two standard clinical measures of the elastic properties of the lung are static lung compliance and maximal static recoil pressure.

Static lung compliance, Cst,L, is determined over the linear portion of the pressure–volume curve, between FRC and a lung volume corresponding to FRC plus 0.5 L. Normal values vary among laboratories, ranging from 0.147 to 0.375 L/cmH_2 O, with a mean of 0.262 L/cmH_2O. Some variability is related to age and sex; Cst,L decreases with age and is higher in males than in females.

Maximal static recoil pressure is the recoil pressure at TLC. Once again, normal values vary. Data from one series of 51 normal subjects.[23] are shown in Table 33-4.

In disease states characterized by an increased elastic recoil pressure, such as diffuse interstitial fibrosis, the pressure–volume curve is shifted to the right and the static lung compliance decreases (Fig. 33-12A and B). The increased elastic recoil pressure contributes to a

TABLE 33-4 Normal Maximal Static Recoil Pressures for Adults (cmH_2O)

	Male Age (Yr)			Female Age (Yr)		
	25–35	36–64	65–75	25–35	36–64	65–75
Mean ± SD	35.9 ± 8.5	33.0 ± 8.7	33.0 ± 2.9	36.4 ± 5.8	25.7 ± 4.0	23.7 ± 3.9
Range	24.0–48.0	21.5–48.0	17.0–42.2	21.0–48.0	20.0–30.0	18.0–31.6

Source: Data from Knudson RJ, Clark DF, Kennedy TC, et al. Effect of aging alone on mechanical properties of the normal adult human lung. J Appl Physiol. 1977;43:1054–1062.

decrease in FRC and TLC. By expressing the volume axis of the pressure–volume curve in terms of *percent predicted TLC* (Fig. 33-12B), instead of *absolute TLC* (Fig. 33-12A), the reduction in maximal lung volume is clearly evident; that is, maximal recoil pressure is increased, despite the reduced TLC.

In contrast to the effects of fibrosis, emphysema, which destroys alveolar walls and enlarges alveolar spaces, reduces lung elastic recoil pressure (Pel). This change increases both TLC and FRC. The shift of the pressure–volume curve upward and to the left (Fig. 33-12A and B) indicates that lung compliance increases and that the maximal recoil pressure decreases. If the volume axis is expressed as percent predicted TLC (Fig. 33-12B), the increase in lung volume is more clearly demonstrated.

As noted previously, disorders affecting primarily the chest wall can also significantly alter the elastic properties of the respiratory system. Among these are obesity, kyphoscoliosis, and fibrothorax. These disorders limit chest wall excursion and lung expansion and reduce FRC. In addition, they produce decreases in static compliance of the lung and chest wall and maximal recoil pressure.

RESPIRATORY MUSCLE STRENGTH

Ventilatory performance depends not only on the mechanical properties of the lungs and chest wall, but also on the strength of the respiratory muscles. Evaluation of respiratory muscle strength was undertaken as early as the mid-19th century. Subsequently, using simplified methods of measurement, Black and Hyatt established normal values (Table 33-5).[24]

The maximal pressure generated by an isometric contraction varies directly with the resting length of the muscle. Consequently, values for maximal inspiratory and expiratory pressures depend on the lung volume at which the tests are performed (Fig. 33-13).[25] When TLC is less than 70% of the predicted value, the maximal expiratory pressure will be low. Similarly, when RV exceeds 40% of the predicted TLC, the maximal inspiratory pressure will be low.

The only equipment required for measurement of maximal inspiratory or expiratory pressure is an aneroid vacuum and pressure gauge. To determine maximal expiratory pressure, the patient is urged to inspire fully to TLC and then to expire as forcefully as possible into the gauge. The highest pressure attained and held for at least 1 second is the *maximal expiratory pressure* ($P_{E_{max}}$). The *maximal inspiratory pressure* ($P_{I_{max}}$) is determined by having the patient inspire maximally from the gauge after having expired completely to RV. The value recorded is the lowest pressure attained and held for at least 1 second.

Measurement of maximal static respiratory pressures is particularly important in evaluating respiratory muscle weakness in patients with neuromuscular disease, as described in Chapters 84 and 85 . In such patients, spirometric tests are often normal, despite respiratory muscle weakness, because maximal pressures are not required to achieve maximal expiratory flow rates (see Flow–Volume Curves).

Another useful function of these measurements is in examining patients whose coordination in performing spirometry or whose degree of motivation is suspicious In such patients, determination of maximal pressures is often helpful in determining whether optimal efforts are being expended during pulmonary function testing (see Approach to Interpreting Commonly Performed Pulmonary Function Tests).

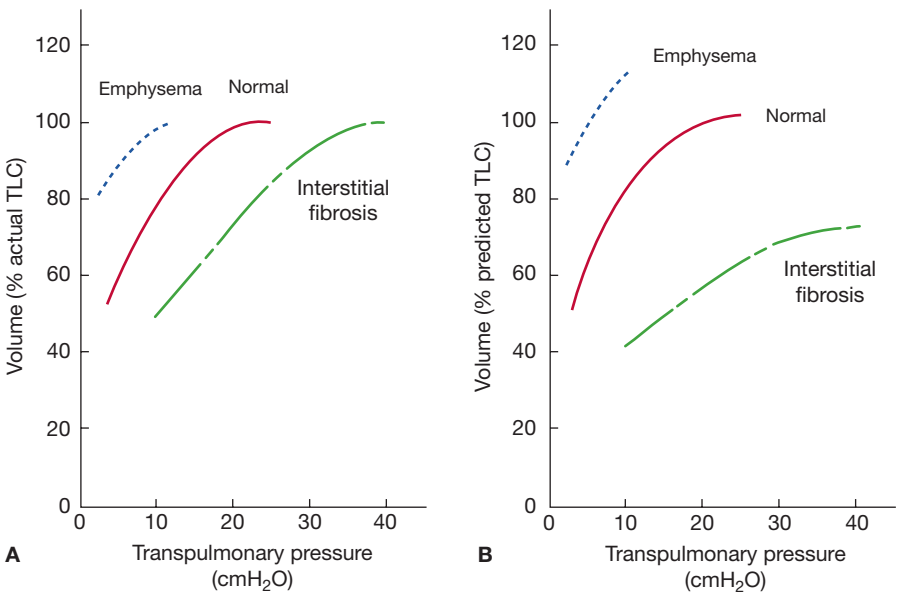

Figure 33-12 Pressure–volume curves of the lungs in health and disease. **A.** Volume expressed as percent of actual TLC. Differences in transpulmonary pressures in normal and diseases states are evident. Changes in lung volume that occur with disease are demonstrated on the plots. **B.** Volume expressed as percent of predicted TLC. In addition to the differences in transpulmonary pressures, alterations in lung volumes in the disease states are evident.

TABLE 33-5 Prediction Equations and Lower Limits of Normal for Maximal Inspiratory ($P_{I_{max}}$) and Maximal Expiratory ($P_{E_{max}}$) Pressures (cmH_2O)[a]

	$P_{I_{max}}$		$P_{E_{max}}$	
	Predicted Mean (cmH_2O)	Lower Limit of Normal	Predicted Mean (cmH_2O)	Lower Limit of Normal[b]
Male	143 − (0.55 × age)	71	268 − (1.03 × age)	111
Female	104 − (0.51 × age)	39	170 − (0.53 × age)	88

[a]*Age range = 20–86 yr.*
[b]*Independent of age.*
Source: Data from Black LF, Hyatt RE. Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696–702.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The static tests of pulmonary function described in the previous section are based on measurements of volume and pressure made while airflow is arrested. These static tests are particularly useful in defining the elastic properties of the respiratory system. Considerable additional information can be gained from tests done during airflow – that is, under "dynamic" conditions.

Although measurements of static lung volumes began about 300 years ago, the assessment of pulmonary function during airflow began in 1933, when the test now known as the *maximal voluntary ventilation* (MVV) was first proposed. This test did not become popular until a few years later, when Cournand and Richards developed regression equations to determine normal values. Subsequently, investigators proposed that the volume of air expired during specific time intervals be determined. In 1955, determination of the average airflow during the middle half of a forced expiratory vital capacity was described. Determination of these indices of dynamic lung function is now generally part of the battery of tests, both static and dynamic, included under the designation *spirometry.*

The more practical tests of dynamic function can, for convenience, be divided into four categories: FVC, flow–volume curves, MVV, and airway resistance. Other dynamic tests, including assessment of airway reactivity and the function of small airways, will be considered separately.

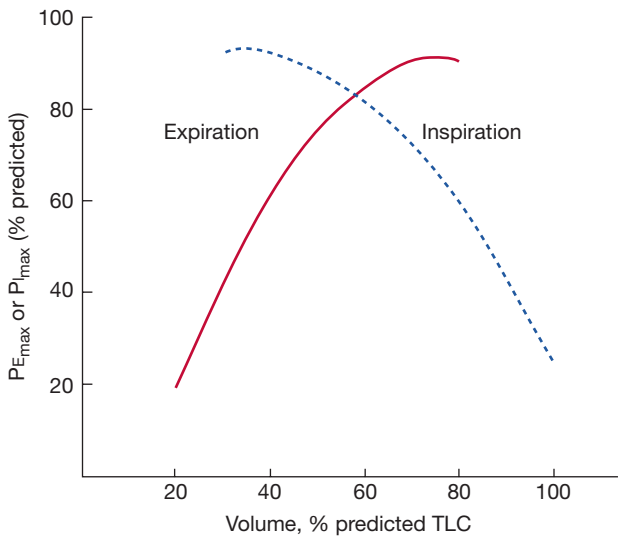

Figure 33-13 Effect of lung volume on maximal inspiratory *(dashed line)* and maximal expiratory *(solid line)* pressures. See text for discussion.

■ FORCED VITAL CAPACITY

Both expiratory and inspiratory measurements of the FVC are routinely made in pulmonary function laboratories. Unless otherwise specified, FVC refers to the forced *expiratory* maneuver.

Forced Expiratory Vital Capacity

The forced expiratory vital capacity is measured during expiration. The maneuver entails two steps: a full inspiration to TLC, followed by a rapid, forceful, maximal expiration (to RV) into a spirometer. The forced expiratory vital capacity (FVC) is normally equal to the relaxed or slow vital capacity (VC). However, a discrepancy between FVC and VC appears in obstructive disease of the airways: the FVC is less than the VC.

The relationship between expired volume and time during an FVC maneuver is used to determine airflow during expiration and the volume of air expired within designated intervals; these values provide an indirect measure of the flow-resistive properties of the lung. The FVC is displayed in one of the two ways: expired volume plotted against time (Fig. 33-14) or airflow plotted against lung volume – that is, an expiratory "flow–volume curve" (see below). The normal volume–time display of the FVC consists of a smooth curve with a gradually and progressively decreasing slope. Irregularities in the curve suggest either a failure of coordination or a suboptimal

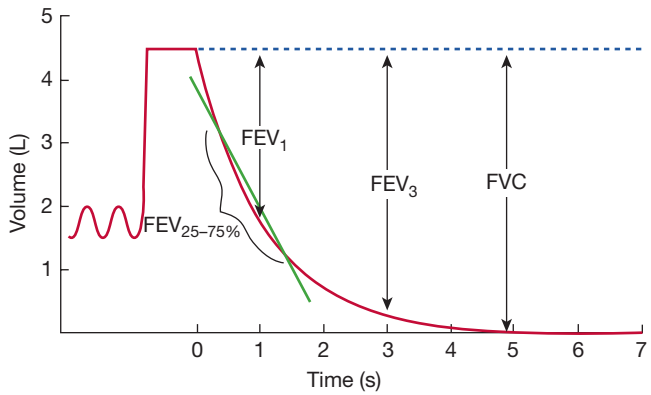

Figure 33-14 Forced expiratory vital capacity maneuver. After an initial period of tidal volume breathing, the patient inspires maximally to TLC and then exhales as rapidly and as forcefully as possible into a spirometer. Shown on the left of the tracing are a series of tidal volume breaths and the maximal inspiration to TLC. The forced expiration begins at time 0. Nearly all the volume is exhaled in the first 3 seconds of the maneuver. The values for FVC, FEV_1, and FEV_3 are measured from the maximal inspiratory level. The $FEF_{25–75\%}$ is the slope of the line connecting the points on the volume–time trace that correspond to 25% and 75% of the FVC.

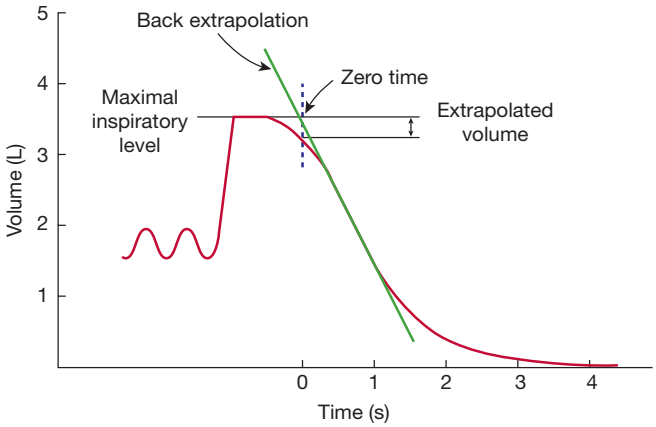

Figure 33-15 Technique of back extrapolation for determining the zero time in calculation of FEV_1. Zero time is determined as the point of intersection of a tangent drawn through the steepest portion of the spirogram and a line drawn horizontally through the maximal inspiratory level.

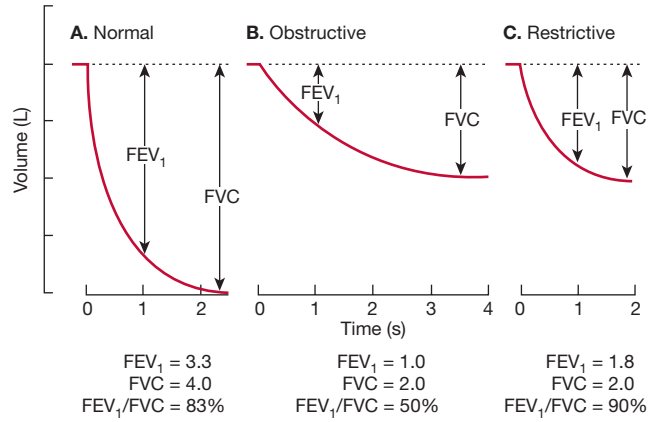

Figure 33-16 Representative spirograms from a normal subject (**A**), a patient with obstructive lung disease (**B**), and a patient with restrictive lung disease (**C**), obtained during a forced expiratory vital capacity maneuver. In the normal subject, expiration is completed within 3 seconds, and 83% of the volume is expired in the first second ($FEV_1/FVC\% = 83$). In the patient with obstructive disease, expiration is prolonged, and only half the volume is expired in the first second ($FEV_1/FVC\% = 50$). In the patient with restrictive disease, although the magnitude of the reduction in exhaled volume is the same as in the obstructed patient, most of the volume is exhaled within the first second ($FEV_1/FVC\% = 90$).

effort. At times, the onset of the forced expiration is unclear (Fig. 33-15) because of hesitation on the part of the patient. When this occurs, the start of expiration ("zero time") is determined with the "back extrapolation" method (Fig. 33-15).[8] A tangent taken through the part of the curve with the steepest slope is extrapolated back to the maximal inspiratory volume; the point of intersection is considered to be the time of onset of expiration.

Several values are commonly determined from the volume–time plot of the FVC (Table 33-6, Fig. 33-14): (1) the *volume expired in the first second*, expressed either as an absolute volume (FEV_1) or as a percentage of the FVC ($FEV_1/FVC\%$); (2) *the volume expired in the first 3 seconds*, expressed either as an absolute volume (FEV_3) or as a percentage of the FVC ($FEV_3/FVC\%$); and (3) *the forced midexpiratory flow rate* ($FEF_{25–75\%}$). The $FEF_{25–75\%}$ is determined by locating the points on the volume–time curve corresponding to 25% and 75% of the FVC and then calculating the slope of a straight line passing through those two points. The slope of this line represents the average airflow over the midportion of the FVC.

Although the *relaxed* or *slow vital capacity* (VC) may be normal or only modestly reduced in patients with obstructive disease of the airways, the volume–time relationship of the FVC maneuver is usually distinctly abnormal in such patients (Fig. 33-16A and B). Most obvious is a flattening of the slope of the curve at any given lung volume, reflecting the reduced airflow. In addition, the duration of the forced expiratory maneuver is prolonged. Normally, expiration is complete within 6 seconds; in obstructive airway disease, expiratory airflow may continue for 10 to 12 seconds. These changes in the expiratory airflow reduce the FEV_1 and FEV_3, the $FEV_1/FVC\%$, the $FEV_3/FVC\%$, and the $FEF_{25–75\%}$.

Restrictive lung disorders reduce the slow vital capacity. However, the *configuration* of the volume–time relationship may not be abnormal (Fig. 33-16C). Although the FEV_1 and FEV_3 are reduced because of the reduced vital capacity, the $FEV_1/FVC\%$ and $FEV_3/FVC\%$ remain normal or even exceed normal values. Often, because of the reduced vital capacity, the $FEF_{25–75\%}$ is also less than predicted.

Forced Inspiratory Vital Capacity

Measurement of the forced inspiratory vital capacity (FIVC) consists of two steps: (1) full expiration to RV, followed by (2) a rapid maximal inspiratory effort (Fig. 33-17). The rate of airflow over the middle half of the forced inspiratory vital capacity ($FIF_{25–75\%}$) is determined using a procedure similar to that described previously for the $FEF_{25–75\%}$.

In normal subjects, the $FIF_{25–75\%}$ is greater than the $FEF_{25–75\%}$. Since inspiratory flow is more dependent on effort than is expiratory

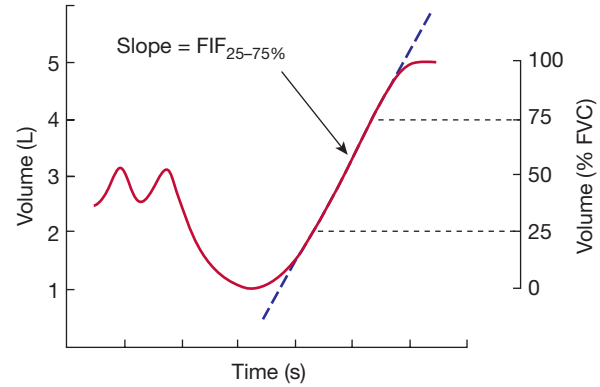

Figure 33-17 Forced inspiratory volume–time curve. The $FIF_{25–75\%}$ is the slope of a line between the points on the trace corresponding to 25% and 75% of the inspired volume.

TABLE 33-6 Values Obtained from Forced Expiratory Volume–Time Curves

FVC (BTPS) (L)	Forced vital capacity; the total volume expired
FEV_1 (BTPS) (L)	Volume of air expired in the first second
$FEV_1/FVC\%$	Volume of air expired in the first second, expressed as percent of the FVC
$FEV_3/FVC\%$	Volume of air expired in the first 3 s, expressed as percent of the FVC
$FEF_{25–75\%}$ (BTPS) (L/s)	Forced midexpiratory airflow

Note: BTPS, body temperature and pressure, saturated with water vapor.

flow, a fall in the $FIF_{25–75\%}$ is usually a more sensitive indicator of respiratory muscle dysfunction or a suboptimal effort than is the $FEF_{25–75\%}$. When airway resistance is high, a disproportionate fall in $FIF_{25–75\%}$ relative to $FEF_{25–75\%}$ suggests an extrathoracic site of airway obstruction (see Approach to Interpreting Commonly Performed Pulmonary Function Tests).

■ FLOW–VOLUME RELATIONSHIPS

In addition to analysis of the relationship between volume and time depicted on a spirogram, examination of the relationship between flow and volume provides useful information about lung function. A flow–volume curve, which shows the relationship between lung volume and maximal airflow as lung volume changes during a forced expiration, is shown in Figure 33-18. The test comprises four phases of breathing into a spirometer: (1) tidal breathing for several breaths, (2) a maximal inspiratory effort to TLC, followed by (3) a maximal expiration to RV done as forcefully and quickly as possible, and (4) another maximal inspiratory effort to TLC. Volume is displayed on the horizontal axis and airflow on the vertical axis. Airflow is measured at the mouth using a pneumotachograph; volume is measured either by integrating the pneumotachographic record during expiration or as a change in TGV, determined by a pressure-corrected flow plethysmograph. The records obtained by the two techniques for determining volume differ because the body plethysmograph senses compression of intrathoracic gas during a forced expiration, whereas measurements of volume made at the mouth do not (Fig. 33-19). Differences between curves obtained with the two techniques for measuring volume are most marked in patients with airway obstruction in whom considerable gas compression occurs during a forced expiration.

For the sake of comparison, tracings of flow versus volume and volume versus time, recorded during the same FVC maneuver and aligned by using a common volume axis as the abscissa, are shown in Figure 33-20. Selected measurements are more evident in one tracing or the other – for example, maximal expiratory flow in the flow–volume curve and volume expired in 1 second (FEV_1) in the volume–time curve.

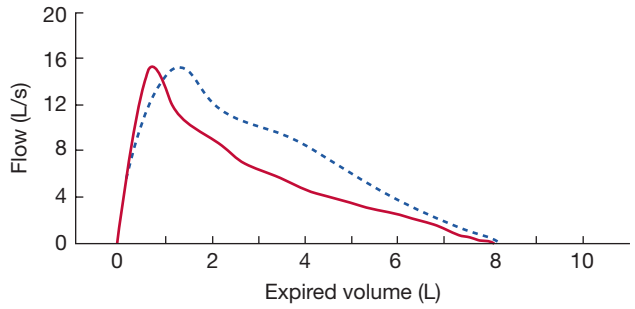

Figure 33-19 Comparison of the flow–expired-volume curve *(solid line)* with a simultaneously recorded flow–thoracic-gas-volume curve *(dashed line)*. The difference between the two curves results from the compression of gas in the lungs during a forced expiration.

Comparison of serial curves from a single person or curves from different subjects requires that the curves be aligned on the volume (horizontal) axis so that points of maximal inspiration or maximal expiration coincide. As may be seen in Figure 33-21A, which illustrates typical curves from a normal subject and two patients, one with pulmonary fibrosis and the other with obstructive airway disease, the information provided by this form of representation is limited; that is, the vital capacities and airflows from the patients are abnormally low. The limitation stems from the fact that the change in volume during expiration is shown relative to the *maximal inspiratory level* rather than to an *absolute volume* of gas in the lungs – that is, RV or TLC. When RV or TLC is known so that absolute volumes can be plotted on the horizontal axis (Fig. 33-21B), additional insight is gained into the flow–volume relationship depicted in Figure 33-21A. The patient with obstructive disease of the airways manifests a reduction in expiratory airflow at elevated lung volumes,

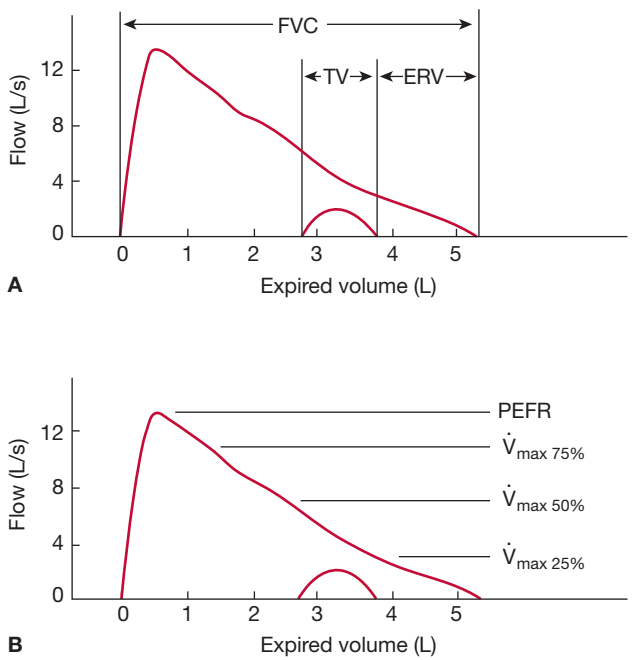

Figure 33-18 Flow–volume plots during forced expiration *(outer trace)* and quiet expiration *(inner trace)*. **A.** The subdivisions of lung volume. **B.** The common flow measurements. PEFR = peak expiratory flow rate; $\dot{V}_{max,75\%}$, $\dot{V}_{max,50\%}$, and $\dot{V}_{max,25\%}$ = flows at 75%, 50%, and 25% of the vital capacity, respectively.

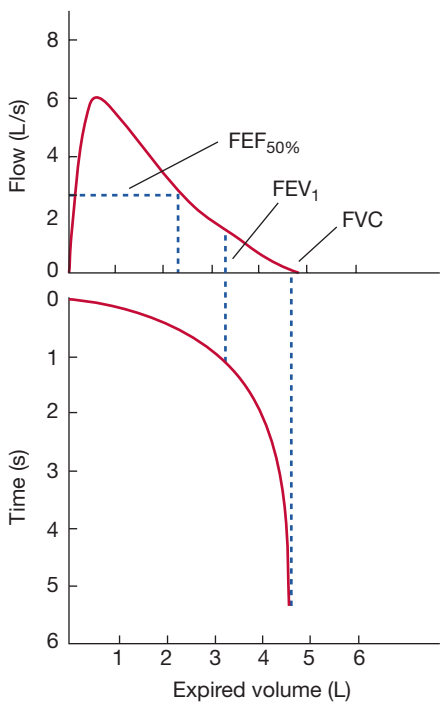

Figure 33-20 Flow–volume and volume–time curves depicting the same forced expiration aligned along a common volume axis (abscissa). Points corresponding to the FEV_1, FVC, and $FEF_{50\%}$ obtained from the volume–time plot are shown on the flow–volume curve.

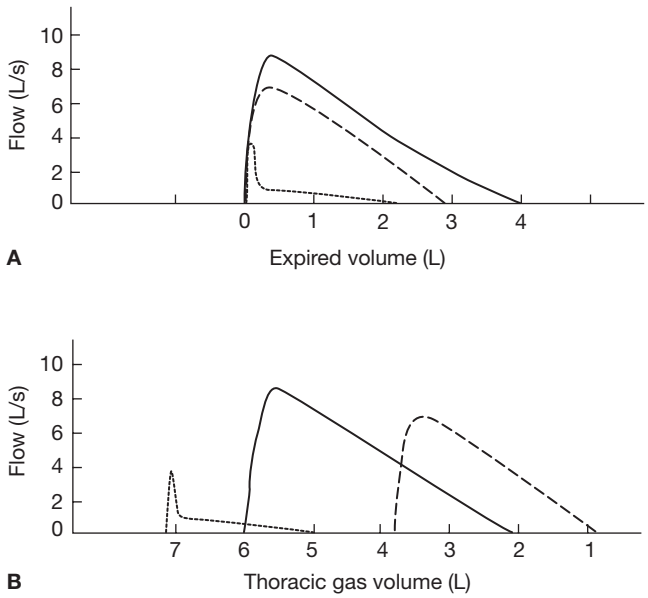

Figure 33-21 Airflow at different lung volumes. **A.** Flow–volume curves aligned at TLC. **B.** Flow–volume curves displayed relative to thoracic gas volume. Although the curves aligned at TLC (**A**) show striking differences in the pattern of airflow, they provide no insight into the relationship between lung volumes and airflow. See text for discussion.

which should enhance airflow. In contrast, the reduced rate of airflow in the patient with pulmonary fibrosis is normal, or even supranormal, when the lung volume at which the airflow occurs is taken into account; that is, the reduced airflow is primarily a function of the reduced lung volume, rather than of airway obstruction.

MAXIMAL VOLUNTARY VENTILATION

The previous considerations of dynamic lung function focus on a single timed maximal expiratory or inspiratory maneuver. In contrast, the MVV depends on the movement of air into and out of the lungs during continued maximal effort throughout a preset interval (Fig. 33-22). The MVV is a simple, informative test that provides an overall assessment of effort, coordination, and the elastic and flow-resistive properties of the respiratory system.[26,27]

In performing the test, the patient is urged to breathe as hard and as fast as possible. As a rule, the patient automatically adjusts

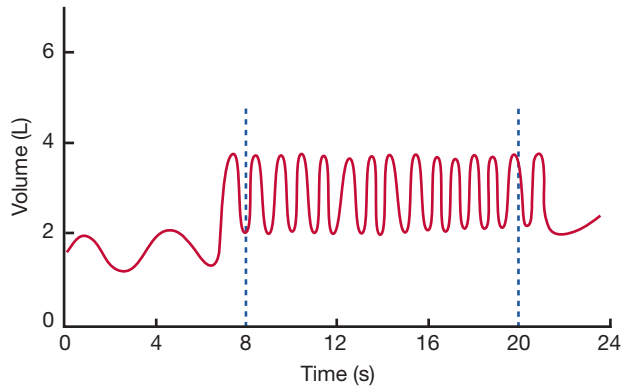

Figure 33-22 Maximal voluntary ventilation (MVV). After a period of relaxed breathing, the subject breathes rapidly and as forcefully as possible. The total volume of air inspired over 12 seconds and expressed in L/min is the MVV.

frequency and tidal volume for optimal performance. However, extremes of frequency or tidal volume are to be avoided, since neither panting nor slow deep breathing leads to the highest possible values. The total volume that is expired during a 12-second interval, expressed in liters per minute (BTPS), is the MVV. In some patients the test cannot be done because of an inability to continue the necessary effort for 12 seconds.

A normal value for MVV indicates that the overall integrated performance of the respiratory system is intact, thereby excluding moderate to severe restrictive or obstructive disease. In addition, a normal value suggests that the elastic and flow-resistive properties of the respiratory system, respiratory muscle strength, coordination of respiratory performance, and motivation of the patient are all normal. Although this test is very useful in detecting overall disturbances in integrated performance and diffuse tracheobronchial and pulmonary parenchymal diseases, other tests are required to pinpoint specific disorders.

The difference between the MVV and the resting minute ventilation is the *breathing reserve.* At one time, a low breathing reserve was correlated with the breathlessness in lung diseases. However, this determination is now primarily of historical interest.

RESPIRATORY RESISTANCE

Total respiratory resistance (Rrs) is the resistance to airflow and chest expansion offered by the airways (Raw), chest wall (Rw), and lung tissue (Rti):

$$Rrs = Raw + Rw + Rti$$

The overall resistance of the respiratory system can be determined with a technique employing forced oscillation (see Small-Airway Function). However, further methodologic refinements permitting determination of *pulmonary resistance* – the sum of airway and tissue resistances (Raw + Rti) – have not proved to be worthwhile clinically, particularly since measurement of transpulmonary pressure with an esophageal balloon is necessary. Other variations of the determination of resistance measurements have also been explored. However, the only clinically useful measurement of resistance is airway resistance, which is now routinely determined in pulmonary function laboratories.

AIRWAY RESISTANCE

Airway resistance (Raw) is defined as the ratio of the driving pressure (P) for flow to the actual rate of airflow ($\dot{V}$) along the airways – that is, the mouth, nasopharynx, larynx, and central and peripheral airways:

$$Raw = \frac{\Delta P}{\dot{V}}$$

where ΔP, the drop in pressure over the entire length of the airways, is determined as the difference between alveolar pressure (P_A) and pressure at the mouth (Pm) or airway opening (Pao).

Although airflow and pressure at the airway opening are easily measured, the difficulty in measuring alveolar pressure prevented the routine determination of airway resistance until DuBois and colleagues introduced the plethysmographic technique in 1956.[28]

With this technique, the patient, seated in the body plethysmograph, pants at a rate of about two breaths per second while airflow is measured using a pneumotachograph. During inspiration and expiration, gas in the alveoli is alternately rarefied and compressed, causing changes in pressure within the sealed plethysmograph. The relationship between plethysmograph pressure and airflow during the panting maneuver is displayed on the X and Y axes of an oscilloscope (Fig. 33-23).

While the panting continues, a shutter at the airway opening is closed so that airflow is transiently interrupted. Using the

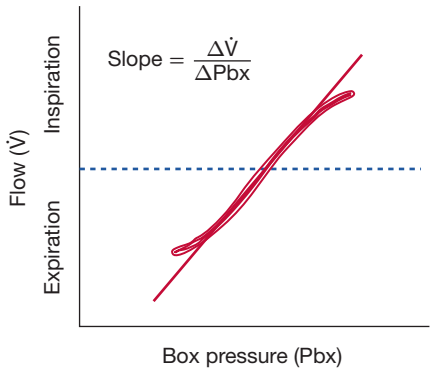

Figure 33-23 Plot of airflow (V̇) versus body plethysmograph pressure (Pbx). The slope of this curve, in the range of 0 to 0.5 L/s of inspiratory flow, divided into the slope of the loop obtained when the shutter is closed (see Fig. 33-7) provides a measure of airway resistance (Raw).

technique employed in the determination of FRC, changes in pressure in the plethysmograph (equivalent to changes in lung volume) and at the mouth are displayed on the X and Y axes, respectively, of the oscilloscope (Fig. 33-6). However, since airflow is zero while the shutter is closed, the pressure at the mouth equals alveolar pressure (Pao = P_A).

Panting while the shutter is open allows the determination of the relationship between airflow (V̇) and plethysmograph pressure (Pbx) – that is, V̇/Pbx. Similarly, panting against a closed shutter enables the determination of the relationship between alveolar pressure (P_A) and plethysmograph pressure – that is, P_A/Pbx. Airway resistance is calculated by dividing the slope of the loop obtained by plotting P_A versus Pbx while the shutter is closed by the slope obtained by plotting V̇ versus Pbx while the shutter is open:

$$\text{Raw} = \frac{P_A / Pbx}{\dot{V} / Pbx} = \frac{P_A}{\dot{V}}$$

where

Raw = airway resistance, $cmH_2O/L/s$
P_A = alveolar pressure, cmH_2O
V̇ = airflow, L/s

Raw is measured during a panting maneuver for several reasons:[29] (1) The rapid respiratory frequency in panting circumvents the poor low-frequency response characteristics of many plethysmographs. (2) The small inspired and expired volumes minimize temperature fluctuations in the plethysmograph that would otherwise occur as tidal breaths of air at body temperature are exchanged with breaths of air at room temperature. (3) During panting, the glottis remains open, thereby minimizing its contribution to overall airway resistance. Use of plethysmographs linked to microprocessors that automatically correct for temperature-related volume differences has made possible the determination of airway resistance during quiet breathing instead of during panting.

Airway resistance varies inversely with lung volume; it is low at large lung volumes and increases curvilinearly as lung volume and, consequently, airway diameters are reduced (Fig. 33-24A).[30] In contrast, the inverse of airway resistance, airway *conductance*, is linearly related to lung volume (Fig. 33-24B). Interpretation of a given value for airway resistance or airway conductance requires that the lung volume at which the measurement is made be taken into account. *Specific conductance* (SGaw) is calculated by dividing airway conductance by the lung volume.

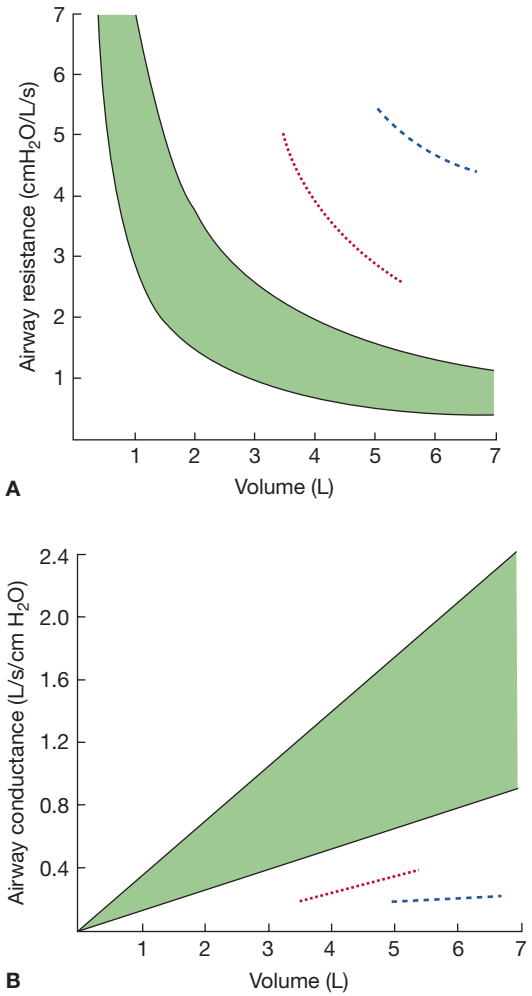

Figure 33-24 The relationship between airway resistance (**A**) and airway conductance (**B**). The shaded area represents the predicted normal range. Values are shown for an asthmatic patient before *(dashed line)* and after *(dotted line)* bronchodilator therapy. Airway resistance increases as lung volume decreases. Conversely, airway conductance, the inverse of resistance, decreases as lung volume decreases.

Defining the range of normal for Raw is difficult because of the lack of data obtained from populations sorted into smoking and nonsmoking groups and because of the inter- and intraindividual variations of Raw with lung volume. One classification scheme proposed for defining normal and abnormal Raw in adults in whom FRC exceeds 2 L is given in Table 33-7.

At times, an apparent discrepancy occurs between forced expiratory flow rates and values for airway resistance. For example,

TABLE 33-7 Categorization of Increased Airway Resistance (Raw)

Category	Raw ($cmH_2O/L/s$)
Mild	2.8–4.5
Moderate	4.54–8.0
Severe	>8.0

Source: Data from Ries A and Clausen JT: In Wilson AF (ed). Pulmonary Function Testing. Indications and Interpretations, Orlando, FL, Grune and Stratton; 1985.

although the FEV_1 and $FEF_{25-75\%}$ may be abnormally low (suggesting some degree of airway obstruction), Raw may be within normal limits (arguing against appreciable airway obstruction). This apparent contradiction arises because Raw is determined during *inspiration,* when airways are enlarged because of surrounding negative pleural pressure, whereas FEV_1 and $FEF_{25-75\%}$ are determined during a forceful *expiration,* when airways are compressed by high positive pleural pressures. Therefore, the discrepancy is simply a manifestation of dynamic airway obstruction in which the narrowing is confined to expiration.

■ MEASUREMENT OF EXHALED NITRIC OXIDE

Over the last two decades, the important role of nitric oxide (NO) in a variety of biologic processes has been described.[31] The concept that NO is a marker of airway inflammation, and, hence, has a potential role as a measure of airway function in the setting of inflammatory airway diseases, has been investigated.[32,33] Studies have demonstrated that, at least in asthma, levels of exhaled NO are elevated during exacerbations (when other measures of airway inflammation show activity), even in the absence of symptoms or changes in spirometry.[34,35] Exhaled levels of NO may also be helpful in classifying the severity of asthma.[36] Levels of NO decrease with inhaled corticosteroid use and rise with corticosteroid tapering. Some advocate measurement of exhaled NO as part of routine chronic asthma management.[31]

Standards have been developed for measuring exhaled NO levels.[31] While exhaled NO measurement has not yet assumed the status of a "standard" pulmonary function test, pulmonary function laboratories will likely soon add the test to their repertoires.

AIRWAY REACTIVITY

The dynamic tests of airway function described previously are designed to determine intrinsic properties of the airways in a subject breathing room air at rest. In many clinical situations, such as evaluation of chronic cough, assessment of airway hyperresponsiveness is desirable. This section reviews *bronchoprovocation testing* (BPT),[37,38] which assesses reactivity of the airways to selected pharmacologic or environmental agents.

■ BACKGROUND

One test of bronchial reactivity that has been incorporated into routine pulmonary function testing is determination of the effect on airflow of administration of a nebulized bronchodilator agent. However, bronchoprovocation tests are designed to quantify the degree of bronchoconstriction following the application of a particular stimulus. A number of tests of bronchial reactivity are currently in clinical use (Table 33-8). Among the agents used for inhalation challenges are methacholine, histamine, carbacholine, and specific antigens chosen in accord with the patient's history. In addition to the inhalation challenge tests in which pharmacologic agents are used, tests of bronchial reactivity may be based on inhalation of cold or dry air, isocapnic hyperventilation, or exercise.

■ INDICATIONS FOR BRONCHOPROVOCATION TESTING

The principal indication for BPT is a history suggestive of bronchospasm induced by an environmental or occupational agent, generally in the setting of normal pulmonary function tests (including determination of airflow before and after administration of an inhaled bronchodilator). For example, comparison of FEV_1 before and after administration of a pharmacologic agent such as methacholine or histamine can be useful in establishing the diagnosis of asthma. Also, inhalation of a suspected specific antigen may be useful in uncovering asthma when skin tests are equivocal, or in proving that asthma is occupation related. In some instances, exercise testing may disclose airway hyperreactivity in persons who are free of bronchoconstriction while at rest. Airway hyperresponsiveness to methacholine may presage an accelerated decline in pulmonary function.[39] However, the impact of therapy with agents like inhaled bronchodilators or corticosteroids in preventing progression is unclear.

TABLE 33-8 Tests of Bronchial Reactivity

Test	Reference
Inhalational challenges	
Pharmacologic agents	
Methacholine	Chai et al. *J Allergy Clin Immunol.* 1975;56:323–327
Histamine	Chai et al. *J Allergy Clin Immunol.* 1975;56:323–327
Carbocholine	Orehek et al. *Br Med J.* 1975;1:123–125
Specific antigens	
Toluene diisocyanate	Salvaggio. *J Allergy Clin Immunol.* 1979;64:646–649
Bacillus subtilis	Salvaggio. *J Allergy Clin Immunol.* 1979;64:646–649
Pollen	Spector. *J Allergy Clin Immunol.* 1979;64:580–586
Molds	Spector. *J Allergy Clin Immunol.* 1979;64:580–586
House dust	Spector. *J Allergy Clin Immunol.* 1979;64:580–586
Exercise-induced asthma	
Cold-air challenge	Strauss et al. *N Engl J Med.* 1977;297:743–747
Dry-air challenge	Hahn et al. *Am Rev Respir Dis.* 1984;130:575–579
Isocapnic hyperventilation	Eschenbacher et al. *Am Rev Respir Dis.* 1985;131:894–901

■ METHODS OF BRONCHOPROVOCATION TESTING

Several methods of BPT are in general clinical use. These include methacholine challenge, exercise challenge, and antigen challenge, each of which is described briefly in subsequent sections.

Inhalation Challenge: Methacholine

Inhalation challenge using methacholine has become popular because of standardization of the technique, ease and safety of performing the test, and high sensitivity of the test in detecting asthma.[40,41] Methacholine is a synthetic cholinergic agent that evokes airway smooth muscle constriction. Because baseline pulmonary function and breathing pattern influence the site of deposition of the inhaled methacholine particles and, thereby, the response, a standard method for aerosolizing the agent is used to ensure reproducible results.[42]

One method in common use is that of intermittent aerosol generation. Standardization entails the delivery of a 0.6-second pulse of airflow at 20 $lb/in.^2$ to a nebulizer, which, in turn, discharges particles that range from 0.3 to 4 μm in diameter into the airways. Methacholine for delivery by aerosol is prepared in concentrations ranging from 0.1 to 25 mg/mL using bicarbonate-buffered isotonic saline (containing 0.4% phenol) as the diluent. The cumulative dose delivered is expressed in inhalation units. One inhalation unit is equivalent to the single inhalation of a solution containing 1 mg of methacholine per milliliter (Table 33-9).

TABLE 33-9 Concentrations and Cumulative Doses of Methacholine Employed in the Methacholine Challenge Test

Methacholine Concentration (mg/mL)	Cumulative Dose (Inhalation Units)[a]
0.1	0.5
0.5	3
1.0	8
2.0	18
5.0	43
10.0	93
25.0	218

[a]*After five inhalations of a nebulized solution containing methacholine in a concentration of 1 mg/mL.*

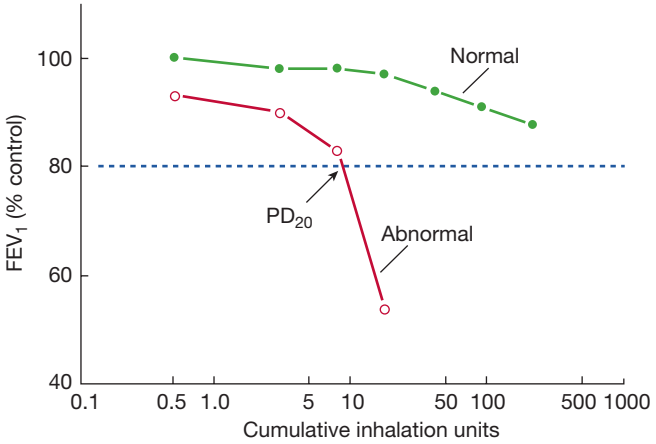

Figure 33-25 Plot of FEV_1,% control versus cumulative dose of methacholine administered by inhalation (logarithmic scale), to a normal subject and a subject with hyperreactive airways. The PD_{20} is the cumulative dose, which results in a 20% drop in the FEV_1 from the baseline measurement (after inhalation of diluent alone). In the subject with normal airway reactivity, the maximal cumulative dose of methacholine administered fails to elicit a 20% drop in FEV_1.

At the outset, the patient is challenged with five inhalations containing only aerosolized diluent. The necessity of the diluent step has been recently questioned. In addition to adding time and expense, it may force a greater absolute drop in FEV_1 needed to prove bronchial hyperreactivity. A fall in FEV_1 below 90% of the baseline value (i.e., the prechallenge control FEV_1) establishes that the airways are hyperreactive, and therefore, the test is terminated. However, if the FEV_1 does not fall below 90% of the control value, increasing concentrations of methacholine are given in stepwise increments of five-breath inhalations. The breaths are taken slowly from FRC to TLC. Then, 1 to 1.5 minutes after each dose, an FVC maneuver is performed. The interval between each increase in concentration is kept to a minimum because the response is judged in terms of the *cumulative* dose. However, the deep inspiration that immediately precedes the expiratory portion of the FVC maneuver may decrease bronchomotor tone in airways narrowed by methacholine. This effect lasts up to 6 minutes, thus limiting the shortest acceptable interval between dosage steps.[43] If the postchallenge FEV_1 falls below 80% of the control FEV_1, or if the patient experiences cough or chest tightness at any step, the test is stopped. The magnitude of the bronchoconstrictor response to inhalational challenge is related to the control FEV_1. A lower baseline FEV_1 (even in the normal range) correlates with increased bronchial reactivity.[44–47] Additional measurements of dynamic airway function (e.g., specific conductance) may provide supplemental data but also prolong the study. Another dosing option in use is the 2-minute tidal breathing protocol. This protocol typically yields results similar to the one described previously.

The results are plotted on four-cycle semilog graph paper: the number of cumulative inhalation units, expressed logarithmically, against the FEV_1, as percent of control (Fig. 33-25). A curve is constructed through the points; the dose corresponding to the point at which the FEV_1 is 80% of the control FEV_1 is designated as the *provocation dose,* or PD_{20} FEV_1.

Exercise Challenge

Persons without a history of asthma who develop cough, wheezing, or dyspnea after exercise may have exercise-induced bronchospasm (EIB). In these individuals, an exercise test may prove useful in establishing the diagnosis. Such exercise testing in asthmatics can be useful to assess the degree of impairment during exercise, or the impact of therapies.

Several factors that may influence the outcome of the test should be kept in mind. The temperature and humidity of the laboratory should be tightly controlled. Some centers use dry air inhalation during exercise. In addition, the duration of the test needs to be monitored. The goal of testing for EIB is to produce at least 4 minutes of exercise at the target heart rate and ventilation. Exercise should not continue for more than 6 to 8 minutes, in order to avoid "run-through" of the bronchospasm – that is, reversal at the end of the test.

The type of exercise also influences the outcome. As a rule, the more intense the exercise, the more likely is bronchoconstriction to occur. Free-range running provides the most potent stimulus for bronchoconstriction, followed by treadmill running, bicycle ergometry, swimming, and walking. An asthmatic may swim comfortably at a level of exercise that is incapacitating on the treadmill. The motor-driven treadmill or electromagnetically braked cycle ergometer are the preferred modes of exercise for formal testing.

The FEV_1 is the most useful measurement made during testing for EIB. Measurements are made just before and immediately after the exercise and at 5-minute intervals for the following 30 minutes. A decrease in FEV_1 of 10% or more below the pre-exercise value constitutes a positive test. Some have suggested that a decrement of 15% is of greater diagnostic value. False-positive responses can occur in patients with vocal cord dysfunction or abnormal posterior arytenoid motion.

Inhalation Challenge: Antigen

Compared with the relatively safe methacholine challenge test, BPT using a specific antigen is unpredictable and potentially hazardous. Since establishing the minimum dose required to induce bronchoconstriction is difficult, too much of the antigen may be given. A late response, far more severe than the initial one, often develops about 6 hours after the challenge. Despite these reservations about antigen challenge, testing is warranted under certain circumstances: to uncover a particular agent in the environment that causes bronchoconstriction, to establish the diagnosis of occupational asthma, to prove that bronchoconstriction is caused by a particular antigen after routine skin tests have failed to support the clinical suspicion, and to convince a skeptical patient about the cause of his or her asthma. Recommendations for preparing concentrations of antigens and the technique of antigen challenge testing are specific to the antigen in question and may be found in the literature. These tests should only be performed in laboratories which have considerable experience in BPT.

TABLE 33-10 Bronchoprovocation Testing: Precautions and Contraindications

- Baseline FEV_1/FVC% <60 (relative) or <50 (absolute)
- Recent upper respiratory tract infection
- Recent influenza vaccination
- Recent administration of bronchodilator
- Ingestion of caffeine within 6 h before testing
- Cold-air breathing, hyperventilation, exercise within 6 h before testing
- Recent acute myocardial infarction or cerebrovascular accident, uncontrolled hypertension, or known aortic aneurysm

PRECAUTIONS AND CONTRAINDICATIONS

Although the overall risk of serious complications is low, bronchoprovocation tests may be unnecessary, invalid, or even dangerous in some circumstances (Table 33-10). For example, the patient who manifests appreciable airway obstruction by conventional testing may develop life-threatening airway narrowing during a bronchoprovocation test. In such a patient, a simple bronchodilator study would be more appropriate and informative. If bronchodilators fail to reverse the increase in airway resistance, and if it is important to prove that bronchial hyperreactivity does exist, BPT is sometimes done, with extreme caution, on another day, as antigen dosages are titrated carefully and details of the procedure monitored closely.

Absolute contraindications include severe airways obstruction (FEV_1 <50% predicted), myocardial infarction or stroke in the preceding 3 months, uncontrolled hypertension, or known aortic aneurysm. Moderate airflow limitation, pregnancy, lactation, and concurrent use of cholinesterase inhibitor medication represent relative contraindications.

A recent viral upper respiratory tract infection can cause airway hyperreactivity for up to 6 weeks in normal subjects. Similarly, influenza vaccination increases responsiveness to inhalation challenges in asthmatics for a few days to a week. In these conditions, BPT should not be undertaken until the sensitization effects of the infection or vaccination have worn off. Also, bronchodilators, including caffeine, should be withheld for at least 6 hours before a bronchoprovocation test, if possible, in order to prevent blunting of the bronchoconstrictor response. Finally, cold air, hyperventilation, and exercise should be avoided for at least 6 hours before testing in order to prevent the induction of a refractory period or late response that would overlap the test results.

SMALL-AIRWAY FUNCTION

Up to this point, discussion of tests of dynamic lung function has addressed the tracheobronchial tree as a unit. However, in a variety of common clinical settings, including asthma, COPD, cigarette smoking, lung transplantation complicated by bronchiolitis obliterans syndrome, ARDS, and cystic fibrosis,[48–52] structural (and functional) abnormalities of the airways may be centered primarily in the small, peripheral airways – that is, those 2 mm or smaller in diameter. Because of their small contribution to airway resistance, estimated to be about 10% to 38% (at a lung volume equivalent to 50% of VC), the small airways can undergo considerable damage before the usual tests of either static or dynamic lung function become abnormal.[53,54] Consequently, efforts have been made to utilize tests aimed at early detection of small-airway disease in the hope of early intervention to limit progression of the disease.

Once obstructive disease of the peripheral airways arises, the small airways' contribution to overall resistance increases, and abnormalities in their function may be detected using specialized tests (see below), or, in some cases, analysis of selected aspects of the expiratory VC maneuver. In particular, abnormal values for $FEF_{25–75\%}$, in conjunction with normal values for FVC and FEV_1, are often useful in identifying small-airway disease. The basis for this approach is that $FEF_{25–75\%}$ measures airflow during the effort independent part of the FVC, when the small airways contribute substantially to the limitation of airflow.

A number of specialized tests of small airways' function have been developed over the last several decades, and some have found resurgent use in evaluating selected patient populations.[48] Several, along with their underlying physiologic basis, are described in subsequent sections.

FORCED OSCILLATION TECHNIQUE AND IMPULSE OSCILLOMETRY

The forced oscillation technique (FOT) and a variation of FOT, impulse oscillometry, are based on assessment of airway impedance and a component of airway impedance, airway resistance. Using a loudspeaker applied to the airway opening and measuring pressure and flow over a range of oscillation frequencies, airway resistance can be measured and compartmentalized into segments reflecting resistance in medium-to-large and small airways. In normals, over an oscillatory range of 5 to 25 Hz, respiratory resistance and its major component, airways resistance, are frequency independent. With development of airways obstruction, respiratory resistance becomes frequency-dependent. Furthermore, as small airways narrow or close, a component of impedance distinct from resistance – reactance (a concept which refers to the "out-of-phase" relationship between pressure and flow during oscillation and which is ascribed to energy storage, as determined by the elastic properties of the respiratory system) – is significantly affected, particularly when measured during the expiratory phase of respiration.[48,51,52,55]

DYNAMIC COMPLIANCE

Dynamic compliance, defined as the change in lung volume during airflow produced by a given change in transpulmonary pressure, is normally independent of breathing frequency. However, under conditions of nonuniformity of ventilation throughout the lung, increases in breathing frequency are associated with a fall in dynamic compliance. This frequency dependence of compliance was first noted in a patient with emphysema.[56,57]

During the test, the patient, with an esophageal balloon in place, first inspires maximally to TLC and then expires to the resting end-expiratory position (FRC); the patient then breathes at a normal tidal volume and respiratory rate (15 breaths per minute). In order to enable the patient to monitor these parameters, tidal volume and the resting end-expiratory level are displayed on an oscilloscope within sight of the patient. At the same time, changes in tidal volume and transpulmonary pressure are displayed on another oscilloscope (Fig. 33-26). The slope of the line connecting the end-inspiratory and end-expiratory points on the pressure–volume loop – that is, the points of zero airflow – is the dynamic compliance. This procedure is repeated with breathing frequencies of 30 and 60 breaths per minute. Values for dynamic compliance (Cdyn,L) at the various frequencies are expressed as a ratio of the dynamic compliance to the static inspiratory compliance (Cst,L) or as a percentage of Cst,L (Fig. 33-27) for the same range of tidal volumes.

In normal subjects, Cdyn,L/Cst,L remains above 0.8, even at frequencies greater than 60 breaths per minute. However, in the presence of obstructive disease of the small airways, Cdyn,L/Cst,L falls progressively to values below 0.8 as breathing frequency increases. It is worth emphasizing that interpretation of frequency dependence of compliance with regard to small-airway disease is valid only if the static compliance and overall airway resistance are normal. Abnormalities in these other measurements indicate

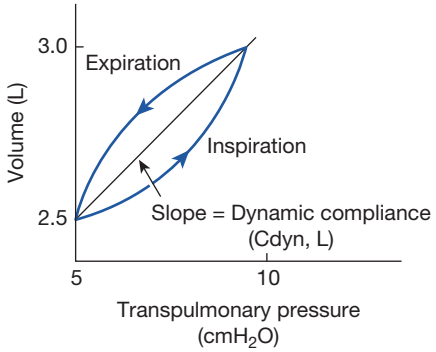

Figure 33-26 Measurement of dynamic lung compliance (Cdyn,L). During the inspiratory and expiratory phases of the respiratory cycle, a loop relating volume to transpulmonary pressure is generated. The slope of a line drawn through the points of zero airflow (at end inspiration and end expiration) is the dynamic compliance. Determination of Cdyn,L can be done at a variety of respiratory frequencies to assess the frequency dependence of compliance (Fig. 36-27).

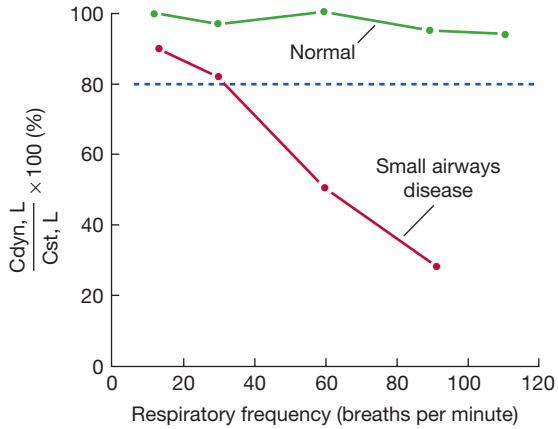

Figure 33-27 Determination of frequency dependence of dynamic compliance. Dynamic compliance is determined as shown in Figure 36-26 and is expressed as a percentage of static lung compliance (Cdyn, L/Cst, L × 100,%) at a variety of respiratory frequencies. Normally, Cdyn,L is ≥80% of Cst,L and is independent of respiratory frequency. In patients with obstructive airway disease, including those with disease limited to the small airways, Cdyn,L falls relative to Cst,L as respiratory frequency increases.

disease that is not likely to be confined to the small airways and for which frequency dependence of dynamic compliance is another manifestation. The physiologic basis for the fall in Cdyn,L/Cst,L as respiratory frequency increases is the presence of unequal time constants throughout the lung (see above).

■ SINGLE-BREATH NITROGEN WASHOUT, MULTIPLE BREATH NITROGEN WASHOUT, AND CLOSING VOLUME

In 1949, Fowler described the single-breath nitrogen washout test for assessing the uniformity of ventilation throughout the lungs. In performing this test, the patient first expires maximally to RV before filling his or her lungs by taking a maximal breath of 100% O_2. During the subsequent expiration, the concentration of nitrogen at the mouth is continuously recorded and plotted against the volume of expired gas. Originally, interest focused on the initial part of the tracing that depicts the changing concentration in expired nitrogen as the first 750 to 1200 mL of gas is exhaled. Over this range, the change in nitrogen concentration in persons with normal lungs is less than 2.5%. In contrast, when disease of the lungs or tracheobronchial tree results in abnormal intrapulmonary distribution of inspired gas, the change in nitrogen concentration exceeds 2.5%.

Almost 20 years later, Fowler's test was modified to include a bolus of xenon at the beginning of inspiration and to record the concentration of xenon during the following expiration.[58] Abrupt changes in the concentration of expired xenon as RV was approached suggested that important information about the small airways could be obtained from the terminal portion of the curve.

These observations with xenon rekindled interest in Fowler's original technique and also directed attention to the terminal portion of expiration. The procedure is depicted in Figure 33-28. To perform the maneuver for this measurement, the seated patient

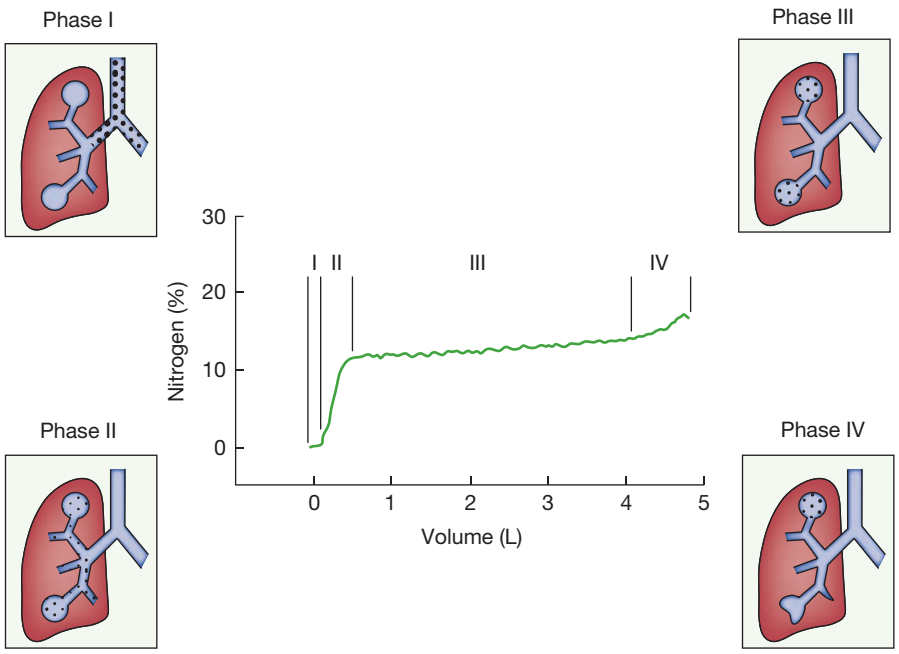

Figure 33-28 Contributions of different lung regions to the nitrogen concentration–volume curve obtained during the single-breath nitrogen washout test. See text for discussion.

takes two deep breaths of air and then expires to RV. At the end of this maximal expiration, a valve is opened so that the patient can take a full breath of 100% O_2 to TLC. The patient then expires slowly to RV while N_2 concentration and expired volume are recorded continuously.

Four distinct phases can be identified in the continuous record relating N_2 concentration to expired volume. Phase I, the initial expirate, contains virtually no N_2, since it derives from the O_2-containing dead space. Phase II represents a mixture of gases from the dead space and the alveoli. Phase III is due to a mixture of gases from alveoli located at the apices, midlung fields, and bases. Phase IV, characterized by an upward shift in N_2 concentration, is caused by closure of alveoli in the dependent parts of the lungs at low lung volumes. This final expirate derives from alveoli in the middle and upper regions of the lungs, where N_2 concentrations are higher than at the bases.

The explanation for these phases resides in the intrapulmonary distribution of gases during the respiratory maneuvers used in performing the test. In the normal upright person, a gradient of pleural pressures exists from apex to base, so that pleural pressure is more negative at the apices than at the bases. Because the alveoli at the bases operate on a lower portion of their pressure–volume curve (Fig. 33-11), they expand more than do apical alveoli per unit change in pleural pressure. However, the less negative pleural pressures and decrease in elastic recoil pressure at the bases also cause small airways to close during expiration as lung volume approaches RV. Thus, the pleural pressure gradient from top to bottom of the chest causes nonuniform distribution of gas within the normal upright lungs.

In the single-breath nitrogen washout test, a breath of 100% O_2 is taken, starting from RV. At RV, small basal airways are closed. Therefore, at the start of the O_2 breath, the N_2-containing air remaining in the dead space is preferentially drawn into the middle and apical lung zones as 100% O_2 gradually replaces air in the dead space. As the inspiration continues, the small airways at the bases open. Since their compliances are greater than those in the middle or at the top of the upright lungs, the inspired O_2 is then preferentially distributed to the bases.

During the expiration from TLC, the four phases then represent, as indicated above, the sequential emptying of dead-space gas and a mixture of dead-space and alveolar gas, followed by mixtures of alveolar gases from different parts of the lungs, as determined by the preceding intrapulmonary distribution of inspired O_2.[59]

The volume from the onset of phase IV to the completion of the full expiratory maneuver is termed the *closing volume* (CV). In healthy young adults, the normal closing volume averages about 10% of the VC. Narrowing or obstruction of small peripheral airways causes closing volume to enlarge. The closing volume also increases progressively as people grow older, so that by the age of 50, the closing volume sometimes reaches 25% of the VC. Cigarette smokers consistently experience an increase in closing volume. In both aging normal persons and cigarette smokers at any age, a decrease in pulmonary elasticity seems to be responsible for the increase in closing volume.

HELIUM–OXYGEN FLOW–VOLUME CURVES

In 1963, the effects of changes in gas density and viscosity on maximal expiratory flow throughout the vital capacity range were described.[60] Almost 10 years later, gas-density-related and viscosity-related concepts were applied to determine the site of airway obstruction in asthma. These principles were then applied for the specific purpose of detecting obstruction of small airways when other tests of pulmonary function were within normal limits.[61] While application of helium–oxygen flow–volume curves in the assessment of small airways function is physiologically elegant, the test is rarely performed in clinical practice.

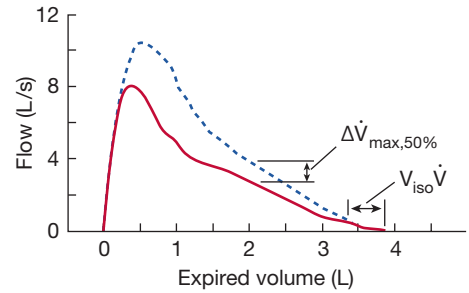

Figure 33-29 Maximal expiratory flow–volume curves generated in breathing room air *(solid line)* and breathing a helium–oxygen mixture *(dashed line)*. The airflows achieved with the less dense helium mixture are higher than those with air at all but the lowest lung volumes. The point of first intersection of these two curves demarcates the volume of isoflow ($V_{ISO}\dot{V}$). The difference between the flows achieved when 50% of the vital capacity has been expired is the $\Delta\dot{V}_{max,50\%}$. The use of these measurements as indicators of small-airway disease is described in the text.

The use of a helium–oxygen mixture to detect small-airway disease requires comparison of two maximal expiratory flow–volume curves, one that is generated while the patient breathes air and the other while the patient breathes helium and oxygen (Fig. 33-29). At least three maximal expiratory flow curves are obtained with room air and three with helium–oxygen.[29]

In normal subjects, at lung volumes greater than 10% of the VC, the primary site of resistance to airflow is in the larger airways, where flow is turbulent and, therefore, density dependent. At these lung volumes, the flow attained with the helium–oxygen mixture will be higher than that attained with air. At lung volumes less than 10% of the VC, the primary site of resistance is in the smaller airways, where flow is laminar and, therefore, not density dependent. In this circumstance, the less dense helium mixture has no effect on flow (Fig. 33-29). In disease of the small airways, the primary site of resistance shifts at large volumes from the larger to the smaller airways. As a result, the flow-enhancing effect of the less dense gas disappears at volumes well above 10% of the VC.

In practice, two sets of maximal expiratory flow–volume curves are obtained, one while the subject is breathing air and the other after three VC breaths of the helium–oxygen mixture to replace at least 95% of the alveolar N_2. Comparisons are then made of the superimposed curves (Fig. 33-29). One comparison is made at 50% of the VC in order to compare maximal expiratory flows (i.e., the $\Delta\dot{V}_{max,50\%}$); the other is at the volume at which the flows become identical – that is, the *volume of isoflow* ($V_{iso}\dot{V}$).[62] The curves are superimposed at RV or TLC, as long as the vital capacities of each curve are within 2.5% to 5.0% of the largest VC recorded.[29]

The percentage change in expiratory flow while breathing helium–oxygen compared to air at 50% of the VC, $\Delta\dot{V}E_{max,50\%}$, is calculated as

$$\Delta\dot{V}E_{max,50\%} = \frac{\dot{V}E_{max,50\%}(\text{helium–oxygen}) - \dot{V}E_{max,50\%}(\text{air})}{\dot{V}E_{max,50\%}(\text{air})} \times 100$$

where $\dot{V}E_{max,50\%}$ (helium–oxygen) and $\dot{V}E_{max,50\%}$ (air) are the expiratory flows at 50% of the VC during helium–oxygen and air breathing, respectively. As noted previously, the volume of isoflow is normally less than 10% of the VC; when it is increased, it indicates small-airway obstruction. The $\Delta\dot{V}E_{max,50\%}$ is also specific for small-airway disease, and unlike the closing volume, it is considered to be unaffected by changes in the elastic properties of the lung. Questions remain, however, about the validity and sensitivity of tests of density dependence of flow in assessing small-airway disease. Although they

are conceptually attractive, the practical value of helium–oxygen flow–volume curves in detecting small-airway disease is debatable.

GAS EXCHANGE FUNCTIONS

Traditional measurements of the gas exchange functions of the lung include oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide elimination ($\dot{V}_{CO_2}$), respiratory dead space (V_D), alveolar gas composition ($P_{A_{O_2}}$ and $P_{A_{CO_2}}$), diffusing capacity for carbon monoxide ($D_{L_{CO}}$), and arterial blood gas tensions (Pa_{O_2} and Pa_{CO_2}). These determinations require a steady state of the ventilation and circulation and constant body stores of O_2 and CO_2. A steady state with respect to O_2 implies that O_2 uptake measured at the mouth equals the rate of O_2 transport across the alveolar membrane, and that, in turn, both rates are equal to O_2 consumption by the tissues. The same type of definition applies to CO_2 exchange in the tissues, in the alveolar capillaries, and at the mouth.

VENTILATION, OXYGEN UPTAKE, AND CARBON DIOXIDE ELIMINATION

The total volume of air breathed per minute ($\dot{V}_E$) is the *minute ventilation.* It is equal to the product of the tidal volume (V_T) and the breathing frequency (f). As a rule, minute ventilation is determined by measuring the volume of expired gas relative to time. When the measurement is performed manually, the necessary equipment includes gas-collecting bags, low-resistance directional valves, a stopwatch, and a device for measuring gas volume. In practice, the patient, with nose clip in place, breathes through a mouthpiece for at least 3 to 5 minutes while expired gas is vented to the atmosphere. This preliminary period is intended to put the patient at ease and to achieve a steady state of respiration and circulation. When a steady heart rate and breathing pattern are achieved, a valve is turned without the patient's knowledge, and expired gas is collected for 3 minutes.

The minute ventilation is determined by dividing the total volume of expired gas collected in the spirometer by the time of collection (3 minutes). The average tidal volume is obtained by dividing $\dot{V}_E$ by the number of breaths per minute. Values for minute ventilation and tidal volume are expressed in terms of body conditions (BTPS). In the resting adult, the minute ventilation is typically 6 to 8 L/min; the corresponding tidal volume is 0.4 to 0.6 L.

The quantity of CO_2 in inspired air is negligible. Consequently, the amount of CO_2 produced per minute ($\dot{V}_{CO_2}$) can be calculated as the product of the expired volume of ventilation ($\dot{V}_E$) and the concentration of CO_2 in the expired air ($F_{E_{CO_2}}$):

$$\dot{V}_{CO_2} = \dot{V}_E \times F_{E_{CO_2}}$$

Oxygen uptake ($\dot{V}_{O_2}$) is calculated as the difference between the amounts of O_2 in inspired and expired air:

$$\dot{V}_{O_2} = (\dot{V}_I \times F_{I_{O_2}}) - (\dot{V}_E \times F_{E_{O_2}})$$

where

$\dot{V}_I$ = inspired volume of ventilation, L/min
$F_{I_{O_2}}$ = concentration of O_2 in the inspired air
$F_{E_{O_2}}$ = concentration of O_2 in the expired air

In the steady state, O_2 uptake by alveolar capillary blood exceeds CO_2 output from alveolar capillary blood. As a result, the expired volume of gas is less than the corresponding inspired volume. Since N_2 does not undergo exchange in the lungs, the difference between CO_2 output and O_2 uptake results in a higher concentration of N_2 in expired air than in inspired air. Based on the change in nitrogen concentration, the inspired volume of ventilation can be calculated from the expired volume of ventilation:

$$\dot{V}_I = \dot{V}_E \frac{F_{E_{N_2}}}{F_{I_{N_2}}}$$

where

$F_{E_{N_2}}$ = concentration of N_2 in expired air
$F_{I_{N_2}}$ = concentration of N_2 in inspired air

In the normal, resting subject who is tested after several hours of fasting, the ratio of CO_2 output to O_2 uptake, the *respiratory exchange ratio* (R), is about 0.8. The respiratory exchange ratio at any instant is calculated by simultaneously determining the P_{O_2} and P_{CO_2} in an alveolar gas sample. As indicated above, in the steady state, the R determined by sampling alveolar gas equals the R of alveolar capillary blood, which, in turn, equals the R of the tissues. The steady-state R, when alveolar gas, blood, and tissue are all in dynamic equilibrium, is the *respiratory quotient* (RQ). Hence, in the steady state, when the O_2 and CO_2 stores of the body are not changing, the RQ, reflecting cellular metabolism, can be determined by analyzing alveolar gas for O_2 and CO_2.

Unlike tidal volume and ventilation, which are expressed in terms of BTPS, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are given in terms of standard temperature and pressure, dry (STPD).

DEAD SPACE

Not all of the air breathed participates in gas exchange. Part of each breath remains in the mouth, nose, pharynx, larynx, trachea, bronchi, and bronchioles. This volume, the *anatomic dead space,* is about equal, in milliliters, to the subject's ideal body weight, in pounds (e.g., about 150 mL in a typical adult male). Inspired air reaching alveoli that are not exposed to pulmonary capillary blood also does not participate in gas exchange. This volume plus the anatomic dead space equals the *physiologic dead space.* In a normal person, the anatomic and physiologic dead spaces are virtually identical and constitute about one-third of the tidal volume.

Determination of the physiologic dead space has proved to be of practical importance in a variety of clinical conditions. It is calculated by considering each breath (V_T) to consist of dead space (V_D) and an alveolar volume that participates in gas exchange (V_A):

$$V_T = V_D + V_A$$

Physiologic dead space can be calculated using a modification of the *Bohr equation,* which recognizes that all of the test gas expired derives from two sources: the physiologic dead space and the alveolar gas-exchanging volume. If we use CO_2 as the marker gas, the total amount of CO_2 eliminated per minute equals the sum of the CO_2 coming from the dead space per minute and from the alveolar compartment per minute:

$$\dot{V}_E \times F_{E_{CO_2}} = (\dot{V}_D \times F_{I_{CO_2}}) + (\dot{V}_A \times F_{A_{CO_2}})$$

where

$\dot{V}_E$ = minute ventilation, L/min
$F_{E_{CO_2}}$ = fractional concentration of CO_2 in expired gas
$\dot{V}_D$ = minute dead space ventilation, L/min
$F_{I_{CO_2}}$ = fractional concentration of CO_2 in inspired gas
$\dot{V}_A$ = minute alveolar ventilation, L/min
$F_{A_{CO_2}}$ = fractional concentration of CO_2 in alveolar gas.

Since, in a subject breathing room air, $F_{I_{CO_2}}$ is practically zero, the last equation is generally simplified as follows.

$$V_E \times F_{E_{CO_2}} = V_A \times F_{A_{CO_2}}$$

where V_E and V_A represent volumes of ventilation, rather than rates.

Recalling that $V_A = V_T - V_D$ and substituting partial pressures for the fractional concentration terms, the relationship becomes

$$V_E \times P_{E_{CO_2}} = (V_T - V_D)\, P_{A_{CO_2}}$$

where $P_{E_{CO_2}}$ and $P_{A_{CO_2}}$ are the partial pressures of CO_2 in mixed expired gas and alveolar gas, respectively.

Assuming that arterial blood and alveolar gas are in equilibrium with respect to CO_2, when Pa_{CO_2} is substituted for $P_{A_{CO_2}}$ and the equation rearranged, it becomes

$$V_D = V_T \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2}}$$

Thus, if arterial blood is sampled during collection of expired gas, and if the partial pressures of CO_2 in expired gas and arterial blood are determined, the physiologic dead space can be calculated. In order for the physiologic dead space to be separated from the total dead space determined by the above equation, the dead space of the apparatus is subtracted from the value for total dead space.

■ ALVEOLAR GAS COMPOSITION

In normal subjects, values for P_{O_2} and P_{CO_2} in an end-tidal sample approximate mean alveolar values. However, when imbalances exist in alveolar ventilation and blood flow because of lung disease, inhomogeneity in alveolar gas composition often invalidates the use of end-tidal gas tensions as a measure of mean alveolar gas composition.

In practice, mean alveolar P_{O_2} ($\bar{P}A_{O_2}$) and mean alveolar P_{CO_2} ($\bar{P}A_{CO_2}$) are often determined indirectly. Arterial P_{CO_2} is assumed to equal mean alveolar P_{CO_2} on the grounds of the narrow arteriovenous difference for P_{CO_2} across the lungs, the high solubility of CO_2, and the presumed role of pulmonary capillary blood as a tonometer. Mean alveolar P_{O_2} is calculated using the alveolar gas equation:

$$\bar{P}A_{CO_2} = \bar{P}I_{O_2} - \bar{P}A_{CO_2}\left[FI_{O_2} + \frac{1 + FI_{O_2}}{R}\right]$$

The alveolar gas equation takes advantage of the fact that the total pressure of gases in the alveoli is equal to the sum of the partial pressures of the individual gases. This equation simply states that the mean alveolar P_{O_2} is the difference between inspired P_{O_2} and mean alveolar P_{CO_2}, allowing for a correction factor when the respiratory exchange ratio differs from 1.0.

■ DIFFUSING CAPACITY

The diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) can be determined by steady-state, rebreathing, and single-breath methods. The most frequently used method is a modification of the single-breath method first described in 1915 and subsequently modified in 1957.[63] Although the single-breath test has been shown to exhibit a large interlaboratory variation, it has proved to be a valuable measure of lung function in a wide variety of disease states. In fact, with continuing refinement of the standards,[6,64,65] the variability, which may be as much as 12% or greater, is likely to decrease; however, the variability will probably not be reduced to the range for vital capacity measurements (about 4%).

The diffusing capacity is intended to provide an estimate of the rate at which test molecules – usually CO – move by diffusion from alveolar gas to pulmonary capillary blood. Factors that influence the measurement are the physicochemical properties of the test gas, the extent and thickness of the alveolar capillary barrier, the resistance to diffusion offered by the red blood cell membrane, and the reaction rates of the test gas and hemoglobin, and pulmonary capillary blood volume. As a rule, the diffusing capacity is interpreted as an index of the surface area engaged in alveolar capillary diffusion. Clinical entities that can reduce the diffusing capacity include parenchymal lung diseases, particularly interstitial lung disease, emphysema, pulmonary hypertension, and anemia. Polycythemia and alveolar hemorrhage syndromes, on the other hand, may increase the diffusing capacity.

Carbon monoxide has emerged as the most practical test gas because of its affinity for hemoglobin. The diffusing capacity for CO is defined as the amount of CO transferred per minute per mm Hg of driving pressure:

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{\bar{P}A_{CO} - \bar{P}C_{CO}}$$

where

$D_{L_{CO}}$ = the diffusing capacity of the lung for CO, mL/min/mm Hg (STPD)
$\dot{V}_{CO}$ = the amount of CO transferred, mL/min
$\bar{P}A_{CO}$ = the mean alveolar PCO, mm Hg
$\bar{P}C_{CO}$ = the mean capillary PCO, mm Hg.

Since the blood P_{CO} in nonsmokers is essentially zero, the term $\bar{P}C_{CO}$ is customarily neglected. In practice, $D_{L_{CO}}$ is determined by calculating $\dot{V}_{CO}$ as the difference between inspired and expired samples and estimating the mean alveolar P_{CO}. Generally, one of the two techniques is used to determine $D_{L_{CO}}$: the single-breath or the steady-state technique.

The Single-Breath Method

The breathing maneuvers required for the single-breath method consist of tidal breathing for a few breaths, unforced expiration to RV, and then a single full, rapid inspiration of a gas mixture containing approximately 0.3% CO and an inert gas – traditionally, 10% helium (some newer systems use methane). The breath is held for 10 ± 2 seconds and then rapidly expired. An inspiratory time of less than 4 seconds, and a sample collection of no more than 3 seconds are required. Longer expiratory times and sample collection time greater than 3 seconds should be noted in the test report. The initial portion of the expirate containing dead-space gas is discarded; the remainder is collected, and the concentrations of CO and helium are measured.[63] A variety of automated systems are commercially available for performing the single-breath diffusing capacity. However, the essential components in all systems are a source of the special inspired gas mixture, a device for measuring the volume of gas inspired and expired, rapid response analyzers to measure the concentration of gases (see below), a timer, and appropriate valving and collection devices to trap the desired portion of the expirate.

The diffusing capacity of the lung for CO is calculated according to the following equation.

$$D_{L_{CO}} = \frac{V_A \times 60}{(\text{barometric perssure} - 47)} \times \text{time} \times \text{In}\frac{F_{A_{CO}}, \text{initial}}{F_{A_{CO}}, \text{final}}$$

where

V_A = alveolar volume
$F_{A_{CO}}$, initial = alveolar concentration of CO at the start of breath hold
$F_{A_{CO}}$, final = alveolar concentration of CO at the end of breath hold.

The concentration of CO in the alveoli at the start of the period of breath holding ($F_{A_{CO}}$, initial) is calculated from the inspired concentration of CO and, for helium-based systems, the inspired concentration of helium and the expired concentration of helium, according to the equation

$$F_{A_{CO}}, \text{ initial} = \frac{F_{E_{He}}}{F_{I_{He}}} \times F_{I_{CO}}$$

where

$F_{E_{He}}$ = expired concentration of helium
$F_{I_{He}}$ = inspired concentration of helium
$F_{I_{CO}}$ = inspired concentration of CO

The concentration of CO in the alveoli at the end of the breath-holding period ($F_{A_{CO}}$, final) is equal to the concentration of CO in the expired gas. The alveolar volume (V_A) is determined in one of two ways. Originally, V_A was calculated as the sum of the RV, determined by the closed-circuit helium or body plethysmograph techniques described previously, and the volume of inspired gas, as recorded on the spirometer. Later, V_A came to be calculated from the single-breath dilution of helium that occurs during the determination of $D_{L_{CO}}$. Finally, the time of breath holding is measured (in seconds) from the spirometer recording of the maneuver.

Although the single-breath method is relatively simple and has the advantage of requiring no blood samples, breath holding is clearly artificial, and the maneuver is difficult for dyspneic patients. Therefore, a steady-state method is sometimes used.

The Steady-State Method

In the steady-state method, a gas mixture containing 0.1% carbon monoxide is breathed until the rate of CO uptake from the lung is constant.[66] CO uptake ($\dot{V}_{CO}$) is determined from the difference between the amount of CO in the inspired and expired gas using an equation similar to that presented previously for calculation of O_2 consumption.

Comparison of Single-Breath and Steady-State Methods

Certain differences between the single-breath and steady-state techniques merit special mention.[29] The single-breath method is more popular because it is relatively easy to perform; it is well standardized, and it is less effected by nonuniformity of ventilation in comparison to the steady-state method. However, one drawback is that the patient is required to perform an inspiratory vital capacity maneuver of at least 88% of the VC and to hold his or her breath for 10 seconds. Another is that the test is extremely difficult to perform during exercise. The steady-state method is more attractive intrinsically than the single-breath method, since it requires no respiratory maneuvers and can be done during exercise. However, it does require an arterial blood sample (for determination of P_{CO_2}), and it is technically more difficult to perform.

The steady-state method for determining diffusing capacity tends to give lower values for the resting subject than does the single-breath method. The discrepancy is generally attributed to the fact that the surface area for diffusion is smaller during the quiet tidal breathing employed in the steady-state method than during the full inspiration to TLC, as required in the single-breath method. Also, during quiet breathing, some areas of the lung receive considerably less ventilation than during a breath hold at TLC.

Factors Other than Diffusion that Influence Test Results

A low $D_{L_{CO}}$ need not indicate a diffusion defect. A number of additional respiratory and nonrespiratory factors may reduce or increase the $D_{L_{CO}}$. A reduction in the lung volume alone can reduce the $D_{L_{CO}}$. Therefore, some laboratories "normalize" the diffusing capacity for lung volume by dividing $D_{L_{CO}}$ by alveolar volume – a manipulation that assumes a linear relationship between $D_{L_{CO}}$ and V_A, which is not the case.

Anemia artificially decreases the $D_{L_{CO}}$ as determined by either method, but the effect of low hemoglobin concentration can be adjusted by application of a correction factor.[67] Conversely, polycythemia and intrapulmonary hemorrhage tend to increase the value for $D_{L_{CO}}$. In fact, an unexpectedly high value for $D_{L_{CO}}$ may be a helpful clinical clue in detecting radiographically occult pulmonary hemorrhage.

Although the equation for $D_{L_{CO}}$ assumes that the CO back pressure in blood is negligible, the blood of a heavy smoker sometimes contains as much as 10% carboxyhemoglobin. Such levels of carboxyhemoglobin will be accompanied by appreciable concentrations of dissolved CO in the plasma. The resulting back pressure of CO will reduce the $D_{L_{CO}}$. A correction equation may be applied to adjust the $D_{L_{CO}}$ for this effect.

Altitude also affects the $D_{L_{CO}}$.[6] Pa_{O_2} falls with increasing altitude above sea level. The reduction in Pa_{O_2} allows CO to diffuse more rapidly into the blood. A specific adjustment should be made for inspired oxygen partial pressure.

Measurement of diffusing capacity is quite useful in the evaluation of patients with a number of pulmonary conditions. Decrement in $D_{L_{CO}}$ has been shown to predict exertional hypoxemia. In addition, $D_{L_{CO}}$ levels have been correlated with disease severity and prognosis in primary pulmonary hypertension, idiopathic pulmonary fibrosis, and alveolitis associated with systemic sclerosis.

■ ARTERIAL BLOOD GAS COMPOSITION

The determination of arterial P_{O_2} and P_{CO_2} provides useful information about the overall efficiency of external gas exchange. Heavy reliance is placed upon them for this purpose in managing acute respiratory failure, particularly in intensive care units. Less dramatic, but important, is their use in a variety of other settings (e.g., exercise testing) and for assorted calculations (e.g., the alveolar–arterial O_2 gradient and respiratory dead space).

Technique for Sampling Arterial Blood

Arterial blood is sampled either through an indwelling arterial catheter or by percutaneous arterial puncture. Sampling through an indwelling catheter avoids the acute changes in ventilation that sometimes result from apprehension and pain associated with percutaneous puncture.

Three anatomic sites are generally used for obtaining arterial blood samples: the radial, brachial, and femoral arteries. For several reasons, the radial artery is the preferred sampling site. Because of its superficial location at the wrist, the radial artery is easy to palpate and easy to compress by direct pressure, facilitating hemostasis when sampling is complete. In addition, no large veins lie in its immediate vicinity. Furthermore, the ulnar artery usually provides an adequate collateral circulation to the hand in the rare instance of postsampling thrombosis of the radial artery.

Arterial blood samples are drawn anaerobically into plastic or glass syringes coated with heparin. Because room air at sea level has a P_{O_2} of approximately 150 mm Hg and a P_{CO_2} of approximately zero mm Hg, air bubbles in the syringe will artificially increase the arterial P_{O_2} and reduce the arterial P_{CO_2}. The sample either is immediately analyzed or is placed on ice in order to minimize the metabolism of blood cells, particularly the white cells. If the icing precaution is neglected and the analysis is delayed, the Pa_{CO_2} of the sample will increase and the Pa_{O_2} and pH will decrease; the rate of change depends on the temperature of the sample and the elapsed time before analysis (Table 33-11).[68]

TABLE 33-11 In vitro Changes in Arterial Blood Gas Values at 37°C

Measurement	Change Over 10 min
pH (units)	−0.01
P_{CO_2} (mm Hg)	+1.000
O_2 content (vol%)	−0.001

Source: Data from Kelman GR, Nunn JF. Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH, and base excess for time and temperature. J Appl Physiol. 1966;21: 1484–1490.

TABLE 33-12 Effect of Altitude on Mean Alveolar and Arterial O_2 Pressures

Altitude (Feet)	Barometric Pressure (mm Hg)	Ambient P_{O_2} (mm Hg)	Alveolar P_{CO_2} (mm Hg)
0	760	159	103
1000	733	154	98
2000	707	148	94
3000	681	143	90
4000	656	138	85
5000	632	133	81
6000	609	128	77
8000	565	118	69
10,000	523	110	61
12,000	484	101	54

Source: Data from Wasserman K. Cardiovascular manifestations of respiratory insufficiency. Clin Notes Respir Dis. Fall; 1973;12(2):3–10.

TABLE 33-13 Classification of Primary Respiratory Disorders of Acid–Base Balance

Disorder	Definition
Acute respiratory alkalosis (acute alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal (<36 mm Hg), with accompanying alkalemia (pH >7.44)
Chronic respiratory alkalosis (chronic alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal, with pH normal (or near normal) due to renal compensation and lowered serum bicarbonate concentration (<19 mEq/L)
Acute respiratory acidosis (acute alveolar hypoventilation	Pa_{CO_2} above upper limit of normal (>44 mm Hg), with accompanying acidemia (pH <7.36)
Chronic respiratory acidosis (chronic alveolar hypoventilation)	Pa_{CO_2} above upper limit of normal, with pH normal (or near normal) due to renal compensation and elevated serum bicarbonate concentration (>30 mEq/L)

Interpretations

Analysis of arterial blood gases as part of pulmonary function testing is based primarily on determination of Pa_{O_2}, Pa_{CO_2}, and pH. As a rule, these parameters are measured directly. Other values, including O_2 saturation, bicarbonate concentration, and base excess (or deficit), are usually calculated. This section deals with the interpretation of Pa_{O_2}, Pa_{CO_2}, and pH. Additional consideration of arterial blood gases, with particular reference to acid–base balance, is found in Chapter 17.

Arterial P_{O_2} (Pa_{O_2}) The physiologic determinants of normal Pa_{O_2} have been described elsewhere. For example, normal values for arterial P_{O_2} depend on altitude (Table 33-12). Therefore, normal values for arterial P_{O_2} in Denver (altitude of approximately 1500 m) are less than those at sea level by about 20 mm Hg.

Arterial P_{O_2} also decreases with age. A regression equation can be used to predict the decrease:[69]

$$Pa_{O_2} = 109 - 0.43 \text{ (age in years)}$$

The standard deviation of this relationship is ±4.10 mm Hg.

A third physiologic influence is body position. Assumption of the supine position causes abdominal contents to displace the diaphragm cephalad, thereby closing small airways at the lung bases and creating ventilation-perfusion inhomogeneities that decrease Pa_{O_2}.

Many more pathologic conditions than physiologic states can lower Pa_{O_2}. In each instance, however, arterial hypoxemia may be attributed to one or more of the following generic mechanisms: alveolar hypoventilation, ventilation-perfusion mismatch, diffusion impairment, and venous admixture ("shunt"). Considerations of the individual disorders within these categories and the mechanisms leading to hypoxemia are found throughout this book.

Arterial P_{CO_2} (Pa_{CO_2}) and pH In a steady state, the level of Pa_{CO_2} reflects the level of alveolar ventilation. In the absence of a disorder in metabolic acid–base balance, an increase or decrease in Pa_{CO_2} beyond normal limits indicates a primary disorder in alveolar ventilation. A summary of these disorders and useful criteria for distinguishing among them, based on arterial blood gas composition, are given in Table 33-13.

Acute *respiratory alkalosis,* produced by alveolar hyperventilation, is characterized by hypocapnia (Pa_{CO_2} < 36 mm Hg) and an appropriately elevated pH (>7.44). In time (e.g., 24 hours or more), renal compensation occurs, and the concentration of bicarbonate in serum decreases. If alveolar hyperventilation continues, a chronic respiratory alkalosis, partly or completely "compensated," ensues.

A low Pa_{CO_2} is not necessarily indicative of a primary disturbance in alveolar ventilation. Instead, it may be a consequence of respiratory compensation (partial or complete) for metabolic acidosis; this possibility is signaled by the coexistence of hypocapnia and a low pH (<7.36). Since the kidney and respiratory system do not overcompensate for acid–base derangements, the coexistence of hypocapnia and acidemia suggest the presence of two primary disturbances.

Acute respiratory acidosis, caused by alveolar hypoventilation, is characterized by an abnormally high Pa_{CO_2} (>44 mm Hg) and a subnormal pH (<7.36). Again, in time (24 hours or more), renal compensation for the primary respiratory disorder restores the serum bicarbonate concentration and blood pH toward normal. A high value for Pa_{CO_2} may also reflect respiratory compensation for a primary metabolic alkalosis ($[HCO_3^-] > 30$ mEq/L). In this circumstance, however, blood pH will be abnormally high (pH > 7.44), rather than low. In general, the elevation in Pa_{CO_2} in compensation for metabolic alkalosis does not exceed about 55 mm Hg. A Pa_{CO_2} exceeding this value in the setting of a metabolic alkalosis suggests the likely coexistence of a primary respiratory acidosis.

This discussion has been limited primarily to alterations in arterial blood gas values in primary respiratory acidosis or alkalosis. Metabolic derangements often complicate the picture. These disorders are considered elsewhere (Chapter 17).

■ TESTING FOR AIR-TRAVEL-RELATED HYPOXEMIA

Travel in commercial jet airliners typically results in exposure of passengers and crew to conditions equivalent to about 6000 to 8000 ft above sea level. For individuals with normal pulmonary gas exchange, the resulting Pa_{O_2} falls within a clinically acceptable range. However, for many patients with lung disease, the resulting Pa_{O_2} may well be problematic, even in those patients who do not require supplemental oxygen at sea level. Consequently, assessment of patients with chronic lung diseases, particularly COPD and interstitial lung diseases, has become part of the repertoire of tests offered by many pulmonary function laboratories.[70–74] One approach to estimating the resultant Pa_{O_2} during air travel is based upon use of regression equations (Fig. 33-30). Using the patient's resting Pa_{O_2} at

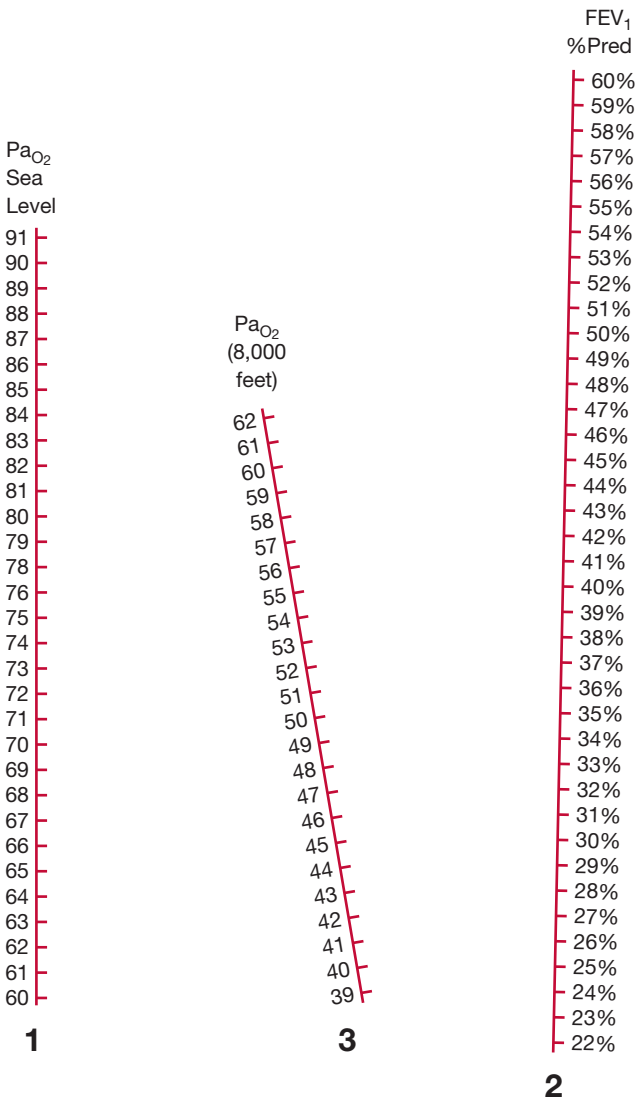

Figure 33-30 Nomogram for predicting in-flight oxygen tension. Using a straight edge, the patient's resting Pa_{O_2} at sea level (*Column 1*) is aligned with his or her FEV_1 percent of predicted (*Column 2*). The expected in-flight Pa_{O_2} (*Column 3*) is estimated as the value where the line crosses the center scale. *(Data from Dillard TA, Berg BW, Rajagopal KR, et al. Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. Ann Intern Med. 1989;111:362–367; and Knudson RJ, Slatin RC, Lebowitz MD, et al. The maximum expiratory flow-volume curve: Normal standards, variability, and effects of age. Am Rev Respir Dis. 1976;113:587–600.)*

sea level and his or her FEV_1 percent of predicted, the expected in-flight Pa_{O_2} can be estimated. Some experts advocate use of the nomogram for determining which patients ought to undergo hypoxia inhalation testing (HIT), while others advocate performance of HIT for all traveling patients at risk for in-flight hypoxemia.

HIT is based on the observation that exposure to hypoxic gas mixtures can reproducibly mimic the Pa_{O_2} arising under true hypobaric conditions. Exposure to 15.1% oxygen for 20 minutes reliably duplicates the resultant Pa_{O_2} at 8000 ft. During performance of the test, the patient, with nose clips in place, breathes from a reservoir though a mouthpiece. The electrocardiogram is monitored, and arterial blood gases are obtained at the conclusion of the test. Supplemental oxygen can then be titrated and prescribed according to the findings.

The British Thoracic Society (BTS) has published recommendations for use of supplemental oxygen during air travel, based on the patient's oxygen saturation at sea level and the presence or absence of risk factors.[71]

The BTS recommends no in-flight supplemental oxygen if the oxygen saturation at sea level is >95%; if the oxygen saturation is 92% to95%, supplemental oxygen is recommended if additional risk factors are present, including: hypercapnia, FEV_1 <50% predicted, lung cancer, interstitial lung disease with fibrosis, chest wall or respiratory muscle disorders, need for mechanical ventilation, cardiac or cerebrovascular disease, or travel within 6 weeks of hospital discharge following an acute exacerbation of chronic lung or heart disease. Supplemental oxygen is also recommended if oxygen saturation is <92% or if the patient uses supplemental oxygen at sea level, for whom an increase in oxygen flow during flight is advised.

The BTS also recommends supplemental oxygen for patients whose Pa_{O_2} on challenge testing (using an FI_{O_2} of 15% for 20 minutes) is <50 mm Hg and, possibly, for those whose Pa_{O_2} is between 50 and 55 mm Hg; in the latter group, a walk test may be helpful.[71]

CONTROL OF BREATHING

The rate, depth, and pattern of breathing reflect a complex interplay of neurohumoral and chemical regulatory mechanisms that drive the respiratory apparatus. Tests used to evaluate the control of breathing, based on assessment of the ventilatory response to controlled hypercapnia or hypoxia, are uncommonly performed in the clinical setting. However, since these tests highlight important physiologic mechanisms that affect the level and pattern of ventilation, they are summarized in subsequent sections.

VENTILATORY RESPONSE TO CO_2

The ventilatory response to changes in Pa_{CO_2} is linear over a broad range (Fig. 33-31). Determination of the ventilatory response to controlled hypercapnia generally is based on one of the two methods: the steady-state method[75] or the rebreathing method.[76]

Steady-State Method

After a control period in which CO_2-free air is breathed to establish a baseline, the patient is subjected to two or more periods of breathing CO_2-enriched air. Care is taken to achieve a steady state of ventilation and circulation during each exposure. Especially at the higher concentrations of inspired CO_2, at least 10 to 20 minutes is required for a steady state to be reached in alveoli, arterial blood, cerebrospinal fluid, and the chemosensitive areas of the brain. The ventilatory response to CO_2 is then determined from a plot of $\dot{V}_E$ versus Pa_{CO_2}. In patients without underlying lung disease, end-tidal CO_2 concentration is often substituted for Pa_{CO_2}. In addition, in order to eliminate the influence of variations in arterial PO_2 on the

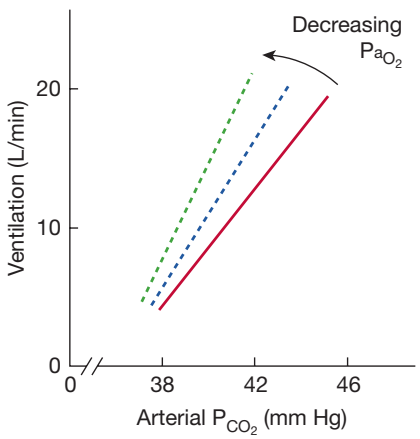

Figure 33-31 Linear relationship between minute ventilation ($\dot{V}_E$) and arterial P_{CO_2}. The dashed lines show the increased slope of the relationship of $\dot{V}_E$ versus P_{CO_2} as Pa_{O_2} decreases.

ventilatory response to CO_2, the inspired gas is enriched with O_2 during the control and test periods.

Rebreathing Method

This method entails rebreathing a CO_2-enriched gas mixture from a bag for approximately 4 minutes. The validity of the approach requires rapid equilibration of CO_2 among alveolar gas, arterial and mixed venous blood, and the chemosensitive areas of the brain. The bag is filled at the outset with a mixture of 7% CO_2 in O_2; O_2 is substituted for air in this mixture to avoid the ambiguity of a hypoxic stimulus to ventilatory drive.

The result of the CO_2 rebreathing test is described by the use of two terms: (1) the *slope* of the line relating change in ventilation response to change in end-tidal P_{CO_2} ($\Delta\dot{V}E/P_{CO_2}$), determined by using the method of least squares linear regression analysis, and (2) the *x-intercept* of the relationship between $\dot{V}E$ and end-tidal P_{CO_2}.

Normal Response to CO_2 and Modifying Influences

As indicated above, the normal increase in ventilatory response to increasing concentrations of inspired CO_2 is linear. Normal responses are categorized as low (<1.5 L/min/mm Hg), intermediate (1.5–5.0 L/min/mm Hg), or high (>5.0 L/min/mm Hg). Most normal persons (about 80%) have an intermediate ventilatory response. A variety of factors, both genetic and environmental, seem to influence the ventilatory response to CO_2 (Table 33-14).

■ VENTILATORY RESPONSE TO HYPOXIA

The response to acute hypoxia in normal persons is largely determined by the peripheral arterial chemoreceptors, as long as the level of hypoxia is mild to moderate. Even at sea level, the level of arterial P_{O_2} in normal persons provides an appreciable chemoreceptor drive, accounting for about 10% of the minute ventilation. Unlike the linear response of $\dot{V}E$ to progressive hypercapnia, the response to hypoxemia is curvilinear (Fig. 33-32). The magnitude of the ventilatory response to a decrease in arterial P_{O_2} depends on the Pa_{CO_2}, increasing as the concentration of CO_2 in arterial blood is increased.

As may be seen from the hyperbolic curves in Figure 33-32, the rate of change in ventilation is greater over the lower range of oxygenation (when Pa_{O_2} falls below 60 mm Hg). Not shown in Figure 33-32 is the depression of ventilation brought about by severe hypoxemia, presumably because of the central depressing effect of severe hypoxia on respiratory neurons.

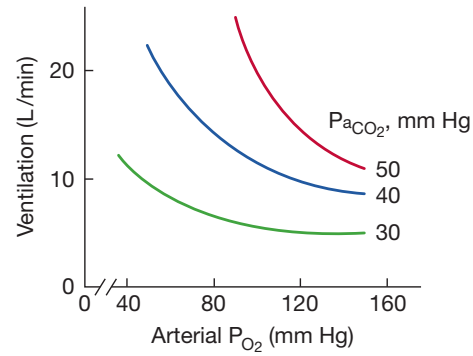

Figure 33-32 The curvilinear relationship between ventilation and arterial P_{O_2} at various levels of arterial P_{CO_2}. The rate of change of ventilation as P_{O_2} falls (slope) increases precipitously at a P_{O_2} of approximately 60 mm Hg when P_{CO_2} is 40 mm Hg. The abrupt increase in ventilation occurs at a higher P_{O_2} when the level of P_{CO_2} is elevated, and at a lower P_{O_2} when the prevailing P_{CO_2} is lower.

Although tests for assessing the ventilatory response to hypoxia are less well standardized than those for measuring the hypercapnic response, they, too, may be conveniently categorized into steady-state and nonsteady-state methods. In one steady-state method,[75] successive ventilatory responses are determined to a series of increasingly severe hypoxic gas mixtures, each administered for at least 10 minutes; Pa_{CO_2} is kept constant by the addition of CO_2 to the inspired gas mixture as hypoxia-induced hyperventilation develops. In another, the effect of hypoxia on the slope of the plot of $\dot{V}E$ versus P_{CO_2} as P_{O_2} is lowered from hyperoxic (at least 200 mm Hg) to hypoxic (40 mm Hg) levels is determined. The normal response to diminished inspired oxygen concentrations is characterized by an increase in sensitivity (slope) without a change in the CO_2 threshold.

TABLE 33-14 Factors Associated with an Altered Ventilatory Response to CO_2

Factor	Reference
Depressed Response	
Endurance training	Byrne-Quinn et al. *J Appl Physiol*. 1971;30:91–98
Aging	Peterson et al. *Am Rev Respir Dis*. 1981;124:387–391
Genetic/racial predilection	Beral et al. *Lancet*. 1971;2:1290–1294
Metabolic alkalosis	Koboyashi et al. *Am Rev Respir Dis*. 1993;147:1192–1198
	Heinemann and Goldring. *Am J Med*. 1974;57:361–370
Narcotics, barbiturates, and other CNS depressants	Lambertsen. *Handbook of Physiology*. Section 3: Respiration, vol I. Washington, DC: American Physiological Society; 1964: 545–555
Neurologic disorders (encephalitis, brain stem disease)	Plum, Brown. *Ann NY Acad Sci*. 1963;109:915–931
Myxedema	Zwillich et al. *N Engl J Med*. 1975;292:662–665
	Duranti et al. *Am J Med*. 1993;95:29–37
Obesity-hypoventilation syndrome	Zwillich et al. *Am J Med*. 1975;59:343–348
Chronic obstructive pulmonary disease (COPD)	Flenley, Millar. *Clin Sci*. 1967;33:319–334
Accentuated Response	
Metabolic acidosis	Heinemann, Goldring. *Am J Med*. 1974;57:361–370
Drugs (e.g., aminophylline, salicylates, thyroxine, progesterone)	Lambertsen. *Handbook of Physiology*. Section 3: Respiration, vol I. Washington, DC: American Physiological Society; 1964: 545–555

Three nonsteady-state techniques are currently in use. In the hypoxic rebreathing test,[77] the subject rebreathes a hypoxic gas mixture containing 7% CO_2. As arterial hypoxemia intensifies, causing an increase in ventilation and in CO_2 elimination into the closed circuit, the P_{CO_2} in the system is held constant at a predetermined level by the diversion of a fraction of the expired gas through a CO_2 absorber. The ventilatory response is determined at two or more levels of P_{CO_2}, since the hypoxic response is influenced by P_{CO_2}. An alternative rebreathing test[78] induces progressive hypoxemia by adding N_2 to the inspired gas mixture over a 20-minute period. Finally, in a relatively simple test, the patient induces a transient drop in arterial P_{O_2} by inhaling pure N_2 for a few breaths. The relationship between $\dot{V}E$ and Pa_{O_2} is plotted; the slope of the relationship is the sensitivity to hypoxia. Because the duration of the hypoxia is brief, presumably only the peripheral chemoreceptors are stimulated. No adjustment is made for the drop in P_{CO_2} that occurs during the hypoxia-stimulated increase in ventilation.

Finally, in a relatively simple test,[79] a transient drop in arterial P_{O_2} is induced by having the patient inhale pure N_2 for a few breaths. The relationship between $\dot{V}E$ and Pa_{O_2} is plotted; the slope of the relationship is the sensitivity to hypoxia. Because the duration of the hypoxia is brief, presumably only the peripheral chemoreceptors are stimulated.

Normal Responses to Hypoxia and Modifying Influences

The normal ventilatory response to acute hypoxia varies among individuals. Several factors may influence the relationship (Table 33-15). A high ventilatory response to CO_2 may be associated with a high sensitivity to hypoxia; in addition, higher levels of arterial P_{CO_2} are associated with a higher ventilatory response to hypoxia. Interestingly, a long duration of hypoxia before the test period, as is the case for example, in native residents at high altitude and persons with cyanotic congenital heart disease, a blunted response to acute hypoxia is observed. Finally, a variety of other clinical disorders, including myxedema and hypothyroidism, autonomic nervous system dysfunction, chronic narcotic addiction, and the chronic use of methadone, are characterized by a reduced hypoxic response.

TABLE 33-15 Factors Associated with an Altered Ventilatory Response to Hypoxia

Factor	Reference
Depressed Response	
Long-standing hypoxia	
High-altitude dwelling	Severinghaus et al. *Respir Physiol.* 1966;1: 308–334
Congenital cyanotic heart disease	Blesa et al. *N Engl J Med.* 1977;296: 237–241
Aging	Kronenberg et al. *J Clin Invest.* 1973;52: 1812–1819
Hypothyroidism	Zwillich et al. *N Engl J Med.* 1975;292:662–665
Riley–Day syndrome	Edelman et al. *J Clin Invest.* 1970;49:1153–1165
Chronic use of methadone	Marks. *Am Rev Respir Dis.* 1970;108:1088–1093
Following carotid endarterectomy	Wade et al. *N Engl J Med.* 1970;282: 823–829
Accentuated Response	
Heightened CO_2 response	Rebuketal. *J Appl Physiol.* 1973;35: 173–177
Hypercapnia	Rebuck, Woodley. *J Appl Physiol.* 1975;38: 16–19

■ NONVENTILATORY MEASURES OF VENTILATORY DRIVE

Measurement of ventilation in response to acute hypoxia or hypercapnia provides a useful index of respiratory output when the ventilatory apparatus (thorax, diaphragm, abdominal muscles, lung, and airways) is normal. This situation obviously does not apply in certain neuromuscular disorders in which the thorax and diaphragm behave abnormally. In addition, it does not apply in some instances of pulmonary disease, notably obstructive airway disease, in which the respiratory apparatus may not be capable of responding normally, even though it is intact and chemosensitivity is normal. In this instance, a decrease in ventilatory response may be attributable to the excessive mechanical load placed on the muscles of respiration.

When ventilation fails to provide a reliable measure of the ventilatory drive (efferent discharge from the respiratory neurons), the diaphragmatic electromyograph (EMG) or the pressure generated by the inspiratory muscles during the first 0.1 second of an occluded inspiration (the $P_{0.1}$)[80] has been used for the clinical assessment of the control of breathing.

The electrical activity of the diaphragm is directly related to neural activity of the phrenic nerve. Therefore, it provides a measure of efferent neural traffic to the diaphragm. The diaphragmatic EMG may be recorded in patients by placing the tip of an esophageal catheter, containing bipolar electrodes, at the level of the diaphragm.

The second approach to obtaining a nonventilatory measure of ventilatory drive is the determination of $P_{0.1}$, which is the negative pressure generated by the inspiratory muscles during the first 100 milliseconds of an inspiratory effort made against an occluded airway. During this brief period, contraction of the respiratory muscles is virtually isometric, and the force generated correlates with activity recorded by the diaphragmatic EMG.

In performing the test, airflow in the inspiratory line of the breathing circuit is randomly interrupted during the preceding expiration. The 100-millisecond period has proved to be so brief as to be imperceptible, thereby obviating any corrective action by the subject during the breath against the occlusion. However, the $P_{0.1}$ is far from foolproof. A major concern is that $P_{0.1}$ is affected by resting lung volume: $P_{0.1}$ is reduced when FRC is abnormally high, a common occurrence in obstructive disease of the airways.

ASSESSMENT OF INTEGRATED FUNCTIONS: 6-MINUTE WALK TEST

A complete evaluation of a patient with respiratory symptoms often requires assessment of exercise capacity, in addition to traditional pulmonary function tests and radiographic studies. A number of exercise studies can be employed, including cardiopulmonary exercise tests (Chapter 34), cardiac stress tests, and exercise-induced bronchospasm protocols. One of the most widely used, practical modalities is the 6-minute walk test (6MWT). Despite its simplicity, the 6MWT has become a powerful tool in the evaluation of functional status and prognosis of patients with a variety of functional impairments.

■ TECHNICAL ASPECTS

The 6MWT is performed indoors. There is an initial period of rest in a chair for at least 10 minutes, during which baseline vital signs are taken. The patient then stands and is asked to rate baseline dyspnea and overall fatigue using the Borg scale (from 1 to 10). The patient, walking at a comfortable pace, completes 60-m laps on a walking course which is 30 m in length. Cones are used to mark

the turnaround points. For patients using supplemental oxygen, the oxygen is delivered at standard rate, or as prescribed by a physician, or as determined by protocol. The patient should not carry or push the oxygen source during testing. The number of laps and a postwalk Borg scale assessment are recorded, as is the total distance walked over 6 minutes (6MWD).

Although pulse oximetry during the 6MWT is considered optional, it has become standard at many institutions. In some cases, pulse oximetry can be used to titrate levels of oxygen supplementation. Obtaining a high-quality oximeter signal is imperative.

A number of sources of variability are inherent in 6MWT. A modest training effect has been reported when two studies are performed within 1 week. Concomitant medication use can also impact the 6MWT. Improved test performance, for example, occurs after bronchodilator use in patients with COPD. Shorter height, female sex, and higher body weight are associated with reduced performance.[81] Despite these factors, the 6MWT has been found to have excellent reproducibility, especially when performed in evaluation of specific clinical entities, such as idiopathic pulmonary fibrosis.[82]

Several modifications of the 6MWT are in clinical use. During a *shuttle-walking test*, the patient walks on a 10 m course while the walking speed is increased every minute until the patient cannot reach the turnaround point within the set time. The *timed walk test (TWT),* which has been designed for patients with idiopathic pulmonary fibrosis, has three stopping criteria based on changes in oxyhemoglobin saturation.

Absolute contraindications to performing the 6MWT include unstable angina or myocardial infarction within 1 month of the study. Resting tachycardia of greater than 120 beats per minute, systolic blood pressure greater than 180 mm Hg, or diastolic blood pressure greater than 100 mm Hg are relative contraindications. The study should be terminated if the patient develops chest pain, severe dyspnea, leg cramps, diaphoresis, or profound oxyhemoglobin saturation.

INTERPRETATION

Although the 6MWT is limited in its inability to provide objective measures of functional capacity, such as oxygen uptake, the test provides very useful clinical information. In addition, it realistically represents the patient's functional capacity during physical effort that more closely reflects his or her daily activity. Reliable reference equations establishing standard performance during a 6MWT in healthy patients are not currently available.

The 6MWT has several indications, including, most notably, measurement of the response to a number of medical and surgical interventions. Pulmonary rehabilitation clearly improves 6MWT performance in patients with COPD, while pharmacologic interventions for pulmonary arterial hypertension and heart failure, among other disorders, have also been shown to favorably affect test results. Lung transplantation (unilateral and bilateral) and lung volume reduction surgery for emphysema have been shown to significantly improve results of the 6MWT.

6MWT also has been used to assess functional status in patients with COPD, cystic fibrosis,[83] heart failure, and peripheral vascular disease, and in determining eligibility for, and timing of, lung transplantation. In the absence of well-established reference standards, the clinical value of performing a single test in these patient groups is limited. Serial studies are likely to be more useful than a single 6MWT.

Recently, a number of publications have established the value of the 6MWT in predicting morbidity and mortality from heart and lung disease. Results from the test have been shown to have an inverse relationship with mortality in severe COPD. Walk distance and velocity, as well as magnitude of oxyhemoglobin desaturation, are correlated with survival in idiopathic pulmonary fibrosis. Similar correlations have been made in heart failure and primary pulmonary hypertension.

Finally, at some institutions, results of the 6MWT are utilized to not only establish the presence of exertional hypoxemia, but also to titrate supplemental oxygen with activity.

QUALITY CONTROL IN THE PULMONARY FUNCTION LABORATORY

Meaningful interpretation of pulmonary function tests requires confidence in the accuracy and reproducibility of results provided by the pulmonary function laboratory. Previously, it was tacitly assumed that all data from all laboratories, especially when reported as "percent predicted," were equally reliable. In recent years, the fallacy of this assumption has been explicitly recognized, and steps have been taken to standardize equipment and procedures and to ensure accuracy, reproducibility, and uniformity in testing and reporting.[6,8] To accomplish this goal, both analytical and nonanalytical factors must be taken into account.

NONANALYTICAL FACTORS IN QUALITY CONTROL

A familiar example of a confounding influence that may distort test results is the anxious patient who pauses outside the laboratory door to "calm the nerves" by smoking one or more cigarettes before undergoing pulmonary function testing. Cigarette smoking before the diffusing capacity of the lungs is determined can generate enough carboxyhemoglobin to reduce a normal value to subnormal levels.

Another example of a nonanalytical factor is the failure to achieve patient understanding and comfort for tests that usually require patient cooperation. Unfortunately, a preliminary explanation before the patient arrives at the laboratory or prior exposure of the patient to the laboratory and its personnel is usually impractical. Use of explanatory sheets or descriptive brochures may prove helpful. If such materials are not available, laboratory personnel are obligated to make the patient comfortable and even perform "practice runs" before undertaking final testing.

When the patient arrives at the pulmonary function laboratory, an assessment should be made of his or her prior experiences. Did the patient undergo other tests or procedures that could alter the outcome of the pulmonary function tests in question? Is the patient fatigued or in pain? Should a period of rest precede the tests in order to ensure optimal performance? If delay is impractical, the test report should include the fact that the patient was fatigued or in pain.

Medication use before pulmonary function testing can seriously affect the results. For example, self-administration of bronchodilators before testing can artificially enhance tests of airflow. If medications have been taken before the patient arrives at the laboratory, the time of administration should be part of the record. Also, a request for pulmonary function test results for patients who regularly take bronchodilators should indicate whether the tests are to be done without interruption of the regular schedule of medications, whether bronchodilators are to be discontinued before the test is done, or whether regular bronchodilators are to be discontinued so that the effects of bronchodilation can be tested. Appropriate comments about bronchodilators are part of the report.

A major nonanalytical cause of misinterpreting results is the inappropriate application of predicted normal values to the patient population by the laboratory (see Approach to Interpreting Commonly Performed Pulmonary Function Tests). For example, normal values based on data obtained using physically fit hospital personnel do not necessarily apply to those who have a sedentary existence. Noncomparable race, as well as lifestyle, may complicate comparisons. Anthropologic differences among control and test populations are not easily reconciled. Extraordinary height, weight, or age cannot be easily extrapolated if corresponding subjects are not represented in the control group. Using patient-reported height, rather

than making measurement of patient height, may introduce an error in the selection of appropriate normal values.[84] Comparison of control and test results at different altitudes can be invalid if due regard is not paid to the influence of hypoxia on certain measurements (e.g., diffusing capacity).

ANALYTICAL FACTORS IN QUALITY CONTROL

Performance of pulmonary function tests is replete with opportunities for error. The equipment, techniques, use of control values, and calculations are potential sources of error. In an attempt to minimize errors, standardization of techniques has been advocated. For example, with respect to performing the FVC maneuver, guidelines have been established for the number of attempts required, acceptable variability between efforts, and methods for selecting test data in order to arrive at acceptable results. To avoid misuse of spirometers, criteria have been set for minimal performance with respect to capacity, accuracy, and frequency response of various spirometers; in addition, standards have been developed for determining the single-breath diffusing capacity. Potential sources of discrepancies – such as breath-holding time, concentration of hemoglobin, dead space of the equipment and the patient, F_{IO_2}, volume of the alveolar sample, number of tests, and acceptable variability in results – are taken into account.

QUALITY CONTROL OF TEST RESULTS

Guidelines for standardization play a major role in reducing discrepancies between laboratories. However, measures are also required to ensure accuracy and reproducibility within any given laboratory. Among the elements of control that merit consideration are calibration, validation of calibration, and performance of a control measurement. *Calibration* is the adjustment of an instrument's output so that it validly reflects a known input. *Verification of calibration* entails introduction of the same known input and demonstration that the correct output is reproduced. *Performance of a control measurement* refers to the testing of a substrate that has known properties, similar to those usually tested, to prove the accuracy of the instrumentation.

One example of the application of these principles is blood gas analysis. Use of control measurements derived from tonometered blood or commercially prepared buffer solutions is now widespread. Another example is assessment of diffusing capacity[85] and routine incorporation of simulator testing in its measurement.[86]

Unfortunately, similar controls do not exist for pulmonary function tests. Therefore, laboratory technologists have the responsibility for continuing to be alert, not only with respect to faithful observance of guidelines for standardization, but also to detect in-house sources of error – for example, a leak in the system, malfunction of gas analyzers, faulty analog-to-digital converters, and faulty electronics that reduce frequency response.

RESPONSIBILITY AND COST IN QUALITY CONTROL

All who work in the laboratory must be concerned with quality control[87] and resist the frequent temptation to cut corners. Time has to be set aside for the technologist to care for and calibrate equipment, to establish proper control values for the laboratory, to search for inconsistencies in the data and interpretation, and to keep up with changing standards. Also, equipment and supplies, including calibrating syringes and calibrating gases, are expensive. However, when put into the balance, the cost and waste of producing erroneous results exceed, by far, the expense of practicing quality control.

INFECTION CONTROL

Given the relatively close contact between patients and technical staff during performance of pulmonary function tests, the issue of infection control is one that must be carefully considered. To date, the role of pulmonary function equipment in transmission of disease appears to be minimal. Although the presence of potential pathogens on laboratory mouthpieces, valves, and tubing has been well documented, implication of these organisms in the transmission of disease has not been established. Nevertheless, the potential hazards should be recognized and appropriate care exercised.

Infection control begins with practice of the basic principles of hygiene. Hand washing between patients and use of protective gloves by staff when they are handling potentially contaminated equipment are important considerations. Care must be taken in working with mouthpieces, nose clips, and any other implements that come in contact with mucosal surfaces. These devices, if reused, should be disinfected or sterilized after each use. Other equipment – manifolds, tubing, etc. – should be sterilized on a regular basis. In fact, guidelines from the ATS call for the disinfection or sterilization before reuse of any equipment surface with visible condensation from expired air.[6,88]

Because of recent growing concern over cross-contamination among patients and laboratory personnel, manufacturers now produce a variety of in-line filters and disposable pneumotachographs. Care should be taken, however, to assure that response characteristics of the test equipment are not driven to unacceptable levels by use of these devices. Current literature on this topic should be consulted regularly.

APPROACH TO INTERPRETING COMMONLY PERFORMED PULMONARY FUNCTION TESTS

A standard battery of pulmonary function tests is commonly used to identify and quantify abnormalities in the performance of the respiratory system. An organized approach to interpreting these studies is critical. Once a patient's baseline values are established, the tests are valuable in tracking the course of the disorder and its response to treatment.

Results of pulmonary function tests are interpreted by comparing individual patient data with reference or predicted values for normal subjects.[89,90] Ideally, predicted values should be generated from large groups of well-defined, normal or healthy subjects with proper distribution of anthropometric characteristics such as sex, age and height, and ethnic background. Despite dedicated attempts to improve prediction formulas, however, many still fail to take into account important sources of discrepancy, such as the racial and ethnic backgrounds of the patients and the control population, the effects of altitude and exposure to air pollution, and effects of inordinate body size or old age. As a result, not all sets of predicted normals are applicable in pulmonary function laboratories outside the immediate vicinity of the patient populations from whom the data were collected.[91] Extrapolation beyond the characteristics of the reference population should be avoided.

Published guidelines from a joint Task Force of the ATS and ERS recommended that in the United States, ethnically appropriate reference equations from the National Health and Nutrition Examination Survey (NHANES) III be used for individuals aged 8 to 80 years. The Task Force did not recommend any specific set of reference equations for laboratories in Europe, but it suggested the need for an investigation conducted throughout Europe to derive contemporary equations for prediction of normal lung function.

The same ATS/ERS Task Force recommended that each pulmonary function test result falling below the fifth percentile of the frequency distribution of values measured in the reference population be considered abnormal. If normal test results fall in a normal distribution, values below the fifth percentile can be estimated using Gaussian statistics. If the distribution of normal values is non-Gaussian, the lower limit of normal is estimated using a nonparametric technique, for example, the 95th percentile method. Traditionally, but without a sound statistical basis, most laboratories have used an arbitrary cut-off of 80% predicted to define normal. While this method may be reasonable in children, errors may arise if it is applied to adult test results.

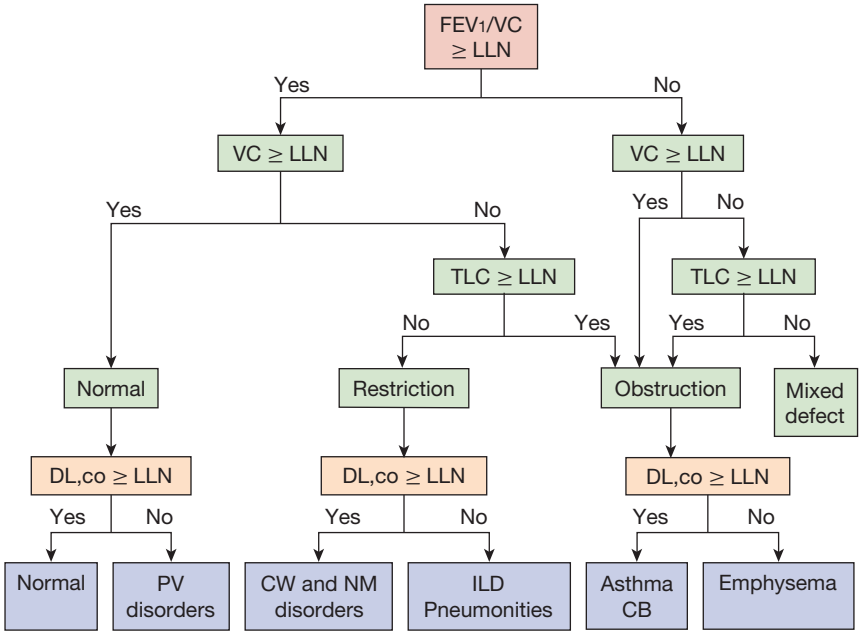

Figure 33-33 Proposed sequence of test review in the interpretation of pulmonary function tests. See text for discussion. LLN, lower limit of normal; PV, pulmonary vascular; CW, chest wall; NM, neuromuscular; ILD, interstitial lung disease; CB, chronic bronchitis. *(Reproduced with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.)*

INTERPRETATION SCHEME AND CLASSIFICATION OF ABNORMAL PATTERNS

A variety of schemes have been proposed for sorting out abnormalities in pulmonary function test results. Many are based on initial categorization of findings reflective of one of the four basic patterns described in the following paragraphs.

An *obstructive* pattern stems from narrowing of any portion of the airways – from upper airway to bronchioles less than 2 mm in diameter – that results in a reduction of maximal airflow in relation to maximal volume.

A *restrictive* pattern is elicited by diseases of the lung, chest wall, pleural space, or neuromuscular respiratory apparatus that reduce lung volumes, particularly TLC, and vital capacity.

A *combined obstructive–restrictive* pattern results from pathologic processes that reduce lung volumes, vital capacity, and airflow, and that also include an element of airway narrowing.

Finally, *abnormal gas transfer* may be noted as part of one of the aforementioned patterns or in isolation and reflects an abnormality in the alveolar capillary membrane, impairing oxygen uptake from alveolar gas to pulmonary capillary blood.

Overlap among categories is not uncommon. For example, widespread interstitial disease, as in idiopathic pulmonary fibrosis, often shows a pattern that indicates important components of both restrictive disease and abnormal gas transfer.

One useful sequence recommended by the ATS/ERS Task Force for analyzing a conventional battery of pulmonary function test results is illustrated in Figure 33-33.

Analysis begins with evaluation of the ratio of FEV_1 to VC. While, historically, the ratio of FEV_1 to FVC (FEV_1/FVC%) served as the basis for distinguishing obstructive disorders from normality or restrictive disease, the ATS/ERS Task Force currently recommends using as the denominator the FVC, *or* the VC ("slow" VC or SVC), *or* the FIVC, whichever is greatest. If the ratio is less than the lower limit of normal (i.e., below the fifth percentile) and the VC (defining VC as any of the three previously noted vital capacity measurements) is at or above the lower limit of normal, the pattern is obstructive. If TLC is not at or above the lower limit of normal, a mixed obstructive–restrictive pattern is suggested. Distinction between asthma and chronic bronchitis on the one hand, and emphysema on the other, is based upon whether the D_{LCO} is normal (asthma or chronic bronchitis) or reduced (emphysema). The previous practice of using a value for FEV_1/FVC% of less than 70% to define obstruction results in misdiagnosis of airway obstruction in men over 40 years and women over 50 years of age, as well as overdiagnosis of COPD in elderly, asymptomatic nonsmokers.

If FEV_1/VC and VC are each equal to or greater than the respective lower limits of normal, spirometry is considered normal; measurement of the D_{LCO} can then help distinguish between normal pulmonary function and pulmonary vascular disorders. If VC is below the lower limit of normal, a reduced TLC supports a diagnosis of restriction, while a normal TLC indicates an obstructive pattern. Once again, in the setting of a restrictive pattern, measurement of D_{LCO} can be used to distinguish between pulmonary parenchymal disorders and disorders of the chest wall or respiratory muscles. Note that according to these guidelines, an obstructive pattern may be diagnosed in the setting of a *normal* FEV_1/VC, if VC is reduced and TLC is normal or elevated.

Once the predominant abnormality is defined with initial pulmonary function testing, the whole battery may not be necessary in following the course of the disease or in assessing its response to treatment. For example, particular determinations, such as spirometry, may suffice in patients with airway diseases. Notably, according to the ATS/ERS guidelines, the severity of the abnormality in each of the obstructive, restrictive, or mixed patterns is expressed on the basis of the FEV_1 (Table 33-16). Standards have been established for

TABLE 33-16 Grading of Severity of Abnormal Spirometry Based on FEV_1

Severity	FEV_1 Percent Predicted
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

Source: Modified with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.

TABLE 33-17 Conditions Associated with Reduced Peak Inspiratory ($P_{I_{max}}$) and Expiratory ($P_{E_{max}}$) Pressures

Condition	$P_{I_{max}}$	$P_{E_{max}}$
Poor effort	↓	↓
Fatigue	↓	↓
Neuromuscular disease	↓	↓
Increased lung volume	↓	N
Decreased lung volume	N	↓

Note: ↓, decreased; N, normal.

defining significant changes in results over time: A 15% or greater change in FVC or in FEV_1, or a greater than 10% change in $D_{L_{CO}}$ is considered significant.

ASSESSING RESPIRATORY MUSCLE STRENGTH AND EFFORT

One additional measurement that is frequently useful in assessing results of routine spirometry is assessment of respiratory muscle strength. Respiratory muscle strength is expressed in terms of peak inspiratory ($P_{I_{max}}$) and peak expiratory ($P_{E_{max}}$) pressures, determined under static conditions.[24] The technique was outlined in a previous section. Any of a number of factors may be responsible for low peak inspiratory or expiratory pressures (Table 33-17): suboptimal effort, fatigue, weakness of the respiratory muscles, deformity of the chest wall, or intrinsic diseases of the lungs or chest wall. Although the first three factors characteristically reduce both peak inspiratory and expiratory pressures, disease of the lungs or chest wall often reduces, selectively, one or the other peak pressure. Thus, diseases that reduce lung volumes (e.g., widespread interstitial fibrosis) and shorten the length of the expiratory muscles at the end-inspiratory position generally reduce maximal expiratory pressure. Conversely, diseases that increase lung volume, such as obstructive airway disease, by decreasing the inspiratory muscle length at end-expiration generally reduce maximal inspiratory pressure.

If airflow during spirometry is reduced, determination of the peak inspiratory and expiratory pressures may be helpful in suggesting the mechanism. Many pulmonary function tests depend on the cooperation of the patient. Poorly reproducible peak flows that are consistently subnormal raise the question of poor effort. Conversely, consistently low values that occur despite maximal effort may signal neuromuscular disease.

ADDITIONAL DETAILS OF PULMONARY FUNCTION TEST RESULTS IN AN OBSTRUCTIVE PATTERN

Included in the obstructive pulmonary disorders (Table 33-18) are chronic obstructive diseases of the airways (chronic bronchitis and emphysema), bronchiectasis, asthma, small-airway disease, and upper-airway obstruction.

Except for diseases confined to the small airways, as noted previously, the hallmark of the obstructive pattern is a reduction in the FEV_1/VC%. Notably, some healthy subjects have a reduced FEV_1/FVC% and an FEV_1 in the normal range. The clinical significance of these findings is unclear. Results of additional tests (e.g., lung volumes, $D_{L_{CO}}$, assessment of bronchodilator responsiveness) may help distinguish those with airway obstruction from true normals.[92] Measurement of airway resistance (Raw) or specific airway conductance (SGaw) may be useful in assessing airway obstruction in subjects unable to perform a maximal forced expiratory maneuver.

Changes in lung volume commonly accompany the abnormal findings on spirometry, but, as indicated in Figure 33-33, lung volume measurement is not mandatory in establishing the presence of obstruction. Frequently, but not invariably, lung volumes are abnormally high. Typically, all three lung volumes – RV, FRC, and TLC – are increased.

In addition to uncovering the pattern of chronic obstructive airway disease described above, certain additional tests provide insight into the sites and mechanisms of obstructive airway disease.

Reversible Versus Irreversible Obstructive Airway Disease

The response to inhaled bronchodilators traditionally has been used to help distinguish between chronic obstructive airway disease (chronic bronchitis and emphysema), in which airway resistance is virtually fixed, and asthma, in which bronchoconstriction is a prominent feature. This is an oversimplification, since a sizable minority of patients with COPD manifest a bronchodilator response. Furthermore, the absence of a bronchodilator response in a laboratory setting does not necessarily predict lack of a clinical response.

A universally agreed upon definition of reversibility is lacking. Expressing change in FEV_1 or FVC as percent of predicted values may be more advantageous than expression of changes in the values relative to baseline. In general, an increase in FEV_1 or FVC of at least 12% above baseline *and* an absolute increment of at least 200 mL is considered evidence of significant bronchodilation. If the increase in spirometric values is not significant, a decrease in lung volumes toward normal may be an indication of bronchodilator responsiveness.

TABLE 33-18 Causes of an Obstructive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Reduced Airflow
Chronic obstructive pulmonary disease (COPD)		
Chronic bronchitis	Large and small (<2-mm diameter) airways	Narrowing of airways by fibrosis, secretions, edema
Emphysema	Lung parenchyma	Loss of lung elastic recoil
Cystic fibrosis	Large and small airways	Narrowing of airway by fibrosis, retained secretions, edema Loss of elastic recoil
Asthma	Large and small airways	Narrowing of airways by smooth muscle contraction, edema, retained secretions
Small-airway disease	Small airways	Narrowing, stenosis of small airways
Upper-airway obstruction	Major, central airways (trachea, main bronchi)	Anatomic or functional narrowing of upper airway

Chronic Bronchitis Versus Emphysema

Although chronic bronchitis and emphysema usually coexist, occasionally one or the other exists in virtually pure form. Two pulmonary function tests have proved valuable in distinguishing between the two – diffusing capacity (D_{LCO}), which is routinely measured, and static lung compliance (Cst,L), which is uncommonly measured clinically. Emphysema, characterized by a loss of alveolar units and a decrease in alveolar surface area, is associated with a low D_{LCO}, whereas the D_{LCO} in chronic bronchitis is usually normal or near normal.

The loss of alveolar units in emphysema also causes a decrease in the elastic recoil pressure of the lungs. As a result, Cst,L is increased in emphysema, whereas it is usually not appreciably altered in chronic bronchitis.

Small-Airway Disease

In obstructive disease of the small airways (i.e., those less than 2 mm in diameter), expiratory flow is usually normal, except at low lung volumes; that is, the FEV_3 and $FEF_{25–75\%}$ are abnormally low. Other, uncommonly performed tests for isolated, small-airway disease, including the helium–oxygen flow–volume loop, nitrogen washout test, and frequency dependence of dynamic compliance, would also be anticipated to be abnormal. Lung volumes and D_{LCO} are normal. Bronchodilators are virtually without effect.

The practical value of tests of small-airway function is problematic. At one time, high hopes were held that early detection of small-airway disease might reinforce measures, such as cessation of smoking, that would prevent or arrest progression to irreversible obstructive disease of the airways. However, enthusiasm for testing for small-airway disease has waned, since it is still unclear if small-airway disease is a reversible phase in the evolution of clinically significant obstructive airway disease that affects larger bronchi.

Upper-Airway Obstruction

The designation *upper-airway obstruction* is an umbrella for anatomic or functional narrowing of the large upper airways – the larynx, extra- and intrathoracic trachea, and lobar bronchi. Although upper-airway obstruction of any cause may reduce expiratory or inspiratory airflow, an alteration in the contour of the flow–volume loop has proved to be the most reliable abnormality in conventional pulmonary function testing. The observation from routine spirometry that the ratio of FEV_1 to peak expiratory flow rate (PEFR) exceeds 8 mL/L/min should prompt careful performance and review of the flow–volume loop, as described later.

Upper-airway obstruction can be divided into three major types: (1) fixed obstruction, (2) variable extrathoracic obstruction, and (3) variable intrathoracic obstruction.[93]

A *fixed obstruction,* such as tracheal narrowing by scar tissue at the site of a previous tracheotomy, is one in which the geometry and cross-sectional area of the lesion do not change during the respiratory cycle. Characteristically, both inspiratory and expiratory flows are affected about equally (Fig. 33-34A).

A *variable obstruction* is one in which the configuration of the obstructive lesion changes with the phases of respiration. Depending on its location in the tracheobronchial tree (extra- or intrathoracic), this type of lesion usually affects predominantly either inspiration or expiration.

The inspiratory arm of the flow–volume loop is primarily affected by a *variable extrathoracic* obstruction, leaving the expiratory limb relatively unaffected (Fig. 33-34B). The abnormal configuration of the flow–volume loop is attributable to the following sequence: during forced expiration, tracheal pressure exceeds atmospheric, so that the degree of obstruction decreases; conversely, during forced inspiration, intratracheal pressure becomes less than atmospheric and the trachea tends to collapse.

The expiratory arm of the flow–volume loop is primarily affected by a *variable intrathoracic* obstruction (Fig. 33-34C). The following sequence is responsible for producing this abnormality in the flow–volume loop: during forced expiration, as pleural pressure reaches and then exceeds intratracheal pressure downstream from the lesion (i.e., toward the mouth), the obstruction tends to increase; conversely, during a forced inspiration, as intratracheal pressure exceeds pleural pressure, the intrathoracic obstruction decreases.

Variable intrathoracic lesions often coexist with obstructive airway disease. In considering a variable intrathoracic lesion, the respective roles played by obstructive disease of the airways (i.e., chronic bronchitis, emphysema, and asthma) and an obstructive upper-airway lesion (anatomic or functional) in deforming the flow–volume loop must be determined. Fortunately, this distinction is often possible. Although both upper-airway obstruction and obstructive airway disease (reversible and irreversible) do decrease maximal expiratory flow, the shapes of the flow–volume cures are frequently quite distinctive (Fig. 33-34C and D). Thus, in obstructive airway disease, despite a decrease in airflow, the

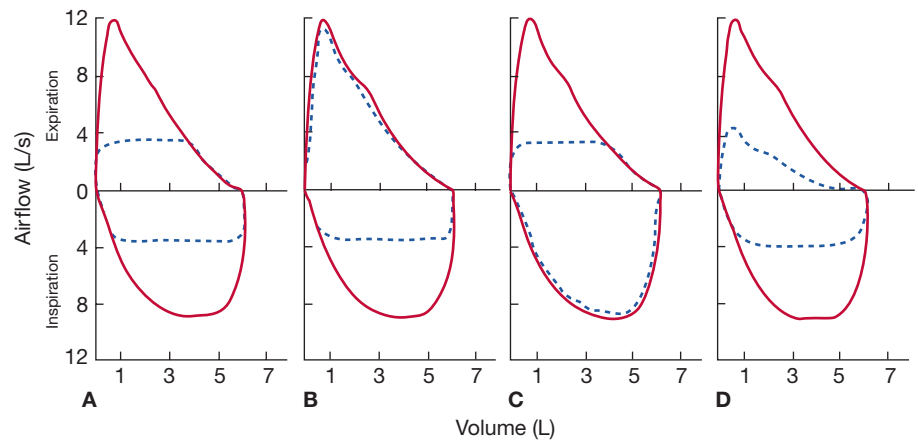

Figure 33-34 Schematic flow–volume loops in four pathologic conditions. **A.** In a fixed upper-airway obstruction, both inspiratory and expiratory limbs are truncated. **B.** In a variable extrathoracic obstruction, the inspiratory limb is flattened while the expiratory limb is not altered. **C.** In a variable intrathoracic obstruction, the expiratory limb is flattened while the inspiratory portion is unchanged. **D.** In chronic obstructive airway disease, although expiratory airflow is reduced, the tapering in airflow during expiration is generally maintained so that the configuration of the loop is different from that in variable intrathoracic obstruction.

TABLE 33-19 Distinguishing Features of Disorders Producing an Obstructive Pattern

Disorder	FEV_1	FVC	FEV_1/VC%	Response of FEV_1 to Administration of Bronchodilator	Tests of Small-Airway Function	Lung Volumes	D_{LCO}	Flow–Volume Loop
COPD								
Chronic bronchitis	↓	↓	↓	NC	ABN	↑	NL	ABN
Emphysema	↓	↓	↓	NC	ABN	↑	↓	ABN
Asthma	↓	↓	↓	↑	ABN	↑	NL	ABN
Small-airway disease	NL	NL	NL	NC	ABN	NL	NL	NL
Upper-airway obstruction	↓	↓	↓	NC	NL or ABN	NL or ↑	NL	ABN[a]

[a]*Configuration frequently characteristic for upper-airway obstruction.*
Note: ↓, decrease; ↑, increase, NC, no significant change; NL, normal; ABN, abnormal.

expiratory limb of the loop generally retains its normal configuration (Fig. 33-34D) – that is, an early peak in flow, followed by gradual tapering. In contrast, in upper-airway obstruction (fixed and variable intrathoracic), the expiratory limb is flat and flow is decreased throughout most of expiration (Fig. 33-34C).

In addition to changes in the shape of the flow–volume loop, clues from routine pulmonary function tests often alert the clinician to the possibility of upper-airway obstruction. As noted previously, when FEV_1/PEFR >8, the possibility of upper-airway obstruction should be considered. Finally, the presence of any of the following may also provide clues: $FEF_{50\%}/FIF_{50\%}$ of at least 1, where $FEF_{50\%}$ and $FIF_{50\%}$ are the forced expiratory flow at 50% of FVC and the forced inspiratory flow at 50% of FIVC, respectively; $FIF_{50\%}$ less than 100 L/min; and $FEV_1/FEV_{0.5}$ at least 1.5.

Distinguishing test features of disorders producing an obstructive pattern are summarized in Table 33-19.

■ ADDITIONAL DETAILS OF PULMONARY FUNCTION TEST RESULTS IN A RESTRICTIVE PATTERN

The restrictive pattern (Table 33-20) characteristically occurs in several groups of disorders including: (1) a primary disorder of the lung parenchyma in which functional tissue is lost through disease (e.g., an alveolar filling process, such as pneumonia, tumor, atelectasis, or fibrosis); (2) surgical removal of lung tissue (e.g., lobectomy); (3) constrictive disease of the pleura and chest wall (e.g., extensive pleural fibrosis, large pleural effusion or pleural mass, kyphoscoliosis, obesity); and (4) neuromuscular diseases, notably those in which the generation of respiratory force is reduced (e.g., disorders of the spinal cord, peripheral nerves, neuromuscular junction, and muscle).

The diagnosis of restriction is based upon the finding of a normal FEV_1/VC and reduced VC in the setting of a decreased TLC. While TLC generally is reduced in most disorders producing a restrictive pattern, FRC is usually preserved in disorders characterized by decreased respiratory force (e.g., the neuromuscular disorders) and is reduced in the others. In neuromuscular disorders, ERV is decreased because of loss of expiratory force, so that RV is often increased. In the other types of restrictive disorders, RV is usually reduced.

Whether or not the D_{LCO} is reduced in the restrictive disorders depends on the underlying disease process. Primary parenchymal disorders and removal of lung tissue decrease the diffusing surface area and reduce D_{LCO}. Diseases of the pleura and chest wall that limit thoracic excursion during the inspiratory vital capacity maneuver, which is part of the technique for determining D_{LCO}, also reduce this measurement.

■ ADDITIONAL DETAILS OF PULMONARY FUNCTION TEST RESULTS IN A MIXED OBSTRUCTIVE–RESTRICTIVE PATTERN

Occasionally, a battery of pulmonary function tests demonstrates features of both obstructive and restrictive patterns. Most often, the mixed pattern is characterized by a low FEV_1/VC% (indicating obstructive airway disease) and VC and reduced TLC (indicating coexisting restrictive disease).

A number of disorders can produce the mixed obstructive/restrictive pattern. Sarcoidosis and interstitial fibrosis, when severe, generally result in this pattern because the parenchymal disease causes restriction and narrowing of the airways by adjacent fibrosis, evoking signs of airway obstruction. The mixed pattern also occurs in complicated situations when there is more than one cause – for example, a lobar pneumonia or large pleural effusion occurring in a patient with underlying chronic bronchitis or emphysema.

■ ISOLATED DECREASE IN THE EFFICIENCY OF GAS TRANSFER

An isolated reduction in the D_{LCO} suggests one of the two possible abnormalities: (1) interstitial lung disease that is so mild as not to affect measurements of airflow or lung volume, or (2) widespread occlusive disease of the pulmonary microcirculation (e.g., due to an inflammatory process or multiple small emboli). In occlusive vascular disorders, tests of airflow and lung volume are usually normal.

TABLE 33-20 Causes of a Restrictive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Pulmonary Function Test Abnormality
Primary parenchymal disease	Lung parenchyma	Loss of lung tissue ⟶ reduced volumes and flows
Surgical removal of lung tissue	Lung parenchyma	Loss of lung tissue ⟶ reduced volumes and flows
Diseases of pleura and chest wall	Pleura, chest wall	Limited expansion of thoracic cavity ⟶ reduced volumes and flows
Reduced generation of expiratory force	Central nervous system, peripheral nerves, neuromuscular junction, muscles of respiration	Reduced muscle tension ⟶ reduced expiratory flow, atelectasis

TABLE 33-21 Categorization of Reduction in Efficiency of Gas Transfer: Measurement of $D_{L_{CO}}$

Severity	$D_{L_{CO}}$, Percent Predicted
Mild	>60, but less than lower limit of normal
Moderate	40–60
Severe	<40

Source: Modified with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.

Although other disorders can also decrease $D_{L_{CO}}$, almost invariably they also reduce airflow, lung volumes, or both. Quantification of the degree to which the $D_{L_{CO}}$ is reduced by any of these processes is indicated in Table 33-21. Notably, interlaboratory differences are substantial for measurements of $D_{L_{CO}}$.

SUMMARY OF APPROACH TO INTERPRETATION

Pulmonary function tests are designed to detect common disorders. Test interpretation relies heavily on recognition of major patterns of abnormality (Table 33-22). These patterns often suggest pathogenetic mechanisms and are helpful to the clinician in arriving at a diagnosis. The degree of abnormality provides a quantitative measure of the extent of involvement at a particular time. Moreover, repeated testing makes it possible to pace and quantify the course of the illness and to assess the effects of therapeutic interventions.

TABLE 33-22 Characteristic Alterations in Pulmonary Function Tests According to the Major Patterns of Abnormality

Pattern	Airflow (FEV_1/VC%)	Airflow Response to Bronchodilators	Volumes	Lung $D_{L_{CO}}$
Obstructive				
Irreversible	↓	↔	↑	↔ or ↓
Reversible	↓	↑	↑	↔
Small-airway disease	↓	↔	↔	↔
Upper-airway obstruction	↓	↔	↔ or ↑	↔
Restrictive				
Parenchymal disease	↔ or ↑	↔	↓	↓
Surgical resection	↔	↔	↓	↓
Pleural, chest wall disease	↔	↔	↓	↔
Reduced expiratory force generation	↔	↔	↓	↔
Mixed obstructive–restrictive	↓	↔ or ↑	↓	↓
Isolated reduction in efficiency of gas transfer	↔	↔	↔	↓

Note: ↓, decreased; ↑, increased; ↔, no change or normal.

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CHAPTER 34

Principles and Applications of Cardiopulmonary Exercise Testing

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INTRODUCTION

Cardiopulmonary exercise (CPX) testing draws on the recognition that the thorax represents a metabolic gas transport unit, the function of whose requisite components – diaphragm, heart, lungs, rib cage, and corresponding skeletal muscles – is to transport O_2 to and CO_2 from metabolizing tissues. Unit O_2 and CO_2 transport must adjust to physiological and pathophysiological stresses that augment the body's consumption of oxygen ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$). During strenuous levels of muscular work, for example, $\dot{V}_{O_2}$ may rise eightfold, accompanied by increased $\dot{V}_{CO_2}$. Cardiovascular or ventilatory disease can disrupt the unit's functional integrity. With severe disease, an abnormality in respiratory gas transport may be apparent at rest, when the body's O_2 requirements are modest. Resting function is preserved with less severe expressions of disease, but abnormal respiratory gas transport becomes apparent when the unit is stressed by an elevation in $\dot{V}_{O_2}$.

CPX testing includes the monitoring of respiratory gas exchange ($\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$), and its components, tidal volume and respiratory rate, together with blood pressure, heart rate, and the electrocardiogram. CPX testing represents a useful approach in the clinical evaluation of a whole host of disorders and circumstances. This chapter addresses physiological principles and the clinical application of CPX testing in the evaluation of major disorders that impair heart or lung function. The chapter is by no means an exhaustive review. For a more detailed discussion of specific entities, the interested reader is referred to several other textbooks.[1,2]

PRINCIPLES, DEFINITIONS, AND CLINICAL APPLICATION OF CARDIOPULMONARY EXERCISE TESTING

The metabolic gas transport unit, also referred to as the "cardiopulmonary unit," links metabolizing tissues to the atmosphere and its supply of O_2. O_2 transport to tissues must be precise and based upon prevailing need. CO_2 produced by tissues must be eliminated into the atmosphere in an equally efficient manner.

RESTING OXYGEN UPTAKE AND TRANSPORT

Concepts and calculations pertaining to $\dot{V}_{O_2}$ and O_2 content, transport, and extraction are reviewed in Table 34-1. The heart and lungs accommodate to the metabolic requirements of tissues; they must do so on a moment-to-moment basis, according to physiological priorities. Tissue requirements for O_2 dictate a certain $\dot{V}_E$ and cardiac output. In an average-sized person, resting $\dot{V}_{O_2}$ averages 250 mL/min or 3.5 mL/min/kg body weight (one metabolic equivalent) and is associated with a $\dot{V}_E$ of 8 to 10 L/min and cardiac output of 4 to 6 L/min. O_2 transport, also termed O_2 delivery, ranges between 730 and 1040 mL/min and is more than adequate to satisfy resting $\dot{V}_{O_2}$. On average, 25% of arterial O_2 content is extracted by tissues. O_2 delivery and extraction each increase during physiological stress in proportion to the elevation in O_2 demand. Factors that normally determine O_2 availability at rest and during exercise include cardiac output, hemoglobin concentration and its percent saturation, and O_2 extraction.

EXERCISE OXYGEN UPTAKE AND TRANSPORT

$\dot{V}_E$ and O_2 delivery must each rise during exercise. Strenuous work can raise $\dot{V}_E$ 8 to 10 times its resting level. Ventilation normally poses no limitation on the ability of tissues to carry out aerobic work. By contrast, the extent to which cardiac output rises during progressive work is less dramatic. In untrained subjects, cardiac output increases four to five times its resting value. Cardiac output rises 600 mL/min for every 100 mL/min increment in $\dot{V}_{O_2}$. This is considered the normal "gain" setting between the heart and its cardiac output and $\dot{V}_{O_2}$. O_2 availability during physical activity is further ensured by enhanced O_2 extraction and circulatory autoregulation. Reflexive and humoral influences produce vasoconstriction in less

TABLE 34-1 Oxygen Utilization, Content, Transport, and Extraction

$\frac{O_2 \text{ utilization}}{250 \text{ mL/min}}$	$\begin{cases} = \text{Cardiac output} \cdot (\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}) \\ = 5000 \text{ mL/min} \cdot (19 \text{ mL/dL} - 14 \text{ mL/dL}) \end{cases}$
$\frac{\text{Arterial } O_2 \text{ content}}{19 \text{ mL/dL}}$	$\begin{cases} = \text{Hemoglobin} \cdot \%\text{ saturation} \cdot O_2 \text{ combining capacity} \\ = 14 \text{ g/dL} \cdot 0.96 \cdot 1.34 \text{ mL/g} \end{cases}$
$\frac{\text{Venous } O_2 \text{ content}}{14 \text{ mL/dL}}$	$= 14 \text{ g/dL} \cdot 0.96 \cdot 1.34 \text{ mL/g}$
$\frac{\text{Arteriovenous } O_2 \text{ difference}}{5 \text{ mL/dL}}$	$\begin{cases} = \text{Arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content} \\ = 19 \text{ mL/dL} - 14 \text{ mL/dL} \end{cases}$
$\frac{O_2 \text{ transport}}{950 \text{ mL/min}}$	$\begin{cases} = \text{Cardiac output} \cdot \text{arterial } O_2 \text{ content} \\ = 5000 \text{ mL/min} \cdot 19 \text{ mL/dL} \end{cases}$
$\frac{O_2 \text{ extraction}}{25\%}$	$\begin{cases} = \frac{\text{Arteriovenous } O_2 \text{ difference}}{\text{Arterial } O_2 \text{ content}} \cdot 100\% \\ = \frac{19 - 14}{19} \cdot 100\% \end{cases}$

Source: Reproduced with permission from Weber KT. Gas transport and the cardiopulmonary unit. In: Weber KT, Janicki JS, eds. Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, PA: Saunders; 1986.

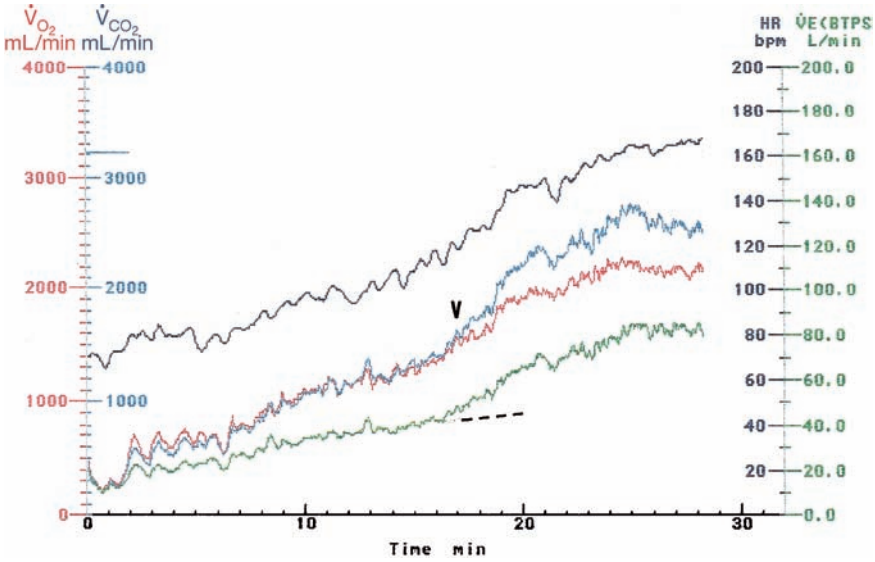

Figure 34-1 Cardiopulmonary exercise response in a 40-year-old man without heart or lung disease. Shown are 2 minutes of standing rest, followed by incremental treadmill exercise. Individual responses *(color coded)* include oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$), and heart rate (HR). Maximal O_2 uptake, a plateau in $\dot{V}_{O_2}$ was attained after the crossover of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ *(arrowhead)*, representing the AT and accompanied by a disproportionate (broken line) rise in $\dot{V}_E$.

metabolically active tissues, permitting a greater apportionment of blood flow to exercising muscle.

Physiological limits to the elevation in cardiac output (i.e., cardiac reserve) and O_2 extraction (approximately 75%–80% of arterial O_2 content) determine aerobic capacity of untrained subjects to incremental exercise. Beyond these physiological limits, any additional increment in work is not accompanied by an elevation in O_2; a plateau in $\dot{V}_{O_2}$ is attained and is termed the *maximal oxygen uptake* ($\dot{V}_{O_{2max}}$). CPX test results, including $\dot{V}_{O_{2max}}$, are shown in Figure 34-1 for a 40-year-old man without clinically apparent heart or lung disease. Shown are individual responses in $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, and heart rate during progressive increments in treadmill work. A $\dot{V}_{O_{2max}}$ of 2198 mL/min (27.2 mL/min/kg) was attained. This is a true plateau in $\dot{V}_{O_2}$, with $\dot{V}_{O_2}$ remaining invariant for 2.5 stages (5 minutes) of exercise.

$\dot{V}_{O_{2max}}$ should not be equated or used synonymously with peak $\dot{V}_{O_2}$ achieved during symptom-limited exercise. $\dot{V}_{O_{2max}}$ reflects a person's aerobic capacity—a physiological capacity of the cardiovascular system. In an average-sized, untrained person whose maximum cardiac output and arteriovenous oxygen difference are 20 L/min and 12 mL/dL, respectively, a $\dot{V}_{O_{2max}}$ of 2400 mL/min is expected. In athletes, a greater cardiac reserve and enhanced capacity for oxidative metabolism by trained skeletal muscle are available, providing for greater aerobic capacity. In patients with heart disease, whose ability to raise cardiac output during exercise is impaired, $\dot{V}_{O_{2max}}$ is proportionally reduced (see above).

CARBON DIOXIDE PRODUCTION

The right heart "accepts" metabolically produced CO_2, and the alveolar exchange surface expels CO_2 into the atmosphere. CO_2 is a major respiratory stimulant that maintains eucapnia. Seventy-five to 80% of O_2 is converted to CO_2. Accordingly, resting $\dot{V}_{CO_2}$ averages 190 mL/min and represents a *metabolic source* of CO_2. The resting $\dot{V}_{CO_2}/\dot{V}_{O_2}$ ratio, or respiratory gas exchange ratio (R), typically ranges between 0.75 and 0.85. The absolute value of R depends on the proportion of carbohydrates and fats available from the diet. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ rise in proportion to one another during physical activity as long as an adequate amount of O_2 is available to sustain oxidative metabolism.

With strenuous levels of muscular work, $\dot{V}_{O_2}$ rises to a level where the heart is unable to provide O_2 at a commensurate rate. Consequently, tissue O_2 availability becomes inadequate. Working skeletal muscle enhances its use of less efficient anaerobic metabolism to derive energy. This leads to lactate production from working muscle beyond that normally produced. This *nonmetabolic source* of CO_2 is derived from rapid buffering of the lactate by bicarbonate; the CO_2 generated serves as a respiratory stimulant. The accompanying increase in $\dot{V}_E$ maintains eucapnia and raises the respiratory gas exchange ratio above that associated with aerobic metabolism. Anaerobic metabolism during a progressive exercise test is heralded by this disproportionate rise in $\dot{V}_E$ and $\dot{V}_{CO_2}$ relative to $\dot{V}_{O_2}$. The corresponding level of $\dot{V}_{O_2}$ at which anaerobic metabolism occurs is termed the *anaerobic threshold* (AT).[1] The point during exercise at which $\dot{V}_{CO_2}$ exceeds $\dot{V}_{O_2}$ and $\dot{V}_E$ rises disproportionately is shown in Figure 34-1. Anaerobiosis normally occurs when 60% or more of a person's aerobic capacity has been attained. For the 40-year-old man whose exercise response is shown in Figure 34-1, the AT occurred at a $\dot{V}_{O_2}$ of 18.8 mL/min/kg, or 69% of his $\dot{V}_{O_{2max}}$.

CLINICAL APPLICATION OF CARDIOPULMONARY EXERCISE TESTING

Patients with cardiovascular or respiratory disease of mild-to-moderate severity frequently note limiting symptoms of fatigue or breathlessness during physical activity. Because their quality of life is compromised, they seek or are referred for medical evaluation. Re-creating muscular work in a monitored setting permits an evaluation of the nature and severity of such symptoms and the relative importance of abnormal heart or lung function. This strategy provides information surpassing that available from static measures of heart and lung function, such as ejection fraction, lung volumes, or airflows, determined at rest. The continuous monitoring of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, respiratory rate, and tidal volume during incremental exercise can be performed simply and on a breath-by-breath basis. Data shown in Figure 34-1 are displayed throughout the test. The choice of a particular CPX test (see above) depends on the nature and expression of the clinical disorder and the particular problem to be addressed. For most clinical evaluations, isotonic forms of exercise are used. Isotonic work is an acceptable, negotiable, and reproducible form of exercise for patients with heart or lung disease.

It should be noted, however, that while noninvasive CPX testing may help determine the impairment in aerobic capacity, abnormalities in ventilation with exercise, and their severity in patients with lung disease, these parameters are not necessarily diagnostic. For example, $\dot{V}_{O_{2max}}$, AT, or exercise $\dot{V}_E$ do not identify the underlying structural defect responsible for a patient's abnormal response. This may require invasive monitoring during CPX testing to identify specific hemodynamic abnormalities. Echocardiography and specialized pulmonary function studies may be required. The physician must draw upon sound clinical judgment and complementary laboratory tests to derive an understanding of the nature and severity of the heart or lung disease.

NONINVASIVE TREADMILL EXERCISE

Walking represents a common daily exercise rather than a specialized skill. A patient who walks into the physician's office or down a hospital corridor can walk on a treadmill at 1.0 or 1.5 mph, zero grade. Treadmills are programmable. The Bruce protocol, which employs marked increments in treadmill speed and slope over short periods in the evaluation of myocardial ischemia, may not be useful for patients with limited exercise tolerance. A modified Naughton protocol of gradually progressive exercise (Table 34-2) serves to stress the cardiopulmonary unit for patients with heart or lung disease who have a wide range of exercise tolerance. In this protocol, the first two stages of exercise represent very low workloads and are a warmup for patients with heart or lung disease of minor severity; the stages represent near-maximal exercise for patients with more advanced disease.

$\dot{V}_{O_2max}$ is defined as $\dot{V}_{O_2}$ that remains invariant (<1 mL/min/kg for 30 seconds or more) despite an increment in workload. An invariant $\dot{V}_{O_2}$ for at least two stages of exercise is preferred (Fig. 34-1). $\dot{V}_{O_2max}$ follows the AT, and this definition of $\dot{V}_{O_2max}$ presumes that the AT has already been achieved. The AT generally occurs at 60% of a patient's aerobic capacity. $\dot{V}_{O_2max}$ associated with incremental treadmill exercise provides a greater aerobic capacity than does cycle ergometry because it works a larger group of muscles.[3] A patient's aerobic capacity to incremental treadmill exercise is used to grade the functional impairment (Table 34-3). $\dot{V}_{O_2max}$ is an objective measure of functional status—in contradistinction to the New York Heart Association classification, which is based on perceptions and biases of the patient and physician. Treadmill O_2max determination is reproducible in patients with a wide variety of cardiovascular disorders.[2] A $\dot{V}_{O_2max}$ of under 20 mL/min/kg has been selected as the cutoff for grading impaired aerobic capacity; adult men and women, including the elderly (over 65 years of age), have an expected $\dot{V}_{O_2max}$ of more than 20 mL/min/kg.[4]

The duration of symptom-free treadmill exercise should not be equated with $\dot{V}_{O_2max}$. Treadmill time suffers from not having an objective, quantitative end-point. Differences in gait and body weight create different levels of work for equivalent stages of treadmill exercise. Symptom-limited exercise time is subject to patient motivation and physician bias.[5] Peak heart rate attained with exercise is also a less precise measure of $\dot{V}_{O_2max}$. This is particularly true in patients with atrial fibrillation.

Determination of the AT can be defined according to one or more criteria.[1] These include (1) a disproportionate rise in $\dot{V}_{CO_2}$, $\dot{V}_E$, or R relative to $\dot{V}_{O_2}$ and (2) a disproportionate rise in end-tidal CO_2 relative to end-tidal O_2. These criteria can best be applied to breath-by-breath respiratory gas exchange data. In our laboratory, a simpler strategy is used. The AT is identified as the level of $\dot{V}_{O_2}$ attained during treadmill work after the plots of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ cross, when R exceeds 1.0. Figure 34-1 depicts the crossover in $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ from breath-by-breath gas exchange data monitored throughout incremental treadmill exercise. It also demonstrates the point at which $\dot{V}_E$ rises disproportionately. Measured days or weeks apart, this noninvasive determination of the AT is reproducible in a wide range of patients with cardiac or circulatory failure and correlates with lactate threshold (see above).[2,6,7]

The normal ventilatory response to incremental treadmill exercise consists of an increase in $\dot{V}_E$ created by an increase in respiratory rate and tidal volume. Ventilatory reserves, represented by maximal voluntary ventilation (MVV) and vital capacity determined during routine pulmonary function testing, are only partly utilized during light, moderate, and maximal exercise by normal persons. The ratio of maximal exercise $\dot{V}_E$ to MVV reflects use of this ventilatory reserve. Exercise $\dot{V}_E$ in normal subjects and patients with predominant cardiovascular disease rarely exceeds 50% of MVV.[8] The same is true of the ratio between maximal exercise tidal volume and vital capacity. These limitations in ventilatory responses are consistent with a ventilatory effort that can be voluntarily sustained at rest without the appearance of fatigue or breathlessness.

TABLE 34-2 Modified Naughton Treadmill Exercise Protocol

Stage	Speed	Grade	Physical Activities
1	1.0	0	Driving a car
			Sitting and writing or eating
2	1.5	0	Dressing; knitting
			Walking to bathroom
			Light auto repair
3	2.0	3.5	Shave self in bathroom
			Wash entire body
			Food shopping
4	2.0	7.0	Sexual activity
			Raking leaves
			Plastering
5	2.0	10.5	Stacking firewood
			Mowing lawn (powered)
			Walking downstairs
6	3.0	7.5	Scrubbing floors
			Gardening
			Walking upstairs
7	3.0	10.0	Lifting and carrying 65–80 lb
			Carpentry
			Climbing hills (no load)
8	3.0	12.5	Digging
			Snow shoveling
			Climbing stairs (20-lb load)
9	3.0	15.0	Beyond this level, work loads are equal to very vigorous exercise (e.g., skiing, basketball)
10	3.4	14.0	
11	3.4	16.0	
12	3.4	18.0	
13	3.4	20.0	
14	3.4	22.0	

Source: Reproduced with permission from Weber KT, Janicki JS, McElroy PA. Cardiopulmonary exercise (CPX) testing. In: Weber KT, Janicki JS, eds. Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, PA: Saunders; 1986.

TABLE 34-3 Classification of Cardiac and Circulatory Failure

Class	Severity	V_{O_2max} (mL/kg/min)	Anerobic Threshold (mL/kg/min)	Predicted Cardiac Index (L/m²/min)
A	Mild to none	>20	>14	>8
B	Mild to moderate	16–20	11–14	6–8
C	Moderate to severe	10–16	8–11	4–6
D	Severe	6–10	5–8	<4

Source: Adapted with permission from Weber KT, Janicki JS, McElroy PA. Pulmonary hypertension. In: Weber KT, Janicki JS, eds. Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, PA: Saunders; 1986.

An oximeter, worn on either an earlobe or a finger, provides noninvasive monitoring of arterial O_2 saturation during exercise. This is a useful screening procedure in patients in whom O_2 desaturation might be anticipated (e.g., those with congenital heart disease with right-to-left shunt, restrictive or obstructive lung disease, or pulmonary vascular disease). Normal subjects and patients with chronic cardiac or circulatory failure do not develop arterial hypoxemia (arterial O_2 saturation under 90%) during exercise. In patients in whom O_2 desaturation is evident from oximetry, confirmatory evidence from direct measurement of arterial blood gases during repeat exercise may be advisable.

Thus, incremental treadmill exercise can be used to determine the following: the AT with a submaximal test, the AT and $\dot{V}_{O_2max}$ with a maximal test, the ventilatory response to submaximal or maximal exercise, and arterial O_2 desaturation during submaximal or maximal exercise.

INVASIVE TREADMILL EXERCISE

Invasive hemodynamic monitoring may be necessary to better define the nature and severity of an underlying cardiopulmonary disorder.[2] A triple-lumen flotation catheter can be safely used for hemodynamic monitoring during upright exercise. The hemodynamic response to incremental treadmill exercise in normal subjects is characterized by a progressive rise in cardiac output, accomplished with minimal elevations in left and right ventricular filling pressures. The rise in cardiac output occurs because of an increment in stroke volume, which is most apparent at low and moderate workloads, and because of an elevation in heart rate, which accompanies the entire exercise response. Systemic O_2 extraction rises progressively with incremental exercise to exceed 70% at maximal workloads. A rise in mixed venous lactate concentration, as observed with pulmonary arterial blood sampling, occurs when O_2 extraction exceeds 60% and when the subject is working at greater than 60% of $\dot{V}_{O_2max}$.

Systolic and mean arterial pressures rise during upright exercise. Because of skeletal muscle vasodilatation, arterial diastolic pressure remains essentially invariant during exercise. Systemic vascular resistance falls by 50% to approximately 600 dynes·s·cm^{-5} during incremental, isotonic treadmill exercise. In normal persons, pulmonary artery systolic, mean, and diastolic pressures rise only minimally with exercise and only with higher workloads. Pulmonary vascular resistance, like systemic vascular resistance, falls 50% to about 60 dynes·s·cm^{-5} during incremental isotonic exercise.

CHRONIC CARDIAC FAILURE

In physiological terms, *cardiac failure* is defined as an impairment in cardiac output secondary to a disease process affecting the myocardium. Ischemic heart disease and dilated cardiomyopathies are examples of disease entities that can result in chronic cardiac failure. $\dot{V}_{O_2max}$ and the AT each predict cardiac reserve and, thereby, the severity of cardiac failure. These parameters further serve to objectively demonstrate a patient's functional capacity, which is not predicted from the cardiac ejection fraction. Patients with an ejection fraction under 20% may still be able to swim.

SYSTOLIC DYSFUNCTION

In patients with chronic cardiac failure, $\dot{V}_{O_2max}$ attained during incremental treadmill exercise is primarily a function of maximal cardiac output.[8,9] This conclusion has been confirmed by numerous studies.[10–14] An impairment in aerobic capacity is gauged according to the exercise AT and $\dot{V}_{O_2max}$ and assigned a functional class as reviewed in Table 34-3. These parameters are, in turn, used to predict maximal exercise cardiac index (or cardiac reserve). Examples of $\dot{V}_{O_2max}$ and the AT attained by two patients with chronic cardiac

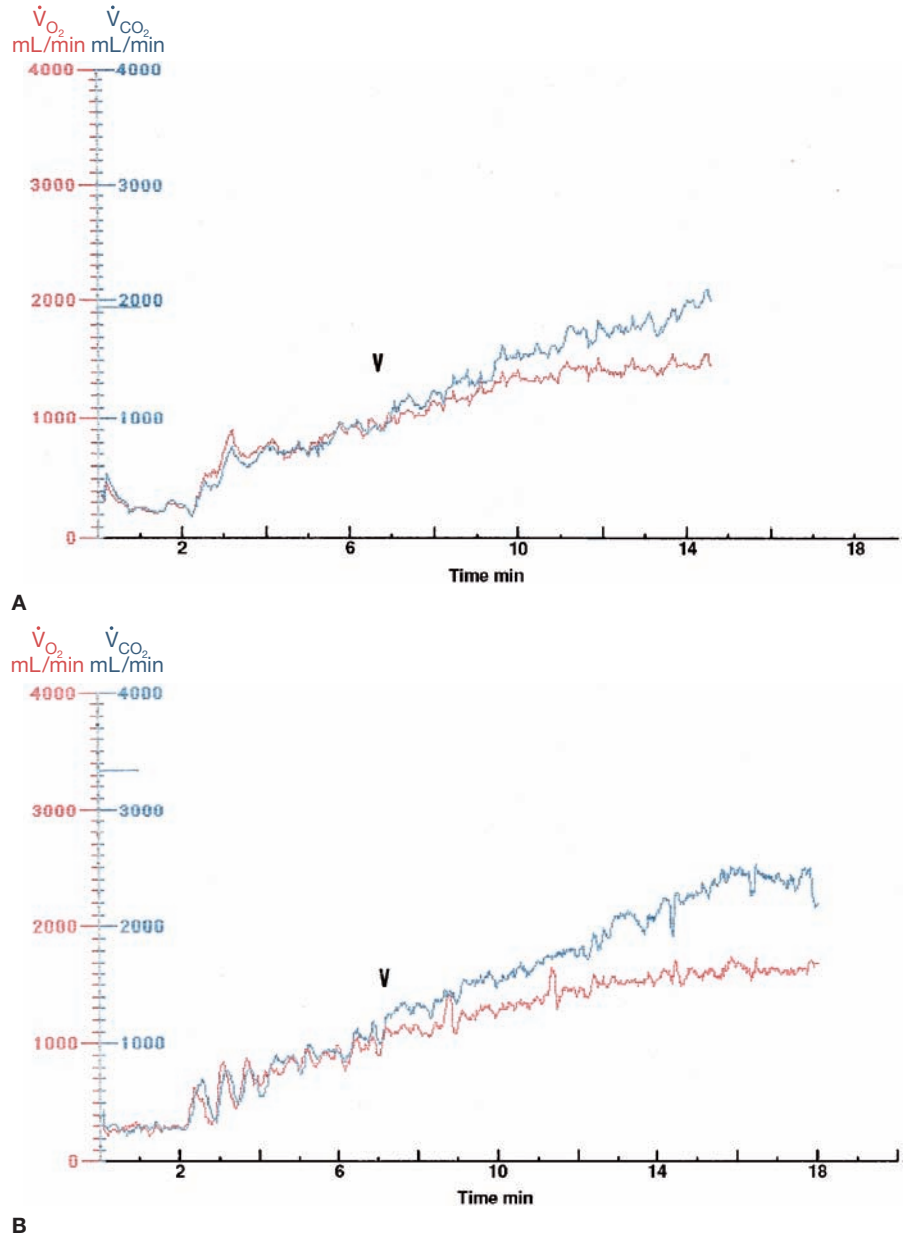

Figure 34-2 Cardiopulmonary exercise test results for a 45-year-old woman (**A**) and a 40-year-old man *(right panel)*, each with ischemic heart disease and chronic cardiac failure. Only $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are shown, to better demonstrate the anaerobic threshold (AT) and $\dot{V}_{O_2max}$ attained by each patient. On the left, the AT was seen with a $\dot{V}_{O_2}$ of 11.6 mL/min/kg and a $\dot{V}_{O_2max}$ of 16.5 mL/min/kg. This represents a functional class B response. The AT and $\dot{V}_{O_2max}$ are 8.5 and 13.7 mL/min/kg, respectively (**B**). This corresponds to functional class C.

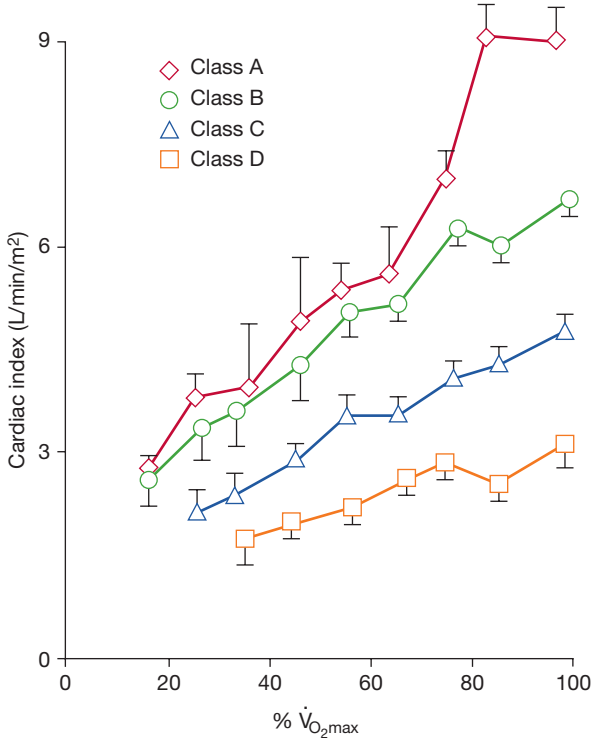

Figure 34-3 Relationship between treadmill exercise cardiac index and normalized aerobic capacity for patients with chronic cardiac failure of diverse origin and severity, subdivided according to each functional class. *(Reproduced with permission from Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol. 1985;55(2):22A–31A.)*

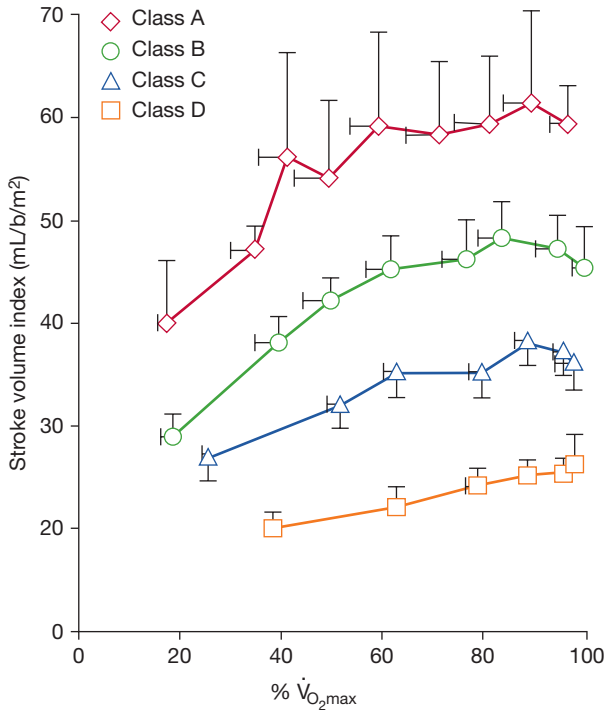

Figure 34-4 Relationship between treadmill exercise stroke volume index and normalized aerobic capacity for patients with chronic cardiac failure of varying severity, as expressed by each functional class. *(Reproduced with permission from Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol. 1986;55(2):22A–31A.)*

failure (one class B, the other class C) are given in Figure 34-2. To measure $\dot{V}_{O_2max}$ in such patients, they must be exercised to exhaustion. The AT is achieved at submaximal workloads short of exhaustion; it, too, stratifies the degree of cardiac dysfunction.

Validation of these concepts was obtained during treadmill exercise using invasive measures of cardiac output and mixed venous lactate concentration.[15,16] Patients had chronic cardiac failure of varying severity (classes A to D), due to either ischemic or myopathic heart disease. In each exercise class, the arteriovenous O_2 difference rose to 12 mL/dL or more at maximum exercise, corresponding to a systemic O_2 extraction in excess of 70%, suggesting that O_2 extraction reached maximal physiological levels. The reduction in aerobic capacity of a patient with chronic cardiac failure is, therefore, due primarily to impaired cardiac reserve. The cardiac output–O_2 relation to progressive treadmill exercise for these patients is given in Figure 34-3. For each exercise class, cardiac output is presented as a percentage of $\dot{V}_{O_2max}$ (set equal to 100%) that existed at rest and throughout each stage of exercise. Cardiac output rose by 600 mL/min/m^2 for each dL/min/m^2 increase in $\dot{V}_{O_2}$ in each class. This indicates that the heart responds to tissue O_2 requirements irrespective of the severity of heart failure, but it is limited by the maximal cardiac output it can attain. Differences in cardiac output achieved at peak exercise are seen between classes. Progressive reductions in cardiac reserve are responsible for different aerobic capacities observed in these patients. $\dot{V}_{O_2max}$, therefore, serves as a noninvasive measure of peak exercise cardiac output and is given for each functional class in Table 34-3.

The cardiac output response to exercise is a function of the rises in stroke volume and heart rate. Responses in stroke volume for patients with chronic cardiac failure are shown in Figure 34-4 for each exercise class. In class A and B patients, stroke volume rises 50% during lighter workloads that represent less than 60% of $\dot{V}_{O_2max}$; at larger workloads, further increments in stroke volume are less apparent. A 25% rise in stroke volume occurs at submaximal exercise in class C patients, whereas in class D patients, exercise stroke volume is no different from its resting value. Exercise stroke volume is a result of several factors, including systolic wall stress, mitral or tricuspid regurgitation that may appear during exercise, and depressed myocardial contractility.

For each functional class of chronic cardiac failure, the heart rate–$\dot{V}_{O_2}$ response to upright incremental exercise is represented by a common slope.[17] The average slope is 3.6 beats/min for every 1-mL/min/kg increment in $\dot{V}_{O_2}$. Peak heart rate achieved is a function of maximal workload performed. Maximal exercise heart rate is, therefore, different for each class. In class D patients, the elevation in heart rate is the sole mechanism by which cardiac output rises during exercise.

Some patients with chronic cardiac failure deviate from this heart rate– $\dot{V}_{O_2}$ relation by having an inappropriate sinus tachycardia, either at rest and throughout exercise or simply during exercise. In the presence of a reduced ejection fraction and ventricular dilation, this inappropriately rapid heart rate further compromises exercise cardiac output and reduces aerobic capacity. β-Adrenergic receptor blockade is useful in attenuating resting or exercise heart rate under these circumstances.[18] Such chronotropic dysfunction (see below) to exercise may also apply to patients with chronic atrial fibrillation. An example of an inappropriate rapid heart rate relative to incremental treadmill exercise (Naughton protocol) is given in Figure 34-5 for a patient with atrial fibrillation and dilated cardiomyopathy of uncertain origin.

As in normal persons, lactate production appears in patients with chronic cardiac failure when systemic O_2 extraction exceeds 60%. Mixed venous lactate concentration during exercise rises above resting values when 60% or more of $\dot{V}_{O_2max}$ is attained.[7,16] Given

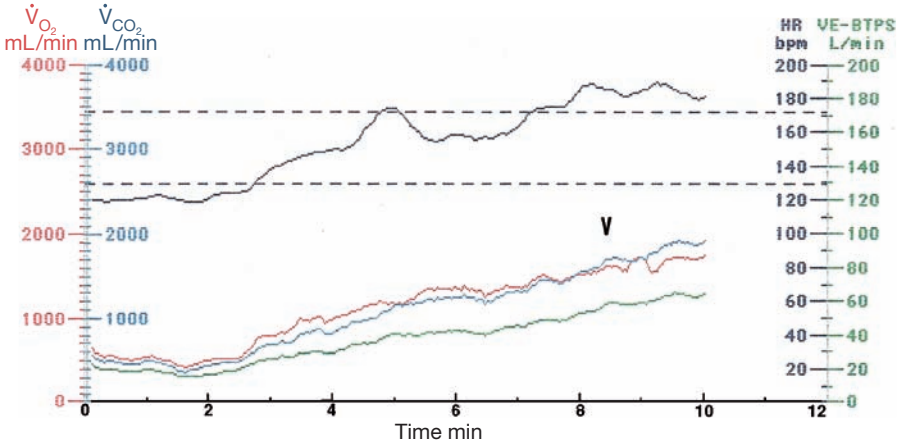

Figure 34-5 Cardiopulmonary exercise test results in a 48-year-old man with atrial fibrillation and dilated (idiopathic) cardiomyopathy. Note the rapid heart rate at rest and throughout incremental treadmill exercise. Predicted maximum heart rate range in this patient is shown by the broken lines. He achieved this rate during the first stage of exercise and exceeded it during the last stage of exercise. This is an inappropriate heart rate response. The AT is 13 mL/min/kg *(arrow)*, in keeping with functional class B. He did not achieve $\dot{V}_{O_2max}$ and, therefore, had a peak $\dot{V}_{O_2}$ of 15 mL/min/kg.

differences in aerobic capacity between exercise classes, different workloads are associated with this lactate threshold (Fig. 34-6). In class D patients whose cardiac output response is limited, the lactate threshold occurs at very light workloads ($\dot{V}_{O_2}$ of 5–8 mL/min/kg). Corresponding values for class C, B, and A patients are 8 to 11 mL/min/kg, 11 to 14 mL/min/kg, and more than 14 mL/min/kg, respectively. Thus, lactate threshold and $\dot{V}_{O_2max}$ reflect the severity of chronic cardiac failure as given in Table 34-3. A noninvasively determined AT based on measurements of respiratory gas exchange, as discussed previously, corresponds to the invasively measured lactate threshold.[7,12,16,19]

Exercise left ventricular filling pressure, as gauged from an occlusive wedge pressure recording, rises to a different degree in each exercise class with chronic cardiac failure (Fig. 34-7). In class A patients, the rise in wedge pressure during isotonic exercise rarely exceeds 18 mm Hg. This resembles a normal response. In class B patients, more dramatic elevations in exercise wedge pressure – to 25 mm Hg or higher – are frequently noted. Resting filling pressure is increased in class C and D patients; a further rise may be seen during upright exercise, often to levels in excess of 30 mm Hg. Despite these marked levels of pulmonary venous pressure, patients do not develop evidence of pulmonary congestion after exercise. Moreover, elevations in wedge pressure neither would predict exercise cardiac reserve and aerobic capacity nor are responsible for exertional dyspnea in these patients. Dyspnea corresponds with the lactate threshold and a disproportionate rise in $\dot{V}_E$ relative to $\dot{V}_{O_2}$.[8,16,20,21] Patients can be encouraged to exercise to exhaustion, attaining $\dot{V}_{O_2max}$ in the presence of dyspnea. In patients with acute cardiac failure, pulmonary congestion and dyspnea correlate with the elevation in wedge pressure; pulmonary edema occurs when hydrostatic pressure exceeds the colloidal osmotic pressure of 25 mm Hg and these patients should not be exercised.

$\dot{V}_E$ rises appropriately during incremental exercise in patients with chronic cardiac failure. The response in $\dot{V}_E$ most closely corresponds to $\dot{V}_{CO_2}$ throughout exercise (aerobic and anaerobic work) and is sufficient to sustain alveolar ventilation, thereby preventing hypoxemia and hypercapnia. Maximum $\dot{V}_E$ attained with exercise is less than 50% of MVV. Thus, these patients do not exhaust their ventilatory reserve in responding to exercise, even when their pulmonary compliance may be adversely elevated as a result of chronic pulmonary congestion and elevations in pulmonary venous pressure that appear with exercise. To minimize the work of breathing during exercise, class C and D patients use a pattern of rapid, shallow breathing to increase $\dot{V}_E$. Thus, the rise in tidal volume during exercise above its resting value is modest and compatible with a substantial portion of each breath being wasted in ventilation of anatomic dead space.[8] The response of class A and B patients more closely approximates that of healthy persons, in whom respiratory rate rises progressively during incremental exercise and the rise in tidal volume occurs early during the transition from rest to low-level exercise.

■ DIASTOLIC DYSFUNCTION

In 30% or more of patients with symptomatic heart failure, primary diastolic dysfunction is held responsible. The ejection fraction is normal or only minimally impaired in these patients. Diastolic dysfunction relates to an inability of the left ventricle to accommodate left atrial and pulmonary venous blood flow during diastole without a marked increase in filling pressure. Abnormal diastolic relaxation and filling typically appear in patients with chronic ischemic heart disease (with previous myocardial infarction), in those with hypertensive heart disease, and especially in elderly women. Responsible mechanisms are thought to include abnormal tissue structure, as occurs with

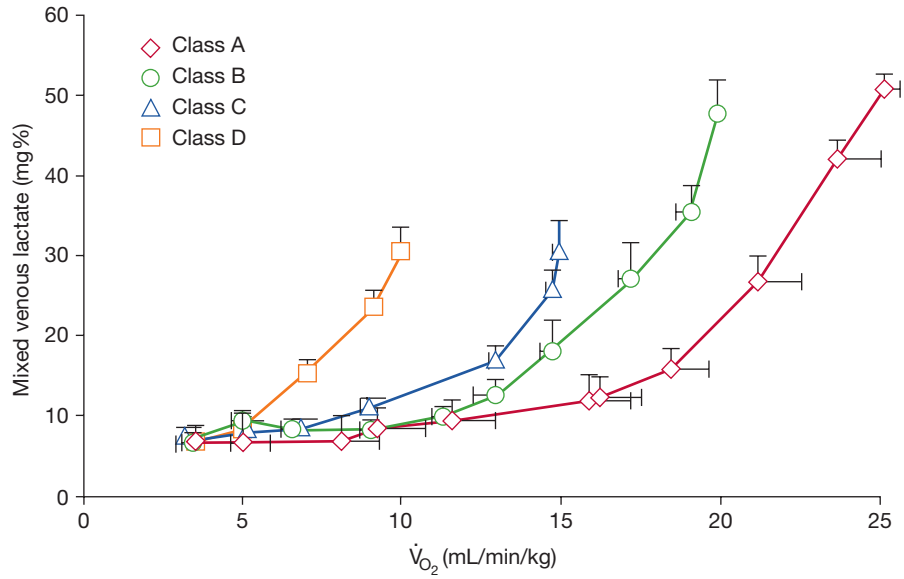

Figure 34-6 Relationship between mixed venous lactate concentration and $\dot{V}_{O_2}$ to incremental treadmill exercise for patients with chronic cardiac failure of varying severity, as expressed by each functional class. *(Reproduced with permission from Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol. 1987;55(2):22A–31A.)*

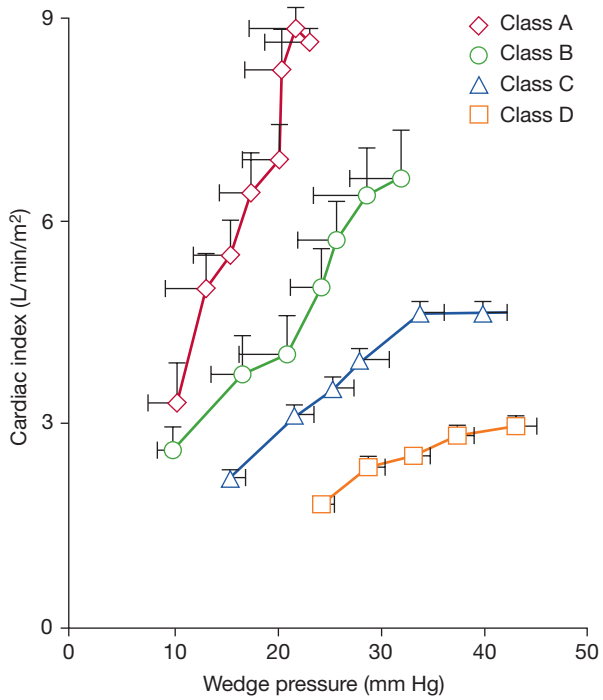

Figure 34-7 Relationship between treadmill exercise cardiac index and occlusion wedge pressure in patients with chronic cardiac failure, subdivided according to functional class. *(Reproduced with permission from Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol. 1988;55(2):22A–31A.)*

fibrous tissue accumulation or amyloid infiltration and abnormal calcium handling by sarcoplasmic reticulum. Factors extrinsic to the myocardium may also be contributory. Examples include the interaction between the pressure- or volume-overloaded right ventricle with the left ventricle and leftward shift of the interventricular septum and the interplay between the heart and pericardium.

Invasive CPX testing, together with incremental bicycle exercise, has been used to address the hemodynamic response of patients with primary diastolic dysfunction.[22] Most patients studied had systemic hypertension, and many were elderly; all had a clinical history of pulmonary congestion. Peak exercise $\dot{V}_{O_2}$ was reduced, owing to a reduction in exercise cardiac output and stroke volume responses; arteriovenous O_2 difference rose above 10 mL/dL. The level of $\dot{V}_{O_2}$ achieved with exercise correlated with peak cardiac output response. In comparison to age-matched controls, expected exercise-associated increments in left ventricular end-diastolic volume were not seen and were accompanied by increased left ventricular filling pressure. Thus, abnormalities in diastolic filling abrogated the Frank–Starling mechanism, thereby restricting the rise in exercise cardiac output; this finding may serve to explain symptoms of fatigue and breathlessness that these patients experience on exertion.

Primary diastolic dysfunction has been observed in patients following cardiac transplantation[23] in whom there is an abnormal blunting of stroke volume and heart rate responses to exercise. Despite the slower exercise heart rate in the transplanted, denervated heart, in which diastolic filling periods would accordingly be longer, diastolic dysfunction is present, limiting the exercise cardiac output response. Abnormal diastolic function has also been observed in the elderly and contributes to impaired exercise cardiac output response.[24]

■ CHRONOTROPIC DYSFUNCTION

Cardiac reserve in exercise depends not only on systolic and diastolic functions but also on heart rate and rhythm, including a coordinated contraction of the atria and ventricles. CPX testing has been used to address the contribution of abnormal heart rate and rhythm on the AT and $\dot{V}_{O_{2max}}$, broadly categorized here as chronotropic dysfunction. This includes abnormal sinus tachycardia, bradyarrhythmias, atrioventricular dissociation, and atrial fibrillation. CPX testing has proved useful in the evaluation of pacemaker function and technique.[25] Improvements in the AT at submaximal levels of work have been demonstrated for single-chamber, activity-triggered pacing compared with fixed-rate atrial or ventricular pacing. It too can help determine the optimum upper rate limit in heart failure patients with pacemakers. This can be determined by the highest pacing rate which still produces an increase in oxygen consumption.[26] With recent advancements in pacemaker technology, cardiac resynchronization therapy (CRT) is being increasingly offered to patients with heart failure. In a study involving CRT patients undergoing CPX testing, significant increments in peak $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ at AT and all ventilation and metabolic parameters were noted. Patients with baseline $\dot{V}_{O_2}$ of less than 14 mL/min/kg had the most benefit.[27] Similarly, patients with severe heart failure and atrial fibrillation had better hemodynamic performance with chronic biventricular pacing than left ventricular pacing alone.[28]

Some patients with chronic cardiac failure deviate from this heart rate– $\dot{V}_{O_2}$ relation by having inappropriate sinus tachycardia, either at rest and throughout exercise, or simply during exercise. In the presence of reduced ejection fraction and ventricular dilation, this inappropriately rapid heart rate further compromises exercise cardiac output and reduces aerobic capacity. Under these circumstances, β-adrenergic receptor blockade is useful in attenuating the resting or exercise heart rate. Such chronotropic dysfunction (see below) to exercise may also apply to patients with chronic atrial fibrillation. An example of an inappropriate rapid heart rate during incremental treadmill exercise (Naughton protocol) is given in Figure 34-5 for a patient with atrial fibrillation and dilated cardiomyopathy of uncertain origin.[29]

■ SURVIVAL AND PROGNOSIS

Various gas exchange parameters have been used to assess prognosis in patients with heart failure, including AT, peak $\dot{V}_{O_2}$, and $\dot{V}_E/\dot{V}_{CO_2}$ slope (a marker of ventilatory efficiency).[13,30–33] $\dot{V}_{O_2}$ at AT and $\dot{V}_{CO_2}$ slope are less subject to patient motivation or premature cessation of exercise and hence are more useful parameters. Class D patients with little or no exercise cardiac reserve (see Table 34-3) with AT <8 mL/min/kg have a marked reduction in 1- and 2-year survival as contrasted to Class A and B patients with respective exercise cardiac index responses of >8 and 6 to 8 L/min/m^2.[13,30,31] $\dot{V}_{O_2}$ at AT combined with $\dot{V}_E/\dot{V}_{CO_2}$ is a better prognostic indicator than peak $\dot{V}_{O_2}$ alone.[34] A low peak Pa_{CO_2} with exercise is responsible for the prognostic power of $\dot{V}_E/\dot{V}_{CO_2}$ slope and by itself is also an independent predictor of prognosis.[35] Resting end-tidal CO_2 has been shown to be a predictor of cardiac-related events.[36] Another $\dot{V}_{O_2}$ kinetics parameter that is a strong predictor of survival and less dependent on motivation is the mean response time ($\dot{V}_{O_2}$ deficit/Δ $\dot{V}_{O_2}$).[37] In the recovery period, slow normalization of $\dot{V}_{O_2}$ is associated with poor prognosis.[38]

The fluctuations in breathing patterns and its association with prognosis have also been studied in heart failure. Cyclic fluctuations in $\dot{V}_E$ at rest that persist during effort (external oscillatory ventilation) are associated with poor prognosis, whereas oscillations at rest alone are not.[39–41]

■ EFFICACY OF MEDICATIONS

The response to various heart failure medications on gas exchange and hemodynamics has been studied. Patients with heart failure taking spironolactone had a significant increase in peak oxygen consumption, D_{LCO}, and membrane diffusing capacity.[42,43] In a study in which losartan was added to an ACE inhibitor, there was

a significant increase in peak $\dot{V}_{O_2}$ and exercise capacity;[44] however, in another study in which candesartan was added, there was no increase in the peak $\dot{V}_{O_2}$ or exercise capacity.[45] Peak $\dot{V}_{O_2}$ has been used as a prognostic marker in heart failure, but in a study involving patients with chronic heart failure taking carvedilol, peak $\dot{V}_{O_2}$ was not found to be a useful prognostic marker.[46]

EXERCISE TRAINING

Exercise training leads to an improvement in exercise tolerance and peak $\dot{V}_{O_2}$ in patients with heart failure who have left ventricular dysfunction.[47] Exercise training in moderate stable heart failure results in favorable qualitative, rather than quantitative, changes in skeletal muscle.[48] Correction of maximum oxygen uptake for skeletal muscle mass, rather than total body mass, is a more sensitive measure of changes associated with exercise training.[48] Only progressive/increasing workload seems to markedly improve oxygen uptake.[49]

ISCHEMIC HEART DISEASE

Ischemia can be diagnosed with the help of ST segment changes during incremental exercise on treadmill or an ergometer during CPX testing. The sensitivity and specificity of ST changes for ischemia is not high. Parameters of gas exchange on CPX testing can be used to improve the diagnostic ability of the exercise-induced ST changes. Using O_2 pulse flattening duration and $\Delta \dot{V}_{O_2}/\Delta$ work rate slope with ST changes, the sensitivity and specificity for diagnosing ischemia improved from 46% to 66%, respectively, to 87% and 74%, respectively.[50] Myocardial stress/rest scintigraphy was used as the standard for detecting ischemia in this study. In another study, exercise cardiac output estimated from $\dot{V}_{O_2}$ at AT correlated with multivessel coronary artery disease, adverse cardiac events and clinically driven revascularization.[51] In postmyocardial infarction patients undergoing 3 weeks of exercise training, a significant improvement in $\dot{V}_{O_2}$ was found.[52]

Parameters of gas exchange measured during CPX testing have proven useful in the diagnosis of ischemia. Myocardial ischemia produces transient depression of left ventricular systolic function and, consequently, a reduction in stroke volume and cardiac output. Graphically, this decline in cardiac output should be reflected in a decline in the rate of increase in oxygen consumption per workload ($\Delta \dot{V}_{O_2}/\Delta$ Work Rate [WR] in watts). Thus, a blunted slope of $\Delta \dot{V}_{O_2}/\Delta$ WR should reflect myocardial ischemia. This analysis of gas exchange has been compared to SPECT myocardial scintigraphy. CPX testing demonstrates improved sensitivity and specificity in the detection of myocardial ischemia. Another valid parameter for the detection of myocardial ischemia is a flattening of the graph of O_2 pulse (mL/beat).[50] As is the case with heart failure, peak $\dot{V}_{O_2}$ and AT are prognosticators of adverse prognosis in patients with ischemic heart disease.

CPX testing has been utilized to assess the presence of right ventricular dysfunction in patients following an inferior myocardial infarction. Right ventricular dysfunction was analyzed utilizing echocardiographic parameters. Patients with right ventricular infarction had significantly lower oxygen consumption than those who had suffered an inferior infarction without right ventricular involvement.[53]

CHRONIC CIRCULATORY FAILURE

Circulatory failure, in physiological terms, refers to an inability of the heart to raise its cardiac output in a manner commensurate with prevailing $\dot{V}_{O_2}$. Responsible factors are extrinsic to the myocardium and include such entities as valvular heart disease, intrinsic pulmonary vascular disease, pericardial disease, and anemia.

VALVULAR HEART DISEASE

Mitral or aortic valve disease may alter the functional integrity of the cardiopulmonary unit by impairing the heart's ability to increase cardiac output in accordance with $\dot{V}_{O_2}$. Pathophysiological alterations within the unit that result from chronic valvular disease and that determine the clinical course and outcome following valve replacement include right heart overload and structural remodeling of the pulmonary vasculature and lung interstitium. The more marked the preoperative impairment in cardiac reserve, the poorer the long-term prognosis. Similarly, the greater the elevation in pulmonary vascular resistance, the more delayed is its return to normal levels and the slower the postoperative abatement of symptoms. The decision for surgical intervention requires an assessment of cardiopulmonary status—one that can be assessed noninvasively and monitored over time to detect a decline in cardiac reserve. Noninvasive CPX testing serves this purpose. Because of the heightened risk of syncope and the myocardial ischemia and arrhythmias that can occur during exercise in patients with aortic valvular stenosis, these patients should exercise with extreme caution, if at all.

Incompetence of the mitral and aortic valves is an example of a disorder that can result in chronic circulatory failure. Each creates a volume overload on the left ventricle. The onset of ventricular dysfunction is generally unpredictable and may initially appear only during vigorous levels of physical activity. As dysfunction progresses, symptoms appear at lower levels of activity and, finally, at rest.

Resting cardiac output is often not distinguishable among class A, B, C, or D patients with mitral or aortic regurgitation. Cardiac reserve is reduced, however, and, accordingly, so is aerobic capacity.[2] No impairment in systemic O_2 extraction has been reported. Thus, as in chronic cardiac failure, any observed decrease in aerobic capacity must be due to a decline in maximal forward cardiac output. To the extent that cardiac output can rise, the exercise cardiac output– $\dot{V}_{O_2}$ relation is preserved among these classes, averaging 600 mL/min/m^2 for every dL/min/m^2 rise in $\dot{V}_{O_2}$. Responses in cardiac output and wedge pressure for each exercise class are given in Figure 34-8. As in chronic cardiac failure, marked elevations in wedge pressure are seen in class C and D patients; this is also true for class B patients with mitral or aortic regurgitation. However, these

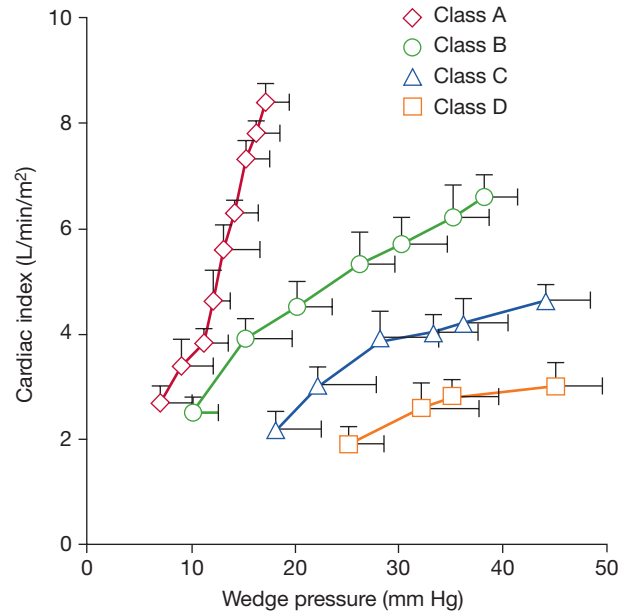

Figure 34-8 Relationship between treadmill exercise cardiac index and wedge pressure in patients with chronic mitral or aortic regurgitation, divided according to functional class. *(Reproduced with permission from Weber KT, Janicki JS (eds). Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia: WB Saunders; 1986.)*

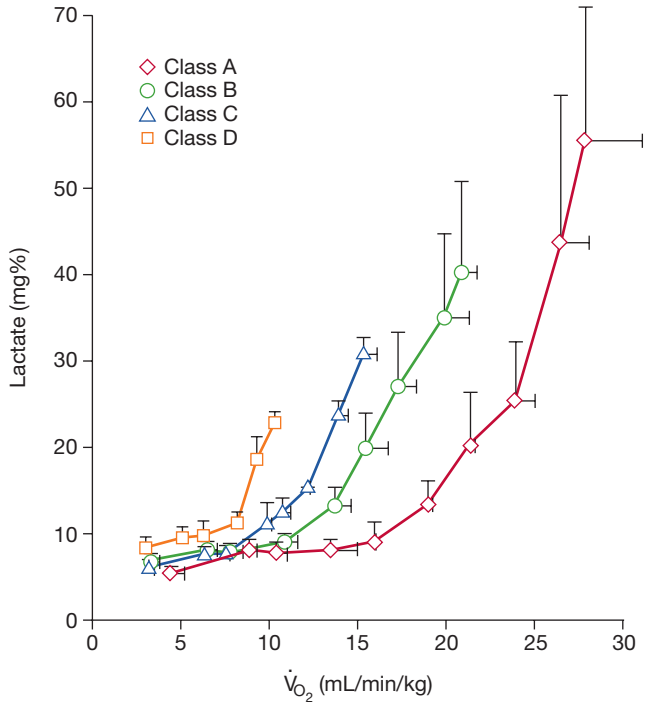

Figure 34-9 Relationship between mixed venous lactate concentration and $\dot{V}_{O_2}$ observed during incremental treadmill exercise in patients with chronic mitral or aortic regurgitation. As in chronic cardiac failure, the lactate threshold (lactate >12 mg/dL) occurs at different levels of $\dot{V}_{O_2}$, depending on functional class. *(Reproduced with permission from Weber KT, Janicki JS (eds). Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia: WB Saunders; 1986.)*

patients do not develop clinical evidence of pulmonary congestion following exercise, and dyspnea correlates with the lactate threshold. Exercise wedge pressure does not presage aerobic capacity or functional class in these patients.

AT can be used as an alternative measure in patients with valvular incompetence who are unable to attain $\dot{V}_{O_{2max}}$. The lactate threshold occurs at 60% to 70% of the patient's aerobic capacity and corresponds to a level of systemic O_2 extraction of 60% or more. Figure 34-9 depicts the response in mixed venous lactate concentration as a function of O_2 for each exercise class with mitral or aortic regurgitation. As in patients with chronic cardiac failure, the lactate threshold occurs at progressively lower levels of work as the severity of valvular disease increases.[2] The invasively measured lactate threshold correlates well with the valve obtained using noninvasive respiratory gas exchange measurements (see above).

The reduced mitral valve orifice that accompanies rheumatic mitral valvular stenosis leads to left atrial chamber enlargement, pulmonary venous hypertension, and right heart pressure overload. Pulmonary vascular resistance in most patients ranges between 200 and 600 dynes·s·cm^{-5}. Mitral stenosis is responsible for reduced left ventricular filling at rest and during exercise. An exercise-associated rise in heart rate reduces the diastolic filling period to further curtail left ventricular filling.

Cardiac output fails to rise appropriately with exercise in patients with chronic circulatory failure due to mitral stenosis.[2] For most symptomatic patients, cardiac output fails to rise appropriately during symptom-limited exercise because of a limited stroke volume response. Systemic O_2 extraction increases markedly with exercise, as do pulmonary capillary wedge and mean pulmonary artery pressures. Preoperative assessment of mitral stenosis should include not only calculation of mitral valve area but also exercise test-determined cardiac reserve and functional status. A decision regarding surgery should be based on these objective measures and clinical judgment, not simply on a laboratory-based calculation of reduced valve area.

A preoperative assessment of valvular surgery patients by CPX testing can help predict the degree of postoperative recovery. Preoperative peak $\dot{V}_{O_2}$ of 19 mL/min/kg and greater in patients undergoing surgery for mitral and aortic regurgitation correlates with higher percentage of patients attaining NYHA Functional Class I at 1 year after surgery.[54,55] $\dot{V}_{O_{2max}}$ along with AT has been used to follow progress of postoperative rehabilitation and training in valve surgery patients.[56,57] Exercise parameters can be helpful in assessing patients with valvular disease patients in whom there is a discrepancy between symptoms and echocardiographic data. A $\dot{V}_{O_{2max}}$ less than 75% predicted in moderate-to-severe mitral stenosis correlates with higher transvalvular gradients and higher pulmonary artery pressures at the end of exercise than does a $\dot{V}_{O_{2max}}$ greater than 75% of max predicted.[58]

In the absence of pulmonary arterial hypertension in patients undergoing mitral valve replacement, the presence of significant tricuspid regurgitation is associated with lower $\dot{V}_{O_{2max}}$ and AT and steeper $\dot{V}_E/\dot{V}_{CO_2}$ than when significant tricuspid regurgitation is absent.[59]

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy, the best known genetically determined cardiovascular condition, is marked by significant left ventricular hypertrophy, which may be asymmetric, concentric, or localized (apical). Two major clinical concerns in the disorder are the risk of sudden death and the difficulty in making the diagnosis when the classic asymmetric septal hypertrophy and the classic hemodynamic findings are absent. Exercise testing, in general, is a simple, but imprecise, method to screen for malignant dysrhythmias. CPX testing has been useful in distinguishing the physiologic left ventricular hypertrophy of athletes from hypertrophic cardiomyopathy.[60] Peak $\dot{V}_{O_2}$ is significantly higher in the athletes. A peak $\dot{V}_{O_2}$ 20% above predicted $\dot{V}_{O_{2max}}$ separates this group from those with genetically proven hypertrophic cardiomyopathy. A number of patients with hypertrophic cardiomyopathy experience symptoms of fatigue and dyspnea which do not correlate with hemodynamic findings. CPX testing can separate real from perceived symptoms. The percent predicted peak $\dot{V}_{O_2}$, combined with a quality of life questionnaire, appears to be helpful in making this distinction.[61]

OBSTRUCTIVE SLEEP APNEA

CPX testing can safely be performed in patients with sleep apnea to evaluate abnormalities in gas exchange and the response to continuous positive airway pressure therapy. Patients with moderate or severe obstructive sleep apnea have impaired exercise capacity, low peak $\dot{V}_{O_2}$, and low AT.[62] The abnormal parameters on CPX testing can be improved with continuous positive airway pressure therapy. In one study involving severe sleep apnea, 2 months of nasal continuous positive airway pressure treatment resulted in higher right ventricular ejection fraction, peak $\dot{V}_{O_2}$, peak $\dot{V}_{O_2}$, AT, and oxygen pulse.[63]

Patients with heart failure who have central sleep apnea have an increased mortality rate compared to those without it. Patients with heart failure often lack the classical symptoms of central sleep apnea and, hence, its presence may be underestimated. Treating central sleep apnea in heart failure has beneficial effects on cardiac function. Patients with heart failure with central sleep apnea have a highly augmented ventilatory response to exercise. This is manifested by a significantly increased slope of $\dot{V}_E/\dot{V}_{CO_2}$, which correlates with the severity of sleep apnea. Thus, patients with heart failure who have an increased $\dot{V}_E/\dot{V}_{CO_2}$ slope should be considered for a full sleep study to confirm the presence of sleep apnea.[64]

CONGENITAL HEART DISEASE

Patients with cyanotic congenital heart disease have limitations in exercise tolerance. CPX testing can be used to objectively assess their exercise limitation and ventilatory efficiency.

In a study of 25 adults with uncorrected cyanotic congenital heart disease, peak oxygen uptake and Pa_{O_2} were significantly reduced compared with normal subjects, while Pa_{CO_2} was only slightly reduced. Ventilatory efficiency, expressed as $\dot{V}_E/\dot{V}_{CO_2}$, was found to be markedly impaired at rest and during exercise. $\dot{V}_E/\dot{V}_{CO_2}$ correlated more strongly with patients' symptoms than hypoxemia and peak oxygen uptake.[65] For the corresponding NYHA class, patients with adult congenital heart disease and patients with heart failure had no significant differences in peak $\dot{V}_{O_2}$.[66]

CPX testing has also been used for assessing the response to transcatheter closure of atrial septal defect in adult patients. Improved peak oxygen uptake, peak oxygen pulse, and vital capacity have been reported following closure.[67] In one study, improvements in the prolonged $\dot{V}_{O_2}$ slope and $\dot{V}_{CO_2}$ slope were noted, reflecting improvement in recovery from maximal exercise.[68]

Tricuspid valve surgery in patients with Ebstein's anomaly produces reduced right ventricular volumes, increased pulmonary blood flow, and increased left ventricular filling and cardiac output. This is reflected by an increased $\dot{V}_{O_{2max}}$.[69]

PULMONARY HYPERTENSION

Pulmonary hypertension is expressed as an abnormal elevation in resting or exercise pulmonary artery pressure (see Chapter 72). Chronic left heart failure with attendant elevated left atrial pressure remains the most common cause of pulmonary *venous* hypertension. Pulmonary *arterial* hypertension (PAH) accompanies intrinsic pulmonary vascular disease or arteriolar vasoconstriction associated with hypoxemia due to intrinsic lung disease. PAH creates right ventricular pressure overload and an impediment to left ventricular filling. Accordingly, exercise cardiac output is compromised and aerobic capacity declines. PAH represents an example of chronic circulatory failure.

Patients with PAH have been studied with elective right heart catheterization using a triple-lumen flotation catheter and subsequent exercise testing.[2] Resting and peak treadmill exercise hemodynamic responses are given in Table 34-4. At rest, right heart and pulmonary arterial pressures exceeded the normal range. Right ventricular systolic pressure at rest was in excess of 50 mm Hg, and in one-quarter of patients it approximated or exceeded left ventricular (and systemic arterial) systolic pressure. Resting wedge pressure was normal in these patients. Calculated pulmonary vascular resistance exceeded the upper range of normal (170 dynes·s·cm^{-5}) in all patients; in more than one-third, it was above 1000 dynes·s·cm^{-5}, approximating systemic vascular resistance.

Peak cardiac output attained with maximal exercise for each functional class (Table 34-3) is similar to that observed for chronic cardiac failure and valvular heart disease. The impairment in exercise cardiac output is related to the extent to which pulmonary vascular resistance is elevated. Patients with a markedly elevated resting pulmonary vascular resistance (above 1000 dynes·s·cm^{-5}) proved to be functional class D. In this group of patients with intrinsic pulmonary vascular disease, arterial O_2 desaturation during exercise was not observed, emphasizing the importance of compromised cardiac reserve—a function of the inability of the right ventricle to generate sufficient pulmonary blood flow to sustain left ventricular filling and, thereby, systemic blood flow. Patients with PAH stopped exercising because of breathlessness or fatigue or both; none experienced retrosternal chest pain, light-headedness, or syncope; none developed arrhythmias. In most, it was possible to determine the $\dot{V}_{O_{2max}}$; in all, the AT could be attained (see above). CPX test results for a 42-year-old woman with PAH are shown in Figure 34-10.

Patients with PAH have significant ventilation–perfusion mismatch; during exercise ventilation is increased. This abnormality in ventilatory inefficiency is reflected by the reduction in end-tidal CO_2 (pET_{CO_2}). The reduction in end-tidal CO_2 is proportional to the decrease in percent predicted $\dot{V}_{O_2}$ and increase in the mean pulmonary artery pressure. In normal subjects, the pET_{CO_2} increases from rest to AT, whereas in patients with PAH, the pET_{CO_2} decreases from rest to AT.[70] On CPX testing the slope of regression between CO_2 production and minute ventilation can also be used to assess the ventilation–perfusion mismatch. The $\dot{V}_E/\dot{V}_{CO_2}$ slope is greater in patients with PAH compared with cardiac dysfunction and the same peak $\dot{V}_{O_2}$. Conversely, for the same $\dot{V}_E/\dot{V}_{CO_2}$ slope, patients with LV dysfunction have a lower peak $\dot{V}_{O_2}$.[71]

Measurement of CPX testing-based parameters in PAH is reliable and reproducible, even in patients with limited exercise tolerance. The parameters correlate well with the decrease in D_{LCO} and NYHA class.[72,73] Even in children with pulmonary hypertension, peak $\dot{V}_{O_2}$ strongly correlates with pulmonary vascular index.[74] CPX testing can be used for the objective assessment of safety and efficacy of treatment strategies in patients with PAH.[75–77] Peak $\dot{V}_{O_2}$ is an independent, strong predictor of survival in these patients.[78]

TABLE 34-4 Resting and Peak Exercise Hemodynamics for Patients with Nonhypoxic Pulmonary Vascular Disease and Pulmonary Hypertension

		Resting	Exercise
PA	(mm Hg)	29 ± 9	47 ± 20
RVSP	(mm Hg)	52 ± 30	86 ± 37
RVDP	(mm Hg)	7 ± 4	16 ± 10
PCW	(mm Hg)	10 ± 3	22 ± 14
PVR	(dynes · s · cm^{-5})	412 ± 319	302 ± 331
CO	(L/m^2/min)	2.8 ± 1.6	5.3 ± 2.2
AP	(mm Hg)	106 ± 6	130 ± 8
Art O_2 sat	(%)	97 ± 2	96 ± 2

PA, mean pulmonary artery pressure; RVSP and RVDP, right ventricular systolic and diastolic pressures, respectively; PCW, wedge pressure; PVR, pulmonary vascular resistance; CO, cardiac output; AP, mean arterial pressure.
Source: Adapted with permission from Weber KT, Janicki JS. Pulmonary Hypertension. In: Weber KT, Janicki JS, eds. Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, PA: Saunders; 1986.

CHRONIC LUNG DISEASES

In a normal subject performing maximal exercise, minute ventilation rarely exceeds 50% of MVV; in addition, tidal volume uncommonly exceeds 50% of vital capacity. Given this large ventilatory reserve, exercise is normally not limited by ventilation. This is not the case in patients with lung disease, in whom ventilatory reserve is reduced. A number of factors may limit exercise in patients with lung disease, including altered lung mechanics, impaired gas exchange and resultant hypoxemia, pulmonary hypertension, or respiratory muscle fatigue.

OBSTRUCTIVE LUNG DISEASE

Exercise intolerance commonly accompanies chronic obstructive pulmonary disease (COPD), with dyspnea limiting physical activity to modest levels of work. Patients with COPD have a higher $\dot{V}_E$ for any given workload; this is largely due to increased dead space ventilation. Given their reduction in MVV and greater exercise $\dot{V}_E$, these patients often exercise with a $\dot{V}_E$/MVV ratio that exceeds 75%.

Use of such a large portion of the ventilatory reserve cannot be sustained, accounting for breathlessness and termination of exercise. In patients with moderate or severe COPD, this generally occurs before they reach their AT, implying a ventilatory, rather than cardiac, limitation to exercise. The workload at which patients terminate exercise represents a peak $\dot{V}_{O_2}$; it is not their $\dot{V}_{O_2max}$, as can be attained in patients with chronic cardiac or circulatory failure in whom ventilatory responses pose no limitation to exercise.

In severe emphysema, D_{LCO} is reduced, in keeping with alveolar capillary destruction. In such patients, a significant fall in arterial O_2 saturation often appears during exercise. This is in contrast to patients with chronic bronchitis, in whom O_2 saturation may actually increase. The improvement in oxygenation in these patients is a result of improved ventilation in areas with low ventilation–perfusion ratios. D_{LCO} portends exercise-induced arterial O_2 desaturation. Patients with a D_{LCO} less than 55% of predicted are most likely to experience hypoxemia with exercise. Arterial hypoxemia limits effort tolerance, for several reasons: (1) reduced O_2 delivery to exercising muscle, including those associated with respiration; (2) increased chemical drive to respiration, with a corresponding inappropriate $\dot{V}_E$ for a given level of work; and (3) secondary pulmonary vasoconstriction.

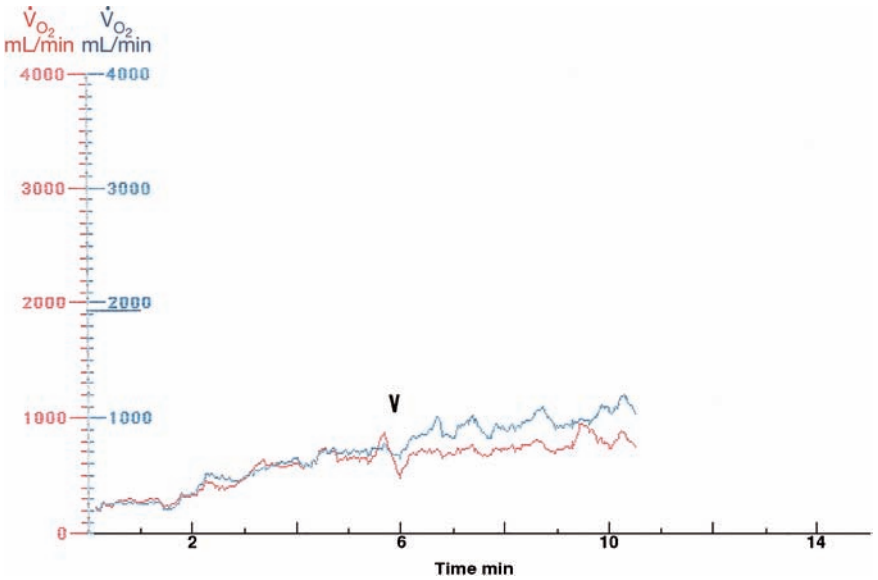

Figure 34-10 Cardiopulmonary exercise test results for a 42-year-old woman with pulmonary arterial hypertension of uncertain origin. The first 2 minutes represent standing rest. The patient attained the AT (7 mL/min/kg) during stage 2 of exercise (1.5 mph, 0 grade) and a $\dot{V}_{O_2max}$ of 10 mL/min/kg, corresponding to functional class D.

By measuring $\dot{V}_{O_2}$ peak in patients with COPD undergoing CPX testing, an objective assessment of exercise capacity can be made. Peak $\dot{V}_{O_2}$ in severe COPD correlates with resting FEV_1% predicted, total treadmill time, and total metabolic equivalent values.[79] CPX testing can better define respiratory limitations than pulmonary function testing alone in patients with COPD filing for disability due to shortness of breath.[80]

The increase in breathing capacity with exercise in COPD, measured by the ratio of $\dot{V}_E$/MVV, correlates with peak $\dot{V}_{O_2}$ and can be predicted by FEV_1/FVC measured during resting pulmonary function testing.[81] In chronic COPD, peak $\dot{V}_{O_2}$ can be estimated by equations that take into account the distance walked by the patient and the lung function tests. However, the correlation between measured and estimated peak $\dot{V}_{O_2}$ is not strong enough to predict exercise capacity. If peak $\dot{V}_{O_2}$ has to be used for clinical decision making, it should be measured, rather than estimated.[82] In COPD, skeletal muscle abnormalities have been described and contribute to reduced exercise capacity. Peak $\dot{V}_{O_2}$ in COPD correlates well with fat-free mass, a bioimpedance index of muscle mass.[83] In patients with COPD, physiologic parameters measured by CPX testing have prognostic implications as well. Based on multivariate analysis the Pa_{O_2} slope ($\Delta Pa_{O_2}/\Delta \dot{V}_{O_2}$) is most closely associated with survival.[84] Similarly, Pa_{O_2max}, along with FEV_1, has been found to independently predict mortality.[85] Overall, a linear relationship exists between peak $\dot{V}_{O_2}$ and pulmonary function testing parameters in COPD.[86]

■ RESTRICTIVE LUNG DISEASE

Patients with known interstitial lung disease, a diverse group of disease entities, experience limiting dyspnea on exertion. This may be secondary to reduced ventilatory reserve or development of arterial O_2 desaturation. The evaluation of exercise performance may also be useful in patients who complain of dyspnea out of proportion to their pulmonary function studies. Dyspnea on exertion may appear in a patient with an abnormal chest radiograph before pulmonary function studies are abnormal. Exercise testing may be indicated in these patients to detect abnormal ventilatory reserve and its response over time. Patients with interstitial lung disease tend to breathe at a higher respiratory rate and lower tidal volume than do normal subjects for any given $\dot{V}_{O_2}$. Because they have a reduced MVV, their ability to exercise is limited by nearly full utilization of their reduced ventilatory reserve.

As in patients with airway disease, the D_{LCO} is a good predictor of arterial O_2 desaturation during exercise in patients with interstitial lung disease. Most patients with a D_{LCO} below 60% develop desaturation. If a patient has a normal D_{LCO}, he or she is unlikely to develop exercise-induced arterial O_2 desaturation. Measurement of D_{LCO} can be used to screen patients for exercise studies. Finally, the degree of arterial O_2 desaturation during exercise correlates with the reduction in D_{LCO}.

CPX testing is a sensitive test for gas exchange abnormalities. In one study involving biopsy-proven sarcoidosis, CPX testing predicted pulmonary dysfunction earlier than did physical examination, chest radiography, and spirometry.[87,88] In another study involving survivors of severe acute respiratory distress syndrome, aerobic capacity using CPX testing was found to be below normal in 41% of patients in whom mild pulmonary function abnormalities were not enough to explain low exercise tolerance.[89] CPX testing has been used for procuring prognostic information in patients with interstitial lung disease. Peak $\dot{V}_{O_2}$ in patients with parenchymal lung disease awaiting transplant, along with Pa_{O_2} slope, has been used to predict survival.[90,91] In other parenchymal lung diseases, such as cystic fibrosis, breathing reserve index at AT has been used to distinguish ventilatory-limited patients from those without ventilatory limitations.[92]

EVALUATION OF EXERTIONAL DYSPNEA

Normally, a person is unaware of the act of breathing and the fact that 500 to 750 mL of air enters and leaves the lungs 10 to 15 times each minute. $\dot{V}_{O_2}$ increases secondary to normal or abnormal chemical stimuli (e.g., hypercapnia, hypoxemia, acidemia) or anxiety. When breathing is perceived to be inappropriate relative to the level of physical activity, it is considered an abnormal awareness of breathing that is termed breathlessness, shortness of breath, or dyspnea.[2] Dyspnea on exertion is common in patients

with heart disease, pulmonary parenchymal or airway disease, and pulmonary vascular disease. Deformities of the chest wall and diseases associated with weakness of the respiratory muscles are also accompanied by exertional breathlessness. Dyspnea may seriously hinder a patient's ability to carry out muscular work, thereby compromising quality of life. The evaluation of dyspnea includes requisite historical information that characterizes its nature, onset, severity, relationship to exercise, and the patient's underlying physical condition and customary daily activity. Other associated symptoms – such as palpitations, anginal chest pain, and lightheadedness – must be taken into consideration.

An objective and reliable estimate of dyspnea on exertion and its severity can be gauged from exercise testing. Dyspnea occurs when $\dot{V}_E$ is excessive relative to $\dot{V}_{O_2}$ and when $\dot{V}_E$ is driven by chemical stimuli or altered lung mechanics. Dyspnea with exercise can appear when $\dot{V}_E$ occupies an excessive proportion of MVV. An estimation of MVV can be derived by multiplying the patient's FEV_1 by 35. As a corollary, maximal encroachment on the vital capacity by exercise tidal volume cannot be sustained for long. Such ventilatory effort poses a substantial workload on respiratory muscles. An MVV maneuver during pulmonary function testing cannot be sustained for more than a few seconds, while more than 70% of the MVV cannot be sustained by normal subjects for more than several minutes. Hence, the ventilatory response to exercise that is associated with dyspnea in patients with heart or lung disease follows a similar pattern of short-lived, near-maximal ventilation.

The patient with pulmonary vascular disease or advanced interstitial lung disease may be unable to sustain alveolar ventilation during exercise at a level commensurate with that required for adequate arterial O_2 saturation. Consequently, hypoxemia may compound the patient's exercise response and be responsible for a heightened chemical drive to respiration. In the case of COPD, the need to move air through a partly obstructed tracheobronchial tree creates an added workload on respiratory muscles. Air flows in these patients are already compromised at rest and must increase with exercise; they may approach peak expiratory flows observed with maximal effort during pulmonary function testing.

Patients with mild, moderate, or severe cardiac or circulatory failure rarely use more than 50% of their ventilatory reserve at maximal exercise, and they do not experience arterial O_2 desaturation during exercise. If one estimates MVV from the FEV_1 (as noted earlier), for an FEV_1 of 1, 2, or 3 L, MVV is expected to equal 35, 70, or 105 L, respectively. In patients with chronic cardiac or circulatory failure, exercise maximum $\dot{V}_E$ has been found to range between 62 and 29 L/min for class A through D patients, respectively. Hence, unless there is a major reduction in MVV (or in FEV_1 to <3 L), these patients will not have a ventilatory limitation to exercise. Finally, patients are able to cross their AT and, if encouraged, may reach their point of exhaustion attaining $\dot{V}_{O_2max}$. By monitoring the breath-by-breath response in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during exercise, the physician can immediately determine when the patient has achieved the AT and $\dot{V}_{O_2max}$. These end-points are not attained in the patients with lung disease or those with coexistent heart and lung disease in whom the respiratory system is the primary limitation to exercise. Table 34-5 summarizes the salient features used to differentiate primary ventilatory from cardiac or circulatory failure as the cause of exertional dyspnea, as detected by exercise testing.

OTHER APPLICATIONS OF CARDIOPULMONARY EXERCISE TESTING

CPX testing, with its ability to foretell cardiac and ventilatory reserves, has proved useful in clinical decision making in a variety of circumstances, including assessment of a patient's candidacy for cardiac transplantation and preoperative assessment of risk.

TABLE 34-5 Ventilatory versus Cardiac/Circulatory Failure as the Predominant Cause of Exertional Dyspnea

Ventilatory Failure
1. Exercise maximum $\dot{V}_E$ utilizes >70% of MVV
2. Exercise-associated arterial hypoxemia
3. Failure to cross AT and to achieve $\dot{V}_{O_2max}$
Cardiac/Circulatory Failure
1. Cross AT and can achieve $\dot{V}_{O_2max}$
2. Maximum exercise $\dot{V}_E$ does not exceed 50% of MVV
3. Does not develop arterial hypoxemia with exercise

MVV, maximal voluntary ventilation; AT, anaerobic threshold.

CARDIAC TRANSPLANTATION

The severity of chronic cardiac and circulatory failure is gauged according to $\dot{V}_{O_2max}$ and the AT (Table 34-3) and is used to predict exercise cardiac reserve. This approach has been applied to patients with systolic dysfunction secondary to chronic ischemic heart disease or dilated (idiopathic) cardiomyopathy, who are considered potential candidates for cardiac transplantation. The ejection fraction or resting hemodynamic parameters (e.g., resting cardiac index or wedge pressure) do not help predict the severity of cardiac failure or functional capacity and are no longer a mainstay in decision making. The same is true for subjective evaluation of functional status using the New York Heart Association criteria. Incremental exercise testing, with identification of AT and peak $\dot{V}_{O_2}$ achieved thereafter, has emerged as a valuable tool to objectively address cardiac reserve and functional capacity and which predicts survival.[30,31,93–95] In fact, consensus has been reached on recommending transplantation based on clinical criteria, in combination with functional stratification based on exercise test results.[96] Class D patients, having little or no cardiac reserve, have a marked reduction in 1- and 2-year survival and, therefore, are candidates for urgent transplantation. Class C patients with a modest increment in exercise cardiac output are probable candidates. On the other hand, class A patients in whom cardiac reserve remains intact, or class B patients in whom cardiac reserve is only minimally impaired, do not have an adequate indication for transplantation. Decision is deferred, and serial exercise studies are used to assess recovery or deterioration in the setting of optimal medical therapy.

Incremental exercise testing may also provide useful information after cardiac transplantation, including recovery of cardiac and ventilatory reserves. The importance of diastolic dysfunction in limiting exercise tolerance following cardiac transplantation was reviewed earlier. A blunted heart rate response to exercise is expected in these patients owing to cardiac denervation. Such chronotropic incompetence is demonstrated in Figure 34-11, along with exercise test results.

Recipients of lung or heart/lung transplant do not experience the degree of return in cardiac reserve and gas exchange as do patients with heart transplant alone. These patients experience considerable exercise limitation and reduced maximum oxygen uptake despite normalization of resting cardiopulmonary function. Such limitation may be a function of peripheral factors, such as abnormalities in the peripheral circulation and peripheral neuromuscular function.[97] CPX testing may be utilized to predict survival in lung transplant recipients. Lower exercise capacity as defined by lower percent predicted peak $\dot{V}_{O_2}$ appears to have prognostic value.[98]

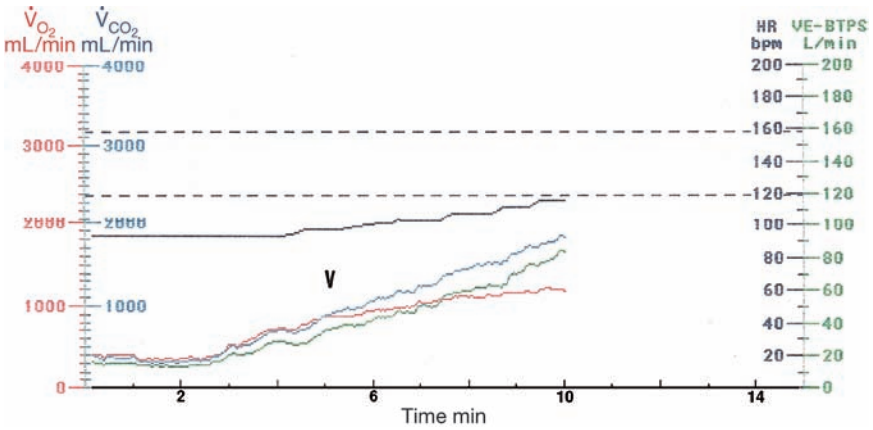

Figure 34-11 Cardiopulmonary exercise test results for a 62-year-old male cardiac transplant recipient. During this incremental treadmill test he attained an AT and $\dot{V}_{O_{2max}}$ of 8 and 11 mL/min/kg, respectively. Note the blunted heart rate response (predicted peak heart rate range shown as *broken lines*).

SURGICAL RISK ASSESSMENT

Preoperative incremental exercise testing has proved useful in assessing postoperative morbidity and mortality in the elderly and patients with underlying heart or lung disease who are scheduled for major intrathoracic or intra-abdominal surgery. The premise underlying this approach is based on recognition that during and after surgery, there may be a need to call on cardiac and ventilatory reserves—namely, the ability to increase cardiac output and maintain O_2 delivery, and to increase $\dot{V}_E$ and prevent hypoxemia. Several studies have demonstrated the utility of measuring the AT and peak $\dot{V}_{O_2}$, using exercise testing, in addressing these reserves and in identifying patients prone to postoperative complications.[99–101] Pulmonary function testing proved insensitive in forecasting postoperative course. Class C and D patients, with little or no cardiac reserve, had a greater number of morbid and mortal events following surgical interventions than did class A or B patients. Class A patients had few, if any, postoperative complications and no mortality. The risk of complications could, therefore, be gauged best by a patient's preoperative aerobic capacity.[99–102] The direct assessment of the AT or $\dot{V}_{O_{2max}}$ and prediction of cardiac reserve, and, by inference, ventilatory reserve supersede the value of an age-determined impairment in aerobic capacity.

AT is a particularly important parameter in assessing preoperative risk. It gives an objective assessment independent of patient motivation and does not require excessive amounts of exercise. In a large study of elderly patients undergoing major intro-abdominal surgery, an AT of less than 11 mL/min/kg along with preoperative ischemia was associated with high mortality.[100] Patients evaluated by CPX testing with unfavorable AT can be electively admitted to intensive care units and their hemodynamics optimized before major surgery.[100,103] Risk stratifying based on AT is even better at predicting patients who are not at risk for adverse events.[100,103]

Patients undergoing other major surgeries, such as radical esophagectomy with three-field lymphadenectomy, have also been risk stratified by CPX testing. Extensive fluid shifts are expected in the postoperative period with surgical interventions on the lymphatic system. CPX testing can provide a thorough assessment of the cardiopulmonary reserve in such patients. In a study involving such patients, a peak $\dot{V}_{O_2}$ of 800 mL/min/m^2 was associated with low risk of complications.[104] In another study involving patients with abdominal aortic aneurysm repair. a higher percentage of patients with adverse complications had a peak $\dot{V}_{O_2}$ less than 20 mL/min/kg.[105] Peak $\dot{V}_{O_2}$ has also been used to risk stratify liver transplant patients. Patients dying within 100 days of transplantation are more likely to have peak $\dot{V}_{O_2}$ <60% of predicted and AT <50% of predicted peak $\dot{V}_{O_2}$ compared with survivors.[106]

Patients with lung cancer have a high likelihood of concomitant COPD and coronary artery disease due to the common risk factor of smoking. Surgery might offer the only chance of cure in these patients and often implies resection of a variable portion of the lung tissue surrounding the cancer to ensure eradication. Removal of functional lung tissue in an already compromised cardiopulmonary system resection can be risky. It is imperative that a preoperative assessment of cardiopulmonary reserve be made before such a surgery (see Chapter 103). By performing preoperative CPX testing in patients being considered for lung cancer resection surgery, an objective assessment of the cardiopulmonary reserve can be made. Peak $\dot{V}_{O_2}$ has been used to risk stratify these patients, along with FEV_1 and D_{LCO}.[107] Correcting peak $\dot{V}_{O_2}$ for weight and expressing it as a percentage of predicted improves the predictive power of peak $\dot{V}_{O_2}$. Elderly patients, female patients, and patients with short stature may have a peak $\dot{V}_{O_2}$ below the absolute cutoff value, but they may still be eligible for surgery when peak $\dot{V}_{O_2}$ is expressed as percentage predicted.[108]

The predictive value of peak $\dot{V}_{O_2}$ is greater in patients with a FEV_1 <70%.[109] Peak $\dot{V}_{O_2}$ <50% of predicted is associated with a high complication rate. Patients with peak $\dot{V}_{O_2}$ >50% predicted can undergo surgery without excess mortality.[108] A peak $\dot{V}_{O_2}$ <10 mL/min/kg is generally considered prohibitive for surgery.[110] Risk stratification based upon peak $\dot{V}_{O_2}$ is particularly useful in assessing patients for lung resection who have borderline pulmonary function (predicted postoperative FEV_1 or D_{LCO} <40%). In these patients, a peak $\dot{V}_{O_2}$ <15 mL/min/kg is associated with an increased risk, and peak $\dot{V}_{O_2}$ <10 mL/min/kg carries a very high risk of postoperative complications.[111]

SUMMARY

CPX testing provides for an extensive evaluation of patients having diseases and disorders of the cardiorespiratory unit. The diagnostic information provided extends far beyond that obtained by testing of heart and lung function measured at rest, or by standard exercise testing with electrocardiographic monitoring. Position papers on CPX testing should be consulted for further diagnostic and prognostic stratification.[112,113]

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CHAPTER 35

Diagnostic Bronchoscopy, Transthoracic Needle Biopsy, and Related Procedures

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INTRODUCTION

Gustav Killian reported his experience with the first bronchoscopy in 1898. Technological advances during the next century facilitated development of bronchoscopy as a pivotal diagnostic and therapeutic tool in pulmonary medicine. Although a number of bronchoesophagologists contributed to refinement of the technique based upon use of a rigid instrument, the advent of flexible fiberoptic bronchoscopy, pioneered by Ikeda in 1967, opened new horizons to clinicians. More recently, transthoracic needle biopsy (TTNB) has been added to the pulmonologist's diagnostic armamentarium, although it is now most frequently performed by radiologists under CT guidance.

This chapter comprises an overview of bronchoscopy, TTNB, and related techniques. Following a general discussion of bronchoscopy and associated general instrumentation, indications for the technique and patient preparation are considered. Specific applications of diagnostic bronchoscopy are discussed. Subsequently, safety factors related to bronchoscopy and complications of the technique are reviewed. Finally, TTNB is described.

GENERAL INSTRUMENTATION

The initial bronchoscope, developed by Killian in Europe and further perfected by Chevalier Jackson in the United States, was a rigid metal tube that permitted either spontaneous or mechanical ventilation. With development of fiberoptic and advanced electronic technology, the flexible bronchoscope has, to a large extent, replaced the rigid bronchoscope for most diagnostic and some therapeutic indications. Therapeutic interventional bronchoscopy, including the use of rigid bronchoscopes, is discussed in Chapter 36.

FLEXIBLE FIBEROPTIC AND VIDEOBRONCHOSCOPY

Although the optical resolution of early fiberoptic bronchoscopes was inferior to that of rigid devices, their flexibility, ease of manipulation, and simplicity of use, which permit rapid examination under topical anesthesia, have made flexible bronchoscopy the primary endoscopic procedure in pulmonary diseases.

Unlike the larger-bore rigid bronchoscope, the flexible bronchoscope varies from ultrathin – allowing for neonatal endoscopy – to larger, adult size therapeutic devices. The diameter of the working channel permits aspiration of secretions or introduction of accessories required for diagnostic purposes (see Bronchoscopy Technique). With flexible bronchoscopy, the patient's ventilation is assured by airflow around the bronchoscope, between the external wall of the device and the tracheobronchial tree. Thus, the appropriate selection of bronchoscope size is crucial.

Fiberoptic systems have largely been replaced by videobronchoscopes, which utilize a miniaturized CCD camera at the tip of the scope that provides electronic transmission of images to a television monitor. Flexible bronchoscopes are more fragile and more prone to damage than are rigid metal instruments. Appropriate care and adherence to safety techniques during procedures, as well as during routine cleaning and maintenance of the instruments, help assure extended instrument life and reduce repair costs.

ULTRATHIN BRONCHOSCOPES

Ultrathin bronchoscopes, flexible scopes with external diameters ≤3 mm, were initially developed for pediatric applications; however, these have now incorporated larger working channels, allowing for their use in the diagnosis of peripheral pulmonary lesions in adults.[1,2] Ultrathin bronchoscopes can be advanced to more peripheral bronchi than conventional bronchoscopes under direct observation, allowing for examination of sixth- to eighth-generation bronchi. Ultrathin scopes may be particularly useful when combined with additional diagnostic tools, such as navigational bronchoscopy and radial ultrasound probes (see Ultraminiature Radial Probes and Navigational Bronchoscopy).

DIAGNOSTIC BRONCHOSCOPY ACCESSORIES

The working channel of the fiberoptic or videobronchoscope, although of relatively small diameter, allows the insertion of various diagnostic and therapeutic accessories.

■ BIOPSY FORCEPS

Simple visualization of lesions is usually not sufficient to determine a precise diagnosis and to guide management. Pathological confirmation through biopsy is frequently required. A variety of instruments with improved distal control (i.e., control beyond the tip of the bronchoscope) have been developed that permit tissue cutting and retrieval of biopsy specimens.

The cutting cups of biopsy forceps may be round or elliptic and may have smooth or jagged edges. The use of nonserrated edges, however, seems to reduce tissue trauma and the concomitant risk of bleeding. The biopsy procedure is simple and generally associated with only minimal complications in the case of a visible lesion. Even peripheral lesions, which are not visible through the bronchoscope, may be biopsied. With diffuse parenchymal or interstitial lung disease, specimens may be obtained without fluoroscopic guidance. With smaller or focal lesions, however, the diagnostic yield of biopsies increases when fluoroscopy is used. The development of new electromagnetic and remote guidance systems suggests that further improvement in the diagnostic yield of bronchoscopic biopsies can be expected.

■ BRONCHIAL BRUSHES

Lesions not accessible to direct biopsy with a forceps can at times be approached with a bronchial brush. This device consists of a rigid central wire surrounded by brushes of various sizes and shapes. To-and-fro movement of the brush against the adjacent tissue produces minor trauma but enables collection of ample specimens for cytological or microbiological analysis.

In some clinical circumstances, there is a need to obtain an uncontaminated specimen from the lower respiratory tract for microbiological studies. A brush protected by an additional sheath and tip may be passed through the working channel of the bronchoscope (protected brush specimen, as discussed later). In these cases, special attention is needed not to use an excessive amount of local anesthetic or saline lavage, since these solutions contain bacteriostatic material that may inhibit microbial growth. The diagnostic yield depends on use of proper technique, appropriate choice of brush, and careful collection and preservation of the specimen.

■ NEEDLES FOR ASPIRATION AND BIOPSY

The first performance of a transbronchoscopic needle aspiration (TBNA) through a rigid bronchoscope was reported by Schieppati in 1958. Wang et al.[3] then developed a flexible needle technique using a fiberoptic bronchoscope in 1978. Initially, several models of needles were designed to obtain cytological material; subsequently, histological specimens from peribronchial mediastinal and hilar lymph nodes were obtained with larger-bore needles. These biopsy needles are also useful in the diagnosis of endobronchial and submucosal lesions and can serve as a complementary technique to percutaneous needle aspiration of peripheral pulmonary nodules or masses.

The tip of the needle is protected by a metal hub during the insertion and withdrawal to avoid damage to the flexible scope. Perforation of the working channel of the scope may occur if the needle is advanced in an exposed position. The diagnostic yield depends on two factors: Optimization of the bend of the tip of the bronchoscope and proper performance of bronchial wall puncture by the needle through the intercartilaginous space. Familiarity with the type of needle used increases the success rate.

TBNA is generally safe, although pneumothorax and hemomediastinum can occur. Clinically significant bleeding is extremely rare, particularly when a 22-gauge needle is used, even if a major vessel is inadvertently punctured or if the patient suffers from superior vena cava syndrome.

ENDOBRONCHIAL ULTRASOUND

Among the new diagnostic modalities available to chest physicians, endobronchial ultrasound (EBUS) has unquestionably had the most profound impact.[4] Two major barriers to EBUS development existed: Ultrasound probe size and sound wave transmission in air-filled structures. Ultrasound engineering advances allowed the former barrier to be overcome. The latter was surmounted by developing an integrated, fluid-filled balloon surrounding the EBUS probe, thereby allowing for a sound wave–transducing medium interface to exist between the ultrasound probe and airway wall (i.e., ultrasonographic coupling).

Ultrasound frequency is an important consideration for EBUS application. Lower frequencies give better penetration depth with less resolution; higher frequencies provide better spatial resolution, but less penetration depth. For EBUS applications, the frequencies range from 7.5 to 30 MHz. Currently, there are three EBUS probes available for different applications: (1) Ultraminiature radial probes (20 and 30 MHz), (2) radial balloon probes (20 MHz), and (3) convex probe or curvilinear EBUS (CP-EBUS). Each of these is discussed in greater detail later.

■ ULTRAMINIATURE RADIAL PROBES

Ultraminiature EBUS (UM-EBUS) was developed to allow for improved assessment and sampling of peripheral pulmonary lesions (Fig. 35-1A). There are two ultraminiature radial probes currently available, with diameters of 1.4 and 2.0 mm, allowing insertion into bronchoscopes with working channels of 2.0 and 2.6 mm, respectively. When a lesion is reached with the probe, the usual normal lung "snowstorm" appearance is replaced by a focal ultrasound alteration that can be marked by fluoroscopy, a guide sheath (GS), or both fluoroscopy and GS (Fig. 35-1B and Video 35-1). After the lesion is localized, the GS can be left in place, allowing for guided biopsies of the lung using forceps, brush, or needle biopsy.

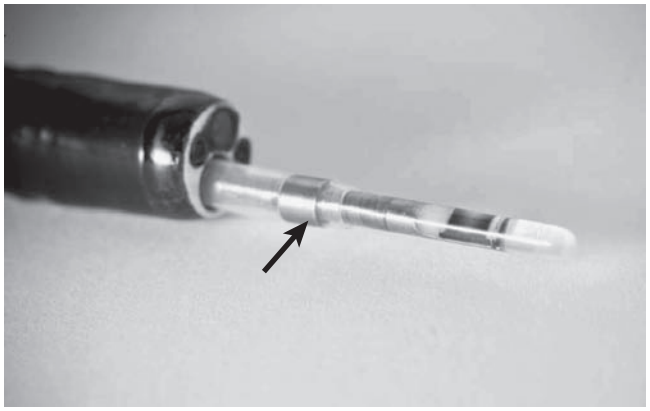
■ RADIAL BALLOON PROBE

To overcome the ultrasonographic coupling problem with UM-EBUS probes in the central airways, a radial EBUS probe was developed; the probe is inserted into an outer sheath with a distal tip balloon. The balloon is filled with saline to provide a fluid medium to allow for sound wave transmission from the probe to the airway wall. The radial balloon EBUS (RB-EBUS; Olympus Corporation, Tokyo, Japan) probe provides <1-mm resolution with a 360-degree visualization of paratracheal and peribronchial structures (Fig. 35-1). Five to seven layers of the tracheal and proximal bronchial wall have been described using RB-EBUS.[5]

■ CONVEX PROBE EBUS

The convex probe EBUS (CP-EBUS) bronchoscope, introduced in 2005, has a built-in curvilinear ultrasound transducer with a

Video 35-1 The ultraminiature (UM)-EBUS probe is used via the working channel of a fiberoptic bronchoscope to identify a focal lung lesion. When the lesion is reached with the probe, there is an alteration in the ultrasound image, with replacement of the usual normal lung "snowstorm" appearance by the presence of a denser focal lesion that surrounds the centrally located probe. *Access at www.fishmansonline.com*



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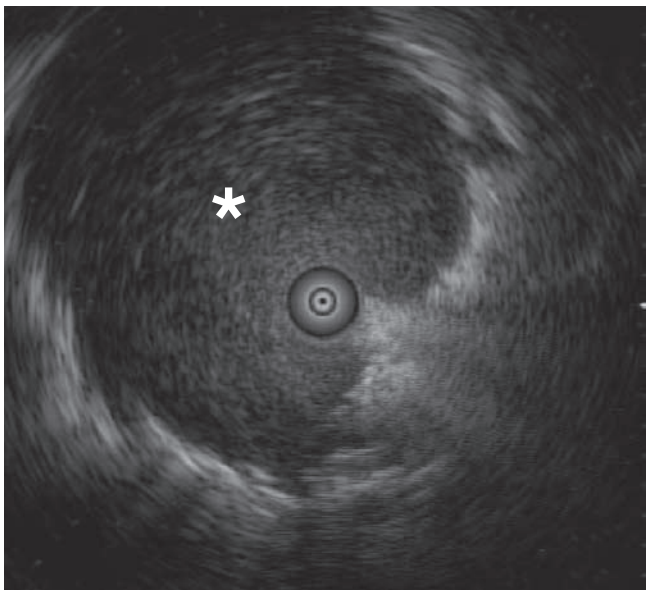


B

Figure 35-1 **A.** The ultraminiature (UM)-EBUS probe contains a circulating ultrasound crystal that provides a 360-degree view of the surrounding structures when full airway ultrasonographic coupling occurs. The probe is inserted through a guide sheath (*arrow*; Olympus Corporation, Tokyo, Japan), which can remain in the airway on UM-EBUS probe removal to allow for instrument guidance for biopsy. **B.** This UM-EBUS image demonstrates a focal lung lesion *(asterisk)* surrounding the probe.

larger distal diameter (6.9 mm) compared with a standard bronchoscope. White light videobronchoscopy occurs at a 35-degree oblique angle with EBUS at 90 degrees from the longitudinal axis. Dedicated biopsy needles (21 or 22 gauge) are inserted through the 2-mm working channel to perform aspirations of the target lesion (Fig. 35-2A). Real-time EBUS imaging displays needle penetration through the tracheobronchial wall into the target during the biopsy maneuver (Fig. 35-2B). If there is difficulty in achieving adequate EBUS images because of poor ultrasonographic coupling, a saline-filled balloon surrounding the transducer can be used to improve image quality. In addition, Doppler capabilities allow vascular structure differentiation, which minimizes the risk of unintended vascular puncture.

NAVIGATIONAL BRONCHOSCOPY

A recent advance in the evaluation of peripheral pulmonary lesions and mediastinal and hilar adenopathy has been the development of navigational approaches, such as electromagnetic navigational bronchoscopy (EMB) and virtual bronchoscopy (VB) (Fig. 35-3).[6–9]

EMB utilizes an electromagnetic board to generate a magnetic field around the patient, a magnetic sensor probe, an extended working channel, and three-dimensional integration of CT scan reconstruction and bronchoscopy position. In essence, this system works on the same triangulation principle as a global positioning system and allows the bronchoscopist to direct the FB through the airways to the target.

VB-based approaches utilize virtual navigation by creating a CT scan–based "road map" that can be overlaid onto real-time endoscopic images. Navigational systems can be used in conjunction with ultrathin bronchoscopies combined with radial EBUS probes and GSs to confirm that a lesion has been reached and to maintain the position for acquisition of diagnostic material. The role of navigational bronchoscopy in the evaluation of peripheral pulmonary nodules is discussed later.

In addition to diagnostic indications, navigational bronchoscopy is increasingly used for targeted cancer therapeutic delivery, including guided stereotactic radiosurgery, fiducial placement, or implantation of radiotherapy monitoring devices.[10,11]

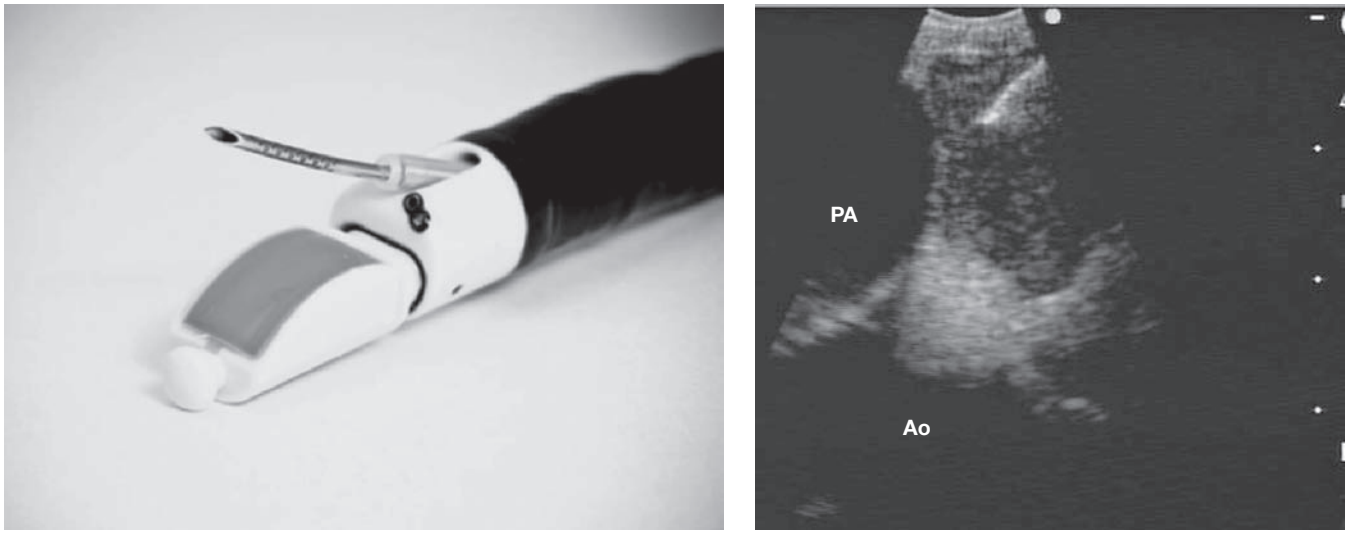
Navigational bronchoscopy systems may be limited in general application by their high capital cost and training necessary for optimal system utilization. At the current time, the greatest experience and yield with these technologies has occurred in centers of excellence, with results unlikely to be reproducible in less experienced centers.

PATIENT PREPARATION AND MONITORING DURING BRONCHOSCOPY

Success of bronchoscopy, whether diagnostic or therapeutic, depends, in large part, on proper preparation of the patient, including relief of anxiety, muscle relaxation, cough suppression, and adequate anesthesia. Time spent in achieving these goals will be well worth it in reducing the risks of complications and in increasing the ease of performance of the procedure. As with any other procedure, analysis of the risk–benefit ratio helps reduce the complication rate. During and shortly after the procedure, appropriate monitoring of hemodynamic parameters (heart rate, rhythm, and blood pressure), oxygenation, and ventilation contributes to the safety of bronchoscopy.

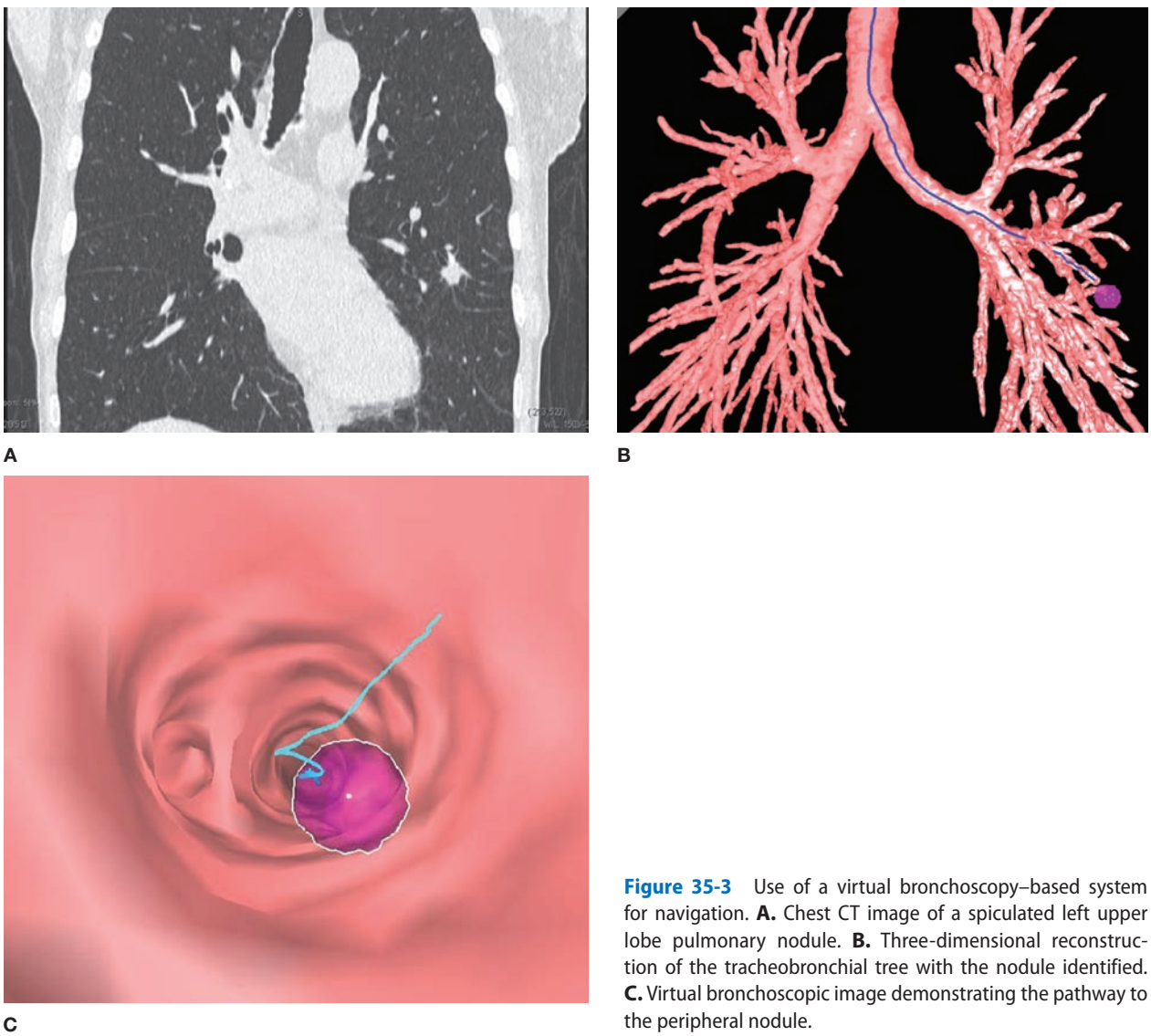
Most flexible bronchoscopies are performed after patient premedication with sedative agents and the use of bronchoscopically instilled lidocaine for local anesthesia of the upper airway, larynx, and tracheobronchial tree. Most frequently, moderate sedation is achieved using a combination of a short-acting benzodiazepine (e.g., midazolam) and a narcotic agent (e.g., fentanyl). Intravenous propofol may also be used to provide moderate sedation and appears to provide similar results in terms of patient satisfaction and degree of hypoxia, with the advantage of a faster recovery time.[12] Because the use of propofol can lead to deep sedation, it is important that these patients receive careful monitoring. Deep sedation (i.e., a deeper state of depressed consciousness with potential for compromised airway function and spontaneous respiration) and general anesthesia are increasingly being employed given the shift of diagnostic and therapeutic bronchoscopy toward more complex and lengthier diagnostic procedures.

Anticholinergic medication (e.g., atropine or glycopyrrolate) has been advocated by some to reduce the risk of vasovagal reactions and to minimize airway secretions, thereby allowing for better examinations of the tracheobronchial tree. However, in a large randomized trial comparing these two drugs with placebo, glycopyrrolate, but not atropine, led to a reduction in airway secretions.[13] There was no significant reduction in cough, patient discomfort, oxygen desaturation, or procedure time with either drug. Current recommendations discourage the use of these agents during bronchoscopy.[12]



A B

Figure 35-2 **A.** The convex probe (CP)-EBUS TBNA (BF-UC160 F-OL8; Olympus Corporation, Tokyo, Japan) videobronchoscope has an integrated ultrasound probe that scans 90 degrees perpendicular from the longitudinal axis, a 35-degree forward oblique video view, and a 2.0-mm working channel through which a dedicated biopsy needle can be passed. Distal tip dimples on the needle provide an echogenic surface to reflect ultrasound waves to allow needle visualization. **B.** This CP-EBUS image demonstrates a left paratracheal lymph node with the ascending aorta (Ao), the pulmonary artery (PA), and the needle present in the lymph node.



A B C

Figure 35-3 Use of a virtual bronchoscopy–based system for navigation. **A.** Chest CT image of a spiculated left upper lobe pulmonary nodule. **B.** Three-dimensional reconstruction of the tracheobronchial tree with the nodule identified. **C.** Virtual bronchoscopic image demonstrating the pathway to the peripheral nodule.

BRONCHOSCOPY TECHNIQUE

Central components of the routine bronchoscopic technique are discussed later.

■ ASSESSMENT OF AIRWAY ANATOMY AND FUNCTION

Thorough bronchoscopic evaluation begins with examination of the upper airways. Special attention should be paid to the integrity of air passages and the function of the nasopharynx and larynx. The vocal cords should be examined for the presence of polyps and tumors and for evidence of cord paralysis.

Once upper airway inspection is completed, a systematic evaluation of the lower respiratory tract should be performed. Critically important is the distinction among normal anatomy, anatomic variations without clinical significance, and frankly pathological conditions. These considerations have important implications regarding potential diagnostic and therapeutic approaches. For example, finding an abnormal branching of a bronchus may be of no clinical significance. On the other hand, such an abnormality could explain symptoms of frequent infections due to impaired ventilation and drainage of the affected area. Special skills and observational experience are required for bronchoscopic examination after surgery, especially following creative bronchoplastic procedures or lung transplantation.

Assessment of airway integrity, with special attention to dynamic changes in airway caliber during either relaxed breathing or forced expiration and coughing, may be crucial in determining appropriate therapeutic maneuvers. Flexible bronchoscopy is superior to rigid bronchoscopy for this assessment. Relaxation and prolapse of the membranous portion of the trachea and main bronchi secondary to destruction of elastic connective tissue may account for exacerbations of expiratory airflow obstruction. On the other hand, finding localized, posttraumatic chondromalacia has very different therapeutic implications. On the basis of these bronchoscopic determinations, the choice of performing an open surgical approach or bronchoscopic therapeutic correction may be made.

Bronchoscopic examination generally permits evaluation and localization of congenital or postsurgical pathological changes in bronchial integrity, such as tracheoesophageal or bronchopleural fistulas. Bronchoscopic observation and early diagnosis of bronchial rupture after chest trauma also greatly influence further therapy and prognosis. The same is true for evaluation of postsurgical anastomoses following reconstructive surgery or lung transplantation.

Advances in airway management of critically ill patients who require prolonged intubation or tracheotomy have resulted in a lower incidence of tracheal injuries. Tracheal injuries documented by bronchoscopy are not rare, however. Important complications of tracheotomy include tracheal stenosis, tracheomalacia, and tracheoinnominate artery fistula. Complications specific to the use of percutaneous tracheotomy, which is increasingly used in the intensive care unit, include flaps of cartilage protruding into the tracheal lumen and extraluminal placement of the tracheostomy tube. Such complications can have significant bearing on clinical outcome.

■ EVALUATION OF TRACHEOBRONCHIAL MUCOSA

Careful examination of the mucosal surface is crucial in the formulation of differential diagnosis. Rapid development of granulation tissue is frequently associated with reaction to a foreign body. Inflammatory mucosal reactions, although not very characteristic, should raise the possibility of mycobacterial infection, nonspecific viral and nonviral infections, and other granulomatous diseases, such as sarcoidosis.

The distinction between normal, pale-pink mucosa and hypervascular areas in the tracheobronchial tree may provide important diagnostic clues. Most frequently, changes in mucosal coloration are associated with an inflammatory reaction due to bronchitis. These findings are, however, very distinctive from small hemangiomas or vascular distentions due to compression by enlarged, neoplastic lymph nodes. Similarly, a network of small mucosal lymphatics may be visible, with lymphatic interruption due to surgery, radiation therapy, fibrosis, or malignancy. This is most frequently associated with local edema, which contributes to airflow obstruction. In addition, distinct and characteristic mucosal discoloration can be observed in Kaposi sarcoma.[14–16]

Video 35-2 White light and autofluorescence bronchoscopy (AFB) demonstrating a focal airway lesion at the carina between the lingua and superior division of the left upper lobe. The lesion demonstrates abnormal autofluorescence, manifested by a brownish color on AFB. The remainder of the airway examination demonstrates normal green fluorescence. *Access at www.fishmansonline.com*

Ulcerations of the mucosa are more characteristic of Wegener granulomatosis or malignancy. Loss of the usual mucosal luster and presence of a roughened surface may alert the expert bronchoscopist to an early infiltrative or neoplastic process. Previously sustained injuries are characterized by the formation of mucosal and submucosal fibrosis, resulting in airway retraction or distortion.

Autofluorescence bronchoscopy (AFB) permits observation and analysis of tracheobronchial mucosal surfaces using the discriminant characteristic of tissue autofluorescence (Video 35-2). It is well known that when stimulated with light of a specific wavelength, normal tissues emit specific fluorescence. Changes in the structural integrity of the same tissues due to pathological processes modify or suppress the autofluorescence. The fluorescent emissions are too low in intensity to be seen by the human eye. With the use of a monochromatic light source, computer-controlled image analysis, and a sophisticated camera attached to a fiberoptic bronchoscope, the airways can be examined for varying degrees of autofluorescence as an indicator of early-stage malignant changes. The acquisition of images is obtained in real time and helps in the detection of minute areas of change in normal tracheobronchial mucosal fluorescence. Biopsies from areas of abnormal fluorescence increase the rate of detection of small, premalignant (dysplasia) or early malignant (carcinoma in situ) lesions in the tracheobronchial tree. Confirmation is provided by biopsy of the suspect or abnormal areas under direct bronchoscopic control, followed by pathological review.

Although AFB may provide the ability to localize these early lesions with greater sensitivity than white light bronchoscopy (WLB),[17–20] longitudinal studies demonstrate that only 0% to 9% of moderate dysplastic foci and 0% to 32% of severe dysplastic foci progress to CIS or invasive cancer,[21–23] and 60% to 65% of moderate/severe dysplastic lesions regress or resolve spontaneously.[21] The uncertainty of the natural history of central airway dysplastic lesions, combined with the increasing incidence of peripheral adenocarcinomas not accessible to bronchoscopic visualization, makes it unlikely that AFB will find a role as a routine screening tool for lung cancer in large populations.

Narrow band imaging (NBI) uses a unique filter to select light wavelengths that preferentially are absorbed by hemoglobin, thereby permitting superior microvasculature detection. Because angiogenesis occurs preferentially in dysplastic and neoplastic lesions, NBI may identify early dysplastic lesions better than WLB or AFB. Early studies with NBI in high-risk patients demonstrated its ability to detect lesions that could not be visualized by WLB, with a similar sensitivity to AFB.[24,25] A recent study compared WLB, AFB, and NBI in the same patients who presented for airway surveillance and revealed similar sensitivity for AFB and NBI, but improved specificity with NBI for detecting abnormal lesions.[24] Although current clinical applications for AFB and NBI are limited, they may play a role in future risk stratification, prognostication, or chemoprevention trials in high-risk patients.

Video 35-3 This video demonstrates the findings on "alveoloscopy" using a confocal microscopy probe (Cellvizio™, Mauna Kea Technologies, Paris, France). A thin probe is advanced into the distal lung parenchyma through the working channel of a flexible bronchoscope and is able to image autofluorescence of structures of the lung. In particularly, elastin in the alveolar wall is readily detected, and therefore allows for visualization of the architecture of the alveolus, including areas of breakdown in the alveolar wall as may be seen in emphysema. In addition, intra-alveolar macrophages emit significant autofluorescence and are therefore readily visualized with the Cellvizio™ probe. These are the cells seen to be mobile within the elastin-containing alveolar walls on the video. Type I and type II pneumocytes are not readily visualized with this technology. *Access at www.fishmansonline.com*

Another promising technique, optical coherence tomography (OCT), is analogous to ultrasound imaging except that infrared light waves, rather than acoustic waves, are used.[26–31] By using light instead of sound waves, OCT overcomes the major limitations of ultrasound in the lung: The inability to image through air and its poor spatial resolution. At present, OCT can resolve structures as small as 3 μm, rendering this imaging technique superior to conventional CT or magnetic resonance imaging for detecting microscopic airway abnormalities. The ability to acquire such precise views in real time may have important clinical implications in the near future.[32,33] A similar modality, fibered confocal fluorescence microscopy (FCFM) is based on confocal microscopy that allows thin section imaging via use of a flexible fiberoptic miniprobe that can be introduced through a fiberoptic bronchoscope. This technology does not rely on light reflectance as in OCT, but rather cellular and tissue autofluorescence upon laser excitation. This technique may offer the possibility of an "optical biopsy" of peripheral lung lesions in the future (Video 35-3).

EVALUATION OF PERIBRONCHIAL STRUCTURES

The trachea and bronchi are surrounded by mediastinal and parenchymal structures. Developmental or pathological changes in these organs may be noted during bronchoscopic evaluation. An enlarged goiter or thymus can compress upper airways, resulting in airflow obstruction. Lymphadenopathy may produce structural changes, including widening of the carina due to subcarinal involvement and compression of other bronchi—as, for example, in the right middle lobe syndrome. Calcification of peribronchial lymph nodes may result in erosion of the bronchial wall and formation of a broncholith. These lesions are potential sources of obstruction, infection, or dangerous hemoptysis.

Development of the techniques of standard TBNA and EBUS-TBNA provide diagnostic options for the evaluation of peribronchial structures that pose much less risk and a lower complication rate than mediastinoscopy; in addition, they are less costly.

PERFORMANCE OF BRONCHIAL AND PARENCHYMAL BIOPSIES

Improvements in bronchoscopic instrumentation since the days of Chevalier Jackson have permitted performance of endobronchial biopsies, as well as biopsy of peripheral lung lesions. Knowledge of the underlying disease process has a significant influence on the choice of specific diagnostic procedures and risk of complications. In the case of diffuse lung diseases, such as sarcoidosis, use of fluoroscopy has not been demonstrated to improve the diagnostic yield of transbronchial biopsies (TBBs). Fluoroscopy is useful, however, in providing information regarding the proximity of the forceps to the pleura and in more rapidly establishing the diagnosis of complications (e.g., pneumothorax).

Bronchoscopically visible lesions are generally biopsied with minimal risk; if bleeding occurs, it can usually be controlled easily

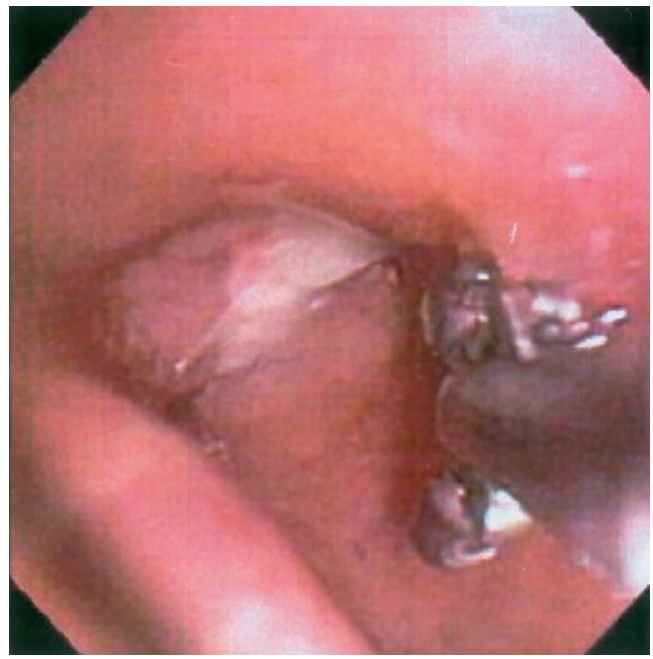


Figure 35-4 "Hot" forceps biopsy of a vascular endobronchial lesion. Use of the electrocautery forceps allows for safe, hemostatic biopsy of friable or vascularized endobronchial lesions (such as bronchial carcinoids), while obtaining pathologically interpretable tissue biopsy specimens.

(Fig. 35-4). The diagnostic yield of bronchoscopy for peripheral lesions depends on a number of factors, including lesion size, its location in the lung, and on the relationship between the lesion and bronchus. The presence of a bronchus sign on chest CT predicts a much higher yield of bronchoscopy for peripheral lung lesions. In these cases, fluoroscopy is mandatory to assure proper positioning of the cytology brush, biopsy forceps, or needle. An exciting new area is the potential application of radial EBUS in evaluation of peripheral pulmonary nodules. Radial probe EBUS allows for acquisition of diagnostic tissue via TBB performed with fewer passes; it may permit differentiation between benign and malignant nodules based entirely on nodule architecture. In the future, peripheral EBUS nodule characterization may even obviate the need for pathological diagnosis in certain patients with suspicious nodules.

The diagnosis of various infectious diseases can be established using a variety of transbronchoscopic sampling techniques. The role of bronchoscopic biopsy has been reaffirmed in immunocompromised hosts, in whom documentation of the precise pathogen is crucial for appropriate therapy. For example, while the presence of cytomegalovirus (CMV) in bronchoalveolar lavage (BAL) fluid may not be diagnostic, documentation of intracellular inclusion bodies on a biopsy specimen is practically pathognomonic. Simple, cost-effective transbronchoscopic tissue sampling can obviate much more complicated, expensive, and higher-risk thoracic surgical procedures.

SAMPLING OF AIRWAY AND ALVEOLAR CONSTITUENTS

Bronchoscopy provides easy and relatively safe access to material in the tracheobronchial tree and distal alveolar spaces. A variety of studies are routinely performed on specimens obtained from the airways and alveolar spaces using several techniques. For example, aspirated secretions can be sent for microscopy and culture to determine the offending organism in cases of infection or suspected infection. Cytological analysis of bronchoscopically obtained materials can provide proof of malignancy. With the advent of lung transplantation, the success of the procedure depends, in large measure, on the early diagnosis of rejection or infection in these immunocompromised

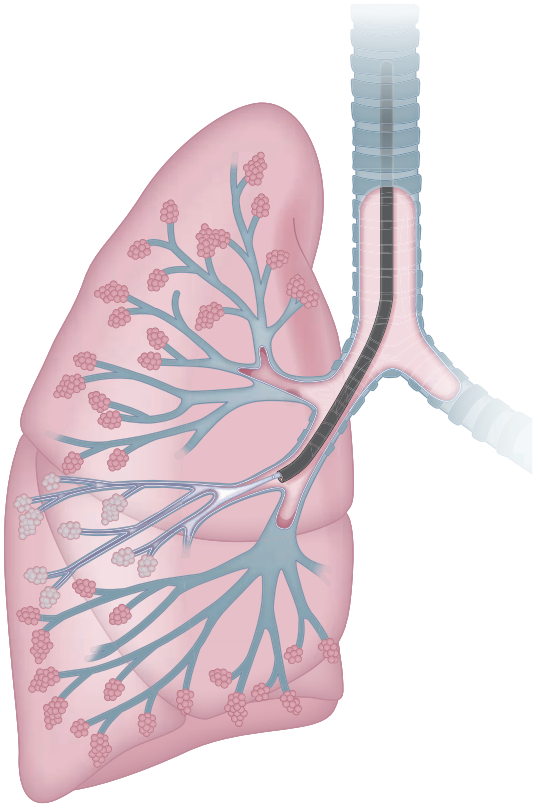


Figure 35-5 Bronchoalveolar lavage is performed by wedging the tip of bronchoscope in the segmental bronchus of interest. Normal saline is instilled into the distal air spaces, and then collected by suctioning back into a sterile container.

subjects. The most commonly employed bronchoscopic techniques for sampling the airways and alveolar spaces include "bronchial washing," bronchial brushing, and BAL.

■ BRONCHOALVEOLAR LAVAGE

A very useful bronchoscopic technique is BAL.[34,35] BAL is safe, even in critically ill patients, when biopsy or brushings may be contraindicated because of the risk of bleeding. Normal saline solution, devoid of any bacteriostatic material, is instilled into distal air spaces through the "wedged" bronchoscope and then aspirated through the instrument's suction channel (Fig. 35-5). The fluid collected in this manner is analyzed for gross appearance to detect possible alveolar hemorrhage. The fluid may also be subjected to a variety of tests, depending on the clinical circumstances: Microbiological testing, specific cytological analysis and cell count, immunological parameters, presence of various biochemical mediators related to pathological processes, tissue markers, polymerase chain reaction, electron microscopy, flow cytometry, and DNA probes.

Overall, the diagnostic yield of BAL is very much dependent on specific patient characteristics, underlying pathological process, and many technical factors.

INDICATIONS FOR DIAGNOSTIC BRONCHOSCOPY

Although there are several indications for diagnostic bronchoscopy (Table 35-1), evaluation of a lung nodule or mass and mediastinal staging of a lung cancer are the most common. There are many other potential indications, some of which are discussed subsequently.[36]

■ BRONCHOGENIC CARCINOMA

Bronchoscopy plays a central role in the evaluation of lung masses and nodules, including those suspicious for bronchogenic carcinoma.

TABLE 35-1 Indications for Diagnostic Flexible Bronchoscopy

Signs and symptoms
Hemoptysis
Stridor
Unilateral wheezing
Hoarseness
Unexplained chronic cough
Infections
Pneumonia in immunocompromised host
Nonresolving pneumonia
Cavitary lesion
Diffuse lung disease
Interstitial lung disease
Diffuse alveolar damage and hemorrhage
Drug-induced lung disease
Malignancy
Lung nodule or mass
Endobronchial tumor
Suspected airway invasion by adjacent malignancies (e.g., esophagus or thyroid)
Early detection (positive sputum cytology/negative CT scan)
Mediastinal or hilar lymphadenopathy or mass
Mediastinal staging or restaging
Other airway disorders
Mucus plugging
Foreign body aspiration
Benign airway stricture (e.g., idiopathic, granulomatosis with polyangiitis [formerly known as Wegener granulomatosis], sarcoidosis, or tuberculosis)
Intensive care
Bronchoscopy-guided intubation (difficult airway)
Endotracheal tube position
Miscellaneous
Lung transplant
Bronchopleural fistula
Aerodigestive fistula
Chest trauma
Chemical/thermal injury of airways
Preoperative and postoperative for lung resection surgery

Source: Reproduced with permission from Casal RF, DE Ost, GA Eapen. Flexible Bronchoscopy. Clin Chest Med. 2013;34(3):341–352.

Diagnosis

Bronchoscopy most commonly is performed in the evaluation of patients with suspected lung cancer. It remains the most commonly used modality for the diagnosis of bronchogenic carcinoma and plays an important role in staging of the disease, as well. Centrally located lesions generally may be approached using flexible bronchoscopy with minimal risk. Bronchogenic carcinoma of the central airways may manifest as exophytic mass lesions with partial or total bronchial lumen occlusion, as peribronchial tumors with extrinsic compression of the airway, with submucosal tumor infiltration, or with some combination of these entities. The mucosal abnormalities seen with peribronchial tumors or with submucosal infiltration often are subtle—the airways should be examined closely for

Video 35-4 Demonstrated in this video is the utilization of a standard 22-gauge Wang™ transbronchial aspiration needle (MW-122, ConMed, Utica, NY) for sampling of a partially necrotic endobronchial lesion in the right main stem bronchus. The advantages of bronchoscopic needle aspiration of endobronchial lesions include decreased bleeding risk compared to endobronchial biopsy or brushing; facilitation of sampling of material from the center of the lesion avoiding necrotic surface; and the ability to obtain real-time feedback through rapid on-site evaluation (ROSE) of aspirates by cytopathology. *Access at www.fishmansonline.com*

characteristic changes such as erythema, loss of bronchial markings, and nodularity of the mucosal surface.

Central lesions usually are sampled using a combination of bronchial washes, bronchial brushings, and endobronchial biopsies. The yield of bronchoscopy is highest for endoscopically visible lesions, with a diagnostic yield of approximately 90%.[37] Attempts should be made to obtain biopsy specimens from areas of the lesion that seem viable. Endobronchial needle aspiration (EBNA) to obtain a "core" biopsy from centrally located tumors should be considered, particularly if the lesion appears necrotic (Video 35-4). For submucosal lesions, EBNA can be performed by inserting the needle into the submucosal plane at an oblique angle; in patients with peribronchial disease causing extrinsic compression, the needle should be passed through the bronchial wall into the lesion. For all of these indications, EBNA has been shown to increase the diagnostic yield over conventional sampling methods.

Evaluation of Peripheral Lesions and Lung Nodules

The evaluation of peripheral lesions or lung nodules remains a common dilemma for chest physicians. A balance between pretest probability of a specific diagnosis and the complication risk associated with a biopsy method must be assessed.[38] Surgical biopsy offers a superior yield at the cost of increased cost and morbidity. TTNB has a high yield, but it carries a 15% to 25% risk of pneumothorax.[39–41] Although bronchoscopy has the advantage of a low complication risk, it has been hampered by a significantly lower diagnostic yield than these other modalities.

The yield of flexible bronchoscopy for peripheral pulmonary lesions, defined as lesions that are not visible beyond the segmental bronchi, is significantly lower than for central lesions. The overall sensitivity of standard bronchoscopy, based on studies that used a combination of TBB, cytology brush, BAL, and TBNA is 78% for peripheral disease.[42–58] Success depends on several factors, including lesion size, distance from the proximal airways, and the presence of a bronchus sign. The bronchus sign on CT may reflect the relationship of a tumor with the airway, and it has been categorized into four patterns by Tsuboi[59]: type I, in which the bronchial lumen is patent up to the tumor; type II, in which the bronchus is contained in the tumor mass; type III, in which the bronchus is compressed, narrowed, and displaced by the tumor, but the bronchial mucosa is intact; and type IV, in which the proximal bronchus is narrowed by the submucosal and peribronchial spread or tumor or by the enlarged lymph nodes (Fig. 35-6). TBB has the lowest diagnostic yield for lesions with a type III or IV tumor–bronchus pattern. In these cases, the use of peripheral TBNA may improve the overall diagnostic yield of bronchoscopy.

A recent study evaluating the use of conventional diagnostic bronchoscopy for screen-detected nodules demonstrated a diagnostic yield of only 13.5%, with a negative predictive value of 47.6%.[60] Given this poor performance, conventional bronchoscopy should not be performed in the evaluation of small, peripheral pulmonary nodules.[39,54] The use of guided bronchoscopic approaches (e.g., navigational bronchoscopy, UM-EBUS, or ultrathin bronchoscopy) has significantly improved the diagnostic yield of small, peripheral pulmonary

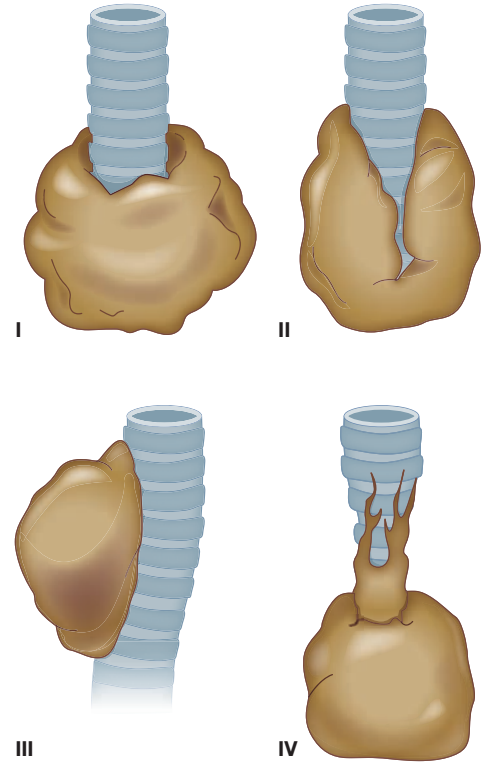


Figure 35-6 Tsuboi classification of tumor–bronchus relationship. (see text for details)

lesions. In a randomized comparison of traditional, fluoroscopically guided TBBs versus UM-EBUS–guided TBB, no statistical difference was found in establishing a diagnosis for lesions greater than 3 cm; however, for lesions smaller than 3 cm and for lesions smaller than 2 cm, the sensitivity of EBUS-guided TBB remained at 75% and 71%, whereas that of standard TBB fell dramatically to 31% and 23%, respectively.[61] Similar improvements have also been reported with the use of EMB- or VB-based systems for peripheral pulmonary lesions.

A recent meta-analysis of 30 studies with >3000 nodules reported a combined diagnostic yield of 70% for all available guided bronchoscopic techniques.[62] The diagnostic yield was influenced by the size of the primary lesion, with a yield of 61% for lesions <2 cm and 82% for lesions >2 cm.[62] Several other factors have also been described that impact the likelihood of obtaining diagnostic tissue using guided bronchoscopy: Ability to place UM-EBUS probe completely within a lesion (as opposed to adjacent to it), presence of a bronchus sign on CT scan, location in the middle lobe or lingula, and distance from the visceral pleura.[63–66] The use of TBNA in addition to conventional diagnostic procedures (TBB and BAL) in UM-EBUS–localized lesions also significantly improves diagnostic yield.[67]

Although it is increasingly clear that guided approaches are better than conventional bronchoscopy for smaller lesions, there are few comparative studies guiding the selection of a particular modality. In one randomized study of EMB alone, UM-EBUS alone, or EMB followed by confirmatory UM-EBUS, there was a significantly higher yield with the combined approach (combination, 88%; UM-EBUS, 69%; EMN, 59%),[68] suggesting that the highest yield may come from combined diagnostic modalities. However, a recent randomized study comparing ultrathin bronchoscopy with and without VB did not demonstrate any significant difference in the overall diagnostic yield (67% vs. 60%), although VB-assisted bronchoscopy was better for lesions in the RUL, lesions invisible on plain films, and lesions in the peripheral third of the lung.[69] Further studies are needed to help define the utility and specific indications for combination approaches for the diagnosis of peripheral lung lesions.

Video 35-5 This video demonstrates use of a 22-gauge EBUS-TBNA aspiration needle (Olympus, Center Valley, PA) to sample a left hilar node. The convex probe-EBUS scope is used to identify the left hilar node, allowing visualization of the TBNA needle entering the node in real time. The TBNA needle can be seen entering the left hilar node from the upper left portion of the video. The to-and-fro needle movement allows for collection of lymph node aspirate material. *Access at www.fishmansonline.com*

Staging

Bronchoscopy is an important modality for establishing lung cancer stage. In patients with potentially resectable tumors, a thorough airway examination helps confirm the absence of a concomitant, radiographically occult lesion. For lesions that involve the central airways, it is important to document the extent of disease and the degree of involvement of the main stem bronchi and main carina.

The use of CP-EBUS allows for real-time visualization and TBNA of hilar and mediastinal lymph nodes (Video 35-5). Sampling of lymph nodes using EBUS-TBNA is now commonly performed for nodal staging in patients with lung cancer. This technique frequently allows the establishment of both diagnosis and nodal stage, obviating the need for, and avoiding the risks associated with, sampling of the primary parenchymal lesion. TBNA has proved particularly useful with the employment of rapid on-site evaluation (ROSE), in which a cytopathologist present in or near the bronchoscopy suite can evaluate specimens in real time.

In general, patients with lung cancer may be separated into four categories with respect to intrathoracic radiographic characteristics, as suggested by the American College of Chest Physicians (ACCP) guidelines on lung cancer staging (Fig. 35-7).[70] In radiographic pattern A, mediastinal infiltration is extensive, with encircling of vessels and airways. In this case, the risk of malignant involvement can be assumed, and biopsy to establish diagnosis should be performed by the safest method available for that particular case. In pattern B, there is discrete lymph node enlargement that can be measured by CT, which may also be FDG-avid. In this case, sampling is recommended as the likelihood of mediastinal involvement is high and requires confirmation. In radiographic pattern C, the presence of a central tumor or suspected N1 disease makes the likelihood of mediastinal node involvement relatively high (20%–25%), necessitating invasive sampling. In the final group (i.e., those with a

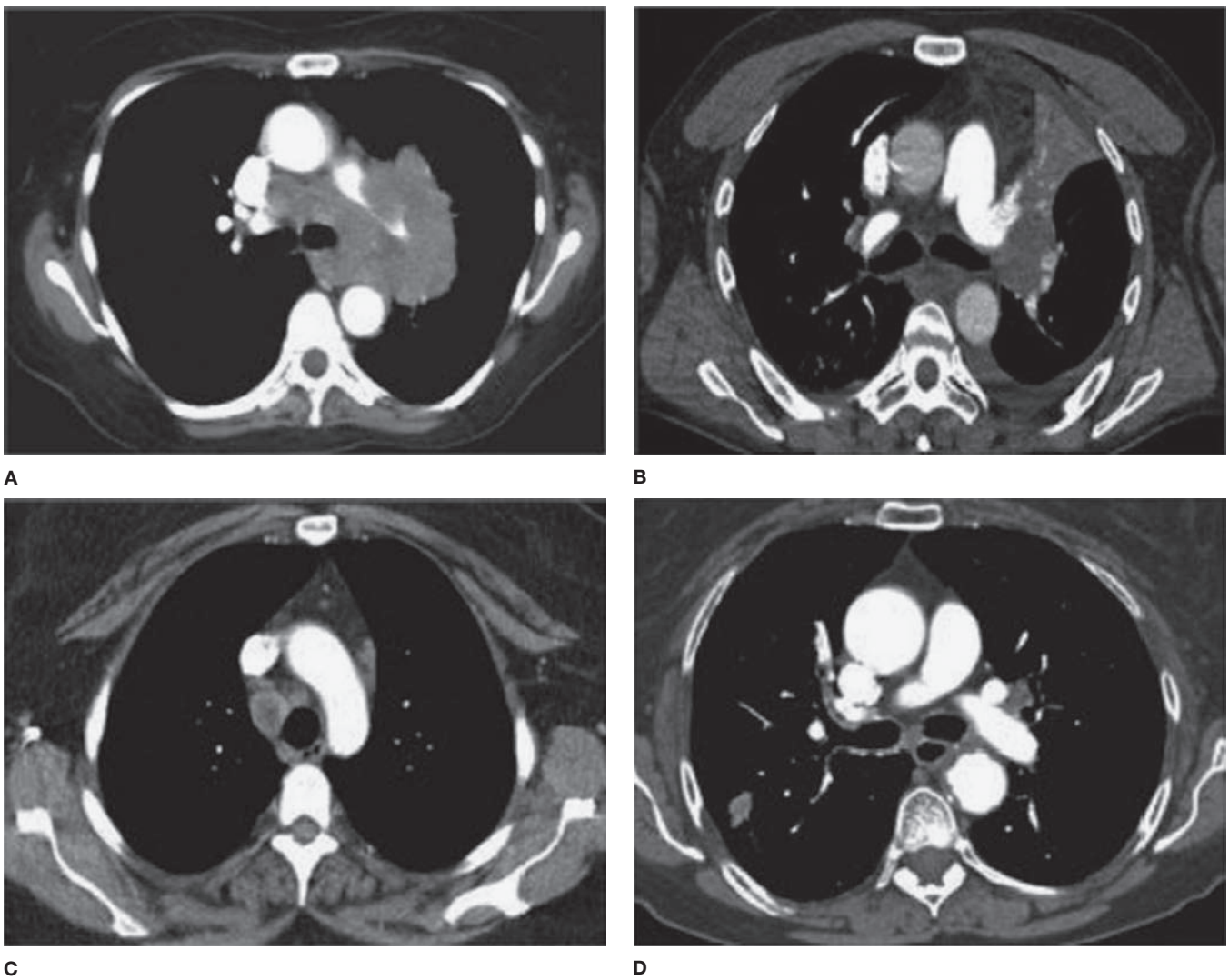


Figure 35-7 American College of Chest Physicians intrathoracic radiographic (CT scan) categories of lung cancer. **A.** Mediastinal infiltration by tumor. **B.** A central tumor or a tumor with enlarged N1 nodes, but a normal mediastinum. **C.** Enlarged discrete N2,3 nodes. **D.** A peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes. *(Reproduced with permission from Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S–250S.)*

peripheral clinical stage I tumor), the chance of either distant metastases or mediastinal involvement is quite low (radiographic group D), especially if the mediastinum is also normal by positron emission tomography (PET) scan. The decision to pursue invasive staging should be considered on an individual case basis.

Several systematic reviews have confirmed that the sensitivity of EBUS-TBNA is equivalent to that of mediastinoscopy.[70–73] A recent randomized study of 241 patients with potentially resectable NSCLC compared mediastinoscopy alone to a combined approach of EBUS-TBNA and EUS-FNA, followed by surgical staging if the needle technique did not identify nodal metastases.[74] The needle approach followed by mediastinoscopy resulted in a significantly greater sensitivity (94%) compared to the other approaches and resulted in fewer unnecessary thoracotomies. One limitation to this approach has been the difficulty in many centers to operationalize a combined EBUS-TBNA and endoscopic ultrasound (EUS)-FNA procedure. Interestingly, recent studies have shown that the EBUS-TBNA scope can be used through both the airway and the esophagus, resulting in similar results.[75,76] The ACCP guidelines now recommend that a needle approach should be used first when performing mediastinal staging. However, because of a relatively high false-negative rate, a negative result with a needle technique should prompt consideration of surgical staging methods.

EVALUATION OF HEMOPTYSIS

One of the most frequent indications for bronchoscopy is hemoptysis. Bronchoscopic evaluation can be of help in determining the precise location and source of bleeding. The choice of instrument (rigid vs. flexible scope) and timing of the procedure are dictated by clinical circumstances.[77] Studies have shown that active bleeding and its site are visualized more commonly with early bronchoscopy (within 48 hours) than with more delayed examination.[77–79] In the case of a normal chest radiograph and hemoptysis, trace signs of bleeding are commonly seen, but not the site of origin.[80] In these circumstances, examination using an ultrathin flexible instrument may be beneficial in identifying the source of bleeding in a peripheral airway once the more proximal airways have been cleared of blood by a therapeutic scope. In some instances, bronchoscopy is useful not only as a diagnostic method, but also to perform therapeutic maneuvers (see Chapter 36, Interventional Bronchoscopy).

PULMONARY INFECTIONS

Bronchoscopy is a useful technique in the diagnosis of pulmonary infections, allowing for the collection of respiratory samples for evaluation with special stains and culture. Several common clinical areas in which bronchoscopy may play an important diagnostic role are described subsequently.

Pneumonia

In general, bronchoscopy is not indicated for the diagnosis of community-acquired pneumonia, which is currently treated empirically with appropriate antibiotic therapy; however, bronchoscopy is likely to be useful in cases of nonresolving pneumonia,[81,82] defined as a lack of improvement or worsening of symptoms despite a minimum of 10 days of antibiotic therapy or failure of radiographic abnormalities to resolve after 2 to 3 months. The causes of nonresolving pneumonia are myriad and include inadequate antibiotic therapy, resistant or highly virulent organisms, impaired host defenses, obstructing endobronchial lesions, or a noninfectious cause. Although controversial, bronchoscopy should be considered in these patients.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as a pneumonia occurring more than 48 hours after intubation and initiation of mechanical ventilation.[83,84] VAP is usually suspected when an intubated, mechanically ventilated patient has signs of infection and an abnormal chest radiograph. Intubated patients experience colonization of their upper and lower airways with nosocomial organisms; because of an abnormal mucociliary clearance mechanism, these patients are at greater risk for developing pulmonary infections. In addition, mechanically ventilated patients are often treated empirically with broad-spectrum antibiotics and, therefore, are at greater risk for infection with resistant organisms and unusual lower respiratory tract pathogens. Guidelines support the use of either a quantitative or semiquantitative strategy in the diagnosis of VAP.[83] Quantitative sampling can be performed using endotracheal aspirates, or BAL or protected specimen brush (PSB) collected with or without a bronchoscope.[83,85]

Quantitative BAL entails the performance of a standardized BAL, with infusion of at least 120 mL of saline for adequate sampling of a pulmonary subsegment. Quantitative culture of the aspirated material is performed to determine the number of colony-forming units (CFUs) recovered.

PSB uses a double catheter system in which an outer cannula and distal, biodegradable plug protect the bronchoscopic brush within the inner cannula from contamination with secretions in the upper airway and suction channel of the bronchoscope. When the bronchoscope is positioned proximal to the segmental orifice of interest, the PSB inner cannula is advanced into a subsegment and the protective distal plug ejected. The brush is then advanced peripherally, rotated gently, and retracted into the inner cannula. The inner cannula is subsequently retracted into the outer cannula and the bronchoscope removed from the airway. The distal portion of the catheter is cleaned with 70% alcohol and the brush clipped into saline solution under sterile conditions. The PSB is then submitted for quantitative bacterial culture within 15 minutes of performance of the procedure.

The threshold for diagnosis of VAP using PSB is 10^3 CFU/mL. PSB has higher specificity than sensitivity for the presence of VAP—a positive result greatly increases the likelihood that pneumonia is present. For quantitative BAL, a threshold of 10^4 or 10^3 CFU/mL is used for diagnosis of VAP.[86] The detection of VAP by quantitative BAL culture has a sensitivity of 40% to 90% and a specificity of 45% to 100%.[86] Because a larger proportion of lung parenchyma is sampled with BAL, this may be a better method than PSB for VAP diagnosis. However, samples contaminated by upper airway secretions (based on a high percentage of squamous epithelial cells) should be interpreted with caution. There are likely a number of factors that affect the diagnostic yield of the bronchoscopic methods, such as a change in antibiotics before sampling, inadequate technique in sampling, and lack of a gold standard for comparison.

Infections in Immunocompromised Patients

Pulmonary infections in immunocompromised patients constitute the most common complication in this population and represent an important contributor to mortality. Such infections are increasingly common, reflecting the expanding use of aggressive chemotherapeutic regimens and the ever increasing number of solid organ and hematopoietic stem cell transplantations. The differential diagnosis of pulmonary infiltrates is broad in scope; however, most cases are caused by infectious agents, including bacterial, fungal, viral, and mycobacterial pathogens.[87] Bronchoscopy is the most commonly used diagnostic procedure in these patients and should be performed as early as possible, because a delay in diagnosis of longer than 5 days has been shown to significantly increase mortality.

The sensitivity of bronchoscopy varies, depending on the immunocompromised population studied and the specific etiological disorder. In non–human immunodeficiency virus (HIV)-infected patients, the yield of BAL for *Pneumocystis jirovecii* pneumonia (known previously as *Pneumocystis carinii* pneumonia [PCP])

is approximately 80%, compared with a greater than 90% yield observed in HIV-seropositive patients.[88,89] This difference is due to the much lower organism load present in non–HIV-seropositive subjects. Although empirical therapy often is initiated in patients suspected of having PCP infection, bronchoscopy should be performed in most cases to confirm the diagnosis. Bronchoscopic lung biopsy may increase the diagnostic yield of BAL for diagnosis of PCP infection, particularly in the non–HIV-infected population.[88] Bronchoscopy also has a high diagnostic yield for CMV; however, because CMV cultures from BAL are not specific, the diagnosis of CMV pneumonia should be limited to patients with pathological evidence of CMV infection demonstrated by the presence of CMV inclusion bodies on BAL or biopsy. Although bronchoscopy also is useful for the diagnosis of aspergillosis – the sensitivity is approximately 50% – the disease often is peripheral and patchy and, thus, is not easily diagnosed by BAL or bronchoscopic biopsy. Overall, in immunocompromised patients with infiltrates, the diagnostic yield of bronchoscopy varies from 30% to 80% and is impacted by factors such as the prevalence of an infectious etiology, timing of bronchoscopy, and use of prophylactic antibiotics.[90–97]

Mycobacterial Infections

In cases in which pulmonary tuberculosis is suspected, the initial diagnostic evaluation should consist of serial examination of sputum for the presence of acid-fast bacilli in stained smears. Ideally, induced sputum samples should be obtained. If sputum study results are negative, or if a patient is unable to produce sputum and tuberculosis is still suspected, bronchoscopy with BAL and biopsy should be performed. The use of bronchoscopy allows for the opportunity to establish a rapid diagnosis (by positive smear or histopathology), providing the potential for earlier intervention and treatment while awaiting culture results. Bronchoscopy should be performed with appropriate infection control precautions to minimize the risk of nosocomial transmission. A bronchoscopy may cause the patient to produce sputum for several days afterward; these specimens also should be collected and analyzed, if possible.

The utility of bronchoscopy in establishing a rapid diagnosis varies widely in the literature, with reported diagnostic yields of 30% to 70%, although the overall yield of culture is considerably higher.[98] One study has shown an improvement in diagnostic yield from 58% to 81% with use of UM-EBUS–guided biopsy and washings.[99] The yield in patients with miliary tuberculosis, in whom sputum smears frequently are negative, is approximately 70%. Bronchoscopy also is useful in tuberculosis manifesting as an endobronchial lesion or with mediastinal and hilar adenopathy, in which case, diagnostic tissue may be obtained with TBNA.

Human Immunodeficiency Virus Syndrome

The introduction of highly active antiretroviral therapy (HAART) has resulted in a sharp decline in the incidence of opportunistic infections in HIV-infected patients. Nevertheless, infectious complications remain one of the most common indications for bronchoscopy in this population. PCP remains the most frequent serious opportunistic infection in HIV-seropositive patients. Bronchoscopy with BAL remains the preferred diagnostic procedure for this disease, although in select centers, use of sputum induction has had a relatively high diagnostic yield and may mitigate the need for bronchoscopy. As previously mentioned, bronchoscopic lung biopsy may increase the diagnostic yield of BAL.[88] Empirical therapy often is initiated in patients with suspected Pneumocystis infection; such therapy can impair the diagnostic yield of BAL if the procedure is not performed within 24 hours. In patients receiving pentamidine prophylaxis, the diagnostic yield is decreased unless the upper lobes are sampled.[100–102] Several PCR assays have been tested on BAL fluid, induced sputum, and oral wash specimens; these generally have been more sensitive, but less specific, than traditional microbiological methods.

Bronchoscopy also plays an important diagnostic role in HIV-positive patients with infections caused by mycobacteria, including tuberculosis, atypical bacterial pneumonias, and various fungal infections. Kaposi sarcoma, caused by human herpesvirus type 8 (HHV8), can manifest with violaceous endobronchial plaques that typically occur at airway bifurcations; pulmonary parenchymal involvement is characterized by lymphangitic infiltration of tumor, leading to the development of nodules and masses.

DIFFUSE LUNG DISEASES

A wide range of acute and chronic pulmonary disorders are capable of causing a diffuse interstitial lung disease pattern of injury. These processes include infection, neoplasm, pulmonary edema, alveolar hemorrhage, alveolar proteinosis, occupational lung diseases, drug-induced disease, and various types of idiopathic or collagen vascular disease–associated interstitial lung disease. The pattern of lung injury should first be evaluated using high-resolution chest CT imaging, which helps to narrow the differential diagnosis and, in some cases, is virtually diagnostic of certain disorders. In many cases, it is still necessary to obtain samples for cytological and histological evaluation to confirm a specific diagnosis and to help exclude other possible disorders.

The most common bronchoscopic procedures used to help establish the diagnosis in diffuse lung disease are BAL and TBB. The findings on high-resolution CT (HRCT) can be used to determine the best location for BAL or TBB. In truly diffuse disease, the right middle lobe and the lingula are the best locations for BAL; with these sites, ease of access and good fluid retrieval are typical. BAL should be performed using a total of 100 to 200 mL of saline instilled in multiple aliquots. It is important to obtain a reasonable sampling of the alveolar spaces for the necessary cellular analysis.

The value of BAL is well documented in the diagnosis of diffuse parenchymal diseases, and findings may be diagnostic in eosinophilic pneumonia, eosinophilic granuloma, and pulmonary alveolar proteinosis.[36] In most other diffuse disorders, BAL findings are mostly supportive of a suspected diagnosis (Table 35-2) and helps to rule out potential infectious etiologies. In disorders such as sarcoidosis, hypersensitivity pneumonitis, and organizing pneumonia, the use of BAL in combination with bronchoscopic lung biopsy can often establish the diagnosis and avoid the need for surgical lung biopsy. For example, with pulmonary sarcoidosis, the diagnosis usually is established by a combination of BAL and biopsy findings. The BAL can be used to exclude the presence of tuberculosis and fungal infections and may demonstrate the characteristic high CD4+/CD8+ ratio seen in sarcoidosis, whereas bronchoscopic biopsy specimens may demonstrate the classic finding of noncaseating granulomas. In general, TBB should be performed in several affected areas, and at least five or six specimens should be taken. The sensitivity of TBB for diagnosis of sarcoidosis is only approximately 60% to 70%, and many patients require further invasive testing, such as surgical lung biopsy.[103,104]

In patients with mediastinal and hilar adenopathy, needle techniques for lymph node sampling should also be considered, as this can provide diagnostic evidence of noncaseating granulomas in 80% to 90% of cases.[105–110] A recent randomized study showed endosonographic needle approaches to have a greater diagnostic yield when compared with bronchoscopic lung biopsy.[111] The addition of TBNA to TBB results in an improved overall diagnostic yield in suspected cases of sarcoidosis.[105] At present, the data suggest that all patients with suspected sarcoidosis should undergo a needle technique for lymph node sampling, but it is unclear if bronchoscopic biopsy should be performed in all cases, given the added risk of pneumothorax and hemorrhage. The presence of mediastinal and hilar adenopathy, with or without parenchymal lung changes, also

TABLE 35-2 BAL Findings in Diffuse Lung Disease

Diffuse Lung Disease	Typical BAL Cellular Pattern	T lymphocyte CD4/CD8 Ratio	Other Relevant BAL Findings
Sarcoidosis	↑ Total cell count ↑ Lymphocytes	↑	-
Hypersensitivity pneumonitis	↑ Total cell count ↑ Lymphocytes	↓	Neutrophils can be increased with recent exposure to antigen
Chronic beryllium disease	↑ Total cell count ↑ Lymphocytes	↑	BAL lymphocyte proliferation with beryllium salts
Asbestosis	↑ Neutrophils	↑	Ferruginous bodies
Idiopathic pulmonary fibrosis	↑ Neutrophils ↓ Lymphocytes	-	-
Cryptogenic organizing pneumonia	↑ Neutrophils ↑ Lymphocytes	↓	Foamy macrophages
Pulmonary alveolar proteinosis	Variable	-	Milky fluid and foamy macrophages with PAS-positive material
Drug-induced lung disease	Variable	↓	Foamy macrophages with amiodarone exposure
Pulmonary Langerhans cell histiocytosis	↑ Total cell count Variable differential	-	CD1+ Langerhans cells
Eosinophilic pneumonia	↑↑ Eosinophils	-	Eosinophil counts greater in acute than in chronic pneumonia

Source: Reproduced with permission from Casal RF, DE Ost, GA Eapen. Flexible Bronchoscopy. Clin Chest Med. 2013;34(3):341–352.

raises the possibility of lymphoma. In these cases, TBNA samples should also be evaluated with flow cytometry for evidence of clonal proliferation to exclude the possibility of lymphoma.

Bronchoscopy has a limited role in the diagnosis of idiopathic pulmonary fibrosis (IPF).[112] A nonspecific increase in levels of neutrophils, eosinophils, and, less commonly, lymphocytes has been documented in BAL fluid. Histological evidence of IPF generally requires documentation of a number of pathological changes consistent with usual interstitial pneumonia. This is often difficult with bronchoscopic biopsies, which are frequently limited by the small size of the specimen obtained and lack of histological preservation because of mechanical crushing of the tissue. Cryobiopsy may improve the yield of bronchoscopy in IPF, as it allows for increased size of the obtained specimens with increased amounts of alveolated lung parenchyma. In cases in which the diagnosis of IPF is probable or definite on the basis of clinical and HRCT criteria, bronchoscopy (and surgical lung biopsy) is not required. In situations in which the HRCT findings are not atypical for IPF, bronchoscopy can be performed to evaluate for the presence of other potential etiological disorders. If the specific diagnosis cannot be established on the basis of BAL and TBB findings, surgical lung biopsy should be considered.

COMPLICATIONS OF BRONCHOSCOPY

Bronchoscopy is a potentially hazardous procedure. Complications are generally due to inappropriate preparation of patients before bronchoscopy, effects of local or general anesthesia, and manipulation of various instruments. Appropriate training and experience of the bronchoscopist and supporting team are crucial in reducing the rate of complications.

Any diagnostic or therapeutic manipulation should be considered in relation to the underlying condition of the patient, localization of the area of investigation, and other surrounding structures in the thorax. It is essential to develop good communication between the bronchoscopist and other members of the team. While the bronchoscopist concentrates on the field of work – which, as seen through the bronchoscope, is two-dimensional – other team members are responsible for monitoring the patient (oxygen saturation, blood pressure, heart rhythm, etc.) and checking and maintaining the adequacy of ancillary equipment (suction, oxygenation, and accessories such as forceps, balloons, catheters, and laser light guides). Risks are decreased if, for example, special attention is paid to the control of accessories during their manipulation beyond the tip of the bronchoscope. Premature deployment of the needle biopsy device or inappropriate bending of the bronchoscope while an instrument is inside the flexible portion can result in perforation of the bronchoscope. Activation of the laser with a broken light guide inside the bronchoscope or inadequate protrusion of the tip of the fiber beyond the bronchoscope may result in airway fires or severe burns to the patient. Attention to details and proper maintenance of the equipment, including accessories, enhance safety for the patient and staff. Diagnostic yield and therapeutic results are also improved. Overall, when bronchoscopy is performed by an experienced endoscopist, backed up by a well-trained team and appropriate facilities, mortality and morbidity are very low.

■ ANESTHESIA AND RELATED BLOOD GAS ABNORMALITIES

Approximately half of the life-threatening complications of diagnostic bronchoscopy are associated with the risk of topical anesthesia and sedation. Risk is significantly increased in the elderly, and in those with serious concomitant illnesses. Predisposing factors include cardiovascular disease, chronic pulmonary disease, renal and hepatic dysfunction, seizures, and altered mental status. Mild sedation, anxiolysis, muscular relaxation, and anterograde amnesia increase patient cooperation and permit quicker and less traumatic procedures. Doses of benzodiazepines, opiates, propofol, and topical anesthetics must be adjusted if there is underlying organ dysfunction. In the event of severe respiratory depression from excess sedation, flumazenil and naloxone can be administered to reverse the effects of benzodiazepines and narcotics.

Inadequate topical anesthesia potentiates coughing, gagging, and patient discomfort and increases the risk of injury during bronchoscopy. However, topical anesthetics such as lidocaine, the

most frequently used agent, are absorbed systemically through the respiratory mucosa, increasing the risk of cardiac or central nervous system toxicity. Although rare, these complications are more likely to occur in patients with underlying low cardiac output, hepatic dysfunction, and oropharyngeal candidiasis.

Another, less frequent complication of excessive lidocaine use is methemoglobinemia and resultant tissue hypoxia. This condition should be suspected when cyanosis occurs following the procedure in combination with low oxygen saturation, but a higher than expected Pa_{O_2} for the degree of cyanosis, and low oxygen saturation. Sampling of arterial blood reveals chocolate-brown blood. Methemoglobinemia occurs because lidocaine causes the rate of hemoglobin oxidation to exceed the reductive capacity of erythrocytes, leading to accumulation of methemoglobin. The diagnosis of this disorder can be made using co-oximetry. Treatment with methylene blue (1–2 mg/kg body weight) should be administered to symptomatic patients or when methemoglobin levels exceed 30%.

Introduction of the bronchoscope under general anesthesia or under conscious sedation with topical anesthesia frequently results in a decrease in oxygenation and in hypoventilation, with demonstrable increases in Pa_{CO_2}. The mechanism responsible for hypoxemia include acute upper airway obstruction, hypoventilation, and ventilation–perfusion mismatching. In patients with underlying chronic lung disease, severe hypoxemia may occur, triggering life-threatening cardiac arrhythmias. Skillful manipulation of rigid and flexible bronchoscopes reduces the risk of injury to the upper airways, which can result in life-threatening laryngospasm during or after completion of the procedure. Particular caution must be exercised in patients with underlying bronchospastic disorders, superior vena cava syndrome, or history of angioedema.

All patients undergoing bronchoscopic procedures should be monitored continuously (electrocardiogram, blood pressure, O_2 saturation, and, if indicated, expiratory CO_2 concentration). Use of supplemental oxygen during the procedure should be routine. Bronchoscopy probably should not be performed in patients who are unable to maintain adequate oxygenation on full ventilator support with high levels of supplemental oxygen.

Significant oxygen desaturation may occur during BAL. The degree of desaturation is directly related to the duration of the procedure and the volume of lavage fluid used. Return to the prebronchoscopy level of O_2 saturation may be prolonged after removal of the bronchoscope, and supplemental O_2 should be continued throughout the procedure and during the postbronchoscopy observation period.

FEVER AND INFECTION

Appearance of transient fever after bronchoscopy, reported in 5% to 30% of procedures, generally does not require any therapy. The incidence of fever is increased in the elderly, in those with underlying chronic pulmonary disease or documented endobronchial obstruction, and in those with bronchoscopic interventions for malignancy. The incidence of fever and extension of pulmonary infiltrates increase with the volume of BAL fluid and the total number of pulmonary segments lavaged. In most cases, these complications resolve spontaneously within 24 hours. However, persistent fever in the setting of progressive radiographic infiltrates suggests postprocedure pneumonia and necessitates antibiotic therapy. The incidence of postbronchoscopic infections is higher in immunocompromised hosts and those with chronic suppurative lung disease (e.g., cystic fibrosis). There have also been reports of purulent pericarditis and mediastinitis following TBNA of mediastinal nodes or masses.[113,114]

In high-risk cardiac patients, including those with prosthetic valves, prior endocarditis, complicated cyanotic heart disease, or surgically constructed systemic-pulmonary shunts, American Heart Association guidelines indicate that prophylactic antibiotics are optional prior to flexible bronchoscopy.

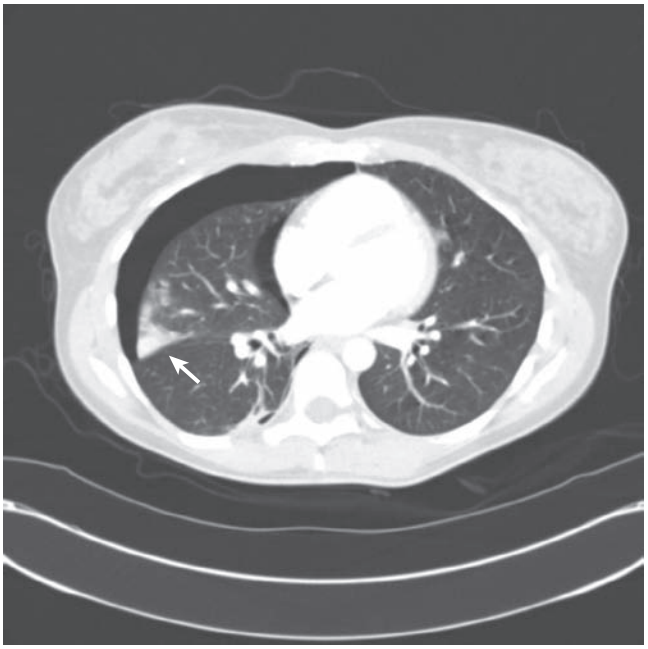


Figure 35-8 CT image demonstrating a pneumothorax of the right lung following transbronchial lung biopsy. An area of focal hemorrhage in the lateral right upper lobe *(white arrow)* as a result of biopsy can also be seen.

PNEUMOTHORAX

Most of the serious complications related to diagnostic bronchoscopy have been reported in association with performance of TBBs. Pneumothorax following TBB occurs in 4% to 5% of cases, (Fig. 35-8) although a recent population-based study suggested pneumothorax rates of approximately 1%.[115–124] The impact of fluoroscopy on the incidence of pneumothorax remains controversial. Uncontrolled studies have not found a difference in the incidence of pneumothorax following TBB when performed with and without fluoroscopy.[125]

The risk of pneumothorax is not related to the size of the bronchoscopic biopsy forceps. The incidence of pneumothorax is increased, however, in immunocompromised hosts. This is likely due to the increased risk of pneumothorax associated with PCP. The risk is also elevated in mechanically ventilated patients, with peripheral lung biopsies, and in the presence of bullous lung disease. For these reasons, a postbronchoscopic expiratory chest radiograph is routinely performed. In rare cases, the development of pneumothorax can be delayed, with patients developing the complication after discharge. In case of a significant pneumothorax, a chest tube should be inserted immediately to avoid oxygen desaturation or tension physiology.

HEMORRHAGE

One of the most frequently reported complications related to bronchoscopy is hemorrhage. Clinically significant bleeding as a consequence of diagnostic bronchoscopy is reported to occur in 1% to 4% of cases, but it is more likely to occur after TBB and brushings.[123,124,126,127] Although hemorrhage may also occur from inadvertent perforation of pulmonary vessels during TBNA, this is a very rare complication. Bleeding is more common in patients with immunosuppressed state, thrombocytopenia, uremia, liver disease, pulmonary hypertension, concurrent anticoagulation, and those on positive pressure ventilation.

The incidence of postbronchoscopy hemorrhage in uremic patients is reported as high as 45%. Consequently, a blood urea nitrogen (BUN) level above 30 mg/dL or a creatinine level above

3 mg/dL should be considered relative contraindications to bronchoscopy. TBB or brushing should not be performed if the platelet count is below 50,000/mm^3. Thrombocytopenic patients may receive platelet transfusions if biopsy is necessary. Similarly, coagulopathic patients should receive vitamin K, fresh frozen plasma, or cryoprecipitate prior to the procedure and biopsy.

Increasingly, patients referred for bronchoscopy are receiving antiplatelet therapy. Importantly, aspirin use has not been shown to increase hemorrhage risk, and it generally does not require discontinuation prior to diagnostic bronchoscopy.[128] In contrast, the risk of bleeding from clopidogrel therapy is very high following TBB.[129] If TBBs are necessary, clopidogrel should be discontinued 5 to 7 days prior to the procedure. We also recommend discontinuation prior to TBNA, although the risk of major bleeding is lower, and successful TBNA can be performed without discontinuation. In cases where clopidogrel therapy cannot be discontinued (e.g., recent coronary artery stenting), careful assessment of the goals of bronchoscopy should be considered and the need for TBB should be clearly defined.

TRANSTHORACIC NEEDLE BIOPSY

TTNB has proved a valuable diagnostic procedure in patients with a variety of thoracic radiographic abnormalities.

■ INDICATIONS AND CONTRAINDICATIONS

TTNB was first used for the diagnosis of pulmonary disease in 1883, when Leyden performed the procedure on three patients with pneumonia. Since that time, many published series have described the use of TTNB for the diagnosis of a variety of benign and malignant thoracic lesions.[130–139] The approach to biopsy may employ either an aspiration approach or an approach based on procuring histological samples with use of cutting needles. The use of histological samples provides improved diagnostic accuracy in lymphoma, both Hodgkin and non-Hodgkin varieties, in which anatomic structure is important in delineating the type of lymphoma, and in distinguishing between clonal, neoplastic processes, and inflammatory conglomerations of lymphocytes. Histological specimens may also improve the yield in the diagnosis of pulmonary hamartomas, characterized by the presence of cartilage or adipose tissue.

The major indications for TTNB include evaluation of solitary lung nodules and masses, (Fig. 35-9) mediastinal and hilar lesions, metastatic disease to the lung from a known extrathoracic malignancy, chest wall invasion by lung carcinoma, and pulmonary consolidation or infiltrates that are likely to be of infectious origin.

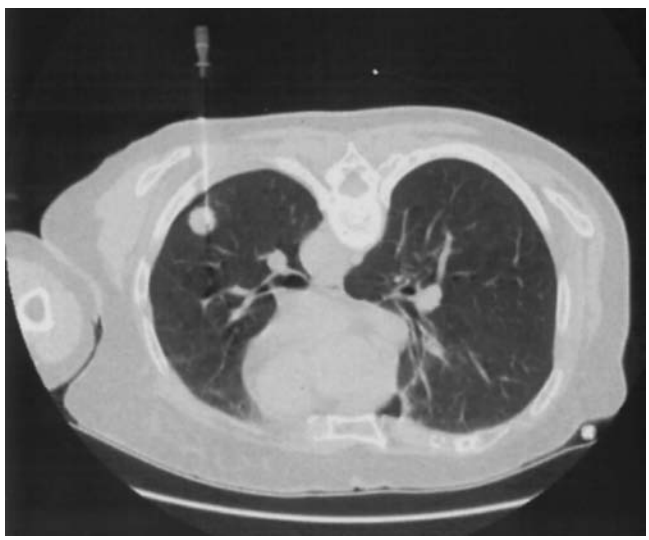


Figure 35-9 Transthoracic needle aspiration of pulmonary nodule. CT scan image of TTNA performed for a 2-cm right lower lobe nodule using a 22-gauge Westcott needle (Becton Dickinson & Co, Franklin Lakes, NJ). The needle can be seen entering the nodule. *(Used with permission of Ana Kolansky, MD.)*

With the "reemergence" of thoracoscopy and development of video-assisted and robotic-assisted thoracic surgical techniques, patients can more easily undergo complete excision of pulmonary nodules. In the past, many pulmonologists performed TTNB as the initial diagnostic procedure for intrapulmonary lesions, especially those in the lung periphery. Physicians are now faced with the dilemma of whether to send patients directly to thoracoscopic biopsy for a definitive answer. Two commonly used strategies – the use of PET or serial CT scanning – can be used to obtain additional evidence regarding the likelihood of malignancy. In appropriately selected patients, the presence of a PET-positive lesion or a lesion increasing in size on serial CT scans may obviate the need for TTNB.

Few absolute contraindications to TTNB exist. These include an uncooperative patient or one with an intractable cough, as patients must be able to suspend respirations for 5 to 10 seconds while the needle crosses the pleura. In addition, TTNB is absolutely contraindicated in patients with a suspected pulmonary hydatid cyst because of the risk of capsule rupture and systemic dissemination. Relative contraindications include bullous emphysema, pulmonary arterial hypertension, and coagulation or platelet disorders. Patients with bullous emphysema are at increased risk of developing symptomatic or tension pneumothoraces after biopsy, although most induced pneumothoraces are small and can be treated conservatively. Those with pulmonary hypertension who undergo TTNB have a higher chance of developing pulmonary hemorrhage and significant hemoptysis.

■ TECHNIQUE

Proper technique in performing TTNB is critical in obtaining adequate material for reliable interpretation. In addition to the mechanics of needle insertion and aspiration, the choice of needle type and careful specimen processing are important aspects of the procedure.

Choice of Needle

Many needle types are available for TTNB.[140,141] They vary in both length and width. In the early 1960s, TTNA was performed using large-bore cutting needles; significant hemorrhagic complications were reported. More recently, thin-needle aspiration has become standard, with devices ranging in size from 18 to 22 gauge. Coaxial needle systems have been introduced for the purpose of obtaining multiple samples from a single pleural penetration. These systems are also useful for procuring specimens for histological evaluation.

Radiographic Guidance and Biopsy Planning

Although TTNB can be performed under fluoroscopic or ultrasound guidance, CT is now the most commonly used image guidance approach for this procedure. CT can be used either intermittently during the procedure to guide needle placement, or with CT fluoroscopy (CTF), which allows for near real-time acquisition of images to guide needle adjustments. The diagnostic yield from either of these CT-based approaches appears to be similar.

Ultrasound-guided biopsies should be considered for peripheral lung lesions that extend to the pleural edge, or for the diagnosis of mediastinal masses. Ultrasound guidance also offers the advantage of real-time lesion imaging, easy portability, and absence of exposure to ionizing radiation for both the clinician and the patient.

Biopsy planning is an important step and should be performed prior to the procedure. Considerations include choosing a needle path that avoids traversal of bullae, vessels, and bronchi. Crossing of interlobular fissures should also be avoided, as this increases the risk of pneumothorax.[142] In cases with more than one lesion, a more peripheral lesion is preferred to decrease the amount of lung

traversed during needle insertion. In addition, upper lobe lesions are preferred over the lower lobe because of less respiratory motion in the upper lobes.

There are a number of different biopsy needles available for use, varying in length, gauge, and sampling mechanism. In general, needles can be divided into those used for aspiration, cutting needles for histological evaluation, and automatic core biopsy needles. The choice of biopsy needle depends on various factors, including characteristics of the lesion, amount of tissue desired, and operator preference.

Needle Insertion

The lesion is localized using CT guidance, and the overlying skin is marked and anesthetized with 1% or 2% lidocaine. The needle is first inserted through the skin into the subcutaneous tissues. The needle is then advanced to the level of the pleura, followed by verification of the needle position and angle by CT. The needle is then advanced in one motion through the pleura to the prescribed length. The needle position can be confirmed prior to biopsy.

Ideal aspiration technique necessitates having the tip of the needle as close to the center of the lesion as possible. If an aspiration or cutting needle is used, the inner stylet should be removed. A syringe is attached to the needle hub. While suction is applied, the needle tip is advanced and withdrawn about 0.5 to 1 cm within the lesion. The needle is then removed from the chest, suction is released, and the aspirated material is flushed into a specimen container. Several samples should be obtained to increase the diagnostic yield. With a necrotic mass, aspiration should also be performed in peripheral locations of the lesion to obtain viable cells and to decrease the risk of false-negative results.

A coaxial technique can also be employed using a larger entry needle, which is advanced into the lesion, followed by a smaller biopsy needle that can be passed through the lumen of the larger needle into the lesion. This approach allows multiple passes into the lesion without repositioning of the needle with each pass.

■ RESULTS

TTNB has an excellent success rate in the diagnosis of primary or metastatic pulmonary malignancies, with meta-analyses demonstrating pooled sensitivity of 90% (95% CI, 88%–91%);[54] lower yields are seen for lesions smaller than 1.5 cm.[135,139,143] CT guidance yields better performance when compared with fluoroscopy.[144] Aspiration biopsies have similar sensitivity to biopsies performed with cutting needles, but a poorer ability to determine a specific diagnosis from benign lesions. There is also concern that aspiration samples provide a lower likelihood of yielding sufficient tissue for molecular analysis, which is increasingly required in patients diagnosed with lung cancer.

Major causes of false-negative results in malignant disease are inadequate sampling of the lesion and aspiration in an area of necrosis or postobstructive pneumonia. In addition, small, central malignant lesions may be difficult to diagnose accurately. Aspiration of vascular tumors, such as angiosarcoma, carcinoid, or metastatic renal cell carcinoma, may yield a bloody aspirate with few, if any, malignant cells. False-positive results are extremely rare (1%–2%) and are typically reported in the setting of inflammatory processes, such as tuberculosis, radiation fibrosis, organizing pneumonia, and pulmonary infarction.

In the absence of a specific benign diagnosis, a lung biopsy that is negative for malignancy does not rule out the presence of neoplastic disease, especially if the biopsy was unsatisfactory. The degree of suspicion of malignancy in a particular clinical situation becomes extremely important in dictating the next step following a negative TTNB. For a smoker with a high risk of bronchogenic carcinoma, the proper course may lead to videothoracoscopic biopsy of the lesion, whereas in a young, otherwise healthy nonsmoker, close observation with serial CT scans may be the preferred option.

■ COMPLICATIONS

As mentioned previously, the most common complication of TTNB is pneumothorax; incidence rates reported in the literature vary from 8% to 61%. A recent population-based analysis reported a rate of pneumothorax of 15%, with 7% of all biopsies resulting in a pneumothorax requiring management with a chest tube.[40] Preexisting lung disease – in particular, bullous emphysema – is the most significant predisposing factor to development of pneumothorax after TTNB.[142,145–148] The vast majority of patients who develop clinically significant pneumothoraces after the procedure have an underlying diagnosis of chronic obstructive pulmonary disease. Other risk factors are smaller nodule size, crossing more than one pleural surface with the needle, needle size, and increased patient age.[142,145–148] Factors such as depth of lesion and increased number of transthoracic passes are controversial.[145,149]

Uncommon complications of TTNB include hemorrhage and hemoptysis, reported in approximately 1% of all biopsies. Although these are typically minor, one large study reported a transfusion requirement in 18% of cases with hemorrhage.[40] Cases of fatal hemorrhage from tracheobronchial obstruction from clot and subsequent asphyxia after use of large-bore (18-gauge) cutting needles have been reported.

Air embolism is a rare complication caused by creation of a communication between atmospheric air and a pulmonary vein. To minimize this risk, the needle should never be left open to air while in the chest, and the patient should be discouraged from deep breathing, straining, or coughing during the procedure. The procedure should be halted and the needle withdrawn if the patient is actively coughing. If an air embolism is suspected, 100% oxygen should be administered through a nonrebreather face mask and the patient placed in the left lateral decubitus position, with the head down: This position optimizes capture of air in the right heart. The patient should be transferred immediately to a hyperbaric chamber.

SUMMARY

Technological advances in diagnostic bronchoscopy continue to improve our ability to perform minimally invasive, accurate evaluations of the tracheobronchial tree and to perform an ever increasing array of diagnostic procedures. The continued development of imaging technologies and ancillary tools will certainly provide improvements in many of the modalities described earlier. Future improvements will include refinements in video and ultrasound imaging technology and the development of newer modalities, such as molecular imaging. This will be accompanied by further improvements in the ancillary tools, such as miniaturization of diagnostic accessories and further refinements in steerable probes that will allow improved access to peripheral regions of the lung. These opportunities will need to be accompanied by well-designed studies to delineate the appropriate use of these techniques in clinical practice.

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CHAPTER 36
Interventional Bronchoscopy

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INTRODUCTION

The first interventional bronchoscopy (also referred to as therapeutic bronchoscopy throughout this chapter) was performed by Gustav Killian in 1897 when he removed a pork bone from the right mainstem bronchus of a patient. For nearly 70 years bronchoscopy was predominantly a therapeutic procedure performed for foreign body extraction. Two events shifted the landscape of bronchoscopy—the lung cancer epidemic and the development of flexible bronchoscopy by Shigeto Ikeda in 1967. Following an escalation in lung cancer incidence, malignant airway obstruction requiring therapeutic intervention became much more common than foreign body extraction. As a result, new tools were developed to address malignant airway obstruction based upon a minimally invasive bronchoscopic approach. In addition, bronchoscopy-based technology has been developed to address chronic obstructive pulmonary disease (COPD) and asthma. Application of the technology has entered clinical trials and may alter the therapeutic options for these diseases processes. This chapter presents an overview of interventional bronchoscopy modalities that can be utilized for benign and malignant airway obstruction, COPD, and asthma.

INDICATIONS FOR INTERVENTIONAL BRONCHOSCOPY

Many potential indications for interventional bronchoscopy have been recognized, including malignant airway obstruction, benign airway obstruction, and foreign body extraction, among others. (Table 36-1). The majority of therapeutic bronchoscopies performed today are undertaken for management of malignant airway obstruction, most commonly from lung cancer. It is estimated that up to 40% of patients with lung cancer develop symptomatic airway obstruction at some point during their disease process. Although lung cancer is the most common source of malignant airway obstruction, any primary thoracic malignancy, or any malignancy with pulmonary metastases, may result in symptomatic airway obstruction. Regaining airway patency to palliate symptomatic dyspnea and other respiratory symptoms may have significant impact on the quality of life of patients with advanced malignancy.

Benign airway obstruction etiologies are listed in Table 36-2 and consist of a variety of localized inflammatory and systemic conditions. Although the etiologic airway process is benign and not malignant, the interventions and management of these complex processes is far from benign to the patient. Interventional bronchoscopy techniques can often correct the presenting symptoms; however, the stenosis and symptoms often recur and patients may require repeat procedures to maintain airway patency. Selected patients may need to proceed with airway resection of the benign stenotic airway segment.[1]

Most patients with airway obstruction have clinical symptoms; dyspnea as the most common patient complaint. Depending on the rapidity of airway obstruction, dyspnea may have a rapid onset, or more commonly, an insidious evolution that gradually limits the patient activities. It is not uncommon for a family member to recognize this limitation more readily than the patient. As the airway obstruction worsens, the patient may begin to have orthopnea, which is a harbinger of an evolving critical airway obstruction. Other symptoms, such as cough, inability to clear secretions, chest discomfort, or fever from post obstructive pneumonia may develop. Early intervention is important to prevent worsening respiratory compromise or death.

SPECIAL CONSIDERATIONS FOR PATIENT PREPARATION, SEDATION, AND MONITORING

All patients undergoing bronchoscopy should undergo a complete pre-bronchoscopy evaluation, including a medical history, physical examination, and chest imaging. Although routine laboratory tests are not required, each evaluation should be individualized on the basis of patients' underlying conditions and therapeutic procedures planned. CT scan is important to assess the degree of airway involvement and to plan interventions to be undertaken.

Sedation and analgesia for patients undergoing interventional bronchoscopy must be considered carefully. Stable patients who can lay flat without distress can undergo bronchoscopy with moderate sedation. Should the patient have moderate or severe respiratory distress or be unable to lay flat, strong consideration should be given to additional monitoring or anesthesiology procedural assistance. Patients with high oxygen requirements may require endotracheal intubation to reduce the risk of developing hypoxemic respiratory failure during moderate sedation. Moreover, if patients are unable to lie flat, they may require an initial upright bronchoscopy under minimal sedation to temporize luminal diameter before undergoing general anesthesia and more definitive interventional bronchoscopy.

Similar to diagnostic bronchoscopy, if a patient is stable for moderate sedation, topical analgesia of the oropharynx and airways should be achieved with lidocaine, followed by administration of a combination of a short-acting benzodiazepine (e.g., midazolam) and a narcotic (e.g., fentanyl).[2] Rigid bronchoscopy is most safely

TABLE 36-1 Indications for Interventional Bronchoscopy

Hemoptysis
Atelectasis from inspissated secretions
Foreign body removal
Tracheobronchial tree neoplasms (primary or metastatic)
Direct bronchoscopic debulking
Laser therapy
Electrocautery/Argon plasma coagulation
Cryotherapy
Brachytherapy
Photodynamic therapy
Stent placement
Airway strictures and stenoses
Rigid bronchoscopic dilation
Stricture/stenosis incision
Balloon tracheobronchoplasty dilation
Stent replacement
Lung lavage (pulmonary alveolar proteinosis)
Bronchoscopic drainage—lung abscess
Endotracheal tube and percutaneous tracheostomy placement
Treatment of persistent air leak
Evolving therapies for emphysema
Bronchial thermoplasty in severe asthma

TABLE 36-2 Etiologies of Benign Tracheobronchial Stenosis

Endotracheal intubation
Tracheostomy tube
Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
Amyloidosis
Sarcoidosis
Tuberculosis
Inflammatory bowel disease
Idiopathic
Trauma
Lung transplantation
Post resection or airway repair
Trauma
Recurrent stenosis after prior stenosis resection
Sleeve resection
External beam radiotherapy or high dose-rate brachytherapy (HDRB)
Photodynamic therapy
Thermal injury from fire exposure
Tracheobronchopathia osteochondroplastica
Postpneumonectomy syndrome
Fibrosing mediastinitis
Large vascular aneurysms

performed with a patient receiving general anesthesia and breathing spontaneously or being ventilated with a jet ventilator.[3] General anesthesia with inhaled anesthetics (e.g., sevoflurane) should be avoided in favor of total intravenous anesthesia in order to avoid exposure of the bronchoscopist to inhaled anesthetics when the ventilator circuit is open. With appropriate planning and monitoring, the vast majority of patients can undergo interventional bronchoscopy with low complication rates.

TYPES OF AIRWAY OBSTRUCTION

Figure 36-1 demonstrates the three main types of airway obstruction that may be encountered: purely intrinsic (A), purely extrinsic (B), or a combination of both intrinsic and extrinsic airway obstruction (C). Attention to preprocedural CT scan imaging allows fairly accurate assessment of these components and permits the therapeutic bronchoscopist to plan an approach. For lesions that are purely intrinsic, direct bronchoscopic debulking with rigid bronchoscopy, thermal ablation, or snare extraction, with or without stent placement, is appropriate. For purely extrinsic lesions, no tumor is present to debulk, and modalities used in purely intrinsic disease cannot be employed because of the risk of airway perforation. Extrinsic lesions are most amenable to balloon bronchoplastic dilatation and endoluminal stent placement. For mixed intrinsic–extrinsic lesions, all tumor removal modalities, as well as dilatation and stent placement, are feasible.

■ ENDOLUMINAL AIRWAY OBSTRUCTION

Endoluminal obstruction of the tracheobronchial tree may result from various benign and malignant processes. The most common cause of endobronchial obstruction is advanced lung carcinoma. In patients with inoperable central airway tumors, restoration of airway patency may provide palliation and may even prolong life, particularly in the case of impending respiratory failure or postobstructive pneumonia.

Signs and symptoms of central malignant airway obstruction vary, but often include progressive dyspnea and functional limitation, wheezing, cough, stridor, hoarseness, hemoptysis, and chest pain. A careful pretreatment evaluation should be performed to distinguish symptoms attributable to focal tracheobronchial lesions from those related to underlying obstructive lung disease, parenchymal lung disease, or both. Although pulmonary function testing and thoracic imaging techniques, such as chest CT, may be useful in the evaluation of a patient with suspected malignant airway obstruction, bronchoscopy, either rigid or flexible, remains the diagnostic and therapeutic "gold standard." Increasingly, however, three-dimensional reconstruction CT imaging, so-called "virtual bronchoscopy," is being applied as a reliable noninvasive method of assessing the nature and extent of malignant airway obstruction, thereby allowing preprocedural intervention planning.

The bronchoscopic approach to management of malignant airway obstruction depends on the lesion location, presence or absence of associated extrinsic compression, and degree of clinical urgency. Rigid bronchoscopic debulking using adjunctive thermal ablation is recommended when airway recanalization must be performed on an emergency basis. If endobronchial obstruction is accompanied by marked extrinsic compression, stent placement may be beneficial.

The complexity of a lesion is equally important in determining the best approach to therapeutic bronchoscopy. Benign tracheal webs often are managed using laser or electrocautery-mediated resection alone, whereas complex fibrotic strictures may warrant the combination of rigid bronchoscopic or balloon dilation, thermal incision, and stent placement. For focal tracheal stenosis in patients at low risk for complications, surgical resection with primary reanastomosis should remain the treatment of choice.

■ EXTRINSIC AIRWAY COMPRESSION

Extrinsic airway compression usually results from malignant involvement of structures adjacent to the central airways, such as mediastinal lymph nodes or the esophagus, but it may be associated with a benign process, such as fibrosing mediastinitis, tuberculosis, aneurysmal dilatation of the aorta, or sarcoidosis. The clinical signs and symptoms of extrinsic airway compression often mimic those of endobronchial obstruction. The diagnosis is established on the basis of bronchoscopic detection of marked airway narrowing in the absence of an endoluminal mass.

Therapeutic options in the management of extrinsic airway compression are limited. Ablative endoscopic approaches, such as laser therapy, cryotherapy, PDT, and electrocautery are contraindicated because of the lack of demonstrable benefit and risk of airway perforation. Although some patients with malignant disease may benefit from endobronchial brachytherapy, tracheobronchial stent placement is the palliative treatment of choice for patients with symptomatic extrinsic airway compression.

TYPES OF THERAPEUTIC BRONCHOSCOPY INTERVENTIONS

A wide variety of therapeutic bronchoscopic interventions may be offered. Each is described in subsequent sections.

■ RIGID BRONCHOSCOPY

The initial bronchoscope, developed by Killian, and further optimized by Chevalier Jackson, was a rigid metal tube that permitted either spontaneous or mechanical ventilation.[4] Over the decades, rigid bronchoscopes of various lengths and sizes that are adaptable for diverse applications in children and adults have become available. Although the flexible bronchoscope has, to a large extent, replaced the rigid scope for most diagnostic and some therapeutic indications, rigid bronchoscopy still has vital therapeutic applications.

Modern rigid bronchoscopy systems are equipped with optical capabilities to allow better direct, magnified, circumferential

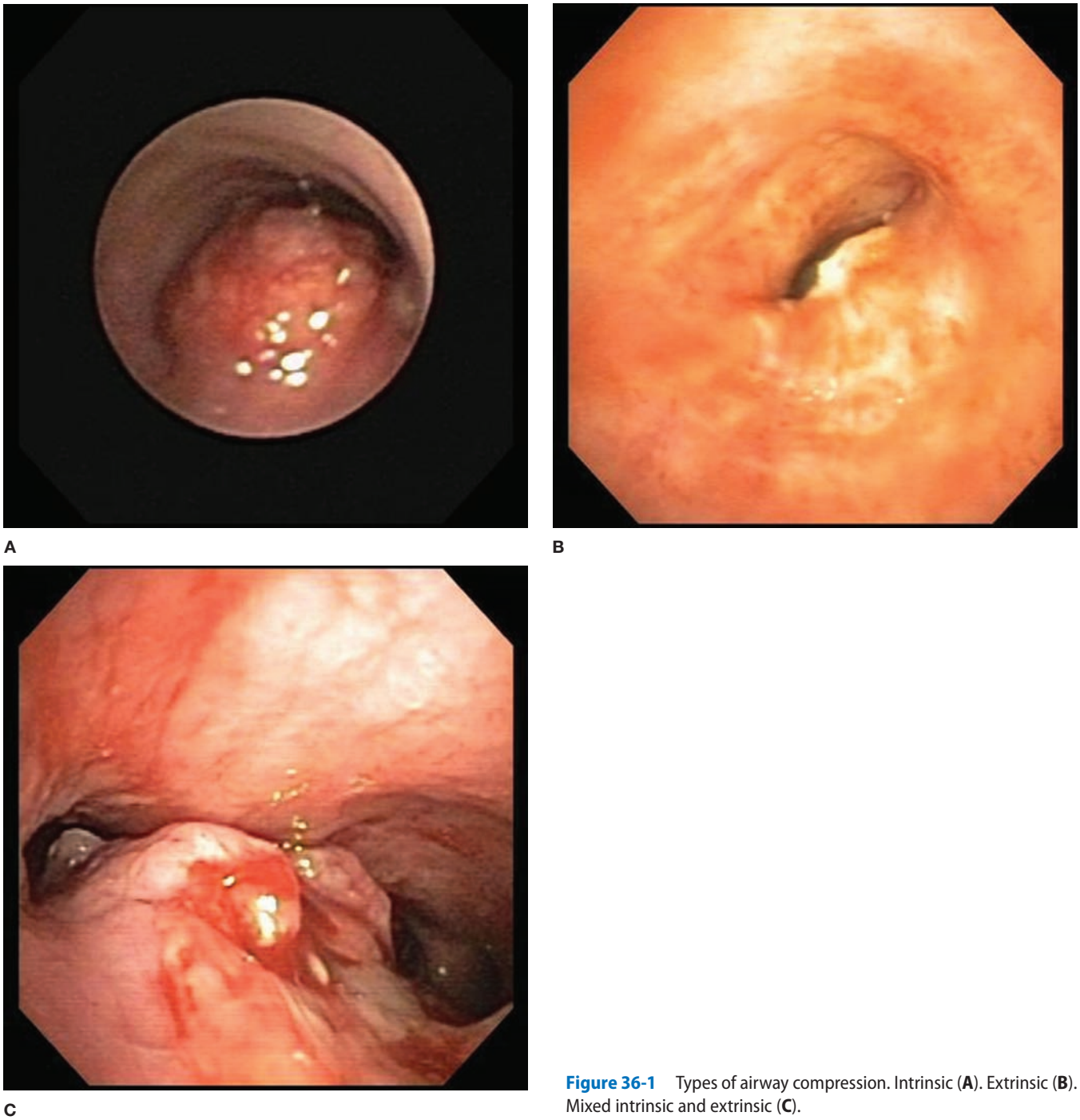
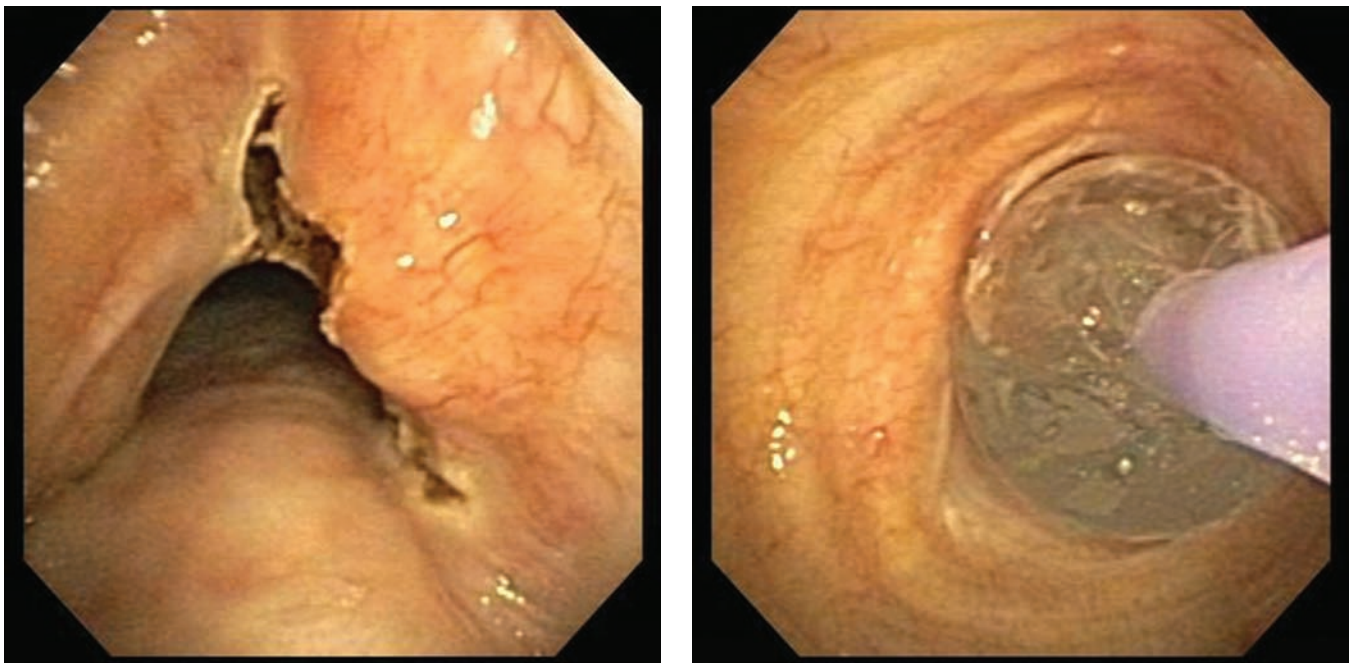


Figure 36-1 Types of airway compression. Intrinsic (**A**). Extrinsic (**B**). Mixed intrinsic and extrinsic (**C**).

illumination and visualization. The main advantage of rigid bronchoscopy over flexible bronchoscopy is its luminal working diameter, which allows multiple therapeutic instruments to be utilized simultaneously while ventilating the patient. Rigid bronchoscopy allows a number of therapies, such as laser photocoagulation, placement of endobronchial stents, balloon dilation, electrocautery, argon beam coagulation, and cryotherapy to be performed safely and effectively. Perhaps most importantly, in the setting of malignant airway disease or obstruction, a rigid bronchoscope can be used to "core out" large bulky airway tumors more efficiently and effectively than any thermal modalities (Video 36-1). Initial rigid bronchoscopic debulking, followed by thermal modality ablation to cauterize remaining tumor is common.[5] For benign, fibrotic airway stenosis, the rigid bronchoscope becomes a very effective modality to partially debulk stenotic tissue and to dilate the stenosis.[6] In experienced centers, rigid bronchoscopic airway recanalization remains the treatment of choice for serious or life-threatening tracheobronchial obstruction.

The main complication from rigid bronchoscopy is dental injury from the scope cracking or fracturing teeth. Other complications, such as oropharyngeal laceration, arytenoid cartilage disarticulation, or vocal cord injury, are possible. Meticulous care upon rigid

Video 36-1 A patient with a right paratracheal mass who underwent diagnostic and therapeutic bronchoscopy. Endoluminal tumor growth was present along the right lateral tracheal wall. The video demonstrates effective and efficient use of rigid bronchoscopy to mechanically debride tumor. *Access at www.fishmansonline.com*



A B

Figure 36-2 Electrocautery incisions were made into the benign stenotic lesion (**A**). Following incision, balloon bronchoplasty dilatation was performed (**B**).

bronchoscope intubation is critical to avoid these possible complications. Intrathoracic complications, such as airway perforation, major bleeding from tumor debulking, and pneumothorax or pneumomediastinum are also possible but are infrequent in experienced hands.

■ BALLOON TRACHEOBRONCHOPLASTY

Balloon dilatation has become an attractive alternative to rigid bronchoscopy for management of airway obstruction in benign and malignant airway obstruction, especially in anatomic locations where a rigid bronchoscope cannot enter or the luminal diameter is too narrow to allow safe rigid bronchoscope passage. High-pressure balloons of various lengths and diameters specifically designed for the tracheobronchial tree are readily available. These balloons are filled with saline or radio-opaque contrast media, advanced to the site of interest through the bronchoscope, and inflated until the desired diameter is attained.

In the setting of benign stenosis, an initial defect in the stenosis is often made with a thermal modality so as to control the stenotic release point (Fig. 36-2). This approach has been used successfully in benign stenoses from endobronchial tuberculosis, idiopathic subglottic stenosis, and post-transplant anastomotic strictures.[7] It is less successful when used alone to treat airway compromise accompanied by extrinsic airway compression, as the initial bronchoscopic improvement often rapidly returns to its original position as the extrinsic process persists. Complications of balloon tracheobronchoplasty include bronchospasm, chest pain, mucosal laceration, airway perforation, bleeding, postprocedure airway edema, pneumothorax, and pneumomediastinum.

■ BRONCHOSCOPIC LASER THERAPY

Perhaps the most widely known technique in therapeutic bronchoscopy is laser photocoagulation or photoablation. Table 36-3

TABLE 36-3 Therapeutic Bronchoscopy Ablation Modalities

Therapy	Type of Lesion Therapy	Type of Bronchoscope	Rapidity of Positive Result	Repeatability
Mechanical debridement	Endoluminal or submucosal	Rigid or flexible (rigid preferable)	++++	+
Laser	Endoluminal	Rigid or flexible (rigid preferable)	++++	++++
Argon plasma	Endoluminal	Rigid or flexible	++++	++++
Brachytherapy	Endoluminal or submucosal	Flexible	+	+
Cryotherapy	Endoluminal	Rigid or flexible	++	+++
Balloon dilation	Endoluminal or submucosal with extraluminal compression	Rigid or flexible (rigid preferable)	++++	++++
Photodynamic therapy	Endoluminal	Flexible	++	+++
Electrocautery	Endoluminal	Rigid or flexible	+++	++++
Stent	Endoluminal with extraluminal compression	Rigid or flexible (Dumon stent requires rigid bronchoscope; Wall stents and Gianturco stents require fluoroscopy)	++++	+++

Video 36-2 A patient who presented with a new right mainstem obstruction from lung cancer. The video shows Nd:YAG tumor coagulation and debulking. *Access at www.fishmansonline.com*

compares characteristics of the laser modality compared with other modalities to be presented later. Lasers produce a beam of monochromatic, coherent light that induces tissue vaporization, coagulation, hemostasis, and necrosis. Although primarily useful in endoluminal malignant tumor ablation, bronchoscopic laser therapy also is beneficial in other tracheobronchial disorders, including inflammatory strictures, obstructive granulation tissue, amyloidosis, and benign tumors, such as hamartomas and lipomas.

Since the initial report of endobronchial laser ablation of an obstructive neoplasm by Laforet in 1976, several types of lasers have become available for management of tracheobronchial obstruction.[8] The carbon dioxide (CO_2) laser, used primarily by otolaryngologists, allows shallow tissue penetration (to a depth of 0.1–0.5 mm) and very precise cutting, but it has minimal hemostatic properties. With the development of other laser modalities, the CO_2 laser has minimal current application in endobronchial tumor ablation, and its role remains primarily in management of laryngeal lesions.

For therapeutic bronchoscopy, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser ablation is most commonly used (Video 36-2). It provides tissue penetration to a depth of 3 to 5 mm, superior coagulation and improved hemostasis, but at the cost of less cutting precision. Nd:YAG laser procedures may be performed through a rigid or flexible bronchoscope. Success rates and complications directly related to laser therapy are not different when the procedure is performed through a rigid bronchoscope with the patient under general anesthesia, or through a flexible bronchoscope with use of topical anesthesia and moderate sedation.

Use of Nd:YAG laser photoablation therapy as a single modality is associated with a recanalization rate >90% for endobronchial obstruction of large central airways; however, it is less successful in treating peripheral lesions or extrinsic airway compression.[9,10] Nd:YAG laser photocoagulation may be an important treatment tool for patients with airway obstruction caused by benign endoluminal tumors. The Nd:Yap (yttrium-aluminum-perovskite) laser, with a patented wavelength of 1.34 μ wavelength, is purported to have better water absorption at that wavelength, improving the power-to-effective ratio compared with traditional Nd:YAG laser and carrying a lower complication risk.

Although endobronchial laser therapy generally is safe and well tolerated, it may be complicated by cardiac arrhythmias, airway perforation, pneumothorax, hemorrhage, hypoxemia, or endobronchial fire.[11,12] Endoluminal laser utilization requires careful consideration of the lesion anatomic location and configuration relative to vital intrathoracic structures. If the lesion is in close proximity to the esophagus or pulmonary artery, endobronchial laser therapy carries risk for fistula formation. Laser therapy in a patient with tracheobronchial narrowing caused by extrinsic compression may result in airway perforation. In rare cases, pulmonary edema or fatal pulmonary venous gas embolism have been reported.[13] Patients with standard silicone endotracheal tubes or silicone tracheobronchial stents, and those who require high concentrations of supplemental oxygen, are at increased risk for endobronchial fire. The bronchoscopist needs to ensure the inspired oxygen level is, ideally, <40%, especially if the patient is receiving mechanical ventilator support during the procedure. Fortunately, the overall risk of endobronchial fire is <0.1%.

■ ENDOBRONCHIAL ELECTROCAUTERY AND CRYOTHERAPY

Electrocautery and cryotherapy are cost-effective alternatives to laser therapy for the management of tracheobronchial lesions and obstruction, as equipment expenses are substantially less compared to laser therapy. Penetration depth and per treatment effectiveness may be less than with laser therapy.

Video 36-3 A patient with a history of renal cell carcinoma who presented with dyspnea and left lung atelectasis. CT scan demonstrated left mainstem bronchus obstruction. The video shows a rigid bronchoscopy with electrocautery snare excision and removal of a large polypoid renal carcinoma metastasis. The point of airway attachment was then cauterized using electrocautery. *Access at www.fishmansonline.com*

As with the Nd:YAG laser, both electrocautery and cryotherapy may be administered through either a rigid or flexible bronchoscope. Electrocautery effects on tissue are similar to those of Nd:YAG laser, with tissue destruction induced by coagulative necrosis (Video 36-3). Argon plasma coagulation (APC) is similar to electrocautery except that it uses argon gas to conduct the electrical current rather than a contact probe. Electrocautery and APC have a 1- to 3–mm penetration depth and are, therefore, more suitable for the treatment of superficial and spreading lesions (Video 36-4).

In contrast with electrocautery or APC, cryotherapy induces tissue necrosis through hypothermic intracellular crystallization and microthrombosis. Specially designed cryoprobes are inserted through the bronchoscope until they contact target tissue. Cryoprobe activation introduces liquid nitrous oxide or liquid nitrogen through a small orifice in the probe under pressure, resulting in rapid cryoprobe cooling with creation of an "ice ball" (approximate temperature, 20°C) at the probe tip on target tissue. This freezing effect is maintained for approximately 20 seconds; the area is then allowed to thaw, and freezing is repeated 2 to 3 times to achieve necrosis by cellular rupture from repeated cycles of intracellular micro-crystallization.

Electrocautery, APC, and cryotherapy have been used successfully to relieve airway obstruction and treat hemoptysis caused by benign and malignant tracheobronchial tumors, polyps, and granulation tissue.[5,9,14–19] These modalities have been used effectively in radiographically occult mucosal lung cancer, carcinoma in situ, and mucosal dysplasia. Cryotherapy may be advantageous in cryoextraction of foreign bodies that can be frozen to the probe and removed.[20] This technique works very well for mucoid plugs or blood clots in large airways where other modalities may be associated with some difficulty in successful removal. Due to the repeat treatment cycles needed to achieve effect, cryotherapy is not ideal for efficient relief of symptomatic airway obstruction.

Although the range of complications from electrocautery and cryotherapy are the same as those discussed for laser therapy, the most common complication of each is bleeding secondary to disruption of endobronchial tumor without full-tissue coagulation. The estimated incidence of clinically significant bleeding in patients treated with electrocautery is 2.5%. Rarely, gas embolism can occur with APC.[21,22]

■ ENDOBRONCHIAL BRACHYTHERAPY

Endobronchial brachytherapy refers to bronchoscopic radiation delivery to a localized airway lesion; it is often referred to as high dose-rate brachytherapy (HDRB) due to high radiation dosage delivery to a focused area. The technique aims to delivery therapeutic radiation to localized lesions while minimizing risk to nontarget tissues.

Video 36-4 This patient had a prior bronchoscopy for minor hemoptysis; endobronchial biopsies demonstrated carcinoma in situ. The video demonstrates argon plasma coagulation ablation of the involved sites from prior biopsies. *Access at www.fishmansonline.com*

Endobronchial brachytherapy involves the bronchoscopic insertion of a thin, hollow "afterloading" catheter across an area of interest (usually malignant) under direct bronchoscopic and fluoroscopic guidance. The catheter is left in place and the patient travels to a radiation oncology department where radioactive beads are inserted into the catheter at the desired location for a predetermined period, depending on the dose rate.

Relief of airway obstruction is the primary goal of HDRB, although curative treatment may be attempted in more advanced lesions by combining HDRB with external beam irradiation in selected patients. HDRB is not effective for rapid airway recanalization due to its delay in response of 14 to 21 days. It is best used as an adjunct to rigid bronchoscopy with or without thermal tumor ablation, endobronchial stent placement, or conventional external beam irradiation to recanalize an obstructed airway. HDRB appears safest and most effective for management of central airway lesions. Among patients with malignant airway obstruction, recanalization rates range from 60% to 90%, with decreased dyspnea, cessation of hemoptysis, and relief of cough in most cases.[16,23,24] HDRB has also been shown to be effective for radiographically occult, minimally invasive cancer in central airways, CIS, or mucosal dysplasia. Moreover, reports of the utility of HDRB in management of benign granulation tissue in lung transplant recipients or patients with or subglottic stenosis have been reported.[25–27]

Serious complications of HDRB can occur, particularly massive hemoptysis, from bronchovascular fistula formation secondary to necrosis of the airway wall and adjacent vascular structures. Because of the risk of fatal hemorrhage, every effort should be made to rule out central vascular tumor involvement before application of HDRB.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) currently is FDA-approved for palliation of malignant airway obstruction and as an alternative to surgery in selected patients with minimally invasive central lung cancer or CIS. PDT works on the principle that certain compounds, such as hematoporphyrin derivatives or aminolevulinic acid (ALA), function as photosensitizing agents, rendering malignant cells susceptible to damage from monochromatic light. Tumor necrosis occurs as a result of oxygen free radical formation and ischemic vasculature necrosis mediated by thromboxane A_2 release.

The selective PDT effect on malignant cells is thought to be due to greater photosensitizing agent uptake and retention in neoplastic cells compared with normal cells; the exception is reticuloendothelial cells, particularly those in the skin. The relative tumor selectivity is most pronounced within 24 to 48 hours after photosensitizing agent infusion; therefore, treatment of the bronchoscopically targeted lesion should be performed within that time frame. Maximal tissue necrosis occurs 24 to 48 hours after light administration and requires repeat bronchoscopy to debride the necrotic and sloughed area treated. Due to the delayed onset of PDT action, it is not useful in patients with acute respiratory distress from evolving airway obstruction.

Ideal candidates for PDT include patients with airway obstruction caused by malignant endobronchial masses with minimal extrinsic airway compression, and patients with minimally invasive central airway tumors. Although surgical resection remains the treatment of choice for early lung cancer, some patients refuse surgery or have tumors that are deemed inoperable because of high surgical risk. In these cases, PDT may represent an appropriate alternative. Response rates are highest in patients with small tumors and minimal airway penetration depth.[28,29] In patients with bulky tumors, endobronchial PDT may substantially reduce the obstruction, with objective increases in spirometric measurements and subjective improvement in dyspnea and quality of life; however, treatment is not curative.[30] Endoluminal metastatic tumors may also be treated successfully with PDT.

Complications of PDT include increased skin photosensitivity and hemoptysis resulting from extensive tumor necrosis into a vascular structure. Cutaneous photosensitivity, similar to a sunburn, occurs in up to 20% of patients in various reported series; it may be obviated by adequate sunlight precautions. Sensitivity to sunlight after photosensitizer administration may persist for 6 weeks or longer.

TRACHEOBRONCHIAL STENTING

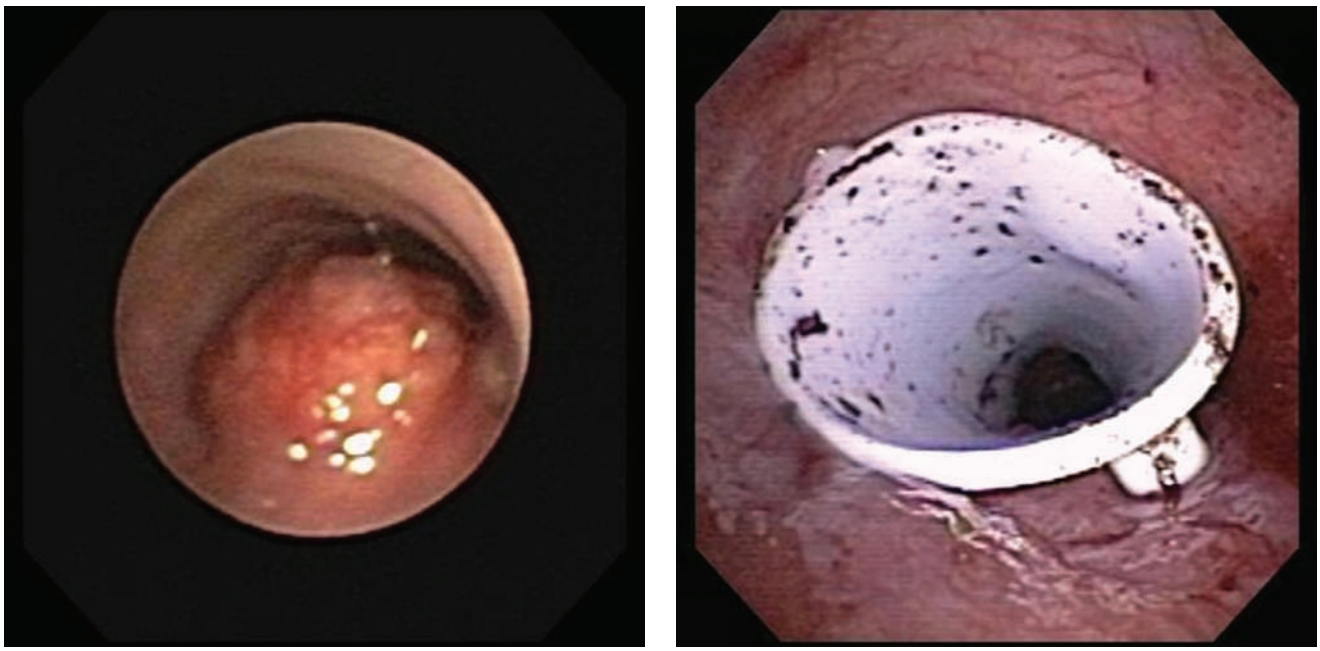
The medical term, "stent" refers to any device designed to maintain the integrity of hollow tubular structures, such as the airways, coronary arteries, or esophagus. Anecdotal reports of attempts to implant stents in the tracheobronchial tree date back to 1915. The Montgomery T-tube, designed in the 1960s, was the first reliable, dedicated airway stent.[31] However, stent implantation in the lower trachea and bronchi did not become standard medical practice until 1990, when Jean Francois Dumon reported the safety and ease of placement of a dedicated silicone airway stent.[32]

Two main types of endobronchial stents are in use today—silicone or self-expanding metal (SEMS). Silicone stents generally are placed by rigid bronchoscopy with the patient under general anesthesia. Silicone stents are relatively inexpensive (~$500 USD) compared with SEMSs (~$2000 USD). Bifurcated silicone stents also are available and have been effectively used in the management of carinal compression associated with malignant tumors, tracheoesophageal fistulas, and tracheobronchomalacia.

Unlike silicone stents, SEMSs may be placed using flexible bronchoscopy and require less technical rigor than silicone stent placement. The main limitation with SEMS is that uncovered varieties may induce mucosal inflammation and granulation tissue formation which may require repeat endoscopic intervention to maintain airway patency.[33–35] For this reason, SEMSs have an FDA black-box warning against their utilization in *benign* airway stenosis, unless all other treatment options, including silicone stenting, have been explored and failed. An exception to this warning applies in bronchial anastomotic dehiscence in lung transplantation. In this setting, insertion of a temporary uncovered SEMS across the dehiscence exploits the fact that focal granulation tissue may develop and promote dehiscence closure.[36]

Endobronchial stents have a critical role in multimodality bronchoscopic approaches to both benign and malignant airway obstruction. Airway obstruction caused by locally advanced lung carcinoma may be treated with a combination of thermal tumor ablation and stent implantation to regain and preserve airway lumen diameter by preventing tumor ingrowth (Fig. 36-3). Stent placement may be combined with balloon dilatation in the endoscopic management of benign fibrotic strictures. Most large studies of endobronchial stent placement have demonstrated impressive efficacy.

Dumon and colleagues reported excellent clinical outcomes and few complications with silicone stent placement in patients with malignant airway obstruction; a lower success rate was noted among patients with tracheal stenosis caused by other disorders.[32] Success, broadly defined as symptomatic relief, in limited studies has been reported to be achieved in between 78% and 98%, although none of the early trials used objective measures to determine efficacy.[37–39] In a small study in patients who were intubated because of respiratory failure secondary to unresectable tracheobronchial and mediastinal disease, stent placement facilitated extubation in most.[40] Stent placement benefits seem to persist in patients who survive for a period of several months or years after stent implantation. Long-term follow-up data are derived from patients with benign disease, since the mean follow-up period in patients with malignant airway obstruction usually does not exceed 3 to 4 months.



A B

Figure 36-3 A large tumor nearly completely obstructs the tracheal lumen (**A**). Manual debulking using a rigid bronchoscope dramatically improved airway luminal diameter. An endotracheal silicone stent was placed to prevent tracheal re-occlusion (**B**).

Complications from endobronchial stents include stent migration, granulation tissue formation, tumor overgrowth, stent bacterial colonization and recurring infection, stent fracture, and inspissated secretions clogging the stent. In addition, massive and fatal hemorrhage associated with stent erosion into central vascular structures can occur.

Stenting for Tracheobronchomalacia

Diffuse or focal tracheobronchomalacia is, perhaps, the most challenging disorder encountered by the therapeutic bronchoscopist. Cartilaginous tracheobronchomalacia reflects tracheal or main bronchi circumferential exhalation airway collapse due to loss of structural integrity of the airway cartilaginous rings. Membranous, or crescentic, tracheobronchomalacia, also known as excessive dynamic airway collapse (EDAC), is manifested by intact cartilaginous rings, but anterior displacement of the posterior membrane during exhalation to variable degree as a result of posterior membrane laxity. This condition is commonly seen with COPD, asthma, obesity, and chronic cough. Dynamic CT scanning may suggest tracheobronchomalacia or EDAC, but the gold standard remains flexible bronchoscopy performed to assess airway collapse with the patient breathing spontaneously.[41] Focal airway malacia may be a complication of long-standing intubation or an anastomotic complication after lung transplantation.[42]

The endoscopist must maintain restraint in therapeutic interventions for patients with tracheobronchomalacia or EDAC. Management of diffuse tracheobronchomalacia should focus on identifying and treating any underlying conditions that may perpetuate cartilaginous inflammation (e.g., relapsing polychondritis) and airway collapse. If the tracheobronchomalacia is symptomatic and progressive despite systemic therapy, initial consideration for tracheostomy should be entertained. If symptoms are not resolved with tracheostomy, or if they recur or progress after an initial improvement, evaluation for placement of a silicone bifurcation Y stent should be undertaken. These patients may also require nighttime ventilator support. Patients with EDAC may benefit from a trial of silicone stent placement as well, but this should not be considered definitive therapy.[43,44] For those who benefit in terms of decreased respiratory symptoms and improved pulmonary function, silicone stent removal, followed by surgical plication or buttressing of the posterior membrane, can be performed with acceptable clinical outcomes.[43,45] For many patients with focal tracheomalacia, particularly from postintubation injury, surgical resection with primary reanastomosis may be the best therapeutic option. If patients are not surgical candidates or prefer to avoid surgery, silicone stent placement often will provide the structural integrity necessary to obviate patient symptoms, but at the risk of long-term stent complications.

■ MANAGEMENT OF HEMOPTYSIS

Bronchoscopy may be of value in hemoptysis for several reasons: to identify site of bleeding, to provide endobronchial therapy to reduce or stop bleeding, to clear blood clots that might impair gas exchange, or to place an endoluminal blocking device to prevent further airway occlusion with blood. Because of visualization difficulties during active bleeding, instruments with large and maximally effective suction channels should be used. Rigid bronchoscopy generally is preferred with massive bleeding or when the need to remove large clots is anticipated.

In attempts to cease bleeding, iced saline or an epinephrine solution can be instilled into a bleeding airway or applied topically onto a proximal bleeding site in attempt to induce vasoconstriction. In addition, balloon catheters can be placed into the bleeding airway to tamponade bleeding and prevent proximal airway soilage in hope of generating a hemostatic clot. Large endobronchial blockers are available to occlude the entire right or left mainstem bronchus to control bleeding. Other effective methods for control of proximal visible bleeding sources, particularly from endobronchial neoplasms, are thermal modalities, such as Nd:YAG laser or APC photocoagulation.[46] Recent reports have demonstrated the benefit from endobronchial packing accomplished with either flexible or rigid bronchoscopy using oxidized regenerated cellulose, which isolates the segmental or subsegmental bleeding site and promotes endobronchial clot formation by induction of fibrin polymerization.[47,48] Frequently, these procedures are temporizing, while definitive management with surgery or bronchial artery embolization is considered.[49]

FOREIGN BODY REMOVAL

Bronchoscopy was developed primarily for foreign body removal; prior to the lung cancer epidemic, foreign body removal represented the overwhelming indication for bronchoscopy for decades.

Foreign body aspiration is more likely to occur in children than in adults, with most foreign bodies occurring in children younger than 3 years. In children, the foreign body most often lodges in a mainstem bronchus, whereas in adults foreign bodies usually are wedged distally, most commonly in the right lower lobe. Before bronchoscopic extraction was possible, most foreign body aspirations resulted in high morbidity and mortality, commonly from postobstructive pneumonia. Today, foreign bodies can be removed with either flexible or rigid bronchoscopy, depending on local expertise and foreign body size and composition. If available, rigid bronchoscopy remains the tool of choice for foreign body removal due to several factors: a larger access channel, which permits use of larger and more adaptable retrieval tools; protection of the vocal cords from trauma upon (foreign body) removal; and ability to provide and maintain ventilation.

Various instruments have been developed for use with bronchoscopy for foreign body removal, including grasping forceps, balloon catheters, retrieval baskets, snares, and magnetic extractors. The instrument choice depends on the foreign body material composition, size, shape, and location in the tracheobronchial tree. Grasping forceps may be helpful in the retrieval of hard objects with an irregular surface. Smooth objects or organic material (e.g., nuts, food particles) may require use of expandable baskets or a combination of balloon catheters, suction devices, and grasping forceps. Balloon catheters frequently are used to dislodge a foreign body and bring it proximally into a larger airway before its removal with other instruments.

SECRETION ASPIRATION

According to a survey of bronchoscopists in the United States, removal of retained secretions is cited as a leading indication for therapeutic bronchoscopy. Aspiration of bronchoscopic secretions may be indicated in patients with respiratory muscle weakness (e.g., due to underlying neuromuscular disease or the postoperative state) who cannot generate adequate cough for secretion clearance. In critically ill or mechanically ventilated patients, removal of secretions and mucus plugs usually can be rapidly achieved with flexible bronchoscopy. For ease of secretion removal, a flexible scope with a large diameter suction channel is ideal. The secretion volume and viscosity may dictate the interval necessary for bronchoscopy procedures to relieve segmental or lobar atelectasis from inspissated mucus plugs. Bronchoscopic secretion aspiration should not be considered "routine" in the postoperative period or in other conditions in which good chest physiotherapy and maintenance of adequate pulmonary toilet may be more effective.

Two specific disorders are worth highlighting in the context of therapeutic bronchoscopy: pulmonary alveolar proteinosis (PAP) and allergic bronchopulmonary aspergillosis (ABPA). In PAP, large-volume repeated bronchoalveolar lavage has been used for therapeutic clearance of alveolar material composed predominantly of surfactant.[50,51] For patients with more extensive disease or impaired gas exchange, the standard approach is sequential whole-lung lavage.[52] In ABPA, lavage with saline solution may be insufficient to remove tenacious secretion impactions (described as "plastic bronchitis"), and use of bronchoscopic forceps or snare may prove helpful.

CLOSURE OF BRONCHOPLEURAL FISTULA

Prolonged air leaks may be encountered following primary or secondary spontaneous pneumothorax, particularly in the setting of underlying parenchymal lung disease; however, they are more commonly seen pulmonary resection. Current management for prolonged air leaks usually includes prolonged chest tube drainage using a Heimlich valve, attempts at surgical repair, pleural blood patch, or pleurodesis.

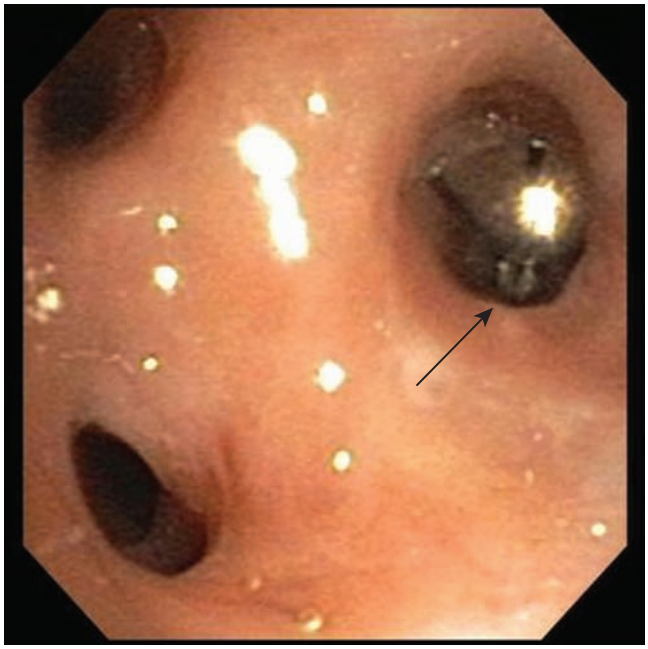


Figure 36-4 A patient presented with a spontaneous pneumothorax from severe emphysema. A chest tube was placed in the left chest and a persistent air leak was noted. Balloon occlusion localized the leak to the left upper lobe anterior segment. A one way endobronchial valve was placed *(arrow)* with complete air leak resolution.

Therapeutic bronchoscopy may be a useful adjunct to prolonged air-leak intervention in confirming suspected bronchopleural or alveolopleural fistulae and in specifying their precise location. The most common approach is to perform selective balloon catheter airway occlusion while observing the chest tube air-leak rate and volume. Depending on the fistula location and size, bronchoscopic procedures can be attempted with the goal of occluding and sealing the bronchopleural fistula. It is much more difficult to achieve fistula obliteration in an area of infected lung or recurrent malignancy. Many different techniques for permanent closure have been reported. Several potentially useful agents have been described, including surgical gel, autologous airway blood patch, and thrombin injection to create fibrin clot, among a variety of others.[53–55] In addition, laser photocoagulation or hypertonic saline injection surrounding small, proximal bronchopleural fistulas has been reported to be beneficial. Recent reports suggest that the placement of one-way endobronchial valves may effectively lead to complete or partial resolution in the large majority of patients with prolonged air leaks from diverse causes (Fig. 36-4).[56–59]

BRONCHOSCOPIC TREATMENTS FOR COMMON BENIGN LUNG CONDITIONS

One of the major advances in therapeutic bronchoscopic use over the past decade has been the development of experimental bronchoscopic interventions for highly prevalent lung diseases, such as asthma and emphysema.

BRONCHOSCOPIC EMPHYSEMA TREATMENT

The National Emphysema Treatment Trial (NETT) demonstrated the role of lung volume reduction surgery (LVRS) as the first major surgical intervention for emphysema to improve patient symptoms, as well as mortality, in certain patient subsets.[60] Unfortunately, these benefits were associated with an approximate 5% procedural mortality and substantial perioperative morbidity, including prolong air leaks and cardiac arrhythmias. These factors have spurred

Video 36-5 The video demonstrates fluoroscopic deployment of an investigational endobronchial coil for treatment of emphysema. *Access at www.fishmansonline.com*

development of minimally invasive, bronchoscopic approaches to achieve similar outcomes as the NETT trial, but without the considerable morbidity observed.

The bronchoscopic lung volume reduction (BLVR) approaches under ongoing evaluation utilize a range of techniques, including airway occlusion using silicone plugs (the Endobronchial Watanabe Spigot); insertion of one-way bronchial valves; creation of artificial noncompressible communications ("bypass tracts") between cartilaginous airways and emphysematous parenchyma,[61] injection of a biologic glue to promote scarring,[62] treatment of affected lung segments with steam,[63,64] and placement of endobronchial coils (Video 36-5).[65]

Endobronchial valves have been studied most extensively and are designed to limit ventilation to the most severely involved lung regions in emphysema in an effort to reduce total lung volume, residual volume, and dynamic hyperinflation.[66,67] When placed correctly, the valves allow one-way flow of secretions and air out of the occluded pulmonary segment but prevent air entry beyond the valve (Video 36-6). The major advantage of the bronchial valves is reversibility; that is, the valves generally are removable with minimal risk to the patient. Preliminary studies have suggested that collateral ventilation across incomplete fissures may reduce bronchial valve effectiveness.[68]

Results from the first randomized study of endobronchial valves, a double-blinded, sham-controlled multicenter trial of the Zephyr endobronchial valve, demonstrated modest increases in forced expiratory ventilation in 1 second (FEV_1) and 6-minute walk distance at 6 months; unfortunately, there was an increased rate of complications, including COPD exacerbations and hemoptysis.[69] This valve is available for placement in Europe and Asia, but it is not approved in the United States at this time. One of the major downsides of the biologic approaches to induce scarring and atelectasis is development of permanent lung tissue destruction, with no option for reversibility in the event of worsening lung function or development of cancer. These approaches remain under investigation. Selecting the best technology for use in appropriate patients will be key; it is unlikely that a single approach will apply to all patients with emphysema.

BRONCHIAL THERMOPLASTY

Chronic asthma is a major cause of morbidity, increased health care utilization and cost, and death. Bronchial thermoplasty (BT) is a new bronchoscopic procedure that delivers controlled radiofrequency energy to the bronchial wall of conducting airways with the intent of inhibiting airway smooth muscle contractile function and attenuating bronchoconstriction during asthma exacerbations.

BT is performed using a radiofrequency device that delivers thermal energy to the bronchial wall during an outpatient bronchoscopic procedure. Three separate procedures are performed in order to treat all accessible upper and lower lobe airways ranging from 3 to 10 mm in diameter (Fig. 36-5). The initial randomized, multicenter Airway Intervention with Radiofrequency (AIR) trial in patients with moderate-to-severe disease demonstrated decreased asthma exacerbations

Video 36-6 A patient with severe, heterogeneous, upper lobe-predominant emphysema who was enrolled in a clinical trial of endobronchial valves. The video demonstrates valve deployment device positioning and valve deployment. *Access at www.fishmansonline.com*

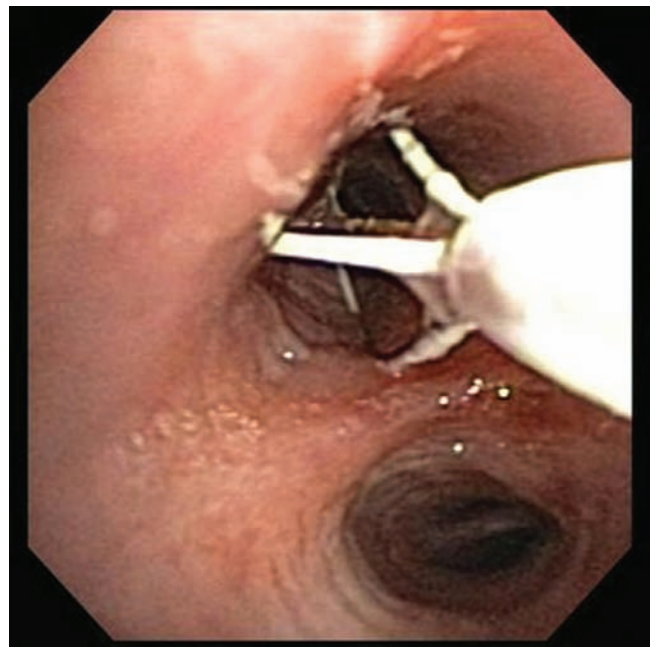


Figure 36-5 Radiofrequency array used in the airway for bronchial thermoplasty in patients with severe asthma.

in the group undergoing BT compared with patients on standard medical treatment alone.[70] This study was followed by a randomized, sham-controlled, multicenter trial (AIR2) which demonstrated significant improvement in the primary end point—asthma-related quality of life.[71] Although an increase was noted in early post-treatment asthma exacerbations requiring emergency department visits and hospitalizations, long-term follow-up data showed decreased asthma-related health care utilization for patients undergoing BT compared with those undergoing the sham procedure.[72] Based on these data, BT received FDA approval for patients with severe asthma in April 2010, but procedural reimbursement remains problematic with most private insurers. Studies are ongoing to collect additional safety data and to assess the durability of the treatment effect.

SUMMARY

Technologic advances in bronchoscopy continue to improve the pulmonologist's ability to perform minimally invasive, accurate evaluations of the tracheobronchial tree and to implement an ever-increasing array of therapeutic and palliative airway interventions. The role of therapeutic bronchoscopy will continue to evolve as further improvements are made in bronchoscopes, accessory equipment, imaging techniques, and novel technologies to treat lung diseases in which bronchoscopy was once thought to have no role. Therapeutic bronchoscopy may soon be used to provide treatment for conditions that traditionally have been treated with surgery. The major challenges in adopting many new bronchoscopic techniques into routine clinical practice will be ensuring adequate procedural competence and having well-designed studies to delineate the appropriate use of the interventions.

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CHAPTER 37

Diagnostic Thoracic Surgical Procedures: Thoracoscopy, VATS, and Thoracotomy

Robert E. Merritt

INTRODUCTION

Thoracoscopy, video-assisted thoracic surgery (VATS), and thoracotomy are well-established surgical techniques used by thoracic surgeons to diagnose benign and malignant diseases involving the thorax.

Thoracoscopy first emerged as a diagnostic tool in the early 20th century when therapeutic pneumothorax became the surgical treatment of choice for tuberculosis. In 1910, Hans Christian Jacobaeus performed the first thoracoscopic intrapleural pneumolysis for collapse therapy in the treatment of tuberculosis.[1–3] He used a rigid cystoscope with a light source to access the pleural cavity and perform a pneumolysis. After development of effective antimicrobial therapy for tuberculosis, thoracoscopy evolved as an effective diagnostic procedure to evaluate pleural effusions and pleural disease.[4] During direct diagnostic thoracoscopy, a fiberoptic mediastinoscope or bronchoscope was placed through a small intercostal incision; pleural fluid could be aspirated and sent for analysis (Fig. 37-1). In addition, the parietal pleura, visceral pleura, fissures, hilum, and diaphragm could be inspected directly.[5]

By 1990, thoracoscopy evolved into VATS. Development of high-resolution video cameras and endoscopic linear mechanical stapling devices allowed the expansion of application of VATS into the diagnosis and treatment of pulmonary nodules and interstitial lung diseases (ILDs).[6,7] The use of diagnostic thoracotomy has declined significantly since the emergence of VATS; however, the diagnostic thoracotomy may be necessary in cases in which VATS is not feasible (Table 37-1).

TECHNICAL CONSIDERATIONS

VATS is performed in the operating room under general anesthesia. A double-lumen tube is placed to isolate the lungs to enable establishment of one-lung ventilation, which is essential for performing the procedure. The use of one-lung ventilation creates sufficient space for maneuvering within the hemithorax to perform the planned procedure. Carbon dioxide (CO_2) insufflation can also be used to provide additional working space within the chest cavity by lowering the position of the diaphragm. The more inferiorly located diaphragm provides better exposure of the costophrenic sulci and lower lobes. When CO_2 is used, the maximum insufflation pressure is maintained below 6 mm Hg to avoid decreased venous return to the right heart and associated hypotension.

The typical VATS procedure utilizes three to four incisions that range from 5 to 12 mm in size. The incisions are usually arranged in a triangular configuration, with the area of interest located in the center of the triangle. (Fig. 37-2) A 5- or 10-mm fiberoptic thoracoscope is connected to a video camera and is most commonly inserted into the most inferiorly placed VATS incision (Fig. 37-3). The chest cavity is clearly visualized on a video monitor and the parietal pleura, visceral pleura, hilum, diaphragm, and mediastinum can be directly inspected. Upon completion of the procedure, a chest tube is inserted under direct visualization through one of the VATS incisions to evacuate air and pleural fluid during the early postoperative period. Simple diagnostic VATS procedures are typically well tolerated, and patients can be discharged after 1 to 2 days in the hospital. Currently, the disease processes assessed using VATS are listed in Table 37-2.

MANAGEMENT OF PLEURAL DISEASE

Both malignant and benign diseases of the pleura may be diagnosed and managed with VATS. Although thoracentesis (including pleural fluid cytology analysis) is the initial diagnostic tool of choice for an undiagnosed pleural effusion, VATS procedures provide a higher diagnostic yield: 90% to 100% compared to 60% to 80% for thoracentesis.[8–10] When the diagnosis of a pleural effusion is not determined following thoracentesis, VATS can be utilized to obtained pleural fluid and pleural biopsies for definitive diagnosis.

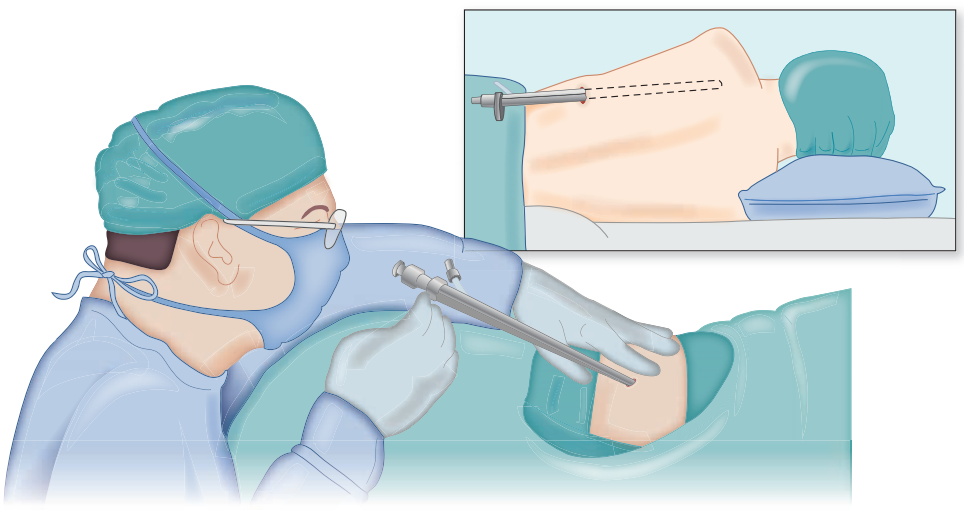

Figure 37-1 Use of a rigid bronchoscope as a thoracoscope.

TABLE 37-1 Contraindications to Video-Assisted Thoracic Surgery (VATS)

Severe hypoxia
Previous pneumonectomy or bilobectomy
Mechanical ventilator dependence
Severe chronic obstructive pulmonary disease
Pleural adhesions
Previous pleurodesis procedure
Coagulopathy
Recent acute myocardial infarction
Severe pulmonary hypertension

Malignant pleural effusions usually present as a result of an obstruction of subpleural lymphatics and are associated with advanced primary lung cancer or metastatic epithelial carcinomas that involve the lung. VATS may provide both diagnostic and therapeutic value in the management of malignant pleural effusions. A pleurodesis can be achieved by instilling chemical agents, such as talc, doxycycline, bleomycin, or tetracycline into the pleural cavity to promote pleural adhesion formation. The process obliterates the potential space between the parietal pleura and visceral pleura, thus preventing accumulation of pleural fluid. Efficacy rates in the range of 94% to 96% for VATS pleurodesis for malignant pleural effusions have been reported,[11,12] along with a morbidity rate of 2.6%.[12] In essence, the VATS approach for diagnosis and management of malignant pleural effusions is highly effective because it provides minimally invasive access to the thoracic cavity for sampling of fluid and pleural tissue, and it enables lysis of loculated adhesions and instillation of a chemical pleurodesis agent.

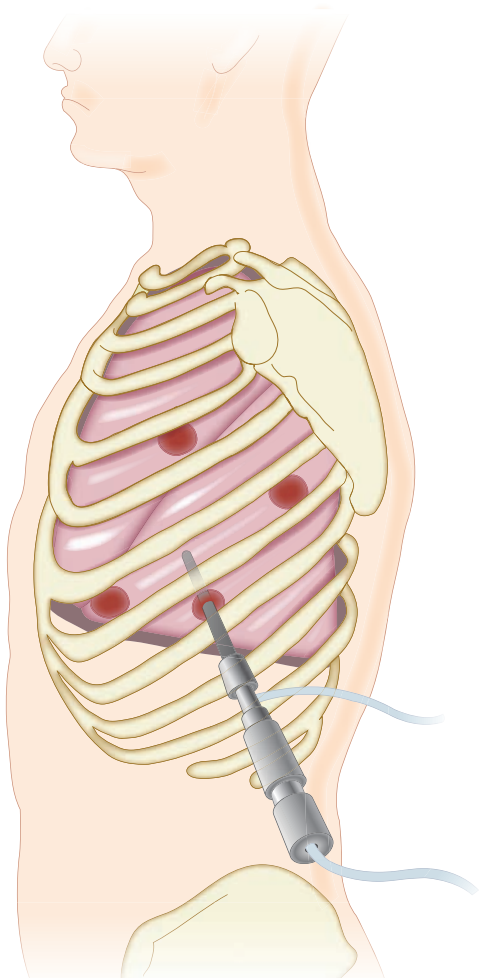

Figure 37-2 Placement of VATS incisions.

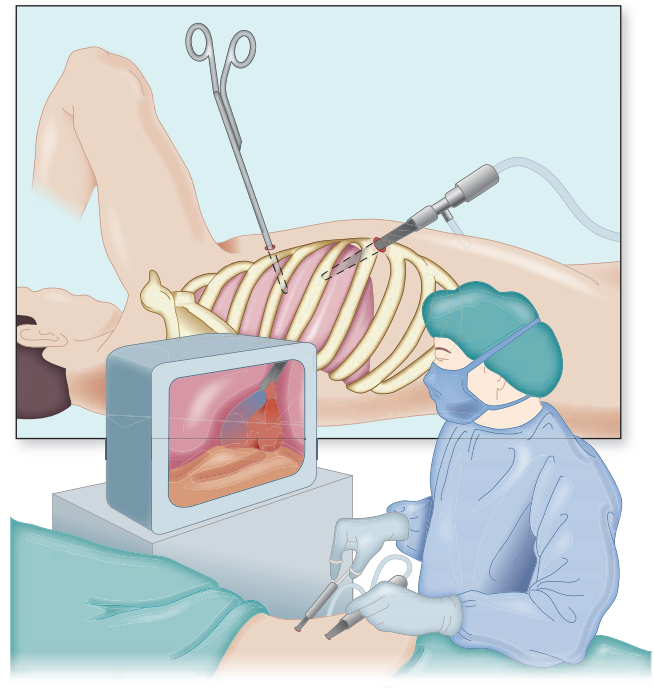

Figure 37-3 Placement of the thoracoscope through the most inferior of the VATS incisions. A video camera is connected to the thoracoscope and the image displayed on a video monitor.

The most common benign condition involving the pleura is an infection of the pleural space or empyema. Patients who present with pneumonia often have associated pleural effusions, which may be either a parapneumonic effusion or an empyema (see Chapter 76). The pleural fluid should be sampled with thoracentesis to enable the distinction between parapneumonic effusion and empyema. If the pleural fluid Gram stain or culture is positive for a pathogen, or if the fluid pH is less than 7.1, an empyema is diagnosed.

The classification of empyema is based on the temporal evolution of the pleural space infection and dictates the optimal management.

TABLE 37-2 Current Indications for Video-Assisted Thoracic Surgery (VATS)

Diagnosis of pleural effusion
Drainage of empyema
Pleurodesis
Diagnosis of a suspicious pulmonary nodule
Biopsy of the pleura
Lung biopsy for diagnosis of interstitial lung disease
Resection of pulmonary metastatic nodules
Resection of primary lung carcinoma
Biopsy of mediastinal lymph nodes
Resection of blebs or bullae for treatment of spontaneous pneumothorax
Drainage of pericardial effusion

Video 37-1 Use of VATS in drainage of empyema. *Access at www.fishmansonline.com*

Video 37-2 Use of VATS in evaluation of indeterminate pulmonary nodule. *Access at www.fishmansonline.com*

Three phases of empyema have been described: (1) The *exudative phase*, an initial phase characterized by free-flowing purulent fluid within the pleural space. Simple drainage with chest tube thoracostomy and intravenous antibiotics are usually sufficient to manage the pleural effusion. (2) The *fibropurulent phase*, characterized by loculated pleural fluid collections and fibrinous exudative deposits on the visceral pleural surfaces. In this phase, the empyema often requires a VATS or thoracotomy to lyse adhesions, break up loculations, and promote drainage of the purulent pleural fluid (Video 37-1). (3) The *fibrous phase*, characterized by formation of a thick, fibrous rind on the visceral pleural surface of the lung. A thoracotomy is usually required to achieve a complete decortication.

Early decortication using a VATS-based approach during the fibropurulent phase is highly effective and may significantly decrease morbidity associated with empyema.[13] VATS offers a decided advantage over simple chest tube thoracostomy because of multiple factors: (1) Loculated purulent fluid may be completely drained, since adhesions are directly visualized and lysed during VATS. (2) Atelectatic lung may be reexpanded under direct vision. (3) Chest tubes can be placed in the appropriate position for optimal drainage in the postoperative period.

The definitive drainage of purulent fluid associated with empyema using VATS can significantly improve patient outcomes and prevent progression to a fibrothorax, which often requires an open thoracotomy.

■ EVALUATION OF LUNG PARENCHYMAL DISEASE

Diagnosis of the solitary pulmonary nodule remains one of the most common indications for VATS. A widely cited, multi-institution, randomized study demonstrating a 20% reduction in lung cancer mortality using low-dose computed tomography (CT) to screen for lung nodules in patients at risk for lung cancer[14] will certainly increase enthusiasm for screening programs and enhance detection of indeterminate pulmonary nodules.

Currently available modalities for the diagnosis of indeterminate solitary pulmonary nodules include high-resolution CT, positron emission tomography (PET), CT-guided fine-needle aspiration (FNA), and VATS. In a randomized trial for evaluation of solitary lung nodules, CT scans performed with intravenous contrast administration have been shown to have an overall accuracy rate of 77%, sensitivity of 98%, and specificity of 58%.[15] The coupling of PET scan-based images with CT scans is often useful to determine if a lung nodule is hypermetabolic, which increases the probability of malignancy (see Chapter 32). In cases of granulomatous diseases, PET scans may generate false-positive results, as inflammatory cells readily accumulate the tracer employed, 18-fluorodeoxyglucose (18F-FDG). The sensitivity and specificity of PET–CT scanning in the evaluation of indeterminate solitary pulmonary nodules have been reported at 92% and 90%, respectively.[16]

Development of VATS has improved the diagnostic yield in evaluation of indeterminate solitary pulmonary nodules. This minimally invasive technique is well tolerated. Patients experience less postoperative pain and recover more quickly compared with patients who undergo conventional open thoracotomy.

Pulmonary nodules located in the outer third of the lung parenchyma are ideally suited for VATS wedge excisional biopsy. For lung lesions smaller than 10 mm, localization can be facilitated using transthoracic wire placement into the area of the lesion under CT guidance prior to the VATS procedure. In addition, the technique of navigational bronchoscopy (see Chapter 36, Sterman) can be employed to inject dye or place fiducial markers in close proximity to small nodules that might be difficult to locate during VATS. The diagnostic yield for VATS using wedge excision of a pulmonary nodule approaches 100%. Furthermore, since morbidity and mortality rates are exceedingly low, the VATS technique is ideal for evaluation of indeterminate pulmonary nodules (Video 37-2).

Although diffuse ILDs often present with characteristic patterns on CT scanning, histologic confirmation is often necessary to determine appropriate treatment. Reports indicate that in as many as 84% of cases of ILD evaluated with surgical lung biopsy, the course of therapy is altered by the biopsy findings.[17]

The VATS technique has been shown to result in less postoperative pain and lower morbidity compared with thoracotomy performed for purposes of lung biopsy.[18,19] Furthermore, in a randomized, controlled clinical trial, VATS and thoracotomy appear equivalent in postoperative outcomes when performed for diagnosis of ILD.[20]Given this diagnostic equivalency, and, in the author's experience, reduced postoperative pain, shorter hospital stay, and faster recovery associated with VATS, it remains the preferred diagnostic technique for patients with ILD who are ambulatory and have sufficient pulmonary reserve to tolerate one-lung ventilation. Thoracotomy is reserved for patients who are ventilator-dependent and too hypoxic to tolerate one-lung ventilation.

SUMMARY

Thoracoscopy, VATS, and thoracotomy are valuable diagnostic tools employed in the evaluation of benign and malignant diseases of the pleura and lung. VATS has emerged as a primary diagnostic method for diagnosis and treatment of malignant pleural effusions and empyema. In addition, VATS has improved the diagnostic yield in evaluation of indeterminate solitary pulmonary nodules. VATS has largely replaced diagnostic thoracotomy for ILD, since VATS results in less postoperative pain, shorter hospital stay, and faster postoperative recovery.

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CHAPTER 38

Evaluation of Respiratory Impairment and Disability

Akshay Sood

INTRODUCTION

Management of a patient with chronic lung disease does not end with its treatment. Those with chronic pulmonary disorders need additional assistance and guidance on issues related to respiratory impairment, including causation or attribution; apportionment; eligibility for, and access to, various compensation systems; workplace modifications or removal from the workplace; and vocational and other forms of rehabilitation. Unfortunately, most physicians avoid providing these services, often with disastrous socioeconomic and medical consequences for the patient.

Multiple reasons underlie the general attitude of physician reluctance in addressing impairment. These include a fear and poor understanding of the legal system as it relates to work-related diseases, pervasive confusion about various compensation systems, a mistaken notion that those who seek impairment assistance are usually malingerers, lack of training in impairment evaluation, and a desire to avoid uncompensated efforts in the context of an already burdensome clinical schedule. This chapter provides an understanding of this complex, but ignored, area in clinical pulmonary medicine.

TERMINOLOGY

This field of impairment and disability evaluation bridges medicine and law; hence, its terminology, drawn from both fields, can be confusing. The terms, impairment and disability, are often used interchangeably, but they are not synonymous. In 1980, the World Health Organization issued a statement defining *impairment* as, "any loss or abnormality of psychological, physiologic, or anatomical structure or function," and *disability* as, "any restriction or lack, resulting from impairment, of ability to perform an activity within the range considered normal for a human being."[1] The resulting social and occupational disadvantage is designated as handicap.

For a patient with chronic lung disease, the goal of respiratory impairment evaluation is objective measurement of the extent of loss of function, primarily through application of pulmonary function or exercise testing. The physician plays a key role in impairment evaluation. On the other hand, the impact of the respiratory impairment on a person's ability to perform day-to-day activities is called disability, which is typically determined through application of administrative and legal instruments by experts in these areas. The experts not only rely upon the evaluation of impairment provided by the physician, but also take into consideration other social and legal issues, as well as the energy requirements of the occupation. Impairment may occur without disability, and disability may occur without measurable impairment. Furthermore, two individuals with exactly the same respiratory impairment may suffer differing impacts on their lives, and consequently, have different levels of disability.

Respiratory impairment may be *temporary* or *permanent*. In contrast to temporary impairment, permanent impairment is not expected to improve with time or treatment. Disability may be *partial* or *total*. Total disability implies that an individual is unable to perform any work of the kind that he or she has the skills and qualifications to perform. Partial disability implies that an individual is able to perform some, but not all, of the work.

Causation or *attribution* refers to whether an exposure has been a "substantial" contributing factor in either causing or exacerbating lung disease. The level of certainty required in determining causation for occupational lung disease is different from the usual standard of 95% certainty used in medical research. The commonly accepted standard of certainty for occupational cases is that the

illness is substantially caused, or exacerbated by, an occupational exposure on a "more probable than not" basis, or a level of certainty greater than 50%.

Apportionment describes the relative contribution of multiple factors to the total respiratory impairment. For instance, both chronic inhalational asbestos exposure and cigarette smoking may be contributory factors to lung cancer. From a scientific perspective, it is usually difficult, if not impossible, to "apportion" the relative roles of multiple exposures in causation of an individual's complex, multifactorial disease. Physicians are often asked to state their opinion on apportionment in the context of the body of available knowledge in that area.

IMPAIRMENT SYSTEMS COMMONLY USED IN THE UNITED STATES

Patients seeking an impairment evaluation can be usually classified into three general types: (1) Those with advanced lung disease who apply for disability benefits under the Social Security Impairment program, (2) those with work-related lung disease who apply under the Workers' Compensation System (but also other programs, such as the Black Lung Benefits Act for coal mine workers), and (3) those who develop lung disease while working for certain employers, such as the Veterans Administration. The most commonly used impairment guidelines in the United States are the Social Security Impairment program and the Workers' Compensation System. Each are discussed in greater detail in subsequent sections.

■ SOCIAL SECURITY IMPAIRMENT

The US Social Security Administration incorporates two programs that provide financial and rehabilitative benefits to disabled individuals. Both require objective demonstration of disability using medical standards set forth in the Social Security Act.

The first program is orchestrated through Title II of the Act, known as Social Security Disability Insurance. The program is available to individuals who are insured as a result of their contributions to the Social Security trust fund (through federal taxes paid on employment earnings during their work careers). The second is orchestrated through Title XVI of the Act, known as supplemental security income, or SSI. This program is available to disabled individuals who have limited income or resources and who are not covered by contributions to the Social Security trust fund. For adults, the definition of disability is the same whether application for benefits is made under Title II or Title XVI of the Social Security Act. The Social Security Administration defines disability as, "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months." The methods used for disability evaluation under Social Security are important for the physician to understand for two reasons: (1) Disability designation under Social Security is a common and important source of financial support for many patients who are under the care of pulmonary physicians and (2) the pulmonary physician often takes an active role in helping determine eligibility under this program.

Evaluation of disability under Social Security is a staged process, beginning with application to a local Social Security field office or the Office of Disability Determination Services (DDS). The Office of DDS gathers objective medical information primarily from the treating physician, who is the preferred source of medical evaluation. If the available information is insufficient to make a determination of disability, the DDS may purchase additional testing and/or request examination from a consultant, such as a pulmonary physician.

The Social Security Administration has decided that certain specific impairments of each major body system are severe enough to prevent a person from engaging in any gainful employment and, therefore, serve as prima facie evidence that disability exists. These impairments have been codified as the Listings of Impairments.[2] Listings under the respiratory system include specific categories of disease severity, including chronic respiratory disorders; asthma; cystic fibrosis; pneumoconiosis; bronchiectasis; mycobacterial, mycotic, and other chronic persistent infections of the lung; cor pulmonale due to chronic pulmonary vascular hypertension; sleep-related breathing disorders; and lung transplant.

If a claimant cannot meet the severity criteria of the Listings, the claimant may still receive an award of benefits by presenting pertinent medical information to the DDS. An initial judgment may then be made by the DDS, but the claimant has the right to challenge an unfavorable decision and to have it reviewed by other members of the DDS staff. If the decision is still unfavorable, the claimant may appeal to the Office of Hearings and Appeals for review by an administrative law judge, who may request expert physician testimony before making a decision. Once again, the claimant may request that an unfavorable decision be reviewed by an appeals council.

The Social Security program has some unusual requirements that distinguish it from other compensation programs: (1) The program requires a "hard copy" of the volume–time curve of a recent spirogram obtained following administration of inhaled bronchodilator when obstruction is present. (2) The program incorporates arbitrary, height-specific cut points for spirometric lung function for deciding impairment status; these cut points are not determined by race, ethnicity, age, or gender. (3) The program accepts an arterial blood gas measured during steady-state *submaximal* exercise at a work rate of 5 metabolic equivalents (METs) for rating impairment in gas exchange. (4) The program denotes the patient as either impaired or not impaired, rather than specifying a percent impairment. In this setting of binary categorization, those considered impaired under Social Security criteria are expected to have a level of impairment sufficient to prevent working for a period of 1 year or longer. (5) Unlike Workers' Compensation programs, the Social Security program does not focus on occupational causation. The sole criterion for granting benefits is whether or not the claimant is able to participate in gainful employment. (6) The Social Security program also takes into account impairment from coexisting nonpulmonary conditions, such as substance abuse.

A major revision to the Social Security impairment criteria was proposed in February 2013.[3] Although the revision has not yet been approved, it is expected that the program will drop its requirements for hard copy spirometric tracings, add age and gender to the spirometric criteria, and add height and gender to the diffusing capacity criteria. If approved, it is also expected to be the first major impairment program to accept graphical printouts of pulse oximetry on room air at rest or after a 6-minute walk test for evaluating gas exchange impairment.

■ WORKERS' COMPENSATION SYSTEM

The Workers' Compensation system is a "no-fault" system of medical care and disability insurance in which private insurers or self-insured employers pay benefits to an employee sustaining an injury or illness due to workplace exposure. Under Workers' Compensation rules, workers cannot sue their employer for injury or illness.

The rules for the Workers' Compensation system vary from one state to another, but they usually follow one of the six editions

of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment.[4] The various editions of the AMA Guides contain markedly different sets of recommendations on impairment evaluation, so one must choose the right edition for the purpose. Use of the wrong edition may result in an erroneous impairment rating. While other guidelines are available on the Internet without charge, use of web-based AMA Guides carries a fee.

The sixth edition of the AMA Guides uses a standardized grid that incorporates five classes of impairment severity.[4] The grids incorporate objective, test-based key criteria for defining the impairment class, along with other criteria for fine-tuning the severity grade within a given class. Among the various objective tests, *the most severely affected test result is used to define the impairment class*.

Although the American Thoracic Society (ATS) has also developed consensus guidelines for rating impairment from chronic respiratory conditions and asthma,[5,6] these guidelines may not be accepted by a specific compensation program. While the AMA Guides generally follow the ATS schema, there exist substantial differences between the two guidelines.

FIVE GENERAL STEPS FOR IMPAIRMENT RATING

Five steps constitute the process of completing a respiratory impairment evaluation.

The first step is confirmation of the diagnosis of lung disease. Because of the medicolegal nature of the evaluation, the physician should have greater certainty of the medical diagnosis than is sometimes used in clinical practice. In other words, objective confirmation of the diagnosis is preferable.

The second step is defining maximal medical improvement (MMI). MMI occurs at the point when, following maximal therapy, no further clinical or physiologic improvement is expected to occur (although deterioration might). If therapy has not been maximized, the physician should either delay impairment evaluation or give a temporary rating. A permanent impairment evaluation should be performed only at, or after, MMI has been reached.

The third step is identifying the correct guideline for rating impairment. As discussed previously, several compensation systems exist, each with its own unique guideline. Therefore, identification of the compensation system for which the patient is eligible is essential, and the evaluating physician must be familiar with the specific guideline to be used. Of course, some patients may be eligible for more than one compensation program and may apply for more than one program contemporaneously.

The fourth step is to supplement the history and physical examination findings with appropriate objective tests. Performance of these tests should strictly adhere to standards of the ATS.[7–10]

The fifth and final step requires writing a comprehensive report of the patient's history, physical examination, and review of objective tests. The assessment should provide clear and accurate answers, in lay terms, to the questions asked. The evaluation should state the diagnosis and whether MMI has been reached, and it should make note of the presence and degree of respiratory impairment. The specific impairment scheme used, including the specific page and table of the guideline used, should be referenced. In work-related respiratory disorders, causation, apportionment, and work restrictions should also be addressed, as requested.

GENERAL APPROACH FOR EVALUATING RESPIRATORY IMPAIRMENT

After determining patient eligibility for a specific compensation system, as described previously, the physician gathers data that is relevant to rating respiratory impairment. In general, impairment criteria are based upon history, physical examination, and objective test results.

The medical history focuses on detailed past and present occupational history, tobacco use and environmental exposures, presence and severity of respiratory symptoms, such as dyspnea, cough, sputum production, and wheezing, and medication history. Relevant features in the physical examination include breathing pattern, shape of chest wall, adventitious lung sounds, cyanosis, digital clubbing, and evidence of cor pulmonale.

RESTING PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) (Chapter 33) are the cornerstone for rating respiratory impairment and should be performed according to the most recent ATS standards.[7–10] Spirometry and diffusing capacity are the key PFTs for assessing respiratory impairment for chronic respiratory conditions. Postbronchodilator spirometry is used when airflow limitation is present. Methacholine challenge tests are used for rating impairment for asthma under the AMA Guides.[4]

Resting and exercise-related hypoxemia, derived from arterial blood gas results and adjusted for altitude and arterial P_{CO_2} level, may be used under the Social Security impairment system to classify gas exchange abnormalities. However, arterial blood gas sampling needs to be repeated within 3 weeks to 6 months of the first sample.[3] Although the presence of hypoxemia was previously used to rate impairment as severe under the fifth edition of the AMA Guides, the sixth edition does not include hypoxemia in the rating of respiratory impairment since it is considered invasive and difficult to standardize.[4]

Adjustment of PFTs for race, ethnicity, and gender is recommended by most impairment guidelines, with the notable exception of the Social Security impairment system, which currently uses uniform height-specific cut points for all individuals, irrespective of race, ethnicity, and gender.[2] Thus, under this system, older women are more likely to be rated as disabled than are younger men.

According to the sixth edition of the AMA Guides, specific NHANES III reference standards for spirometry should be used for Caucasian Americans, Mexican Americans, and African Americans.[4,11] For the remaining population subgroups, no clear guidelines are provided. Corrected single-breath carbon monoxide diffusing capacity (D_{LCO}) is used under the AMA Guides, ATS guidelines, and Social Security Impairment guidelines for impairment rating, but it is not used under the Veterans Administration guidelines. Crapo's reference standards for D_{LCO} are used for comparison with measured values.

The cut points for impairment classification, as suggested by the various impairment guidelines (Tables 38-1–38-3) are set arbitrarily and may differ from those recommended for assessing degree of lung disease severity by other professional organizations, such as the 2005 ATS statement[8] or by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[13] Some investigators have suggested that lung function thresholds should be expressed as a z-score, which converts a raw measurement on a test to a standardized score expressed in units of standard deviations.[14,15] This strategy, although scientifically valid, is not currently used for impairment evaluation.

Methacholine bronchoprovocation tests are useful for assessing bronchial hyperresponsiveness and in rating impairment from asthma under the AMA Guide and ATS guidelines (Tables 38-1 and 38-2).[4,6] The methacholine PC_{20} (provocative concentration of methacholine, expressed as mg/mL that results in at least 20% drop in FEV_1 compared to the pretest baseline) is a key parameter for rating asthma impairment under the sixth edition of the AMA Guides.[4] The performance of methacholine bronchoprovocation tests should also strictly adhere to the ATS guidelines.[16]

TABLE 38-1 Classification of Respiratory Impairment from Chronic Lung Diseases, Using the Sixth Edition of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment

American Medical Association Class	Class 0	Class 1: 2–10% impairment of the whole person	Class 2: 11–23% impairment of the whole person	Class 3: 24–40% impairment of the whole person	Class 4: 45–65% impairment of the whole person
Severity grade (%)		A (2%), B (4%), C (6%), D (8%), E (10%)	A (11%), B (14%), C (17%), D (20%), E (23%)	A (24%), B (28%), C (32%), D (36%), E (40%)	A (45%), B (50%), C (55%), D (60%), E (65%)
Objective Tests					
FVC (% predicted)	≥80% predicted and	70–79% predicted or	60–69% predicted or	50–59% or	<50% or
FEV_1 (% predicted)	≥80% predicted and	65–79% predicted or	64–55% predicted or	45–54% or	<45% or
FEV_1/FVC%	>Lower limit of normal and/or >75% predicted) and	N/A	N/A	N/A	N/A
D_{LCO} (% predicted)	≥75% predicted	65–74% predicted	55–64% predicted	45–54%	<45%
$\dot{V}_{O_2max}$					
mL/kg/min	>25 or	22–25 or	21–18 or	15–17 or	<15 or
METs	>7.1	6.1–7.1	5.1–6.0	4.3–5.0	<4.3
History					
	No current symptoms and/or intermittent dyspnea that does not require treatment	Dyspnea controlled with intermittent or continuous treatment or intermittent mild dyspnea despite continuous treatment	Constant mild dyspnea despite continuous treatment or intermittent moderate dyspnea despite continuous treatment	Constant moderate dyspnea despite continuous treatment or intermittent severe dyspnea despite continuous treatment	Constant severe dyspnea despite continuous treatment or intermittent extreme dyspnea despite continuous treatment
Physical Findings					
	No current signs of disease	Physical findings not present with continuous treatment or intermittent mild physical findings	Constant mild physical findings despite continuous treatment or intermittent moderate physical findings	Constant moderate physical findings despite continuous treatment or intermittent severe physical findings	Constant severe physical findings despite continuous treatment or intermittent extreme physical findings

FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; D_{LCO}, diffusing capacity of carbon monoxide; $\dot{V}_{O_2max}$, measured maximal exercise capacity; MET or metabolic equivalent is the multiple of basal oxygen consumption, approximately 3.5 mL/kg/min; N/A, not applicable.

Source: Reproduced with permission from American Medical Association. The pulmonary system. In: Rondinelli RD, ed. Guides to the Evaluation of Permanent Impairment. 6th ed. American Medical Association; 2008:77–99. Copyright 2008. American Medical Association. All Rights Reserved.

EXERCISE TESTS

Maximal cardiopulmonary exercise tests are difficult to perform due to need for specialized equipment and trained personnel, are expensive and not readily available, and carry a risk to the patient. Test performance should strictly adhere to the ATS guidelines.[17] Clear agreement on the role of exercise tests in the evaluation of respiratory impairment is lacking. Generally, in cases in which subjective dyspnea is disproportionate to the resting PFT results,

TABLE 38-2 American Thoracic Society's (ATS) Classification of Respiratory Impairment[5]

Impairment Class	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired
Work ability		Usually able to perform most jobs	Diminished ability to perform many jobs	Unable to meet physical demands of most jobs including travel to work
FVC (% predicted)	≥80%	60–79%	51–59%	≤50%
FEV_1 (% predicted)	≥80%	60–79%	41–59%	≤40%
FEV_1/FVC	≥75%	60–74%	41–59%	≤40%
D_{LCO} (% predicted)	≥80%	60–79%	41–59%	≤40%
$\dot{V}_{O_2max}$ (mL/kg/min)	≥25 (or 7.1 METs)			≤15 (or 4.3 METs)

FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; D_{LCO}, diffusing capacity of carbon monoxide; $\dot{V}_{O_2max}$, measured maximal exercise capacity; MET or metabolic equivalent is the multiple of basal oxygen consumption, approximately 3.5 mL/kg/min.

Source: Data from Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. Am Rev Respir Dis. 1986;133(6):1205–1209. This document was published in 1986 and is currently in revision. Certain aspects of this document may be out of date and caution should be used when applying these in clinical practice or other usages.

TABLE 38-3 Impairment Rating Guidelines for Chronic Obstructive Lung Diseases using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY		
Height without Shoes (cm)	**Height without Shoes (in)**	**FEV_1 Equal to or Less than (L, BTPS)**
≤154	≤60	1.05
155–160	61–63	1.15
161–165	64–65	1.25
166–170	66–67	1.35
171–175	68–69	1.45
176–180	70–71	1.55
≥181	≥72	1.65

(B) VETERANS ADMINISTRATION
Chronic Bronchitis
Pronounced (100% rating): with copious productive cough and dyspnea at rest; PFTs showing a severe degree of chronic airway obstruction with symptoms of associated severe emphysema or cyanosis and findings of right-sided heart involvement
Severe (60% rating): with severe productive cough and dyspnea on slight exertion and PFTs indicative of severe ventilatory impairment
Moderately severe (30% rating): persistent cough at intervals throughout the day, considerable expectoration, considerable dyspnea on exercise, rales throughout chest, beginning chronic airway obstruction
Moderate (10% rating): considerable night or morning cough, slight dyspnea on exercise, scattered bilateral rales
Mild (0% rating): slight cough, no dyspnea, few rales
Emphysema
Pronounced (100% rating): intractable and totally incapacitating; with dyspnea at rest, or marked dyspnea and cyanosis on mild exertion; severity of emphysema confirmed by CXR and PFTs
Severe (60% rating): exertional dyspnea sufficient to prevent climbing one flight of steps or walking one block without stopping; ventilatory impairment of severe degree confirmed by PFTs with marked impairment of health
Moderate (30% rating): with moderate dyspnea occurring after climbing one flight of steps or walking more than one block on a level surface; PFTs consistent with findings of moderate emphysema
Mild (10% rating): with evidence of ventilatory impairment on PFTs and/or definite dyspnea on prolonged exertion
(C) AMA GUIDES AND ATS GUIDELINES
Use criteria outlined in Tables A and B respectively in the text

FEV_1, forced expiratory volume in the first second; BTPS, body temperature and pressure saturated with water vapor.
For mixed obstructive and restrictive lung diseases with gas exchange impairment, evaluate under any of the criteria listed in Tables 38-3(A), 38-6(A), or 38-7.
Social Security impairment system has separate guidelines for patients with bronchiectasis.
Source: Data from Social Security Administration and Veterans Administration.[2,12]

or when PFTs are difficult to interpret because of submaximal performance, cardiopulmonary exercise tests may be considered. Such tests may also help identify unanticipated coexisting conditions, such as cardiovascular or pulmonary vascular disease, as the cause of exercise limitation.

Exercise testing may also be useful in determining whether an individual can perform a specific job with a known energy requirement. Under the ATS guidelines, the estimation of impairment from oxygen consumption at peak exercise ($\dot{V}_{O_2peak}$) is based on the widely held, but untested, assumptions that a worker involved in manual labor can comfortably work at 40% of $\dot{V}_{O_2peak}$ (corresponding to lower limit of generally accepted normal values for anaerobic threshold) for prolonged periods,[5] and that $\dot{V}_{O_2}$ requirements can be assigned to specific occupations. Individuals whose $\dot{V}_{O_2peak}$ is ≤15 mL/kg/min would be uncomfortable performing most jobs because they would find it difficult to travel back and forth to their place of employment (Table 38-2).[5] Unfortunately, data on $\dot{V}_{O_2}$ requirements of most jobs in modern workplaces are not currently available. Furthermore, jobs with the same title may vary considerably in their $\dot{V}_{O_2}$ requirements from one work site to another.

Submaximal exercise tests at a workload of approximately 17 mL O_2/kg/min (5 METs) or less of exercise can be performed at steady state to obtain arterial blood gases, which are then used to evaluate impairment of gas exchange under the Social Security impairment system when criteria for neither obstructive nor restrictive disorders are met. Use of submaximal exercise tests is however not currently recommended by any other impairment guideline.

IMAGING

Imaging studies are primarily useful for confirming the diagnosis of lung disease. They are less useful in rating respiratory impairment, since the correlation between radiographic abnormality and physiologic dysfunction is imperfect.

Chest radiographic evidence of pneumoconiosis is rated according to the 2011 International Labor Organization's (ILO) International Classification of Radiographs of Pneumoconiosis scheme (also called "B-reading"). The 2011 standards extended the applicability of the Classification to digital chest radiographs. The extent or profusion of small-sized parenchymal opacities is rated as 0, 1, 2, or 3. An intermediate score of 1/0 (i.e., profusion of small opacities greater than 0 but less than 1 profusion score) is often used to confirm the presence of pneumoconiosis.

Some determinations of respiratory impairment are not dependent on PFTs. They are based on environment-related diagnoses

(e.g., occupational asthma or hypersensitivity pneumonitis) and warrant proscription of continuing exposure to inciting agents). In addition, impairment may be based upon prognosis (e.g., unresectable lung cancer) or public health considerations (e.g., pulmonary tuberculosis).

SCIENTIFIC RATIONALE FOR CHOICE OF TESTS USED FOR IMPAIRMENT EVALUATION FOR CHRONIC RESPIRATORY DISORDERS

Impairment evaluation for chronic respiratory conditions is based upon PFT values at rest and with exercise. The premise for these tests is that $\dot{V}_{O_2peak}$ reasonably measures ability to work, and that resting PFTs, such as forced expiratory volume in 1 second (FEV_1) and D_{LCO}, reasonably predict $\dot{V}_{O_2peak}$ values.

OXYGEN CONSUMPTION AT PEAK EXERCISE AS THE GOLD STANDARD FOR MEASURING ABILITY TO WORK

Most of the available medical literature appears to support the view that $\dot{V}_{O_2peak}$ value, expressed as mL/kg/min, is the gold standard for assessing impairment.[18,19] With exercise on a cycle ergometer, $\dot{V}_{O_2}$ increases linearly with external work,[17] and $\dot{V}_{O_2peak}$ represents the maximal work an individual can perform during a short burst of activity. Some have advocated use of percent predicted $\dot{V}_{O_2peak}$ values (i.e., loss of aerobic capacity), instead of $\dot{V}_{O_2peak}$ expressed in mL/kg/min (i.e., remaining aerobic ability) for evaluating impairment in patients with respiratory disease, since the latter approach overestimates impairment in older and obese subjects Fig. 38-1.[20,21] In addition, some consider the value for $\dot{V}_{O_2}$ at anaerobic threshold ($\dot{V}_{O_2}AT$) as a better index for work ability than $\dot{V}_{O_2peak}$.[21] Individuals are unable to sustain work rates above anaerobic threshold values. However, no major guidelines currently use percent predicted $\dot{V}_{O_2peak}$ values or $\dot{V}_{O_2}AT$ to rate impairment.

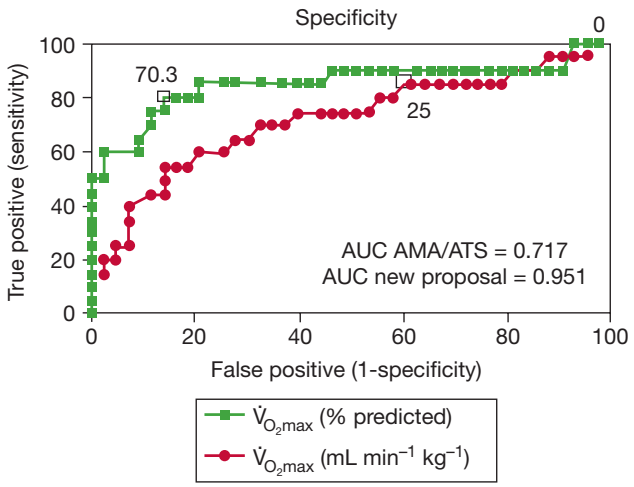

Figure 38-1 Receiver operating characteristics (ROC) curves of two classifications (AMA/ATS vs. new classification proposed by Neder et al.), using the $\dot{V}_{O_2}$ at anaerobic threshold ($\dot{V}_{O_2}AT$) as the "gold standard." The *open squares* represent the cutoffs for normality for $\dot{V}_{O_2peak}$ using the two classification schema. Neder et al. have advocated the use of percent predicted $\dot{V}_{O_2peak}$ values (i.e., loss of aerobic capacity) instead of $\dot{V}_{O_2peak}$ in mL/kg/min (i.e., remaining aerobic ability) for the evaluation of impairment in patients with respiratory disease since the latter approach overestimates impairment in older and obese subjects. AMA, American Medical Association; ATS, American Thoracic Society; AUC, area under the ROC curve; $\dot{V}_{O_2}$, oxygen consumption. *(Reproduced with permission from Neder JA, Nery LE, Bagatin E, Lucas SR, Ancao MS, Sue DY. Differences between remaining ability and loss of capacity in maximum aerobic impairment. Braz J Med Biol Res. 1998;31(5):639–646.)*

COMPARISON OF RESTING PULMONARY FUNCTION TESTS WITH OXYGEN CONSUMPTION AT PEAK EXERCISE

Low values for resting PFTs (i.e., FEV_1 or D_{LCO}) predict low $\dot{V}_{O_2peak}$ levels; poor scores on the Short Physical Performance Battery (tests that assess lower extremity function); less distance walked during the 6-minute walk test; and a greater risk of self-reported functional limitation.[22,23]

FEV_1 is linearly correlated with $\dot{V}_{O_2peak}$ levels,[23] but the reported correlations vary widely between studies, resulting in variance values ranging from 0.25 to 0.71.[23–28] Use of absolute versus percent predicted values largely yield similar correlation measures.[27] Although some studies demonstrate that FEV_1 and forced vital capacity (FVC) have similar predictive value for $\dot{V}_{O_2peak}$ levels,[27] most report FEV_1 to be a stronger predictor than FVC. A 2005 ATS statement indicated that percent predicted FEV_1, rather than FVC, should be used to categorize severity of impairment for all respiratory diseases.[8] The predictive ability of FEV_1 for $\dot{V}_{O_2peak}$ increases if it is used in combination with another variable, such as D_{LCO}, minute ventilation ($\dot{V}_E$), or dead space ventilation measure during exercise (V_D/V_T).[27] D_{LCO} does not predict $\dot{V}_{O_2peak}$ among healthy controls,[24] but it does so among subjects with COPD and those with occupational lung diseases, where it may account for a variance of 0.25 to 0.76 in various studies.[26,27,29]

Despite the previously noted correlations in population studies, resting PFTs cannot accurately predict $\dot{V}_{O_2peak}$ values among individuals, particularly those with occupational lung diseases. In a comparison study of impairment ratings obtained using simultaneous resting PFTs and cardiopulmonary exercise tests conducted in 216 ambulatory patients with COPD, the two methods resulted in similar impairment rating in only 30.1%. Ratings were similar between the two methods in the extreme subgroups of normal or severely impaired individuals. 61.1% were found to be less impaired according to exercise testing than according to resting PFTs, and 8.8% were more impaired according to exercise testing than resting PFTs (Table 38-4). These data suggest that use of resting PFTs and exercise testing for rating impairment often yields discrepant results.

TABLE 38-4 Degree of Impairment, as Assessed by Resting Pulmonary Function Tests and Cardiopulmonary Exercise Tests[a19]

Degree of Impairment	Resting PFT (%)	CPET (%)
None	6	28
Mild	26	36
Moderate	38	20
Severe	30	16

PFT, pulmonary function test; CPET, cardiopulmonary exercise test; FEV_1, Forced expiratory volume in 1 second.

[a]Among 216 ambulatory patients with COPD with mean percent predicted FEV_1 of 54.1 ± 16.8% and mean age of 57.9 ± 6.9 years

Source: Reproduced with permission from Fink G, Moshe S, Goshen J, et al. Functional evaluation in patients with chronic obstructive pulmonary disease: pulmonary function test versus cardiopulmonary exercise test. J Occup Environ Med. 2002;44(1):54–58.

PFTs other than FEV_1 and D_{LCO} may also help predict $\dot{V}_{O_2peak}$ values. These include inspiratory capacity in flow-limited obstructive diseases;[30] peak inspiratory pressure in chronic obstructive diseases;[26] exercise ventilation ($\dot{V}_E$) in both obstructive and restrictive lung diseases;[27] and submaximal exercise tests, including 6-minute walk test duration.[20] Use of these tests is however not currently recommended by any impairment guideline. Performance of maximal voluntary ventilation (MVV) is not recommended except under the Black Lung Benefits Act.[31] MVV is markedly effort dependent and bears a fixed relationship with FEV_1;[32] therefore, it is of limited value.

Further, both baseline oxygen saturation and the lowest oxygen saturation measured with a finger oximeter probe during a submaximal test correlate with $\dot{V}_{O_2peak}$ in patients with idiopathic pulmonary fibrosis,[20] but not in those with COPD.[33]

ASTHMA

Unlike most chronic respiratory conditions, asthma is an episodic disease, and impairment evaluation for asthma is particularly difficult. Therefore, most impairment rating schemes incorporate separate guidelines for rating asthma impairment.

DETERMINANTS OF WORK ABILITY IN ASTHMA

Among subjects with methacholine-confirmed asthma, a lower self-reported work ability is associated with lower PC_{20} value (i.e., higher degree of airway hyperresponsiveness), greater clinical severity of disease (based on minimum medication need to maintain asthma control), and the presence of respiratory symptoms in the workplace.[34] However, no relationships are evident with regard to baseline FEV_1 or FVC in both unadjusted and adjusted analyses.[34] Although controversial, methacholine PC_{20} (see Chapter 33) has been accepted as the key parameter for rating asthma impairment under the sixth edition of the AMA Guides.[4]

COMPARISON BETWEEN RESPIRATORY SYMPTOMS AND PC_{20}

For most subjects with asthma, greater breathlessness perceived during asthma attacks is not correlated with greater decline in peak expiratory flow rate [35] or with a lower PC_{20}.[36]

COMPARISON BETWEEN MINIMUM MEDICATION NEED AND PC_{20}

Almost all medications used to treat asthma improve PC_{20} values, that is, decrease bronchial hyperresponsiveness.[37–49] In one study, patients with asthma with the minimum medication needed to control symptoms were divided into four groups: (1) those who required no medication; (2) those who required short-acting β_2-agonist occasionally, but not daily; (3) those who required daily short-acting β_2-agonist; and (4) those who required additional inhaled corticosteroid dosing. The mean PC_{20} value was highest in group 1 and lowest in group 4; the differences between each group were significant.[50] Minimum medication need is, therefore, an important predictor for both work ability and airway hyperresponsiveness in asthma.

COMPARISON BETWEEN PERCENT PREDICTED FEV_1 AND PC_{20}

In a small clinical population of smokers and nonsmokers, as well as in a population of subjects with asthma with concomitant stable bronchiectasis, baseline FEV_1 has been shown to correlate with methacholine PC_{20} values.[51]

IMPAIRMENT RATING FOR ASTHMA

Impairment ratings for episodic diseases like asthma are problematic; the rating schemes differ dramatically as well (Tables 38-5A–38-5C).

The methacholine PC_{20} is the key parameter for rating asthma impairment under the sixth edition of the AMA Guides (Table 38-5B).[4] On the other hand, PC_{20} and extent of FEV_1 reversibility are given less weight than are either minimum medication need or postbronchodilator FEV_1 in the multicomponent asthma impairment scoring scheme recommended by the 1993 ATS guidelines (Table 38-5C).[6] Under Social Security impairment criteria, patients with asthma may be rated by FEV_1 or by a clinical history of frequent, severe exacerbations, despite maximal asthma therapy; a methacholine PC_{20} measurement is not required (Table 38-5A). On the contrary, AMA Guides and ATS guidelines do not

TABLE 38-5A Impairment Rating Guidelines for Asthma Using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY
(1) Asthma with chronic asthmatic bronchitis: evaluate under the criteria for chronic obstructive airway disease (Table 38-3A)
(2) Attacks, in spite of prescribed treatment and requiring physician intervention, occurring at least once every 2 mo, or at least 6 times a year. Each in-patient hospitalization >24 h for control of asthma counts as two attacks. An evaluation period of at least 12 consecutive months must be used to determine the frequency of attacks
(B) VETERANS ADMINISTRATION[a]
Pronounced (100% rating): asthmatic attacks very frequently with severe dyspnea on slight exertion between attacks and with marked loss of weight or other evidence of severe impairment of health
Severe (60% rating): frequent attacks of asthma (one or more attacks weekly), marked dyspnea on exertion between attacks with only temporary relief by medication; more than light manual labor precluded
Moderate (30% rating): asthmatic attacks rather frequent (separated by only 10–14-d intervals) with moderate dyspnea on exertion between attacks
Mild (10% rating): paroxysms of asthmatic type breathing (high-pitched expiratory wheezing and dyspnea) occurring several times a year with no clinical findings between attacks
(C) AMA GUIDES AND ATS GUIDELINES
Use scoring criteria in Tables 38-5B and 38-5C, respectively

[a]*In the absence of clinical findings of asthma at time of examination, a verified history of asthmatic attacks must be on record.*

Source: Data from Social Security Administration and Veterans Administration.[2,12]

TABLE 38-5B Classification of Respiratory Impairment from Asthma, using the Sixth Edition of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment

Class	Class 0	Class 1	Class 2	Class 3	Class 4
Whole person impairment rating (%)	0	2–10%	11–23%	24–40%	45–65%
Severity grade (%)		A (2%), B (4%), C (6%), D (8%), E (10%) (minimal)	A (11%), B (14%), C (17%), D (20%), E (23%) (mild)	A (24%), B (28%), C (32%), D (36%), E (40%) (moderate)	A (45%), B (50%), C (55%), D (60%), E (65%) (severe)
Clinical parameters (minimum medication need)	No medication required	Occasional bronchodilator, not daily	Daily low-dose inhaled steroid (<500 µg beclomethasone or equivalent)	Daily medium or high-dose inhaled steroids (500–1000 µg beclomethasone or equivalent) and/or short periods of systemic steroids and a long-acting bronchodilator. Daily use of steroids (systemic and inhaled) and daily use of maximum bronchodilators	Asthma not controlled by treatment
Maximum postbronchodilator percent predicted FEV_1	>80%	70–80%	60–69%	50–59%	<50%
PC_{20} (key factor)[a]	6–8 mg/mL	3–5 mg/mL	>0.5–3 mg/mL	0.25–0.5 mg/mL	0.125–0.24 mg/mL

FEV_1, forced expiratory volume in the first second; PC_{20}, provocative concentration of methacholine associated with 20% decrease in FEV_1 from baseline.
[a]The methacholine PC_{20} is the key parameter for rating asthma impairment. If PC_{20} cannot be obtained, postbronchodilator percent predicted FEV_1 is used as the key factor.
Source: Reproduced with permission from American Medical Association. The pulmonary system. In: Rondinelli RD, ed. Guides to the Evaluation of Permanent Impairment. 6th ed. American Medical Association; 2008.

incorporate frequency of acute exacerbations in the impairment rating for asthma. Given the efficacy of currently recommended asthma therapies, frequent emergency room visits or hospitalizations generally reflect inadequate treatment and failure to achieve the objectives of treatment. The AMA Guides and ATS guidelines instead use minimum medication need for asthma control as a better reflection of the severity of disease for the purpose of impairment assessment than frequency of asthma exacerbations. Hence, it is easy to see why impairment ratings for the same patient with asthma might vary widely among various compensation systems.

Impairment rating for occupational asthma is even more problematic. In these cases, both temporary and long-term impairment evaluation should be performed.[6] Temporary impairment for patients with sensitizer-induced occupational asthma should be performed after removing the worker from exposure. Early cessation of exposure improves prognosis in sensitizer-induced occupational asthma. Sometimes, physiologic tests may be normal, and symptoms and need for treatment may subside after early cessation of exposure, resulting in 0% measureable impairment. However, such an individual should be considered as100% disabled on a permanent basis from working in a job that exposes him or her to the specific sensitizing agent.[6] It is not necessary to wait for long-term impairment rating to initiate vocational rehabilitation in such a case.[6] The long-term impairment evaluation is performed using the rating systems devised for nonoccupational asthma at least 2 years after cessation of exposure, when improvement has been shown to plateau.[52]

PNEUMOCONIOSES

According to the AMA Guides, those who develop pneumoconiosis should limit further exposure to the offending agent, "particularly if radiographic changes have occurred at a relatively young age or if there is associated physiologic impairment."[4] It follows that an older patient who is nearing retirement, with minimal radiographic change after a long history of exposure, could elect to continue in the workplace under the assumption of a lower risk of developing future disabling disease. Such discretionary decisions should be made based on a discussion between the patient and physician.[4] While the Veterans Administration has specific guidelines for impairment ratings for pneumoconiosis, the Social Security construct is based upon standard criteria for assessing impairment from any chronic respiratory disorder, as listed in Tables 38-3(A), 38-6(A), and 38-7.[2]

COAL WORKERS' PNEUMOCONIOSIS

In 1972, the Black Lung Benefits Act set eligibility criteria for the awarding of benefits to coal miners and their survivors in the United States. The Act defines pneumoconiosis as, "a chronic dust disease of the lung and its sequelae, including respiratory and pulmonary impairments arising out of coal mine employment." This definition encompasses two classes of coal dust–related lung diseases: medical or "clinical" pneumoconioses and statutory or legal pneumoconioses. Medical or "clinical" pneumoconioses include diseases that pulmonologists usually consider as pneumoconioses (such as coal workers' pneumoconiosis, anthracosis, anthracosilicosis, massive pulmonary fibrosis, silicosis, or silicotuberculosis). Statutory or legal pneumoconioses include any chronic restrictive or obstructive pulmonary disease arising out of coal mine employment, including chronic bronchitis and emphysema.

A coal miner applying for Black Lung benefits must show that he or she has pneumoconiosis, that the pneumoconiosis resulted from coal mine employment, and that it has resulted in "total disability," defined as inability to perform usual coal mine work. The miner must supply medical evidence of pneumoconiosis that includes (1) a chest radiograph, along with a report of the findings using the ILO classification system; (2) a physician report detailing the occupational, medical, and smoking history, as well as all manifestations of chronic respiratory disease; (3) spirometric results (including MVV); (4) altitude-adjusted arterial blood gas results; and (5) biopsy or autopsy evidence, if available.

TABLE 38-5C American Thoracic Society's (ATS) Asthma Impairment Rating Guideline

(A) POST-BRONCHODILATOR FEV_1	
Score	**FEV_1 (%Predicted)**
0	>lower limit of normal
1	70–lower limit of normal
2	60–69
3	50–59
4	<50

(B) REVERSIBILITY OF FEV_1 OR DEGREE OF AIRWAY HYPERRESPONSIVENESS[a]		
Score	**%FEV_1 Change**	**PC_{20} (mg/mL)**
0	<10	>8
1	10–19	8–>0.5
2	20–29	0.5–>0.125
3	≥30	≤0.125

(C) MINIMUM MEDICATION NEEDS[b]	
Score	**Medication**
0	No medication
1	Occasional bronchodilator, not daily, and/or occasional cromolyn, not daily
2	Daily bronchodilator and/or daily cromolyn and/or daily inhaled low-dose inhaled steroid (<800 µg beclomethasone or equivalent)
3	Bronchodilator on demand and daily high-dose inhaled steroid (>800 µg beclomethasone or equivalent) or occasional course (1–3/y) of systemic steroid
4	Bronchodilator on demand and daily high-dose inhaled steroid (>1000 µg beclomethasone or equivalent) and daily systemic steroid

(D) SUMMARY OF IMPAIRMENT RATING CLASSES	
Impairment Rating	**Sum of Scores from Sections A, B, and C**
0	0
I	1–3
II	4–6
III	7–9
IV	10–11
V	Asthma not controlled despite maximal treatment, i.e., FEV_1 remaining <50% despite use of ≥20 mg Prednisone per day

FEV_1, forced expiratory volume in the first second; PC_{20}, provocative concentration of methacholine associated with 20% decrease in FEV_1 from baseline.

[a]When the postbronchodilator FEV_1 value is above the lower limit of normal, the PC_{20} value should be determined and used for rating of impairment; when the postbronchodilator FEV_1 value is <70% of the predicted value, the degree of reversibility is used; when the FEV_1 value is between 70% of the predicted value and the lower limit of normal, either the degree of reversibility of FEV_1 or the PC_{20} can be used.

[b]The need for minimum medication should be demonstrated by the treating physician, for example, previous records of exacerbations when medications have been reduced.

Source: Adapted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis. 1993;147(4):1056–1061. Official journal of the American Thoracic Society. This document was published in 1993 and is currently in revision. Certain aspects of this document may be out of date and caution should be used when applying these in clinical practice or other usages.

Chest radiographic findings are accepted to show pneumoconioses if they demonstrate the presence of either small parenchymal opacities of at least category 1/0 profusion or large opacities. The absence of radiographic evidence of pneumoconioses makes medical or clinical pneumoconioses unlikely, but it may be noted in patients with statutory or legal pneumoconiosis.[31] Spirometry must meet the 1979 ATS repeatability criteria that require the maximum FVC and FEV_1 be within 5% or 100 mL, whichever is greater.[53] The arterial blood gas analysis may be performed at rest or with exercise. The Department of Labor has published detailed tables of FEV_1, FVC, and MVV, as well as arterial blood gas values delineating criteria for "total disability."[31]

UNITED STATES DEPARTMENT OF ENERGY EMPLOYEES IN NUCLEAR WEAPONS FACTORIES

The US Energy Employees' Occupational Illness Compensation Program Act (EEOICPA) was enacted to provide compensation and medical benefits to workers who acquired disease in the course of their work in the nuclear defense industry. Those eligible include employees and former employees of the Department of Energy at nuclear weapons factories, as well as private contractors and subcontractors at those locations. In addition to exposure to silica, asbestos, or mixed dusts that occurred during uranium ore extraction, many workers were also exposed to beryllium (used in the manufacture of ballistic missile nose cones) and radiation.

TABLE 38-6 Impairment Rating Guidelines for Restrictive Lung Diseases using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY		
Height without Shoes (cm)	**Height without Shoes (in)**	**Vital Capacity Equal to or Less than (L, BTPS)**
≤154	≤60	1.25
155–160	61–63	1.35
161–165	64–65	1.45
166–170	66–67	1.55
171–175	68–69	1.65
176–180	70–71	1.75
≥181	≥72	1.85
(B) VETERANS ADMINISTRATION		
Leaves the rating to the judgment of the physician, according to symptoms, anatomical extent, pulmonary functions and complications.		
(C) AMA GUIDES AND ATS GUIDELINES		
Use criteria outlined in Tables 38-6A and B, respectively		

BTPS, body temperature and pressure saturated with water vapor.
In severe kyphoscoliosis, the measured span between the fingertips when the upper extremities are abducted 90 degrees should be substituted for height.
For mixed obstructive and restrictive lung diseases with gas exchange impairment, evaluate under any of the criteria listed in Tables 38-3A,38-6A, or 7.
Source: Data from Social Security Administration and Veterans Administration.[2,12]

In contradistinction to Black Lung evaluation, the Part E of the EEOICPA has adopted the standards of the fifth edition of AMA Guides to the Evaluation of Permanent Impairment as the method of rating impairment.

LUNG CANCER

According to the AMA Guides, lung cancer is a cause of severe impairment for the period extending from the time of diagnosis to 1 year, thereafter. If no evidence of tumor is found at reevaluation at 1 year, then impairment is recalculated on the basis of the degree of physiologic impairment present at that time. On the other hand, if there is evidence of tumor, the patient remains classified as severely impaired.

Under the Social Security system, lung cancer produces impairment if it is unresectable, is incompletely resected, is recurrent or metastatic, is of small cell histology, is a squamous cell cancer with

TABLE 38-7 Social Security Impairment Criteria for Evaluating Chronic Impairments of Gas Exchange due to Clinically Documented Pulmonary Disease

(1) Arterial blood gases demonstrating values of Pa_{O_2} and simultaneously determined Pa_{CO_2} measured while at rest (breathing room air, awake and sitting, or standing), in a clinically stable condition on at least two occasions, 3 or more weeks apart within a 6-mo period, equal to or less than the values specified below or arterial blood gas values during steady-state exercise breathing room air (level of exercise equivalent to or less than 17.5 mL O_2 consumption/kg/min or 5 METs), equal to or less than the values specified below.

Pa_{CO_2} (in mm Hg) and	At test sites <3000 ft above sea level, Pa_{O_2} ≤ (in mm Hg)	At test sites 3000–6000 ft above sea level, Pa_{O_2} ≤ (in mm Hg)	At test sites >6000 ft above sea level, Pa_{O_2} ≤ (in mm Hg)
≤ 30	65	60	55
31	64	59	54
32	63	58	53
33	62	57	52
34	61	56	51
35	60	55	50
36	59	54	49
37	58	53	48
38	57	52	47
39	56	51	46
≥40	55	50	45

Or

(2) Diffusing capacity for carbon monoxide less than 10.5 mL/mm Hg/min (single-breath method) or less than 40% of predicted normal. (All methods, actual values and predicted normal values and the sources of the predicted value should be reported).

Source: Data from Social Security Administration.[2]

metastasis beyond hilar nodes, or is one of other histologic types with metastasis to hilar lymph nodes. Under the Veterans Administration system, degree of impairment is not categorized clearly, but rather, is left to the judgment of the physician.

SLEEP APNEA

Impairment ratings for sleep apnea are problematic and vary widely among compensation systems. Resting and exercise PFTs are not useful for rating impairment related to sleep apnea. Therefore, the AMA Guides recommend assessment of complications of sleep apnea, such as the presence of cor pulmonale or polycythemia, and rate the complications according to the appropriate organ systems. Any "add-on" for strictly defining respiratory impairment must be determined by a sleep specialist and should not exceed 3% of total impairment.[4] Under the Social Security system, sleep apnea is rated according to criteria for cor pulmonale, obesity, or organic mental disorders.[2]

AMERICANS WITH DISABILITIES ACT

Although many physicians think of impairment assessment as an evaluation that follows injury, or termination of employment, or is undertaken at an advanced stage of lung disease, in reality, important assessments are also made prior to the start of a job. Until recently, people with physical impairment were excluded from employment because of an unreasonable fear that an impaired employee would be a detriment at the workplace. The Americans with Disabilities Act (ADA), which was enacted by the United States in 1992, produced a fundamental change in the way in which physical impairments are viewed at the workplace.

Many of the regulations established by the ADA deal with removal of physical barriers that prevent impaired workers from entering and functioning within the workplace. Others are specifically directed at removing bias and prejudice from the opportunity to enter the workforce. While the ADA has not altered the methods of impairment evaluation used by physicians, it does have a substantial impact on the timing of evaluations and the way the evaluations are reported and used. For instance, while preemployment physical examinations were commonly requested by employers prior to enactment of the ADA, they are no longer allowed, due to the perceived risk that a qualified individual might be excluded from employment because of an impairment that has little or nothing to do with the job requirements. Before making a job offer, employers are no longer allowed to ask if a prospective employee has a physical impairment, although they may ask if he or she can perform the duties of the job. Once a job offer is made and accepted, physical examination is permissible to confirm that the job can be performed in a safe and acceptable manner. In fact, the employer is legally permitted to make a job offer conditional on the applicant passing a physical examination, as long as the same physical requirements are required for every employee in the same job category. These examinations, known as preplacement physicals, must deal only with job-related issues and must be consistent with business necessity.

The other major change in the determination of work-related physical fitness is that businesses are required to make "reasonable" accommodations for physical impairments, as long as the impairments do not interfere with the essential requirements of the job. Employers are not, however, required to make unreasonably extensive changes to a work area or to undertake "action requiring significant difficulty or expense" to accommodate an otherwise qualified applicant.

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PART 4

Obstructive Lung Diseases

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CHAPTER 39

Pathology of Chronic Obstructive Pulmonary Disease: Diagnostic Features and Differential Diagnosis

Joanne L. Wright
Andrew Churg

Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking, but also after exposure to biomass fuels. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airway resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it may be difficult to prove associations between physiologic abnormalities and pathologic changes. The Global Initiative on Obstructive Lung Disease (GOLD), recently revised,[1] classifies patients with COPD purely upon indices of airflow and thus far there is only limited integration with pathologic findings.

This chapter presents the pathologic features of COPD and how these findings can be differentiated from other lesions associated with airflow obstruction.

HISTORY OF PATHOLOGIC DESCRIPTIONS OF COPD

The word emphysema is derived from Greek and means "to blow into," hence "air-containing" or "inflated." Although "voluminous lungs" and lungs "turgid particularly from air" were described respectively by Bonet in 1679[2] and Morgagni in 1769,[3] the first description of enlarged airspaces in emphysema in the human, together with illustrations, was furnished by Ruysh in 1721,[4] followed by Matthew Baillie in 1807, who not only clearly recognized and illustrated emphysema, but also pointed out its essentially destructive character.[5,6]

Laennec,[7] writing in the early 1800s, made a number of seminal contributions to the basic descriptions of pathologic changes in COPD. He was the first to make a clear-cut distinction between interstitial emphysema and emphysema proper, and related the enlarged airspaces to the clinical syndrome of emphysema. He also recognized that air trapping and increased collateral ventilation were features of emphysematous lungs, and that the peripheral airways were the primary site of obstruction in emphysema. Furthermore, he noted that airspaces enlarged with increasing age, and he distinguished these changes from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and to clearly describe the pathology of bronchiectasis.

Little of major importance was added to the gross descriptive morphology of emphysema for almost the next 150 years. The foundation of modern knowledge of the pathologic anatomy of pulmonary emphysema was laid by J. Gough in 1952[8] when he described centrilobular emphysema and distinguished it from panlobular emphysema. The paper section technique developed by Gough and Wentworth[9] was largely responsible for this advance, as it made examinations of sections of entire inflated lungs possible and simple (Fig. 39-1). A comprehensive microscopic description of emphysema was then provided by McLean,[10,11] who demonstrated the relationship of destruction to inflammatory alterations of the bronchioles, and also discussed alterations of the vasculature.

LESIONS OF THE LUNG PARENCHYMA IN COPD: EMPHYSEMA

A major problem in describing the pathologic features of emphysema has been the lack of a generally accepted and easy to apply definition. In 1959, a Ciba Guest Symposium defined emphysema in anatomic terms as "a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls."[12] Subsequent definitions differed in that destruction of respiratory tissue became a requirement[13–15]: "Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls." This requirement separates emphysema from enlargement of airspaces unaccompanied by destruction, the latter now being termed overinflation.

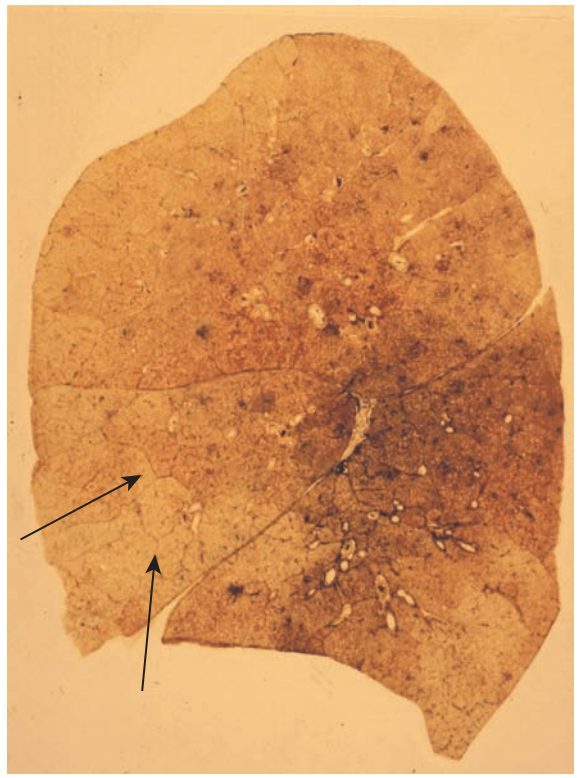


Figure 39-1 Gough sagittal section. Paper mount. Normal lung.

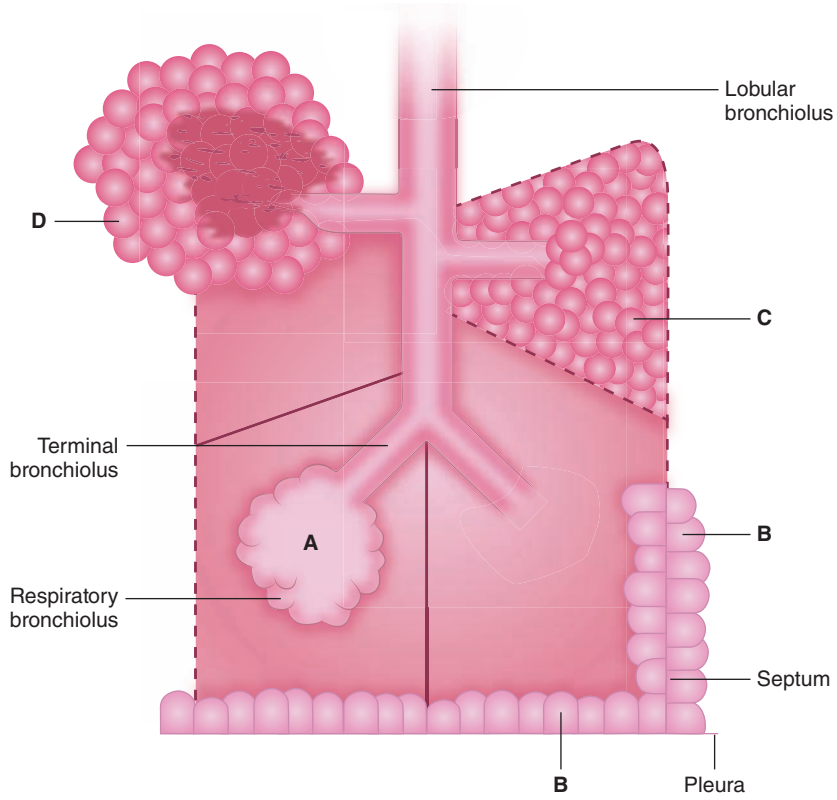


Figure 39-2 Anatomic varieties of emphysema. **A.** Centriacinar (centrilobular). **B.** Paraseptal (distal acinar). **C.** Panacinar (panlobular). **D.** Irregular (scar). The *dashed lines* mark the edge of the acinus. Only centriacinar and panacinar emphysema are commonly observed in COPD, although paraseptal emphysema often can be found in focal areas in lungs with centriacinar emphysema.

Destruction has been similarly difficult to define in an unambiguous way. A committee of the National Institutes of Health[16] proposed that destruction was present when "there was nonuniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost." They recognized that emphysema was a subset of airspace enlargement defined as "an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction." While these definitions, when strictly applied, would eliminate airspace enlargement due to overinflation or failure of septation, they would not eliminate airspace enlargement due to reorganization of the airspaces, such as is found in honeycomb lung. This may be part of the confusion when combined emphysema and fibrosis is considered (see the section below).

CLASSIFICATION OF EMPHYSEMA

Not only is emphysema defined in terms of lung structure, it is also classified in similar terms; therefore, several anatomic definitions are important. The part of the lung involved in emphysema is the acinus, which is defined as the unit of lung structure distal to the terminal bronchiole (final generation membranous bronchiole) and that consists of three orders of respiratory bronchioles: a single order of alveolar ducts, followed by the alveolar sacs, and finally the alveoli. Alveolar ducts are entirely alveolated and characteristically contain smooth muscle around the mouths of their alveoli. While the walls of alveolar sacs are also formed entirely by alveoli, muscle is absent. Alveolar pores of Kohn (also known as vents, stomata, or fenestrae) are normal components of adult alveoli, responsible for collateral ventilation. However, they may also be an initial site of destruction in the development of emphysema, particularly centriacinar emphysema.

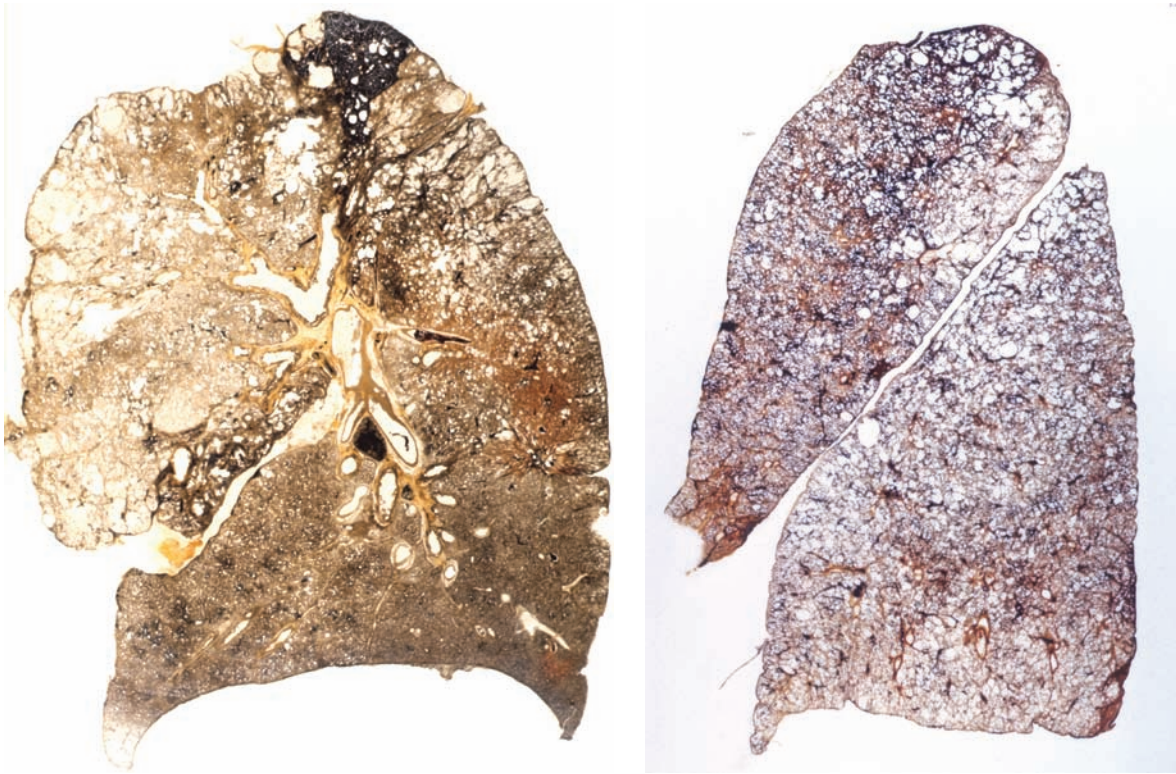
The acinus is a three-dimensional anatomic structure, but it cannot be easily identified by gross examination. What can be seen instead on the surface of lung slices is the secondary lobule of Miller, defined as the tissue bounded on four sides by interlobular septa or pleura (see Fig. 39-1). Lobules vary tremendously in size, but are generally 2 to 4 cm on a side, and contain between three to five acini. The terminal bronchiole and subtending respiratory bronchioles tend to be situated in the center of the lobule. For this reason "centrilobular" emphysema and "panlobular" emphysema are reasonable and widely used approximations for the more accurate "centriacinar" and "panacinar" emphysema (see below).

The ways in which the acini are involved determine the classification of emphysema. There are four recognized patterns (Fig. 39-2). The acinus (and lobule) may be more or less uniformly involved; this is panacinar (panlobular) emphysema. The proximal portion of the acinus (center of the lobule) may be dominantly involved; the best term for this lesion is proximal acinar emphysema, although the usual term is centrilobular or centriacinar emphysema. Alternately, the proximal portion of the acinus may be normal, and the distal part (alveolar sacs and ducts) may be dominantly involved. This is distal acinar emphysema, more commonly referred to as paraseptal emphysema since the lesion is accentuated along lobular septa where the peripheral parts of the acini lie. Finally, the acinus may be irregularly involved, producing irregular emphysema or paracicatricial emphysema, so called because it is usually associated with obvious adjacent scarring.

MORPHOLOGY OF EMPHYSEMA

CENTRILOBULAR EMPHYSEMA

This destructive lesion of the respiratory bronchioles has a number of characteristic features on gross examination of the lung. In the *classical* lesion, the enlarged, destroyed respiratory bronchioles coalesce in series and in parallel to produce sharply demarcated



A B

Figure 39-3 Pathologic subtypes of emphysema. **A.** Predominantly centriacinar emphysema. Emphysema is more severe in upper lobes. **B.** Predominant panacinar emphysema. Emphysema is more severe in the lower lobes.

emphysematous spaces, separated from the acinar periphery (the lobular septa), by intact alveolar ducts and sacs of normal size. The walls of the emphysematous spaces and adjacent tissue characteristically contain variable amounts of black pigment.

The lesions vary qualitatively as well as quantitatively even within the same lung. There is striking irregularity of involvement of lobules, and even within the same lobule.[17,18] The lesions are usually more common and become more severe in the upper than in the lower zones of the lung (Figs. 39-3A and 39-4A,B).[19–24] Most affected are the upper lobe, particularly the posterior and apical segments, and the superior segment of the lower lobe. In cases of severe CLE, the destruction proceeds toward the periphery of the lobule, and the distinction between CLE and PLE becomes blurred.

In CLE, alveolar pores are abnormal in size and shape, and occasionally contain epithelial debris and macrophages. Although there are numerous pores of variable size in the emphysematous areas,[25] there are also increased numbers of pores in the grossly normal areas, and accentuation of these changes in the center of the lobule.[26] Thus, it appears that in CLE the pores of Kohn are possibly the initial site of destruction.

There is increased cellularity in the alveolar walls of cigarette smokers,[27] and when this has been quantified, the parenchyma in severe emphysema has increased numbers of neutrophils, macrophages, eosinophils, and both CD4 and CD8 T lymphocytes.[28] There is also a significant inflammatory cell infiltrate in the airspaces in severe emphysema, with the same cell types increased.[28] Although not readily apparent grossly or on standard histologic stains, use of histochemical stains or biochemical analysis demonstrates that collagen is increased in both centrilobular and panlobular emphysema.[29–31]

■ PANLOBULAR EMPHYSEMA

The recognition of mild panlobular emphysema is very difficult. The normal lung has a very characteristic appearance when seen through a dissecting microscope: The multifaceted alveoli form a contrast to the larger, cylindrical conducting structures that are alveolar ducts and respiratory bronchioles. In panlobular emphysema the distinction between alveolar ducts and alveoli becomes lost as alveoli lose their sharp angles, enlarge, and then lose their contrast in size and shape with the ducts, resulting in simplification of the lung architecture, with formation of small box-like structures. As the process becomes worse, the architectural derangement becomes more obvious, with progressive effacement and loss of the orderly arrangement of the lung until little remains other than the supporting framework of vessels, septa, and bronchi. The best way to see panlobular emphysema grossly is to examine lung slices immersed in a water or fixative bath and then immediately after removal from the bath. The immersed specimen shows enlarged airspaces and, when the slices are lifted from the bath, panlobular emphysema can be suspected because the lung parenchyma "falls away" from the supporting structures and protrudes slightly above them. In contrast to centrilobular emphysema, panlobular emphysema is usually worse in the lower lobes (Fig. 39-3B).

Histologic examination is a sensitive method of recognizing panlobular emphysema. The pattern is again one of simplification with diminishing contrast between alveoli and alveolar ducts (Fig. 39-4C,D). Despite the greater extent of tissue destruction, in panlobular emphysema the pores of Kohn are more uniform and inconspicuous than those found in centrilobular emphysema.[32]

Panlobular emphysema is the characteristic lung lesion seen in α1-antitrypsin deficiency,[33] but may also occur as a consequence of permanent obliteration of airways (obliterative bronchiolitis, constrictive bronchiolitis). Most often, obliteration of airways results in collapse of the distal lung parenchyma and dilatation of the bronchi proximal to the obliterated airways. This is the sequence of events in postinfective bronchiectasis. In some instances, however, the lung parenchyma does not collapse, but remains fully expanded or

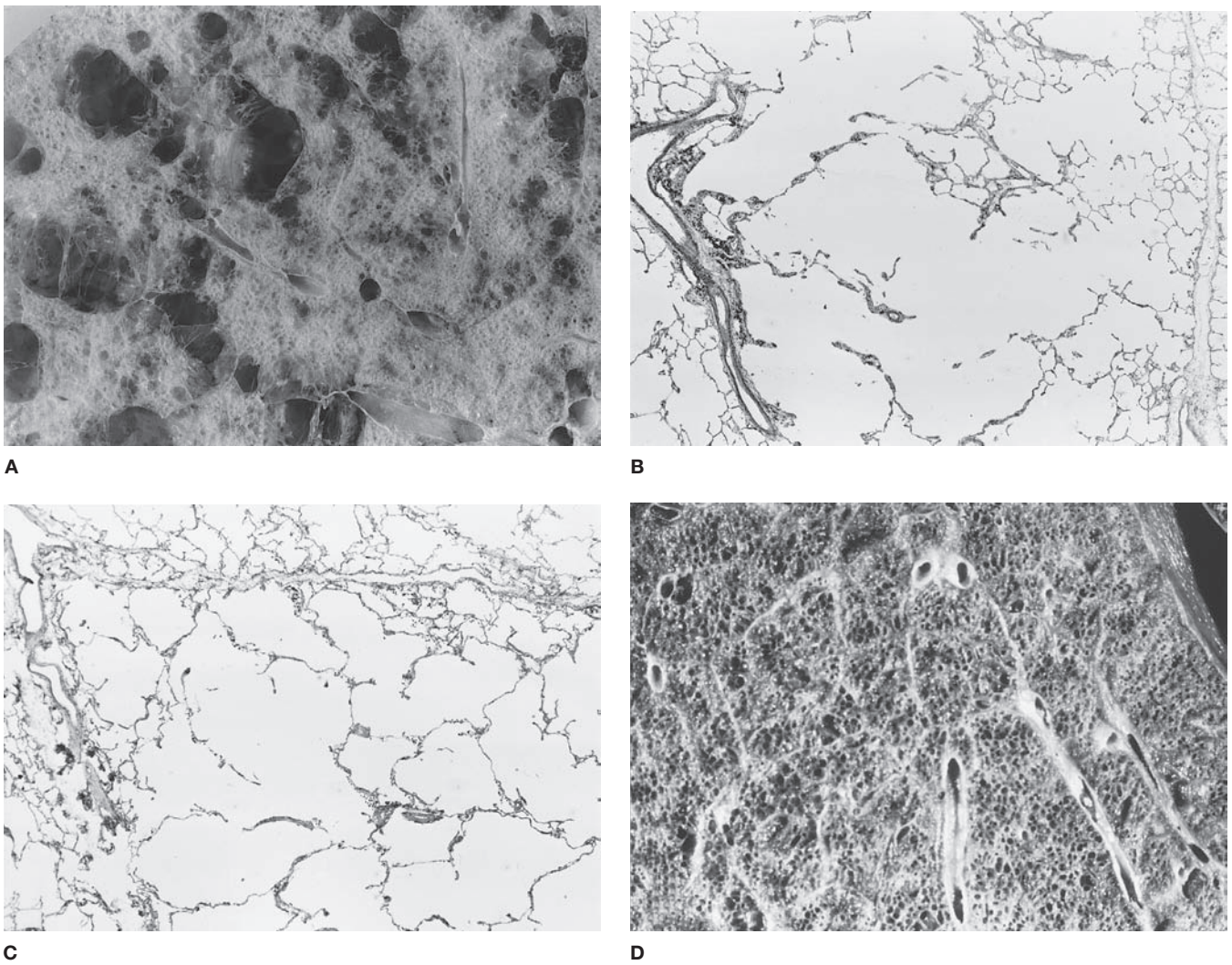


Figure 39-4 **A, B.** Gross and histologic sections illustrating centriacinar; and (**C, D**) panacinar emphysema. **A.** Cut surface from a lung with centriacinar emphysema showing holes in the center of lobules surrounded by relatively normal parenchyma. The severity varies among lobules. **B.** Microscopic section showing that the airspace enlargement in centriacinar emphysema is most marked adjacent to the abnormal respiratory bronchiole, corresponding to the center of the lobule. Also, some of the alveolar walls of the abnormal airspaces are thickened and fibrotic (H&E, ×16). **C.** Cut surface of a lung slice showing how the entire lobule is uniformly affected in panacinar emphysema. **D.** Microscopic section demonstrating that in panacinar emphysema, the airspaces adjacent to the lobular septa are enlarged to the same degree as those in the center of the lobule (H&E, ×16).

becomes emphysematous. The parenchymal sequel to bronchial and bronchiolar obliteration depends on the extent of the obliteration and the amount of collateral ventilation between adjacent airspaces distal to unobstructed airways. If collateral ventilation is present, then the units distal to the obliterated airways will remain expanded by virtue of the air reaching them by collateral ventilation, producing overexpansion and destruction of lung parenchyma beyond the obliterated airways. The terms Swyer–James or MacLeod syndrome are applied when this process affects most of one lung but spares the other.

■ DISTAL ACINAR EMPHYSEMA: PARASEPTAL EMPHYSEMA

The original description of distal acinar emphysema is generally credited to Loeschcke,[34] who described collections of subpleural bullae. It was Heard,[24,35] however, who first noted that the lesions could extend into the substance of the lung, where they lay along the septa, and coined the term "paraseptal" emphysema. Since the distal part of the acinus (alveolar sacs and ducts) is dominantly involved, emphysema is most striking adjacent to the pleura (superficial emphysema or mantel emphysema), along lobular septa (paraseptal emphysema), at the margins of lobules and acini (periacinar emphysema), and along vessels and airways, which, when cut longitudinally, display a linear pattern. The characteristic morphology is that of multiple contiguous, enlarged airspaces, varying from <0.5 mm to >2 cm in diameter.

Paraseptal emphysema is usually limited in extent, and is found most commonly along the anterior and posterior parts of the upper lobe and along the posterior surface of the lower lobe. When extensive, it is usually more severe in the upper half of the lung. Gough has stressed that it is associated with fibrosis of the tissue between the enlarged airspaces, and this is certainly a common finding.[36] Paraseptal emphysema is frequently found in association with centriacinar emphysema,[20] but it is most known for its association with spontaneous pneumothoraces in young thin adults.[37]

■ IRREGULAR EMPHYSEMA

Irregular emphysema is logically named, because the acinus is indeed irregularly involved in it. Irregular emphysema is almost invariably

TABLE 39-1 Differential Diagnosis of Airspace Enlargement

	Distribution	Enlarged Structure
Centrilobular emphysema	Upper lobes, center of lobule	Alveolar ducts, alveoli
Panlobular emphysema	Lower lobe, uniform in lobule	Alveoli
Paraseptal emphysema	Apical, adjacent to septum	Alveoli
Irregular emphysema	No typical site, adjacent to scars	Alveoli
Aging	Uniform in lung	Alveolar ducts
Compensatory alterations	Uniform in lung	Alveoli
Obstructive alterations	Affected area	Alveoli
Genetic alterations	Uniform in lung	Lack of septation
Asthma	During acute attack	Alveoli
Honeycomb lung	Variable—often subpleural	Total remodeling

adjacent to a scar, giving name to the synonyms scar or paracicatricial emphysema. Most scars within the lung are usually small and the emphysema is limited in extent. The severity of irregular emphysema depends on the extent of damage to lung tissue, and multiple scars through the lung may lead to multiple foci of irregular emphysema.

DIFFERENTIAL DIAGNOSIS OF EMPHYSEMA

GAS TRAPPING

The lungs of an asthmatic who has succumbed during an attack are usually characterized by gas trapping, and thus remain inflated, with focal areas of atelectasis (Table 39-1). In a patient with long-standing asthma who has died from other causes, or has had a lung resection, there may still be areas of atelectasis. Focal bronchiectasis can be found also, particularly in the anterior segment of the upper lobe. However, parenchymal destruction is not a feature of asthma, and thus gross, microscopic, and morphometric analyses will all be normal in the chronic asthmatic.

NONEMPHYSEMATOUS AIRSPACE ENLARGEMENT

Although not part of the differential diagnosis of COPD, non-emphysematous airspace enlargement also occurs in infancy. In congenital lobar hyperinflation (emphysema), the lobes are over-inflated rather than emphysematous, but in some instances they may be polyalveolar.[38,39] Some other genetic abnormalities will also give enlarged airspaces, but this is due to failure of septation with a simplified rather than a destroyed alveolar framework.

At the other side of the age spectrum, the term senile emphysema was once used to describe the enlarged airspaces found in the aged. On gross examination, lungs round out with increasing age. An analysis of Gough sections showed increases in anteroposterior distance, height, perimeter, and area of the lung up to the age of 59 years. After this age, only the anteroposterior diameter continued to increase significantly, thus "rounding" the lung dimensions.[40] This change is due to an increase in the volume proportion of alveolar duct air,[41] with shallower and flatter alveoli,[42] a process termed ductectasia. There is no evidence of lung destruction; thus, the condition does not fulfill the criteria for emphysema.

If a part of the lung collapses or is removed, the remaining lung can expand to fill the increased amount of space available, a process known as compensatory overinflation. The exact way that this happens and the limits of the process are unknown. However, no tissue destruction has occurred and, by definition, this is not emphysema. It is not clear how much larger the overinflated lung can become, or how it expands to reach the new and larger volume. It is generally thought that the possible extent of overinflation is modest and that all the parts of the acinus are equally expanded.

Obstructive overinflation can occur in adults, and two mechanisms may be involved. In one, the obstruction in the bronchus may act as a ball valve, so that air enters on inspiration but does not leave on expiration. Alternatively, the bronchus may be completely obstructed and air may be trapped behind channels of collateral ventilation. Whatever the mechanism, the affected part of the lung can expand considerably. Obstructive overinflation differs in a number of ways from compensatory overinflation, although, in both, the lung contains too much air per unit of lung and lung tissue.

HONEYCOMB LUNG

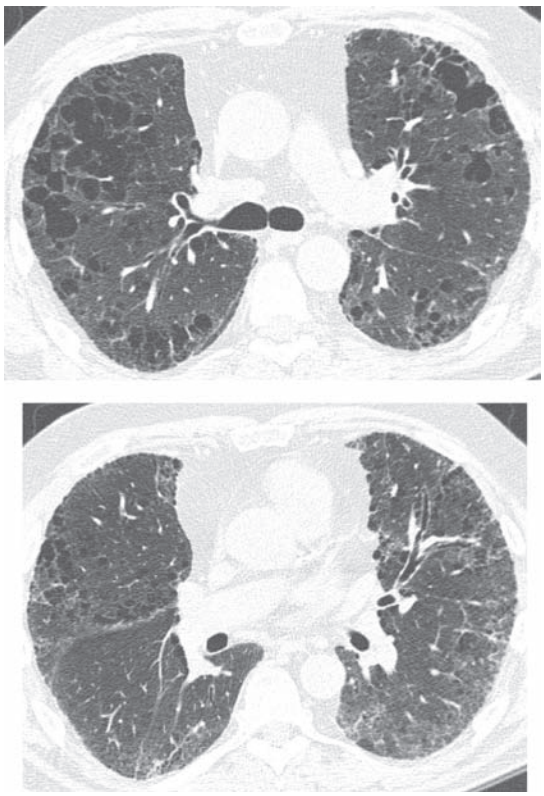
The airspace enlargement that occurs in cryptogenic fibrosing alveolitis (usual interstitial pneumonia [UIP]) and other fibrotic lung diseases could possibly be confused with emphysema. While honeycomb spaces are enlarged airspaces, they are the result of parenchymal remodeling with formation of new airspaces, rather than destruction of normal airspaces, and thus have thickened and irregular walls with none of the structure of an acinus. They are lined by bronchiolar epithelium, and often contain mucus; the walls have abundant and well-collagenized connective tissue, which may also contain impressive amounts of muscle and sometimes fat. There is usually interstitial inflammation in the form of varying degrees of lymphocytic and plasma cell infiltration.

COMBINED EMPHYSEMA AND FIBROSIS

Despite the definition of emphysema, which limits fibrosis, the significance of a mixture of fibrosis and emphysema has recently been reevaluated in relationship to its clinical, radiologic, and pathologic components.[43] The problem is that people who smoke cigarettes not only can develop respiratory bronchiolitis-interstitial lung disease (RB-ILD), but also have a higher incidence of developing UIP (idiopathic interstitial fibrosis), and mixtures of these with emphysema are not uncommon. When the combination of emphysema and UIP occurs, lung volumes can be preserved, but the diffusing capacity becomes markedly decreased, and pulmonary hypertension develops, with its associated significant negative prognosis. CT scans generally show centrilobular or mixed centrilobular and paraseptal emphysema in the upper lobes, with increased reticular markings and honeycomb remodeling in the lower lobes. Pathologically, there is both gross and microscopic emphysema and interstitial fibrosis with fibroblast foci in the areas of active fibrosis.[44] We have recently reviewed this topic with a focus on the pathologic differential diagnosis (Fig. 39-5A–D).[45]

LESIONS OF THE LARGE AIRWAYS IN COPD

The majority of studies in this area have focused upon the lesions present when the clinical signs and symptoms of chronic bronchitis are also present.



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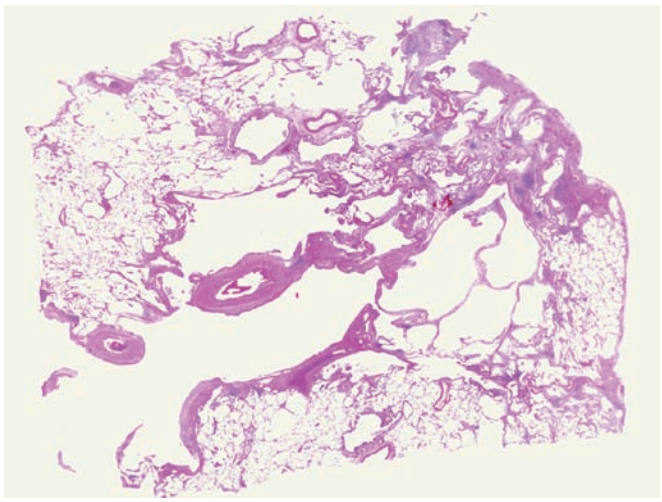

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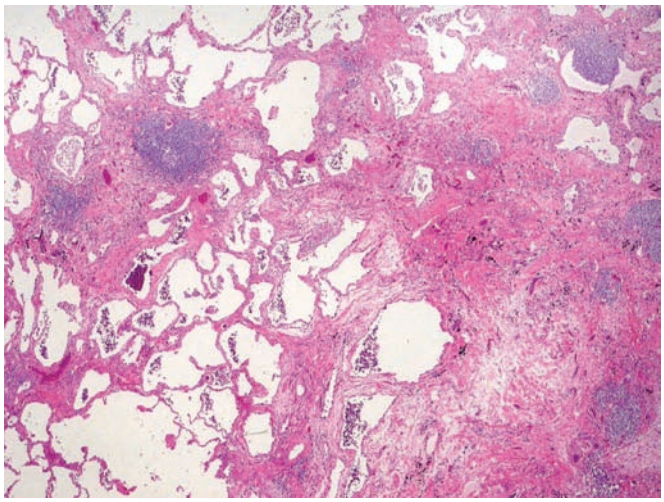


D

Figure 39-5 Combined fibrosis and emphysema in a case of chronic (fibrotic) hypersensitivity pneumonitis. **A.** Computed tomography scan from upper zone *(top)* shows emphysema and a suggestive of reticulation; lower image from midlung zone shows extensive reticulation indicating the presence of underlying fibrosis. **B.** Gross photo (sagittal slice) from this case showing marked upper zone emphysema, with fibrosis evident in the most posterior portion of the upper lobe, and the posterior portions of the lower lobe. **C.** Whole mount from the upper lobe. There are large emphysematous spaces, several with extensive surrounding fibrosis; at higher magnification, many of these fibrotic rims had fibroblast foci (not shown), indicating that this process is really interstitial fibrosis stretched around pre-existing emphysema. **D.** Image from lower lobe showing a UIP-like area, a common finding in chronic hypersensitivity pneumonitis. Elsewhere there were noncaseating granulomas (not shown). *(Reproduced with permission from Wright JL, Tazelaar H, Churg A. Fibrosis with Emphysema. Histopathology. 2011;58(4):517–524 (This document was published in 1993. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages).)*

■ GROSS FINDINGS

Gross lesions in the large airways are few and subtle. Bronchial pits are the dilated openings of one or more mucus glands into the epithelium. They are most often found along the margins of the cartilaginous rings and at the bifurcations of the airways. In nonbronchitis the pits can be seen using a hand lens or a dissecting microscope, but in chronic bronchitis, the ducts may be distended with mucus and the mucus may protrude into the lumen of the bronchus and be visible grossly. It is not correct to refer to these as diverticula. First, these are protrusions of normal ducts; and second, they do not extend through all of the muscle coats of the bronchial wall.

While enlarged bronchial pits are the most obvious gross lesions in COPD, careful examination of lung specimens will show that the bronchi do not taper progressively as they approach the pleura,[46] and they also display prominent circular ridges, probably due to bands

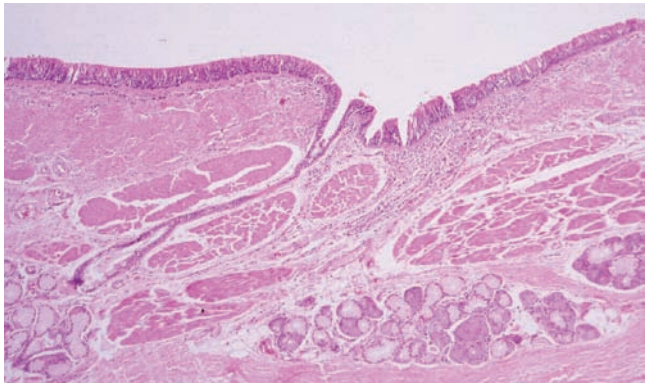


Figure 39-6 Large airway from a subject with chronic bronchitis. The overall wall is thickened with inflammation and fibrosis, and there is prominence of the smooth muscle in addition to the bronchial mucus glands.

of hypertrophic smooth muscle.[47,48] Gross mucus may be present in the airway lumen, particularly in subjects with chronic bronchitis.[49]

■ MICROSCOPIC FINDINGS

The intraluminal mucus found in the airways of subjects with COPD contains a mixed population of epithelial cells and acute and chronic inflammatory cells; large numbers of neutrophils can be found during an exacerbation.

Detailed microscopic analysis of the large airways in COPD reveals alterations in the entire airway wall (Fig. 39-6). Epithelial changes are mild in degree and are not necessarily consistent from patient to patient. Epithelial sloughing can occur, but in most instances the epithelium is generally intact and shows only mild goblet cell or squamous cell metaplasia, both of which appear to be more marked if the subject has symptoms of chronic bronchitis.[50,51] The reticular basement membrane thickness is within the normal range.

The thickness or area of mucus glands in subjects with COPD in general, or chronic bronchitis in particular, is increased over a population mean, but has a distribution that extensively overlaps that of normals and asthmatics.[52–55] Interestingly, there appears to be a decreased percentage of serous acini in these glands, a feature that apparently does not occur in asthma (discussed below).[56]

Thickening of the inner wall (area internal to the muscular layer) appears to be the most consistent component of airway wall thickening in the large airways of subjects with COPD, and appears to be generalized.[57,58] This increase in thickness can be partially attributed to edema and hyperemia of the bronchi,[59] but is also due to an increase in fibrous tissue or other matrix proteins.

In the large airways of subjects with COPD, increases in the thickness of the muscular layer have not been consistently identified. Although some studies[60] have found that the average proportion of muscle in main, lobar, and segmental bronchi was approximately doubled in patients with chronic bronchitis and airflow obstruction, others have found that a substantial number of patients fell within the normal range.[54,55,61]

Alteration in the amount of cartilage in COPD does not appear to be a consistent finding. While some studies[59,62,63] described cartilage atrophy in chronic bronchitis and/or emphysema, or circumferentially arranged cartilage that extended farther distally in nonbronchitis than bronchitis,[64] this was not supported by other reports.[54,65] However, histologic signs of cartilage damage, as judged by loss of cellular or pericellular metachromasia and vacuolated or empty lacunae can be consistently identified.[66]

The large airways in COPD show a mild, usually mixed, inflammatory infiltrate. Bronchus-associated lymphoid tissues (BALT) is not consistently found, but its frequency appears to be considerably higher (82%) in smokers than nonsmokers (14%).[67] Bronchial biopsy analysis consistently shows an increase in CD8 T cells, with eosinophils and neutrophils found during exacerbations (reviewed in Refs.[50,68]). Chronic inflammation can also be found around the bronchial glands, particularly in subjects with chronic bronchitis.[69]

DIFFERENTIAL DIAGNOSIS

■ ASTHMA

In asthma the large airways are not dilated, but mucus plugs are classically identified in the large airways of subjects with fatal or near-fatal asthma,[70] and the mucus may be continuous with that present in the ducts of the mucus glands (Table 39-2). Visible bronchial pits are not a standard feature of asthma, and although the airway wall may be thickened, this is usually not apparent grossly.

In the large airways of subjects with asthma, desquamation of the epithelium is a common feature,[71,72] and this may be worse in people who have persistent rather than intermittent activity. Sloughing of cohesive epithelial clusters produces the creola bodies found in cytology specimens. Goblet cell metaplasia can be marked in both asthma and bronchiectasis,[73] but there is a considerable degree of variability, so that this feature cannot be used in isolation to distinguish among

TABLE 39-2 Pathologic Differential Diagnosis of Large Airway Lesions in COPD

	Dilatation	Structural Distortion	Pits	Glands	Submucosal Fibrosis	Basement Membrane	Epithelium	Lumenal Mucus	Cartilage	Muscles
Chronic bronchitis	✓	Fibrosis and inflammation	✓	✓	✓	X	Goblet cell metaplasia	✓	✓	✓/X
Asthma	Focal	Focal	X	✓	✓	✓	Goblet cell metaplasia	✓	X	✓
Bronchiectasis	✓	Fibrosis and inflammation	✓	✓/X	✓	X	Focal goblet cell metaplasia	✓	✓	X
Tracheobronchopathia osteoplastica	✓	Bony nodules	X	X	X	X	X	X	✓	X
Tracheomegaly	✓	X	Diverticula	X	X	X	X	X	X	X
Relapsing polychondritis	✓	✓	X	X	X	X	X	X	✓	X

Check mark indicates that the feature is present; X indicates that the feature is absent.

the airways of subjects with COPD, asthma, and bronchiectasis. These epithelial cell changes result in an overall thickening of the epithelium in asthma, but not in COPD.[58] In asthma, the reticular basement membrane (lamina reticularis) is characteristically thickened. This alteration occurs early in the course of disease, and remains even when the asthma is mild or well controlled (reviewed in Ref.[56]).

The airways of asthmatics demonstrate a greater severity of inner wall thickening, with values double those found in patients with COPD.[58] The increase in thickness is due to variable increases in fibrous tissue, inflammatory cells, edema fluid, and vascular prominence.[50,56] Analysis of the muscular wall in subjects with severe or fatal asthma compared with normals or those with COPD shows a marked increase in amount of muscle, with a lesser increase in asthmatics who died with rather than from their asthma (discussed in Ref.[74]). There has also been a suggestion that the increase in muscle mass may occur relatively early during childhood.[56]

Neutrophils are the predominant cells present in the mucus of patients with bronchiectasis, while eosinophils and accompanying Charcot Leyden crystals are the hallmark of asthmatic mucus. As noted, the cartilaginous destruction present in polychondritis is severe and associated with chronic inflammation, thus easily distinguishing the two processes. Depending upon the severity of the inflammation in bronchiectasis, there may be significant cartilaginous destruction.

Airways from fatal and near-fatal asthma also contain isolated aggregates of lymphoid cells, roughly in the same proportion as that present in COPD.[75] However, in asthma, by contrast to COPD, there is an inflammatory infiltrate consisting of activated eosinophils, and activated CD4 T cells in the submucosa,[76] and both mast cells and neutrophils within the glands.[70] There is little in the literature regarding the inflammatory cell infiltrates present in the airway walls in bronchiectasis. Compared with asthma, there appear to be fewer eosinophils, but a similar population of CD45 (as opposed to any specific subtype) lymphocytes, with both cell types having a greater density in the inner, as opposed to the outer aspect of the airway.[77]

BRONCHIECTASIS

In bronchiectasis, there is by definition an abnormal and permanent dilatation of the bronchi, and this is usually present to a much greater degree than is found in COPD, and is often accompanied by airway distortion. There is exaggeration of the muscular ridges and the presence of multiple bronchial gland–based pits. The large airway walls can be thickened and/or irregularly thinned as a result of inflammation and fibrosis, and there is often inspissated mucus or actual purulent material.

MISCELLANEOUS CONDITIONS

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterized by a marked dilatation of the trachea and major bronchi, with diameters 5 to 10 cm above normal values.[78] In this condition there are multiple true diverticula, with out-pouchings formed of membranous tracheal tissue between the cartilaginous rings,[79] with atrophy or absence of elastic fibers.[80]

Patients with tracheobronchopathia osteoplastica have an obstructive pulmonary function pattern[81]; however, unlike the trachea and large airways in COPD, cartilaginous and bony nodules are present in the subepithelial space (submucosa). Relapsing polychondritis[82,83] shows variable dynamic expiratory and/or inspiratory obstruction depending on the size and location of the airways involved. In this disease, however, the obstruction is due to impaired airway clearance of inflammatory debris, and an ineffective cough because of dynamic upper airway collapse. The airways are dilated and the walls are thickened because of the extensive fibrosis and chronic inflammation due to the immunologic nature of this condition. In particular, the cartilaginous plates show extensive destruction.

LESIONS OF THE SMALL AIRWAYS IN COPD

In the context of COPD, small airways refer to airways with an internal diameter of 2 mm or less. In COPD, intraluminal mucus can be found in the small airways, and there appears to be an overall relationship between the degree to which the airways are occluded by mucus and the FEV_1.[84] Goblet cells are rare in normal small airways, but goblet cell metaplasia is a frequent finding in the airways of patients with COPD.[85–87]

Similar to the large airways, there is alteration of all of the small airway wall compartments in patients with COPD (Fig. 39-7). These changes result in an overall decrease in the internal bronchiolar diameter and, as assessed by a conformity index, produce significant deformity. Similar results are obtained from three-dimensional reconstructions.[74] Detailed measurements of the airway walls show that the increased wall thickness is due to increases in the epithelium, subepithelial fibrous tissue compartment (submucosa, lamina propria), smooth muscle, and adventitia.[58,84] While there is no direct evidence, it seems appropriate that these changes would result in airway obliteration, a process which appears to happen relatively early in airflow obstruction, with the number of airways in patients with severe airflow obstruction reduced to one-tenth of the numbers calculated in the normal lung (see Fig. 39-8A,B).[88] Although the adventitia is thickened, there is a loss of alveolar attachments to the airway wall,[89] an important process because it allows early airway collapse on expiration.

One of the earliest histologic abnormalities that can be detected in cigarette smokers is the presence of macrophages in the lumen of the respiratory bronchioles.[90] However, an inflammatory infiltrate can also be identified within the walls of both membranous and respiratory bronchioles in subjects with COPD. When examined in conjunction with the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) stage, the proportion of airways which had measurable neutrophils appear to be increased in GOLD stages 2 to 4, and airways with measurable macrophages show a progressive increase from GOLD stage 0 to 4, while there does not seem to be any alteration in the percentage of airways that contain eosinophils among the GOLD stages.[91] The percentage of airways with CD4, CD8, and B cells also increase with GOLD stage, but when these data are expressed as total accumulated volume, only the B cells and CD8 cells show progressive increases. The presence of lymphoid follicles is markedly increased in GOLD stages 3 and 4. Interestingly, histone deacetylase 2 (HDAC2) appears to be downregulated in the

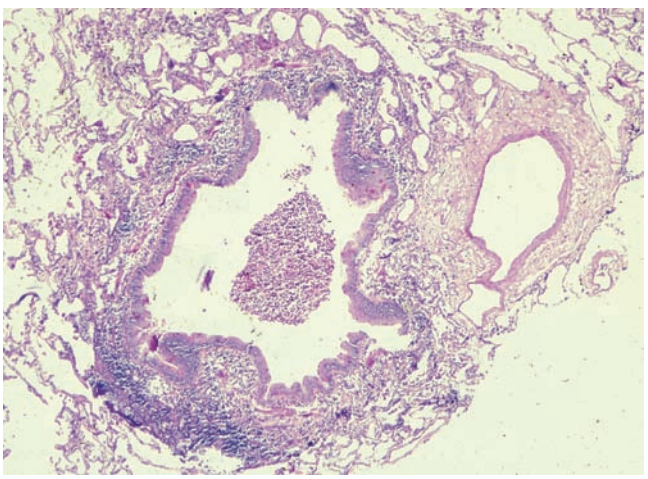
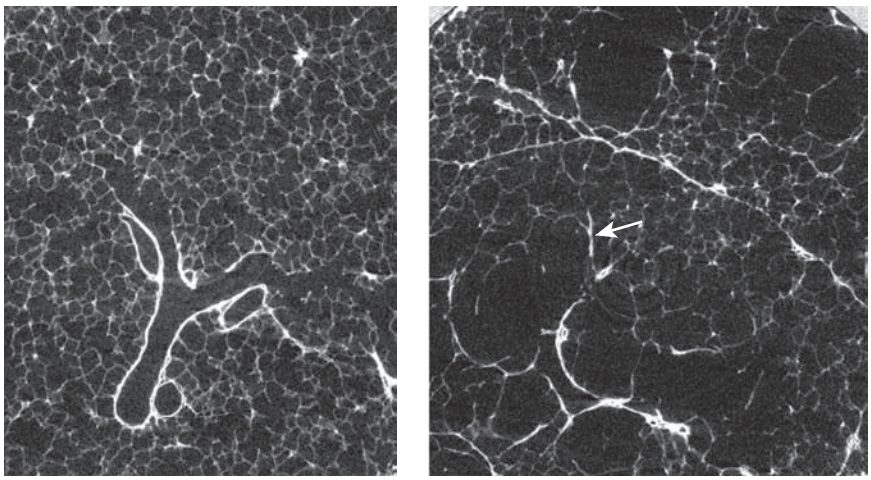


Figure 39-7 A small airway from a subject with COPD. The lumen contains mucus and inflammatory debris. There is goblet cell metaplasia of the epithelium. The subepithelial (submucosal) layer is increased in thickness due to an increase in fibrous tissue and inflammatory cells.



A B

Figure 39-8 **A.** Micro-CT scan image of an airway from a normal lung. Note the regular progression from membranous bronchiole to respiratory bronchiole to alveolar duct. **B.** Micro-CT scan image of an airway from a lung with centrilobular emphysema. Note the irregular airway emptying into a centrilobular hole. Partially obliterated airway is seen at the *arrow*. *(Figures used with permission of Dr. James C Hogg.)*

small airways of smokers with COPD,[92] a finding which may be of considerable importance since downregulation of the HDAC system is associated with a pro-inflammatory cytokine profile.

DIFFERENTIAL DIAGNOSIS

ASTHMA

Mucus plugs and goblet cell hyperplasia are markedly increased in the small airways of asthmatics[73,93] and this increase is generally much greater than that seen in COPD. In addition, the basement membrane thickness is approximately 20% greater than that found in either normals or patients with COPD.[73] The peripheral airways of asthmatics have an inflammatory infiltrate that features lymphocytes and eosinophils,[73,77,94] with many of the inflammatory cells in the adventitial, as opposed to the submucosal compartment. The data regarding the vessels in the submucosa are controversial, with some studies suggesting that they are congested, but not increased in number, in asthmatics compared with COPD (discussed in Ref.[74]), and others demonstrating an increased number of vessels, but a lesser total area in asthma compared with COPD.[95] Although smooth muscle is increased in asthmatics, the increase is not as great as that present in the large airways.[96] Moreover, the distribution of smooth muscle increase in the bronchial tree may be quite different, with some patients displaying a generalized increase, while in others the increase is restricted to the larger airways.[97] Overall, the small airways in asthmatic subjects who have died because of their disease have a greater area of subepithelial fibrous tissue, smooth muscle, and adventitial fibrous tissue than do subjects who died with their disease, which in turn have a greater area than do the airways of subjects with COPD.[98] Thus, although the same qualitative changes are present in both asthmatics and COPD, they are more severe in asthmatics and most severe in cases of fatal asthma. Interestingly, there appears to be a loss of alveolar attachments in cases of fatal asthma,[99] although this is less than that present in the airways of patients with COPD.

FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis is characterized by narrowing of the bronchioles due to adventitial and subepithelial lymphoid follicles, and accompanied by a lymphoplasmacytic inflammatory infiltrate.[100] The condition is classically found in patients with rheumatoid arthritis or those with IgA deficiency. This process can mimic severe COPD small airway disease, but the inflammatory infiltrate is generally magnified compared to COPD, while there is little goblet cell metaplasia in the airway epithelium.

PANBRONCHIOLITIS

The presence of foamy macrophages in the airway wall and lumen and extending down into the alveolar ducts and alveoli is a feature of the condition known as panbronchiolitis, originally described in Japan but now known to occur worldwide.[101,102] Follicular hyperplasia of the peribronchiolar lymphoid tissue is frequent, and bronchiolectasis is found in the more advanced lesions.

CONSTRICTIVE BRONCHIOLITIS

The term constrictive bronchiolitis appears to have been coined by Gosink et al.[103] In constrictive bronchiolitis, the airway lumen is occluded by a progressive thickening of the subepithelial (submucosal) space. Both the membranous and respiratory bronchioles are involved, and show transmural inflammatory cell infiltrates, occasionally with epithelial necrosis. Mucus plugs can also be identified. As the process evolves, the inflammatory infiltrate wanes, and greater amounts of fibrous tissue can be demonstrated both in the peribronchial and subepithelial portions of the airway, acting to narrow or obliterate the airway lumen.[104] Lesions of constrictive bronchiolitis, particularly in the organized phase, may be difficult to demonstrate, and may require elastic stains to outline the obliterated airway. Thus, the lesions in COPD differ from constrictive bronchiolitis only in degree.

Mineral dust–induced airway disease is a distinctive type of constrictive bronchiolitis, characterized by a stereotypic response of the small airways to high doses of particulate, regardless of the specific mineral dust involved. The lesions consist of fibrosis and thickening of the walls of both the membranous and respiratory bronchioles, sometimes extending down the alveolar ducts, the latter finding providing diagnostic discrimination from tobacco smoke–induced airway disease, which tends not to involve the alveolar ducts. Pigment deposition is highly variable, and is not a diagnostic feature.[105] Other forms of constrictive bronchiolitis may be related to ingestion of toxic compounds such as *Sauropus androgynus* ingestion,[106–109] *or* related to diffuse neuroendocrine cell hyperplasia.[110–113]

PROLIFERATIVE BRONCHIOLITIS

The lesions of proliferative bronchiolitis have been elegantly described and illustrated.[114–116] Within the lumens of the membranous and respiratory bronchioles are plugs of organizing fibroblastic (granulation) tissue. Occasionally, ulceration of the epithelium can be seen, and early lesions may have fibrin. The granulation tissue is formed of a pale matrix with proliferating spindle cells, accompanied by chronic inflammatory cells. As the lesions age, the granulation tissue usually shrinks and contracts. However, in a certain proportion of cases, the bronchiolar cells proliferate over the granulation tissue, and incorporate it into the subepithelial space, leaving an irregular airway lumen.

Although acute bronchiolitis, be it bacterial or viral in nature, is usually easily distinguished from the lesions of COPD by the presence of extensive epithelial damage, healed lesions may

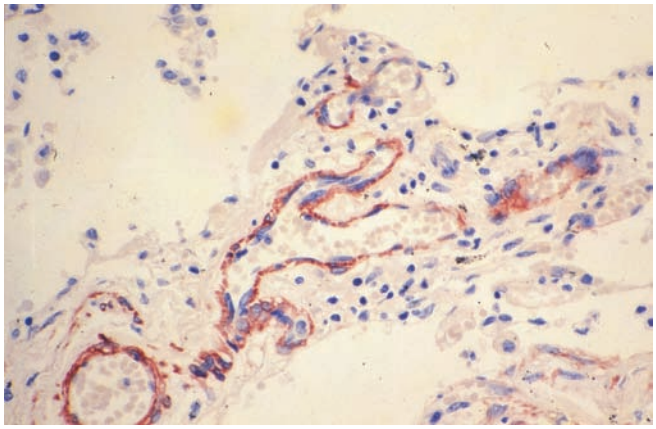


Figure 39-9 A small pulmonary artery from a subject with COPD. These vessels, situated adjacent to the alveolar ducts, are normally poorly muscularized, but in this case, the vessel has a distinct circumferential muscular layer.

show nonspecific airway fibrosis and chronic inflammation, or the residua of proliferative bronchiolitis. Interestingly, latent adenoviral infection has been suggested as a contributor to airflow obstruction in adults by amplifying the inflammatory response in the bronchioles of cigarette smokers.[117] Airway disease complicating other diseases may also need to be distinguished from that of COPD. For example, posttransplant bronchiolitis[115,118] or airway disease in patients with inflammatory bowel disease (both Crohn disease and ulcerative colitis)[119] include both proliferative and constrictive bronchiolitis. Inflammatory bowel disease may also have large airway involvement.

LESIONS OF THE VESSELS IN COPD

There are no consistent alterations in the large elastic pulmonary arteries of subjects with COPD. Atheromata can be found,[120] but unless there is pulmonary hypertension, the incidence is probably not greater than that found in a carefully matched population.

Cigarette smokers, with or without pulmonary hypertension, have an increase in arterial muscle media thickness as well as intimal fibrosis in the muscular arteries, and progressive muscularization of the small arterioles (reviewed in Ref.[121]). Increases in intimal thickness with longitudinal muscle formation are a common feature in lungs of patients with COPD (Fig. 39-9).[11,122,123] There appears to be a progressive increase in the numbers of smaller muscularized arteries, percent medial thickness, and percent intimal thickness of muscularized arteries from nonsmokers, to smokers without obstruction, to smokers with airflow obstruction.[124]

The lesions of primary pulmonary hypertension and hypertension secondary to vascular shunting also include intimal fibrosis and increased muscular media thickness. Intimal fibrosis is often cellular in its early phases, but progresses to concentric laminar fibrosis, which can almost totally obliterate the vessel lumen. These changes are of much greater severity than those identified secondary to COPD. Vasculitis, fibrinoid necrosis, and plexiform lesions are never found in COPD. Lesions of chronic thromboembolic disease include eccentric intimal thickening, and the occasional formation of webs due to recanalization of the thrombi.

NONPATHOLOGIC, CT SCAN–BASED, EVALUATION OF TISSUE COMPARTMENTS IN COPD

CT scanning has provided useful information on the lung parenchyma, airways, and pulmonary vasculature in patients with COPD.

EMPHYSEMA

The advent of high-resolution CT scanners has allowed identification of even mild emphysema, and can distinguish between emphysema and senile lung airspace enlargement. When combined with general morphometric principles, emphysema can be quantified, and emphysema progression can be monitored.[125–128]

AIRWAYS

Evaluation of this compartment is in its developmental phase, with much of the work being performed on phantom airways or in large animals. In humans, thin-section CT scans are able to demonstrate evidence of airway wall remodeling in the more proximal airways (first- to sixth-generation airways) of subjects with COPD or asthma, and it has been suggested that changes in these airways can be extrapolated to the smaller airways.[129] Certainly, the data do suggest that these measurements correlate with lung physiology, independent from emphysema.[130]

PULMONARY ARTERIES

Measurements of the mainstem pulmonary artery are easily performed on CT scans using contrast, and these data have shown prognostic significance. Evaluation of the smaller vessels is much more difficult, but initial work has found that determination of the total cross-sectional area of the vessels which have an individual cross-sectional area of less than 5 mm^2 have a significant negative correlation with pulmonary arterial pressure, at least in patients with severe emphysema.[131,132]

SUMMARY

There are a number of pathologic alterations of the lung in COPD. These involve almost all of the lung compartments, including the parenchyma, vasculature, and large and small airways. These changes can overlap the pathologic findings present in other diseases associated with airflow obstruction, or other diseases that are manifested in the lung. It is important to be able to make the distinction among these diseases. Although the pathologic alterations roughly correlate to alterations in pulmonary function, it is important to remember that their individual contributions are not well worked out. Thus, it may be difficult on an individual patient basis to proceed from a clinical classification such as the GOLD classification to a mechanistic/pathologic explanation of the airflow obstruction. Advances in CT scanning technology have allowed evaluation and quantification of emphysema, and there is developing work suggesting that evaluation of the airways and pulmonary arterial system may also be possible.

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CHAPTER 40

Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology, Pathogenesis, and α1-Antitrypsin Deficiency

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Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow obstruction that is not fully reversible and for which there is no other explanation for the obstruction. The obstruction is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gas. Unlike earlier definitions, this definition does not mention emphysema or chronic bronchitis. According to criteria set by the Global Initiative for Obstructive Lung Disease,[1] airflow obstruction is present when there is a reduction of the postbronchodilator FEV_1/FVC ratio below 0.7 and its severity is graded by the percentage of the postbronchodilator FEV_1 of the predicted normal FEV_1 (Table 40-1). However, 0.7 as the cutoff value for the FEV_1/FVC ratio has been controversial as it may be too high for all age groups and lead to misdiagnosis of COPD in healthy middle-aged and older individuals.[2] Alternatively, use of the lower limit of normal (LLN) for the FEV_1/FVC ratio has been recommended,[3] but it is uncertain whether this criterion improves the detection of clinically significant COPD or prognosis in elderly individuals.[4,5] Classification of COPD by GOLD has undergone further refinement recently with addition of self-reported severity of dyspnea and history of COPD exacerbations.[1] Chapter 42 comments further about risk stratification.[6]

EPIDEMIOLOGY

COPD is a major health problem worldwide.[7,8] Its prevalence is being recognized increasingly in countries at all levels of development.[9] An ever-increasing number of smokers and an expanding number of elderly people are major factors in the surge in the worldwide prevalence of COPD. In a study from Canada, 27.6% of individuals reaching the age of 80 were diagnosed with COPD by a physician over the preceding 14 years.[10] In large areas of the world where indoor air pollution is generated by burning biomass for heating and cooking, COPD is prevalent among nonsmokers, especially women.[11] Moreover, COPD is not restricted to smokers in developed countries. Of 4291 never-smokers over age 40, involving 14 developed countries, 5.6% met criteria for moderate to severe COPD, of whom 81.2% were undiagnosed.[12]

At present, COPD is the third most common cause of death in the United States.[13,14] As might be expected from the mortality figures, surveys indicate a high prevalence of COPD. The 2011 Behavioral Risk Factor Surveillance System (BRFSS), which is a state-based telephone survey of the US civilian adult population aged >18 years, found that 6.3% of US adults (an estimated 15 million nationwide) were told that they have COPD by a healthcare provider and a large percentage of these individuals reported having had spirometry.[15] Another survey, the 2010 National Health Interview Survey of approximately 27,000 adults in US households, yielded an estimate of 5 million adults in the United States with emphysema and

TABLE 40-1 Classification of Airflow Limitation in Patients with $FEV_1/FVC < 0.7$

Severity Stage	Postbronchodilator FEV_1
1: Mild	$FEV_1 \geq 80\%$ predicted
2: Moderate	$50\% \geq FEV_1 < 80\%$ predicted
3: Severe	$30\% \geq FEV_1 < 50\%$ predicted
4: Very severe	$FEV_1 < 30\%$ predicted

Source: Modified with permission from Vestbo J, Hurd SS, Augusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(4):347–365.

TABLE 40-2 Risk Factors for COPD

Environmental	Host-based
Smoking	Genetic
Indoor air pollution	Airway hyperreactivity
Occupation	
Low socioeconomic status	

10 million with chronic bronchitis, not all of whom may have airflow obstruction.[16] Although these figures are impressive, they may be an underestimate, since COPD is likely to be unrecognized in some groups such as elderly persons living in poverty. Other statistics support these national surveys. Among 1575 cigarette smokers, aged 30 or older, with a 10 or more pack-year smoking history, approximately 20% met spirometric criteria for COPD.[17]

The number of deaths due to COPD in the United States has been rising. In 2008, COPD was the primary cause of death in 141,090 Americans.[14] and was a comorbidity in many other deaths. The number of women dying of COPD now exceeds men and has more than doubled in recent decades. Based on the Third National Health and Nutrition Examination Survey (NHANES III), life expectancy is shortened by 5.8 years for men aged 65 with GOLD stage 4 COPD and by an additional 3.5 years if smoking has continued.[18]

ETIOLOGY

Risk factors for the development of COPD are environmental and host based (Table 40-2). In developed countries, smoking tobacco is the predominant risk factor. However, as noted above, never-smokers also develop COPD and women predominate in this cohort.[11,12] In places where solid fuels are burned, indoor air pollution is probably the dominant risk factor. Other factors associated with COPD include second-hand tobacco exposure, age, level of education, tuberculosis, hospitalization for respiratory illness before the age of 10 years (see further comment below), a family history of COPD, and the number of years worked in dusty jobs.[19] Clearly, multiple risk factors may be present in a single individual.

■ ENVIRONMENTAL

Smoking

A history of smoking is present in 80% to 90% of the individuals with COPD in developed countries. In the United States an impressive level of overlap exists between the geographic distribution of smokers and the geographic distribution of individuals who have been told they have COPD (Fig. 40-1). In a European study involving 6836 individuals with normal spirometry, age 20 to 44, smoking was the most commonly recognized risk factor for the development of new COPD over a decade.[20] Deterioration of FEV_1 correlates with pack-years of smoking, but the relationship between amount of smoking and risk of COPD is unpredictable on an individual basis (Fig. 40-2), In the Million Women Study conducted in the United Kingdom, that involved 232,461 current, 328,417 former smokers, and 619,774 never-smokers at baseline, the relative risk of death from chronic lung disease, presumably mostly COPD, over a 12-year follow-up was increased about 35-fold among middle-aged women who smoked.[21] Among former smokers, the age at smoking cessation affects the subsequent rate of deterioration of lung function. The rate is closest to never smokers for those who quit prior to age 30, but even for those who quit after age 40, deterioration is less than in continued smokers (Fig. 40-3).

The effects of gender on the risk of developing COPD from smoking are unclear. Women may be more susceptible to lung injury from smoking than men as they show more lung function reduction in association with lower total exposure and they predominate among individuals with early onset of COPD[22] and never-smokers with COPD. However, among individuals with advanced COPD treated with long-term oxygen therapy, men have a higher mortality rate than women, a difference that cannot be explained by comorbidities.[23] Some data indicate racial disparities in the risk of developing COPD, with African Americans showing similar severity of COPD to whites with lesser pack-years of smoking.[24,25] Hispanic ethnicity appears to confer protection from the risk of COPD and a reduced risk of accelerated decline in lung function due to smoking.[26]

According to statistics from the Center for Disease Control and Prevention (CDC), in 2010 there were an estimated 45.3 million smokers in the United States representing 19.3% of all adults over age 18.[27] The percentage was similar in African Americans and whites. Smoking was present in 21% of men and 17% of women. Hispanics and Asians had the lowest percentage of smokers at 12% and 9%, respectively, while the percentage was highest at 27% among American Indian/Alaska Natives. Beyond age 65 the incidence of smoking was 9.5%. The number of smokers worldwide is predicted to be 1.5 to 1.9 billion in 2025.[28] Thus, COPD will continue to be a profound health problem well into the future.

Among smokers who have already sustained reductions in FEV_1, the consequences of continued smoking on ventilatory function are more impressive than when all smokers are grouped together.[29] The Lung Health Study, which followed middle-aged smokers for 11 years, found accelerated decline in those who already had a reduced FEV_1 at the start.[30] Despite these findings, progressive decline in the FEV_1 is not inevitable among individuals with COPD (Fig. 40-4).[31,32]

Environmental Tobacco Smoke Exposure or Second-Hand Smoke

Environmental tobacco smoke exposure (ETS) is implicated in loss of many years of life of adults and children in the United States, with notable sensitivity among African Americans,[33] but COPD, specifically, as a cause of the life shortening due to ETS is not clear[34] Controlled experimental studies with normal volunteers indicate that short-term exposures to ETS at levels comparable to those in real-life situations have effects on serum cytokine levels and pulmonary function that if recurrent or chronic might translate into COPD.[35,36] However, when smoking and other risk factors are controlled both workplace and home ETS but not prenatal ETS increase the risk of development of COPD.[37] Data regarding in utero effects of maternal smoking on lung growth and subsequent risk of childhood wheezing or asthma are becoming evident. However, doubt exists regarding the quantitative impact on the development of COPD in individuals with only prenatal exposure. It seems likely that similar to cystic fibrosis, individuals with enhanced genetic risk factors could be adversely modulated by ETS,[38] but to date no definitive proof of gene-by-environment interactions for ETS have been demonstrated. The data does not suggest that ETS is harmless but rather it is less definitively causal of COPD as an independent risk than chronic smoking or occupational exposures.[37] Avoidance in individuals with existing lung disease is clearly indicated given the association with exacerbation. The attitude that there is no risk-free dose of ETS, is likely the safest approach; this applies to all ETS-related diseases and not just COPD.[34]

Indoor Air Pollution

As stated above, indoor air pollution from burning solid fuels such as wood and animal dung for cooking and heating is widespread in parts of the world. This practice exposes women and children to high concentrations of smoke containing respirable particles and complex gas mixtures for many hours daily and thus the risk of COPD. It compounds the risk of COPD in smokers who are more likely to be men in these settings. Cough and sputum occur among those

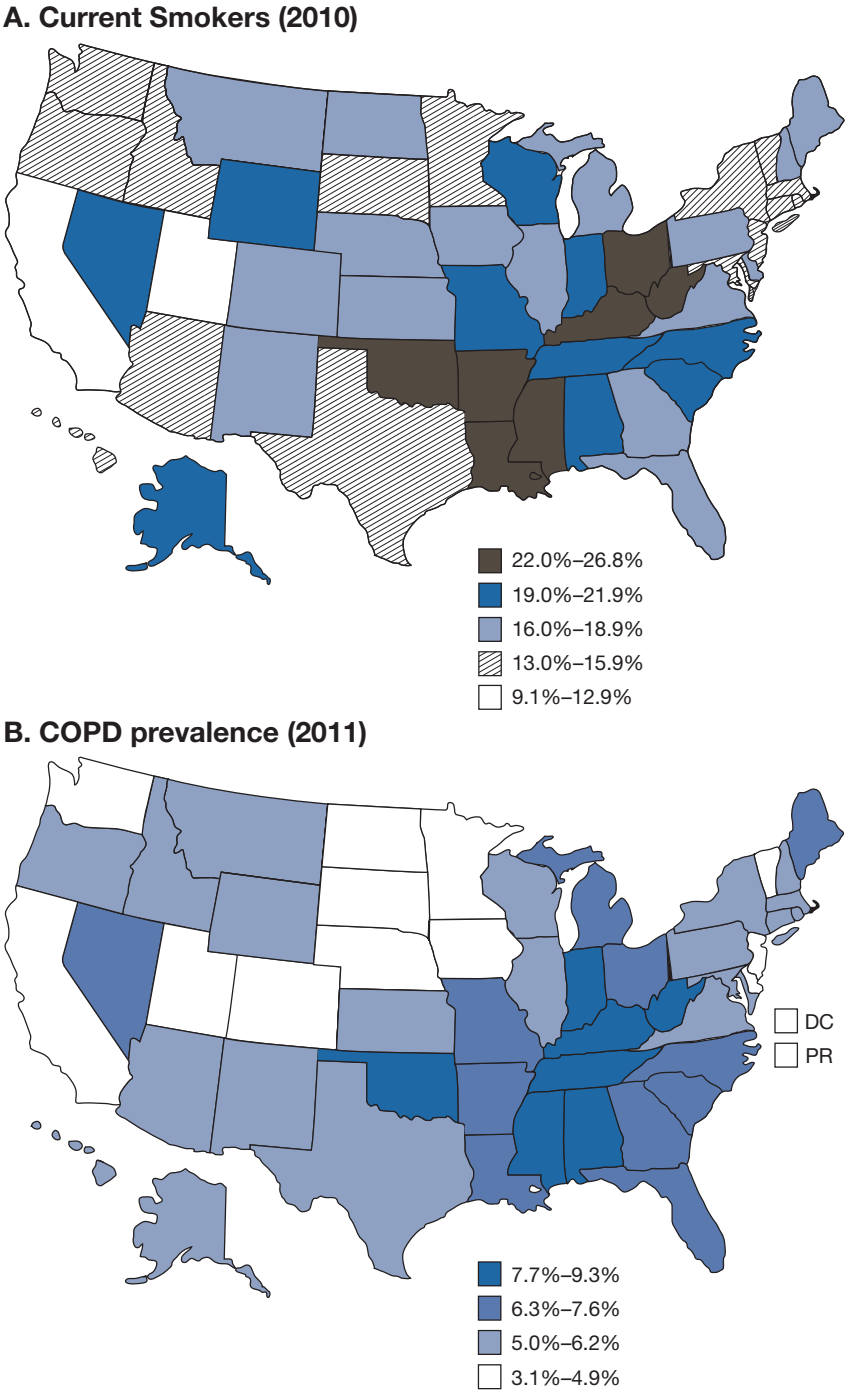


Figure 40-1 **A.** Percentage of persons aged ≥18 years who were current cigarette smokers, by state. Behavioral Risk Factor Surveillance System, United States, 2010. Persons who reported smoking at least 100 cigarettes during their lifetime and who, at the time of the survey, reported smoking cigarettes every day or some days. **B.** Age-adjusted prevalence of chronic obstructive pulmonary disease (COPD) among adults—Behavioral Risk Factor Surveillance System, United States, 2011. Based on an affirmative response to the question, "Has a doctor, nurse, or other health professional ever told you that you have COPD, emphysema, or chronic bronchitis?" (***A.*** *Reproduced with permission from Vital Signs. Current Cigarette Smoking Among Adults Aged ≥18 Years—United States, 2005–2010. Morbidity and Mortality Weekly Report. 2011;60(35):1207–1212.* ***B.*** *Reproduced with permission from Chronic Obstructive Pulmonary Disease Among Adults—United States, 2011. Morbidity and Mortality Weekly Report. 2012;61(46):938–943.)*

exposed to indoor air pollution and an association with COPD is evident.[39,40] Abatement of bronchitic symptoms coincident with measures that reduce the levels of smoke strongly implicates the indoor air pollution.[41] The World Health Organization estimates that more than 1 million people a year die of COPD precipitated by indoor air pollution.[42] International advocacy organizations such as the Global Alliance for Clean Cook-stoves seek to curb indoor air pollution.

Occupation

The possibility that occupation-related inhalation of particulates and gases carries a risk for COPD was slow in gaining acceptance, but acceptance is widespread now.[43,44] The delay was understandable since smoking among workers in certain occupations was a confounding factor. Also, workers beginning jobs with a high risk of causing lung disease typically have better lung function than normal (the "healthy worker" phenomenon), obscuring work-related effects among relatively young workers. In addition, among cohorts of workers, those with COPD may drop out, causing an underestimate of risk in follow-up studies of individuals still working.

Despite these problems, studies from different groups around the world, urban and rural, workforce-based and community-based, clearly implicate occupations producing exposures to dusts, gases, and fumes as risk factors for COPD.[44] The American Thoracic Society has estimated that the occupational contribution to the population burden of COPD is 15%.[45] Apart from the well-recognized risk of occupations involving exposure to organic and inorganic dusts, less obviously "risky" occupations, such as construction, plastics manufacturing, and utility work may carry an increased risk of COPD.[46] The risk of adverse occupational exposure is particularly

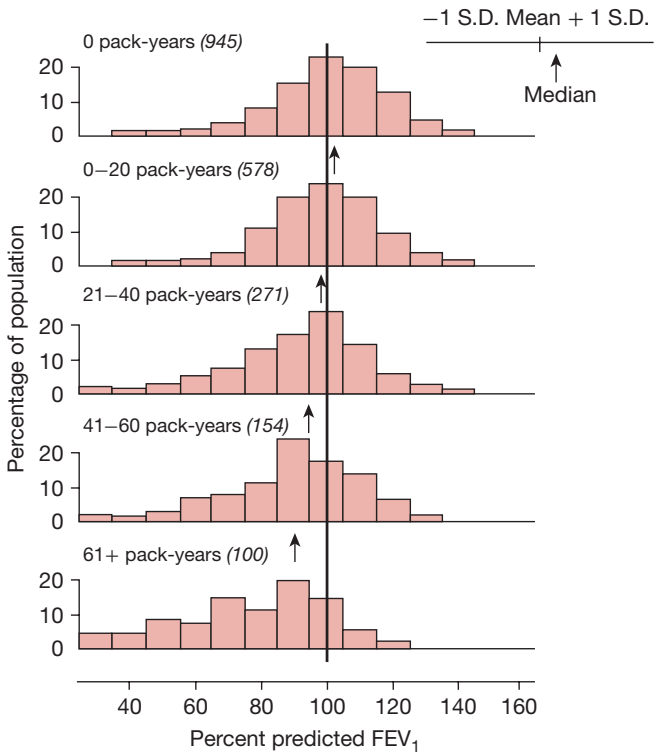


Figure 40-2 Distribution of percent predicted FEV_1 in adults with varying pack-years of smoking. Subjects with "respiratory trouble" before age 16 are excluded. The proportion of smokers with normal expiratory airflow decreases with increasing pack-years. Nevertheless, many smokers have a normal FEV_1 despite large cigarette-smoking histories. Means, medians, and ± standard deviation of the data for each group are shown in the abscissas. The numbers in parentheses are the numbers of subjects. *(Reproduced with permission from Burrows B, Knudson RJ, Cline M, et al. Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis. 1977;115:195–205.)*

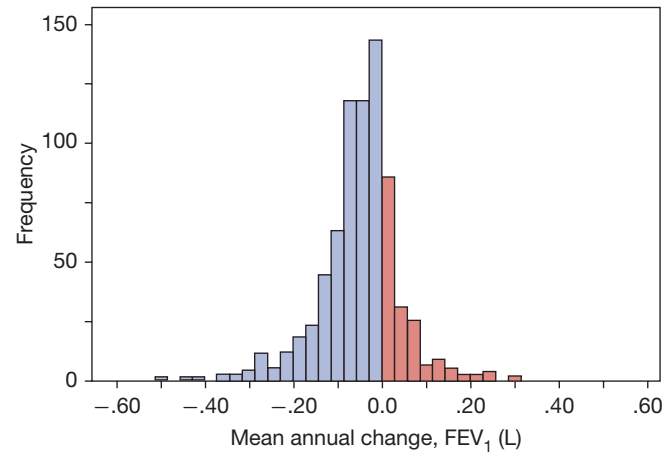


Figure 40-3 Histogram of the mean annual FEV_1 decline (L) for 751 patients with COPD followed for a median of 64 months and up to 10 years, having an average of 5.44 annual measurements, average age 66 years, 92% male, stratified by ATS/ERS and GOLD severity classification as follows: 32 (4%) mild (FEV_1% ≥80); 256 (34%) moderate (FEV_1% 50–79); 245 (33%) severe (FEV_1% 30–49); and 218 (29%) very severe (FEV_1% <30). *(Reproduced with permission from Casanova C, de Torres JP, Aguirre-Jaíme A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184(9):1015–1021.)*

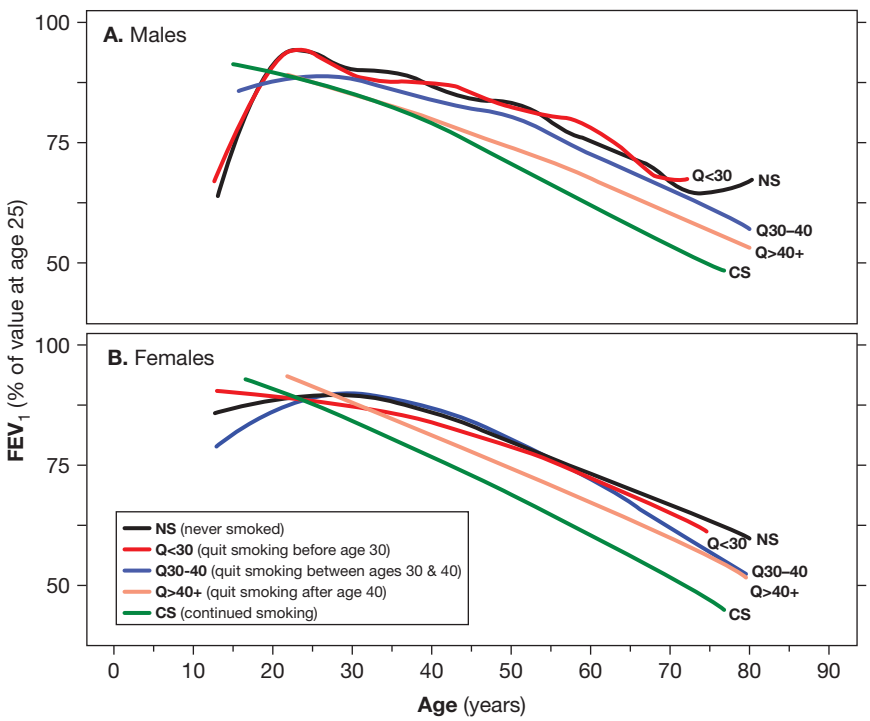


Figure 40-4 The effect of age of quitting smoking on FEV_1. Mean FEV_1 values (expressed as percent of its value at age 25) in smokers who quit smoking before the age 30 (Q < 30), between 30 and 40 years of age (Q30–40) and after age 40 (Q40+). Curves from healthy never smokers (NS) and continuous smokers (CS) are included for comparison. **A.** Males. **B.** Females. The mean annual FEV_1 decline for males was 15.5 mL in quitters before age 30, 24.0 mL in quitters 30 to 40 years of age, and 28.9 mL in quitters after age 40; for females, the values were 10.4 mL quitting before age 30, 16.5 mL in quitters between 30 and 40 years of age, and 21.0 mL in quitters after the age of 40. *(Reproduced with permission from Kohansal R, Martinez-Camblor P, Agustí A, et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med. 2009;180(1):3–10.)*

important in workers who smoke or have other factors that raise their risk for COPD, such as α1-antitrypsin deficiency.[47]

Childhood Lower Respiratory Tract Infections

Since the status of lung function in very early childhood predicts ventilatory function many years later,[48] it is plausible that lower respiratory tract infections (LRIs) during childhood might adversely affect lung development and increase the risk of developing COPD later in life. However, lung function in children who had pneumonia up to age 2 infrequently had reduced lung function 10 years after the infection.[49] If there was a ventilatory defect, it was most often restrictive. Where reduced airflow was observed, an adenovirus was the predominant class of pathogens responsible for the pneumonia. It is notable that COPD exacerbations may leave only a minor lasting effect on airflow. Continued smokers enrolled in the Lung Health Study had only an additional loss of 7 mL of FEV_1 per year for those having one exacerbation per year, while among those who had quit smoking, exacerbations had no permanent effect on the FEV_1.[50]

LOW SOCIOECONOMIC STATUS

A low socioeconomic status is a risk factor for COPD. The relationship may be linked to an increased amount of smoking and other factors, including deficient medical care for respiratory infections, occupational exposure to inhaled particulates, and increased exposure to household allergens. The importance of smoking is evident. In the United States in 2011, 45% of adults with a General Education Diploma (GED) were smokers compared to 10% of individuals with a college degree, and among adults living below the poverty level, 33% were smokers in contrast to 20% of individuals living above the poverty level.[51]

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Individuals with human immunodeficiency virus (HIV) who smoke have an increased risk of COPD or more specifically emphysema development.[52–54] The risk appears to be modulated by activation of alveolar macrophages with evidence of enhanced production of matrix metalloproteinases (MMPs) in these individuals.[55] Although HIV can infect macrophages,[56] it is unclear if this is a direct alteration due to HIV infection or a response to some downstream alteration of the suppression of innate immune responses, like chronic *Pneumocystis* infection.[57] The occurrence of COPD and pulmonary hypertension in smokers with HIV appears to be more common in individuals with a high viral load and lower CD4 cell counts and not an adverse consequence of antiretroviral therapy.[58] However, emphysema is not reversible and relation to viral load or recovery of CD4 cell counts is not straightforward. Other health issues like malnutrition may contribute. A multicenter study about the lung in HIV supported by the National Insitutes of Health is underway.

HOST BASED

Genetics

The field of COPD genetics is moving rapidly so that capturing this subject is aiming at a moving target. Aggregation of COPD in families and concordance of pulmonary function in twin studies have established a role for genetic predisposition to COPD.[59–61] Moreover, the occurrence of reduced maximal expiratory airflow among nonsmoking first-degree relatives of individuals with early-onset COPD provides further support.[62] Perhaps most compelling is the marked variability in development of COPD among smokers. Dissecting specific genetic factors that increase the risk of COPD has proven difficult. α_1-AT deficiency illustrates this difficulty,[63] where even among individuals with an identified genetic risk factor, wide, unexplained variability in the occurrence of COPD exists.[64]

However, deficiency of functional α_1-AT represents the best-known genetic risk for COPD (see below). In this example genetic mutations discovered in small initial sample sizes can be replicated in larger analysis despite a significant gene-by-environment interaction. To this end, very rare mutations in the coding sequence of elastin cause cutus laxa and can also lead to COPD.[65–67] Although Marfan and Ehler–Danlos syndromes cause lung parenchymal blebs[68] and in mouse models demonstrate developmental of airspace enlargement,[69,70] no human cohort has demonstrated clear penetration of a fixed obstructive lung disease phenotype.[71]

Polymorphisms of genes involved in protease–antiprotease balance, antioxidant function, inflammation, and immune responses have been implicated in COPD in studies utilizing candidate gene approaches (Table 40-3).[72–74] However, none of these polymorphisms are consistently confirmed in other cohorts or large genome-wide association studies of lung function or COPD (Table 40-4).[75–78] Failure of confirmation may indicate flaws in previous studies, but differences in COPD phenotypes, ethnic background, or other factors might explain discrepancies between previous studies and subsequent data. Despite misgivings of reproducibility in candidate gene studies it should be noted a minor allele frequency (MAF) of less than 5% typically excludes rare polymorphisms from GWAS style studies. Rare alleles may be quite important if the effect is large as demonstrated by α_1-AT (SerpinA1) (Table 40-3).

TABLE 40-3 Examples of COPD-Related Genes from Candidate Approach Studies

Gene Symbol	Functional Category	Locus	Polymorphism	MAF[a]
SERPINA1	Antiprotease	14q32	rs28929474=A	0.01
MMP12	Protease	11q22	rs2276109=G	0.07
MMP1	Protease	11q22	rs1799750=del	0.45
SOD3	Antioxidant	4p15	rs1799895=G	0.02
HMOX1	Antioxidant	22q13	rs3074372 $(GT)_n$>33	0.13[b]
EPHX1	Detoxifying	1q42	rs2234922=G	0.19
GSTM1	Detoxifying	1p13	rs366631=T	0.19
ADRB2	Adrenergic	5q32	rs1800888=T	0.01
TGFB1	Cytokine	19q13	rs2241712=A	0.35

SERPINA1 (α1-antitrypsin) included for appreciation of allelic frequency of genes discovered by candidate gene approach or meta-analysis of candidate genes.
[a]Minor allele frequency (MAF) from 1000 Genomes or from [b]study when not available.

TABLE 40-4 Examples of COPD-Related Genes from Genome Wide Association Studies of Spirometry (prebronchodilator)

Gene Symbol	Functional Category	Locus	Polymorphism	MAF[a]	Association
TNS1	Cell adhesion to matrix	2q35	rs2571445=G	0.33	FEV_1
FAM13A	Signal transduction	4q22	rs7671167=T	0.48	COPD, FEV_1/FVC
HHIP	Lung development	4q31	rs11100860=G	0.39	COPD, FEV_1/FVC
HTR4	Serotonin receptor	5q33	rs3995090=C	0.47	COPD, FEV_1
AGER	Glycosylation receptor	6p21	rs2070600=T	0.07	FEV_1/FVC
THSD4	TGFβ signaling	15q23	rs12899618=G	0.12	FEV_1/FVC
CHRNA3/5[b]	Nicotine addiction	15q25	rs8034191=T	0.21	COPD, FEV_1/FVC
IREB2[b]	Iron homeostasis	15q25	rs2568594=G	0.32	FEV_1/FVC
BICD1	Telomere/senescence	12p11	rs10844154=A	0.38	Emphysema
TMEM26	Transmembrane protein	10q21	10761570=T	0.44	Decline in FEV_1

[a]*Minor allele frequency (MAF) from 1000 Genomes, Polymorphism studied is not always minor allele.*
[b]*Polymorphism no longer significant for association with physiology measures when only nonsmokers evaluated.*

Traits like emphysema quantified by CT lung density, subjective dyspnea, and 6-minute walk distance can also be utilized as each trait has been independently associated with prognosis in COPD. Of note, analysis based on radiographic emphysema characterization does not seem to reveal the same genetic locations as airway physiology–based phenotyping (Table 40-4),[79] possibly reflecting the advantage of extending genetic evaluation to other reproducible quantitative phenotypes, as differential genetic susceptibility to disease characteristics may reveal distinct independent pathways within the larger COPD population.

Very large GWAS studies of physiologic traits used to define COPD (FEV_1, FEV_1/FVC ratio) in populations that include nonsmokers and individuals too young to have COPD increase the understanding of how genetic factors interact with the environmental etiologic factors. For example, lung development and smoking habit may be teased out by examining COPD-susceptibility loci for association with the same traits in nonsmokers or younger individuals. This is important, as polymorphisms related to nicotine addiction[80] (e.g., CHRNA3/5) need to be separated from polymorphisms that mark susceptibility to smoke exposure given the difficulty with quantifying lifetime smoke exposure. On the other hand, polymorphisms related to genes involved predominantly in lung development (e.g., HHIP) will result in alterations of the physiologic traits even in never-smokers, but may also augment increased susceptibility to smoking.[81] It is notable that the different approaches of genetic analysis have not yielded as much cross-confirmation in COPD as has been seen in other diseases, despite the fairly large size of recent GWAS studies. In addition, although the same approaches have been utilized in asthma, a diagnosis that relies on the same physiologic traits, the polymorphisms discovered in asthma do not overlap COPD associated pathways.[82–84] This distinct genetic framework of COPD versus asthma supports many years of work in mouse models defining divergent immune pathways in these two common airway diseases.[85]

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is present when there is an acute, temporary decline in maximal expiratory airflow in response to inhaling potential bronchoconstricting agents such as methacholine or histamine. In individuals with COPD, AHR is associated with accelerated decline of FEV_1 and therefore is a negative prognostic marker.[86] In the Lung Health Study, AHR was second to smoking as an important determinant of decline in FEV_1 and was not related to the initial level of obstruction. AHR was greater in women smokers than men smokers.[86] Although AHR decreased after smoking cessation and bronchodilator responsiveness improved, bronchodilator responsiveness did not correlate with the rate of FEV_1 decline.[87]

A major question about the relationship of AHR to COPD involves consideration of the so-called "Dutch hypothesis," which ascribes a role of allergy to the development of COPD. Observations that argue against AHR as a cause of COPD are that smokers typically do not show AHR until their FEV_1 is already reduced and that experimental induction of emphysema can lead to AHR.[88] It is plausible that AHR may be a consequence of emphysema, as airway wall stiffness and parenchymal tethering are affected by the extracellular matrix.[89] If unmeasured emphysema is also connected to AHR, this may contribute to the gender bias and decline rate findings as emphysema presence may predict accelerated future decline regardless of smoking habit.[90] As noted, the genetic distinction of asthma and COPD polymorphisms would also favor a great proportion of COPD having a nonasthmatic origin.

PATHOPHYSIOLOGY

A persistent reduction in FEV_1/FVC is the defining physiological feature of COPD. Increased airway resistance, increased residual volume (RV), increased RV/total lung capacity ratio (RV/TLC), decreased inspiratory capacity, decreased maximum voluntary ventilation (MVV), abnormal distribution of ventilation, and ventilation–perfusion mismatching are also typical physiological features.

■ AIRFLOW OBSTRUCTION

The low FEV_1 and low FEV_1/FVC in COPD are not reversible with inhaled bronchodilators, although small improvements are common, especially if responsiveness is tested with both ipratropium and albuterol.[91] Thus, COPD differs from asthma, in which inhaled bronchodilators can produce large improvements in FEV_1. Maximal inspiratory flow may be relatively well preserved in the presence of a low FEV_1/FVC and a low FEV_1. A reduced FEV_1 with a normal FEV_1/FVC and normal TLC should not be interpreted as an obstructive ventilatory defect. This pulmonary function pattern is called nonspecific and infrequently progresses to COPD.[92]

The FEV_1 is the result of the balance between the elastic recoil of the lungs promoting expiratory flow and the resistance of the airways that limits flow during performance of an FVC. In normal lungs, as well as in lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil and the cross-sectional area of the airways falls leading to an increase in airway resistance. The decrease in

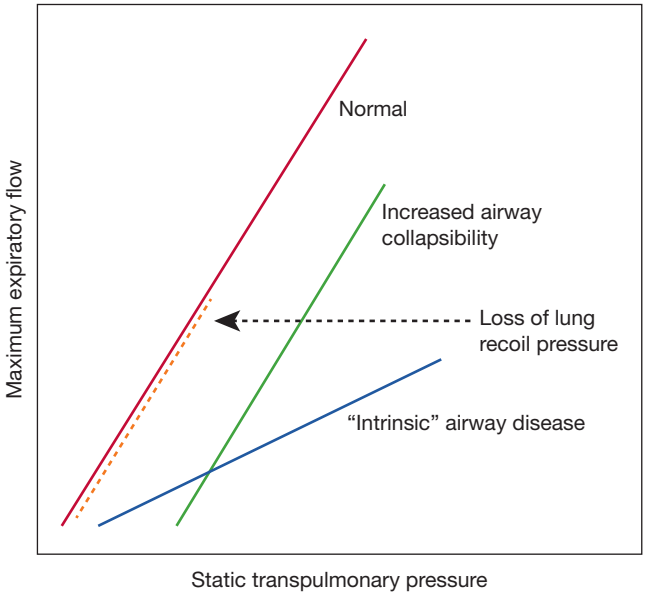


Figure 40-5 Analysis of reduced maximum expiratory flow in COPD from maximum expiratory flow versus lung recoil pressure curves. With loss of lung recoil pressure – that is, "emphysema" (heavy interrupted line) – the slope of the flow–pressure curve remains normal, but the curve terminates at lower pressure than normal. With intrinsic airway obstruction – that is, "bronchitis" – the slope is reduced. Increased airway collapsibility, which may be a result of decreased elastic recoil, causes the curve to be displaced to the right. Commonly in COPD, the flow–pressure curve has premature termination and a decreased slope and is shifted rightward, indicating that decreased elastic recoil, increased airway resistance, and increased airway collapsibility are all involved in causing the reduced maximum expiratory flow. *(From Pride NB, Milic-Emili J. Lung mechanics, in Calverley PMA, Pride NB [eds]. Chronic Obstructive Pulmonary Disease. London, Chapman & Hall; 1995.)*

flow coincident with the decrease in lung volume is apparent on the expiratory limb of the flow–volume curve (Fig. 40-5). In mild COPD the abnormality in airflow is evident only at lung volumes at or below functional residual capacity, appearing as a "scooped out" lower part of the descending limb of the flow–volume curve. In advanced COPD, the entire curve demonstrates decreased expiratory flow. By measuring pressure–volume and pressure–flow relationships it is theoretically possible to assess the relative importance of decreased elastic recoil ("emphysema") from increased airway resistance ("small airway disease") as the cause for the reduced FEV_1 As discussed below, the correlation between FEV_1 and small airway pathology is strong and likely contributes to the reduction independent of the correlation of FEV_1 with emphysema.

There is wide variability in COPD in the relationships between FEV_1, exercise tolerance, and quality of life.[93] Variability also extends to the relationship between the FEV_1 and alveolar gas exchange. However, the Pa_{O_2} and oxygen saturation usually remain near normal until the FEV_1 has decreased to about half of the predicted normal while elevation of the Pa_{CO_2} seldom occurs until the FEV_1 is less than about one-fourth of the predicted.[94] Thus, other causes of hypoxemia or an elevated Pa_{CO_2}, such as the obesity hypoventilation syndrome, should be considered in patients with abnormal arterial blood gases and only mild to moderate COPD. Similarly, pulmonary hypertension and right ventricular failure do not occur unless COPD is severe and associated with chronic hypoxemia (Pa_{O_2} <55 mm Hg). Diastolic dysfunction is common in the general population, where COPD is prevalent, and should be considered when pulmonary hypertension is discrepant with COPD severity.

ABNORMAL DISTRIBUTION OF VENTILATION AND VENTILATION–PERFUSION MISMATCHING

Abnormal distribution of ventilation results from the heterogeneity of the pathologic process affecting airways and lung parenchyma. This heterogeneous ventilation results in ventilation–perfusion mismatching that is characteristic of COPD. Abnormality in the distribution of ventilation is evident in the pattern of nitrogen washout during breathing of 100% oxygen. The nitrogen washout is delayed because of regions that are poorly ventilated, and the shape of the nitrogen washout curve reflects compartments with different washout rates due to regional differences in compliance and airway resistance. Radioisotopic ventilation scanning with ^{133}xenon also reveals regional heterogeneity of ventilation in COPD, but can also demonstrate the ability of airway mucus to trap xenon tracer.

The multiple inert gas elimination technique (MIGET), which enables quantification of the ventilation–perfusion profile, has demonstrated different ventilation–perfusion patterns among patients with advanced COPD (Fig. 40-6). In one pattern, the

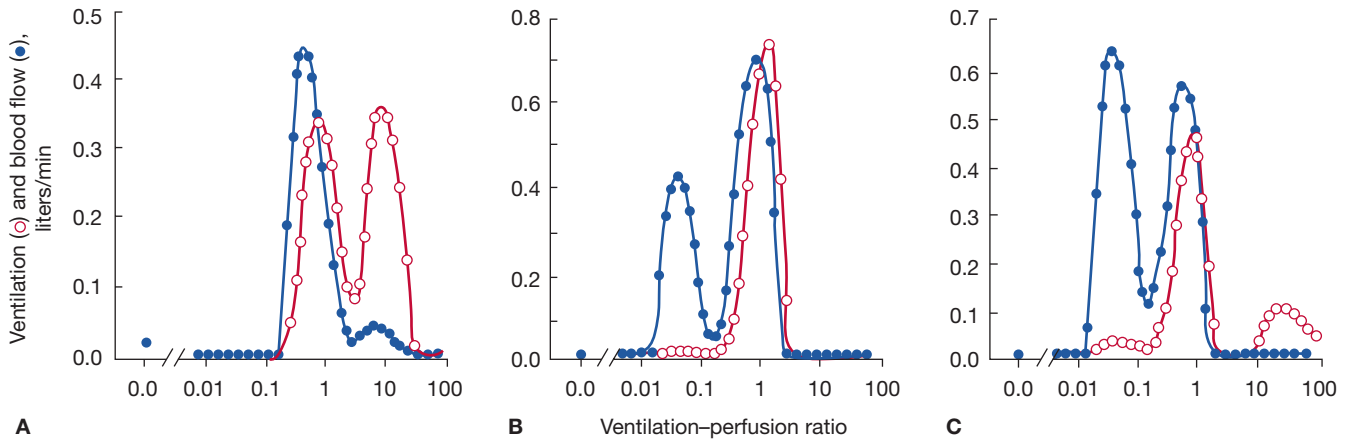


Figure 40-6 Ventilation–perfusion distributions in three persons with COPD determined by the multiple inert gas elimination technique (MIGET). **A.** Regions of high ventilation–perfusion characteristic of "emphysematous," type A COPD. **B.** Regions of low ventilation–perfusion characteristic of "chronic bronchitis," type B COPD. **C.** Regions of both high and low ventilation–perfusion characteristic of many people with COPD. In the normal person, not shown, ventilation–perfusion virtually overlaps and peaks at about a ventilation–perfusion ratio of 1. *(Reproduced with permission from Wagner PD, Dantzker DR, Dueck R, et al. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest. 1977;59(2):203–216.)*

so-called type A ("pink puffer") COPD, there is a substantial amount of ventilation distributed to high ventilation–perfusion regions. This likely reflects actual loss of vascular elements in conjunction with the pathologic changes of the gas exchange parenchyma. In a second pattern, called type B ("blue bloater") COPD, there is a substantial amount of pulmonary blood flow perfusing low ventilation regions. This simple classification was important historically in the development of understanding COPD pathophysiology, but has fallen out of use because most people with COPD are not easily classified as either type A or type B. They have both high and low ventilation–perfusion regions.

Ventilation–perfusion mismatching accounts for essentially all of the reduction in Pa_{O_2} that occurs in COPD, so modest elevations of the inspired oxygen concentration are effective in treating hypoxemia. If hypoxemia is difficult to correct, other problems such as right- to left-sided intracardiac or intrapulmonary shunting need to be considered in addition to COPD.

HYPERINFLATION

Increases in total lung capacity, functional residual capacity (FRC), residual volume, and the residual volume to total lung capacity ratio (RV/TLC) are common in COPD. These abnormalities may be beneficial in that they help to preserve expiratory airflow by increasing lung elastic recoil and the cross-sectional areas of airway lumens. However, they have adverse effects. They displace the diaphragm into a flattened position causing a number of adverse effects (Fig. 40-7). In addition, they put the thoracic cage at a mechanical disadvantage so that inspiration requires work rather than being passively assisted by the elastic recoil of the chest wall. These abnormalities of increased lung volume may increase further with exertion because reductions in airflow in diseased lungs reduce expiratory volume during rapid breathing. This phenomenon, called dynamic hyperinflation, adds to the workload on the inspiratory muscles while further reducing their mechanical advantage. Dynamic hyperinflation is an important mechanism of dyspnea with exertion in COPD.[95]

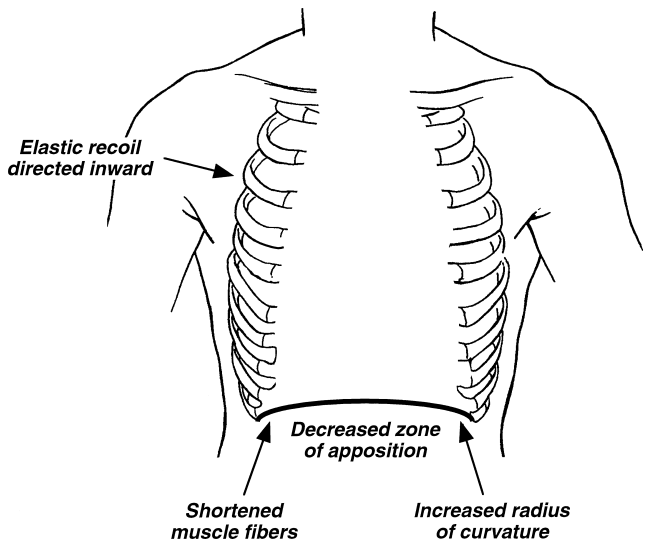


Figure 40-7 Detrimental effects of hyperinflation on diaphragmatic function. Hyperinflation causes flattening of the diaphragm, which (1) decreases the zone of apposition between the diaphragm and the abdominal wall, hindering rib cage movement; (2) shortens diaphragmatic muscle fiber length, decreasing the force that can be generated by the diaphragm; (3) increases the radius of curvature of the diaphragm, thereby decreasing transpulmonary pressure (at constant tension); and (4) directs diaphragmatic muscle fibers medially, impairing inflation with diaphragmatic contraction. In addition, hyperinflation prevents the thorax from assisting inspiration during tidal breathing because the resting volume of the thorax is above the volume at which the rib cage recoils outward during inspiration. *(Reproduced with permission from Yusen RD, Lefrak SS. Evaluation of patients with emphysema for lung volume reduction surgery. Washington University Emphysema Surgery Group, Semin Thorac Cardiovasc Surg. 1996;8(1):83–93.)*

Hyperinflation of the residual volume and FRC reduce the inspiratory capacity, which has prognostic significance that is independent of FEV_1. In one study of individuals with moderate to severe COPD, those whose ratio of inspiratory capacity to total lung capacity was less than 25% had a much shorter life span than those with a ratio greater than 25%, even though the two groups had comparable percent predicted FEV_1.[96]

DYSPNEA

People with COPD typically seek medical care because shortness of breath limits their activities and quality of life. Dyspnea is seldom a complaint until the FEV_1 has fallen below about 60% of predicted. However, the correlation between FEV_1 and exercise limitation is not strong. Some individuals are relatively free of dyspnea despite a severely reduced FEV_1. Commonly, the discomfort associated with breathing is associated with inspiration rather than expiration.[97] Measurement of dyspnea has proven complicated.[98] A number of indices are in use.

An increased sense of effort relating to the pressures needed from the respiratory muscles relative to their maximum pressure-generating capacity is thought to be an important factor in causing the dyspnea associated with COPD. Signals of "length-tension inappropriateness" from the respiratory muscles due to hyperinflation are another factor. Dynamic hyperinflation, as described above, exaggerates these problems for respiratory muscles. Also, impulses from airways undergoing abnormal dynamic compression during exhalation have been described. Hypoxemia and hypercapnia play only a small role during periods of clinical stability. Oxygen administration may decrease breathlessness by reducing ventilation during exertion and through poorly understood direct effects not associated with changes in ventilation.

PHYSIOLOGICAL–PATHOLOGICAL CORRELATIONS

In 1968, Hogg and colleagues observed that airways 2 mm or less in internal diameter normally contribute only a minor part of the total airway resistance, but that these airways are the principal sites of increased airway resistance in COPD.[99] For many years, the physical basis for small airway resistance in COPD was considered to be a combined result of emphysema causing small airway instability and collapse along with multiple anatomic abnormalities narrowing the lumens of small airways. Because emphysema and small airway pathology are both common in individuals with COPD their relative contributions to airflow obstruction have been difficult to discern.

Fixed reduction in airflow is associated with several specific pathologic findings in the small airways of advanced COPD (Fig. 40-8). Small airways in the lungs of individuals with COPD typically show goblet cell metaplasia, replacement of Clara cells with mucus-secreting cells, and infiltration of the airway walls by inflammatory cells that, in severe disease, include an increased surface area of lymphoid follicles.[100] The cellular changes are accompanied by increased connective tissue in the subepithelial and adventitial compartments of the airway walls.[100] Alveolar tissue surrounding small airways normally provides radial traction on bronchioles at points where alveolar septa attach. Loss of these bronchiolar attachments as a result of proteolytic destruction may contribute to airway distortion, narrowing, and instability.

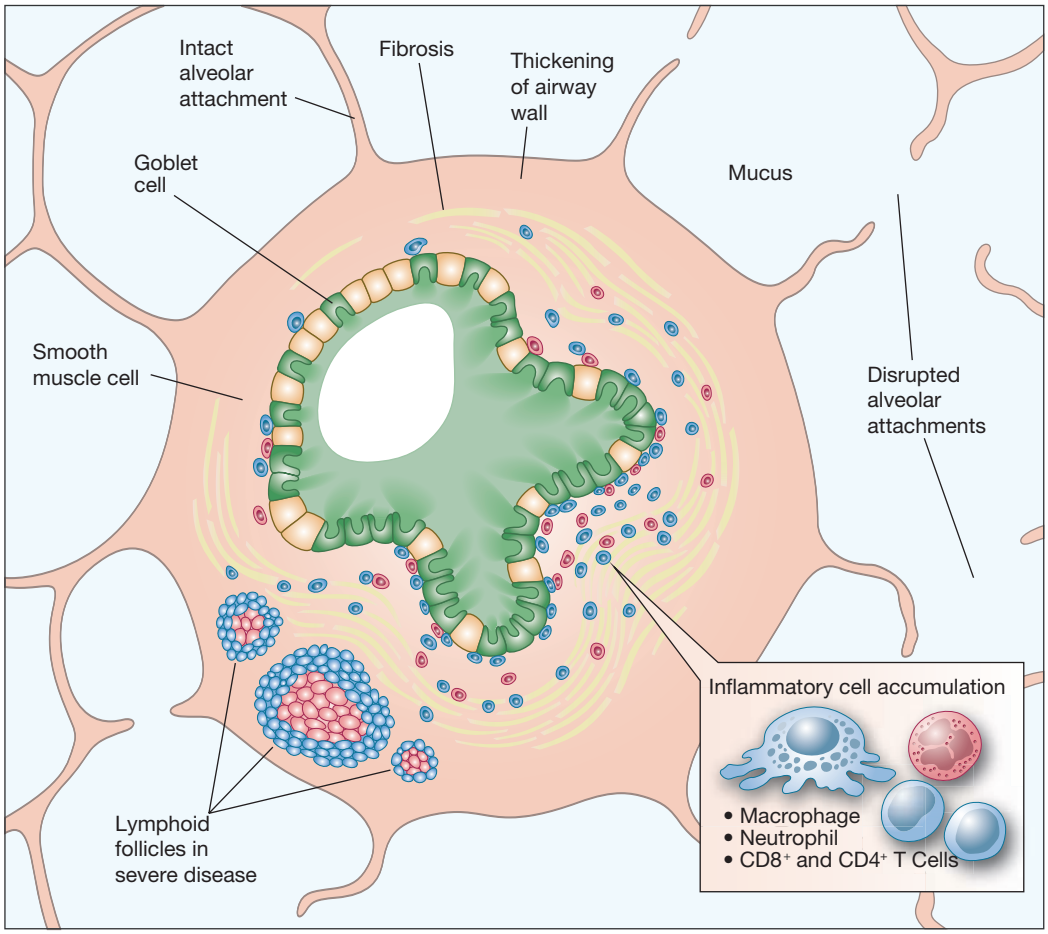


Figure 40-8 Pathologic lesions in small airways in COPD. Multiple abnormalities lead to partial obstruction of the lumen and altered shape and mechanical properties of the airways. *(Reproduced with permission from Senior RM, Silverman EK. Chronic obstructive pulmonary disease. In: Nabel EG, ed. ACP Medicine: Pulmonary, Hamilton, Ontario. Canada: Decker Publishing; 2011.)*

Although pathologic studies suggested the numeric loss of very small airways seen at autopsy is insufficient to produce the degree of airway resistance increases seen early in COPD, recent radiologic studies have confirmed there is a significant loss of visible (2–2.5-mm diameter) airways before radiographic emphysema is present.[101] Indeed, the loss of small airways can be impressive, reaching 90% in severe COPD. The large-scale pathologic loss of terminal airways in advanced disease will contribute significantly to the small airway resistance[101] but whether radiographic loss of small airway surface area in early disease is pathologic destruction, severe wall thickening or mucus plugging that obscures the lumen below the radiographic resolution is not yet clear. However, more severe airflow obstruction is clearly associated with increases in thickness of all components of the airway wall.[100] The greatest relative increase in components of the airway wall is in the connective tissue–rich adventitial layer but the epithelial layer, the lamina propria, and the smooth muscle–containing layer all demonstrate significant increases in advanced disease and small airway mucus plugs have been demonstrated to be significantly associated with airflow limitation in severe disease. Thus, overall, compared to small airway pathology and radiologic loss of small airways, emphysema occurs late in the development of COPD and appears to have a limited role in causing the airflow obstruction in early COPD.[102]

PATHOGENETIC MECHANISMS

COPD represents the clinical expression of complex alterations in structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis, altered phenotype of lung cells, and remodeling of the extracellular matrix (Fig. 40-9). Numerous mediators, most notably proteinases, oxidants, and cytokines, are involved in these processes. Studies in genetically altered mice have proven invaluable in helping to elucidate the pathogenesis of COPD, especially emphysema.

■ INFLAMMATION

Innate Immune Responses

As reflected in the definition of COPD, inflammation occupies a central role in current thinking about the pathogenesis of COPD. The inflammation paradigm is that smoking and other types of inhaled irritants lead to recruitment of innate inflammatory cells to the lungs and airways and that products of these recruited cells injure lung tissue and disrupt normal mechanisms of lung repair. Indeed, inflammation is prominent in airways and lung parenchyma in biopsies, surgical specimens, and postmortem material from individuals with COPD.[100,103–105] Other indicators of inflammation are increased inflammatory cells in bronchoalveolar lavage fluid (BALF)[106–108] and sputum[109–111] and increased volatile products of inflammatory cells in exhaled breath.[112,113] Systemic inflammation is also present in current smokers, with elevations in white blood cell counts, neutrophil subsets, or liver-derived acute phase reactants.[114–116] Inflammatory cells associated with COPD in the lung include predominantly neutrophils,

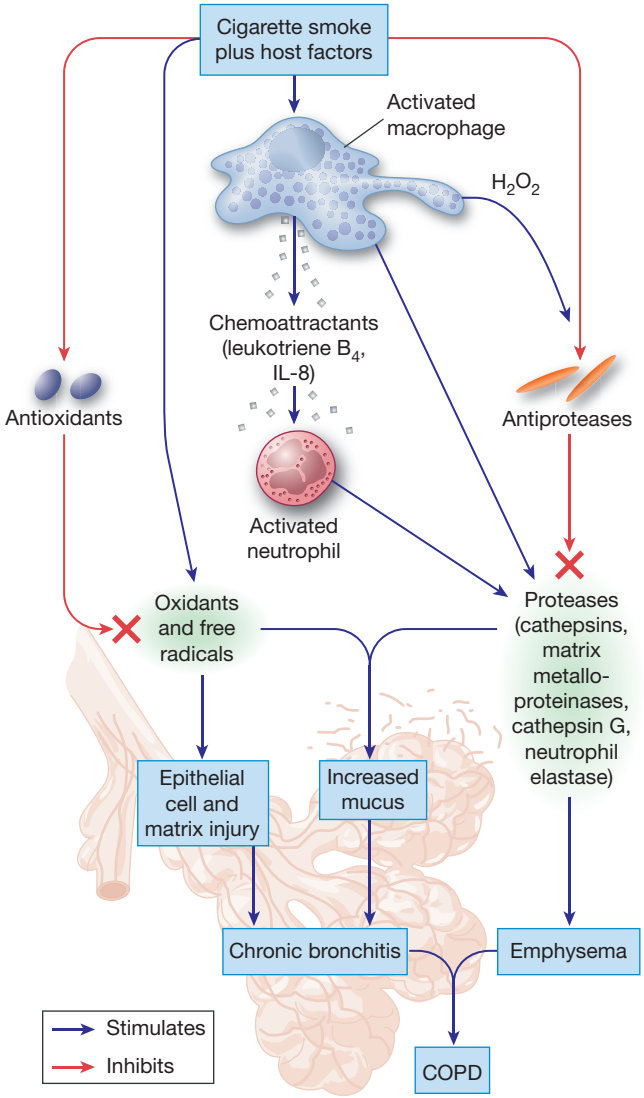


FIGURE 40-9 The pathogenesis of COPD from smoking. Smoking stimulates resident cells to release factors that recruit inflammatory cells to the lungs. The various inflammatory cells that accumulate in the peripheral tissues of the lungs release proteinases and oxidants that damage or degrade extracellular matrix in the walls of alveoli, alveolar ducts, and respiratory bronchioles. In addition, agents in smoke and those released by inflammatory cells inactivate proteinase inhibitors such as α1-antitrypsin, and cause senescence and apoptosis of lung cells that produce extracellular matrix. Products of the damaged extracellular matrix, such as peptides of degraded elastin, are chemotactic for inflammatory cells; thus degradation of the extracellular matrix may lead to a feedback loop that perpetuates inflammation. These matrix-derived products may also elicit immune responses that lead to destruction of extracellular matrix. Not shown are the role of mechanical forces that may also promote deformation of lung tissue. *(Reproduced with permission from Senior RM, Silverman EK. Chronic obstructive pulmonary disease. In: Nabel EG, ed. ACP Medicine: Pulmonary, Hamilton, Ontario. Canada: Decker Publishing; 2011.)*

macrophages, and sometimes eosinophils, but also dendritic cells and lymphocytes (see Acquired Immune Responses). Once the inflammatory process is initiated by smoking the process may persist long after smoking has stopped.[117] Systemic neutrophil counts generally decrease within weeks but activated alveolar macrophages may be present even years after smoking cessation.[117–119]

Unlike nonsmokers, macrophage accumulations are found specifically in respiratory bronchioles, even in young smokers, and BALF from smokers contains many fold increases in macrophages compared to the numbers in BALF from nonsmokers.[120,121] Besides releasing proteinases that might degrade the extracellular matrix of the lung,[122] alveolar macrophages in COPD make chemotactic factors that recruit other inflammatory cells to the lungs. Likewise, structural cells of the lungs in COPD produce proteinases and chemotactic factors for inflammatory cells.[123,124] Expression of interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1), for example, are upregulated in bronchiolar epithelium in COPD.[125,126] Peptides of elastin are chemotactic for inflammatory cells and may act as epitopes for T-cell responses.[127–129] In mice, genetically induced overexpression of cytokines, such as IL-13 or γ-interferon by lung cells leads to emphysema via a robust innate immune response, with inflammatory cell proteinases being integral in emphysema pathogenesis.[130–132]

Acquired Immune Responses

Cellular and humoral immunity may also be involved in emphysema pathogenesis or the continued progression after smoking cessation. CD4+ and CD8+ T cells and B cells accumulate in alveolar and airway tissue in COPD and form bronchus-associated lymphoid tissue (BALT) in the walls of small airways.[100] The increasing BALT presence in small airways correlates with severity of GOLD stage.[100] In mice, exposure to antibodies directed at endothelial cells alone elicits alveolar septal cell destruction and emphysema.[133] Speculation about antigens for immunologically driven emphysema in patients include microbial pathogens, peptides altered by tobacco smoke, and peptides released from lung extracellular matrix.[128,129,134] Difficulties in distinguishing cellular and humoral responses to microbial colonization of advanced airway disease in COPD from pathologic self-directed immune responses will require further study,[135] but more targeted immunosuppresion in treating advanced COPD has not yet shown benefit.[136,137] Intrinsic in this issue is the accelerated emphysema in smokers with HIV, but that may be complicated by direct virus infection inducing macrophage alterations, rather than suppression of acquired immune responses.[55,56]

■ PROTEINASE–ANTIPROTEINASE IMBALANCE

The discovery in the 1960s of α_1-AT deficiency associated early-onset emphysema and the production of emphysema in experimental animal models with elastolytic enzymes have promoted the imbalance of proteinases relative to their inhibitors as a key factor in emphysema development.[138,139] Although additional mechanisms, like apoptosis and oxidant stress, have been uncovered in recent years, the importance of proteinase excess continues to prevail as an important mechanism in emphysema development.

Proteinases of several biochemical classes, and different specific inhibitors, are implicated in the pathogenesis of emphysema. Serine proteinases, especially neutrophil elastase, and several matrix metalloproteinases, have been the proteinases for which there are the most data.[140–143] It is notable that both neutrophils, which are the source of neutrophil elastase and MMP-12 from alveolar macrophages are largely related to continued smoking. Progression after smoking cessation may follow different pathways. As discussed in the genetics section many of these genes have been implicated in candidate gene studies but not genome-wide association studies (Tables 40-4 and 40-5).[144–146] Although neutrophil elastase and its main inhibitor α_1-AT have predominated the proteinase–antiproteinase imbalance hypothesis, MMPs appear prominent in mouse models and in samples from smokers and individuals with COPD. It is likely a combination of many local imbalances involving different proteinases and antiproteinases contribute to the progressive lung destruction.

TABLE 40-5 Proteinases That May Affect the Lung Parenchyma

Proteinase	Cell of Origin
Neutrophil elastase	Neutrophil (monocyte)
Proteinase 3	Neutrophil (monocyte)
Cathepsin G	Neutrophil (monocyte, mast cell)
MMP-1[a]	Macrophage, epithelial cell
MMP-9 (Gelatinase B)	Macrophage, neutrophil, eosinophil, fibroblast, epithelial cell
MMP-12 (Macrophage elastase)	Macrophage
Cathepsin L	Macrophage
Cathepsin S	Macrophage

Note: Parentheses denote minor cellular sources.
[a]Lacks elastase activity.

Several aspects of proteinases in COPD should be noted, as a straightforward destructive mechanism only is likely an oversimplification. In addition to destruction of lung elastin and other matrix components, proteinases process cytokines and surface receptors involved in the inflammatory and immune responses.[147–151] Inflammatory cells may not be the exclusive sources of the proteinases as structural cells also produce matrix-degrading proteinases.[152] Even the apparently simple emphysema model of placing elastases in the lungs of experimental animals results in complex responses that can be altered by nonproteinase-related mechanisms including stem cell and immunologic responses.[153,154] It must also be emphasized that little is known about proteinases in the pathogenesis of the small airway pathology of COPD. Virtually all of the information about proteinases in COPD pertains to emphysema pathogenesis despite clear evidence of small airway obliteration in advanced disease.

OXIDANT–ANTIOXIDANT IMBALANCE

Reactive oxygen species in cigarette smoke or released by inflammatory cells and structural cells of the lungs in response to smoke may lead to lung injury (see Chapter 41). Up to 20 mg of tar may be deposited in a smoker's lung per cigarette smoked. This tar contains more than 10^{17} stable, long-lived radicals per gram. The gas phase of tobacco smoke contains 10^{15} organic radicals per puff of smoke, although in general these small oxygen- and carbon-centered species are more short-lived and reactive than the radicals in the particulate phase. In addition, tobacco smoke appears to "prime" neutrophils and alveolar macrophages to generate elevated amounts of reactive oxygen species, such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. The lung tissue of smokers contains significantly more iron than that of nonsmokers,[155] providing a catalyst for the production of hydroxyl radicals from H_2O_2. This is of interest given the finding of an iron-binding protein polymorphism in the genome wide association studies of smokers with COPD, IREB2 (Table 40-4). Smokers also demonstrate increased production of neutrophil myeloperoxidase,[106,112] which is capable of yielding oxidized halogens such as hypochlorous acid (HOCl). Oxidants modify and inactivate proteins, such as protease inhibitors (α_1-AT and secretory leukoprotease inhibitor), and histone deacetylase 2 (HDAC2), which is involved in glucocorticoid mediated anti-inflammatory responses. Oxidants can affect lipids, DNA, and some specific end products, such as 4-hydroxy-2-nonenal (4-HNE) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), may be markers of COPD.[156,157]

Oxidants can promote inflammation and proteinase expression, facilitate proteinase-mediated extracellular matrix degradation by enhancing matrix molecule susceptibility to proteolytic cleavage, and participate in nonenzymatic degradation of matrix molecules like type I collagen. In experimental animals the combination of cigarette smoke and elastase leads to greater emphysema than either insult alone, suggesting that these insults do not elicit identical responses.[158] Animal models of antioxidant deficiency result in increased susceptibility to both cigarette smoke and direct elastase-induced disease.[159–161]

APOPTOSIS AND SENESCENCE

Emphysematous human lung specimens demonstrate increased apoptotic and senescent cells compared to healthy lung specimens.[162,163] An early theory of emphysema development was that alveolar vascular destruction preceded loss of alveolar tissue. Consistent with this early theory, the blockade of vascular endothelial growth factor (VEGF) signaling in alveolar endothelial cells or genetic downregulation of VEGF production in alveolar epithelium produces apoptosis and noninflammatory emphysema in rodents.[164] In vitro, cigarette smoke induces apoptosis of several lung cell types.[157,165,166] An important feature of experimental models of emphysema due to apoptosis is that there is minimal inflammation.[167] Of interest, the BICD1 gene polymorphism linked to emphysema (Table 40-4) encodes for a protein in the apoptosis pathway.[79] In contrast to the expanding body of information linking emphysema to apoptosis, there is only scant information about apoptosis of the cells of small airways in COPD.[168] Much remains to be learned about apoptosis in the context of COPD airway disease.

Senescence of lung cells as a cause of emphysema stems from the knowledge of alveolar loss with aging and animal models[169,170] where accelerated aging results in emphysematous changes. Lung fibroblasts isolated from human lungs with COPD demonstrate increased markers of senescence and senescent fibroblasts do not maintain the extracellular matrix.[171] However, much of the information regarding telomeres in human COPD relates to inflammatory cell telomere shortening, with telomere length being a biomarker of chronic lifelong inflammatory excess present in individuals with COPD.[172] Whether lung epithelial cells are driven to an injury-related replicative senescence is unknown, but human diseases of telomere deficiency and excess alveolar epithelial apoptosis tend to result in pulmonary fibrosis and not COPD.[173,174]

MUCUS HYPERSECRETION

Airway mucus is a normal protective barrier that is constantly replenished and cleared in health (see Chapter 6). Mucin glycoproteins, the main components of mucus, have a core protein rich in serine and threonine, to which carbohydrates and cysteine residues are attached. Mucus is secreted from submucosal glands and airway goblet cells. In COPD there is hyperplasia of goblet cells and hypertrophy of glands with an increase in the ratio of glandular mucus cells to serous cells. The changes in COPD are associated with an alteration of the mucus proteins (MUCs) to favor a predominance of MUC5B over the typical MUC5AC form, and an increase in the MUC2 form, which is uncommon in normal lung mucus.[175,176] Other alterations in the mucus layer in COPD include greater acidity, less mucin glycosylation, and decreased antimicrobial peptides. Mediators responsible for mucus hypersecretion include proteinases, cytokines, oxidants, and epidermal growth factor receptor (EGFR) ligands.[177,178] The negative charge of mucus glycoproteins results in sequestration of proteases, volatile hydrocarbons and possibly preservation of the hydration of the ciliated layer, resulting in protection of the underlying lung and likely improved carcinogen clearance. However, the symptoms of mucus hypersecretion are common complaints in individuals with COPD; quantity and location of mucus may be particularly important in symptomantic COPD.

Determining the relationship between chronic cough and sputum in patients with COPD and the natural history of COPD

has been elusive.[179] Reports vary from finding weak to strong correlations between cough and sputum production and COPD progression, COPD exacerbations, and mortality.[180–182] A relationship between chronic mucus hypersecretion in small airways and adverse outcomes is plausible as histological analysis of small airway pathology in COPD demonstrated that the extent of small airway luminal obstruction by mucus correlated with the GOLD stage and was inversely correlated with survival after lung volume reduction surgery.[104] Whether the mucus glycoproteins are a beneficial factor that mark the degree of inflammation (e.g., a biomarker of inflammation) or are themselves a pathologic factor in the severity of symptoms or progression of disease is an important question, as treatment of mucus hypersecretion without adequate suppression of the inciting inflammation may result in undesired consequences.[182,183]

PATHOGENESIS OF EMPHYSEMA

GENERAL CONCEPTS

Emphysema is defined as "a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis."[184] However, studies since this definition was enunciated indicate increased collagen per unit volume of airspace wall in emphysematous tissue[185] and active expression of elastin production (Fig. 40-10).[186] Thus, emphysematous lung tissue should be viewed as actively undergoing remodeling rather than as inert. Further indications of activity in emphysematous lung tissue include the presence of many inflammatory cells[103] and cellular changes of apoptosis and senescence.[187]

Degradation of lung elastin by elastase activity from inflammatory cells is probably the predominant mechanism for emphysema in most smokers. However, the biology of emphysema is clearly complex and still incompletely understood. It includes inflammatory cell recruitment, proteinase–antiproteinase imbalance, oxidant–antioxidant imbalance, and responses of lung cells to proteinases and oxidants from inflammatory cells and to constituents of tobacco smoke. It may also involve humoral and cellular immunity. Degradation of extracellular matrix components besides elastin, particularly collagens, may be an important feature. In some situations, apoptosis of lung cells may precede degradation of extracellular matrix. Senescence of lung cells, a recently identified phenomenon in emphysema, has unclear implications, but suggests that lung repair mechanisms are depressed.

According to the proteinase–antiproteinase hypothesis, there is a constant or episodic release of proteinases, active at neutral pH, into the lung parenchyma. These proteinases come principally from inflammatory cells (Table 40-5). Under normal conditions circulating proteinase inhibitors, especially α_1-AT, and inhibitors produced locally in the lungs, permeate lung tissue and prevent these proteinases from digesting the structural proteins of the lungs (Table 40-6). Emphysema results when the balance between proteinases and

TABLE 40-6 Proteinase Inhibitors in the Lung

Inhibitor	Cell of Origin	Class of Proteinases Inhibited
α1-antitrypsin	Hepatocyte (mononuclear phagocyte)	Serine[a]
α2-macroglobulin	Hepatocyte, lung fibroblast (macrophage)	Serine, MMP[b], Cysteine
TIMPs (1,2,3,4)[c]	Resident lung cell	MMP
SLPI[d]	Resident lung cell (macrophage)	Serine[e]
Elafin	Large-airway epithelial cell	Serine
Cystatin C	Bronchial epithelial cell (macrophage)	Cysteine

Note: Parentheses denote minor cellular sources.
[a]*α1-antitrypsin has its greatest affinity for neutrophil elastase.*
[b]*Matrix metalloproteinase.*
[c]*Tissue inhibitors of metalloproteinases.*
[d]*Secretory leukocyte protease inhibitor.*
[e]*SLPI does not inhibit proteinase 3 (PR3).*

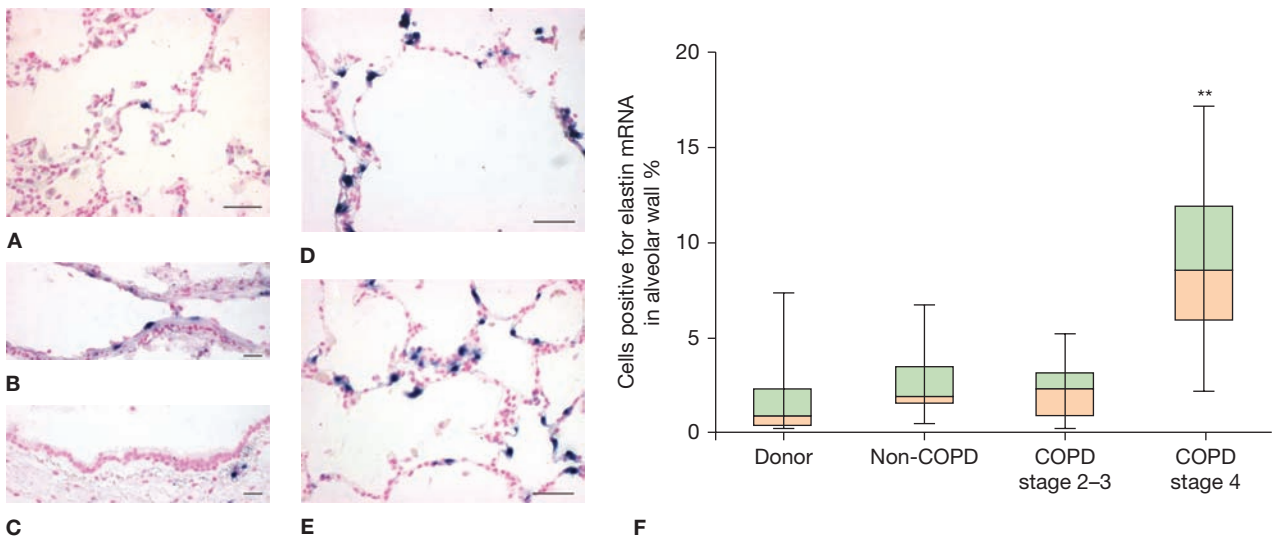


Figure 40-10 Active expression of elastin production in severely emphysematous lung removed for lung transplantation. Elastin mRNA *(blue signal)* as detected by in situ hybridization is rarely detected in donor lungs in (**A**) parenchyma, (**B**) intralobal pulmonary arteries or (**C**) airways, but is prevalent in parenchyma of GOLD 4 COPD lungs in regions with moderate (**D**) and severe (**E**) alveolar enlargement. Quantification of cells positive for elastin mRNA (**F**) reveals significantly higher elastin expression in alveolar walls of GOLD 4 COPD lungs compared to donor lungs or less severe COPD lungs. *(Reproduced with permission Deslee G, Woods JC, Moore CM, et al. Elastin expression in very severe human COPD. Eur Respir J. 2009;34(2):324–331.)*

antiproteinases in lung tissue tilts in favor of proteinases due to increased proteinase release into the tissue and/or a reduction in the antiproteinase content in the tissue. The proteolytic events leading to emphysema occur in microenvironments adjacent to lung cells; proteinase–antiproteinase balance may not be reflected in measurements of large samples of emphysematous lung tissue.

An important addition to ideas about proteinases and destruction of lung extracellular matrix has come from studies linking mechanical stresses on lung tissue and proteolytic events. Proteolytic damage resulting in local loss of structural integrity of lung tissue increases tissue susceptibility to proteinases.[187] As some fibers are lost, the load on remaining fibers increases, propagating mechanical failure analogous to mechanical failure of a partially cut rope under strain.[188] Biochemically, when lung tissue is overstretched new binding sites for proteases are exposed, increasing the rate of proteolysis.[189] Accordingly, a vicious cycle linking proteinases and tissue destruction may exist.

LUNG ELASTIC FIBERS

Because α_1-AT inhibits neutrophil elastase and papain is a potent elastase, the original observations linking proteinases to emphysema led to the concept that destruction of alveolar elastic fibers is key to emphysema development.[139] Indeed the proteinase–antiproteinase hypothesis of emphysema pathogenesis was originally the "elastase–antielastase hypothesis."

Structurally, the extracellular matrix of the lung is organized into three interdependent cable systems: (1) an axial system that extends from the central airways through the peripheral airways to the alveolar ducts; (2) a parenchymal system that comprises the matrix of the alveolar septae; and (3) a peripheral system that arises from the visceral pleura and extends into the interlobular septae, forming a fibrous sac around the lung. Distal to the respiratory bronchioles, the axial system forms a helix encircling the alveolar ducts, extending into the interstitium of alveolar walls. Elastic fibers, of which elastin is the main component, loop around alveolar ducts, form rings at the mouths of the alveoli, and penetrate as wisps into the alveolar septae, where they are concentrated at bends and junctions (Fig. 40-11). Elastic fibers, which possess rubberlike reversible extensibility, come under tension and provide elastic recoil throughout the respiratory cycle. Unlike elastic fibers, the interstitial collagen fibers in alveolar septa are nondistensible and have high tensile strength. They can be thought of as relaxed ropes that straighten during inspiration and become taut at total lung capacity.

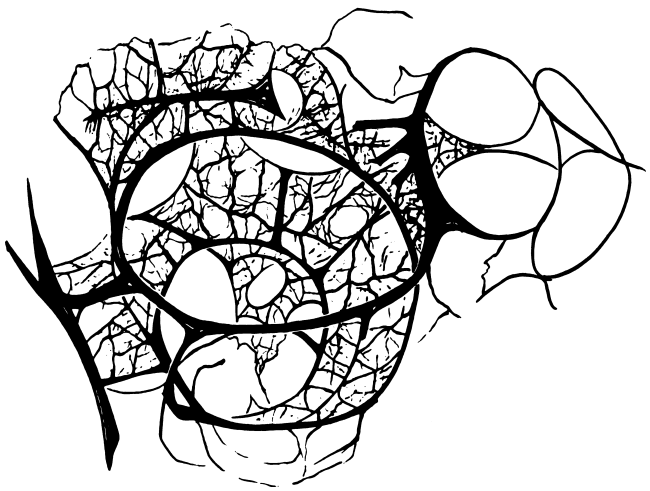


Figure 40-11 Alveolar elastic fiber network. Artist's sketch of the elastic fibers in the parenchyma of human lung showing how elastic fibers form a helix encircling the alveolar ducts and penetrate into alveolar septae. *(Reproduced with permission from Pierce JA, Ebert RV. Fibrous network of the lung and its change with age. Thorax. 1965;20(5):469–476.)*

Elastin is resistant to many proteinases, most notably the collagenases that cleave interstitial collagens. However, there are a number of enzymes that may come into contact with the lung that can degrade elastin (Table 40-5). Elastic fibers in the lung normally last a full human life span.[190] Histological studies of emphysematous lung tissue support the hypothesis that elastic fibers are perturbed in emphysema. There are fragmented elastic fibers in α_1-AT deficiency and poorly formed elastic fibers and clumps of elastin in smokers with centriacinar emphysema.[191] The latter changes appear to be from aberrant synthesis of new elastin and resemble the findings in the lungs in emphysema induced experimentally with elastase.

Animal models employing elastase-induced emphysema have shown acute depletion of elastin following an intratracheal injection of human neutrophil elastase, followed by a burst of synthesis of extracellular matrix including elastin.[192] Over a few weeks, the elastin content of the lungs returns to normal, although the lungs still display emphysema. The elastic fibers, like the elastic fibers in human emphysema, appear disorganized. New elastin gene expression occurs even in severe emphysema in humans (Fig. 40-10). However, there are significant barriers to effective repair of damaged elastic fibers in the mature lung. When elastic fibers are damaged enough to fail under load, there is no mechanism for cells to recreate a structure with a length many times the size of each cell. The injured adult lung lacks the mechanical and morphogen gradients that initiate alveolar formation during development, and may also be unable to coordinate the expression of the many components necessary for functional elastic fiber synthesis.

LUNG COLLAGEN TURNOVER

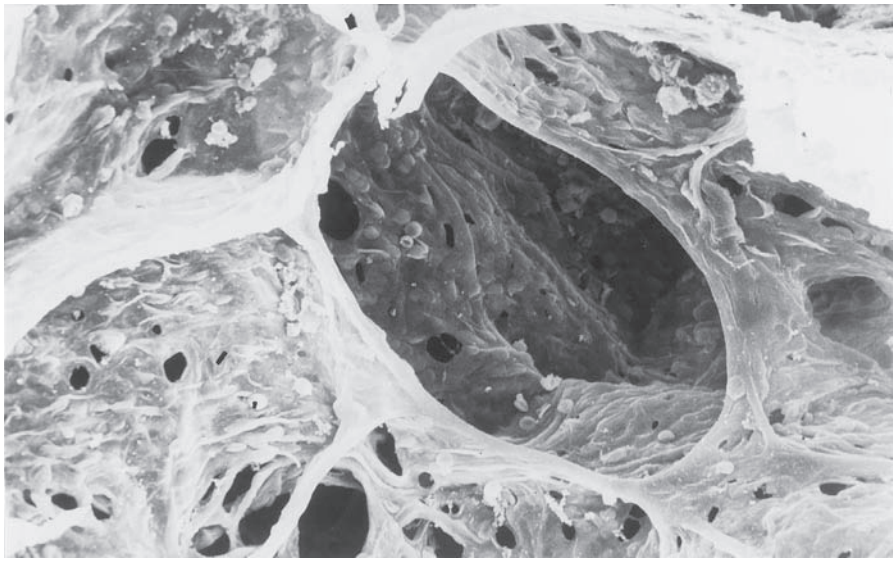
Although elastic fiber destruction dominates thinking about the proteolytic basis for the pathogenesis of emphysema, degradation of alveolar wall collagen and aberrant collagen deposition in alveolar tissue may also be involved. Indeed, in some forms of experimental emphysema collagen destruction appears to be the critical event. Mice genetically engineered to harbor a transgene that leads to expression of human MMP-1 (collagenase) in lung tissue develop structural changes typical of emphysema.[140] and these changes are due to destruction of alveolar type III collagen.[193] In these models, emphysema occurs without obvious disruption and faulty resynthesis of elastic fibers as the elastic fibers in these lungs look normal. Expression of MMP-1 by alveolar epithelial cells in human emphysematous tissue fits with the idea that collagenolytic activity plays a role in emphysema.[152]

Analogous to elastin peptides promoting emphysema in mice exposed to cigarette smoke (128), a peptide derived from collagen, proline–glycine–proline (PGP), is a neutrophil chemoattractant, associated with COPD and experimental emphysema.[194] PGP is generated by the sequential breakdown of collagen by MMPs 8 and 9 and prolyl endopopetidase.[195] Blocking PGP reduces emphysema in mice exposed to cigarette smoke.[196]

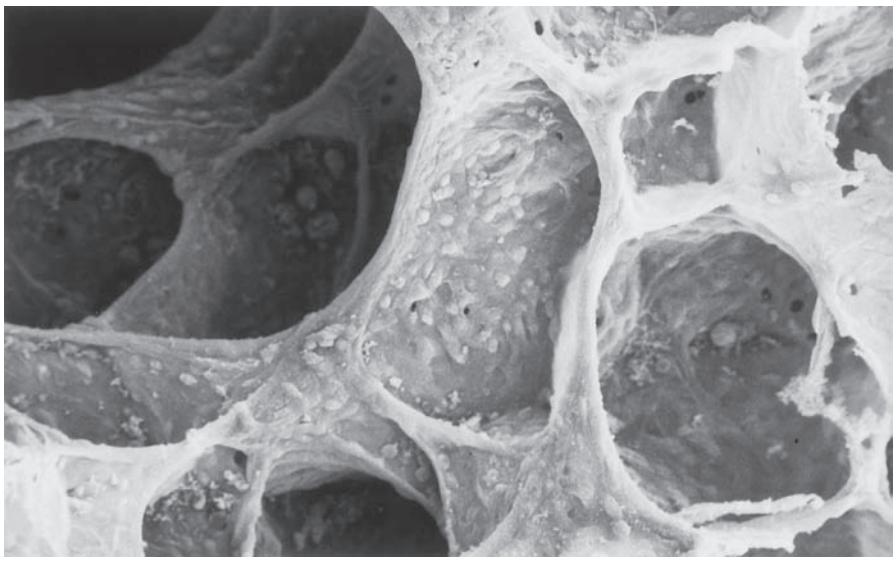
In emphysematous lungs the pores of Kohn are larger and more numerous than in normal lungs (Fig. 40-12). Because interstitial collagens and basement membrane collagens are prominent in alveolar walls, it is plausible that collagenous structures undergo degradation in the process of generating of these interalveolar pores.

ALPHA 1-ANTITRYPSIN DEFICIENCY

In 1963 Laurell and Erikson described α_1-AT deficiency and its association with COPD.[197] Ever since then, α_1-AT deficiency has played an important role in the clinical and basic science aspects of COPD.[198]



A



B

Figure 40-12 Holes in alveolar walls in early emphysema. Scanning electron micrographs of alveolar walls from surgically resected specimens: lung with mild emphysema (**A**) and nonemphysematous lung (**B**). Holes are more numerous in alveolar walls in the emphysematous lung than in the normal lung. Original magnification ×250. *(Reproduced with permission from Nagai A, Inano H, Matsuba K, et al. Scanning electron microscopic morphometry of emphysema in humans. Am J Respir Crit Care Med. 1994;150 (5 Pt 1):1411–1415.)*

■ BACKGROUND

Human plasma contains at least six proteins that function as proteinase inhibitors. Together, they make up about 10% of the total plasma protein. At a concentration of 100 to 273 mg/dL (~18–50 μmol/L) in adults with a normal phenotype, Pi MM,[199] α_1-AT has the highest concentration of all of the plasma proteinase inhibitors. α_1-AT is a member of a family of serine proteinase inhibitors called serpins (SERPINA1).

α_1-AT is a glycoprotein of 52 kDa synthesized primarily by hepatocytes. Mononuclear phagocytes and bronchial epithelial cells are other less abundant cellular sources. α_1-AT consists of a single polypeptide chain of 394 amino acids. Carbohydrate side chains account for 12% of the α_1-AT molecular mass. The 12.2-kb gene, *SERPINA1*, that encodes α_1-AT is on the proteinase inhibitor (PI) locus on chromosome 14. The α_1-AT gene has seven exons and six introns. Exons four through seven code for the mature protein. The first two exons and a segment of the third exon are encoded in the transcript expressed in macrophages, but not in hepatocytes. α_1-AT is an acute-phase reactant. Plasma levels rise with trauma, estrogen therapy, use of birth-control pills, and during pregnancy, however the levels do not rise to normal among individuals with severe deficiency.

Inhibition of neutrophil elastase and other serine proteinases by α_1-AT involves cleavage by the proteinase of the reactive site of α_1-AT between methionine[358] and serine[359] and formation of an enzyme-inhibitor complex that renders the proteinase inactive. Because the complex is quite stable, inactivation is essentially permanent. α_1-AT has a higher affinity for neutrophil elastase than trypsin or other serine proteinases. It is notable that oxidation of the critical methionine residue results in a 2000-fold reduction in the rate of association with neutrophil elastase.[200] The capacity of α_1-AT to inhibit serine proteinases besides trypsin has led some authors to call the protein α_1-PI or α_1-antiproteinase, but the name α_1-AT has become a fixture.

Apart from inhibition of serine proteinases, α_1-AT has numerous other activities. These include promoting immune tolerance, reducing production of proinflammmatory cytokines, and protecting various cell types from cell death through inhibition of caspases.[201–207]

From the genetic standpoint, α_1-AT disease is an autosomal recessive disorder, which means that one mutated α_1-AT allele from each parent must be transmitted to the affected offspring. Thus, for example, on average if MZ parents have four children, there will be two that are MZ and one each will be MM and ZZ. More than 120 different α_1-AT alleles are known,[208] most of which are single nucleotide polymorphisms (SNPs) that do not alter expression of the protein or

its function and so have no clinical significance. Letters are used to specify the allelic variants. The original letters were chosen to reflect electrophoretic mobility: F = fast, M = medium, S = slow, and Z = ultraslow. Homozygosity for the M allele, Pi MM, is present in about 95% of adults in the United States. Homozygosity for the Z allele, Pi ZZ, is associated with severe deficiency of α_1-AT (<15% of normal) and accounts for virtually all of the individuals with severe α_1-AT deficiency. In the United States, the prevalence of the Pi ZZ phenotype is about 1 in 3000 people; worldwide, it is estimated that there are 3.4 million persons with severe α_1-AT deficiency, mainly Pi ZZ.[209]

Heterozygosity of the M allele with an S or Z allele is very common. In the United States, 3% to 8% of the adult population are Pi MS heterozygotes and 2% to 4% are Pi MZ heterozygotes. Pi MS and Pi MZ individuals have mean blood α_1-AT levels 75% and 57% of normal, respectively. Pi MS heterozygosity does not carry an increased risk of COPD.[210] The relationship of Pi MZ heterozygosity to the risk of COPD has been controversial, but recent studies indicate that Pi MZ individuals have slightly impaired air flow, measured as FEV_1/FVC or FEV_1/VC ratios, and slightly more emphysema on CT scans than matched Pi MM individuals.[211]

The abnormality in the Z α_1-AT protein is a point mutation in a single nucleotide at codon 342 that results in coding for lysine instead of glutamic acid. This amino acid substitution changes the charge attraction between the amino acids normally present in positions 342 and 290 in α_1-AT and prevents the formation of a fold in the molecule. With this change in tertiary structure, the molecule is susceptible to dimerization with another α_1-AT molecule that can result in polymerization of α_1-AT in the endoplasmic reticulum. Polymerization impedes secretion of the protein from hepatocytes and explains the low levels of α_1-AT in plasma and other body fluids. In contrast to the Z variant, the S variant of α_1-AT, which involves a single nucleotide substitution of glutamic acid[264] with valine, polymerizes more slowly than the Z protein and does not accumulate in the liver.

Polymers of Z type α_1-AT are chemotactic and recruit neutrophils to the lungs.[212,213] Oxidation of α_1-AT, as occurs with exposure to cigarette smoke, promotes polymerization of Z type α_1-AT.[214] Together, these findings suggest a pathway for the increased risk of COPD in Pi ZZ smokers. An unfolded protein response (UPR) in monocytes and other cell types may be another pathway for increasing the risk of COPD associated with Pi ZZ. According to this paradigm, activation of a UPR occurs in cells that make ZZ α_1-AT which leads to an inflammatory phenotype of increased cytokine production and activation of the NF-kB pathway.[215] Thus, in both of these pathways, a key feature is increased inflammation, which leads to increased proteinase and oxidant stress burdens in tissues. Moreover, compared to M α_1-AT, Z type α_1-AT has a slower rate of association with neutrophil elastase than does M α_1-AT.[216] The net result is that the α_1-AT produced by Pi ZZ individuals is less effective than M protein.

Quantification of serum α_1-AT is done routinely by immunoassay. To confirm an immunoassay showing severe deficiency, specialized laboratories use isoelectric focusing to phenotype α_1-AT (Fig. 40-13). To definitively identify α_1-AT genotypes, analysis is performed with molecular probes.[217]

CLINICAL ASPECTS

Severe α_1-AT deficiency may present in adults as chronic respiratory symptoms (COPD, unremitting asthma, and bronchiectasis), liver disease, (chronic virus–negative hepatitis, cirrhosis, and hepatoma) or skin disease (panniculitis).[198] In practice, however, about 80% of patients are discovered because of respiratory symptoms and most of the rest are detected by screening for α_1-AT deficiency prompted by finding the deficiency in a family member with lung disease. In middle-aged and older individuals with chronic respiratory symptoms, the disease is often not diagnosed for more than 5 years after the onset of the symptoms.[218]

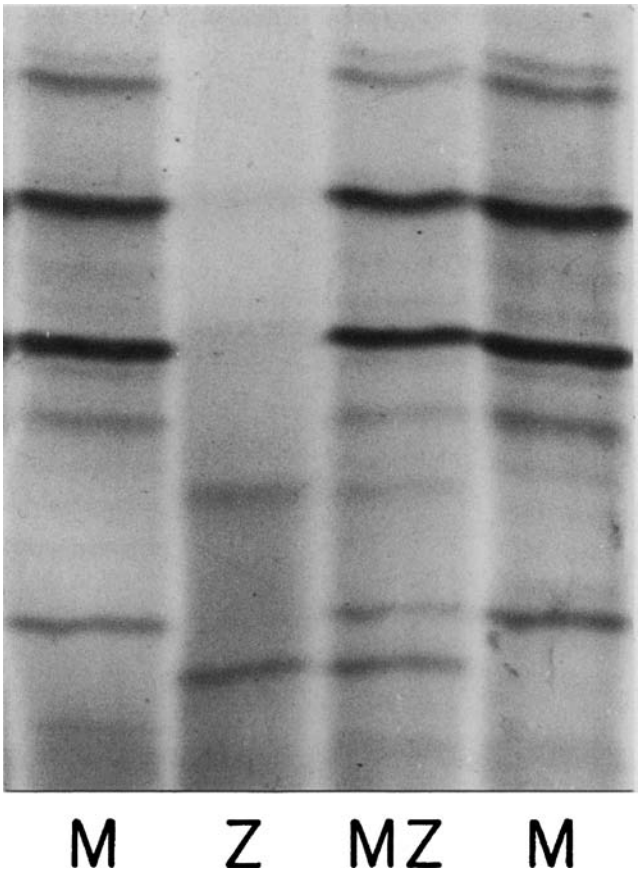


Figure 40-13 Patterns of Pi M, Pi Z, and Pi MZ α_1-AT on isoelectric focus. By this analysis, α_1-AT has microheterogeneity and thus appears as multiple bands. Pi M and Pi Z have distinctly different band patterns, while Pi MZ has a pattern that combines the patterns of both Pi M and Pi Z. *(Used with permission of John A. Pierce, MD.)*

Lung Disease

The classic patient with Pi Z α_1-AT deficiency presents with the typical symptoms of COPD, but is younger than usual, often around age 40. The patient has an increased total lung capacity, a decreased D_{LCO} and radiographic studies show hyperlucent lower lung fields reflecting the predominance of emphysema in those regions (Fig. 40-14). This classic patient reports a mild smoking history relative to the severity of COPD and a family history of chronic respiratory symptoms in parents, siblings, and other close relatives.

In fact, however, there are many exceptions to this classic clinical picture of Pi Z α_1-AT deficiency. Wheezing, cough and sputum mimicking asthma, or chronic bronchitis, that are poorly responsive to standard therapy may be the predominant symptoms. Radiographic emphysema may be modest relative to the severity of the airflow obstruction and may have upper lobe predominance of emphysema,[219] and no other family members may have chronic respiratory symptoms, including siblings who are discovered to have the same level of deficiency as the patient. Discovery of SNPs in genes associated with COPD indicate that modifier genes may account for the differences in COPD occurrence between individuals who share the PiZ phenotype.[220] Because the pulmonary presentation of α_1-AT deficiency often deviates from the classic presentation, experts in this field have advised that everyone diagnosed with COPD be screened for α_1-AT deficiency and that screening be extended to people with certain other conditions (Table 40-7).[221]

About 10,000 individuals in the United States are recognized to have severe α_1-AT deficiency, but estimates from gene frequency

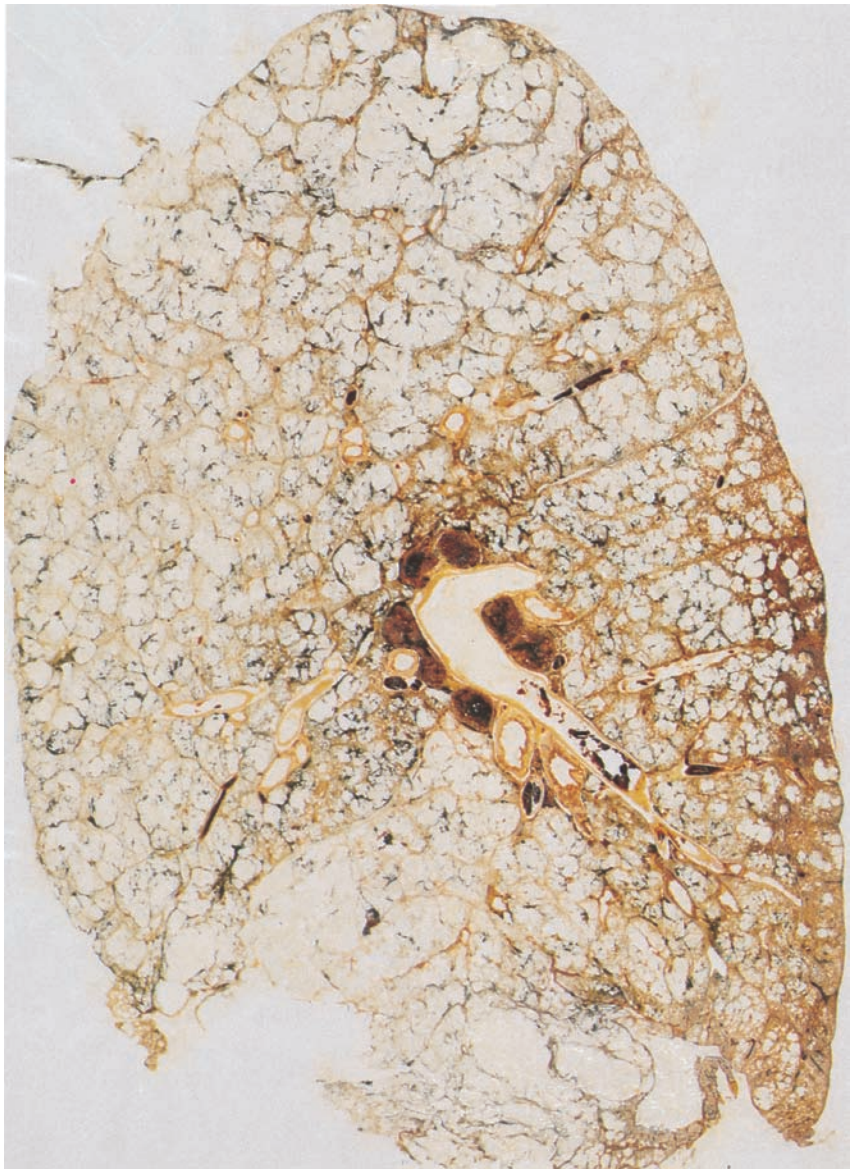


Figure 40-14 Lung pathology of Pi Z-type α_1-AT deficiency. Panacinar emphysema that is worst in the lung base. Paper-mounted whole lung section.

TABLE 40-7 Clinical Situations for Assessment of α_1-AT Status

Early-onset COPD (age of 45 yr or less)
Early-onset emphysema (age 45 yr or less)
Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
Emphysema with prominent basilar hyperlucency
Asthma with airflow obstruction that is incompletely reversed after aggressive treatment
Bronchiectasis without evident etiology
Otherwise unexplained liver disease
Necrotizing panniculitis
Antiproteinase 3-positive vasculitis (C-ANCA [antineutrophil cytoplasmic antibody] positive vasculitis)
Family history of any of the following: emphysema, bronchiectasis, liver disease, panniculitis

Source: Data from American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society Statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818–900.

calculations suggest a much larger number, at least 100,000. The discrepancy between known and unknown individuals reflects the fact that many severely deficient individuals are clinically well and, as noted above, clinicians commonly do not consider the diagnosis even among symptomatic individuals. Irrespective of the precise number, the point is that unrecognized deficiency is common. In a recent study involving 3457 individuals with moderate or more severe fixed airflow obstruction undergoing routine pulmonary function testing at 19 US medical centers, 0.63% had severe α_1-AT deficiency (ZZ and SZ) and 10.88% were MS or MZ heterozygotes.[222] Extrapolating these figures to the large number of people with COPD countrywide yields a large number of severely deficient people.

Smoking hastens the development of COPD in most people with severe α_1-AT deficiency. The typical Pi Z individual who smokes has respiratory symptoms by age 40. Besides smoking, male gender and a history of asthma are also associated with worse lung function among deficient individuals.[223] Specific occupational exposures may also impart increased risk of disease,[224–226] but studies of nonindex cases and screened individuals confirm that smoking is the predominant risk factor associated with increased mortality.[227]

Although emphysema is the predominant lung pathology associated with Pi Z α_1-AT, bronchiectasis has been reported to be common.[228] However, this finding has not been universal and it

remains unknown whether bronchiectasis is more prevalent in these individuals than among individuals with comparable COPD and a normal α_1-AT phenotype.[229] Among patients with bronchiectasis due to nontuberculous mycobacterial (ATM) pulmonary infections, heterozygous α_1-AT abnormalities are common, but the basis for this association is obscure as most of the affected individuals do not have severe α_1-AT deficiency.[230]

Liver Disease

Pi Z α_1-AT deficiency can present as liver dysfunction in infancy ranging from asymptomatic jaundice to liver failure. In most instances, the clinical manifestations are mild and resolve spontaneously, but α_1-AT deficiency represents one of the main indications for liver transplantation in children. In adults, liver abnormalities may be limited to tests of liver function. However, among Pi Z individuals who live beyond age 60, liver abnormalities are common and may overshadow respiratory symptoms. Indeed, among those individuals who have not smoked and for other unexplained reasons have avoided significant pulmonary function deterioration, hepatic cirrhosis and associated complications is the predominant terminal illness. In such individuals there is also a high incidence of hepatic cell carcinoma.[231]

THERAPY

Therapy for COPD associated with α_1-AT deficiency includes the standard measures for COPD—cessation of smoking, inhaled bronchodilators and inhaled corticosteroids, pulmonary rehabilitation, pneumococcal and influenza vaccinations, and supplemental oxygen (see Chapter 42). Lung volume reduction surgery has not proven as successful as in individuals with normal α_1-AT.[232] Because progression of disease tends to be slow, qualifying for lung transplantation seldom has urgency.

Up to the present time, the only specific treatment has been the so-called augmentation therapy that consists of weekly intravenous administration of α_1-AT isolated from pooled plasma obtained from healthy individuals, of which several preparations are commercially available. This therapy should be limited to individuals with severe α_1-AT deficiency; for lack of need and expense it is not recommended for MZ heterozygotes.[233] The effectiveness of augmentation therapy has been most evident in individuals with reductions in FEV1 of 30% to 65% predicted.[221] Delivery of α_1-AT by inhalation may improve the convenience of augmentation in the future. Safe and effective genetic approaches to achieve permanent correction of α_1-AT deficiency have not yet been developed, despite efforts with α_1-AT–carrying vectors and transplantation with stem cell–derived hepatocytes that carry normal genes.[234–237]

From the standpoint of liver disease, α_1-AT antitrypsin deficiency is a paradoxical situation in that there is a severe systemic deficiency of α_1-AT despite substantial production of α_1-AT by the liver. The distinction between what is happening in the liver and what is happening systemically is clinically important. Infusions of α_1-AT, or other techniques under investigation for boosting systemic α_1-AT levels, can compensate for severe systemic α_1-AT deficiency and so help protect the lung, but these approaches do not correct or ameliorate problems associated with the accumulation of abnormal α_1-AT in liver cells. At present, liver transplantation is the only treatment for the liver defect. Drugs to promote degradation of hepatocyte accumulations of Z antitrypsin, presumably the underlying mechanisms for liver injury,[238,239] or to prevent α_1-AT polymerization in the liver are under investigation.[240]

CONCLUDING COMMENT

Better understanding of COPD is imperative. This potentially disabling and fatal disease is already epidemic in many countries and appears destined to become a worldwide epidemic in coming decades due to indoor air pollution from use of solid fuels and trends of smoking prevalence.

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CHAPTER 41

Cigarette Smoking and Smoking Cessation

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GENERAL BACKGROUND

Native Americans discovered the use of the tobacco plant, *Nicotiana tabacum*, during antiquity. By the time Columbus arrived in America, tobacco use was widespread throughout the Western Hemisphere and was well integrated into Native American cultures. Production of tobacco and its trade represented a major economic activity in the pre-Columbian Americas. Early European explorers learned of the tobacco plant from Native Americans, and by the mid-17th century tobacco was widely used in Europe.

The most important, but not the only, active psychopharmaceutical drug contained in the leaves of the tobacco plant is nicotine.[1,2] Nicotine is a major metabolic product of the tobacco plant, and it is likely that it evolved as a protection against insect predators, as nicotine is a potent insect neurotoxin.[3] Interestingly, nicotine has been exploited in this regard as a commercial insecticide. Nicotine, however, is the major addicting substance in tobacco, although the addiction to tobacco is more complex than addiction to nicotine alone. Other psychoactive compounds are also present in tobacco smoke, including monoamine oxidase inhibitors.[4] These may have either direct effects or interact with other psychoactive drugs.[1,2] In addition, conditioned behavior and social interactions are important drivers of smoking.[5–8]

Nicotine is a potent euphoriant. On a molar basis, nicotine is more active than such euphoria-inducing drugs as cocaine, amphetamine, or morphine.[9] Nicotine elicits complex effects on the central nervous system (CNS), which are discussed in more detail below. Many of these effects, however, are perceived as desirable, accounting for the popularity of smoking. For example, nicotine ameliorates anxiety, reduces perception of pain,[10] mitigates symptoms of depression,[11] and induces a sense of well-being[9] while causing a state of arousal.[12] In contrast to many euphoriants that impair cognition, nicotine can improve task performance and attention time by measurable degrees in nonhabituated individuals and may have beneficial effects on cognition.[12]

Despite its perceived benefits, smoking of tobacco has long been controversial. King James of England wrote in 1604 "[Smoking is] a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible Stygian smoke of the pit that is bottomless.[13]" The Surgeon General's Report of 1964 outlined the convincing evidence for the health consequences of smoking.[14] Since that time there has been a gradual increase in efforts to control tobacco use and the associated health consequences. Changes in social attitude, public health efforts, and both pharmacologic and nonpharmacologic approaches have been developed that have meaningful benefits. The current chapter will focus on treatment designed to help a smoker achieve abstinence.

NICOTINE ADDICTION

Nicotine exerts its biologic effects on "nicotinic" receptors, a subset of cholinergic receptors, whose endogenous ligand is acetylcholine.[15,16] Nicotinic receptors are homo- or heteropentamers that bind two ligand molecules and form an ion channel.[17] In man, 17 genes code for distinct component chains, resulting in a very large number of potential pentamers, although only a relatively few are believed to have a biologic role. In the brain, nine alpha and three beta receptors are expressed. However the major receptors are composed of complexes (alpha4)(beta2), (alpha3)(beta4), and (alpha7). The (alpha4)(beta2) complex incorporates other subunits, particularly (alpha5), (alpha6), or (beta3), and these may modulate the effects of ligands, including nicotine.[17] The $(alpha4)_3(beta2)_2$ receptor is believed to be particularly important in the addicting effects of nicotine. Deleting the (beta2) receptor in mice eliminates behavioral responses to nicotine, while mutations in the gene can result in markedly increased sensitivity to nicotine.[18] The $(alpha7)_5$ receptor, for example, is believed to mediate some of the cognitive effects of nicotine, including sensory gating and learning.[18,19] In contrast the muscarinic receptors, the other major class of cholinergic receptors, are single chain G-protein–coupled receptors. Nicotine has no effect on these receptors.

Nicotinic receptors are ion channels and upon binding of nicotine, permeability of the channel is increased.[15–18] For example, binding of nicotine to the $(alpha4)_3(beta2)_2$ allows influx of calcium. This, in turn, modulates release of neurotransmitters. It is likely that the behavioral responses to nicotine result from the actions of many neurotransmitters, but dopamine is believed to be a major mediator of nicotine effects. In this context, dopamine is a key mediator of pleasure and reward and is required for the reinforcing effects that lead to drug self-administration in animal models.[20] As such, dopaminergic signaling is believed to be key in the pathogenesis of many addictions and compulsive behaviors. Nicotine also modulates the release of other neurotransmitters, including glutamate and gamma-amino butyric acid (GABA). Interestingly, chronic administration of nicotine desensitizes neurons that release GABA, which inhibits dopamine release. In contrast, there is no desensitization of glutamate release, which augments dopamine release. Chronic nicotine exposure, therefore, can lead to further augmentation, nicotine-induced dopamine release.[21,22] Moreover, the CNS alterations that occur following nicotine administration can be very long lasting; for example, alterations in nicotine receptor levels in rats exposed in utero persist until adult life.[23] The adolescent brain may be particularly sensitive to long-term alterations induced by nicotine.[24] This may account for the sensitivity of adolescents to addiction. Persistent changes in the brain may also account for the observation that, even after achieving abstinence, a smoker is at risk for relapse and if relapse occurs, the smoker reverts to the previous "steady-state" habit much more rapidly than that habit developed initially.

Nicotine is contained in the leaves of the tobacco plant. Nicotine is a weak base and as a result will be charged in acidic environments. Many forms of tobacco, such as cigars and chewing tobacco, are alkalinized, which results in uncharged nicotine that can be more readily absorbed through the buccal mucosa. Thus, cigar smokers do not have to inhale to achieve desired blood nicotine levels. The process of smoking a cigarette is more complex.[25] Air sucked through the burning end of a cigarette becomes heated. As the hot air passes down the bole of a cigarette, it causes the nicotine in the tobacco to volatilize. As the mixture cools, the nicotine condenses on smoke particles resulting in a nicotine aerosol. Conventional cigarettes have been designed so that the resulting particle size is ideal to reach the alveolar structures of the lung. Uncharged nicotine is lipid soluble and is rapidly absorbed from the alveolar gas into the

pulmonary capillary blood and then into the arterial circulation. Inhaled nicotine, therefore, reaches the brain in about ½ a circulation time or about 15 to 20 seconds. In its neutral form, nicotine readily crosses the blood–brain barrier and exerts its psychoactive effects. A cigarette, therefore, is a very effective means of delivering nicotine to the brain. It also allows a smoker to control the dose of delivered drug with considerable precision.

After absorption, nicotine distributes into various body pools. This results in a marked difference between arterial and venous nicotine levels and a rapid drop in nicotine levels upon completion of a cigarette.[26] Nicotine is then catabolized by several enzymes. The most important of these is CYP2A6 which oxidizes nicotine to cotinine and cotinine to hydroxycotinine.[27] Nicotine can also be oxidized by alternative CYP450 enzymes and may be inactivated and excreted by glucuronidation. Genetic variants in nicotine metabolizing enzymes can influence smoking behavior. In normal metabolizers, nicotine is cleared with a half-life of about 2 hours. As a result, nicotine levels increase throughout the day for individuals who smoke steadily. The increase in nicotine levels can result in levels believed to fully saturate all nicotinic receptors.[1,2] In this setting, it is likely that smoking behavior is more dependent on conditioned responses than on psychopharmacologic effects of nicotine. Conversely, nicotine levels fall at night. The drop in nicotine levels is thought to initiate the early stages of withdrawal. Importantly, the lower levels allow for nicotinic receptors to be in the unbound state. As a result, the first cigarette in the morning can have a large psychodynamic effect. This is well recognized by smokers who will often report that the "most enjoyable" cigarette is the first one smoked in the morning. In addition, the drop in nicotine levels is thought to initiate the early stages of withdrawal. How long it takes a smoker to smoke the first cigarette of the day, therefore, serves as a gauge of addiction, with short times indicating stronger addiction. Smoking within 30 minutes of awakening is a key question in the Fagerstrom test for nicotine dependence.[28]

Several lines of evidence support genetic influences on smoking behavior.[29–32] Twin studies suggest that genetics accounts for about 50% of the variance in smoking. Interestingly, there appears to be a genetic basis for withdrawal symptoms.[33] A number of genes have been suggested to play a role in both candidate gene and in genome-wide association studies. Although many of the candidate genes have been difficult to reproduce, an extremely strong signal has been consistently observed in a region of chromosome 15 that includes the genes for three nicotinic receptors.[34] Among COPD patients, this region is also associated with intensity of smoking assessed by cigarettes smoked per day, suggesting it may be related to intensity of addiction.[35] As might be expected of a gene related to smoking behavior, this region has also been strongly linked to the risk for several smoking-related diseases.[36–39] Candidate genes include not only genes in the dopamine pathway, but also other neurotransmitter pathways as well as cell adhesion molecules that are thought to contribute to long-term memory and neural adaptation.

Genetic variation in nicotine metabolizing enzymes has received particular attention.[31] Many, but not all studies have demonstrated that individuals with variants in CYP2A6 who metabolize nicotine slowly smoke fewer cigarettes and maintain lower cotinine and carbon monoxide levels consistent with their requiring less total intake.[35,40,41] Consistent with a reduced level of smoking, some studies have shown reduced risk for cancer in slow metabolizers.[42,43] Similarly, better lung function has been reported among individuals with haplotypes associated with slow metabolism compared to those with genes associated with rapid metabolism who smoke the same number of cigarettes.[44]

It is plausible that the slower decline in blood nicotine levels associated with slow nicotine metabolism makes these individuals less likely to experience withdrawal. In addition, the persistence of nicotine may decrease the "reward" of smoking. Both of these effects may contribute to increased likelihood that a slow metabolizer can achieve abstinence from smoking[40] and better quit rates have been observed among slow metabolizers in clinical trials.[31,45] On the other hand, slow metabolizers who are experimenting with smoking may have higher and more sustained nicotine levels. Consistent with this, a prospective study of adolescents observed a threefold risk of becoming a regular smoker among slow metabolizers.[46]

Smoking cigarettes is more complex than nicotine addiction. Conditioned behaviors also play a key role.[1,2] In this context, a smoker typically inhales 10 puffs per cigarette. This would be 300 puffs for a 1½ pack per day smoker or more than 100,000 puffs annually. In addition, smoking frequently occurs in recurrent settings: after eating, when irritated, when bored, when sad, in specific social settings, etc. As such, smoking becomes associated with these settings which serve as operant cues to induce smoking behavior. Nicotine, moreover, has been demonstrated to increase both the intensity of operant conditioning as well as its persistence.[6,47] The development of addiction to tobacco, therefore, involves not only development of addiction to nicotine, but also acquisition of conditioned behaviors, which nicotine facilitates. Because these cue-mediated behaviors can be very persistent, they are major causes of relapse.

Tobacco addiction most commonly begins in late childhood or adolescence,[48–51] although smoking can begin in young adulthood.[52,53] Historically, in the United States, the peak incidence for developing a regular tobacco habit is in adolescence. Individuals who do not acquire a habit prior to age 20 were unlikely to do so as adults.[48] The demographics of smoking initiation were well known to the tobacco industry. Marketing campaigns designed to promote the image of specific brands of cigarettes were carefully designed and were exceedingly effective in leading to logo recognition among children as young as kindergartners[51,54] and contributed to brand selection among American adolescents. The susceptibility of children to these campaigns was a major driver in leading to the current ban on tobacco advertising in media likely to be seen by children. Importantly, since most exploratory smoking occurs in peer-related social settings, the social context of smoking is a crucial variable in determining smoking initiation.[51,55,56]

Most children who begin to smoke do so on an occasional basis. Within a few years, however, a regular habit may develop. Most often this habit is characterized by smoking only a few cigarettes daily. As noted above, slow metabolizers may be particularly susceptible to addiction due to higher nicotine levels and longer persistence.[46] The number of cigarettes smoked, however, generally increases for the first 8 to 10 years. Important variations on this pattern exist, suggesting biologic differences among smokers. Some smokers achieve a "mature addiction" very rapidly. In contrast, as many as 15% of smokers, termed "chippers," may continue to smoke episodically and may not be fully addicted.[57,58]

Smoking is more common among those with psychiatric disorders.[59–61] This includes individuals with depression, anxiety disorders, and cognitive disorders such as schizophrenia as well as other drug dependencies. The basis for this relationship is unclear. Nicotine has modest antidepressant and antianxiety effects, and the suggestion has been made that some individuals with mood disorders may smoke to "auto-medicate." Alternatively, it has been suggested that smoking and psychiatric disorders may share common genetic risk factors. Another possibility is that smoking early in life may lead to alterations in the CNS that may lead, in turn, to psychiatric disorders. In support of this, smoking more commonly precedes first psychotic episodes.[61] Whatever the mechanisms, the concurrent presence of psychiatric disorders can complicate efforts to achieve smoking abstinence.

Once a smoker achieves a "mature" addiction, cigarette consumption typically remains very constant. Interestingly, the smoker

appears to adjust both nicotine intake and number of cigarettes smoked independently. If supplemental nicotine is administered, smokers will often reduce their nicotine consumption.[62] Alternatively, if smoking is restricted, for example, by decreasing the number of cigarettes available, smokers will alter their smoking strategy, for example, by smoking each cigarette more deeply, to maintain a relatively constant nicotine intake.[63] Similarly, acidification of the urine increases while alkalinization slows nicotine clearance, and there are corresponding increases and decreases in nicotine intake that are achieved with no change in the number of cigarettes smoked.[64] Rather, smokers alter the way in which individual cigarettes are smoked, that is, the depth and duration of inhalation and the number of puffs, thus modifying the nicotine absorbed. Consistent with self-regulation of nicotine administration, low–nicotine-content cigarettes do not result in lower nicotine consumption.[65] This illustrates the complexity of smoking where both nicotine addiction and conditioned behaviors contribute.

While the pathogenetic mechanisms underlying withdrawal symptoms are incompletely understood, it is generally believed that some withdrawal symptoms are related to decreases in nicotine blood levels below certain thresholds. Variations in nicotine metabolism would be expected to affect the timing of symptom onset. Some smokers, for example, may experience nicotine withdrawal at night when sleep interferes with nicotine intake.[66] The concept that nicotine replacement can help ameliorate withdrawal symptoms by maintaining nicotine blood levels is also an important concept underlying nicotine replacement as an aid to smoking cessation. In addition, susceptibility to specific symptoms may be genetically determined.[67,68]

SMOKING AS A PUBLIC HEALTH PROBLEM

Cigarette smoking is a major public health problem and is perhaps the most important cause of preventable disease. The number of deaths attributed to cigarette smoking in the United States has been estimated to be well in excess of 400,000 annually and has been for many years.[69,70] This exceeds deaths attributed to other specific causes.[71] The health burden attributable to smoking parallels smoking prevalence. As a result, smoking-induced disease is becoming more common in the developing world where smoking prevalence has been increasing, particularly in specific subpopulations such as young and middle-aged males.[72] In the United States, where comprehensive tobacco control programs have reduced smoking prevalence, the burden of tobacco-related disease has begun to decrease.[73–75] Smoking can cause disease through a variety of mechanisms, which are reviewed in other chapters. However, some pathophysiologic effects persist after cessation. Smoking-related disease, therefore, will continue to be a major health problem for many decades.

Since Dr. Luther Terry released the first Surgeon General's report on smoking and health in 1964,[14] the prevalence of adult smokers in the United States has dropped from 40% to under 20%.[75] Antismoking awareness has increased worldwide to the extent that smoking bans have become commonplace in public buildings, workplaces, and public transportation. In 1984, Surgeon General C. Everett Koop[76] proclaimed that the United States' number one health goal was to achieve a smoke-free society by the year 2000." Unfortunately, this goal was not achieved, but the importance of the public health initiatives that followed, evidenced by the overall incidence of smokers in the adult population in the United States, continues to decrease.[73–75] A more realistic goal of adult smoking reduction to 12% in the United States was put into place through the Healthy People 2010.[77] Whether this goal will be obtained remains to be determined; however, it still highlights the importance of a smoke-free society. The greatest reductions in smoking have been in states with the most comprehensive tobacco control programs, supporting the effectiveness of currently available interventions.

Public health approaches to control smoking-related disease begin with the social factors that are key in initiating and maintaining smoking.[51] The experience a child has with the initial attempts at smoking appear to be important as is an individual's attitude toward smoking, that is, the "image" of the smoker, peer pressure, parental cigarette use, and availability.[51,78,79] Social attitudes can account for very low smoking prevalence in some groups. These observations support attempts to place restrictions on smoking in public places and other efforts to "de-normalize" smoking.[51]

As in ancient America, the use of tobacco products has become well integrated into modern cultures worldwide. Tobacco is a multibillion dollar industry. In some regions, tobacco is a crucial cash crop in an agricultural economy. In addition, the manufacturing, distribution, marketing, and sale of tobacco products employ many individuals worldwide. Taxation on tobacco products has become an important means for the support of many governments. Thus, any changes in tobacco usage are likely to have economic impacts well beyond any health effects.

The use of tobacco not only has an economic role, but a cultural one as well. In some societies, for example, certain Native American tribes, tobacco usage has religious significance. In other groups, tobacco usage is associated with a strong cultural "image." Often this image may have been created through direct efforts of the tobacco industry to market their product. In this regard, advertising messages promoting the image of the cigarette smoker as rugged, independent, and masculine or as sophisticated, independent, and feminine have been developed.[80,81] While these images of cigarette smoking have their origins in advertising campaigns, the effectiveness of such marketing programs cannot be underestimated.[51,79] The portrayal of these images in media, such as film, may help promote smoking, which supports restrictions on advertisements as part of public health initiatives directed at tobacco control.[51,82,83] Whatever the reasons, cigarettes clearly have a cultural significance. The social and economic impact of tobacco usage, therefore, must be considered when attempting to deal with smoking as a public health problem.

In an effort to combat the public health ramifications of tobacco usage in the United States, the Master Settlement Agreement was signed into effect in 1998.[84] It served as a measure to recoup what states had lost through Medicaid expenditures due to smoking-related illnesses and as a measure to fine the tobacco industry for deceitful actions. Four major United States tobacco companies awarded 46 states $206 billion to be paid over 25 years and to be utilized as the states saw fit. Four states had previously settled separately. Unfortunately, since its inception, many states have failed to use the funding for tobacco control causes, instead using it to fill budget deficits or to support other state programs. Among many other actions, the agreement also prohibited advertisements targeted at youth and permitted access to tobacco industry documents. Based on current understanding of the complex factors that interact to cause tobacco addiction, these approaches are rational. The issues are also complex and controversial. It is likely that social and public health interventions will continue to evolve and be part of ongoing political debate.

Smoking prevention. As noted above, smoking initiation is generally a pediatric problem.[51] Precisely why some children begin smoking is not fully understood, although both social and genetic factors contribute as discussed above.[51] Currently as many as 40% of American children will experiment with cigarettes, of whom one-fourth will eventually smoke by the twelfth grade.[85] A number of factors are believed to contribute, including the child's social environment and the child's attitude toward smoking, which appears to be based, in large part, on the smoking behavior of parents, friends, and peer group role models.[51,78,79] Attitudes toward smoking appear

to be important factors leading to smoking initiation, which may depend, at least in part, on advertising and marketing programs, hence the effectiveness of bans on advertising. The reasons for initiating smoking, however, are not entirely environmental, as several lines of investigation (see above) suggest a genetic basis for smoking as well. These concepts support the basis for interventions to reduce smoking initiation. Interventions aimed at altering the social milieu have benefit.[86] Participation in sporting activities is associated with lower rates of smoking initiation.[48,87]

A second approach to limiting smoking initiation is to restrict the sale of tobacco products to minors. Many states have legal restrictions on such sales. In many cases, however, these laws are not enforced. Active enforcement, however, can lead to a decrease in sales to minors[88] and a decrease in both experimental smoking and in regular cigarette use among younger smokers,[89] although the general effectiveness of these measures is unclear.[90] For such measures to be effective, they must be uniformly enforced in the community, and vending machines must be made inaccessible to minors.[91,92] Another approach to restrict tobacco usage by minors is taxation.[93] While there is controversy over how "elastic" purchase of tobacco is,[94] increasing price decreases use, and this effect may be particularly prominent among less addicted smokers.[93] Inasmuch as adolescents may have less disposable income, the effect may be even greater among adolescents. Some analyses support an association between higher price, particularly through taxation and lower smoking initiation and prevalence.[95] However assessment of the specific effectiveness is difficult methodologically.

Measures aimed at restricting tobacco sales to minors may lead to a deferral for smoking initiation, as young adults remain at risk for[52,53] smoking initiation. Thus, if measures are effective at delaying smoking initiation among children, parallel measures may also be required to affect smoking initiation among older adolescents and young adults. Currently available data suggest that smoking behavior among high school students decreased steadily since the initiation of efforts designed to reduce initiation (Fig. 41-1). There does not appear to be a corresponding increase in smoking among older individuals, which supports the concept that smoking prevention is a legitimate and achievable public health goal. While it is difficult to determine the effectiveness of specific public health initiatives,[96] the evidence is clear that smoking rates can be decreased by population-based measures and that states with the most comprehensive programs have achieved the greatest gains.[51,73–75]

SMOKING CESSATION

BACKGROUND AND GENERAL APPROACH

Smoking should be regarded as a primary addictive disorder.[97] This contrasts with the "classic" view of smoking as a "habit" or "life style choice." An estimated 75% of Americans wish to quit but only 3% are able to achieve prolonged abstinence in any year, which indicates the involuntary nature of the established addiction.[98] In addition, current concepts suggest smoking should be regarded as a chronic relapsing disorder. In this context, a "cessation attempt" should be regarded as an attempt to induce a remission. The abstinent smoker, moreover, should always be viewed as at risk for relapse. The goal for therapy is to induce a remission that is as durable as possible. However, the clinician needs to be prepared to reinduce remission in the event that relapse occurs. In this context, smokers who are "quit" should remain in active surveillance, and relapses should not be regarded as "failures." In this model, the health consequences of smoking should be regarded as secondary effects. Importantly, there are health benefits of cessation that are well established. These are the subject of the Surgeon General's Report (2014).

Current recommendations are to assess smoking and willingness to quit at every visit.[97,99,100] Interestingly, success in quitting may be related to acute problems that may have motivated a patient to be willing to consider quitting (see Stages of Change).[101] This acute motivation may be present even if the acute event is not directly related to smoking, and the clinician should be ready to utilize these windows of opportunity. In contrast, not inquiring about smoking can have adverse effects. Not asking is thought to send three messages: (1) that the physician does not care if the patient smokes; (2) that the physician does not have an effective intervention to offer; and/or (3) that the physician does not think that the patient will be able to quit. All of these "nonmessages" have negative effects, particularly as smokers gradually make the decision to quit. A sense of empowerment and control over the behavior is believed to be key to making and succeeding in a quit attempt[102] and to subsequent risk of relapse.[103] Inadvertently eroding a patient's sense of mastery is an unanticipated adverse consequence of not asking about smoking. In addition, many patients are unaware of the potential available therapies; appropriate information can increase motivation to engage in quit attempts. Smokers unwilling to make a quit attempt should be encouraged as much as possible, provided with specific information if desired and reminded that the issue will be brought up again in the future.

Approach to a Quit Attempt

A smoking quit attempt should be approached in a similar way to induction of remission from cancer. As with cancer, each patient should be given the best chance of achieving remission. In general this will require two classes of intervention: nonpharmacologic approaches and pharmacotherapy, which should be used together to optimize success.

Evaluation

As with the management of any complex disease, smokers should undergo an initial organized assessment.[97,100] Motivation or reason to

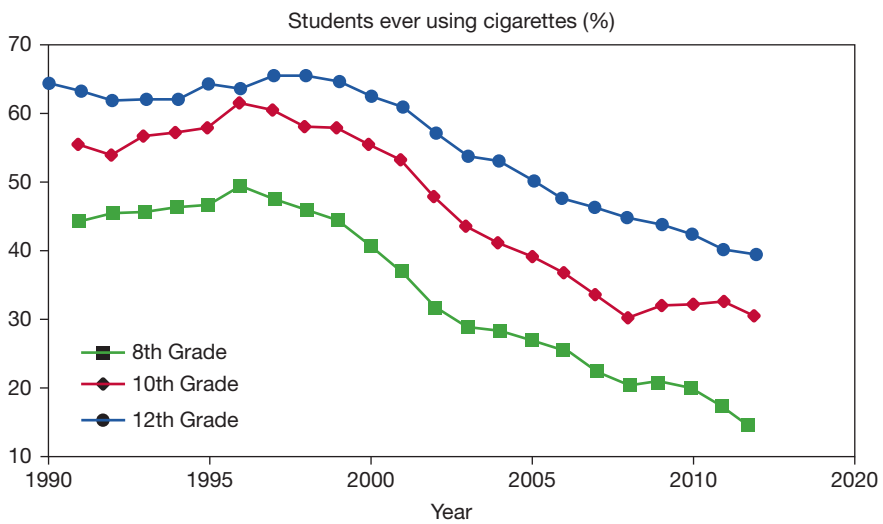

Figure 41-1 Prevalence of ever smoking among American Youth. *(Data from Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Decline in teen smoking continues into 2012. Monitoring the Future Press Release. University of Michigan News Service, Ann Arbor.)*

TABLE 41-1 Items and Scoring for Fagerstrom Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	After 60 min	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Source: Used with permission of K.O. Fagerstrom.

quit and the patient's confidence in their ability to stop smoking, that is, self-efficacy, should be assessed. For patients who indicate they are not currently interested in quitting, the goal is simple: to move them through the stages of change[104] so a quit attempt will be made. For some, this may be as simple as providing information about health risks. For others, it may be information about effective interventions.

The intensity of addiction can be assessed with the Fagerstrom test for nicotine dependence (Table 41-1).[28] The most important question is time to first cigarette, and smokers who smoke within 30 minutes of awakening are usually heavily addicted to nicotine. These patients and those with Fagerstrom scores ≥7 comprise a group of individuals likely to benefit from nicotine replacement therapy (NRT) or varenicline. In contrast, patients with low Fagerstrom scores who are able to cope with smoke-free environments for an extended time period (>4 hours) without developing discomforting withdrawal symptoms, may not require NRT. For these individuals, the benefit of pharmacologic support is unknown.

Past experience with quit attempts should be reviewed. Many patients will have a number of prior tries. Individuals who had particular difficulty with withdrawal symptoms should be prepared for this, and medications can be gauged to attempt to mitigate their intensity. Approaches that achieved abstinence, but were followed by relapse, should be considered as they are likely to succeed again. In these cases, interventions should be guided by reducing risks of relapse.

■ NONPHARMACOLOGIC APPROACHES

Nonpharmacologic approaches provide the smoker with guidance and support as progress is made through a quit attempt.[97,99,100] It is likely that effective support improves adherence with pharmacotherapy and results in therapeutic synergy. In addition, conditioned responses, that is, cue-driven behaviors, are largely dealt with thorough behavioral strategies. This generally requires individual interviews to define individual smoking patterns. These patterns can also help identify situations that increase risk of relapse. In general, success increases with the intensity of support,[97,99,100] but most smokers will decline referral to intensive programs and will receive only the support provided in the office setting. The remainder of this section summarizes commonly used approaches.[97,99,100,105]

Stages of Change and Smoking Cessation

The Stages of Change model has been very useful to guide behavioral support. Prochaska and DiClemente[104] described the smoking cessation process as involving five stages: precontemplation, contemplation, preparation, action, and maintenance. These stages are viewed as a continuum with smokers progressing sequentially through each stage. In the precontemplation stage, smokers are not interested in quitting smoking and will likely be nonresponsive to direct intervention. Smokers in the contemplation stage are considering quitting smoking and may be receptive to a physician's advice about the risks and benefits of quitting. In the preparation stage, smokers are actively preparing to quit. The action stage encompasses both initial abstinence and the 6-month postcessation period. The maintenance period commences after the 6-month abstinence period. It is rare for a smoker to progress successfully through these stages in the initial quit attempt. The cycle will likely be repeated several times before smoking a prolonged abstinence, that is remission, is achieved. Thus the clinician must be encouraging and willing to support repeated attempts.

The National Cancer Institute's (NCI) recommended model for smoking intervention is based, in part, on five NCI supported trials involving more than 30,000 patients and was later expanded by the Public Health Service.[97,99,100] This approach, popularly referred to as "the five A's," emphasizes the role of medical professionals to ask patients about their smoking status, assess their willingness to make a quit attempt, advise smokers to stop, assist them in their stop smoking efforts, and arrange for follow-up visits to support the patient's efforts. This approach utilizes brief intervention techniques and emphasizes the role of physicians as facilitators in the quitting process.

Simple advice has been assessed in a number of studies, and meta-analysis suggests a small but significant benefit of these limited interventions.[100] Physician advice is effective both in the outpatient and hospital setting and may also be effective when given by letter, email, or telephone.[106–108]

Group Counseling

Group counseling programs for smoking cessation are offered by several commercial and voluntary health organizations. These programs are similar in content and typically include lectures, group interactions, exercises on self-recognition of one's habit, some form of tapering method leading to a quit day, development of coping skills, and suggestions for relapse prevention. Group counseling programs sponsored by voluntary health organizations are generally the best cost value for smokers.[97,99,100] However, these programs are generally limited to large metropolitan areas and are offered on a sporadic basis. One-year success rates associated with group counseling programs are typically in the 15% to 35% range.[97,99,100] The high success rates are likely affected by selection bias, that is, participants may be more motivated to quit.

Gradual Reduction Versus Abrupt Abstinence

Gradual reduction or tapering intuitively appears to offer smokers the least abrasive way to stop smoking, and may be effective for some.[109–111] However, gradually cutting down can be stressful when smokers attempt to reduce their cigarette use below their critical blood nicotine threshold. At this stage, smokers may begin to experience tobacco withdrawal symptoms. Rather than suffer prolonged discomfort, many taperers will gradually return to their customary cigarette levels and will not succeed in quitting. One of the negative consequences of tapering is that this method can strongly reinforce

the smoker's belief of their underlying need for cigarettes, that is, it can undermine self-efficacy. Combining tapering with pharmacotherapy to prevent withdrawal may be useful in this setting,[110] but this is not an FDA-approved use for any medication. Abrupt abstinence is often stressful and can lead to tobacco withdrawal symptoms. However, within a few weeks of total abstinence, complete abstainers experience less frequent cigarette cravings than taperers and are less prone to relapse. Cigarette tapering is often a component of many group programs in which gradual cigarette reduction is used as a preparatory stage leading toward a target quit day.

Educational Techniques

For years, cigarette smoking was viewed as largely a social or psychological habit. As such, the ability to quit was viewed as a measure of personal motivation and psychological willpower. Motivation to stop smoking, combined with sufficient psychological resources, was seen as a driving force behind successful cigarette abstinence. Thus, if smokers could be educated about the health risks of cigarette smoking, they could theoretically become sufficiently motivated and psychologically empowered to quit. Unfortunately, anticipated benefits of the smoking cessation value of educational awareness messages were overly optimistic and simplistic. Educational programs to aid smoking cessation have produced disappointing results with high long-term failure rates.[97,99,100] Nevertheless, education about smoking is still regarded as a useful activity, particularly when the information can address problems of specific interest to individual patients. In this regard, as noted above, a major predictor of success is "self-efficacy," which is the patient's sense that they are likely to succeed. Education that improves self-efficacy should be a therapeutic goal.

Other Modes

The goal of hypnosis in smoking cessation is to enable the smoker to achieve an altered state of consciousness to enhance the ability to quit. Controlled trials of hypnosis have generally been unable to document long-term smoking cessation efficacy. While one meta-analysis suggested the possibility of a treatment effect,[112] this was not supported in another meta-analysis.[113] Aversive conditioning is based on the premise that smoking is a learned response that can be extinguished by creating an association between smoking and a negative sensation. By design, adversive conditioning techniques can produce smoker discomfort and are now rarely employed. However, there are few recent studies, and a treatment benefit cannot be excluded.[112] Acupuncture has been advocated, but controlled trials with "sham" acupuncture have not clearly demonstrated an effect. Meta-analyses have not been conclusive, but suggest the possibility of an effect.[112,114]

Resources Available

The resources available to support smoking cessation vary among communities. Some have readily available and affordable group programs, while these may be unavailable in other places. Toll-free tobacco quit lines are currently provided by many countries, including the United States and Canada. Telephone counseling is an effective smoking intervention.[108] Thus, clinicians should encourage every smoker who wishes to quit to utilize a National Quit Line (e.g., in the United States: 1-800-Quit-Now). Additional support can be found via the internet using smokefree.gov. Using this approach, a smoker can choose to talk with a telephone specialist with either internet instant messaging or telephone support. Both methods are designed to provide smokers with a personalized quit plan that would be available in most clinical settings.

■ PHARMACOLOGIC TREATMENT

Three classes of agents, nicotine replacement, bupropion, and varenicline, are approved to aid smoking cessation.[115] In addition, two other agents, clonidine and nortriptyline are supported by guidelines for "off-label" use as secondary agents. In addition, several other agents are under active investigation and have shown promise.[97,99,100] As noted above, combination of nonpharmacologic support and pharmacotherapy optimizes success in achieving abstinence.[97,99,100] The remainder of this section summarizes currently available pharmacotherapy.

Nicotine Replacement Therapies

Five nicotine replacement therapies are approved for use to aid in smoking cessation. Lozenges, polacrilex (gum), and transdermal systems are available over the counter (OTC). Nasal spray and a nicotine inhaler are available with a prescription. Other nicotine preparations, including nicotine toothpicks and e-cigarettes, have been developed and marketed as consumer products. Their efficacy and safety in smoking cessation remains undetermined. Initial concerns about potential hazards of concurrent smoking while using NRT led to warnings against this practice. However, the Food and Drug Administration recently (April, 2013) removed this warning from the OTC formulations, as the benefits of smoking cessation greatly exceed any potential hazards.

NRT is usually started on the scheduled quit day. The concept is to replace nicotine that would be absorbed from cigarettes and thereby reduce the intensity of withdrawal. Smokers will, however, experience withdrawal symptoms albeit with less intensity. In clinical trials, the five approved formulations have demonstrated about twofold increases in quit rates above placebo when used alone[97,99,100] and one trial comparing gum, inhaler, and nasal spray found no difference in efficacy.[116] They differ, however, in their pharmacokinetics.[117] The transdermal systems provide the slowest delivery of nicotine, but maintain steady-state levels throughout the day. The other formulations allow episodic dosing. A common practice is to combine a transdermal system with another formulation, a "patch-plus" regimen.[118,119] This allows a smoker to increase nicotine delivery at times of urges. Clinical trial data supports better success with combined NRT compared to monotherapy.[97,99,100]

Nicotine Polacrilex Gum Nicotine polacrilex gum was the first NRT to gain FDA approval. It is now commercially available OTC in 2 and 4-mg forms. In nicotine polacrilex, nicotine is bound to a resin that contains a buffering agent to improve delivery of nicotine through the buccal mucosa. The rate of chewing can influence the rate of nicotine release. In addition, acid foods or drinks convert nicotine base to its salt, which, because of its charge, does not cross the buccal mucosa. To be absorbed into the venous circulation, the nicotine-containing saliva must be retained in the mouth as long as possible. If swallowed, the nicotine can cause local irritation of the stomach. When absorbed into the portal circulation, high first-pass metabolism in the liver limits blood nicotine levels. If chewed properly, absorption takes place gradually, and blood levels peak after about 30 minutes.[117] Ad lib use of 2-mg nicotine polacrilex is associated with blood nicotine levels less than 40% of customary smoking. The 4-mg dose is recommended for individuals who are heavier smokers or who have had discomforting tobacco withdrawal symptoms on the 2-mg dose.[97] A fixed dosage regimen rather than ad lib usage may have better success,[120] perhaps because it can produce higher blood nicotine levels. A common recommendation is that a smoker use one piece of gum every 1 to 2 hours for the first 6 weeks after quitting followed by gradual reduction over 6 weeks. Many smokers continue to use gum at times of craving for an extended time and some can use sufficient gum to sustain nicotine addiction without smoking.

Although effective in clinical trials, less successful results have been observed with nicotine gum in general practice and unsupervised settings. This may be due, in part, to requirement that the gum

be chewed properly. Adverse effects from the gum include exacerbation of local effects: temporomandibular joint (TMJ) disease, trauma to dental appliances, sore jaw, oral irritation or ulcers, and excess salivation; effects from swallowed nicotine: hiccups; and effects from systemic absorption of nicotine: nausea, vomiting, abdominal pain, constipation, diarrhea, palpitations, and headache. Use of the gum is not recommended in individuals with poor dentition or who have dental appliances.[115]

Nicotine Polacrilex Lozenge A nicotine polacrilex lozenge is also available "over the counter." Chewing is not required, but acid food and/or beverages will impair absorption as with gum. Dosing, absorption, and duration of therapy with the lozenge are similar to those for the gum.[121] Because it is not chewed, the lozenge does not share the problems of exacerbating TMJ disease or damaging dental appliances. Other side effects are similar to those of the gum.

Transdermal Nicotine The primary advantage of transdermal patch delivery systems are ease of use and controlled drug delivery. Several formulations are available "over the counter." In general, they achieve nicotine blood levels roughly 40% to 50% of that achieved by customary smoking of about 30 cigarettes daily.[117] Transdermal nicotine systems have been repeatedly found to reduce tobacco withdrawal symptoms and significantly enhance smoking cessation rates.[97,99,100] Unlike nicotine polacrilex gum, transdermal nicotine systems and the nicotine lozenge have improved quit rates in primary care settings.[101,122] This difference is likely due to the ease of patch use in this setting. The recommended use period for patches varies according to product, but a minimum of 4 weeks of therapy is probably required to help achieve long-term abstinence.

Patches are most commonly worn at night, which provides a level of nicotine when a smoker awakes. Often this is a time when the individual is at risk to relapse, since the low nicotine levels are associated both with withdrawal and with increased effect of the smoked cigarette. On the other hand, delivery of nicotine at night may disturb sleep, particularly through vivid dreams or insomnia. Spontaneous long-term use of the patch has not been observed, suggesting that the very slow kinetics of nicotine delivery with this system is insufficient to sustain addiction effectively.[123] In addition, perhaps due to the partial replacement of nicotine, most smokers on patches will still experience some tobacco withdrawal symptoms during the first few days of quitting. While these symptoms will likely be less severe compared to quitting cold turkey, some patients will be tempted to smoke and wear patches. Early concerns about increased cardiac risk among individuals who smoked while wearing the patch have not been substantiated. In fact, reduced smoking may decrease cardiac events.[124–126]

Nicotine Inhaler The nicotine inhaler is a plastic nicotine-containing cartridge that fits on a mouthpiece. Nicotine is released when air is inhaled through the device, which is similar in size to a cigarette. The nicotine is not effectively delivered to the lungs as the particle size is too large. Rather, it is deposited and absorbed through the buccal mucosa, which results in pharmacokinetics that resemble nicotine polacrilex. Blood levels depend on the frequency of inhalations but can be about one-third of conventional smoking. Usual dosing is 6 to 16 cartridges per day for 6 to 12 weeks followed by gradual reduction over 6 to 12 weeks. Because the use of the inhaler recapitulates many of the actions associated with smoking: preparation of the device, oral stimulation, inhalation, etc.; it may be particularly effective in smokers for whom these behaviors are particularly strongly conditioned. In addition to the adverse effects described for the lozenge, the inhaler may cause irritation of the throat and mouth and may precipitate bronchospasm in individuals with reactive airways.

Nicotine Nasal Spray The nasal spray delivers nicotine to the nasal mucosa through which it is absorbed. It has the most rapid pharmacokinetics of the currently available nicotine replacement formulations but does not reproduce that of a cigarette.[117] Nasal irritation is very common, particularly when initiating therapy. The recommended dose is one to two sprays per hour for 3 months with a maximum of 80 sprays per day. Because the spray can deliver large amounts of nicotine, it may be particularly effective for heavily addicted smokers. It also likely has a greater risk of nicotine overdose and may have a greater potential to sustain a long-term addiction.

Combination Therapy Although not approved by drug regulatory agencies, various combinations of nicotine replacement may have utility for selected individuals who need higher doses. In particular, combination of a transdermal system with an ad lib modality has been demonstrated to increase quit rates.[97,99,100,122,127] Because of its increased success, it is recommended by some as initial therapy.[115]

Bupropion

Bupropion is approved as an antidepressant, and it is also effective as an aid for smoking cessation.[97,99,100,128] It is believed to act by potentiating dopaminergic and noradrenergic signaling. The formulations for depression and for smoking cessation have different trade names, which has clinical relevance. First, an appropriate diagnosis is often required for reimbursement. Second, care is needed not to prescribe bupropion under one name to an individual already taking it under its other name, as over dosage can result.

In clinical trials, bupropion approximately doubles quit rates compared to placebo. Subjects with a history of depression, however, appeared to benefit from bupropion but did not with nicotine replacement, suggesting that bupropion may be a superior initial choice in such individuals. Combination of nicotine replacement with bupropion has been assessed and appears more effective than either agent alone.

The currently recommended dose is 150-mg daily for 3 days followed by 150-mg twice daily. Because the drug is excreted slowly, steady state-levels are achieved after 6 to 7 days. For this reason, the quit date should be scheduled after a week of therapy so that blood levels are established. As the 150-mg once daily dose was nearly as effective as the 150-mg twice daily,[129,130] many practitioners use the lower dose routinely. The appropriate duration of therapy is not established. Clinical trials that formed the basis for approval treated for 7 weeks, although a 12-week course is commonly recommended. With prolonged therapy, there is an increase in secondary quits, and therapy for 1 year resulted in more quits than therapy for 7 weeks.

The drug is generally well tolerated. The most common adverse effects are dry mouth, insomnia, agitation, and headache. In combination with nicotine replacement, an increase in blood pressure may also occur. Bupropion reduces seizure threshold and a seizure risk of 0.1% has been reported. Because of its reduction in seizure threshold, bupropion is contraindicated among those predisposed to seizures, or with anorexia nervosa or bulimia.

In 2008, the FDA first noted that both bupropion and varenicline (see below) had a "possible association (with) suicidal events."[131] The benefits of smoking cessation were felt to outweigh any potential risks, and the medicines were not withdrawn from the market. However, both labels now contain a black box warning, suggesting that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts. Most practitioners make a routine practice of reassessing patients 3 to 7 days after the quit day to both monitor for adverse effects and to provide additional support for the quit attempt. In this context, a second visit has been demonstrated to greatly improve success.[97,99,100]

Varenicline

Varenicline is a partial agonist at the (alpha4)(beta2) nicotinic receptor.[132] As such, it can partially activate the receptor thereby mitigating withdrawal symptoms. In addition, by occupying the receptor, it can

prevent nicotine from acting, and thus can reduce the rewarding and reinforcement effects associated with nicotine. This may be particularly important in preventing a lapse from becoming a full relapse once abstinence has been achieved. Both of these effects are supported by evidence from clinical trials.[133–136] Varenicline consistently improves success in quitting compared to placebo by an effect of two- to fourfold.[97,136] In addition, head-to-head trials have demonstrated superiority compared to bupropion.[133,134] Fewer data compare varenicline to NRT, and a recent meta-analysis failed to show a difference, though superiority of varenicline could not be excluded.[136]

Varenicline is given orally. Usually medicine is started at 0.5-mg once daily for 3 days followed by 0.5-mg twice daily for 4 days and then 1-mg twice daily for 3 months. Individuals who have achieved abstinence at 3 months may have less relapse if therapy is continued for an additional 3 months. A quit date is usually recommended for 1 week after starting medication, but success has been reported with a broader window of quit dates from 1 to 5 weeks that was comparable to a fixed quit rate.[137,138] This increased flexibility may be an advantage in starting a quit attempt when patients are seen for problems other than smoking cessation.

The most common adverse reactions are nausea, insomnia, visual disturbances, syncope, and skin reactions. The incidence of nausea is reduced with the dose titration described above.[139] The most serious concerns with varenicline have been with psychiatric and cardiovascular side effects. Varenicline has the same boxed warning as bupropion, indicating that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts.[131] However, clinical trials have failed to confirm psychiatric adverse effects, although they cannot be fully excluded.[140] A meta-analysis that reported significant increase in cardiovascular events[141] was felt to be methodologically flawed as it excluded studies with no events.[142] A subsequent meta-analysis that included all available studies found no difference between varenicline and placebo, although a small difference may be present.[142] Currently the FDA recommends that patients taking varenicline be alert for development of new or worsening symptoms of cardiovascular disease.[143] Varenicline has also been associated with accidental injuries from falls and vehicular accidents.[144] This has resulted in an FDA advisory regarding operating heavy machinery while using varenicline.[145]

Off-Label Agents

Clonidine Clonidine is an α-adrenergic agonist active in the CNS that is used to treat hypertension. A number of clinical trials have evaluated its efficacy in smoking cessation and have generally shown a trend toward benefit, although individual trials have generally not been statistically significant, and its use is supported by a meta-analysis.[146] The Department of Health and Human Services (DHHS) guidelines suggest it can be used by experienced practitioners comfortable with the drug.[97,99,100] Major adverse effects of clonidine are drowsiness, fatigue, dry mouth, and postural hypotension.

Nortriptyline Nortriptyline is a tricyclic antidepressant that has been evaluated for efficacy in smoking cessation in several studies. Both individual studies and meta-analyses support its benefit as an aid to smoking cessation,[128,147] and it is also recommended as a possible second-line agent for practitioners comfortable with its use by the DHHS guidelines.[97,99,100] Major adverse effects of nortriptyline include drowsiness and dry mouth. As with other tricyclics, CNS and cardiovascular effects, including arrhythmias, may occur.

Investigational Drugs

A number of other agents approved for other uses have also been assessed for smoking cessation. None are currently recommended off-label by established guidelines, although several are under investigation. These include topiramate, an antiseizure medication that has been evaluated for several addictions, including combined alcohol and tobacco addiction, and selegiline, an agent used as an adjunct in the treatment of Parkinson disease that has also shown promise in smoking cessation.[148] Several other agents have been assessed. Selective serotonin reuptake inhibitor (SSRI) antidepressants have been demonstrated to be without benefit.[128] Opiate antagonists and anxiolytics have generally been without benefit,[97,99,100,149] but buspirone remains controversial as studies have been mixed.

Nicotine vaccines are also under investigation. Antibodies can be made to nicotine, if it is presented bound to an appropriate carrier.[150,151] The antibodies then bind nicotine reversibly. By slowing the delivery of nicotine to the brain, the vaccine would distort the pharmacokinetics of a cigarette. These investigational agents may have utility for long-term relapse prevention or for prevention of smoking initiation. However, phase 3 trials have not shown clinical benefits to date.[150]

■ PRACTICAL CONCERNS DURING THE QUIT ATTEMPT

Approach

As noted above, the first step is to have a patient willing to make a quit attempt. Current practice is to optimize the chance for success with each attempt. In general this will be achieved with nonpharmacologic support combined with pharmacotherapy. The more active the nonpharmacologic support the greater the likelihood of success. Patients will vary, however, in the type of support they will accept. It is also important to select an appropriate pharmacotherapy. Many practitioners initiate treatment with NRT, because of greater experience and reduced potential for adverse effects. The "patch-plus" regimen that combines a transdermal system with an ad lib formulation is often recommended.[97,99,100,115] Bupropion may be more appropriate for individuals with a history of depression.[152] Varenicline has the greatest efficacy, but is often reserved for secondary attempts to induce a remission from smoking.[115] The quit date should be linked to the pharmacotherapy: generally this is 1 week after initiating bupropion or varenicline and on the same day as initiating NRT. Varenicline may offer some flexibility, with a quit date 1 to 5 weeks after starting treatment.[138] A follow-up visit should be scheduled about 10 days after initiating bupropion or varenicline to check for side effects. A follow-up in the immediate postquitting period is associated with improved success. This may be particularly important for cessation attempts that begin in hospital.[153]

Withdrawal Symptoms

The first 3 days of abstinence are usually the most difficult. Tobacco withdrawal symptoms (Table 41-2) generally peak during the first 72 hours then gradually subside over a 3- to 4-week period. These symptoms can include restlessness, anxiety, difficulty concentrating, irritability, frustration, depression, and an almost unrelenting craving for cigarettes. Common suggestions to help smokers cope with these

TABLE 41-2 Nicotine Withdrawal Symptoms (DSM-IV)

Dysphoric or depressed mood
Insomnia
Irritability, frustration, or anger
Anxiety
Difficulty concentrating
Restlessness
Decreased heart rate
Increased appetite or weight gain

early withdrawal symptoms in addition to NRT can include: (1) Be active. Increased activity may curtail some of the drive to smoke. (2) Use deep breathing exercises. The simplest breathing exercise involves nothing more than extended breath holding followed by slow exhalation through pursed lips. (3) Avoid high-risk situations for smoking during the first 3 weeks of quitting. (4) Use plenty of cinnamon gum or chewable candies. (5) Combat strong urges to smoke: The urge to smoke will go away whether one smokes or not.

Cravings

Of all the symptoms associated with nicotine withdrawal, cravings to smoke are the most persistent. Unlike the other symptoms, cravings can also recur long after abstinence is achieved. During the second and third weeks of abstinence, the craving waves usually occur less frequently, but can sometimes catch smokers off guard because of their unexpected intensity. The decrease in frequency is greater than the decrease in intensity, and cravings can be precipitated months and years after abstinence if precipitated by specific cues. In this context, cravings recapitulate, in some ways, the grief response. Relapse is commonly associated with concurrent alcohol consumption. It is likely that alcohol, and the associated situations in which it is consumed, serves both as a cue leading to craving and decreases the inhibitions that may prevent smoking. Ex-smokers should be aware of these moments of hazard.

Depression

At some time during the first 3 months of abstinence, some smokers may experience depression. For many this depression is mild and transient. For a small minority of smokers, quitting smoking may produce a clinical depression that may require antidepressant therapy, counseling, or return to smoking. Depressive symptoms are associated with relapse.[154]

Weight Gain

One of the most disheartening components of quitting smoking is weight gain.[97,99,100] Rapid weight gain is common during the first 6 to 8 weeks of cigarette abstinence. This is followed by a more gradual increase in weight to roughly 4-kg at 6 months. Average weight gain at 10 years following cessation is 4.4 and 5.0-kg for males and females, respectively. The health risks associated with postcessation weight gain are unknown but are likely surpassed by the health benefits of stopping smoking.

■ RISKS OF SMOKING CESSATION

Smoking cessation may be associated with some hazards in selected cases. Nicotine and other components of cigarette smoke may have a significant antidepressant effect, and many endogenously depressed individuals may have empirically found smoking helped alleviate their symptoms. Depression is a well-recognized manifestation of the nicotine withdrawal syndrome. At times, this depression can be of major clinical importance. Exacerbations of ulcerative colitis are more common in former smokers and may develop at times long after smoking cessation.[155] These potential adverse effects should not minimize the importance of smoking cessation, but the clinician should be prepared to address them when necessary. Anecdotal reports have suggested that asthma may worsen following cessation. However, smoking generally makes asthmatics worse[156] and induces resistance to the therapeutic effects of inhaled glucocorticoids. Thus, asthma symptoms generally improve with smoking cessation.[157] Some smokers report an increase in cough in the weeks following cessation. However, among individuals with chronic bronchitis, symptoms of cough and sputum production decrease dramatically in the months following cessation.[158,159]

■ SPECIAL POPULATIONS

Smoking cessation approaches for special populations are generally the same as for the general population.[97,99,100] Smoking cessation treatment can be started in hospital at the time of acute illness.[153] Success will be dependent on adequate follow-up and support. Interestingly, withdrawal symptoms may be particularly mild in hospital, perhaps because there are few options to smoke. Concurrent treatment of individuals hospitalized with psychiatric illness for smoking cessation can be successful and does not compromise treatment of the comorbid psychiatric problem.[97,99,100] Treatment of pregnant smokers has been extensively reviewed.[97,99,100]

Smoking is a major risk factor for COPD. All three approved forms of pharmacotherapy: NRT,[160] bupropion,[161] and varenicline[162] have demonstrated efficacy in the COPD population.

HARM REDUCTION

A more controversial approach for smokers who are unwilling or unable to quit at all, is that the health consequences may be partially addressed by reducing the exposure to smoke-derived toxins. This approach, termed "harm reduction," has been the subject of several reviews, including an Institute of Medicine report.[163,164] Four general categories of harm reduction are theoretically possible: (1) administration of agents to counteract the effects of cigarette smoking; (2) smoking reduction; (3) development of less toxic tobacco products; and (4) alternate nicotine delivery systems. It is important to recognize that clear health benefits have not been established for any of these approaches, however.

Since cigarette smoking is thought to cause its effects through pathogenetic mechanisms that are at least partially defined, it is appealing to use such mechanisms as targets for therapeutic intervention. In this regard, antioxidants to ameliorate the oxidant-induced injury caused by cigarette smoke, and protease inhibitors to bolster the antiprotease defenses are both potential therapies. While conceptually appealing, no data exist to suggest that any such approach is of benefit in continuing smokers.

Pharmacologic support may facilitate reduction in smoking. The observation that most smokers maintain a relatively constant nicotine intake creates the possibility that nicotine replacement can help sustain smoking reduction. Smoking reduction has also been achieved with several formulations of nicotine replacement, and there is some evidence for physiologic benefit. Short-term smoking reduction, facilitated with the use of nicotine polacrilex gum, was associated with improvements in lower respiratory tract inflammation assessed by bronchoscopy and bronchoalveolar lavage in a group of heavy smokers.[165,166] In patients with cardiac disease who reduced smoking, there were measurable improvements in cardiac function that were associated with improved oxygen delivery to the heart due to reduced carbon monoxide.[125]

Reducing the delivery of cigarette smoke toxins while still providing the smoker with a satisfactory cigarette has been pursued by some tobacco companies. This was a major motivation in the development of filtered cigarettes and of low-tar, low-nicotine cigarettes. Unfortunately these approaches do not reduce, and may actually increase, exposure to smoke-derived toxins. As most smokers maintain constant nicotine intake, many smokers compensate for altered smoke composition by simply smoking more or by changing the way in which they smoke each cigarette.[167,168] By causing an altered smoking strategy, filtered and low-yield cigarettes may actually deliver more toxins.

Many of the cigarette-derived toxins are generated as a result of pyrolysis.[25] As a result, tobacco products that do not burn have the promise to yield fewer toxins. Several cigarette-like devices have been developed with similar goals. Some burn small amounts of processed tobacco together with a carbon heat source to have a taste that more closely resembles a cigarette.[169] Others electrically heat the tobacco.

Whether the electronic cigarette will be effective as an alternative to smoking at present remains to be determined.[164] Because of its widespread use, the electronic cigarette has become particularly controversial. This has led to reviews and position statements relating to these products.[170,171] Potential harm-reduction products appear to deliver less toxins in standardized smoking regimes. However, limited data are available on physiologic effects. In one study, a reduction in lower respiratory tract inflammation and airway metaplasia was observed among heavy smokers who switched to a harm-reduction product.[172] Whether such products are associated with health benefits, however, remains to be determined.

Nonburned tobacco products may also have advantages. Moist snuff, which has low nitrosamine content due to its processing, has been widely used for several decades in Sweden. It has been associated with a measurable decrease in a number of tobacco-related diseases among Swedish men compared to cigarettes, but not compared to abstinence.[173–176]

Harm-reduction strategies may have unforeseen problems. Reduced-risk products, or smoking reduction strategies may encourage smokers to continue and thus discourage quit attempts. Available data, however, suggest the opposite. Smokers who switch to harm-reduction products or who reduce with pharmacologic support appear to have an increased rate of subsequent quits. It may be that the sense of mastery that comes with the reduction effort helps make smokers "able" to quit. There are other potential hazards. Reduced-risk products, for example, might be particularly appealing for individuals beginning smoking both because they may be easier to smoke and because they are not perceived as having significant risks. Finally, if use of reduced-risk products erodes the social climate that discourages smoking, such products could increase use of conventional cigarettes.

CONCLUSION

Cigarette smoking is a complex social and medical issue. The physician has a particularly important role in curbing smoking. Not only must the physician participate in efforts to reduce smoking as a citizen, but as a protector of public health and a possessor of specific expertise in healthcare matters, the physician must take an active role in health promotion. Such a role includes discouraging smoking initiation among younger patients, encouraging and assisting smoking patients to quit, and participating in social efforts designed to reduce smoking at various levels.

For individuals who are smokers, the clinician needs to approach smoking as a chronic relapsing disorder for which a range of effective treatments are available. These include nonpharmacologic and pharmacologic therapies and optimal results from a combined approach.

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CHAPTER 42

Course and Treatment of Chronic Obstructive Pulmonary Disease

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Robert A. Wise

In past decades, the treatment of chronic obstructive pulmonary disease (COPD) has been approached by many physicians and patients alike with a nihilistic attitude, assuming that the disease was progressive, incurable, and untreatable. More recently, as our understanding of the clinical epidemiology and value of therapy of COPD has improved, this attitude has changed. Physicians have come to approach COPD in the same way as other chronic diseases, such as diabetes, rheumatoid arthritis, and coronary artery disease. With modern comprehensive treatment, the diagnosis of COPD is compatible with prolonged survival, good quality of life, and independent functional status for many who have this illness. The purpose of this chapter is to summarize the current understanding of the course of COPD and best approaches to treatment.

OVERVIEW OF COPD

COPD is a disorder that is characterized by slow emptying of the lung during a forced expiration. In practice, this is measured as the forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio, and the arbitrary definition of airflow obstruction is generally taken to be an FEV_1/FVC ratio lower than 0.70.[1] Because the rate of emptying of the lung falls with advancing age, many elderly individuals demonstrate airflow obstruction even in the absence of a clinical diagnosis of COPD. For this reason, an alternative criterion to define airflow obstruction incorporates lower limit of normal thresholds instead of the fixed ratio criteria.[2] Several disorders cause chronic airflow obstruction—long-standing asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, lymphangioleiomyomatosis, panbronchiolitis, silicosis, Sjögren syndrome, and diffuse interstitial processes such as eosinophilic granuloma and sarcoidosis. The diagnosis of COPD is usually limited to individuals who have chronic airflow obstruction associated with tobacco smoke or some other noxious inhalant, and it is usually not difficult to distinguish it from other causes of chronic airflow obstruction. The most commonly associated clinical disorders associated with COPD are emphysema and chronic bronchitis. *Emphysema* is defined anatomically by airspace enlargement due to disappearance of alveolar septae (see Chapter 39). This leads to the characteristic loss of elastic recoil, which, in turn, causes slowing of airflow from the lungs, hyperinflation, and air trapping (see Chapter 40). *Chronic bronchitis* is characterized by chronic cough and sputum production, which is present in about one out of three people with early COPD. Chronic cough and sputum production in cigarette smokers is often, but not always, associated with chronic airflow obstruction. When chronic mucus hypersecretion is associated with airflow obstruction, it is often called *chronic obstructive bronchitis*. The anatomic correlates of chronic bronchitis are mucus gland hyperplasia and goblet cell metaplasia in large- and medium-sized airways.[3] Patients with COPD also have *small- and medium-sized airway involvement* with inflammation, narrowing, tortuosity, mucus plugging, and fibrosis that contributes to the airflow limitation. As the disease evolves, there is obliteration of small airways. Some patients with a long-standing history of asthma develop airflow obstruction that is not completely reversible, episodes of cough and wheeze, and chronic sputum production. These individuals are often classified as having *chronic asthmatic bronchitis* and tend to have a somewhat better prognosis for survival than those with typical tobacco-related COPD. Physicians have a tendency to classify women as having asthma and men as having COPD despite similar medical histories.

NATURAL HISTORY OF COPD

COPD results from an increase in the rate of decline in lung function over time. Normal nonsmoking adults lose FEV_1 at a rate of 30 mL/yr, thought to be the consequence of the aging-related loss of elastic recoil of the lung. Persons who develop COPD may start in early adulthood with lower levels of lung function and also have increased rates of decline.[4,5] Studies of patients with COPD show an average annual decline in FEV_1 of 45 to 69 mL/yr (Fig. 42-1A). However, there may be considerable heterogeneity between patients and over time.[6,7] This leads to the insidious loss of ventilatory reserve capacity that often is asymptomatic and unrecognized by patients and physicians alike. Chronic bronchitis may be dismissed as an innocent "smoker's cough" because patients fail to understand that it is abnormal to produce daily sputum. As ventilatory reserve decreases, people with mild COPD tend to limit strenuous activities, so breathlessness with activities of daily living is not ordinarily an early symptom of the disease. When the ventilatory reserve decreases to the extent that mild exertion such as climbing stairs, bed making, or carrying groceries is limited, patients tend to seek medical advice. In some cases, the first clinical presentation of disease is an acute episode of bronchospasm, dyspnea, or even respiratory failure in association with a respiratory infection or exposure to respiratory irritants. Thus, the onset of COPD may appear precipitous even though it is the cumulative result of decades of progression.

People who discontinue smoking with mild to moderate degrees of airflow obstruction cease the rapid decline in FEV_1, and have better survival (Fig. 42-1B).[8] The improvement in survival depends largely upon the stage of disease. Persons who quit smoking with earlier disease have better outcomes compared with those who continue to smoke or those who quit smoking later in the disease. Once the disease is advanced, the inflammatory response persists and the proportional loss of lung function tends to progress. Because there are many years of asymptomatic decline in lung function, it is possible to diagnose COPD with forced expiratory spirometry before the disease is apparent and implement aggressive smoking intervention programs. There is a consensus that smokers with respiratory symptoms should be tested for COPD with spirometry. However, there is debate whether it is of value to screen for COPD among all cigarette smokers.[9] Opponents of using spirometry for case-finding argue that the finding of a normal test would not alter physician behavior because all smokers should be encouraged to quit. It has also been argued that a normal spirometry test might provide a false sense of complacency for active smokers. Those who support the use of spirometry for COPD case-finding argue that early detection and aggressive smoking intervention have been proved to halt disease progression and improve survival, and the finding of abnormal spirometry may encourage patients and healthcare professionals to be more aggressive with smoking cessation. Moreover, some evidence points to the benefits of drug therapy in terms of lung function decline and survival in patients with mild to moderate airflow obstruction.[10–12] While these data arise from post hoc analysis, the findings are promising.

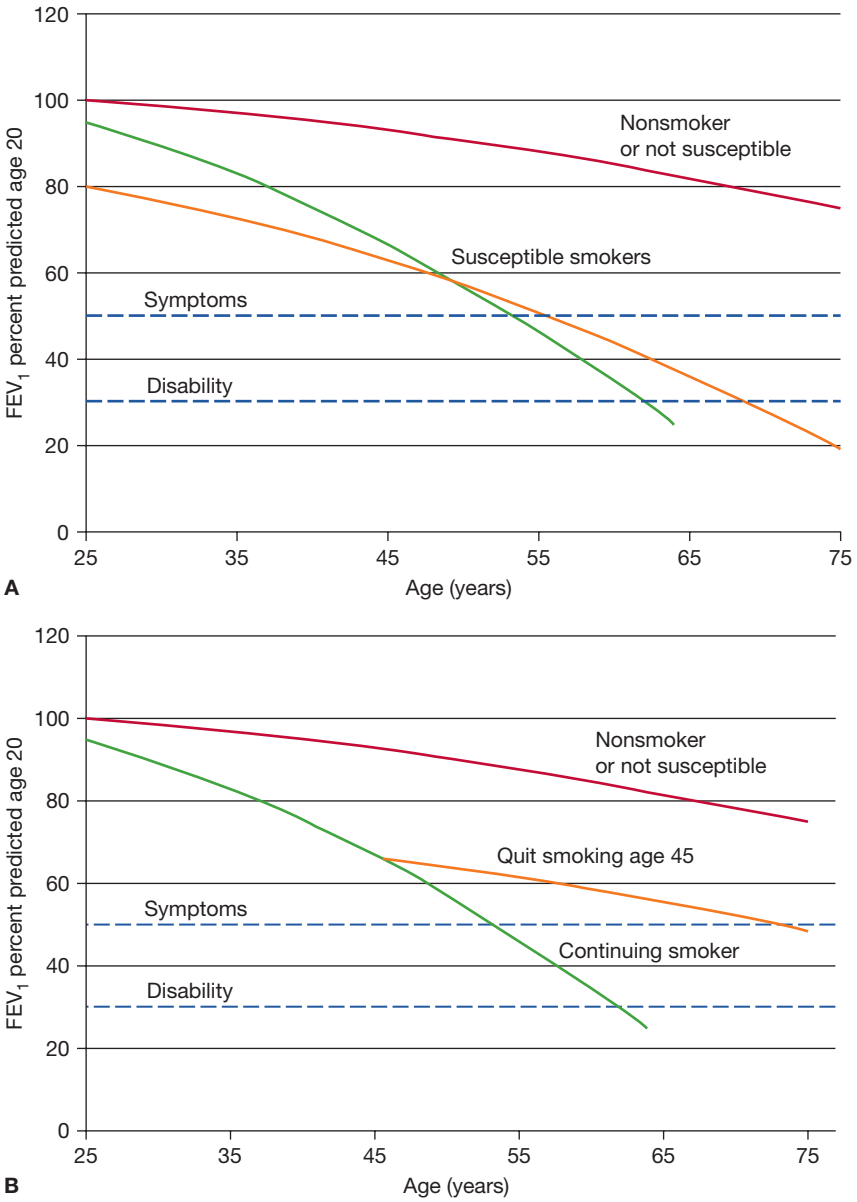


Figure 42-1 **A.** The natural history of COPD is presented for three hypothetical individuals. Pulmonary function is plotted as the percent of predicted lung function for a young adult who has attained maximal lung growth. Those who do not smoke, or are not susceptible to cigarette smoke typically lose about 25% of their young adult lung function throughout life. Individuals are susceptible to the adverse effects of smoking because of increased decline of lung function, or low lung function in young adult life. Although the abnormality of lung function is detectable for many years, symptoms do not develop until there is loss of approximately 50% of lung function *(upper dashed line)*, which occurs in middle age or later. If the disease progresses, it may lead to substantial disability within a decade of the onset of symptoms *(lower dashed line)*. **B.** The natural history of COPD is displayed for a hypothetical continuing smoker, and an individual who quit smoking at age 45. The axes are identical to those in (**A**). If an individual ceases smoking in the asymptomatic phase of COPD, the rate of decline of lung function reverts toward normal. In this example, the detection of abnormal lung function and cessation of smoking has a substantial effect of delaying the onset of respiratory symptoms. This plot is modified from the work of Fletcher and Peto and is commonly referred to as Fletcher curves. *(Reproduced with permission from Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645–1648.)*

With the progression of COPD comes progressive exercise limitation.[13] This is due to the increased work of breathing as ventilation increases with exercise. With increased respiratory rate, patients develop dynamic hyperinflation—a condition in which the end-expiratory lung volume does not return to the static end-expiratory volume of functional residual capacity (FRC). The hyperinflation that occurs causes increased work of breathing and exacerbates dyspnea. An indicator of dynamic hyperinflation is the inspiratory capacity (IC), which progressively falls with increasing ventilation. Measures that reduce dynamic hyperinflation, increasing IC, can improve exercise capacity. These include alterations in breathing pattern, oxygen supplementation, and use of inhaled bronchodilators.

As COPD progresses, ventilation–perfusion inhomogeneity causes an increase in the alveolar–arterial oxygen difference. Eventually, alveolar hypoxemia leads to pulmonary hypertension, which becomes manifested as cor pulmonale. The alveolar hypoxemia may be compounded by alveolar hypoventilation—manifested by arterial hypercapnia. Physical findings indicative of cor pulmonale are venous engorgement, edema, and physical findings of pulmonary hypertension and right ventricular failure including accentuated pulmonic second heart sound, right ventricular heave, tricuspid regurgitation murmur, hepatojugular reflux, and ascites. Chest imaging shows central enlargement of the pulmonary arteries. Once cor pulmonale is clinically apparent, survival is markedly reduced in proportion to the elevation of pulmonary artery pressure. Chronic respiratory failure is defined by chronic hypoxemia (sea-level resting Pa_{O_2} ≤60 mm Hg or 8 kPa) with or without attendant hypercapnia (Pa_{CO_2} >45 mm Hg).

Patients with advanced COPD may restrict their activities to a bed-and-chair lifestyle because of severe exercise incapacitation. This limitation can lead to social isolation, depression, and skeletal muscle deconditioning, which, in turn, further restrict activity and impair quality of life. Protein and calorie malnutrition occurs as the consequence of impaired nutritional intake caused by dyspnea.[14] Malnutrition is augmented by increased metabolic demands caused by increased basal oxygen consumption, inefficient skeletal muscle oxygen utilization, and cachexia-producing cytokines such as tumor necrosis factor-α (TNF-α).[15]

DIAGNOSIS OF COPD

Physical examination and chest imaging are insensitive methods for diagnosis of COPD. Physical findings of hyperinflated lungs such as low-lying diaphragm, decreased breath sounds, and hyperresonant chest percussion are highly specific for COPD, but usually only in

TABLE 42-1 Conditions Suggesting α1-Antitrypsin Deficiency

Early-onset emphysema (age under 45 yr)
Emphysema in a nonsmoker
Emphysema predominantly in lung bases (panacinar)
Necrotizing panniculitis (Weber–Christian disease)
c-ANCA positive vasculitis (e.g., Wegener granulomatosis)
Family history of early-onset emphysema or non–smoking-related emphysema
Bronchiectasis without other etiology

advanced disease.[16] One study has suggested that a distance between the thyroid cartilage and the sternal notch less than 4 cm in a smoker older than age 45 is highly indicative of the presence of COPD.[17] Clubbing of the fingers is rare in COPD and, if present, suggests another diagnosis such as bronchiectasis, asbestosis, or lung cancer. High-resolution computed tomography (HRCT) of the lung is useful in establishing the presence of emphysema. Quantitative analysis of HRCT is a promising technique for early detection of emphysema. α_1-Antitrypsin deficiency is an uncommon, but not rare, condition associated with premature emphysema. Testing for α_1-antitrypsin deficiency is indicated in those most likely to have the disorder (see Chapter 40 and Table 42-1). Some experts advise that all patients with COPD should be tested for α_1-antitrypsin deficiency because treatments are available for those with the most severe form of deficiency.[18] HIV/AIDS is also associated with premature emphysema and accelerated lung function decline,[19,20] and screening for HIV should be performed for persons with emphysema and HIV risk factors such as intravenous drug use or high-risk sexual activity.

The diagnosis of COPD, classification of its severity, and progression of the disease can be monitored with spirometry, a simple, noninvasive, and inexpensive test. The FEV_1/FVC ratio, reflecting the rate of emptying of the lung, is used to define the presence of an obstructive ventilatory defect, commonly defined as a ratio less than 0.70 or below the lower limit of normal. Once airflow obstruction is established, the severity of the airflow limitation is classified by the reduction of FEV_1 compared with a healthy reference population. Table 42-2 shows the widely used GOLD classification of severity based on the FEV_1. Lung volume measurements, by plethysmography, helium dilution, nitrogen washout, or single-breath methods typically show hyperinflation (elevated TLC) and air trapping (elevated residual volume [RV]), and thus are useful to exclude restrictive lung diseases. The carbon monoxide diffusing capacity (D_{CO}) is an indicator of emphysema and is roughly inversely correlated with the anatomic extent of emphysema in patients who have an FEV_1 greater than 1.0 L.

TABLE 42-2 Classification of Severity of Airflow Limitation in COPD

GOLD Classification	Characteristics
I Mild COPD[a]	FEV_1 ≥80% predicted
II Moderate COPD[a]	FEV_1 50–79% predicted
III Severe COPD[a]	FEV_1 30–49% predicted
IV Very severe COPD[a]	FEV_1 <30% predicted or <50% predicted with room air Pa_{O_2} <60 mm Hg (8.0 kPa)

[a]*Postbronchodilator FEV_1/FVC less than or equal to 0.70.*
Source: Data from the 2011GOLD COPD guidelines, www.goldcopd.com; Celli BR, MacNee W. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.

TABLE 42-3 Modified Medical Research Council Dyspnea Scale (mMRC Scale)

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Source: Data from Celli BR, MacNee W. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.

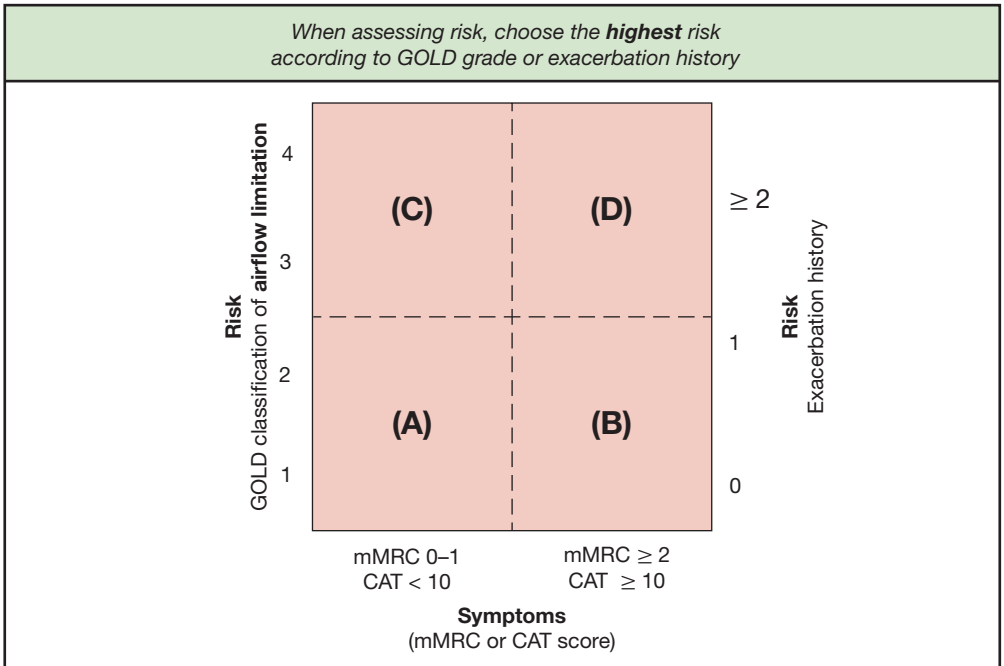
CLASSIFICATION OF COPD

Classification of COPD involves determination of symptoms and assessment of risk. Symptoms are determined using standardized questionnaires (**see** Table 42-3 and **www.catsonline.org**), while risk assessment is defined by severity of ventilatory limitation and exacerbation history. Based on symptoms and risk of exacerbations, individuals are grouped into one of four different patient categories (see Fig. 42-2). The categories are informative for determining prognosis and treatment of COPD. Additional instruments are available for quantifying the impact of COPD.[21]

PROGNOSIS OF COPD

The prognosis in COPD may vary widely. Physicians are poor prognosticators of survival in COPD.[22] In part, this is because the disease is one of widely varying rates of progression, and, in part because death is often due to susceptibility to intercurrent illness and other smoking-related illness such as lung cancer rather than progressive respiratory failure. Recent studies have demonstrated heterogeneity in lung function decline, with some patients with COPD having little or no decline in FEV_1 over time.[6,7]

Several factors have been identified that predict poor survival in COPD. These include low FEV_1, active smoking status, hypoxemia, poor nutrition, the presence of cor pulmonale, resting tachycardia, low exercise capacity, severe dyspnea, poor health–related quality of life, anemia, frequent exacerbations, comorbid illnesses, and low D_{CO}.[23] Patients with an FEV_1 less than 35% predicted have about 10% mortality per year.[24] If a patient reports that they are unable to walk 100 m without stopping because of breathlessness, the 5-year survival is only 30%.[25] A multidimensional prognostic index that takes into account several indicators of COPD prognosis is the BODE index (*b*ody mass index [BMI], *o*bstructive ventilatory defect severity, *d*yspnea severity, and *e*xercise capacity).[26] See Table 42-4 for calculation of the BODE prognostic score. The components are derived from measures of the BMI (weight in kg/height m^2), FEV_1 percent predicted, and the modified Medical Research Council dyspnea score (Table 42-3). A BODE score greater than 7 is associated with a 30% 2-year mortality; whereas a score of 5 to 6 is associated with 15% 2-year mortality. If the BODE score is less than 5, the 2-year mortality is less than 10%. In settings where the 6-minute



Patient category	Characteristics	Spirometric classification	Exacerbations per year	mMRC	CAT
A	Low risk, Less symptoms	GOLD 1–2	≤1	0–1	<10
B	Low risk, More symptoms	GOLD 1–2	≤1	≥2	≥10
C	High risk, Less symptoms	GOLD 3–4	≥2	0–1	<10
D	High risk, More symptoms	GOLD 3–4	≥2	≥2	≥10

Figure 42-2 Combined COPD assessment. An understanding of the impact of COPD on an individual patient combines assessment of symptoms and future risk of exacerbation. To use this figure, first assess symptoms with the modified medical research council (mMRC) or COPD assessment test (CAT) scale and determine if the patient has less symptoms (mMRC <2 or CAT <10) or more symptoms (mMRC ≥2 or CAT ≥10). Next, assess the risk of future exacerbation by determining prior exacerbation history and severity of airflow limitation with high risk of future exacerbation in individuals with GOLD airflow classification 3 to 4 or ≥2 exacerbations in the prior year (future risk should be determined by the method indicating higher risk). With this figure, individuals are stratified into one of four categories (A, B, C, D). which helps describe the burden of disease and informs potential treatments. *(Reproduced with permission from Global Strategy for the Diagnosis, Management, Prevention of COPD, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.org.)*

walk test is not available, the ADO index (*a*ge, *d*yspnea and *o*bstruction) also provides useful prognostic information (Table 42-5).[27] The ADO index ranges from 0 to 10 points, with each point increase in the index associated with a 42% increase in odds of death at 3 years for patients with longstanding and severe COPD.

TREATMENT OF STABLE COPD

The goals of treatment of COPD are to prevent progression and complications of the disease, relieve symptoms, improve exercise capacity, improve quality of life, treat exacerbations, and improve survival.[28,29] Efforts are being made to standardize the most optimal treatment guidelines for COPD.[30]

■ EDUCATION

The diagnosis of COPD can be a life-changing event for people, so understanding the nature and prognosis of the disease is an important and underemphasized aspect of care. There is a wide divergence of understanding of the implications of having COPD, and many patients do not understand that COPD comprises both the diagnoses of emphysema and chronic bronchitis. Table 42-6 lists

TABLE 42-4 Calculation of the BODE Index[a]

Variable	Points on the BODE Index 0	1	2	3
FEV_1 (% predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
mMRC dyspnea scale	0–1	2	3	4
Body mass index (kg/m^2)	>21	<=21		

[a]*The BODE index is calculated as the sum of points from each row.*
Source: Adapted with permission from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–1012.

TABLE 42-5 Calculation of the ADO Index[a]

Variable	Points on the ADO Index 0	1	2	3	4	5
FEV_1 (% predicted)	≥65	36–64	≤35	–	–	–
mMRC dyspnea scale	0–1	2	3	4	–	–
Age (yr)	40–49	50–59	60–69	70–79	80–89	≥90

[a]*The ADO index is calculated as the sum of points from each row.*
Source: Adapted with permission from Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet. 2009;374(9691):704–711.

TABLE 42-6 Patient Education Topics for Office Management of COPD

Risk factors for COPD
Smoking cessation advice and instruction
Reduction of noxious environmental exposures
Immunization for influenza and pneumococcus
Respiratory hygiene and avoidance of infections
Nature and prognosis of COPD
Indications, dose, benefits, and adverse effects of medications
Proper inhaler and nebulizer use
Strategies to improve adherence with prescribed treatment
Pacing, arm support, and other strategies to minimize dyspnea
Importance of regular exercise and social interaction
Options for pulmonary rehabilitation programs
Recognition and early treatment of exacerbations
Indications for and proper use of supplemental oxygen
Options for surgical management if indicated
Advanced directives for end-of-life care

topics that should be discussed with COPD patients. It is neither possible nor effective to cover all of these topics in a single session, so several sessions with repetition and expansion of the educational messages are necessary. Supplemental written materials or referral to a health educator is also necessary for many patients. Local and national volunteer health organizations provide useful educational materials and group educational sessions (e.g., www.copdfoundation.org, www.lung.org). Special counseling is needed for patients with α_1-antitrypsin deficiency and their family members to determine whether genetic testing is necessary or desired. In patients with advanced disease, discussions about end-of-life planning and advance directives regarding life support are often welcomed by patients and initiate discussions between the patient and family. Patients should be encouraged to discuss information that they obtain from newspapers or the Internet, as some may be instructive, but others are incorrect. Physicians should be prepared to deal with patients' sense of guilt, as many view COPD as a self-induced disease. Caregivers need to address the reality that COPD is often stigmatized by patients, their families, and other healthcare providers. The physician should let the patient understand that nicotine dependence is a strong physical addiction and difficulty quitting smoking is not a measure of moral weakness or lack of will. The general message provided should be realistic, but positive. Current treatments for COPD can usually improve quality of life, restore activity levels, maintain social interactions, and reduce the frequency of complications.

PREVENTION OF COPD PROGRESSION AND COMPLICATIONS

Presently, there are no proven treatments that prevent the progression of COPD in patients who continue to smoke cigarettes. *Smoking cessation*, however, does prevent the excessive decline in lung function and should be a primary goal for physicians caring for COPD patients. Patients with mild or moderate COPD may not know that they have underlying lung disease that can be halted by smoking cessation,[4] or may adopt a fatalistic attitude that it is too late for help. Even severely impaired patients who are dyspneic at rest or use continuous oxygen may continue to smoke cigarettes or relapse after quitting. A smoking history should be obtained at each patient encounter because many patients fail to volunteer the extent of their smoking or report a smoking relapse following cessation. In patients who do smoke, achieving cessation should be a primary and persistent goal of treatment.[31] Approaches to smoking cessation are given in detail in Chapter 41. For patients who do smoke, a direct, unambiguous, and personalized smoking cessation message should be given by the physician. The message should emphasize the harm of continued smoking, the benefits of cessation in terms of activities that are meaningful for the individual, and the understanding that smoking cessation is a realistic and achievable goal. Techniques of motivational interviewing are readily learned and are effective in changing health behaviors.[32] Assistance with pharmacologic adjuncts such as nicotine replacement therapy, varenicline, or bupropion and referral to smoking cessation groups should be offered. Follow-up of smoking status and repeated smoking cessation messages should be performed at each encounter.

Exposure to respiratory irritants should be avoided in the workplace as well as the home. Although heavy occupational dust exposure rarely is the primary cause of COPD, exposure to dusty occupational jobs in smokers can increase the lung function deterioration from smoking and increase symptoms of cough and sputum.[33] In developing countries, heavy exposure to particulates from burning of biomass fuels is associated with COPD, even in the absence of cigarette smoking.[34] Efforts to improve indoor air quality may be effective in reducing symptoms and disease progression. Respiratory protective equipment should be worn by COPD patients exposed to heavy dust concentrations. There is no level of FEV_1 that absolutely prohibits the use of respiratory protective equipment, but patients with COPD often experience untoward breathlessness with these masks because of the increased dead space and increased inspiratory resistance. Thus, many COPD patients need to change their work environment if they cannot tolerate protective devices. If COPD is complicated by allergy or overlaps with allergic asthma, environmental control measures should be instituted to the extent that these strategies are helpful. Smoking of marijuana and cocaine may cause airway irritation, and although there is no convincing evidence that they contribute to progression of COPD, their use ought to be discouraged.[35]

Pneumococcal vaccination is recommended, although the evidence of its particular efficacy in COPD is lacking.[36] Annual *influenza immunization* can prevent or attenuate this potentially fatal infection. The killed vaccine is preferred, as cold-attenuated live influenza vaccines have not been approved for use in older patients and those with underlying lung disease. High-potency influenza immunization is recommended for older patients who may have an impaired immune response to the vaccine. During influenza epidemics, the use of neuraminidase inhibitors such as zanamivir and oseltamivir can minimize severity of infection if taken within 48 hours of onset of illness and are useful against both influenza A and B, and may limit the spread of infection. Peramivir, an injectable form of neuraminidase inhibitor, is now available for treatment of individuals with respiratory failure.

Replacement therapy with α_1-antitrypsin should be considered for those individuals with severe deficiency. Observational studies suggest that individuals with moderate degrees of impairment (FEV_1 35%–65% predicted) appear to benefit most in terms of preservation of lung function and improved survival.[37] The human plasma–derived preparation of α_1-antitrypsin is administered intravenously in a dose of 60 mg/kg weekly. Although the replacement treatment is derived from pooled human plasma, the risk of viral transmission is low and immunization for hepatitis B is not mandatory before initiating therapy.

DRUG THERAPY

Over the past several decades, the evidence base for use of drug therapy in COPD has expanded, and provides an objective and generally optimistic picture that such treatment is effective. Bronchodilators and anti-inflammatory agents are used to reverse bronchoconstriction, improve lung function, improve quality of life, exercise capacity, and prevent exacerbations. Recent evidence however suggests that a

combination of inhaled steroids and long-acting bronchodilators may improve survival as well as reduce exacerbations.[38–40] Proposed future drug treatments that might alter progression of COPD are under active investigation, including inhibitors of cytokines, proteases, and oxidative stress. There is a poor correlation between the effect of bronchodilating drugs on lung function and symptom relief, so monitoring of treatment requires attention to patient-centered outcomes as well as lung function. Small amounts of bronchodilation can cause considerable improvement in functional capacity through decrease in dynamic exercise hyperinflation; and reduction in days of exacerbation can make considerable improvement in patients' quality of life.

The usual approach to drug treatment for COPD is to sequentially add agents using the minimum number of agents and the most convenient dosing schedule, starting with the agents having the greatest benefit, best tolerance, and lowest cost. One approach to step-up therapy is provided in Figure 42-3. Inhaled bronchodilators are the foundation of treatment for COPD. They are given on a regular basis to maintain bronchodilation and on an as needed basis for relief of symptoms.[41,42] Most breathless patients benefit from regular use of a maintenance bronchodilator. Both β-agonist and anticholinergic classes are available in short-duration (4–6 hours) and long-duration (12–24 hours) forms (Table 42-7). The choice of bronchodilator class and duration of effect depends upon the preference of the patient and the cost of the preparation. Combination of different classes of bronchodilators is often more effective than increasing the dose of a single agent, and combination inhalers can simplify treatment regimens. Patients with advanced COPD often use a combination of bronchodilators, including long-acting maintenance anticholinergics and β-agonists as well as symptomatic use of shorter-acting bronchodilators. Individuals with exacerbations may benefit from a combination inhaler of corticosteroids and long-acting bronchodilator. Long-acting oral preparations of theophylline are useful adjuncts in cases in which inhaled medication is too expensive or not acceptable for the patient. Chronic use of systemic corticosteroids should be reserved for individuals with very frequent or life-threatening exacerbations in those cases where discontinuation of steroids

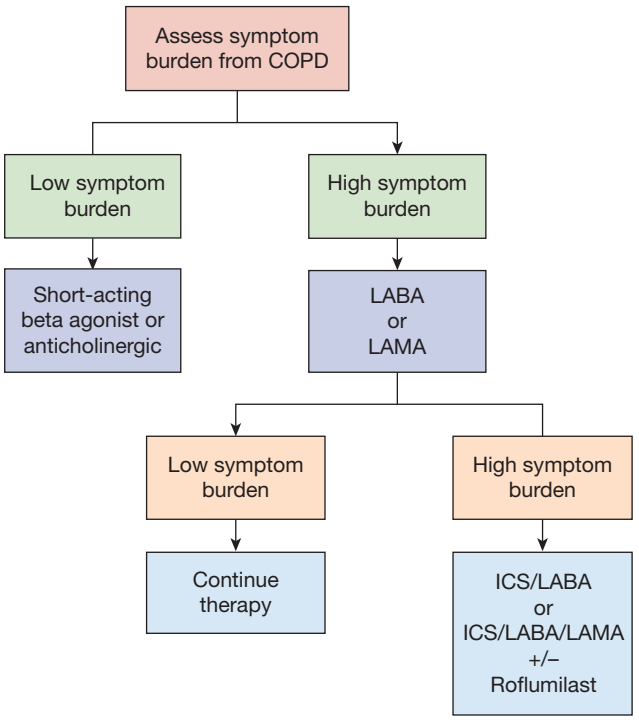


Figure 42-3 Decision tree for pharmacologic treatment of COPD. Treatments are determined by symptom burden, which is determined by assessment of dyspnea and COPD exacerbation risk. If patients are stable for 6 to 12 months, consideration should be given to trial reductions of treatment. In addition to pharmacologic interventions described here, treatment should also include preventative measures, smoking cessation counseling, pulmonary rehabilitation, and advanced therapies. LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

TABLE 42-7 Inhaled Bronchodilators

Drug Name	Dosage/Frequency	Formulation
β-Sympathomimetics		
Olodaterol		Soft Mist inhaler, 5 μg
Albuterol	2 inhalations q4–6h	Metered-dose inhaler, 90 μg/puff
	3 mL nebulized q4–6h	Nebulized solution 1.25–2.5 mg/3 mL
Levalbuterol	2 inhalations q4–6h	Metered-dose inhaler, 45 μg/puff
	3 mL nebulized TID	Nebulized solution 0.63–1.25 mg/3 mL
Salmeterol	1 inhalation BID	Dry powder inhaler, 50 μg/dose
Formoterol	1 capsule inhaled BID	Dry powder inhaler, 12 μg/capsule
	2 mL nebulized BID	Nebulized solution 20 μg/2 mL
Arformoterol	2 mL nebulized BID	Nebulized solution 15 μg/2 mL
Indacaterol	1 capsule daily	Dry powder inhaler, 75 μg/capsule
Anticholinergic Bronchodilators		
Ipratropium	2 puffs q4–6h	Metered-dose inhaler, 17 μg/puff
	2.5 mL nebulized q6–8h	Nebulized solution 0.5 mg/2.5 mL
Tiotropium	1 inhalation daily	Dry powder inhaler 18 μg/dose
Aclidinium	1 inhalation BID	Dry powder inhaler 400 μg/dose
Combination Therapies		
Ipratropium/albuterol	1 puff q6h	Soft Mist inhaler, 20 μg ipratropium and 100 μg albuterol
Umeclidinium/vilanterol		Dry powder inhaler, 62.5 μg/25 μg

cannot be tolerated. Response to treatment is judged by symptomatic improvement, functional status, frequency of exacerbations, and spirometry. If patients are doing well for 6 to 12 months on a stable treatment regimen, then it is reasonable to see if a trial withdrawal of one of the drug components can be tolerated.

Inhaled corticosteroids do not effectively alter the progression of COPD in those who continue to smoke. Inhaled corticosteroids are most useful in patients who have an overlap between asthma and COPD and those who have frequent exacerbations. Inhaled corticosteroids can reduce the frequency of exacerbations and slow the decline in quality of life.[39] In patients with chronic bronchitis and obstructive lung disease, inhaled corticosteroids improve pulmonary function, and the results are additive to those achieved with long-acting bronchodilators.[39,43] The efficacy of inhaled corticosteroids cannot be predicted based on the response to oral corticosteroids, so it is not necessary to conduct an oral steroid trial before initiating this treatment. Combined corticosteroid and long-acting bronchodilator inhalers are available in the United States and throughout the rest of the world and can simplify the treatment regimen. Inhaled corticosteroids, although poorly absorbed, probably do contribute to steroid side effects such as cataracts, capillary fragility, and osteoporosis in susceptible individuals. High doses of inhaled corticosteroids are associated with increased risk of pneumonia.[44] In most cases, the risk is low compared to the benefit of treatment, but it is prudent to prescribe the lowest effective dose. In patients who are at risk for osteoporosis (i.e., older age, cigarette smoking, low exercise) as most patients with COPD are, it is prudent to recommend prophylactic treatment such as calcium supplements and vitamin D. In those with established osteoporosis, bisphosphonates are advised. Monitoring for osteoporosis with DEXA bone scans is guided by the overall clinical situation and is not required for all patients using inhaled corticosteroids.

Adverse effects of inhaled therapy can occur. Inhaled anticholinergic agents are generally very safe. They may lead to an increased frequency of supraventricular arrhythmias, acute urinary retention in those with bladder outlet obstruction, or acute narrow-angle glaucoma if sprayed in the eye. β-Agonists, both short acting and long acting, may lead to side effects such as tremor, tachycardia, or hypokalemia.

Inhaled agents are administered by metered-dose inhaler (MDI), dry powder inhaler (DPI), or as a nebulized solution. The selection of route of administration is made by cost and convenience of the device because all are similarly effective if used properly. Many patients find that it is difficult to coordinate an MDI, and addition of a spacer device is helpful. There are many forms of DPI, some more intuitive to use than others, so specific instruction and demonstration is required by most patients. Nebulizers are easier for patients to coordinate, but each treatment takes longer to complete, and they require additional effort to maintain cleanliness. Although nebulized medications are more expensive overall, the cost of the medication is often covered by insurance, so many patients prefer nebulizers for financial considerations.

Adherence with inhaled medication, particularly when it does not provide immediate symptom relief is poor. Typically about half of patients do not take their medication in the dose or quantity prescribed. Reasons for this include a lack of understanding of the role of the medication, failure of the medication to provide meaningful benefit, complexity of the treatment program, and expense of the treatment. Many patients do not want to confide poor adherence to their physician, so it is important for the physician to ascertain this information in a way that does not interfere with the relationship with the patient. For example, a physician could inquire, "It is often difficult for patients to remember to take all of their medications. Has this been a problem for you?" or "Are you able to afford all your medication?" or "Do you think that your medicines are working for you?" If nonadherence is a problem, the treating physician can undertake actions to improve adherence, such as simplification of the medication program, education about the benefits of treatment, linking drug use to established habits such as meals or tooth brushing, or prescribing less costly drugs.

Proper use of MDIs is difficult for many patients to learn and retain. Repeated review and training of patients in MDI use is an important component of treatment of COPD and asthma. The inhaler should be held about 4 cm from the mouth to minimize deposition of larger droplets in the mouth. The patient should exhale to FRC and take a slow inhalation to TLC over about 5 seconds. The slow inhalation diminishes impaction of particles in the mouth and larynx. At the initiation of inspiration the patient should actuate the MDI one time. After full inspiration, the patient should hold the breath for about 10 seconds to permit settling of particles in the distal airspaces. If the patient finds that hoarseness or mouth irritation occurs with inhaler use, this can often be corrected by use of a spacer, slowing the rate of inspiration, and rinsing the mouth after each inhaler use. Although waiting a period of time between inhalations or between different MDIs is sometimes recommended for optimal effect, the benefit is small compared with the inconvenience and risk of worsening adherence. Therefore, it is usually appropriate to permit the patient to take additional inhalations as soon as he or she has rested a few seconds.

If the patient has difficulty coordinating the actuation of the MDI with inspiration, a spacer device or holding chamber can be used. This device is placed directly in the mouth and the MDI can be actuated prior to inspiration. DPIs usually require less coordination than MDIs, but there are many different devices, some rather complicated to use. Very frail patients may not have adequate inspiratory flow to effectively use a DPI. Therefore, each device requires individual instruction and review of technique. (For a compendium of patient instructions, see http://www.ginasthma.com/OtherResources.asp.)

Theophylline is taken as a long-acting oral preparation once or twice daily. Although it is possible to monitor blood levels, because the drug is protein bound there is a poor correlation between efficacy or adverse effects and serum levels. Theophylline is a bronchodilator; it improves arterial oxygenation and exercise tolerance.[45] If typical side effects such as nausea, vomiting, tremor, or tachyarrhythmias occur, the dose should be adjusted irrespective of serum levels. Prescriptions for theophylline to treat COPD have diminished in recent years because of the availability of long-acting inhaled agents. However, theophylline is still an effective second-line drug for patients who show benefit or prefer inexpensive oral medications. Theophylline has other putative pharmacologic actions that might be beneficial for the COPD patient: improvement in diaphragm contractility, prevention of respiratory muscle fatigue, increased ventilatory drive, potentiation of catecholamine function, prevention of microvascular permeability, increased mucociliary clearance, prevention of late-phase antigen responses, inhibition of mast cell histamine release, and suppression of leukocyte activation. Evidence has suggested that the anti-inflammatory effect of theophylline is mediated by augmentation of steroid effects through activation of histone deacetylase (HDAC), an effect that is of particular importance in COPD patients who have lower HDAC activity.[46]

Roflumilast is a more specific inhibitor of phosphodiesterase-4, which is a mild bronchodilator with anti-inflammatory properties. It is marketed in the United States for reduction of exacerbations of COPD in individuals with chronic bronchitis.[47]

Oral corticosteroids are effective for treatment of COPD exacerbations. About 10% to 20% of chronic symptomatic patients show substantial short-term improvement in pulmonary function, but it is not possible to identify these patients based on clinical characteristics alone. Because of the well-defined long-term adverse effects of systemic corticosteroids, and the ill-defined long-term benefits, most patients should not be maintained on long-term oral or systemic corticosteroids. Patients with COPD who are on

chronic corticosteroids can most often taper the dose at the equivalent of 5 mg of prednisone per week, and exclusively reserve their use for exacerbations. Long-term low doses of oral corticosteroids are occasionally needed by patients who cannot afford or tolerate inhaled agents, and who suffer frequent exacerbations. Patients on long-term systemic steroids should receive prophylaxis for osteoporosis with calcium and vitamin D or bisphosphonates, and should be instructed about the need for stress-dose steroids for acute illnesses.

Long-term macrolide antibiotics should be used sparingly in patients with COPD who do not have symptomatic bronchiectasis. Macrolides, which have immunomodulatory properties, have been demonstrated to reduce the frequency of exacerbations in patients susceptible to frequent exacerbations.[48] Thus, the use of long-term antibiotics may have a role in those susceptible to frequent, severe exacerbations.

Mucolytic agents to control mucus hypersecretion with the use of expectorants and physical means such as high-frequency chest wall oscillation is not of proven benefit in improving lung function, although symptoms are sometimes improved. N-acetylcysteine is a mucolytic with antioxidant properties does not prevent exacerbations, nor does it alter the decline in FEV_1. The role of antioxidant mucolytics such as N-acetylcysteine or carbocysteine is unclear but may have a role in reducing exacerbations.[49,50]

Opiates can be effective in the management of severe dyspnea related to COPD. Given differential response to these therapies, as well as the associated potential for respiratory depression, short acting and low-dose preparations should be initially used. While typically associated with severe, end-stage management in the hospice setting, short-acting opiates can be considered in patients with less severe lung impairment but symptomatic dyspnea refractory to pharmacotherapy, oxygen supplementation, and rehabilitation.

EXERCISE AND REHABILITATION

Regular prudent self-directed exercise is recommended for all individuals with COPD to prevent the muscle deconditioning that often accompanies the disorder. Individuals should be encouraged to perform at least 20 to 30 minutes of constant low-intensity aerobic exercise such as walking at least three times per week. Even the most severely impaired patients with COPD can usually attain an exercise regimen of 30 minutes of walking at 1 mph (i.e., one-half mile in 30 minutes). It is important to instruct patients that they should exercise to a level of dyspnea that is tolerable for the entire exercise period. Patients should understand that dyspnea, by itself, is not injurious to the heart or lungs, but patients should pace themselves to avoid severe dyspnea that disrupts activity, can lead to panic reactions, and is distressing to onlookers. Patients who demonstrate desaturation with exertion may be prescribed supplemental oxygen for exercise. Some may benefit in terms of exercise capacity and training effect even if they do not have demonstrable oxygen desaturation.[51] Many patients, particularly those with marked hyperinflation, find that they can ambulate better with the use of a rolling walker that supports the arms, improving the mechanical advantage of the accessory muscles in the neck.

Formal rehabilitation programs offer a comprehensive approach to exercise training, patient education, nutritional counseling, group support, and psychological support that cannot be efficiently provided in the physician's office. Rehabilitation programs are established as an effective component of COPD management and should be offered to patients who have substantial limitation in daily activities. A detailed discussion of rehabilitation is provided in Chapter 43.

NUTRITIONAL SUPPORT

In patients with very severe COPD (FEV_1 less than 35% predicted) about half show protein–calorie malnutrition.[52] Reasons for this include increased resting metabolic demands, inadequate caloric intake due to dyspnea and anorexia, and possibly elaboration of cachexia-associated inflammatory cytokines such as TNF-α, IL-1, and IL-6. Patients with a BMI of less than 90% of normal have increased mortality and decreased exercise capacity. Muscle wasting and loss of bone mass may be present even in patients who have normal BMI.[53] Although clinical trials of nutritional supplementation have been disappointing, it is prudent to monitor body weight in COPD patients and encourage caloric supplementation as needed since those patients who do gain weight show improved survival.[54] High-fat diets have the theoretical advantage of offering higher caloric content with lower CO_2 production than high carbohydrate diets, but there is no convincing evidence that this strategy is clinically superior to a well-balanced diet. For patients with less advanced disease, a balanced diet with avoidance of overweight or underweight is a rational goal. In particular, patients with mild to moderate disease who quit smoking tend to gain excessive weight, which might adversely affect lung function.[55]

SLEEP DISORDERS IN COPD

Sleep disturbances, including insomnia and daytime hypersomnolence, are common symptoms in patients with COPD,[56,57] and are often overlooked because of the focus on breathlessness and exercise intolerance. The causes for sleep symptoms are multifactorial and include anxiety, depression, resting hypoxemia, nocturnal bronchospasm, sleep apnea, and nocturnal oxygen desaturation (NOD). Patients with COPD often relate insomnia to a fear of suffocation or death during sleep, a situation that may respond to repeated reassurance, cognitive therapy, or small doses of anxiolytics or antidepressants. Patients with resting hypoxemia treated with low-flow nasal oxygen often report improved sleep quality. Nocturnal bronchospasm, more common among those with an asthmatic component to their disease, may respond to longer-acting bronchodilators, or rearrangement of the dosing schedule to provide nocturnal coverage. In some cases, treatment for gastroesophageal reflux by elevation of the head of the bed and prescription of acid suppressant drugs can help. Sleep apnea syndrome, probably not more common in COPD patients than the general community, has particularly severe complications in COPD. Patients with COPD and sleep apnea, the so-called "overlap syndrome" are prone to develop pulmonary hypertension and daytime hypercapnia.[58] Accordingly, symptoms of sleep apnea such as snoring, intermittent nocturnal breathing, and daytime hypersomnolence should be sought in patients with COPD. If present, then formal sleep studies and treatment with continuous positive airway pressure (CPAP) are indicated. NOD is common during rapid eye movement sleep in patients with COPD. The causes are not entirely understood, but contributing factors include hypoventilation, ventilation–perfusion mismatch, respiratory muscle dysfunction, and increases in upper airway resistance. NOD is thought to be associated with poorer sleep quality and pulmonary hypertension. It is controversial whether NOD is associated with poorer survival. However, small studies have shown inconclusive results about the utility of treating NOD.

Current guidelines do not recommend that all patients with COPD have nocturnal oxygen monitoring, nor do they recommend treatment with supplemental oxygen or nocturnal ventilation if NOD is found. Many physicians, though, will prescribe these diagnostic studies and treatments for selected symptomatic patients, and most insurance companies will provide reimbursement for such treatment. Patients who have resting room air daytime hypoxemia should be prescribed nocturnal oxygen at the same flow rate as used during the day, and it is usually not necessary to monitor nocturnal oxygen saturation in such patients.

MANAGEMENT OF DEPRESSION

Depression is a common comorbidity in individuals with COPD. The recognition and treatment of depression is important as this comorbidity is associated with poorer prognosis, increased risk of

exacerbations, and poor health status. While there is little evidence to suggest that depression should be treated differently in COPD patients, pulmonary rehabilitation has been shown to reduce depression with COPD.

AIR TRAVEL

Patients with COPD should not avoid air travel, but must be aware of the medical and regulatory issues that are involved.[59] Modern airplanes are pressurized to an equivalent altitude of approximately 5000 to 8000 ft, but may, on occasion, pressurize to an equivalent altitude of 10,000 ft without providing emergency oxygen. Many patients with COPD who do not use sea-level oxygen can tolerate short flights without supplemental oxygen. As flight distance becomes longer, the flying altitude becomes higher and the cabin pressure becomes lower, so transcontinental or transoceanic flights should prompt medical advice. The general rule of thumb used by the commercial airline industry is that patients who can ambulate 50 m without stopping are safe for air travel. A more conservative approach is to estimate the Pa_{O_2} during air travel by performing a high altitude simulation test. High altitude simulation can be performed by administering 15% oxygen via a face mask or by using 100% nitrogen in a 40% Venturi mask.[60] If the oxygen saturation falls below 86% or 50 mm Hg, then supplemental oxygen is recommended. Formulas are available to estimate altitude hypoxemia from sea-level room-air blood gases. Figure 42-4 provides a nomogram for estimating altitude Pa_{O_2} from sea-level room-air arterial oxygen tensions.[61] If estimated altitude Pa_{O_2} is used, it is prudent to prescribe oxygen for estimated altitude Pa_{O_2} of 54 mm Hg or lower. Patients who use oxygen supplementation at sea level should increase their resting oxygen prescription by a flow rate of 2 L/min. For patients with COPD who travel by air frequently, low-cost finger pulse-oximeters that are marketed to airplane pilots can be used to adjust their oxygen flow.

Airlines have inconsistent policies with respect to providing supplemental oxygen for travelers, so it is important to check with the airline service desk before booking travel. The United States Federal Aviation Administration has promulgated regulations that permit some approved portable oxygen concentrators to be carried on board by passengers as personal luggage with a physician's statement of need. These may be rented from oxygen supply companies or specialized websites.

LONG-TERM OXYGEN THERAPY

In addition to smoking intervention in early COPD, treatment of resting daytime hypoxemia with oxygen is a treatment that prolongs survival.[62–64] The two strongest indications for prescription of long-term oxygen therapy are (1) resting room-air Pa_{O_2} ≤55 mm Hg or oxygen saturation ≤88% while a person is in usual state of health; and (2) resting room-air Pa_{O_2} 56 to 60 mm Hg or oxygen saturation 88% to 89% with supporting evidence of chronic hypoxemia such as polycythemia, pulmonary hypertension, cor pulmonale, or psychological impairment. Oxygen is usually administered by nasal cannula, with the flow rate adjusted to maintain a resting saturation greater than 90%. The usual starting flow rate is 2 L/min, although some patients with severe hypercapnia require lower flows. A few patients, particularly those with concomitant interstitial pulmonary disease or cardiac disorders, require higher flow rates.

The most convenient and cost-effective oxygen source at home is usually a concentrator device that uses a molecular sieve to extract oxygen from room air. For ambulation, small compressed air cylinders, portable concentrators, or liquid oxygen reservoirs that can be carried provide patients with the ability to leave their homes. Conserving devices such as reservoirs or demand valves permit portable ambulatory oxygen tanks to last up to 10 hours. Compressed oxygen cylinders or liquid oxygen reservoirs should be provided to patients who use electrically driven oxygen concentrators for emergency use in the event of a power failure. Ideally, oxygen should be used constantly 24 hours per day. At least 18 hours of oxygen per day, however, has been shown to have substantial benefit over 12 hours per day. If continuous oxygen supplementation is prescribed following an exacerbation of COPD, it is recommended to check arterial oxygen levels in 6 weeks, as many patients will no longer require oxygen.

Nasal drying or congestion is a common symptom for those who use continuous oxygen. This may be alleviated to some extent by alternating the nasal cannula from one nostril to the other or placing it in the mouth for periods. Copious watery nasal secretions often respond well to ipratropium nasal spray, and dry, crusted nasal mucosa is treated with hourly instillations of saline nasal spray.

Smoking or exposure to any open flame is prohibited by the danger of fire and airway burns in those who use oxygen. This is a surprisingly common cause of burns in the United States, with estimates that up to 50% of patients on oxygen continue to smoke to some extent.[65] Accordingly, it is safer to counsel patients to discontinue oxygen while smoking or cooking over an open flame if they insist on doing these activities. Patients at particular risk are those who live alone, have cognitive impairment, and do not have functioning smoke detectors.

Oxygen delivery via a transtracheal catheter is an option for selected patients who cannot tolerate other oxygen delivery methods, and who can attend to the regular maintenance of the catheter. High-flow humidified nasal cannulas are also an option for individuals who need high concentrations of oxygen but who cannot tolerate a facemask.

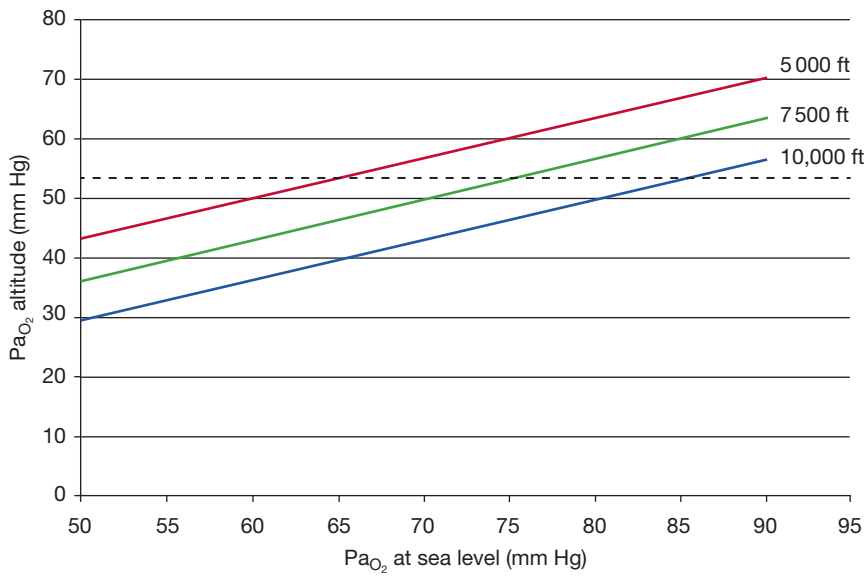


Figure 42-4 Estimated Pa_{O_2} at altitude based on resting sea-level arterial oxygen tension. Isopleths are drawn for the range of cabin pressures that occur on commercial aircraft. The dashed line is drawn at 54 mm Hg, which indicates a threshold for prescribing supplemental oxygen for air travel. *(Data of Gong H Jr, Tashkin DP, Lee EY, et al. Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. Am Rev Respir Dis. 1984;130:980–986.)*

Ambulatory oxygen, although not shown to improve survival, may be provided for patients who desaturate with exertion. Some, but not all, patients show improved exercise capacity and reduced breathlessness. There is a growing body of evidence that suggests that oxygen supplementation may also benefit COPD patients who do not have exercise desaturation by reduction in minute ventilation and diminution of dynamic hyperinflation.[51] Because it permits greater exercise intensity, oxygen supplementation is also a useful adjunct for aerobic conditioning during pulmonary rehabilitation.

COMPLICATIONS

COPD EXACERBATIONS

Exacerbations are characterized by worsening cough, dyspnea, and sputum production beyond normal day-to-day variation. These exacerbations are associated with acute deterioration of lung function during the exacerbation and may also accelerate the longitudinal loss of lung function. Acute exacerbations of COPD are a major cause of hospitalization, healthcare costs, morbidity, and mortality in COPD. Exacerbations have been associated with respiratory viral infections including rhinovirus, respiratory syncytial virus, influenza, adenovirus, and metapneumovirus. Bacterial infections or superinfections are also associated with COPD exacerbations. The most frequent pathogens are *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptoccous pneumoniae*. In patients who have been treated with antibiotics, gram-negative bacteria may also be present. Severe air pollution, especially particulates, sulfur dioxide, ozone, and nitrogen dioxide have been associated with elevated risk for hospitalization due to COPD. On average, patients with COPD have two to three exacerbations per year, but there is wide variation, and the frequency of exacerbations is only roughly correlated with severity of airflow obstruction. The best predictor of future exacerbations is a past history of frequent exacerbations,[66] and these are more common in patients with chronic cough and sputum production. Only half of COPD exacerbations come to the attention of treating physicians, and many of these eventually resolve without specific treatment. The management of these exacerbations depends upon the severity. Indications for hospital evaluation or hospitalization are listed in Table 42-8. Arterial blood gas studies and chest radiographs are useful for evaluating etiology and severity of acutely ill patients. Spirometry during the acute exacerbation is usually not helpful in predicting the severity or duration of the exacerbation.

For patients treated at home, increasing the frequency and intensity of inhaled short-acting bronchodilators for several days is effective in mild exacerbations. A hand-held inhaler and spacer are usually effective, but a nebulizer may be needed for those who cannot coordinate well or who have severe dyspnea. Increasing dyspnea accompanied by a change in the quantity or color of phlegm is usually an indication of bacterial infection and should prompt initiation of antibiotics. The choice of antibiotic is determined by severity of the underlying disease, resistance patterns of likely pathogens, and likelihood of treatment failure (Table 42-9). After initiation of therapy, the antibiotic treatment should be tailored based on sputum cultures.

A course of corticosteroids, equivalent to 30 to 60 mg of prednisone for 7 to 14 days, will shorten the duration of symptoms for patients with exacerbations managed as outpatients.[67,68]

For patients admitted to the hospital, intensification of inhaled bronchodilator treatment, systemic corticosteroids, and antibiotics are administered.[69] Controlled oxygen supplementation should be provided at the lowest level needed to reverse hypoxemia and minimize the induction of hypercapnia. The selection of the oral or intravenous route for antibiotics and corticosteroids is determined by the severity of the illness and the ability of the patient to tolerate oral medication. Evaluation for the cause of the exacerbation does not have to be extensive if it responds to initial treatment and conforms to the patient's usual exacerbation pattern. Sputum culture for resistant bacterial strains, a chest radiograph for exclusion of pneumonia and pneumothorax, and an electrocardiogram for exclusion of myocardial ischemia and arrhythmia are useful tests in all hospitalized patients. Echocardiography for assessment of ventricular function, and Doppler venous flow studies, radionuclide, or computed tomographic lung imaging for evaluation of pulmonary thromboembolism need to be performed in selected cases. Usually a 2-week course of steroids is sufficient for hospitalized patients.

Treatment in an intensive care setting should be undertaken for patients with severe exacerbations or those who require more constant attention (Table 42-8). For patients with respiratory failure,

TABLE 42-8 Indications for Hospitalization in COPD

Indications for Hospital Assessment or Admission for COPD Exacerbation
Sudden onset of new or severe symptoms (e.g., dyspnea)
Inability to sleep or eat because of dyspnea
Severe or very severe underlying COPD
Onset of new physical findings (e.g., edema, cyanosis, change in mental status)
Failure to respond to initial medical treatment
Associated comorbidities (e.g., cardiac, renal, hepatic failure, or diabetes)
Diagnostic uncertainty (e.g., suspected pneumonia or pulmonary embolism)
Unusual presenting symptoms
Older age or frailty
Inadequate home or social support
History of poor adherence with treatment
Indications for ICU Admission for COPD Exacerbation
Severe dyspnea unresponsive to initial treatment
Change in mental status (e.g., confusion, lethargy, coma)
Persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis
Need for sedation or narcotic pain control

Source: Data from 2011 GOLD COPD guidelines (www.goldcopd.com) and 2004 ATS/ERS Standards for treatment of COPD.

TABLE 42-9 Antimicrobial Treatment of COPD Exacerbations

First Line
Amoxicillin 500–875 mg PO TID
Doxycycline 100 mg PO BID
Alternatives
Amoxicillin/clavulanate 875 mg PO BID
Azithromycin 500 mg, then 250 mg PO QD × 4 d
Clarithromycin 500 mg PO BID
Second-generation cephalosporins
Severe COPD or previous antibiotics
Levofloxacin 500–750 mg PO QD × 7 d
Ciprofloxacin 500 mg PO QD × 7 d

noninvasive mask ventilation has proved to be an effective strategy to avert endotracheal intubation, shorten duration of illness, and improve outcomes.[70] Attention needs to be paid to selecting and fitting a comfortable well-sealed mask, and providing a ventilator that minimizes the patient's work of breathing and triggering effort. When noninvasive mask ventilation is not successful in sustaining ventilation, or the patient is too ill to use the mask, endotracheal intubation and mechanical ventilation are needed to treat respiratory failure. The mechanical ventilator should be set to provide minute ventilation that does not overventilate the patient and cause alkalemia, which may ultimately impede liberation from the ventilator. The inspiratory flow rates and inspiratory to expiratory time ratios should be adjusted to provide a prolonged duration of expiration to minimize dynamic hyperinflation (auto-PEEP), which can lead to dyspnea, discoordination, and barotrauma. Weaning and liberation from mechanical ventilation can be hindered by anxiety, oversedation, mucus secretions, intravascular volume overload, myocardial ischemia, or respiratory muscle deconditioning. Survival after an episode of acute respiratory failure for COPD patient with hypercarbia is about 50% at 2 years after discharge, with about half of the patients being readmitted to the hospital within 6 months.[71]

PNEUMOTHORAX

COPD is thought to be the most common cause for secondary spontaneous pneumothorax. A pneumothorax can either cause an acute symptomatic exacerbation of COPD from rupture of a bleb, or may occur during the course of an exacerbation as a consequence of hyperinflation or mechanical ventilation. Because this is a life-threatening but quickly treatable cause for worsening respiratory failure in COPD, it should always be considered in the differential diagnosis for worsening dyspnea in COPD. The physical examination can be misleading because diminished breath sounds are a component of the underlying disease. Imaging studies are usually diagnostic, but at times it can be difficult to distinguish a pneumothorax from an over-distended bulla. If the patient's clinical situation can tolerate it, imaging with inspiratory and expiratory views, or chest computed tomograms can be helpful. In the intensive care unit, upright and cross-table lateral views sometimes show mobility of the pleural air.

Urgent treatment for the patient in extremis is performed by aspirating the pleural space at the second intercostal space anteriorly in the midclavicular line. Definitive emergency treatment is placement of a thoracostomy tube, which should be done with care to avoid laceration of a bulla and creation of a bronchopleural fistula. In patients with advanced COPD, recurrence of a pneumothorax can be life-threatening, so definitive pleural sclerosis with surgical or medical thoracoscopy should be considered.

COR PULMONALE

Pulmonary hypertension and consequent right ventricular failure, *cor pulmonale*, are usually the consequence of chronic alveolar hypoxia, with secondary contributions from destruction of the alveolar capillary bed, lung hyperinflation, and increased blood viscosity.[72] Diagnosis of pulmonary hypertension and right ventricular failure can be difficult, as physical findings of venous engorgement, and right ventricular hypertrophy and dilatation are late signs. Peripheral edema is poorly correlated with resting right atrial pressure and may reflect fluid retention from activation of the renin–angiotensin–aldosterone system. Functional imaging studies including echocardiography or radionuclide ventriculography are more probative for evaluation of right ventricular function. Doppler echocardiographic measures of pulmonary artery systolic pressure correlate weakly with severity of pulmonary hypertension by right heart catheterization.[73] Once cor pulmonale is present, survival is diminished. If the pulmonary artery pressure exceeds 25 mm Hg, the average 5-year survival is diminished by 50%.[74]

The primary treatment of cor pulmonale consists of continuous oxygen to overcome hypoxemia and diuretic to optimize volume status. Calcium channel blockers and other vasodilators can dilate the pulmonary circulation, but they worsen hypoxemia and their benefit is not established. Phlebotomy increases exercise capacity when the hematocrit exceeds 55%, but persistent erythrocytosis suggests inadequate oxygen supplementation or another cause. Anticoagulation, which is considered beneficial in severe pulmonary vascular hypertension of other causes, is of uncertain benefit in patients with pulmonary hypertension caused by COPD.

SUPRAVENTRICULAR ARRHYTHMIAS

Supraventricular tachyarrhythmias are common in patients with COPD, as a consequence of right atrial enlargement, increased endogenous adrenergic tone, hypoxemia, and drug treatment—specifically theophylline and anticholinergic bronchodilators. Treatment is similar to that in nonpulmonary patients; however, the presence of COPD should not prevent evaluation for treatable causes of arrhythmias such as pulmonary embolism, hyperthyroidism, or valvular heart disease, which may be difficult to diagnose in COPD patients.

HYPERCAPNIA

Chronic hypercapnia secondary to alveolar hypoventilation can be considered an adaptive response to obstructive lung disease by decreasing the work of breathing, preventing respiratory muscle fatigue, and allowing a diminished sensation of dyspnea. The adverse effect of chronic hypercapnia is the development of alveolar hypoxia and consequent pulmonary hypertension. Accordingly, the approach to chronic hypercapnia is the use of supplemental oxygen in controlled concentrations. In patients who are very sensitive to oxygen, it is preferable to provide oxygen in controlled concentrations with Venturi masks rather than nasal cannula.

Nocturnal ventilation has been effective in reducing daytime hypercapnia in patients with neuromuscular disease and kyphoscoliosis. Short-term trials have shown divergent effects of nocturnal ventilation in patients with COPD. A 2-year controlled long-term trial of nocturnal ventilation in hypercapnic patients with COPD has shown modest improvement in symptoms and quality of life, and a trend toward reduced hospitalization, but only small improvements in daytime hypercapnia.[75] Thus, based on our current state of knowledge, long-term nocturnal ventilation ought to be reserved for selected symptomatic patients with frequent hospitalizations who can tolerate the treatment.

ADVANCED TREATMENTS

For patients who have far-advanced disease evidenced either by severe breathlessness or short life expectancy, more aggressive treatments should be considered. Undertaking these treatments requires thoughtful consideration by patients and their families, and frank discussion of the risks and benefits by the medical caregivers.

LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) is a surgical procedure that involves stapled resection of 20% to 30% of the lung bilaterally, usually from the apices. The procedure is equally safe and effective, done by median sternotomy or video-assisted thoracoscopy (VATS). The theory behind this procedure is that the remaining lung expands to fill the thorax, thereby increasing its elastic recoil pressure, which improves expiratory airflow. The reduction of lung volume permits the diaphragm to attain a more normal, domed configuration, which improves its mechanical efficiency. Moreover, the preferential removal of unventilated bullae reduces residual volume, permitting an increase in the vital capacity. While some patients show substantial

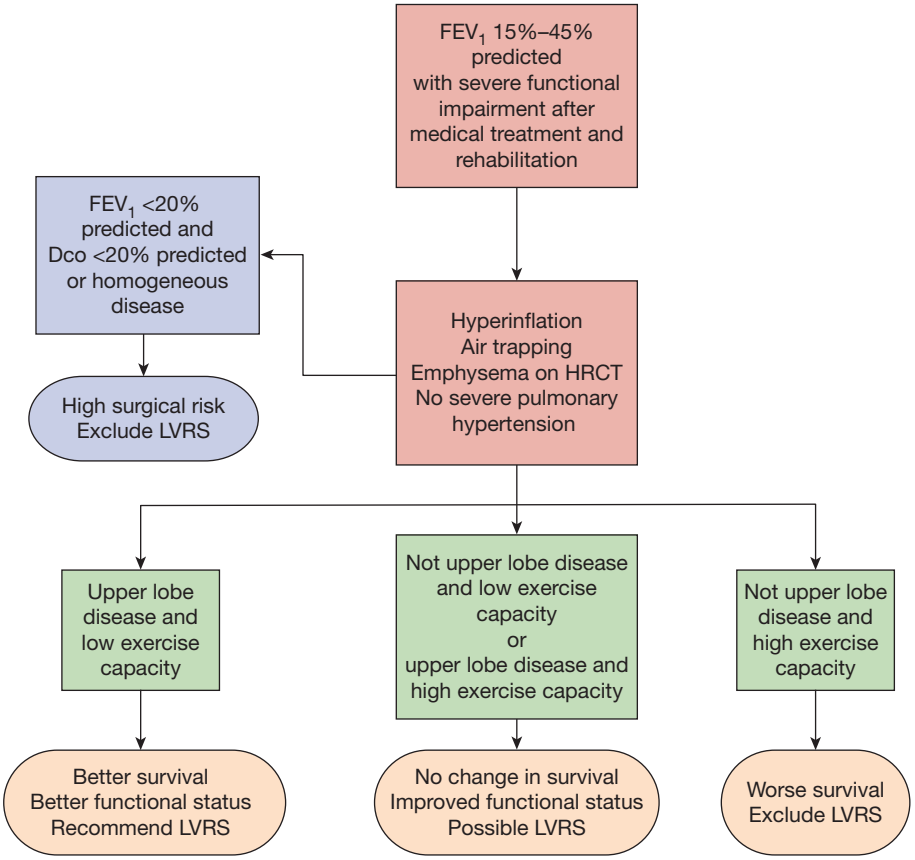


Figure 42-5 Decision tree for selection of candidates for lung volume reduction surgery (LVRS) based on distribution of emphysema on high-resolution computed tomogram (HRCT) and functional impairments.

physiological and symptomatic improvement following LVRS, many do not.[76] An algorithm for selection of patients for LVRS, based on distribution of emphysema and functional measures, is presented in Figure 42-5. Generally, LVRS should not be done on patients with an FEV_1 less than 20% predicted and either diffusing capacity less than 20% predicted or diffuse homogeneous emphysema on HRCT, because these patients have high surgical mortality. The group of patients who fare best with LVRS are those who have emphysema predominantly in the upper lung zones and low exercise capacity despite pulmonary rehabilitation. These patients have improved survival after LVRS and show improved functional status and quality of life. Conversely, patients without upper lobe predominance (i.e., lower lobe emphysema or homogeneous emphysema) and who have adequate exercise capacity after rehabilitation, have worse outcomes after LVRS. In selected cases, resection of a pulmonary nodule may be accompanied by LVRS as an attempt to improve postoperative functional status. Although LVRS was originally proposed as a temporizing measure while patients were awaiting lung transplantation, most LVRS candidates are not suitable candidates for lung transplantation. However, prior LVRS does not alter the outcome of subsequent lung transplantation.

Surgical resection of a single large bulla is rarely indicated for treatment of COPD. Isolated giant bullae are usually the result of an expanding congenital cyst. The generally accepted indication for resection of a single large bulla is that it occupies more than one-third of the hemithorax and causes compression of normal lung. Some believe that a preserved D_{CO} is an indicator of those most likely to improve following a bullectomy.

Preliminary studies with nonsurgical approaches to lung volume reduction using a variety of techniques to induce atelectasis of a target lobe are under investigation. In a study of COPD patients with severe airflow obstruction, hyperinflation and heterogeneous emphysema, placement of endobronchial valves for a bronchoscopic LVRS was associated with modest improvements in relevant clinical outcomes, although these results are balanced by an increased risk of infection and COPD exacerbation.[77,78] Selection of patients with proper anatomy appears to be important predictors of success to these nonsurgical approaches. These methods may ultimately provide an alternative approach to surgical LVRS for patients with severe COPD.

LUNG TRANSPLANTATION

In younger patients with advanced disease, lung transplantation should be a treatment consideration. Criteria for lung transplantation referral in patients with COPD are an FEV_1 below 25% predicted, BODE index greater than 5, hypercapnia, resting hypoxemia, secondary pulmonary hypertension, and accelerated decline in FEV_1 in patients under the age of 60 to 65 years.[79] For additional information see Chapter 107 (lung transplantation).

CHRONIC VENTILATOR SUPPORT

Some patients remain on long-term ventilator support following an episode of acute respiratory failure. Most often these patients are treated in a long-term ventilator unit, but some can be managed at home with adequate support. In some cases, the goal of long-term ventilator support is to provide rehabilitation via respiratory care, nutrition, and exercise to eventually be liberated from the ventilator entirely or for substantial portions of the day. In other cases, the goal of care is to provide comfort and support for terminal care without attempts at rehabilitation. Whatever the goal, a coordinated team of physicians, respiratory therapists, physical therapists, nutritionists, social workers, psychologists, and nurses are needed to undertake the care of these patients. The treatment of long-term ventilator patients differs from the treatment of acute respiratory failure in the intensive care unit. Ventilators are less sophisticated in terms of modes of ventilation and monitoring, but more portable. Ventilation is often performed with an uncuffed tracheostomy with

an air leak to avoid complications at the cuff site. Sufficiency of ventilation is judged by noninvasive measures of oxygenation and patient comfort. Narcotics in small doses are administered for relief of dyspnea. Diagnostic studies and invasive testing are performed less frequently than in critical care units. Although the care in long-term ventilator units is complex and expensive, the quality of life experienced by patients in chronic ventilator units is similar to that of patients confined to a bed-and-chair existence by other chronic maladies. The survival of COPD patients on long-term mechanical ventilation is less than those on such treatment for neuromuscular diseases, in part, because of their older age and comorbidities.[80]

CONCLUSIONS

COPD develops insidiously. However, the disease can be easily detected with simple spirometric testing before symptoms occur, and cessation of smoking can slow or even halt the disease progression and prolong survival. Once the disease is symptomatic, a coordinated, comprehensive, and individualized approach to treatment, both pharmacologic and nonpharmacologic, can increase functional status, prevent complications, and improve the quality of life. Exacerbations of COPD can range from those that are nuisances to those that are life-threatening, but treatment can shorten the duration of illness and improve outcomes. In advanced disease, treatments including surgical approaches are directed toward relief of symptoms and prolongation of survival. Thus, although there is certainly need for improvement in our treatment of symptomatic COPD, current treatments are effective and a nihilistic attitude is not warranted.

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CHAPTER 43

Rehabilitation in Chronic Obstructive Pulmonary Disease and Other Respiratory Disorders

Andrew L. Ries

Rehabilitation for patients with chronic lung diseases is well established as a means of enhancing standard pharmacologic and other therapies in controlling and alleviating symptoms and optimizing functional capacity.[1–4] The primary goal of any rehabilitation program is to restore the patient to the highest possible level of independent function. This goal is accomplished by helping patients and significant others learn more about the underlying disease, treatment options, and coping strategies. Patients are encouraged to participate actively in providing their own health care, become more independent in daily activities, and be less dependent on health professionals and expensive medical resources. Rather than addressing solely reversal of the disease process, rehabilitation focuses on improving disability from disease.

Historically, pulmonary rehabilitation strategies were developed and have been used primarily for patients with chronic obstructive pulmonary disease (COPD). However, pulmonary rehabilitation has also been applied successfully to patients with other chronic lung conditions, including interstitial diseases, cystic fibrosis, bronchiectasis, and thoracic cage abnormalities.[3,5–7] It has been used successfully in the evaluation and preparation of patients for surgery, such as lung transplantation and volume reduction lung surgery, and in maximizing recovery after surgery.[8–11] Pulmonary rehabilitation has been used to facilitate patient recovery from acute processes such as acute lung injury, or exacerbations of chronic lung disease requiring mechanical ventilation or acute hospital care. Pulmonary rehabilitation is appropriate for any patient with stable lung disease who is disabled by respiratory symptoms. Even patients with advanced disease may benefit if they are selected appropriately and realistic goals are set.

This chapter defines pulmonary rehabilitation and outlines issues related to patient selection and evaluation. Key components of a pulmonary rehabilitation program are described and results of rehabilitation programs reviewed. Finally, the role of rehabilitation prior to and following lung surgery is reviewed.

DEFINITION

In 2006, the American Thoracic Society and European Respiratory Society adopted the following definition:

> Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce healthcare costs through stabilizing or reversing systemic manifestations of the disease.[2]

This definition focuses on three important features of successful rehabilitation. First, the program is *multidisciplinary.* Pulmonary rehabilitation programs utilize expertise from various healthcare disciplines that is integrated into a comprehensive, cohesive program tailored to the needs of each patient. Second, the program is tailored to the *individual.* Patients with disabling lung disease require individual assessment of needs, individual attention, and a program designed to meet realistic individual goals. Third, the program addresses *multidimensional outcomes* that include physical, psychological, and social function as well as healthcare utilization.

The interdisciplinary team of healthcare professionals in pulmonary rehabilitation may include physicians, nurses, respiratory and physical therapists, psychologists, exercise specialists, and others with appropriate expertise. The specific team make up depends upon the resources and expertise available, but it usually includes at least one full-time staff member. Responsibilities of team members generally cross disciplines.[12]

Within this general framework, successful pulmonary rehabilitation programs have been established in both outpatient and inpatient settings and with different formats. A key to success is a dedicated, enthusiastic staff that is familiar with respiratory problems and can relate well to pulmonary patients and motivate them.

PATIENT SELECTION

Any patient with symptomatic chronic lung disease is a candidate for pulmonary rehabilitation (Table 43-1). Appropriate patients are aware of disability from their disease and are motivated to participate actively in their own care to improve their health status. Patients with mild chronic disease may not perceive their symptoms to be severe enough to warrant a comprehensive care program. On the other hand, patients with severe disease who are bed bound may be too limited to benefit greatly.

Criteria based on arbitrary lung function parameters or age alone should not be used in selecting patients.[1] Pulmonary function is not a good predictor of symptoms, function, or improvement after rehabilitation.[13] Chronic lung disease is commonly associated with systemic features that contribute to functional limitations and may benefit from rehabilitation.[14] In general, selection should be based upon a person's disability from their disease, potential for improvement, and motivation to participate actively in a comprehensive self-care program. Also, pulmonary rehabilitation is not a primary mode of therapy. Patients should be stabilized on standard medical therapy and should not have other disabling or unstable conditions that might limit their ability to participate fully in the program and to concentrate on the necessary tasks.

The ideal patient for pulmonary rehabilitation, then, is one with functional limitation from moderate to severe lung disease who is stable on standard therapy, not distracted or limited by other serious or unstable medical conditions, willing and able to learn about his or her disease, and motivated to devote the time and effort necessary to benefit from a comprehensive care program.

TABLE 43-1 Patient Selection Criteria for Pulmonary Rehabilitation

Symptomatic chronic lung disease
Stable on standard therapy
Functional limitation from disease
Relationship with primary care provider
Motivated to be actively involved in and take responsibility for own health care
No other interfering or unstable medical conditions
No arbitrary lung function or age criteria

PATIENT EVALUATION

The initial step is screening patients to ensure appropriate selection and to set realistic individual and program goals. The evaluation process includes the following components: interview, medical evaluation, psychosocial assessment, diagnostic testing, and goal setting (Table 43-2).

INTERVIEW

The screening interview is an important first step. It serves to introduce the patient to the program, review the medical history, and identify psychosocial problems and needs. Family members and significant others should be included. Communication with the primary care provider is important to establish the vital link for the rehabilitation staff to clarify medical questions prior to the program and facilitate subsequent recommendations. Care and attention in this initial evaluation helps in setting goals compatible with everyone's expectations as well as appropriate programmatic objectives.

MEDICAL EVALUATION

Reviewing medical history helps to identify the patient's lung disease and assess its severity. Other medical problems that might preclude or delay participation may be identified. Available laboratory data should be reviewed, including pulmonary function and exercise tests, rest and exercise arterial blood gas measurements, chest radiographs, electrocardiogram, and pertinent blood tests. Program

TABLE 43-2 Components of a Comprehensive Pulmonary Rehabilitation Program

Patient evaluation
Interview
Medical evaluation
Psychosocial assessment
Diagnostic testing
Pulmonary function
Exercise
Arterial blood gases/oximetry
Goal setting
Program content
Education
Respiratory and chest physiotherapy instruction
Bronchial hygiene
Breathing retraining techniques
Oxygen
Exercise
Psychosocial support

staff can then determine the need for any additional information or action before the program begins.

PSYCHOSOCIAL ASSESSMENT

Successful rehabilitation requires attention not only to the patient's physical problems but also to psychological, emotional, and social issues. Patients with chronic illnesses experience psychosocial difficulties as they struggle to deal with symptoms they may not fully understand.[15]

Neuropsychological impairment is common in patients with chronic lung diseases and cannot be accounted for solely on the basis of age, depression, or organic disease. Commonly, such patients become depressed, frightened, anxious, and more dependent on others to care for their needs. Progressive dyspnea is a frightening symptom and may lead to a vicious "fear–dyspnea" cycle: With progressive disease, less exertion results in more dyspnea, which produces more fear and anxiety, which, in turn, lead to more dyspnea. Ultimately, the patient avoids any physical activity associated with both of these unpleasant symptoms.

In addressing these problems, the initial evaluation should assess the patient's psychological state and pay attention to "psychosocial clues" that may be apparent during the screening interview (e.g., level of family and social support, the patient's living arrangement, activities of daily living, hobbies, and employment potential). Important clues in initial interviews to the patient's emotional state may be evident in nonverbal communication, such as facial expression, physical appearance, handshake, and personal space (distance between individuals when conversing). Cognitive impairment that may limit the patient's ability to participate fully in the rehabilitation program may be identified. Family members and significant others may provide valuable insight and should be included in the screening process and program whenever possible.

DIAGNOSTIC TESTING

Planning an appropriate rehabilitation program requires accurate, current information. The complexity of the testing procedures performed depends upon individual patient and program goals as well as the facilities and expertise available.

Pulmonary function testing is used to characterize lung disease and quantify impairment. Spirometry and lung volume measurements are most useful. Other tests (e.g., diffusing capacity, maximal respiratory pressures to assess muscle strength) can be added as needed.

Exercise testing helps to assess the patient's exercise tolerance and to evaluate changes in arterial blood gases (e.g., hypoxemia or hypercapnia) with exercise.[16,17] This may also uncover coexisting diseases (e.g., heart disease). The exercise test is also used to establish a safe and appropriate prescription for subsequent training.

Maximal exercise of patients with chronic lung disease is limited largely by their breathing reserve, though chronic lung diseases are increasingly recognized as being associated with systemic effects that may also contribute to exertional symptoms (e.g., muscle fatigue). Simple pulmonary function tests such as spirometry can be used to estimate a patient's capacity for sustained breathing (maximal ventilation) during exercise. The forced expiratory volume in 1 second (FEV_1) is most useful in this regard. However, lung function only provides an estimate of an individual patient's maximum work capacity. Exercise tolerance depends also on the patient's perception and tolerance of the subjective symptom of breathlessness. Therefore, it is important to exercise patients to assess their physical function and symptom tolerance.

Exercise evaluation for rehabilitation is most easily performed with the type of activity planned for training (e.g., treadmill for a walking training program). Laboratory exercise testing is most commonly performed using either (1) rapid, progressive, incremental levels to a symptom-limited maximum or (2) defined steady-state levels.[16,18] The former is most useful for determining exercise tolerance and the limitations to maximum performance. The latter may be preferred for assessing training prescriptions. Simpler exercise tests, such as the 6-minute walk test, have been used increasingly in recent years to measure exercise tolerance outside of a laboratory setting.[19] These timed distance walk tests measure the maximum distance a person can walk within a defined period (e.g., 6 minutes). Such tests have the advantage of requiring less equipment and technical expertise; however, attention must be paid to the details of testing procedures because variations in factors such as the walking course, patient instructions, encouragement during tests, use of oxygen or monitoring devices, and number of tests performed will influence the results. Also, these tests do not provide the detailed physiologic data typically included in more formal laboratory exercise tests.

Measurement of arterial blood gases at rest and during exercise is important because of the frequent but unpredictable occurrence of exercise-induced hypoxemia.[20] Arterial blood gas sampling during exercise makes testing more complex. The noninvasive estimate of arterial oxygen saturation by cutaneous (e.g., pulse) oximetry is useful for continuous monitoring, but it has limited accuracy (95% confidence limits, ±4–5%).[21]

GOALS

After a patient's medical, physiologic, and psychosocial state have been evaluated, specific goals should be set that are compatible with his or her disease, needs, and expectations. Goals should be realistic in light of the objectives of the program. Family members and significant others should be included in this process so that everyone understands what can and cannot be achieved. Programs should evaluate individual patients to document changes before and after pulmonary rehabilitation with standardized outcome measures of exercise tolerance (e.g., 6-minute walk distance) and symptoms (e.g., dyspnea) or health status (e.g., health-related quality of life).

PROGRAM CONTENT

Comprehensive pulmonary rehabilitation programs typically include several key components: education, instruction in respiratory and chest physiotherapy, psychosocial support, and exercise training (Table 43-2). Often, the various components are provided simultaneously; for example, during an exercise session, a patient may learn and practice breathing techniques for symptom control while being encouraged and supported by staff or other patients. Although there is no consensus regarding the optimal duration of a pulmonary rehabilitation intervention, typical programs last 6 to 12 weeks with 2 to 3 sessions per week, each session including several hours of supervised exercise training and individual or group education and psychosocial interventions.

EDUCATION

Successful pulmonary rehabilitation depends upon an understanding of lung disease and active involvement by patients and important others in providing social support. Education is an integral component; even patients with severe disease can gain a better understanding of their disease and learn specific means to deal with problems. Instruction can be provided individually or in small groups, but it should be adapted to different learning abilities. Topics discussed commonly include normal lung function, chronic lung disease, medications, nutrition, travel, stress reduction and relaxation, reasons to call the physician, and planning a daily schedule. Individual instruction and coaching may be provided on the use of respiratory therapy equipment and supplemental oxygen, breathing techniques, bronchial drainage, chest percussion, energy-saving techniques, and self-care tips. The general philosophy is to encourage patients to assume responsibility for their own care and become partners with their physician in providing the care.[22]

Despite the importance of education, it is unlikely that increased patient knowledge alone will lead to improved health status. It is more difficult to change patient attitudes and behaviors. Patients require specific, individualized treatment strategies, instruction, and reinforcement. Thus, education is a necessary but not sufficient component of pulmonary rehabilitation.

RESPIRATORY AND CHEST PHYSIOTHERAPY TECHNIQUES

Patients with chronic lung disease use, abuse, and are confused about respiratory and chest physiotherapy techniques. In pulmonary rehabilitation, each patient's needs for respiratory care techniques should be assessed and instruction provided in proper use. These techniques may include chest physiotherapy to control secretions; breathing retraining techniques to relieve and control dyspnea and improve ventilatory function; and proper use and care of respiratory equipment, including nebulizers, metered dose inhalers, and supplemental oxygen.[23]

BRONCHIAL HYGIENE

Patients with chronic lung diseases frequently have abnormal lung clearance mechanisms that increase problems with retained secretions and infection. Therefore, rehabilitation programs teach a variety of chest physiotherapy techniques for secretion control (e.g., coughing, postural drainage, chest vibration, and percussion). These are important for patients who experience excess mucus production during exacerbations as well as for those with chronic sputum production. The use of mucolytic agents to reduce viscosity of secretions is of questionable benefit.[24,25]

BREATHING RETRAINING TECHNIQUES

Pulmonary rehabilitation typically includes instruction in breathing techniques, such as diaphragmatic and pursed lips breathing—techniques aimed at helping patients relieve and control breathlessness, improve their ventilatory pattern (i.e., slower respiratory rate and increased tidal volume), prevent dynamic airway compression, improve respiratory synchrony of the abdominal and thoracic musculature, and improve gas exchange.[26] Review of studies evaluating these techniques indicates that improvement in symptoms (e.g., dyspnea) is a more consistent finding than are measurable changes in physiological parameters. The diaphragmatic breathing technique is a maneuver in which the patient consciously coordinates abdominal wall expansion with inspiration and slows expiration through pursed lips. The primary effect is to slow respiratory rate and increase tidal volume. Pursed lips breathing is commonly taught to pulmonary patients, particularly those with COPD. This technique was observed by Laennec as early as 1830 and was advocated as a physical exercise for pulmonary patients in the early part of the twentieth century. As a maneuver assumed naturally by many patients with respiratory disease, pursed lips breathing is characterized by tensing the lips and narrowing the mouth opening during expiration. The aim is to slow expiration and maintain positive airway pressure to "stent the airways open" and prevent collapse.[27]

OXYGEN

When chronic oxygen therapy is required, available delivery methods should be reviewed to help select the best system for the patient's needs. Supplemental oxygen is beneficial for patients with severe resting hypoxemia. Long-term continuous oxygen therapy has been clearly shown to improve survival and reduce mortality and morbidity in hypoxemic patients with COPD.[28,29] The benefits of supplemental oxygen for nonhypoxemic patients or those with intermittent hypoxemia (e.g., during exercise or sleep) are less clearly defined. Although continuous oxygen therapy is feasible and safe, maintaining patients on supplemental oxygen presents several challenges. Handling equipment is particularly difficult for physically disabled and frail patients. Therefore, it is important to assess each person's oxygen needs and provide appropriate instruction.[30]

Several new developments have improved the efficiency of gas delivery systems and patient compliance with continuous oxygen therapy. Liquid oxygen provides more gas with less weight than tanks of compressed gas, particularly in portable systems. Oxygen conserving devices may increase the efficiency of delivery, reducing flow requirements and prolonging the life span of portable gas sources. Transtracheal oxygen delivery may help to improve compliance and avoid problems with nasal catheters; however, patients must be instructed carefully in caring for the catheter.[31]

EXERCISE

Exercise is important in pulmonary rehabilitation.[32,33] Considerable evidence supports favorable responses to exercise training in patients with chronic lung diseases.[3] Benefits are both physiological and psychological. Patients may increase their maximum capacity and endurance for physical activity, even though objective measures of lung function do not usually change. Patients may also benefit from learning to perform physical tasks more efficiently. Exercise training provides an ideal opportunity for patients to learn their capacity for physical work and use and practice methods for controlling dyspnea (e.g., breathing and relaxation techniques). Of all the components in a comprehensive pulmonary rehabilitation program, exercise is probably the most costly and labor-intensive, considering the personnel, equipment, and expertise required. Principles of exercise for patients with lung disease differ from those based on normals or other patient populations because of differences in the limitations to exercise and the problems encountered in training.

Many approaches have been used to train the person with chronic lung disease. To be successful, the program should be tailored to the individual's physical abilities, interests, resources, and environment. For general application, techniques should be simple and inexpensive. As in normals and other patients, benefits are largely specific to the muscles and tasks involved in training. Patients tend to do best with activities and exercises for which they are trained. Walking programs are particularly useful. They have the added benefit of encouraging patients to expand social horizons. In inclement weather, many can walk indoors (e.g., at shopping malls). Other types of exercise (e.g., cycling, swimming) are also effective. Patients should be encouraged to incorporate regular exercise into daily activities they enjoy (e.g., golf, gardening). Since many persons with chronic lung disease have limited exercise tolerance, emphasis during training should be placed on increasing endurance. Changes in endurance with rehabilitation are often greater than changes in maximal exercise tolerance and allow patients to become more functional within their physical limits. Increase in maximum exercise is also possible as patients gain experience and confidence. Resistive training is also used commonly in rehabilitation and can lead to significant increases in muscle strength that are important for many activities of daily living.[34]

EXERCISE PRESCRIPTION

Selecting a training target based upon a predetermined percentage of predicted maximal heart rate or ($\dot{V}_{O_2}$) is a well-established practice for normals or patients without underlying pulmonary disease. However, in patients with chronic lung diseases, the best method of choosing an appropriate training prescription is less clearly defined. Exercise tolerance in pulmonary patients is typically limited by maximal achievable ventilation and breathlessness. Such patients frequently do not reach their limits of cardiac or peripheral muscle performance.

Much controversy exists regarding the appropriate training intensity target for patients with chronic lung disease. Use of a target heart rate has been advocated by some, although it is recognized that such a target may not be reliable for patients with more severe disease.

Many patients with lung disease can be trained at a high percentage of maximal exercise tolerance, with work levels approaching or even exceeding the maximal level reached on the initial exercise test. In a study of 52 patients with moderate to severe COPD, patients were able to perform endurance exercise testing at an average workload of 95% of their baseline maximum.[35] After 8 weeks of training, these patients were training at 86% of the baseline maximum. In fact, many patients with severe COPD were exercising at levels exceeding their baseline maximum. In another study that examined 59 patients with moderate to severe COPD who trained at levels near their ventilatory limits, a mean peak exercise ventilation of 100% of measured maximal voluntary ventilation was achieved after 12 days of training and at 3 months of follow-up.[36] These findings suggest that even patients with advanced disease can be trained successfully at or near maximal exercise levels.

Based on the findings noted previously, some pulmonary rehabilitation programs define exercise targets and progression during training more by symptom tolerance than heart rate, work level, or other physiological measurements. Ratings of perceived symptoms (e.g., breathlessness) help teach patients to exercise to "target" levels of breathing discomfort. A typical approach is to begin training at a level that the patient can sustain with reasonable comfort for several minutes and then to increase the time or exercise level according to symptom tolerance. Patients are encouraged to exercise daily and increase exercise duration up to 15 to 30 minutes of continuous activity. This graduated program helps patients to achieve a goal of improved tolerance for tasks of daily living, which often require a period of sustained activity.

BLOOD GAS CHANGES

A major problem in planning a safe exercise program for patients with lung disease is the potential for worsening of hypoxemia with exercise. Patients who are not hypoxemic at rest may develop changes in arterial oxygenation that cannot be predicted reliably from resting measurements of pulmonary function or gas exchange.[20] Normal individuals do not become hypoxemic with exercise. In patients with obstructive lung disease, Pa_{O_2} changes unpredictably during exercise. In patients with mild COPD, Pa_{O_2} typically does not change with exercise; in fact, it may even improve. However, in patients with moderate to severe COPD, Pa_{O_2} may increase, decrease, or remain the same. Patients with interstitial lung disease commonly develop worsening oxygenation with exercise.

Based on these observations, it is important to evaluate a patient's oxygenation status both at rest and during exercise. Such testing is also used to prescribe oxygen therapy at rest and with physical activity. With the availability of convenient, portable systems for ambulatory oxygen delivery, hypoxemia is not a contraindication to safe exercise training.

OTHER TYPES OF EXERCISE

Exercise programs for pulmonary patients typically emphasize lower extremity training (e.g., walking or cycling). Since exercise conditioning is largely specific to the muscles and tasks involved in training other forms of exercise may be particularly valuable for persons with chronic lung diseases.

Upper Extremity Training

Many patients with chronic lung disease report disabling dyspnea with daily activities involving the upper extremities (e.g., lifting, grooming) at much lower work levels than with the lower extremities. Upper extremity exercise is accompanied by a higher ventilatory demand for a given level of work than is lower extremity exercise. Given the aforementioned muscle specificity of training, upper extremity exercises may be important in helping pulmonary patients cope better with common daily activities.[37]

Ventilatory Muscle Training

The potential role of ventilatory muscle fatigue as a cause of respiratory failure and ventilatory limitation in patients with chronic lung disease has stimulated attempts to train the ventilatory muscles. Techniques of isocapnic hyperventilation, inspiratory resistive loading, and inspiratory threshold loading have been shown to improve function of the respiratory muscles in both normals and patients. In normals, respiratory muscle function does not limit exercise tolerance; therefore, specific respiratory muscle training is unlikely to be of clinical benefit. In patients with COPD, the patient group most extensively studied, improvement in general exercise performance from ventilatory muscle training alone has not been demonstrated consistently. Thus, the role of respiratory muscle training as a routine component of pulmonary rehabilitation has not been clearly established.

PSYCHOSOCIAL SUPPORT

An essential component of pulmonary rehabilitation is psychosocial support, the goal of which is to help patients combat progressive feelings of hopelessness and an inability to cope with chronic, progressive disease.[15] Depression is common in patients with chronic pulmonary disorders, as are anxiety (especially anxiety over dyspnea), denial, anger, and isolation. Patients become sedentary and dependent upon family members, friends, and medical services to provide for their needs. Excessive concern over other physical problems and psychosomatic complaints arise. Sexual dysfunction and fear are common and represent often unspoken consequences of chronic lung disease. Patients may also demonstrate cognitive and neuropsychological dysfunction, possibly related to or exacerbated by the effects of hypoxemia on the brain.

Psychosocial support is provided best by a warm and enthusiastic staff who can communicate effectively with patients and devote the time and effort necessary to understand and motivate them. Family members and significant others should be included in activities so that they can understand the disease and help the patient cope. Support groups are also effective. Patients with severe psychological disorders may benefit from individual counseling and therapy. Psychotropic drugs should generally be reserved for patients with more severe psychological dysfunction.

BENEFITS OF PULMONARY REHABILITATION

A growing body of evidence supports the expected results and benefits of pulmonary rehabilitation in the management of patients with chronic lung disease (Table 43-3). Evidence-based guidelines were

TABLE 43-3 Results of Pulmonary Rehabilitation

Decreases in
Medical resource utilization (e.g., hospitalizations, emergency room visits)
Respiratory symptoms (e.g., breathlessness)
Psychological symptoms (e.g., depression, fear)
Increases in
Quality of life
Physical activity
Exercise tolerance (endurance, maximal level of activities of daily living, strength)
Knowledge
Independence
Return to work possible
No change in lung function
Possible prolonged survival

published by a joint effort of the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) in 1997 and updated in 2007.[3,38] The 2007 ACCP/AACVPR Panel made and rated 26 recommendations and statements regarding pulmonary rehabilitation. Of these, seven were given the highest rating representing strong evidence and documented benefits. These included improvements in lower extremity exercise training, dyspnea, and health-related quality of life and the decline in benefits over 12 to 18 months from a 6- to 12-week intervention. They also felt that there was high-quality evidence supporting exercise in pulmonary rehabilitation regarding both high and low intensity training, increase in muscle strength and muscle mass from strength training, and upper extremity training. Other benefits with moderate level evidence included greater physiologic benefits from higher exercise training intensity, incorporation of education in pulmonary rehabilitation, and benefits for some patients with chronic respiratory diseases other than COPD. It should be noted that once a patient is stabilized on a standard drug treatment regimen, lung function (e.g., spirometric flow rates, lung volumes) does not change after pulmonary rehabilitation.

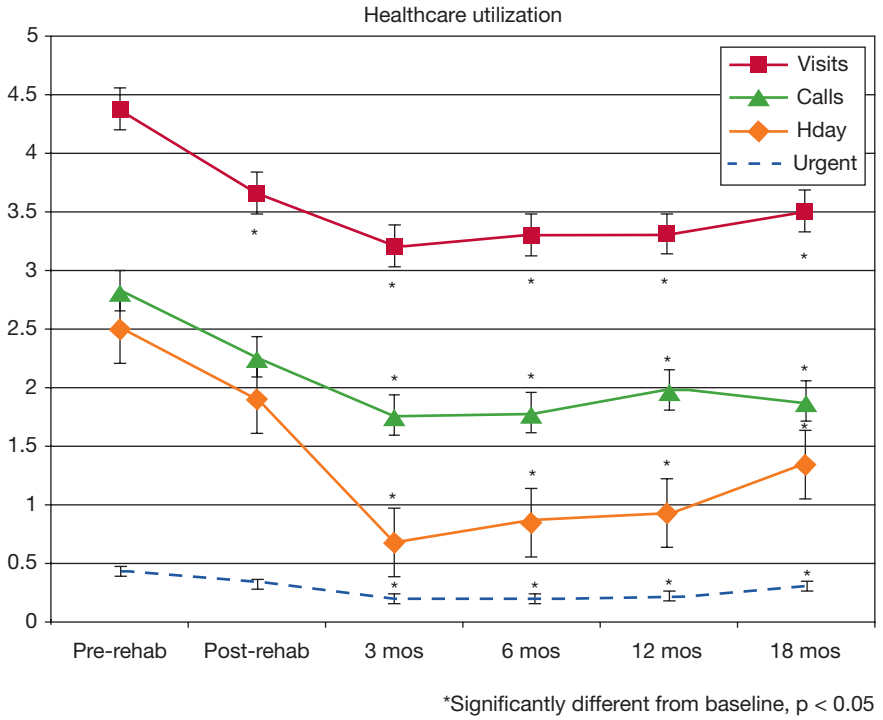

Figure 43-1 Changes in healthcare utilization over 18 months after pulmonary rehabilitation in a collaborative study of 647 patients in 10 centers in California. Results are presented as mean ± SE. *(Reproduced with permission from California Pulmonary Rehabflitation Collaborative Group: Effects of pulmonary rehabfl itation on dyspnea, quality of life and health care costs in California. J Cardiopulmonary Rehabfl. 2004;24:52–62.)*

In addition to the ACCP/AACVPR Guidelines, several other reviews support the benefits of pulmonary rehabilitation. The ATS/ERS Statement of Pulmonary Rehabilitation provides a systematic review and concludes that there is strong and growing evidence for improvement in exercise endurance, dyspnea, functional capacity, and quality of life and reduced healthcare utilization from pulmonary rehabilitation.[2] In a 2006 Cochrane Review, Lacasse et al.[39] analyzed 31 randomized trials in patients with COPD and concluded that rehabilitation forms an important component of the management of COPD. They reported statistically and clinically significant improvement in important domains of quality of life (dyspnea, fatigue, emotions, and patients' control over disease). Improvement in measures of exercise capacity was slightly below the threshold for clinical significance.

Benefits and cost savings associated with pulmonary rehabilitation have been demonstrated not only in highly specialized centers, but also in community-based practice settings.[3,40] A collaborative study of 647 patients in 10 centers in California reported significant improvements in dyspnea and health-related quality of life along with substantial reduction in measures of healthcare utilization over 18 months of follow-up.[41] (Fig. 43-1). Similar findings with a reduction in hospital and intensive care unit days in the year after compared with the year before pulmonary rehabilitation were reported by a consortium of 11 centers in Connecticut and New York in 128 patients.[42] In addition, pulmonary rehabilitation following a hospital admission for acute exacerbation may reduce subsequent hospital admission and mortality.[43]

PULMONARY REHABILITATION AND LUNG SURGERY

In recent years, surgical options for patients with severe, disabling lung disease have been used more frequently. Lung surgery in these patients represents new challenges and may further compromise already reduced lung function. Pulmonary rehabilitation has been found to be a valuable adjunct in preparing the patient for surgery or in postsurgery recovery.

LUNG TRANSPLANTATION

Pulmonary rehabilitation is recommended and used commonly in both the preoperative and postoperative phases of lung transplantation programs.[8,9,44] Although the general strategies of rehabilitation may be similar, the individual and program goals and specific program components differ (Table 43-4).

TABLE 43-4 Goals of Pulmonary Rehabilitation in Lung Transplantation

Pretransplant
Maintain and increase mobility and exercise tolerance
Monitor disease progression
Prevent complications
Provide education about
Underlying disease
Transplantation procedures
Self-care and self-assessment
Provide psychosocial support during waiting period for patients and families
Posttransplant
Improve physical work tolerance
Monitor clinical status and assess symptoms and oxygenation
Prevent complications
Reinforce self-care and self-assessment
Encourage compliance with medical regimen
Provide psychosocial support for adaptation to new demands and expectations

PRETRANSPLANT REHABILITATION

Patients with advanced lung disease who are candidates for lung transplantation are usually evaluated by the transplant team and then referred for pulmonary rehabilitation after their transplant candidacy is approved. Rehabilitation staff evaluate the patient to assess needs and plan an appropriate program that can be maintained throughout a waiting period, which may last months to years. Since these patients have advanced disease with limited life expectancy, the goals in the preoperative period differ from those that typically apply to rehabilitation in chronic lung disease.

The overall goals of pretransplant pulmonary rehabilitation are to maintain function, monitor disease progression, prevent complications, provide education about the underlying lung disease and lung transplantation, and offer psychosocial support for patients and families in coping with the stresses of waiting for a potentially life-saving procedure. Although patients may have some initial improvement in exercise tolerance or endurance as they begin rehabilitation, the primary goal for these patients is to maintain mobility and exercise capacity. Exercise sessions also provide an excellent means to monitor disease progression and to detect, at an earlier stage, problems that commonly occur (e.g., increased breathlessness or reduced arterial oxygenation with exercise).

The goals of education in the pretransplant period are to teach patients about their underlying lung disease, the transplant procedure itself, and expectations following transplantation. Patients can also be taught techniques for self-care and self-assessment that will be useful before and after surgery. The psychosocial stresses of waiting for transplantation are considerable. Many patients feel as though their lives are "on hold." Some may have moved away from family and social support networks to live close to the transplant center. Providing support for patients and families during this time, whether through formal group support sessions or informal contact with supportive staff and other patients, helps patients cope better with these problems.

POSTTRANSPLANT REHABILITATION

After lung transplantation, patients must learn to cope with a new level of function, new expectations, and a new set of problems. Rehabilitation for patients in this phase can facilitate physical reconditioning, help implement self-care and assessment techniques, and facilitate coping with the psychosocial adaptations to a new life-style.

Goals of exercise training after rehabilitation are improved physical work tolerance and continued assessment of symptoms and oxygenation as early warning signs of complications, including rejection and infection. Educational goals are focused on self-care and assessment and the importance of compliance with a new medical regimen. Psychosocial support can assist with adaptation to a new set of stresses related to additional demands and expectations from both patients for themselves and significant others. Patients who are used to being sick, disabled, and cared for by others may now be expected to be well, independent, return to work, and provide support for others.

LUNG VOLUME REDUCTION SURGERY

Pulmonary rehabilitation has been recommended as an important modality in the evaluation for and preparation of patients for this procedure as well as in the postoperative recovery phase.[11,45] Since these patients have severe, disabling chronic lung disease, they are typically good candidates for pulmonary rehabilitation. Enrolling patients in rehabilitation prior to surgery has the advantage of optimizing their functional status, improving physical and psychological symptoms, helping them learn more about their disease and alternative treatment options, and improving their skills for coping and actively co-managing their disease. Patients can then make an informed decision about surgical treatment based upon their optimal level of baseline function. After surgery, similar to the posttransplant period, rehabilitation helps patients to adapt to new levels of function and to reassess symptoms and oxygenation needs.

REHABILITATION AFTER LUNG RESECTION

Patients who undergo pulmonary resection frequently experience a significant increase in symptoms and reduced functional status. This is particularly true for patients with underlying chronic lung disease. Most commonly, surgery is used to treat patients with thoracic neoplasms who are deemed to have resectable disease and are operative candidates. Following resection, these patients with already limited lung function have to learn to adapt to a new, lower level of function.[46,47]

Similar changes may be observed in patients who undergo radiation therapy. Patients in a stable phase of their treatment or in remission may be appropriate candidates for pulmonary rehabilitation. Improvement in health status, physical and psychological symptoms, exercise tolerance, and quality of life – as well as reduced healthcare burdens – are potential benefits. These patients' survival may be as limited by their underlying lung disease as by their treated malignancy.

SUMMARY AND FUTURE OF PULMONARY REHABILITATION

Pulmonary rehabilitation has been well established as a means of improving functional status and reducing the disability and economic burden of the growing number of patients with chronic lung diseases. In adopting a broad rehabilitation medicine perspective, such programs provide interdisciplinary expertise directed toward the needs of the individual disabled patient.

Much of the experience in pulmonary rehabilitation has been in patients with COPD. However, it is clear that similar benefits can result for patients with other disabling pulmonary conditions. Pulmonary rehabilitation may also play an important role in the preoperative evaluation, preparation, and postoperative recovery of patients undergoing surgical procedures, including lung transplantation, lung volume reduction surgery, and lung resection. In many parts of the world, a major challenge for the widespread application of pulmonary rehabilitation to the large number of patients with chronic lung diseases relates to acceptance by health policy makers and health insurers about the benefits and cost savings associated with this treatment. In the United States, for instance, Medicare, the major government sponsored health insurance program that sets standards for many health insurers, recently implemented a national coverage policy for pulmonary rehabilitation.[48] This is a major step forward; however, the current relatively low reimbursement rates have threatened the financial viability of many existing programs. It is hoped that, with time and experience, the benefits of pulmonary rehabilitation as an effective, preventive health intervention that can improve patient outcomes and reduce healthcare costs will be better recognized.

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CHAPTER 44
The Biology of Asthma

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Asthma is characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person.[1] More than 18 million adults and 7 million children are affected in the United States alone, making asthma one of the most common chronic diseases in this country.[2] Attempts to elucidate the underlying pathophysiology of the disease have led to the realization that asthma truly is a protean disease with various cell types and mechanisms playing variable but important roles in each patient. This degree of mechanistic variation explains the numerous phenotypes of this disease as well as the differences in response to treatment.

By the simplest definition, the pathogenesis of asthma involves bronchoconstriction, airway inflammation, and airway hyperresponsiveness.[3] It is, however, the complex interplay between these factors that defines the disease in general and specifically in an individual patient. A closer examination of the factors involved in each of these components allows a better understanding of this complex disease.

THE ACUTE INFLAMMATORY RESPONSE IN ASTHMA

Perhaps the best illustration of the features of the acute inflammatory response, that is central to the pathogenesis of asthma, is the reaction to the initial and then subsequent exposures to inhaled antigen. While important cellular and molecular mediators will be described later in greater detail, a brief review of the acute inflammatory response serves as a foundation upon which further concepts can be introduced to illustrate the variable but persistent changes that occur in the airway in asthma. When a novel antigen is introduced to the airway of an at-risk individual, it initially becomes trapped in the mucus lining the airway. Here it can be taken up by antigen presenting cells, most notably dendritic cells, which are distributed through the epithelium of the airways.[4,5] After the uptake of allergen, the dendritic cells travel to pulmonary lymph nodes whereby the antigen is presented to naïve $CD4^+$ T cells.[5] Signals derived from the dendritic cell determine which type of $CD4^+$ T cell will be produced. Prior to this event, the dendritic cell is influenced by a complex network of molecular signals that are derived from airway epithelial cells and other local cell types. In allergic inflammation, for example, thymic stromal lymphopoietin (TSLP) and granulocyte–monocyte colony stimulating factor (GM-CSF), which are derived from bronchial epithelial cells, and induce the dendritic cell to promote T_H2 differentiation of naïve $CD4^+$ T cells, thus setting up an environment favorable to the eventual development of allergic inflammation.[5] Upon rechallenge with the sensitizing antigen, these now T_H2 differentiated $CD4^+$ T cells are recruited back to the airway by other signals, such as the chemokines CCL17 and CCL22, secreted by dendritic cells.[6] Upon arrival in the airway, the $CD4^+$ T_H2 cells become key sources of the T_H2 cytokines, namely IL-4, IL-5, and IL-13, which serve as the molecular catalysts to establish a framework for acute allergic inflammation.[6]

After rechallenge with antigen, the local environment of the airways is now rich with T_H2 cytokines, which act on other cell types, either present or recruited to the airway, to propagate the acute allergic inflammatory response. B cells, in the presence of IL-4 and IL-13, are influenced to produce antigen-specific IgE, which binds to high-affinity IgE receptors (FcεRI) on mast cells (MC). When inhaled antigen cross-links the membrane-bound IgE on the mast cells, a variety of preformed and synthesized meditators are released to cause bronchoconstriction, airway edema, and local tissue damage.[7] Mast cells also release chemoattractants such as leukotrienes and cytokines, to recruit a variety of other cells, including eosinophils, basophils, neutrophils, and lymphocytes, which then contribute to the late phase inflammatory response.[7] The eosinophil appears to be, in most cases, the most important and abundant inflammatory cell associated with the late phase response and possibly contributes to the subsequent airflow obstruction.[8] The vast numbers of mediators the eosinophil produces are reviewed later in the chapter. Eosinophil products can cause local tissue damage, mucus hypersecretion, increased vascular permeability, smooth muscle contraction, and a sustained inflammatory response whereby other cell types are recruited to the site of inflammation to perpetuate the reaction.[7,8] The roles of neutrophils and basophils in the pathogenesis of the acute and late-phase allergic inflammatory responses are less well defined.

While the acute allergic response to allergen illustrates the pattern of inflammation seen in asthma, it should be noted that other forms of inflammation can and do play important roles in asthma. Viral respiratory infections, especially with human rhinovirus (HRV), are important triggers for asthma exacerbations.[9] The response to HRV is a primarily T_H1 driven response with increased production of IL-8 and IL-1β and the appearance of airway neutrophilia, as opposed to the strong T_H2 response seen after allergen exposure.[9,10] In asthma, there is evidence that diminished production of the type I and III interferons, antiviral cytokines, may be deficient in some patients with asthma thus leading to increased risk for viral respiratory infections and a greater susceptibility to exacerbations of asthma.[9,10]

This pattern of acute- and late-phase inflammatory response to antigen is, however, a central component of asthma. Chronic inflammation is a later development of the disease and will be described later. Many of the cell types and inflammatory mediators seen in asthma were briefly touched upon in the preceding paragraphs and will now be further developed.

CELL TYPES IN ASTHMA

A study of the pathogenesis of any complex disease begins at the cellular level. The importance of cells of the immune system, including mast cells, basophils, $CD4^+$ T cells, eosinophils, neutrophils, macrophages, dendritic cells, and T lymphocytes, as well as their molecular mediators has long been recognized and appreciated in the development and regulation of inflammation. The contribution of airway smooth muscle cells, especially in relationship to the acute asthmatic response, has also been well documented. More recently, epithelial cells of the airway have become the focus of intense research and emerging importance to both acute and chronic inflammation in asthma. Their role in airway inflammation, and especially in the airway remodeling as is seen in the chronic forms of asthma, is being increasingly cited as a major contributor to the severity of this disease.

CELLS OF THE IMMUNE SYSTEM IN ASTHMA

The contributions of each of the aforementioned immune system cell types in the pathogenesis of asthma are considered below.

Mast Cells

Human mast cells are derived from the same $CD34^+/cKit^+$ hematopoietic stem cell population that also gives rises to eosinophils, basophils, neutrophils, and monocytes.[11] They are resident cells in most tissues of the body and are commonly found in association with blood vessels, nerves, and surfaces that have contact with the external environment.[12] Mast cells exist in two types in humans and are differentiated by their immunohistochemical staining properties.[13] MC_T mast cells contain only the neutral protease tryptase, while MC_{TC} mast cells contain chymase, carboxypeptidase A_3, and cathepsin G-like protease in addition to tryptase.[13–15] In normal lung tissue, mast cells are located in the subepithelium of the bronchi, bronchioles, and alveolar walls and are almost exclusively of the MC_T type.[13] This distribution of mast cell types is also seen in mild asthma. In severe asthma, however, mast cells in the submucosa are decreased in number and are primarily of the MC_{TC} type.[16] MC_{TC} mast cells are also seen in the airway epithelium of severe asthma, a finding not seen in normal lungs or in milder disease.[16] Mast cells increasingly infiltrate airway smooth muscle bundles in asthma where they likely contribute to ongoing bronchoconstriction through release of their mediators.[17]

While mast cells appear to have some importance in nonallergic asthma as well, they are essential components of the allergic (IgE-mediated) response seen in many asthma patients.[18] Antigen-specific IgE molecules bind allergen and cross-link high-affinity IgE receptors (FcεRI) present on the mast cell surface. This results in the release of preformed mediators, such as histamine, tryptase, chymase, and heparin, as well as tumor necrosis factor-alpha (TNF-α) and vascular endothelial growth factor (VEGF) in some cases (Fig. 44-1).[19] Upon activation, mast cells also generate and release newly synthesized mediators, which contribute to the ongoing inflammatory milieu. These include leukotrienes (predominantly LTC_4), prostaglandins (predominantly PGD_2), thromboxane A_2, platelet activating factor (PAF), growth factors including GM-CSF, fibroblast growth factor-2, and VEGF, and various other cytokines including TNF-α, IL-4, IL-5, IL-8, and IL-13 (Fig. 44-1).[19,20]

The effect of mast cell mediator release contributes to numerous features in the asthmatic response.[7] Histamine, leukotrienes, and the various proteases increase mucus production. Prostaglandins, leukotrienes, thromboxane A_2, and histamine cause bronchoconstriction and increase vascular permeability. The various proteases cause local tissue damage and are important in the activation of various protein precursors. Finally, synthesized cytokines contribute to the recruitment, differentiation, and activation of other inflammatory cells, resulting in the propagation of the inflammatory response.

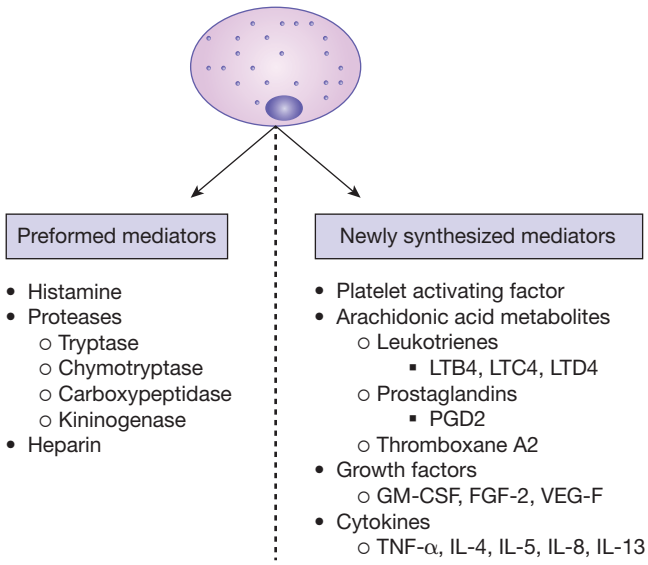

Figure 44-1 The mast cell and its mediators. GM-CSF, granulocyte-monocyte colony stimulating factor; FGF-2, fibroblast growth factor 2; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor alpha.

Basophils

In addition to sharing a common progenitor cell, basophils share many similarities with mast cells, with the exception that basophils are present primarily in the peripheral circulation. Both cells express FcεRI on their cell surface and release both preformed, as well as newly synthesized mediators and cytokines, upon cross-linking by IgE–antigen complexes. The major preformed mediator released from basophils is histamine. Preformed heparin and tryptase are also released, albeit at lower concentrations than mast cells.[21] Basophils synthesize and release LTC_4 upon activation, but unlike mast cells, they do not produce PGD_2.[21] Upon activation, basophils produce large quantities of IL-4 and IL-13, cytokines that play an important role in the T_H2 differentiation, which will be discussed later.[21] More recently, two other roles of basophils in the pathogenesis of asthma have been discovered, both of which also play important roles in T_H2 differentiation. First, basophils can act as antigen presenting cells via their expression of major histocompatibility complex (MHC) class II and co-stimulatory molecules.[22] Second, basophils, along with eosinophils, are also the primary target of IL-33, a potent promoter of allergic inflammation and T_H2 polarization.[23]

Eosinophils

Eosinophils, like basophils and mast cells, are granulocytes derived from $CD34^+$ hematopoietic stem cells. Early eosinophil production is highly dependent upon the presence of GM-CSF and IL-3.[24] Eosinophil precursors are recruited to the airway in asthma as the result of cytokine and chemokine signaling, which involves IL-5, eotaxins, RANTES, macrophage inflammatory protein (MIP)-1α, and macrophage chemotactic factors 2,3, and 4 (MCP-2,3,4).[25] IL-5 is critically important for the terminal differentiation of eosinophils and release from the bone marrow.[24]

Once in the airway, eosinophils are activated and contribute to the inflammatory response through releasing a wide variety of mediators including cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, tumor necrosis factor-α [TNF-α] and transforming growth factor-α and β [TGF-α and TGF-β]), chemokines (MIP-1, MCP-2, RANTES and eotaxin), and lipid mediators (PGE_1, PGE_2, thromboxane B_2, PAF, LTC_4) (Fig. 44-2).[26,27] Eosinophils secrete granule proteins, which are important in the eosinophil's primordial role as the primary defender against parasites, as well as in the pathogenesis of asthma.[26,28] Eosinophils contain both primary and secondary granules. The primary granules contain Charcot–Leyden crystal protein, while the secondary granules contain the four principal cationic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO).[26] These cationic proteins play various roles in the pathogenesis of asthma including the induction of mast cell and basophil degranulation (ECP and MBP), increasing airway mucus production (ECP), and formation of reactive oxygen species (EPO) (Fig. 44-2).[26]

Over the past 30 years, the role of the eosinophil in asthma has undergone considerable re-evaluation. Since the discovery of the eosinophil by Ehrlich in 1879 and the later discovery that Ehrlich's cells were present in the sputum of asthmatic patients, the eosinophil has been viewed as the primary effector cell in asthma.[29] Studies have noted that peripheral blood eosinophilia is a characteristic of asthma and often in relationship to disease severity, and that eosinophilic infiltrates were found in the airways of asthma patients at autopsy, regardless of whether asthma was the primary cause of death.[30,31] Later studies detected increased eosinophils and eosinophil products

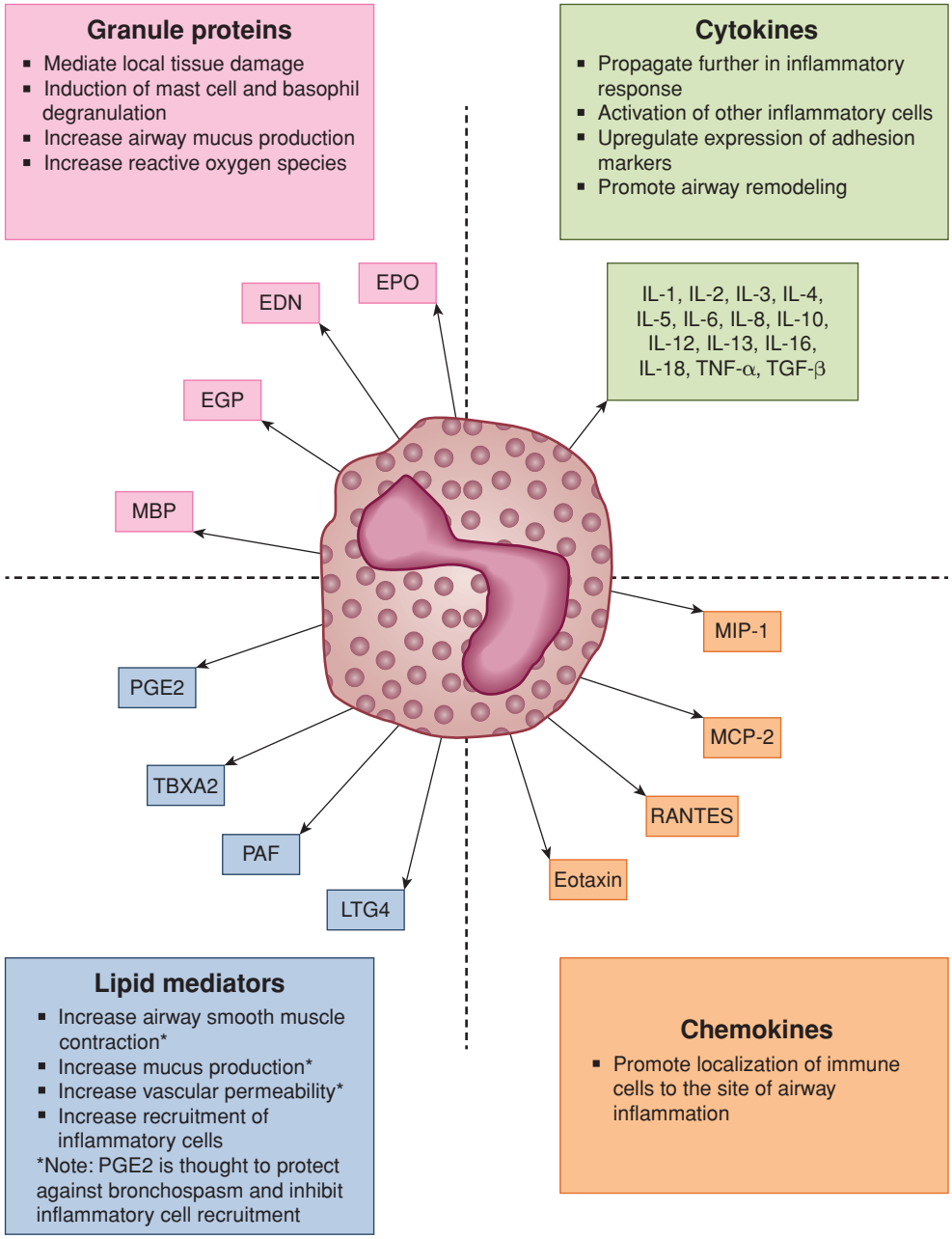

Figure 44-2 Eosinophil products in asthma. EPO, eosinophil peroxidase; EDN, eosinophil-derived neurotoxin; ECP, eosinophil cationic protein; MBP, major basic protein; PGE_2, prostaglandin E2; $TBXA_2$, thromboxane A_2; PAF, platelet activating factor; LTC_4, leukotriene C4; RANTES, regulated upon activation normal T cell expressed and secreted; MCP-2, monocyte chemotactic protein 2; MIP-1, macrophage inhibitory protein 1; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta.

in bronchoalveolar lavage (BAL) fluid after antigen challenge.[32] The view that the eosinophil was the principal effector of asthma was largely unchallenged until the new millennium brought new therapies, including monoclonal antibodies to IL-5, into evaluation.

The importance of IL-5 to the differentiation and survival of the eosinophil has been previously noted. Initial studies with monoclonal antibodies to IL-5 in asthma showed a decrease in sputum and peripheral blood eosinophilia, as expected, but failed to demonstrate significant benefit in a wide variety of clinical outcome measures, that is, symptoms or improved airflow obstruction.[33,34] Although this lack of effect on parameters of clinical asthma was a surprise, it led to an increasing interest in the heterogeneity of asthma with the realization that eosinophils may play greater or lesser roles in different patients.

Later studies with anti-IL-5 were conducted in patients who had persistent eosinophilia despite treatment with inhaled corticosteroids (ICS), and in these patients were noted clinical outcomes, the prevention of exacerbations.[35,36] Eosinophils play an important role in a certain subset of asthma, but the contribution of their role appears to be defined by phenotypes and is not necessarily generalizable to the entire asthmatic population. Finally, eosinophils are likely a prime contributor to airway remodeling seen in chronic asthma, and will be discussed in this capacity later in the chapter.

Neutrophils

Neutrophils are granulocytes derived from $CD34^+$ hematopoietic stem cells and are normally present in the bloodstream, as well as in various tissues, including the lung. They contain primary (azurophilic) and secondary (specific) granules, which contain a variety of antimicrobial enzymes, neutral proteases, and acid hydrolases.[37] Neutrophils are attracted to the airway by various cytokines and

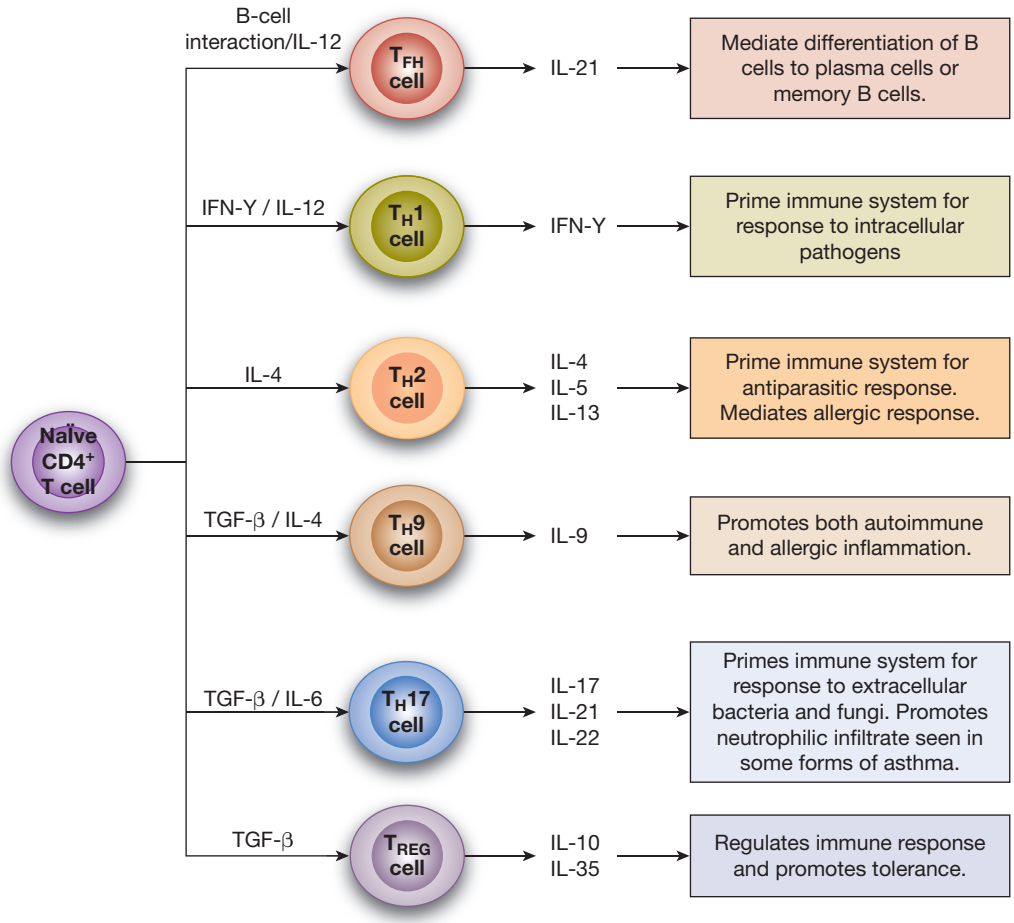

Figure 44-3 $CD4^+$ T Lymphocyte subsets. IFN-γ, interferon gamma; TGF-β, transforming growth factor beta; TFH cell, T follicular helper cell; T_{REG} cell, regulatory T cell.

chemokines including IL-8, IL-17, and granulocyte colony stimulating factor (G-CSF).[38,39] Airway neutrophilia can be seen in many respiratory conditions, viral respiratory infections, COPD, and asthma.[10,39]

The role of neutrophils in response to viral respiratory infections was introduced previously. In response to inoculation with a respiratory virus, such as HRV, dendritic cells, and other mononuclear cells produce proinflammatory cytokines and chemokines, which recruit neutrophils to the airway.[10] Neutrophils contribute to the inflammatory milieu by secreting cytokines such as TNF-α, IL-1, IL-8, and IL-18, to attract other inflammatory cells, upregulate cytokine production, and produce airway inflammation and enhance bronchial hyperresponsiveness.[40] Neutrophil products, such as elastase, can have more direct effects on the airway and cause mucus production.[10] In addition, because neutrophils are found in severe asthma, they are proposed to play a more prominent role in this phenotype.[41] Prominent neutrophilic inflammation has been noted in the sputum of patients with severe asthma exacerbations, in BAL fluid from patients with noninfectious status asthma, and in autopsy specimens from the airway in patients with acute, fatal asthma.[42–44] Other studies have demonstrated subgroups of patients with chronic asthma in whom the primary inflammatory cell type is neutrophils rather than eosinophils.[45,46] These patients are often more difficult to treat and less responsive to treatment with corticosteroids.

Lymphocytes

Unlike the previously discussed cell types, T cells are lymphocytes and derived from the common lymphoid progenitor. Numerous subsets of T cells have been identified and are important contributors to asthma, including $CD4^+$ helper T cells and their subsets (T_H1, T_H2, T_H9, and T_H17), $CD8^+$ cytotoxic T cells, and regulatory T cells (T_{REG}).

$CD4^+$ helper T cells recognize antigens presented to them by antigen presenting cells (APCs) and, in turn, secrete cytokines to influence the inflammatory response. In the airway, the dendritic cell is the most important APC and its role will be described later. A complex series of events involving cytokines and various transcription factors determines whether $CD4^+$ T cells will differentiate into T_H1 cells, T_H2 cells, T_H9 cells, or T_H17 cells (Fig. 44-3).[47]

T_H2 cells are recognized as the primary drivers of inflammation in asthma and allergic disease. When T_H2 cells encounter antigen presented by dendritic cells, they produce IL-4, IL-5, and IL-13, all of which play critical roles in the pathogenesis of asthma and are part of the clinical disease as demonstrated by detection of increased levels of these cytokines in the BAL fluid of patients with asthma.[48,49] IL-4 increases IgE production by plasma cells. As mentioned previously, IL-5 is critical in the terminal differentiation and homing of eosinophils to the airway. IL-13 also increases IgE production and plays a prominent role in airway hyperresponsiveness and tissue remodeling.[50]

The role of T_H1 cells in asthma is not as well defined as T_H2 cells. Although it has been presumed that T_H1 cells counteract the asthma-inducing effects of T_H2 cells, this likely is an over-simplification. T_H1 products have been shown to be increased during asthma exacerbation.[51] Some studies have also suggested that T_H1 cells may play a more prominent role in chronic severe asthma as evidenced by increased levels of the primary T_H1 cytokine, interferon-γ (IFN-γ), in the BAL fluid of patients with severe asthma.[52]

T_H9 cells are a relatively newly defined cell population whose primary cytokine is generation of IL-9. T_H9 cells function similarly to T_H2 cells in that they increase allergic inflammation. Mast cells are the primary IL-9 receptor-bearing cell, and T_H9 cells are important contributors to the previously described increased mast cell activation seen in asthma.[20] Because mast cells also produce VEGF and fibroblast growth factor-2, T_H9 cells likely contribute to airway remodeling seen in chronic asthma.[20]

The role of T_H17 cells in asthma is an area of intense research. With the identification of subphenotypes of asthma patients with primarily neutrophilic inflammation, the role of IL-17 (the primary cytokine produced by T_H17 cells) in asthma has become of considerable interest. Although IL-17 is found to be increasingly expressed in patients with severe asthma,[53] it is, however, also found in high concentrations in patients with mild asthma (FEV_1 >70% predicted) and these values correlate negatively with the PC_{20}.[54] Thus, while T_H17 cells most certainly play a role in patients with primarily neutrophilic asthma, they are also likely important in milder forms of disease as well.

The primary function of $CD8^+$ cytotoxic T cells is the destruction of human cells that are infected with viruses or other intracellular pathogens. $CD8^+$ T cells also likely play a role in asthma, though the extent of their contribution has yet to be fully elucidated.[50] IL-4 and IL-5 producing $CD8^+$ T cells are present in the airways of asthmatic patients.[55] IL-5 production by $CD8^+$ T cells is increased in the presence of a viral respiratory infection, and the overall cytokine production by $CD8^+$ T cells correlates with asthma severity.[56,57] Whether $CD8^+$ T cells function as direct contributors or bystanders in the worsening of asthma has yet to be determined.[50]

T_{REG} cells also appear to play a critical role in asthma development. T_{REG} cells serve to limit inflammatory responses and promote immune tolerance through the production of IL-10 and TGF-β.[50,58] In patients with asthma and other allergic disorders, T_{REG} cells appear to be less effective in limiting T_H2 inflammation.[59,60] However, after allergen immunotherapy, for example, T_{REG} cells increase in the nasal mucosa and may act to promote allergen tolerance.[61] Interestingly, farm exposure early in life is associated with a decreased incidence of allergic disease and asthma, a fact that may be related to increased numbers and function of T_{REG} cells in infants living in this environment.[62]

Natural killer cells (NK cells) are members of the innate immune system and serve as a first line of defense against infections. Their role in the pathogenesis of asthma has yet to be fully elucidated. They obviously appear in response to viral respiratory infections, and NK cells increase during asthma exacerbations.[63] NK cells are capable of producing numerous cytokines including IFN-γ, IL-4, IL-5, and IL-13.[64] NK cells from patients with atopic asthma are skewed toward the production of IL-4 as opposed to IFN-γ upon activation.[64] IFN-γ production by NK cells is also inhibited by prostaglandin D2, a T_H2-promoting lipid mediator produced by mast cells.[65] NK cells may also play a role in "dendritic cell editing" by killing immature dendritic cells, which might influence a certain type of T_H response.[66]

Macrophages and Dendritic Cells

Macrophages and dendritic cells are descendants from the $CD34^+$ hematopoietic stem cell and arise from a common committed precursor cell.[67] Macrophages arise from circulating monocytes and function, primarily, to clear debris and microbes from the airway. They may also function as antigen presenting cells, although this role is likely less important than that of the dendritic cell.[68] Alveolar macrophages may further differentiate into M1 or M2 subsets based on exposure to various cytokines and toll like receptor (TLR) agonists.[67] M1 macrophages are "classic" macrophages, and clear microbes from the airway. They also produce cytokines, such as IL-12, IL-6, and TNF-α, as well as high levels of nitric oxide (NO).[67] M1 macrophages have traditionally been described as suppressing allergic inflammation, primarily through their secretion of T_H1 cytokines such as IL-12; this is not fully resolved.[67]

Differentiation into M2 macrophages is influenced by an environment rich in T_H2 cytokines such as IL-4 and IL-13, thus implicating their role in asthma. When compared with M1 macrophages, M2 macrophages are poor at clearing intracellular pathogens.[67] They release cytokines such as IL-13 and thus are likely contribute to the airway hyperresponsiveness.[67]

Dendritic cells are the lung's primary presenter of antigen to T cells. Their role as the primary APC places the dendritic cell at a critical junction in determining what type of T cell response will be directed toward the antigen (i.e., T_H1, T_H2). Dendritic cells in humans exist in two broad categories: the myeloid dendritic cell (mDC) and the plasmacytoid dendritic cell (pDC). While both types of dendritic cells are present in the human lung, their anatomic localization within the lung is poorly understood. [5] Upon encountering antigen in the airway, dendritic cells migrate to local lymph nodes where they present antigen to T lymphocytes. Both pDC and mDC levels increase in the airway (and coincidently decrease in the blood) after exposure to inhaled allergen.[69–71] Because dendritic cells lie close to the epithelial barrier, they receive numerous signals from epithelial cells, which can influence their effect on T cells. TSLP is produced by epithelial cells and promotes dendritic cells to direct T_H2 differentiation and recruit T_H2 cells to the airway.[5] Other epithelial cell–derived factors, such as GM-CSF, TNF-α, CCL-20, IL-1β, and TNF-related apoptosis-inducing ligand (TRAIL), have similar T_H2 promoting effects.[5] pDC represent the lung's primary source of IFN-α, a potent antiviral cytokine, and they are recruited to the lung during times of viral infections.[72] As viral infections commonly precede asthma exacerbations and may predispose infants to develop asthma, this role of the pDC cannot be understated.[73] The importance of pDC to the development of asthma was illustrated by a recent study which showed that decreased pDC levels in childhood was directly correlated to increased number and severity of viral respiratory infections, increased episodes of wheeze, and increased asthma diagnosis.[74] The function of mDC is not as well known in human asthma, but the role of both dendritic cell types in contributing to the development and propagation of the disease will continue to be an important area of asthma research.

RESIDENT CELLS OF THE AIRWAY

The roles of airway smooth muscle cells and airway epithelial cells in the biology of asthma are considered below.

Airway Smooth Muscle

Given that bronchospasm and bronchial constriction are critical components of asthma, it is intuitive that the cell type responsible for this component, the airway smooth muscle cell, would be a key factor in asthma pathogenesis and pathophysiology. While its importance seems obvious, the details of why airway smooth muscle function is so different in the asthmatic airway compared with the normal airway have been elusive. It has been well documented that the smooth muscle layer surrounding the airway is thicker in asthma compared to nonasthmatic controls. These difference are due to both smooth muscle hypertrophy and hyperplasia.[75] Increased inflammatory cells, including mast cells, can be found within the smooth muscle bundles of asthmatic airways, and the interplay between these cells, the airway epithelium, and the smooth muscle layer, is an important determinant of the asthmatic response.[17] Numerous cytokines, chemokines, and growth factors are involved in this interaction including those produced by the airway smooth muscle cell itself and those produced by other cell types with which the airway smooth muscle cell communicates. Airway smooth muscle cells in asthma are more prolific producers

of these cytokines, and this function likely plays a role in their ability to proliferate more rapidly than those of nonasthmatic subjects.[76]

The treatment of asthma has long focused on preventing or reversing contraction of bronchial smooth muscles. β2-agonists, both short and long acting, have long been key to the treatment of asthma, and these medications act directly on the airway smooth muscle. More recently, debulking of airway smooth muscle, with the use of bronchial thermoplasty, has shown improvement in asthma control, which, in theory, further supports the role that airway smooth muscle plays in asthma pathophysiology.[77,78]

Airway Epithelial Cells

The epithelial lining of the airway is an area of intense research, and its importance, beyond being a simple anatomic barrier, is being increasingly recognized and appreciated. The airway epithelium represents a vast surface area (100 m^2) that is in contact with some 10,000 L of inhaled air daily.[79] As the area of initial contact between the lung and the external airborne environment, functions of the airway epithelium are likely key to determine the body's response to airborne substances.

The airway epithelium is composed of three major cell types: the ciliated columnar epithelial cell, the mucus-secreting goblet cell, and the surfactant secreting Clara cell.[79] Both overproduction of mucus by goblet cells and underproduction of important anti-inflammatory peptides by Clara cells have been noted in patients with asthma.[80,81] The tight junctions between epithelial cells have also been noted to be defective in patients with asthma, which can serve to decrease the ability of the airway epithelium to act as a protective barrier.[79] The airway epithelium in asthma is also less capable of defending itself against reactive oxygen species, a defect that leads to further damage to this airway barrier.[82] Epithelial cells in asthma produce lower amounts of Type I interferon in response to respiratory viruses, which can increase the severity to respiratory infections and promote asthma exacerbations.[83] TSLP promotes T_H2-driven inflammation and is overproduced by epithelial cells in asthmatic patients, thus providing a crucial link between the airway epithelium and the T_H2 type inflammation seen in asthma.[84,85] Finally, epithelial cells are capable of secreting endothelins, which are peptides with significant bronchoconstrictive activity.[86]

MOLECULAR MEDIATORS IN ASTHMA

The above-mentioned cells are able to initiate, perpetuate, coordinate, and regulate the inflammatory process with the synthesis and secretion of several different classes of molecular mediators. These mediators have a variety of functions, as discussed below.

CYTOKINES

Cytokines are small–molecular-weight glycosylated signaling molecules that are secreted by a number of different cell types with autocrine, paracrine, or endocrine directive activities.[87] Cytokine is a broad term and includes many subcategories including interleukins, interferons, and growth factors.[87] Cytokine secretion is usually a brief, self-limited event. It may, however, require new mRNA and protein synthesis, which takes place over a matter of hours rather than seconds or minutes.[88] A variety of cytokines have been implicated in the regulation of airway inflammation and thus in the pathogenesis of asthma (Table 44-1).[89] The support for cytokine involvement in inflammation was first obtained by the detection of these mediators in the airways of patients with asthma, particularly in bronchoalveolar lavage fluid after allergen challenge and in situ hybridization of retrieved cells or biopsy materials.[90,91]

The overall effect of the complex cytokine network in the airway depends on a number of factors, including the relative abundance of the various cytokines, their ability to recruit and perpetuate the actions of inflammatory cells such as eosinophils and lymphocytes, and their ability to amplify or suppress inflammation by interacting with structural cells such as fibroblasts, endothelial cells, and epithelial cells. There is no question, however, that cytokines are key mediators in the pathogenesis of the chronic inflammation characteristic of asthma.

CHEMOKINES

The chemokines are small–molecular-weight proteins, 8 to 12 kD, that are classified into four categories based on the organization of specific cysteine residues in their protein sequence: XC, CC, CXC, CX_3C.[92] The predominant function of chemokines is the recruitment or chemotaxis of inflammatory cells.[92] Some chemokines also have additional signaling function. There are corresponding families of chemokine receptors for each class of chemokines. Notably, there is considerable overlap and redundancy in the chemokines and their target receptors.

Since the localization of inflammatory cells into the airway is dependent to a large extent on chemotaxis via chemokine signaling, the chemokine receptors have become an attractive target for asthma therapy. There are currently chemokine receptor inhibitors for CCR5 as well as others in development as potential therapy for asthma.[93,94]

IgE

The initial association of IgE with asthma was based on several epidemiological studies.[95–97] With the increased understanding of the role of mast cell mediators in the pathogenesis of asthma, the importance of IgE in triggering mast cell activation and the resulting airway inflammation has been underscored. This relationship between IgE levels and asthma, and its function, led to the development of a humanized monoclonal antibody directed to IgE for asthma therapy.[98] This antibody (omalizumab, Xolair®) has been shown to be effective in the treatment of severe asthma, specifically allowing a significant reduction in dosage of corticosteroids and prevention of asthma exacerbation, further supporting a key role of IgE in asthma.[99]

LEUKOTRIENES

The leukotrienes (LT) are a family of lipid compounds generated from the metabolism of arachidonic acid via the lipoxygenase pathway (Fig. 44-4).[100] These compounds are typically not preformed

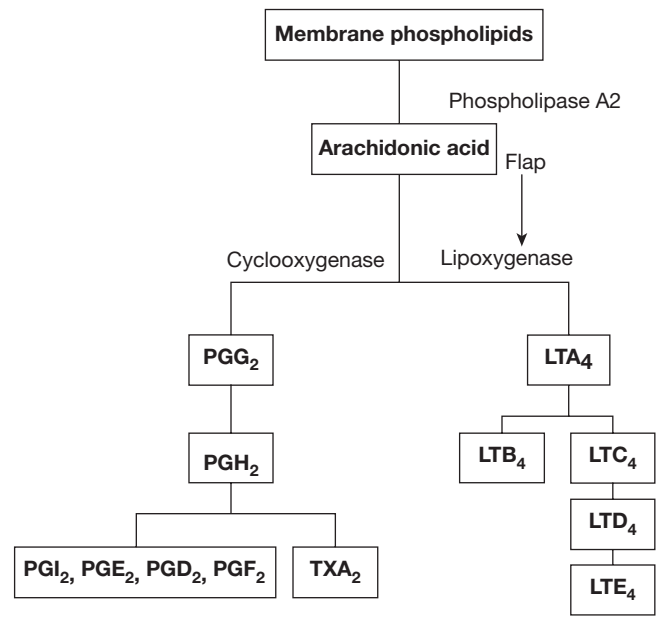

Figure 44-4 Formation of arachidonic acid metabolites. PG, prostaglandin; TXA_2, thromboxane A_2; LT, leukotriene; FLAP, 5-lipoxygenase activating protein.

TABLE 44-1 Cytokines and Lipid Mediators in Asthma

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Interleukins		
IL-1	DCs, monocytes, macrophages, mast cells, B and T cells, neutrophils, endothelial cells, airway epithelial cells	*Basophils*: Increased production of cytokines and histamine *DCs*: Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Macrophages*: Increased cytokine production *Mast cells*: Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *B cells*: Increased antibody production *T cells*: Increased proliferation—especially for T_H2 and T_H17 cells
IL-2	$CD4^+$ T Cells	*T cells*: Increased survival and proliferation, increased T_H2 cytokine production
IL-3	T Cells, mast cells	*Basophils*: Increased survival and release of IL-4, IL-6, and histamine *Eosinophils*: Increased degranulation *Mast cells*: Increased survival and histamine release *Hematopoietic stem cells*: Increased production of mast cells, basophils, neutrophils, eosinophils, macrophages, erythrocytes, megakaryocytes, and dendritic cells
IL-4	T cells, mast cells, basophils, eosinophils	*Airway smooth muscle cells*: Increased airway hyperresponsiveness *Basophils*: Increased recruitment *Eosinophils*: Increased recruitment *Goblet cells*: Increased mucus production *Mast cells*: Increased recruitment, upregulation of FCεRI *B cells*: Increased class switching to IgE, upregulation of FCεRII *T cells*: Increased recruitment, increased T_H2 differentiation, increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells
IL-5	T cells, mast cells	*Basophils*: Increased proliferation, maturation, and functional activation *Eosinophils*: Increased proliferation, chemoattraction, maturation, functional activation, and degranulation
IL-6	Macrophages, DCs, mast cells, neutrophils, B and T cells, endothelial cells, airway epithelial cells	*T cells*: Increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells, promotes differentiation of T_H17 cells, downregulation of T_{REG} cells
IL-7	Bone marrow stromal cells	*Eosinophils:* Increased activation and survival *B cells:* Increased proliferation and survival *T cells*: Increased maturation and survival
IL-8	Airway epithelial cells, neutrophils, eosinophils, monocytes/macrophages	*Eosinophils*: Chemoattraction *Neutrophils*: Chemoattraction
IL-9	T cells	*Mast cells*: Increased recruitment and maturation, increased expression of proteases, upregulation of FCεRI *T cells*: Increased growth and proliferation
IL-10	Monocytes/macrophages, B cells, T cells (specifically T_{REG} cells)	*DCs*: Inhibits expression of co-stimulatory molecules thus inhibiting T_H cell activation *Eosinophils*: Inhibits survival, recruitment, and maturation *Monocytes/macrophages*: Downregulates MHC Class II expression, downregulates inflammatory cytokine production *T cells*: Downregulates IFN-γ and IL-2 production by T_H1 cells and IL-4 and IL-5 production by T_H2 cells
IL-11	Airway epithelial cells, eosinophils, airway smooth muscle cells	*Airway epithelial cells:* Regulate proliferation *Macrophages:* Inhibit production of TNF-α, IL-1, IL-12 *B cells:* Increases immunoglobulin production *T cells:* Inhibits production of TH1 cytokines, Increases IL-4 and IL-10 production
IL-12	Dendritic cells, B cells, macrophages	*NK cells*: Increased IFN-γ production *T cells*: Increased IFN-γ production, increased TH1 differentiation, decreased T_H2 and T_H17 differentiation

(continued)

TABLE 44-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-13	Mast cells, T cells	*Airway epithelial cells*: Increased permeability, increased mucus production, production of inducible nitric oxide synthase *Airway smooth muscle cells*: Increased airway hyperreactivity *Eosinophils*: Promotes migration and survival *Macrophages*: Activation and enhanced MHC Class II expression *B cells*: Increased class switching to IgE and production of IgE
IL-14	T cells	*B cells*: Increased proliferation, suppression of Ig secretion
IL-15	Monocytes/macrophages, DCs	*DCs*: Increased activation and survival, increased production of IFN-γ *Mast cells*: Increased survival *Monocytes/macrophages*: Increased phagocytic activity, increased production of IL-8, IL-12, MCP-1 *Neutrophils:* Increased survival and phagocytic activity, increased IL-8 production *NK cells*: Increased maturation and survival, increased production of IFN-γ, TNF-α, and GM-CSF *T cells*: Increased proliferation of memory $CD8^+$ T cells, Increased proliferation of T_H17 cells
IL-16	T cells, airway epithelial cells, DCs, eosinophils, mast cells	*DCs:* Increased chemoattraction *Eosinophils*: Increased chemoattraction *Monocytes/macrophages*: Increased chemoattraction, upregulation of MHC class II expression *T cells:* Increased migration, maturation, and proliferation
IL-17	T cells, NK cells	*Airway epithelial cells:* Increased production of IL-6, IL-8, G-CSF, PGE_2 *Eosinophils*: Increased chemoattraction *Neutrophils*: Increased production from stem cells, increased chemoattraction
IL-18	DCs, monocytes, macrophages, neutrophils, airway epithelial cells	*Basophils*: Increased production of cytokines and histamine *DCs*: Increased cytokine production, upregulation of MHC and costimulatory molecules *Macrophages*: Increased cytokine production *Mast cells*: Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK cells*: Increased IFN-γ production. *T cells*: Promotes T_H1 differentiation.
IL-19	Monocytes	*T cells*: Increased production of T_H2 cytokines and downregulation of IFN-γ production
IL-20	Monocytes	Unclear
IL-21	T cells	*B cells*: Increased proliferation of IgA, IgG, IgM producing plasma cells and decrease in IgE producing plasma cells *T cells*: Increased differentiation into T_H17 cells, upregulation of T_H1 cytokine production
IL-22	T cells, NK cells	*Respiratory epithelial cells*: Increased production of antimicrobial peptides
IL-23	DCs	*Macrophages*: Increased TNF-α production *T cells*: Increased IL-17 production, promotion of T_H17 differentiation
IL-24	Monocytes, T cells	Unclear
IL-25	Airway epithelial cells, eosinophils, mast cells	*T cells*: Increased production of T_H2 cytokines
IL-26	Monocytes, T cells	Unclear
IL-27	Macrophages, DCs	*T cells*: Increased differentiation into IL-10 producing T_{REG} and T_H1 cells, decreased development of T_H2 and T_H17 cells
IL-28 (IFN-λ2,λ3)	DCs	Inhibits viral replication *DCs:* Increase ability to stimulate production of T_{REG} cells
IL-29 (IFN-λ1)	DCs	Inhibits viral replication *DCs*: Increase ability to stimulate production of T_{REG} cells
IL-31	T cells	*Airway epithelial cells*: Attenuate proliferation of epithelial cells
IL-32	NK cells, Airway epithelial cells, T cells	*Macrophages*: Upregulation of proinflammatory cytokines *Airway epithelial cells*: Decreased production of proangiogenic factors

TABLE 44-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-33	Endothelial cells, airway epithelial cells, dying cells	*Basophils*: Increased production of cytokines and histamine *DCs*: Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Eosinophils:* Increased proliferation, survival, and chemokine production *Macrophages:* Increased cytokine production *Mast cells*: Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK cells*: Increased IFN-γ and T_H2 cytokines *T cells*: Promotes T_H2 differentiation, enhances release of T_H2 cytokines
IL-35	T_{REG} cells	*T cells*: Decreased production of T_H2 cytokines, suppression of T cell proliferation
IL-36	Airway epithelial cells	*T cells*: Increased T_H1 differentiation
IL-37	Hematopoietic cells	*Macrophages*: Decreased secretion of proinflammatory cytokines *Airway epithelial cells*: Decreased secretion of proinflammatory cytokines
Interferons		
IFN-α	Monocytes/macrophages	*Virus infected cells*: Inhibition of viral replication
IFN-β	Monocytes/macrophages	*Virus infected cells*: Inhibition of viral replication
IFN-γ	T cells, NK cells	*Macrophages*: Differentiation, activation, and expression of Fcγ receptor. Increased cytokine production *T cells*: Increased differentiation to T_H1 cells, increased cytotoxicity of $CD8^+$ T cells
IFN-λ	See above	See above
Growth factors		
bFGF	Endothelial cells	*Fibroblasts*: Proliferation and extracellular matrix formation
G-CSF	Monocytes, fibroblasts, airway epithelial cells	*Neutrophils*: Proliferation and differentiation
GM-CSF	T cells, airway epithelial cells, macrophages	*DCs:* Maturation *Eosinophils:* Increased survival, degranulation *Macrophages*: Differentiation, increased survival, increased cytokine production *Neutrophils*: Increased chemotaxis and survival
M-CSF	Fibroblasts, endothelial cells, macrophages, airway smooth muscle cells	*Hematopoietic stem cells*: Differentiation of monocytes
PDGF	Platelets, monocytes, macrophages	*Fibroblasts*: Proliferation and chemoattraction
SCF	Bone marrow stromal cells, fibroblasts	*Mast cells*: Chemoattraction, induction of histamine release, differentiation, proliferation
TGF-β	Eosinophils, T cells, macrophages, airway epithelial cells, endothelial cells, airway smooth muscle cells	*Fibroblasts*: Chemoattraction and increased conversion to myofibroblasts, increased synthesis of collagen *Macrophages:* Chemoattraction *Neutrophils*: Chemoattraction *T cells:* Increased differentiation of T_{REG}, T_H9, and T_H17 cells, inhibition of T_H1 and T_H2 differentiation
VEGF	Macrophages, airway epithelial cells, T cells, eosinophils	*Airway smooth muscle cells*: Hyperplasia and increased airway hyperresponsiveness *DCs:* Increased proliferation and activation *Endothelial cells*: Increased angiogenesis and vascular permeability *Airway epithelial cells:* Increased proliferation, mucus production *Fibroblasts*: Promotion of subepithelial fibrosis
Other		
TNF-α	Monocytes/macrophages, DCs, mast cells, eosinophils, neutrophils, B and T cells, airway epithelial cells, airway smooth muscle cells, fibroblasts	*Airway epithelial cells*: Upregulation of adhesion molecules *Airway smooth muscle cells*: Increased airway hyperresponsiveness *Endothelial cells*: Upregulation of adhesion molecules *Eosinophils*: Chemoattraction, increased activation *Fibroblasts*: Increased conversion to myofibroblasts *Macrophages*: Chemoattraction *Mast cells*: Increased histamine release *Neutrophils*: Chemoattraction *T cells*: Increased activation and cytokine release

(continued)

TABLE 44-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
TSLP	Airway epithelial cells	*DCs*: Increased ability to attract T_H2 cells *Eosinophils*: Induced release of proinflammatory cytokines and chemokines *Mast cells*: Increased production of T_H2 cytokines *T cells*: Increased differentiation to T_H2 cells
Lipid Mediators		
Mediator	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Leukotrienes		
Dihydroxy acid leukotriene (LTB4)	DCs, monocytes/macrophages, neutrophils	*B lymphocytes*: Increased expression of CD23, CD54, and CD105 *DCs*: Recruitment, increased skewing of T_H0 cells to T_H1 type *Eosinophils*: Recruitment *Mast cells*: Recruitment *Monocytes/macrophages*: Increased production of IL-6, TNF-α, MCP-1 *Neutrophils*: Recruitment and activation *Airway smooth muscle cells*: Increased proliferation *T lymphocytes:* Recruitment
Cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4)	DCs, eosinophils, mast cells, monocytes/macrophages	*Airway smooth muscle cells*: Bronchoconstriction *DCs*: Increased migration to lymph nodes *Endothelial cells*: Increased vascular permeability and upregulation of adhesion molecules *Eosinophils*: Recruitment *Goblet cells*: Increased mucus production *Mast cells*: Increased production of IL-5, IL-8, TNF-α, and MIP-1β *Monocytes/macrophages*: Increased production of MCP-1, TNF-α, and MMP-9 *T lymphocytes*: Increased T_H2 immune response
Prostanoids		
PGD_2	Mast cells	*Airway smooth muscle cells*: Bronchoconstriction *Eosinophils*: Recruitment, increased degranulation *Monocytes/macrophages*: Increased cytokine production *Neutrophils*: Inhibition of activation *T lymphocytes*: Recruitment, increased production of T_H2 cytokines, inhibition of IFN-γ production
PGE_2	Airway smooth muscle cells, airway epithelial cells, endothelial cells, macrophages	*Airway smooth muscle cells*: Inhibition of allergen-induced bronchoconstriction *Eosinophils:* Inhibits recruitment *Monocytes/macrophages*: Decreased cytokine production, downregulation of MHC Class II expression *T cells*: Decreased proliferation, decreased T_H2 cytokine production
PGI2 (Prostacyclin)	Endothelial cells, monocyte/macrophages	*Endothelial cells*: Vasodilatation *Eosinophils*: Inhibition of recruitment *T cells*: Increased IL-10 production
Thromboxane A_2	Platelets, endothelial cells, monocyte/macrophages	*Airway smooth muscle cells*: Bronchoconstriction *Eosinophils*: Recruitment

and stored in cells for release upon activation; rather, they are rapidly synthesized following activation of the source cell. LTC_4, LTD_4, and LTE_4 are potent bronchoconstrictors that are produced by several cell types, including eosinophils and mast cells, whereas LTB_4 is a neutrophil attractant.[100] The leukotrienes are also able to increase mucus secretion in the airway and facilitate a plasma leak generating edema in the airway.[100,101] Leukotriene receptor antagonists (e.g., montelukast, Singulair®) are currently used in the treatment of asthma.[102] Although effective in some patients, the leukotriene modifiers have limitations as regards overall potency, thus raising questions as to what are the conditions, or phenotypes, in which leukotrienes dominate.[103]

Prostanoids

The prostanoids (PG) are a family of lipid compounds generated from the metabolism of arachidonic acid via the cyclooxygenase pathway (Fig. 44-4).[104] Most of the prostanoids, that is, PGD_2, PGF_2, and TXA_2, are potent bronchoconstrictors and products of several

cell types including eosinophils and mast cells.[104] However, another prostanoid, PGE_2, has bronchodilatory and anti-inflammatory activity.[105,106] The use of nonsteroidal anti-inflammatory medications to inhibit cyclooxygenase activity has not been shown to have an appreciable effect on airway inflammation. It has been observed that PGD_2 is the predominant prostanoid involved in asthma.[107] Therefore, specific PGD_2 receptor antagonists are currently being considered to ameliorate some of the bronchoconstriction in asthma.[108–110]

NITRIC OXIDE

The role of nitric oxide (NO) in the pathogenesis of asthma remains unclear. NO is continually synthesized at low levels in the airways of normal subjects. Sources of NO in the respiratory tract include airway epithelial cells, smooth muscle cells, sensory nerves, endothelial cells, and macrophages.[111] At low levels, NO is a bronchodilator and vasodilator that antagonizes endothelin and has protective effects in the airway.[111] Higher levels of NO are found in asthma, secondary to increased inducible NO synthase expression, and may be detrimental to airway epithelium.[112] This may be mediated by the ability of NO to react with superoxide anion in inflamed tissue to produce biologic oxidants that contribute to ongoing tissue damage and chronic asthmatic inflammation.[111] The production of NO is also thought to reflect the level or severity of airway inflammation. Thus, exhaled NO measurement has been utilized successfully as a tool to reflect the extent of airway inflammation as a measure of asthma control.[112]

GRANULE PROTEINS

Granulocytes, that is, mast cells, basophils, eosinophils, and neutrophils, are capable of releasing granule proteins, many of which has been proposed to play significant roles in the pathogenesis of asthma.

Insights into the kinetics and importance of mast cell mediators have been obtained from measurements of BAL histamine and tryptase.[113] These studies have demonstrated that mast cell activation is an early event, with elevated BAL histamine and tryptase levels being seen 12 minutes after endobronchial antigen challenge; the levels of tryptase returning to normal 48 hours after antigen challenge.[113] The levels of histamine remain elevated after 48 hours, raising the possibility that non-mast cells (e.g., basophils) are subsequently recruited and activated to produce histamine at these later points or that mast cells generate and continue to release histamine over time following an initial activation.[113] Furthermore, BAL of allergic asthmatic subjects had only moderately elevated levels of tryptase at baseline but higher concentrations of tryptase following antigen challenge.[113]

Histamine is capable of inducing bronchoconstriction, increasing vascular permeability to cause edema, and increasing mucus secretion.[114] The role of tryptase is not well established, although there are data to suggest that it can activate inflammatory cells such as eosinophils, mast cells, and epithelial cells by cleaving a family of protease activated receptors (PARs) on their cell surfaces.

Major basic protein (MBP) is the principal protein constituent of eosinophil granules. It is toxic to epithelial tissues, induces airway hyperresponsiveness, and causes histamine release from basophils.[115] ECP is more cytotoxic to the epithelium than MBP and damages target cells by membrane pore formation.[116] Eosinophil-derived neurotoxin (EDN), as the name implies, damages myelinated neurons.[117] EPO differs from neutrophil and monocyte myeloperoxidases (MPOs); it causes LTC_4 and LTD_4 degradation and causes histamine release from mast cells.[118]

Neutrophil release of MPO and neutrophil elastase enhances host defense functions but is also potentially injurious to normal tissues, including airway epithelium.[119] The primary granules of neutrophils contain MPO and lysozyme as well as hydrolases and proteinases, which are important in tissue penetration by neutrophils.[119] Secondary granules contain lysozyme and collagenases, which can also potentially damage airway tissue.[119] Neutrophil granule proteins are considered toxic to airway epithelium and tissue.

REMODELING IN ASTHMA

As occurs in most chronic inflammatory disorders in which there is an "injury–repair" cycle, tissue remodeling is a key component of asthma. Airway remodeling in asthma involves epithelial changes, increases in smooth muscle mass, increased angiogenesis, increased fibroblast/myofibroblast activity, increased fibrosis, and many other important changes that affect the structure and function of the large and small airways of the lung.[120] Prolonged infiltration of inflammatory cells and the cytokines, chemokines, and growth factors, which they generate, contribute to these structural changes, which help define the features of asthma in some patients.

As mentioned previously, airway epithelium serves not only as an anatomic barrier, but also as a key player in asthma pathogenesis. Defects in airway epithelium are ubiquitous in human asthma and, when injury occurs, the repair process has been likened to a chronic wound, which may not heal normally as a result of repetitive and ongoing insults.[121] As with other types of chronic wounds, the body attempts to heal the epithelial damage by promoting the release of growth factors from the underlying mesenchyme. This, in turn, leads to increased extracellular matrix deposition, fibrosis, and size and number of airway smooth muscle cells.[122] These even have been likened to the function of the epithelial–mesangial trophic unit (EMTU), a key component of early lung morphogenesis, which, in a sense, becomes reactivated in chronic asthma.[122] The consequence of prolonged epithelial injury is a protracted release of proinflammatory cytokines and profibrogenic growth factors such as TGF-β. When these reactions are combined with the inflammatory milieu derived from the immune cells recruited to the airway by this long-term damage, the effects of these morphologic changes are manifested in chronic airflow obstruction, which is often resistant to pharmacologic treatment, and results in permanent airflow obstruction.

PHENOTYPIC CLUSTERS IN ASTHMA

Several recent studies have begun to identify phenotypes, or subphenotypes, of asthma. These studies have confirmed that asthma is a very heterogeneous disease.[123,124] Specifically, studies by Haldar and colleagues in the United Kingdom used sputum eosinophilia, in addition to measurements of atopic status and other characteristics, to identify these subphenotypes.[123] Interestingly, they identified a cluster of patients with symptomatic disease who had very little eosinophilic involvement and lacked evidence of atopic sensitization. Other groups fit a more "classic" pattern of asthma with evidence of eosinophilic involvement and atopic sensitization. Other clusters fell somewhere between the two. This study, and others, are probing the heterogeneity of the disease and discovering the reasons behind differences in disease course and response to conventional asthma therapy.

CONCLUSION

Asthma is a complex disease in which the contributions of many different immune cells, structural cells, molecular mediators, and external factors combine to produce acute and chronic inflammation and airflow obstruction. The study of these different factors has led to a greater understanding and appreciation of the breadth of this disease and a recognition of its complexity and heterogeneity. It has also led to the realization that different phenotypes of asthma exist and treatment of asthma based on the specific phenotype represents an emerging, potentially more specific and effective possibility. Over the last decade, many new advances in therapy have been made that target specific inflammatory mediators in asthma. The fact that these have not been universally successful speaks to the heterogeneity and redundancy of asthma. As research delves further into the pathogenesis and pathophysiology of asthma, many more

targets will emerge, which will hopefully lead to novel therapies to improve the lives of asthmatic patients and with these interventions greater insight into the effects of individual mediators and in whom they may be relevant.

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CHAPTER 45
Asthma: Epidemiology

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Asthma is a clinical syndrome that affects 25 million Americans and accounts for 12.7 million medical visits yearly. One-third of those afflicted with asthma are children under the age of 18 years. It is estimated that roughly half of these children received their diagnosis prior to the age of 6 years. As a result, the origins of asthma are believed to have a clear genomic component that is often manifested in early childhood. The clinical course of this illness is influenced greatly by exposures, including respiratory viruses, indoor allergens, maternal tobacco smoke, and other physical and social aspects of the environment. Thus, this clinical disease has important consequences in childhood and may have important consequences for adult obstructive lung disease.

Asthma is an extremely common clinical problem and the most common cause of hospitalization for children in the United States. The estimated total annual costs of asthma care is rising dramatically and totaled approximately $56 billion in 2007 in the United States,[1] representing a $3 billion increase since 2002. These costs include $50.1 billion per year in medical expenses, $3.8 billion per year in missed school or lost work days, and $2.1 billion per year in premature deaths. The paradox of this illness is that despite important strides in understanding etiologic environmental factors and mechanisms of airway inflammation characteristic of the syndrome, its prevalence and morbidity remain unacceptably high. Although asthma morbidity and mortality rates have been steady over the last few years, the rates are dramatically higher than 25 years ago and continue to be very significant, particularly for urban minority groups, low-income populations, and children.

The purpose of this chapter is to describe trends in asthma epidemiology, specifically prevalence, hospitalization, and mortality. In so doing, we examine potential reasons for these trends, and the recent research on the interactions of genes and environment. We also examine the relationship of the intermediate phenotypes of airway hyperresponsiveness and allergy to the asthma syndrome and consider a variety of risk factors for asthma occurrence. We conclude with a review of asthma natural history and the implications of the current trends.

DEFINITIONS AND PREVALENCE

In 2007, the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPPR3)[2] defined asthma as

> a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Because asthma is a clinical syndrome, there is no gold standard for its diagnosis. As such, physicians employ nonstandardized algorithms for making the diagnosis, such as a history of wheezing or a parental history of asthma in conjunction with a favorable response to a bronchodilator to identify the asthmatic patient. Frequently, age, gender, and other patient characteristics such as smoking status or response to allergen may influence a physician's diagnosis. Rarely are tests of airway responsiveness used to investigate symptomatic patients in the clinical setting.

In general, epidemiologic surveys have tended to rely on historical or questionnaire sources to identify patients with asthma. Asthma cases have been identified, either by physicians or surveys of population groups in whom the definition of who is asthmatic has been left to the patients themselves, surrogates, or the report of the diagnosis having been made by the patient's physician. Clearly, each of these methods of identifying asthma patients has inherent weaknesses. One must, therefore, assume that some bias in the reporting of cases is present and that the biases in each method of gathering data are different.

The National Health Interview Survey (NHIS) is an annual random population household interview survey that provides information on asthma prevalence in the United States. Its data demonstrate an almost doubling of asthma prevalence over the last quarter century,

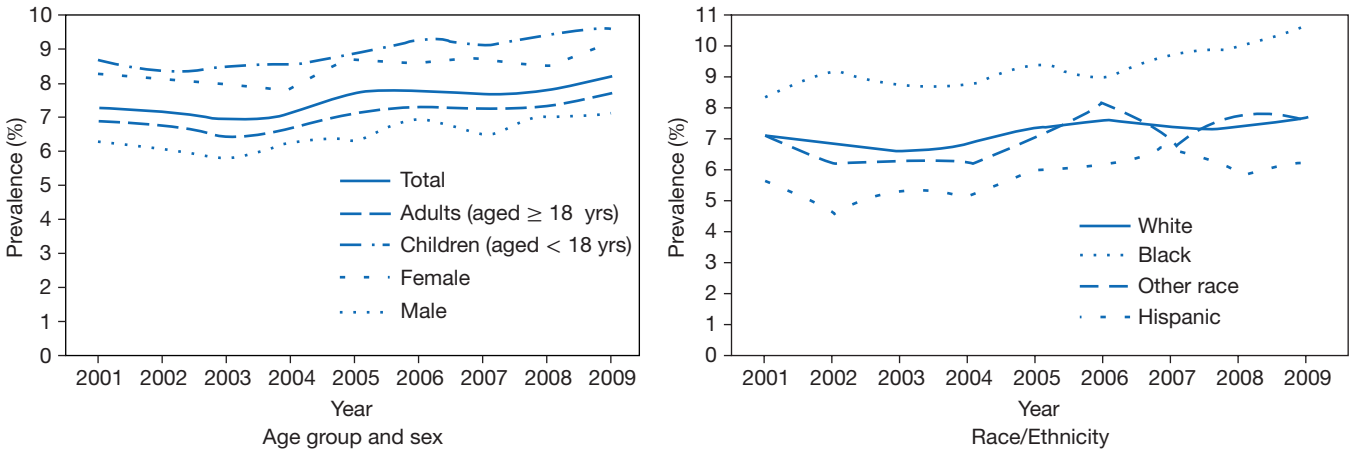

Figure 45-1 Current asthma prevalence figures from the National Health Interview Survey (NHIS), United States, by age group, sex, and race/ethnicity. Prevalence measures include persons who answered "yes" to the questions: "Have you ever been told by a doctor or other health professional that [you/your child] had asthma?" and "Do [you/your child] still have asthma?" *(Reproduced with permission from Vital signs: asthma prevalence, disease characteristics, and self-management education. United States, 2001–2009. MMWR Morb Mortal Wkly Rep. 2011;60(17):547–552.)*

from 3.2 per 100 population in 1981 to 5.5% per 100 in 1996.[3] In 1997 the NHIS questions and methodology were modified, limiting comparisons of prevalence before and after 1997. Instead of asking whether the respondent or a family member had had asthma over the past 12 months the newer version asks, "Have you ever been told by a doctor or other health professional that you had asthma?" (lifetime prevalence). Information about adults can no longer be obtained from a family member or proxy. If the response is affirmative, an "attack" question is asked, "During the past 12 months have you had an episode of asthma or asthma attack?" Beginning in 2001, if the lifetime prevalence response was positive, a point prevalence or "Current" measure was added asking, "Do you still have asthma?" The data from the "Current" question, is most comparable with previous data, but not exactly the same. Most recent data from the CDC, which analyzed data from the NHIS, indicated a plateau in asthma prevalence from 2001 through 2003, but prevalence has continued to rise since then (Fig. 45-1).[4] The prevalence in children under 18 years remains higher than adults, for example, in 2009, 9.6 per 100 compared with 7.7 (Fig. 45-1).

There is a difference in prevalence by racial/ethnic groups. Until 1997 racial groups were classified as black or white with black population having slightly higher 12-month prevalence. Beginning in 2003, racial and ethnic classification was expanded to include Hispanics. The most recent data from 2009 shows that prevalence was 11.1 for black non-Hispanics, 6.3 for Hispanics, and 8.1 per 100 for white non-Hispanics.[4] It is noteworthy that the rate for Hispanics of Puerto Rican descent was 14.2 per 100.[5]

The current data show a significant modification of prevalence by gender, in that males tend to predominate in the younger age group, whereas gender ratios equalize in the pubertal years, and females predominate throughout the rest of the adult life. For example, the current prevalence for males less than 18 years in 2009 was 11.3 per 100 compared with 7.9 for females, but in adults 18 years and older female prevalence (9.7 per 100) is almost twice that for males (5.5 per 100).[4] Thus, age and gender play an important role in modifying disease prevalence. In addition, there also appears to be some regional variation in asthma prevalence rates. Asthma prevalence was highest in the Northeast (9.3%), followed by the Midwest (8.8%), the West (7.7%), and the South (7.5%).[4]

ASTHMA HEALTHCARE USE

Drawing from data from multiple national surveys, the analyses performed by the CDC suggest that hospitalization and emergency

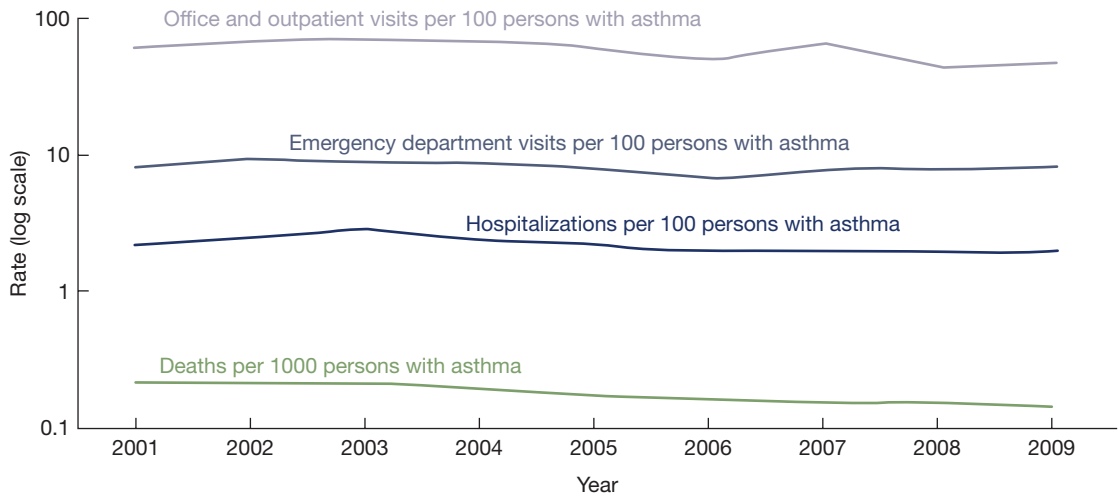

Figure 45-2 Asthma healthcare encounters per 100 persons with asthma, and asthma deaths per 1000 persons with asthma: United States, 2001 to 2009. *(Reproduced with permission from Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS Data Brief. 2012;(94):1–8.)*

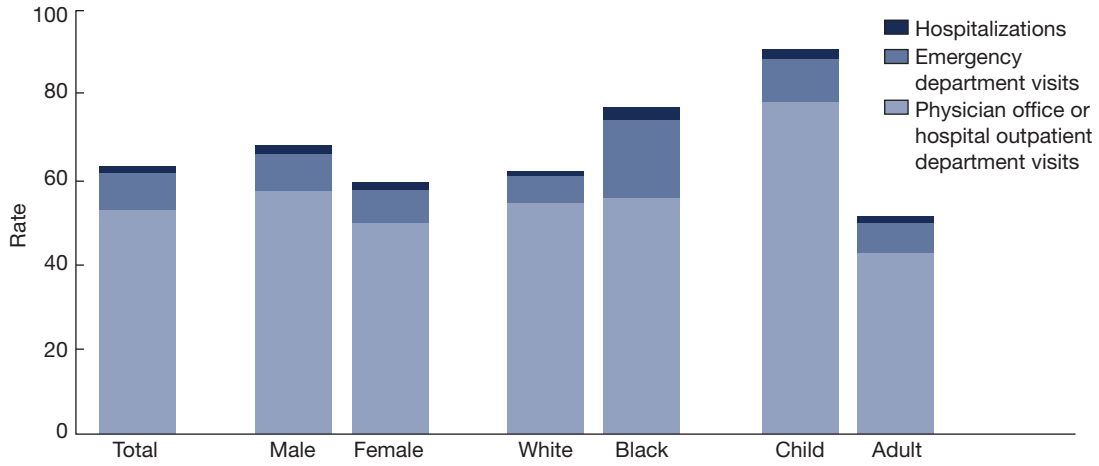

Figure 45-3 Asthma healthcare encounters per 100 persons with asthma: United States, 2001 to 2009. Hospitalizations are three times more frequent and emergency department visits almost five times more frequent among blacks. Healthcare utilization is more frequent in children than adults. *(Reproduced with permission from Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS Data Brief. 2012;(94):1–8.)*

department (ED) visit rates for asthma have remained stable from 2001 to 2009, a period of rising prevalence (Fig. 45-2).[6] Asthma visits in primary care settings (defined as physician offices and hospital outpatient departments) declined during this period. Asthma healthcare use is known to vary by demographic characteristics. For the period 2007 to 2009, asthma healthcare use across all healthcare settings was greater for children than for adults (Fig. 45-3): outpatient visit rates for children (0–17 years) averaged 78.7 per 100 persons with asthma versus 42.5 for adults; ED visits for children averaged 10.7 per 100 persons with asthma versus 7.0; while hospitalization rates were similar for both groups (2.1 per 100 persons with asthma for children vs. 1.9 for adults).[6] With respect to gender, for the 2007 to 2009 period, males had higher annual average outpatient visit rates than women (57.6 per 100 persons with asthma for men vs. 49.8 for women), while ED visit and hospitalization rates were about the same for both sexes (8.7 ED visits per 100 persons with asthma for males vs. 7.6 for women, and 1.8 hospitalizations per 100 persons with asthma for males vs. 2.0 for women). With respect to race, asthma outpatient visits per 100 persons with asthma were similar for black (54.9) and white (56.0) persons, but ED visits were three times higher in blacks (18.4 per 100 persons with asthma) than whites (6.1 per 100 persons with asthma), and hospitalizations were two times higher in blacks (2.8 per 100 persons) than whites (1.3 per 100 persons).

TRENDS IN ASTHMA MORTALITY

Asthma mortality rates in the United States are quite low. Recent data show that for the period 2007 to 2009, the asthma death rate per 100 persons with asthma was 0.015.[6] Figure 45-4 shows the trends in asthma mortality in the United States between 1980 and 2004.[7] There is an overall decline in deaths since 1998, although 11% of that decline can be attributed to the new coding instituted in 1999. As seen in Figure 45-2, the decline in death rates for asthma has continued through 2009. However, the downward trend in countrywide asthma mortality belies pockets of very high prevalence, morbidity, and mortality in urban minority populations. For instance, in 2009, blacks had a greater likelihood of dying from asthma than whites (Rate ratio = 1.93).[8]

These mortality rates do not represent a public health concern in an absolute sense, as the number of deaths is still very low. However, the rates do represent a clear public health concern because almost all asthma deaths are preventable, and certain urban and minority areas have extremely high mortality rates, suggesting inadequate care practices.

INTERMEDIATE PHENOTYPES

There are two intermediate phenotypes that contribute to the asthmatic syndrome: airway responsiveness and allergy. Both have a genetic component, and both are influenced by environmental factors. We will discuss these phenotypes and their interrelationship to each other and to asthma.

AIRWAY RESPONSIVENESS

Airway responsiveness is measured by quantifying decline in lung function caused by using increasing doses of a bronchoconstrictive stimulus, such as histamine or methacholine (see Chapter 33). When the patient's FEV_1 decreases by 20% from its initial value, or after a maximum stimulus dose has been administered, the test is terminated. The dose at which this drop occurs is called the *provocative dose* (PD_{20}). Individuals who manifest a PD_{20} at a low dose of

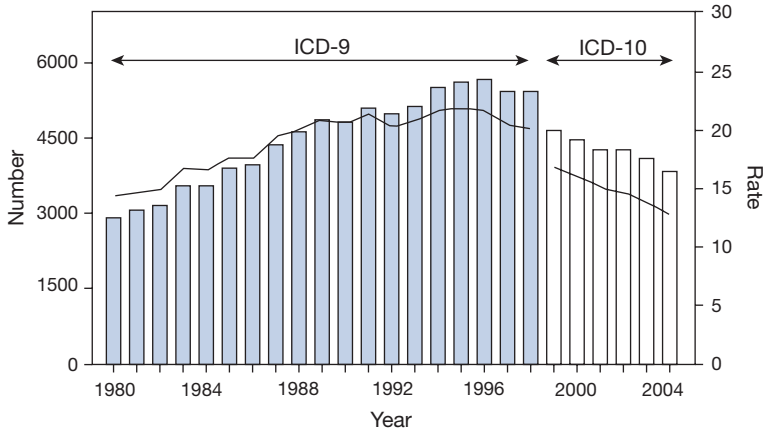

Figure 45-4 Asthma mortality trends, by year and International Classification of Diseases (ICD), United States, 1980 to 2004. Since1980, deaths from asthma rose. Beginning in 1998, both the overall number of deaths and the rate have clearly declined. However, a new mortality coding scheme was implemented in 1999. About 11% of the decline in asthma deaths can be attributed to the new coding scheme. *(Reproduced with permission from Moorman JE, Rudd RA, Johnson CA, et al. National surveillance for asthma–United States, 1980–2004. MMWR Surveill Summ. 2007;56(8):1–54.)*

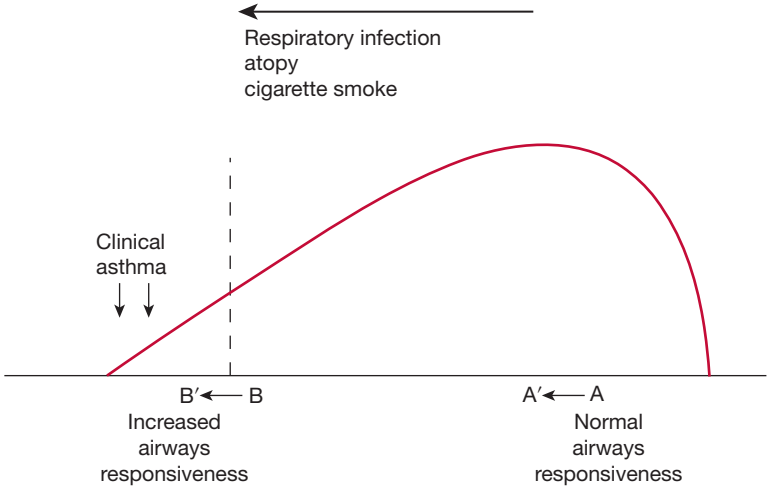

Figure 45-5 The effect of environmental exposures on the population distribution of airway responsiveness acting to move people in a more responsive direction. *(Reproduced with permission from Brown RW, Weiss ST. The influence of lower respiratory illness on childhood asthma: defining risk and susceptibility. Semin Respir Infect. 1991;6(4):225–234.)*

stimulus are said to have increased airway responsiveness and are hyperresponsive to the inhaled agent.

Cross-sectional population-based surveys of children and adults conducted in many different countries and using a variety of techniques for measuring airway responsiveness have shown that the prevalence of airway hyperresponsiveness is upward of 20% in the general population,[9–11] with women having a higher prevalence than men The prevalence of increased airway responsiveness exceeds the prevalence of asthma by two- to fivefold.

These studies have also demonstrated that airway responsiveness is log normally distributed in the general population. An example of this is given in Figure 45-5. In this population-based study of the distribution of histamine airway responsiveness, symptomatic or asthmatic subjects appear at the more responsive end of the distribution, but there is considerable overlap with asymptomatic subjects.[8] Other population-based studies have confirmed that a large number of asymptomatic subjects manifest increased airway hyperresponsiveness to this agent.

It has been well demonstrated in studies of both children and adults that airway hyperresponsiveness antedates and predicts the development of asthma.[12–16] Increased airway responsiveness carries at least twice the risk for the development of asthma in children and young adults. However, increased airway responsiveness is a necessary, but not a sufficient condition for the development of asthma. In all likelihood, subjects who are genetically predisposed have increased airway responsiveness.[15] They then encounter environmental stimuli that generate airway inflammation. The inflammation then moves them in the direction of greater responsiveness and the development of respiratory symptoms. This theoretical paradigm is graphically depicted in Figure 45-5.[17]

A variety of mechanical factors influence airway responsiveness. First, and most important, is the level of lung function. Individuals with lower levels of lung function are more likely to have increased airway responsiveness.[18–20] In part, this is simply a mathematical phenomenon. Since airway responsiveness is expressed as a percent change from baseline, the baseline value will obviously be important in determining the level at which an individual would be considered responsive (i.e., have a PD_{20}). This can be best understood with a simple mathematical example. A man with a 5-L FEV_1 would be required to drop his prechallenge level of lung function by 1 L to achieve a PD_{20} for FEV_1. In contrast, a man with a 500-mL FEV_1 will only need to drop his FEV_1 by 100 mL to achieve a comparable PD_{20} for FEV_1. Other factors, such as the central deposition and distribution of the inhaled aerosol, the fact that airflow is inversely proportional to the fourth power of the airway radius, and baseline bronchomotor tone all contribute to the relationship of lung function to airway responsiveness. For this reason, airway responsiveness is likely to be increased at the extremes of age (i.e., in children and older adults) and reduced in young adults between the ages of 15 and 45 years.[19]

■ ALLERGY

Allergy refers to immediate (Type 1) hypersensitivity to environmental antigens. It is characterized by wheal and flare reactions to skin testing with common environmental antigens, usually with appropriate clinical history. Atopy is the demonstration of allergy and familial aggregation of this trait.

Initially described over 20 years ago by Mosmann and colleagues,[21–23] the Th1–Th2 dichotomy has been helpful in explaining the pathophysiology of the allergic response. This model is also the basis for clinical research seeking to understand the development of asthma. Antigen presenting cells (APCs) display peptide antigens, either allergenic or infectious, on their cell surfaces for recognition by naïve T cells (Th0).[24] Th0 differentiate into Th1 or Th2 cells, depending on the nature of the antigen, the characteristics of the APC, local concentration of cytokines, and other cofactors not fully understood.[25] Th1 cells secrete IFN-γ, while Th2 cells secrete IL-4 and IL-5. (see Chapter 44). For example, activation of APC by microbial products results in production of IL-12 and Th0 cells differentiate into Th1 cells. The presence of IL-4 results in differentiation of Th0 cells into Th2 cells. Th2 cells promote allergic inflammation through the production of cytokines including IL-4, IL-5, and IL-13. IL-4 and IL-13 induce B lymphocytes to differentiate into IgE-producing plasma cells. IL-5 secreted by Th2 cells results in eosinophil production and resistance to apoptosis.[26] A Th1 response results in activation of macrophages and natural killer cells and production of IgG1, which plays a role in complement binding and opsonization. Th1 and Th2 cells cross-regulate each other. That is, IFN-γ inhibits Th2 proliferation and IL-4 inhibits IFN-γ–induced macrophage activation. T-regulatory (Treg) cells are recently characterized cells that inhibit Th1 and Th2 cells.[27] These cells are characterized by their secretion of IL-10 and transforming growth factor (TGF)-β, and, via the expression of Foxp3, lead to suppression or proliferation of other T cells.[28,29] Tregs also suppress effector cells of allergic inflammation (e.g., basophils, eosinophils, and mast cells),[30,31] and regulate IgE production.[32] Thus, it is likely that Tregs play a role in airway tolerance in the prevention of asthma.[33]

Since the initial description of the Th1/Th2 dichotomy, it has become clear that mechanisms involved in asthma and the allergic response are much more complicated. The role of the epithelium and upstream pathways has become clearer (as reviewed in Williams et al.[34]). Initial activation occurs in the epithelium, upon interaction of allergen and/or pathogen (damage)-associated molecular patterns and toll-like receptors. Early response cytokines, including thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 (previously termed IL-17E) are released in the local tissue environment. These set off a cascade of events that include dendritic cell skewing to a phenotype that supports differentiation of Th2 cells, and also expansion of innate immune effector leukocytes secreting IL-4, IL-5, and IL-13 leading to a Th2 inflammatory response. Other cytokines are now recognized to play a role in the acute response and chronic inflammation characteristic of asthma and allergies, including IL-9, IL-17, IL-22, among many others.[26,35]

CLINICAL MARKERS OF ALLERGY

Many clinical allergy markers have been utilized in epidemiologic studies of asthma. Total or allergen-specific IgE, measured by serologic testing, or specific allergen skin testing, assess sensitization as well as exposure to environmental antigens and frequently are used to determine the prevalence of allergic responsiveness. Skin test reactivity depends on at least three separate factors: (1) an intact immune system; (2) the presence of IgE-sensitized mast cells that release mediators when exposed to antigen; (3) and skin that can respond to histamine with the development of an inflammatory response, including erythema and induration. Although these manifestations of an allergic response depend on prior exposure to an environmental antigen, they do not measure or take into account the level of exposure in the environment.

Total serum IgE, although used in epidemiologic studies, has relatively limited value in the diagnoses of atopic diseases, with the exception of allergic bronchopulmonary aspergillosis. Total and specific IgE levels correlate with each other and with skin test results, but no level of total IgE avoids misclassifying a significant proportion of those with and without allergic diseases. The limitations in clinical information imposed by these tests reduce their utility when they are used in epidemiologic studies.

Total and specific IgE measurements appear to be comparable in males and females. Both increase with age and peak approximately at the age of 15 years. After this time, there is a progressive decline, although the decline in skin test reactivity exceeds the reduction in total serum IgE, perhaps related to local factors in the skin.

It is believed that IgE responses to inhalant allergens are commonly set in early childhood. In early life, the immune system is characterized by immature humoral and cellular responses. Initially thought to be unresponsive, in fact, the neonatal response is strongly biased toward a Th2 function.[36–38] As the neonate grows and the immune system matures, there is a shift toward a more balanced immune response in healthy individuals. The process by which this shift comes about is the object of intense research. For example, it is known that potent neonatal Th1 responses can be induced under specific circumstances (e.g., infections).[39–42] Immunomodulatory agents that can promote neonatal Th1 immunity are the subject of current research.[43,44] Thus, sensitization, that is, production of IgE directed at environmental antigens, is not only a function of genetic susceptibility, dose, timing, and duration of allergen exposure, but likely reflects early exposure to other environmental antigens, particularly microbial or viral organisms. One hypothesis of the development of atopic disease, the "hygiene hypothesis," states that the prevention of Th2-mediated disorders is dependent upon early exposure to infectious agents. That is, respiratory or gastrointestinal infections may stimulate macrophages to produce interferon-α and IL-12 that stimulate NK cells to produce IFN-γ, which would inhibit the development of a Th2-type response. The Tucson Children's Respiratory Study, a birth cohort of 1246 subjects, noted that children who had a nonwheezing lower respiratory tract illness before 9 months of age had lower total IgE levels at 9 months and 6 years of age when compared with children who had no lower respiratory illnesses before 9 months of age.[45,46] These children were also less likely to be atopic than those who had no lower respiratory tract illnesses. These investigators also found that children exposed to more siblings at home or to day care in the first 6 months of life, presumably exposed to more infections, were protected from the development of asthma between ages 6 and 13 years.[47] Findings from some other cohorts have shown similar effects of early life exposure to day care or more siblings on asthma risk.[48–50] On the other hand, several other birth cohorts have found either that early day care exposure had no effect on asthma development or that it increased the risk for asthma and asthma-like symptoms in children.[51–54] This research confirms the complexity of environmental influences on the immune system.

RELATIONSHIP OF AIRWAY RESPONSIVENESS AND ALLERGY TO ASTHMA

Atopy and increased airway responsiveness are independent factors, both of which are related to the asthma phenotype. While the prevalence of atopy is higher among asthmatics than nonasthmatics, the association may not be causal. Systematic reviews have shown that at a population level, there is no correlation between the prevalence of atopy and the prevalence of asthma.[55–57] It is likely that there are common factors that raise the risk of both conditions. Studies that have investigated phenotypes of asthma using clustering methods have shown that there are asthma cases that are predominantly atopic with positive skin test reactivity, eosinophilia, and a younger age of onset, whereas there are other clusters that are predominantly nonatopic with neutrophilia and an older age of onset.[58,59]

Atopy and airway responsiveness may also occur together. Studies have shown that individuals who are sensitized to an allergen have bronchospasm when exposed to that allergen,[60,61] but individuals may have airway hyperresponsiveness without atopic manifestations. The introduction of omalizumab, a recombinant, humanized anti-IgE antibody, is helping to elucidate the relationship of airway responsiveness and allergy. Omalizumab lowers total serum IgE and reduces eosinophils in sputum.[62–64] In some studies it has allowed reduction of corticosteroid therapy, but in others it has failed to show reduction in airway hyperresponsiveness, supporting the notion that airway hyperreactivity and allergy have other separate influences.

Since the first report of a longitudinal relationship between exposure to higher levels of dust mite allergen and the development of asthma,[65] researchers have explored the relationship between exposure to allergen and the subsequent development of asthma. A birth cohort design has been used to examine this relationship. Preventing loss of participants to follow-up makes these studies difficult to conduct. It is also difficult to measure exposure to allergen, that is, to quantify inhalation by subjects, while accounting for intermittent and varying exposure over time and place. Nevertheless, most studies have investigated exposure to allergens in house dust early in life. Furthermore, there is an imperfect correlation among skin test reactivity, total serum IgE level, and peripheral blood eosinophil count, such that no single phenotypic marker completely defines the atopic state. These longitudinal studies have shown that exposure to high levels of allergens early in life increases the risk for sensitization and atopy.[66,67] However, the effect on asthma appears to depend on the atopic status of the parents. In children of atopic parents, exposure to high levels of allergen in early life increased the risk of asthma in childhood,[66] whereas in studies where cohorts were not selected for parental atopy, there was no significant effect of exposure to allergens in early life and asthma risk in childhood.[67,68] These studies suggest the theme that asthma and allergies have some common determinants but are likely separate entities, and that genetic susceptibility likely interacts with environmental exposures in determining risk for the development of asthma.

GENETIC SUSCEPTIBILITY AND GENE–ENVIRONMENT INTERACTIONS

Geneticists describe asthma as a complex disease, a disease in which many genes influence the development and phenotype of asthma, each having only a small influence. Since the human genome project was completed in 2000, remarkable advances have been made in identifying asthma genes.

There are two main types of genetic studies: linkage studies and association studies. In an association study, candidate genes are examined to determine a statistical association between polymorphism in the gene and asthma phenotypes; either cases and controls or trios can be used. These studies focus on known pathophysiology. An extension of the candidate gene association study is the genome-wide association study (GWAS). In this case, a panel of

markers, commonly single nucleotide polymorphisms (SNPs) and numbering 500,000 to over 2 million, are genotyped and association analysis is conducted to find associations with asthma phenotypes. This type of association study is hypothesis free and does not focus on known pathophysiology.

Linkage studies start with families with well-characterized phenotypes such as asthma. Genes within families are examined for linkage, the sharing of genes markers that may be located near or at the disease gene. Association studies are then used to follow-up and "fine map" the linkage peak. These studies focus on novel genes.

To date, five genes *ADAM 33*,[69] *DPP10*,[70] *PHF11*,[71] *NPSR1*,[72] and *HLA-G*,[73] have been identified by linkage and fine mapping. One gene *ORMDL3*[74] has been identified by GWAS. Two large meta-analyses of asthma GWAS have been conducted in European and ethnically diverse US populations,[75,76] with surprising consistency in results. In both of these studies, SNPs at or near four loci achieved genome-wide levels of significance in their *p*-values: the 17q21 locus (*ORMDL3/GSDML*), the *IL1RL1/IL18R1* locus, *TSLP*, and *IL33*.

ENVIRONMENTAL RISK FACTORS

Below we present some of the most important environmental risk factors for the development or exacerbation of asthma not discussed earlier.

PERINATAL FACTORS

Prematurity carries an increased risk for the development of asthma. A recent review and meta-analysis showed that infants born at less than 37 weeks' gestation are at greater risk for developing asthma than term infants.[77] Prematurity also is associated with bronchopulmonary dysplasia,[78] a disease characterized by increased airway responsiveness and asthma symptoms. Some investigators have found that low birth weight independent of prematurity has been associated with asthma risk.[79,80] The strength of the association between prematurity and/or low birth weight on asthma or asthma symptoms appears be greatest in very young children, but the effects decrease over time.[81,82] Note that blacks have higher rates of prematurity than whites; thus, prematurity may contribute to racial differences in asthma prevalence and morbidity. Young maternal age (i.e., <20 years) has not been shown to have a consistent independent association with the development of asthma. Despite much research, there is no conclusive evidence that breastfeeding influences atopic sensitization or the development of asthma.[83,84]

Recent studies have focused on maternal diet during pregnancy and its effect on the development of asthma and allergies, with the hypothesis that nutritional deficiency or excess may lead to programming of the fetus for adult disease.[85] These studies have mostly used nutrient intake estimates derived from food frequency questionnaires that assess how often a particular standard serving of a food or drink is eaten. The responses to the questionnaire, in conjunction with a database of nutrient composition of foods, are then used to calculate the amount of a particular nutrient over a specified time period.[86] A few studies have measured the particular nutrient in either maternal or cord blood samples. A meta-analysis found that there was weak support for protective effects of higher maternal intakes of vitamin A, E, and zinc for the prevention of asthma in children.[87]

VITAMIN D

In the strict sense of the word, vitamin D is not a vitamin, since humans are able to produce the compound in the skin upon exposure to the UVA rays from the sun. While the first report of an effect of vitamin D on asthma and allergies appeared in 1934,[88] research into the effects of vitamin D did not begin in earnest until the last decade. There are two opposing hypotheses regarding the role of vitamin D in asthma. Wjst and Dold[89] suggested that fortification of food with vitamin D and the widespread use of multivitamins in childhood contributed to the rise in asthma and allergies. On the other hand, given the documented decrease in the levels of the circulating form of vitamin D in population studies,[90] Litonjua and Weiss hypothesized that the increasing prevalence of vitamin D deficiency led to the increase in asthma prevalence worldwide.[91]

With regard to the development of asthma and allergies, four cohort studies have reported beneficial effects of a higher maternal intake of vitamin D in pregnancy on outcomes in their children.[92–95] However, other studies have not replicated these findings.[96–99] More consistent results have been found with regard to the role of vitamin D in disease severity or treatment. These studies have shown that asthmatics with higher circulating vitamin D levels have greater lung function,[100,101] lower risks for exacerbations,[102,103] and generally more severe indices of disease.[104] Clinical trials of vitamin D supplementation to prevent asthma development and to prevent exacerbations are ongoing.

INDOOR AND OUTDOOR ALLERGENS

Indoor allergen sources include animals (cats, dogs, rodents), insects (mites, cockroaches), and fungi. Allergens are well-known precipitants of asthma exacerbations and increased morbidity.[105,106] There has been some recent investigation as to whether exposure to pets early in life would be useful in preventing asthma,[107–109] but a recent pooled analysis of 11 European birth cohorts did not find any effect of pet ownership on asthma and allergic rhinitis in school age children.[110] It is noteworthy that animal allergens, particularly cat allergen, can be found in settled dust and in circulating air in homes, school classrooms, and other buildings that never housed a cat.[111–113]

House dust mites are ubiquitous in all but very dry climates and exposure and sensitization to mite body and fecal allergens is associated with asthma.[65,66] Mites infest fabrics, including mattresses, bedding, floor coverings, and upholstered furniture. The use of wall-to-wall carpets has increased exposure to mites. Covering mattresses and pillows with vapor-permeable fine weave materials, washing bedding in hot (>30°F) water, vacuuming weekly, and removing carpets, especially from the bedroom, reduce mite levels.[114,115]

Whether reducing exposure results in improvement in asthma outcome has been the focus of several studies,[116,117] with inconsistent results. A Cochrane meta-analysis of 54 trials using varying methods of mite-allergen reduction (physical methods, chemical methods, and a combination) concluded that there was no clinical benefit of dust mite allergen reduction.[118] Adherence to the demanding protocols for control of mite exposure is difficult and may not always result in sufficient reduction in personal aeroallergen exposure. More recent studies have focused on multifaceted intervention programs that target other environmental exposures (e.g., environmental tobacco smoke [ETS]) in addition to allergen avoidance, and may have more promise than single allergen avoidance.[119–123]

Sensitization to cockroach has been shown to be associated with the development of asthma and asthma morbidity.[106,124] Although the presence of this allergen is not limited to low-income homes, it has not been studied in more affluent settings. Removal of this allergen is difficult and more research is needed to evaluate the impact on asthma of allergen removal.[125–127]

Home, school, and workplace dampness and the presence of fungi have been associated with reports of respiratory symptoms.[128] Sensitization to molds has also been shown to be associated with greater asthma morbidity.[129]

Day care establishments may be sources of indoor allergens, including pets, insects, and fungi.[130] They also may be sources of gram-negative bacterial endotoxin and lipopolysaccharides, which induce Th1 activity and have been hypothesized to be protective against the development of allergy and asthma. However, longitudinal studies have not consistently supported this notion. A recent

study of 3963 children found no effect of early day care attendance on the development of asthma symptoms, airway hyperresponsiveness, and allergic sensitization at 8 years of age.[51]

Outdoor allergens include trees, grass, and weed pollen constituents. Susceptible individuals may have increased asthma symptoms at times of pollination.[131] For example, in the Northeast and Midwest grass pollinates in May and June and ragweed in late August and September. Pollens most closely linked to exacerbations of asthma in at-risk individuals are trees such as birch, oak, and Western red cedar; grasses; and ragweed. A recent study, however, suggests that asthmatics react to airborne allergens regardless of their sensitization status.[132] This will require further study.

SMOKING AND ENVIRONMENTAL TOBACCO SMOKE

Maternal cigarette smoking is a major risk factor for the development of asthma in the first year of life. Both a meta-analysis[133] and a pooled analysis[134] showed that the risk of developing asthma ranges from around 40% to 85% greater among children born to mothers who smoked during pregnancy compared to children born to mothers who did not smoke. This effect appears to be strongest in children who developed asthma before 2 years of age.[133]

ETS exacerbates asthma in children of all ages.[135] Wilson and coworkers[136] evaluated a cotinine-feedback behavioral intervention administered to caregivers that successfully reduced ETS exposure and healthcare utilization by children with asthma at 1-year follow-up. However, in a follow-up study, the effect was only seen in children at highest risk for exacerbation.[137] In adults, cigarette smoking is associated with the development of airway hyperreactivity.[138] Whether this hyperreactivity represents asthma or COPD can be difficult to determine. Cigarette smoking in asthma produce a synergistic and accelerated decline in lung function.[139,140] In addition, the response to corticosteroid therapy used for asthma is reduced in active smokers.[139]

OTHER POLLUTANTS

Outdoor pollutants implicated in the development or exacerbations of asthma include ozone, sulfur dioxide, particulate matter, and components of motor vehicle exhaust.[141,142] Measuring exposure to potential pollutants is difficult and correlating exposure with symptoms and exacerbations of disease is very expensive. Most monitoring of pollutants is from fixed external stations. Sometimes proxy measures of pollutant exposure, such as traffic counts, are used. Although potentially more accurate, monitoring of personal exposures is particularly difficult and expensive.[143] Assessing which of the many possible simultaneous outdoor inhalants affects asthma morbidity is also a formidable task. Conclusions drawn from such data may be indirect. An example is the observation that asthma morbidity is highest among low-income individuals who tend to live in less desirable areas, which are frequently those with high traffic volumes and pollution.

There has been much interest in indoor environmental pollutants, such as nitrogen dioxide, sulfur dioxide, volatile organic compounds, and particulate matter, and their possible association with asthma, particularly in inner city homes.[144,145] As with studies of outdoor pollution difficulties in measurement over time, controlling for other exposures such as allergens, infectious agents, and social determinants of health, while linking exposures to symptoms and physical findings makes research challenging.

RACE/ETHNICITY AND SOCIOECONOMIC STATUS

As discussed at the beginning of this chapter, asthma prevalence and especially morbidity and mortality are higher in blacks than whites. Whether these racial differences in asthma prevalence, hospitalization, and mortality are solely due to inadequate treatment and access to medical care remains unclear, but there is indisputable evidence of unequal treatment of minority and low-income groups by health professionals.[146] In addition, environmental factors that are the products of poverty, such as urban crowding, exposure to tobacco smoke or other pollutants or allergens contribute to these findings.[147] A recent line of research to explain some of the racial and socioeconomic disparities in asthma has focused on the effect of stress and violence in the pathogenesis of asthma and morbidity related to asthma.[148,149] These studies have shown that exposure to stress or violence is related to asthma in children, even after adjusting for socioeconomic status.

There is much current debate about the relative importance of social and genetic effects and/or gene–environment interactions that might account for the health disparity seen in asthma and other diseases. In most studies race and ethnicity are not well defined and socioeconomic factors tend to be inseparably linked to ethnicity and race. Perceptions of a person's race influence social experiences including those with the health system. In a recent survey, black and Hispanic women were more likely to report a doctor's diagnosis of asthma and less likely to report a diagnosis of hay fever or eczema. However, these women had higher mean total IgE levels and were more likely to be sensitized to aeroallergens.[150] The investigators concluded that these findings could represent either underdiagnosis by medical personnel (e.g., fewer referrals to an allergist or other specialist) or underreporting of symptoms by patients. They also concluded that it was unlikely that genetics alone could explain the differences in sensitization and that these differences more likely were related to differences in housing and community environmental exposures.

As our cultural and ethnic diversity increases, communication between patient and healthcare provider becomes more complicated and miscommunication more likely. In addition, prior experiences of discrimination or perceived discrimination contribute to distrust of the health system.[151,152] These may result in mistrust of the medical advice, or refusal of treatment and poor adherence and thus contribute to health disparities. One study found patients' beliefs in the risks over the benefits of inhaled steroids to be associated with lower adherence.[153] In focus groups, blacks with moderate or severe asthma who reported their adherence was influenced by reliance on their own assessment of asthma control over that of the health provider. They expressed concern about adverse effects of inhaled steroid therapy and several had misperceptions of their risks. Such misperceptions can be addressed in the patient–provider encounter. Adherence was also adversely affected by the cost of the medication or its copay and insurers' approval policies and restricted formularies.

OBESITY

Obesity has reached epidemic proportions in the United States and has been related to asthma in cross-sectional and longitudinal studies. A number of mechanisms for this relationship have been proposed.[154,155] Some of these mechanisms may begin early in life to confer risk for both disorders.[156,157] A mechanical effect is postulated to be the result of decreased tidal volume and decreased functional residual capacity leading to reduced ability of the smooth muscles to stretch and thus respond to changes in respiration with exercise. Obesity enhances gastroesophageal reflux, a condition associated with asthma. Immune effects also have been postulated. For example, certain inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 are expressed by adipocytes. TNF expression is increased in asthma exacerbations and may have a role in amplifying the inflammatory response of asthma. IL-6 stimulates a Th1 response, which may contribute to the inflammation of severe asthma. Leptin, a product of adipocytes, is a member of the IL-6 cytokine family. Whether or not leptin plays a role in asthma is unknown. Because asthma in adults is more common in women and because estrogen is increased in obesity, estrogen has been hypothesized to play a role in a link between asthma and obesity but no such role has been demonstrated.

Since asthma and obesity are both complex diseases, it is possible that some genetic susceptibilities are shared (pleiotropy).[157] There is some evidence for this in that there are regions of the human genome important for both asthma and obesity, such as chromosome 6p, which contains the gene for TNF. Alternatively, it is possible that obesity is related to asthma as an epiphenomenon; that is, there are shared lifestyle or social exposures, for example, physical exercise or diet, that influence both obesity and asthma. Obesity is more prevalent in the same socioeconomic groups in which asthma is more prevalent. No randomized interventional studies have been completed showing that weight reduction ameliorates asthma. Clearly, more research is needed.

■ ACETAMINOPHEN

It has been postulated that acetaminophen use may increase the risk of developing asthma due to its pro-oxidant effects (by depletion of the antioxidant glutathione in lung tissue).[158] Several studies have reported on the association of acetaminophen use, either in pregnancy, in early life, and in adulthood, and the development of asthma.[159–162] However, the issue with studies that investigate over-the-counter medications such as acetaminophen is the possibility of confounding by indication, meaning that these individuals have comorbidities (e.g., respiratory infections) for which they may take the acetaminophen for its antipyretic or analgesic effects. To address this, investigators of the Melbourne Atopy Cohort Study found that when they adjusted for the frequency of respiratory infections, the association between acetaminophen use and asthma at age 6 or 7 years disappeared.[163] Therefore, while more studies need to be done, it is not likely that taking acetaminophen in usual doses is a cause of asthma.

■ RESPIRATORY ILLNESS

Many epidemiologic studies have shown a prominent association between lower respiratory tract viral infections and wheezing illnesses in infancy and increased risk of chronic childhood asthma.[164,165] Respiratory syncytial virus (RSV) has drawn particular attention, since it is the major cause of bronchiolitis in children and RSV infection is associated with IgE production, airway inflammation, and increased airway responsiveness. Human rhinoviruses (HRVs) which are a more common cause of upper and lower respiratory infections than RSV, may also cause bronchiolitis,[166] and have also been associated with asthma onset.[167] This is particularly true of the newly identified type C rhinoviruses. Respiratory tract infections by parainfluenza viruses, influenza virus, and human metapneumovirus during infancy are all associated with childhood wheezing.

It is hypothesized that susceptibility to asthma associated with viral infection in early life results from the interaction of developmental, genetic, and environmental factors. Developmentally, infancy is a time of pulmonary alveolarization and a time when the immune system has not reached full maturity. Several studies have now documented the synergy of allergen sensitization and respiratory infections in the risk for developing asthma. Kusel et al.[168] showed that among sensitized children, the risk for developing asthma by the age of 6 years was almost double that of children who were not sensitized. Jackson and colleagues[167] showed that while HRV was the dominant factor in developing asthma by the age of 6 years, the risk was highest when concomitant allergen sensitization was present.

Atopic status and airway hyperresponsiveness may be important genetically determined characteristics that influence whether RSV, HRV, or other respiratory viral infections increase the risk of developing asthma. Most children who wheezed only during the first 2 years of life had lower levels of lung function when evaluated at the age of 2 and 6 years. In contrast, children who wheezed early in life and who were still wheezing at the age of 6 years had normal lung function, but statistically elevated serum total IgE levels when studied during the first year of life. When restudied at the age of 6 years, they had elevated IgE, but lung function had deteriorated and was below that of individuals who had never wheezed.[45] This has led to the hypothesis that there are two wheezing syndromes associated with lower respiratory tract infection in young children. One occurs in children with small airway caliber who lack airway hyperresponsiveness, and have excellent prognosis. The other syndrome, which represents early-onset asthma, is associated with increased prevalence of allergic markers, bronchial hyperreactivity, and a significant decrease in lung function over the first 6 years of life.

Viral respiratory illnesses trigger asthmatic exacerbations. A number of studies have demonstrated a close temporal relationship at the individual and population levels, between virus infection and asthma exacerbations. These studies have also demonstrated that (1) asthmatics may be more susceptible than normal subjects to viral lower respiratory infections;[169–171] for example, in a surveillance study of 5.3 million children aged 17 years or younger during the 2003 to 2009 influenza seasons and the 2009 pandemic, Dawood and colleagues[170] found that 32% and 44%, respectively, of the children hospitalized had asthma; (2) in contrast to viral infections, bacterial infections are not associated with asthmatic exacerbations, although agents such as *Mycoplasma* and *Chlamydia* may be involved with persistence of asthma;[172] (3) viruses precipitate a high percentage of severe (vs. mild) asthmatic exacerbations; during the 2009 influenza pandemic, a greater proportion of asthmatics required intensive care;[170] and (4) viral infections can induce nonspecific increases in airway responsiveness and airway obstruction.[173–175]

PROGNOSIS

The prognosis of asthma in early childhood has been clarified substantially by data from the Tucson Children's Respiratory Study.[45,46] These investigators followed a cohort of children through the first 6 years of life. They characterized four groups of children: "persistent wheezers," who wheezed both before and after the age of 3 years; "transient early wheezers," who wheezed before the age of 3 years and then stopped; "transient late wheezers," who wheezed after the age of 3 years but not before; and "never wheezers." Totally 40% of all children in the Tucson Children's Respiratory Study cohort wheezed in the first year of life.

Significant predictors of persistent wheezing, and hence children at greatest risk for developing chronic asthma were young maternal age, IgE level at 9 months, parents with asthma, maternal cigarette smoke exposure in utero, abnormal lung function at birth, and male gender. It is likely that early-life wheezing is predominantly a mechanical factor and less due to severe and chronic airway inflammation. It also seems unlikely that allergen exposure predominates as a factor in early childhood.

The characteristics of older children who wheeze are atopy, female gender, and active and passive cigarette smoking. By preadolescence, atopy and environmental allergen exposure are important risk factors for wheezing in children.

In roughly half of all childhood asthmatics, symptoms decrease or disappear by late adolescence and early adulthood. Characteristics that suggest a good prognosis include male gender, precipitation of attacks by viral respiratory illness, and children with airway parenchymal desynapsis (i.e., large lungs but small airways). These children are predominantly male, and, although often atopic, still are likely to outgrow their asthma. In a longitudinal study of children from East Boston, initially 5 to 9 years of age followed over a 13-year period, the effect of asthma on lung growth was different for boys than girls.[176] Boys with asthma had larger growth in vital capacity than boys without asthma and tended to have mild disease. This was associated with fewer hospitalizations for asthma, despite somewhat greater prevalence than in girls. Asthmatic girls, however, had persistent reductions in FEV_1 and were more likely to be hospitalized

for asthma, despite an initially reduced prevalence relative to the boys. These data are consistent with asthma being milder in boys in that the boys are more likely to "outgrow" their asthma. In contrast, the Childhood Asthma Management Program (CAMP) followed lung function of 1041 children (420 girls and 621 boys) with mild to moderate persistent asthma, who participated in a clinical trial of asthma treatment.[177] The authors used lung function data of 5415 nonasthmatic children from the Harvard Six Cities Study for comparison. In children of both sexes aged 6 to 18 years, the FEV_1/FVC ratio was significantly lower and FVC was significantly higher for asthmatic children, compared to nonasthmatic children. In contrast to the East Boston study, boys had lower FEV_1 between the ages of 10 to 18, whereas there were no significant differences in girls. Taken together, these studies suggest that asthma that starts in early life (i.e., by the age of 6 years) leads to decrements in lung function that are persistent through adolescence. These patterns have been borne out in other longitudinal studies (reviewed by Grad and Morgan[178]).

In both adolescents and adults, airway responsiveness predicts the development of asthma[12–16] and antedates and predicts accelerated decline in lung function.[179,180] Both persistent symptoms[181] and active smoking[140] conferred more rapid rates of lung function decline in longitudinal studies. The severity of adult asthma is clearly predicted by the severity of childhood asthma, and the persistence of symptoms in childhood and early adulthood is associated with reduced lung function and more severe disease later in adult life.

IMPLICATIONS OF CURRENT TRENDS IN PREVALENCE, MORBIDITY, HOSPITALIZATIONS, AND MORTALITY

Although prevalence, morbidity, and hospitalizations have remained stable recently, these absolute levels remain unacceptably high, particularly for certain minority groups and low-income populations. Risk factors such as obesity, prematurity, young maternal age, and cigarette smoking are all associated with these same patient groups, speaking about social and healthcare disparities. There are many vulnerable groups for which no data on asthma prevalence and morbidity yet exist. Certainly, genetic differences exist from patient to patient. These differences must be better characterized. Understanding the influence of gene–gene and gene–environment interactions is crucial. Gene–environmental interactions must be carefully studied for all exposures, and particularly for the exposure of socioeconomic status and cultural groups.

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CHAPTER 46

Asthma: Clinical Presentation and Management

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ASTHMA—A HETEROGENEOUS DISEASE

Asthma is a chronic inflammatory disorder of the airways characterized by marked variability in airflow obstruction that is often reversible, either spontaneously or with treatment.[1] This inflammation presents clinically in susceptible patients with recurrent symptoms of wheezing, chest tightness, cough, and, occasionally, dyspnea and contributes to the heightened airway hyperresponsiveness to specific and nonspecific stimuli; a pathognomonic feature of asthma. Increased airway hyperresponsiveness manifests in patients as intolerance to smoke, dust, air pollution, and strong odors, where exposure to such agents in healthy individuals does not induce such symptoms. Asthma is not a single disease entity with a unique pathogenesis, but rather recognized to be a clinical syndrome and heterogeneous disease;[2] that is, asthma comprises multiple endotypes that manifest common symptoms, but have distinct and probably different pathophysiologic and etiologic mechanisms with an interplay between genetic and environmental factors. This phenotypic heterogeneity in the expression of asthma is multidimensional and includes variability in pathologic, clinical, and physiologic parameters among different patients.[3]

RISK FACTORS FOR ASTHMA

Several risk factors for asthma are considered below.

■ ATOPY AND ALLERGENS

The most important factor predisposing to asthma is atopy (Table 46-1). Asthma has been classified as *atopic* (extrinsic) *or nonatopic* (intrinsic) depending on the suspected role of allergens as etiologic factors. Atopic asthma involves an exaggerated immune response characterized by immunoglobulin E (Ig-E) activation and mast cell degradation. Atopy can be clinically elicited with a positive skin prick test or specific antibodies to IgE in serum against common aeroallergens such as house dust mite, grass and tree pollens, cat and dog fur, rodents (in laboratory workers), and cockroaches (in inner city populations). House dust mite is recognized as a significant cause of asthma throughout the developed world, although the relative importance of different indoor allergens may vary among populations. Patients with atopic asthma commonly suffer

TABLE 46-1 Risk Factors and Triggers Involved in Asthma

Endogenous Factors	Environmental Factors	Triggers
Atopy	Allergens–indoor	Allergens (especially house dust mite, animal dander, cockroach, indoor fungi, perennial allergens, and seasonal pollens)
Airway hyperresponsiveness	Allergens–outdoor (fungi, pollens)	Changes in the weather (cold air, thunderstorms)
Ethnicity	Obesity	Drugs (angiotensin-converting enzyme inhibitors, aspirin, β-blockers, NSAIDs)
Gender	Occupational sensitizers	Exercise and hyperventilation
Genetic predisposition	Parasitic infections	Extreme emotional expression (laughing, stress)
	Respiratory infections (early childhood, viral)	Irritants (household sprays, paint fumes)
	Socioeconomic status	Respiratory infections
	Tobacco smoking (active and passive)	Sulfur dioxide and pollutant gases
		Tobacco smoking

from other atopic diseases, including allergic rhinitis that may be seasonal (hayfever), and may be found in over 80% of asthmatic patients; allergic conjunctivitis; and atopic dermatitis (eczema). Nonatopic asthmatic patients (approximately 10%) have a negative skin prick test, normal serum IgE concentrations, and usually show later onset of disease (adult-onset asthma). In this group, their asthma is more severe, persistent, there is more sensitivity to aspirin and commonly they have concomitant nasal polyps. This classification, although appropriate from a pathologic perspective, does not readily help clinicians as it does not aid in establishing an etiologic diagnosis nor does it help in defining treatment strategies.[4] There is a high prevalence of atopy among nonasthmatics and a large percentage of skin prick sensitive persons report no allergic symptoms. Around 50% of asthma can be attributed to atopy in the developed world and the prevalence of atopy among asthmatics is mainly determined by the general prevalence of atopy in the population.[5,6] In addition, the immunopathology in bronchial biopsies and sputum in patients with nonatopic asthma appear to be identical to that found in atopic asthmatic patients. Therefore, the finding that an asthmatic is atopic does not imply that the disease is allergic in nature or, that atopy is causing asthma. Moreover, respiratory tract viruses have emerged as the most frequent triggers for exacerbations in both children and adults and may play a more prominent role than allergens as triggers of acute exacerbations in most patients.[7] House dust mites are the most common indoor allergen, where particles excreted from the digestive tract contain the principal allergen *Dermatophagoides pteronyssinus*. Other main sources of inhaled indoor allergen are cat and dog fur, and cockroaches (Table 46-1). Although asthmatic symptoms often improve when the allergen is removed, rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma.

Although allergens are often triggers of acute exacerbations of asthma, allergens themselves may induce subclinical airway inflammation that may lead to enhanced airway responsiveness and greater susceptibility to the provocative effects of other triggers such as respiratory viral infections and exercise. In this regard, it is important to understand the distinction between triggers and etiologic risk factors. A trigger is any agent capable of inducing or exacerbating asthma and whereas triggers may lead to symptoms, they do so only in susceptible persons who already possess the underlying asthmatic diathesis.

VIRAL INFECTIONS

Acute upper respiratory tract viral infections are the commonest triggers of exacerbations of asthma and most are due to rhinovirus infections. Viral infections not only give symptoms of the common cold and cause acute inflammatory rhinitis, but may also play a role in asthma development and potentially, airway remodeling through increasing inflammation in the lower airways.[8] Asthma is recognized to be more common in children who have had croup or lower respiratory tract infections in early life, although viral infections in the absence of atopy do not appear to be risk factors for the development of asthma.[9] Other viruses commonly implicated in acute exacerbations of asthma are respiratory syncytial virus, influenza virus, and parainfluenza virus. Bacterial infection with species of *Mycoplasma* and *Chlamydia* are also associated with exacerbations of asthma, whereas other bacterial infections are not.

OCCUPATIONAL EXPOSURE

Occupational asthma accounts for approximately 5% of all adult cases of asthma, and the disease can often be classified according to its etiology. In these circumstances, not only is the specific agent that triggers the symptoms known, but the same agent is usually the underlying cause of asthma.

EXERCISE-INDUCED ASTHMA

Many asthma patients have worsening of symptoms on or after physical exercise and another category of asthma is exercise-induced, where exercise per se is not the cause of, but rather one of many nonimmunologic triggers that produce symptoms in patients who already have the disease. In this condition, the trigger is thought to be the drying of the airway mucosa as a result of hyperventilation that leads to osmotically induced mast cell mediator release and bronchospasm.

OBESITY

Obesity is a major risk factor for asthma where abdominal obesity (waist circumference) and general obesity (BMI) both show a strong correlation with the risk of new-onset asthma.[10]

DRUGS

Drugs that may worsen asthma control include β-blockers, occasionally angiotensin-converting enzyme (ACE) inhibitors, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs).

CLINICAL PRESENTATION AND DIAGNOSIS

Asthma is a clinical diagnosis made on the basis of a medical history of typical symptoms, consideration to provocative factors, and supported with objective confirmation of variable airflow obstruction. As the disease is heterogeneous in its presentation and severity, the clinical features of asthma show great variability both between individual asthmatics, and also within the same patient over time. It is also important to recognize that asthma is often associated with different comorbidities including allergic rhinitis, atopic dermatitis, rhinosinusitis, gastroesophageal reflux disease, diabetes, depression, obesity, all of which may affect the clinical expression and severity of the disease.[11] The following clinical features and laboratory assessments are important in the consideration of the diagnosis of asthma.

MEDICAL HISTORY

The typical symptoms of asthma are paroxysmal wheezing, cough, breathlessness, and chest tightness, which may temporally be related to exposure to triggers or exercise. Cough may be productive of clear or yellow/green discolored sputum, where the latter may be tenacious and difficult to expectorate and reflect the underlying airway inflammation rather than a respiratory infection. Indeed, cough may be present in isolation to other symptoms and as the sole manifestation of an episode of asthma.[12] Breathlessness may occur as a result of the dynamic lung hyperinflation that accompanies acute asthma episodes and patients may report the sensation of difficulty in "getting air in" their lungs. Exertional symptoms may not be apparent if the patient's ability to exert themselves is limited by other health conditions such as rheumatologic or cardiac disease and, therefore, asthma may be underdiagnosed in the elderly. No single symptom is specific or more significant for asthma, although wheezing is a useful sign, as nonasthmatics rarely report frequent wheezing. In younger patients, the symptom of chest tightness is helpful, since it occurs more often in association with asthma than with other pulmonary or cardiac disorders. The pattern of symptom occurrence, the precipitating or aggravating factors, and the profile of a typical exacerbation are important elements in the clinical evaluation.

In patients with poorly controlled asthma, symptoms may temporally evolve slowly over days or weeks, or present abruptly. The severity and frequency with which symptoms occur varies greatly within the asthmatic population. The recurrent paroxysmal nature of symptom presentation is characteristic of asthma and symptoms improve, sometimes rather spontaneously, although usually with treatment. Nocturnal episodes are common in adult asthmatics and typically patients awake in the early hours of the morning with symptoms.

Distinguishing whether nocturnal symptoms are due to asthma, angina, or gastroesophageal reflux may be difficult, but early-morning asthma symptoms are usually relieved with administration of inhaled bronchodilators, in contrast to cardiovascular symptoms which occur at any time during the night and, gastroesophageal reflux which tends to usually cause symptoms soon after the patient reclines at night.

Chest symptoms that vary by season and are accompanied by symptoms of irritation of other mucus membranes, such as conjunctivitis and rhinitis, are typical of allergic asthma. Triggers such as indoor allergens of house dust mite, cockroach, and animal dander proteins are more likely to result in perennial symptoms, whereas pollens and some mold spores are likely to provoke seasonal symptoms. The presence of rhinosinusitis, nasal polyps, conjunctivitis, or eczema, coupled with a family history of asthma or atopy, may further support the diagnosis of asthma. Symptoms after heavy exertion, especially in the cold air, are highly suggestive of exercise-induced asthma and typically, patients experience symptoms at the end of exercise, rather than during its performance. Excessive coughing after exercise in the absence of wheeze may also be a sign of asthma. Premenopausal women with asthma may experience a deterioration of asthma control perimenstrually.[13] The medical history should elicit risk factors for asthma (Table 46-1), and special consideration should address symptoms induced by aspirin or those associated with the patient's occupation.

■ ASTHMA AND ASPIRIN SENSITIVITY

The association of asthma and sensitivity to aspirin or other NSAIDs is well established.[14] Aspirin-sensitive asthma affects approximately 5% of all asthmatics, although it is more common in patients with severe asthma (~20%) and in those frequently hospitalized for their asthma. This subtype of asthma is usually characterized by a tetrad of asthma, nasal polyps, chronic hypertrophic eosinophilic sinusitis, and aspirin intolerance. Classically, perennial rhinitis is the first symptom in this syndrome, preceding the development of aspirin sensitivity, and then followed much later by nasal polyps that are usually bilateral and originate from the turbinates and the paranasal sinuses. Even in small doses, aspirin typically causes wheezing, facial flushing, rhinorrhea, and conjunctival irritation. Although aspirin-induced asthmatic episodes often resemble allergic reactions, there is no evidence that immunolglobulin (Ig)-E–related mechanisms are at work. Aspirin-induced asthma is due to blockade of cyclooxygenase 1 by nonsteroidal anti-inflammatory drugs and has been associated with enhanced leukotriene production and mast cell activation, but the cellular pathways responsible for these events remain unclear. The diagnosis of aspirin sensitivity is made on the basis of the clinical history and can be confirmed by a provocative aspirin challenge, although this test carries a potential health risk of anaphylaxis for the patient.

Aspirin-sensitive asthma usually responds to standard therapy with inhaled corticosteroids (ICSs), although the condition is associated with severe asthma, who are a group of patients often refractory to treatment with inhaled and oral CS. Potentially, antileukotriene therapy should be efficacious in these patients, but have been found to be no more effective compared to their use in patients with allergic asthma. Aspirin desensitization may sometimes be needed, and should only be performed in specialized centers. In all asthmatic patients with aspirin sensitivity, the nonselective cyclooxygenase (COX) inhibitors should be avoided, but when an anti-inflammatory analgesic is needed, the selective COX-2 inhibitors are usually safe to use.

Occupational Asthma

Occupational asthma is asthma arising de novo that is initiated as a consequence of exposure to a specific etiologic agent in people without prior asthma. In contrast, work-exacerbated asthma is defined as the worsening of asthma, that is already pre-existing or concurrent, triggered by nonspecific irritants in the workplace.[15] Occupational asthma may be classified into (i) that caused by a sensitizing agent in the workplace (sensitizer-induced asthma) where the specific sensitizing agent causes asthma through an identified underlying immunologic mechanism and (ii) asthma caused by exposure to irritant compounds (irritant-induced asthma) where the exposure agent is not considered to be sensitizing.[16] Table 46-2 highlights the causes of both sensitizer-induced occupational asthma and the common agents responsible for irritant-induced occupational asthma. The diagnosis of occupational asthma is based on a demonstrable link between asthma symptoms and workplace exposure, showing work-related variability in measurements of lung function made serially.[16] Classically, a typical history of asthma-like symptoms during the working week and improvement over the weekend or on vacation are elicited and symptoms may occur either during exposure to the etiologic substance, or they may be delayed until the evening or night after the work day. Early detection and avoidance of occupational asthma is important where, if the patient is removed from exposure within the first 6 months of symptoms, there is usually complete recovery.

TABLE 46-2 Causes of Occupational Asthma

Sensitizing Agent-Induced Asthma	
Agent	**Workers at Risk**
Acrylate	Dental workers; adhesive handlers
Anhydrides	Workers using epoxy resin for plastics
Animal protein allergens	Veterinary workers; animal handlers
Cereals (grains)	Bakery workers; grain workers; farmers
Dyes	Textile workers
Enzymes	Pharmaceutical workers; bakery workers; laboratory workers
Formaldehyde, glutaraldehyde	Hospital and healthcare workers
Gums	Carpet makers
Isocyanates	Installers of insulation; manufacturers of plastics; rubbers and foam; spray painters
Latex	Healthcare workers; rubber workers
Persulfate	Hairdressers
Seafoods	Seafood handlers and processors
Wood dusts	Forestry workers; sawmill workers; carpenters

Common Agents Responsible for Irritant-Induced Asthma
Acids (acetic, hydrochloric, sulfuric)
Alkaline dust
Ammonia
Bleach
Chlorine
Cleaning agents
Diesel exhaust
Endotoxins
Formalin
Mustard
Oxide (calcium)
Paints (heated)

■ PHYSICAL EXAMINATION

The most typical physical finding in asthma is wheezing on auscultation, which is usually caused by turbulent airflow through narrowed

airways. Wheezing may be heard throughout the chest and is classically polyphonic, present to a greater extent during expiration, although it may also be heard during inspiration. The quality and character of wheezing is not specific to asthma or to the severity of the underlying disease. There may be no abnormal physical findings when asthma is under control yet conversely, in cases of very severe airway obstruction, breath sounds and wheezing may be absent. Examination of the upper respiratory tract may reveal clinical signs of rhinitis, sinusitis, or nasal polyps.

During an acute exacerbation of disease, physical signs of increased ventilation may be observed with the use of accessory muscles of respiration and chest signs of hyperinflation. A sign of severe airway obstruction is pulsus paradoxus, which is the exaggerated decrease in systolic blood pressure during inspiration by >10 mm Hg. As ventilatory effort can be diminished with respiratory muscle fatigue, pulsus paradoxus may be absent, but its absence does not preclude severe airway obstruction. Stridor is a high-pitched inspiratory sound and indicates airflow turbulence in the upper airways. In the acute setting, stridor should prompt a review of causes such as epiglottitis or foreign body, and in chronic presentation conditions such as upper airway tumors, tracheal–bronchial stenosis, vocal cord dysfunction/paralysis, and airway narrowing due to thyroid enlargement should be excluded.

LABORATORY INVESTIGATION

The diagnosis of asthma is usually apparent from the medical history with symptoms of variable and intermittent airway obstruction and objective measurements of lung function and spirometry support the diagnostic process. Similarly, the clinical history provides relevant information regarding the relationship between symptoms and allergen exposure, but skin prick testing and serology may be useful in identifying specific allergic triggers of asthma. Radiologic examination of the thorax, blood tests, and body plethysmography are not routinely indicated, unless there is some uncertainty in the diagnosis, where these tests may be used to exclude other conditions that may mimic asthma or complicate its clinical presentation.

LUNG FUNCTION TESTS

Peak flow meters are portable devices, readily available for patient use, that measure the peak expiratory flow (PEF). Serial readings of PEF that vary by more than 20% either spontaneously or in response to treatment are supportive of a diagnosis of asthma. Twice-daily PEF measurements, morning and evening, may also demonstrate diurnal variation, which is a typical feature of asthmatic patients.

Spirometry measures the expiratory volume and flow of air using forced maneuvers from full lung inflation, as a function of time. Simple spirometry is important for objectively demonstrating airflow obstruction, confirming the diagnosis of asthma, establishing the severity of the disease, and monitoring the response to therapy. Patients with asthma typically show a reduced forced expiratory flow in 1 second (FEV_1), reduced PEF, preserved forced vital capacity (FVC), and an FEV_1/FVC ratio of 0.7 or greater, but with worsening disease, FEV_1 less than 60% predicted the FEV_1/FVC ratio is more usually <0.7.[17] Home PEF monitoring may be of diagnostic use, confirming the diurnal variations in airflow obstruction, especially in patients who demonstrate normal spirometry during clinic visits. Spirometry also allows the assessment of the flow–volume loop, which shows a reduced maximum expiratory flow.

Bronchodilator reversibility is a measure of the magnitude of airway smooth muscle relaxation. A postbronchodilator increase in FEV_1 of >12% and 200 mL is often considered evidence of reversible airway obstruction, where measures are taken 15 minutes after an inhaled short-acting β_2-agonist (SABA). However, this level of increase is arbitrary and lacks sensitivity or specificity for detecting asthma. In addition, bronchodilator reversibility is diminished in well-controlled asthmatic patients, so it is not a good measure of asthma severity or response to therapy. In some patients, bronchodilator reversibility may be demonstrated by a 2- to 4-week trial of oral corticosteroids (prednisone or prednisolone 30–40 mg daily). Bronchodilator reversibility may also occur in patients with chronic obstructive pulmonary disease (COPD), and although asthma and COPD are distinct diseases, an "overlap syndrome" is described between the two conditions.[18–20]

BODY PLETHYSMOGRAPHY

Whole-body plethysmography is rarely required to establish a diagnosis of asthma in family practice, but may help in patients where there is diagnostic uncertainty. In stable asthma, measurement of the lung volumes may reveal an increase in residual volume, which reflects airway closure at a lung volume that is higher than normal. Air trapping is typically seen in patients with severe asthma. Airway resistance is characteristically increased and, during acute episodes of disease exacerbation, functional residual capacity and total lung capacity may also be observed to be increased. Measurement of the diffusing capacity of the lung (D_{LCO}) may also differentiate patients with COPD from those with asthma. In stable asthma, D_{LCO} is usually normal, but there may be a small increase in some patients. In contrast, patients with COPD typically have a reduced D_{LCO}, which reflects alveolar septal destruction and loss of pulmonary capillary volume—characteristic features of emphysematous patients.

BRONCHIAL CHALLENGE TESTING

Assessing bronchial hyperresponsiveness (BHR) is a sensitive tool that, although not routinely undertaken in clinical practice, may be helpful in diagnosing asthma, particularly when there is diagnostic uncertainty in the context of normal pulmonary function tests and unexplained chest symptoms (see Chapter 33).[21] Bronchial challenge tests assess the abnormally increased airway hyperresponsiveness observed in patients with asthma, by detecting the exaggerated response to inhaled bronchoprovocative agents. The provocation agents can be classified into two categories: direct and indirect. Direct stimuli such as histamine and methacholine, which are normally used in the clinic, act on airway smooth muscle receptors, whereas indirect stimuli act through intermediate pathways that include the release of mast cell mediators, and/or through local and central neurologic reflexes. Indirect stimuli include adenosine monophosphate (AMP), mannitol, exercise, hypertonic saline, and isocapnic hyperventilation.

Increased BHR is typically defined as the inhaled concentration of the bronchoprovocative agent that reduces FEV_1 by 20% (PC_{20}). This criterion for the test has maximal sensitivity but not maximal specificity and thus, when a diagnostic PC_{20} threshold of ≤8 mg/mL is used, pharmacologic challenges are sensitive tests with a high negative predictive value, that is, a PC_{20} >8 mg/mL excludes a diagnosis of asthma with a high degree of accuracy. Similarly, a positive result, although consistent with is not diagnostic for asthma. False-negative results can be obtained in patients who experience only intermittent symptoms and are tested when they are asymptomatic. The prevalence of abnormal responsiveness in nonatopic, nonasthmatic subjects who have no history of prior respiratory problems ranges between 5% and 10%. Knowledge of family history, personal atopy, and comorbidities clearly improves the prediction that abnormal airway responsiveness predisposes to the subsequent development of asthma.[22]

Technical factors related to the test procedure must be strictly controlled and follow standard operating procedures that include: the aerosol generation, the method of inhalation (intermittent versus continuous), and the measurement and calculation of the response. Medications such as β_2-agonists, theophylline, long-acting muscarinic antagonists, and CSs may influence the test and decrease

airway responsiveness. Measuring BHR may have additional utility in the management of asthma. Patients whose disease is considered to be clinically controlled, may still have BHR and underlying airway inflammation and studies have shown that using AHR to guide treatment with ICSs, leads to an additional improvement in symptoms, lung function, and airway biopsy findings, compared with conventional assessment.[23]

Exercise testing of patients using cycle, treadmill, or free running challenges is occasionally undertaken to show postexercise bronchoconstriction if there is a suggestive history of exercise-induced asthma.[24] In professional athletes, asthma may be both under- or overdiagnosed and objective confirmation by appropriate lung function testing with bronchodilator or exercise challenge is often needed. Allergen challenge is rarely utilized in the routine management of patients with asthma and should only be undertaken by a specialist center if a specific causative or occupational agent is to be identified, such as aspirin.

BLOOD TESTS

Blood tests are usually not helpful in establishing the diagnosis of asthma. The eosinophil count in the peripheral blood film may be raised in atopic conditions and eosinophilia may support a diagnosis of asthma; however, a normal level does not rule out atopy or exclude asthma. In patients receiving CSs, eosinophilic counts may be normal or low. Because of their poor sensitivity and specificity, blood eosinophil counts are not recommended in the routine monitoring of asthma severity or as a barometer of airway inflammation. Markedly high levels may be present in disorders such as tropical parasitic eosinophilia, allergic bronchopulmonary aspergillosis (ABPA), Churg–Strauss syndrome, and Loeffler's syndrome as discussed elsewhere in this volume. In these hypereosinophilic conditions, clinical suspicion may warrant additional blood tests directed to ruling out vasculitis or ABPA, which are uncommon causes of asthma symptoms.

Total serum immunoglobulin E (IgE) may be measured in patients. Epidemiologic studies demonstrate an association between asthma and total serum IgE levels, standardized for sex and age. There is also a relationship between total serum IgE and asthma in patients with negative skin tests. Importantly, total IgE levels are used to calculate the dose of the anti-IgE antibody therapy, omalizumab, when it is used for asthma treatment as discussed below in Anti-IgE Monoclonal Antibodies. Blood tests of specific IgE to inhaled allergens, radioallergosorbent testing (RAST), and immunoCAP may help identify or confirm allergy to specific allergens, such as house dust mite, cockroach, *Aspergillus* species, pollens, or animal dander.

In acute exacerbations of disease, arterial blood gases may reveal hypoxemia and the arterial Pa_{CO_2} may be reduced due to hyperventilation. With a severe exacerbation, the arterial Pa_{CO_2} may rise due to respiratory muscle fatigue and an inability to maintain the required alveolar ventilation.

SKIN TESTS

If the clinical history suggests specific aeroallergens are important triggers or when asthma symptoms in a patient are accompanied by other symptoms typical of allergic disease, such as conjunctivitis or rhinitis, skin prick tests may be helpful to determine whether the patient is allergic, and to investigate the role of specific allergens as a cause of asthma. Sensitivity to a particular allergen such as house dust mite, cockroach, *Aspergillus* species or animal dander can be verified by skin tests or in vitro serum antibody studies (see above). Antihistamines and antidepressants should be avoided when undertaking testing as these drugs can interfere with the response. Positive responses on skin prick testing may help encourage patients to undertake allergen avoidance measures or, in selected cases, may help develop immunotherapy regimens.

CHEST IMAGING

Chest radiography is usually unremarkable and normal in patients with mild-to-moderate asthma; however, in more severe disease, nonspecific findings such as hyperinflation, prominent hilar vessels, and bronchial wall thickening may be seen. In patients with an exacerbation of their symptoms, chest radiography may be useful to exclude a pneumothorax. Consolidation shadowing in the lung usually indicates pneumonia or eosinophilic infiltrates in patients with ABPA. High-resolution computed tomography (HRCT) of the chest may identify atelectasis, bronchial wall thickening, or areas of bronchiectasis in patients with severe asthma, but these changes are not diagnostic of asthma. Emphysema is absent. Multidetector computed tomography (MDCT) undertaken in inspiration and expiration provides additional information concerning the tracheobronchial tree during the entire respiratory cycle.

EXHALED NITRIC OXIDE

The measurement of fractional nitric oxide gas in the exhaled breath (FeNO) of patients is being utilized as a noninvasive test to assess intrapulmonary eosinophilic inflammation.[25] Portable, compact hand-held devices allow FeNO measurements to be undertaken at the bedside and in family practice. Typically, asthmatic patients have elevated FeNO levels compared with healthy subjects, which correlate with the amount of eosinophils in sputum. ICSs and oral leukotriene receptor antagonists have been shown to decrease FeNO levels. These observations suggest a possible role for FeNO as an index of asthma disease severity, as a test of treatment efficacy and, in the assessment of patient adherence with asthma therapy. Measurements of FeNO have also been used successfully to titrate inhaled steroids without any loss of asthma control; thus, FeNO may be used as a tool in conjunction with other clinical measures to optimize asthma management as recommended by guidelines, that is, achieving disease control using the lowest doses of medications possible. In the research environment, FeNO can be partitioned into that arising from the central bronchial/conducting airways, or to that generated in peripheral alveolar regions, allowing an assessment of the site of intrapulmonary inflammation.[26,27] Patients with severe refractory asthma have shown greater alveolar NO concentrations compared to those with mild asthma.

SPUTUM EXAMINATION

The sputum differential count may be helpful. Induced sputum eosinophil counts have been used as an endpoint in clinical trials of therapeutic agents targeted at patients with eosinophilic lung diseases like asthma.[28] Research studies have shown sputum eosinophilia predicts clinical outcomes, particularly asthma exacerbations, when CSs are withdrawn. Induced sputum eosinophil counts have also been shown to guide anti-inflammatory treatment in patients with asthma in a management strategy that minimizes eosinophilic inflammation.[23] However, induced sputum remains a research tool as it is rather an unpleasant procedure for the patient and further studies are needed before measurement of sputum eosinophils can be widely used as a biomarker to monitor patients in clinical practice.

DIFFERENTIAL DIAGNOSIS

There are a number of conditions to consider in the differential diagnosis of asthma and these are listed in Table 46-3. Usually, it is not difficult to differentiate asthma from other conditions causing wheeze and dyspnea. The degree of diagnostic accuracy is probably dependent on the age of the patient, where the diagnosis in young adults is usually not difficult since there are few other conditions that mimic asthma or confound its clinical presentation. With increasing age, cardiovascular disease and other forms of chronic lung disease are more common, and the differential diagnosis of episodic chest symptoms is broader.

TABLE 46-3 Differential Diagnosis of Asthma

Upper Airway	Pulmonary	Cardiac	Other
Foreign body	Allergic bronchopulmonary aspergillosis (ABPA)	Angina	Anemia
Postnasal drip	Bronchiectasis	Left ventricular failure	Carcinoid
Upper airway obstruction	Churg–Strauss syndrome	Mitral valve disease	Functional
Vocal cord dysfunction	COPD		Gastroesophageal reflux
Tracheobronchomalacia	Cystic fibrosis Interstitial lung disease Lung cancer Pneumonia Pneumothorax Sarcoidosis		Hyperventilation Mastocytosis Obesity

Patients with upper airway obstruction can mimic severe asthma, and typically these patients present with localized wheeze and stridor of the large airways. Assessing the flow–volume loop in such patients will reveal a reduction in inspiratory flow as well as expiratory flow, and bronchoscopy can demonstrate the site of narrowing in the upper airways. Vocal cord dysfunction can be assessed using nasoendoscopy, which allows the observation of abnormalities in the movement of the vocal cords, and is most helpful when adduction of the cords is detected in the presence of the patient's symptoms.[29] Persistent wheezing auscultated in a localized area of the chest wall may indicate endobronchial obstruction due to lung cancer or a foreign body. Eosinophilic pneumonias and systemic vasculitis, including the Churg–Strauss syndrome and polyarteritis nodosa may be associated with wheezing and their systemic clinical manifestations may help in their identification.

COPD is usually easy to differentiate from asthma. The symptoms in patients with COPD are more persistent, show less variability, are progressive, and usually exhibit minimal reversibility to bronchodilator agents. The literature highlights an "overlap syndrome," where COPD patients have features of asthma with increased sputum eosinophils and a response to oral corticosteroids; these patients probably have both diseases concomitantly.[20] Important cardiologic causes to consider include left ventricular failure, where usually bibasal lung crackles are present in contrast to the scattered polyphonic wheeze in asthma. Anemia should always be thought of as a cause of dyspnea, especially in elderly patients. The symptoms of gastroesophageal reflux disease (GERD) may be mistaken for those of asthma; however, it is important to recognize that GERD is common in patients with asthma and has been identified as a potential trigger for asthma symptoms.[30]

TREATMENT OF ASTHMA

Treating asthmatic patients is generally straightforward; with effective and safe drugs, most asthmatics are now managed by family doctors. The successful management of asthma requires an appreciation of the heterogeneity of the disease with respect to etiology, clinical presentation, severity, natural history, and response to therapy. It is unlikely that a single management approach will work for all patients and hence, treatment should be tailored to the individual patient. It will also be recognized that symptom severity in patients varies over time with periods of remission that are interspersed with acute exacerbations, and thus the patient should be monitored regularly and treatment should be modified on an ongoing basis to meet the patient's current needs. There are several aims in the management of patients with asthma (Table 46-4) and although prominence has been placed on drug therapy, there are important patient-orientated approaches that focus on correct inhaler usage, emphasize self-management action plans, and address environmental control.

TABLE 46-4 Aims of Asthma Therapy

Control symptoms
Prevent (or minimize risk of) exacerbations
Eliminate emergency visits
Maintain lung function as close to as normal levels as possible
Decrease diurnal variation, especially nocturnal
Maintain normal levels of daily activities, including exercise
Eliminate or minimize adverse effects from medicine

INHALER DEVICES

Drug delivery to the lungs via the inhaled route remains the cornerstone of therapy for patients with asthma. Inhaled therapy targets drug directly to the lungs and allows a distinct therapeutic advantage over systemic therapy with the use of smaller drug doses, a more rapid onset of therapeutic action, and decreased adverse effects. There are several types of inhaler device and drug delivery systems used in clinical practice for the management of asthma and these include the pressurized metered-dose inhaler (pMDI), spacers, dry powder inhalers (DPIs), and nebulizers.[31] There are potentially over 250 device drug combinations available and this leads to confusion in prescribing among healthcare practitioners. Indeed, studies have shown that not just patients, but healthcare workers are uncertain about the correct use of inhaler devices and physician's knowledge, in particular, remains poor and may be related to a lack of education and instruction about inhaler usage during their training.[32] It has been shown that training and counseling patients in their inhalation technique can increase their adherence to device usage, and patients may be assessed with respect to their suitability for a particular inhaler device by using portable handheld meters that assess inhalation flows. Evidence-based guidelines from the American College of Chest Physicians,[33] recommend the following points for healthcare practitioners to consider when choosing an inhaler for their patient; the clinical condition and disease severity; availability of the inhaler device for the drug prescription; the patient's ability to use the selected device correctly; consideration given to using the same device type for all drugs; the setting and convenience of outpatient and inpatient use; the time required for drug administration; cost and reimbursement; and the inhaler preference of the patient as well as the prescriber. The advantages and disadvantage of the common inhaler device types are shown in Table 46-5.

PRESSURIZED METERED-DOSE INHALERS

The pMDIs contain the drug as a liquid suspension or solution with propellant in a sealed canister and, other formulation ingredients may be present such as ethanol, chemical preservatives, flavoring agents, and surfactant. Most inhaler therapies are now free of chlorofluorocarbon (CFC) propellants having being replaced by non–ozone-depleting propellants such as hydrofluorocarbons (HFCs). Upon actuation of the pMDI canister, there is quick vaporization of the propellant and this provides the force to aerosolize and propel the liquid drug out of the canister at high velocity. Vaporization of the

TABLE 46-5 Advantages and Disadvantages of Inhalation Devices

	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	Compact and portable	High oropharyngeal deposition
	Multi-dose	Difficulty in hand–mouth coordination
	Quick treatment time	Propellants may cause "cold Freon" effect and affect climate change
	Drug in sealed canister	Difficult to assess empty canister
	Inexpensive	
Dry powder inhaler (DPI)	Compact and portable	Need adequate inhalation flow to disperse drug
	Quick treatment time	High oropharyngeal deposition
	Breath-actuated function removes need for coordination	Humidity can cause drug degradation
		Patients may be intolerant to additives, e.g., lactose
Nebulizers	Large doses of drug can be given	Bulky, cumbersome, and expensive
	Can be used with relaxed tidal breathing	Wasted drug in nebulizer reservoir
	Suitable for young, old, and acutely ill patients	Variation in aerosol output performance between models
	Many drug solutions can be aerosolized	Time consuming
		Need for power source
		Regular cleaning and maintenance

propellant also causes cooling of the drug aerosol which can sometimes give rise to the "cold Freon effect," which is the sensation experienced by some patients of cold aerosol hitting the back of their oropharynx, which can stop them from inhaling the drug and sometimes cause paradoxical bronchospasm. Some of the formulation ingredients added to pMDIs described above, have been shown to cause bronchospasm, wheeze, and cough in asthmatic patients. pMDIs are compact, portable, and inexpensive devices. Recent advances in the technologic design of pMDIs include the addition of a dose counter.

Optimal clinical efficacy with a pMDI is obtained when the device is actuated at the start of a deep and slow inhalation lasting for 5 seconds followed, at the end of inspiration, by a breath-hold pause of 10 seconds. Failure to inhale slowly and deeply with pMDIs is a more common mistake than the actual patient coordination between inhalation and actuation. However, the latter problem is more pertinent in elderly patients and add-on spacer attachments, device-holding adaptors, and breath-actuated pMDIs have been developed to overcome this. Breath-actuated metered-dose inhalers utilize the patient's inspiratory force to trigger and activate the inhaler device, although it has been shown breath-actuated pMDIs offer no advantage over patients with good conventional pMDI inhaler technique. In contrast, breath- "coordinated" devices are different from breath-"actuated" metered-dose inhalers in that they do not depend upon the patient's inspiratory flow for actuation and help patients achieve coordination with aerosol inhalation.

SPACERS

Spacer devices are used with pMDIs and are designed to assist in the delivery of inhaled drug to the lungs by promoting ease of pMDI use, and reduce oropharyngeal deposition by slowing the high velocity of the emitted aerosol cloud. The plastic walls of the spacer trap the large dug particles and this decreases oropharyngeal impaction, which may lead to a decrease in local unwanted side effects, particularly with CSs, and also a reduction in systemic adverse effects by minimizing the amount of drug absorbed via the gastrointestinal tract. In addition, increasing the distance the aerosolized drug travels (by using the spacer as an extension attachment to the pMDI device), slows the emitted aerosol cloud and allows more evaporation of the propellant, leading to relatively smaller drug particles that have a greater potential to deposit within the lungs. Spacers include valve-holding reservoir chambers with a one-way inhalation valve in the mouthpiece only allowing airflow through the chamber when the patient inhales; simple extension devices that are nonvalved add-on products that require a reasonably good amount of coordination; and reverse-flow devices where the aerosol spray is actuated away from the patient into a collapsible reservoir chamber or bag through which outside air is entrained to provide the airflow stream for inhalation.

Spacer devices each differ in their design characteristics and should be prescribed only with the pMDI they are compatible with, as each spacer–inhaler combination has distinct aerosol output characteristics.[34] To reduce the electrostatic charge in spacers which can significantly contribute to decreased drug available to be delivered to the lungs, spacers should be primed with the pMDI prior to use, and one-dose actuation at a time from a pMDI into the spacer device should be employed as opposed to simultaneous multiple-dose administrations. Spacers should be washed with ionic detergent and air dried. Antistatic spacer devices are available and can be used.

DRY POWDER INHALERS

DPIs are propellant-free devices that contain finely milled powdered drug particles bound into loose aggregates or, drug particles associated with larger carrier molecules such as lactose. DPI devices are breath-actuated in their operation, and critically rely on the patient's inspiratory effort to deaggregate the drug from its carrier particle to achieve optimal delivery and deposition within the lungs. Studies have shown that DPIs are highly dependent on the patient's inspiratory flow for therapeutic success, and have observed that patients with asthma and those with COPD use suboptimal inspiratory flows from DPIs leading to low pulmonary deposition.[35]

DPIs can be classified into single-dose delivery systems that either require drug to be individually loaded into the inhaler prior to use or where individual doses are dispensed from punctured gelatin capsules. In contrast, multiple-dosing delivery DPIs avoid the inconvenience associated with repeated drug loading and can be divided into "multi-dose" or "multi–unit-dose" systems. Multi-dose systems deliver drug that is metered from a powder reservoir, whereas multiple–unit-dose devices either contain drug sealed in individual foil blisters, or drug sealed in pockets on a moving strip. Deterioration of the drug may occur in damp and humid conditions, and so all these devices should be stored in a dry environment.

A newer generation of DPIs have been developed that rely less on the patient's inspiratory effort, requiring either lower inhalation flows to aerosolize the drug or, in some circumstances, deliver the drug wholly independent of the patient's breathing maneuver.

NEBULIZERS

The main types of nebulizer commonly used in clinical practice can be divided into two categories: ultrasonic and jet nebulizers.[36] Ultrasonic nebulizers utilize the vibration from a piezoelectric crystal at a high frequency to produce aerosol clouds for inhalation from the liquid drug. Ultrasonic nebulizers are smaller and less noisy compared to jet nebulizers, but are usually less robust, more expensive, and not as effective in nebulizing liquid suspensions of drug. Jet nebulizers use either compressed gas or an electrical compressor to generate aerosolized particles. High-velocity air streams are generated and directed through a narrow Venturi opening, across the liquid drug solution/suspension, to produce aerosolized droplets within the nebulizing chamber.

Nebulizers require tidal breathing at rest for effective use and do not require much patient coordination. However, it is recognized that there is great variation in the aerosol output generated from each of the different nebulizer devices, and the inhalation maneuver will affect drug delivery to the lungs that can be greatly reduced with crying, as may occur with children, or when there are shallow and rapid inhalations.[37] Consideration should be given to the nebulizer–facemask combination as incorrect mask insertion into the nebulizer may give rise to unwanted deposition of drug onto the face and eyes, particularly in children. Generally, nebulizer devices are large, lack portability, and have a longer treatment time than conventional inhalers.

There are now a newer generation of nebulizer devices that offer a marked improvement in the efficiency and precision of pulmonary drug delivery.[38] These devices are more costly as units compared to conventional nebulizers, but may be cost-effective by decreasing drug loss from the nebulizer chamber particularly during exhalation, and overall by delivering a reduced drug dose to the lungs but more effectively. Nebulizer systems have also been developed that control the patient's inhalation maneuver so as to minimize the variability in dose delivery that occurs during use, and there are systems that provide feedback to the patient and allow an assessment of patient compliance.

THERAPEUTIC DRUGS

A wide variety of agents are used in the management of asthma.

BRONCHODILATORS

Bronchodilators reverse the bronchoconstriction of asthma, principally by acting to relax airway smooth muscle, and this results in the rapid relief of symptoms. Bronchodilators are not adequate enough to control asthma in patients with persistent symptoms, as they have little effect on the underlying airway inflammation. The classes of bronchodilators in current clinical use include β_2-adrenergic agonists, anticholinergics, and theophylline, where β_2-agonists are the most efficacious.

β_2-Adrenergic Agonists

Inhaled β_2-adrenergic agonists are the drugs of choice for relief of respiratory symptoms due to acute airway obstruction.

Mode of Action β_2-Agonists activate β_2-adrenergic receptors resulting in an increase in intracellular cyclic AMP, which leads to relaxation of airway smooth muscle cells. β_2-Agonists act as functional antagonists; that is, they prevent and reverse the contraction of airway smooth muscle cells by bronchoconstrictors, and it is this action that mainly accounts for their efficacy as bronchodilators in asthma. These drugs also have nonbronchodilator effects that include the inhibition of mast cell mediator release, the inhibition of sensory nerve activation, and a reduction in plasma exudation, which may be clinically useful.[39]

Clinical Use SABAs, such as albuterol and terbutaline, have a rapid onset of action and a 3- to 6-hour duration of activity. This pharmacodynamic characteristic of a rapid onset of bronchodilation allows these drugs to be used as quick-relief medications or "relievers" on an as-needed basis. As a matter of caution, increasing use of SABA indicates that asthma is not controlled and patients should be reviewed. At recommended doses, inhaled β-agonists have few adverse effects, although when used at higher doses by nebulizer, patients may experience short-lived side effect. Long-acting β_2-agonists (LABAs) include formoterol and salmeterol. Both drugs are given twice daily by the inhaled route and have a duration of action of over 12 hours. In particular, formoterol has an onset of action as rapid as albuterol and can be used as a "reliever" component in fixed-dose combinations of LABA with ICS medication. LABA should not be used as monotherapy for the control of asthma of any severity and should not be given in the absence of ICS therapy as they do not control the underlying inflammation. However, fixed-dose combinations of LABA with ICS are now increasingly used in the management of asthma and have proved to be highly effective in improving the control of asthmatic patients, reducing disease exacerbations, and allowing asthma to be controlled using lower doses of CSs.[40] Studies have also shown the clinical benefits of LABA/ICS fixed combinations compared with the monocomponents administered using two separate inhalers. Interestingly, the combination of formoterol and budesonide, and recently formoterol and beclomethasone dipropionate, have been demonstrated to be effective when used as both a controller and reliever agent, and thus provides the advantage of a single device used for both purposes.[41]

Adverse Effects The commonest adverse effects of β_2-agonists are palpitations and muscle tremors, which are unusual with the inhaled route and seen more commonly with high-dose nebulizer therapy and in elderly patients. The safety of β_2-agonists has been an issue of concern. An association has been demonstrated between the amount of SABA used and asthma deaths, but thorough analyses demonstrate that the increased use of rescue SABA implies poor asthma control, which itself is a risk factor for asthma death. A slight increase in deaths from asthma has been observed with the use of LABA, but this is most likely related to the lack of use of parallel ICS, as the LABA therapy on its own fails to suppress the asthmatic airway inflammation, and this highlights the need to always use ICS when LABA are given which can most suitably be achieved by using a combination ICS/LABA inhaler.[42] Patients should also be reminded to avoid β-adrenergic receptor–blocking drugs, including those contained in topical ophthalmic preparations, as they can precipitate severe and sometimes life-threatening asthmatic episodes. Accordingly, β-blockers are contraindicated during acute asthma exacerbations and the risk–benefit ratio should be considered before they are used in stable patients with asthma. Some patients experience deterioration in their asthma control following inhaled β-agonist treatment and possible mechanisms and contributory factors include paradoxical bronchospasm, increased BHR, and tolerance to the drug. With prolonged exposure to a drug, down-regulation of the β-receptor may occur and this can limit therapeutic efficacy; that is, lead to tachyphylaxis to treatment. Indeed, β-receptor mutations and gene polymorphisms have been implicated in influencing the response to inhaled β-agonists.[43]

Anticholinergics

Anticholinergic agents are another class of drugs to be considered in asthma management.

Mode of Action Muscarinic receptor antagonists, such as ipratropium bromide, induce airway smooth-muscle relaxation by blocking

muscarinic receptors on airway smooth muscle, inhibiting vagally mediated cholinergic tone and preventing mucus secretion.[39]

Clinical Use In general, the anticholinergic drugs are not as efficacious compared to the β_2-agonists as bronchodilator agents. Anticholinergics prevent the cholinergic reflex component of bronchoconstriction, whereas in contrast, β_2-agonists inhibit all bronchoconstrictor mechanisms. Hence, anticholinergics tend only to be used as add-on bronchodilator treatment in asthmatics who remain uncontrolled on other inhaled therapy. In the treatment of acute severe asthma, high doses of anticholinergic therapy may be given by nebulizer, but should only be given following β_2-agonist treatment as anticholinergics do not have such a fast onset of bronchodilation. A combination preparation of albuterol and ipratropium bromide is available for nebulization therapy. It has recently been shown that the long-acting anticholinergic drug tiotropium may be as useful as an asthma treatment, as it is in patients with COPD, although the drug is currently not licensed for the treatment of patients with asthma.

Adverse Effects Adverse effects are usually not a concern with anticholinergics as there is minimal absorption into the systemic circulation, but the most commonly experienced side effect is dry mouth, and in elderly patients, glaucoma and urinary retention can occur.

Theophylline

Oral theophylline was primarily used as an adjunct bronchodilator treatment, but due to its narrow therapeutic index and adverse effect profile, together with the availability of safer and more effective alternatives, theophylline is now infrequently used in patients with asthma.[44]

Mode of Action Theophylline inhibits phosphodiesterases in airway smooth muscle cells, which increases intracellular cyclic AMP and this leads to a bronchodilator effect. However, the doses required for bronchodilator activity commonly cause adverse effects, which are mainly a consequence of direct phosphodiesterase inhibition. Theophylline has been shown to exhibit anti-inflammatory effects, which are likely to arise through different molecular pathways; for example, theophylline has been shown to stimulate a key nuclear enzyme, histone deacetylase-2, which is an important intracellular mechanism for switching off inflammatory genes that have been activated.

Clinical Use Theophylline is normally administered as an oral slow-release formulation either once or twice a day, as this results in more steady plasma concentrations compared to standard theophylline tablets. In severe asthmatic patients, theophylline may be used as an add-on bronchodilator treatment, although plasma concentrations of 10 to 20 mg/L are typically needed, and these levels are usually associated with adverse effects. In contrast, the anti-inflammatory effects of theophylline seem to occur at plasma levels below the traditional therapeutic range of 10 to 20 mg/L, and at low doses, the drug is better tolerated. Low-dose theophylline has additive effects to ICS and is particularly helpful in severe asthmatic patients, where withdrawal of theophylline may result in clear worsening of asthma control. Intravenous aminophylline is now seldom used for the treatment of asthmatic patients, only very rarely in those with acute severe asthma exacerbations.

Adverse Effects The adverse effects of theophylline are directly related to drug levels in the plasma and are infrequently observed at concentrations below 10 mg/L. The measurement of plasma theophylline may be useful in determining and guiding the correct clinical dose. Headaches, nausea, and vomiting are the commonest adverse effects, which arise from the inhibition of phosphodiesterase. Palpitations and diuresis may be troublesome, and with higher plasma concentrations, epileptic seizures, cardiac arrhythmias, and death may occur due to adenosine A_1-receptor antagonism. Oral theophylline is well absorbed through the gastrointestinal route and is largely inactivated in the liver by the enzyme CYP450 and so, drugs that inhibit CYP450 activity such as allopurinol and erythromycin may increase plasma levels of theophylline with consequently, a greater potential for adverse effects.

CORTICOSTEROIDS

Corticosteroids (CSs) are potent anti-inflammatory agents and when administered by the inhaled route are the most effective therapy available for treating and controlling asthma, and have greatly contributed to a reduction in asthma mortality in the Western world.[45]

Mode of Action

CSs reduce the number and activation of inflammatory cells in the airways. The reduction in eosinophils, activated T lymphocytes, and surface mast cells in the airways contribute to the lessening in the airway hyperresponsiveness that is seen with CS therapy. There are several molecular mechanisms underlying the action of CS on airway inflammation and the main pathways center on the inhibition of transcription factors NF-κB and AP-1, which switch off the transcription of multiple activated genes encoding inflammatory proteins such as cytokines, chemokines, inflammatory enzymes, and adhesion molecules. Another key mechanism in the action of CS is the inhibition of the recruitment of histone deacetylase-2 to the inflammatory gene complex, which reverses the histone acetylation associated with increased gene transcription. CSs increase the expression of β_2-receptors and this may contribute to the complementary clinical effects observed when CS are combined with LABA.[46] Transcriptional activation is responsible for most of the endocrine and metabolic adverse effects of CS.

Clinical Use—Inhaled Corticosteroids

CSs are usually administered by the inhaled route for maintenance controller therapy in patients with asthma. ICS have been shown to prevent the symptoms of asthma, reduce severe exacerbations rates, improve lung function, and reduce airway hyperresponsiveness. Early and timely treatment with ICS appears to avert the irreversible changes in airway function that occur with chronic asthma. Patients with persistent asthma stabilized on ICS experience increased exacerbations when treatment is withdrawn, indicating that ICS suppress symptoms and inflammation, but do not cure the underlying disease. ICS are beneficial in treating asthmatic patients of any age and at any stage of disease severity. They are first-line therapy for patients with persistent asthma and are usually administered twice a day, although ICS may be effective given once a day in some patients with mild symptoms. The dose–response curve of ICS is relatively flat, meaning that higher doses are only incrementally better than low-to-medium doses. If low-to-medium doses of ICS do not control persistent asthma symptoms, it is usual practice now to add a LABA, preferably as a combination of the two drugs delivered from a single inhaler device.

Clinical Use—Systemic Corticosteroids

Oral CSs are reserved to treat acute exacerbations of asthma. Typically prednisolone or prednisone 30 to 45 mg is given once daily for 5 to 10 days and on finishing the course of treatment, no tapering of the dose is required. Some asthmatic patients, especially those with more severe disease, require maintenance treatment with oral CS and in these patients it is important to determine the lowest dose necessary to maintain asthma control in light of the greater potential for adverse effects with higher doses. CSs may also be administered intravenously (methylprednisolone or hydrocortisone) for the treatment of acute severe asthma, although studies show oral CSs are as equally efficacious and easier to take.

Adverse Effects

ICS may give rise to local oropharyngeal adverse effects such as oral candidiasis, dysphonia, and hoarseness, but these may be lessened with the use of a spacer device. There exist concerns about the systemic adverse effects of ICS from swallowing of the oropharyngeal dose and lung absorption, but these depend upon the individual pharmacokinetic properties of the different CS and overall, studies show that ICS have minimal systemic adverse effects.[47] At higher drug doses, ICS may suppress plasma and urinary cortisol levels, and in prepubertal children it has been shown that the initial decrease in attained height from ICS persists as a reduction in adult height, but is not progressive or cumulative and is approximately a loss of 1 cm. Most importantly, ICS allow the effective control of asthma symptoms and disease, and maintenance therapy may decrease the need and number of prescribed courses of oral CS, and thus, reduce the total-body systemic exposure to CS in general.

Oral CS gives rise to greater systemic adverse effects than ICS, with a greater potential in those on chronic maintenance therapy. Adverse effects include bruising, diabetes, truncal obesity, osteoporosis, duodenal and gastric ulceration, hypertension, mood and behavioral changes, proximal myopathy, and cataracts. It is important to assess and monitor bone density if patients are administered chronic oral CS therapy so that preventive treatment for osteoporosis with bisphosphonates or estrogen in postmenopausal women may be initiated if levels of bone density are borderline or low. If CS adverse effects are a considerable problem, steroid-sparing agents may occasionally be considered.

■ ANTILEUKOTRIENES

Leukotriene pathway inhibitors are a group of compounds that alter the pathophysiologic effects of leukotrienes derived from the 5-lipoxygenation of arachidonic acid. Two classes of agents are available: inhibitors of the 5-lipoxygenase enzyme (zileuton) and cysteinyl-leukotriene receptor type-1 antagonists (montelukast, zafirlukast, and pranlukast).[48]

Mode of Action

Cysteinyl-leukotriene receptor type-1 antagonists inhibit the smooth muscle bronchoconstriction, microvascular leakage, and eosinophilic airway inflammation that occur through activation of cys-LT_1-receptors. These agents predominantly act on the inflammatory mediators produced by mast cells in asthma, and also to a lesser extent on mediators produced by eosinophils.

Clinical Use

Antileukotrienes have less effect on airway inflammation and provide modest clinical benefit compared to ICS. ICSs are more effective anti-inflammatory agents and clinically superior in controlling asthma than antileukotrienes. Antileukotriene treatments may be useful as add-on therapy to selected mild asthmatic patients on low-dose ICS, although these agents are less efficacious than add-on therapy with LABA. Antileukotrienes may be helpful when CS use is poorly tolerated or not desired by the patient, or there is concomitant rhinosinusitis. These drugs are usually given orally once or twice a day.

Adverse Effects

Antileukotrienes are usually well tolerated, but can sometimes give rise to gastrointestinal upset, hepatotoxicity, and hypersensitivity reactions including anaphylaxis and angioedema.

■ CROMONES

Cromolyn sodium and nedocromil sodium are classified as asthma-controller drugs. Their main mechanisms of action seem to be to inhibit sensory nerve and mast cell activation, and therefore they are effective in blocking trigger-induced asthma such as allergen- or exercise-induced symptoms. However, these drugs have a short duration of action, requiring up to four times a day inhalation, and consequently have somewhat little benefit in the long-term control of asthma. They are popular in the treatment of children with asthma because they are remarkably safe, although they are inferior to ICS with respect to most relevant clinical outcomes, and low-dose ICSs are now favored in children as they are more efficacious and have an established safety profile.

■ CORTICOSTEROID-SPARING TREATMENTS

Some patients experience serious adverse effects with CS therapy, especially oral CS therapy in those with severe asthma, and in an attempt to minimize CS exposure and reduce patient requirement, various immunomodulatory treatments have been tried. Many agents have been utilized as steroid-sparing therapies including azathioprine, colchicine, cyclosporin A, gold, methotrexate, and intravenous gamma globulin; but none of these treatments have shown long-term efficacy and importantly, each has been associated with a high-risk adverse effect profile and cannot be recommended to be used in lieu of CSs.

■ ANTI-IGE MONOCLONAL ANTIBODIES

Omalizumab is a monoclonal antibody to IgE that inhibits IgE-mediated reactions by neutralizing serum IgE without binding to cell-bound IgE. It is used as an adjunctive agent for atopic asthmatic patients who are dependent on CS therapy.[49] Studies in patients with moderate-to-severe CS-dependent asthma show an improvement in asthma control, a reduction in the number of disease exacerbations, and a significant steroid-sparing effect. However, anti-IgE treatment is very expensive and appropriate only for specific patients who have a high circulating IgE within a precise range and are not controlled on maximal doses of inhaled and/or oral CS therapy. Omalizumab is usually given as a subcutaneous injection every 2 to 4 weeks and is relatively safe with few significant adverse effects, although anaphylaxis has occasionally been reported. A 3- to 4-month trial of therapy should be undertaken to ascertain any objective benefit with this treatment.

■ IMMUNOTHERAPY

Allergen immunotherapy is of benefit in highly selected patients with defined allergic triggers.[50] Asthmatic patients with a single specific allergic trigger and concomitant nasal symptoms derive the greatest benefit than patients with multiple allergic triggers. Allergen-specific immunotherapy (ASIT) involves the repeated administration of allergen products to induce immunologic and clinical tolerance to the specific allergen. ASIT may be given subcutaneously and studies have supported efficacy by this route of administration, but there is a risk of adverse effects including anaphylaxis. In contrast, sublingual ASIT has recently been shown to be an effective and safe alternative in patients with seasonal allergy, although data for perennial allergies related to asthma is lacking.

■ NONPHARMACOLOGIC MANAGEMENT

Alternative therapies may be popular and more acceptable with some patients and include acupuncture, breathing control, chiropraxy, homeopathy, hypnotherapy, and yoga; but placebo-controlled studies show these treatments lack efficacy and they should not be clinically recommended.[51] The concern with these therapies is that they may lead to discontinuation of effective drug therapy and destabilize asthma control in patients. However, as these therapies are considered not to be harmful, patients may utilize them as an adjunct to their conventional pharmacotherapy.

■ FUTURE TREATMENTS

Although current asthma therapy with CSs and β_2-agonists are effective in controlling disease symptoms in the majority of patients, poorly controlled asthma still remains a problem in a considerable

proportion of patients.[52] Poor adherence to prescribed controller therapy contributes to poor asthma control, and the use of combination LABA/ICS therapy delivered by a single inhaler device and/or the use of combination LABA/ICS therapy as both a controller and reliever agent, may partly address this problem. Indeed, the majority of current inhaler devices target their treatment to the large airways of the lung and research is ongoing to assess the clinical implications of targeting inhaled therapy to the peripheral lung regions, where they may be ongoing untreated inflammation additionally contributing to the patient's clinical state.[53] Asthma continues to remain an unmet need as the life-long treatments currently used only address the clinical symptoms and have little effect on the underlying structural alterations associated with asthma. There is also pressing need for the development of novel therapies for patients who have side effects with systemic CSs.[54]

Ultra–long-acting bronchodilators with once-daily dosing have been approved for COPD but not for asthma, and these treatments have allowed the production of several combination therapies incorporated with once-daily CS are in development.

CS resistance is a particular problem in patients with severe asthma, and several molecular mechanisms have been elucidated that may lead to novel therapeutic approaches, including the reversal of this resistance by drugs such as theophylline and nortriptyline. New treatments have been developed to control disease in very select groups of asthmatic patients. In patients with severe eosinophilic asthma (<5% of all asthmatic patients) despite treatment with high doses of CSs, blocking antibodies against interleukin-5 have been shown to reduce disease exacerbations. In contrast, anti–TNF-α antibodies have not been shown to be effective in patients with severe asthma. Several other blockers of specific mediators such as prostaglandin D(2), IL-9, and IL-13 are in clinical trials in patients with subtypes of severe asthma. New broad-spectrum anti-inflammatory treatments are in clinical development and include phosphodiesterase-4, NF-κB, and p38 MAP kinase inhibitors, but these drugs act on signal transduction pathways that are common to many immune cells, and present the risk of troublesome adverse effects particularly by the parenteral route and hence, there is ongoing research into their delivery by the inhaled route.

Studies of the steroid-sparing effects of macrolide antibiotics in asthma management have yielded discordant results. Macrolides might benefit some patients with infection by atypical bacteria, but recent results are not encouraging, although there could be an effect in patients with predominant neutrophilic asthma.

Bronchial thermoplasty has recently been advocated in selected patients with severe asthma and may be of benefit, and clinical studies although limited have demonstrated improved outcomes.[55]

MANAGEMENT OF CHRONIC ASTHMA

Management guidelines in asthma now focus on the control of asthma symptoms using a stepwise approach to drug therapy.[1] There has been a shift away from treatment based on disease severity with the realization that asthma does not necessarily remain in the same category permanently, but may change over months or years and that patients may move up or down in their asthma severity based on factors such as the presence of allergens, the incorrect/correct use of medications and treatments, and lack of adherence to the prescribed treatment regimen. If control at a particular step is not adequate, then treatment should be increased to the next level. The principles of therapy embody the fact that effective treatment should lead to better asthma control and allow the patient to move to a less severe category, and therefore for ongoing management of asthma, classification by level of control may be more relevant and useful. The aims of chronic therapy in asthma are highlighted in Table 46-2.

The Global Initiative for Asthma (GINA) stratifies patients into four categories of the level of asthma control; controlled (where therapy is maintained or stepped down); partly controlled (where consideration is given to stepping up therapy); uncontrolled (where treatment is stepped up until symptom control is achieved); and exacerbation (where patients are treated according to the exacerbation algorithms).[1] The characteristics that contribute to determining the level of control involve an assessment of the following: daytime symptoms experienced in the last week; limitations in activities of daily living; nocturnal symptoms or awakenings the need for rescue reliever medication during the week; lung function; and the number of exacerbations (if any) in the last week and last year.

STEPWISE TREATMENT

The stepwise approach to asthma management is a description of the levels of treatment required to achieve good asthma control.[1] Some patients may experience acute worsening of asthma control, such as those with a concomitant upper respiratory tract infection, and may need to step up more than one step at a time.

Step 1

For all asthma patients, a SABA delivered by a metered-dose inhaler is all that is required and gives relief of acute symptoms. The increasing use of a reliever medication more than three times a week, or triggering of symptoms from exercise, provide an indication that controller therapy is needed. An important, but often overlooked part of asthma management relates to measures to control environmental triggers. Recognized triggers that worsen asthma control in the patient such as aeroallergens or occupational agents should be avoided, although this is not always possible. Patients with asthma may also have several triggers; therefore the impact of avoiding a single trigger will vary considerably between patients. However, complete removal from exposure to house dust mite has been shown to reduce asthma severity and airway hyperresponsiveness.

Guidelines recommend that influenza vaccination should be administered in adult asthmatics. However, where studies suggest it is unlikely to induce asthma exacerbations, there is no conclusive evidence regarding the efficacy of vaccination on influenza-related asthma complications or a reduction in exacerbations of asthma. Asthmatic patients, especially the elderly or those with comorbid conditions that increase the risk of death from influenza infection, should receive inactivated influenza vaccine if there are no other contraindications. The CDC recommends a single dose of Pneumovax for adults from 19 to 64 who have chronic illnesses, including asthma.

Steps 2–3

When patient symptoms are no longer intermittent, the addition of a long-term controller medication on a scheduled daily basis is recommended, and the treatment of choice for all patients is an ICS to alleviate the underlying airway inflammation. It is usual to start with a low-to-intermediate dose of ICS twice daily (e.g., 200 μg beclomethasone dipropionate (BDP) or equivalent BID) and if symptoms are controlled after 3 months the dose should be stepped down. However, if symptoms persist and are not controlled, a LABA should be added as a fixed combination drug with an ICS delivered from a single inhaler device, as studies show a clinical advantage compared with the monocomponents administered using two separate inhalers. Indeed, low-dose ICS with LABA therapy has been shown to be as efficacious at high-dose ICS treatment.[56] The dose of the ICS should be adjusted up or down accordingly to the need for rescue inhaler treatment and to the control of the patient symptoms. Alternative add-on therapies to ICS that can be considered include low doses of slow-release oral theophylline or an antileukotriene, but these are less effective than the LABA/ICS combination.

Step 4–5

In patients with worsening symptoms, the addition of low-dose slow-release oral theophylline to high-dose LABA/ICS may be

helpful. Recently, it has been shown that the addition of the inhaled long-acting anticholinergic tiotropium bromide to LABA/ICS treatment in patients with poorly controlled asthma, significantly decreases asthma exacerbations and improves bronchodilator lung function.[57] In patients with severe asthma who fail to achieve symptom control, maintenance therapy with systemic oral CSs may be indicated, and there should always be an aim to titrate down to the lowest possible daily (or every other day) dose that maintains asthma control. Occasionally, anti-IgE therapy with omalizumab may be tried in patients who are CS dependent and continue to remain uncontrolled, but this treatment is only suitable for highly selected patients. Allergen-specific immunotherapy may be considered in this group; however, the risk of severe events including death is highest in patients with severe asthma.

STEP-DOWN TREATMENT

Once asthma patients achieve stable symptoms and have stable peak flow readings, it is important to slowly decrease therapy to find the optimal dose to control symptoms. Indeed, asthma severity may fluctuate and improve with time, owing to improved disease management, changes in environmental exposure, or because of the natural history of the disease, and most asthma guidelines recommend a step-down approach once patients are controlled.[1] Overtreatment of patients, particularly with ICS, can cause significant morbidity and adverse effects, especially in moderate-to-severe asthmatics. It may also be unnecessarily costly. Unfortunately, in such patients there is a tendency to maintain a static treatment regimen, even after symptoms are controlled and clinical stability is achieved. Studies have now supported the notion that stable asthmatic patients on high-dose ICS may be overtreated and that reductions in the inhaled dose can be achieved without significant increases in asthma exacerbations, visits to the family practitioner, or recourse to oral CS use.[58] A gradual reduction in medications starting with the treatment with the greatest toxicity should be attempted once stability is achieved and sustained for several months, and symptoms should be monitored on a long-term basis using both objective lung function and subjective symptom measures. Most patients should be maintained on an ICS, and this treatment should not be stopped as this provides anti-inflammatory protection. In those asthmatic patients that needed admission to hospital and/or ventilatory support, a longer period of stability on maintenance therapy may be justified before consideration of a step-down treatment approach.

MANAGEMENT OF REFRACTORY ASTHMA

Most asthmatic patients are controlled with appropriate stepwise therapy, but approximately 5% of asthmatics are difficult to control, do not remain symptom free despite maximal inhaled therapy, and may require maintenance treatment with oral CSs. In this group of patients, a thorough investigation of factors aggravating or contributing to poor asthma control should be undertaken. It is important to check adherence with medication and inhaler technique, particularly if the patient's disease is unstable despite the maximal recommended dose of therapy. Nonadherence with medication remains an important factor for the poor control of asthma and may be particularly manifest with ICS, as patients may be concerned about adverse effects or describe lack of immediate clinical benefit from this treatment. Monitoring adherence to ICS therapy in the clinic is difficult as there are no useful plasma measurements that can be made, however in contrast, the measurement of plasma cortisol suppression and absolute plasma drug concentrations may be useful in monitoring adherence to oral CSs. Evidence suggests nonadherence may be commoner in those with psychosocial problems or depression and these conditions should be actively sought and addressed during the clinical assessment. A detailed review of factors such as exposure to environmental allergens, unidentified occupational agents, or drugs that worsen asthma control such as aspirin or β-blockers should also be undertaken. Asthma may coexist with a number of disorders that can affect lung function, and the successful management of asthma often requires treatment of these associated conditions that are thought to aggravate asthmatic symptoms. Rhinosinusitis and gastroesophageal reflux disease are the most common of the disorders associated with poorly controlled asthma.

The relationship between rhinosinusitis and asthma is well established as described in the "united airway disease hypothesis," where treating the inflammation of allergic rhinitis in the upper airways has been shown to translate into improved asthma control.[59,60] It has also been postulated that poor asthma control may arise as a result of the inability of current inhaler devices to target drug therapy to the ongoing inflammation in the peripheral lung regions, and possibly treatment of this lung compartment with targeted anti-inflammatory therapy may result in improved symptoms.[53] In spite of the lack of data from meta-analyses which fail to show a consistent effect of antireflux therapy on asthma symptoms and lung function, many clinicians will assess and treat the possibility that gastroesophageal reflux disease may be aggravating asthma.[61]

As discussed earlier, patients with vocal cord dysfunction may present with wheeze and stridor and an escalation in asthma therapy. This disorder can be assessed using nasoendoscopy to observe abnormalities in the movement of the vocal cords, and if confirmed patients should be weaned off CSs. Speech therapy intervention may be helpful. Bronchoscopy or MDCT to exclude tracheobronchomalacia may be considered. A reconsideration of the potential differential diagnoses should be explored in the refractory asthmatic patient and this may require specialist referral (Table 46-3).

Patients who require high doses of oral CSs to maintain asthma control are referred to as CS-"dependent" asthmatics. In contrast, patients with complete CS-"resistant" asthma show a failure to respond to high-dose oral CS therapy, but this is very uncommon affecting less than 1 in 1000 patients. Several molecular mechanisms have been implicated in CS resistance and the impairment of their anti-inflammatory action, and this has led to the identification of new drug targets for future therapies.[62] There is evidence that in asthmatic patients who smoke (approximately 20% of the population), smoking itself hinders the anti-inflammatory action of CSs leading to relative CS resistance with the need for higher drug doses to achieve asthma control. It is recognized that smoking asthmatics compared to nonsmoking asthmatics have a faster decline in lung function, more severe asthma, more frequent hospital admissions, and a higher risk of death. Smoking cessation should be strongly pursued in this group as this intervention has been shown to reduce CS resistance and improve lung function.

Some asthmatic patients have unstable disease with rapid variations in lung function that may lead to recurrent and severe attacks of asthma, despite appropriate treatment for the disease.[63] These patients may be divided into type I brittle asthma, where there is a sustained pattern of chaotic peak flow variability on a daily basis or; type II brittle asthma, where asthma symptoms and lung function are well controlled, but there are abrupt and unpredictable falls in peak flow that may be catastrophic and result in sudden death. These patients are difficult to treat as they do not usually respond to maximal high-dose CS therapy but rely and need subcutaneous epinephrine injections. The assessment of treatment adherence and education on allergen avoidance is particularly important in these patients and they should wear an identification bracelet of their condition. The importance of carrying a portable epinephrine autoinjector at all times and being taught to self-administer this treatment should be a central part of their management.

ASTHMA EDUCATION AND MONITORING

Asthma education and training is important as patients need to understand the disease, its management, how to use inhalers properly, adverse effects of treatment, and importantly when to use reliever and controller treatments. Education may improve adherence to treatment recommendations and also engage the patient in self-management strategies particularly in terms of recognizing their symptoms, identifying and avoiding asthma triggers, objectively measuring any deterioration in their asthma control, and treating exacerbations of asthma at their earliest stages by stepping up their therapy. Educating the patient in the self-administration of oral CSs and access to healthcare advice are also important elements in a management program, which are designed to reduce emergency hospitalizations and patient morbidity. Studies have shown that written personal patient action plans result in better asthma control, reduced emergency room visits and hospitalizations, and decreased morbidity in both adults and children. Written plans are particularly useful and recommended in patients with unstable disease who have frequent exacerbations. The additional provision of a program of educational sessions (one-to-one or in small groups) with a knowledgeable healthcare professional has been shown to be more effective than written materials alone. Like drug therapy, the educational program and the method and frequency of reinforcement should be tailored to the patient's individual needs. Patients should be reassured that with proper treatment, their symptoms and occasional exacerbations can be minimized, and in most cases a normal lifestyle and life expectancy can be anticipated.

Home monitoring of asthma symptoms and control is an important aspect of self-management programmers. PEF measurements allow patients to be monitored on a long-term basis with relative ease using hand-held, compact, portable devices. Asthma treatment guidelines recommend patients use PEF measurements not only to monitor the course of the disease, but also to dictate self-administered treatment regimens.[1] Indeed, studies show improvements in measures of asthma control when peak flow measurements are used by patients (in relation to their personal best peak flow) to adjust medication usage. However, despite the advantages of written plans highlighted above, the US Centers for Disease Control and Prevention (CDC) analyzed asthma data from adults and children between 2001 and 2009 in a national health interview survey and showed that only one-third of patients with asthma reported being given a written asthma action plan, and just over two-thirds of patients had been taught the appropriate response to symptoms of an asthma attack.[64] It should be recognized that not all patients are capable of comprehending and executing complicated treatment plans. There are also concerns that peak flow–guided self-management may lead to overtreatment with medication, and hence the potential for increased morbidity due to adverse effects. Similarly, patients with severe asthma in whom self-management plans are more readily recommended, may tend to use more oral CSs where it may be unclear whether the increased use is appropriate or medically warranted (although the increase in medication may be initially viewed as a potential benefit of peak flow monitoring). Action plans should be written using clear, simple language and individualized based on patients' understanding of their asthma, its severity, and their demonstrated ability to comply with instructions.

MANAGEMENT OF ACUTE SEVERE ASTHMA

Asthma is characterized by exacerbations of disease, which can lead to substantial morbidity, occasional mortality, and considerable medical and economic costs. Patients with asthma fear disease exacerbations as they can be life-threatening and exacerbation-prone patients seem to be at increased risk for attacks of near-fatal asthma. Analysis of asthma mortality data identifies that patients experience worsening symptoms and deterioration in asthma control of a period of several hours to several days, before the event.[65] Indeed, life-threatening episodes can develop in any asthmatic patient, but particularly those patients with severe and poorly controlled disease; those who frequently access the emergency room; or patients who are hospitalized, are all recognized to be at high risk of life-threatening events. The importance of educating all patients with asthma should not be underestimated, as well as their carers, and in particular healthcare professional should identify and closely monitor such at-risk patients.

CLINICAL FEATURES

Patients with a moderate exacerbation of their disease notice a deterioration in their asthma control by an increase in daytime and nocturnal symptoms of cough, chest tightness, wheeze, and dyspnea, that do not respond to their usual maintenance therapy and require more reliever drug. A history of prodromal symptoms may be elicited that precede an asthma attack, such as itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom). A fall in home peak flow recordings also signify a worsening of asthma and the GINA guidelines classify exacerbations based on the peak flow into mild (PEF >80% predicted), moderate (PEF between >60% and 80% predicted), and acute severe (PEF between <60% predicted).[1] Patients may become so breathless in acute severe exacerbations that they become exhausted, unable to talk freely in complete sentences, and show life-threatening features of confusion, agitation, and cyanosis. Clinical examination usually shows an increased respiratory rate, hyperinflation, and tachycardia. In acute severe asthma, pulsus paradoxus (the accentuated decrease in systolic blood pressure [>10 mm Hg] during inspiration), may be present. Life-threatening signs are a silent chest, bradycardia, and hypotension. Investigations will show a marked fall in PEF and spirometric values; hypoxemic saturations on air and arterial blood gases may reveal a low Pa_{O_2}, and initially a low Pa_{CO_2} usually due to hyperventilation. In life-threatening situations the PEF will be <30% of predicted, oxygen saturation (Sa_{O_2}) measured by pulse oximetry <92% and, arterial blood gases on air will show a Pa_{O_2} <60 mm Hg (8 kPa) and a rising Pa_{CO_2} will indicate impending respiratory failure and requires immediate monitoring and therapy. A chest radiograph is not routinely recommended in the absence of a suspected pneumothorax, pulmonary consolidation, failure to respond to treatment satisfactorily, or a requirement for ventilation.

PHARMACOLOGIC TREATMENT

The cornerstone of therapy for worsening asthma control requires the escalation of both ICSs and quick-relief inhaled β_2-agonists.[1] Exacerbations of asthma should never be treated by escalating bronchodilators alone and asthma fatalities usually result when patients fail to promptly seek medical attention. Studies have shown patients dying from asthma commonly self-medicate with escalating doses of reliever bronchodilator medication in the preceding days to an asthma attack. A short course of oral CS therapy for at least several days may be needed to control and prevent a mild–moderate exacerbation and tapering of the dose should be undertaken with close outpatient follow-up. Very mild or subacute exacerbations in asthmatics with mild persistent disease may be managed in some cases by escalating the dose of ICSs in cases in which patients are taking low-doseCS. In less severe exacerbations, patients who promptly respond to treatment in the emergency department may be discharged but close outpatient follow-up is essential.

In patients with an acute severe exacerbation presenting to the emergency department, oxygen at high concentrations and high flows should be given continuously by face mask to achieve oxygen saturations (Sp_{O_2}) of between 94% and 98%. Hypoxemia is to be avoided at all costs, as patients die from hypoxemia in acute asthma and oxygen therapy is critical to prevent death in severe acute asthma, so continuous monitoring of oxygen saturation is needed until there is a meaningful response to treatment.

High doses of inhaled SABA given either by nebulizer (oxygen-driven) or via a pMDI with a spacer should be the first-line agents in acute asthma and be administered as early as possible. While generally well tolerated, occasionally nebulized bronchodilators cause arrhythmia and continuous electrocardiogram monitoring is required. In those patients in whom inhaled therapy cannot be used reliably, or in severely ill patients with impending respiratory failure, intravenous β_2-agonists may be given. In patients not responding, nebulized anticholinergic treatment (ipratropium bromide) may be added as they provide additional bronchodilation. Systemic CSs should be given in adequate doses in all cases of acute severe asthma for at least 5 days or until recovery and should be tapered after this response over a 2-week period, particularly in cases of severe asthma exacerbations. In patients unable to take oral CSs, intravenous therapy (e.g., hydrocortisone) should be administered in the emergency department.

A single dose of intravenous magnesium sulfate for patients has been shown to be effective when added to inhaled β_2-agonists. It is relatively well tolerated and can be considered in patients with acute severe asthma who have not had an initial good response to inhaled bronchodilator therapy, or in those with life-threatening features.

Patients should be referred to the intensive care unit for intubation and ventilation if they have acute severe or life-threatening asthma that is failing to respond to therapy indicated by: a deteriorating PEF, worsening hypoxemia, a normal or rising Pa_{CO_2}, poor respiratory effort, and exhaustion or confusion. Intravenous aminophylline may be used, but the risks of toxicity are much greater than when inhaled β_2-adrenergic agonists are used. Sedatives should never be given as they may depress ventilation, and antibiotics should not be routinely administered, unless there are clinical or radiologic signs of pneumonia.

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CHAPTER 47

Aspirin- and Exercise-Induced Asthma

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Asthma is well known to be triggered by specific immune factors such as aeroallergen exposures. There are, however, several important nonallergic triggers for the development of asthmatic bronchial obstruction. Two of the most important are aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDS) and exercise. Both can provoke airway responses in the setting of established symptomatic aeroallergen-induced asthma or in isolation. These two nonspecific triggers may also share pathophysiologic mechanisms, including mast cell and leukotriene-related pathways, and may be related to vascular response–mediated airway narrowing.

ASPIRIN-INDUCED ASTHMA

The first report of aspirin-induced asthma (AIA) was that of Hirschberg in 1902. Six decades later, the association between aspirin sensitivity, asthma, and nasal polyps was documented in a classic paper by Samter and Beer.[1] In 1928, the clinical importance of sensitivity to aspirin was highlighted by van Leewen, who challenged 100 asthmatics with aspirin, provoking bronchoconstriction in 16. Several others[2,3] have made similar observations, documenting a prevalence of aspirin sensitivity in asthmatics that ranges from 5% to as high as 30%, depending on the characteristics of the asthmatics studied (severity increases risk) and the criteria applied to make the diagnosis.

Aspirin was originally recognized as the first drug capable of precipitating asthma. With the development of chemically related analgesic and nonsteroidal anti-inflammatory drugs (NSAIDs) after 1950, other agents were found to exacerbate asthma. In a study of 781 asthmatics observed over a period of 2 years, drugs were noted to provoke asthmatic airway responses in 10.5% of patients.[4] Reactions to NSAIDs were thought to be responsible for 77% of all cases, with aspirin accounting for two-thirds of the reactions to NSAIDs, or nearly 50% of all cases of drug-induced asthma. Therefore, although aspirin is the most common drug to induce asthma and the most common NSAID to cause asthma, other NSAIDs are responsible for an important number of these reactions.

CLINICAL PRESENTATION

Reactions to aspirin take two distinct forms: Cutaneous—most commonly characterized by urticaria and angioedema,[5] and respiratory—characterized by rhinoconjunctivitis and bronchospasm.[6] The cutaneous reactions that develop after the ingestion of NSAIDs include hives with or without angioedema, may develop in individuals with a history of chronic urticaria or healthy individuals, and are the result of exposure to a single drug in this class or to one of multiple NSAIDs.[5] The wide spectrum of underlying variables suggests that the pathogenic processes leading to these clinical presentations are diverse. The fact that a great majority of patients were able to tolerate the same NSAIDs before the development of the urticarial process, suggests that the NSAIDs interact with an underlying urticarial tendency but do not directly and independently cause the hives. This explains why the avoidance of NSAIDs does not eliminate the urticarial symptoms in all patients. However, the identification of the reaction as one provoked by a single or by multiple NSAIDs is fundamental to develop a therapeutic plan in these subjects, to provide guidance with respect to the restriction of exposure to the inciting agent in this therapeutic class.

The respiratory manifestations of aspirin sensitivity involve both the upper (nasal) and lower airway (asthma), and are generally temporally linked. Sometimes, upper respiratory symptoms, typically rhinitis, precede the development of lower respiratory reactions to these agents. AIA can occur on a background of established asthma or can appear de novo without previous asthma symptoms. This observation has led to the use of more accurate descriptors for this condition including, aspirin-induced asthma (AIA) or aspirin-exacerbated respiratory disease (AERD), the latter a more inclusive term that extends beyond the lower airway manifestations (asthma), to include the upper airway (nasal and sinus mucosa).

The typical presentation of this syndrome is characterized by an initial complaint of upper respiratory symptoms, similar to those caused by a viral illness. The syndrome peaks in the third decade of life. Upper respiratory symptoms become persistent and extend to involve the nasal mucosa and paranasal sinuses. Marked eosinophilia is often observed in the setting of chronic rhinitis, and nasal polyps. A detailed history documenting a relationship between the ingestion of aspirin and/or NSAIDs and the upper and lower respiratory symptoms helps to establish the connection between these agents and the development of nasal polyps. Typically, though symptoms may improve, the inflammation persists despite substantially reduced or absent exposure to aspirin or NSAIDs.

In addition to Samter's classical description of nasal polyps, asthma, and aspirin sensitivity,[1] the documentation of sinusitis involving one or several paranasal sinuses at some point in the disease in almost all patients is an additional feature of the syndrome.[7] The nasal and sinus inflammation is often accompanied by anosmia, recurrent sinus infections often leading to recurrent surgeries to remove polyps to provide relief for the chronic sinus congestion. Opacification of one or more sinuses on plain radiographs can be seen in 90% of these patients, while sinus CT has a higher sensitivity to detect mucosal thickening resulting from chronic hyperplastic eosinophilic sinusitis, and air fluid levels.

Atopy does not seem to be the main pathogenic mechanism in AIA. This observation is based on evidence from multiple sources and includes the observation that many patients with AIA are not atopic; with a rate of positive aeroallergen skin testing between 30% and 60%, a substantial proportion exhibit negative skin tests and IgE levels in the normal range. The documentation of NSAID-specific IgEs has not been successful, and the peripheral blood eosinophilia, complement activation, and serum histamine elevation seen after acute aeroallergen challenge of atopic asthmatics, are absent after acute aspirin challenge. Thus, the term, pseudoallergy has been used to describe some of the AIA reactions.

In contrast, the typical reaction after aspirin ingestion in these patients is the slow development (within ½ to 4 hours, mean 50 minutes) of nasal congestion with profuse rhinorrhea, cutaneous flushing involving the head and neck, conjunctivitis, and bronchial obstruction, the latter usually manifested as wheezing. A typical reaction provoked by an oral challenge under laboratory conditions is illustrated in Figure 47-1. In severe reactions, headache, nausea and vomiting, and acute hypercarbic respiratory failure culminating in death can occur. Life-threatening responses with faster kinetics have also been reported with systemically administered NSAIDs such as ketorolac.[8]

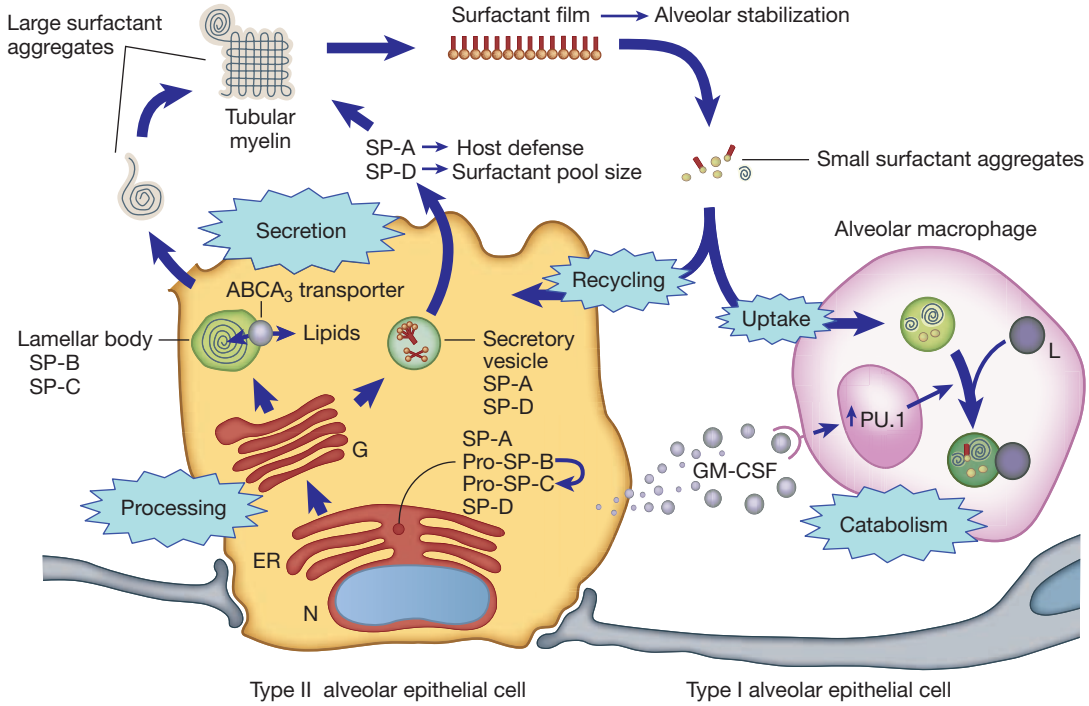

Figure 47-1 Typical reaction to aspirin in AIA. The timeline illustrates the kinetics of respiratory compromise and nasoocular symptoms after graded aspirin or placebo challenge. IPPB, intermittent positive-pressure ventilation with β-adrenergic agonist bronchodilator. *(Data from Stevenson DD, Simon RA. Aspirin sensitivity: Respiratory and cutaneous manifestations, in Middleton E Jr, et al (eds). Allergy: Principles and Practice. St. Louis, CV Mosby. 1993;1747–1767.)*

Combined cutaneous and respiratory reactions (i.e., true urticarial eruptions in association with asthma) occur in <3% of cases.[9]

■ GENETICS

In contrast to classic atopic asthma, which patients develop during childhood and adolescence, AIA typically occurs in individuals in the third to fourth decade of life. An original report by Lockey describing a consanguineous family suggested an autosomal recessive pattern.[10] However, a subsequent report by Von Maur indicated an autosomal dominant pattern.[11] The late onset of the disease points to important environmental influences that may play a significant role in the development of the syndrome. Both genders are affected by the disease; however, the prevalence is higher in women than men.

Notwithstanding the lack of familial association in most cases, one study did show an increase in the expression of *HLA-DQW2* in a group of patients.[12] A later study showed increased expression of *HLA-DPB1*0301* (Odds ratios: 4.4 and 5.3) and decreased expression of *DPB1*0401* (OR: 0.42 and 0.48) in AIA versus normals and nonaspirin-sensitive asthmatics, respectively, among Europeans.[13] Korean investigators confirmed a higher risk of AIA in patients carrying *HLA-DPB1*0301*, while those carrying *HLA-DRB1*1302* and or *DQB1*0609* exhibited a higher risk of aspirin-induced urticaria.[14]

Several genes in the arachidonic acid pathway have been associated with molecular defects responsible for aspects of the pathogenesis of the disease. The single nucleotide polymorphism (SNP) rs730012 (A-444C) in the Leukotriene C4 synthase *(LTC4S)* gene was associated with higher gene expression in blood eosinophils and higher relative risk of AIA (2.62; 95% CI: 1.38, 4.98) in Europeans with AIA.[15] An additional study from the same group showed a functional and gender association of the rs20417 SNP (G-765C) in the *COX-2* promoter region in AIA patients with more severe disease.[16] A Japanese group found an association between the rs4794067 SNP in the *TBX21* gene, the human analogue for the *T-bet* gene in mice, that, when absent, had previously been shown to result in airway eosinophilia and hyperresponsiveness. The rs4794067 polymorphism was in linkage disequilibrium with a synonymous coding 390A-G SNP in exon 1 and was significantly associated with AIA.[17] Another study showed heightened transcription or polymorphisms in the 5-lipooxygenase activating protein *(ALOX5AP)* gene in AIA.[18] New insight may result from the recent observation of selective expression in AIA patients of cysteinyl leukotriene type 2 receptor, but not type 1 receptor, expressed by infiltrating inflammatory cells of the upper airway, not observed in aspirin-sensitive patients with chronic allergic rhinitis and normal controls.[19]

The number of genetic studies in AIA has increased significantly over the last decade, with the advent of high throughput technologies. The majority of studies have used a candidate gene approach, with some positive associations. The interpretation of the evidence suggests that the development of AIA is the result of the interaction between multiple polymorphisms and the environment; however, some of these findings in specific populations may not be generalizable to all individuals with disease due to different allelic frequencies and individual environmental risk factors that modify the AIA phenotype.

Gene expression profiling of nasal polyps of individuals with AIA has shown higher levels of periostin expression;[20] this observation is particularly relevant for both the upper and lower airway, since periostin is also secreted by bronchial epithelial cells and is associated with TGF-β stimulation and increased extracellular matrix deposition in the airway of asthmatics.[21]

■ CROSS-REACTIVITY

Cross-reactivity of aspirin with other NSAIDs was first recognized in 1967 by Vanselow and Smith.[22] This report was followed by others of reactions to structurally unrelated NSAIDs, which suggested that these reactions were not atopic in nature. It was subsequently shown that the ability of these drugs to provoke asthma in susceptible patients was related to their ability to inhibit cyclooxygenase (COX), and that the degree of cross-reactivity with aspirin was related

to the degree to which these agents inhibited COX in vitro.[23,24] Subsequently, the discovery of isoforms of COX has revealed that the dominant form that is inhibited by low doses of aspirin and is capable of eliciting airways responses in AIA is COX-1. Drugs that are less potent inhibitors of COX-1, but are structurally related to aspirin (e.g., sodium salicylate), at clinical doses, do not provoke AIA.

The association of AIA with the COX-1 isoform of the enzyme has been strengthened by studies with specific inhibitors of COX-2, which, at clinical doses, nearly completely spare inhibition of COX-1. Two separate studies have shown convincingly that selective inhibitors of COX-2 (celecoxib and rofecoxib) do not provoke airway changes typical of AIA in patients known to have the disorder, or in those who were challenged in the laboratory de novo in the process of diagnosing the disease.[25,26] In individuals challenged with celecoxib, including high doses, no reaction was seen (Fig. 47-2).[27,28] The increased risk of thrombotic cardiovascular events with rofecoxib and celecoxib, has limited the evaluation of these effects in larger populations of individuals with AIA. A list of NSAIDs reported to provoke AIA and those not associated with AIA is given in Table 47-1.

Curiously, although at least two studies involving nearly 100 subjects showed that a later generation, highly specific COX-2 inhibitor, etoricoxib, did not provoke acute responses with doses up to 120 mg,[29,30] another study showed a small, though detectable risk of cutaneous reactions after challenge with etoricoxib.[31] In one case report involving a single patient, challenge with etoricoxib was associated with a reduction of FEV_1 and development of rhinorrhea 30 minutes after a 60 mg dose. Thus, although the vast majority of patients with ASA may not develop symptoms when administered COX-2 inhibitors, confirmation of ability to tolerate these agents with formal testing may be the most conservative approach.

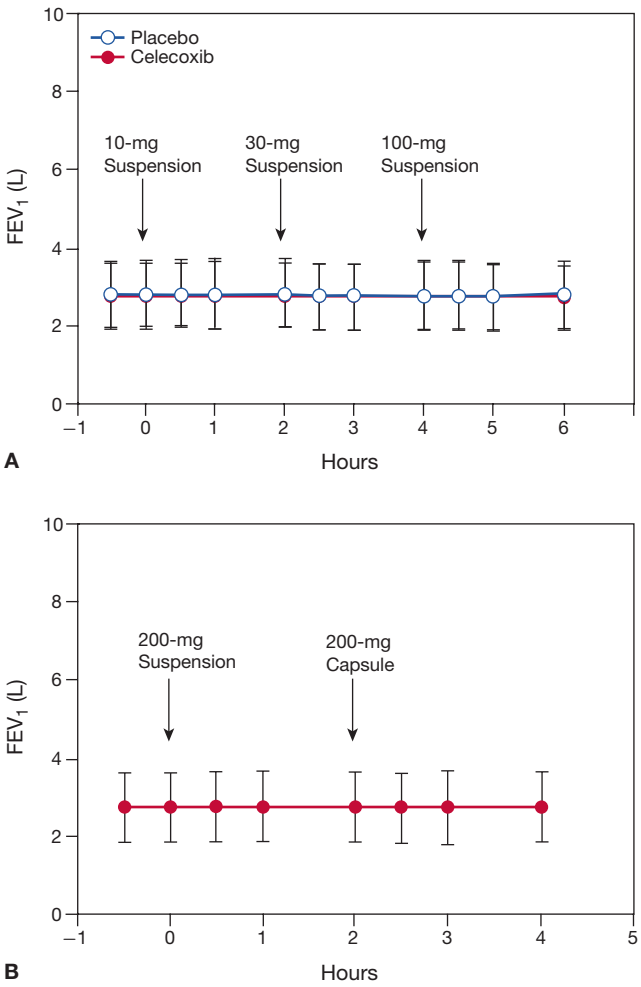

Figure 47-2 Lack of airway bronchoconstriction to increasing doses of a COX-2 inhibitor in aspirin-sensitive asthmatics. FEV_1 measured before and after oral challenge. **A.** Double-blind crossover challenge. **B.** Open label challenge. *(Reproduced with permission from Gyllfors P, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclo-oxygenase 2-selective drug celecoxib. J Allergy Clin Immunol. 2003;111(5):1116–1121.)*

TABLE 47-1 NSAIDs in Aspirin-Induced Asthma (AIA)

NSAIDs that Can Provoke Airway Narrowing in AIA
Carboxylic acids
Salicylates
Acetylsalicylic acid (aspirin, Easpirin, Zorpin)
Acetic acids
Indomethacin (Indocin)
Sulindac (Clinoril)
Tolmetin (Tolectin)
Diclofenac (Voltaren)
Ketorolac (Toradol)
Zomepirac (Zomax)
Propionic acids
Ibuprofen (Motrin, Advil, Nuprin)
Naproxen (Naprosyn)
Fenamates
Meclofenamate (Meclomen)
Mefenamic acid (Ponstel)
Enolic acids
Piroxicam (Feldene)
NSAIDs and Analgesics that Appear to Be Well Tolerated in AIA
Sodium salicylate
Choline salicylate
Salicylamide
Dextropropoxyphene
Acetaminophen in low doses
Selective COX-2 inhibitors

A number of other analgesics have long been considered to be well tolerated in patients with AIA. They are also listed in Table 47-1. However, some analgesics, formerly considered safe for use by these patients, were subsequently shown to be capable of provoking bronchospasm if given in large doses. For example, doses generally greater than 1000 mg of acetaminophen, and salicylate, at doses of 2000 mg or greater, can provoke significant declines in FEV_1 in some aspirin-sensitive asthmatics. Reactions to high doses of these drugs, when they occur, tend to be milder than those seen with aspirin. A similar phenomenon has been observed with meloxicam and nimesulide, drugs that inhibit COX-2 somewhat more than COX-1. At typical clinical doses they are generally well tolerated in patients with AIA; however, at high doses, cross-reactions may be observed.

The documentation of NSAID-specific IgE antibodies and anaphylactic reactions to NSAID after a period of sensitization is much less common than non–IgE-mediated reactions, which tend to occur after first exposure. However they must be considered in the

differential diagnosis in the appropriate clinical situation. Avoidance of the specific NSAID involved prevents relapses.[32]

An interesting association of AIA with sensitivity to hydrocortisone has been made. After several case reports of the association, two studies[33] demonstrated that a small percentage of patients with aspirin-induced asthma may experience acute bronchospasm (15–30 minutes) after the intravenous or intramuscular injection of hydrocortisone. The vehicles and diluents used in the hydrocortisone preparations could not be linked to the reactivity. One of these studies showed no bronchoconstrictor response to methylprednisolone, dexamethasone, or betamethasone when given intravenously, indicating that these potent anti-inflammatory steroid preparations, related to hydrocortisone but with different side chain chemical structure, could be used safely.[34] The mechanism of this reaction is not known, though corticosteroids can reduce phospholipase PLA2 activity (generally decreasing eicosanoid production) and broadly inhibit isoforms of COX, especially COX-2.[35]

PATHOGENESIS

The combination of epidemiologic data, genetic and genomic information, with the observation that COX-2 inhibitors exhibit a relatively safe profile in individuals with AIA has pointed to key aspects of the pathophysiology of AIA. The main theory supports an alteration in the balance between leukotrienes and prostaglandins generated by the lipooxygenase- and COX-dependent pathways of arachidonic acid metabolism (Fig. 47-3). Other attempts to explain the spectrum of symptoms are based on the release of other mediators, most likely from mast cells, basophils, or platelets. These theories include upregulation of mast cell–basophil mediator release by substances not yet identified that affect mast cell membranes, increased histamine production by basophils of patients with aspirin-induced asthma in comparison to normal subjects, decreased production of prostaglandin E2 (PGE2) with enhanced production of leukotriene B4 (LTB4) by AIA basophils, and enhanced aspirin-induced release of serotonin and other mediators by AIA platelets.[9,36] It has been proposed that complement activation may be important in these processes.[37] However, the role of complement activation in AIA has been questioned by data showing no significant changes in CH50 and C4 levels in patients experiencing an asthma exacerbation after acute oral aspirin challenge.[38]

Alterations in arachidonic acid metabolism appear to play a central role in AIA. The major pathways of COX and lipooxygenase metabolism of arachidonic acid are illustrated in Figure 47-3. Arachidonic acid is derived from membrane phospholipid by phospholipase A2. It is then metabolized via the COX pathway to prostaglandins (COX-2 > COX-1) and thromboxanes (COX-1 > COX-2) or via the lipooxygenase pathway to sulfidopeptide (cysteinyl) leukotrienes. The leukotrienes have a variety of effects, including the induction of contraction of bronchial smooth muscle. In contrast, the prostaglandins, in particular PGE2, act as bronchodilators and may inhibit T cell–mediated inflammatory responses in the lung. Aspirin and the other NSAIDs that cause AIA inhibit COX-1 activity. A shift occurs after the administration of aspirin or appropriate doses of these other agents, shunting approximately 90% of the arachidonic acid metabolism to the 5-lipooxygenase pathway, decreasing prostaglandin and thromboxane production, and increasing leukotriene generation. In comparison to normal controls, patients with AIA generate leukotrienes in exaggerated quantities after aspirin challenge. Discovery that AIA patients produce less of the anti-inflammatory mediators lipoxins and 15-epimer lipoxin might enhance effects of this shift.[39] AIA patients may also be more sensitive than normal subjects to the bronchoconstrictor properties of leukotrienes (particularly LTE4) and more susceptible to the loss of the bronchodilating and potentially anti-inflammatory effects of PGE2. The data supporting these conclusions are briefly summarized below.

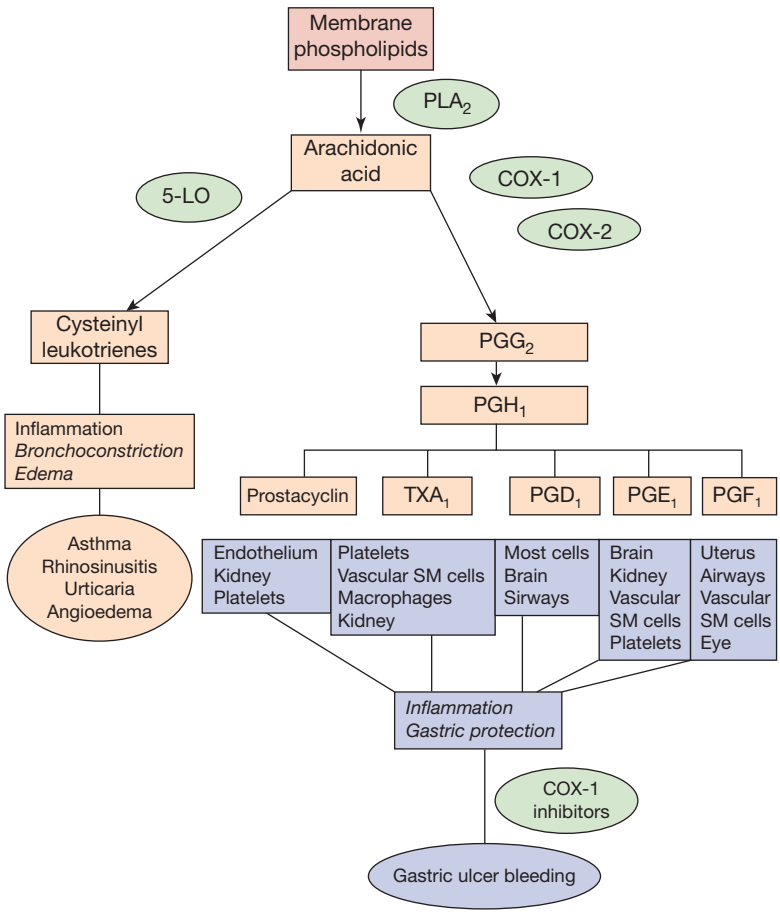

Figure 47-3 Enzymatic pathways of arachidonic acid metabolism. *(Reproduced with permission from Sanchez-Borges M, et al. Cutaneous reactions to aspirin and nonsteroidal anti-inflammatory drugs. Clin Rev Allergy Immunol. 2003;24(2):125–135.)*

Several groups have analyzed the nasal lavage fluid from aspirin-sensitive and control patients and found inducible levels of cysteinyl leukotrienes and plasma proteins when patients with AIA received oral or nasal aspirin challenges.[40,41] One study found that LTC4 and LTD4 levels were not significantly induced in normal subjects, but could be induced to some degree in patients with allergic rhinitis and in those with isolated nasal polyps (rising 93% and 69% above baseline levels, respectively).[41] Similarly, although histamine levels rose significantly in the AIA group (greater than threefold increase in total protein) they did not rise significantly in the control groups. Analysis of the nasal lavage fluids showed impressive increases in lactoferrin and lysozyme, suggesting that submucosal glands are stimulated in this process.

In a follow-up study, the cellular source of these nasal abnormalities was investigated by analysis of nasal lavage fluid after induction by aspirin challenge for the presence of mast cell tryptase and eosinophil cationic protein (ECP).[40] Significant increases in nasal tryptase, histamine, and cysteinyl leukotrienes were observed after AIA was provoked in these patients. ECP levels at baseline were variable and did not

increase significantly after challenge. A similar study before and after intranasal challenge with aspirin revealed changes in the vascular permeability of patients with AIA, an associated influx of eosinophils coupled with increased ECP, and an associated increase in tryptase suggestive of mast cell activation.[42] These findings are consistent with earlier work[8] that documented similar increases in blood tryptase (4 hours) and urinary LTE4 levels (6 hours); the decreases in blood eosinophil counts demonstrated could be associated with eosinophil recruitment at the tissue level after aspirin challenge.

The metabolism of arachidonic acid in the lung has not been studied as extensively. The available data show both similarities and differences with findings in the nose and circulation. For example, bronchoalveolar lavage fluid (BALF) obtained 30 minutes after inhalation of threshold doses of lysine–aspirin contained decreased levels of COX-dependent mediators (PGE2, PGD2, thromboxane B2 [TXB2], and PGF2α). However, only small increases in LTE4 and 5-hydroxyeicosatetraenoic acid (HETE) levels were noted. Lysine–aspirin inhalation also did not produce a significant rise in tryptase levels in BALF and led to a significant fall in ECP levels despite baseline eosinophil and ECP levels, which were higher in the AIA group than in placebo-treated nonasthmatic individuals.[43] The authors postulated that the altered pulmonary eicosanoid production might be related to eosinophilic inflammation in the airways of patients with AIA.

Additional understanding of the mechanism of bronchospasm in AIA has been gained by other investigators who used inhibitors of leukotriene effector function. One study administered a specific sulfidopeptide leukotriene receptor antagonist via inhalation and noted that it attenuated aspirin-induced asthma in five of six subjects by 43% to 74%.[44] This was followed by a double-blind, placebo-controlled, crossover study that showed that a specific leukotriene receptor antagonist given as a single oral dose 1 hour before perithreshold lysine–aspirin inhalant provocative challenge could almost completely block the development of aspirin-induced bronchospasm.[45] This was achieved without evidence of any direct bronchodilatory effect of the drug before lysine–aspirin challenge, confirming that leukotriene receptor antagonist was effective in preventing analgesic-induced (dipyrone) bronchospasm.

The effects of leukotrienes in the lung can also be modulated by blocking 5-lipooxygenase activation. The efficacy of this approach was demonstrated in a randomized, double-blind, crossover study in which the 5-lypooxygenase inhibitor zileuton (600 mg orally, four times a day, for 6–8 days before aspirin challenge) led to a greater than 70% reduction in baseline urinary LTE4 excretion, a greater than 60% reduction in mean maximal urinary concentration of LTE4 after aspirin challenge, and almost complete suppression of subthreshold and threshold oral aspirin-induced bronchospasm.[46] In addition, nasoocular, gastrointestinal, and cutaneous manifestations were reduced to the levels of symptoms produced by placebo challenge. Similar data have been generated with the cysteinyl leukotriene receptor antagonists montelukast and zafirlukast.[44,45,47]

Analysis of mast cells isolated from patients with AIA shows that the overproduction of cysteinyl leukotrienes by these cells is very sensitive to the regulatory role of PGE2, suggesting an additional molecular mechanism to account for the excess sensitivity to the COX inhibition associated with NSAIDS in AIA.[48] Altered cellular cross talk involving platelets and leukocytes has been recently recognized as a potential source of excess cysteinyl leukotrienes in individuals with AIA through a biologic mechanism known as transcellular biosynthesis.[49]

In summary, although the mechanism of AIA remains incompletely understood, there appears to be a clear role for lipooxygenase products in the pathogenesis of the disorder. The available data also suggest that mast cells, stimulated by aspirin directly or indirectly, discharge their leukotriene mediators in large amounts into nasal secretions, but may not play the same role in the lung. The presence of increased numbers of eosinophils and altered eosinophil phenotype may be more relevant to the pathophysiology in the lung and may be linked to the airway inflammation that characterizes this disorder. This probably reflects their recruitment secondary to the release of mast cell–derived mediators, including leukotrienes and cytokines.

DIAGNOSIS

Despite the characteristic clinical features of AIA, diagnostic evaluation is fundamental, given the presence of false positive and negative diagnosis based on clinical history alone.[27] Several *in vitro* assays have been described in individuals with AIA; however, their standardization and availability as diagnostic tests has not materialized. This ranges from cellular assays, to biomarkers in serum, induced sputum, and exhaled condensate, to assays performed on saliva and on urine.[36,50] The use of provocation tests with aspirin or NSAIDS for persons suspected to have this disorder (Table 47-2) is used in the diagnosis of AIA employing protocols using single-blind or double-blind approaches.

A traditional protocol begins with a 3 mg dose of aspirin, although higher initial doses (30 mg) have been recently advocated.

TABLE 47-2 Diagnosis of Aspirin-Induced Asthma (AIA): Aspirin Challenge Protocols

Single-Blind Oral 3-Day Aspirin Challenge			
	Test Days		
Time	1	2	3
0	Placebo	ASA 30 mg	ASA 100–150 mg
3 h	Placebo	ASA 45–60 mg	ASA 150–325 mg
6 h	Placebo	ASA 60–100 mg	ASA 325–650 mg
Double-Blind Oral Aspirin Challenge			
Both tester and patient are blinded to eliminate potential bias.			
Bronchial Challenge with Lysine–Aspirin			
Time (min)	Challenge (Lysine–Aspirin in mg/mL)		
0	Placebo		
45	Placebo		
90	11.25		
135	22.5		
180	45		
225	90		
270	180		
315	360		
350	360 (10 breaths)		
Patients receive four breaths of all doses of lysine–aspirin unless otherwise indicated.			

Source: Data from DD Stevenson. Aspirin and NSAID sensitivity. Immunol Allergy Clin N Am. 2004;24:491–505; Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in Middleton E Jr, Reed CE, Ellis EF (eds). Allergy: Principles and Practice. St. Louis, CV Mosby, 1993; Phillips GD, Foord R, Holgate ST. Inhaled lysine-apirin as a bronchoprovocation procedure in aspirin-sensitive asthma: Its repeatibility, absence of a late-phase reaction, and the role of histamine. J Allergy Clin Immunol. 1989;84:232–241.

If reactions occur at this dose, patients are easily treated. The dosage is then increased to a maximum of 650 mg over a 3-day period. Due to concerns regarding the safety of the protocol, the use of leukotriene antagonists to decrease the rates of severe lower respiratory tract reactions during provocation tests has gained popularity.[51] The improvement in the safety profile for the oral aspirin challenge has also allowed reduction in the time needed to complete the protocol from 3 to 2 days. Spirometric pulmonary function is monitored serially during the challenge to assess the degree of bronchial obstruction. Airway reactivity to methacholine is not a viable surrogate for spirometry, since aspirin does not consistently alter methacholine sensitivity. Aspirin challenge should probably be reserved for use in centers experienced in its application and adverse effects. An alternative to oral challenge, used in some centers in Europe and elsewhere for the diagnosis of AIA, is the inhalation of stabilized lysine–aspirin, followed by serial lung function measurements, or nasal provocation with aspirin or lysine–aspirin followed by serial rhinomanometry or acoustic rhinometry.[52] Since lysine–aspirin is not available for clinical use in the United States, intranasal ketorolac challenge has been advocated as an alternative.[53]

TREATMENT

Given the particular pathophysiologic characteristics of AIA, optimal treatment of patients with AIA requires knowledge of the best approaches to treat acute aspirin-induced bronchial symptoms and associated nasal and sinus pathology. No specific therapy has emerged which can be recommended for the routine treatment of acute bronchospasm provoked by NSAIDs. Corticosteroids are not effective after acute aspirin ingestion, and theophylline and cromolyn sodium play no definite role.[9] Treatment of symptoms after acute ingestion, therefore, relies mainly on β-adrenergic agonists to reverse bronchospasm, and topical vasoconstrictors for both nasal congestion and eye symptoms. Frequent applications of these agents usually are necessary to maintain nasal and airway potency over the 2- to 6-hour reaction duration. On a chronic basis, the treatment of AIA depends on the correct diagnosis and avoidance of aspirin and other COX inhibitors that could cross-react to induce acute bronchospasm. Patients should be instructed that many over-the-counter medications contain aspirin or other NSAIDs, and they should carefully read package inserts before using any medication.

Drug treatment of AIA should focus on treating the underlying asthma and the strict avoidance of aspirin and cross-reacting NSAIDs. Currently, there also appears to be no role for systemic corticosteroids or theophylline in the prevention of AIA. Some investigators have found that antihistamines such as clemastine and mast cell stabilizers such as ketotifen, cromolyn, and nedocromil can have prophylactic efficacy.[54–56] However, not all subjects on these drugs are protected against bronchoconstriction after aspirin challenge. 5-lipooxygenase inhibitor zileuton was not found to be effective in preventing FEV_1 decline or nasoocular reactions to direct aspirin challenge,[57] although it had been previously shown to improve chronic asthma symptoms when added to conventional therapy in another study.[58] In contrast, experience with the cysteinyl leukotriene receptor antagonists has been variable, but mostly positive[56,59,60] and may be more effective in those who carry the variant C allele of LTC4S than in noncarriers.[61] Pretreatment with inhaled or systemic steroids or long-acting β-agonist (salmeterol) was shown to at least partially attenuate aspirin-induced respiratory lung function declines. The failure of tacrolimus (0.1 mg/kg), (a drug which could potentially affect both T cell generated cytokine responses and prevent release of mast cell histamine and leukotrienes) to prevent aspirin-induced respiratory reactions in patients with AERD on aspirin challenge in another study[62] suggests that this agent cannot be relied upon to prevent reactions from aspirin and cannot be used to facilitate "silent" aspirin desensitization of the patient with AERD.

In cases in which aspirin (or cross-reacting NSAIDs) cannot be avoided (i.e., in the setting of cardiovascular prophylaxis) or the efficacy of prophylactic measures cannot be assured, aspirin "desensitization" can be considered. Protocols are available for selected patients (Fig. 47-4).[63] These methods can effectively protect many from experiencing symptoms on exposure to aspirin or NSAIDs and will maintain this level of desensitization as long as aspirin is ingested indefinitely at doses of 325 to 650 mg a day. In a study of 25 aspirin-sensitive asthmatics, such therapy was shown to reduce nasal symptoms by 67% and asthma severity by 48%.[63,64] In the largest study of its kind, 172 patients with AERD were desensitized,

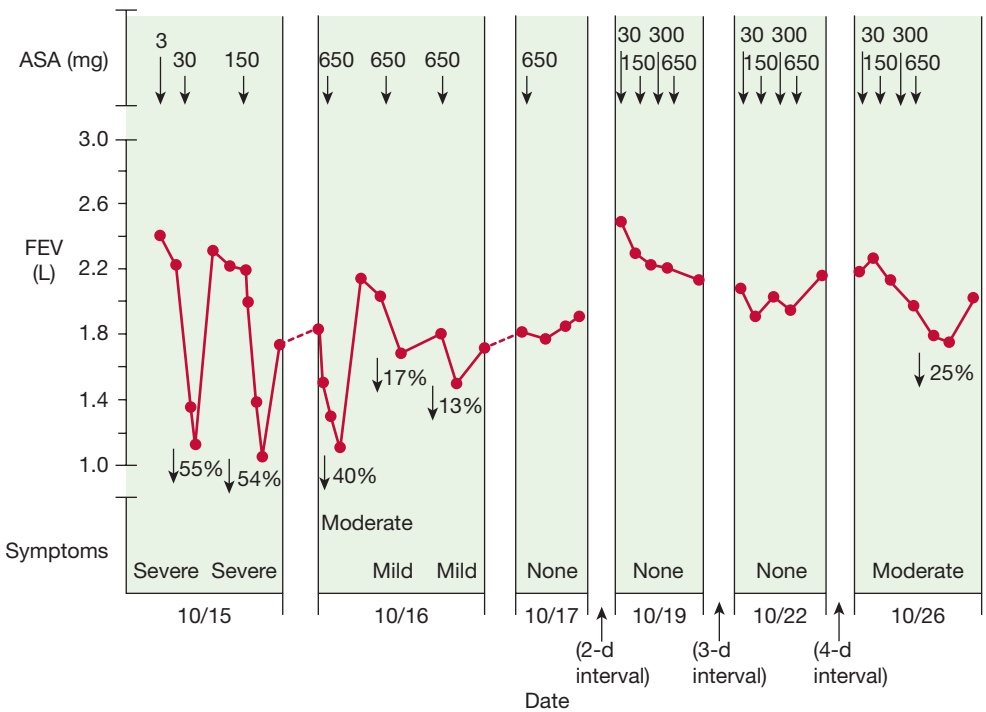

Figure 47-4 Airway desensitization to aspirin challenge in AIA. Timeline of respiratory function and overall symptoms after serial aspirin dosing. The reappearance of respiratory compromise and symptoms after 4 days without aspirin shows the need for continuous aspirin administration to maintain desensitized state. *(Data from Pleskow WW, et al. Aspirin desensitization in aspirin-sensitive asthmatic patients: Clinical manifestations and characterization of the refractory period. J Allergy Clin Immunol. 1982;69:11–19.)*

treated with 1300 mg of aspirin each day and followed for 1 to 5 years.[65] Clinical improvements were noted over the first 6 months, including reduction in dose of systemic corticosteroid and improvement in global assessments, which were maintained, but not further enhanced, during the remainder of the study. Approximately 67% (115 of 172) improved, 16 failed to improve, 24 discontinued because of aspirin-related side effects, and another 17 dropped out for other reasons.

It is interesting to note that although there are some reports of increased methacholine reactivity developing in patients soon after aspirin challenge,[44] baseline methacholine responsiveness does not seem to be successfully downregulated by aspirin desensitization. Also, there is no firm evidence that aspirin desensitization leads to abatement in skin disease in those with aspirin–urticaria syndrome.

Inhaled PGE2 was shown to prevent bronchoconstriction in a high proportion of patients challenged with inhaled L-lysine–aspirin in two small studies. In two studies[66] using misoprostol, a stable analogue of PGE1, prior to challenge with L-lysine–aspirin (400 μg 1 hour before) or predetermined threshold dose of aspirin (400 before, followed by then 200 μg with the provocative dose of aspirin), evidence was provided of some protection in 7 of 11 patients ($p = 0.024$) and in 6 of 7 patients (statistically only significant at time points 3 hours after challenge), respectively. To test whether asthma symptoms might improve on treatment with misoprostol, another group performed a double blind crossover study that showed that misoprostol, given for a period of 6 weeks (at dose of 800–1600 μg per day) led to a small improvement in nasal symptomatology without any effect on asthma control in 17 patients with proven AIA.[66] Thus, evidence of a specific method to control AIA apart from desensitization methods described above, has not been proven to be reliable. Fortunately, for those who require aspirin to prevent disease, such as those on low-dose aspirin, given for cardiovascular prophylaxis, the threshold needed to provoke airway and skin reactions is above that of the dose required for cardiovascular prophylaxis.

The potential contribution of chronic sinusitis to asthma exacerbations is well established. Aspirin sensitivity, chronic sinusitis, and nasal polyposis are well documented to coexist in AIA. Thus, the presence of these upper airway disorders must be considered in patients with AIA and effective treatment instituted if they are identified. High-dose topical intranasal corticosteroids can shrink polyp tissue and prevent obstruction of nasal passageways. In the setting of chronic sinusitis, standard approaches – including topical vasoconstrictors, antihistamines, and antibiotics – should also be utilized. Surgery to drain sinuses and remove polyps has been shown to be effective in the short term; however, polyps can regrow and the sinusitis often recurs.[2] The initial approach to nasal polyps in AIA is medical management, with aspirin desensitization playing an important role to decrease symptoms and improve postoperative outcomes in those requiring endoscopic sinus surgery, however, there is limited data on long-term follow-up in patients with nasal polyposis and AIA.[67] In selected cases where aspirin predominantly provokes nasal symptoms, administration of intranasal lysine–aspirin at increasing weekly doses successfully desensitized such patients and prevented regrowth of polyps.[68] A more recent and larger (though, due to drop-outs, under-powered randomized clinical trial) employed a crossover design after withdrawal of intranasal steroids. Lower doses of lysine–aspirin were administered more frequently (16 mg intranasally every 48 hours).[69] Results showed encouraging immunohistochemical changes characterized by a decreased expression of CysLT1 receptor on nasal submucosal inflammatory cells from turbinate tissue, but no clinical (diary scores of nasal and chest symptoms) or objective improvement on rhinometry. Two US studies that piloted the use of intranasal ketorolac administration with a modified aspirin challenge have shown the ability of ketorolac to induce nasal and lower respiratory reactions as part of the diagnostic element of the challenge. In addition, the administration of ketorolac prior to the modified aspirin challenge has the ability to decrease the severity of the FEV_1 decline, the frequency of laryngospasm and other extrapulmonary reactions. The rate of partial to complete desensitization was estimated at 77% for the intranasal portion of the protocol.[53] An additional advantage was the shortening in the duration of the desensitization.[70]

Despite aspirin desensitization and careful treatment of commonly associated sinusitis, a significant proportion of AIA patients do not achieve complete control of asthma or nasal symptoms. It is postulated that this may reflect permanently remodeled airways or residual allergic triggers that require specific allergy control measures and anti-inflammatory therapy. Evaluation of the effect of strict allergen avoidance, specific allergen immunotherapy, more intensive local management of the inflamed nasal mucosa and anti-IgE treatment in this scenario may better clarify the role of atopy in persistence of symptoms after aspirin desensitization.

EXERCISE-INDUCED ASTHMA

The first report of exercise-induced asthma (EIA) is attributed to John Floyer in 1698.[71] Nearly 300 years later, interest in this subject grew when it was recognized that exercise or hyperventilation could provoke asthma attacks. EIA can be defined as a condition in which vigorous physical activity triggers acute airway narrowing in persons with heightened airway reactivity.[72] It appears that EIA is always associated with the asthmatic diathesis, although EIA can be seen before other characteristic features of asthma emerge. Various reports indicate that EIA is common, affecting between 50% and 90% of all asthmatics[73] and 40% of patients with allergic rhinitis without known asthma.[74] Some have suggested that all asthmatics can be shown to manifest airway narrowing to thermal provocations of sufficient intensity, whether induced by exercise or hyperventilation. Other susceptible persons are first degree relatives of asthmatics, atopic "nonasthmatics," and patients with cystic fibrosis. Approximately 10% of pediatric patients can be found to have EIA, a higher prevalence than that of clinical asthma.

Elite athletes may be more predisposed to developing EIA.[75] Surveys conducted of athletes at the Atlanta (summer) and Nagano (winter) Olympic Games, showed a prevalence of 16% to 17%. The prevalence may actually be higher in those who are regularly exposed to high minute ventilation of cold, dry air typical of winter sports. In some studies the prevalence of EIA reported in figure skating (35%), and ice hockey (35%)[75] may be responsible for driving the overall incidence of EIA in winter sports to as high an estimate as 23%.[76]

CLINICAL PRESENTATION

Several societies have adopted a definition of EIA as clinical asthma where exercise triggers symptoms.[77] This is important given the recognition of exercise-induced bronchoconstriction (EIB) in individuals without asthma. Patients with EIA generally manifest a series of fairly predictable symptoms and alterations in pulmonary function that can be assessed by laboratory testing (Fig. 47-5). Normal persons and asthmatics generally first respond to exercise with bronchodilation, probably mediated by the release of catecholamines.[78,79] This response is short-lived, peaking at midexercise, and is followed by return of normal baseline airway tone at the end of exercise. In patients with EIA, the transient bronchodilation and reversal are followed by bronchoconstriction coincident with

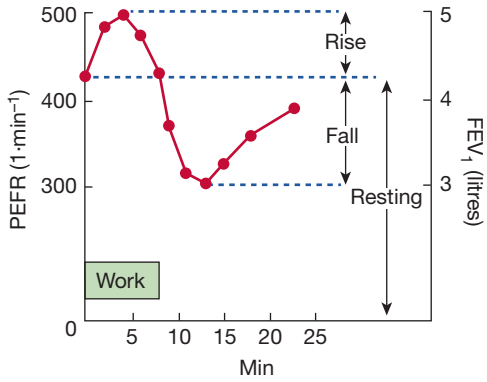

Figure 47-5 Typical pulmonary function changes induced by exercise in EIA. Transient bronchodilation during exercise and bronchospasm after exercise are noted. *(Data from Anderson SD. Is there a unifying hypothesis for exercise-induced asthma? J Allergy Clin Immunol. 1984;73:660–665.)*

symptoms of cough, wheezing, dyspnea, and chest tightness typical of asthmatic attacks. Typically, when they are provoked with a brief, intense exercise period in the laboratory, maximal bronchoconstriction occurs 5 to 10 minutes after the cessation of exercise and lasts for 30 to 60 minutes (Fig. 47-4). Rarely does this form of bronchoconstriction result in ventilatory failure, although it can limit the performance of trained athletes.

In addition to asthma after exercise, many athletes describe dyspnea during exercise. If these athletes are able to continue to exercise despite the initial airway obstruction and increase their level of activity, relief of bronchoconstriction often occurs. This is associated with symptomatic improvement that is described as "running through the attack." The development of dyspnea during exercise is ostensibly related to the development of bronchoconstriction at lower work intensities (simulating a postexercise state), which is reversed by interval training at higher intensities (simulating an exercise state). This has been taken as evidence that airway function during exercise reflects a balance between bronchoconstrictor and protective bronchodilator influences, and that this balance can be influenced by rapid changes in exercise intensity.[75,78]

The reproducibility of EIA is highly dependent on the specific characteristics of the stimulus- and patient-related factors. The net influence of exercise intensity, the temperature and humidity of the inspired air, the presence of allergens and pollutants in the environment, and the patient's baseline airway reactivity are fundamental in determining whether exercise will lead to bronchoconstriction. If asthma is better controlled at baseline, EIA may be more difficult to provoke. If climatic conditions vary, even though asthma is not well controlled, EIA may fail to develop. Classic work has shown that for a fixed minute ventilation, cold, dry air inspired during exercise is more likely to provoke EIA than warm, humid air.[79,80] Thus, EIA is more likely to occur with jogging outdoors during the winter than with swimming indoors. A recent study in children showed that exercise-induced wheeze was associated with an increased rate of urgent medical visits independently of asthma severity or socioeconomic factors, suggesting that EIB may be a surrogate marker of poorly controlled asthma rather than a distinct asthma phenotype.[81]

It is interesting to note that about 50% of patients with EIA will not manifest a bronchoconstrictive response if rechallenged with the same stimulus within 60 minutes and thus appear to be in a "refractory state." Neither baseline airway obstruction nor the degree of obstruction provoked by exercise can be used to determine who will be refractory to repeated exercise challenges. Furthermore, after 3 hours, even patients who were refractory to repeated challenge will regain ability to bronchoconstrict with exercise.

PATHOPHYSIOLOGY

The heterogeneity of responses present in EIA and bronchoconstriction, are influenced by the fundamental differences in the types of exercise and the environmental aspects of specific disciplines. Despite the attempt to categorize EIA as a unique entity the truth is that this is almost impossible. Two pathogenic schemas have been proposed for the bronchoconstriction seen in EIA. The two theories focus on the roles of (1) heat exchange, water loss, and airway rewarming; and (2) airway inflammation. The role of inflammation as a reaction to these stimuli or as an enhancer of the effects of these two pathophysiologic pathways is likely tied to leukotrienes and related lipooxygenase products.

Heat Exchange and Water Loss

During tidal breathing, heat (via conduction and evaporation) and water (via evaporation) are transferred from the mucosa of the upper airways to the entering air. Since exercise requires marked increases in minute ventilation, surpassing the volume of air that can be inspired through nasal structures, air enters directly through the mouth, bypassing the normal warming and conditioning function of the nose. The lower respiratory mucosa then attempts to compensate for the function of the bypassed nose. Heat and water fluxes first occur. The lower airways are cooled and dried and are subject to rewarming by warm blood carried by the bronchial circulation.

In the late 1970s, a number of investigators postulated that EIA was the result of increased heat loss in the airway. This was based on the observation that cold, dry air caused a greater fall in FEV_1 than did hot, dry air[82] and on correlations between heat exchange and the degree of bronchoconstriction. Others, however, showed that the temperature of the inspired air was not crucial to inducing bronchoconstriction, and that temperatures of dry inspired air that varied by as much as 60 degrees could still provoke airway narrowing.[80,83] This suggested that airway evaporative water loss might be more important than airway cooling. The water loss was predicted to change the osmolarity of the cellular and extracellular components of the airway wall, stimulating increased bronchial blood flow to increase the delivery of water.[80] In addition, bronchial wall hyperosmolarity was hypothesized to increase the release of proinflammatory mediators from resident airway immune cells such as mast cells.[82] This concept was supported by work that demonstrated that changes in the humidity of inspired air, and not temperature, determine the magnitude of EIA. Further support for this construct came from studies using cold gas mixtures with different water-carrying capacities, which showed a significant correlation between evaporative heat loss but not total heat loss or temperature gradient on the airway response.[84]

In apparent contrast to these data is the considerable body of work that does not support the concept that osmolar changes precipitate EIA. The most important of these showed that increasing minute ventilation at constant humidity increases the severity of EIA.[74] The combination of overlapping mechanisms including airway cooling, airway dehydration and osmolar changes account for the pathogenic features responsible for EIA, rather than a single mechanism.[114]

Airway Rewarming

An important theory that also remains to be unequivocally proven is that offered by McFadden, who proposed that the process of airway rewarming is active in the pathogenesis of the airway narrowing that occurs in EIA.[85] This theory postulates that loss of heat associated with exercise transiently leads to decreased bronchial blood flow.

At the end of exercise, the bronchi undergo reactive hyperemia characterized by vascular engorgement. This leads to airway caliber compromise and airway wall edema. The strongest support for this theory arises from studies showing that the severity of EIA could be controlled by regulation of the thermal gradient during exercise and the rate of rewarming after exercise. The presence of an elevated airway permeability index in individuals with EIA is associated with the severity of EIB,[86] suggests that individuals with abnormal vascular permeability may be more susceptible to larger fluid shifts and airway physiologic changes associated with exercise. Sodium ingestion also seems to affect vascular volume and increase airway inflammation in the setting of exercise.[87]

In summary, there is evidence that associates exercise-induced bronchoconstriction with a sequence of events that includes heat loss, water loss, and airway rewarming. The degree to which these temperature and water alterations contribute to the pathogenesis of EIA is still, however, a topic of debate and investigation.

Inflammation and EIA

Theories postulating a role for inflammatory mediators in the pathogenesis of EIA have recently received new support and are being harmonized with the already considerable evidence supporting a role for inflammation in the pathogenesis of other forms of asthma. New information in exercise suggests that those predisposed to EIA, specifically elite athletes, may manifest a degree of airway inflammation that had not been previously appreciated. Instead of demonstrating a lower rate of EIA, allowing a potentially higher level of exercise performance, which might be expected on the basis of selection of those best equipped to excel in sports, elite athletes appear to exhibit a paradoxically higher incidence of EIA and a higher degree of airway inflammation without necessarily manifesting a higher prevalence of underlying clinical asthma.

Older data on the role of inflammation in EIA did not necessarily support this link. One study analyzing the characteristics of bronchoalveolar lavage (BAL) fluid from patients with EIA 12 minutes after exercise failed to find evidence for mast cell mediator release since BAL histamine, tryptase, LTC4, and PGD2 levels were not altered. Similarly, studies performed 1 hour and 25 hours after exercise did not reveal significant differences in BAL cellularity or in histamine or tryptase levels.

In contrast, one group studying elite cross-country skiers, found elevated airway T lymphocytes and eosinophils compared to controls.[88] Several others have demonstrated changes in exhaled NO, which generally decreased with exercise, suggesting a high basal level and ventilatory clearance of this gas associated with airway inflammation,[75] while another observed increases in plasma adenosine after exercise.[89] A different group documented the presence of a late phase airway response after exercise that was demonstrable in 50% of competitive athletes studied.[90] Most importantly, the new concept that these changes might be provoked by exercise, rather than be a reflection of underlying inflammation in those who manifest EIA, is supported by Helenius,[91] who showed that athletes who stopped high-level training and modulated the amount of exercise they subsequently pursued, experienced reduced asthma symptoms and diminished bronchial responsiveness to histamine. Additional observations using exhaled breath condensate (EBC) have shown elevations of cysteinyl leukotrienes,[92] RANTES and eotaxin,[93,94] after exercise. RANTES has also been found to be elevated in the EBC of asthmatic children with EIB after exercise challenge.

Leukotrienes in EIA To determine whether leukotrienes play a role in the pathogenesis of EIA, LTD4 receptor antagonists and 5-lipooxygenase inhibitors have been employed. Studies using an intravenous LTD4 receptor antagonist 20 minutes before exercise demonstrated significant attenuation of the maximal provoked bronchoconstriction and mean time to recover from bronchoconstriction (8 minutes for the treatment group vs. 33 minutes for placebo).[95] Similar results were noted by others using oral or inhaled leukotriene antagonists. In general, although the protection was relatively small, it was significant and equivalent in potency to inhaled cromolyn.

The results obtained with peptidoleukotriene antagonists are consistent with those obtained when the effects of a 5-lipooxygenase inhibitor on bronchoconstriction induced by cold, dry air were evaluated. In the most important study of this kind,[96] a 5-lipooxygenase antagonist was an effective as cromolyn or terbutaline in augmenting respiratory heat exchange. Thus, leukotrienes may well mediate the airway inflammation and contribute to the pathogenesis of EIA.

GENETICS AND GENOMICS

Little information is available on the potential genetic underpinnings of EIA, however, some of the observations from genetic and genomic studies are summarized here. Using microarray analysis, a group demonstrated enhanced transcription of 5-lipooxygenase (ALOX5) and 5-lipooxygenase activating protein (ALOX5AP) genes.[18] A more recent study examined the transcriptional profile of induced sputum after an exercise challenge and identified the upregulation of transglutaminase 2 (TGM2), a molecule associated with an increase in the activity of secreted phospholipase A2, the rate-limiting step on eicosanoid formation.[97] The same investigators described the predominant role of airway MUC5AC expression during exercise challenge in a similar setting.[98]

Other investigators have provided evidence of leukotriene C4 synthase (A-444C) promoter polymorphisms in association with greater severity of EIA in studies conducted in a large cohort of Korean children with asthma.[99] However, these polymorphisms are not associated with montelukast responsiveness in a subsequent pharmacogenomics study of the same population.[100] These observations suggest the potential existence of disease-modifying genes in exercise-induced bronchospasm.

DIFFERENTIAL DIAGNOSIS

The diagnosis of EIA is most accurately established by employing validated exercise protocols coupled with pulmonary function testing. However, patients are commonly given a presumptive diagnosis based on their history and physical examination. Important points in the clinical history include the level and type of exercise that provokes asthma, the timing of symptom onset, situations that modify symptom onset, environmental conditions and the precise symptoms experienced. Many of the symptoms of EIA can mimic other conditions that would require an entirely different therapeutic approach (Table 47-3). For example, chest

TABLE 47-3 Differential Diagnosis of Exercise-Induced Asthma

Cardiac Disease	Functional Abnormalities
Coronary ischemia	Vocal cord dysfunction
Mitral valve prolapse	Panic disorders
Atrial myxoma	General
Cardiomyopathy	Deconditioning
Arrhythmias	Anemia
Lung Disease	
Fixed airway obstruction	
Interstitial lung disease	
Exercise-induced cough	

tightness with exercise should be unequivocally distinguished from coronary ischemia. Other cardiac disorders that can mimic EIA are arrhythmias, cardiomyopathies, atrial myxoma, and mitral valve prolapse, all of which can manifest with dyspnea and wheezing. The presence of a murmur, click, or other findings on physical examination should help to identify patients with these conditions. Exercise-induced anaphylaxis can also mimic EIA but will generally exhibit skin manifestations (urticaria), and respiratory symptoms will be less prominent. Two other conditions that have been reported to mimic EIA are fixed glottal and tracheal obstruction, which become noticeable with the increased ventilation of exercise and exercise-induced vocal cord/arytenoids dysfunction, not present at rest. Some have also suggested that panic disorders and the excessive tachypnea associated with deconditioning can be confused with EIA. Symptoms due to these other conditions generally are greatest during exercise provocation rather than afterward, when airflow limitation due to EIA usually reaches its peak.

Exercise-induced cough is another phenomenon that can mimic EIA. Both may be induced by changes in the osmolarity of the airways reflecting water loss from the respiratory tract during exercise, the inhalation of humid air also prevents both phenomena. However, EIA and exercise-induced cough respond differently to β-adrenergic agonists, suggesting that they are mediated by different underlying mechanisms. It is postulated that exercise-induced cough is the direct result of the osmolarity changes provoked by airway drying, whereas EIA is due to the mediator release that results from the process of airway drying. Therefore, although nearly all patients with EIA cough with exercise provocation, there are patients who have exercise-induced cough without bronchospasm, and thus do not have EIA.

■ PHYSIOLOGIC DOCUMENTATION

Because a simple history or cough or wheezing may not reliably predict EIA, especially in those in whom a trial of preventive measures has not been successful, formal exercise testing may be required.[75] The clinician needs to document airflow obstruction that reaches a peak just after provocation, during the recovery period. In athletes, the presence of EIA and EIB has major implications in their exercise performance and management. In addition, societies and committees have created practice guidelines to assist in the documentation of EIA.[77,101,102] Bronchial provocation tests (BPT) are used to identify airway hyperresponsiveness and they can be classified as indirect and direct. Indirect tests include exercise, the inhalation of dry air (isocapnic hyperventilation [ISH], also known as eucapnic voluntary hyperpnea), hypertonic saline, and mannitol. The direct methods include methacholine, histamine, carbachol and AMP inhalation.

Indirect methods trigger airway hyperreactivity through different mechanisms that affect the release of inflammatory mediators and cause bronchoconstriction. Exercise provocation, whether performed on an ergometer or a treadmill, leads to significantly greater increases in heart rate, metabolic rate, and oxygen consumption. Exercise, but not ISH, is accompanied by increased numbers of circulating basophils and increased circulating catecholamines and cAMP. The differences in the last two parameters probably explain why the bronchodilatory response that characterizes exercise is not provoked by ISH. The bronchoconstriction induced by ISH is similar to that induced by exercise in terms of magnitude, time course, and refractory period. Two main advantages over exercise include the ease with which the ISH protocol can be standardized and the finding that oxygen consumption and heart rate are not increased with ISH. As a result, ISH is useful in differentiating EIA from occult cardiac disease and is especially valuable when elderly or cardiac patients are being evaluated.

The most commonly used ISH protocol for the diagnosis of EIA in the United States is that published by O'Byrne et al.[103] and modified by Philips et al. (Fig. 47-6).[104] This is accomplished by registering changes in pulmonary function in response to varying rates of ventilation using dry air with a fixed CO_2 content of 4.9% to maintain isocapnia. Each ventilatory challenge is performed for 3 minutes, with spirometry performed at intervals thereafter (usually 2, 5, and 10 minutes after the end of hyperventilation). Serial increase in hyperventilation is performed until maximal voluntary ventilation is reached. If the FEV_1 falls greater than 10% after provocation, the test is considered positive, confirming the diagnosis of EIA. Although some have pointed out that it is not necessary to condition air to subfreezing temperatures to perform the test, Scandinavian investigators showed that assessing bronchoconstrictor responses to whole-body exposure to very cold air significantly increased the number of asthmatic patients who experienced bronchoconstriction. Others have pointed out the need to assess athletes in the field performing in the sport in which they compete, since they may not have a significant drop in FEV_1 symptoms during in the laboratory during challenge.[75]

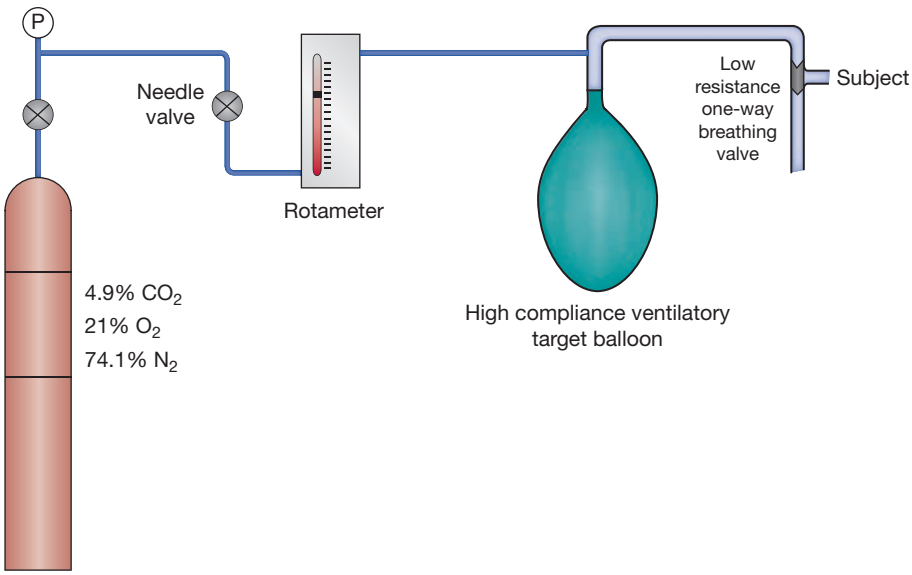

Figure 47-6 Apparatus for isocapnic hyperventilation challenge to diagnose EIA. *(Data from Phillips YY, et al. Eucapnic voluntary hyperventilation of compressed gas mixture: A simple method for bronchial challenge by respiratory heat loss. Am Rev Respir Dis. 1985;131:31–35.)*

To optimize the validity, repeatability and practicality of exercise testing for the diagnosis of EIA, a variety of testing protocols have been pursued. Unfortunately, the criteria used to define a positive test in these studies are different, making standardization difficult. Although the optimal diagnostic algorithm for the assessment of EIA is still lacking,[72,75] data reported on athletes from the 2002 Olympic Winter Games,[105] compared eucapnic voluntary hyperventilation (EVH) with exercise testing outdoors in the cold (20°C and 45% humidity). The EVH test for 6 minutes with cold dry air was determined to perform best in assessing the presence of EIA.

The mannitol inhalation test relies on the airway fluid changes to incremental doses of this hyperosmolar dry powder. This bronchial provocation agent was approved by the FDA in 2010 and is available for adults and children older than 6 years of age. A decline in FEV_1 equal to or larger than 10% is considered positive. In a similar fashion, the inhalation of hypertonic saline (4.5%) takes advantage of the same physiologic principle to evaluate for the presence of bronchoconstriction. The most popular direct challenge method is the methacholine challenge test, supported by its standardization and reproducibility; it has been approved by the International Olympic Committee Medical Commission.

In addition to the difficulties inherent in the standardization of the challenge protocol, the clinician must be aware of situations that can lead to false-negative evaluations. Specifically, it is important that all drugs that can potentially attenuate bronchoconstrictor responses – such as calcium channel blockers, methylxanthines, cromolyn, and β-adrenergic agonists – be discontinued for a sufficient period before the evaluation.

TREATMENT

A variety of nonpharmacologic and pharmacologic approaches have been employed in treatment of EIA.

Nonpharmacologic Treatments

The treatment of EIA is influenced by the underlying process driving this response. In patients with asthma who experience EIA, optimization of the asthma therapy is the first step. Inhaled steroids attenuate the development of EIA during laboratory provocation and increase the threshold for the development of EIA clinically. Prophylactic measures to prevent EIA include avoiding exercises that expose the patient to cold, dry air and favoring those in which the patient breathes humid air during exercise. Patients can reduce the severity of their EIA by breathing through the nose rather than through the mouth during exercise. Face masks (e.g., 3M Cold Weather Mask) can be effectively used by the many people who find it impossible to breathe through the nose during intense exercise.

It is still unclear whether physical training and improvement in work capacity can relieve symptoms of EIA. Training ought to be useful, at least theoretically, since a better-trained athlete may require a lower mandatory minute volume—which may lead to less water loss from the airways and less severe EIA. Pre-exposure of patients with EIA to air high in ozone in two studies performed in Los Angeles and Toronto showed that EIA was not enhanced. This suggests that choosing a day to exercise on the basis of ozone will not help prevent EIA. A series of repeated short sprints has been shown to be effective in inducing the refractory state, which might then allow the athlete to maximally exercise without developing EIA.[106] A warm up period to induce the refractory period has been advocated by some to improve performance in the competitive athlete.[107] A high-intensity interval warm-up in recreational athletes prior to an exercise challenge resulted in improved FEV_1, and this protective effect was increased when used in combination with salbutamol.[108] A systematic review of the effect of warming-up prior to exercise found that interval and variable-intensity protocols are effective short-term strategies to prevent EIB.[109]

A low sodium diet has also been advocated as a nonpharmacologic intervention in individuals with EIA, based on the observation that those with a low sodium diet had smaller declines in FEV_1 with exercise compared to those ingesting normal or high amounts of sodium.[110]

TABLE 47-4 Treatment of Exercise-Induced Asthma (EIA)

Treatment Immediately Before Exercise (10–20 min before)	Treatment of Underlying Disease (Days Before)
β-Adrenergic agonists	Goal: Improved asthma control
Cromolyn sodium	Inhaled corticosteroids
Nedocromil	Systemic corticosteroids
? Anticholinergics	? Theophylline
? Inhaled furosemide	
Leukotriene receptor antagonists	

Pharmacologic Treatment

Several classes of drugs have been shown to prevent EIA if administered just before (10–15 minutes) exercise. The list includes β-adrenergic agonists, cromolyn sodium, anticholinergics, and possibly rapid-release theophylline (Table 47-4).[75,103] β-Adrenergic agonists are the most effective drugs for use against EIA and, therefore, are the mainstay of therapy. They have a rapid onset of action and are 90% effective in preventing EIA when used just before exercise. They are especially useful if the patient has some reversible airway obstruction, since they also improve lung function before exercise. Long-acting β-adrenergic agonists (LABA) have also been found to be effective in preventing EIA. The duration of protection they confer may approach 10 hours or more. It is interesting to note that the cough so often associated with EIA appears to occur independent of the bronchospasm provoked by exercise. Although exercise-induced airway narrowing is prevented by the inhalation of β-adrenergic agonists before exercise, the cough is not.

Cromolyn sodium also has been shown to attenuate bronchoconstriction in most patients with EIA. This medication is not a bronchodilator and, therefore, does not reverse bronchoconstriction. Cromolyn does, however, have two advantages over other agents. First, it does not contribute to tachycardia and is therefore useful in elderly patients or patients with cardiac compromise. In addition, cromolyn has been shown to prevent the late bronchoconstrictor response to exercise. Related drugs (including nedocromil, minocromil, and oxatomide, but not ketotifen) have been shown to be similarly effective against EIA. Anticholinergics, such as ipratropium bromide, prevent airway narrowing after exercise in a high percentage of patients with EIA. They are especially useful in those who experience a rapid bronchodilating effect of the drug. The slower onset of action for most patients, however, limits their utility after bronchodilation has occurred.

Theophylline has weak bronchodilatory effects, high side-effect profile, and slow onset of action and is not recommended for routine use as pretreatment for EIA. However, it has been shown to confer protection against EIA if 100 to 200 mg is taken 2 hours before exercise. Other orally administered drugs that are not commonly used, but have the potential to be helpful in preventing EIA, are terbutaline, albuterol (2 hours before exercise), some alpha adrenergic agonists, and verapamil if taken 1½ hour before exercise as well as

the inhaled antihistamine clemastine.[78] In addition, terfenadine was shown by one group to prevent EIA.[111]

For athletes, organizations including the World Anti-Doping Association and International Olympic Committee, have developed standards that incorporate physiologic documentation of bronchial hyperresponsiveness, including bronchoprovocation tests, permitting use of certain medications, particularly short acting β-agonists.[112] Due to concerns related to doping, all practitioners involved in the management of athletes should review the specific guidelines developed by the appropriate governing bodies. Some of these agencies include the World Anti-Doping Agency (WADA; http://www.wada-ama.org/), International Olympic Committee (IOC; http://www.olympic.org/ioc), National Collegiate Athletic Association (NCAA; http://www.ncaa.org/), and US Anti-Doping Agency (www.usantidoping.org), among others.

Despite the observation that inhaled furosemide can prevent EIA in adults and children, their use for this indication has not evolved as standard therapy. Leukotriene antagonists have been advocated by some and shown to be effective, especially if treatment with short acting β-agonists in insufficient.[75] Because of their low side-effect profile, leukotriene antagonists would appear to be well suited as single agents for use against EIA. However, additional head-to-head studies showing efficacy during exercise need to be conducted before these agents can be recommended over inhaled β-adrenergic agonists in routine prophylaxis against EIA. A recent study showed that the combination of inhaled budesonide and montelukast, was superior to either agent alone, shortening the duration of EIB.[113]

Management needs to be tailored to individual needs and response to therapy. Despite the mechanistic differences seen in EIA and EIB, an approach that optimizes underlying asthma control is key, since the two syndromes are associated with impaired airway function. In individuals with chronic asthma, EIB seems to be a marker of suboptimal control, and an increase of controlling agents is advocated.[77,114]

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CHAPTER 48

Allergic Bronchopulmonary Aspergillosis (Mycosis) and Severe Asthma with Fungal Sensitivity

Geoffrey L. Chupp

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory disease of the lung, characterized by an allergic inflammatory response to colonization of the airways by *Aspergillus fumigatus* or other fungi. The entity was first described in 1952 by Hinson et al., and then again in 1967, when Scadding recognized an association between the disease and proximal bronchiectasis in areas previously affected by infiltrates (predominantly in the upper lobes).[1,2] The first adult case of ABPA was reported in the United States in 1968.[3] Although most cases entail hypersensitivity to *Aspergillus* spp. (especially *A. fumigatus*), the finding of a virtually identical clinical syndrome associated with immune sensitivity to *Candida albicans* (most commonly), *Helminthosporium*, *Alternaria, Curvularia lunata, Drechslera hawaiiensis, Stemphylium languinosum, Saccharomyces cerevisiae*, or *Pseudallescheria boydii* has led some to use the term *allergic bronchopulmonary mycosis* to describe the syndrome.[4] However, since the predominant causative organism is *A. fumigatus* and the commercially available laboratory testing is for this organism, ABPA is primarily designated as the diagnosis. In addition, a new entity has been recently recognized that appears to be on the continuum between fungal allergy, at one end, and ABPA at the other: severe asthma with fungal sensitivity (SAFS).[5]

The precise prevalence of ABPA is unknown, in part due to variability in diagnostic criteria used in various studies, the lack of distinction between ABPA and mold-sensitive asthma, and delays in the diagnosis of patients with long-standing disease; however, it is clear that ABPA is a relatively common entity. Estimates are that true ABPA complicates approximately 7% to 14% of cases of chronic steroid–dependent asthma and approximately 7% to 15% of cases of cystic fibrosis (CF).

Most cases of ABPA are recognized in the third to fifth decade of life, but they may present during childhood. In some patients, it is likely that ABPA starts early in life and continues, unrecognized, until adulthood. Interestingly, familial cases have been reported, suggesting that genetic factors underlie development of ABPA.[6,7] The spectrum of disease is broad. Patients may be asymptomatic, have mild-to-moderate asthma, or have severe and debilitating disease, leading to lung transplantation. However, if recognized early and managed aggressively, ABPA is treatable and may remit indefinitely; progressive lung damage can be avoided.

For the purposes of this discussion, the focus is on ABPA. However, clinicians should be cognizant that diagnostic testing for other fungi needs to be pursued when organisms other than *Aspergillus* spp. are suspected. In addition, the newly defined form of asthma noted previously, SAFS, is discussed and differentiated from ABPA.

PATHOGENESIS

Although the pathogenesis of ABPA is poorly understood, it is believed to be the result of an exaggerated immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal) species.[8] *Aspergillus* spp. are globally ubiquitous, thermotolerant fungi that reside in decaying organic matter and colonize most domestic environments, including carpets and air duct systems.

In humans, airborn *Aspergillus* spores or conidia that are inhaled are immunologically inert, and in normal individuals are cleared by innate immune system mechanisms to maintain airway homeostasis. However, in susceptible individuals, conidia colonize airways, germinate into somatic hyphae that stimulate a chronic allergic inflammatory response that results in tissue injury and, ultimately, dictates the clinical features of ABPA. In contrast to a true infection in which fungal hyphae invade the lung parenchyma, colonization of the airways with germinating fungal spores represents an abnormal state that contributes to the exaggerated Th2 inflammatory response without clear tissue invasion. While a detailed understanding of the mechanisms that drive this process remains poorly understood, it appears that susceptibility to *Aspergillus* colonization and development of clinical disease depend on host factors, such as genetic background, T-cell responsiveness to *Aspergillus* antigens, the magnitude of tissue response to *Aspergillus*, and the level of environmental exposure to this ubiquitous fungus.

Investigations into the genetic risk factors associated with ABPA have identified several candidate genes, suggesting that the pathogenesis of ABPA requires both host and environmental factors.[9] Best characterized is the association between gene mutations in the CF transmembrane conductance regulator (CFTR) and the pathogenesis of ABPA.[10,11] CFTR mutations are more common among patients with ABPA compared with the general population or with individuals with severe asthma without sensitivity to *A. fumigatus*. Another genetic link to ABPA is that Th2-type T-cell reactivity to selected *Aspergillus* antigens is determined by the presence of MHC Class II DR2 or DR5 alleles, which may predispose patients to the disease, whereas the MHC DQ2 allele may be protective.[12,13] In addition, investigators have determined that there is an increased prevalence of polymorphisms in the promoter region of the pathogen associated molecular pattern receptor, Toll (TLR) 9, in individuals with ABPA compared with controls or patients with SAFS.[14] We recently determined that children with severe asthma and ABPA are more likely to carry the Chitotriosidase 1 (CHIT1) exon 10 mutation.[15,16] Individuals with the exon 10 mutation have lower levels of, or lack, chitinase activity in serum and are unable to degrade chitin, a structural polysaccharide in the cell wall of lower life forms such as *A. fumigatus*.[17–19]

At the microscopic level, ABPA is characterized by an intense eosinophilic and mononuclear cell inflammatory response, leading into areas of parenchymal scarring, airway remodeling, and bronchiectasis.[20,21] Immunologic studies demonstrate the presence of a type I hypersensitivity reaction, with elevated serum levels of total IgE and *A. fumigatus*-specific IgE in individuals with ABPA. In addition, patients have evidence of an exaggerated Type III hypersensitivity reaction, indicated by the presence of *A. fumigatus-specific* IgG antibodies (classically called "precipitins" or precipitating antibodies) and circulating immune complexes during disease exacerbations. A type IV cell-mediated immune reaction may also be at work, based on the finding of dual (immediate and delayed) cutaneous reactions and *in vitro* lymphocyte transformation to *A. fumigatus* antigen stimulation in some patients.[22,23]

A substantial amount of work has been done on the immune response in ABPA, demonstrating that several cell types and pathways are involved in the pathogenesis of this destructive variant of

asthma.[17,18] A pathogenetic role for helper T lymphocytes is suggested by a number of findings, including the presence of increased numbers of airway Th2 cells and elevated levels of soluble interleukin 2 receptors (suggesting T-cell activation) in the circulation of persons with active ABPA[24]; the derivation of *A. fumigatus*-specific T-cell clones with T helper–2 (Th2) patterns of cytokine production from the blood of patients with ABPA[25,26]; positive correlations between activated T-cell number, levels of the T-cell–derived cytokines IL-4 and IL-5, and number of airway eosinophils in the disease; the critical role IL-5 plays in murine models of ABPA[27–34]; and increased reactivity of Th2 cells to *A. fumigatus* antigens among patients with ABPA as compared with patients with asthma and skin reactivity to *Aspergillus*.

In addition to lymphocytes, eosinophils and basophils may contribute to local airway injury, and neutrophils likely play a role in airway inflammation and tissue damage in ABPA, as evidenced by the fact that sputum IL-8 levels correlate with sputum neutrophilia, matrix metalloproteinase levels, and FEV_1 among patients with ABPA.[35,36]

It is also clear that the fungus itself contributes substantially to the pathogenesis of disease. *A. fumigatus*-derived proteases likely cause epithelial cell injury and protective barrier disruption, triggering immune hypersensitivity by inducing inflammation or by allowing increased penetration of fungal antigens into the airway wall.[37] *Aspergillus*-derived proteases may also stimulate proinflammatory cytokines, such as IL-8, and release of growth factors; proteases may also cause tissue damage, leading to bronchiectasis.[36]

A variety of other *Aspergillus*-derived antigens (including cytotoxins and heat shock proteins) with demonstrated ability to bind IgE and IgG derived from the blood of patients with ABPA have also been shown to drive both the IgE (hypersensitivity) and IgG immune responses. *A. fumigatus*-derived proteases with antibody-binding capacity may also amplify the inflammatory response. *A. fumigatus* antigens, such as Aspf1 (a cytotoxic protein), Aspf2 (a fibrinogen binding protein), Aspf5 (a metalloprotease), Aspf6 (manganese superoxide dismutase), Aspf8 (a ribosomal protein), Aspf13 and Aspf18 (serine proteases), as well as Aspf3 and Aspf4, have all been implicated in these processes. Finally, host response to *Aspergillus fumigatus* antigens includes surfactant proteins (SP) A and D, which may play a protective role against ABPA by interfering with binding between *A. fumigatus* antigens and IgE. Notably, however, SPD levels do not correlate with acute exacerbations of ABPA in humans.[38–40]

CLINICAL FEATURES

Although ABPA typically presents in patients with a history of difficult-to-control asthma, the spectrum of presentation is highly variable and should be considered in any patient with difficult-to-control asthma and hypersensitivity to *A. fumigatus* (Table 48-1).[40] Typical presenting complaints are often nonspecific and include dyspnea, wheezing, poor asthma control, cough (sometimes productive of thick, brown mucus plugs), malaise, low-grade fever, and occasionally, hemoptysis. There may be an antecedent history of recurrent asthma exacerbations in conjunction with pneumonias without a culture-identified bacterial source. In addition, atopy with rhinitis, drug allergy, and/or allergic conjunctivitis are also common. It is often not until a patient has been repeatedly ill over weeks to months and unresponsive to standard treatments that the diagnosis is considered.[41] As patients with SAFS have the same clinical presentation, differentiation from ABPA is based on interpretation of laboratory testing and radiographic studies.[40]

DIAGNOSTIC GUIDELINES

In general, the diagnosis of ABPA is based on appropriate clinical features in combination with supporting radiologic and serologic findings. While there are no absolutely specific diagnostic criteria, similar guidelines have been proposed by multiple expert panels to aid clinicians in the diagnosis of ABPA (Table 48-1).[20,42] These guidelines have evolved over time and have been recently updated by several societies. Although there is no agreement on clinical criteria that should trigger screening for ABPA, in most asthma centers, all asthmatics with difficult-to-control asthma are screened by checking an eosinophil count, total IgE, and radioallergosorbent test for 22 aeroallergens, including *A. fumigatus and Alternaria.*

TABLE 48-1 Criteria for the Diagnosis of ABPA

Seropositive ABPA (ABPA-S)
History of asthma (almost always difficult to control)
Elevated total serum IgE (usually >1000 IU/mL)
Immediate skin test reactivity to *Aspergillus fumigatus* OR elevated specific serum IgE to *A. fumigatus*
Presence of serum precipitins (by gel diffusion) or elevated specific serum IgG to *A. fumigatus*
ABPA central bronchiectasis (ABPA-CB)
Above criteria are positive
Central bronchiectasis by high-resolution CT scan or CXR
Other supportive clinical findings
Peripheral blood eosinophilia (often absent, especially if patient is on oral or inhaled corticosteroids)
Patchy, fleeting infiltrates (often absent, especially if patient is on oral corticosteroids)
Expectoration of brown mucus plugs
Mucoid-impacted bronchi evident on radiographic studies
Sputum culture positive for *A. fumigatus*

Using the Patterson criteria (Table 48-1), ABPA may be considered to exist in two different forms: ABPA-seropositive (S) and ABPA-central bronchiectasis (CB).

Patients with ABPA-S usually display all of the following diagnostic criteria proposed by Greenberger and Patterson: (1) history of asthma; (2) total IgE >1000 IU/mL; (3) elevated serum anti-*AF* IgE and IgG (twofold higher than *A. fumigatus* allergic asthma controls); (4) positive immediate hypersensitivity skin test to *A. fumigatus*; and/or (5) serum anti-*A. fumigatus* IgG antibodies to *A. fumigatus*. The last criterion is considered positive when either the double gel diffusion, enzyme-linked immunoassay (ELISA), or fluorescent enzyme immunoassay (FEIA) are positive for anti-*AF* IgG antibodies.[43]

Patients with ABPA-S have normal chest radiographic studies, with no evidence of bronchiectasis. In contrast, patients with ABPA-CB have the classic features of advanced disease (expectoration of mucus plugs or sputum culture positive for *A. fumigatus*) and are positive for all of the criteria of ABPA-S listed earlier. Patients with ABPA-CB also have central bronchiectasis on high-resolution CT scanning or chest X-ray.[44,45] Patients with ABPA-S tend to have fewer symptoms, lower IgE levels, less severe airflow obstruction, and fewer exacerbations than do persons with ABPA-CB. Although IgE levels fluctuate with disease activity, a normal IgE level in a symptomatic, untreated patient with asthma virtually excludes the diagnosis.[46] It remains unclear whether ABPA-S is a milder form of the disease (e.g., representing a different host response) or an earlier stage of illness. Identification of *Aspergillus* (or other relevant fungus) in the sputum and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* (by prick test or intradermal) are also common clinical features of ABPA. Rare cases lacking a history of asthma, but meeting the other major diagnostic criteria, have been reported.[41]

TABLE 48-2 Criteria for the Diagnosis of Severe Asthma with Fungal Sensitivity (SAFS)

1. History of poorly controlled asthma (>500 μg/d of fluticasone or the equivalent, near continuous oral corticosteroids for >6 mo, or >2 oral steroid tapers per year)
2. Total serum IgE <1000 IU/mL
3. Positive immediate skin test reactivity to *Aspergillus fumigatus* OR elevated specific serum IgE to *A. fumigatus*
4. Absence of serum precipitins (by gel diffusion) and elevated specific serum IgG to *A. fumigatus*
5. No radiographic evidence of bronchiectasis or infiltrates

SEVERE ASTHMA WITH FUNGAL SENSITIVITY

The broad spectrum of clinical, laboratory, and radiographic abnormalities evident in patients with asthma with fungal allergy has led to the description of additional diagnostic categories of allergic fungal disease. The most relevant of these diagnoses is based on studies that demonstrate that antifungal therapies are effective in patients with poorly controlled asthma that have some of the criteria for ABPA-S, but do not reach the threshold for diagnosis. These patients have been designated as having SAFS.

Whether SAFS is a unique disease or is on the continuum from asthma to ABPA remains unclear. However, the primary distinction is that patients with SAFS have a milder allergic reaction and lack the exaggerated IgG response that is typical of patients with ABPA. Therefore, patients with SAFS are difficult to distinguish from patients with ABPA, and especially ABPA-S, as the clinical features are identical between the two entities and both lack radiographic abnormalities.

The diagnosis of SAFS is based on the interpretation of *Aspergillus*-specific immunologic studies. The diagnostic criteria for SAFS (Table 48-2) overlap substantially with ABPA-S and include: (1) severe uncontrolled asthma (treatment requirement of >500 μg/d of fluticasone or the equivalent, need for near continuous oral corticosteroids for 6 months or >2 oral steroid tapers per year); (2) positive skin prick test or RAST for *A. fumigatus* or other fungi; (3) total serum IgE (<417 IU/mL or <1000 ng/mL)); and (4) absence of IgG against *A. fumigatus* (by ELISA, gel diffusion, or FEIA).

In general, patients with SAFS typically have normal radiographic studies and a milder immunologic response that may be identified in patients with milder asthma. Although it remains unclear whether these patients are on the continuum from asthma to ABPA or are at risk of progressing to frank ABPA, the importance of identifying such patients is based on several studies indicating that antifungal therapies may significantly improve asthma control and reduce oral corticosteroid exposure.[47–49]

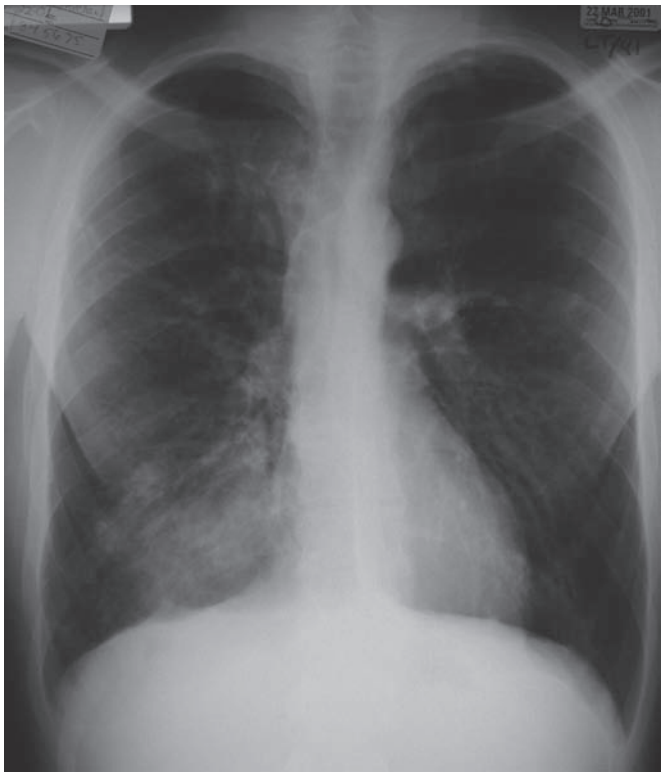
The differential diagnosis of ABPA is broad and includes corticosteroid-dependent asthma without ABPA, SAFS, chronic obstructive pulmonary disease (COPD), chronic necrotizing aspergillosis, tuberculosis, parasitic infections, hypersensitivity pneumonitis, Churg–Strauss syndrome, acute eosinophilic pneumonia (including drug-induced pneumonitis), chronic eosinophilic pneumonia, lymphoma, idiopathic hypereosinophilic syndrome, autoimmune disease, crack cocaine use, CF, and other causes of bronchiectasis. In addition, the diagnosis of ABPA in patients with mold-sensitive asthma and CF poses particular diagnostic challenge. This is especially true in asthmatics, since, by definition, bronchiectasis is absent; furthermore, serum precipitins to *Aspergillus* spp. may be present in up to 10% of patients with positive immediate skin tests to *Aspergillus* and in up to 25% of asthmatics, making distinction from ABPA-S difficult.

Persons with mold-sensitive asthma or ABPA may have peripheral blood eosinophilia and/or elevated serum total IgE levels. However, most persons with ABPA have 2- to 20-fold higher serum levels of *Aspergillus*-specific IgE and total IgE than do mold-sensitive asthmatics without ABPA. A more confusing diagnostic conundrum occurs when considering the diagnosis of ABPA in patients with CF, because patients with CF alone may manifest chronic airflow obstruction, recurrent exacerbations with infections and/or bronchoconstriction, underlying bronchiectasis, pulmonary infiltrates, chronic sputum production, *Aspergillus* colonization of the airways, and positive serum precipitins.

Distinguishing ABPA in patients with CF is critical, because infectious CF exacerbations and the presence of ABPA require different treatments. The steroid treatment required for ABPA may be detrimental in the setting of infection, yet antibiotics alone given for infection may be inadequate to control the inflammation associated with ABPA. Among patients with CF, factors associated with the risk of ABPA include adolescent age, atopy, severe lung disease, and colonization with *Pseudomonas aeruginosa*. ABPA should be suspected in patients with CF who develop clinical deterioration, exhibit a greater than fourfold increase in total serum IgE (especially >1000 IU/mL), have immediate cutaneous reactivity to *Aspergillus* or increased *Aspergillus*-specific IgE or IgG, and show a change in baseline CXR. Annual screening of total serum IgE is recommended; if the level rises >500 IU/mL, immediate cutaneous hypersensitivity testing for reactivity to *A. fumigatus* or testing for serum anti-*A. fumigatus* IgE is recommended.[11,50] The presence

TABLE 48-3 Clinical Stages of ABPA

Stage I: Acute
Acute asthma symptoms
Elevated serum IgE (>1000 IU/mL)
Peripheral blood eosinophilia (may be absent in patients treated with oral corticosteroids)
Fleeting infiltrates on chest X-ray (may be absent in patients treated with oral corticosteroids)
Positive specific IgE, IgG, skin test reactivity, or precipitins to *Aspergillus fumigatus*
Responds to steroids/antifungal therapy
Stage II: Remission
Resolution of symptoms
Resolution of pulmonary infiltrates
Improvement in eosinophilia and *A. fumigatus* specific blood abnormalities
Stage III: Exacerbation/Recurrence
Recurrence/worsening of clinical symptoms
Recurrent pulmonary infiltrates
Rising IgE levels
Stage IV: Steroid-Dependent Asthma
Refractory steroid-dependent asthma
Persistently elevated serum IgE levels
Persistently elevated *A. fumigatus*–specific blood abnormalities
Stage V: Fibrotic Lung Disease
Refractory steroid-dependent asthma
Fibrotic lung disease (irreversible obstructive and restrictive defects with impaired diffusing capacity)
Chronic bronchiectasis symptoms (sputum production, frequent infections)



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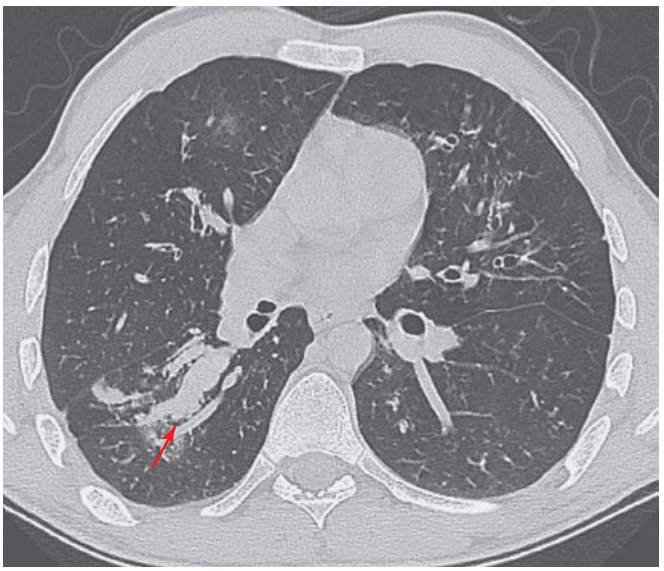

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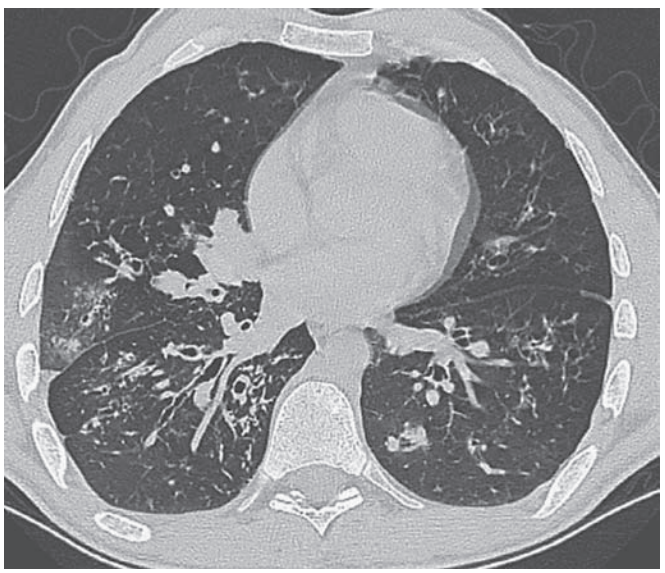

C

Figure 48-1 A 27-year-old man with a history of moderate asthma, recurrent bronchitis, and mild hemoptysis. Serologic studies were consistent with ABPA (IgE, 9490 IU/mL) and radiographic studies were consistent with bronchiectasis. **A.** PA chest X-ray shows hyperinflated lungs, bronchial dilatation, and right lower lobe opacity consistent with mucoid impaction. **B.** High-resolution CT scan image of impacted bronchus *(arrow)* and chronic inflammatory changes. **C.** Dilated central bronchus consistent with cylindrical/central bronchiectasis.

of IgE reactive against the purified *Aspergillus* allergens Aspf3 and Aspf4 may be useful in distinguishing patients with ABPA and CF or *Aspergillus*-sensitive asthma from patients without ABPA.[10]

■ CLINICAL STAGING OF ABPA

Five clinical stages of ABPA have been recognized, based on clinical, serologic, and radiographic characteristics (Table 48-3). A modified version proposed by the International Society for Human and Animal Mycology (ISHAM) has not been widely adopted.[20,51]

Using the classic staging system, Stage I, the *acute* stage, is characterized by symptoms of moderate-to-severe asthma, elevated total IgE (typically >1000 IU/mL), elevated anti-*A. fumigatus* IgE or hypersensitivity skin test to *A. fumigatus*, infiltrates on chest radiograph (with or without proximal bronchiectasis), peripheral blood eosinophilia (frequently >2000/mm^3), and positive precipitating or anti-IgG antibodies to *A. fumigatus* (up to fivefold concentration of serum may be required for detection of the precipitating antibodies).

Patients with stage II ABPA have disease that is in *remission*. This stage is characterized by the resolution of symptoms, radiographic clearing, and decreased stabilization of total IgE levels. Remissions are of varying length, may last several months to years, or may be permanent, allowing corticosteroid treatment to be tapered or discontinued.

Patients with stage III ABPA have *recurrent* disease or disease *exacerbations* (Fig. 48-1). This stage of ABPA is common and is characterized by development of new pulmonary infiltrates and, usually, a substantial increase in total IgE. Elevation of IgE may precede clinical or radiologic worsening during this stage; an isolated increase in the severity of bronchospasm does not constitute an exacerbation

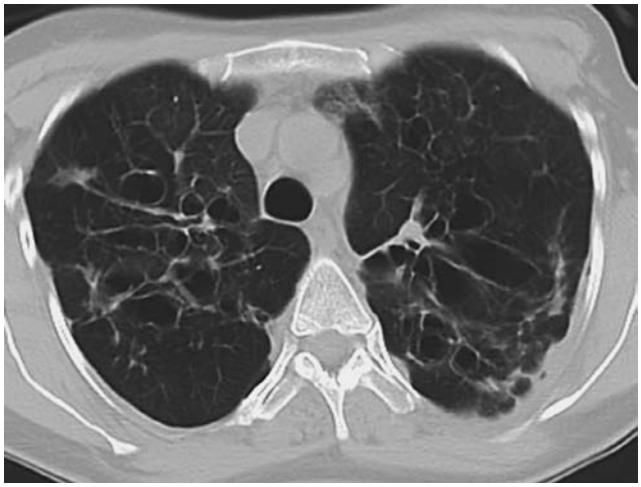

Figure 48-2 Representative CT image of the lungs of a 41-year-old woman who presented with Stage-V ABPA after a long history of mild asthma (IgE, 1500 IU/mL). Pulmonary function studies demonstrated severe combined obstructive and restrictive defects. CT shows bilateral upper lobe scarring and emphysematous changes.

in the absence of a change in biomarkers. Although a majority of disease exacerbations are associated with a concomitant increase in symptoms, exacerbations may occur in the absence of any increase in symptoms. Indeed, since up to one-third of patients with radiographic infiltrates may be asymptomatic, evolving progressive lung damage may remain unrecognized. Total serum IgE levels should be monitored every 1 to 2 months for at least a year after diagnosis, and chest radiographs should be performed intermittently. *Aspergillus*-specific IgA levels may also be elevated in the acute or exacerbation stages of disease. Exacerbations are more likely to occur during seasons or in environments when mold counts are high.

Stage IV ABPA is defined as *steroid-dependent asthma*. In stage IV disease, total IgE, *Aspergillus* precipitins, and *Aspergillus*-specific IgE and IgG typically remain elevated, despite chronic steroid therapy. The frequency of exacerbations may increase.

Stage V is defined as *pulmonary fibrosis*. Stage V patients have prominent symptoms of dyspnea; are often steroid dependent because of persistent bronchospasm; frequently have chronic sputum production, recurrent respiratory infections, and irreversible pulmonary function abnormalities (obstruction, restriction, and/or gas exchange abnormalities), and may have cyanosis or clubbing. The serologic profile of patients with stage IV disease persists during stage V. Stage V disease is generally thought to be the consequence of longstanding, often unrecognized, disease, but it may occur occasionally among patients with little prior clinical evidence to suggest the diagnosis (Fig. 48-2).

DIAGNOSTIC STUDIES

In addition to the blood abnormalities described earlier, analysis of BAL fluid from patients with ABPA often reveals a moderate eosinophilia (especially in steroid-naive patients) and increased levels of *Aspergillus*-specific IgE and IgA, but not IgG. On bronchoscopy, mucoid impaction may be evident, and bronchial brushings may reveal mucus that contains aggregates of eosinophils, fungal hyphae, and eosinophil-derived Charcot–Leyden crystals. The finding of hyphae-filled mucus plugs is considered pathognomonic for ABPA. Pulmonary function tests typically reveal an obstructive ventilatory defect (due to bronchospasm or mucus impaction of the bronchi) during Stages I, III, IV, and often, V and may not correlate with the duration of ABPA or asthma. Patients with Stage V disease typically also have a restrictive ventilatory defect and a reduced D_{LCO} (Fig. 48-2).

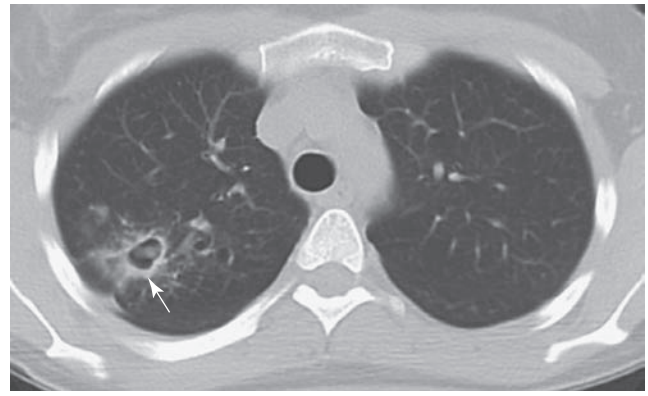

Figure 48-3 A 21-year-old woman with ABPA, who responded to treatment with oral corticosteroids and chronic antifungal therapy, developed an aspergilloma and hemoptysis *(arrow)*. Amphotericin paste injection failed and the patient ultimately underwent a right upper lobe lobectomy.

The typical radiographic manifestations of ABPA include parenchymal infiltrates and bronchiectasis (Figs. 48-1–48-3). The infiltrates are often irregular and transient (1–6 weeks). They have a predilection for upper lobes, although all lobes may be affected. The bronchiectasis is classically cylindric and proximal (central), occurring within the proximal two-thirds of the lung (Fig. 48-1B). Mucoid impaction in dilated bronchi leads to a characteristic (but nonspecific) radiographic appearance of ABPA termed the "finger in glove" opacity. "Tramline shadows" (parallel linear shadows extending from the hilum in bronchial distribution and reflecting longitudinal views of inflamed, edematous bronchi), "toothpaste shadows" (representing mucoid impaction of the bronchi), "ring shadows" (dilated bronchi with inflamed bronchial walls seen on end), local consolidation, or lobar collapse are also common features. Involvement of the small airways may lead to centrilobular nodules and branching tree-in-bud opacities (Fig. 48-1). Less common radiographic findings include bullous changes, pneumothorax, pleural effusion, cavitating nodular lesions, aspergilloma (Figs. 48-2 and 48-3) and migratory parenchymal opacities, some of which have a ground-glass appearance. High-resolution CT scanning is the most reliable noninvasive means of detecting proximal bronchiectasis.

Open-lung biopsy is usually not required to establish the diagnosis of ABPA. Histopathologic findings include intense bronchocentric inflammation with prominent eosinophilia, as well as lymphocytes, plasma cells, and monocytes. Bronchi may be filled and/or impacted with copious mucus plugs containing fibrin, Charcot–Leyden crystals, Curschmann spirals, and fungal hyphae. Bronchiectasis of segmental and subsegmental bronchi may be evident. Regions of bronchocentric granulomatosis, eosinophilic pneumonia, eosinophilic microabscess, lymphocytic or desquamative interstitial pneumonitis, proliferative or obliterative bronchiolitis, lipoid pneumonia, or interstitial fibrosis may also be seen.

TREATMENT

The goals of treatment for individuals with ABPA consist of controlling symptoms, preventing exacerbations, and preserving normal lung function.

Systemic corticosteroids are the mainstay of therapy for ABPA. Without treatment, ABPA may cause significant irreversible lung damage due to bronchiectasis and pulmonary fibrosis. Therefore, initiation of appropriate treatment early in the course of disease is essential. Although most data are derived from small uncontrolled trials, and definitive proof that corticosteroid therapy prevents the development of central bronchiectasis is lacking, retrospective

studies suggest that early therapeutic intervention using corticosteroids may prevent progression to lung fibrosis.

Therapy for Stage I or III disease should include prednisone, 0.5 to 1 mg/kg a day for 2 weeks, followed by 0.5 mg/kg every other day for 6 to 8 weeks. A subsequent taper (by 5–10 mg every 2 weeks) over the ensuing 3 months may then be tried. The duration of treatment must be guided by activity and severity of disease, with an aim of minimizing cumulative exposure to systemic corticosteroids. A low maintenance dose (e.g., 5.0–7.5 mg/d) may be required long term to control the disease and prevent recurrence in some patients.

Corticosteroid therapy leads to relief of symptoms and decreases in airflow obstruction, decreases (>35%) in serum IgE, reductions in peripheral blood eosinophils, and resolution of pulmonary inflammation and infiltrates. IgE levels should be monitored within a few months of an acute episode or exacerbation and should be followed every 2 months thereafter since levels may rise, reflecting disease activity, prior to an exacerbation or in the absence of clinical symptoms. Escalation of steroid therapy should be considered if IgE levels rise more than 100%. The CXR should be monitored within the first year of an acute episode or exacerbation and may be followed yearly thereafter if the disease is quiescent. Pulmonary function testing should be followed closely as well.

Although treatment of acute exacerbations is believed to be helpful in preventing fibrotic complications of ABPA, it is not known if early detection and treatment of disease flares has any effect on disease progression. Therefore, high-dose systemic corticosteroid treatment of asymptomatic individuals is not recommended. Patients with CF and ABPA flares may derive symptomatic or functional improvement from steroid treatment. However, patients with CF who are on steroids should be followed closely for development of invasive aspergillosis. It is unclear whether development of ABPA alters the course of CF disease progression.

Although not advocated as primary treatment, inhaled corticosteroids are useful for control of bronchospasm and may help minimize the dose of systemic steroid necessary to control wheezing. They have been used occasionally as a steroid-sparing agent for the treatment of symptomatic exacerbations and pulmonary infiltrates, and they may help maintain stability of lung function. In addition, adjuvant treatment with bronchodilators and antibiotics also helps control bronchospasm and secondary respiratory infections.

In the last decade, development of oral antifungal agents has brought new hope to patients with ABPA.[52,53] Even though the current concept is that ABPA is not a classic "infection," evidence is mounting to support use of the antifungal agent, itraconazole, in patients with ABPA. Presumably, the agent minimizes the degree of fungal colonization.

In one randomized controlled study, itraconazole (200 mg twice daily for 16 weeks) led to significant reductions in corticosteroid dose, decreased IgE levels, greater resolution of pulmonary infiltrates, and gains in exercise tolerance or pulmonary function.[54] Several clinical studies have demonstrated that treatment with itraconazole also reduces *Aspergillus* antibody titers and eosinophilia compared with placebo.

Itraconazole treatment (200 mg/d or every other day) is generally recommended for patients with ABPA who are steroid dependent, have frequent relapses, and in whom the cost and risks are thought not to outweigh the potential benefits. Itraconazole also has demonstrated utility in ABPA associated with CF. If itraconazole is used, steady-state blood levels can be checked after 1 to 2 weeks, 4 hours after the dose is given, to assess drug absorption.[55]

Since itraconazole interferes with the hepatic metabolism of several medications, including cyclosporine, oral hypoglycemics, tacrolimus, terfenadine, cisapride, and midazolam, particular caution should be exercised with its use among patients taking any of these medications. In addition, physicians must be mindful of adrenal insufficiency associated with itraconazole treatment among patients with ABPA using inhaled corticosteroids, as itraconazole may cause reduced steroid clearance and/or possible direct suppression of adrenal steroid production. Interval screening for adrenal insufficiency should be considered among such persons. In contrast, the efficacy of itraconazole in ABPA may be less among persons taking agents that raise gastric pH, as an elevated gastric pH may dramatically reduce drug absorption.

Other antifungal agents, including nystatin, amphotericin B, miconazole, clotrimazole, and natamycin, are generally ineffective in controlling ABPA. Ketoconazole may be effective, but its utility is limited by hepatotoxicity. Efficacy of voriconazole has not yet been studied in ABPA, but anecdotal reports from our center and others suggest similar results to itraconazole.[56–59]

Finally, the new biologically engineered antibody directed against IgE, omalizumab, is an intriguing consideration for use in ABPA, but the agent has not been extensively studied in large randomized trials. Given that the recommended dosing of this biologic is based on patient weight and serum IgE level, many patients with ABPA are outside of the dosing nomogram. However, multiple case reports and small series indicate that at conventional doses (up to 375 mg subcutaneously every 2 weeks), administration may improve disease activity and spare oral corticosteroid dosing.[60–69]

In addition to medical therapy, all patients with ABPA-related bronchiectasis should be prescribed standard airway clearance treatments, including hypertonic saline and mucus clearance valves or percussion vests, depending on the severity of disease. In addition, patients with ABPA should avoid areas and environmental conditions associated with high mold counts, such as decomposing organic materials and moldy indoor environments. One should consider the use of HEPA filters if such exposures are unavoidable.

PROGNOSIS

With appropriate treatment, long-term control of ABPA is feasible, and durable remissions are common. Treatment of Stage I disease using corticosteroids typically results in decreased sputum production, improved control of bronchospasm, >35% reduction in total IgE within 8 weeks, clearing of precipitating antibodies, and resolution of radiographic infiltrates. IgE levels typically do not completely normalize, but rather, they decrease by approximately one-half of peak levels seen in the acute stage. Progression of Stage IV disease to pulmonary fibrosis may be prevented if patients are maintained on low-dose steroids; most patients with Stage V disease have a stable course over several years. Persons with an FEV_1 persistently <0.8 L have a worse prognosis.

In addition to severe airflow obstruction and pulmonary fibrosis, long-term complications of ABPA occasionally include the development of an aspergilloma (Fig. 48-3), chronic or recurrent lobar atelectasis, allergic *Aspergillus* sinusitis, or *Aspergillus* tissue invasion and semi-invasive *Aspergillosis*. Transplantation has been undertaken successfully among patients with ABPA. However, post-transplant recurrence of ABPA has been reported.

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SECTION 10 Other Obstructive Disorders

CHAPTER 49

Upper Airway Obstruction in Adults

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Meir H. Kryger

INTRODUCTION

The upper airway is conventionally described as being made up of all the structures that conduct air between the carina and the nares and includes the trachea, larynx, pharynx, nasal airway, and oral airway. Upper airway structures may change their physiologic function in response to pressures around them, and anatomic structures near them. Thus, physiologically, the segments of the upper airway behave differently when they are subject to pleural pressures (anatomically intrathoracic) or ambient pressures (anatomically extrathoracic). Furthermore we now know that extrathoracic airway function may change with posture, sleep/wake state, and the function and anatomy of tissues surrounding the airway.

The upper airway evolved anatomically in humans to subserve several important functions including swallowing, breathing, and vocalization.[1] The multifunctionality of the upper airway increases the risk of certain diseases (e.g., aspiration and sleep apnea).[2] These functions require that different segments of the airway have differing properties. The trachea receives some support by the tracheal rings, the nasal airway is surrounded by rigid structures, and the oral airway has a rigid boney roof, the hard palate. On the other hand, the pharyngeal airway does not have rigid structures supporting it. It is a collapsible tube whose patency is maintained by muscles whose function is affected by arousal state (sleep/wake, and more specifically during sleep, the stage of sleep), the structures around it, and posture. Thus, the pharyngeal airway is divided anatomically and physiologically into the nasopharynx, retropalatal oropharynx, retroglossal oropharynx, and hypopharynx.

Clinically significant obstruction in adults may occur anywhere within the upper airway. Common etiologies of upper airway obstruction (UAO) include neoplasia, scar formation, skeletal facial malformations, infection, inflammatory disorders, trauma, extrinsic compression related to pathology of adjacent structures, and functional changes related to posture and sleep/wake state. Airway obstruction may be classified as extrinsic, intrinsic, or mixed (Fig. 49-1).

UAO can be acute and life-threatening, or chronic and resulting in significant symptoms, some of which may not even relate to the respiratory system. Initial management of acute UAO focuses on securing the airway and stabilizing the patient. Often the intervention is surgical. Some diseases require bypassing the obstruction using translaryngeal intubation or tracheostomy. Definitive long-term management depends on the underlying etiology and physiology, and may include both medical and surgical interventions. The still evolving fields of imaging and interventional pulmonology offer new diagnostic and management modalities. This chapter provides an overview of acute and chronic UAO in adults and focuses on clinical presentation, assessment, etiology, and management. Obstructive sleep apnea is covered in Chapter 99 of this volume.

HISTORICAL PERSPECTIVE

Acute UAO can be so distressing to the patient and to those around him/her that it is not surprising that tracheostomy has been used as a treatment for at least 3000 years, as described in ancient Egyptian tablets and Greek and Roman writings.[3] Tracheostomy was considered dangerous because it might lead to catastrophes (e.g., laceration of the carotid artery) or infections that may not be controlled. Even Hippocrates warned about the dangers of tracheostomy. By the mid-16th century, the tracheostomy had been performed to relieve UAO caused by a pharyngeal abscess.

Although the procedure was already widely known within the medical profession in the 18th century, it was seen as potentially very dangerous. The first president of the United States, George Washington, died of acute UAO likely caused by epiglottis while his doctors (who were familiar with tracheostomy) treated him with blood letting.[4] During the 19th century, the procedure was used to treat UAO caused by croup and diphtheria.

By the early 20th century, nonsurgical treatments were used to treat UAO; for example, rigid bronchoscopy was used to remove foreign bodies from the trachea.[5] The flexible fiberoptic bronchoscope was introduced in 1966, and the next four decades saw the introduction of many diagnostic and therapeutic modalities including: Nd:YAG laser, video

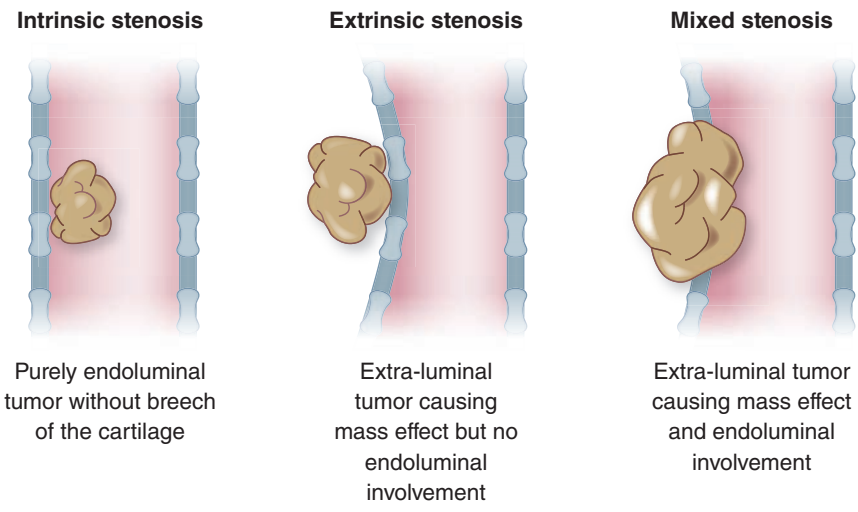


Figure 49-1 Classification of airway tumor involvement. **A.** Intrinsic stenosis. Purely endoluminal tumor without breech of the cartilage. **B.** Extrinsic stenosis. Extraluminal tumor causing mass effect but no endoluminal involvement. **C.** Mixed stenosis. Extraluminal tumor causing mass effect and endoluminal involvement.

bronchoscopy, airway stenting, endobronchial ultrasonography, endobronchial electrocautery, cryotherapy, argon laser coagulation, thermal laser therapy, photodynamic therapy (PDT), brachytherapy, and percutaneous tracheostomy.[6]

There are newly described causes of UAO and novel imaging techniques, both radiographic and endoscopic, which are in evolution to detect and quantify UAO. Treatment strategies are continuously advancing. The incidence of malignancy and related obstruction of the upper airway has increased due in part to tobacco use and exposure to modern environmental toxins. It is estimated that 20% to 30% of lung cancer patients present with symptomatic airway obstruction. The exact prevalence, however, is unknown as a result of the nihilistic view of lung cancer, particularly in the setting of advanced disease. Complications of endotracheal intubation and tracheostomy have become well-recognized causes of benign upper airway stenosis and malacia. Again, it is likely that this pathology is underreported and many people are inappropriately treated for asthma or other chronic peripheral airway diseases. Improvement in pharmacologic agents to treat infectious, inflammatory, and malignant etiologies, as well as developments in radiation oncology, have influenced the management of UAO. More recently, advances involving anesthetic agents and anesthesia techniques, along with development of sophisticated surgical procedures for reconstruction of the larynx, trachea, and bronchi, have had a considerable impact on the management of this condition. Development of new endoscopic and imaging techniques and introduction of interventional pulmonology also have proved useful in the management of UAO.

In the mid-1960s it became apparent that UAO occurred in some patients only during sleep and until the mid-1980s the only effective treatment was tracheostomy, which was used to bypass the segment of the airway obstructing during sleep.[7] Up to that era, the main focus of the laboratory diagnosis of pulmonary disease was for patients with obstructive intrathoracic disease and soon the importance of being able to diagnose UAO became apparent.[8] Soon the notion of using positive airway pressure to overcome UAO was established.[9]

CLINICAL FEATURES

Upper and lower airway obstruction may present with similar symptoms (e.g., shortness of breath, noisy breathing) and physical findings (e.g., wheezing, diminished breath sounds). Asthma and chronic obstructive pulmonary disease, common causes of lower airway obstruction, are often incorrectly assumed to be causing the patient's symptoms.

Significant UAO may be asymptomatic for a prolonged period of time, resulting in delayed presentation, diagnosis and possibly a catastrophic outcome. When UAO develops or worsens acutely, asphyxia and death may result within minutes to hours. When UAO develops slowly, diagnoses may be delayed or incorrect, and, in the case of malignancy in the upper airway, may lead to incurable disease.

Dyspnea and noisy breathing, the most common symptoms of UAO, are often prominent during exercise and also may be intensified or relieved by a change in body position. The patient may indicate that breathing is labored while supine and may experience sleep disordered breathing in the forms of obstructive sleep apnea or upper airway resistance syndrome (see Chapter 99). Therefore, daytime somnolence may be a prominent feature of UAO. In severely affected patients, peripheral edema as a result of cor pulmonale may be present as a consequence of chronic hypoxemia and hypercarbia during sleep and wakefulness.

In most cases, significant anatomic obstruction precedes the development of symptoms. By the time dyspnea on exertion occurs, the airway diameter at the site of obstruction is likely to be reduced to about 8 mm. Shortness of breath at rest often develops when the airway diameter is about 5 mm, and stridor is now often present. Stridor is a loud, musical sound of constant pitch that usually indicates the presence extrathoracic airway obstruction most often affecting the larynx or upper trachea.

Unlike wheezing, which is a feature of diffuse peripheral airway obstruction and occurs primarily during expiration, stridor usually occurs during inspiration and is loudest in the neck. The sound can usually be appreciated without using a stethoscope. Although one would expect to be able to distinguish stridor from wheezing coming from lower airways, sound recordings from the neck and chest have shown that the sounds from the asthmatic wheeze and stridor have similar frequencies. Hence there may be errors in diagnosis and a UAO caused by a tumor or foreign body may be mistakenly treated as asthma.

Breathing maneuvers that increase inspiratory airflow, such as forced inspiration or voluntary hyperventilation, accentuate the intensity of stridor. Neck flexion may change the loudness of stridor. When the obstructing lesion is fixed, both inspiratory and expiratory stridorous sounds may be heard. At times, the character of a patient's voice may be a clue to the presence of UAO. Hoarseness may be a sign of a laryngeal abnormality. Muffling of the voice may be present when vocal cords are paralyzed.

LABORATORY ASSESSMENT

Just as UAO must be quite advanced before development of symptoms, physiologic abnormalities do not become apparent on lung function testing until severe obstruction occurs. Studies of subjects breathing through tubes of varying diameters suggest that UAO must narrow the airway lumen to less than 8 mm in diameter to produce abnormalities on a flow–volume loop. This corresponds to an obstruction of more than 80% of the normal median diameter of the tracheal lumen. The forced expiratory volume in 1 second (FEV_1) remains above 90% of control until a 6-mm orifice is created. Therefore, spirometry, which is often the first screening test for pulmonary symptoms, may not be an effective way to detect upper airway abnormalities. The peak expiratory flow rate (PEFR) and maximal voluntary ventilation (MVV) are more sensitive than the FEV_1 in detecting UAO. Of note, a noncritical airway may become so with a lesser degree of obstruction in the context of airway secretions, edema, or bleeding.[10]

The flow–volume loop, which is a recording of maximal inspiratory and expiratory flows at various lung volumes, is an important tool for the diagnosis of UAO. The configuration of the normal flow–volume loop is shown in Figure 49-2. During a forced expiratory maneuver from total lung capacity (TLC), the maximal flow achieved during the first 25% of the forced vital capacity is dependent on effort, that is, an increase in driving pressure (effort) may result in increased flow. During the remaining 75% of the forced vital capacity maneuver, flow is determined by the mechanical properties of the lungs and is not effort dependent. During this portion of forced exhalation, a linear deceleration of flow is caused by dynamic compression of the intrathoracic airways (Fig. 49-3A). An increase in effort and therefore pleural pressure causes further compression of the intrathoracic airways and a further limitation of airflow. At higher lung volumes, flow may be limited by a UAO. At low lung volumes, flow may not be affected by a UAO, since measurement of flow in this effort-independent portion of the curve represents the function of the peripheral airways. Since the FEV_1 reflects a large portion of flow at these lower lung volumes, it is not a sensitive test for UAO. Because the PEFR reflects flow at higher lung volumes, it may be abnormal when the FEV_1 is not.

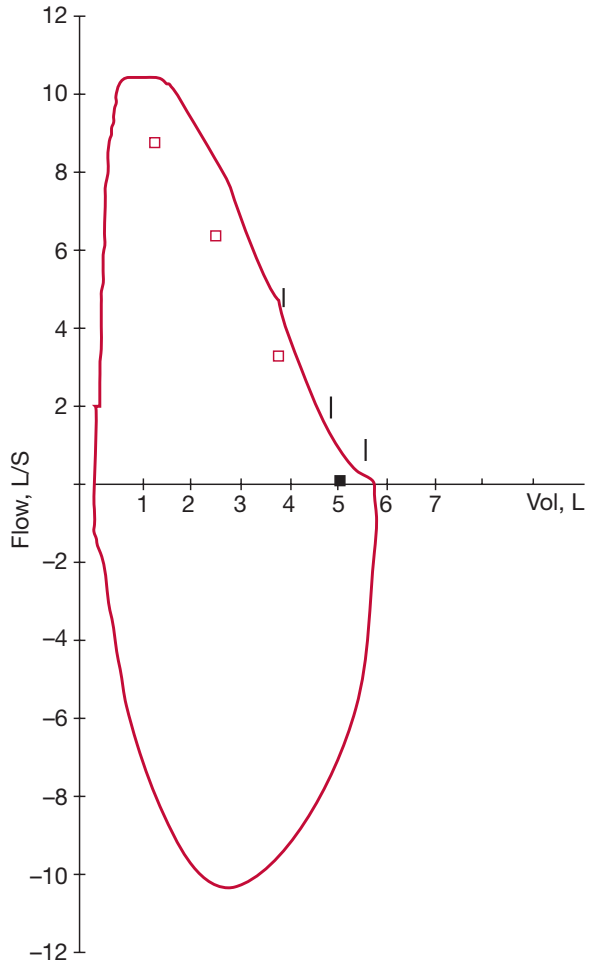


Figure 49-2 Normal flow–volume loop following maximal expiratory *(above)* and inspiratory *(below)* effort. Small vertical lines denote seconds.

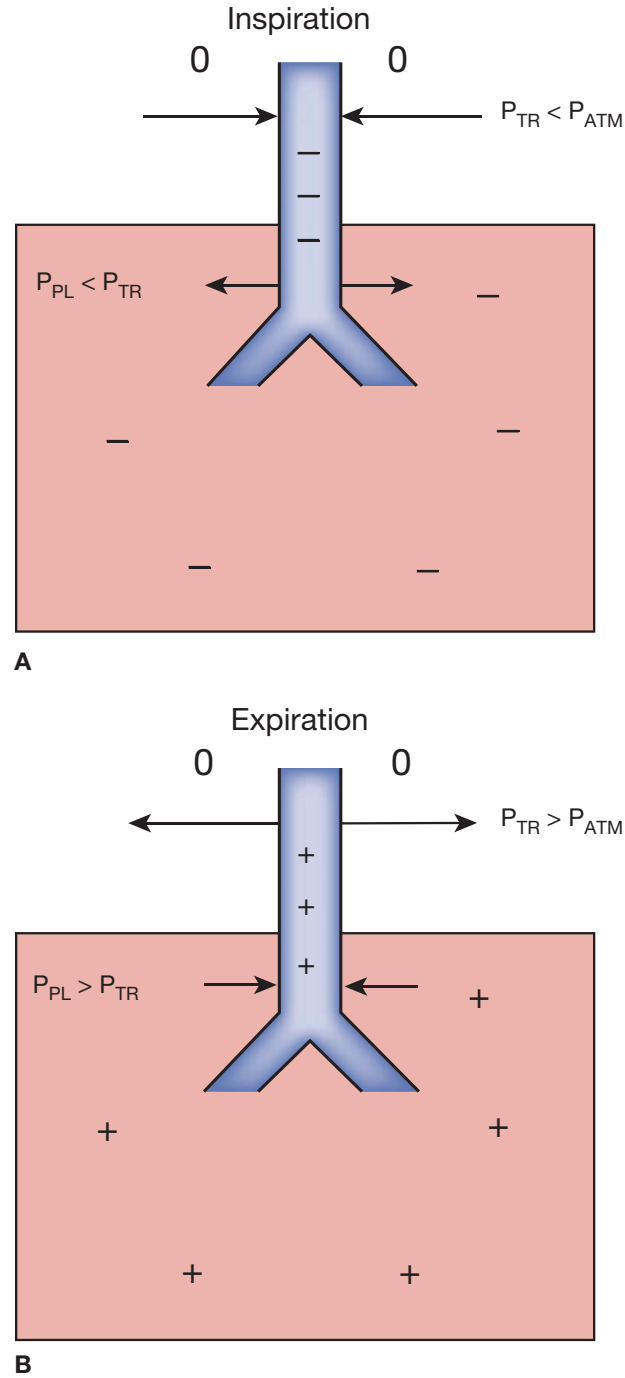
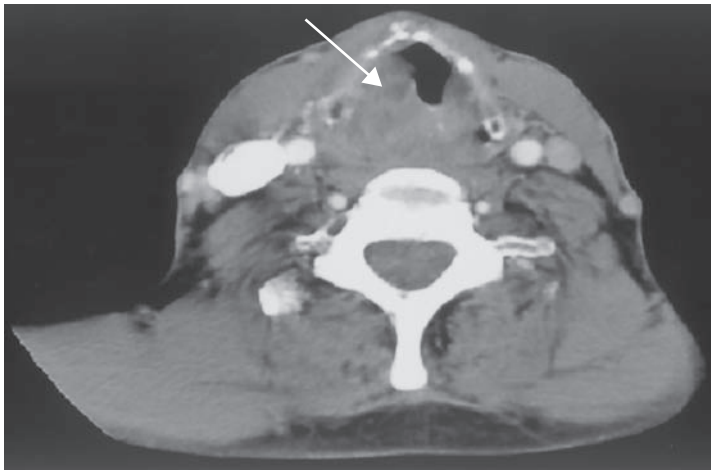


Figure 49-3 Forces acting on intra- and extrathoracic airway walls during inspiration and expiration. 0, atmospheric pressure; +, positive pressure; −, negative pressure. **A.** During inspiration, extrathoracic tracheal pressure (P_{TR}) falls below atmospheric pressure (P_{ATM}), favoring narrowing of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) becomes negative, favoring airway enlargement *(arrows)*. **B.** During expiration, the extrathoracic tracheal pressure (P_{TR}) becomes positive and, therefore, greater than P_{ATM}, favoring enlargement of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) is positive, causing dynamic compression of the intrathoracic trachea *(arrows)*.

In generating the flow–volume loop, forced inspiratory flow is limited by effort during the entire inspiratory maneuver. Flow increases from residual volume to near the midportion of the curve, where it becomes maximal at the peak inspiratory flow rate. Flow then declines until TLC is reached. The pressure surrounding the extrathoracic portion of the upper airway is atmospheric. The turbulent nonlaminar airflow, which occurs during forced inspiration and causes airway pressure to fall in this portion of the airway, favors slight narrowing of the extrathoracic airway (Fig. 49-3B). Peak inspiratory flow, therefore, is less than peak expiratory flow in normal subjects. Because of the dynamic compression of the intrathoracic airways that occurs during exhalation, flow during the middle of inspiration, that is, the forced inspiratory flow at 50% of the forced vital capacity ($FIF_{50\%}$), is usually greater than flow during the middle of forced expiration, that is, the forced expiratory flow at 50% of the forced vital capacity ($FEF_{50\%}$). Typical patterns of the flow–volume loop may be seen, depending on whether the obstruction to flow is "fixed" or "variable," and whether the site of the obstruction is above or below the thoracic outlet or suprasternal notch.

Fixed obstructions of the upper airway are those in which the cross-sectional area does not change in response to transmural pressure differences during inspiration or expiration. A fixed obstruction may occur in either the intrathoracic or extrathoracic airways. Irrespective of the site of the obstruction, a fixed lesion results in the flattening of the inspiratory and expiratory phases of the flow–volume loop. A *variable obstruction* is one that responds to transmural pressure changes, eliciting varying degrees of obstruction during the respiratory cycle. Since the stresses on the intrathoracic and extrathoracic airways are different, changes seen in the flow–volume loop vary according to the site of the obstruction.



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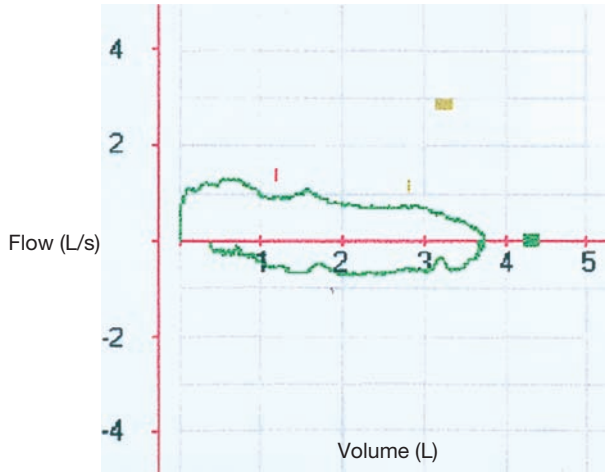


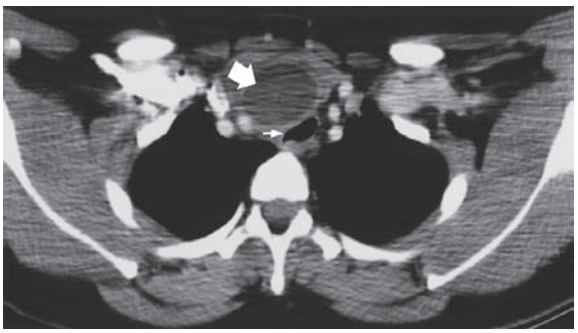
B

Figure 49-4 **A, B.** Flow–volume loop in fixed upper airway obstruction due to laryngeal abscess in a 56-year-old man who developed persistent wheezing, hoarseness of voice, and intermittent stridor for 3 months after a brief intubation for asthma exacerbation. Computed tomography scan of the neck (**A**) shows a laryngeal abscess with significant impingement on the laryngeal inlet. The flow–volume loop (**B**) demonstrates a plateau of flow during inspiration and expiration; the $FEF_{50\%}/FIF_{50\%}$ ratio is near 1.

A number of conditions have been associated with nondistensible narrowing of the upper airway and fixed airway obstruction. Benign strictures and malignancy are common examples. Maximal inspiratory and expiratory flow–volume loops with fixed obstruction show constant flow, represented by a plateau during both inspiration and expiration (Fig. 49-4A,B). On the expiratory curve, the plateau effect is seen in the effort-dependent portion of the curve near TLC; very little change is noted in the effort-dependent portion near residual volume. Since the inspiratory curve is similar in appearance, the ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is normal (close to 1). The forced inspiratory volume in 1 second (FIV_1) and FEV_1 are nearly the same in fixed UAO.

Unilateral vocal cord paralysis is a common cause of variable extrathoracic obstruction. A variable extrathoracic airway obstruction increases the turbulence of inspiratory flow, and intraluminal pressure falls markedly below atmospheric pressure. This leads to partial collapse of an already narrowed airway and a plateau in the inspiratory flow loop (Fig. 49-5A,B). Expiratory flow is not significantly affected, since the markedly positive pressure in the airway tends to decrease the obstruction. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is high (usually greater than 2). Similarly, the FEV_1 is greater than the FIV_1.

A variable obstruction in the intrathoracic airways reverses the situation. A predominant reduction in maximal expiratory flow is associated with a relative preservation of maximal inspiratory flow. This association occurs because intrapleural pressure becomes decidedly positive during forced expiration and causes dynamic compression of the intrathoracic airways. The obstruction caused by an intrathoracic lesion is accentuated and a plateau in expiratory flow occurs on the flow–volume loop (Fig. 49-6A,B). A plateau of flow suggests that the lesion has caused the airway lumen to reach its minimal size. A flow peak may precede the plateau, suggesting that the obstruction may not affect flow until a certain lung volume is reached. During inspiration, intrapleural pressure is markedly negative; therefore, the obstruction is decreased. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is very low and may approach 0.3. Similarly, the FEV_1 is considerably lower than the FIV_1. Although the flow ratios are similar to those seen in patients with COPD and chronic asthma, these disorders are distinguished from UAO by the appearance of the flow–volume loop. Thus, the expiratory curve in patients with COPD and asthma is primarily altered in the effort-independent portion of the curve, leading to a characteristic shape unlike the plateau configuration of a UAO (Fig. 49-7).



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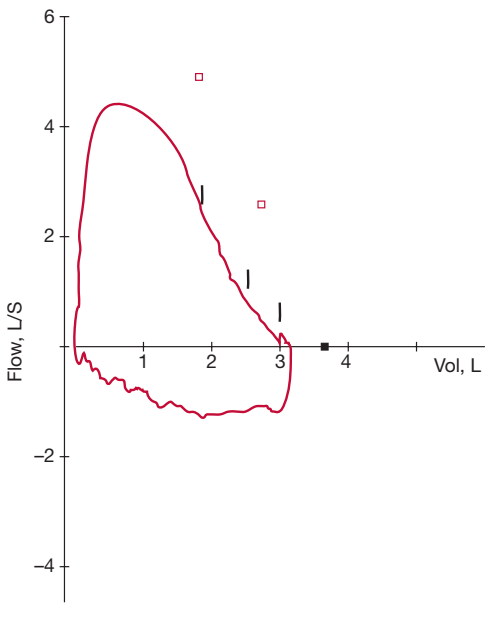
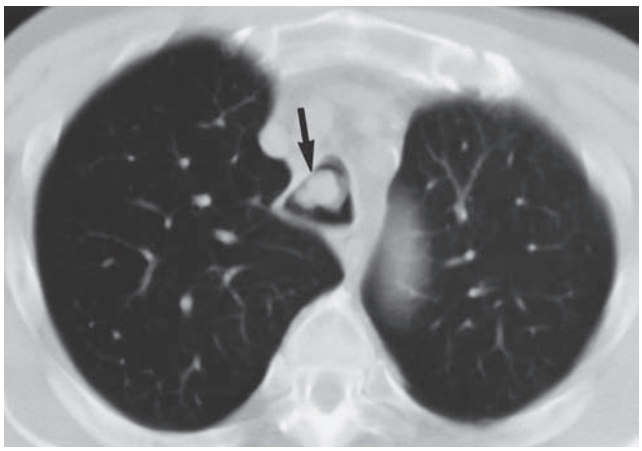


B

Figure 49-5 Variable extrathoracic obstruction due to thyroid cyst in a 32-year-old woman with dyspnea on exertion. **A.** Computed tomography of the neck shows a 10- × 4-cm cystic mass *(large arrow)* in the thyroid gland compressing the trachea *(small arrow)*. **B.** Flow–volume loop shows inspiratory obstruction. $FEF_{50\%}/FIF_{50\%}$ is very high, and the inspiratory curve is flattened.



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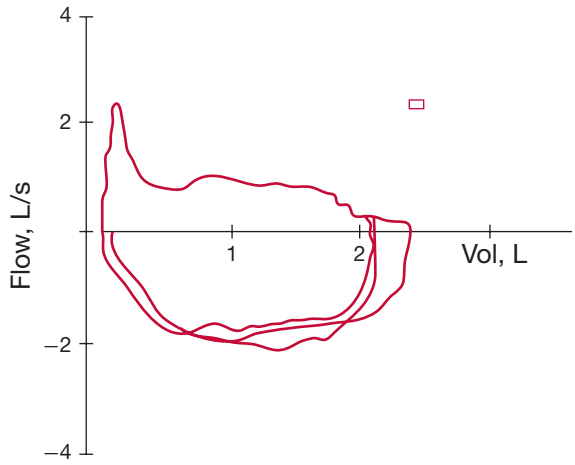


B

Figure 49-6 Variable intrathoracic obstruction due to squamous cell carcinoma of the trachea. **A.** Computed tomography of the chest shows a tracheal lesion *(arrow)*, which was not readily apparent on plain chest radiograph. **B.** Superimposed flow–volume loops show a plateau of expiratory flow preceded by a peak of flow at higher lung volumes. The forced inspiratory flow is preserved in comparison to expiratory flow, but it is also reduced. $FEF_{50\%}/FIF_{50\%}$ is 0.4.

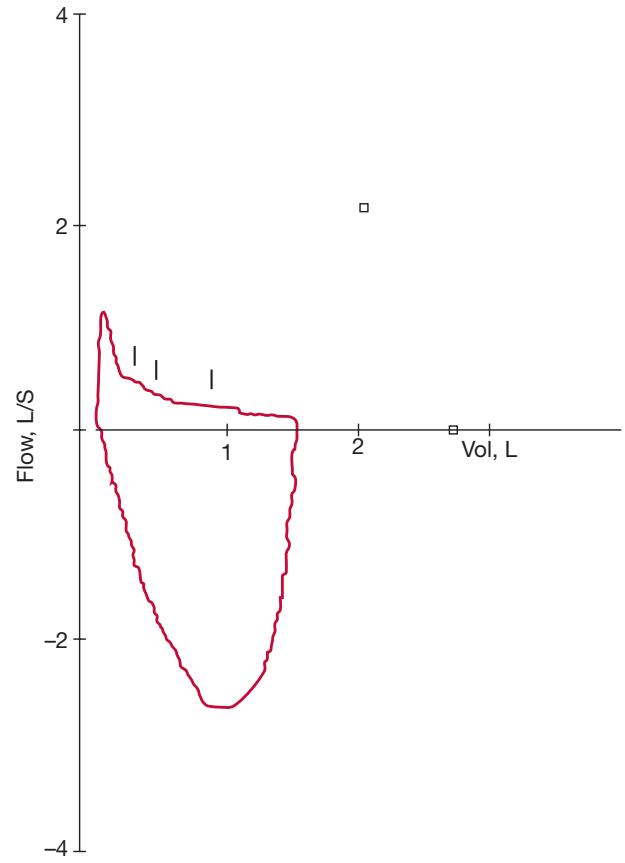


Figure 49-7 Flow–volume loop typical of chronic obstructive lung disease. Very low $FEF_{50\%}/FIF_{50\%}$ and typical curvilinear shape are noted.

When a hospital laboratory or physician's office is not equipped to perform flow–volume loops, results of other tests, such as routine spirometry, may be helpful. If the forced spirogram shows that the PEFR is reduced disproportionately to the reduction in FEV_1, a UAO should be suspected. Other findings that suggest the diagnosis include a ratio of less than 1.0 for the inspiratory flow between 25% and 75% of the inspired vital capacity ($FIF_{25–75\%}$) and a value of less than 1.0 for the expiratory flow between 25% and 75% of the expired vital capacity ($FEF_{25–75\%}$). Another indication is an FEV_1 that is decreased to the same degree as the $FEF_{25–75\%}$. The MVV may also be a useful test, since it measures both inspiratory and expiratory flows. A ratio of MVV to FEV_1 of less than 25% is often found with UAO. Whenever the MVV is reduced in association with a normal FEV_1, a diagnosis of UAO should be considered.

In contrast to the situation in patients with diffuse obstructive disease of the lower airways (e.g., COPD, asthma), the distribution of ventilation in the lungs is normal, and ventilation–perfusion mismatch does not occur. Hypercarbia is not seen unless the degree of obstruction is very severe, although nocturnal hypercarbia may occur while daytime levels of P_{CO_2} are normal. Hypoxemia is also not present except during exercise and with severe airflow limitation, when it may accompany increases in the level of P_{CO_2}. In contrast to asthma and many instances of COPD, the airflow obstruction caused by an upper airway lesion does not resolve following the inhalation of a bronchodilator unless there is also a component of small airway disease that is often the case.

IMAGING

When acute airflow obstruction occurs as a result of an abnormality of the extrathoracic airway, roentgenographic studies of the soft tissues of the upper chest and neck in the emergency setting may be helpful (Fig. 49-8). However, computed tomography (CT) has afforded the most important approach to imaging of the extrathoracic airways (Fig. 49-9). The standard chest roentgenogram is often not helpful in detecting the presence, or the cause, of UAO. Occasionally, in patients with chronic airway obstruction, generalized hyperinflation of the lungs may occur; in the absence of asthma or COPD this finding may raise suspicion of occult disease in the central airways. The trachea is usually well visualized on the posteroanterior (PA) and lateral views in chest roentgenograms of good quality. It is located in the midline and is moderately deviated at the level of the aortic arch. However, many standard roentgenograms are underpenetrated so that the trachea may become a "blind spot." In one study, only 13 of 53 tracheal tumors were evident to the radiologist on the standard PA roentgenogram. The use of digital imaging techniques may avoid such pitfalls. However, thoracic CT studies have become the procedure of choice for imaging the upper airway.

The sensitivity of CT scanning for detecting upper airway disease surpasses that of the routine chest roentgenogram (97% vs. 66%, respectively). Helical CT (HCT) scanning minimizes artifacts due to respiratory motion and provides imaging of the whole thoracic volume during a single breathhold.[11] The technique represents

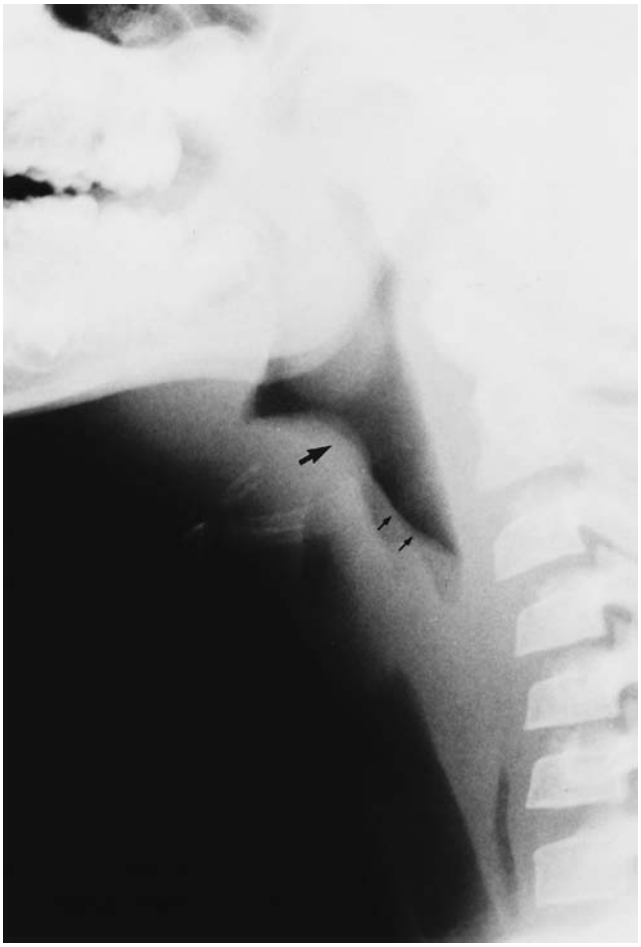


Figure 49-8 Acute epiglottitis. Lateral soft tissue radiograph of the neck of a patient with stridor shows swelling of the epiglottis *(large arrow)* and loss of normal convexity of the edematous aryepiglottic folds *(small arrows)*.

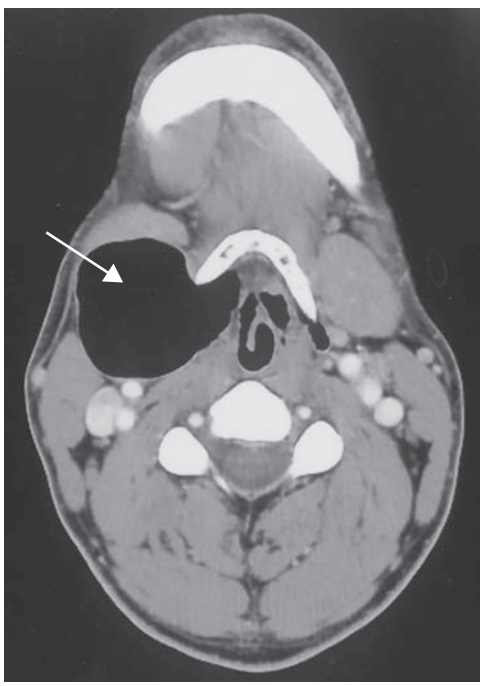
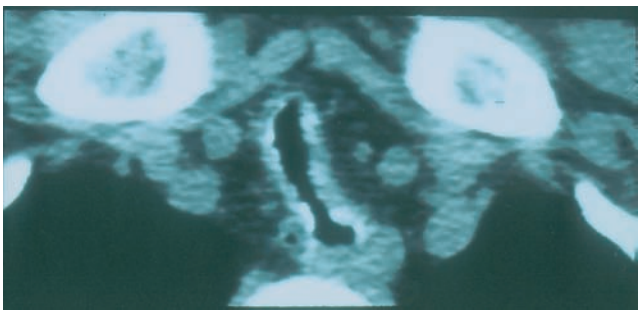


Figure 49-9 Computed tomography scan of the neck demonstrating a large laryngocele compressing the lateral wall of the larynx *(arrow)* causing positional air flow obstruction.



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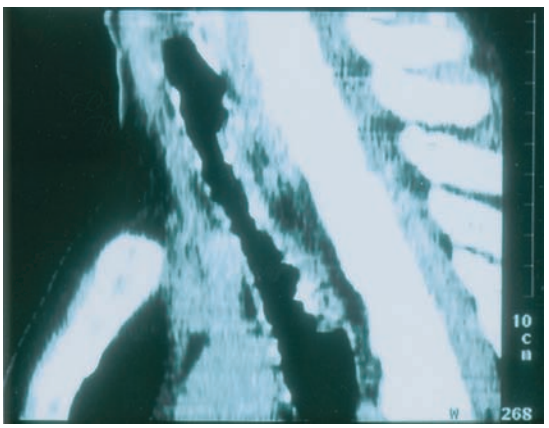


B

Figure 49-10 **A.** Computed tomography scan of the chest demonstrating marked narrowing of the trachea with intraluminal calcified nodular projections in a patient with tracheopathia osteoplastica. **B.** Computed tomography scan of the chest demonstrating multiplanar reformation of the trachea in the sagittal plane of the same patient.

an improvement over conventional CT scanning in that it allows detection of intraluminal, submucosal, and extraluminal lesions (Figs. 49-10A,B and 49-11). Since the early 1990s, HCT has become the preferred noninvasive modality for evaluation of the central airways. The use of HCT using multidetector technology and thin collimation provides high-resolution images of the entire thorax, improved special resolution, greater speed of image acquisition, and

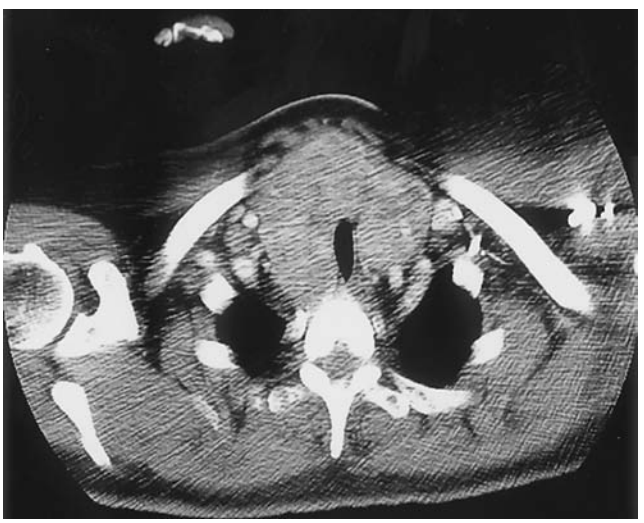
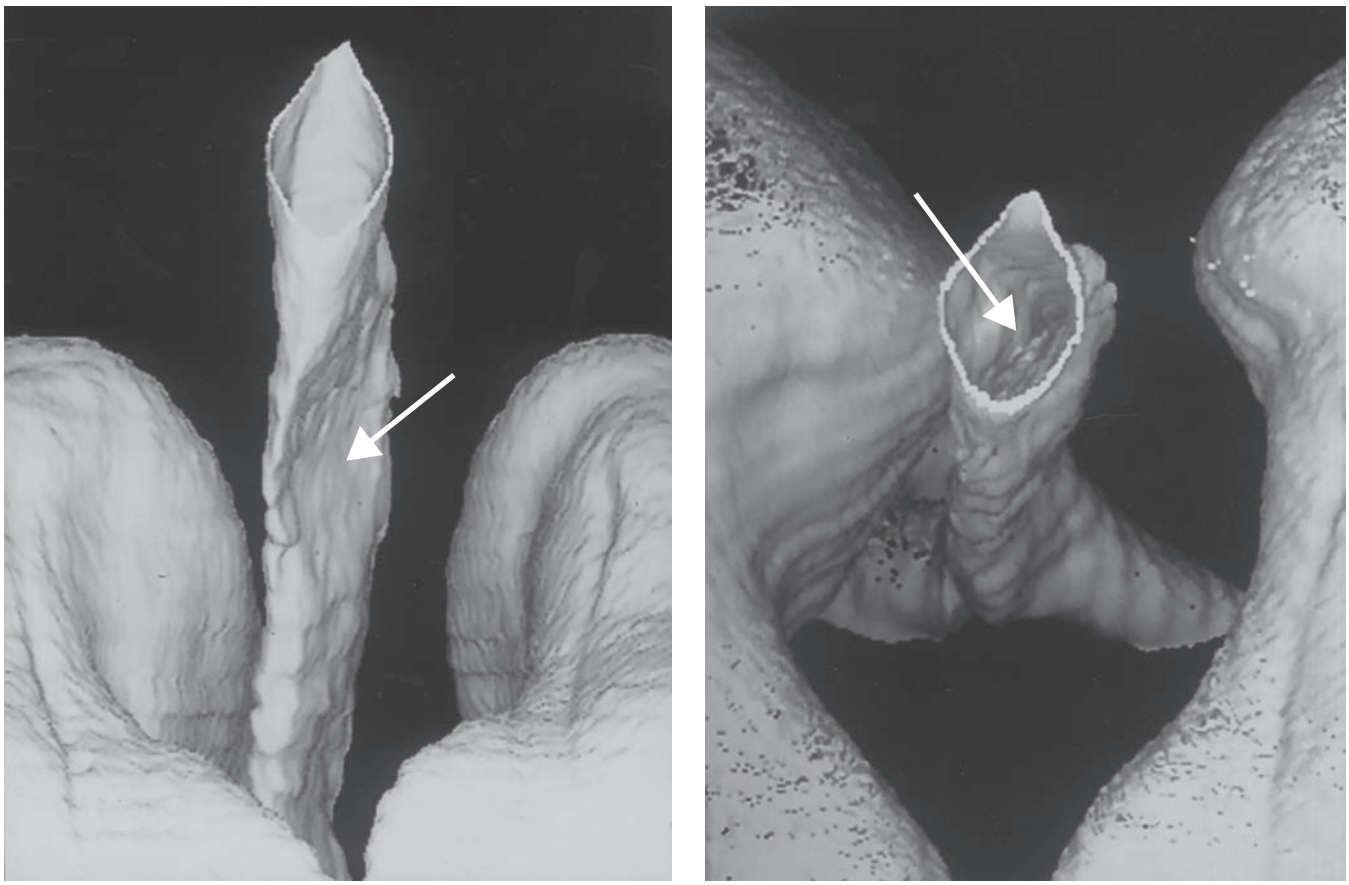


Figure 49-11 Computed tomography scan of the chest demonstrating marked extraluminal compression of the trachea caused by intrathoracic goiter.



A B

Figure 49-12 Helical computed tomography scan of the chest with three-dimensional reconstruction of the upper airway showing focal tracheal compression *(arrows)* (**A, B**.)

excellent contrast enhancement. HCT techniques using multiplanar and three-dimensional reconstruction can provide virtual images of the thorax that enhance the perception of local and diffuse anatomic lesions of the upper airways (Fig. 49-12). The images may demonstrate the degree of tracheal widening or narrowing, show the location and longitudinal extent of abnormalities, assess tracheal wall thickness, and demonstrate associated extratracheal diseases.

The use of paired inspiratory dynamic and expiratory multislice HCT has proved helpful for the diagnosis of tracheomalacia. Because the maximal degree of collapse in tracheomalacia usually occurs during exhalation rather than at end expiration, dynamic expiratory imaging is preferable to end-expiratory imaging. If complete collapse is not demonstrated during expiration, then one should confirm the diagnosis by quantitatively measuring the degree of airway luminal narrowing during expiration. Tracheomalacia is generally defined as a reduction in cross-sectional area of greater than 50% on expiratory images; however, this cut point may not be discriminatory enough to detect clinically significant tracheomalacia.[12]

Another novel CT-based imaging technique is virtual bronchoscopy. The use of volumetric imaging allows for an intraluminal three-dimensional reconstruction of the airways and surrounding tissues. The technique has been used with a high degree of accuracy in assessing the width, length, and contour of fixed airway lesions, but it has not been effective in defining dynamic airway lesions, such as excessive dynamic airway collapse.

Magnetic resonance imaging (MRI) is another modality that may be used to assess the central airways and surrounding mediastinal structures. MRI provides a multiplane image of the chest without the need for contrast material. However, the technique is best used to investigate vascular structures surrounding central airways, such as vascular rings or aneurysms that may compress the trachea, rather than the airways themselves, which are better visualized using CT scanning.

ENDOSCOPY

Bronchoscopy and direct laryngoscopy provide a real-time morphologic and functional evaluation of the upper airway. Imaging techniques are often limited by their inability to document the dynamic nature of many airway lesions and may underestimate the extent of an obstruction.

With respect to laryngeal disease, endoscopy allows the operator to determine whether the vocal cords are mobile or fixed in abduction or adduction or alternatively moving paradoxically. This valuable information can help guide management. In cases of traumatic or thermal injury to the airways, edema, laryngeal fracture, or carbonaceous materials can be readily identified.

CAUSES OF UPPER AIRWAY OBSTRUCTION

UAO may be observed in a wide variety of settings, including infections, trauma (including iatrogenic), vascular disorders, and a wide variety of benign and malignant tumors. Each is discussed below.

INFECTION

A broad variety of infections may eventuate in UAO.

Deep Cervical Space Infections

Deep cervical space infections occur in potential spaces bounded by the deep cervical fascia. The cervical fascia is divided into a

superficial and, a more complex, deep layer. This configuration and complexity divides the neck into functional units. Infection can spread along the planes formed by the cervical fascia. Infections affecting the deep neck tissues may result in life-threatening UAO.

Patients with deep cervical space infections may present with sore throat, odynophagia, neck swelling, pain, fever, and dyspnea. Stridor and profound respiratory difficulty are signs of significant UAO. Parapharyngeal, peritonsillar, submandibular, and retropharyngeal abscesses appear to be common locations in adults. The bacteriology and initiating event of deep cervical infections appear to have changed over time.

Mixed infections caused by aerobic and anaerobic infections are common and have been reported in up to two-thirds of cases.[13] *Streptococcus viridans* and *Klebsiella pneumonia* are common pathogens. *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Escherichia coli*, and *Haemophilus influenzae* are other agents that are commonly reported. Alpha and beta hemolytic *streptococci* appear to have significantly declined in frequency. Overall, an odontogenic origin is probably most common, with upper respiratory tract infections as an important etiology in children. Intravenous drug abuse, mandibular fractures, iatrogenic and noniatrogenic traumatic injury to the upper airway, underlying malignancy, and poor underlying immune status are associated conditions. Ludwig's angina – an infection of the submandibular space and the floor of the mouth – is potentially lethal and is commonly associated with significant UAO. This entity is usually a cellulitic process and can affect the submandibular spaces bilaterally. Many cases with true Ludwig's angina require tracheostomy.

Treatment of deep cervical infections involves maintenance of oxygenation and ventilation by securing an adequate airway, administration of appropriate antibiotics, and when indicated, use of surgical drainage. Complications of deep cervical infections include UAO, Lemierre's syndrome (see next paragraph), distant infection, septic embolization, carotid artery rupture, pulmonary embolism, direct extension of infection resulting in mediastinitis and empyema, and rupture of the abscess during intubation or other interventions.[14]

One particularly virulent cervical infection, known as Lemierre's syndrome, arises from a nasopharyngitis or peritonsillar abscess. This lateral pharyngeal space infection results in suppurative thrombophlebitis of the internal jugular vein, septicemia, and metastatic abscess formation, particularly in the lungs and joints. *Fusobacterium necrophorum* is usually the causative agent and has been cultured from blood in over 80% of cases. Symptoms begin with a sore throat, fever, and painful swelling in the neck, followed by tender lymphadenopathy and tenderness along the sternocleidomastoid muscle (representing thrombophlebitis of the internal jugular vein). Dysphagia, trismus, and UAO may occur as a result of swelling of the lateral pharyngeal space. Contrast-enhanced CT scan of the neck is most useful in establishing the diagnosis of thrombosis of the internal jugular vein and may demonstrate soft tissue abscesses, fasciitis, and myositis, which may require extensive surgical debridement. Without the use of early and appropriate antibiotics, such as high-dose penicillin with metronidazole, or monotherapy with clindamycin, the mortality rate approaches 100%.

Epiglottitis

Epiglottitis is an infectious process that causes variable degrees of inflammation and edema of the epiglottis and supraglottic structures. Supraglottitis may be more appropriate term in adults, since the supraglottic structures usually are involved with variable involvement of the epiglottis. This condition can be life-threatening. Its prevalence is 0.18 to 9.7 cases per million adults; the mortality rate may be as high as 7.1%. Clinical presentation includes odynophagia, with inability to swallow secretions, sore throat, dyspnea, hoarseness, fever, tachycardia, and stridor. In one review, 44% of the patients had a normal routine oropharyngeal examination.[15]

Fiberoptic laryngoscopy is necessary to make the diagnosis. The procedure is safe in adults with suspected epiglottitis and should be done without delay. Radiographic studies can be helpful in ruling out other etiologies with similar presentations and in evaluating potential complications. However, the airway must be secured, and radiographic studies should not delay diagnosis or management.

Supraglottitis may involve the base of the tongue, uvula, pharynx, and false vocal cords. The disease may be increasing in prevalence among adults and declining in children, perhaps, reflecting introduction of *Haemophilus b* conjugate vaccines. Young adult males are commonly affected. The disorder appears to be more prevalent in colder, winter months and in smokers. Blood cultures are positive in less than one-third of cases. Although *Haemophilus influenzae* is the most common organism isolated in children, adult supraglottitis may be caused by a variety of organisms, including *Haemophilus influenzae, pneumococci*, group A *streptococci, S. aureus, Streptococcus viridans*, a variety of anaerobic organisms, mycobacteria, fungi, and viruses. Throat cultures can be helpful in diagnosis and management; however, treatment should not be delayed while awaiting culture results.

Illicit drug use may be associated with epiglottitis, with inhalation of heated objects (e.g., metal pieces from a crack cocaine pipe or the tip of a marijuana cigarette) causing thermal injury to supraglottic structures. Signs, symptoms, and roentgenographic and laryngoscopic findings are similar to infectious epiglottitis.

Initial antibiotic therapy using a third-generation cephalosporin or extended-spectrum penicillin is reasonable. The prevalence of resistant organisms should be taken into account when choosing empiric antibiotic coverage. Corticosteroids often are used in management of acute epiglottitis despite lack of evidence to support their use. Based on anecdotal case reports, epinephrine is also used.

Patients should be observed closely and experienced staff should be available immediately to secure the airway by intubation or surgical approach, if needed. Securing the airway is extremely important in patients who develop stridor and other signs of significant airway obstruction. Mortality in this group has been reported to be as high as 17.6%.[16]

Laryngotracheobronchitis and Bacterial Tracheitis

Laryngotracheobronchitis, often called croup, is commonly seen in children who present with hoarseness, barking cough, shortness of breath, and stridor. This is an acute viral illness characterized by narrowing of the subglottic area. Adult croup is a rare condition. Rare instances of diphtheric croup have been described in adults. Noninfectious membranous tracheitis related to trauma also has been reported.

Acute bacterial tracheitis refers to involvement of the subglottic trachea by bacterial infection and usually follows an episode of viral laryngotracheobronchitis. Thick, purulent exudates and mucosal edema may cause symptoms of UAO. *S. aureus* appears to be the predominant organism. Prompt antibiotic therapy, close observation with attention to airway compromise, and frequent suctioning are important. Data to suggest effectiveness of steroids or epinephrine in adults are lacking.

Rhinoscleroma is a chronic, progressive granulomatous infection of the upper airway that may cause airflow obstruction. This disorder affects primarily the nose and paranasal sinuses, but also may involve the nasopharynx, larynx, trachea, and bronchi. The causative organism is *Klebsiella rhinoscleromatis*. Rhinoscleroma is endemic in Africa, Asia, and South America and is rare in North America. About 5% of patients have diffuse narrowing of the trachea.[17] Prolonged antibiotic therapy with trimethoprim/sulfamethoxazole is effective.

Tuberculosis

The incidence of laryngeal tuberculosis may be on the rise due to the epidemic caused by the human immune deficiency virus. This form of the infection is relatively uncommon, accounting for less than 1% of tuberculosis cases. Laryngeal tuberculosis may present as progressive hoarseness and ulceration or a laryngeal mass. In the appropriate clinical context, a positive purified protein derivative (PPD) skin test and acid-fast bacilli in sputum may suggest the diagnosis. However, a biopsy from the laryngeal abnormality usually is required. Biopsy features include granulomatous inflammation, caseating granulomas, and acid-fast bacilli. The true vocal cords and epiglottis are the areas most affected. Treatment with antituberculous medications is usually adequate and should be instituted promptly, since the disease is highly contagious. Surgical interventions, including tracheostomy, are reserved for airway obstruction and long-term complications and, in one report, were required in 12% of the cases.[18]

Endobronchial tuberculosis may result in significant airflow limitation that is related to the initial lesion or subsequent stricture formation. A barking cough and sputum production are common findings. The diagnosis of tuberculosis can be delayed while the diagnosis of malignancy is being entertained. Early diagnosis and treatment with antituberculous medications should decrease the development of fibrostenosis and resultant airflow limitation. The role of steroids in reducing the incidence of fibrostenotic complications remains unclear and controversial. Management may require endoscopic or surgical approaches.

UPPER AIRWAY TUMORS

Both head and neck cancers and tracheal tumors may cause UAO.

Head and Neck Cancer

The great majority of cancers that impact the upper airway are squamous cell carcinomas, and the incidence of oropharyngeal cancer appears to be increasing in some countries (Fig. 49-13).[19] Other less common cancers occurring in the oropharynx include salivary gland carcinomas, lymphomas, and lymphoepitheliomas. Tobacco and alcohol abuse represent the most significant risk factor for the development of head and neck cancers. Other risk factors may include a diet poor in fruits and vegetables,[20] and infection with the human papillomavirus (HPV), especially HPV-type-16.[21–23] A 23% decline in head and neck cancers has been observed in the United States over the last three decades. The reported incidence was 10.8 cases per 100,000 per year from 2005 to 2009, as compared with 14.6 cases per 100,000 per year from 1976 to 1983.[24,25]

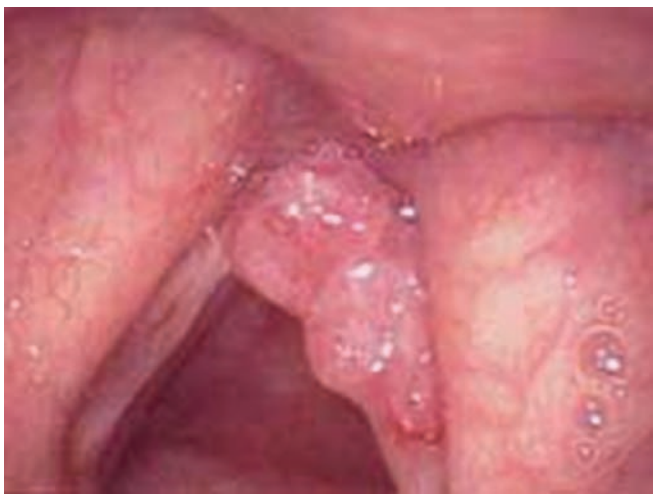


Figure 49-13 Laryngeal squamous cell carcinoma.

The clinical manifestations of head and neck cancer depend on the location and stage. Cancers at the base of the tongue and pharyngeal walls are insidious. These cancers grow either in an infiltrative or exophytic pattern. Because of the lack of pain fibers at the base of the tongue, these tumors are often asymptomatic until they are far advanced. The most common location of a primary tumor of the oropharynx is the anterior tonsillar pillar or tonsil. Symptoms of these cancers include hoarseness, hemoptysis, sore throat, dysphagia, referred otalgia due to cranial nerve involvement, and trismus due to pterygoid muscle involvement. Life-threatening UAO may be seen. Five percent of newly undiagnosed laryngeal cancers (a subcategory of head and neck cancers) present with severe dyspnea or stridor and may require emergency laryngectomy or tracheostomy. Patients who have had head and neck surgery for cancer have a very high prevalence of obstructive sleep apnea.[26]

TRACHEAL TUMORS

Tumors that originate in the trachea are uncommon, and make up only about 2% of all tumors that form in the upper airway. Although rare, when they do occur, approximately 80% of tracheal tumors are malignant. Primary tracheal cancers are rare with a reported incidence of 0.1 per 100,000 per year.[27] Adenoid cystic carcinoma and squamous cell carcinoma comprise the majority of primary malignant tracheal tumors. Squamous cell carcinoma is almost always associated with cigarette smoking. These tumors grow quickly, and in nearly half of cases, they are often too large to be removed by the time they are discovered. Adenoid cystic carcinoma grows much more slowly, and has not been found to be related to smoking. Men and women have the same risk for this type of cancer, and it is commonly diagnosed around the age of 40 years. Dyspnea, cough, hemoptysis, wheeze, and stridor are frequent presenting symptoms. Surgery remains the most effective management. Emergency treatment with procedures to recannulize the airway, including airway stenting, may be necessary pending definitive surgery. Postoperative radiation therapy appears useful for primary tracheal malignancies, particularly when surgical margins are positive. Palliative radiation is used for local control when surgery is contraindicated. Five-year survivals for adenoid cystic and squamous cell carcinomas are reported at 52% and 39%, respectively.[28] Favorable prognostic factors include negative airway margins at the time of resection and adenoid cystic histology.

More commonly, malignancies found in the trachea result from direct extension of primary lung cancer or regional extension to the lymph nodes (Fig. 49-14). Metastases to central airways

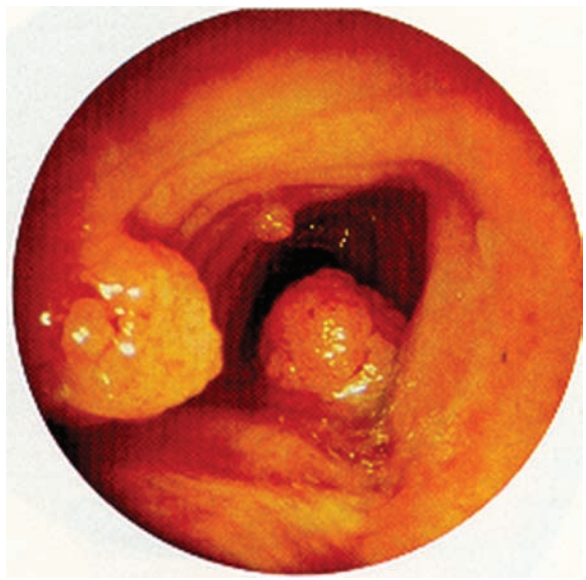


Figure 49-14 Squamous cell carcinoma of the lung.

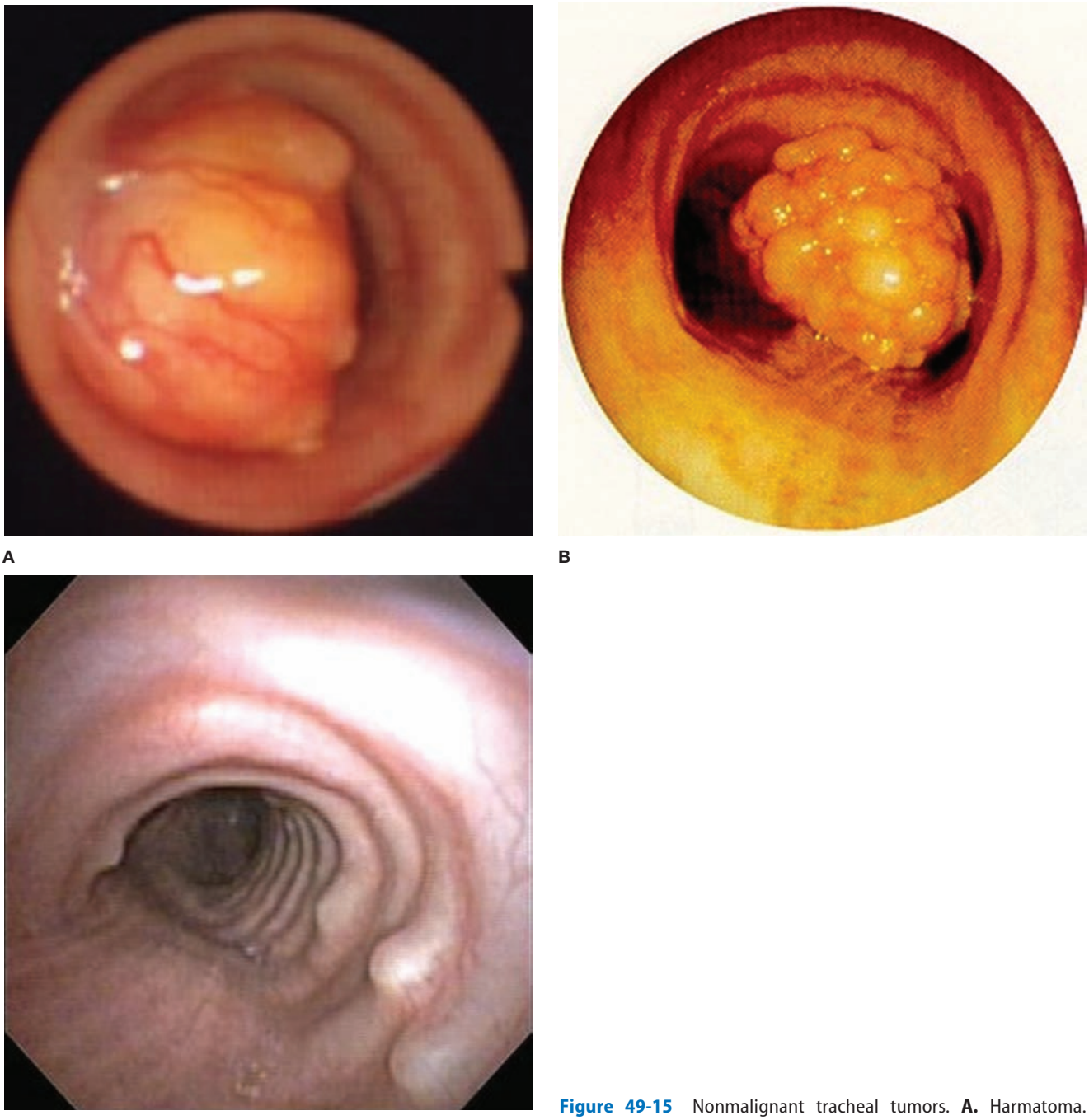


Figure 49-15 Nonmalignant tracheal tumors. **A.** Harmatoma. **B.** Papillomatosis. **C.** Chondromas.

from nonpulmonary malignancies are uncommon, although endobronchial metastases from breast, colorectal, renal, ovarian, thyroid, uterine, testicular, nasopharyngeal, and adrenal carcinomas, as well as sarcomas, melanomas, and plasmacytomas have been described. In an autopsy series of over 1300 patients with solid tumors, metastatic disease to central airways occurred in 2%.[29] The mediastinal lymph nodes are also a common site for disease involvement from hematologic malignancies such as lymphoma.

Nonmalignant tracheal tumors include papillomas, chondromas, and hemangiomas (Fig. 49-15). Chondromas are the most common type of benign tracheal tumor. It is formed from the cartilage rings of the trachea, and has the potential to become malignant over time. Recurrent respiratory papillomatosis in adults, caused by human papilloma virus types 6 or 11 (or, much less commonly, types 16 or 18) may result in UAO and death. Although the larynx is most commonly affected (Fig. 49-16), the tracheobronchial tree may be involved, with a predilection toward areas with prior mucosal injury, including tracheostomy sites and tracheal injuries. Lesions tend to progress down through the tracheobronchial tree. Pulmonary parenchymal involvement is rare, but it may be severe, and bronchiectasis, pulmonary nodules, and abscess formation may occur. Malignant transformation is also possible. The course of the disease is difficult to predict. Recurrent endoscopic interventions (debulking), with attendant risk of airway stenosis, are often required. It is important to minimize intervention unless clinically relevant obstruction exists due to concerns regarding extension secondary to airway injury. No controlled trials on the role of antiviral therapy have been conducted. Available data suggest beneficial effects of intralesional cidofovir. Favorable effects also have been reported with the use of interferon-A. Chemotherapy, radiation therapy, and

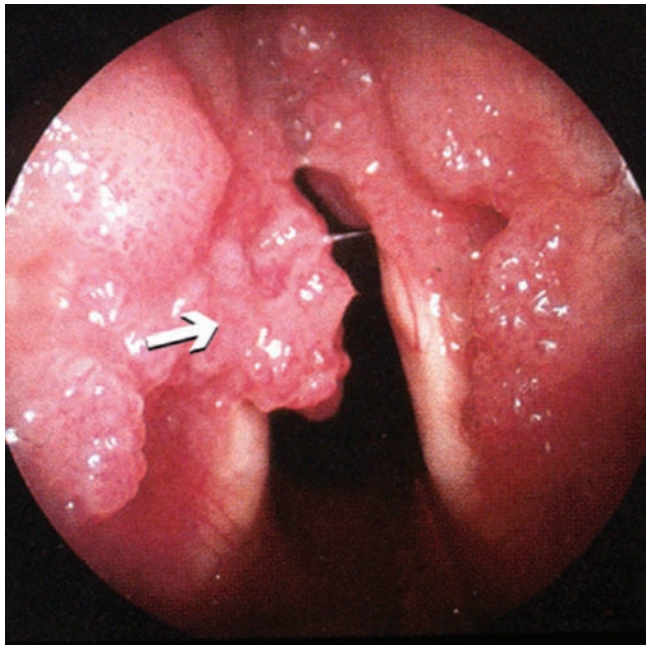


Figure 49-16 Recurrent laryngeal papillomatosis *(arrow)*.

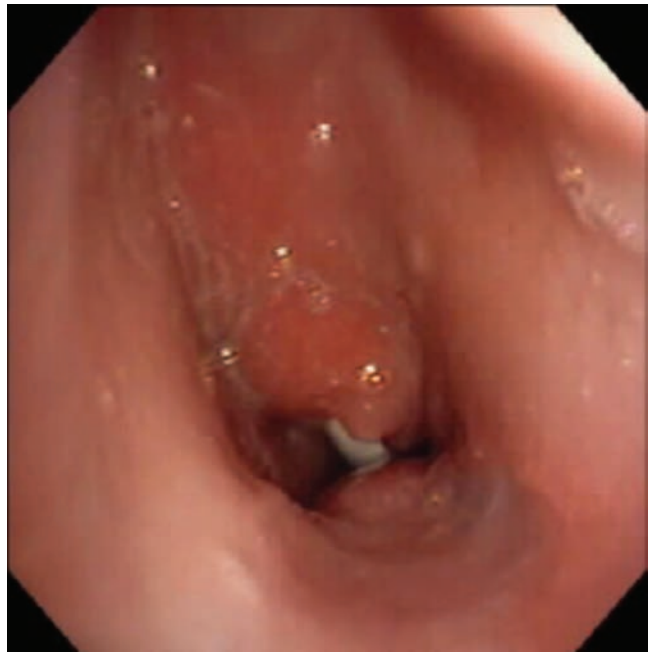


Figure 49-17 Posttracheostomy stenosis.

targeted surgical resection are utilized for confirmed malignant transformation.

■ LARYNGEAL AND TRACHEAL STENOSIS

Common causes of laryngeal and tracheal stenosis include prior intubation and tracheotomy. However, many other causes have been reported.

Postintubation and Posttracheotomy

Concentric scar formation in the larynx or trachea may lead to narrowing and obstruction to airflow. Significant stenosis, defined as obstruction exceeding 50% of the lumen, can lead to serious symptoms and functional limitations.

Endotracheal intubation, tracheostomy, and prior laryngotracheal instrumentation account for most cases of laryngotracheal stenosis. The reported frequencies of tracheal stenosis following tracheostomy or laryngotracheal intubation vary widely (0.6–65%) (Figs. 49-17 and 49-18).[30,31] Although injury to the laryngotracheal airway is common following intubation or tracheostomy, the incidence of symptomatic stenosis, demonstrated by radiographs or bronchoscopy, appears to be much lower (<2%). A recent 8-year retrospective review from Lahey Clinic identified certain patient demographics associated with an increased incidence of postintubation and posttracheostomy stenosis. These included female gender (75%), obesity (66%), diabetes mellitus (35.4%), hypertension (51.6%), and cardiovascular disease (45.1%) and current smoker (38.7%).[32]

Tracheal stenosis in the region of the tube cuff is related to pressure-induced ischemic injury of the mucosa and cartilage and its risk can be minimized by use of large-volume, low-pressure cuffs. The duration of translaryngeal intubation also affects the frequency and severity of laryngotracheal stenosis.

Stenosis following tracheostomy may be above the stoma, at the level of the stoma, at the cuff site, or at the tip of the cannula. Damage to the cartilage above the stoma is a common cause of tracheal stenosis after tracheostomy. In addition to ischemic mucosal injury and ischemic chondritis, anterior and lateral tracheal wall damage, with "buckling in" fractures of the cartilage, is an important factor. The fractures can be minimized by avoiding excessive pressure on the cartilage during the procedure, selecting the appropriate size and length of the tracheostomy tube, avoiding infection, and using the lowest possible cuff pressure.

Percutaneous tracheostomy is growing in popularity as an alternative to the standard procedure. The ideal anatomic site for percutaneous tracheostomy is between the second and third, or the first and second, tracheal rings (not the subglottic space). The incidence of symptomatic tracheal stenosis following percutaneous tracheostomy is comparable to the incidence that occurs after open techniques. When symptomatic tracheal stenosis and tracheomalacia are included as long-term complications, the incidence has been reported to be less than 2.5%.[33]

Other Causes of Tracheal Stenosis

Other causes of laryngeal and tracheal stenosis are uncommon. They include airway trauma, including external injury; inhalational burns, irradiation; tracheal infections, including bacterial tracheitis, tuberculosis, and diphtheria; granulomatosis with polyangiitis

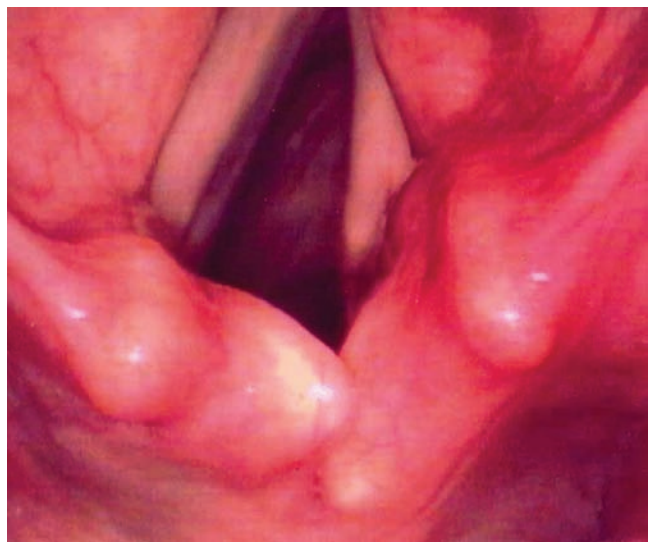


Figure 49-18 Postintubation trauma.

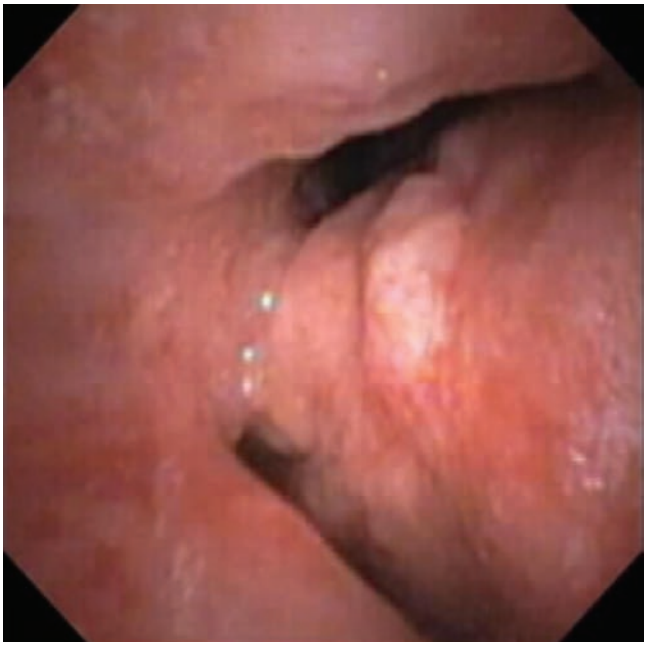


Figure 49-19 Airway sarcoid.

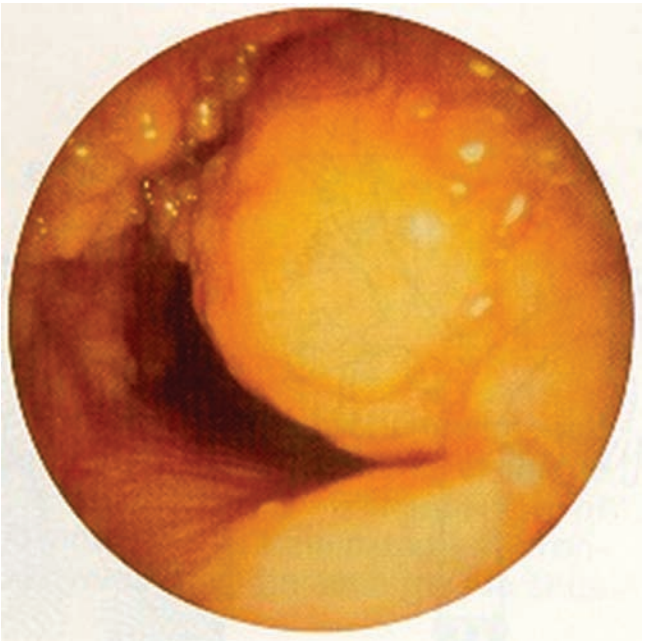


Figure 49-20 Amyloid pseudotumor.

(formerly known as Wegener granulomatosis); sarcoidosis; amyloidosis; collagen vascular diseases, including relapsing polychondritis, polyarteritis; inflammatory bowel disease; and congenital disorders.

Granulomatosis with polyangiitis may present with significant subglottic stenosis, a complication reported in 16% to 23% of patients. Subglottic stenosis may be the only manifestation of Wegener's granulomatosis and have a clinical course distinct from other manifestations of the disease. Endoscopic biopsy of suspected sites of involvement is positive in only 5% to 15% of cases.

Sarcoidosis may be associated with granulomatous infiltration and obstruction of the upper airways (Fig. 49-19). Laryngeal involvement is more common, but tracheal stenosis has been described. Radiographs may show diffuse tracheal stenosis, which progresses despite corticosteroid therapy. Bronchoscopy may reveal extensive tracheal narrowing.

Pulmonary amyloidosis includes tracheobronchial manifestations. The chest roentgenogram may show diffuse narrowing and wall thickening involving a long tracheal segment. Involvement is diffuse and circumferential, often with ossification of the amyloid deposits (Fig. 49-20). Bronchoscopy demonstrates multiple plaques on tracheal walls or localized tumor-like masses.

Relapsing polychondritis is a rare systemic disease characterized by recurrent episodes of inflammation of cartilaginous structures. Respiratory manifestations are often severe and may be life-threatening. Inflammation occurs in all cartilage types, including the elastic cartilage of the ears and nose, hyaline cartilage of all peripheral joints, and axial fibrocartilage. The most common presenting symptom is pain in the external ear due to auricular chondritis. Respiratory tract involvement may develop years after the first occurrence of auricular chondritis. Symptoms include hoarseness, aphonia, and choking. Tenderness over the thyroid and laryngeal cartilages may be present. When the trachea is involved, endoscopic examination shows inflammation and stenosis. CT demonstrates major airway collapse caused by destruction of cartilaginous rings or airway narrowing due to inflammatory edema and fibrosis. CT findings also include diffuse, smooth thickening of the trachea and proximal bronchi; thickened, densely calcified cartilaginous rings; tracheal wall nodularity; and diffuse narrowing of the tracheobronchial lumen. The posterior tracheal membrane is spared.[34]

Tracheopathia osteoplastica is a rare, benign disease of the trachea and major bronchi in which cartilaginous or osseous nodules project into the airway lumen, often causing considerable airway deformity. The posterior membranous portion of the tracheal wall is spared. The disorder may begin just below the larynx, but most often it affects the lower two-thirds of the trachea. Extension into the proximal portions of the major bronchi may be noted. The condition usually occurs over the age of 50 years and may cause severe airflow obstruction. Its etiology is unknown.

On rare occasion, inflammatory bowel disease produces tracheobronchial stenosis and severe airflow obstruction. The associated airway mucosal inflammation may be steroid responsive early in the course of illness. If fibrosis ensues, medical management has limited success.

Laryngopharyngeal reflux may contribute to subglottic stenosis and, when documented, merits treatment.

Idiopathic progressive subglottic stenosis may be diagnosed in the absence of a clear, underlying etiology. Since most affected patients are females, a hormonal etiology has been proposed. However, estrogen receptors have not been demonstrated in specimens studied.[35]

In addition to medical management, repeated rigid and flexible bronchoscopy-based interventions aimed at reestablishing airway patency may be necessary, particularly in those who are not considered to be surgical candidates or in those with simple web-like stenoses. In cases of web-like stenosis, radial incisions sparing the posterior membrane are made and then the airway dilated either using a balloon or the rigid bronchoscope barrel. With respect to more complex stenosis, endoscopic intervention is generally considered a bridge in patients considered good operative candidates with potentially resectable disease. There exists concern on the part of many experts that repeated endoscopic intervention may result in extension of the area of scar rendering potentially resectable stenoses no longer amenable to surgical intervention.[36] Unfortunately resection and reanastomosis is limited by the length of trachea to be resected.[37,38] A multidisciplinary approach incorporating medical and surgical specialists as described by Brichet is utilized in many centers.[39]

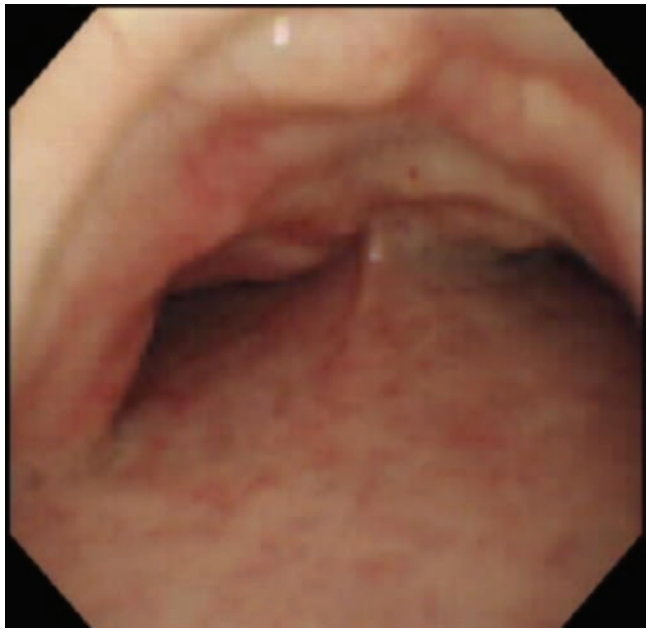


Figure 49-21 Bronchoscopic view of tracheomegaly or Mounier-Kuhn syndrome.

TRACHEOMALACIA

Tracheomalacia refers to loss of tracheal rigidity and resulting susceptibility to collapse. Tracheomalacia may be diffuse or localized to a tracheal segment. The affected portion may be intrathoracic, in which airway obstruction is accentuated during expiration. Less common is extrathoracic obstruction resulting from cervical malacia, in which airway obstruction is most marked during inspiration. Tracheobronchomalacia is the term used to describe the condition when the mainstem bronchi are involved.

Tracheomalacia in adults may be classified as congenital or acquired. The congenital form, described more extensively in children, is related to a variety of congenital disorders and associated syndromes. The disorder may persist into adult life and is referred to as "idiopathic giant trachea," "tracheomegaly," or the "Mounier-Kuhn syndrome" (Fig. 49-21). Bronchiectasis and recurrent respiratory infections are common. Tracheal diverticuli have been reported in more advanced disease. Although atrophy of the longitudinal elastic fibers and muscularis layer has been described, the etiology of these changes is unclear. The diagnosis is made when the diameters of the trachea or right or left mainstem bronchi exceed the upper limits of normal by 3 or more standard deviations. In a recent article by O'Dell, patients with tracheobronchomalacia attributable to Mounier-Kuhn were found to benefit symptomatically from airway stenting and tracheobronchoplasty.[40]

Acquired or secondary tracheomalacia in adults may be related to a variety of conditions.[41] Tracheostomy and endotracheal intubation are probably the most common etiologies. Usually, limited, focal weakness of the trachea and excessive dynamic airway collapse are present. Tracheomalacia may be caused by conditions that are associated with chronic pressure on the tracheal wall, inflammation of the cartilaginous support or mucosa, interference with tracheal blood flow, or chronic infection. Traumatic injury to the central airways or surgical interventions also may lead to tracheomalacia.

Symptoms of tracheomalacia include dyspnea, a seal-barking paroxysmal cough, recurrent pulmonary infections, and respiratory failure in a small subset.[42] Many of these patients will also have decreased exercise tolerance and in severe cases impaired quality of life.

Tracheomalacia is diagnosed by using direct bronchoscopic visualization to confirm significant narrowing of the tracheal lumen during regular, forced expiration. Assessment of the central airways using end-expiratory, dynamic, three-dimensional CT images is useful. Application of continuous positive airway pressure (CPAP) has been reported as beneficial as pneumatic splint for the airways. Tracheobronchoplasty may be useful in selected patients and has been shown to improve quality of life and exercise tolerance.[42] Optimal medical management includes treatment of associated infections and of distal airway disease.

EXTRINSIC COMPRESSION OF THE CENTRAL AIRWAY

The upper airway is subject to extrinsic compression by a variety of pathologies that involve adjacent structures. The compression may affect the intrathoracic trachea or extrathoracic trachea and upper airway.

Mediastinal Masses and Lymphadenopathy

Rarely, mediastinal masses present with serious limitation to airflow that develop either acutely or indolently. Common symptoms include chest pain, fever, dyspnea, and cough. Based on one large series, approximately 40% of mediastinal masses are malignant; 25% are cystic. The anterosuperior compartment is the most common site of mediastinal malignancies. Thymic neoplasms and lymphoma are the most common malignancies, followed by neurogenic tumors and teratomas. Both Hodgkin and non-Hodgkin lymphomas may be manifested by severe respiratory compromise due to airway compression. A similar syndrome may be due to a metastatic tumor to the mediastinal lymph nodes arising from bronchogenic or other carcinomas.

Patients with large mediastinal masses present a challenge during the perioperative period because of the potential for development of acute UAO and other respiratory complications. In adults, complete airway obstruction during induction of anesthesia is rare. Serious pulmonary complications develop intra- and postoperatively in about 4% and 7% of patients, respectively. Complications may occur while the patient is placed in the supine position, during induction, or following extubation. Patients with severe symptoms, including stridor, and those with greater than 50% airway obstruction appear at high risk for respiratory complications; asymptomatic patients are at significantly less risk. Patients with reduced peak expiratory flow and mixed obstructive–restrictive patterns on pulmonary function testing also appear to be at increased risk for postoperative complications.

Middle mediastinal masses include benign cysts that are bronchogenic, enterogenous (duplication), pericardial, pleural, and thymic in origin. Most bronchogenic cysts are asymptomatic. However, some evoke cough, chest pain, and dyspnea. Severe respiratory distress and compressive symptoms can occur. Usually, cyst contents appear to have the density of water on CT or MRI. Mucoid contents may give the impression of solid appearance on CT. Surgical resection and transthoracic or transbronchial drainage are options for management. Surgical intervention appears to be the preferred treatment in patients who are symptomatic. The role of interventions, including surgery, in asymptomatic patients is controversial. Enterogenous cysts are usually removed surgically.

Enlarged mediastinal lymph nodes that compress the airway may arise from infectious and noninfectious benign etiologies. One notable example is fibrosing mediastinitis, defined as the presence of excessive mediastinal fibrous tissue that tends to invade and destroy normal structures. The entity is thought to represent a reaction to an infectious granulomatous disease, especially histoplasmosis. The incidence in populations exposed to histoplasmosis remains low. Constriction of the central airways and vessels and the resulting cardiopulmonary limitations may develop several years after the initial infection. Hemoptysis is common, as are cough, dyspnea, and chest

pain. CT imaging shows mediastinal fibrosis, calcification, and compression of mediastinal structures. Bronchoscopic findings include concentric airway narrowing and mucosal edema with hyperemia. Unfortunately, hemoptysis tends to be recurrent, and the disease does not respond to corticosteroids or antifungal agents. Surgical intervention is generally ineffective and may be hazardous.

Neck and Thyroid-Related Causes

Retrosternal extension of a diffuse goiter may cause extrathoracic or intrathoracic airway obstruction. Up to 90% of patients with substernal goiter report respiratory symptoms. A choking sensation occurs in about one-third of patients with diffuse thyroid enlargement and 14% in patients with solitary thyroid nodules. Orthopnea is prevalent when the goiter is intrathoracic and may be enhanced by obesity. Flow–volume loops show evidence of UAO in one-third of patients. Lack of correlation has been reported between symptomatic obstruction and CT findings.[43]

Laryngoceles and saccular cysts, which are abnormal dilatations of the laryngeal saccule (ventricle), are uncommon. Saccular cysts usually are filled with mucus. Laryngoceles communicate with the laryngeal lumen, resulting in air-filled structures noted on radiographic studies. Laryngoceles may be internal (i.e., confined to the larynx), external (i.e., extending into the thyrohyoid membrane superiorly), or combined. Most are asymptomatic. Hoarseness, dysphagia, pain, or signs of airway obstruction or infection may occur. A neck mass during the valsalva maneuver may be detectable. Pyocele formation (i.e., infection in the laryngocele) may result in airway obstruction, aspiration pneumonia, or infection of the lateral pharyngeal space. The incidence of laryngeal carcinoma in association with laryngoceles makes close evaluation necessary. Endoscopic and surgical approaches may be employed in management.

Parathyroid cysts may be located in the neck or mediastinum. Fifty percent are accompanied by clinical hyperparathyroidism. Paroxysmal symptoms of airway obstruction can develop. Surgical excision is the treatment of choice; results are generally good.

Cervical osteophytes, common in the elderly, are related to either degenerative spinal arthritis or more generalized idiopathic skeletal hyperostosis; the osteophytes may be associated with dysphagia. In addition, airway narrowing and ulcerations due to osteophytes have been reported. The airway compression may make even elective endotracheal intubation difficult, despite adequate preoperative evaluation.

Finally, significant upper airway compression may arise from cervical lymph node involvement with infectious or malignant disorders, hematomas or pseudoaneurysms (related to trauma, surgical interventions, central line placement, or coagulation abnormalities), abscess formation, or other expanding lesions in the soft tissue of the neck.

Diseases of the Esophagus

Involvement of the trachea, glottis, or vocal cords by advanced esophageal cancer is common and associated with a poor prognosis; estimated 1-year survival is less than 10%. Airway obstruction requiring stent placement is associated with a median survival of 1 to 4 months after the placement. Tracheal obstruction may develop if an esophageal stent is placed in the setting of significant tracheal compromise. Development of tracheoesophageal fistula represents a devastating complication.

Placement of stents simultaneously in the trachea and esophagus is effective palliation for a tracheoesophageal fistula.[44] If such double stenting is anticipated for a fistula or for simultaneous esophageal and tracheal obstructions, the tracheal stent is placed first to ensure patency of the airway, followed by the esophageal stent. Palliative external or local radiation therapy, chemotherapy, or other treatment modalities (e.g., PDT) may be effective with or without accompanying airway interventions. The risk of esophageal disruption and rupture should be considered if stenting is performed after these local measures are employed.

Achalasia may cause a variety of pulmonary complications, including cough, aspiration with pneumonia or abscess formation, and rarely UAO. Tracheal compression by a dilated megaesophagus is the usual etiology. Ensuring patency of the airway and decompressing the esophagus are necessary in urgent management.

Vascular Abnormalities

Vascular rings, defined as anomalies of the aortic arch or its branches that compress the trachea or esophagus, are rare in adults (incidence <0.2%). Respiratory symptoms are common.

Right-sided aortic arch occurs in less than 0.1% in adults and may be associated with complete vascular rings, while double aortic arch and right-sided aortic arch with aberrant left subclavian artery appear to be the most common etiologies of vascular rings in adults.

The right-sided aortic arch usually crosses over the right mainstem bronchus and descends on either the right or the left side. The vascular ring is usually completed by the ligamentum arteriosum arising from the descending aorta, an aberrant left subclavian artery, or an aortic diverticulum. With a double aortic arch, the left arch crosses over the left main-stem bronchus and joins the descending aorta to complete the ring; the ligamentum arteriosum does not contribute to the vascular ring. Symptoms, resulting from malacia of the compressed airway and resultant dynamic airway obstruction, may be misdiagnosed as exercise-induced asthma. An increase in aortic diameter due to rising blood pressure during exercise, intravenous fluid administration, or anatomic changes with aging may contribute to symptoms. Surgical intervention is indicated in symptomatic patients.

Pulmonary artery sling with anomalous origin of the left pulmonary artery from the right pulmonary artery is very rare in adults. In neonates, the condition is symptomatic and can be fatal without surgical intervention. However, in adults the condition is usually diagnosed incidentally on imaging a patient who has no significant symptoms. This disorder may be associated with a complete tracheal ring, forming the "sling-ring" complex. This condition may present with a right paratracheal mass noted on the chest radiograph.

Compression of the trachea by large aortic or innominate artery aneurysms or pseudoaneurysms may occur and complicate management in the perioperative period. Surgical repair is indicated to relieve symptoms.

FOREIGN BODY ASPIRATION

Foreign body aspiration, more common in children than adults (in whom the peak incidence is in the sixth decade), is usually recognized from the patient's history. Foreign bodies commonly lodge in the bronchi after migrating through the trachea. In adults, food products are the most commonly aspirated material. The penetration syndrome, defined as the sudden onset of choking and intractable cough after aspirating a foreign body, with or without vomiting, is often followed by persistent cough, fever, chest pain, dyspnea, and wheezing. Impairment of the normal protective airway mechanisms is common; among the frequent associations are neurologic disorders, trauma with loss of consciousness, sedative or alcohol use, poor dentition, and advanced age. Emergency measures, entailing a food extractor or the Heimlich maneuver, can be life-saving. Flexible bronchoscopy is usually successful in removing foreign bodies, although back-up rigid bronchoscopy should be available and is preferred as the primary procedure at some centers. A complicating chemical bronchitis from aspiration of vegetables or nuts may affect visualization and management of the foreign body. Certain nut oils also cause a significant foreign body mucosal reaction resulting in the development of granulation tissue that may be misdiagnosed as endobronchial tumor.

TRAUMA

A variety of traumatic injuries may eventuate in UAO.

Facial Trauma

Emergency access to the airway is necessary in up to 6% of cases of facial trauma complicating motor vehicle accidents and other causes of crush injuries. If intubation is difficult or impossible due to the injury or related airway obstruction, emergency cricothyroidotomy or tracheostomy must be considered.

Laryngotracheal Injuries

Blunt and penetrating injuries to the laryngotracheal airway are rare. Without a high index of suspicion, clinicians may miss the diagnosis. The incidence of penetrating injuries appears to be increasing.

Stridor, wheezing, dysphonia, hemoptysis, and general neurologic deficits are common. Cervical crepitus and subcutaneous emphysema also may be present. Cervical ecchymoses and hematomas, pneumomediastinum, and pneumothorax should prompt consideration of a laryngotracheal injury.

Management includes prompt securing of the airway, but blind endotracheal intubation should be avoided, since it carries the risk of complete airway obstruction. Some experts recommend tracheostomy as the primary airway management strategy. Awake fiberoptic intubation can be useful. Flexible fiberoptic laryngoscopy, rigid or flexible bronchoscopy, and CT imaging may be helpful in assessing the degree of injury. Unfortunately, the mortality of laryngotracheal injuries remains high (20%–40%). Thoracic injuries and closed head injuries are commonly associated pathologies that can influence management and prognosis.

Inhalation Injuries

Thermal and chemical injuries to the upper respiratory tract may lead to serious consequences, including airway obstruction. Unfortunately, the mortality rate increases significantly when burns are accompanied by inhalational injury. Symptoms can be delayed in becoming manifest, making early recognition and intervention vital in the management of patients with inhalational injuries. The presence of cough, dyspnea, hoarseness, or loss of consciousness, or the findings of singed nasal hairs, carbonaceous sputum, or burns involving the face indicate a high likelihood of inhalation injury.

Early flexible bronchoscopy remains important in evaluation and management of patients with inhalation injuries, enabling the assessment of the extent and severity of the injury, procurement of samples for bacteriologic studies, and bronchoscopic intubation, as necessary. Translaryngeal intubation is the standard method of securing the airway in inhalation injury; early tracheostomy is used in some centers. A role for prophylactic corticosteroids or antibiotics is currently not supported by published reports. Significant tracheal stenosis may develop in patients who survive the initial insult, especially when translaryngeal intubation or tracheostomy is necessary.

ENDOTRACHEAL TUBE–RELATED TRAUMA

Postextubation stridor due to glottic edema, laryngospasm, or laryngotracheal stenosis is a serious event. Reintubation rates for UAO due to endotracheal tube–related trauma in critically ill patients have been reported to range from 4% to 33%. An "acceptable" rate is considered to be 5% to 15%. The cuff leak test does not accurately predict success or failure of extubation. Although the efficacy of corticosteroids or racemic epinephrine in the management of postextubation stridor is not substantiated, both are used extensively in clinical practice.

Translaryngeal intubation may also produce vocal cord paralysis, accounting for 10% to 15% of all cases. Paralysis may be unilateral or bilateral. Affected patients may present with hoarseness or airway obstruction. Findings may occur immediately after extubation or be delayed. Prolonged intubation, use of a large endotracheal tube (number 8 or larger), placement of the tube cuff close to the vocal cords, or use of excessive cuff pressure are risk factors. The condition usually resolves spontaneously within 10 weeks.

Vocal cord (contact) granuloma may develop 4 to 6 weeks after intubation. Symptoms include prolonged hoarseness, exertional dyspnea, and stridor. Management, using antireflux medications, inhaled and systemic corticosteroids, antibiotics, botulinum toxin injection, speech therapy, smoking cessation, and rest of the voice are usually successful. Surgical intervention is reserved for cases that fail conservative management.

On occasion, dislocation of the arytenoid cartilages occurs during intubation. Rheumatoid arthritis that affects the cricoarytenoid cartilage is a risk factor for this condition. Rigid bronchoscopy or surgical interventions may be needed to reduce the dislocation. Other disorders that may cause complications during intubation include hyperostosis of the cervical spine due to ankylosing spondylitis and cricoarytenoid joint disease due to systemic lupus erythematosus.

NEUROMUSCULAR DISORDERS

Neuromuscular disorders may affect the bulbar muscles, many of which surround the upper airway (Fig. 49-22). When this occurs, resistance to airflow is increased, and the flow–volume loop often shows an inspiratory flow plateau typical of variable extrathoracic UAO. In addition, a pattern of flow oscillations during inspiration ("sawtooth pattern") may be seen.[45] The abnormal flow pattern, first noted in patients with sleep apnea,[46] is commonly seen in extrapyramidal disorders, myasthenia gravis, and motor neuron disease; it may also be seen in patients who have functional stridor and wheezing (see Vocal Cord Dysfunction section). In extrapyramidal disorders, the flow oscillations correspond to vocal cord tremor. In motor neuron diseases, muscle denervation causes irregular muscle fasciculation, resulting in tremor of upper airway muscles.

Upper airway symptoms may be seen in Shy–Drager syndrome with extrapyramidal involvement and in Parkinson disease.[47,48] Patients may present with symptoms of chronic dyspnea or with stridor and respiratory failure relieved by endotracheal intubation or tracheostomy. Bilateral vocal cord paralysis may also occur with familial bulbar spinal muscle atrophy, postpoliomyelitis syndrome,

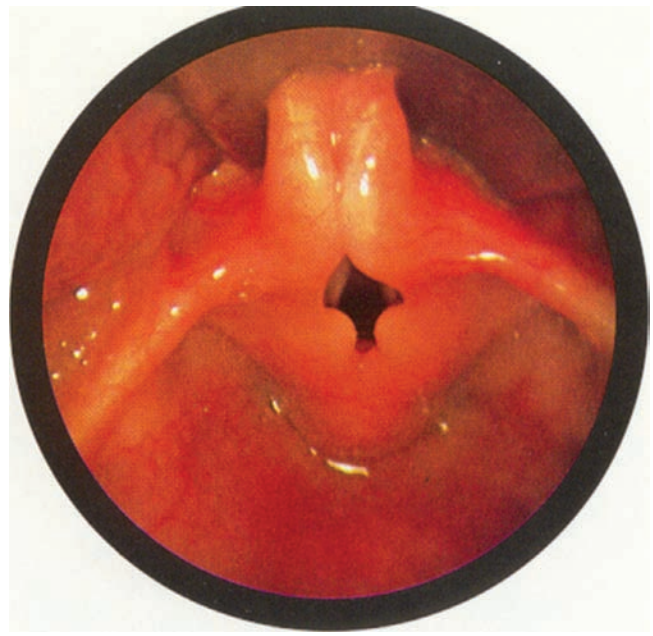


Figure 49-22 Laryngomalacia.

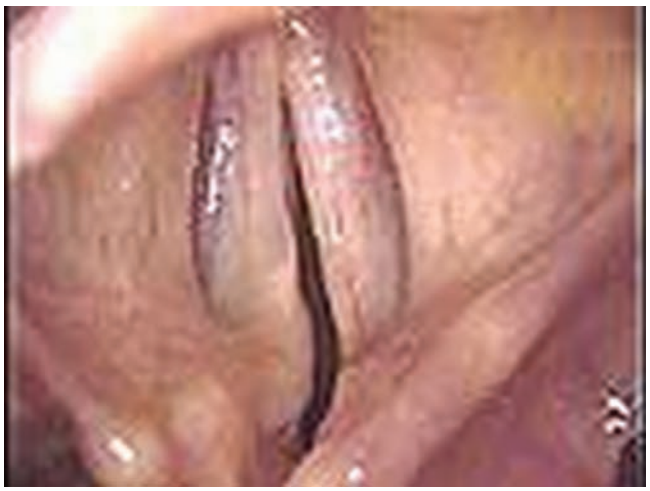


Figure 49-23 Bilateral vocal cord paralysis.

Parkinson disease, multiple sclerosis, acute poliomyelitis, amyotrophic lateral sclerosis, Guillain–Barré syndrome, brain stem stroke, and large cerebral hemisphere stroke. Dystonic extrapyramidal reactions due to neuroleptic medications (e.g., haloperidol) may cause significant UAO. The usual reactions to these medications are akathisia, dyskinesia, dysarthria, and dystonic reactions, such as torticollis. Laryngeal–pharyngeal dystonia may cause severe upper airway dysfunction, and if not reversed, symptoms can last for days or lead to respiratory arrest.

BILATERAL VOCAL CORD PARALYSIS

Bilateral vocal cord paralysis is a serious condition resulting in nocturnal stridor, oxygen desaturation, sleep disruption or, in extreme cases, acute respiratory failure (Fig. 49-23). Thyroidectomy is the most common cause of bilateral recurrent laryngeal nerve injury, with its consequent bilateral vocal cord paralysis.[49] As mentioned earlier, bilateral vocal cord paralysis may occur with numerous neurologic conditions. Nonneurologic causes include endotracheal intubation injury, laryngeal trauma, infection, and thoracic aortic aneurysm. Bilateral vocal cord paralysis results in abnormalities of inspiratory flow and a distinctive flow–volume loop.

Spontaneous recovery of vocal cord motility is rare after surgical injury of the recurrent laryngeal nerve. For those patients showing no spontaneous functional recovery, several surgical techniques to achieve a glottic space enlargement are available. CO_2 laser endoscopic surgery has led to shorter hospitalization and higher patient compliance.[50,51] Endoscopic surgeries include arytenoidectomy with or without posterior true and false cord cordectomy. Surgeries aim to improve breathing with minimal deglutition impairment and improve quality of voice. Restenosis of the glottis space is the main problem that leads patients to reoperations.

VOCAL CORD DYSFUNCTION

The glottis plays an active role in adjusting airflow, both voluntarily and through reflex control from laryngeal and lung receptors. During a normal respiratory cycle, the vocal folds widely abduct during inspiration and slightly adduct during expiration. Occasionally, the glottis can become dysfunctional in the absence of organic disease. The disorder, most commonly called vocal cord dysfunction or paradoxical vocal fold motion, is characterized by paradoxical closure of the vocal cords intermittently during inspiration. The glottis angle formed by the true vocal folds can become acute and cause airflow obstruction during inspiration and/or expiration. The mechanism is unknown, but likely multifactorial. Laryngeal hypersensitivity has been associated with reflux, upper respiratory tract infections, postnasal drip, irritants, exercise, as well as psychogenic factors.

Signs and symptoms of vocal cord dysfunction resemble those of laryngeal edema, laryngospasm, vocal cord paralysis, or asthma. Wheezing or stridor and shortness of breath are typical and are often so dramatic that they suggest acute asphyxia and respiratory failure. Intubation and other emergency measures are used frequently. However, symptoms are often brief and may remit without intervention. Distinguishing physical examination findings include tracheal localization of wheezing or stridor with absent peripheral airway expiratory wheezing; however, it should be understood that this might also occur during severe asthma attacks.

On pulmonary function testing, patients with vocal cord dysfunction typically have normal spirometry without evidence of obstructive ventilatory defect. Some may demonstrate a pattern of variable extrathoracic airway obstruction, resulting in an increase in the ratio of $FEF_{50\%}$ to $FIF_{50\%}$. Some patients show a pattern of "sawtoothing," or fluttering of the inspiratory limb of the flow–volume loop, representing fluctuations in the abnormal cord motion (Fig. 49-24). Often, attempts to perform the flow–volume loop maneuver generate variable results from test to test. A normal alveolar–arterial oxygen gradient and absence of bronchial hyperresponsiveness are other clues to the diagnosis.

The diagnosis of vocal cord dysfunction is confirmed during direct visualization of the vocal cords during an attack. The anterior

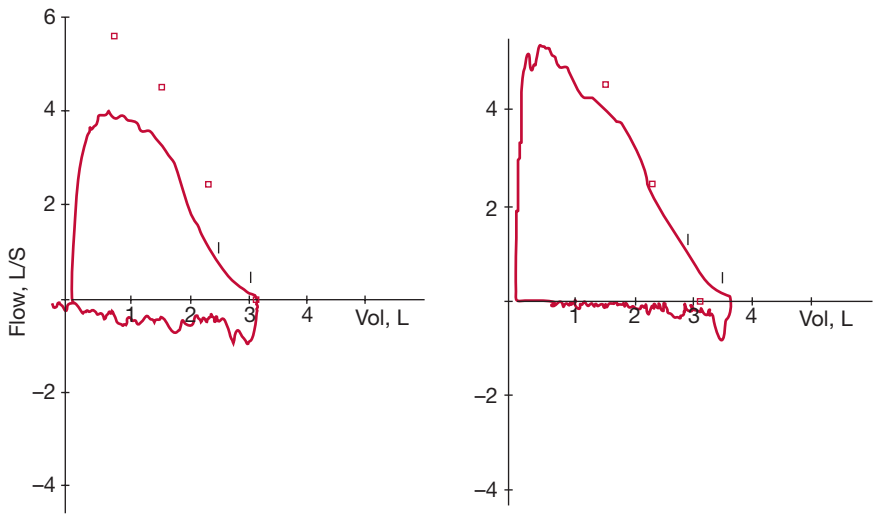


Figure 49-24 Variable extrathoracic obstruction due to vocal cord dysfunction. Two consecutive flow–volume loops from a young woman with inspiratory stridor. Variable effort accounts for the differences in configuration. $FEF_{50\%}/FIF_{50\%}$ in each is very high. The inspiratory loop is flat and demonstrates a sawtooth pattern. This pattern has also been associated with sleep apnea syndrome and various neuromuscular disorders.

two-thirds of the vocal folds adduct and give the presence of a posterior diamond-shaped chink in the folds during inspiration.[52]

The true prevalence of the disorder is unknown because it is often mistakenly diagnosed as asthma, and many patients in fact have both vocal cord dysfunction and asthma. Patients without asthma are predominantly women who have been misdiagnosed as having asthma for an average of 5 years. Typically, patients have been treated with large doses of oral corticosteroids, and have experienced frequent emergency room visits, hospitalizations, and endotracheal intubations.

Psychiatric disorders are common in these patients. Major psychiatric disorders, personality disorders, and sexual and physical abuse are commonly uncovered. Whereas many patients are unaware of their self-induced wheeze or stridor, others appear to derive secondary gain from their symptoms and manifest factitious illness. A high index of suspicion is warranted when the adventitious sounds are loudest over the neck in a patient who presents with wheezing, stridor, or both. Despite their respiratory distress, patients often have little difficulty completing full sentences and can hold their breath; the laryngeal-induced sounds disappear during a panting maneuver.

Treatment includes discussion of the diagnosis with the patient, discontinuation of unnecessary medications, and referral to a speech therapist or psychotherapist. The response to bronchodilator therapy is usually poor. Administration of an inhaled helium–oxygen mixture may alleviate symptoms during an acute attack.

ANGIOEDEMA

Angioedema is characterized by well-demarcated swelling of the face, lips, tongue, and mucus membranes of the nose, mouth, and throat. When the larynx is involved, UAO may occur and is fatal in as many as 25% of patients. In most instances, the cause of angioedema is unclear; prior exposure to common allergens, such as drugs, chemical additives, and insect bites should be suspected.

Contrary to what might be thought, the most common causes of angioedema are not IgE initiated. They include reactions to histamine-releasing drugs, such as narcotics and radiocontrast materials, to aspirin and other nonsteroidal anti-inflammatory drugs, and to angiotensin-converting enzyme inhibitors. Hereditary angioedema, a rare cause of UAO, is an autosomal-dominant trait that occurs in all races. The underlying mechanism is a deficiency in production or function of C1 esterase inhibitor, a serum protease inhibitor that regulates the complement, fibrinolytic, and kinin pathways. Hereditary angioedema is characterized by painless nonpitting edema of the face and upper airway. The disorder usually begins in childhood and becomes more prominent in adolescence. Swelling progresses over many hours and then resolves spontaneously over 1 to 3 days. Despite the slow progression, death may occur from laryngeal obstruction. Physical stimuli (cold, heat, stress) and circulating immune complex diseases (e.g., due to serum sickness or systemic lupus erythematosus) are also known to cause angioedema.

Emergency management includes foremost securing the airway. Epinephrine is used for allergic angioedema. Administration of corticosteroids and antihistamines are often used, although current evidence suggests that such a therapy is rather ineffective in kinin-induced angioedema.[53] Thus, symptom-related medical care should be provided until the swellings have disappeared. Approaches targeting the kallikrein–kinin system, such as kallikrein inhibitors[54] and bradykinin type-2 receptor antagonists[55] may improve pharmacotherapy. It is probable that these drugs may also be beneficial in patients with bradykinin-mediated drug-induced angioedema.

MISCELLANEOUS ETIOLOGIES

Postpneumonectomy syndrome refers to compression of the left main bronchus between the aortic arch and left pulmonary artery following a right pneumonectomy. The syndrome also may be seen following a left pneumonectomy, sometimes in the setting of a right-sided aortic arch. Mediastinal repositioning prostheses, with or without additional fixation methods, may be useful in selected patients.

Mucus ball formation related to transtracheal oxygen catheters has been described. Although transtracheal oxygen delivery decreases supplemental oxygen flow requirements by approximately 50% during rest and 30% during activity, development of symptomatic mucus balls (occurring in up to one-third of patients) remains a major disadvantage of the technique. Death and life-threatening events secondary to airway obstruction have been reported.

MANAGEMENT OF UPPER AIRWAY OBSTRUCTION

Key elements in the management of UAO include general principles, securing the airway, and specific interventions.

GENERAL MANAGEMENT

The primary goals in management of any patient with UAO are assurance of adequate oxygenation and ventilation and management of the underlying condition. If airway obstruction is partial, and the patient's condition is stable, close monitoring and diagnostic studies are appropriate. Depending upon the underlying etiology, temporary measures may include close observation in an intensive care unit, elevation of the head of the bed, administration of humidified oxygen, use of a helium–oxygen inhalation mixture (see next paragraph), systemic corticosteroids, and inhaled racemic epinephrine, pending definitive medical or surgical management.

A helium–oxygen gas mixture (heliox) may be useful in management of UAO when the obstruction is temporary and reversible. The physiologic rationale for heliox is based upon a reduction in work of breathing achieved through administration of a low-density gas. In particular, heliox has a lower density than does oxygen, room air, or a mixture of the two, resulting in conversion of the predominantly turbulent flow at the site of obstruction to a more laminar pattern. Furthermore, since laminar flow requires a smaller pressure gradient than turbulent flow to achieve the same flow rate, the accompanying work of breathing is less (see Chapter 10). The major limitation of the modality is an inability to deliver gas with an inspiratory fraction of oxygen ($F_{I_{O_2}}$) of more than 40%. Despite physiologic evidence and clinical reports of efficacy, prospective, randomized studies demonstrating improved outcome in patients receiving heliox are lacking, as are data supporting use of corticosteroids or inhaled epinephrine in airway obstruction from a variety of causes.

SECURING THE AIRWAY

Although under controlled circumstances, a significant portion of the so-called difficult airways and intubations may be identified in the course of a thorough preoperative assessment, the patient with impending airway obstruction presents a challenge. Under such circumstances, a critical first concern is deciding whether an artificial airway is needed emergently.[56] Regardless of the airway utilized, emphasis is placed on ensuring adequate oxygenation and ventilation.

Airways judged unsafe for routine management may be addressed according to the "difficult airway algorithm" recommended by the American Society of Anesthesiologists (see also Chapter 146).[57] A difficult airway is defined as a clinical circumstance in which a conventionally trained anesthesiologist experiences difficulty using face mask ventilation, endotracheal intubation, or both.

Airway access in emergency situations may be challenging because the patient frequently is critically ill and can deteriorate quickly. The likelihood of a difficult intubation can be estimated by using the Mallampati score or a modification of the score to assess potential laryngeal exposure and prospects for adequate airway visualization.

A number of parameters, such as mouth opening distance, jaw size, thyromental distance, and cervical range of motion, have been

incorporated into airway assessment scoring systems; each parameter has limited sensitivity and specificity. Combining scoring systems provides better accuracy of prediction. The "rule of threes," which is a useful, simple bedside tool, predicts successful direct laryngoscopy if the examiner can place three finger breadths (~6 to 7 cm) between the upper and lower teeth, the mandible and hyoid bones, and the thyroid cartilage and sternal notch. In the emergency setting of UAO, the most experienced physician available should secure the airway. Appropriate equipment and monitoring, along with back-up resources for alternative and invasive airway management, should be available.

A variety of invasive and noninvasive techniques are available as alternatives to standard, laryngoscopy-guided orotracheal intubation. Invasive methods include surgical and/or percutaneous tracheostomy, surgical and percutaneous transtracheal (needle) cricothyrotomy, translaryngeal guided or "retrograde" intubation, fiberoptic endotracheal intubation, and use of a rigid ventilating bronchoscope. Noninvasive techniques include use of specialized laryngoscope blades, Glidescope™, guiding and lighted stylets, directional tip control tubes, and esophageal–tracheal (Combitube) or laryngeal mask airways. In selected circumstances, tactile intubation, nasotracheal intubation, or blind orotracheal intubation may be employed.

CRICOTHYROIDOTOMY

Cricothyroidotomy (either surgical or based on Seldinger technique) has a long history of use in emergency access to the airway when more conservative approaches fail or are contraindicated. Currently, surgical cricothyroidotomy is performed by surgeons, anesthesiologists, and intensive care specialists. In early reports, a high incidence of laryngeal stenosis during intermediate and long-term follow-up was noted, perhaps related to the presence of infectious laryngeal disease or the use of large-bore tubes. In addition, the risk of subglottic stenosis also appears high in patients with prolonged prior intubation. Hence, although the procedure is useful for short-term airway control, tracheostomy should be considered if prolonged airway access is required.

TRACHEOSTOMY

Most tracheostomies are performed on intubated patients in the intensive care unit. Percutaneous tracheostomy is rapidly becoming the method of choice in the intensive care unit and is associated with acceptable intraoperative and postoperative complication rates. Advantages of the technique over the traditional procedure include low cost, short procedure time, low complication rate, and elimination of the need to transport critically ill patients to the operating room. Adaptation of percutaneous techniques for emergency situations also has been described.

In a review of over 1100 patients who underwent tracheostomy, 76% were performed in patients who required prolonged ventilation, 6% for UAO, 7% for extensive maxillofacial trauma, and 11% as an adjunct for head and neck or chest surgeries; only 0.26% were performed as emergency procedures. Overall mortality was 0.7%.[58]

INTERVENTIONAL BRONCHOSCOPIC TECHNIQUES

Interventional bronchoscopy is discussed in chapter 36. Use of these techniques for managing UAO is well established and is briefly summarized in the following paragraphs.

Rigid bronchoscopy allows oxygenation, ventilation, and application of various diagnostic and therapeutic interventions, including debridement of obstructing lesions, control of bleeding, and removal of foreign bodies. Complications include anesthetic risks, barotrauma, damage to teeth, lips or gums, airway perforation, bleeding, and mucosal injury.

Thermal modalities may be used to devitalize tissue prior to mechanical debridement or to cauterize the base of lesions following debulking. Electrocautery, laser (Nd-Yag, CO_2, i.e., Yap), argon plasma coagulation, and cryotherapy can be applied through rigid or flexible bronchoscopy. Side effects include bleeding, perforation, airway fire and damage to cartilage.

Photodynamic therapy is based on the principle of targeted tissue apoptosis after local activation of a systemically injected photosensitive chemotherapeutic agent. In essence, PDT creates a phototoxic cell reaction when nonthermal laser light is applied by bronchoscopy and activates a drug trapped in these target cells. The major disadvantage of this technique is that the tissue necrosis occurs within 48 to 72 hours and as such the ability to debride the airway is delayed for several days. Bleeding and obstruction from necrotic tumor and edema are potential immediate complications. PDT may also result in airway perforation.

Standard cryotherapy, based on repeated freeze–thaw cycles to achieve cell necrosis and tissue damage is used in benign and malignant disorders of the upper airway. Cryotherapy has excellent hemostatic effects; the incidence of perforation or bleeding is low. Due to the delayed beneficial effect, cryotherapy is not usually used under emergent conditions. In recent years a cryobiopsy technique has been developed in which the tissue is simply frozen to the probe and then sheared from the surface, obviating the thaw cycle. Applied in this fashion, cryotherapy can be used for the immediate treatment of airway obstruction. In addition, cryotherapy has the advantage over other thermal modalities in that cartilage is cryoresistant.

Finally, external beam radiation and brachytherapy are useful modalities for palliative management of airway obstruction and hemoptysis. For external beam radiation, unwanted exposure of adjacent structures is a limiting factor, while hemorrhage, radiation bronchitis, and fistulae with surrounding structures are known complications of radiotherapy. The maximal effect of all radiation techniques is delayed days to weeks and there is a risk of worsening of obstruction during therapy due to airway edema.

AIRWAY STENTS

Airway stents are used in the palliative management of both benign and malignant airway obstruction.[59] Available tracheal stents include expandable metal, silicone, and hybrid prostheses. Major complications include stent migration, granulation tissue formation, and stent interference with mucociliary clearance. In a series of over 1500 patients who had stents placed for UAO due to benign or malignant disorders, stent migration was reported in 9.5%, granulation tissue formation in 7.9% and obstruction in 3.6%. Due to concerns regarding stent fracture, the FDA posed a warning on the use of metallic airway stents for benign disease. Currently, metallic stents are only recommended in benign disease for patients who are not candidates for or have failed a trial of silicone stent placement.

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CHAPTER 50

Cystic Fibrosis

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Cystic fibrosis (CF) is a common inherited disease that has a high frequency in Caucasians. The disorder affects all exocrine glands, with symptoms involving the lungs and pancreas usually dominating the clinical picture. Even though the gene responsible for CF and its gene product, an integral membrane glycoprotein, have been identified, two aspects of the disease make CF particularly difficult to both diagnose and manage. First, there is tremendous variability in the degree and pattern of involvement of organs in different persons. In addition, we lack information about the precise details of the molecular and cellular pathogenesis of the disease. This chapter focuses on the pathophysiology and management of CF. Our current understanding of the genetics and underlying molecular biology is highlighted. Complications of the disorder are addressed, and a brief discussion of relevant psychosocial and reproductive issues is provided. Finally, potential future directions in treatment are described.

GENETICS

CF demonstrates an autosomal-recessive pattern of inheritance. In the United States, the incidence of the disease is approximately 1 in 3000 in Caucasians, 1 in 6000 in Hispanics, and 1 in 10,000 in African Americans. The frequency of unaffected heterozygote carriers of a CF mutation is estimated to be 1 in 26 in persons of Northern European ancestry.

CF is caused by mutations in a single gene named the *cystic fibrosis transmembrane conductance regulator* (CFTR). This gene was identified with an approach known as positional cloning, which permitted mapping of the gene, without prior knowledge of the biochemical defect, through use of polymorphic DNA markers. The first genetic marker that was found to be linked to CF was paraoxonase. In 1985, the demonstration of the linkage of CF to two DNA markers, D7S15 and D7S8, and to the *met* oncogene established the localization of the CF gene to the long arm of chromosome 7. Following a series of molecular cloning experiments, which included "chromosome walking" and "jumping," a candidate gene was identified. This was proved to be the CF gene in 1989, largely through the discovery of a frequent mutation.[1,2]

The CF gene spans approximately 230 kb of DNA and contains 27 exons. The mRNA is 6.5 kb and is detected in a variety of tissues, including lungs, pancreas, and sweat glands, which are predominantly affected in pathogenesis of the disease. The deduced polypeptide was predicted to be an integral membrane glycoprotein containing 1480 amino acids (Fig. 50-1) (see "Pathogenesis" below). Several major and minor splicing variants in the transcripts have been described in individuals with and without CF. In most cases, however, the significance of the alternative splicings is not clear.

The most common CF mutation, and the first to be described, is a three-base deletion in exon 10 that causes a deletion of phenylalanine from position 508 (ΔF508 or F508del) of the CFTR glycoprotein. This mutation accounts for 66% of CF mutations.[3] However, more than 1900 CF mutations have now been reported, and the list continues to grow. In addition, a number of benign sequence variations have been described. A listing of the most common mutations and their relative frequency is included in Table 50-1. The large number of mutations makes accurate detection of a satisfactory percentage of carriers extremely difficult, and carrier screening for the general population has not been recommended or implemented. Testing for 32 of the most common mutations is widely available; such testing will detect approximately 90% of the carriers in Caucasians of Northern European descent. In families with an affected individual and known mutations, prenatal diagnosis and

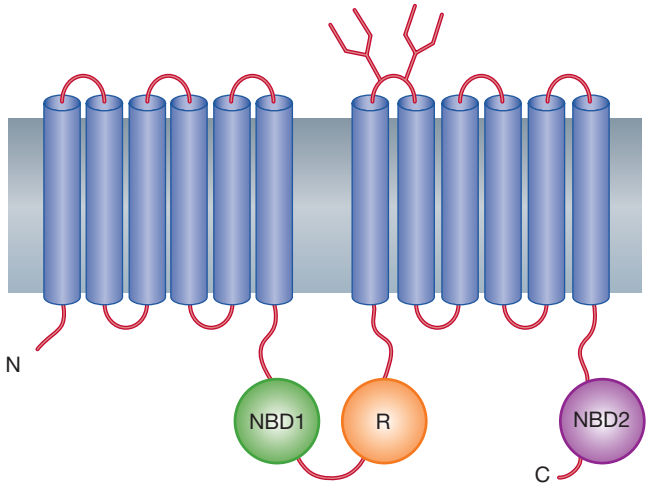


Figure 50-1 Domain model of the cystic fibrosis transmembrane conductance regulator (CFTR). Based on hydrophobicity plots, CFTR has 12 transmembrane-spanning domains, two nucleotide (N) binding domains (NBD 1 and NBD 2), and a regulatory (R) domain. The 12 transmembrane domains form the ion channel "pore." In the closed state, the "R" domain is believed to obstruct the channel. Channel opening requires binding of two adenosine triphosphates (ATPs) to the nucleotide binding domains. This model is similar to other ATP-binding cassette transporter proteins that bind ATP and transport ions or micronutrients. *(Modified with permission from Riordan J, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science; 245(4922):1066–1073.)*

carrier testing using direct detection of mutations is accurate and available. In families with a member diagnosed as having CF, but with undetected mutations, sequencing of the complete CFTR coding region and critical intronic regions is now also available to detect rare mutations.

PATHOGENESIS

Discovery of the gene responsible for CF and description of its product, CFTR, have provided the necessary foundation for understanding the pathogenesis of the disorder at the molecular and cellular levels. CFTR is an integral membrane glycoprotein of approximately 170 kD that is expressed in epithelial cells of affected organs. CFTR contains 1480 amino acids, which are arranged in 12 transmembrane domains, two nucleotide binding domains, and a putative regulatory domain (Fig. 50-1). The most common mutation, F508del, is a three-base deletion that causes deletion of phenylalanine from position 508, located in the proposed first nucleotide-binding domain. The original structural model, which was based on hydrophobicity plots, has proved to be essentially correct in its main features. CFTR shares many structural features with the "adenosine triphosphate (ATP)-binding cassette" transporter family, which includes P glycoproteins, as well as a number of bacterial transporters. CFTR has been clearly shown to function as an apical chloride channel in airway epithelial cells.

The localization of CFTR to the apical aspect of airway epithelial cells, to the ciliated duct of submucosal gland cells, and to submucosal serous cells, and the role of CFTR as an apical chloride channel fits nicely with the simplest hypothesis to account for the pathogenesis of pulmonary disease in CF. Decreased secretion of chloride and water by airway epithelial cells results in dehydrated mucus (Fig. 50-2). However, CFTR may have other functions, such as regulation of other ion channels, including the epithelial sodium channel. Loss of CFTR causes increased reabsorption of sodium; increased epithelium sodium channel activity alone alters regulation of ions and water, resulting in mucus obstruction of airways. CFTR transports bicarbonate; loss of CFTR function may result in acidification of the small intestinal lumen and, possibly, the airway lining fluid. Alternatively, CFTR may also function in *intracellular* membranes (e.g., endoplasmic reticulum, endosomes, phagosomes, and clathrin-coated vesicles). A consequence of the altered function of CFTR in intracellular membranes may explain abnormalities of CF glycoproteins: Increased sulfation of respiratory mucins, with decreased sialylation and increased fucosylation of both secreted and membrane glycoproteins. Altered glycosylation of airway glycoproteins may significantly impact

TABLE 50-1 Most Common CFTR Mutations in the United States

Name of Mutation	Frequency (%)	Population with High Prevalence
ΔF508	66	
G542X	2.4	Spanish
G551D	2.1	English
3120+1G→A	1.5	African American, Arabian
W1282X	1.4	Jewish-Ashkenazi
N1303K	1.3	Italian
R553X	0.9	Hispanic
621+1G→T	0.9	Multiethnic
1717–1G→A	0.7	Italian
3849+10kbC→T	0.7	Hispanic
R117H	0.7	
1898+1G→T	0.4	East Asian
ΔI507	0.3	Hispanic
2789+5G→A	0.3	
G85E	0.3	
R347P	0.2	
R334W	0.2	Multiethnic
R1162X	0.2	Multiethnic
R560T	0.2	
3659delC	0.2	
A455E	0.2	
2184delA	0.1	
S549N	0.1	Multiethnic
711+1G→T	0.1	
R75X	0.2	Hispanic
406–1G→A	0.2	Hispanic
I148T	0.2	Hispanic/French
2307insA	0.2	African American
A559T	0.2	African American
ΔF311	0.2	African American
G480 C	0.2	African American
405+3A→C	0.2	African American
S1255X	0.2	African American

Data based on the most frequent mutations found overall in the United States. Source: Adapted with permission from Bobadilla JL, Macek M Jr., Fine JP, et al. Cystic fibrosis: A worldwide analysis of CFTR mutations-correlation with incidence data and application to screening. Hum Mutat. 2002;19(6):575–606.

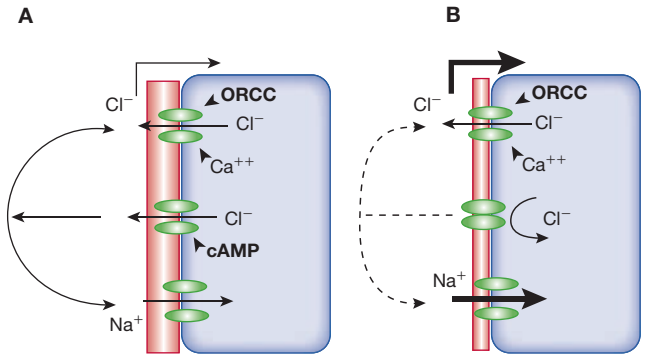


Figure 50-2 Simplified model of ion transport in airway epithelium. **A.** Normal airway cell with multiple apical ion channels. At the top, two different chloride channels are represented, the outwardly rectifying chloride channel (ORCC) and the Ca^{++}-gated chloride channel. In the center, cyclic adenosine monophosphate (cAMP)-gated cystic fibrosis transmembrane conductance regulator (CFTR) is shown. The apical sodium channel is depicted at the bottom. Experimental data suggest that CFTR interacts with the other channels, although the type of interaction is not clear *(solid arcs)*. **B.** CF cell with nonfunctioning cAMP-gated apical chloride transport. The function of the other channels is affected in an unknown manner *(dashed arc)*. The net result of ion channel activity on the pericellular fluid composition *(hatched area)* is under investigation. Many questions remain concerning the function of CFTR and ion transport in the airway.

bacterial–epithelial interactions and innate immune functions in the lung.[4]

In addition to the effect of CFTR on epithelial ion channels and glycoprotein processing, loss of CFTR function negatively impacts innate immunity and accentuates inflammation. Absence of CFTR function is associated with impaired bacterial killing in vitro and defective function of antimicrobials including human β-defensin 1 and lysozyme. Absence of CFTR is also associated with increased interleukin-8 (IL-8) production and decreased IL-10 in vitro. In the CF airway, excessive neutrophil elastase cleaves complement and immunoglobulins, interfering with bacterial opsonization. CF airways have increased oxidant stress due to neutrophilic inflammation and reduced antioxidants such as glutathione. Together, these factors synergistically increase the inflammatory milieu in the airways in CF.

A long-standing impediment to progress has been the absence of a completely suitable animal model. A number of mouse models of CF have been developed and while these have been useful in understanding some features of the disease such as the regulation of inflammation, a drawback has been the absence of spontaneous development of lung disease.[5] Two recently developed animal models in the ferret[6] and pig[7] have shown promise in developing some features of the early lung disease of CF.

CFTR mutations have been grouped into five classes,[8] depending on the effect of the mutation on the expression, processing, and function of the protein (Fig. 50-3). The most common mutation, F508del, is a processing mutation in which very little of the mutant protein reaches the apical surface. If the mutant protein escapes normal intracellular processing, however, F508del protein functions normally in the apical membrane. Furthermore, only 25% of normal CFTR transcripts are properly processed and transported to the cell surface. The remaining 75% are degraded before being processed. These data suggest that one therapeutic strategy to overcome the defect in CF is to disrupt normal intracellular processing mechanisms. A phase III clinical trial is in progress to test a therapeutic small molecule which is based on this concept.

PATHOPHYSIOLOGY

In CF, all exocrine glands appear to be affected primarily, albeit to varying degrees. Because exocrine glands perform highly specialized functions in a variety of organs – for example, in the skin, respiratory tract, gastrointestinal tract, and reproductive system – the number of possible symptoms and complications in CF is large. Table 50-2 highlights the complications and symptoms of CF according to the age groups in which they most often occur.[9] Obstruction of exocrine ducts by viscous secretions appears to play a cardinal role in the pathogenesis of almost all manifestations of the disease. In 10% to 20% of patients, the initial manifestation is often *meconium ileus* – that is, obstruction of the intestine by thick, viscous meconium stool. Chronic pulmonary disease, pancreatic insufficiency, and focal biliary cirrhosis progress gradually throughout the course of the disease, albeit at different rates in different patients. Progressive obstruction of exocrine ducts is a regular feature of the disease except in sweat glands, where obstruction of ducts has not been implicated in pathogenesis.

RESPIRATORY TRACT

In the lungs, hypersecretion of viscid mucus and chronic bacterial infection combine to produce a progressive and distinctive type of

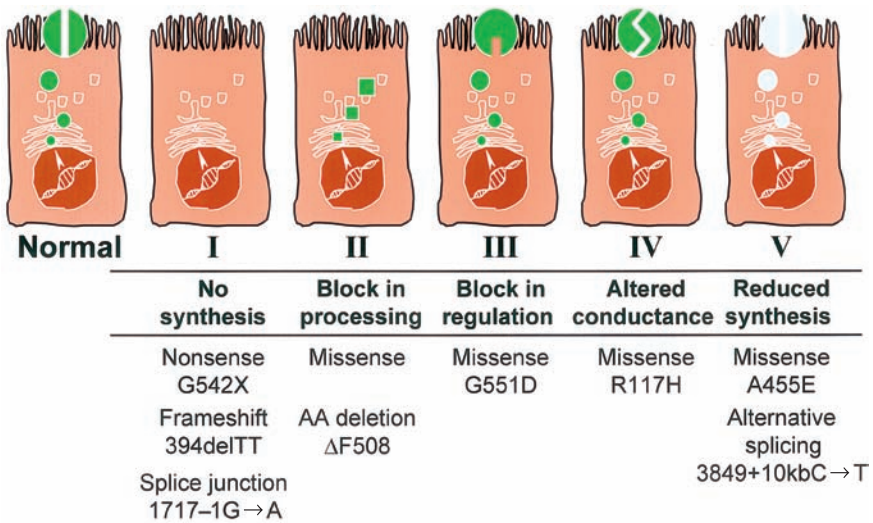


Figure 50-3 Classification of cystic fibrosis transmembrane conductance regulator (CFTR) mutations by molecular and biochemical abnormalities. This schematic depicts the effect of different classes of CFTR mutations on expression and function in the cell. Class I mutations block mRNA transcription. Class II mutations prevent normal CFTR protein processing and localization. Class III mutations permit CFTR localization at the apical membrane but inhibit chloride channel conductance. Class IV mutations result in partial chloride channel conductance. Class V mutations affect transcription, translation, or protein processing resulting in reduced CFTR expression at the apical membrane. Examples of mutations in each class are depicted below the cell models. Epithelial cell models with finger-like projections depict cilia at the apical surface. Fully processed CFTR protein is depicted by the *gray circles* embedded among the cilia at the apical surface of the cells. *(Adapted with permission from Zielenski J1, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. Annu Rev Genet. 1995;29:777–807.)*

TABLE 50-2 Presenting Signs and Symptoms of CF

Infancy	Childhood	Adolescence/Adult
Positive prenatal test for CF mutations or hyperechoic bowel on ultrasound	Pulmonary infection with *Staphylococcus* and *Pseudomonas*	Chronic bronchitis with bronchiectasis
Positive CF newborn screen	Malnutrition with steatorrhea and pancreatic insufficiency	Pansinusitis
Meconium ileus	Heat prostration with hypoelectrolytemia and metabolic alkalosis	Hemoptysis
Obstructive jaundice	Atypical asthma with clubbing and/or bronchiectasis	Recurrent pancreatitis
Edema with hypoproteinemia and hypothrombinemia	Esophageal varices and/or hyperplenism	Cholelithiasis
Failure to thrive	Nasal polyps	Chronic abdominal pain and constipation
Salty taste and/or salt loss syndrome		Obstructive apnea
Rectal prolapse		CF-related diabetes
Intestinal obstruction with or without intussusceptions/volvulus		Osteopenia
Recurrent pneumonia/bronchiolitis		Chronic respiratory failure

chronic obstructive airway disease that eventually leads to diffuse, severe bronchiectasis. The earliest pathologic lesions are found in the distal bronchioles. Whether the viscid secretions are primary or are secondary to chronic bacterial infections remain unsettled. In favor of a primary disturbance is the demonstration of mucus obstructing submucosal gland ducts in the airways of neonates with CF, who have not yet developed any evidence of bacterial infection or chronic colonization of the airways. With the use of sophisticated culture methods, bacterial pathogens can almost invariably be isolated from the respiratory tract of patients with CF. The most common pathogens isolated from sputum cultures are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Less commonly found are *Escherichia coli, Klebsiella,* and *Haemophilus influenzae*. In later stages of the disease, *Pseudomonas* usually predominates. By adulthood, more than 80% of patients are colonized with *P. aeruginosa*. Chronic infection with *P. aeruginosa* elicits an anaerobic milieu within mucus plugs in the CF airway.[10] Using anaerobic culture conditions, large numbers of anaerobes, particularly *Prevotella, Veillonella*, and *Propionibacterium*, were detected in CF sputum but not in induced sputum from healthy volunteers.[11] There is a correlation between *P. aeruginosa*–positive cultures and presence of the anaerobes. Multidrug-resistant organisms (MDROs) are detected in CF sputum cultures with higher prevalence and chronicity apparently associated with acute and chronic administration of antibiotics to suppress *P. aeruginosa*. These pathogens include *Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, and *Burkholderia cepacia complex*. Other opportunistic pathogens including *Aspergillus* and nontuberculous mycobacteria have also been detected more commonly in CF sputum cultures. There is still controversy concerning whether these MDRO are actively contributing to CF lung disease or are commensal pathogens present in bronchiectatic airways.

Neutrophil-dominated lower airway inflammation also plays a primary role in the pathogenesis of the characteristic central bronchiectasis of CF.[12] Bronchoalveolar lavage fluid (BALF) demonstrates increased neutrophils and various cytokines, especially IL-8, even in infants whose BALF is sterile.[13,14]

Typically, respiratory secretions increase when a patient with CF, already chronically colonized with *Pseudomonas,* develops a viral respiratory tract infection. In turn, the increase in secretions leads to a gradual increase in cough and sputum production and then to an exacerbation of the pulmonary disease, usually manifested by increase in respiratory rate; retraction of the chest during inspiration; and diffuse, coarse inspiratory crackles. Leukocytosis is common. The chest radiograph demonstrates worsening hyperinflation. Both peribronchial thickening and nodular or cystic densities are more marked than usual. Pulmonary function tests show a worsening over baseline. Usually, residual volume (RV) increases; forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) decrease; the forced expiratory flow between 25% and 75% of the exhaled vital capacity ($FEF_{25–75\%}$) also decreases. Treatment using antibiotics and chest physiotherapy generally succeed in restoring most indices of pulmonary function to, or almost to, baseline. However, *Pseudomonas* and *Staphylococcus* persist in sputum cultures.

The most attractive hypothesis to account for the pattern of response to treatment is that therapy reduces the number and, probably, virulence of organisms. Despite the virtual return to baseline after an exacerbation, however, the cumulative effect of repeated episodes is progressive bronchiectasis or atelectasis, or a combination of the two, accompanied by a gradual and irreversible decrease in pulmonary function. The striking degree of airway destruction and relative sparing of the pulmonary parenchyma at autopsy are shown in Figure 50-4. A simplified scheme illustrating the evolution of the process is shown in Figure 50-5.

GASTROINTESTINAL TRACT

Although pancreatic function may be either normal or abnormal at birth, it gradually becomes increasingly abnormal in most patients with CF as the pancreatic ducts become progressively obstructed by thick, viscous secretions from the exocrine portion of the organ; pancreatic enzymes that are trapped within the ducts lead to autodestruction of the pancreas. A cycle of destruction and obliteration of the ducts is set into motion, leading to cystic dilatation of ducts proximal to sites of obstruction and fibrosis of the body of the pancreas. In advanced stages of the disease, pancreatic fibrosis sometimes causes obliteration of the islets of Langerhans and, consequently, diabetes. This concept has been challenged by the notion that CFTR may have a direct effect on β-cell dysfunction as, discussed in the next section.

The liver and biliary tract are also affected in CF. Here too, the primary mechanism appears to be obstruction of small intrahepatic bile ducts by abnormally viscid secretions, leading to accumulation of toxic bile acids, depletion of hepatic antioxidants, and subsequent liver injury. CFTR is localized to the apical surface of the bile duct epithelium and not in the hepatocytes. Risk factors for liver disease appear to be male sex, meconium ileus, PiZ heterozygous state, and transforming growth factor-β1 (TGF-β1) polymorphisms. Elevated liver enzymes can be seen intermittently in 40% to 50% of patients with CF. Hepatic steatosis is frequently seen and may be related to malnutrition, essential fatty acid, choline and carnitine deficiency. Focal biliary cirrhosis, multilobular cirrhosis, and portal hypertension are also seen. Some newborn infants with CF develop the *inspissated bile syndrome,* characterized by prolonged obstructive jaundice starting at 2 to 8 weeks of age. The jaundice often clears

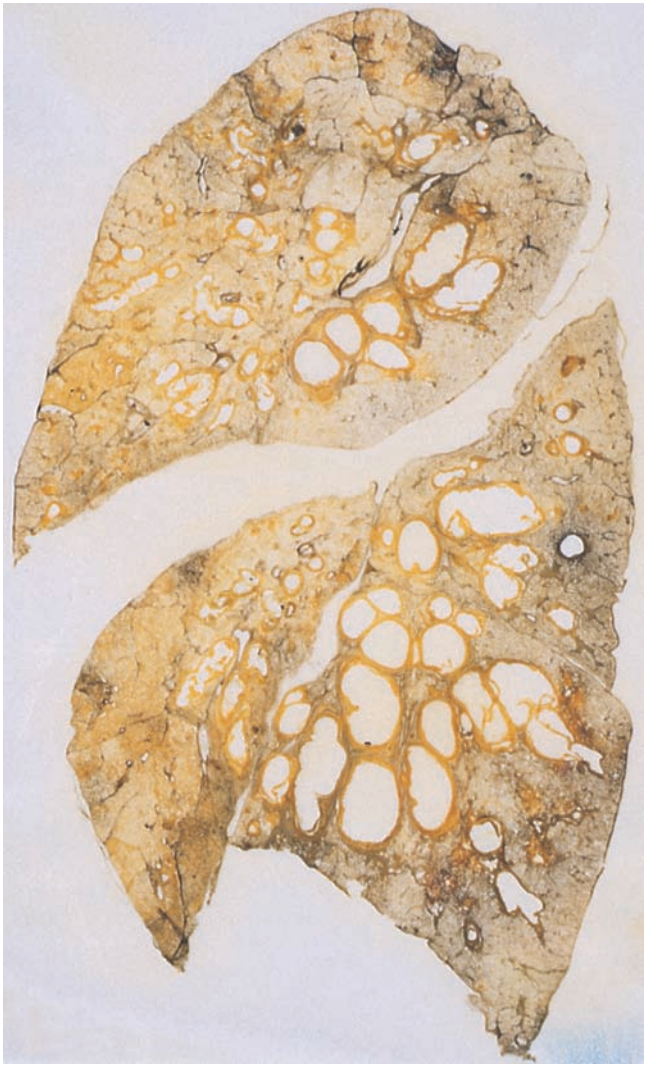


Figure 50-4 Section of lung from autopsy of a patient with CF, demonstrating remarkable dilation of large airways and preservation of intervening pulmonary parenchyma. *(Used with permission of Dr. S. Moolten.)*

without therapy. Gall bladder anomalies may be seen in about 24% to 50% of patients and include microgall bladder, gall stones, and gall bladder dysfunction.[15] The most striking pathologic change in the intestines is hyperplasia of the mucus glands and goblet cells. Biochemical abnormalities in intestinal mucins may contribute to malabsorption of specific nutrients and bile acids. Much of the malabsorption in CF can be corrected by administration of pancreatic enzyme replacement therapy (PERT). However, the abnormal mucins may lead to slowing of intestinal transit time; the slowing, combined with maldigestion of food substances, sometimes causes fecal impaction in the terminal ileum and ileocecal area, a condition referred to as *meconium ileus equivalent* or distal intestinal obstruction syndrome. The fecal impaction, in turn, occasionally causes volvulus or intussusception of the bowel (Fig. 50-6).

■ ENDOCRINE INSUFFICIENCIES

Important CF-associated endocrine disorders are discussed below.

Cystic Fibrosis–Related Diabetes

Diabetes mellitus is a common comorbidity in CF and increases in frequency with increasing age. According to data from University of Minnesota where annual cystic fibrosis–related diabetes (CFRD) screening is recommended for all patients ≥6 years, CFRD affects 2% of children, 19% of adolescents, and 40% to 50% of adults.[16]

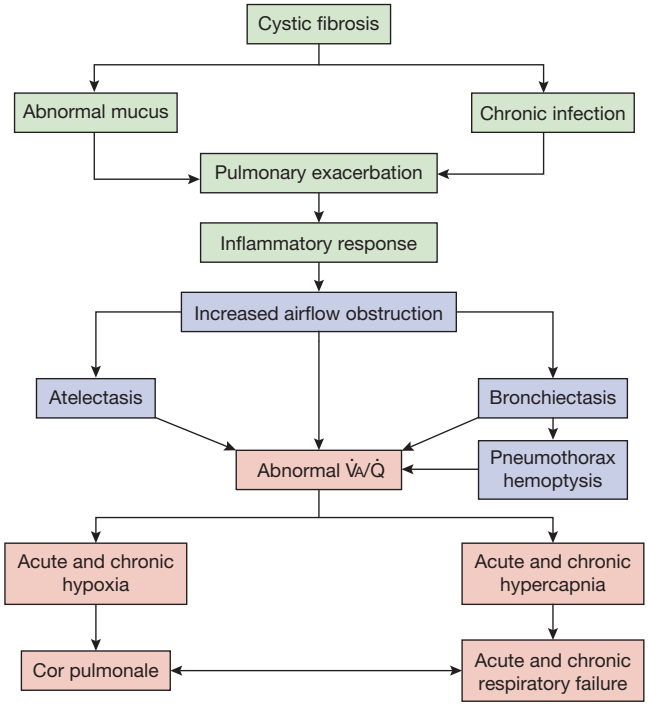


Figure 50-5 Simplified scheme for pathogenesis and progression of pulmonary disease in CF.

Similarly, CFRD was found in over a third of 775 patients of age ≥6 years undergoing CFRD screening over a 15-year period.[17]

Underscoring its relevance, CFRD has been associated with decreased survival,[18–24] worse pulmonary function, and lower BMI.[23] Declines in pulmonary function and nutritional status have been observed even prior to the CFRD onset.[22,25] Moreover, less significant glucose impairments are associated with greater declines in nutritional status over the previous year in children[25]; these findings suggest more subtle glucose abnormalities may be clinically relevant in CF. Microvascular complications, such as retinopathy, nephropathy, and neuropathy also occur in CFRD but may be limited to those individuals with fasting hyperglycemia (FH).[17]

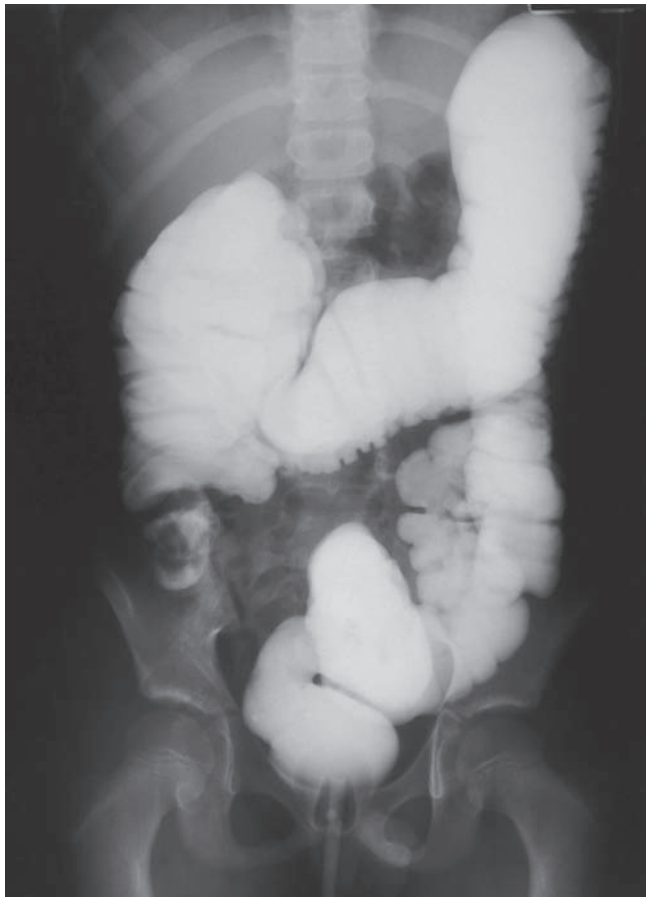
Fortunately, early identification and treatment of CFRD appear to curb the impact of CFRD upon survival.[16] Insulin treatment of adults with CFRD without FH improves BMI,[26] and small studies have found insulin treatment improves weight in children even prior to development of CFRD.[27–29]

As described above, CFRD is considered an insulin-deficient state. In fact, delayed and blunted insulin secretion in response to a glucose load or meal prevails even in the setting of "normal" glucose tolerance in CF,[30–32] and these abnormalities progress with worsening glucose intolerance.[30,32,33] This progressive decline in insulin secretion has traditionally been considered a product of "collateral damage" extending from obstructive damage to the exocrine pancreas.

This "bystander" model has been challenged in more recent years. Animal models suggest CFTR may play a direct role in β-cell dysfunction.[34,35] For instance, CFTR knockout ferrets demonstrate glucose abnormalities and insulin secretion defects as newborns.[35] Moreover, the T2DM GWAS-implicated gene, *TCF7L2*, which may contribute to the defective insulin secretion that underlies T2DM, confers an even stronger risk of CFRD. In addition, disturbances in secretion/function of incretins, gut-secreted hormones that potentiate insulin secretion, have been described in CF[36] and in T2DM.[37–40,44–47]

Osteoporosis/Vitamin D Deficiency

Low bone mineral density occurs in as many as 85% of adults with CF. The origin of osteoporosis in CF is multifactorial and is attributed to



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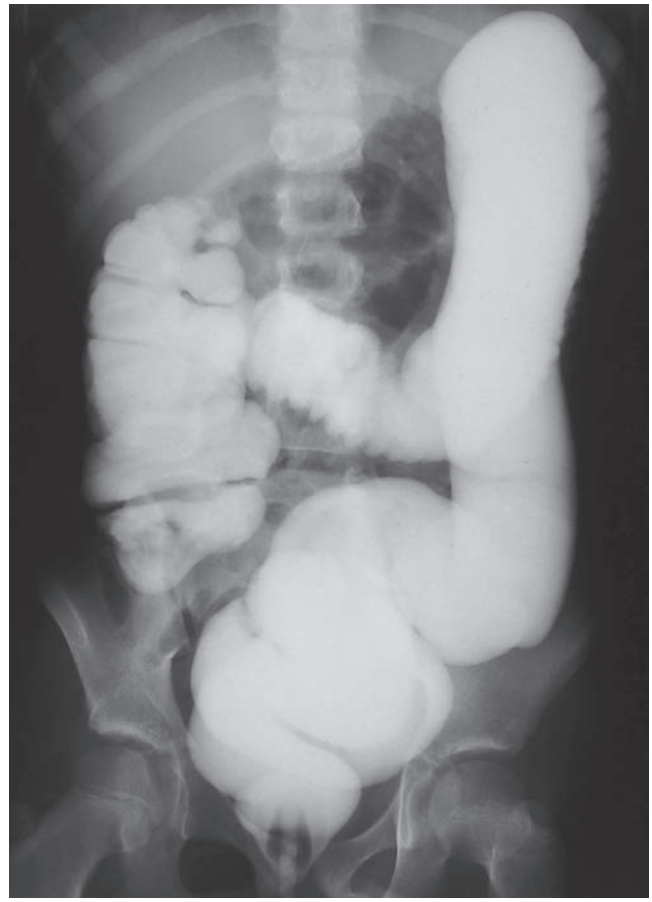

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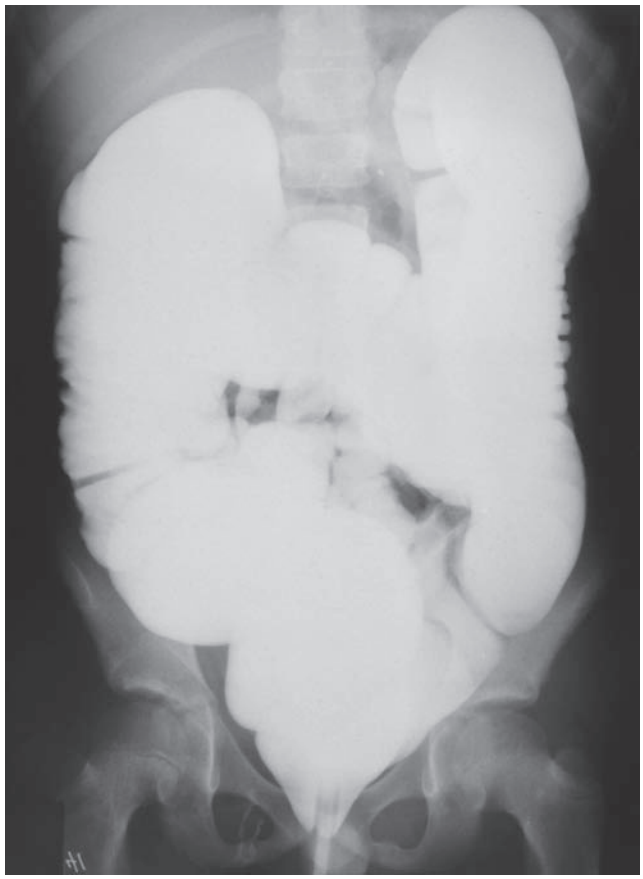


C

Figure 50-6 Distal intestinal obstruction syndrome (DIOS). **A.** Presenting Gastrografin enema of a child who had crampy abdominal pain and a right lower–quadrant mass. Fecal impaction with intussusception is demonstrated. **B.** Partial resolution of the obstruction following Gastrografin administration. **C.** Complete resolution of the intussusception and fecal impaction.

pancreatic insufficiency and malnutrition and poor growth, CFRD, deficiencies in vitamin D, vitamin K, and calcium levels, elevated inflammatory cytokines, pubertal delay, diabetes, and exposure to glucocorticoids.[41] Bone histology in clinically stable CF adults is significant for decreased cancellous bone volume and decreased connectivity.[42] Importantly, the sequelae of low bone density in CF patients include increased risk of vertebral and rib fractures, approximately twice as great as the general population, and increased risk of kyphosis.

■ REPRODUCTIVE ORGANS

Except for an increase in viscosity and an abnormal midcycle fern-ing pattern in cervical mucus, no consistent pathologic changes occur in the female reproductive tract in patients with CF. In the male reproductive tract, however, the vas deferens is either atretic or absent at birth. Although the pathogenesis of this lesion is not certain, viscous secretions may contribute to obstruction in utero, followed by failure of development of the vas deferens. Spermatogenesis and testicular development are otherwise normal. Because of either partial or complete obstruction of the vas deferens, approximately 98% of males with CF are aspermic.

■ SWEAT GLANDS

The sweat glands of patients with CF manifest no distinctive histologic changes. Nonetheless, their function is abnormal. Micropuncture experiments have shown that the precursor solution secreted by the sweat glands is isotonic to plasma, both in CF patients and in normal subjects. In normal persons, as the sweat flows along the duct of the gland, sodium and chloride are reabsorbed, so that by the time the opening at the skin surface is reached, sweat is hypotonic to plasma with respect to both sodium and chloride concentrations. In CF, the relative impermeability to chloride ions is thought to be responsible for the elevated chloride and sodium concentrations which are the basis for the diagnostic test, the quantitative pilocarpine iontophoresis sweat test, and are also responsible for the characteristic increase in potential differences across isolated, perfused sweat glands from CF patients.

DIAGNOSIS

The diagnosis of CF requires the demonstration of abnormally high concentrations of sodium and chloride in the sweat of a person who has the characteristic history and symptoms of CF. The most prominent clinical features are chronic pulmonary disease and pancreatic insufficiency. The most compelling family history for the diagnosis is CF in a sibling. If the clinical picture and/or the family history support the diagnosis, and if two sweat tests using the quantitative pilocarpine iontophoresis method are clearly positive, the diagnosis of CF can be made with assurance. Identification of two pathologic mutations, in addition to the characteristic clinical picture, is accepted as a criterion for the diagnosis. However, CF is a complex syndrome (Table 50-2) whose clinical manifestations are sometimes subtle. In addition, the family history is not always straightforward. Therefore, a high index of suspicion, coupled with a battery of clinical tests, is sometimes required to establish the diagnosis, especially in adolescents or young adults.

Since CF occurs with a high frequency in the general population, the diagnosis should be considered routinely in a broad array of differential diagnoses. Although Table 50-2 categorizes symptoms according to the age at which they most often occur, symptoms at any age should prompt consideration of the diagnosis of CF.

The most consistent feature of CF is an abnormally high concentration of sodium and chloride in sweat. Measurement of the chloride concentration is recommended for clinical testing. The only reliable sweat test is based on iontophoresis of pilocarpine, followed by quantitative determination of the concentration of chloride in an adequate, measured volume of sweat. Guidelines for the proper performance of a sweat test have been published.[43] In children, concentrations of chloride of less than 40 mEq/L are usually regarded as normal. However, the average of values for sodium and chloride concentrations is about 20 mEq/L for normal subjects and 95 mEq/L for those with CF. In children, values between 40 and 60 mEq/L are traditionally considered borderline elevated; such values call for further evaluation. As a result of recent experience with CF newborn screening, it has been suggested that sweat chloride values above 30 mEq/L may be diagnostic in the first few months of life.

The concentration of sodium and chloride in sweat increases gradually with age. Conditions other than CF in which the concentrations of sodium and chloride in sweat are abnormally high include malnutrition, adrenal insufficiency, hereditary nephrogenic diabetes insipidus, ectodermal dysplasia, and fucosidosis. Except in some instances of malnutrition, these conditions are readily distinguished from CF.[44] The finding of abnormal concentrations of sodium and chloride in sweat should automatically prompt evaluation of the patient to determine if, and to what extent, other organs are affected.

Genetic analysis can be used to confirm the diagnosis of CF. In patients with minimal symptoms, the diagnosis of CF can be made with certainty if two CF-associated alleles are present. As mentioned previously, screening for 32 of the most common alleles yields an overall sensitivity of 90% due to undetected alleles. Therefore, a negative mutation analysis does not rule out a diagnosis of CF, and atypical patients should be followed carefully.

Newborn screening is now standard practice in the United States.[45] The initial stage of screening often uses the neonatal blood spot to determine the concentration of immunoreactive trypsinogen. If this is elevated, secondary screens vary in individual states from repeat immunotrypsinogen determination to F508del or 25 to 32 mutation screen. The screening programs have a sensitivity ranging from 87% to 99%. Risks versus benefits and the relative costs of the screening programs are being evaluated to determine the best approach. Infants with positive newborn screens for CF are referred to CF centers for sweat test confirmation. It has been proposed that infants who have a positive newborn screen, but do not otherwise fulfill the criteria for a diagnosis of CF,[45] should be termed as having "CFTR metabolic syndrome"[46,53] and at a minimum they should be followed in a CF center until their status can be clarified.

CLINICAL EVALUATION

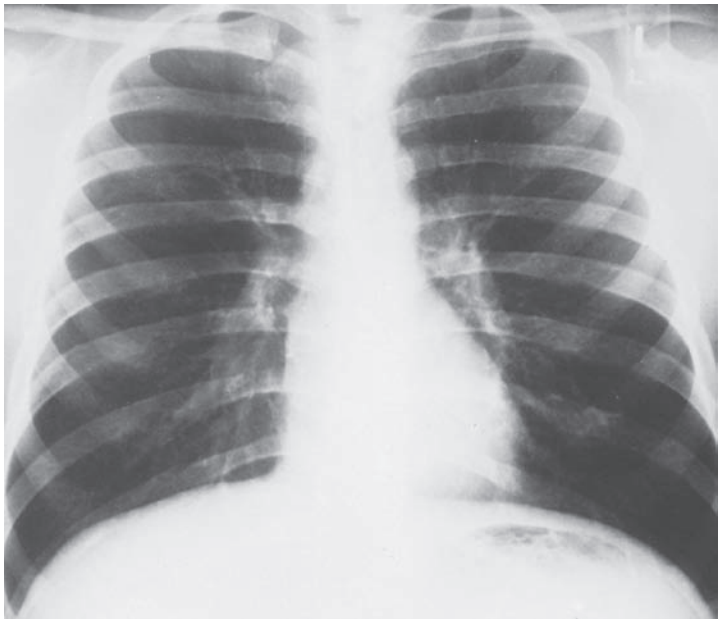
The evaluation of patients with CF includes chest radiography, tests of pulmonary performance, sputum culture, and assessment of pancreatic, endocrine, hepatic, and reproductive functions. Each is described below.

■ PULMONARY ASSESSMENT

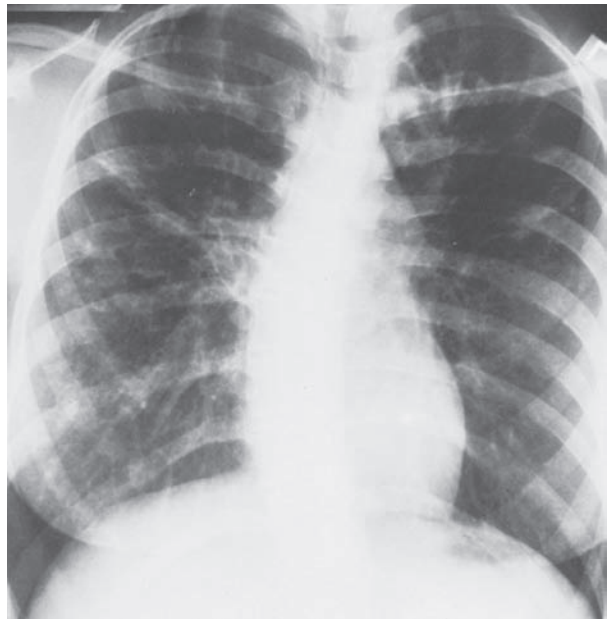
Pulmonary assessment includes chest radiography; measurement of pulmonary function, including that of small airways; and evaluation of gas exchange.

Chest Radiography

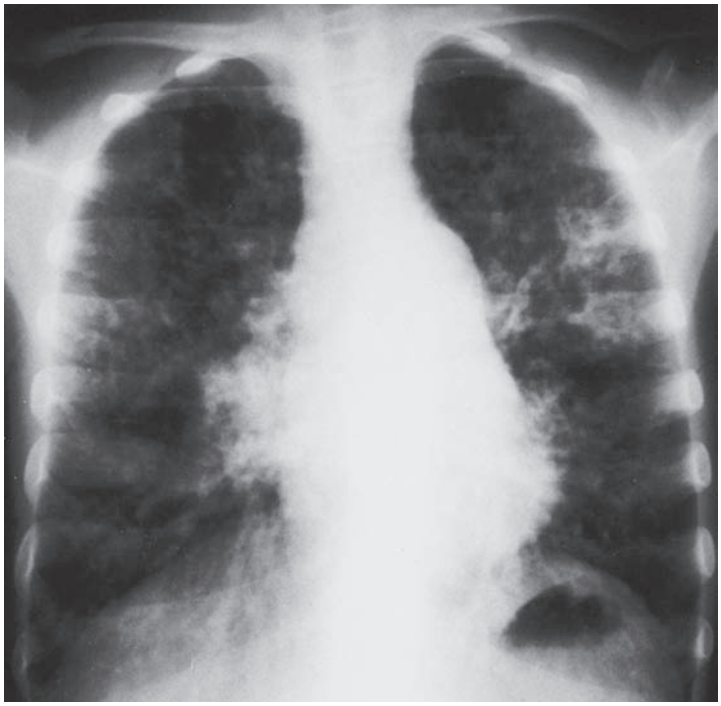
Rarely is the chest radiograph completely normal in CF. In the person with minor pulmonary symptoms, the manifestations may be questionable (e.g., mild hyperinflation and minimal peribronchial thickening). However, the radiographic findings become more distinctly abnormal as the disease increases in severity. Peribronchial thickening, which is often most prominent in the upper lobes of the lungs early in the course of the disease, usually progresses to affect all lobes. In the advanced stage of pulmonary involvement, ring shadows, cystic lesions, and nodular densities are increasingly apparent, as are areas of bronchiectasis and atelectasis. The central pulmonary artery often enlarges in the middle stages of the disease, but the cardiac silhouette remains within normal limits until the disease is far advanced. The variability in the chest radiograph is illustrated in Figure 50-7 for three siblings with CF when each was 17 years old.



A



B



C

Figure 50-7 Chest radiographs of three siblings with CF taken when the patients were 17 years of age. **A.** Mild hyperinflation; otherwise normal. Patient is now 32 years old and has been hospitalized once for treatment of electrolyte depletion. **B.** Diffuse peribronchial thickening, mild hyperinflation, and cystic changes in both upper lobes. The patient was hospitalized seven times for pulmonary exacerbations, once for diabetes, and once for hemoptysis. She died at age 34 following complications from lung transplantation. **C.** Severe hyperinflation, diffuse peribronchial thickening, multiple infiltrates, and increased pulmonary vascular markings and heart size. The patient died 1 month later from respiratory failure complicated by congestive heart failure.

High-resolution computed tomography (HRCT) scans are more sensitive than plain radiographs. The most common abnormalities described are bronchiectasis, peribronchial thickening, mosaic perfusion, air trapping, and mucus plugging.[47] Early bronchiectasis is easily detected on the CT scan, even when routine chest radiographs are normal, as seen in Figure 50-8. CT scan abnormalities may be detected prior to a change in pulmonary function tests. Chest CT scan abnormalities have been detected in asymptomatic newborn infants diagnosed by newborn screening.[48] Currently, there are no standard recommendations for CT use due to the radiation exposure incurred by these studies.

Pulmonary Performance

The lungs of patients with CF are usually morphologically and functionally normal at birth. Over time, accumulation of tracheobronchial secretions and recurrent infections progressively impair pulmonary function in almost all patients. In the fully developed clinical syndrome, all the pulmonary function abnormalities seen in chronic bronchitis, emphysema, and asthma may occur. However, one complicating regular feature of CF – bronchiectasis – modifies pulmonary performance. Chronic, local infection and airway damage increase the compliance of bronchiectatic airways, resulting in airway collapse during rapid expirations or cough. The usefulness of pulmonary function testing in CF is twofold: Tracing the natural history of the disease and assessing the value of therapeutic interventions.

The earliest stages of the pulmonary disorder are the most difficult to quantify. In infants, tests are limited almost entirely to those that do not depend on the patient's understanding and cooperation. A variety of methods to measure infant pulmonary function have been devised; one method, the raised volume rapid thoracoabdominal compression technique, requires sedation of infants but provides values most similar to standard spirometric values, and has detected reduced

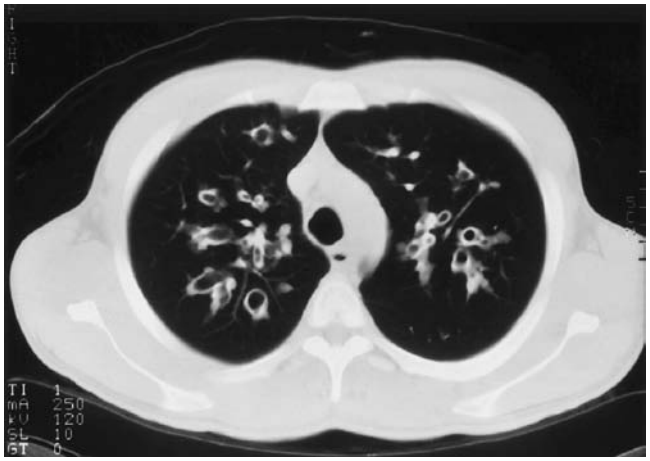


Figure 50-8 High-resolution chest computed tomography scan from a patient with CF. Marked bronchiectasis with peribronchial thickening is shown in the upper lobes.

pulmonary function in infants with CF[49] Nitrogen multiple breath washout or lung clearance index, can be performed in preschool age children and detects early ventilation inhomogeneity that correlates with airflow obstruction by spirometry.[50] After age 6, pulmonary function tests originally designed for adults may be performed quite readily on children. Changes in pulmonary performance throughout the natural history of CF can be described with confidence.

Obstruction in Small Airways

The small airways – that is, the bronchioles – are vulnerable to obstruction early in the course of CF. At this stage, as in cigarette smokers, results of tests for small airway disease are apt to be abnormal, while those of tests for obstruction of large airways are still normal. Three factors interact in causing the obstruction: (1) Intrinsic disease of the smaller airways, often in association with bronchiectasis in the proximal, larger airways; (2) viscid secretions, impaired ciliary action, and impaired cough; and (3) progressive decrease in lung elastic recoil.

The progressive reduction in lung elastic recoil in CF is predominantly a function of overinflation due to intrinsic airway disease, rather than loss of pulmonary parenchyma. This mechanism differs from that in chronic bronchitis and emphysema, in which the combined effects of parenchymal destruction and overinflation are responsible for the decrease in elastic recoil. Emphysema is not a regular feature of CF. In some patients, emphysema occurs only late in the course of the disease (Fig. 50-4).

Airway smooth muscle tone increases only slightly in CF. Exercise elicits bronchodilation, followed shortly thereafter by bronchoconstriction. Both the bronchodilation and bronchoconstriction are far less impressive in CF than in asthma. Indeed, exaggerated bronchomotor responses in CF raise the possibility of superimposed asthma. In distinguishing between contributions to airway obstruction by intrinsic airway disease caused by CF and asthma, maximal expiratory flow–volume curves are sometimes helpful.

Because of the bronchiolar locus of the early lesions in CF, abnormalities in breathing frequency–dependent tests (e.g., dynamic lung compliance), in volume-dependent tests (e.g., closing volume), and in maximal expiratory flow ($\dot{V}E_{max}$) at low lung volumes are demonstrable, even though results of tests of large airway function (e.g., FEV_1 and airway resistance) are still normal.

Change in Lung Volumes

As with chronic bronchitis, emphysema, and asthma, RV in CF increases. Thereafter, an increase in functional residual capacity and, sometimes, in total lung capacity is seen. As CF lung disease progresses, air trapping increases in severity and is manifest as an elevated ratio of RV to total lung capacity. This change decreases the compliance of the lung and increases the work of breathing.

Abnormalities in Gas Exchange

Early in the evolution of the pulmonary abnormalities in CF – that is, when tests of small airway function alone are abnormal – ventilation–perfusion abnormalities usually result in widening of the alveolar–arterial oxygen gradient and an increase in the ratio of dead space to tidal volume (V_D/V_T). These abnormalities portend increasing inhomogeneities in alveolar ventilation and blood flow as the affected child grows to adulthood. The diffusing capacity for carbon monoxide ($D_{L_{CO}}$) is low at rest and does not increase normally during exercise. This observation is difficult to reconcile with the preservation of the gas-exchanging surface of the lungs (in the absence of emphysema) until late in the course of the disease (Fig. 50-4).

As obstructive disease of the airways progresses and exaggerates the imbalances between alveolar ventilation and blood flow, arterial hypoxemia develops; pulmonary hypertension, cor pulmonale, and right ventricular failure follow, in turn. Late in the course of the disease, hypercapnia and respiratory acidosis contribute to the final picture of respiratory failure. At this juncture, the ventilatory response to inhaled CO_2 is depressed. Bouts of infection punctuate the course of the illness; during each episode, pulmonary function deteriorates, but it usually returns toward baseline, except in the preterminal stages of the disorder.

■ SPUTUM CULTURE

The unique respiratory flora isolated from sputum or oropharyngeal cultures from patients with CF is helpful in establishing the diagnosis and in guiding the antimicrobial therapy for acute exacerbations. In many patients with CF, *P. aeruginosa* and *S. aureus* are found alone, or in combination with other organisms, in the sputum. There is growing evidence of correlations between different organisms and CF lung disease progression. The presence of mucoid *Pseudomonas* is important because acquisition of mucoid *Pseudomonas* predicts more rapid progression of CF lung disease.[51] Similarly, acquisition of methicillin-resistant *S. aureus* is associated with a decline in pulmonary function[52] and worse survival.[53] Infection with *B. cepacia complex* organisms may be aggressive with rapid deterioration of clinical status or may have an indolent course; the presence of mucoid-positive organisms appears to be protective.[54] Chronic antibiotic therapy to suppress *Pseudomonas* has improved clinical outcomes but has also led to a greater number of MDROs identified in sputum, including *S. maltophilia* and *A. xylosoxidans*. Chronic colonization with *S. maltophilia*, induces a serologic response and independently correlates with progression in airflow obstruction.[55]

In addition to bacteria, sputum cultures for detection of molds and nontuberculous mycobacteria are helpful to guide therapy for patients with acute exacerbations unresponsive to antibiotic therapy, or for patients with unexplained progression of lung disease. Allergic bronchopulmonary aspergillosis (ABPA) complicates CF lung disease,[56] and recent evidence suggests that *Aspergillus fumigatus* may also be associated with airway infection or allergy-triggered asthma in the absence of ABPA.[57] The prevalence of nontuberculous mycobacteria ranges from 7% to 24% with the most frequent species identified as *Mycobacterium avium complex* and *Mycobacterium abscessus*.[58]

■ PANCREATIC FUNCTION

The evaluation of pancreatic function is an important part of establishing the diagnosis of CF, since almost 90% of patients have pancreatic insufficiency. Infants with pancreatic insufficiency due to CF can present with failure to thrive and loose or frequent stools.

However, visual appearance does not always correlate with the degree or presence of fat malabsorption. Currently the diagnosis of pancreatic insufficiency can be made by measuring fecal elastase (FE)-1 levels and assessment of the degree of malabsorption is best accomplished by the determination of the coefficient of fat malabsorption. The FE-1 test is performed on a random single stool sample. It is easy to obtain and in patients with CF, a human enzyme-linked immunosorbent assay (ELISA) for FE has a sensitivity of 98% to 100% and a specificity of 93% to 100%, even while patients are taking pancreatic enzyme supplements.[59] Also available is a polyclonal assay that detects human as well as porcine elastase and should not be used to diagnose pancreatic insufficiency in patients already on pancreatic enzyme supplementation. There is some debate as to the value used for the diagnosis of pancreatic insufficiency.[60] The coefficient of fat absorption is performed by collecting stools for 72 hours while the patient is ingesting a high-fat diet (documented on a 3-day diet record) and analyzing the stool fat content. A malabsorption coefficient of greater than 7% is usually considered abnormal. Patients with CF usually have a malabsorption coefficient around 20% to 30%. The test is not popular with families who find the stool collections very unappealing. Pancreatic stimulation tests are the most accurate measurement of pancreatic function but are invasive, cumbersome, and at this time are not clinically available.

Cystic Fibrosis–Related Diabetes

Because the onset of CFRD is generally insidious, and FH tends to be a late manifestation, annual CFRD screening with an oral glucose tolerance test (OGTT) starting by age 10 is recommended.[61,62] Based upon the fasting, 1-hour, and 2-hour plasma glucose (PG0, PG1, and PG2) during the OGTT, the following glucose tolerance categories are defined.

- Normal glucose tolerance (NGT) = PG1 <200 mg/dL and PG2 <140 mg/dL
- Indeterminate = PG1 ≥200 mg/dL but PG2 <140 mg/dL
- Impaired glucose tolerance (IGT) = PG2 ≥140 and <200 mg/dL
- CFRD = PG2 ≥200 mg/dL
  Without FH = PG0 <126 mg/dL
  With FH = PG0 ≥126 mg/dL

Contrary to what one might expect, isolated impaired fasting glucose (PG0 100–125 mg/dL) is not associated with worse survival, nutritional status, pulmonary function, or progression to CFRD.[63] Over 10 years, FH occurs in 60% of patients with CFRD without FH at baseline.[17] At least in children, increased plasma glucose at 1 hour during the OGTT predicts increased risk of progression to CFRD.[64]

Additional CFRD screening measures include fasting and postprandial glucose measurements during hospitalizations for acute illness.[61,62] Home glucose monitoring should also occur periodically during and after continuous overnight enteral feeds as well as during intercurrent illnesses, intravenous antibiotic therapy, and glucocorticoid treatment.[65] While an elevated hemoglobin A1C (>6.5%) is consistent with CFRD, the HbA1C tends to underestimate overall glucose intolerance in CF patients and is not generally recommended for CFRD screening.

Osteoporosis/Vitamin D Deficiency

Patients with CF are at risk for vitamin D deficiency and osteoporosis. Annual serum 25-hydroxy vitamin D levels should be monitored. In addition, in all adults and children greater than 8 years with risk factors for osteopenia including malnutrition, chronic glucocorticoid use, moderate-to-severe airway obstruction (FEV_1 <50% predicted), or history of fracture or delayed puberty, a DXA scan should be obtained to monitor bone mineral density.[41]

LIVER FUNCTION

Evaluation of liver function (transaminases, bilirubin, gamma glutamyl transferase [GGT]) is an important part of the evaluation of CF. Transient elevations of serum transaminases can be often seen and may be related to intercurrent illnesses and medications. However, these tests can often be relatively normal, even in patients with mild or moderate focal biliary cirrhosis. The prothrombin time is sometimes prolonged, owing to a combination of malabsorption and decreased synthesis of clotting factors by the liver. Obtaining a level of protein induced by vitamin K absence-II (PIVKA-II) to assess vitamin K status can be helpful in these instances. A liver ultrasound with Doppler should be performed in patients with persistently elevated liver function tests. Fatty liver, cirrhosis, splenomegaly, varices, and reversal of portal blood flow can be seen on ultrasound. Occasionally, patients present with bleeding esophageal varices from advanced cirrhosis and an upper endoscopy is helpful diagnostically and therapeutically.

SEMEN ANALYSIS

Occasionally, a man who is found to have aspermia during the course of an evaluation for infertility is found to have CF. In men with CF, a complete semen analysis is part of the evaluation. Azoospermia is found in more than 98% of men with the disorder.

MUTATION ANALYSIS

There are currently over 1900 mutations associated with CF (http://www.genet.sickkids.on.ca/cftr/). A new initiative, The Clinical and Functional TRanslation of CFTR (CFTR2) (www.cftr2.org), funded by NIH, the US CFF, and Sequenom, is a website dedicated to publishing the functional implications of CFTR mutations. Patients homozygous for the most common mutation, F508del have pancreatic insufficiency; patients with CF who have pancreatic insufficiency tend to have a worse prognosis. F508del is one of the major mutations classified as disease causing; other mutations are associated with CF-related disorders, and yet other mutations have no known clinical importance or unknown significance. Several mutations, including R117H, are associated with pancreatic sufficiency and a mild phenotype. Interestingly, the phenotype of R117H is linked to the expression of the polyT and polyTG intronic domains found 5' to exon 9. A T5 polymorphism expressed with R117H results in congenital bilateral absence of the vas deferens (CBAVD) or idiopathic pancreatitis, and may be complicated by mild lung disease. In contrast, R117H associated with T7 or T9 may have no manifestations of CF or CF-related disease.[66]

Certain alleles associated with CF (e.g., 3849+10kbC→T) are associated with nasal polyposis and bronchiectasis but normal sweat test results. The diagnosis of CF can be made with confidence in these patients. More problematic are persons with atypical presentations, normal sweat test results, and at least one CF-associated mutation. More extensive genotyping should be attempted for all patients with a high clinical suspicion for CF (see "Genetics") because mutation analyses will be used to determine eligibility for mutation-specific protein-correcting therapies. For example, therapy for CF patients with the G551D mutation with the CFTR potentiator ivacaftor® results in astonishing improvements in respiratory tract symptoms, weight gain, and shift from positive to borderline sweat chloride values (see "Therapy," "Genetics," and "Future Directions").[67]

Patients with the same genotype may have dramatically different phenotypes, supporting the concept that modifier genes play an important role in determining the CF phenotype. Three large GWAS consortia are collaborating to define modifier genes associated with lung disease severity[68] and with specific disease manifestations such as CFRD,[69] liver disease,[70] and meconium ileus.[71] Investigations using these large well-characterized cohorts recruited by the consortia have identified chromosomal regions of interest but have not yet confirmed gene targets or polymorphisms that confer increased risk of severe lung disease. Using a hypothesis-driven

approach, several potential candidate modifier genes for severity of lung disease were identified, including α_1-antitrypsin, HLA antigens, nitric oxide synthase, mannose-binding lectin, TGF-β, tumor necrosis factor-α (TNF-α), and β_2-adrenergic receptor. However, none of these genetic polymorphisms were validated as gene modifiers by GWAS analysis in the combined consortia.

ATYPICAL CLINICAL PRESENTATIONS

Atypical clinical presentations confound the diagnosis of CF in adults; a high index of suspicion is required to establish the diagnosis. Approximately 6% of all CF is diagnosed after age 18. Late presentations of CF tend to occur in persons with pancreatic sufficiency; indeed, overweight or well-nourished persons may have CF. Recovery of unusual gram-negative organisms, mucoid *Pseudomonas* species, or *S. aureus* from sputum of asthmatics with persistent sputum production, chest radiographic abnormalities, or clubbing should prompt referral for sweat testing. Recurrent sinusitis and nasal polyposis may be the only manifestations of CF in a mildly affected person. Isolation of *P. aeruginosa* from deep nasal cultures should raise the suspicion of CF. Frequently, the sinus findings on CT mimic fungal sinusitis, demonstrating concentric, inhomogeneous material. Occasionally, persistent inflammation produces bony destruction that is mistaken for previous surgical intervention. Sweat testing and referral to a CF center should be considered for men with azoospermia or CBAVD. The clinical entity, "CFTR-related disease" has recently been defined by an international working group. CFTR-related disease encompasses patients with evidence of CFTR dysfunction who do not meet the criteria for CF disease (e.g., only one CFTR mutation, a normal sweat test, and single organ involvement). CFTR-related diseases include CBAVD, idiopathic pancreatitis, and diffuse bronchiectasis.[72]

TREATMENT

Intensive, comprehensive CF treatment programs designed to deal with particular symptoms, correct deficiencies, and prevent progression and complications of the disease have led to a dramatic increase in the median age of survival. Although the value of comprehensive treatment is beyond question, far less certain are the utility of each component of the treatment plan and the level of each component necessary in a given patient. At present, the best approach still appears to be determination of the type and degree of abnormality in individual patients and design of a treatment program that will improve or maintain function of the organ systems affected. Two recent reviews highlight the evidence supporting each component of CF therapy.[73,74] To ensure that the treatment regimen meets the needs of the individual patient, that necessary treatment is not omitted, or that side effects of prescribed treatments do not go unnoticed, it is often desirable to hospitalize the patient for diagnosis and evaluation. Hospitalization also provides an excellent opportunity for counseling the patient, parents, and family about the diverse aspects of the diagnosis, treatment, prognosis, and inheritance pattern of CF. Hospitalization provides the opportunity to monitor the response of individual patients to each component of the therapeutic program.

An important aspect of the care of patients with CF is the network of more than 100 CF centers that exist throughout the United States and the larger network throughout the world. CF centers use a team approach to the care of patients. A CF care team usually includes physicians, nurses, respiratory therapists, physical therapists, nutritionists, social workers, and genetic counselors.

■ MANAGEMENT OF PULMONARY DISEASE

Management of CF-related pulmonary disease focuses on chronic respiratory management and treatment of acute exacerbations.

Chronic Maintenance Therapy

More than 90% of the patients with CF die from respiratory failure or pulmonary complications. The goals of treating the pulmonary disorder in CF are to prevent and treat the complications of airway obstruction and infection. Although management of the pulmonary disorder consists of many components applied in combination,[75] the individual components of therapy are discussed separately below.

Chest Physiotherapy

Almost all treatment programs for CF include a strategy intended to clear pulmonary secretions to prevent complications arising from airway plugging by viscous secretions. Chest physiotherapy – that is, "percussion and postural drainage" – performed regularly, is the most widely prescribed method. In infants and young children, chest physiotherapy is generally performed routinely, twice daily. Percussion and postural drainage technique has been modified to exclude head-down positioning which increased the risk of GE reflux and increased the duration of acute exacerbations of cough in infants.[76] In addition to manual chest percussion and postural drainage, there are several other effective modalities for chest physiotherapy. These alternative measures include the high-frequency chest-wall oscillation (HFCWO) vest; the flutter device, a small pipe–like device that produces an oscillating resistance during a forced expiratory maneuver; the acapella device that produces both positive expiratory pressure (PEP) and an oscillating resistance during forced expiratory maneuver; PEP mask; intrapulmonary percussive ventilation; autogenic drainage and active cycle of breathing; and exercise.[77]

Overall, due to the difficulty in designing unbiased, well-controlled trials with sufficient power to unequivocally distinguish efficacy between treatments, evidence does not exist to demonstrate superiority of one airway clearance mechanism over another. Therefore, the recommendations based on expert opinion are that airway clearance should be initiated in asymptomatic infants because they develop signs of lung disease within the first few months of life, and that patients should be offered and instructed in a variety of methods so that they can select the methods that they deem provides the most subjective benefit.[78] Some form of physiotherapy that is effective in mucus clearance is required daily because without chest physiotherapy, pulmonary function deteriorates.[79] At present, most CF centers recommend that all patients with CF attempt to maintain clearance of pulmonary secretions with a method that is applied regularly (e.g., twice daily). An additional recommendation is that chest physiotherapy be applied more often during an exacerbation of the chronic pulmonary infection. Unfortunately, the recommendation of chest physiotherapy on a regular basis – a time-consuming and often arduous form of treatment – is difficult to implement without considerable support and encouragement from family and health professionals.

Mucolytics and Inhaled Hypertonic Saline

A number of mucolytic agents have been tried over the years. One that has endured is *N*-acetylcysteine. In the test tube, this agent is quite effective in dissolving mucin components and in decreasing the viscosity of sputum from patients with CF.[80–82] Although some centers who have outstanding pulmonary outcomes, have used this agent as a standard part of the chronic regimen as an adjunct to airway clearance therapy in CF, others have been reluctant to use it because of a lack of randomized controlled trials.[83] One CF center which has a track record of outstanding CF outcomes recommended using *N*-acetylcysteine in combination with sodium cromolyn and albuterol (W. Warwick, personal communication). We continue to recommend its use to our CF patients. Interestingly, *N*-acetylcysteine was found to activate CFTR Cl^- conductance in cultured epithelial cells.[84]

In 1994, Pulmozyme, a DNA-cleaving enzyme, was approved for use in patients with CF following a large phase III multicenter trial.[85] More than 900 patients were enrolled for a 6-month period. Three dosing regimens were employed: Placebo, 2.5 mg inhaled once

daily, and 2.5 mg inhaled twice daily. The treatment groups showed a 5% improvement in FEV_1 over placebo, as well as a slightly lower relative risk of exacerbation of lower respiratory tract infection after 6 months. There was no difference between the once- and twice-daily treatment groups. A second study revealed that Pulmozyme, inhaled once daily over 96 weeks, maintained pulmonary function and decreased the relative risk of respiratory tract exacerbations in young CF patients with normal FEV_1 (≥85%).[86] Currently, this drug is in fairly widespread use for CF. However, questions regarding patient selection and timing and duration of use of this expensive drug remain unanswered.

Abnormal homeostasis of airway surface fluid results in dehydrated secretions and impaired mucociliary clearance. As a strategy to improve airway surface hydration and airway clearance, inhaled hypertonic therapy was evaluated. Patients with CF, age 6 years and older, inhaled 7% hypertonic saline twice daily following a bronchodilator for 48 weeks; results revealed only a modest improvement in FEV_1, but a significant reduction in the number of pulmonary exacerbations and days lost from school or work.[87] Inhaled 7% hypertonic saline did not decrease the frequency of pulmonary exacerbations in CF infants and children less than 6 years of age,[88] and therefore did not meet the primary outcome for approval as a maintenance therapy in this age group. However, in a subset of infants tested, infant pulmonary function testing revealed an improvement in $FEV_{0.5}$ in the hypertonic saline group suggesting that this therapy may be useful and considered on an individual basis.

Bronchodilators and Anti-Inflammatory Agents

Bronchodilators are often used in treating the pulmonary manifestations of CF. Their use should be individualized. For example, in many patients, bronchospasm that is reversible with bronchodilators at one point in the course of the illness may prove refractory a short time later. Some patients undergo deterioration in pulmonary function following use of bronchodilators. In infants who are audibly wheezing, a bronchodilator can be tried. In older patients, pulmonary function testing provides a more objective and quantitative measure of bronchodilator effectiveness.

Corticosteroids have been used with good results in infants with severe obstructive airway disease that does not respond to antibiotics and bronchodilators and in patients with CF in whom the pulmonary disease is complicated by severe asthma or allergic bronchopulmonary aspergillosis (ABPA). Preliminary observations initially suggested that patients with CF would benefit from long-term administration of alternate-day corticosteroids, based on the presumption that corticosteroids would decrease the airway inflammatory response. However, in a large, placebo-controlled, multicenter trial of alternate-day corticosteroids administered in two dosage regimens (1 mg/kg and 2 mg/kg), the development of many side effects precluded a general recommendation for long-term corticosteroid treatment in CF.[89] Subgroup analysis led to the suggestion that patients with moderately severe obstructive airway disease and those with chronic *Pseudomonas* infection might benefit from treatment for periods of less than 1 year. Beneficial effects were sufficient to prompt further studies of anti-inflammatory agents in CF. A controlled 4-year trial of high doses of ibuprofen in 40 patients with CF showed improvement in the rate of decline of pulmonary function in children.[90] Questions remain whether side effects that might accrue with continued therapy will justify the gains. In concert, these two studies suggest that future development of a lung-specific anti-inflammatory agent with fewer systemic side effects may offer a promising approach.

Antibiotics

Two major innovations using antibiotics have been implemented as part of the regimen of maintenance therapy for CF. First, inhaled therapies have been demonstrated to successfully eradicate initial *Pseudomonas* infection and postpone chronic colonization in three large prospective trials of patients with CF in North America and in Europe.[91–93] Second, chronic inhaled and/or oral antibiotic therapies successfully decrease the progression of lung disease related to chronic *Pseudomonas* infection. In addition to these therapies, it is important to emphasize that person-to-person transmission of *P. aeruginosa* and other opportunistic microbes is another source for chronic colonization. In healthcare facilities for CF patients, contact isolation precautions are recommended.[94]

Chronic airway colonization/infection with *P. aeruginosa* promotes progression of lung disease. Hoiby et al. championed early treatment of *P. aeruginosa*–positive sputum cultures with inhaled colistin and oral ciprofloxacin, even in the absence of symptoms, as a modality to prevent chronic colonization.[95] The EPIC trial[91] tested four randomized regimens: Cycled therapy versus culture-driven therapy; and 28 days of inhaled tobramycin inhalation solution (TIS) in the presence or absence of 14 days of oral ciprofloxacin. Approximately 80% of patients remained free of *P. aeruginosa* for the duration of the study (18 months) with no difference concerning time to first pulmonary exacerbation attributed to regularly cycled therapy or the addition of ciprofloxacin. The ELITE study[92] was an open label randomized study comparing 28 to 56 days of inhaled TIS which revealed approximately 90% eradication at the end of therapy with 66% to 69% of patients having *Pseudomonas*-free cultures at the end of the 27-month study. In addition, a trial comparing inhaled colistin and oral ciprofloxacin to inhaled TIS and oral ciprofloxacin showed no difference between regimens in eradication with approximately 62% to 65% of patients with *Pseudomonas*-free cultures at 6 months.[93] Therefore, although the evidence from these three studies supports antibiotic eradication of new *Pseudomonas* infection, there is no consensus yet for a specific therapeutic regimen.

Another approach that has been advocated is suppression of chronic *Pseudomonas* colonization by alternating monthly cycles of inhaled antibiotics. Inhaled, preservative-free TIS, 300 mg twice daily for 28 days on and 28 days off, improved pulmonary function (FEV_1 increased by 10%) at the end of the third treatment cycle (20 weeks) compared to placebo.[96] Recently, inhaled aztreonam, 75 mg three times per day, was tested in an open label study of cycling monthly regimen for patients with chronic *P. aeruginosa* infection.[97] Patients reported improved symptoms and pulmonary function during on-therapy months with sustained weight gain over the 18-month duration of the study. Currently, prospective clinical trials are evaluating the efficacy of continuous alternating inhaled antibiotics compared to on–off cycling inhaled antibiotics.

Another antibiotic which has been studied as a chronic therapy in CF is azithromycin. Azithromycin, 250 mg or 500 mg thrice weekly, was evaluated in CF patients colonized with *P. aeruginosa*. After 6 months of therapy, patients on azithromycin had a modest improvement in FEV_1 (6.2%), increased weight gain, and decreased rates of pulmonary exacerbations.[98] Although macrolide antibiotics have been reported to have anti-inflammatory properties,[99] there is no direct evidence of azithromycin-induced anti-inflammatory activity in CF. One concern about inhaled tobramycin, inhaled aztreonam, and oral azithromycin as chronic therapies is the risk of bacterial resistance and selection for growth of MDRO. In addition, questions regarding selection of patients and timing and duration of treatment remain unanswered.

CFTR Potentiators and Correctors

The most exciting breakthrough in CF therapies was announced in 2011 with the proof-of-concept demonstration that an oral drug, ivacaftor®, corrected the physiologic impact of a CFTR mutation, G551D. The G551D mutant CFTR protein is expressed at the cell surface but does not conduct chloride or regulate other ion channels. Ivacaftor® was discovered using a high throughput screening approach.[100] In a

phase III randomized, placebo-controlled, double-blind trial for CF patients with at least one copy of G551D mutation, ivacaftor®, administered orally, 150 mg twice per day for 48 weeks, increased FEV_1 percent predicted by 10.6%, decreased risk of pulmonary exacerbations by 55%, improved CF quality of life (CFQL) respiratory symptom scores by 8.6 points, decreased sweat chloride values by 48 mmol/L, and was associated with an average 2.7-kg weight gain.[67] Currently, other mutations similar to G551D are being tested as potential ivacaftor® targets. Importantly, other compounds that potentially correct F508del CFTR are being tested. One lead compound, VX-809 has been reported to decrease sweat chloride values in a dose-dependent manner.[101] VX-809 will be combined with ivacaftor® for complementary combined therapy to enhance both processing and functioning of F508del-CFTR in homozygous patients.

Management of Acute Exacerbations of CF Bronchitis

During the past few decades of treatment of CF, antibiotics have proven to be the key element responsible for increased survival. A reasonable approach balances the dangers of overzealous administration of antibiotics against progressive airway damage and bronchiectasis resulting from untreated infection. The approach is based on sputum culture at the time of diagnosis and at regular intervals thereafter.

When signs and symptoms herald an exacerbation of pulmonary infection (i.e., increased cough or sputum production, dyspnea, decreased exercise tolerance, decreased appetite) or new abnormalities on the physical examination (i.e., increased respiratory rate, use of accessory muscles, changes on auscultation of the chest including decreased breath sounds, new crackles or wheezes, weight loss), new abnormalities on the chest radiograph, or a decline in pulmonary function tests, chest physiotherapy is increased and appropriate antibiotics are given orally, or for severe exacerbations, intravenously.

Currently useful agents for treating staphylococcal infections include dicloxacillin, cephalexin, the third-generation penicillin–clavulanic acid combinations, and macrolides. Early in the course of the pulmonary disease, a small fraction of *Pseudomonas* strains may be sensitive to tetracycline, trimethoprim/sulfamethoxazole, or chloramphenicol. Occasionally, even *Pseudomonas* strains considered resistant according to laboratory sensitivity tests apparently respond to these antibiotics. A mechanism that has been proposed to account for this phenomenon is that even though the antibiotic is not bactericidal, it may inhibit either growth of the organism or its production of exotoxin and proteases. Ciprofloxacin, a quinolone derivative that can be given orally, is initially effective against many strains of *Pseudomonas* and has gained widespread use in the outpatient management of CF. A major disadvantage in its use is that resistance often develops after a few courses of treatment.

For treatment of a severe pulmonary exacerbation of CF caused by methicillin-resistant *Staphylococcus*, vancomycin or linezolid are indicated. For *Pseudomonas,* a combination of an aminoglycoside given intravenously and a semisynthetic penicillin is generally used. This combination is presumed to act synergistically on *Pseudomonas*, and the *Pseudomonas* is less likely to become resistant to either antibiotic.

The most popular antibiotic combination currently in use is tobramycin and ceftazidime. To achieve high levels of antibiotics in the airways and in secretions, the aminoglycoside is generally administered in higher doses, 10 mg/kg/d instead of 7.5 mg/kg/d. A recent randomized trial comparing once-daily versus three-times–daily regimens of tobramycin revealed that once-daily IV therapy provided equivalent efficacy with less nephrotoxicity in children.[102] Dosing should be titrated for serum peak levels of 20 to 30 mg/L and trough levels of 1 mg/L or less.

Third-generation penicillins and cephalosporins, piperacillin, and ceftazidime; carbapenems, imipenem and meropenem; and the latest β-lactam, aztreonam, are also quite effective against *Pseudomonas.* When given alone, resistance often develops quickly. Usually, these agents are used in combination with an aminoglycoside. Because the sensitivity and resistance patterns of the *Pseudomonas* often change, various combinations are tried at different times, with clinicians relying on sensitivities from recent isolates to determine which is most effective for the particular strain of *Pseudomonas.* For other resistant gram-negative organisms, such as *B. cepacia, S. maltophilia,* and *Achromobacter xylosoxidans,* other antibiotic combinations are indicated, including ceftazidime, meropenem, ciprofloxacin, minocycline, aztreonam, chloramphenicol, or trimethoprim/sulfamethoxazole.

Staphylococcus, Pseudomonas, and other gram-negative organisms, such as *B. cepacia, A. xylosoxidans,* and *S. maltophilia*, once found in the sputum, are rarely eradicated. However, most other manifestations of an exacerbation of pulmonary disease abate during a 2-week course of antibiotics administered intravenously; for example, the densities seen on the chest radiograph decrease, the white blood cell count decreases, fever and respiratory rate decrease, and pulmonary function test results, which often deteriorate at the start of an exacerbation, return to their previous baseline. Although many patients begin to show improvement after 5 to 7 days, most CF centers continue antibiotics intravenously for at least 2 weeks to decrease the relapse rate and to avoid a decrease in the interval between exacerbations. Indeed, some centers routinely recommend a 3- to 4-week course of intravenous antibiotics to treat an exacerbation of a pulmonary infection. In the occasional-hospitalized patient who experiences a relapse or manifests an increase in symptoms shortly after administration of intravenous antibiotics is stopped, long-term intravenous administration of an aminoglycoside can be continued with use of a heparin lock. This technique may be helpful in allowing the patient to return home while still receiving effective doses of aminoglycosides.

Nutritional Support

Patients with CF should have a detailed nutrition assessment at diagnosis and annually as per the CFF guidelines.[60] Nutritional status should be screened at every visit. Patients are prescribed a high-calorie balanced diet. The CFF recommends that for infants and young children (0–2 years) weight for length be maintained at the 50th percentile and that children and adolescents (2–20 years of age) have their BMI percentile at the 50th percentile. Although it is true that pulmonary function is the predominant factor in determining morbidity and mortality in CF, it is becoming increasingly clear that overall patient status is closely tied to nutritional status. Importantly, achieving and maintaining normal nutritional status is associated with maintenance of lung function in young children and adults. Calorie goals are often 110% to 120% of usual calorie requirements. At these caloric intakes, protein intake is often adequate to meet needs. Patients are encouraged to achieve calorie goals by the ingestion of calorically dense foods. If this is hard to achieve, calorie boosters (vegetable oils, butter, and cheese) are recommended followed by the use of high-calorie supplements (shakes). Calorie needs may be increased in patients with chronic lung disease, malabsorption, and chronic liver disease. Nocturnal nasogastric feeds may be used in the short term for aggressive nutritional rehabilitation, and patients who need long-term support have placement of a gastrostomy tube for ease of care. Typically standard formulas are used but some patients with feeding intolerance and poor weight gain benefit from hydrolyzed formulas. Intravenous or parenteral nutrition is rarely used, but may be required in patients who have had GI surgery.

Pancreatic status (insufficiency or sufficiency) should be determined and monitored as needed. The mainstay in managing the pancreatic insufficiency of CF is PERT which consists of enteric-coated capsules containing amylases, proteases, and lipases. PERT should be ingested before meals that contain protein, fat, or complex

carbohydrates. Dosing guidelines have been developed by the CFF. Fibrosing colonopathy or the development of colonic strictures is a complication that appears to be related to high PERT doses exceeding 10,000 lipase units/kg/d and was first noted following the introduction of high-potency pancreatic enzymes.[103] Most patients can be managed with pancreatic enzyme doses within the published guidelines. Patients who require higher pancreatic enzyme doses should be evaluated by a dietitian and a pediatric gastroenterologist.

Patients with pancreatic insufficiency are at risk for fat-soluble vitamin deficiency. Guidelines also exist for vitamin supplementation and CF-specific vitamin products are available.[60] It is recommended that fat-soluble vitamin status be monitored annually and additional supplements (Vitamin D) may be required if levels are still low. It is very unusual for patients with CF to be vitamin A deficient if they are on a CF-specific vitamin preparation. Supplemental salt is needed by patients to prevent salt depletion. Salt is added to infant formula and children and adults are encouraged to salt their foods liberally and to take salt-containing liquids and snacks during hot weather and periods of increased physical activity.

MANAGEMENT OF CYSTIC FIBROSIS–RELATED DIABETES

Insulin is the treatment of choice for CFRD, and ideally the regimen is customized to fit the needs of the individual patient. Combinations of basal (long-acting) and bolus (rapid-acting) insulins are used in the treatment of CFRD with FH. In the absence of FH, premeal rapid-acting insulin is the main treatment approach. Frequent meals, snacking, and "grazing" are not uncommon in CF, and the requirement of multiple daily injections can be prohibitive for some individuals. The insulin pump offers flexibility and can negate the need for frequent injections.[104] Moreover, calories are not restricted in CFRD although either avoidance of foods of low nutritional value (sugared soda or confection) or their consumption in combination with complex carbohydrates, protein, and fats is useful in avoiding excessive hyperglycemia. Pancreatic enzyme replacement also appears to improve meal-related glucose excursion.[36] The role of treatment of prediabetes and early insulin deficiency in preserving pancreatic β-cell function, pulmonary function, and nutritional status has yet to be defined.

NATURAL HISTORY AND PROGNOSIS

A comprehensive treatment program for CF has unequivocally improved overall survival of patients. Fifty years ago, the median survival was only a few years of age. For the 5-year period from 2007 to 2011 the median predicted survival was 36.8 years of age (CF Foundation Patient Registry, 2011 Annual Data Report, Bethesda, MD). However, because CF is a complex disorder that affects different organs to different degrees, it is difficult to describe a "typical course" for a patient with CF. Some patients die in childhood or adolescence, while others survive well beyond age 40.

An important determinant of the natural history of CF is the severity of the pulmonary disease and the rate at which it progresses. Although most patients' condition improves in response to therapy, skillful management does less to influence the course of the severely affected than that of the mildly affected patient.

A variety of scoring systems have been devised for CF. The clinical scoring system devised by Shwachman and Kulczycki and the chest radiograph scoring system devised by Brasfield and associates are widely used. However, although these and more elaborate scoring systems are useful in categorizing patients according to the severity of illness, none has proved useful in prognosticating the course of an individual patient.

Because CF is a genetic disease, the question of a familial pattern of severity is often raised. Figure 50-7 shows chest radiographs of three siblings with CF; the radiographs demonstrate mild, moderate, and severe disease in individuals in the same family. The capsule histories, which are included in the figure legend, also illustrate the variability in courses experienced.

Patients with CF can be categorized not only with respect to severity of illness, but also with regard to survival. For example, more than half of patients with CF who underwent surgery for meconium ileus before 1965 died in the first 2 months of life. Although this situation had improved markedly by 1976, the survival rate for patients with meconium ileus was still not as good as for all other patients with CF. In addition, the survival rate was much lower for females than for males, especially in adolescents. In recent years, differences between the patients in these groups have declined or disappeared. Because of improvements in the collection of mortality statistics, comparison of current data with those from previous years may be somewhat misleading, but 50% survival age has not been increasing as rapidly in recent years as in the 1970s and 1980s. Furthermore, there is a difference in outcomes among individual CF centers.

COMPLICATIONS

The course of CF is often characterized by a gradual decrease in pulmonary function, punctuated by further abrupt declines during exacerbations. Malnutrition, when present despite therapy, usually correlates best with the severity of the pulmonary disease. However, the course of CF may be suddenly altered by certain complications of the disease.

HYPOELECTROLYTEMIA AND METABOLIC ALKALOSIS

Hypoelectrolytemia and metabolic alkalosis are serious complications that are especially apt to occur during periods of hot weather, when losses of sodium and chloride increase. Electrolyte depletion may be life-threatening, especially in infants and young children (Table 50-3). Prompt fluid replacement with isotonic saline is critical.

INTESTINAL OBSTRUCTION

Intestinal obstruction in patients with CF may be related to distal intestinal obstructive syndrome (DIOS), volvulus, intussusception, and adhesions from prior surgery. Acute or chronic crampy abdominal pain can be seen in patients with CF with pancreatic insufficiency and pancreatic sufficiency. This is most often due to DIOS which is related to intestinal dysmotility, poor hydration of intestinal contents, and malabsorption. Typically the pain is in the right lower quadrant of the abdomen and is related to a buildup of stool in the terminal ileum, cecum, and ascending colon. Treatment consists of adequate fluid and electrolyte intake, use of polyethylene glycol solutions, and treatment of malabsorption. If the obstruction is incomplete and manifested solely by a tender right lower–quadrant mass, then the above-described measures are used. Nasogastric infusion of polyethylene glycol solutions is also used successfully in the hospitalized patient. If these measures are unsuccessful or the patient has an obstruction, then hyperosmolar contrast enemas are administered by a radiologist

TABLE 50-3 Hypoelectrolytemia and Metabolic Alkalosis in Two Cystic Fibrosis Patients

Patient	Serum Electrolytes, mEq/L				Serum pH
	Na	K	Cl	CO_2	
No. 1	123	2.2	49	48	7.60
No. 2	125	2.4	55	41	7.63

Source: Modified with permission from Scanlin TF. Cystic fibrosis, in Fleisher G, Ludwig S (eds). Textbook of Pediatric Emergency Medicine. Baltimore: Williams & Wilkins; 1983.

after hospitalization is required. It is important that patients are well hydrated, that the terminal ileum is cleared of stool and that an abdominal x-ray is performed to document clearance of stool prior to the patient being discharged from the hospital. Adherent stool/mucus may serve as the leading edge for a volvulus or intussusception (Fig. 50-6) and surgical consultation may be required. Careful pre- and postoperative management is essential to avoid the deterioration in pulmonary function that may follow the use of anesthesia.

LIVER DISEASE

Liver disease is often asymptomatic and can be detected by evaluation of liver function tests on routine yearly studies. Assessment of liver status (synthetic function) and anatomy (abdominal ultrasound with Doppler) are important in the diagnosis of cirrhosis and portal hypertension. Only a small percentage of patients with significant liver disease will need liver transplantations unlike other chronic liver diseases seen in children. Liver biopsy is recommended in patients in whom an etiology other than CF liver disease needs to be established.[105] It is recommended that other causes of liver disease be ruled out and that patients receive hepatitis A and B immunizations. There is a paucity of data to support the routine use of ursodeoxycholic acid in patients with CF-related liver disease. However, this medication is often used in doses of 10 to 20 mg/kg/d as a choleretic agent to improve bile flow.[59] Persistent hepatomegaly or splenomegaly, or complications of portal hypertension establish significant liver involvement. Patients may develop esophageal varices as a result of portal hypertension and present with upper gastrointestinal bleeding. Once bleeding has been identified as due to varices and hemoptysis has been excluded, therapeutic endoscopy (sclerotherapy or band ligation) is required. For patients with complications of portal hypertension, transjugular intrahepatic portosystemic shunting or surgical portosystemic shunts can effectively decompress esophageal varices by decreasing portal pressure as a bridge to liver transplantation.

Liver transplantation is another option for many patients with CF who have end-stage liver disease. Indications include significant synthetic dysfunction, unresponsive or recurrent esophageal varices with recurrent upper GI bleeding, ascites, and encephalopathy. Patients need to be evaluated by a hepatologist. Ideal candidates are those with an FEV_1 of at least 50% of predicted. Colonization with a multidrug-resistant or panresistant strain of *Pseudomonas* is a relative contraindication to transplantation. In patients in whom poor pulmonary function or drug-resistant pulmonary infection is an issue, double organ (liver and lung) transplantation may be considered. Despite concerns about worsening airway infection during transplant-associated immunosuppression, liver transplantation in patients with CF does not worsen their pulmonary status.[106]

ATELECTASIS

Atelectasis of a lung segment or lobe sometimes occurs in CF. Acute atelectasis is generally associated with few symptoms (Fig. 50-9A). If it is untreated, however, the end result of atelectasis is a severely bronchiectatic segment or lobe (Fig. 50-9B). Vigorous chest physiotherapy, in conjunction with antibiotics, is often successful in reexpanding the affected lung region. Bronchoscopy is occasionally helpful. As a rule, however, bronchoscopy is no more effective than chest physiotherapy and pulmonary pharmacotherapy. Resection of a persistently atelectatic or bronchiectatic lobe is undertaken only when the remaining areas of the lung are in relatively good condition, overall pulmonary function is good, and the evidence convincing that the affected segment is responsible for intolerable symptoms (fever, cough, or sputum production).

PNEUMOTHORAX

Recurrent pneumothorax is common in CF, particularly in older patients (Fig. 50-9C). Tension pneumothorax occurs in up to 30% of patients with CF who develop pneumothorax. Tube thoracostomy is indicated when the pneumothorax occupies more than 10% of the area of the hemithorax seen on the posteroanterior chest radiograph. Because the frequency of recurrence of pneumothorax is high, attempts are often made at the time of the initial event to achieve chemical or surgical pleurodesis. Surgical pleurodesis is more effective at preventing recurrence of a pneumothorax and is no longer considered a contraindication to lung transplantation.

HEMOPTYSIS

Expectoration of a small amount of blood-streaked sputum is a fairly common occurrence in CF and is generally managed by intensifying home therapy for pulmonary infection. In contrast, hemoptysis (the expectoration of at least 30–60 mL of fresh blood) requires hospitalization, even with a chest radiograph that is virtually unchanged (Fig. 50-9D). The probable mechanism underlying most instances of hemoptysis in CF is the erosion of an area of localized infection into a bronchial vessel. Massive hemoptysis (blood loss of 240 mL) is uncommon in CF. However, it represents a potentially life-threatening situation. Bronchoscopy, and sometimes thoracic surgery, may be required to control the hemorrhage. Bronchial artery embolization has been used successfully in patients with CF and is now the treatment of choice when a physician experienced in the procedure is available.[107]

INFECTION WITH UNUSUAL ORGANISMS

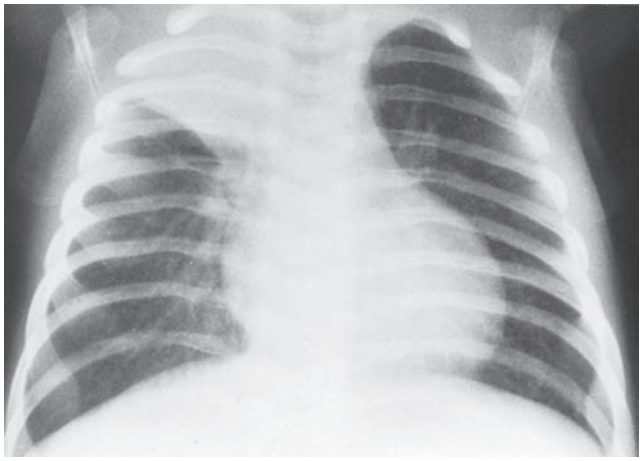
CF produces central bronchiectasis, even though the disease initially is in the small bronchioles. Bronchiectatic airways are frequently colonized with unusual organisms, including *Aspergillus* and atypical mycobacteria. As is the case with pathogenic bacteria, eradication of these organisms from the airways is virtually impossible. The focus of therapy is directed toward verifying that the organisms are resulting in worsening of the disease and controlling the infection, rather than effecting a microbiologic cure.

Mycobacteria

The prevalence of infection with atypical mycobacteria in CF mandates surveillance for these organisms in sputum cultures at least annually.[108] When atypical mycobacteria are cultured, antimicrobial sensitivities should be obtained. A decision about therapy for isolation of atypical mycobacteria is based on the likelihood that the organism is contributing to airway infection and a decline in pulmonary function. Isolation of the same organism on several occasions, positive smears, presence of progressive chest radiographic changes, further decline in pulmonary status despite vigorous antipseudomonal (or antistaphylococcal) therapy, persistent night sweats, and fever are clinical clues that the atypical mycobacteria are contributing to disease. Demonstration of tissue infection with transbronchial lung biopsy is rarely recommended. A clinical database has been established by the CF Foundation to track results of treatment for atypical mycobacterial infections in patients with CF. The current standard for therapy is treatment with several antimicrobials for synergy and to prevent development of resistance.

Aspergillus

In an analogous fashion, molds, especially *Aspergillus,* are occasionally isolated from patients with CF. Approximately 5% to 15% of patients have ABPA. The diagnosis of ABPA in CF is difficult because of overlapping symptoms between the two disorders. Diagnostic criteria for ABPA are (1) reversible airway obstruction, (2) proximal bronchiectasis, (3) history of pulmonary infiltrates, (4) skin test positivity to aspergillus antigens, (5) precipitating serum antibodies to *A. fumigatus*, (6) elevated total serum immunoglobulin E (IgE), (7) elevated specific serum IgE and serum immunoglobin G (IgG) to *Aspergillus,* and (8) peripheral eosinophilia. A negative skin test for *Aspergillus* effectively rules out the diagnosis of ABPA. During the



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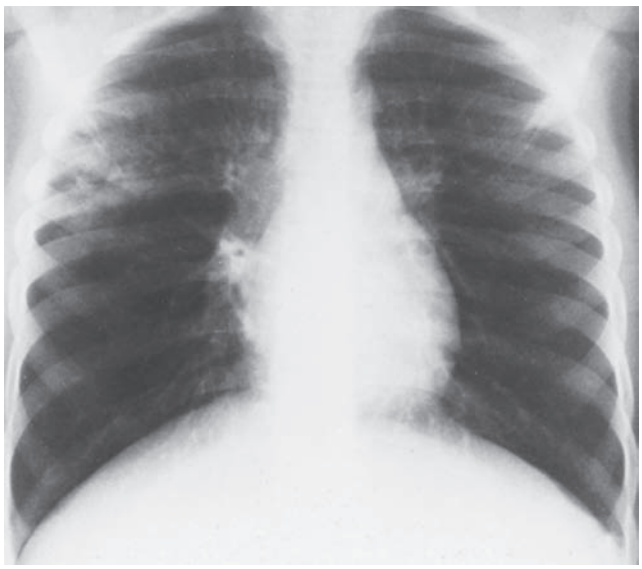

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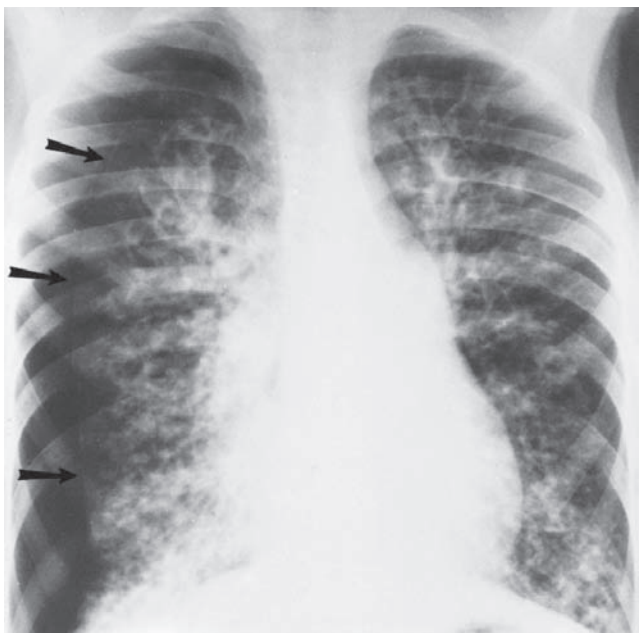

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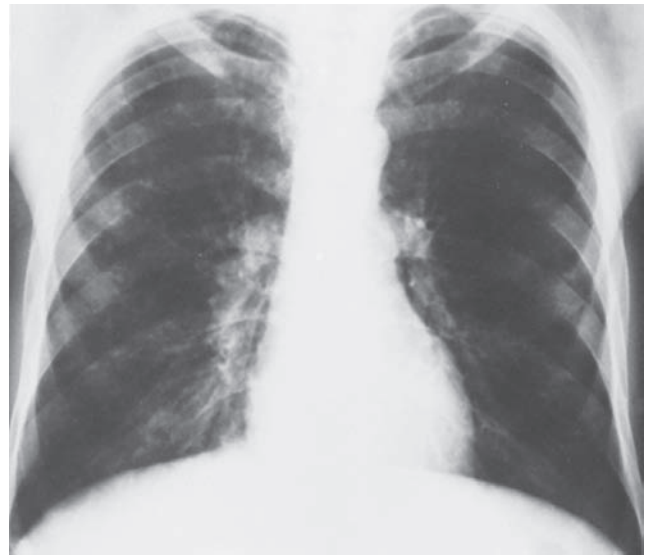

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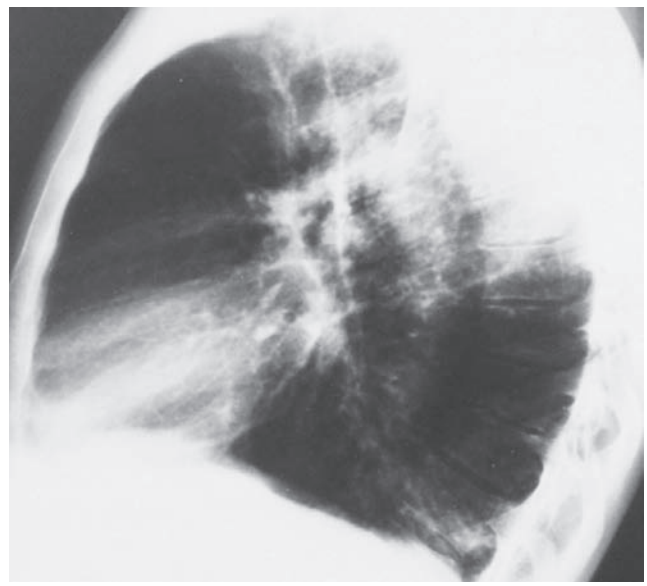

E

Figure 50-9 Chest radiographs of patients with pulmonary complications of CF. **A.** Atelectasis of the right upper lobe in a 4-month-old boy. The atelectasis resolved with antibiotics and chest physiotherapy. **B.** The same patient at 9 years of age with mild hyperinflation, central bronchiectasis, resolving right upper lobe infiltrate. The diagnosis of allergic bronchopulmonary aspergillosis was made, and the patient improved after treatment with prednisone. **C.** Pneumothorax of the right lung *(arrows)* in a 13-year-old boy. The pneumothorax resolved after tube thoracostomy and tetracycline sclerosis. The patient died 3 years later from respiratory failure with congestive heart failure. There were no recurrences of the pneumothorax. **D, E.** A 43-year-old man showing hyperinflation and diffuse peribronchial thickening. The radiograph was taken during an episode of significant hemoptysis, and no acute changes were seen on the radiograph.

active phase of ABPA, elevations in total IgE and eosinophil count are seen. Rises in *Aspergillus*-specific titers (IgE and IgG) are more specific for ABPA than are serum precipitins. ABPA in patients with CF is treated with corticosteroids and itraconazole. The level of total IgE is used to follow the activity of the disease.

Gram-Negative Bacteria

In the late 1970s and early 1980s, the importance of *B. cepacia* (formerly *Pseudomonas cepacia* [PC]) was recognized. *B. cepacia* is a gram-negative, oxidase-positive rod that is uniformly resistant to polymyxin and, frequently, panresistant. Isolation of *B. cepacia* requires plating on special oxidative fermentive polymyxin B bacitracin lactose (OFPBL) or PC agar plates to retard growth of other gram-negative rods and enhance growth of *B. cepacia.* The plates must be maintained for a minimum of 4 days. *B. cepacia* colonization has been associated with septicemia, which is very rarely seen with *P. aeruginosa.* The clinical course after acquisition of *B. cepacia* may be fulminant, with death occurring in a matter of months. However, most patients' disease follows a more benign course. Carefully controlled epidemiologic studies are needed to better define risk factors and to establish the true virulence of *B. cepacia.* Experimental evidence exists that at least one strain of *B. cepacia* may be transmitted in an epidemic fashion. The combination of a poor clinical course after acquisition of *B. cepacia* and the evidence supporting epidemic transmission has led to cohorting or isolation of patients with CF infected with *B. cepacia,* as recommended by the CF Foundation and the Centers for Disease Control (CDC).

In addition to being colonized with *Pseudomonas* and *Burkholderia* species, patients with CF may be colonized with other gram-negative, oxidase-positive organisms, such as *S. maltophilia, Pseudomonas oryzihabitans,* and *A. xylosoxidans*. These are pathogenic organisms, similar in importance to *P. aeruginosa*. Antibiotic therapy should be directed toward these bacteria when they are isolated from the patient with CF who is experiencing an acute exacerbation. The prolonged, prophylactic, aggressive use of antibiotics in CF has led to emergence of resistant organisms. A multiply resistant *Pseudomonas* is an organism that is resistant to all agents in at least two different classes of antibiotics. Resistance to oral fluoroquinolones occurs after about 3 weeks of therapy; if the agent is withheld, the organism occasionally becomes sensitive again.

■ RESPIRATORY FAILURE

As the pulmonary disease of CF progresses and the degree of hypoxia increases, patients are at risk to develop pulmonary hypertension and cor pulmonale. An increase in hypoxia often occurs during exacerbations of the pulmonary disease. During the acute episode, antibiotic treatment for the underlying pulmonary disorder is intensified and supplemental oxygen is added. Expectant monitoring and aggressive treatment of nocturnal hypoxemia (maintaining $Sa_{O_2} \geq 95\%$) prevent the onset of cor pulmonale. When respiratory failure develops in CF, that is, hypercarbia (Pa_{CO_2} at least 55 mm Hg) in addition to hypoxemia, management becomes extremely difficult. Noninvasive mechanical ventilation using bilevel positive airway pressure has been used successfully in patients with end-stage CF awaiting lung transplant; it improved oxygenation, reduced respiratory rate, and was successfully transitioned to home nocturnal use.

Mechanical ventilation is generally instituted when an acute episode, such as viral pneumonia or status asthmaticus, thrusts the patient into acute respiratory failure. This approach is particularly indicated in the patient who has had good pulmonary function before the acute episode. Mechanical ventilation is less apt to be successful if the patient has previously experienced a bout of respiratory failure. When respiratory failure marks the end of a chronic course of progressive pulmonary insufficiency despite adequate medical therapy, mechanical ventilation is usually unhelpful. None of the indications or contraindications for mechanical ventilation is absolute; however, and the clinical outcome depends, to a large extent, on the availability of a dedicated and skilled intensive care team experienced in caring for patients with CF.

■ COMPLICATIONS RELATED TO LUNG TRANSPLANTATION

Lung transplantation has emerged as an option for patients with end-stage CF.[109] Despite initial concerns about immunosuppression in patients with suppurative lung disease, the outcome for those with CF who undergo lung transplantation is among the best reported for this procedure. Timing for lung transplantation has changed with the adoption of a Lung Allocation Score (LAS) which takes into consideration parameters to predict 1-year survival, with a transplant versus without a transplant, and medical urgency. The impact of this organ allocation system is a dramatic decrease in the number of patients on the waiting list for transplantation and a significant shortening of wait times for transplantation.

One major complication postlung transplantation for CF patients is the risk of infection due to resistant organisms. Colonization with *B. cepacia complex*, or rapidly growing mycobacteria such as *M. abscessus*, has been reported to negatively impact survival.[110] *Aspergillus* may cause invasive infections in the parenchyma or the anastomosis site. Other complications, not specific to CF patients, include acute and chronic graft rejection. Acute graft rejection is associated with a humoral immune response to donor HLA antigens and complement activation.[111] Importantly, acute graft rejection is a negative prognostic factor for chronic graft rejection. Chronic allograft rejection is characterized by obliterative bronchiolitis following transplantation. Obliterative bronchiolitis is a progressive occlusion of the bronchiolar lumina by inflammatory cells and submucosal fibrosis. Transient improvement in airflow is seen following augmentation of immunosuppression. About 50% of transplant patients develop obliterative bronchiolitis after the second year following the procedure. The disease pursues a relentless downhill course, with a median survival of about 2 years following the initial diagnosis.

The poor prognosis associated with obliterative bronchiolitis has several important implications for patient selection and timing of referral for transplantation. First, the main reason for seeking lung transplant is to improve the quality of life, rather than to improve survival. Second, the timing of referral for lung transplantation needs to be calculated to optimize the candidate's fitness for transplant yet delay transplant until absolutely necessary considering the risk of developing obliterative bronchiolitis.

Results from clinical studies may aid with proper timing of referral for lung transplantation in CF. CF patients with severe airflow obstruction as indicated by FEV_1 less than 30% of predicted have a 50% 2-year mortality. Other important clinical parameters useful in determining the timing of transplantation are the presence of hypoxemia (Pa_{O_2} under 55) and hypercarbia (Pa_{CO_2} above 50). Of interest, in both single and multivariate analyses, female gender is associated with an increased relative risk, suggesting that for female patients, referral for lung transplantation should be considered at an even earlier stage.

Because CF is a multisystem disorder, both management and proper selection of patients are more complicated than for other diseases managed with lung transplantation. Among the most difficult challenges presented by patients with CF before transplantation is the microbiology of their lower airways. As discussed previously, colonization with multidrug-resistant *B. cepacia*, specifically the genotype, genomovar III, has been associated with a poor clinical outcome. For poorly understood reasons, patients with CF metabolize drugs differently from those without CF, complicating the dosing of medications, including cyclosporine. The difficulties in achieving an optimal drug dose may be related to malabsorption or enhanced excretion of the drug. Nutritional issues also complicate the posttransplantation management of patients with CF. About

50% of all patients with CF over 30 years of age are overtly diabetic, and administration of corticosteroids induces diabetes in another 10%. Maintenance of proper nutrition is important in CF, especially for rapid postoperative recovery. Finally, gastroesophageal reflux may negatively impact pulmonary outcomes following transplantation. Despite all the special challenges to successful lung transplantation posed by patients with CF, their actuarial survival is quite good. The median survival is 7.1 years, reinforcing the tenet that lung transplantation is done principally to improve quality of life.

PSYCHOSOCIAL ISSUES

A number of psychosocial issues are important in the management of patients with CF. Special circumstances should be recognized for adults with the disorder.

GENERAL

Careful attention to the emotional, social, and financial well-being of the patient with CF and his or her family has considerable value in favorably influencing the course of the disease. At the time of diagnosis, it is important to strike an optimistic note while educating the patient about the illness and its management. As part of the early encounter with the patient, the importance of identifying and reinforcing the emotional and financial strengths of the family, as well as weaknesses that will need buttressing, should be recognized. Medical care for CF patients is costly, especially if hospital admissions are required. Many states have programs for children with disabilities that provide support for patients and families. Several states have also established special programs for adults with CF.

As the disease runs its course, counseling and feedback about disease progression are essential. As the patient and family go about setting educational, career, and family goals, they need guidance in realistic planning. It is vital that the physician develop and maintain a positive attitude. The patient who gives up hope is liable to undergo rapid deterioration. Conversely, even patients with severe pulmonary disease can continue to function well and be productive. At the stage when medical therapy is of no further avail, however, the patient and family require considerable emotional support to accept the inevitable. In recent years, many CF centers have allowed patients to die at home, rather than in the hospital. The family requires specific instructions about how to provide physical and emotional comfort for the patient in the home. Usually, home visits by some members of the CF team are required. Not all families have the strength or resources to care for the patient dying at home.

SPECIAL CONSIDERATIONS IN ADULT PATIENTS

In the 5-year period spanning 2007 to 2011, the median life expectancy for patients with CF was about 37 years (CF Foundation Patient Registry, 2011 Annual Data Report, Bethesda, MD). Managing a chronic illness becomes more complicated when patients must also begin to manage their independence and make life decisions regarding education, marriage, children, careers, insurance, and self-care. Intense support for both patients and their families is required. Patients with a relatively mild clinical course of disease form healthy and satisfying relationships in a manner similar to that of their healthy, age-matched peers. With advanced disease, patients with CF have more difficulty in forming intimate relationships. Disturbances in body image, decreased mobility, and lack of opportunity to meet suitable partners are cited as reasons for the decreased ability to form intimate relationships in the severely affected young adult with CF.

The adult patient with CF faces unique problems with self-care. Families of patients with CF provide a tremendous amount of care that is expensive and time-consuming to replace for the independently living adult. When the disease flares, patients must "step up" their level of care at precisely the time when they are least able to do so. Judicious use of hospitalization and home care must be provided if the patient is to recover. The trend toward home management of a pulmonary exacerbation using intravenous antibiotics alone ignores the obvious contributions of nutrition, airway clearance, and rest toward resolution of the problem.

REPRODUCTIVE ISSUES

More than 98% of male patients with CF are sterile, secondary to bilateral absence of the vas deferens. Microsurgical epididymal sperm aspiration (MESA), coupled with in vitro fertilization, has been successful in producing pregnancies in a few carefully selected patients. Not all males with CF are sterile, however. In addition to counseling, these men should be offered semen analysis.

Pregnancy for women with CF is increasingly common, and several important issues remain unsolved. In 2004, 191 women with CF were pregnant (CF Foundation Patient Registry, 2004 Annual Data Report, Bethesda, MD). This stands in marked contrast to the total of 13 pregnancies in 10 patients recorded from 1960 to 1966 (data from the 1994 CF Foundation Data Registry).

Maternal clinical status before pregnancy is the most important prognostic factor of maternal outcome. In a study of 25 women with 38 pregnancies, no significant difference was seen between pre- and postgravid gas exchange or nutritional status. A small, but statistically significant, decline in spirometry was noted. However, the decline was not outside the range of expected decline for the natural progression of the disease. More severely affected women suffered an irreversible decline in clinical status during pregnancy. Without an appropriately matched control group of nongravid women with CF, it was not possible to determine whether pregnancy per se was responsible for the decline or whether the decline is a reflection of the natural history of the disease. Comparison of matched groups of pregnant and nonpregnant and CF women from a registry suggested that there was no difference in the rate of decline between these groups. However, the pregnant women received a greater number of therapies and more intense monitoring of their health.[112]

Recommendations about pregnancy for women who are either mildly affected or severely affected is straightforward. For the woman with moderately compromised pulmonary status (i.e., FVC under 50%–60% of predicted), an overall assessment of the clinical situation is recommended, although no firm guidelines can be given. Increased incidence of fetal prematurity is noted in women with a pregravid FVC below 50% of predicted, lending additional weight against recommending pregnancy to women with moderate-to-severe airflow obstruction. In any woman with CF who is contemplating pregnancy, thorough evaluation and treatment of nutritional deficiencies and pulmonary exacerbations are required. Frequent use of antibiotics is unavoidable, and the teratogenic risk of many antibiotics is unknown. Despite this theoretical risk, good maternal and fetal health depends on aggressive management of pulmonary exacerbations, including use of antibiotics. Management of the gravid patient with CF is best accomplished in a CF center that has a program in high-risk obstetrics. A European consensus panel has published detailed guidelines for the management of pregnancy in women with CF.[113]

For men with CF who opt for MESA and for women with CF who are contemplating pregnancy, all offspring are obligate heterozygotes for CF. These offspring need to be counseled that their risk of having a child with CF is about 1 in 50 if the genotype of the spouse is not known. Although genetic testing of children from affected parents is not recommended, they should receive genetic counseling on reaching adolescence. Parents with CF also need to consider the ethical issues of a premature parental death and its effect on the family. If the spouse of an individual with CF is a known carrier of a CF mutation, the availability of in vitro fertilization with preimplantation genetic testing provides a method to avoid having a child who is affected with CF.

Discovery of the CF gene in 1989 led to the hope that prenatal diagnosis might eventually decrease the incidence of the disease. There is a suggestion that this may in fact be occurring.[114]

FUTURE DIRECTIONS

To further enhance survival in CF, physicians must look into insights gained from basic research. Although much work needs to be done, much has already been accomplished, warranting a realistic expectation that major breakthroughs will soon occur in the treatment of the disorder.

Progress toward cure of CF will require a multidisciplinary approach. Management of the lung disease in CF will probably be based on combined methods. However, the momentum gained from recent improvements in our understanding of the molecular details of CFTR structure and function provides a basis for realistic optimism that specific therapy will result in better outcomes for patients with CF. As described above, specific single molecule therapy has already become a reality for CF patients who have the G551D mutation. A phase III trial of the combination of two small molecules for the most common CF mutation, F508del, is underway. Newer compounds that are based on a better understanding of the structure and function of CFTR[115–117] are already progressing from the bench to bedside.

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CHAPTER 51 Bronchiolitis

Gary R. Epler

DISEASES OF THE BRONCHIOLES

Diseases of the bronchioles occur throughout the bronchiolar structures, from bronchiolar airways to alveolar ducts and alveoli (Table 51-1). Acute and chronic bronchiolitis are seen from near the bronchi, all the way to the respiratory bronchioles; constrictive bronchiolitis is seen in the midbronchioles, while diffuse panbronchiolitis occurs from the distal bronchioles to the respiratory bronchioles, and smoker's bronchiolitis involves the respiratory bronchioles. Bronchiolitis obliterans organizing pneumonia (BOOP) includes both the terminal bronchioles and alveoli and is discussed in Chapter 57.

New bronchiolar disorders continue to be described, including diffuse panbronchiolitis and smoker's bronchiolitis. New causes of bronchiolitis obliterans have also been described, including lung transplantation, pulmonary microcarcinoids, *Sauropus androgynous* vegetable drink, and food-flavoring. This chapter includes a discussion of the pathological, clinical, radiographic findings, and treatment of the bronchiolar airway disorders.

BRONCHIOLAR ANATOMY

Bronchioles are noncartilagenous small airways which are usually 1 mm or less in diameter; they have been called the bridge between the bronchi and alveoli.[1] The bronchioles have cartilage and mucus glands that are commonly found in the bronchi, but bronchioles also contain ciliated epithelium, smooth muscle, and Clara cells.[2] Clara cells are columnar cells with apical surfaces capable of secreting proteins and surfactant. Neuroendocrine cells are common in the proximal bronchioles.

More distal in the airways are approximately 30,000 terminal bronchioles that have an average diameter of about 0.6 mm. These bronchioles have circular smooth muscles in the their walls; the surface cilia gradually disappear distally. Terminal bronchioles branch into 224,000 respiratory bronchioles that differ from the bronchioles: respiratory bronchioles have two to three alveolar structures in the walls containing columnar cells with cuboidal type II cells and squamous type I cells. These structures terminate in 13.8 million alveolar ducts and 300 million alveoli.

TABLE 51-1 Clinical Classification of the Bronchiolar Diseases

Airway diseases
• Acute and chronic bronchiolitis
• Respiratory bronchiolitis
• Follicular bronchiolitis
• Diffuse panbronchiolitis
• Bronchiolitis obliterans
Interstitial diseases
• Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
• Bronchiolitis obliterans organizing pneumonia (BOOP)

THE CLINICAL SPECTRUM OF THE BRONCHIOLAR DISEASES

The wide variety of bronchiolar diseases that may be seen in clinical practice are discussed below.

■ ACUTE AND CHRONIC CELLULAR BRONCHIOLITIS

Acute and chronic cellular bronchiolitis is characterized pathologically as acute or chronic inflammation of the bronchioles without a fibrotic component.[3] The inflammation may be submucosal, mural, or peribronchiolar. Clinically, this is a common respiratory illness in children that is caused by several infectious agents, including *Mycoplasma*, adenovirus, influenza, parainfluenza, herpes virus, and adenoviruses. In the adult, bronchiolitis is rare and caused by similar viruses. Symptoms include a flu-like illness with persistent nonproductive cough of several weeks duration. There is generally no wheezing and no airflow obstruction. The chest x-ray is normal. The illness usually subsides over time. Cough suppressants may be utilized. Sometimes, a brief course of corticosteroid therapy is given for a severe, relentless cough. If symptoms are not responsive to corticosteroid therapy or if symptoms worsen, the illness may be fibrotic constrictive bronchiolitis – a disorder with a different clinical course and prognosis.

■ RESPIRATORY BRONCHIOLITIS

Respiratory bronchiolitis is sometimes called smoker's bronchiolitis, as cigarette smoking is almost always the cause of this lesion.[3] The characteristic histological feature is the accumulation of tan-brown macrophages in the lumens of respiratory bronchioles and adjacent alveoli-often seen as an incidental finding in cigarette smokers. For example, respiratory bronchiolitis was found in 70 of 79 (88.6%) smokers who underwent surgery for spontaneous pneumothorax.[4] There are usually no clinical symptoms associated with this type of respiratory bronchiolitis. Treatment is smoking cessation.

In some situations, respiratory bronchiolitis may extend into the interstitium and is referred to as respiratory bronchiolitis-interstitial lung disease (RB-ILD). Affected individuals have shortness of breath, bilateral crackles, reticulonodular opacities on chest radiography, decreased vital capacity, and decreased diffusing capacity. Treatment is smoking cessation, but often a course of corticosteroid therapy is needed for resolution.

■ FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis is characterized by hyperplastic lymphoid aggregates forming 1- to 2-mm peribronchiolar nodules.[3] Follicular bronchiolitis is often limited to a pathological description with no clinical counterpart. It occurs in the connective tissue disorders, such as rheumatoid arthritis. In some patients, there may be cough, sputum production, and small linear radiographic opacities.[5]

■ DIFFUSE PANBRONCHIOLITIS

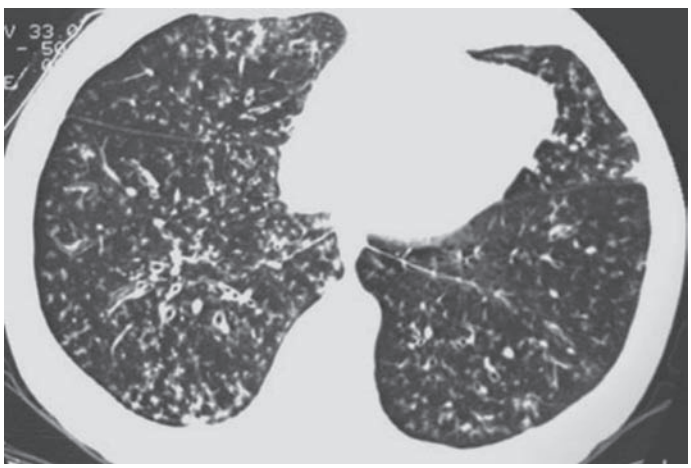
Diffuse panbronchiolitis was first described in the 1960s and is characterized by chronic inflammation and lymphofollicles of the respiratory bronchioles and adjacent centrilobular regions, with infiltration of histiocytosis, plasma cells, and lymphocytes.[6] There is also an interstitial accumulation of foam cells in the walls of respiratory bronchioles and adjacent alveolar ducts and alveoli (Fig. 51-1). The disorder is largely restricted to the Asian countries, but diffuse panbronchiolitis has been reported in the United States, Australia, Canada, and Spain.[7–10] The disorder has been reported in Kartagener syndrome.[11] In recent years, there appears to be a major decrease in the incidence and prevalence of diffuse panbronchiolitis in Japan.[12]

Symptoms include chronic cough, sputum production, shortness of breath, and almost all individuals have chronic paranasal sinusitis. Rhonchi and crackles are common. Radiographic findings show hyperinflation and diffuse small nodular opacities bilaterally. Pulmonary function testing shows airflow obstruction with decreased forced expired volume in one second (FEV_1) and FEV_1 to forced vital capacity (FEV_1/FVC) ratio. Hypercapnia and cor pulmonale occur late. There is often an associated increase in the cold-hemagglutinin titer. There appears to be a major susceptibility gene located between the HLA-A and HLA-B loci on the short arm of chromosome six.[13]

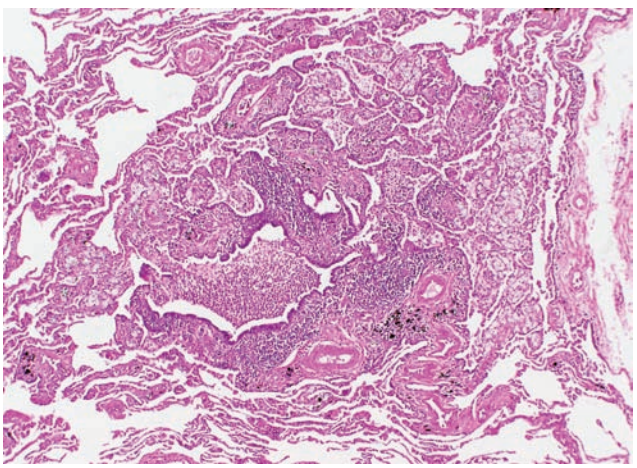
The disorder is progressive. In the past, diffuse panbronchiolitis was a fatal disease with a 10-year survival of less than 20% in patients with *Pseudomonas aeruginosa* infection. However, the introduction of low-dose, long-term erythromycin and other macrolides has resulted in a dramatic improvement in survival. Among Chinese patients, Li et al.[14] showed azithromycin, 500 mg once daily, for 3 months and 500 mg three times weekly for 6 to 12 months, resulted in complete cure in 27.5% of patients, elimination of symptoms in 70.6%, and a 5-year survival of 94.1%. The macrolides may prevent influx of neutrophils into the alveoli, decrease interleukin-8, and interfere with the pathological potency of *P. aeruginosa*.[15]

■ BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans is an important lesion because it can be severely disabling and deadly. Traditionally, bronchiolitis obliterans



A



B

Figure 51-1 Diffuse panbronchiolitis. **A.** The chest CT scan shows bilateral centrilobular nodules with branching showing "tree-in-bud" pattern. **B.** The pathology micrograph shows chronic inflammation of the respiratory bronchioles, with interstitial accumulation of foam cells in the walls of the respiratory bronchioles, adjacent alveolar ducts, and alveoli. *(Used with permission of Dr. Kenneth W. Tsang, Queen Mary Hospital, Hong Kong, China; and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*

TABLE 51-2 Pathological Findings of Bronchiolitis Obliterans

Constrictive bronchiolitis
• Concentric fibrotic lesion of the mid to distal bronchioles
• The lesion surrounds the lumen, causing extrinsic narrowing and obliteration
• Distortion of the lumen and mucostasis
• Muscle layer hypertrophic early, atrophic late, and replaced by fibrotic tissue in end-stage disease
• May be patchy and focal
• Late stage includes traction bronchiectasis and bronchiolectasis
Proliferative bronchiolitis
• Intraluminal polypoid myxoid fibroblastic tissue arising with the bronchiole wall.
• May be organized polypoid granulation tissue from the bronchioles to the respiratory bronchioles including the alveoli
• No disruption of the lung architecture
• No traction bronchiectasis

has been used as a clinical term to describe irreversible fibrosis of the bronchiolar airway that is idiopathic or occurs after accidental toxic fume inhalation or a viral pneumonia. However, pathologists may see two distinctive lesions that, in turn, have a different clinical course and response to treatment.

Histologically, the two lesions are *proliferative bronchiolitis* and *constrictive bronchiolitis* (Table 51-2). Depending on severity, obliteration of the bronchioles, the obliterans term, may or may not occur with these lesions. The histological distinction between these two lesions is that constrictive bronchiolitis arises in a concentric fashion outside the bronchiole walls as a fibrotic lesion, and proliferative bronchiolitis arises from within the bronchiole walls as an inflammatory lesion.

The term *bronchiolitis obliterans* is used in this chapter, as it has been used by clinicians for more than a hundred years and almost always reflects the fibrosing, constrictive, pathological lesion.[16] The proliferative lesion is often self-limiting and less severe, or responds to corticosteroid therapy with complete resolution; it usually does not result in the clinical label of bronchiolitis obliterans.

Proliferative bronchiolitis is an inflammatory bronchiolitis characterized by intraluminal polypoid connective tissue masses of myxoid fibroblastic tissue which resembles granulation tissue that arises from within the bronchioles.[1] Central clusters of mononuclear inflammatory cells may be found in these polypoid masses. This type of bronchiolitis includes organized polypoid granulation inflammatory tissue in the distal bronchiole airways, respiratory bronchioles, alveolar ducts, and alveoli in the form of BOOP[17] Additional distinctive histological findings with proliferative bronchiolitis associated with BOOP include no disruption in the lung architecture, interstitial fibrosis, absence of traction bronchiectasis, or histological honeycombing (Fig. 51-2).

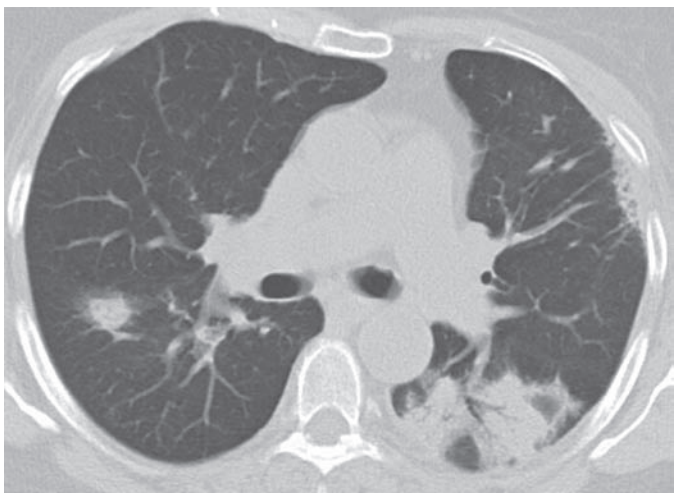
Constrictive bronchiolitis is a fibrotic, concentric bronchiolitis lesion with or without complete obliteration (Fig. 51-3). This lesion is usually seen in the mid to distal area of bronchioles and does not extend into the respiratory bronchioles or alveoli. The lesion is characterized by a peribronchiolar fibrotic process that surrounds, rather than fills, the lumen, resulting in extrinsic compression and obliteration of the airway.[3] There is mural thickening by submucosal collagenous fibrosis with progressive concentric narrowing associated with luminal distortion, mucus stasis, and chronic inflammation.[18]

Constrictive bronchiolitis was called "fibrosing bronchiolitis" in the German pathology literature.[19] The lesion preferentially involves membranous bronchioles and is characterized by fibrosis of the stroma and narrowing the lumen in a concentric fashion. The muscle layer may be hypertrophic in early lesions, atrophic in late stages, and replaced by fibrotic tissue at the end stage. Visscher and Myers noted that constrictive bronchiolitis is often patchy and focal, making the diagnosis difficult from a transbronchial biopsy; advanced cases may be especially inconspicuous because of lack of active inflammation and disappearance of bronchioles.[20]

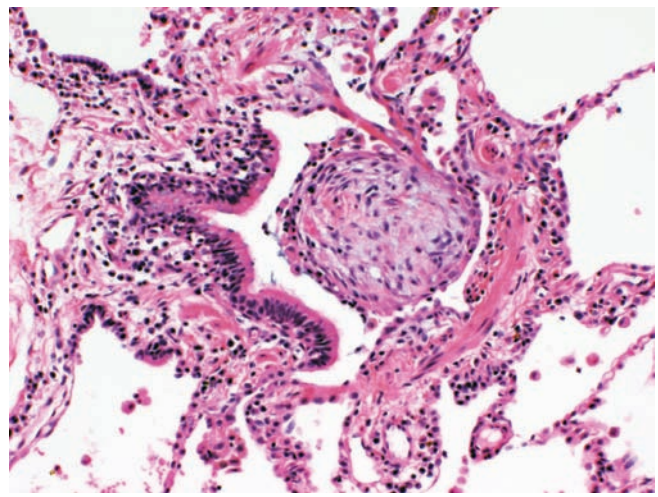
There are several causes of bronchiolitis obliterans and associated systemic disorders (Table 51-3).

Idiopathic Bronchiolitis Obliterans

Idiopathic bronchiolitis obliterans occurs among individuals who have no obvious inciting agent or associated systemic disorder,

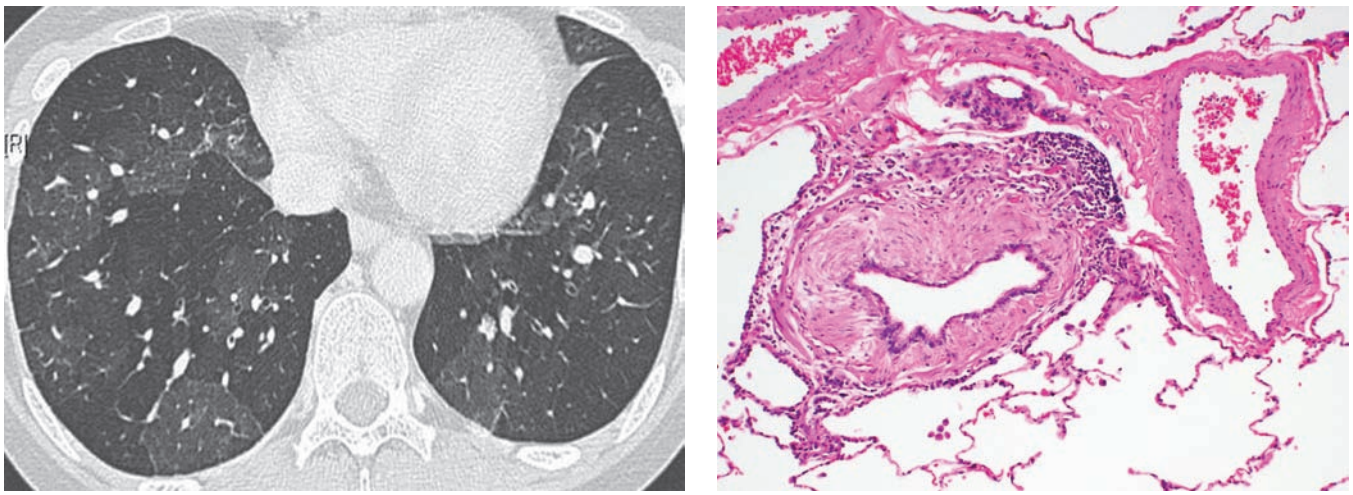


A



B

Figure 51-2 Bronchiolitis obliterans organizing pneumonia. **A.** The chest CT scan shows bilateral patchy ground-glass opacities, air bronchograms, and peripheral-based triangular infiltrates. **B.** The pathology micrograph shows organized polypoid granulation tissue filling the distal bronchiole and extending into the alveoli. *(Used with permission of Dr. Ritu R. Gill, Chest Radiology, Brigham and Women's Hospital, Boston, and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*



A B

Figure 51-3 Constrictive bronchiolitis. **A.** The expiratory chest CT scan shows the mosaic pattern of air trapping seen from obliterated bronchioles. **B.** The pathology micrograph shows extrinsic fibrosis of the bronchiolar wall in a concentric manner constricting and obliterating the bronchiolar lumen. *(Used with permission of Dr. Ritu R. Gill, Chest Radiology, Brigham and Women's Hospital, Boston, and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*

and who have airflow obstruction and constrictive bronchiolitis histologically. This disorder continues to be exceedingly rare. Symptoms begin with a nonproductive cough, and shortness of breath develops later. Physical examination shows no wheezing but may demonstrate an unusual finding of early inspiratory crackles. The crackles occur early because of the scarring around the midbronchiole airways, causing snapping closure of the airways and resultant crackling sound.

TABLE 51-3 Clinical Classification of Bronchiolitis Obliterans

Idiopathic
Toxic fumes
Post-respiratory infections
Connective tissue disorders
Drug-related
Organ transplantation
• Lung
• Bone marrow and stem cell
Aspiration
Neuroendocrine hyperplasia
Microcarcinoids
Sauropus androgynous
Stevens-Johnson Syndrome
Primary biliary cirrhosis
Miscellaneous diseases
• Ataxia-telangiectasia
• IgA nephropathy
• HIV
• Paraneoplastic pemphigus and paraneoplastic autoimmune multi-organ syndrome (PAMS)
• Swyer–James syndrome
• Inflammatory bowel disease

Pulmonary function studies show irreversible decrease in the FEV_1 and FEV_1/FVC with no improvement after bronchodilator inhalation. The diffusing capacity is highly variable, from increased, to normal, to markedly decreased.

The chest roentgenogram is often normal or shows hyperinflation. High-resolution chest CT scans during inspiration and expiration can be helpful for establishing a diagnosis (Fig. 51-1). For example, a 65-year-old woman with idiopathic bronchiolitis obliterans had a normal chest CT scan in the inspiratory study, but the expiratory study showed extensive lobular air trapping.[21] These expiratory images show low-attenuation areas in the secondary pulmonary lobules, resulting in a typical mosaic pattern with scattered areas of low attenuation. Additional thin-section CT findings include constriction of the pulmonary vessels within the low-attenuation areas, expiratory air trapping, bronchial dilation, and sometimes, centrilobular nodules or branching linear densities.[22]

Treatment consists of high-dose corticosteroids such as prednisone with an initial dose of 60 mg daily, followed by lower-dose therapy for usually one year in patients who respond. For those who do not respond by three months, corticosteroids are discontinued and employed for life-threatening exacerbations. Immune-suppression treatment can be utilized and lung transplantation for individuals with life-threatening and severe disease.

Patients who survive the initial episode may stabilize for several years or progress to end-stage airflow disease and cor pulmonale.[23] For example, a 43-year-old woman had idiopathic bronchiolitis obliterans for 24 years and showed relentless progression of airway obstruction with 19 admissions for respiratory failure.[24] The autopsy in this patient showed complete obliteration of smaller airways. The FEV_1 decreased from 1.06 L to 0.40 L terminally.

Myong et al.[25] described three women aged 41 to 54 who developed cough and progressive shortness of breath during 6 months to 10 years; lung tissue showed constrictive bronchiolitis with bronchiolar airway obliteration. The thin-section CT scans showed low-attenuation changes of the mosaic pattern. None responded to corticosteroid treatment. One woman died 8 months after the diagnosis from lymphoma and the other two were stable.

Toxic Fume Bronchiolitis Obliterans

Toxic fume bronchiolitis obliterans is a three-phase response disease. The exposure usually occurs from an accidental explosion

resulting in nose, throat, and eye irritation with no major respiratory symptoms. Phase one is an asymptomatic latency period of 6 to 12 hours after exposure. Phase two begins suddenly with acute-onset respiratory failure and acute respiratory distress syndrome. Successful treatment results in another asymptomatic latency period of 7 to 10 days. Phase three then occurs as constrictive bronchiolitis with irreversible airflow obstruction, progressive shortness of breath, and chronic respiratory failure.

This disorder occurs after accidental exposures to sulfur dioxide fumes, nitric acid fumes, and nitrogen dioxide in freshly filled corn silos. Unusual accidental exposures to toxic fumes may cause this lesion. For example, two workers in a lithium battery factory were accidentally exposed to thionyl chloride, and one of them developed findings consistent with bronchiolitis obliterans.[26] This acidic compound is used in the manufacturing process and produces sulfur dioxide and hydrochloric acid fumes when in contact with water.

Smoke inhalation bronchiolitis obliterans was described in a 23-year-old man who was in a fire while sleeping in his newly constructed house.[27] He was unconscious when rescued. There was cough and mild dyspnea after recovery. He returned 3 years later because of persistent dyspnea. He had finger clubbing, an FEV_1 of 0.90 L, and an FEV_1/FVC of 34%. The burning synthetic structural materials used to build his house produced gases containing acrolein, formaldehyde, acetaldehyde, nitrogen dioxide, and sulfur dioxide.

There has been a report of bronchiolitis obliterans from mustard gas occurring from a chemical warfare attack in a 37-year-old man who had cough, sputum production, shortness of breath, and airflow obstruction for 14 years after the exposure.[28] Later, investigators[29] used high-resolution chest CT scan findings for the diagnosis of bronchiolitis obliterans in a group of individuals exposed to the same mustard gas attack. They treated 18 individuals with bronchodilator treatment and 18 with interferon gamma-1b and 7.5 mg of prednisolone. Patients had baseline FEV_1 values of 49.3% and 48.7% predicted, respectively. Both groups improved after 6 months of treatment; however, the group treated with interferon gamma had a significantly higher posttreatment FEV_1 of 66.3% compared to 57.3% for the group treated with bronchodilators ($p = 0.001$).

King et al.[30] reported constrictive bronchiolitis among 38 US soldiers returning from Iraq and Afghanistan and found a common exposure to a sulfur-mine fire in 2003 among 28 of them.

A 42-year-old police officer exposed to the dust in the cloud from the New York City World Trade Center disaster of September 11, 2001 developed decreased FEV_1 and FEV_1/FVC in April 2002.[31] The lung biopsy showed regions of constrictive bronchiolitis. He was treated with oral corticosteroid therapy and azithromycin. By April 2003, pulmonary function studies had returned to normal values.

An unusual radiographic appearance of scattered lung cysts has been reported in a 49-year-old woman with severe airflow obstruction and constrictive bronchiolitis.[32]

Diacetyl appears to be a common exposure among artificial butter flavoring workers who developed constrictive bronchiolitis. A report of nine microwave popcorn factory workers showed airflow obstruction among the mixers, and biopsy of some individuals showed constrictive bronchiolitis.[33] Investigators[34] have reported that four workers at a cookie factory who were exposed to diacetyl developed severe and persistent airflow obstruction, with FEV_1 ranging from 25% to 44%. Lung biopsy showed constrictive bronchiolitis and bronchiolar airway distortion.

Post-Respiratory Infection Bronchiolitis Obliterans

Post-respiratory infection bronchiolitis obliterans may occur after adenovirus pneumonia, influenza or parainfluenza pneumonia, or after *Mycoplasma* pneumonia.[35] Cough develops several days after the initial infection. Chest radiographs may show diffuse reticulonodular opacities early but are normal or show hyperinflation late. Expiratory, high-resolution chest CT scans show low-attenuation mosaic pattern. Tissue shows constrictive bronchiolitis with extensive scarring that obliterates many of the bronchioles, corresponding clinically with severe airflow obstruction. At this stage, the lesion is not responsive to corticosteroid medication. Lung transplantation has been utilized for severe post-*Mycoplasma* pneumonia bronchiolitis obliterans.[36]

Connective Tissue Bronchiolitis Obliterans

Connective tissue bronchiolitis obliterans occurs most commonly in rheumatoid arthritis and has been reported in scleroderma, lupus erythematosus, and Sjögren's syndrome.[37,38]

Rheumatoid arthritis-related constrictive bronchiolitis often has a poor prognosis. Among 25 individuals with rheumatoid arthritis and bronchiolitis obliterans, most had severe airflow obstruction, often with an FEV_1 less than 1 L, and the process was not responsive to corticosteroids.[39] The outcome was poor, as chronic respiratory failure occurred in 40% of the patients; four patients died.

Drug-Related Bronchiolitis Obliterans

Drug-related bronchiolitis obliterans has been reported with penicillamine and gold used for treatment of rheumatoid arthritis. The penicillamine-related bronchiolitis obliterans has a poor prognosis, sometimes requiring lung transplantation for management.[40] Fatal bronchiolitis obliterans has been reported in a 12-year-old girl with juvenile rheumatoid arthritis after a 6-month course of intramuscular gold.[41] Although cause and effect are difficult to confirm for both of these agents, patients receiving these medications who develop unexplained cough or dyspnea need to be evaluated for the possibility of bronchiolitis obliterans.

Bone-Marrow Transplantation Bronchiolitis Obliterans

Bone-marrow transplantation bronchiolitis obliterans occurs much less frequently as allogeneic stem-cell transplantation has become so common; however, bronchiolitis obliterans may occur in up to 9% of allogeneic bone-marrow recipients.[42] Bronchiolitis obliterans occurs only after graft-versus-host reaction, and therefore, is rarely seen after autologous bone-marrow transplantation. As complications of chronic graft-versus-host develop after 100 days, bronchiolitis obliterans is usually seen 6 to 12 months after transplantation. Donor type-2 T-helper lymphocytes appear to be the primary mediators. The pathological lesion is concentric bronchiolar fibrosis typical of constrictive bronchiolitis. There is generally a poor response to corticosteroid therapy; mortality ranges from 40% to 100%.[42] Living donor lobar lung transplantation has been used successfully for bone-marrow transplant-related bronchiolitis obliterans.[43]

Stem-Cell Transplant Bronchiolitis Obliterans

Stem-cell transplant bronchiolitis obliterans has replaced bone-marrow transplantation-associated bronchiolitis obliterans as allogeneic hematopoietic stem-cell transplantation has become more widespread (see Chapter 95). The prevalence of bronchiolitis obliterans ranges from 2% to 3% among all allogeneic recipients to 6% among those who develop chronic graft-versus-host disease (cGVHD).[44] These data underestimate the incidence of bronchiolitis obliterans (26%) when using an annualized rate of decline in FEV1 of 5%. Those with cGVHD had a rate of 30%, but more importantly, they had a mortality rate of 40% at 10 years. cGVHD is the major risk factor for bronchiolitis obliterans, as high as 80% of patients with bronchiolitis obliterans are preceded with cGVHD. Other risk factors include low IgG levels, use of peripheral blood stem cells, poor pretransplant lung function, and respiratory infection during the first 100 days. Biopsy specimens performed early show bronchiolitis, fibrous obliteration of the respiratory bronchioles, and inflammatory cell infiltrates; later lesions show constrictive bronchiolitis with circumferential fibrosis. The mechanism of bronchiolitis

obliterans is based on chronic rejection that may involve donor cytotoxic T cells.

Preventive treatment of stem-cell transplantation bronchiolitis obliterans consists of early and aggressive treatment of respiratory infections and cGVHD. Treatment includes high-dose systemic corticosteroids and immunosuppression with calcineurin inhibitors, sirolimus, azathioprine, and anti-thymocyte globulin. Prognosis continues to be poor despite treatment and supportive care, with an overall survival rate of 44% at 2 years and 13% at 5 years.[44]

In a study of 2087 allogeneic stem-cell transplantation recipients from 1994 to 2005, there were 57 (2.8%) who developed bronchiolitis obliterans.[45] The time interval between transplantation and bronchiolitis obliterans ranged from 83 days to 907 days with a median time of 335 days. Acute graft-versus-host disease was not found to be a risk factor, whereas cGVHD was a significant risk factor. The development of bronchiolitis obliterans was related to the stem-cell source, with related peripheral blood stem-cell transplantation (3.83%) the highest. Unrelated bone-marrow transplantation (2.91%) and cord-blood transplantation (2.65%) were lower, with related bone-marrow transplantation (1.62%) the lowest. The outcome among these 57 patients showed that 8 (16.7%) improved, 10 (21.7%) showed no change, and 28 (60.9%) died; the cause of death was respiratory failure in 17 (60.7%).

The high-resolution chest CT findings in bronchiolitis obliterans among patients receiving allogeneic stem-cell transplantation shows geographic hypoattenuation and air trapping with subpleural predominance.[46] In some patients, the geographic hypoattenuation involved more than half of both lungs.

Extracorporeal photodynamic therapy has been used for the treatment of cGVHD and bronchiolitis obliterans.[47] The role of this treatment in the management of bronchiolitis obliterans in stem-cell transplantation recipients has not yet been established. Some patients have improved pulmonary function.

Mesenchymal stem-cell treatment was used for one patient. A 38-year-old patient received peripheral blood stem cells from her sibling and developed bronchiolitis obliterans 8 months later with an FEV_1 <0.7 L.[48] She was treated experimentally with human bone marrow–derived mesenchymal stem cells from her sister on day 275 and on day 305, resulting in disappearance of symptoms and improved pulmonary function. This may be an effective treatment on a case-by-case basis, but at this time, there are too many unknown variables involved to advocate its use (e.g., absence of large scale studies, availability of a standardized source of mesenchymal cells, and an understanding of potential carcinogenic effects).

Lung Transplant Bronchiolitis Obliterans

Lung transplant bronchiolitis obliterans has emerged as the most important clinical complication among lung transplant recipients since the mid-1980s and has continued to plague thoracic surgeons and patients, with minimal change in occurrence and mortality (see Chapter 107).

The terminology has become the bronchiolitis obliterans syndrome (BOS), which is a clinical classification based on FEV_1. The classification was developed because BOS is a common problem among lung transplantation recipients. The approach eliminates the need for low-yield transbronchial biopsy or other invasive procedure to establish a definitive diagnosis of bronchiolitis obliterans. A clinical severity classification has been used.[49] A National Institutes of Health (NIH) diagnostic classification of BOS in cGVHD[50] has also been developed (Table 51-4).

Many years after the initial description of bronchiolitis obliterans occurring in lung transplant recipients, BOS remains a common process with devastating consequences.[51] At least one-half of lung transplantation recipients surviving 5 years will develop airflow obstruction. BOS has not declined significantly in incidence, and no totally effective treatment is available.

TABLE 51-4 Bronchiolitis Obliterans Syndrome (BOS) Classifications

BOS clinical severity classification	
BOS 0	FEV_1 >90% of baseline and $FEF_{25–75}$ >75% baseline
BOS 0-p	FEV_1 81–90% of baseline and/or $FEF_{25–75}$ ≤75%
BOS 1	FEV_1 66–80% of baseline
BOS 2	FEV_1 51–65% of baseline
BOS 3	FEV_1 50% or less of baseline
NIH chronic graft-versus-host BOS classification	
1. FEV_1 <70% predicted or FEV_1/FVC <70%	
2. Expiratory HRCT showing air trapping, small airway thickening or bronchiectasis, residual volume >120% predicted, or constrictive bronchiolitis by pathology	
3. Absence of respiratory infection	

The frequency and severity of acute cellular rejection continues to be the major risk factor. For example, a study showed that lung transplant recipients who had more than three episodes of acute rejection in any 12-month period eventually had a 100% incidence of bronchiolitis obliterans.[52] Both types of acute rejection are involved, including acute vascular rejection and lymphocytic bronchiolitis.

Primary graft dysfunction (PGD) is a term used for a process that occurs during the initial postoperative phase characterized by pulmonary edema and acute respiratory failure. This process has been associated with high perioperative mortality and is a risk factor for the subsequent severity of bronchiolitis obliterans.[53]

A classification system for PGD (Table 51-5) has been established based on oxygenation and the presence of pulmonary edema.[54]

Daud et al.[55] found that among 334 lung transplant recipients, 130 (39%) had grade-one PGD, 69 (20%) had grade-two, and 70 (21%) had grade-three. All grades were associated with increased risk of bronchiolitis obliterans, with a risk ratio ranging from 1.73 for grade-one to 2.53 for grade-three. This risk was independent of acute rejection.

Innate immunity may play a role in development of postlung transplant bronchiolitis obliterans. There are several risk factors that activate this innate system, including prolonged ischemic time, cytomegalovirus (CMV) pneumonia, *Aspergillus* colonization, PGD, gastroesophageal reflux disease (GERD), and community respiratory virus infections.[51]

Autoimmunity as a mediator in BOS has been proposed as a biphasic rejection.[56] The first phase is recurrent tissue injury from airway insults, and the second phase is sequestered self-antigens and fragments released into the lung, triggering autoreactive T-cell proliferation and autoantibody production.

TABLE 51-5 Classification of Primary Graft Dysfunction (PGD)

PGD grade 0: $Pa_{O_2}/F_{I_{O_2}}$ >300 mm Hg
PGD grade 1: $Pa_{O_2}/F_{I_{O_2}}$ >300 mm Hg and pulmonary edema
PGD grade 2: $Pa_{O_2}/F_{I_{O_2}}$ 200–300 mm Hg and pulmonary edema
PGD grade 3: $Pa_{O_2}/F_{I_{O_2}}$ <200 mm Hg and pulmonary edema

$Pa_{O_2}/F_{I_{O_2}}$: Arterial oxygen (mm Hg) to the fraction of inspired oxygen.

Eberlein et al.[57] found that an oversized allograft can be associated with improvement, including higher expiratory airflows, and less frequent occurrence of BOS. Circulating fibrocyte levels correlated with BOS after lung transplantation.[58] Levels of KL-6, a high–molecular-weight human MUC1 gene mucin, are increased and correlated with the level of FEV_1 decline in lung transplantation recipients.[59] Bourdin et al.[60] showed that donor Clara cell secretory protein polymorphism is a risk factor for BOS. Gastroesophageal reflux, a cause of bronchiolitis obliterans, occurs in as many as 50% of lung transplant recipients, and early fundoplication may improve rates of bronchiolitis obliterans and survival.[61]

Chronic productive cough and shortness of breath were commonly reported as symptoms in early reports, but bronchiolitis obliterans is now diagnosed earlier than in the past, and these symptoms may not be present. Gradual onset of progressive shortness of breath is the most common symptom. Early inspiratory crackles may be heard. The decreases in FEV_1 may be mild to severe and life-threatening.

The chest x-ray is often normal; however, the combination of newly decreased FEV_1 and the expiratory high-resolution chest CT scan showing mosaic pattern have virtually become diagnostic.[62]

Management of lung transplantation bronchiolitis obliterans begins with early and aggressive treatment of acute organ rejection, including both the acute vascular rejection and lymphocytic bronchiolitis. Treatment of bronchiolitis obliterans generally includes a calcineurin inhibitor, a purine synthesis inhibitor, and a corticosteroid.

The calcineurin inhibitor tacrolimus has become an alternative to cyclosporine, with evidence for similar survival and a decrease in episodes of acute rejection with use of tacrolimus.[63] In addition, compliance with tacrolimus appears to be better than cyclosporine. New-onset diabetes after transplantation is a major complication of tacrolimus, and there is an increased risk of infections.

Mycophenolate mofetil (MMF) has generally replaced azathioprine[64] as the purine synthesis inhibitor. Both alloimmune and nonalloimmune mechanisms are involved in development of bronchiolitis obliterans; therefore, vigorous treatment of infections is needed at all times during the posttransplant period.

Extracorporeal photopheresis (ECP) appears to be effective for early treatment of BOS. It consists of the patient's white blood cells being exposed to ultraviolet light in the presence of 8-methoxypsoralen in a photoactivation chamber.[65,66] In a study of 60 lung transplant recipients, ECP treatment decreased the rate of the FEV_1 decline and improved FEV_1 actual value by 25% in patients. In addition, the rate of decline in lung function was sustained over both the 6- and 12-month period.[65] In a study of 1012 lung transplant recipients, 194 developed BOS and 51 received ECP.[66] There were 31 (61%) who responded to the therapy and showed sustained stabilization of the FEV_1 for at least 6 months. Responders showed significantly greater survival and less need for re-transplantation. Treatment was more effective when given soon after the diagnosis of BOOP.

The macrolides, such as erythromycin, appear to be an effective treatment in a subset of patients with BOS. The finding of bronchoalveolar lavage neutrophils may distinguish responders from nonresponders.[67] The process in the responders is referred to as neutrophilic reversible allograft airway dysfunction (NRAD).[68] An additional important finding about azithromycin is that this agent may reduce gastroesophageal reflux in lung transplant recipients, further decreasing the risk of constrictive bronchiolitis.[67] Early treatment resulted in responders having more lower-grade BOS.[69] A thin-section CT study showed patients with NRAD had more centrilobular nodularity at the beginning of treatment, and they had improved bronchus dilation, consolidation, and air trapping.[70]

The six-minute walk test can be useful for monitoring lung transplant recipients with bronchiolitis obliterans. In a 2009 study, patients who walked farther than 330 m had a median survival of 1178 days, compared to 263 days for lung recipients who walked less.[71]

A 2011 study of traffic air pollution as estimated by the proximity of the home to a major road showed that lung transplant recipients living near a major road within 171 m were 2.06 times more likely to develop BOS and 2.20 times more likely to die than patients living far away.[72]

Aspiration Bronchiolitis Obliterans

Aspiration bronchiolitis obliterans was first reported in 1908 occurring in a 2.5-year-old child who aspirated a prune pit that eventually caused respiratory failure and death.[73] Activated charcoal used for management of a medication-related suicide attempts has been reported as a cause of bronchiolitis obliterans.[74] Massive gastroesophageal reflux has been reported as a cause of bronchiolitis obliterans in a patient who later underwent a gastrojejunostomy that relieved the symptoms and prevented recurrent aspiration, accompanied by a corresponding improvement in the FEV_1.[75]

Neuroendocrine Hyperplasia-Related Bronchiolitis Obliterans

Neuroendocrine hyperplasia-related bronchiolitis obliterans has been reported to occur among six patients who developed shortness of breath and fibrotic bronchioles.[76] In a case report of a 65-year-old man who had 20 years of shortness of breath and a severely decreased FEV_1 of 19% predicted, neuroendocrine hyperplasia with fibrotic narrowed bronchioles was observed.[77] In addition, in another report of two women who had airflow obstruction and unexplained cystic lung disease, biopsies showed showed diffuse idiopathic neuroendocrine cell hyperplasia.[78]

Carcinoid-Related Bronchiolitis Obliterans

Carcinoid-related bronchiolitis obliterans has occurred in patients with multiple tumorlets and microcarcinoids located within the bronchioles, resulting in bronchiolitis obliterans and airflow obstruction.[38,79]

Sauropus Androgynus Bronchiolitis Obliterans

Sauropus androgynus bronchiolitis obliterans has been reported among women who consume this leafy vegetable. It is cultivated in India, Malaysia, Indonesia, China, and Vietnam. The leaves are boiled and blended with pineapples or guavas to make a mixed vegetable-fruit juice which is consumed for its alleged effects of body weight reduction and blood pressure control. The leaves contain the alkaloid papaverine. Among 194 patients in Taiwan, the obstructive ventilatory defect was irreversible and resulted in progressive deterioration in some patients resulting in lung transplantation.[80] In a report of five patients in Japan, the illness occurred 6 months after ingestion; four were mothers and daughters, and none improved with corticosteroid treatment.[81]

Stevens–Johnson-Related Bronchiolitis Obliterans

Stevens–Johnson-related bronchiolitis obliterans has been described in a woman who developed progressive dyspnea 12 days after developing diffuse oral erythematous lesions and blisters after antibiotic therapy.[82] She developed progressive respiratory failure and died 2 months later. Autopsy showed constrictive bronchiolitis with obliterated bronchioles.

Primary Biliary Cirrhosis Bronchiolitis Obliterans

Primary biliary cirrhosis bronchiolitis obliterans has been reported in a 39-year-old woman.[83] Early there was improvement from corticosteroid therapy, but later deterioration and death. Lung tissue showed concentric submucosal fibrosis and scarring, constricting the lumen of the airway, consistent with constrictive bronchiolitis and bronchiolar airway obliteration.

Paraneoplastic Autoimmune Multi-Organ Syndrome Bronchiolitis Obliterans

Paraneoplastic autoimmune multi-organ syndrome bronchiolitis obliterans, also referred to as paraneoplastic pemphigus-related bronchiolitis obliterans, has been reported in several patients.[38,84–86] A patient with myasthenia gravis died from bronchiolitis obliterans after surgical resection of a Castleman tumor.[84] Another patient had this paraneoplastic syndrome and developed constrictive bronchiolitis.[85] In a 2009 report from Mayo Clinic of three patients, all had severe airflow obstruction, with FEV_1 <1 L.[86] Two of them died and the third had stable chronic respiratory failure. A case report describes a 44-year-old woman with Castleman tumor and paraneoplastic syndrome; autopsy showed partial obliteration of the bronchiolar lumen by fibrolymphocytic tissue and dense inflammatory infiltrates surrounding the bronchioles. The oral mucosa, skin and bronchioles showed similar immunophenotypes.[87]

Swyer–James Syndrome Bronchiolitis Obliterans

Swyer–James syndrome bronchiolitis obliterans is not congenital in origin but is secondary to respiratory infection occurring during infancy.[38,88] Respiratory infections that can cause this syndrome include measles, whooping cough, tuberculosis, *Mycoplasma* pneumonia, influenza A, and adenovirus types 3, 7, and 21.

Miscellaneous Systemic Disorders Associated with Bronchiolitis Obliterans

Bronchiolitis obliterans has been reported in four patients with *ataxia-telangiectasia* who died from respiratory failure secondary to bronchiolitis obliterans.[89] Another report describes an elderly man with renal failure from *IgA nephropathy* characterized by diffuse crescentic glomerulonephritis who died from progressive respiratory failure and bronchiolitis obliterans.[90] *HIV-related bronchiolitis obliterans and* [91] *inflammatory bowel disease bronchiolitis obliterans* have been reported.[38]

SUMMARY

In summary, the bronchiolar airway diseases include acute and chronic bronchiolitis, follicular bronchiolitis, diffuse panbronchiolitis, and bronchiolitis obliterans. Acute bronchiolitis is usually transient, whereas diffuse panbronchiolitis responds to macrolide therapy. Postlung transplantation bronchiolitis obliterans continues to be a major problem, with minimal change in frequency or response to treatment.

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CHAPTER 52

Bullous Disease of the Lung

Fernando J. Martinez

DEFINITION

A *bulla* is an air-containing space within the lung parenchyma that arises from destruction, dilatation, and confluence of airspaces distal to terminal bronchioles and is larger than 1 cm in diameter (Fig. 52-1).[1] Its walls are composed of attenuated and compressed parenchyma. Bullae occur in various clinical contexts: (1) with emphysema ("bullous emphysema"); (2) with pulmonary fibrosis, as in the late stages of sarcoidosis or complicated pneumoconiosis; (3) in so-called "vanishing lung," in which the parenchyma is rapidly replaced by multiple bullae; and (4) in lungs that are otherwise normal ("bullous lung disease") and, therefore, likely secondary to a mechanism different from that of bullae occurring in conjunction with emphysema (Table 52-1).[2,3]

Distinctions are drawn between bullae, blebs, and cysts (Table 52-2).[2] A *bleb* is an accumulation of air between the two layers of the visceral pleura that arises when the thin covering of the bleb ruptures and permits entry of air (Fig. 52-1). *Cysts* are epithelial-lined cavities that may resemble bullae on radiographs.[3] Many fall into the category of developmental anomalies and include mixtures of mesenchymal and epithelial components that are normally present in the lung. The pathologic nature of these cystic lesions is reflected

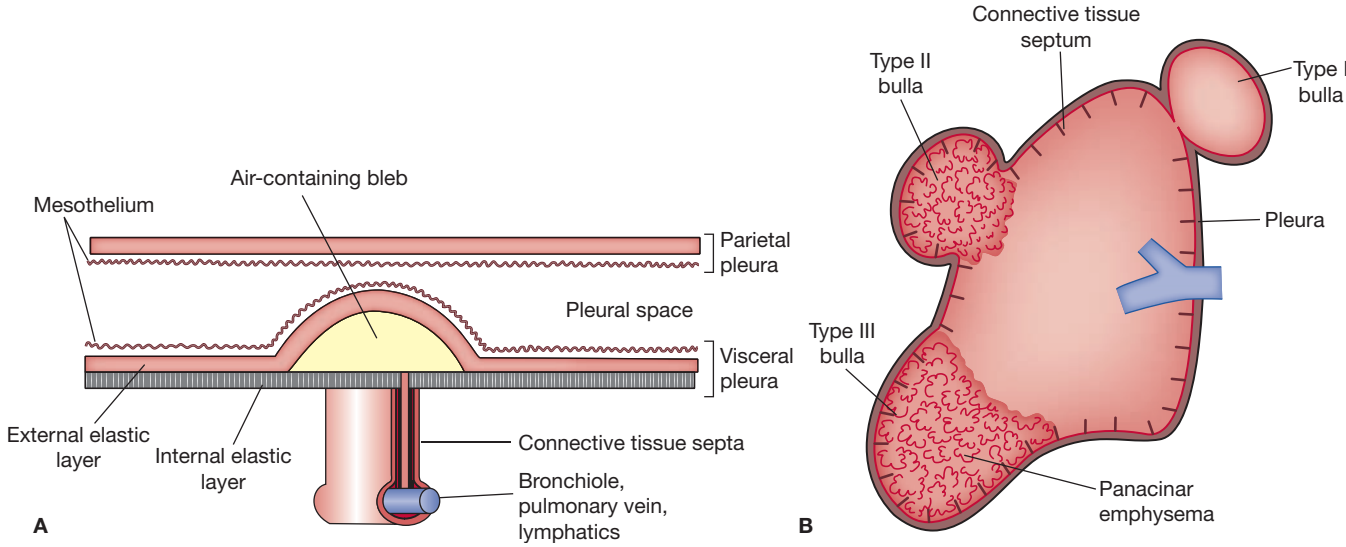


Figure 52-1 Blebs and bullae. **A.** Development of a bleb. A bleb is an accumulation of air within the pleura that is not confined by connective tissue septa within the lung. Air that escapes within the substance of the lungs makes its way to the surface, separating the internal from the external elastic layers on the visceral pleura. **B.** Different types of bullae. In contrast to a bleb, a bulla is confined by connective tissue septa of the lung and is deep to the internal elastic layer of the visceral pleura. Three different types of bullae are shown arising from a lung that has been removed from within the chest wall. A type I bulla is shown at the apex, a type II is in the middle zone, and a type III is arising at the base. The short *dark lines* denote connective tissue septa. Panacinar emphysematous parenchyma is present within the types II and III bullae. *(Adapted with permission from Reid L. The Pathology of Emphysema. Chicago: Year Book; 1967:211–240.)*

in their names: "cystic adenomatoid malformations," "peripheral bronchogenic cysts," "congenital polycystic disease," and "atypical bronchopulmonary sequestration."[1]

The term *bullous disease* is reserved for multiple bullae in lungs that are otherwise normal.[2] This entity is different in etiology and pathogenesis from that in which bullae occur in conjunction with underlying chronic obstructive pulmonary disease (COPD). Confusion occasionally arises between the two entities because some pathologists regard bullous disease as a subset of panacinar emphysema.[1] However, this view is not useful as (1) panacinar emphysema tends to occur in the lower lobes, whereas bullous disease favors the upper lobes; (2) the natural history of the two disorders is quite different; and (3) panacinar emphysema has certain distinctive features not shared by bullous disease. Bullae may occur not only as part of obstructive lung disease, but also as a complication of fibrotic lung disease (Table 52-1).

TABLE 52-1 Classification of Bullae

Primary
Vanishing lung syndrome
Single giant bulla
Bullous lung disease
Secondary
Emphysema
Paraseptal
Panacinar
Centriacinar
Pulmonary fibrosis
Sarcoidosis
Idiopathic pulmonary fibrosis
Progressive massive fibrosis
Conglomerate silicosis
Fibrotic tuberculosis
Other fibrotic lung disorders
Familial disorders
α_1-antitrypsin deficiency
Ehlers–Danlos syndrome
Salla disease
Marfan syndrome
Fabry disease
Cutis laxa

ETIOLOGY

Bullae may originate in a variety of clinical and pathogenetic settings: (1) with emphysema of distal acini; (2) in the setting of cigarette smoking; (3) in conjunction with scar tissue formation, which "traps" areas of normal lung, enlarges airspaces by traction on surrounding intact alveoli, or produces retraction or shrinkage of intact walls of adherent alveoli; (4) in the setting of intravenous drug abuse; (5) as a result of chronic inflammation and destructive

TABLE 52-2 Characteristics of Blebs, Bullae, and Cysts

	Bleb	Bulla	Cyst
Site	Within visceral pleura	Arises within secondary lobule	Lung parenchyma or mediastinum
Size	1–2 cm	1 cm to 75% of a lung	2–10 cm
Lining	Elastic laminae of the pleura	Connective tissue septa	Epithelium
Associated condition	Spontaneous pneumothorax	Bronchogenic carcinoma	Respiratory infection

changes in terminal and first-order respiratory bronchioles, resulting in airspace distention from delayed emptying; and (6) with α_1-antitrypsin deficiency.[2,4,5]

CLASSIFICATION

Bullae are classified anatomically into three main types (Fig. 52-1B).[1,2] Type I bullae are characterized by a narrow neck that connects the bullae with the pulmonary parenchyma. This type of bulla may be caused by overinflation of a volume of flawed lung tissue. The walls of type I bullae are thin, and their interiors are empty. Type I bullae are usually found at the lung apices and along the edges of the lingula and middle lobes. They often occur in association with paraseptal emphysema. Scanning electron microscopy has demonstrated that the thin neck is a consistent feature and that pleural mesothelial cells on the external surface are either reduced in number or completely absent; bundles of collagen fibers lie naked and separated from one other by small pores or crevices.

Type II bullae arise from the subpleural parenchyma and are characterized by a neck of panacinar emphysematous lung tissue. The interior of these airspaces consists of emphysematous lung in which blood vessels are still present. In contrast to type I bullae, the outer wall is formed by pleura covered with intact mesothelial cells. Although connective tissue septae are present within the bullae, they are not found in the wall. Type II bullae may occur anywhere in the lung, but they are most frequent in the upper lobe, at the anterior surface of the middle lobe, and over the diaphragm.

Type III bullae consist of slightly hyperinflated lung connected to the rest of the lung by a broad base extending deep into the parenchyma. This type is believed to represent an atrophic form of emphysema.

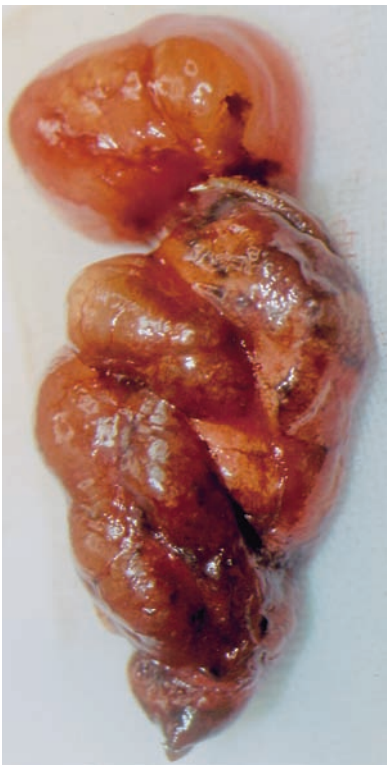
PATHOGENESIS

Several hypotheses have been proposed over the years for how bullae develop, although none have been proved.[1,2,3,6] These include (1) weakness of the alveolar walls predisposes to the formation of bullae, particularly at the apices of the lungs, where pleural pressures are most negative. This theory underscores the proclivity of bullae for the upper lobes and stresses the influence of mechanical forces acting upon flawed tissue. (2) Inflammatory disease of a bronchiole leads to progressive air trapping and "tension airspaces." (3) Disordered collateral ventilation produces the findings. (4) The same mechanisms responsible for generalized emphysema are operative in the formation of bullae. (5) Underlying paraseptal emphysema produces bullous disease.

Of all the hypotheses, that of underlying paraseptal emphysema is the most popular.[1,2] The hypothesis envisages destruction of alveoli adjacent to connective septae or the pleura. The pattern relates to the fact that capillaries in alveolar walls that abut connective tissue septa are less numerous than elsewhere because of a sparse network of arterioles and arteries in peripheral alveoli. Consequently, these regions of the acinus have less vascularity and greater compliance.

Dynamic computerized tomography and intrabulla pressure measurements have raised questions about the theory that bullae are formed by positive pressure within the airspace.[1,7] The lung surrounding a bulla is less compliant than the bulla itself; accordingly, the pressure necessary to inflate the surrounding lung is greater than that necessary to inflate the bulla. The pressure within a giant bulla has been found to be the same as pleural pressure. Therefore, when a bulla and its surrounding lung are exposed to the same negative pleural pressure, the bulla fills preferentially and completely like an inflated paper bag, prior to the surrounding lung inflating. Further inspiration increases the elastic recoil pressure, thereby exerting a greater retractive force on the lung parenchyma and enlarging the airspace. Nevertheless, bullae can be removed from within the lung while still maintaining their volume, indicating a positive intrabulla pressure.

Bullae within the intact chest are molded and compressed to fit adjacent anatomic configurations. However, if the lung is released from these constraints (e.g., when removed from the chest cavity), bullae project as shiny bubbles at the lung surface (Fig. 52-2).



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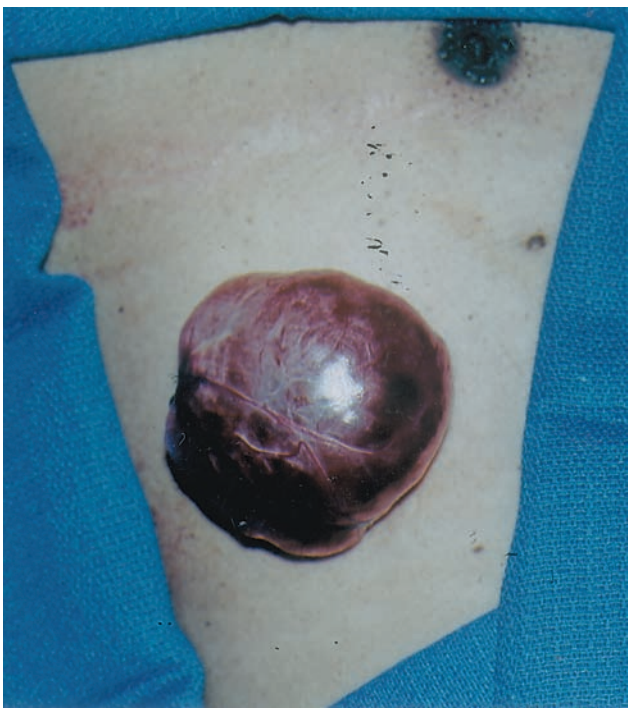

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Figure 52-2 **A.** Surgically resected specimen with a bulla projecting from the lung surface. **B.** A bulla is shown projecting through a previous chest tube insertion site onto the surface of the skin.

Within the thoracic cavity, large bullae cause crowding of adjacent lung parenchyma, and structures such as bronchi are displaced, stretched, and narrowed over the bullae surfaces. Very large airspaces can expand across the midline or even extend into the neck. Bullae represent more than just overexpanded alveoli, because the remnants of bronchioles and their accompanying vessels sometimes persist as trabeculae within the bullae. Interlobular septae can be incorporated into the wall as the airspace expands from within the secondary lobule.

Two important risk factors for bullous emphysema are cigarette smoking and α_1-antitrypsin deficiency. Many patients with bullous emphysema are cigarette smokers, and most bullous lesions are associated with paraseptal or centriacinar emphysema. Although bullous emphysema is typically found in young males, elderly patients with α_1-antitrypsin deficiency who are lifelong nonsmokers may develop bullous changes in later life. A hereditary predisposition to bullous emphysema is also suggested by its association with a variety of rare familial disorders, including Fabry disease, Salla disease, cutis laxa, Ehlers–Danlos syndrome, and Marfan syndrome.[1] Giant bullous emphysema has also been reported with histologic changes of placental transmogrification—a rare, benign lung disease of unknown etiology in which the lung shows bullous changes or, rarely, cysts or nodules.[8,9] Lung pathology demonstrates papillary structures similar to placental villi surrounding the pulmonary epithelium. The tight skin mouse, which has a dominant mutation for the elastase gene and is characterized by multiple connective tissue abnormalities, serves as a unique model for bullous emphysema.[10]

DISTRIBUTION OF BULLAE

As noted previously, the tendency for bullae to occur in the upper lobes is usually attributed to the greater mechanical stresses imposed on the lung apices than bases. Because intrapleural pressure near the lung apices is more negative than at the bases, apical alveoli are subjected to greater expanding stresses than are basal alveoli. Radioactive gas studies and in situ freezing techniques have demonstrated that alveoli in the upper lung zones are considerably larger than those in the lower zones. Gravity also plays a role, as the upright lung behaves like a coiled spring, which, when allowed to dangle in the upright position, shows larger gaps between coils at the top than the bottom.

Engineering techniques used to study the distribution of stresses in aircraft have been applied to the analysis of stresses on the lung.[1] These have shown that the larger expanding stresses at the apices are directed primarily in a vertical direction, and to a lesser extent, laterally. The stresses tend to increase with expansion of the lung, but they are present also when the lung volume decreases below functional residual capacity (FRC). The increase in apical stress at low lung volumes has been attributed to an increase in the rigidity of the lungs as residual volume is approached.

EVALUATION AND DIAGNOSIS

In asymptomatic individuals, bullae may be detected in the course of routine chest radiography. Small bullae rarely become visible on the chest radiograph but are usually easily visible by computed tomography (CT). As a rule, small bullae usually produce no symptoms, signs, or discernible alterations in pulmonary function.[11] However, rupture of one or more bullae may lead to spontaneous pneumothorax (see below). In some patients bullae give rise to progressive dyspnea or chest pain (Fig. 52-3A,B).[12] On occasion, a patient with bullous lung disease develops sudden, severe breathlessness secondary to development of a spontaneous pneumothorax[13] or sudden increase in bulla size due to air trapping. In patients with known bullous disease infection in a bulla can occur (see below). Radiographically, infection is usually identified by the appearance of an air–fluid level (Fig. 52-4A).[4–6] The physical findings in a patient with one or more bullae usually reflect the overall state of the lungs. Only infrequently do giant bullae reach a size sufficient to cause a localized decrease in regional air entry, with absent breath sounds and increased resonance to percussion.

LABORATORY

Routine laboratory testing in the evaluation of bullae includes the measurement of hemoglobin and hematocrit to identify if anemia is contributing to respiratory symptoms and to assess for possible secondary polycythemia due to chronic hypoxemia.[1,12] Measuring an α_1-antitrypsin level should be obtained to diagnose α_1-antitrypsin deficiency.[14] Finally evaluation of arterial blood gases, performed while the patient is breathing room air if possible, is generally indicated in patients with severe respiratory insufficiency and those being evaluated for possible bullectomy.[12] As noted in Table 52-3, a Pa_{CO_2} greater than 45 mm Hg is considered a relative contraindication for bullectomy.[15]

IMAGING

Imaging techniques used in the evaluation of bullous lung disease include chest radiography, computed tomography, and nuclear medicine-based studies.

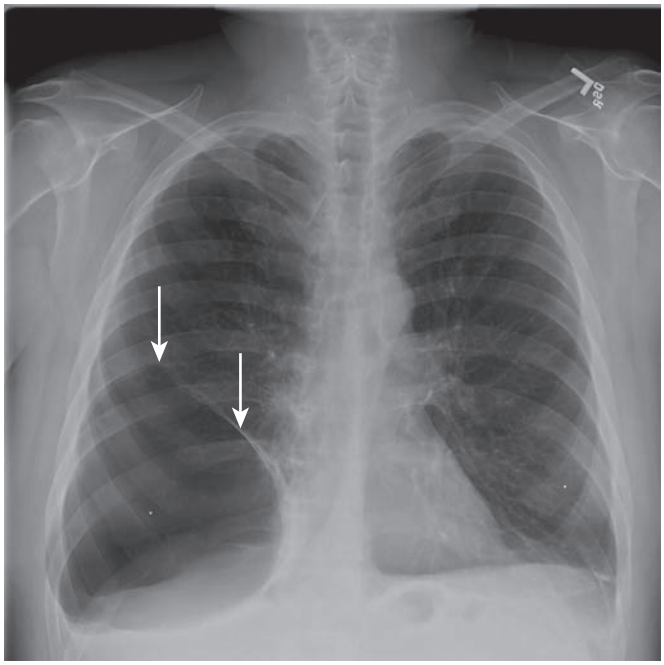
Chest Radiography

Although routine chest radiography is the most practical method for identifying the presence of bullae, the technique generally discloses less than 50% of bullae identified on CT.[16,17] In a given patient, serial radiographs taken over years are invaluable in tracing evolution of the disease.[11] The presence of the condition is suggested by areas of increased radiolucency that are sharply delineated by fine radiopaque lines representing the walls of the bullae. These lines, or "hairline shadows," are composed of compressed and fused interlobular septae or pleura.[10,18] Because the hairline shadows appear incomplete on the chest radiograph, they delineate only segments of the bulla wall (Fig. 52-3A). Distinction between hairline shadows produced by a bulla, and thicker, sometimes irregular, walls of a cavity is usually not difficult. More difficult is distinguishing bullae from cysts. The presence of other radiologic signs of emphysema or fibrotic lung disorders suggests that the cystic structure is a bulla.[13] Similarly, distinguishing between a large bulla and pneumothorax may be challenging.[12,19] In general, the pleural line associated with a large bulla is usually concave relative to the lateral chest wall, whereas the pleural line associated with a pneumothorax is convex relative to the lateral chest wall.[12] Similarly observation of "the double-wall sign" (i.e., the presence of air on both sides of the bulla wall) may be helpful in identifying the findings as due to a bulla.[18]

A chest radiograph obtained after forced expiration is sometimes helpful in demonstrating the presence of bullae: air trapping during the expiratory maneuver accentuates their outline by preventing a decrease in their size as the surrounding lung empties.[3] Large bullae sometimes displace the mediastinum contralaterally and may even compress the opposite lung.

Computed Tomography

CT provides valuable anatomic information about the size, number, and relationships of bullae, as well as crowding of adjacent lung and disposition of the pulmonary vasculature (Fig. 52-3B).[20–22] Bullae are identified as areas of radiolucency that usually do not contain blood vessels and that are confined by visible walls. High-resolution computed tomography (HRCT) shows that large bullae are frequently associated not only with distal acinar (paraseptal) emphysema, but also with centriacinar emphysema—the type of emphysema usually associated with cigarette smoking.[20]



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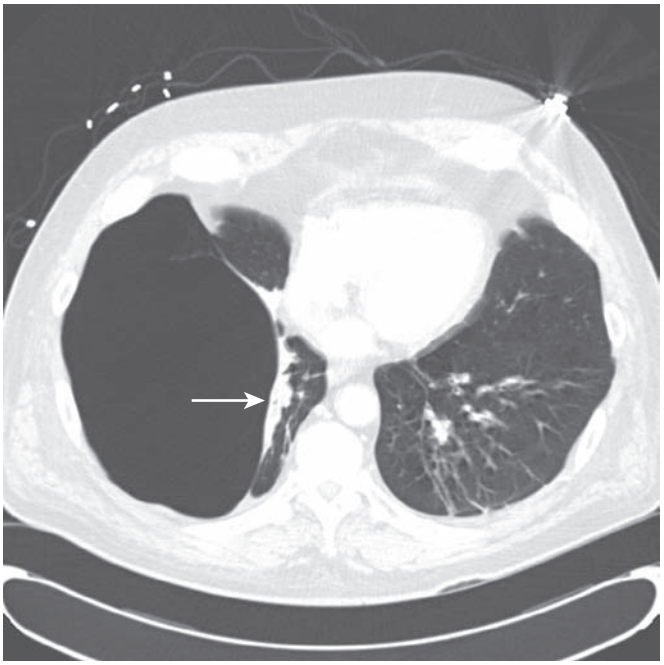

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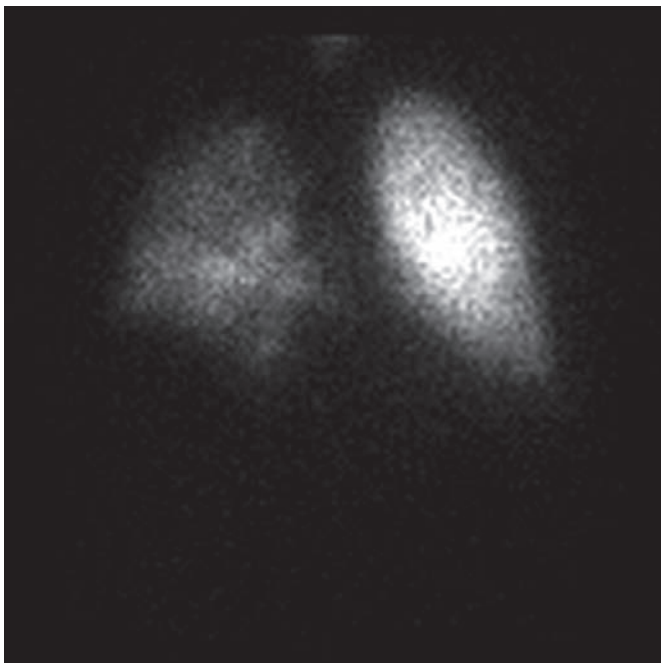

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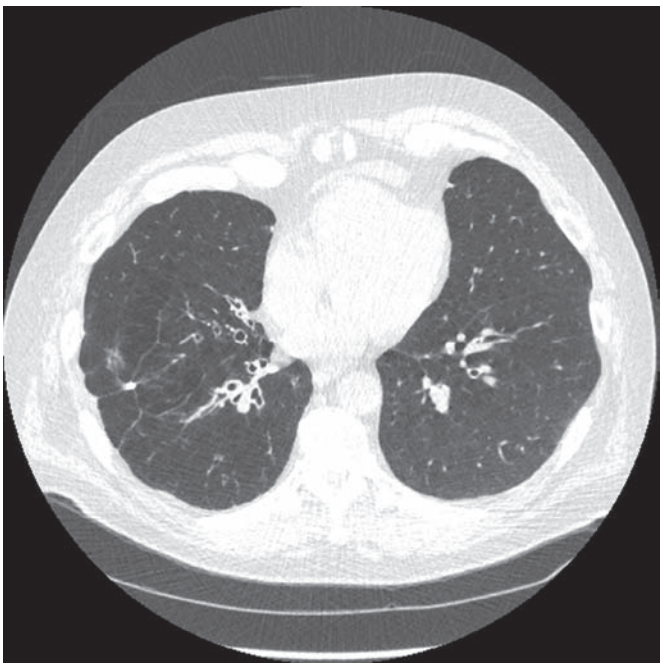

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Figure 52-3 **A.** Chest radiograph demonstrating a right lower lobe bulla. Note the demarcating lines, or "hairline shadows" *(arrows)*. **B.** CT image of the lungs demonstrating the right lower lobe bulla with compressed lung *(arrow)*. **C.** Perfusion scintigraphy demonstrating decreased perfusion to the right lower lung zone. **D.** CT image of the lung following surgical resection of the right lower lobe bulla.

These observations are consistent with the hypothesis that peripheral airspaces in paraseptal emphysema may coalesce to form larger bullae that may crowd normal adjacent lung. In addition, CT has shown that when bullae occur in the context of generalized emphysema, the extent of bullous emphysema correlates poorly with measurements of pulmonary function, and that the main determinant of respiratory function is the severity of emphysema in the bullous-free parts of the lung.[23]

On chest CT, giant bullae are predominantly located in the upper lobes and are generally subpleural.[12] However, in patients with α_1-antitrypsin deficiency, bullae are most commonly located at the lung bases. Approximately half of the patients have bilateral bullae (Fig. 52-4), and, occasionally, deviation of the mediastinal structures to the contralateral side may be noted.[12] CT has been used to create three-dimensional reconstructions of bullae, which can then be used to calculate bullae volumes (Fig. 52-5).

Nuclear Imaging

Lung scanning using radionuclide-based techniques may provide useful preoperative information in evaluating patients with bullous lung disease.[24] A lung perfusion scan provides a semiquantitative assessment of regional blood flow (Fig. 52-3C); results of ventilation

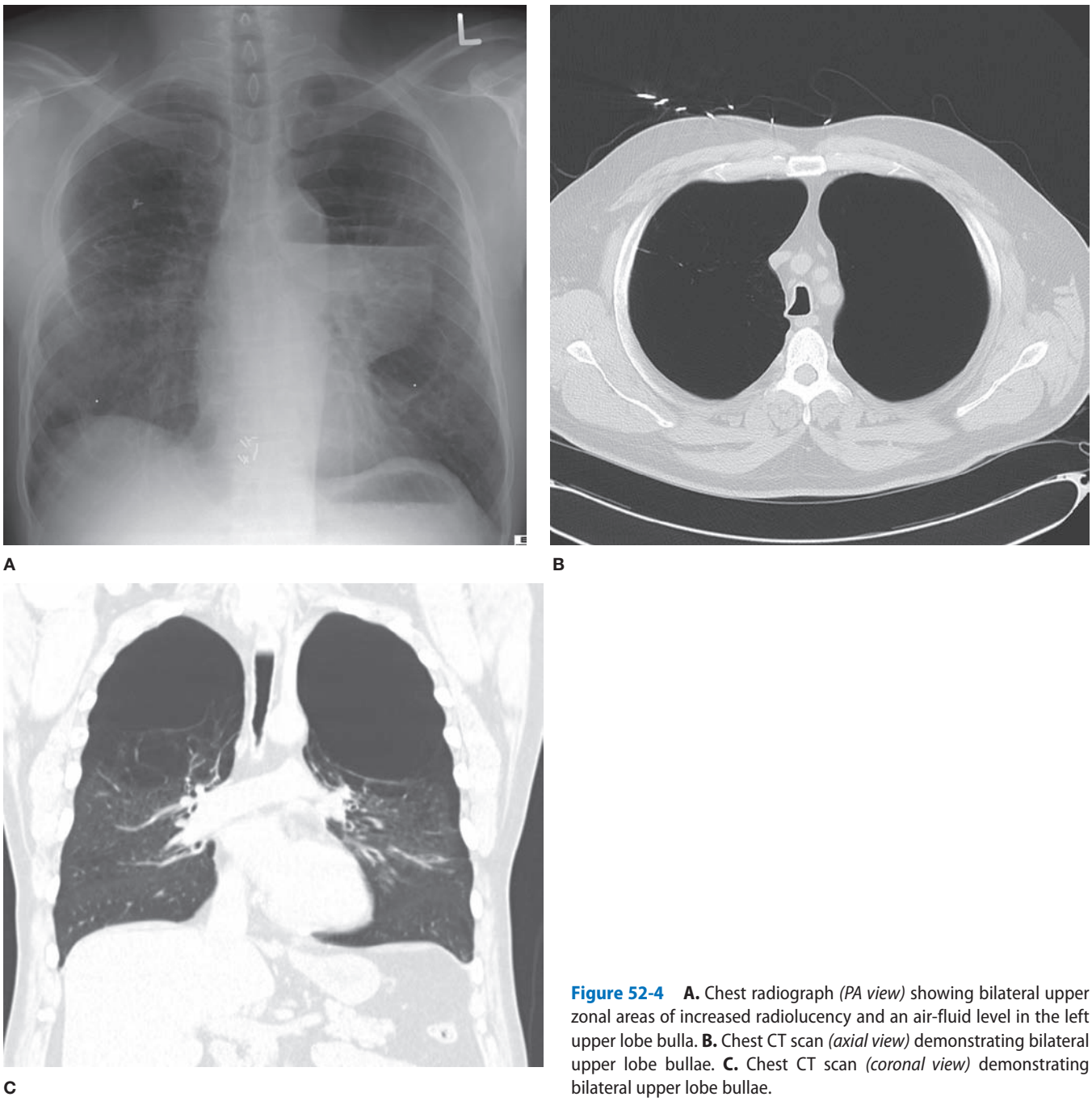


Figure 52-4 **A.** Chest radiograph *(PA view)* showing bilateral upper zonal areas of increased radiolucency and an air-fluid level in the left upper lobe bulla. **B.** Chest CT scan *(axial view)* demonstrating bilateral upper lobe bullae. **C.** Chest CT scan *(coronal view)* demonstrating bilateral upper lobe bullae.

scans vary with the technique. A single-breath scan using ^{133}xenon often fails to demonstrate ventilation of a bulla, whereas a continuous ventilation scan often shows slow filling and emptying of the structure.[24,25] Complete lack of communication between the airways and bulla is reflected in the absence of filling during all phases of the continuous ventilation scan.

■ PULMONARY PHYSIOLOGY

Clinical evaluation of bullous lung disease is aided by assessment of pulmonary function, pulmonary mechanics, exercise performance, and the pulmonary circulation.

Pulmonary Function Tests

Pulmonary function tests have considerable practical value in distinguishing between individuals with localized bullae in whom intervening lung is normal (bullous disease), and those in whom localized bullae are part of obstructive airways disease (bullous emphysema) (Table 52-4).[12] The distinction is important, since those with obstructive airways disease are generally poor surgical candidates because of impaired pulmonary function.

In individuals with bullous disease, the volume of air in the lungs can be estimated using plain radiography, CT, body plethysmography, or other pulmonary function test methods for determining lung volume, including closed circuit (helium dilution) and open circuit (nitrogen washout) techniques.[12,15] The volume of air trapped in a bulla can be determined as the difference between the functional residual capacities determined plethysmographically and by open or closed circuit methods (Table 52-4). This difference is due to the relative inability of the inert gas used in the circuit methods to enter the bulla.

Pulmonary Mechanics

Distinction between widespread obstructive airways disease with concomitant bullae and bullous lung disease has practical

TABLE 52-3 Potential Indications and Contraindications for Classical Bullectomy[a]

Parameter	Indications	Contraindications
Clinical	Young age (<50 y)	Age >50 y
	Rapid progressive dyspnea despite maximal medical therapy	Comorbid illness
	Ex-smoker	Cardiac disease
		Pulmonary hypertension
		>10% weight loss
		Frequent respiratory infections—chronic bronchitis
		Ongoing tobacco use
Physiologic	Normal or slightly ↓ FVC	FEV_1 <35% predicted
	FEV_1 >40% predicted	"Low" trapped gas volume
	Little bronchoreversibility	Decreased D_{LCO}
	"High" trapped lung volume	
	Normal or near-normal D_{LCO}	
	Normal Pa_{O_2} and Pa_{CO_2}	
Imaging	*CXR*—bulla >1/3 hemithorax	*CXR*—vanishing lung syndrome
	CT—large and localized bulla with vascular crowding and normal, compressed pulmonary parenchyma around bulla	Poorly defined bullae
		CT—multiple ill-defined bullae in underlying lung
	Angiography—vascular crowding with preserved distal vascular branching	*Angiography*—vague bullae; disrupted vasculature elsewhere
	Isotope scan—well-localized matching defect with normal uptake and washout for underlying lung	*Isotope scan*—absence of target zones, poor washout in remaining lung

[a]*Data from www.thoracic.org/copd.*

significance, since surgical lung resection in generalized emphysema offers a less certain therapeutic response than does resection of giant bullae in the absence of widespread obstructive lung disease (Table 52-3).[12] As large bullae expand, they initially cause relaxation of adjacent elastic lung tissue; with continued expansion, adjacent lung is compressed. Relaxation of the surrounding pulmonary parenchyma results in a decrease in radial traction on airways, thereby increasing airflow resistance. The effects of bullectomy on respiratory mechanics are inconsistent. Generally, resection of a large bulla increases lung static elastic recoil (by allowing for decompression of elastic lung parenchyma) and decreases airways resistance.

The diffusing capacity (D_{LCO}), rather than lung elastic recoil, is usually determined to aid in distinguishing between widespread emphysema and localized bullae, as more widespread loss of alveolar surface area in emphysema reduces the D_{LCO}; indeed, the D_{LCO} correlates better with morphologic estimates of emphysema than do most other tests.[12,15] Although the combination of a decreased D_{LCO} and reduced static elastic recoil pressure favors the diagnosis of widespread emphysema rather than localized bullae, both measurements may also be decreased by bullae that compress adjacent normal lung (Table 52-3).[3] Respiratory muscle strength, assessed by measurements of maximal inspiratory and transdiaphragmatic pressures, improves after bullectomy in some patients with bullous emphysema.[26]

Exercise Testing

In patients with a few circumscribed bullae and otherwise normal lungs, exercise testing reveals that the alveolar–arterial difference in Pa_{O_2}, ratio of dead space to tidal volume, D_{LCO}, and arterial oxygenation remain normal or near normal with exercise.[11] On the other hand, in patients in whom bullae are associated with panacinar emphysema, the alveolar–arterial difference in Pa_{O_2} is widened at rest and during exercise.[27] The latter group of patients also may develop arterial hypoxemia during exercise. The Pa_{O_2} tends to hover around the upper limit of normal at rest and during exercise, and the ratio of dead space to tidal volume is higher than in patients with normal intervening lung. The steady-state D_{LCO} is also reduced and fails to increase normally during exercise.

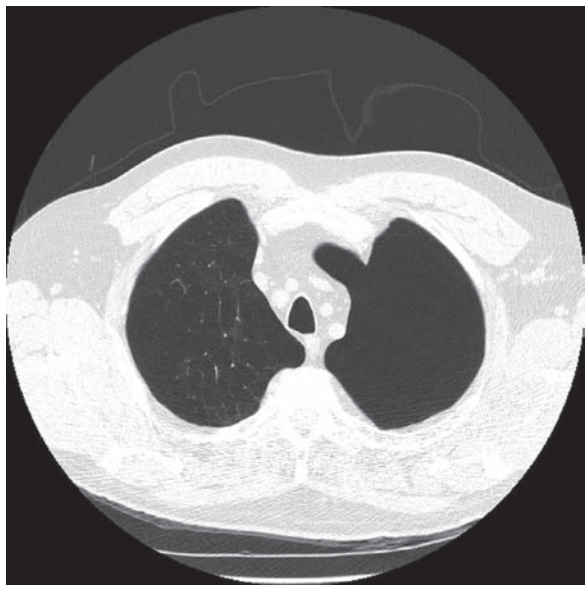
Patients in whom bullae are associated with chronic bronchitis also show a widened alveolar–arterial difference in Pa_{O_2} and an increase in the ratio of dead space to tidal volume at rest. However, in these patients the decrease in Pa_{O_2} during exercise is modest, even though the Pa_{O_2} at rest is abnormally high and increases further during exercise (indicating progressive alveolar hypoventilation).[2]

Pulmonary Circulation

In general, resting pulmonary arterial pressure and blood flow are within normal limits in patients with bullous lung disease (i.e., the bullae act like "amputated" segments of lung); the volume of the vascular bed available for recruitment as cardiac output increases is limited.[1,2] However, in patients in whom bullous disease has severely reduced the extent of the pulmonary vascular bed, pulmonary arterial pressure may be elevated at rest and during exercise; in a few instances, pulmonary and cor pulmonale may be observed.[1,2] Exercise in bullous lung disease is generally associated with an excessive increase in pulmonary arterial pressure as increases in pulmonary blood flow are not effectively accommodated by the restricted vascular bed.[2] Underlying pulmonary disease further exaggerates the increase in pulmonary artery pressure during exercise.

COMPLICATIONS

The major complications of bullous lung disease are fluid accumulation (including infection) in the bulla, spontaneous pneumothorax, bronchogenic cancer, chest pain, and hemoptysis.



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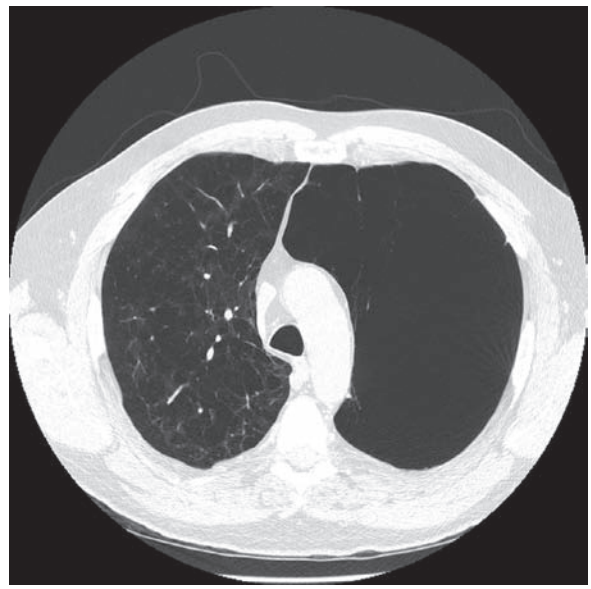

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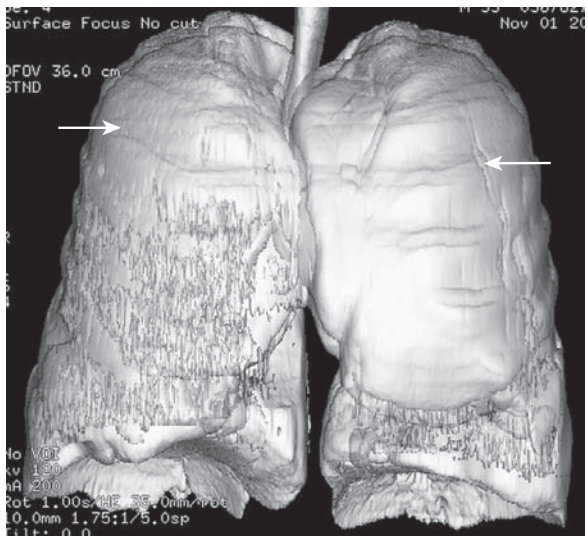

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Figure 52-5 **A.** Chest CT *(axial view)* showing bilateral upper lobe bullae. **B.** Chest CT *(axial view)* demonstrating larger left upper lobe compared to right upper bulla. **C.** Chest CT (*coronal view;* three-dimensional reconstruction) demonstrating bilateral upper lobe bullae *(arrows)*.

TABLE 52-4 Pulmonary Function Tests

Test	Bullous Disease	Obstructive Airways Disease and Bullae
TLC, L	N	N ↑
RV, L	N	↑
FRC, L	N	↑
FRC,[a] L	↑	↑
RV/TLC%	N	↑
FEV_1, L	N ↓	↓
FVC, L	N ↓	↓
FEV_1/FVC%	N	↓
MVV, L/min	N	↓
D_{LCO}/V_A, (mL/min/mm Hg)/L	N	↓
Raw, cm H_2O/L/s	N ↑	↑
Cst, exp, L/cm H_2O	N ↑	↑
Pst, TLC, cm H_2O	N ↓	↓

Note: N, normal; ↑, increased; ↓, decreased.
[a]FRC determined by body plethysmography.

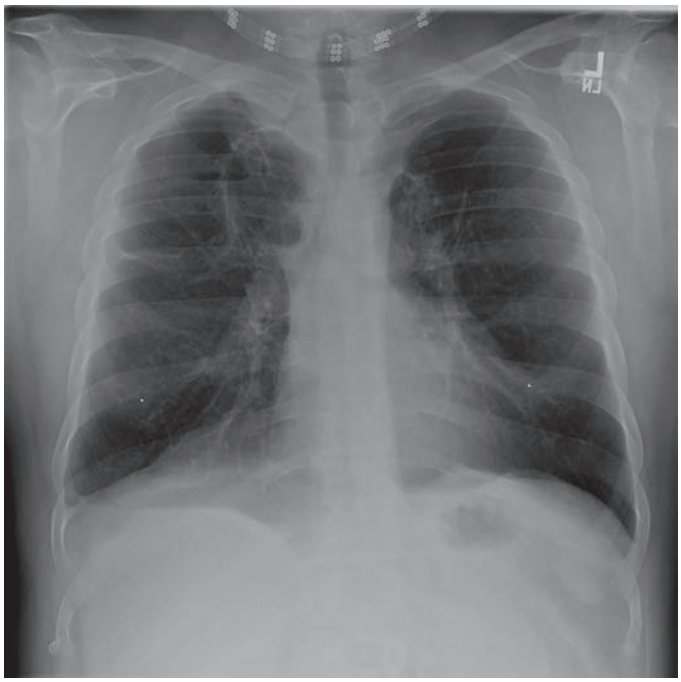
■ FLUID ACCUMULATION

The determination that an air–fluid level is within a bulla and not in a newly formed cyst or cavity is generally based on the new appearance of fluid in a previously known bulla or the presence of other bullae (Fig. 52-6).[12] CT of the chest is indicated to assure that the air–fluid level is within a bulla and to identify any surrounding pneumonia, adjacent pulmonary nodule, or an increase in wall thickness of the bulla. The latter aids in differentiating an air–fluid level within a bulla from other disorders such as tuberculosis, fungal disease, lung abscess, or cavitary bronchogenic lung cancer. These processes typically have substantially thicker cavity walls.

The presence of a fluid level within a bulla, especially if the bulla is located subpleurally, occasionally prompts the mistaken diagnosis of a loculated hydropneumothorax. CT is helpful in separating these two conditions.

Benign, Sterile Bullous Fluid

Benign, sterile fluid accumulations in a bulla can result from adjacent pneumonia or from poorly functioning bronchial communications with inadequate drainage of normally accumulating fluid.[28] In asymptomatic patients who have a thin-walled bulla without



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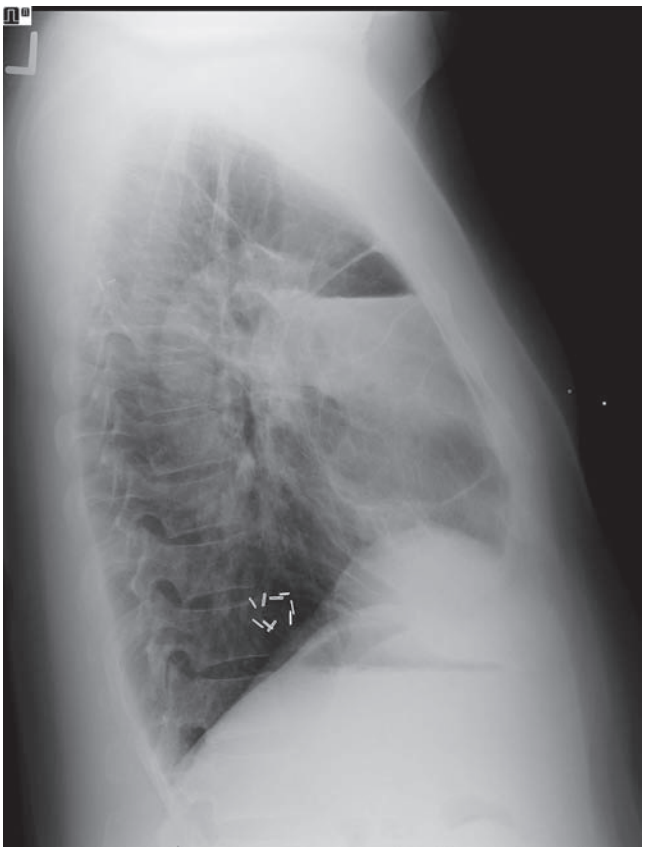

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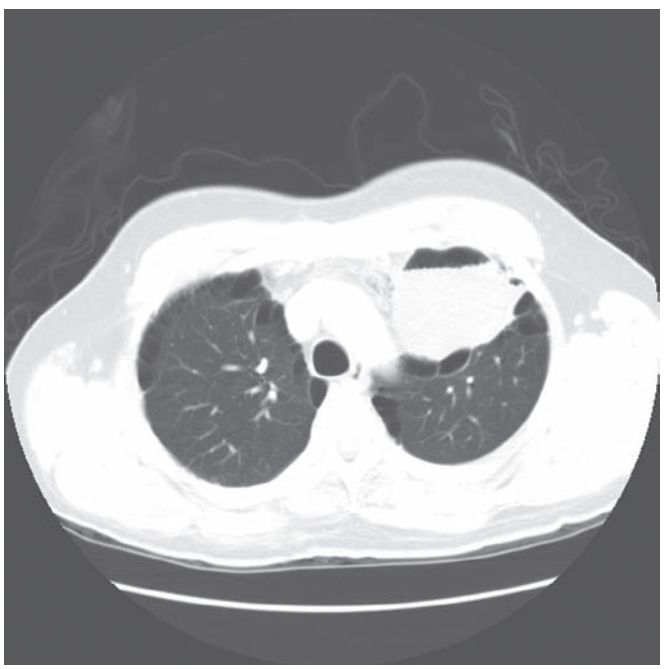

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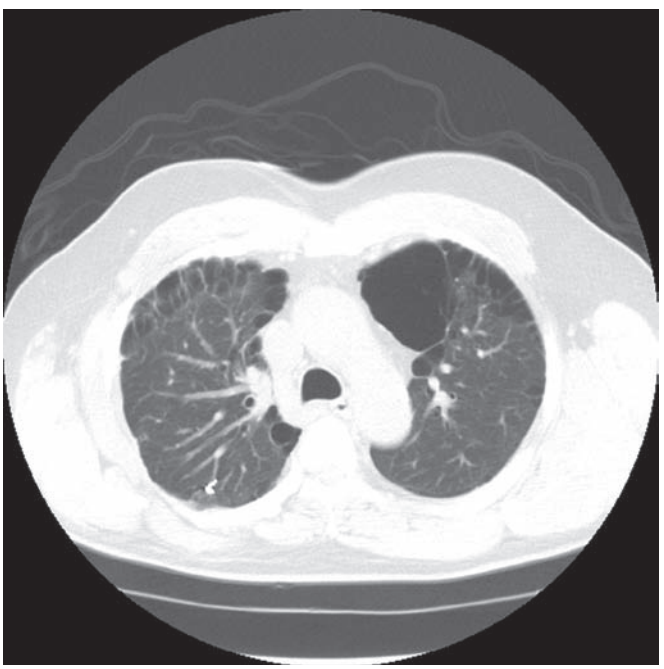

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Figure 52-6 **A.** AP chest radiograph demonstrating an air–fluid level in a left upper lung bulla. **B.** Lateral chest radiograph demonstrating air–fluid level in a left upper lung bulla. **C.** CT image of the infected left upper lobe bulla. **D.** CT image of the same bulla after a prolonged course of antibiotics.

chest CT evidence of an adjacent pneumonitis or nodule, continued observation without specific therapy is appropriate.[4] Close radiologic evaluation is typically performed at 6- to 12-week intervals to ensure that an infection or bronchogenic carcinoma is not present. In patients with clinical and radiographic evidence of adjacent pneumonia antibiotic therapy is indicated.[29] The air–fluid level may persist for weeks to months after resolution of active infection.

Infected Bulla

A superinfection within a bulla can occur with clinical manifestations including fever, cough, purulent sputum production, dyspnea, and pleuritic chest pain. Laboratory findings may include leukocytosis and positive sputum cultures. When clinical and radiographic findings suggest an infected bulla, empiric antibiotics should be initiated based on a regimen similar to that used for community-acquired pneumonia in a patient with COPD.[4,12] Bacterial species that have been identified from infected bullae include methicillin-resistant *Staphylococcus aureus* (MRSA), Bacteroides, *Pseudomonas aeruginosa*, and mycobacteria.[30–32] Treatment is sometimes prolonged and may require parenteral or intrabulla administration, since poor drainage of the bulla inevitably slows resolution of the disease process.[33] The course of the infection should be followed by interval chest radiographs, in part as bulla infection has been associated with bronchogenic cancer.[34] If a patient does not improve with empiric antibiotics percutaneous aspiration of bullous fluid can be performed under CT guidance to confirm the presence of infection and to identify the antibiotic sensitivities of the infecting organism.[4,30] It should be recognized that percutaneous aspiration carries an increased risk of pneumothorax and empyema.[12] Tube thoracostomy[35] and endoscopic drainage have also been utilized.[36]

■ PNEUMOTHORAX

Spontaneous pneumothorax may be a complication of paraseptal emphysema, particularly in patients who continue to smoke. The typical presentation is a sudden onset or worsening of dyspnea with or without pleuritic chest pain. Ultrastructural assessments suggest the possibility of air leaking through the wall of the bullae with sloughling of mesothelial cells,[37] while lung density measures suggest a valve like effect with air trapping.[38] A few case reports have described a pneumothorax occurring when a bronchogenic carcinoma eroded through the wall of a bulla.[39]

Tube thoracostomy drainage of pleural air is often required; this depends on the size of the pneumothorax and the degree of respiratory impairment.[12,40,41] Patients with ruptured bullae also tend to have prolonged air leaks, along with pleural and parenchymal infections. Subsequent management is directed at preventing recurrence. For patients with a bulla and a secondary spontaneous pneumothorax, pleurodesis using mechanical abrasion of the pleura via video-assisted thoracoscopic surgery (VATS) can be considered.[39,41,42] For patients with minimal surrounding diffuse emphysema, a bullectomy can be performed at the time of pleurodesis; for those with diffuse bullous emphysema, pleurodesis is often performed without bullectomy.[12]

■ BRONCHOGENIC CANCER

Primary lung cancer has been reported to be associated with bullous lung disease.[43–46] Presenting manifestations include pneumothorax and hemoptysis.[46] The increased incidence of lung cancer may be due to the fact that lung cancer occurs more frequently in fibrotic lungs that are, themselves, predisposed to development of bullae.[1] Other explanations for the increased incidence of malignancy include dystrophic changes in lung parenchyma caused by bullous disease or persistence of carcinogens in poorly ventilated bullae.[1] The CT appearances for bronchogenic cancer complicating bullae include a nodule or mass extruding from the wall of the bulla, a nodule or mass confined within the lumen, a soft tissue density thickening the wall of the bulla, a pneumothorax, and an air–fluid level.[37,47–50]

■ CHEST PAIN AND HEMOPTYSIS

Chest pain may occur with a bulla and is attributed to overdistention of the structure.[12] The pain is angina-like and located retrosternally. The symptom is sometimes so severe as to constitute an indication for surgical intervention. Hemoptysis, which is occasionally massive, can result from rupture of blood vessels within the walls of bullae.[51]

TREATMENT

Many patients with bullous lung disease can be managed medically.[52] Because the natural history of a bulla is unpredictable, patients with bullous disease should be monitored by chest radiography at regular intervals to ensure that the disease is stable. Occasionally, bullae enlarge suddenly and rapidly for no apparent reason; alternatively, they may shrink or disappear.[50,53,54]

■ MEDICAL MANAGEMENT

The finding of a bulla in an asymptomatic patient calls for reassurance, a recommendation for annual chest radiography, advice to stop smoking, and an alert to the need for a prompt visit to a physician should symptoms develop. Activities that promote rupture of bullae (e.g., contact sports and scuba diving) should be proscribed.[1,14] Chronic bronchitis, asthma, or emphysema associated with bullae require treatment in their own right. For patients with α_1-antitrypsin deficiency augmentation therapy with antiproteases may be appropriate.[14] Endobronchial therapy with endobronchial valves (see Chapter 36) has been recently reported.[55–57]

■ SURGICAL MANAGEMENT

Although randomized trials of giant bullectomy have not been performed, the potential benefits of elective bullectomy have been described in a number of case series.[15,58,59] In general, significant symptomatic and functional improvements have been reported for 5 or more years in 60% to 90% of patients.[15,58,59] Patients with diffuse emphysema tend to deteriorate faster than patients without diffuse emphysema.[59] A systematic review of bullectomy reported that hypoxemia was more likely to improve compared with spirometric parameters or D_{LCO}.[59] Patients with radiographic evidence of compressed lung were the most to likely experience improved oxygenation.[59] Perioperative mortality ranges from 0% to 7% for bullectomy via open thoracotomy; patients with diffuse emphysema seem to experience a higher mortality rate.[59] Causes of death include pneumonia, respiratory failure, pulmonary embolism, and cardiovascular complications.

■ INDICATIONS

The most common indication for bullectomy is severe dyspnea due to a bulla occupying 30% or more of the hemithorax or spontaneous secondary pneumothorax.[22,60,61] A key challenge for the clinician is selecting the optimal patient for bullectomy. A key factor suggesting that bullectomy may be beneficial is a bulla that occupies greater than 50% of the hemithorax with radiographic evidence that the bulla is compressing adjacent normal pulmonary parenchyma (Table 52-3; Fig. 52-3A,B).[15,58] An overall enumeration of criteria reported to define patients who are most likely to benefit from bullectomy is presented in Table 52-3.

As noted in Table 52-3 physiologic data have been reported to provide valuable information in guiding the decision to perform bullectomy. The majority of patients who undergo bullectomy have an FEV_1 less than 80% predicted but greater than or equal to 40% predicted; these thresholds have been supported by case series.[60]

Similarly, patients likely to benefit have physiologic evidence of air trapping (e.g., total lung capacity [TLC] >100% predicted, residual volume [RV] >150% predicted).[62] Some have suggested that the difference in lung volume measured by body plethysmography versus helium dilution techniques can be compared to estimate the volume of nonventilated lung. A larger nonventilated volume suggests a more favorable response to bullectomy.[15,58]

CONTRAINDICATIONS

As noted in Table 52-3 features associated with a less favorable result following bullectomy include older age, ongoing cigarette smoking, significant comorbid disease, lower pulmonary function (FEV_1 and D_{LCO}), hypercapnia, poorly defined bullae on chest imaging, and pulmonary hypertension.[59,60,62–68] Similarly, patients with chronic sputum production or frequent lung infections have been suggested to be less likely to improve.[58,59]

PREOPERATIVE EVALUATION AND MANAGEMENT

The preoperative evaluation for bullectomy includes pulmonary function testing and imaging as noted earlier. Underlying COPD should be treated aggressively with an appropriate combination of inhaled medications and pulmonary rehabilitation.[58] Preoperative cardiac evaluation is appropriate given the increased risk of cardiovascular comorbidity among patients with COPD.[69]

ANESTHETIC MANAGEMENT

Standard monitoring during the procedure includes blood pressure, pulse oximetry, capnography, core temperature, and continuous electrocardiography.[70] Arterial and central venous pressure monitoring are not mandatory but frequently utilized.[58] Bullectomy is typically performed under general anesthesia.[70] Short-acting anesthetic agents are preferred over longer-acting agents to facilitate early extubation.[70] Intravenous agents are typically used for induction of anesthesia, as severe bullous disease may make the uptake and distribution of inhalational agents erratic.[70] A thoracic epidural catheter is usually placed for administration of epidural anesthetic agents during and/or after surgery.[70]

After anesthetic induction, appropriate positioning, and sterile draping, an endotracheal tube that allows isolation of ventilation to one lung is placed to administer single lung ventilation to the nonoperative lung and to enable deflation of the operative lung.[70] Immediately postoperatively patients are assessed for anemia, cardiac ischemia, electrolyte abnormalities, hypercapnia, hypoxemia, and inadequate lung reexpansion.[70] If these factors are acceptable, the patient may be extubated; in the majority of cases this occurs in the operating room.[71]

OPERATIVE APPROACH AND TECHNIQUES

Although many surgeons prefer an open approach for bullectomy there is increasing application of VATS techniques.[62,72–74] When an open thoracotomy is performed, the posterolateral approach is generally used for unilateral bullous disease, while median sternotomy is often utilized for resection of bilateral bullae.[62] The amount of lung resected in addition to the main bulla is dependent on a balance between removing diseased tissue to optimize reexpansion of compressed tissue while avoiding resecting healthy lung tissue and minimizing prolonged air leak around the suture line.[22,59] For a single bulla that is well-demarcated and has a clear, narrow pedicle, a simple stapled excision is adequate. When the bulla is broad based or when numerous bullae merge indistinctly, a broad stapled wedge resection is usually necessary.[71] Lobectomy and segmentectomy may be utilized in unusual settings.[61,62,75]

Ablation or excision of bullae can be achieved by a variety of surgical methods, including plication, laser ablation, and excision with a stapler.[22,58] The latter is the most frequently utilized. Numerous approaches are utilized to minimize postoperative air leaks, including applying exogenous materials to buttress staple sutures (e.g., bovine pericardial or polytetrafluoroethylene strips), fibrin sealant to areas of air leak intraoperatively, and creating a "pleural tent."[76–80] The Brompton technique, or modified Monaldi procedure, utilizes a limited thoracotomy to visualize the bulla, insufflation of the bulla with iodized talc, and drainage of the bulla for several days with a Foley catheter under water seal.[66,81,82] Talc is subsequently instilled into the pleural cavity to achieve pleurodesis.

The postoperative approach includes careful attention to respiratory status, pain control, minimizing bronchoconstriction and hyperinflation, monitoring for development or worsening of a pneumothorax, and prevention of thromboembolic disease.[58] Attention to the proper function of chest tubes is key to minimize the negative implications of pneumothorax. Thoracostomy tubes are generally left in place until the lung is fully expanded and there is no evidence of air leak. In those patients with persistent slow air leaks a minichest tube with a unidirectional flutter valve (e.g., Heimlich valve) can be used to facilitate discharge of the patient. The management of postoperative pain to ensure early mobilization of the patient and effective cough is crucial to minimize complications.[71]

SUMMARY

Recognition of bullous lung disease and its causes, classification, and underlying pathophysiology have important clinical implications. Careful clinical, radiographic, and physiologic assessment allows identification of patients whose dyspnea may be substantially improved through a variety of medical, surgical, and bronchoscopic interventions.

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CHAPTER 53
Bronchiectasis

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Bronchiectasis (*broncos,* airways; *ectasia*, dilatation) is a morphologic term used to describe abnormal, irreversibly dilated and thick-walled bronchi. This is an anatomic definition that evolved from Laennec's original description in 1819 of ectatic bronchi in pathologic specimens. Bronchiectasis represents the end stage of a variety of pathologic processes that cause destruction of the bronchial wall and its surrounding supporting tissues. Etiologies include prior lung infection, systemic inflammatory disorders, and genetic disorders of host defense, however, bronchiectasis is considered to be idiopathic in up to half of the affected individuals. The clinical manifestations include chronic cough and copious mucopurulent expectoration.[1] Bronchiectasis shares many features with chronic bronchitis, including inflamed and easily collapsible airways, airflow obstruction on spirometry, and frequent exacerbations.

PREVALENCE

Bronchiectasis was a common disabling and fatal condition in the pre-antibiotic era and remains more common in medically underserved regions of the world. Overall, it is an important cause of suppurative lung disease with a significant impact on the quality of life of affected individuals and on the health system as patients utilize many medical care resources including frequent clinic visits, hospitalizations, diagnostic imaging such as high-resolution computed tomography scan (HRCT) of the chest and parenteral antibiotics.[2] In the United States, the overall prevalence has been estimated to be 52 per 100,000, but varies by age. In persons aged 18 to 34 years the prevalence is approximately 4.2 per 100,000 but in those who are 75 years old or it is estimated to be greater than 272 per 100,000. There are an estimated 110,000 affected individuals in the United States.[3] In most series, 60% of affected individuals are women. The incidence is higher in some ethnic groups living in isolated regions including the native peoples in Alaska, Maori populations in New Zealand and the Pacific, and Aboriginal groups in Central Australia. In North America and Europe, improved health care has decreased the incidence, thus bronchiectasis due to cystic fibrosis (CF) and other genetic diseases now significantly contribute to the fraction of affected adults.

PATHOPHYSIOLOGY

The pathogenesis of bronchiectasis is not known in many cases, and in others may vary with etiology, so that the pathophysiology often remains descriptive. Gross pathology reflects chronic changes so that initial changes of injury proposed to lead to initial airway obstruction are not often observed. The abnormal bronchial dilatation in bronchiectasis principally affects the medium-sized bronchi, but typically extends to the distal bronchi and bronchioles. On gross examination of surgically resected or autopsied lungs, the affected bronchi and bronchioles are so prominent as to be visible all the way to the pleural surface. These dilated and ectatic bronchi are commonly filled with purulent secretions. The affected bronchi show transmural inflammation, mucosal edema, cratering, ulceration, and neovascularization. The bronchial epithelium may show a polypoidal appearance due to underlying granuloma formation and lymphoid aggregates, ridging due to bronchial smooth muscle hypertrophy, and pitting due to the dilated bronchial mucus glands. Severe cases may show denudation of epithelial lining, with destruction of underlying elastic laminae, smooth muscle, and cartilage with fibrotic changes replacing these structures. Dilated and tortuous bronchial arteries may be seen secondary to the development of extensive bronchial-pulmonary anastomoses.

Microscopically, bronchiectasis is associated with airway epithelial remodeling characterized by mucus cell metaplasia, and decrease in ciliated cells. In other regions, cuboidal and squamous metaplasia predominate. Intense infiltration of the bronchial wall with neutrophils, lymphocytes, and monocytes is common. Hypertrophy of bronchial glands, and lymphoid hyperplasia are also seen.

Various explanations have been advanced for the phenomenon of bronchiectasis after bronchial obstruction. Following bronchial obstruction, airways proximal to the collapse are exposed to strong dilating forces caused by the difference in the atmospheric pressure in the bronchi and the negative pressure in the pleural space. Over time, these forces acting on weakened, inflamed airways may result in permanent and pathologic airway dilatation. The presence of surrounding lung fibrosis, atelectasis, and loss of lung volume leading to regional increases in local retractile lung forces may also play a role. Animal experiments suggest that obstruction may facilitate the development of bronchiectasis by interfering with bronchial clearance and promoting bacterial infection, bronchial wall inflammation, and weakening.

It has long been recognized that the pathologic changes are associated with chronic bacterial infection, independent of the initial cause of bronchiectasis. The concept of the "vicious cycle" of recurrent infectious and inflammatory insults proposed by Peter Cole et al.,[4] 37 years ago has largely been accepted. The cycle is initiated by an infection and an airway insult in a host at genetic risk. This vicious cycle theory proposed that chronic bacterial endobronchial infection and inflammation damage or destroy mucociliary defenses, leading to secretion stasis, which in turn propagates furthers bacterial infection, and increases airway inflammation and bronchial dilatation. Specific primary defects in innate host defense (e.g., IgG deficiency) have been identified as causative.[5] Furthermore, acute bacterial infection and chronic biofilm formation in the airways alone are not sufficient to produce true bronchiectasis. Impaired airway epithelial cell function, immune response, or other systemic inflammatory conditions resulting in insufficient airway clearance are additionally required. Once injury ensues, the appearance of *Pseudomonas aeruginosa* in the respiratory tract of bronchiectasis patients on a chronic or recurring basis has been associated with worsening airway clearance and airway obstruction, resulting in impaired health-related quality of life (HQOL) and worsened lung function.[6] This may be due to the ability of this organism to release virulent exotoxins, form biofilms on tissue surfaces, and easily develop hypermutable *P. aeruginosa* strains resistant to antibiotics, all factors perpetuating and propagating bronchial damage.

Specificity biochemical and molecular markers of non-CF bronchiectasis are not established and robust animal models of bronchiectasis have not been developed. Early biochemical changes are proposed related to infection and reflect a stereotyped host immune response. Later in disease, neutrophils, macrophages, and monocytes, along with their products are abundant. At both stages, cytokines such as tumor necrosis factor-a (TNF-a) and interleukin-8 may be elevated, providing a sustained signal for inflammatory cell recruitment.[7] Neutrophil- and macrophage-derived elastases and proteases isolated in large quantities in sputum have been proposed to contribute to airway injury and subsequent chronic bronchiectasis pathology.[8]

CLINICAL FEATURES

The classic clinical manifestations of bronchiectasis are daily cough and mucopurulent sputum production. Cough is invariably present and often may be the only symptom for years. Purulent, tenacious sputum production, frequently worse in the morning (having accumulated during recumbency in sleep) is present in most patients. Sputum production may be intermittent, being affected by recurrent infections, bronchial plugging, and antibiotic therapy. "Dry bronchiectasis" presenting as cough, minimal sputum expectoration, and/or hemoptysis is occasionally described. Hemoptysis may be seen in 40% to 70% of patients and may vary from blood streaks to large clots. Increasing cough, dyspnea, and volume and darkening of sputum color, fever, hemoptysis, and chest pain are hallmarks of acute exacerbations. Often patients give a history of recurrent chest infections, although single episodes of severe pneumonia, tuberculosis, or pertussis with secondary pneumonia may also result in bronchiectasis.

On physical examination chest auscultation usually reveals findings of early and midinspiratory crackles as well as diffuse rhonchi and prolonged expiration. Bronchial breath sounds may be heard in severe cases or patients with a complicating pneumonia. Digital clubbing and hypertrophic pulmonary osteoarthropathy, although common in the pre-antibiotic era, are rarely seen now. In advanced cases, there may be evidence of respiratory insufficiency and cor pulmonale.[9]

PREDISPOSING OR ASSOCIATED CONDITIONS

Previously bronchial damage secondary to childhood respiratory tract infections such as pneumonia, pertussis, complicated measles, and tuberculosis were implicated as common causes of bronchiectasis. However, with the early use of antibiotics and childhood immunizations, the focus has shifted from postinfectious to intrinsic host defense causes. Often regarded as a condition in which extensive investigation is unlikely to yield treatable causes, recent studies have shown results to the contrary (Table 53-1). Most series from referral centers identified an association or contributing cause in approximately 50% of patients. Careful investigation and the identification of the genetic basis for immune and other disorders of innate airway defense have reduced the number of idiopathic cases and increased the number of individuals that may considered for specific therapy. The overall impact of these efforts is a bimodal distribution in the age of adult patients with bronchiectasis composed of those with genetic causes first presenting in childhood and an elderly population, typically composing the idiopathic group.

INFECTION

A number of pulmonary infections have been associated with the development of bronchiectasis. Complicating secondary infections with adenovirus, herpesvirus, and bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* contribute to the severity of a necrotizing bronchopneumonia. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella* infections typically do not cause bronchiectasis, but may be chronically present within bronchiectatic airways. Necrotizing pneumonias secondary to chronic aspiration or bronchial obstruction are often complicated by parenchymal destruction and bronchiectasis. Tuberculosis can result in bronchiectasis by several mechanisms. Bronchiectasis may be a consequence of tuberculous bronchitis, postobstructive bronchial damage secondary to posttuberculous bronchial wall stenosis, and extraluminal bronchial obstruction by enlarged tuberculous lymph nodes.

The association of nontuberculous *Mycobacterium (NTM)* with bronchiectasis is well documented. CT scan of the chest in such cases is relatively specific, showing small irregular nodules in the middle lobe or lingula, but other parts of the lung may be affected. While traditionally considered a secondary pathogen in an abnormal host or a colonizer in damaged lungs (bullous emphysema, cavitary lung disease) it is now recognized that NTM can cause bronchiectasis in apparently normal hosts. A recent study of individuals with idiopathic bronchiectasis infected with NTM demonstrated shared features with primary ciliary dyskinesia (PCD) (slow cilia beat frequency, low nasal nitric oxide) suggesting the presence of either an underlying genetic or acquired defect.[14] One phenotype for NTM-associated bronchiectasis seems to involve predominantly slender white women 50 to 70 years old with kyphoscoliosis. An underlying primary lung disease or immune defect has not been identified in this subpopulation.[15]

BRONCHIAL OBSTRUCTION

Localized bronchiectasis may also been seen in middle-lobe syndrome, and is usually caused by intraluminal or extraluminal obstruction

TABLE 53-1 Associated Factors and Etiologies of Bronchiectasis

Author, Year	Anwar et al., 2013[10]	Altenburg et al., 2013[11]	McShane et al., 2012[5]	Li et al., 2005[12]	Pasteur, 2000[13]
Patients (*n*)	**189**	**83**	**106**	**136**	**150**
Age (mean)	**66**	**62**	**61**	**12**	**53**
Etiology or Association					
Immunodeficiency	2	2	18	52	12
Postinfection	46	28	10	5	44
Aspiration	2	1	12	25	6
Primary ciliary dyskinesia	2	1	3	20	4
Alpha-1 antitrypsin deficiency	2	1	12	0	0
Congenital structural malformation	0	1	1	5	1
Allergic bronchopulmonary aspergillosis	7	2	1	0	11
Asthma	6	14	0	0	0
Rheumatoid arthritis	9	0	13	0	6
Hematologic (Stem-cell transplant)	0	0	15	0	1
Inflammatory bowel disease	5	0	3	0	2
Idiopathic (%)	82(43)	27(17)	7(6)	35(26)	80 (53)

secondary to tumor, enlarged lymph nodes, or abnormalities of bronchial structure and branching. Endobronchial adenomas, fibromas, chondromas, and lower respiratory tract papillomatosis causing partial airway obstruction and bronchiectasis have been described.

■ ASPIRATION/INHALATION AIRWAY INJURY

Aspiration or inhalation of foreign matter, such as noxious fumes or particulates into the airways, may result in bronchiectasis. This may involve aspiration of oropharyngeal secretions containing microaerophilic and anaerobic bacteria, leading to a necrotizing pneumonia. Refluxed material from the esophagus or stomach containing food particles, gastric, biliary, and pancreatic secretions, and gut microbes may enter and damage airways, especially if the aspiration events are large and repeated. Depressed sensorium (stroke, alcohol and drug use, seizure, postanesthetic), neuronal or spinal cord dysfunction (amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia), defective laryngeal function (postsurgery, postirradiation), esophageal disorders (dysmotility, achalasia, tracheoesophageal fistula), and gastric disorders (gastric outlet obstruction) influence the likelihood and frequency of aspiration. Bronchiectasis may present years after foreign body aspiration (aspiration is often unrecognized), although bronchiectasis has been seen to occur in animals as soon as 2 to 8 weeks after experimental foreign body introduction into the bronchial tree. GERD is the most common condition in this category contributing to the risk of bronchiectasis CCDC.

■ CYSTIC FIBROSIS

CF is a common cause of bronchiectasis in the United States and other developed countries (see Chapter 50). This is an autosomal recessive, monogenic disorder that presents most commonly in childhood as a multisystem disease. However, 3% to 7% of patients with CF are diagnosed in adulthood, and due to improvements in therapy, there are now more adults over 18 years old with CF than younger individuals. CF is caused by a genetic deficiency in the Cystic fibrosis transmembrane conductance regulator (CFTR). Approximately 2000 mutations in the CF gene have been identified. Clues suggesting CF as a cause of bronchiectasis include upper lobe radiographic involvement and sputum cultures showing mucoid *P. aeruginosa* or *S. aureus*. The diagnosis of CF rests on a combination of clinical criteria accompanied by sweat chloride values above 40 to 60 mmol/L. However, intermediate or normal sweat chloride values may be seen in patients with clinical manifestations of CF and genetically confirmed CF. Screening for other mutations in the CFTR gene may be necessary in these circumstances. Measurement of the electrical potential difference across the nasal epithelium, available in specialized centers, is sometimes used to corroborate the diagnosis.

■ PRIMARY CILIARY DYSKINESIA

PCD is a genetically heterogeneous syndrome caused by defect in motile cilia. The true prevalence is unknown but estimated to affect 1:20,000 to 1:100,000 people.[16] The tissue-specific location of cells with motile cilia reflects the clinical features including chronic otitis media, rhinosinusitis, bronchiectasis, infertility, and laterality defects including situs inversus. PCD has an autosomal-recessive inheritance pattern and has been ascribed to mutations in over 30 genes to date that are estimated to account for approximately 60% of all cases. The involvement of many genes in this syndrome is consistent with the knowledge that over 2000 proteins are involved with cilia assembly, structure and function. The ciliary axoneme contains nine outer and two inner pairs of microtubules that are connected to dynein motor proteins forming characteristic structures of motor complexes called inner and outer dynein arms that can be observed by transmission electron microscopy of preparations of cilia from respiratory epithelial cells. Known causative genes in PCD encode proteins for dynein motors (e.g., DNAI1, DNAI2, DNAH5, DNAH11), cilia motor regulation and structural assembly (e.g., RSPH4 A, RSPH9, CCDC39, CCDC40) and motor complex preassembly (e.g., DNAAF1, DNAAF2, HEATR2).[16]

In 1933 Kartagener described the PCD syndrome, as the triad of situs inversus, bronchiectasis, and either nasal polyps or recurrent sinusitis, while the description by Afzelius in 1976 of the defects in the ultrastructure of ciliary dynein arms revealed the basis of this condition.[17,18]Thus, clinical findings include, respiratory distress in neonates, recurrent respiratory tract infections, bronchiectasis, situs inversus, infertility, and heterotaxy in approximately 50%. Laterality defects are the result of motile cilia defects in the embryonic node, a midline structure transiently present during early development that contains cilia. Directional movement of fluid in the node activates downstream programs that establish left and right sidedness of organs. In the absence of flow, *situs solitus* (normal left-right), *situs inversus* (fully reversed right-left, functional organs), or intermediate states may occur resulting in cardiac defects. Thus, individuals with congenital heart disease may also have cilia dysfunction, complicating exacerbation of pulmonary disease in heart failure.[19] Hydrocephalus due to dysfunction of the motile cilia of the brain ventricles is exceedingly rare.

In a study of 94 patients from 68 families, Noone et al.[20] showed that cough was seen in 100% of patients, bronchiectasis (98%), sinusitis (47%), otitis media (92%), and situs inversus (46%). Although most patients with PCD are identified in childhood, this disorder may not be accurately diagnosed until adulthood. Like CF, bronchiectasis occurs in children and is progressive, however in contrast to CF, lung disease is not as severe and lifespan is usually normal.

Accurate testing for PCD is technically demanding and should be performed in specialized centers.[21] Nasal nitric oxide (NO) is emerging as the most sensitive screening test, with levels of NO being characteristically low, a feature that can be shared with CF.[20] Once CF is excluded (e.g., by sweat test), then nasal NO together with clinical features provides high specificity for diagnosis. Ciliated epithelial cells obtained from the inferior or middle turbinate using a sterile cytology brush may be studied for ciliary beat pattern and frequency using digital high-speed video imaging. This requires experienced observers. Abnormalities in ciliary beat have been correlated to ultrastructural defects, but normal ciliary motion cannot fully exclude PCD since some mutations are associated with near normal beat frequencies. Axonemal structure of respiratory cilia may be visualized by transmission electron microscopy and defects in dynein arms, peripheral and central tubules, radial spokes, and basal bodies may be seen. These studies are technically challenging and no structural abnormalities may be found in cases of PCD,[22] particularly when mutations involve regulatory proteins. Genetic testing is available in some research centers.

■ COPD AND BRONCHIECTASIS

Cigarette smoking causes COPD but is probably not an etiology for bronchiectasis although there is overlap in clinical characteristics that have prognostic and management implications. The phenotype includes frequent exacerbations requiring medical attention in an urgent care setting,[23] HRCT scans that have both emphysema and bronchiectasis portend a reduced prognosis,[24] obstructive impairment on pulmonary function, and sputum microbiology that contains *P. aeruginosa*.[6,25,26]

■ ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD)

Unimpeded neutrophil elastase contributes to the alveolar destruction of emphysema in AATD. Abundant elastin in airways could also be subject to destruction. There may be a spectrum of disease with heterogeneous lung conditions rather than simply pure emphysema in patients with AATD. Small case series have identified

bronchiectatic changes in patients with AATD. Cuvelier et al. measured AAT alleles in patients with known bronchiectasis and healthy blood donors. They did not find any significant differences in AAT alleles between patients with bronchiectasis and control individuals except in those patients with both emphysema and bronchiectasis. There were more abnormal alpha-1 alleles in those patients with coexisting emphysema and bronchiectasis. They concluded that bronchiectasis might be a consequence of emphysema.[27] In a study of 74 patients by Parr et al. with AATD (PiZ phenotype), 70 out of 74 were found to have bronchiectasis on HRCT scan. They defined clinically significant bronchiectasis as patients with regular sputum production and HRCT findings of bronchiectasis affecting four or more lobes.[28] Fifty-seven patients had bronchiectasis in four or more bronchopulmonary segments. Twenty (27%) met the criteria for clinically significant bronchiectasis. In general, those with more severe bronchiectasis had more severe emphysema. Whether there is a common pathway that contributes to both emphysema and bronchiectasis in patients with AATD or whether emphysema predisposes to bronchiectasis is still unknown.[28]

■ ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease caused by the ubiquitous fungus *Aspergillus fumigatus* and usually occurs as a complication of persistent asthma or CF. The excessive mucus production and impaired mucociliary clearance in these conditions allow the inhaled conidia of *Aspergillus* to persist and germinate, releasing exoproteases and other fungal products that further compromise clearance, breach epithelium, and activate immune responses. ABPA is characterized by a marked local and systemic eosinophilia, an elevated level of *A. fumigatus*—specific IgG and IgE antibodies, as well as a nonspecific elevation of total IgE. Clinically, ABPA manifests as difficult-to-control or recurring episodes of asthma, pulmonary infiltrates, and central bronchiectasis that may progress to fibrosis. Criteria have been established for the diagnosis of ABPA in the non-CF as well as the CF population.[29]

■ INFLAMMATORY DISORDERS

Inflammatory and fibrotic processes affecting large and small airways may be seen in several rheumatic diseases and autoimmune states. Significantly higher frequencies of bronchiectasis (20%–35%) have been found in *rheumatoid arthritis* (RA) patients undergoing HRCT, both in symptomatic (30%) and asymptomatic (8%) patients, and was independent of smoking status. Bronchiectasis may precede or follow the development of RA, and the coexistence of both conditions is considered to portend a reduced survival.[30] *Sjögren syndrome* may also be complicated by bronchiectasis presumed to be secondary to the effects of inspissated bronchial secretions causing atelectasis and bronchial wall destruction.[31] *Relapsing polychondritis* may be complicated by bronchiectasis in regions of recurring pneumonia as well as regions free of infection. It is not clear whether the chondritis itself or the recurrent infections predispose to bronchiectasis. Inflammatory bowel disease such as *chronic ulcerative colitis* is associated with bronchiectasis. The pathogenesis remains unknown, although autoimmune and immune complex deposition theories have been proposed. This variant of bronchiectasis does not respond to colectomy and has been known to appear and progress after colectomy. Bronchiectasis seen in sarcoidosis is usually traction bronchiectasis secondary to parenchymal and peribronchial fibrosis. Endobronchial sarcoid may result in localized bronchiectasis secondary to obstruction, atelectasis, and bronchial wall destruction.[32]

■ IMMUNE DEFICIENCIES

Bronchiectasis is associated with defects in both cellular and humoral immunity. Bronchiectasis is found in HIV and HTLV-1 infected individuals.[33] It is also associated with acquired immunodeficiencies associated with stem-cell transplant and chemotherapy.[5,12] Recurrent sinopulmonary infections and bronchiectasis are associated with defects in humoral immunity and hypogammaglobulinemia. Several forms of antibody deficiency have been linked with the development of bronchiectasis, including X-linked agammaglobulinemia, common variable immunodeficiency, IgA deficiency, and IgG subclass deficiency (usually IgG-G2 and IgG-G4).[34] The issue of subclass deficiency (in the presence of normal or near-normal levels of total IgG) as a cause of bronchiectasis is controversial due to the wide range of values in normal individuals and the difficulties involved in accurately measuring these levels. An immunizing challenge with common humoral bacterial antigens, such as capsular polysaccharides of *H. influenzae* and *S. pneumoniae* followed by measurement of antibody titers 4 to 6 weeks later, may help establish the presence of such a deficiency. The lack of an antibody response is suggestive that humoral deficiency is present.[35] Early diagnosis of these conditions and replacement with intravenous immunoglobulin significantly reduces infections and prevents bronchiectasis, although the efficacy of this treatment in patients with selective IgM, IgA, and IgG subclass deficiency remains controversial. Standard doses in adults of 300 mg/kg by intravenous infusion every 4 weeks have been proved to reduce rates and severity of respiratory infections, but higher doses of 600 mg/kg appear more efficacious in reducing respiratory exacerbations and preserving pulmonary function in some patients.[36] Hyper-IgE syndrome is accompanied by recurrent lower respiratory infections leading to bronchiectasis and cystic lung destruction. Respiratory infection with *Pseudomonas* is a contributor to mortality.[37]

DIAGNOSIS OF BRONCHIECTASIS

The diagnosis of bronchiectasis is based on history, clinical features, and radiologic demonstration of bronchiectatic airways. The diagnostic evaluation in these patients is largely aimed at identifying potentially treatable underlying causes of bronchiectasis (Table 53-2). After confirming the diagnosis with chest imaging, CBC with differential

TABLE 53-2 Clinical Approach to the Patient with Suspected Bronchiectasis

History	Recurrent lower and/or upper respiratory tract infections, pneumonia
	Daily mucopurulent sputum production
Initial studies	CBC with differential
	Chest x-ray
	Immunoglobulins IgG, IgM, IgA
	Sputum: bacterial culture and sensitivity, mycobacteria, fungi
Confirms diagnosis	Chest CT (non-contrast)
Other studies	Sweat chloride and/or genetic panel for CFTR alleles
	Allergic bronchopulmonary aspergillus panel (IgE, precipitins, or skin test)
	Bronchoscopy (for cultures, obstruction)
	Nasal nitric oxide
	Alpha-1 antitrypsin level; phenotype
	Pulmonary function (spirometry pre- and postbronchodilator)
	Serum antibody response to bacterial antigen challenge, e.g., pneumococcal vaccine

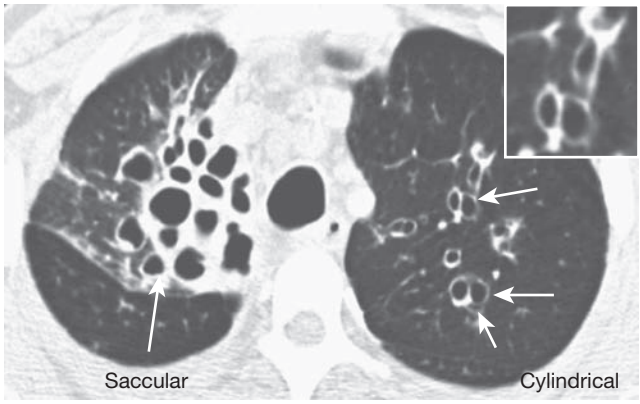

Figure 53-1 Chest computed tomography. *(Left chest) Cylindrical* bronchiectasis: dilated and thickened airways *(arrows and insert). (Right chest) Saccular* or cystic bronchiectasis: very dilated airways clustered into saccules, cysts, or grapelike clusters *(arrow)*.

for eosinophils, serum immunoglobulins IgG, IgA, and gM, sweat chloride or genetic CF testing, sputum culture for bacteria, mycobacteria, and fungi are productive starting tests. Subsequent testing will depend on clues from the history and likelihood of other conditions.

CHEST RADIOGRAPH

The chest x-ray may be abnormal and show the presence of increased pulmonary markings, ring-like structures, atelectasis, dilated and thickened airways (tram lines), and mucus plugging (finger-in-glove) appearance; however, the chest radiograph may be normal even in the presence of bronchiectasis.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY

HRCT is now the defining test for the diagnosis of bronchiectasis. HRCT can accurately diagnose bronchiectasis, localize, and describe areas of parenchymal abnormality, and identify bronchiolar abnormalities and mucus plugging. It also can identify focal areas of air trapping as an indicator of small airway disease (mosaic attenuation).

Airway dilatation can be gauged when seen in cross section. A luminal diameter more than 1.5 times the adjacent vessel is indicative of bronchiectasis (Figs. 53-1 and 53-2). Other findings include bronchial wall thickening and small airway plugging with debris (tree-in-bud) (Figs. 53-2 and 53-3). The distribution and pattern of

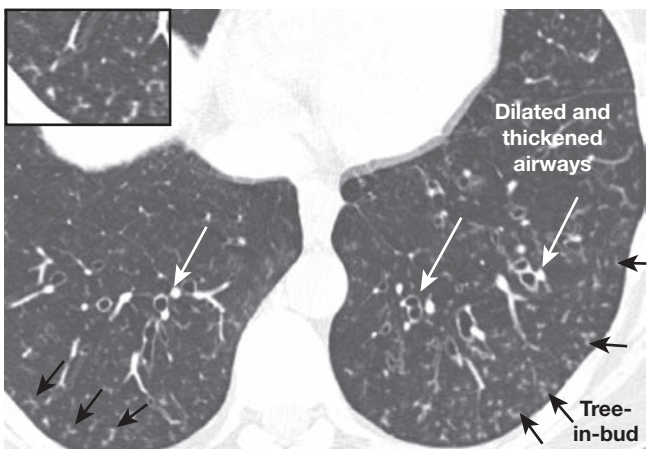

Figure 53-2 Chest computed tomography. Extensive peripheral branching opacities of tree-in-bud *(black arrows)*. Dilated and thickened airways *(white arrows)*.

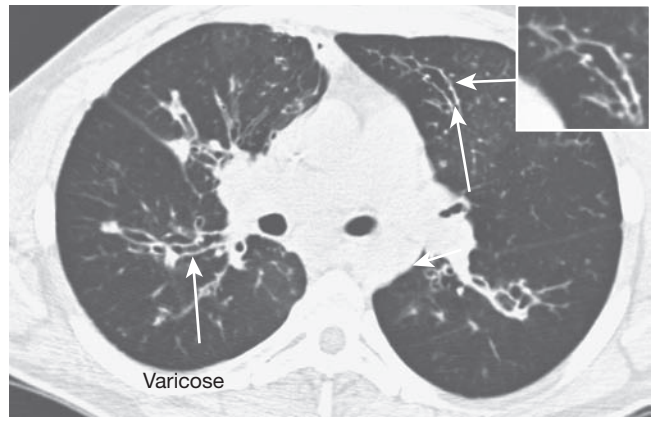

Figure 53-3 Chest computed tomography shows *varicose* bronchiectasis: dilated airways with irregular thickened mucosa *(arrows)*.

bronchiectasis may implicate a specific cause. Cartier et al.[38] found that bilateral predominantly upper lobe bronchiectasis is seen most commonly in CF, ABPA, and sequelae of tuberculosis. A middle-lobe distribution with irregular ground glass nodules is very characteristic of NTM.[15] A lower lobe predominance is seen in most other causes. HRCT scoring systems for CF have been developed to identify disease at an early stage, grade severity, monitor disease progression, and utilize as endpoints in clinical trials. With similar CT findings in bronchiectasis, these scoring systems may be applicable for non-CF bronchiectasis.[39] PCD children have been assessed with one of these scoring systems and correlated with pulmonary function and compared to age and gender-matched CF children and adults.[40]

Bronchiectasis may be classified by pathologic features and radiographic appearance. Reid[41] described a correlation between pathologic and bronchographic findings in bronchiectasis; since then, this has been the most widely used classification. In *cylindrical* bronchiectasis, the bronchi are regularly outlined (tubular), dilated in diameter, with straight walls, often coming to a straight abrupt end instead of a tapering end due to obstruction of the peripheral bronchial tree by secretions, casts, and inflammatory wall edema. *Varicose* bronchiectasis (illusion to varicose veins) is marked by the presence of irregular dilatations, outpouchings, and tortuosity of the airways. *Saccular* (cystic) bronchiectasis is characterized by the presence of cystic distortion of the distal airways that may be focal or more generalized, resulting in saccules that appear as a cluster of grapes (Fig. 53-1 *arrows and inset*). Traction bronchiectasis, a term used to describe the dilated airways seen in diffuse pulmonary fibrosis secondary to fibrous tissue traction and elevated negative intrathoracic pressure, should be distinguished from usual bronchiectasis, because of the lack of intrinsic airway pathology and paucity of sputum expectoration. Congenital bronchial cysts (central and peripheral) are developmentally abnormal cystic bronchial structures, often filled with mucus and lined with respiratory epithelium. While usually lacking connection with the parent bronchus and distal alveoli, if infected they may communicate and mimic localized bronchiectasis. Intralobar bronchopulmonary sequestration too may become infected and communicate with the bronchial tree, mimicking localized bronchiectasis.

PULMONARY FUNCTION

Pulmonary function is usually abnormal. The degree of impairment depends not only on the nature and extent of the morphologic abnormalities of bronchiectasis, but also on the presence or absence of associated COPD. Thus, patients with mild localized bronchiectasis and no chronic bronchitis may have normal lung function tests. Spirometry will often show a pattern of airflow obstruction, with normal or reduced forced vital capacity (FVC), reduced forced

TABLE 53-3 Microbiology in Bronchiectasis

Author, Year	Li et al., 2005[12]	Angrill et al., 2002[7]	Pasteur et al., 2000[13]	Nicotra et al., 1995[45]
Mean age (y)	**12**	**53**	**58**	**57**
Patients (*n*)	**136**	**42**	**150**	**123**
Microbiologic Flora (%)				
Haemophilus influenzae	53(40)	11(26)	52(35)	37(30)
Pseudomonas aeruginosa	15(11)	4(9)	46(31)	38(31)
Streptococcus pneumoniae	23(18)	6(14)	20(13)	13(11)
Staphylococcus aureus	5(4)	NA	NA	9(7)
Moraxella catarrhalis	3(2)	2(5)	30(20)	3(2)
Nocardia	0	NA	NA	4(3)
Anaerobes	1(1)	NA	NA	2(1)
Mycobacteria	0	NA	NA	49(40)
Aspergillus	1(1)	1(2)	3(2)	6(5)
Two or more organisms	21	NA	NA	60

expiratory volume in 1 second (FEV_1), and reduced FEV_1/FVC ratio. In some patients with accompanying atelectasis and/or parenchymal and pleural scarring, restrictive or mixed/obstructive and restrictive physiology may be seen with reduced FVC and normal FEV_1/FVC ratios. The Lung Clearance Index (LCI; multiple breath nitrogen washout) is another method to detect airflow obstruction. The LCI has been used to detect early airflow obstruction in CF and may be more sensitive than changes in spirometry. In bronchiectasis the LCI is reproducible and correlates better with abnormalities on chest CT than FEV1.[42]The diffusing capacity for carbon monoxide is initially normal but may decrease with progressive disease. Impaired oxygenation is highly variable, most likely due to heterogeneity among patients in anatomic disease distribution.

MICROBIOLOGY

The sputum of patients with bronchiectasis is frequently found to be colonized with potentially pathogenic microorganisms (Table 53-3). The most frequent microorganisms isolated are *H. influenzae*, *S. pneumoniae*, and *P. aeruginosa* and are often implicated as the cause of exacerbations. Sequencing of lung microbiota in patients with bronchiectasis demonstrates both diversity of communities and a predominance of *Haemophilus*, *Pseudomonas*, and *Streptococci* in stable patients and during exacerbations.[43,44] Colonization with *P. aeruginosa*, in particular, has been associated with more severe impairment of lung function, more intense inflammatory response, and more extensive lung disease independent of the cause of bronchiectasis.[6] Instances of airway colonization with other potential pathogens that may require specific treatment include *Nocardia asteroides*, *A. fumigatus*, and nontuberculous mycobacteria. Anaerobic bacteria are identified in genomic surveys of airway microbiota of individuals with non-CF bronchiectasis; however, there is no direct implication for therapy.[43,44]

TREATMENT

The management of bronchiectasis is aimed at treating underlying conditions, controlling infection, reducing inflammation, improving bronchial hygiene, and surgical resection of focal bronchiectasis or severely affected segments or lobes. With few quality clinical trials for guidance, treatment often has to be tailored to the specific needs, tolerances, and preferences of individual patients.

CONTROL OF INFECTION

Since infection plays a major role in the causation and perpetuation of bronchiectasis, reducing the microbial load and associated inflammatory mediators remains a cornerstone of therapy. Antibiotics are indicated to treat an acute exacerbation. Antibiotics are directed at commonly isolated pathogens such as *H. influenzae* and *P. aeruginosa*. Oral fluoroquinolones are often used as initial antibiotic choices for treatment durations of 10 to 14 days. In the face of failure to respond to treatment or the occurrence of frequent exacerbations over short periods of time, sputum cultures and sensitivity tests should be performed to help define antibiotic selection and/or aid in alternative diagnoses, for example, atypical mycobacteria or fungus. Severe exacerbations due to *P. aeruginosa* require the intravenous administration of antipseudomonal antibiotics and potential hospitalization.

The role of prophylactic/suppressive antibiotics remains controversial. Several approaches to the prescription of suppressive antibiotics exist, including daily antibiotics, antibiotics given for 1 to 2 weeks each month, as well as more prolonged courses lasting weeks to months.

The use of daily, twice weekly, and thrice weekly macrolides (erythromycin, azithromycin) as biologic response modifiers in CF and diffuse panbronchiolitis has generated considerable interest regarding a role in the treatment of bronchiectasis. In the EMBRACE and BAT trials, azithromycin was associated with a decrease in exacerbations compared with placebo. However, no significant difference was noted in lung function.[11,46] In the BAT trial gastrointestinal intolerance and macrolide resistance was common. Similarly, in the BLESS study, erythromycin decreased the number of exacerbations and ameliorated the decline in lung function but with a consequential development of macrolide resistance.[47] Macrolides have been shown to have several biologic effects not related to their antibacterial properties. These include effects on nuclear transcription factors with downregulation of proinflammatory cytokines, suppression of iNOS, reduced adhesion molecule expression, reduced neutrophil chemotaxis and degranulation, cytoprotection against phospholipids, improvement in mucus rheology, reduction in bronchial hyperreactivity, effects on *Pseudomonas* biofilm production, and quorum sensing function.[48]

Administration of antibiotic aerosols (chiefly tobramycin 300 mg nebulized twice daily and aztreonam 75 mg three times daily) are effective in CF. Pilot studies of non-CF bronchiectasis have demonstrated a reduction in *Pseudomonas* density and even eradication of *Pseudomonas* in some patients, although side effects were also noticed, including increased cough, wheezing, dyspnea, tinnitus, voice alteration, and tobramycin resistance.[49] The effects of other aerosolized antibiotics, such as colistin, ciprofloxacin,[50]

and gentamicin[51] alone, or in rotation with tobramycin need to be assessed for efficacy and side effects.

NTM-associated bronchiectasis should be considered in patients not responding to antibacterial therapy. The diagnosis requires two or more separate expectorated sputum collections with positive cultures for NTM or one positive culture from a bronchial wash and radiologic evidence of progressive infiltrates, multiple nodules, or cavitation on chest imaging. American Thoracic Society guidelines provide treatment guidance for the individual NTM species.[52]

ABPA responds to oral prednisone in doses of 0.5 to 1 mg/kg per day. The addition of antifungal azoles (itraconazole 400 mg/day for 2 months; then 200 mg/day; or voriconazole 300 mg twice daily)[53] may confer additional benefits in terms of reducing fungal burden, steroid dose, and exacerbations. Early and appropriate therapy for ABPA may prevent or delay permanent airway destruction. Because of its relapsing course, monitoring of clinical, radiographic, and serologic responses (IgE) is necessary.

BRONCHIAL HYGIENE

Airway mucus clearance is a problem in bronchiectasis. Chest percussion and postural drainage have been the traditional method of facilitating mucus clearance. The onerous and labor-intensive nature of physical therapy procedures such as chest wall percussion and postural drainage, and potential issues of hypoxemia and chest discomfort may result in poor patient compliance. These issues have led to a search for alternative therapies. Autogenic drainage, mechanical vibration with ultrasonic devices, positive expiratory pressure, and flutter valve devices have been shown to achieve good airway clearance provided the patient has motivation, breath control, and the neuromuscular function to perform. An intrapulmonary percussive ventilation device and vibratory vest help provide mucus clearance in patients unable to perform the other techniques.[54] Studies document increased sputum expectoration using all these methods, with no method being demonstrably more effective or preferred. Thus, it is recommended that patients should choose their modality based on ability, motivation, preference, needs, and resources.

MUCUS CLEARANCE

Mucus hypersecretion is a prominent feature of bronchiectasis and little is known about the effects of current therapies, because of the difficulties in quantifying mucus hypersecretion in clinical studies, both at baseline and in response to treatment. Maintenance of hydration with oral and/or intravenous fluids is considered useful in preventing inspissated sputum retention. Humidification of inhaled air or oxygen as an adjunct to airway clearance techniques has been shown to significantly increase the wet weight of sputum produced. The use of nebulized normal or hypertonic saline may be considered as adjuncts to bronchial hygiene, although bronchospasm may be associated with the use of these agents. A randomized multicenter study evaluating the efficacy of aerosolized DNAse in non-CF bronchiectasis did not find it efficacious in this group of patients.[55] Rather it was associated with increased pulmonary exacerbation rates, hospitalizations, antibiotic use, and a fall in FEV_1 and FVC. The antiosmolar agent, mannitol, has shown efficacy to stabilize pulmonary function and reduce exacerbations.[56]

BRONCHODILATORS

Bronchodilators, such as beta agonists or anticholinergics, are used in patients with bronchiectasis, since these patients show signs of airflow obstruction and hyperreactivity. Formoterol in addition to budesonide has been shown to reduce symptoms and improve scoring on an HQOL questionnaire as compared to budesonide alone.[24]

Anti-inflammatory Therapy Persistent endobronchial inflammation is known to play a significant role in the pathogenesis of bronchiectasis, and anti-inflammatory therapy may be beneficial. The role of inhaled steroids (fluticasone) in bronchiectasis was evaluated by Tsang et al.,[57] who found reduced sputum volume and purulence, and reduced rates of exacerbations.

SURGERY

Bronchiectasis is usually a diffuse disease and surgical extirpation of affected areas is often not feasible. However, in selected cases surgical resection of the most severely affected segments, bleeding segments, or areas harboring resistant tuberculosis or atypical mycobacteria may confer significant benefits in terms of symptom control, reduction of tenacious sputum production, elimination of large-volume bronchial bleeding, reduction of acute infective episodes, and improved quality of life. The surgical approach varies according to the centers offering this treatment, with some preferring a video-assisted thoracoscopy approach, while others recommend the lateral thoracotomy approach. The complications associated with surgery include spread of infection, bleeding, prolonged air leak, and poor lung expansion following surgery.[58]

Lung transplantation is now considered a viable option in advanced cases, when earlier the risks of persistence of infection in the face of prolonged immunosuppression seemed prohibitive. The outcomes of patients receiving lung transplantation in non-CF bronchiectasis were reported from the United Kingdom. Fifty-four patients underwent bilateral lung transplantation between 1997 and 2007. The mean age was 54 and the median transplant list waiting time was 309 days. The median survival time for transplant recipients was 8 years.[59]

MISCELLANEOUS

While not evaluated specifically for bronchiectasis, vaccinations against *S. pneumoniae* and influenza should be considered in these patients. Smoking cessation should be emphasized as a matter of routine. Patients with advanced bronchiectasis with evidence of exercise and/or nocturnal desaturation should be considered for oxygen supplementation to delay the onset of pulmonary hypertension and cor pulmonale and improve exercise tolerance. Pulmonary rehabilitation and inspiratory muscle training may be considered, as these modalities have been documented to improve exercise tolerance.[60]

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PART 5

Interstitial and Inflammatory Lung Diseases

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CHAPTER 54

Interstitial Lung Disease: A Clinical Overview and General Approach

Danielle Antin-Ozerkis

INTRODUCTION

Commonly, interstitial lung disease (ILD) presents with dyspnea on exertion, diffuse bilateral infiltrates on chest imaging, and restriction with diffusion impairment on physiologic testing. When tissue is obtained, the lung parenchyma may contain any combination of abnormalities, including inflammation, fibrosis, and granulomas. While many forms of ILD are extremely rare, there are some, such as idiopathic pulmonary fibrosis (IPF) and sarcoidosis that are seen commonly in general pulmonary practice. Masqueraders of ILD such as infection, pulmonary edema, and malignancy will be encountered in the assessment of an abnormal chest radiograph, and distinguishing these from true ILD is crucial.

ILD refers to a heterogeneous collection of more than one hundred distinct lung disorders that tend to be grouped together because they share clinical, radiographic, and pathologic features. These disorders are sometimes called diffuse parenchymal lung disease (DPLD) to make the point that the interstitium is not the only compartment of the lung affected. Entities such as organizing pneumonia or pulmonary alveolar proteinosis may cause an alveolar filling process. Respiratory bronchiolitis and chronic hypersensitivity pneumonitis may center on the airway, involving this compartment as well. Occasionally, purely airway-centered diseases like bronchiolitis obliterans may be initially identified as an ILD because of overlapping radiographic findings. A structured approach is necessary since treatments may vary considerably depending on the diagnosis.

Diagnosis is based upon a comprehensive history, a careful physical examination, as well as review of laboratory data, physiologic studies, radiography, and in some cases, pathologic tissue obtained from lung biopsy. Multidisciplinary review is an important part of the process and can have a significant impact on diagnostic and management decisions. For each patient, decisions regarding diagnostic approach and therapy must be individualized based upon the patient's respiratory status, comorbid medical conditions, and personal approach to medical care.

DIAGNOSTIC APPROACH TO ILD

Several classification schemes for ILD have been proposed, which include histopathologic and clinical characteristics.[1] The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus panel classification system was published in 2001 and has recently been revised.[2] One approach is given in Figure 54-1.

It is often helpful in the case of any individual patient to incorporate a combination of historical, clinical, radiographic, and pathologic features. Distinguishing those patients who have a known cause for their ILD (e.g., connective tissue disease, occupational or environmental exposure, or drug toxicity) from those who do not (e.g., IPF, sarcoidosis) is an important first step. Clinical features, such as acuity of onset, may help to classify disease as well. For example, the subacute time course of a patient with organizing pneumonia will be quite different than the insidious onset of dyspnea in IPF. The radiographic pattern of IPF will be characterized by bibasilar traction bronchiectasis and honeycombing, while sarcoidosis may demonstrate upper lobe-predominant nodular opacities with retraction and volume loss. Histopathologic characterization may range from acute inflammation to granulomatous involvement, or fixed fibrosis and collagen deposition.

It is important to note that the names used to describe the clinical entities themselves must be distinguished from the radiographic and

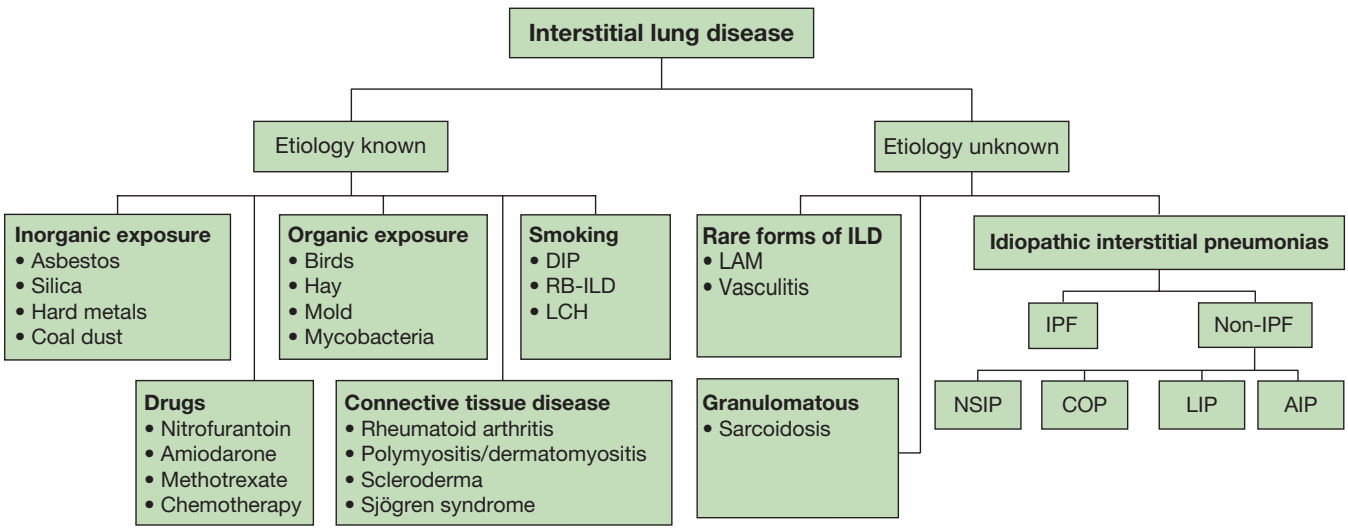

Figure 54-1 An overview of ILD classification. DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis interstitial lung disease; LCH, Langerhans cell histiocytosis; LAM, lymphangioleiomyomatosis; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; COP, cryptogenic organizing pneumonia; LIP, lymphocytic interstitial pneumonia; AIP, acute interstitial pneumonia. *(Data from ATS/ERS classification, 2001.)*

TABLE 54-1 Time Course of Disease Onset

Acute
Cryptogenic organizing pneumonia
Acute eosinophilic pneumonia
Acute hypersensitivity pneumonitis
Diffuse alveolar hemorrhage
Acute interstitial pneumonia
Acute exacerbation of idiopathic pulmonary fibrosis or other ILDs
Subacute to Chronic
Connective tissue disease–associated ILD
Idiopathic pulmonary fibrosis
Sarcoidosis
Chronic hypersensitivity pneumonitis
Occupational lung disease
Nonspecific interstitial pneumonia
Desquamative interstitial pneumonitis
Respiratory bronchiolitis interstitial lung disease
Lymphocytic interstitial pneumonia
Chronic eosinophilic pneumonia

pathological terms used to describe the findings. For example, IPF is the clinical entity associated with a usual interstitial pneumonia (UIP) pattern on chest CT and on pathology. However, the finding of a UIP pattern alone does not ensure a diagnosis of IPF, as this may also be seen in other entities, such as the connective tissue diseases.

CLINICAL HISTORY

The typical presentation of ILD is nonspecific and may include vague pulmonary complaints, such as dyspnea on exertion or cough, and an abnormal radiograph. In some cases the time course of the disease may suggest certain forms of ILD (Table 54-1). The acute forms of ILD must be distinguished from respiratory infections and pulmonary edema due to congestive heart failure.

It is important to consider key features of the patient. For example, the differential diagnosis for dyspnea and diffuse infiltrates on chest radiograph will vary markedly between immunocompetent patients and those who have undergone organ or bone marrow transplantation, are neutropenic from recent chemotherapy, or who have advanced HIV disease. In the immunocompetent host, it is often after a lack of response to antibiotics or diuretics that ILD is suspected. Other clinical features may affect the presentation as well. In elderly or disabled patients, musculoskeletal issues may limit mobility and dyspnea may be a late symptom. In a patient with other cardiopulmonary disease, relatively minor ILD may cause an earlier onset of disabling dyspnea and the discovery of ILD for this reason. It is helpful to attempt an objective quantification of the degree of dyspnea, such as the distance the patient walks before becoming breathless or the number of steps climbed before a rest must be taken.

Often a persistent cough after a respiratory infection leads to the initial chest radiograph. While other respiratory symptoms are less common, they may help focus the differential diagnosis. For example, a history of wheezing may suggest an airway-centered process such as hypersensitivity pneumonitis, eosinophilic pneumonia, or sarcoidosis.[3] Substernal chest pain is commonly described by patients with sarcoidosis.[4] Pleuritic chest pain may herald serositis in a patient with connective tissue disease, or pneumothorax in cystic lung diseases such as lymphangioleiomyomatosis (LAM) and Langerhans cell histiocytosis (LCH).[5–7] Hemoptysis may suggest diffuse alveolar hemorrhage, though it is not present in most cases.[8]

SYSTEMIC SYMPTOMS

Connective tissue disease is a frequent cause of ILD, and patients may come with a pre-existing diagnosis. However, most will not and it is incumbent on the physician to search carefully for suggestions of underlying autoimmune disease, as the pulmonologist may be the first to make such a diagnosis, prompted by the onset of ILD. In some cases, nonspecific systemic symptoms such as night sweats, fever, fatigue, or weight loss suggest an underlying inflammatory condition. In others, one can arrive at a specific diagnosis by merely performing a thorough review of systems. For example, careful questioning regarding dermatologic symptoms may lead to the discovery of dermatomyositis as demonstrated by a heliotrope rash, Gottron's papules, or "mechanic's hands," all of which may be relatively specific features that do not bother the patient. Patients with underlying systemic sclerosis (scleroderma) may give a history of skin tightness and thickening, telangiectasias, Raynaud's phenomenon, or digital pitting. Papular eruptions, lupus pernio, and erythema nodosum may be seen in sarcoidosis.[9] Patients with systemic lupus erythematosus (SLE) may describe malar rash, photosensitivity skin reaction, or hair loss.

Gastrointestinal symptoms may be indicative of underlying esophageal motility problems related to connective tissue disease such as systemic sclerosis and polymyositis, or may be the root cause of the ILD itself. In particular, symptoms suggestive of acid reflux (chest burning or pressure, cough after meals, regurgitation of food) should be sought. Chronic, intermittent aspiration can lead to progressive fibrotic lung disease from recurrent lung injury. Patient descriptions of coughing or choking while eating or noting food "going down the wrong pipe" are suggestive of frank aspiration and could lead to a discovery of progressive neuromuscular diseases such as amyotrophic lateral sclerosis (ALS), cerebrovascular accidents, or other causes of oropharyngeal and laryngeal dysfunction.[10] Other gastrointestinal complaints, such as bloating and diarrhea, may suggest inflammatory bowel disease or bacterial overgrowth due to bowel dysmotility in systemic sclerosis.

Musculoskeletal complaints can be helpful in identifying underlying connective tissue disease as well. In particular, arthralgias, morning stiffness, joint swelling and erythema, and deformities may be evidence of an underlying inflammatory disorder such as rheumatoid arthritis, Sjögren syndrome, or mixed connective tissue disorder. Swollen fingers ("sausage digits") may be observed in systemic sclerosis and polymyositis. Raynaud's phenomenon manifests as either blue/purple discoloration or whiteness of the digits (fingers or toes) in the cold. In some cases this may be quite profound and can even be associated with digital ulcerations and, rarely, digital gangrene. This finding is most suggestive of underlying scleroderma, mixed connective tissue disease, SLE, and antisynthetase syndrome.[11]

Ophthalmologic symptoms may direct the clinician toward particular clinical entities. Inquiries regarding dry eyes or the use of eye drops may uncover sicca syndrome, as seen in Sjögren syndrome and overlap connective tissue diseases. Patients with a history of uveitis may have underlying SLE or sarcoidosis. Neurologic symptoms may suggest vasculitis or sarcoidosis.

A detailed review of systems may uncover sequelae of longstanding ILD. Increasing edema, syncopal events, or exertional chest discomfort may indicate severe pulmonary hypertension and *cor pulmonale* in the patient with advanced fibrotic lung disease and hypoxemia. Alternatively, in a patient with systemic sclerosis, these findings might indicate a second primary problem such as pulmonary arterial hypertension. The presence of palpitations or syncope in a patient with sarcoidosis can lead to a diagnosis of cardiac sarcoidosis.

The review of systems will sometimes also lead to a related secondary diagnosis. For example, more typical causes of exertional chest discomfort, such as cardiac ischemia, may be truly present and may be exacerbated by exertional desaturation. This is particularly important to remember, as patients with underlying immune-related diseases appear to be at increased risk for coronary artery disease.[12]

In addition, pleuritic chest pain, leg swelling, and increasing dyspnea should prompt consideration of acute pulmonary embolism, as patients with ILD are at increased risk for this complication.[13,14]

PAST MEDICAL HISTORY

As mentioned, a prior diagnosis of connective tissue disease (systemic sclerosis, rheumatoid arthritis, SLE) is extremely pertinent for patients with ILD. In the case of HIV disease, specific forms of lung disease such as lymphocytic interstitial pneumonia (LIP) are more commonly observed. A prior history of acute or chronic kidney disease might suggest underlying vasculitis, pulmonary–renal syndromes, or connective tissue disease. A history of liver disease could suggest sarcoidosis, primary biliary cirrhosis, or underlying genetic abnormalities resulting in short telomere length.[15–17] A history of facial nerve paralysis (Bell's palsy) might represent unrecognized sarcoidosis.[18]

OCCUPATIONAL HISTORY

The occupational history should be thorough, including a review of all jobs held in the past. In particular, attention should be paid to any occupation in which a history of exposure to organic or inorganic products was present (Table 54-2). Specific inquiries may be made regarding a history of construction work, including demolition, plumbing, and electrical work. The patient should be questioned about employment in factories and manufacturing plants, the electronics industry, metal working, stone cutting, and mining. The clinician should specifically inquire about exposure to asbestos, silica, hard metals, and beryllium, as workers often know when these have been present in their work environment.[19,20] Inquiries may additionally be made regarding the jobs held by the household contacts of patients. For example, spouses may have been subjected to significant levels of dust inhalation via clothing worn by the worker.[21] In cases where a relevant exposure has occurred, details should be obtained regarding the worker's specific duties, the typical proximity to the exposure of interest and any use of respiratory protection. In some cases, related respiratory illnesses in coworkers can raise suspicion. There may be a long latency period between the exposure and the onset of symptoms and radiographic changes, so the occupational history must explore jobs held many years in the past. A history of farm work or other agricultural employment should raise suspicion for an environmental cause of ILD. Exposure to moldy hay, bird feathers and droppings, and a variety of organic products can lead to chronic hypersensitivity pneumonitis.

TABLE 54-2 Occupational Interstitial Lung Disease

Occupation	Type of ILD	Exposure
Electrician Plumber Pipe fitter Construction worker Ship builder Insulation installer	Asbestosis	Asbestos
Stone cutter Miner Sand blaster	Silicosis	Crystalline silica dust
Metal grinder	Giant cell interstitial pneumonia Hard metal lung disease	Hard metals Cobalt Tungsten carbide
Metal worker Factory workers Nuclear weapons Aircrafts Electronics Ceramics Golf clubs Bicycle frames	Berylliosis	Beryllium
Coal worker	Coal worker's pneumoconiosis	Coal dust
Paint sprayer Plastic worker	Chemical worker's lung	Isocyanates
Bird breeder	Bird breeder's lung	Bird droppings Bird feathers
Farm worker Haying Mushroom compost	Farmer's lung Mushroom worker's lung	Thermophilic bacteria
Office worker	Humidifier lung Ventilation pneumonitis	Fungi/Molds
Lifeguard	"Hot tub" hypersensitivity pneumonitis	*Mycobacteria*

ENVIRONMENTAL HISTORY

Organic exposures are also frequently encountered in household and office settings. For example, humidification systems may be contaminated with mold.[22] Hot tubs and other aerosolized water sources have led to lung disease related to the growth of *Mycobacterium avium*.[23] The exposure history should include a thorough inquiry regarding the home heating and humidification system, a history of water damage, or visible evidence of significant mold growth on walls. An assessment of the timing of any water damage relative to the onset of the lung disease can be helpful. Domestic birds are a common source of feathers and dropping antigen. Bird owners often have multiple birds and have owned birds for many years. Frequently, these pets are considered to be cherished members of the family, residing in bedrooms and main living spaces. A history of hobbies and materials used should also be obtained.

Cigarette smoke is one of the most common environmental exposures and is strongly linked with several forms of ILD, including desquamative interstitial pneumonitis (DIP), respiratory bronchiolitis-ILD, and LCH. Cigarette smoking has been identified as a risk factor for IPF.

MEDICATION HISTORY

Numerous drugs have been implicated in the development of ILD, ranging from acute pneumonitis to chronic fibrotic lung disease (Table 54-3). The use of several commonly prescribed drugs should be sought. Nitrofurantoin, used for suppression of recurrent urinary tract infections, may lead to severe ILD.[24] Amiodarone, used for management of atrial and ventricular arrhythmias, is known to lead to lung toxicity.[25] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used and may lead to eosinophilic and other inflammatory lung disease.[26] While less frequently used in the general population, a history of recent chemotherapy should trigger suspicion for drug-related lung disease.[27] Similarly, a history of immunemodulating drug use, such as in the treatment of rheumatoid arthritis or Crohn's disease is suspicious.[24,25,28] So many drugs have been reported in association with ILD that it is recommended to review the patient's entire medication history thoroughly with this in mind. A helpful online source of information is: http://www.pneumotox.com. This independent resource is compiled and regularly updated by members of the University Hospital in Dijon, France, and the GEPPI (Groupe d'Etudes de la Pathologie Pulmonaire Iatrogène). It lists all reports of suspected drug-induced lung disease, categorizes the radiographic patterns observed, and gives an assessment of the quality of the compiled information.

TABLE 54-3 Drugs Implicated in Interstitial Lung Disease

Antibiotics	**Chemotherapeutic**
Nitrofurantoin	All-trans retinoic acid (ATRA)
Minocycline	Alpha-interferon
Cephalosporins	Antithymocyte globulin
Antiarrhythmic	Bleomycin
Amiodarone	Busulfan
Tocainide	Carmustine (BCNU)
Anti-inflammatory	Chlorambucil
Azathioprine	Colony-stimulating factors (GM-CSF)
Etanercept	Cyclophosphamide
Gold salts	Cytosine arabinoside
Infliximab	Docetaxel
Methotrexate	Geftinib
NSAIDs	Gemcitabine
Penicillamine	Interleukin-2
Sulfasalazine	Irinotecan
Neurologic/Psychiatric	Melphalan
Carbamazepine	Mitomycin C
Phenytoin	Paclitaxel
Drugs of Abuse	Procarbazine
Cocaine	Vinorelbine
Heroin	**Other**
Talc	Bacille Calmette-Guérin (BCG)
	Mineral oil
	Radiation

Source: Data from Camus. Drug-induced and iatrogenic infiltrative lung disease. Clinics in Chest Med. 2004;25:479–519.

FAMILY HISTORY

Most forms of ILD are not heritable, though several do have a genetic component. When heritable disease is suspected, it is important to consider both systemic disorders as well as those that primarily affect the lung. In particular, by considering a patient's concomitant medical history or the history of family members, specific diagnoses may be uncovered. Several inborn errors of metabolism (Gaucher disease and Niemann-Pick, for example) are inherited in an autosomal recessive fashion. Other rare diseases such as Hermansky–Pudlak syndrome, Burt–Hogg–Dubé syndrome, and neurofibromatosis type I are autosomal dominant disorders.[29] The cystic lung disease, LAM may be associated with mutations in the tuberous sclerosis complex (TSC) genes, in which systemic hamartomas are present, including a high incidence of renal angiomyolipomas.[29]

The telomere shortening syndromes that lead to dyskeratosis congenita may lead to a phenomenon known as genetic anticipation, in which telomere lengths are progressively shortened in subsequent generations. This leads to the earlier onset of more severe disease in each subsequent generation. In the case of IPF, mutations in the telomerase genes have been demonstrated among 8% to 15% of familial cases and among 1% to 3% of patients with sporadic disease.[17] Several other genes have been linked with the onset of IPF, including those involved in the regulation of surfactant protein C and MUC5B.[30,31] There may be familial predisposition to sarcoidosis, but inheritance is more complex, involving an interaction of genetic and environmental factors.[32]

PHYSICAL EXAMINATION

Most patients with pulmonary fibrosis have lung findings characterized by fine, inspiratory, basilar "Velcro" crackles and many will have digital clubbing. In contrast, patients with nonfibrotic lung disease may have clear lung fields on auscultation. The location of the abnormal breath sounds may be suggestive of the underlying diagnosis, such as the upper lobe findings in silicosis and sarcoidosis in contrast to the lower lobe abnormalities in IPF. Additional breath sounds such as wheezing and inspiratory squeaks can indicate airway disease, which may focus the examiner's differential diagnosis on airway-centered diseases such as bronchiolitis, sarcoidosis, and hypersensitivity pneumonitis. These additional sounds should not be present in a patient with IPF.

Other cardiopulmonary manifestations of disease should also be sought. Signs of pulmonary hypertension and right heart failure include an increased P2 component, a right ventricular heave, elevated jugular venous pressure, and lower extremity edema.

Dermatologic and musculoskeletal signs of connective tissue disease, including skin rashes, sclerodactyly, skin thickening, digital ulceration, "mechanic's hands," synovitis, joint deformities, Raynaud's phenomenon, and telangiectasias, may be extremely helpful in narrowing the differential diagnosis. Less common findings such as cutaneous neurofibromas or café-au-lait spots in neurofibromatosis, albinism in Hermansky–Pudlak syndrome, and facial angiofibromas, periungual fibromas, and Shagreen patch in TSC may all be key features only recognized through a careful and focused search.

CHEST IMAGING

Findings on chest radiography and high-resoluaion computed tomography are discussed below.

CHEST RADIOGRAPH

An abnormal chest radiograph is often the first indication of underlying ILD. The pattern and distribution of abnormalities often help in formulating a differential diagnosis (Table 54-4). For example, sarcoidosis, silicosis, and LCH are among the diseases with an upper lobe predominance, while IPF, connective tissue disease–associated ILD, and asbestosis are all lower lobe predominant. Peripheral alveolar opacities are typical findings in organizing pneumonia and chronic eosinophilic pneumonia. The chest radiograph is also helpful for assessing lung volumes. In particular, fibrotic lung disease such as IPF leads to small lung fields whereas lung volumes are maintained and may even demonstrate hyperinflation in diseases such as LAM and LCH. In many cases, the presence of lymphadenopathy, with hilar fullness observed on chest radiograph, is the feature that leads to an accurate diagnosis, such as in sarcoidosis.

HIGH-RESOLUTION CHEST COMPUTED TOMOGRAPHY

High-resolution computed tomography (HRCT) of the chest is significantly more sensitive than chest radiograph for abnormalities in ILD. Characteristic patterns observed on HRCT can be quite specific in some cases. For example, the characteristic radiographic features of IPF are collectively known as the "UIP pattern," since these features have been demonstrated to confidently predict the presence of pathologic UIP when surgical biopsy is obtained (Table 54-5).[33,34] This pattern consists of peripheral, subpleural, basilar-predominant reticular opacities in combination with basilar honeycombing and without features, such as ground-glass opacities, cysts or nodules, to suggest another form of ILD.[35] When these features are accurately recognized, patients can be spared a surgical biopsy for diagnosis (Fig. 54-2).

Several radiographic patterns have been identified that help to focus the differential diagnosis (Table 54-4). In particular, a peripheral reticular pattern, that is basilar predominant may be seen in IPF, NSIP, and connective tissue disease–associated ILD (Fig. 54-3). Nodular infiltrates may suggest sarcoidosis, hypersensitivity pneumonitis, and LCH, though the nature of the nodules

TABLE 54-4

Distribution of ILD	
Upper lung zone	**Lower lung zone**
Sarcoidosis	Usual interstitial pneumonia (UIP/IPF)
Silicosis	Nonspecific interstitial pneumonia (NSIP)
Coal worker's pneumoconiosis	Connective tissue disease–associated ILD
Hypersensitivity pneumonitis	Asbestosis
Langerhans cell histiocytosis	Desquamative interstitial pneumonia (DIP)
Berylliosis	
Chronic eosinophilic pneumonia	
Pattern of ILD	
Peripheral reticular	**Ground glass**
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	NSIP
Nonspecific interstitial pneumonia	Cryptogenic organizing pneumonia
	Eosinophilic pneumonia (chronic or acute)
	Pulmonary edema
Nodular	Infection (opportunistic or viral)
Sarcoidosis	Alveolar hemorrhage
Berylliosis	Hypersensitivity pneumonitis
Hypersensitivity pneumonitis	Desquamative interstitial pneumonia
Langerhans cell histiocytosis	Sarcoidosis
Silicosis	Pulmonary alveolar proteinosis
Metastatic disease	
Talcosis	**Cystic**
Granulomatous polyangiitis (formerly known as Wegener's granulomatosis)	Lymphangioleiomyomatosis
Respiratory bronchiolitis ILD	Langerhans cell histiocytosis
	Lymphocytic interstitial pneumonia
	Pneumocystis jiroveci pneumonia (PCP)

Source: Data from Diagnostic Thoracic Imaging, Miller W. McGraw Hill; 2006.

and their location may make one or another diagnosis more likely (Fig. 54-4). The finding of diffuse cystic abnormalities leads to a specific differential diagnosis, including LAM, LCH, and LIP. The term "ground glass" refers to areas of lung tissues with increased attenuation, but not enough to obscure or distort lung architecture, blood vessels, and lymphatics. Alveolar opacities are a related finding and reflect more dense attenuation of lung tissue, sometimes containing air bronchograms. Many forms of ILD are characterized by ground-glass and alveolar opacities. When observed in characteristic distributions, such as the peripheral, patchy alveolar opacities in cryptogenic organizing pneumonia (COP) and chronic eosinophilic pneumonia, they are quite suggestive of an underlying pathologic pattern (Fig. 54-5).[36] However, the radiographic appearance in such cases is nonspecific and other testing, including lung biopsy, may be required for diagnosis.

TABLE 54-5 Radiographic Characteristics of the UIP Pattern

"Definite UIP"
Peripheral, subpleural distribution
Basilar predominance
Reticular markings and traction bronchiectasis
Honeycombing
Absence of inconsistent features
Atypical for a "Definite UIP"
Upper or mid lung predominance
Peribronchovascular distribution
Ground-glass abnormality (out of proportion to reticulation)
Profuse micronodules
Multiple, bilateral, discrete cysts
Diffuse, bilateral, mosaic attenuation or air trapping
Consolidation

Source: Data from Schmidt. Respirology. 2009;14(7):934–939.

LABORATORY TESTING

Routine laboratory testing, while often normal, may lead to the diagnosis of a previously unrecognized systemic disease, or may be suggestive of the underlying lung disease. Its importance may also lie in the discovery of associated conditions, such as elevated liver enzymes or hypercalcemia in sarcoidosis, or renal insufficiency in pulmonary renal syndromes and other connective tissue disease with renal involvement. Other examples include the presence of peripheral eosinophilia in chronic eosinophilic pneumonia, Churg–Strauss syndrome, drug reaction, and other forms of vasculitis. Anemia may worsen symptoms of dyspnea in the setting of ILD and may reflect an underlying hemolytic condition, or chronic gastrointestinal blood loss in inflammatory bowel disease. In addition to eliciting causes for the ILD, recognition of underlying chronic organ dysfunction will also help determine the ability of the patient to tolerate treatment.

More advanced testing is often necessary, including serologic testing for underlying connective tissue disease (Table 54-6). Many of the tests listed here are employed by ILD centers in the evaluation of patients newly presenting with diffuse lung disease, though no clear standard exists. Importantly, ILD can be the sole manifestation or the presenting feature of a connective tissue disease, making a careful evaluation for previously unrecognized autoimmune disease essential.[37]

PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) are a mainstay in the pulmonologist's armamentarium in the evaluation and management of ILD. Importantly, they assist in assessing the severity of disease and help determine prognosis in many forms of disease.[38,39] They are a relatively noninvasive method to gauge disease progression and measure response to therapy.[40] The testing typically include spirometry, measurement of lung volumes, and diffusing capacity. Exercise testing, such as the 6-minute walk test, is particularly important for patients with ILD.

Typically, spirometry in most forms of ILD demonstrates a restrictive ventilatory defect due to decreased compliance and increased recoil of the lung parenchyma.[41] The presence of obstruction suggests either concomitant obstructive lung disease, often from prior smoking exposure, or the presence of an airway-centered lung ILD such as LCH, LAM, or sarcoidosis. Decreased static lung volumes confirm the presence of restriction. In the case of airway-centered

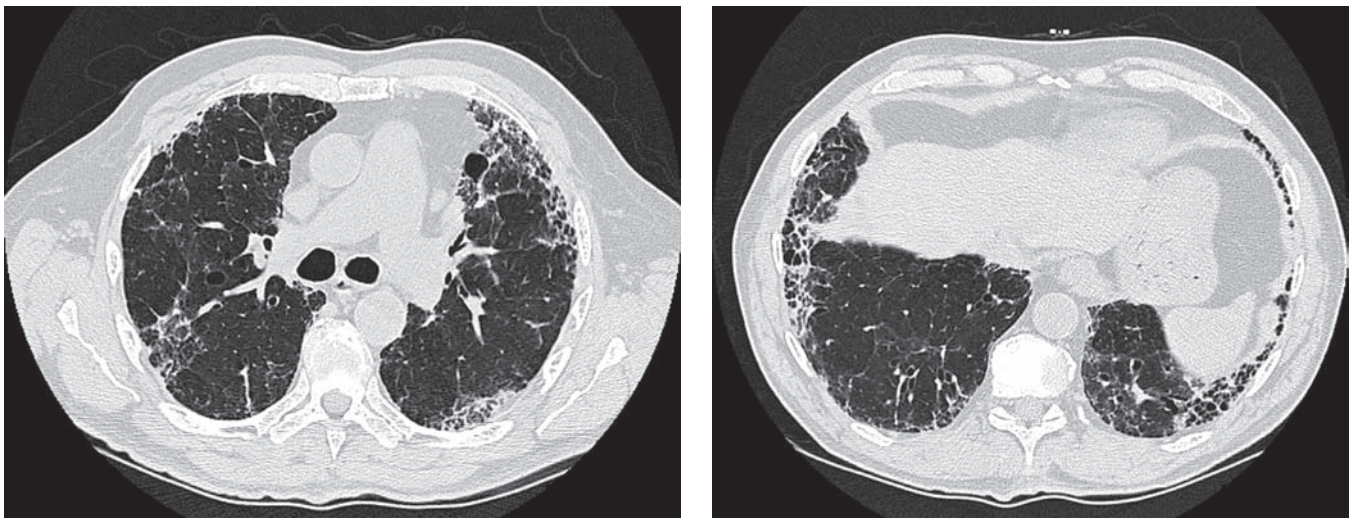

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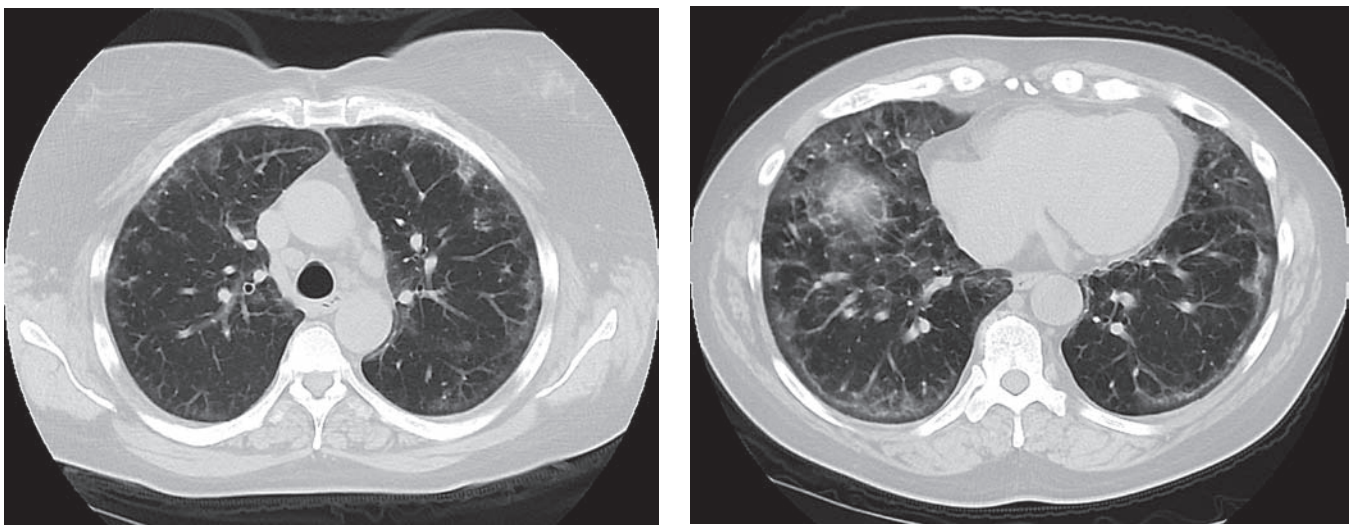
Figure 54-2 An 82-year-old man with progressive dyspnea and a usual interstitial pneumonia (UIP) radiographic pattern. High-resolution (1.25-mm thick sections) CT images at the level of the midthorax (**A**) and lower thorax (**B**) show peripheral reticular markings with architectural distortion and small subpleural cysts/honeycombing. Ground-glass opacities and other features atypical for IPF are absent. The patient had no exposures and no clinical evidence of connective tissue disease. The final diagnosis was idiopathic pulmonary fibrosis (IPF). No lung biopsy was performed, as a diagnosis was made based upon CT criteria alone.

diseases, the lung volume measurements may indicate unrecognized air trapping and hyperinflation.

Diffusion impairment, demonstrated by a decrement in the diffusing capacity (D_{LCO}), is frequently observed in ILD and is often the earliest physiologic abnormality.[42] The decreased D_{LCO} reflects the presence of either fibrotic tissue or inflammatory cells (or both) in the interstitium of the lung, leading to a defect at the level of the alveolar–capillary membrane. The diffusion impairment is typically lower than predicted by alveolar volume.[41] With activity, exertional desaturation is a frequent occurrence among patients with ILD, and which may predict prognosis in certain forms of ILD.[43–45] Formal 6-minute walk testing is quite useful, additionally offering an assessment of exercise capacity in terms of distance walked, heart rate response, and causes for exercise discontinuation (including leg discomfort or chest pain). However, if this is not available, measurement of pulse oximetry with ambulation in the hallway or with stair climbing can offer important information, including an understanding of reasons for the patient's dyspnea as well as a marker of disease severity.

BRONCHOSCOPY

Bronchoscopy is a generally well-tolerated procedure that can be quite useful in the diagnosis of DPLD. It allows inspection of the upper and lower airways, bronchoalveolar lavage (BAL), and the performance of transbronchial lung biopsy. All may be completed as an outpatient procedure, with relatively minimal sedation.



A B

Figure 54-3 A 55-year-old woman with progressive dyspnea on exertion. She had finger swelling and Raynaud phenomenon, with an antinuclear antibody titer of 1:2560 (nucleolar). Axial CT image through the midthorax (**A**) and lower thorax (**B**) show ground-glass opacities in a peripheral distribution, reticular markings, and mild architectural distortion. Subpleural sparing is evident. These findings are all compatible with a nonspecific interstitial pneumonia (NSIP) pattern. The final diagnosis was scleroderma lung disease.

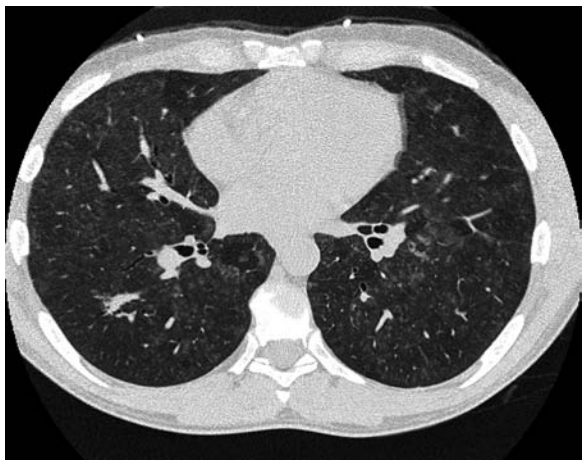


Figure 54-4 A 47-year-old man who enjoyed soaking in the hot tub after exercising at the gym developed dyspnea and hypoxemia. He improved clinically with removal from the presumed source of exposure. High-resolution CT images at the level of the midthorax demonstrate diffuse centrilobular ground-glass nodules as well as areas of lobular lucency, consistent with air trapping. These findings are consistent with subacute hypersensitivity pneumonitis.

BAL allows the sampling of the protein and cellular components of the lung fluid. Tests typically performed on this fluid include cell count and differential, cytology, and a variety of viral assays and microbiologic cultures, depending on the clinical scenario. In some cases, the BAL fluid appearance itself may be diagnostic, for example with the finding of progressively bloody lavage specimens in diffuse alveolar hemorrhage.[46] Similarly, the presence of milky white or tan BAL fluid–containing debris that settles out suggests pulmonary alveolar proteinosis. Periodic acid–Schiff (PAS) staining confirms the diagnosis.

Specific testing on BAL fluid, including cell count and differential, can be diagnostic in the correct clinical context. BAL eosinophilia (>25%) indicates an eosinophilic process, and in combination with the clinical scenario of acute respiratory failure with bilateral alveolar opacities on chest radiograph suggests acute eosinophilic pneumonia. Significant BAL lymphocytosis suggests the presence of a granulomatous ILD, suggestive of hypersensitivity pneumonitis, drug reaction, or cellular NSIP when greater than 50%.[46] A high ratio of CD4+/CD8+ T lymphocytes may be specific, not sensitive for sarcoidosis, though this is not considered a diagnostic test.[46,47] BAL neutrophilia has not been shown to be helpful in distinguishing among the idiopathic ILDs.[48] Notably, increasing patient age may shift the cellular composition of BAL fluid toward lymphocytes and neutrophils so results should be interpreted cautiously.[49]

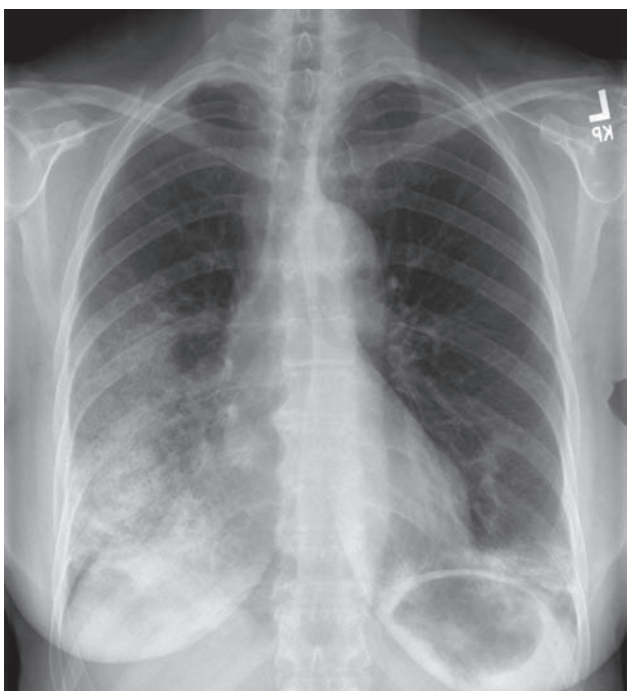
Specialty testing on BAL fluid may also be important to consider. BAL can accurately confirm a work exposure, for example a positive

TABLE 54-6

Serologic Testing in ILD

Test	Disease
ANA	Scleroderma, SLE, MCTD
SSA	Sjögren syndrome, Polymyositis
SSB	Sjögren syndrome
CK Aldolase Jo-1 Myositis-associated antibodies	Polymyositis, dermatomyositis
Jo-1 Myositis-associated antibodies	Antisynthetase syndrome
Scl-70 Anticentromere antibody	Scleroderma
RF CCP	Rheumatoid arthritis
RNP Antihistone antibody	Mixed connective tissue disease
p-ANCA, c-ANCA	ANCA-associated vasculitis

ANA, antinuclear antibody; CK, creatine kinase; ESR, erythrocyte sedimentation rate; SSA, anti-Ro antibody; SSB, anti-La antibody; RF, rheumatoid actor; CCP, cyclic citrullinated peptide; RNP, ribonucleoprotein; CRP, C-reactive protein; ANCA, antineutrophil cytoplasmic antibody.



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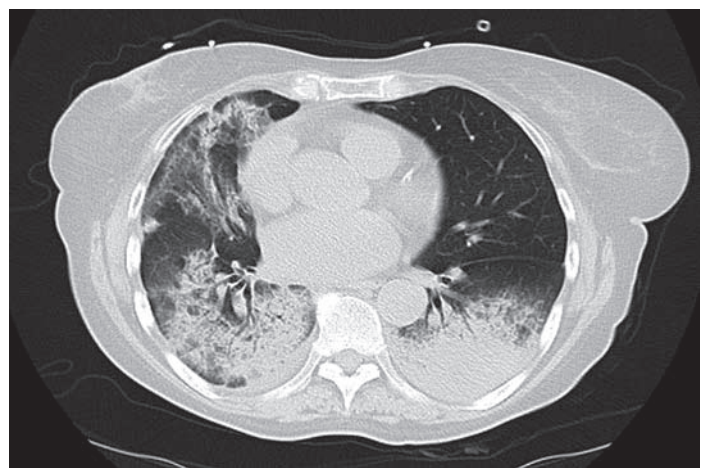

B

Figure 54-5 A 58-year-old woman with organizing pneumonia (OP) secondary to radiation for breast cancer. Frontal chest radiograph (**A**) demonstrates ground-glass and alveolar opacities. High-resolution CT images at the level of the midthorax (**B**) demonstrate both ground-glass opacities and areas of consolidation. She had complete response to corticosteroid therapy.

lymphocyte proliferation assay in chronic beryllium disease or the presence of asbestos bodies in asbestosis.[50] The demonstration of CD1a positive cells on flow cytometry may lead to a diagnosis of LCH, and clonal cell populations may be demonstrated in the BAL fluid of patients with pulmonary lymphoid malignancies.[46,51] Much research has focused on identifying molecular and cellular profiles to predict prognosis and response to therapy, however BAL is not widely used for this purpose outside the research setting.[52]

One of the major reasons to obtain BAL fluid in the diagnosis and treatment of ILD is to rule out infection, either as a primary cause of the diffuse lung disease, or as a secondary complication of immunosuppressive therapy. In the immunocompromised host, BAL fluid is highly sensitive for the diagnosis of bacterial, viral, fungal, and mycobacterial diseases.[53] Specialized staining may identify *Pneumocystis jiroveci* infection, endemic fungi, and mycobacterial disease. Immunofluorescent antibody and polymerase chain reaction (PCR) assays are now commonly utilized, and significantly increase yield.[46,54,55]

Transbronchial biopsy is safe, with risk for pneumothorax of approximately 1% and significant bleeding less than 2%.[56,57] Biopsy forceps are introduced via the flexible bronchoscope and tissue samples are obtained with fluoroscopic guidance. Multiple passes are made, with yield improving when more than four specimens are obtained.[58] Despite the relatively small size of these specimens as compared with surgical lung biopsy, diagnostic information in certain forms of ILD are particularly amenable to diagnosis by bronchoscopy, especially granulomatous diseases such as sarcoidosis, hypersensitivity pneumonitis, and drug toxicity.[59]

SURGICAL LUNG BIOPSY

Despite a high yield in certain forms of lung disease, the utility of transbronchial biopsy for most of the idiopathic interstitial pneumonias (such as IPF, NSIP, and LIP) is low and surgical biopsy is often required for accurate diagnosis.[60] The usual technique is video-assisted thoracoscopic surgery (VATS) that has a low morbidity and mortality in selected populations.[61] VATS biopsy should be performed by surgeons familiar with the techniques needed for ILD diagnosis. Wedge biopsies are taken from three separate lobes, and include areas of normal appearing lung; when only the most affected areas are sampled, specimens demonstrate end-stage honeycomb lung and the procedure may be nondiagnostic. Risks of VATS include prolonged air leak, bleeding, infection, and incisional site pain.[62] Generally, the length of hospital stay after a VATS procedure is 2 to 3 days, though a few centers perform VATS biopsy as an outpatient procedure in selected patients.[63] For most patients, there is no significant loss of lung function; however, cases of acute exacerbation of IPF following biopsy have been reported.[62,64] Patients must be able to tolerate general anesthesia with single lung ventilation.[62] Risk factors for complications and mortality include advanced respiratory failure as indicated by high P_{CO_2} and/or severe hypoxemia, significant pulmonary hypertension, problems with clotting, and immunosuppression.[65,66] Patients older than 65 years of age have morbidity and mortality rates no different than younger patients, though those over 75 may have higher rates of air leak.[67,68] Preoperative cardiac evaluation should be considered since many patients undergoing biopsy for ILD are older, or have a significant smoking history.[69]

A comprehensive approach including the clinical history, laboratory testing, and radiographic appearance can help assess if pathologic information is needed for accurate diagnosis. If a specific cause for the ILD can be identified, such as underlying connective tissue disease or a temporally correlated drug or environmental exposure, pathologic tissue may not change management and may not be worth the operative risk. When no etiology of the lung disease can be found, the radiographic appearance is crucial to help determine if surgical biopsy is needed. The most important question to be answered with biopsy is whether the patient has IPF or some other form of idiopathic interstitial pneumonia.[70] Specific features on HRCT are highly predictive of the histopathologic finding of UIP, the histologic correlate of IPF (Table 54-5).[33,34] An assessment of the HRCT as "definite UIP" by an experienced observer can spare some patients a surgical biopsy in the correct clinical setting.[35] When most features are present, but honeycombing is not, the pattern is called "possible UIP" and it is this group in which surgical biopsy is the most helpful. The differential diagnosis in these cases includes NSIP, UIP, and chronic hypersensitivity pneumonitis and radiographic appearance alone cannot be used to make an accurate diagnosis.[71,72] Each case should be assessed individually before a decision to pursue biopsy is made. In some, it may not be necessary and in others, though potentially helpful, the risk of the procedure outweighs the benefit of the information gained.

PATHOLOGY AND MULTIDISCIPLINARY REVIEW

Several major pathologic patterns are described in the idiopathic interstitial pneumonias, including granulomatous ILD, UIP, NSIP, and organizing pneumonia. However, these same patterns may be observed in patients with systemic diseases and other causes for ILD and therefore the pathology must be interpreted within the context of the clinical scenario and radiographic studies. It has been demonstrated that the final diagnosis will often change after a group discussion involving clinicians, radiologists, and pathologists.[73] The diagnosis also frequently differs between academic and community-based physicians, with academic physicians being less likely to arrive at a diagnosis of IPF.[74]

The UIP pattern is the histologic correlate of IPF and has specific features, including a heterogeneous appearance in which areas of fibrosis and honeycombing are interspersed with areas of normal lung. The changes are most pronounced in the periphery of the lung and should not predominantly involve the airways. Fibroblastic foci should be present and atypical features should be absent. The most recent guidelines offer categories in which the pathologist may interpret the pattern as "UIP," "Probable UIP," "Possible UIP," "Unclassifiable fibrosis," and "Not UIP."[75] These, in combination with the HRCT and clinical features, will lead to a definite, probable, possible IPF diagnosis, or one of "Not IPF." However, the clinical context must always be considered as a UIP pattern is not completely specific for IPF. For example, a patient with a history of bird exposure, whose HRCT demonstrates upper lobe predominance with lobular areas of air trapping, may have UIP on biopsy, but the final diagnosis will be chronic hypersensitivity pneumonitis. A patient with morning stiffness, deforming arthritis, positive serology for anti-CCP antibodies and UIP will be given a diagnosis of rheumatoid arthritis–associated ILD.

Granulomatous histology may be observed in idiopathic disease such as sarcoidosis, but may be present in many other forms of ILD, including drug toxicity and hypersensitivity pneumonitis. In addition to ILD, the possibility of diffuse infections, including mycobacterial disease, must always be kept in mind. The morphology and location of the granulomas, as well as the appearance of the surrounding tissue, must be considered in combination with the clinical features.[76] For example, a history of beryllium exposure in combination with sarcoidal granulomas on pathology will change the diagnosis to chronic beryllium disease. A patient with diffuse centrilobular ground-glass nodules, a history of humidifier use, and loosely formed granulomas on histology most likely carries a diagnosis of subacute hypersensitivity pneumonitis.

Nonspecific interstitial pneumonia is characterized by interstitial inflammation and fibrosis in a homogeneous pattern, as opposed to the heterogeneity of UIP. It may range from predominantly cellular to fibrotic in nature, with interstitial thickening but without significant honeycomb change (Fig. 54-6).[77] While this pattern may be idiopathic, it is much more commonly associated with connective

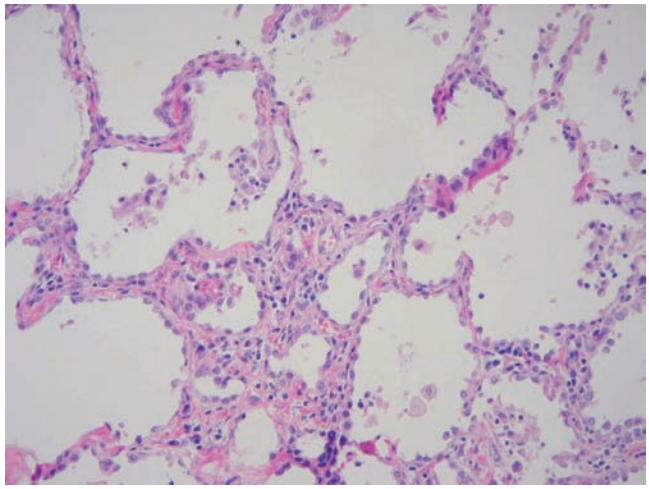

Figure 54-6 Nonspecific interstitial pneumonia (NSIP). There is diffuse, homogeneous septal fibrosis with a mild mononuclear infiltrate, as well as mild diffuse type II cell hypertrophy. No organizing pneumonitis, fibroblast foci, granulomas, or eosinophilic infiltrate are seen. Honeycombing is absent. There is a very mild accumulation of alveolar macrophages in the alveoli. 20× objective. *(Used with permission of Robert Homer, MD, PhD, Yale School of Medicine.)*

tissue disease. For example, a patient with a history of Raynaud's syndrome, skin thickening, diffuse ground-glass opacities on HRCT, and pathologic NSIP is likely to have underlying systemic sclerosis.

Organizing pneumonia is characterized histopathologically by intra-alveolar granulation tissue containing myofibroblasts and connective tissue (Fig. 54-7). The finding of organizing pneumonia on histopathology should prompt an exhaustive search for a cause before being called COP, which is idiopathic. For example, a patient with peripheral alveolar opacities on chest imaging and features of OP on biopsy who is found to have taken chronic nitrofurantoin as suppressive therapy for urinary infections may be suffering from drug toxicity. Likewise, a patient with OP who has muscle weakness, papular lesions on the hands, and heliotrope rash likely carries a diagnosis of dermatomyositis.

TREATMENT

Approach to treatment includes general and specific measures, as discussed below.

■ REMOVAL FROM EXPOSURES

The treatment of ILD varies with the specific diagnosis. Importantly, if any causative exposure can be identified, this should be eliminated. For example, if a drug reaction is suspected, that drug should be discontinued. For environmental exposures, the situation may require more extensive remediation. For example, in addition to removal of birds from the home, extensive cleaning of upholstery, window coverings, and ventilation systems may be required. The cleaning should not be performed by the patient. Even these measures may not remove all residual antigen, and removal of the patient from the location may be necessary.[78] In the case of extensive water damage and mold growth, significant demolition and reconstruction may be necessary. In the case of occupational exposures, some situations may be addressed by altering the particular job being done by the patient, changing the substances used, or using protective respiratory equipment, but others may require complete removal from the suspected exposure.[79] In many cases, patients' livelihoods may be at stake, involving severe financial consequences, disability, and workers' compensation. Identification of a workplace hazard for a patient may lead to the discovery of a public health issue or one that affects the health of coworkers.[80] Referral to and coordination with an Occupational Medicine specialist may be necessary to appropriately assess and remediate home and workplace exposures.

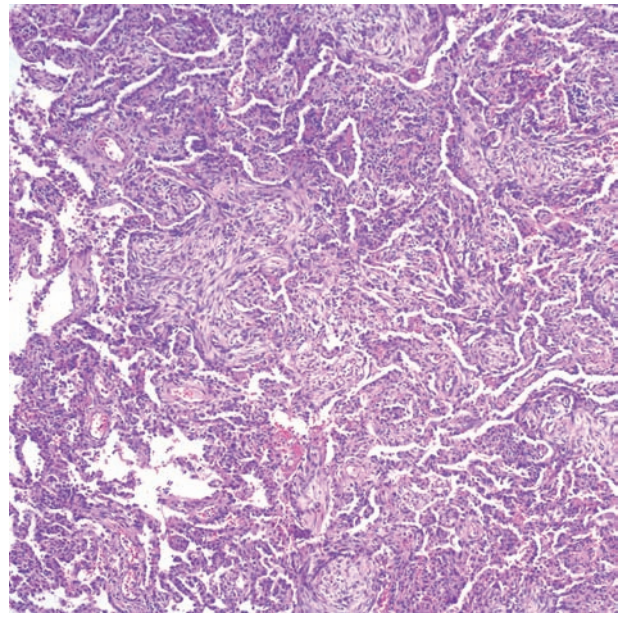

Figure 54-7 Organizing pneumonia (OP). There is fibromyxoid granulation tissue within alveolar ducts accompanied by a lymphoplasmacytic infiltrate. Notable is the absence of hyaline membranes, necrosis, neutrophilic or eosinophilic infiltrate, granulomas, and established fibrosis. 10× objective. *(Used with permission of Robert Homer, MD, PhD, Yale School of Medicine.)*

■ IMMUNOSUPPRESSIVE THERAPY

Some forms of ILD, including COP, connective tissue disease–associated ILD, and sarcoidosis, may demonstrate a favorable response to corticosteroids and other immunosuppressive agents.[81] However, in diseases such as IPF, what was once thought to be standard of care (prednisone plus azathioprine) has been demonstrated to carry harm without potential for benefit.[82] When considering the use of these drugs, an assessment should be made regarding the likelihood of response as well as the relative risks and benefits of the therapy.

The many side effects of corticosteroids include glucose intolerance, bone loss, cataract development, and mood instability.[83] Increased risk for infection may be substantial.[84] Some inflammatory diseases such as COP, CEP, and sarcoidosis can be quite sensitive to corticosteroids and relatively quick weaning to low dosages may be feasible and effective. In disorders such as connective tissue disease–associated ILD, when a more prolonged course of therapy is anticipated, the early addition of steroid sparing medications, such as azathioprine or mycophenolate mofetil, can permit lower doses of corticosteroids to be used. Certain forms of ILD, including scleroderma lung disease, vasculitis with alveolar hemorrhage, and severe cases of connective tissue disease–associated ILD may require drugs such as cyclophosphamide, which carry increased risk for severe side effects. Such medications should only be prescribed by practitioners familiar with the use and toxicities of these agents.

When actively treating ILD, objective measures of improvement, including PFTs, exercise oximetry, and chest radiography should be employed to avoid the unnecessary continuation of therapy. In particular, when corticosteroids are used, there is often an initial boost in mood and energy level that may not correspond to actual improvements in lung function. If no clinical improvement is seen after 3 to 6 months of therapy, discontinuation of immunosuppressive therapy should be strongly considered.

ANTIFIBROTIC DRUGS

For progressive fibrotic lung diseases, particularly IPF, the lack of adequate treatment options has led to a search for new therapies. In particular, pirfenidone, a small-molecule drug which appears to have antifibrotic properties, may stabilize lung function and is approved for use in Japan, Europe, and Canada and is currently being evaluated for approval in the United States. Multiple phase II and III studies of novel agents for IPF and for scleroderma-ILD are ongoing.

SUPPORTIVE THERAPY

Supportive therapy directed at improving quality of life and decreasing respiratory symptoms should be a part of the approach to care of all patients with ILD. Formal exercise testing in the PFT laboratory offers a standardized approach to the assessment of oxygen needs. However, a check of oximetry with simple ambulation in the hallway or with stair climbing can uncover the need for oxygen supplementation. The use of oxygen for patients with ILD is encouraged to maintain saturations >90% both at rest and with exercise.[85] No data exist regarding the impact of nocturnal oxygen use on mortality in ILD, but this is often utilized based upon data suggesting that nocturnal hypoxemia has a significant negative impact on quality of life.[86] Home and portable systems should be used to encourage ease of use and mobility. Collaboration among physicians, patients, and oxygen providers can help identify the ideal system for each patient.

The role of pulmonary rehabilitation has been studied in chronic obstructive lung disease and leads to increased muscle strength and improved endurance.[87] Similar improvements may be evident in the fibrotic lung diseases.[88,89] In addition to the potential benefits of improved muscle strength and stamina, patients with ILD may also benefit from the ongoing education regarding oxygen use, breathing and pacing techniques, and social support.[90] As patients with chronic lung disease frequently suffer from anxiety and depression, pulmonary rehabilitation may benefit patients by identifying these issues, leading to appropriate specialist referrals.[91]

TREATMENT OF COMORBIDITIES

Several common comorbidities should be sought among patients with ILD. In particular, an assessment for underlying coronary artery disease should be undertaken when dyspnea on exertion is present, as the risk for ischemic heart disease is increased among patients with IPF.[92,93] Due in part to prior tobacco exposure, patients with IPF have an increased risk of developing lung cancer.[85] Nodules should be individually assessed based on size, appearance, and growth. No specific screening recommendations for this patient population exist. The prevalence of obstructive sleep apnea appears to be quite high among patients with ILD, even in the absence of excessive sleepiness or large body habitus, although these features are important to assess.[94–96] There is a high prevalence of gastroesophageal reflux (GERD) among patients with IPF, though only a minority have symptoms.[97,98] Studies have suggested that GERD may be intimately involved in the pathogenesis of IPF and be linked with progression of disease.[99] The evaluation and treatment of GERD in patients with ILD is an evolving field. Based on existing data, it is not clear how aggressive therapy should be. If symptoms exist, therapy is typically utilized. However, whether to seek evidence of asymptomatic GERD through more invasive testing and whether to treat such patients is not clear.[85]

In addition to native comorbidities, side effects from therapy should be assessed. In particular, the use of corticosteroids can lead to weight gain, fluid retention, diabetes, and osteoporosis. Glucocorticoid-induced osteoporosis may be prevented by the use of calcium and vitamin D supplementation early in the course of steroid use.[100] Fracture risk assessment can identify patients in whom bisphosphonate therapy is indicated.[100]

Pulmonary hypertension develops in a significant number of patients with ILD and may be due to the effects of chronic hypoxia and the focal destruction of capillaries in fibrotic lung tissue.[101] Pulmonary hypertension contributes to progressive diffusion impairment and may contribute to progressive respiratory failure. It is important to ensure that no other cause for the pulmonary hypertension can be identified. For example, a concomitant pulmonary arterial vasculopathy, such as seen in scleroderma or MCTD should be sought, as specific therapy for the pulmonary arterial hypertension may be indicated in those circumstances.[102] In addition, common causes of pulmonary hypertension, such as left-sided systolic or diastolic cardiac dysfunction may be present.[103] Right heart catheterization can distinguish between the various etiologies of pulmonary hypertension and is often required, as echocardiogram has limited sensitivity and specificity in this population.[101] Whether to utilize pulmonary vasodilator therapy in patients with PH secondary to ILD is uncertain at this time. There is concern that use of these medications may worsen ventilation–perfusion matching, however some patients may have symptomatic and functional improvement.[104]

PALLIATIVE CARE

Symptom control is particularly important for patients with all stages of ILD. Pulmonary rehabilitation is encouraged to improve dyspnea in all symptomatic patients. The breathlessness due to advanced ILD may be treated with oxygen supplementation, low-dose opiates and anxiolytics.[105] Cough can be quite problematic and difficult to control; low-dose opiates may be of some benefit and low dose corticosteroids are occasionally used, understanding their long-term risk.[85] Evaluation for acid and nonacid reflux should be considered whenever intractable cough persists.

Palliative care services and hospice referral are appropriate for advanced ILD to maintain a focus on the physical, psychological and spiritual needs of patients and their families.[106] Prognosis in ILD may be uncertain, depending upon the specific diagnosis, the severity of disease, and progressiveness already demonstrated.[107] Particularly in IPF, the likelihood of either progressive respiratory failure or acute decline due to exacerbation should be discussed. End-of-life discussions and advanced directives regarding mechanical ventilation should be broached.[106]

LUNG TRANSPLANTATION

Although lung transplantation has significant associated morbidity and mortality, it is an important and potentially life-extending alternative for patients with progressive fibrotic lung disease. Most patients with ILD referred for lung transplantation have IPF, and for those with advanced disease, survival after lung transplantation is superior to the natural history of their disease.[108] Patients must have a strong social support system as well as the emotional and physical ability to tolerate a complex medical regimen of immunosuppressive therapy.[109]

The timing of listing is complicated in ILD, since the rate of progression is difficult to predict, and abrupt exacerbation of disease may occur.[110] Historically, patients with IPF had high mortality while on lung transplant waiting lists. With newer systems of prioritization, patients with severe IPF are often transplanted quickly, making the correct timing of listing important.[111] In general, a severely impaired D_{LCO} (<39%) as well as advanced fibrosis on HRCT predict poor survival and are considered to be triggers for active listing.[112] Regardless of ILD diagnosis, severe and progressive impairments in pulmonary function predict earlier mortality.[113] Early referral to a lung transplant center is useful as it allows full evaluation and education earlier in the disease course.

CONCLUSION

The approach to ILD includes a careful history and physical examination, with a focus on identifying an etiology for the ILD. Important considerations include a complete investigation of environmental, occupational, and drug exposures as well as a thorough search for underlying connective tissue disease. Laboratory tests, pulmonary physiologic studies, radiography, and biopsy of lung tissue may be necessary. Multidisciplinary review is an essential part of the diagnostic evaluation. Decisions regarding diagnostic and therapeutic approach must be individualized.

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CHAPTER 55

Systemic Sarcoidosis

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Sarcoidosis is a multisystem disorder characterized by noncaseating granulomatous inflammation at sites of disease.[1] Although any organ can be involved, the disease most commonly affects the lungs and intrathoracic lymph nodes. A diagnosis of sarcoidosis is most securely established from compatible clinical and radiologic findings, confirmed by a biopsy showing noncaseating epithelioid granulomas in more than one organ and the exclusion of granulomatous disorders of known cause. Clinical, epidemiologic, and family studies support the hypothesis that sarcoidosis is triggered by exposure to microbial agents in individuals with a genetic susceptibility to the disease. The clinical course is highly variable, with a mortality rate of <1% to 5%. Corticosteroids remain the mainstay of treatment for patients with threatened organ failure or progressive disease.

HISTORICAL PERSPECTIVE

Jonathan Hutchinson was the first to describe a case of sarcoidosis in 1887; he called it Mortimer's malady, after one of his patients who presented with face and limb skin lesions. In 1889, Besnier of Paris described a 34-year-old man with violaceous skin lesions of the nose, ear lobules, and central face; he proposed that the lesions were a variant of lupus erythematosus leading to its designation as "lupus pernio." In 1899, Caesar Boeck first described the characteristic noncaseating granulomas in a patient with peripheral lymphadenopathy and skin nodules. He proposed the term *multiple benign sarcoids of the skin* because he thought the granulomatous changes resembled sarcomatous tissue. Subsequently, descriptions of sarcoid-type lesions in the eyes, bones, lungs, and salivary glands were made, but the systemic and unifying nature of sarcoidosis was not recognized for almost 20 years.

The view that sarcoidosis is a systemic disorder is largely based on the work of Jorgen Schaumann, a Swedish dermatologist, who in 1914 presented the view that Besnier lupus pernio and Boeck's multiple sarcoids were manifestations of the same disease termed "lymphogranulomatose benigne," thought to represent a variant of tuberculosis. In 1935, Williams and Nickerson reported that intradermal inoculation of a suspension of sarcoidosis tissue resulted in firm papules in patients with suspected sarcoidosis. Ansgar Kveim demonstrated that these papules contained sarcoidosis-like granulomas on biopsy. Louis Siltzbach and others would demonstrate in worldwide studies that this "Kveim" reaction was positive (showed granulomas) in up to 80% of sarcoidosis and was highly specific for the disease. Sven Löfgren of Sweden in the 1940s noted that sarcoidosis frequently begins with asymptomatic bilateral hilar adenopathy or with acute erythema nodosum. In the 1950s, corticosteroids were reported to be successful in treating sarcoidosis. More recently, the tools of cell and molecular biology have advanced our understanding of the immunologic, genetic, and etiologic basis of sarcoidosis, but have not yet led to breakthroughs in the development of safe, effective therapies or cure.

EPIDEMIOLOGY

Sarcoidosis is found worldwide, although the frequency of the disease varies among different geographic regions. Accurate measurements of disease prevalence are unknown, because many people with sarcoidosis are asymptomatic and there is neither sensitive nor specific diagnostic tests. Estimated prevalence rates between 10 and 40 cases per 100,000 population are reported in North America, southern Europe, and Japan.[2] Higher prevalence rates are noted in Sweden, Denmark, and US Blacks. More than 80% of cases occur in persons between 20 and 50 years of age, with a second peak in women more than 50 years of age.[1] Sarcoidosis is rare in the preadolescent period.[3] The lifetime risk for developing sarcoidosis has been estimated as 1.4% and 1.0% in women and men of Scandinavian countries, respectively, whereas one US study calculated a lifetime risk "in women and men of 2.7% and 2.1% in Blacks and 1.0% and 0.7% in Whites, respectively" in a midwestern city.[4] Based on autopsy studies, the prevalence of sarcoidosis is likely underestimated.[5] Whether the incidence of sarcoidosis is changing remains unknown given a lack of studies over the past decade.[6]

The frequency of different clinical manifestations of sarcoidosis also varies among geographic regions and ethnic groups, and is influenced by gender. Erythema nodosum is common in Scandinavian countries and Ireland, but found in less than 5% of Black or Japanese patients. In contrast, lupus pernio appears more frequently among Black populations. In Japan, over 50% of patients may have cardiac sarcoidosis.[7] Several studies suggest that race is an important determinant of disease severity with Black populations more likely to have persistent disease and greater mortality than White populations.[4,8] In the United States, 40% to 80% of mortality from sarcoidosis is from advanced pulmonary disease, with higher rates observed in Blacks and women.[9,10] In Sweden and Japan, cardiac involvement is the leading cause of death from sarcoidosis. Overall, mortality rates directly related to sarcoidosis approximate <1% to 5% depending on the study setting.[11,12]

ETIOLOGY

The cause of sarcoidosis remains uncertain. Since sarcoidosis was first described, investigators have postulated an infectious cause of the disease based on the clinical similarities to tuberculosis. Environmental exposures are linked to sarcoidosis due to seasonal clustering of the disease with a predilection for winter and early spring months in both northern and southern hemispheres.[13] Geographic variation and time–space clustering also support a role for environmental factors in sarcoidosis.[14] Occupational associations have been described for healthcare professionals, firefighters, military personnel, and workers involved in the lumber industry. Chronic beryllium disease causes a granulomatous pneumonitis histologically identical to pulmonary sarcoidosis in less than 5% of exposed workers following immunologic sensitization to beryllium.[15] However, there is no evidence that beryllium is a cause of systemic sarcoidosis.[16] An increased risk of a "sarcoidosis-like" pulmonary disease was documented in first-response rescue workers exposed to the heavy dust burden from the World Trade Center disaster; a minority of these workers had multisystem disease confirming a likely diagnosis of multisystem sarcoidosis.[17,18]

The US-based multicenter study of sarcoidosis etiology called ACCESS (A Case Control Etiologic Study of Sarcoidosis) compared 706 newly diagnosed, biopsy-proven sarcoidosis cases to age-, sex-, and race-matched controls.[19,20] Results from the study showed an absence of environmental or occupational associations positively linked to sarcoidosis risk that carried an odds ratio (OR) greater than 2.0 and an exposure prevalence of greater than 5% (prestudy goal). Weak positive associations (OR ~1.5) were found for insecticide use at work, mold/mildew exposures at work, and musty odors, suggesting possible links to microbial-rich environments. Sarcoidosis was not associated with exposure to heavy metals including beryllium, wood dusts, or rural residence as previously hypothesized. The ACCESS study found a robust negative association of smoking and sarcoidosis risk, confirming earlier studies. The

lack of a single, dominant exposure associated with sarcoidosis risk is consistent with the concept that gene–environment interactions are important in causing disease.

Many studies have directly examined a role for infectious agents in sarcoidosis given the clinical similarities to mycobacterial disease. A meta-analysis of studies published between 1980 to 2006 identified a 10- to 20-fold greater likelihood of detecting mycobacterial nucleic acids (DNA, RNA) in sarcoidosis tissues than control tissues.[21] The authors and their colleagues used a limited proteomic approach to identify potential pathogenic antigens in sarcoidosis tissues based solely on the biochemical properties of the Kveim reaction, a delayed granulomatous skin reaction to sarcoidosis tissue extracts.[22] Using homogenized sarcoidosis tissue extracts, mass spectrometry, and protein immunoblotting, we identified the mycobacterial catalase-peroxidase protein (mKatG) as a candidate pathogenic antigen.[23] This unbiased approach was not predicated on any *a priori* hypothesis regarding specific pathogenic microbes or autoantigens, supporting a mycobacterial link to sarcoidosis etiology. Several groups have demonstrated that as many as 70% of sarcoidosis patients have lung and blood T-cell responses to mycobacterial antigens including mKatG, *Mycobacterium tuberculosis* ESAT-6, Ag85, superoxide dismutase.[24–26] Several studies report extensive overlap in peripheral blood gene expression between individuals with sarcoidosis and tuberculosis infection, further supporting a mycobacterial etiology of sarcoidosis.[27–29]

Japanese investigators find *Propionibacterium acnes* DNA in 80% to 98% of sarcoidosis tissues from Japan and Europe but also in 0% to 60% of control tissues.[30] An animal model of granulomatous lung inflammation induced by *P. acnes* has been reported.[31,32] However, a role for *Propionibacteria* in sarcoidosis remains unclear because of the frequent detection and recovery of these organisms from tissues and evidence of immune responses to these commensal organisms in nonsarcoidosis control individuals. Other microbial agents, such as *Borrelia burgdorferi*, *Chlamydia pneumonia,* or *Rickettsia helvetica* have been implicated in sarcoidosis from tissue or serologic studies, but these latter studies all lack wider confirmation. High titers of antibodies against lymphotropic DNA viruses (Epstein–Barr virus, cytomegalovirus, and human herpesvirus type 6) and HTLV1 have been described in patients with sarcoidosis but may reflect generalized B-cell activation in sarcoidosis, since a viral origin has not been substantiated by viral cultures or tissue analysis.

Despite the evidence for linking some microbes to sarcoidosis etiology, there is no histopathologic or microbiologic evidence that viable mycobacterial organisms or other pathogenic organisms are present in sarcoidosis tissues. Cell-wall deficient microbes have been suggested to cause sarcoidosis, but none are supported by independent, reproducible studies.[33] Although direct demonstration of an infectious etiology remains unproven, many investigators favor the hypothesis that certain classes of microbial organisms trigger sarcoidosis in those with genetic susceptibility.

Some investigators hypothesize an etiologic association with autoimmunity, perhaps triggered by an infectious agent through molecular mimicry. In support of this concept, sarcoidosis is associated with features of autoimmunity, such as antinuclear antibodies, rheumatoid factor, hypergammaglobulinemia, and immune complexes. Sarcoidosis patients often express low titer autoantibodies of unclear significance, although no disease-specific autoantibody profile has been identified. One recent study identified several potential autoantigens such as vimentin, ATP synthase, and lysyl-tRNA whose derived peptides stimulated Th1 lymphocytes in the blood or lung of sarcoidosis patients, suggesting these responses may help sustain chronic inflammation.[34]

GENETICS

Family and case control association studies provide strong evidence for a genetic influence on the risk of developing sarcoidosis and in determining clinical expression of the disease. Familial clustering of sarcoidosis occurs in 3% to 14% of patients, with a greater frequency among Black compared with White populations. The US ACCESS study found siblings of sarcoidosis cases have a higher relative risk (RR) (OR ~5.8) than parents (OR ~3.8).[35] The significantly higher adjusted familial RR estimates reported for Whites in both the US ACCESS study (RR ~18) and in a UK study with mostly Whites (RR ~36–73) and Blacks (RR ~2.8), suggest that genetic factors have a greater influence in susceptibility to sarcoidosis in Whites than Blacks.

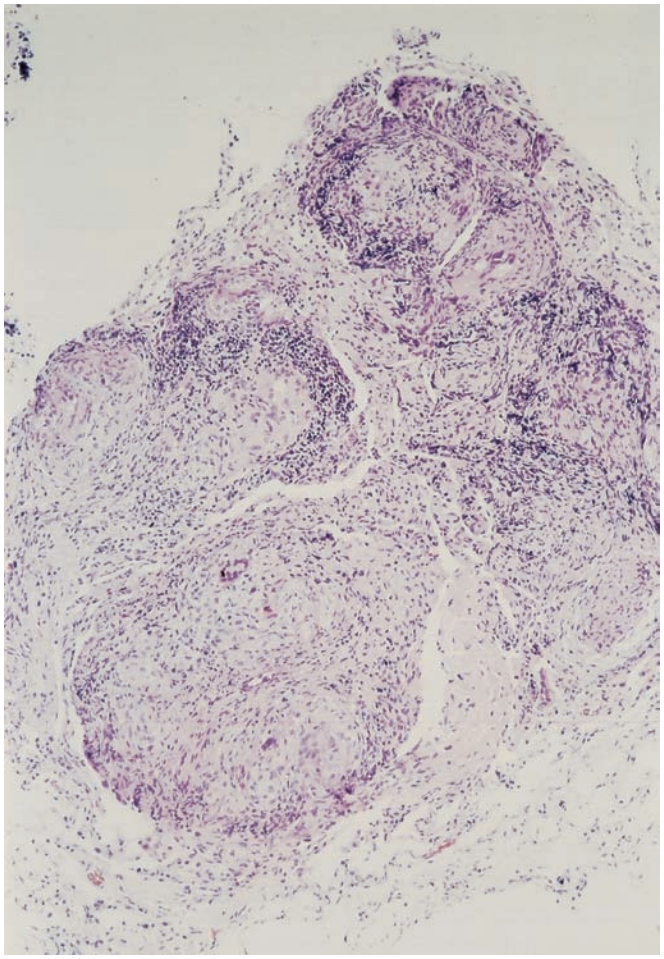
Early studies examined the role of HLA class I alleles using serologic techniques. The HLA-B8 allele has most consistently been associated with disease susceptibility, increasing sarcoidosis risk in Whites from the United States and Europe but not in Blacks or Japanese.[36–38]

The role of HLA class II alleles has been intensively studied in sarcoidosis. HLA-DR3 has been associated with sarcoidosis susceptibility, while HLA-DR1 and -DR4 alleles have been associated with disease protection in Scandinavian and European populations. Using molecular genotyping, the ACCESS study found a significant association between HLA-DRB1*1101 in both Blacks and Whites, while HLA-DRB1*1501 was associated with sarcoidosis risk only in Whites.[39] Other studies find the class II HLA-DR17 (DR3) haplotype and specifically HLA DRB1*0301 or the closely linked DQB1*0201 alleles to be associated with favorable outcomes (Löfgren syndrome, acute arthritis, stage I chest radiograph, or remission within 2 years) in European and Japanese populations.[40,41] The DRB1*1501 or the closely linked DQB1*0602 alleles were associated with more severe or chronic disease in a Danish cohort. HLA-DPB1 and DQB1 alleles have been associated with disease susceptibility in some studies, although linkage disequilibrium makes it difficult to separate from effects of HLA-DR alleles.[42] One study identified four DR and nine DQ gene polymorphisms associated with increased risk of developing sarcoidosis.[43] Since the pockets within the HLA class II sequence determine specific antigenic peptide binding, these results are consistent with the existence of etiologically important antigens in sarcoidosis. Family linkage studies employing genome-wide microsatellite analysis confirm the importance of genes from the MHC locus in determining susceptibility to sarcoidosis.[44] These data support a consensus view that MHC class II alleles are the major contributor to disease susceptibility across different ethnic populations in sarcoidosis, likely through binding specific pathogenic antigens.

Non-HLA genes have been the subject of multiple case control studies but most candidate genes linked to sarcoidosis lack replication. A meta-analysis concluded that polymorphisms of the tumor necrosis factor (TNF) gene located within the MHC locus is associated with a 1.5-fold increase risk of developing sarcoidosis.[45] There appears to be no increased risk associated with polymorphisms in genes encoding angiotensin-converting enzyme (ACE) or vitamin D receptor.

Genome-wide association studies of both familial and sporadic sarcoidosis incident cases have identified multiple chromosomal regions that may contribute to sarcoidosis susceptibility, suggesting multiple small genetic effects may influence risk. German and US investigators reported that the butyrophilin-like 2 (*BTNL2*) gene is associated with sarcoidosis risk in White and to a lesser extent, Black populations.[46,47] In addition to increased risk for disease susceptibility, recent studies suggest that BTNL2 polymorphisms may associate with chronic active disease.[48,49] Since *BTNL2* is a member of the B7 receptor family that functions in T-cell costimulation, a plausible hypothesis links the *BTNL2* gene with T-cell immunity and sarcoidosis susceptibility.

German investigators reported novel genetic loci at chromosome 6p12.1, and 11q13.1 to be associated with sarcoidosis susceptibility.[50,51] This group also identified risk associations with annexin A11, which has been also associated with Crohn disease.[52] Other studies have



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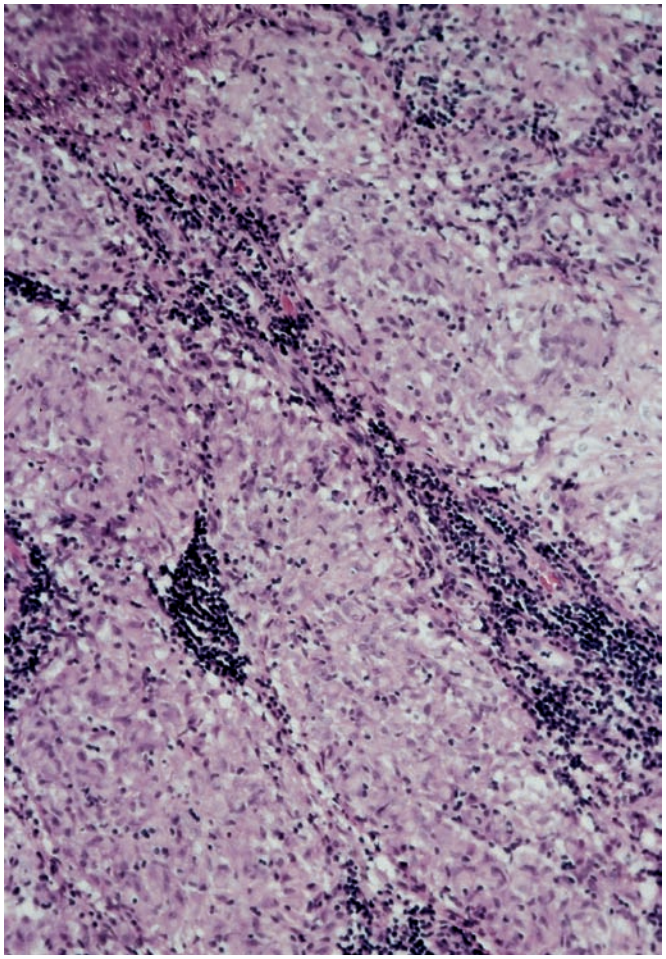


B

Figure 55-1 Photomicrographs of noncaseating granulomatous inflammation in sarcoidosis. **A.** Thoracoscopic lung biopsy showing extensive parenchymal involvement with granulomas, multinucleated giant cells, and mononuclear cell inflammation (×80). **B.** Mediastinal lymph node biopsy showing typical discrete epithelioid granulomas (×200).

identified additional loci including 10p12.2 to have associations with both sarcoidosis and inflammatory bowel disease.[53,54]

PATHOLOGY

The pathologic hallmark of sarcoidosis is the presence of discrete, noncaseating, epithelioid cell granulomas (Fig. 55-1). The dominant cell in the central core is the epithelioid cell, thought to be a differentiated form of a mononuclear phagocyte. CD4 lymphocytes and mature macrophages are typically interspersed throughout the epithelioid core, whereas both CD4+ and CD8+ T cells and B lymphocytes may be seen in the periphery of the granuloma. Occasionally, focal fibrinoid but not caseating necrosis may be seen. Giant cells, often containing cytoplasmic inclusions such as calcium and iron-laden Schaumann bodies and Hamazaki–Wesenberg bodies are scattered throughout the inflammatory locus. These features are not specific for sarcoidosis, as similar histopathologic findings can be seen in infections, berylliosis, Crohn disease, and local "sarcoid reactions" that occur near neoplastic, foreign body, or chronic inflammatory areas.

In the lung, granulomas tend to form along perivascular, peribronchial, and septal regions, areas rich in lymphatic vessels. In the lung, a mononuclear cell infiltration composed predominantly of lymphocytes is often present in the adjacent interstitium. Granulomas in sarcoidosis may resolve or undergo fibrosis, leaving a stellate scar or hyalinized ghost of a former granuloma.

PATHOPHYSIOLOGY

Important considerations in the pathophysiology of sarcoidosis are discussed below.

■ IMMUNOPATHOLOGY

Experimental models indicate that the first step in granuloma formation involves the tissue deposition of poorly soluble antigenic material. An initial innate immune response involves the recruitment and activation of antigen-presenting cells such as macrophages or dendritic cells expressing pattern recognition receptors and Toll-like receptors (TLRs). This results in the phagocytosis and degradation of antigenic proteins, generating peptide: MHC complexes that are displayed on the cell surface for analysis by CD4+ T cells. The resulting adaptive immune response is characterized by the expression of effector cytokines dominated by either a type 1 T helper cell (Th1; IFNγ), Th2 (IL4/IL13), or Th17 (IL17/IL21/IL22) response, depending on the nature of the antigen and host genetic/epigenetic factors.[55] Granuloma formation is orchestrated by the subsequent release of cytokines, chemokines, and other mediators by activated innate and adaptive immune cells. Granulomatous inflammation is downregulated with clearance of antigen along with release of anti-inflammatory mediators such as transforming growth factor-b (TGFβ) and IL10 by local immune cells.[56,57]

The immunopathology of sarcoidosis can be modeled in this experimental context (Table 55-1). Sites of granulomatous

TABLE 55-1 Hallmarks of the Pathobiology of Sarcoidosis

Pathology of noncaseating epithelioid granulomas
Genetic susceptibility determined primarily by HLA genes of MHC locus
Oligoclonal expansion of αβ+T cells consistent with antigen-driven inflammation
Polarized Th1 immunity with upregulated Th1 cytokines and chemokines at sites of disease
Potential contribution of Th17 immune responses
Reduced regulatory T-cell function
Microbial triggers with mycobacterial or propionibacterial organisms most commonly implicated
Serum amyloid A dysaggregation within granulomas provides a mechanism for chronic disease

inflammation such as the lung contain activated T cells and mononuclear phagocytes that express the same proinflammatory cytokines and chemokines that have been shown experimentally to be critical in granuloma formation.[58] Lung T cells are predominantly of the CD4 T helper, CD45R0 "memory" phenotype, express the activation markers, VLA-1 (very late activation antigen-1, CD49a) and HLA-DR molecules. Sarcoidosis alveolar macrophages (AMs) spontaneously produce TNF, interleukin-6 (IL6), IL1α, IL15, osteopontin, and the Th1 regulatory cytokines, IL12 and IL18 as well as increased amounts of lysozyme, ACE, and reactive oxygen species. Sarcoidosis AMs express increased density of the costimulatory molecules, CD80, CD86, and CD40, consistent with their enhanced antigen-presenting capability. Dendritic cells likely play a critical role in regulating local immune responses in sarcoidosis but have been the focus of few studies.[59–61] TNF is considered to be a major effector cytokine of granuloma formation in sarcoidosis (and therapeutic target) as enhanced release of TNF by BAL cells is associated with persistent disease.[62] Other proinflammatory cytokines such as IL1, macrophage migration inhibitory factor, IL6, and osteopontin are upregulated in sarcoidosis. Consistent with upregulated proinflammatory cytokine expression, there is increased activation of the transcription factor NF-κB in the lung of sarcoidosis patients,[63] and downregulation of the inflammation-suppressive transcription factor, peroxisome proliferator–activated receptor-γ.[64]

Studies of T-cell receptor (TCR) gene expression provide direct evidence that sarcoidosis is an antigen-driven disorder. Oligoclonal expansions of T cells expressing specific Vβ- or Vα-specific TCR gene segments have been found in the lung (BAL T cells), skin (Kveim biopsy sites), and blood.[65,66] The best studied example involves the remarkable expansion of Vα2.3 (AV2S3)+ BAL T cells from HLA-DRB1*0301-positive Scandinavian patients with sarcoidosis.[67] The specific antigens driving these clonally expanded T-cell populations remain uncertain but may include autoantigens such as vimentin and microbial antigens such as mKatG.[34] These studies provide evidence that oligoclonal T-cell expansions in sarcoidosis are driven by conventional antigens.

TH1 AND TH17 IMMUNITY

There are compelling data that sarcoidosis is characterized by dominant Th1 cytokine production compartmentalized to sites of inflammation.[68,69] Multiple studies confirm that pulmonary sarcoidosis is associated with enhanced expression of Th1 associated IFNγ, IL12, and IL18 in the lung but low or undetectable levels of IL4 or IL5. Characteristic of a Th1 response, the Th1-differentiation transcription factors, T-bet (T-box, expressed in T cells), and STAT-1 and its phosphorylated form are upregulated in sarcoidosis.[70,71] Consistent with Th1 polarization, most sarcoidosis BAL T cells express a functional, high-affinity IL12 receptor and the chemokine receptors CXCR3 and CCR5. This dominant Th1 polarization is characteristic of sarcoidosis at time of diagnosis and after years of known disease.

The role of Th17 responses in sarcoidosis is uncertain. Several studies show upregulated Th17 responses in sarcoidosis blood and tissues,[72,73] with release of IL17 and IL22,[74] but others show decreased or no upregulated Th17 responses in sarcoidosis compared to control subjects.[75–77] Despite an established role for Th17 effector T cells in granulomatosis with polyangiitis (GPA), (formerly known as Wegener granulomatosis) and tuberculosis,[78,79] whether Th17 responses play a critical role in disease outcome or can substitute for the polarized Th1 responses documented in sarcoidosis needs further study.

IMMUNOREGULATORY CELLS

Regulatory T cells (Tregs) maintain immune homeostasis by suppressing the function of antigen-presenting cells and effector T cells. Several groups have reported that FoxP3-positive natural Tregs (nTreg) accumulate at sites of granulomatous inflammation in sarcoidosis but may have reduced function in suppressing proinflammatory cytokine expression and granuloma formation.[80–82] Diminished numbers of immunoregulatory natural killer T (NKT) cells have also been reported and may contribute to chronic active sarcoidosis.[83] Whether the functional impairment of nTreg or NKT cells in sarcoidosis are primary defects or secondary to the hyperimmune Th1 responses in sarcoidosis remains uncertain.

One group studied the effects of nebulized vasoactive intestinal peptide (VIP) in sarcoidosis and found it significantly reduced TNF production by BAL cells.[84] This effect was associated with an increased frequency of lung CD4+CD127-CD25+ Tregs. Since VIP converted naïve CD4+CD25-T cells into CD4+CD25+FoxP3+ Tregs in vitro, the authors suggested inhaled VIP as a potential treatment of immune-mediated lung diseases including sarcoidosis.

MECHANISMS OF PULMONARY FIBROSIS

The mechanisms that promote pulmonary fibrosis in sarcoidosis remain uncertain. IFNγ has direct antifibrotic effects,[85] but this pleotropic cytokine may mediate fibrosis by enhancing lung injury.[86] There is evidence that sarcoidosis AMs transition to an alternative profibrotic M2-like phenotype in fibrotic pulmonary sarcoidosis with upregulated expression of chemokines such as CCL18.[87] The lack of evidence for IL4 upregulation in sarcoidosis suggests that IL10 or IL13 may foster this profibrotic macrophage phenotype.[88]

Increased expression of TGFβ, fibronectin, insulin-like growth factor-1 (IGF-1), laminin, and matrix metalloproteases by sarcoidosis AMs may promote a fibrosis-permissive environment in chronic active sarcoidosis through the recruitment and activation of fibroblasts.[69,89] While increased TGFβ is associated with the presence of structural lung disease among sarcoidosis patients,[90,91] the exact role of TGFβ in sarcoidosis remains unclear since it not only has profibrotic but immunoregulatory effects.

SERUM AMYLOID A DYSAGGREGATION HYPOTHESIS

The major challenge of sarcoidosis is to understand what drives chronic granulomatous inflammation given the lack of evidence for an active mycobacterial or other viable microbial infection in sarcoidosis tissues at any point in the disease. The lack of evidence of viable pathologic organisms in sarcoidosis tissues occurs in the context of often long-term treatment with corticosteroid, immunosuppressive or anti-TNF therapy in these patients. This observation, together with evidence of nonviable remnants of mycobacterial or other microbial DNA in sarcoidosis tissues, and relevant immune responses to these

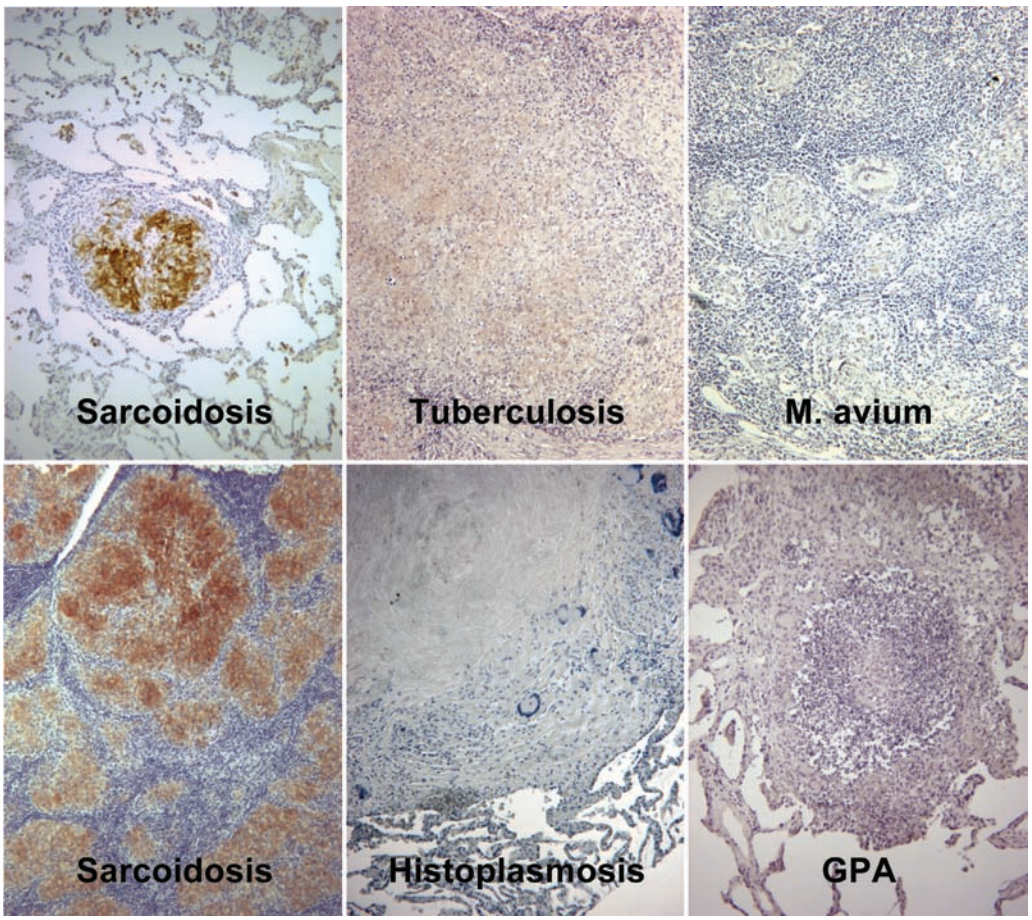


Figure 55-2 Immunohistochemistry showing focal deposition of serum amyloid A *(brownish stain)* in tissues from patients with sarcoidosis but little or no staining for SAA in tuberculosis, *Mycobacterium avium* infection, histoplasmosis, or granulomatosis with polyangiitis (GPA).

organisms, suggests that specific microbes may trigger sarcoidosis, but that a local hyperpolarized Th1 response results in permanent immune control of the triggering infectious agent.

The authors and their colleagues recently reported on a potential mechanism for chronic granulomatous inflammation in sarcoidosis involving the host protein serum amyloid A (SAA).[92,93] Our investigation of SAA was based on our recognition that the granuloma-inducing component in Kveim reagent had physicochemical properties that closely resemble amyloid or prion proteins.[94] SAA is an amyloid precursor protein and acute phase reactant[95] that was previously reported to be upregulated in the blood of sarcoidosis patients as an inflammatory biomarker.[96–98] We reported that SAA was highly concentrated within sarcoidosis granulomas unlike all other granulomatous disorders examined (Fig. 55-2). Our studies showed SAA could promote experimental granulomatous lung inflammation and stimulated the expression of TNF, Th1-related cytokines, and immunoregulatory IL10 by lung BAL cells from sarcoidosis patients, effects mediated in part through TLR-2. We hypothesized that the pathobiology of sarcoidosis is caused by the induction, misfolding, and progressive aggregation of insoluble SAA within granulomas in an amyloid-like process (Fig. 55-3). Tissue SAA and its released peptides then promote the subsequent feed-forward amplification of local Th1 responses to pathogenic antigens at sites of granulomatous inflammation to promote slowly progressive chronic inflammation centered around insoluble SAA as a nidus for granuloma formation.

CLINICAL FEATURES

The clinical features of sarcoidosis are discussed in detail below.

■ CLASSIFICATION

The clinical manifestations and course of sarcoidosis vary greatly (Table 55-2). Although any organ of the body can be affected, the lungs or intrathoracic lymph nodes are involved in more than 90% of patients with sarcoidosis. Patients may manifest with no symptoms or develop acute, subacute, or indolent manifestations. Systemic constitutional symptoms such as fever, fatigue, malaise, and weight loss are seen in over 50% of patients and may be disabling. One classification scheme with prognostic information categorizes patients based on their initial manifestations as follows: asymptomatic, acute sarcoidosis with or without erythema nodosum, sarcoidosis with symptoms or signs of pulmonary disease for less than 2 years, chronic pulmonary sarcoidosis of more than 2 years, and dominant extrapulmonary sarcoidosis. Two years represent an arbitrary but useful reference point for distinguishing patients who usually, but not always, have long-term disease.

Rare manifestations of sarcoidosis include unusual patterns of organ involvement, the result of granulomatous inflammation developing in unusual locations for sarcoidosis, or when sarcoidosis is associated with a second disorder (Table 55-2). In general, rarer manifestations reflect the known pathophysiology and clinical behavior of more common organ involvement.

■ ASYMPTOMATIC SARCOIDOSIS

Up to two-thirds of patients are asymptomatic but have sarcoidosis diagnosed after an incidental radiographic finding of bilateral hilar adenopathy. Occasionally, interstitial infiltrates are seen in association with intrathoracic adenopathy in asymptomatic patients, most commonly in Whites.

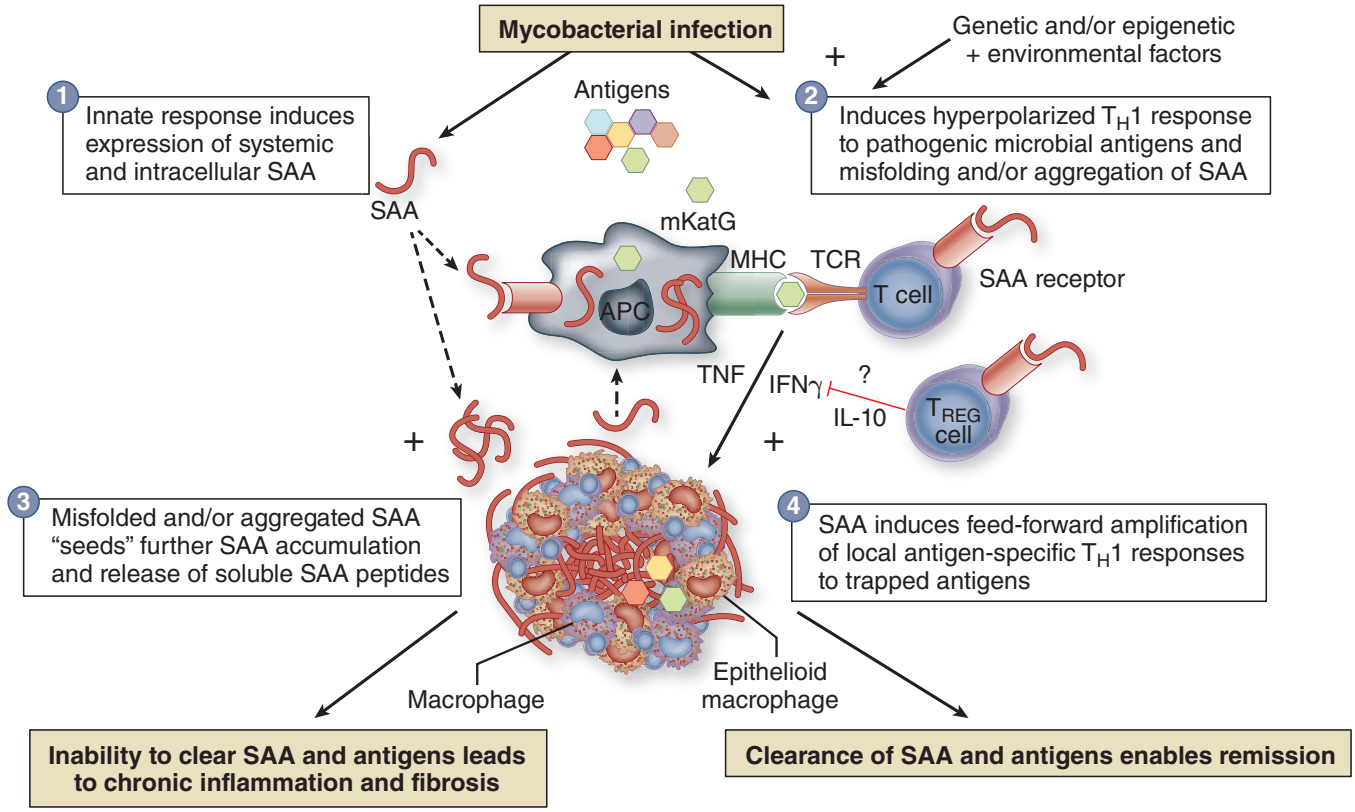


Figure 55-3 Serum Amyloid A dysaggregation as a disease-defining pathway for chronic sarcoidosis. In this scenario, misfolded amyloid-like SAA aggregates serve as "seed" that provides a poorly soluble nidus and a template for further SAA aggregation within sarcoidosis granulomas. SAA and SAA peptides released from the granulomas stoke a feed-forward stimulation of macrophages and T cells that amplifies polarized Th1 responses to local pathogenic antigens with production of TNF, Th1 promoting cytokines and IL10 (which partially dampens the inflammatory response). These effects are mediated in part through TLR2. Persistent tissue antigens may derive from degradation-resistant pathogenic microbial antigens such as mKatG, new antigens trapped by the granuloma matrix and cells or from induction of autoimmune responses. This pathobiologic course continues unabated unless there is clearance of SAA and local pathogenic antigens with downregulation of Th1 responses. Although the model depicts mycobacterial organisms as inciting agents, nonmycobacterial microbes or environmental agents could trigger a similar pathobiologic outcome. *(Reproduced with permission from Chen ES, Moller DR. Sarcoidosis–scientific progress and clinical challenges. Nat Rev Rheumatol. 2011;7(8):457–467.)*

■ ACUTE SARCOIDOSIS WITH OR WITHOUT ERYTHEMA NODOSUM

Sarcoidosis may manifest with the acute onset of erythema nodosum associated with bilateral hilar adenopathy, fevers, polyarthritis, and often uveitis, known as Löfgren syndrome. Erythema nodosum is characterized by tender reddish nodules several centimeters in diameter, usually located on the lower extremities; histologic examination shows panniculitis, not granulomas. The polyarthritis is often severe and incapacitating, typically involving the ankles, feet, knees, and occasionally, wrists, and elbows. Approximately 10% of patients with this syndrome have a normal chest radiograph. Löfgren syndrome is more common in European and White populations, but found in less than 5% of Blacks with sarcoidosis. Some patients manifest acute arthritis, bilateral hilar lymphadenopathy, and constitutional symptoms without erythema nodosum. In either case, the prognosis is excellent for remission in 70% to 80% of patients, typically within several months.

■ PULMONARY SARCOIDOSIS

Respiratory symptoms occur in 40% to 60% of patients.[99] The most common symptoms are cough and shortness of breath, usually of a progressive, insidious nature. The cough is usually nonproductive and may be severe. Dyspnea is typically worse with exertion. Sputum production and hemoptysis are frequent in patients with fibrocystic sarcoidosis that is often associated with bronchiectasis. Ill-defined chest pain is a frequent complaint, possibly caused by nerve irritation from inflammation, scarring, or lymph node enlargement in the chest. Chest tightness and wheezing are common with endobronchial disease or fibrocystic changes. These symptoms are usually poorly responsive to bronchodilators, except in those with reversible airway hyperreactivity. Physical findings are infrequent, with lung crackles heard in less than 20% of patients; clubbing is rare.

Chest Imaging

The chest radiograph is abnormal in more than 90% of known cases and carries prognostic information. Chest radiographs are categorized by international convention: stage 0 (<15%) denotes a normal chest X-ray; stage I (30% to 50%) shows symmetric bilateral hilar adenopathy often with right paratracheal adenopathy; stage II (40% to 60%) and stage III (10% to 20%) indicate the presence of pulmonary infiltrates with (stage II) or without (stage III) bilateral hilar adenopathy; stage IV (<15%) shows obvious scarring with fibrocystic changes with cephalad hilar retraction (Fig. 55-4). The hilar adenopathy often has a symmetric "potato node" appearance and calcifications are uncommon. Infiltrates most commonly appear as linear or reticulonodular markings in the middle and upper lung fields, but occasionally can present with patchy, focal alveolar consolidations mimicking infectious pneumonia, granulomatosis with polyangiitis (GPA), eosinophilic pneumonia, or malignancy. Less frequently, a miliary pattern is observed but would warrant exclusion

TABLE 55-2 Clinical Manifestations of Sarcoidosis

Organ System (Percent Clinical Disease)	Major/Uncommon Manifestations
Pulmonary (>90%)	Restrictive, obstructive impairment, reduced diffusing capacity, fibrocystic disease, bronchiectasis/pulmonary vasculitis, mycetomas, cavitating nodules, lobar atelectasis, tracheal or bronchial stenosis, superior vena cavae syndrome, pleural disease, pneumothorax
Constitutional symptoms (>50%)	Fevers, night sweats, malaise, excessive fatigue, unintentional weight loss
Upper respiratory tract and oral cavity (5–10%)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis/saddle nose deformity, respiratory failure from upper airway obstruction, sleep apnea
Ocular (20–30%)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis/granulomatous orbital inflammation
Skin (20–30%)	Erythema nodosum, chronic nodules and plaques, lupus pernio, alopecia/subcutaneous sarcoidosis, ichthyosis, alopecia, scar granulomas
Hepatic/Abdominal (10–20%)	Hepatosplenomegaly, jaundice, cirrhosis, abdominal/retroperitoneal lymphadenopathy/massive hepatomegaly, jaundice with pruritus, cirrhosis with portal hypertension, massive splenomegaly, pancreatic mass, gastric involvement, small or large intestine involvement, appendicitis
Cardiac (5–20%)	Arrhythmias, heart block, cardiomyopathy, sudden death/valvular disease, pericardial disease, ventricular or atrial mass
Neurologic (5–10%)	Facial and other cranial neuropathies (e.g., Bell palsy) aseptic meningitis brain mass, seizures, obstructing hydrocephalus, hypothalamic hypopituitarism, myelopathy, polyneuropathy, peripheral neuropathies, small fiber neuropathy/optic chiasmal involvement, cerebritis (white matter involvement), cerebral vascular occlusion, encephalitis, corpus callosum involvement, hydrocephalus, Horner syndrome, Argyll Robertson or Adie pupil, cerebellar involvement, pseudotumor cerebrei, brain stem involvement, transverse myelitis, intraspinal mass, cauda equina or spinal root involvement, mononeuritis multiplex
Exocrine gland (10–20%)	Salivary, lacrimal, and parotid gland enlargement, sicca syndrome/Heerfordt syndrome, hypopituitarism, diabetes insipidus, thyroid mass, thyroiditis, parotid mass, dacryoadenitis, sicca syndrome
Hematologic (20–30%)	Peripheral or retroperitoneal lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia/hypogammaglobulinemia, lymphedema, idiopathic thrombocytopenic purpura (ITP)
Joints and musculoskeletal (10–20%)	Polyarthritis, Achilles tendinitis, heel pain, polydactylitis, bone cysts, myopathy/polymyositis, bone cysts—long bones, skull, vertebrae
Endocrine (10–30%)	Hypercalciuria, hypercalcemia, hypopituitarism, diabetes insipidus
Renal (<5–10%)	Renal calculi, nephrocalcinosis, renal failure
Genitourinary (<5%)	Ovarian or uterine mass, dysmenorrhea, testicular mass, epididymitis/uterine mass, ovarian involvement, menometrorrhagia, testicular mass, epididymitis, intermittent azoospermia
Psychosocial manifestations (30–60%)	Depression, pain, fatigue

of tuberculosis, hypersensitivity pneumonitis, chronic beryllium disease, or lymphangitic carcinomatosis. While stage IV sarcoidosis is associated with a poor prognosis, the recent ACCESS study affirms the weak correlation between stages I, II, or III chest radiographs and clinical status.[12,100] Unusual radiographic signs of sarcoidosis include pneumothorax, mycetoma, isolated nodule or mass, lobar atelectasis, or pleural effusions.

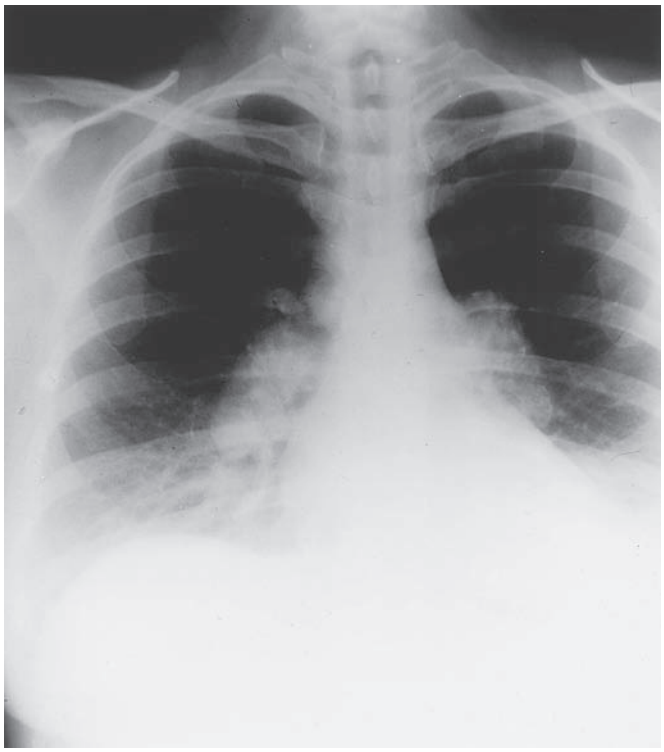
Chest computed tomography (CT) typically demonstrates that infiltrates tend to be central, following bronchovascular structures. Ground-glass infiltrates or honeycombing can also be seen. The adenopathy of sarcoidosis typically appears as multiple discrete enlarged lymph nodes rather than amorphous, mass-like growths more suggestive of malignancy. CT of the chest is often useful in the evaluation of patients with suspected sarcoidosis and to help plan bronchoscopic biopsy of enlarged lymph nodes, define unusual radiographic features, fibrocystic disease, or bronchiectasis.

Pulmonary Function Tests

Pulmonary function may be normal even when the chest radiograph demonstrates pulmonary infiltrates. However, restrictive impairment with reduction in lung volumes, forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), is common, particularly when pulmonary infiltrates are present on chest radiograph. Reduction in diffusing capacity can be seen in association with restrictive impairment or as an isolated deficit. Obstructive impairment is as common as restrictive impairment, particularly in advanced fibrocystic disease or endobronchial disease. A subgroup of patients have bronchial hyperresponsiveness and airway obstruction that may respond to bronchodilators. Resting hypoxemia and exercise O_2 desaturation are typical when there is severe obstructive or restrictive impairment. CO_2 retention is unusual except in advanced pulmonary disease.

Pulmonary Hypertension

Pulmonary hypertension represents an important complicating factor of pulmonary sarcoidosis because it is associated with increased mortality. In patients with end-stage pulmonary sarcoidosis awaiting lung transplantation, pulmonary hypertension is associated with a fivefold increased rate of mortality.[101,102] Overall, ~6% of patients with sarcoidosis have pulmonary hypertension, but is seen in over 70% of patients with advanced lung disease. In patients with dyspnea disproportionate to pulmonary function impairment, pulmonary hypertension may be seen in 50% of cases.[103] The causes of pulmonary hypertension include extensive interstitial lung disease with loss of pulmonary capillary bed, granulomatous pulmonary vasculitis, pulmonary arterial impingement by lymphadenopathy or traction lung scarring of bronchovascular bundles, left heart dysfunction, or rarely, pulmonary venous occlusion.[104] Patients typically present with progressive dyspnea. Echocardiography is a useful screening technique, but right heart catheterization is needed to confirm clinically significant pulmonary hypertension.



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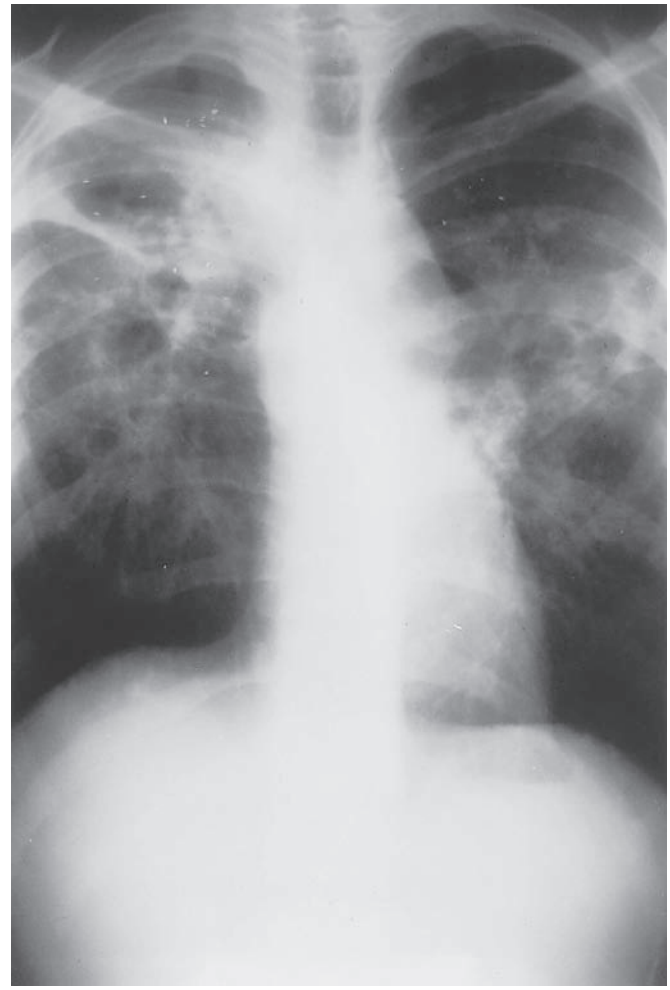

B

Figure 55-4 Chest radiographs of pulmonary sarcoidosis. **A.** Stage II sarcoidosis pattern with prominent, discrete "stand-away" hilar nodes, right paratracheal adenopathy, and fine reticulonodular infiltrates. **B.** Fibrocystic sarcoidosis with extensive scarring, bullous and cystic changes, hilar retraction, and parenchymal infiltrates.

Necrotizing Sarcoid Granulomatosis

This disorder is characterized by large, confluent, noncaseating granulomas involving both pulmonary arteries and veins but without systemic vasculitis, and is often considered a variant of pulmonary sarcoidosis.[105] Patients may be asymptomatic or have cough, dyspnea, fever, chest pain, or constitutional symptoms. Chest radiographs typically demonstrate multiple, usually noncavitating, nodules. Pleural disease with pleurisy or pleural effusions occurs in the majority of patients and may be a clue to the diagnosis. Most patients have spontaneous improvement or a rapid response to corticosteroid therapy.

■ EXTRAPULMONARY SARCOIDOSIS

Many patients have manifestations of granulomatous inflammation in one or more organ systems either in addition to pulmonary involvement or without evidence of pulmonary disease (Table 55-1). The presence of these characteristic extrapulmonary manifestations may help distinguish sarcoidosis from other systemic diseases. Defining clinically significant organ involvement remains a challenge despite improved imaging techniques.

Sarcoidosis of the Upper Respiratory Tract and Oral Cavity

Sarcoidosis of the upper respiratory tract (SURT) occurs in 5% to 10% of patients, usually involving the nasal sinuses or laryngeal structures. Symptoms of nasal congestion, sinusitis, and intermittent epistaxis are often chronic and unresponsive to decongestants or topical corticosteroids. Chronic disease or surgical intervention may result in destruction of the nasal septum and a "saddle nose" deformity. Laryngeal sarcoidosis may manifest with severe hoarseness, stridor, or acute respiratory failure secondary to upper airway obstruction. Frequently, laryngeal sarcoidosis is associated with chronic skin lesions, lupus pernio, or sinus disease. Oral and pharyngeal sarcoidosis is rare, but may manifest with macroglossia, tongue mass, or palatal mass with cartilaginous or bone destruction.

Ocular Sarcoidosis

Ocular involvement is detected in approximately 20% to 30% of patients, more frequently in Black populations.[1] Uveitis is the most common manifestation and is often associated with bilateral hilar adenopathy. The uveitis is more commonly anterior, and may be unilateral or bilateral, with either granulomatous or nongranulomatous features. Granulomatous conjunctivitis is less common. Optic neuritis, or severe chorioretinitis, may present dramatically with blindness. The International Workshop on Ocular Sarcoidosis (2006) has proposed seven clinical signs of ocular inflammation consistent with sarcoidosis including mutton-fat keratic precipitates, nodules in the iris, stroma, or trabecular meshwork, optic disk, and periphlebitis.[106]

Cardiac Sarcoidosis

Although myocardial sarcoidosis is clinically apparent in less than 10% of cases in the United States at initial diagnosis, autopsy studies

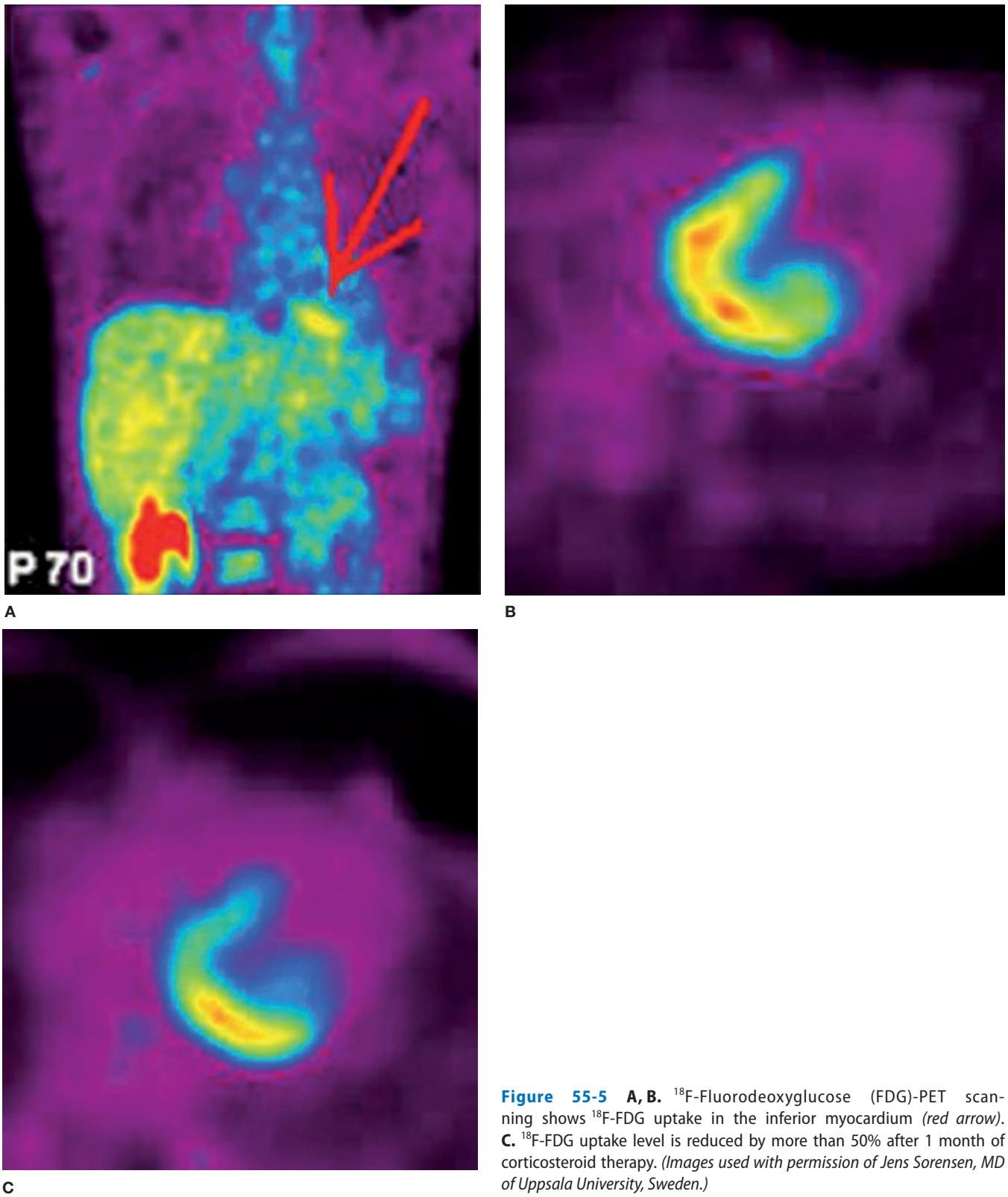

Figure 55-5 **A, B.** ^{18}F-Fluorodeoxyglucose (FDG)-PET scanning shows ^{18}F-FDG uptake in the inferior myocardium *(red arrow)*. **C.** ^{18}F-FDG uptake level is reduced by more than 50% after 1 month of corticosteroid therapy. *(Images used with permission of Jens Sorensen, MD of Uppsala University, Sweden.)*

suggest the prevalence may be greater than 20% in the United States and greater than 50% in Japan.[107,108] Arrhythmias, heart block, or sudden death may be the initial manifestation due to involvement of the conduction system. Myocardial inflammation can lead to dilated cardiomyopathy and congestive heart failure, local akinesia, or aneurysms. Myocardial mass, valvular dysfunction from papillary muscle dysfunction, pericarditis, and myocardial ischemia are rarer manifestations.[109] Radiographic scanning using thallium or technetium sestamibi myocardial scanning, cardiac MRI or cardiac PET reveal myocardial inflammation in a distribution not defined by normal coronary vascular anatomy (Fig. 55-5). The severity of pulmonary involvement does not appear to predict the presence or severity of cardiac sarcoidosis.

Neurosarcoidosis

Neurologic manifestations of sarcoidosis are varied and are estimated to occur in 10% to 20% of patients with sarcoidosis.[110] Cranial neuropathies, with unilateral or bilateral seventh nerve (Bell) palsy being the

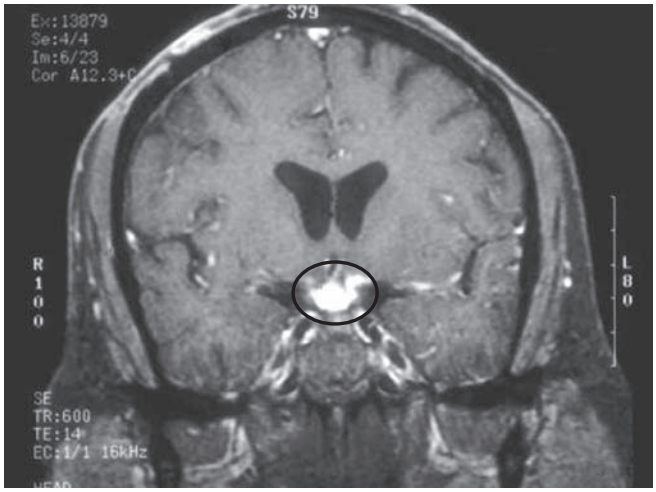

Figure 55-6 Sarcoidosis involving the optic chiasm *(circle)* resulting in blindness.

most common, often resolve spontaneously or with corticosteroids but may recur years later. Optic neuropathy may result in sudden blindness (Fig. 55-6). Impingement of the recurrent laryngeal nerve may cause vocal cord dysfunction. The more typical presentations of sarcoidosis in the brain include a basilar meningitis or aseptic encephalitis, sometimes associated with hypothalamic pituitary dysfunction leading to diabetes insipidus, hypogonadism, or hyperprolactinemia. Meningeal granulomatous masses may mimic meningioma. Spinal cord involvement is rare and can present as a transverse myelitis or mass-like lesion resulting in paraparesis, hemiparesis, back and leg pains mimicking radiculopathy. Peripheral neuropathies account for about 20% of cases of neurosarcoidosis, typically presenting as mononeuritis multiplex or a predominant sensory deficit. The presence of a small fiber neuropathy has been demonstrated in a subset of patients with sarcoidosis and can contribute to chronic pain, excessive fatigue, and autonomic dysfunction.[111]

Cutaneous Sarcoidosis

Chronic skin sarcoidosis is seen in approximately 25% of patients, usually manifesting as plaques or subcutaneous nodules and is more common and severe in Blacks. Typically, the plaques are located around the hairline, eyelids, ears, nose, and extensor surfaces of the arms and legs. Lupus pernio is a disfiguring form of cutaneous sarcoidosis of the face, with violaceous plaques and nodules covering the nose, nasal alae, malar areas, and areas around the eyes. Erythema nodosum is a nongranulomatous panniculitis seen in acute sarcoidosis.

Hepatic Sarcoidosis

Liver biopsies show granulomatous inflammation in over 50% of patients, but clinical manifestations are much less frequent. Active hepatic inflammation may be associated with fever, tender hepatomegaly, or pruritus that may mimic primary biliary cirrhosis except that autoimmune serologies are negative. Characteristically, the serum alkaline phosphatase and γ-glutamyltransferase are elevated proportionately higher than the transaminases or bilirubin, although the latter may be observed with advancing liver dysfunction. Progressive cirrhosis occurs in a subset of patients if not treated.

Gastrointestinal Sarcoidosis

Sarcoidosis involvement of the gastrointestinal tract is rare. Occasionally, direct esophageal involvement may cause dysphagia, but more commonly this symptom may be caused by extensive mediastinal lymphadenopathy that impinges esophageal motility. Gastric sarcoidosis may manifest as dyspepsia, abdominal pain, or gastric nodule. Although autopsy studies show scattered granulomas in the gut, clinically symptomatic intestinal sarcoidosis is rare.

Abdominal Sarcoidosis

A variant of sarcoidosis, often called abdominal sarcoidosis, manifests with liver, spleen, and often bone marrow involvement with hypercalcemia or abdominal lymphadenopathy. Constitutional symptoms are frequent with fevers and fatigue. This "triad" pattern may be seen with or without pulmonary involvement; in the latter instance, intra-abdominal malignancy must be excluded.

Hematologic Sarcoidosis

Persistent, bulky, painful, or disfiguring adenopathy is seen in <10% of patients, most commonly involving the cervical, supraclavicular, axillary, or epitrochlear lymph nodes. Splenomegaly occurs in <10% of patients, and may be massive and associated with hypersplenism. Because many of the clinical features of sarcoidosis and lymphoma are similar, clinicians should employ heightened awareness to exclude malignancy in patients with a known diagnosis of sarcoidosis who experience new onset of adenopathy and splenomegaly.[112]

Peripheral blood lymphopenia is common in sarcoidosis.[113] Granulomas in the bone marrow are found in about 20% of patients who come to autopsy but usually do not cause symptoms. A known feature of sarcoidosis is the impaired cutaneous response to common antigens that elicit delayed-type hypersensitivity reactions, seen in >30% of patients. The mechanism is unknown but may be related to alterations in regulatory T-cell function.

Joint and Musculoskeletal Sarcoidosis

Arthralgias are a frequent complaint in sarcoidosis. A short-lived polyarthritis is typical of acute sarcoidosis, usually associated with erythema nodosum. Chronic joint disease is found in less than 5% of patients. Joint cartilaginous erosion is rare, but "punched out" bony lesions with cystic changes and loss of bony trabeculae may be seen in subchondral locations. Cystic lesions of the long bones, pelvis, sternum, skull, and vertebrae are uncommon. Symptomatic myopathy with marked elevation of serum creatinine phosphokinase, aldolase, aspartate aminotransferase, weakness and tenderness is uncommon. Typically, the myositis from sarcoidosis is responsive to systemic immunosuppression, and recalcitrant cases prompt consideration of alternative diagnosis such as inclusion body myositis.[114]

Exocrine Gland Sarcoidosis

Granulomatous inflammation of salivary, parotid, and lacrimal glands results in enlarged, tender glands, and/or sicca syndrome with dry mouth and dry eyes in less than 5% of patients with sarcoidosis. The association of fever, parotid enlargement, facial palsy, and uveitis is known as uveoparotid fever, or Heerfordt syndrome, and is usually accompanied by bilateral hilar adenopathy.

Endocrine Sarcoidosis

Abnormal calcium metabolism is found in sarcoidosis; hypercalciuria is more frequent than hypercalcemia. These abnormalities are due primarily to increased conversion of 25(OH) vitamin D metabolites to active $1,25(OH)_2$ vitamin D by tissue macrophages and epithelioid cells at sites of granulomatous inflammation.[115] Hypothalamic/pituitary insufficiency may be a manifestation of neurosarcoidosis.

Renal Sarcoidosis

Kidney stones are the most frequent manifestation of renal sarcoidosis, usually related to abnormal calcium metabolism. Renal failure due to nephrocalcinosis may result from chronic, often asymptomatic hypercalcemia or hypercalciuria. Granulomatous involvement of the kidneys occurs but is rarely the cause of significant renal dysfunction.

Genitourinary Sarcoidosis

Sarcoidosis of the reproductive system has been estimated to occur in less than 1% of clinically diagnosed cases and in 5% of autopsy cases. Genitourinary manifestations of sarcoidosis in men include testicular masses and acute epididymitis-orchiditis. In women, sarcoidosis may manifest with uterine or ovarian involvement that may cause dysmenorrhea or mimic malignancy or fibroids.

Psychosocial Manifestations

A Dutch study found the prevalence of depression was 4% in asymptomatic patients and 30% in symptomatic patients with sarcoidosis while the prevalence of depression was found to be 60% in a US study of both White and Black patients with sarcoidosis.[116,117] In this latter study, depression was associated with the female sex, lower socioeconomic status, poor access to care, and increased disease severity, but not race.

Fatigue is commonly reported and may be disabling for a subset of patients.[118] The prevalence of pain in sarcoidosis is unclear, but clinical experience suggests it is common with frequent reports of arthralgias, myalgias, headache, and chest pain. The cause of pain is often multifactorial with causes ranging from direct granulomatous inflammation of bones, joints, muscles, or peripheral nerves to small fiber neuropathy. A subset of patients meets diagnostic criteria for fibromyalgia. In addition to its association with pain, small fiber neuropathy may cause autonomic dysfunction with gastrointestinal dysmotility, incontinence or retention, sicca syndrome, flushing, sweats, orthostatic hypotension, and sexual dysfunction.[119]

■ ASSOCIATED CONDITIONS

Important selected conditions associated with sarcoidosis are discussed briefly below.

Sarcoidosis and Pregnancy

There is usually little long-term effect on the course of sarcoidosis from pregnancy. In contrast to diseases such as asthma and systemic lupus that may progress during pregnancy, spontaneous improvement in chronic sarcoidosis has been reported in some patients during pregnancy, although exacerbations often follow several months after delivery. The reasons for the temporary clinical improvement are not known but might be related to suppressed Th1 immunity during pregnancy associated with enhanced Treg function.

Altered Th1 Immunity

Sarcoidosis is associated with several clinically disparate situations associated with altered, enhanced Th1 immunity. The clearest example involves the administration of Th1-promoting therapeutics such as IFNα, IFNγ, IL2, and IFNβ that may be associated with initiation or recrudescence of sarcoidosis.

Common Variable Immunodeficiency Granulomatous inflammation has been identified in several immunodeficiency states, particularly in patients with hypogammaglobulinemia secondary to common variable immunodeficiency (CVID). Within subsets of patients with CVID, case series reports suggest that a diagnosis of concurrent sarcoidosis can be inferred by a compatible history of systemic illness and confirmed by biopsy.[120] In other CVID patients who present with dominant pulmonary manifestations, a recently described CVID-associated granulomatous-lymphocytic interstitial lung disease may be present and is often resistant to treatment.[121] Since CVID occurs at any age, a high index of suspicion must be maintained, particularly in sarcoidosis patients who have recurrent infections or in any child with sarcoidosis given the low frequency of sarcoidosis in this age group.

Human Immunodeficiency Virus Sarcoidosis may develop in HIV-infected patients with immune reconstitution following initiation of highly active antiretroviral therapy, perhaps from reconstituted Th1 immunity.[122] Granulomatous inflammation of the lungs or skin is most often reported.

Autoimmune Disorders Sarcoidosis is associated with a variety of disorders of the immune system, such as Crohn's disease, ulcerative colitis, primary biliary cirrhosis, scleroderma, Sjögren syndrome, autoimmune hemolytic anemia, and autoimmune endocrinopathies.[123] Given the rarity of some of these disorders, it is reasonable to postulate that these associations are the result of a common immune disturbance, with altered Th1 immunity that may predispose to both disorders.

Recently, a syndrome of immune-mediated disorders in patients with elevated serum IgG4 levels has been described, commonly presenting as adenopathy, constitutional symptoms, and mass-like tumors.[124] Granulomatous inflammation is observed in a subset of such patients and can mimic sarcoidosis.[125,126]

Cancer Noncaseating granulomas may be seen in or nearby 3% to 10% of tumors and in approximately 4% of regional draining lymph nodes. Less commonly, multi-system granulomas consistent with systemic sarcoidosis develop in patients with a recent or past diagnosis of cancer or following chemotherapy treatment. Often the diagnosis is established by biopsy of enlarged lymph nodes or lung where the presurgical diagnosis is recurrent malignancy. There is usually little functional lung impairment from pulmonary sarcoidosis in these instances, and treatment is often unnecessary with eventual remission. A possible link involves dysregulated Th1/Th2 immunity, a premise supported by several cases of sarcoidosis developing in patients with changes that result in deletion of several Th2 genes (IL4, IL13, CSF2).[127]

Pediatric Sarcoidosis

Sarcoidosis is rare in the preteen ages. In the teenage years, clinical manifestations and prognosis in children is similar to that of adults.[128] Early onset disease in children under 5 years of age typically involves skin, eye, and joint involvement that can mimic juvenile rheumatoid arthritis or Blau syndrome, an autosomal dominant granulomatous disease caused by a NOD2 mutation.[129] This form of sarcoidosis carries a much worse prognosis than disease presenting in older children.[130,131] Pediatric sarcoidosis may also be associated with CVID.

Sarcoidosis in the Elderly

There is a second peak incidence of sarcoidosis between 50 and 65 years. In the ACCESS study, one-third of patients were over the age of 50.[132] Recurrent sarcoidosis after many years, even decades of apparent remission, is also seen, often manifesting with new onset neurologic involvement, or recurrent manifestations of original organ involvement.

DIAGNOSTIC APPROACH

There is no reliable, noninvasive screening test to help confirm a diagnosis of sarcoidosis. A diagnosis of sarcoidosis is based on compatible clinical and radiologic manifestations together with a tissue biopsy demonstrating noncaseating granulomatous inflammation and exclusion of other granulomatous disorders. Exceptions to this approach include patients who manifest with Löfgren syndrome in areas with a low prevalence of histoplasmosis, which may mimic Löfgren syndrome, in which case most experts believe a biopsy is not necessary.[133] Many experts suggest that patients with asymptomatic bilateral hilar adenopathy with presumptive stage I sarcoidosis do not need biopsy unless atypical features are present, given a low pretest probability for alternative diagnoses and the risks for potential complications of a diagnostic biopsy.[134,135] Clinical involvement of more than one organ system helps exclude local granulomatous reactions to foreign bodies, infection, or malignancy.

In general, the easiest accessible biopsy site can be approached to confirm a diagnosis of sarcoidosis. Biopsy of a skin or conjunctival

nodule, enlarged superficial lymph node, or lacrimal gland may help to establish a diagnosis. Noncaseating granulomas on a liver or bone marrow biopsy are nonspecific and support a diagnosis only when competing diagnoses such as infection, drug reaction, or malignancy are excluded.[136]

When a more easily accessible site is not available, biopsy by fiberoptic bronchoscopy remains the most common approach because of its high yield and relative safety. The diagnostic yield of transbronchial biopsy (TBB) is estimated to be >40% even in patients with a stage I chest radiograph and approaches 80% in the presence of lung infiltrates.[137] Transbronchial lung biopsy in advanced fibrocystic sarcoidosis has a low yield, owing to extensive fibrotic changes. Sampling by endobronchial mucosal biopsy (EMB) and transbronchial needle aspiration (TBNA) of thoracic lymph nodes provides additional sensitivity when combined with TBB.[137] The sensitivity of endoscopic bronchial ultrasound (EBUS)-guided TNBA has been found to be superior to standard TBNA in diagnosis of sarcoidosis, but in cases of suspected lymphoma, mediastinoscopy may be needed for histologic diagnosis.[138]

Bronchoalveolar lavage obtained as part of a diagnostic bronchoscopy remains an important method for excluding infectious causes of granulomatous inflammation. Some studies suggest a CD4:CD8 ratio >3.5 of BAL T cells supports a diagnosis of sarcoidosis, but may not differentiate some infectious or noninfectious inflammatory lung diseases.

A diagnosis of cardiac sarcoidosis is usually established by a noncardiac biopsy confirming systemic sarcoidosis along with consistent myocardial imaging studies or rhythm disturbances (Fig. 55-5). Endomyocardial biopsy is positive in <20% of cardiac sarcoidosis owing to sampling inefficiencies and the infrequency of right ventricular involvement; thus a negative biopsy never excludes cardiac sarcoidosis.[139]

A diagnosis of neurosarcoidosis is usually confirmed by biopsy of a non-CNS site. Rarely, brain biopsy is needed to exclude infectious or malignant disease.

For organs that are rarely involved in sarcoidosis, directed biopsy of the involved tissue is often recommended to exclude alternative causes, even when there is documentation of a prior biopsy that confirmed an original diagnosis of sarcoidosis. For organs that are difficult to biopsy, ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, or contrast enhanced MRI scanning have replaced gallium[67] scans in helping define sites of clinically occult inflammation that could provide an alternative biopsy approach.[140]

Laboratory tests are generally not helpful in confirming a diagnosis of sarcoidosis but may assist in establishing an alternative diagnosis, such as autoimmune disease. A diagnostic biomarker has not been identified for sarcoidosis. Serum ACE (SACE) levels are elevated in 30% to 80% of patients with clinically active disease from activated epithelioid cells and macrophages at sites of inflammation, but can be also seen in infectious granulomatous diseases, lymphoma, primary biliary cirrhosis, and thyroid disease and lack specificity for use as a diagnostic tool.[141]

CLINICAL ASSESSMENT

Once a diagnosis is established or suspected, an initial evaluation should consist of tests to evaluate the presence and extent of pulmonary involvement and assess the presence and severity of extrathoracic disease (Table 55-3).

Specialized testing is indicated when symptoms or signs suggest extrapulmonary sarcoidosis. Guidelines for when and how to screen for potential cardiac involvement remain uncertain.[142] Given the risk for sudden death, screening for cardiac sarcoidosis is recommended whenever symptoms such palpitations, near-syncope, or syncope are present.[143] A second-level screening may include a Holter monitor, signal-averaged ECG, and echocardiogram to detect conduction abnormalities, heart rate variability, or myocardial dysfunction. Advanced cardiac imaging with cardiac MRI with gadolinium enhancement or cardiac PET scanning is recommended for those patients with continued uncertainty of possible cardiac sarcoidosis.[144] Unexplained dyspnea or chest pain may also be suggestive for sarcoidosis but may also prompt investigations for other etiologies such as pulmonary hypertension. Thallium or technicium sestamibi myocardial scanning is useful to exclude coronary artery disease and may detect patchy fixed or reverse ischemia–perfusion defects consistent with myocardial inflammation or fibrosis.[145] Electrophysiologic testing may be indicated to exclude arrhythmias not detected by routine studies and assess indications for prophylactic cardiac pacemaker or implantable defibrillator to reduce the risk of sudden death. There is no consensus on risk stratification of patients with known cardiac sarcoidosis for placement of an implantable defibrillator, but is typically recommended for patients with moderate or severe cardiomyopathy or serious ventricular arrhythmias.[109,146]

Evaluation for possible CNS and spinal sarcoidosis should include MRI with gadolinium enhancement, now considered the optimal test to detect characteristic inflammatory lesions[147]. The distribution of inflammatory loci has a propensity for periventricular and leptomeningeal areas, although the images are nonspecific, and can be produced by infectious, malignant, or occasionally demyelinating disease. A normal scan does not exclude neurosarcoidosis, particularly for cranial neuropathies or in the presence of corticosteroid therapy. Examination of the cerebrospinal fluid is less often performed today, but may be useful by demonstrating characteristic lymphocytic pleocytosis and/or elevated protein levels. In suspected cases of peripheral neuropathy or myopathy, EMG or nerve conduction studies or rarely, tissue biopsy, may help to establish a link to sarcoidosis. Specialized evaluation including skin biopsy analysis of intraepidermal nerve fiber density may be considered to confirm cases of small fiber neuropathy.[148]

TABLE 55-3 Recommended Tests in the Clinical Evaluation of Systemic Sarcoidosis

All Patients	Organ-Specific Testing for Suspected Involvement
Chest radiograph or chest CT	Cardiac: Echocardiogram, Holter monitoring, thallium or sestamibi myocardial scan, cardiac MR, cardiac PET
Pulmonary function tests: Spirometry, diffusion capacity, lung volumes	Neurologic: Brain or spine MRI with gadolinium enhancement, cerebrospinal fluid examination, nerve conduction studies, small fiber nerve analysis
Ophthalmologic examination	Upper respiratory tract: Flow–volume loop, ENT evaluation
Complete metabolic panel	Endocrine: Pituitary function tests; thyroid function tests
Complete blood count with differential count	
Electrocardiogram	
Purified protein derivative (PPD) skin test	

CLINICAL COURSE AND PROGNOSIS

A clinical framework can be constructed to assist in decisions regarding monitoring and planning treatment strategies. First, organ involvement usually defines itself early in the disease. For example, only 23% of patients in the ACCESS study were found to have one or more new

organ systems involved with sarcoidosis during a 2-year follow-up evaluation; the presence of extrapulmonary involvement at presentation was a risk factor for new organ development.[100] Second, patients who undergo remission usually do so within the first 2 to 3 years. Clinical experience suggests sarcoidosis rarely recurs after a prolonged period of remission, with exceptions most often involving neurologic or ocular manifestations. Third, patients with chronic sarcoidosis generally have progressive, unremitting organ impairment. High rates of relapse are observed in patients (>50%) requiring systemic immunosuppressive medications compared with those who experience spontaneous disease remission (<10%).[149–151] In these patients, the rate of progression varies from individual to individual, as does their response to treatment. A waxing–waning clinical course is uncommon except for a subset of patients with neurologic or ocular manifestations or occasionally recurrent erythema nodosum. Fourth, prognosis in sarcoidosis is strongly influenced by the initial manifestations of disease. Patients with Löfgren syndrome have remission rates of 70% to 80%. An initial stage I chest radiograph is associated with a 60% to 90% remission rate. Patients manifesting with type II chest radiographs have a poorer outcome, with spontaneous remission occurring 40% to 70% of the time. A stage III chest radiograph is associated with remission in only 10% to 20% of patients. Patients with extensive pulmonary fibrosis (stage IV) rarely undergo remission.

Currently, a consensus recommendation is that treatment decisions are best based on repeated clinical examinations and direct measurement of organ function and not on laboratory markers of disease "activity."[152] SACE levels tend to correlate with the extent of granulomatous inflammation throughout the body particularly when interpreted in the context of known polymorphisms of ACE alleles and usually decrease in response to corticosteroids or with disease remission, but the test is highly variable, correlates poorly with functional assessments of disease activity and has no prognostic value.[153] Similarly, BAL parameters such as the proportion of CD4 lymphocytosis or the CD4:CD8 ratio of BAL T cells have been inconsistent in predicting outcomes. Many inflammatory molecules have been proposed as helpful biomarkers for disease activity including sIL2R, TNF, and neopterin but are not reliable prognostic indicators. More recently, studies suggest transcriptomic signatures may be useful for prognosis, but there are no currently validated markers useful for clinical purposes.[154] Monitoring for at least 3 years following presumed "disease remission" is recommended; longer periods of observation are indicated for patients with serious pulmonary or extrapulmonary manifestations.

TREATMENT

A variety of approaches have been utilized in the treatment of sarcoidosis and are outlined in this section.

INDICATIONS

There have been attempts to provide evidence-based recommendations for treatment of sarcoidosis, but the lack of placebo-controlled clinical trials in this highly heterogeneous disease have made firm conclusions problematic. Most physicians agree that corticosteroid or other systemic therapy is indicated for the manifestations listed in Table 55-4.

Indications for treatment must take into account the overall excellent prognosis for most patients with sarcoidosis, particularly for patients with stage I disease, for whom systemic therapy is usually not required. Symptomatic or local therapy is recommended whenever possible. Löfgren syndrome is usually managed with bed rest and nonsteroidal anti-inflammatory drugs; corticosteroids are recommended when symptoms, particularly arthritis, are disabling and persistent. The following consensus recommendations from the British Thoracic Society and the Thoracic Societies of Australia, New Zealand, and Ireland are shown in Table 55-5.[155]

TABLE 55-4 Indications for Treatment of Sarcoidosis

Threatened organ failure—severe ocular, cardiac, or neurologic disease
Progressive or persistent pulmonary disease
Uveitis unresponsive to topical corticosteroids
Persistent hypercalcemia, renal or hepatic dysfunction
Palpable splenomegaly or hypersplenism
Severe myopathy
Disfiguring skin disease
Painful lymphadenopathy
Severe fatigue and weight loss

SYSTEMIC TREATMENT

There are no FDA-approved systemic therapies for sarcoidosis.

CORTICOSTEROID THERAPY

Corticosteroids remain the cornerstone of therapy for sarcoidosis. Although controversy exists regarding the overall effectiveness of corticosteroids in altering the long-term course of the disease, there is no disagreement that corticosteroids provide prompt symptomatic relief and reverse organ dysfunction in most patients with the degree of reversibility dependent on the extent of pre-existing fibrosis. Case series and several but not all clinical trials support the view that corticosteroids favorably affect disease outcome in chronic pulmonary sarcoidosis. One large study by the British Thoracic Society

TABLE 55-5 Consensus Approach to Treatment of Sarcoidosis

1. Treatment is not indicated for asymptomatic patient with only intrathoracic lymphadenopathy
2. Treatment is not indicated in asymptomatic patient with pulmonary infiltrates and mildly abnormal lung function and stable disease
3. Oral corticosteroids are the first line of therapy in patients with progressive disease determined by radiology or lung function, significant symptoms or extrapulmonary disease requiring treatment
4. Treatment with prednisone (or equivalent) 20–40 mg/d initially for 4 wk, then reduced to a maintenance dose that will control symptoms and disease progression for a period of 6–24 mo
5. Bisphosphonates are recommended to minimize steroid-induced osteoporosis
6. Inhaled corticosteroids are not of significant benefit as initial treatment or for maintenance therapy. Inhaled corticosteroids may be considered for symptom control (cough) or bronchial hyperreactivity in a subgroup of patients
7. Steroid-sparing immunosuppressive or anti-inflammatory treatments only have an undefined role in sarcoidosis, but should be considered in patients when corticosteroids are not controlling the disease or side effects are intolerable. At present, methotrexate is the treatment of choice if there are no relative contraindications for its use. Azathioprine is often used when methotrexate is contraindicated or not tolerated
8. Lung (and heart) transplantation should be considered in end-stage pulmonary and cardiac sarcoidosis

Source: Data from Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63(Suppl 5):v1–v58.

found long-term improved lung function in patients with stage II or III pulmonary disease treated with daily corticosteroid therapy compared with a group treated intermittently with corticosteroids based on symptoms.[149]

Optimal dosing of corticosteroid therapy has not been established by clinical trials. Most authorities suggest that initial treatment of pulmonary sarcoidosis usually does not require more than 20 to 40 mg per day of prednisone followed by a slow taper to a maintenance dose of 5 to 15 mg per day of prednisone. A qod regimen of prednisone in patients may be effective in some but not all patients. Treatment is usually continued for a minimum of 6 to 24 months, since premature attempts to taper off steroids are likely to result in relapse of disease. Inhaled steroids appear to have limited effectiveness in chronic pulmonary sarcoidosis and are not recommended as sole therapy. Overall, recurrent progressive pulmonary disease occurs in more than 20% of patients as oral corticosteroids are tapered or discontinued.

■ ALTERNATIVE AGENTS

Several classes of drugs have been reported to be beneficial in subgroups of patients with sarcoidosis but none of these drugs has been proved effective by rigorous clinical trials.

Nonimmunosuppressive Drugs

Case series suggest hydroxychloroquine is effective in many patients with mucocutaneous sarcoidosis, hypercalcemia and occasionally, as a steroid-sparing agent in systemic sarcoidosis. Ocular toxicity is rare, and its overall safety profile provides a rationale for an early trial of this drug. Chloroquine may be efficacious in treating lupus pernio, SURT, or sinus disease, which is often recalcitrant to other therapies, although ocular toxicity has limited its use.

The tetracyclines, minocycline, and doxycycline, may be effective in a subgroup of patients with mild cutaneous sarcoidosis but rarely as a steroid-sparing drug in systemic disease. These antibiotics have mild anti-inflammatory effects, which probably account for their mechanism of action given that other antibiotics with similar antimicrobial activity have not been found effective in sarcoidosis.

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory effects that was found to be effective in early pulmonary sarcoidosis in one study.[156] Other experiences have not been as favorable with responses in less than 10% of patients, generally those with mild pulmonary or systemic sarcoidosis.

Melatonin was found to be beneficial in a small case series of patients with generally mild disease but wider experience has not confirmed its efficacy.

Thalidomide was found in one study to be beneficial in over 80% of patients with severe skin sarcoidosis (lupus pernio unresponsive to other therapies), but was not effective in pulmonary sarcoidosis.[157] Given the drug's well-known teratogenicity and potential to cause peripheral neuropathy and sedation, the drug is recommended only in patients refractory to other treatments.

Immunosuppressive Drugs

Clinical experience in sarcoidosis suggests that all immunosuppressive therapies share the following characteristics: beneficial responses are seen in no more than 50% to 70% of patients; responses may take 3 to 6 months or longer; low-dose corticosteroid therapy is often needed for synergistic effect to obtain adequate suppression of granulomatous inflammation. Dosing and monitoring for these therapies should follow the recommendations of the American College of Rheumatology.[158]

Methotrexate is often the first immunosuppressive therapy used as an alternative therapy for refractory pulmonary or systemic sarcoidosis when corticosteroid and antimalarial therapies are ineffective or poorly tolerated. Hepatic, pulmonary, and renal toxicities limit the use of the drug. Azathioprine has shown benefit in small clinical trials and is used by some authorities as an initial potent steroid-sparing therapy. Clear advantages of methotrexate or azathioprine over low-dose corticosteroids in the routine management of sarcoidosis have not been established. Other immunosuppressive agents, such as mycophenylate mofetil, leflunomide, or cyclophosphamide, have been found beneficial in a small series of patients with manifestations of sarcoidosis refractory to corticosteroids.

Small studies have shown that cyclosporine and FK506, drugs known to inhibit T-cell activation, are not effective in pulmonary or ocular sarcoidosis or in suppressing recurrent sarcoidosis in transplants. Given their toxicities, consensus is to avoid these medications until new studies demonstrate potential benefits.

Anti-TNF Therapies

The scientific basis for the use of TNF inhibitors in sarcoidosis is firmly established based on the role of TNF in experimental models of granuloma formation. One multicenter study found infliximab to be effective in one of several primary end points (improved FVC after 24 weeks of therapy), although the effect was modest.[159] Etanercept was not shown to be effective in a smaller clinical trial of pulmonary sarcoidosis.[160] Anecdotal cases suggest adalimumab may be effective in some patients with sarcoidosis, although larger studies are lacking. Given the risk profiles of current immunosuppressive drugs, additional clinical trials of these agents are warranted but most authorities reserve these therapies after failure of one or more immunosuppressive drugs.

■ SPECIAL CIRCUMSTANCES

Several special considerations in the management of systemic sarcoidosis warrant particular mention.

Fibrocystic Sarcoidosis

Advanced pulmonary sarcoidosis may be complicated by mycetomas, usually from *Aspergillus fumigatus* that colonize pre-existing cystic spaces. The fungi rarely cause invasive disease. Spontaneous resolution may be seen. The benefit of antifungal agents has not been established but may be used for serious hemoptysis. Massive hemoptysis associated with mycetomas or bronchiectasis may be life-threatening, requiring therapeutic embolization of the appropriate bronchial or collateral artery for control. Surgery is usually not feasible because of the severe restrictive lung disease.

Pulmonary Hypertension

Moderate or severe pulmonary hypertension is an independent predictor of reduced survival in patients with advanced lung disease awaiting lung transplantation. Studies suggest drugs used to treat primary pulmonary hypertension may improve dyspnea and pulmonary hypertension but no study has yet demonstrated survival benefit.[161–163] Further studies are underway to determine the role of these therapies in sarcoidosis.

Cardiac Sarcoidosis

Several large case series find prognosis in cardiac sarcoidosis, and response to treatment is related to the degree of cardiac dysfunction. Treatment of cardiac sarcoidosis consists of antiarrhythmic therapy, diuretics, and afterload-reducing agents for specific cardiac abnormalities. Although randomized trials are lacking, studies from Asia, Europe, and the United States consistently report that corticosteroids in moderate doses are associated with improved cardiac function and outcomes.[164,165] Maintenance doses often range between prednisone 10 to 25 mg a day, although higher doses may be needed for intractable arrhythmias. Immunosuppressive drugs are frequently used as steroid-sparing agents since treatment often must be maintained for years. Automatic implantable

cardioverter-defibrillators (ICDs) may prevent sudden death in patients with serious arrhythmias; guidelines for prophylactic placement of ICDs or pacemakers have not yet been established.

Neurosarcoidosis and Ocular Sarcoidosis

High doses of oral corticosteroids or high-dose pulse intravenous therapy are often indicated for serious ocular or CNS disease, such as optic neuritis or encephalitis followed by maintenance corticosteroid or immunosuppressive therapy. Anterior uveitis can usually be treated with topical ophthalmologic steroid drops. Systemic immunosuppression may be necessary in cases of severe or recurrent disease, but aggressive treatment of neurosarcoidosis is generally associated with favorable outcomes.[166] Small fiber neuropathy typically does not reliably respond to corticosteroid therapy, prompting trials of neuropathic drugs, TNF-inhibitors or other novel agents.[167,168]

Pregnancy

Corticosteroids are the only drugs recommended for use during pregnancy because of the potential of other steroid-sparing drugs to cause fetal toxicity or teratogenicity. Sometimes, spontaneous abatement of chronic sarcoidosis occurs in pregnant patients, allowing a temporary reduction in steroid dosage. After pregnancy, however, an exacerbation often occurs, requiring a return to the original maintenance dose.

Quality of Life

There is increasing recognition of the need to treat depression and pain to improve quality of life in patients with these manifestations. The utility of nonpharmacologic treatments, such as exercise training or rehabilitation, merits investigation because of the impact of these problems in sarcoidosis patients.

Lung and Heart Transplantation

Successful lung, heart–lung, and heart transplantations have been performed in patients with advanced pulmonary sarcoidosis or cardiomyopathy. Although noncaseating granulomas have been found in some transplanted lungs or hearts, these findings do not appear to significantly affect outcome. Outcomes for lung transplant in sarcoidosis are similar to other interstitial lung diseases.[169–171]

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CHAPTER 56

Idiopathic Pulmonary Fibrosis

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OVERVIEW

In simplest terms, pulmonary fibrosis equates with the growth of "scar" in the lung. Scarred lung can assume any one of a variety of patterns; these patterns define unique pathologic phenotypes. When scar assumes a patchy distribution and appears to emanate from the pleural surface, it is recognized as the "usual" type—otherwise known as usual interstitial pneumonia (UIP). The disease in which UIP manifests without cause or trigger is called idiopathic pulmonary fibrosis (IPF). IPF is, therefore, a type of pulmonary fibrosis (also known as interstitial lung disease [ILD]). IPF is recognized by a unique compilation of clinical, radiographic, and pathologic features. IPF causes breathlessness, disability due to respiratory insufficiency and, in most instances, eventually leads to death.

While there are many causes of ILD, IPF is the most common form of ILD and certainly the most serious. IPF is characterized by an inexorable progression of interstitial pulmonary fibrosis that results in restrictive lung disease and worsening gas exchange. Death from respiratory failure is reported to ensue within 5 years of diagnosis in the majority of patients.

By definition, IPF is UIP in the absence of cause or explanation. It is equally important to remember what IPF is not. IPF is not pulmonary fibrosis from chronic aspiration, drug toxicities, environmental exposures (such as chronic hypersensitivity pneumonitis), and collagen vascular diseases, even if the pattern of fibrosis resembles UIP. Therefore, the diagnosis of IPF can only be made by excluding other possibilities. One of the major challenges in diagnosing IPF is the reasonable exclusion of other potential causes of pulmonary fibrosis. This requires a careful clinical and diagnostic evaluation; and often verges on areas of clinical uncertainty.

IPF typically comes to medical attention later in life, beginning in the sixth decade. IPF is rarely the cause of ILD in patients under the age of 40. The predominant presenting symptoms of IPF are exertional breathlessness and a dry, harassing cough. These are nonspecific complaints shared by a variety of pulmonary and cardiac diseases. In particular, exertional breathlessness is often attributed to advancing age by patients in their sixties and seventies, leading to delays in seeking medical evaluation. In addition, many patients are poorly conditioned and overweight and attribute their symptoms of breathlessness to these circumstances. In addition to nonspecific clinical symptoms, initial nonspecific radiographic findings also fail to trigger prompt medical evaluation. Fine peripheral linear radiographic opacities on plain chest radiographs, predominantly in the lower lung zones, may be interpreted as chronic and nonspecific pulmonary fibrosis, which often does not elicit an alarming response. Delay in diagnosis is therefore the norm. However, in recent years important scientific advances have improved the understanding of IPF pathogenesis; new therapeutic trials are under way and this has increased the enthusiasm for an early diagnosis of IPF.

HISTORICAL PERSPECTIVE

A brief review of the evolution in our understanding of IPF illustrates the contributions made by earlier investigators and account for much of the confusion that many clinicians have regarding IPF. One of the challenges in defining IPF has been the variety of antiquated terms formerly used to describe pulmonary fibrosis. While there are many causes of ILD in general, and pulmonary fibrosis in particular, it is important to note that IPF is a unique disease, although it had not been formally codified until recently when a group of expert pulmonologists, radiologists, and pathologists collaborated on a classification of ILD. Reviewing the history of IPF will both clarify the present terminology and distinguish contemporary nomenclature from the outmoded terms encountered in earlier literature.

Fibrosis of the lung was long recognized in association with infection or dust inhalation. In the 19th century, pulmonary fibrosis was known as "cirrhosis" of the lung. Yet little attention was paid to this form of respiratory illness.[1] Interest in pulmonary fibrosis was ignited in 1944 when Drs. Louis Hamman and Arnold Rich published a seminal paper describing "acute diffuse interstitial fibrosis of the lungs."[2] Hamman and Rich reported a series of unusual cases that shared a unique clinical presentation featuring idiopathic subacute respiratory failure followed by death. Their report was complete with pathologic findings from autopsy. They described thickening of the alveolar interstitium and areas of dense fibrotic scar tissue within the lung. This was the first pathologic depiction of pulmonary fibrosis and, to this day, is considered an accurate portrayal. In retrospect, the cases of Hamman and Rich best fit a diagnosis of the fibrosing interstitial pneumonia now known as acute interstitial pneumonitis (AIP).[3] Yet in the 1940s, the "Hamman–Rich syndrome" became synonymous with IPF. So it remained for the next three decades.

Over the years, clinical reports of pulmonary fibrosis suggested a number of alternate presentations that were referred to as "variants" of the Hamman–Rich syndrome.[4] This included cases that exhibited a rather protracted duration of illness compared to the "classic" Hamman and Rich cases. It was also noted that pulmonary fibrosis occurred in patients who suffered from the "rheumatoid group of collagen diseases." An assortment of abnormal patterns was noted under the microscope. Eventually, the breadth of the Hamman–Rich syndrome encompassed a heterogeneous mixture of clinical manifestations and a variety of histologic forms of pulmonary fibrosis with no distinction made between systemic and limited illness nor any concession to the prognostic implications of an acute versus chronic presentation.

In the 1960s authors began to regularly substitute the term "IPF" for "acute diffuse interstitial fibrosis."[5,6] A debate began concerning the chronicity of this disease, with some authors suggesting a slow course punctuated by "terminal complications,"[5] while others reported an average illness of no more than 2 years.[6]

The term "fibrosing alveolitis" was introduced in England in 1964.[7] Cryptogenic fibrosing alveolitis (CFA) became the preferred term for pulmonary fibrosis in the European literature and it is essentially synonymous with IPF. This term was originally meant to improve upon its predecessor by capturing pathologic features in a manner that was more precise and descriptive. CFA refers to the interalveolar location of the inflammation in pulmonary fibrosing as compared with the intra-alveolar inflammation of infectious pneumonia. This interalveolar septal inflammation was dubbed "alveolitis." It was maintained that alveolitis was responsible for the subsequent development of fibrosis and it was first suggested that corticosteroids be used to treat alveolitis and therefore pulmonary fibrosis.

The most important advance came in 1964 with the publication of an improved and safe technique for performing open lung biopsy.[8] With this procedure, it became possible to carry out a widespread analysis of lung tissue from patients with suspected

pulmonary fibrosis. Before long there were new insights into the pathology associated with fibrotic lung disease.

In 1969 Liebow and Carrington[9] heralded the modern era of ILD histopathology with the notion that idiopathic interstitial pneumonia (IIP) could be split into separate pathologic subtypes. They described distinct patterns of IIP that were identified by examination of lung biopsy specimens with light microscopy. Moreover, these subtypes were found to predict prognosis and response to treatment. Based on their research findings, Liebow and Carrington produced the first detailed histopathologic classification of IIP. They created five categories that were termed UIP, desquamative interstitial pneumonia (DIP), bronchiolitis obliterans interstitial pneumonia (BIP), lymphocytic interstitial pneumonitis (LIP), and giant cell interstitial pneumonia (GIP). More recent observations have led to a modification of this classification of IIP subtypes.[10,11] New categories have been added, such as respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) and nonspecific interstitial pneumonia (NSIP).[10,11]

Simultaneously, a revolution in thinking about the pathogenesis of IPF affected the way in which experts talked about the disease. Researchers at the National Heart, Lung, and Blood Institute (NHLBI) were major proponents of an "inflammatory theory" of pathogenesis as originally proposed by European investigators. This theory was based on studies at the NHLBI throughout the 1970s during which excessive amounts of inflammatory cells were identified in bronchoalveolar lavage (BAL) fluid obtained from IPF patients.[12] The NHLBI agreed with European researchers who had coined the term "alveolitis" and the NHLBI also endorsed corticosteroid treatments. The inflammatory theory has since fallen from favor, mostly as a consequence of corticosteroid inefficacy, and the term "alveolitis" has also fallen out of vogue.

A new hypothesis has replaced the "inflammatory theory" of IPF. This new concept proposes that IPF is the result of alveolar epithelial injury, which is then followed by aberrant repair mechanisms. This theory emerged from landmark ultrastructural studies performed in the mid-1980s.[13,14] Using electron microscopy, it was discovered that the alveolar epithelial cells were injured in IPF. In addition, foci of subepithelial fibrosis were first described. This concept of injury and repair was modified and expand on by subsequent investigators.[15]

In 1997 a modified version of Liebow's pathologic classifications were proposed.[16] The new classification scheme reinforced acceptance of certain categories within the context of an updated understanding of ILD pathogenesis. For instance DIP and UIP categories were retained in the new classification scheme. Some original categories were discarded and two modern categories were added. RB-ILD was recognized in the spectrum of smoking-related lung diseases and a provisional category, NSIP, was also added.[16,17] This modern pathologic classification became the basis for a consensus statement that finally standardized the nomenclature of ILD and IPF for the very first time.

In 2002 a panel of experts convened sponsored jointly by the American Thoracic Society and the European Respiratory Society.[18] This panel released an official statement for the purpose of providing a new and comprehensive classification of IIP that considered all clinical, radiographic, and pathologic features. The diseases recognized by the 2002 ATS/ERS classification of IIP are IPF, NSIP, cryptogenic organizing pneumonia (COP), acute interstitial pneumonia, RB-ILD, DIP, LIP. Further classification of IPF has been undertaken by joint consensus statements of the American Thoracic Society, and European Respiratory Society, in 2000 and 2010.[19,20] These statements attempt to offer strict definitions for each subtype of IIP with practical guidelines for diagnostic purposes. The benefit of attempting to utilize precise definitions is to provide a uniformity of diagnostic decisions in both clinical practice and in research.

Despite the utility of rigorously defining IIP (and IPF), there are several potential pitfalls. For instance, the current classification system relies upon an assumption that each specific IIP is a discrete clinical entity. There has never been validation of this assumption by careful phenotyping and prospective trials. In addition, these definitions are heavily reliant on surgical pathology, suggesting that pathology be considered the "gold standard"; however, evidence shows even expert pathologists can have difficulty agreeing on pathologic classification.[21] This continues to create confusion and difficulty in the diagnosis of IIPs and IPF. Hopefully continued refinement of consensus guidelines, greater expertise of clinicians and greater identification and use of genetic signatures/biomarkers will lead to more confident separation of the IIPs and a clear definition of IPF.

EPIDEMIOLOGY

Below are considered the incidence and prevalence of IPF, along with risk factors and associated familial and genetic factors.

INCIDENCE, PREVALENCE, AND VITAL STATISTICS

The epidemiology of IPF is difficult to determine and the available data are of limited value. It has been principally assessed by large population studies using death certificates and/or medical coding as the principle component for determination of disease. The main criticism of these studies is that surgical lung biopsy (SLB) was rarely performed or incorporated into the criteria used for analysis, although SLB remains the gold standard of diagnosis. In addition, many of these studies have not incorporated the up-to-date definition of the disease and use disparate methodologies to develop their assessments of the epidemiology of IPF.[22,23] The most recent update of the diagnostic criteria for IPF may help to clarify these difficulties but will also make it difficult to compare data over time. Early studies from Great Britain and from the United States suggest that IPF is widely underreported.[24,25] Though this is probably still the case heightened clinical awareness of the disease and the greater availability of high-resolution computed tomography (HRCT) appear to be changing the landscape; and this may explain recent studies that suggest an increasing incidence of the disease.[22]

The precise incidence and prevalence of IPF remains difficult to determine. However, there are several studies worth considering. Coultas et al.[26] utilized a population-based registry in which cases were determined using a combination of medical records, pathology reports, and death certificates. With this data, the prevalence/annual incidence was estimated at 20.2/10.7 cases per 100,000 males and 13.2/7.4 per 100,000 females.

Recent studies by two different groups have attempted to update and further define these estimations.[27,28] Both studies employed sensitivity analyses to examine the impact of diagnostic reliability; they examined the epidemiology of IPF using both narrow- and broad case definitions. Fernandez et al.[27] reported a prevalence of 27.9 per 100,000 people, using a narrow case definition, and 63.0 per 100,000 people using a broad case definition; similarly, annual incidence was estimated at 8.8/100,000 and 17.43/100,000 using the narrow and broad definitions respectively. Raghu et al.[28] relied on yet another North American database and reported a prevalence of 14.0 per 100,000 persons with their narrow definition and 42.7 per 100,000 persons with their broad case definition; annual incidence was reported as 6.8 and 16.3 per 100,000 persons for narrow and broad definitions respectively. It is important to point out that Fernandez et al. and Raghu et al. used different definitions of IPF in their separate studies, which likely accounts for some of the difference in the incidence and prevalence between the two studies. In European epidemiologic studies, there is even wider variation in case definition and reported incidence and prevalence; though some authors have claimed that IPF is more common in the United States than in Europe.[23]

Mortality data is equally difficult to determine, as data is scant and varies by country and race. Retrospective longitudinal studies have suggested that median survival is 2 to 3 years from time of diagnosis.[29–33] However, new information is coming from the placebo arms

of recent clinical trials. This data suggests that survival time may be greater than previously expected.[34–36] As a result of this emerging data, the actual mortality of IPF therefore remains without clear definition.

RISK FACTORS

IPF remains a disease without known pathogenesis, which makes the definition of risk factors problematic. Despite this shortcoming, a few case-control observational studies have identified potential risk factors that include age, gender, smoking status, environmental exposures, gastroesophageal reflux, and viral infections. The identification of these risk factors remains just associations as research identifying causality is either ongoing or inconclusive. Despite the lack of clear causality these risk factors can help to identify patients who have higher risk of developing IPF.

Age/Gender

The incidence of IPF undoubtedly increases with age and appears to have a higher predilection for men. Patients with IPF are usually between 40 and 70 years old. Two-thirds of IPF cases present in patients over the age of 60 years, with a mean age of 66 years at the time of diagnosis.[19] IPF occurs infrequently amongst those younger than 40 years and rarely affects children, if at all. Several studies stratified the incidence and prevalence of IPF by age.[26–28,37,38] Amongst adults aged 35 to 44 years the prevalence was 2.7 cases per 100,000 persons. In contrast, the prevalence for individuals older than 75 years was greater than 175 cases per 100,000.[26] Other studies in both USA and Europe have demonstrated similar findings.[23] In addition, there appears to be a higher incidence and prevalence of IPF in males than in females with the notable exception of a study in Norway, which identified a higher incidence and prevalence in females.[37]

Smoking

Another risk factor that emerges from case-control studies is a history of cigarette smoking. The prevalence of tobacco use in patients with IPF is high, ranging from 41% to 83%.[19,39] A meta-analysis of five case-control studies demonstrated that IPF patients were significantly more likely to report a history of smoking than controls with an odds ratio of 1.58 (95% CI 1.27–1.97).[40] There may even be a dose–response relationship. Baumgartner et al.[41] reported that IPF patients with a greater than 21-pack-year smoking history had an odds ratio of 2.26 (95% CI = 1.3–2.8) compared to individuals with less than a 20-pack-year history. This finding was corroborated in a subsequent study.[42] Despite the association, a mechanistic link between smoking and IPF remains undefined.[43]

Environmental Exposures

A number of papers have implicated environmental exposures to such particulate materials as metal and wood dusts.[20] In a related finding, an increased incidence of IPF was noted in industrial centers of the southeastern United States and central regions of the United Kingdom.[44] There is also an association between farming and risk of IPF.[40] A specific association exists between exposure to livestock and the risk of developing IPF though this seems to be strongest at exposures greater than 5 years.[45] At this point these types of risk factors are only associations as the causative link to environmental exposures remains undefined.

Viral Infections

Several articles have implicated a variety of viruses such as the Epstein–Barr virus, influenza virus, cytomegalovirus, and hepatitis C.[46–48] All are found with higher incidence amongst patients with IPF. The best studies are of herpes viruses (including EBV, CMV, human herpes virus 7 and 8). Tang et al.[49] identified DNA from herpes virus in 33 patients with IPF. Herpes virus antigens have also been detected by immunohistochemistry in type II alveolar epithelial cells from IPF patients but were not seen in cells from patients with normal lungs.[49–51] The significance of these findings remains unclear because there is still no evidence to support a pathogenic mechanism for IPF involving viruses. Interestingly, new animal models have shown a role for viral infection in the development of experimental fibrosis.[52,53] Despite the suggestive evidence of virus in human IPF cells and potential mechanistic links from animal modeling, direct causal links to human disease remain undefined.

FAMILIAL AND GENETIC FACTORS

Familial cases of IPF have been described in dozens of reports. The clinical features of familial IPF are indistinguishable from those of the nonfamilial form, except that the familial form may have an earlier age of onset.[54] Familial IPF or familial interstitial pneumonia (FIP) is defined by at least two members of a primary biologic family (parent, child, siblings) presenting with a characteristic appearance of IPF that is confirmed by biopsy. Familial IPF seems to account for 0.5% to 2% of all cases of IPF.[55]

In 2000, a report was published describing 25 families and comprising 67 cases of familial IPF.[55] In this report the mean age at time of diagnosis was 56 years. Only half of the patients were smokers. The male-to-female ratio was 2:1 in contrast to earlier reviews of FIP, which suggested an inverted male-to-female ratio. This was followed by a larger study of FIP published in 2005.[56] This impressive report described a much larger cohort of 111 families with 309 affected family members. Most of these subjects were identified as having probable or definite IPF by the American Thoracic Society/European Respiratory Society diagnostic criteria. Interestingly, correlation with biopsy specimens suggested that FIP could present with a variety of pathologic patterns (other than UIP), even within the same family. This study revealed a mean age at diagnosis of 68.3 years, with a slight male predominance (55%) and an increased association with cigarette smoking (even after controlling for age and gender differences). Analysis of pedigrees confirmed vertical transmission and provided strong evidence for an autosomal dominant inheritance pattern of disease with variable penetrance.

These accounts of FIP provide compelling evidence for genetic factors that predispose to the development of IPF. One such factor is a mutation in the gene that encodes surfactant protein C (SPC) gene.[57] Other studies have implicated mutations in the gene for surfactant protein A; and mutations in the genes that encode telomerase reverse transcriptase and the telomerase RNA template.[58,59] By leveraging genomic linkage, investigators have recently described a common polymorphism in the promoter of MUC5B, which is associated with both FIP and sporadic IPF.[60] This was followed by a large genome-wide association study of patients with IIPs, which identified additional genetic loci suggesting potential genetic markers of disease.[61] This data is opening up insights into potential genetic pathways of this disease and confirms a generally understood concept that there is a combination of genetic factors and environmental exposures, which account for the significant disease heterogeneity observed in individual patients. While these studies provide useful insights they do not define a direct causal link at present. Several candidate genes have been selected, because of their bearing on proposed mechanisms of the disease, and these genes are currently under investigation.

CLINICAL PRESENTATION

In this section, we discuss important aspects of the clinical presentation of IPF.

DIAGNOSIS

Differential

In the setting of exertional breathlessness, the hallmark of IPF is a predominance of radiographically visualized lower lung zone reticular opacities that spread out over time to involve an ever

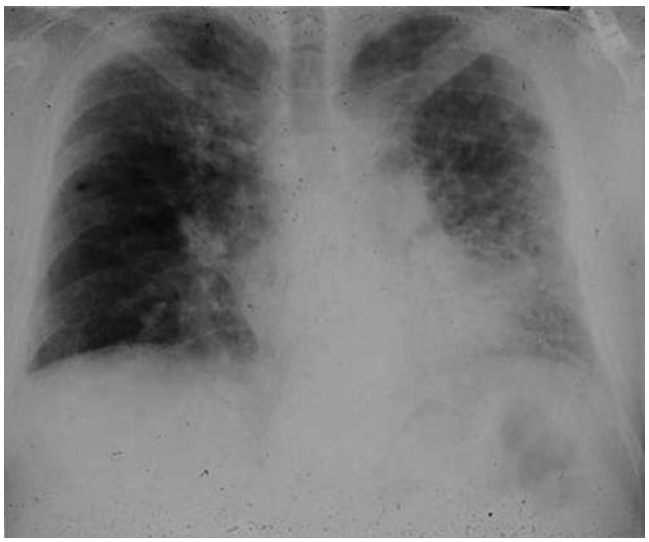


Figure 56-1 Posteroanterior chest radiograph of a 67-year-old man with progressive dyspnea revealing bilateral reticular infiltrates with lower lobe predominance.

enlarging area of lung parenchyma (Fig. 56-1). The differential diagnosis of IPF includes the other IIP, connective tissue diseases (principally scleroderma and rheumatoid arthritis), chronic hypersensitivity pneumonitis, environmental exposures, occupational exposures, chronic aspiration, and heritable conditions such as the Hermansky–Pudlak syndrome. The aforementioned disorders all present with exertional dyspnea coupled with radiographic abnormalities indicative of an interstitial pulmonary disorder.

HRCT has emerged as the single most important diagnostic modality in ILD. A number of diseases share a radiographic pattern that is similar to IPF, in other words, reticular abnormalities are demonstrated by HRCT with a tendency to involve the lower lobes. Examples include asbestosis, chronic aspiration, radiation pneumonitis, chronic hypersensitivity pneumonitis, end-stage sarcoidosis, and congenital disorders such as Gaucher disease, Niemann–Pick disease, and tuberous sclerosis–lymphangioleiomyomatosis. The presence of extensive ground-glass opacities on HRCT should prompt the consideration of an alternative diagnosis such as DIP, cellular NSIP, or acute hypersensitivity pneumonitis. Other IIP that are included in the differential diagnosis of IPF are fibrotic NSIP and COP.

History

Patients with IPF typically present with exertional dyspnea and a nonproductive cough. The dyspnea begins insidiously and is usually progressive. Dyspnea is the most prominent symptom in IPF. Associated systemic symptoms can occur but are not common. Systemic symptoms may include weight loss, low-grade fevers, fatigue, arthralgias, or myalgias.

Patients will often have symptoms for longer than 6 months before seeking medical attention. It is not unusual for symptoms to be present for up to 2 years before an initial consultation is arranged with a pulmonary specialist. Patients are frequently evaluated and treated for other ailments, such as asthma or heart failure, before IPF is identified as the final diagnosis. Because most patients present over the age of 60 where coronary artery disease is highly prevalent, many patients are referred for a cardiac evaluation before pursuing a pulmonary evaluation.

The patient's age is an essential clue to the recognition of IPF. While IPF mostly occurs in older patients (>50 years), the other ILDs are more common among the young or middle-aged (examples include sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis).

A history of cigarette smoking is a vital piece of information. While IPF, DIP, and PLCH are diseases found in former and current smokers, other diseases such as hypersensitivity pneumonitis are rare among the smoking population.

It is critical to obtain a detailed occupational history with particular attention to exposures such as asbestos, silica, or any other respiratory toxins. This history is necessary to exclude the presence of pneumoconiosis. It is equally important to inquire about exposure to molds and/or pets in the home environment as this information may suggest a diagnosis of hypersensitivity pneumonitis.

A general health history, including an accounting of all medications, can be revealing. A review of systems may uncover photosensitivity, Raynaud phenomenon, dry eyes, or dry mouth that implies a connective tissue disorder. Certain drugs have been associated with pulmonary fibrosis, most notably nitrofurantoin, bleomycin, and amiodarone.

Physical Examination

In most patients the physical examination reveals fine, bibasilar inspiratory crackles, known as "Velcro rales." As the disease progresses, rales can extend toward the upper lung zones. Clubbing is found in up to 50% of patients with IPF. Resting arterial oxygen saturation may be normal but desaturation is expected with exercise. Extrapulmonary involvement does not occur in IPF. Thus the physical examination is otherwise unremarkable in the early stages of the disease.

Later in the course of disease weight loss, cyanosis, and signs of pulmonary hypertension with cor pulmonale may become apparent. Findings at this stage include an accentuated pulmonic second heart sound, presence of a third heart sound, a right ventricular heave, and edema of the lower extremities.

Routine Laboratories

A routine laboratory evaluation is not helpful except for its role in ruling out other causes of diffuse parenchymal lung disease. Polycythemia is a rare finding despite the frequency of chronic hypoxemia. Elevation of systemic inflammatory markers (i.e., erythrocyte sedimentation rate or C-reactive protein level) or the presence of hypergammaglobulinemia is found in IPF yet such findings are nondiagnostic. The lactate dehydrogenase activity is often elevated but is also nonspecific. Up to 30% of patients with IPF may have positive tests for antinuclear antibodies or rheumatoid factor. These titers are not generally high. The presence of a high titer of autoantibodies suggests connective tissue disease while an elevated angiotensin-converting enzyme level or antineutrophil cytoplasmic antibodies indicates alternative diagnoses.

■ PULMONARY FUNCTION AND PHYSIOLOGY

Pulmonary function tests in IPF normally identify a restrictive ventilatory defect with reductions of total lung capacity (TLC), functional residual capacity (FRC), and the residual volume (RV). These changes are the result of diminished lung compliance. Pressure–volume studies will yield a curve that is shifted downward and to the right, indicative of lost lung compliance. As the disease progresses, compliance decreases further. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) will also be decreased.

Unless a complicating airways disease is present (e.g., chronic obstructive pulmonary disease [COPD]), isovolume flow rates are preserved. While functional alterations associated with small airways disease have been reported in IPF, this description is exclusive to smokers and likely represents a concurrent smoking-related airways disorder.[62]

Impaired gas exchange is demonstrated by the measurement of a lowered diffusing capacity. The decline of diffusion capacity may even precede the development of abnormal lung volumes. Resting arterial blood gases are usually normal in IPF or else they will reveal mild hypoxemia with a respiratory alkalosis. Patients with

IPF have tachypnea and often develop a pattern of rapid-shallow breathing. The work of breathing is increased in IPF. While no chemical changes can explain the observed hyperventilation, it is felt that rapid respiratory rates are secondary to altered mechanical reflexes resulting from an increase in elastic recoil and elastic load. The major cause of hypoxemia is ventilation and perfusion (V/Q) mismatching, not anatomic shunting or reduced oxygen diffusion as was previously suspected.[62]

During exercise, patients with IPF and may exhibit evidence of pulmonary hypertension, even in early cases that have preserved lung function at rest. Pulmonary hypertension can also be present at rest, and is an expected finding, once the vital capacity drops below 50% of predicted or the diffusing capacity falls below 45% of predicted. The presence of pulmonary hypertension may be a predictor of poor outcome yet may not correlate with lung function.[63]

RADIOLOGY

Conventional Chest Radiograph

The chest radiograph is abnormal in nearly all patients with IPF (Fig. 56-1). Yet, in up to 10% of patients with histologically proven IPF, the chest film might be normal. In most of these cases, the use of HRCT will uncover evidence of the disease.[20]

The most common abnormalities seen on a conventional chest film are reticular opacities. In other words there is an appearance of net-like linear and curvilinear densities. Reticular markings may be found bilaterally, in an asymmetrical distribution with a predilection for the lower lobes. A course reticular pattern on the plain radiograph, taking the form of translucent "honeycombing," will emerge late in the course of disease and portends a poor prognosis. The chest radiograph lacks specificity for the diagnosis of IPF. The correct diagnosis is made on the conventional radiograph in less than 50% of cases. In addition, the interpretation of conventional radiographs with an interstitial pattern shows poor interobserver agreement. Studies have examined this particular characteristic and report that concordance between radiologists is only 70%.[64,65]

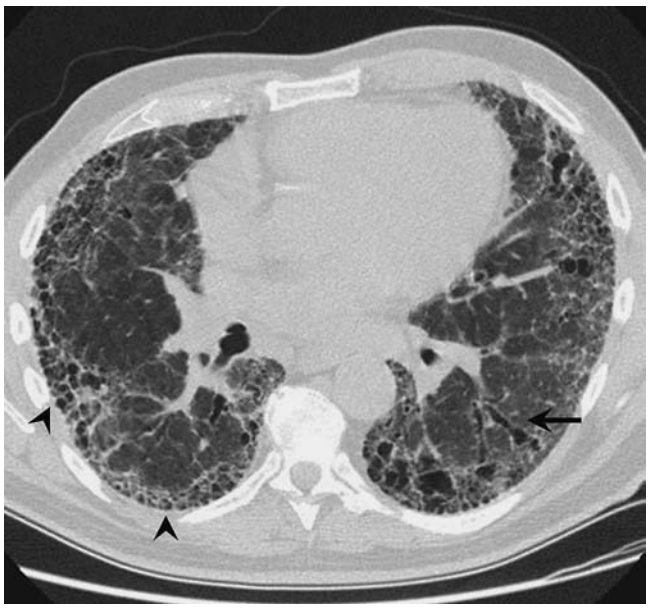


Figure 56-2 Computed tomography scan illustrates the "classic" features of idiopathic pulmonary fibrosis (IPF). Bilateral, peripheral, and subpleural reticular infiltrates are evident. The presence of advanced fibrosis is indicated by honeycomb changes *(arrowheads)* and traction bronchiectasis *(arrow)*. These features permit experienced clinicians to make a confident radiographic diagnosis of IPF.

High-Resolution Computed Tomography

Development of the high-resolution CT scanner has revolutionized the diagnostic evaluation of the ILDs. HRCT allows a detailed examination of the lung parenchyma by creating 1- to 2-mm thin slices of the chest. HRCT uses a computerized reconstruction algorithm to maximize spatial resolution. This generates much improved image clarity such that the specificity of interpretations is increased, interobserver variability is reduced, and the overall accuracy of diagnosis is enhanced. HRCT scanning allows for the earlier diagnosis of IPF and permits the identification of alternate patterns of disease. The primary role of HRCT in the diagnostic evaluation of ILD is the discrimination of typical IPF from the other ILDs. Given the utility and availability of scanners, HRCT has become the primary diagnostic tool for identifying IPF.

The HRCT appearance of IPF is characterized by patchy, predominantly peripheral, predominantly subpleural, and bibasilar reticular opacities (Fig. 56-2). Ground-glass opacities can be found, but should occupy no more than a limited amount of territory. Areas that are severely involved with reticular markings may also demonstrate traction bronchiectasis. The presence of subpleural honeycombing (small, round translucencies with a density equal to that of air), traction bronchiectasis, and thickened interlobular septae will increase the specificity of the CT scan for diagnosing IPF. Several studies have examined the diagnostic accuracy of HRCT scans in IPF.[64–68] Studies were conducted in which observers were asked to determine a radiographic diagnosis that was then compared with the histopathology of UIP as the "gold standard." In the hands of experienced observers, radiographic diagnosis of IPF has a reported specificity and positive predictive value for IPF histology that exceeds 90%.[66–68] However, the "confident" HRCT is not a sensitive tool for the diagnosis of IPF.[66] The full spectrum of a "confident" radiographic pattern will only be seen in two-thirds of biopsy-proven IPF. One-third of IPF cases will not show a definitive CT pattern and would be missed if the HRCT was relied upon exclusively (Fig. 56-3). In such cases, and in the right clinical context, an SLB should be considered to clarify the diagnosis. Nonetheless it has become apparent that, in the right clinical setting, an experienced radiologist can diagnose IPF by the HRCT with considerable accuracy, obviating the need for biopsy.

Given the evolving importance of HRCT in the diagnosis of IPF, CT scan criteria were defined during the most recent expert consensus statement on the diagnosis of IPF.[20] HRCT patterns were

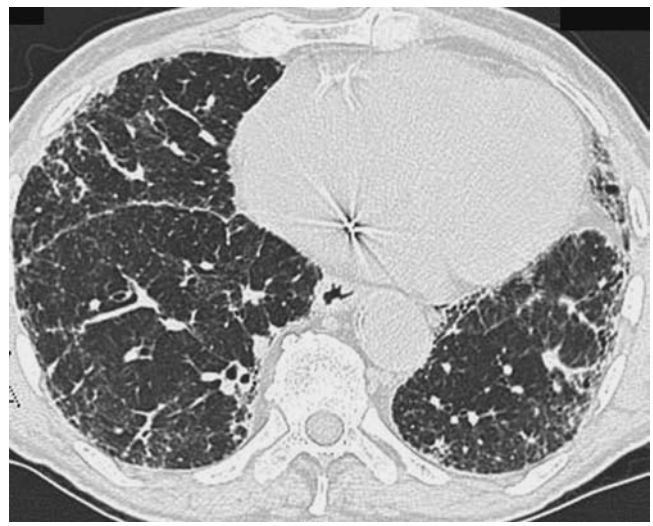


Figure 56-3 Computed tomography scan of an 81-year-old man with biopsy-proven idiopathic pulmonary fibrosis. A peripheral distribution of reticular opacities is demonstrated. Honeycombing and traction bronchiectasis are notably absent. In the absence of specific findings, a surgical lung biopsy was needed to make a diagnosis.

separated into three groups: A UIP pattern; a possible UIP pattern; and a pattern labeled "inconsistent with UIP." The UIP pattern has four features: (1) Subpleural, basal predominance of disease; (2) reticular abnormality; (3) honeycombing with or without traction bronchiectasis; and (4) absence of any inconsistent features. The inconsistent features include (1) upper or midlung predominance; (2) peribronchovascular predominance; (3) extensive ground-glass abnormalities that are greater than the amount of reticulation; (4) profuse micronodules; (5) multiple discrete cysts that are located away from areas of honeycombing; (6) diffuse mosaic attenuation/air trapping; and (7) consolidation in bronchopulmonary segments.[20] Features defined as consistent with a "possible UIP pattern" were those of the UIP pattern except without evidence of honeycombing.

BRONCHOALVEOLAR LAVAGE

An enormous amount of scientific information has been obtained by analyzing the content of BAL fluid from patients with IPF. Notable increases of immune cells (neutrophils, eosinophils, and activated alveolar macrophages) are present in BAL fluid from IPF. In addition, BAL has aided in the identification of cytokines, growth factors, and other cellular products that are now implicated in the pathogenesis of IPF. As a research tool, BAL has been immensely valuable. However, the role of BAL in the clinical diagnosis of IPF remains limited. Though much effort has been invested in evaluating the clinical utility of this modality, study results have been contradictory and generally disappointing.[69] Most samples of BAL from IPF patients demonstrate simultaneous increases of several effector cell types including neutrophils (70%–90% of patients); eosinophils (40%–60% of patients); and lymphocytes (10%–20% of patients).[20] Despite this finding, studies have failed to demonstrate a clear distinction amongst pulmonary diseases based upon the predominant type of cell in the BAL fluid.[62] As a consequence of this, in standard practice, BAL is no longer generally recommended for the routine evaluation of IPF.

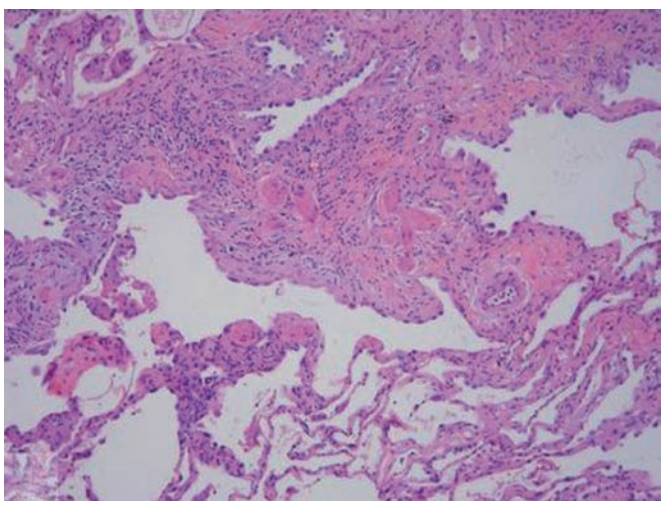
PATHOLOGY

Previously, SLB was recommended to confirm all cases of suspected IPF. With the advent and availability of HRCT this is no longer the case, as the positive predictive value of HRCT is comparable and in some studies better than that of biopsy.[70] Despite this fact, SLB remains critical to the diagnosis of IPF in the context of HRCT scans that are equivocal (e.g., without the full complement of radiographic features that are expected in IPF). Biopsy may be achieved by either open thoracotomy or by video-assisted thoracoscopy (VATS). VATS is preferred as it has been associated with less morbidity and shorter hospital stays compared to open biopsy. An SLB provides the best sample from which to distinguish UIP from other forms of IIP. The recommendation is that the SLB be taken from at least two lobes, preferably the upper and lower lobes. The basis of this recommendation is from studies that identified that different pathologies could exist in different sections of the lung. Despite the coexisting patterns, if one of these had UIP pathology then the patient's clinical course followed that of the UIP pathology.[71] Transbronchial biopsies are less helpful in identifying IPF lesions because the small size of the sample prohibits the pathologist from identifying all the necessary features for a confident pathologic diagnosis of IPF.

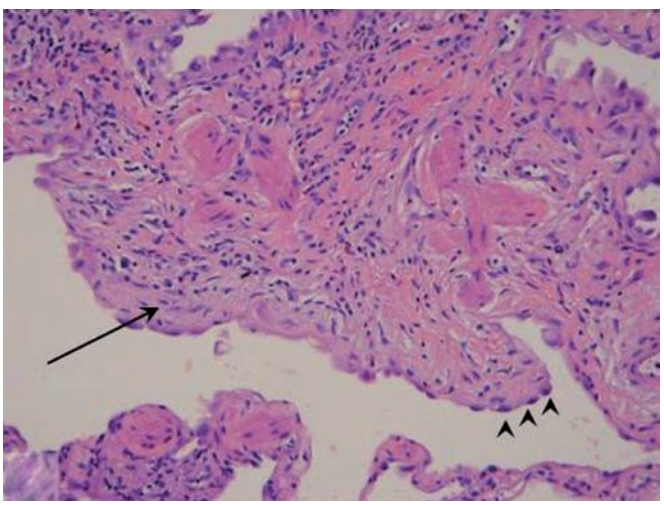
The gross appearance of an IPF sample may be normal but often has a distinctive nodular pleural surface that has been likened to cirrhosis. The histopathologic lesion associated with IPF is UIP. This lesion is defined by a variegated structure. Normal lung alternates with patchy collagen fibrosis (Figs. 56-4 and 56-5). The fibrosis takes the form of alveolar septal thickening with a predominantly subpleural distribution. Whirls of fibroblasts embedded in a loose extracellular matrix embody the fibroblastic foci that are found in numerous quantities at the leading edge of dense scar (Figs. 56-4 and 56-5). Interstitial inflammation is present but remains scant and confined to areas of fibrosis. This limited inflammation consists of lymphocytes and plasma cells. Associated hyperplasia of the type 2 pneumocytes is found within areas of active inflammation. Areas that contain dense collagen may develop cystic structures, which may be filled with mucin or lined by bronchiolar epithelium. These cysts are referred to as microscopic honeycomb change. Hyaline membranes and organized alveolar exudates are absent. Occasionally alveolar macrophages are present.

The UIP pathologic pattern exhibits a wide range of severity with regards to the extent of honeycomb change and the extent of involved lung. A history of smoking may alter the histopathologic appearance of UIP. Emphysematous change can be superimposed upon UIP. Pigmented alveolar macrophages, the hallmark feature of RB-ILD and DIP pathologic patterns, may be present in small number in UIP lesions from former or current smokers.

The UIP pattern can be found in other diseases besides IPF. The presence of granulomas in a UIP lesion favors a diagnosis of fibronodular sarcoidosis or chronic hypersensitivity pneumonitis. Asbestos bodies found within a UIP pattern suggest the diagnosis of asbestosis.



A



B

Figure 56-4 **A.** Low-magnification photomicrograph of usual interstitial pneumonia (UIP) showing the characteristic heterogeneous involvement of the parenchyma. Zones of interstitial fibrosis are seen alternating with areas of normal lung. **B.** Higher magnification demonstrates enlarged cystic air spaces lined with hyperplastic alveolar epithelium *(arrowheads)*. Beneath the mucosal layer is an advancing region of young fibrosis containing loose extracellular matrix *(pale pink staining)* and fibroblasts *(arrow)*.

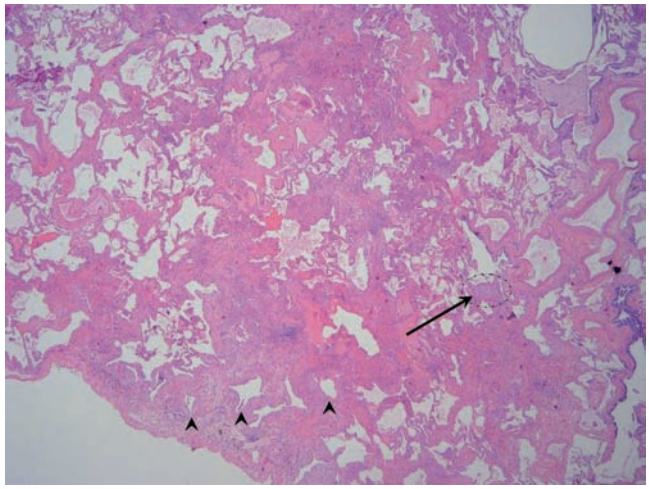


Figure 56-5 Scanning view of usual interstitial pneumonia (UIP) demonstrates the characteristic variegated appearance of UIP. Note the honeycomb change *(arrowheads)* present in the region of dense fibrosis adjacent to the pleural surface. A fibroblast focus *(arrow)* is seen at the leading edge of advancing fibrosis.

The histopathologic pattern of UIP can also be found in several conditions other than IPF. UIP can be found in association with connective tissue diseases, asbestosis, chronic hypersensitivity pneumonitis, the Hermansky–Pudlak syndrome, neurofibromatosis, or in the setting of a toxic drug reaction (typically after administration of either bleomycin, methotrexate, nitrofurantoin, or amiodarone; [this is a partial list]). The identification of these conditions is largely a matter of correlation with the clinical history. It is important to note that the presence of honeycombing on biopsy is a nonspecific finding with a broad differential. Honeycombing is a common endpoint for a myriad of pathologic processes. Although honeycombing carries the connotation of end-stage fibrosis it can also occur in a focal distribution after any lung injury. Seen alone, honeycombing is not indicative of IPF.

To standardize the pathologic definition of UIP, a set of consensus criteria were established to represent expert opinion.[20] The consensus definition allows for four pathologic categories: The UIP pattern; a probable UIP pattern; a possible UIP pattern; and a pattern referred to as "not UIP." The UIP pattern requires (1) evidence of marked fibrosis/architectural distortion generally with honeycombing in a predominant subpleural distribution; (2) patchy involvement of the fibrosis in the lung parenchyma; (3) presence of fibroblastic foci; and (4) absence of features such as hyaline membranes, organizing pneumonia, granulomas, predominant airway-centered pathology, inflammatory cell infiltrate away from honeycombing or pathologic features suggestive of another disorder. The "probable" UIP pattern requires (1) evidence of marked fibrosis/architectural distortion with or without honeycombing; (2) absence of either patchy involvement or fibroblastic foci but not both; plus (3) an absence of features such as hyaline membranes, organizing pneumonia, granulomas, etc. In the right clinical context, "probable" UIP can be considered when honeycomb changes alone are present in the SLB. The "possible" UIP pattern incorporates (1) patchy or diffuse fibrosis within the pulmonary parenchyma; (2) in the absence of other criteria for a UIP pattern; and (3) in the absence of the features such as hyaline membranes, etc.

DIAGNOSTIC ALGORITHM

The objective is to secure an accurate diagnosis of IPF. The task is critical, to provide patients with accurate prognostic information; and, also to define cohorts for clinical/therapeutic trials. As previously discussed, the central issue is that the diagnosis of IPF is a diagnosis of exclusion. However, complete exclusion of other diagnostic possibilities is a daunting challenge. For one, there are multiple studies demonstrating significant interobserver disagreement between pulmonologists, radiologists, and pathologists especially when their decisions are made in isolation from each other's expertise.[21,72,73] By corollary, a multidisciplinary approach to diagnosis has been shown to improve diagnostic accuracy. The multidisciplinary approach requires real-time collaboration between the diagnosing physicians: The pulmonologists, radiologists, and pathologists involved with the case. If these groups are not available, then referral of patients to a center where this expertise is available is recommended.[20]

Given the complexity of making an accurate diagnosis, and the lack of definitive molecular biomarkers to aid such a diagnosis, practical diagnostic algorithms have relied on the practices and opinions of a consensus of experts. It must be noted that such diagnostic criteria (adopted from expert opinion) have never been validated. The most recent expert diagnostic guideline was endorsed by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT).[20] In the revised 2011 guidelines, SLB is no longer considered an absolute necessity for a definitive diagnosis. Rather, HRCT may qualify as a surrogate in appropriate circumstances. As per the ATS/ERS/JRS/ALAT statement, the diagnosis of IPF requires (1) exclusion of other known causes of ILD; and (2) either (a) UIP pattern from SLB, supported by a UIP pattern of fibrosis on HRCT; or (b) UIP pattern by HRCT alone (in patients not subjected to an SLB).[20] In clinical practice, the most critical (yet most challenging) factor is to exclude other known causes of ILD. This requires a careful history, physical examination, and evaluation with a focus on environmental/work place exposures; medication use; family history; clinical evidence connective tissue disease (oftentimes, the evidence is subtle); and other comorbidities.

A diagnostic algorithm follows: Patients with suspected IPF in whom there are no identifiable causes of ILD will undergo HRCT scans of the chest; if there is definitive evidence of a UIP pattern on the HRCT, then the diagnosis is complete. If the HRCT pattern is equivocal, SLB can be considered to clarify the diagnosis. Prior to SLB, the safety of such an invasive procedure must be weighed against the utility of a definitive diagnosis (in other words, a careful risk–benefit analysis is indicated). Expert consultation with a multidisciplinary group of ILD experts is recommended in this setting. A UIP or probable UIP pattern on biopsy was felt to confirm the diagnosis of IPF in the setting of a HRCT pattern, which is defined as a possible UIP pattern. An HRCT possible UIP pattern in the setting of a not UIP pathology pattern was defined as not IPF. In this algorithm, if the HRCT scan was inconsistent with UIP, and the pathology was a UIP pattern then this was determined to be possible IPF. Per the algorithm, these types of cases require a multidisciplinary discussion to resolve any potential inconsistencies and come to a consensus diagnosis.

Although this algorithm provides a clear path toward the diagnosis of IPF several caveats must be considered. This algorithm is based on experience and expert opinion; it has never been validated in prospective studies. It also requires a high level of expertise (to define the radiographic, clinical, and pathologic evidence) that may not be available in all clinical settings. Such diagnostic algorithms and diagnostic criteria are best suited to defining populations for clinical research. A much more elegant and streamlined approach is needed for standard clinical practice. As of yet, this state of art is lacking.

NATURAL HISTORY AND PROGNOSIS

The natural history of IPF has never been fully defined. IPF is felt to be a progressive disorder of subjective and objective decline in pulmonary function ultimately resulting in death. The exact length of time from diagnosis to mortality has been difficult to clearly define. Studies utilizing the modern definition of IPF first reported median survival between 2 and 5 years from the time of diagnosis.[29] Recent data from the placebo arms of clinical trials suggest longer survival.[34,36] There

are few, if any, reports of long-term survival with biopsy-proven IPF/UIP.

Several factors have combined to create barriers preventing the further, more rigorous description of the natural history of IPF. First, the diagnosis of IPF can be challenging and, not infrequently, the presence of "early" disease gets overlooked. Patients develop IPF in the later decades of life and often attribute their symptoms to old age. When their disease eventually comes to medical attention, there may be further delay in diagnosis because the symptoms are nonspecific. Most patients with IPF are evaluated for other diseases before a diagnosis of pulmonary fibrosis is considered. Moreover, the interstitial markings found on a chest radiograph are subtle and tend to go unnoticed or else simply get disregarded as clinically unimportant. Experts in IPF agree that patients usually have symptoms for 2 or more years before receiving a definitive diagnosis. It is therefore apparent as to why many older cohorts are enriched with advanced, late-stage IPF. The epidemiology is shifting with the advent and more commonplace use of HRCT, which may detect interstitial markings and pick up the diagnosis of IPF at an earlier stage.

The other major issue is that there is clear heterogeneity in the clinical course of individual patients. This heterogeneity has led to the consideration that there are several possible natural histories of IPF.[20] This determination is the result of observations that have occurred over clinical trials especially in circumstances that placebo groups have had different clinical trajectories despite similar clinical definition of disease. The majority of patients appear to follow a slowly progressive clinical course, though others appear to have a more rapid course. Selman et al.[74] described different clinical groups based on the length of symptoms prior to diagnosis. The patients who had symptoms <6 months (rapid progression) prior to diagnosis had higher mortality than those who had symptoms for more than 24 months (slow progression). In the "rapid progression" patients there were associated alterations to their gene expression profile, as well as increased BAL active matrix metalloproteinase-9 and fibroblast migration. What influences these different clinical courses is not well known or understood.

■ ACUTE EXACERBATION OF IPF

Japanese investigators made the initial observation that patients with IPF can experience episodes of sudden decline, which they characterized as acute exacerbations.[75] Recent observations from the placebo arm of two randomized clinical trials have suggested that acute exacerbations may be more common that previously appreciated.[33,76,77] The acute exacerbation of IPF (AE-IPF) is characterized by a sudden worsening of symptoms and has been associated with hypoxemia and new radiographic infiltrates. It is important in making the diagnosis of AE-IPF to rule out infection, congestive heart failure, and pulmonary embolism. AE-IPF typically occurs in patients with established IPF however it has been recognized that AE-IPF can form the initial presentation of IPF as well, mimicking AIP. Patients with established IPF satisfy the criteria for an acute exacerbation if they have (1) previous or concurrent diagnosis of IPF; (2) unexplained development or worsening of dyspnea in the past 30 days; (3) HRCT with evidence of new ground-glass opacities superimposed on the background of a radiographic pattern of UIP; (4) no evidence of pulmonary infection; and (5) exclusion of alternative causes.[76] Histopathologic examination of AE-IPF commonly reveals a UIP pattern with superimposed diffuse alveolar damage (DAD) characterized by diffuse alveolar septal thickening within a pale matrix that includes hyaline membranes and fibrin. UIP with superimposed organizing pneumonia has also been reported in AE-IPF. The prognosis of AE-IPF is poor. Series of patients with AE-IPF reported in-hospital mortality rates between 78% and 96%.[77–80] Mortality is strongly associated with the need for mechanical ventilation. The etiology of AE-IPF is poorly understood and remains an area of active research.

■ PROGNOSIS

While accurate predictions of the prognosis of IPF are essential for clinical decision making, such predictions remain challenging for a variety of reasons. Still, rudimentary predictions can be based on pathologic, physiologic, and radiographic information. In addition, various composite scores have been developed for prognostic purposes.

■ PATHOLOGIC PREDICTORS

One of the most important features of the spectrum of illness encompassed by IIP is the fact that pathologic patterns predict survival. In the late 1990s it was recognized that the UIP pathologic pattern had a precise correlation with clinical parameters and with outcome.[17] Survival is significantly worse amongst patients whose biopsy contains a UIP pattern as compared to either NSIP or other patterns of fibrosis.[29] Within biopsy specimens, specific traits have also been correlated with survival.[33] The degree of cellularity does not seem to affect survival nor does the degree of fibrosis. However, the number of fibroblastic foci has been shown to predict survival. Fibroblastic foci have been linked to high mortality and large declines in physiologic measures such as the FVC and diffusion capacity.[81]

■ PHYSIOLOGIC PREDICTORS

Baseline pulmonary function as a determinant of prognosis has not been reproducible,[82–90] though more recent studies utilizing standardized definitions and involving patients with earlier disease suggest that it may have better prognostic value than initially appreciated.[91–93] Changes in pulmonary function over time have been more clearly correlated with measures of long-term survival. For instance, a 10% decline in FVC over 6 months, or a 15% decline in D_{LCO} over 6 months, predicts shortened survival.[91,94] For this reason, clinical trials in IPF have utilized changes in FVC as a clinical outcome measure to assess drug efficacy,[95] though some disagreement exists on this issue.[96] In clinical practice, at the present time, the use of decrements in pulmonary function remains an important objective means of assessing clinical disease progression.

An issue that affects the predictive value of physiologic variables in IPF is the confounding influence of coexistent emphysema. This problem is addressed by the composite physiologic index (CPI), which corrects for emphysema by combining several physiologic measures into a single-weighted score.[97] The formula for the CPI includes diffusion capacity, FVC, and FEV_1 in its calculations. The CPI was validated by comparison with HRCT. In addition, it was shown that the CPI is a more accurate prognostic determinant than any individual test of pulmonary function.

■ RADIOGRAPHIC PREDICTORS

The utility of HRCT in predicting the outcome of IPF is supported by a study, which compares HRCT patterns to biopsy.[98] Patients who had both an HRCT and a biopsy were analyzed and it was found that an HRCT pattern consistent with UIP correlated pathologically with the UIP pattern. However, an indeterminate HRCT pattern could be a manifestation of either UIP or NSIP. Patients with combined pathologic UIP and radiographic "confident UIP" had a worse outcome compared to patients with pathologic UIP and an indeterminate HRCT.

■ COMPOSITE SCORES

Some authors have proposed that a composite scoring system for IPF would have better predictive value than measuring individual disease-related factors. The first clinical, radiologic, and physiologic (CRP) scoring system was developed in 1986 and employed seven variables that accounted for parameters such as dyspnea, specific radiographic findings, and physiologic function.[99] This CRP score was validated through comparison to histopathology in a group of

26 patients. No single component of the CRP score had a better correlation than the composite score.

Over time further scoring systems have been developed. In 2001, a CRP score was derived to predict death rather than just histopathology.[82] A large cohort of patients was followed prospectively to devise the revised CRP score, utilizing multivariate statistical models to identify significant disease-related parameters. The revised CRP score incorporates age, smoking status, the presence of clubbing, TLC, arterial oxygen during maximal exercise, radiographic infiltrates, and radiographic findings consistent with pulmonary hypertension. The revised CRP score ranges from 0 to 100, with higher scores indicating more severe disease. Five-year survival can be predicted in individual patients by calculating a CRP score employing the published formulas and then referencing published survival curves. This system was felt to be cumbersome and therefore Collard et al. developed a simplified staging system from retrospective data of three large cohorts in California, Minnesota, and Italy (Ley B Annals of Internal Medicine 2012).[100] Utilizing gender; age; physiology, which included FVC and D_{LCO}(GAP) patients with IPF could be grouped into stages I, II, or III and that had defined 1-, 2-, and 3-year predicted mortality rates. This simple system using readily available clinical and physiologic data could provide important prognostic data for patients at the time of initial evaluation and assist with immediate management decisions.

PATHOGENESIS

IPF is a complex disorder and many pathogenic events have been observed. Despite significant research effort, no definitive, unifying hypothesis has yet emerged. Multiple pathways have been implicated in both experimental models of pulmonary fibrosis and patients with IPF. Despite this information, drug targets to modify these pathways have thus far been largely ineffectual. It remains distinctly possible that there is no single common pathway that results in the IPF phenotype; but rather, a combination of multiple factors that lead to aberrant wound healing, progressive fibrosis, and diffuse scar formation. Although more questions than answers currently exist, great strides are being made to elucidate new mechanisms in IPF pathogenesis.[101,102]

A primary change in our understanding of the pathogenesis of IPF has been a movement away from inflammation as the driver of the fibrotic response in the IPF lung. "Inflammation" dominated the field in the 1970s and 1980s and was based largely on the observation that BAL fluid from patients with IPF had increased numbers of inflammatory cells (mostly neutrophils and eosinophils) relative to normal individuals.[103–108] The concept that permeated the literature in that era was that IPF resulted from an unremitting inflammatory response to an exogenous insult, culminating in progressive fibrosis. By targeting the inflammatory response, the belief was that fibrosis could be limited or prevented. Unfortunately, it now appears that the data are more likely explained by structural abnormalities in lung architecture (traction bronchiectasis) that result in airway inflammation but do not appear to be causative of the fibrosis inflammation.[17,109] This is further supported by the pathologic observation that there is a lack of inflammation at the leading edge of the fibrosis and the fact that patients with IPF do not respond to systemic immunosuppression with corticosteroids. As a consequence of this understanding the overall research into mechanisms of IPF has made a clear transition from the belief of a primary "inflammatory-driven" process to one that focuses on dysfunctional repair of alveolar epithelial cells with generation of profibrotic mediators, activation of fibroblasts, and resultant scarring.[101]

BASEMENT MEMBRANE INJURY

A unique feature of the UIP pathologic pattern is a loss of integrity of the subepithelial basement membrane. This has been definitively demonstrated through the use of electron microscopy.[14] Basement membranes in IPF are denuded of the usual type I pneumocytes. It is theorized that loss of this protective epithelial barrier results in further oxidative injury that degrades basement membranes. At the same time it appears that hyperplastic type II pneumocytes are abundantly present. This likely represents an attempt at epithelial cell regeneration. While the exposed basement membrane may provide the signal for epithelial growth, new epithelial cells cannot attach to a damaged membrane. The result is a "frustrated" epithelial cell response with failure to signal a termination of epithelial cell proliferation. Further examination of tissue from patients with IPF has confirmed an irregular pattern of alveolar epithelial cell proliferation, concurrent with dysregulation of the proteins that control the cell cycle.[110,111]

An accumulation of growth factors in IPF may originate from the persistent proliferative response of epithelial cells. A downstream consequence of "frustrated" epithelial cell regeneration would be recruitment of fibroblasts and myofibroblasts through the release of such growth factors. In essence, the signal to recruit and maintain a pool of mesenchymal cells (fibroblasts) might originate from an inability to successfully re-epithelialize the alveolar lining surface.

ALVEOLAR EPITHELIUM

Multiple lines of investigation suggest that the alveolar epithelium is critically involved in the pathogenesis of IPF.[53,109,112] The prevailing hypothesis is that repetitive low-level injury to a vulnerable or susceptible alveolar epithelium drives the pathologic features of IPF.[102] Why IPF alveolar epithelium is more vulnerable appears to be from a combination of age-related and genetic factors that are not clearly defined but being actively investigated.

Epithelial Apoptosis/Injury

An emerging body of literature supports alveolar epithelial cell injury and apoptosis as important features of IPF and in the development of experimental pulmonary fibrosis. Electron microscopic studies of human IPF tissue demonstrate injury and apoptosis of alveolar epithelial cells.[14] BAL from patients with IPF has established the presence of proapoptotic proteins.[113] In the bleomycin model of lung injury and fibrosis in animals, fibrosis can be abrogated by various approaches to inhibit epithelial cell apoptosis.[114–116] These include a reduction in experimental fibrosis by inhibiting the Fas–Fas ligand pathway, angiotensin production, or caspase activation.

In addition direct inhibition of apoptotic pathways, factors that cause epithelial cell apoptosis are critical to the development of fibrosis. Evidence suggests that fibroblasts produce angiotensin peptides that lead to epithelial apoptosis. Other researchers have demonstrated that transforming growth factor-β (TGF-β) is involved with promoting epithelial cell apoptosis.[117] Oxidant injury may also promote epithelial cell death and several studies of IPF patients have confirmed excessive oxidant production as well as glutathione deficiency.[118–120] Tumor necrosis factor-α (TNF-α) has been shown to promote alveolar epithelial cell apoptosis in vitro.[121] In a mouse model, knockout of the TNF-α receptor confers resistance to bleomycin-induced lung fibrosis, while overexpression of TNF-α in the mouse has been associated with an increase in experimental fibrosis.[122] Patients with IPF are known to exhibit an exaggerated expression of TNF-α, which may contribute to epithelial injury.[123]

Evidence of direct injury to the alveolar epithelium suggests that this may be an important model of pulmonary fibrosis. Utilizing a transgenic mouse directing expression of human diphtheria toxin receptor in SPC-expressing cells, it was shown that targeted injury of type II epithelial cells resulted in the development of experimental lung fibrosis.[124] The development of fibrosis in this targeted epithelial cell injury is dependent on plasminogen activating factor 1 and the recruitment of monocytes and macrophages into the lung.[125,126]

Endoplasmic Reticulum Stress

Mutations of surfactant proteins A2 and C have been associated with familial types of pulmonary fibrosis and suggest a potential genetic mechanism for alveolar epithelial injury.[57,58,127–130] In alveolar epithelium, during both homeostatic and inflammatory conditions, surfactant proteins are regularly produced. This production requires appropriate and coordinated folding and packaging of the proteins in the endoplasmic reticulum (ER) prior to their release.[131] When this folding does not occur correctly, the cell experiences ER stress, which results in activation of the unfolded protein response (UPR) a cellular pathway designed to limit the deleterious consequences of misfolded proteins.[132] The fact that mutations in these proteins were associated with pulmonary fibrosis suggested that misfolding of these proteins could result in cellular stress and thereby enhance the vulnerability of the epithelium.[51] Using a mouse model that expressed a mutant form of SPC, Lawson et al.[133] demonstrated that misfolded SPC caused ER stress and thereby activating the UPR. Despite this activation the mice did not spontaneously develop pulmonary fibrosis but rather required a secondary challenge with bleomycin or viral infection.[133,134] With secondary challenge, the mice exhibiting enhanced ER stress were more susceptible to fibrosis. A growing body of literature suggests that the UPR response is defective with advancing age, which may provide a direct link to IPF as it is a disease of advanced age. ER stress and secondary insults provide an attractive model for IPF as this model system has the potential to link both genetic- and age-related disease factors to microinjuries and a vulnerable epithelium.

■ THE FIBROBLAST

The hallmark of pulmonary fibrosis is the development and expansion of scar tissue in the lung. In this context, patients develop progressive respiratory failure associated with unrelenting accumulation of extracellular matrix in the gas-exchanging regions. The generally accepted predominant sources of this matrix are fibroblasts. In IPF, fibroblasts accumulate in areas of advancing fibrosis and are associated with regions of alveolar epithelial hyperplasia, a.k.a. the fibroblast foci. Though not completely unique to IPF[101] (they can be found in small numbers in NSIP), fibroblastic foci are pathognomonic for IPF.[135] Supporting their importance two groups have observed that a large number of fibroblast foci within lung biopsies correlate with a worse prognosis in IPF.[33,81]

Myofibroblast

One of the hallmarks of IPF pathology is the development of a subset of cells called myofibroblasts.[136] Much attention has been focused recently on the role of the myofibroblast in the pathogenesis of IPF. The defining characteristics of myofibroblasts are positive staining for α-smooth muscle actin (α-SMA) and production of new collagen. Myofibroblasts have contractile properties critical to normal wound healing, though they only appear transiently in this circumstance.[137] In IPF lung biopsies, myofibroblasts have been described in abundance especially in the fibroblastic foci.[138] Myofibroblasts have also been shown to accumulate in bleomycin-induced lung fibrosis.[139] Immunohistochemical studies have suggested that they are important in the production of newly synthesized collagen.[139] The source of these myofibroblasts and the reasons for their persistence in IPF lung are just starting to be clarified.[140]

Origin of Fibroblasts and Myofibroblasts

The source of fibroblasts has been a subject of intense research and debate. Several possibilities include resident lung fibroblasts, bone marrow progenitors called fibrocytes, and epithelial cell transition in a process called epithelial to mesenchymal transition (EMT).

Evidence has accumulated over the past several years that suggests that bone marrow–derived cells may contribute to the pool of lung fibroblasts in IPF. In an animal model of experimental lung fibrosis it was shown that fluorescently tagged bone marrow–derived cells trafficked to the lung where they became a source of collagen expression.[141] Interestingly these bone marrow–derived cells did not express α-SMA, nor did they express α-SMA when stimulated in vitro with TGF-β, suggesting that they are not capable of acquiring the myofibroblast phenotype. Another group of researchers observed that a newly defined cell type migrated into the lungs of animals following bleomycin injury called fibrocytes.[142] Fibrocytes are a recently recognized cell type of hematopoietic origin that circulate in the peripheral blood and have been suggested to play a role in wound repair.[143] They also have been implicated in the pathogenesis of hypertrophic scars, scleroderma, and asthma-related airway fibrosis.[144] Fibrocytes are present in the blood of patients with IPF and appear to be a marker of disease progression.[145] Still, the exact role of these cells (and their relationship to the fibroblast) remains unclear due to the lack of specificity in lineage-tracing markers.

Another possibility is that the fibroblasts in IPF are derived from the alveolar epithelium. A transformation of cell type from epithelium to mesenchyme is a well-documented phenomenon that takes place during embryogenesis. In culture, it has been shown that isolated type II alveolar epithelial cells (AEC2) exhibit a loss of AEC2 markers and express fibroblast markers when stimulated with TGF-β, a critical fibrogenic factor. Whether this occurs in IPF remains a point of controversy with some studies demonstrating colocalization of AEC2 and fibroblast markers[146] and others that do not observe evidence of this phenomenon.[147] To address this question in vivo, lineage-tracing experiments were performed. Initial studies utilized a fragment of the human SPC promoter to drive the expression of a lineage label to track AEC2 cells.[148,149] Tracking AEC2 cells after TGF-β or bleomycin exposure suggested that these cells were a significant source of mesenchymal cells in experimental lung fibrosis. In contrast to these observations, alternative in vivo lineage tracing using a knock-in allele of the SPC gene directing inducible expression of a fluorescent lineage tag in mature AEC2 cells did not demonstrate evidence of EMT after bleomycin.[150] This work suggested a complex and heterogeneous proliferation of mesenchymal cells in experimental lung fibrosis. None of the cells that they explored appeared to be the origin of myofibroblasts.[150] Determining the origin of these cells remains an area of active investigation.

Fibroblast Phenotypes and Functions in IPF

Various growth factors that influence fibroblast function have been shown to be produced in the lung tissue of patients with IPF and also shown to mediate the pathogenesis of experimental fibrosis.[151,152] Examples include keratinocyte growth factor, TGF-β, insulin-like growth factor-1 (IGF-1), platelet-derived growth factors (PDGF-A and PDGF-B), fibroblast growth factor-2, and hepatocyte growth factor. Many of these growth factors activate tyrosine kinase signaling pathways that promote fibroblast proliferation and matrix production.

TGF-β is a critical mediator of lung fibrosis in animal models.[153] Several studies have shown that antagonizing TGF-β prevents the development of lung fibrosis.[154] Alternatively, targeted overexpression of TGF-β has been shown to produce progressive pulmonary fibrosis.[155] Evidence suggests that TGF-β has the capacity to promote epithelial cell transformation into a mesenchymal phenotype.[146] Studies have suggested that fibrosis is attenuated in the setting of targeted loss of TGF-β signaling in epithelial cells[156,157] and that epithelial expression of the integrin αvβ6 responsible for the activation of latent TGF-β is also critical to the development of fibrosis.[158] TGF-β also induces the differentiation of fibroblasts to myofibroblasts.[159,160] This effect appears to be dependent on NADPH oxidase 4.[161]

Secreted factors that influence fibroblast migration may also be important to fibrogenesis. The production of CXCL10 by innate immune cells may be critical to fibroblast migration and fibrogenesis.[162–164] Recent work highlighted lysophosphatidic acid (LPA) as an additional chemotactic factor for fibroblasts.[165] LPA interacting with

its cognate receptor LPAR1 is critical for recruitment of fibroblasts. LPA was increased in the BALF from IPF patients and inhibition of LPAR1 markedly attenuated the migration of fibroblasts to IPF BALF.

It appears that IPF fibroblasts have an enhanced proliferative capacity as compared to non-IPF fibroblasts.[166,167] The mechanism of enhanced proliferation is not fully elucidated but data suggest that several pathways may be involved. These include defective fibroblast/extracellular matrix interactions, aberrant activation of PI3 K/Akt/S6K1 signaling pathways, and genome-wide derangements in translation control.[168–171] The derangements in transcriptional control have the potential to allow IPF fibroblasts to circumvent normal negative feedback signals that would inhibit fibroblast proliferation and therefore limit fibrogenesis.

It has also been suggested that IPF fibroblasts have the capacity to invade through tissue. Such an invasive capacity might lead to the destruction of the basement membrane and collapse of alveolar tissue, both hallmarks of IPF pathology. It was recently shown that IPF fibroblasts may spontaneously invade an artificial matrix in an in vitro model.[172] It was also shown that targeted overexpression of hyaluronan, an extracellular matrix component, in myofibroblasts resulted in enhanced invasive capacity.[173] The invasive capacity of human IPF fibroblasts could be abrogated by either blockade of CD44 (the receptor for hyaluronan) or inhibition of hyaluronan synthase 2 (the enzyme responsible for HA production).[173] The importance of fibroblast capacity to invade matrix was also demonstrated in mice where there was deletion in regulators of G-protein–coupled receptor functioning called β-arrestins. β-Arrestin null mice were protected from experimental fibrosis and both mouse and IPF fibroblasts had suppression of fibroblast invasion when β-arrestins were inhibited.[174]

TREATMENT

Treatment for IPF is discussed below. Both pharmacologic and nonpharmacologic approaches are considered.

PHARMACOTHERAPY

The management of patients presents several challenges, namely (1) whom to treat; (2) when to treat; and (3) how to select treatment. In IPF, selection of treatment has been a contentious issue due to lack of drugs conferring a survival benefit, physiologic improvement, or quality of life (QOL) benefit. Recently, this landscape has changed due to a combination of promising novel treatment pathways and two recent clinical trials demonstrating positive outcomes in the treatment of IPF.

Historically, treatment strategies have been directed at suppressing the inflammatory processes of IPF. This strategy was employed despite histologic evidence demonstrating that inflammation is but a meager component of this disease. Alternative therapeutic agents were then developed to inhibit cytokines, proteases, oxidants, and mesenchymal growth factors. Several clinical trials have been undertaken over recent years to study these pathways. More recently potential targets for treatment have shifted to targeted therapies directed at the specific pathways that appear to mediate fibrogenesis. The goal continues to remain to prevent the onset and progression of fibrosis as there remains little evidence to support the notion that mature fibrosis can ever be reversed.

Corticosteroids and Immunosuppressants

Corticosteroids have never been studied head-to-head against placebo to determine their benefit in treating IPF. Retrospective studies have failed to demonstrate benefit from steroid monotherapy.[175] The most recent consensus guidelines on IPF recommend against the use of steroid monotherapy for the treatment of IPF.[20] Combination immunosuppressant therapy (steroid plus azathioprine, for instance) is also lacking for evidence of efficacy. Current guidelines recommend against the use of combination immunosuppressant therapy as the limited evidence in support of its benefit does not outweigh concerns for associated morbidity and mortality with such treatment. This opinion relies heavily on new data from a trial that compared the use of prednisone and azathioprine to placebo (the PANTHER trial).[176] The study was halted early due to an excess of mortality in the arm of the trial receiving combination prednisone and azathioprine.

N-acetylcysteine

Previous studies have demonstrated both an increased oxidant burden in the epithelial-lining fluid from patients with IPF as well as diminished antioxidant capacity.[118,119] These studies formed the basis for a controlled study comparing prednisone and azathioprine to prednisone, azathioprine, and N-acetylcysteine (NAC).[177] The results of this study showed that NAC slowed the deterioration of FVC and diffusion capacity after 1 year to a statistically significant extent. There was a high dropout rate in both arms and there was no difference in mortality. In order to address these concerns, an arm of the PANTHER trial was designed to compare NAC to placebo. The results of this study failed to demonstrate a change in either the primary or secondary endpoints. These results suggest that NAC does not have a benefit in IPF patients who had evidence of mild-to-moderate impairment in pulmonary function (FVC >50% predicted and D_{LCO} >30% predicted). The effect on later stage disease and other interstitial lung diseases is not known.

Pirfenidone

Pirfenidone is an orally administered agent with anti-inflammatory, antioxidant, and antifibrotic properties. There is evidence to suggest that pirfenidone has efficacy in slowing the progression of IPF. The first study of pirfenidone evaluated 105 Japanese patients with IPF using a 2:1 randomization and a physiologic endpoint incorporating gas exchange with exertion.[178] The study was discontinued prematurely due to concern over excess morbidity in the placebo group though it failed to demonstrate efficacy as measured by the primary endpoint. However, there were differences in FVC at the end of the study that stimulated interest in further clinical trials. As a result of this observation, two large international efficacy trials were completed.[179] In one of these studies a statistically significant reduction in the decline of FVC was observed in the active arm (patients who took 2403 mg/d of pirfenidone daily). However, the other trial, with a nearly identical protocol, failed to demonstrate efficacy. Based on this data and the data from the Japanese trial, pirfenidone was approved for use in Japan and in the European Union. Similar approval did not occur in the United States. A new phase III trial was undertaken at the request of the United States Food and Drug Administration (FDA) to clarify the concern over the results of the CAPACITY trials. In the ASCEND trial, 555 patients with idiopathic pulmonary fibrosis were randomized to receive 2403 mg of oral pirfenidone or placebo and then followed for 52 weeks. The enrolled patients had: (1) mild to moderate functional impairment, defined by an FVC range from 50–90% perdicted; (2) D_{LCO} range from 30–90% predicted; (3) FEV_1/FVC >0.80; and (4) 6-minute walk distance >150 meters. In recently published data from the ASCEND trial, pirfenidone was associated with a significant reduction in the proportion of patients who had a decline of 10% or greater in their predicted FVC. Additionally, there was a significant increase in the numbers of patients who demonstrated no decline in FVC. In a combined analysis of the ASCEND and CAPACITY trials, pirfenidone was associated with a decrease in both all-cause and IPF-related mortality. On the basis of these results, pirfenidone is in the process of being re-evaluated by the FDA for approval as a therapy for IPF in the United States.

Thalidomide

Thalidomide is a drug with a variety of properties including anti-inflammatory, immunomodulatory, and antiangiogenic effects.[180–182] In animal models thalidomide has attenuated pulmonary fibrosis after bleomycin challenge.[183] When a small open label trial was performed, hoping to assess the safety and efficacy of this drug as a disease-modifying agent, a reduction of cough was serendipitously

observed. This led to a follow-up randomized crossover design study in which thalidomide was shown to significantly reduce cough and improve QOL in patients with IPF.[184] Since cough is a particularly debilitating aspect of IPF this could represent a potential future therapy to impact QOL in this disease.

Tyrosine Kinase Inhibitor BIBF 1120 (Nintedanib)

BIBF 1120 is a triple tyrosine kinase inhibitor with efficacy on fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and on platelet-derived growth factor (PDGF).[185] The activation of these pathways has been implicated in the pathogenesis of experimental fibrosis. In a 12-month phase II trial (the TOMORROW trial) patients who received 150 mg of BIBF 1120 twice daily had a trend toward reduction in the decline of FVC.[186] In addition, there was an improved QOL and a reduction in acute exacerbations of IPF. These results led to a phase III trial. This was designed as two identical phase III studies called INPULSIS-1 and INPULSIS-2. The INPULSIS trials tested the effect on IPF disease progression over 52 weeks using 150 mg of twice daily nintedanib (formerly BIBF 1200) versus placebo. The inclusion criteria included patients diagnosed with idiopathic pulmonary fibrosis based on established criteria.[20] In addition, the participants' HRCT scans and biopsies, if available, were reviewed by a central radiologist or pathologist to confirm the diagnosis. Enrolled subjects had a FVC which was >50% of the predicted value and a D_{LCO} from 30–79% of predicted values. Published data from the two trials indicated that patients who received nintedanib demonstrated a statistically significant reduction in the rate of decline in lung function compared with the placebo group. In the INPULSIS-2 trial, there was a significant reduction in the time to first acute exacerbation of IPF. This was not replicated in the INPULSIS-1 trial data. The most common side effect for the medication was diarrhea. On the basis of this study, nintedanib is pending evaluation for approval for use in the United States.

Gastroesophageal Reflux Therapy

It has been observed that IPF patients have a high prevalence of gastroesophageal reflux disease (GERD). A retrospective cohort study identified that GERD treatment in IPF patients was associated with an increased length of survival and reduced radiographic evidence of fibrosis.[187] The contribution of this observation to the pathogenesis of the disease is unknown as no rigorous prospective studies have been performed. Nevertheless, pursuing the diagnosis of GERD in IPF patients appears warranted and, when identified, treatment according to established practice guidelines is appropriate.

■ NONPHARMACOLOGIC THERAPY

The roles of lung transplantation and additional nonpharmacologic measures are presented briefly below.

Lung Transplantation

Lung transplant remains the only therapeutic intervention of proven benefit in IPF. Transplant has been reserved for patients at the advanced stages of IPF and the 5-year survival data approach 50%. However, complications of lung transplant remain common and severe. Among the most important complications and the major cause of long-term mortality following lung transplant is bronchiolitis obliterans syndrome (BOS). BOS is an enigmatic process characterized by progressive fibrosis of terminal and respiratory bronchioles leading to an inexorable decline in transplant function. New therapeutic approaches are sought to control BOS. Therapy for BOS is limited at this time.

Supplemental Oxygen

Patients with hypoxemia (Pa_{O_2} <55 mm Hg or Sp_{O_2} <88%) at rest or during exercise can be managed with supplemental oxygen. There is evidence in patients with COPD, which suggests that supplemental oxygen relieves exercise-induced hypoxemia and improves exercise performance. Studies examining QOL in patients with IPF emphasize the importance of maintaining a patient's independence and participation in physical activities. In one study that examined QOL in IPF patients, no difference was found between patients receiving supplemental oxygen compared to those who were not receiving oxygen. Thus, any concern can be put to rest that supplemental oxygen would have a deleterious effect on QOL domains such as "self-esteem," "dependence on therapy," and "body image."[188]

Pulmonary Rehabilitation

Patients with IPF should be encouraged to enroll in pulmonary rehabilitation programs. Although pulmonary rehabilitation has not yet been shown to be effective in the IPF population, recent evidence suggests the possibility of benefit from a tailored exercise program. Exercise capacity in the IPF population has been correlated with quadriceps strength, which implies that training of the lower extremities would increase exercise capacity in IPF much the same as it does in COPD.[189] Furthermore, it has been shown that overall QOL is impaired in IPF, with specific defects in areas of physical health and perceived social independence. Therefore it has been suggested that pulmonary rehabilitation programs for IPF be designed to include education and psychosocial support elements with the goal of improving coping skills affecting a better QOL.[188]

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CHAPTER 57

Idiopathic Interstitial Pneumonias Other Than Idiopathic Pulmonary Fibrosis

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INTRODUCTION

The idiopathic interstitial pneumonias (IIPs) encompass a subcategory of interstitial lung diseases (ILDs) that pose significant diagnostic and management challenges. The general diagnostic approach to these disorders is discussed elsewhere in this textbook (Chapter 54), as is the diagnosis and management of idiopathic pulmonary fibrosis (IPF), (Chapter 56). This chapter details the classification, diagnosis, and management of non-IPF forms of IIPs including nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), and lymphocytic interstitial pneumonia (LIP). Historical perspectives, current definitions, and epidemiologic information will be provided along with clinical aspects, imaging, and pathologic findings. Each section ends with a discussion of current therapeutic options. This information is summarized in Table 57-1.

NONSPECIFIC INTERSTITIAL PNEUMONIA

The important entity of nonspecific interstitial pneumonia is discussed below.

DEFINITION AND HISTORICAL PERSPECTIVES

In 1994, the term "nonspecific interstitial pneumonia" (NSIP) was developed by Katzenstein and Fiorelli[1] to describe a histologic pattern that demonstrates a temporally uniform appearance of interstitial inflammation and fibrosis This definition was further refined in 1998, when Katzenstein went on to formally designate NSIP as a distinct category within the IIPs.[2] While most sources are in agreement about the presence of NSIP as a distinct *histologic* entity, the existence of NSIP as a distinct *clinical* entity remains controversial.[3–5] For example, the American Thoracic Society (ATS) reports that in one review of 193 cases of NSIP, only 67 cases (or approximately one-third) were truly idiopathic while the rest were associated with a discrete diagnosis. As a result, when a radiographic or pathologic diagnosis of NSIP is made, clinicians should search for one of the underlying conditions with which this pattern is known to be associated.

UNDERLYING DISEASE ASSOCIATIONS

Nonidiopathic NSIP is associated with a number of underlying causes.[5,6] NSIP is the most prevalent form of ILD to complicate connective tissue diseases (CTD) and as such is frequently the histologic pattern seen when ILD complicates polymyositis and dermatomyositis,[7] Sjögren syndrome,[8] and systemic sclerosis (SSc).[9] NSIP is seen in rheumatoid arthritis though far less commonly than is usual interstitial pneumonia (UIP).[10] NSIP is also encountered in the setting of hypersensitivity pneumonitis,[11] drug reactions,[12] and in some forms of familial ILD.[13] Some cases of apparently idiopathic NSIP may later develop CTD, indicating that NSIP is a forme fruste of CTD.[14]

CLINICAL PRESENTATION

NSIP most commonly affects nonsmoking middle-aged adults between 40 and 60 years of age and has a female predilection.[1,4,15] Like most other IIPs, NSIP tends to present with the subacute onset of dyspnea and cough. Lung examination frequently reveals bilateral crackles though in some settings lungs will be clear. Extrapulmonary examination may provide clues to an underlying CTD (Chapter 60). For example, the presence of a heliotrope rash, shawl-like rash, and digital edema/desquamation (the so-called "mechanic's hands") suggests underlying dermatomyositis. The presence of telangiectasis, calcinosis, and sclerodactyly suggests a diagnosis of scleroderma. The presence of joint effusions and radial deviation of the MCP joints suggests an underlying diagnosis of rheumatoid arthritis. Clubbing is seen only rarely.

Patients sometimes present without an established diagnosis. In this case, a complete history regarding occupational, environmental, and medication exposures must be obtained. In addition, because idiopathic NSIP is frequently associated with CTD, an exhaustive rheumatologic history should be obtained. This includes questions regarding the presence of arthralgias, swallowing difficulties, myopathic symptoms, rash and mechanic's hands commonly encountered in antisynthetase syndrome, ocular and/or salivary gland dryness associated with Sjögren syndrome, and Raynaud phenomenon and swallowing difficulties that are characteristic of SSc. While most sources recommend serologic testing in the diagnosis of NSIP, there exist no standardized practice guidelines in this area. At minimum, ANA and rheumatoid factor should be ordered, along with extractable nuclear antigens (which include Jo-1 and Scl-70) and anticyclic citrullinated peptide (anti-CCP). Serum creatine phosphokinase (CPK) and aldolase are useful in the diagnosis of myositis. Because hypersensitivity pneumonitis may also present with NSIP, antigen testing for mold or birds is sometimes performed though the clinical relevance of a positive (or negative) test is unclear and as such these tests are insufficient for diagnostic purposes.

PULMONARY FUNCTION TESTING

Pulmonary function testing demonstrates a restrictive ventilatory defect characterized by a preserved FEV_1/FVC ratio and a depressed FVC, TLC, and D_{LCO}. The presence of obstructive physiology should raise suspicion of an alternate or superimposed diagnosis.

CHEST IMAGING

The imaging appearance of NSIP may vary, depending on if it is cellular, fibrotic, or mixed. Chest radiograph may be normal in patients with early disease or show nonspecific interstitial markings and ground-glass opacities mostly in the lower lobes with more advanced disease. Distribution of disease at CT is typically peripheral and lower lobe predominant, but may also involve the upper lobes without an obvious apicobasal gradient and can be patchy or peribronchovascular in distribution as well.[16–19] The most common CT findings include ground-glass density and reticular markings with or without traction bronchiectasis (Figs. 57-1 and 57-2). Honeycombing is sometimes seen in fibrotic NSIP but is usually not the dominant feature.[18,19]

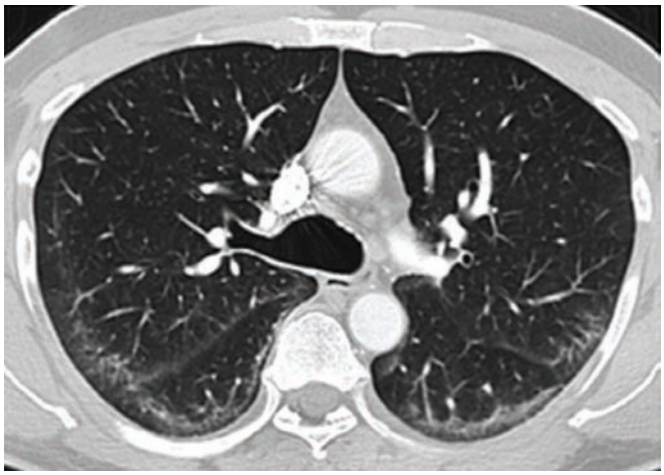
PATHOLOGY

When a tissue biopsy is required for diagnosis of NSIP, video-assisted thoracoscopic surgery (VATS) is the procedure of choice because this approach yields sufficient tissue to accurately diagnose the IIPs. The original description of NSIP categorizes its temporally uniform appearance of fibrosis and inflammation into three groups:

TABLE 57-1 Key Features of Idiopathic Interstitial Pneumonias

Features	IPF/UIP	NSIP	COP	AIP	DIP/RB-ILD	LIP
Mean age of onset	60s	50s	50s	50s	40s	50s
Duration of illness	Chronic	Subacute to chronic	Subacute	Acute	Subacute to chronic	Chronic
Frequency of diagnosis	47–64%	14–36%	4–12%	Rare	10–17%	Rare
Smoking	Up to 2/3	Uncommon	Up to 1/2	Unknown	Most	Unknown
HRCT	Peripheral, subpleural; basilar predominant; reticular opacities; traction bronchiectasis architectural distortion and honeycombing	Peripheral, subpleural; basal, symmetric; ground-glass opacities, reticular markings, traction bronchiectasis	Patchy, bilateral, subpleural and peribronchovascular consolidation	Diffuse consolidation and ground-glass opacities often with lobular sparing	DIP: peripheral or diffuse ground-glass opacities, reticular markings, +/− small cysts RB-ILD: bronchial wall thickening; centrilobular nodules; patchy ground-glass opacity	Diffuse; centrilobular nodules; ground-glass opacities; septal thickening; thin-walled cysts
Key pathologic features	Variegated temporal appearance; scant inflammation; patchy fibrosis; fibroblastic foci; honeycomb change	Uniform temporal appearance; prominent inflammation; variable, diffuse fibrosis; rare honeycomb	Uniform temporal appearance; moderate inflammation; intra-alveolar (Masson bodies) fibroblast proliferation; foamy macrophages	Structural cell death responses; acute inflammation; hyaline membranes may be present	Uniform temporal appearance DIP: diffuse variable moderate fibrosis with diffuse intra-alveolar macrophage accumulation RB-ILD: peribronchilar intra-alveolar macrophage accumulation with only focal, mild fibrosis	Diffuse interstitial infiltration, infiltrates comprises T and/or B cell lymphocytes, plasma cells, macrophages, lymphoid hyperplasia
Prognosis	50–70% mortality in 5 y	<10% mortality in 5 y	Rare deaths	50–60% mortality at 1 mo	5% mortality in 5 y	Not well defined
Response to steroids	Poor response	Responsive (particularly cellular)	Responsive	Unknown	Responsive	Not well defined

Source: Data from American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee. 2001. Am J Respir Crit Care Med. 2002;165(2):277–304.



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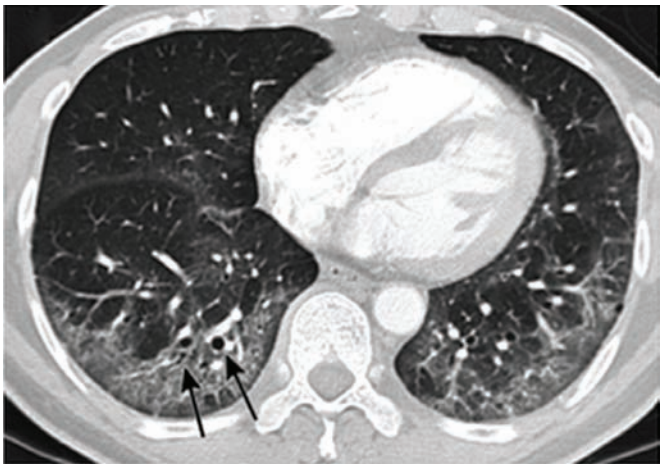

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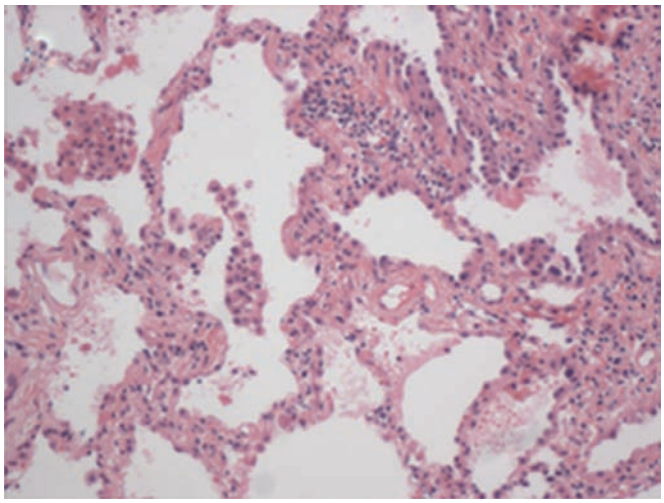


C

Figure 57-1 A 60-year-old male with antisynthetase syndrome and cellular nonspecific interstitial pneumonia (NSIP). High-resolution CT images through the upper (**A**) and lower (**B**) thorax demonstrate peripheral and lower lobe predominant ground-glass opacities with mild reticular markings and minimal traction bronchiectasis *(arrows)*. **C.** Open lung biopsy revealed temporally uniform septal thickening and inflammation consistent with a cellular NSIP. *(Pathology images used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

those dominated by active inflammation (later called, "cellular" NSIP [Fig. 57-1]), those dominated by established fibrosis (later called, "fibrotic" NSIP [Fig. 57-2]), and those demonstrating a combination of inflammation and fibrosis (later called, "mixed" NSIP.[1])

■ CLINICAL COURSE, OUTCOME, AND TREATMENT

Patients with NSIP demonstrate a good to fair prognosis as shown by several studies. Those individuals with cellular NSIP can expect 74% survival at 5 years[20] and this specific pathologic pattern is associated with reduced event-free survival compared to the fibrotic forms.[21] Similarly, radiographic changes that would be expected to accompany fibrotic NSIP such as honeycombing have been associated with reduced survival, as have progressive dyspnea and desaturation during 6-minute walk test.[20]

■ PHARMACOLOGIC THERAPY

Immunosuppression is commonly employed in the management of NSIP but the lack of prospective, randomized controlled trials in this area means that evidence for a therapeutic effect of these agents is lacking. For cases of exposure-related NSIP related to drugs or inhalations, cessation of the offending agent is the initial treatment strategy. In very mild situations this intervention may be sufficient but oftentimes patients with significant disease burden radiographically or physiologically require treatment with systemically administered immunosuppressive agents. Patients with arterial hypoxemia at rest or during exercise require the administration of supplemental oxygen. Patients with exercise impairment may benefit from pulmonary rehabilitation. Finally, due to the rapid deterioration that is sometimes encountered in patients with NSIP, referral for orthotopic lung transplantation (OLT) should be considered for any eligible patient.

The use of immunosuppression is based on the rationale that the inflammation seen on pathology at least partially contributes to disease. Most of the immunosuppressive agents used to treat NSIP have not been formally evaluated in prospective, randomized clinical trials and all of them have significant toxicities. Thus, the decision to embark upon a course of immunosuppression should be considered in light of the risk–benefit ratio. Similarly, when treating a patient with NSIP in the setting of CTD, the management of these medications is best performed with the patient's rheumatologist because since the pulmonary and systemic involvement may demonstrate independent responses, systemic effects must be monitored as well. Patients should be seen frequently and should have lab monitored monthly in order that serious and potentially fatal side effects can be recognized in a timely fashion.

Corticosteroids

Despite a lack of clinical trials in this area, expert opinion recommends a trial of corticosteroid therapy in patients with NSIP. Patients are typically treated with 1 mg/kg per ideal body weight of oral prednisone for several months and then assessed for evidence of objective response on PFTs or HRCT.[16] The side effects of steroid therapy are well-known and include diabetes, bone complications, cataracts, hypertension, weight gain, and opportunistic infection so patients should be followed closely with serial monitoring blood chemistry and CBC. Due to these

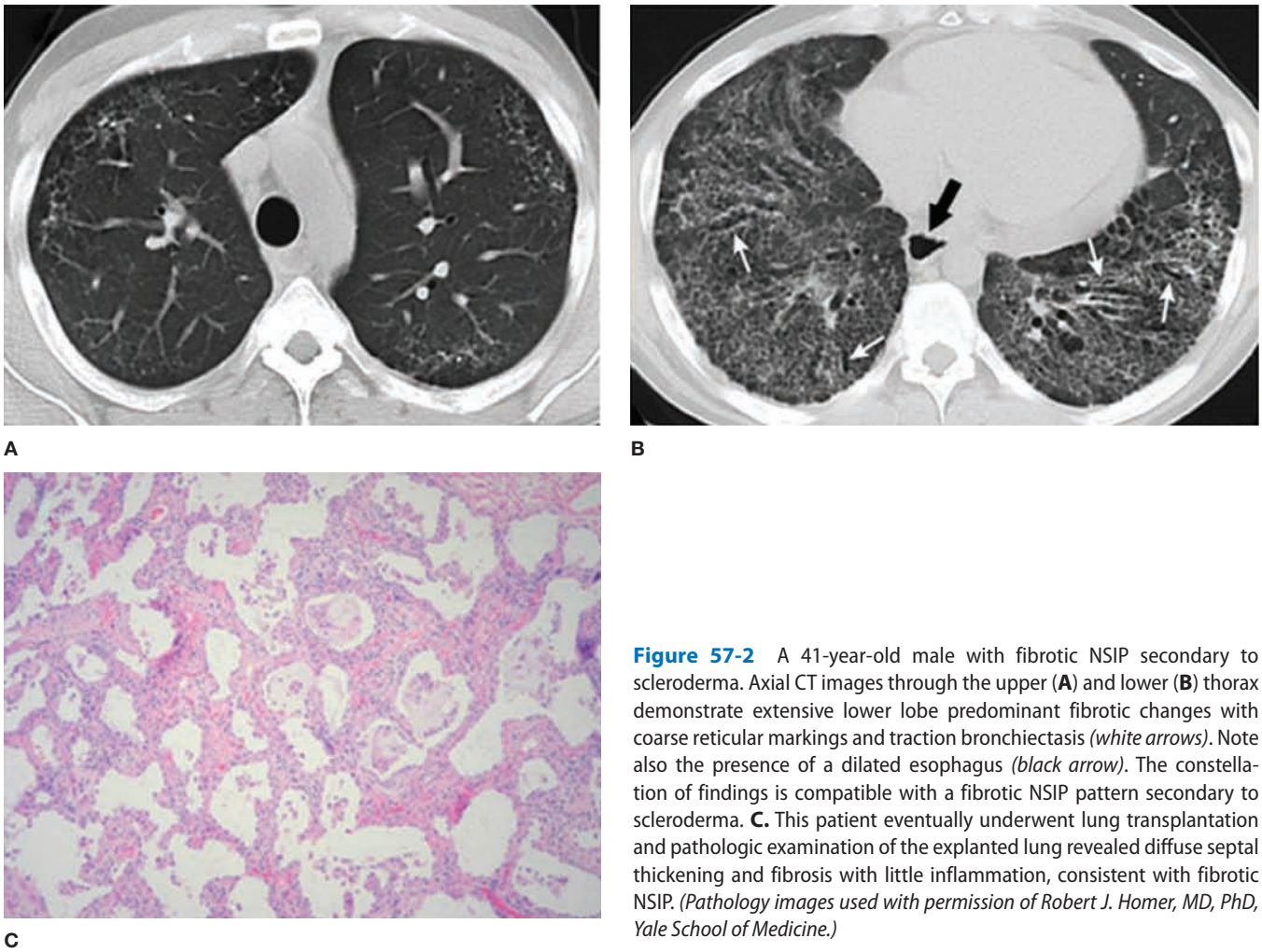


Figure 57-2 A 41-year-old male with fibrotic NSIP secondary to scleroderma. Axial CT images through the upper (**A**) and lower (**B**) thorax demonstrate extensive lower lobe predominant fibrotic changes with coarse reticular markings and traction bronchiectasis *(white arrows)*. Note also the presence of a dilated esophagus *(black arrow)*. The constellation of findings is compatible with a fibrotic NSIP pattern secondary to scleroderma. **C.** This patient eventually underwent lung transplantation and pathologic examination of the explanted lung revealed diffuse septal thickening and fibrosis with little inflammation, consistent with fibrotic NSIP. *(Pathology images used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

toxicities, every attempt to transition the patient to a steroid-sparing agent is made once the patient has responded to therapy.

Azathioprine

Azathioprine is a commonly used alternate therapy used in patients with NSIP. The evidence for this approach derives from an early study of subjects with IIPs in which a small subset comprised in part of patients with NSIP were found to improve. There have since then been no large-scale clinical trials in this area though one small case series found that patients with fibrotic NSIP experienced improved outcomes when treated with combination therapy of prednisone and azathioprine.[20] Because azathioprine carries several risks including bone-marrow suppression and hepatotoxicity most centers perform genotyping for thiopurine methyltransferase prior to initiation of therapy and when a mutation is uncovered reduce dosage accordingly though evidence for this approach is currently lacking.

Cyclophosphamide

Cyclophosphamide (Cytoxan™) is used in patients with significant or rapidly progressive lung involvement. In a prospective study comparing patients with confirmed fibrotic NSIP versus those with UIP/IPF receiving pulse therapy with methylprednisolone followed by low-dose prednisone and cyclophosphamide, 33% of subjects with NSIP improved with steroids alone and 66% improved with combined therapy. In contrast, only 15% of the subjects with UIP/IPF demonstrated clinical improvement at either timepoint.[22] Further suggestion of efficacy was provided by a small retrospective study in which patients with known or suspected NSIP showed stabilization of lung function following 6 months of therapy. Perhaps the best evidence for a therapeutic benefit of Cytoxan™ was seen in patients with SSc-ILD (most of whom have NSIP) randomized to placebo or Cytoxan™. A small but significant improvement in lung function was noted in those subjects assigned to the treatment arm[23] though subsequent analysis found this effect to dissipate after 2 years.[24] Because cyclophosphamide is associated with many side effects including bone-marrow suppression, hemorrhagic cystitis, and the long-term risk of bladder cancer and hematologic malignancies, its use is reserved for severe and progressive cases of NSIP and it is recommended that it only be used by experienced practitioners with appropriate monitoring.

Other Immunosuppressive Agents

Several case series indicate that mycophenolate mofetil (MMF) may be efficacious in delaying lung function decline in patients with SSc-ILD.[25,26] Because most of these patients have NSIP, these studies are viewed as providing direct evidence of a potential role for MMF in the management of this form of ILD. A large-scale randomized controlled trial of MMF versus cyclophosphamide is currently underway in for the treatment of SSc-ILD. MMF is started at 500 mg b.i.d. and titrated up to a maximum dosage of 2000 mg b.i.d. This agent is pregnancy category D due to its teratogenic potential. A role for tacrolimus in the treatment of NSIP is supported by one retrospective series[27] of patients with polymyositis- and dermatomyositis-related ILD. However, because no large-scale studies have been performed, consideration of this agent for the treatment of NSIP should be considered on a case-by-case basis and patients should be managed with physicians who are experienced in the interpretation

of serum levels. The most feared side effect is renal toxicity, which can in some cases be permanent and lead to kidney failure.

CRYPTOGENIC ORGANIZING PNEUMONIA

The entity of cryptogenic organizing pneumonia was described over 30 years ago. Important clinical aspects and associations are described below.

DEFINITION AND HISTORICAL PERSPECTIVES

First described by Davison[28] and Epler[29] in the early 1980s, cryptogenic organizing pneumonia (COP) was categorized as an IIP in a 2002 working group sponsored by the ATS and the European Respiratory Society (ERS).[16] The pathologic hallmark of COP consists of whorls of myofibroblasts and inflammatory cells in a connective tissue matrix within the distal airspaces. This nonspecific pathologic pattern is termed "organizing pneumonia" and is found in a variety of settings such as in the context of infection, drug toxicity, posttransplant, radiation exposure, or rheumatologic conditions. Therefore, it is only in the absence of an associated condition or inciting factor that clinicians may establish a diagnosis of COP. Thus, the diagnosis of COP rests on an integrated assessment of clinical symptoms, radiographic patterns, compatible histopathologic features, when available, and the exclusion of other associated causes and conditions.

The pathology was initially called "bronchiolitis obliterans organizing pneumonia" (BOOP) and this term initially dominated the North American literature and was included in the seminal paper by Katzenstein and Myers in 1998.[30] Given clinical confusion between the term BOOP and the distinct airway-centered disease of bronchiolitis obliterans syndrome ("BOS"), the terminology was changed in 2002. However, because many cases of COP are associated with an underlying etiology, the inclusion of COP as an "idiopathic" interstitial pneumonia has also been confusing for some. Perhaps most perplexing to clinicians is the fact that the disease in COP dominates the airspaces and not the interstitium. However, the working group justified the inclusion of COP within the IIPs because in clinical practice COP is part of the differential diagnosis of other IIPs, and because interstitial inflammation and fibrosis may be present in COP.

CLINICAL PRESENTATION

Similar to other IIPs, the epidemiology of COP is not well characterized though it seems to affect both genders equally with a mean age of onset of 58 years. Nonsmokers or former smokers may be affected more frequently than current smokers.[31] The classic presentation of COP includes an initial prodromal flu-like illness and symptoms of fever, cough, and dyspnea. Complaints such as hemoptysis, chest pain, arthralgias, or myalgias are uncommon. Chest auscultation may be clear or may reveal crackles. Patients are frequently treated with multiple courses of antibiotics before being diagnosed. The presence of systemic symptoms and/or findings consistent with CTD should lead to careful investigation for an associated underlying disease.[32]

UNDERLYING ASSOCIATIONS

A diagnosis of *COP* requires exclusion of associated causes. It has been suggested that gastroesophageal reflux with silent aspiration may play a role in the development of OP; however, this association has not been firmly established.[33] Many viral, bacterial, fungal, and parasitic infections have been implicated[31,34] as has influenza A H1N1 flu.[35] OP is a frequently encountered manifestation of drug-induced lung disease caused by antibiotics such as nitrofurantoin, medications such as phenytoin, amiodarone, sulfasalazine,[36] and illicit drugs such as cocaine.[37] Occupational exposures are also associated with an OP pattern of lung injury including but not limited to the aerosolized textile dye Acramin FWN, titanium nanoparticles in paint, and certain chemicals used in spice processing.[38–40] OP has been reported in patients with dermatomyositis-polymyositis[41–46] as well as other conditions such as rheumatoid arthritis,[47–49] scleroderma,[50–52] and systemic lupus erythematosus.[53–55] Rheumatologic serologies can be helpful in identifying the presence of disease because this form of lung injury may present as the initial manifestation of systemic disease. OP may be present in other inflammatory diseases such as in patients with Crohn's disease and ulcerative colitis.[56] Radiotherapy treatment is also associated with the development of OP particularly after treatment for breast cancer 3 to 6 months following therapy. Compared to radiation pneumonitis which is fairly well circumscribed and characterized by retracted lung and traction bronchiectasis, postradiotherapy OP occurs diffusely, is migratory, and is highly steroid responsive.[57] OP can also occur following transplantation of lung or bone marrow. While BOS is the most commonly reported lung injury pattern in patients experiencing lung transplant rejection, OP patterns have also been described.[58,59] Similarly, bone-marrow transplant recipients may develop OP as a manifestation of transplant rejection, graft-versus-host disease, or idiopathic pneumonia syndrome.[60–62] OP can also complicate malignant or hematologic conditions such as various forms of acute and chronic leukemias and lymphomas.[63]

PULMONARY FUNCTION TESTING

Similar to other IIPs, a restrictive ventilatory defect, characterized by a reduction in total lung capacity is generally present. In a subset of patients, an obstructive ventilatory defect can be found. Hypoxemia is typically mild although in a subgroup of patients with infiltrative opacities severe hypoxemia may be seen.[64,65]

CHEST IMAGING

OP displays a variable imaging appearance. The CXR usually shows nonspecific patchy areas of consolidation. Sometimes the imaging appearance mimics infectious pneumonia with lobar consolidation that is unresponsive to antibiotics. Peripheral, patchy, and peribronchovascular areas of ground-glass opacity and consolidation are the most classic CT appearance (Fig. 57-3).[16,17,66] Nodular areas of ground glass and consolidation as well as fleeting or migratory areas of consolidation can also be seen with OP.[16,17,66] Findings suggestive of fibrosis such as reticulation, architectural distortion, traction bronchiectasis, and honeycombing are not typically present with this entity. An area of ground-glass opacity surrounded by a rim of increased density, also known as the atoll (or reverse-halo) sign, when present, is strongly suggestive of OP[66] but can also be present with other entities such as vasculitis, certain infections, or pulmonary infarction.

PATHOLOGY

When the clinical presentation and chest imaging is insufficient for a confident diagnosis of COP, bronchoscopy with transbronchial biopsy or surgical lung biopsy can be employed. Bronchoalveolar lavage (BAL) typically reveals significant accumulation of lymphocytes, neutrophils, and eosinophils. Transbronchial biopsies may be performed to make a diagnosis; however, the quantity of lung tissue obtained during these procedures is quite small and may be insufficient to fully evaluate the spectrum of pathology that may exist within the lung parenchyma.[67–69] Thus, larger lung tissue specimens obtained by VATS are frequently used to provide the opportunity for more thorough analyses.

The pathology of OP is characterized by intraluminal plugs of inflammatory debris within the alveolar ducts and surrounding alveoli. The plugs consist of buds of granulation tissue, whorls of fibroblasts and myofibroblasts in a connective tissue matrix referred to as Masson bodies (Fig. 57-3). OP patterns can be seen concomitantly in patients with NSIP or UIP and may in certain patients represent an exacerbation of underlying ILD. In this setting, interpretation of the pathology in the context of the radiographic and clinical features can greatly aid in accurate diagnosis.

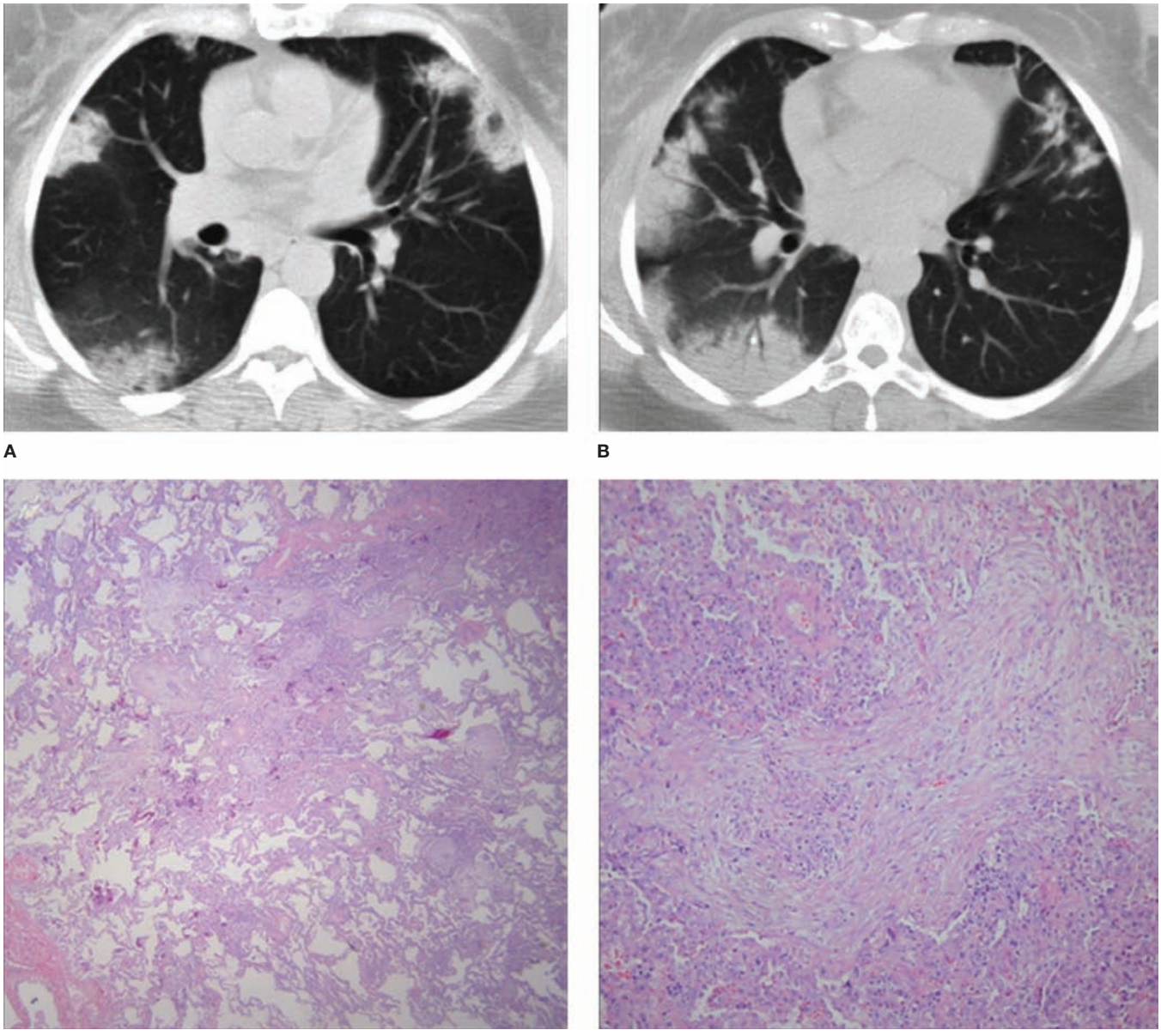


Figure 57-3 A 50-year-old female with cough and dyspnea secondary to organizing pneumonia (OP). Axial CT images through the mid (**A**) and mid to lower (**B**) thorax demonstrate multifocal, peripheral areas of consolidation with a distribution compatible with OP. Low (**C**) and high (**D**) power views of lung tissue from this patient reveal a patchy organizing pneumonia pattern of exudates, fibroblasts, and inflammatory cells. *(Pathology images used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

■ CLINICAL COURSE, OUTCOME, AND TREATMENT

Patients with mild or asymptomatic disease may not require treatment.[70] When compared to other fibrotic lung diseases such as IPF, COP is impressively steroid responsive though a significant proportion of patients, ranging from 13% to 58%, experience relapse. Fortunately, relapses are not associated with poorer long-term outcomes and death is very infrequent.

■ PHARMACOLOGIC THERAPY

Historically, a 6-month course of treatment has been advised. More recently, shorter 3-month durations of corticosteroids have been recommended to avoid unnecessarily prolonged courses of steroids in patients who do not relapse.[32] Macrolide antibiotics[71] and steroid-sparing agents[72,73] have been used as alternative immunosuppressants for individuals with COP or secondary OP. However, the clinical utility of these approaches has not been completely validated. It is not known whether individuals with secondary causes of OP experience different long-term outcomes from individuals with COP.

While the majority of COP patients have favorable prognosis, a subset of patients present with a rapidly progressive and fatal form of OP. Some investigators have suggested that such cases represent an overlap group with acute interstitial pneumonia or acute respiratory distress syndrome (ARDS). In another series, AFOP, an acute fibrinous organizing pneumonia pattern was reported. In AFOP, organizing pneumonia and intra-alveolar fibrin balls are present.[74] Nonetheless, the literature does suggest that a small subgroup of COP patients suffer a progressive fibrotic course. Alternative forms of immunosuppression such as cyclophosphamide have been used in such rapidly deteriorating patients though experience with this approach is at best limited and the clinical utility is not entirely clear.[72]

RESPIRATORY BRONCHIOLITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE AND DESQUAMATIVE INTERSTITIAL PNEUMONIA

The entities of respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia are part of a spectrum of disorders affecting smokers. Important clinical and pathologic considerations in these two entities are described below.

DEFINITION AND HISTORICAL PERSPECTIVES

While regarded clinically as two discrete forms of IIPs, RB-ILD and DIP are generally thought of as representing ends of a continuous spectrum of disease primarily affecting tobacco smokers. The diagnostic distinction persists due to evidence indicating that RB-ILD and DIP have divergent natural histories and prognoses. The pathologic hallmark of both diseases features cytoplasmic accumulation of golden-brown pigment in macrophages. RB-ILD pathology appears to reflect inhalational exposure as findings center around the bronchioles with peribronchiolar inflammation and fibrosis. In contrast, DIP involves the airways but also extends into the alveolar space and may even include mild to moderate associated interstitial fibrosis. Because RB-ILD and DIP reactions are frequent and often incidental findings in the lung tissue of smokers, formal clinical diagnosis of RB-ILD or DIP hinges upon the presence of symptomatic, radiographic, and functional impairment. Taken together, DIP and RB-ILD account for up to 15% to 20% of patients with biopsied IIPs.[75–78]

CLINICAL PRESENTATION

Patients diagnosed with RB-ILD and DIP are typically males in the fourth or fifth decade of life with an average 30 pack-year smoking history. Affected patients report nonspecific complaints of progressive dyspnea and nonproductive cough. Physical examination may be normal but might reveal dry inspiratory crackles and clubbing as seen in other forms of ILDs. Extrapulmonary findings are usually absent.

UNDERLYING ASSOCIATIONS

Tobacco smoke exposure accounts for the most cases of RB-ILD and DIP, despite their categorization as "IIPs." In fact, it has been reported that up to 90% of RB-ILD and DIP cases are causatively linked to tobacco smoke.[75] However, in one review of 49 cases, it was noted that only 60% of DIP patients versus 93% of RB-ILD patients had a prior smoking history.[79] Although the lower prevalence of smoking in this study compared to prior studies may reflect referral bias, investigators should remain cognizant that such pathologies can occur independently of smoking. When viewed in this light, it is relevant that a number of exposures have been reported in association with DIP such as marijuana smoking, diesel fume, beryllium, copper, fire extinguisher powder, asbestos, and certain chemicals used to process textiles.[79–82] DIP has also been reported as a complication of autoimmune disorders including rheumatoid arthritis and scleroderma[50,52,80,83] and has occurred in association with infections such as hepatitis C, cytomegalovirus, and aspergillus.[84–86] Finally, idiopathic DIP has also been reported.[79] Genetic factors seem unlikely to play a dominant role; however, a few studies particularly among children and sibling studies have implicated genetic abnormalities of surfactant function, such as mutations in SP-B, SP-C, and ABCA-3 genes[87–89] though the applicability of these studies to the adult IIPs described herein remain uncertain. The difficulty in determining the contribution of other exposures may occur because when evaluating individuals with a smoking history, clinical providers dismiss the possible contribution of alternate etiologies. Furthermore, since many individuals with conditions such as rheumatologic disease do not proceed to lung biopsy, the specific underlying pathology of the associated IIP may remain unconfirmed and individuals may be assumed to have NSIP.

PULMONARY FUNCTION TESTING

Patients with RB-ILD often manifest a restrictive physiologic pattern with concomitant reduction in $D_{L_{CO}}$. However, given the bronchiolocentric nature of the pathology, a mixed pattern with some elements of obstruction may also be seen. DIP patients generally demonstrate restrictive ventilatory defects along with reductions in diffusion capacity. Hypoxemia may be seen in more severely affected patients. On occasion spirometry and lung volume impairments seem less severe compared to the patient's clinical status. This phenomenon may be due to the mixed or obstructive patterns seen due to the airway-centered nature of RB-ILD or concomitant smoking-related lung pathologies such as chronic obstructive pulmonary disease (COPD).

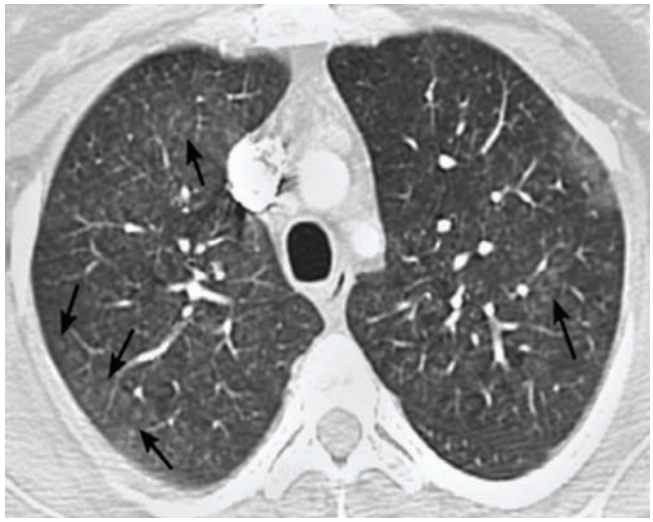
CHEST IMAGING

The imaging findings of RB-ILD are usually subtle and not visualized on CXR. CT findings include subtle, mild diffuse or upper lobe predominant, centrilobular ground-glass nodules, and patchy ground-glass densities (Fig. 57-4).[16,17,90,91] Ancillary findings associated with cigarette smoking may also be present such as bronchial wall thickening from chronic bronchitis and tissue rarefaction and bullae reflecting emphysema. The main alternative diagnosis in a patient with centrilobular ground-glass nodules on CT is subacute hypersensitivity pneumonitis. However, the ground-glass nodules with hypersensitivity pneumonitis are usually not as subtle as those seen with RB-ILD. Similar to the CXR findings in RB-ILD, the CXR in DIP are usually quite faint and although sometimes hazy, nonspecific, ground-glass opacities may be present. Ground-glass opacities that are usually peripherally located (Fig. 57-5), but which can also be diffuse, are the most common finding seen on CT.[26,62,86,87] Other CT findings include reticular markings and small cysts, which may indicate a component of fibrosis[26,62,86,87] can be seen but more extensive fibrotic changes such as traction bronchiectasis and honeycombing are rare. In addition, bronchial wall thickening and emphysema may be seen here as well.[87] When peripheral ground-glass opacities exist in this disease, the differential diagnosis includes NSIP, OP, and chronic eosinophilic pneumonia.

PATHOLOGY

The diagnosis of RB-ILD and DIP hinges upon a comprehensive clinical assessment integrating history, physical examination, PFTs, and HRCT. Because the histopathology of DIP and RB-ILD may exist in the lung tissue of asymptomatic smokers, pathology alone does is not diagnostic. Bronchoscopy may have a role in ruling out other processes resembling RB-ILD or DIP. BAL reveals characteristic pigmented macrophages. A pronounced eosinophilia has also been reported in the BAL specimens of some DIP patients. Investigators have suggested that in the appropriate clinical setting and BAL profile, transbronchial biopsy showing RB may be sufficient to support the diagnosis of RB-ILD. Nonetheless, for both RB-ILD and DIP surgical lung biopsy may be necessary to formally establish the diagnosis as well as exclude alternative causes.

The pathologic hallmark of RB-ILD and DIP centers around the accumulation of pigmented macrophages, commonly referred to as smoker's macrophages. These macrophages contain iron and display glassy eosinophilic cytoplasm with a finely granular, yellowish-brown pigment that likely contains components of tobacco smoke. In heavy smokers, the pigmentation may become coarser making the distinction from hemosiderin deposition seen in chronic alveolar hemorrhage more challenging.[79,92] Clinicians must also differentiate the common pathologic finding of respiratory bronchiolitis (RB), first described by Niewoehner in 1974, from the specific disease entity referred to as RB-ILD.[93] In the 1980s, Myers described the phenomena of RB-ILD characterized by the intensified RB response.[94] Lung tissue from RB-ILD may demonstrate a chronic inflammatory



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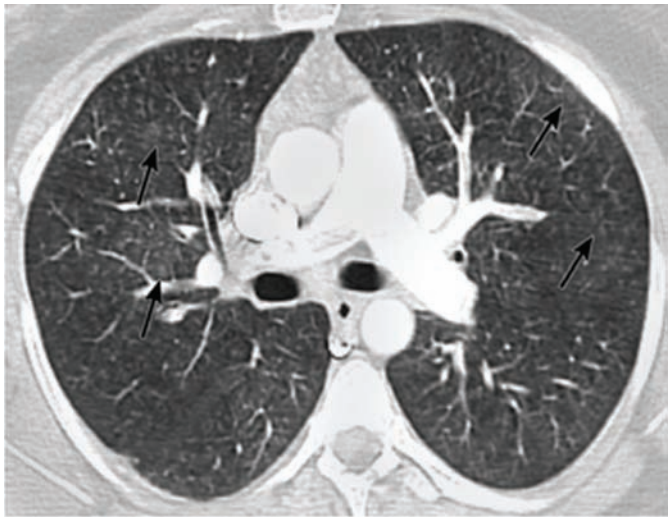

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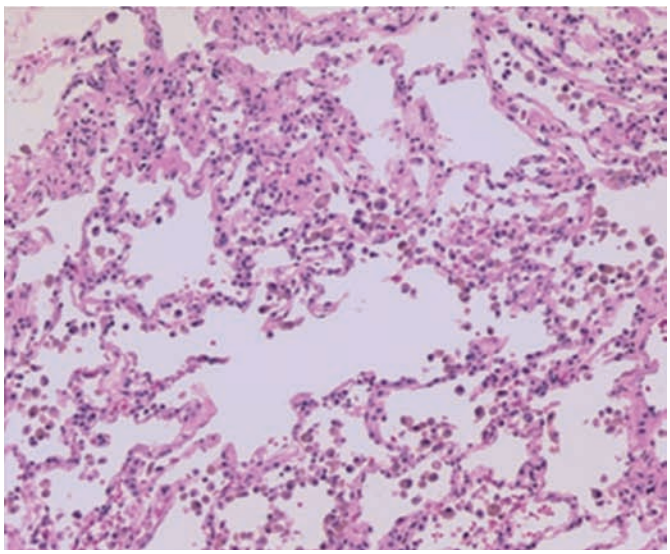


C

Figure 57-4 A 42-year-old male with smoking history and chronic cough secondary to respiratory bronchiolitis-interstitial lung disease (RB-ILD). High-resolution CT images through the upper (**A**) and mid (**B**) thorax show diffuse, centrilobular ground-glass nodules *(arrows)*. These findings are compatible with the pathologic pattern of RB-ILD, which features the peribronchial accumulation of pigmented macrophages. Note the relative sparing of the alveolar space (**C**). *(Pathology images used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

cell infiltrate as well as a peribronchiolar fibrotic pattern more pronounced as compared to uncomplicated RB (Figs. 57-4 and 57-5). Churg has proposed that an RB-ILD diagnosis should be differentiated from RB in smokers when individuals demonstrate evidence of significant functional and physiologic impairment along radiographic abnormalities.[95]

First described by Liebow in 1965,[96] DIP was highlighted as a diagnostic entity in a 1978 study by Carrington.[97] Comparison of DIP and RB-ILD reveals that in DIP the macrophages extend more diffusely into the lobule in contrast to the more limited peribronchiolar involvement found in RB-ILD and that interstitial fibrosis, giant cells, and eosinophils are more commonly found in DIP (Fig. 57-5). Pathologists must exclude the presence of alternative ILDs on biopsy. A clinical diagnosis of RB-ILD or DIP necessitates overall assessment of the patient incorporating pathologic and radiographic findings, functional impairment and exclusion of other diagnostic considerations pathologically and radiographically.

■ CLINICAL COURSE, OUTCOMES, AND TREATMENT

Patients with RB-ILD or DIP are generally characterized by less fibrosis and experience a more favorable prognosis compared to IPF, perhaps in part due to the finding that smoking cessation and corticosteroids are often effective therapies in RB-ILD and DIP patients.[77,78,98] Progressive disease is uncommon in RB-ILD and is more often seen in patients with DIP as one study found that 33% of DIP patients versus 64% of RB-ILD patients experienced objective radiographic or physiologic improvement.[75] Similarly, another study found that 26% of patients with DIP died compared to no patients in the RB-ILD, a finding that confirmed prior work by Carrington and Yousem.[92,97,99]

Smoking Cessation

The cornerstone of treatment for these diseases includes tobacco smoking cessation. In patients with mild to moderate symptoms and impairment a period of observation after smoking cessation is reasonable. Many patients stabilize and improve; however, concomitant corticosteroid therapy often confounds interpretation of the efficacy of smoking cessation alone[77] and earlier studies by Carrington and Yousem failed to comprehensively characterize the effect of smoking cessation. Additional confounders that complicate assessment of improvement include the presence of other smoking-related lung pathologies such as emphysema whose contribution to impairment will not generally respond to any intervention.

Corticosteroids

When symptoms and impairment are severe, treatment with systemic corticosteroids may be of benefit. A 6- to 9-month course of therapy starting at a level of 40 to 60 mg/d for 6 weeks is reasonable.

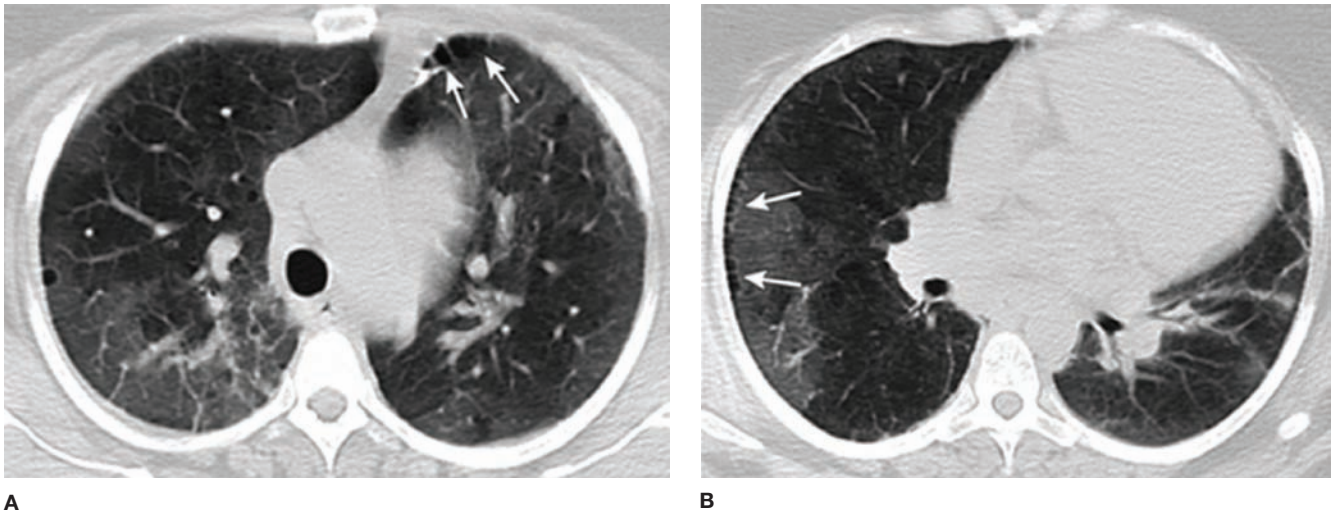


Figure 57-5 A 36-year-old female with significant cigarette smoking history, cough, and dyspnea. Axial CT images through the upper (**A**) and lower (**B**) thorax demonstrate bilateral, patchy, and peripheral ground-glass opacities. Small bullae along the pleural surfaces compatible with paraseptal emphysema are also present *(arrows)*. The ground-glass opacities did not resolve on follow-up imaging so the patient underwent video-assisted thoracoscopic surgery (VATS) and pathology revealed desquamative interstitial pneumonia (DIP) shown in (**C**), demonstrating the peribronchial and intra-alveolar accumulation of pigmented macrophages. *(Pathology image used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

The role of alternative immunosuppressants that are used in other ILDs have been less well defined in RB-ILD and DIP although macrolide antibiotic therapy has been reported to be an effective steroid-sparing treatment in DIP.[100] Lung transplantation may be necessary for patients with severe progressive disease. Recurrence of disease after transplant has been reported.[99]

ACUTE INTERSTITIAL PNEUMONIA

The original description of acute interstitial pneumonia dates back over 75 years. Clinical hallmarks of this entity are described below.

■ DEFINITION AND HISTORICAL PERSPECTIVE

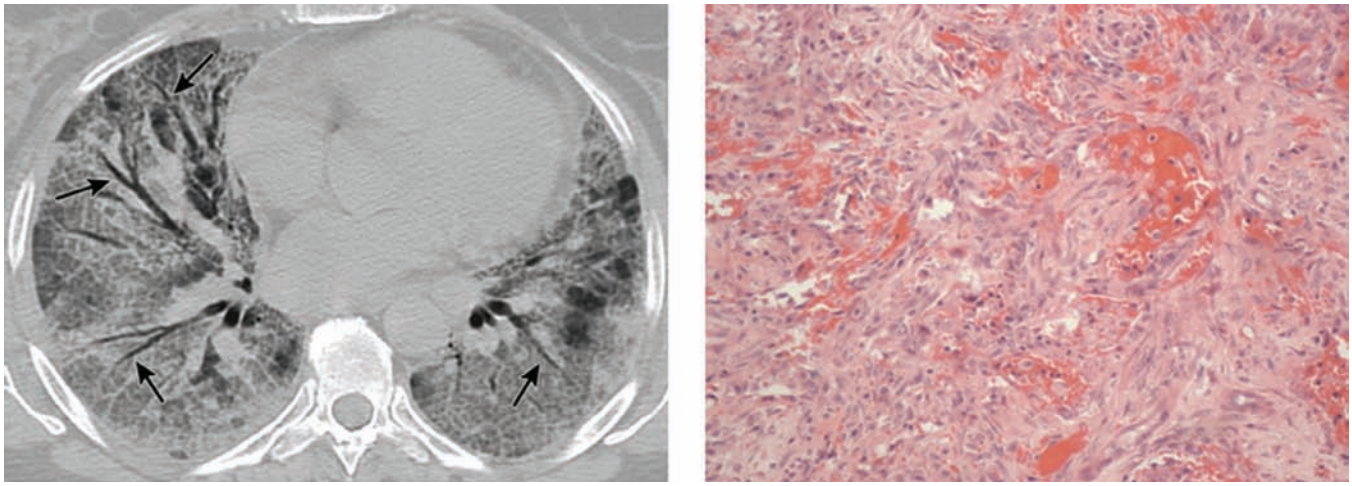
Acute interstitial pneumonia, also called "AIP" or "Hamman–Rich syndrome," was first described by Hamman and Rich in 1935 and is a rare and fulminant IIP.[101] Current ATS/ERS diagnostic criteria for AIP include the following[16]: (1) rapidly progressive clinical course (≤2 months) leading to respiratory failure; (2) exclusion of infectious, toxic, autoimmune, or any other known cause of ARDS; (3) diffuse alveolar damage (DAD) on biopsy specimens (see below); (4) radiologic findings consistent with ILD; and (5) absence of chronic lung disease.

■ CLINICAL PRESENTATION

AIP is quite rare and most frequently presents in previously healthy individuals with no prior lung disease. The disease has no gender predominance and most commonly affects patients over 40 years old with a mean age of 50 to 55 years.[102–104] Unlike most other IIPs,[102] AIP typically presents as the acute onset of fever (75%), cough (70%), and rapidly progressive dyspnea (90%)[105] with many patients reporting the sensation of an infectious prodrome. Most patients are hypoxemic upon presentation and rapidly progress to respiratory failure requiring mechanical ventilation. Physical examination frequently reveals tachypnea and bilateral crackles in all lung fields. Signs of chronic lung disease such as clubbing are uncommon and argue against a diagnosis of AIP while the presence of skin or joint abnormalities might suggest an underlying autoimmune process. While initial management focuses on stabilizing the patient's respiratory status, diagnostic evaluation should be undertaken. Once cardiogenic pulmonary edema has been ruled out by EKG, cardiac enzymes, and echocardiogram, causes of noncardiogenic pulmonary edema and ARDS should be evaluated. Given the broad array of diseases and exposures associated with the development of ARDS, this assessment should include careful exposure history including medications and occupational hazards, as well as a complete rheumatologic history. The serologic and muscle enzyme testing described earlier for NSIP may also be valuable in this setting.

■ UNDERLYING ASSOCIATIONS

The differential diagnosis of AIP is broad and includes left heart failure, diffuse alveolar hemorrhage, OP, hypersensitivity pneumonitis, UIP/IPF, and DIP. AIP can generally be distinguished from these entities based on careful history, examination of chest films, and ancillary tests described earlier. Once the AIP diagnosis has been established, it is imperative to further seek underlying causes



A B

Figure 57-6 A 45-year-old female with acute shortness of breath. High-resolution CT image through the thorax (**A**) demonstrates diffuse ground-glass opacities involving every lobe. Within areas of ground-glass opacity are reticular markings and traction bronchiectasis *(arrows)* suggestive of organization and underlying fibrosis. Lung tissue obtained at autopsy revealed findings of diffuse alveolar damage which was including obliteration of the alveolar space with structural cell death responses, acute inflammation, and hyaline membrane formation (**B**). *(Pathology image used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

such as collagen vascular disease such as antisynthetase syndrome[106] or lupus[107]; therapeutic exposures such as certain chemotherapies, biologic therapies, radiation, hyperoxia[108,109]; illicit drugs such as heroin or cocaine[110]; toxic exposures such as smoke inhalation and other gases[108]; massive transfusion,[111] fat embolism, aspiration,[112] and infections such as atypical pneumonias (mycoplasma[113] or legionella[114]) and viral infections (influenza).[115] AIP should also be differentiated from acute exacerbations of underlying IIPs or other pre-existing forms of underlying lung disease.

■ PULMONARY FUNCTION TESTING

Most patients are too ill to undergo pulmonary function testing but a restrictive ventilatory defect and impaired diffusion capacity would be expected.

■ CHEST IMAGING

AIP is radiographically and pathologically indistinguishable from ARDS. Imaging findings depend upon whether the early, exudative phase or chronic, fibrotic phase is present. Diffuse consolidation and ground-glass opacities are typically seen in the early, exudative phase, with the dependent areas of lung being more affected.[16,17,116] The early, exudative phase is difficult to distinguish radiographically from other entities such as cardiogenic or noncardiogenic edema, diffuse infection or diffuse hemorrhage. In patients who survive the acute phase (sometime after the first week), in addition to the lung consolidation, findings of underlying fibrosis such as architectural distortion, traction bronchiectasis, with or without honeycombing, become apparent at imaging and are usually more severe in the nondependent portions of the lung (Fig. 57-6).[16,17,116]

■ PATHOLOGY

If microbiologic testing yields negative sputum culture and viral studies, bronchoscopy with BAL is next performed to rule out undiagnosed infection or alternate diagnosis. There is generally no role for transbronchial biopsy in the diagnosis of AIP as when a tissue diagnosis is required, surgical lung biopsy is the preferred approach. A pathologic diagnosis of DAD demonstrates diffuse and extensive cell death accompanied hyaline membranes, which are histologically apparent layers of fibrin mixed with necrotic epithelium. This material lines the alveolus and reflects the severity and acuity of the injury (Fig. 57-6). As the injury progresses, it evolves into its organizing phase, which can either resolve into relatively normal lung or result in lung fibrosis.

■ CLINICAL COURSE, OUTCOMES, AND TREATMENT

The fulminant and often untreatable nature of AIP endows this disease with a particularly high mortality. More than 50% of patients die during hospitalization and most patients die within 6 months of diagnosis. Those who survive are at risk for disease recurrence or the development of other forms of ILD. However, a small fraction of survivors may experience complete recovery of lung function.[103,105] Treatment is detailed below and is aimed at supporting the patient and attempting to limit the acute injury and inflammation.

Nonpharmacologic Therapy

The mainstay of therapy for AIP is supportive care.[103,105] This includes supplemental oxygen or mechanical ventilation, adequate sedation, nutritional support, and prevention of ICU-related complications such as stress-induced ulcers, venous thromboembolism, catheter-related bloodstream infections, and ventilator-associated pneumonias.

Pharmacologic Therapy

High/pulse-dose glucocorticoid therapy is frequently administered to patients suffering from AIP though, due to the rarity and often grave nature of AIP, there have been no clinical trials assessing efficacy of this treatment.[105] Therefore, the evidence supporting this approach is anecdotal and is, in fact, based on case reports that showed a conflicting survival benefit.[102,105,117] For example, in the largest case series published in 1990, of 29 patients treated with glucocorticoids, survival was 45% in the treated group versus 33% in the untreated group.[102] Similarly, in smaller series of only eight patients treated with pulse-dose steroids, seven patients survived.[117] Conversely, a different study of nine patients treated with 8 mg/kg of methylprednisolone found a mortality of 100% with this regimen.[105] Despite this lack of clear benefit, expert opinion recommends continuation of high-dose steroids for several days followed by a maintenance dose of the equivalent of prednisone 60 mg/d that can be tapered over the ensuing weeks if the patient survives.[103,105]

The side effects of high-dose steroids cannot be understated. In addition to the long-term side effects described earlier, short-term risks in the ICU include hyperglycemia, immunosuppression, neuromuscular complications, and delirium. Thus, in some settings when steroids are contraindicated or a steroid-sparing agent is required, practitioners might employ a trial of nonsteroid-based therapy. Use of other agents such as azathioprine, cyclosporine,[118] Cytoxan™, and vincristine have been reported in AIP though these agents are not recommended for routine use.[112] OLT has been successful in several patients with respiratory failure attributed to AIP. However because these patients are frequently too unstable for transfer to a transplant center, the utility of OLT in AIP is at best limited.

LYMPHOID INTERSTITIAL PNEUMONIA

The final entity discussed within this group of idiopathic interstitial pneumonias is lymphoid interstitial pneumonia.

DEFINITION AND HISTORICAL PERSPECTIVES

In 1969, Liebow and Carrington developed the term "lymphoid interstitial pneumonia" (LIP) to describe a benign polyclonal infiltration of the alveolar space and interstitium with mature B or T cells. LIP exists within a spectrum of lymphoproliferative disorders affecting the lung and as such its classification as an IIP has been debated. Furthermore, the malignant potential of LIP is not well defined[119,120] but all sources agree that identification of monoclonal features effectively rules out LIP and points to a malignant etiology.[121,122] However, because the clinical and radiographic features overlap with the other IIPs in terms of differential diagnosis[123] and treatment approach, the most recent ATS and ERS statement on IIPs retained LIP within this classification.[16] LIP is also sometimes seen in children; however, because this chapter addresses the adult IIPs, pediatric LIP will not be discussed.

CLINICAL PRESENTATION

Given its rarity, the demographics of LIP are difficult to define but the available data indicate that this diagnosis is more commonly seen in women and that the mean age of onset is during the fifth decade of life.[16,124] LIP typically presents as slowly progressive cough and dyspnea over several years.[124] Systemic symptoms are rare though fever, weight loss, chest pain, and joint aches have been reported.[16,124] Chest auscultation may be normal or may reveal crackles as the disease progresses.[25,42] Extrapulmonary findings may include lymphadenopathy or joint findings consistent with an underlying diagnosis of Sjögren syndrome or rheumatoid arthritis. Findings consistent with severe lung disease such as clubbing, are rarely detected.[16] Laboratory examination may reveal mild anemia. Quantification of serum immunoglobulins reveals either a polyclonal gammaglobulinemia or a monoclonal increase in either IgG or IgM up to 75% of patients.[122,125] Immune complexes are sometimes seen but only infrequently.[126]

UNDERLYING DISEASE ASSOCIATIONS

Most cases of LIP are associated with an underlying cause such as Sjögren syndrome[127] or immunodeficiency such as severe combined immunodeficiency and HIV.[42,43] LIP has also been reported in association with rheumatoid arthritis,[128] Hashimoto disease,[129] pernicious anemia,[130] chronic active hepatitis,[131] systemic lupus erythematosus,[132] autoimmune hemolytic anemia,[125] primary biliary cirrhosis,[122] and hypogammaglobulinemia.[130,133] LIP is also seen in association with certain viral infections including Epstein–Barr[134,135] and human T cell lymphotropic virus type I (HTLV-I).[136,137] Truly idiopathic LIP accounts for less than 20% of cases.[124] Thus, as with NISP, a diagnosis of LIP should prompt a dedicated search for an underlying cause.

PULMONARY FUNCTION TESTING

When present, PFT abnormalities include a restrictive defect characterized by reduced FVC and TLC, an impaired D_{LCO}, and, potentially, hypoxemia.[138]

CHEST IMAGING

The imaging findings of LIP are variable and depend upon the underlying disease process. The CXR reveals nonspecific findings such as bilateral reticular markings and hazy, ground-glass opacities. As with the other IIPs, LIP is much better characterized by HRCT. Diffuse, patchy, or lower lobe predominant ground-glass opacities with reticular markings and small cysts is the pattern most commonly seen on CT in patients with AIDS, and can be difficult to distinguish from viral or opportunistic infections such as pneumocystis or CMV pneumonia.[17,139] Thickened bronchovascular bundles, septal thickening, and centrilobular nodules are less commonly present. LIP in patients with Sjögren syndrome typically manifests as bilateral, thin-walled cysts of varying sizes (but usually larger than the cysts seen in AIDS-associated LIP) scattered throughout the lungs with intervening normal lung parenchyma (Fig. 57-7).[16] Often times a vessel appears to be associated with (or adjacent to) the wall of a cyst, thus the term "perivascular cyst." Ground-glass opacities may exist as well.[16,123,140] The main differential diagnosis for this appearance would include other causes of cystic lung disease, such as lymphangioleiomyomatosis (in a female patient), Langerhans cell histiocytosis (in a cigarette smoker), and pneumocystis pneumonia (in immunocompromised patient) though the latter two entities usually manifest with upper lobe predominant cysts.

PATHOLOGIC FINDINGS

LIP pathology demonstrates a dense interstitial lymphoid infiltrate containing lymphocytes, plasma cells, and histiocytes, in combination with Type II cell hyperplasia (Fig. 57-7). The alveolar septa are extensively infiltrated. Lymphoid follicles with germinal centers are often seen.[16,122] Honeycombing and nonnecrotizing granulomas are sometimes detected[122] along with intra-alveolar organization and macrophage but when these latter aspects are the dominant pathologic feature, the diagnosis of LIP should be reconsidered.[16]

NATURAL HISTORY, CLINICAL COURSE, AND TREATMENT

Little is known about the clinical course and prognosis of LIP. The results of several case series suggest that approximately 50% of patients improve, 10% remain stable, and 40% will die of disease within 2 years even when treated with immunosuppression.[122,124,141] Those patients surviving are subject to a small but significant chance of progression to pulmonary lymphoma[122] as well as increased risk of serious and potentially fatal infections related either to the underlying cause of LIP (inherited or acquired immunodeficiency) or to the immunosuppressive therapies used to treat this disease.

Idiopathic LIP

Treatment for LIP in part depends upon the patient's symptoms and the underlying cause. Asymptomatic patients with mild, idiopathic disease are typically subject to careful longitudinal follow-up with serial PFTs and chest imaging because a small percentage of these patients will spontaneously improve.[16] Patients who deteriorate over time, or those who are highly symptomatic or significantly impaired upon initial diagnosis, are offered treatment with immunosuppression. While there exist no data regarding the safety or efficacy of glucocorticoids in patients with idiopathic LIP,[16] extrapolation of case series of patients with CTD-associated LIP (in which approximately 50% of patients show some evidence of response) suggests potential benefit.[141] Patients are typically started on the equivalent of 1 mg/kg (ideal body weight) oral prednisone for 8 to 12 weeks after

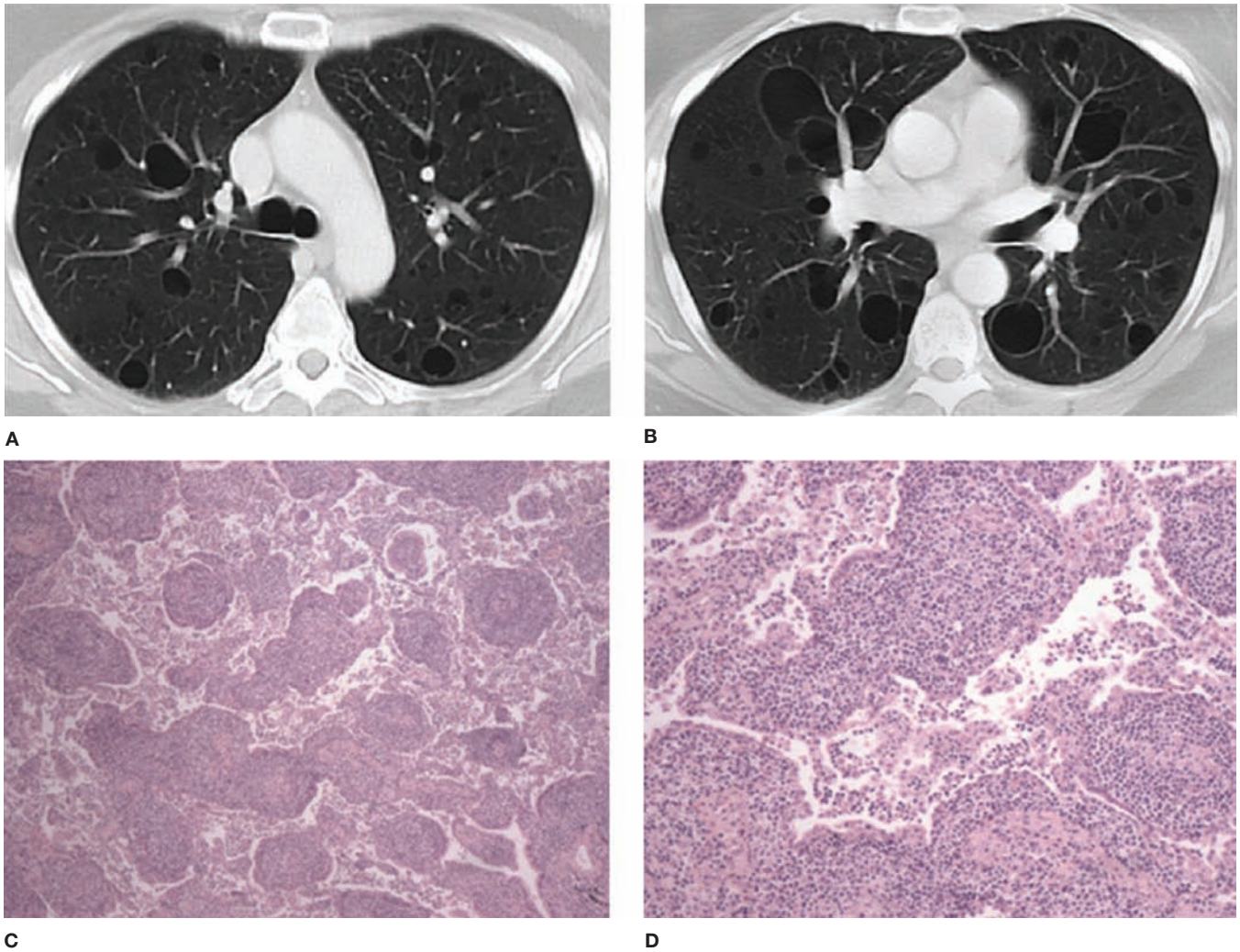


Figure 57-7 A 51-year-old female with Sjögren syndrome and lymphocytic interstitial pneumonia (LIP). Axial CT images through the upper (**A**) and mid (**B**) thorax show multiple thin-walled cysts of varying sizes bilaterally involving the upper and lower lobes. Note the presence of normal lung parenchyma between the cysts. Low (**C**) and high (**D**) power views of LIP lung tissue reveal a dense interstitial infiltrate containing lymphocytes, plasma cells, and histiocytes, combined with Type II cell hyperplasia and increased alveolar macrophages. *(Pathology images used with permission of Robert J. Homer, MD, PhD, Yale School of Medicine.)*

which chest imaging and PFTs are repeated. Those patients who demonstrate an objective response may continue their prednisone at a tapered dose for several months longer; those patients who do not respond generally have therapy discontinued or are offered an alternate disease modifying agent such as cyclosporine or azathioprine. Again, it should be noted that the evidence for this approach is scarce and the risk of side effects, and possible lack of efficacy, should be weighed against the potential benefit inherent in this class of drugs. In addition, patients on long-term steroid therapy should be offered prophylaxis against pneumocystis pneumonia and should be monitored for bone health.

Nonidiopathic LIP

Management of LIP in the setting of CTD is similar to that of idiopathic LIP and in fact the use of immunosuppression in this population is based on stronger evidence.[124,141] Treatment of LIP in the setting of HIV usually involves institution of HAART as in many patients this intervention will reduce symptoms and improve both radiographic disease burden and lung physiology.[142–144] For those patients whose disease persists despite use of HAART, glucocorticoids are commonly used though evidence for this regimen precedes the HAART era.[138,145] As with idiopathic and CTD-related LIP, pneumocystis prophylaxis should be strongly considered for patients with HIV-related LIP that are treated with immunosuppression.

CONCLUSION

The non-IPF IIPs are characterized by diverse presentations, underlying associations, natural history, and response to therapy. Given the complexity of diagnosis and management, these diseases are best managed by highly experienced practitioners using a multidisciplinary approach.

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CHAPTER 58

Hypersensitivity Pneumonitis

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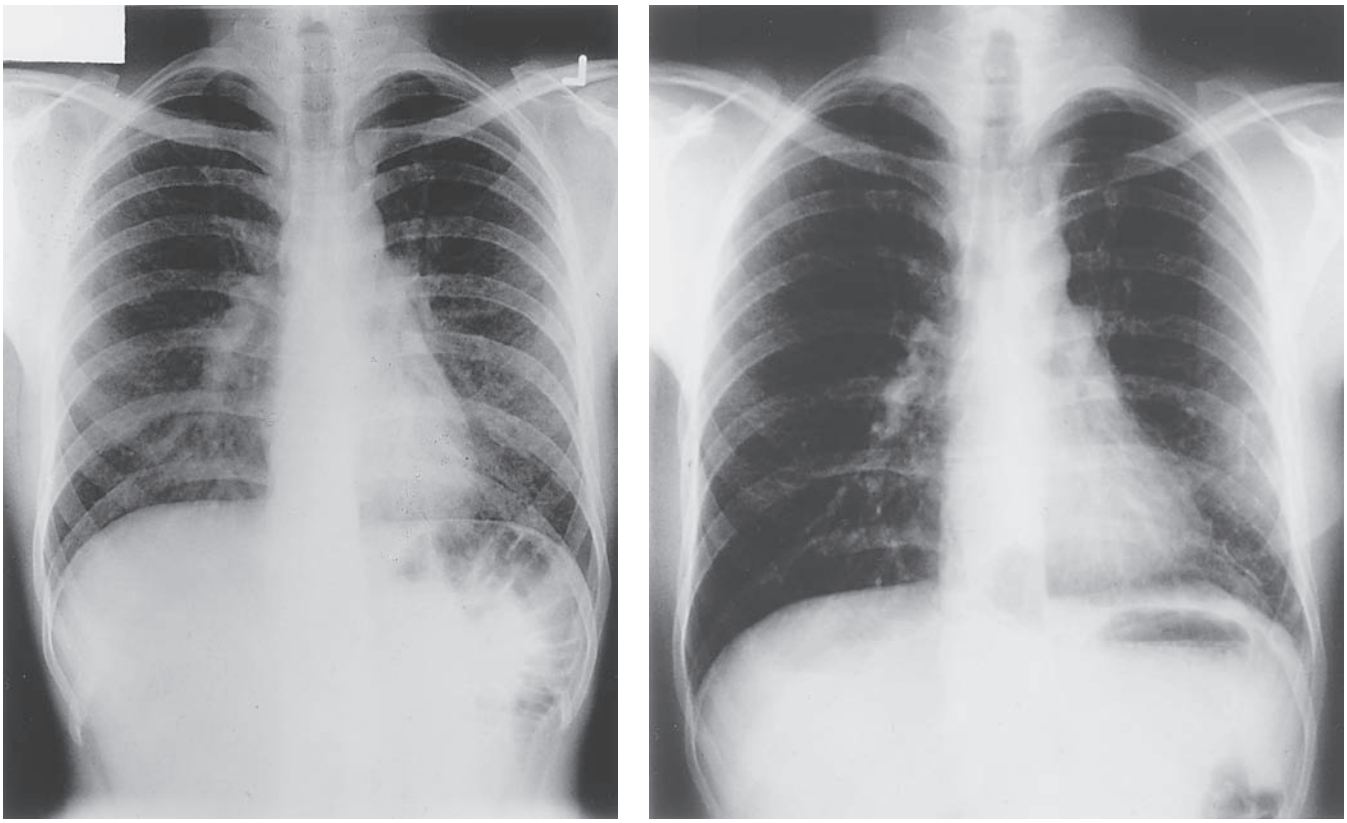
EPIDEMIOLOGY AND ETIOLOGIES

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a spectrum of interstitial, alveolar, and bronchiolar lung diseases resulting from immunologically induced inflammation in response to inhalation of a wide variety of different materials that are usually organic or low–molecular-weight chemical antigens (or haptens), which may lead to irreversible lung damage. Despite the terms *hypersensitivity* and *allergic,* HP is not an atopic disease and is not associated with increased IgE or eosinophils. The prevalence of HP is quite variable in different populations, presumably because of differing intensity, frequency, and duration of inhalation exposure, and also probably due to host factors that have yet to be identified. Once thought to be a relatively rare disease, it is becoming more frequently recognized as awareness is of the limitations of classical diagnostic criteria has increased. Among pigeon breeders, 8% to 30% of members of pigeon-breeding clubs who participated in surveys exhibited evidence of HP, so-called pigeon breeder's disease (Fig. 58-1). Among farmers, 0.5% to 5% have symptoms compatible with HP, so-called farmer's lung disease. The prevalence of symptoms is lower in farms that use hay-drying methods that decrease exposure to the responsible antigens and increased after a wet summer season.

The population at risk and the season of exposure vary with the type of HP. For example, most cases of farmer's lung disease occur in cold, damp climates in late winter and early spring, when farmers (usually male) use stored hay to feed their livestock. Pigeon breeder's disease occurs chiefly in men in Europe and the United States but predominantly in women in Mexico, owing to differing patterns of exposure, but without a seasonal preference in either population. Bird fancier's disease in Europe and the United States occurs in subjects who keep domestic birds and does not exhibit a predilection to either sex. Japanese summer-type HP occurs mostly in women without an occupation outside the home in June to September in warm, moist parts of the country. The disease has been reported in children as well, though rarely.

In contrast to other pulmonary diseases, there is a curious predominance (80%–95%) of nonsmokers in all examples of HP, which is substantially higher than the proportion of nonsmokers in similarly exposed individuals without HP.[1] The mechanisms of this phenomenon are unknown, but could include anti-inflammatory effects of nicotine. This clinical finding suggests that the presence of



A B

Figure 58-1 **A.** Chest radiograph of a patient with pigeon breeder's disease with fever, dyspnea, and bibasilar rales. The patient had kept pigeons for 5 years and presented with fever, dyspnea, and myalgias approximately 8 hours after cleaning the pigeon coop. He had serum antibody to pigeon dropping extract. Note bilateral lower lobe 2- to 3-mm nodules. **B.** Chest radiograph of the same patient 2 weeks later without specific treatment. Note clearing of the lower-lobe nodules and the staples in the left chest from the open lung biopsy.

active smoking may be evidence against the diagnosis of HP, although this has not been consistently observed.[2]

An important feature of HP is the great variability of susceptibility among exposed populations and the apparent resistance to illness of most exposed persons. Possible reasons include differences in exposure, or differences in the host response to exposure, which may be inborn and/or acquired. There are no differences in the prevalence of atopy or HLA-A, B, or C haplotypes in exposed subjects with and without HP,[1] although there may be an alteration in the prevalence of several HLA-DR and -DQ alleles.[3]

Several case-control studies have identified single nucleotide polymorphisms (SNPs) that are disproportionately represented in patients with HP and have accordingly garnered interest as potential pathogenetic determinants. Compared with healthy controls of the same ethnic heritage, a Mexican cohort with HP was found to have SNPs in MHC class II genes encoding a family of transporters associated with antigen processing (TAP).[4] Mexican HP patients also more frequently possess the KQ genotype of the PSMB8 gene, which codes for a constituent of the low–molecular-weight proteosome required for peptide processing and eventual presentation in the context of class I MHC.[5] SNPs in the interleukin-6 (IL-6) gene have been correlated with higher levels of epithelial neutrophil-activating protein (CXCL-5) in the BAL fluid of HP patients,[6] but the clinical implications of cytokine gene variation in this disease are undefined. An increased prevalence of a particular polymorphism in the tumor necrosis factor-α (TNF-α) promoter has been reported in patients with pigeon breeder's disease compared with exposed subjects without pigeon breeder's disease,[7] as well as protective variants in the tissue inhibitor of metalloproteinase-3 (TIMP3) promoter in exposed subjects without pigeon breeder's disease,[8] the possible significance of which is discussed below (see Immunopathogenesis).

A large number of agents are associated with HP, shown in Table 58-1. Some types of HP have apparently disappeared from their originally described clinical settings (e.g., bagassosis in Louisiana) but presumably exist in areas with similar agricultural or industrial settings. In addition, other forms of HP are being newly recognized (e.g., potato riddler's lung and machine operator's lung). Both the disappearance of previously described examples of HP and the appearance of new examples are due to changing agricultural or industrial practices that result in changes of exposure of subjects to antigenic material that can cause HP. At the present time farmer's lung disease, bird fancier's disease, ventilator lung, and Japanese summer-type HP are the most commonly recognized forms of HP.

Recognition of new examples of HP usually requires a cluster of new cases with a unifying exposure history, underscoring the importance of obtaining at least a basic occupational and avocational history whenever possible. Such diligence revealed that a group of musicians developed HP from instruments contaminated with *Mycobacteria* in the case of trombonists[9] and by molds in the case of a saxophonist.[10] Use of a new metalworking fluid (MWF) led to recognition of machine operator's lung in an auto parts–manufacturing facility due to clustering of cases and a common unusual exposure (*Pseudomonas* in cooling fluid). Highly sensitive genomic testing applied to MWF used in the automotive and nonautomotive industries suggests that HP risk may be associated with microbial colonization patterns,[11] particularly the presence of *Mycobacterium immunogenum*.

CLINICAL FEATURES

The manifestations of the disease may be acute, subacute, or chronic. The stereotypical acute clinical presentation includes transient fever, hypoxemia, myalgias, arthralgias, dyspnea, and cough that occur 2 to 9 hours after exposure and resolve in 12 to 72 hours without specific treatment (sometimes longer after a particularly intense exposure). Patients exhibit tachypnea, bibasilar rales, and occasionally cyanosis. There is usually peripheral blood leukocytosis with neutrophilia and lymphopenia (without eosinophilia), and BAL neutrophilia. Subacute or intermittent disease may result from repeated exposures, and manifest as productive cough, dyspnea, fatigue, and weight loss. There may be BAL lymphocytosis, frequently (though not always) with a predominance of $CD8^+$ T lymphocytes.

The chronic form is clinically more insidious, and patients may lack a history of acute episodes, but present with a gradual onset of cough, dyspnea, fatigue, and weight loss. Symptoms are usually present for months to years. There is typically no fever, but tachypnea and bibasilar dry rales are usually present. This form of the disease may be difficult to distinguish from idiopathic pulmonary fibrosis (IPF). Symptoms and signs of cor pulmonale are not uncommon at presentation.

The reasons for the different clinical presentations (i.e., acute, subacute, and chronic) of HP are not clear, but could include differences of intensity and duration of exposure (low-intensity long-duration exposure tending to cause chronic HP; high-intensity short-duration exposure tending to cause acute HP). This is most clearly demonstrated in HP due to bird exposure. Long-term exposure to low amounts of bird antigens is associated with chronic HP. Pigeon breeder's disease has different presentations in different geographic areas, manifesting as an acute HP in some and chronic HP in others. Intermittent exposure of pigeon breeders to large amounts of pigeon antigens in the United States and Europe is associated with acute disease and a good prognosis, whereas chronic exposure to a few household pigeons in Mexico is associated with chronic disease and a much poorer prognosis. In the United States and Europe, pigeon breeders keep their animals in an enclosure separate from their living areas, which they visit periodically so that exposure is intermittent. In Mexico, birds are often kept in living quarters so that exposure is constant. It is of interest that bird antigens can persist in a room for substantial lengths of time (>18 months) after removal of the birds,[12] so that Mexicans with pigeon breeder's disease might be exposed to pigeon antigens for prolonged periods even after removal of the pigeons. Therefore, pigeon breeder's disease in Mexico resembles bird fancier's disease in the United States and Europe in type of exposure, clinical presentation, and prognosis. It differs greatly from the acute HP that characterizes the pigeon breeder's disease in the United States and Europe. Since the relevant antigens are similar in these two examples of bird-associated HP, it is likely that the type of exposure, and not the antigen characteristics, determines clinical presentation and prognosis. The recognition of a new example of HP is usually associated with the acute form, which is likely related to the relative ease in making the association of acute disease and an acute exposure.

The previous discussion indicates that HP, and particularly chronic HP, may be more prevalent than is readily apparent and may often be confused with other diseases, such as chronic bronchitis or IPF. The latter may be particularly important because detailed histories are not always obtained from patients with IPF, the serum antibody levels to the agents responsible for HP tend to wane after cessation of exposure, and chest high-resolution computed tomography (CT) scans of chronic HP can resemble those of IPF.

RADIOGRAPHIC FEATURES

The chest radiographs of patients with acute and chronic HP differ significantly. In acute HP, chest radiographs demonstrate diffuse poorly defined nodular radiodensities, often with areas of ground-glass radiodensities or occasionally even consolidation. These radiodensities tend to occur in the lower lobes and spare the apices. Linear radiodensities (presumably representing

TABLE 58-1 Etiologies of Hypersensitivity Pneumonitis

Disease	Antigen Source	Probable Antigen
Farmer's lung disease	Moldy hay	*Thermophilic actinomycetes, M. faeni (S. rectivirgula), Thymus Vulgaris, Aspergillus* spp.
Bagassosis	Moldy pressed sugarcane (bagasse)	*Thermophilic actinomycetes, Thermoactinomyces Sacchari, T. vulgaris*
Mushroom worker's disease	Moldy compost and mushrooms	Thermophilic actinomycetes, *M. faeni, T. vulgaris, Aspergillus* spp., Mushroom spores
Suberosis	Moldy cork	*Penicillium* spp.
Malt worker's lung	Contaminated barley	*Aspergillus clavatus*
Maple bark disease	Contaminated maple logs	*Cryptostroma corticale*
Sequoisis	Contaminated	*Graphium* spp., redwood dust, *Pullularia* spp.
Soybean lung	Soybeans in animal feed	Soybean hull antigens
Wood pulp worker's disease	Contaminated wood pulp	*Alternaria* spp.
Wood dust HP	Contaminated wood dust	*Bacillus subtilis, Alternaria*
Compost lung	Compost	*Aspergillus* spp., *T. vulgaris*
Cheeseworker's disease	Cheese or cheese casings	*Penicillium* spp.
Wood trimmer's disease	Contaminated wood trimmings, at times in sawmills	*Rhizopus* spp., *Mucor* spp.
Thatched roof disease	Dried grasses and leaves	*Saccharomonospora viridis*
Greenhouse lung	Greenhouse soil	*Aspergillus* spp., *Penicillium* spp., *Cryptostroma corticale*
Coffee worker's lung	Green coffee dust	Unknown
Potato riddler's lung	Moldy hay around potatoes	*Thermophilic actinomycetes, M. faeni, T. vulgaris, Aspergillus* spp.
Tobacco worker's disease	Mold on tobacco	*Aspergillus* spp.
Wine grower's lung	Mold on grapes	*Botrytis cinerea*
Woodman's disease	Mold on bark and fuel chips	*Penicillium* spp.
Soy sauce brewer's lung	Fermentation starter for soy sauce	*Aspergillus oryzae*
Domestic allergic alveolitis	Decayed wood	*Serpula lacrymans, Leucogyrophana pinastr, Paecilomyces variotii, Aspergillus fumigatus*
Riding school lung	Hay in horse stall	*Thermophilic actinomycetes, M. faeni (S. rectivirgula), T. vulgaris*
Stipatosis	Esparto grass (Stipa tenacissima), used to make plaster	Esparto grass antigens
Pigeon breeder's disease	Avian droppings, feathers, serum	Altered serum/feather proteins
Turkey handler's disease	Turkey products	Turkey proteins
Chicken breeder's lung	Chicken feathers	Chicken feather proteins
Bird fancier's lung	Domestic and wild bird products	Bird proteins
Duvet lung	Duvet and pillow	Goose proteins
Laboratory worker's HP	Rat fur	Rat urine protein
Pituitary snuff taker's disease	Pituitary powder	Vasopressin
Shell lung	Oyster or mollusk shell	Shell proteins
Miller's lung	Grain weevils in wheat flour	*Sitophilus granarius* proteins
Sericulturist's lung	Silkworm larvae	Silkworm larvae proteins
TDI HP	Toluene di-isocyanate	Altered proteins (albumin + others)
MDI HP	Diphenylmethane diisocyanate	
HDI HP	Hexamethylene diisocyanate	
TMA HP	Trimetallic anhydride	Altered proteins
Ventilator lung	Contaminated humidifiers, dehumidifiers, air conditioners, heating systems	*Thermophilic actinomycetes, T. candidus, T. vulgaris, Penicillium* spp., *Cephalosporium* spp., *Amoebae, Klebsiella* spp., *Candida* spp.
Basement lung	Contaminated basement (sewage or mold)	*Cephalosporium spp., Penicillium* spp.
Sauna taker's disease	Sauna water	*Aureobasidium* spp.
Detergent worker's disease	Detergent enzymes	*Bacillus subtilis*
Japanese summer house HP	House dust, bird droppings	*Trichosporon cutaneum*
Hot-tub lung	Mold on ceiling	*Cladosporium* spp.
Tractor lung	Contaminated tractor, cab air conditioner	*Rhizopus* spp.
Machine operator's lung	Contaminated metal working fluid	*Pseudomonas* spp.
Fertilizer lung	Contaminated fertilizer	*Streptomyces albus*
Sax lung	Saxophone mouthpiece	*Candida albicans*

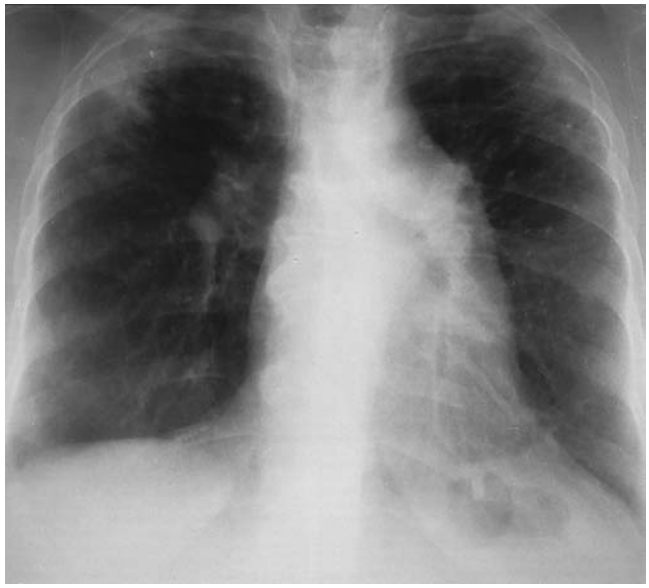


Figure 58-2 Chest radiograph of a patient with bird fancier's disease who presented with progressive dyspnea and weight loss. She had kept two to three parakeets in her home for 15 years and did not notice episodic fever or acute dyspnea. She had positive serum precipitins to parakeet serum, severe restrictive disease, and resting hypoxemia. Note the diffuse radiodensities, loss of volume of the upper lobes, and pulmonary hypertension.

areas of fibrosis from previous episodes of acute HP) may also be present. The nodular and ground-glass densities tend to disappear after cessation of exposure, so the chest radiograph may be normal after resolution of an acute episode of HP (Fig. 58-2). High-resolution CT scans often demonstrate ground-glass densities better than chest radiographs and at times reveal diffusely increased pulmonary radiodensities. They may also become normal after resolution of an acute episode. Pleural effusions or thickening, calcification, cavitation, atelectasis, localized radiodensities (coin lesions or masses), and intrathoracic lymphadenopathy are rare.

In chronic HP, chest radiographs are notable for diffuse linear and nodular radiodensities, with sparing of the bases and upper-lobe predominance, and volume loss (Fig. 58-3). Pleural effusions and thickening are very unusual, although subcutaneous emphysema (presumably as a consequence of pleural rupture due to bronchiolitis and lobular overinflation) has been reported.

High-resolution CT scans of patients with chronic HP demonstrate several patterns. Most commonly there are multiple centrilobular nodules 2 to 4 mm in diameter throughout the lung fields, with some areas of ground-glass radiodensities, especially in the lower lobes (Fig. 58-4). Unlike sarcoidosis, the nodules are seldom attached to the pleura or bronchovascular bundles, and the border between the nodules and the surrounding lung is well demarcated. There are also well-delineated areas of increased radiolucency, which are presumably overinflated pulmonary lobules subserved by partly occluded bronchioles. The ground-glass densities and micronodules tend to resolve after cessation of exposure. Although these findings are suggestive of HP, they are found in only a subset (50%–75%) of patients with HP, and high-resolution CT scans of the lungs of patients with HP can resemble those of patients with IPF. In cases of chronic avian-related HP, honeycombing and airspace consolidation on high-resolution CT scans are independently associated with increased mortality risk, even after controlling for spirometric and demographic

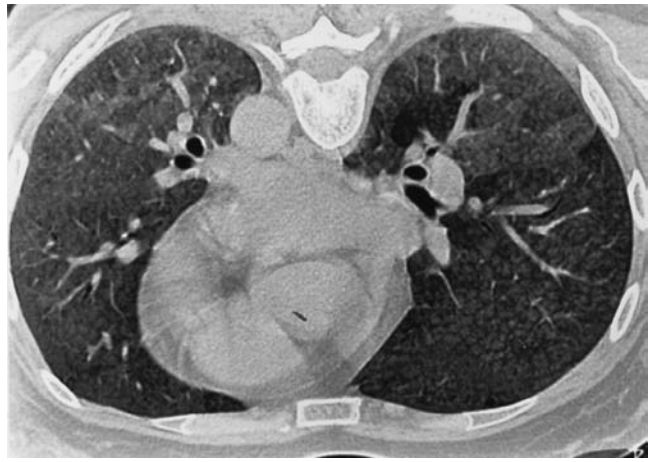


Figure 58-3 High-resolution CT scan of a nonsmoking patient with exposure to both birds and shells who presented with progressive dyspnea and weight loss and had hypoxemia and a restrictive ventilatory defect. Note the diffuse nodular radiodensities in the lower lobes, with areas of ground-glass densities posteriorly.

variables.[13] Emphysematous abnormalities are also commonly detected by high-resolution CT scans in nonsmoking patients with farmer's lung disease.

■ LABORATORY FINDINGS

Patients with acute HP often have a peripheral blood leukocytosis with neutrophilia and without eosinophilia. Prominent cellular abnormalities may also be seen in their BAL fluid, which may be useful in supporting the diagnosis of HP. At time points greater than 5 days after the last exposure, a two- to fourfold increase in BAL fluid leukocytes and lymphocytosis (typically 30%–70% of total cells) are frequently noted. In most instances of HP, the BAL fluid lymphocytes are virtually all $CD3^+$ (T lymphocytes), with a relative increase of $CD8^+$ cells, so that the CD4:CD8 ratio is usually less than 1 (normally 2–2.5, as in peripheral blood).[14] This profile varies considerably with the stage of disease. Indeed, only 33 of 98 HP patients (34%) in one case series displayed a lymphocytic $CD8^+$ alveolitis.[15] Findings of a higher $CD4^+$:$CD8^+$ ratio, fewer $\gamma\delta$ T cells,

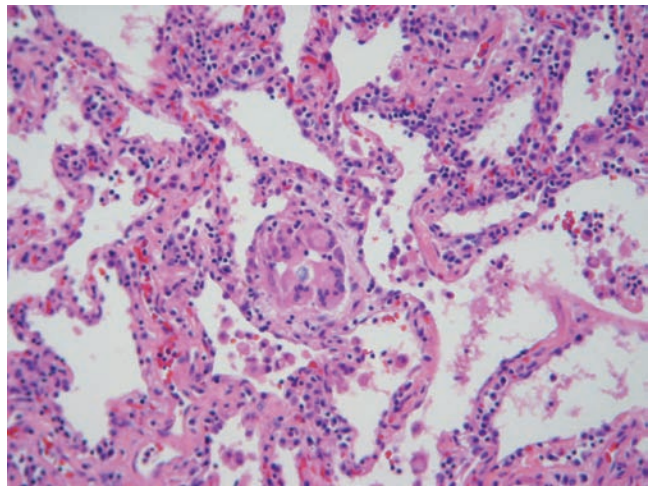


Figure 58-4 Low power view (20×) of H&E-stained section of surgical lung biopsy from a patient with bird fancier's disease. There are nonspecific interstitial mononuclear inflammation and loosely formed granulomatous lesions.

and more terminally differentiated memory $CD4^+$ and $CD8^+$T cell subsets in BAL fluid from patients with chronic HP compared to that from patients with subacute HP suggest that fibrosis may be related to a shift toward Th2 immunity in the lung.[16] Furthermore, BAL lymphocytosis may persist for years following clinical improvement and apparent removal from antigen exposure. Conversely, exposed asymptomatic individuals may exhibit BAL lymphocytosis, further limiting its utility in diagnostic evaluation. After recent (<48 h) exposure, as well as in advanced disease, the lavage is frequently characterized by BAL fluid neutrophilia.[17] The concentrations of IgG, IgM, IgG, and albumin are increased in BAL fluid, presumably a nonspecific manifestation of pulmonary inflammation.

Many patients with HP have easily demonstrable antibodies (typically IgG, IgM, and IgA) to the offending material in the serum, detectable by a variety of methods. Since antigen preparations are not standardized, it is difficult to be confident of the meaning of a negative result; therefore negative "HP panel" does not exclude the diagnosis of HP. Furthermore, since serum antibody is also present in many exposed, but not ill, subjects in virtually the same amounts as in patients with HP, the presence of antibody should be considered supporting data in the proper clinical context.

In asymptomatic pigeon breeders, the prevalence of antibody to pigeon antigens is 30% to 60%. In farmers, the prevalence of anti-*Micropolyspora faeni* serum antibody is 2% to 27%. The occurrence of serum antibody is not consistently related to apparent exposure (i.e., hours of exposure or intensity of exposure) in most instances of HP. This may be related to a threshold effect, so that most exposures are above the minimum required to induce antibody and increases above that threshold are not associated with increases of the prevalence of antibody. In addition, serum antibody tends to wane after cessation of exposure, so patients with chronic HP who have not been exposed for some time may not have demonstrable antibody. In farmer's lung disease, approximately 50% of patients with initially positive serum antibody to *M. faeni (Saccharopolyspora rectivirgula)* lose demonstrable antibody 6 years after cessation of exposure. Farmers who continue to farm also lose detectable antibody (35%–50% in 5 years),[18] and some asymptomatic farmers who were initially negative later develop antibody without farmer's lung disease. In pigeon breeder's disease and bird fancier's disease, approximately 50% of patients with initially positive serum antibody to avian antigens lose demonstrable antibody 2 to 3 years after cessation of exposure. Therefore, it is possible that patients with HP will have no detectable serum antibody owing to either use of an inappropriate antigen in the assay or the waning of antibody in time since the last exposure.

Nonspecific markers of inflammation, such as increased sedimentation rate and C-reactive protein, are often elevated during an acute episode of HP, though are quite nonspecific. In contrast to sarcoidosis, the serum angiotensin-converting enzyme levels are usually not elevated. Skin tests (either immediate or delayed type) to detect sensitization to the suspected antigens are not useful, since extracts of agents that cause HP produce nonspecific reactions that do not indicate sensitization and do not discriminate between sensitized and nonsensitized subjects.

Pulmonary function tests may be restrictive, obstructive, or mixed. There is an increased lung elastic recoil, and usually decreased diffusing capacity. Arterial hypoxemia with hypocapnia reflecting an increased alveolar-arterial oxygen gradient either at rest or after exercise is common. However, 39 of 177 patients (22%) with $D_{L_{CO}}$ data available to the HP Study Group displayed normal diffusion capacity, defined as a $D_{L_{CO}} \geq 80\%$ predicted at the time of diagnosis.[19] Many patients with HP (20%–40%) exhibit increased nonspecific airway reactivity, and 5% to 10% also develop clinical asthma.[20] The increased airway reactivity and asthma tend to diminish after cessation of exposure.

DIAGNOSIS

The symptoms, signs, and laboratory findings of acute HP can resemble those of many other lung diseases, including pulmonary edema, organic dust toxic syndrome (ODTS), inhalation fever, chronic bronchitis, and some pneumoconioses. Acute HP is also often confused with infectious pneumonia (viral, mycoplasma, or chlamydia in subjects exposed to birds). Subacute HP is characterized by a more gradual onset of cough, fatigue, dyspnea, and weight loss, and such symptoms may also develop with intermittent acute attacks. There is considerable overlap in the presentations of acute and subacute HP, in contrast to chronic progressive HP (discussed below).

Chronic bronchitis in nonsmoking farmers and bird breeders is more common than HP, and may share overlapping immunopathogenic mechanisms with HP. The finding of serum precipitins is more frequent in farm workers with chronic bronchitis than those who are asymptomatic. ODTS has been seen in some of the same populations exposed to materials that cause HP, although its cause is likely mycotoxins from bioaerosols contaminated with toxin-producing fungi. ODTS can occur in a larger proportion of the exposed population than HP and is characterized by transient fever, dyspnea, nonproductive cough, peripheral blood leukocytosis, and BAL fluid neutrophilia. The manifestations commonly include diffuse opacities on chest radiograph, restrictive ventilatory defects, reduced $D_{L_{CO}}$, and bronchiolitis obliterans without granulomas on lung biopsy. Diffuse alveolar damage may occur in severe cases. In contrast to HP, prior sensitization is not required (as indicated by the absence of serum antibodies). Patients presenting with ODTS tend to have more intense exposure of shorter duration than those who present with farmer's lung disease. Another disease caused by exposure to the some of the same agents associated with HP is inhalation fever. This is manifested as fevers, chills, malaise, headaches, and myalgias without prominent pulmonary findings, although mild dyspnea and cough may occur. The onset usually occurs 4 to 12 hours after exposure. Usually there are normal lung volumes and diffusing capacity. The clinical syndrome remits after 12 to 24 hours without specific therapy. Symptoms and signs are exaggerated following an exposure that occurs after a period of nonexposure (such as vacations or weekends), but then become blunted despite continued exposure ("Monday illness"). All signs and symptoms of inhalation fever remit after cessation of exposure, and there are no permanent physiologic or radiographic changes.

In contrast to acute and subacute HP, the classic or typical clinical findings are usually not present in chronic HP. The chronic form of HP often resembles IPF, and these entities may be extremely difficult to distinguish. The differential diagnoses also includes other causes of pulmonary fibrosis (e.g., drug reactions, rheumatologic disease, asbestosis, radiation). Further complicating matter is the frequent lack of clear history of acute episodes. In addition, removal from the presumptive offending agent may result in little or no clinical improvement at this stage.

A thorough and complete occupational and avocational history is essential to the diagnosis of all forms of HP. The history should seek to establish a link between a particular exposure (at work, at home, or elsewhere) and previous episodes of "pneumonia." Knowledge of other exposed persons with similar symptoms should be sought. Evidence of repetitive appropriate symptoms and laboratory and radiologic abnormalities associated with exposure to a particular environment is also highly suggestive of HP. In questionable instances, a "natural exposure" (i.e., documentation of appropriate symptoms and laboratory abnormalities after exposure to a suspect environment) can be used to diagnose HP. A "natural exposure" challenge should not be considered positive unless there is objective

evidence of a change in temperature, total peripheral white blood cell count, chest radiograph (or high-resolution CT scan), or a decrease in diffusing capacity (or arterial P_{O_2}). If the history suggests a relationship between exposure and pulmonary symptoms, evidence of sensitization and the nature of the pulmonary inflammatory response should be determined. Sensitization is indicated by the presence of serum antibody to an agent known to cause HP. A large proportion of lymphocytes in BAL fluid (usually over 40%) is highly suggestive of, though not specific for, HP.

A variety of tools exist that have utility in the diagnosis of HP, all of which have advantages and disadvantages. One of the difficulties in assessing the value of diagnostic methods in HP is the vagueness of the "gold standard."[21] Though most would agree that the presence of poorly formed, airway-centered nonnecrotizing granuloma on lung biopsy in a patient with exposure to a known offending agent is supportive enough to be "diagnostic," these features are commonly absent, and a number of histologic variants have been described (see below).[22,23] Since the utility of lung biopsy, absent classic features, is largely supportive, several prediction rules have been devised to determine the probability of a diagnosis of HP based upon clinical features. One such model, developed by the Hypersentitivity Pneumonitis Study Group,[24] examined a cohort of 400 patients with suspected HP and found six significant predictors retrospectively (116 were ultimately diagnosed with HP). These were then validated prospectively in 261 patients (83 of whom were eventually given the diagnosis). It should be noted that the ultimate determination, or gold standard, was the consensus of experts, in many cases without tissue. Although not ideal, at the current level of understanding of the nature of HP, this may be the best method available.[21] The criteria used in this study were (1) exposure to a known offending antigen, (2) positive precipitating antibodies to the offending agent, (3) recurrent episodes of symptoms, (4) inspiratory crackles on physical examination, (5) symptoms occurring 4 to 8 hours after exposure, and (6) weight loss. The probability of having HP was determined based upon the presence or absence of these predictors. The probability of HP ranged from 0% in those patients with none of the predictors to 98% in patients with all six of these features. Exposure to a known offending antigen was the strongest clinical predictor with an odds ratio of 38.8. In cases lacking a compatible exposure history, the diagnosis of HP was made only after further investigation, including supportive findings on lung biopsy (discussed below). It should be emphasized that these clinical prediction rules are of little value in chronic HP, which is usually a more difficult diagnostic problem (often even when histopathology is available). Of course, in the evaluation of individual patients, the threshold for further investigation clearly depends upon the clinical setting and the consequences of the diagnosis.

HISTOPATHOLOGY

A lung biopsy specimen is generally required when there is significant doubt about the diagnosis. Transbronchial lung biopsies often do not provide sufficient material to fully establish the presence and interrelationships of granulomas, bronchiolitis, and interstitial inflammation, so either open or thoroscopically obtained lung biopsies may be necessary. These often reveal chronic interstitial and alveolar inflammation with infiltration of plasma cells, mast cells, macrophages, and lymphocytes, usually with poorly formed nonnecrotizing granulomas (Figs. 58-4 and 58-5). The inflammation usually extends from the terminal bronchioles into the parenchyma. Foamy macrophages are usually evident in the alveoli. There is often bronchiolitis as well as bronchiolitis obliterans. Organizing pneumonia is also present in up to 50% of patients with HP (Fig. 58-6). Conversely, patients with recognized bronchiolitis obliterans with organizing pneumonia (BOOP) may have underlying HP, whether or not other histologic manifestations are evident.

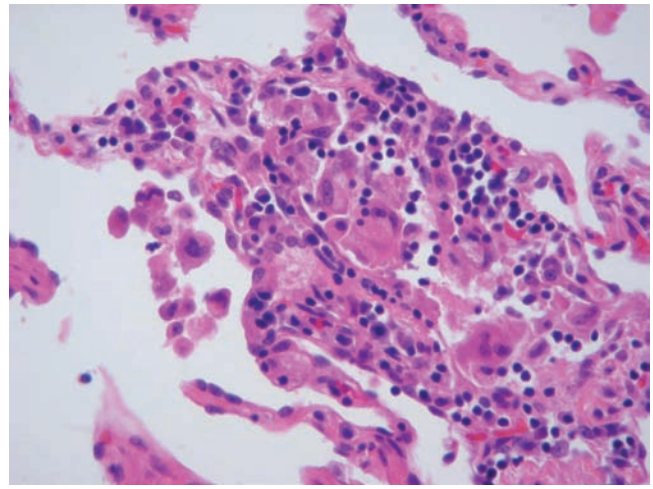


Figure 58-5 Higher power view (40×) of the section shown in Figure 58-4.

Varying degrees of interstitial fibrosis are also often present. The granulomatous interstitial inflammatory responses of HP and sarcoidosis can be difficult to differentiate, though in HP these are usually smaller, poorly differentiated, loosely arranged and contain more lymphocytes and fewer multinucleated giant cells. In contrast to sarcoidosis, the interstitial inflammatory cell infiltrate in HP occurs distal as well as proximal to the granulomas. The granulomas of HP also tend not to occur in groups and tend not to occur near bronchi or in subpleural locations. Instead, they are usually adjacent to bronchioles and are often single. In the absence of granulomas, the pattern may resemble that of nonspecific interstitial pneumonitis, though the bronchiolocentric nature of the lesions and the presence of giant cells or organizing pneumonia may be clues suggesting underlying HP.

The predominant pattern of inflammation and fibrosis in a patient's lung biopsy stands to inform his or her prognosis. In a study of 110 patients with pigeon breeder's lung, the survival rate was highest for those with biopsy specimens displaying a nonspecific interstitial pneumonia (NSIP) pattern and lowest for those with changes of UIP.[24] Interestingly, the survival prediction for patients with typical HP biopsy findings fell between the Kaplan–Meier curves for patients with NSIP and UIP in this investigation. Another

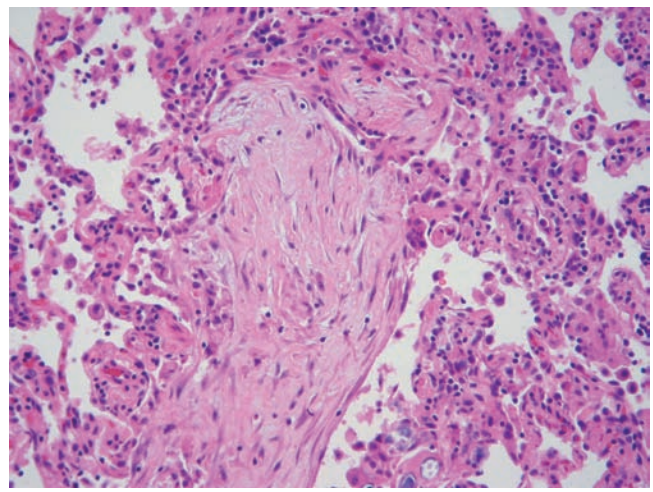


Figure 58-6 Organizing pneumonitis in a patient with bird fancier's disease.

study that considered more diverse causes of HP demonstrated that survival is considerably shorter for patients with UIP-like and fibrotic NSIP-like histology compared to those with isolated peribronchiolar fibrosis.[25] Therefore, lung biopsy results may play an important role in counseling patients about the anticipated natural history of their disease.

The specific histologic changes of HP, when present, are quite helpful in making the diagnosis. However, the granulomas and respiratory bronchiolitis may not be present years after cessation of exposure, so only interstitial inflammation and fibrosis remain in many subacute and most chronic cases.[26] Although these findings might be useful in supporting the clinical diagnosis of HP, they would be insufficient to confirm it.

IMMUNOPATHOGENESIS

Considerable evidence obtained over the past 25 years suggests a primary role for T cell–mediated events in the pathogenesis of HP. A contribution of humoral immunity, especially in acute HP, has not been excluded however. The presence of serum antibody in patients with HP and the timing of symptoms after exposure (2–9 hours) led to the hypothesis that HP represents an example of immune complex–mediated lung disease. Therefore, it is possible that immune complexes initiate the injury upon antigen exposure, which is then perpetuated and amplified by T cell activities. By the time the disease is clinically evident, lung tissue gene expression profiles indicate T cell–driven inflammation (in contrast to the profiles of IPF and NSIP).[27] The T cell responses evident in HP are notable for the predominance of $CD8^+$ cells and the expression of interferon-gamma (IFN-γ), the prototypic cytokine of type 1 inflammatory processes. Expression of IFN-γ–dependent chemokines, such as CXCL9 and CXCL10, is also observed in HP lungs, which undoubtedly serves to amplify the type 1 inflammation. Not unexpectedly, $CD8^+$ T cells in BAL of HP patients strongly express CXCR3, the receptor for both of these chemokine.[28]

Although the Th1 response has canonically defined HP, recent evidence suggests that dysfunctional regulatory T cells (Tregs) are involved with a loss of tolerance to inhaled antigens. Broadly speaking, these $CD4^+Foxp3^+$ lymphocytes suppress the activity of Th1 and Th2 effector cells, which is important for antigen self-recognition and the prevention of autoimmune diseases.[29] Compared to Tregs from BAL and blood of healthy controls, those obtained from HP patients cannot suppress T-lymphocyte activation in vitro, perhaps because of IL-17 production, given that significantly higher IL-17 levels are found in sera and BAL samples from the latter population.[30] The importance of Th17 polarized $CD4^+$ T cells in generating fibroinflammatory lung injury has been described in mice using *S. rectivirgula*.[31] This murine model has also been used to demonstrate that Tregs concurrently reduce IFN-γ production and pulmonary infiltration by $CD4^+$ and $CD8^+$ lymphocytes.[32] Whether Tregs and/or Th17 immunity explain the clinical heterogeneity of HP has yet to be determined.

In animal models of HP, macrophage-derived cytokines such as IL-1, IL-6, IL-12, and TNF-α (as well as a variety of chemokines) play a central role in models that entail intrapulmonary administration of various antigenic substances.[33] TNF-α, produced by activated macrophages as well as $CD8^+$ T cells, likely participates both in the amplification of the inflammation and the activation/degranulation of neutrophils recruited to the alveolar space.[34,35] Interestingly, polymorphisms in the TNF-α promoter have been reported in a group of patients with farmer's lung disease, which correlated with higher serum levels of TNF-α after challenge with hay dust, compared with a group of sensitized asymptomatic controls.[7] Two small genetic susceptibility studies in Mexican[8] and Dutch[36] patients with bird fancier's disease found protective polymorphisms in the tissue inhibitor of metalloproteinase-3 (TIMP-3) gene, which is involved in the inhibition of metalloproteinases associated with extracellular matrix turnover. TIMP-3 has also been identified recently as the primary inhibitor of TNF-α–converting enzyme (TACE/ADAM-17), and this enzyme is responsible for processing TNF-α to its soluble form, which is intensely proinflammatory.[37] The TIMP-3 polymorphism was not found in patients with IPF or NSIP.[8] It is therefore reasonable to speculate that the expression and/or proteolytic processing of TNF-α is important in the pathogenesis of HP, though clearly this leaves much to be explained concerning the varying clinical pictures of the disease.

PROGNOSIS AND TREATMENT

Prognosis varies considerably with the type of HP and even the geographic location. For example, farmer's lung disease has a good prognosis in Quebec, even in farmers who continue to farm. However, farmer's lung disease in Finland often results in significant physiologic impairment and even death. Pigeon breeder's disease has a good prognosis in the United States and Europe, whereas the same disease in Mexico has a 30% 5-year mortality.[38] The reasons for these differences are not clear but may include differences in the nature of the antigen and the exposure.

Identification of the offending antigen is critical to effective avoidance, which is the primary intervention in all forms of HP. This is not always practical when the exposure is occupational, such as in farmer's lung disease. In addition most farmers who continue to be exposed may fare no worse than those who leave their farms.[39] Nevertheless, removal from exposure to the offending antigen(s) is usually sufficient to resolve symptoms and physiologic abnormalities. Measures to reduce antigenic burden may include protective equipment and reducing microbial contamination of the home or work environment. Elimination of excess moisture, reduction in humidity, repair of water damaged materials, regular cleaning of humidifiers, ventilation, and air conditioning equipment all contribute to reduction in mold and other microbial colonization, which may predispose to sensitization. Removal of birds from the home of patients with bird fancier's disease is a critical aspect of treatment, but antigens may persist for extended periods despite thorough cleaning of the home environment.[12]

Systemic glucocorticosteroids are usually required to treat severely symptomatic patients, although there is no formal evidence that such treatment is associated with long-term abatement of symptoms or radiologic or pulmonary function test abnormalities.[30,40] The usual treatment is prednisone or prednisolone, 40 to 60 mg a day for 2 weeks, followed by a gradual decrease over 2 to 4 weeks. Patients with farmer's lung disease treated with prednisolone, compared with those not treated with prednisone, demonstrated slightly more rapid resolution of some radiologic (ground-glass opacities) and some physiologic abnormalities than untreated patients (slight improvement of diffusing capacity, no difference in lung volumes or arterial P_{O_2}). However, there were no differences between the groups 6 months after the diagnosis of HP. The evidence mentioned earlier suggests that systemic steroids may slightly increase the rate of resolution of acute pulmonary inflammation but have little or no effect on chronic residue of HP.

If patients are removed from exposure before there are permanent radiologic or physiologic abnormalities, the prognosis is excellent, with little evidence of long-term ill effects. If removal from exposure is impossible, the use of efficient masks during exposure can result in prevention of acute HP and an excellent prognosis. The prognosis varies considerably with different types of HP. In general, bird fancier's disease carries a worse prognosis than other forms of HP, though even this varies considerably depending on the specific nature of the exposure. It appears that long-term low-level exposure is associated

with a poorer prognosis, whereas short-term intermittent exposure is associated with a more favorable one. Unfortunately, many patients with chronic HP present with pulmonary fibrosis and physiologic abnormalities that are only partly reversible after cessation of exposure. The specific nature of histopathologic findings on biopsy in these patients at the time of diagnosis may help predict subsequent clinical course of the disease.[41] Not surprisingly, patients with organizing pneumonia/BOOP or cellular NSIP have a better prognosis than those with fibrotic NSIP or other patterns of fibrosing pneumonitis.

SUMMARY

In conclusion, HP is an immunologically mediated lung disease likely mediated primarily by T cell responses to inhaled antigens. The diagnosis requires careful history, appropriate laboratory tests, and lung biopsy in selected cases. Avoidance of exposure is usually associated with a good prognosis, and corticosteroids are indicated in severely symptomatic patients. Because of constantly changing environmental exposures, new examples of HP are continually being described, and represent an ongoing challenge in patients presenting with undefined interstitial lung disease.

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CHAPTER 59
Radiation Pneumonitis

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Roy Decker
Sara Rockwell

INTRODUCTION

The discovery of X-rays by Roentgen in 1895 and of radium by the Curies in 1898 revolutionized medicine at the turn of the 20th century. Roentgen's first paper on X-rays illustrated the power of diagnostic imaging with a remarkably detailed radiographic image of Frau Roentgen's hand. As researchers around the world built vacuum tubes and acquired radioactive sources for their studies, it rapidly became apparent that these invisible radiations could produce dangerous, and even lethal, injuries.[1–3] Erythema, chronic dermatitis, ulceration, loss of hair, and eye injuries were soon reported in patients who received large doses of radiation during prolonged fluoroscopy procedures. Even greater injuries were reported among the physicians, technicians, and scientists who performed diagnostic procedures or laboratory studies using unshielded X-ray-generating equipment and highly radioactive sources. The development of these radiation injuries suggested that radiation might be useful in the treatment of cancer; indeed, patients with cancer were treated with radiation therapy as early as 1896.[1–3]

Radiation was found to inhibit the growth of tumors, but this benefit came with the cost of injury to normal tissues within the irradiated areas. Because of the very low energies of the early X-ray and gamma-ray sources, radiotherapy in its early days was limited to using poorly penetrating radiations, which delivered much higher doses of radiation to skin than to even very superficial tumors. As a result, severe early radiation reactions in the skin limited the doses of radiation that could be delivered to tumors. Studies of these skin reactions led to the development of the concept of normal tissue tolerance and an appreciation of the benefits of "fractionated" radiotherapy, using multiple treatments with small doses of radiation.[2] The relative sensitivity of the lung to injury from radiation became apparent early in the development of radiation oncology. The clinical syndromes of dyspnea, cough, fever, and radiographic infiltrates occurring weeks to months after irradiation of the thorax were dramatic enough to be described as early as 1922.[4]

The field of radiation oncology has matured immeasurably over the last century and has incorporated significant advances from fields as diverse as theoretical and applied physics, radiation biology, pathology, cell biology, and immunology.[1,2,5–7] The importance of advances in physics and engineering to the maturation of radiation oncology is especially notable.[2,7] These advances have led to the development of modern linear accelerators capable of delivering very high-energy, deeply penetrating radiations, which can be used to deliver high radiation doses with great precision to tumors deep within the body. Precise systems for radiation dose measurement, or *dosimetry,* rapid computers, and precise algorithms for the rapid computerized three-dimensional planning of individualized radiotherapy treatments based on computed tomography (CT) scans and magnetic resonance imaging (MRI) studies have been developed. These advances have changed the dose-limiting toxicities of radiation therapy from painful early reactions in the skin to life-threatening late reactions in the normal tissues invaded by and surrounding the tumors, including the lung.

For clinicians interested in pulmonary medicine, understanding radiation pneumonitis is important. An understanding of radiation injury to the lung can be useful in understanding other lung diseases. Because the chemical mediators of radiation effects, both beneficial and harmful, are free radicals, the pathway leading to radiation injury in the lung overlaps with those leading to many other lung injuries.[8,9] In addition, understanding radiation pneumonitis has practical value to physicians in many areas of medicine. Approximately one in three people in the United States will be diagnosed with cancer at some point in their lifetimes. Over half of these patients will be permanently cured of their malignancies. Approximately 65% of all patients with cancer receive radiotherapy at some point in the treatment of their malignancies, and radiotherapy seems destined to remain an important component of cancer treatment for the foreseeable future. Because of this, every physician can expect to care for many patients who are receiving radiotherapy or have received radiotherapy at some point in the past.

In addition to the association of radiation therapy with acute or subacute pulmonary disease, recent studies of plutonium workers have shown an excess incidence of pulmonary fibrosis.[10] These

findings, which are supported by data from a large number of studies in experimental animals, show that lung injury may be produced by inhalation of insoluble particulate radionuclides that are deposited in lung tissue and produce long-term irradiation of the tissue.

Respiratory diseases are also known to be a cause of increased late morbidity and mortality in the survivors of the atomic bombs in Hiroshima and Nagasaki.[11] Therefore, radiation injury to lung is possible in cases in which people are exposed to high levels of inhaled radionuclides or external irradiation through their occupations, accidents, or acts of war or terrorism.[9] A working knowledge of the basics of radiobiology and radiation oncology is important to every physician and healthcare provider. An understanding of the potential toxicities of radiotherapy and other exposures to radiation, including radiation pneumonitis, can be critical to patient care.

Many neoplasms involving the thorax are treated with regimens that include the use of radiotherapy to produce either cure or palliation. Radiotherapy is principally a localized, anatomically based modality. The success of radiotherapy hinges on delivering radiation selectively to the sites of malignant disease, while sparing to the maximal extent possible the uninvolved normal tissues.[1,2,5] To plan radiotherapy treatments effectively, the radiation oncologist must have a sophisticated appreciation of the malignancy being treated and understand its biologic behavior, patterns of local and metastatic spread, radiosensitivity, and factors that influence the responses of individual patients to therapy. The radiation oncologist must also consider the effects of radiation on normal tissues within the treatment volumes.

Many factors, including radiation dose, fractionation pattern, volume of the tumor and involved margins, prior or planned use of other therapies such as surgery or systemic chemotherapy, and presence of other diseases influence both the probability of controlling the neoplasm and of producing toxic reactions. For cancers of the lung, esophagus, pleura, breast, and chest wall, as well as for lymphomas involving the thorax, optimal treatment frequently involves use of multiple overlapping X-ray beams and possibly electron beams, planned to encompass all of the cancer-containing tissues. Although treatments are carefully planned to include the smallest possible amount of healthy normal tissue, some normal tissue will necessarily be included in the radiation fields. The radiation sensitivity of the specific tissues in the irradiated fields and the acceptable level of risk for complications combine to limit the dose of radiation that can be administered. The planning of radiotherapy always involves a balance of benefit and risk, because the probabilities of controlling the malignancy increase with increasing radiation dose, but the probabilities and severities of the potential complications increase with dose as well.

To illustrate the mechanisms involved in planning radiotherapy treatments, a treatment plan is depicted in Figure 59-1A. The first panel shows the isodose distribution for treatment of a stage IIIB non–small-cell lung cancer, using a color-wash display in which the highest radiation dose is shown in red and lower doses in shades of yellow, green, and blue. This represents the sum of multiple radiation portals using intensity-modulated radiation therapy (IMRT), in which computer-based planning is used to deliver high dose to the tumor target with specific dose limits to normal tissue structures, such as the spinal cord, esophagus, heart, and lungs. The volume of normal lung receiving significant radiation can be readily appreciated.

The radiation dose delivered to the lung tissue is shown in a cumulative dose–volume histogram, in Figure 59-1B, which integrates the percentage of the volume of the organ at risk (on the vertical axis) receiving the specified cumulative radiation dose (on the horizontal axis). While this is a simplified representation of a complex dose/volume relationship, this formalism has become important in analyzing radiation dose delivery and correlating dosimetry with treatment outcome. In the illustration, the volume of lung receiving greater than or equal to 20 Gy is referred to as the V_{20}. In this case, the V_{20} is 35%, which predicts at least a 25% risk of grade 2 or greater pneumonitis (see discussion below, Clinical Syndromes). In Figure 59-2, the patient's pretreatment CT scan (panel A) is shown in comparison to a 3-month postradiation scan (panel B). The latter demonstrates radiation-induced inflammatory changes corresponding to the high-dose region of the radiotherapy. In this case, these changes were associated with increasing dyspnea, cough, and a decrease in diffusion capacity. Panel C shows slowly resolving changes, with persistent pulmonary fibrotic changes, on a CT scan obtained 1 year post treatment.

In the case presented, if the malignancy is cured, or the patient experiences the desired improvement in symptoms with minimal or manageable toxicity from the radiotherapy, the treatment is a success even if accompanied by radiographic changes or by other subclinical damage to the lung or other organs. Overt pulmonary toxicity is, however, a potential consequence of thoracic radiotherapy that sometimes overshadows the benefits of treatment.

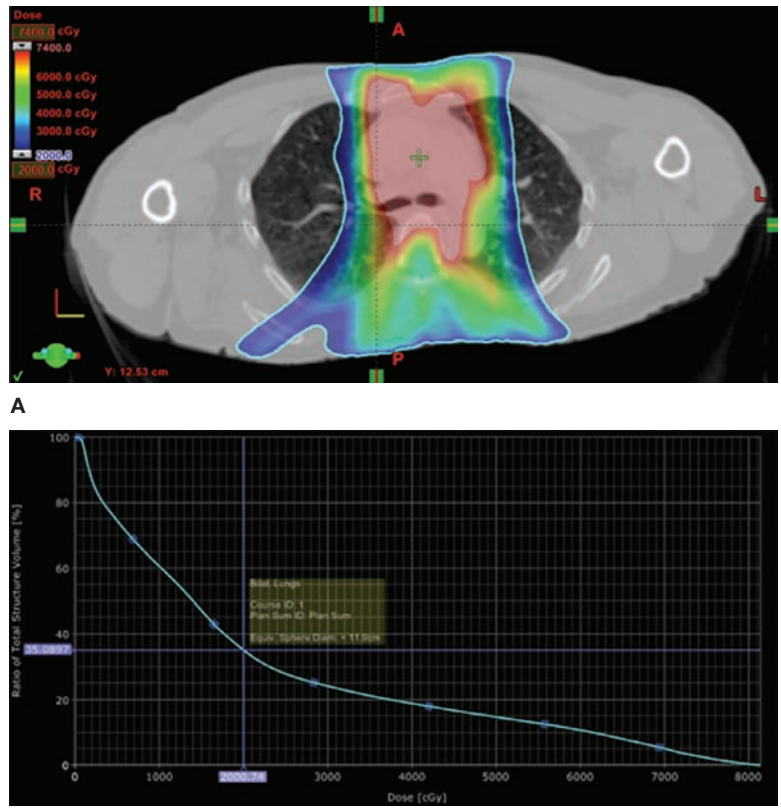
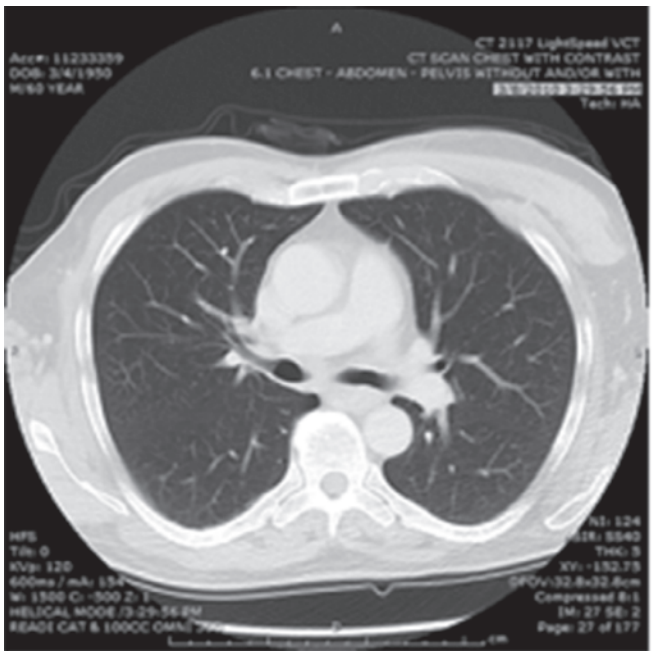


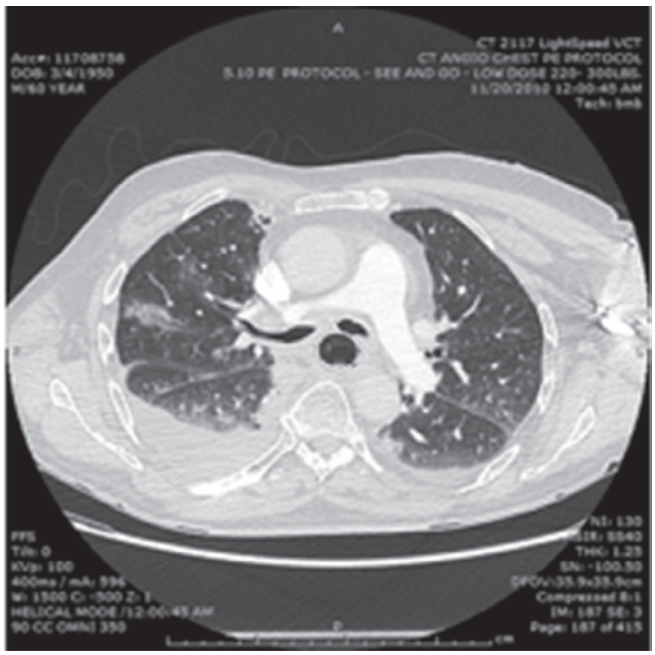
Figure 59-1 A 60-year-old man with stage IIIB non–small-cell lung cancer was treated with radiotherapy and concurrent cisplatin-based chemotherapy. The plans for his radiation treatments are summarized. **A.** The isodose distribution from a complex multifield radiation plan is overlaid on a treatment-planning CT scan. Using a color-wash format, radiation dose is demonstrated from 20 Gy *(green)* to 70 Gy *(red)*. **B.** Cumulative dose–volume histogram of the entire treatment course for bilateral lung tissue. The volume of normal lung receiving 20 Gy or more (V_{20}) is 35%.

BRIEF OVERVIEW OF RADIOLOGIC PHYSICS

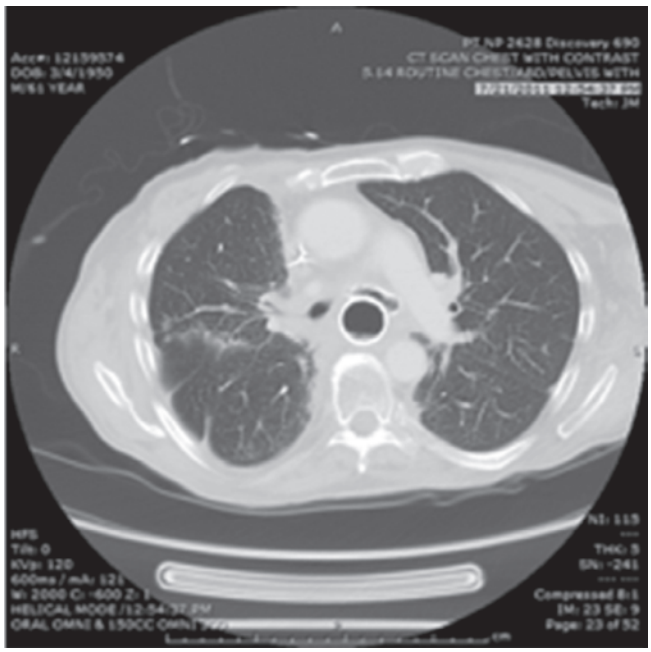
External beam radiotherapy is generally delivered using X-rays or gamma rays. Both of these radiations are high-energy electromagnetic waves or photons that are able to cause ionizations when



A



B



C

Figure 59-2 The same patient as in Figure 59-1, developed a progressive dyspnea and nonproductive cough. A comparison of chest CT imaging from before treatment (Panel A) and 3 months after treatment (**Panel B**) demonstrated interstitial infiltrates and ground-glass changes in a distribution consistent with the prior radiation, as well as the development of new pleural effusions. This is consistent with radiation pneumonitis, and the patient was treated with corticosteroids. He symptomatically improved over several months. A chest CT scan at 1 year (**Panel C**) shows residual fibrotic changes in the paramediastinal region. **Panels** (**B**) and (**C**) also show bronchial and esophageal stents placed for palliation of a tracheoesophageal fistula.

interacting with matter.[7] The only difference between them lies in the manner in which they are produced: Gamma-ray photons are emitted from atomic nuclei during the decay of radioactive atoms, and X-rays are produced when high-energy electrons strike a target material and interact with the electron shells of atoms in that target, causing them to emit X-ray photons (the *bremsstrahlung effect*). After its emission, an individual X-ray photon is indistinguishable from a gamma-ray photon. Thus, although the discussion below uses X-rays as examples, the principles are equally applicable to radiotherapy using high-energy gamma rays (e.g., from cobalt-60 teletherapy units or brachytherapy using implanted radioactive sources).

The X-rays used for diagnostic imaging are in a relatively low-energy range, in which the dominant interaction of photons with matter is through the "*photoelectric effect*." In this process, absorption of a photon causes an electron to be ejected from the inner shell of an atom. The probability of photoelectric interactions increases as a function of the cube of the atomic number, that is, as Z^3. Consequently, large, heavy atoms absorb low-energy diagnostic X-rays much more efficiently than smaller, lighter atoms.

Diagnostic radiology capitalizes on the large differences between the absorption of low-energy X-rays in materials with different compositions, for example, air, soft tissue (which is 70% water and, therefore, composed primarily of the small atoms hydrogen and oxygen), bone (with its high calcium content), and administered contrast agents containing barium, iodine, or other heavy atoms. The differences in absorption are used to image anatomical structures. In contrast, high-energy X-rays used in radiotherapy interact with matter primarily by a phenomenon called the "*Compton effect,*" in which X-rays cause ionization of atoms via interactions with their outer electron shells. The Compton effect is not dependent on the atomic number, but is, instead, a function of the electron density. Because the electron densities of most biologic tissues are relatively uniform,

for the purposes of most radiotherapy dosimetry, it is reasonable to assume that a patient is of uniform density, equivalent to water.

An important caveat to radiation dosimetry involves the standard specification of doses in tissues that include a large proportion of air, such as the lung. As a single X-ray beam penetrates through water or tissue, the dose received by the tissue falls progressively, generally as an exponential function of distance. Because of its markedly lower density, air absorbs less radiation energy and, therefore, attenuates the X-rays less than does tissue or water. With the quantitative knowledge of lung density that can now be derived from CT scanning, algorithms have been devised to estimate the inhomogeneity in the absorbed dose resulting from differences in the density of lung and other soft tissues.[7,12] These heterogeneity corrections show that routine dosimetric calculations, which assume uniform density, underestimate the radiation doses to lung and tissues beyond the lung by 5% to 25%.

Although the effect of tissue heterogeneity is a very important consideration when quantifying the radiation dose delivered to the lungs, one must remember that doses delivered to the thorax and the lungs historically have been reported in the medical literature *without* heterogeneity corrections. Moreover, because the preponderance of clinical data concerning lung tolerance have been determined and reported using older dosimetric algorithms, which assume that lung has water-equivalent density, the impetus to change dose reporting is tempered by the desire to avoid confusion between the newer and older literature. The reader should assume, unless explicitly stated otherwise, that the historic radiation doses given in this chapter, or for that matter any publication, are not necessarily corrected for lung density. Most modern radiotherapy planning systems now include the ability to account for tissue heterogeneity. Without such corrections, actual dose delivery to the chest region is modestly higher than the nominal doses reported. However, the variability of the actual dose delivery is highly individual and only recently has been accounted on a routine basis with improvements in computerized treatment planning.

Radiation dose is currently reported using the unit of the Système International (SI), the gray (Gy). The Gy is a measure of the energy absorbed by 1 kg of tissue; 1 Gy = 1 J/kg. The former unit of absorbed dose, called the "rad" (an acronym for "radiation absorbed dose") was measured with the CGS system; by definition, 1 rad = 100 ergs per gram. To compare old and recent literature, one must remember that 1 Gy = 100 rad. Despite the fact that it is not an approved SI unit, some radiotherapy literature avoids this conversion by giving the dose in centigray (cGy), where 1 cGy = 0.01 and Gy = 1 rad. Other measures of radiation dose seen in the literature include the roentgen, the Sievert, and the rem.

The roentgen measures radiation *exposure,* rather than energy *absorption,* and refers specifically to the amount of ionization produced in air under standard conditions (1 R = 1 electrostatic unit/cc = 2.58×10^{-4} coulombs/kg of "standard air" at a density of 1.29×10^{-4} g/cm^3 at 0°C and 760 torr). This unit is frequently encountered in the radiation dosimetry literature, not only because it was historically used as a measure of dose, but also because many widely used radiation monitors (e.g., ionization chambers) directly measure radiation exposure at the surface of the body. The dose absorbed by tissue is then calculated from this exposure.

The radiation protection literature uses the unit of "equivalent dose," the Sievert (Sv), which is calculated as the absorbed dose (in Gy) multiplied by a "weighting factor" that considers the differing biologic effects of different radiations. Although the weighting factors for some radiations, such as neutrons and alpha particles, can be as high as 20, the weighting factors for X-rays, gamma rays, and electrons are all defined as 1. For most purposes in diagnostic and therapeutic radiology, therefore, 1 Sv = 1 Gy. The Sv replaces the older unit of equivalent dose, the rem (1 Sv = 100 rem). Unfortunately, the literature on radiation-induced lung injury includes papers using all of these different units, creating great confusion for readers. For simplicity, all doses in this chapter have been converted to Gy.

RADIOBIOLOGY OF RADIOTHERAPY

When X-rays pass through tissue, a complex series of physical and chemical reactions occurs.[1,13,14] As the X-rays interact with atoms along their path, energy is absorbed, and energetic fast electrons are ejected. These fast electrons travel through tissue, producing secondary ionizations, which lead within milliseconds to the generation of a variety of highly reactive free radical species. Because biologic materials are about 70% water, ions and free radicals derived from water (e.g., H, OH, H_2O^+, H_3O^+) are the main reactive species produced. These ions and radicals react with each other and with other nearby molecules, creating a wide variety of chemically reactive species and producing many kinds of damage in biologic macromolecules. Because DNA contains information that is critical to the cell, while most other molecules can be replaced readily, damage to DNA is the most important biologic effect of irradiation. Radiation produces a wide variety of lesions in DNA, including single- and double-strand breaks, damaged bases and loss of bases, as well as chromosomal breaks and rearrangements. If these lesions are not repaired, the result can be permanent mutations or changes in chromosomal structure that lead to the death of the cell or changes in its behavior.

The cytotoxic effects of radiation are the basis for both the antineoplastic effects and the toxicities of radiotherapy. A theoretical concern is that radiotherapy may produce a mutation in a previously normal cell that leads to the development of a new malignancy. Although radiation-induced malignancies do occur and are a primary concern in considerations of environmental and occupational exposures,[1,11,13] malignant transformation is, fortunately, a rare enough event at the doses used in radiotherapy that the risk of inducing a second cancer in an individual patient is very small relative to the great benefit of curing the existing malignancy.[5] The greater risk to the patient lies in the fact that radiation is not selectively toxic to the tumor cells, but instead, kills both normal and malignant cells within the treatment field.

Although the radiochemical reactions that lead to cytotoxic damage are complete within milliseconds after the end of irradiation, cells dying from radiation injury do not die immediately. In fact, soon after irradiation, radiation-sterilized cells are indistinguishable from cells that ultimately survive irradiation in their appearance, metabolic activities, and even rates and patterns of proliferation. Most radiation-sterilized cells ultimately die during mitosis, but they may first undergo one or even several divisions, producing an abortive clone of sterile cells, all of which ultimately die and disintegrate through apoptosis, necrosis, mitotic catastrophe, senescence, autophagy, or other pathways of cell death.[15,16] This delayed cytotoxicity underlies many of the effects seen in radiotherapy. Rapidly growing tumors, for example, generally begin shrinking sooner than slowly growing tumors, and many tumors continue to shrink progressively for months after radiotherapy.[13,17] Analogously, radiation reactions in normal tissues reflect the normal patterns of cell turnover in the tissue.

After irradiation, nonproliferating, terminally differentiated cells continue to perform their differentiated functions throughout their normal life spans. Other cells that are not proliferating at the time of irradiation likewise continue to function normally until they are recruited into proliferation, perhaps months or even years after irradiation; when they begin to proliferate, their progeny die. Rapidly proliferating cells, such as mucosal or intestinal epithelium or nucleated blood and bone marrow cells, die within a few days of irradiation, leading to the familiar early radiation reactions of epilation, desquamation, mucositis, and hematologic depression.[3,5] Some cell types, especially hematopoietic cells, may be induced by radiation-induced damage to enter a pathway of

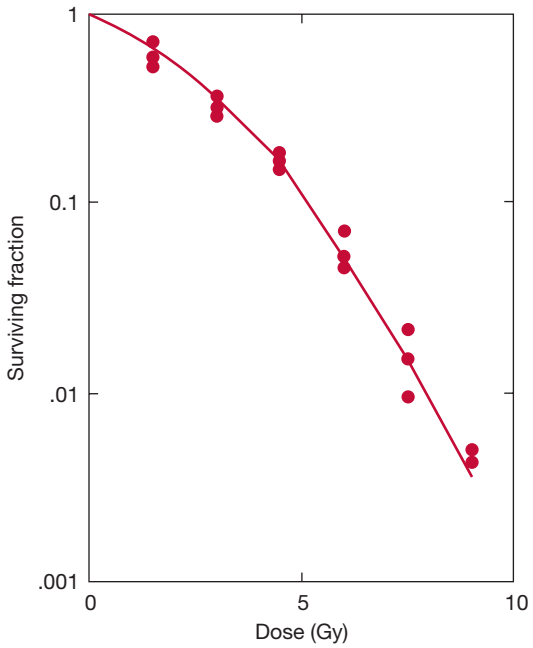


Figure 59-3 Survival of lung cells treated with different doses of radiation. Cells were explanted from mouse lungs, irradiated in vitro, and assayed for viability using a colony formation assay. *(Reproduced with permission from Guichard M, Deschavanne PJ, Malaise EP. Radiosensitivity of mouse lung cells measured using an in vitro colony method. Int J Radiat Oncol Biol Phys. 1980;6(4):441–447.)*

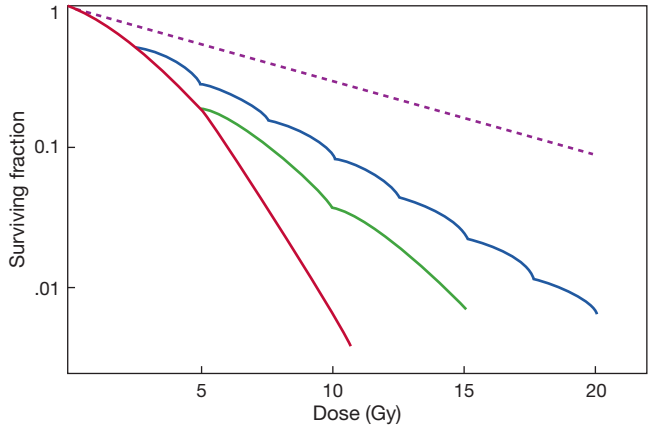


Figure 59-4 Effect of fractionated irradiation and low-dose rate irradiation on cell survival. The survival curve for lung cells treated with a single dose of radiation is redrawn from Fig. 59-3. The calculated effect of dividing the radiation dose into several daily treatments with 5 Gy/fraction or 2.5 Gy/fraction is illustrated. The *dashed line* illustrates the survival curve that would be expected for irradiation delivered continuously at a low-dose rate over several hours, allowing repair and proliferation to occur during treatment. Changes in the cytotoxicity of radiation with fractionation and at low-dose rates lead to decreased injury in lungs irradiated with analogous regimens.

programmed cell death that leads to apoptosis; the role of early and delayed apoptosis in determining the response of tumors and normal tissues to radiotherapy is the subject of intensive investigation.

A typical survival curve for mammalian cells, obtained using mouse lung cells, is shown in Figure 59-3. As a first approximation, cell survival falls exponentially as the radiation dose increases. Statistically, this implies that each incremental dose of radiation has the same cytotoxic effect; that is, each incremental dose kills the same proportion of the viable cells that were present in the population at the beginning of that irradiation. Very low doses of radiation have somewhat lesser effects; the shoulder on the cell survival curve reflects the ability of the cells to accumulate and tolerate or repair some of the damage produced by radiation.

The effect of the repair of radiation damage can be seen when the radiation dose is divided into two or more treatments separated by hours or days, rather than being delivered in a large single dose. Dividing, or "fractionating," the radiation dose allows cells to repair damage to their DNA and to proliferate between treatments.[1,5] As a result, there is less cytotoxicity from a fractionated treatment regimen than from the same total radiation dose delivered as a large single fraction (Fig. 59-4). Smaller fractions produce less cytotoxicity than larger fractions. Similarly, the cytotoxic effects of radiation are diminished when the radiation is delivered continuously at a low-dose rate, over hours or days, allowing repair and proliferation to occur during irradiation (Fig. 59-4).

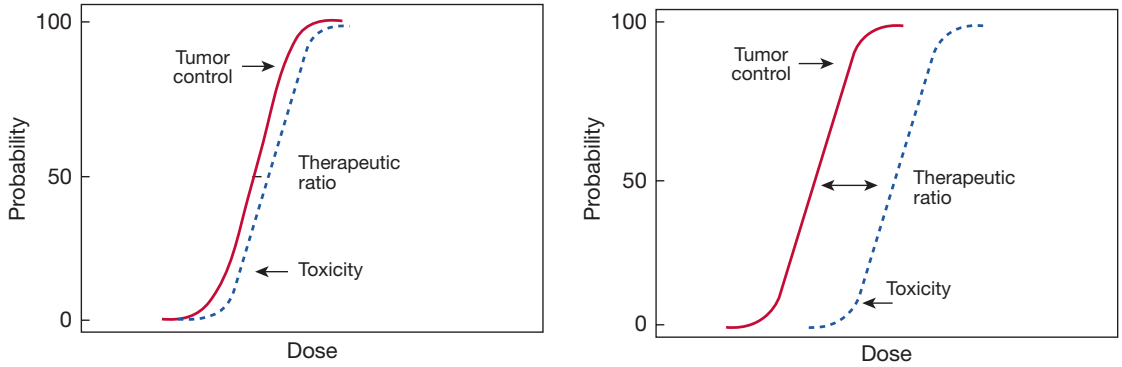
Fractionating therapeutic irradiations or delivering the radiation at low-dose rates generally appears to increase the therapeutic ratio by protecting normal tissues against radiation injury, while producing a smaller increase in the relative radioresistance of the tumor; treatment outcomes are thereby improved. This increase in the therapeutic ratio is thought to reflect qualitative and quantitative differences between normal and malignant cell populations, including differences in the intrinsic radiosensitivity of the critical cells and in the patterns of cell proliferation and cell loss, as well as differences in the ability of the normal and malignant cells to repair radiation damage. Empiric observations of patients treated with radiotherapy, laboratory experiments with tumors and normal tissues in rodents, and studies with cells in culture have all been used to guide the development of the clinical fractionation schedules now in use. This optimization process is ongoing and will undoubtedly continue, incorporating new information about the repair of radiation damage in normal and malignant cells and about the physiologic factors that modulate development of late radiation injuries in specific normal tissues. In addition, efforts will continue in the development of new technologies for targeting and delivering radiation.

In this process, as in any change in cancer therapy, the critical parameter is the therapeutic ratio (Fig. 59-5). A new treatment regimen is superior *only* when it produces an increased effect on the tumor without an equivalent increase in toxicity to critical normal tissues, reflected in an increase in the therapeutic ratio and therapeutic gain. The art of radiotherapy lies in the design of treatment fields that minimize radiation doses to normal tissues and in the development of treatment regimens that use all available information on the biology of the tumor and of the critical normal tissues.

PATHOPHYSIOLOGY OF RADIATION PNEUMONITIS

Much of our current understanding of the pathophysiology of radiation injury to the lungs is derived from animal experimentation. Translation of animal data to human conditions is always problematic, because differences in the biology and physiology of different species may preclude direct and definitive extrapolation from animals to humans.[9,13,18] Instead, studies with experimental animals must be designed to identify physiologic factors and biologic mechanisms that can be used to interpret clinical data and suggest avenues for clinical investigations.

Data on radiation pneumopathy in humans is fragmentary and complicated by the variability in the patients treated with thoracic irradiation. Most studies of radiation pneumonitis include patients with a variety of malignancies who have been treated with different irradiation regimens, often in combination with chemotherapy and surgery. Moreover, patients vary widely in age and the presence of



Increasing the therapeutic ratio, either by selectively increasing the effect on tumor or by selectively protecting normal tissues from injury, produces therapeutic gain.

Figure 59-5 The therapeutic ratio is the critical factor determining the success of cancer therapy.

other diseases and risk factors. Therefore, our current understanding of radiation injury to the lung remains incomplete. What is known suggests a complex, multifactorial mechanism of injury and disease progression that reflects cytotoxic effects on both epithelial and endothelial tissues. Inflammatory responses involved in this injury cascade include transient increases in reactive oxygen and nitrogen species, macrophage infiltration and activation, oxidative stress, induction of interstitial fibrosis with regional tissue hypoxia, and disordered cytokine and cellular signaling—including profibrogenic transforming growth factor-beta (TGF-β), proangiogenic hypoxia-inducible factor-1 alpha (HIF-1α), and vascular endothelial growth factor (VEGF).[8,9,14,19–25] Similarities to lung injuries resulting from cancer chemotherapy, other drugs, inhaled chemicals, oxygen toxicity, immune reactions, and idiopathic pulmonary fibrosis are intriguing, especially when one considers that many of these diseases include pathologic responses to free radical chemical species and are likely to reflect similar underlying initial lesions.

Partial-lung resection and localized irradiation have certain similarities: Their effects are largely localized to the treated areas and, consequently, depend on the number of pulmonary lobules or alveolar–capillary units functionally destroyed. Thus, the volume of lung irradiated is an important determinant of toxicity. Consequently, the radiation oncologist plans treatment to minimize the volume of lung receiving high radiation doses, just as the thoracic surgeon plans lung resection with due consideration to anticipated residual lung function. Of course, this simple analogy has its limitations. For example, inactivation of enough lobules by radiation increases the ventilatory dead space and could lead to shunting and ventilation–perfusion mismatching. However, in clinical practice, extensive shunting generally is not observed.[26] In fact, postradiation radionuclide ventilation–perfusion scans tend to show both underperfusion and underventilation that is dose dependent in irradiated areas of partially irradiated lungs.[27] In most cases, radiation injury in lung conforms to the radiation treatment fields, but in some, effects outside the treated areas are observed, with localized radiation inducing a more generalized or diffuse hypersensitivity pneumonitis.[28]

The effects of radiotherapy on the lung reflect the proliferation patterns of the different cellular components of the terminal capillary–alveolar units.[29] Type I pneumocytes are the dominant epithelial cells of the lung, covering about 83% of the alveolar surface. Type I pneumocytes are normally nonproliferating and do not proliferate in response to injury. Consequently, they are thought to be relatively resistant to the cytotoxic effects of radiation.

Type II pneumocytes, which comprise about 16% of the cells in the human lung, are the principal source of surfactant that modifies alveolar surface tension to prevent atelectasis. Type II pneumocytes have turnover times of about 1 month. In response to certain injuries, these granular pneumocytes can be induced both to undergo rapid mitosis and differentiate into type I pneumocytes.

Endothelial cells comprise about 30% of the cells in human lungs and form a continuous layer between the blood and the lung tissue. Although endothelial cells are classified in most tissues as stromal cells, endothelial cells in lung are actually parenchyma, because they are critical to the function of this organ. Capillary endothelial cells are a constantly renewing population, with an estimated turnover time on the order of 2 months. Endothelial cells can be induced into rapid compensatory proliferation after injury; therefore, radiation may result in depletion of both type II pneumocytes and endothelial cells.

Several lines of evidence suggest that radiation injury is related primarily to cytotoxic damage, especially to the surfactant-producing type II pneumocytes and vascular endothelial cells. Although clinical signs of pneumonitis require weeks to develop, laboratory studies reveal evidence of lung injury within hours after large single doses of radiation.[6,22,30–32] Shortly after irradiation, electron microscopy may detect abnormalities in surfactant-containing lamellar bodies. There is an increase in surfactant in bronchoalveolar lavage specimens within hours of irradiation that persists for several weeks. Ultrastructural evidence of endothelial cell damage is also seen soon after lung irradiation, and a rapid increase in capillary permeability occurs, reflecting loss of integrity of cell junctions, intracellular vacuolization, cellular pleomorphism, and sloughing of the basement membrane. Capillary occlusion by cellular debris and microthrombi may occur at high doses.

The clinical course of lung injury occurs later and includes a pneumonitic phase, developing weeks to months after radiation, followed by a fibrotic phase, developing months to years later. To explain the two clinical phases, Rubin and Casarett's original model of radiation lung toxicity suggested that the pneumocytes and endothelium represented two separate and distinct cellular targets, and that damage to pneumocytes led to pneumonitis, while vascular damage led to fibrosis. This older model is now thought to be incorrect; current data[19,20,22,29,33–38] suggest that the pneumonitic and fibrotic processes both are manifestations of a common pathway of injury and response.

Histologically, one can recognize a typical sequence of events developing in the lung after large doses of radiation.[6,21,30] Within days to weeks, vascular congestion and intra-alveolar edema and exudation occur, followed by infiltration of inflammatory cells and epithelial desquamation. Weeks later, collagen fibrils are deposited within areas of injury and interstitial edema, leading to a thickening of alveolar septa similar to that in hyaline membrane disease. The probability and severity of these changes are quite variable and depend on such factors as the radiation dose and treatment volume. The severity of the damage and volume of tissue affected determine whether a pneumonitic picture becomes clinically evident. Resolution of inflammatory infiltrates and alveolar exudates, which

can be improved by anti-inflammatory agents such as glucocorticoids, correlates with symptomatic improvement and resolution of radiographic opacities in the affected lung.

Inflammatory cells, particularly alveolar macrophages, migrate into areas of radiation injury. This induces an ensuing cytokine cascade and mediates the host response,[9,20,22,25] similar to that which occurs in other inflammatory conditions, which can lead to pulmonary fibrosis.

Rubin et al. have detected a biphasic increase in mRNA expression for the proinflammatory cytokines IL-1α, IL-1β, and TNF-α at 2 and 8 weeks after radiation.[22] Preliminary clinical trials also suggest that elevated serum levels of IL-6 before and during radiotherapy predict an elevated risk of radiation pneumonitis. Beginning 24 hours following radiation, TGF-β, a cytokine that mediates fibrotic responses, increases.[21] Elevated levels of VEGF may be detected 2 weeks later. Tissue hypoxia accompanies the inflammatory response. Clinical data implicating TGF-β as a predictive marker for pneumonitis, however, have been mixed. Collagen gene expression is also appreciably increased corresponding to the fibrotic changes seen histologically. These studies suggest that early and persistent elevations of cytokine production and alterations of intercellular signaling are critical to the development of radiation reactions in the lung. There is increasing evidence from studies with inbred mice that genetic differences, age, and past health and treatment history modulate the development and severity of fibrosis and hyaline membrane formation, thus determining the nature of the late toxic lesion and the time of development of radiation pneumotoxicity.[9,33,34]

The processes described earlier lead to pathologic changes that conform spatially to the areas to which localized radiation was administered. Interestingly, it has been discovered that radiation can also induce an allergic alveolitis. This is observed infrequently as a diffuse pneumonitis, or occasionally as a patchy, transient bronchiolitis obliterans organizing pneumonia (BOOP; see Chapter 57) occurring outside the treated fields. In its most severe form, the result is the acute respiratory distress syndrome (ARDS; see Chapter 141). Morgan and Breit[28] have suggested that this form of radiation-induced pneumonitis be termed "sporadic". The occurrence of the syndrome actually may be more common than appreciated. One series showed a 2.3% incidence of BOOP in women undergoing whole breast radiotherapy, occurring outside the radiotherapy fields four or more months after exposure.[39] Bronchoalveolar lavage in humans and in experimental animals frequently shows a significant increase in activated T-helper ($CD4^+$) lymphocytes, temporally related to irradiation and occurring equally in the irradiated lung and the contralateral, nonirradiated lung. Gallium scanning may also show bilateral uptake not corresponding to the treated regions. Frequent reports of autoantibodies, including antibodies to collagen, in the sera of patients with cancer even before treatment suggest the possibility that malignancy-associated autoimmune reactions may be involved in the syndrome.

CONFOUNDING EFFECTS OF CHEMOTHERAPY

Many cytotoxic drugs employed as antineoplastic agents can produce pulmonary toxicity (see Chapter 65).[40–42] Bleomycin, which has been extensively studied, kills cells by generating reactive free radical species similar to radiotherapy and may give rise to both pneumonitis and fibrosis.[42] Doxorubicin, mitomycin C, irinotecan, and gefitinib have been associated with lung toxicity, as have the antimetabolites (methotrexate, cytosine arabinoside, gemcitabine, fludarabine, and the nitrosamines) and the podophyllotoxins (etoposides, paclitaxel, and docetaxel). Interestingly, lung injury has also been reported after treatment with immune modulators, including interferons, IL-2, and TNF-α.

As high-dose alkylating agent chemotherapy is used more frequently in the setting of bone marrow or peripheral stem cell transplantation, agents such as cyclophosphamide, BCNU, and busulfan have been associated increasingly with clinically significant pneumonitis. The direct toxicity of many widely used anticancer drugs to the lungs sounds a note of caution for those considering development of treatment protocols combining systemic chemotherapy with lung irradiation. Moreover, the concurrent administration of antineoplastic agents and radiotherapy may make it difficult to discern to what degree pulmonary injury in an individual patient is related to radiotherapy alone.

Animal studies addressing changes in respiratory rates and/or death resulting from lung injury show that the severity of the lung injury can be increased when doxorubicin, bleomycin, cyclophosphamide, mitomycin C, dactinomycin, or vincristine are administered along with radiation.[43,44] No enhancement has been documented in studies with 5-fluorouracil, cisplatinum, carboplatinum, hydroxyurea, vinblastine, or methotrexate, despite reports of lung toxicity from methotrexate alone.

As a wide variety of cytokines and molecularly targeted agents are now available for pharmacologic administration, modulation of radiation injury by these biologic agents needs increased study. Interferons have been shown both to increase and decrease radiation lung toxicity, whereas interleukins 1 and 2 may have protective effects. Some radiation-drug interactions in the lung have been shown to be schedule dependent, with the effect of the combination varying with the sequence and the time between treatments with the two agents.[43,44] Additive, subadditive, and even supra-additive toxicities may be observed in rodents when single treatments with the same dose of radiation and drug are given over a 24-hour period, but in different sequences and different times between treatments. Such findings highlight the complexities of combined-modality therapy and the difficulty of using animal data to plan clinical treatment regimens.

Data from several specific clinical situations show that regimens combining radiation with particular chemotherapy agents can produce significant risks of pneumonitis. As summarized in reviews of chemotherapy and radiation-induced pneumonitis, docetaxel, mitomycin C, gemcitabine, and irinotecan given concurrently with radiotherapy seem to elevate the risk of pneumonitis or lung toxicity.[45,46] On the other hand, drugs that are commonly used in lung cancer concurrent with radiotherapy, such as cisplatin, carboplatin, paclitaxel, and etoposide, do not consistently elevate the risk of pneumonitis; alternatively, the clinical data regarding pneumonitis risk so commonly include these chemotherapy agents that the risk may already be incorporated into consideration.[47–51] Older clinical data from pediatric trials strongly suggest that administration of concurrent doxorubicin or actinomycin D with thoracic radiotherapy generally should be avoided or, alternatively, that the radiation doses should be reduced significantly where these drugs are used.

Sequential treatment with doxorubicin or actinomycin D and radiation is less likely to produce lung injury. However, a phenomenon termed "radiation recall" has been well described, in which either of these two drugs given even several months after radiotherapy will produce an inflammatory reaction in the region corresponding to the radiation treatment fields.[52] Although this reaction is best known in skin, it also has been well documented in the lungs in several case reports and has been produced in experimental animals. Radiation recall probably reflects the fact that the irradiated areas of the lung still retain residual, subclinical injury, which is exacerbated into clinical pneumonitis as a result of the additional injury from the drug. Therefore, the biologic basis of the recall phenomenon is analogous to that of the residual radiation injury, which decreases the ability of heavily irradiated lung tissue to tolerate a second course of radiotherapy delivered months or years later.[5,6,37]

CLINICAL SYNDROMES

Radiation oncologists conventionally divide clinical toxicities into acute and late effects,[5,6] with both radiation pneumonitis and fibrosis considered late toxicities. Several grading systems for pneumonitis

TABLE 59-1 Toxicity Criteria for Pneumonitis

Scoring System	Grade 1	2	3	4	5
CTCAE	Asymptomatic; radiographic findings only	Symptomatic; not interfering with ADL	Symptomatic; interfering with ADL; O_2 indicated	Life-threatening ventilatory support indicated	Death
RTOG/EORTIC (LENT-SOMA)	Asymptomatic or mild symptoms (dry cough), with radiographic findings	Moderately symptomatic (severe cough fever)	Severely symptomatic	Severe respiratory insufficiency; continuous oxygen/assisted ventilation	Death
SWOG (33)	Asymptomatic or symptoms not requiring steroids with radiographic findings	Initiation of or increase in steroids required	O_2 required	Assisted ventilation necessary	Death

CTCAE, common terminology criteria for adverse events; ADL, activities of daily living; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; LENT-SOMA, late effects on normal tissue-subjective, objective, management and analytic scales; SWOG, Southwest Oncology Group. Source: Reproduced with permission from Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. Int J Radiat Oncol Biol Phys. 2005;63(1):5–24.

have been developed for scoring lung injury during clinical trials (Table 59-1).

■ ACUTE MANIFESTATIONS

It is relatively uncommon to observe acute pulmonary toxicity during the administration of fractionated radiotherapy. However, at relatively high therapeutic doses (50–60 Gy), acute radiation changes in the tracheobronchial tree can be expected. Bronchoscopic examination is likely to reveal erythematous mucosa, with thickened secretions that can accumulate in and obstruct the airways. Although a majority of patients remain asymptomatic, occasional patients experience an irritative, dry cough. Antitussive agents, such as codeine, adequate hydration, and reassurance are usually all that are required to manage this problem. Once radiotherapy has been completed, the bronchial epithelium regenerates and heals over several weeks, accompanied by resolution of symptoms.

■ LATE MANIFESTATIONS

The clinical course of late radiation injury to the lungs is biphasic, with both inflammatory and fibrotic components.[19,30,32]

Radiation Pneumonitis

A pneumonitic process frequently becomes evident 6 weeks to 6 months following radiotherapy. At this time, radiographs show alveolar opacities that generally conform to the treatment portals. The severity of radiation pneumonitis varies dramatically from patient to patient, even in those receiving identical therapeutic regimens. In most cases, the pneumonitis is asymptomatic, even though radiologic abnormalities are quite common, as noted in some prospective studies, in which as many as 50% of patients who have completed a course of thoracic radiotherapy were asymptomatic.

When symptomatic, this syndrome is often characterized by the abrupt onset of fever, cough, and dyspnea. The severity of symptoms depends on the extent of radiotherapy, increasing with the treated volume and with the radiation dose. Symptoms in patients irradiated to limited lung volumes or to relatively low doses may consist of low-grade fever, cough, congestion, and chest fullness or discomfort. Any hemoptysis tends to be minimal. In more severe situations, dyspnea, high fever, and cough occur. When large volumes of normal lung receive high radiation dose, acute radiation pneumonitis is more likely and can be extremely severe, producing respiratory distress. The radiation oncologist is probably most likely to see clinically significant radiation pneumonitis that can be life-threatening when it occurs as a rare and unanticipated consequence of standard treatment, despite appropriate treatment planning designed to minimize the volume of lung treated with high doses of radiation. Fortunately, with well-planned radiotherapy, severe radiation pneumonitis is a rare event. Milder pneumonitis is not uncommon, but is readily manageable.

It is important to distinguish radiation pneumonitis from infection, recurrent tumor (particularly with lymphangitic spread), drug reactions, congestive heart failure, and other respiratory disorders. These distinctions may not be easy; one series from Duke suggested that up to 28% of patients with radiation-associated lung toxicity have complex comorbidities that make it difficult to assign a definitive diagnosis.[53] Bacterial, fungal, viral, and pneumocystis pneumonias can be quite difficult to differentiate from pneumopathy induced by chemotherapy or radiation.

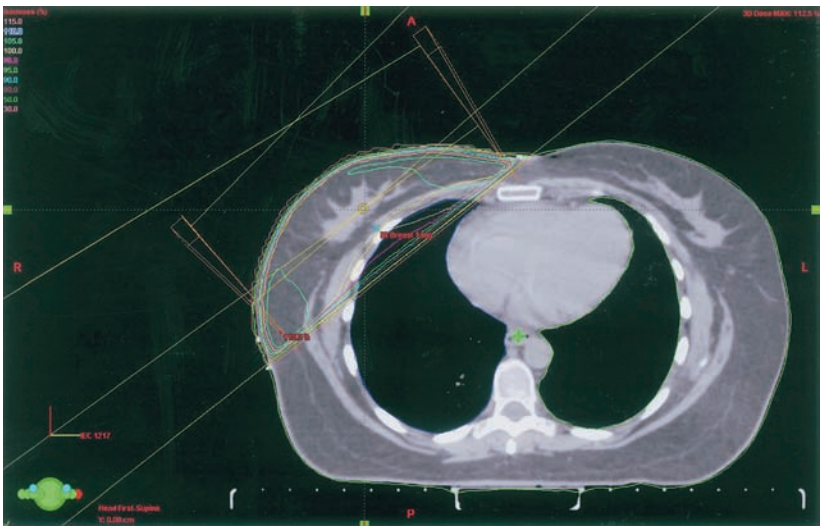
Aids in the differential diagnosis include the clinical course and temporal relationship between the irradiation and respiratory illness. Definition of the radiographic pattern of the infiltrate is also very useful, because radiation pneumonitis often conforms to the outline of the sharply demarcated radiation portal (Figs. 59-2 and 59-6). Bronchoscopy and lung biopsy can also be helpful diagnostic tools to direct therapeutic decisions. Ruling out infection is particularly important, because treatment of symptomatic radiation pneumonitis relies on supportive care in conjunction with corticosteroids.

Doses of glucocorticoids generally can be tailored to the severity of the symptoms. Asymptomatic pneumonitis may be managed with close observation. Severe cases generally warrant treatment with prednisone (or its equivalent) at a dose of 0.5 to 1 mg/kg per day in divided doses. Response rates between 20% and 100% have been reported, and dramatic clinical and radiographic responses are not infrequently seen. Steroids should be tapered slowly after the patient is stabilized, because it is common to see a recrudescence of symptomatology when steroids are discontinued too rapidly. Failure to respond to steroid therapy is an adverse prognostic factor that suggests the prospect of rapid disease progression.

Most studies show at least a transient decline in pulmonary function in patients who receive radiation to a significant lung volume (i.e., patients with lung cancer receiving a potentially curative course of fractionated radiotherapy). There may be a transient reduction in FEV_1 and FVC 3 to 6 months post radiation. Carbon monoxide diffusing capacity (D_{LCO}) may be reduced over a similar time course, but typically to a greater degree relative to baseline.[54] Absent the development of radiation fibrosis, these parameters tend to recover toward the patient's baseline, reaching maximal recovery at approximately 12 months.

Radiation Fibrosis

A more indolent fibrotic process may follow either subclinical or symptomatic radiation pneumonitis.[19,30,32] This begins several



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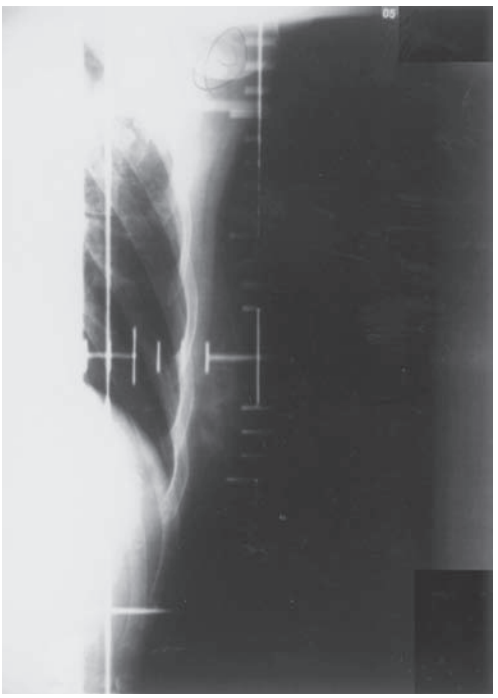

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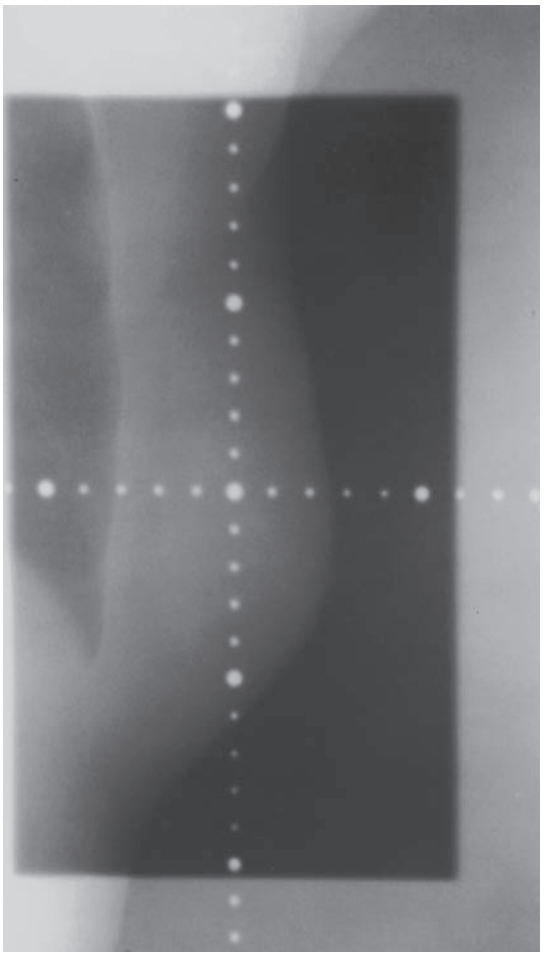

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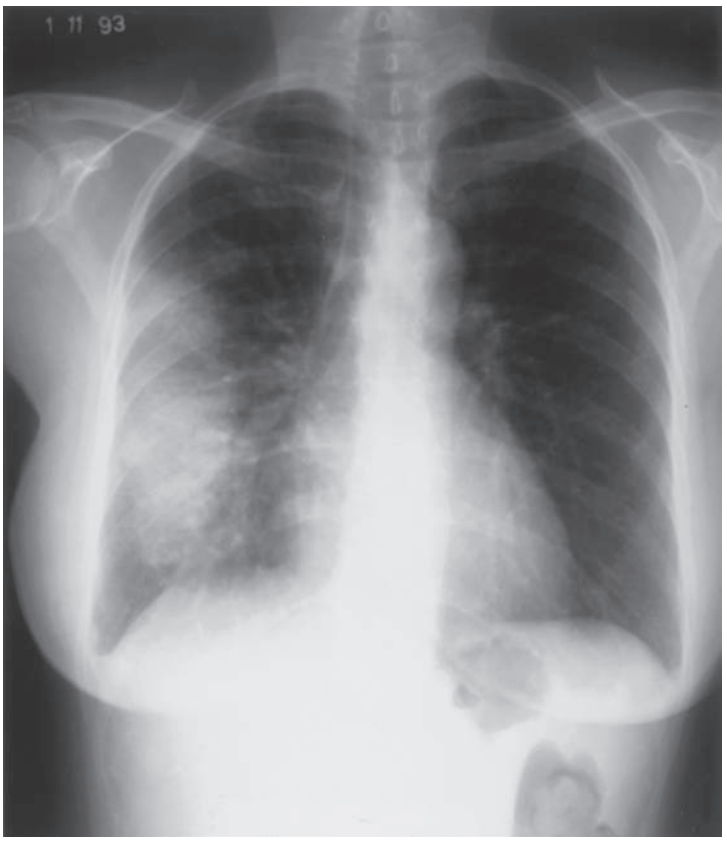
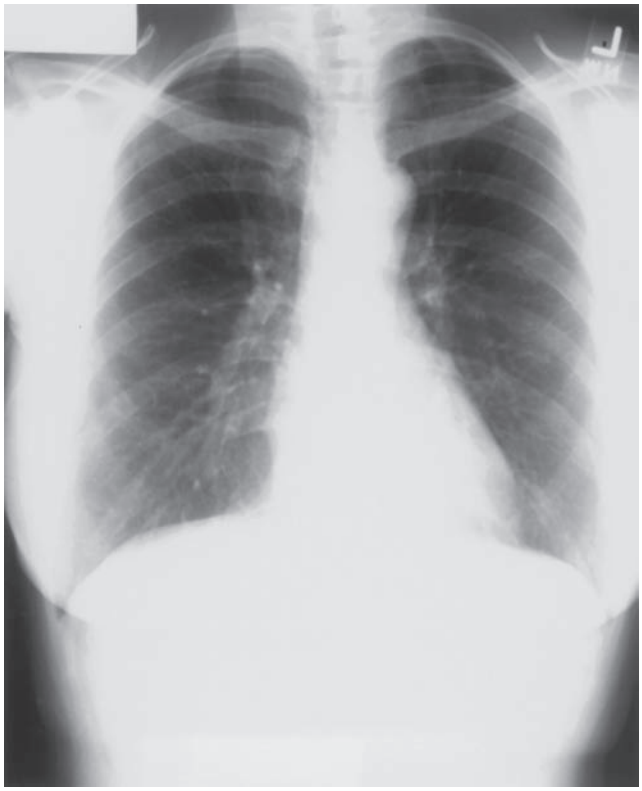


D

Figure 59-6 A 52-year-old woman found a nontender lump in her right breast and subsequently underwent a lumpectomy for a localized 1.4-cm diameter infiltrating ductal carcinoma. The axillary lymph nodes were negative. The patient was placed on Tamoxifen and underwent radiotherapy to the right breast, using tangential fields, to 50 Gy in 25 fractions over 36 days. **A.** A radiation dose distribution of the photon fields overlying the right breast and chest wall. This was followed by boost radiation treatments to the surgical bed for an additional 14 Gy in seven fractions. **B**, **C.** The simulation and port films, respectively, of the whole-breast treatments, highlighting the different interactions of low-energy and high-energy X-rays with tissues. Four months after radiotherapy, the patient developed radiation pneumonitis characterized by fever, cough, and dyspnea requiring hospitalization. **D.** A right-lung opacity that does not correspond to normal anatomic structures but does correspond to her treatment fields. *(continued)*



E

Figure 59-6 *(Continued)* **E.** The patient responded dramatically to steroids, with resolution of radiographic findings on follow-up chest radiographs.

months after radiotherapy and peaks in radiographic severity several years later. Fibrosis tends to occur in, or adjacent to, areas of prior pneumonitis,[33] but it can also occur in the absence of clinically overt radiation pneumonitis. Fibrotic changes and the retraction of the lung parenchyma from scarring occur in the irradiated regions (Fig 59-2). When the volume of lung irradiated is relatively small and the remaining lung parenchyma contains sufficient respiratory surface area, the changes tend to be asymptomatic.

With increasing relative volumes of pulmonary fibrosis, a spectrum of symptomatology is possible, ranging from mild dyspnea on exertion to severe fibrosis with respiratory compromise, chronic cor pulmonale, cyanosis, and finger clubbing. At the severe end of the spectrum, the syndrome can be life-threatening. In general, in the absence of other underlying lung disease, symptoms are mild when less than 25% to 30% of total lung parenchyma is involved.

Radiation-induced Pleural Reactions

Pleuritis may also be seen 2 to 6 months following radiation. It can be associated with pleuritic chest pain, a pleural friction rub, and an exudative pleural effusion. Large effusions are, however, distinctly unusual in the absence of other pathology. Like radiation pneumonitis, radiation-induced pleuritis may heal without significant residue, or it may proceed through a fibrotic phase that generates pleural thickening.

Radiation-induced Bronchial Stenosis

With improvements in the technical delivery of radiotherapy, recent clinical trials for lung cancer have emphasized escalation of the administered radiation dose. Stereotactic body radiotherapy (SBRT) utilizes —three to five large fractions (i.e., >10 Gy per fraction), delivering significantly higher biologically effective doses than are feasible with conventional fractionated radiotherapy.[55] As a result, there is an increasing appreciation that, particularly for perihilar tumors, radiation-induced fibrosis may result in bronchial stenosis or necrosis, causing postobstructive atelectasis, volume loss, and functional impairment.[56–58] Clinically, this complication needs to be differentiated from recurrent tumor; bronchoscopy or positron emission tomography (PET) imaging may be of help. One retrospective series in which radiation doses ranged from 60 Gy to as high as 86 Gy demonstrated that radiation-induced bronchial stenosis may occur in up to 25% of patients; the incidence directly correlates with radiation dose.[59] However, severe bronchial injury is rare with fractionated chest radiotherapy using conventional doses.

DEFINING THE RADIATION TOLERANCE OF THE LUNGS

While we customarily refer to radiation doses that can be delivered safely either to the whole body or to a particular organ, radiation *tolerance* is usually defined as the dose that yields a 5% risk of severe late radiation injury.[60] When discussing the tolerance of the lungs, one must consider several different therapeutic situations. The tolerance of the lung varies with the volume of lung tissue irradiated.[5,35,60,61] In addition, single-dose irradiations, fractionated irradiations, and irradiations given at low-dose rates each pose different risks of injury, and therefore, they must be considered separately.[5,38,62] Additional injury from surgery or chemotherapy or from a prior course of radiotherapy also must be considered, as must the confounding effects of injury to lung tissue from coexisting cardiopulmonary disease and from the underlying malignancy.

Infections and immunologic reactions are also important. The clinical endpoints used to define a case of radiation pneumonitis vary as well, because the severity of the lung injury spans a wide spectrum of diagnostic signs and clinical symptoms. Moreover, with improvements in imaging and three-dimensional dose-calculation algorithms, there is a concerted effort within the radiation oncology community to better define dose–volume determinants for a variety of organ radiation-related toxicities. Known as QUANTEC (quantitative analysis of normal tissue effects in the clinic), this broad compilation of data shows that there are strong correlations of pneumonitis risk with radiation dose, fractionation, and tissue volume.[63] Given the heterogeneity of clinical circumstances and biologic data in general, it is not surprising that the medical literature that defines the risks for radiation pneumonitis and fibrosis is extremely complex and often difficult to interpret.

■ WHOLE-LUNG IRRADIATION

A good starting point for considering lung tolerance is analysis of the effects of irradiating the entire lung. This construct has direct clinical relevance because there are several circumstances in which the entire lung is irradiated. These include total-body irradiation (TBI) for bone marrow or hematologic stem cell transplantation, hemibody irradiation for palliation of widespread metastatic disease, and whole-lung irradiation given electively or therapeutically for relatively radiosensitive tumors, such as Wilms tumor, Ewing sarcoma, or Hodgkin lymphoma. These are often circumstances in which chemotherapy is administered as well.

Published experience from the Princess Margaret Hospital in Toronto[12,64–67] provides some of the best data regarding whole-lung tolerance. Investigators from that institution have an extensive experience with delivering upper hemibody irradiation to different doses and varying fractionation patterns. They reported in 1978 on a cohort of 245 patients, most with metastatic solid tumors, who received single-fraction, upper hemibody irradiation at dose rates of 0.3 to 0.8 Gy/min to doses of up to 10 Gy.[64] The actuarial incidence of acute radiation pneumonitis, defined as the sudden onset of cough, dyspnea, and opacities visible on chest radiographs at about 16 weeks following treatment, was strikingly dose dependent

TABLE 59-2 Actuarial Incidence of Radiation Pneumonitis after Single-fraction Whole-lung Irradiation

Uncorrected Dose	Patients	Pneumonitis (%)
<6 Gy	49	2.7
6 Gy	24	17.5
8 Gy	149	35.6
10 Gy	23	83.9

Source: Data from Fryer Fitzpatrick PJ, Rider WD; CJH, et al. Int J Radiat Oncol Biol Phys. 1978;4:931–936.
Note: Doses are not corrected for heterogeneity in tissue density.

(Table 59-2). The doses shown in Table 59-2 were not corrected for heterogeneity in density.[12] When doses are corrected, resulting in an upward estimation of the doses actually received by the lungs, analysis yielded the sigmoid-shaped curve shown in Figure 59-7.

Using heterogeneity-corrected data, the incidence of pneumonitis is estimated to be negligible for single doses less than about 7.5 Gy. Other published data regarding upper hemibody single-fraction irradiation are in general agreement with these findings.

Careful analysis suggests that the single-fraction data might predict an unacceptable risk for pneumonitis when single-fraction TBI is utilized in the setting of bone marrow transplantation (BMT). The most important treatment factor making single-fraction TBI in the range of 8 to 10 Gy (uncorrected for heterogeneity) tolerable is that treatments generally are given at a low-dose rate (less than or equal to 0.1 Gy/min) over 1 to 2 hours.[38,68] In Seattle, where hundreds of patients with leukemia have undergone BMT after TBI, using single fractions of 10 Gy (uncorrected) delivered at dose rates on the order of 0.08 Gy/min, the incidence of pneumonitis is roughly 25%. Review of transplant-related single-fraction TBI with variable dose rates shows incidences of clinical lung injury varying from 25% to 70%.[65,69–71]

Studies in mice show that the toxicities of TBI can be improved further by fractionating the irradiation, as well as by delivering radiation at a low-dose rate. This concept is supported by a randomized clinical trial comparing low-dose rate, single-fraction TBI (10 Gy)

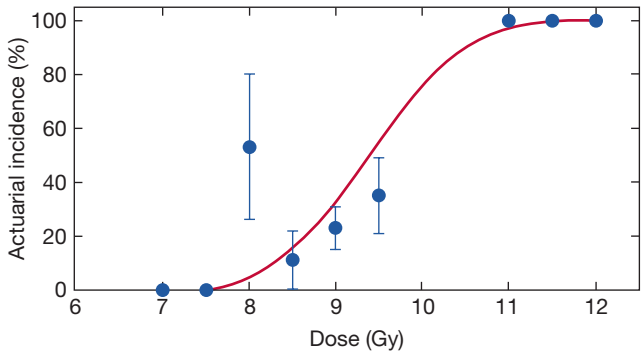


Figure 59-7 Incidence of radiation pneumonitis in patients receiving single-dose, whole-lung irradiation at dose rates of 0.3 to 0.8 Gy/min. Unlike most doses given in the text, doses on this figure *are* corrected for heterogeneity in density. The effect of this correction can be seen by comparing these data with those in Table 59-1, which were derived from an earlier analysis by the same group and are presented using uncorrected doses. *(Reproduced with permission from Van Dyk J, Keane TJ, Kan S, et al. Radiation pneumonitis following large single dose irradiation: a re-evaluation based on absolute dose to lung. Int J Radiat Oncol Biol Phys. 1981;7(4):461–467.)*

with low-dose rate, fractionated TBI (12 Gy in six fractions over three days) for patients with acute myelogenous leukemia in first remission. A significant improvement in event-free survival was noted with fractionation, mainly because of an improvement in early mortality.[68] Interstitial pneumonitis was decreased from 26% to 15% with fractionation. Other studies have corroborated a reduced incidence of pneumonitis to less than 20% without increasing the rate of tumor recurrence using fractionated TBI.[72–74] Within a range of 1.5 to 2 Gy per fraction given once or twice daily, there is no significant increase in pneumonitis risk using doses up to 15 Gy.[72,75,76] Nevertheless, total dose delivered to the lung is a key determinant of pneumonitis risk.[65,77] In addition, at many transplant centers it has become common practice to utilize lung transmission blocks to attenuate the lung dose and thereby reduce the risk of pneumonitis, in part by compensating for the heterogeneity in tissue density due to the air within the lungs.[71]

Another radiobiologic approach to reduce the incidence of interstitial pneumonitis has been to lower the dose rate at which the radiation is delivered—in essence, a kind of continuous fractionation. While efficacious,[78,79] treatment times of 2 to 3 hours are impractical and poorly tolerated by patients. Within the context of fractionated TBI schemes, instantaneous dose rates of 0.05 to 0.18 Gy/min generally have been employed due to practical considerations. Whether or not higher instantaneous dose rates are detrimental in the context of fractionated TBI remains unclear. One small study comparing dose rates of 0.075 versus 0.15 Gy/min for TBI prescribed to 12 Gy in six fractions reported pneumonitis risks of 13% and 43%, respectively, for these dose rates, although there were many confounding covariates.[80]

Pneumonitis in the BMT setting has a multifactorial etiology, reflecting not only the effects of radiation, but also the effects of chemotherapy, graft-versus-host disease (GVH), lung injury from tumor, opportunistic infections, and other risk factors.[69,71,81] Cyclophosphamide is almost universally given with TBI. The addition of other drugs is based on institutional treatment policies; many of these anticancer drugs are known to injure the lung.[41,42] BMT conditioning regimens that do not use TBI (which often use high-dose busulfan in place of radiation) in fact have rates of interstitial pneumonitis comparable to regimens that include TBI. The presence of GVH is also important, not only because GVH causes lung injury directly, but also because the drugs used to control GVH injure the lung. Perhaps, for this reason, T-cell-depleted transplants, which produce less GVH, tend to have lower risk for pneumonitis.[82]

Whole-lung irradiation has been used in the treatment of widespread lung metastases. In two published series, a combined total of 70 patients with osteosarcoma who received elective whole-lung irradiation to prevent pulmonary metastases (which is not currently a standard practice pattern) received 15 to 17.5 Gy in 10 fractions. None of these patients developed pneumonitis.[19] Similarly, in a series of 40 patients who received 20 to 25 Gy of thoracic irradiation in 1.5-Gy fractions to treat pulmonary metastasis, no cases of pneumonitis were reported.[19] This and other clinical experience with fractionated whole-lung irradiation in the nontransplant setting and in the absence of chemotherapy indicate that the following dose schemes should have a relatively low risk (<5%) for radiation pneumonitis: 25 Gy given in 20 fractions over 4 weeks or 20 Gy given in 10 fractions over 2 weeks. (All doses noted are without heterogeneity corrections.)

Historically, radiotherapy for Hodgkin disease has used whole-lung treatment in situations in which there is massive mediastinal adenopathy, hilar adenopathy, or overt pulmonary disease treated with chemotherapy. Risks of symptomatic pneumonitis ranging from 7% to 35% have been reported, with the risk highly dependent on the total radiation dose and the fractionation pattern.[19,83] When the whole lung is to be irradiated, available data suggest that the lungs should be treated through transmission blocks, rather than using open fields. This reduces both the total dose and the dose per fraction to the lungs,

thereby reducing the risk of symptomatic pneumonitis to 4% to 7% over a broad range of total lung doses of 10 to 20 Gy.

There is a suggestion that the addition of mediastinal irradiation to fractionated whole-lung radiotherapy increases the risk of pneumonitis. To many oncologists, the risk of radiation pneumonitis from such a treatment seems too great. As a result, such patients are often treated primarily with chemotherapy (often with adjuvant low-dose radiotherapy), even though these regimens also produce significant risks for lung toxicity. In the setting of pulmonary metastases, the addition of low-dose radiotherapy to the whole lung after chemotherapy is controversial. There are few clinical data to quantify risks and benefits, but doses of 10 to 16 Gy, given in 0.7- to 1.5-Gy fractions, are associated with only modest risk.[19,83]

Lung radiotherapy using 12 to 14 Gy for pulmonary metastases in pediatric patients with Wilms tumor (who also receive sequential doxorubicin and actinomycin D) is associated with a 10% incidence of pneumonitis.[84] Long-term follow-up in such children also shows restrictive lung disease, with total lung and vital capacities approximately 70% of the predicted values. In children receiving thoracic irradiation, inhibition of normal growth and development of the lung parenchyma and bones as a result of radiotherapy also produces significant morbidity. The effects of radiation on growth and development and the radiosensitivity of growing tissues raise special concerns in the treatment of pediatric patients.[5]

■ PARTIAL-LUNG IRRADIATION

The role of partial-lung irradiation in the treatment of various malignancies and assessment of its risks are considered below.

Assessment of Risk

Estimating the risks of radiation pneumopathy for individual patients receiving fractionated external beam radiotherapy is a daunting task, because so many confounding factors must be considered. With lung cancer, the tumor size and location influence the volume of adjacent normal lung that must be irradiated. The volume irradiated should determine the number of capillary–alveolar units destroyed and, therefore, should influence the risk of symptomatic radiation pneumonitis and fibrosis.[29] This qualitative prediction is borne out by clinical experience, but quantifying the risks is not straightforward. The lung region irradiated is also important, because the upper lung regions contribute less to gas exchange than do the lower regions. Treatment-related factors such as total dose, dose per fraction, and overall treatment time are also important, as are the other confounding factors described in the preceding sections.[32]

Patients begin radiotherapy with a wide range of pulmonary function, reflecting age, smoking history, and the presence or absence of underlying cardiopulmonary disease. Because regional pulmonary fibrosis may be partially compensated by functional lung parenchyma, pretreatment lung status influences the severity of symptoms. The clinical endpoints used to measure lung injury are quite varied and include symptom and quality-of-life scores; radiographic changes, such as changes in CT-assessed lung density, pneumonitis, and fibrosis; and other objective measures.[32]

Pulmonary function tests are global measure of organ function that correlate imperfectly with symptomatology after partial-lung irradiation. A large tumor mass may cause localized obstructive or restrictive changes in lung function or phrenic nerve dysfunction, any of which may improve or worsen as the tumor shrinks with treatment. These factors add to the variability produced by patient-to-patient differences in the treatment volume, dose, fractionation, etc. Thus, radiotherapy-induced changes in global lung function with regard to gas exchange, physiologic dead space, shunting, ventilation–perfusion mismatch, and respiratory surface area, as measured by arterial blood gases, spirometry, and $D_{LCO,}$ are complex and highly individualized.

Several clinical studies have attempted to predict radiotherapy-induced changes in FEV_1 by superimposing radiation treatment portals on quantitative ventilation and perfusion scans.[85–88] Unfortunately, the simple notion that the proportion of lung irradiated should match the drop in FEV_1, akin to the highly useful preoperative assessment of predicted postresection lung function, has not been verified. In fact, a report from the Massachusetts General Hospital[88] examining global and regional pulmonary function in patients with lung cancer showed improvement in pulmonary function in 52% of patients and a mild decline in 37%; the decline was predicted from changes in radionuclide scans in only 11%. Similar observations have been made in nonoperative lung cancer patients.[86] Whereas the mean pretreatment FEV_1 of 1.71 ± 0.67 L declined to an average of 1.15 ± 0.43 L after treatment, the change was not consistent: Posttreatment FEV_1 was improved in 19% of the patients, unchanged in 53%, mildly decreased in 22%, and decreased below predicted levels in 5%. The technique of superimposing radiation treatment portals over quantitative lung perfusion scans is, therefore, of limited utility in predicting pneumonitis in individual patients. In fact, it has been suggested that the diffusing capacity is a more sensitive indicator of tolerance to radiotherapy.[85]

Unfortunately, there are no firm tests or data to guide the development of tolerable regimens of radiotherapy for patients with borderline lung function, except that we know the treatment volumes should be minimized. If the initial FEV_1 is below 1.0 L or D_{LCO} is less than 50% of predicted, large-volume radiotherapy (e.g., elective nodal irradiation for lung cancer) may well be too hazardous. Despite its limitations, quantitative perfusion scanning in selected patients may give a worst-case scenario and help the radiation oncologist decide on dose and treatment volume.

The quantitative relationship between the volume of lung irradiated and toxicity has only recently been studied in any systematic fashion. An interesting set of mouse data published by investigators at MD Anderson showed a clear shift in dose–response curves for changes in respiratory rate and pulmonary death as a function of the volume of lung irradiated.[35] As expected, the region of the lung irradiated was important: Effects were more pronounced when the well-perfused base of the lung was irradiated, rather than the less well-perfused apex. The response to lung irradiation was quite heterogeneous, even within mice of the same age and sex, from a single highly inbred mouse strain, maintained in microbiologic isolation under rigorously controlled environmental conditions. The morbidity and symptomatology observed in the individual mice was not always reflected in the histology findings found after necropsy.

In patients, radiation dose–volume histogram analyses derived from detailed three-dimensional treatment evaluations and applied to an empirical normal tissue complication model show only a fair correlation between volume and risk of complications.[61,89] Nevertheless, it is common practice to evaluate dosimetric parameters, such as V_{dose} or mean lung dose (MLD), in an effort to predict the risk of pneumonitis prospectively. The V_{dose} (i.e., $V_{20\ Gy}$ or $V_{30\ Gy}$) parameter is defined as the percentage of total volume receiving greater than the threshold dose (i.e., 20 Gy or 30 Gy, respectively). The MLD is defined as the average dose delivered to the whole lungs. These simple metrics predict pulmonary risk based on a single-radiation dose point, used as a mean or threshold.

More complex dosimetric models have also been derived that fit observed normal tissue complication probabilities (NTCPs) to functions that include more comprehensive evaluations of low- and high-dose partial-volume organ exposures using standard radiobiologic models. These approaches may have broader applicability across various radiation treatment techniques, but they are infrequently used because of their complexity. Recently, a multidisciplinary effort, the QUANTEC (see above), was undertaken to summarize the published three-dimensional dose–volume/toxicity

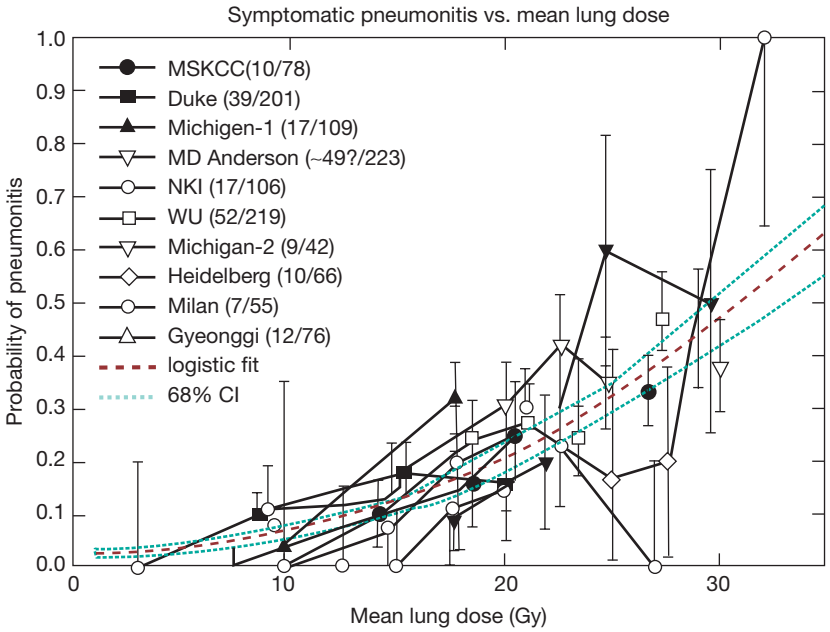


Figure 59-8 Probability of symptomatic pneumonitis versus mean lung dose; data from 10 clinical studies with *dashed line in red* fit by logistic Lyman–Kutcher–Burman dose–volume histogram model with one standard deviation shown in *light blue curves*. *(Reproduced with permission from Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 1;76(3 Suppl):S70–S76.)*

data in the literature, review NTCP modeling, and provide practical guidance for radiotherapy treatment planning.[63] From collected data in the QUANTEC effort, the risk of radiation pneumonitis is less than 20% when the MLD is less than approximately 20 Gy, when V_{20} <30 to 35 Gy, or when V_5 <60%. These predicted risks apply to patients receiving conventional fractionation of 1.8 to 2 Gy per day and are less relevant when the dose per day is greater than 2 Gy.

For hypofractionated treatments, such as SBRT, where doses in excess of 10 Gy per day are given in one to five fractions, the incidence of radiation pneumonitis is significantly lower.[90] This is primarily because the target volume for this type of treatment is quite small. While the risk of symptomatic pneumonitis does seem to follow a radiation dose-volume relationship similar to that seen in conventionally fractionated treatment, specific dose threshold guidelines have not yet been definitively elucidated. In one large series, the risk of grade 2 or greater pneumonitis was 17% when the MLD was >4 Gy, compared with 4% for lower values, and this risk was 16% when the V_{20} was >4% compared with 4% when V_{20} was <4%.[90] The American Association of Physicists in Medicine (AAPM) Task Group 101 report included a first approximation of tissue tolerance doses for SBRT.[91] For lung, they recommended 12.4 Gy to no more than 10 cc, and 11.6 Gy to no more than 15 cc of lung for three-fraction SBRT, and no more than 13.5 and 12.5 Gy to 10 and 15 cc for five-fraction SBRT.

In patients undergoing pneumonectomy for mesothelioma who will then require radiotherapy, dosimetric parameters to avoid pneumonitis of the remaining lung are even more stringent: V_{20} should be below 4% to 10% and MLD should be below 8 Gy.[92] QUANTEC has reviewed over 70 reports on dose–volume parameters and the risk of pneumonitis, selecting the largest series for use in performing a meta-analysis of complication probability models.[61] Such clinical data is challenging to interpret, owing to a host of confounding covariates. However, there are clear trends showing increasing pneumonitis risk with increasing radiation dose. Figure 59-8 shows the risk of symptomatic pulmonary complications as a function of MLD from 10 studies.

Investigators at Duke[93] and the Netherlands Cancer Institute[94,95] have attempted to refine the correlation of dose–volume histograms with toxicity by factoring out nonfunctioning lung using lung perfusion scans. In patients with lung cancer, particularly those with chronic obstructive pulmonary disease (COPD), areas of hypoperfusion separate from tumor are seen frequently; irradiation of such irreversibly hypoperfused lung may not contribute additional toxicity. Such a "functional" dose–volume histogram analysis has not been proven to be of clinical value, but it does provide an interesting analytical framework. The existing data show a direct correlation between regional changes in ventilation, perfusion, or CT density with increasing radiation dose to that region (Fig. 59-9).[96]

Perhaps the most accurate and clinically relevant approach to estimating risks for symptomatic radiation pneumopathy is to study a large group of patients who receive a relatively standard dose and fractionation scheme for a specific disease. As discussed earlier, the variability of the treatment volumes for individual patients with diseases such as lung cancer, as well as the frequent coexistence of other lung diseases, especially COPD from tobacco use, makes this a difficult task.

More complex prediction models that factor in baseline $D_{L_{CO}}$, serum cytokine levels, or tumor locations in upper versus low lobes have yielded variable improvements in prognostication. Similar data regarding the incidence of radiation fibrosis are quite difficult to obtain, largely because of the wide spectrum of severity in symptomatology. Clinical experience suggests that radiographic fibrosis is rare below 20 Gy and common above 40 to 50 Gy, with symptoms of respiratory insufficiency dependent on the volume of injured lung and the presence of coexisting lung disease.

Lung Cancer: Local Tumor Boosting

In the treatment of lung (and, perhaps, esophageal) cancer, it is quite standard to boost the primary tumor and a small volume of the lung to total cumulative doses above 50 Gy, commonly to 60 to 70 Gy. Clinical data, notably the dose-escalation lung cancer trials of the

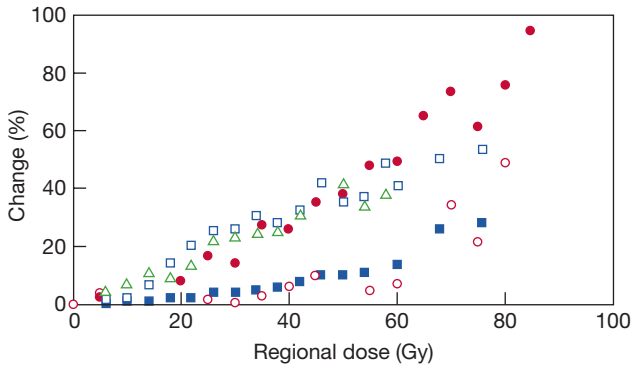


Figure 59-9 Regional changes in ventilation, perfusion, and computed tomography (CT) density from partial lung radiotherapy as a function of regional radiation dose: data from Duke University (Duke) and Netherlands Cancer Institute (NKI). Symbols in graph represent: (●) reduction in perfusion-Duke; (¡) increase in CT density-Duke; (■) change in air-filled fraction-NK; (□) reduction in perfusion-NKI; and (Δ) reduction in ventilation-NKI. *(Reproduced with permission from Marks LB, Yu X, Vujaskovic Z, et al. Radiation-induced lung injury. Semin Radiat Oncol. 2003;13(3):333–345.)*

Radiation Therapy Oncology Group, suggest that increasing doses to small volumes from approximately 50 to approximately 65 Gy is not associated with a significant increase in lung toxicity,[97] probably because the number of nonfunctional alveoli is not increased by this increase in dose. In most series of patients receiving radical thoracic radiotherapy, the risk of symptomatic radiation pneumonitis is usually about 10% to 20%, and some degree of radiographic fibrosis is almost universal.

Breast Cancer

Breast cancer radiotherapy, whether after lumpectomy or after mastectomy, typically uses opposed tangential beams, as depicted in Figure 59-6, which irradiate a volume of lung anterolateral to a plane demarcating the midchest to the lateral axillary line to doses of 45 to 50 Gy in 23 to 25 fractions. The volume of the ipsilateral lung irradiated can be estimated for individual patients from the simulator films and is typically about 20% of the lung volume. If the supraclavicular and axillary nodes are irradiated as well, the anterior treatment portals are matched to the tangential chest wall fields. As a result, the apex of the lung (roughly another 10%–15% of ipsilateral lung volume) is also irradiated. The incidence of symptomatic pneumonitis from tangential fields alone is roughly 0.5%, with some series documenting an increased risk with increasing lung volume.[98,99] It is desirable to keep the irradiated volume below approximately 25%, if possible. Nodal irradiation increases the risk for pneumonitis to 0.5% to 1.5%. Risk further increases to as high as 9% when chemotherapy is given concurrently. The risk of pneumonitis is much lower when chemotherapy and radiation are given sequentially.[98]

Early-stage Hodgkin Disease

Radiotherapy for early-stage Hodgkin lymphoma, using moderate doses (40–45 Gy in 1.5–2 Gy fractions) and large volumes to treat lymph node-bearing regions, has represented a remarkable success story in oncology.[5,100] Because it now has produced very high cure rates in a young patient population, allowing for extended follow-up over several decades, this experience also has produced considerable data regarding late radiation toxicities.

With the protocols employed, the chest is irradiated with treatment portals, generically called "mantle fields," as depicted in Figure 59-10. With modern radiation techniques that use sequential shrinking fields, the incidence of symptomatic radiation pneumonitis is 3% to 4%. The risk of pneumonitis increases to roughly 10% when full doses of both chemotherapy and radiation to a mantle field are given sequentially, even when bleomycin is not part of the regimen.

Studies on pulmonary function in patients with Hodgkin disease suggest that a transient reduction in FEV_1 and vital capacity, on the order of 5% to 20%, occurs 3 to 9 months after radiotherapy, corresponding to the period of pneumonitis. There tends to be some recovery by about 1 year. Late follow-up of pulmonary function in patients with Hodgkin disease[100] further suggests that mantle field radiotherapy is associated with small, and, for the most part, clinically insignificant, reductions in vital capacity and D_{LCO}. These decreases in pulmonary function tests were associated with minor, if any, symptomatology, even for treatment regimens that included sequential chemotherapy with doxorubicin or bleomycin.

Primary radiotherapy for Hodgkin disease is now rarely practiced. Decades of follow-up in patients cured of their lymphomas show a steady increase in secondary cancers as well as cardiac complications. As a consequence, clinical trials have shown improved disease-free survival over 5 to 10 years with primary chemotherapy. In this setting in which lower-dose (20–30 Gy) involved-field radiotherapy is often delivered after chemotherapy, the incidence of clinical pneumonitis is quite low, although small changes in spirometry and diffusion capacity may be detected in up to 50% of the patients. Longer-term follow-up of toxicities from combined-modality therapy in Hodgkin disease is in progress.

PROGNOSTIC ASSAYS AND FUTURE TRENDS

Our understandings of the molecular and cellular mechanisms of radiation injury in general, and radiation pneumonitis in particular, are still evolving and improving. We hope that increased understanding of these processes will lead to new approaches for avoiding radiation injury to the lung, for modulating the development of injury or ameliorating its symptomatology, and for identifying patients at unusually high risk of injury. Several different lines of investigation leading to these ends are being pursued.

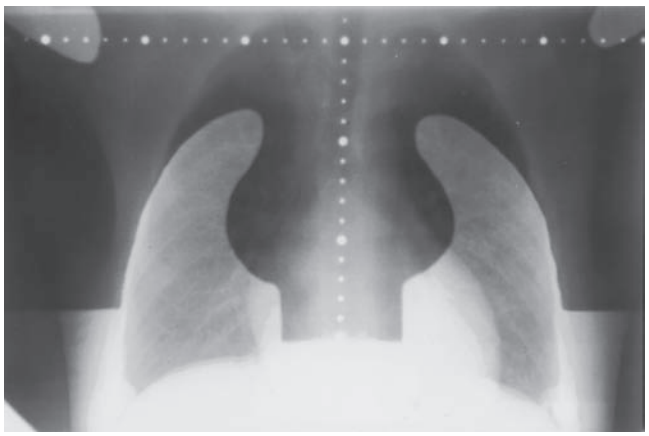
Innovations in radiation therapy techniques are under active investigation. These include modifications in the dose rates, fractionation patterns, and radiation dose distributions used in radiation therapy regimens for specific diseases. Improvements in diagnostic imaging that allow better identification of tumor-involved regions, computerized treatment planning and dosimetry systems, improved patient immobilization systems, the use of multiple "noncoplanar, noncoaxial" radiation portals (three-dimensional conformal radiotherapy), and the use of multiple radiation fields that have variable rather than uniform spatial intensities (intensity-modulated radiotherapy) are now standard techniques in the radiotherapy clinic.

Proton radiotherapy takes advantage of the "Bragg peak," in which the radiation dose is deposited at a well-defined maximum depth that depends on the proton energy to produce very precise, highly localized dose distributions. This type of charged-particle radiation technique is being explored in the hope that the approach will enable the radiotherapist to increase the dose to the tumor while decreasing the volume of surrounding normal tissue irradiated to high doses.

Four-dimensional treatment planning to take into account respiratory motion, along with deep inspiration breath-hold methods, are also being examined in an effort to better limit the volume of normal tissue exposed to radiotherapy. In addition, refinements in combined-modality therapy may also lead to the development of regimens that increase the therapeutic ratio for the treatment of thoracic tumors and, therefore, decrease the risk and severity of radiation pneumonitis after effective antineoplastic therapy.

The risk of developing radiation pneumonitis varies dramatically in different patients. To a certain extent, increased risk can be predicted from identifiable risk factors, such as prior treatment with thoracic radiotherapy, treatment with pneumotoxic drugs, or the existence of lung disease from other causes. However, even when the known risk factors are considered, the risk of symptomatic injury after radiotherapy varies dramatically from patient to patient. Studies with mice indicate that genetic factors contribute to individual variability in the development of late radiation injury in the lung.[34] This raises the possibility that pretreatment measurements of genetic or proteomic polymorphisms or of enzyme or cytokine levels in the lung, analyses of changes in cytokine levels during treatment or of tissue response to cytokines, or some other relevant measure may be useful in predicting patients at high risk for the development for pneumotoxicity.[36]

Assays of surfactant levels shortly after irradiation predict radiation pneumonitis in some rodent studies but have not predicted radiation pneumonitis in individual patients in the clinical trials performed to date. TGF-β1, a cytokine that mediates fibrosis, is currently the subject of intense investigation. Serum levels of TGF-β1 have been reported to predict pulmonary toxicity after high-dose chemotherapy for breast cancer[101] and may also predict for breast fibrosis from radiotherapy,[102] but its application to predicting toxicities after radiotherapy for lung cancer has been tenuous and controversial due to the fact that TGF-β1 correlates with adverse dosimetric parameters, thus eliminating any independent prognostic importance as a biomarker.[32,103–106] Nevertheless, there is laboratory evidence that antagonists of TGF-β1 receptors may someday be useful in the clinic.[107]



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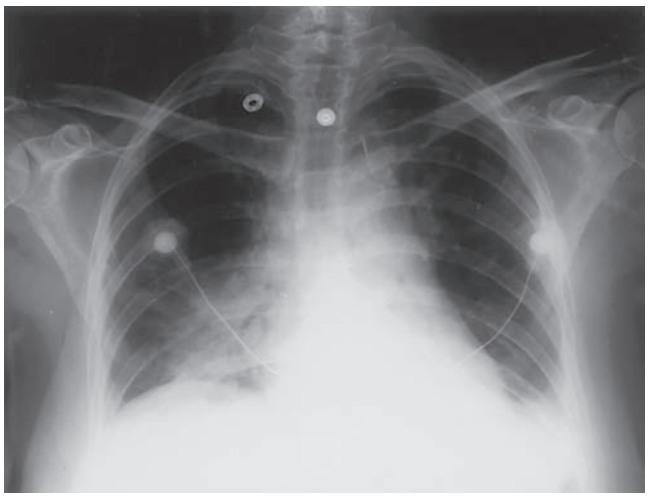

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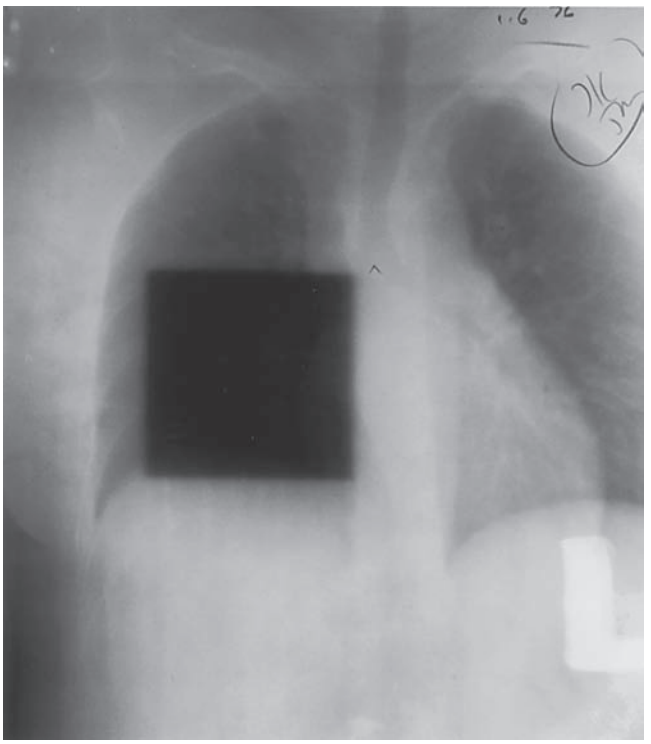

B

Figure 59-10 **A.** Shows the port film for a "mantle field" used for treatment of a patient with Hodgkin lymphoma. Note the effect of the lung blocks in reducing the dose to large volumes of the lung. (In this example, the whole heart/pericardium is not being treated.) A 30-year-old female underwent mantle field and subdiaphragmatic radiotherapy (not shown) for early-stage Hodgkin lymphoma. Ten years later, a recurrence in the right lower lobe and mediastinum was treated with MOPP-type chemotherapy and low-dose involved-field radiotherapy. The treatment field to the right lung, shown in (**B**), was irradiated to 15 Gy in 10 fractions, in addition to the 40 Gy given to the mantle field 10 years previous. Radiation pneumonitis occurred 6 months later, as seen in (**C**). This responded to prednisone. Twenty years later, the patient remains well and free of recurrence.

Assays of other cytokines such as interleukins, IL-6 and IL-1α are being explored clinically in studies that suggest high positive predictive values for pneumonitis.[108] Similarly, analyses of the intrinsic radiosensitivity in vitro of fibroblasts from patient biopsies have been suggested as a possible approach to measuring the general risks of individual patients for radiation injury. Such assays have proved useful in planning treatments for patients with the genetic disease ataxia telangiectasia (AT), which leads to unusual radiosensitivity. One intriguing study of AT polymorphisms in a cohort of lung cancer patients treated with chemoradiation does suggest increased susceptibility to radiation pneumonitis with certain genotypes.[109] Prognostic assays predicting high or low risks for radiation pneumopathy could be used to guide clinical decision making and plan optimal therapy for individual patients.

Insights into the physiology underlying the development of radiation pneumopathy may also lead to the development of regimens that prevent the development of this disease or ameliorate its symptomology.

The "radioprotector," amifostine (Ethyol, WR2721) has been examined extensively because of its widespread distribution into most normal tissues, limited distribution into tumors, and its activity as a free radical scavenger, which results in a decrease in radiation cytotoxicity. Amifostine has been of variable benefit in reducing mucositis or xerostomia in patients with head and neck cancer undergoing radiotherapy (without apparent effect on tumor control). This has led to analogous clinical investigations of amifostine to prevent pneumonitis.

Several small phase III trials in lung cancer suggested a benefit to amifostine during thoracic radiotherapy, with a decrease not only in pneumonitis, but also in radiation esophagitis as well.[110] A large multi-institutional trial sponsored by the Radiation Therapy Oncology Group involving 242 patients, however, failed to document a difference in pneumonitis rates with amifostine.[111] The trial has been criticized for its twice a day fractionation scheme, in which amifostine was administered with only one fraction each day, the unusually high patient dropout rate of 19% due to toxicity, and the fact that 52% of patients did not receive their intended dose of amifostine.

The development of radiation pneumopathy has not been appreciably altered by the use of prophylactic steroids, antibiotics, or anticoagulants. The use of gamma interferon in conjunction with radiation actually worsened pneumonitis in recent clinical trials.[112] Beta interferon is under clinical investigation. Nutritional factors and neutraceuticals merit further consideration, as subclinical vitamin

A deficiency has been shown to increase radiation injury in the rat lung[113] and genistein decreases effects in irradiated mouse lungs.[114]

Numerous other approaches are being investigated in laboratory studies, including the use of captopril, superoxide dismutase analogs, lovastatin, pentoxifylline, IL-11, and inhibitors of TGF-β.[9,115] Captopril, which is an angiotensin-converting enzyme (ACE) inhibitor used clinically for the treatment of hypertension and heart failure, is especially promising in laboratory studies. As a thiol compound, captopril can act as a free radical scavenger. It can also form copper complexes, which have superoxide dismutase-like activity. Moreover, in animal studies, captopril has vascular effects and can inhibit platelet aggregation, perhaps mediated by IL-2 release, which ameliorate radiation injury to pulmonary endothelium and decrease pulmonary fibrosis.[116,117]

One retrospective clinical review failed to demonstrate a benefit for ACE inhibitors in general, but it did not specifically evaluate captopril and may have been further confounded by including older radiation techniques.[118] Two clinical series of lung cancer patients treated with chemoradiation have shown a significant decrease in pneumonitis associated with the incidental use of ACE inhibitors.[119,120] Experiments in a mouse model suggest that captopril administration subsequent to radiation exposure may mitigate radiation lung injury.[121] In another mouse study, another experimental agent having superoxide dismutase activity, EUK-207, mitigated lung injury following thoracic irradiation.[122]

Lovastatin, a cholesterol-lowering drug that inhibits 3HMG coenzyme A reductase and also has potent anti-inflammatory effects, improved survival and reduced pulmonary infiltration by macrophages and lymphocytes in a murine model of whole-lung irradiation.[123] This approach has not yet been investigated in the clinic.

Pentoxifylline, with or without vitamin E, has been shown to reduce radiation-induced breast or soft tissue fibrosis[124–126] and has been proposed as a potential agent for mitigating pulmonary fibrosis. A number of promising compounds, some in clinical use for other indications, have been proposed for clinical testing as agents for mitigating radiation-induced lung injuries.

All attempts to modulate the development of radiation pneumonitis must be pursued cautiously, however, because these therapeutic strategies are based on biologic epiphenomena and rely on an incomplete understanding of the mechanisms by which radiation pneumopathies are produced. In testing such interventions, as with any alteration of cancer therapy, it will be critical to consider the effects of the intervention on the response of the malignancy, as well as its effects on normal tissue injury; the intervention will be of value only if it increases the therapeutic ratio.

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CHAPTER 60

Pulmonary Manifestations of the Collagen Vascular Diseases

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Marvin I. Schwarz

Pleuropulmonary involvement associated with the collagen vascular diseases occurs frequently. All the structures within the respiratory tract may be affected, either separately or in combination. This includes the respiratory muscles, the pleura, the conducting airways, and the lung parenchyma—the small airways, the interstitium, or the pulmonary vessels. Moreover, these patients experience an increased incidence of community-acquired pneumonia as well as pneumonia associated with the immunosuppressive drugs employed for treatment. Anti–tumor necrosis factor-α (anti–TNF-α) agents increase the risk for infections, particularly mycobacterial pathogens, both tuberculous and nontuberculous. Cytotoxic drugs, particularly methotrexate and gold, can also induce various noninfectious interstitial reactions, which are often difficult to distinguish from a primary interstitial complication of a collagen vascular disease.[1]

Although most pulmonary complications appear in an established case of a collagen vascular disease, lung disease may precede the more typical systemic manifestations.[2] For example, in both rheumatoid arthritis and polymyositis–dermatomyositis, the interstitial lung disease may precede the joint and muscle disease for several months to several years. This is also the case, but to a lesser extent, for scleroderma. In one study, 19% of patients initially diagnosed with idiopathic pulmonary fibrosis developed a collagen vascular disease over a period of 1 to 11 years, primarily rheumatoid arthritis or polymyositis–dermatomyositis. These individuals were younger and more likely to be women. Pleuritis with or without effusion sometimes heralds the onset of rheumatoid arthritis or systemic lupus erythematosus (SLE). An acute immunologic pneumonitis or diffuse alveolar hemorrhage has been reported to be the signal event in SLE, polymyositis–dermatomyositis, and mixed connective-tissue disease.

The incidence of the pleuropulmonary complications (Table 60-1) is variable. Interstitial lung disease is reported to be as high as 60% in premortem and 100% in postmortem studies in scleroderma. In contrast, interstitial lung disease in ankylosing spondylitis is an uncommon event. In general, the incidence of interstitial lung disease is increasing for most of the collagen vascular diseases, primarily due to increased recognition and more sensitive screening techniques such as high-resolution computed tomography and bronchoalveolar lavage, which will detect abnormalities in both asymptomatic as well as symptomatic patients with normal chest radiographs. Prior studies assessing the incidence of disease relied on physiologic testing, which included spirometry, lung volumes, and diffusing capacity but did not measure rest and exercise gas exchange, which is the most sensitive physiologic marker of interstitial lung disease and pulmonary vascular disease.

PULMONARY PARENCHYMAL, VASCULAR, AND AIRWAY PATHOLOGY IN THE COLLAGEN VASCULAR DISEASES

The spectrum of pathologic changes in the lung parenchyma, pulmonary vasculature, and airways are considered below, prior to a discussion of clinical findings in individual collagen vascular diseases.

INTERSTITIAL LUNG DISEASE

Interstitial involvement is a common manifestation of the collagen vascular disorders, presenting with a number of different

TABLE 60-1 Pulmonary Complications of the Collagen Vascular Diseases

	Relative Frequency (0–4)						
Manifestation	SLE	RA	SS	PM-DM	MCTD	AS	Sjögren's
Respiratory muscle dysfunction	2	1	0	2	1	0	0
Aspiration pneumonia	0	0	3	3	2	0	2
Primary pulmonary hypertension	2	1	4	1	2	0	0
Vasculitis	2	2	0	1	1	0	0
Interstitial lung disease	2	3	4	3	2	1	3
Capillaritis + DAH	2	1	1	1	1	0	0
Bland DAH	2	0	0	0	1	0	0
Diffuse alveolar damage	2	0	0	2	1	0	0
Nonspecific interstitial pneumonitis	2	3	3	3	3	0	1
Lymphocytic interstitial pneumonitis	1	2	1	0	0	0	3
Usual interstitial pneumonitis	2	3	2	2	2	1	1
Honeycomb lung	1	2	4	3	2	1	1
Bronchiolitis obliterans organizing pneumonia	1	3	1	3	2	0	1
Bronchiolitis	1	2	1	0	1	0	1
Obliterative bronchiolitis	0	2	0	0	0	0	1
Pleural effusion	2	3	1	0	2	0	1
Parenchymal nodules	0	2	0	0	0	0	1

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SS, systemic sclerosis (scleroderma); PM-DM, polymyositis-dermatomyositis; MCTD, mixed connective-tissue disease; AS, ankylosing spondylitis; Sjögren's, Sjögren syndrome; DAH, diffuse alveolar hemorrhage.

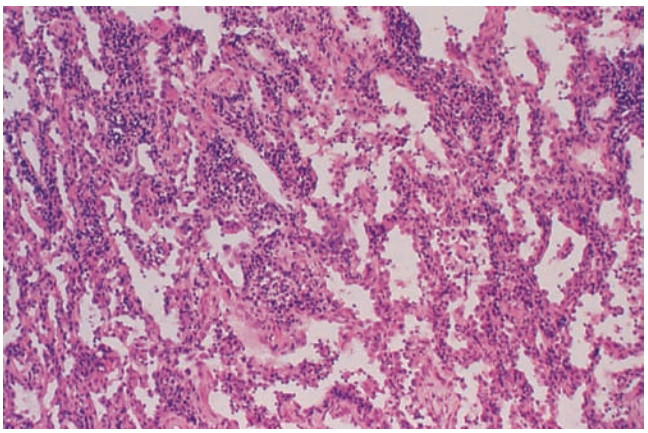


Figure 60-1 Nonspecific interstitial pneumonitis (NSIP) in rheumatoid arthritis. There is a lymphoplasmacytic infiltration of the interstitial compartment with minimal collagen deposition.

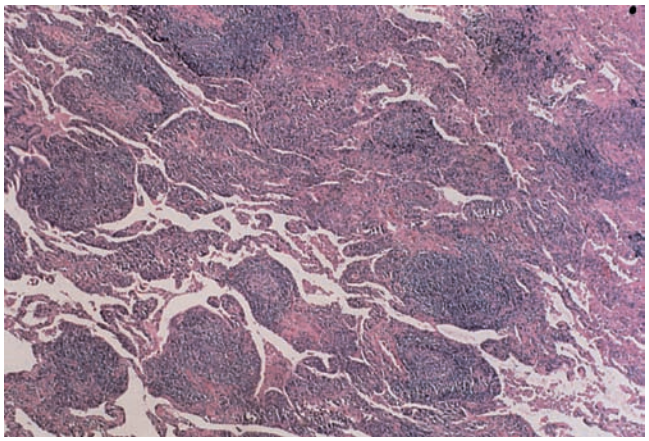


Figure 60-2 Lymphocytic interstitial pneumonitis in a patient with primary Sjögren syndrome. There is a dense lymphocytic infiltrate, broadening the interstitium and lymphoid follicles.

inflammatory responses within the lung. Each response may represent a different form of lung injury or response to injury. Defining which response is underlying a patient's interstitial lung disease has important prognostic and therapeutic significance.

Diffuse alveolar damage (DAD) is the underlying histologic lesion that is also seen in the acute respiratory distress syndrome, idiopathic acute interstitial pneumonitis (Hamman–Rich syndrome), severe viral pneumonias, and cytotoxicity from some drugs. This damage consists of a mixed interstitial inflammatory infiltrate, interstitial edema and fibrin deposition, and characteristic intra-alveolar hyaline membrane formation. Intra-alveolar red blood cells (diffuse alveolar hemorrhage) may be present in severe cases. With progression, there is intra-alveolar organization, intra-alveolar and interstitial fibrosis, alveolar collapse, and the development of an end-stage fibrotic or "honeycomb" lung. An acute immunologic pneumonia, seen in SLE (acute lupus pneumonitis) and in polymyositis–dermatomyositis, may also demonstrate this underlying histologic appearance.

Nonspecific interstitial pneumonitis (NSIP) refers to a spectrum of histologic features with varying degrees of lymphoplasmacytic infiltration of the interstitium and collagen deposition (Fig. 60-1). In the cellular form, lymphoplasmacytic interstitial inflammation exists with associated type II alveolar epithelial cell hyperplasia. In the fibrosing form, the inflammation is accompanied by a temporally and spatially homogeneous deposition of collagen (fibrosis). Architectural distortion or honeycombing may occur in advanced cases and the presence of fibrosis dramatically changes the clinical course and prognosis to one resembling that seen in usual interstitial pneumonitis (UIP) (see below). NSIP is most frequently seen in patients with rheumatoid arthritis, polymyositis–dermatomyositis, mixed connective-tissue disease, and scleroderma.

Lymphocytic interstitial pneumonitis refers to a monotonous infiltration of the interstitium by mature lymphocytes (Fig. 60-2). These lymphocytes tend to form germinal centers within the interstitium as well as displaying an angiocentric distribution. Other features of lymphocytic interstitial pneumonia include macrophagic giant cells, granuloma formation, and amyloid deposition. Lymphocytic interstitial pneumonitis can progress to UIP and end-stage honeycomb lung. Among the collagen vascular diseases, this pneumonitis most commonly accompanies the primary form of Sjögren syndrome and, to a lesser extent, the secondary form of Sjögren syndrome appearing with other collagen vascular diseases, particularly rheumatoid arthritis.

UIP is the underlying lesion of idiopathic pulmonary fibrosis and can also appear in all the collagen vascular diseases. It consists of varying degrees of mononuclear cell infiltration and fibroblastic proliferation leading to collagen deposition within the alveolar interstitium (Fig. 60-3). With progression, this fibrotic reaction results in marked distortion of the lung architecture and what remains are 2- to 3-mm cystic spaces lined by metaplastic epithelium, the so-called honeycomb lung (Fig. 60-4). Other features of UIP include type II epithelial cell hyperplasia producing a "hob-nailed" appearance on the alveolar surface, collections of intra-alveolar macrophages, and smooth-muscle proliferation within the interstitium. Additional abnormalities seen in collagen vascular disease-associated UIP but not in patients with idiopathic pulmonary fibrosis may include: focal chronic pleuritis, lymphoid follicles with germinal center formation, perivascular collagen deposition, and an increase in CD4+ T lymphocytes, especially in rheumatoid arthritis.

Organizing pneumonia, previously termed bronchiolitis obliterans organizing pneumonia, is a distinctive histologic lesion that follows a variety of insults to the alveolar structures including drugs, infection, radiation, and an idiopathic variety. Organizing pneumonia can also complicate the collagen vascular diseases, particularly rheumatoid arthritis and polymyositis–dermatomyositis. Three features comprise the histologic picture: (1) intra-alveolar space and intra-alveolar ductal fibroblastic proliferation with early collagen deposition (Masson bodies), (2) inflammatory polyps consisting of fibroblasts and mononuclear cells protruding into the lumens of respiratory and terminal

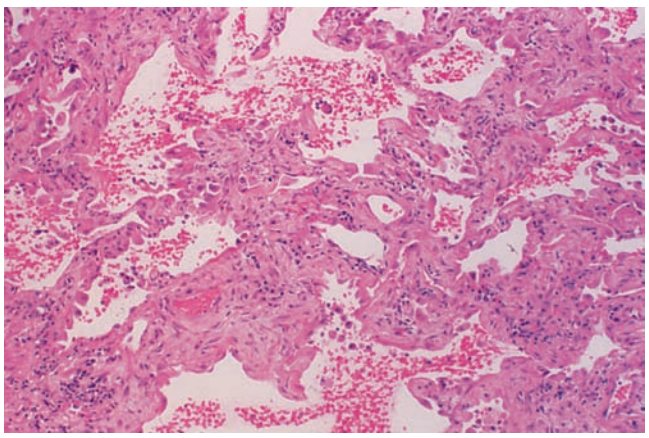


Figure 60-3 Usual interstitial pneumonia (UIP) in a patient with rheumatoid arthritis. There is broadening of the interstitium by varying degrees of mononuclear cell infiltration and collagen deposition.

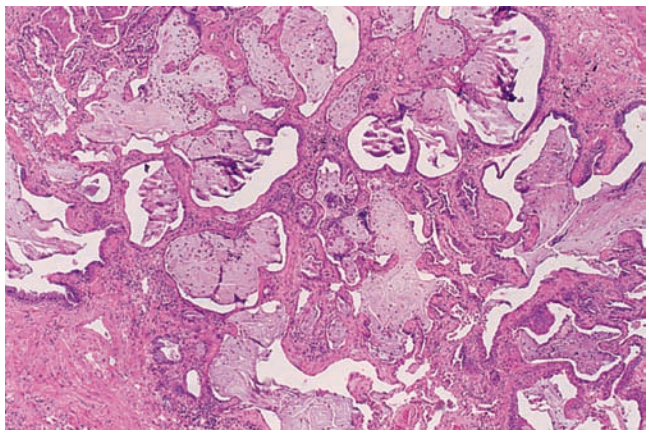


Figure 60-4 Advanced UIP in a patient with scleroderma (honeycomb lung). Normal alveolar tissue is replaced with broad bands of fibrous tissue lined by metaplastic epithelium and filled with inspissated mucus producing a cyst-like network. *(Used with permission of the Armed Forces Institute of Pathology [AFIP].)*

bronchioles, and (3) alveolar septal lymphoplasmacytic infiltrate with type II pneumocyte hyperplasia within affected areas (Fig. 60-5). Bronchiolitis obliterans organizing pneumonia has the potential for being a completely reversible lesion; however, with continuing injury it may progress to end-stage fibrosis and honeycomb lung.

PULMONARY VASCULAR DISEASE

A form of pulmonary artery hypertension, which most commonly appears in patients with scleroderma and is now being increasingly recognized in SLE, rheumatoid arthritis, and mixed connective-tissue disease, is histologically identical to the syndrome of idiopathic pulmonary artery hypertension (IPAH) seen in young women without collagen vascular disease, formerly known as primary pulmonary hypertension. This is a proliferative disorder (plexogenic arteriopathy) affecting the arterioles and small muscular pulmonary arteries. This form of pulmonary hypertension must be differentiated from secondary forms as a result of hypoxic vasoconstriction induced by interstitial lung disease or severe emphysema. In the plexogenic variety, there is endothelial cell intimal proliferation and smooth muscle cell proliferation causing medial thickening with a resultant "onion ring" configuration and luminal obliteration. In the secondary forms

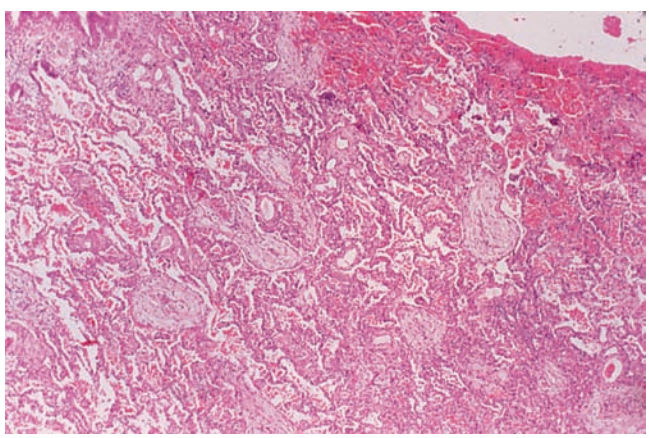


Figure 60-5 Bronchiolitis obliterans organizing pneumonia in a patient with rheumatoid arthritis. There is a mononuclear cellular infiltration of the interstitium without collagen deposition as well as alveolar duct and intra-alveolar fibroblastic proliferation and early collagen production.

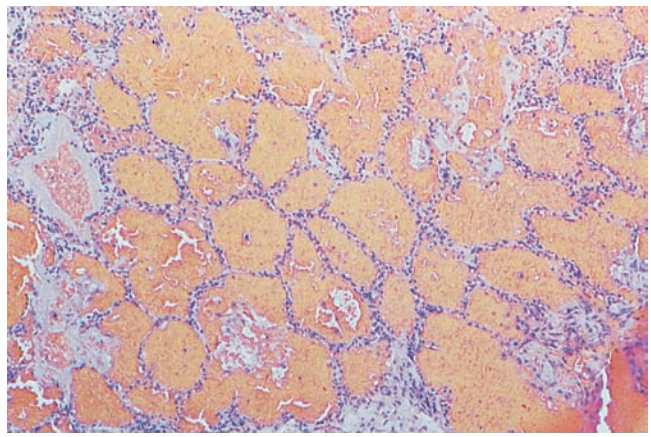


Figure 60-6 Bland diffuse alveolar hemorrhage in SLE. There is little if any interstitial reaction except for type II pneumocyte epithelial cell hyperplasia. The alveolar spaces are filled with red blood cells.

of pulmonary hypertension due to hypoxia, medial hypertrophy is the primary finding. In patients with SLE and the antiphospholipid syndrome, pulmonary artery hypertension may develop as a result of recurrent pulmonary emboli and mimic the clinical picture of IPAH.

Vasculitis refers to an acute inflammatory angiodestructive process resulting in fibrinoid necrosis of the vascular wall. In the collagen vascular diseases, this is most often a small-vessel vasculitis involving arterioles and small muscular pulmonary arteries. Although uncommon, this is seen with greatest regularity in SLE and less frequently in rheumatoid arthritis, polymyositis–dermatomyositis, and mixed connective-tissue disease. Often accompanying the arteriolitis is the lesion of pulmonary capillaritis (see below).

DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage is recognized by the accumulation of red blood cells within the alveolar spaces, and with recurrent episodes, intra-alveolar and interstitial hemosiderin is deposited and fibrosis may result. There are two different histologic subtypes seen in diffuse alveolar hemorrhage. One is devoid of inflammation and is referred to as *bland hemorrhage* (Fig. 60-6). It is therefore similar in histologic appearance to idiopathic pulmonary hemosiderosis. The other, pulmonary capillaritis is a unique neutrophilic infiltration of the alveolar interstitium, which results in necrosis and loss of integrity

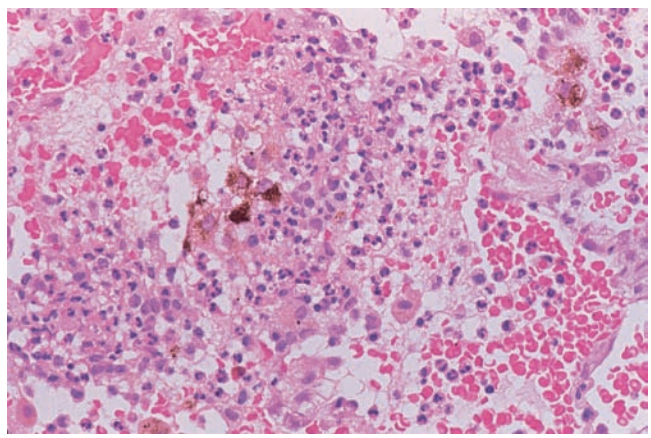


Figure 60-7 Low-power view of pulmonary capillaritis in a patient with SLE. There is marked thickening of the interstitial compartment and infiltration by acute and chronic inflammatory cells. The alveolar spaces are filled with red blood cells and neutrophils.

of the alveolar–capillary basement membrane, capillary destruction and thrombosis, and a leakage of red blood cells into the alveolar space (Fig. 60-7). A unique feature in pulmonary capillaritis is that many of the infiltrating neutrophils are undergoing fragmentation (leukocytoclasis), and others appear as densely staining apoptotic cells. Nuclear debris ("dust") subsequently accumulates within the necrotic, edematous interstitium, and intra-alveolar compartments while red blood cells freely leak into the interstitial matrix due to capillary destruction. Capillary and arteriolar thrombosis, organizing pneumonia, and type II epithelial cell hyperplasia may also be seen.

Capillaritis is most commonly seen in the systemic vasculitides, particularly granulomatosis with polyangiitis (GPA/Wegener granulomatosis) and microscopic polyangiitis (MPA), the small-vessel variant of polyarteritis nodosa. Of the collagen vascular diseases, both bland pulmonary hemorrhage and diffuse alveolar hemorrhage secondary to pulmonary capillaritis appear most commonly in SLE. Cases of pulmonary capillaritis have also been reported to occur in rheumatoid arthritis, Sjögren syndrome, polymyositis–dermatomyositis, and mixed connective-tissue disease.

■ BRONCHIOLITIS

Bronchiolitis refers to an inflammatory-fibrotic process involving the terminal and respiratory bronchioles and possibly the surrounding alveolar structures. Respiratory bronchiolitis is primarily seen in smokers with or without an associated collagen vascular disease. There is also a primary form of cellular bronchiolitis that complicates the collagen vascular diseases, most often appearing in rheumatoid arthritis and Sjögren syndrome. Histologically, there is a mononuclear cell infiltration of the wall of the bronchiole without impingement of the bronchiolar lumen. In contrast, in bronchiolitis obliterans, or obliterative bronchiolitis, there is a concentric fibrous obliteration of the bronchiolar lumen leading to a severe obstructive lung disease (Fig. 60-8). Bronchiolitis obliterans is most often reported as a complication of rheumatoid arthritis.

■ PARENCHYMAL NODULES

Noninfectious inflammatory parenchymal nodules occur in both rheumatoid arthritis and Sjögren syndrome. In rheumatoid arthritis the nodules are referred to as the *necrobiotic* or *rheumatoid nodules*. These lesions are found both in the pleura and lung parenchyma and are identical in appearance to a subcutaneous rheumatoid nodule. In the lung parenchyma, these nodules are located in the interlobular septa and in the subpleural parenchyma. The necrobiotic nodule is comprised of palisading histiocytes, giant cells, and other mononuclear cells surrounding an area of fibrinoid debris (Fig. 60-9). In Sjögren syndrome, a rounded lesion known as pseudolymphoma can occasionally be detected on the chest radiograph. Pseudolymphoma is considered to be a localized form of lymphocytic interstitial pneumonia and is made up of a dense infiltrate of lymphocytes and histiocytes with occasional granuloma formation. There is a potential risk for malignant transformation in pseudolymphoma as well as in the other forms of lymphocytic interstitial pneumonia.

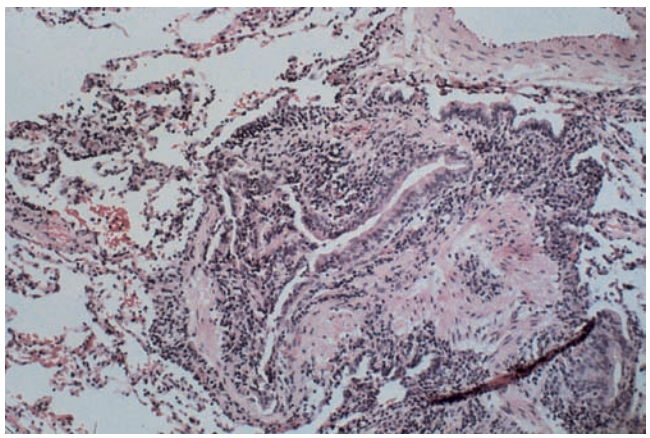


Figure 60-8 Obliterative bronchiolitis in rheumatoid arthritis. There is a marked reduction of the luminal diameter due to concentric fibrous obliteration and dense chronic inflammation. *(Reproduced with permission from Schwarz MI, Lynch DA, Tuder R. Bronchiolitis obliterans: The lone manifestation of rheumatoid arthritis. Eur Respir J. 1994;7(4):817–820.)*

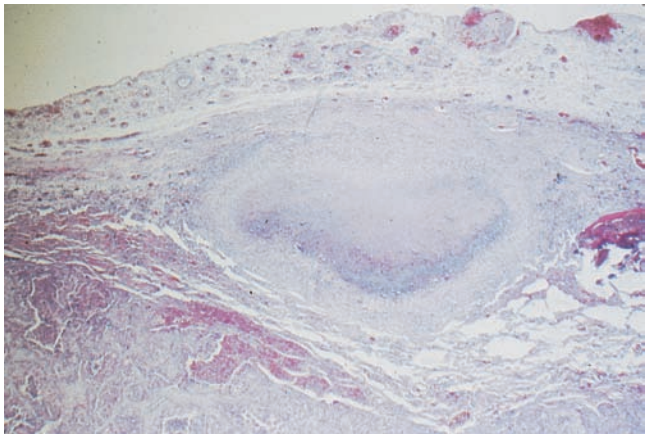


Figure 60-9 Typical subpleural location of a necrobiotic rheumatoid nodule. There is a central area of fibrinoid debris surrounded by palisading histiocytes.

SYSTEMIC LUPUS ERYTHEMATOSUS: CLINICAL FEATURES

SLE is characterized by the production of antibodies against various cellular antigens derived from the nucleus, cytoplasm, or cell membrane. Tissue injury appears to be associated with the development of immune complexes, the presence of low serum complement levels, and the production of antibodies to native DNA. Pleuropulmonary involvement in SLE occurs in the vast majority of patients (97.8%), with pleuritis (77%), bacterial infections (58%), and diffuse alveolar hemorrhage (26%) being the most common.[3,4] Lung injury is thought to be the result of an immune complex-mediated injury and appears to increase in incidence depending on the age of the patient, duration of illness, pleuritis, and the presence of specific autoantibodies. Pulmonary vascular and shrinking lung syndrome appear to be associated with the development of the anti-RNP autoantibody.[5] A number of syndromes (Table 60-2) are associated with acute respiratory-type illness in SLE. Patients with SLE who present with a febrile illness, cough with or without productive sputum, and new pulmonary infiltrates must be considered

TABLE 60-2 Acute Lung Syndromes in Systemic Lupus Erythematosus

Community-acquired or immunocompromised pneumonia
Pleurisy
Pulmonary embolization
Uremic pneumonitis
Cardiogenic pulmonary edema
Acute reversible hypoxemia syndrome
Acute lupus pneumonitis
Diffuse alveolar hemorrhage

to have an infectious pneumonia, although acute lupus pneumonitis and diffuse alveolar hemorrhage may have a similar presentation.[6] Infection can be community-acquired or a complication of immunosuppressive therapy. Infectious pneumonia represents the most common cause of pulmonary disease in SLE, and infections in general represent the most common reason for death (33%–77%).[7] Bronchoalveolar lavage is often helpful in excluding an infectious pneumonia in the immunocompromised SLE patient.

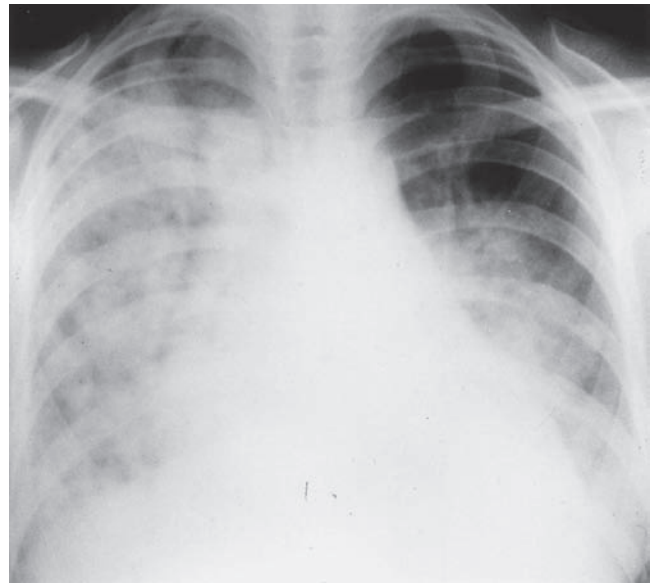
Another important consideration in an acutely dyspneic SLE patient is pulmonary embolism, a complication reportedly occurring in up to 25% of patients and a significant cause of mortality.[8] The occurrence of thromboembolic disease correlates with the presence in the serum of acquired antiphospholipid antibodies (lupus anticoagulant or anticardiolipin).[9] The most common epitope(s) to which antibodies exist in these patients is β_2-glycoprotein I. A more appropriate term may therefore be anti-β_2–glycoprotein syndrome. Up to a third of patients with SLE have the antiphospholipid syndrome. Thrombocytopenia, recurrent venous or arterial thrombosis, hemolytic anemia, leg ulcers, and recurrent fetal loss are also manifestations of antiphospholipid syndrome.

Other causes for acute respiratory failure in patients with SLE include a volume overload state, due either to renal failure or to congestive heart failure secondary to myocarditis. Uremic pneumonitis with underlying DAD is also a possible cause of an acutely dyspneic SLE patient with renal failure. A syndrome, *acute reversible hypoxemia*, occurring in acutely ill SLE patients who are experiencing systemic exacerbations has been described.[10] These patients have hypoxemia and a widened alveolar–arterial oxygen gradient, but both the chest radiograph and ventilation–perfusion lung scans are normal. It is postulated that there is complement-activated neutrophil aggregation in the pulmonary vasculature. The hypoxemia improves with immunosuppressive therapy. Given the high incidence of antiphospholipid syndrome in SLE, acute reversible hypoxemia should be considered only after excluding thromboembolic disease.

■ ACUTE LUPUS PNEUMONITIS

Acute lupus pneumonitis is a clinical syndrome with an underlying histology of DAD, bronchiolitis obliterans organizing pneumonia, NSIP, or a combination of these.[11] Acute lupus pneumonitis mimics an acute infectious pneumonia and may be the presenting manifestation of SLE in up to 50% of patients. In those with an established diagnosis, it also appears during a flare-up of the other systemic manifestations of SLE, particularly pleuritis, pericarditis, arthritis, and nephritis. Acute lupus pneumonitis is reportedly more common in the postpartum period. It frequently recurs and cases have been documented that have progressed to a more chronic interstitial lung disease (UIP). Fortunately, acute lupus pneumonitis is a relatively uncommon complication, occurring in less than 5% of patients.

Bilateral alveolar infiltrates, which can be patchy or densely consolidated and often accompanied by pleural effusions and cardiomegaly due to underlying pericardial effusion or myocarditis (Fig. 60-10A), are present on chest radiographs at presentation. White blood cell counts and sedimentation rates are elevated and serum complement is often low. Immunopathologic studies reveal the presence of complement as well as antibodies to IgG and DNA in some patients, supporting the concept of an immune complex pathogenesis (Fig. 60-10B). Because of the difficulty in distinguishing acute lupus pneumonitis from an infectious pneumonia, a bronchoalveolar lavage and sometimes an open (thoracoscopic) lung biopsy are indicated prior to instituting anti-inflammatory and immunosuppressive therapy. Acute respiratory failure in acute lupus pneumonitis often requires assisted mechanical ventilation. The mortality rate has been reported to be as high as 50%, with the causes of death in patients with acute lupus pneumonitis being due to respiratory failure, another complication of SLE (nephritis, cerebritis), or a superimposed infection.



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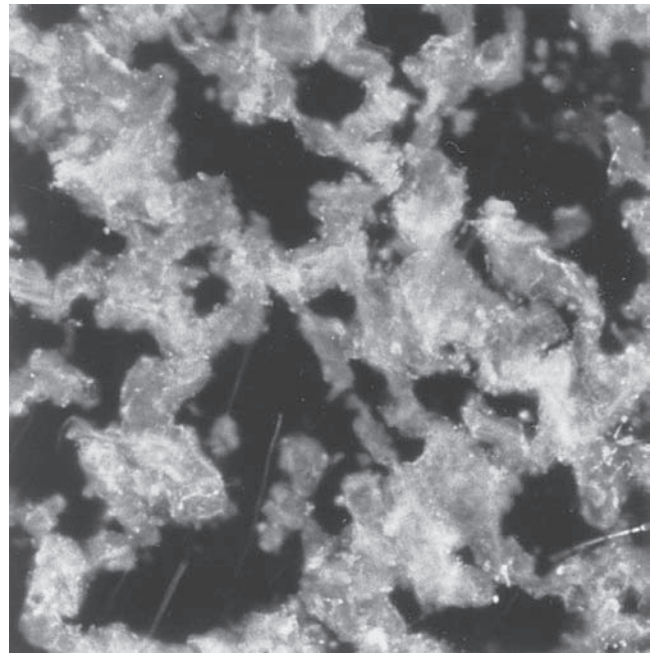


B

Figure 60-10 Acute lupus pneumonitis. **A.** The chest radiograph demonstrates diffuse alveolar filling with cardiomegaly (pericardial effusion vs. myocarditis). There is also a left pleural effusion. **B.** The immunofluorescent study demonstrates granular immune complex deposition in the alveolar interstitium.

■ DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage, although rare, may be a presenting manifestation of SLE. In several cases, recurrent diffuse alveolar hemorrhage was present for years prior to the diagnosis of SLE.[12] The majority of cases, in contrast to acute lupus pneumonitis, first appear in a well-documented case of SLE. Diffuse alveolar hemorrhage accounts for 1% to 4% of SLE-related hospitalizations.

Diffuse alveolar hemorrhage can also present with symptoms reminiscent of an infectious pneumonia or acute lupus pneumonitis, and the additional symptom of hemoptysis raises the possibility of this diagnosis. Hemoptysis is present in 30% to 50% of patients during their initial presentation, but up to 90% will have hemoptysis

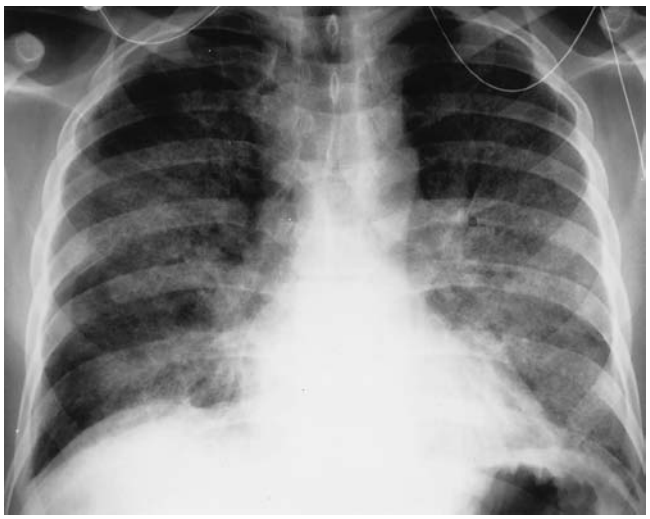


Figure 60-11 Diffuse alveolar hemorrhage in SLE. There are diffuse alveolar infiltrates without cardiomegaly or pleural effusions.

during their subsequent course. Routine laboratory work demonstrates a falling hematocrit, and in 60% to 90% of patients an active glomerulonephritis is invariably present. A progressive serosanguineous bronchoalveolar lavage may be the first clue to this diagnosis. Diffuse alveolar infiltrates are present on chest radiography (Fig. 60-11), but in contrast to acute lupus pneumonitis, pleuritis and pericarditis are not prominent features. Pathologic changes that are reminiscent of both acute lupus pneumonitis (DAD and NSIP) and diffuse alveolar hemorrhage with or without pulmonary capillaritis are not unusual in a single biopsy specimen.[13] The mortality rate is approximately 50% and is independent of the underlying histopathology (bland hemorrhage vs. pulmonary capillaritis). Recurrent DAH is common and should be expected in the absence of therapeutic intervention.

There are no controlled clinical trials for the treatment of either acute lupus pneumonitis or diffuse alveolar hemorrhage. Once infection has been excluded, corticosteroids are the mainstay of therapy. Intravenous methylprednisolone, 1 to 2 g daily in divided doses for 3 to 4 days before tapering, should be considered. Concomitant oral or parenteral cyclophosphamide or azathioprine is commonly administered, given the associated incidence of lupus nephritis. Plasmapheresis, immunoglobulin therapy, and rituximab have been used successfully, consistent with the proposed immune complex pathogenesis.[14–17]

LUPUS PLEURITIS

Pleurisy and pleural effusion are the most common primary pulmonary complications of SLE, occurring in 50% to 80% of patients. Pleurisy and/or a pleural effusion may also be the presenting and sole manifestation of the disease. They are usually recurrent and may accompany more severe complications such as acute lupus pneumonitis or nephritis. Patients complain of pleuritic pain, fever, and dyspnea. The chest radiograph may be normal (dry pleurisy) or demonstrate small to moderate pleural effusions (massive effusions are rare), which are bilateral in 50% of patients. When unilateral, there is no predilection for either side.

Effusions are serous or serosanguineous and exudative in nature. The white cell counts range from 5 to 10,000 cells/mm.^{3} Early on, neutrophils predominate, but with time mononuclear cells appear. These characteristics are nonspecific and are often seen with infectious parapneumonic effusions. In contrast to rheumatoid arthritis, the pleural fluid glucose concentration in lupus pleuritis is not reduced. Rheumatoid factor may be positive in lupus pleuritis. Pleural fluid complement levels are abnormally decreased in lupus, with both total complement activity and C3 and C4 reduced. A positive double-stranded pleural fluid DNA titer is nonspecific as opposed to the serum test, since it has been found in pleural effusions due to malignancy and tuberculosis. The most helpful measurement is the pleural fluid antinuclear antibody titer. Levels greater than 1:160 are very suggestive of lupus pleuritis. Examination of the pleural tissue reveals infiltration with plasma cells and lymphocytes, and, with repeated episodes, pleural fibrosis supervenes. Occasionally, a vasculitis of the pleural vessels is detected, and immune complex deposition has been reported. Corticosteroid treatment is effective for relief of pleural pain, but time to resolution of the pleural effusion is quite variable and probably unaffected by this treatment. In the unusual case, recurrent lupus pleuritis may result in massive pleural fibrosis and lung entrapment, necessitating a pleural stripping procedure.

While pleural effusions and pleurisy are common in patients with SLE, a broad differential diagnosis should be considered. The increased incidence of infectious complications, thromboembolic disease, and pulmonary hypertension in SLE predisposes patients to parapneumonic effusions and empyema, congestive heart failure, and effusions secondary to thromboembolic disease.

INTERSTITIAL LUNG DISEASE

Clinically significant interstitial lung disease is an uncommon pulmonary manifestation in SLE but UIP, lymphocytic interstitial pneumonitis, NSIP, and organizing pneumonia have all been reported. UIP is known to appear following acute lupus pneumonitis and in some cases has been documented to appear as an independent insidious disease. Using high-resolution computed tomography, 38% of patients with SLE patients with normal chest radiographs demonstrate pulmonary abnormalities consistent with some form of interstitial lung disease. In those who develop interstitial lung disease, a prior episode of acute lupus pneumonitis and an insidious onset of dyspnea are often noted. The prevalence of interstitial lung disease is increased in the subset of SLE patients with features suggestive of a mixed connective-tissue disease.

In patients who develop the insidious form of interstitial lung disease, the diagnosis of SLE is present for several years, and no other pattern of organ involvement predicts its appearance. These patients have progressive dyspnea and cough with interstitial infiltration on the chest radiograph. High-resolution computed tomography indicates combinations of ground-glass attenuation, inter- and intralobular septal thickening, and honeycomb change. Pulmonary function tests reveal a restrictive pattern with reduction in the diffusing capacity and hypoxemia accentuated by exercise. Response to therapy, either corticosteroids alone or in combination with cyclophosphamide or azathioprine, depends upon the underlying histology. Those cases with underlying NSIP or organizing pneumonia are more likely to respond to treatment than those who demonstrate excess collagen deposition and cystic honeycomb formation.

PULMONARY VASCULAR DISEASE

Idiopathic pulmonary hypertension due to plexogenic arteriopathy was previously thought to be an uncommon complication of SLE. It is now estimated to occur in 1% to 9% of patients.[18,19] This form of pulmonary hypertension is associated with Raynaud phenomenon, digital vasculitis, serositis, antibodies to ribonucleoprotein, rheumatoid factor, antiphospholipid antibodies, and most recently antiendothelial cell antibodies. Patients complain of dyspnea and fatigue but have normal chest radiographs. In advanced cases, pulmonary arterial enlargement appears. Spirometry and lung volumes are normal, but there is often an isolated reduction of the diffusing capacity for carbon monoxide as well as gas exchange abnormalities. Ventilation–perfusion lung scanning and, occasionally, pulmonary

arteriography are indicated, particularly in those patients with the antiphospholipid syndrome who have a potential for recurrent small pulmonary emboli. Therapeutic options include vasodilator therapy, anticoagulation, immunosuppression with cyclophosphamide, and transplantation.

Vasculitis in SLE is more likely to be discovered in lung biopsy specimens, demonstrating either diffuse alveolar hemorrhage or acute lupus pneumonitis as opposed to being an isolated finding. Autopsy series indicate small-vessel vasculitis in 20% of cases.

BRONCHIOLITIS

Five percent of SLE patients are reported also to have obstructive physiology. Obliterative bronchiolitis has been documented in SLE, but is rare in contrast to rheumatoid arthritis. Organizing pneumonia, with inflammatory polyps protruding into bronchiolar lumens, is one of the interstitial patterns that occurs in acute lupus pneumonitis and in chronic interstitial lung disease in SLE, but this entity causes restriction rather than obstructive lung disease. Bronchiectasis may occur in up 20% of patients but is often asymptomatic. Large airway involvement including tracheal and subglottic stenosis, vocal fold paralysis, epiglottitis, and necrotizing tracheitis have all been reported, but are rare.

RESPIRATORY MUSCLE DYSFUNCTION

It is estimated that weakness of the diaphragm and other respiratory muscles is found in 25% of patients with SLE. This accounts for the previously unexplained findings of dyspnea without evidence of interstitial or pulmonary vascular disease. These patients have subsegmental atelectasis, an elevated diaphragm on chest radiograph (Fig. 60-12), and restrictive physiology. This has been referred to as *unexplained dyspnea and shrinking lungs syndrome.* Although there is a reduction in static lung volumes, the diffusing capacity, when corrected for alveolar volume, remains normal, thereby distinguishing respiratory muscle dysfunction from interstitial lung disease. The likely explanation for this is a reduction in the transdiaphragmatic pressure generated during maximal inspiration, which in turn reduces static lung compliance, producing the linear atelectasis seen on the chest radiograph. Moreover, in the patients with respiratory muscle weakness, no evidence for a generalized neuromuscular disease can be found. The pathogenesis of respiratory muscle dysfunction remains unexplained, although phrenic nerve conduction abnormalities have been excluded.[20] Abnormal diaphragmatic activation, due in part to voluntary inhibition due to pleuritic pain, may contribute to diaphragmatic dysfunction in this disorder. Clinical variables associated with the development of shrinking lung syndrome include: pleuritis, double-stranded DNA antibody and RNP antibody seropositivity, serositis, and a prolonged course of SLE.[5] Corticosteroids are not a frequently effective treatment modality. Rituximab has been used successfully in the treatment of shrinking lung syndrome, albeit anecdotally in nature.[21] Progression is uncommon and most patients stabilize. Positive-pressure ventilation, particularly at night, may improve these patients' daytime symptoms, although there is limited evidence available. Rituximab has been used successfully in patients with respiratory muscle dysfunction with significant physiologic improvement.[21]

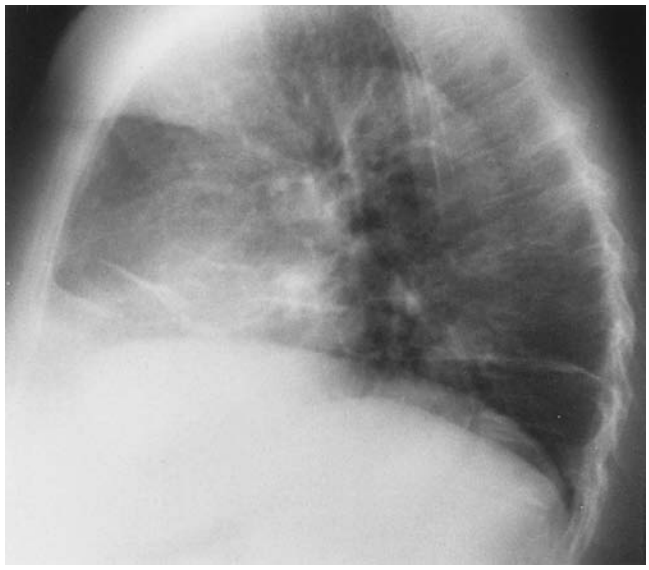


Figure 60-12 Diaphragmatic dysfunction in SLE. There is diaphragmatic elevation resulting in plate-like atelectasis.

RHEUMATOID ARTHRITIS: CLINICAL FEATURES

Rheumatoid arthritis classically affects the articular surfaces, but pleuropulmonary complications are responsible for significantly increased morbidity and mortality.[22] Most often cited is a 50% incidence for these complications, but it is likely that this underestimates their frequency.[23] Rheumatoid arthritis–associated interstitial lung disease abnormalities may be present in over 60% of patients with RA and are clinically asymptomatic during the initial assessment.[24] In those that manifest symptoms, the presence of RA-ILD, which approximates 10%, is associated with increased mortality.[25–27] Pleuropulmonary complications are more apt to occur in patients with more severe chronic articular disease, with high titers of rheumatoid factor, and in patients who have subcutaneous nodules, as well as other systemic complications such as cutaneous vasculitis, myocarditis, pericarditis, ocular inflammation, and Felty syndrome. An association between smoking and an increased risk for the development of pleuropulmonary disease, radiographic progression, and nodule formation in rheumatoid factor–seropositive patients has been reported. More recent observations series suggest that in those patients with anticitrullinated protein antibodies (anti-CCPs) there is an increase in parenchymal lung abnormalities, independent of current or prior tobacco exposure, supportive of the hypothesis that anti-CCPs are important in the pathogenesis of lung disease in RA.[28,29] Pleuropulmonary disease may occur in seronegative patients and both cytolytic and biologic therapies, commonly employed for treatment, can induce an interstitial lung disease, which is often difficult to distinguish from the primary forms complicating rheumatoid arthritis.[30] Moreover, interstitial lung disease, pleuritis, and occasionally obliterative bronchiolitis may be the first and only manifestation of the rheumatoid state in up to 20% of patients, preceding the articular manifestations by months to years.

PLEURISY AND PLEURAL EFFUSION

Pleural disease in a postmortem series was found in 40% of patients with rheumatoid arthritis. The incidence of clinically apparent pleural disease is closer to 5%, and the majority of patients experience mild symptoms. In approximately 20% of the patients who develop pleural complications, they do so prior to the onset of articular disease. In patients with rheumatoid arthritis, pleural complications are more common in men and occur most frequently during episodes of active articular disease and in patients with subcutaneous rheumatoid nodules.

Pleural disease is often first discovered on routine chest radiograph, and both pleural fibrosis and effusions have been reported to occur in asymptomatic patients. In more recent series using multidetector CT imaging, pleural thickening was noted in 49% of patients and did not correlate to the presence of symptoms.[31] Pleural effusions can be unilateral or bilateral and coexist with interstitial lung disease or necrobiotic nodules. Symptomatic patients present with pleuritic pain, dyspnea, and occasionally fever. The effusion

is an exudate by protein and lactic dehydrogenase criteria, and, if chronic, cholesterol concentrations are increased. Other characteristics include a low pleural fluid pH (<7.2), thought to be due to impaired carbon dioxide exit from the pleural space. The leukocyte counts can be as high as 15,000 cells/mm^3 and consist of a mixture of neutrophils and mononuclear leukocytes. As in SLE, the total and individual complement components are low, and the rheumatoid factor level is increased. The presence of rheumatoid factor in pleural fluid has also been reported with tuberculosis, malignancy, and other infectious diseases. A low pleural fluid glucose concentration, thought to be due to a defect in glucose transport, is characteristic of rheumatoid effusions. Up to 40% of patients have pleural fluid glucose levels less than 10 mg/dL, and 75% have levels under 50 mg/dL. It has been stated that cytologic examination of the pleural fluid, which demonstrates a background of necrotic debris, spindle-shaped macrophages, and multinucleated histiocytes, is characteristic of a rheumatoid effusion. Necrobiotic nodules are thought to be involved in the pathogenesis of the pleural effusions, but transthoracic pleural biopsy only occasionally will demonstrate this finding.

Treatment is not indicated for asymptomatic cases; however corticosteroids, when used for active articular disease, are also effective in hastening the resolution of the pleural effusion. Rarely, is any other form of intervention such as intrapleural corticosteroids necessary for these patients. In the unusual case, pleural fibrosis with resultant lung entrapment occurs, requiring surgical intervention. Spontaneous pneumothorax due to rupture of a necrobiotic nodule, another uncommon complication, necessitates tube thoracostomy, and with persistence of the bronchopleural fistula, surgical intervention is indicated.

■ PULMONARY VASCULAR DISEASE

In general, pulmonary vascular disease is the least common pleuropulmonary complication in rheumatoid arthritis. The fibroproliferative plexogenic arteriopathy typical of scleroderma and SLE is an infrequent complication. When it does occur, Raynaud phenomenon is commonly present. The chest radiograph reveals normal lung fields and enlarged pulmonary arteries, and there is an isolated reduction of the diffusing capacity for carbon monoxide as well as hypoxemia.

Small-vessel vasculitis in rheumatoid arthritis occurs in the setting of diffuse alveolar hemorrhage due to pulmonary capillaritis and is a very rare event in rheumatoid arthritis. Several cases have been well documented and, in one, antineutrophilic cytoplasmic antibody to myeloperoxidase (p-ANCA) was present in the serum. Treatment with intravenous methylprednisolone, followed by oral corticosteroid preparations in addition to cyclophosphamide, is indicated for this complication.

■ NECROBIOTIC (RHEUMATOID) NODULE

Radiographically visible parenchymal rheumatoid nodules are infrequently seen in a rheumatoid population (1%). If present, necrobiotic nodules are more common in men, particularly those who smoke, with active articular disease and high rheumatoid factors, and in those who have subcutaneous nodules. The nodules are primarily a radiographic finding, subpleural in distribution, and asymptomatic in most. Cavitation and rupture may occur rarely and are associated with pneumothorax, pleural effusions, and hemoptysis. Radiographically, the nodules can be single or multiple with upper- and midzone predilection, and approximately 50% will undergo cavitation due to the large amounts of proteolytic enzymes in these lesions. The size is variable, and nodules up to 7 cm have been reported. Spontaneous resolution and recurrence are to be expected. Continuous growth, although possible, should prompt a more aggressive diagnostic approach. In most cases, no treatment is required. The major problem is differentiating the necrobiotic nodule from either malignant or infectious granulomatous disease, particularly given the increased risk of lung cancer in patients with RA.[32]

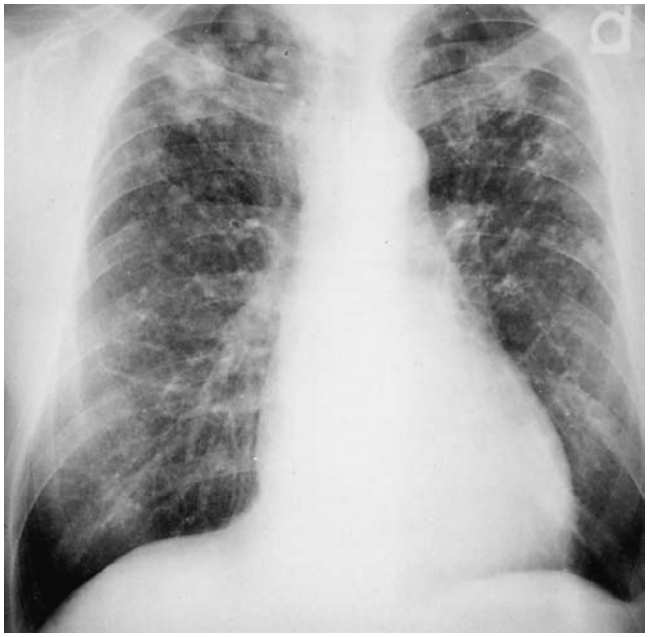


Figure 60-13 Caplan syndrome in a patient with rheumatoid arthritis and silicosis (hard-rock miner). There are multiple small nodules in the middle and upper lung representing the silicosis. In addition, multiple upper-zone rheumatoid nodules are present.

Caplan syndrome refers to a radiographic picture that developed in Welsh coal miners with rheumatoid arthritis and a pneumoconiosis.[33] It consists of the sudden appearance of discrete nodules primarily in the upper lobes that are histologically identical to the necrobiotic nodule (Fig. 60-13). The incidence of necrobiotic nodules is higher in rheumatoid patients with underlying pneumoconiosis, including coal workers' pneumoconiosis, silicosis, and asbestosis, than it is in a general rheumatoid population.

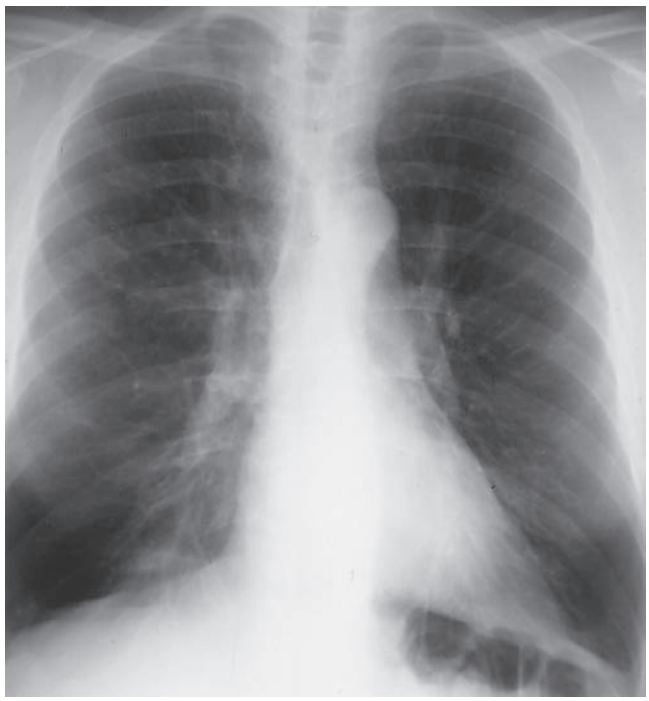
■ AIRWAY DISEASE

Upper airway involvement by the rheumatoid process most commonly involves the cricoarytenoid joint, causing difficulty with inspiration and occasionally resulting in stridor. A sore throat, hoarseness, and globus sensation are other common complaints. The prevalence of this complication, although asymptomatic in the majority of cases, approaches 50% when computed tomography screening is employed. Clinically significant disease can be detected by performing flow–volume loops, which indicate a variable extrathoracic obstruction of the inspiratory loop. Cricoarytenoid arthritis may further complicate endotracheal intubation and should be considered in all patients with rheumatoid arthritis requiring general anesthesia.

Bronchiolitis obliterans or obliterative bronchiolitis is a well-recognized cause of progressive and often severe obstructive lung disease in patients with rheumatoid arthritis.[34] The majority of patients develop bronchiolitis subsequent to the diagnosis of RA. Of note, bronchiolitis obliterans may be the initial manifestation of RA in a small group of patients.[35] This complication was first thought to be a consequence of either penicillamine or gold therapy, but many cases have appeared in the absence of either treatment. The onset of obliterative bronchiolitis is insidious, with patients complaining of progressive dyspnea and cough while having a normal or hyperinflated chest radiograph (Fig. 60-14A). It was thought that this complication was limited to women, but this is not the case. Physical examination reveals a generalized reduction of breath sounds and

occasionally an inspiratory squeak. Physiologic testing reveals varying degrees of airflow limitation and hyperinflation, and the diffusing capacity may be normal or reduced. High-resolution computed tomography demonstrates adjacent areas of decreased and increased attenuation (geographic pattern), suggesting air trapping, which may be further identified by expiratory imaging (Fig. 60-14B). The response to therapy is poor. Some patients have responded to treatment with a combination of corticosteroids and cyclophosphamide, but the majority of cases progress to hypercapnic respiratory failure.

Another form of bronchiolitis seen in rheumatoid arthritis is a respiratory or follicular bronchiolitis, consisting of a dense infiltration of lymphocytes and plasma cells surrounding the terminal and respiratory bronchioles. Cough and dyspnea are common symptoms. Chest radiographs may be normal or demonstrate a fine nodular pattern more predominant in the middle and lower lung zones. High-resolution computed tomography reveals a pattern of follicular bronchiolitis in up to 33% of patients with RA, demonstrating centrilobular nodules and bronchiectasis (Fig. 60-15).[31] There is usually no physiologic evidence for airflow limitation or reduced lung volumes, but rather gas exchange abnormalities dominate the physiologic picture. Treatment with corticosteroids yields variable results.



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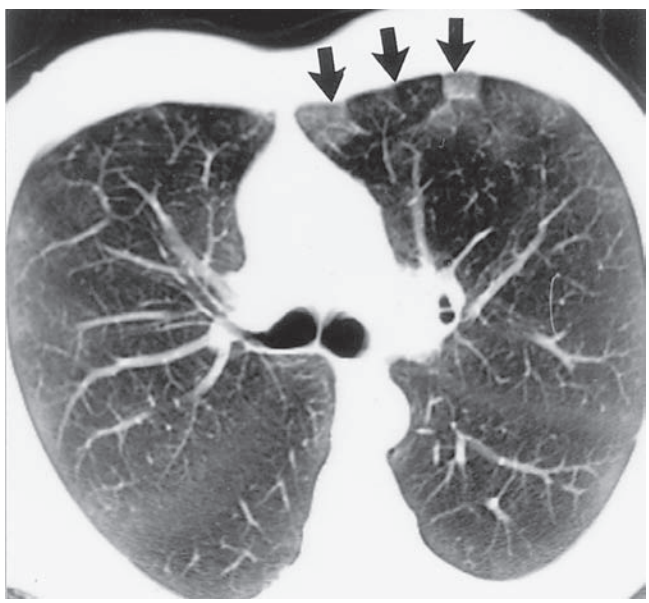


B

Figure 60-14 Obliterative bronchiolitis in a patient with rheumatoid arthritis. **A.** The chest radiograph is normal except for hyperinflation. **B.** A high-resolution computed tomography demonstrating areas of increased and decreased attenuation *(arrows)*.

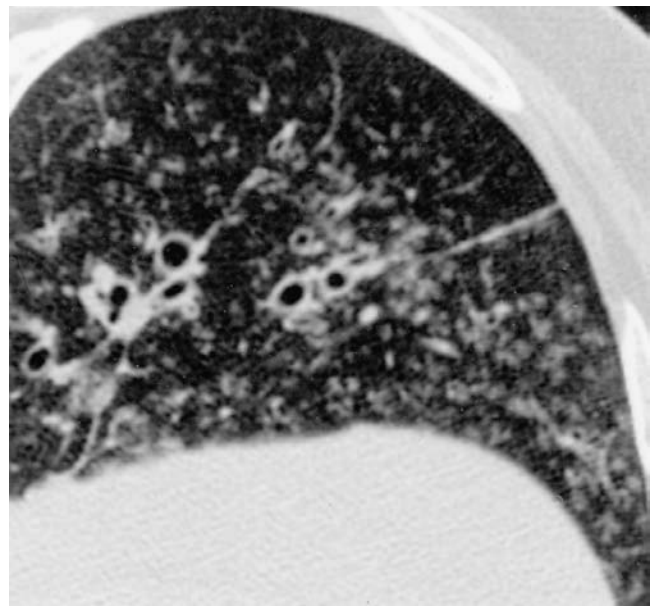
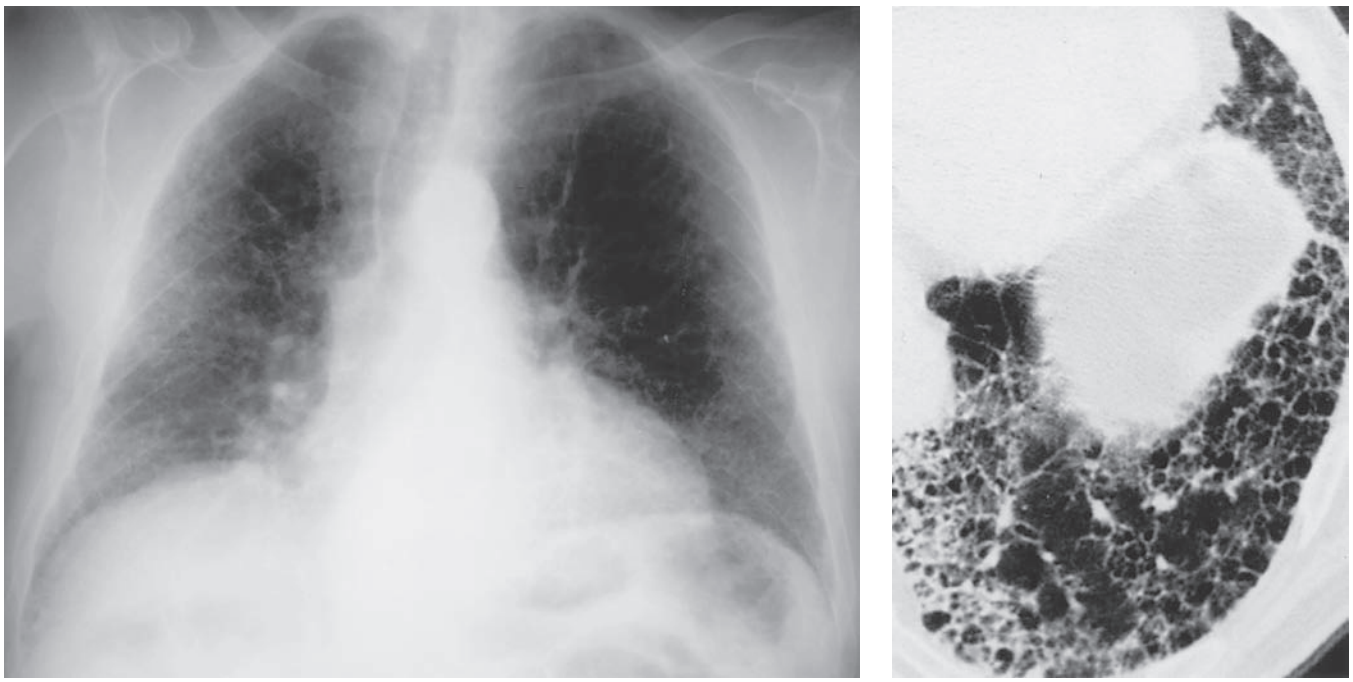


Figure 60-15 Follicular bronchiolitis in rheumatoid arthritis. High-resolution computed tomography demonstrating multiple centrilobular nodules.

Diffuse panbronchiolitis has been reported in Japanese patients with rheumatoid arthritis. In both diffuse panbronchiolitis and rheumatoid arthritis, an association with HLADR4 and B54 haplotypes has been reported, suggesting a common genetic predisposition.[36,37]

INTERSTITIAL LUNG DISEASE

Interstitial lung disease is a relatively common complication in patients with rheumatoid arthritis. In contrast to most connective-tissue diseases, interstitial lung disease is more common in males than females (3:1), individuals who have late-onset disease, high-titer rheumatoid factors, and in those who smoke. It is not unusual for interstitial lung disease to precede the articular manifestations for a period of months to years. The incidence of this complication in a rheumatoid population is difficult to determine, being reported in 5% to 40% of patients depending upon the methods of detection. The use of bronchoalveolar lavage indicating alveolar inflammation and high-resolution computed tomographic scans indicating various interstitial changes, often in the face of a negative chest radiograph, are difficult to interpret. This is because follow-up studies determining whether these patients developed clinically apparent interstitial lung disease are lacking. Furthermore, some parenchymal changes described on computed tomography such as bronchiectasis have very little, if any, clinical significance. It is likely that clinically important interstitial lung disease occurs in 5% to 10% of patients with rheumatoid arthritis, the most common forms being UIP and NSIP. These patients are dyspneic and complain of cough. Physical examination reveals bibasilar crackles, clubbing of the digits, and evidence of cor pulmonale when pulmonary hypertension appears secondary to hypoxic vasoconstriction. The chest



A B

Figure 60-16 UIP in rheumatoid arthritis. **A.** Chest radiograph demonstrating lower zone and peripheral reticulonodular infiltrates. **B.** High-resolution computed tomography demonstrating a cystic network (honeycomb lung) at the lung base in a patient with advanced disease.

radiograph and computed tomographic scan demonstrate varying degrees of interstitial infiltrates with predilection for the lung bases and lung periphery (Fig. 60-16A). Other features include ground-glass attenuation on computed tomography with mixed alveolar–interstitial infiltrates on chest radiograph indicating a component of NSIP. Both imaging studies in advanced disease reveal the presence of honeycomb lung (Fig. 60-16B).

Several other interstitial reactions, which produce subacute or chronic symptoms, complicate rheumatoid arthritis. The first is organizing pneumonia, which can present with identical symptoms to UIP and preempt the onset of the articular disease as well. The chest radiograph (Fig. 60-17) and computed tomography scan differ from that seen in UIP because the infiltrates are primarily alveolar and localized, patchy, or diffuse. The second interstitial reaction is lymphocytic interstitial pneumonia, which occurs when rheumatoid arthritis is complicated by Sjögren syndrome. In addition to dyspnea and cough, these patients complain of dry mouth and eyes (xerophthalmia and xerostomia). The chest radiograph indicates patchy alveolar infiltrates primarily seen at the lung bases. In contrast to patients with primary Sjögren syndrome in which large cystic structure may develop within the lung, parenchymal cysts are uncommon in patients with RA-ILD. Eosinophilic pneumonia has been reported as a pleuroparenchymal complication of rheumatoid arthritis and may be the primary presentation of the disease. Acute interstitial pneumonitis is a rare, acute form of interstitial lung disease in rheumatoid arthritis. While it may occur as a result of an immunologic injury to the lung, medication-related pulmonary toxicity and opportunistic infections should be considered. Finally, fibrobullous disease, similar to that seen in ankylosing spondylitis, has been reported in rheumatoid arthritis and may precede the articular manifestations of the disease.

It is important to establish the underlying histology, since response to therapy and prognosis differs. Unless the imaging studies indicate end-stage honeycomb lung, which can also result from unresponsive or recurrent organizing pneumonia, lymphocytic interstitial pneumonia, or UIP, further evaluation is indicated. Bronchoalveolar lavage will not necessarily help differentiate between these three histologic pictures, but the finding of increased lymphocytic percentages as opposed to neutrophils and eosinophils indicates the potential for therapeutic responsiveness. Alveolar infiltrates and increased lymphocyte percentages are seen in lymphocytic interstitial pneumonitis. Organizing pneumonia is associated with increases in neutrophil, eosinophil, and lymphocyte percentages as well as radiographic alveolar infiltrates. The finding of increased

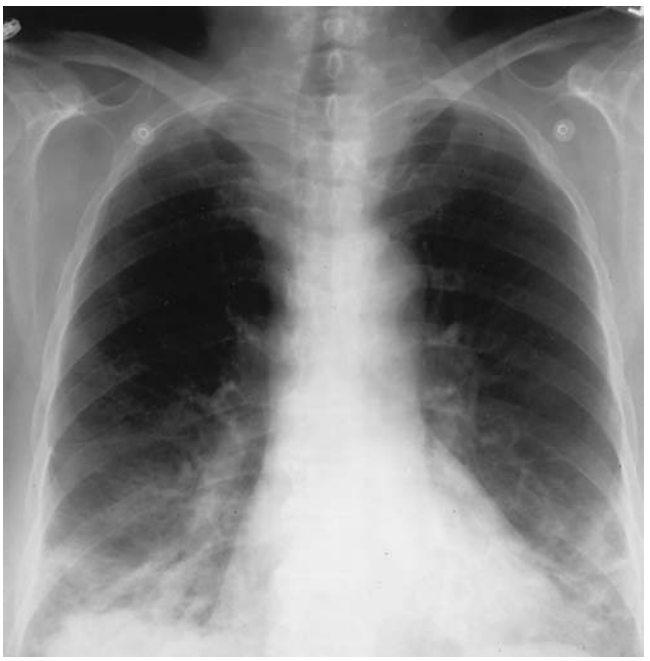


Figure 60-17 Bronchiolitis obliterans organizing pneumonia in rheumatoid arthritis. Chest radiograph demonstrating lower-zone mixed alveolar-interstitial infiltrates.

neutrophil and eosinophil percentages in suspected underlying UIP is an indicator of poor prognosis. Therefore, patients with lymphocytic interstitial pneumonitis and organizing pneumonia are more treatment-responsive when compared to those with UIP. If imaging studies and bronchoalveolar lavage cellular analysis are not definitive, thoracoscopic open lung biopsy should be considered. Treatment consists of a corticosteroid preparation and often the addition of cytotoxic drugs in the nonresponsive cases. As opposed to the idiopathic variety of organizing pneumonia, in which 66% of cases have favorable responses to corticosteroid medications, those associated with collagen vascular diseases are less responsive to treatment, often recur with tapering of the treatment regimen, and can progress to honeycomb lung. While the histopathology may be similar between rheumatoid arthritis and idiopathic pulmonary fibrosis, improved survival exists for those with rheumatoid arthritis–associated UIP but the long-term prognosis remains poor.[25,26,38]

Gold-induced pneumonitis must be differentiated from the primary forms of interstitial lung disease in patients with rheumatoid arthritis, particularly since the underlying histology can be similar, indicating varying degrees of NSIP and organizing pneumonia.[39] Dyspnea and cough usually begin 4 to 6 weeks following initiation of therapy, and peripheral eosinophilia occurs in a minority of cases. Occasionally, the chest radiograph will demonstrate upper- as opposed to lower-zone mixed alveolar interstitial infiltration. Bronchoalveolar lavage indicates a predominance of lymphocytes, and differentiation from rheumatoid interstitial lung disease can only be made after withdrawal of the drug results in remission. In severe cases with marked gas exchange abnormalities, corticosteroid therapy will occasion prompt reversal.

Methotrexate given in relatively low weekly doses (10–20 mg) is associated with the development of an interstitial disease in rheumatoid patients. No correlation with age, sex, duration of disease, or weekly or cumulative dose could be found. Conflicting data suggest that rheumatoid patients with underlying primary rheumatoid lung disease are predisposed to develop methotrexate pneumonitis. In rheumatoid patients treated with methotrexate, the incidence of methotrexate pneumonitis is 1% to 11%. The clinical onset is relatively acute with cough, fever, dyspnea, and new mixed alveolar and interstitial pulmonary infiltrates on chest radiograph. Increased white blood cell counts with mild eosinophilia, elevated sedimentation rates, and increased serum lactic dehydrogenase are nonspecific findings. Bronchoalveolar lavage indicates lymphocytosis and should be performed to rule out an infectious etiology. Lung tissue reveals an NSIP, organizing pneumonia, and granuloma formation reminiscent of a hypersensitivity pneumonitis. In patients who develop this clinical syndrome while on methotrexate, the drug should be discontinued since progression to end-stage fibrosis may occur. With life-threatening respiratory failure, corticosteroids given intravenously are an effective therapy.

The advent of TNF-α antagonists has revolutionized therapy for patients with rheumatoid arthritis. Their efficacy in the treatment of pleuroparenchymal complications remains unknown, with conflicting data having been reported. Of concern in those patients being treated with these agents should be the increased risk of infections, particularly both typical and atypical mycobacteria and fungi, as well as common bacterial pathogens. Several series suggest a temporal association between the use of biologic therapies and the development of ILD. It remains unclear if the association is temporal or causative.[30,40–43]

SCLERODERMA: CLINICAL FEATURES

Scleroderma or systemic sclerosis is an inflammatory-fibrotic disease that results in deposition of excessive extracellular matrix in the skin and several visceral organs including the lungs, heart, kidneys, and gastrointestinal tract. Two subtypes of systemic sclerosis exist: diffuse and limited. In diffuse systemic sclerosis, extensive skin involvement of the extremities, face, and torso exists with accompanying marked visceral involvement that is progressive in nature. The limited form, or CREST variant (*c*alcinosis, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias), has a more protracted course in most patients and usually affects an older subset of patients. Pulmonary disease contributes significantly to both the morbidity and mortality of patients. The pathogenesis, although not well understood, involves a complex interaction among immune cells, endothelial cells, and fibroblasts. In addition to the excessive extracellular matrix, which in the lung results in interstitial fibrosis, endothelial cell damage with intimal thickening of pulmonary and systemic arteries occurs, leading to luminal obliteration. This may result in a form of idiopathic pulmonary hypertension.

The lung is involved in the great majority of cases of scleroderma, with postmortem series indicating a 70% to 100% incidence.[44] Most patients with scleroderma develop dyspnea during the course of their illness due either to interstitial lung disease or pulmonary hypertension. Both bronchoalveolar lavage and high-resolution computed tomographic scans, in the face of normal chest radiographs, have indicated interstitial lung disease in both symptomatic and asymptomatic patients (Fig. 60-18). Although unusual, interstitial lung disease and pulmonary hypertension have preceded the dermatologic manifestations, defined as systemic sclerosis sine scleroderma.[45] Despite the lack of skin involvement, the course in systemic sclerosis sine scleroderma does not significantly differ from the more common forms, with exception of a greater tendency toward the development of pulmonary hypertension.

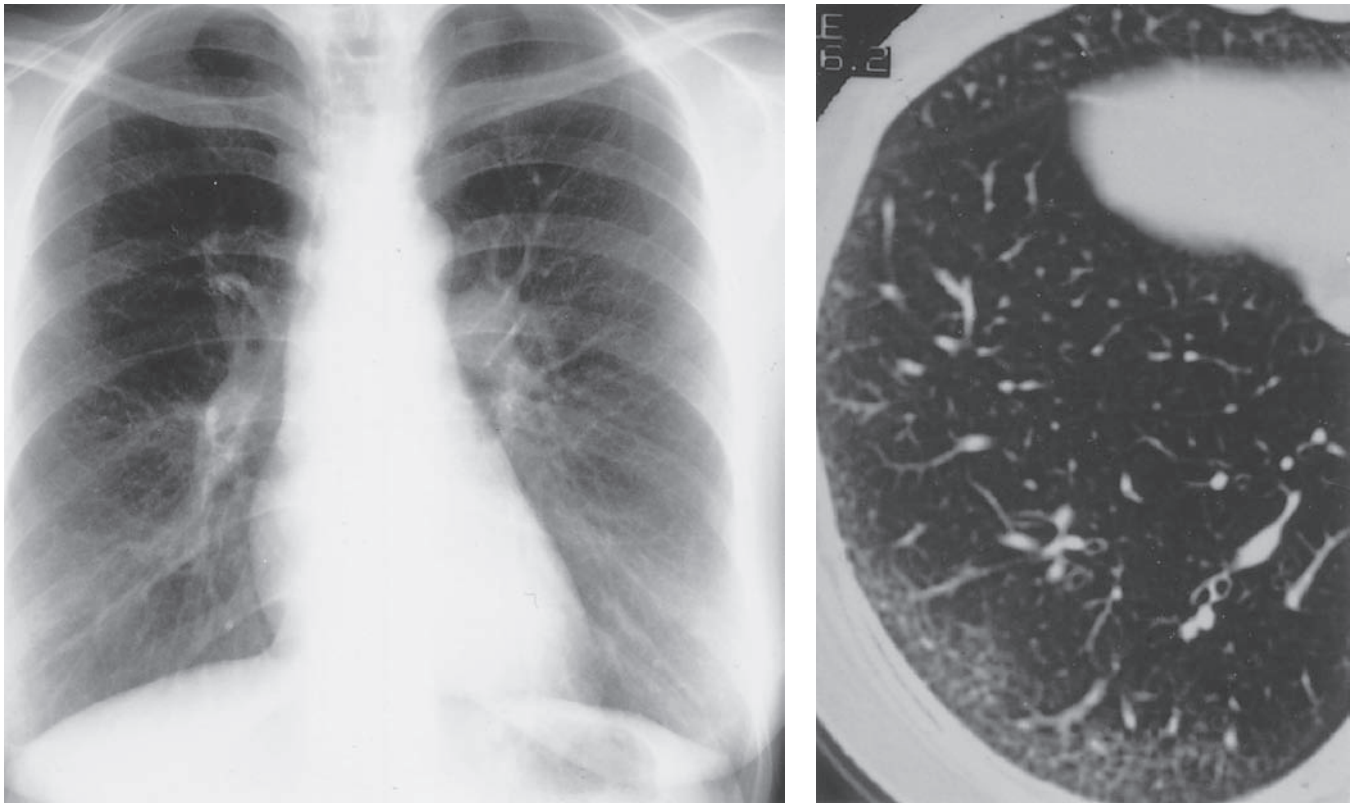
PLEURAL DISEASE

Although pleural fibrosis and adhesions are reported to be present in 40% of patients with scleroderma in postmortem studies, clinically apparent pleural thickening or pleural effusions on chest radiographs are considerably less frequent. The exception to this is pleural effusions secondary to congestive heart failure due to a scleroderma-associated cardiomyopathy.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease, progressing to honeycomb lung, is the most common pulmonary complication of scleroderma, occurring in 30% to 100% of cases. A high-resolution computed tomographic study indicated a greater than 90% incidence of this abnormality with up to two-thirds of patients having normal chest radiographs. As many as 60% of patients who undergo bronchoalveolar lavage will demonstrate an abnormal inflammatory cell distribution. Chest radiographic and physiologic screenings indicate somewhat lower prevalence. The significance of the bronchoalveolar lavage and computed tomographic findings remain unclear, since no longitudinal follow-up is available. Following the histologic reclassification of idiopathic interstitial pneumonias, the most common underlying histology in systemic sclerosis is NSIP with honeycomb lung. UIP, unclassifiable fibrosing interstitial lung disease, and rarely, organizing pneumonia and granulomatous lung disease resembling sarcoidosis have also been reported.[46] It was previously thought that interstitial lung disease in scleroderma was primarily a fibrotic disorder. However, recent information derived from high-resolution computed tomography demonstrating ground-glass attenuation, which indicates more cellular disease, bronchoalveolar lavage revealing increased inflammatory cell populations, and biopsy material demonstrating cellular infiltration of the interstitium indicates the presence of a cellular inflammatory response.[47] This predates the development of fibrosis, consistent with the cellular subtype of NSIP. It is likely that the inflammatory phase in most cases is clinically silent.

Interstitial lung disease is more likely to occur in diffuse systemic sclerosis, although it may also complicate limited systemic sclerosis, formerly referred to as the CREST syndrome. Dyspnea on exertion



A B

Figure 60-18 **A.** Normal chest radiograph in a dyspneic patient with scleroderma. **B.** High-resolution computed tomography of the same patient demonstrating reticular interstitial infiltrates.

progressing to dyspnea at rest and cough are the predominant symptoms. Bibasilar crackles are heard, but clubbing is unusual due to the capillary destruction in the nail beds. Physical findings of cor pulmonale eventually appear. Bibasilar interstitial infiltrates followed by more diffuse changes, loss of lung volume, honeycomb cysts, and pulmonary hypertension are the typical radiographic features. Scleroderma was the first interstitial lung disease in which scar carcinoma (adenocarcinoma or alveolar cell carcinoma) was reported. Several reports suggest an increased incidence of lung neoplasms in patients with scleroderma.[48,49] Physiologic testing eventually reveals restrictive lung disease, preserved flow rates, and a reduced diffusing capacity. Early on, the aforementioned measurements may be normal, and hypoxemia and a widened alveolar–arterial oxygen gradient at rest and heightened by exercise may be the only physiologic abnormality. A disproportionally greater reduction[50] of the diffusing capacity, when compared to lung volumes, most likely indicates the presence of idiopathic pulmonary hypertension due to plexogenic arteriopathy, particularly in the limited form of systemic sclerosis.

Other forms of interstitial lung disease seen in scleroderma include lymphocytic interstitial pneumonitis in those cases associated with Sjögren syndrome; rare cases of diffuse alveolar hemorrhage, and DAD in association with exacerbations of fibrotic lung disease in scleroderma have been reported.

Immunosuppression is the mainstay of treatment, with corticosteroids and cyclophosphamide being the agents of choice. The NHLBI-sponsored Scleroderma Lung Health Study confirmed prior retrospective studies suggesting improved lung function in those patients treated with cyclophosphamide. Although the improvement in lung function is of questionable clinical significance, a therapeutic effect is expected in those with ground-glass attenuation on HRCT imaging, a lymphocytic or eosinophilic predominant bronchoalveolar lavage, and a cellular interstitial pneumonia on lung biopsy.[51,52] Unfortunately, the durability of response to cyclophosphamide was limited as the majority of physiologic benefit waned after 12 months of discontinuation of treatment.[53] Mycophenolate mofetil and rituximab have been reported to benefits patients with progressive disease in scleroderma.[54–57] The efficacy of mycophenolate is currently the focus of an ongoing study sponsored by the National Institutes of Health.

PULMONARY VASCULAR DISEASE

Pulmonary hypertension, due to a plexogenic arteriopathy involving the pulmonary arteries, occurs in approximately 10% of cases of scleroderma and is primarily seen in the limited form (CREST syndrome). In this form of scleroderma, pulmonary hypertension may coexist with interstitial lung disease. Patients present with a gradual onset of dyspnea and increasing fatigue. Physical examination and chest radiograph may initially be normal, and, with disease progression, physical and radiographic signs of pulmonary hypertension appear. Lung volumes and airflow parameters are maintained, unless there is concomitant interstitial lung disease. Typically there is an isolated reduction in the diffusing capacity as well as progressive hypoxemia. Prior to the use of vasodilator therapy, the mean survival following a diagnosis of pulmonary hypertension was approximately 2 years. Treatment with continuous intravenous prostacyclin, phosphodiesterase type 5 inhibitors, and endothelin antagonists have improved the quality of life and exercise performance. Improved survival has been suggested with the use of these agents, specifically in those patients with isolated pulmonary arterial hypertension, in contrast to those with ILD-associated pulmonary hypertension.[58]

ASPIRATION PNEUMONIA

There is a high incidence of esophageal dilatation and decreased peristalsis (dysmotility) in patients with scleroderma, particularly in

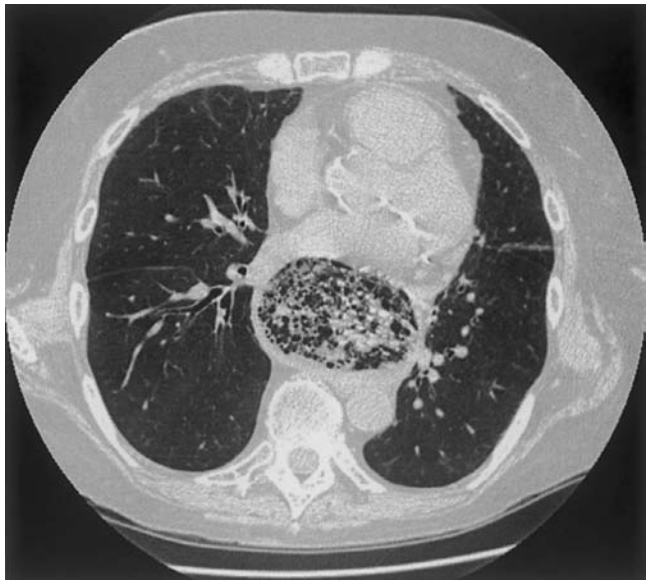


Figure 60-19 Mild peripheral, linear, ground-glass opacities in both lungs with marked thickening of the esophageal wall and severe dilatation of esophageal lumen with extensive debris filling the lumen in a patient with limited systemic sclerosis.

the limited variety (Fig. 60-19). This leads to dysphagia, heartburn, gastroesophageal reflux, and possibly aspiration with subsequent pneumonia.[59] It has long been held that reflux and aspiration contribute to the development of interstitial lung disease, albeit with a paucity of direct evidence.[60] In scleroderma, several different abnormalities contribute to the risk of reflux and aspiration: altered peristalsis, reduced lower esophageal pressure, presence of a hiatal hernia, gastroparesis, and autonomic nerve dysfunction.[61] Aggressive treatment to reduce the risk of reflux and aspiration is recommended despite inconclusive evidence to suggest an association. Behavioral modification and pharmacologic acid suppression are the initial interventions. In refractory situations, fundoplication may be considered in the appropriate patient, particularly in those with advanced lung fibrosis awaiting transplantation in an attempt to decrease the incidence posttransplantation bronchiolitis obliterans and chronic rejection.[62–64]

POLYMYOSITIS-DERMATOMYOSITIS: CLINICAL FEATURES

Polymyositis is a systemic autoimmune disorder characterized by an inflammatory myopathy. Dermatomyositis differs from polymyositis in that prominent skin involvement, characterized by a heliotropic rash and/or erythematosus scaling over the proximal interphalangeal joints, termed *Gottron papules* or *rash*, occurs with less severe myositis. In polymyositis–dermatomyositis, pulmonary complications are common and important causes of morbidity and mortality and as seen in other connective-tissue diseases, often predate or overshadow the muscle or skin manifestations. Pulmonary involvement has been reported in up to 40% of cases.[65] In contrast to the other collagen vascular diseases, in polymyositis–dermatomyositis primary involvement of the airways and pleura do not routinely occur. Pulmonary hypertension secondary to plexogenic arteriopathy has been reported on several occasions, most often in cases in which a crossover with scleroderma was suspected.

■ ASPIRATION PNEUMONIA

Aspiration pneumonia is a common pulmonary complication, occurring in 10% to 20% of patients with polymyositis–dermatomyositis; almost half of the patients complain of dysphagia as well. This complication results from an inflammatory myositis affecting the striated muscle of the hypopharynx and upper third of the esophagus. As a result, there is loss of normal swallowing function and failure to protect the airway. Aspiration is more likely in those patients with extensive skin or muscle involvement given the associated myositis.

■ RESPIRATORY MUSCLE DYSFUNCTION

Hypercapnic respiratory failure requiring assisted ventilation, due to extensive myositis involving the respiratory muscles and diaphragm, is an uncommon event (5% prevalence). In those patients presenting with unexplained hypercapnic respiratory failure, polymyositis–dermatomyositis as well as demyelinating neuromuscular disorders should be considered. With less extensive involvement of these muscles, however, there is a reduction in cough generation and the potential for the development of hypostatic pneumonia and atelectasis due to mucus plugging. Weakness can also cause a restricted physiologic defect with resulting tachypnea and dyspnea in the face of a normal diffusing capacity, normoxia, and hyperventilation. Respiratory muscle dysfunction as the cause of restrictive lung disease can best be demonstrated by measurement of the maximal pressure generated during both phases of the respiratory cycle. Sequential measurements are useful for monitoring the disease course and response to treatment.

■ INTERSTITIAL LUNG DISEASE

The prevalence of interstitial lung disease in polymyositis–dermatomyositis ranges from 5% to 30%.[66,67] The incidence is significantly higher in certain populations. In Japan, it approached 40% to 80% in one series. As in the other collagen vascular diseases, the use of bronchoalveolar lavage and high-resolution computed tomography for screening increases the documented incidence. In those screened with high-resolution CT imaging, the incidence approaches 78% within 3 years of diagnosis.[68]

Although UIP was previously reported to be the predominant histologic type of interstitial lung disease seen in polymyositis–dermatomyositis, NSIP now appears to be most common, based on the revised classification system for idiopathic interstitial pneumonias. DAD, organizing pneumonia, and diffuse alveolar hemorrhage secondary to pulmonary capillaritis may also occur.[69] All forms of interstitial lung disease may precede, appear simultaneously with, or follow the muscle or skin manifestations. There is no relationship between interstitial lung disease and the extent of muscle or skin disease, the level of creatinine phosphokinase elevation, or the presence of serum rheumatoid factor or antinuclear antibodies. There is, however, a relationship between interstitial lung disease and a serum antibody directed against the cellular enzymes tRNA-synthetases, the most common of which being known as anti–Jo-1.[70] This antibody appears in 25% of patients with polymyositis–dermatomyositis in total, but in 50% of patients with interstitial lung disease and in 13% of patients without lung disease. Depending on which tRNA-synthetase antibody is present, different clinical phenotypes may occur with varying degrees of myositis and lung involvement.[71,72]

All forms of interstitial lung disease in polymyositis–dermatomyositis are more common in women. Several clinical syndromes occur and are associated with the underlying interstitial lung disease. The most common presentation is chronic cough and progressive dyspnea due to NSIP with varying degrees of fibrosis.[73] Digital clubbing is rarely, if ever, seen. Chest radiographs demonstrate reticulonodular infiltrates, and with disease progression there is a reduction of the lung volume and the development of radiographic honeycomb lung and pulmonary hypertension. Physiologic testing indicates a restrictive pattern with a low diffusing capacity. Response to treatment depends upon the underlying histology, the more cellular disease being more responsive. In

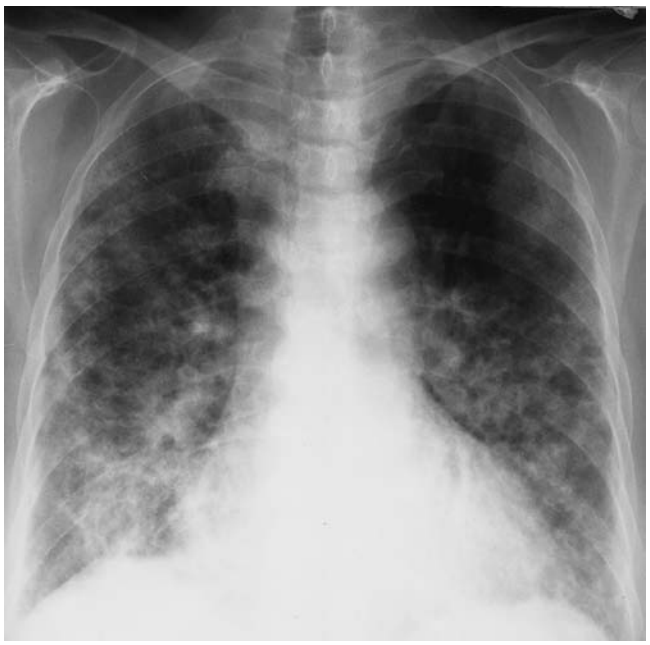


Figure 60-20 Bronchiolitis obliterans organizing pneumonia in a patient with polymyositis-dermatomyositis and acute symptoms. Chest radiograph demonstrating diffuse patchy alveolar infiltrates.

corticosteroid-resistant patients, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, intravenous immunoglobulins, and rituximab have been used with efficacy.[74]

In polymyositis–dermatomyositis, an acute pulmonary presentation with a clinical and radiographic picture reminiscent of a diffuse infectious pneumonia may occur and is associated with a poorer prognosis. The underlying lesion is DAD. Severe respiratory failure occurs, and recovery is unusual in spite of aggressive anti-inflammatory and immunosuppressive therapy. Organizing pneumonia may have either an acute or subacute presentation (Fig. 60-20). The differentiation from DAD becomes important because of the marked disparity in treatment outcome and survival. In organizing pneumonia, corticosteroid responsiveness with or without an additional agent is the rule rather than the exception. Diffuse alveolar hemorrhage due to pulmonary capillaritis may also occur.[75] This complication appears simultaneously with the onset of the muscle disease. Hemoptysis may or may not be present. As with other forms of pulmonary capillaritis, immunosuppression with corticosteroids and cyclophosphamide is utilized and been efficacious.

MIXED CONNECTIVE-TISSUE DISEASE: CLINICAL FEATURES

Patients with mixed connective-tissue disease have features of SLE, polymyositis–dermatomyositis, and scleroderma. Mixed connective-tissue disease is characterized by elevated titers of a specific antinuclear antibody directed against nuclear ribonucleoprotein (anti-RNP). Because of the similarity of mixed connective-tissue disease to the aforementioned collagen vascular diseases, pleuropulmonary complications are frequent, occurring in 20% to 80% of cases.[76,77]

PLEURAL DISEASE

Although pleurisy has been reported to occur in 40% of cases, pleural effusions are uncommon, appearing in approximately 5% of cases.[78] Effusions have been characterized as exudative in nature, but limited information is available in the literature.

PULMONARY VASCULAR DISEASE

Pulmonary hypertension may be caused by recurrent pulmonary emboli, hypoxic vasoconstriction secondary to interstitial lung disease, or plexogenic arteriopathy, as occurs in SLE and scleroderma. This is a significant problem for these patients; however, the incidence is unknown but may be less common than previously believed.[79] These patients, primarily women, present with dyspnea and fatigue. They have normal chest radiographs except for pulmonary arterial enlargement and an isolated reduction in the diffusing capacity for carbon monoxide. The prognosis in pulmonary hypertension secondary to mixed connective-tissue disease is similar to that noted in pulmonary hypertension seen in scleroderma and SLE. In contrast to patients without pulmonary arterial hypertension, 5-year survival is decreased from 96% to 73%.[80,81]

Medium-sized pulmonary artery vasculitis has been reported in mixed connective-tissue disease, with evidence suggesting immunologic-mediated injury with deposition (IgG, C_3) in the vascular walls. Circulating lupus anticoagulant (antiphospholipid syndrome) may also complicate the course of patients with mixed connective-tissue disease, predisposing them to thromboembolic disease.[82] It is in these patients that recurrent small pulmonary emboli may mimic the clinical picture of idiopathic pulmonary hypertension.

ASPIRATION PNEUMONIA

Patients with mixed connective-tissue disease, presenting with predominant features of scleroderma or polymyositis–dermatomyositis, are predisposed to esophageal dysmotility and dilatation, which can be a significant problem leading to reflux esophagitis and recurrent aspiration pneumonia. The presence of radiographic evidence of ILD closely associates with esophageal dilation and motor dysfunction, suggesting a common pathobiology.[83]

RESPIRATORY MUSCLE DYSFUNCTION

In those patients with features of polymyositis–dermatomyositis, an inflammatory myositis with respiratory muscle involvement may lead to hypercapnic respiratory failure or a restrictive lung disease with the development of hypostatic pneumonia.

INTERSTITIAL LUNG DISEASE

The incidence of interstitial lung disease in mixed connective-tissue disease is increased in comparison to other collagen vascular diseases, with greater than 50% of patients having abnormal high-resolution CT imaging abnormalities.[84] The histologic pattern of NSIP and/or UIP are noted, both of which may progress to honeycomb lung, particularly in those patients with the features of scleroderma. As with the other connective-tissue diseases, this interstitial lung disease manifests as progressive dyspnea, bibasilar reticulonodular infiltrates on chest radiograph, and physiologic parameters with low lung volumes and a reduction in the diffusing capacity for carbon monoxide.

Diffuse alveolar hemorrhage has been reported in a few cases of mixed connective-tissue disease and is similar in presentation to that in SLE. It is assumed that the histology is one of either bland pulmonary hemorrhage or pulmonary capillaritis but remains unknown.[85]

SJÖGREN SYNDROME

Sjögren syndrome refers to a triad of xerophthalmia, xerostomia, and polyarthritis. This autoimmune exocrinopathy is characterized by lymphocytic infiltration of the lacrimal and salivary glands.[86] A primary form, occurring in the absence of another collagen vascular disease, and a secondary form, associated with one of the other collagen vascular diseases, most frequently rheumatoid arthritis, exist.[87] A strong female predominance exists in Sjögren syndrome (90%). A positive rheumatoid factor (95%) and antinuclear antibodies in a speckled pattern (80%) are to be expected, as well as positive tests for antibodies to extractable nuclear antigens (anti-SSA, anti-SSB), which are specific for the primary form of the syndrome.

AIRWAY DISEASE

Lymphocytic infiltration and destruction of airway mucus glands result in desiccation of the tracheobronchial tree in Sjögren syndrome.[88] Patients may develop hoarseness, cough, inspissation of secretions resulting in luminal obstruction and atelectasis, recurrent pneumonias, and bronchiectasis. There is a high incidence of obstructive ventilatory dysfunction in these patients, secondary to follicular bronchiolitis. Obliterative bronchiolitis, constrictive bronchiolitis, and bronchiolectasis have also been reported.

INTERSTITIAL LUNG DISEASE

In primary Sjögren syndrome, patients present with a nonproductive cough, dyspnea on exertion, or asymptomatic radiographic abnormalities. As occurs in the lacrimal and salivary glands, interstitial lung disease in these patients is the result of lymphocytic infiltration of the lung parenchyma. This occurs in two forms, lymphocytic interstitial pneumonitis and, less commonly, pseudolymphoma. Both of these lesions have the potential for lymphomatous conversion. Lymphocytic interstitial pneumonitis is an interstitial lung disease in which cough, dyspnea, and restrictive physiology manifest. Because lymphocytes may also infiltrate the alveolar spaces as well as the interstitium, the radiologic studies indicate mixed alveolar and interstitial infiltrates. In a subset of patients, variably sized cystic lesions with associated ground glass may be the only radiographic abnormality (Fig. 60-21). The development of pleural effusions or the appearance of hilar or mediastinal adenopathy should be investigated further as it may suggest a malignant transformation to a lymphoma. Lymphocytic interstitial pneumonia is responsive to anti-inflammatory agents such as corticosteroids. Occasionally, cytolytic therapy, such as azathioprine or cyclophosphamide, is required but remains of unproven benefit. Cyclosporine has also been recommended as an additional agent in corticosteroid-resistant cases. Rituximab, an anti-CD20 monoclonal antibody, may be beneficial in selected patients but further controlled studies are required to better assess its efficacy in primary Sjögren syndrome. While the majority of patients will respond to immunosuppressive therapy, a subset of patients progress to fibrotic lung disease with honeycomb change.

Pseudolymphoma is a tumor-like proliferation appearing as single or multiple masses on the chest radiograph. It is often difficult to distinguish from a malignant lymphoma and it has been suggested that pseudolymphoma, which is considered to be a localized form of lymphocytic interstitial pneumonitis, is a premalignant lesion.[89] When associated with a monoclonal gammopathy, malignant transformation to lymphoma is suggested.[90]

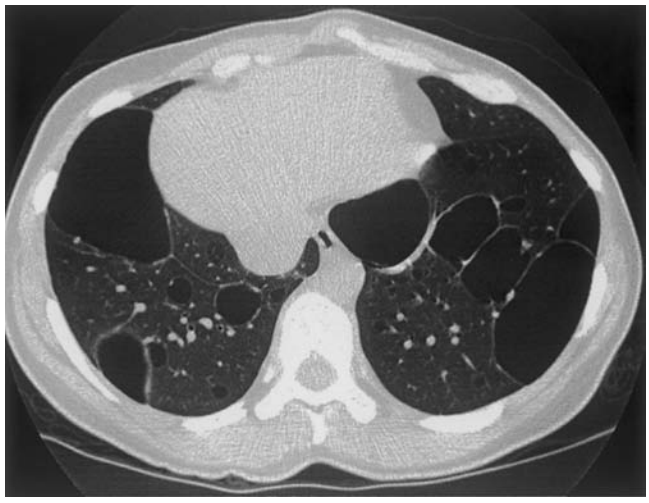


Figure 60-21 Multiple cysts of varying sizes scattered throughout both lungs in a patient with Sjögren syndrome and lymphocytic interstitial pneumonia.

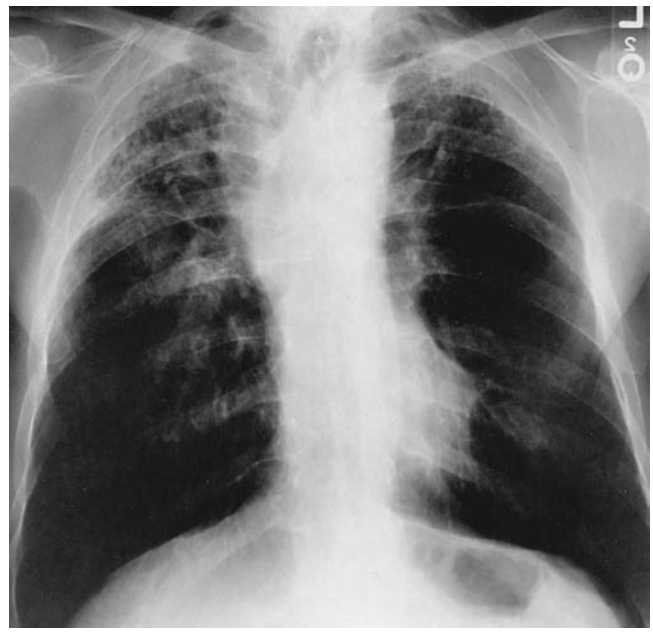


Figure 60-22 Ankylosing spondylitis. Chest radiograph demonstrating bilateral upper-zone fibronodular infiltrates.

Interstitial lung disease occurs more commonly in the secondary forms of Sjögren syndrome and most likely represents a complication of the associated collagen vascular disease.[2] The histologic pattern in secondary Sjögren syndrome mimics that seen in rheumatoid arthritis, with NSIP, UIP, and organizing pneumonia reported. UIP is uncommon in the primary form of Sjögren syndrome.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is one of the seronegative spondyloarthropathies that may eventually result in fixation of the chest wall and a mild to moderate restrictive lung disease. Muscular involvement, in contrast to polymyositis–dermatomyositis, does not occur and diaphragmatic function is preserved, limiting ventilatory failure given the preserved respiratory muscle function.

The incidence of interstitial lung disease complication is reportedly less than 2%.[91] In contrast to the other collagen vascular diseases that primarily affect the basilar portion of the lung, ankylosing spondylitis has a predilection for the upper lung zones, only appears late in the course of the chronic spondylitis, and never precedes it.[92] Interstitial lung disease often appears as fibrocystic disease on the chest radiograph (Fig. 60-22) and is difficult to distinguish from apical lung infections such as tuberculosis. Histologically, it is a fibrosing process with cystic formation. Progressive dyspnea and cough are the predominant symptoms, and treatment with corticosteroids is ineffective and therefore not suggested. Etanercept may afford patient a short-term benefit with improvements in spinal mobility and pulmonary physiology.[93] The most serious complication of this apical fibrocystic disease is infection with invasive aspergilla species as well as atypical mycobacteria. Further, saprophytic colonization of the cysts by aspergilla species (aspergilloma) may induce life-threatening hemoptysis.

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CHAPTER 61

Pulmonary Langerhans' Cell Histiocytosis

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INTRODUCTION

Pulmonary Langerhans' cell histiocytosis is part of a large spectrum of disorders characterized by abnormal organ infiltration by Langerhans' cells, which are highly differentiated cells in the monocyte-macrophage line that are also found in the dermis of the skin, reticuloendothelial system, pleura, and lung. Clinically, these disorders vary greatly, ranging from mild, single-organ disease to acute, disseminated life-threatening presentations. Depending on the sites involved and severity, the entity now referred to as Langerhans' cell histiocytosis has been previously defined as eosinophilic granuloma, Hand–Schüller–Christian disease, and Letterer–Siwe disease. A more recent and simplified system of classification includes Langerhans' cell histiocytosis with single-organ involvement or with multisystem involvement.[1]

Pulmonary Langerhans' cell histiocytosis is an uncommon, smoking-related, interstitial lung disease that primarily affects young adults. Usually, lung involvement occurs in isolation; less frequently, involvement of other systems, for example, bone, skin, pituitary gland, is seen. Although there is some similarity to other diffuse interstitial lung diseases, pulmonary Langerhans' cell histiocytosis, as a specific disease entity, is distinct in its clinical, radiologic, and pathologic manifestations.

EPIDEMIOLOGY

The true incidence and prevalence of pulmonary Langerhans' cell histiocytosis are unknown. Studies in which diagnoses were confirmed by lung biopsy showed that pulmonary Langerhans' cell histiocytosis is an uncommon, if not rare, disease.[2,3] A Japanese study of discharge diagnoses in hospitals with 200 beds estimated the disease prevalence at 0.27 and 0.07 per 100,000 population in males and females, respectively.[4] These reports may underestimate the true incidence of the disease, as lung biopsy is not performed in all cases of pulmonary Langerhans' cell histiocytosis, and some patients exhibit no symptoms or experience spontaneous remission. Occupational or geographical predisposition has not been reported.

Of note, nearly all affected persons report a current or prior smoking history. Thus, tobacco smoke is thought to play a key role in the pathogenesis of pulmonary Langerhans' cell histiocytosis of adulthood. Other diffuse parenchymal lung diseases associated with cigarette smoking are respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonitis.[5]

Most patients with pulmonary Langerhans' cell histiocytosis present to medical attention in young adulthood (20–40 years of age). Pulmonary Langerhans' cell histiocytosis, however, may present in any age group. Older literature suggested a male preponderance; however, recent literature suggests an equal sex distribution, with increasing presentations in middle age. In general, women tend to present at an older age than men. These differences in prevalence may reflect the changing smoking habits of women in our society. For unknown reasons, whites are affected much more commonly than blacks or Asians, in whom this disease is very rare.

Pulmonary Langerhans' cell histiocytosis has reportedly been associated with a number of malignancies and may be a premalignant condition. Lymphoma, both Hodgkin's and non-Hodgkin's, and other hematologic and solid cancers have been reported in association with pulmonary Langerhans' cell histiocytosis.[6] However, the evidence regarding this association is inconclusive. Malignancies may precede, follow, or occur concomitantly with the diagnosis of the interstitial lung disease. The carcinogenic effects of cigarette smoke are probably responsible for some of these tumors; thus, other components of tobacco may be responsible for pulmonary Langerhans' cell histiocytosis. Given the complexity of factors involved in the pathogenesis of cancer and pulmonary Langerhans' cell histiocytosis, it has been difficult to define the effects of tobacco on the pathogenesis of malignancies in patients with pulmonary Langerhans' cell histiocytosis. Possibly, shared genetic predisposition factors may also have a role in the development of malignancies in patients with the disorder.[7]

NATURAL HISTORY AND CLINICAL PRESENTATION

Patients with pulmonary Langerhans' cell histiocytosis come to medical attention in a variety of ways: as an incidental diagnosis that is suggested by a screening chest radiograph, after pneumothorax, or with respiratory or constitutional symptoms. Symptomatic patients most often have a nonproductive cough (56%–70%), dyspnea (40%), chest pain (10%–21%), fatigue (~30%), weight loss (20%–30%), and fever (15%). Pleuritic pain and acute dyspnea with a spontaneous pneumothorax can be a recurrent problem in as many as 25% of patients. Pleural thickening or effusion is rarely seen in the absence of a history of pneumothorax. Hemoptysis (13%) is occasionally reported, and it should prompt consideration of superimposed infection (e.g., *Aspergillus*) or tumor.[8]

Cystic bone lesions are present in 4% to 20% of patients with pulmonary Langerhans' cell histiocytosis and may produce localized pain or a pathologic bone fracture. The precise number of patients with bone lesions is not known because complete bone surveys are not routinely performed. Skeletal involvement may be either the sole symptomatic manifestation of pulmonary Langerhans' cell histiocytosis or may precede the more typical pulmonary manifestations. The radiographic pattern is not diagnostic. In most instances, the lesions are solitary and affect the flat bones. Central nervous system involvement with diabetes insipidus (approximately 15% of patients) is also seen and is believed to portend a poor prognosis. Skin involvement may also be present in adults with pulmonary Langerhans' cell histiocytosis.

Skin lesions are usually erythematous, maculopapular, or nodular. In these patients, the scalp is often involved by characteristic seborrheic and crusted lesions.[9]

The physical examination is usually unremarkable. On chest examination, crackles are uncommon. Digital clubbing is also uncommon. Secondary pulmonary hypertension (PH) may occur and is probably underrecognized. Manifestations of cor pulmonale are seen in advanced stages. Routine laboratory studies are usually unrevealing; the peripheral eosinophil count is normal.[1]

PATHOGENESIS

The pathogenesis of adult pulmonary Langerhans' cell histiocytosis is still poorly understood. However, the nearly universal association with cigarette smoking strongly implies causation. Smoke may activate alveolar macrophages through bombesin-like peptides. Bombesin is a neuropeptide produced by neuroendocrine cells, which are increased in the lungs of smokers.[10] Bombesin-like peptides are chemotactic for monocytes, are mitogenic for epithelial cells and fibroblasts, and stimulate cytokine secretion. Several antigens in cigarette smoke, including tobacco glycoprotein, may stimulate macrophage and epithelial cell production of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), dendritic cell chemokines, for example, chemokine (C-C motif) ligand 20 (CCL20), osteopontin, and tumor necrosis factor-α (TNF-α) that promote recruitment and activation of Langerhans' cells.[11] In fact, GM-CSF and TNF-α have been found in the lesions of patients with Langerhans' cell histiocytosis and have been shown to facilitate the in vitro generation of Langerhans' cells from CD34+ hematopoietic stem cells.[12] TNF-α and other cytokines, for example, tumor necrosis factor-β (TNF-β), may also stimulate fibroblasts leading to fibrosis.[13] Moreover, tobacco glycoprotein may also cause an abnormal differentiation of T lymphocytes and a reduction in interleukin (IL)-2 release by lymphocytes, thereby enhancing survival or proliferation of Langerhans' cells (Fig. 61-1).[14]

Abnormalities in immune function, with a nonspecific increase in immunoglobulin G (IgG) in bronchoalveolar fluid, circulating and tissue-bound immune complexes, and abnormalities in T-cell function, have been observed in association with pulmonary Langerhans' cell histiocytosis and may be important in the pathophysiology of this disorder.[15] It is possible, however, that these findings represent nonspecific consequences of a generalized activation of immune effector cells.

Recent studies report high serum levels of IL-17A during active Langerhans' cell histiocytosis, IL-17A synthesis by dendritic cells of patients with multisystem Langerhans' cell histiocytosis, and an IL-17–dependent pathway for dendritic cells fusion, showing that IL-17 may play a role in pathogenesis, although its significance in pulmonary Langerhans' cell histiocytosis is not known.[16] Some studies suggest that the pathogenesis of pulmonary Langerhans' cell histiocytosis entails alterations of the expression of the adhesion molecules that regulate interactions between white blood cells and endothelial cells.[17,18] One important adhesion molecule for neutrophils that is expressed by endothelial cells is intercellular adhesion molecule-1 (ICAM-1). ICAM-1 expression by Langerhans' cells has been demonstrated in biopsy specimens of subjects with Langerhans' cell histiocytosis. Expression of other leukocyte adhesion molecules, such as the β_1 and β_2 integrins, has also been noted.[19] The significance of these findings and their relevance to pulmonary Langerhans' cell histiocytosis remain to be elucidated.

Alternatively, a viral infection has been suggested as the underlying cause of generalized Langerhans' cell histiocytosis. However, there are no convincing data to suggest a role for viral infection as a cause of pulmonary Langerhans' cell histiocytosis.[20] Although clonality of histiocytes has been shown in children and adults with multisystem Langerhans' cell histiocytosis or unifocal bone disease, pulmonary Langerhans' cell histiocytosis appears to be primarily a reactive process to cigarette smoke in which nonmalignant clonal evolution of LCH cells may occur in the setting of abnormal Langerhans' cell hyperplasia in the airways.[21,22]

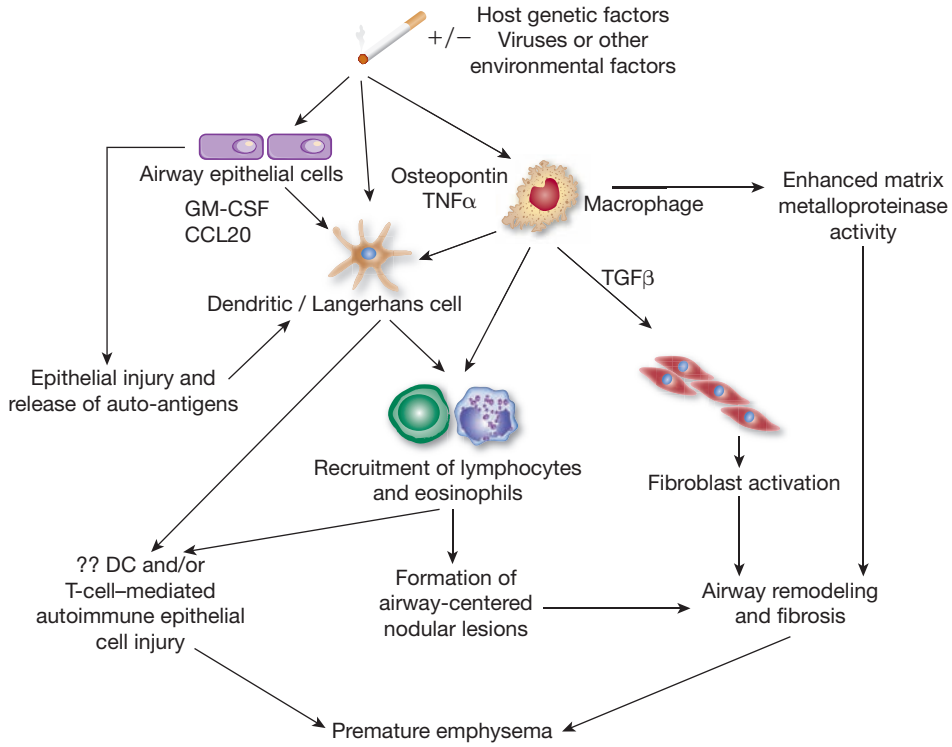


Figure 61-1 The primary event in the pathogenesis of pulmonary Langerhans' cell histiocytosis probably involves cigarette-smoke–induced recruitment to the lung and activation of Langerhans' cells, a process that may result from a variety of potential mechanisms. Antigens in cigarette smoke, including tobacco glycoprotein (TGP), may stimulate alveolar macrophages and epithelial cells to produce cytokines or other factors that enhance recruitment and activation of Langerhans' cells. Cigarette smoke may also directly activate Langerhans' cells to secrete cytokines (such as TNF or GM-CSF) that mediate local accumulation of inflammatory cells, with resultant formation of nodules. Uptake of cigarette-smoke antigens by alveolar macrophages or Langerhans' cells may also promote local expansion of T lymphocytes and further inflammation. Through the action of tobacco glycoprotein, reduced interleukin-2 secretion by lymphocytes may occur, thereby enhancing local survival and proliferation of Langerhans' cells. T lymphocytes may further stimulate B-lymphocyte activation, promoting secretion of antibodies and immune-complex formation. Fibroblast activation and fibrosis may result from the local synthesis of tumor growth factor-β (TGF-β) and by alveolar macrophages. *(Reproduced with permission from Suri HS, Yi ES, Nowakowski GS, Vassallo R. Pulmonary langerhans cell histiocytosis. Orphanet J Rare Dis. 2012;7:16.)*

HISTOPATHOLOGY

The pathologic cell type of pulmonary Langerhans' cell histiocytosis is the Langerhans' cell, a differentiated cell of the monocyte-macrophage line (Fig. 61-2). Langerhans' cells are distinguished by a pale-staining cytoplasm and large convoluted nucleus. Electron microscopy may demonstrate the classic pentalaminar cytoplasmic inclusion known as a Birbeck granule (Fig 61-3). Langerhans' cells are also characterized by the presence of the CD1a antigen on the cell surface, a feature not found in other cells of histiocytic origin. Langerhans' cells also react with anti-S-100 antibody, but this reactivity can also be observed in other cell types. More recently, langerin, a type II mannose lectin that is constitutively associated with Birbeck granules, has been identified as a specific marker of Langerhans' cells.[23] Although this cell can be found in association

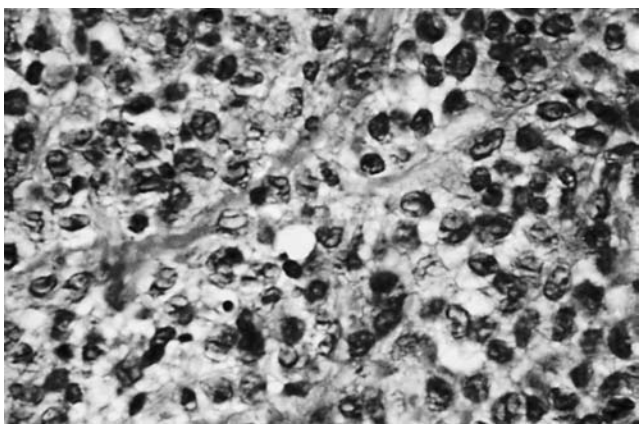


Figure 61-2 Lung tissue in pulmonary Langerhans' cell histiocytosis. The Langerhans' cells are typical. A characteristic longitudinal groove is seen along the center of some cells (×96.)

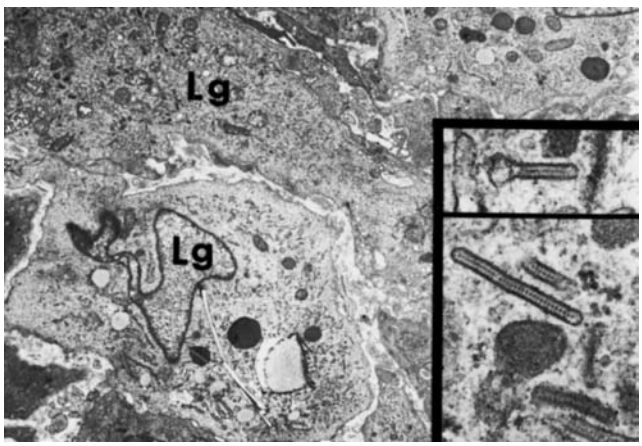


Figure 61-3 Electron micrograph of Langerhans' cell (Lg) of the lung. Typical X bodies (Birbeck granules) are seen in the two insets.

with cigarette smoking in otherwise healthy persons and with other pulmonary pathologies (e.g., idiopathic pulmonary fibrosis) or in normal lung, its presence is characteristic of pulmonary Langerhans' cell histiocytosis. In pulmonary Langerhans' cell histiocytosis, the Langerhans' cells are characteristically found in clusters and significantly outnumber those seen in other lung diseases. Absolute quantitative guidelines for diagnosis of pulmonary Langerhans' cell histiocytosis have not been established.

Early inflammatory lesions center around the smaller bronchioles and usually contain a mixture of Langerhans' cells, eosinophils, lymphocytes, and neutrophils. The cells appear to invade the bronchiole, destroying the bronchiolar wall in an eccentric fashion. The lesions often affect pulmonary arterioles and venules, so that the disorder can be described as having a bronchovascular distribution.

Pseudodesquamative interstitial pneumonia (characterized by the accumulation of alveolar macrophages in the alveolar parenchyma between pulmonary Langerhans' cell lesions) and respiratory (smoker's) bronchiolitis (with pigmented macrophages filling the lumen of bronchioles and the surrounding alveolar spaces) have also often been found on lung biopsy.[3,8] In addition, intraluminal fibrosis was often present (86% of specimens). The fibrosis was characterized by mural incorporation, alveolar obliteration, and intraluminal buds. It was mild in extent in 59% of specimens, moderate in 20%, and marked in 9%. These findings support the hypothesis that intraluminal fibrosis serves as a mechanism for alveolar collapse, with progression to interstitial fibrosis and lung remodeling.[8]

Interstitial fibrosis and small cyst formation with a middle- to upper-zone predominance occur in advancing disease. This middle- to upper-zone predominance differs from that of idiopathic pulmonary fibrosis, which generally has a lower-zone predominance. More advanced lesions extend widely into the lung parenchyma that surrounds the bronchovascular structures and produce the so-called stellate lesions that are characteristic of this disorder.[3] Kambouchner et al.[24] used three-dimensional reconstructions of serial histologic sections to demonstrate that pulmonary Langerhans' cell histiocytosis lesions are elongated, sheath-like structures of variable diameter that extend proximally and distally along bronchioles and do not necessarily have a spherical morphology (Fig. 61-4).

Older lesions are relatively acellular, lacking Langerhans' cells entirely and producing a diffuse interstitial pathology that can be difficult to distinguish from other forms of end-stage pulmonary fibrosis, with extensive areas of fibrosis and honeycombing accompanying the cystic lesions. The mechanism for cyst formation is unknown. It may be a consequence of central necrosis of older stellate lesions. Alternatively, the cysts may occur as a result of secondary inflammatory foci in relatively avascular areas distal to more advanced bronchovascular lesions. Finally, these cysts may form, in part, because of obstruction of the more proximal airway by the stellate lesions (traction emphysema).

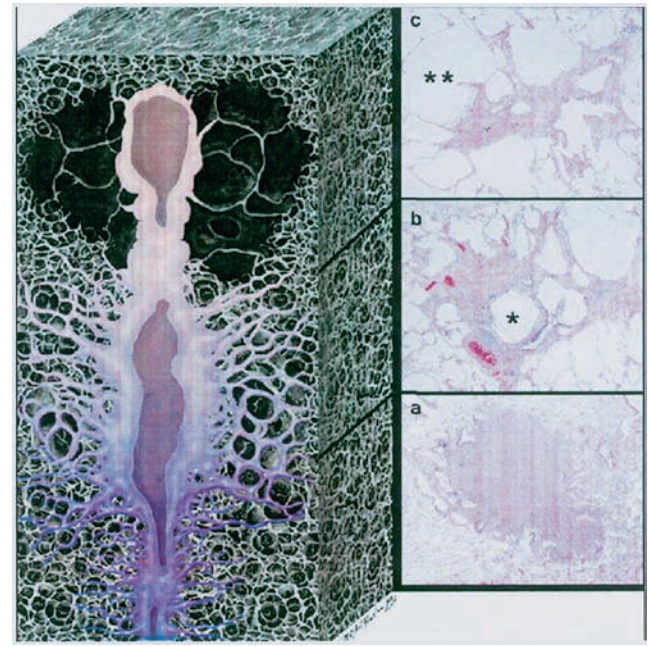


Figure 61-4 Three-dimensional appearance of a pulmonary Langerhans' cell histiocytosis (PLCH) lesion. Artist's rendering, based on the reconstructions by Kambouchner et al.,[24] illustrates the elongated morphology and variable cellular and fibrotic composition of PLCH with correlative histologic sections. As a PLCH lesion evolves, the nodule of densely packed cells (*bottom*, A) is centripetally replaced by fibrous tissue and ultimately becomes a stellate scar (*top*, C). This continuum of change may be evident within a single lesion. PLCH lesions are bronchiolocentric and propagate both proximally and distally along the small airways. The involved bronchiolar lumen may become either dilated or obliterated. The histologic sections correspond to the early, middle, and late phases of PLCH. In the early phase (*a*), there is a densely cellular nodule with delicate stellate extensions along the adjacent alveolar walls (original magnification, ×12; H&E stain). As the disease progresses (*b*), cellularity diminishes as fibroblasts replace the lesion (original magnification, ×19.2; H&E stain). Note that the stellate extensions have become more prominent, the central bronchiole (*) is dilated, and adjacent alveolar spaces have coalesced because of focal destruction of alveolar walls (paracicatricial airspace enlargement). In the final phase (*c*), the characteristic Langerhans' cell histiocytosis is absent and only a fibrous, stellate scar remains (original magnification, ×24; H&E stain). This phase is often accompanied by paracicatricial airspace enlargement (**). *(Used with permission of the Armed Forces Institute of Pathology (AFIP).)*

RADIOLOGY

The appearance of Langerhans' cell histiocytosis on routine chest x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are described below.

CHEST RADIOGRAPH

The radiographic appearance of pulmonary Langerhans' cell histiocytosis may be very characteristic. The combination of ill-defined or stellate nodules (2–10 mm in size), reticular opacities, upper-zone cysts or honeycombing, preservation of lung volume, and costophrenic angle sparing are believed to be highly specific for this disorder.[25] Typically, in keeping with the pathology, the reticular or nodular opacities are seen in the middle to upper zone (Fig. 61-5). The total lung volume is most often normal, although both hyperinflation and reduced volume have been described. In addition to pulmonary Langerhans' cell histiocytosis, other interstitial diseases that may present with an increased lung volume are lymphangioleiomyomatosis, chronic hypersensitivity pneumonitis, stage III sarcoidosis, constrictive bronchiolitis, and any interstitial lung disease in an individual with emphysema.

Small cysts and nodules are the radiographic hallmark of pulmonary Langerhans' cell histiocytosis (Fig. 61-6A); occasionally miliary disease is seen. Hilar or mediastinal adenopathy in pulmonary Langerhans' cell histiocytosis is rare and should prompt consideration of malignancy as a secondary diagnosis. Pleural thickening is most often due to treated pneumothorax, since pleural involvement by the primary disease process is uncommon. Bone lesions can occur in any bone, including the ribs. On rare occasions, patients come to medical attention with a solitary pulmonary nodule that, on biopsy, proves to be pulmonary Langerhans' cell histiocytosis.[26]

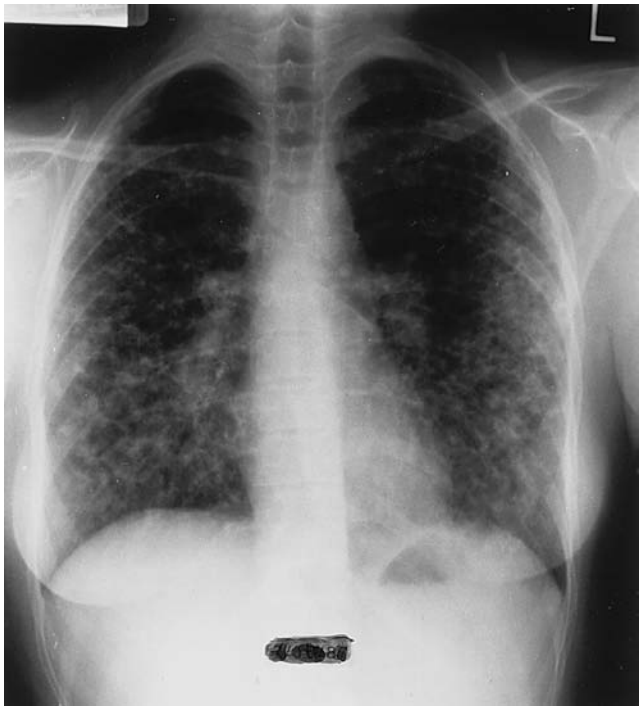


Figure 61-5 Pulmonary Langerhans' cell histiocytosis in a 22-year-old woman. Chest radiograph demonstrates the classic features of profuse ill-defined nodules, reticulonodular opacities, cysts, costophrenic angle sparing, and preservation of lung volumes.

■ COMPUTED TOMOGRAPHY

The combination of multiple cysts and nodules with a middle- to upper-zone predominance with interstitial thickening in a young smoker is so characteristic as to be diagnostic of pulmonary Langerhans' cell histiocytosis (Fig. 61-6B). The nodules can be well or poorly defined. Occasionally, they can be large and bizarrely shaped (Fig. 61-6C). Cysts may vary in shape, size, and wall thickness from a few to several millimeters. Honeycombing can be seen in advanced disease.[27,28] Serial chest CT scanning often suggests a sequence of progression from nodular to cavitating to cystic lesions over time.[29] Moreover, the CT pattern seems to reflect the histopathologic evolution of lung lesions, with cystic changes prominent in the advanced, fibrotic stages of the disease.[30]

The degree of cyst formation is often underappreciated with routine chest radiography. Thus, this progression may explain a number of "spontaneous remissions" in the literature reported before the routine use of thin-section CT scanning.[31] Although the extent of the cystic lesions present on HRCT at one point in time has been correlated with impaired lung function, the utility of serial CT scanning in managing these patients has yet to be determined.[32,33]

■ MAGNETIC RESONANCE IMAGING

The role of MRI in pulmonary Langerhans' cell histiocytosis is limited to evaluation of bone and central nervous system lesions.

■ POSITRON EMISSION TOMOGRAPHY

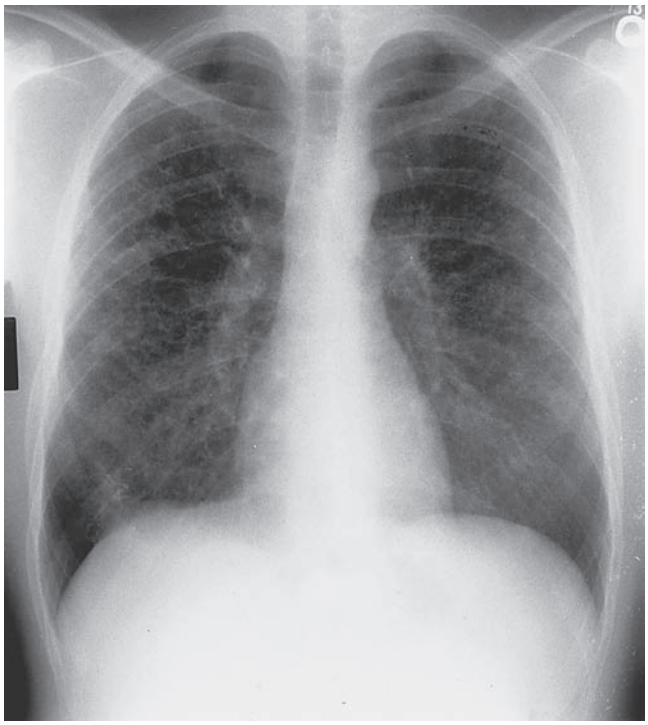
Fluorodeoxyglucose (FDG)-PET scan imaging has shown to be useful in quantifying disease activity, with positive scan results seen in patients with nodular, inflammatory lung disease. Moreover, FDG-PET scan may provide valuable information regarding extrapulmonary involvement in patients with a known diagnosis of pulmonary Langerhans cell histiocytosis. Nevertheless, the mean maximum standardized uptake value (SUV) of the PET scan-positive lesions may vary significantly, suggesting that PET scan imaging cannot reliably distinguish between the benign, inflammatory nodular lesions of Langerhans' cell histiocytosis and malignant lesions.[34]

PHYSIOLOGIC TESTING

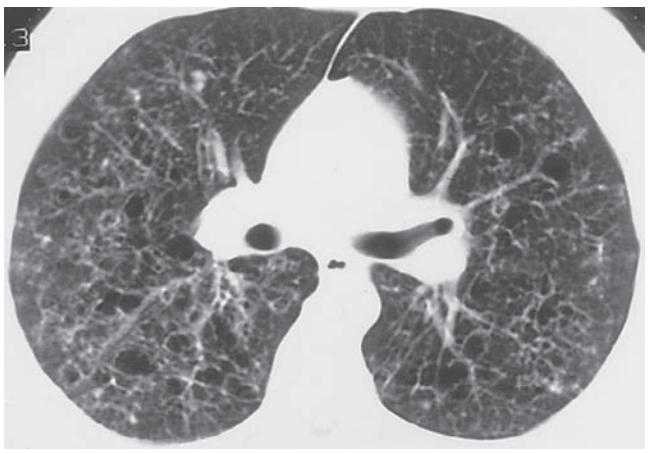
Basic physiologic assessment in Langerhan's cell histiocytosis includes pulmonary function and exercise testing.

■ PULMONARY FUNCTION TESTING

Pulmonary function testing of subjects with pulmonary Langerhans' cell histiocytosis may demonstrate all possible patterns of function abnormality—normal, obstructive, restrictive, or mixed. In general, total lung capacity (TLC) is well preserved, with nearly normal airflow. Most often, the diffusing capacity (D_{LCO}) is disproportionately reduced.[7,22,24] This pattern of pulmonary function abnormality suggests pulmonary vascular involvement by the disease process.

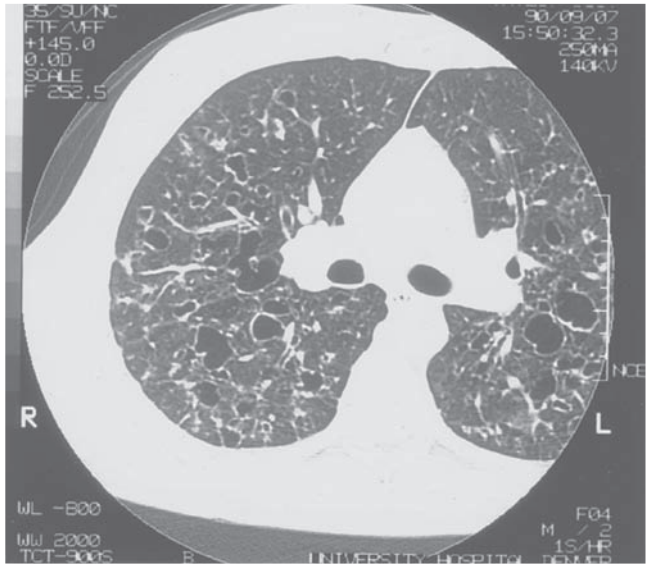


A



B

Figure 61-6 Pulmonary Langerhans' cell histiocytosis in a 33-year-old man. **A.** Chest radiograph reveals reticulonodular opacities in midlung zones, cysts, costophrenic angle sparing, and preservation of lung volumes. **B.** Conventional CT scan helps confirm the presence of bilateral reticulonodular opacities and cysts. *(continued)*



C

Figure 61-6 *(Continued)* **C.** High-resolution CT with thin section shows more clearly that the reticulonodular or emphysematous changes on chest radiography are actually cysts. In this instance, few nodules are present. The cysts vary markedly in size and may be larger than 10 mm. The cysts are bizarre in shape, and many are closely related to pulmonary arteries, often mimicking bronchiectasis.

In the experience at San Giuseppe Hospital in Milan, among 35 patients with pulmonary Langerhans' cell histiocytosis, an obstructive functional pattern was present in 43% of subjects. 10.5% of patients had a restrictive pattern and 3.5% a mixed pattern; 43% of patients showed normal airflow and volumes. A reduction in D_{LCO} was evident in 78% of patients.

Airflow limitation is sometimes associated with reactive airways; significant improvement may occur after administration of a bronchodilator. When present, reactive airways disease may reflect coexisting chronic obstructive pulmonary disease (COPD).

The mean alveolar–arterial difference in P_{O_2} (AaP_{O_2}) may be normal at rest, but the subset with more severe disease had a markedly elevated AaP_{O_2} and required supplemental oxygen. Resting pH and Pa_{CO_2} were most often normal. Thus, the resting arterial blood gas was a very insensitive indicator of disease.[35]

■ EXERCISE TESTING

Clinically, we have observed that patients with established pulmonary Langerhans' cell histiocytosis generally demonstrate a limitation in physical activity and intolerance for exercise that is out of proportion to their pulmonary function abnormalities.

In our cross-sectional study of 23 subjects with pulmonary Langerhans' cell histiocytosis, a marked decrease in exercise capacity, as measured by either work achieved (mean + SEM, 54 ± 4% of predicted) or oxygen utilization ($\dot{V}_{O_2}$, 44% ± 3) at maximal exercise, was found.[35] The oxygen pulse at maximal exercise was reduced to 56 ± 3%. The anaerobic threshold was decreased to 33% ± percent of expected $\dot{V}_{O_{2max}}$ (it was ≤40% in all subjects). The maximal ventilatory response ($\dot{V}_{E_{max}}$, 83 ± 5%) was excessive for the maximal level of work. The maximal ventilatory response was not limiting, and the $\dot{V}_{E_{max}}$ was well below predicted ventilatory ceilings. Gas exchange abnormalities were reflected in increasing AaP_{O_2} differences as the level of exercise increased. In addition, alveolar dead space to tidal volume ratio (V_D/V_T), a parameter believed to reflect pulmonary vascular function, was either abnormally elevated or failed to decrease

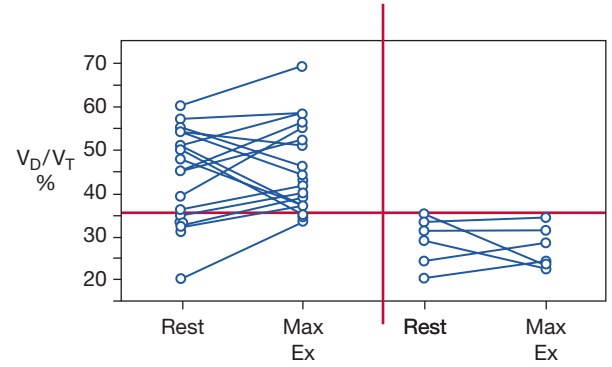


Figure 61-7 Dead space to tidal volume ratio (expressed as percentage, V_D/V_T%) at rest and maximal exercise (max ex) in patients with pulmonary Langerhans' cell histiocytosis (n = 23). Seventeen patients demonstrated either an abnormal V_D/V_T at rest or response to exercise *(left panel)*. Six patients had a normal V_D/V_T at rest and normal response to exercise *(right panel)*. *(Data from Crausman RS, Jennings CA, Tuder R, et al. Pulmonary histiocytosis X: Pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med. 1996;153:426–435.)*

in most patients (Fig. 61-7). This abnormality suggested either pathologic or functional involvement of the pulmonary vasculature.

Two linear regression models derived from pulmonary function indices predicted 73% (r^2 = 0.73) and 75% (r^2 = 0.75) of the variability in the maximal achieved workload and predicted oxygen consumption at maximal exercise, respectively. The following equation was derived for the maximal achieved workload:

$$\text{Maximal achieved workload} = 0.884 - (0.0088 \times V_D/V_T \text{ baseline}) - (0.002 \times RV) + (0.0044 \times D_{LCO}) \quad (1)$$

Here the partial r^2 was V_D/V_T baseline (r^2 = 0.40, p = 0.0007), RV (0.19, 0.001), and D_{LCO} (0.15, 0.004). Figure 61-8 shows the regression model for the predicted oxygen consumption at maximal exercise.

Analysis of the composite results suggests that exercise intolerance in subjects with pulmonary Langerhans' cell histiocytosis is

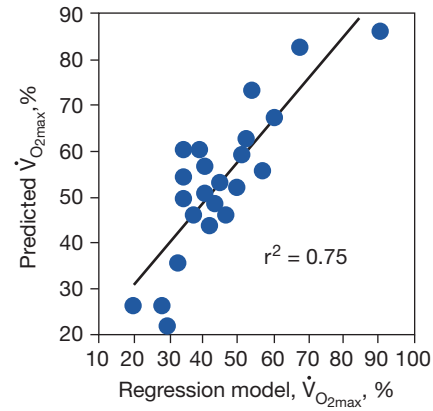


Figure 61-8 Correlation between predicted oxygen consumption at maximal exercise ($\dot{V}_{O_{2max}}$ and predicted $\dot{V}_{O_{2max}}$ from the linear regression model): $\dot{V}_{O_{2max}}$ = 0.062 − (0.0074 * baseline V_D/V_T) − (0.0014 * RV) + (0.0017 * baseline $P(Aa)_{O_2}$) + (0.0011 * D_{LCO}); r^2 = 0.75. *(Data from Crausman RS, Jennings CA, Tuder R, et al. Pulmonary histiocytosis X: Pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med. 1996;153:426–435.)*

due to a combination of mechanical factors and pulmonary vascular involvement by pulmonary Langerhans' cell histiocytosis.[35]

Precapillary PH is a complication of advanced pulmonary Langerhans' cell histiocytosis and is associated with increased mortality.[36] Severe PH has been reported in a high percentage of patients referred for lung transplantation.[37,38]

In patients with respiratory insufficiency, chronic hypoxemia is a relevant factor, but the pathophysiology of PH in pulmonary Langerhans' cell histiocytosis is likely to be multifactorial, with other contributors including abnormal pulmonary mechanics and vascular remodeling. Histopathologic analysis of patients with end-stage disease shows proliferative vasculopathy involving muscular arteries and frequent venular involvement, with aspects of veno-occlusive disease.[37] The degree of PH appears not to be related to variables of pulmonary function; in a subgroup of patients, vasculopathy worsened, although parenchymal and bronchiolar lesions were unchanged, consistent with intrinsic pulmonary vascular disease.[37]

DIAGNOSTIC EVALUATION

The history and physical examination are the first steps in the diagnostic evaluation of a patient suspected of having pulmonary Langerhans' cell histiocytosis. Unfortunately, the signs and symptoms of pulmonary Langerhans' cell histiocytosis are generally nonspecific and often point to other, more common pulmonary diagnoses.[7,22] For example, wheezing, cough, and dyspnea in a 50-year-old patient with a prominent smoking history are much more commonly due to COPD than to pulmonary Langerhans' cell histiocytosis. However, when present, a history of recurrent pneumothorax, diabetes insipidus, or bone pain can be helpful. A smoking history is a consistent but not an essential component of the history, since pulmonary Langerhans' cell histiocytosis may occur without an antecedent smoking history especially in a young adult.

Most evaluations for pulmonary Langerhans' cell histiocytosis are prompted by an abnormal chest radiograph. As previously noted, the chest CT, if classic, may be diagnostic, and should, therefore, be obtained in all who are suspected of having this disease. We recommend high-resolution chest CT as a prebiopsy step in the evaluation of any patient with diffuse interstitial lung disease suspected of having pulmonary Langerhans' cell histiocytosis. A sufficiently characteristic chest CT, in association with the appropriate history, is believed by many to obviate the need for tissue confirmation. It should be noted that most often chest CT scans in pulmonary Langerhans' cell histiocytosis are not diagnostic and may be confused with chest CT scans of lymphangioleiomyomatosis, hypersensitivity pneumonitis, sarcoidosis, or idiopathic pulmonary fibrosis. In these instances, further diagnostic evaluation is warranted.

Bronchoalveolar lavage (BAL) fluid may be of diagnostic value in cases of suspected pulmonary Langerhans' cell histiocytosis.[39] The total number of cells recovered is usually increased (as expected in smokers), and a modest increase in the concentration of neutrophils and eosinophils is common. In active disease, the total number of lymphocytes recovered may also be increased, and the CD4:CD8 ratio may be decreased. Langerhans' cells in BAL fluid may be recognized by their characteristic reactivity with anti-S-100 protein antibodies or peanut agglutination antigen. These cells are also OKT-6 (CD1) positive, are identified by a specific monoclonal antibody (MT-1), and contain characteristic Birbeck or pentilaminar bodies on electron microscopic evaluation (Fig. 61-3).

Quantitative criteria for the definitive diagnosis of Langerhans' cell histiocytosis based on BAL fluid Langerhans' cell numbers have not been conclusively established. A BAL cell differential with more than 5% Langerhans' cells strongly suggests the diagnosis. Lower proportions of Langerhans' cells may be seen in current smokers, in patients with other interstitial lung disorders, in bronchoalveolar carcinoma, or even in normal subjects. Thus, the mere presence of Langerhans' cells is of little diagnostic value, and the effective sensitivity of this tool seems to be lower than previously believed.[40] BAL is also useful to exclude other inflammatory or infectious lung diseases.

When tissue confirmation is sought, transbronchial biopsy may be performed, but the patchy nature of the disease, with a focal distribution of the lesions, the potential for sampling error, and the inability to obtain sufficient tissue may account for the substantial number of false-negative or nondiagnostic biopsies.[41] Open, video-guided thoracoscopic lung biopsy, is generally definitive and may be done with a minimal operative risk. Tissue reactivity with the monoclonal antibody CD1 (OKT-6) distinguishes Langerhans' cells from other histiocytes and can be a useful diagnostic adjunct. It may be performed on routinely fixed tissue and is less expensive than electron microscopy.

In patients with progressive disease and extensive fibrosis, the number of Langerhans' cells in either tissue specimens or BAL fluid decreases dramatically. Diagnosis at this stage may be difficult, regardless of the laboratory methods used. In most cases, the combination of transbronchial lung biopsy and BAL, supplemented with the identification of CD1-positive cells in tissue and BAL fluid, is highly likely to result in the correct diagnosis.

TREATMENT AND PROGNOSIS

The natural history of pulmonary Langerhans' cell histiocytosis is extraordinarily variable, with some patients experiencing spontaneous remission of symptoms and others progressing to end-stage fibrotic lung disease and severe respiratory failure. A poor outcome in pulmonary Langerhans' cell histiocytosis has been associated with older age at the time of diagnosis, severe airway obstruction, reduced carbon monoxide diffusing capacity, and the need for corticosteroid therapy during follow-up.[42] Most subjects who continue to smoke demonstrate gradual progression; regression of disease is noted following smoking cessation.[43] Therefore, it is important to stress smoking cessation (Fig. 61-9). Patients with radiographic sparing of

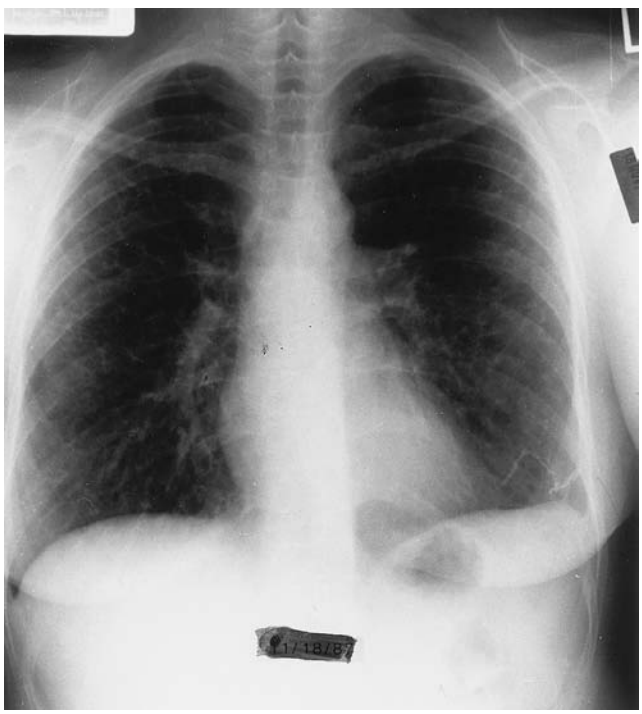


Figure 61-9 Follow-up chest radiograph in a 22-year-old woman obtained 4 months after the initial film shown in Figure 61-6. After an open lung biopsy performed on the left, she was told to stop smoking and treated with prednisone. The chest radiograph shows marked clearing of the ill-defined nodules and preservation of lung volumes.

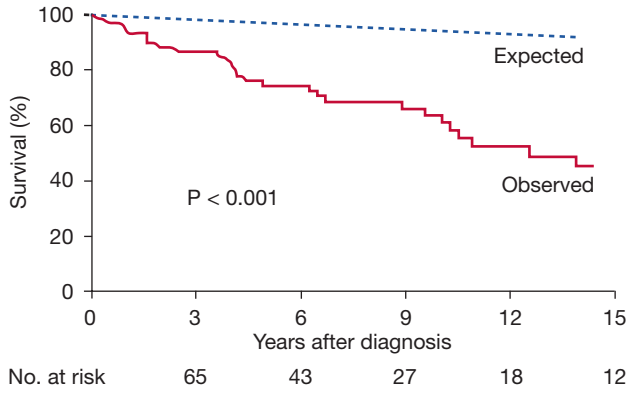


Figure 61-10 Kaplan–Meier analysis of expected and observed survival among 102 adults (40 men and 62 women) with pulmonary Langerhans' cell histiocytosis. The expected survival was defined as that for age- and sex-matched members of the general US population. The median follow-up period after the diagnosis of pulmonary Langerhans' cell histiocytosis was 4 years (range, 0–23). There were 33 deaths, 15 of which were attributable to respiratory failure. Survival was significantly shorter than that expected for healthy persons of the same sex and calendar year of birth ($p < 0.001$). *(Reproduced with permission from Vassallo R, Ryu JH, Schroeder DR, et al. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med. 2002;346(7):484–490.)*

the costophrenic angle are more likely to remain stable or to improve than are patients with involvement of the costophrenic angle.

Although corticosteroids have historically been employed in patients with progressive disease, their efficacy in the treatment of pulmonary Langerhans' cell histiocytosis has not been proved. Cytotoxic therapy, which may be of value in the treatment of disseminated disease, has not shown to be effective in pulmonary Langerhans' cell histiocytosis.

Recently, cladribine (2-chlorodeoxyadenosine), an agent cytotoxic for lymphocytes and monocytes, has been reported to have some efficacy in patients with progressive pulmonary Langerhans' cell histiocytosis.[44,45] Cladribine has been used successfully alone or in combination with an alkylating cytostatic agent and corticosteroids in a small number of adult patients with a multisystem or aggressive multifocal form of Langerhans' cell histiocytosis.[46] A randomized controlled trial is needed to assess the effectiveness and tolerance of cladribine in a larger population of patients. Successful use of therapy for PH has been reported in patients with Langerhans' cell histiocytosis.[47,48]

Radiotherapy for symptomatic bone lesions may be palliative. Radiation is not useful in the treatment of the pulmonary manifestations. Lung transplantation has been successfully accomplished in a number of centers. It is a viable option for selected patients with end-stage disease or severe PH. Recurrence of pulmonary Langerhans' cell histiocytosis after lung transplantation has been reported, especially in patients who resumed smoking after the transplant.[49]

The rate of recurrence of pneumothoraces is high in the absence of interventions to prevent additional episodes. Pleurodesis may be needed in patients with recurrences.[50]

Figure 61-10 shows a Kaplan–Meier analysis of expected and observed survival among adults with pulmonary Langerhans' cell histiocytosis.

ACKNOWLEDGMENT

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CHAPTER 62

Pulmonary Lymphangioleiomyomatosis

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Joel Moss

Lymphangioleiomyomatosis (LAM) is a multisystem disorder, predominantly affecting women, which is characterized by cystic lung lesions, abdominal angiomyolipomas (AML) and lymphatic abnormalities, for example, lymphatic tumors, chylous effusions.[1–5] These pathologic features are caused by the proliferation of a neoplastic smooth muscle–like LAM cell that also has characteristics of melanocytes.[6] Inherited and sporadic forms of LAM have been described. Sporadic LAM is caused by somatic mutations in an unknown susceptible cell of the tuberous sclerosis complex (TSC) 2 (*TSC2*) gene.[7,8] LAM also occurs in TSC, an autosomal dominant disorder resulting from germline mutations in the *TSC1* or *TSC2* genes that is characterized by widespread hamartomas in several organs including the brain, heart, skin, kidney, eyes, lung, and liver, and occurs in 1 of 6000 live births.[9]

EPIDEMIOLOGY

Until the establishment of LAM registries,[1] LAM was considered to be a fatal disease of women of child-bearing age for which oophorectomy, antiestrogen therapy, and lung transplantation were the only therapeutic options.[10–13] LAM is now best defined as a chronic disease of post- and premenopausal women with a life expectancy spanning decades.[14] Sporadic LAM is an uncommon disease occurring in approximately 4.9/1,000,000 women.[15] Although the association of TSC and cystic lung disease has long been recognized,[11–13] little is known about the prevalence and the natural history of LAM in TSC (TSC-LAM). The prevalence of cystic lung disease in women with TSC was reported to range from 30% to 40%; in male patients, it has been estimated to be 13%.[16] Males with TSC tend to have milder, subclinical lung involvement.

CLINICAL PRESENTATION

Patients with LAM often present with a history of progressive dyspnea. Pneumothorax, another common presentation of LAM, is often recurrent, occurring in about 50% to 60% of patients.[1–4] The size of the lung cysts, as seen on high-resolution computed tomography (HRCT) scans (Fig. 62-1A), appears to parallel the incidence of pneumothorax; higher incidence of pneumothorax is seen in patients with larger cysts.[17] Other modes of presentation include chylothorax, abdominal lymphangioleiomyomas, chylous ascites, hemoptysis, chyluria, chyloptysis, and hemorrhage caused by renal AML (Table 62-1).[1,5,18] Lymphatic involvement in LAM occurs in the posterior mediastinum, retroperitoneal and pelvic areas and includes lymphadenopathy, chylous effusions, and lymphangioleiomyomas.[5,18] AML are benign tumors, usually localized in the kidneys and found in approximately 90% of patients with TSC-LAM and 30% of those with sporadic LAM (Table 62-1).[1,5,18] The physical examination of LAM patients may disclose wheezing, pleural effusions, ascites, or intra-abdominal masses. In patients with TSC, typical skin lesions or signs of brain involvement may be evident.[9]

PATHOLOGY

Gross examination of lung sections shows cysts ranging in size from 0.2 to 2 cm.[6,19] Microscopically, cysts characterize lung lesions and proliferation of LAM cells in the walls of cysts and along blood vessels, lymphatics, and bronchioles (Fig. 62-1B1,B2), causing airways narrowing, vascular wall thickening, lymphatic disruption, and venous occlusion are observed.[6,19] Focal hemosiderosis may be present. Often LAM cells grow in a haphazard, disorderly fashion.[6,19] Two types of LAM cells have been described. Small, spindle-shaped cells predominate in the center of the lung nodules; epithelioid cells with large cytoplasm predominate at the periphery.[6,19] Both cell types react with antibodies against smooth muscle–cell antigens (e.g., smooth muscle α-actin, vimentin, desmin). The epithelioid cells also react with human melanin black antibody (HMB-45), a monoclonal antibody that recognizes gp100, a premelanosomal protein encoded by the *Pmel17* gene (Fig. 62-1B2, inset).[6,19] Spindle-shaped LAM cells react with proliferating cell nuclear antigen, indicating that these cells are more proliferative.[6] Receptors for estrogen, progesterone, insulin-like growth factors, angiotensin II, hyaluronic acid (CD44), chemokines, and erythropoietin have been identified in LAM cells.[20–27]

AML are highly vascular tumors comprising smooth muscle–like cells, immature, poorly differentiated blood vessels, and fatty tissue (Fig. 62-1D).[6,19] Tumors vary in size from 1 mm to more than 15 cm in diameter.[18,19] Smooth muscle–like cells found in AML have the same immunocytochemical properties as lung LAM cells (Fig. 62-1D).[6,19] All the major cell types in AML (vascular, fat, smooth muscle) may have mutations in the TSC genes.[7,8] The blood supply of AML originates from the renal arteries or aberrant vessels and may completely disrupt normal kidney architecture.[18,19] Hilar, mediastinal, and retroperitoneal lymphadenopathy may be seen.[18,19] The thoracic duct may be thickened and dilated.[19] Lymphangioleiomyomas consist of encapsulated lymphatic masses of varying sizes comprising chyle-filled cysts, with infiltration of LAM cells, displaying the immunoreactivity profile of LAM lung cells, arranged in fascicular, trabecular or papillary patterns and associated with slit-like vascular channels (Fig. 62-1F).[6,19]

PATHOGENESIS

Sporadic LAM is caused by proliferation of neoplastic LAM cells that have mutations or deletions in the *TSC2* (16p13) gene.[7,8] Consistent with Knudson's "two-hit" hypothesis of tumor development,[28] loss of heterozygosity of *TSC2* has been reported in LAM cells isolated from lung, blood, chyle, urine, and AML from both sporadic LAM and TSC-LAM patients.[8,29–31] LAM cells having identical mutations were identified in AML and lungs of the same patient.[8,31] LAM cells from patients receiving lung transplantation have been detected in the donor lung, suggesting migration from other sites, such as the kidney or lymphatic system, to the lungs.[32,33] The metastatic properties of LAM cells were also demonstrated by the presence of LAM cells in blood, urine, expectorated chyle and pleural, or abdominal chylous fluid of LAM patients.[29,30] LAM cell clusters, consisting of LAM cell aggregates covered by lymphatic endothelial cells, which have been proposed to originate from lung LAM lesions, have also been identified in chylous fluid.[34] Potential sources of lung LAM cells include AML, the lymphatic system, and the uterus,[35] in which case they may originate from abnormal leiomyoma.

A role of estrogens in the pathogenesis of LAM has been suggested by its predominance in premenopausal women, worsening of lung disease during pregnancy or following the administration of estrogens[36,37] and the presence of estrogen and progesterone receptors in lung and angiomyolipoma LAM cells.[20–22] Estrogens promote the proliferation of TSC-null rat ELT3 leiomyoma–derived cells

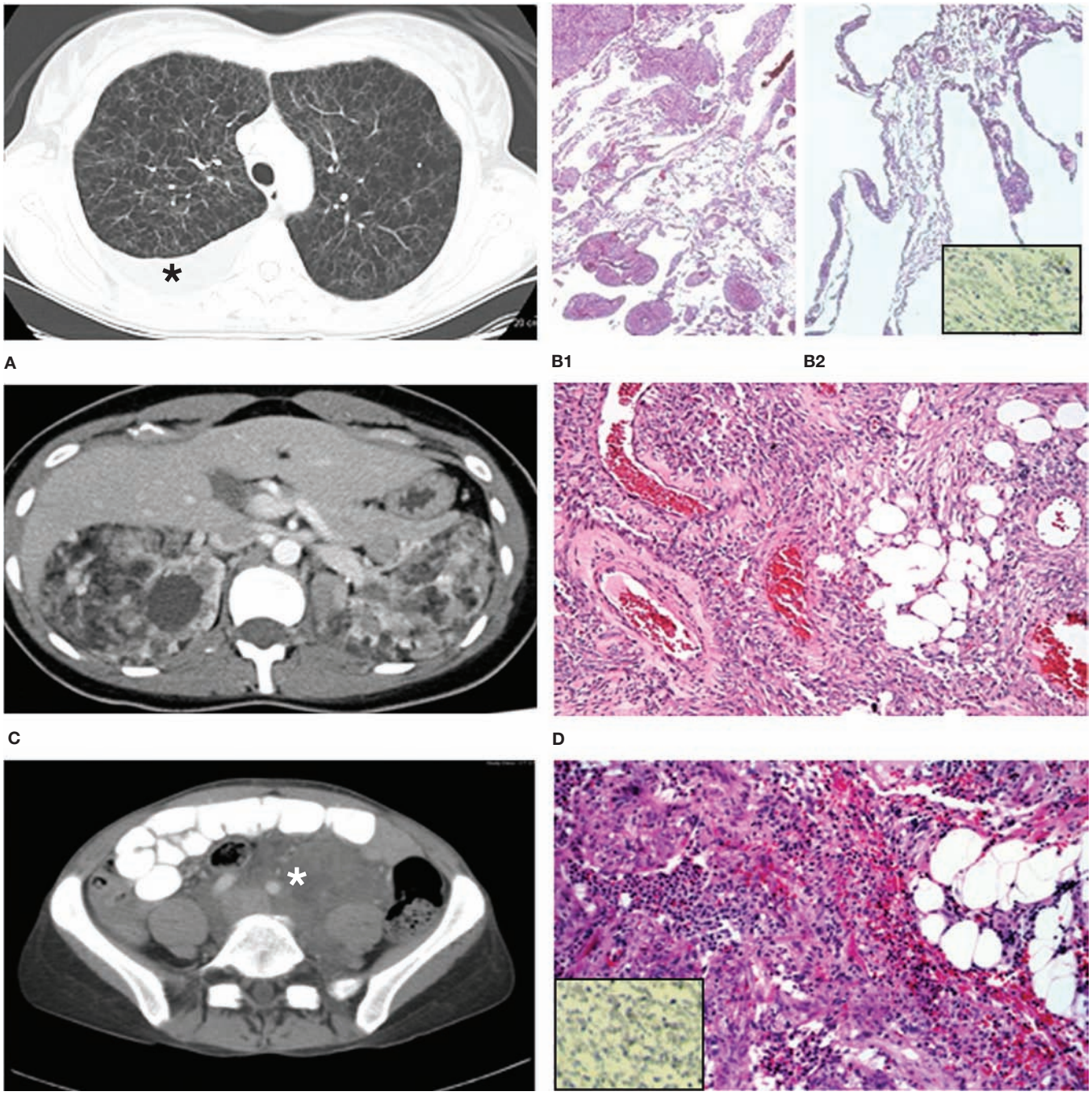

Figure 62-1 Computed tomography scans showing pulmonary and extrapulmonary images of patients with LAM, and the corresponding histopathologic findings. **A.** Multiple thin-walled cysts scattered throughout the lungs that have completely replaced the normal lung parenchyma. The *black asterisk* indicates the presence of a right pleural effusion. **B1 and B2.** Histopathology of the lung showing characteristic nodular smooth muscle cell–like infiltrates and cystic lesions. Inset image on **B2** shows immunocytochemistry of lung tissue showing reactivity with monoclonal antibody HMB45. **C.** Bilateral angiomyolipomas in a patient with TSC-LAM. The fatty, low-density component is clearly visualized. **D.** Histopathology of AML showing smooth muscle cell–like infiltrates, fatty tissue, and poorly differentiated vascular structures. **E.** Large, fluid-filled lymphangioleiomyoma (*white asterisk*) surrounding vascular structures. **F.** Histologic appearance of a lymphangioleiomyoma showing smooth muscle–like cells arranged in fascicular, trabecular or papillary patterns. Inset image on **F** shows immunocytochemistry of lymphangioleiomyoma tissue showing reactivity with monoclonal antibody HMB45.

in vitro, and the growth of subcutaneous tumors in a nude mouse xenograph system.[38] Estrogens stimulate the growth of human angiomyolipoma $TSC2^{-/-}$ cells, increase the survival and metastatic properties of $TSC2^{-/-}$ ELT3 cells in mice, and enhance matrix metalloproteinase (MMP)-2 activity of LAM lung-derived cells, thereby promoting cell invasiveness.[39–41]

The mechanism by which interstitial LAM cell proliferation causes lung cyst formation is unknown.[42] It has been proposed that compression of the airways by LAM cells leads to distention of the terminal airspaces and cyst formation.[6,19] It has also been proposed that degradation of lung elastic fibers is a major cause of the cystic lesions.[42] Matrix metalloproteinases, which play a role in

TABLE 62-1 Clinical and Physiologic Features of Patients with Sporadic LAM and TSC-LAM

Demographics	TSC-LAM	Sporadic LAM
Number of patients	34	196
Age of LAM diagnosis	39.0 ± 1.6	41.4 ± 0.7
Signs and symptoms		
Dyspnea	70.6%	73.5%
Pneumothorax	47.1%	56.9%
Wheezing	58.8%	44.4%
Cough	26.5%	31.6%
Hemoptysis	20.6%	32.1%
Pleural effusions	5.9%	23.5%
Lung function		
Airflow obstruction	37.5%	60.8%
Low diffusion capacity	38.2%	60.3%
Normal spirometry	53.1%	30.7%
Extra-pulmonary LAM		
Number of patients	67	256
Renal angiomyolipoma	32%	93%
Hepatic angiomyolipomas	2%	33%
Lymphangioleiomyomas	6%	29%
Ascites	6%	10%

TSC-LAM, Lymphangioleiomyomatosis associated with Tuberous Sclerosis Complex.
Source: Data from Ryu JH, Moss J, Beck GJ, et al. The NHLBI Lymphangioleiomyomatosis Registry, Characteristics of 230 Patients at Enrollment. Am J Respir Crit Care Med. 2006;173:105; Avila NA, Dwyer AJ, Rabel A, et al. Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis, comparison of CT features. Radiology. 2007;242:277.

TABLE 62-2 Cardiopulmonary Exercise Abnormalities in LAM

Decreased $\dot{V}_{O_{2max}}$
Decreased work rate
Decreased oxygen pulse
Decreased breathing reserve
Decreased Pa_{O_2}
Increased $\dot{V}_E/\dot{V}_{CO_2}$ at AT
Increased $\dot{V}_D/\dot{V}_T$
Increased A-a/O_2 gradient

[a] $\dot{V}_{O_{2max}}$, peak oxygen uptake; Pa_{O_2}, arterial oxygen tension; $\dot{V}_E/\dot{V}_{CO_2}$, ventilatory equivalent for CO_2; AT, anaerobic threshold; $\dot{V}_D/\dot{V}_T$, dead space ventilation ratio; A-a/O_2, alveolar arterial oxygen tension difference.
Source: Data from Crausman RS, Jennings CA, Mortensen RL, et al. Lymphangioleiomyomatosis: the pathophysiology of diminished exercise capacity. Am J Respir Crit Care Med. 1996;153:1368; Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al. Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2003;168:1427.

lung remodeling and lymphangiogenesis, are associated with LAM lesions.[43] LAM nodules contain MMP2, MMP9, MMP1, and MMP activators (MT1-MMP), and their inhibitors (TIMPs).[44,45] Levels of TIMP-3, which inhibits some MMP, were reportedly reduced in LAM lesions.[45,46] Compared with normal subjects, serum levels of MMP-9 were higher in patients with LAM,[47] suggesting that an imbalance between MMP and their inhibitors may contribute to lung destruction.[48] Growth of TSC2-null lesions was associated with an increase in MMP activity and vascular endothelium growth factor D (VEGF-D).[48] Elastic fibers were demonstrated in alveoli of mice with TSC2-null lesions[48] and human lung LAM nodules show disrupted elastic fibers. The presence of lymphatic spaces in the LAM nodules and strong immunoreactivity towards vascular endothelium growth factor C (VEGF-C), VEGF-D, vascular endothelium growth factor receptor (VEGFR) 3, and podoplanin, markers of lymphatic endothelial cells, led to the hypothesis that disorganized lymphangiogenesis enhances metalloproteinase expression and lung remodeling.[48] Some combination of these mechanisms may be the best explanation for the pathogenesis of cystic lung destruction.

PULMONARY PHYSIOLOGY

Airflow obstruction was seen in approximately 61% of patients with sporadic LAM[1,49]; normal spirometry was present in about 31%. The remaining patients had restrictive disease. By comparison, normal lung function was observed in 53% of patients with TSC-LAM (Table 62-1).[1] Increased gas trapping may be also present. The cause of airflow limitation in LAM has been attributed to alveolar destruction,[50] but a study of pulmonary mechanics showed that lung elastic recoil was not significantly reduced.[51] Instead, upstream airway resistance was increased, suggesting increased airways resistance as the major cause of airflow obstruction.[51,52] Reduced diffusing capacity (D_{LCO}) occurred in approximately 60% of sporadic LAM patients.[1] Most patients have both decreased FEV_1 and D_{LCO}, but some patients have only a reduced D_{LCO}.[49] Gas exchange, especially during exercise, is often abnormal (Table 62-2).[52,53] An abnormal ventilatory response with excessive minute ventilation and reduced breathing reserve are seen during exercise. Baseline and exercise dead space to tidal volume ratio and alveolar–arterial oxygen difference (A-a/O_2) are increased both at rest and during exercise.[52] The primary determinants of exercise limitation in LAM are airflow limitation, decreased breathing reserve, dynamic hyperinflation,[52–54] and limitation of oxygen transfer due to loss of alveolar capillary surface area. The latter exerts a significant effect upon exercise performance, because the increase in physiologic dead space produces excessive ventilation. The interdependence between airflow obstruction, which produces a decrease in the ventilatory reserve, and cystic lung destruction, which affects gas exchange during exercise, leads to severe impairment in exercise performance.[52,53] Pulmonary hypertension may also contribute to reduce oxygen transfer during exercise.[55]

RADIOLOGY

Chest radiographic findings in LAM range from being normal, to showing a reticular or nodular irregular shadowing or, in advanced stages, severe cystic changes. Computed tomography (CT) demonstrates diffuse, well-defined, round thin-walled cysts scattered throughout the lungs. Cysts vary in size from a few millimeters to up to 2 cm (Fig. 62-1A).[56,57] Additional findings are pleural effusions and lung opacities caused by chyle (Fig. 62-1A). Correlation between the extent of the cystic parenchymal replacement, as measured by high-resolution chest CT (HRCT), and the severity of the disease, as determined by spirometry, D_{LCO} or exercise performance, has been reported.[53,57–61] Computer analysis of HRCT can quantify the extent of cystic changes and detect abnormalities in areas adjacent to the cysts that may appear to be radiographically normal[60,61]; these emphysematous changes were also seen by histopathology.[61]

Abdominal CT and ultrasonography studies may show renal AML, abdominal lymphadenopathy, lymphangioleiomyoma, ascites, and dilatation of the thoracic duct.[18] AML occur predominantly in the kidney and liver and are recognized by their characteristic appearance consisting of areas of fatty density, intermixed with more dense

areas and normal-appearing renal parenchyma (see Fig. 62-1C).[18] Atypical AML lacking adipose tissue have a predominance of epithelioid LAM cells and radiologically may mimic renal cell carcinoma. Lymphangioleiomyomas appear as well-circumscribed masses of variable dimensions, comprising a wall and a central fluid-rich region (Fig. 62-1E).[18] Diurnal variation in size of lymphangioleiomyomas has been demonstrated by CT and ultrasound, which may help differentiating them from malignant tumors and explain worsening of symptoms during day time.[62,63]

DIAGNOSIS

The characteristic CT scan appearance and its histologic features on open or thoracoscopic lung biopsy can diagnose LAM. Transbronchial lung biopsy may yield adequate sample size for pathologic diagnosis.[64,65] The diagnosis of LAM should be strongly suspected in any woman who presents with progressive dyspnea, recurrent pneumothorax, or a chylous pleural effusion.[1–5] The differential diagnosis includes pulmonary emphysema, asthma, chronic extrinsic allergic alveolitis, Langerhans cell histiocytosis, sarcoidosis, Birt–Hogg–Dubé syndrome, and follicular bronchiolitis. Definite LAM may be diagnosed in the presence of a characteristic HRCT and a lung biopsy showing the pathologic features of LAM or a characteristic lung HRCT and (1) angiomyolipoma, (2) chylous effusion, (3) lymphangioleiomyoma or lymphadenopathy, and (4) TSC.[66] A diagnosis of probable LAM may be established in the presence of a characteristic HRCT and a compatible clinical history or a characteristic HRCT and angiomyolipoma or chylous effusions. Possible LAM may be diagnosed in the presence of a characteristic or compatible HRCT.[66]

Serum VEGF-D, a lymphangiogenic factor, is increased in the serum of patients with LAM compared to normal individuals and is a measure of lymphatic involvement in LAM.[67–70] In the appropriate clinical and radiologic setting, a VEGF-D serum level equal or greater than 800 pg/mL is unlikely to be found in other cystic lung diseases and appears to be diagnostic of LAM.[69,70]

PROGNOSIS

The clinical course of LAM is highly variable. The estimated median transplant-free survival time for LAM patients in the United States is 29 years from symptom onset and 23 years from diagnosis.[71] The estimated 10-year transplant-free survival is 86%. Age appears also to affect survival, as rapid decline in lung function is more common in younger premenopausal patients.[49,72] Patients whose lung tissue shows predominance of cystic lesions tend to have worse lung function and prognosis than those with more LAM cell infiltrates.[73]

The severity of lung involvement in LAM may be assessed in patients who had a lung biopsy using the LAM Histology Score (LHS), which grades the extent of replacement of normal lung tissue by cystic lesions and LAM cell infiltrates.[74] The amount of tissue involvement is graded semiquantitatively based on percent of lung tissue involved: LHS-1, <25%; LHS-2, 25% to 50%; and LHS-3, >50% lung tissue. LHS-2 and LHS-3 scores and the presence of hemosiderin-laden macrophages are associated with decreased survival.[74] Patients with more cystic disease are likely to have lower FEV_1 and D_{LCO}, lower peak oxygen uptake ($\dot{V}_{O_{2max}}$), and more exercise-induced hypoxemia.[53,75]

The severity of lung disease in LAM can be also graded by HRCT. HRCT findings correlate with lung function tests, gas exchange, and exercise performance.[53,56–59] HRCT computer analysis can quantify the percentage of lung volume affected by cysts and evaluate the texture of areas not involved with cysts.[60,61] Using these methods, percentage of lung volume occupied by cysts was found to correlate with FEV_1, residual volume, and D_{LCO}.[60,61]

The simplest method of assessing the severity of lung disease in LAM is pulmonary function testing.[1,49] Most patients have airflow obstruction and impaired gas exchange. Early in the disease, a significant number of patients may have normal spirometry or only mild airflow obstruction, along with a marked decrease in diffusion capacity. In these patients, the severity of disease is best graded by tests of gas exchange such as D_{LCO}, arterial blood gases, A-a/O_2 gradient, cardiopulmonary exercise testing, and 6-minute walk test.[52,53,59] Exercise-induced hypoxemia may occur in the presence of near-normal D_{LCO} and FEV_1.[53] Correlation between $\dot{V}_{O_{2max}}$ and LHS scores, and between CT severity grade and A-a/O_2 gradient, dead space/tidal volume ratio, and $\dot{V}_{O_{2max}}$ have been demonstrated.[53,58–61] Rates of functional decline over time may help in defining the course of disease, that is, whether it is rapidly or slowly progressive. Sequential lung function testing every 3 to 6 months is warranted to assess the progression of disease.[49,72] A positive response to bronchodilators occurs in 25% to 30% of LAM patients.[75,76] Patients who respond to bronchodilators tend to have a predominantly cellular pattern of LAM lung lesions and greater rates of decline in FEV_1.[75] A low initial D_{LCO} was also reported to be a predictor of accelerated loss of FEV_1.[77]

OTHER PROGNOSTIC INDICATORS

There is some evidence that older age and/or menopause are associated with slower disease progression.[49,72] Patients who present with exertional dyspnea and hemoptysis tend to have more severe disease, greater rates of progression of disease, and lower survival than those with a history of pneumothorax.[78] This may be due to either a delay in diagnosis or an insidious course in those who present with dyspnea. Lymphatic involvement, for example, chylous effusions, lymphadenopathy, lymphangioleiomyomas, may be associated with a more severe form of disease.[68,79,80] Correlation between LHS and the expression of VEGF-C has been reported.[80] Serum levels of VEGF-D are especially elevated in patients with lymphatic abnormalities and show a correlation with D_{LCO} and HRCT scan grading of severity of lung disease.[68,79,80] Measurement of serum VEGF-D may be of value in establishing a diagnosis and grading the severity of disease and response to therapy.

TREATMENT

Treatment includes general principles of management and specific therapeutic interventions.

GENERAL PRINCIPLES OF MANAGEMENT

LAM patients should be told about the chronic nature of LAM and be advised to lead, as much as possible, a normal life. If there is an excess body mass, they should be encouraged to lose weight, engage in physical activities, and exercise regularly. The limits of exercise should be dictated only by the severity of their lung disease. Sports involving physical contact and martial arts should be avoided because of potentially causing bleeding from AML. Patients should be advised to continue with normal activities, and be allowed to travel by land or air except to high altitude locations, depending on disease severity. The risk of life-threatening pneumothorax associated with air travel is minor. However, if patients should experience sudden onset of breathlessness or chest pain, pneumothorax should be excluded prior to travelling. An arterial blood gas may help to determine whether a patient may travel by air without supplemental oxygen. A 6-minute walk test or a cardiopulmonary exercise test to uncover exercise-induced hypoxemia and determine the need for supplemental oxygen is recommended. Patients who desaturate during exercise should be given supplemental oxygen at flow rates adjusted to sustain oxygen saturation above 88% to 90%. Patients should be advised against using estrogen-containing contraceptives and avoid phytoestrogen-rich food.

SPECIFIC THERAPIES

Specific therapies include antiestrogen therapy, mTOR inhibitors, matrix metalloproteinase inhibitors, statins, and inhibitors of autophagy.

Antiestrogen Therapy

Oophorectomy, progesterone, and gonadotrophin-releasing hormone (GnRH) analogs have been employed in the treatment of LAM. Case reports and uncontrolled studies claimed a beneficial effect of antiestrogen therapies.[81] Taylor et al.[13] however, found no benefit from oophorectomy and improvement in dyspnea only in 2 of 19 patients treated with progesterone. A reduced rate of decline in FEV_1 and D_{LCO} was reported in premenopausal patients treated with progesterone.[72] However, when patients with short-term follow-up were excluded from the analysis, the effect of progesterone was not significant.[72] In a retrospective study, no difference was observed in disease progression between patients treated with or not treated with progesterone.[49] Data from studies that assessed the effect of GnRH analogs have also been inconclusive.[82,83] Experimental data however, appear to provide a rational for hormonal manipulations in the treatment of LAM.[38–41] Further studies aimed at suppressing estrogen secretion with aromatase inhibitors (i.e., letrozole) are undergoing a clinical trial (clinicaltrials.gov) in postmenopausal women in whom the main source of estrogens are the adrenal glands (Frank X. McCormack P.I. ClinicalTrials.gov Identifier:NCT01353209).

Mammalian Target of Rapamycin (mTOR) Inhibitors

Since the discovery that TSC genes *TSC1* and *TSC2* were involved in the pathogenesis of LAM, major advances were made in treatment of LAM. *TSC1* and *TSC2* are tumor suppressor genes that encode respectively, hamartin and tuberin (Fig. 62-2).[84–87] These proteins form a cytosolic complex that regulates the intracellular serine/threonine kinase mTOR, which integrates growth factor, energy, and stress signaling, thereby regulating cell growth, proliferation, and survival.[84,85] Two different complexes involving mTOR, mTORC1, and mTORC2, have been identified.[85–87] Tuberin, which exists in a complex with hamartin, is a GTPase-activating protein for the guanine nucleotide–binding protein Rheb (Ras homolog enriched in brain), promoting the formation of inactive Rheb-GDP from active Rheb-GTP.[85] Inhibition or absence of tuberin, as occurs with *TSC2* gene mutations, results in accumulation of active Rheb-GTP, leading to stimulation of mTORC1, which results in phosphorylation of S6 kinase and eukaryotic initiation factor 4E-binding protein, and increased translation and cell growth.[85]

Sirolimus is an immunosuppressant drug that forms a complex with FK506-binding protein-12 and inhibits mTORC1.[85,88] Sirolimus provides only partial inhibition of mTORC1 and has some inhibitory effect on mTORC2 signaling (Fig. 62-2B).[87,89,90] In experimental models, sirolimus was shown to decrease tumor size in animals with a germline mutation of *TSC2*.[91] Treatment with a sirolimus analog decreased the severity of renal cystadenomas and liver hemangiomas in $TSC2^{+/-}$ mice, and decreased tumor growth and improved survival of nude mice with $TSC2^{+/-}$ tumors.[92] In human subjects with TSC or LAM who had AML, treatment with sirolimus decreased tumor size by half after 1 year of therapy.[93] Following withdrawal of sirolimus, the angiolipomas partially regained their size. Subsequent studies have confirmed these findings.[94–96] The most recent study found that 42% of 79 patients with AML, treated with everolimus, responded with a 50% reduction in tumor size after 24 weeks of therapy.[96] Sirolimus also appears to be effective in reducing the size of giant-cell astrocytomas in patients with TSC.[97,98]

The effect of sirolimus on pulmonary function was examined in 89 patients with LAM (MILES trial). Forty-six patients were treated with sirolimus and 43 with placebo for 12 months and followed for an additional year after discontinuation of therapy.[99] Compared to the placebo group, the sirolimus group had improvements

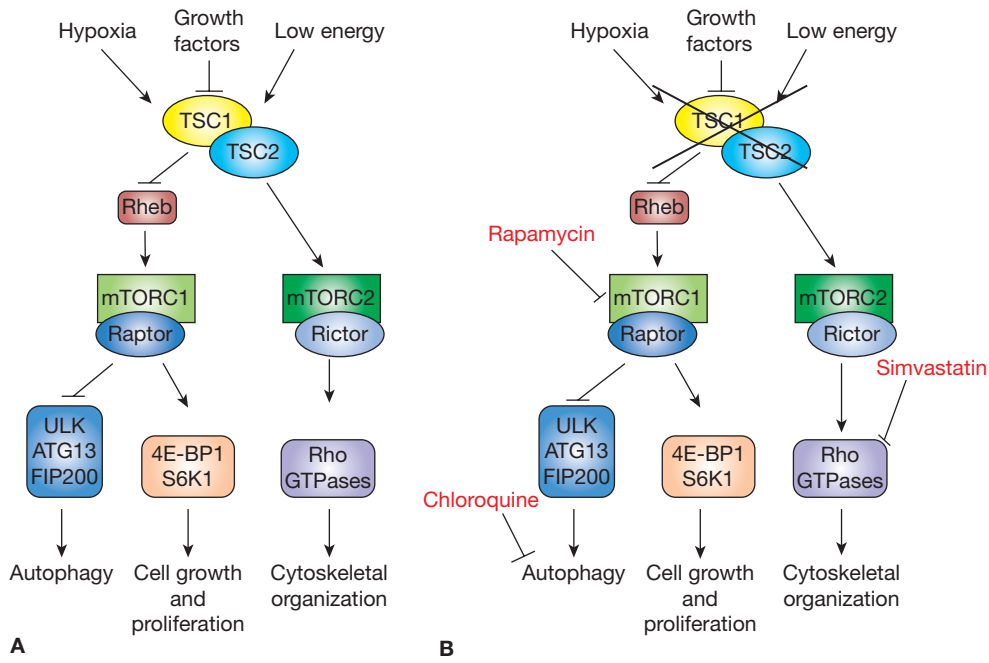

Figure 62-2 Simplified scheme of the mTOR signaling pathways. **A.** TSC1/2 integrates multiple signals, such as growth factors, energy state and hypoxia, to control cell growth and proliferation. Growth factors stimulate several signaling pathways leading to phosphorylation of TSC2 and its inactivation. TSC1/2 negatively regulates mTORC1 through its actions on Rheb, while it positively regulates mTORC2. Activation of mTORC1 leads to cell growth and proliferation and inhibition of autophagy. mTORC2 regulates the actin cytoskeleton through Rho GTPases, which affects cell migration and morphogenesis. **B.** mTORC1 is acutely inhibited by sirolimus (rapamycin) treatment. mTORC2 is sensitive to prolonged rapamycin treatment, which may affect mTORC2 assembly and function. Simvastatin inhibits Rho GTPases, whereas chloroquine inhibits autophagy by blocking fusion of autophagosomes with lysosomes. mTOR, mammalian target of rapamycin; Rheb GAP, Ras homolog enriched in brain GTPase-activating protein; S6K1, S6 kinase 1; 4E-BP1, factor 4E binding protein 1; raptor, regulatory associated protein of mTOR; rictor, rapamycin-insensitive companion of mTOR; ULK 1, UNC-51–like kinase 1; ATG13, autophagy-related protein 13; FIP200, focal adhesion kinase family interacting protein of 200 kDa.

from baseline of FVC, FEV_1, quality of life, and functional performance. After discontinuation of sirolimus, decline of lung function resumed and paralleled that of the placebo group.[99] In another study, 19 patients with either rapidly progressive lung disease or lymphangioleiomyomas and chylous effusions were treated with sirolimus for approximately 2.5 years. Instead of the expected decrease in lung function, an increase in FEV_1 and D_{LCO} was observed.[100] Nine patients experienced complete resolution of their chylous effusions and abdominal lymphangioleiomyomas.[100]

Based on the findings in the MILES trial we recommend that sirolimus be given to patients in whom lung function is declining rapidly. We also recommend sirolimus therapy for LAM patients with symptomatic lymphangioleiomyomas and chylous pleural effusions or ascites.[100,101] The role of sirolimus in patients with normal or stable lung function or very slow rates of decline is unclear. Currently the starting dose of sirolimus is 2 mg/d. Sirolimus serum levels must be monitored and dosage adjusted to attain serum trough levels between 5 and 15 ng/mm, a range thought to be therapeutic for patients with renal transplants.[99] Adverse events associated with sirolimus therapy include oral mucosa ulcers, hypertension, hyperlipidemia, proteinuria, increased serum creatinine, infections, acne, amenorrhea, and sirolimus-related interstitial pneumonitis. Close patient monitoring is recommended. Given the limited experience with sirolimus in the treatment of LAM, it is not known whether treatment must be continued for life or whether resistance to sirolimus may eventually develop.

Matrix Metalloproteinase Inhibitors

Doxycycline is a MMP inhibitor that affects MMP production in TSC-null ELT3 cells,[102] and inhibits MMP2 secretion by TSC-null mouse embryonic and human LAM cells.[103] A potential role of doxycycline in the treatment of LAM was suggested by a report of one patient with LAM in whom treatment with doxycycline decreased urinary MMP levels and improved lung function.[104] A decrease in serum and urine levels of MMP-9 and MMP-2 in 34 patients treated with doxycycline has been reported.[105] A controlled study showed that it is unlikely that doxycycline has a useful effect in LAM.[105A]

Statins

There is evidence that both mTORC1 and mTORC2 are necessary for tuberin-dependent cell proliferation and survival.[106] In the absence of tuberin, RhoA activity is increased, resulting in increased cell survival.[106] Since sirolimus primarily suppresses mTORC1 signaling, there is a rational for new therapies targeting mTORC2 signaling. Statins inhibit both sirolimus-sensitive and sirolimus-insensitive mechanisms of TSC-null cell growth by inhibiting RhoA GTPase activity.[107] In one study, atorvastatin was shown to inhibit the growth of *TSC2*$^{-/-}$ ELT-3 cells and mouse embryonic fibroblasts while decreasing Rheb-GTPase activity and function.[107] A synergistic effect of simvastatin and sirolimus in inhibiting proliferation of TSC2-null cells and TSC-null tumor growth has been described.[106] This effect appears to be specific for simvastatin; in a mouse model of TSC, atorvastatin failed to reduce the size of liver and renal tumors.[108] In a mouse model of LAM, simvastatin prevented alveolar space enlargement and, combined with sirolimus, blocked MMP upregulation, reducing TSC2-null lesions and alveolar destruction.[48] However, in a retrospective study, it was found that the rate of decline in lung diffusion for patients treated for hypercholesterolemia with statins was greater than that of their matched off-statin therapy controls.[109]

Inhibitors of Autophagy

Autophagy is a mechanism by which cells maintain energy homeostasis and recycle proteins and organelles.[110] Autophagosomes are formed that encapsulate damaged organelles or cellular debris and fuse with lysosomes to degrade their contents.[111] Autophagy is controlled by signaling from mTOR, and the human homolog of ATG1 (ULK1) kinase complex, comprising ULK1, Atg13, and Atg17; mTORC1 is a major regulator of autophagy.[111–113] Under conditions of cellular stress, mTORC1 is downregulated, triggering autophagy. mTOR inhibitors such as sirolimus stimulate autophagy by causing phosphorylation of Atg13, which interacts with ULK1 and inhibits the formation of autophagosomes which increases autophagy and, within limits, increases cell survival.[110–113] Since LAM cells have been shown to have low levels of autophagy, blockade of mTOR signaling with sirolimus may result in increased survival of LAM cells.[114,115] Hydroxychloroquine and its analogs inhibit the growth of cancer cells and induce cell death by blocking autophagy.[113–115] The combination of mTORC1 inhibition with sirolimus and inhibition of autophagy with hydroxychloroquine was found to be more effective than either treatment alone in inhibiting the survival of TSC2-null cells and the growth of TSC2-null xenograph tumors, as well as the spontaneous development of renal tumors in *TSC2*$^{+/-}$ mice.[115] Inhibition of autophagy with hydroxychloroquine could potentially complement the effect of sirolimus in the treatment of LAM. These observations provide a rational for testing the effect of chloroquine and sirolimus in LAM patients. A current study (SAIL trial) testing the effects of sirolimus and hydroxychloroquine is ongoing (Elizabeth Henske P.I.; ClinicalTrials.gov Identifier:NCT01687179).

TREATMENT OF COMPLICATIONS

Treatment of well recognized complications of LAM and special considerations are discussed below.

■ PNEUMOTHORAX

Small pneumothoraces may be treated conservatively by chest tube drainage. Because of the high rate of pneumothorax recurrence if air leak persists or the pneumothorax recurs, chemical or surgical pleurodesis by video-assisted thoracoscopy should be considered.[3,116] Chemical sclerosis, pleurectomy, mechanical abrasion, and talc poudrage are most effective.[116] Talc pleurodesis may result in fibrothorax that can complicate removal of the lung at the time of transplantation.[3,116] The risk of developing a pneumothorax during air travel appears to be small.[117]

■ CHYLOUS EFFUSIONS AND LYMPHANGIOLEIOMYOMAS

Chylous effusions and lymphangioleiomyomas may compromise respiratory function and cause abdominal pain, urinary frequency, obstipation, tenesmus, and peripheral edema. Abdominal symptoms may suggest malignancy.[63,118–120] Frequent drainage of chylous effusions may result in protein loss, lymphopenia, and weight loss.[100,121] Several treatments such as low fat diet, pleuro-peritoneal or peritoneal-venous shunts, have been employed but there is little experience with these therapeutic modalities in LAM.[122,123] The same is true of treatment with somatostatin and octreotide.[124,125] The finding that sirolimus is effective in decreasing the size of chylous effusions and lymphangioleiomyomas strongly suggests that instead of undertaking invasive procedures such as pleurodesis, symptomatic patients should be treated with sirolimus.[100,126]

■ ANGIOMYOLIPOMAS

AML occur primarily in the kidney, although other organs, for example, liver, may be involved.[127] Small AML, for example, less than 4 cm in diameter, are well tolerated and are associated with well-preserved renal function.[127] The principal complication of larger AML is bleeding. Embolization, rather than resection, is recommended to preserve kidney function.[128–130] Severe pain may be also an indication for selective embolization of the tumor. Prophylactic embolization may be undertaken in patients with large AML and no known episodes of bleeding but evidence favoring this approach is lacking. Indeed, embolization appears to be of little value in the long-term management of AML.[130] Since treatment with sirolimus reduces tumor size in about 44% to 50% of the patients, it may also prevent bleeding and

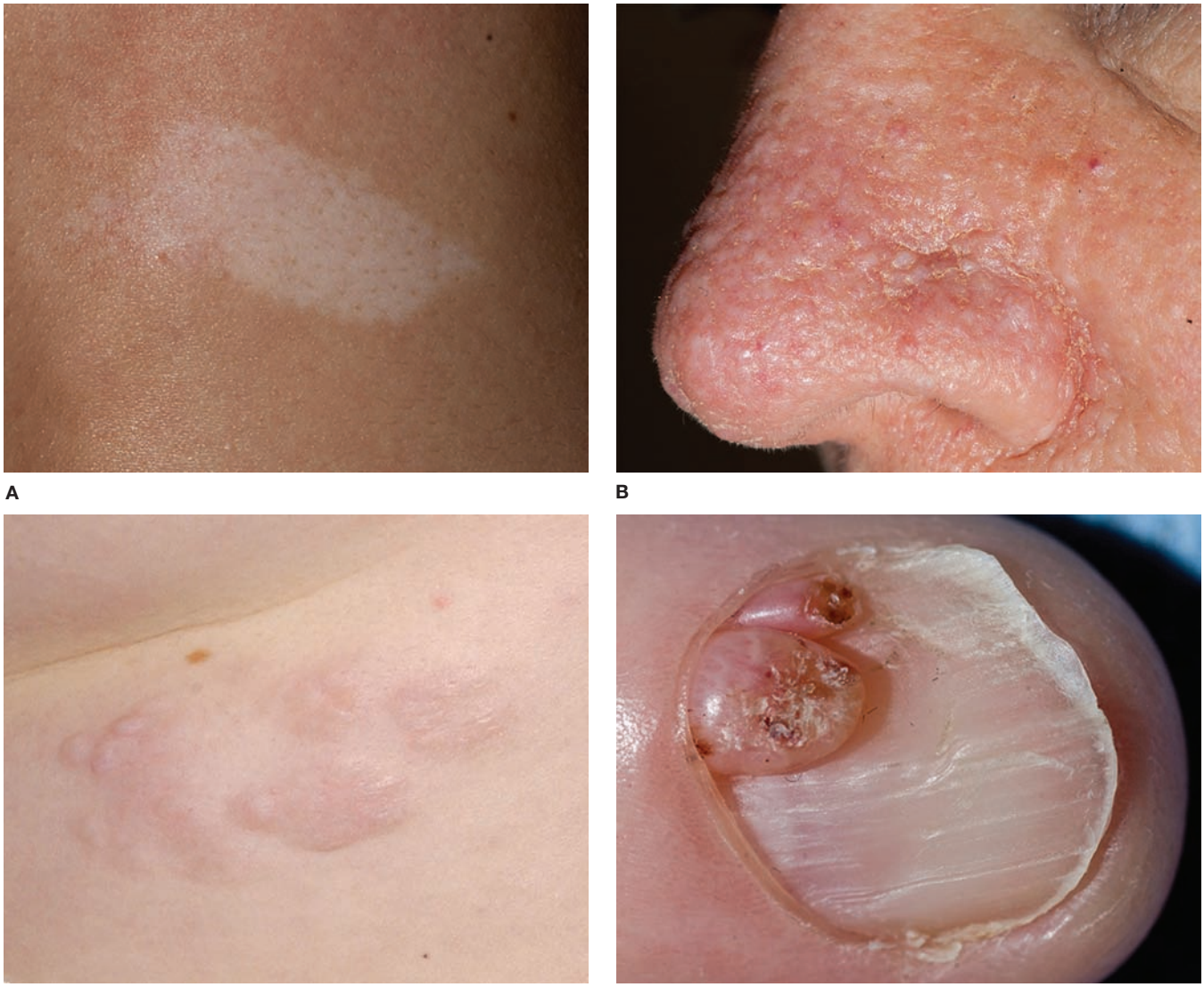

Figure 62-3 Skin manifestations of TSC in an adult women. **A.** Large hypomelanotic macule on the back. **B.** Multiple facial angiofibromas involving the nose and adjacent cheek. **C.** Shagreen patch on the lower back. **D.** Periungual fibroma near the fingernail.

the need for embolization or surgical intervention.[99–102] Accordingly, treatment with mTOR inhibitors is currently the initial approach for the treatment of large AML. Arterial embolization, which has a response rate similar to mTOR inhibitors, should be reserved for patients with acute bleeding or those who do not respond or do not tolerate sirolimus therapy.[93–95,130] Discontinuation of sirolimus therapy may result in return of the AML to its original a size.

■ PREGNANCY

Of 353 pregnancies recorded in the LAM registry, 66.9% resulted in live birth, 16.7% had spontaneous abortion and 15% had therapeutic abortion.[1] Twenty-two percent of those who had been pregnant experienced worsening of respiratory symptoms during pregnancy.[1] Patients who were diagnosed with LAM during pregnancy had more premature births, higher frequency of dyspnea, pneumothorax, and chylothorax than those diagnosed either before or after pregnancy.[131] These data, along with anecdotal reports of worsening symptoms during pregnancy,[132] raise the question whether LAM patients should be advised not to become pregnant. In patients with moderate to severe disease or those in whom lung function is declining rapidly, pregnancy should be discouraged. Instead, these patients should be treated with sirolimus. Patients with mild disease who wish to become pregnant should be told about the potential risks (e.g., pneumothorax, decline in lung function) and advised that with close medical and obstetrics monitoring they have a chance of having a normal pregnancy and delivering a normal child.

■ LUNG TRANSPLANTATION

Except in advance stages, dyspnea at rest is not a major feature of LAM. Exercise limitation and hypoxemia requiring supplemental oxygen are major factors affecting the ability of the patient to conduct activities of daily living. Consequently, patients with an FEV_1 less than 1 L and a D_{LCO} less than 30% predicted receiving supplemental oxygen might be comfortable at rest. In the series of Pechet et al.[133] preoperative FEV_1 and D_{LCO} were respectively, 20 ± 8 and 23 ± 9% predicted and there was resting hypoxemia prior to transplantation. The average 6-minute walk test distance was 250 m. The 5-year survival was 69%.[133–135] The European experience is similar to that of the USA.[136] Before transplantation is considered, lung function needs to be severely compromised because LAM patients with very low FEV_1 and D_{LCO} on supplemental oxygen may live for many years. We suggest that lung transplantation be considered when FEV_1

and D_{LCO} are less than 30% predicted, and the patient is on continuous supplemental oxygen and unable to carry out activities of daily living. Importantly, the patient should rate her quality of life as being poor and be certain that she wishes to undergo lung transplantation.

TUBEROUS SCLEROSIS COMPLEX

TSC is a multisystem autosomal-dominant disorder that affects men and women equally. Its frequency is 1 in 12,000 to 14,000 children under the age of 10, or 1 in 6000 births.[9] It is characterized by mental retardation, seizures, facial angiofibroma, periungual fibromas, Shagreen patches, cortical tubers, giant-cell astrocytomas, and cardiac rhabdomyomas (Fig. 62-3).[9] The association of TSC and cystic lung disease has long been reported in the literature,[137] but little is known about the natural history of LAM in the presence of TSC (TSC-LAM). Initially the prevalence of clinically significant LAM in TSC was thought to be relatively low, ranging from 0.6% to 2.3% of TSC patients.[137–140] However, subsequent studies showed that the prevalence of lung cysts in women with LAM ranges from 26% to 38%.[141–143] Lung cysts were demonstrated in only 13% of men with TSC.[16] If it is accepted that visualization of four or more cysts in the lungs of a TSC patient equates the presence of LAM, then the prevalence of LAM in males may be as high as 38% but the lung disease is mild.[144] The NHLBI LAM registry reported data from 34 TSC patients who were known to have LAM or were later confirmed to have LAM.[1] In a study comparing CT features of 67 patients with TSC-LAM and 256 patients with sporadic LAM,[145] severe disease was present in 25% of TSC-LAM patients versus 40% of sporadic LAM patients (Table 62-1). Renal AML occurred in 93% of TSC-LAM patients and in only 32% of sporadic LAM subjects. Lymphangioleiomyomas and chylous effusions were more common in sporadic LAM. Sclerotic bone lesions were very common in patients with TSC-LAM.[146]

Lung disease in TSC tends to be milder than in sporadic LAM, often comprising only a few cysts scattered throughout the lungs. These patients have subclinical disease and usually are diagnosed with LAM only because they have TSC. TSC patients who initially present with characteristic symptoms of pulmonary LAM may have more severe lung disease and a clinical course similar to patients with sporadic LAM.

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CHAPTER 63

Benign Metastasizing Leiomyoma

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Joel Moss

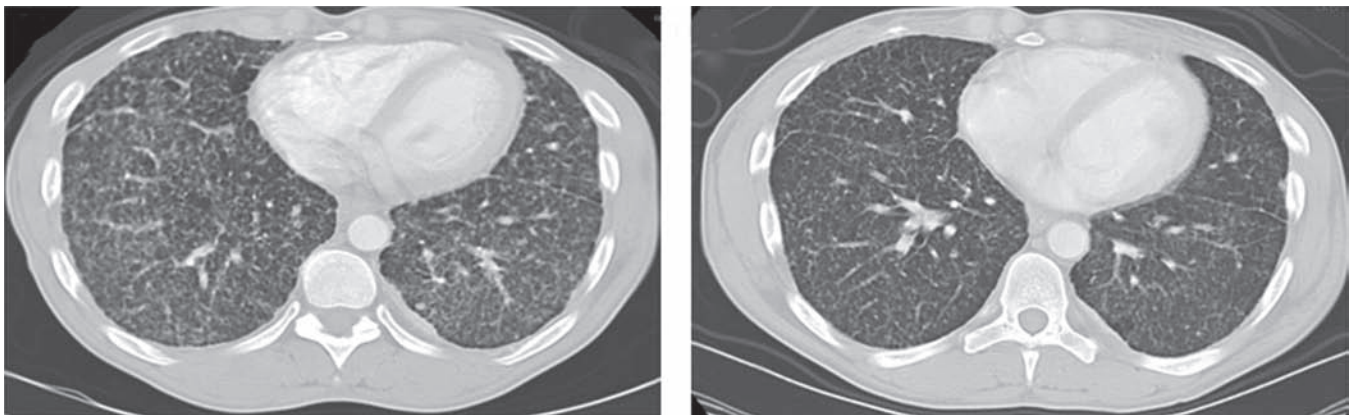
Benign metastasizing leiomyoma (BML) is a rare disease of women, which is characterized by noninvasive, well-circumscribed tumors composed of differentiated smooth muscle cells, localized to sites other than the uterus.[1–5] Lungs and lymph nodes[6] are the most common sites involved, but BMLs have also been identified in the mediastinum,[7,8] retroperitoneum,[9] vascular channels,[10] bone,[11] heart,[12] skeletal muscle,[13] and soft tissues.[14] Pulmonary BML has been associated primarily with uterine leiomyomas and has been mainly diagnosed in patients who have undergone uterine myomectomy or hysterectomy.[1,4]

The first report of BML, in 1939, described a 36-year-old woman who presented with dyspnea and wheezing. Chest X-rays showed multiple lung nodules. At autopsy, lymph nodes, uterus, and lungs showed nodules of smooth muscle cells with identical morphology[15] and the term "metastasizing fibroleiomyoma of the uterus" was adopted. This term was later abandoned and the name BML was proposed because of the metastatic behavior of this disease.

Pathologically, BML lung nodules resemble hamartomas (the most common benign lung tumor), low-grade leiomyosarcomas, and nodules of proliferating smooth muscle cells.[16] Pulmonary BML is usually asymptomatic and presents with either single or multiple lung nodules of varying sizes.[17] The tumors do not appear to invade adjacent tissues.[18] BML, however, represents a diagnostic and therapeutic challenge because of its pathogenesis and metastatic potential.

EPIDEMIOLOGY

The occurrence and prevalence of pulmonary BML is unknown. There are over 100 cases of BML reported in the literature but only a few studies reported more than one case. BML is a rare disease, found primarily in premenopausal women who have undergone surgical procedures for treatment of uterine leiomyomas.[1,4,18] However, cases of lung BML have also been reported in women with no history of these surgical procedures.[19] Leiomyomas, including BML of the lung, may be found in women and, to a lesser extent, in men and children.[20] There is no ethnic or racial preference for BML and this differs from uterine leiomyoma, which is more frequent in African-American women.[21] Cases of BML have been reported from countries all over the world[4,22] including, but not limited to, the United States,[19] Portugal,[23] Brazil,[24] China,[25] India,[14] South Korea,[13] Japan,[26] and Turkey.[6]



A B

Figure 63-1 Nodular structures in BML. High-resolution computed tomography (HRCT) shows multiple diffuse small bilateral nodules before (**A**) and after treatment (**B**). *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, Kotz HL, Moss J. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2):438–442.)*

CLINICAL PRESENTATION

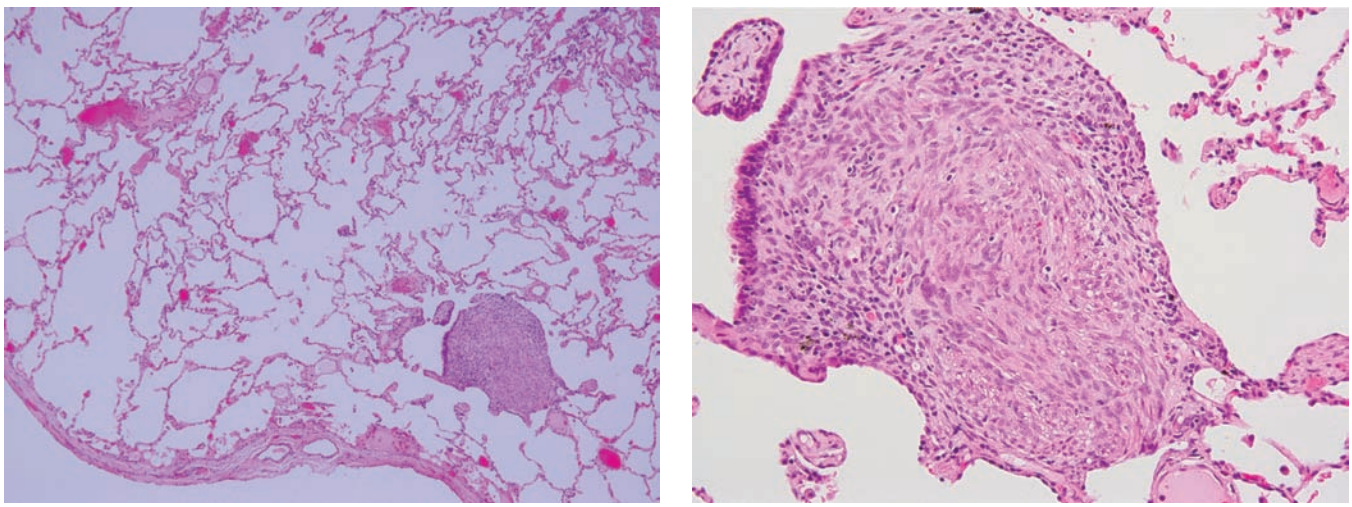
Most cases of lung BML have been identified as an incidental finding on imaging procedures performed for other purposes (Fig. 63-1).[1] BML nodules may present in premenopausal women as unilateral or bilateral tumors with no specific lobar distribution.[17,27] A number of different types of uterine tumors (e.g., leiomyoma, smooth muscle tumors of uncertain malignant potential, leiomyosarcomas, other smooth muscle tumors, endometrial stromal tumors) are associated with the diagnosis of BML. BML may present with respiratory symptoms including cough, wheezing, dyspnea, and chest pain.[15,17,19,28,29] BML lung nodules have been detected in women in a few months to over 30 years after they have undergone uterine myomectomy or hysterectomy.[30]

PATHOLOGY

BML lung lesions consist of well-circumscribed nodules ranging in size from few millimeters to several centimeters in diameter.[1,4] The lung tumors are composed of well-differentiated proliferative smooth muscle cells that form intersecting fascicles and show positive immunoreactivity toward actin, desmin, and caldesmon (Fig. 63-2).[4,31] Most of these cells also react with antibodies against receptors for estrogen and progesterone.[1,3,22]

Benign lung nodular or mass lesions may be either of epithelial or mesenchymal origin.[32] BML lesions consist of well-differentiated smooth muscle cells, which form lung nodules with low cellularity, exhibiting low mitotic index and no nuclear atypism. The lung nodules do not invade the surrounding tissue and lack evidence of necrosis. Since most of the BML cases are discovered after hysterectomy or myomectomy, it would be important to identify the type of uterine cell causing the tumor. BML cells without a clearly distinct smooth muscle phenotype may exhibit unusual growth patterns.[33] In general, BMLs have been classified as benign tumors of mesenchymal origin.

BML lesions contain vascular structures as determined by anti-CD34 antibody reactivity within nodules adjacent to vessels. BML lesions express variable levels of p53, but the role of this tumor suppressor in BML cells has not been reported.[31] BML lung lesions also show reactivity with antibodies against proliferating cell nuclear



A B

Figure 63-2 Histologic section of proliferative areas of lung BML. Tissue section shows proliferative smooth muscle cells forming fascicles characteristic of leiomyomas and BML. **A, B.** Show low- and high- resolution pictures of lung proliferative nodules. *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, Kotz HL, Moss J. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2): 438–442.)*

antigen (PCNA). In contrast to what is seen in leiomyomatous hamartoma, most of the histopathologic sections of lung BML are not reactive with the monoclonal antibody Human Melanoma Black-45 (HMB-45), which recognizes Pmel17,[31] a melanosomal protein expressed in cells from lung hamartomas, PEComas (perivascular epithelioid cells), and lymphangioleiomyomatosis (LAM).[34] BML nodules are in most of the cases not reactive to antibodies against EMA, CD10, CD117, TTF-1, BCL-2 GPAP, calretinin, and cytokeratin chromogranin. S-100 is expressed at very low levels in BMLs. PEComas of the uterus with pulmonary metastases have a similar presentation to BML but the proliferating smooth muscle cells are mostly nonreactive to HMB-45.[19,35,36] Thus, BML lung nodules appear to have distinct pathologic characteristics.

It has been proposed that leiomyomas should be classified as benign or malignant based on the number of mitotic figures. If 10 mitotic figures per 10 high power field (HPF) are present, the tumor is classified as a neoplasm and if there are more than 5 mitotic figures per 10 HPF it should be considered a leiomyosarcoma. Benign lesions should have less than 5 mitotic figures per HPF.[37] The fact that BML lesions contain less than 5 mitotic figures per HPF, identifies them as a benign tumor.

It is possible to identify cancer cells based on their molecular phenotype,[38,39] however, the molecular characteristics of BML cells remain unknown. Expression of the micro-RNA 221 (miR-221), which has been correlated with different malignancies,[40] appears to differentiate leiomyosarcoma from BML.[41] Molecular assays of X-chromosome inactivation have shown that it is very likely that the lung and uterine cells have a similar origin.[42] BMLs proliferate without telomeric changes, suggesting that their proliferative behavior is independent of telomeric attrition as is the case in other malignant diseases.[43,44] Cytogenetic studies of BML lung tumors have shown that the cells have abnormalities in several chromosomes. BML tumors from five cases showed 19q and 22q terminal deletions.[45] Interestingly, a single case showed multiple chromosomal deletions from cells isolated from different metastatic sites.[46] Rearrangement of the 6p21 region was correlated with changes in the high mobility group A1 gene (*HMGA1*). Chromosomal translocation and mutations have been associated with HMGIC in leiomyomas but they have not been identified in the leiomyomas present in BML patients. It has been possible to correlate the proliferative behavior of BML cells with chromosomal translocations present in other noninvasive tumors.[45–47]

Some of the factors potentially involved in the development of uterine leiomyoma are basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-β) and granulocyte macrophage colony–stimulating factor (GM-CSF),[48] although a role for these factors in the pathogenesis of BMLs has not been defined. Analysis of BML tumor cells from different sites suggests a clonal origin.[42] The balanced karyotype of BMLs is consistent with the findings seen with leiomyomas.[49] The clonality of these tumors should be interpreted with caution due to the fact that the founding mutation has not been identified in any case.

PATHOGENESIS

BMLs are considered mesenchymal tumors not mixed tumors of the uterus. Although there are different types of leiomyomas (e.g., mitotically active, cellular, hemorrhagic cellular, atypical, epitheliod, myxoid, vascular, lipoleiomyomas), the type of leiomyoma associated with BML has not been determined. Hamartomas, the most common tumor of the lung, are seen in both genders. PEComas of the uterus with pulmonary metastases may have a similar presentation to BML but these tumors express Pmel7, and are recognized by the monoclonal antibody HMB-45.

The source of the cells that form the lung nodules remains unknown, but due to the strong association with uterine leiomyomas, it is believed that the main source of the cells is the uterus. It has been proposed that those cells responsible for the formation of pulmonary BML are derived from (a) low-grade tumors; (b) cells dislodged from uterus at the time of myomectomy and hysterectomy; (c) metastasis from uterus or an unknown site; (d) proliferation of lung smooth muscle cells; and/or (e) simultaneous-independent development of multiple leiomyomas.

LOW-GRADE TUMORS

Although other tumors may occur in patients with BML including leiomyosarcoma, adenocarcinoma,[50] breast carcinoma, and skeletal muscle tumors, their association with BML is not clear. Leiomyomas of the esophagus, lung, and uterus are found in association with multiple endocrine neoplasia type I (MEN1) but loss of heterozygosity for MEN1 has not been investigated in BML, as is the case in many MEN cases.[51] Tumors characterized as low-grade leiomyosarcomas and high-grade leiomyosarcomas do not appear to metastasize to the lung; these tumors occur mainly in the abdominal cavity.[52] It has also been proposed that BML could be an intermediate tumor stage leading to a malignant leiomyosarcoma[7] but high-grade leiomyosarcomas involving the lung reappear in a short period of time following surgery.[52] Low-grade leiomyosarcomas do not express progesterone and estrogen receptors as is the case in BML. Thus, it is very unlikely that BMLs arise from low-grade malignancies.

CELLS DISLODGED FROM UTERUS AT THE TIME OF MYOMECTOMY AND HYSTERECTOMY

Since pulmonary BML has been associated with hysterectomy and myomectomies, it has been postulated that some of the uterine cells move into the blood circulation at the time of surgery and migrate to the lung where they remain and grow at a slow rate.[18] Lung BML has been associated with tumors in the retroperitoneal cavity,[9] pelvis, and the para-aortic lymph nodes arguing against the passive passage of cells from uterus to lung.[18] The presence of BML tumors in the pelvic region is not in agreement with the concept that uterine cells became dislodged and seeded the lung. Although most cases of BML report multiple pulmonary tumors after hysterectomy, few cases describe the occurrence of nodules before hysterectomy.[53] BML has been correlated with endometriosis as BMLs and endometriosis have a similar course and may develop after hysterectomy or myomectomy.[3,4] Estrogen and progesterone receptors are found in lung BML cells and uterine leiomyomas, which are the most likely source of the cells. However, it is not clear if lymphatics or blood vessels are involved in the metastatic process leading to pulmonary BML.

METASTASIS FROM UTERUS OR UNKNOWN SITE

Due to the fact that BMLs are present in multiple sites, it is possible that either uterine smooth muscle cells or cells from other non-uterine sites metastasize to the lung. Forty percent of leiomyomas or myomas possess specific chromosomal abnormalities.[49] Uterine leiomyomas comprise smooth muscle cells with the extracellular matrix containing a high collagen content. Lung BML nodules however, do not have a high content of extracellular matrix. Leiomyomas contain high concentrations of estrogen[54] and progesterone[55] receptors, which drive the proliferation of cells in response to their ligands. In addition, leiomyomas contain large amounts of aromatase,[56] an enzyme involved in estrogen synthesis.[57] The presence of leiomyomas in lung, lymph nodes, muscular tissue, heart, vascular structures, retroperitoneal cavity, and parietal pleura[58] suggest a metastatic process.[9,12] Leiomyomatosis of the uterus does not tend to metastasize to the lung[59] but BML can present with uterine vascular invasion,[25] supporting a metastatic model. Similar patterns of X-chromosome (human androgen receptor) inactivation suggest that there is a single BML cell source, which is the uterus.

PROLIFERATION OF LUNG SMOOTH MUSCLE CELLS

BML nodules could originate from proliferative lung smooth muscle cells as is the case in primary leiomyoma.[60] However, pathologic sections of a primary pulmonary leiomyoma lacked immunoreactivity for estrogen and progesterone receptors as is found in BML.[61]

SIMULTANEOUS INDEPENDENT DEVELOPMENT OF LEIOMYOMAS AT MULTIPLE SITES

Multiple BML tumors have been identified in some cases and it is possible that they occur independently or via a metastatic process.[13] Since initial mutations have not been identified, it is possible that the mutations occur independently in the different sites. Experimental models to study BML are not available. Interestingly, N-nitroso compounds promoted formation of tumors in lung, reproductive and mammary organs.[62] In fact, chronic treatment of mice with N6-(Methylnitroso) adenosine (m6(NO)Ado) caused tumors in lungs and reproductive tract.[62] These findings support the idea that BML could be promoted by carcinogenic processes.

Metastatic dissemination of BML cells appears to be the most accepted mechanism for localization of BML to the lungs. BML cells could metastasize via the lymphatics, hematologic spread, coelomic metaplasia, and intraperitoneal seeding.[3] Galactins have been identified in pathologic sections of BML lesions, suggesting that these proteins could play a role in cell transformation, regulation of apoptosis and cell growth, cell adhesion during metastasis, and regulation of tumor invasiveness.[63] Molecular studies support the notion that BML metastasis to the lung is promoted by the inherent properties of BML cells and is not a mere by-product of the surgical procedures.

PULMONARY PHYSIOLOGY

Few studies have evaluated lung function in patients with BML.[19,29,52,64] In one study, a patient was followed for more than 10 years and serial pulmonary function tests were obtained.[19] Initially, the patient presented with diminished vital capacity and total lung capacity (TLC) without any evidence of airflow obstruction or impairment in diffusion capacity (Fig. 63-3). As the disease progressed, the patient experienced a decline in diffusion capacity that could be accounted by the decline in lung volumes. In response to antiestrogen therapy, an increase in vital capacity and TLC were observed. In this case, the pathophysiologic profile was consistent with that of an interstitial lung disease.

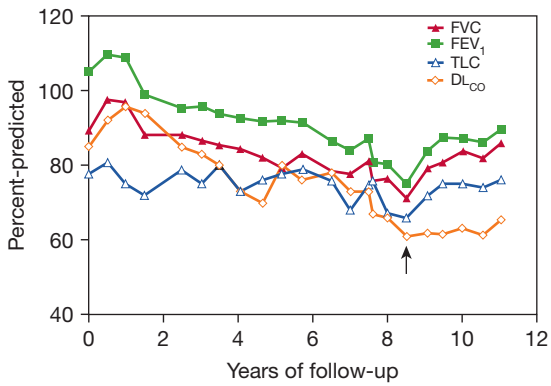


Figure 63-3 Changes in lung function before and after leuprolide acetate therapy. The patient was followed for 8.5 years before therapy and for over 2 years after therapy. Respiratory parameters, for example, forced vital capacity (FVC), force expiratory volume in the first second (FEV_1), total lung capacity (TLC), diffusion capacity for carbon monoxide (D_{LCO}), declined prior to therapy but improved following treatment with leuprolide. *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, Kotz HL, Moss J. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2):438–442.)*

RADIOLOGY

BML nodules may be identified by chest X-rays, computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). The nodular structures observed in BML are well circumscribed. Bilateral pulmonary BML nodules are more common than unilateral nodules. Lung BML may occasionally present with cystic lung destruction.[19] Fluorodeoxyglucose-positron emission is negative in BML and may be used to differentiate BML from other tumors. BMLs and tumors such as adenomas, bronchoalveolar carcinomas, carcinoid tumors, and low-grade lymphomas also have low glycolytic activity.[65] ^{18}F-FDP-PET however, can distinguish a BML from leiomyosarcoma, which is a more glycolytically active tumor and may be found in association with BML.[6] CT and magnetic resonance has also been used to identify BML lesions in the retroperitoneal space and pelvic cavity.[66] Leiomyomas can be easily recognized on pelvic examination. The dimensions and locations of the fibroids may be identified by ultrasound.[67] Since, in most instances the lung nodules are detected by incidental X-rays, a chest X-ray may be warranted after a woman is diagnosed with uterine leiomyomas.

DIAGNOSIS

The differential diagnosis of BML nodular lesions include infectious or neoplastic metastatic lesions.[68] BMLs are usually asymptomatic but may result in lung-related symptoms.[69] Diagnosis requires a compatible medical history and pathologic analysis of biopsies and/or surgically removed tumor. CT-guided, transbronchial or open lung biopsy may be used to establish the diagnosis.[37] Although most cases of pulmonary BML are asymptomatic, some patients present with dyspnea, cough, wheezing, chest pain, chylothoraces, and pneumothoraces. The respiratory symptoms of BML are more prevalent in younger patients. The manifestations of BML in other sites such as uterus, heart, and lymph nodes, for the most part, may be nonspecific. The symptoms of uterine fibroids include abnormal uterine bleeding, pelvic pressure/pain, and reproductive dysfunction. Some of these symptoms have been reported in patients diagnosed with BML prior to myomectomy or hysterectomy.[3,19] BML patients do not present with dysregulated levels of tumor biomarkers, for example, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9, also called cancer antigen 19-9 or sialylated Lewis (a) antigen (CA19-9), carcinoma antigen 15-3 (CA 15-3), cancer antigen-125 (CA-125), cytokeratin 19 fragment (CyFRA21-1), neuron-specific enolase (NSE), alpha-fetoprotein (AFP), hyperglycosylated hCG (HCG-β), beta-2-microglobulin *(β2-MG)*.

Differential diagnosis of BML includes primary pulmonary leiomyoma, primary pulmonary leiomyosarcoma, metastatic leiomyomatosis of an extrauterine source, pulmonary hamartomas, and lymphangioleiomyomatosis (LAM).[1] BML, depending on location, has been classified as intravenous leiomyomatosis and disseminated BML.[9] BML lung nodules have been associated primarily with leiomyomas. Lung hamartomas are associated with other cancers and express the melanogenic protein Pmel17.[70] High-grade leiomyosarcomas may involve the lung. In leiomyosarcomas, the mean time to recurrence is 19 months and metastasis to the lung is seen in 16% of patients for low-grade and 70% for high-grade leiomyosarcomas. Low-grade leiomyosarcomas do not express progesterone and estrogen receptors, which distinguish them from BML. Leiomyomatosis peritonealis disseminata could be one of the confounding diagnoses to consider when a BML patient presents with peritoneal lesions.[9] The slow growth of BMLs could be mistaken by other potential causes of lung nodules for example, infectious processes (fungal, parasitic and tuberculosis), metastatic cancers, benign neoplasms (e.g., chondrohamartomas, hamartomas, BML),

amyloidosis, mucoid impaction syndromes, multiple arteriovenous malformation, paraffinoma, plasma cell granuloma, rheumatoid nodules, sarcoidosis, silicosis.[68]

PROGNOSIS

The prognosis of patients with BML is favorable. Although most cases of BML present with multiple pulmonary tumors after myomectomy and hysterectomy, few cases reported the presence of these nodules before hysterectomy.[53] There are only scattered reports where BML was described as a cause of death. Other cancers detected in association with BML could influence prognosis.

TREATMENT

There is no standard treatment for BML. Treatment involves tumor resection and manipulation of hormonal status. Lung tumors may regress at menopause and during/after pregnancy, supporting a role for estrogen in BML.[71] Treatments have been adapted from those used for uterine leiomyoma, and include hysterectomy, myomectomy, dilation of the cervix, uterine artery embolization and endometrial ablation, and scrapping of the uterus (curettage).

Oophorectomy has been reported to improve lung function and cause regression of the lung tumors.[29,64,72–76] Another line of treatment has involved antiestrogenic therapy. Gonadotropin-releasing hormone (GnRH) analogs (e.g., Lupron) have been used to reduce estrogen levels.[10,19,77] Other drugs include the selective estrogen receptor modulators (SERMs), e.g. raloxifene.[24,64,78] Aromatase inhibitors such as anastrozole[64] have been shown to be effective treatments. Progesterone therapy has also proven to be effective.[79–81] However, there have been some cases of BML refractory to progesterone and aromatase inhibitors.[82] Treatments of uterine leiomyoma have also included combination of GnRH analogs and aromatase inhibitors.[64,83] Patients with BML have been treated with a single drug or combination of drugs,[22,83] e.g. leuprolide acetate, letrazole, leuprolide acetate and aromatase inhibitors, and antiprogestin (CDB-2914)[22,83] e.g., In some cases total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) has been combined with drugs. Although bilateral oophorectomy has been the most commonly used treatment, unilateral oophorectomy has been effective in treating some BML tumors.[74] It is important to consider loss of bone mineral density due to antiestrogenic therapies. The slow-growing behavior of BML suggests that these tumors can be left untreated unless the patient becomes symptomatic.

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CHAPTER 64

Depositional Diseases of the Lungs

Robert J. Homer

INTRODUCTION

Deposits of endogenous body constituents or exogenous materials in amounts sufficient to deform structure and impair function can occur virtually anywhere in the body. Deposits of endogenous materials in the lungs or airways cause a variety of diseases (Table 64-1). These may have different clinical manifestations, depending on localization (i.e., pulmonary parenchyma or conducting airways). This chapter deals with a few of these manifestations: amyloidosis; diffuse pulmonary calcification; alveolar microlithiasis; diffuse alveolar hemorrhage (DAH) syndromes; and idiopathic pulmonary hemosiderosis. Others are discussed elsewhere in this text.

AMYLOIDOSIS

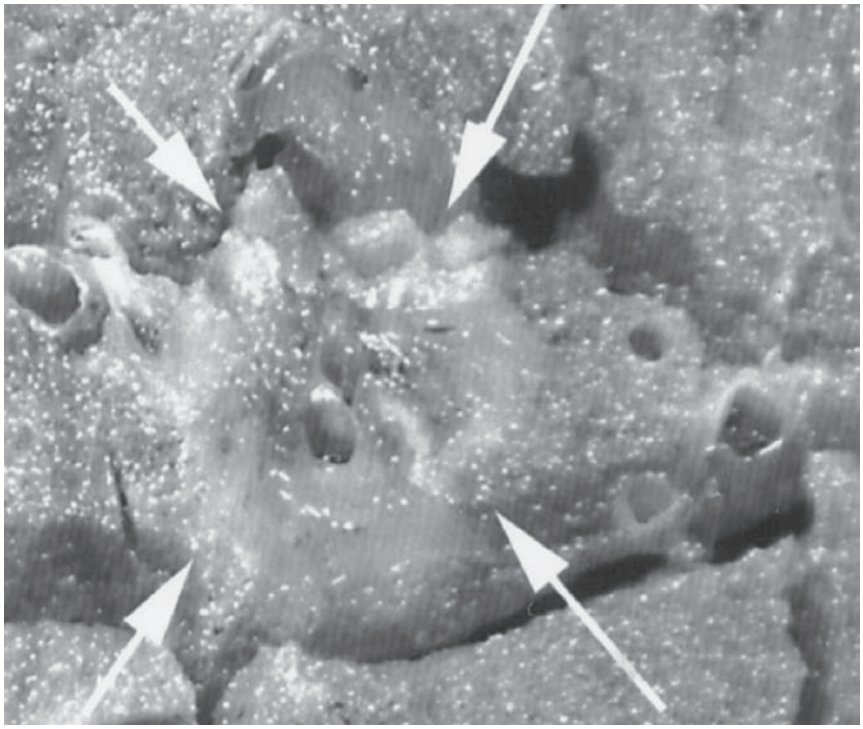
Characteristics of amyloid and the various forms of pulmonary amyloid are considered below.

NATURE OF AMYLOID

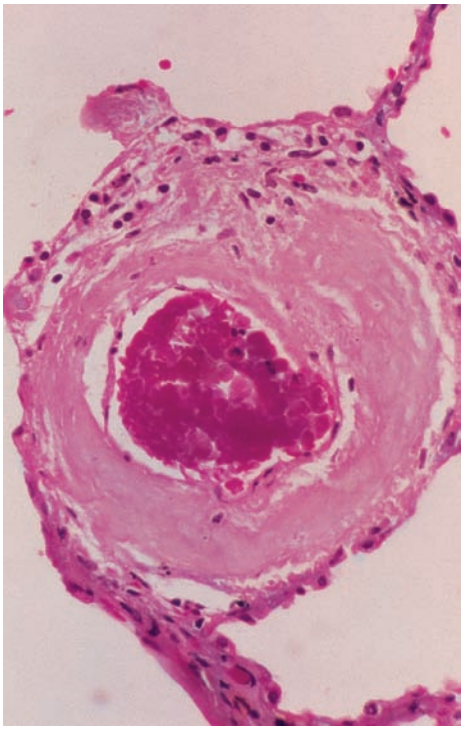
Amyloidosis refers to the extracellular deposition of amyloid, a fibrillar, proteinaceous, insoluble material that has characteristic light, ultrastructural, and histochemical features (Fig. 64-1). Electron microscopic examination of amyloid reveals a dominant (95%) fibrillar component with distinctive periodicity, associated with a lesser (5%) pentagonal doughnut-shaped glycoprotein component, physically and chemically identical in all forms of amyloid, which is derived from a soluble plasma protein, soluble amyloid P protein (SAP). Amyloid also includes various glycosaminoglycans and certain apolipoproteins (E and J). Radiographic diffraction studies of amyloid show the fibrils to be arrayed in a β-pleated sheet configuration.

TABLE 64-1 Depositional Diseases of the Lungs

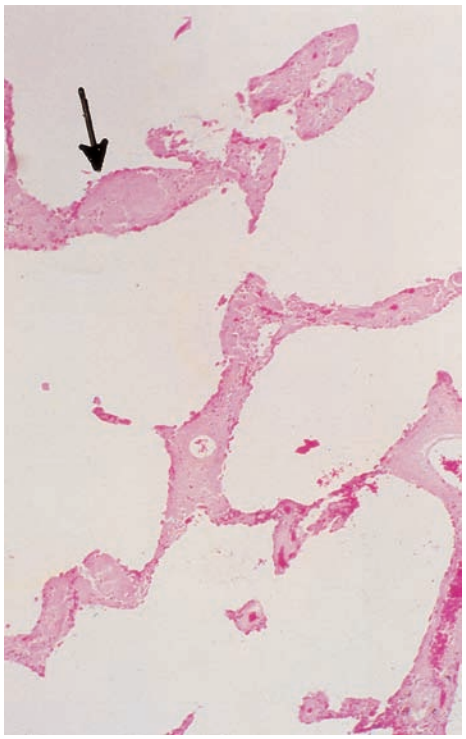
Biologic Material	Disease
Interstitial Deposition	
Amyloid	Amyloidosis
Water	Interstitial edema
Calcium	Metastatic calcification
Alveolar Deposition	
Surfactant	Alveolar proteinosis
Water	Alveolar edema
Calcium	Alveolar microlithiasis
Blood and hemosiderin	Alveolar hemorrhage syndromes



A



B



C

Figure 64-1 Amyloid deposition. **A.** Amyloidoma. Cut surface of lung with *white arrows* indicating a dense, wax-like lesion that is characteristic of nodular amyloid. Incidental finding at autopsy. *(Used with permission of Leslie A. Litzky, MD, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.)* **B.** The typical amorphous appearance of amyloid is seen deposited within the wall of a pulmonary venule. *Green* birefringence on polarized light examination after staining with *Congo red* will confirm the amyloid nature of the deposit (H&E ×700). **C.** Amorphous amyloid in the alveolar interstitial space. *Arrow* indicates a thickened alveolar septum (H&E ×420).

This accounts for the ordered binding of the histochemical stain Congo red such that Congo red–stained amyloid appears apple-green under polarized light.[1,2] When amyloid is deposited in tissues it may produce atrophy of parenchymal cells (e.g., glomeruli), interference with mechanical function (e.g., heart and lungs), or impaired vasoconstriction of blood vessels, leading to hemorrhage (e.g., lungs and gastrointestinal tract). Other mechanisms of tissue injury are also hypothesized including direct tissue toxicity.[3]

While the main fibrillar component of amyloid can be derived from any one of 27 precursor proteins,[2] only a few are common in systemic disease, including immunoglobulin light-chain, serum amyloid–associated (SAA) protein (a family of acute phase reactants), transthyretin (TTR, a prealbumin molecule that binds and transports thyroxine and retinol), and β_2-microglobulin.[1,4–6] The established amyloid fibril nomenclature is based on the chemical nature of the fibril protein, where an A, for amyloid, is followed by a suffix that is an abbreviated form of the parent or precursor protein. These forms of amyloidosis are therefore known as AL, AA, ATTR, and Aβ_2M, respectively. An entity related to amyloidosis is light-chain deposition disease (LCDD) in which tissue deposits are also

derived from immunoglobulin light chains and are similar to amyloid by light microscopy, but show granular deposition by electron microscopy and do not stain with Congo red.[7] It seems likely that the biochemical properties of the light chain determine the nature of the deposit produced.

AL amyloidosis usually occurs in association with a neoplastic clonal proliferation of B cells or plasma cells which produce a monoclonal immunoglobulin or immunoglobulin fragment (monoclonal gammopathy). The neoplastic clone may clinically manifest as multiple myeloma or lymphoma (generally lymphoplasmacytic lymphoma) or may be subclinical (formerly known as primary amyloidosis), causing bone-marrow plasmacytosis. Most often the protein source is a λ-light chain, either intact or the amino terminal fragment. Amyloid-associated (AA) amyloidosis (previously referred to as secondary amyloidosis) is associated with a chronic increase in serum acute-phase reactants. It was formerly seen predominantly in patients with chronic infections (e.g., tuberculosis, leprosy, and chronic osteomyelitis) but is now seen more commonly with noninfectious chronic inflammatory diseases (e.g., rheumatoid arthritis, familial Mediterranean fever, Crohn disease, and heroin abuse with "skin popping").[1,6] TTR is deposited in familial amyloid polyneuropathies and senile systemic amyloidosis (ATTR amyloidosis).[5] β_2-microglobulin deposition ($A\beta_2M$ amyloidosis) is seen in patients with chronic renal failure on dialysis.

■ PULMONARY INVOLVEMENT IN AMYLOIDOSIS

It is important to distinguish secondary involvement of the respiratory tract in patients with systemic disease from localized pulmonary involvement with the latter being much less common than the former.[4,8,9] Tracheobronchial amyloid deposition and nodular parenchymal amyloid deposition (amyloidoma) (Fig. 64-1A) most often occur as isolated phenomena, whereas diffuse interstitial deposition is more often seen in systemic amyloidosis. In addition to pulmonary involvement per se, amyloidosis may also cause symptoms in any portion of the respiratory tract or there may be secondary effects from deposition in other organs. For example, deposits in the tongue may be extensive enough to cause obstructive sleep apnea. Persistent pleural effusions may be due to both pleural and cardiac disease.[10] Diaphragmatic deposition may lead to respiratory failure. Pulmonary hypertension is a rare complication.[11] The vast majority of cases of pulmonary amyloidosis can be categorized as tracheobronchial amyloidosis, nodular parenchymal amyloidosis, and diffuse septal amyloidosis.

Nodular Parenchymal Amyloidosis

Solitary amyloid nodules (amyloidomas) are commonly incidental radiographic findings in asymptomatic individuals (Fig. 64-1).[4,8] When multiple, such nodules may be associated with cough, dyspnea, or hemoptysis. These nodules have no distinctive features, although occasionally, they may show radiographic evidence of calcification or cavitation. Usually the diagnosis of an amyloid nodule is made after surgical resection. Occasionally, the diagnosis has been made by transbronchial biopsy or percutaneous fine-needle aspiration. However, surgical excision of one or more nodules may be prudent, since, on rare occasion, amyloid deposition occurs within a pulmonary neoplasm (e.g., a primary neoplasm such as atypical carcinoid or a metastatic neoplasm such as medullary carcinoma from the thyroid). It is possible that advances in biochemical analysis of the amyloid (see below) may influence this decision, but this is not yet commonly discussed in the literature.

Nodular parenchymal amyloidosis most often represents AL. Histologically, the amyloid deposit is often associated with an intense inflammatory reaction consisting of plasma cells, macrophages, and multinucleated giant cells. Interestingly, when the accompanying plasma cells have been analyzed for clonality, they are more often polyclonal than monoclonal. In such cases, the inflammatory cells may therefore be a local reaction to the presence of amyloid, rather than the source of the amyloid precursor light chains. In a few instances, nodular amyloidosis has been associated with a histologically apparent low-grade pulmonary lymphoma. Rare cases of AA amyloidosis have also been reported. Clinical follow-up of nodular parenchymal amyloidosis unassociated with systemic or, frankly, neoplastic disease is generally benign.[8]

Tracheobronchial Amyloidosis

Amyloid deposition in the tracheobronchial tree can produce either plaques or tumoral masses.[4,9] The more common presentation as plaques is diffuse and multifocal, and represents submucosal deposition of amyloid. Diffuse or proximal involvement of the airways is apt to be symptomatic, producing cough, stridor, or hemoptysis. Less commonly, deposition of amyloid in the tracheobronchial tree produces a solitary mass, which mimics an endobronchial neoplasm with signs of bronchial obstruction or hemorrhage. Tracheobronchial amyloid deposition, like parenchymal nodule amyloid, is most often of light-chain derivation and a localized phenomenon. Again, like nodular amyloidosis, this form is rarely associated with systemic disease. Both types of airways lesions can be readily identified by bronchoscopic examination. However, as is the case with amyloid deposition at all sites, with biopsy there is a risk of hemorrhage. Although localized tumoral masses may be treated by excision or observation, more diffuse involvement may be treated by laser ablation, stents, or radiation. Involvement of proximal airway leads to significant mortality while involvement of distal or mid airway has generally good prognosis.

Diffuse Interstitial Amyloidosis

Widespread, *diffuse interstitial amyloidosis* of the pulmonary parenchyma may produce either a reticulonodular or miliary pattern on the chest radiograph.[4,8,12] The deposition of amyloid may involve the alveolar septal interstitium, the walls of small blood vessels, or both (Fig. 64-1B,C). Such pulmonary involvement occurs most often in patients with systemic amyloidosis, derived from either immunoglobulin light-chain or AA protein. Pulmonary interstitial amyloid deposition in secondary involvement is rarely sufficiently severe to produce clinical manifestations but, uncommonly, it may produce progressive dyspnea, hemoptysis, or restrictive pulmonary function tests. It is thought that the morbidity and mortality of diffuse septal amyloidosis in patients with systemic disease is related to concurrent cardiac amyloidosis with which tissue burden closely correlates, possibly explaining why septal amyloidosis by itself in this setting is not of more significance.[4] On the other hand, primary diffuse interstitial pulmonary amyloidosis has been considered to have a relatively poor prognosis.[4,12]

■ DIAGNOSIS AND TREATMENT OF AMYLOIDOSIS

Diagnosis of amyloidosis requires tissue examination and Congo-red staining and/or electron microscopy. The biochemical nature of the amyloid fibril in patients with systemic amyloidosis cannot be predicted from clinical manifestations alone.[13–18] Even in patients with a known plasma cell dyscrasia, if amyloid is detected, it should not be assumed that this represents AL amyloid since a significant number of patients with familial or senile type amyloid also have plasma cell dyscrasias. Historically, a variety of immunohistochemical and immunofluorescence tests were used, combined with genetic testing; but these commonly required frozen tissue, which were technically challenging and did not always provide an answer. More recently, improved immunohistochemistry and biochemical techniques have become available and are applicable in formalin fixed paraffin embedded tissue.[13–17,19–21] Published data show these approaches are highly robust and generalizable to multiple clinical scenarios although they have not yet been reported in patients with isolated pulmonary disease.

While it is beyond the scope of this chapter to discuss therapy in depth, it is important to note that therapy for systemic disease is

entirely dependent on the specific peptide responsible. In cases of systemic AL amyloidosis, there has been considerable progress in treatment with introduction of myeloma type therapy with high-dose prednisone and mephalan therapy combined with use of hematopoietic stem-cell transplantation. Newer agents also appear promising such as thalidomide and related compounds and especially bortezomib which targets plasma cells.[3] In contrast, treatment for AA amyloidosis focuses on the underlying inflammatory disease but may also include small molecule inhibitors.[6] Systemic senile amyloidosis due to deposition of transthyretin (ATTR) has also been approached with small molecule inhibitors.[5] In some cases of hereditary disease, either small molecule inhibitors or organ (liver, heart) transplantation has been explored.[5] The significance of these therapies for lung-limited disease is unclear since localized disease is typically treated with ablative therapy such as stents, radiation, laser treatment, resection, and other localized methods. The more recent systemic therapies have not yet been reported in patients with lung-limited disease.

DIFFUSE PULMONARY CALCIFICATION

Calcification of the pulmonary parenchyma can occur by a variety of mechanisms.[22] Dystrophic calcification refers to the deposition of calcium salts, most often crystalline hydroxyapatite, in dead tissue such as within the healing granulomas of tuberculosis or sarcoidosis. It can also be seen in various other conditions such as in pulmonary hypertension, other post infectious conditions or pneumoconiosis. This type of calcification is usually localized; its distinctive radiographic features are sometimes diagnostically helpful. It is rarely of any clinical significance beyond that of the underlying condition.

Metastatic calcification refers to the deposition of calcium salts, usually amorphous, in normal tissues (Fig. 64-2). This latter type of calcification occurs in association with some derangement of calcium metabolism, such as primary hyperparathyroidism, secondary hyperparathyroidism of chronic renal failure, hypervitaminosis D, the milk-alkali syndrome, sarcoidosis, or increased bone turnover due to multiple myeloma or metastatic carcinoma.

Although metastatic calcification can occur in almost any tissue of the body, it occurs most often in the lungs, kidneys, and the stomach (tissues with more alkaline pH), and the walls of blood vessels. Metastatic calcification in the lungs usually affects the interstitium of the alveolar septa and the walls of bronchioles and pulmonary vessels, sometimes localizing on elastic fibers.

Clinical manifestations of diffuse pulmonary calcification are unusual, occurring most often in patients who are in chronic renal failure, particularly in those on chronic hemodialysis. Radiographically, metastatic calcification usually takes the form of a diffuse interstitial infiltrate, sometimes with fine nodularity. Less often, confluent patchy consolidation mimicking pneumonia may be seen. Although the calcific nature of the infiltrate is often apparent on routine chest radiograph, computed tomography (CT) scan is more sensitive both in detecting the interstitial deposits and in revealing their calcific nature. Moreover, CT scan may also demonstrate calcification of chest wall blood vessels, circumstantially implicating calcification as the cause of pulmonary parenchymal abnormalities. Recognition of the calcific nature of the infiltrate is furthered by scanning with ^{99m}technetium.

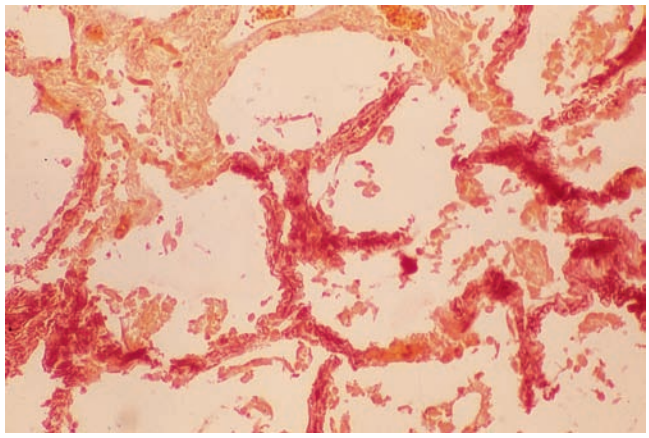


Figure 64-2 Metastatic calcification of alveolar septa in a renal dialysis patient. Photomicrograph shows calcium forming a *dark red* precipitate within the alveolar septa (Alizarin red ×280).

Only rarely do the patients manifest dyspnea or arterial hypoxemia, and pulmonary function tests tend to not show signs of restrictive pulmonary disease. Unexplained dyspnea in a patient with chronic renal failure or hypercalcemia in the presence of a normal chest radiograph should lead to consideration of high-resolution computed tomography (HRCT) or technetium scanning. Rarely, respiratory failure may develop although death from metastatic calcification is typically due to cardiac disease.

The mechanism responsible for diffuse pulmonary calcification is unknown. Although high levels of parathyroid hormone or a marked increase in the calcium-phosphate solubility product occur in some patients, diffuse calcification can occur in the absence of either. Ultrastructural observations of minimal, presumably early, lesions show selective deposition of calcium on elastic fibers, suggesting that they may serve as the initial nidus. In contrast to their apparent role in alveolar microlithiasis, extracellular matrix vesicles do not appear to be involved.

ALVEOLAR MICROLITHIASIS

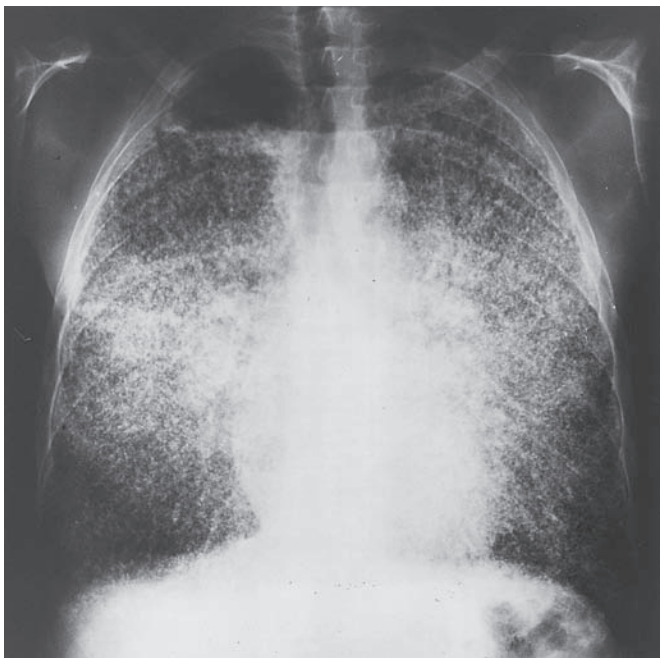
Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disorder characterized by intra-alveolar accumulation of spherical calcified concretions (called calciferites, calcospherites, or microliths), in the absence of any known calcium metabolism disorder.[23] This disorder usually presents with an abnormal chest radiograph from an asymptomatic patient (Fig. 64-3). Presentation can occur at any age, although symptoms usually occur in third or fourth decade of life. The chest radiograph and/or HRCT are diagnostic, showing a sand-like micronodulation throughout the lung fields. This is caused by the presence of innumerable minute calcified spherules filling the alveolar spaces. Although not usually required, bronchoalveolar lavage or biopsy can confirm the diagnosis. Biopsy shows calcified spherules filling alveolar spaces (Fig. 64-3).

Although usually asymptomatic at the time of presentation, alveolar microlithiasis typically progresses to end-stage lung disease, but the rate of progression is highly variable. When it does, the findings are those of restrictive pulmonary disease or exercise-induced pulmonary hypertension. No therapy has proven effective but lung transplantation has been performed successfully in a few patients.

The disease is due to a mutation in a type IIb sodium-phosphate cotransporter (SLC34A2) gene. As surfactant phospholipids are metabolized, phosphate is liberated and the transporter is needed to eliminate the excess phosphate from the alveolar space. In the absence of this transporter, increased phosphate levels lead to microlith formation. While this is most dramatic in the lungs, other organs can also be affected. The accumulation of microliths ultimately leads to loss of vital capacity by mass effect as well as by inducing underlying parenchymal fibrosis.

ALVEOLAR HEMORRHAGE SYNDROMES

Pulmonary hemorrhage most commonly arises from endobronchial diseases (tumors, bronchiectasis, bronchitis).[24] However, there is a subset of patients in whom bleeding originates at the level of the alveoli and who are referred to as having DAH.[25] Symptoms range from cough, fever, and dyspnea alone to respiratory failure. While hemoptysis is common, it is not universal, even when DAH is severe. In these



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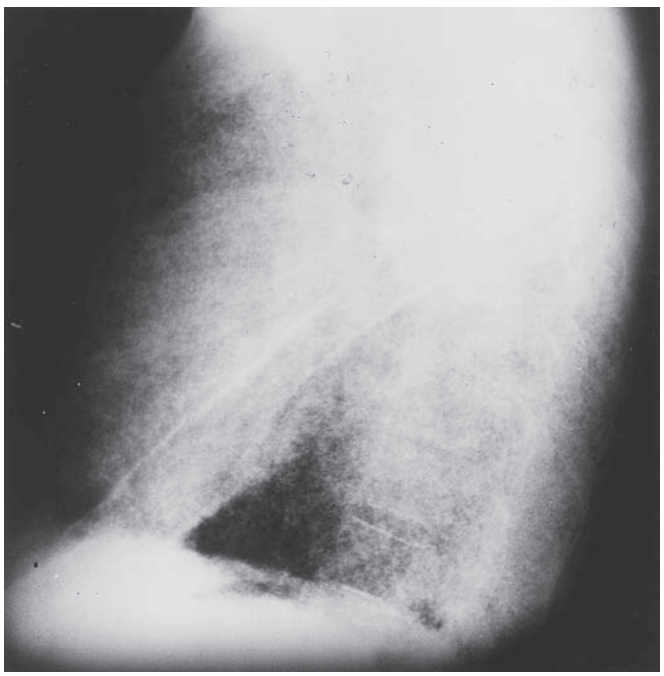

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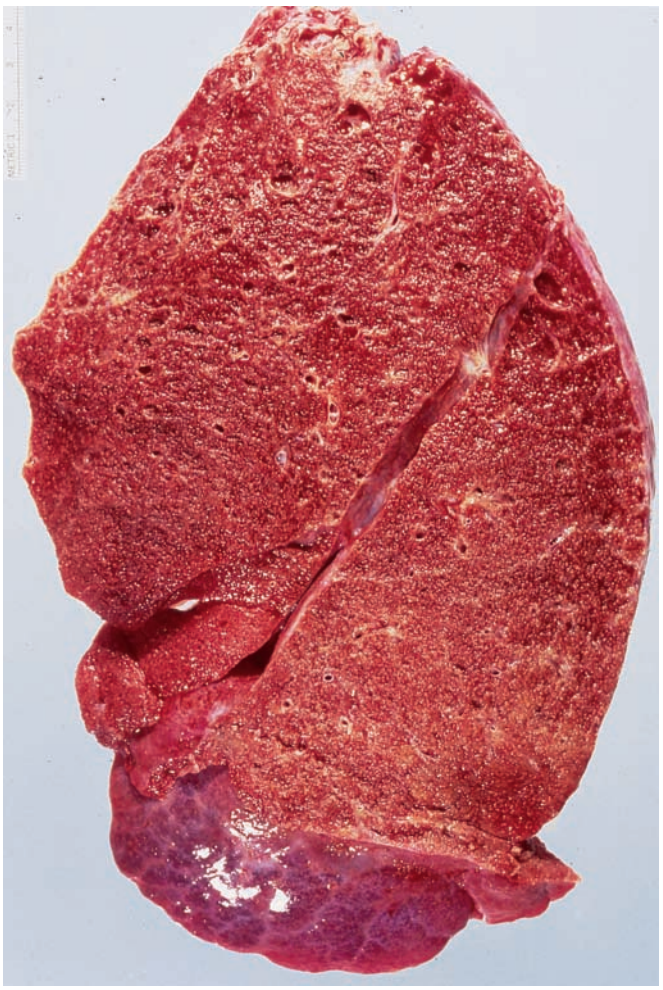

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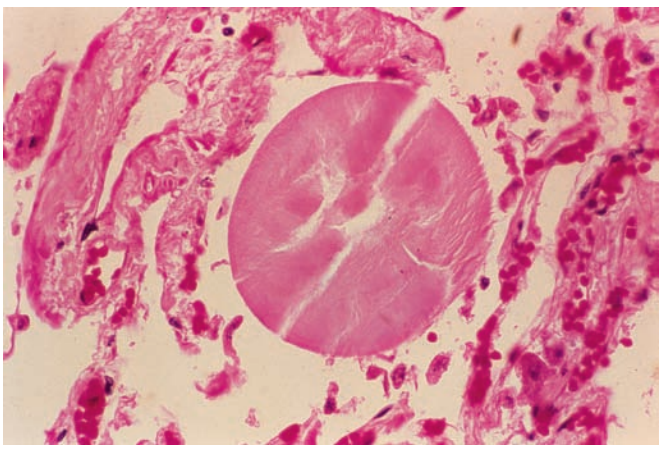

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Figure 64-3 Alveolar microlithiasis in a 46-year-old man admitted for nonpulmonary problems. History included slight dyspnea on exertion and previous episodes of "pneumonia" in 1947, 1950, and 1952. Clinical examination revealed severe restrictive lung disease, pulmonary hypertension, and cor pulmonale. Diagnosis confirmed by lung biopsy. **A and B.** Posterior–anterior and lateral chest radiographs demonstrate innumerable, tiny calcified nodules throughout both lung fields. Thin, lucent lines on each side represent normal pleura visualized between the calcified pulmonary parenchyma and the chest wall. Emphysematous blebs in the apices displace the calcifications. **C.** Cut surface of explanted lung from a patient undergoing lung transplantation for primary alveolar microlithiasis. Note the fine nodularity which correlated with the chest radiographs. *(Used with permission of Leslie A. Litzky, MD, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.)* **D.** Photomicrograph demonstrating a typical calcospherite in an alveolar space (H&E ×1120).

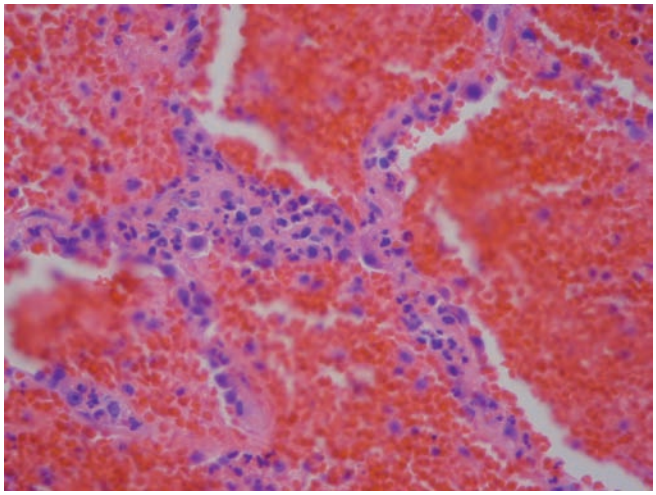


Figure 64-4 Capillaritis as a cause of pulmonary hemorrhage. Note the neutrophils in the alveolar septum (in *center* of image) and the blood and fibrin in the alveolar spaces (H&E ×100).

cases, the diagnosis can be suspected due to a falling hemoglobin level. Evaluation of serial bronchoalveolar lavage aliquots in such patients may show a progressive increase in bloody return, as opposed to endobronchial disease, in which bleeding tends to clear. Bronchoalveolar lavage is also useful to exclude infection in patients with DAH.

The damage to alveolar septa may either be due to immunologic mechanisms (immune complex, antineutrophil cytoplasmic antibody [ANCA], antiglomerular basement antibodies, antiphospholipid antibodies) or to nonimmunologic causes. This distinction is largely, although not perfectly, captured in the presence or absence of the pathologic finding of capillaritis (Fig. 64-4 and Table 64-2).[26]

TABLE 64-2 Causes of Diffuse Alveolar Hemorrhage

Diffuse Alveolar Hemorrhage without Pulmonary Capillaritis
Inhalational toxins (trimetallic anhydride, crack cocaine)
Mitral stenosis
Severe coagulopathy (iatrogenic, renal failure, thrombocytopenia)
Nonspecific inflammation (diffuse alveolar damage, pulmonary gangrene, endocarditis)
Neoplasm/hamartomatous (angiosarcoma, lymphangioleiomyomatosis, tuberous sclerosis)
Pulmonary vascular disease (pulmonary veno-occlusive disease, capillary hemangiomatosis)
Idiopathic pulmonary hemosiderosis
Diffuse Alveolar Hemorrhage with Pulmonary Capillaritis
ANCA-associated vasculitis (granulomatosis with polyangiitis [formerly known as Wegener granulomatosis], microscopic polyangiitis, Churg–Strauss syndrome)
Immune complex—associated with vascular disease (Behçet disease, Henoch–Schönlein purpura, systemic lupus erythematosus, rheumatoid arthritis, mixed connective-tissue disease, polymyositis)
Isolated pauci-immune pulmonary capillaritis
Diffuse Alveolar Hemorrhage with or without Capillaritis
Goodpasture syndrome
Systemic lupus erythematosus
Primary or secondary antiphospholipid syndrome
Drug-induced pulmonary hemorrhage

Capillaritis is characterized by infiltration of alveolar walls by inflammatory cells, usually neutrophils, but sometimes eosinophils or monocytes, with fibrinoid necrosis of the alveolar and vessel wall. However, due to the absence of supporting structures, alveolar necrosis leads to wall breakdown so rapidly that this latter feature may be hard to appreciate. In order to distinguish this process from simple margination of neutrophils, there should be evidence for neutrophils undergoing apoptosis (pyknosis and nuclear fragments). Distinction from infection requires determination that there is minimal accumulation of inflammatory cells within alveoli. The pathologic diagnosis of pulmonary hemorrhage itself requires that there is either hemosiderin-laden macrophages or evidence of hemophagocytosis, since the blood that is commonly seen in lung biopsies may be due to surgery alone. If this evidence is absent, clinical criteria for DAH should be used.

Nonimmunologic mechanisms are quite diverse and include diffuse alveolar damage, inhalation of toxins, coagulopathy, and mitral valve disease, among others listed (Table 64-2).[25] While the presence or absence of capillaritis is a useful way to think about these diseases, the decision about whether to actually perform a biopsy in these cases is challenging as interpretation of these biopsies is difficult, there is potential sampling error, and there is a significant risk of surgery to these patients. These problems limit this procedure's utility while alternative diagnostic schemes usually allow diagnosis in absence of biopsy.

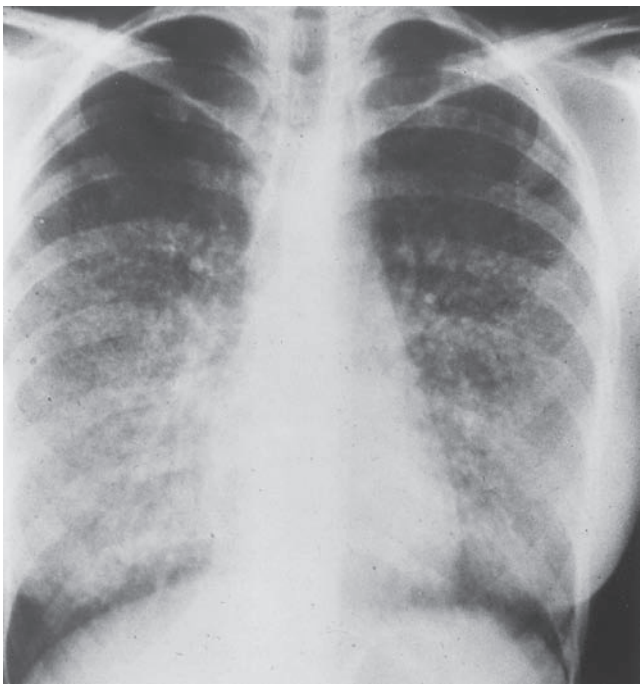
■ GOODPASTURE SYNDROME

This entity was originally described as an association of alveolar hemorrhage with glomerulonephritis.[27,28] It was later determined that pulmonary and renal damage in many such patients was mediated by antibodies that are specifically directed against a component of glomerular and other capillary basement membranes, most often the α_3-chain of type IV (basement membrane) collagen. The anti-basement membrane antibodies cause pulmonary hemorrhage only in genetically predisposed individuals, after some injury such as cigarette smoke, viral respiratory infection, or hydrocarbon vapor inhalation exposes alveolar capillary basement membranes to the immune system.[29] Although there are other causes of concomitant alveolar hemorrhage and glomerulonephritis, Goodpasture syndrome is generally reserved for disease mediated by antiglomerular basement membrane antibodies (anti-GBM antibodies).

Goodpasture syndrome can present with a broad spectrum of clinical findings. The "classic" patient presents with massive hemoptysis, dyspnea, diffuse alveolar infiltrates on chest radiograph (Fig. 64-5) and overt glomerulonephritis, often with acute renal failure.[30] However, some patients present with only hemoptysis and subsequently develop overt renal disease months or even years later. On occasion, patients present with acute glomerulonephritis due to anti-GBM antibodies and either develop pulmonary hemorrhage subsequently or never develop pulmonary hemorrhage. Without pulmonary hemorrhage, the entity should not be called "Goodpasture syndrome."

The histologic findings on lung biopsy in Goodpasture syndrome are not diagnostic. Routine light microscopy reveals intra-alveolar hemorrhage, usually associated with intra-alveolar hemosiderin-laden macrophages (Fig. 64-5).[24,31] There may be no evidence of vasculitis, capillaritis, interstitial or intra-alveolar inflammation, or necrosis. In some cases, subtle capillaritis may be present. In either case, nonspecific reparative proliferation of the alveolar-lining cells may be present.

While the diagnosis of Goodpasture syndrome can be made by detecting anti-GBM antibodies in the patient's serum, the sensitivity and specificity of various methods to detect these antibodies vary considerably. The gold standard remains the detection of the linear pattern of immunofluorescence on a lung or kidney biopsy. However, only occasionally will immunofluorescence microscopy



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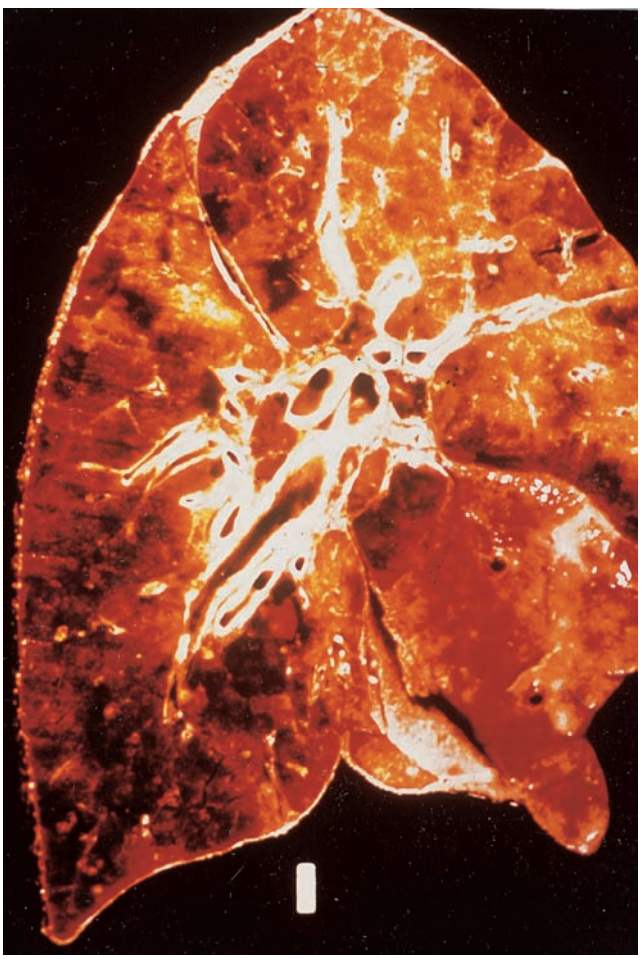

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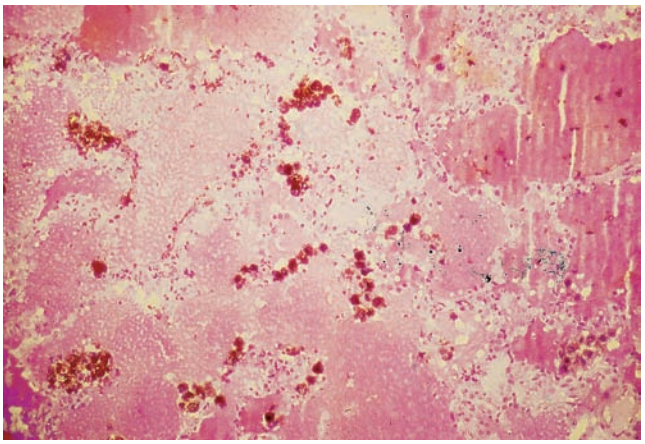

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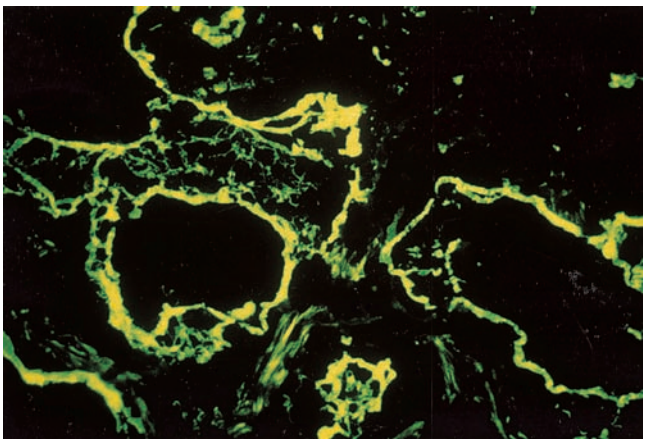

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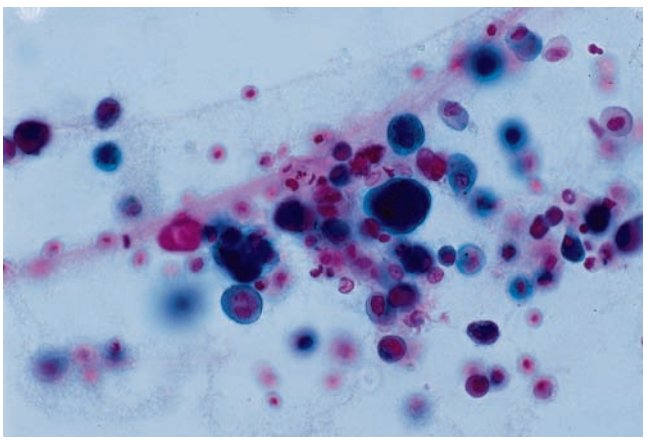

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Figure 64-5 Goodpasture syndrome. **A.** Chest radiograph showing bilateral alveolar infiltrates, predominantly in the middle and lower lung fields. **B.** Autopsy specimen showing cut surface of lung with massive alveolar hemorrhage. *(Used with permission of Dr. Richard Garnett, Reid Memorial Hospital, Richmond, IN.)* **C.** Photomicrograph of intact alveoli, containing both red blood cells and hemosiderin-laden macrophages (H&E ×45). **D.** Immunofluorescent demonstration of immunoglobulin-lining alveolar surfaces in a uniform distribution (fluoresceinated anti-IgG ×113). **E.** Smear of bronchoalveolar lavage demonstrating hemosiderin-laden macrophages (*Prussian blue stain*; original magnification ×132). *(Used with permission of Dr. David Lyon, Iankenau Lankenau Hospital, Wynnewood, PA.)*

show diagnostic linear deposits of immunoglobulin and/or complement along alveolar capillary walls (Fig. 64-5D). In contrast, kidney biopsy in Goodpasture syndrome is usually diagnostic. Conventional light microscopy shows nonspecific focal or diffuse glomerulonephritis which may be crescentic and necrotizing.

When pulmonary hemorrhage due to Goodpasture syndrome is life-threatening, plasmapheresis for rapid lowering of circulating levels of anti-GBM antibody and administration of intravenous corticosteroids and cyclophosphamide to suppress antibody synthesis can be life-saving.[25,28,30] If the patient is not in advanced renal failure at the time of diagnosis, chronic immunosuppression with a combination of corticosteroids and cyclophosphamide can prevent progressive renal damage. If irreversible renal failure has already occurred, the patient can eventually be successfully transplanted once anti-GBM antibodies have disappeared from the serum. Elimination of the antibodies usually can be achieved by immunosuppression alone; in some instances, pretransplant nephrectomy may be required.

ANCA-ASSOCIATED PULMONARY VASCULITIS

The ANCA-associated vasculitides, granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) and microscopic polyangiitis (MPA), represent the most common cause of immunologically mediated DAH.[25,26,30,32] These have been associated with the development of autoantibodies directed against cytoplasmic components of neutrophils (and monocytes), the ANCAs. Detection of ANCAs entails the use of indirect immunofluorescence and heterologous antibodies against human immunoglobulin to detect autoantibodies bound to neutrophils of affected patients. Ethanol fixation of the neutrophils prior to antibody staining produces one of two patterns when autoantibodies are present: (1) a finely granular centrally accentuated cytoplasmic localization (c-ANCA); or (2) a perinuclear localization (p-ANCA). The usual targets of these antibodies have been identified as proteinase 3 for c-ANCA and myeloperoxidase for p-ANCA. Both antigens are found in the primary azurophilic granules of neutrophils. When ethanol is used as the fixative, the cellular granules are disrupted; the positively charged myeloperoxidase molecules then migrate toward the negatively charged nucleus to produce the perinuclear pattern, and the neutral proteinase 3 molecules remain dispersed in the cytoplasm to produce the cytoplasmic pattern. To maximize diagnostic accuracy, dual testing by fluorescence and an antigen-specific solid phase assay is required. Otherwise, a high degree of clinicopathologic correlation is required for correct interpretation of these tests. Some patients with ANCA-associated alveolar hemorrhage also have antibasement membrane antibodies in the serum. These antibodies are directed against basement antigens other than those seen in Goodpasture syndrome and are thought to be a secondary phenomenon, rather than of pathogenic significance.

Overt DAH occurs in approximately 15% of patients with GPA or MPA. Depending on the specific syndrome present, alveolar hemorrhage may be isolated, associated with glomerulonephritis, or associated with widespread systemic vasculitis. In patients with ANCA-associated vasculitis, the occurrence of DAH is a poor prognostic indicator, although among survivors, complete recovery of lung function is common. Therapy does not depend on diagnosis of MPA versus GPA, and is based on immunosuppression with steroids and cyclophosphamide possibly augmented with plasmapheresis. Nevertheless, patients with GPA/c-ANCA/proteinase 3 have worse outcomes with higher mortality and recurrence rate. While Churg–Strauss syndrome (CSS) is classified among the ANCA-associated vasculitides, DAH due to CSS is extraordinarily rare.

Rarely, patients present with isolated pulmonary capillaritis with no serologic or clinical evidence for a systemic disorder.[33] These patients respond to immunosuppression but relapses occur.

ANTIPHOSPHOLIPID ANTIBODY–ASSOCIATED ALVEOLAR HEMORRHAGE

Patients with serum antibodies directed against membrane phospholipid (antiphospholipid syndrome or APS) display hypercoagulability.[25,34] Clinically, this manifests as peripheral arterial and venous thrombosis, fetal wastage in pregnant women, and thrombocytopenia. Pulmonary involvement can include pulmonary thromboembolism, pulmonary hypertension, diffuse alveolar damage, or rarely DAH. The latter produces fever, dyspnea, and diffuse pulmonary infiltrates on chest radiograph. Alveolar hemorrhage in APS has been associated with alveolar capillaritis with or without immune complex deposition and with microvascular thrombosis in the lungs. The combination of both thrombosis and hemorrhage greatly complicates therapy.

Antiphospholipid antibodies were first detected in patients with systemic lupus erythematosus (SLE) and were formerly known as the lupus anticoagulant because they prolong some laboratory tests of clotting. APS can occur in the absence of SLE. How often these antibodies play a role in pulmonary hemorrhage due to SLE is unknown, as there are other possible mechanisms in that syndrome (see below). In patients with isolated APS and alveolar hemorrhage, corticosteroid treatment, sometimes supplemented by cyclophosphamide, can result in a favorable outcome.

COLLAGEN VASCULAR DISEASE AND IMMUNE COMPLEX–ASSOCIATED PULMONARY HEMORRHAGE

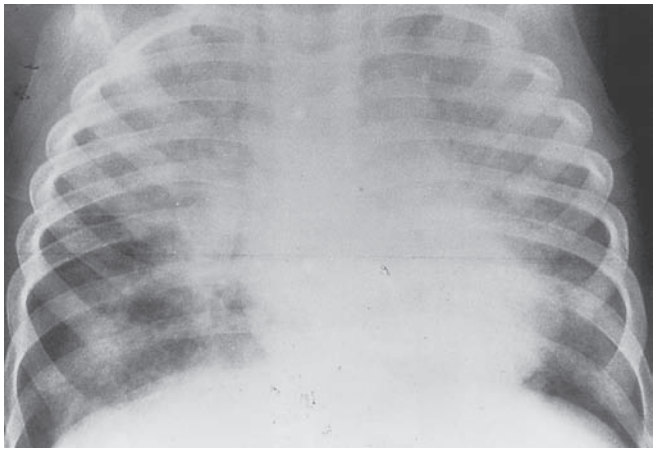
DAH also occurs as a rare complication of certain connective-tissue disease syndromes, most often SLE but also rheumatoid arthritis, progressive systemic sclerosis, and mixed connective-tissue disease.[35] Particularly in SLE, other causes of alveolar hemorrhage must be considered, including infection, uremia, and coagulopathy. When such causes have been eliminated, alveolar hemorrhage is sometimes found to be associated with capillaritis, with interstitial pneumonitis, or with immunofluorescent or ultrastructural evidence of immune complex deposition in alveolar septa. However, none of these disorders are consistently associated with pulmonary hemorrhage in SLE. Early diagnosis and treatment with corticosteroids and cytotoxic drugs are associated with favorable outcomes, although relapse is not uncommon.

DRUG-INDUCED PULMONARY HEMORRHAGE

There is a long list of drugs, both therapeutic and drugs of abuse, associated with vasculitis. The clinical spectrum ranges from isolated mild skin disease to severe multiorgan systemic disease, usually due to a small vessel vasculitis. Some of these drugs can induce an ANCA-associated vasculitis. DAH due to ANCA-associated pulmonary capillaritis is well documented for propylthiouracil, D-penicillamine, allopurinol, diphenylhydantoin, and minocycline. Drug-induced ANCA-associated vasculitis should be treated with cessation of all potential causative agents as well as immunosuppression. Once the offending drug has been eliminated, the possibility of relapse seems low.

NONIMMUNOLOGIC CAUSES OF DIFFUSE ALVEOLAR HEMORRHAGE

There is a wide range of conditions that are associated with DAH with no capillaritis seen on biopsy and which are due to a wide variety of specific conditions, including toxins, neoplasms, nonspecific inflammation, infection, coagulopathy, and pulmonary vascular disease.[25] While all the previously mentioned diseases and syndromes have been excluded as likely possibilities, there still remains a small group of patients who develop recurrent DAH in the absence of extrapulmonary disease and with no evidence of an immune etiology. These patients are considered to have idiopathic pulmonary



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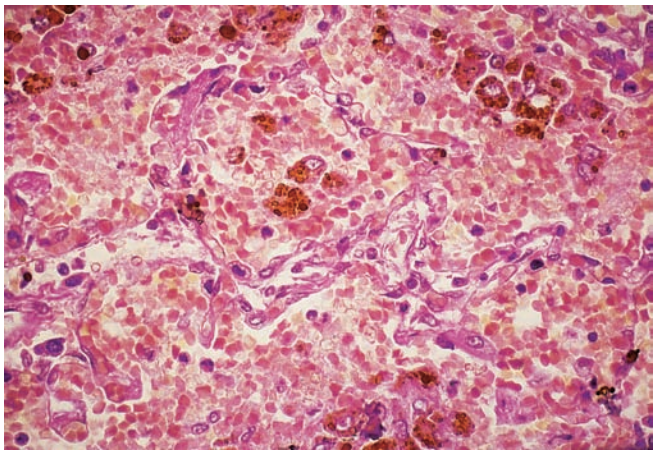

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Figure 64-6 Idiopathic pulmonary hemosiderosis in a 21-month-old child with anemia soon after birth. Iron stain of the sputum showed hemosiderin-laden macrophages. **A.** Chest radiograph showing extensive, bilateral, almost punctate densities throughout both lung fields, most prominent in the perihilar regions where an alveolar filling pattern appears. **B.** Photomicrograph of lung at autopsy, showing intact alveoli containing degenerating red blood cells and hemosiderin-laden macrophages. Immunofluorescence studies for immunoglobulin and complement deposition were negative (H&E ×31). *(Used with permission of Department of Pathology, St. Christopher's Hospital for Children, Philadelphia.)*

hemosiderosis, a diagnosis of exclusion (Fig. 64-6).[30,36] Clinically, the patients form a heterogeneous group with respect to the onset and course of disease, which range from fulminant and fatal to chronic relapse with eventual chronic pulmonary insufficiency due to interstitial fibrosis, to spontaneous remission with little or no residual deficit. The disease usually affects children and young adults. Pathologic examination reveals nonspecific alveolar hemorrhage without evidence of inflammation, vasculitis, or immune complex deposition. Only a few observations on ultrastructure are available. These include focal disruption, smudging, or lamination of alveolar capillary basement membranes.

The pathogenesis of this condition remains unknown, and there are no associated antibodies or other serum markers in the idiopathic cases. However, the clinical and morphologic similarities to some cases of alveolar hemorrhage of known immune pathogenesis, the occasional responsiveness to immunosuppressive therapy, the occasional association with celiac sprue – a presumably immunologic disease of the small intestine – and frequent association with a nonspecific elevation of serum IgA, all point to an as yet unelucidated immune pathogenesis. Rarely, children with hypersensitivity to cow's milk (Heiner syndrome) can present with DAH.

If the diagnosis proves to be idiopathic pulmonary hemosiderosis, high-dose corticosteroid therapy with or without cyclophosphamide and plasmapheresis is useful in controlling acute bleeding, but the long-term effectiveness of these measures in preventing recurrence or progression of this disease is unknown.

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PART 6

Drug-Induced Lung Diseases

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CHAPTER 65

Pulmonary Toxicity Related to Chemotherapeutic Agents

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INTRODUCTION

Toxicities related to medications comprise a major category of iatrogenic illness. Many agents used for cancer treatment have the potential to cause pulmonary toxicity. As the horizon for treatment options has broadened with our ever-expanding understanding of biological mechanisms fundamental to neoplasia, so has the spectrum of pulmonary complications related to new therapies. Further, with availability of new therapeutic modalities, patients with cancer are living longer, and may, in their long-term survivorship, display delayed toxicities related to treatment. Consequently, for the pulmonologist, drug-induced lung disease is an area of growing complexity.

Chemotherapeutic agents, therapeutic radiation, and biological response modifiers are used in a wide range of regimens, and their use is further complicated by the use of hematopoietic support and bone marrow or stem cell transplantation. Many are, directly or indirectly, associated with pulmonary toxicity. An estimated 5% to 10% of patients undergoing chemotherapy ultimately develop therapy-related pulmonary complications.[1–3] This chapter reviews the evaluation of patients with suspected chemotherapy-induced pulmonary toxicity, as well as the potential toxicities associated with specific classes of drugs.

APPROACH TO THE PATIENT WITH SUSPECTED CHEMOTHERAPY-INDUCED PULMONARY TOXICITY

The differential diagnosis of patients with cancer receiving treatment who develop pulmonary complications is often very challenging, particularly as the diagnosis of drug-induced pulmonary toxicity is typically one of exclusion. Patients most often present with nonspecific constitutional or respiratory complaints. In many cases, symptoms and physical signs may be minimal or even absent. In these situations, the only evidence of an ongoing pulmonary process may be an abnormal chest radiograph (Table 65-1).

The diagnosis of lung disease caused by chemotherapeutic agents poses a particular challenge to the clinician, as there are several complicating features inherent to the oncology patient population.

First, treatment may be given in multidrug regimens or in combination with other modalities such as radiation therapy, bone marrow transplantation, or stem cell transplantation. Assigning pulmonary toxicity to a single drug or modality within such a regimen is often impossible. Moreover, the combined toxicity of two or more drugs or a single drug with radiation therapy may exceed the individual toxicities of those drugs.

Second, patients undergoing chemotherapy are often immune suppressed, either from the malignancy itself or from myelosuppressive or immunosuppressive effects of their treatment. These patients are therefore susceptible to opportunistic infection, which may be indistinguishable radiographically from drug toxicity. This is particularly challenging, as the lung is the most common site of serious infection in patients with cancer. It has been estimated that a relative minority (5%–30%) of pulmonary complications in immunocompromised patients are actually due to drug toxicity; hence it is important to remember that infection is still the most likely culprit when pulmonary decompensation occurs. Since changing a treatment regimen may affect the chance for cure or prolongation of survival, reasonable certainty of drug-related complications necessarily involves exclusion of infection.

Third, cancers themselves may mimic lung disease. This is particularly true in cases of lymphangitic tumor spread or metastases to the lung parenchyma or pleura.

Fourth, toxicity from some drugs appears to be related to cumulative dosage levels. However, adverse reactions may occur even with a low cumulative dose, when clinical suspicion for toxicity is low.

Finally, pulmonary toxicity due to a single chemotherapeutic agent may present with several different syndromes that vary clinically, radiographically, and temporally. While a severe pulmonary reaction acutely following drug administration usually raises suspicion of drug toxicity, as patients survive for longer periods of time it is becoming increasingly clear that toxicity due to some chemotherapeutic agents may be delayed by months to even years after treatment. In such situations, clinical suspicion of drug toxicity may be low.

Monitoring for potential pulmonary toxicity in the patient undergoing chemotherapy requires ongoing clinical vigilance. Symptoms such as cough, dyspnea, or chest discomfort may be mild or even absent. Radiographic findings may be equally subtle. Even if clinical symptoms and radiographic abnormalities are present and severe, they are usually nonspecific. The possibility of adverse drug effects must be considered within the complex medical context inherent to the patient with cancer undergoing physically challenging or immunosuppressive treatment.

PULMONARY PHYSIOLOGICAL TESTING

Pulmonary physiological testing has been utilized in surveillance of patients receiving drugs with potential for pulmonary toxicity. A multitude of investigations studying the utility of pulmonary function testing (PFT) in monitoring pulmonary effects related to administration of chemotherapy have been reported, but the

TABLE 65-1 Differential Diagnosis of Radiographic Abnormalities in Cancer Patients

Pulmonary toxicity related to chemotherapy or other medication
Infection
Primary malignancy
Lymphangitic tumor, metastatic disease, leukemic infiltration
Radiation lung injury
Acute respiratory distress syndrome
Interstitial lung disease, unrelated to drug toxicity
Pulmonary edema (cardiogenic)
Pulmonary thromboembolism
Pulmonary hemorrhage
Transfusion-related acute lung injury

application of these findings to clinical management has been a subject of debate.

Various physiological abnormalities have been described, the most common of which are decreases in lung volumes and diffusing capacity for carbon monoxide (D_{LCO}). Patients receiving chemotherapy who are monitored serially by PFT frequently demonstrate physiological abnormalities in the absence of clinical signs of toxicity.[4–6] Abnormalities in D_{LCO} in particular have been thought by some to be indicative of early-onset, drug-related pulmonary injury. Most such studies have been performed in patients receiving bleomycin, busulfan, or carmustine. Discontinuation of drug, with or without initiation of treatment, including corticosteroids, typically results in improvement. Whether early intervention based on D_{LCO} abnormalities in the absence of clinical symptoms decreases the likelihood of long-term pulmonary impairment related to toxicity is unclear. Conversely, in situations of clinically evident drug toxicity accompanied by PFT abnormalities, withdrawal of culprit therapy may not be paralleled by improvement in physiological measurements. For example, in a study examining pulmonary function in 116 long-term (5–13 years after treatment) survivors of Hodgkin disease in Norway, nearly 30% of patients had exertional dyspnea with associated pulmonary function abnormalities.[7] Multivariate analysis of these patients identified chemotherapy with a combination of bleomycin and anthracyclines as the sole significant predictor of lung function impairment. In all patients in whom drug toxicity is of concern, consideration must be given to the possibility that discontinuation of a specific treatment might result in substitution of less effective therapy.

A number of factors further complicate the practice and interpretation of PFT in the oncology population. Many physiological parameters are effort dependent. The ability of a patient to consistently perform test maneuvers may be affected by weakness, pain, or the use of analgesic or sedating medications. Reproducibility of results therefore may be a significant concern in patients whose functional status and strength are impaired by their malignancy or its treatment. Many patients have anemia induced by malignancy, medication, or chronic illness. Since D_{LCO} is affected by hemoglobin concentration, it is critical that appropriate corrections for anemia be made. Patients with cancers may also be subject to processes other than drug toxicity that will affect PFT results. Primary pulmonary malignancy, metastatic lung disease, infection, thoracic or abdominal surgical procedures, and a host of other clinical situations may all independently cause variation in physiological measurements. Therefore, identifying pulmonary physiological abnormalities specific to drug effect may prove very difficult.

Ultimately, even though the predictive value of baseline or serial PFT remains unclear, most clinicians will continue to rely on such testing as screening and monitoring tools. Though there are no definitive data that toxicity can be averted by physiological monitoring, we are limited by the absence of other means of identifying toxicity early enough to prevent severe pulmonary disease. Though the presence of subclinical abnormalities does not imply that patients will develop irreversible lung disease, these abnormalities may dictate closer monitoring, or even the withdrawal of drug. Conversely, normal physiology cannot predict abrupt toxicity that may produce profound pulmonary injury. As always, medical decisions based on pulmonary physiological findings must be made in the context of the patient's clinical situation as a whole.

■ DIAGNOSTIC EVALUATION

Given the potential impact of pulmonary drug toxicity on a patient's present and future cancer treatment, it is important to establish this diagnosis as firmly as possible. Thoughtful and judicious use of invasive procedures plays an important role in that evaluation.

The approach to the cancer patient in whom drug toxicity is suspected should parallel the approach to any immunocompromised patient with diffuse or localized lung disease (see Chapter 123). Because clinical features are usually not specific, sampling of respiratory tract secretions and/or lung tissue may be critical to this evaluation. Direct sputum examination or culture may suggest specific pathogens or may be diagnostic of infections such as invasive fungal disease, *Pneumocystis jiroveci* pneumonia, or tuberculosis. In the absence of diagnostic sputum findings, invasive procedures may be necessary. Fine-needle aspiration of the lung may be useful with focal lesions. However, the utility of this procedure in diffuse lung disease is relatively low. This is particularly problematic for patients with drug-induced pulmonary toxicity, which often presents with a diffuse interstitial pattern on chest radiograph. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy has become central to the evaluation of both diffuse and localized lung disease in the immunocompromised host. The procedure is associated with a low rate of major complications. Diagnostic yield varies widely, reflecting the broad range of disease processes that can involve the lung in the immunocompromised patient. Highest diagnostic yields are obtained in patients with infections; lower yields are seen in interstitial inflammatory processes, which may include toxicity from drugs. However, even in situations in which a specific etiology is not identified, exclusion of infection by bronchoscopy often provides clinically useful information.

Open or thoracoscopic lung biopsy is associated with the highest diagnostic yield and can be performed with low complication rates even in critically ill patients. If drug-induced pulmonary injury is suspected, surgical biopsy may be necessary to definitively exclude other causes of lung disease.

The evaluation of a patient in whom chemotherapy-related pulmonary toxicity is a consideration clearly presents significant challenges. Clinicians must be vigilant in the evaluation and management of patients receiving chemotherapeutic regimens. An awareness of potential iatrogenic complications related to drug therapy is, therefore, essential.

CYTOTOXIC ANTIBIOTICS

A variety of cytotoxic antibiotics have been associated with pulmonary toxicity (Table 65-2). Important examples are discussed below.

■ BLEOMYCIN

Bleomycin, a cytotoxic antibiotic produced by *Streptomyces vermiculus*, is used in the treatment of various malignancies, including lymphomas, germ cell tumors, and squamous cell cancers of the head and neck.[8] Unfortunately, it has significant potential for pulmonary toxicity due to relative lack of the inactivating enzyme bleomycin hydrolase in the lungs.[9] The most severe complication is interstitial pneumonitis progressing to fibrosis and respiratory failure, though there are also less severe syndromes, including organizing pneumonia and hypersensitivity pneumonitis.[10]

The pulmonary toxicities of bleomycin have been studied extensively, primarily in animal models. Endothelial injury via oxidative stress is the sentinel event, followed by the influx of inflammatory cells (predominantly macrophages, neutrophils, and lymphocytes), development of perivascular edema, elaboration of inflammatory cytokines, and, ultimately, fibroblast activation and fibrosis (Fig. 65-1).[11] A variety of mediators have been implicated in bleomycin-induced lung injury, including tumor necrosis factor α (TNFα), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), and interleukin-1 (IL-1).[10] Human studies have demonstrated activation of in vitro alveolar macrophages in response to bleomycin,[12] and patients treated with bleomycin for testicular cancer demonstrate a rise in serum TNFα 3 to 24 hours after drug administration.[13] The continued expression of TNFα and IL-1 may predispose to the production of TGF-β and promotion of dysregulated collagen production and fibrosis. Animal studies have shown that bleomycin-induced pulmonary toxicity can

TABLE 65-2 Cytotoxic Antibiotics

Drug	Pulmonary Syndrome	Treatment	Comments
Bleomycin	Chronic pneumonitis; pulmonary fibrosis; rare fulminant variant with acute respiratory failure	Discontinue drug; corticosteroids	Risk factors: Cumulative dose >400 units; supplemental oxygen; therapeutic radiation; renal insufficiency; age >70 y; additional cytotoxic drugs
	Hypersensitivity-type lung disease	Discontinue drug; corticosteroids	Dyspnea, cough, skin rash, and peripheral eosinophilia
	Chest pain syndrome	Discontinue drug	Associated with drug infusion
Mitomycin C	Chronic pneumonitis; pulmonary fibrosis; rare fulminant variant after single dose	Discontinue drug; corticosteroids	Risk factors: Oxygen therapy; therapeutic radiation; additional cytotoxic drugs
			May relapse after withdrawal of corticosteroids
	Acute dyspnea and/or bronchospasm	Discontinue drug; bronchodilators; supportive care; consider corticosteroids	Risk factors: Vinca alkaloid use; may develop noncardiogenic pulmonary edema and/or chronic interstitial disease
			Can recur with rechallenge of vinca alkaloids
	Hemolytic uremic syndrome	Discontinue drug; supportive care; poor response to plasmapheresis or corticosteroids	Microangiopathic hemolytic anemia thrombocytopenia, renal insufficiency, noncardiogenic pulmonary edema; rare hemorrhage
Actinomycin D	"Radiation recall" pneumonitis	Discontinue drug	Effect may be longstanding

be ameliorated or prevented by antibodies to TNFα and TGF-β, or receptor antagonists to IL-1; knockout of the TNFα receptor has also demonstrated protective effects.[14–16] Bleomycin also induces direct free-radical damage after oxidation of the bleomycin-Fe (II) complex; this effect has been mitigated by iron depletion with chelators both in vitro and in vivo.[10]

The incidence of bleomycin-induced pneumonitis varies from 6% to 18%, though this figure may be higher depending on the criteria used for diagnosis and the presence of other chemotherapeutic agents in a multidrug regimen; overall mortality is estimated at 3% or less, depending on risk factor subgroup.[10,17]

Several risk factors for severe bleomycin-induced pneumonitis have been identified: (1) Toxicity appears to correlate with higher cumulative dosages. While fatal injury has been observed after administration of <100 units, there is a significant escalation in toxicity with total doses over 400 units, and severe toxicity develops in 20% of patients receiving >500 units.[18] (2) Exposure to high concentrations of supplemental oxygen, particularly in the setting of general anesthesia, may create a synergistic toxic effect. This is primarily based on animal data, including a study which demonstrated a 75% increase in mortality in hamsters treated with bleomycin and 70% oxygen for 72 hours versus bleomycin alone.[19] As a result, high fractions of supplemental oxygen are generally avoided whenever possible in clinical practice, and the evidence substantiating human risk has been largely anecdotal. There have also been case reports of recrudescence in patients exposed to even modest levels of supplemental oxygen several months after bleomycin exposure, so caution in limiting oxygen exposure for at least 6 months after treatment appears warranted.[20] (3) Thoracic irradiation prior to, concomitant with, or subsequent to, bleomycin administration may be associated with an increase in toxicity. This "radiation recall" may extend outside the original port of irradiation, and may last for years after bleomycin therapy. More recent data suggests that the augmented risk from consolidative radiation therapy may be attenuated if there is an interval of at least 28 days between chemotherapy and radiation.[21] While there is still certainly an increase in pulmonary symptoms during treatment for patients receiving combined therapy, and patients must be closely monitored, long-term sequelae may be less pronounced than originally feared.[22] (4) Since bleomycin is excreted by the kidneys, and is often coadministered with potentially nephrotoxic agents, decreased creatinine clearance below 35 mL/min is associated with increased risk of toxicity.[23] (5) The risk for pulmonary toxicity rises proportionately for every decade after 30 years, and patients over 70 years of age are at particular risk.[24] (6) Concurrent use of

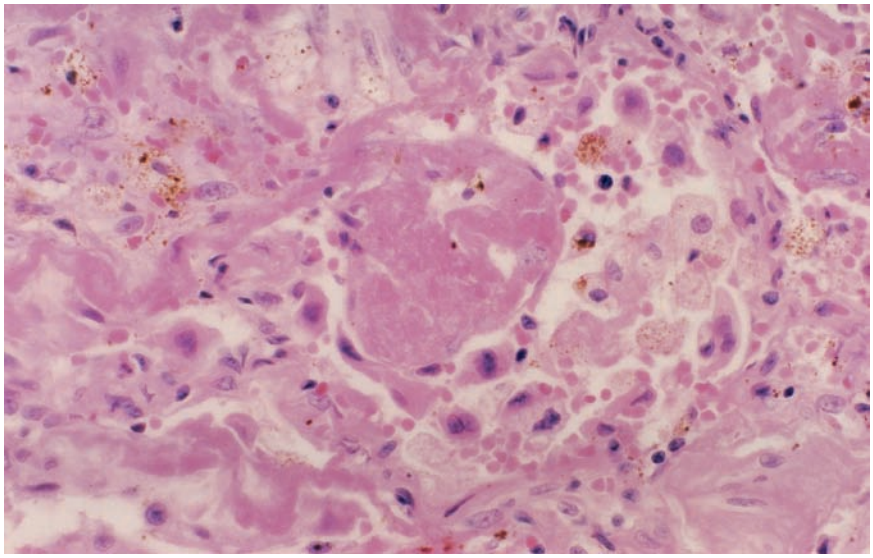


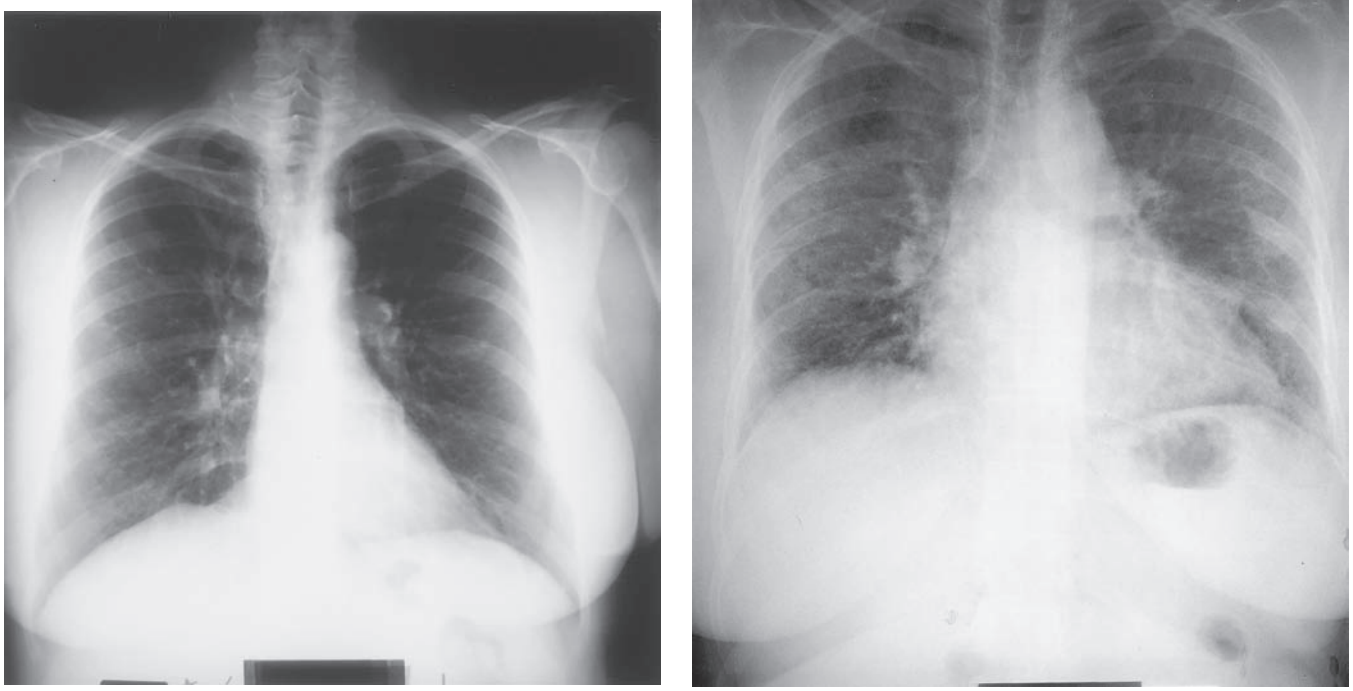
Figure 65-1 Lung biopsy specimen from a patient with clinical and radiographic evidence of bleomycin-induced pulmonary toxicity shows drug effect with acute and chronic changes. The alveolus contains an exudate of fibrin, which is undergoing organization and is surrounded by alveolar macrophages. The large and atypical cells are markedly reactive alveolar type II pneumocytes. The alveolar wall itself is scarred with collagen deposition by the spindle-shaped fibroblasts. *(Used with permission of Dr. Darryl Carter, Professor of Pathology, Yale University School of Medicine.)*

other chemotherapeutic regimens, including gemcitabine, cisplatin, and drugs in the ABVD regimen, may result in synergistic toxicity.[21,22] Though these effects have not been clearly reproducible in all cases, convention has been to reduce bleomycin dosage in drug regimens in which this synergy is a concern. (7) Smoking appeared to confer an increased risk of bleomycin toxicity in one study,[25] however this has not been confirmed in other studies, and may be confounded by the presence of other risk factors. (8) Similarly, though there have been case reports of increased incidence of bleomycin toxicity in patients receiving granulocyte colony–stimulating factor (G-CSF), likely due to increased cytokine induction, larger series have not clearly demonstrated a relationship.[26]

The clinical presentation of bleomycin-induced pneumonitis is usually subacute and insidious, occurring within a few weeks to 6 months after treatment.[10] A more fulminant presentation with acute respiratory failure has been reported but is far less common. Patients generally present with dyspnea, nonproductive cough, and low-grade fever, though some patients may be asymptomatic. Substernal or pleuritic chest pain occurs, but is infrequent. Common physical findings include hypoxemia and fine bibasilar crackles; rhonchi and a pleural rub may also develop.[27] Chest radiograph usually shows bilateral reticular or fine nodular infiltrates with a basilar predominance, often beginning at the costophrenic angles (Fig. 65-2A,B). Loss of lung volume with diaphragmatic elevation is also commonly seen. However, various radiographic patterns including alveolar infiltrates, lobar consolidation, organizing pneumonia, asymmetric lung involvement, pneumothorax, pneumomediastinum, and even lung nodules have been described. Computed tomographic (CT) scanning, particularly high-resolution computed tomography (HRCT) scanning, is more sensitive in the evaluation of radiographic abnormalities and may be useful in patients who have spirometric or clinical evidence of toxicity but negative chest radiographs (Fig. 65-3); CT scanning provides more accurate assessment of anatomic distribution of disease that correlates well with lung function impairment.[28] Most patients receiving bleomycin demonstrate a decrease in $D_{L_{CO}}$ over the course of therapy, though only a small percentage of these patients will go on to manifest clinical signs of pulmonary toxicity, which is typically also associated with restrictive ventilatory defect.[29]

Bleomycin may also cause an acute hypersensitivity syndrome of dyspnea, cough, and rash immediately following administration of drug. Lung biopsy in these cases shows eosinophilic infiltration, and changes consistent with hypersensitivity pneumonitis; peripheral eosinophilia may also be observed. These cases show a particularly favorable response to steroid therapy.[30] An acute chest pain syndrome has also been reported in 1% of patients; it occurs during infusion, resolves with termination of drug, and does not appear to predict other pulmonary toxicity from bleomycin.[31]

Discontinuation of drug is recommended for patients with clinically significant bleomycin-induced toxicity, and may be sufficient treatment for individuals with mild presentations. For more significant disease, corticosteroids are usually given in the range of 60 to 100 mg of prednisone per day for 4 to 8 weeks, with slow taper over the following 4 to 6 months guided by clinical stability of the patient. It should be noted that the steroid responsiveness of bleomycin-induced pulmonary toxicity is highly variable, with more responsive cases likely representing hypersensitivity pneumonitis or organizing pneumonia.[10] Improvement often occurs within weeks of drug cessation, but complete resolution may take up to 2 years; patients may be left with residual radiographic and/or physiological abnormalities, particularly if fibrosis has developed. Though a number of promising agents have been explored in animal models, none have yet been shown to be effective in humans.



A B

Figure 65-2 Posteroanterior chest radiographs of a 56-year-old woman with cervical carcinoma (**A**) before and (**B**) after chemotherapy with a bleomycin-containing regimen. Note the decrease in lung volume and diffusely increased interstitial lung markings in the post-chemotherapy radiograph.

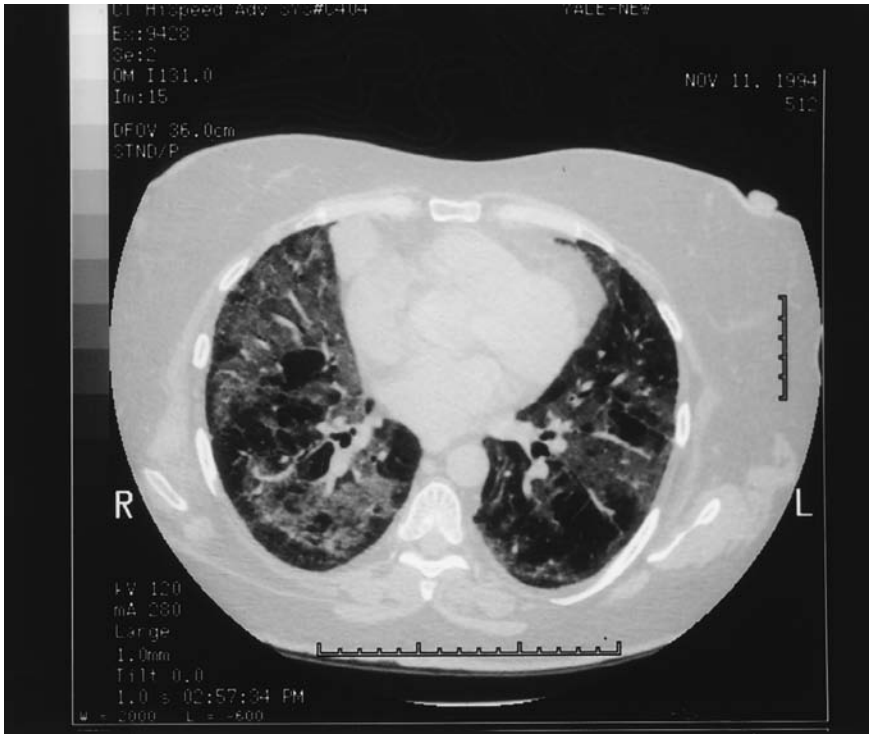


Figure 65-3 Chest computed tomography (CT) scan of same patient as in Figure 65-2, taken at the time of radiograph in Figure 65-2. Note the patchy distribution of bilateral infiltrates, whose extent is clearly delineated by CT.

■ MITOMYCIN C

Mitomycin C is an alkylating agent derived from *Streptomyces caespitosus*. It is used in multidrug regimens for multiple solid organ malignancies including non–small-cell lung, breast, gastric, pancreatic, cervical, prostate, and bladder cancers.[32] The incidence of pulmonary toxicity due to mitomycin is variably reported between 2% and 38% (with clinically relevant toxicity likely <10%), and appears to be potentiated by concurrent administration of other agents, particularly vinca alkaloids.[32] Though typically associated with intravenous therapy, cases of significant pulmonary toxicity have been reported in patients receiving both intravesicular and intraperitoneal mitomycin C.[33,34] Mitomycin C lung injury presents with multiple distinct pulmonary syndromes, including interstitial pneumonitis and fibrosis, bronchospasm, acute lung injury, thrombotic microangiopathy, venoocclusive disease with pulmonary hypertension, and pleural disease.

The most common form of mitomycin-induced lung toxicity is a chronic pneumonitis with pulmonary fibrosis similar to that seen with bleomycin; it similarly appears potentiated by exposure to supplemental oxygen and radiation.[35] Some studies have suggested a dose–response effect, with increased risk of toxicity after cumulative doses ranging from 20 to 39 mg/m^2, though this finding has not been consistently reproducible.[28,29] The exact mechanism of injury is unknown, though several have been proposed, including lipid peroxidant injury, hypersensitivity reactions, or immune complex–mediated disease.[36] Pulmonary toxicity usually occurs after 2 to 12 months of therapy, though a more fulminant form of acute lung injury has been reported after a single dose.[36]

Clinically, patients present with a subacute syndrome of cough and progressive dyspnea, often with fatigue and sometimes with pleuritic chest pain.[37] Fever is less common. Chest radiographs usually show bilateral interstitial infiltrates, occasionally with alveolar or fine nodular patterns. PFTs demonstrate a restrictive pattern with impairment in D_{LCO}, though degree of impairment correlates poorly with prognosis.[6] Histologically, biopsy specimens show mononuclear cell infiltration, alveolar-lining cell hypertrophy, collagen deposition, and alveolar septal thickening; type II pneumocyte enlargement and lymphocytic or eosinophilic infiltration have also been described. This syndrome may respond to discontinuation of drug and institution of corticosteroids at an initial dose of 60 mg/d tapered over a 4- to 6-week period; patients may demonstrate relapse once steroids are discontinued.[37]

The second syndrome of mitomycin-induced pulmonary toxicity is primarily seen in patients who have also received vinca alkaloids. While drugs of this latter category (vinblastine, vinorelbine, and vindesine) confer little in the way of risk of pulmonary toxicity when used alone, they may precipitate a syndrome of acute pulmonary toxicity when given concurrently with or subsequent to administration of mitomycin C.[38] Patients present with rapid onset of dyspnea or bronchospasm hours to weeks after exposure; symptoms generally abate in 12 to 24 hours with cessation of drug, supportive care, and bronchodilators. In some cases, however, bilateral interstitial infiltrates or noncardiogenic pulmonary edema may also develop, and patients may go on to develop chronic interstitial lung disease with permanent physiological impairment.[39] Rechallenge with vinca alkaloids alone, independent of mitomycin C, can also result in recrudescence of symptoms.[38]

The third syndrome of mitomycin C toxicity is a microangiopathy, with a presentation similar to thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP–HUS); in the case of mitomycin C microangiopathy, it is also associated with acute lung injury and respiratory failure in 50% of cases.[40] Pulmonary alveolar hemorrhage in this setting has also been described.[41] The mechanism of toxicity appears related to endothelial injury in the pulmonary vasculature. Unfortunately, prognosis is poor, and patients with chemotherapy-induced TTP–HUS respond poorly to the plasma exchange and corticosteroids that are the mainstay of therapy; there are case reports of successful treatment with rituximab, though it should be noted that these patients did not have respiratory failure.[42,43]

In addition, mitomycin C has been implicated in two cases of fatal pulmonary hypertension caused by pulmonary venoocclusive disease in patients with non–small-cell lung cancer (NSCLC) treated prior to surgical resection.[44] There have also been reports of pleural toxicity, with exudative effusions and pleural fibrosis.[6]

■ ACTINOMYCIN D

Actinomycin D is an older antitumor antibiotic derived from *Streptomyces*, which is still used in the treatment of Ewing sarcoma, rhabdomyosarcoma, Wilms tumor, and gestational choriocarcinomas. While this drug is not often associated with primary lung toxicity, it may potentiate "radiation recall" pneumonitis in patients who have received prior thoracic irradiation.[45]

ALKYLATING AGENTS

Alkylating agents (Table 65-3) have been implicated in chemotherapeutic agent–related lung disease. Important examples are described below.

The chemotherapeutic properties of the alkylating agents result from the formation of covalent linkages (alkylation) of DNA

TABLE 65-3 Alkylating Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Cyclophosphamide	Chronic pneumonitis; pulmonary fibrosis	Discontinue drug; corticosteroids	Risk factors: High cumulative dose; additional cytotoxic drugs; supplemental oxygen; therapeutic radiation Toxicity may occur years after treatment is completed Pleural fibrosis may occur in late-stage disease
Busulfan	Chronic pneumonitis; pulmonary fibrosis	Discontinue drug; consider corticosteroids	Risk factors: Cumulative dose >500 mg Often occurs after cessation of drug; prognosis poor
Oxaliplatin	Eosinophilic pneumonitis; organizing pneumonia; diffuse alveolar damage	Discontinue drug; corticosteroids	Risk factors: Pre-existing interstitial lung disease
Chlorambucil Melphalan Ifosfamide	Chronic pneumonitis; pulmonary fibrosis	Discontinue drug; consider corticosteroids for patients with hypersensitivity features	Clinical pulmonary toxicity is rare with exception of high-dose melphalan (>200 mg/m^2)

components.[46] Nitrogen mustards are the prototypic alkylating agents and were the first drugs to be used as modern cancer chemotherapy, but many other drugs also exert antineoplastic effects by alkylation. Alkylating agents that have been associated with pulmonary toxicity include derivatives of nitrogen mustards (cyclophosphamide, melphalan, chlorambucil, ifosfamide), alkyl sulfonates (busulfan), platinum-based therapies (oxaliplatin), and the nitrosoureas (carmustine/BCNU, lomustine/CCNU). The nitrosoureas are considered in a separate section below.

CYCLOPHOSPHAMIDE

Cyclophosphamide is widely used in the treatment of many malignancies, including lymphomas, breast and ovarian cancers, and a variety of other solid tumors. It may be used as part of myeloablative conditioning regimens prior to bone marrow or peripheral blood stem cell transplantation. It is also used alone or in combination with corticosteroids in the treatment of autoimmune diseases and systemic vasculitides.[3] The overall incidence of cyclophosphamide-induced lung injury is less than 1%, though as with other agents, increased pulmonary toxicity may occur in the setting of radiation therapy, oxygen supplementation, or combination treatment with other cytotoxic agents.[47]

Cyclophosphamide is administered as an inactive prodrug that is metabolized by the liver, and to lesser extent, in the lung, to 4-hydroxycyclophosphamide, phosphoramide mustard (responsible for alkylation and DNA cross-linking), and acrolein (responsible for the hemorrhagic cystitis which can complicate therapy).[48] Though the exact mechanism of cyclophosphamide-induced injury to the lung is unknown, in vitro models suggest contributions from oxidative stress, and upregulation of TGF-β, increase in collagen synthesis and, ultimately, fibrosis.[49] Cyclophosphamide toxicity lacks a clear dose–response relationship in humans, possibly due to genetic variations in drug metabolism.[50] In addition, the pharmacokinetics of both the inactive parent compound and the active alkylating derivative can be affected by variations in the cytochrome P450 superfamily of enzymes, as well as by interactions with other drugs. Therefore, functionally higher exposure to active drug may occur in the setting of substances that induce hepatic enzyme activity, such as rifampin, phenytoin, and alcohol, or with decreased renal clearance.

As with a number of other chemotherapeutic agents, cyclophosphamide-induced pulmonary toxicity may present either early in the course of treatment or in a delayed, progressive fashion that may begin years after treatment is completed. In cases where pulmonary symptoms occur long after exposure, an association with the drug may be difficult to identify. Clinical features are nonspecific, including nonproductive cough, dyspnea, fatigue, and fever. Occasionally, patients are asymptomatic but are discovered to have radiographic abnormalities compatible with drug toxicity. Chest radiographs and CT scans usually show evidence of bilateral interstitial lung disease (either bilateral reticular or nodular markings with ground-glass opacities or, later, fibrosis) but may also show pleural fibrosis in late-stage disease.[51] This latter radiographic finding may be helpful in distinguishing cyclophosphamide-associated interstitial lung disease from the idiopathic interstitial pneumonias.

Histological findings in the lung are not specific. Lung biopsy in these patients is primarily useful for exclusion of other identifiable causes of interstitial lung disease in immunocompromised patients, including infection and malignancy. When used to treat nonneoplastic lung disease, the distinction between underlying lung disease from a systemic syndrome and lung disease exacerbated by drug toxicity is often very difficult to delineate. When cyclophosphamide is used as a chemotherapeutic agent, its identification as the specific etiology of lung injury may also be difficult, as it is rarely used alone, pinpointing specific toxicity to a single agent may be impossible. Like other agents, cyclophosphamide may have synergistic toxicity with therapeutic thoracic radiation, high levels of supplemental oxygen, and other chemotherapeutic drugs with potential for lung injury.[52]

Cyclophosphamide-induced lung injury may cause significant morbidity, and a high clinical suspicion for pulmonary toxicity should result in prompt discontinuation of the drug. Early-onset pneumonitis can occasionally be fatal, but when recognized quickly, prognosis is generally favorable and recovery, though slow, is expected for most individuals. Discontinuation of the drug alone may be sufficient, though most patients also receive glucocorticoid therapy. The optimal regimen and magnitude of benefit in these cases remain unclear.[53] Unfortunately, late-onset toxicity follows an irreversible and progressive course, which appears steroid unresponsive; mortality due to progressive respiratory failure exceeds 60%.[51]

BUSULFAN

Busulfan, previously used as a treatment for chronic myelogenous leukemia (CML) prior to the advent of oral tyrosine kinase inhibitors, is now mainly used as a component of conditioning regimens for bone marrow and stem cell transplantation. Toxicity may develop within weeks of exposure, but is more typically insidious, with the average onset of symptoms more than 3 years after treatment.[3] Estimates of frequency vary widely, with an average of approximately 6%.[54] Because of the indolent nature of CML, patients were often treated for months to years with busulfan. Though it was generally well tolerated in this setting, patients receiving a cumulative dose above 500 mg appeared to be at higher risk for pulmonary complications.[55]

Currently, busulfan is used in combination with other chemotherapeutic agents in conditioning regimens prior to bone marrow and stem cell transplantation. Pulmonary complications in this situation are not uncommon though it is difficult to clearly attribute toxicity to busulfan rather than other causes including infection (notably cytomegalovirus), radiation therapy, and other drugs (particularly etoposide).[56,57] In long-term comparisons of patients receiving busulfan and cyclophosphamide versus total body irradiation prior to allogeneic transplantation, bronchiolitis obliterans was far more frequent in the former group (26% vs. 5%), while rates of pneumonitis were similar; this raises the concern that the main source of pulmonary toxicity in busulfan-based conditioning regimens may be an increase in chronic pulmonary graft versus host disease.[58]

Symptoms of busulfan lung injury usually present insidiously, weeks to years after exposure, with cough, progressive dyspnea, fever, fatigue, and weight loss. Chest radiographs typically show bilateral interstitial infiltrates with a basilar predominance. Pathological findings are consistent with other cytotoxic drug–induced pulmonary injuries, with type II pneumocyte hyperplasia, dysplasia, and desquamation into alveolar spaces. Fibroblast proliferation, collagen deposition, and fibrosis are usually evident. Desquamation and accumulation of alveolar debris can be severe in some cases, yielding a pattern similar to pulmonary alveolar proteinosis; unfortunately, total lung lavage is usually ineffective in such cases.[3,59]

There is no specific treatment for busulfan-induced pulmonary injury, except withdrawal of the drug. However, due to the delayed nature of presentation, patients are often no longer on therapy by the time toxicity is detected; thus, treatment is largely supportive. Though some spontaneous improvement may occur, when there is clinically evident busulfan-induced pulmonary toxicity the prognosis for recovery is generally poor. Corticosteroids have anecdotally been reported to be of benefit but, as with most chemotherapeutic agents, no prospective studies are available.[3] Given the possibility of late-onset pulmonary toxicity, it seems prudent that long-term follow-up of recipients of bone marrow or peripheral blood stem cell transplants with busulfan-based conditioning regimens should include pulmonary evaluation. However, guidelines for identification or treatment of pulmonary toxicity in this situation are lacking.

OTHER ALKYLATING AGENTS

Chlorambucil and melphalan are both slow-acting nitrogen mustards. Chlorambucil has an important role in the treatment of lymphoreticular malignancies including chronic lymphocytic leukemia (CLL) and has also been used in the treatment of nonneoplastic diseases, such as rheumatoid arthritis and sarcoidosis. Though pulmonary toxicity is less common than with other alkylating agents, occurring in less than 1% of patients, mortality from irreversible fibrosis when it occurs exceeds 50%.[60] As with busulfan, chlorambucil may be administered over a prolonged time in the treatment of CLL, but there does not appear to be a clear relationship between toxicity and either cumulative dose or duration of therapy. The number of cases of reported chlorambucil pulmonary toxicity is relatively small, thus no distinct clinical pattern has emerged. In cases of chlorambucil-related interstitial pneumonitis, BAL has demonstrated a CD8+ T cell alveolitis suggestive of hypersensitivity reaction.[61] Given the possibility of hypersensitivity pneumonitis, clinical suspicion should prompt immediate discontinuation of the drug, and administration of corticosteroids can be considered in patients with progressive pulmonary disease.

Melphalan has traditionally been used in the treatment of multiple myeloma, but, like other alkylating agents, it is now used to treat a variety of malignancies. High-dose melphalan (200 mg/m^2 or more) is used in conditioning regimens prior to stem cell transplantation and has been associated with fatal pneumonitis and fibrosis.[62] Since large series of such patients are not available, the incidence of pulmonary toxicity associated with high-dose melphalan given in these situations is not known. As these types of treatments become more widely available, new data should define whether pulmonary toxicity related to melphalan or other alkylating agents is indeed more prevalent than has been historically appreciated.

Ifosfamide is an alkylating agent that is structurally related to cyclophosphamide. It is used in the treatment of lymphoma and acute and chronic leukemias, as well as in solid tumors including sarcomas, ovarian cancer, and breast cancer. Dose limitation is usually related to bladder toxicity. Clinically evident ifosfamide-induced pulmonary toxicity appears to be rare and typically presents as interstitial pneumonitis.[63] It has also been described as a cause of acquired methemoglobinemia; this should be considered in the differential for patients on ifosfamide presenting with dyspnea, cyanosis, or altered mental status.[64]

Oxaliplatin is a platinum-derivative cytotoxic agent primarily used as part of multidrug regimens with 5-fluorouracil and leucovorin (FOLFOX) for treatment of colorectal cancer, as well as for treatment of pancreatic, breast, ovarian, and NSCL cancers. Though pulmonary complications are relatively rare, variable patterns of lung toxicity have been reported with FOLFOX regimens, including eosinophilic pneumonia, organizing pneumonia, and diffuse alveolar damage.[65–68] The timing, severity, progression, and prognosis of individual cases have been heterogeneous, probably owing to the diversity in pathological mechanisms. Some cases have demonstrated complete resolution with withdrawal of drug, with or without administration of corticosteroids, but others have nonetheless progressed rapidly to respiratory failure and death.[66,68] In some cases, patients were successfully rechallenged with 5-fluorouracil and leucovorin, indicating oxaliplatin as the likely culprit in the original drug reaction.[65,67] Mechanism of toxicity is still poorly understood, and likely multifactorial; glutathione depletion has been suggested based on the mechanistic role in oxaliplatin-induced hepatic injury, and an anecdotal case report of an individual who improved when treated with a combination of corticosteroids and N-acetylcysteine.[69,70] Patients with pre-existing interstitial lung disease, even when subclinical, may be at increased risk for oxaliplatin toxicity, progression of underlying interstitial disease, or both.[70] Individuals with baseline physiological and radiographic abnormalities, even in absence of symptoms, should be monitored carefully, and the threshold for withdrawal of drug and trial of corticosteroids should be low. It is unclear whether prophylactic N-acetylcysteine might be of benefit in these cases.

ANTIMETABOLITES

Antimetabolites are associated with lung injury (Table 65-4). Representative examples are discussed below.

METHOTREXATE

Methotrexate is an antimetabolite used to treat malignancies, as well as connective tissue diseases and other inflammatory conditions, including sarcoidosis and psoriasis. When used in high doses for the treatment of cancers, the incidence of pulmonary toxicity is estimated at 1% to 8%. The exact nature of methotrexate causing pulmonary toxicity in the context of cancer treatment is less well defined than in treatment of inflammatory diseases. Methotrexate, as a chemotherapeutic agent, would rarely be used alone, making interpretation of its role in any pulmonary syndrome challenging. In patients with rheumatoid arthritis, polymyositis, and other collagen vascular diseases, the potential for a variety of pulmonary manifestations related to the underlying disease can make the diagnosis of methotrexate-induced pneumonitis challenging.

The diagnostic criteria of Searles and McKendry (Table 65-5) are frequently employed in an effort to determine whether pulmonary involvement is related to methotrexate.[71] Though the criteria have

TABLE 65-4 Antimetabolites

Drug	Pulmonary Syndrome	Treatment	Comments
Methotrexate	Chronic pneumonitis; pulmonary fibrosis	Corticosteroids; discontinue drug	Most common syndrome of methotrexate-induced lung toxicity; risk factors: older age, pre-existing lung disease, diabetes, previous use of disease-modifying drugs, hypoalbuminemia
	Hypersensitivity-type lung disease	Corticosteroids; discontinue drug	May resolve even if drug is continued, but can progress to fibrosis
	Acute chest pain syndrome	Discontinue drug	Often accompanied by pleural effusions
	Noncardiogenic pulmonary edema	Supportive care; discontinue drug	Associated with intrathecal administration
Cytosine arabinoside	Noncardiogenic pulmonary edema	Supportive care; discontinue drug	Onset of symptoms usually occurs within days of initiation of treatment; risk factor: cumulative dose
	Cryptogenic organizing pneumonia	Discontinue drug; corticosteroids	Risk factors: combined therapy with anthracyclines or interferon-α
Fludarabine	Hypersensitivity-type lung disease; interstitial pneumonitis	Discontinue drug	Toxicity is uncommon; treatment associated with increased incidence of delayed opportunistic infections
Gemcitabine	Dyspnea	Occurs within hours of dose	Usually self-limited
	Interstitial lung disease; noncardiogenic pulmonary edema	Discontinue drug; corticosteroids; diuretics	Risk factors: combination treatment with taxanes or bleomycin

not been validated in a prospective cohort, they may be useful in situations where methotrexate pulmonary toxicity is a consideration.

In a multicenter case-control study of methotrexate-induced lung toxicity in patients with rheumatoid arthritis, Alarcon et al.[72] identified risk factors associated with the development of pneumonitis, including age greater than 60 years (associated with a sixfold increase in risk of pneumonitis compared with those <50 years of age), prior history of rheumatoid pleuropulmonary disease, diabetes, previous use of disease-modifying antirheumatic drugs, and hypoalbuminemia. Toxicity does not appear to have dose dependency, but daily versus weekly administration and higher weekly doses of methotrexate have been suggested as associated with increased risk, as well as pre-existing lung disease, prior PFT abnormalities, and the presence of renal insufficiency.[1,73–75] Synergistic toxicity has been reported with combination therapy using cyclophosphamide. Tapering of corticosteroid therapy or adrenalectomy may also increase the risk of methotrexate-induced toxicity.[1,76]

TABLE 65-5 Diagnosis of Methotrexate Pneumonitis

Diagnostic criteria:

- Acute onset of shortness of breath
- Fever (>38.0°C)
- Tachypnea (≥28 breaths/min) with nonproductive cough
- Radiographic evidence of interstitial or alveolar infiltrates
- WBC ≤15,000
- Negative blood or sputum cultures for pathogenic organisms (required)
- Pulmonary function tests demonstrating restrictive disease with low diffusion capacity
- Pa_{O_2} <55 mm Hg on room air (at presentation)
- Biopsy histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic microorganisms

Presence of methotrexate pneumonitis:

- Definite: at least 6 of 9 criteria
- Probable: 5 of 9 criteria
- Possible: 4 of 9 criteria

Source: Data from Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. J Rheumatol. 1987;14(6):1164–1171.

Methotrexate is a folate analog; its therapeutic effect is related to its ability to inhibit cellular proliferation by inducing deficiencies of folate coenzymes, and ultimately to decreased synthesis of DNA and RNA.[77] The mechanism(s) of methotrexate-induced lung injury is unknown. Clinically, toxicity presents with several syndromes. The most common of these is development of a symptom complex characterized by fever, dyspnea, cough, malaise, and myalgias, usually within weeks after initiation of therapy. Chest radiography usually shows diffuse interstitial infiltrates. Chest radiography may demonstrate unilateral or bilateral effusion, a nodular appearance, or hilar and/or mediastinal adenopathy, or may be normal. Rash is present in up to 17% of patients and peripheral blood eosinophilia in up to 40% of patients. BAL in this setting may show a lymphocytic alveolitis, suggestive of a hypersensitivity reaction. However, illness may resolve even with continuation of the drug, and rechallenge does not necessarily result in relapse, suggesting that hypersensitivity may not be the true mechanism of injury. This presentation of methotrexate-induced pulmonary toxicity parallels the hypersensitivity-type syndrome that is sometimes observed with bleomycin. As some patients may go on to develop chronic pneumonitis and pulmonary fibrosis, the drug is generally withdrawn when toxicity occurs.

Pulmonary toxicity from methotrexate may also present as a more insidious subacute syndrome of interstitial lung disease. Symptoms including cough, fever, dyspnea, headache, and malaise typically occur within 4 months after the initiation of treatment. Radiographically and clinically this syndrome more closely resembles the type of chronic pneumonitis seen with other cytotoxic drugs and has been reported with all routes of methotrexate administration (oral, intravenous, intrathecal). In contrast to the lung injury associated with many other chemotherapeutic agents, the pneumonitis caused by methotrexate appears, in general, to be responsive to corticosteroids. Pathological findings in the lung parallel those seen with lung injury due to other cytotoxic drugs, with interstitial and alveolar inflammation and fibrosis.[3] In addition, eosinophilic

infiltration of the interstitium, as well as granulomatous inflammation, may be observed. These latter findings are again suggestive of a potential hypersensitivity-type mechanism of inflammation.

Methotrexate-induced lung injury may also appear as an acute syndrome with pleuritis and pleural effusion. Respiratory distress progressing to noncardiogenic pulmonary edema has been described after intrathecal administration of the drug and may be neurogenic in origin.

The prognosis with methotrexate-associated lung toxicity is generally thought to be favorable. As noted, symptoms and radiographic abnormalities may resolve even with continuation of treatment. The use of corticosteroids is generally recommended, though prospective trials of this intervention are not available.

CYTOSINE ARABINOSIDE

Cytosine arabinoside (Ara-C) is a pyrimidine nucleoside analog that rapidly inhibits DNA synthesis. It is important in the treatment of acute leukemias and non-Hodgkin lymphoma. Pulmonary toxicity parallels intensity of treatment; high-dose regimens are associated with a 5% to 44% incidence of acute or subacute respiratory insufficiency.[1,78,79] Symptoms include fever, cough, dyspnea, and tachypnea; their onset may coincide with chemotherapeutic treatment or may be delayed for up to several weeks after treatment is initiated. Hypoxemia may be present. The chest radiograph generally shows a diffuse interstitial or alveolar pattern.

The pathogenesis of pulmonary toxicity due to Ara-C is unknown, but it appears to result in a syndrome of noncardiogenic pulmonary edema. In an autopsy series of 181 patients who died of acute leukemia, Haupt et al.[80] described a group of 42 patients who had received Ara-C within 30 days of death and who had moderate to severe pulmonary edema. Lung pathology showed protein-rich infiltrates in both alveoli and interstitium. Twenty-eight of these 42 patients had no other identifiable cause of their pulmonary edema. In these cases, Ara-C was thought to be the most likely precipitant. Treatment for Ara-C lung toxicity is standard supportive care for noncardiogenic pulmonary edema. Administration of corticosteroids has been recommended by some authors but is of unclear benefit.

Ara-C has also been associated with cryptogenic organizing pneumonia when administered with anthracyclines or interferon-α.[81,82] The pulmonary manifestations typically occur within a few weeks to 2 months after drug exposure and are characterized by fever, shortness of breath, and radiographic infiltrates that may be either lobar or nodular. All patients reported to date have achieved resolution of their pulmonary disease, either spontaneously or with the use of corticosteroids. Overall mortality associated with Ara-C–induced pulmonary toxicity ranges from 6% to 13%.[1,3,78,80–82]

FLUDARABINE

Fludarabine monophosphate is a purine nucleotide analog used in the treatment of CLL, low-grade non-Hodgkin lymphoma, and a variety of other lymphoproliferative disorders. A major clinical issue related to pulmonary complications with fludarabine therapy is the profound immunosuppression that may persist for months after treatment. The persistent nature of this immunosuppression is unusual when compared to other chemotherapeutic agents. The risk of opportunistic infections, including *P. jiroveci* pneumonia is increased by the use of corticosteroids in this setting. Therefore, symptomatic pulmonary disease in patients treated with fludarabine within this time frame is most likely to be related to infection.

Pulmonary toxicity from fludarabine, including interstitial pneumonitis and acute eosinophilic pneumonitis, is uncommon but has been described.[83–85] Helman et al.[83] reported the largest series to date, which included nine patients with fludarabine-related pulmonary toxicity out of a total of 105 patients (8.6%) treated with fludarabine over an 11-year period at a single institution. Toxicity did not correlate with age, prior treatment regimens, or history of prior lung disease, but occurred more frequently in patients with CLL compared to those with other lymphoproliferative disorders. The onset of symptoms ranged from 3 to 6 days after therapy, with radiographs notable for new interstitial or mixed interstitial and alveolar infiltrates. BAL fluid revealed increased cellularity without a consistently predominant cell type. Multifocal nodular pulmonary infiltrates have also been described.[85]

Biopsy specimens most commonly reveal diffuse, chronic interstitial inflammation and fibrosis, although in some cases granulomas have been observed, suggesting the possibility of a hypersensitivity reaction. In the report by Helman et al., patients with fludarabine-associated pulmonary toxicity generally demonstrated subjective and objective improvement with corticosteroid therapy. Most patients responded within days, although more delayed responses were possible. Recrudescence of noninfectious pulmonary infiltrates has been described with fludarabine retreatment; thus, fludarabine should be avoided in future regimens in patients who have developed drug-related pulmonary toxicity.

GEMCITABINE

Gemcitabine is a pyrimidine analog used in the treatment of cancers of the lung, pancreas, ovary, and uroepithelium. It is structurally similar to cytosine arabinoside. Gemcitabine is generally well tolerated when used as a single agent, which may make it appealing for use in older patients. Myelosuppression is its major toxicity. The most common respiratory complaint is dyspnea, which occurs in less than 1% of patients.[86] Dyspnea may occur within hours to days of treatment and is generally self-limited. More serious pulmonary side effects, including interstitial lung disease, pulmonary fibrosis, and acute respiratory distress syndrome, are reported much more frequently when gemcitabine is used in combination with other chemotherapeutic agents. Gemcitabine appears to have a reasonable safety profile when given with carboplatin, a treatment regimen often used for NSCLC.[5] However, severe pulmonary toxicity appears to be much more common when gemcitabine is given in combination with taxanes or bleomycin.[87–90] Acute respiratory distress has been reported with these regimens, with development of noncardiogenic pulmonary edema characterized radiographically by mixed interstitial and alveolar infiltrates. Though responses to diuretics and corticosteroids have been noted, severe pulmonary complications in this setting can be fatal. Histological evaluation most commonly reveals type II pneumocyte hyperplasia, interstitial inflammation, and hyaline membrane formation, consistent with acute lung injury. Some patients with ultimately fatal outcome have demonstrated early symptomatology, including dyspnea, hypoxemia, and radiographic infiltrates to a milder degree with prior doses of gemcitabine. Such findings should raise consideration for discontinuation of gemcitabine.

NITROSOUREAS

The nitrosoureas (Table 65-6) include carmustine or BCNU (1,3-bis-(2-chloroethyl)-1-nitrosourea), lomustine or CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), semustine or methyl-CCNU, and chlorozotocin. These cytotoxic drugs are active against a variety of neoplasms. BCNU and CCNU are highly lipophilic and can cross the blood–brain barrier, which makes them particularly useful in the treatment of central nervous system malignancies. BCNU is also used in high-dose conditioning regimens prior to bone marrow or stem cell transplantation for a variety of malignancies, including breast cancer, Hodgkin and non-Hodgkin lymphomas, multiple myeloma, and gliomas.

CARMUSTINE (BCNU)

Of the nitrosoureas, BCNU has been most extensively studied. Like bleomycin, this drug has been used in animal models of lung injury.

TABLE 65-6 Nitrosoureas

Drug	Pulmonary Syndrome	Treatment	Comments
Carmustine (BCNU)	Early-onset interstitial lung disease Late-onset pulmonary fibrosis	Discontinue drug; corticosteroids May appear years after treatment	Risk factors: total dose, female sex, underlying lung disease, cigarette smoking, combination treatment with other cytotoxic drugs
Lomustine Semustine Chlorozotocin	Interstitial lung disease	Discontinue drug	By extrapolation, toxicities and risk factors probably parallel BCNU

Intraperitoneal injection of BCNU in rats results in granulomatous inflammation and interstitial fibrosis, which progresses even after withdrawal of drug. Oxidant lung injury may play a role in the pathogenesis of toxicity as BCNU is known to inhibit glutathione reductase in pulmonary macrophages and reduces lung glutathione stores; however, the exact mechanisms by which pulmonary fibrosis occur are not well defined.

Like bleomycin, the toxicity of BCNU appears to be dose related. In a study of 94 patients with Hodgkin lymphoma who received chemotherapeutic regimens including BCNU, doses less than 475 mg/m^2 were associated with a 15% incidence of pulmonary toxicity; doses ranging between 475 and 525 mg/m^2 with a 32% incidence; and doses in excess of 525 mg/m^2 with a 47% incidence of pulmonary toxicity.[91] Treatment of intracranial gliomas may result in substantially higher cumulative BCNU doses. Very high doses (>1200–1500 mg/m^2) result in pulmonary toxicity in as many as 20% to 50% of patients.[91–93] Of note, BCNU may be used in single high doses pre–bone marrow or stem cell transplantation or may be given sequentially over longer periods of time. Whether the pattern of administration of a given total dosage has an impact on the potential for lung injury is unknown. Reported risk factors contributing to the development of pulmonary toxicity with BCNU include underlying lung disease, a history of smoking, previous or simultaneous treatment with other chemotherapy agents (including cyclophosphamide or bleomycin), chest radiotherapy, and female sex; of these, higher dose of drug and female sex are most consistently reported as related to development of pulmonary fibrosis.[92,94–98]

Pulmonary fibrosis related to BCNU falls into two patterns: An early-onset group that typically occurs within days to weeks of treatment or up to 3 years, and a late-onset group that may present years later. Early-onset pulmonary injury appears to be an underappreciated event. In a study of 152 patients treated for breast cancer with a regimen of BCNU (600 mg/m^2), cyclophosphamide, and cisplatin followed by stem cell transplantation, 59% developed a significant decrease in D_{LCO} at a median time after treatment of 45 days.[92] The vast majority of patients had subclinical disease and appeared to have improvement in their pulmonary status with initiation of corticosteroid therapy. Early-onset toxicity can also present as fulminant lung injury with progression in some cases to fatal pulmonary fibrosis.[97–99]

Late-onset pulmonary toxicity, typically presenting as pulmonary fibrosis, may occur years after BCNU treatment. In 1990, O'Driscoll et al.[95] first reported their observations on this phenomenon in survivors of childhood brain tumors. Of 31 original patients, 14 died of their tumors. In their last report in 2004 of a 25-year follow-up of the 17 survivors, 9 (53%) had died of complications related to pulmonary fibrosis.[100,101] Two patients died within the first 3 years after chemotherapy, four died between 6 and 13 years after chemotherapy, and three died between 13 and 25 years after chemotherapy. Furthermore, of the remaining eight patients still surviving, seven had radiographic and physiological evidence of pulmonary fibrosis. Thus, in this population of children treated with high-dose BCNU, late toxicity in the lung was extremely common and of severe clinical consequence.

The clinical presentation of BCNU-induced lung toxicity is variable. As noted, it may present as fulminant acute respiratory failure but more commonly presents insidiously with asymptomatic physiological abnormalities or radiographic evidence of pulmonary fibrosis. Symptoms of this latter subacute course include cough, fatigue, and progressive dyspnea. Chest radiograph is rarely normal in symptomatic patients, usually showing bilateral interstitial infiltrates with a basilar predominance. However, in O'Driscoll's series of patients with childhood brain tumors treated with high-dose BCNU and who developed late-onset pulmonary fibrosis, patients demonstrated an upper lobe predominance to the distribution of fibrotic changes.[95,100,101] Patients with an acute presentation may present with confluent alveolar infiltrates. Pneumothorax has been described in a number of cases and may be bilateral (Fig. 65-4). Pulmonary physiology generally shows a restrictive ventilatory defect, with diffusion abnormalities and eventually hypoxia. As with bleomycin-related lung injury, D_{LCO} may decrease without radiographic or clinical evidence of disease. While it has been suggested that a decrease in D_{LCO} may be the earliest sign of pulmonary toxicity, prospective evaluation of screening pulmonary function studies in the diagnosis of BCNU-induced lung toxicity has not been adequately studied. However, in light of the frequency and severity with which BCNU-associated pulmonary injury appears to occur, PFT may be helpful in identifying patients at risk and in whom administration of corticosteroids might be considered. Since BCNU toxicity is, unfortunately, common, and the likelihood of progression of BCNU-related lung injury to significant pulmonary fibrosis is seemingly high, it could be argued that surveillance with PFT should be considered, particularly if high doses of drug are to be given.

Pathological changes in the lung from BCNU parallel those seen with other cytotoxic agents. Type II pneumocyte hyperplasia and dysplasia, fibroblast proliferation, and deposition of proteinaceous material in alveoli have been described. However, inflammation tends not to be a prominent histological feature, and the cardinal feature of BCNU-induced lung toxicity appears to be interstitial fibrosis. In some cases, angiocentric necrotizing granulomatous inflammation or, more rarely, pulmonary venoocclusive disease may be seen.

The prognosis for patients with BCNU-induced lung injury is poor. For patients with early-onset lung toxicity, treatment with corticosteroids may be effective. One study of patients with breast cancer for whom BCNU was administered as part of treatment with high-dose chemotherapy followed by stem cell transplantation suggested that inhaled corticosteroids might be helpful in preventing pulmonary toxicity.[102] Late-onset pulmonary fibrosis related to BCNU does not appear to respond to corticosteroid therapy. The primary approach to BCNU toxicity should be to administer the lowest possible effective dose and monitor closely for signs of toxicity. Long-term treatment remains supportive. With the known long potential delay in the onset of signs of toxicity, long-term pulmonary follow-up is also warranted.

OTHER NITROSOUREAS

The other nitrosoureas used as chemotherapeutic agents, lomustine (CCNU), semustine (methyl CCNU), and chlorozotocin, have also been described to cause pulmonary toxicity. In general, these drugs have been used less widely than BCNU and in smaller cumulative doses. Their described lower incidence of pulmonary toxicity is likely due to these factors. As with BCNU, toxicity tends to present

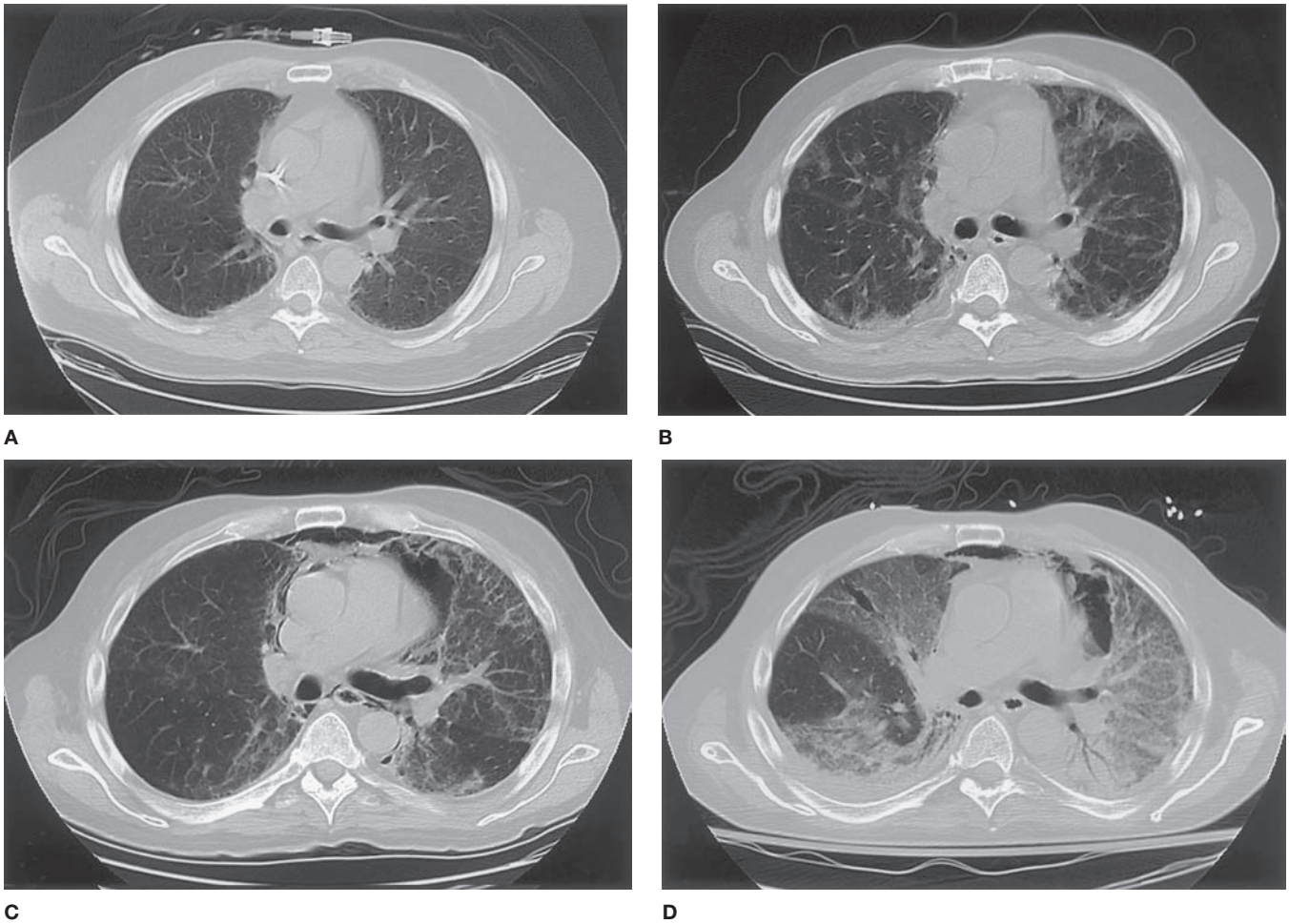


Figure 65-4 Serial chest computed tomography scans of a 54-year-old man with a history of Hodgkin lymphoma, treated with a BCNU-containing regimen. The dates of the examinations span 6 months from (**A**) to (**D**). Note the progression of diffuse interstitial patchy infiltrates, starting with the baseline normal study in (**A**). Pneumomediastinum and left pneumothorax are seen in (**C**) and (**D**). Bronchoscopy was performed between examinations (**B**) and (**C**), and demonstrated no evidence of infection. The patient had progressive dyspnea and respiratory insufficiency and eventually died of respiratory failure.

insidiously with interstitial pneumonitis and pulmonary fibrosis. However, given their close chemical relation, the potential for severe lung toxicity as seen with BCNU must be taken into consideration when using other drugs of this class.

MOLECULARLY TARGETED AGENTS

Examples of molecularly targeted agents (Table 65-7) include epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (gefitinib and erlotinib), BCR-Abl tyrosine kinase inhibitors (imatinib and dasatinib), and anaplastic lymphoma kinase (ALK) inhibitors (crizotinib).

EGFR TYROSINE KINASE INHIBITORS: GEFITINIB AND ERLOTINIB

Small molecule inhibitors of the EGFR tyrosine kinase were the first successful molecularly targeted agents effective for patients with NSCLC and virtually revolutionized the approach to treatment of this group of patients (Fig. 65-5).

Gefitinib was the first EGFR tyrosine kinase inhibitor available for clinical use. In a prospective study involving over 3000 patients treated with gefitinib for NSCLC in Japan, 4% of patients developed interstitial lung disease by 12 weeks of treatment with gefitinib, compared with 2.1% in patients treated with cytotoxic chemotherapy.[103] Studies done around the world have noted that pulmonary toxicity appears to vary geographically, being seen more commonly in Asian, as opposed to Caucasian or African populations.[104–106] Toxicity typically occurs fairly early in the course of treatment, with median exposure from 24 to 42 days. Withdrawal of drug appears in most cases to be helpful, but inexorable progression to end-stage respiratory failure and death occurs in approximately 31% of patients with gefitinib-induced pulmonary toxicity. Histological evaluation in patients who have succumbed to this illness has revealed diffuse alveolar damage. Risk factors associated with a higher likelihood of developing toxicity include older age, cigarette smoking, pre-existing interstitial lung disease, and poor performance status.[103,106]

The mechanism of gefitinib-induced lung injury remains a subject of investigation. EGFR is known to be upregulated in response to lung injury, and may be important in promoting type II pneumocyte hyperplasia in response to injury. In murine models, gefitinib has been demonstrated to result in more severe lung fibrosis in animals exposed to bleomycin. The increased frequency of this toxicity in patients with pre-existing pulmonary fibrosis lends credence to the hypothesis that gefitinib impairs the regeneration of alveolar epithelial cells in response to injury.

Erlotinib is the EGFR tyrosine kinase inhibitor used most commonly in the United States, as gefitinib is not available for clinical

TABLE 65-7 Molecularly Targeted Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Gefitinib	Interstitial lung disease; pulmonary fibrosis	Discontinue drug	Usually occurs within first 3 mo of treatment; risk factors: older age, cigarette smoking, pre-existing lung disease, Asian ethnicity
Erlotinib	Interstitial lung disease	Discontinue drug	Risk factors: pre-existing lung disease
Imatinib	Pleural effusions	Diuretics	
	Interstitial lung disease	Discontinue drug; corticosteroids	Risk factors: pre-existing interstitial lung disease
Dasatinib	Pleural effusions	Diuretics	
	Pulmonary arterial hypertension	Discontinue drug	
Bevacizumab	Pulmonary hemorrhage	Supportive care; discontinue drug	Risk factors: cavitary tumor, squamous cell histology
Cetuximab	Bronchospasm, stridor	Discontinue drug; supportive care; corticosteroids	May occur during infusion; risk factors: asthma, atopy, history of allergic reactions
Rituximab	Interstitial pneumonitis; cryptogenic organizing pneumonia	Discontinue drug; corticosteroids	
	Bronchospasm, stridor, angioedema	Discontinue drug; supportive care; corticosteroids	May occur during infusion
Trastuzumab	Bronchospasm, hemodynamic instability	Discontinue drug	May occur during infusion
	Interstitial lung disease	Discontinue drug; corticosteroids	

treatment purposes.[93,107,108] While pulmonary toxicity manifesting as interstitial lung disease is also described with erlotinib, the incidence of this complication appears to be lower compared to gefitinib. This may reflect geography, as erlotinib has predominantly been used outside of Asia, but the exact incidence of erlotinib-associated interstitial disease is not clearly defined. In a study comparing treatment of patients with advanced NSCLC with erlotinib combined with carboplatin and paclitaxel followed by maintenance erlotinib versus placebo in combination with the two cytotoxic agents, there were no differences in overall survival.[109] However, five severe cases of interstitial disease occurred in the erlotinib group, compared to one in the placebo group; three cases were fatal, were all in the erlotinib group and were thought to be related to drug toxicity.[110] The time course of lung injury appears to be similar to gefitinib, with appearance of pulmonary injury typically occurring within weeks of initiation of treatment. The presence of underlying interstitial lung disease appears to be a risk factor for the development of drug toxicity.[111]

BCR-Abl TYROSINE KINASE INHIBITORS: IMATINIB AND DASATINIB

Imatinib was the first clinically available and prototypic molecularly targeted therapy. Developed in the 1990s, it is a small molecule tyrosine kinase inhibitor that suppresses proliferation of cells expressing the BCR-Abl fusion protein. The fusion gene created by translocation of the Abl-1 ("Abelson") gene on chromosome 9 to a part of the "breakpoint cluster region" (BCR) gene on chromosome 22 is the "Philadelphia chromosome," a hallmark for CML. Imatinib is used for treatment of patients with CML as well as gastrointestinal stromal tumors.

The most common pulmonary complication related to administration of imatinib is the development of pleural effusions. This reflects the propensity of patients receiving imatinib to retain fluid in various anatomic compartments.[112] Less commonly, imatinib has been associated with the development of interstitial lung disease; underlying fibrotic lung disease may be a predisposing factor.[113,114] In small series, corticosteroids have been reported as potentially beneficial; rechallenge is generally not recommended, but has been reported without recurrent lung disease.[113]

Almost inevitably, tumor resistance to the small molecule tyrosine kinase inhibitors occurs, due to development of new point mutations in the tumor kinase, resulting in resistant clones of cells and relapse of disease. Second generation BCR-Abl tyrosine kinase inhibitors include dasatinib and nilotinib. Like imatinib, these drugs may cause fluid retention and pleural effusions and have generated reports of associated interstitial lung disease.[115,116] Perhaps more concerning, a number of case reports have been published identifying pulmonary hypertension in patients treated with dasatinib.[117,118] Withdrawal of drug does not necessarily result in reversal of the elevation of pulmonary pressures, so rechallenge should not be attempted. Pulmonary hypertension has not been reported as a complication of imatinib.

ALK INHIBITORS: CRIZOTINIB

Crizotinib inhibits the ALK and has been useful in patients with NSCLC demonstrating the EML4-ALK fusion oncogene. Interstitial lung disease has been reported with crizotinib treatment.[119] As this drug is used only in a relatively small population of lung cancer patients with the specific targetable mutation, clinical information relating to potential lung injury is limited.

MONOCLONAL ANTIBODIES

Monoclonal antibodies have been increasingly employed to treat a variety of malignancies. Pulmonary toxicity has been reported with their use.

BEVACIZUMAB

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) with activity against breast, colon, renal, and NSCL cancers. Improved response rates for locally advanced and metastatic NSCLC are observed when bevacizumab is added to traditional chemotherapy.[120] In a series including 99 patients

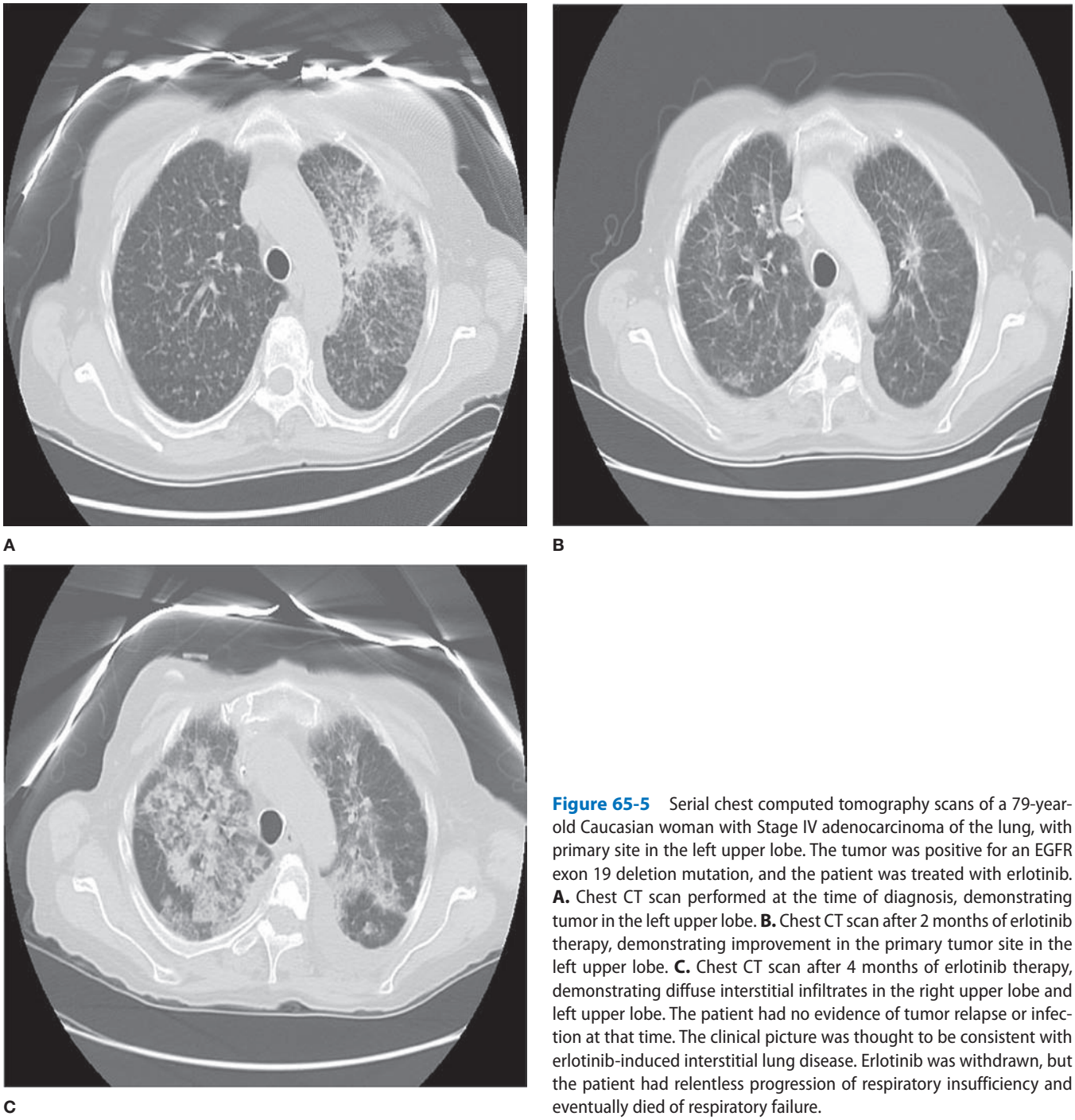


Figure 65-5 Serial chest computed tomography scans of a 79-year-old Caucasian woman with Stage IV adenocarcinoma of the lung, with primary site in the left upper lobe. The tumor was positive for an EGFR exon 19 deletion mutation, and the patient was treated with erlotinib. **A.** Chest CT scan performed at the time of diagnosis, demonstrating tumor in the left upper lobe. **B.** Chest CT scan after 2 months of erlotinib therapy, demonstrating improvement in the primary tumor site in the left upper lobe. **C.** Chest CT scan after 4 months of erlotinib therapy, demonstrating diffuse interstitial infiltrates in the right upper lobe and left upper lobe. The patient had no evidence of tumor relapse or infection at that time. The clinical picture was thought to be consistent with erlotinib-induced interstitial lung disease. Erlotinib was withdrawn, but the patient had relentless progression of respiratory insufficiency and eventually died of respiratory failure.

with newly diagnosed stage IIIB or IV or recurrent NSCLC, six patients developed serious bleeding complications including hemoptysis or hematemesis.[121] Four of the six patients died as a result of the hemorrhage. All six cases of hemorrhage appeared to be tumor related, with four of the six patients having squamous cell histology. Radiographically visible cavitation or necrosis was seen in five of the six cases of hemorrhage. As a result, current clinical investigations of regimens including bevacizumab generally exclude patients with cavitary pulmonary disease or squamous cell histology.

CETUXIMAB

Cetuximab is a chimeric monoclonal antibody directed against EGFR. Infusion of cetuximab may be associated with symptoms suggestive of anaphylaxis, including bronchospasm or stridor. In severe cases, respiratory compromise may be life-threatening. Risk factors for the development of these complications include a history of asthma, atopy, or allergic reactions.[122,123]

RITUXIMAB

Rituximab is a chimeric monoclonal antibody directed against the CD-20 antigen on B lymphocytes; it has demonstrated activity against non-Hodgkin lymphoma. It is increasingly used in inflammatory processes, including connective tissue diseases, autoimmune disorders, and solid organ transplantation. Like cetuximab, rituximab can be associated with infusion reactions, which, in severe form, may include bronchospasm and angioedema. Pulmonary parenchymal toxicity, while rare, is well described.[124–126] In one series of 107 patients with NHL receiving a regimen including

rituximab, 9 of 107 patients developed interstitial pneumonitis associated with fever, dyspnea, and cough.[126] Treatment with glucocorticoids resulted in improvement. Retreatment was attempted in four patients, two of whom developed recurrence of interstitial disease; therefore, rechallenge is usually not recommended.

The clinical syndrome of rituximab-induced pulmonary toxicity typically begins insidiously with cough and dyspnea, which may progress with subsequent reexposure to rituximab. Development of hypoxemia in association with parenchymal ground-glass opacification on CT scan has been noted. Histological examinations have revealed reactions typical of cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia, as well as interstitial inflammation with T lymphocytes and extensive arterial thrombosis. While fatal outcomes have been reported, generally this entity has responded well to withdrawal of rituximab and administration of corticosteroids.

■ TRASTUZUMAB

Trastuzumab is a humanized monoclonal antibody directed against the HER2 protein expressed by some breast and gastroesophageal tumors. Infusion reactions with trastuzumab are common; in severe cases, symptoms may include bronchospasm and hemodynamic instability. Rarely, patients with breast cancer receiving trastuzumab may develop acute pulmonary toxicity, with interstitial pneumonitis, organizing pneumonia, or acute respiratory distress syndrome; in some cases, glucocorticoids have been used successfully.[127,128]

MISCELLANEOUS AGENTS

A number of other agents used in treating malignant disease have been reported to be associated with pulmonary toxicity (Table 65-8). Representative examples are discussed below.

■ ALL-TRANS RETINOIC ACID

All-*trans* retinoic acid (ATRA) is a vitamin A derivative that has proved beneficial in the treatment of acute promyelocytic leukemia (APL). Activity of ATRA occurs through the induction of maturation of malignant cells into mature neutrophils. A constellation of symptoms and signs called the "differentiation (retinoic acid) syndrome," characterized by fever, weight gain related to volume overload and edema, respiratory distress with interstitial or alveolar infiltrates, pleural or pericardial effusions, hemodynamic instability, and renal insufficiency may occur from 2 to 21 days after drug initiation.[129,130] Pulmonary alveolar hemorrhage has been described as a rare complication.[131] The syndrome is frequently, although not universally, seen coincident with the development of a pronounced leukocytosis.[132]

Differentiation syndrome is not described with treatment on non-APL malignancies with ATRA. Radiographic features of the syndrome include pleural effusions, cardiomegaly, increased pulmonary blood volume, and widened vascular pedicle. Less frequently seen are prominent septal lines, nodules, ground-glass opacities, or parenchymal consolidation with air bronchograms. In the setting of diffuse alveolar hemorrhage, HRCT reveals poorly defined centrilobular nodules and diffuse ground-glass opacification.

Histological examination most commonly reveals infiltration of the lung parenchyma with maturing myeloid cells, with or without pulmonary hemorrhage. Fibrinoid necrosis and pulmonary capillaritis have also been described. The syndrome is thought to result from endothelial damage resulting in edema, hemorrhage, fibrinous exudates, and infiltration of neutrophils. The mechanism of ATRA-mediated pulmonary toxicity is poorly understood, but is thought to reflect systemic release of inflammatory cytokines.[133] Increased expression of cell adhesion molecules on leukemic cells has been demonstrated after ATRA administration, as has increased endothelial expression of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). In addition, elevated levels of interleukin-1β (IL-1β), IL-6, and TNFα have been observed and may promote leukocyte activation, contributing to tissue injury.

The incidence of the differentiation syndrome varies between 5% and 27% in the published literature.[129,132,134] Mortality rates vary from 5% to 29%. Prompt initiation of corticosteroids may be associated with improved outcome. Continuation of ATRA does not appear to be absolutely contraindicated, as long as corticosteroids are administered in a timely fashion. In cases with severe manifestations, discontinuation of ATRA seems reasonable, although reintroduction of drug on resolution of the syndrome is only infrequently met with recurrence.

■ INTERLEUKIN-2

Interleukin-2 (IL-2) is a glycoprotein secreted by activated lymphocytes. IL-2 therapy alone, or in conjunction with lymphokine-activated

TABLE 65-8 Miscellaneous Agents

Drug	Pulmonary Syndrome	Treatment	Comments
All-*trans* retinoic acid	"Differentiation syndrome"	Discontinue drug; corticosteroids	Treatment regimens for acute promyelocytic leukemia using all-*trans* retinoic acid should include corticosteroids
Interleukin-2	Cardiogenic edema, pleural effusions	Diuretics; supportive care	Vascular leak syndrome; risk factors: cumulative dose; administration of LAK cells
Procarbazine	Hypersensitivity-type pneumonitis	Discontinue drug	
	Interstitial lung disease	Discontinue drug	
Paclitaxel	Dyspnea, bronchospasm	Decrease infusion rate; corticosteroids and/or histamine antagonists	Pretreatment with histamine antagonists and/or corticosteroids reduces incidence
	Interstitial pneumonitis	Discontinue drug	Tends to occur within days to weeks after administration of drug
Docetaxel	Pleural effusions; noncardiogenic pulmonary edema	Discontinue drug; diuretics; supportive care	Pretreatment with corticosteroids may decrease incidence
	Interstitial pneumonitis	Discontinue drug	
Vinca alkaloids	Noncardiogenic pulmonary edema, interstitial pneumonitis, bronchospasm	Discontinue drug; corticosteroids	Risk factor: concurrent treatment with mitomycin C

killer (LAK) cells, has proved beneficial in patients with metastatic renal cell carcinoma or melanoma. Pulmonary complications related to IL-2 largely relate to cardiovascular instability with a vascular leak syndrome. This can result in cardiogenic, as well as noncardiogenic, pulmonary edema and may be associated with hypotension, renal insufficiency, and pleural effusions.

Several mechanisms have been identified that may explain the increase in capillary permeability. IL-2–activated lymphocytes produce a variety of cytokines, including tumor necrosis factor and IL-1. These may alter endothelial permeability and are thought, for example, to contribute to the septic shock syndrome. IL-2 also may promote the adhesion of natural killer cells to the capillary endothelium, thus altering vascular integrity. Furthermore, IL-2 is also associated with toxicity in multiple other organs, including the heart. Therefore, IL-2–induced cardiac dysfunction may contribute to the development of pulmonary interstitial edema.

IL-2 appears to have a cumulative dose-dependent lung toxicity that seems to be compounded by LAK cell administration.[135,136] Lung toxicity does appear to be reversible. In most cases, clinical and radiographic abnormalities resolve within several days after cessation of therapy. IL-2 has also been administered via inhalation to treat pulmonary metastases in patients with renal cell carcinoma and melanoma. The inhalational route of IL-2 appears to abrogate the risk of pulmonary toxicity, while demonstrating efficacy against intrapulmonary metastatic disease.[137]

PROCARBAZINE

Procarbazine is a cytotoxic drug used primarily in the treatment of lymphoma; it is associated with hypersensitivity pneumonitis in a small number of patients. This syndrome typically is seen after the second or third cycle of chemotherapy, although earlier as well as later occurrences have been described. Cough, dyspnea, and fever are typical symptoms, with the development of radiographic interstitial and/or alveolar infiltrates. A variable response to corticosteroids is reported, and rechallenge with procarbazine is associated with recurrence of the syndrome in the majority of patients.

TAXANES

Paclitaxel is a member of the taxane family, which functions through inhibition of microtubule disassembly and disruption of the G2 and M phases of the cell cycle. Paclitaxel has activity against a variety of carcinomas, including breast, ovarian, and NSCL cancers. There is a high incidence (up to 30%) of acute hypersensitivity reactions associated with paclitaxel infusion, with symptoms including dyspnea, bronchospasm, urticaria, and hypotension. Decreasing the infusion rate and/or administration of corticosteroids and histamine antagonists greatly reduces the frequency of this reaction to 1% to 2%. Paclitaxel has also been associated with the development of interstitial pneumonitis occurring days to weeks after paclitaxel administration, and should be suspected in those who develop interstitial infiltrates following paclitaxel therapy.[138–140]

Docetaxel has a much lower incidence of acute hypersensitivity reactions than paclitaxel.[90,141–143] Docetaxel is, however, associated with a syndrome of fluid retention related to capillary leak.[142] This syndrome is characterized by the development of peripheral edema, pleural effusions, or ascites, and is mitigated by pretreatment with corticosteroids. Interstitial pneumonitis has been associated with docetaxel administration, and may progress to respiratory failure and death.[90,141,143] This syndrome may occur as early as 1 to 2 weeks after administration of the drug. Biopsies have been reported to reveal histological changes consistent with drug-induced hypersensitivity pneumonitis or diffuse alveolar damage. As opposed to many cases of drug-induced hypersensitivity, this reaction may have a protracted course prior to recovery.

VINCA ALKALOIDS

The vinca alkaloids given as sole agents are rarely associated with pulmonary toxicity. However, the combination of vinblastine, vindesine, or vinorelbine with mitomycin C has been reported to be associated with noncardiogenic pulmonary edema, interstitial pneumonitis, and bronchospasm, often in conjunction with more diffuse endothelial dysfunction (see earlier section on mitomycin C).[36] Vinorelbine as a sole agent has been associated with dyspnea in less than 5% of cases; it occurs within hours of dosing, and generally responds to bronchodilators and corticosteroids.[144] Respiratory distress with pulmonary edema and interstitial pneumonitis has also been rarely described.

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CHAPTER 66

Drug-Induced Pulmonary Disease Due to Nonchemotherapeutic Agents

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INTRODUCTION

Drugs have long been recognized as having the potential to cause pulmonary injury. The precise incidence of drug-induced lung disease is difficult to ascertain, because the signs and symptoms of disease are shared by many other pulmonary conditions and diseases. An analysis of a database of approximately 9 million patients from the United Kingdom describes an incidence density of 0.7 per 100,0000 patient years for interstitial disease related to drugs over a 12-year period (1997–2008).[1] These data reflect only a portion of the impact of drug-induced respiratory disease, because the alveoli, upper and lower airways, pleura, pulmonary vasculature, muscles of respiration, and the central nervous system governing respiratory control are all susceptible to injury from ingested, inhaled, and parenterally administered agents. As the categories and varieties of therapeutic drugs continue to increase, clinicians will encounter disease from new culprit drugs in addition to well-established drug reactions. Web-based data repositories, such as www.pneumotox.com, can serve as useful tools for the clinician, as they provide frequent updates based on the emerging literature on drug toxicities.

As the clinician-scientist explores the literature on drug-induced lung injury, it is critical to recognize that not all associations between drug use and respiratory dysfunction imply a definitive causal link between a specific drug and the injury pattern described. The literature needs to be cautiously interpreted before concluding that the reported associations are actually due to the implicated drug rather than a confluence of clinical conditions. This chapter addresses a broad array of drug classes implicated in pulmonary toxicity. Chemotherapeutic agents are discussed separately.

GENERAL PRINCIPLES OF DRUG-INDUCED LUNG DISEASE

The lung has an enormous surface area on which blood-borne substances (therapeutic medications, nutritional supplements, illicit drugs, or toxins) actively interact with lung tissue. Drug-related pulmonary toxicity, however, is a rare event. Reactions typically occur in a small minority of individuals exposed to a given agent. In most cases, lung injury appears to be an idiosyncratic event and cannot be predicted by dose, latency from drug initiation, duration of exposure, or pharmacologic characteristics of the drug. Often, there is no characteristic clinical presentation or pathognomonic histologic pattern of injury associated with a given drug, although certain histologic patterns of lung injury may occur more frequently than others. Thus, establishment of a diagnosis of lung toxicity is frequently a diagnosis of exclusion (see Table 66-1).

It may be inferred from the idiosyncratic nature of toxicity that there are host-specific risk factors that influence development of pulmonary toxicity. The factors influencing individual susceptibility may be: (1) genetically determined, (2) due to concurrent exposures to medications or environmental factors, (3) related to the individual's comorbid disease, or (4) a function of a combination of these factors.

Genetic predisposition to drug-induced injury is not fully characterized. While drug metabolism occurs primarily in the liver, through the action of the cytochrome P450 family of enzymes, the lung also is an active site of drug biotransformation, with cytochrome P450 enzyme levels estimated as 10% to 15% of those in the liver. In addition, the existence of lung-specific cytochrome P450 isoenzymes implies lung-specific metabolism of drugs.[2] Host-specific enzyme polymorphisms affecting drug metabolism may confer increased risk of toxicity on certain individuals.[3,4]

MECHANISMS OF PULMONARY INJURY

Mechanisms of lung injury include: (1) oxidant injury, (2) immunological and inflammatory cell–mediated injury (including immune complex–mediated injury), (3) interference with matrix formation, (4) abnormal protease/antiprotease balance, and (5) interference with lipid metabolism.

Mechanisms of lung toxicity are less well characterized than are other organ toxicities. The role of drug-induced oxidant injury is well established for nitrofurantoin, and it may be the mechanism of injury of other drugs, as well. Biotransformation of these drugs results in generation of reactive oxygen species, including hydrogen peroxide (H_2O_2), the hydroxyl radical (•HO), and superoxide anion (O_2^-•), which promote lipid peroxidation, glutathione depletion, and, consequently, cellular dysfunction or cell death.[2]

Immunologically mediated injury is undoubtedly important as well. The observation that drug metabolite–protein adducts can act as immunogens, resulting in hypersensitivity reactions or other immunologically mediated tissue injury likely applies to the lung, as well as to other organs.[5,6] Lymphocytic or neutrophilic alveolitis and inflammatory cell interstitial infiltrates are present in many cases of drug-induced lung injury, and the elaboration of chemokines and proteases by these cells may lead to cellular injury. Complement-mediated injury has been implicated for drugs causing noncardiogenic pulmonary edema (ARDS), particularly opiates and β-agonists.

Amphiphilic compounds, such as amiodarone, quinidine, and some β-blockers are passively sequestered in the lung within macrophages and type II alveolar cells. The role of disruption of phospholipid metabolism as a consequence of this sequestration has been well established for amiodarone-mediated lung injury, as discussed below.

TABLE 66-1 General Principles of Drug-Induced Lung Injury

Clinical presentation is nonspecific
Injury occurs with variable latency from drug initiation
Lung injury is often dose-independent
Pulmonary toxicity may be unrelated to the drug's pharmacologic properties
Acute, subacute, and chronic reactions may be caused by a drug
A variety of histopathologic patterns may be induced by a drug
Diagnosis of drug-induced injury is often made by exclusion
Resolution of injury may occur with drug discontinuation alone
Rechallenge with the suspected culprit drug is *not* recommended

IMPACT OF CONCURRENT EXPOSURES OR CONDITIONS

The harmful effect of concurrent oxygen administration in association with the chemotherapeutic agent, bleomycin, has been well established. It has been suggested that the apparent increased risk of amiodarone toxicity in patients who have had thoracic surgery (see below) may be a result of the impact of intraoperative high oxygen tensions.[7] However, high oxygen tension does not substantially increase the risk of toxicity for most nonchemotherapeutic agents. It is plausible that the additive effect of oxidant injury may be more relevant for some individuals than others. There are evolving data that other exogenous factors, such as cigarette smoke, may influence lung injury through induction of cytochrome P450 enzymes.

DIAGNOSTIC APPROACH TO THE PATIENT WITH SUSPECTED DRUG-INDUCED LUNG DISEASE

Confirmation of suspected drug-induced pulmonary toxicity is often a diagnostic challenge. No definitive criteria exist by which to establish the diagnosis of drug-induced disease, but the diagnosis may be inferred if: (1) there is a history of drug exposure; (2) clinical, radiologic, and histopathology are consistent with previously reported toxicity; (3) alternate diagnoses are excluded (e.g., infection, systemic or idiopathic diseases); and (4) findings regress with drug discontinuation and/or treatment. Recrudescence of the lung injury following rechallenge with the culprit drug is further confirmation of drug-induced disease, but rechallenge is *not* recommended due to the substantial risk of morbidity and/or mortality.

Recognition of a patient's risk of drug-induced injury is the first step in the diagnostic process. Drug-induced lung disease occurs with prescribed drugs, over-the-counter drugs, herbal or alternative medicine preparations (many of which contain a variety of substances that could be implicated as culprit agents), and illicit drugs. Patients may be reluctant to offer accurate information about their use of alternative medicines or supplements, and the clinician must skillfully elicit the history.

The challenge of diagnosis is further compounded by the fact that the latency from the onset of drug use to development of a toxic reaction can be highly variable, such that the temporal relationship between the pulmonary findings and the culprit drug is not readily apparent. Furthermore, many drugs (e.g., amiodarone and nitrofurantoin) can cause acute, subacute, or chronic pulmonary toxicity. Moreover, new drugs will continue to come on the market, some of which will inevitably cause lung disorders. Often the potential for drugs to cause toxic reactions will only be recognized once the drug has been in use for a sufficient length of time to allow a low frequency event, such as drug-induced toxicity, to be recognized.

In many cases, drug reactions are idiopathic, rather than dose-dependent reactions, and are unpredictable in that they are unrelated to the drug's intended pharmacologic properties. Exceptions to these observations include (1) amiodarone, for which there is an increased risk of toxicity with higher daily maintenance dosages, and for which the associated histopathology is related to amiodarone's pharmacologic properties; and (2) heroin, methadone, aspirin, propoxyphene, ethchlorvynol, and colchicine that cause pulmonary toxicity only in the setting of overdose.

A diagnosis of drug-induced lung toxicity is often difficult to establish, because patients with this condition typically come to medical attention with nonspecific symptoms, radiologic findings, and laboratory data. The clinical presentation of drug-induced lung disease may be similar to that of other disorders, including infection, hypersensitivity pneumonitis due to environmental antigens, eosinophilic lung disease, systemic rheumatologic or collagen vascular disease, and idiopathic interstitial pneumonias. High-resolution computed tomography (HRCT) has utility in characterizing the lung injury, but it does not confidently predict the histologic pattern of drug-induced injury.[8,9] Even in cases in which lung tissue is obtained by biopsy, the histopathologic features may not fully distinguish drug-induced disease from the disorders or conditions mentioned earlier.

An additional consideration is that the underlying disease for which a drug is given may produce pulmonary findings similar to drug-induced lung disease. For example, rheumatoid arthritis may cause pulmonary infiltrates with similar radiographic appearance and histology to toxic reactions induced by the methotrexate, gold, or penicillamine used to treat the rheumatoid arthritis.

Once the clinician has established that a patient has (1) a recognized, identifiable risk of drug-induced lung toxicity, and (2) history, physical examination, laboratory data, and radiographic findings compatible with known patterns of lung injury, then further cytopathologic or histologic evidence may be warranted to further establish the diagnosis. The technique of bronchoalveolar lavage (BAL) is used in the diagnostic evaluation of patients with interstitial lung diseases (ILDs). Analysis of BAL fluid is most useful when it is used in conjunction with a comprehensive clinical history and HRCT.[10] BAL cytologic analysis and culture can be particularly useful to exclude typical or atypical bacterial, fungal, viral, or parasitic infections in patients with suspected drug-induced lung injury. BAL may be helpful in diagnosing diffuse lung malignancies, such as lymphangitic spread of tumor or diffuse pulmonary lymphoma.[11] BAL can also provide evidence of alveolar hemorrhage, whether bland or vasculitic in origin. The grossly cloudy BAL fluid that settles with gravity is consistent with pulmonary alveolar proteinosis, which is a reported pattern of injury associated with disease-modifying, antirheumatoid arthritis drugs.[12]

The cellular differential of the BAL fluid may help narrow the diagnosis in suspected drug-induced pulmonary disease. The most common BAL cellular profile in drug-induced disease is lymphocytosis; a cell differential of ≥25% lymphocytes should earn drug-induced ILD a place on the differential diagnosis of any presentation of ILD. Recent guidelines for the use of BAL do not recommend routine measurement of lymphocyte subsets on all patients with ILD. However, if a lymphocyte alveolitis is suspected or confirmed, the subset measurement may be justified.[10] The T suppressor (CD8+) lymphocyte subset is commonly reported in drug-induced lung disease, as seen in hypersensitivity pneumonitis. BAL T helper (CD4+) predominance has been associated with immunomodulatory drug injury, including methotrexate, sirolimus, and temsirolimus.[13,14] Other cellular profiles occur in drug-induced disease: Eosinophils and neutrophils are variably present.[15–17] A percentage of eosinophils ≥25% is consistent with acute or chronic eosinophilic pneumonia, which may be seen as a result of drug injury.

Lung tissue obtained bronchoscopically or surgically may help characterize the injury pattern and may support the diagnosis of drug-induced injury. However, lung biopsy is not essential to establish the diagnosis. The histologic patterns seen in drug-induced injury, whether usual or nonspecific interstitial pneumonia (NSIP), organizing pneumonia with or without bronchiolitis obliterans, eosinophilic pneumonia, or granulomatous inflammation are histologically indistinguishable from other etiologies of these lung injury patterns.

Adjunctive testing for serum markers has been studied in the context of drug-induced lung injury. Serum markers, including surfactant proteins (SP-A, SP-D), KL-6, and ADAM8 have been associated with drug-induced injury but have not entered into the diagnostic armamentarium for most routine clinical evaluations.[18–21] Similarly, drug-specific lymphocyte stimulation testing and lymphocyte migration inhibition testing have been shown to be useful in the diagnosis of drug-induced lung disease by some investigators, but have not been found to be sufficiently and clinically helpful to enter mainstream clinical practice.[22–25]

CLINICAL AND HISTOPATHOLOGIC PATTERNS OF INJURY

The entire respiratory system – upper and lower airway, pleura, lung parenchyma, pulmonary vasculature, muscles of respiration,

and the central nervous system governing respiratory control – is susceptible to the adverse effects of drugs. Of these areas, injury to the parenchyma is the most important cause of morbidity and mortality.

Respiratory disease may occur as the sole consequence of drug toxicity, or it may be one manifestation of a systemic drug-induced syndrome. For example, systemic hypersensitivity syndromes, such as drug rash with eosinophilia and systemic symptoms (DRESS), may be induced by drugs, particularly the aromatic anticonvulsants.[26] Drug-induced systemic lupus erythematosus (SLE) may occur, with or without pulmonary involvement, from exposure to β-blockers, amiodarone, angiotensin-converting enzyme inhibitors (ACEIs), hydralazine, procainamide, isoniazid, methyldopa, minocycline, and tetracycline, among others. In addition, drugs (e.g., phenytoin, hydralazine, propylthiouracil, D-penicillamine, and cocaine, among others) can cause the clinical picture of a pulmonary–renal syndrome, with evidence for pulmonary and renal vasculitis with renal failure.

Parenchymal injury may manifest itself in the interstitial, alveolar, and/or vascular compartments. Of the processes affecting the lung parenchyma, interstitial involvement is the most common. The major histopathologic forms of ILD – cellular and fibrotic NSIP and usual interstitial pneumonia (UIP) – have been reported to occur as an adverse effect of drugs. Unfortunately for diagnostic clarity, among the many case reports citing the presence of ILD, many have no tissue confirmation of the precise lung histology, and older case reports were published before the current guidelines for classification of ILDs were established. However, it seems likely that much of the previously reported drug-induced ILD would now be classified as either cellular or fibrotic NSIP. Virtually all histopathologic types of ILD have been reported to occur in association with drugs, including organizing pneumonia (with and without obliterative bronchiolitis), usual interstitial pneumonitis, eosinophilic pneumonia, desquamative interstitial pneumonitis, and hypersensitivity pneumonitis. It is important to recognize that few drugs have been reported to cause a single histopathologic pattern of parenchymal injury, and in the cases of many drugs, several patterns of injury may occur (Table 66-2).

NONSPECIFIC AND USUAL INTERSTITIAL PNEUMONIAS

The radiographic and histologic definitions of NSIP and UIP have been defined in the American Thoracic Society/European Respiratory Society (ATS/ERS) international, multidisciplinary consensus statements of 2002 and 2013.[27,28] Whether drug-induced, idiopathic, or due to systemic disease, the radiographic and histologic features are largely indistinguishable, and it is the clinical scenario that is critical to the differential diagnosis. Older literature on drug-induced lung disease does not necessarily conform to recent consensus definitions of NSIP, UIP, or otherwise unclassified interstitial pneumonias, making older case series somewhat difficult to interpret. Culprit drugs leading to these interstitial pneumonias include antimicrobials, antirheumatics, tumor necrosis factor (TNF) antagonsists, β-adrenergic antagonists, antiarrhythmics, anti-inflammatory drugs, antipyretics, and immunosupressants (see Table 66-2).

BRONCHIOLITIS OBLITERANS AND ORGANIZING PNEUMONIA

Organizing pneumonia (OP) with or without histopathologic evidence of obliterative bronchiolitis is a frequently reported pulmonary reaction to medications. The histologic pattern seen in drug-induced parenchymal injury is indistinguishable from cryptogenic organizing pneumonia (COP) or other causes of bronchiolitis obliterans organizing pneumonia (BOOP). The histology consists of plugs of loose connective tissue, or granulation tissue that fills respiratory bronchioles, alveolar ducts, and alveolar spaces. This may be accompanied by mild interstitial inflammation with preserved architecture. Radiographic findings of BOOP are typically bilateral, patchy areas of consolidation that are often subpleural, with a tendency to lower lobe predominance or distribution along the bronchovascular bundle.

Many of the drugs that have been reported to cause BOOP are commonly used medications. Among the implicated antimicrobials are cephalosporins, minocycline, nitrofurantoin, amphotericin B, and interferons. One of the most utilized antiarrhythmic agents, amiodarone, is known to cause BOOP, as are the anticonvulsants, carbamazepine and phenytoin, and the anti-inflammatory agents, gold, penicillamine, and sulfasalazine. In patients treated for rheumatoid arthritis (RA) with gold or penicillamine, it is important to distinguish between drug-induced OP and infiltrates reflecting a pulmonary manifestation of the underlying RA itself. A variety of other agents reported to cause obliterative bronchiolitis are listed in Table 66-2.

The clinical presentation of drug-associated OP or BOOP is similar to that of the idiopathic disease, which is now referred to as COP. Symptoms include shortness of breath, nonproductive cough, and, in some cases, low-grade fever and/or pleuritic chest pain. The chest radiograph typically shows bilateral patchy infiltrates that may be migratory over serial radiographs, with interval normal chest radiographs despite continuous drug exposure. As with other interstitial lung disease, the utility of BAL is primarily to exclude an infectious etiology of the infiltrates. There is no specific BAL cellular profile characteristic of OP or BOOP. Lung biopsy reveals characteristic histopathology, identical to that of COP. Patients with drug-induced OP or BOOP may have spontaneous resolution of disease when the offending drug is discontinued, but oral corticosteroids may be used to accelerate disease resolution if the patient is symptomatic.

EOSINOPHILIC LUNG DISEASE

Drug-induced eosinophilic lung disease may mimic other eosinophilic pulmonary syndromes, including simple eosinophilic pneumonitis (Loeffler's syndrome), chronic eosinophilic pneumonia, acute eosinophilic pneumonia, pulmonary infiltrates with peripheral eosinophilia (PIE), and Churg–Strauss syndrome (see Chapter 71). The differential diagnosis of eosinophilic lung disease includes drug-induced injury and a search for the culprit drug is an integral part of the diagnostic evaluation. Although the clinical presentation of drug-induced eosinophilic pneumonia may be identical to idiopathic conditions, several distinctions can be made. In idiopathic eosinophilic pneumonia, symptoms affect the lung exclusively, while in drug-induced eosinophilic pneumonia, respiratory symptoms may be accompanied by systemic symptoms, such as rash and fever. Marked peripheral blood eosinophilia (>1000 cells/mL) suggests drug-induced pneumonitis, rather than acute idiopathic eosinophilic pneumonia, in which the eosinophilia tends to be more modestly elevated or normal.

The diagnosis of drug-induced eosinophilic pneumonia is supported by peripheral blood and/or pulmonary eosinophilia in a setting of exposure to a suspect drug. The diagnosis may be established when other eosinophilic lung diseases are excluded. When evaluating a patient with pulmonary eosinophilia, it is particularly important to exclude infectious causes of eosinophilia so as to avoid promoting progressive infection and/or death by use of corticosteroid treatment for presumptive drug-induced eosinophilic pneumonia. Tropical pulmonary eosinophilia caused by filarial infection should be suspected if the patient has a consistent travel history. Schistosoma and Paragonimus westermani are other potential pathogens to be excluded. Strongyloides, Ascaris, and Toxocara are indigenous to the United States and are known to cause pulmonary

TABLE 66-2 Histopathologic Diagnosis or Clinical Syndrome and Strength of Association with Drug

Histopathologic Diagnosis or Syndrome	Drug	Strength of Association
Interstitial Infiltrate/ Fibrosis (acute, subacute, or chronic)	Amiodarone	++++
	ACE Inhibitor	+
	Azathioprine	++
	β-Adrenergic blockers	+
	Carbamazepine	+
	Cocaine	++
	Erlotinib	++
	Flecainide	++
	Fluoxitine	++
	Gold salts	++
	Hydrochlorothiazide	++
	Interferon-α/β	+
	mTOR inhibitors	+++
	Mesalamine	+
	Methotrexate	+++++
	Nitrofurantoin	++++
	Penicillins	+
	Phenytoin	++
	Rifampicin	+
	Rituximab	++
	Statins	++
	Sulfasalizine	+
	TNF-α antagonists	++
	Venlafexine	+
OP/BOOP	Amiodarone	++
	Amphotericin B	+
	β-Adrenergic blockers	++
	Carbamazepine	+
	Cephalosporins	+
	Cocaine	++
	Gold	+
	Interferon-α/β	+
	mTOR inhibitors	++
	Methotrexate	+
	Minocycline	+
	Nitrofurantoin	++
	D-Penicillamine	+
	Phenytoin	+
	Rituximab	++
	Sulfasalazine	+
	Talc	+
Eosinophilic lung disease	Antibiotics	++
	Carbamazepine	+
	Cocaine	++
	Ethambutol	+
	Fluoxitine	+
	Heroin	+
	Infliximab	+
	Minocycline	++
	NSAIDs	++
	Penicillins	++
	Sulfonamides	++
	Tacrolimus	+
	Tetracycline	++
	L-tryptophan (OTC preparation)[a]	++
	Venlafexine	+
Pulmonary and/or systemic hypersensitivity	Aspirin	+++
	Carbamazepine	+
	HAART	+
	Hydralazine	++
	Infliximab	+
	Minocycline	+
	NSAIDs	+
	Phenytoin	++
	Sulfasalazine	+
	Sulfonamides	+
	Valproate	++
	Vancomycin	+
	Venlafexine	+
Lupus-like Syndrome	ACE inhibitor	++
	Amiodarone	++
	β-Adrenergic blockers	++
	Carbamazepine	+++
	Hydralazine	++
	Infliximab	++
	Interferon-α/β	+
	Isoniazid	++
	Methyldopa	+++
	Minocycline	++
	Procainamide	++
	Statins	+
	Sulfasalazine	++
	TNF-α antagonists	+++
	Zafirlukast	+
Bronchospasm/Cough	Acetylcysteine	++
	Amiodarone (cough)	++
	Aspirin	++++
	ACE inhibitor	+++++
	Adenosine	++
	β-Adrenergic blockers	++++
	ARB (cough)	+
	Carbamazepine	+
	Cephalosporins	++
	Clarithromycin	+
	Cocaine	+++
	Etanercept	+
	Heroin	+++
	Interferon-α/β	++
	NSAIDs	++++
	Penicillins	+
	Proton pump inhibitors	++
	Radiocontrast	+
	Statins (cough)	++
	Venlafexine	+

TABLE 66-2 Histopathologic Diagnosis or Clinical Syndrome and Strength of Association with Drug *(Continued)*

Histopathologic Diagnosis or Syndrome	Drug	Strength of Association
Noncardiogenic pulmonary edema/ ARDS	Amiodarone	+++
	Amitriptyline	++
	Amphotericin	++
	Aspirin/NSAID overdose	++
	Carbamazepine	+
	Cocaine	++
	Cyclosporin	+
	HCTZ	++
	Heparins	+
	Interferon-α/β	+
	Methotrexate	++
	Neuroleptics	++
	Nitrofurantoin	+
	Opiate overdose	+++
	Propofol	+
	Propylthiouracil	+
	Radiographic contrast	++
	Rituximab	++
	Tocolytic agents (e.g., terbutaline, ritodrine)	+
	Tricyclic antidepressants	+++
DAH: Bland or vasculitis	Amiodarone	++
	Aspirin	+
	Azathioprine	+
	Clopidigrel	+
	Cocaine	+
	Epoprostenol	++
	Etanercept	+
	Heparin	++
DAH: Bland or vasculitis	Heroin	+
	Hydralazine	+ (vasculitis)
	Immunoglobulins	+
	LTRAs	++ (vasculitis)
	mTOR inhibitors	++
	Methotrexate	++
	Minocycline	+ (vasculitis)
	Nitrofurantoin	+ (vasculitis)
	Penicillamine	++ (bland/ vasculitis)
	Phenytoin	+ (vasculitis)
	Propylthiouracil	++ (vasculitis)
	Radiocontrast	+
	Sildenafil	+
	Sulfonamides	+++ (vasculitis)
	TNF-α antagonists	+
	Thrombolytics	++
	Warfarin	++
	Valproate	+
	Pulmonary hypertension	++++
	Aminorex	+++
	Buprenorphine	++
	Flenfluramine	+++
	Metamphetamine	++
	Methadone	+
	SSRI	++
	Talc	++
	L-tryptophan (OTC preparation)[a]	++

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; LTRA, leukotriene receptor antagonist; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter; TNF, tumor necrosis factor.
[a]Withdrawn from the market.

infiltrates and peripheral blood eosinophilia. Missing the diagnosis of a fungal infection can be lethal. Aspergillus is a ubiquitous fungus that can be difficult to diagnose as a pulmonary pathogen. BAL eosinophilia may be present without definitive evidence of invasive fungal infection, which may require a tissue biopsy for diagnosis. Coccidioides immitis is endemic in the southwestern United States, and infection can result in peripheral blood eosinophilia and pulmonary infiltrates. Serologic testing for antibodies to Coccidioides and sputum or BAL cultures are useful studies to exclude coccidioidomycosis.

Specific testing for drug reactions, such as drug-specific lymphocyte transformation tests, has been used to implicate a culprit drug. However, the clinical utility of such tests is uncertain, especially because a negative assay does not exclude the diagnosis.

Successful management of drug-induced eosinophilic lung disease is achieved by identification and discontinuation of the inciting drug. Typically, resolution of symptoms in drug-induced eosinophilic lung disease occurs with discontinuation of the culprit drug, frequently without the need for corticosteroids. In contrast, idiopathic chronic eosinophilic pneumonia may require months of treatment with corticosteroids, and relapse may occur as steroids are tapered. Relapse of the disease as steroids are tapered is rare in drug-induced eosinophilic disease; recrudescence of the lung infiltrates suggests an alternate diagnosis.

■ HYPERSENSITIVITY SYNDROMES

Systemic hypersensitivity syndromes with granulomatous inflammation of the lung may be caused by a number of drugs, most commonly the aromatic anticonvulsants, phenytoin, and carbamazepine, as well as nonsteroidal anti-inflammatory drugs (NSAIDs), minocycline, and sulfonamides, among others. DRESS has been reported primarily with the anticonvulsants and, in some cases, is accompanied by pulmonary histopathology consistent with BOOP, ILD, or granulomatous inflammation.

Not all cases of pulmonary hypersensitivity are accompanied by rash or other systemic symptoms. The clinical presentation of drug-related pulmonary hypersensitivity typically consists of acute onset of dyspnea, cough, and fever. The radiographic pattern is one of diffuse reticular or peripheral alveolar infiltrates, sometimes accompanied by pleural effusion. In most cases, drug discontinuation results in disease resolution. A minority of individuals (10%) have persistent radiographic abnormalities after several months, and

rarely, progressive disease may occur despite drug withdrawal. In these cases, a trial of corticosteroids is reasonable if the diagnosis has been well established.

ALVEOLAR INJURY: NONCARDIOGENIC PULMONARY EDEMA AND ACUTE RESPIRATORY DISTRESS SYNDROME

Alveolar disease occurs in the form of noncardiogenic pulmonary edema, diffuse alveolar damage (DAD) or acute respiratory distress syndrome (ARDS), and both bland and vasculitic diffuse alveolar hemorrhage (DAH). (Vasculitis due to drugs is discussed in the separate section below.)

Noncardiogenic pulmonary edema may be precipitated by numerous drugs, including aspirin, opiates, calcium channel blockers, some diuretics (e.g., hydrochlorothiazide and acetazolamide), intravenous and inhaled pulmonary vasodilators (e.g., epoprostenol and nitric oxide), methotrexate, TNF-alpha radiographic contrast media, tocolytics, and oxytocin, among others.[29] The onset of drug-induced pulmonary edema typically occurs in close temporal proximity to ingestion of the culprit drug and does not have a variable latency of onset.

A variety of mechanisms are implicated in the development of pulmonary edema. Increased pulmonary capillary permeability is the likely cause of aspirin-induced, interleukin-2–induced, and ethchlorvynol-induced edema. Volume expansion and sodium retention likely cause the pulmonary edema associated with the use of β2-sympathomimetic tocolytic agents. Opioid-induced edema is mediated by neurogenic reflex and deposition of immunoglobulin and complement in the lung.[30] Although the mechanisms of pulmonary edema may vary, frequently the resolution of symptoms is prompt within days of drug discontinuation.

Pulmonary edema is common in salicylate intoxication, and the risk is correlated with the degree of intoxication. A prevalence of alveolar edema as high as 20% to 30% has been reported for aspirin-intoxicated adults. An increased risk of edema is associated with chronic aspirin ingestion, older age, positive smoking history, neurologic disease, and proteinuria.[31,32]

In many cases reported as drug-induced ARDS, this condition is considered as a clinical syndrome of lung injury, rather than a specific histopathologic pattern of disease. If we examine the more specific histopathology of DAD, many cases of drug-induced injury have been reported to have these histologic characteristics and diffuse ground-glass attenuation on CT imaging of the lung. The more commonly implicated drugs associated with DAD are amiodarone, methotrexate, rituximab, and many chemotherapeutic agents.

DIFFUSE ALVEOLAR HEMORRHAGE, VASCULITIS, AND PULMONARY–RENAL SYNDROMES

Drug-induced DAH is infrequently reported in the literature on drug-induced pulmonary disease. DAH should be suspected in patients with unexplained ground-glass infiltrates or consolidation, accompanied by anemia. Hemoptysis is not required for the diagnosis, and may be absent in as many as one-third of patients with DAH.

The classification of DAH is based on histopathologic findings and includes (1) capillaritis, (2) bland hemorrhage due to drug-induced coagulopathies, and (3) DAD, the histopathologic finding in ARDS.

Pulmonary capillaritis has been described as an adverse effect of many drugs, but strong associations with its development are reported for relatively few drugs. One of the best-characterized toxicities presenting as DAH is that from propylthiouracil.[33] The DAH is a manifestation of a systemic vasculitic syndrome characterized by leukocytoclastic vasculitis, glomerulonephritis, and pulmonary capillaritis. Use of propylthiouracil induces antineutrophil cytoplasmic antibodies (ANCAs) in as many as 46% of patients, although only a minority of these develop pulmonary toxicity; pathogenesis may be mediated by antimyeloperoxidase antibodies.[34,35] Cases of pulmonary or systemic vasculitis also have been reported for diphenylhydantoin, hydralazine, nitrofurantoin, and leukotriene receptor antagonists. In the case of the last group of drugs noted, there has been considerable discussion as to whether the vasculitis is a toxic effect of the leukotriene antagonists or whether withdrawal of oral corticosteroids leads to identification of pre-existing Churg–Strauss granulomatous vasculitis. At least some reported cases of Churg–Strauss syndrome are unrelated to steroid withdrawal and appear to represent a rare complication of leukotriene antagonists.

Bland hemorrhage without capillaritis can occur (1) in the setting of therapeutic and supratherapeutic anticoagulation, (2) with the use of inhibitors of platelet aggregation (e.g., clopidigrel), and platelet glycoprotein IIa/IIIb inhibitor therapy, and (3) as a complication of thrombolysis. Drug combinations may increase the risk of pulmonary hemorrhage. For example, when therapeutic anticoagulation is combined with epoprostenol for management of pulmonary hypertension, the risk of hemorrhage is compounded.[36] Bland DAH related to D-penicillamine, amiodarone, and cocaine is discussed in the sections on individual drugs in later sections.

Drug-induced DAD may lead to bland DAH and has been reported for amiodarone, nitrofurantoin, minocycline, methotrexate, gold, cocaine, and chemotherapeutic agents.

COUGH AND ANGIOEDEMA

Cough induced by ACEIs is well characterized in several case series.[36–40] The overall reported incidence of cough ranges from 5% to 25%. Women are more at risk of developing cough than are men.[37,39,41] The latency from initiation of use to the onset of cough is variable, ranging from 1 week to 15 months. A prior diagnosis of asthma has not been found to be a significant risk factor for the development of ACEI-associated cough. While some series have reported increased nonspecific bronchial hyperresponsiveness among subjects with cough, others have not. Symptoms typically resolve promptly after a week to 1 month after discontinuation of the drug, but occasionally resolution may take as long as 3 months.[41] Angiotensin receptor blockers induce cough in approximately one-third of patients in whom ACEI-induced cough has been diagnosed.[42] Less frequent side effects of ACEIs include PIE, SLE, and subacute ILD, but these do not typically appear in conjunction with ACEI-induced cough.

Angioedema to ACEIs is a potentially life-threatening complication of these medications. Edema more commonly affects the face (57%) and less commonly affects the floor or roof of mouth and tongue (26%). In 17%, the oropharynx and glottis are involved.[43] Presenting symptoms may range from simple edema of the lips and/or face to respiratory failure requiring ventilatory support. The latency for onset is even wider than that for cough, ranging from 4 weeks to 4 years after onset of ACEI use. In one series, 70% presented within the first month of treatment.[44]

Numerous case series have reported a higher incidence of angioedema among African Americans, and a higher risk of intubation among those affected in this racial group.[43,44] Angioedema formation is likely due to elevation of circulating bradykinin as a result of ACEI-induced inhibition of its degradation, leading to vasodilatation and capillary leak. The effect of impaired bradykinin degradation may be compounded in individuals with genetically based deficiency of other bradykinin metabolizing enzymes. Most experts recommend treatment for angioedema with corticosteroids, H1- and H2-blockers, and, in some case, epinephrine.

BRONCHOSPASM AND ANAPHYLAXIS

Drug-induced bronchospasm is a relatively common side effect of many categories of medications (see Table 66-2).[45] Bronchospasm is mediated by a variety of mechanistic pathways including (1) IgE-mediated anaphylaxis, (2) non–IgE-mediated anaphylactoid reactions, (3) alteration in the cyclooxygenase (COX) and

lipoxygenase pathways, and (4) other pharmacologic mechanisms, such as β-blockade.[46,47]

Brochospasm triggered by drugs is more common in subjects with underlying asthma, atopy, or bronchial hyperreactivity. These reactions are more common in women than in men, and there appears to be familial predisposition to reactions to some drugs.[48] Symptoms range from mild chest tightness and dyspnea on exertion to respiratory failure in susceptible individuals.

In the United States, medications are the primary cause of anaphylaxis in adults and antimicrobials have been implicated as the cause of 0.7% to 10% of cases of severe bronchospasm. Penicillin remains the most important cause of anaphylaxis, accounting for up to 75% of cases annually.[49,50] Aspirin and NSAIDs are commonly implicated in bronchospasm, in one series accounting for as many as 24% of bronchoconstrictive reactions, ranging from mild to severe reactions.[49,51] (Aspirin and NSAIDs are discussed in the sections below.) Other agents more commonly implicated in bronchospasm and anaphylaxis include sulfonamides, omalizumab, halothane, heparins, protamine, insulin, and neuromuscular blocking agents.

■ BRONCHIOLITIS

Agents that have been reported to cause small airway inflammation (bronchiolitis) include medications used in the treatment of RA, such as D-penicillamine, gold, and tiopronin. The bronchiolitis in these cases may be fatal.[52–55] Interpretation of earlier literature on D-penicillamine and gold-induced bronchiolitis is complicated by the fact that RA itself can cause bronchiolitis.[56] Use of these agents has been largely supplanted by disease modifying antirheumatic drugs, immunosuppressants, and biologics, but the implicated agents may still be used in certain cases. Drug-induced bronchiolitis typically causes shortness of breath, with or without wheezing, and cough. Spirometry may not detect small airway disease until obstruction is severe, but high-resolution CT imaging protocols may show centrilobular nodules and/or tree-in-bud opacities, as well as mosaic attenuation of the lung parenchyma, reflective of airtrapping.[57]

■ PULMONARY HYPERTENSION

Pulmonary hypertension (see Chapter 72) is a relatively infrequent complication of drug therapy, but because of the subtlety of the onset of disease, paucity of symptoms until significant vascular compromise has occurred, and potential for eventual vascular collapse and death, it is critical to recognize drug-induced pulmonary hypertension early in its course. Among the drugs known to cause pulmonary hypertension are cocaine, other illicit stimulants, anorexigens, and toxic contaminants of food and nutritional supplements (e.g., tryptophan).[58]

The association of appetite suppressants with pulmonary hypertension dates to the late 1970s when reports of unexplained "primary" pulmonary hypertension were first published. The "epidemic" of pulmonary hypertension was linked to the use of aminorex fumarate, an amphetamine-derived appetite suppressant that came into use because its potential for addiction and abuse was lower than that of amphetamine. The use of aminorex was associated with a significant rise in the incidence of pulmonary hypertension, primarily among women in Germany, Austria, and Switzerland. Development of disease occurred as early as weeks to months from the onset of use of the drug, with a dose-dependent risk as high as 2 in 100. The mechanism of action on the pulmonary vasculature is through the release of catecholamines, including dopamine. The epidemic subsided as the drug's use declined.

The aminorex epidemic was followed by the introduction of fenfluramine, a phenylethylamine, like amphetamine and aminorex. Fenfluramine had been shown to be equally effective for weight reduction as an amphetamine, without the potential for abuse.

Satiety is normally accompanied by the release of serotonin, which acts on central serotonin 2_C receptors. Fenfluramine and racemic dexfenfluramine mimic normal satiety through competitive inhibition of the serotonin transporter, leading to release of serotonin from intracellular stores. These agents were used primarily in Europe throughout the 1980s. Case reports of users with pulmonary hypertension were published in Britain as early as 1981, but use of these agents persisted through the 1980s.

Two landmark reports supported a causal relationship between pulmonary hypertension and the use of fenfluramine and dexfenfluramine. The first was published in 1993, describing a cohort of young-to-middle–aged users of the anorexigens who developed pulmonary hypertension indistinguishable from idiopathic primary arterial pulmonary hypertension.[59] This was followed in 1996 by the findings of the International Primary Pulmonary Hypertension Study Group, which published a case-control series of 95 patients with pulmonary arterial hypertension.[60] An odds ratio (OR) of 23.1 for development of disease was found among those who had used an anorexigen for more than 3 months, with an estimated incidence of one to two cases per million users per year. Further support for a causal link is contained in the surveillance study of pulmonary hypertension among anorexigen users in the United States. Fenfluramine was withdrawn from the market in 1995 due to its association with increased risk for pulmonary hypertension, as well as its role in the development of valvular heart disease in users of the fenfluramine–phentermine combination anorexigen, known as "fen-phen."[61]

Epidemics of pulmonary hypertension also have been reported due to contaminants in a specific manufacturer's rapeseed oil in Spain, and from use of an over-the-counter L-tryptophan preparation that resulted in the eosinophilic myalgia syndrome, characterized by a systemic syndrome, which included acute lung injury and pulmonary hypertension.

The reason(s) that some individuals develop drug-related pulmonary hypertension while others do not has not been clearly defined. One putative risk may be polymorphisms of a cytochrome P450 enzyme, CYP 2D6, which is the primary enzyme for metabolism of fenfluramine.[62] Other risk factors have yet to be characterized.

TOXICITY ASSOCIATED WITH SELECTED DRUGS

The following drugs have been selected for discussion because (1) they are very commonly used, or (2) have important forms of toxicity associated with their use, or (3) have more recently entered into our pharmacologic armamentarium and, therefore, are likely associated a lower level of awareness of their potential toxicity to the respiratory system.

■ CARDIOVASCULAR DRUGS

Important examples of cardiovascular agents associated with pulmonary toxicity are highlighted in the sections that follow.

Amiodarone

Amiodarone is an iodinated, benzofuran-derivative antiarrhythmic used for management of life-threatening supraventricular and ventricular arrhythmias. Both amiodarone and its major metabolite, desethylamiodarone, are cationic, amphiphilic compounds with high lipid solubility, causing the drug to accumulate in a variety of tissues. The elimination half-life of amiodarone is 30 to 60 days. However, the concentration of amiodarone in lung tissue can be 100- to 500-fold higher than serum levels and the drug has been found in lung tissue as long as 1 year after discontinuation of therapy. These pharmacokinetic characteristics contribute to the drug's potential toxicity and impact treatment strategies.

One of amiodarone's biochemical effects is to impair normal phospholipid catabolism by phospholipases, thereby leading to cellular phospholipidosis. The accumulation of phospholipids in the cell may cause direct cellular injury and secondary tissue inflammation. Evidence supports cellular injury through production of

the unstable aryl radical as amiodarone is deiodinated, leading to reactive oxygen species formation and cell death.[63] The impairment of phospholipid metabolism results in the lamellar inclusions and lipid-laden foamy macrophages that characterize the histology seen on lung biopsy and BAL. These findings are characteristic of amiodarone exposure and are not indicative of toxicity unless accompanied by the lung injury patterns discussed below.

Adverse reactions to amiodarone have been reported in a variety of tissues, including the lung, liver (liver function abnormalities and increased tissue attenuation on radiographic imaging), thyroid (thyrotoxicosis), skin (discoloration), and cornea. The first reports of amiodarone pulmonary toxicity were published in 1980 and were followed by larger series of patients as amiodarone was tested in the United States in early-to-middle 1980s. Based on two trials published in 1987, the clinical picture of amiodarone pulmonary toxicity emerged as a syndrome of pulmonary infiltrates and respiratory symptoms, most often cough and dyspnea of subacute or chronic onset, accompanied by fever, malaise, and chest discomfort in 50% of those affected. In one series, 11 of 171 patients (6.4%) treated with 400 to 1200 mg of amiodarone developed pulmonary disease. In the other series, 15 of 154 subjects (9.7%) developed disease.[64–66] The time from initiation of therapy to development of symptoms was 61 to 465 days in one series and 30 to 720 days in the other. Subsequent reports have further refined these initial observations.[67]

Disease Prevalence and Risk Factors for Amiodarone Toxicity Based on the analysis of administrative databases in Quebec, approximately 4% of amiodarone users with atrial fibrillation carry a diagnosis of pulmonary fibrosis, alveolar or interstitial lung disease or ARDS.[68] Earlier studies reported the incidence of pulmonary toxicity to range from 0.1% to 10%. Predisposing risk factors for the identification of amiodarone pulmonary toxicity include older age, higher daily dosages, male gender, renal disease, and pre-existing lung disease.[68] The risk of pulmonary toxicity is dependent on daily dose: In one series, 0.1% to 0.5% of patients on 200 mg per day developed amiodarone pulmonary toxicity, while as many as 50% of those using the highest dosages (e.g., 1200 mg per day) were affected.[69] Most reports of amiodarone toxicity have been of subjects receiving doses greater than 400 mg daily. The lower doses of amiodarone that are more commonly used are considered to be safer than higher doses; however, toxicity has been reported at doses as low as 200 mg per day.[68,70]

Pre-existing lung disease may enhance the risk of toxicity, but not all studies have shown this to be the case. It is not clear whether there is actually higher incidence of toxicity in those with pre-existing lung disease, or if prior disease results in earlier perception of symptoms and attention to pulmonary causes of dyspnea. The AFFIRM (Atrial Fibrillation Follow-up of Rhythm Management) trial reported a higher risk of diagnosis of amiodarone lung toxicity if the patient had pre-existing pulmonary disease; however, there was no higher risk of either pulmonary death or all-cause mortality.[71] Patients with atrial fibrillation and amiodarone used in the setting of chronic obstructive pulmonary disease (COPD) had a hazard ratio of 2.53 (2.2–2.89) compared to those without COPD.[68] It is acceptable to use amiodarone in the setting of pre-existing lung disease if vigilance is maintained for the development of symptoms suggestive of amiodarone toxicity. Prospective studies have suggested that a decrement in diffusing capacity from baseline is a poor predictor of amiodarone toxicity. Therefore, there are no formal recommendations for screening pulmonary function tests during amiodarone use. However, it is reasonable to obtain a baseline pulmonary function test, including diffusing capacity measurement, and to follow the patient with symptom-driven testing, thereafter.

Exposure to high concentrations of supplemental oxygen may increase the risk of amiodarone pulmonary toxicity. Several authors have suggested that amiodarone pulmonary toxicity may be triggered by administration of high concentrations of supplement oxygen, or that oxygen may act in synergy with amiodarone to enhance cellular injury.[72–74] A high index of suspicion for amiodarone toxicity, therefore, should be maintained especially if high concentrations of oxygen were used perioperatively, and if high loading doses of amiodarone were initiated for the management of perioperative cardiac arrhythmias. Similarly, serious consideration to amiodarone lung toxicity is warranted if high concentrations of oxygen are used for management of respiratory failure. A less substantiated risk factor may include use of intravenous iodinated contrast media. Rapidly progressive, fatal ARDS attributed to amiodarone toxicity has been reported following pulmonary angiography.[75] A protective effect against amiodarone pulmonary toxicity by ACEIs is supported in several publications.[76–78]

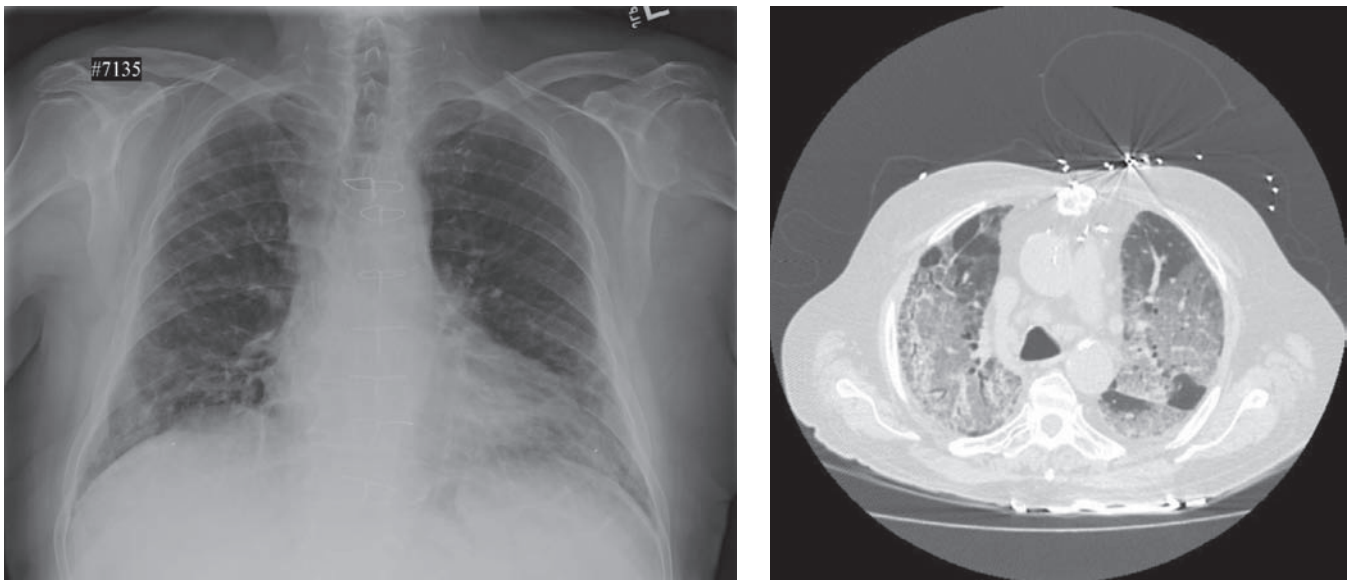
Clinical Presentation of Amiodarone Toxicity The typical clinical presentation of amiodarone pulmonary toxicity is nonproductive cough and dyspnea, sometimes accompanied by pleuritic chest pain, fever, malaise, and/or weight loss. Symptom onset is most often 6 to 24 months into treatment (100–150 g cumulative dose), but ranges from a few days to 10 years into therapy. Most subjects have an insidious onset of symptoms over several months, but fatal amiodarone-induced pulmonary toxicity occurring 2 weeks into therapy has been reported.[79]

The earliest abnormality identifiable on pulmonary function testing of affected individuals is impairment in diffusing capacity for carbon monoxide (D_{LCO}) There may be an accelerated decline in the D_{LCO} as the disease progresses, accompanied by mild restrictive physiology. Since a low D_{LCO} is not specific for amiodarone toxicity, a decline should not necessarily prompt discontinuation of the drug, but should trigger evaluation for possible cause(s) of the impairment.

Radiographic and Histologic Findings of Amiodarone Toxicity The radiographic and histologic findings associated with amiodarone pulmonary toxicity are not stereotypic (Fig. 66-1). While the most common pattern observed is subacute ILD, there are also many reports of organizing pneumonia and pulmonary fibrosis, and fewer reports of nodules (which can be fluorodeoxyglucose [FDG]-avid on PET imaging), ARDS, and SLE. Reports of PIE and DAH are rare.[67,80]

Typical radiographic findings in patients with subacute or chronic onset of disease are diffuse or patchy, interstitial or mixed alveolar–interstitial infiltrates, which are either bilateral or unilateral. Mild cases of toxicity may be characterized by a diffuse ground-glass pattern on HRCT, often in a peripheral, subpleural distribution.[81] Focal and patchy areas of higher attenuation may be superimposed on the ground-glass opacification. Alveolar opacities may correspond to areas of organizing pneumonia that are indistinguishable from idiopathic BOOP. Amiodarone toxicity should be considered in cases of migratory infiltrates that are consistent with BOOP but that are poorly responsive to steroids. Amiodarone-induced fibrosis occurs in 5% to 7% of patients diagnosed with amiodarone pneumonitis and may be present at disease presentation. A coarse interstitial pattern in the periphery of the lung, accompanied by traction bronchiectasis, is characteristic. Honeycombing is rare.

Laboratory Analysis in Amiodarone Toxicity Laboratory analyses have little utility in the differential diagnosis of amiodarone-associated lung toxicity. Common laboratory abnormalities include mild leukocytosis and elevation in serum lactate dehydrogenase (LDH). Earlier trials of amiodarone identified elevated sedimentation rates (ESRs) (i.e., a range of 39–150 mm/h) in 9 of 11 patients with pulmonary toxicity,[64] but nonspecificity of the ESR makes this test less useful in the clinical setting. Identification of a value for brain natriuretic peptide (BNP) that is normal, or at a patient's baseline, may be useful in distinguishing pulmonary causes of dyspnea from congestive heart



A B

Figure 66-1 **A.** Baseline chest radiograph before initiation of amiodarone. **B.** Amiodarone lung toxicity. ARDS superimposed on mild underlying fibrosis at 3 months after initiation of amiodarone in an 80-year-old man with progressive dyspnea. Dyspnea began insidiously approximately 1 month after amiodarone load.

failure. Laboratory findings that are investigational include elevated serum levels of KL-6, a mucin glycoprotein secreted by proliferating type II pneumocytes, and surfactant protein SP-D.[21,82] Elevations of the latter may be an early marker of amiodarone pulmonary toxicity, but the sensitivity and specificity of these tests is uncertain, and neither has a place in routine clinical evaluation of amiodarone toxicity.

Diagnostic Evaluation and Management of Amiodarone Toxicity The challenge to the practitioner considering the diagnosis of amiodarone pulmonary toxicity is that the differential diagnosis is extensive for dyspnea with pulmonary infiltrates in patients with known cardiac disease. Cardiogenic and noncardiogenic etiologies must be excluded. Consideration must be given to cardiac conditions, including ischemic and nonischemic cardiomyopathies, diastolic dysfunction, mitral valve disease, aortic stenosis, and atrial fibrillation. Noncardiogenic causes may include infections; the broad range of idiopathic interstitial pneumonias; malignant causes of infiltrates (e.g., lymphangitic spread of tumor or lymphoma); systemic diseases, such as sarcoidosis, amyloidosis, or autoimmune disease; exposures to inhaled agents (e.g., occupational inorganic dust exposures, or organic inhalations, with subsequent development of hypersensitivity pneumonitis); and exposures to drugs other than amiodarone.

The risk of invasive workup must be weighed against those of empiric therapy, which includes drug discontinuation and, possibly, corticosteroids. BAL may reveal a lymphocytosis, often with a predominance of CD8+ lymphocytes, reflective of a lymphocytic alveolitis. This finding, however, is not consistently reported, and some affected individuals may have elevated BAL neutrophils as well. Significant BAL eosinophilia is rare. Abundant alveolar macrophages with a "foamy" cytoplasm, indicative of undigested phospholipids, are found in all subjects chronically exposed to amiodarone and are not indicative of pulmonary toxicity per se. Hemosiderin laden macrophages are infrequently found, since alveolar hemorrhage is rare. As the BAL findings are neither sensitive nor specific for amiodarone pulmonary toxicity, the role of BAL in the diagnosis is controversial.

Lung biopsy findings, however, may support the diagnosis of amiodarone toxicity. Earlier reports of amiodarone pulmonary toxicity describe DAD of variable severity in all affected subjects. Those more severely affected had evidence of acute DAD, with abundant hyaline membranes and reactive type II pneumonocytes lining the alveoli, while others showed organizing DAD with interstitial and intra-alveolar proliferation of fibroblasts and prominent type II pneumocytes. All cases had abundant "foamy" macrophages in the alveolar spaces. The foamy appearance of the cytoplasm is due to the presence of lamellar bodies (~1 μm in diameter) containing lipid particles, reflecting the disrupted lipid metabolism caused by amiodarone. The foamy macrophages or histiocytes are not indicative of toxicity; in fact, similar vacuolated histiocytes and parenchymal cells may be found in the thyroid, liver, and skin of treated individuals without clinical evidence of cellular dysfunction.

The diagnosis of amiodarone pulmonary toxicity is supported by the presence of lamellar bodies in macrophages, pneumocytes, bronchiolar epithelium, and/or endothelial cells, but the diagnosis cannot be made unless there is also evidence of interstitial lymphocytic infiltrates or fibrosis with alveolar distortion. Histologic findings may also fit the description of fibrotic NSIP or bronchiolitis with organizing pneumonia, and combinations of histologic findings may occur. Despite the early reports, few patients with amiodarone pulmonary toxicity have DAD pathologically unless they fit the clinical picture of ARDS. Alveolar hemorrhage may be present, but it is not a common feature of amiodarone toxicity.[83]

In contrast to other types of drug-induced pulmonary toxicity, resolution of amiodarone-induced toxicity does not often occur with discontinuation of the drug alone. Amiodarone becomes sequestered in tissues and the clearance of drug is typically prolonged. Depending on the severity of respiratory symptoms, practitioners often may need to treat affected patients with corticosteroids. Specific dosages of prednisone have not been studied for efficacy, but 0.5 to 1 mg/kg is a reasonable starting point in most cases. Due to the pharmacokinetic characteristics of amiodarone, the required duration of therapy may be as long as several months, and recrudescent disease after tapering of corticosteroids is not uncommon.

β-Adrenergic Receptor Blockers

The most common adverse effect of β-adrenergic blockers on the respiratory system is precipitation of bronchospasm in asthmatics and patients with reactive airway disease. The high frequency of clinically significant bronchospasm in hypertensive

asthmatics treated with nonselective β-adrenergic blockers, such as propranolol, requires that these agents be avoided in asthmatics. β1-Receptor–selective agents and the mixed α- and β-receptor blockers, labetalol, are better tolerated but should be used with considerable caution in asthmatics. The use of β-adrenergic blockers is not contraindicated in patients with COPD. Many individuals with COPD tolerate β-adrenergic blockers without significant decrement in their lung function. Patients with COPD who have clinical or spirometric evidence of variable airflow obstruction responsive to bronchodilators should be observed carefully for bronchospasm upon initiation of these agents; the cardiac benefit of β-blockade in these subjects may outweigh any risk.

Pulmonary parenchymal injury associated with the use of β-adrenergic blockers is not common, but it warrants mention because of the ubiquitous use of these agents. Subacute interstitial infiltrates, PIE, and pulmonary edema have been reported in conjunction with the use of acebutolol, propranolol, labetalol, nadolol, and pindolol. Thus, the clinician should be vigilant for these reactions from using β-adrenergic blockers as a class. SLE has reported with the use of acebutolol, propranolol, labetalol, and pindolol.

Hydralazine

Hydralazine-induced pulmonary disease is not common, but it can be associated with systemic autoimmune disease that is potentially fatal even when recognized.[84] Half of the patients on daily doses of greater than 200 mg have a positive ANA, however only 10% of these patients develop clinical symptoms. The most important reported complication of long-term use of hydralazine is drug-inducedLE, which occurs more frequently if daily dosing is greater than 200 mg or the cumulative dose exceeds 100 g. In addition, there have been cases of pulmonary–renal syndrome associated with the use of hydralazine.[85] Pleuropulmonary manifestations occur in 30% of affected subjects, and isolated pulmonary parenchymal disease is rare. Subacute ILD/NSIP, organizing pneumonia, and DAH also have been documented.

Hydrochlorothiazide

The most commonly reported pulmonary side effect of the diuretic hydrochlorothiazide (HCTZ) is noncardiogenic pulmonary edema or ARDS.[86] Pulmonary edema was first reported in 1968 as a potentially life-threatening complication of HCTZ use. The onset of symptoms is typically acute and less often occurs later in the course of HCTZ use. Typical symptoms and signs include acute dyspnea and hypoxemia; fever, tachycardia, hypotension, and shock may accompany the dyspnea. Immunologically mediated capillary leak has been suggested as a possible mechanism of action. IgG deposition in the alveolar membrane and elevated serum IgM have been reported. Management is supportive, and symptom resolution typically occurs in a few days. Rechallenge with HCTZ can cause recrudescent pulmonary edema and is not recommended. Since HCTZ is a widely used diuretic, frequently used in patients with cardiovascular disease who are prone to pulmonary edema, the true incidence of drug-induced noncardiogenic pulmonary edema may be underreported.

Procainamide

Procainamide, used in the treatment of supraventricular and ventricular arrhythmias, is frequently cited as a cause of drug-induced lupus (DIL). Among patients using procainamide for over 2 months, as many as 50% to 90% develop serum antinuclear antibodies (ANAs), and of these, 10% to 30% may develop symptomatic DIL. Slow acetylators develop DIL at lower doses of procainamide and earlier in their course of treatment.[87] Symptoms associated with drug-induced disease are indistinguishable from those of idiopathic SLE, and may include fever, rash, arthralgias, Raynaud disease, myositis, vasculitis, and serositis. Among affected subjects, 40% to 80% exhibit pleuropulmonary manifestations characteristic of SLE, such as pleuritis, with pleural effusion and/or diffuse parenchymal infiltrates. Of these findings, pleural disease is more common, while parenchymal infiltrates are present in fewer than half of affected individuals.[88] The pleuritis of DIL may produce pleural fluid with characteristics indistinguishable from those of spontaneous SLE: high pleural fluid ANA (≥1:160), high pleural fluid to serum ratio of ANA (≥1), and LE cells. More severe myositis also may affect respiratory muscle function and result in ventilatory insufficiency, perhaps potentiated by competitive blockade of the acetylcholine receptor by procainamide. The absence of renal or central nervous system involvement is suggestive of DIL, but it is otherwise difficult to differentiate drug-induced disease from other SLEs on clinical grounds. The absence of anti–double-stranded DNA, normal complement levels, and identification of antibodies to histone complex H2A-H2B support the diagnosis of DIL.

Unlike idiopathic SLE, DIL may resolve over several weeks simply with discontinuation of the drug and without the use of corticosteroids or immunosuppressants. More severely affected patients may benefit from oral corticosteroids, which appear to accelerate symptom resolution. A positive ANA without signs or symptoms of local or systemic disease need not warrant discontinuation of procainamide. Relapse after symptom resolution does not occur unless the drug is reintroduced.

■ STATINS

Statins are widely used 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Injury has been reported for various statin compounds and appears to be a class effect. Clinicians are more familiar with the well-reported myositis and hepatotoxicity associated with statins than they are pulmonary side effects.[89] Based on Food and Drug Administration reports of adverse events and the medical literature, lung injury occurs in 0.01% to 0.04% of patients with side effects attributed to statin use.[90] Although the incidence of adverse pulmonary events among all statin users is low, the widespread use of this class of drugs makes lung injury a potentially important side effect.

As with other drugs, the latency, radiographic and histopathologic pleuropulmonary manifestations associated with statins are variable. The latency between initial use and onset of injury ranges from 1 week to 120 months (mean, 34 months; SD, ±35 months).[91] The most common presenting complaints are nonspecific: dyspnea, cough, and fever. The predominant radiographic findings are ground-glass and alveolar opacities that are diffuse in distribution, sometimes with patchy consolidation. Fewer subjects exhibit interstitial infiltrates or fibrosis, and pleural effusion is reported, but is rare.[91,92] Analysis of BAL fluid shows no characteristic predominant cellular profile. Foamy macrophages suggesting pulmonary phospholipidosis have been observed in some, but not all cases. When obtained, biopsies demonstrate histopathology consistent with NSIP or hypersensitivity pneumonitis.[90,92–94] The mechanism of lung injury from statins is not fully characterized, but a role of NLRP3 inflammasome activation has been proposed.[95]

Resolution of statin-induced lung disease has been achieved with drug discontinuation, with or without corticosteroid therapy.

■ ANTICONVULSANTS

Various types of pulmonary injury may result from exposure to phenytoin. Among the reported patterns of injury are pulmonary hypersensitivity reactions, which may be a component of systemic hypersensitivity (see the prior discussion of DRESS). Two fatal cases of apparent polyarteritis nodosum and necrotizing vasculitis have been reported. The histologic findings in subacute phenytoin lung toxicity are most consistent with NSIP, but lymphocytic interstitial pneumonitis and BOOP have been described, as well. In

some cases, parenchymal findings are accompanied by peripheral blood eosinophilia, suggesting PIE syndrome. The presence of cold hemagglutinins has been reported. Carbamazepine has also been reported to cause systemic and pulmonary hypersensitivity syndromes.

■ ANTIRHEUMATIC AND ANTI-INFLAMMATORY DRUGS

Pulmonary toxicity has been reported with aspirin non-steroidal anti-inflammatory drugs (NSAIDs), and a number of drugs used in the management of rheumatologic disorders.

Aspirin

The most common pulmonary reaction associated with aspirin use is bronchospasm, which may occur with therapeutic dosing in aspirin-sensitive individuals. Aspirin and NSAIDs induce bronchoconstriction by diverting arachidonic acid metabolites toward the lipoxygenase metabolic pathway, thereby leading to enhanced leukotriene-mediated airway inflammation and bronchoconstriction. Less commonly reported pulmonary complications of aspirin use include PIE syndrome, DAH, pulmonary hypersensitivity, vasculitis, and ARDS.

Acute salicylate poisoning produces symptoms of central nervous system toxicity (tinnitus, vertigo, nausea, vomiting, and hyperventilation) in mild to moderate overdose, and may result in coma, severe metabolic acidosis, and noncardiogenic pulmonary edema with critical overdoses. Pulmonary edema occurs in as many as 30% of patients with severe salicylate poisoning and may result in respiratory failure, often exacerbated by severe metabolic acidosis. Risk factors for salicylate toxicity include increased age and chronic aspirin ingestion. Management of severe toxicity includes supportive intensive care and sodium bicarbonate infusion to promote drug excretion.

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are widely used and generally well tolerated. However, NSAIDs may cross react with aspirin, producing a variety of allergic and pseudoallergic reactions affecting upper and lower airways.[96] NSAIDs cause bronchospasm in susceptible individuals with symptoms range from mild to severe. NSAIDs also cause anaphylactic reactions through the same mechanisms as that for aspirin.

The bleeding tendency induced by NSAIDs is well known, and reports exist of pulmonary hemorrhage associate with their use. DAH has been reported for ketorolac tromethamine in subjects without an underlying bleeding diathesis, but the histopathology leading to DAH has not been characterized.[97]

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor used as an anti-inflammatory and immunosuppressant, as well as a chemotherapeutic agent when used in higher doses. Despite the availability of newer antirheumatic drugs, methotrexate has retained its position as a first-line disease-modifying agent for the management of RA. Methotrexate affects cell replication through inhibition of dihydrofolate reductase, the enzyme that converts folic acid to its active coenzyme, tetrahydrofolate, allowing it to serve as one-carbon carriers in the synthesis and repair of DNA. The major nonpulmonary side effects of methotrexate correlate with the degree of folate deficiency. In contrast, pulmonary toxicity does not correlate with folate deficiency and may be seen at doses as low as 7.5 mg/wk, a conventional starting dose for treatment of RA. Conditions that have been identified as risk factors for toxicity include diabetes (OR, 35.6), hypoalbuminemia (OR, 19.5), rheumatoid pleuropulmonary disease (OR, 7.1), previous use of other disease-modifying agents (e.g., gold, sulfasalazine, or penicillamine), and older age (OR, 5.1).[98]

Methotrexate-induced pulmonary toxicity typically occurs within the first 2 years of treatment, but it can occur as early as 1 month into therapy. Pulmonary symptoms are most often subacute in onset, presenting over days to weeks, and include dyspnea, cough, fever, and less frequently, chest pain (<10%).[99] Symptoms may also develop acutely.[100] Radiographic changes are interstitial and bilateral in 50% of cases, but may also include a mixed alveolar–interstitial pattern that may appear as ground-glass opacities on high-resolution CT imaging.[99] Fibrotic changes are less common.

Diagnosis is challenging in cases of suspected methotrexate-induced pulmonary toxicity and RA, because similar clinical presentations may occur as a manifestation of RA itself. The most important diagnosis to exclude is infectious pneumonia, including that from opportunistic organisms. A diagnosis of methotrexate-induced lung disease is suggested by a predominance of lymphocytes, rather than neutrophils, on BAL.[14,22] The lymphocytic BAL fluid of methotrexate-induced hypersensitivity pneumonitis often has a CD8-predominant profile (low CD4:CD8 ratio), but not exclusively so. It appears that the type inflammatory cells may predict disease severity. In one study of 56 cases of methotrexate pulmonary toxicity, a lymphocyte-predominant BAL fluid was associated with late onset of symptoms (>6 months from drug initiation) and lower mortality than in those with neutrophil-predominant BAL.[101] Histopathology is varied and may demonstrate ill-formed granulomas suggestive of hypersensitivity pneumonitis, changes of chronic interstitial pneumonitis, BOOP, and/or DAD. PIE syndrome has also been reported.[99]

As with other pulmonary toxicities, prompt drug withdrawal is critical; resolution follows in the majority of patients. Corticosteroids may accelerate recovery in those with severe disease or symptoms refractory to drug withdrawal alone. Fatalities have been reported in subjects rechallenged with methotrexate, but rechallenge has been tolerated in others, arguing against hypersensitivity as the mechanism of injury in some subjects.

D-Penicillamine

D-Penicillamine is used as an anti-inflammatory agent in the management of rheumatoid arthritis. Although currently used less frequently than disease-modifying antirheumatic drugs (DMARDs), its pulmonary manifestations are important to recognize, as mortality from penicillamine pulmonary toxicity can be as high as 5%.

Penicillamine is a heavy metal chelating agent that has inhibitory effects on T-lymphocytes, impairs fibroblast proliferation, and decreases levels of rheumatoid factor and immune complexes. DAH and subacute interstitial infiltrates are the two most frequently reported histologic patterns of penicillamine-induced lung toxicity. Other patterns of pulmonary injury associated with its use include chronic alveolitis, PIE, and hypersensitivity pneumonitis.

Penicillamine is one of the few drugs that cause a pulmonary–renal syndrome, including a clinical presentation similar to Goodpasture syndrome.[102,103] The syndrome occurs infrequently among patients on penicillamine therapy for rheumatic disease, and also has been reported in patients given penicillamine as a chelating agent in Wilson disease—findings which support the hypothesis that the pulmonary findings are not simply a manifestation of the underlying collagen vascular disease.[104] Diagnosis is supported by high serum titers of ANA; antiglomerular basement membrane (anti-GBM) antibodies are typically absent from the serum. Pulmonary vasculitis is absent. Renal histopathology is that of crescentic glomerulonephritis, similar to that of Goodpasture syndrome; immunoglobulin deposition is absent. No specific risk factors have been identified for penicillamine-induced pulmonary–renal syndrome.

Symptoms at presentation include cough, dyspnea, hemoptysis, and hematuria. Symptom onset has been reported from 10 months to 20 years after drug initiation. No definitive dose–response relationship has been defined but there are reports of toxicity at doses as low as 300 mg

per day and as high as 3.5 g per day. Coalescing, bilateral alveolar infiltrates characterize the radiographic findings, resulting in severe hypoxemia. BAL reveals an increase in the concentration of red blood cells on serial lavage and the presence of hemosiderin-laden macrophages, both of which characterize DAH. The syndrome may progress to include respiratory and/or renal failure. Mortality from penicillamine-induced pulmonary–renal disease has been reported to be as high as 50%. Survivors in one series were all left with residual radiographic abnormalities. Many patients become hemodialysis dependent despite treatment. Therefore, prompt identification and treatment are warranted.

Drug withdrawal, accompanied by high-dose corticosteroids, is the cornerstone of therapy. Adjunctive treatment with cyclophosphamide or azathioprine is often offered, although studies definitively supporting their use do not exist. In the absence of anti-GBM antibodies, plasmapheresis is not warranted.

Penicillamine may also induce interstitial lung disease, including hypersensitivity pneumonitis and/or bronchiolitis obliterans. In some cases, the findings are accompanied by alveolitis. A sister drug, bucillamine, has also been reported to cause centrilobular, ground-glass opacities and thickening of interlobular septae.

Gold Salts

The immunomodulatory properties of gold have been recognized since the 1920s, when the first cases of RA treated with chrysotherapy were reported. The first reports of gold-induced pulmonary toxicity followed in 1948.

Gold remains a therapeutic option for the treatment of RA that is refractory to other agents. It also has a role in the management of juvenile RA, ankylosing spondylitis, and pemphigus. As with methotrexate and penicillamine, the toxic reaction of gold must be distinguished from pulmonary disease related directly to the underlying RA.

One of the largest reviews of 140 patients with gold-related pulmonary toxicity identified distinguishing features.[25] The pattern that emerged from this review is one of cough and dyspnea as the most common presenting symptoms, with half of the patients exhibiting fever, as well. More than one-third of patients have an erythematous skin rash. Peripheral blood eosinophilia is a common finding. The onset of symptoms is typically early in the course of treatment, often within the first 4 months. Gold-induced pulmonary toxicity affects women more often than men (4:1). The mean age of onset of disease is in the sixth decade of life. A restrictive ventilatory defect is characteristic. The diffusing capacity is reduced in over 90% of affected individuals. The radiographic injury patterns seen include ILD, hypersensitivity pneumonitis, and BOOP.[105,106]

Diagnostic evaluation may include BAL, which typically shows a lymphocytic-predominant fluid, including CD8+ lymphocyte predominance.[106,107] This finding, in conjunction with a positive in vitro gold lymphocyte proliferation assay, strongly supports the diagnosis of gold-induced pulmonary toxicity. The diagnostic features suggest that the gold-induced toxicity can be a hypersensitivity reaction.

Treatment of gold-induced lung toxicity necessitates discontinuation of the drug. Longitudinal data reveal that gold-induced impairments in diffusing capacity may take months to resolve. Rarely, disease progression may occur after discontinuation of the gold. Refractory or progressive symptoms may be treated with prednisone at 30 to 60 mg per day.

Sulfasalazine and Mesalazine

Sulfasalazine is used as a DMARD and also is commonly employed in the treatment of inflammatory bowel disease, as is mesalazine. Both agents have been associated with pulmonary toxicity, most commonly interstitial pneumonias, including NSIP.[108,109] Sulfasalazine has been reported to cause BOOP.[110,111] BOOP has been associated with mesalazine, as well.[112] Mesalazine has been associated with eosinophilic pneumonia when taken orally and when it is used as a suppository.[113]

Biologic Agents

Rituximab is a CD20-directed, B-cell–depleting monoclonal antibody used in the treatment of RA. granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), and microscopic polyangiitis. Many case reports regarding its pulmonary toxicity have been reported in the literature, with clinical presentations ranging from dyspnea and mild hypoxemia to fatal respiratory failure.[114] Clinical disease occurs in three different time courses, most commonly as a subacute onset of dyspnea 2 weeks following rituximab infusion, often several cycles into therapy.[115–117] Radiographic imaging shows bilateral diffuse interstitial infiltrates or ground-glass opacities. Less common presentations include acute onset of ARDS within hours of first infusion of the drug and chronic, insidious onset of disease.[115] Histopathology may include obliterative bronchiolitis.[118]

TNF antagonists are used in the management of rheumatic diseases. The most important pulmonary side effects of these agents are pneumonias due to bacteria, mycobacteria, Pneumocystis jiroveci, and fungi, occurring in 1.4% of patients treated with etanercept and 2.4% of those treated with infliximab. Among noninfectious pulmonary disorders associated with the use of anti-TNF therapies, interstitial pneumonitis is the most common manifestation of drug-induced disease. Interstitial pneumonitis was reported in 0.5% of 5000 Japanese subjects treated with infliximab and in 0.6% of over 7000 subjects who received etanercept.[119,120]

The reliability of case reports for demonstrating a definite causal link between monoclonal antibody use and pulmonary toxicity is complicated by the fact that interstitial pneumonitis is part of the spectrum of disease in patients with rheumatologic disorders. In addition, biologics are often administered to those with more severe manifestations of disease in whom lung disease is often present. In a large case series of autoimmune disease induced by TNF antagonists, 24 cases of interstitial pneumonitis were noted among 233 subjects studied.[121] In a review summarizing case series and reports published between 1990 and 2010, the mean time of onset of respiratory symptoms for subjects receiving biologic was 26 weeks, with 50% of cases occurring within the first 2 months.[122] Sarcoid-like granulomatosis has been frequently reported with the use of etanercept.[122,123] Among cases of sarcoid-like disease associated with monoclonal antibody therapies, 50% were compatible with stage 2 sarcoidosis, and two-thirds of all cases resolved with discontinuation of biologic therapy.[122]

Etanercept and infliximab have also been associated with development of drug-induced lupus, presenting with pleural effusion and/or pericarditis, along with positive ANA and antihistone or anti–double-stranded DNA antibodies.[124,125] The lupus-like conditions subside with drug discontinuation.

Adalimumab, a new TNF-α antagonist used in management of RA , also has been reported to cause pulmonary toxicity. Reports indicate lung injury occurring months to years into therapy. Patients usually present with dyspnea, cough, and a radiographic pattern are consistent with interstitial pneumonitis. Acute onset of lung injury has reported within 1 hour of dosing of this agent.[126] Symptoms may begin subtly as mild cough following a treatment cycle and progress with each subsequent injection.[127] Imaging shows patchy ground-glass opacities, with or without consolidation and patchy fibrosis.[127,128] In one case, patchy fibrotic interstitial disease was seen initially, followed by resolution after drug withdrawal, and then recurrent injury characterized by areas of ground-glass opacification after rechallenge.[129] Patients usually require corticosteroids to achieve clinical resolution.

■ IMMUNOSUPPRESSANTS

Sirolimus and everolimus are immunosuppressive agents used in the management of patients with solid organ transplants. They function as inhibitors of mammalian target of rapamycin (mTOR)

and suppress organ rejection through inhibition of growth factor–induced smooth muscle cell proliferation and migration; they also inhibit T- and B-cell activation.

Sirolimus was introduced into clinical use in the late 1990s. Sirolimus-induced pneumonitis in solid organ transplant recipients is an important consideration in the differential diagnosis of dyspnea with interstitial infiltrates after exclusion of infection. Case reports of sirolimus-induced pulmonary toxicity began to appear in the literature in 2000, when the drug was first implicated as the cause of biopsy-proven BOOP in a renal transplant recipient. A dose–response relationship is suggested, because dose reduction appears to ameliorate the pneumonitis. However, toxicity may occur despite therapeutic serum sirolimus levels and can occur as early as 2 weeks into therapy. However, it occurs more often after at least 6 weeks of therapy.

A case series of 24 patients further characterized the drug reaction. Most patients in the series exhibited a radiographic pattern of patchy peripheral consolidations consistent with BOOP, while four patients had reticular and ground-glass opacities.[130]

The BAL of subjects with sirolimus lung toxicity is typically lymphocytic (19 of 24 subjects); ≥5% eosinophilia was present in four cases.[130] Lymphocyte subsets have not been consistently reported, but some authors have described CD4+ predominance in the BAL.

The histology is consistent with BOOP and/or granulomatous interstitial pneumonitis, characterized by noncaseating granulomas in the bronchial wall and surrounding granulomatous inflammation.[131,132]

Cases of DAH have also been reported associated with sirolimus, and in some cases have been fatal.[133,134]

Discontinuation of sirolimus is necessary for syndrome resolution. Complete recovery is typically achieved in all patients by 6 months.

Everolimus has been shown to cause mild, reversible pulmonary toxicity.[135] It has also been implicated in fatal respiratory failure presenting initially with cough and dyspnea and accompanied by patchy alveolar infiltrates. Despite drug withdrawal and treatment with corticosteroids, the patient described in the case report progressed to respiratory failure and DAH.[136]

ANTIMICROBIAL DRUGS

The most commonly reported clinical syndrome for all classes of antimicrobials is pulmonary infiltrates with PIE. Among the reports of antibiotic-associated PIE syndrome are many cases of minocycline- and erythromycin-induced PIE, and fewer cases associated with penicillins, tetracyclines, sulfonamides, and cephalosporins. Cases of PIE have also been reported with the use of antituberculous drugs, including isoniazid, rifampin, and ethambutol.

Nitrofurantoin

Nitrofurantoin is one of the most commonly implicated antimicrobial agents that causes pulmonary toxicity. Although its peak usage worldwide was probably in the 1980s, it remains a widely used antibiotic for management of chronic urinary tract infections. Pulmonary toxicity may have significant clinical impact if the affected patient has underlying cardiopulmonary disease. Since the drug is used primary in the elderly population, in whom cardiopulmonary disease is common, recognition of its potential contribution to a patient's respiratory decline is important.

The clinical spectrum of respiratory disease caused by nitrofurantoin is broad. The onset of symptoms is highly unpredictable and of variable latency. The severity of disease varies; and the histopathology is diverse. Ninety percent of the earliest reported cases of nitrofurantoin pulmonary toxicity were acute in onset, occurring within days to weeks of treatment initiation. These patients presented with fever (80%), cough, dyspnea, rash (20%), arthralgias, and peripheral eosinophilia. As reports of toxicity have continued to populate the literature, it has become clear that subacute and chronic presentations also are common (Fig. 66-2).

It is inevitable that many cases may be missed due to the long latency between the initial dose and the onset of clinical symptoms. The median time to diagnosis in one series was 4 months; however, some diagnoses were made as long as 5 years after drug initiation. Among those with chronic symptoms, the most common histopathologic pattern is that of chronic interstitial pneumonitis, with fewer reported cases of BOOP and granulomatous interstitial disease.[137] High-resolution CT findings in 18 patients with chronic nitrofurantoin lung injury showed bilateral ground-glass opacities in all subjects (diffuse in 30%, and with a middle to upper lung zone predominance in 40%). Irregular linear opacities were present in 30%, consolidation in 30%, and traction bronchiectasis in 10% (one subject).[138]

Many other histopathologic patterns and clinical syndromes have been reported, including pulmonary edema, ARDS, vasculitis, DAH, SLE, PIE, and nodules. Bronchospasm and anaphylaxis related to antimicrobials is discussed in the section on those conditions.

INTERFERON-α AND PEGYLATED INTERFERON-α_2b

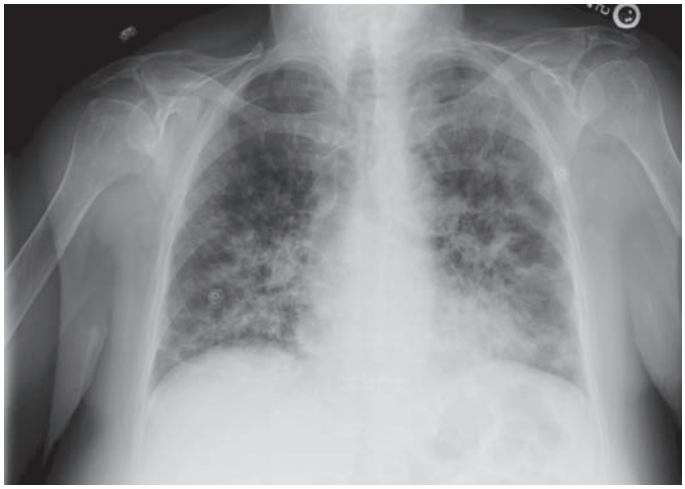
The rising prevalence of chronic hepatitis C worldwide, and its treatment with interferon-α and pegylated interferon-α_2b, has brought with it reports of pulmonary toxicity, most commonly interstitial infiltrates and BOOP. Systemic side effects are common among patients using interferon, and typically include flu-like symptoms of fatigue, headache, anorexia and myalgias. Pulmonary symptoms occur infrequently. Ribavirin, a synthetic nucleoside analog is often used in conjunction with either interferon-α or pegylated interferon-α_2b to enhance the antiviral activity of the interferons. Ribavirin is associated with dyspnea and cough, but it has not been reported to cause pulmonary toxicity when used alone. The reported rate of significant pulmonary interstitial disease and/or BOOP is as high as 6% among patients receiving high-dose daily interferon for hepatitis C, and <1% among patients on conventional three-times-weekly dosing schedules of interferon-α and ribavirin.[139]

The occurrence of interstitial disease among users of interferon-α is not exclusive to those with hepatitis, and it has been reported in patients on interferon therapy for chronic myelogenous leukemia and myelofibrosis as well. Most cases of pulmonary toxicity occur within several weeks of initiation of therapy and resolve with discontinuation of the medications.

Several case reports or small series of cases characterize the association of de novo sarcoidosis or recrudescent sarcoidosis with interferon-α and interferon-α_2a used in chronic hepatitis C.[140] The incidence of sarcoidosis among patients receiving interferon is not well established, but has been reported to be as high as 5% among patients receiving treatment with interferon-α_2a for hepatitis C.[141]Although most of the reports of sarcoidosis have been in patients undergoing treatment for hepatitis C, it also can occur in the setting of treatment of hematological malignancy. Interferon-associated pulmonary sarcoidosis occurs along with manifestations of disease involvement of other sites, including cutaneous, parotid, liver, ocular, and cardiac diseases. Prompt withdrawal of the drug is advised, and corticosteroids may be necessary for disease resolution.

OPIATES AND ILLICIT DRUGS

Complications of illicit drug use are numerous and encompass toxic injury to the lung related to use of the drug itself, and the associated infectious sequelae of venous cannulation, including endocarditis, septic embolization, and HIV-associated opportunistic infection. The prevalence of tuberculosis among drug users puts these individuals at high risk of active tuberculosis as well. Opiates or other sedatives may cause altered mental status and impairment of the gag reflex, substantially increasing the risk of aspiration pneumonia. Pulmonary parenchymal disease may also be caused by talc or other inert substances used to "cut" the drugs. Recognition of these



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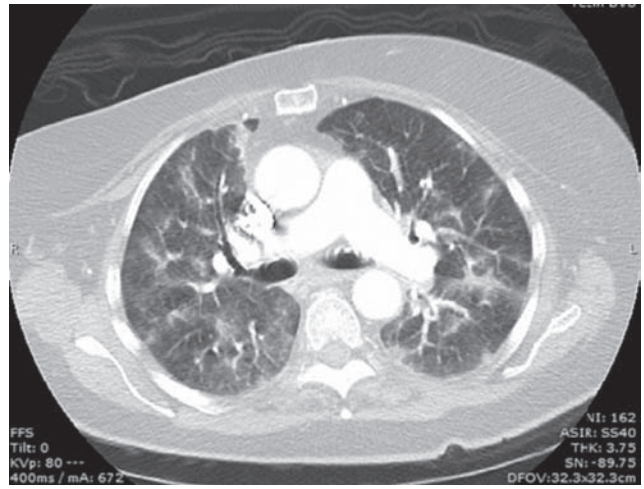

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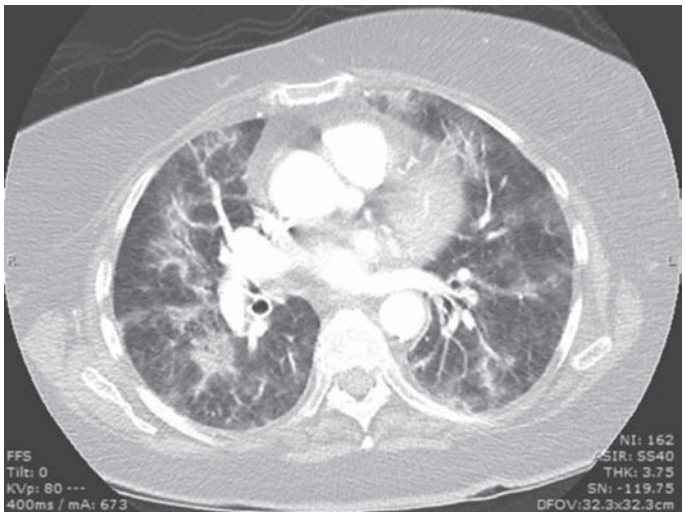

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Figure 66-2 **A.** Chest radiograph of an 80-year-old woman 1 year after initiation of nitrofurantoin for recurrent urinary tract infection. **B, C.** CT scan: Patchy ground-glass opacities and consolidation consistent with nitrofurantoin-induced bronchiolitis obliterans—organizing pneumonia. *(Used with permission of Ami Rubinowitz, MD.)*

conditions unrelated to direct toxicity of the drug broadens the differential diagnosis of respiratory symptoms in users of illicit drugs.[142]

Heroin

Overdoses of heroin and other narcotics have long been known to cause pulmonary edema. One of the earliest reports of drug-induced lung disease was by Osler in 1880, in which he described pulmonary edema in an opiate addict and ascribed the edema to the opiate use. For unknown reasons, the frequency with which heroin-induced pulmonary edema (HIPE) occurs appears to have decreased in recent decades. In one series of patients compiled between 1968 and 1970, 48% of 149 patients with heroin overdose had pulmonary edema on presentation.[143] The presence of pulmonary edema was associated with increased mortality (18.3% vs. 8.7% if pulmonary edema was absent). A more recent case series describes a much lower incidence of pulmonary edema: 2.1% cases of heroin overdose.[144] It is unclear whether the change in epidemiology of HIPE relates to a change in the additives to illicit heroin or other factors. In the latter series, one-third of the patients required intubation and mechanical ventilation, but the hypoxemia of HIPE resolved within 48 hours of presentation.

The literature does not conclusively indicate the mechanism of HIPE. Some studies have reported higher protein levels in pulmonary edema fluid of HIPE than in cardiogenic pulmonary edema, supporting increased capillary permeability as the mechanism.[145] There are reports of significant acute inflammation in the lung tissue of narcotic abusers who were examined postmortem.[146] Other reactions associated with heroin use include acute bronchospasm.

Pulmonary disease associated with illicit injection drug use may be unrelated to the drug itself. Talc used to cut heroin or inert substances used in pills that are crushed and injected produce foreign-body granulomatous reactions in the pulmonary vasculature and interstitium. A longitudinal study of six patients with pulmonary talcosis described characteristic radiographic findings, consisting of a diffuse, micronodular pulmonary infiltrate that evolved into coalescent conglomerates, often in the upper lobes, similar in appearance to those of progressive massive fibrosis. These alterations may be accompanied by emphysematous changes in the lower lobes, which may result in pneumothoraces. Other pulmonary complications of injection drug use include septic emboli, abscess formation, bronchiectasis, and bullae independent of apical fibrotic reactions.

Cocaine

Cocaine may be injected intravenously, inhaled nasally, or smoked. It is the last noted route that is most frequently associated with respiratory symptoms and pulmonary injury. Cocaine is typically smoked as "crack" cocaine, an alkaloid derivative of cocaine hydrochloride that is mixed with ether or alcohol. Respiratory symptoms typically develop acutely, within hours of use, and include cough, hemoptysis, chest pain, and shortness of breath. Bronchospasm, which may be severe enough to precipitate respiratory failure, has been reported with and without a prior history of asthma. The radiographic appearance may

be consistent with ARDS, and the histopathology that of DAD, with or without alveolar hemorrhage.[147] Capillaritis, accompanied by glomerulonephritis, has been reported, but is not typically present.

PRINCIPLES OF TREATMENT AND DISEASE RESOLUTION

Prompt recognition of drug-induced lung disease affords patients the greatest chance of clinical and radiographic recovery, before irreversible lung injury occurs. In most cases of drug-induced pulmonary injury, discontinuation of the culprit drug is sufficient for regression of clinical symptoms and most or all of the radiographic findings. The decision to treat with corticosteroids must be individualized, based on the severity of the clinical picture and the expected rapidity of symptom resolution. For example, amiodarone pulmonary toxicity frequently requires oral corticosteroid administration unless the symptoms are very mild, because of the long serum half-life of the drug. Recrudescence of lung injury is rare among other implicated drugs in the absence of reexposure to the culprit drug. Overall, corticosteroids are used with apparent success, but controlled studies to determine therapeutic efficacy are lacking, and the infrequent occurrence of most drug toxicities will not allow this treatment to be convincingly studied in clinical trials.

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CHAPTER 67

The Lungs in Patients with Inborn Errors of Metabolism

Timothy Craig Allen

INTRODUCTION

Inborn errors of metabolism, also termed "inherited metabolic disorders," are a group of inherited systemic conditions involving various types of chemical imbalances that cause disease and affect essentially all organs to a greater or lesser degree.[1–9] Each of the diseases is characterized by a specific genetic defect that causes an abnormality of an enzyme necessary for the degradation of some chemical substance.[2] The disruption of degradation leads to disease due to the deficiency of a substance or to the pathologic accumulation of a substance.[2,5] The first inborn errors of metabolism were identified about a century ago. Sir Archibald Garrod coined the phrase in 1902.[10] Today, there are over 500 inborn errors of metabolism identified.[11]

The diseases that comprise the inborn errors of metabolism are individually rare; however, taken together, they affect about 1 in 1000 people.[2] The majority of the diseases making up the inborn errors of metabolism exhibit autosomal recessive inheritance; however, X-linked recessive inheritance occurs with some diseases, and, less commonly, autosomal dominant inheritance is seen.[5] The majority of these diseases are pediatric; however, with the identification of attenuated variants, and with improved survival, they are today's conditions that must be considered in patients of all ages.[2] Tissue biopsy may be necessary for specific diagnosis; however, given that these disorders typically present with unexpected findings, high clinical suspicion and careful radiologic evaluation are usually the key to faster and more accurate diagnoses. Particularly as newer and more effective therapies being designed require earlier diagnoses, radiology plays a central role in diagnosis, and clinical–radiologic correlations are increasingly important.[2] Although metabolic specialists with expertise in the various inborn errors of metabolism are present in large academic centers and tertiary care centers, pediatricians and primary care physicians are typically the first physicians to whom patients with these diseases present themselves.[5]

Some of the diseases that make up the inborn errors of metabolism can be placed into a few broad groups; these include disorders of amino acid metabolism, organic acidurias, urea cycle defects, disorders of ketogenesis and ketolysis, disorders of fatty acid oxidation, lysosomal storage disorders, and mitochondrial disease.[2] While the lung is not typically a primary site of clinical disease in patients with inborn errors of metabolism, the lungs are involved with many inborn errors of metabolism, and in some diseases, clinically significant lung disease may occur.[1,12] Of course, the lungs may be involved with infections as a secondary feature in many types of chronic diseases, including inborn errors of metabolism; however, this chapter focuses on several specific inborn errors of metabolism for which lung disease may be a clinically significant feature.

ACID SPHINGOMYELINASE DEFICIENCY (NIEMANN–PICK DISEASE TYPES A AND B)

Acid sphingomyelinase (ASM) deficiency, an autosomal recessive condition, has a phenotype that occurs in a continuum, with severe, neuropathic disease with early symptoms and resulting in death in infancy or early childhood designated as Niemann–Pick disease type A (NPA), and nonneuropathic disease with generally later onset and milder symptoms designated as Niemann–Pick disease type B (NPB).[13–17] Patients with NPA typically show hepatosplenomegaly by about 3 months of age. The hepatosplenomegaly may ultimately become massive, and children are often dead within 3 years. Psychomotor development in patients with NPA typically is limited to not more than the 12-month level, after which deterioration occurs. NPB patients generally show milder hepatosplenomegaly and may survive to adulthood; however, progressive and clinically significant pulmonary changes are frequent in these patients.[14,18,19] Diagnosis is made by showing less than 10% normal residual ASM activity in peripheral blood lymphocytes or cultured skin fibroblasts.

Patients with NPA often exhibit radiographic changes of interstitial lung disease due to sphingomyelin storage within pulmonary macrophages, and they may exhibit low arterial blood oxygen levels. Respiratory infections are common, and not infrequently culminate in respiratory failure and death.[13,20,21] Patients with NPB, who have generally milder disease, may develop pulmonary complications at any age.[21,22] Most patients with NPB exhibit radiographic changes of interstitial lung disease, even while their individual symptoms may vary dramatically; their radiographic changes often do not correlate with the severity of pulmonary function abnormalities.[14,18] Cystic lung disease has also been reported in association with NPB.[23] Whole lung lavage has been attempted for symptomatic treatment of patients with NPB.[24]

Radiographically, patients show nodular infiltrates and linear strands, with a predominantly basilar honeycomb pattern.[19,25] Histologically, the lungs demonstrate predominantly normal architecture, with airspaces filled with Niemann–Pick cells—enlarged histiocytes with finely vacuolated cytoplasm (Figs. 67-1 and 67-2).[26] If necessary, CD68 immunostain may be used to establish their presence. These collections of cells have been termed "sea blue histiocytosis," due to the vivid blue staining with May–Grunwald Giemsa stain. Pulmonary fibrosis may occur over time (Fig. 67-3).

NIEMANN–PICK DISEASE TYPE C

Niemann–Pick disease type C (NPC) is a rare, autosomal recessive inborn error of metabolism characterized by impaired intracellular lipid trafficking and accumulation of cholesterol and glycosphingolipids in the brain and other tissues.[27–34] It is diagnosed by

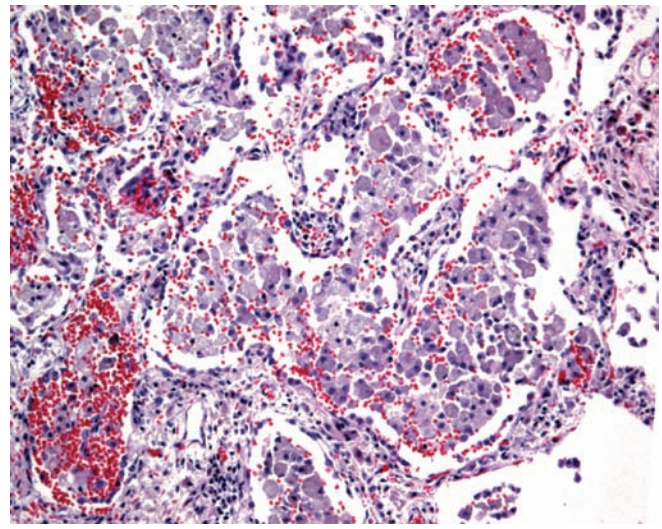

Figure 67-1 Low power image of lung in Niemann–Pick disease showing collections of foam cells within alveoli.

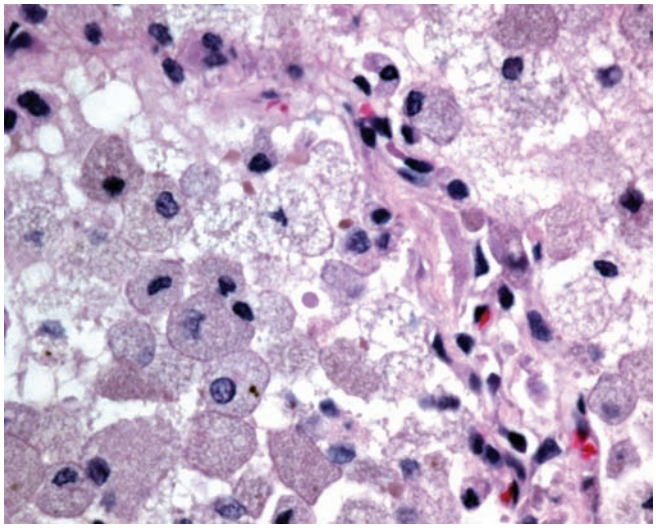

Figure 67-2 High power image of lung in Niemann–Pick disease showing enlarged histiocytes with finely vacuolated cytoplasm within the alveolar spaces.

biochemical tests that show impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. Patients typically have saccadic eye movement abnormalities or vertical supranuclear gaze palsy; cerebellar signs, such as ataxia, dystonia/dysmetria, dysarthria, and dysphagia; gelastic cataplexy; and epileptic seizures[27,33] are given symptomatic treatment for cataplexy, dystonia, and seizures, as well as physical therapy to maintain as much independent mobility as possible. Approximately 95% of NPC cases are due to mutations of the NPC1 gene, with the remainder due to mutations of the NPC2 gene.[27]

NPC may produce symptoms in patients of any age; and initial presentation may occur from neonatal to adult periods. Infants often have nonspecific symptoms that make exact diagnosis difficult. Along with liver disease, infants may present with often-fatal pulmonary failure due to impaired gas exchange due to lung infiltration with foam cells. Patients presenting in childhood or adolescence, or as adults, typically do not have pronounced pulmonary involvement.[30–32,35] Pulmonary alveolar proteinosis may occur in patients with NPC2 disease; possibly due to loss of normal NPC2 protein expression in alveolar macrophages and accumulation of functionally inactive cholesterol-rich surfactant.[33,34,36] Bronchoalveolar lavage has been reported to improve pulmonary symptoms in children with foam cell infiltrates.[37] Histologic features are similar to those seen in patients with NPA and NPB.

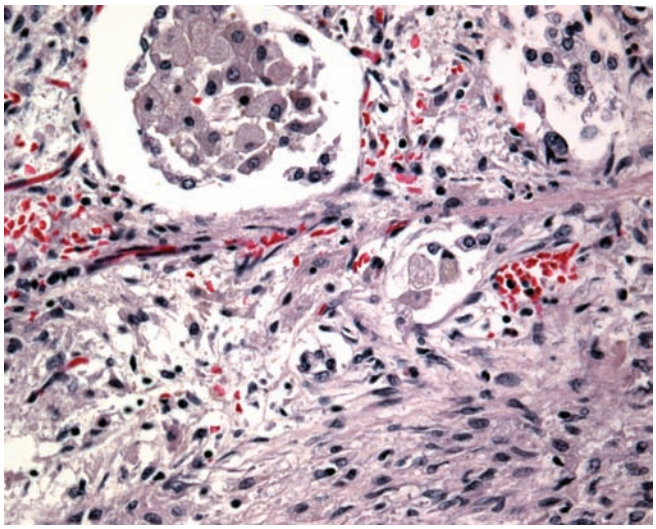

Figure 67-3 High power image of lung in long-standing Niemann–Pick disease showing developing pulmonary fibrosis.

GAUCHER DISEASE

Gaucher disease (GD), an autosomal recessive disease, is due to inadequate lysosomal enzyme glucosylceramidase activity, with the resulting accumulation of glucosylceramide, the enzyme's undegraded substrate, as well as other glycolipids.[12,15,38–40] The substrate arises primarily from the breakdown of red blood cells and other tissue cells. The undegraded substrate is then taken up by monocytes and macrophages. Central nervous system involvement with GD may be caused by membrane ganglioside turnover; however, neuron death may also play a role.[41]

GD encompasses three main clinical subtypes, as well as two additional subtypes, each with characteristic features. Type 1, 2, and 3 GD frequently show lung involvement. Type 1 GD is characterized clinically by bone disease, including osteonecrosis, lytic and sclerotic lesions, and osteopenia; anemia; thrombocytopenia; and hepatosplenomegaly; however, affected patients do not typically show central nervous system involvement. Type 2 and type 3 GD are both characterized by central nervous system involvement with disease; however, type 2 GD patients typically present with disease before age 2, exhibit poor psychomotor development, and rapidly deteriorate, with death occurring usually between ages 2 and 4. Patients with Type 3 GD, in contrast, typically present before age 2, but progress slowly, with some patients surviving to adulthood. There are also two additional subtypes, for which lung involvement is not characteristic. Cardiovascular GD shows mitral value and aortic valve calcification, corneal opacities, and supranuclear opthalmoplegia. Perinatal lethal GD shows nonimmune hydrops fetalis or skin abnormalities.

GD may be caused by mutations in Saposin C and acid-β-glucosidase.[42] Diagnosis of GD requires the demonstration of inadequate glucosylceramidase activity in peripheral blood leukocytes or other cells. Treatments include enzyme replacement therapy or substrate reduction therapy.[43–46]

Pulmonary involvement in patients with GD includes pulmonary hypertension, lobar consolidation, and interstitial lung disease.[1,12,15,38,47,48] Pulmonary hypertension is a typical finding in GD patients with hepatic disease, perhaps because of the patients' inability to detoxify gut-derived factors that affect pulmonary endothelium, with resultant pulmonary hypertension. Pulmonary hypertension may also occur in patients with GD without liver disease.[47] Some patients with type 1 GD without pulmonary disease may, nonetheless, exhibit rapid fatigability, possibly due to GD-caused circulatory impairment.[12,48,49]

Histologically, GD cells infiltrate liver, spleen, and bone marrow. Lung involvement is common in pediatric patients and less common in adults.[50] Lung involvement may be clinically significant in as many as one-third of patients.[51] GD cells most often involve septal capillaries; this is thought to be the cause of GD-associated pulmonary hypertension.[51] Infants and children may also demonstrate intra-alveolar involvement. GD cells have also been found to cause substantial septal thickening and patchy involvement in a lymphatic distribution.[51] The characteristic Gaucher cell has a "wrinkled paper" appearance (Fig. 67-4), highlighted with Periodic acid-Schiff (PAS) staining. Gaucher cells are CD68 negative, in contrast to alveolar macrophages, which show CD68 positivity.[52]

FABRY DISEASE

Fabry disease (FD) is an X-linked lysosomal storage disease caused by a deficiency of α-galactosidase A enzyme activity, resulting in globotriaosylceramide accumulation in a variety of tissues, including cardiomyocytes, smooth muscle cells, and endothelial cells.[53–55]

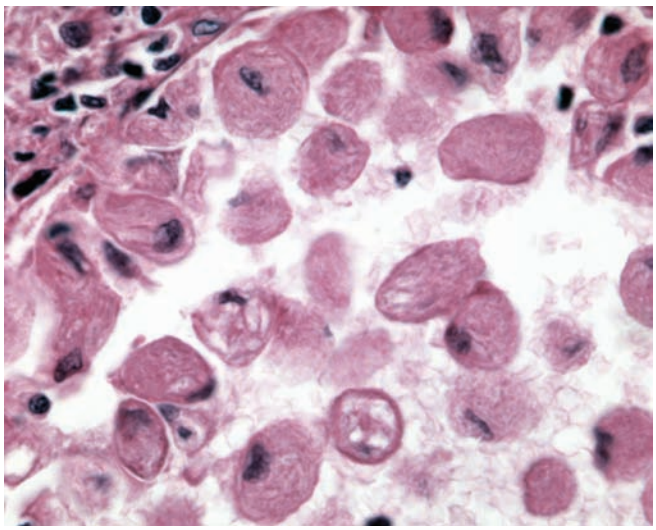

Figure 67-4 High power image of Gaucher cells within an alveolar space showing its characteristic "wrinkled paper" appearance.

Males with less than 1% enzyme activity develop the classic form of FD, which typically present in childhood or adolescence and is characterized by proteinuria, corneal and lenticular opacities, angiokeratomas, hypohidrosis, and periodic episodes of markedly painful extremities. By the third to fifth decades, gradually worsening renal function usually leads to end-stage renal disease. If an adult with FD survive their renal disease, they typically succumb to cerebrovascular or cardiovascular disorders. If men exhibit greater than 1% enzyme activity, however, they typically exhibit a renal variant, with resultant end-stage renal disease, but without extremity pain or skin lesions. Alternatively, they may exhibit a cardiac variant, which typically presents in men in their 50s to 70s. Findings include proteinuria, mitral value insufficiency, cardiomyopathy, and left ventricular hypertrophy; end-stage renal disease is absent.

Female patients with FD, who are heterozygous for the disease, often exhibit later onset of findings and milder symptoms than males; however, their presentations may range from essentially asymptomatic throughout life to symptoms mimicking their male counterparts with classic FD.

Diagnosis in males is made by showing α-galactosidase A enzyme deficiency in leukocytes, cultured cells, or plasma. Enzyme measurement is not a reliable test for females; some carriers have decreased enzyme activity, but others show normal activity. Enzyme testing for a mutation in *GLA*, the gene associated with FD, is necessary for diagnosis in female carriers. Males essentially always show a *GLA* mutation. Enzyme replacement therapy is typically used in male patients and symptomatic female carriers.[49,53,54]

Pulmonary involvement may occur in both males and females with FD.[12,56–58] Patients typically exhibit dyspnea, wheezing, and findings of chronic bronchitis; pulmonary function tests may show obstruction.[59] Radiologic changes may be minimal and do not correlate with the severity of pulmonary dysfunction. Histologic diagnosis of FD typically involves identification of laminated inclusions in type II pneumocytes and capillary endothelium.[58] Lamellar inclusions have been reportedly identified cytologically in alveolar macrophages, ciliated epithelial cells, and goblet cells by examination of induced sputum, bronchial brushings, and bronchoalveolar lavage specimens.[58,60,61]

HERMANSKY–PUDLAK SYNDROME

Hermansky–Pudlak syndrome (HPS), also termed oculocutaneous albinism syndrome, is a rare autosomal recessive multisystem disease involving disorders of intercellular trafficking. HPS is characterized by tyrosinase-positive oculocutaneous albinism, a platelet storage pool deficiency that causes bleeding diatheses, and, in some cases, pulmonary fibrosis.[62–71] Patients with HPS exhibit congenital nystagmus, decreased visual acuity, iris transillumination, and variable skin and hair hypopigmentation.[72] Approximately 15% of patients may also develop granulomatous colitis.[63–65,73] HPS is diagnosed based on clinical characteristics and ultrastructural absence of platelet-dense bodies.[74] Patients often exhibit easy bruising and prolonged bleeding.

HPS, including its subtypes, has been shown to be caused by mutations in several genes. These include *HPS1*, causing HPS-1; *AP3B1*, causing HPS-2, *HPS3*, causing HPS-3; *HPS4*, causing HPS-4; *HPS5*, causing HPS-5; *HPS6*, causing HPS-6; *DTNBP1*, causing HPS-7; *BLOC1 S3*, causing HPS-8; and *BLOC1 S*, causing HPS-9.[65,66,75]

Pulmonary involvement in patients with HPS generally presents clinically and radiologically as pulmonary fibrosis. Patients generally become symptomatic by the fourth decade; lung disease is progressive and restrictive in nature. Death may ensue within a few years following onset of pulmonary symptoms.[76] Pulmonary fibrosis is typically found in HPS1, HPS2, and HPS4; it is particularly prevalent in patients with HPS1 from Puerto Rico.[64,72,77–83] Pulmonary fibrosis is not characteristic of HPS3, HPS5, or HPS6. Lung transplantation may be appropriate for some patients with HPS.[84]

The basis for the pulmonary fibrosis is unknown; however, a postinflammatory response has been hypothesized as the causative factor.[85] Pirfenidone treatment has been attempted in patients with HPS with pulmonary function greater than 50% of normal, with some benefit.[77] Histologically, the pulmonary fibrosis may show a pattern of usual interstitial pneumonia or nonspecific interstitial pneumonia.[72,86] Ceroid–filled macrophages fill airspaces and the lung interstitium (Figs. 67-5–67-7) and may be identified with bronchoalveolar lavage.[86]

CHOLESTERYL ESTER STORAGE DISEASE

Cholesteryl ester storage disease (CESD), a rare autosomal recessive disease, is characterized by lysosomal acid lipase/cholesteryl ester hydrolase deficiency.[87] Most patients with CESD have some enzyme activity; individuals with complete enzyme deficiency are diagnosed as having Wolman disease.[88] In patients with CESD, there is deposition of cholesteryl ester generally in the liver, bone marrow, bowel, and spleen. Gastrointestinal bleeding, often occult, and hepatomegaly are frequently identified.[89] Patients usually survive well into adulthood, ultimately dying from chronic hepatic failure or premature atherosclerosis.[87]

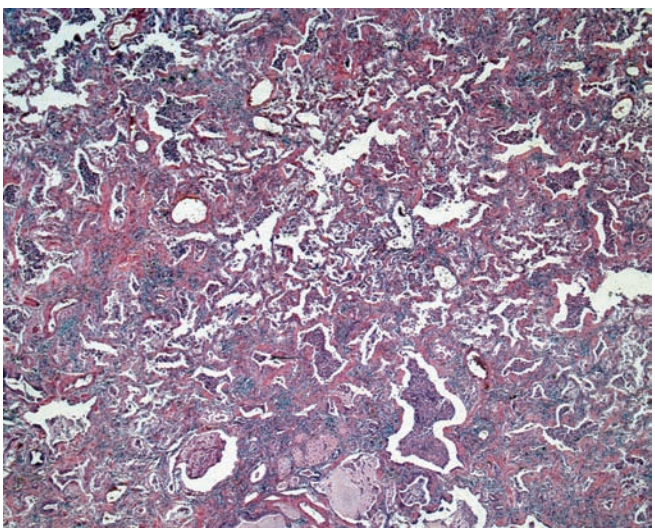

Figure 67-5 Lower power image of lung in Hermansky–Pudlak syndrome showing a nonspecific interstitial pneumonia-like pattern.

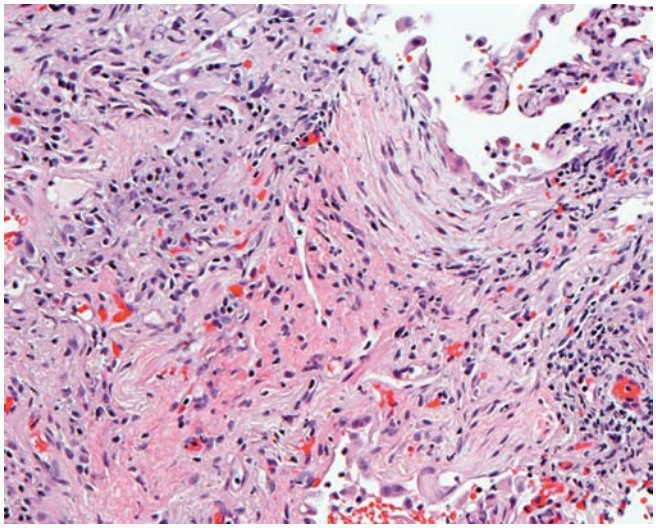

Figure 67-6 Medium power image of lung in Hermansky–Pudlak syndrome showing a usual interstitial pneumonia-like pattern.

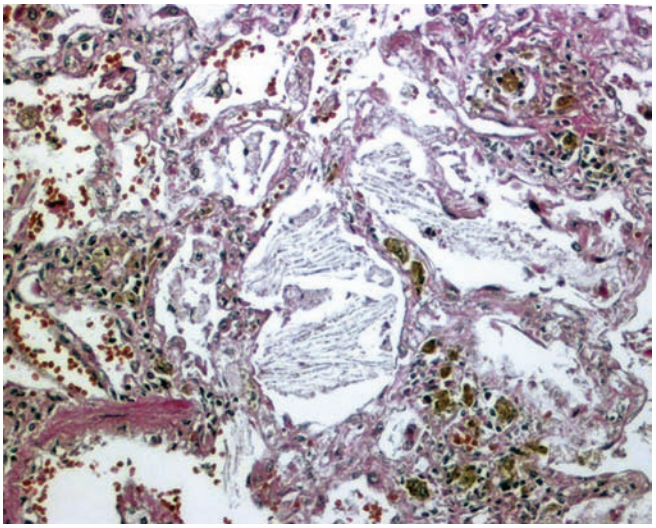

Figure 67-8 Medium power image of lung in cholesteryl ester storage disease showing cholesteryl ester accumulation within alveolar macrophages, and interstitial fibroblasts.

Pulmonary involvement in CESD is uncommon; however, it may occur due to accumulation of cholesteryl esters within alveolar macrophages and interstitial fibroblasts (Figs. 67-8 and 67-9). Pulmonary arteries may also develop from cell deposits within the intima, which may be complicated by associated reactive fibrosis.[90,91] Treatment of pulmonary involvement in patients with CESD is supportive; however, for most patients, pulmonary involvement is not life-threatening.[90]

MUCOPOLYSACCHARIDOSIS TYPE I

Mucopolysaccharidosis Type I (MPS1), an autosomal recessive disease, is a progressive multisystem disease due to a lysosomal storage disorder caused by deficiency of the enzyme α-L-iduronidase.[92,93] Patients with MPS1 show varying levels of severity. The diagnoses of Hurler syndrome, Hurler–Scheie syndrome, and Scheie syndrome have shown generally overlapping clinical features and no biochemical differences; therefore, currently, patients are clinically diagnosed as having either Severe MPS1 (formerly Hurler syndrome) or Attenuated MPS1 (formerly Hurler–Scheie syndrome and Scheie syndrome). The diagnosis of MPS1 is based on demonstration of insufficient α-L-iduronidase activity in plasma, in cultured fibroblasts, or peripheral blood leukocytes. Treatment may include enzyme replacement therapy and bone marrow transplantation.[92–95] Attenuated MPS1 patients may show pulmonary disease, including changes in forced vital capacity, and respiratory complications are often the cause of death.[96]

MUCOPOLYSACCHARIDOSIS TYPE II

Muopolysaccharidosis type II (MPSII), also termed Hunter syndrome, is inherited as an X-linked recessive disease. MPSII is a multisystem disease characterized by the pathologic lysosomal storage of glycosaminoglycans.[97–99] Most patients are males, with carrier females showing clinical features only rarely. Patients with MPSII typically show central nervous system involvement, predominantly a progressive deterioration of cognitive functions. Patients generally have macrocephaly, with or without communicating hydrocephalus, hoarseness, hearing loss, macroglossia, splenomegaly, hepatomegaly, short stature, dysostosis multiplex, and joint contractures.[98,99] Patients may also exhibit cardiac findings and progressive airway disease in severe cases. Patients frequently do not survive their second decade.

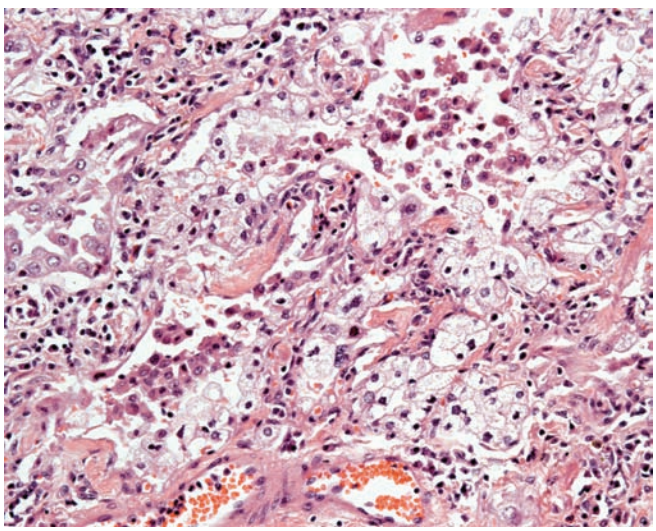

Figure 67-7 High power image of lung in Hermansky–Pudlak syndrome showing ceroid-filled histiocytes within alveolar spaces.

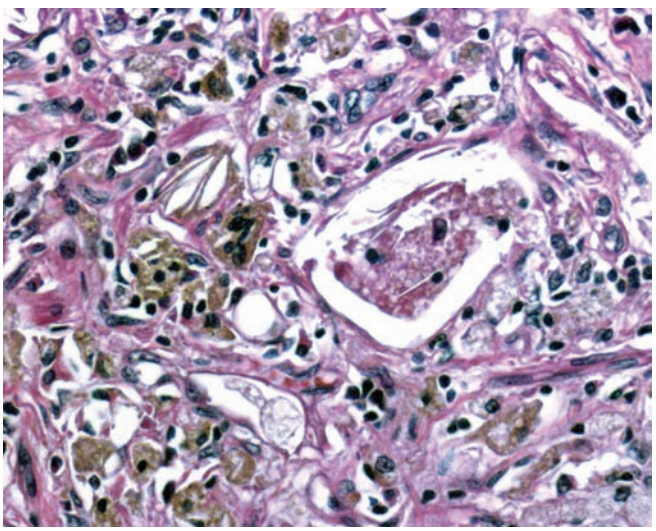

Figure 67-9 High power image of lung in cholesteryl ester storage disease showing alveolar macrophages containing cholesteryl esters.

Clinical manifestations and progression may vary significantly; severity should be considered to be on a continuum. Some patients with milder forms of disease show normal intelligence into early adulthood and survive into the sixth decade.[97,98]

To confirm clinical suspicion, testing for deficient iduronate sulfatase enzyme activity in plasma, fibroblasts, or white blood cells may be performed. Diagnosis may be confirmed by molecular testing of *IDS*, the gene associated with MPSII. Until recently, treatment has been supportive only.[97] Bone marrow transplantation has been attempted, but has not been successful.[100] Treatment with enzyme replacement therapy is currently being studied in patients with MPSII.[98,101–104]

Patients with MPSII often show frequent upper respiratory infections as an early feature of disease. Progressive airway narrowing due to accumulation of glycosaminoglycans in the tongue, upper airway, and trachea usually cause symptomatic airway obstruction.[97,99] Ultimately, progressive airway obstruction with associated sleep apnea requires tracheostomy. Along with airway obstruction, hepatomegaly and splenomegaly, thick pulmonary secretions, and chest wall stiffness.[98]

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CHAPTER 68

Alveolar Hemorrhage Syndromes

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Michael C. Fishbein
Tisha Wang

Diffuse alveolar hemorrhage (DAH) is a potentially catastrophic complication of myriad immune and nonimmune disorders.[1–3] Clinical features are broad, but hemoptysis, infiltrates on chest radiographs, hypoxemia, and progressive respiratory insufficiency are common to diverse etiologies.[2] Nonimmune causes of alveolar hemorrhage include endobronchial tumors, arteriovenous malformations or aneurysms, ulcerative tracheobronchitis, hemorrhagic pneumonia, bronchiectasis, congestive heart failure, uremia, thrombocytopenia or coagulopathy, pulmonary venoocclusive disease, infections, and massive pulmonary embolism.[4,5] These nonimmune causes need to be excluded in patients with severe alveolar hemorrhage. Depending upon the clinical scenario, coagulation profiles and ancillary tests (e.g., echocardiogram, chest computed tomographic [CT] pulmonary angiography, fiberoptic bronchoscopy) may be required to establish a specific diagnosis. In addition, other causes of diffuse parenchymal infiltrates (but without severe alveolar hemorrhage) share features in common with DAH syndromes (e.g., cryptogenic organizing pneumonia, hypersensitivity pneumonia, pulmonary alveolar proteinosis, and diverse interstitial or alveolar lung disorders). A discussion of these disorders is beyond the scope of this chapter, which focuses primarily on immune-mediated causes of DAH.

AUTOIMMUNE CAUSES OF ALVEOLAR HEMORRHAGE: DIFFERENTIAL DIAGNOSIS

Autoimmune DAH results from diffuse injury to the pulmonary microvasculature (termed *capillaritis* or *endotheliitis*) (Table 68-1).[6,7] Systemic necrotizing vasculitides[8,9] (principally microscopic polyangiitis [MPA][10,11] and Wegener's granulomatosis [12] account for most cases of autoimmune DAH.* Other causes of autoimmune DAH include antiglomerular basement membrane (anti-GBM) antibody disease,[13–15] connective tissue disease (CTD) (principally systemic lupus erythematosus [SLE]),[16] exogenous agents or drugs.[17] In many of these disorders, rapidly progressive glomerulonephritis (RPGN) is present concomitantly.[18,19] In most patients with autoimmune DAH and glomerulonephritis (GN), anti-GBM antibody and immune complexes are lacking.[19] The term *pauci-immune glomerulonephritis* has been used to refer to this group of patients, who encompass a heterogeneous group of disorders.[20,21] (discussed in detail below).

Idiopathic pulmonary hemosiderosis (IPH), a rare cause of recurrent DAH with no renal or extrapulmonary component, occurs primarily in children[22–24] and remains a diagnosis of exclusion.

Differentiation of these diverse syndromes can usually be accomplished by serological studies and by kidney biopsy. In such cases, lung biopsy is not required. GN can be demonstrated in the great majority of patients with DAH complicating granulomatosis with polyangiitis (GPA)[12] or MPA.[7,10,11] By contrast, the kidneys may be spared in DAH associated with CTD,[16] bone marrow transplant recipients,[25,26] or immunocompromised patients.[27,28] Urinalysis (to look for microscopic hematuria, red cell casts, and proteinuria) and measurement of renal function should always be done in the diagnostic evaluation of DAH. Findings consistent with GN warrant a prompt and aggressive evaluation that should include percutaneous needle biopsy of the kidney.

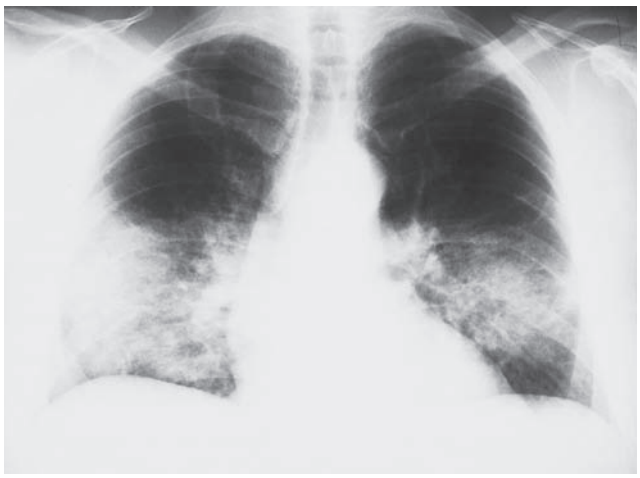
CLINICAL FEATURES OF AUTOIMMUNE ALVEOLAR HEMORRHAGE

Irrespective of etiology, the clinical, radiographic, and histopathological features of DAH may be similar.[1,2,6] Classical findings are hemoptysis, diffuse alveolar infiltrates, hypoxemia, renal failure, and iron-deficiency anemia.[2,7] However, the clinical spectrum is wide, and many of these features may be subtle or absent. In this context, the diagnosis of DAH may be difficult, as signs and symptoms overlap with diverse etiologies of diffuse alveolar infiltrates. Prompt diagnosis and institution of therapy is vital to avert early mortality from DAH and late sequelae from end-stage renal failure. Chest radiographs typically reveal bilateral alveolar infiltrates, often with a batwing appearance. However, focal, and even unilateral, patterns indistinguishable from pneumonia may occur. Following cessation of bleeding, infiltrates markedly improve or normalize within 24 to 72 hours (Fig. 68-1). A presumptive diagnosis of DAH can often be made by a combination of clinical and serological findings and bronchoalveolar lavage (BAL) fluid. Grossly bloody BAL fluid (with progressively more blood with serial aliquots),[1,2,7] large numbers of hemosiderin-laden macrophages,[8,27] and the absence of purulent secretions or ancillary evidence for infection strongly support DAH as a cause of pulmonary infiltrates. Ancillary studies including serologies, renal function tests, and urinalysis may support the diagnosis.

TABLE 68-1 Etiology of Autoimmune Diffuse Alveolar Hemorrhage

Antiglomerular basement membrane antibody disease (Goodpasture's syndrome)
Antineutrophil cytoplasmic antibody (ANCA)-mediated vasculitis (e.g., granulomatosis with polyangiitis, microscopic polyangiitis, Churg–Strauss syndrome, pauci-immune glomerulonephritis)
Idiopathic rapidly progressive glomerulonephritis
Collagen vascular disease (e.g., systemic lupus erythematosus)
Immunocompromised status (e.g., bone marrow transplant, AIDS)
Exogenous agents or drugs (e.g., trimellitic anhydride, isocyanates, D-penicillamine, cocaine)
Idiopathic pulmonary hemosiderosis (pathogenesis unknown)

*The Boards of Directors of the American College of Rheumatology (ACR), American Society of Nephrology (ASN), and the European League Against Rheumatism (EULAR) have recommended a gradual shift from honorific eponyms to disease-descriptive or aetiology-based nomenclature. The leadership of these three organizations tasked an international group of senior academicians expert in the care of patients with vasculitis and engaged in research in the field to provide the medical community with proper descriptive terms instead of the names for Wegener's granulomatosis, Churg–Strauss syndrome, and Behçet syndrome. The move toward a vasculitis terminology based on pathology, rather than historical reference, was triggered by evidence that Dr Friedrich Wegener was a member of the Nazi party before and during World War II. Falk RJ, Gross WL, Guillevin L, Hoffman GS, Jayne DR, Jennette JC, Kallenberg CG, Luqmani R, Mahr AD, Matteson EL, Merkel PA, Specks U, Watts RA; American College of Rheumatology; American Society of Nephrology; European League Against Rheumatism. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Arthritis Rheum*. 2011:863–4.



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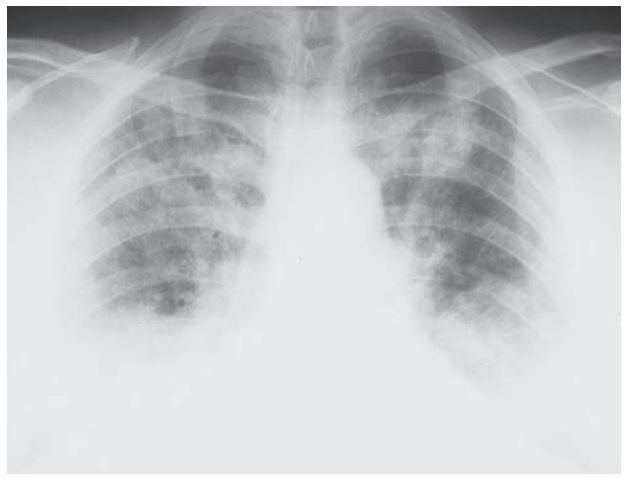

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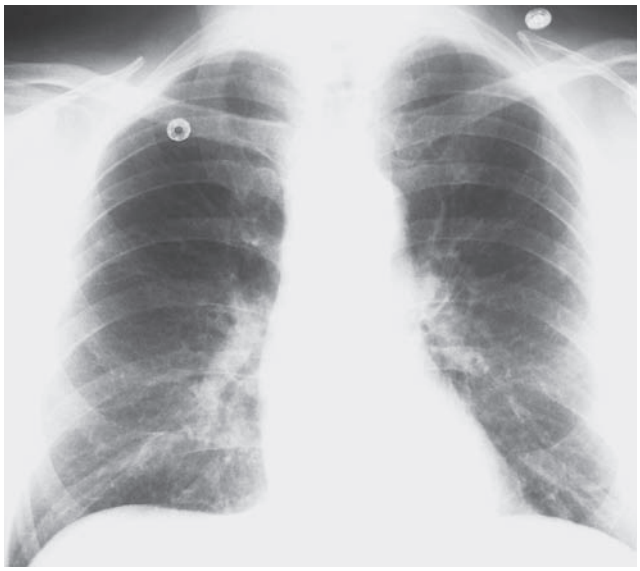


C

Figure 68-1 **A.** Idiopathic rapidly progressive glomerulonephritis. Posterior–anterior (PA) chest radiograph from a 52-year-old man with rapidly progressive glomerulonephritis, hemoptysis, and bilateral alveolar infiltrates, consistent with alveolar hemorrhage. Bronchoalveolar lavage demonstrated blood-tinged fluid and numerous hemosiderin-laden macrophages. **B.** Idiopathic rapidly progressive glomerulonephritis. PA chest radiograph from the same patient 18 months later with diffuse bilateral alveolar infiltrates representing recurrent massive alveolar hemorrhage. He was treated with pulse methylprednisolone (1 g daily for 3 days), followed by a gradual corticosteroid taper. **C.** PA chest radiograph from the same patient 3 weeks later demonstrating complete resolution of the alveolar infiltrates.

DIAGNOSIS

THE ROLE OF LUNG BIOPSY

The role of lung biopsy in the diagnosis of DAH and the determination of its etiology is controversial. We believe the risks of open or thoracoscopic lung biopsy are excessive in patients with severe DAH and respiratory failure. Postoperative complications such as infection and air leaks may be exacerbated by the corticosteroid or immunosuppressive agents used to treat many of these immune-mediated DAH syndromes. Furthermore, histological features are usually nonspecific. Predominant findings are extensive intra-alveolar hemorrhage and necrotizing pulmonary capillaritis (endotheliitis) (Fig. 68-2).[6–8] Capillaritis is characterized by neutrophilic infiltration of capillaries, fragmented neutrophils (leukocytoclasis), and necrosis of the capillary walls (Fig. 68-3).[8] Loss of the integrity of the alveolar–capillary basement membrane results in leakage of red blood cells and neutrophils into the alveolar space.[2] Hemosiderin-laden macrophages (siderophages) accumulate within the alveolar spaces and interstitium; their presence is a clue to prior episodes of alveolar hemorrhage (Figs. 68-2B,C and 68-4).[8]

Capillaritis was initially described as a marker of systemic vasculitis, but may also be observed in myriad disorders associated with DAH (e.g., SLE,[16] CTD,[2] anti-GBM disease,[14] bone marrow[25,26] or lung[29] transplant recipients, and drug-induced DAH).[1,6,7] An associated venulitis and arteriolitis may sometimes be present, but larger vessels are spared.[8] Capillaritis is subtle and often overshadowed by DAH filling the alveolar spaces.

Pulmonary capillaritis can be diagnosed by transbronchial biopsy, but this diagnosis is made with greater confidence when larger biopsy specimens are obtained by video-assisted thoracoscopy or limited thoracotomy.[6] Additional pathological features may be seen in patients with underlying granulomatous vasculitis (e.g., granulomas, necrosis, or eosinophils).[6,8] Nongranulomatous inflammation in airways and lung interstitium, interstitial fibrosis, diffuse alveolar damage (DAD), fibrinous pleuritis, and organizing pneumonia have also been described in DAH associated with anti-neutrophil cytoplasmic antibody (ANCA) vasculitic syndromes.[8] It should be emphasized that histological findings of alveolar hemorrhage and capillaritis, although distinctive, are nonspecific.[7] Immunofluorescent (IF) stains (of lung or kidney) or serological markers (e.g., anti-GBM antibody or ANCA) are required to differentiate the various causes of autoimmune DAH (Table 68-2).[6–8] Linear deposits of immunoglobulin G (IgG) along alveolar septa is pathognomonic for anti-GBM disease.[13,14] A granular, or "lumpy-bumpy" pattern of immune complex deposits may be seen in SLE, systemic necrotizing vasculitis, or immune complex–mediated idiopathic RPGN.[6] In ANCA-associated capillaritis, immune complexes are usually lacking (hence the term *pauci-immune*).[10,11,30] When immune DAH is suspected, a portion of the lung biopsy can

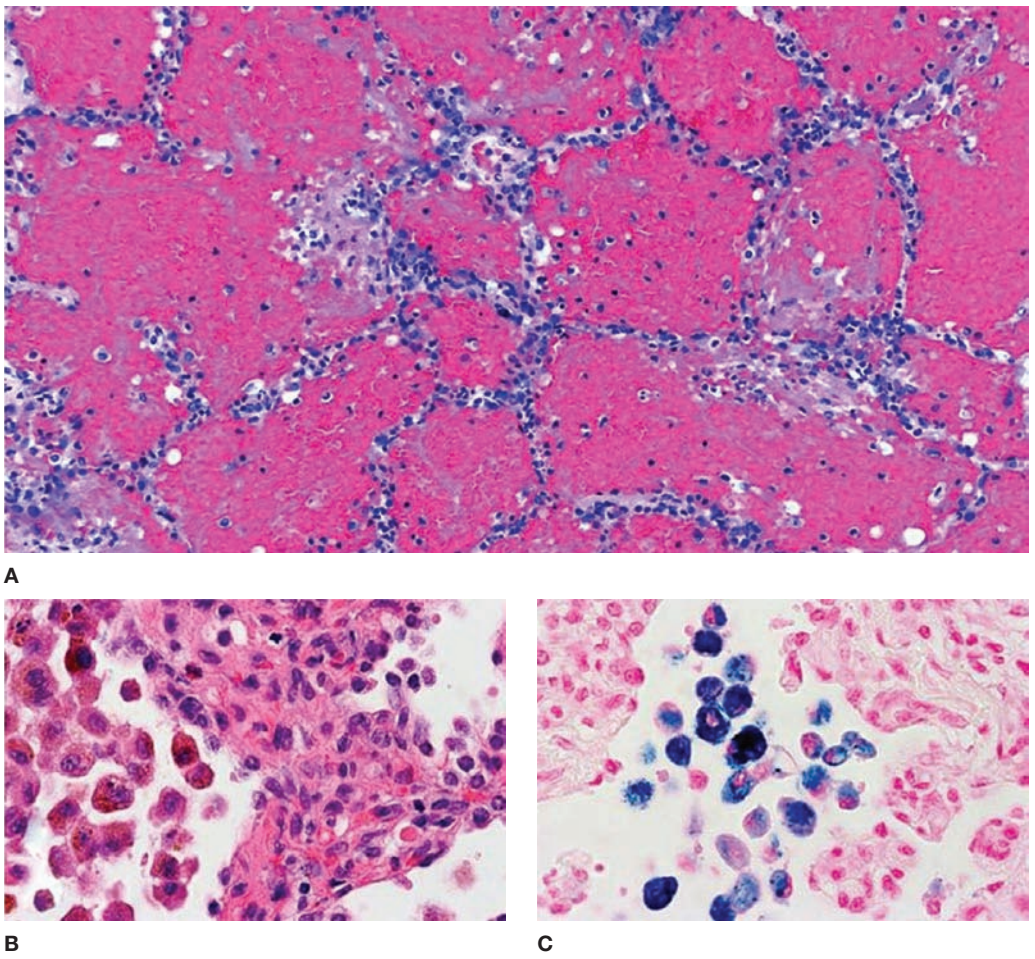


Figure 68-2 Alveolar hemorrhage. **A.** Acute hemorrhage with blood-filling alveolar spaces (H&E stain, ×40). **B.** Pigment-laden alveolar macrophages (H&E, ×200) shown in (**C**) to be full of iron (blue cytoplasm) indicative of prior hemorrhage (Prussian blue stain, ×200).

be frozen for IF stains, but IF stains of lung tissue are logistically difficult, and nonspecific background staining may lead to misinterpretation. When GN is present concomitantly, kidney IF stains are more sensitive and reliable.

Despite the greater accuracy of surgical lung biopsy in evaluating DAH, fiberoptic bronchoscopy with BAL is usually adequate to exclude infectious etiologies and support the diagnosis of DAH.[1] Bloody or serosanguinous BAL fluid (consistent with active or recent bleeding)[1,2,7] or hemosiderin-laden macrophages[8,27] (a clue to prior episodes of alveolar hemorrhage) may be sufficient to justify initiation of therapy provided clinical and serological features are consistent. Thoracoscopic lung biopsy may be useful in *noncritically ill* patients with suspected DAH when ancillary studies, kidney biopsy, and BAL are nondiagnostic.

■ THE ROLE OF PERCUTANEOUS KIDNEY BIOPSY

Necrotizing GN is a cardinal (albeit nonspecific) feature of most immune-mediated DAH syndromes.[19,31] The histological spectrum is varied, ranging from mild mesangial thickening to severe crescentic GN. Vasculitis of renal arterioles is rarely found, even in granulomatous vasculitides. Because of the strong association of autoimmune DAH and GN, percutaneous kidney biopsy should be performed in any patient with suspected DAH who has abnormalities on urinalysis or renal function tests. Conventional hematoxylin and eosin (H&E) stains are nonspecific, but the demonstration of glomerular inflammation with necrosis and crescents supports the diagnosis of an immune-mediated etiology (Fig. 68-5).[19,31,32] IF stains may clarify the nature of the underlying disorder. Bright linear IF staining along glomerular basement membranes (GBMs) is pathognomonic for anti-GBM disease (Fig. 68-6).[13,33] A lumpy-bumpy IF pattern, consistent with deposits of immune complexes, is found in some cases of CTD[16] and in idiopathic immune complex–mediated GN.[34] Negative IF stains are characteristic of the pauci-immune GN of necrotizing vasculitis.[19,30,35,36] Serologies are critically important in defining the underlying disorder responsible for DAH (particularly ANCA, anti-GBM antibody, and antinuclear antibodies). Recognizing the different pathogenetic mechanisms of these DAH syndromes is important, as the prognosis and treatment strategies differ.

■ THERAPY OF IMMUNE-MEDIATED ALVEOLAR HEMORRHAGE

Irrespective of etiology, the most immediate concern in patients with severe immune DAH is to control intrapulmonary bleeding, which may be fatal. Besides general supportive measures, corticosteroids are considered part of standard therapy for all immune-mediated DAH syndromes. For severe cases (e.g., severe hypoxemia, respiratory failure), high-dose "pulse" methylprednisolone (1000 mg daily for 3 days) should be given (irrespective of underlying etiology), even while pursuing a diagnostic workup.[1,7] Delaying pulse therapy in a critically ill patient for even a few hours may be catastrophic. Rapid resolution of bleeding can occur, often within 24 to 72 hours of initiation of therapy (Fig. 68-7). Following the 3-day pulse, corticosteroids (dose of methylprednisolone 60 to 120 mg per day or equivalent) should be continued for a few days, until control of the

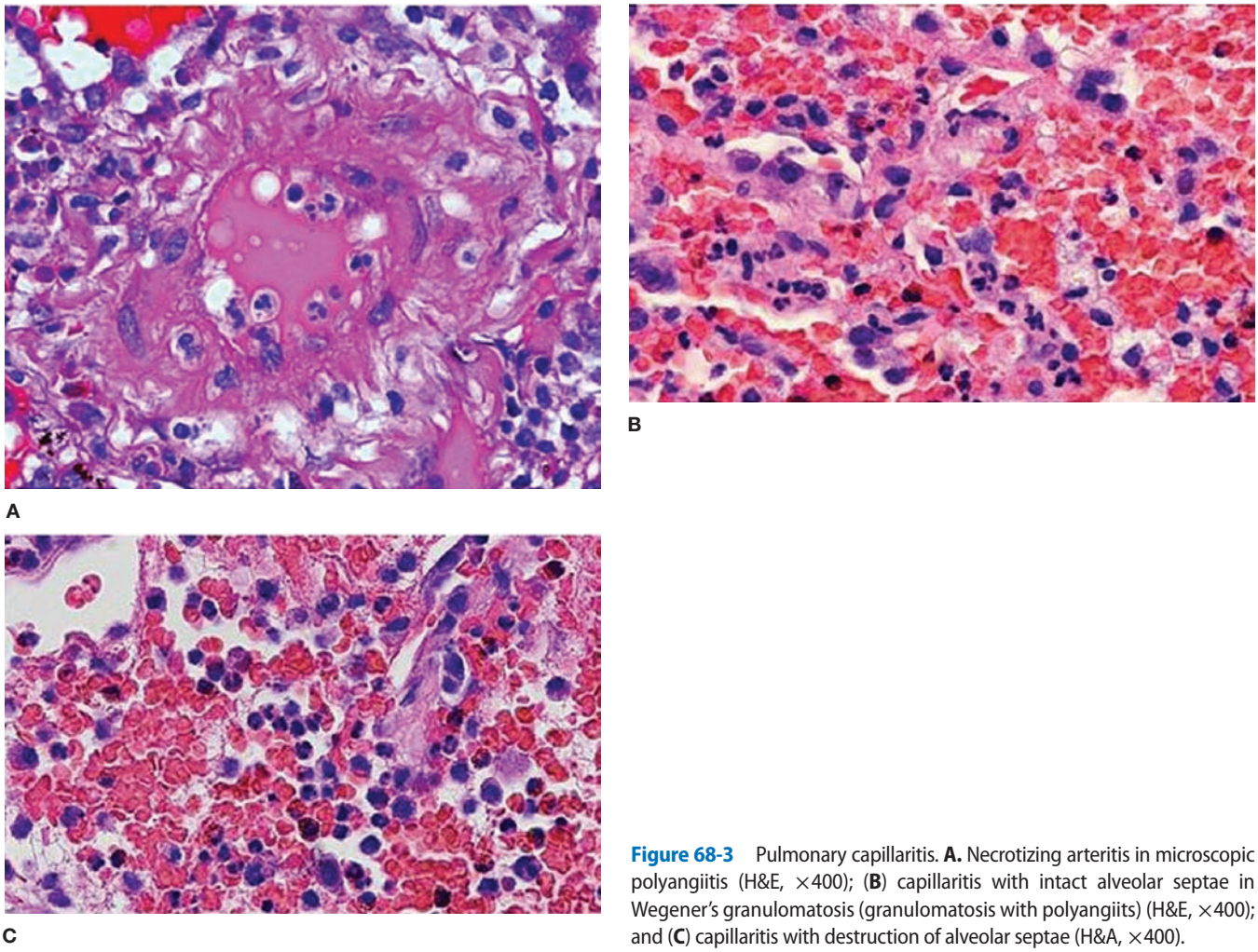


Figure 68-3 Pulmonary capillaritis. **A.** Necrotizing arteritis in microscopic polyangiitis (H&E, ×400); (**B**) capillaritis with intact alveolar septae in Wegener's granulomatosis (granulomatosis with polyangiits) (H&E, ×400); and (**C**) capillaritis with destruction of alveolar septae (H&A, ×400).

bleeding and extrapulmonary manifestations has been achieved. The subsequent dose and rate of corticosteroid taper need to be individualized, based upon clinical, radiographic, and serological response. The presence of renal involvement, vasculitis, or progression of DAH on corticosteroids is an indication for adding cyclophosphamide (CYC) (or occasionally other immunosuppressive agents).[1,18,37] Rituximab may be as effective, and possibly more effective than CYC for ANCA-associated vasculitis,[38,39] but data are limited for DAH.

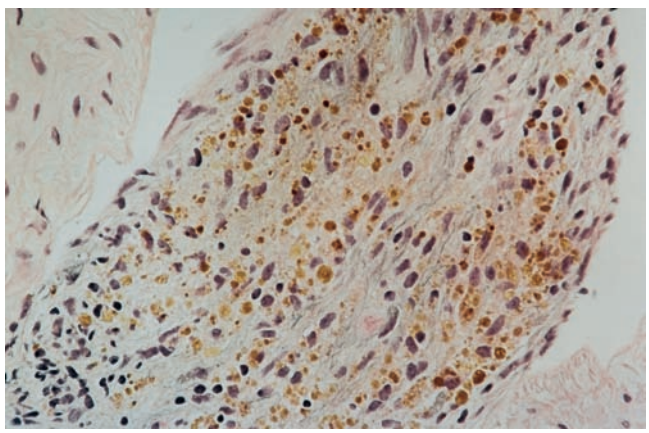


Figure 68-4 Hemosiderin-laden macrophages (siderophages) are prominent in the alveolar interstitium in a patient with recurrent alveolar hemorrhage (H&E). *(Used with permission of Joseph Fantone, MD.)*

Plasmapheresis is a central component of therapy for anti-GBM disease[13,14] but has no *routine* role for other disorders.[11,12,40,41] However, plasmapheresis may have an adjunctive role in patients with autoimmune DAH and severe renal insufficiency (i.e., serum creatinine >4 mg%)[41,42] and in patients with severe or progressive DAH refractory to corticosteroids or immunosuppressive agents.[43] Measures to ensure adequate oxygenation are also essential. Mechanical ventilatory support, often with positive end-expiratory pressure, may be necessary in fulminant cases of DAH, to prevent death due to refractory hypoxemia. Transfusion of red blood cells may be required to maintain an acceptable hematocrit (more than 25%) and adequate blood pressure. In the sections that follow, we discuss each of the autoimmune DAH syndromes individually.

SPECIFIC SYNDROMES

■ GOODPASTURE'S SYNDROME

Clinical Features

Anti-GBM disease (Goodpasture's syndrome), the prototype of pulmonary renal syndromes, accounts for 18% to 32% of immune-mediated DAH.[3,13,15,31,44] Classically, anti-GBM disease manifests as DAH and RPGN.[13,14,33,45] In 30% to 50% of patients with anti-GBM disease, GN occurs *without* DAH; DAH alone is rare (<5%).[14,15] Anti-GBM disease typically affects individuals between 20 and 45 years of age with a distinct male predominance.[14,45] The incidence has been estimated as 1 to 3 cases per million population per year.[46,47] The etiology is not known, but exposure to inhaled hydrocarbons,[46] cigarette smoke,[45] cocaine,[15] and antecedent viral

TABLE 68-2 Autoimmune Diffuse Alveolar Hemorrhage: Pathology and Serology

	Lung Pathology		Renal Pathology		
	Histopathology	Immunofluorescence	Histopathology	Immunofluorescence	Serology
ABMA disease (Goodpasture's syndrome)	±Capillaritis	Linear	Variable	Linear	ABMA (±p-ANCA)
Granulomatosis with polyangiitis	Capillaritis (±granulomatous)	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (c-ANCA ⋙ p-ANCA)
Microscopic polyangiitis	Capillaritis	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (p-ANCA or c-ANCA)
Systemic lupus erythematosus	Capillaritis	Granular	Variable	Granular	ANA
Idiopathic pulmonary hemosiderosis	±Capillaritis	Negative	Normal	—	Negative

ABMA, antibasement membrane antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophilcytoplasmic antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody.

illnesses, particularly influenza, have been cited as risk factors.[14] The demonstration of anti-GBM antibodies in tissue (typically kidney)[33] or in serum[13,14] is the cornerstone of the diagnosis.

The clinical expression of anti-GBM disease is highly variable. Most patients present with progressive dyspnea, diffuse alveolar infiltrates, and hypoxemia; hemoptysis occurs in 45% to 94%.[13–15,48] GN is a cardinal feature.[33,47,49,50] Microscopic hematuria, red cell casts, or proteinuria are almost always present. Gross hematuria occurs in up to 41% of patients.[14] Azotemia is noted in 55% to 71% of patients at presentation.[13,48] Fatigue and weakness are common.[14] In the absence of therapy, progressive renal insufficiency ensues, often resulting in end-stage renal failure within days to weeks of the onset of symptoms.[13] Oliguria, severe renal failure, or greater than 50% crescents on renal biopsy are associated with a poor prognosis and low rate of recovery of renal function.[13,14,33,51] The course may be fulminant, with severe renal failure and explosive, life-threatening DAH.[13,14] Chest radiographs typically reveal dense bilateral alveolar infiltrates, often with air-bronchograms. With cessation of bleeding, infiltrates may resolve within 24 to 36 hours. Pleural effusions are rare and suggest an alternative diagnosis. Pulmonary function tests are rarely helpful in the acute setting of DAH.[14,15] Bloody or serosanguineous BAL fluid (that worsens with serial aliquots) suggests DAH but is nonspecific.[8] Anemia is present in more than 90% of cases and may be profound. Serum iron and ferritin levels are usually decreased, reflecting diminished iron stores. Factors associated with a higher incidence of DAH include cigarette smoking,[15] exposure to high concentrations of oxygen, upper respiratory tract infections, and increased hydrostatic (pulmonary capillary) pressures.[13,14]

Serological assays for anti-GBM antibody are invaluable in confirming the diagnosis and monitoring the adequacy of therapy.[14,47] Radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) for anti-GBM antibody are highly sensitive (>95%) and specific (>97%)[13,14] but are performed in only a few laboratories. Results are usually not available for several days. Since delay in institution of therapy may preclude a favorable outcome, percutaneous renal biopsy is usually performed while awaiting the results of serum assays. Although disparate results have been reported, the height of serum anti-GBM antibody titer correlated with the prognosis of renal disease in some studies.[48,52] Further, changes in anti-GBM titer over time may be a guide to efficacy of therapy.[14] Treatment can be tapered and discontinued after the antibody has disappeared from the circulation (usually within 3–6 months).[15] Up to one-third of patients with circulating anti-GBM antibodies have concomitant ANCA (usually MPO).[13,32,53] Other serological studies are negative or nondiagnostic.

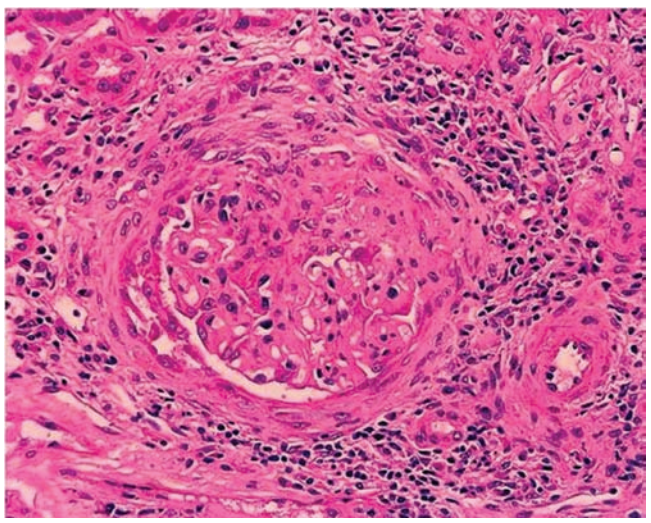


Figure 68-5 Segmental necrotizing and crescentic glomerulonephritis due to vasculitis (H&E).

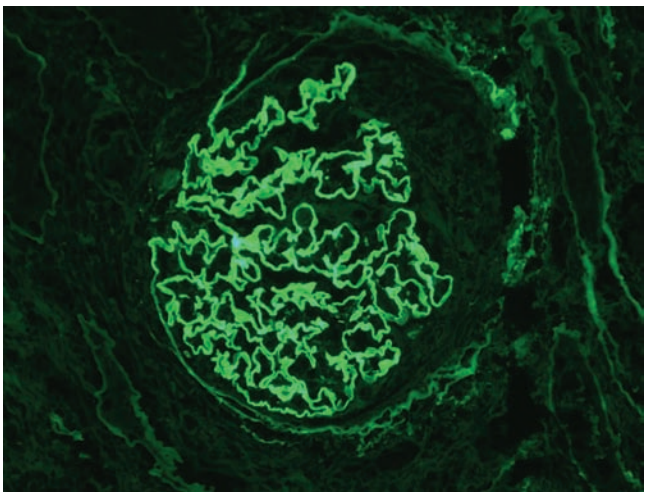
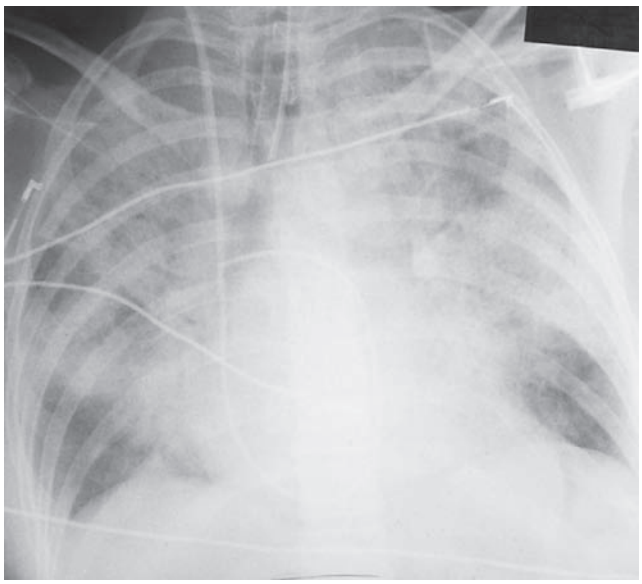
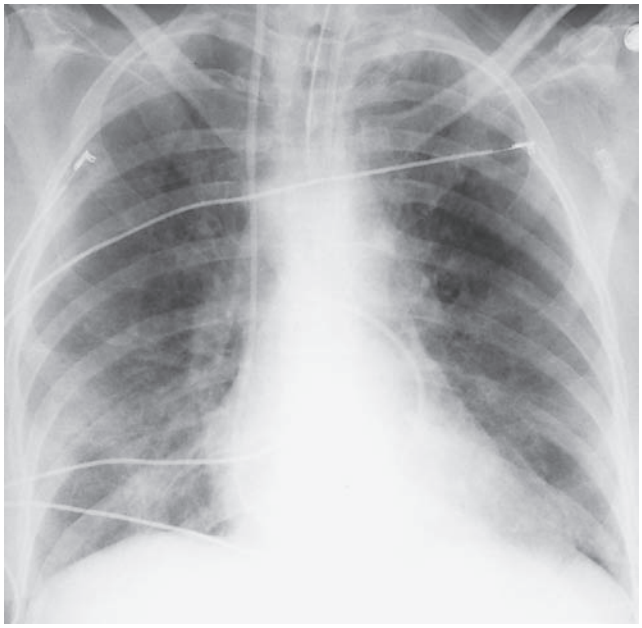


Figure 68-6 Linear immunofluorescent staining along glomeruli due to deposition of anti-glomerular basement membrane (anti-GBM) antibody.



A



B

Figure 68-7 **A.** Alveolar hemorrhage due to microscopic polyarteritis (MPA). Posterior–anterior (PA) chest radiograph demonstrating massive alveolar infiltrates involving all lobes. Because of the severity of respiratory failure (requiring 16 cmH_2O of positive end-expiratory pressure to achieve acceptable oxygenation), no lung biopsy was performed. Urinalysis demonstrated numerous red cells and occasional red cell casts. Serum creatinine was 1.4 mg%. Pulse methylprednisolone (1 g daily × 3 days) was initiated, and renal biopsy was scheduled for the following morning. **B.** Alveolar hemorrhage due to MPA. PA chest radiograph from the same patient 12 hours following initiation of pulse methylprednisolone. Marked improvement in alveolar infiltrates is evident. Renal biopsy demonstrated glomerulonephritis and a necrotizing vasculitis involving renal arterioles; no granulomas were present. Cyclophosphamide (2 mg/kg per day) was instituted, and corticosteroids were continued. Within 5 days, the infiltrates had cleared completely and serum creatinine was 0.6 mg%.

HISTOPATHOLOGY

Percutaneous kidney biopsy is the preferred invasive procedure to substantiate the diagnosis of anti-GBM disease.[15] Light microscopy demonstrates a proliferative or necrotizing GN, often with cellular crescents.[14,33] Over time, the crescents may fibrose, and frank glomerulosclerosis, interstitial fibrosis, and tubular atrophy may be observed.[33] Although these microscopic features are nonspecific, IF stains are the cornerstone of the diagnosis. Bright linear deposits of IgG and complement (C3) along GBM are pathognomonic of anti-GBM disease (Fig. 68-6).[14,33] All four subclasses of IgG are represented, but IgG_1[54,55] and IgG_3[55] predominate in anti-GBM disease. Rare cases of linear deposits of IgM or IgA have been described.[15] Lung biopsies are rarely necessary,[14] as the histological features on renal biopsy are usually adequate to establish the diagnosis. When lung biopsy has been done, extensive hemorrhage predominates[6,8] with accumulation of hemosiderin-laden macrophages within the alveolar spaces.[14] Foci of DAD and capillaritis may also be found.[6] Interstitial or intra-alveolar inflammation is minimal or absent. Extensive necrosis or large-vessel vasculitis is not found. Similar histopathological features may be seen with a wide gamut of immune-mediated DAH syndromes.[6,8] IF stains of lung tissue may be diagnostic, provided a clear linear pattern of immunofluorescence is present. However, IF stains are technically difficult in lung tissue and autofluorescence may obscure the linear IgG deposits.

PATHOGENESIS

Antibodies are directed against the α3 chain of type IV collagen, an antigen highly expressed in both alveolar and GBMs.[13,15,54] Anti-GBM antibodies bind the GBM and activate complement, initiating an inflammatory pathway that elicits injury.[13] In addition to circulating antibodies, autoreactive T lymphocytes directed against the α3 antigen are key mediators for development of RPGN.[15,56] Immunoglobulin synthesis and deposits of IgG along the alveolar and glomerular capillary basement membranes then ensue. Anti-GBM disease is monophasic, and during the course of the disease, self-tolerance is restored.[13] Late relapses are rare.[13] This tolerance may be achieved by regulatory CD4+ and CD25+ T cells[15,57] or anti-idiotypic (blocking) antibodies,[54] but this remains speculative.

The pathogenesis of anti-GBM disease is unknown, but both genetic[15,58] and environmental factors[54] may play roles. Patients with anti-GBM disease preferentially express certain immunoglobulin Gm allotypes and links between anti-GBM disease and the HLA-DR2 histocompatibility antigen have been noted.[13,15] Exposure to cigarette smoke, hydrocarbon-containing solvents, hard-metal dust, influenza A2 virus, chlorine gas, and D-penicillamine have been associated with anti-GBM disease.[13–15] These exogenous factors may injure the basement membrane, resulting in increased capillary permeability, exposing the Goodpasture's antigen (α3 chain), which is then recognized as foreign, eliciting a T-helper cell response.[15,54]

TREATMENT

Before the availability of the current therapy and renal dialysis, mortality exceeded 90%.[13] Plasmapheresis was introduced as a therapeutic option for anti-GBM disease in the 1970s,[49] and was quickly adopted worldwide and incorporated in all clinical trials. Currently, with the combination of plasmapheresis, corticosteroids (CSs), and CYC, mortality has been reduced to less than 20%.[13–15] Because of the rarity of anti-GBM syndrome, only one small randomized trial compared immunosuppressive therapy with the *combination* of immunosuppressive therapy *plus* plasma exchange.[49] In that study, plasmapheresis plus immunosuppressive therapy was associated with more rapid disappearance of anti-GBM antibody and improved renal function than treatment with immunosuppressive agents *alone*.[49] The optimal extent and duration of plasma exchanges have not been defined. Most

investigators advocate plasma exchange daily or every other day for 2 to 3 weeks, until the clinical course has improved and serum anti-GBM antibodies are nondetectable.[13,41] Immunosuppressive therapy is required to inhibit antibody production and rebound hypersynthesis, which may occur following discontinuation of plasma exchange.[13] Treatment of acute, life-threatening DAH in Goodpasture's syndrome is similar to other autoimmune disorders. Pulse methylprednisolone (1 g daily for 3 days) is given, followed by a gradual corticosteroid taper.[14] Either CYC (oral or IV pulse) or azathioprine should be initiated once the diagnosis of anti-GBM disease is substantiated. Most investigators favor CYC over azathioprine,[13–15] but studies comparing these agents have not been done. CYC is maintained for the duration of therapy, unless complications such as leukopenia necessitate dose reduction. The corticosteroid dose is gradually tapered over several months. Immunosuppressive or cytotoxic therapy may be discontinued within 3 to 6 months provided a sustained remission has been achieved and anti-GBM antibodies have disappeared.[13,15] Circulating anti-GBM antibodies usually clear within 8 weeks, irrespective of the initial titer. Early relapse (within the first 2 months) may occur when circulating antibodies are still present. This typically manifests as DAH. Risk factors for relapse include infection, volume overload, and cigarette smoking.[15] Late recurrence, associated with renewed antibody synthesis following a remission, is rare.[14] In summary, aggressive therapy with plasmapheresis, corticosteroids, and immunosuppressive agents has dramatically improved prognosis.[14,15,51] With this approach, 5-year survival exceeds 80%, and fewer than 30% of patients require chronic dialysis.[14,15] Early recognition and treatment of this syndrome are critical, as the prognosis for recovery of renal function depends upon the initial extent of injury.[32,50] Recovery of renal function can be expected in patients with minor functional impairment. By contrast, patients manifesting initial serum creatinine greater than 4 mg/dL, oliguria, or greater than 50% crescents on renal biopsy rarely recover and usually progress to end-stage renal failure requiring chronic dialysis.[32,50] In one study of 71 patients with anti-GBM disease (all were treated with steroids, immunosuppressive agents, and plasmapheresis), renal survival was linked to extent of renal failure at presentation.[51] Renal survival rates at 1 year were as follows: 8% among 39 patients requiring dialysis at presentation; 82% among 13 patients with creatinine >5.7 but not requiring dialysis; 95% among 19 patients with initial serum creatinine <5.7 mg%. Renal transplantation has been successful in patients with irreversible renal failure, provided serum anti-GBM antibodies are undetectable.[59,60]

Systemic Vasculitis

DAH is a common complication of MPA[10,11] and granulomatosis with polyangiitis (GPA) (formerly called Wegener's syndrome)[12,61] and rarely complicates Churg–Strauss syndrome (CSS),[62,63] Behçet disease,[64] mixed cryoglobulinemia,[65] Henoch–Schöenlein purpura,[66] and other systemic necrotizing vasculitides.[1,37] Classic polyarteritis nodosa (PAN) rarely involves the lung.[8,67] Necrotizing small-vessel vasculitis accounts for the majority of autoimmune DAH syndromes.[1,8] RPGN is usually present in each of these DAH syndromes, but the disease is sometimes limited to the kidneys or lungs. Circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (ANCA) have been detected in most patients with these "pulmonary–renal syndromes,"[7,34,37,68] suggesting a common pathogenesis and mechanism of lung injury in these diverse vasculitic disorders.

ANCA-Associated Vasculitides

Goodpasture's syndrome (anti-GBM disease) was the first of the pulmonary–renal syndromes to be immunologically characterized.[14,15] Subsequent studies documented immune complexes in serum or renal tissue in subsets of patients with pulmonary–renal syndromes, particularly SLE[16] and immune complex–mediated GN.[69] However, more than two-thirds of patients with pulmonary–renal syndromes are mediated by ANCA antibodies without anti-GBM or immune complexes (i.e., pauci-immune).[1,34,37] Depending upon clinicopathological features, some patients with pauci-immune GN and DAH may meet criteria for GPA or CSS, while others exhibit a multisystemic small-vessel vasculitis but lack granulomatous inflammation of the respiratory tract. In this context, the term *microscopic polyangiitis* is used.[10,11,70] The availability of serum assays for ANCAs has profoundly influenced the classification of immune DAH and GN. ANCA-positive patients with pauci-immune DAH and GN (*formerly* given a diagnosis of idiopathic RPGN and DAH) are now considered to have MPA.[11] The spectrum of ANCA-associated diseases is not limited to patients with pulmonary–renal syndromes but includes individuals with MPA limited to the lung (i.e., manifesting as DAH) or kidney (i.e., necrotizing GN).[11] To avoid further confusion, brief definitions of the major ANCA-associated vasculitides are outlined below.

■ GRANULOMATAOSIS WITH POLYANGIITIS, GPA (FORMERLY CALLED WEGENER'S GRANULOMATOSIS)

GPA, the most common of the pulmonary vasculitides, typically involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis (see Chapter 83).[12] The annual incidence of GPA has been estimated at 4 to 12 cases per million.[12,46,71,72] Alveolar hemorrhage is a rare complication of GPA, reflecting diffuse injury to the lung microvasculature (i.e., capillaritis) (Fig. 68-8).[1,6] In this context, RPGN is present in more than 90% of patients.[6,12] The salient histopathological features of GPA include small-vessel vasculitis (involving capillaries, arterioles, venules), geographic necrosis, hemorrhagic infarcts, a mixed inflammatory cellular infiltrate, and a granulomatous component.[6,8,12] Circulating c-ANCAs (PR3 epitope) have been detected in more than 90% of patients with active generalized GPA and in 40% to 70% with active regional GPA.[12,68,73–75] Oral CYC (2 mg/kg per day) plus prednisone has been the initial treatment of choice for GPA for more than 3 decades.[12,76,77] With this regimen, remissions are achieved in 70% to 93% of patients, with early mortality rates of less than 15%.[76–81]

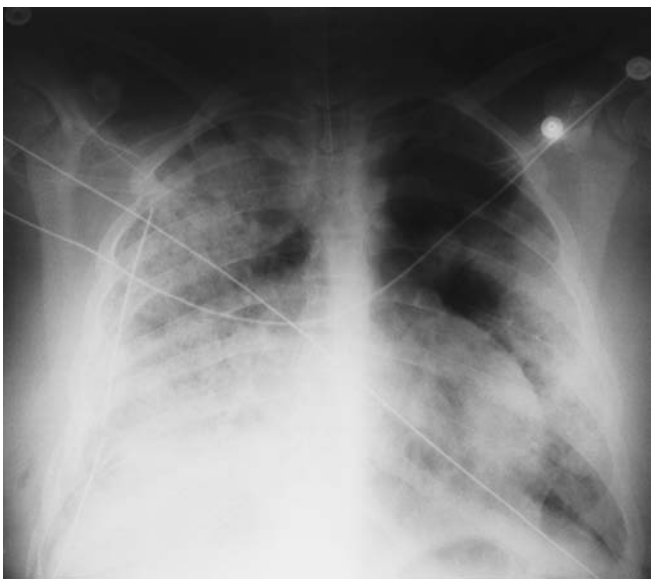


Figure 68-8 Granulomatosis with polyangiitis (GPA) (formerly called Wegener's granulomatosis. Posterior–anterior (PA) chest radiograph demonstrated bilateral alveolar infiltrates in a 13-year-old girl with hemoptysis and respiratory failure. A right chest tube is in place from an open lung biopsy performed 2 days earlier. Open lung biopsy demonstrated capillaritis and massive alveolar hemorrhage. Pulse methylprednisolone, followed by oral cyclophosphamide and prednisone, was associated with a complete remission.

By 3 to 6 months, assuming complete remissions are achieved, azathioprine[78,79] or methotrexate[79] can be substituted for CYC. Treatment should be continued for a minimum of 12 to 18 months (total duration).[12,77] Relapses can be treated with CYC and prednisone. Methotrexate may be used in patients with limited disease or those experiencing significant toxicity from CYC.[82,83] Rituximab may be as effective, and possibly more effective than CYC for GPA and AAV.[38,39,84–86] However, whether rituximab should be used with corticosteroids alone or corticosteroids combined with CYC has not been clarified. Further, the role for long-term maintenance therapy with rituximab has not been studied.[84–86] Additional studies are required to assess indications for rituximab, appropriate dosing and frequency of administration, role for concomitant therapy, and long-term side effects. Trimethoprim/sulfamethoxazole may have an adjunctive role (together with CYC and prednisone) to reduce relapse rates,[87] but should not be considered as primary therapy.

CHURG–STRAUSS SYNDROME (ALLERGIC ANGIITIS AND GRANULOMATOSIS)

CSS, also termed *allergic angiitis* and *granulomatosis,* is a rare, small-vessel vasculitis associated with a prominent allergic component, asthma, and eosinophils in blood or involved tissues (see Chapter 83).[63,88] CSS involves capillaries, venules, and arterioles.[63] Granulomas, eosinophils, and palisading histiocytes in extravascular tissues are hallmarks of the disorder[88,89] and distinguish CSS from other vasculitides.[8,63] The annual incidence of CSS has been estimated at 0.6 to 6.8 cases per million.[46,71,88,90] In the classic form of CSS, vasculitis develops after a several-year history of atopy or asthma.[89] Pulmonary involvement is nearly invariably present.[63,88,89] Asthma is present in 96% to 100%; focal infiltrates on chest radiographs, in 30% to 70% of cases.[63,88,89] DAH is a rare complication of CSS. In a French series of 112 patients with CSS, moderate DAH was observed in 3/43 ANCA-(+) patients and in 5/69 ANCA-negative patients.[91] DAH was cited in only 1/32 patients in a Spanish series,[92] and 1/19 in an Italian series.[93] Severe DAH has only rarely been reported in CSS.[94,95] Constitutional symptoms may herald the onset of vasculitis.[88] Extrapulmonary manifestations include mononeuritis multiplex (63%–93%); skin (50%–78%); cardiac (16%–56%); kidney (16%–49%); skin (50%–78%); gastrointestinal (GI) tract (17%–58%).[63,88] Factors associated with a worse prognosis include cardiac or GI tract involvement, renal insufficiency; age >65 years.[96]

The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood eosinophil count are elevated in more than 80% of patients during the acute phase of vasculitis or exacerbations.[62,70,88,89] Circulating ANCAs (primarily p-ANCA) have been detected in 40% of patients with CSS.[88,91,97] Interestingly, the presence of ANCA was associated with a higher incidence of renal involvement and pulmonary hemorrhage, but a lower frequency of cardiac involvement.[97]

A variety of treatment regimens have been employed for CSS including corticosteroids, immunosuppressive or cytotoxic agents, and plasmapheresis (alone or in combination).[62,88,96] Corticosteroids achieve remissions in more than 80% of patients with CSS and are first-line therapy for mild to moderate cases of CSS.[88,98,99] Oral or pulse CYC (or other immunosuppressive agents such as azathioprine or mycophenolate mofetil) should be added for severe or multisystemic disease or corticosteroid-recalcitrant cases or when unfavorable prognostic factors are present.[40,62,88,96,98] Plasmapheresis should be considered as adjunctive therapy for ANCA-positive CSS patients with severe pulmonary–renal syndrome.[42]

MICROSCOPIC POLYANGIITIS

MPA (formerly termed *microscopic polyarteritis* or *polyangiitis overlap syndrome*) typically presents with GN and pulmonary capillaritis manifesting as DAH.[10,11] Clinical and serological features of MPA overlap with GPA and CSS.[11,70] MPA is rare, with an annual incidence of 2.1 to 17.5 cases per million.[46,71,90] As its name implies, MPA involves small vessels (arterioles, venules, or capillaries); extension to larger vessels occurs in a minority of cases.[100] Small vessels are always spared in classic PAN.[67,100] In contrast to GPA or CSS, neither granulomas nor eosinophils are prominent in MPA.[11,100] Circulating ANCAs are present in 50% to 90% of patients with MPA,[11,70,100] suggesting a relationship with other ANCA-associated vasculitides. By contrast, circulating ANCAs are present in fewer than 20% of patients with classic (macroscopic) PAN.[100] A necrotizing, crescentic pauci-immune GN is nearly invariably present in MPA[11,100] but is rare in classic PAN.[67] Alveolar hemorrhage, which is rarely observed in classic PAN, occurs in 30% to 50% of patients with MPA and is often the dominant and most life-threatening manifestation.[10,11,70]

Corticosteroids, CYC, and plasmapheresis, alone or in combination, have been used to treat MPA.[11,70,78] Response rates and long-term survival have generally been similar with the various regimens. Most investigators use oral CYC (2 mg/kg per day) plus prednisone (1 mg/kg per day, with gradual taper), similar to the regimen used for GPA. With this approach, favorable responses are achieved in more than 80% of patients; 10-year survival exceeds 70%.[11,70,78] By 3 to 6 months, once complete remissions have been achieved, azathioprine, methotrexate, or mycophenolate mofetil may be substituted for CYC.[11,78] As was discussed in the section on GPA, rituximab may be as efficacious as CYC-containing regimens for AAV,[38,39,84–86] but data are limited.

ANCA-ASSOCIATED PULMONARY RENAL SYNDROMES: CLINICAL FEATURES

The clinical and radiologic manifestations of ANCA-associated DAH are similar to other immune causes. Acute necrotizing GN is nearly always present, but the renal lesion is nonspecific.[34,35,101] Distinguishing the specific underlying disorder may be difficult. The pathological lesions in ANCA-associated diseases share characteristic features, regardless of the organ affected. The three key histopathological findings are a segmental (focal) distribution of vascular injury, infiltration with neutrophils, and fibrinoid necrosis.[11,70,100] The latter results from lysis of the vascular wall, allowing plasma coagulation factors to enter the interstitium and come into contact with thrombogenic substances, generating fibrin. Neutrophils that infiltrate vessel walls undergo disruption and karyorrhexis, leading to the typical leukocytoclastic pattern of injury in capillaries and venules.[100] ANCA-associated vascular injury is accompanied by few, if any, immune deposits (pauci-immune).[19] However, the presence of immune deposits may be associated with more severe renal injury.[34] The salient lesion of renal vasculitis is a segmental necrotizing GN, usually accompanied by extracapillary proliferation of Bowman capsule (crescents) (Fig. 68-5).[11] Depending on the duration and extent of renal injury, varying degrees of glomerular fibrosis and sclerosis may be seen.[19] Vasculitis affecting the kidney often involves only the glomerular capillaries; macroscopic arteritis is seldom apparent.[100] When the lung is involved, the histopathology is nonspecific, demonstrating only capillaritis and intra-alveolar hemorrhage.[7] Immune deposits are absent.

Clinical features of ANCA-associated DAH syndromes overlap. Striking elevations in the ESR and CRP may be observed in all the syndromes, particularly when disseminated vasculitis is present.[11,88] Anemia and leukocytosis are common. Marked eosinophilia is characteristic of CSS[89] but is not a feature of MPA[11] or GPA.[12] Extrapulmonary and extrarenal manifestations suggesting small-vessel vasculitis (e.g., palpable purpura, leukocytoclastic vasculitis, mononeuritis multiplex, arthralgias or arthritis, ocular disease, sinusitis) may direct biopsies at these sites. Histological features of granulomatous vasculitis are consistent with GPA or CSS whereas granulomas are lacking in MPA.[11,100] Radiographic features may discriminate granulomatous vasculitides from MPA. In GPA (and less

commonly in CSS), focal nodular or cavitary mass lesions may be seen.[12] These are not found in MPA.[11] The diagnosis of CSS can usually be readily established by a pronounced eosinophilic component in the blood or in extravascular sites.[67,89] However, discriminating GPA from MPA may be difficult or impossible as small-vessel vasculitis is common to both disorders. By definition, GPA is associated with concomitant granulomatous inflammation, typically, but not invariably involving the upper and lower respiratory tracts.[12] The latter may lead to the highly distinctive features attributed to GPA including sinusitis, otitis media, nasal or laryngotracheal ulcerations, subglottic stenosis, and cavitary pulmonary nodules.[12]

Characteristics of ANCA

The identification of circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (i.e., ANCA) represented a major advance in the classification and understanding of vasculitis.[68,75] Using ethanol-fixed granulocytes incubated with patient serum, two distinct patterns of ANCA are identified by IF techniques: cytoplasmic (c-ANCA) and perinuclear (p-ANCA) (Fig. 68-9). The p-ANCA pattern is an artifact of fixation causing movement of the target antigens to a perinuclear location. These differing IF patterns reflect distinct antigenic specificities.

In both radioimmunoassays and ELISA, the antibody responsible for c-ANCA is directed against proteinase 3 (PR3).[68,75] The p-ANCA pattern is usually due to an antibody to myeloperoxidase (MPO).[68,75] MPO-ANCA is usually associated with small-vessel vasculitis, but multiple p-ANCA antibodies directed against a variety of antigens (e.g., cathepsin G, lactoferrin, and elastin) may be seen in nonvasculitic inflammatory disorders including CTD and inflammatory bowel or liver disease.[68,75] Therefore, while c-ANCA is more than 90% specific for small-vessel vasculitis, p-ANCA is nonspecific. In untreated GPA, circulating c-ANCA (PR3-ANCA) is detected in more than 70% of patients; the incidence is lower (40% to 65%) in patients with limited disease (e.g., involvement confined to the upper respiratory tract).[12] By contrast, p-ANCA (MPO-ANCA) is rarely found in GPA. Circulating ANCAs are present in more than 70% of patients with MPA[7,11,70] and 30% to 70% of patients with CSS.[62,67,88] In MPA either c-ANCA or MPO-ANCA may be present, but MPO is more common.[70] Circulating ANCAs have been found in fewer than 20% of patients with classic PAN.[67] When present, antibodies have shown MPO antigenic specificity. Individual patients almost never have both c-ANCA and p-ANCA. Most ANCAs are of the IgG class. However, IgM ANCAs associated with severe DAH have been described, either concomitant with IgG-ANCA or in the absence of IgG-ANCA.[102] It is unknown how often patients with ANCA-negative vasculitis would be ANCA-positive if reagents that detected IgM antibodies were used.

The antigenic specificities of ANCA (i.e., PR3 or MPO) may provide clues to the nature of the underlying disorder and may assist in categorizing the type of disease, but overlap exists.[68,75] Biopsies are important to differentiate the nature of the underlying vasculitic disorder. For example, patients with c-ANCA and small-vessel vasculitis may be misclassified as MPA if clinically inapparent areas of granulomatous inflammation are overlooked. For clinical purposes, distinguishing GPA from MPA is not critical, because therapy and management are similar.[78] Circulating p-ANCA (MPO) or c-ANCA (PR3) are present in more than 70% of patients with pauci-immune necrotizing GN (renal vasculitis).[30,68,75,103] ANCA-negative patients usually have disease limited to the kidney. Nearly all patients with concomitant DAH have circulating ANCA. Indeed, a negative ANCA provides strong evidence against vasculitis as the cause of DAH and GN. When applied to patients with RPGN, a positive ANCA almost invariably predicts pauci-immune necrotizing GN. In the setting of clinical, laboratory, and radiologic features that are highly suggestive of DAH and RPGN, a positive c-ANCA or MPO-ANCA, together with a negative anti-GBM and ANA assay, is virtually diagnostic of systemic vasculitis (e.g., GPA or MPA). Similarly, a positive ANCA (usually MPO-ANCA) is sufficient to diagnose lung-limited MPA, provided the clinical presentation is typical of DAH and nonimmune causes of DAH have been excluded. Most patients previously diagnosed as having idiopathic IPH likely had lung-limited MPA or ANCA-associated pulmonary capillaritis.

Problems with using serum ANCA to diagnose vasculitis arise when the clinical presentation is ambiguous. The low incidence of vasculitis in the general population dictates that the positive predictive value of ANCA will be low when applied indiscriminately. Routine assay of serum ANCA in patients with nonspecific respiratory complaints yields a high rate of false-positive results. Given the risks of immunosuppressive therapy, misinterpretation of ANCA may lead to devastating consequences. Accordingly, results of serum ANCA assays must be interpreted in light of the entire clinical picture.

Anti-GBM disease and vasculitis have traditionally been viewed as distinct clinicopathological entities. However, up to 30% of patients with anti-GBM disease (as evidenced by anti-GBM antibody in serum and linear deposits of IgG in kidney biopsy) also have serum MPO-ANCA.[7,32,15] The coexistence of ANCA and anti-GBM antibodies is almost certainly not a chance occurrence, given the rarity of both antibodies in the general population.[15] It is possible that ANCA initiates vascular injury, and anti-GBM antibody then forms in response to the damaged basement membrane.

The role of ANCA in the pathogenesis of vasculitis is uncertain, but these antibodies probably mediate vascular damage.[68,74,75,104] Sera from patients with either c-ANCA or MPO-ANCA induce neutrophils to undergo

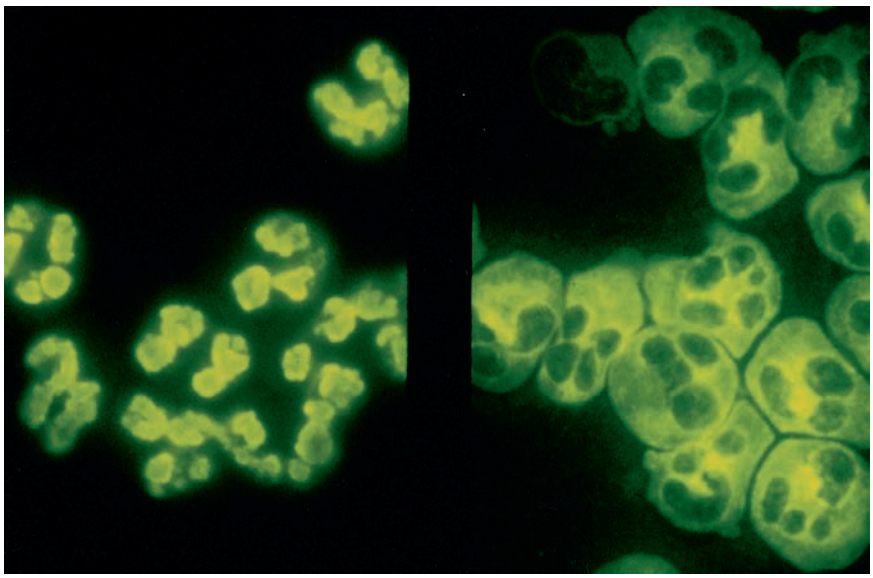


Figure 68-9 Indirect immunofluorescent stains demonstrating two distinct types of antineutrophil antibodies. On the left panel, note the perinuclear pattern of immunofluorescence characteristic of p-ANCA (myeloperoxidase epitope). On the right panel, a coarse granular pattern of immunofluorescence within the cytoplasm is evident, characteristic of c-ANCA (proteinase-3 epitope).

a respiratory burst with release of reactive oxygen species and proteolytic enzymes.[104] Cytokine-primed neutrophils are stimulated by ANCA to damage human endothelial cells in vitro.[104] These observations, together with correlations of ANCA titer with clinical disease in humans (although imperfect), suggest that ANCAs are not innocent markers of vasculitis but play a crucial role in mediating vessel injury.[68,75,104]

Therapy

Therapy of DAH due to ANCA-associated syndromes depends on the underlying disorder and the extent and severity of symptoms. Irrespective of etiology, the most immediate concern in patients with severe immune DAH is to control intrapulmonary bleeding, which may be fatal. Besides general supportive measures, high-dose "pulse" methylprednisolone (followed by a tapering regimen of corticosteroids) should be given. The presence of renal involvement *or* progression of DAH on corticosteroids is an indication for adding CYC (with or without empiric plasma exchange).[18] Plasma exchange has been used, with anecdotal successes, as therapy for ANCA-associated systemic vasculitis with severe renal insufficiency[43,105–109] or DAH.[43] Because ANCA may play a pivotal role in mediating tissue injury, plasmapheresis may be beneficial in selected patients (particularly those with DAH[43] or severe renal failure, i.e., serum creatinine >4 mg%[41,42] or dialysis-dependent).[105,107,109,110] When plasma exchange is used to treat ANCA-associated DAH, it may be preferable to use an apparatus that efficiently removes both IgM and IgG, because of the reported association of IgM-ANCA and DAH.[110] Protein A immunoadsorption has also been used to treat patients with DAH and GN,[111] in the hope of removing pathogenic antibodies without producing the side effects of plasma exchange. Additional strategies for patients resistant to conventional therapies include high-dose, intermittent intravenous immunoglobulin G (IVIG).[112] The mechanism of action is uncertain but may involve binding of ANCA idiotype by anti-idiotype antibodies in the intravenous IgG preparation.[112]

The role of serial ANCA determinations in following patients with vasculitis is controversial. We do not base therapeutic decisions on the ANCA titer alone. However, a rising titer should alert the clinician to the possibility of disease exacerbation and clinical follow-up should be intensified. Serial ANCA titers may help differentiate disease relapse from nonimmune causes of pulmonary infiltrates. However, ANCA titers do not obviate the need to aggressively evaluate patients with vasculitis presenting with a new pulmonary process while receiving immunosuppressive therapy.

CONNECTIVE TISSUE DISORDERS

■ SYSTEMIC LUPUS ERYTHEMATOSUS

Alveolar hemorrhage is a rare, but potentially catastrophic, complication of SLE, with mortality rates as high as 50%.[16,113–115] In one large tertiary care center, 19 episodes of DAH were observed among 15 patients with SLE, accounting for 3.7% of hospitalizations for complications of SLE.[16] Alveolar hemorrhage complicating SLE is almost invariably accompanied by other manifestations of active SLE.[16,113,114,116] Alveolar hemorrhage is rarely the sole or presenting feature of SLE.[16,116] Clinical and radiographic features of DAH complicating SLE are similar to other DAH syndromes. However, in SLE-associated DAH, GN is usually, but not uniformly, present.[16,113,114] Diffuse, bilateral alveolar infiltrates, dyspnea, and hypoxemia are characteristic (Fig. 68-10). Hemoptysis is noted in a minority of patients at presentation, obscuring the diagnosis.[16,114,116] The diffuse pulmonary infiltrates must be differentiated from other pulmonary complications of SLE[117] including lupus pneumonitis, opportunistic infections, congestive heart failure, uremia, or pulmonary embolism.

Lung biopsy may be needed to exclude alternative diagnoses and corroborate the diagnosis of DAH. However, the risk of lung biopsy may be substantial in critically ill patients with fulminant DAH and respiratory failure. In addition, as with other immune DAH syndromes, histopathological features of DAH complicating SLE are nonspecific. The dominant feature is intra-alveolar hemorrhage and capillaritis, without macroscopic necrosis.[16] The small-vessel necrotizing vasculitis rarely extends to arterioles and small muscular arteries in addition to capillaries. Granular deposits of IgG or C3 (consistent with immune complexes) have been found in up to 50% of cases of DAH complicating SLE.[16,118] Because of its potential morbidity, we rarely advise surgical lung biopsy to diagnose DAH. Provided clinical features are consistent, the diagnosis of DAH can often be established by fiberoptic bronchoscopy with BAL and transbronchial lung biopsies. Transbronchial biopsies may demonstrate foci of capillaritis with intra-alveolar hemorrhage, but due to sampling error, these features may be missed. However, the presence of gross blood in the airways or serosanguineous BAL fluid, large numbers of hemosiderin-laden macrophages, absence of purulent sputum, and lack of infectious organisms by appropriate stains strongly supports the diagnosis of autoimmune DAH and justifies institution of therapy. Transbronchial lung biopsies may be deferred in acutely ill patients with severe DAH and respiratory failure. In this context, BAL alone is adequate, primarily to exclude local or infectious causes of bleeding.

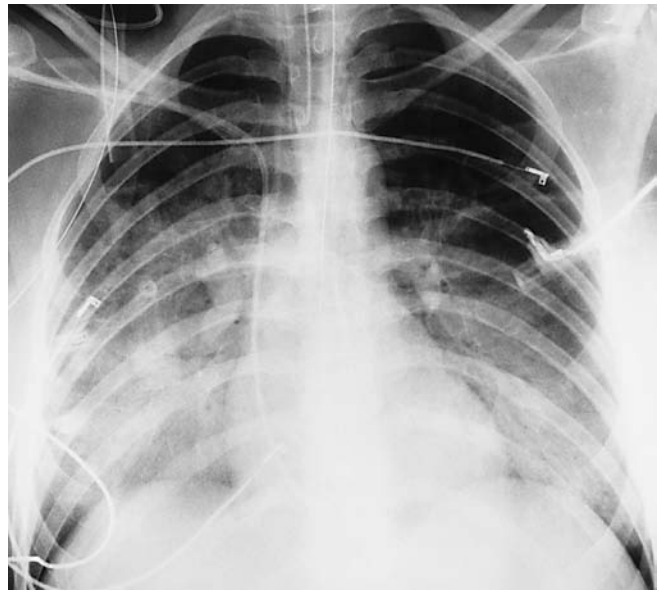


Figure 68-10 Systemic lupus erythematosus (SLE). Posterior–anterior (PA) chest radiograph reveals extensive bilateral alveolar infiltrates in a 22-year-old woman with SLE, hemoptysis, and anemia.

Due to the rarity of this syndrome, prospective, controlled trials evaluating therapy have not been performed. As with other causes of immune DAH, high-dose IV pulse methylprednisolone (1 g daily for 3 days), followed by gradual steroid taper is the mainstay of therapy.[16,115,116] Immunosuppressive or cytotoxic agents may be considered for DAH refractory to corticosteroids.[114–116,119] The role of plasmapheresis has not been elucidated, but anecdotal successes have been cited for severe DAH complicating SLE.[16,110,115,120] We reserve plasmapheresis for patients with severe DAH refractory to corticosteroids and/or cytotoxic agents. Rituximab was efficacious in anecdotal cases of SLE-associated DAH refractory to immunosuppressive agents.[119]

■ OTHER CONNECTIVE TISSUE DISORDERS

Anecdotal reports of DAH, with or without capillaritis, have been described in association with rheumatoid arthritis,[121] scleroderma,[122] mixed connective tissue disease,[121] polymyositis,[123]

antiphospholipid antibody syndrome,[124] Henoch–Schönlein syndrome,[125] and Behçet disease.[64] The clinical spectrum ranges from minimal hemoptysis to life-threatening respiratory failure. In addition to capillaritis and DAH, additional histopathological features on lung biopsies include vasculitis of small and medium muscular pulmonary arteries, DAD, and organizing pneumonia. In view of the rarity of DAH complicating these diverse CTDs, data regarding therapy are limited. High-dose (pulse) intravenous methylprednisolone is advised as initial treatment. In patients with fulminant or corticosteroid-recalcitrant disease, CYC, alone or combined with plasmapheresis,[110,122] should be added.

ALVEOLAR HEMORRHAGE IN IMMUNOCOMPROMISED HOSTS

Alveolar hemorrhage may occur in immunocompromised patients.[27,126] Alveolar hemorrhage may reflect injury to pulmonary endothelial or epithelial cells (secondary to chemotherapy or radiation toxicity), thrombocytopenia (secondary to bone marrow toxicity), pulmonary edema, pulmonary malignancies, and diverse infectious and nonspecific interstitial pneumonias.[126] The incidence of DAH in severely immunocompromised hosts with hematologic malignancies or bone marrow transplants has varied from 11% to 64%.[25,126] The variable frequency in large part is due to differing diagnostic criteria for the diagnosis of DAH. Subclinical alveolar hemorrhage (as evidenced by increased numbers of hemosiderin-laden macrophages in BAL) occurs in up to one-third of immunocompromised hosts with pulmonary infiltrates and may reflect pulmonary endothelial or epithelial injury from diverse causes.[27] Nonimmune causes of DAH in this patient population include coagulopathy, thrombocytopenia or platelet dysfunction, renal failure, congestive heart failure, bronchopulmonary Kaposi sarcoma, and diverse infections.[27,28]

ALVEOLAR HEMORRHAGE COMPLICATING BONE MARROW TRANSPLANTATION

DAH occurs in approximately 5% (range 2%–31%) of hematopoietic stem cell transplantation (HSCT) or bone marrow transplant (BMT) recipients receiving pre-BMT conditioning with high-dose chemotherapy or radiation therapy.[25,26,127–130] Opportunistic infections or thrombocytopenia account for some cases of DAH,[26,128,129] but a distinct syndrome of DAH in this population unrelated to infection is well accepted.[126,127] The incidence of DAH is similar among autologous and allogeneic HSCT recipients.[25,127,130] Risk factors for DAH include age >40 years,[128,130] myeloablative conditioning,[25,128,130] thoracic[131] or total body irradiation,[25,132] acute severe graft versus host disease (GVHD),[128,132] severe oral mucositis,[133] renal failure,[25,133] airway inflammation or increased proportions of bronchial neutrophils and eosinophils,[134] and leukocyte recovery.[25,134] Thrombocytopenia or coagulopathy do not predict DAH.[25,131,133] DAH usually develops within 10 to 40 days after BMT, but may develop earlier or later.[127,131,132] Case reports of DAH developing immediately following autologous bone marrow transfusion suggest that components within the transfusion (e.g., dimethylsulfoxide [DMSO] for cryopreservation of blood stem cells) may mediate acute lung injury in some cases.[135]

Progressive dyspnea, hypoxemia, and respiratory failure are typical.[25,128,130] Even with extensive DAH, hemoptysis is uncommon (<20%).[127,130,134] Chest radiographs *initially* demonstrate predominantly interstitial opacities, which evolve to diffuse alveolar opacities, with a confluent alveolar pattern involving all lobes. Serosanguineous or frankly bloody BAL fluid,[127,128,130] with negative stains for infectious organisms, support the diagnosis of DAH. Lung biopsies or necropsies typically reveal histological features of both DAD and DAH.[129,133,134,136] However, the risk of lung biopsy is excessive in critically ill patients, many of whom are thrombocytopenic.[130] Hence the diagnosis is made by clinical, radiographic, and BAL findings.[127,130]

The clinical course of DAH is variable, but severe respiratory failure requiring mechanical ventilation is common.[127,133] Mortality rates in patients with DAH are high (60-day mortality ranging from 48% to 84%).[26,127,128,133] In one study, hospital mortality was lower among autologous (28%) compared to allogeneic (70%) SCT recipients and early onset DAH (within 30 days of transplant) (32% mortality) compared to 70% for late-onset DAH.[127] Secondary infections are serious and potentially lethal.[26,126,128,129]

Multiple mechanisms may mediate alveolar hemorrhage in this patient population. Diffuse injury to the pulmonary microvasculature, secondary to chemotherapy or radiation therapy, coupled with a heightened inflammatory response in the airways, appear to be operative.[25] Bleeding may be amplified by a precipitating factor such as coagulopathy, pulmonary edema, GVHD, or infections. DAD, a pathological hallmark seen in toxic lung injury from chemotherapy, radiation therapy, or viral infections, is frequently observed in lung biopsies or necropsies in bone marrow recipients with DAH.[127] An association between microangiopathy and DAH in patients receiving BMT for hematologic malignancies was cited.[137] Neutrophils and other inflammatory cells likely play important roles in the pathogenesis of DAH. The onset of DAH frequently coincides with marrow recovery and reappearance of neutrophils within the circulation or BAL fluid. Influx of neutrophils may promote the lung injury by release of oxygen radicals, proteases, and other phlogistic mediators.[25,134] Hematopoietic growth factors (e.g., granulocyte colony–stimulating factor) may exacerbate alveolar damage and capillary leakage by increasing neutrophil influx into the lungs.[25]

High-dose pulse IV corticosteroids are considered standard of care for DAH,[25,26,127,129] but randomized, controlled studies are lacking and a survival benefit has not been established. Unfortunately, DAH or bloody BAL fluid may be seen in infectious causes of pneumonia (particularly due to cytomegalovirus [CMV] or *Aspergillus* spp.),[130] and high-dose corticosteroids could be disastrous under these circumstances. Infectious etiologies must be rigorously excluded. Among patients who respond favorably to corticosteroids, the dose can be gradually tapered over 2 to 6 weeks.[25,127] A more prolonged course is appropriate for patients with GVHD or other complications requiring long-term corticosteroid therapy. Anecdotal response to recombinant factor VIIa was cited in one allogeneic SCT recipient with DAH.[138]

ALVEOLAR HEMORRHAGE COMPLICATING HIV INFECTION

DAH can complicate human immunodeficiency virus (HIV) infection. The incidence and clinical significance of DAH is not clear, as additional pulmonary processes (e.g., opportunistic infections;[139] Kaposi sarcoma[140]) are usually present.[28] Subclinical episodes of alveolar hemorrhage are common, as studies in HIV-infected patients with pulmonary infiltrates detected more than 20% hemosiderin-laden macrophages in BAL fluid in 15% to 44% of patients.[27,28] In one study of 203 HIV-infected patients with pulmonary symptoms who underwent BAL, alveolar hemorrhage (AH) was detected in 73; however, AH was severe in only eight patients and AH did not affect survival.[28] Thrombocytopenia, coagulopathy, renal failure, hydrostatic pulmonary edema, CMV pneumonia, and Kaposi sarcoma were more frequent in patients with AH compared to HIV-infected controls without AH.[28] Pulmonary capillaritis has been cited in occasional patients, most of whom had concomitant opportunistic infections. CMV pneumonia has been implicated as a cause of DAH in HIV-infected patients.[139] CMV exhibits tropism for endothelial cells, and CMV may induce vascular injury or thrombotic microangiopathy. Antiviral therapy (e.g., ganciclovir) may be curative for CMV-associated DAH. Opportunistic pathogens[139] or endobronchial Kaposi sarcoma[140] account for most cases of DAH in HIV-infected individuals. The incidence and appropriate therapy of DAH of unknown etiology in the setting of acquired immunodeficiency syndrome (AIDS) has not been defined.

ALVEOLAR HEMORRHAGE DUE TO EXOGENOUS AGENTS

Certain exogenous agents or drugs[7,17] (e.g., trimellitic anhydride,[141] isocyanates,[142] D-penicillamine,[143] cocaine,[144] diphenylhydantoin,[145] propylthiouracil,[146] hydralazine,[147] sulfasalazine,[147] allopurinol,[1,147] all-*trans*-retinoic acid (ATRA),[148] minocycline[149] are rare causes of DAH. An exhaustive list of drugs capable of causing DAH is available on www.pneumotox.com. Circulating ANCAs, GN, and DAH have been linked with some agents (particularly d-penicillamine,[143] hydralazine,[150] propylthiouracil,[146] methimazole, and carbimazole[151]). Lung biopsies have rarely been performed in these cases of DAH. However, pulmonary capillaritis (without immune deposits) is the most common finding.[7,17]

ATRA, a therapeutic agent for acute promyelocytic leukemia, may be associated with "retinoic acid syndrome," characterized by fever, thrombosis, pulmonary infiltrates, and DAH.[148,152] The onset is 2 to 21 days after initiation of treatment. In this circumstance, ATRA is continued but high-dose IV corticosteroids should be administered.

Propylthiouracil can cause a systemic small-vessel vasculitis with necrotizing GN, leukocytoclastic vasculitis, ANCAs, and DAH secondary to pulmonary capillaritis.[146,147] Withdrawal of the drug may be associated with resolution of the disease, but corticosteroids or immunosuppressive agents are indicated in patients with severe DAH or renal failure.

A variety of chemotherapeutic agents (e.g., bischloroethyl nitrosourea [BCNU], carmustine, CYC, methotrexate, mitomycin C, bleomycin, or busulfan) may cause lung injury and fibrosis.[17,153] In some cases, DAH may result from epithelial injury and injury to the alveolar capillary basement membranes.[17] In this context, fatality rates are high (more than 50%).[17,153] High-dose corticosteroids are recommended, but efficacy is uncertain.

Trimellitic anhydride (TMA), a chemical used in manufacturing plastics and epoxy resins, may elicit pulmonary hemorrhage and anemia.[141,142] Most patients with DAH secondary to TMA exposure recover within a few days following removal from the offending environment. An immune mechanism is likely, as circulating IgG antibodies against trimellitic protein were found in some patients with DAH, suggesting TMA acts as a hapten.[142] TMA may cause asthma, rhinitis, and hemolytic anemia mediated by IgE antibodies directed against trimellitic protein. Animal models of TMA-induced lung disease have also been developed.[141] Induction of serum antibodies against epitopes of TMA produced acute lung injury in animals, mediated by at least two types of humoral antibodies. It is also possible that TMA may exert a direct toxic effect on alveolar endothelium. This syndrome is exceptionally rare, as only sporadic cases have been described. Exposure to isocyanates in spray paint has been linked to occupational asthma and (in a few cases) DAH.[154] The mechanism is likely mediated by high levels of IgE and IgG antibodies against diisocyanates.[142] Thus, exposure to TMA or isocyanates, and possibly other chemicals, can elicit hemorrhagic pneumonitis, likely mediated by circulating antibodies (IgG or IgE) and immune complexes.

Smoking, snorting, or intravenous "crack" cocaine has been associated with hemoptysis and varying degrees of DAH,[144,155] including rare fatalities. Histopathological features of cocaine-induced DAH are nonspecific, but include DAD, acute or chronic DAH, interstitial pneumonitis/fibrosis, and intra-alveolar edema.[156] The mechanism of DAH is not clear but may relate to direct toxic injury from cocaine or its contaminants, vasospasm, or a combination of both mechanisms. This syndrome typically reverses with cessation of exposure. The frequency of clinically significant DAH associated with inhaled or intravenous use of cocaine has not been established.

When drug- or hapten-induced DAH is suspected, immediate avoidance of the implicated agent or drug is essential. For acute or severe cases, a brief course of high-dose corticosteroids is warranted. Plasmapheresis or cytotoxic agents may be considered for fulminant cases refractory to corticosteroids, but data supporting their use are lacking.

Finally, coagulopathies, severe thrombocytopenia, or the use of anticoagulants, thrombolytic agents, or platelet inhibitors may rarely cause DAH.[157–159] In this context, the histology is "bland" without evidence for capillaritis or acute inflammation.

ALVEOLAR HEMORRHAGE DUE TO MOLDS

Acute, life-threatening DAH in infants identified fungal contamination as the etiology.[160,161] Exposure to *Stachybotrys chartarum* and other toxigenic fungi elicits the syndrome.[160] *Stachybotrys chartarum* produces several classes of toxins including hemolysins, proteinases, macrocyclic trichothecenes, phenylspirodrimanes, and others.[160] Acute respiratory distress, progressing to respiratory failure requiring mechanical ventilatory support, may occur.[160] High-dose IV corticosteroids are warranted for acute DAH. Long-term management mandates removal of infants from the residential environment to avoid relapse.[160,161] This syndrome has rarely been reported in adults, but must be considered in water-damaged homes or environs where mold/fungal contamination exists.[161]

IDIOPATHIC PULMONARY HEMOSIDEROSIS

IPH is an exceptionally rare cause of DAH that occurs primarily in infants and children.[23,162–164] The estimated incidence is 0.2 to 1.2 cases per million.[22,165] Many children with IPH have a history of milk or gluten sensitivity.[166] A subset of adults with celiac sprue manifest IPH,[167] which may respond to elimination of gluten from the diet.[168] Clinical features of IPH are similar to immune causes of DAH, but extrapulmonary or renal involvement is lacking.[23] Serum or tissue antibodies (including ANCA, immune complexes, anti-GBM antibody) are also absent. A diagnosis of IPH can be made *only* when other specific causes of DAH have been *reliably* excluded. Most early series of IPH, published in the 1960s and 1970s, antedated the availability of serologies and immunohistochemical assays (e.g., ANCA, anti-GBM antibody, etc.).[169,170] It is likely that most cases formerly diagnosed as IPH in adults had ANCA-associated vasculitis, MPA, or underlying CTD.

The onset of the disease is typically in infants and young children (<5 years old).[23,162] The clinical course of IPH is variable, but recurrent episodes of DAH over several years are characteristic.[23,164,171] Spontaneous remissions without long-term sequelae have been cited in up to 25% of cases.[164] Sequelae of recurrent episodes of DAH include pulmonary fibrosis, progressive respiratory failure, and cor pulmonale.[23,164,171] Early studies cited median survival rates of 3 to 6 years,[162,165] but more recent studies suggest a more favorable prognosis, with many patients surviving >10 to 15 years.[164,171] During acute episodes, chest radiographs demonstrate bilateral alveolar infiltrates. Following cessation of bleeding, chest radiographs may normalize within 1 to 2 weeks. Reticulonodular infiltrates may be observed as the process is resolving or with recurrent episodes (Fig. 68-11). CT reveals areas of ground-glass opacification, representing foci of alveolar hemorrhage. Thickening of interlobular septae and honeycombing may be observed in a subset of patients who progress to pulmonary fibrosis.[172] Hemoptysis may be absent, particularly in young children who may be unable to expectorate blood. Iron-deficiency anemia is characteristic and can be profound.[23,164,171,173] Iron deficiency may persist despite normal total body iron stores, because hemosiderin within alveolar macrophages is not available to developing erythrocytes. Siderophages may be found in sputum, BAL fluid, or tracheal or gastric aspirates in patients with recent episodes of DAH.[22,164,171] Lung biopsies may reveal fresh areas of alveolar hemorrhage or patchy interstitial fibrosis and aggregates of hemosiderin-laden macrophages from prior episodes of alveolar hemorrhage (Fig. 68-12).[23,164]

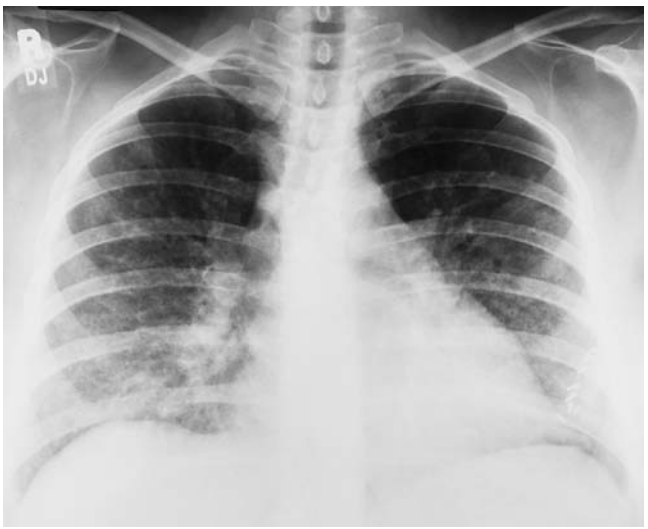


Figure 68-11 Idiopathic pulmonary hemosiderosis (IPH). Posterior–anterior (PA) chest radiograph demonstrates bilateral reticulonodular infiltrates in a 28-year-old woman with IPH confirmed 10 years earlier by open lung biopsy.

The pathogenesis of IPH is not known. In children, associations between IPH and cow's milk hypersensitivity, celiac disease,[173] IgA monoclonal gammopathy, autoimmune hemolytic anemia, and autoimmune thyrotoxicosis have been suggested,[164] but a pathogenetic link has not been substantiated. Resolution of pulmonary symptoms following elimination of milk products or gluten from diet[167,173] supports a role for exogenous factors in the pathogenesis in at least some cases. No genetic basis has been found, but clusters within families have been described.[170,174]

In view of the rarity of IPH, optimal therapy is not clear. Corticosteroids are considered the mainstay of therapy,[22–24,163] but controlled studies evaluating therapeutic regimens have not been done. Because IPH is life-threatening, most physicians treat acute episodes with daily corticosteroids and taper to the lowest dose that appears to control the disease. Long-term (and possibly indefinite) therapy may be required to prevent recurrences. Favorable responses have been cited with azathioprine,[175] CYC,[176] or other immunosuppressive agents[171] in patients failing corticosteroids. Chronic immunosuppressive agents may improve prognosis for patients with corticosteroid-recalcitrant disease or patients experiencing repetitive relapses of DAH.[171] In this context, we prefer azathioprine over CYC given the heightened risk of neoplasia and gonadal toxicities associated with the long-term use of CYC.[177]

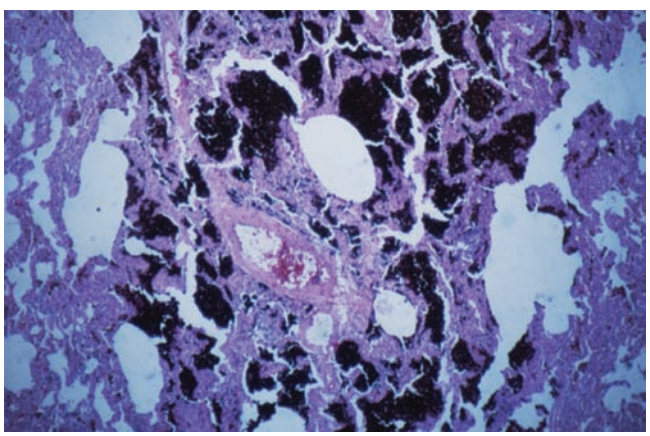


Figure 68-12 Idiopathic pulmonary hemosiderosis (IPH). Photomicrograph demonstrating extensive deposits of hemosiderin within alveolar interstitium (Prussian blue stain).

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CHAPTER 69

Aspiration-Related Pulmonary Disorders

Paul E. Marik

Pneumonia—"Captain of the Men of Death"

—William Osler[1]

Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[2] An assortment of pulmonary syndromes may occur following aspiration depending on the quantity and nature of the aspirated material, the chronicity of aspiration, as well as the nature of the host's defense mechanisms and the host's response to the aspirated material. The most important syndromes include "*aspiration pneumonitis*" or Mendelson's syndrome, which is a chemical pneumonitis caused by the aspiration of gastric contents, and "*aspiration pneumonia*," an infectious process caused by the aspiration of oropharyngeal secretions colonized by pathogenic bacteria.[2] While there is some overlap between these two syndromes they are distinct clinical entities. In addition, a variety of pulmonary conditions have been described from chronic recurrent occult aspiration, most notably "*diffuse aspiration bronchiolitis*."[3] Other aspiration syndromes include airway obstruction, lung abscess, exogenous lipoid pneumonia, chronic interstitial fibrosis, and *Mycobacterium fortuitum* pneumonia. This chapter will focus on the pathophysiology, clinical features and management of aspiration pneumonitis, aspiration pneumonia, and diffuse aspiration bronchiolitis.

ASPIRATION PNEUMONITIS

Aspiration pneumonitis is best defined as acute lung injury following the aspiration of regurgitated gastric contents.[2] This syndrome occurs in patients with a marked disturbance of consciousness such as drug overdose, seizures, coma due to acute neurologic insults, massive cerebrovascular accident, following head trauma and during anesthesia. It is important to emphasize that aspiration pneumonitis only occurs in patients who have a depressed level of consciousness with impairment of airway protective reflexes. In clinical practice, drug overdose is the most common cause of aspiration pneumonitis, occurring in approximately 10% of patients hospitalized following a drug overdosage. Adnet and Baud[4] demonstrated that the risk of aspiration increases with the degree of impairment in consciousness (as measured by the Glasgow Coma Scale). Historically, the syndrome most commonly associated with aspiration pneumonitis is Mendelson's syndrome, reported in 1946 in obstetric patients who aspirated while receiving general anesthesia.[5] Mendelson's original report consisted of 44,016 nonfasted obstetric patients whom he studied between 1932 and 1945, of whom more than half received an "operative intervention" with ether by mask without endotracheal intubation. He described aspiration in 66 patients (1:667). Although several of the patients were critically ill from their aspiration, recovery was usually complete within 24 to 36 hours and only two patients died (1:22,008).

Although aspiration is a widely feared complication of general anesthesia, clinically apparent aspiration in modern anesthesia practice is exceptionally rare, and in healthy patients the overall morbidity and mortality are low (see section below). The risk of aspiration is greatly increased in patients intubated emergently in the field, emergency room or in the ICU. In these patients every effort should be made to reduce the risk of aspiration; this includes removing dentures and clearing the airway and in certain circumstances placing a nasogastric tube to empty the stomach prior to intubation. If there is an immediate risk of airway compromise

endotracheal intubation should be performed prior to placement of a nasogastric tube. However, if the patient is likely to have a full stomach (upper GI bleed, small bowel obstruction, ileus, etc.) it may be prudent to place a nasogastric tube prior to endotracheal intubation. When intubating emergently, suction equipment must be immediately available and rapid-sequence induction using cricoid pressure should be performed.

PATHOPHYSIOLOGY

Mendelson emphasized the importance of acid when he showed that unneutralized gastric contents introduced into the lungs of rabbits caused severe pneumonitis indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid.[5–7] However, if the pH of the vomitus was neutralized before aspiration, the pulmonary injury was minimal. Experimental studies have demonstrated that the severity of lung injury increases significantly with the volume of the aspirate and inversely with its pH, with a pH of less than 2.5 being required to cause aspiration pneumonitis. However, the stomach contains a variety of other substance in addition to acid. Several experimental studies have revealed that aspiration of small, particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate is above 2.5.[8,9] These studies suggest that cell recruitment and expression of inflammatory mediators are most pronounced after injury with combined acid and small food particles. These data are supported by findings in patients where the most severe lung injury was observed in patients following aspiration with particulate food matter.[10,11]

Aspiration of gastric contents results in a chemical burn of the tracheobronchial tree and pulmonary parenchyma with an intense parenchymal inflammatory reaction. The proinflammatory cytokines including tumor necrosis factor-α and CXC chemokines are crucial to the development of aspiration pneumonitis by mediating neutrophil recruitment. Once localized to the lung, neutrophils play a key role in the development of lung injury through the release of oxygen radicals and proteases. Gastric acid prevents the growth of bacteria and therefore the contents of the stomach are normally sterile. Bacterial infection, therefore, does not play a significant role in the early stages of acute lung injury following aspiration of gastric contents. However, acid aspiration pneumonitis reduces host defenses against infection increasing the risk of superinfection.[12] The incidence of this complication has, however, not been well studied. Furthermore, experimental models suggest that acid aspiration pneumonitis "primes the lung" making secondary infection more severe.[12,13] Colonization of the gastric contents by potentially pathogenic organisms may occur when the gastric pH is increased by the use of antacids, histamine-2 (H2) receptor blockers, or proton pump inhibitors. In addition, gastric colonization by gram-negative bacteria occurs in patients receiving enteral feedings, as well as in patients with gastroparesis and small bowel obstruction. In these circumstances the pulmonary inflammatory response is likely to result from both bacterial infection and the inflammatory response of the gastric particulate matter.

ANESTHESIA AND ASPIRATION PNEUMONIA

Aspiration pneumonitis has traditionally been regarded as the major cause of serious anesthetic complications. However, with the recognition of the importance of this complication, and the fact that it is largely preventable, the risk of aspiration pneumonitis in modern anesthesia is very low. Nevertheless, aspiration pneumonitis is an important perioperative complication and remains the commonest cause of anesthesia-related death. The risk of aspiration with modern anesthesia is reported to be between 2.9 and 4.7 per 10,000 general anesthetics (about 1 in 3000 anesthetics) with a mortality of approximately 1:125,000, accounting for between 10% and 30% of all anesthetic deaths.[14,15] Warner et al.[7] published data from a study of 215,488 anesthetics and observed 67 episodes of aspiration in adults (3.1 per 10,000 patients) undergoing general anesthesia. In a recent study involving 99,441 patients undergoing nonobstetrical anesthesia, perioperative pulmonary aspiration occurred in 14 patients (1 in 7103 procedures).[16] All 14 patients has one or more risk factors for aspiration. The Thai Anesthesia Incident Monitoring Study prospectively recorded reports on aspiration from 51 hospitals across Thailand during a 6-month period in 2007.[17] Twenty-eight reports met the definition of pulmonary aspiration (denominator not reported). Most of the incidents occurred in American Society of Anesthesiology (ASA) class 1 to 2 patients (85.7%), during day time hours (64.3%), and when the anesthesiologists were in charge (67.9%). Eleven incidents (39.3%) occurred during induction, seven (25%) during maintenance, and seven (25%) during the emergence phase. All the incidents except one (96.4%) were considered human error and 25 (89.2%) were preventable. Thirteen patients (46.4%) had major physiologic changes and 10 (35.7%) of them required unplanned ICU admission. Ten patients (35.7%) needed prolonged ventilator support and two (7.14%) of them died.

The most definitive and extensive review on the risk of airway problems associated with intubation was reported by Cook et al.[18,19] who summarized the findings of the 4th National Audit Project of the Royal College of Anaesthetists. In this 1-year prospective audit, the authors examined the occurrence of serious airway complications in anesthesia, ICUs, and emergency departments of all the National Health Service hospitals in the United Kingdom. The authors found 184 cases that met the inclusion criteria: 133 from anesthesia, 36 from ICUs, and 15 from emergency departments. A concurrent national census of anesthesia activity over a 2-week period was performed to provide denominator data for anesthesia, which indicated 2.9 million anesthetic procedures annually, resulting in a nominal incidence (using the 133 anesthesia events) of one serious airway complication per 22,000 anesthetics. In total, 38 deaths were attributable to airway complications, and the death rate was 16 of 133 (12%) in anesthesia, 18 of 36 (50%) in the ICUs, and 4 of 16 (25%) in the emergency departments. Pulmonary aspiration of gastric contents was the commonest cause of death and brain damage. A supraglottic airway was the planned technique in more than 50% of death or brain damage cases. A statistical analysis of the reports suggested that as few as 25% of relevant incidents may have been reported. The authors therefore suggest that this audit provides an indication of the lower limit for the incidence of such complications.

Emergency surgery (particularly, trauma and abdominal surgery with delayed gastric emptying) procedures performed at night, inadequate anesthesia, obesity, elderly immobilized patients, and obstructive sleep apnea have been associated with a higher risk of aspiration.[15,20] Obtunded adults and children with known gastroesophageal reflux are more likely to aspirate even without narcotic or sedative impairment of airway reflexes. The factors increasing the risk for aspiration are listed in Table 69-1. Patients who are at risk before surgery are also at increased risk during the postoperative period when immobility, residual effects of anesthetic agents, and narcotics combine to decrease protective airway reflexes.[21–23]

The incidence of aspiration appears higher in obstetric patients as highlighted by the pioneering study of Mendelsohn.[5] A study from 1973 reported an incidence of 1 in 6000 obstetric patients receiving general anesthesia for vaginal deliveries and 1 in 430 for cesarean section patients.[24] In more recent studies, an aspiration incidence of 1 in 1547 and 1 in 1431, respectively, were described for cesarean section under general anesthesia,[21,23] and a recent audit showed an incidence of 1 in 900 women undergoing cesarean section.[22] The risk of pulmonary aspiration is, therefore, at least double or three times as high as in general surgical patients. Pregnant women are at increased risk of aspiration because of gastroesophageal reflux and delay in gastric emptying.[25,26]

TABLE 69-1 Factors Increasing the Risk of Perioperative Aspiration

Recent eating
Delayed gastric emptying
Diabetic neuropathy
Opioids
Paralytic ileus
Small bowel obstruction
Pregnancy
Emergency surgery
Obesity
Obstructive sleep apnea
Reflux esophagitis
Achalasia
Esophageal stricture
Previous gastric bypass surgery
Traumatic brain injury
Cerebral infarction/bleed

Gastroesophageal reflux is common in pregnancy and can be demonstrated even in the absence of symptoms. There is no difference in basal and evoked gastric acid secretion in pregnancy but there is a reduction in lower esophageal barrier pressure, which is likely to be a progesterone effect present from early pregnancy. The surgical procedure may itself increase aspiration risk through the adoption of lithotomy or Trendelenburg positions or the creation of a pneumoperitoneum.

The laryngeal mask airway (LMA) does not reliably protect the lungs from regurgitated stomach contents and should be avoided in patients at an increased risk for aspiration.[27,28] In a meta-analysis of 12,901 low-risk cases, where the standard contraindications to the use of the LMA were followed (e.g., absence of gastrointestinal pathology, obesity, history of reflux, or emergency surgery), only 3 cases of aspiration were identified, an incidence of 2.3 per 10,000.[29]

Inadequate reversal of neuromuscular blockage at the end of surgery is an important risk factor for aspiration. After the administration of nondepolarizing neuromuscular blocking agents, it is essential to ensure adequate return of normal neuromuscular function. Residual paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and the hypoxic ventilatory drive.[30] These factors significantly increase the risk for aspiration. Adequate recovery of postoperative neuromuscular function cannot be guaranteed without objective neuromuscular monitoring. Good evidence-based practice dictates that clinicians should always quantitate the extent of neuromuscular blockade by objective monitoring (train-of-four monitoring).[30] To exclude clinically significant residual neuromuscular blockade, the train-of-four ratio, when measured mechanically or by electromyography, must exceed 0.9. If sufficient recovery (i.e., train-of-four $\geq$0.9) has not been documented objectively at the end of the surgical procedure, the neuromuscular block should be antagonized.

Prevention of Aspiration During Anesthesia

In recent years more liberal preoperative fasting guidelines have been promoted. In healthy adults without an increased risk of regurgitation or aspiration solids should be avoided after midnight; however, a light meal such as dry toast may be considered up to 6 hours before anesthesia and clear liquids such as water, coffee without milk, or fruit juice can be given up to 2 hours before induction.[31,32] Meta-analyses of randomized controlled trials comparing fasting times of 2 to 4 hours *versus* more than 4 hours report smaller gastric volumes and higher gastric pH values in adult patients given clear liquids 2 to 4 hours before a procedure and this approach is currently endorsed by the ASA.[33]

Preoperative antacids, H2 receptor blockers, proton pump inhibitors, and prokinetic agents have been used to reduce the volume and/or acidity of the gastric contents. There is, however, a lack of data indicating that any of these drugs reduce the risk of aspiration pneumonitis.[34] The routine use of these drugs is not recommended by the ASA guidelines.[33] However, it is not unreasonable to use these drugs in patients at an increased risk of aspiration. It is however important to realize that it takes time for the clinical effects of the acid suppressive drugs to manifest and these drugs should therefore be dosed at least 2 hours prior to induction.[35]

Standard teaching suggests that rapid-sequence induction with cricoid pressure should be performed when intubating patients at an increased risk of aspiration. Cricoid pressure, known as the Sellick maneuver, is designed to occlude the cervical esophagus by compressing it between the cricoid cartilage and the vertebral bodies.[36] Passively regurgitated gastric contents are therefore prevented from entering the pharynx. Neither rapid-sequence induction nor cricoid pressure has been prospectively studied and proven to decrease the incidence of aspiration. Rapid-sequence induction shortens the time between the onset of unconsciousness and securing the airway, which may be of benefit if the aspiration risk is high. However, the use of cricoid pressure is controversial.[37] The esophagus cannot be reliably occluded between the cricoid cartilage and the vertebral bodies. Studies in volunteers (men and nonpregnant women) clearly show that the esophagus often does not lie in the midline or that cricoid pressure displaces the esophagus laterally without occluding it.[38] More recent data suggest that the hypopharynx posterior to the cricoid cartilage is in continuity with the esophageal inlet and this hypopharyngeal area is occluded with the Sellick maneuver.[39] Cricoid pressure is often applied incorrectly or without the appropriate amount of force and may reduce visualization of the vocal cords and impede intubation. Although not proven to reduce the risk of aspiration during emergent intubations, cricoid pressure is currently considered the standard of care in this situation.

CLINICAL PRESENTATION

Aspiration of gastric contents can present dramatically with a full-blown picture that includes gastric contents in the oropharynx, wheezing, coughing, shortness of breath, cyanosis, pulmonary edema, hypotension, and hypoxemia; this may progress rapidly to severe ARDS and death (see Fig. 69-1). However, many patients may not develop signs or symptoms associated with aspiration, while others may develop a cough or wheeze. In some patients aspiration may be clinically silent manifesting only as arterial desaturation with radiologic evidence of aspiration. Warner et al.[7] studied 67 patients who aspirated while undergoing anesthesia. Forty-two (64%) of these patients were totally asymptomatic, 13 required mechanical ventilatory support for more than 6 hours and 4 died.

MANAGEMENT OF ASPIRATION PNEUMONITIS

The upper airway should be suctioned following a witnessed aspiration. Endotracheal intubation should be considered in patients who are unable to protect their airway. While common practice, the prophylactic use of antibiotics in patients with suspected or witnessed aspiration is not recommended. Similarly, the use of antibiotics shortly after an aspiration episode in a patient who develops a fever, leukocytosis, and a pulmonary infiltrate is discouraged as it may select for more resistant organisms in a patient with an

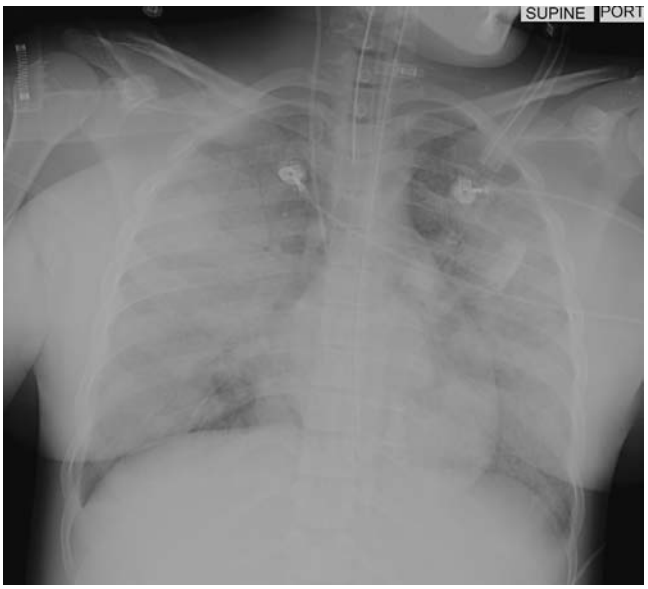

Figure 69-1 Anteroposterior chest radiograph demonstrating bilateral alveolar infiltrates following aspiration of gastric contents (aspiration pneumonitis).

uncomplicated chemical pneumonitis. However, empiric antimicrobial therapy is appropriate in patients who aspirate gastric contents in the setting of small bowel obstruction or in other circumstances associated with colonization of gastric contents (acid-suppressive therapy, tube feeds). Antimicrobial therapy should be considered in patients with an aspiration pneumonitis that fails to resolve within 48 hours. Empiric therapy with broad-spectrum agents is recommended. Antimicrobials with anaerobic activity are not routinely required. Recently serum procalcitonin has emerged as a biomarker that has been postulated to be able to discriminate bacterial infections from nonbacterial inflammatory disorders.[40] El-Solh et al.[41] investigated the predictive accuracy of serum procalcitonin in distinguishing aspiration with bacterial pneumonia from "sterile" aspiration pneumonitis. In this study serum procalcitonin levels had poor diagnostic value in separating bacterial pneumonia from aspiration pneumonitis based on quantitative bronchoalveolar lavage culture.

IMMUNOMODULATING AGENTS

Corticosteroids have been used in the management of aspiration pneumonitis since 1955.[42] However, limited data exist on which to evaluate the role of these agents, with only a single prospective, placebo-controlled study having been performed. In this study, Sukumaran et al.[43] randomized 60 patients with "aspiration pneumonitis" to methylprednisolone (15 mg/kg/day for 3 days) or placebo. The patients were subdivided into two groups; a younger group with drug overdose as the predominant diagnosis and an older group with neurologic disorders. Radiographic abnormalities improved more rapidly in the steroid group, as did oxygenation. The number of ventilator and ICU days was significantly shorter in the overdose patients who received corticosteroids; however, these variables were longer in the neurologic group receiving this therapy. There was no significant difference in the incidence of complications or mortality. The results of this study are somewhat difficult to interpret as it is likely that the patients in the overdose group had true "aspiration pneumonitis" while many patients in the neurologic group probably developed "aspiration pneumonia." Wolfe et al.[44] performed a case-controlled study of 43 patients with aspiration pneumonitis, of whom 25 received high-dose corticosteroids (approximately 600 mg prednisolone/day for 4 days). While there was no difference in mortality, secondary gram-negative pneumonia was reported to be more frequent in the steroid group (7/20 vs. 0/13); however, ventilator days tended to be less in this group (4.3 vs. 9.8 days). Based on this limited data it is not possible to make evidence-based recommendations on the use of corticosteroids in patients with aspiration pneumonitis.

In animal models, a number of pharmacologic interventions including inhaled B_2 agonists, pentoxifylline, antiplatelet drugs, and omega-3 fatty acids have been shown to attenuate the acute lung injury following acid aspiration.[45–50] The role of these interventions in patients remains to be tested; however, due to their inherent safety, these agents should be considered in patients with severe acid aspiration pneumonitis.

ASPIRATION PNEUMONIA

Aspiration pneumonia refers to the development of a radiographic infiltrate and clinical features consistent with pneumonia in a patient with risk factors for increased oropharyngeal aspiration (see Fig. 69-2). Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep. Presumably, the low virulent bacterial burden of normal pharyngeal secretions together with forceful coughing, active ciliary transport, and normal humoral and cellular immune mechanisms result in clearance of the inoculum, without sequelae. However, if the mechanical, humoral, or cellular mechanisms are impaired or if the aspirated inoculum is large enough, pneumonia may follow. Any condition that increases the volume and/or bacterial burden of oropharyngeal secretions in the setting of impaired host defense mechanism may lead to aspiration pneumonia. Indeed, in stroke patients undergoing swallow evaluation there is a strong correlation between the volume of the aspirate and the development of pneumonia.[51] Factors that increase oropharyngeal colonization with potentially pathogenic organisms and that increase the bacterial load may augment the

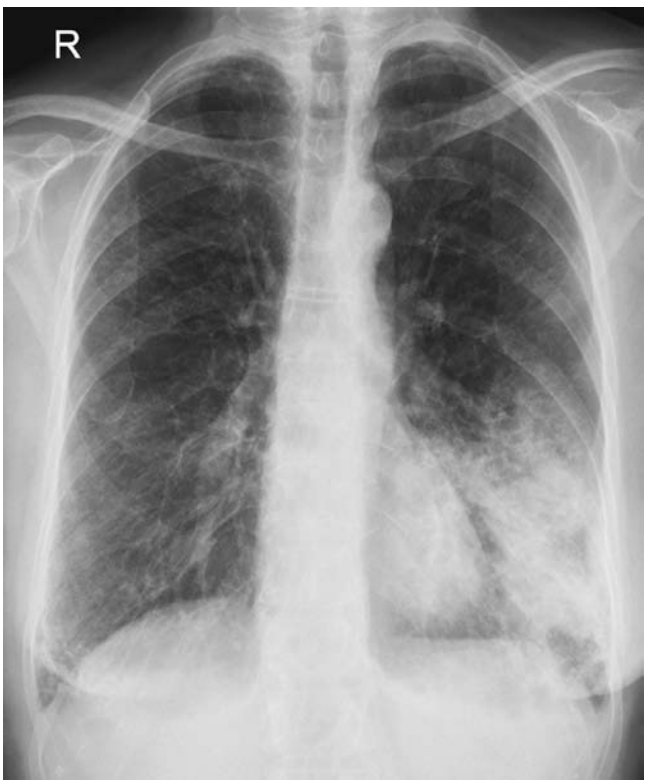

Figure 69-2 Anteroposterior chest radiograph demonstrating a left lower lobe aspiration pneumonia.

risk of aspiration pneumonia. The clinical setting in which pneumonia develops largely distinguishes aspiration pneumonia from other forms of pneumonia. However, there is much overlap. This is illustrated by the fact that otherwise healthy elderly patients with "community-acquired pneumonia" (CAP) have been demonstrated to have a significantly higher incidence of silent aspiration when compared with age-matched controls.[52]

EPIDEMIOLOGY

The lack of specific and sensitive markers of aspiration makes the epidemiologic study of aspiration syndromes difficult. Furthermore, most studies do not make the distinction between aspiration pneumonitis and aspiration pneumonia. Nevertheless, several studies list "aspiration pneumonia" as the cause of CAP in 5% to 15% of cases.[53,54] CAP is a major cause of morbidity and mortality in the elderly and it is likely that aspiration is the major cause of pneumonia in these patients. Epidemiologic studies have demonstrated that the incidence of pneumonia increases with aging, with the risk being almost six times higher in those over the age of 75, compared to those less than 60 years of age.[55,56] The attack rate for pneumonia is highest among those in nursing homes.[57]

DYSPHAGIA IN PATIENTS WITH ASPIRATION PNEUMONIA

Swallowing is a complex function, with both voluntary and reflexive components. Five cranial nerves and more than 50 muscles in the head and neck are involved in oropharyngeal swallowing. Both brainstem and cortical areas are involved in the neural processing of swallowing. The coordination of swallowing requires bilateral input from the sensorimotor cortex with descending input to the brainstem medullary swallowing center.[58] Functional and anatomic imaging studies have identified several sites that play an important role in swallowing, including the primary sensorimotor cortex, insula, anterior cingulate, internal capsule, basal ganglia, and thalamus. The swallowing process can be divided into oropharyngeal phase and esophageal phase.[59] The oropharyngeal phase includes biting and chewing in the oral cavity, and the transport of food into the pharynx. In simplified terms, this process is accompanied by elevation and anterior movement of the larynx to meet with the epiglottis for protection of the airway. It is followed by passage of the bolus through the upper esophageal sphincter into the esophagus (esophageal phase). During the esophageal phase, the lower esophageal sphincter relaxes and food is pushed into the stomach by peristalsis and gravity.

Dysphagia refers to the difficulty in swallowing. The severity of dysphagia varies from moderate difficulty to complete inability to swallow. Dysphagia is the major risk factor leading to aspiration pneumonia. In addition, dysphagia contributes significantly to protein-energy malnutrition and dehydration. Impairment in any component of the swallow mechanism including anatomical abnormities of the upper airway or esophagus can lead to dysphagia. Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarction, though it has more recently been shown to occur in isolated cerebral infarctions as well. Furthermore, dysphagia is commonly associated with silent cerebral infarction.

Dysphagia is remarkably common in Westernized nations and is a major cause of morbidity and mortality. Indeed, aspiration pneumonia is probably the final common pathway by which most chronically ill patients die. It has been estimated that over 16 million senior citizens in the United States suffer from dysphagia.[60] Furthermore, an additional 300,000 to 600,000 patients develop dysphagia each year in the United States from neurologic disorders.[61] Dysphagia affects more than 30% of patients who have had a cerebrovascular accident; 52% to 82% of patients with Parkinson disease; 84% of patients with Alzheimer disease, up to 40% adults aged 65 years and older, and more than 60% of elderly institutionalized patients.[62] The efficiency of the swallow mechanism decreases with aging, increasing the risk of aspiration and pneumonia in the elderly. Kikuchi et al. evaluated the occurrence of silent aspiration in otherwise "healthy elderly patients" with CAP and age-matched control subjects using indium[111] chloride scanning.[52] Silent aspiration was demonstrated in 71% of patients with CAP compared to 10% in control subjects. The impaired swallow mechanism in the elderly can be attributed to diminished sensation, silent cerebral infarction, cerebral atrophy, a delay in the synapse conduction in the afferent inputs to the central nervous system, and lingual weakness (sarcopenia) caused by aging.[63,64]

RISK FACTOR FOR DYSPHAGIA

The major risk factors for dysphagia are listed in Table 69-2. In patients with an acute stroke the incidence of dysphagia ranges from 40% to 70%.[65] Dysphagic patients who aspirate are at an increased risk of developing pneumonia.[66,67] Although dysphagia improves in most patients following a stroke, in many the swallowing difficulties follow a fluctuating course with 10% to 30% continuing to have dysphagia with aspiration.[68,69]

The Cough Reflex in Patients with Aspiration Pneumonia

An intact cough reflex is an important respiratory defense mechanism. Sekizawa et al.[70] demonstrated a marked depression of the cough reflex in elderly patients with pneumonia. Furthermore, the greater the derangement of the cough reflex, the greater the risk of pneumonia.[71] Nakazawa et al.[72] demonstrated impairment of the swallow and the cough reflex in elderly patients with aspiration pneumonia but not in patients with dementia who had no prior history of aspiration pneumonia. Angiotensin-converting enzyme (ACE) modulates the cough reflex. Along with its effects that cleave angiotensin I to angiotensin II, ACE also metabolizes the protussive peptides, substance *P* and bradykinin. Substance P, which is released from vagal sensory nerves in the pharynx and upper airways, mediates the cough reflex. One study found that substance *P* levels in sputum were reduced substantially in elderly patients with pneumonia.[73] Bradykinin, an inflammatory peptide that mediates cough due

TABLE 69-2 Risk Factors for Dysphagia and Aspiration Pneumonia

Cerebrovascular disease
Ischemic stroke
Hemorrhagic stroke
Subarachnoid hemorrhage
Degenerative neurologic disease
Alzheimer dementia
Multi-infarct dementia
Parkinson disease
Amyotrophic lateral sclerosis (motor neuron disease)
Multiple sclerosis
Head and neck cancer
Oropharyngeal malignancy
Oral cavity malignancy
Esophageal malignancy
Other
Scleroderma
Diabetic gastroparesis
Reflux esophagitis
Presbyesophagus
Achalasia

to ACE inhibitors, sensitizes airway sensory nerves and enhances the cough reflex. A number of reports indicate that the insertion/deletion (*I*/*D*) polymorphism of the ACE gene (ACE DD allele) is associated with an increased risk of pneumonia.[74,75] Furthermore, the use of ACE inhibitors is associated with a reduced risk of aspiration pneumonia (see the section that follows).

FACTORS THAT INCREASE THE RISK OF PNEUMONIA IN PATIENTS WHO ASPIRATE

While the presence of dysphagia and the volume of the aspirate are key factors that predispose patients to aspiration pneumonia, a number of other factors play an important role.[51] Colonization of the oropharynx is an important step in the pathogenesis of aspiration pneumonia. The elderly have increased oropharyngeal colonization with pathogens such as *Staphylococcus aureus* and aerobic gram-negative bacilli (e.g., *Klebsiella pneumoniae* and *Escherichia coli*). Although this increased colonization may be transient, it underlies the increased risk in the elderly of pneumonia with these pathogens. Furthermore, colonization of dental plaque may be an important risk factor for aspiration pneumonia.[76] The defects in host defenses that predispose to enhanced colonization with these organisms are uncertain; however, dysphagia with a decrease in salivary clearance and poor oral hygiene may be major risk factors.[77] Residents of long-term care facilities are prone to poor oral health due to lack of oral hygiene care as well as conditions of peridental and/or dental disease. Langmore et al.[78] reported that in elderly patients the number of decayed teeth and never or only occasionally brushing teeth were independent predictors of aspiration pneumonia. Similarly, Azarpazhooh and Leake [79] performed a systematic review that demonstrated that the presence of cariogenic and periodontal pathogens in dental plaque and saliva and decayed teeth were independent predictors of aspiration pneumonia. Awano et al.[80] demonstrated that persons with 10 or more periodontal pockets had an increased risk of death from pneumonia. Proton pump inhibitors increase gastric and oropharyngeal colonization with potentially pathogenic organisms. Gulmez et al.[81] reported that the concurrent use of proton pump inhibitors in patients over the age of 60 increased the risk for community-acquired (aspiration) pneumonia.

DIAGNOSIS AND MANAGEMENT OF ASPIRATION PNEUMONIA

There is no "gold standard" test to diagnose aspiration pneumonia. Furthermore, in patients with aspiration pneumonia, unlike the case of aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient with known risk factors for aspiration develops clinical features compatible with pneumonia (fever, shortness of breath, purulent sputum) with an infiltrate in a characteristic bronchopulmonary segment (see Fig. 69-2). In patients who aspirate in the recumbent position the commonest sites of involvement are the posterior segments of the upper lobes and the apical segments of the lower lobes. In patients who aspirate in the upright or semirecumbent position the basal segments of the lower lobes are favored. The usual picture is that of an acute pneumonic process, which runs a course similar to that of a typical CAP. Untreated, however, these patients appear to have a higher incidence of cavitation and lung abscess formation.[82]

Antimicrobial therapy is indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs as well as the patient's premorbid condition. This includes such factors as whether the aspiration occurred in the community or in a healthcare facility (healthcare-associated pneumonia [HCAP]) and patient characteristics such as alcoholism, oral hygiene, intravenous drug abuse, and the recent use of antibiotics or acid suppressive therapy.[83] In otherwise "healthy" outpatients a narrow-spectrum antibiotic which targets organisms such as *Streptococcus pneumoniae, S. aureus,* and *Haemophilus influenzae* is recommended. However, most patients with aspiration pneumonia have risk factors for colonization and infection with aerobic gram-negative organisms and require treatment with antimicrobials such as third generation cephalosporins, fluoroquinolones, piperacillin, or carbapenems.[83–86] In addition, vancomycin or linezolid should be considered in patients at risk of infection with methicillin-resistant *S. aureus* (MRSA). Although commonly prescribed (and often considered the standard of care) antimicrobials with specific anaerobic activity are not routinely warranted. The anaerobic bacteria that colonize the oropharynx are intrinsically of low virulence. In an experiment dating back to 1930, Smith introduced bacteria isolated from patients with Vincent angina into the lungs of rabbits.[87] Cultures of a single organism failed to produce pneumonia; only when multiple different organisms were instilled into the lungs did the animals develop pneumonia (synergistic anaerobic infection). In the most rigorous study to date, El-Sohl et al.[86] performed protected quantitative bronchial sampling in 95 patients with severe aspiration pneumonia. Out of the 67 pathogens identified, gram-negative enteric bacteria were the predominant organisms isolated (49%), followed by anaerobic bacteria (16%) and *S. aureus* (12%). A single anaerobic bacterium was isolated from 11 patients usually in association with a gram-negative pathogen. Although seven cases with anaerobic isolates received initially inadequate antimicrobial therapy, six had effective clinician response. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum and patients with a necrotizing pneumonia or lung abscess on chest radiograph.[2,83–85]

ASSESSMENT AND MANAGEMENT OF DYSPHAGIA

All elderly patients with CAP, as well as patients with a recent cerebrovascular accident and those with degenerative neurologic diseases should be referred to a speech and language pathologist (SLP) for a formal swallow evaluation (Video 69-1).[67,88] Those patients with dysphagia require the formulation and implementation of an individualized management strategy. A clinician's bedside assessment of the cough and gag reflex is unreliable in screening for patients at risk of aspiration. Because objective swallowing evaluation can be performed with a nasogastric tube or feeding tube in place, it is not necessary to remove the tube (and interrupt enteral feedings) to evaluate dysphagia. Similarly, there is no contraindication to leaving a nasogastric tube in place to supplement oral alimentation.[89]

The management of patients with dysphagia requires the coordinated expertise of a number of healthcare professionals, including the patient's primary care physician, pulmonologist, SLP, clinical dietician, occupational therapist, physiotherapist, nurse, oral

Video 69-1 An 82 year-old male admitted with PNA, required multiple intubations and eventual tracheostomy. Fiberoptic endoscopic evaluation of swallowing (FEES) completed with #5XLT proximal/cuffless tracheostomy (patient capped on room air) and Dobhoff feeding tube in place. FEES revealed a severe pharyngeal dysphagia. There is pooling of secretions throughout pharynx/larynx (valleculae and pyriform sinuses) with aspiration of secretions. With pureed texture there is residue throughout the pharynx suggestive of generalized reduced pharyngeal contraction. The residue in the valleculae is a result of reduced base of tongue retraction, epiglottis dysfunction, and poor hyoid elevation. The residue in the pyriform sinuses is a result of cricopharyngeus dysfunction/inadequate upper esophageal sphincter opening. There is a delayed pharyngeal swallow response with nectar consistency with bolus spilling to the pyriform sinuses resulting in + aspiration before/during/after the swallow response due to reduced arytenoid tilt and vocal fold adduction. *(Used with permission of Randy Dubin.) Access at www.fishmansonline.com*

hygienist, dentist, as well as the patient's primary caregivers. The goal is to optimize the safety, efficiency, and effectiveness of the oropharyngeal swallow to maintain adequate nutrition and hydration and to improve oral hygiene. Enhanced quality of life, wherever possible, should direct management and oral intake (when possible) is preferred over tube feeding. A fundamental principle of rehabilitation is that the best therapy for any activity is the activity itself; as swallowing may be considered the best therapy for swallowing disorders, rehabilitation should be aimed at identifying ways of ensuring safe and effective swallowing in individual patients. Current treatment for dysphagia includes prevention of aspiration in the form of diet and fluid modifications, compensatory maneuvers, position changes, and rehabilitation exercises.[90] Diet modification is a common treatment for dysphagia. Modifications in food consistency are individually determined by means of the clinical swallow and/or videofluoroscopic swallow evaluation. Reduction in bolus volume and enhancement of bolus viscosity significantly improve the safety of swallowing and reduce the risk of aspiration.[63] The SI physical unit of dynamic viscosity is the pascal-second (Pa·s). The prevalence of aspiration is maximal with water and thin fluids (20 Pa·s) and decreases with nectar (270 Pa·s) and pudding (3900 Pa·s) viscosity boluses.[63] By increasing the viscosity or thickness of the food or liquid bolus in patients with oral sensory or motor deficits, the material is less likely to escape from the oral cavity, fall into the laryngeal inlet, or penetrate the incompletely sealed larynx during the delay before pharyngeal swallowing starts. Videofluoroscopic studies have demonstrated that increasing viscosity of liquids to pudding viscosity significantly reduces the risk of aspiration.[91,92] In addition to changes in diet, maintenance of oral feeding often requires compensatory techniques to reduce aspiration or to improve pharyngeal clearance. A variety of behavioral techniques are used, including modifications in posture, head position and respiration, as well as specific swallowing maneuvers. The chin-down posture has been suggested to reduce the risk of aspiration.[92–94] Welch et al.[95] noted that the posterior shift of anterior pharyngeal structures with the chin-down posture improved airway protection. The preferred intervention in patients with dysphagia and the impact of these interventions on the risk of aspiration pneumonia is however unclear.[96]

Neuromuscular electrical stimulation (NMES) is a relatively new treatment for oropharyngeal dysphagia.[97–99] NMES for dysphagia entails applying electrodes to the muscles of the head and neck, and stimulating those muscles that are weakened or hemiparetic by means of electric pulses. This is generally combined with the subject swallowing food or fluids that are predetermined to represent the most appropriate consistency that the person can tolerate without aspiration. Further research on the effects of NMES is warranted before surface electrical stimulation can be recommended as treatment of dysphagia

Tube Feeding

Tube feeding is not essential in all patients who aspirate. Short-term tube feeding, however, may be indicated in elderly patients with severe dysphagia and aspiration in whom improvement of swallowing is likely to occur. Nakajoh et al.[71] demonstrated that the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared to those who received tube feeding (54.3 vs. 13.2%, $p < 0.001$), despite the fact that the orally fed patients had a higher functional status (higher Barthel index). The *FOOD* trials consisted of two large randomized studies that enrolled dysphagic stroke patients.[100] In the first trial, patients enrolled within 7 days of admission were randomly allocated to early tube feeding or no tube feeding. Early tube feeding was associated with an absolute reduction in risk of death of 5.8%. The second trial allocated patients to early nasogastric feeding or early feeding via a percutaneous endoscopic gastrostomy (PEG) tube. PEG feeding was associated with an absolute increase in the risk of death of 1% and an increased risk of death or poor outcome of 7.8%. Patients with a PEG were less likely to be transitioned to oral feeding than the nasogastric group and were more likely to be living in an institution. This may in part explain the higher mortality of the PEG-fed patients. Furthermore, it was interesting to note that PEG-fed patients were more likely to develop pressure sores, suggesting that these patients may have been nursed differently. The results of the FOOD trials suggest that dysphagic stroke patients should be fed early via a nasogastric or feeding tube and transitioned to oral feeding as their dysphagia resolves. Those patients whose dysphagia does not resolve may be candidates for placement of a PEG tube.

Oral Hygiene

Dental plaque as well as "tongue coating" serves as a reservoir of potentially pathogenic organisms.[76] Occupants of residential homes have been shown to have poor oral hygiene and rarely receive treatment from dentists and oral hygienists.[101] An aggressive protocol of oral care will reduce colonization with potentially pathogenic organisms and decrease the bacterial load, measures that have been demonstrated to reduce the risk of aspiration pneumonia.[102–105] Oral care should not be overlooked in edentulous patients as "tongue cleaning" is associated with a decreased oropharyngeal bacterial load.[106,107]

Pharmacologic Management

The neurotransmitter, Substance P, is believed to play a major role in both the cough and swallow sensory pathways. ACE inhibitors prevent the breakdown of Substance P and may theoretically be useful in the management of patients with aspiration pneumonia. A number of studies have demonstrated a lower risk of aspiration pneumonia in stroke patients treated with an ACE inhibitor compared to other antihypertensive agents.[108,109] This observation was initially noted in Japanese patients and it has been suggested that this benefit was restricted to Asian populations.[110] Furthermore, it has been postulated that lipophilic ACE inhibitors may be more beneficial than hydrophilic ACE inhibitors.[111] However, a population-based case-control study from the United Kingdom demonstrated that the current prescription for an ACE inhibitor was associated with a reduction of the risk of pneumonia in the general population (OR 0.75, 95% CI 0.65–0.86).[112] Nicergoline (Sermion, Pfizer), an ergot alkaloid derivative, has been demonstrated to upregulate Substance P and improve dysphagia with an efficacy similar to that of ACE inhibitors.[113] Additional studies are required with this drug to determine its role in preventing aspiration pneumonia.

Sedative medication has been demonstrated to increase the risk of pneumonia in residents of long-term-care facilities and should, therefore, be avoided.[114] The prescription of phenothiazines and haloperidol should be very carefully considered, as they reduce oropharyngeal swallow coordination, causing dysphagia.[115,116] Medications that dry up secretions, including antihistamines and drugs with anticholinergic activity, make it more difficult for patients to swallow and should therefore also be avoided.[115,117]

DIFFUSE ASPIRATION BRONCHIOLITIS

Occult aspiration can result in lung damage with a variety of radiographic, clinical, and histologic manifestations. Occult aspiration in the elderly is usually associated with esophageal dysmotility, gastroesophageal reflux disease (GERD) as well as neurologic impairment (dysphagia) and frequently presents with acute onset of symptoms while sleeping.[118] Diffuse aspiration bronchiolitis is a distinct clinical entity that was first defined by Matsuse et al.[3] in 1996 as a syndrome characterized by chronic bronchiolar inflammation from recurrent aspiration of foreign matter (food). Their case series was based on autopsy findings and represented an elderly, chronically debilitated

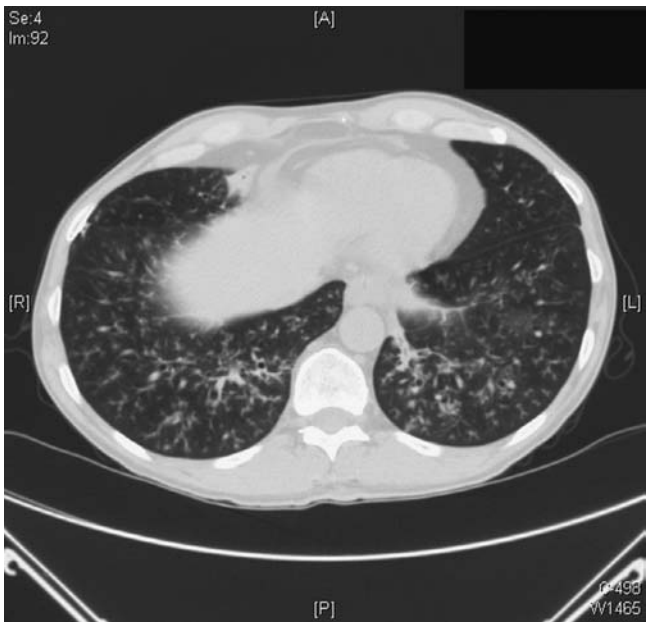

Figure 69-3 CT scan of patient with diffuse aspiration bronchiolitis.

population. Dysphagia was recorded in over half of the patients with two-thirds being bedridden. Diffuse aspiration bronchiolitis should be suspected in elderly patients with recurrent episodes of bronchorrhea, bronchospasm, and dyspnea. However, this syndrome has been reported in middle-aged patients (mean age 50 years) with "asymptomatic" GERD.[119] Typical findings on the chest radiograph include the presence of regional or disseminated small nodular shadows and hyperlucency. Airspace consolidation is relatively rare. Chest CT scans demonstrate diffuse centrilobular nodules with a tree-in-bud pattern (Fig. 69-3).[120] It is likely that this disease is underrecognized and therefore often inappropriately managed.

CONCLUSIONS

Aspiration pneumonitis and pneumonia are common clinical syndromes. Aspiration pneumonitis follows the aspiration of gastric contents, usually in patients with a marked decreased level of consciousness. Treatment of aspiration pneumonitis is essentially supportive, however, corticosteroids and other immunomodulating agents may have a role in these patients. Aspiration pneumonia occurs in patients with dysphagia and usually presents as a "CAP" with a focal infiltrate in a dependent bronchopulmonary segment. Patients with aspiration pneumonia require treatment with broad-spectrum antibiotics and management of the underlying dysphagia. Diffuse aspiration bronchiolitis presents with radiographic evidence of widespread centrilobular and tree-in-bud opacities; clinicians must be aware of the possibility of occult aspiration in order to make the correct diagnosis.

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CHAPTER 70

Pulmonary Alveolar Proteinosis Syndrome

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Takuji Suzuki

Pulmonary alveolar proteinosis (PAP) syndrome is characterized by the accumulation of surfactant in alveoli and terminal airways resulting in hypoxemic respiratory failure.[1] This fascinating syndrome continues to serve as a paradigm for disease discovery and development due to a globalized collaborative network, employment of diverse clinical, basic, and translational research approaches, and active patient involvement. While PAP occurs in many clinical settings including recently identified genetic etiologies, its molecular basis is now known in more than 90% of cases, and the molecular basis of the role of granulocyte macrophage colony–stimulating factor (GM-CSF) in surfactant homeostasis has been defined. Diseases associated with PAP can be grouped into primary PAP, secondary PAP, and congenital PAP based primarily on pathogenesis involved. Primary PAP is caused by impairment of GM-CSF–dependent surfactant clearance by alveolar macrophages and accounts for approximately 90% of all cases.[2] Secondary PAP occurs as a consequence of a comorbid condition that impair surfactant clearance by alveolar macrophages and accounts for about 5% of cases.[3] Congenital PAP is a clinically distinct and pathogenically heterogeneous group of genetic disorders associated with the production of abnormal surfactant and accounts for about 5% of cases.[4] Because of its increased frequency and greater research attention, primary PAP will be the focus of this chapter and data for secondary and congenital PAP will be provided where available.

PATHOGENESIS

In their initial description of PAP in 1958, Rosen et al.[5] established that the material accumulating within alveoli in PAP was composed of lipids, proteins, and a small amount of carbohydrate. Research over the past two decades has shown that in more than 90% of patients pathogenesis is driven by disruption of GM-CSF signaling, which blocks terminal differentiation of alveolar macrophages thereby

impairing their ability to clear surfactant.[2] GM-CSF is a 23-kDa cytokine produced by respiratory epithelium and other cells[6,7] initially identified by its ability to stimulate the formation of macrophage and granulocyte colonies from hematological progenitors and subsequently shown to stimulate functions in mature myeloid and other cells. GM-CSF is expressed similarly in humans and mice and its effects are mediated by binding to cell surface receptors composed of a GM-CSF–binding α-chain (CD116) and an affinity-enhancing β-chain (CD131). Ligand binding activates intracellular signaling via multiple pathways including signal transducer and activator of transcription 5 (STAT5) regulating diverse functions of myeloid cells including survival, differentiation, proliferation, and priming of specific host defense functions.[8,9] GM-CSF also has poorly understood effects of alveolar epithelium. In primary PAP, pathogenesis is caused by disruption of GM-CSF signaling by neutralizing GM-CSF autoantibodies in autoimmune PAP or by recessive mutations in *CSF2RA* or *CSF2RB* (encoding GM-CSF receptor α-chain [CD116] or β-chain [CD131], respectively) in hereditary PAP.[1,2,10–13]

■ SURFACTANT HOMEOSTASIS

Surfactant is vital to lung function and acts at the air–liquid–tissue interface to prevent alveolar wall collapse. It is composed of 90% lipids (largely phospholipids), 10% proteins (surfactant protein [SP]-A, -B, -C and -D), and less than 1% carbohydrate.[14] SP-B and SP-C are hydrophobic phosphoproteins that contribute significantly to the surface active properties of surfactant.[15] SP-A and SP-D are hydrophilic collectin family members that contribute to lung host defense.[16] Surfactant lipids and proteins are synthesized, stored, and secreted into the alveoli by type II alveolar epithelial cells. In the extracellular space, surfactant "large aggregates" contribute to formation of a film that lowers surface tension and stabilizes the alveolus.[17] Surfactant is expelled from the film as "small aggregates" that are internalized by type II cells and alveolar macrophages in roughly equal amounts (Fig. 70-1). Type II cells recycle and catabolize internalized surfactant equally via mechanisms that are poorly understood but do not appear to involve regulation by GM-CSF.[17–19] In contrast, alveolar macrophages exclusively catabolize internalized surfactant under the positive regulatory control of GM-CSF.[20,21]

■ ANIMAL MODELS OF PAP

The discovery that GM-CSF knockout ($GM\text{-}CSF^{KO}$) mice develop a pulmonary disease indistinguishable from primary PAP provided the first real pathogenic clue (Fig. 70-2).[22,23] In these mice, neither production of surfactant by type II cells, nor its uptake by alveolar macrophages was impaired.[22,24] Rather, surfactant clearance by alveolar macrophages was impaired.[25] Replacement of GM-CSF in the lungs by direct instillation or expression of its cDNA in airway epithelium corrected the lung disease.[26–28] Disruption of the GM-CSF receptor β gene (i.e., $Csf2rb^{KO}$ mice) caused a similar lung phenotype[29] that could be corrected by bone marrow transplantation, which indicated the critical cell type driving pathogenesis was myeloid (i.e., alveolar macrophages) not epithelial (i.e., type II cells) in origin.[30] Surfactant clearance in $GM\text{-}CSF^{KO}$ alveolar macrophages could be corrected by retroviral expression of PU.1, a transcription factor normally expressed in murine alveolar macrophages in vivo under tight regulatory control of pulmonary GM-CSF.[31] These studies established that GM-CSF, via PU.1, was required for surfactant clearance in alveolar macrophages (Fig. 70-3).[20] Recently, passive immunization with human PAP patient–derived neutralizing GM-CSF autoantibodies resulted in recapitulation of the cardinal pathological features

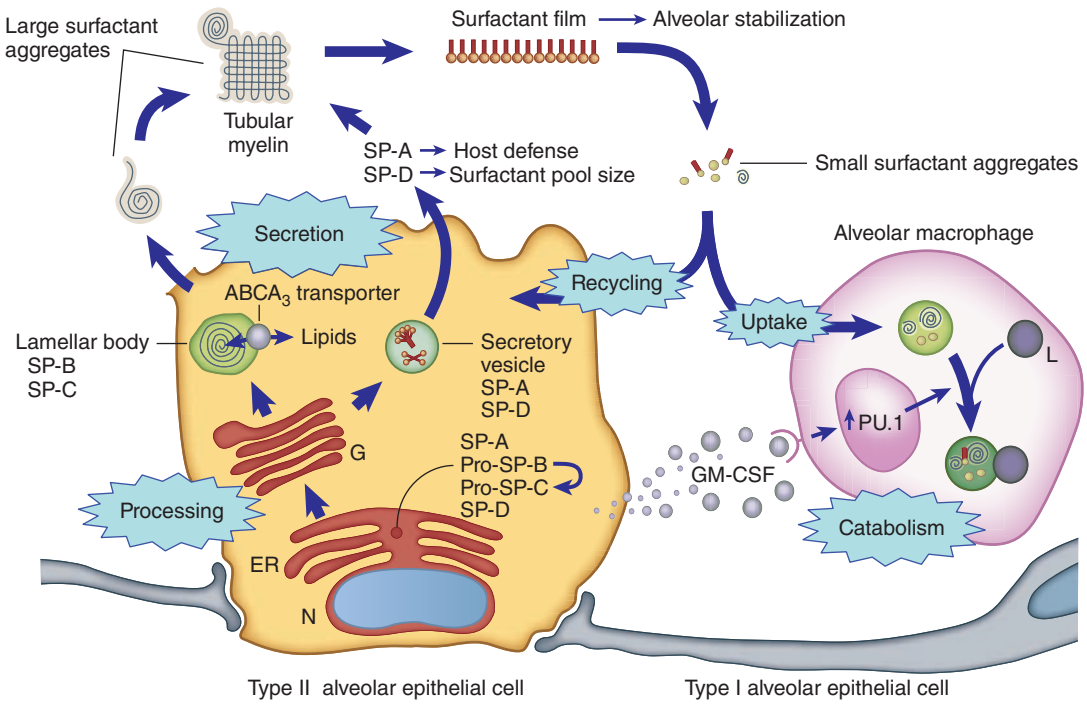

Figure 70-1 Schematic illustration depicting mechanisms of surfactant production, recycling, and catabolism. Surfactant phospholipids and proteins are synthesized in type II alveolar epithelial cells that line pulmonary alveoli. Surfactant B and C precursor proteins are processed, transported to lamellar bodies, and then secreted into the alveolar space where they interact with surfactant protein A to form tubular myelin. Surfactant monolayers and multilayers are formed from tubular myelin and function to reduce surface tension at the air–liquid–tissue interface, thus stabilizing the alveoli. Surfactant remnants are taken up and either catabolized or reutilized by type II alveolar epithelial cells. Alveolar macrophages play a critical role in surfactant homeostasis by taking up and catabolizing surfactant remnants. GM-CSF is required to maintain surfactant homeostasis and acts by stimulating catabolism of surfactant lipids and proteins in alveolar macrophages. *(Reproduced with permission from Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. Hum Mol Genet. 2004;13[Spec No 2]:R207–R215.)*

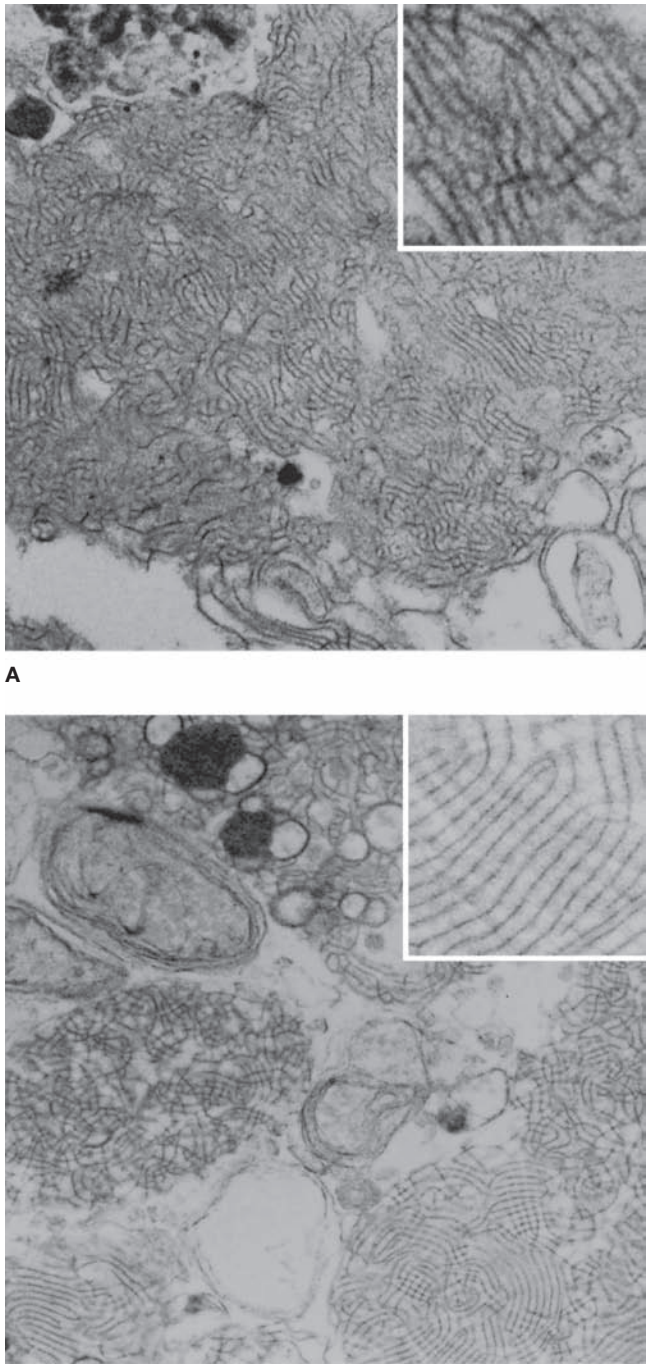

Figure 70-2 Ultrastructural appearance of the sediment from the lungs of a human patient with primary PAP (**A**) and a GM-CSF–deficient mouse (**B**). Note the presence of lamellated, fused membrane structures and amorphous debris (uranyl acetate, ×30,000).

of autoimmune PAP in nonhuman primates.[32,33] The abnormalities induced in alveolar macrophage included impaired GM-CSF signaling, GM-CSF–dependent gene expression (including PU.1), and surfactant clearance and increased neutral lipid accumulation resulting in foamy appearing alveolar macrophages. These animal models provide strong support for disruption of GM-CSF signaling as the critical driver of PAP pathogenesis. As a model of secondary PAP, depletion of alveolar macrophages has been shown to increase lung surfactant pool size in rats.[34] Congenital PAP models have been created in mice by disruption of the genes required for normal surfactant production *(Sftpb*, *Sftpc*, *Abca3)*.[35–37]

■ PRIMARY PAP

Autoimmune and hereditary forms of primary PAP are considered below.

Autoimmune PAP

In 1999, the Nakata group discovered that idiopathic PAP (also reported as acquired PAP) was specifically associated with high levels of neutralizing anti–GM-CSF autoantibodies (Fig. 70-4).[10] Subsequently, these autoantibodies were shown to be (1) polyclonal, primarily comprised of immunoglobulin G subclass 1 (IgG_1) and IgG_2 with smaller amounts of IgG_3 and IgG_4, (2) have a very high affinity for GM-CSF in the 3 to 20 pM range, and (3) capable of neutralizing GM-CSF, and (4) eliminating GM-CSF bioactivity in vivo.[38,39] Notwithstanding, several findings were difficult to reconcile. GM-CSF autoantibodies were also present in healthy individuals, albeit at lower levels,[39] and the antibody levels in PAP patients did not correlate with disease severity.[40] The recapitulation of PAP in healthy nonhuman primates by passive immunization with PAP patient–derived GM-CSF autoantibodies firmly established their critical role in pathogenesis.[32,33] The low autoantibody levels in healthy individuals and lack of correlation with disease severity in PAP patients was explained by a model in which constitutive in vivo stimulation of GM-CSF–dependent myeloid cell functions (including surfactant clearance) declined with increasing GM-CSF autoantibody level until a critical threshold was reached where function became zero.[39,41] The threshold level was identified and similar in humans and nonhuman primates.[33,39] These studies provide strong evidence that GM-CSF autoantibodies were pathogenic and led to a recommendation to change the name from "idiopathic PAP" to "autoimmune PAP."[41]

Hereditary PAP

While humans with GM-CSF deficiency have not been identified to date, in 2008, a GM-CSF autoantibody-negative child was found to have compound heterozygous mutations in *CSF2RA* (encoding GM-CSF receptor α) as the cause of familial PAP.[11] Additional patients were identified by exploiting use of a biomarker, increased serum GM-CSF, to screen sera from a repository including patients with PAP of unknown etiology, which identified a cohort of patients with PAP-causing *CSF2RA* mutations (Fig. 70-4).[42] Subsequently, *CSF2RB* mutations were identified as a cause of hereditary PAP.[12,43] Detailed characterization were done including molecular cloning and expression studies to recapitulate the receptor dysfunction established that the pathogenesis of hereditary PAP is caused by recessive or compound heterozygous mutations in the *CSF2RA* or *CSF2RB* genes.[11,12,42,43] A variety of mutation types were identified as the cause of hereditary PAP including missense mutations, nonsense mutations, small insertions and deletions, exon deletion, and gene deletion.[2] Together, these studies defined the clinical presentation, pathogenesis, diagnosis, and therapy of hereditary PAP.

■ SECONDARY PAP

Results from a national registry recently confirmed that secondary PAP occurs in association with a heterogeneous group of underlying diseases including hematological disorders, primarily myelodysplasia (76%–88% of cases), infectious diseases (2%–3%), other autoimmune diseases (7%), immunosuppression after organ transplantation (7%), and in nonhematological malignancies (5%).[44] Secondary PAP also occurs in association with (and presumably due to) heavy inhalation exposure to inorganic dusts (e.g., silica, titanium, aluminum) and other gasses and fumes, or as a consequence of systemic infections, for example, during human immunodeficiency virus (HIV) infection.[45] Secondary PAP appears to be caused by a reduction in the numbers or clearance capacity of alveolar macrophages, consistent with macrophage depletion studies in rats.[34]

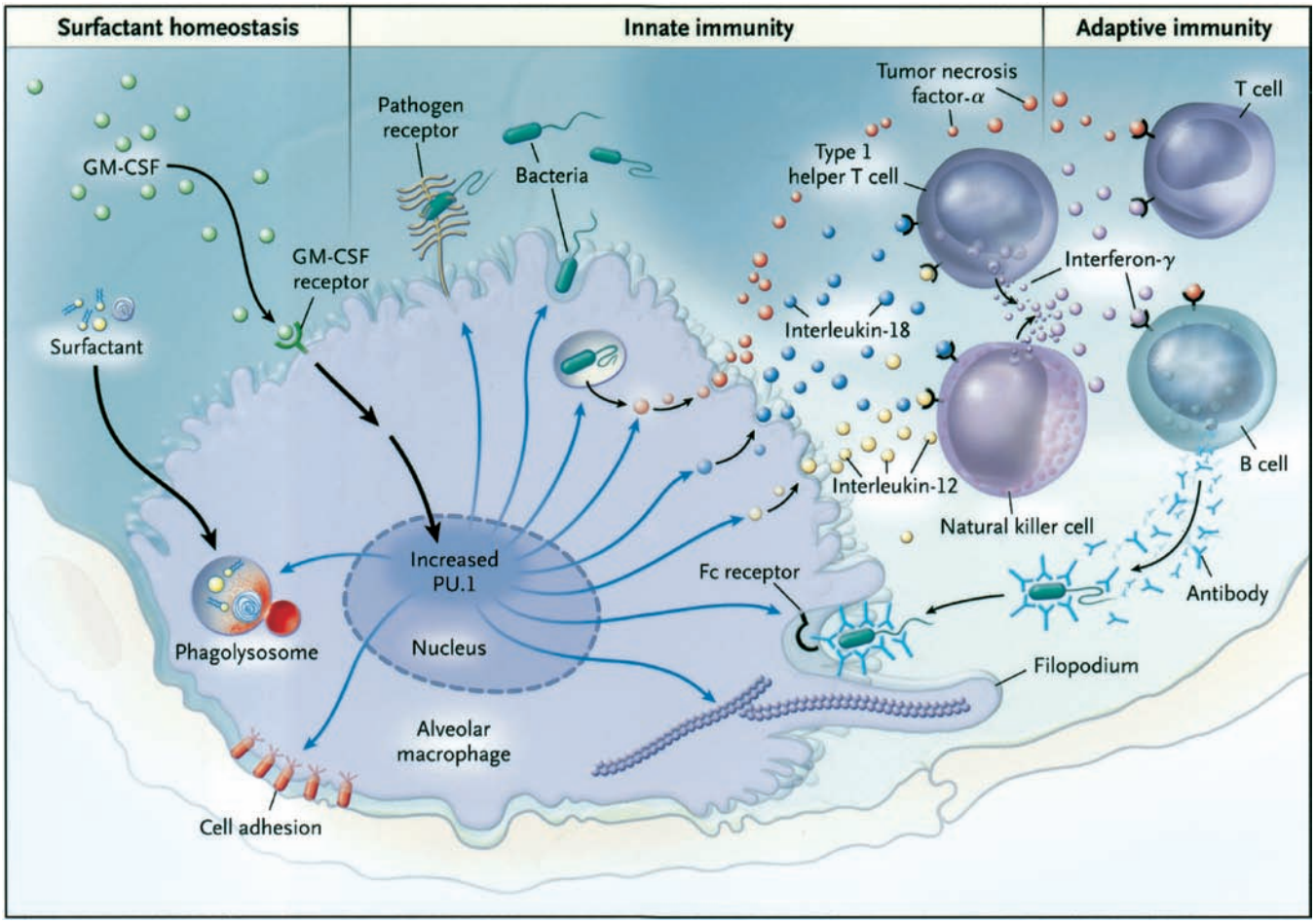

Figure 70-3 Role of GM-CSF in modulating the function of alveolar macrophages in mice. Pulmonary GM-CSF stimulates increased levels of the transcription factor PU.1 in alveolar macrophages in the lungs in vivo. Alveolar macrophages from mice deficient in GM-CSF have a number of functional defects including defects in cellular adhesion, catabolism of surfactant proteins and surfactant lipids, expression of pathogen-associated molecular pattern receptors (e.g., toll-like receptors and the mannose receptor), toll-like–receptor signaling, phagocytosis of pathogens, intracellular killing of bacteria (independent of uptake), pathogen-stimulated secretion of cytokines (tumor necrosis factor-α, interleukin [IL]-12, and IL-18), and Fc-receptor–mediated phagocytosis. Cytoskeletal organization is abnormal and may in part account for defects in phagocytosis. The ability of alveolar macrophages to release IL-12 and IL-18 severely impairs the interferon-γ response to pulmonary infection, thus impairing an important molecular connection between innate and adaptive immunity in the lung. Retroviral-mediated expression of PU.1 in alveolar macrophages from GM-CSF knockout mice corrects all these defects, suggesting that GM-CSF stimulates terminal differentiation of the macrophages primarily through the master transcription factor PU.1. The *blue arrows* represent the functions regulated by PU.1 that are affected by the absence of GM-CSF. *(Reproduced with permission from Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003;349(26):2527–2539.)*

■ CONGENITAL PAP

PAP occurs in neonates, infants, and children in association with various defects in the genes encoding SP-B, SP-C, ABCA3 – a lipid transporter expressed in type II alveolar epithelial cells, or TTF-1 – a transcription factor essential for lung development and surfactant expression.[4,46–49] In contrast to primary and secondary PAP that are caused by reduced surfactant clearance, these disorders result from production of abnormal surfactant. While surfactant accumulation does occur to varying degrees in surfactant production disorders, these disorders are clinically, histopathologically, and pathogenically distinct from primary and secondary PAP (see below).

■ THE EMERGING ROLE OF GM-CSF IN INNATE IMMUNITY

GM-CSF^{KO} mice have increased susceptibility to a broad range of microbial pathogens, increased mortality from spontaneous infections,[50,51] and numerous host defense defects in macrophages and neutrophils.[31,52] In macrophages, all these diverse defects could be corrected by forced expression of PU.1 (Fig. 70-3).[31] Similar defects are present in alveolar macrophages and neutrophils from humans and nonhuman primates with disruption of GM-CSF signaling.[2] GM-CSF^{KO} mice also have systemic immune and inflammatory abnormalities[51] including reduced severity in arthritis models,[53] an observation that has led to conduct the human trials of GM-CSF signaling disruption as therapy of rheumatoid arthritis.[54,55] These and other studies lead to an emerging understanding of the important roles that GM-CSF plays in the regulation of alveolar macrophage terminal differentiation, the basal functional capacity of circulating neutrophils, and in autoimmune and inflammatory diseases.[56]

EPIDEMIOLOGY

The epidemiology of PAP remains poorly defined. Results from a national registry study estimated the incidence and prevalence of autoimmune PAP in Japan to be approximately 0.49 and 6.2 per million in the general population, respectively.[57] In a subsequent report from the registry,[44] 40 cases of secondary PAP were identified premortem resulting in a prevalence estimate of approximately 0.3 per million. The incidence and prevalence of congenial PAP are unknown. In recent reports from specialized clinical centers, the

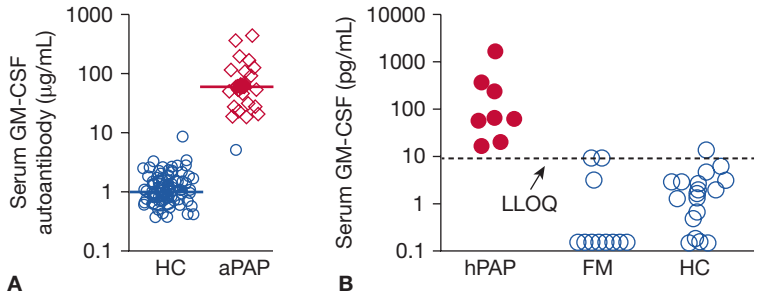

Figure 70-4 Biomarkers of use in identifying individuals with primary PAP. **A.** Serum GM-CSF autoantibody concentration. Shown are data for healthy controls (HCs) and patients with aPAP (autoimmune PAP). *(Reproduced with permission from Uchida K, Nakata K, Suzuki T, et al. GM-CSF autoantibodies and myeloid cell immune functions in healthy individuals. Blood. 2009;113(11):2547–2556.)* **B.** Serum GM-CSF concentration. Shown are data for children with hereditary PAP (hPAP) caused by recessive *CSF2RA* or *CSF2RB* mutations, members of their immediate family who were health (FM), or unrelated HCs. The lower limit of quantification (LLOQ) of the assay was 7.8 pg/mL *(dashed line)*. The serum levels of GM-CSF (median, interquartile range) in children with hPAP (52 pg/mL [28–101 pg/mL]) were increased compared with healthy family members (0.0 pg/mL [0.0–3 pg/mL]) and unrelated health controls (0.0 pg/mL [0.0–1.9 pg/mL]) ($n = 8, 11, 30$, respectively; $P < 0.001$; Kruskal–Wallis analysis of variance on ranks with comparisons using Dunn's method). *(Reproduced with permission from Suzuki T, Sakagami T, Young LR, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Crit Care Med. 2010;182(10):1292–1304.)*

age at the time of diagnosis of autoimmune PAP in years (median/mean, number of patients, country) were 52 (248, Japan),[57] 42 (241, China),[58] 43 (70, Germany),[59] 40 (81, Italy),[60] although the diagnosis has been made in children as young as 3 years (unpublished). In these reports, the male/female ratio varied from 1.3 to 2.2 overall but was close to one in nonsmokers. Autoimmune PAP occurs in various ethnic backgrounds including Hispanic, Asian, Black, and white and in wide geographic distribution.

CLINICAL FEATURES

PRESENTATION

Autoimmune PAP typically presents as progressive dyspnea of insidious onset in previously healthy adults between the ages of 20 and 50 years, but has presented in children as young as 3 years old and in the elderly. In several series, dyspnea occurred in 67% to 94% of patients, followed by cough (23%–66%) and fatigue (49%) whereas fever (4%–11%) and sputum production (1%–4%) were less common.[57–60] In the Japanese registry study, one-third of patients were asymptomatic and identified only by mandatory health screening programs.[57] A history of diffuse pneumonia that is poorly responsive or unresponsive to antibiotic therapy is sometimes present and should raise the suspicion of PAP. The physical examination is often normal but commonly includes crackles especially in dependent areas and cyanosis is occasionally present in severe cases. Digital clubbing is typically absent. Hereditary PAP presents in remarkably similar fashion but at a mean age of 4.8 ± 1.6 years.[42] Secondary PAP has been reported to present at a median age of 49 years, most frequently accompanied by exertional dyspnea (40% of cases) followed by fever (38% of cases).[44] In patients with lung disease associated with abnormal surfactant production, dyspnea, crackles, and digital clubbing may be present.

RADIOGRAPHIC APPEARANCE

The chest radiograph in primary PAP usually reveals bilateral symmetrical alveolar opacities located centrally in mid- and lower-lung zones, often with a perihilar predominance resembling the "bat wing" appearance of pulmonary edema but without other signs of left-sided heart failure (Fig. 70-5A,C). The peripheral lung is commonly spared, resulting in lucency along the diaphragmatic, mediastinal, and peripheral borders. High-resolution computed tomography (HRCT) scanning reveals a characteristic geographical pattern of ground-glass opacification with superimposed interlobular septal and intralobular thickening, commonly referred to as "crazy paving" (Fig. 70-5B,D) that is characteristic of PAP but not diagnostic.

LABORATORY FINDINGS

In primary PAP, routine blood counts and chemistries are usually normal in primary PAP with the exception of serum lactate dehydrogenase (LDH), which is increased two- to threefold and correlates well with the degree of functional impairment as determined by physiological testing and arterial blood gas analysis. A number of biomarkers have been identified in autoimmune PAP including increased serum levels of GM-CSF autoantibody, SP-A, SP-B, SP-D, KL-6, CEA, Cyfra-21-1, cytokeratin 19, and others.[1,57,59–61] Many of these biomarkers are also increased in hereditary PAP.[11–13,42,43] Importantly, serum GM-CSF is specifically elevated in hereditary PAP but not in autoimmune PAP, which was important in identifying an initial cohort of patients for study (Fig. 70-4).[42] Biomarkers of secondary and congenital PAP have been less well studied.

LUNG FUNCTION

In primary PAP, spirometry and lung volume testing is usually normal or near normal but may show a restrictive pattern of impairment with modest reduction in the vital capacity and total lung capacity (TLC) and a disproportionate reduction of the carbon monoxide diffusing capacity (D_{LCO}). Arterial blood gas analysis in symptomatic patients reveals hypoxia caused by ventilation–perfusion inequality and intrapulmonary shunting, resulting in a widened alveolar–arterial diffusion gradient ($A\text{-}a_{DO_2}$).

BRONCHOSCOPIC FINDINGS

The bronchoscopic appearance of the airways in primary PAP is normal but white, frothy proteinosis material is occasionally seen.[42,59,60,62] The bronchoalveolar lavage (BAL) fluid is opaque and has a milky or waxy appearance and develops a thick layer of sediment upon standing overnight (Fig. 70-6). The sediment consists of large, acellular, eosinophilic bodies in a diffuse background of granular material that stains with periodic acid-Schiff (Fig. 70-7A). The cellular fraction contains large, foamy macrophages (Fig. 70-7B), smaller monocyte-like macrophages, and lymphocytes with relatively few neutrophils unless infection is also present. SP is increased and electron microscopy reveals the presence of lamellar bodies and tubular myelin that are characteristic of surfactant (Fig. 70-2).

LUNG PATHOLOGY

Macroscopically, the cut surface of the lung in autoimmune PAP reveals a patchwork of 2- to 3-cm grayish-yellow regions of firm consolidation that exudes fatty material. Microscopically, alveoli and terminal airspaces are filled with a fine eosinophilic material (Fig. 70-7C) that stains strongly for SPs (Fig. 70-7D).[1] In primary PAP, the alveolar wall and interstitial architecture are usually well preserved but occasionally, lymphocytosis and fibrosis can be seen. The vasculature appears normal. Electron microscopy reveals characteristic, concentrically laminated surfactant structures within the granular material and in alveolar macrophages. The gross and microscopic appearance of the lung in hereditary PAP

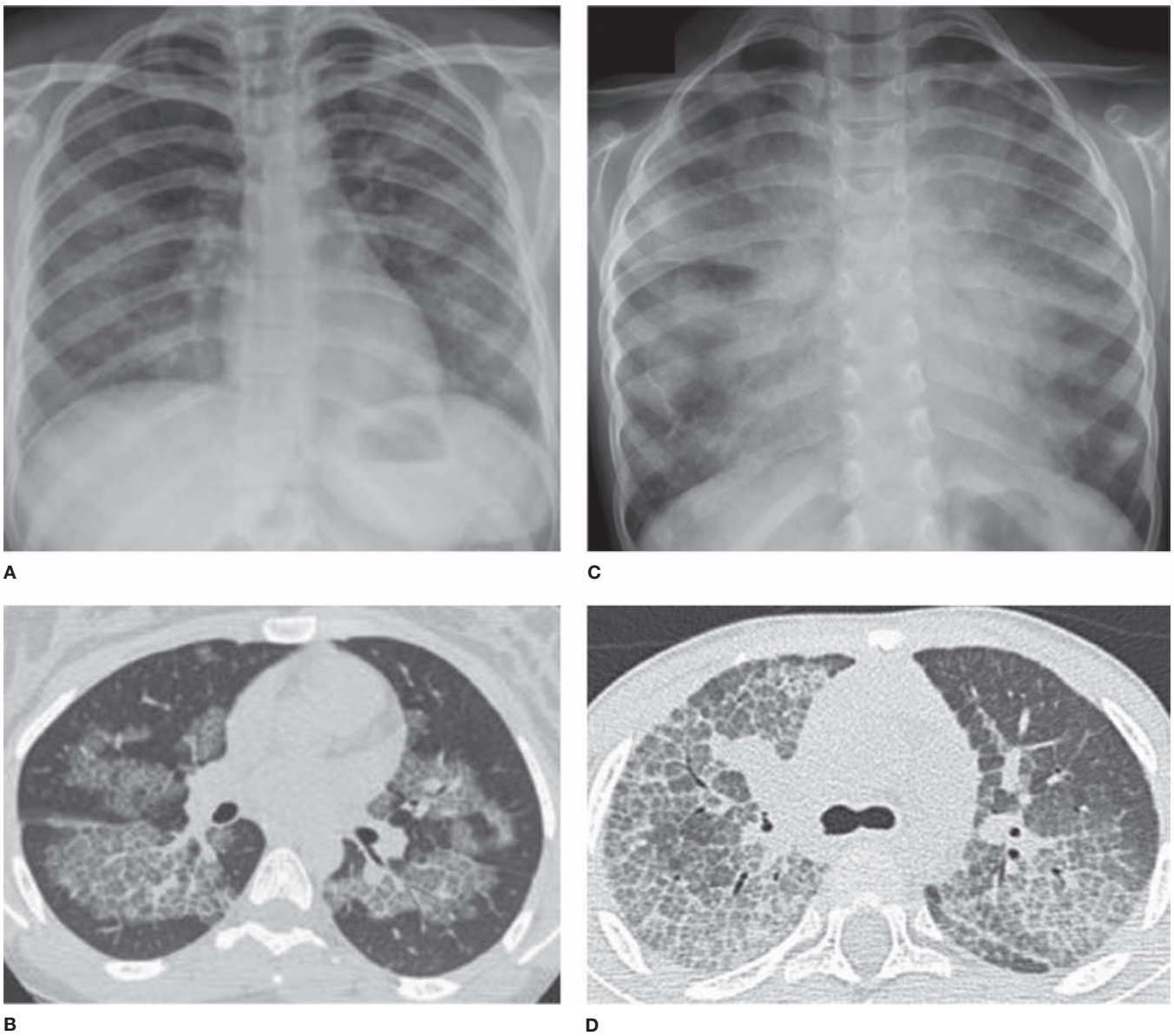

Figure 70-5 Radiographic appearance of primary PAP. **A.** Chest radiograph of a 25-year-old woman autoimmune PAP. **B.** Corresponding chest high-resolution computed tomographic (HRCT) scan. **C.** Chest radiograph of a 6-year-old girl with compound heterozygous *CSF2RA* mutations. **D.** HRCT of a 3-year-old girl with recessive null *CSF2RA* mutations.

is similar.[11–13,42,43] The lung pathology in secondary and congenital PAP varies significantly depending on the disease.

■ SECONDARY INFECTIONS

Individuals with autoimmune PAP have an increased risk of infections, which contribute significantly to increased morbidity and mortality.[1,61] Although pathogens commonly seen in community- and hospital-acquired lung infections are sometimes identified, opportunistic organisms are often responsible and can include Nocardia, Mycobacterium, Aspergillus, Cryptococcus, and others. Infections can occur at both pulmonary and extrapulmonary sites supporting the concept that a systemic defect in host defense is present secondary to defects in the antimicrobial functions of macrophages and neutrophils.[31,51,52,63]

DIAGNOSIS

While PAP syndrome can be suspected based on historical, physical, radiographic lung function findings, further studies are needed to exclude other conditions in the differential diagnosis such as hypersensitivity pneumonitis, pulmonary edema, pneumonia, and interstitial lung diseases. Traditionally, transbronchial or surgical lung biopsy have been considered necessary and are commonly used to identify the syndrome. However, none of these approaches *including lung biopsy* are capable of identifying the specific disease causing PAP. In contrast, the development and testing of several disease-specific and semi-specific biomarkers is particularly useful. The serum-based GM-CSF autoantibody ELISA initially established by Nakata[10] has been refined[38,39,52,62] and recently evaluated in a multinational validation study that demonstrated a sensitivity and specificity for a diagnosis of autoimmune PAP of 100%.[64] Similarly, an increase in serum GM-CSF appears to be both sensitive and specific for a diagnosis of hereditary PAP.[65] In both these diseases, the STAT5-phosphorylation index test can be helpful in establishing disruption of GM-CSF signaling.[66] Secondary PAP can usually be distinguished from primary PAP on the basis of the clinical context and histological or immunohistochemical evaluation of lung biopsy

Figure 70-6 Lavage fluid obtained during the whole lung lavage procedure of a patient with autoimmune PAP has a characteristic turbid appearance and a sediment that forms upon standing. The marked opacity and sediment of the fluid observed at the beginning (left bottle) shows progressive clearing by the end of the procedure (right bottle).

specimens. Further, disease mimics like *Pneumocystis pneumonia* can be distinguished by specific histological staining. That radiographic abnormalities are often increased out of proportion to the severity suspected on clinical grounds is of diagnostic utility but its practical application requires a high degree of clinical suspicion.

NATURAL HISTORY

Prospective, longitudinal studies of the natural history of PAP have not been done. However, experience from several large retrospective and cross-sectional PAP cohorts (number of patients) at tertiary referral centers in Japan (248), China (241), Germany (70), and Italy (81) have recently been reported.[57–60] The "time-to-diagnosis" ranged from 9 to 11 months similar to a prior report by Seymour.[57–61] Most patients had stable disease with mild, persistent symptoms while some had spontaneous remission or progressive disease. Spontaneous remissions occurred in 5% to 7% of 399 patients[57,59,60] confirming a previous estimate of 6% in 410 patients by Seymour.[61] In Seymour's study, the 5-year survival was 85% without therapy and 95% with whole lung lavage therapy.[61] Of the deaths attributable to PAP among 303 patients, 47 were due to respiratory failure from PAP, 12 were from infections, and 1 was from cardiac arrest during whole lung lavage (WLL) therapy (see below).[61] The prognosis of secondary PAP is worse than primary PAP due to linkage with the underlying disease with an estimated 5-year survival of between 20% to 40%.[44] The prognosis of congenital PAP varies, ranging widely from death at birth for SP-B deficiency and some ABCA3 mutations to respiratory insufficiency or failure from interstitial lung disease in adolescence or adulthood for SP-C mutations and some ABCA3 mutations.[4,48]

THERAPY

Therapy of PAP varies by disease. In autoimmune PAP, therapy is required by most but not all patients and is usually initiated when symptoms become limiting. In secondary PAP, treatment is aimed at the underlying clinical condition although WLL can be effective. In congenital PAP, therapy is generally limited to supportive care although SP-B deficiency has been treated successfully by lung transplantation.[67]

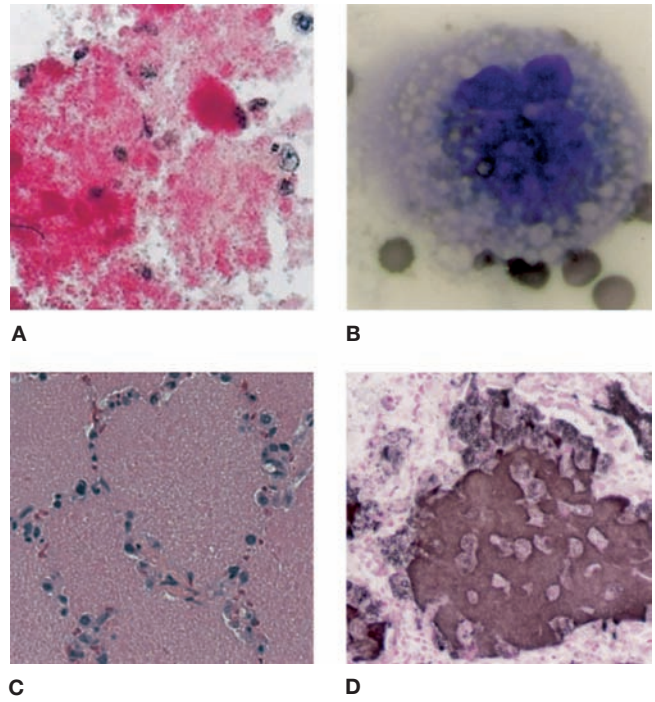

Figure 70-7 Cytological, pathological, and immunohistochemical appearance of the lipoproteinaceous material from patients with autoimmune alveolar proteinosis. **A.** Positive periodic acid-Schiff staining of the sediment from bronchoalveolar lavage (×100). **B.** Cytological appearance of a typical "foamy" alveolar macrophage. **C.** Histopathological appearance of the lung biopsy specimen from a 10-year-old child with primary PAP. Note the homogeneous staining pattern, normal alveolar wall architecture, and the absence of inflammatory cells (H&E, ×200). **D.** Immunohistochemical staining reveals the presence of abundant accumulation of surfactant protein A in a lung biopsy specimen (human anti–surfactant protein A immunostain, ×200).

■ WHOLE LUNG LAVAGE

WLL remains the most widely used therapy of primary PAP[57–61] and is still the recommended standard approach. It can be helpful in secondary PAP but has little to no utility in congenital PAP, likely due to the extensive parenchymal derangement present in these latter patients. In independent cohorts, WLL was used in 54% to 90% of a combined total of 899 patients.[51,57–60] While indications vary among centers, some of the recommendations include a histopathological diagnosis of PAP; Pa_{O_2} <60 mm Hg; A-a_{DO_2} gradient >40 mm Hg; shunt fraction >10% to 12%; or severe dyspnea at rest or with exercise. The WLL procedure itself also varies among centers. It requires general anesthesia, endotracheal intubation, and simultaneous mechanical ventilation of one lung while repeatedly filling and draining the other lung with warm saline with or without chest percussion to emulsify and physically remove the alveolar surfactant. Infusion volumes of up to 50 L per lung have been used in adults but may reach diminishing return above 20 L. Other variations include use of extracorporeal or hyperbaric oxygen. While specific therapeutic response criteria have not been defined, most patients experience clinical, physiological, and radiographic improvement following WLL.[68] Physiological parameters demonstrated to improve with lavage include increases in forced vital capacity (FVC), TLC, D_{LCO}, Pa_{O_2} at rest and with exercise, and a decrease in A-a_{DO_2} and shunt fraction. WLL improves the 5-year survival from 85±5% to 94±2%.[61] Two studies have reported a duration of response to WLL of 15 months.[60,61] Sequential lobar lavage has been used although its clinical utility is unclear.

EXPERIMENTAL APPROACHES

Our improved understanding of PAP as a disease driven by reduced GM-CSF–dependent surfactant clearance in alveolar macrophages has stimulated the development of specific pharmacological therapy. One such strategy is based on augmentation with recombinant human GM-CSF and several clinical studies have demonstrated therapeutic efficacy with this approach.[62,69–75] Both subcutaneous and inhaled administration have been used but the latter appears more efficacious. In 39 patients with unremitting/progressive autoimmune PAP, 62% of the patients receiving inhaled GM-CSF therapy had improvement in the A-a_{DO_2} gradient.[69] Radiographic improvement was also seen,[69] which in a separate study, was documented by quantitative densitometry of the chest HRCT.[75] Notwithstanding, GM-CSF therapy of autoimmune PAP is still in development and many questions remain unanswered including the optimal dosage, frequency of administration, duration of therapy. While no drug-emergent toxicities have been identified, formal safety studies of inhaled GM-CSF therapy have not been done but have been requested by the FDA and are currently underway with support from the National Institutes of Health Therapeutics for Rare and Neglected Diseases (TRND) program. Another approach aimed at GM-CSF autoantibodies is anti–B lymphocyte immunotherapy, which is used to deplete anti–GM-CSF autoantibody-producing cells.[76–78] While results are encouraging, the number of patients is small and results should be interpreted cautiously.

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CHAPTER 71

The Eosinophilic Pneumonias

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INTRODUCTION

The association between pulmonary infiltrates and eosinophilia was first identified by Loeffler in 1932. It is now recognized that the eosinophilic pneumonias are a heterogeneous group of disorders characterized by varying degrees of pulmonary parenchymal and/or blood eosinophilia.[1] The precise role that eosinophils play in the pathogenesis of the different eosinophilic pneumonias is not clear. Normally, less than 2% of the leukocyte cell differential in bronchoalveolar lavage (BAL) are eosinophils. The presence of increased BAL and/or tissue eosinophils, and our knowledge of the biology of eosinophils (see Chapter 22) does, however, suggest that they play a variety of roles, including initiation, perpetuation, and amplification of tissue inflammation and injury. These effector functions are no doubt the result of the ability of the eosinophils to release numerous soluble mediators, including granule-derived proteins, arachidonic acid metabolites, proinflammatory cytokines, superoxide anions, metalloproteases, and hydroxyl radicals. The different roles of eosinophils in these disorders can be appreciated when comparisons are made of parasitic infections and disorders such as asthma or allergic bronchopulmonary aspergillosis (ABPA). In the former, eosinophils play a crucial role in eradicating the infectious pathogen; in the latter, the eosinophils accumulate in the lung as a result of immune hypersensitivity and are prominent mediators of tissue injury.

The spectrum of diseases that can be primarily or secondarily associated with blood or pulmonary eosinophilia is shown in Table 71-1. It is beyond the scope of this chapter to discuss each of these disease entities in detail. Instead, discussion will focus on diseases of known or unknown causes in which eosinophilic infiltration of lung tissue is a characteristic feature, including acute eosinophilic pneumonias, tropical pulmonary eosinophilia (TPE), chronic eosinophilic pneumonia (CEP), ABPA, Churg–Strauss syndrome (now termed as eosinophilic granulomatosis with polyangiitis [EGPA]), and idiopathic hypereosinophilic syndrome (HES). Since eosinophilic granuloma of the lung is frequently seen in the absence of blood or tissue eosinophilia, it is considered separately (Chapter 74).

EOSINOPHILIC PNEUMONIAS WITH ACUTE PRESENTATIONS

Acute presentations of eosinophilic pneumonia center on several primary considerations, including Loeffler Syndrome, parasitic infections, drug- and toxin-related disorders, and idiopathic varieties. Each is discussed in the following sections.

LOEFFLER SYNDROME (SIMPLE PULMONARY EOSINOPHILIA)

In 1932, Loeffler first described a clinical syndrome characterized by mild respiratory symptoms, peripheral blood eosinophilia, and transient, migratory pulmonary infiltrates. The term *Loeffler syndrome,* or *simple pulmonary eosinophilia,* has been used to define the numerous similar cases reported subsequently. Immune hypersensitivity to *Ascaris lumbricoides* has been recognized as the likely cause of most of the earliest reported cases, although several other parasitic infections, including hookworms (*Ancylostoma duodenale, Necator Americanus, Necator Brasilensis*), *Strongyloides, Trichinella Spiralis, and Toxocara Canis*[2–4] and exposures to numerous drugs and other agents have also been recognized to induce a Loeffler-like syndrome (see below and Tables 71-2 and 71-3). An identifiable etiologic agent may be lacking in up to one-third of patients.

TABLE 71-1 Diseases Associated with Pulmonary Infiltrates and Eosinophilia

Pulmonary Eosinophilic Syndromes of Known Cause
Parasitic-induced eosinophilic pneumonias (including Loeffler syndrome)
Drug- or toxin-induced eosinophilic pneumonias
Tropical pulmonary eosinophilia
Allergic bronchopulmonary mycosis
Pulmonary Eosinophilic Syndromes of Unknown Cause
Idiopathic acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
EGPA (allergic granulomatosis and angiitis)
Idiopathic hypereosinophilic syndrome
Other Lung Diseases Variably Associated with Eosinophilia
Asthma/allergy
Bronchocentric granulomatosis
Bronchiolitis obliterans–organizing pneumonia
Infections
Fungal (esp. coccidioidomycosis, *Aspergillus, Pneumocystis jirovecii*)
Tuberculosis
Viral
Interstitial lung disease
Idiopathic pulmonary fibrosis
Collagen vascular disease associated
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic granuloma (pulmonary histiocytosis X)
Malignancy
Non–small-cell cancer of lung
Non-Hodgkin lymphoma
Myeloblastic leukemia
Metastatic disease
Miscellaneous (e.g., lung transplantation, lung allograft rejection, ulcerative colitis)

Loeffler syndrome affects people of all ages. It is characterized clinically by the presence of low-grade fever, nonproductive cough, dyspnea (mild to severe), chest discomfort with coughing or deep breathing, and, occasionally, hemoptysis.[3,5] The respiratory manifestations of Loeffler syndrome are usually self-limited, typically resolving in 1 to 2 weeks. Laboratory examination of peripheral

TABLE 71-2 Parasitic Infections Associated with Eosinophilic Pneumonia

Ancylostoma spp.	*Opisthorchis* spp.
Ascaris spp.	*Paragonimus westermani*
Brugia malayi	*Schistosoma* spp.
Clonorchis sinensis	*Strongyloides stercoralis*
Dirofilaria immitis	*Toxocara gondii*
Echinococcus spp.	*Trichinella spiralis*
Entamoeba histolytica	*Trichosporon terrestre*
Necator americanus	*Wuchereria bancrofti*

TABLE 71-3 Drugs and Other Exposures Causing Eosinophilic Pneumonia

Acetaminophen	Levofloxacin
Acetylsalicylic acid[a]	L-Tryptophan[a]
Aluminum	Maloprim
Amiodarone[a]	Mecamylamine
Amitriptyline[a]	Mephenesin carbamate
Ampicillin	Mesalazine
Angiotensin-converting enzyme inhibitors[a]	Methotrexate[a]
Azathioprine	Methylphenidate
Beclomethasone dipropionate	Minocycline[a]
Beryllium	Montelukast
β-Blockers	Naproxen
Bleomycin[a]	Nickel dust (inhalation)
Captopril[a]	Nilutamide[a]
Carbamazepine[a]	Nitrofurantoin[a]
Chloroquine	Nomifensine
Chlorpromazine	Oxaliplatin
Chlorpropamide	Para-aminosalicylic acid
Clarithromycin	Penicillamine[a]
Clofibrate	Penicillin
Cocaine (inhalation)	Pentamidine (inhaled)
Contrast agents	Phenytoin[a]
Cromolyn (inhalation)	Piroxicam
Dantrolene	Procarbazine
Dapsone	Progesterone
Daptomycin[a]	Prontosil
Desipramine	Propylthiouracil[a]
Diclofenac	Pyramethamine
D-penicillamine	Radiation exposure
Dust (inhalation), e.g., World Trade Center	Ranitidine
Ethambutol	Rapeseed oil
Fenbarbamate	Red spider antigens
Fenbufen	Salicylazosulfapyridine
Fludarabine	Scorpion stings
Glafenine	Sertraline
Gold salts[a]	Smoke exposure
Granulocyte macrophage colony–stimulating factor	Streptomycin
Heroin (inhalation)	Sulfa-containing antibiotics[a]
Hydrochlorothiazide	Sulfasalazine[a]
Ibuprofen	Sulindac
Imipramine	Tamoxifen
Indomethacin	Tetracycline
Infliximab	Thiazides
Interferon-alpha	Tolazamide
Interleukins	Tolfenamic acid
Iodinated contrast agents[a]	Trazodone
Isoniazid	Trichloroethane
	Venlafaxine

[a]*Drugs commonly or occasionally reported to cause pulmonary eosinophilia.*

blood from patients reveals moderate-to-extreme eosinophilia, which may be at peak levels as respiratory symptoms resolve and which resolves over several weeks.[4] Expectorated sputum, if present, frequently contains eosinophils and/or Charcot–Leyden crystals.[4,5] Transient, migratory, nonsegmental, bilateral, interstitial, and alveolar infiltrates (often peripheral or pleural based) are evident on the chest radiograph.[3] Infiltrates typically clear after several weeks. Pulmonary function evaluation typically reveals a mild-to-moderate restrictive ventilatory defect with a reduced diffusing capacity for carbon monoxide (D_{LCO}).

When Loeffler syndrome is due to *A. Lumbricoides*, hookworms or other parasites, the pulmonary manifestations are believed to result from a hypersensitivity reaction to the parasite larvae. Following ingestion of *Ascaris* ova, larvae hatch within the small intestine, then cross the intestinal wall to enter the splanchnic, and ultimately the pulmonary circulation. Subsequently, the larvae migrate across pulmonary capillaries into alveoli, mature into adult worms, ascend the large airways, and are swallowed into the gastrointestinal (GI) tract, where they complete their life cycle. The pulmonary manifestations of Loeffler syndrome begin approximately 9 to 14 days following ingestion and occur during the migration of larvae through the lung. *Ascaris suum,* a large roundworm endemic to pigs, can cause a nearly identical syndrome. Cutaneous penetration of larvae is the principal relevant mode of tissue entry for hookworms.

During the pneumonic stage of the illness, *Ascaris* or hookworm larvae may be identified in sputum or gastric aspirates.[4] In keeping with the life cycle of *Ascaris* or hookworms, stool examination for ova and parasites is typically negative until 8 weeks after the onset of the respiratory syndrome.[6] Histologic evaluation of lung tissue is not required for confirmation of the diagnosis. When tissue has been obtained, a characteristic and striking eosinophilic infiltration of interstitium and alveolar–capillary units has been noted. Increased numbers of macrophages have also been appreciated. Tissue necrosis and vasculitis are not features of the disorder. *Ascaris* or hookworm larvae may be identified in the tissue specimen.[4]

Since Loeffler syndrome may be induced by a variety of exposures, a search for an etiologic agent (e.g., parasitic infection or drug reaction) should be undertaken. Bronchodilators and rarely corticosteroids may be used for alleviation of pulmonary symptoms, although these are usually self-limited. In cases due to *Ascaris*, treatment with oral mebendazole (100 mg twice a day for 3 days or a single dose of 500 mg) should be given to prevent late GI manifestations of *Ascaris* infestation, which may include malnutrition, diarrhea, abdominal pain, and/or intestinal obstruction typically 8 weeks or more after onset of respiratory symptoms. Pyrantel pamoate, albendazole, or ivermectin are alternate treatment options.[4] Since stool specimens are negative for ova and parasites early in the illness, clinical follow-up over a 2- to 3-month period is indicated.

■ PARASITIC INFECTIONS

Infections with parasites other than *Ascaris* species are also commonly associated with pulmonary infiltrates and blood or pulmonary eosinophilia.[3–5] The parasites associated with the development of pulmonary eosinophilic syndromes are listed in Table 71-2. The prevalence of infection with each of these organisms varies with geographical location, socioeconomic status, and host immunity. Parasites may infect the lung via direct pulmonary invasion or via hematogenous seeding. In addition to *Ascaris* species, *Strongyloides stercoralis* (an intestinal nematode), *Ancylostoma brasiliensis* (cutaneous helminthiasis, "creeping eruption"), *Ancylostoma duodenale,* and *T. canis* (dog roundworm, "visceral larva migrans") are the parasitic agents most commonly associated with pulmonary eosinophilia in the United States.

Strongyloides is widely distributed in the tropical and subtropical regions.[3] Following initial transcutaneous infection, a Loeffler-like syndrome may occur as larvae migrate through the lungs. Chronic strongyloidiasis occurs as a result of autoinfection, whereby the noninfectious rhabditiform larvae transform within the GI tract into infectious filariform larvae, penetrate the colonic wall or perianal skin, and reinfect the host.[4,5] Chronic strongyloidiasis may be associated with recurrent asthma-like symptoms that may worsen with the administration of corticosteroids. The hyperinfection syndrome results from accelerated autoinfection, and usually occurs in persons with defects in cell-mediated immunity[3] (such as lymphoma, human immunodeficiency virus [HIV] or human-T lymphotropic virus type 1 [HTLV-1] infection, and with chronic corticosteroid use), as well as in persons with underlying GI disease, chronic lung disease, malnutrition, and use of H2 blockers or antacids.[7] It may also occur in healthy persons. Respiratory manifestations include cough, dyspnea, chronic bronchitis, wheezing, hemoptysis, and patchy pulmonary infiltrates, in association with blood eosinophilia. Rarely, acute respiratory distress syndrome (ARDS) has been reported in patients with hyperinfection. GI manifestations are also common, including abdominal pain, paralytic ileus, nausea and vomiting, bowel perforation, and secondary sepsis from gram-negative bacteria. Central nervous system (CNS) manifestations such as meningitis have also been noted.

The diagnosis of *Strongyloides* infection may be established by identification of larvae in sputum, BAL fluid, bronchial brushings, or transbronchial biopsy specimens, pleural fluid or stool. Several stool samples are often required to identify the pathogen.[5] Serologic testing, such as ELISA to detect IgG antibody to *Strongyloides stercoralis* can also be used to establish a diagnosis.[4] Patients at risk for *Strongyloides* hyperinfection syndrome should be screened for the parasite prior to initiation of immunosuppressive therapy.[3]

Thiabendazole (25 mg/kg twice a day for 2 days) or ivermectin (200 μg/kg given orally for 1–2 days) may be used for the treatment of uncomplicated or disseminated strongyloidias.[4] Ivermectin is generally better tolerated in terms of side effects.[5] Albendazole is an alternative agent. Higher dose and longer duration of thiabendizole treatment are needed to treat disseminated strongyloidiasis in immunocompromised persons.[5] The hyperinfection syndrome associated with *Strongyloides* can be difficult to cure. Therapy should be continued until the clinical syndrome resolves and larvae are no longer detectable in the GI tract.

Ancylostomiasis is a nematodal infection endemic to the southeastern coastal regions of the United States, Mexico, and Central and South America.[4,5] The organism is present in soil contaminated by stool from infected domestic animals. It penetrates human skin most commonly through the feet. This results in the development of the "creeping eruption" lesion – a raised, erythematous, serpiginous, tunnel-like, and often itchy lesion on areas of exposed skin.[8] A Loeffler-like syndrome occurs in up to 50% of cases of "creeping eruption." Specific treatment for pulmonary involvement is typically not required as illness is usually self-limited.

Infection with *T. canis* may occur throughout the world and leads to the clinical syndrome of "visceral larva migrans."[4] This syndrome is characterized by hepatomegaly, leukocytosis, fever, hypergammaglobulinemia, and persistent blood eosinophilia.[9] Because the disease most commonly affects young children, a high degree of clinical suspicion is necessary to establish the diagnosis in adults. Respiratory symptoms, including cough and severe wheezing, may occur after ingestion of substantial numbers of larvae. Laboratory evaluation reveals peripheral blood and BAL eosinophilia, elevated serum levels of immunoglobulin E (IgE), and poorly defined, diffuse nodular alveolar infiltrates on chest radiograph.[4] ELISA testing for larval antigens is diagnostic. Although the disease may be self-limited, treatment with thiabendazole, albendazole, mebendazole,

diethylcarbamazine, or corticosteroids may hasten recovery in patients who are severely ill.[3–5]

DRUG AND TOXIN-INDUCED PULMONARY EOSINOPHILIC SYNDROMES

A vast number of drugs and toxic exposures have been associated with the development of pulmonary infiltrates and blood or pulmonary eosinophilia.[1,10–13] A partial list of these medications and exposures is given in Table 71-3, and information regarding pulmonary drug toxicities may also be found on the Internet on the regularly updated web site, www.pneumotox.com. Of the medications implicated, many are commonly used antibiotics, nonsteroidal anti-inflammatory agents, anticonvulsants, cardiovascular medications, and antidepressants.

In addition to medications, a number of toxic exposures may also be associated with eosinophilic pneumonia.[10] For example, eosinophilic pneumonia has been described following radiation therapy for breast cancer, dust or smoke exposure,[14–17] exposure to iodinated contrast agents or 1,1,1-trichloroethane (Scotchguard),[18] and after inhalation of cocaine or heroin.[19–21]

Whereas most cases of drug- or toxin-induced pulmonary eosinophilia are sporadic, outbreaks of pulmonary eosinophilia have occurred following ingestion of rapeseed oil (contaminated with aniline derivatives)[22] or L-tryptophan.[23] The precise incidence of drug- or toxin-induced pulmonary eosinophilia is difficult to assess, since most of the literature pertaining to these syndromes is published in the form of case reports, rather than large series or controlled trials. For the same reason, the precise pathogenesis and the definition of the clinical syndromes associated with individual exposures are difficult to characterize.

In general, drug-induced pulmonary eosinophilic syndromes have an acute or subacute onset and are not always related to either the cumulative dose of drug used or the duration of treatment. Respiratory symptoms vary widely in severity, from a mild Loeffler-like illness with dyspnea, cough, and fever to severe fulminant respiratory failure. The DRESS syndrome consists of acute eosinophilic pneumonia with drug rash and systemic manifestations.[24] Wheezing may be present, but obstructive physiology is not common on pulmonary function testing. Although radiographic findings are not specific, interstitial or alveolar infiltrates are typically evident on chest radiograph (Fig. 71-1), and common high-resolution chest computed tomographic (CT) findings include bilateral consolidation and ground-glass opacities, both of which are frequently peripherally located.

A diagnosis of drug- or toxin-induced eosinophilic pneumonia is based upon a careful review of drug and other exposures (including nonprescription drugs, herbal preparations, street drugs, and environmental exposures). Other causes of eosinophilic lung disease must be excluded. A concurrent skin rash and pleural effusion can support the diagnosis of drug-induced eosinophilic pneumonia. In some cases, testing with lymphocyte proliferation assays may reveal T-cell sensitization to specific drugs. However, the utility of such assays is limited as negative tests do not rule out a drug-induced disorder, and these assays are not widely available for routine clinical use. The prognosis is favorable in most cases. Elimination of exposure to the drug or other toxin usually leads to resolution of symptoms, eosinophilia, pulmonary infiltrates, and normalization of lung function within a month. Supplemental therapy with corticosteroids is not universally required, but it may hasten recovery in patients who are severely ill.

IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA

In contrast to the typically benign Loeffler syndrome, a more severe idiopathic form of eosinophilic pneumonia termed *acute eosinophilic pneumonia* (AEP) has been recognized as a distinct clinical entity.[25–28] Although seen in patients of both genders and any age group, AEP tends to occur in patients between the age of 20 and 40[26,29,30] and is more common in men.[25] AEP is usually idiopathic, occurs commonly in previously healthy persons, and may represent an acute hypersensitivity reaction to an inhaled agent.[28] Similar cases have been reported in persons with a history of chronic myelogenous leukemia, hematopoietic stem cell transplantation[31,32] or HIV infection.[33] Many cases have been reported in patients who have recently commenced smoking,[27,34–36] used flavored tobacco products,[37] or had other changes in smoking habits. The disease may recur when former smokers resume smoking.[35,38] Overall up to 70% of patients with AEP have a history of smoking.[26,39] In addition, cases have been reported in persons treated with venlafexine,[40] minocycline,[26] daptomycin,[11,41] and several other drugs.[26] It has also been reported among persons who have been involved in activities with unusual exposures (including exposure to dust from the World Trade Center collapse in New York City,[14] after military deployment in Iraq,[17] cave exploration, gasoline tank cleaning, plant repotting, woodpile moving, and indoor renovations).[26,42] AEP has also been seen following inhalation of cocaine or heroin[21,43] and in association with H1N1 influenza infection.[1,44] Although none of the patients in the original reported series had atopy or asthma, cases have since been described in persons with a history of atopy. No definite seasonal variation has been identified.

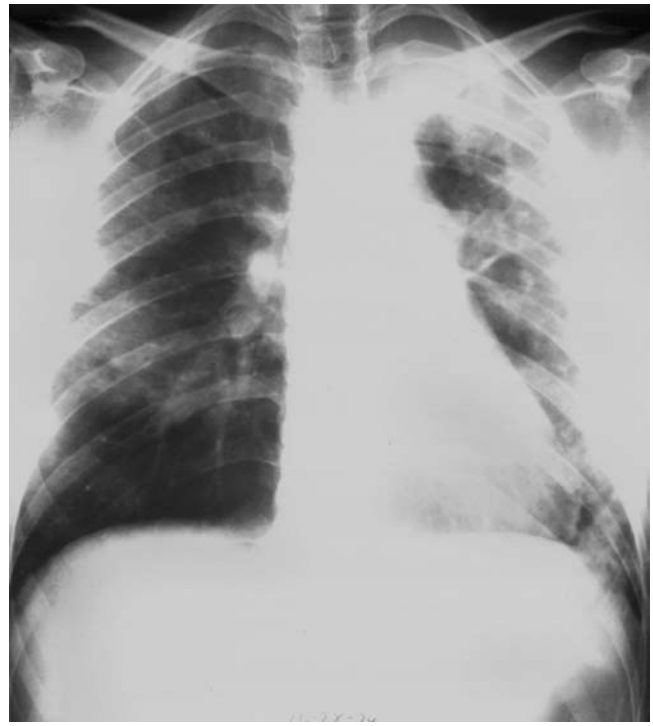


Figure 71-1 Chest radiograph of a 23-year-old woman with acute sulfasalazine-induced eosinophilic pneumonia. Bilateral interstitial and alveolar infiltrates are present.

Idiopathic AEP presents as an acute illness with dyspnea, fever, nonproductive cough, tachypnea, pleuritic chest pain, and hypoxemia (arterial Pa_{O_2} under 60 mm Hg) at times with myalgias.[25,26,39] Symptom duration is typically less than 7 days,[1] although longer courses of up to 30 days have been described. Patients usually have diffuse inspiratory crackles on chest auscultation, wheezing may be present, and rapid progression from mild dyspnea to overt respiratory failure requiring mechanical ventilation is common.[17,26,27] A moderate leukocytosis with left shift is typical,[27] but blood eosinophilia is usually absent at the onset of disease.[17,25,26] Early clinical features may be mistaken for community-acquired pneumonia. Blood eosinophilia may develop later in the course of the disease and may

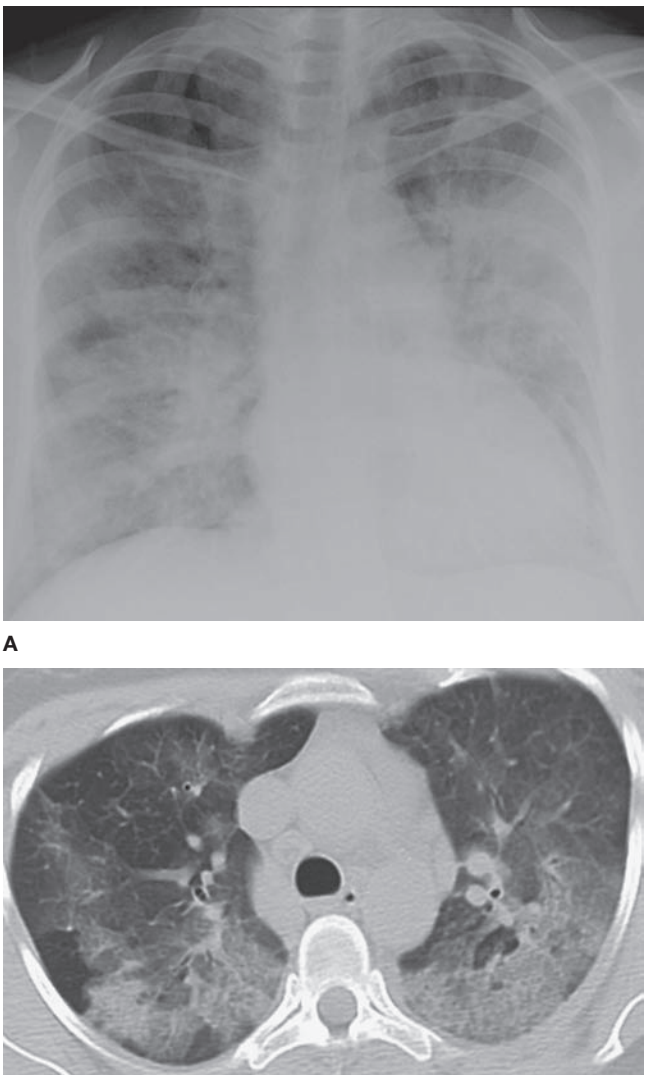


Figure 71-2 Radiographic apœpearance of idiopathic acute eosinophilic pneumonia (AEP). **A.** Diffuse bilateral alveolar and interstitial infiltrates apparent on chest radiograph. **B.** Diffuse parenchymal ground-glass opacity and consolidation evident on computed tomography scan.

provide a clue to the diagnosis.[27,45] Serum IgE levels may be moderately elevated.[26,46] The erythrocyte sedimentation rate (ESR) may be elevated as well. Serum levels of thymus and activation-regulated chemokine (TARC)/CCL17 (a ligand for CCR4 on Th2 lymphocytes) may be elevated and may help to distinguish AEP from other cause of acute lung injury(ALI).[47] Striking eosinophilia (25%–55%) is present in BAL fluid.[17,26,27,45,48] Increased numbers of lymphocytes (up to 20%) and neutrophils (up to 15%) are commonly also present in BAL fluid in AEP.[48] Pulmonary function tests reveal a restrictive ventilatory defect with a reduced D_{LCO} that typically normalize following treatment.[48]

Early in the course of illness, the chest radiograph reveals subtle, patchy infiltrates with Kerley B lines.[26,49] Diffuse, symmetric alveolar and interstitial infiltrates resembling ARDS with a ground-glass or micronodular or reticular appearance (Fig. 71-2A) develop within 48 hours.[50,51] Infiltrates are typically bilateral, although AEP with unilateral infiltrates has been described. Small-to-moderate bilateral pleural effusions are common (affecting up to 50%–70% of patients).[27] Fluid analysis typically reveals a high pH and marked eosinophilia.[51] CT scanning confirms the presence of diffuse parenchymal ground-glass attenuation, inerlobular septal thickening and/or consolidation (Fig. 71-2B), with prominence along bronchovascular bundles, with or without pleural effusion.[49,52] Lymphadenopathy may also be seen.

Light microscopic examination of lung tissue reveals prominent eosinophil infiltration in interstitium and/or alveolar spaces, and bronchial walls.[53] The pathologic pattern of diffuse alveolar damage with hyaline membranes and eosinophilic infiltrates should suggest the possibility of AEP. Lymphocytic infiltration of interstitium, type 2 pneumocyte hyperplasia, and intra-alveolar fibrinous exudate are also common. Granulomas, alveolar hemmorhage, and nonnecrotic perivascular inflammation have been reported.[53] Basal lamina damage is unusual.[49] Extrapulmonary involvement is rare.

The pathogenesis of idiopathic AEP is poorly understood.[26,39] The occurrence of cases following unusual environmental exposures (as noted earlier) suggests these exposures as possible disease-inciting events, perhaps as triggers for a hypersensitivity reaction to an unidentified antigen in susceptible persons. Of note, elevated levels of the fungal cell wall component β-D-glucan have been described in the BAL fluid of some patients with AEP, suggesting a possible association between exposure to fungus and development of disease.

However, the roles of lymphocytes and eosinophils in this disorder have not been fully elucidated. Elevated levels of interleukin (IL)-5, a Th2 lymphocyte–derived cytokine involved in activation and recruitment of eosinophils, have been described in the BAL of patients with AEP.[54] Levels of vascular endothelial growth factor (VEGF), a cytokine induced by IL-5, have also been shown to be elevated in BAL and to correlate with number of eosinophils and levels of IL-5.[55] Elevated BAL levels of IL-18, a cytokine capable of inducing several cytokines known to induce or enhance eosinophilia, have also been identified among patients with acute (and other) forms of eosinophilic pneumonia.[26] Collectively, these findings suggest a role for Th2 lymphocytes and eosinophils in disease pathogenesis. It remains unknown, however, whether the eosinophils initiate the disease process or are a secondary manifestation of the disorder. Alveolar macrophage–derived cytokines may also play a role in the development of AEP.[56]

Idiopathic AEP is a diagnosis of exclusion[51] and should be considered in a patient who presents with an acute febrile illness less than 1 week in duration, apparent ALI or ARDS without a typical antecedent illness. A careful search must be undertaken for other causes of pulmonary infiltrates, especially fungal or other infection, and drug or other exposures. Specimens of blood, sputum, stool, BAL, and often transbronchial biopsy specimens should be obtained for stain and culture as well as serologic testing to rule out viral, bacterial, mycobacterial, fungal, and parasitic infection.[26,39] BAL cell differential should be performed. Elevated blood levels of TARC/CCL17 may distinguish AEP from other causes of ALI, even in the early phase of disease before blood esoinophilia is present.[47] In contrast, levels of KL-6, a marker for alveolar cell damage, tend to be lower in AEP than in other forms of ALI.[47] An elevated fraction of exhaled nitric oxide (FeNO; e.g., levels >23.5 ppb) may also help to distinguish AEP from non-AEP disorders[57] and FeNO levels decreased following corticosteroid treatment. Lower serum IgG levels have also been reported in AEP as compared with other causes of pulmonary eosinophilia.[58]

Idiopathic AEP generally carries an excellent prognosis. Although fatalities have been reported, most patients demonstrate rapid dramatic responses to corticosteroid therapy,[25,26,59] with abatement of fever and respiratory symptoms within 12 to 48 hours and complete resolution of infiltrates, pleural effusion, and pulmonary function impairment usually within 1 month.[27,48] The optimal steroid regimen for the treatment of AEP has not been determined. However, initial doses of methylprednisolone typically used range from 60 to 125 mg administered every 6 hours. After resolution of respiratory failure, oral prednisone (in doses of 40–60 mg per day) may

be continued for 2 to 4 weeks with a subsequent slow taper over the next several weeks.[26,51] Despite the apparent clinical success of steroid treatment, there is no definitive proof that steroids alter the natural history of the disease. Spontaneous disease regression has been reported,[27] and in contrast to idiopathic CEP, absence of clinical relapse is characteristic. Follow-up pulmonary function testing is generally normal, although a small number of patients may demonstrate mild reductions in D_{LCO} or lung volumes.

TROPICAL PULMONARY EOSINOPHILIA

TPE was first described in the early 1940s[60] as a syndrome characterized by fevers, malaise, anorexia, weight loss, paroxysmal dry cough with dyspnea or wheezing, marked peripheral blood eosinophilia, and spontaneous resolution over several weeks' time. In the 1950s and 1960s, filarial infections were recognized as the cause of this disorder.[61] TPE is most prominent in India, Africa, and Southeast Asia, but it may be seen worldwide in filarial-endemic regions.[3,4,62] Disease may also present in nonendemic regions among immigrants or travelers.[62,63] A rare manifestation of parasitic infection, TPE occurs in less than 1% of patients infected with lymphatic filariae (usually introduced by mosquito bite) and results from a hypersensitivity reaction to microfilariae from *Wuchereria bancrofti* and *Brugia malayi*.[5,62,64] Illnesses resembling TPE have also been reported following infection with other parasites. Approximately four times more common in men, most patients with TPE manifest the disease between the age of 25 and 40 years,[4,62] although children and older adults may also be affected. There is no known seasonal or genetic propensity to this disease, and it remains unclear why only such a small percentage of patients with filarial infection develop TPE.

Clinical manifestations of TPE develop months to years after the infection.[4] The most common distinguishing symptom of TPE is spasmodic cough that usually occurs at night.[62] Other typical early symptoms include low-grade fevers, weight loss, fatigue, and malaise. Dyspnea and wheezing, which can be severe, are common, and the clinical presentation may resemble status asthmaticus. Chest pain, muscle tenderness, and cardiac, pericardial, and CNS involvement have also been reported. Rarely, patients remain asymptomatic. Physical examination of patients with TPE is notable for coarse rales or rhonchi and wheezing,[62] although no abnormalities are found in approximately 20% of patients. Generalized lymphadenopathy and hepatosplenomegaly, pericarditis, musculoskeletal or CNS manifestations may be present,[4,62] but they are less common in adults than in children.

Laboratory findings in TPE include extreme peripheral blood eosinophilia[4,5,62] (usually more than 3000 eosinophils per cubic millimeter and up to 90% of the leukocyte differential) that persists for several weeks, although the degree of eosinophilia generally does not correlate well with clinical disease severity or radiographic findings. Blood eosinophils appear degranulated and contain cytoplasmic vacuoles.[62] Total serum IgE is usually elevated (more than 1000 U/mL), and the presence of high titers of filarial-specific IgE and IgG, measured by complement fixation or hemagglutination techniques, confirms the diagnosis.[3,5] Hypergammaglobulinemia results from polyclonal activation of B cells.[4] The ESR, circulating immune complexes, serum IgG, IgM and IgA, and complement (CH50) may be moderately elevated,[4,5] and patients may also have an abnormal electrocardiogram (ECG). Eosinophils may be identified in the sputum,[4,62] and, in those with active disease, BAL typically reveals intense eosinophilia (upto 50% of the differential), elevated levels of total IgE, and filarial-specific IgE, IgM, IgG and fibronectin.[4,5,62] BAL may also contain IgE antibodies to *B. Malayi* BM 23–25 antigen[4,62,65] as well as eosinophil-derived neurotoxin.[5] Pleural fluid, when present, is eosinophilic and also contains elevated IgE.[4] Serum α1-antitrypsin levels are reduced and return to normal with treatment.[4,66] Microfilariae are not found in blood or sputum,[4] and examination of stool or urine for ova and parasites is negative (although patients from endemic countries may be simultaneously infected with other parasites). In contrast, microfilariae have been identified in lung and lymph node tissue, especially when lymphadenopathy is present.

Pulmonary function test findings vary with the duration of disease: They reveal an obstructive ventilatory defect in up to 30% of patients, particularly when symptoms have been present less than 1 month. A restrictive ventilatory defect and reduced D_{LCO}, with or without a concomitant obstructive defect, are typical of long-standing disease.[3–5] Mild arterial hypoxemia may be present.[62] Ill-defined, diffuse reticulonodular infiltrates with a mottled appearance primarily affecting the mid to lower lung fields are characteristic radiographic findings in TPE.[3,4,62] Bronchovascular markings may be prominent and hilar adenopathy and pleural effusions have occasionally been reported.[4,62] The chest radiograph may be normal at the time of presentation in as many as 20% of patients.[62] In rare cases where *Dirofilaria* is the causative agent, the chest radiograph may reveal solitary or multiple nodules thought to represent infarcts caused by parasitic emboli. CT scanning may show mediastinal adenopathy, bronchiectasis, and areas of calcification.[67]

The histopathologic findings in TPE depend on the tissue examined, as well as the stage and duration of the disease.[62] Studies of lung pathology have shown that the early stage of the disease (within the first 2 weeks) is characterized by histiocytic inflammation in the alveolar, interstitial, peribronchial, and perivascular spaces, with preservation of lung architecture.[4] Tiny nodules may be palpable within the lung tissue. One to three months after symptom onset, eosinophilic infiltration with eosinophilic bronchopneumonia and microabscesses is present in lungs of untreated patients. Degenerating microfilariae may be present within the center of the microabscesses, and some destruction of alveolar walls may be evident. Local bronchial walls are also edematous and inflamed, with evidence of epithelial disruption. Long-standing untreated disease is associated with the presence of chronic mixed-cell inflammation (histiocytes, eosinophils, and lymphocytes) in a nodular pattern and the development of pulmonary fibrosis.[4,62] Foreign body–type granulomatous lesions are often present. Lymph node biopsies may reveal degenerating microfilariae or adult worms, surrounded by aggregates of eosinophils, their granule products, and giant cells.

The clinical features of TPE are believed to result from an intense hypersensitivity reaction to microfilarial antigens of *W. bancrofti* and *Brugia malayi*. Although a broad spectrum of clinical disease may be caused by filaria, patients with TPE rarely have other systemic features of filariasis. Canine filarial forms (e.g., *Dirofilaria immitis*) are rarely transmitted to humans but also may be recovered from lung and lymph node specimens. Disease occurs when larvae introduced into the body via insect bites develop into mature filariae.[4] The adult worms, dwelling within the lymphatics, produce microfilariae, which are then trapped in the pulmonary vasculature. The release of antigens from degenerating microfilariae leads to an intense local and systemic inflammatory response. A striking antibody and eosinophilic response, similar to that seen in peripheral blood, is also present within the lung.[4,5,62] Although little is known about the precise mechanisms by which filariae are cleared in patients with TPE, both antibody-dependent mechanisms and eosinophils probably play a role.[4,62] In vitro, both granulocytes and macrophages can bind microfilariae in the presence of IgG, IgE, or complement leading to the death of the organism. The finding of an intense lymphocytic- and plasma-cell infiltrate around microfilariae in tissues suggests that lymphocytes may be important for clearance of the organism. In vitro lymphocyte transformation in response to stimulation with microfilarial antigens can be demonstrated in some cases. The transcription factor NFkB[68]

TABLE 71-4 Diagnostic Criteria for Tropical Pulmonary Eosinophilia

Relevant exposure in endemic area
Paroxysmal nocturnal cough, dyspnea
Infiltrate on chest radiograph
Leukocytosis with eosinophilia
Elevated serum IgE
Elevated serum antifilarial IgE, IgG (*W. bancrofti*, *B. malayi*)
Clinical improvement with diethylcarbamazine treatment

and oxidants[69] are also reported to play an important role in the inflammatory response to TPE. The precise mechanisms by which eosinophils accumulate in the lung and contribute to tissue inflammation in patients with TPE are incompletely understood. Lung (as well as blood) eosinophils appear degranulated by microscopy.[62,70] Elevated levels of eosinophil-derived neurotoxin, an RNase capable of damaging the lung epithelium, have been observed in the BAL fluid of patients with TPE. IgE and eosinophil-, lymphocyte-, mast cell-, or basophil-derived products may contribute to the wheezing and airway hyperresponsiveness that can occur in this disorder.

The diagnosis of TPE is usually established on the basis of the clinical and laboratory findings described earlier including pertinent exposure history. Lung or other tissue biopsies are not typically required. The diagnostic criteria for TPE are summarized in Table 71-4.[62] Biopsy of enlarged lymph nodes (e.g., scalene) may assist in establishing the diagnosis in some cases. A rapid treatment response may provide confirmatory evidence that the correct diagnosis has been made. The differential diagnosis includes Loeffler syndrome, CEP, ABPA, drug reactions, other parasitic infections, HES, and lymphangitic spread of carcinoma. In nonendemic areas, the disease may also masquerade as asthma, atypical pneumonia, sarcoidosis, EGPA, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis, WG), or tuberculosis (TB). Diagnosis in nonendemic regions is often delayed, and a careful review of travel history and a high index of suspicion are necessary to prompt the diagnosis.

Diethylcarbamazine, a piperazine derivative used widely in the treatment of filarial infections, is the therapy of choice for TPE, typically at a dose of 6 mg/kg/d for 14 to 21 days.[4,5,62] Diethylcarbamazine acts by both direct and indirect mechanisms. It is directly filaricidal to both adult worms and microfilariae. It can also enhance the binding of granulocytes, macrophages, antibodies, and complement to the surface of microfilariae. A marked clinical improvement and decrease in eosinophil count usually occurs in the first 7 to 14 days of therapy. Clinical improvement following diethylcarbamazine treatment has been correlated temporally with the resolution of eosinophilic alveolitis. In addition, improvement in pulmonary function, reduction in BAL eosinophilia, a decrease in total and filarial-specific IgE and IgG, increase in serum α1-antitrypsin levels, and radiographic clearing generally occur within 1 to 4 weeks of treatment.[4,62]

The course and prognosis of the acute disease in patients treated with diethylcarbamazine are generally benign, and 3 weeks of diethylcarbamazine therapy is curative in most patients. However, acute relapses related to reinfection or release of microfilaria from existing adult worms do occur in up to 20% of patients.[4] Persons whose α1-antitrypsin levels remain low after initial treatment may be at greater risk of relapse .[4,66] Patients who experience acute relapses often respond to additional treatment with diethylcarbamazine at higher doses of 2 to 4 mg/kg three times a day for 21 to 30 days. Alternatively, mild, chronic inflammation may persist, causing chronic interstitial lung disease, with persistent respiratory symptoms, radiographic findings, and hematologic and serologic abnormalities.[62] Persistent clinical symptoms have been reported over 2- to 5-year follow-up periods in up to 13% of patients with TPE treated with a standard course of therapy. BAL in these patients reveals a mild, persistent eosinophilia. Persons with symptoms of longer duration are less likely to have a favorable treatment response. Alternative antifilarial drugs (e.g., ivermectin) or a trial of corticosteroids may be useful therapies for the chronic variant of the disease,[4,62] although controlled studies of these agents are lacking. A subset of patients with apparent TPE may fail to respond to diethylcarbamazine; whether these patients have diethylcarbamazine-resistant TPE or disease due to other parasites is unclear, as current serologic testing does not distinguish between human lymphatic filarial antigens and antigens on certain other parasites.

Untreated disease usually persists for weeks to months. Untreated TPE may remit spontaneously, but it commonly recurs within months to years. It is important to treat TPE early in the course of the disease, since although seldom fatal, untreated TPE often leads to the development of irreversible pulmonary fibrosis.[63,71]

CHRONIC EOSINOPHILIC PNEUMONIA

CEP was first described as a clinical entity by Carrington et al.[72] in 1969. Although CEP may develop in people of any age, the peak incidence occurs in persons 30 to 45 years of age.[1,73,74] Women are affected approximately twice as often as men, and CEP has been reported during pregnancy and following radiation therapy for breast cancer.[75] The female predominance is less obvious among patients whose disease begins after the age of 60. Most cases occur in Caucasians. Up to two-thirds have adult-onset asthma preceding (by several weeks to years) or arising concurrently with the occurrence of CEP.[1,74,76,77] The asthma is often severe and may lead to fixed airflow obstruction (approximately 10% of patients) despite medical therapy.[76] Most patients with CEP are nonsmokers. In addition, approximately one-third to one-half of patients have antecedent atopy, allergic rhinitis, nasal polyps, or urticaria.[1]

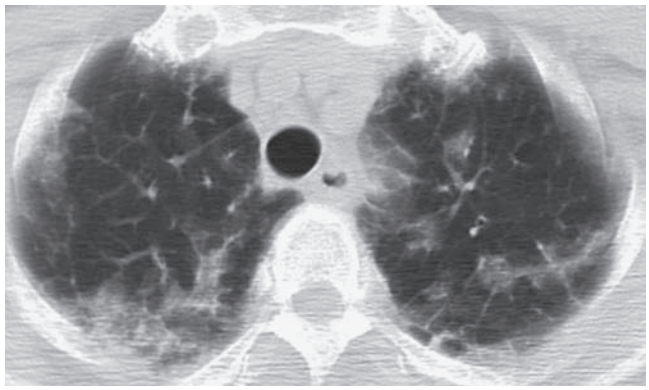
In contrast to idiopathic AEP, CEP typically has a subacute presentation, with symptoms present for weeks to several months before diagnosis.[1,74] Common presenting complaints include dyspnea, low-grade fevers, malaise, drenching night sweats, and moderate (10 to 50 lb) weight loss.[74,77] Cough, often dry initially and later productive of small amounts of mucoid sputum, is a virtually universal finding.[74] Rhinitis or sinusitis may be present. Two of the nine patients described in Carrington's original series had minor hemoptysis. Patients ultimately develop progressive dyspnea, which may be associated with wheezing in those with adult-onset asthma. Very rarely, patients with CEP may also have severe acute respiratory failure or ARDS, with severe hypoxemia requiring mechanical ventilation. There are no major extrapulmonary manifestations of CEP. Rarely, arthralgias, skin rash, diarrhea or colitis, mononeuritis, hepatitis, pericarditis or unexplained heart failure have been described, raising suspicion that there may be a continuum between CEP and EGPA.[74] Indeed, cases have been reported wherein patients initially diagnosed with CEP later developed EGPA.[78,79]

Patients with CEP frequently manifest a moderate leukocytosis. The majority (66%–95%) have peripheral blood eosinophilia (usually $>1000/mm^3$),[74] with eosinophils constituting more than 6%, and typically up to 20% to 30% of their leukocyte differential.[73,80] Leukocyte differentials with up to 90% eosinophils have been noted in this disorder. However, a lack of peripheral blood eosinophilia does not rule out the diagnosis, since eosinophilia may be absent in 10% to 30% of cases.[73,77] Normochromic, normocytic anemia and thrombocytosis may be present. The C-reactive protein levels and the

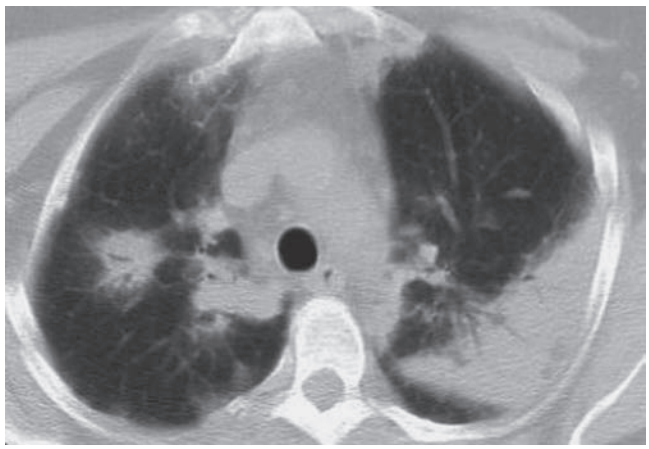
ESR are typically elevated (greater than 20 mm per hour),[74] and IgE levels are elevated in up to one-half of cases. Analysis of BAL fluid reveals increased eosinophils, typically accounting for 40% or more of the white blood cell (WBC) differential, with a range from 12% to 95% reported.[1,74,77,81] Urinary eosinophil-derived neurotoxin levels are also elevated.[82] Blood and sputum cultures routinely fail to identify an infectious etiology in these patients.

The severity of pulmonary function abnormalities depends on the stage and severity of the disease. In the initial stage prior to treatment with corticosteroids, testing may reveal restrictive, obstructive, or normal physiology.[74] Obstructive ventilatory defects, while more common in patients with a history of asthma, are also encountered in patients without pre-existing asthma. Restrictive physiology may result from changes in lung compliance due to acute eosinophilic infiltration of lung parenchyma. Diffusing capacity may be reduced and the alveolar–arterial oxygen gradient may be mildly elevated.[74,77]

In the original series, Carrington et al. described three radiographic features that are characteristic for CEP: (1) peripherally based, progressive dense infiltrates; (2) rapid resolution of infiltrates following corticosteroid treatment, with recurrences in identical locations; and (3) the appearance of infiltrates as the "photographic negative of pulmonary edema."[72,83,84] The pulmonary infiltrates associated with CEP are typically dense and patchy areas of airspace consolidation with ill-defined margins usually affecting the outer two-thirds of the lung fields (Fig. 71-3). Infiltrates are most commonly bilateral, tend to be located in the mid to upper lung zones, and may mimic loculated pleural fluid. They are frequently nonsegmental, subsegmental, or lobar in distribution. The characteristic "photographic negative of pulmonary edema" appearance (which occurs in <50% of cases) results if extensive infiltrates surround major portions of or the entire lung. Pleural effusions and cavitation are rare.[73,85,86] The infiltrates may be migratory in up to 25% of cases. Occasionally, the chest radiograph can be normal.



A



B

Figure 71-3 Radiographic appearance of chronic eosinophilic pneumonia (CEP). Variable computed tomography appearance of infiltrates in two patients with chronic eosinophilic pneumonia. Peripheral upper lobe–predominant infiltrates may have a ground-glass appearance (**A**) or may appear as regions of dense consolidation or nodular opacity (**B**).

Common CT scan findings include ground-glass opacities and areas of consolidation involving the middle and/or upper lung zones in peripheral regions of the lung.[73,87–90] In addition, apparent unilateral or isolated lower lung zone involvement noted on chest radiography may prove to be bilateral and diffuse on CT scanning. Mediastinal adenopathy, which may be evident on conventional chest radiograph, may also be identified on CT scan.[90] Less typical radiographic findings include nodular infiltrates, linear oblique or vertical densities, bronchial wall thickening, pleural effusion, and areas of fibrosis unassociated with anatomic divisions. Findings on CT scan may vary depending on the timing of the CT relative to the onset of symptoms. Typical areas of dense, peripherally located airspace consolidation are found in most cases within the first several weeks of disease onset. Streaky bandlike opacities may appear when symptoms have been present for more than 2 months.

The pulmonary lesions of CEP are characterized histopathologically by varying degrees of leukocytic infiltration of the alveolar airspaces and alveolar septae. These infiltrates are predominantly eosinophilic,[49,72,77] with some associated macrophages, a small-to-moderate number of lymphocytes, occasional plasma cells, multinucleated giant cells, and an associated fibrinous exudate. Unlike AEP, the basal lamina may be disrupted[49] but frank alveolar necrosis is absent. Eosinophilic microabscesses can be found. Focal edema of the capillary endothelium, focal type II epithelial cell hyperplasia, proteinaceous and fibrinous alveolar exudates can also be appreciated. Histologic evidence of proliferative bronchiolitis obliterans or bronchiolitis obliterans–organizing pneumonia may occur in up to one-third of cases, and a mild, nonnecrotizing microangiitis affecting predominantly the small venules may be seen. Biopsy specimens of lymph nodes from patients with intrathoracic lymphadenopathy reveal lymphoid hyperplasia and eosinophil infiltration.

The cause of CEP is unknown. No specific genetic predisposition for the disease has been identified, although CEP has been reported in identical twins, raising the question of a familial tendency toward the disease. An association has been reported between rheumatoid arthritis and CEP[91] but no clear causal relationship has been identified.[92] Although the precise immunopathogenesis of CEP is unknown, evidence suggests that Th2 helper T cells likely have a role in disease pathogenesis. Levels of the cytokines TARC-CCL17 and macrophage-derived cytokine 22 (MDC-22) and macrophage inflammatory protein 1-beta (MIP-1β/CCL14), which help recruit Th2 T cells are increased in CEP.[74,84] Increased levels of the T-cell–derived eosinophil chemoattractant cytokines IL-5, eotaxin, and RANTES (CCL-5) are also elevated in BAL fluid of patients with CEP.[74] Thus Th2 cells likely recruit and attract eosinophils to the lung.[84] The number of regulatory (CD4+CD25+) T-cells is also increased in peripheral blood and BAL in CEP.[93] The potential role of blood and lung tissue lymphocytes in the pathogenesis of CEP requires further study.

Several lines of evidence suggest that eosinophils also play a primary pathogenetic role in the pulmonary tissue damage seen in this disorder. Increased numbers of eosinophils appear in the peripheral blood and bone marrow before the onset of clinical disease, and eosinophilia is the predominant abnormality in BAL fluid. These eosinophils appear to be activated, since they show evidence of degranulation on electron microscopy,[94] eosinophil-derived granule proteins (EDGPs) have been identified microscopically within the

pulmonary parenchyma and microvasculature, increased concentrations of EDGP are identified in BAL fluid from patients with CEP compared to controls, and BAL-derived eosinophils express activation markers including class II major histocompatibility (MHC) antigens.[95] Also, eosinophil-derived neurotoxin[82] and leukotriene E4[96] are identified in the urine of patients with CEP, and inducible nitric oxide synthase (iNOS) is expressed on lung eosinophils.[97] The processes that regulate eosinophil activation and degranulation in CEP are not clear. Evidence showing that class II MHC and other activation markers are expressed by BAL- but not blood-derived eosinophils suggests the presence of an immune inflammatory response compartmentalized within the lung. Data also suggest that eosinophils from the BAL fluid are more resistant to apoptosis than peripheral blood eosinophils in subjects with CEP.[98]

Of interest are the findings that immunoglobulins can augment eosinophil chemotaxis and degranulation in vitro, and that circulating immune complexes and elevated titers of IgE are noted in the context of clinical flares of the disease. To date, however, no clear causal relationship has been established between immunoglobulins and eosinophil activation in CEP. An association between CEP and diffuse pulmonary neuroendocrine cell hyperplasia has also been reported.[99]

The diagnosis of CEP is based on the presence of compatible clinical, radiographic, and BAL findings, and on the inability to document pulmonary or systemic infection or other known causes of eosinophilic lung disease. The clinical signs and symptoms of CEP are nonspecific, however, and blood eosinophilia and typical radiographic features may be absent in some cases. In most reported series, open lung biopsy has been required only rarely to establish the diagnosis. Transbronchial biopsy, usually performed to rule out other diagnostic entities, may reveal eosinophil and mononuclear cell infiltrates. Because of the rapid and dramatic responsiveness of CEP to steroid treatment, a therapeutic trial of steroids is often useful in establishing the diagnosis. Failure to document rapid clinical improvement should alert the clinician to consider other diagnoses. The differential diagnosis of CEP includes drug-induced eosinophilic pneumonia, infection (especially TB, fungal diseases such as cryptococcosis and parasitic disease), sarcoidosis, Loeffler syndrome, desquamative interstitial pneumonitis, cryptogenic organizing pneumonia, ABPA, chronic hypersensitivity pneumonitis, acute idiopathic eosinophilic pneumonia, EGPA, and eosinophilic granuloma.

CEP rarely resolves without therapy and if left untreated may result in pulmonary fibrosis.[100] Corticosteroids are the mainstay of therapy for CEP. Dramatic clinical, radiographic, and physiologic improvements have been documented following steroid treatment in all series reported.[1,74,87] Even patients presenting with severe respiratory failure may respond well to steroid treatment. In most cases, treatment with steroids leads to defervescence within 6 hours, reduced dyspnea, cough, and blood eosinophilia within 24 to 48 hours, resolution of hypoxia in 2 to 3 days, radiographic improvement within 1 to 2 weeks, complete resolution of symptoms within 2 to 3 weeks, and normalization of the chest radiograph within 2 months.[1,73,77] No comparative studies exist to determine optimum treatment doses or duration of steroids, but one recommended regimen is prednisone 0.5 mg/kg/d (40–60 mg a day) continued until 2 weeks after resolution of symptoms and radiographic abnormalities, generally for 4 to 6 weeks. The dose of prednisone can then be tapered slowly by 0.25 mg/kg/d and then continued for the subsequent 8 weeks. Treatment is usually maintained for at least 3 months and optimally for 6 to 9 months; during this phase prednisone dosing can be decreased by 5 mg every 4 weeks. Shorter courses of prednisone may also be effective.[74]

The prognosis of CEP is generally favorable.[101] In steroid-treated patients, morbidity and mortality directly related to CEP are low. Patients may require 1 to 3 years of initial steroid treatment to control the disease,[1] and up to 50% may require long-term maintenance treatment (2.5–10 mg prednisone a day) to remain disease-free.[74] The lowest possible dose of steroid that suppresses disease activity should be used. Some patients may respond to high doses (e.g., 1000–1500 µg/24 h) of inhaled corticosteroids, allowing discontinuation of oral steroids, although inhaled steroids alone as initial therapy are inadequate.

Clinical, hematologic, or radiographic evidence of relapses are common, occurring in 50% to 80% of cases when steroids are tapered or discontinued.[1,73,74,77] Relapses may involve radiographic infiltrates in the same or different anatomic distribution compared to the original disease. Relapsing CEP must be distinguished from the development of new or worsening asthma. No obvious factors exist to identify persons who are likely to relapse or require long-term steroids, although relapses are more common in persons treated initially with a short course (<6 months) of steroids. Regular long-term treatment of patients with CEP and asthma with inhaled corticosteroids may reduce the risk of CEP relapses.[76] Multiple recurrences may occur in anyone. Relapses should be managed by increasing the prednisone dose to ≥40 mg per day until 2 weeks after symptom control has been achieved, with gradual taper thereafter. The reinstitution of steroids generally leads to improvement, and relapses do not appear to indicate a worse prognosis, increased likelihood of treatment failure, or increased morbidity. The anti–IL-5 monoclonal antibody omalizumab has also been used successfully as a steroid-sparing agent in the treatment of CEP.[102]

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (MYCOSIS)

ABPA is a disorder caused by a complex hypersensitivity response to inhaled fungal antigens.[103–110] Since the disease is most commonly induced by *Aspergillus* species, it is usually known as ABPA. When induced by non-*Aspergillus* species, the syndrome is called allergic bronchopulmonary mycosis. A comprehensive discussion of ABPA is provided in Chapter 48. Highlights of the disorder are discussed here.

ABPA occurs most commonly in immunocompetent patients and complicates 1% to 2% of cases of persistent asthma and 7% to 14% of cases of chronic steroid-dependent asthma,[111] most often among patients in their third to fourth decade. It also complicates up to 15% of patients with cystic fibrosis (CF), most often during the teen years.[105,112] Rare cases lacking a history of asthma but meeting the other major diagnostic criteria (summarized in Table 71-5) have

TABLE 71-5 Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

Major[a]
Asthma (ABPA is also common in persons with cystic fibrosis)
Positive immediate hypersensitivity skin-prick test to *Aspergillus*
Precipitating antibodies against *Aspergillus*
Elevated total IgE
Elevated serum *Aspergillus*–specific IgE, IgG
History of pulmonary infiltrates
Peripheral blood eosinophilia
± Central bronchiectasis
Minor
Expectoration of thick brown mucus plugs
Aspergillus in sputum
Dual cutaneous reaction to *Aspergillus*

[a]*The presence of 6 of eight major criteria strongly suggests the diagnosis.*

been reported.[113] The diagnosis of ABPA is based on appropriate clinical features in combination with supporting serologic and radiologic findings.[104]

Patterson and Greenberger[114] proposed five minimal essential criteria needed to establish the diagnosis, including (1) asthma, (2) positive immediate hypersensitivity skin test to *Aspergillus,* (3) total IgE greater than 1000 ng/mL (or >417 IU/mL), (4) elevated serum anti-AF IgE and IgG (more than twofold greater than for asthmatic controls), and (5) serum precipitins to *Aspergillus fumigatus* (AF) or other relevant fungus. These features, as well as a history of current or previous pulmonary infiltrates and/or central bronchiectasis evident on high-resolution CT scan (HRCT) and peripheral blood eosinophils (~10,000 cells/mL), comprise the major diagnostic criteria of ABPA.[103,106,115–118] Expectoration of brown mucus plugs, identification of *Aspergillus* (or other relevant fungus) in the sputum, and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* are also common clinical features of ABPA.

Five clinical stages of ABPA have been recognized: acute illness (stage 1); remission (stage II); exacerbation (stage III); steroid-dependent asthma (stage IV); and fibrotic lung disease (stage V).[104,105,114] The clinical features of these stages are shown in Table 71-6. Two variants of ABPA have been recognized: seropositive ABPA (ABPA-S), wherein the preceding essential criteria are met and there is no evidence of central bronchiectasis; and ABPA with central bronchiectasis (ABPA-CB), wherein the above criteria are met and CB is present.[105,119] It is unclear whether ABPA-S is an earlier stage of disease that precedes ABPA-CB or whether it is perhaps a milder form of the disease.

TABLE 71-6 Clinical Stages of Allergic Bronchopulmonary Aspergillosis

Stage I: Acute
Acute asthma symptoms ± constitutional symptoms
Elevated serum IgE (typically >1000 ng/mL)
Elevated *Aspergillus*-specific IgE and IgG
Infiltrate on chest radiograph
Peripheral blood eosinophilia
Immediate skin reactivity to *Aspergillus*
Positive precipitating antibodies to *Aspergillus fumigatus*
Stage II: Remission
Resolution of symptoms (concurrent decrease in total IgE needed to confirm remission)
Radiographic clearing
Reduction or stabilization of IgE levels (normalization rare)
Stage III: Exacerbation
Recurrence of elevated IgE levels (greater than twofold over baseline)
± Development of a new pulmonary infiltrate on chest radiograph
± Escalation of asthma symptoms
Stage IV: Steroid-dependent Asthma
Difficult to control, steroid-dependent asthma
Persistently elevated total IgE, *Aspergillus* precipitins and *Aspergillus*-specific IgE and IgG despite corticosteroid therapy
± Transient infiltrates and/or bronchiectasis on chest radiograph or CT
Stage V: Fibrotic lung disease
Persistent steroid-dependent asthma
Fibrotic lung disease with gas exchange disturbances
Chronic sputum production and frequent infections common

Typical radiographic manifestations of ABPA include transient, irregular pulmonary infiltrates with a predilection for the upper lobes (Fig. 71-4).[88,120] Other common radiographic features include "finger-in-glove opacities," "tramline shadows," "parallel lines," "toothpaste shadows," "ring shadows," and lobar consolidation (Fig. 71-4). These findings result from bronchial and bronchiolar wall inflammation, edema, and remodeling, and from mucoid impaction of the bronchi with or without parenchymal involvement. As noted, central (proximal) bronchiectasis, another characteristic radiographic manifestation of ABPA, occurs in many, although not all, patients. The presence of high attenuation mucus on HRCT may be a marker for disease severity.[121] ABPA is not typically diagnosed by tissue sampling. Nevertheless, histopathologic findings of ABPA include intense bronchocentric inflammation with eosinophils, lymphocytes, plasma cells, and monocytes, bronchocentric granulomatosis, as well as mucoid impaction of bronchi.[112,116] Fungal hyphae are typically present in mucus plugs without bronchial tissue invasion. The histologic findings may vary in differing parts of the lung and in different stages of the disease.

The features of ABPA are believed to result from a complex immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal species) that includes features of type I, type III, and type IV immune responses.[104] T-helper lymphocytes, neutrophils, eosinophils, genetic susceptibility factors, and the fungus itself all also likely contribute to the pathogenesis of the disease.[103,122]

Typical symptoms include wheeze, cough, dyspnea, and sputum production, at times with expectoration of brownish/black mucus plugs. Other symptoms may include malaise, myalgias, low-grade fever, chest pain, weight loss, or hemoptysis. Respiratory symptoms may at times be absent despite serologic and radiologic evidence of active disease. The diagnosis of ABPA should be considered in any patient with asthma or CF who experiences frequent and/or recurrent exacerbations of respiratory symptoms, and/or the combination of asthma and eosinophilia. Worsening of lung function and/or steroid dependence or failure to improve clinically following antibiotic therapy for a suspected bacterial infection may also suggest the diagnosis in patients with CF.[112,123] The differential diagnosis of ABPA is broad, and in addition to other pulmonary eosinophilic disorders, includes asthma with fungal sensitization without ABPA, refractory asthma without fungal sensitization, aspergillus bronchitis, and other nonfungal infectious bronchitis or pneumonia. ABPA often goes unrecognized, due to overlap of clinical features with these disorders. ABPA may also be challenging to recognize due to the varying clinical presentations at different stages of disease.

Goals of treatment are to control symptoms, preserve normal lung function, and prevent exacerbations and disease progression. Early recognition and aggressive treatment are essential to prevent development of permanent airway remodeling, bronchiectasis, and pulmonary fibrosis.[105] Systemic corticosteroids, with careful patient monitoring of clinical symptoms, IgE levels, and chest radiograph, are the mainstay of therapy.[124–126] Corticosteroid doses that reduce IgE levels by at least half of acute stage levels within 6 to 8 weeks and induce clearing of radiographic infiltrates must be used to control the disease. These doses are typically higher than those needed to control symptoms alone.

The recommended initial prednisone dose is 0.5 mg/kg/d for 2 weeks followed by every other day dosing for 6 to 12 weeks, followed by a gradual taper of 5 to 10 mg every 2 weeks over 3 to 6 months.[105] Children with CF may require higher doses and/or longer duration of treatment. Total serum IgE levels should be measured at the time of diagnosis, at 4 and 8 weeks, and every 2 months thereafter for 1 year.

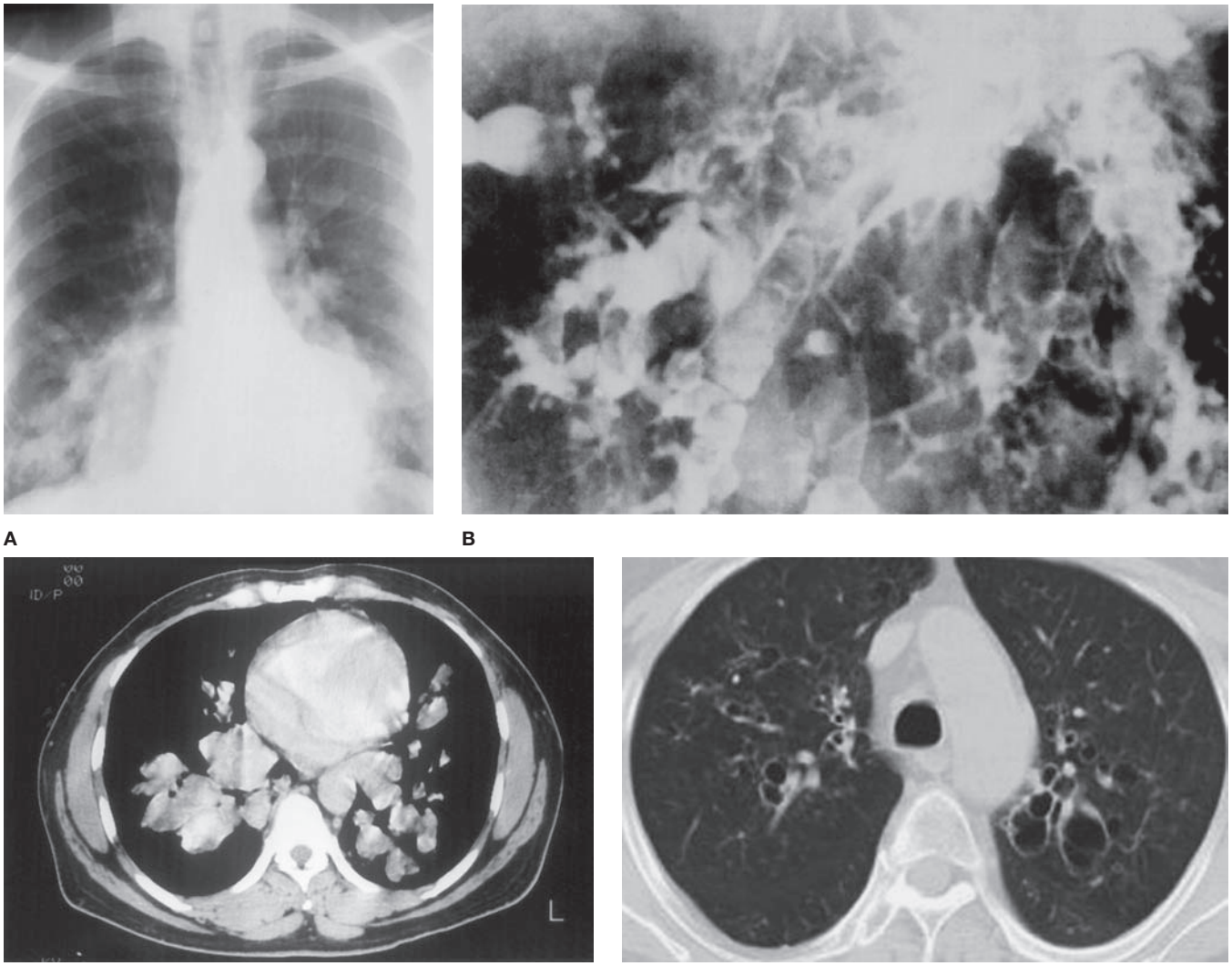


Figure 71-4 Radiographic appearance of allergic bronchopulmonary aspergillosis (ABPA). Extensive infiltrates with tubular configuration and "gloved finger" appearance are present, in this case predominantly in the lower lobes (**A**), the bronchogram (**B**), and computed tomography (CT) of the chest (**C**) reveal extensive proximal bronchiectasis. Extensive mucoid impaction of the bronchi is evident on CT scan (**C**). Central bronchiectasis and tram-track shadows in a patient with ABPA may also be present without mucoid impaction (**D**).

Treatment with the antifungal agent itraconazole can also help control the symptoms and immunologic features and exacerbations of the disease[127–129] and may enable reduction of the systemic corticosteroid dose.[130,131] Voriconazole may be a suitable alernate antifungal agent.[132,133] In case series, the anti-IgE antibody omalizumab has helped to control the disease in steroid-dependent patients with ABPA who have failed itraconazole treatment.[134–137] Bronchodilators and antibiotics help control bronchospasm and secondary respiratory infections. Inhaled corticosteroids alone are inadequate to prevent or treat acute episodes of ABPA. Yearly spirometry should be performed and patients should be monitored for concurrent gastroesophageal reflux, rhinosinusitis, or environmental mold exposures.[105]

CHURG–STRAUSS SYNDROME (EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS)

In 1939, Rackemann and Greene reported a subgroup of patients with polyarteritis nodosa and concomitant allergic disease. Similar findings were reported in the early 1940s by Harkavy. The histopathology and clinical features associated with this disease entity were first described in 1951 by Churg and Strauss, who reported a form of necrotizing vasculitis in several organs, associated with eosinophilic tissue inflammation and extravascular granulomas, occurring in asthmatics, with associated fever and peripheral hypereosinophilia (Churg–Strauss syndrome).[138] This disease entity, now termed eosinophilic granulomatosis with polyangiitis (EGPA), is an uncommon systemic disease.[139–141] An overall prevalence of 10.7 to 13 cases per million inhabitants is estimated among the general population,[142] and up to 64 cases per million persons per year is estimated among patients with a history of asthma. The mean annual incidence has been estimated at 0.5 to 6.8 per million population across various countries.[142]

Approximately 10% of all patients with vasculitis prove ultimately to have EGPA (see also Chapter 74). Nevertheless, the precise incidence of EGPA is unknown due to uncertainties regarding diagnosis and variable clinical presentation. The true incidence of EGPA may be higher than is generally recognized, since the syndrome has many clinical, radiographic, and histologic features in common with other vasculitic, eosinophilic, and granulomatous disease states. The diagnosis of EGPA may be missed if not carefully entertained.

EGPA may occur in patients of any age, but it develops most commonly in patients between the ages of 38 and 50.[1,143,144] It is rare

in persons older than age 65, as well as children and adolescents. However, among affected children, it tends to follow a more aggressive clinical course.[145] There is no clear gender predominance.[142,144] Among women, disease onset has been reported during pregnancy. The MHC complex DRB4 allele may confer genetic risk for the disease.[146,147]

EGPA tends to follow a subacute course, with symptoms ranging over months to years. Historically, three distinct clinical phases of the disease have been recognized: the prodromal phase, the eosinophilic phase, and the vasculitic phase.[148,149] The *prodromal phase* has been characterized by "late-onset" (in the second or third decade) allergic rhinitis and atopy in persons often lacking a family history of atopy. Severe allergic rhinitis, sinusitis, and drug sensitivity are usually present for 8 to 10 years, and up to 30 years before EGPA disease recognition. Asthma is a feature of EGPA in all cases. It typically precedes the onset of vasculitis by 3 to 6 years.[148] The *eosinophilic phase* is typified by the development of marked peripheral blood eosinophilia and eosinophilic tissue infiltration, most commonly of the lung, GI tract, and skin. The *vasculitic phase* is characterized by vasculitis of the small and medium vessels with vascular and extravascular granulomas. The onset of the vasculitic phase is often heralded by development of constitutional symptoms, including fever, malaise, weight loss, arthralgias, myalgias, and increased allergic or asthmatic symptoms. Although the vasculitis tends to occur several years after the onset of allergic manifestations of the disease, in some cases it develops within months of, or concomitant with, the onset of asthma. A short duration between the onset of asthma and vasculitis has been associated with increased severity of vasculitis. During the vasculitic stage, the asthma symptoms may persist and worsen, or they may diminish. When asthma dissipates, it often flares later in the course of illness and may require prolonged steroid treatment. Importantly, not all patients progress sequentially through these phases, and overlap of clinical features between phases is often present. Although EGPA typically affects multiple organ systems, limited forms of disease have also been described.[142,150] Manifestations in the lungs, heart, skin, and nervous system are most common.

Lung involvement occurs in nearly all patients with EGPA.[142] Most of the respiratory manifestations of EGPA occur in the prodromal and eosinophilic phases of the disease. As noted earlier, all patients have asthma at some point in the illness. Upper airway allergic disease, including sinusitis, rhinitis, and polyposis, is seen in 75% to 85% of patients and may be the presenting symptom.[1,142] Unlike granulomatosis with polyangiitis, necrotizing granulomas involving the upper airway are unusual in EGPA. The asthma and upper airway disease usually are long-standing, severe, and often require steroid therapy (systemic or inhaled) to maintain control of symptoms.[142] Spirometry may reveal an obstructive ventilatory defect.[151] A Loeffler-like syndrome with eosinophilic infiltration of the lung parenchyma is seen in 50% to 70% of patients. These patients may develop dyspnea, cough, and wheezing. Their chest radiographs have transient, migratory, patchy, nonlobar, nonsegmental, often peripheral pulmonary infiltrates, with no regional predilection.[152–154] Nodular lesions, reticular opacities, bronchial wall thickening, bronchiectasis, and hilar adenopathy are less common findings. In contrast to granulomatosis with polyangiitis, the allergic granulomas cavitate more rarely. Up to 50% of patients develop unilateral or bilateral pleural effusions,[154] which may be associated with pleuritic chest pain. The chest radiograph may occasionally be normal. HRCT scanning has demonstrated bronchial wall thickening, pulmonary artery enlargement (in comparison to the corresponding bronchi), irregular stellate configuration of some vessels, adenopathy, areas of interlobular septal thickening, and scattered patchy parenchymal opacities with ground-glass, nodular, consolidated, or tree-in bud appearance.[1] Nodules may be present within areas of ground glass.[90,154,155] These findings have been reported to correlate with pathologic findings evident on open lung biopsy such as eosinophilic pneumonia, alveolar hemorrhage, eosinophilic infiltration of the bronchial wall, and septum.[153] Further studies are necessary to determine whether high-resolution CT is useful to stage the disease or establish the diagnosis without tissue biopsy.

Cardiac manifestations generally are not evident on initial presentation of EGPA. However, they typically occur during the vasculitic phase of the disease and are a major source of morbidity and the principal cause of death (in up to 50% of cases) from the disorder.[142,143,156] Patients may be asymptomatic. Progressive congestive heart failure (CHF) occurs in up to 47% of cases because of endomyocardial infiltration by eosinophils[1,157] or ischemic cardiomyopathy resulting from necrotizing vasculitis of the coronary arteries.[158] This coronary vasculitis is fatal up to 60% of the time. Acute pericarditis is present in approximately one-third of cases, and cardiac tamponade has been reported. Constrictive pericarditis may develop over time. Cardiac involvement is more common in persons with EGPA who lack serum ANCA (see below).[159,160]

A wide array of neurologic manifestations may develop in EGPA. Mono- or polyneuropathy (most notably mononeuritis multiplex) is present in 69% to 75% of cases. The common peroneal, ulnar, and internal popliteal nerves are most frequently affected.[142] CNS manifestations occur more rarely and include cranial nerve impairment (especially optic neuritis), seizure, subarachnoid hemorrhage, and cerebral infarction. Skin, GI, renal, and other systemic alterations have been well described in EGPA. Skin findings are present in 40% to 70% of cases and may develop in localized crops. They can manifest as nonthrombocytopenic purpura (particularly on the lower extremities), urticaria, a maculopapular rash, petechiae, ecchymoses, or livedo reticularis. Skin biopsies typically demonstrate eosinophilic infiltration and leukocytoclastic vasculitis.[161] Tender cutaneous or subcutaneous nodules (which may ulcerate) containing extravascular granulomas may preferentially involve the fingers, scalp, and extensor surface of the elbow.[142] GI manifestations of EGPA are present in up to 60% of cases. They can include eosinophilic gastroenteritis or vasculitis that can lead to diarrhea, abdominal pain, intestinal obstruction, cholecystitis, pancreatitis, bleeding, liver function test abnormalities, and bowel perforation.[142] GI disease also carries a poor prognosis[142] and is the second leading cause of death in patients with EGPA. A degree of renal insufficiency occurs in 25% to 50% of patients with EGPA. Eosinophilic interstitial nephritis with necrotizing features is the most common histopathologic finding, but focal segmental glomerulosclerosis, hematuria, and proteinuria also occur.[143,162,163] Severe, difficult-to-control hypertension is also a major sequela of EGPA (in 25%–75% of cases) and may be due to recurrent renal infarction. In contrast to granulomatosis with polyangiitis, overt renal failure is not commonly seen in EGPA.[143] Mild lymphadenopathy (in 30%–40%), rheumatologic manifestations (migratory polyarthralgias, myalgias, temporal arteritis), urologic disease (ureteral, urethral, prostatic), and ocular manifestations (scleritis, uveitis, optic neuropathy, conjunctival nodules)[142] have also been described.

The diagnosis of EGPA is based on clinical features with corroborating laboratory and/or histologic findings. There is no single laboratory test specific for a diagnosis of EGPA. A majority of patients with EGPA have a striking but fluctuating degree of peripheral blood eosinophilia (mean values between 5 and 20,000/mm^3; 20% to 90% of the WBC differential) at diagnosis,[1,142] generally greater than that seen with asthma alone. The

degree of eosinophilia tends to parallel the vasculitis activity[1] and may be suppressed by corticosteroid treatment of asthma. Serum C-reactive protein levels and total IgE levels are elevated (range, 500–1000 U/mL) in 75% of patients. Elevated exhaled breath condensate and BAL fluid concentrations of the eicosanoid 12-HETE can help distinguish EGPA from asthma without EGPA.[164] Elevated blood levels of the Th2 T lymphocyte cytokines IL-4, IL-5, and IL-13[165] as well as serum IgG4,[166] TARC/CCL17,[167] urinary eosinophil–derived neurotoxin,[168] and serum eotaxin-3 levels[169,170] also correlate with disease activity. BAL fluid of patients with active EGPA also contains increased levels of the Th2 cytokines IL-4, IL-5, and IL-10 as compared with inactive EGPA.[171,172] Most patients have a normochromic, normocytic anemia, and moderate elevation of their ESR. Rheumatoid factor titers may be positive, but antinuclear antibodies are usually negative.[142] Hypergammaglobulinemia and circulating immune complexes may also be seen.

Approximately 40% to 60% of patients have positive antinuclear cytoplasmic antibody with a perinuclear staining pattern (pANCA).[159,160,173] The majority of these are directed against myeloperoxidase (MPO-ANCA) and a minority against proteinase 3 (PR3-ANCA). The absence of ANCA does not exclude the diagnosis. Indeed, recent case series suggest that persons positive for ANCA have different clinical features than those without.[174] Persons with positive ANCA (the "vasculitic phenotype") tend to manifest evidence of biopsy-proven vasculitis, purpura, ENT manifestations, peripheral neuropathy, and renal disease but have less cardiac involvement.[159,160,175] In contrast, those without ANCA (the "eosinophilic tissue infiltration phenotype") manifest predominantly with fever, eosinophilic pneumonia, and eosinophilic myocarditis.[159,160,176]

Laboratory examination of pleural fluid, if present, reveals an eosinophil-predominant exudate with low glucose levels.[142] Pleural biopsy shows chronic pleuritis with eosinophilic infiltration. BAL reveals an increased percentage of eosinophils,[177] the magnitude of which is generally less than that seen with CEP or idiopathic HES. However, patients have been described whose BAL fluid leukocyte differential contained 81% eosinophils. Electrocardiogram, echocardiography, N-terminal pro-brain natriuretic peptide and tropinin-1 levels, and/or cardiac MRI are recommended to evaluate patients with suspected EGPA for the presence of cardiac involvement.[142,178,179] ^{18}FDG/^{13}N ammonia positron emission tomography (PET) imaging may also be useful to identify cardiac involvement in EGPA. Magnetic resonance imaging may show T2-weighted signals in subcortical matter suggestive of CNS vasculitis.[142]

Although lung biopsy is rarely required for diagnosis, the histopathologic hallmarks of EGPA vary depending on the stage of illness but include tissue (interstitial, blood vessel, and alveolar) infiltration by eosinophils, eosinophilic necrotizing giant cell vasculitis of small arteries, arterioles, and, to a lesser extent, small veins, venules, and capillaries and perivascular and interstitial eosinophilic granulomas (typically microscopic).[180–182] Both pulmonary and systemic vessels may be affected. The precise histopathology of vascular impairment depends on the stage of the lesion. Early lesions demonstrate eosinophilic infiltration of the vessels and perivascular region (Fig. 71-5). Later lesions are characterized by necrotizing arteritis or vessel obliteration and scarring. The extent of vascular impairment varies from mild, eosinophilic perivascular cuffing to severe transmural inflammation with necrotization. Lesions may be sparse or widespread. In the lung the allergic granulomas may have central necrosis with eosinophilic infammation, may involve interlobular septae and extend along the pleura. Diffuse capillaritis and alveolar hemmorhage has been reported. Eosinophilic lymphadenopathy may also be present. Biopsies of skin, nerve, or muscle may also confirm the diagnosis.[156]

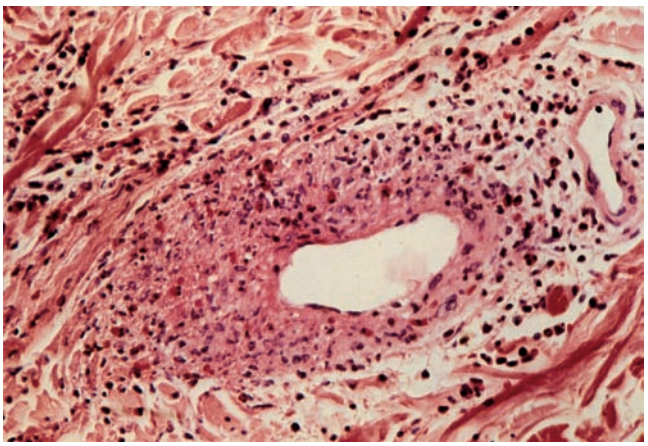


Figure 71-5 Pathologic appearance of small arteriole in Churg–Strauss vasculitis. Intense perivascular inflammation with eosinophilia is present.

The pathogenesis of EGPA remains poorly understood. A possible pathogenic role of antineutrophil cytoplasmic antibody (ANCA) is suggested by the finding of ANCA in 40% to 60% of patients with EGPA.[144] ANCA may contribute to tissue inflammation and injury by activation of inflammatory cells, release of proteolytic enzymes, and generation of oxidative stress[142] but its presence may be a consequence rather than a cause of the tissue injury. As noted previously, the clinical features of EGPA differ between persons with versus without ANCA.[159,160] The strong association with allergy, atopy, eosinophilia, and elevated blood levels of Th2 T lymphocyte-derived cytokines and IgE (especially during the vasculitic phase of the disease) has raised the likelihood of augmented Th2 immunity.[142,172,183–185]

Reductions in T regulatory cells[183,186] and augmented Th1 immunity[187] have also been demonstrated. Eosinophils likely also contribute significantly to the tissue injury[188] since blood, BAL, and urine specimens contain eosinophil-derived cytotoxic granule proteins.[142] Based on these collective findings, it has been proposed that repeated antigenic stimulation in patients with a heightened T-cell and eosinophil response may be important in the development of the disorder. Heightened humoral immunity with immune complex disease may also play a role. Genetic factors including polymorphisms in the IL-10 gene[189] and HLA-DRB107 and HLA-DRB4[146] may be important in predilection to develop EGPA.

The relationship between the pathophysiology of asthma in EGPA to that of asthma without EGPA also remains uncertain. CEP with asthma may precede EGPA in up to 50% of cases. A decrease in the number of blood regulatory T cells (Treg) occurs in persons who develop EGPA following CEP, but not in those with CEP who do not later develop EGPA or in persons with asthma without EGPA.[186,190] This suggests that maintenance of normal numbers of Treg cells may protect against the development of EGPA. Also, a strong association has been noted between the use of leukotriene receptor antagonists (LTRA) and 5-lipoxygenase inhibitors,[172,191–194] as well as other asthma therapies including inhaled glucocorticoids[195,196] and omalizumab[197] and the development of EGPA. These findings raise question as to whether these agents may serve as triggers for the disease. The appearance of EGPA following reduction in systemic corticosteroid dosing in many of these reports raises the likelihood that pre-existing, underlying EGPA that was being treated with corticosteroids is unmasked by the administration of these agents and the reduction in corticosteroid dose. Thus, it remains uncertain whether any of these agents may be causally related to the onset of EGPA. Patients with steroid-dependent asthma, in whom the diagnosis of EGPA has not been demonstrated or entertained, should be monitored closely for evidence of EGPA when steroid doses are

tapered, or when symptoms escalate despite systemic corticosteroid treatment and require intensification of medical therapy. EGPA has also been reported following inhalational use of cocaine,[198] following exposure to other medications, birds, vaccinations, and various infectious pathogens.[13,142]

The diagnosis of EGPA is generally based on clinical features. Various diagnostic criteria have been reported.[148,182] In 1990, the American College of Rheumatology published diagnostic criteria for EGPA,[182] based on assessments of the sensitivity and specificity of the diagnostic criteria used previously. The presence of at least four out of six of the following criteria yielded 85% sensitivity and 99.7% specificity in establishing the diagnosis: (1) asthma, (2) peripheral eosinophilia greater than 10%, (3) mono- or polyarthropathy, (4) migratory or transient pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) extravascular eosinophils in a blood vessel on a biopsy specimen. The presence of asthma or allergy as well as more than 10% eosinophilia was 95% sensitive and 99% specific in distinguishing EGPA among a subgroup of patients with well-documented systemic vasculitis. Subsequently, the Chapel Hill Consensus Conference recommended that diagnostic criteria for EGPA include[1] appropriate clinical setting and histopathology and[2] eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small and medium vessels with associated asthma and eosinophilia.[199] However, these criteria require tissue biopsy and are less sensitive for EGPA than others that have been proposed; hence, they may be less useful to assist diagnosis in the routine clinical setting. Open lung biopsy is the gold standard for tissue biopsy but is rarely necessary. Transbronchial biopsy may reveal the diagnosis if there is alveolar involvement, but is often nondiagnostic. Biopsy of other sites (e.g., skin, pericardium, muscle, nerve, gut), with or without immunostaining, may assist in establishing the diagnosis in selected cases, although demonstration of characteristic histopathologic changes are not essential for establishing the diagnosis. The diagnosis may be elusive since EGPA may be suppressed by corticosteroid treatment for asthma.

The differential diagnosis of EGPA includes polyarteritis nodosa, microscopic angiitis, granulomatosis with polyangiitis, CEP, ABPA, idiopathic HES, Loeffler syndrome, asthma, fungal or parasitic infection, drug-induced vasculitis, sarcoidosis, and Hodgkin lymphoma. EGPA can be distinguished from granulomatosis with polyangiitis since compared with the latter, patients with EGPA have nasal polyps and allergic rhinitis but lack significant necrotizing upper airway lesions and cavitation of lung nodules, and are more likely to have pANCA (in contrast to the c-ANCA seen in granulomatosis with polyangiitis). Also, patients with EGPA are less likely to develop renal failure, and vasculitic neuropathy and asthma/eosinophilia are not typical features of granulomatosis with polyangiitis. EGPA can be distinguished from MPO-ANCA–positive microscopic angiitis since patients with the latter syndrome have leukocytoclastic vasculitis without granulomas and do not have upper airway involvement, asthma, and eosinophilia. Further, unlike EGPA, cardiac involvement is rare in MPO-ANCA–positive vasculitis. EGPA may be difficult to distinguish from idiopathic HES among persons who lack ANCA and/or neuropathy without overt vasculitis.[200] EGPA is more likely among those with lower eosinophil counts who later develop vasculitis.

Patients in whom EGPA goes untreated have a poor prognosis; up to 50% die within 3 months after the onset of vasculitis. As such, efforts at early recognition and treatment are important.

Two randomized controlled trials of therapy for EGPA have been conducted recently.[201,202] The choice of treatment depends in part on the clinical features at the time of diagnosis, since the presence of some features portends a worse prognosis and requires a more aggressive treatment approach.[201–203] Poor prognostic features include age >65 years, cardiac, GI, CNS, and renal involvement (with serum creatinine >150 μmol/L) and absence of ENT involvement.[175,203] In persons *without* poor prognostic features, corticosteroids are the mainstay of treatment and generally lead to dramatic clinical improvement, with disease stabilization or cure. Prednisone, 1 to 1.5 mg/kg/d (or 60 mg per day in adults) is given for 3 to 12 weeks, aiming to eliminate constitutional symptoms and cardiac, renal, neurologic, or other vasculitic manifestations. Higher doses (e.g., 15 mg/kg/d methylprednisolone) are occasionally required for control of life-threatening symptoms. Severe hypertension and mononeuritis multiplex often require prolonged steroid treatment and may be difficult to eliminate. Once the vasculitic phase is controlled, steroids may be tapered, with doses titrated to maintain disease control. Low-dose prednisone (e.g., 5–10 mg) is often given every day or every other day for up to 1 year. Although relapses are uncommon, patients should be followed closely for evidence of clinical deterioration, and should have periodic screening of total WBC and differential, ESR, and IgE levels. Most reports suggest the pANCA is not useful to monitor disease activity or direct therapeutic intervention, but one recent case series demonstrated that ANCA-positive persons had more frequent relapses and lower 5-year relapse-free survival rates than ANCA-negative persons.[175] Treatment with cytotoxic immunosuppressive agents, such as cyclophosphamide or azathioprine, should be administered in patients whose condition fails to improve or have relapses despite steroid treatment.

Persons who have poor prognostic features at the time of disease presentation,[142,204] or who have severe systemic involvement should receive high-dose intravenous methylprednisolone or oral prednisone for 3 days plus induction therapy with cyclophosphamide (2 mg/kg/d orally or 0.6–0.7 g/m^2 intravenously day 1, 15, and 30 and then every 3 to 4 weeks theareafter).[205] Patients treated with cyclophosphamide should be monitored closely for hemorrhagic cystitis, renal insufficiency, bone marrow suppression, bladder fibrosis, and urologic malignancies. Patients with severe disease treated with corticosteroids and cyclophosphamide have better survival than those treated with corticosteroids alone. Azathioprine maintenance therapy (2 mg/kg/d) for 18 to 24 months may be beneficial once remission of disease has been achieved.[142,143,202]

Intravenous immunoglobulin (IvIg) may be beneficial for use in pregnant women and for reducing symptoms and organ involvement and improving long-term disease control among persons with severe organ involvement. The number of blood Treg cells was increased among persons with EGPA treated with IV Ig and conventional therapy.[206] The anti-IL5 antibody mepolizumab has also demonstrated efficacy as a steroid-sparing agent in small uncontrolled case series.[207,208] The immunoregulatory cytokine interferon-α (IFN-α) has led to improved pulmonary function tests, reduction in corticosteroid dose, and decreased WBC count and may be considered as another alternative treatment in persons with refractory disease[209] but may be of limited efficacy and can cause cardiac toxicity. Plasma exchange may also be a successful adjunct treatment in some patients,[142,210] particularly those with ANCA positivity and glomerulonephritis. Finally, rituximab may be effective as an alternate therapeutic agent but further studies are needed to clarify benefits of treatment in EGPA as compared with other forms of ANCA-positive vasculitis.[211] β-Blockers should be avoided in the management of EGPA-related hypertension, owing to the risk of bronchospasm and CHF. Persons undergoing immunosuppressive treatment for EGPA should receive prophylactic treatment to prevent infection with pneumocystis jirovecii.

Prolonged treatment may be necessary to maintain disease control. Long-term overall remission can be achieved in approximately 81% to 92% of patients[142,156]; relapses occur in 25% of cases and are most common within 1 year.[142] In a series of 30 patients collected over the period 1950 to 1974, a median survival of more than 9 years was reported in patients treated with steroids; 1-year survival was 90%, 3-year survival was 76%, and 62% survival was noted at 5 years. More recent studies suggest 85% to 100% survival at 5 years.[1,175,205]

IDIOPATHIC HYPEREOSINOPHILIC SYNDROME

Idiopathic HES is a rare disorder first described in 1968 by Hardy and Anderson. Over the ensuing years, many case reports of severe peripheral eosinophilia and diffuse organ infiltration with eosinophils were described. Several names – including *eosinophilic leukemia, Loeffler fibroplastic endocarditis,* and *disseminated eosinophilic cardiovascular disease* – were used to describe this disease entity. In 1975, Chusid et al. [212] revised the definition of HES to include only cases in which no other underlying cause of hypereosinophilia could be found. HES is now recognized as a clinically heterogeneous syndrome with a wide range of disease severity. Whereas some patients experience a mild, limited form of the disease with minimal involvement of noncritical organs (e.g., skin), others have life-threatening multiorgan dysfunction. Emerging evidence suggests that HES may indeed represent several diseases of distinct etiology that share several features in common.[213–215]

Current consensus defines hypereosinophilia as blood eosinophils $>1.5 \times 10^9$/L on two examinations separated by ≥1 month and/or tissue eosinophilia (defined as >20% of cells in a bone marrow specimen, tissue infiltration defined by a pathologist, and/or marked deposition of EDGP in tissue).[216] The term HES is defined as the presence of hypereosinophilia together with eosinophilic tissue infiltration and organ damage (in the absence of other identifiable cause). HES is a rare disorder. Although persons of any age may be affected, disease onset is most common between 20 and 50 years of age.[217,218] When it occurs in children it often heralds a clonal hematologic disturbance.[218] There is no known racial or ethnic predisposition. Familial cases with autosomal dominant transmission have been reported.

Clinical features and symptoms vary according to the organ system(s) affected. Presenting complaints are often nonspecific and include weakness, fatigue, low-grade fevers, myalgias, cough, angioedema, rash, retinal lesions, and dyspnea. Involvement of virtually every organ system has been described.

Several distinct clinical variants of HES have been recognized.[216,219] Three of the most common are:

1. The myeloproliferative variant (primary/neoplastic HES): In this variant there is clonal expansion of eosinophils related to stem cell, myeloid, or eosinophil neoplasms. Clinical features inlcude anemia, thrombocytopenia, hepatosplenomegaly, elevated leukocyte alkaline phosphatase, circulating immature leukocytes, and elevated B_{12} levels.[220] The most common chromosomal abnormality noted is deletion on 4q12, leading to fusion of genes for and constitutive activation of the tyrosine kinase fusion protein FIP1L1-PDGFRA.[221] Other chromosomal abnormalities have also been reported.
2. The lymphocytic variant (secondary, reactive HES, ~30% of cases): This variant is related to clonal expansion of Th2 T cells with an abnormal surface antigen phenotype (CD3−/CD4+) and increased production of IL-5.[222,223] Increased amounts of IL-4, IL-13, GMCSF, and hypergammaglobulinemia may be present.[224] Skin and soft tissue involvement are the predominant clinical features of this variant.
3. The idiopathic variant (~50% of cases): The disturbances present in the previously noted variants are lacking, but end-organ damage is present.[215]

The respiratory system is affected in an estimated 63% of patients with HES.[225] The most common symptoms include a predominantly nocturnal cough, which is either nonproductive or productive of small quantities of nonpurulent sputum, wheezing, and dyspnea (without evidence of airflow obstruction on spirometric examination). In general, respiratory manifestations are mild.[225] Pulmonary hypertension, ARDS, and pleural effusions (which may be due to CHF) have been reported but are rare. In patients with pulmonary manifestations, the chest radiograph or CT may reveal transient focal consolidation, ground glass opacities or diffuse pulmonary infiltrates (with no predilection for any particular distribution), small nodules, pleural effusion(s), adenopathy, or pulmonary emboli.[212,225] Histopathologic examination of affected lung specimens most commonly reveals intense interstitial infiltration with eosinophils. Less commonly, necrotic areas of parenchyma are found. These are believed to be due to pulmonary microemboli. In contrast to EGPA, significant vasculitis is not present.

Cardiac disease is the major cause of morbidity and mortality in patients with HES.[217,226] The most common cardiac manifestations are relentlessly progressive CHF due to eosinophilic myocarditis and endocarditis, intracardiac thrombi, and endocardial fibrosis.[217] Cardiac involvement in HES, which may be clinically silent, is believed to progress from an initial acute necrosis stage, followed by endocardial thrombus formation and eventually development of fibrosis, which may lead to restrictive cardiomyopathy or valvular dysfunction such as mitral regurgitation.[217] Intracardiac thrombus formation can lead to ischemic embolic events. Bacterial endocarditis has also been noted. The cardiac damage is believed to be mediated at least in part by EDGP . Elevation in serum troponin level can provide a clue to the presence of cardiac involvement in HES.[227] Disturbingly, cardiac involvement correlates poorly with the peripheral blood eosinophilia, hence echocardiographic follow-up at 6-month intervals is recommended. Cardiac MRI also detects eosinophil-mediated cardiac injury[228] or intracardiac thrombus.

Involvement of the central or peripheral nervous system, which occurs in up to 60% of patients, is also a major cause of morbidity.[229] Neurologic manifestations of HES include encephalopathy with neuropsychiatric dysfunction, memory loss, gait disturbances with or without signs of upper motor neuron injury, visual changes, and sequelae of thromboembolic events, including hemiparesis. Peripheral neuropathy with sensory and/or motor axonal loss (no vasculitic or eosinophilic infiltration) is extremely common in HES.

The bone marrow is universally affected with a striking eosinophilia (up to 25%–75% of the differential). Other hematologic manifestations are venous and arterial thromboembolism,[230] anemia, thrombocytopenia, elevated vitamin B_{12} levels, hepatosplenomegaly, and lymphadenopathy (in 12%–20%).

Cutaneous manifestations may include eczema, uritcaria, angioedema, nodular or papular lesions, skin thickening, erythroderma or dermatographia.[217,231] Mucosal ulcerations may develop. As noted, cutaneous manifestations are more likely seen among persons with the lymphocyte HES variant.[223] Urticaria or angioedema generally portend a benign prognosis. Persons with papules are likely to have the FIP1L1-PDGFRA variant.[232] GI (20–30% of patients), renal (10–20%), musculoskeletal, ocular, and endocrine manifestations are all also well described.

Laboratory findings associated with HES include peripheral blood eosinophilia >1.5 × 10^9/L,[212] an elevated total serum IgE (25%–38%), hypergammaglobulinemia, circulating immune complexes (32%–50%), and an ESR above 15 mm/h (68%). Anemia is likely in patients with the myeloproliferative variant.[233] Elevated serum B_{12} and leukocyte alkaline phosphatase levels are also noted. Fungal and parasitic serologies, as well as aspirates of body fluids for ova and parasites, are negative. Of interest is that whereas blood and BAL eosinophilia are both prominent in persons with pulmonary involvement, blood eosinophilia is present and BAL eosinophilia is absent in persons lacking pulmonary manifestations of the disease. This finding has raised the question whether BAL eosinophilia may serve as a marker for the development of pulmonary disease associated with HES.

The organ damage in HES is believed to be due to both eosinophilic infiltration of tissues[234,235] and tissue injury caused by thromboembolic events. Eosinophils probably contribute to tissue damage via antibody-mediated cytotoxicity and the release of toxic granule products such as major basic protein and eosinophil cationic protein. Elevated serum levels of eosinophil cationic protein and major basic protein have been reported, but they do not correlate universally with clinical disease severity. The precise events inciting the extreme eosinophilia in HES are unknown, but several mechanisms have been proposed, including overproduction or abnormal activity of cytokines leading to eosinophilia, and defects in cytokine signaling or signal transduction.

The diagnosis of HES is established by demonstrating multiorgan dysfunction, severe peripheral blood eosinophilia (>1.5 × 10^9/L) on two separate occasions in the absence of any other known causes of peripheral blood eosinophilia. Occasionally, the disease presents with the incidental finding of blood eosinophilia before development of other complications. The total peripheral leukocyte count is typically elevated to above 10,000 (typical range, 10,000 to 30,000), with a preponderance of eosinophils (up to 70%). The leukocytosis may be progressive. Eosinophilic blast transformation was reported to occur at some time during the course of the disease in 28% of 51 patients in one series. Tests recommended to assess for end-organ damage also include serum chemistries, liver function tests, CPK, troponin, EKG, echocardiogram, chest x-ray and/or CT, pulmonary function tests, abdominal CT scan, and tissue biopsy as indicated. Serum tryptase, vitamin B_{12} and Ig levels may also support the diagnosis.[236] In addition, patients with suspected HES should undergo bone marrow aspirate and biopsy, FIP1L1/PDGFRA mutation analysis, and T lymphocyte phenotyping by flow cytometry or karyotype analysis to evaluate for the HES subtypes noted earlier. Proper diagnosis of the HES subtypes has implications for choosing therapy for the disease.

The differential diagnosis of HES includes parasitic infection, acute eosinophilic leukemia, drug-induced hypersensitivity, EGPA, episodic angioedema with eosinophilia, tuberculous or fungal infection, allergic or autoimmune disease, other acute or CEPs, TPE, other lymphoproliferative disorders, and paraneoplastic syndromes. Patients with eosinophilic leukemia have immature eosinophils or blasts in the bone marrow and/or blood, whereas patients with HES typically do not. Patients with HES do not have asthma or vasculitis characteristically associated with EGPA, and patients with episodic angioedema typically lack the multiorgan involvement associated with HES.

Before the discovery of an effective therapy, the prognosis of HES was poor. In one early series, 81% of 48 patients died within 1 year of diagnosis. Overall, without therapy, average survival was 9 months, and 3- to 4-year survival was estimated at 10% to 12%.[212] The greatest mortality occurs within the first year after diagnosis. Death may occur from refractory CHF, azotemia, hepatic failure, venous thromboembolism, a perforated abdominal viscus, or infection. Persons with the myeloproliferative variant of HES (especially those with FIP1L1/PDGFRA positive disease) tend to have an aggressive course with high mortality without treatment. The advent of effective therapy for HES has led to a marked improvement in median survival to more than 10 years.

Patients with the incidental finding of peripheral eosinophilia but without evidence of end-organ dysfunction can be followed closely at 3- to 6-month intervals without specific treatment, as they tend to follow a benign course. Patients should be monitored routinely at 6-month intervals with chemistries, EKG, echocardiogram, and pulmonary function tests as well as monitored for clinical signs of thrombotic complications. Additional monitoring and testing should be done as indicated depending on symptoms and other known organ involvement.

The tyrosine kinase inhibitor imatinib mesylate (initial dose 400 mg per day) is the first line therapy for all patients with the PDGFRA-positive variant of HES.[214,221,237,238] Persons with cardiac involvement should receive concomitant systemic corticosteroid therapy, to avoid further cardiac damage potentially induced by imatinib.[239] Case reports have suggested other tyrosine kinase inhibitors, nilotinib and sorafenib, can be effective alternate therapies in cases of resistance to imatinib therapy.[240,241]

A mainstay of therapy for persons with HES and organ involvement who lack FIP1L1/PDGFRA fusion or other imatinib responsive mutation includes corticosteroids such as prednisone at 1 mg/kg/d for several weeks, with taper of dose attempted to an every-other-day regimen once eosinophil levels are reduced. The mechanisms by which steroids are effective in this disorder are not fully clear. If the disease stabilizes or resolves (e.g., if blood eosinophilia and symptoms are controlled), corticosteroids can be tapered gradually to alternate-day dosing, and should be continued for approximately 1 year at the minimal dose that effectively controls disease activity.[214]

IFN-α, a mediator that suppresses eosinophil function in vitro, has been beneficial in management of HES, perhaps by inhibiting eosinophil proliferation and differentiation. IFN-α should be tried as a second-line agent among patients with HES who fail to respond to corticosteroid treatment or as a steroid-sparing agent for persons requiring high-dose corticosteroids.[214] IFN-α monotherapy should be avoided among persons with lymphocyte-variant disease.[242] Pegylated interferon may be an effective alternate therapy in selected cases.[243] Existing data suggest that another anti-eosinophil strategy, the anti–IL-5 antibody mepolizumab, may reduce symptoms and eosinophilic organ involvement associated with HES, and may be particularly helpful as a steroid-sparing agent in patients with high IL-5 levels (e.g., persons with lymphocyte variant HES lacking the FIP1L1/PDGFRA fusion gene).[244,245] Case reports have also demonstrated efficacy of the anti–CD-52 antibody alemtuzumab that targets eosinophils and T cells in the lymphocyte variant of HES.[246–248]

Hydroxyurea (0.5–1.5 g per day) may be added to the regimen if there is evidence of further disease progression or steroid toxicity,[214] with the aim of reducing the peripheral leukocyte count to the range of 5000 to 10,000. Vincristine may be used as a chemotherapeutic inducing agent in patients with extremely high peripheral WBC counts. Etoposide, chlorambucil, and other chemotherapeutic agents may be effective alternative agents for cases that prove refractory to standard treatment with corticosteroids. Cyclosporine may also be of benefit in controlling the disease, especially when used in combination with corticosteroids.

Allogeneic bone marrow transplantation has also been reported anecdotally to be successful in selected severe cases of HES in which end-organ damage is potentially reversible.[249]

Leukapheresis affords no clear benefit unless there is elevated blood viscosity with associated coagulation. Antiparasitic agents and radiation therapy are ineffective. Anticoaguation with warfarin and/or antiplatelet agents may be needed for management of thromboembolic events.

Favorable prognostic features include a rapid clinical response to treatment with reduction in blood eosinophilia, the presence of angioedema, an elevated IgE, and absence of findings associated with myeloproliferative disorder.[217,236,250,251] Factors associated with a poor prognosis include presence of total blood WBC greater than 100,000/mm^3, myeloblasts in the peripheral blood, refractory CHF, basophilia above 3%, identifiable chromosomal abnormalities in bone marrow cells, and elevated serum B_{12} levels. The mechanisms by which these features are associated with a given prognosis are largely unknown.

APPROACH TO THE EVALUATION OF EOSINOPHILIC PNEUMONIAS

In approaching the patient with pulmonary infiltrates and eosinophilia, one must first establish whether the patient has one of the eosinophilic disorders described in this chapter or a disease process that is secondarily associated with eosinophilia (Table 71-1). A useful algorithmic approach to the evaluation of patients with pulmonary infiltrates and eosinophilia (blood or lung) is shown in Figure 71-6. A careful search for the cause of the disease should be undertaken. A comprehensive medical history should be elicited, with particular attention paid to any antecedent illness (e.g., atopy, rhinitis, asthma, steroid use, immunosuppression), disease exposures, travel, and the duration and nature of the patient's symptoms. One should take special notice of the sequence and timing of events during the course of the illness. In addition to a careful chest examination, a search should be undertaken for physical findings suggestive of extrapulmonary disease (e.g., skin lesions, CHF, hypertension, neurologic abnormalities, musculoskeletal disorders, or GI illness). The nature, distribution, and duration of infiltrates on chest radiograph should be noted. CT scanning of the chest can also provide additional information that may not be apparent on the chest radiograph.

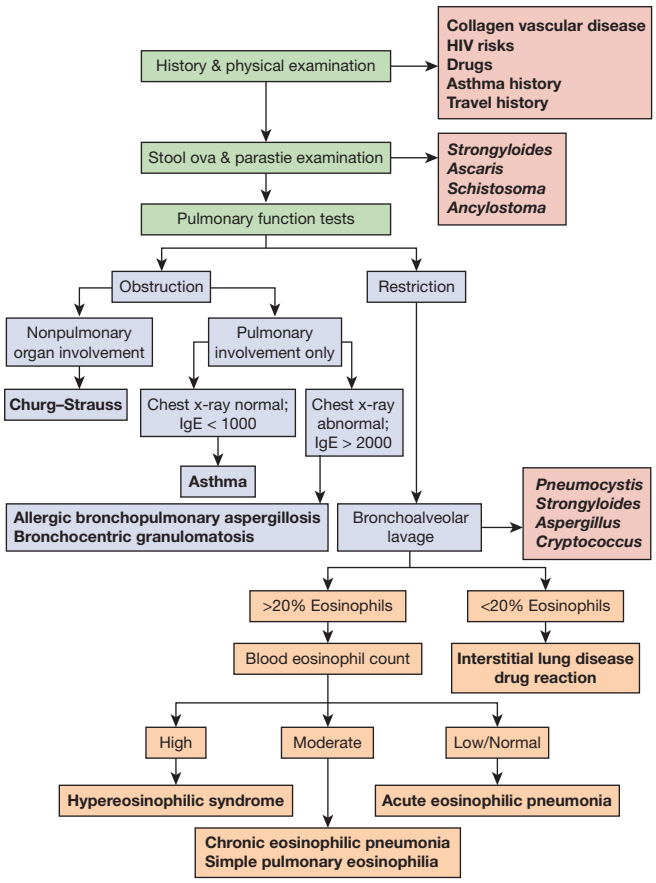


Figure 71-6 Algorithmic approach to evaluation of patients with pulmonary infiltrate and eosinophilia. *(Data from Allen JN, Davis WB. Eosinophilic lung diseases. Am J Respir Crit Care Med. 1994;150: 1423–1438.)*

The workup should include the following additional laboratory data: complete blood count (CBC) with differential, ESR, IgE level, ECG, blood urea nitrogen (BUN), creatinine, liver function tests, urinalysis, sputum cultures, and, when appropriate, sputum cytology. Serologies (e.g., *Aspergillus* precipitins, ANCA, antiparasitic antibodies) are indicated in selected cases. Bronchoscopy with BAL or transbronchial biopsy is important in the evaluation of pulmonary eosinophilic syndromes. The advent of BAL has allowed diagnosis of most cases of eosinophilic pneumonia without open lung biopsy. Normally, BAL fluid contains less than 2% eosinophils. In contrast to diseases associated secondarily with eosinophilia, all the primary pulmonary eosinophilic syndromes are characterized by prominent BAL eosinophilia (more than 20% of the BAL leukocyte differential). The finding of more than 20% BAL eosinophils, viewed in combination with appropriate clinical and radiographic features, is strongly suggestive of the diagnosis of one of these syndromes. BAL and transbronchial biopsy are also useful in ruling out infections (bacterial, fungal, tuberculous, and parasitic), malignancies, and other causes of eosinophil-associated disease. It must be kept in mind that in the context of the overall list of pulmonary diseases associated with more than 5% BAL eosinophilia, the true pulmonary eosinophilic syndromes are rare.

The pulmonary eosinophilic syndromes are at times difficult to distinguish from one another, owing to the substantial amount of overlap among their clinical, radiographic, and histologic features, as well as variable features at different stages of disease. The comparative features of the eosinophilic pneumonias described in this chapter, with regard to several key features, are shown in Table 71-7. The clinical presentation may be acute, subacute, or chronic. Disease may range from mild and self-limited to severe and life-threatening illness. To varying degrees in all the pulmonary eosinophilic syndromes, dyspnea, malaise, low-grade fever, cough, and wheezing are common presenting complaints. Of the diseases considered in detail in this chapter, only EGPA and HES are consistently associated with significant extrapulmonary manifestations. Radiographic infiltrates may be transient in Loeffler syndrome, TPE, EGPA, ABPA, and HES. Blood eosinophilia is present in all the diseases discussed except idiopathic AEP and in a minority of cases of CEP. Variable degrees of elevation of serum IgE are also present. Pulmonary function abnormalities are not specific for these disorders. Except for the diseases caused by parasites, corticosteroids are the mainstay of therapy.

Although the eosinophilic pneumonias can, at times, pose diagnostic difficulties, it is crucial to establish an accurate diagnosis whenever possible. An accurate diagnosis is important because the dose and duration of steroid treatment, prognosis, and follow-up measures for each of these diseases vary widely, and initiation of other specific therapeutic interventions improves outcomes in selected situations. Furthermore, chronic fibrotic lung disease may result from failure to accurately diagnose and treat some of these disorders in a timely fashion, and misdiagnosis with resultant inappropriate therapy (e.g., high-dose steroid treatment of invasive fungal infection masquerading as CEP) may be catastrophic.

TABLE 71-7 Comparative Features of the Pulmonary Eosinophilic Syndromes

	Loeffler's	AEP	TPE	CEP	ABPA	EGPA	HES
Clinical course	Acute	Acute	Acute, subacute, chronic	Subacute	Acute, subacute, chronic	Acute, subacute, chronic	Subacute, chronic
Respiratory Symptoms	Self-limited, mild	Severe	Severe	Mod.–severe	Mod.—severe	Mod.–severe	Mild
H/o allergic disease/asthma	—	±	—	+(30–60%)	Nearly 100%	100%	—
Blood eosinophilia	Mod. to extreme, transient	Absent (delayed)	Extreme	Moderate in most	Typical	Extreme, fluctuating	Extreme, persistent
Sputum/BAL eosinophilia	Prominent	Striking	Prominent	Striking	In some	Prominent	Striking
Elevated serum IgE	±	Moderate elev. in some	High elev.	Mod.–elev. in 50%	Marked elev., fluctuates w/disease	Mod.–elev.	Mod.–elev. in some
Etiologic agent	*Ascaris* spp. *Ancylostoma*, *Strongyloides*, drugs	Unknown	Filarial infection	Unknown	*Aspergillus* (or other fungus)	Unknown	Unknown
Radiographic findings (CXR, CT)	Patchy, often peripheral unilateral or bilateral consolidation and GGO; usually transient, migratory, nonsegmental	Diffuse, alveolar and interstitial GGO and airspace opacities, interlobular septal thickening, pleural effusion	Diffuse, reticulonodular	Predominately, peripheral consolidation and GGO; "photographic negative of pulmonary edema"	Upper lobe–predominant proximal bronchiectasis	Transient, migratory peripheral, rarely diffuse; patchy peribronchial and septal thickening, patchy parenchymal GGO or consolidation, pleural effusion	Transient, focal or diffuse GGO or consolidation
PFTs	± Mild RVD	RVD	OVD early, RVD late, or mixed pattern	Normal, OVD, or RVD	OVD ± RVD	OVD ± RVD	Mild RVD in some
Characteristic diagnostic findings	*Ascaris* larvae in sputum, BAL, gastric aspirate	None	Filaria-specific IgE, IgG, microfilaria in LN/lung	None	See Table 71-5	Histopathology plus appropriate clinical setting	Extreme persistent eosinophilia and multiorgan dysfunction (no other evident cause)
Vasculitis	None	None	None	Occasionally mild, nonnecrotic	None	Characteristic (see text)	None
Extrapulmonary manifestations	GI late, if untreated	None	Cardiac, CNS rare	Very rarely reported	None	Typical of vasculitic phase	Cardiac, neurologic, GI, hematologic, other
Therapy	Mebendazole, if *Ascaris* or hookworm; removal of drug or toxin exposure ± steroids	Corticosteroids	Diethylcarbamazine, Ivermectin	Corticosteroids	Corticosteroids, bronchodilators, antibiotics, antifungals	Corticosteroids, other immunosuppressives (see text)	Depends on disease variant (see text)
Chronic/recurrent disease	None	None	May occur	Common	Typical	May occur (~25%)	Chronicity typical

+, yes or present; −, no or not present; BAL, bronchoalveolar lavage; CT, computed tomography; elev., elevated; GGO, ground-glass opacity; GI, gastrointestinal; h/o, history of; LN, lymph node; mod., moderately; OVD, obstructive ventilatory defect; CXR, chest x-ray (radiograph); PFTs, pulmonary function tests; RVD, restrictive ventilatory defect.

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PART 8

Disorders of the Pulmonary Circulation

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CHAPTER 72

Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature in which an ever increasing resistance to circulatory flow imposes a mounting afterload for the right heart to overcome. Without therapy, and frequently despite it, patients with PAH suffer progressive and inexorable right heart failure, functional decline, and ultimately die. Although rapid progress has resulted in the availability of therapy that can improve the outlook for many patients, long delays in disease recognition are common, exposing patients to prolonged suffering and potentially irreversible harm.

PAH is one of several possible causes of pulmonary hypertension. Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest. It can be due to diseases primarily isolated to the pulmonary vasculature itself, as in PAH, or can be a complication of other diseases, including hypoxemic lung disorders (e.g., chronic obstructive pulmonary disease [COPD]), left heart disease (e.g., systolic, diastolic, or valvular dysfunctions), or thromboembolism.[1,2] Identification of its cause is essential, as appropriate therapy for pulmonary hypertension is aimed at its underlying cause—be that repair of a stenotic mitral valve, bronchodilators for obstructive lung disease or, in the case of PAH, the use of advanced therapies targeted at the pulmonary vasculature.

CLASSIFICATION OF THE PULMONARY HYPERTENSIVE DISEASES

A "sclerosis of the pulmonary arteries" ("Uber Sklerose der Lungen Arterie") without identifiable cause was first described by Ernst von Romberg in 1891.[3] Exclusively descriptive reports of pathologic findings continued until the 1950s when the development of catheterization techniques allowed for hemodynamic evaluation. Using such methods, Dresdale and colleagues described a hypertensive vasculopathy of the pulmonary circulation involving vasoconstriction, elevation of pulmonary arterial pressures (PAPs), and a measurable response to the injection of the nonselective alpha adrenergic antagonist tolazoline.[4] No cause could be identified for the pulmonary arteriopathy and the term primary pulmonary hypertension (PPH) was introduced.[5]

Subsequent classification schemes for diseases-causing pulmonary hypertension have been adopted by international consensus panels. These have evolved from systems based primarily on histopathologic findings to a current model that emphasizes the grouping of entities according to similarities in hemodynamic and clinical characteristics (Table 72-1).[6] Importantly, accurate classification of pulmonary hypertension is essential to guide the rational and appropriate use of medications.

It is important to note the specific nomenclature purposefully adopted in the current classification scheme. The group of patients with PAH is identified as distinct from those patients with other causes of pulmonary hypertension (e.g., due to chronic left heart or respiratory disease). This grouping recognizes similarities in the histologic and many clinical features of patients with identifiable genetic causes of PAH (i.e., those with heritable PAH), collagen vascular or other diseases known to be associated with PAH (Associated PAH), and patients in whom no known associated entity or genetic cause has

TABLE 72-1 Updated Classification of Pulmonary Hypertension[a]

1.	Pulmonary arterial hypertension
1.1	Idiopathic PAH
1.2	Heritable PAH
1.2.1	BMPR2
1.2.2	ALK-1, ENG, SMADS, CAV1, KCNK3
1.2.3	Unknown
1.3	Drug and toxin induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart diseases
1.4.5	Schistosomiasis
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″.	Persistent pulmonary hypertension of the newborn (PPHN)
2.	Pulmonary hypertension due to left heart disease
2.1	Left ventricular systolic dysfunction
2.2	Left ventricular diastolic dysfunction
2.3	Valvular disease
2.4	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3.	Pulmonary hypertension due to lung diseases and/or hypoxia
3.1	Chronic obstructive pulmonary disease
3.2	Interstitial lung disease
3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental lung diseases
4.	Chronic thromboembolic pulmonary hypertension (CTEPH)
5.	Pulmonary hypertension with unclear multifactorial mechanisms
5.1	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

[a]5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.
BMPR2, bone morphogenetic protein receptor type II; CAV1, caveolin 1; ENG, endogin; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.
Source: Adapted with permission from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S43–S54.

been found. This last group is referred to as having idiopathic PAH (IPAH). IPAH replaces the previously (and often loosely) used term "PPH." Abandonment of the term "primary" also is important as a means of discouraging the use of the confusing and clinically inappropriate term "secondary" pulmonary hypertension. Use of such "primary" and "secondary" groupings may inappropriately suggest clinical similarities among the many very different diseases previously referred to as "secondary" pulmonary hypertension (e.g., patients with COPD and those with congenital heart disease). It may also promote a failure to recognize important similarities in clinical features (including appropriate treatment) between what was previously called "primary" pulmonary hypertension and entities inappropriately labeled "secondary" (e.g., patients with Eisenmenger syndrome or HIV infection).

DETERMINANTS OF PULMONARY ARTERY PRESSURE AND PULMONARY VASCULAR RESISTANCE

The pulmonary circulation normally is a high-flow, low-resistance, low-pressure system that carries blood into the pulmonary microcirculation where the blood takes up oxygen and unloads excess carbon dioxide. From early childhood to the fifth decade of life, the mean PAP is approximately 20 mm Hg.[7] PAP is the product of cardiac output (CO) and pulmonary vascular resistance (PVR) as shown in equation 1 (Eq. 1), where PVR is the vascular resistance of the entire lung, including the pulmonary arteries, capillaries, and veins.

$$PAP = CO \times [PVR_{arteries} + PVR_{capillaries} + PVR_{veins}] \quad \text{(Eq. 1)}$$

From this equation, it is clear that PAP can be raised by an increase in CO or an increase in arterial, capillary, or venous resistance. It would be expected then, that during periods of increased CO, such as during strenuous exercise, there would be a significant increase in PAP. However, in a normal healthy individual, the PAP is only slightly increased during periods of increased CO due to the compensatory increase in the cross-sectional area of the pulmonary vascular bed (due to recruitment of previously unperfused vessels and distension of vessels) resulting in a decreased PVR. Arterial distension and optimal recruitment are dependent upon the compliance of the blood vessel walls. Loss of this compliance due to vascular remodeling leads to pulmonary hypertension. As demonstrated in Eq. 1, an increase in PVR of any of the three components of the pulmonary vasculature can lead to an increase in PAP.[8]

Eq. 1 demonstrates the physical laws that govern blood flow in the lungs. To further understand and use this equation, we must know its physical and anatomical foundations. When a liquid (e.g., blood) flows through a cylindrical tubular structure (e.g., a blood vessel), the resistance (e.g., PVR) is inversely proportional to the fourth power of the radius of the lumen of the tube. This is demonstrated by the Poiseuille equation (Eq. 2), where L is the length of the tube (or vessel), r is the inner radius of the tube, and η is the coefficient of viscosity of the liquid (blood). Therefore, even small changes in the radius of a vessel can significantly change the PVR.[8]

$$PVR = (8L\eta)/\pi \times 1/r^4 \quad \text{(Eq. 2)}$$

PULMONARY VASCULAR STRUCTURAL AND FUNCTIONAL CHANGES IN PULMONARY HYPERTENSION

Regardless of the initial genetic or pathogenic trigger, the increased PVR seen in pulmonary hypertension can be attributed to the collective effects of sustained vasoconstriction, vascular remodeling, in situ thrombosis, and increased arterial wall stiffness (Fig. 72-1).[8–13] A rise in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$)

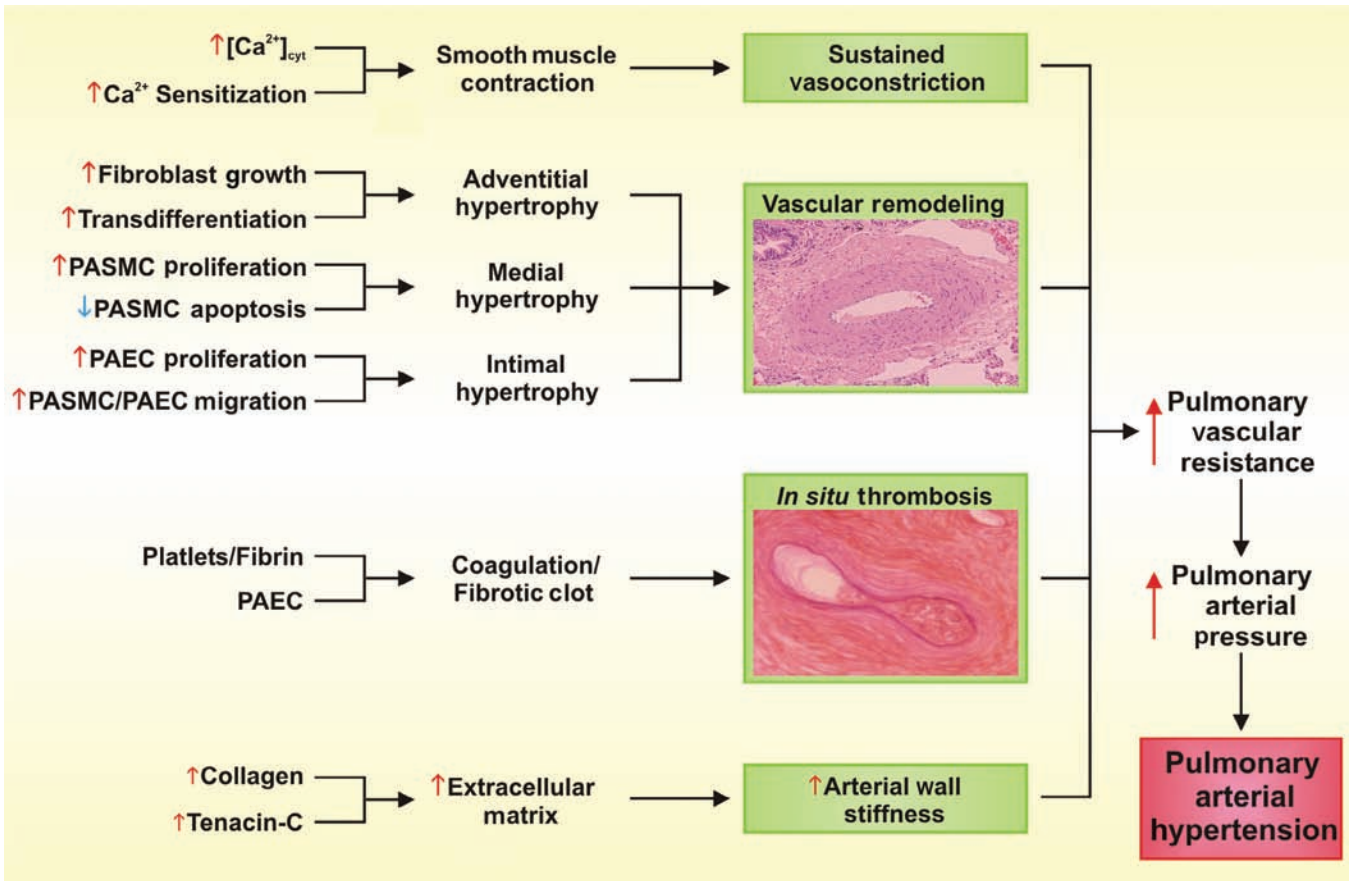


Figure 72-1 Schematic illustration of pathophysiologic components contributing to the development of increased pulmonary vascular resistance, pulmonary arterial pressure, and pulmonary arterial hypertension. *(In situ thrombosis figure reproduced with permission from Zwicke D. PAH and pregnancy: Physiological changes, challenges, and outcomes. Advances in Pulmonary Hypertension. Fall; 2011;10(3).)*

in pulmonary arterial smooth muscle cells is a major trigger for vasoconstriction and a key stimulus for pulmonary arterial smooth muscle cell proliferation and migration, which contributes to vascular remodeling.

SUSTAINED VASOCONSTRICTION

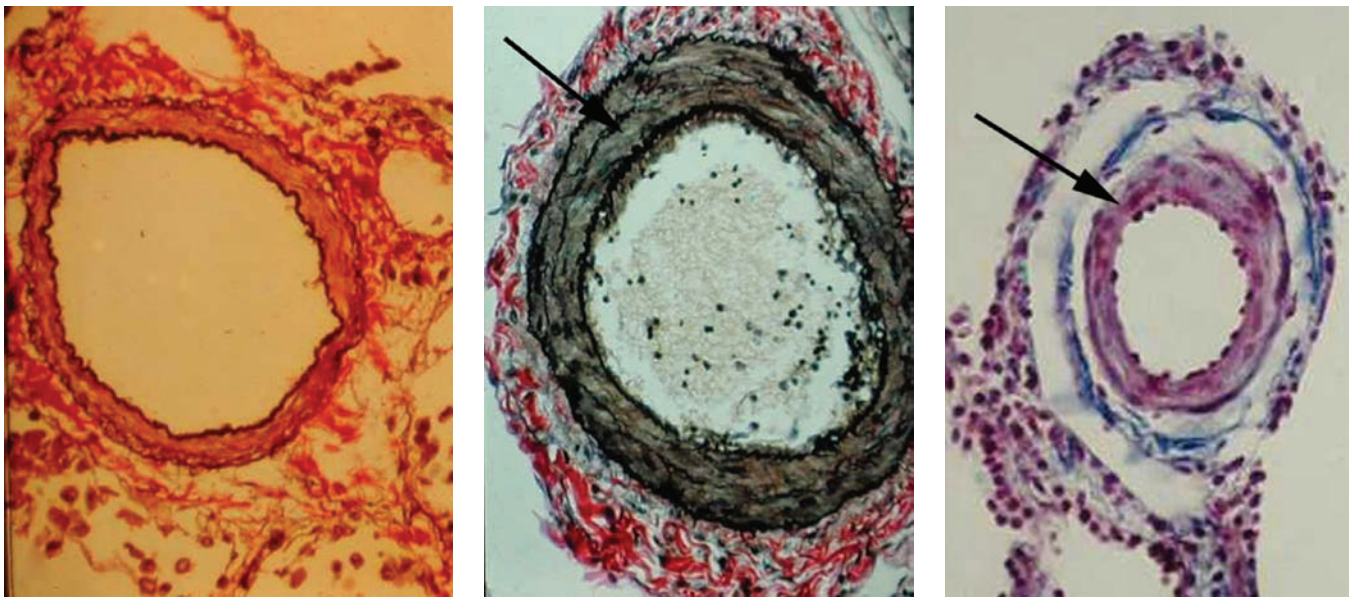
Pulmonary vasoconstriction can be a major contributor to increased PVR and hence PAP. Vasoconstrictive lesions include medial hypertrophy involving an increase in the number and size of pulmonary arterial smooth muscle cells. The elevated PAP and sustained vasoconstriction in PAH can, in turn, enhance pulmonary arterial smooth muscle cell hypertrophy and hyperplasia.[14] Marked smooth muscle hypertrophy can eventually cause medial atrophy, fibrosis, and the subsequent thinning of the media and dilation of the vessel lumen. Extension of pulmonary arterial smooth muscle cells into vessels normally only partially muscularized or nonmuscularized is a common and often prominent feature of precapillary vessels (Fig. 72-2).[15]

Hypoxic pulmonary vasoconstriction is an adaptive mechanism important for redirecting blood flow away from poorly ventilated areas of the lung and into the better ventilated areas to maximize the ventilation–perfusion matching and optimize oxygenation of blood.[16–19] Hypoxia induces vasoconstriction in isolated pulmonary arteries without the endothelium and also induces contraction in a single isolated pulmonary arterial smooth muscle cell model, indicating that hypoxic pulmonary vasoconstriction is an intrinsic property of pulmonary arterial smooth muscle cells. In chronic hypoxia, two factors contribute to increased PAP: vascular remodeling due to pulmonary arterial smooth muscle cell proliferation and sustained vasoconstriction and structural changes that develop within a matter of weeks.[20,21] This remodeling is characterized by thickening of the media of the small pulmonary arteries and arterioles, and by peripheral extension of muscle into minute pulmonary vessels that are normally devoid of muscle (Fig. 72-2).[22] Although the precise mechanism by which hypoxia induces pulmonary vasoconstriction is still somewhat unclear, the signaling pathways initiated in response to acute and chronic hypoxia seem to relate, at least in part, to disrupted Ca^{2+} homeostasis.[8,23]

VASCULAR REMODELING

The thickness and tissue mass of the pulmonary arterial walls are maintained at an appropriate level by a fine balance between proliferation and apoptosis of fibroblasts, pulmonary arterial smooth muscle cells, and pulmonary arterial endothelial cells. Thickening of the wall and luminal narrowing and eventual obliteration can occur if the balance is tipped in favor of cell proliferation. These structural changes that lead to hypertrophy and/or luminal occlusion are referred to as pulmonary vascular remodeling.[24–26] The precise cellular and molecular mechanisms contributing to vascular remodeling are extremely complex. However, vasoconstriction and cellular proliferation share a common pathway. Increased proliferation and hypertrophy of pulmonary arterial smooth muscle cells have been implicated in the development of PAH and these processes, like vasoconstriction, relate in part to disturbed Ca^{2+} homeostasis.[7] Resting $[Ca^{2+}]_{cyt}$ is increased in proliferating pulmonary artery smooth muscle cells compared to growth-arrested cells, demonstrating a role for enhanced Ca^{2+} in both proliferation and vasoconstriction.[27,28] In addition to increased proliferation, decreased apoptosis has been implicated in the development and maintenance of severe pulmonary hypertension,[29] and induction of apoptosis has been shown to promote the regression of hypertrophied pulmonary vascular walls in animal experiments.[30] Hypoxia can induce proliferation of pulmonary arterial adventitial fibroblasts, and in pulmonary hypertension patients, hypoxia induces the appearance of α-smooth muscle actin in the proliferative and matrix-producing fibroblasts, suggesting these cells have transdifferentiated into myofibroblasts.[31] Therefore, fibroblasts may play an important role in vascular remodeling due to hypoxia.

Complex lesions such as plexiform lesions also contribute to vascular remodeling. Plexiform lesions are aneurysmatic dilations of a muscular artery that can occur in very small arteries and arterioles.[8,32] These lesions are often found in patients with IPAH, but they



A B C

Figure 72-2 Vascular remodeling. As compared with a normal vessel (**A**), hypertrophy of smooth muscle cells *(arrow)* is seen in the pulmonary artery of a patient with pulmonary arterial hypertension (**B**). Extension of muscle *(arrow)* into normally nonmuscularized small intra-acinar pulmonary vessels is another prominent feature of pulmonary arterial hypertension (**C**). *(Reproduced with permission from Taichman DB, Snow JL, Pietra GG. Histopathology of pulmonary arterial hypertension. In: Pulmonary Vascular Disease, Mandel J, Taichman DB. Philadelphia: WB. Saunders; 2006.)*

also occur in the lungs of patients with severe PAH associated with left-to-right cardiac shunts, HIV infection, liver cirrhosis, and scleroderma. Although not pathognomonic, the plexiform lesion has been the focus of many studies of the cellular and molecular pathogenesis of PAH.[33–36] They contain collections of proliferating endothelial and smooth muscle cells, together with myofibroblasts and matrix proteins that can partially or completely occlude the vessel lumen. Narrowing or complete obliteration of the parent vessel by intimal thickening is a frequent associated finding, as is destruction of its media. Plexiform lesions often coexist with other obliterative vascular changes such as concentric laminar intimal thickening.[37]

The origin of plexiform lesions is complex and somewhat controversial. Originally, plexiform lesions were considered a congenital malformation.[38] Currently, there are investigators who believe that plexiform lesions develop due to the proliferation of pulmonary arterial smooth muscle cells that transform into myofibroblasts.[39–41] Other investigators propose that, in IPAH patients, plexiform lesions develop due to an endothelial-initiated response to cytokines, growth factors, or vascular injury.[39,41,42] Endothelial cells isolated from the plexiform lesions of IPAH patients proliferate in a monoclonal fashion. However, plexiform lesions from patients with forms of pulmonary hypertension other than IPAH develop from a polyclonal cell population, suggesting different mechanisms contribute to plexiform lesion development in different forms of PAH.[8,43]

IN SITU THROMBOSIS

Monoclonal proliferation of pulmonary arterial endothelial cells, pulmonary arterial smooth muscle cell migration, and accumulation of circulating inflammatory cells, platelets, and progenitor cells can result in occlusion of smaller vessels.[11,42] Thrombosis is frequently seen within the small vessels of patients with PAH. This occurs without evidence of a remote (embolic) source of the thrombus,[44–47] suggesting a local imbalance of pro- and anticoagulant forces. Activation and altered function of the endothelium leading to a shift from anti- to procoagulant activities might be due to the effects of shear stress associated with elevated pressure and/or flow. In addition to altered endothelial cell activity, platelets also promote thrombus formation by releasing vasoactive and mitogenic factors such as thromboxane metabolites and serotonin.[48] These, as well as other platelet-derived products (e.g., platelet-derived growth factor [PGDF], transforming growth factor-beta (TGFβ), and vascular endothelial growth factor [VEGF]) likely also contribute to the remodeling of vessel walls seen in PAH.

INCREASED ARTERIAL WALL STIFFNESS

Increased arterial wall stiffness can also contribute to increased PVR.[49,50] The normal turnover of extracellular matrix proteins is accelerated with remodeling of the vasculature in PAH patients.[51,52] The expression of tenascin-C, for example, is increased in experimental pulmonary hypertension induced by either monocrotaline in rats or increased blood flow in swine.[53–55] Indeed, inhibition of tenascin-C expression by antisense RNA ameliorates monocrotaline-induced pulmonary vascular lesions.[56] Elevated levels of this extracellular matrix protein are also seen on pulmonary arteries of patients with PAH.[57,58] Decreased vascular compliance resulting in the inability to recruit previously unperfused vessels due to increased parenchymal stiffness can also contribute to the development of PAH.[11,42] As a result, there is little capacity for distention and modest increases in pulmonary blood flow can elicit disproportionate elevations in PAPs. This situation is in marked contrast to that of the normal pulmonary circulation, in which an amputation of considerable lung parenchyma rarely suffices, per se, to raise PAPs to pulmonary hypertensive levels, as the remaining vessels retain their normal high capacitance. In some interstitial lung diseases, such as progressive systemic sclerosis, the parenchymal disease and the pulmonary vascular disease can evolve independently. In other connective tissue disorders, such as systemic lupus erythematosis, combinations of interstitial disease and intrinsic vascular abnormalities can contribute to pulmonary hypertension. While there are many structural changes in the pulmonary vasculature that lead to the development of PAH, vasoconstriction and vascular remodeling characterized by intimal, medial, and adventitial hypertrophy are the major structural changes that contribute to the increased PVR/PAP seen in PAH patients.

No single histologic feature distinguishes between the clinical PAH diagnoses. Each of the changes described can be seen in varying proportions in all clinical forms of PAH. For example, the vascular remodeling seen in chronic hypoxia-induced pulmonary hypertension is virtually indistinguishable from that seen in IPAH.[8] The predominant causes of the increased PVR in patients with PAH are sustained vasoconstriction, vascular remodeling, in situ thrombosis, and increased arterial wall stiffness. Persistent pulmonary hypertension, regardless of the cause, can ultimately lead to the development of cor pulmonale with hypertrophy of the right ventricle, its eventual dilation, and ultimately its failure (Fig. 72-3).

PATHOGENIC MECHANISMS OF PULMONARY HYPERTENSION

The pathogenic mechanisms leading to pulmonary hypertension have been conceptualized in six categories (Table 72-2): (1) *passive,* due to obstruction to pulmonary venous outflow (e.g., fibrosing mediastinitis, mitral stenosis, or left heart failure); (2) *hyperkinetic,* due to abnormally high pulmonary blood flow (e.g., left-to-right shunts); (3) *obstructive,* due to pulmonary thromboembolic disease; (4) *obliterative,* due to destruction of the pulmonary vascular bed by parenchymal proliferative disease; (5) *vasoconstrictive,* due to hypoxic vasoconstriction; and (6) *idiopathic* (i.e., without discernible cause).[59] Each mechanism leads to pulmonary vascular remodeling discussed previously, though the progression and reversibility may vary between entities. Other anatomic alterations can be seen in several categories and, over time, distinctions between categories tend to become blurred (e.g., thrombosis may complicate obliterative vascular disease). Also, by the time pulmonary hypertension becomes manifest clinically, the pulmonary arterial tree has undergone considerable remodeling that limits its area and distensibility.

These mechanisms share commonality with the clinical classification of pulmonary hypertension, though overlap of mechanisms occur. The most clearly linked is chronic thromboembolic pulmonary hypertension (CTEPH) with the obstructive mechanism. The most common form of pulmonary hypertension, that related to left heart failure, can also closely be tied to its passive mechanism along with fibrosing mediastinitis, which is classified in group 5 with unclear multifactorial mechanisms. Pulmonary hypertension owing to lung diseases and/or hypoxia, group 3, can be understood as having two primary pathogenic mechanisms, vasoconstrictive in the chronic hypoxic subset and obliterative in the parenchymal disease/fibrosis subset, though these two often overlap. Group 5, pulmonary hypertension with unclear multifactorial mechanisms by definition contains multiple pathogenic mechanisms. Group 1 remains the most diverse and difficult to equate to a particular mechanism as hyperkinetic, vasoconstrictive, obliterative, and other idiopathic mechanisms all contribute to disease pathophysiology.

GENETIC, CELLULAR, AND MOLECULAR MECHANISMS OF PULMONARY ARTERIAL HYPERTENSION

The development of PAH involves increased PVR due to sustained vasoconstriction, vascular remodeling, in situ thrombosis, and increased atrial wall stiffness (Fig. 72-1). Abnormalities in the expression of numerous vasoactive mediators, vasoconstriction mediators, growth factors, and cytokines cause, or result from

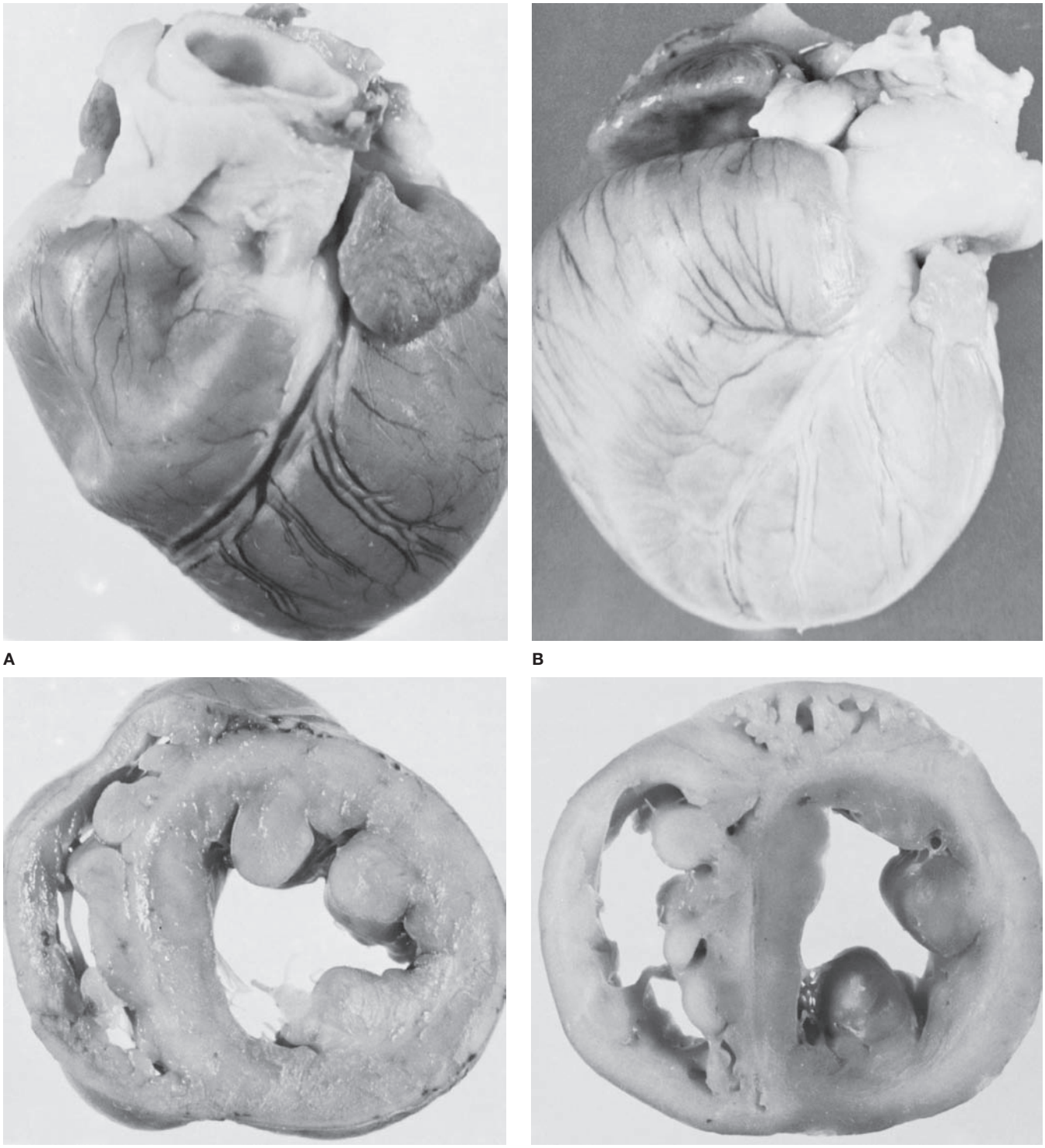


Figure 72-3 Cor pulmonale in experimental pulmonary arterial hypertension in the dog. **A.** Normal heart. **B.** Chronic cor pulmonale secondary to severe pulmonary arterial hypertension. **C.** Cross section of normal heart to show thin wall of the right ventricular cavity. **D.** Cross section of heart with chronic cor pulmonale to show hypertrophy of the right ventricular myocardium and enlargement of the right ventricular cavity. *(Used with permission of Dr. B. Atkinson.)*

changes in pulmonary arterial endothelial cells, pulmonary arterial smooth muscle cells, and platelet function and together result in a thickened vessel wall and markedly narrowed or even completely obliterated lumen. Some of the mechanisms for this combination of uncontrolled vasoconstriction, cell proliferation, and thrombosis are highlighted here.

■ IMBALANCE OF VASOACTIVE MEDIATORS

Relative deficiencies of factors with vasodilatory properties and a simultaneous excess in those promoting vasoconstriction have been noted in both animal models and patients with PAH. In addition to vasoconstriction/dilation, these same factors influence cell proliferation and thrombosis. Deficiencies in the production

TABLE 72-2 Pathogenetic Mechanisms of Pulmonary Hypertension

	Mechanism	Examples
Passive	Pulmonary venous hypertension	Mitral stenosis, left atrial myxoma, fibrosing mediastinitis, pulmonary venoocclusive disease
Hyperkinetic	Increased pulmonary blood flow[a]	Left-to-right intracardiac shunts
Obstructive	Thromboembolic pulmonary vascular disease	High grade obstruction of large pulmonary arteries by organized thromboemboli, multiple pulmonary emboli
Obliterative	Inflammatory and/or proliferative pulmonary vascular disease	Interstitial lung disease, pulmonary arterial hypertension, schistosomiasis
Venoconstrictive	Hypoxia	High altitude, chronic bronchitis and emphysema (COPD)
Idiopathic	Unknown	Drug-associated pulmonary hypertension, portopulmonary hypertension, HIV infection

[a]Most categories overlap to some extent. For example, increased pulmonary blood flow is usually coupled with anatomic changes in the resistance vessels to produce pulmonary hypertension.

of the potent vasodilators nitric oxide (NO) and prostacyclin have each been observed, and indeed both substances have been used as a basis for effective therapies for PAH. Normally produced by vascular endothelial cells, each promotes the formation of cyclic nucleotides (cGMP and cAMP) by pulmonary arterial smooth muscle cells resulting in their relaxation and vasodilation. In addition, both prostacyclin and NO inhibit pulmonary arterial smooth muscle cell proliferation and platelet aggregation. In patients with PAH, the chronic administration of prostacyclin analogs improves hemodynamics, exercise capacity, and survival. The overexpression of NO synthase (NOS) by transgenic animals protects against the development of hypoxia-induced pulmonary hypertension, whereas mice lacking the gene for this enzyme develop severe pulmonary hypertension upon exposure to mild hypoxia.[60–62] In rats, monocrotaline-induced pulmonary hypertension can be prevented, or even reversed, with the administration of endothelial progenitor cells overexpressing human endothelial NOS (eNOS).[63] Inhaled NO has been proposed for the treatment of PAH and persistent pulmonary hypertension of the newborn,[64] however, inhaled NO has limitations regarding dose and duration of the exposure.[65] The inorganic anion nitrite (NO_2^-) is an oxidative product of NO metabolism and can function as an intravascular reservoir of NO bioactivity that can be converted to NO under physiologic and pathologic conditions.[65] Studies have shown that inhaled nebulized nitrite can prevent and reverse established pulmonary hypertension in the monocrotaline-induced rat pulmonary hypertension model.[66,67]

Vasoactive intestinal protein (VIP) also promotes vasodilation and inhibits smooth muscle proliferation and platelet aggregation. VIP levels are reduced in patients with PAH. In a preliminary study of 8 patients with IPAH, treatment with inhaled VIP improved hemodynamics and exercise capacity.[68] The acute effect of inhaled VIP was confirmed in a subsequent study that included patients with multiple etiologies of pulmonary hypertension including IPAH, congenital heart disease, CTEPH, and pulmonary hypertension related to parenchymal lung disease, although the modest effect on hemodynamics had questionable clinical relevance.[69]

INCREASE IN VASOCONSTRICTION MEDIATORS

In addition to deficiencies in vasodilators, excesses of other mediators capable of promoting vasoconstriction, smooth muscle proliferation, or platelet aggregation have been noted in patients with PAH. Thromboxane, an arachidonic acid metabolite produced by endothelial cells and platelets, causes vasoconstriction, platelet aggregation, and is a smooth muscle mitogen. Increased thromboxane metabolites have been documented in the urine of patients with PAH.[48] Attention was focused on the effects of serotonin (5-HT) on the pulmonary circulation by the epidemic of PAH in patients who ingested the appetite suppressants aminorex and fenfluramine.[70] These agents increase plasma 5-HT levels by inducing the release of 5-HT from platelets and interfering with its reuptake.[71] The 5-HT hypothesis was supported by the occurrence of pulmonary hypertension in fawn-hooded rats with an inherited defect in the platelet storage of 5-HT, and by an increase in circulating 5-HT in a patient with platelet storage disease and PAH.[72] 5-HT causes vasoconstriction and is a smooth muscle mitogen (Fig. 72-4). A key regulator of 5-HT action is the 5-HT transporter (5-HTT) whose expression is increased above normal in platelets and the pulmonary arteries of patients with IPAH. The overexpression of the 5-HTT gene in recombinant mice results in worsened hypoxia-induced pulmonary hypertension[73] whereas loss of the gene's function is protective against hypoxia or monocrotaline-induced disease.[74,75] A polymorphism in the 5-HTT gene that increases its activity may confer an increased susceptibility to the development of pulmonary hypertension in patients with COPD.[76] While some studies have suggested a similar role in IPAH,[77] larger data sets have not found such an association.[78] Blockade of the 5-HT receptor has successfully prevented the development and progression of experimental pulmonary hypertension in rats, yet a human trial was not able to show significant decreases in PVR.[79,80]

Endothelin-1 (ET-1) is one of the most potent endogenous vasoconstrictors known. Its expression is increased in the blood and tissues of patients with idiopathic and other forms of PAH and correlates with disease severity.[81–83] In addition to its vasoconstricting properties, ET-1 is mitogenic for both pulmonary arterial smooth muscle cells and fibroblasts (Fig. 72-4).[84,85] ET-1 administration or overexpression in animal models has been shown to result in fibrosis, inflammation, and platelet aggregation.[86,87] ET-1 binds endothelin A (ET_A) and B (ET_B) receptors on the surface of pulmonary arterial smooth muscle cells, resulting in potent vasoconstriction. ET_B receptors on pulmonary arterial endothelial cells increase the production of nitric oxide, resulting in vasodilatation. ET_B receptors are also active in the clearance of endothelin. The net effect of endothelin's vasoconstricting or dilating actions may be both site and context dependent, as both the distribution and relative expression of the ET_A and ET_B receptors differ according to vessel location in normal lung tissue, and are altered in patients with IPAH.[88,89] Indeed, both selective ET_A and dual ET_A/ET_B inhibition improve the hemodynamic derangements and clinical outcome of patients with PAH.[90–92]

INCREASED EXPRESSION OF GROWTH FACTORS

Growth factors that promote the maturation and stabilization of the developing vasculature have also been implicated in the

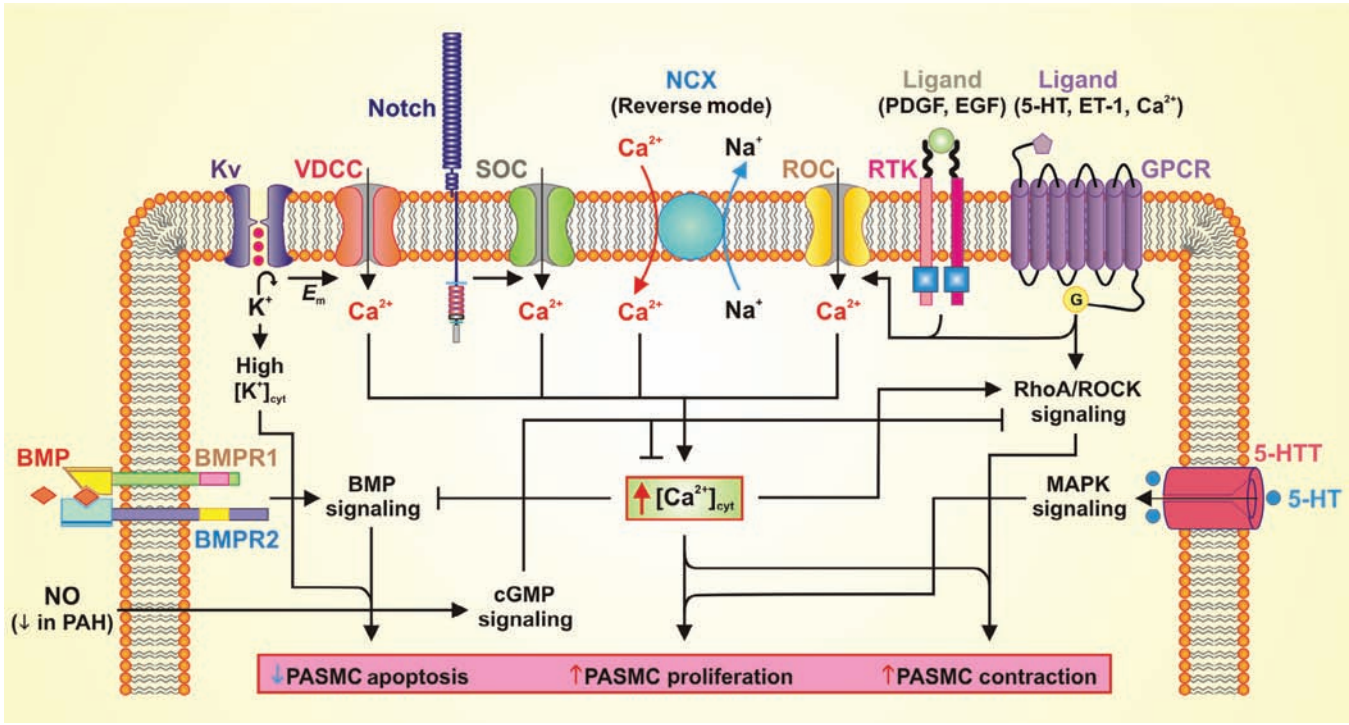


Figure 72-4 Potential mechanisms involved in the development of pulmonary arterial hypertension. Schematic diagram depicting potential mechanisms involved in the development of pulmonary arterial hypertension. BMP, bone morphogenic protein; BMPR, bone morphogenic protein receptor; cGMP, cyclic guanosine monophosphate; E_m, membrane potential; ET-1, endothelin 1; EGF, epidermal growth factor; GPCR, G-protein–coupled receptor; 5-HT, hydroxytryptamine (serotonin); 5-HTT, hydroxytryptamine (serotonin) transporter; Kv, voltage-gated K^+ channel; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NCX, Na^+/Ca^{2+} exchanger; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cell; PDGF, platelet-derived growth factor; ROC, receptor-operated Ca^{2+} channel; RTK, receptor tyrosine kinase; SOC, store-operated Ca^{2+} channel; VDCC, voltage-dependent Ca^{2+} channel.

pathogenesis of PAH. Elevations in angiopoietin 1 and its ligand TIE2 correlate with disease severity in patients with multiple forms of PAH.[93] Angiopoietin 1 is overexpressed in most forms of nonfamilial PAH,[93,94] however, how angiopoietin becomes elevated in these patients is not clear. Several lines of evidence suggest that angiopoietin 1 regulates pulmonary arterial smooth muscle cell hyperplasia in PAH.[9] Interestingly, in an animal model of PAH induced by monocrotaline, the overexpression of angiopoietin is actually protective.[95] Whether this discrepancy represents differences in human versus animal tissues or the differing insults to the vasculature involved is not clear. Another modulator of development, VEGF and its target, tyrosine kinase receptor, are increased in the pulmonary vasculature of patients with PAH. Increased VEGF expression has been reported specifically within plexiform lesions[34,96] where its proangiogenic properties are hypothesized to mediate disordered endothelial cell proliferation.[97] Whether such changes are primary, secondary, or indeed detrimental is not entirely clear. Like elevations in angiopoietin, increases in the expression of VEGF thought to be deleterious in some situations might be beneficial in others that promote the development of pulmonary hypertension. In animal models of hypoxia, the inhibition of VEGF signaling results in proliferative vascular abnormalities[98] and promotion of VEGF signaling is protective against the development of monocrotaline-induced PH.[99]

PDGF along with its receptor, tyrosine kinase, are also found to be increased in the pulmonary vasculature of patients with PAH (Fig. 72-4).[100] PDGF has been implicated in smooth muscle cell proliferation and migration, which is thought to contribute to PAH pathogenesis. The tyrosine kinase inhibitor imatinib has a particular affinity for the PDGF receptor and several small studies have identified a potential benefit in PAH patients.[101] Early human trials have also shown improvements in hemodynamic measurements after treatment.[102]

Cellular microparticles recently have been implicated as vasoactive mediators in PAH. Microparticles represent vesicle fragments of the cell membrane containing various proteins and antigens that are involved in cellular communication.[103] These small particles are released during cell activation or apoptosis and can be derived from multiple cell lines including endothelial cells, platelets, leukocytes, red blood cells, and fibroblasts. Circulating levels of endothelial microparticles are increased in PAH, which may represent endothelial dysfunction and has also been correlated with disease survival.[104] Microparticles, when isolated from rats with hypoxia-induced pulmonary hypertension, have been shown to impair endothelium-dependent vasorelaxation in pulmonary arteries and decrease NO production.[105] Circulating microparticles have also been linked to inflammatory signaling in the lung.[106]

■ INCREASED CYTOKINES AND INFLAMMATION

The close association of systemic inflammatory disorders to IPAH has implicated inflammation as an important factor in vascular remodeling. Numerous cytokines have been implicated in the pathogenesis of PAH including tumor necrosis factor alpha, and interleukins 1b, 2, 4, 6, 8, 10, and 12p70. Early data showed increased levels of IL-1β and IL-6 in IPAH patients[107] and higher IL-6 levels were later found to be associated with mortality.[108] The chemokine fractalkine (CX3CL1) is elevated in CD4 and CD8 T-cells of PAH patients and further studies have shown that CX3CL1 may promote proliferation in pulmonary arterial smooth muscle cells.[109,110] Monocyte chemotactant protein (MCP)-1 is also elevated in serum and lung samples from IPAH patients and may influence monocyte and T-cell recruitment to the diseased lung.[111] Increased expression of Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES) has been found in lung

samples from PAH patients.[112] As a chemoattractant for monocytes and T-cells, RANTES is thought to promote inflammation, but may also play a role in the synthesis of endothelin-1, a potent vasoconstrictor.

FUNCTIONAL CHANGES IN MEMBRANE RECEPTORS AND ION CHANNELS

Important functional changes in membrane receptors and ion channels in IPAH are discussed below.

Ca^{2+} CHANNELS IN IPAH

Sustained vasoconstriction and vascular remodeling are both directly mediated by pulmonary arterial smooth muscle cell contraction and proliferation. A rise in $[Ca^{2+}]_{cyt}$ due to Ca^{2+} influx through various Ca^{2+}-permeable channels in the plasma membrane is a major trigger for pulmonary arterial smooth muscle cell contraction and a key stimulus for pulmonary arterial smooth muscle cell proliferation.[113] Therefore, understanding how the regulation of Ca^{2+} homeostasis is disrupted in IPAH is important to understanding how IPAH develops. Pulmonary arterial smooth muscle cells isolated from IPAH patients have an elevated $[Ca^{2+}]_{cyt}$.[114–117] Ca^{2+} influx through the plasma membrane in pulmonary arterial smooth muscle cells involves multiple Ca^{2+}-permeable channels including (a) voltage-dependent Ca^{2+} channels (VDCC) regulated by changes in membrane potential,[118] (b) receptor-operated Ca^{2+} channels (ROC) activated by interaction of agonist with membrane receptors, and (c) store-operated Ca^{2+} channels (SOC) activated by depletion of Ca^{2+} from the intracellular stores (Fig. 72-4).[8] Decreased expression and/or function of K^+ channels leads to sustained membrane depolarization, activation of VDCC, and increased $[Ca^{2+}]_{cyt}$. Ca^{2+} influx through ROC, termed receptor-operated Ca^{2+} entry (ROCE), and through SOC, referred to as store-operated Ca^{2+} entry (SOCE) is enhanced in IPAH-associated pulmonary arterial smooth muscle cells compared to those from normal controls.[114–117] Several experimental studies have demonstrated increased expression of several proteins involved in ROCE/SOCE such as, TRPC3, TRPC6, STIM2, and Orai2, in pulmonary arterial smooth muscle cells from IPAH patients.[114–117,119,120] In addition, a single-nucleotide polymorphism (SNP) has been identified in IPAH patients that results in enhanced expression and function of TRPC6.[115]

K^+CHANNELS IN IPAH

Vascular tone might also be altered in IPAH by changes in the expression of voltage-gated K^+ (Kv) channels as well as other types of K^+ channels (Fig. 72-4). Their activation normally allows an efflux of K^+ and resultant changes in intracellular Ca^{2+} that promote vasodilation.[121] Gene expression of Kv channel family members is downregulated by hypoxia-induced pulmonary hypertension in rats,[122,123] whereas induction of their expression can reverse the hemodynamic effects of hypoxia.[122,124] The expression of specific Kv channels is also decreased in the lungs of patients with IPAH[125–127] possibly contributing to heightened vasoconstriction resulting from a more depolarized membrane leading to increased $[Ca^{2+}]_{cyt}$ due to activation of VDCC. Kv channels may also mediate the effects of certain drugs. The anorexigens dexfenfluramine and aminorex inhibit smooth muscle Kv channel activity, thus causing pulmonary vasoconstriction.[128] In contrast, enhanced activity of Kv channels may be one mechanism by which sildenafil promotes vasodilation in addition to its activity as an inhibitor of phosphodiesterase-5.[122] One final way in which decreased activity of Kv channels might promote the development of PAH is by inhibiting apoptosis, thus enabling unchecked pulmonary arterial smooth muscle cell proliferation. Apoptosis requires a loss in cell volume as well as the function of specific caspases, both of which require appropriate K^+ movement via Kv channels.[129,130]

G-PROTEIN–COUPLED RECEPTORS IN IPAH

The Ca^{2+}-sensing receptor is a G-protein–coupled receptor in the plasma membrane that can be activated by extracellular Ca^{2+} (and Mg^{2+}), polyamines (e.g., spermine), amino acids and neomycin.[131–134] Activation of the Ca^{2+}-sensing receptor results in activation of intracellular Ca^{2+} signaling pathways that lead to pulmonary arterial smooth muscle cell contraction, proliferation, and migration (Fig. 72-4).[135,136] Like some G-protein–coupled receptors coupled to Gq (e.g., endothelin receptors), Ca^{2+}-sensing receptor activation increases the synthesis of inositol 1,4,5 triphosphate (IP_3) and diacylglycerol via phospholipase C. IP_3 binds to the IP_3 receptor on the sarcoplasmic reticulum (SR) membrane and releases Ca^{2+} from the SR to the cytosol. Depletion of Ca^{2+} from the SR induces Ca^{2+} entry via SOCE, and diacylglycerol directly activates ROCE. In addition to increasing $[Ca^{2+}]_{cyt}$ via ROCE and SOCE, the extracellular Ca^{2+}-induced activation of CaSR also activates other signal transduction pathways (e.g., Akt/mTOR and MAPK/ERK) to induce cellular proliferation.[137–139] A recent study[135] indicates that the extracellular Ca^{2+}-induced increase in $[Ca^{2+}]_{cyt}$ by activation of the Ca^{2+}-sensing receptor is enhanced and the Ca^{2+}-sensing receptor protein expression is upregulated in IPAH-pulmonary arterial smooth muscle cells compared to normal pulmonary arterial smooth muscle cells. These observations suggest that upregulated expression and enhanced function of Ca^{2+}-sensing receptor in pulmonary arterial smooth muscle cells are involved in the development of sustained pulmonary vasoconstriction and pulmonary vascular remodeling in patients with IPAH and animals with experimental pulmonary hypertension. In addition to Ca^{2+}-sensing receptor, many other G-protein–coupled receptors are reported to be involved in PAH such as endothelin receptor, prostacyclin receptor, and serotonin receptor.[48,140,141]

Na^+/Ca^{2+} EXCHANGER IN IPAH

The Na^+/Ca^{2+} exchanger (NCX) is a ubiquitously expressed protein that transports Ca^{2+} across the plasma membrane along the electrochemical gradient of Na^+ and Ca^{2+}.[142] The NCX can operate in either forward mode, transporting 3 Na^+ ions into the cell and 1 Ca^{2+} ion out of the cell, or the reverse mode, transporting 1 Ca^{2+} ion into the cell and 3 Na^+ ions out of the cell, based on the Na^+ and Ca^{2+} concentration gradients and membrane potential. Due to the reverse mode of the NCX, a small increase in the cytosolic Na^+ concentration ($[Na^+]_{cyt}$) can greatly increase $[Ca^{2+}]_{cyt}$. The canonical transient receptor potential (TRPC) channels, such as TRPC6, which is overexpressed in IPAH patients, are permeable to both Na^+ and Ca^{2+}, and for many TRPC channels, the permeability to Na^+ is greater than the permeability to Ca^{2+}. The reverse mode of the NCX has been shown to couple to TRPC6 and localized increases in $[Na^+]_{cyt}$ result in transport of Ca^{2+} into the cell resulting in increased $[Ca^{2+}]_{cyt}$ in pulmonary arterial smooth muscle cells.[143] The NCX is overexpressed in PASMC isolated from patients with IPAH, and is found localized in caveolae along with other G-protein–coupled receptors, ROC, and SOC resulting in a functional coupling of these receptors and contributing to increased $[Ca^{2+}]_{cyt}$, resulting in increased proliferation and contraction of PASCM in patients with IPAH.[116,144]

ALTERED SIGNALING PATHWAYS IN IPAH

Alterations in signaling pathways have been observed in IPAH and are discussed below.

CYCLIC GUANOSINE MONOPHOSPHATE IN IPAH

IPAH is associated with abnormally low levels of the potent pulmonary arterial smooth muscle cell relaxant NO. In pulmonary arterial endothelial cells, NO produced by eNOS freely diffuses across the

cell membrane to pulmonary arterial smooth muscle cells and activates intracellular soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine 5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP then activates cGMP-dependent kinases, which can reduce $[Ca^{2+}]_{cyt}$, inhibit Rho signaling, and inhibit phosphorylation of myosin-binding protein, all of which lead to smooth muscle relaxation.[145,146] In the lung, metabolism of cGMP is controlled by phosphodiesterase 5 (PDE-5). PDE-5 inhibitors block the breakdown of cGMP, leading to vasodilation due to an accumulation of cGMP in the tissue.[147] In 2005, following several clinical studies, sildenafil was approved for the treatment of PAH.[148] Tadalafil was approved for the treatment of PAH in 2009.[149] Both sildenafil and tadalafil share structural similarities with cGMP and inhibit PDE-5 by competitively binding to the catalytic site.[147]

PDGF AND Akt/mTOR SIGNALING IN IPAH

PDGF and its receptor PDGFR have been implicated in the pathogenesis of IPAH. Previous studies have indicated that PDGF increases SOCE in rat and human pulmonary arterial smooth muscle cells, thereby promoting cell proliferation (Fig. 72-4).[119,150] Binding of PDGF to PDGFR leads to activation of phosphatidylinositol 3-kinase (PI3K),[151] which activates Akt. Akt promotes cell growth through the downstream mediator mammalian target of rapamycin (mTOR) or by directly phosphorylating proteins involved in cell cycle regulation and apoptosis.[152] The Akt/mTOR pathway has been shown to be important for pulmonary arterial smooth muscle cell proliferation[150,153] and the development of PAH.[154] Inhibition of mTOR and Akt by rapamycin and Akt inhibitor VIII, respectively, abrogated the PDGF-induced increased SOCE and Ca^{2+} channel expression in normal and PAH-pulmonary arterial smooth muscle cells,[150,155] suggesting that the PDGF-mediated increase in SOCE occurs via the Akt/mTOR pathway. Clinical trials have shown some benefit to the use of imatinib, an orally active PDGFR inhibitor, in patients with severe PAH.[102]

RhoA/ROCK SIGNALING IN IPAH

The RhoA/ROCK signaling pathway is a major mediator of Ca^{2+}-sensitization/desensitization and a key regulator of vascular tone (Fig. 72-4).[156,157] RhoA is a GTP-binding protein that is activated following activation of G-protein–coupled receptors by vasodilators. In addition, RhoA can be activated by serotonin, which enters the cell through its transporter 5-HTT, and by an increase in $[Ca^{2+}]_{cyt}$.[158] Activation of RhoA leads to activation of Rho kinase (ROCK), which increases the Ca^{2+} sensitivity of contraction in pulmonary arterial smooth muscle cells by inhibiting myosin light chain phosphatase and increasing the phosphorylation of myosin light chain kinase, leading to increased contraction of pulmonary arterial smooth muscle cells.[20,21] Recent studies have indicated that the RhoA/ROCK signaling pathway is enhanced in patients with IPAH.[159,160] Small clinical studies have demonstrated that inhibition of the RhoA/ROCK signaling pathway with fasudil, a selective ROCK inhibitor, results in acutely improved pulmonary hemodynamic variables in patients with IPAH.[161,162]

NOTCH SIGNALING IN IPAH

Notch signaling is involved in vascular development and has been implicated in the development of IPAH (Fig. 72-4).[163,164] Both Notch receptors (Notch1-Notch4) and their ligands, Jagged (Jag1 and Jag2) and Delta-like (Dll1, Dll3, and Dll4), are single-transmembrane–spanning proteins that restrict Notch signaling to adjacent cells. After ligand binding, Notch undergoes a series of proteolytic cleavages resulting in the release of the Notch intracellular domain, which translocates to the nucleus where it interacts with recombination signal binding protein for immunoglobulin kappa j region (RBPjκ) to function as a transcription factor resulting in activation of transcription of Notch target genes.[163,165–167] The most commonly induced Notch target genes are the basic helix–loop–helix transcriptional repressors of the *Hes* (*Hairy/Enhancers of Split*) and *Hrt* (*Hes-related transcription factor*) gene families. In addition, Notch signaling has been shown to upregulate expression of PDGFR-β,[168] which is known to be upregulated in IPAH.[155,169] Notch3 signaling has recently been implicated in PAH. Lung tissue from IPAH patients displays increased Notch3 and Notch3 intracellular domain (N3ICD) expression when compared to normotensive patients.[164] In addition, Notch3 and N3ICD expression is increased in two animal models of pulmonary hypertension, hypoxic-induced pulmonary hypertension in mice and monocrotaline-induced pulmonary hypertension in rats.[164] This suggests that the Notch signaling pathway may be an important pathway to target for the development of new drugs for the treatment of IPAH.

GENETIC ALTERATIONS RELATED TO IDIOPATHIC AND FAMILIAL PAH

Identification of bone morphogenetic protein receptor II (BMPR2) gene mutations has led to increasing interest in genetic susceptibility to pulmonary hypertension. As a receptor for the TGFβ super family, BMPR2 is involved in diverse cell growth and differentiation processes in multiple systems. Engagement of a BMP receptor with its ligand normally results in the activation of intracellular mediators (Smads) and their translocation to the cell nucleus and regulation of the transcription of target genes. The resulting activation of some genes and the inhibition of others varies according to the BMP pathway and tissue involved. BMP signaling is essential to both normal vascular development and the maintenance of the normal adult pulmonary vasculature, likely by regulating the growth and apoptosis of endothelial and smooth muscle cells (Fig. 72-4). Loss of such regulation gives rise to pulmonary hypertension.[170] Normally found primarily on endothelium and to a lesser extent smooth muscle cells, the expression of BMPR2 is reduced and its function abnormal in patients with various types of PAH, most notably those with mutations of the *BMPR2* gene.[171] The ability of BMP to inhibit smooth muscle proliferation and induce apoptosis is suppressed in cells isolated specifically from smaller pulmonary vessels in patients with IPAH (e.g., 1 to 2 mm, where occlusive vascular pathologic changes predominate).[29,172,173] Germline mutations in *BMPR2* have been identified in up to 70% of patients with familial PAH, and in 20% of patients with IPAH,[174–180] as well as disease associated with anorexigens,[181] congenital heart disease,[182] and pulmonary venoocclusive disease (PVOD).[183] Nearly 300 different mutations of BMPR2 have been identified.[177]

Further work has identified other genetic alterations in the TGFβ pathway including activin receptor kinase-like 1 (*ALK1*), endoglin (*Eng*), and Smad 8.[184] ALK1 is a receptor for TGFβ and endoglin is its coreceptor; while Smad 8 is a downstream second messenger of BMPR2. Mutations in *ALK1* and *Eng* have been shown to confer susceptibility to the development of PAH in patients with hereditary hemorrhagic telangiectasia.[185,186] In addition, concomitant Thrombospondin-1 gene mutation (*THBS1*) has been detected in a small subset of familial PAH patients with BMPR2 mutations; this mutation has been proposed to further promote pulmonary hypertension development and increase genetic penetrance.[187]

CLINICAL EVALUATION OF PULMONARY HYPERTENSION

The symptoms and signs of PAH are nonspecific, overlapping with many more common entities. As a result, patients experience problematic delays between the time of symptom onset and appropriate diagnosis.[188,189] The problem is usually first suggested by findings suggestive of pulmonary hypertension on an echocardiogram. The evaluation of PAH is predominantly,

TABLE 72-3 Presenting Symptom(s) Attributable to PAH

Symptom	Percentage of Patients at Presentation
Abdominal distention	4%
Chest pain/discomfort	2%
Cough	14%
Dizziness/lightheadedness	15%
Dyspnea at rest	11%
Dyspnea on exertion	86%
Edema	21%
Fatigue	27%
Presyncope/syncope	17%
Palpitations	13%

Source: Data from Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest. 2011;140(1):19–26 and represent percentage of patients with each indicated symptom at the time of initial presentation, from among 2493 patient enrolled in a multicenter United States national registry of patients with pulmonary hypertension (Registry to Evaluate Early and Long-term PAH Disease Management).

TABLE 72-4 World Health Organization Functional Classification of Patients with Pulmonary Hypertension

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Source: Adapted with permission from Rich S. Primary Pulmonary hypertension: executive summary. Evian, France. World Health Organization, 1998.

therefore, the evaluation of pulmonary hypertension more generically: a step-wise process to establishing whether pulmonary hypertension is likely present, and if so confirmation and careful evaluation of the specific cause and classification so as to guide rational therapy.

■ PATIENT HISTORY IN PULMONARY HYPERTENSION

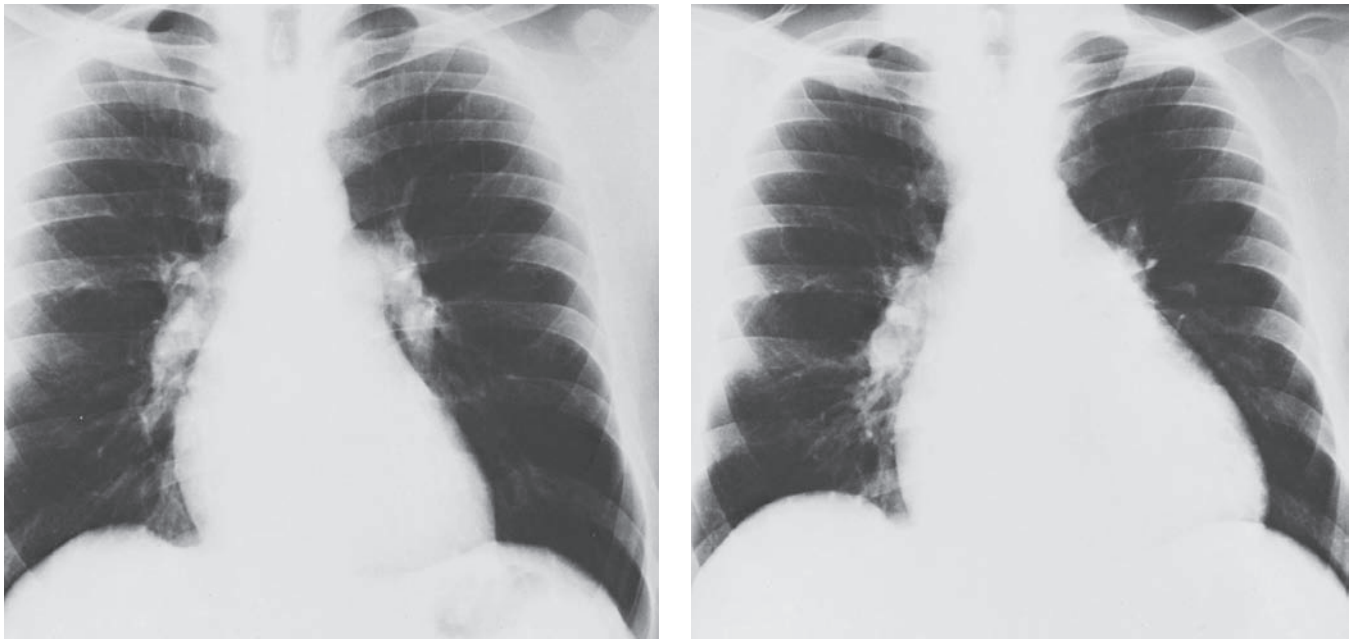
Except for mild breathlessness – often attributed to being "out of shape" – PAH is generally asymptomatic until severe. Because of the nonspecific nature of the symptoms (Table 72-3), underrecognition of the disease by healthcare providers, and its confusion with other conditions, a significant delay between the onset of symptoms and the diagnosis of PAH is common. The mean time from symptom onset until PAH diagnosis was over 2 years in a National Institutes of Health (NIH) registry assembled in the 1980s.[190] Twenty years later, registries in China, France, Germany, and the United States each found that similarly disappointing delays of over 2 years persist.[189,191–193] As a result, diagnosis is delayed until most patients have severe functional impairment, with more than one-half reporting World Health Organization (WHO) functional class III or IV symptoms (Table 72-4).

Symptoms due to pulmonary hypertension are generally difficult to dissociate from symptoms of underlying pulmonary or cardiac disease. In IPAH, the first symptoms generally occur during exertion, usually as dyspnea and, less often, chest pain, dizziness, or syncope.[194] Dyspnea on exertion is by far the most common presenting complaint. Often, because of the lack of other signs or symptoms, it is attributed to physical deconditioning or anxiety. Other initial complaints, particularly easy fatigability and chest discomfort, are often similarly dismissed. Angina-like or nonspecific chest pain is common in patients with severe pulmonary hypertension and generally attributed to right ventricular overload and myocardial ischemia. Chest pain might also occur due to the extrinsic compression of the left main coronary artery by an enlarged pulmonary artery.[195]

In time, in the absence of amelioration of the pulmonary hypertension, right-sided heart failure evolves. Syncope, or light-headedness on exertion, are less common but more ominous complications of pulmonary hypertension. They occur in patients with severe pulmonary hypertension and a fixed low CO. The cause is inadequate cerebral blood flow due to a combination of failure to increase the CO, along with diversion of systemic blood flow toward the exercising muscles. Syncope may also occur at rest in association with the onset of bradycardia, presumably vagal in origin. Hoarseness, due to paralysis of the left recurrent laryngeal nerve, may result from trapping of the nerve between the aorta and the dilated left pulmonary artery (a form of Ortner syndrome). If the right ventricle should fail, lower extremity swelling is common, as are abdominal signs and symptoms including a sensation of "bloating," early satiety, tender hepatomegaly, ascites, and abdominal pain. Symptoms of right ventricular failure and the presence of syncopal events are associated with a worse prognosis. Hemoptysis in the setting of pulmonary hypertension is most often due to pulmonary venous congestion but when mitral stenosis is present, it is generally attributed to bleeding from bronchial veins. Occasionally, hemoptysis occurs in other forms of pulmonary hypertension and may originate in alveolar capillaries, precapillaries, or elsewhere in the pulmonary arterial tree.

Not infrequently, the suspicion of pulmonary hypertension is raised by the presence of a known risk for pulmonary hypertension (e.g., systemic sclerosis) or by serendipitous discovery of right ventricular enlargement by an electrocardiogram or chest radiograph taken for other reasons (Figs. 72-5 and 72-6). Initial recognition of the presence of pulmonary hypertension also frequently occurs in the absence of reported symptoms when an echocardiogram is performed for the evaluation of a murmur. Alternatively, echocardiographic evidence of pulmonary hypertension may be found unsuspectedly when the study is obtained as "routine" evaluation of a patient complaining of any of a number of chest symptoms, including dyspnea. Patients with severe pulmonary hypertension are prone to sudden death and its occurrence may be the first (and last) indication of disease. Death has occurred unexpectedly during normal activities, cardiac catheterization, and surgical procedures, and after the administration of sedatives or anesthetic agents. In a few instances, bradycardia leading to cardiac arrest has preceded sudden death.

An important hint to the presence of pulmonary hypertension is a history of long-standing dyspnea that has not responded to treatment for other more common disorders. Patients have often seen several clinicians before an appropriate diagnosis is made.



A B

Figure 72-5 Radiographic changes in idiopathic pulmonary arterial hypertension. As compared to a chest radiograph 14 months earlier (**A**) enlargement of the cardiac silhouette has occurred in a 30-year-old man in association with increasing dyspnea (**B**). Decrease in the cardiac silhouette occurred in response to chronic pulmonary vasodilator therapy.

Younger patients have frequently been told their symptoms are due to asthma, yet failed to improve significantly with aggressive anti-inflammatory and bronchodilator therapies. In older patients, dyspnea or exercise limitation may have been blamed on COPD, often despite a trivial history of tobacco use. Unfortunately, a further clue in such patients is learning that these "diagnostic" labels were never investigated with pulmonary function testing. Patients should be asked about important symptoms or risk factors that might suggest the presence and cause of pulmonary hypertension. These include symptoms of collagen vascular disease (e.g., dysphagia, skin or joint changes, Raynaud's phenomenon), sleep apnea (e.g., witnessed apneic events, daytime hypersomnolence), history of risks for thromboembolism, HIV infection, liver disease, or anorectic agent use. A history of tobacco use and chronic sputum production, or a known history of asthma with poor control might be important clues to the presence of obstructive airway disease and hypoxia as the cause of pulmonary hypertension. A prior history of interstitial lung disease or any cause of chronic hypoxia must be noted. A careful family history should be taken including inquiring about relatives who suffer(ed) poorly understood cardiopulmonary conditions.

■ PHYSICAL EXAMINATION

A careful physical examination is necessary to recognize the presence of pulmonary hypertension and begin elucidating its cause (Table 72-5). In mild-to-moderate pulmonary hypertension, the physical examination is apt to be unrevealing unless suspicion has been aroused that pulmonary hypertension may be present. Right ventricular enlargement is an important clue but notoriously difficult to detect in its early stages on physical examination. Evidence of pulmonary hypertension, such as prominent closure of the pulmonary valve, is apt to be overlooked or discounted, especially in younger people; recognition of tricuspid insufficiency or a right ventricular gallop is often delayed until pulmonary hypertension becomes severe and has led to heart failure.

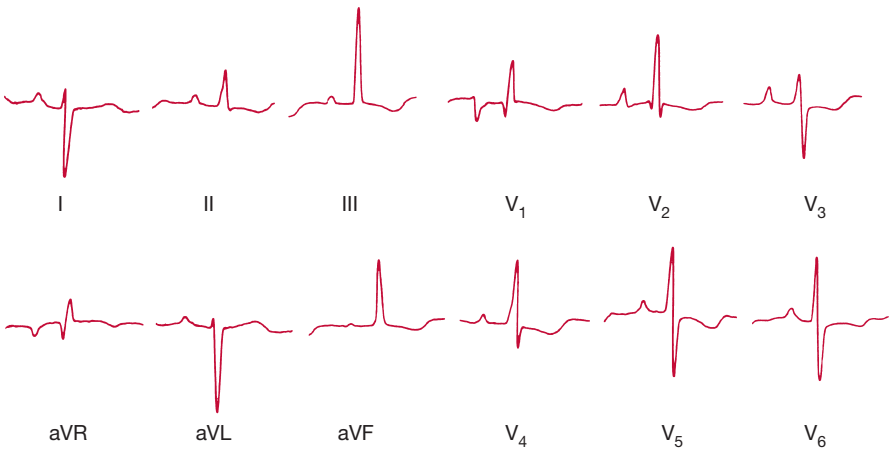


Figure 72-6 Twenty-six-year-old woman in whom the first evidence of primary pulmonary hypertension was by electrocardiography. The record shows marked right axis deviation and dominant R waves over the right precordium consistent with right ventricular hypertrophy.

TABLE 72-5 Physical Examination Findings in Pulmonary Hypertension

Physical Signs that Reflect Severity of PH	
Sign	**Implication**
Accentuated pulmonary component of S2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular "a" wave	Poor right ventricular compliance
Physical Signs that Suggest Moderate-to-Severe PH	
Sign	**Implication**
Moderate-to-severe PH	Tricuspid regurgitation
Holosystolic murmur that increases with inspiration tricuspid regurgitation	
Increased jugular v waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation or both
Hepatomegaly	
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
Physical Signs that Suggest Possible Underlying Cause or Associations of PH	
Sign	**Implication**
Central cyanosis	Abnormal V/Q, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venoocclusive disease
Cardiac systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Crackles, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Crackles, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils, narrowed pharyngeal opening, macroglossia	Disordered ventilation, sleep apnea
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic PH
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

PH, Pulmonary hypertension.

Source: Adapted with permission from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619.

Once pulmonary hypertension is suspected, the physical examination can offer important signs. When symptoms first become manifest, a large *a* wave generally can be detected in the jugular venous pulse. Auscultation usually discloses splitting of the second heart sound with accentuation of the pulmonic component. A sharp systolic ejection click over the region of the pulmonary artery is usually heard. As pulmonary hypertension persists, enlargement of the right ventricle becomes evident as a palpable cardiac impulse near the left sternal border and in the hypogastrium. An important sign of cor pulmonale is a right-sided (ventricular) diastolic (S_3) gallop; it is accentuated by inspiration. Less helpful is the right atrial gallop (S_4), which occurs immediately before the first heart sound and suggests an increase in the filling pressure of the right side of the heart.

In time, tricuspid insufficiency develops. It is manifested by a holosystolic murmur, best heard in the fourth interspace to the left of the sternum; the murmur characteristically increases in intensity during inspiration (as do the third and fourth heart sounds). A prominent *v* wave appears in the jugular pulse, and distended neck veins pulsate with each heartbeat. The onset of right ventricular failure is often marked by discomfort in the right upper quadrant due to hepatic engorgement as well as edema in the lower extremities. The liver often also shows expansive pulsations that are synchronous with the heartbeat. Hydrothorax and ascites are uncommon, even after right ventricular failure has progressed to the stage of hepatomegaly and pedal edema. Systemic arterial hypoxemia is often present. Assessment of oxyhemoglobin desaturation with activity is an important component of the patient evaluation; if desaturation is noted, formal exercise testing to titrate oxygen therapy should be pursued promptly. Late in the disease, many patients develop peripheral cyanosis secondary to a reduced CO and peripheral vasoconstriction; central cyanosis also occurs preterminally in some patients because of right-to-left shunting through a patent foramen ovale.

The physical examination should be focused on the presence of additional signs to indicate a possible cause of pulmonary hypertension. Systemic hypertension, a risk factor for coronary artery disease or diastolic dysfunction, may suggest left-sided heart disease. Abnormal lung sounds might include wheezing suggesting airway obstruction, or crackles suggesting either pulmonary edema or interstitial disease. Additional findings suggestive of lung disease include hyperresonance to percussion or hyperinflation of the thorax (barrel chest) suggestive of COPD or kyphoscoliosis causing a restrictive pattern. Skin changes such as rash or telangiectasias are clues to the presence of collagen vascular disease, as are digital ulcers in patients with the CREST variant of systemic sclerosis. The presence of digital clubbing should also be noted as it may indicate congenital heart disease, certain forms of chronic hypoxic lung disease (e.g., cystic fibrosis or certain interstitial lung diseases) or PVOD.[196] Narrowing of the posterior oropharynx, macroglossia, and a large neck size may suggest obstructive sleep apnea.

DIAGNOSTIC STUDIES

Diagnostic testing is used to confirm the presence of pulmonary hypertension, identify the etiology, assess severity and prognosis, and to help guide appropriate therapy. Table 72-6 lists tests that are essential in the evaluation of pulmonary hypertension.[197] Table 72-7 lists the criteria required for a diagnosis of PAH.

Following a detailed history and physical examination, an electrocardiogram, chest radiograph, and echocardiogram are indicated if there is suspicion of pulmonary hypertension, and often as logical tests to evaluate symptoms such as dyspnea even if concern for pulmonary hypertension has not been raised.

Chest Radiograph and Electrocardiogram

Early in the evolution of pulmonary hypertension, the chest radiograph appears normal. In time, the central pulmonary arteries become increasingly prominent as the peripheral vessels become attenuated, and the cardiac silhouette enlarges (Fig. 72-7). The chest radiograph (together with pulmonary function tests) may also suggest the presence of underlying lung disease. An electrocardiogram should be obtained and may indicate signs of ischemic heart disease or conduction abnormalities. Findings suggestive of the presence of pulmonary hypertension include right axis deviation, right atrial enlargement, and right

TABLE 72-6 Evaluation of Patients with Pulmonary Hypertension

Detection of pulmonary hypertension	Detailed history and physical examination	Suspicion of pulmonary hypertension and possible causes/associations
	Electrocardiogram	Exclude other causes of cardiopulmonary symptoms
	Chest radiograph	
	Echocardiogram (at rest, to consider repeat with exertion)	Evaluate for presence of pulmonary hypertension, assess chamber sizes and function, valvular abnormalities, contrast (bubble) study to evaluate possible shunt
Essential testing	Pulmonary function testing	Exclude intrinsic lung disease
	Overnight oximetry	Screen for sleep-disordered breathing
	Lung (V/Q) scan	Exclude thromboembolism
	Blood serologies (e.g., CBC, liver function, renal function, HIV, ANA, antiphospholipid antibodies)	Exclude collagen vascular disease, liver disease, infection, and other possible causes of pulmonary hypertension
	Oxygen desaturation study	Assess need for supplemental oxygen (rest and exertion)
	6-Minute walk test	Establish baseline
	Right cardiac catheterization	Confirm diagnosis, assess other cardiac causes (shunt); consider left heart catheterization
Contingent testing	Transesophageal echocardiogram	Assess patent foramen ovale (PFO)
		Characterize valvular function
	Computed tomogram of chest	Assess interstitial lung disease, adenopathy
	Polysomnogram	Diagnosis and treatment of sleep-disordered breathing
	Pulmonary angiogram	Assess presence and location of organized thromboemboli and suitability for pulmonary thromboendarterectomy
	Blood studies (BNP, clotting studies, genetic testing)	
	Lung biopsy	Exclude subtle interstitial lung disease vasculitis and other uncommon diseases (PVOD, PCH) to assist planning

Source: Data from Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43 (12 Suppl S):40S–47S.

TABLE 72-7 Requirements for the Diagnosis of Pulmonary Arterial Hypertension

Required Testing	Rationale
Cardiac catheterization: • A mean pulmonary artery pressure ≥25 mm Hg • Pulmonary artery wedge or left ventricular end diastolic pressure ≤15 mm Hg • Pulmonary vascular resistance >3 Wood units[a]	Confirm presence of pulmonary hypertension Exclude left heart disease as the cause of pulmonary hypertension (pulmonary venous hypertension) (Group 2 PH)
PFTs, chest imaging without evidence of more than mild lung disease	Exclude chronic hypoxemic lung disease as cause of PH (Group 3 PH)
Ventilation–perfusion scan without evidence of unmatched perfusion defects	Exclude chronic thromboembolic pulmonary hypertension (Group 4 PH)

[a]*An elevated pulmonary vascular resistance is not included in all published criteria for the diagnosis of PAH.*

ventricular hypertrophy (Fig. 72-6). Arrhythmias are uncommon until late in the course of the disease, when they may contribute to syncopal episodes.

Echocardiogram

When there is suspicion, the echocardiogram is the appropriate first test to assess if pulmonary hypertension is present.[194,198] Indeed, as noted earlier, the unsuspected finding of pulmonary hypertension on an echocardiogram often first brings the issue to attention. A carefully performed Doppler examination is able to quantify the tricuspid regurgitant jet in the majority of cases.[199] A modified Bernoulli equation is used to estimate right ventricular systolic (RVSP = $4v^2$ + right atrial pressure; v = tricuspid jet velocity in meters per second) and is assumed equal to the pulmonary artery systolic pressure when the pulmonic valve is normal. Normal RVSP has been reported as 28 ± 5 mm Hg. Echocardiographic evaluation with exercise is an additional consideration when estimates of RVSP at rest are normal and there is a high suspicion of pulmonary hypertension (e.g., dyspnea in a patient with systemic sclerosis and no other obvious cause).

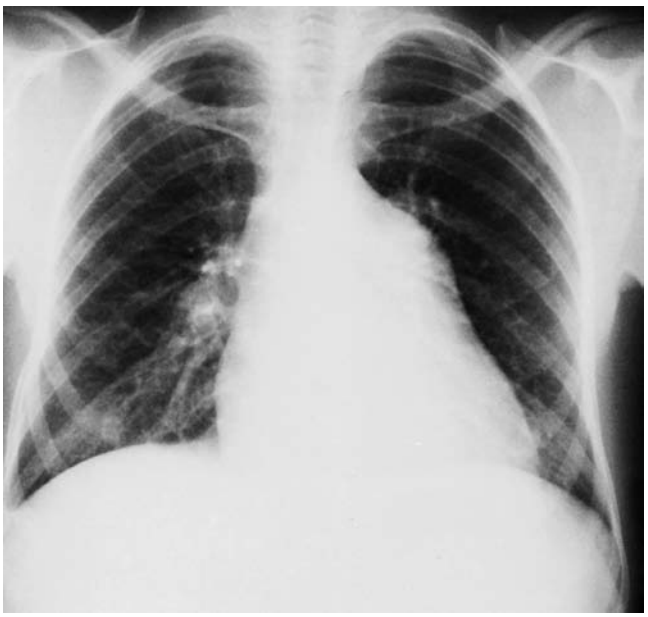


Figure 72-7 Chronic thromboembolic pulmonary hypertension. Prominent central pulmonary arteries in conjunction with the marked pruning of the peripheral tree reflect marked pulmonary hypertension in a patient with a history of multiple pulmonary thromboemboli.

Echocardiographic measurements taken at peak exercise may reveal undue elevations, perhaps signaling the presence of earlier disease. However, normative echocardiographic values of RVSP with exercise have not been well established and whether patients with "exercise-induced" pulmonary hypertension require or benefit from therapies useful for patients with resting pulmonary hypertension is debated.

The echocardiogram also reveals important anatomical and functional information that may assist in identifying the cause of pulmonary hypertension (Table 72-8). Evaluation for a patent foramen ovale and intracardiac or intrapulmonary shunting of blood should be performed (e.g., using "bubble" contrast). Echocardiography can help to rule out related anatomic abnormalities, such as acquired or congenital mitral valve disease or left atrial myxoma. Left ventricular hypertrophy, signs of diastolic noncompliance, decreased systolic function or focal hypokinesis as well as mitral or aortic valvular

TABLE 72-8 Potential Causes of Pulmonary Hypertension that may be Identified by Echocardiography

Conditions that Predispose to Pulmonary Hypertension
Congenital or acquired valvular disease (MR, MS, AS, prosthetic valve dysfunction)
Left ventricular systolic dysfunction
Impaired left ventricular diastolic function (hypertensive heart disease, HCM, Fabry disease, infiltrative cardiomyopathies)
Other obstructive lesions (aortic coarctation, supravalvular AS, subaortic membrane, cor triatriatum)
Congenital disease with shunt (ASD, VSD, coronary fistula, patent ductus arteriosus, anomalous pulmonary venous return)
Pulmonary embolus (thrombus in IVC, right-sided cardiac chamber, or PA; tricuspid or pulmonic valve vegetation)
Pulmonary vein thrombosis/stenosis
Findings that Suggest Specific Disease Entity
Left-sided valve changes (SLE, anorexigen use)
Intrapulmonary shunts (hereditary hemorrhagic telangiectasia)
Pericardial effusion (IPAH, SLE, systemic sclerosis)

Source: Reproduced with permission from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc. and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619.

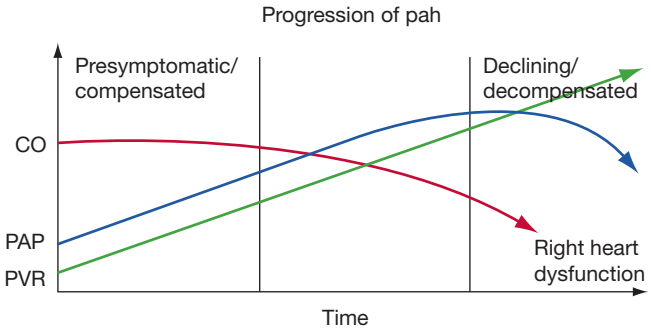


Figure 72-8 Hemodynamic changes during the progression of pulmonary arterial hypertension. With progressive increase in the pulmonary vascular resistance (PVR), the pulmonary artery pressure (PAP) initially increase until a failing right heart can no longer generate the required pressures to maintain cardiac output (CO). At this late stage both the cardiac output and pulmonary pressures may fall. *(Reproduced with permission from Friedman EB, Palevsky HI, Taichman DB. Classification and prognosis of pulmonary arterial hypertension. In: Pulmonary Vascular Disease, Taichman DB. Philadelphia: WB. Saunders; 2006.)*

defects all are vital observations when evaluating the likely cause of pulmonary hypertension. Assessment of right ventricular size and function is essential, as the symptoms caused by pulmonary hypertension and the prognosis of patients with PAH are determined in large measure by the status of the right heart (Fig. 72-8). Indeed, unexplained echocardiographic findings of RV dilation and/or decreased function warrant further investigation regardless of whether pulmonary hypertension appears to be present by echocardiographic estimate. The degree of RV function is often evaluated subjectively, but more quantitative approaches to assessment are becoming more commonly reported, have variably been shown to predict right ventricular output and patient prognosis, and may provide better means of assessing change with disease progression or in response to therapy. Such approaches include evaluation of the tricuspid annular plane systolic excursion, tissue Doppler imaging, and myocardial performance index (Tei-Doppler index).[200] The presence and greater size of a pericardial effusion are also poor prognostic signs.[201–204] Flattening of the intraventricular septum is seen with advanced right heart dilation and failure, and the leftward movement of the septum may impair left ventricular filling (Videos 72-1 and 72-2).

Video 72-1 Short-axis view of an echocardiogram of a patient with pulmonary hypertension demonstrating flattening of the interventricular septum with bowing toward the left ventricle during diastole. The right ventricle is hypocontractile. A small pericardial effusion is demonstrated as well. *(Used with permission of Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.)* **Video 1, still shot 1**: An echocardiogram performed during diastole in the short-axis view demonstrates an enlarged right ventricle (RV), a flattened interventricular septum (IVS) with bowing toward the left ventricle (LV), and a small pericardial effusion (PE). *(Used with permission of Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.)* **Video 1, still shot 2**: An echocardiogram performed during systole in the short-axis view demonstrates an enlarged right ventricle (RV), a flattened interventricular septum (IVS), and a small pericardial effusion (PE). Impaired filling of the left ventricle (LV) during diastole compromises stroke volume. *(Used with permission of Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.) Access at www.fishmansonline.com*

Video 72-2 A four-chamber view of an echocardiogram in a patient with pulmonary hypertension. The right ventricle (RV) is enlarged, dilated, and hypocontractile. The right atrium (RA) is enlarged. The interventricular septum (IS) moves paradoxically toward the left ventricle (LV) during diastole, impairing LV filling. A small pericardial effusion (PE) is demonstrated. *(Used with permission of Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.)* **Video 2, still shot 1**: An echocardiogram in the four-chamber view demonstrating an enlarged, dilated RV and RA, as well as a relatively underfilled left ventricle LV and a small PE. The moderator band (MB) of the right ventricle is well visualized. *(Used with permission of Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.) Access at www.fishmansonline.com*

While the correlation between echocardiographic estimates of pulmonary arterial systolic pressure and measurements taken at right heart catheterization is generally good, there is significant variability and confirmation by catheterization is absolutely required when the presence of pulmonary hypertension will influence the approach to treatment. For example, in the setting of some patients with severe COPD in whom an echocardiogram reveals evidence of pulmonary hypertension, confirmation by right heart catheterization might not impact medical therapy. If, on the other hand, there is consideration of surgical interventions for the COPD (e.g., transplantation or volume reduction), confirmation of the presence of pulmonary hypertension with catheterization may be important. When the diagnosis might be PAH, diagnostic catheterization is absolutely required to confirm the diagnosis and to guide appropriate therapy. Cardiac catheterization in the evaluation of pulmonary hypertension is described in the following section.

Pulmonary Function Testing, Ventilation–Perfusion Scanning, Sleep Studies

Once echocardiographic evidence of pulmonary hypertension has been established, testing for possible causes is in order. Pulmonary function tests, a radionuclide ventilation–perfusion scan, and overnight oximetry are essential to screen for possible underlying obstructive/restrictive lung disease, occult thromboembolism, and sleep-disordered breathing, respectively. Although computed tomographic angiography may reveal the presence of organized thrombus and is frequently useful for evaluation of other possible causes of the patient's symptoms, it is not established to be sufficiently sensitive to exclude CTEPH. Since a diagnosis of CTEPH as a cause of pulmonary hypertension will markedly alter therapeutic approach, its exclusion with a ventilation–perfusion scan remains an essential test (Fig. 72-9). A history or examination findings suggestive of sleep-disordered breathing should prompt performance of overnight oximetry and/or polysomnography. Treatment of significant sleep apnea may be all that is required to treat mild pulmonary hypertension in some patients with preserved right ventricular function who are followed closely for compliance and resolution of pulmonary hypertension.

■ LABORATORY TESTING

Blood tests including HIV antibody, rheumatologic serologies (e.g., ANA), liver function tests, and a complete blood count are essential. Dyspnea due to PAH may the presenting symptom leading to the initial diagnosis of systemic sclerosis or HIV infection, and the presence of either would alter required therapeutic plans. Abnormal liver function should prompt further evaluation for possible portal hypertension as an explanation for PAH.

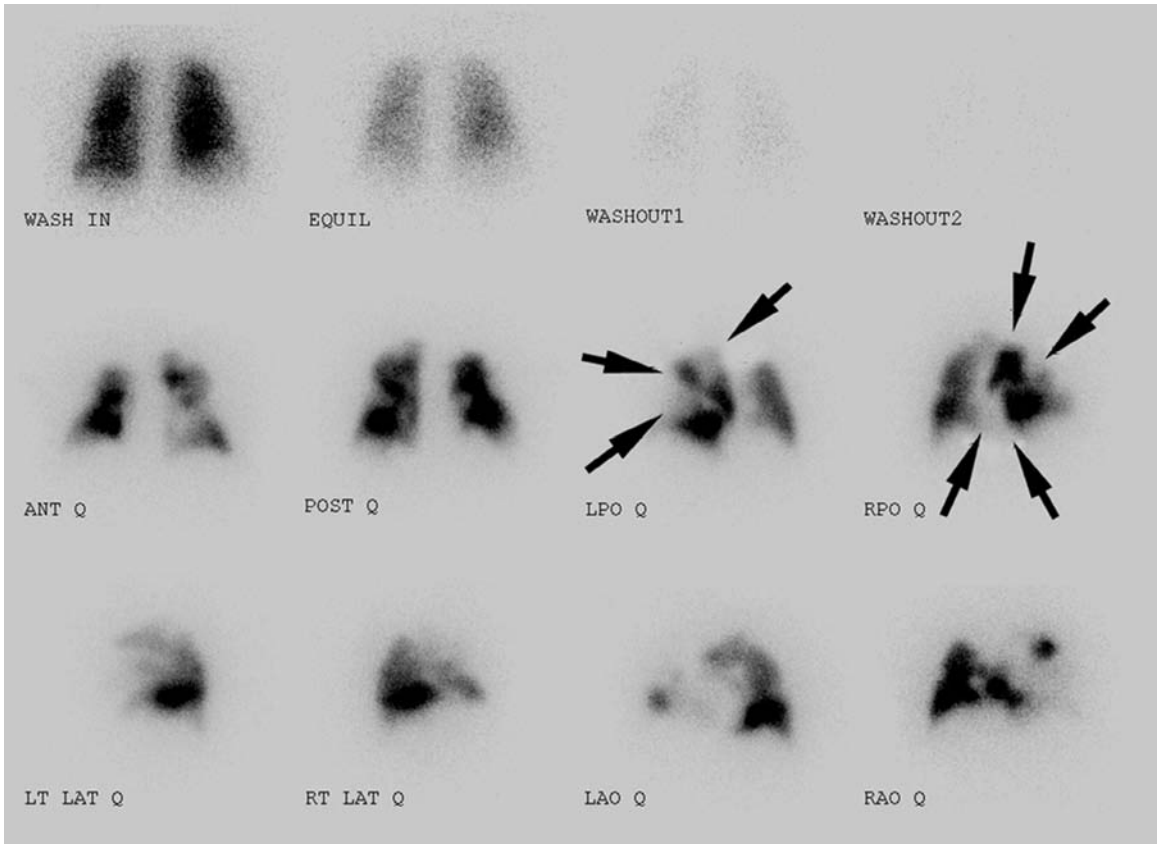


Figure 72-9 Ventilation–perfusion scan in chronic thromboembolic pulmonary hypertension. The top row of images shows normal ventilation; images in the following two rows reveal multiple unmatched perfusion defects, indicated by arrows in the posterior oblique views. *(Image used with permission of Kim Kerr, MD.)*

EXERCISE TESTING AND ASSESSMENT OF OXYHEMOGLOBIN SATURATION

Baseline testing should also include assessments of exercise tolerance and a determination of whether supplemental oxygen is required. A 6-minute walk test is a useful means of assessing exercise capacity and prognosis. It may be useful when choosing initial therapy and serial testing can be helpful in evaluating the response to therapy. Measurements of arterial oxyhemoglobin saturation both at rest and with exertion are important to ensure adequate levels are maintained, and to titrate supplemental oxygen appropriately.

CARDIAC CATHETERIZATION

Right heart cardiac catheterization is required to confirm the diagnosis of pulmonary hypertension, test for important cardiac causes, and in appropriate patients perform vasodilator trials to determine an initial approach to therapy. Both to ensure appropriate interpretation and avoid the need to subject the patient to repeated invasive testing when initial testing is inadequately performed, cardiac catheterization should be performed under the direction of expert operators sufficiently familiar with the evaluation of pulmonary hypertension. Except in those considered to be at very low risk of coronary artery disease, many expert centers also perform a left heart catheterization in all patients. In addition to coronary angiography, measurement of the left ventricular end diastolic pressure (LVEDP) is important to exclude left atrial hypertension (e.g., as seen in diastolic dysfunction) as an important cause of pulmonary hypertension (pulmonary venous hypertension). Although pulmonary artery wedge pressure (PAWP) is routinely obtained during right heart catheterization, it does not always provide an accurate estimate of LVEDP. To maximize the chance of an accurate measurement, PAWP should be made at end expiration and not on the basis of digitally computed "mean" PAWP.[205,206] The PAWP should be measured with equipment leveled at the midchest position (halfway between the table surface and skin surface at the sternum). Discrepant readings between the PAWP and the LVEDP may occur frequently, and so the need for left heart catheterization to directly measure left-sided pressures should be carefully considered given the therapeutic implications of the findings.[207]

During right heart catheterization, serial measurements of blood oxygen saturation should be performed for evidence of a "step up" in oxyhemoglobin saturation suggesting the presence of left to right shunting of blood as an etiology of PAH. Attention should also be paid to the right atrial pressure as significant elevation has been associated with a poorer prognosis. When suspicion of pulmonary hypertension is high and resting pressures are normal, some centers assess values with exercise (e.g., with serial leg lifts, arm raising with weights, or with a stationary bicycle). As noted previously, however, normative values for pressures with exercise have not been well established and whether exercise-induced PAH represents an early stage of disease or alone warrants treatment remains debated.

A diagnosis of PAH requires a mean pulmonary artery pressure greater than or equal to 25 mm Hg, an adequately measured PAWP or a directly recorded LVEDP of less than or equal to 15 mm Hg; an elevated PVR >3 Wood units is also seen and required in some published diagnostic criteria for PAH. The CO is obtained by either thermodilution or use of measured arterial and venous hemoglobin saturations and the Fick principle; the latter is likely more accurate when either significant tricuspid or pulmonary regurgitation is present or the CO is very low. The PVR is calculated as (mean

PA pressure – PCWP)/CO. A normal PVR may be seen if pulmonary hypertension is due to pulmonary venous hypertension, or abnormally high CO (as may occur, for example, in patients with hyperthyroidism, thiamine deficiency, Paget disease of the bone, or arteriovenous fistulae in hereditary hemorrhagic telangiectasia). PH with an elevated CO and normal PVR may also be found in some patients with liver disease (which is to be distinguished from those with PAH associated with liver disease, termed portopulmonary hypertension (POPH) and characterized by an elevated PVR, PH, and a variable CO). It must also be noted that although the hemodynamic profile of patients with PAH (an elevated mean PA with a normal PAWP) may be seen in patients with pulmonary hypertension and pulmonary parenchymal disease (Group 3) but pulmonary function testing and chest imaging distinguish these patients from those with PAH.

In patients with PAH, vasodilator testing is often performed at the time of right heart catheterization to identify those few patients in whom a trial of treatment with oral calcium channel antagonists is appropriate (discussed below). Agents commonly used for acute vasodilator testing include inhaled nitric oxide, intravenous adenosine, or epoprostenol administered by either route.[208–214] Although the definition has varied, a decrease in the mPAP of at least 10 mm Hg to a value less than 40 mm Hg, together with a CO that is unchanged or increased (but not decreased) is generally considered a "positive" acute vasodilator response.[194,215]

Acute vasodilator testing carries significant risk and deaths have been reported.[216] It should not be performed when PVOD is suspected, as the inability of the venous system to accommodate an acute increase in flow may precipitate pulmonary edema.[217] Acute vasodilator testing should be performed only at experienced centers and when the results will influence therapy. Patients who do not demonstrate acute vasoreactivity at the time of right heart catheterization should not receive calcium channel antagonist therapy.

EPIDEMIOLOGY OF PAH

Estimates of the incidence of PAH in studies from France, Scotland, Spain, and the United States range between 2.4 and 7.6 cases per million people. Prevalence estimates range between 15 and 26 cases per million people.[189,191,218–221] Overall, PAH appears to occur more frequently among women (around 2:1) and at a mean age of approximately 50. IPAH and PAH associated with connective tissue diseases appear to be the most commonly recognized in published studies, although limited studies suggest that the burden of schistosomiasis-related disease is likely large.

In the largest such study to date, the mean (±SD) age of patients enrolled in a multicenter US-based national registry of 2525 patients with PAH was 50.1 ± 14.4 years and 79.5% were female. Nearly half of the patients were diagnosed with idiopathic disease (Fig. 72-10). It is important to note that 86% of these were prevalent patients, with a mean of almost 3 years from the time of initial PAH diagnosis until enrollment in the study, thus limiting the ability to extrapolate these data to incident disease.[191]

The prognosis of patients with PAH is worse when hemodynamic variables indicate right heart dysfunction (e.g., elevated right atrial pressure or a depressed CO), and varies according to the specific diagnosis, with PAH associated with scleroderma and portal hypertension portending a worse prognosis than other forms of PAH. Although the outlook appears to have improved with advances in disease management and the availability of multiple drug classes for therapy, many patients continue to require consideration of lung transplantation, and many continue to die. Several risk prediction tools have been recently developed, derived using data from both incident and prevalent patients managed with currently available therapies.[222] One such tool derived and validated with patients in a large US-based cohort is shown in Figure 72-11. This, as well as other risk prediction models, have been validated in populations from other countries.[222–225]

SPECIFIC PAH DISEASE SUBTYPES

In the sections to follow, the various PAH disease subtypes will be discussed in detail.

■ IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

IPAH is a rare disease with an estimated incidence of 1 to 2 cases per million in industrialized countries.[226–228] The paucity of numbers of patients with IPAH and the likelihood that diverse causes and pathogenetic mechanisms can produce the same clinical syndrome have complicated descriptions of its natural history. In the past, certain stereotypes were regarded as the norm: young women with Raynaud's syndrome, with acute onset of dyspnea and fatigue, and death within 3 years. Now it is appreciated that even though there

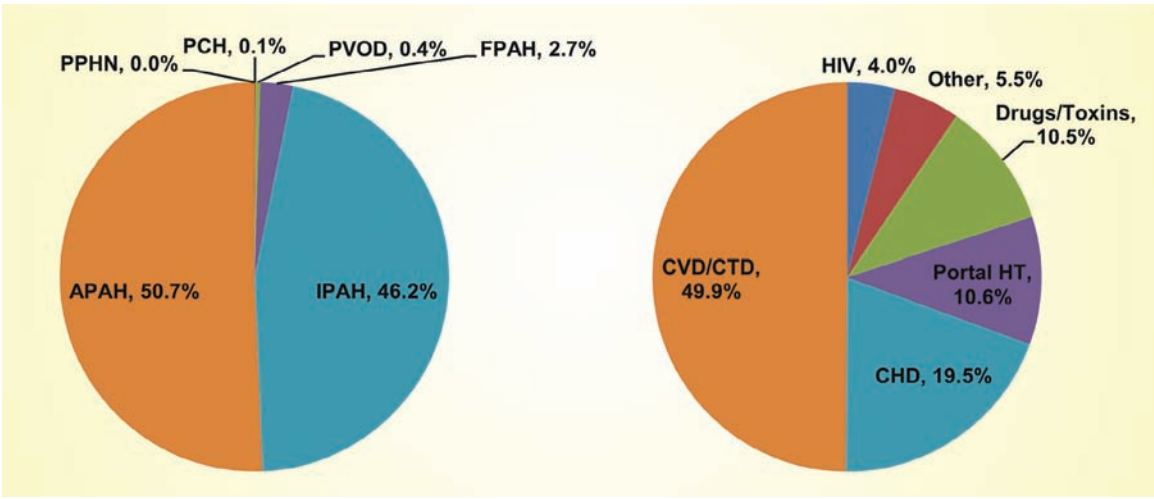


Figure 72-10 Distribution of pulmonary arterial hypertension diagnoses among 2525 prevalent patients in a United States national registry. World Health Organization (WHO) Group I pulmonary arterial hypertension classification of REVEAL patients at enrollment. **A.** WHO Group I PAH classification. **B.** Breakdown of associated PAH subgroup. APAH, associated PAH; CHD, congenital heart disease; CVT/CTD, collagen vascular disease/connective tissue disease; FPAH, familial PAH; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary venoocclusive disease; REVEAL, Registry to Evaluate Early And Long-term PAH Disease Management.

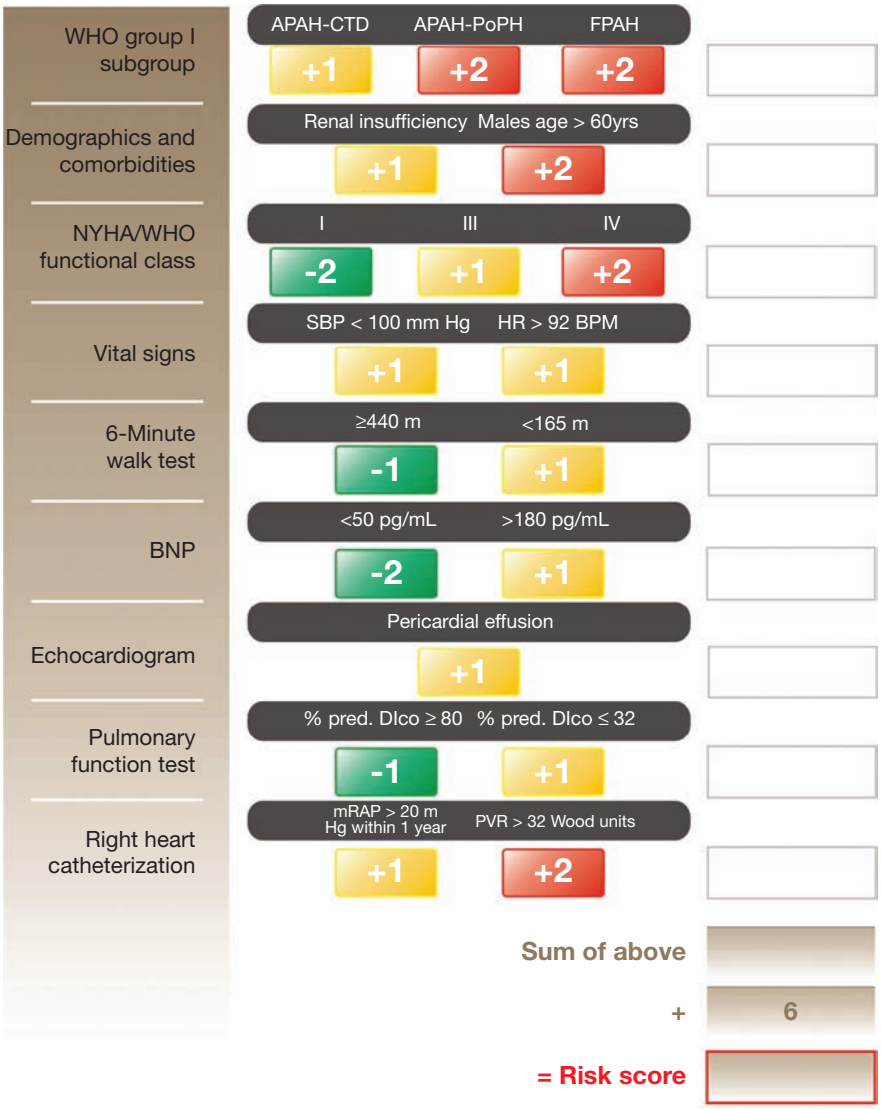


Figure 72-11 REVEAL Registry PAH Risk Score Calculator. Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). In the REVEAL cohort, the average predicted 1-year survival was 95% to 100% in the low-risk group (score <7), 90% to <95% in the average-risk group (score 8), 85% to <90% in the moderately high-risk group (score 9), 70% to <85% in the high-risk group (score 10–11), and <70% in the very high-risk group (score >12). If N-terminal proBNP is available and BNP is not, listed cut points are replaced with <300 pg/mL and >1500 pg/mL. APAH, associated pulmonary arterial hypertension; BNP, brain natriuretic peptide; BPM, beats per minute; CTD, connective tissue disease; $D_{L_{CO}}$, diffusing capacity of lung for carbon monoxide; FPAH, familial pulmonary arterial hypertension; HR, heart rate; mRAP, mean right atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; REVEAL Registry, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP 5 systolic BP; WHO, World Health Organization. *(Reproduced with permission from Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest. 2012;141(2):354–362.)*

is such a subset, prolonged survival in response to medical therapy is not unusual and the disease may affect all ages, both sexes, and different ethnic groups.[229,230]

To overcome the limitations of sporadic reports, the NIH established a nationwide registry in 1981 to collect and analyze data on IPAH (then called PPH). Criteria for entry of a patient into the national registry included normal pulmonary function tests (except for a moderate reduction in diffusing capacity); a right heart catheterization to exclude congenital or left heart disease; perfusion scans and, if inconclusive, pulmonary angiography to exclude CTEPH; and serologic testing to rule out collagen vascular disease. Included in the registry were certain associated diseases, such as hepatic cirrhosis, because the reason for the association was unclear and because of the suspicion that the association might provide a clue to etiology.

By the close of the registry in 1987, data were available on 187 patients.[231] The mean age was 36.4 years and similar for women and men, although the female-to-male ratio was 1.7:1. Few patients were older than 60 years, although race and ethnicity of the cohort was similar to that of the general population. Similar demographic trends have been reported in series from France, Israel, Japan, and Mexico.[228,232,233] Dyspnea was the most common initial symptom and the mean time to diagnosis among patients in the NIH registry was 2 years.

Prognosis of IPAH

Without effective therapy the prognosis of IPAH is very poor. The median survival of patients in the NIH registry was 2.8 years; estimated survival at 1, 3, and 5 years was 68%, 48%, and 34%, respectively.[231] Similar or even poorer figures have been reported absent

effective treatment in other series from various countries.[46,234] Most patients die of right heart failure.

The outlook is worse with more advanced symptoms. NIH registry patients with WHO functional classes III and IV symptoms had a median survival of only 31.5 months, as compared with 58.6 months in patients with milder impairment (Class I or II; Table 72-4). Although the figures have improved, functional status remains a significant indicator of prognosis even with effective advanced therapy.[228,235–238] Functional assessment with a 6-minute walk test, for example, is a useful means of following response to therapy and independently predicts prognosis.[237,239–241] Maximal oxygen consumption has also been used to assess response to therapy and can correlate with survival.[241]

On echocardiogram, an enlargement of the right atrium, the presence of a pericardial effusion and its severity are each associated with an increased risk of death.[201–204] A relative increase in the isovolumetric contraction and relaxation times of the RV as compared to RV ejection time is indicative of RV dysfunction and a significantly poorer prognosis.[242]

Levels of endothelin, catecholamines, and atrial natriuretic peptide have been correlated with disease severity, whereas elevations of uric acid, von Willebrand factor, D-dimer, troponin-T, and brain natriuretic peptide have each been associated with a poorer survival in patients with IPAH.[243–249] More recently, a low serum albumin has been associated with an increased risk of death, independent other measures that would reflect passive hepatic congestion or right heart dysfunction.[204] None of these putative prognostic markers is currently incorporated into clinical decision making.

Hemodynamic variables reflecting the development of right heart failure (an increased right atrial pressure and decreased cardiac index) are associated with a poorer prognosis.[228,233,250,251] Worsened survival has been seen in association with both increasing and decreasing mean pulmonary artery pressures (mPAPs). These observations are not necessarily contradictory. Rather, they reflect the natural history of right heart failure in PAH: mPAP rises initially as the vascular derangements worsen only to fall later as the right heart fails and is no longer able to generate an increased pressure (Figs. 72-8 and 72-12.)

A regression equation based on hemodynamic data from the NIH registry has been used to predict survival.[233,252] Because of the dismal prognosis expected, long-term "control" groups without treatment in clinical trials are unethical and assessments of survival with new therapies have been compared with outcome as predicted by the NIH equation. Such comparisons have suggested improved survival with epoprostenol and endothelin receptor antagonists. These improvements are addressed in the discussion of individual therapies in the following sections. As a growing number of effective drugs are now routinely employed, the relevance of survival estimates based on data from an era lacking effective treatment is questionable. The NIH registry equation may no longer be sufficient for predicting survival given current standards of care and background therapies. Indeed, when applied to a more recent cohort of patients treated with current agents, the NIH equation underestimated survival.[204]

It is not surprising that the prognosis of patients with IPAH who have suffered cardiac arrest is dismal even when resuscitative efforts are initiated promptly. In a retrospective review of the records of over 3000 patients, 132 episodes of attempted cardiopulmonary resuscitation (CPR) following cardiac arrest were identified. Survival at 90 days following CPR was only 6%.[253]

HERITABLE PULMONARY ARTERIAL HYPERTENSION

A family of patients with what was then termed "PPH" was first described by Dresdale in 1951.[4] Thereafter additional families were reported, and Loyd and Newman identified an autosomal dominant

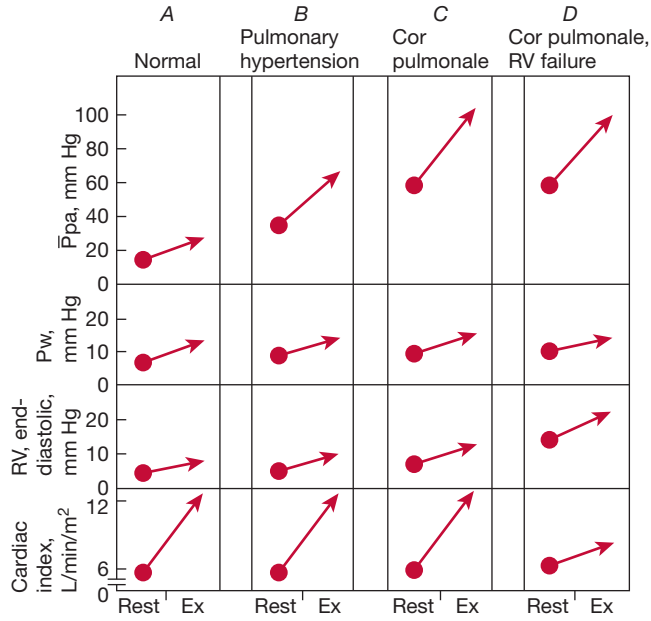


Figure 72-12 Schematic representation of evolution of chronic cor pulmonale. Hemodynamic studies at rest and during exercise in a normal subject (**A**). The stage of pulmonary arterial hypertension (**B**) is succeeded by cor pulmonale (**C**), in which the right ventricle performs normally despite pulmonary arterial hypertension but is known to be enlarged because of radiographic and electrocardiographic findings. Once right ventricular failure supervenes (**D**), cardiac output fails to increase normally during exercise, despite an increase of right ventricular filling pressure (end-diastolic) to abnormally high levels.

pattern of inheritance, a greater tendency for female carriers to manifest clinical disease, and an earlier onset in successive generations (genetic anticipation).[254,255] Linkage analysis led to a marker at chromosome 2q31–32, and mutations in the gene for a member of the TGFβ family of receptors, bone morphogenetic protein receptor II (BMPRII), were identified as the cause of heritable PAH.[175,176,256,257] Mutations in another member of the TGFβ family, ALK1 predispose patients with hereditary hemorrhagic telangiectasia to develop PAH.[185,186,258,259]

TGFβ receptors control an array of cell growth and differentiation systems. BMP signaling is involved in the control of normal vascular development as well as the homeostasis of the adult pulmonary vasculature, likely by regulating the growth and apoptosis of endothelial and smooth muscle cells.[170] In an assessment of mutations from the coding sequence of *BMPRII* in 210 patients, over 140 distinct mutations were identified, the majority predicting premature truncation of the gene transcript. Disease is believed to result from haploinsufficiency, where inadequate quantities of BMPR2 protein are produced for normal function.[177] In addition, the low penetrance observed in heritable PAH suggests that additional environmental factors likely contribute to disease development in genetically susceptible individuals.[260] Up to 70% of patients with heritable PAH have germline mutations in a *BMPRII* allele as do some patients with idiopathic and other associated forms of PAH.[175,176,178–183] Clinically asymptomatic carriers may have evidence of mild pulmonary hypertension on echocardiogram.[261] Common ancestries have been identified that link previously assumed "sporadic" cases of IPAH. Failure to recognize heritable cases of PAH may arise due to incomplete family history taking or reporting, and low disease penetrance, particularly in smaller families.[179,262]

There are no established differences in the approach to treating patients with heritable PAH as compared with IPAH. At present, the clinical evaluation of patients remains the same. Genetic testing of family members should be considered to assess the risk of developing PAH. As a rough guide, there is a one in five chance of PAH developing in a first-order relative who carries a disease-causing *BMPRII* mutation. If genetic testing has not been performed, the risk of disease developing in the first-order relative of a patient with known heritable PAH is approximately one in ten. In the absence of a disease-causing *BMPRII* mutation, the risk of disease is the same as in the general population (estimated at one in a million).[260] Because of the potential interpersonal, psychological, and economic implications of identifying an at-risk genotype, genetic testing should only be performed in conjunction with professional genetic counseling.

■ PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SPECIFIC CONDITIONS

Pulmonary arterial hypertension has been reported in a wide variety of disorders, as discussed below.

Collagen Vascular Diseases

The lungs and the pleura are commonly affected in patients with collagen vascular diseases. Although the incidence in each of the collagen vascular diseases varies, interstitial lung disease is more common than isolated involvement of the pulmonary vasculature. When present, however, PAH is frequently a more rapidly lethal development than interstitial lung disease. It is important in this population to differentiate between pulmonary hypertension associated with interstitial lung disease and the true development of PAH that occurs in the absence of significant interstitial changes. Pulmonary hypertension may also develop due to left heart ischemia or diastolic dysfunction, or to thromboembolic complications of collagen vascular disease.[263] Unfortunately, both interstitial lung disease and true PAH coexist in many patients. Most clinical studies of PAH therapy have excluded patients with collagen vascular diseases and evidence of "significant" restriction (usually defined as an FVC of <70% of predicted values) or interstitial changes on radiographs. Drugs that are efficacious in PAH have not proven effective in the treatment of pulmonary hypertension that accompanies interstitial lung disease. Among patients with systemic sclerosis, PAH occurs most commonly in those with limited disease or the CREST syndrome. Prevalence estimates have ranged significantly, but when investigated with right heart catheterization, PAH has been found in between 7% and 12% of patients.[264,265] The prognosis of patients with scleroderma is worse when their disease is complicated by PAH than by pulmonary fibrosis, even when the latter is severe. Nearly one-half of patients with PAH in the context of scleroderma die within 1 year, compared with a 3-year 50% mortality when the lung is affected by fibrosis alone.[266,267] Even with the use of equivalent therapies, the outcome of patients with PAH associated with systemic sclerosis is less favorable than for IPAH (Fig. 72-13).[90,236,266,268,269]

When estimated by echocardiography, pulmonary hypertension has been identified in approximately 4% to 10% of patients with systemic lupus erythematosis, but as many as 43% when patients are followed prospectively.[270–275] Estimates of prevalence are variable and most were obtained without confirmation by catheterization in patients with mixed connective tissue disease. Regardless of frequency, however, when it is present, PAH appears to be a significant cause of death in these patients. PAH occurs in numerous other rheumatologic disorders, including Sjögren's syndrome and rheumatoid arthritis although firm data on incidence or impact on survival are lacking.

Human Immunodeficiency Virus

Patients infected with the human immunodeficiency virus (HIV) are at increased risk of developing PAH. The mechanism by which HIV predisposes to the development of PAH is not known, but it does not appear to be due to direct viral infection of pulmonary vascular endothelial cells.[276] Infection may cause elevations in local concentrations of growth factors or other mediators such as endothelin to indirectly result in the development of PAH.[277–279]

The estimated annual incidence of PAH among HIV-infected patients is approximately 0.5%, significantly higher than the estimated annual incidence of 1.7 per million in the general population.[226,280] The annual incidence of pulmonary hypertension in a large Swiss cohort of HIV-positive patients appears to be declining, having peaked at 0.24% in 1993 as compared with 0.02% in 2001; this decline was hypothesized to relate to the introduction of highly effective antiretroviral therapies.[281] However, no such change was seen in a French study population, comparing rates of HIV-associated PAH between the early 1990s and 2008.[282] It is unclear, therefore, if better control of HIV infection alters the risk of developing PAH.

Symptoms, hemodynamic findings, and survival of PAH associated with HIV appear to be similar to IPAH.[283] Like IPAH, the prognosis is worse with more advanced symptoms (e.g., WHO functional class III or IV as compared with either I or II). A CD4 lymphocyte count below 212 cells/mm^3 has also been associated with a poorer prognosis.[284] Mortality is more often directly attributable to PAH and right heart failure than to infectious complications.[283,284]

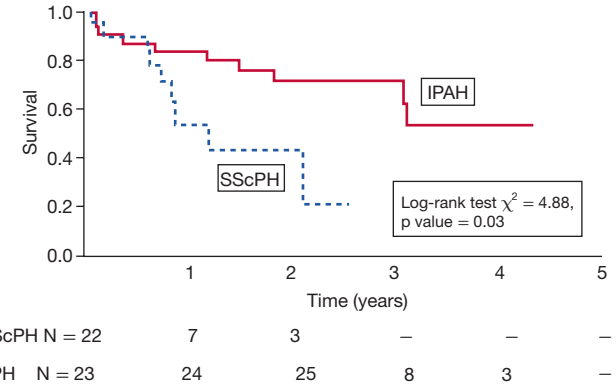


Figure 72-13 Survival of patients with systemic sclerosis–associated pulmonary arterial hypertension is worse than that of patients with idiopathic pulmonary arterial hypertension despite equivalent therapies. *(Reproduced with permission from Kawut SM, Taichman DB, Archer-Chicko CL, et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest. 2003;123(2):344–350.)*

Portal Hypertension

The lung may be affected by chronic liver disease in several ways, including the hepatopulmonary syndrome with the development of vascular dilatations and resultant hypoxemia, the development of pleural effusions (hepatic hydrothorax), and pulmonary hypertension. Liver disease is frequently characterized by a low systemic vascular resistance and high CO; the accompanying increased flow and blood volume result in pulmonary hypertension although the PVR is normal or even decreased. Vascular changes resulting in an elevated PVR, on the other hand, are seen with the development of PAH associated with portal hypertension, also termed POPH. Evaluation of pulmonary hypertension in these patients may be difficult as the high CO state of liver disease may precede or accompany the developmental POPH. Thus, as compared with patients with IPAH, patients with similar degrees of clinical impairment and POPH may display numerically smaller elevations in PVR or decrements in CO.[285]

The pathologic changes seen in POPH are similar to those described in other forms of PAH: vasoconstrictive, proliferative, and obliterative changes including both plexiform and thrombotic lesions.[286,287] The pathogenesis is not well understood and may involve abnormal proliferative (or other) vascular responses, but inducing triggers are not well defined. Portal hypertension might alter the vasoactive mediators to which the pulmonary circulation is exposed because of blood bypassing the liver via portosystemic shunts and returning to the systemic circulation.[288] As in other forms of PAH, altered levels of vasodilators and vasoconstrictors have been observed in patients with POPH.[289,290] Women with portal hypertension appear to be at greater risk for the development of POPH than men, as do patients with autoimmune hepatitis. The severity of portal hypertension does not appear to influence the risk of POPH.[291,292] Predisposing, likely genetic, factors are also believed to determine why only some patients with liver disease develop POPH.[293] The degree to which mutations in *BMPRII* are involved in the development of POPH remains unclear.

The prevalence of PAH in patients with liver disease has not been established. Estimates of up to 16% have been reported in studies screening patients with advanced liver disease.[289,294] In one series of patients evaluated for liver transplantation, the prevalence of POPH was 8.5%.[286] Incidence has not been evaluated. Without effective treatment the prognosis of POPH is poor, with a mean survival of only 15 months reported in one retrospective series of 78 patients.[295] Survival with current therapies is worse for patients with POPH than IPAH. In the REVEAL cohort, despite less severe hemodynamic derangements at the time of enrollment, 5-year survival of 174 patients with POPH was significantly worse than of 1478 patients with IPAH/HPAH (40% vs. 64%, respectively), although the initiation of therapy appeared to have been delayed in POPH as compared to IPAH.[285]

The symptoms and findings on physical examination of POPH reflect the presence of both PAH and of chronic liver disease. While shortness of breath may be overshadowed by abdominal complaints and fatigue, dyspnea becomes prominent as POPH progresses. Differentiating between the contributions of PAH-related cor pulmonale and cirrhosis as the cause of fatigue, edema, and abdominal complaints such as satiety, bloating, and ascites can be difficult.

Compared with IPAH, relatively little is known regarding effective treatments for POPH, due to the small number of patients with POPH and their exclusion from clinical trials. Mild disease usually does not require specific treatment; whether early therapy will prevent progression is unknown. Treatment for more severe disease differs from that of other patients with PAH in that some experts have advised against the use of calcium channel antagonists even if acute vasoreactivity is documented during cardiac catheterization. This concern is based upon the potential worsening of intrahepatic venous gradients by calcium channel antagonists.[296–299] Diuretics are particularly important in POPH due to the frequent presence of both cor pulmonale and cirrhosis causing fluid retention, edema, and ascites. Anticoagulation is less frequently employed due to pre-existing coagulopathy related to underlying hepatic synthetic deficiencies or the presence of splenomegaly and significant thrombocytopenia.

The experience with inhaled or parenteral prostenoids or oral endothelin antagonists or phosphodiesterase-5 inhibitors in the treatment of POPH has been reported in small case series.[300–309] Given the significant incidence of liver function abnormalities associated with endothelin antagonist treatment, there has been concern for their use in patients with POPH. However, bosentan was successfully used in a nonrandomized study of 11 patients with POPH and Child Class A resulting in improvements in hemodynamic values, exercise capacity, and no significant liver toxicity.[310] The potentially more favorable liver toxicity profile of ambrisentan may permit therapy in additional patients with POPH, and the safe use of the drug in this setting has been reported.[311,312]

Many patients with advanced hepatic dysfunction require liver transplantation. The perioperative mortality is significantly increased by the presence of severe PAH, however, and therefore a mean PA pressure above 50 mm Hg is considered a contraindication to transplantation at most centers.[313,314] Effective treatment to lower PAPs has been used in some patients who subsequently underwent orthotopic liver transplantation successfully.[300–303,307,315] It is therefore essential that POPH be recognized in patients being considered for liver transplantation prior to surgery. All potential liver transplant patients should be assessed by echocardiography, and cardiac catheterization should be undertaken when the estimated right ventricular systolic pressure approaches 50 mm Hg. Serial monitoring for the development of pulmonary hypertension should be performed in patients listed for liver transplantation.[316] Unlike the hepatopulmonary syndrome in which liver transplantation results in resolution of the pulmonary vascular abnormality, liver transplantation is not reliably curative of POPH. While some cases of reversal have been reported, POPH has progressed in other patients following transplantation.[296]

Drugs and Toxins

The term "dietary pulmonary hypertension" refers to the fact that substances taken by mouth can damage the pulmonary circulation. In animals, ingestion of *Crotalaria spectabilis*, an annual shrub, causes multiorgan injury, including damage to the lungs. In humans, certain appetite suppressant drugs exert similar effects.

Anorectic Agents—Aminorex and Fenfluramine Derivative

Between 1966 and 1968, an epidemic of PAH erupted in Switzerland, Austria, and Germany where the incidence increased 20-fold.[317] The epidemic followed the introduction in these countries of an appetite-depressant agent, aminorex (2-amino-5-phenyl-2-oxazoline), in November 1965. Although only 2% of those exposed to the drug developed PAH, the relative risk compared to unexposed individuals was 52:1.[318] Aminorex resembles epinephrine and amphetamine in chemical structure; both of these agents release endogenous stores of catecholamines. Aminorex was banned in 1968, and the epidemic subsided. After stopping the drug, the level of pulmonary hypertension decreased or stabilized at a tolerable level in some patients and completely reversed in others. However, in many patients, the disease continued inexorably from pulmonary hypertension to cor pulmonale and death despite discontinuation of the drug. The pathology produced by aminorex in humans was identical with that of IPAH, including plexiform lesions and intimal fibrosis. Unfortunately, attempts to produce pulmonary hypertension by administering aminorex to experimental animals were consistently unsuccessful.

This outbreak had several important epidemiologic implications: (1) A medication taken by mouth could damage pulmonary arteries and arterioles; (2) because only few of the many individuals who used the agent developed pulmonary hypertension, the possibility was raised of genetic susceptibility to injury by aminorex; (3) other anorectic medications that resemble the catecholamines and amphetamines in structure might have similar effects in predisposed individuals (this possibility was reinforced by experience with phenformin, an antidiabetic agent that resembles the amphetamines in structure); and (4) pulmonary hypertension can be reversible, particularly when detected early in its course and before pressures reach systemic levels.

After the aminorex epidemic, a variety of appetite-suppressant medications were used with little heed to the possibility that these agents might cause PAH. Then, in the early 1990s, Brenot et al.[319] called attention to possible association in Europe of PAH and the

use of fenfluramine derivatives for weight reduction, prompting the establishment of an international registry in Europe to assess the incidence and risks of IPAH. Among the 95 patients enrolled in the registry, anorectic agent use was clearly associated with an increased risk of PAH, especially when taken longer than 3 months (odds ratio 23.8). In 1996, Abenheim sounded the alarm that an epidemic might be in the making: the Food and Drug Administration in the United States had approved the use of dexfenfluramine, a fenfluramine derivative, for the long-term treatment of obesity even though experience with long-term use was extremely sparse.[226]

Approval of dexfenfluramine by the FDA was followed by a tremendous increase in sales of this and other anorectic agents. A registry of idiopathic and anorectic agent associated PAH in the United States revealed that use of fenfluramine was strongly associated with the development of PAH (odds ratio 7.5 with greater than 6 months use). A high prevalence of anorectic agent use in patients with other forms of PAH was also seen, suggesting these agents might also precipitate disease in the presence of other risks such as a collagen vascular disease.[320]

Several points were illustrated: (1) Although aminorex and the fenfluramines differ in their pharmacologic characteristics, the pulmonary vascular lesions in the patients who die of pulmonary hypertension after taking either drug are identical; (2) the longer the anorectic agent is used, the more likely pulmonary hypertension is to develop; and (3) the occurrence of pulmonary hypertension in users of anorectic agents likely is related to other determinants of susceptibility, perhaps genetic.

Aminorex and fenfluramine derivatives may cause PAH by altering blood levels of serotonin (5-HT). These agents cause the release of serotonin from storage in platelets and inhibit its reuptake,[71] and serotonin is a potent vasoconstrictor and induces the aggregation of platelets. An additional mechanism by which aminorex and fenfluramine derivatives might contribute to pulmonary vasoconstriction is via the inhibition of potassium channels that mediate vasodilation.[128] An inductive role of anorexigens in promoting the development of PAH in genetically susceptible individuals has also been hypothesized. Genotyping for the presence of mutations in *BMPRII* (with familial PAH) has not revealed a significant number of abnormalities among patients with anorexigen-associated PAH.[181,321]

In one series of 62 patients with fenfluramine-associated PAH evaluated over a 10-year period at a single center in France, the interval from drug exposure to the development of dyspnea was approximately 4 years. Hemodynamic values at the time of diagnosis were similar to a control group of patients with IPAH, although the anorectic agent–exposed patients were less likely to demonstrate acute vasoreactivity and thus be treated with calcium channel antagonists.[322] The approach to therapy for PAH associated with anorectic agent use, however, is similar as for IPAH.

Relatively little is known regarding the prognosis of anorectic agent–associated disease. Data conflict regarding prognosis as compared with IPAH. In one retrospective study of 104 patients with aminorex-associated PAH and 69 with IPAH, survival was better in both groups for patients treated with warfarin, and better overall for the anorectic-agent associated disease patients.[323] With the use of advanced therapies, survival in fenfluramine-exposed patients with PAH appears similar to that of IPAH patients.[322] When matched according to treatments and disease severity, however, a separate study of IPAH and fenfluramine-exposed patients found poorer survival in the anorectic agent group.[324]

Toxic Oil Syndrome

Another episode of dietary pulmonary hypertension unfolded with the occurrence of the "toxic oil syndrome." In May and June 1981, rapeseed oil adulterated with aniline was sold door to door as olive oil in Spain and caused an outbreak of noncardiogenic pulmonary edema.[325] Twenty thousand persons were affected, and approximately 375 died. About 2000 individuals experienced sequelae. As a consequence of close surveillance, the features of three stages of the disease were categorized as early (first 6 months), intermediate (6 months to 2 years), and chronic (persisting years). From the outset, it was clear that the damage was widespread (affecting lungs, liver, skin, nervous system, immune system, muscle, and fat) and that pervasive endothelial injury featured prominently in the pathogenesis of the clinical syndromes.

The early stage was characterized by noncardiogenic pulmonary edema, eosinophilia, and pulmonary hypertension in a subset of patients; these findings resolved within 6 months. The intermediate stage was marked by thromboembolic events, weight loss, and neuromuscular dystrophies; PAH developed in some but often resolved. The chronic stage (particularly 4 and 5 years after the oil was ingested) involved progressive PAH and cor pulmonale. Increasingly evident were vascular lesions of intimal fibrosis and proliferation in association with organized pulmonary thromboemboli. Plexiform lesions were also seen.

Unfortunately, the exact chemical ingredients in the toxic oil responsible for the syndrome remain enigmatic and are unlikely to be identified, since the bootleggers could provide no recipe for the adulterated cooking oil. Nonetheless, the outbreak did show that material taken by mouth – often in small quantities – could cause widespread endothelial injury in the lungs. It also underscored the spontaneous reversibility of the pulmonary hypertension (as well as the ineffectiveness of vasodilators tried at different stages in the disease).

Hemoglobinopathies

Patients with sickle cell anemia and other hemoglobinopathies are at increased risk for the development of pulmonary hypertension. Pulmonary hypertension in this setting has been variably categorized as WHO Group 1 (PAH) or as WHO Group 5 disease. Multiple factors likely contribute to the pathogenesis of pulmonary hypertension in patients with hemolytic states, including recurrent thromboembolism, recurrent infectious or hemolytic crises causing lung damage and hypoxia, asplenia, and the microvascular effects of intravascular hemolysis itself. Hemolysis contributes to the development of pulmonary hypertension by reducing the bioavailability of NO. Hemoglobin is released into the plasma from destroyed red blood cells where it can bind and sequester NO. There is also destruction of the substrate for NO production, L-arginine, by increased levels the enzyme arginase, also released into plasma by hemolysis. Further effects of hemolysis include an increase in the expression of vascular adhesion molecules, platelet activation, the production of free radicals, and elevated levels of endothelin, all of which might contribute to the vasculopathy.[326–328]

The reported prevalence of pulmonary hypertension in patients with sickle cell anemia has ranged from 0% to 40%. Factors influencing this wide range include the age of patients examined, whether the study involved asymptomatic or symptomatic patients, and whether testing involved echocardiography or cardiac catheterization. In one prospective study of 195 adult patients with sickle cell anemia, 32% of patients had echocardiographic evidence of pulmonary hypertension, of which over 90% had the SS phenotype.[329] Pulmonary hypertension is associated with a poorer prognosis in patients with sickle cell anemia.[326,329] Pulmonary hypertension has also been noted in patients with other chronic hemolytic disorders, including thalassemias, hereditary spherocytosis, and paroxysmal nocturnal hemoglobinuria.[330–335]

The hemodynamic findings of pulmonary hypertension associated with sickle cell anemia differ from those seen in patients with idiopathic or other forms of associated PAH. Specifically, the mean PAP tends to be lower and CO higher in patients with sickle cell anemia diagnosed

with pulmonary hypertension than in patients with IPAH. In addition, many patients with hemoglobinopathy and pulmonary hypertension demonstrate a combination of intrinsic pulmonary vascular disease suggested by an elevated vascular resistance together with left heart diastolic dysfunction with an elevated PAWP.[336] As an example, in 20 patients with pulmonary hypertension associated with sickle cell anemia the mean PAP was 36 mm Hg, CO 8.6 L/min, and PCWP 16 mm Hg; one-half of the patients had PAWP values above 15 mm Hg.[337]

The optimal treatment of patients with pulmonary hypertension associated with a hemoglobinopathy has not been established. As markers of ongoing hemolysis correlate with the severity of pulmonary hypertension as well as survival in patients with sickle cell disease, maximizing treatment of the hemolytic anemia is likely an important therapeutic consideration.[326,329] Treatment includes the use of hydroxyurea or transfusions to minimize anemia and ongoing hemolysis. Intravenous prostacyclin can acutely decrease the mean PAP and PVR in patients with PAH associated with sickle cell anemia, but its long-term benefits have not been established.[337] Oral sildenafil has been shown to acutely improve the mPAP, PVR and cardiac index; however, conflicting effects on 6-minute walk distance have been reported.[338,339] Safety concerns such as headache, priapism, and increased hospitalization rates for pain remain incompletely resolved. Improvement with sildenafil has also been reported in a small, uncontrolled series of patients with other hemoglobinopathies but large trials are lacking.[340] Supplemental oxygen to prevent hypoxia should be used as in other forms of pulmonary hypertension. While not studied in patients with hemoglobinopathy for treatment of pulmonary hypertension itself, anticoagulation to prevent thromboembolic complications of sickle cell anemia is also a consideration.

PULMONARY VENOOCCLUSIVE DISEASE

PVOD is a rare form of PAH in which there is even less understanding of mechanisms and less experience with therapy.[217,341] Some combination of pathologic changes on both the arterial and venous sides of the pulmonary circulation is found in all forms of PAH, but arterial changes tend to predominate in most cases. There is patchy occlusion of pulmonary veins by fibrous tissue, intimal thickening, and large numbers of hemosiderin-laden macrophages. Lymphatic dilation in the lung and pleura are additional features, likely related to pulmonary capillary hypertension and consequent chronically increased hydrostatic movement of fluid from the capillaries into the interstitium.

The incidence and prevalence of PVOD are unknown owing at least in part to frequent misdiagnosis as IPAH. Thirteen percent of cases in the NIH registry had histologic changes of PVOD.[37] In a pooling of IPAH patient series in which cases meeting criteria for a diagnosis of PVOD were reported, an incidence of 0.1 to 0.2 cases per million persons in the general population has been estimated.[217] Prospective studies have not been performed, however, and this figure likely underestimates the true incidence of PVOD, as some cases are likely misclassified as either interstitial lung disease or heart failure because of similarities in radiographic appearance.[341] There is no apparent predilection for women (as is seen in IPAH) and patients have been diagnosed from infancy to the seventh decade of life.[342]

The risk factors for PVOD are not well known. As familial cases of this apparently rare disease have been reported, a genetic predisposition has been postulated. Indeed, mutations in *BMPRII* have been identified in several patients with PVOD.[183,342] Case reports of PVOD complicating treatment of cancer with various chemotherapeutic agents (notably mitomycin, bleomycin, carmustine, and gemcitabine) or following bone marrow transplantation suggest that toxic exposures might elicit pathologic vascular responses.[343–356] Other case reports have noted the development of PVOD in association with various thrombophilic states, autoimmune disorders, or following bacterial or viral infection, including HIV.[357–364] More recently, abnormal circulating cytotoxic lymphocyte subpopulations and epigenetic dysregulation within the GNLY gene have been reported in individuals with PVOD, although the significance of such observations remains unclear.[365]

Patients with PVOD usually present with dyspnea and fatigue; symptoms less typical of other forms of PAH such as cough, orthopnea, and hemoptysis have also been observed.[196,366–370] The presence of basilar inspiratory crackles on physical examination favors a diagnosis of PVOD over other forms of PAH although these are clearly nonspecific. Decreased basilar breath sounds might suggest the presence of pleural effusions, which tend to occur more commonly in PVOD.[371,372]

The diagnosis of PVOD is suggested by the triad of pulmonary hypertension, radiographic evidence of pulmonary edema, and a normal PCWP. Unfortunately, all three are not universally present in cases of PVOD and the diagnosis frequently is delayed because of confusing findings during evaluation. As an example, "high probability" findings on ventilation–perfusion scanning, a frequent finding in PVOD, may lead to an erroneous diagnosis of CTEPH.[373] Findings on plain radiographs and CT scans in PVOD include enlargement of the central pulmonary arteries, peribronchial cuffing, Kerley B lines, interstitial infiltrates, and pleural effusions that in other circumstances might suggest left heart failure.[196,374]

In the appropriately placed pulmonary artery catheter with its balloon inflated, there is a static column of blood from the catheter tip to the left atrium and the pressure transduced is reflective of left heart chamber filling pressures (which should be normal in patients with PVOD).[375,376] Obtaining an adequate tracing, however, can be difficult and may require positioning the catheter in multiple areas. Of note, there may be a marked rise in measured pressure and a subsequent slow decline back to normal when saline is flushed through the wedged catheter; this is presumed due to impaired run-off of fluid through the restricted pulmonary venous vessels.

The antemortem diagnosis of PVOD often requires surgical biopsy but this frequently is avoided due to increased operative and anesthetic risk in the setting of severe pulmonary hypertension, particularly given the questionable impact on therapy that establishing the diagnosis produces. However, establishing a diagnosis does provide prognostic information to the patient, may influence the urgency of evaluation for lung transplantation, and may be helpful in avoiding needless and possibly harmful therapies.

The features atypical of other forms of PAH (e.g., radiographic abnormalities "normally" consistent with left heart failure) should prompt caution when considering acute vasodilator testing.[196,374] Acute pulmonary edema, at times life-threatening, has been precipitated by the administration of vasodilators to patients with PVOD.

There are no established therapies for PVOD. Controlled studies have not been performed and only anecdotal reports are available. These describe both positive and negative responses to various agents. Some patients have experienced benefit while others have died with the use of calcium channel antagonists, intravenous epoprostenol, or other advanced therapies.[196,377–382] Glucocorticoids and other immunosuppressive agents have been attempted but experience has been anecdotal, with mixed results, and their use is not generally recommended except in rare cases where a concomitant inflammatory condition exists.[341,383,384] As in other forms of PAH, diuretics and supplemental oxygen should be employed as indicated. Lung transplantation is the only therapeutic option for many patients. The prognosis of patients with PVOD is poor, with most dying within 2 years of diagnosis.

PULMONARY CAPILLARY HEMANGIOMATOSIS

Pulmonary capillary hemangiomatosis is another rare form of PAH with predominant involvement of the pulmonary veins. Pathologically, the findings are those of "pulmonary microvasculopathy" marked by angioproliferative capillary lesions that appear to invade the pulmonary vessels, interstitium, and in some cases the airways.[385,386] The etiology is unknown. Descriptive studies have reported the presence of vascular growth factors as well as markers of altered endothelial cell

proliferation; altered expression of nitric oxide synthase has also been noted.[387–389] A heritable form has been reported to have occurred in three siblings but specific genetic linkage has not been established.[390]

Epidemiologic features of the disease are unknown, as only scattered case reports are available for evaluation. Pulmonary capillary hemangiomatosis may present with dyspnea and episodes of hemoptysis, and cases both with and without associated pulmonary hypertension have been reported. The radiographic findings are described as diffuse bilateral reticulonodular infiltrates, often associated with enlargement of the central pulmonary arteries.[391,392] The prognosis is poor, with most cases reported as fatal, often rapidly. Attempts at treatment with intravenous epoprostenol have resulted in pulmonary edema.[393–395] Successful treatment of several patients has been described with α-interferon; another patient with superimposed endotheliomatosis was stabilized with doxycycline.[396,397] Urgent evaluation for lung transplantation is recommended.

■ SCHISTOSOMIASIS

Schistosomiasis, also referred to as bilharzia or snail fever, is caused by infection with any of several species of the trematode flatworm fluke *Schistosoma.* Typically, humans contract schistosomiasis by contact with shallow water that contains snails that are intermediate hosts of the *Schistosoma* pathogen. Cercariae, the life-cycle stage released from infected snails, may penetrate human skin and after a conformational change to become schistosomulae, reach the lungs.[398] Lung involvement tends to develop after extensive chronic liver involvement and there is debate about the relative contributions of POPH, periovular granulomas in the lungs, and host immunologic changes in producing PAH-like pathologic changes in up to 9% of patients.[399] It is estimated that up to 300 million individuals worldwide have schistosomiasis and as such it is likely to be one of the most numerically important causes of PAH. Patients generally present clinically with dyspnea on exertion and other features similar to PAH due to other causes. Diagnosis requires documentation of PAH via hemodynamic assessments along with clinical and serologic evidence of *Schistosoma* infection.

Much remains unknown regarding the prognosis and optimal approach to therapy. One series of 54 patients in Brazil suggested a more benign course than IPAH patients at the same institution.[400] Treatment with prostenoids, endothelin antagonists, and phosphodiesterase-5 inhibitors appears efficacious in improving hemodynamics and 6-minute walk distance although large randomized trials are lacking.[401] The antischistosomal agent, praziquantel, can reverse pulmonary hypertension and vascular remodeling in murine schistosomiasis although its efficacy in human disease is not documented.[402]

THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

The many facets and challenges in treating pulmonary arterial hypertension are presented below.

■ A CAUTIONARY NOTE: NON-PAH FORMS OF PULMONARY HYPERTENSION

Therapy must be driven by an appropriately established diagnosis.[403] As is noted previously, PAH is but one form of pulmonary hypertension and overall less common than pulmonary hypertension due to parenchymal lung or left heart disorders. Appropriate therapy for pulmonary hypertension due to left heart disease or parenchymal lung disease centers on optimal management of the underlying left heart disorder or lung disease, respectively. Far too often focus on the presence of pulmonary hypertension distracts clinicians' attention from the underlying cause. This not only leads to inappropriate use of drugs that are of established benefit only among patients with PAH, but may be accompanied by a failure to pursue appropriate therapies more likely to relieve a patient's symptoms (such as appropriate fluid management for left heart failure, interventions for coronary artery disease, correction of a mitral or aortic valvular dysfunction, bronchodilators and other inhaled medications for obstructive lung disease, or control of systemic hypertension). Other times, when underlying lung or left heart disorders have been maximally treated and symptoms remain, frustrated clinicians and patients may be driven to "blame" persistent problems on the presence of pulmonary hypertension. They may try drugs approved for treatment of PAH reasoning, "there is nothing else to do," or that, "it couldn't hurt." Unfortunately, such an approach is currently ill-informed and potentially harmful. The use of drugs approved for treatment of PAH in patients with other forms of pulmonary hypertension has not been found to be beneficial and is associated with known harms including exposure to well-established side effects. For example, randomized trials of patients with decreased left ventricular systolic function have raised concerns for worsened heart failure with the use of endothelin receptor antagonists, and have resulted in an increased risk for death with epoprostenol infusion.[404,405] Another randomized trial of patients with COPD and echocardiographic evidence of pulmonary hypertension found use of bosentan worsened hypoxemia and quality of life, and failed to improve exercise capacity.[406] Despite suggestion of improved exercise capacity among patients with left heart dysfunction and pulmonary hypertension treated with sildenafil in a preliminary study, a larger randomized trial found no improvement, and there were more adverse events among the participants who received sildenafil.[407,408] Finally, the high expense of these drugs often must be borne by the patient as well as the healthcare system.

■ GENERAL MANAGEMENT

A variety of pharmacologic and nonpharmacologic interventions are used in treatment of pulmonary arterial hypertension. PAH-specific pharmacotherapy is discussed in a separate section, below.

Exercise and the Avoidance of Deconditioning

Regardless of the cause, patients with pulmonary hypertension and cor pulmonale should be encouraged to maintain as active a lifestyle as possible. Recommendations that the patient minimize exertion for fear of further raising pulmonary pressures generally result only in deconditioning of the muscles and an increase in fatigue and breathlessness when an activity is attempted. Regular, steady aerobic exercise should be encouraged, and is often best initiated under guidance of a pulmonary or cardiac rehabilitation program. Indeed, randomized trials of exercise rehabilitation in patients with PAH or CTEPH have demonstrated not only the safety of exercise in these patients, but improvements in exercise capacity (e.g., 6-minute walk distance) greater than that observed in randomized clinical trails of currently available pharmacologic treatments for PAH. Clinically significant improvements in exercise capacity as well as health-related quality of life occurred in both an intensive exercise regimen beginning with inpatient therapy, as well as a 10-week outpatient program of treadmill walking similar in intensity to that commonly used in pulmonary and cardiac rehabilitation programs.[409,410] In addition to improving strength and endurance, the benefits of a supervised rehabilitation program may include a decrease in the fear many patients with dyspnea experience when initiating exercise programs. Many rehabilitation programs teach techniques to cope with dyspnea when it occurs, allowing exercise to continue. Importantly, activities that cause patients to experience lightheadedness or syncope should be avoided, including hot showers or baths and bending over to lift heavy objects.

Oxygen Therapy

Although controlled studies analogous to those performed in the treatment of COPD have not been conducted,[411] it is recommended that patients with pulmonary hypertension avoid acute hypoxia, as hypoxic pulmonary vasoconstriction will add to the burden on the right ventricle. Oxygen relieves hypoxic pulmonary vasoconstriction, thus decreasing vascular resistance and improving CO.

It also lessens renal vasoconstriction, improving urinary sodium excretion, and alleviates tissue hypoxia by improving oxygen delivery. Measurements of arterial oxyhemoglobin saturation should be performed at rest, with exertion, and with sleep. Levels of arterial oxygen saturation below 90% should prompt supplemental oxygen. Maintenance of adequate oxygen saturation may be difficult in patients with severe pulmonary hypertension in whom a patient foramen ovale allows right-to-left shunting.

Air travel is a particular concern because of the threat of hypoxic pulmonary vasoconstriction. Measurements made during commercial airline flights lasting a mean of 3.6 hours in a series of patients with PAH or CTEPH found that oxyhemoglobin desaturation below 85% occurred in 26% of participants, at a mean cabin pressure of 1971 ± 73 m (6467 ± 240 ft) with the lowest occurring at 1829 m (6000 ft).[412] Over one-third of patients developed symptoms during flight. Although more definitive studies have not been performed, it seems prudent to evaluate pulmonary hypertension patients who plan air travel that will last more than a few hours for in-flight oxygen use, particularly among patients with prior need of supplemental oxygen (including with sleep only). Many pulmonary function laboratories can simulate conditions of high altitude with an inspired oxygen concentration of 15% to determine whether the patient requires supplemental oxygen to maintain adequate oxyhemoglobin saturation. Patients should contact airlines in advance of travel as requirements differ, as do costs (which regrettably may not be covered by insurance). An attractive alternative to stored oxygen systems are portable concentrators, which most airlines will permit patients to carry on board without special arrangements.

Immunizations

Immunizations against influenza and pneumococcal pneumonia are important preventive measures in all patients with pulmonary hypertension and cor pulmonale. Influenza vaccination should occur annually, and administration of the 23-valent polysaccharide pneumococcal vaccine should occur once at the time PH is diagnosed and again when the patient turns 65.

Fluid Management and Diuretics

Careful attention to avoid fluid overload is central to the management of cor pulmonale of any cause. Patients must be educated regarding appropriate dietary habits and to restrict sodium intake to minimize fluid retention and the development of right heart failure. Patients should weigh themselves daily so that any trend toward fluid retention can be reversed before progressive right ventricular overload results in failure that may then be more difficult to reverse and require inpatient treatment.

Management of right heart failure relies heavily on diuretic therapy. Spironolactone is often used to manage mild fluid retention. It may also have beneficial effects in heart failure by modulating neurohormones. Loop diuretics are often required to prevent more significant fluid retention and right heart failure. Indeed, high doses and combinations of diuretics are often required to maintain appropriate fluid balance, but must be used cautiously to avoid electrolyte imbalances and volume depletion.

Digitalis

It is unsettled whether cardiac glycosides should play a role in treating right heart failure. In one series of 17 patients with PAH and right ventricular failure, the intravenous administration of 1 mg of digoxin resulted in a modest increase in CO after 2 hours[413] but longer-term data are lacking. Approximately 25% of patients in the REVEAL registry were using digoxin, [191] but many physicians avoid use of this agent even when right-sided heart failure is evident on account of a lack of sufficient evidence regarding its use in PAH and the potential for toxicity.

Anticoagulation

In the absence of contraindications, anticoagulation with warfarin is recommended for patients with significant IPAH.[191,197] This is reasoned to be of benefit on the basis of autopsy studies revealing in situ thrombosis in both venous and arterial vessels without evidence of an embolic source in a significant proportion of patients with PAH.[44–46] Anticoagulation is also justified on the basis of the increased risk of venous thromboembolic disease in patients with severe heart failure and immobility, and their expected poor tolerance of embolic events. The efficacy of anticoagulant therapy in patients with PAH has never been studied in randomized controlled trials. Uncontrolled observational reports, however, have demonstrated an association between warfarin use and increased survival. In a study of 64 IPAH patients randomized to treatment with calcium channel antagonists or placebo, survival after 5 years was greater among those patients in either group who at their provider's discretion had received warfarin.[414] In a retrospective evaluation of 173 patients with either idiopathic or anorexigen-associated PAH, anticoagulation was associated with a statistically greater survival among the anorexigen agent patients and a trend toward improvement after 5 years of therapy in patients with idiopathic disease.[323] Extrapolating from such studies, warfarin is often prescribed to patients with other forms of PAH but disease-specific data supporting this practice is nonexistent.

The generally recommended target international normalized ratio (INR) for warfarin therapy in patients with PAH is 1.5 to 2.5.[415] The severity of disease (e.g., threshold mean PAP or PVR) at which anticoagulation should be initiated has not been determined. A role for newer, non-warfarin oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban) has not been defined in patients with PAH.

Contraception and Pregnancy

Pregnancy in women with IPAH is associated with a high mortality, on the order of 30% to 50%.[416–418] Expert consensus is that pregnancy should be avoided, and early termination recommended on account of the high maternal mortality.[191,197] Effective contraception should be ensured; if hormonal contraception is chosen, anticoagulation may be advisable to reduce the risk of venous thromboembolism. Although the successful management of pregnancy has been reported,[419] single and multicenter series continue to report high rates of maternal death despite the use of aggressive treatments including intravenous prostenoids.[420–422]

Other Considerations

Patients should be queried about the concomitant use of medications and herbs. Warfarin is particularly apt to be associated with drug–drug interactions. The use of vasoconstrictor or serotonergic medications for unrelated illnesses, such as migraine, should also be undertaken cautiously. Patients taking bosentan are at risk of interaction with such medications as cyclosporine and azole-type antimicrobial agents, and care must be taken to avoid glyburide-containing diabetic therapies. Surgical procedures may entail considerable operative and postoperative risk in patients with hemodynamic compromise from PAH.

Vulnerability of patients with severe PAH to vasovagal events has to be kept in mind. An attack can be precipitated by pain, nausea, vomiting, or straining (Fig. 72-14). The induction of anesthesia and intubation may be a particularly troublesome time. The combination of bradycardia and systemic vasodilation can lead to a precipitous drop in systemic blood pressure. Atropine or a similar agent should be kept at hand during invasive procedures.

■ PAH-SPECIFIC PHARMACOTHERAPY

Treatment of PAH aims to decrease PVR, thereby improving CO. Acute improvements occur in some patients with certain vasodilators. Used chronically, some agents also appear to have cellular

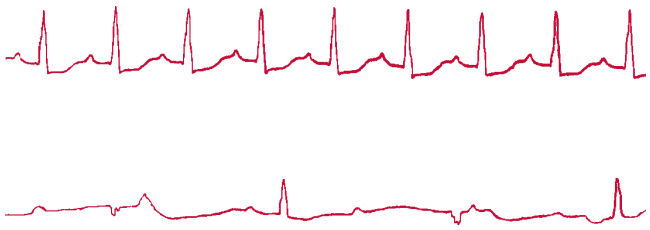


Figure 72-14 Idiopathic pulmonary arterial hypertension. Bradycardia and prolongation of atrioventricular conduction progressed to atrioventricular dissociation while patient was on bedpan. Associated with syncope.

effects that may ameliorate some of the vascular derangements seen in untreated disease. Remarkable progress in the treatment of IPAH has resulted in the availability of multiple therapies and a significantly improved outlook, with many long-term survivors. No currently available medical treatment, however, is curative and despite clinical improvement in many patients that is durable in some, histopathologic changes of vasculopathy remain.[423] Lung transplantation remains an option for some failing medical therapy.

The majority of subjects studied in controlled clinical trials of treatment with calcium channel antagonists, prostenoids, endothelin receptor antagonists, or phosphodiesterase inhibitors have been patients with either IPAH or PAH associated with scleroderma. Since most of these studies compared a single agent to placebo, our knowledge regarding the relative efficacy of available agents is limited by the lack of head-to-head comparisons. In addition, patients treated in earlier studies with epoprostenol were generally sicker than those treated in more recent studies of oral therapies. Finally, only small numbers of patients with heritable or various other forms of PAH have been studied, limiting our ability to draw firm conclusions about efficacy in these less common disorders.

Care must be taken in comparing and applying the results of clinical trials of different pharmacologic agents. Most clinical trials have enrolled patients and assessed response at least in part on the basis of a WHO modification of the New York Heart Association functional assessment of patients with heart failure (Table 72-4), and there appears to be substantial variability in even expert clinicians' judgments of functional class.[424] The 6-minute walk distance has been the most commonly used primary end point in trials of PAH drugs currently available, and with several exceptions improvements in this parameter have been the basis for their approval by the US Food and Drug Administration. The minimal clinically meaningful change in 6-minute walk distance in patients with PAH has been estimated to be between 33 and 42 meters.[425,426] These estimates, however, have been made using data from trials of predominantly treatment naïve patients, and may not be applicable when additional therapies are added.[427,428] Further, trials have mostly been of short duration (12–16 weeks). Additional endpoints such as threshold levels of exercise capacity, indications of clinical deterioration and long-term morbidity or even mortality may emerge as more important metrics to assess individual and combinations of drugs. Assessments of clinical deterioration have been reported as endpoints in several trials of PAH-specific therapy, including, for example, the time until PAH-related hospitalization, death, need for transplantation, or escalation of therapy, but the definitions used have varied.

In addition, the results of long-term follow-up studies (discussed below) must be interpreted with caution. In addition to being open-label (nonblinded) therapy, the selection of patients for therapy was determined at the physician's discretion (nonrandomized) and nonprotocol changes in other therapies occurred. Thus, confident assessments of the benefit or adverse effects of a given agent, comparison to others, and generalization of the findings are not possible. These results are, however, the best descriptions currently available regarding long-term use of these agents.

In general, the choice of initial therapy depends upon an assessment of disease severity and the patient's prognosis and risk for further, rapid deterioration. This judgment involves an assessment of a combination of variables, including hemodynamic and echocardiographic findings, exercise capacity, functional classification, and recent clinical stability of deterioration (Table 72-9). Although more or less "aggressive" approaches have not been compared directly in randomized studies, in general, patients thought to be at lower risk are first treated with an oral agent, whereas

TABLE 72-9 Assessment of Risk in PAH[a]

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class[b]	II, III	IV
6MW distance[c]	Longer (>400 m)	Shorter (<300 m)
CPET	Peak $\dot{V}_{O_2}$ greater than 10.4 mL/kg/min	Peak $\dot{V}_{O_2}$ less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m^2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m^2
BNP[d]	Minimally elevated	Significantly elevated

[a]*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.*
[b]*WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.*
[c]*6MW distance is also influenced by age, gender and height.*
[d]*As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.*
natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak $\dot{V}_{O_2}$, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; WHO, World Health Organization.
Source: Reproduced with permission from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc. and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619.

higher-risk patients are started on parenteral therapy. No single variable determines the choice of therapy. For example, a WHO functional class III patient without rapid recent clinical change and a cardiac index above 2.5 L/min/m^2 might be appropriately treated initially with oral therapy. A WHO class III patient who is either rapidly declining clinically or who has a more severely depressed cardiac index (e.g., below 2 L/min/m^2), however, might be more appropriately managed initially with intravenous prostenoid therapy. Personal preferences often influence a patient's willingness to undertake intravenous therapy. In addition, psychosocial issues, cognitive abilities, and other determinants of patient compliance may make certain therapies unsafe even if otherwise medically indicated.[429]

How best to follow patients treated for PAH, and to adjust medications, also are not well established. In addition to the clinical evaluation, most expert referral centers monitor patients with varying combinations of 6-minute walk distance measurements, echocardiograms, and serum NT-BNP. Some practitioners will repeat the right heart catheterization at regular intervals, while others do so only when a change in clinical status requires repeat diagnostic evaluation to guide further treatment. Which tests and frequencies are best at improving outcomes have not been studied in an organized manner, nor has the relative cost effectiveness of different approaches.

Note that additional therapies approved for the treatment of PAH by the FDA since the completion of this volume include an endothelin receptor antagonist (macitentan), an oral prostenoid (treprostinil) and a soluble guanylate cyclase inhibitor (riociguat). In addition, an up-dated guideline to pharmacotherapy for PAH has been released.[430]

Calcium Channel Antagonists

The calcium channel antagonists diminish vascular tone by preventing an increase in cytosolic calcium concentration through inhibition of both the influx of extracellular calcium and the release of calcium from intracellular stores. The long-term prognosis is good for some IPAH patients who respond acutely to the administration of short-acting pulmonary vasodilators and are treated subsequently with calcium channel antagonists. In one study, the survival rate of acutely vasoresponsive patients treated chronically with oral calcium antagonists was maintained at 94% when measured at 1, 3, and 5 years.[414] Unfortunately, relatively few patients demonstrate acute vasoreactivity (~10% by recent estimates) and of these only about one-half experience a sustained clinical response.[431] Oral calcium antagonists should not be used as vasodilator therapy in the absence of documented acute vasoreactivity. Those failing to demonstrate acute vasoreactivity not only fail to benefit from calcium channel antagonist therapy, but are also prone to adverse side effects including systemic hypotension, decreased CO because of a negative inotropic effects, arrhythmias, salt and water retention, syncope, and death. Acute vasodilator testing as described earlier is therefore required to determine whether a clinical trial of calcium channel antagonist therapy is appropriate.

Patients who do manifest a significant acute pulmonary vasodilator response to short-acting agents should undergo monitored trials of oral calcium channel antagonists while the pulmonary artery catheter is still in place. Increasing doses of nifedipine or diltiazem are usually administered until pulmonary hemodynamics are improved (i.e., there is a significant decrease in PVR and PAP and, ideally, an increase in CO). Agents such as verapamil, which exert negative inotropic effects, should be avoided. Testing is stopped if systemic hypotension or a trend of worsening hemodynamic values is seen. Relatively high doses of calcium channel antagonists are required to promote sufficient pulmonary vasodilation. In some instances, the required daily doses of nifedipine and diltiazem have exceeded 200 mg and 700 mg, respectively.[432] The total daily dose should be divided and administered in two or three doses of long-acting formulations to minimize peak and trough drug effects throughout the day. Patients treated with oral calcium antagonists must be monitored for the development of side effects including systemic hypotension or peripheral edema, as well as for evidence of continued benefit.

Endothelin Receptor Antagonists

Endothelin-1 (ET-1) is a member of the endothelin family of peptides secreted by endothelial cells that promote vasoconstriction and modulate the proliferation of vascular smooth muscle and endothelial cells. ET-1 is overexpressed in the vasculature of patients with various forms of PAH and antagonists of its interaction with its receptors (ET_A and ET_B) have been developed for oral use. A dual ET_A/ET_B and a relatively ET_A-selective antagonist are available.

Bosentan is a dual ET_A/ET_B antagonist that improves hemodynamics, exercise capacity, WHO functional class, and the time to clinical worsening (defined as death, PAH-related hospitalization, need for altered therapy or lung transplantation).[90,433] In a double-blind, randomized, placebo-controlled trial of patients with IPAH and PAH associated with collagen vascular disease (predominantly systemic sclerosis), bosentan improved the 6-minute walk distance by 44 m as compared with placebo at 16 weeks. Exercise capacity improved in IPAH patients, while stabilization or a slowing in the rate of deterioration was observed in patients with systemic sclerosis.[90] The beneficial effects of bosentan on exercise capacity and functional class persist at 1 year with open-label use.[434] In a double-blind, randomized placebo-controlled trial of PAH patients with less severe symptoms (WHO functional class II), bosentan treatment for 6 months improved hemodynamics and 6-minute walk distance as compared to placebo.[435] Survival of IPAH patients treated with bosentan in these trials and their open-label extensions was 96% at 1 year and 89% at 2 years as compared with "expected" survival of 69% and 57%, respectively, as predicted by the NIH registry equation.[92]

Improved hemodynamics and exercise capacity have also been demonstrated with bosentan use in a 16-week randomized controlled trial of patients with Eisenmenger syndrome, with persistent effects seen during a 24-week open-label extension.[436,437] Nonrandomized reports have suggested a benefit of bosentan in other specific PAH populations. A prospective open-label study of 16 patients with PAH associated with HIV infection reported improved hemodynamics, exercise capacity, and quality of life after 16 weeks.[438] Retrospective observational studies have reported the successful use of bosentan in pediatric patients with PAH.[439–442]

Ambrisentan is a relatively ET_A-selective antagonist. In concurrent double-blind, placebo-controlled studies of patients with PAH, 5 and 10 mg daily of ambrisentan for 12 weeks resulted in placebo-corrected improvements in 6-minute walk distance of 31 and 51 m, respectively, in one trial, and 32 and 59 m with 2.5 and 5 mg treatments, respectively, in the other trial. A delay in the time to clinical worsening was seen in one of the trials, and health-related quality of life improved in both.[443] In open-label extension studies, ambrisentan therapy was accompanied by improved hemodynamic values at a median duration of over 1 year and persistent improvements in exercise capacity at 2 years.[444,445]

Bosentan therapy is initiated at 62.5 mg orally twice daily and, if liver function remains normal, increased after 1 month to 125 mg twice daily. Liver function must be monitored monthly as significant elevations may occur; severe elevations (transaminase levels greater than eight times normal) require discontinuation of therapy. Lower rates of elevated transaminases are observed with ambrisentan than bosentan and the FDA-label requirement for monthly liver function monitoring has been removed for ambrisentan, although experts continue to recommend intermittent evaluations. Notable

side effects include peripheral edema (usually readily responsive to diuretics), anemia, and nasal congestion. Bosentan is contraindicated with either cyclosporine or glyburide. Both ambrisentan and bosentan are teratogenic and contraception and pregnancy testing are required for use in women with childbearing potential.

Phosphodiesterase Inhibitors

The relative deficiency of NO-mediated vasodilation and modulation of cell growth in patients with PAH has led to attempts to augment its effects therapeutically. NO acts through the second messenger cGMP, which is metabolized in the lung predominantly by phosphodiesterase 5. Specific inhibitors of phosphodiesterase type 5 (e.g., sildenafil, vardenafil, and tadalafil) can promote acute pulmonary vasodilation.[446]

In a double-blind, randomized placebo-controlled trial of 267 patients predominantly with IPAH but also some with congenital heart or collagen vascular disease, sildenafil administered orally at 20, 40, or 80 mg three times daily improved hemodynamics, exercise capacity, and functional class.[148] Although the time to clinical worsening was not affected in this single trial, the improvement in exercise capacity (51 m as compared with baseline) was maintained over 1 year among the subset of patients continuing open-label use of sildenafil at 80 mg three times daily. No statistically significant dose response was seen in the primary end point, exercise capacity, of this trial and the FDA-approved dosage for treatment of PAH is 20 mg by mouth three times daily. In open-label follow-up of a subset of patients up to 3 years following 12 weeks of randomized therapy with sildenafil, 46% demonstrated continued improvement over baseline exercise capacity, although additional therapies had been added to sildenafil during this period. In a posthoc analysis of patients in this randomized trial who had PAH associated with connective tissue disease (predominantly scleroderma and lupus erythematosis), improvements in exercise capacity, functional class, and hemodynamics were seen. An initial 12-week, double-blind, placebo-controlled trial of sildenafil for treatment of PAH in children aged 1 to 18 years demonstrated efficacy in improving exercise capacity and hemodynamics at some doses, although the optimal regimen requires further study.[447]

A 12-week, double-blind, placebo-controlled trial of four different doses of tadalafil found an overall placebo-corrected increase in 6-minute walk distance of 33 m (although statistically significant only for the highest dose group, 40 mg daily). The time to clinical worsening and quality of life also improved.[149] The trial included both treatment naïve patients with PAH, as well as those already receiving bosentan treatment. The mean improvement in 6-minute walk distance was greater among the treatment naïve participants (44 m) than those already receiving bosentan (23 m). During open-label extension for up to 1 year, improvements in 6-minute walk distance in patients receiving either 20 or 40 mg daily of tadalafil appeared to be maintained.[448] In a 12-week, double-blind, placebo-controlled trial of an additional phosphodiesterase type 5 inhibitor, vardenafil, improved 6-minute walk distance and hemodynamic values.[449]

Common side effects of phosphodiesterase type 5 inhibitors when used to treat PAH are headache, flushing, diarrhea, epistaxis, and myalgias. Systemic hypotension has also occurred, particularly with concomitant nitrate use, and this combination should be avoided.

Prostenoid Therapies

Prostacyclin analogs have played a key role in the management of idiopathic and other forms of PAH. Prostacyclin is a powerful vasodilator (both pulmonary and systemic) as well as an inhibitor of smooth muscle proliferation and platelet aggregation. It is a product of arachidonic acid metabolism and acts, at least in part, by stimulating the intracellular production of cAMP. Its major source is the vascular endothelial cell and deficiencies are noted in patients with PAH. Several synthetic prostacyclin analogs are currently available in the United States for the long-term treatment of PAH, including formulations administered by continuous intravenous infusion (epoprostenol and treprostinil), subcutaneous infusion (treprostinil), and via inhalation (treprostinil and iloprost).

Prostenoid infusion therapy requires a relatively highly functional and compliant patient for safe administration, preferably in conjunction with a strong social support system at home. Intensive patient and family education is required for safe initiation of therapy and, particularly for intravenous infusions, is often performed with the patient hospitalized until appropriate understanding and proficiency in self-care is demonstrated. While appropriate expertise in the management of PAH is required for nonparenteral treatments, parenteral prostenoid therapy in particular requires the support of a dedicated team of nurses and physicians at a program with sufficient expertise, typically with the additional assistance of nurses from specialty pharmacies.[450]

Intravenous Prostenoid Therapy (Epoprostenol, Iloprost, and Treprostinil) The first prostenoid therapy shown in randomized clinical trials to be beneficial in the treatment of PAH was epoprostenol. Because of its short half-life (on the order of only minutes) it requires continuous intravenous infusion. In an initial study, 81 patients with IPAH were randomized to receive epoprostenol infusion or treatment considered "standard" at the time (oral vasodilators, diuretics, cardiac glycosides, and anticoagulants).[451] After 12 weeks of treatment, hemodynamic values were improved in the epoprostenol group (e.g., a 21% decrease in PVR as compared with an increase in control patients) as was the 6-minute walk distance (increased by 31 m compared with a decrease of 29 m). None of the patients treated with epoprostenol died during the study, as compared to a 20% mortality by 12 weeks with conventional therapy. Intravenous epoprostenol therapy for IPAH was approved by the FDA in 1995.

Additional reports have confirmed and extended these observations. Indeed, originally conceived as a "bridge" to lung transplantation in patients with severe PAH, the long-term use of epoprostenol and other treatments was followed by a decrease in the demand for lung transplantation for this indication.[452] In a cohort of 162 IPAH patients treated with intravenous epoprostenol at a center in the United States, the observed 1- and 3-year survival rates were 88% and 62%, compared to rates of 59% and 35% predicted by the NIH registry equation.[238] Remarkably similar results were observed in a cohort in France of 178 epoprostenol-treated patients with IPAH at 1 and 3 years, and somewhat lower survival rates in a cohort of 91 patients at a second United States center. In each case survival was improved over that predicted by the NIH registry equation.[236,237] Unfortunately, however, one-third of patients with IPAH died within 3 years and nearly half by 5 years (Fig. 72-15).[234]

Epoprostenol infusion therapy has also been used in other forms of PAH. A randomized multicenter trial in patients with systemic sclerosis associated PAH (without significant interstitial lung disease) showed improvements in both hemodynamics and exercise capacity.[453] Favorable results of epoprostenol treatment have also been reported in uncontrolled series of patients with systemic lupus erythematosis,[454] congenital left-to-right shunts,[455] anorectic agent use,[322] patients with HIV, POPH,[300] and inoperable CTEPH.[456] Epoprostenol has been used successfully in isolated reports of patients with PVOD. The use of epoprostenol in patient with PVOD must be approached with extreme caution, however, as its use in patients with impeded venous blood flow might precipitate pulmonary edema.[217] Isolated attempts at treating patients with pulmonary capillary hemangiomatosis (also characterized by predominant involvement of the pulmonary veins) have resulted in death.[397] In a single randomized trial of patients with left ventricular dysfunction, the use of epoprostenol was associated with a trend toward increased mortality.

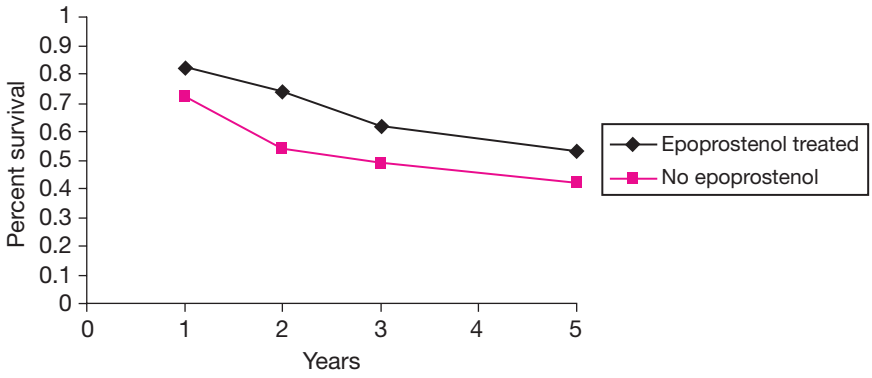


Figure 72-15 The effect of chronically infused epoprostenol therapy on survival in patients ($n = 431$) from multiple series with idiopathic pulmonary arterial hypertension. Survival in the absence of epoprostenol was estimated using a prediction equation derived from observation in the NIH registry of primary pulmonary hypertension at which time effective therapy was not available. *(Reproduced with permission from McLaughlin V V, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines, Chest. 2004;126(1 Suppl):78S–92S.)*

A longer half-life (3 hours) and stability at room temperature prompted the development of treprostinil as an alternative prostenoid analog for intravenous therapy. Treprostinil appears to have acute hemodynamic effects similar to those of epoprostenol.[457] In an uncontrolled 12-week, open-label study of 16 PAH (8 with IPAH and 6 and 2 associated with connective tissue and congenital heart disease, respectively) intravenous treprostinil infusion resulted in an 82-m improvement in 6-minute walk distance as well as improvements in hemodynamic values.[458] In a subsequent 12-week placebo-controlled randomized trial of 44 PAH patients continuously infused treprostinil resulted in an 83-m placebo-corrected increase in 6-minute walk distance and improvements in functional class.[459] Importantly, this randomized study involved the placement of central venous catheters for placebo infusions (that indeed were associated with harm, including a death). This has raised ethical concerns and questions that must be addressed as investigators of therapy in this rare disease face difficulties with recruitment and aim to extend their reach.[460,461]

Intravenously administered iloprost, another prostanoid, is available in some European countries, but not in the United States. In uncontrolled trials it has been used in patients with IPAH, collagen vascular disease associated PAH, and CTEPH.[462–464] The acute hemodynamic effects are similar to those of epoprostenol, but no controlled trials of its efficacy are available. In a retrospective analysis of 50 patients with PAH treated at multiple centers in Germany with intravenous iloprost following insufficient or deteriorating clinical status after the use of oral therapy with endothelin receptor or phosphodiesterase type 5 inhibitors, only approximately 25% had an improved functional class at 3 months, and more than 50% of patients died or required lung transplantation within 1 year.[465]

Epoprostenol therapy is initiated at 1 to 4 ng/kg/min and progressively increased in 0.5 to 1 ng/kg/min increments at intervals dictated by patient response and side effects. Treprostinil is initiated at 0.625 or 1.25 ng/kg/min and similarly increased as dictated by clinical response, typically in increments of 1.25 ng/kg/min. Induced metabolism mandates a need for continuous increases in dosage to maintain improvements in symptoms. Increases are usually required at more frequent intervals initially to relieve symptoms due to PAH (e.g., dyspnea and lightheadedness) although many patients will reach a more stable dosing with less frequently required increases after several weeks to months. Such titration must be closely monitored for prostenoid side effects (nausea, tachycardia, diarrhea, masticatory jaw pain).[450] Even patients lacking an acute vasodilator response (e.g., to infused epoprostenol) have shown improved hemodynamics and exercise capacity after sustained treatment, suggesting that the beneficial effects are not mediated merely through acute vasodilation, but also by altering cell growth.

Intravenous treatment with epoprostenol or treprostinil requires a tunneled venous catheter and thus is associated with a significant risk of bacterial infection. In an evaluation of 1146 patients who received intravenous prostenoid therapy during over 3 years of the multicenter observational US-based REVEAL cohort, an approximate threefold increase in blood stream infections of any type and over sixfold increase in those due to gram-negative organisms was observed among patients receiving intravenous treprostinil as compared with intravenous epoprostenol.[466] A retrospective study by the US Center for Disease Control of data from seven PAH treatment centers also concluded that rates of bloodstream infection were higher with continuous intravenous infusions of treprostinil than epoprostenol. The higher rate of infection did not appear to be due to intrinsic drug contamination,[467] but may have been related to the neutral pH of the treprostinil diluent, as substitution with the basic pH epoprostenol diluent appeared to eliminate the increase in infection rates with treprostinil at one institution.[468]

Prostenoid infusion requires the use of a battery-powered portable infusion pump that must be carried at all times. A back-up medication cassette and pump must also be immediately available as an interruption of only minutes can result in hemodynamic compromise. In theory, the risk with interrupted treprostinil infusion is somewhat lower on account of its longer half-life. The originally available formulation of epoprostenol is unstable at room temperature and must be mixed daily and kept cool with ice packs. Like treprostinil, a more recently approved formulation of epoprostenol has greater stability at room temperature and does not require continuous cooling with ice packs.[469] Treprostinil may be administered with the same infusion pump used for epoprostenol therapy but smaller equipment is available that may potentially allow for more convenient therapy. Preliminary experience suggests that a higher dosage of treprostinil is required than epoprostenol to maintain an improvement in symptoms. Further observation is required to establish whether survival is similarly improved with treprostinil as with epoprostenol. Experience and established duration of benefit is greatest with epoprostenol infusion and it remains an important treatment for severe PAH, and a benchmark against which other therapies are often compared.

Subcutaneous Prostenoid Therapy (Treprostinil) Treprostinil is also available for subcutaneous administration. In a large randomized double-blind placebo-controlled trial of 470 patients with IPAH or PAH associated with congenital heart or collagen vascular disease, subcutaneous treprostinil resulted in improvements in hemodynamic parameters and a modest improvement in 6-minute walk distance of 16 m at 12 weeks.[470] In an open-label extension study of participants previously enrolled in the randomized trial, together with de novo patients,

survival up to 4 years was evaluated in 332 IPAH patient for whom baseline hemodynamic measurements were available. Observed survival was 91% and 72% at 1 and 4 years, respectively, compared with survival rates of 69% and 38% at 1 and 4 years predicted by the NIH registry equation.[471]

The major advantage of subcutaneous treprostinil is avoidance of an intravenous catheter and the associated risk of life-threatening bacteremia. While infections can occur at the subcutaneous infusion site, these are usually mild and manageable with oral antibiotics. Other side effects are similar to those seen with intravenous prostenoid therapy (nausea, diarrhea, flushing, and jaw discomfort). In addition, however, the major drawback of treproprotinil has been a significant incidence of troublesome infusion site pain. This occurred in 85% of patients in the pivotal clinical trial and led to discontinuation in 8%.[470] Out of 860 total patients in the previously noted open-label study, 196 (23%) discontinued subcutaneous therapy due to infusion site pain or reactions.[471] Management strategies to reduce the occurrence and severity of pain have been reported, including initial "dry" catheter insertions with delayed infusion of medication, less frequent site rotations, and the application of topical analgesics and anti-inflammatory agents.[472] For those with severe pain refractory to these measures, narcotic analgesics may be required. Another relative disadvantage is a slower rate of dosage titration as compared to intravenous therapy, making it less attractive for severely ill patients in need of a rapid response. In select patients, however, subcutaneous treprostinil has proven to be effective therapy with minimal side effects and has allowed for avoidance of the risks and inconveniences of intravenous therapy.

Inhalational Prostenoid Therapy (Iloprost and Treprostinil) Inhaled prostenoid therapies have been developed in the hopes of avoiding the need for an invasive delivery system. Iloprost is an inhaled prostacyclin analog. Conflicting results of efficacy were seen in uncontrolled studies,[473–475] but a 12-week randomized, placebo-controlled trial of 203 patients demonstrated a placebo-corrected improvement of 36 m in 6-minute walk distance.[476] Most of the patients studied had IPAH; the remainder had PAH associated with anorectic agent or collagen vascular disease, or had CTEPH. Functional class and quality-of-life measures also improved in association with treatment. Hemodynamic variables were improved at 12 weeks when measured following a dose of iloprost, although preinhalation values were unchanged. As in other trials of PAH therapies, hemodynamic variables were worse compared to baseline following 12 weeks of placebo. Following another 3-month placebo-controlled study, 52 patients received open-label iloprost therapy. At 2 years, 36 (69%) remained on iloprost while treatment was discontinued in 16 patients due to death, lack of efficacy, and adverse events in 2, 6, and 6 patients, respectively. The study included patients with PAH and non-PAH forms of disease. The 2-year event-free survival was 74% in the IPAH patients, as compared to a predicted survival of 63% according to the NIH formula.[477]

Treprostinil is also available for inhalational therapy. A 12-week double-blind, placebo-controlled randomized trial of 235 patients with PAH already receiving either endothelin receptor or phosphodiesterase type 5 inhibition therapies demonstrated an overall 20-m improvement in postinhalation 6-minute walk distance as compared to baseline (14 m in preinhalational distance), as well as improved measures of quality of life. There was no difference in the time until clinical worsening.[478] An open-label extension of 206 patients from this trial found a median 18-m improvement over baseline 6-minute walk distance after 24 months.[479]

In addition to the lack of need for invasive administration equipment, inhaled prostenoid therapy is easier to initiate. Frequent dosing, however, is required (four times daily for treprostinil and between 6 and 9 while awake for iloprost) and compliance may be a challenge. In addition, as the hemodynamic effects wane prior to each administration, whether patients receive the same benefit as with continuously infused prostenoid therapy is unclear.[480]

Iloprost inhalational therapy is initiated at a dosage of 2.5 and increased to 5 μg with the subsequent dose if tolerated. Treprostinil is started at 18 μg (3 breaths) four times a day, with dose escalation suggested every 1 to 2 weeks to a maximum and target dose of 54 μg (nine breaths) four times daily. Inhaled prostenoids are each administered with drug-specific portable delivery devices. Prostenoid side effects are seen with inhalational therapy, including headache, nausea, diarrhea, flushing, and jaw discomfort. Systemic hypotension and syncope may also occur although have not been associated with further clinical deterioration in clinical trials.[476]

Oral Prostenoid Therapy An orally active prostacyclin analog, beroprost, has been studied in two randomized placebo-controlled trials of patients with various forms of PAH and appears to result in a nonsustained improvement in exercise capacity. An initial trial of 130 patients demonstrated an improvement in 6-minute walk distance after 12 weeks of therapy but in a subsequent study of 116 patients the effect was not sustained beyond 6 months.[481,482] Neither trial demonstrated significant hemodynamic improvement as compared with placebo, and beroprost is currently only approved for use in Japan. An oral formulation of treprostinil was ineffective at improving exercise capacity in patients already receiving oral endothelin receptor antagonists or phosphodiesterase type 5 inhibitors.[483]

Combination Pharmacotherapy

Despite the improvements in exercise capacity and functional status that many patients achieve with individual agents, PAH a life-threatening disease and many patients fail to improve with or maintain a positive response to initial treatment, or suffer progressive decline. With further clinical deterioration it is tempting to replace one agent for another. Alternatively, additional agents are added and used in combination. Indeed, 41% of 2438 patients enrolled in the multicenter US-based REVEAL cohort were receiving two PAH-specific therapies (excluding calcium channel antagonists) and 7.5% were receiving three.[191] Unfortunately, despite such widespread adoption of combination therapy, data regarding the most efficacious and safest approach to using multiple drugs in patients with PAH are limited.

In the only randomized controlled study of upfront combination therapy for PAH, 33 patients with IPAH were randomized to receive either bosentan or placebo 2 days after the initiation of epoprostenol. Both groups demonstrated improved exercise capacity and hemodynamics, but no statistically significant difference was seen as a result of the combination therapy. The small sample size may have precluded identification of differences in efficacy or safety.[484] Other randomized trials of combination therapy have involved sequential ("add-on") therapy in which a second PAH-specific agent has been added to the regimen of a patient already on at least one other drug. In a 12-week trial of 67 patients with PAH, the addition of inhaled iloprost to background bosentan therapy resulted in a 26-m increase in 6-minute walk distance as compared with placebo over 12 weeks. Iloprost also delayed the time to clinical worsening in this study.[485] In a 16-week study of 267 PAH patients, the addition of sildenafil (up to 80 mg three times daily) to continuous intravenous epoprostenol infusion increased 6-minute walk distance by 29 m and improved hemodynamic variables and measures of health-related quality of life.[486] Patients on background bosentan therapy experienced a 23-m placebo-corrected increase

in 6-minute walk distance when tadalafil was added in a 16-week trial.[149] In contrast, the addition of oral treprostinil to background endothelin and/or phosphodiesterase type 5 inhibitors for 16 weeks did not improve 6-minute walk distance.[483]

SURGICAL INTERVENTIONS FOR PULMONARY ARTERIAL HYPERTENSION

Lung transplantation is addressed in detail in Chapter 107. Here, it will suffice to note that lung transplantation remains an important consideration for some patients with PAH whose disease fails to respond adequately to medical therapy. Although changes in the method of allocating donor lungs within the United States have improved wait times, mortality on the wait list for patients with PAH remains excessive compared to patients with other indications for lung transplantation.[487] To address this issue, PAH patients who are deteriorating despite optimal medical therapy and who have a cardiac index <1.8 L/min/m^2 or a right atrial pressure >15 mm are now granted special priority.

Atrial septostomy has been performed as a palliative measure, as well a "bridge" to lung transplantation in some patients with severe PAH and symptoms refractory to other therapies. The creation of a right-to-left shunt is aimed at decreasing the pressure overload of the right ventricle, and simultaneously increasing preload of the left ventricle thereby improving systemic perfusion. Controlled studies have not been performed, and evidence-based selection criteria have not been established. Significant palliation of patients has been reported, but deaths have been reported as well.[488] The procedure should only be performed at experienced institutions.[489]

ACUTE COR PULMONALE OR RESPIRATORY FAILURE IN PULMONARY ARTERIAL HYPERTENSION

Patients with PAH may become acutely unstable due to a number of factors, including infection, volume overload with dietary indiscretion, or complications of medicines (Table 72-10). Often a clear acute precipitating source of decompensation is not identified. Regardless of the inciting event,[490] in many patients an acute stress will convert stable cor pulmonale into rapidly progressive hemodynamic failure. Acutely worsened hypoxemia, if not the precipitating cause of the hemodynamic instability will usually develop quickly as well.[491] Although the precipitating events may differ, each tends to lead to a vicious cycle that will result in worsening right ventricular function and hypotension (Fig. 72-16). Increased work of the right heart, be it from acute hypoxia and pulmonary vasoconstriction, or due to fever and infection, will increase ventricular wall stress further impeding ventricular performance. A decreased CO will impede myocardial perfusion, as will the increase in intraventricular pressure. Increases in right ventricular volume and pressure will, through displacement of the interventricular septum and increases in pericardial pressure, impede left ventricular filling and function. The resultant hypoxemia and ventricular ischemia, as well as acidemia from either respiratory insufficiency or poor systemic perfusion, can worsen the situation.

The goals of management are the same as for any patient who is hemodynamically unstable or in respiratory distress: to decrease the demand for oxygen while improving its delivery. Supportive care therefore aims to reverse the hypotension and hypoxemia through judicious fluid management, the reduction of RV afterload, support of cardiac function, and provision of supplemental oxygen and, if necessary, ventilator support (Fig. 72-17). Few data are available to guide the management of acute hemodynamic instability in patients with PAH. Available studies of various agents have frequently been performed in patients with acute right heart dysfunction following cardiac surgery, who generally do not suffer from severe underlying pulmonary vasculature disease. It is similarly important to recognize the limitations in extrapolating data from acute vasodilator trials performed on an elective basis in patients with PAH to the care of a hemodynamically unstable PAH patient.

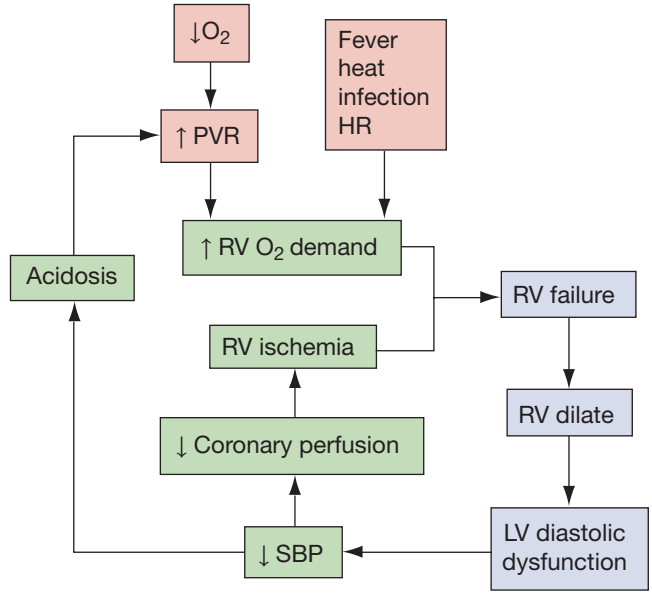


Figure 72-16 Interacting mechanisms in the acute development of worsened right heart function in patients with pulmonary arterial hypertension. A vicious cycle frequently results in both respiratory failure and hemodynamic instability. *(Reproduced with permission from Jeffery ME, Taichman DB. Management of the acutely ill patient with pulmonary arterial hypertension. In: Pulmonary Vascular Disease, Mandel J, Taichman DB. Philadelphia: Elsevier Science; 2006.)*

TABLE 72-10 Clinical Presentations of Patients with Pulmonary Arterial Hypertension with Acute Hemodynamic Instability

Acute recognition/late presentation • Syncope, shock, renal failure, ascities, hypoxemia
Acute medication failure • Medical noncompliance, interrupted infusions • Intolerance (calcium channel antagonist)
Dietary indiscretion/fluid retention
Infection (sepsis with infused therapy)
Fever (environmental causes, infection)
Venous thromboembolism
Medical/surgical procedures/anesthesia
Pregnancy
Tachydysrhythmia (atrial fibrillation, atrial flutter)
Increased activity of underlying disease (flare of systemic lupus erythematosis with worsened PAH that may be responsive to increase immunosuppression)

Source: Adapted with permission from Jeffery ME, Taichman DB. Management of the acutely ill patient with pulmonary arterial hypertension. In: Mandel J, Taichman DB, eds. Pulmonary Vascular Disease. Philadelphia, PA: Saunders/Elsevier; 2006.

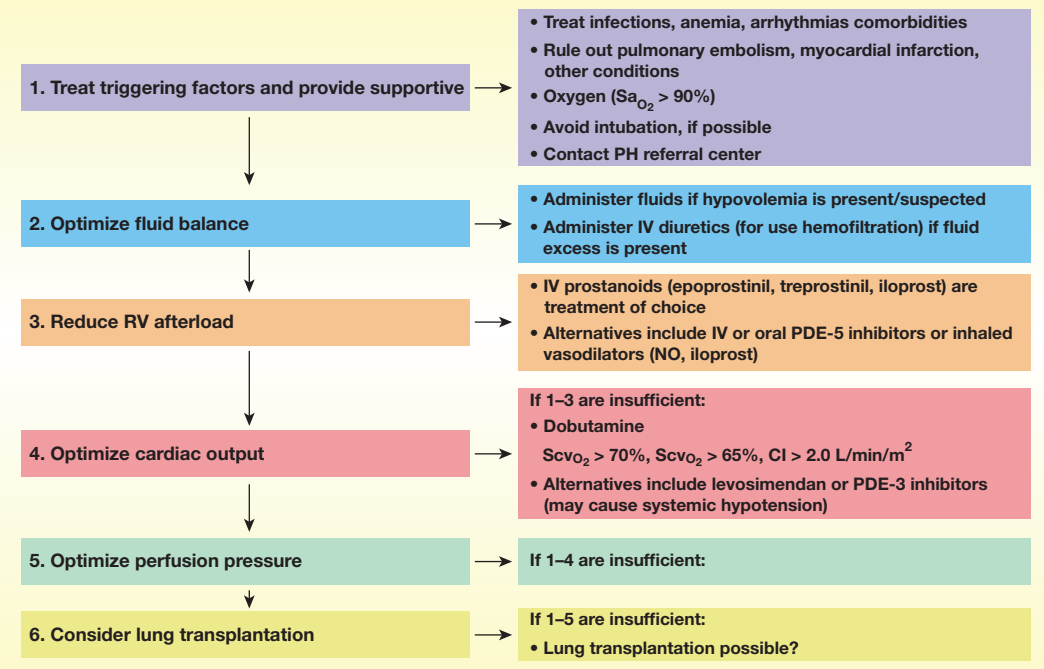


Figure 72-17 Hemodynamic management of critically ill patients with right ventricular failure due to pulmonary arterial hypertension. Which measures are necessary will depend on the individual patient. On many occasions, these treatment strategies need to be administered simultaneously rather than sequentially. CI, cardiac index; IV, intravenous; PDE-5, phosphodiesterase-5; PH, pulmonary hypertension; RV, right ventricular; Scv_{O_2}, central venous oxygen saturation; Sv_{O_2}, mixed venous oxygen saturation. *(Reproduced with permission from Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184(10):1114–1124.)*

Although administration of intravenous fluids is the usual first, and frequently most important, intervention for hypotension causing critical illness, fluid challenges for hypotension in the patient with PAH and right ventricular failure must be pursued cautiously with the clinician paying close attention to the potential for making the situation worse. A fluid challenge is often an appropriate initial measure for hypotension, especially when infection or other factors that might predispose to hypovolemia exist. In many patients with PAH and chronic cor pulmonale, however, acute hypotension is caused or complicated by worsened right heart dilation further impairing both right and left ventricular functions. In such cases, fluid removal is required to recover right ventricular function. Vasopressors may be needed for hemodynamic support while fluid removal is accomplished with diuretics.

There are few data to firmly guide the choice of vasopressors.[492] Norepinephrine or dobutamine are often employed for their inotropic properties, while agents that may constrict pulmonary vessels such as phenylephrine are usually avoided if possible.[493–495] Tachycardia and a resultant further impairment of ventricular filling and output may limit the use of any of these agents. If tolerated, the use of intravenous pulmonary vasodilators (e.g., epoprostenol) may result in significant improvement both acutely and longer term. Attempts to promote pulmonary vasodilatation with intravenous or oral agents are, however, frequently complicated by hypotension from the systemic effects of the drugs. In the setting of acute hemodynamic instability, the use of inhaled agents (iloprost, nitric oxide, aerosolized epoprostenol, or milrinone) is often preferable.[496–498] The phosphodiesterase type 5 inhibitor sildenafil has been administered intravenously in a small series of hemodynamically stable patients with PAH; whether it might prove useful for therapy of critically ill patients has not been studied.[499]

Oxygen is a potent pulmonary vasodilator and should be administered at concentrations adequate to prevent hypoxemia. Mechanical ventilation is avoided if possible due to the hemodynamic effects of positive pressure ventilation as well as required sedatives. Unfortunately, invasive ventilator support may be unavoidable. When mechanical ventilation is required, the same principles apply as in other patients with respiratory failure, although certain points are worth noting in the management specifically of patients with PAH. While intra-alveolar vessels are stretched and their resistance increased with overdistention of alveoli, compression of extra-alveolar vessels with atelectasis at low lung volumes might increase their vascular resistance. Thus, at either extreme PVR might increase. The application of positive end-expiratory pressure must also be done with attention to possible overdistention of alveolar vessels and a resultant increase in their resistance. As hypercarbia tends to promote pulmonary vasoconstriction, lung-protective strategies that permit hypoventilation (and hypercapnea) must be carefully monitored to be certain of overall benefit.[500] Hyperventilation to induce mild alkalemia and pulmonary vasodilation has been used empirically, but with attention to avoid dynamic hyperinflation. Finally, care must be taken to avoid agitation with noxious procedures (such as endotracheal suctioning) that might promote further surges in vascular resistance; sedation and analgesia should be employed judiciously with such procedures.[501]

Some acutely ill patients may be candidates for lung transplantation. Although experience is limited, extracorporeal membrane oxygenation (ECMO) has been used in the successful support of individual acutely ill patients with PAH and right ventricular failure awaiting transplantation.[502,503] Newer dual channel cannulas inserted into the internal jugular vein permit patients to remain ambulatory while on ECMO. A pumpless oxygenation system implanted between the pulmonary artery and left atrium has been used to provide support to acutely ill patients while awaiting lung transplantation.[504]

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CHAPTER 73

Pulmonary Thromboembolic Disease

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INTRODUCTION

Pulmonary thromboembolic disease refers to the condition in which blood clot(s) (thrombus or multiple thrombi) migrate from the systemic circulation to the pulmonary vasculature. Most of these thrombi arise from the deep veins of the lower and upper extremities (deep venous thrombosis [DVT]). From the clinical standpoint, DVT and pulmonary embolism (PE) can be considered a continuum of the same disease, and the two terms are often collectively referred to as venous thromboembolism.

The annual incidence of PE in the United States remains uncertain. In a retrospective analysis of data involving 2218 Olmsted County residents over a 10-year period, community residents who were not hospitalized within a 90 days period had an incidence of PE of 3.6 per 10,000 person-years.[1] A slightly lower incidence of 2.3 per 10,000 person-years was reported in an earlier study in Massachusetts.[2] This translates to an annual incidence of approximately 100,000 cases in the United States. However, the true incidence of PE is likely to be much higher since many cases remain undiagnosed. A recent systematic review revealed that silent PE was present in 32% of patients with DVT.[3] An earlier report estimated that as many as 630,000 patients develop PE every year in the United States with 200,000 related deaths, the majority in patients in whom the diagnosis was never made (Fig. 73-1).[4] Although considerable effort is directed toward the development of new diagnostic techniques and therapeutic agents, a considerable impact on mortality related to the disease would arise from the routine use of prophylactic strategies, an understanding of the often subtle clinical presentation of the disease, and the appropriate application of existing diagnostic techniques.

SOURCES OF EMBOLI

Most cases (80%–95%) of PE occur as a result of thrombus originating in the lower extremity. Thrombus often begins at a site where blood flow is turbulent, such as at a venous bifurcation, or behind a venous valve (Fig. 73-2). When thrombus propagation exceeds the rate of thrombus organization and adherence to the endothelium, part or all of thrombus may break away and migrate via the venous system to the lungs. Most thrombi originate in the deep veins of the

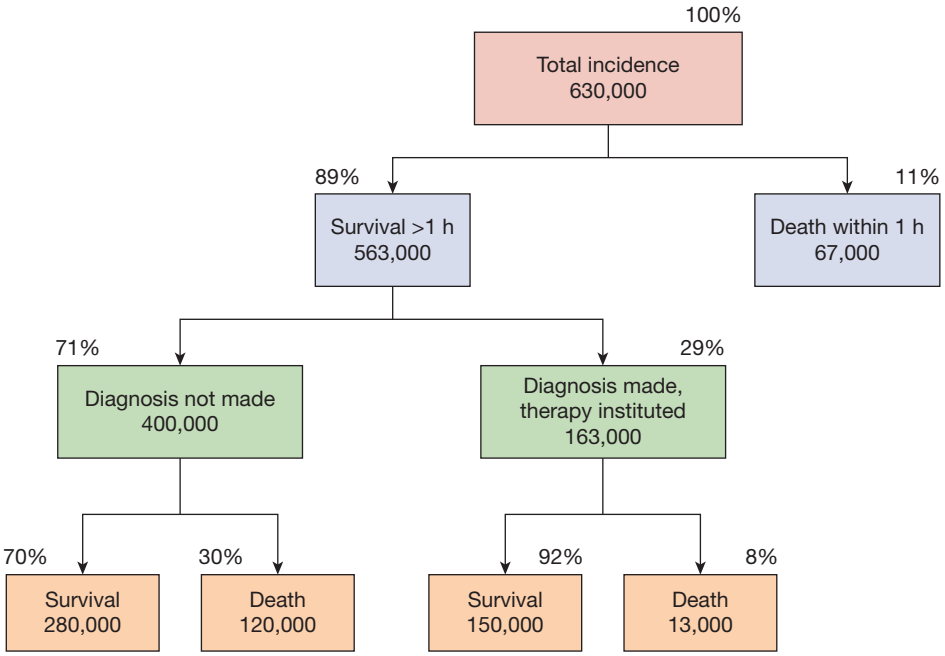

Figure 73-1 Estimated incidence and survival statistics for pulmonary embolism in the United States. *(Reproduced with permission from Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis. 1975;17(4):259–270.)*

calf and propagate proximally to the popliteal and femoral veins. Calf-limited thrombi pose a minimal embolic risk while those that extend into and above the popliteal vein represent the most common source of acute symptomatic PE. This is not meant to imply that calf-limited thrombosis represents a benign condition. Proximal propagation may occur in as many as 15% of untreated patients along with a higher risk of thrombotic recurrence and postphlebitic syndrome.[5]

Emboli may originate from other sources, most often from the pelvic veins, in which case a predisposing factor such as pregnancy, pelvic thrombophlebitis or pelvic infection, prostate disease, or recent pelvic surgery can often be identified. Emboli may also originate from upper extremity thrombosis associated with central venous catheters or intravascular cardiac devices, or may be associated with thoracic outlet obstruction or effort thrombosis (Paget–von Schroetter syndrome).[6] A small number of patients with PE may have evidence of right ventricular thrombus at presentation and this has been associated with more hemodynamic instability and an increase in mortality.[7]

Although the majority of cases of PE are the result of thrombus migration (hence, *thromboembolism*), other materials may occasionally obstruct the pulmonary vascular bed. These include blood-borne parasites (such as schistosomiasis), sickle cell disease, and various "contaminants" of illicit injected drugs (talc, cloth fibers, etc.). Air embolism is usually iatrogenic and typically enters the blood stream accidentally through a central venous catheter. Less commonly, a patient's own tissues or cells may enter the blood stream and lodge in the pulmonary vasculature. Examples include amniotic fluid embolism, which can occur during or immediately after labor or late-term abortion; fat embolism, which is usually associated with long bone fractures; and tumor embolism. PE due to sickle cell disease is caused by "clumping" of abnormal red blood cells in the setting of hypoxia and stress, and can cause both acute respiratory distress as well as a more progressive disease with secondary pulmonary hypertension.

PREDISPOSING FACTORS

Rudolf Virchow first described the phenomena of "embolism" and "thrombosis" in the mid-nineteenth century, and identified three main factors contributing to the formation of venous thrombosis (Virchow's triad): venous stasis, hypercoagulability, and injury to the venous wall (endothelium). One hundred and fifty years later, this basic classification remains useful in helping clinicians stratify individual patient's risk of developing venous thromboembolism (Table 73-1). It is important to recognize that there is an interplay between acquired and genetic risk factors, that multiple mechanisms lead to the development of DVT and/or PE, and that multiple factors can often be found in individual patients.

■ ACQUIRED RISK FACTORS

The risk imposed by a major surgical procedure is well recognized. Without prophylaxis, venous thrombosis occurs after approximately 20% of all major surgical procedures with associated embolism after 1% to 2%.[8] The incidence of thromboembolism without prophylaxis is even higher in orthopedic patients with over 50% of major orthopedic procedures complicated by venous thrombosis.[9] In the absence of prophylaxis, the frequency of fatal postoperative PE ranges from 0.1% to 0.4% in patients undergoing elective general surgery and from 1% to 5% in patients undergoing elective hip or knee surgery, emergency hip surgery, major trauma, or spinal cord injury.

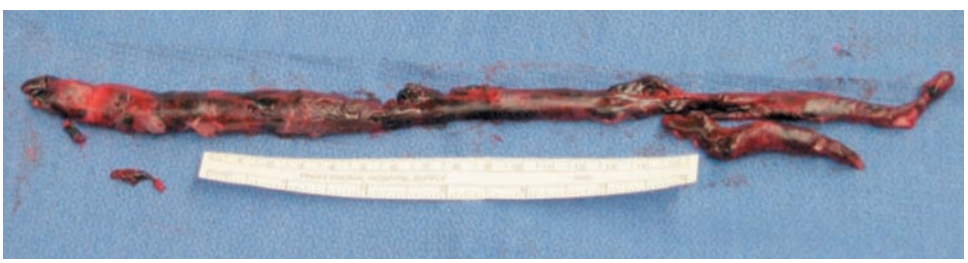

Figure 73-2 Large, well-organized embolus representing "cast" of a lower extremity vein removed from pulmonary artery at pulmonary embolectomy.

TABLE 73-1 Virchow's Triad: Clinical States Predisposing to Venous Thrombosis

Stasis	Immobility
	Bed rest
	Anesthesia
	Congestive heart failure/cor pulmonale
	Prior venous thrombosis
Hypercoagulability	Malignancy
	Anticardiolipin antibody
	Nephrotic syndrome
	Essential thrombocytosis
	Estrogen therapy
	Heparin-induced thrombocytopenia
	Inflammatory bowel disease
	Paroxysmal nocturnal hemoglobinuria
	Disseminated intravascular coagulation
	Protein C and S deficiencies
	Antithrombin III deficiency
Vessel wall injury	Trauma
	Surgery

Major traumatic injuries, most notably those of the head, spine, and pelvis, are also associated with high risk. The basis for this risk is multifactorial, involving all three components of Virchow's triad.

Although initially recognized and studied in surgical patients, it is now appreciated that hospitalized medical patients may be equally prone to develop DVT.[10] In about 80% of the cases, one or more risk factors may be present when extensive investigative testing is performed. Major risk factors include New York Heart Association class III and IV congestive heart failure, chronic obstructive pulmonary disease, sepsis and other inflammatory disorders, advanced age, stroke, critical illness, and prolonged bed rest.

Any prolonged period of immobilization may increase thromboembolic risk and explains the occurrence of thrombosis under such circumstances as paralysis, bed rest, and prolonged air travel. Long distance traveling (economy class syndrome) is associated with a 1.5- to 3-fold increase in thromboembolic risk, depending on the travel duration.[11] Despite the relative increase in risk, the actual incidence of PE associated with air travel is quite low.[12]

Pregnancy is the most common cause of venous thromboembolism in women younger than 40 years old, and if untreated may account for 20% to 50% of all pregnancy-related deaths. Compared with nonpregnant women, the risk of venous thrombotic events is increased fivefold during pregnancy and 60-fold in the first 3 months after delivery.[13,14] The increase may be a result of decreased mobility, pregnancy-related hypercoagulable state (increases in factors II, VII, VIII, X, acquired activated protein C resistance, and decreased free protein S level), and venous obstruction from uterine compression. The incidence is estimated at 0.76 to 1.72 cases per 1000 pregnancies and occurs in roughly equal distribution over all trimesters. Most cases of postpartum DVT occur within the first 6 weeks after delivery. Cesarean section, premature birth, multiple births, preeclampsia, advance maternal age, and maternal history of cardiac disease have all been identified as contributing factors. Interestingly, 90% of all DVT cases are noted in the left leg, presumably because of the anatomic relationship between the uterus and inferior vena cava (IVC).

The use of oral contraceptive agents and hormonal replacement therapy has also been associated with an increased risk of venous thromboembolism.[14,15] Although the risk of venous thromboembolism is higher among users of oral estrogen-containing contraceptives, the absolute risk is low. In terms of oral contraceptive agents, the relative risk of developing venous thrombosis is a four- to sixfold increased risk. There appears to be a synergistic effect of oral contraceptives with obesity.[16]

Hormone replacement therapy appears to be associated with a two- to fourfold increased risk of venous thromboembolism.[17] Studies have suggested that venous thromboembolic risk is lower with transdermal hormone preparations. However, none of these studies are randomized trials. Given that the baseline risk of thrombosis increases with age, the use of hormonal replacement therapy in a postmenopausal population has a considerably higher impact on absolute rates of thrombosis.

Obesity has been associated with venous thromboembolism, particularly in women. The Nurses' Health Study found that a body mass index greater than or equal to 29 kg/m^2 was an independent risk factor.[18] The metabolic syndrome, defined by abdominal obesity, elevation of blood pressure, elevated fasting blood sugar and triglycerides, and low levels of high-density lipoprotein cholesterol, appears to be associated not only with an increased risk of atherosclerotic disease but also of venous thromboembolism.[19]

The risk of venous thromboembolism increases with age. A recent study, using hospital discharge surveys over a 21-year period, found that patients 70 years or older have an approximately 25-fold increased risk, compared with those 20 to 29 years of age.[20] Presumably the difference may be due to decrease in mobility and increase in comorbidities in this population. Elderly patients also appear to have a higher mortality due to PE, and PE is suspected less commonly prior to death in the elderly patient.

Cancer patients, particularly those with primary malignancies from lung, pancreas, breast (mucin-secreting adenocarcinoma), prostate, stomach/colorectal, and genitourinary tracts are at a high risk for venous thromboembolism. Cancer is estimated to increase the risk of venous thromboembolism by four- to sixfold. Patients with cancer also have a higher risk of thromboembolic recurrence and those with venous thromboembolism have a higher overall mortality rate than cancer patients without thrombosis. Multiple factors are probably involved and include the development of abnormalities in the hemostatic system related to the malignancy itself, hemostatic alterations induced by chemotherapeutic agents, immobility, infectious complications, and the presence of chronic indwelling central venous catheters. Although most instances of cancer-associated venous thromboembolism occur after the diagnosis of the malignancy, approximately 5% to 10% of patients with "idiopathic" venous thrombosis have a malignancy diagnosed within the next 2 to 3 years. There is no evidence at this time to recommend an aggressive search for cancer in patients with idiopathic or unprovoked thrombosis. Recent data suggest that a limited approach (routine laboratory testing, chest radiograph, tumor markers, abdominal ultrasound) may have the capacity to identify approximately one-half of malignancies in patients who were negative on routine examination.[21] More extensive screening utilizing chest and abdominal computed tomography (CT) appears to result in excessive false-positive results without an effect on outcome.[22]

Various hematologic conditions such as polycythemia vera, essential thrombocytosis, and acute leukemia may result in significant overproduction of different cell lines, which in turn may increase the risk of venous thromboembolism by increasing blood viscosity (hyperviscosity syndromes) and through the release of

procoagulants.[23] This type of thrombosis seems to occur more frequently in the hepatic or portal veins and may be the presenting symptoms of the underlying disorder.

Paroxysmal nocturnal hemoglobinuria is a rare condition associated with an incidence of venous thromboembolism of approximately 40%.[24] Many cases involve nonlower extremity sites, particularly in the intra-abdominal vessels. The reason for thrombosis is not clear but may be related to a decrease in blood complement levels in these patients.

The presence of antiphospholipid antibodies, most notably the lupus anticoagulant, appears to be an independent risk factor for venous thromboembolism.[25] Among patients with venous thrombosis, a lupus anticoagulant has been reported in 5% to 15% and this abnormality has been estimated to lead to a ninefold increased risk of thrombosis.

The frequency of venous thromboembolism in patients with nephrotic syndrome may be as high as 40%.[26] There is a higher tendency for the thrombosis to present in unusual locations such as the cerebral sinus or as arterial thrombosis. Rarely, thrombosis may also be the presenting symptom of the nephrotic syndrome. The mechanism for venous thromboembolism in these patients is not clear but various factors such as functional or quantitative changes in coagulation factors, diminished fibrinolytic activity, platelet hyperreactivity, and increased blood viscosity have been proposed.

Patients with inflammatory bowel disease are at substantially increased risk of both venous and arterial thromboses.[27,28] The exact pathogenetic mechanism remains unclear. The majority of thrombotic complications occur during an active phase of the disease and inflammatory mechanisms have been proposed.

INHERITED RISK FACTORS

Many patients who develop venous thromboembolism are found to have an inherited risk factor due to either abnormal levels of or functional abnormalities in coagulation factors (inherited thrombophilia). The relative risk of thrombosis varies widely depending on the hemostatic defect. In general, this group of patients tends to be younger (less than 50 years) and has a tendency to develop recurrent venous thromboembolism.

The first known inherited thrombophilic trait was antithrombin III deficiency, originally described in 1965. Subsequently, a number of other genetic mutations associated with venous thromboembolism have been reported. The most common of these inherited predispositions was first described in 1993 by Dahlback and designated as a factor V Leiden mutation.[29] It is the consequence of a single point mutation on the factor V gene (adenine for guanine) resulting in factor Va with diminished sensitivity to the natural anticoagulant effect of activated protein C. Approximately 5% of Caucasians in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native American, African, and Asian populations. The heterozygous state carries a 5- to 10-fold increase in lifetime risk for venous thromboembolism, whereas the risk among patients homozygous for this mutation may be increased 80-fold. Factor V Leiden mutation appears to be an important risk factor for venous thromboembolism during pregnancy, in the postpartum period, and during oral contraceptive use.[30] Compared with women who do not use oral contraceptives and are not carriers of the factor V mutation, the risk of thrombosis among those with both risk factors is increased approximately 30-fold.[31]

Another common mutation has been identified in the 3' untranslated region of the prothrombin gene (substitution of A for G at position 20210) and is present in 2% to 4% of the general population.[32] This mutation results in an overproduction of prothrombin, which is otherwise normal. It is associated with a three- to fourfold increased risk of lower extremity venous thrombosis and appears to act in a synergistic manner with other forms of thrombophilia in increasing both the initial and recurrent thrombosis risk.

In clinical practice, factor V Leiden mutation and prothrombin gene mutation are the most common inherited conditions and account for more than half of the cases of inherited thrombophilia-related venous thromboembolism; three other conditions (deficiencies in antithrombin III, protein C, or protein S) account for most of the remainder. Occasionally one may also encounter venous thromboembolism patients who may have other conditions, particularly related to dysfibrinogenemias. It is important to recognize that, when multiple inherited risk factors coexist (such as factor V Leiden and prothrombin gene mutation), the risk of recurrent venous thromboembolism may increase substantially, and lifelong anticoagulation may be necessary in these patients.

PATHOPHYSIOLOGY

Once detached from their point of origin, emboli travel via the systemic venous system, through the right chambers of the heart, and eventually reach the pulmonary arterial system. The physiologic effects and clinical consequences of pulmonary thromboembolism vary widely, ranging from asymptomatic disease to hemodynamic collapse and death. Major factors that determine the outcome include (1) size and location of emboli; (2) coexisting cardiopulmonary diseases; (3) secondary humoral mediator release and vascular hypoxic responses; and (4) the rate of resolution of emboli.

HEMODYNAMIC CONSEQUENCES

Obstruction of the pulmonary vascular bed by embolism acutely increases right ventricular afterload. The normal pulmonary arterial system is a low-pressure system capable of accommodating substantial increases in blood flow with only modest increases in pressure. The thin-walled right ventricle is poorly equipped to generate the pressure necessary to overcome any significant increase in pulmonary vascular resistance. Compensatory mechanisms exist that allow up to 70% obstruction of the pulmonary vascular bed before right ventricular failure develops.[33–36]

In the absence of pre-existing cardiopulmonary disease, obstruction of less than 20% of the pulmonary vascular bed results in minimal hemodynamic consequences as a result of recruitment and distention of pulmonary vessels. When the degree of pulmonary vascular obstruction exceeds 30% to 40%, modest increases in right ventricular pressure occur, but cardiac output is maintained through an increase in heart rate and myocardial contractility. Compensatory mechanisms begin to fail when the degree of pulmonary artery obstruction exceeds 50% to 60%. Cardiac output begins to fall and right atrial pressure increases dramatically. Mixed venous oxygen saturation falls and a lactic acidosis may develop. With further acute obstruction, the right heart dilates, right ventricular wall tension increases, right ventricular ischemia may develop, the cardiac output falls, and systemic hypotension develops. In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure capable of being generated by the right ventricle appears to be 40 mm Hg (pulmonary artery systolic pressure of approximately 70 mm Hg).[34]

Other factors may affect the hemodynamic consequences of PE. Patients with pre-existing cardiopulmonary disease often have diminished pulmonary vascular reserve and even a relatively minor embolus may result in significant hemodynamic instability (Fig. 73-3). Alternatively, if the right ventricle has had time (months to years) to hypertrophy in response to a gradual increase in demand (left ventricular disease, idiopathic pulmonary arterial hypertension, chromic thromboembolism, etc.) a significantly higher pulmonary artery pressure may be seen.

Several observations suggest that other mechanisms are involved in hemodynamic consequences of acute PE. For example, patients

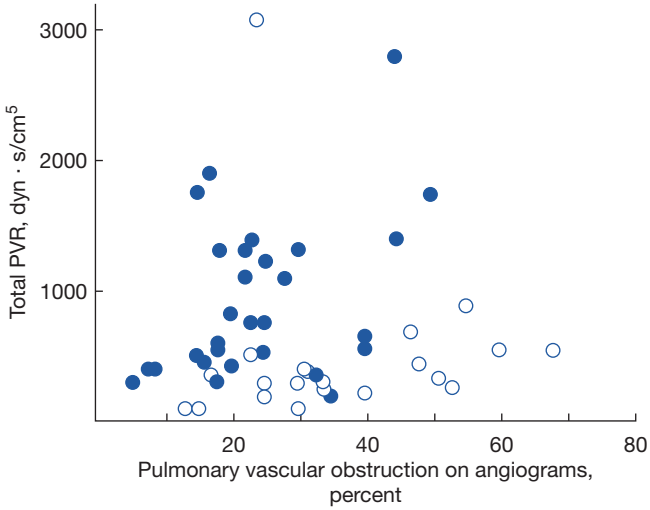

Figure 73-3 Hemodynamic consequences of pulmonary embolism and the underlying state of the pulmonary vasculature. Patients in whom the pulmonary vasculature was previously normal (*open circles*) develop little increase in pulmonary vascular resistance (PVR) until the clot burden exceeds 50%. In those with antecedent cardiopulmonary disease (*solid circles*), the PVR increases appreciably with only modest clot burden. *(Reproduced with permission from Sharma GV, McIntyre KM, Sharma S, Sasahara AA. Clinical and hemodynamic correlates in pulmonary embolism. Clin Chest Med. 1984;5(3):421–437.)*

develop only minimal hemodynamic instability during elective lobectomy, pneumonectomy, or even single lung transplantation despite complete and acute interruption of blood supply during cross-clamping. In the experimental setting, cyproheptadine (a nonselective serotonin antagonist) and ketanserin (a selective serotonin antagonist) have been shown to diminish some of the hemodynamic and airway responses that occur after pulmonary embolization. Certain patients develop disproportionately large and fluctuating pulmonary hemodynamic changes in response to relatively small emboli, suggesting that other mechanisms such as reflex vasoconstriction and release of vasoactive compounds may also be involved.[37,38]

As expected, large or multiple emboli tend to cause more severe symptoms and changes in oxygenation and hemodynamics. Given the large surface area of the peripheral pulmonary vascular bed compared to the central, symptomatic improvement may occur when a large central embolus is fragmented by forces generated by cardiac contractions or even with chest compressions during cardiopulmonary resuscitation. Eventually, the emboli may either resolve by fibrinolysis, or organize and become scar-like tissue that adheres to the vascular endothelium (Fig. 73-4). Recent data suggest that complete resolution is uncommon and that as many as 50% of patients have some residual obstruction 6 months after the embolic event.[39,40]

■ GAS-EXCHANGE ABNORMALITIES

Hypoxemia is the most common immediate physiologic consequence of PE. Obstruction of the pulmonary vasculature prevents systemic venous blood from reaching the pulmonary capillaries of the involved vessels and redirects the blood flow to other parts of the pulmonary vascular bed. This results in an increase in ventilation–perfusion (V/Q) inequality, intrapulmonary shunting, and decreases in the mixed venous O_2 level, thereby magnifying the effect of the normal venous admixture.[41,42] Further shunting and increase in alveolar dead space can also occur as a result of alveolar hemorrhage or to atelectasis related to loss of surfactant. Despite an increase in alveolar dead space, patients with PE often develop hypocapnia. This is thought to be due to hypoxia-induced intrapulmonary reflex

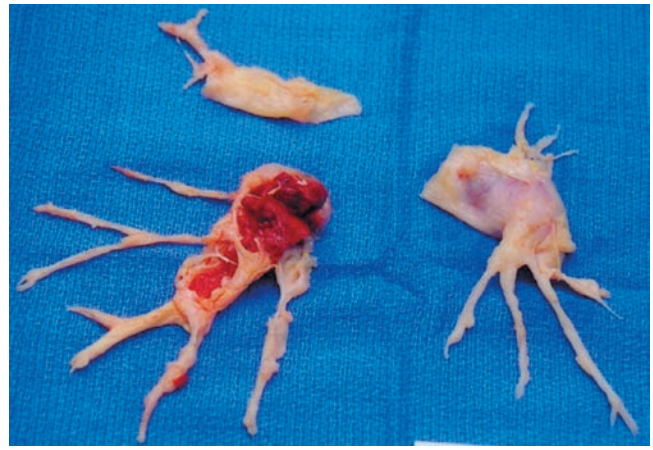

Figure 73-4 Chronic thromboembolic material dissected from pulmonary arteries at pulmonary thromboendarterectomy. Resolution of emboli is occasionally complete but certain patients may be left with significant emboli residua.

vagal stimulation, with resulting hyperventilation. Finally, embolic events large enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale.

One uncommon consequence of PE is pulmonary infarction. Infarction is uncommon because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, bronchial arteries, and airways. Two of these three sources apparently must be compromised before infarction develops (Fig. 73-5). Therefore, in a patient with no coexisting cardiopulmonary disease, infarction is rare.[43] Infarction occurs in approximately 20% of patients with significant cardiac or pulmonary disease that compromise either bronchial arterial flow or airway patency. In patients with left ventricular failure, increased pulmonary venous pressure may decrease bronchial flow and infarction may occur.

DIAGNOSIS OF PULMONARY EMBOLISM

The diagnostic approach to PE has undergone a fundamental transition over the past decade. V/Q scanning, the mainstay of diagnosis for almost three decades, has been relegated to a secondary role. The prospective investigation of pulmonary embolism diagnosis (PIOPED) trial demonstrated the shortcomings of this technique while providing valuable insight into the diagnostic utility of clinical assessment.[44] CT, highly sensitive D-dimer assays, stratification according to clinical assessment, and the application of Bayesian analysis to the diagnostic pathway have become the cornerstones of the current diagnostic approach. What has not changed is the understanding that clinical evidence per se, although capable of raising suspicion of the disease, is incapable of reliably confirming or excluding the diagnosis in the absence of objective testing. Recognition of the clinical signs and symptoms associated with embolism is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway.

■ CLINICAL PRESENTATION

The mainstay for the diagnosis of PE is a high index of suspicion tempered by the reality that most patients with embolism have one or more factors predisposing them to the condition. These predisposing factors need not be major or readily apparent. Advancing age, a period of bed rest, a prolonged air flight, or a minor traumatic injury can result in the development of venous thromboembolism. The absence of a known clinical or thrombophilic predisposition, however, should not dissuade an objective evaluation if the clinical presentation is consistent with embolism.

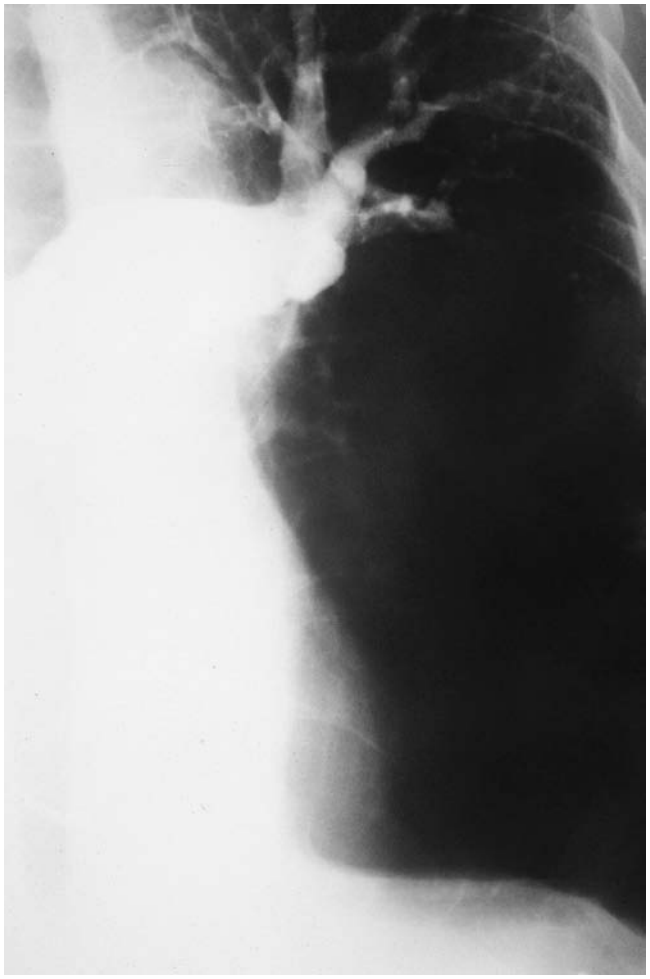

Figure 73-5 Pulmonary angiogram demonstrating thromboembolic obstruction of left pulmonary artery with absent blood flow to lingula and lower lobe. Despite extension obstruction, infarction did not occur as a result of lung's dual blood supply.

Although a somewhat arbitrary classification (as presenting symptoms and signs of embolism frequently overlap), the presentation of acute PE can be categorized into one of the three clinical syndromes: (1) isolated dyspnea; (2) pleuritic pain or hemoptysis; and (3) circulatory collapse.[45,46] Among patients without prior cardiopulmonary disease in the PIOPED study, the syndrome of pleuritic pain or hemoptysis was found to be the most common mode of presentation, occurring in approximately 60% of patients. Isolated dyspnea occurred in approximately 25%, whereas circulatory collapse occurred in 10%.

Two additional modes of presentation are also possible: subclinical clot and chronic, nonresolving or propagating clot. With the increasing use of computed tomographic studies, incidental emboli are occasionally found.[47] Typically, these emboli are found in the peripheral segments of the pulmonary arterial vasculature and do not correlate with any clinical symptoms. At this time, the short- and long-term significance of these incidental findings is not clear. In patients who are known to be at high risk of recurrent disease, such as those with inherited thrombophilia and hormonal use or those with poor cardiopulmonary reserve, it is reasonable to consider treatment with anticoagulation or at least the use of more aggressive prophylactic therapies during at-risk situations, such as prolonged hospitalization or air travel.

Complete anatomic resolution of PE appears to be uncommon. When there is sufficient residual pulmonary vascular obstruction, some patients may develop chronic thromboembolic pulmonary hypertension (CTEPH).[48] Although exact values for frequencies vary, it is estimated that approximately 0.5% to 1% of patients may develop this condition following an initial, symptomatic episode of PE.[49] The diagnosis should be considered even in the absence of a history of acute embolism. Approximately 30% of patients who present with CTEPH do not have a history of precedent acute embolism and are diagnosed during the evaluative process for unexplained dyspnea or pulmonary hypertension.

The most common presenting symptom of acute PE is the sudden onset of dyspnea.[45,46] Dyspnea usually occurs over minutes to hours but in approximately 15% occurs over days. Although usually present at rest, dyspnea may only be noted with exertion. It is important to recognize that dyspnea does not occur in approximately 25% of patients ultimately proven to have embolism. Other symptoms include pleuritic chest pain, cough, leg swelling or pain, and hemoptysis. The most common physical finding is unexplained tachypnea (respiratory rate greater than 20/min) present in approximately 70% of patients with embolism. Less frequent physical findings include rales, tachycardia, and an increased pulmonic component of the second heart sound. Fever may develop some hours after the event and often reaches, but rarely exceeds, 38.3°C.[50]

Obviously, these symptoms and signs are nonspecific (Table 73-2). In the PIOPED study, none of the presenting symptoms or

TABLE 73-2 Incidence of Signs and Symptoms of Pulmonary Embolism

	Massive PE[a] (%)	Submassive PE[a] (%)	Without Pre-existing Cardiopulmonary Disease (%)[b]
Dyspnea	85	82	73
Pleuritic chest pain	64	85	66
Cough	53	52	37
Hemoptysis	23	40	13
Tachypnea	95 (>16 breaths/min)	87 (>16 breaths/min)	70 (>20 breaths/min)
Tachycardia (>100 beats/min)	48	38	30
Increased pulmonic component of second heart sound	58	45	23
Rales	57	60	51
Phlebitis	36	26	11

[a]*Data from NIH-sponsored urokinase and streptokinase clinical trials (Am J Med. 1977;62:355–360).*
[b]*Data from NIH-sponsored PIOPED study (Chest. 1991;100:598–603).*

TABLE 73-3 The Wells' Clinical Prediction Score

Variable	Points
DVT symptoms/signs	3.0
PE likely or more likely than alternative diagnosis	3.0
Heart rate >100	1.5
Immobilization/surgery previous 4 wk	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total Score	**Pretest Probability**
<2.0	Low
2.0–6.0	Moderate
>6.0	High
Dichotomized Score	
≤4	PE unlikely
>4	PE likely

Source: Data from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83(3):416–420.

signs with the exception of the presence of rales, a fourth heart sound, and an increased pulmonic component of the second heart sound could differentiate between those with positive and negative angiograms.[45]

CLINICAL ASSESSMENT

A major advance in the diagnostic approach to PE has been a transition from a purely technique-oriented approach to one that uses Bayesian analysis. In doing so, the pretest probability of the disease, calculated independently of a particular test result using either empiric means or a standardized prediction rule, is calculated. This pretest probability aids in the selection and interpretation of further diagnostic tests to create a posttest probability of the disease. This posttest probability can then be used as a basis for clinical decision making. For PE, a number of such scores have been developed and validated (Tables 73-3–73-5). Wells et al.[51] have prospectively tested a rapid seven-item bedside assessment to estimate the clinical pretest probability for PE. An alternative scoring system, the Geneva score, involved seven variables and required gas exchange and radiographic information.[52] A revised Geneva score requiring eight clinical variables without gas exchange or radiographic information was validated and published.[53] Other clinical decision rules include the PISA rule, the PERC (pulmonary embolism rule-out criteria) rule, and the Charlotte rule.[54–56] Although such scoring systems have not proved to be more accurate than clinical assessment, they do provide a method of standardization that compensates for variability in physician experience and judgment.

LABORATORY FINDINGS

Routine laboratory testing is not useful in confirming or excluding the diagnosis of PE but may be helpful in suggesting other diagnoses. A modest leukocytosis may accompany embolism but rarely exceeds 20,000/mm^3.[57]

As noted, hypoxemia is common in acute PE although the diagnosis cannot be excluded based upon a normal P_{O_2}.[58,59] The more massive the obstruction, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia and,

TABLE 73-4 The Original Geneva Clinical Prediction Score

Variable	Point Score
Age	
60–79 y	1
>80 y	2
Previous DVT or PE	2
Recent surgery	3
Pulse rate >100	1
Pa_{CO_2}, kPa (mm Hg)	
<4.8 (36)	2
4.8–5.19 (36–38)	1
Pa_{CO_2}, kPa (mm Hg)	
<6.5 (<48)	4
6.5–7.99 (48–60)	3
8.0–9.49 (61–71)	2
9.5–10.99 (72–82)	1
Chest radiograph appearance	
Plate-like atelectasis	1
Elevated hemidiaphragm	1
Total Score	**Pretest Probability**
0–4	Low
5–8	Moderate
9–16	High

Source: Data from Ageno W, Becattini C, Brighton T, et al. Cardiovascular Risk Factors and Venous Thromboembolism: a Meta-Analysis. Circulation. 2008;117(1):93–102.

TABLE 73-5 The Revised Geneva Clinical Prediction Score

Variable	Points
Age >65 y	1
Previous DVT or PE	3
Surgery (under general anesthesia) or lower limb fracture within 1 mo	2
Active malignancy (currently active or considered cured <1 y)	2
Symptoms	
Unilateral lower limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate: 75–94 beats/min	3
≥95 beats/min	5
Pain on lower limb deep venous palpation or unilateral edema	4
Total Score	**Pretest Probability**
0–3	Low
4–10	Moderate
≥11	High

Source: Data from Stein PD, Hull RD, Kayali F, et al. Venous thromboembolism according to age: the impact of an aging population. Arch Intern Med. 2004;164(20):2260–2265.

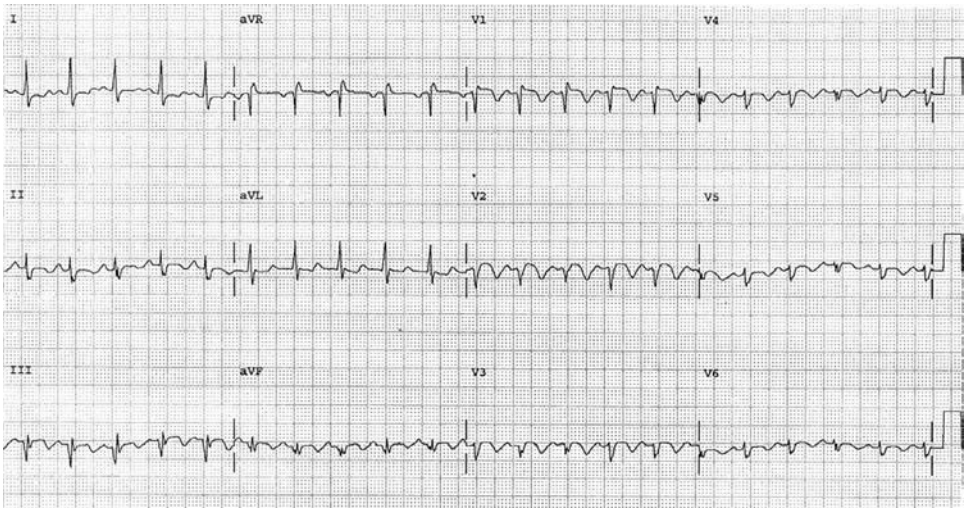

Figure 73-6 Electrocardiogram demonstrating findings consistent with embolism including sinus tachycardia, incomplete right bundle branch block, S1Q3T3 pattern, and inverted precordial T waves.

conversely, acute PE does not necessarily cause hypoxemia or even a widening of the $(A\text{-}a)_{O_2}$ gradient.[58] In the PIOPED trial, no combinations of blood–gas abnormalities were identified that reliably excluded PE. Although most patients with embolism have a low Pa_{O_2}, low Pa_{CO_2}, or high $P(A\text{-}a)_{O_2}$ gradient, the absence of such abnormal values, alone or in combination, did not exclude PE. Hypercapnia resulting from increased dead space ventilation is rare and appears with PE only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation when the embolism occurs.

■ ELECTROCARDIOGRAM

The electrocardiogram is nonspecific in the diagnosis of PE, and its major value may be in identifying other clinical disorders (e.g., acute myocardial infarction and pericarditis) that may be confused with PE. Findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities, and left- or right-axis deviation (Fig. 73-6).[46] Atrial arrhythmias may occur but appear to be more common in patients with underlying cardiopulmonary disease. The S1Q3T3 pattern, commonly considered to be specific for PE, is seen in only a minority of patients. Electrocardiographic findings can offer insight into the extent and hemodynamic consequence of the embolism. The electrocardiogram is rarely normal in the setting of PE associated with right ventricular dysfunction. The presence of an S1Q3T3 pattern, right bundle branch block, or T-wave inversion in leads V1 toV3 in a patient with PE should suggest the presence of right ventricular dysfunction.[60,61]

■ CHEST RADIOGRAPHY

Most patients with PE have abnormal but nonspecific chest radiographic findings.[46,62] Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and mild elevation of a hemidiaphragm. Classic findings of pulmonary infarction – such as Hampton's hump or decreased vascularity (Westermark sign) – are suggestive but infrequent. There is some confusion about the diagnostic configuration of infiltrates due to embolism. These infiltrates, although usually abutting a pleural surface, can be of any shape, not necessarily wedge shaped. Although pleural effusions occur in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle. The main use of the chest radiograph in suspected PE is to exclude alternative diagnostic possibilities such as pneumothorax, which may simulate the disease. A normal chest radiograph in a patient with otherwise unexplained acute tachypnea, dyspnea, or hypoxemia should raise the possibility of PE.

■ D-DIMER

The development of a rapid and accurate blood test capable of diagnosing venous thromboembolism has been the subject of considerable investigative interest. A number of different hemostasiologic markers have been investigated. Of these, D-dimer, alone and in combination with other noninvasive studies has been subjected to the most rigorous clinical evaluation.[63,64] D-dimer testing has proven to be highly sensitive but not specific. Increased levels are present in nearly all patients with venous thromboembolism, but also occur in a wide range of other circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy. Therefore, the role of D-dimer testing is limited to one of venous thromboembolism exclusion. The study is of limited utility in inpatients given the high frequency of positive results in this population.[65]

Multiple assays for D-dimer have been developed with a range of sensitivities and specificities.[66] Highly sensitive assays such as the enzyme-linked immunosorbent assay (ELISA) are capable of excluding venous thromboembolism but are associated with such a high frequency of false-positive results, especially when applied to an inpatient population, as to limit their clinical utility. Less sensitive assays (e.g., latex agglutination, red cell agglutination) lack the ability to exclude venous thromboembolism in isolation but have been used successfully in combination with either a clinical probability estimate or noninvasive diagnostic study. D-dimer testing has been used successfully as part of a number of different diagnostic strategies. Negative results of standardized, highly sensitive assays (ELISA) have proved capable of safely excluding PE in outpatients presenting with a low or intermediate clinical likelihood of the disease. Certain non-ELISA assays are capable of excluding embolism as a stand-alone study in outpatients with a low probability of disease but are more appropriately used in a multibranch diagnostic pathway.

■ VENTILATION–PERFUSION SCANNING

V/Q scanning had been the pivotal diagnostic test for suspected PE for many years but has been replaced by CT imaging. Despite limitations, V/Q lung scanning can provide valuable information if used and interpreted appropriately. The PIOPED trial provided valuable insight into the strengths and limitations of V/Q scanning.[44] A negative study is capable of ruling out the diagnosis of PE with the same degree of certainty as a negative pulmonary angiogram and with a higher degree of certainty than can be achieved by a negative CT scan (Fig. 73-7). The positive predictive value of a "high probability" study (one characterized by multiple, segmental-sized, mismatched

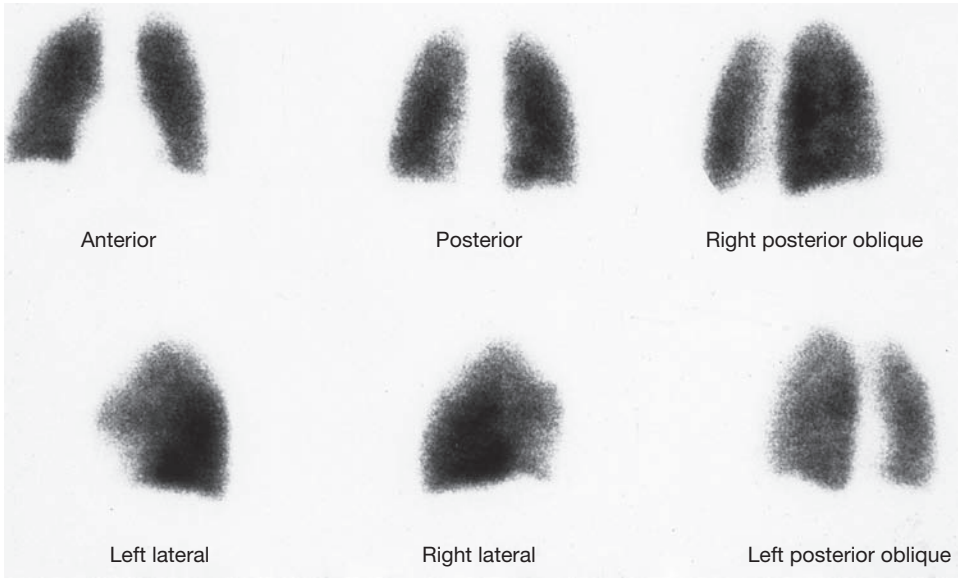

Figure 73-7 Normal six-view perfusion scan. Such a scan finding has a negative predictive value equivalent to a negative pulmonary angiogram and higher than that of a negative computed tomographic study.

defects) approximates 88%; when coupled with a high clinical probability of embolism, the positive predictive value increased to 96% (Fig. 73-8). However, only 28% of patients in PIOPED had scans characterized as high probability or normal, the only categories that can be considered definitive. The majority of patients with PE do not have a high probability scan, whereas the majority of those without embolism do not have a normal scan.

The PIOPED study also undertook to correlate the clinical impression of the likelihood of PE with the interpretation of the lung scan (Table 73-6). When interpretation of the lung scan and clinical assessment were concordant (both high and low probability), diagnostic accuracy was greater than that of the lung scan alone. In contrast, when interpretation of the lung scan and clinical assessment were discordant, the predictive value of the lung scan was decreased. In as many as two-thirds of patients suspected of PE, the combination of the lung scan and clinical assessment were either discordant or indeterminate and failed to diagnose or exclude PE.

There are certain situations in which V/Q scanning may be preferred over CT-pulmonary angiography (CT-PA). IV contrast is not required for V/Q scanning making it a more desirable option in patients with renal dysfunction or a severe iodinated contrast allergy. In addition, with a portable gamma scintillation camera the perfusion portion of the study can be performed at the bedside, which may be a major advantage in a critically ill patient for whom transportation to the CT scanner may be deemed too high risk. The role of V/Q scanning versus CT-PA in pregnancy remains unsettled but V/Q scanning appears to offer similar diagnostic performance in this setting with significantly lower levels of maternal radiation.[67]

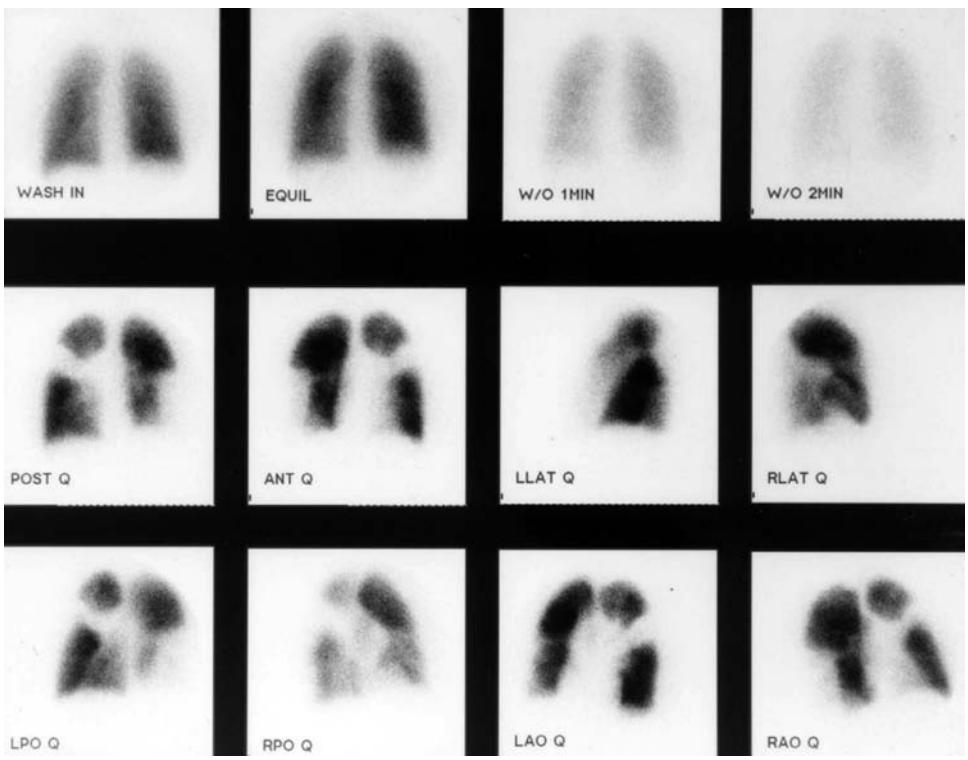

Figure 73-8 "High probability" ventilation/perfusion scan demonstrating normal ventilation and multiple mismatched segmental and larger defects.

TABLE 73-6 Prevalence of Pulmonary Embolism in PIOPED: Value of Correlating Lung Scan Interpretation with Clinical Assessment

		Clinical Assessment		
		High No./Total (%)	Intermediate No./Total (%)	Low No./Total (%)
Lung Scan Interpretation	High Probability	28/29 (96%)	70/80 (88%)	5/9 (56%)
	Intermediate Probability	27/41 (66%)	66/236 (28%)	11/68 (16%)
	Low Probability	6/15 (40%)	30/191 (16%)	4/90 (4%)

Source: Data from Pomp ER, Lenselink AM, Rosendaal FR, et al. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008;6(4):632–637.

■ ECHOCARDIOGRAM

The overall sensitivity of transthoracic echocardiography in PE approximates 50%.[68] Under appropriate clinical circumstances, the detection of unexplained right ventricular volume or pressure overload should suggest the possibility of PE and lead to confirmatory testing. Transthoracic echocardiography has emerged as a potentially important tool for risk assessment and treatment guidance in patients with acute PE. The presence of right ventricular dysfunction on a baseline echocardiogram in normotensive patients appears to represent an independent predictor of an adverse outcome or early death.[69,70] Properly performed transesophageal echocardiography has demonstrated sensitivity and specificity exceeding 90% in the detection of proximal emboli involving the pulmonary trunk and the right and left main pulmonary arteries.[71] Echocardiography also may prove valuable in the evaluation of competing diagnostic possibilities such as right ventricular infarction, endocarditis, pericardial tamponade, and aortic dissection in patients with unexplained shock and evidence of elevated central venous pressure.

■ LOWER EXTREMITY EVALUATION

Duplex ultrasonography, which refers to the combination of Doppler venous flow detection and real-time B-mode imaging, has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity DVT.[72] A number of criteria are used to diagnose DVT, the most reliable of which is noncompressibility of a venous segment. Secondary, less reliable criteria include the presence of echogenic material within the venous lumen, loss of phasicity with respiration, attenuated increase in venous diameter in response to Valsalva, and lack of augmentation of flow in response to calf compression. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may not demonstrate echogenicity. Multiple studies over the past decade have demonstrated sensitivities and specificities exceeding 95% in *symptomatic* patients with proximal DVT.

While duplex ultrasonography is highly sensitive and specific in the diagnosis of DVT in symptomatic patients, its accuracy in the diagnosis of asymptomatic DVT is less clear. A meta-analysis of studies comparing ultrasound to contrast venography in asymptomatic patients found that ultrasound was accurate for the detection of asymptomatic proximal DVT, but the data was limited almost entirely limited to postoperative orthopedics patients.[73] Approximately 30% to 40% of patients with PE will also have signs and/or symptoms of DVT and 60% to 80% will have evidence of proximal DVT when subject to duplex ultrasonography. However, given that the overwhelming majority of patients with suspected PE will not prove to have that diagnosis, duplex ultrasonography as the initial diagnostic study should be reserved for those patients with clinical evidence of DVT and for special populations in which avoidance of radiation or contrast material is preferred.[74–77]

The role of CT venography as a stand-alone test for DVT is limited. CT venography appears to be comparable to ultrasonography with respect to sensitivity and specificity, but it requires contrast injection with its associated risks and radiation exposure. A potential advantage of CT venography is the ability to visualize the pelvic veins and vena cava. The concept of combined CT-PA and venography is attractive. Such an approach would provide visualization of the embolus and its source in a single study as well as potentially increase diagnostic yield in comparison with the use of CT-PA alone.[78] However, the absolute increase in diagnostic yield appears to be modest and comes at the cost of increased expense, substantial pelvic radiation exposure, and the risk of hemorrhagic complications from providing anticoagulation to patients with false-positive studies.

■ MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) techniques for detecting DVT and PE have been investigated. The PIOPED III trial was the largest, multicenter study designed to assess magnetic resonance angiography (MRA) for the diagnosis of PE.[79] Three hundred and seventy-one patients were enrolled in whom PE was confirmed or excluded by CT-PA or V/Q. Approximately 25% of studies were technically inadequate and could not be interpreted. However, this seemed to vary by site (11%–52%) suggesting that some sites may have had more experience and were able to limit their number of inadequate scans. The sensitivity and specificity of MRA among patients with technically adequate scans was 78% and 99%, respectively. These figures fell considerably when the technically inadequate scans were included in the calculations. Sensitivity for PE involving the main or lobar pulmonary arteries was only 79%.

There are patients in whom CT-PA may not be possible due to IV contrast allergy or in whom avoidance of radiation is preferred (e.g., pregnancy). In these patients it seems that MRA may be a reasonable alternative. The risk of gadolinium-related nephrogenic systemic fibrosis has dampened the initial enthusiasm for MRI scanning in patients with renal insufficiency.[80]

■ COMPUTED TOMOGRAPHY

CT-PA has become the first-line imaging test for PE (Fig. 73-9). CT technology has evolved from single detector scanners to 64-multidetector-row CT (MDCT) scanners. Using the latest generation scanners, visualization of the entire chest with submillimeter resolution extending to the sixth generation arteries can now be performed within a single breath hold. The PIOPED II trial, which used predominantly 4-MDCT technology and a composite reference standard, demonstrated sensitivity for the diagnosis of PE of 83%, specificity of 96%, positive predictive value of 86%, and negative predictive value of 97% (Table 73-7).[46] The predictive value of CT-PA varied substantially when clinical assessment was taken into account, with the major variance occurring when there was discordance between the clinical assessment and CT-PA finding. Both the positive predictive value in patients with a low clinical probability and the negative predictive value in those with a high clinical probability were in the range of 60%.

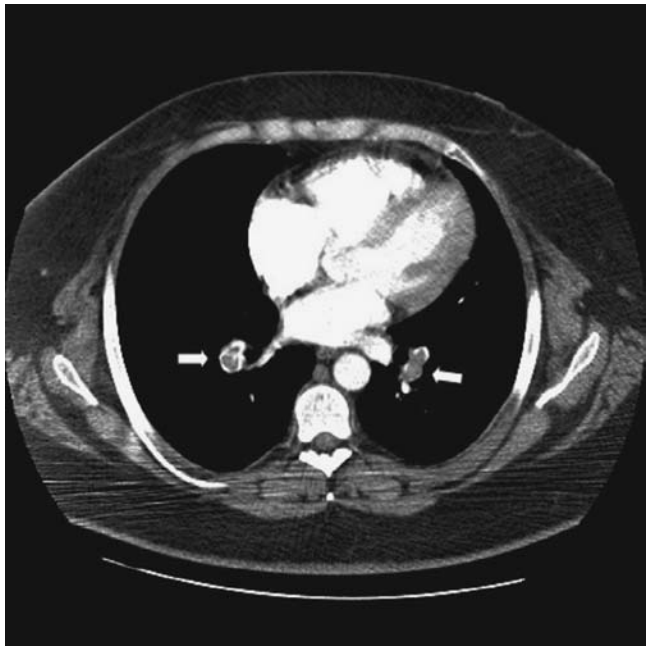

Figure 73-9 Computed tomographic angiogram demonstrating nearly occlusive thrombus in both lower lobe pulmonary arteries (*arrows*).

At the present time, CT can be considered confirmatory in excluding embolism in patients with a low or intermediate likelihood of disease and confirming embolism in patients with intermediate or high probability of disease. When discordance exists between the clinical assessment and CT findings, additional studies should be considered.

Concerns have been raised that the widespread utilization of CT-PA is resulting in the overdiagnosis of PE, defined as diagnosing clinically insignificant disease. The highest level of evidence thus far is a randomized controlled trial by Anderson et al.[81] of pulmonary CT-PA versus V/Q scan for suspected PE that showed comparable mortality and false-negative rates for the two imaging modalities with a 51% higher rate of PE diagnosis for CT. It has been suggested, based on the known natural history of subsegmental embolism, that patients with isolated subsegmental PE do not necessarily need to be treated with anticoagulants provided they meet the following criteria: (1) good cardiopulmonary reserve; (2) no evidence of DVT with serial lower extremity studies; (3) a transient (reversible) major risk factor for PE that is no longer present; (4) no history of central venous catheterization and no history of atrial fibrillation; and (5) a compliant and trustworthy patient who would return for serial noninvasive lower extremity studies.[82] Concerns have also been raised that CT-PA, as a result of its easy availability, is being overutilized in outpatients without adequate patient screening through validated methods such as the Wells criteria/D-dimer model or the PERC.[55,83]

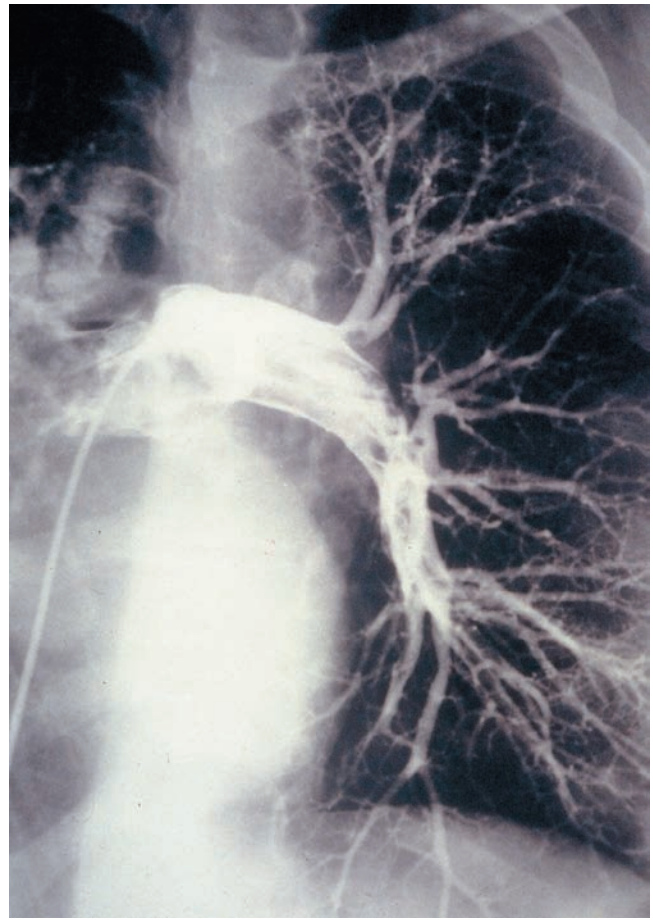

Figure 73-10 Conventional contrast pulmonary angiogram demonstrating extensive embolus within the left main pulmonary artery and extending into lobar branches.

■ CONVENTIONAL PULMONARY ANGIOGRAPHY

Prior to widespread acceptance of CT-PA, pulmonary angiography was considered the accepted "gold standard" for PE diagnosis although it had a number of limitations (Fig. 73-10). It requires expertise in study performance and interpretation. It is invasive and

TABLE 73-7 Prevalence of Pulmonary Embolism in PIOPED II: Value of Correlating CT Interpretation with Clinical Assessment

		Clinical Assessment		
		High No./Total (%)	Intermediate No./Total (%)	Low No./Total (%)
CT Scan Interpretation	**PPV of CTA**	22/23 (96%)	93/101 (92%)	22/38 (58%)
	PPV of CTA-CTV	27/28 (96%)	100/111 (90%)	24/42 (57%)
	NPV of CTA	9/15 (60%)	121/136 (89%)	158/164 (96%)
	NPV of CTA-CTV	9/11 (82%)	114/124 (92%)	146/151 (97%)

PPV of CTA, positive predictive value of computed tomographic angiography; PPV of CTA-CTV, positive predictive value of combined computed tomography angiography + venography; NPV of CTA, negative predictive value of computed tomographic angiography; NPV of CTA-CTV, negative predictive value of computed tomographic angiography + venography.

Source: Data from Galli M, Luciani D, Bertolin G, et al. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101(5):1827–1832.

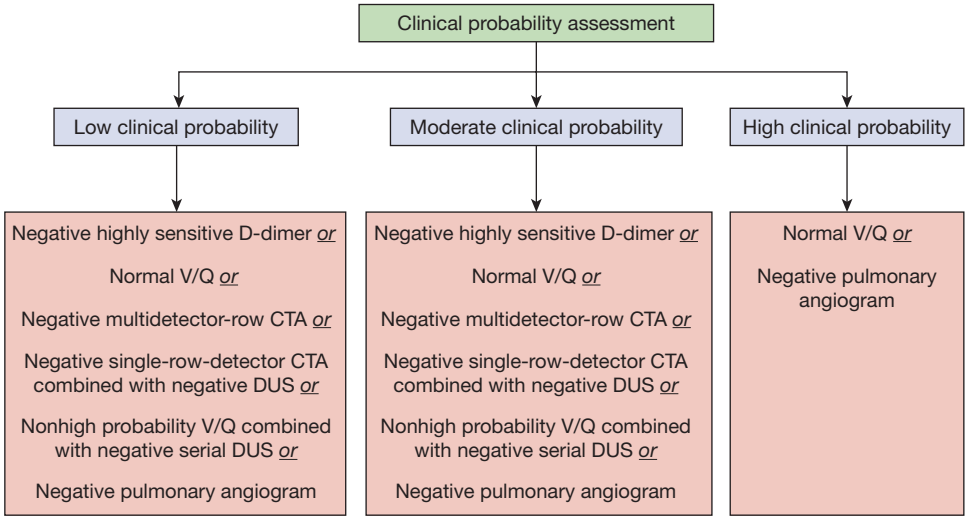

Figure 73-11 Current diagnostic strategies capable of excluding diagnosis of pulmonary embolism.

has associated risks, although published studies suggest that the use of modern techniques and contrast materials has reduced the risk well below its lingering perception. Pulmonary angiography can be performed quite safely if certain safeguards are observed and experienced personnel are involved. In the 1111 angiograms performed in the original PIOPED trial, pulmonary angiography was nondiagnostic in 3% of patients and associated with a major complication rate of 1% and death rate of 0.5%.[84] Major complications occurred more frequently among patients sent for angiography from the medical intensive care unit than in patients from elsewhere (4% vs. 1%). The procedure has other limitations. One is accessibility and the need for transportation. The other limitation is interpretation. Interpretation of pulmonary angiograms is heavily influenced by three factors: the location of the thromboembolic obstruction, the quality of the images, and the experience of the interpreters. Only two angiographic findings are diagnostic of acute embolism: a filling defect and abrupt cutoff of a vessel. Technical adequacy of the angiogram is critical to accurate identification of both. Flow artifacts can falsely suggest a filling defect. It is essential that good vessel opacification be obtained and that the filling defects be identified as real on a sequence of films.

Angiography is reserved for the small subset of patients in whom the diagnosis of PE cannot be established or excluded by less invasive means and for the evaluation of suspected chronic thromboembolic disease.

DIAGNOSTIC APPROACH

The diagnostic approach to PE should be targeted toward the patient population being studied (Figs. 73-11 and 73-12). For outpatients, the use of a clinical prediction rule coupled with D-dimer testing or the use of the PERC criteria can substantially reduce the number of imaging studies performed. In the outpatient setting, D-dimer results would not alter the need for an objective imaging study in patients with a high probability of PE. In patients with a low or intermediate clinical likelihood of PE, a negative D-dimer study is sufficient to exclude the diagnosis, assuming a highly sensitive assay is used. An imaging study should be performed in all patients with a high probability of disease as well as those with a low or intermediate probability whose D-dimer tests are positive.

Patients with signs or symptoms of lower extremity DVT should initially undergo lower extremity duplex ultrasonography. A positive lower extremity study, although not proving PE has occurred, has the same therapeutic implications. Although such an approach will yield a confirmatory study in only about 20% of patients suspected of having PE, it avoids the cost and radiation exposure associated with CT-PA. A negative study is insufficient to exclude the possibility of PE.[77]

In patients without lower extremity symptoms or signs who have a high or intermediate clinical probability of PE, a positive CT-PA confirms the diagnosis. In patients with a low or intermediate clinical probability, a negative CT-PA excludes the diagnosis. The only patients who may require additional testing (duplex ultrasonography and/or conventional angiography) are those in whom the clinical assessment and CT findings are discordant (low clinical probability and positive CT scan or high clinical probability and negative CT scan) unless the CT scan is of adequate quality and demonstrates evidence of PE in the main or lobar arteries in a patient with a low clinical probability assessment.

An approach utilizing V/Q scanning as the primary imaging tool can be used in settings such as pregnancy, contrast allergy,

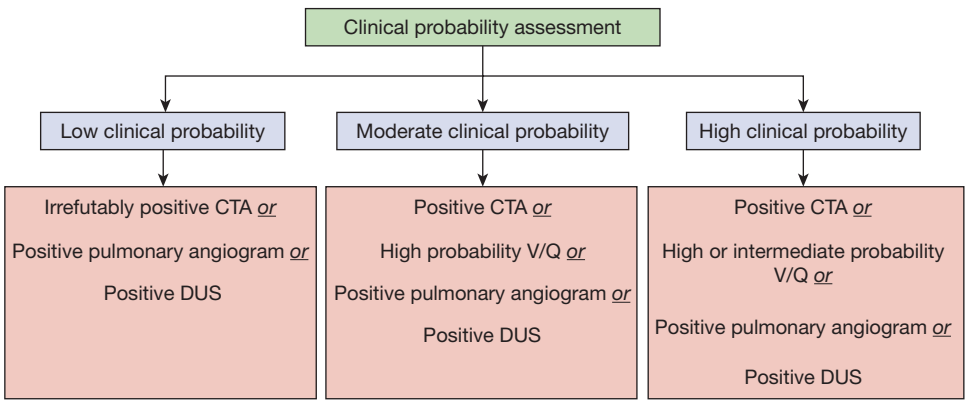

Figure 73-12 Current diagnostic strategies capable of confirming diagnosis of pulmonary embolism.

or renal insufficiency. This approach should be reserved for those with normal chest radiographs and no history of chronic pulmonary disease. Lower extremity evaluation should be considered before chest imaging given the likelihood that the V/Q scan will not be diagnostic. A negative V/Q scan is capable of excluding the diagnosis regardless of the clinical assessment as does a low probability scan in conjunction with a low clinical suspicion. A high probability scan is capable of confirming the diagnosis in patients with a high clinical suspicion. All other circumstances (high clinical probability with low or intermediate V/Q result, intermediate clinical probability regardless of V/Q result, and low clinical probability with a high or intermediate V/Q scan result) require additional testing.[44]

Whatever approach is undertaken, the treating physician should be aware of the type of D-dimer assay, discriminant value of that particular assay, and generation of CT scanner used. "Negative" findings on a low-sensitivity D-dimer assay or a single-row CT scanner have very different implications than similar findings using a highly sensitive D-dimer assay or 64-MDCT scanner.

The role of D-dimer testing and clinical assessment in hospitalized patients is limited. A substantial proportion of hospitalized patients have a positive highly sensitive D-dimer result related to an active inflammatory process, malignancy, recent surgery, liver disease, and even advancing age.[85] In a recent study that evaluated the use of the Wells prediction rule in conjunction with a latex agglutination or rapid ELISA D-dimer assay in hospitalized patients, only 10% of over 600 patients tested fell into the low probability category.[85] Furthermore, comorbid conditions affect the clinical likelihood assessment. Therefore, a far higher proportion of hospitalized patients require an imaging study to confirm or exclude the diagnosis of venous thromboembolism. In patients with limited cardiopulmonary reserve, high clinical probability assessment, and negative CT scan, pulmonary angiography should be considered given the potentially fatal consequences of a recurrent embolic event. In patients with adequate cardiopulmonary reserve under the same circumstances, a strategy incorporating sequential lower extremity evaluation can be undertaken.

TREATMENT

Management of acute PE consists of a systematic approach that involves early intervention, patient risk stratification, selection of therapy, and determination of treatment duration. The goals of therapy in PE are severalfold—to assure adequate oxygenation, provide hemodynamic support, and prevent thrombus propagation and embolic recurrence.

When a diagnosis of venous thromboembolism is suspected, empiric treatment should be considered until the diagnosis is either objectively excluded or confirmed. Given the ready availability of rapid D-dimer assays and CT, diagnostic confirmation or exclusion should require a relatively short period of time. Early empiric treatment should be initiated if diagnostic tests are not readily available. An exception can be made in those patients with a low clinical likelihood of disease, adequate cardiopulmonary reserve, and a high risk of bleeding complications.

The availability of low–molecular-weight heparin (LMWH) potentially allows carefully selected patients to be managed in the outpatient setting as demonstrated in the recently published study.[86] Although there are good data to support treating uncomplicated cases of DVT entirely in the outpatient setting, most physicians still advocate a short period of hospitalization in patients with newly diagnosed acute PE. Hospitalization should be mandatory for older patients who may have less cardiopulmonary reserve, or significant coexisting illnesses, or those who may not be able to follow instructions or have adequate follow-up. Other indications for hospitalization include hypoxemia, hypotension, hemodynamic instability, or sufficient renal disease to contraindicate the use of LMWH or a factor Xa inhibitor.

HEPARIN

Anticoagulation with heparin remains the standard initial therapy. The major anticoagulant effect of heparin is to reduce thrombus propagation and prevent embolic recurrence. Choices include either intravenous unfractionated heparin (UFH) or subcutaneous LMWH preparations. Given that failure to achieve rapid therapeutic levels of anticoagulation appears to be associated with an increased recurrence rate, it is reasonable to attempt to ensure adequate anticoagulation as soon as possible.[87]

Physician practices in the administration of intravenous unfractionated heparin have often resulted in substantial delays before adequate prolongation of the activated partial thromboplastin time (aPTT) is achieved. To overcome these problems, standardized protocols for unfractionated heparin administration and monitoring have been recommended. One commonly employed dosing regimen using an initial intravenous bolus of 80 units of heparin per kilogram followed by a continuous infusion initiated at 18 U/kg/h has been demonstrated to reach therapeutic thresholds more quickly than regimens using fixed dosing.[88] The heparin drip is adjusted based on monitoring of the aPTT, drawn 6 hours after the initial bolus dose, then 6 hours after each dose adjustment, with a target aPTT ratio of 1.5 to 2.5. Because attempts to straddle the lower therapeutic range may result in periods of inadequate anticoagulation, it is prudent to maintain the ratio in the upper range of the recommended target.

More recently, an approach using a fixed dose of subcutaneous unfractionated heparin without aPTT monitoring, administered as an initial dose of 333 U/kg followed by a dose of 250 U/kg every 12 hours, has been demonstrated to be as safe and effective as LMWH in patients presenting with DVT and PE.[89]

With the exception of special circumstances, LMWH preparations have displaced unfractionated heparin as the anticoagulant of choice in uncomplicated venous thromboembolism including PE.[90] Situations in which the use of UFH is appropriate include renal insufficiency, extremes of body weight, and circumstances in which a rapid adjustment or reversal of anticoagulation is needed, such as women in the late stage of pregnancy who may need Cesarean sections, patients with recent surgery or recent history of bleeding, and hemodynamically unstable patients with venous thromboembolism who may need surgical procedures such as emergency embolectomy.

Available evidence suggests that LMWH is at least as effective as unfractionated heparin in treating acute PE.[91] Advantages of LMWH compared with UFH include (1) longer half-life and ease of use; (2) ability to consistently achieve early therapeutic anticoagulation; (3) no need to monitor anticoagulant effects; and (4) reduced incidence of major bleeding complications. There are few data comparing different LMWH preparations. Even though there are differences in their Food and Drug Administration (FDA)-approved indications in the United States, it is not clear if their actions differ significantly.

In general, therapeutic monitoring is not needed with LMWH, but there are situations where the therapeutic effects may be less predictable and monitoring with anti-Xa levels is indicated. Typical examples include (1) patients with antiphospholipid antibodies or other circulating anticoagulants who have elevated baseline aPTT; (2) extremes of body weight (less than 40 kg and greater than 150 kg); (3) significant renal disease (creatinine clearance less than 30 mL/min); (4) pregnancy; and (5) unexplained bleeding or recurrent thrombosis during therapy. A therapeutic target range for peak anti-Xa levels ranges from 0.6 to 1.0 IU/mL, 4 hours after administration. The target range for peak anti-Xa levels with once daily enoxaparin is likely to be greater than1.0 IU/mL whereas it is greater than 0.85 IU/mL with tinzaparin and 1.3 IU/mL and 1.05 IU/mL with nadroparin and dalteparin, respectively.[92]

FACTOR XA INHIBITORS

Fondaparinux, a synthetic pentasaccharide, represented the first in a new class of antithrombotic agents. Unlike unfractionated heparin and LMWH, the antithrombotic properties of fondaparinux are selective for factor Xa. By binding rapidly and strongly to antithrombin, fondaparinux catalyzes specifically the inhibition of factor Xa, which results in inhibition of thrombin generation. It does not bind to other plasma components or platelets, has a half-life of approximately 17 hours, and is excreted almost completely by the kidneys. Fondaparinux was shown to be as effective and safe as intravenous unfractionated heparin in a large, open-label study.[93] It has been approved for prophylaxis in patients undergoing hip, knee, and abdominal surgery as well as for treatment of DVT and PE in conjunction with warfarin.

Rivaroxaban represents the first in a new generation of oral factor Xa inhibitors. In a large, open-label randomized study, rivaroxaban proved noninferior to conventional therapy (LMWH followed by a vitamin K antagonist) in patients with symptomatic DVT.[94] Patients with acute PE were excluded from the acute phase of the study. Although not specifically designed to determine efficacy in acute PE, the incidence of subsequent PE was equivalent between the two study groups. In a subsequent study involving 4832 patients, a fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of PE with or without DVT.[95] Ongoing trials are underway evaluating the efficacy and safety of other oral factor Xa inhibitors, including apixaban and edoxaban in venous thromboembolism.[96]

Intravenously administered direct thrombin inhibitors (lepirudin, argatroban) represent another class of anticoagulant agents that have been approved for the management of patients with venous thromboembolism in the setting of heparin-induced thrombocytopenia (HIT).[97] Their mechanism of action differs from that of heparin and the synthetic pentasaccharides in that they directly inhibit the active site of thrombin and do not require interaction with antithrombin to produce an anticoagulant effect. Argatroban is a synthetic agent derived from arginine. It has a half-life of approximately 45 minutes and is cleared by the liver. Lepirudin is a recombinant polypeptide similar to hirudin. It has a half-life of 40 to 60 minutes and is cleared by the kidneys. Both agents are administered by continuous intravenous infusion and dose adjustments made with monitoring of the aPTT. Both agents affect the international normalized ratio (INR), thereby complicating the transition to oral warfarin therapy. Although demonstrating promise, data supporting the use of fondaparinux in the management of HIT is far less robust than that of the intravenous direct thrombin inhibitors.[98] Based on its size, the drug is less immunogenic than unfractionated heparin or LMWH. Fondaparinux has not been approved by the FDA for this indication.

THROMBOLYTIC THERAPY

Unlike anticoagulants, thrombolytic drugs cause direct lysis of thrombi by increasing plasmin production through plasminogen activation. The potential benefits, however, are often offset by the relatively high incidence of hemorrhagic complications.

Multiple thrombolytic agents are available. Those most studied for the management of acute PE include streptokinase, alteplase (rt-PA), and urokinase, all of which are FDA approved for use in the United States. The PEITHO (pulmonary embolism thrombolysis) trial, a large multicenter study designed to enroll 1000 patients, is currently underway and will evaluate the efficacy and safety of tenecteplase in normotensive patients with evidence of right ventricular (RV) dysfunction.[99]

The exact role of thrombolytic agents in acute PE remains controversial. While thrombolytic therapy does appear to accelerate the rate of thrombolysis, there is no convincing evidence to suggest that it decreases mortality, increases the ultimate extent of embolic resolution when measured at 7 days, reduces thromboembolic recurrence rates, improves symptomatic outcome, or decreases the incidence of thromboembolic pulmonary hypertension.[100] The one issue about which there can be little controversy is that the use of thrombolytic agents is associated with a substantially increased risk of bleeding, including intracranial hemorrhage. Intracranial hemorrhage has occurred in 0.5% to 3.0% of patients treated with thrombolytic agents in trials evaluating the use of these agents in both PE and myocardial infarction.[101]

Based on these data, and assuming there is no contraindication to its use, the use of thrombolytic therapy in PE appears to be appropriate when an accelerated rate of thrombolysis may be considered lifesaving. Specifically, this applies to patients with PE who present with hemodynamic compromise (in whom the mortality rate approaches 30%), patients who develop hemodynamic compromise during conventional therapy with heparin, and patients with PE associated with intracavitary right heart thrombi.[36]

The role of thrombolytic therapy in patients with anatomically massive embolism or echocardiographic evidence of right ventricular dysfunction in the absence of systemic hypotension is less well defined. Risk stratification strategies using echocardiography, troponin levels, or brain natriuretic peptide (BNP) levels are currently under investigation and may help resolve this area of controversy.[102] At the present time, the finding of right ventricular dysfunction on echocardiography in the absence of hemodynamic instability would not appear to serve as a justification for the routine use of thrombolytic therapy. Approximately 40% to 50% of patients with symptomatic PE have echocardiographic evidence of right ventricular dysfunction.[103] Clinical scoring systems have also been constructed capable of estimating 30-day mortality rates in patients with acute PE (Table 73-8).[104,105] However, these scoring systems appear best suited in identifying patients with a low mortality risk who may be suitable for home management rather than those with a sufficiently high mortality risk to justify the use of thrombolytic therapy.

Normotensive patients with evidence of right ventricular dysfunction, as determined by echocardiography or an elevated BNP or troponin level, appear to be at risk for an adverse outcome when

TABLE 73-8 Original and Simplified Pulmonary Embolism Severity Index

Variable	Original PESI	Simplified PESI
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[a]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation <90%	+20	1

Original PESI: Class I, 65 or less; Class II, 66–85; Class III, 86–105; Class IV, 106–125; Class V, >125.
Modified PESI: 0, low risk; 1 or more, high risk.
[a] *Variables combined into a single category of chronic cardiopulmonary disease.*
Source: Modified with permission from Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041–1046.

compared with patients without right ventricular dysfunction. However, until criteria have been established that more clearly define that subset of patients who will benefit from thrombolytic therapy, there is little basis for exposing all such patients to the considerable risk of hemorrhagic complications associated with this intervention. It is hoped that the ongoing PEITHO trial will help resolve this uncertainty.[99]

Because of the side effects and the prolonged period of infusion required, many physicians are reluctant to use thrombolytics in cases of DVT, whether delivered systemically or by local catheter-directed infusion. In selected patients with symptomatic iliofemoral thrombosis, catheter-directed thrombolysis either alone or combined with angioplasty or stent placement may result in increased venous patency and may improve quality of life.[106]

INTERVENTIONAL RADIOLOGIC TECHNIQUES

Interventional thrombus fragmentation represents a potential alternative to systemic thrombolysis or surgical embolectomy for treatment of PE.[107] If the bleeding risk is not exceedingly high, catheter fragmentation may be combined with local or systemic thrombolysis. A wide variety of devices designed to either fragment and/or remove fresh embolic material have been tested in patients with PE.[108] In general, the devices use either pressured saline or a rotating impeller to fragment central thrombi. The fragments are either aspirated through a separate port on the catheter or allowed to migrate distally. Most of the devices appear to be effective, safe, and potentially lifesaving in the presence of central, acute clots. However, none of the devices has been investigated in a large controlled trial, and all commercially available devices have important limitation. These limitations include a risk of paradoxical embolism from the clot fragments. Therefore, the intervention is contraindicated in patients who have an intracardiac communication, such as a patent foramen ovale.

PULMONARY EMBOLECTOMY

Embolectomy has been used for the emergency removal of PE. Small observational studies comparing surgical embolectomy and thrombolytics did not show significant advantage using embolectomy, although there was a trend toward better survival and lower bleeding rates in the surgical group. In a recent review of 3770 patients undergoing surgical embolectomy for acute PE between 1999 and 2008, all-cause inhospital case fatality rate was 28%; mortality was 24% in patients considered stable and 40% in those unstable.[109] Based on current data, it is reasonable to consider surgical embolectomy in patients with persistent hypotension, shock, or cardiac arrest who either failed thrombolysis or have a contraindication to thrombolytic management.

LONG-TERM MANAGEMENT

Long-term management includes use of traditional anticoagulants, including warfarin and heparin, as well as a variety of new pharmacologic agents. In addition, insertion of devices in the inferior vena cava to prevent additional embolic events has been employed.

WARFARIN

Recurrence is common following an acute thromboembolic event. Therefore, treatment should be continued until the benefits of ongoing therapy no longer outweigh the potential risks.

Oral anticoagulation using warfarin, a vitamin K antagonist, is generally used for long-term treatment of venous thromboembolism because of its proven efficacy. Warfarin inhibits gamma carboxylation activation of coagulation factors II, VII, IX, and X as well as proteins C and S. With proper monitoring, less than 3% of patients using warfarin develop significant bleeding. The drug is usually started soon after the initiation of heparin therapy. Use of warfarin without heparin is strongly discouraged as it generally takes 3 to 5 days of warfarin to achieve full therapeutic efficacy. In patients with protein C deficiency, skin necrosis or paradoxical thrombosis may occur in the absence of concurrent heparin therapy.

Warfarin has a narrow therapeutic index and patients are generally monitored closely by measuring the prothrombin time corrected to the reagent being used (the INR). To maximize efficacy while minimizing side effects, an INR range between 2 and 3 is recommended for most patients. Even in the setting of an antiphospholipid antibody, high-intensity warfarin therapy does not appear superior to standard treatment but is associated with an increased incidence of minor bleeding complications.[110,111] Besides bleeding complications, warfarin has been associated with fetal abnormalities particularly when given during the 6th to 12th weeks of gestation. Another rare complication of warfarin use is cholesterol microembolism ("purple toes" syndrome), which is thought to be due to cholesterol crystal release from ulcerated intravascular plaques.[112]

Individuals metabolize warfarin differently and age, genetic variations in CYP2C9 alleles, nutritional factors, and concomitant medications can affect anticoagulant levels significantly. Multiple mechanisms of drug interaction are possible including alterations of absorption (cholestyramine), induction of hepatic CYP450 (barbiturates, carbamazepine), inhibition of CYP3A4 (amiodarone), inhibition of CYP2C9 (metronidazole, clotrimazole), and displacement of protein-bound warfarin (phenytoin).[113]

Suggested dosing regimens involve an initial daily dose of 5 or 10 mg with use of a standardized nomogram to dose adjust based on INR values obtained on days 3 and 5.[114] Beginning with a 10-mg dose appears to hasten the achievement of a therapeutic INR without an increase in bleeding complications.[115,116] Elderly, malnourished, and debilitated patients tend to require less warfarin and the initial dose should be lowered accordingly. Some medical conditions, such as concomitant liver or kidney failure, alcoholism, malignancy, and recent history of gastrointestinal bleeding or trauma, are additional factors that may predict dose titration difficulties and higher risk of bleeding.

To minimize potential subtherapeutic anticoagulation, it is generally recommended that patients should receive at least 5 days of combined heparin and warfarin therapy, including at least 2 days in which the INR is in a therapeutic range before stopping heparin. The safety and effectiveness of both short- and long-term anticoagulation can be optimized by a systematic, evidence-based approach to therapy, often in the context of dedicated anticoagulation management services.[117] In carefully selected patients, self-management of warfarin therapy using INR measurement with "point of care" devices may also be done.[118]

HEPARIN

There are occasional instances in which heparin should be considered for long-term anticoagulation despite the cost and inconvenience associated with subcutaneous administration. Because of the teratogenic potential of warfarin, unfractionated heparin or LMWH should be used in pregnant women who developed venous thromboembolism in the first and possibly early second trimesters. Since the risk of venous thromboembolism may be highest in the postpartum period, anticoagulation should be continued for at least 3 to 6 months, including a minimum of 4 to 6 weeks after delivery. Patients with cancer complicated by thromboembolism appear to have fewer recurrent thromboembolic events and bleeding complications when treated with LMWH compared with warfarin.[119] Whether this is a specific effect of LMWH or simply a reflection of fluctuating INR levels in patients with cancer treated with warfarin is uncertain. LMWH therapy is now recommended over warfarin as

a first-line treatment to reduce the risk of recurrent venous thromboembolism in patients with active cancer.[120]

NOVEL AGENTS

Novel agents have been used successfully for long-term management of patients with venous thromboembolism. As noted previously, rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of PE with or without DVT.[95] Dabigatran, an oral direct inhibitor of thrombin, has also proven effective for long-term management. In the RE-COVER trial involving 2539 patients with acute venous thromboembolism, 786 of whom had PE, dabigatran administered at a dose of 150 mg twice daily after initial treatment with heparin was as effective as warfarin therapy in preventing thromboembolic recurrence while significantly reducing nonmajor bleeding.[121] In the AMPLIFY-EXT (apixaban after the initial management of PE and deep vein thrombosis with first-line therapy-extended treatment) trial, apixaban reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy.[122]

The role of aspirin in the long-term management of patients with venous thromboembolism remains incompletely defined. In the WARFASA (the warfarin and aspirin study) trial, the use of aspirin reduced the risk of thromboembolic recurrence by 40% when given to patients with unprovoked venous thromboembolism following discontinuation of anticoagulant therapy.[123] In the ASPIRE (aspirin to prevent recurrent venous thromboembolism) trial, however, aspirin, as compared with placebo, did not significantly reduce the rate of recurrence of venous thromboembolism but resulted in a significant reduction in the rate of major vascular events, with improved net clinical benefit.[124]

DURATION OF THERAPY

Over the past decade, data have emerged that have significantly changed our recommendation regarding duration of anticoagulation after venous thromboembolism. Central to this change has been awareness that venous thromboembolism often represents a recurrent disease and that the risk for recurrence is based on the initiating factors, persistence or resolution of those factors, and anatomic consequences of the initial event.

Patients with venous thromboembolism associated with a transient risk factor appear to be at a low risk of recurrence. Patients who experience postoperative venous thromboembolism appear to be at lowest risk. However, the annualized risk of recurrent disease is still in the region of 3%.[125] A 3-month course of anticoagulation appears to be adequate in this group (assuming the risk factor has resolved). Patients with idiopathic (unprovoked) thromboembolism have a substantially higher rate of recurrence, corresponding to an annualized event rate of 7.9% per patient-year.[125] In these patients, anticoagulation may simply delay subsequent recurrent thromboembolic events and ongoing risk factors may be present that have yet to be identified. Therefore, it is recommended that strong consideration be given to extended therapy in those with a low risk of bleeding complications.[126] Determining which patients remain at increased risk of thromboembolic recurrence is the target of ongoing investigative efforts. A number of clinical and serologic factors have been identified that predict a higher likelihood of recurrent venous thromboembolism following an initial course of therapy. These include PE as the initial presenting manifestation, age greater than 65, male gender, evidence of residual lower extremity DVT by ultrasonography, and elevated D-dimer levels measured at the end of warfarin therapy and then 1 month after its discontinuation.[127] How these factors should influence decisions about duration of anticoagulation in an individual patient remains to be determined.

In patients with venous thromboembolism associated with an irreversible risk factor, the absolute recurrence risk depends on the underlying disease or condition.[128,129] Patients heterozygous for the factor V Leiden mutation or the prothrombin G20210A mutation, although at higher recurrence risk than those without the mutation, do not appear to warrant prolonged anticoagulation while those homozygous for either of these mutations, or with a combined thrombophilia (i.e., heterozygous factor V Leiden combined with heterozygous prothrombin mutation), do. Patients with antiphospholipid antibody syndrome, those with active cancer, and those with deficiencies of protein S, protein C and antithrombin III are at considerable risk for thromboembolic recurrence and consideration should be given to lifelong therapy. In patients with two or more episodes of recurrent venous thromboembolism, the current recommendation is to consider lifelong anticoagulation with interval reassessment of the risk–benefit ratio. In summary, long-term anticoagulation should be individualized based on the risk for recurrent thromboembolism and bleeding. This is especially true in patients with cancer in whom the recurrent thrombosis risk and bleeding risk are substantially increased.[130] The appropriateness of ongoing therapy should be continuously re-evaluated, and the prophylaxis stopped if the benefit no longer appears to exceed the risk.

VENA CAVA INTERRUPTION AND VENA CAVA FILTER

The concept of vena cava interruption came from the historical practice of surgical ligation (by complete vascular ligation or partial interruption using surgical suture) of the IVC in an attempt to prevent thrombus migration. A variety of vena cava filters are now available, both permanent and temporary, and surgical ligation is rarely performed in the modern era.

The central indication for IVC filter placement is to prevent PE in patients who have a contraindication to anticoagulation. Recent data suggests that the utilization of IVC filters has dramatically expanded over the past decade and that IVC filters are being placed for alternative reasons, including prophylaxis.[131] Much of this expansion in utilization can be attributed to the development of retrievable IVC filters, which in many instances are not removed.[132] Guidelines for filter placement, albeit based on limited data, have been established by the American College of Chest Physicians and the Society of Interventional Radiologists.[133,134] These recommendations are somewhat disparate with the recommendations of the latter society being considerably more liberal than those of the former.

Despite the obvious theoretical benefit, carefully controlled trials that demonstrate the ability of IVC filters to decrease recurrence rates or mortality from PE have not been performed.[135] In one of the largest trials to date examining the effectiveness of IVC filters, 400 patients with proximal DVT were randomly assigned to either standard anticoagulation alone or anticoagulation plus insertion of a Vena Tech, Greenfield, Bird's Nest, or Cardial IVC filter.[136] During the first 12 days after randomization, significantly fewer patients in the IVC filter group suffered PE (1% vs. 5%). However, after a 2-year follow-up period, there were no significant differences in survival or symptomatic PE between the two groups, and a significantly higher rate of recurrent DVT was observed among patients who had received an IVC filter (21% vs. 12%).[137]

Given that IVC filters may decrease the incidence of early, recurrent PE, an argument can be made for their use in patients with residual lower extremity DVT who have suffered hemodynamically massive PE or who have poor cardiopulmonary reserve. Data on the effectiveness of IVC filters purely for prophylactic reasons are limited and randomized controlled trials are warranted to provide better practice-based evidence for or against this indication. Placement of an IVC filter is not a benign procedure and carries several possible

risks including potential DVT formation, filter migration, filter tilt, filter thrombosis, and the possibility of a higher incidence of lower extremity thrombotic events and postthrombotic syndrome.[138,139]

CHRONIC THROMBOEMBOLISM

Anatomic resolution of PE is rarely complete.[39,140] However, resolution in most patients is adequate to permit normalization of pulmonary hemodynamics and exercise tolerance. In some cases, however, the residual thromboembolic burden is sufficiently extensive to cause CTEPH. Estimates of the incidence of CTEPH range from 0.5% to 3.8% following an initial episode of PE to 13.4% following recurrent episodes of venous thromboembolism.[141–143] Approximately 30% of patients who develop CTEPH have no documented history of acute DVT or PE, and this feature greatly impedes the diagnosis. Anticardiolipin antibodies or lupus anticoagulants have been detected in approximately 10% to 20% of patients and elevated factor VIII levels detected in 40%.[144,145] No other defined thrombophilic or fibrinolytic abnormality has been encountered in this population. Age greater than 70, systolic pulmonary artery pressure greater than 50 mm Hg at the time of diagnosis of acute PE or at the time of hospital discharge following acute PE, previous PE, prior splenectomy, ventriculoatrial shunts, the presence of antiphospholipid antibodies, and a larger degree of pulmonary vascular obstruction at the time of acute PE have been identified as risk factors for CTEPH.[146]

The mortality of untreated CTEPH is high, with a 5-year survival of only about 10% in those who have a mean pulmonary artery pressure exceeding 50 mm Hg.[147,148] The treatment of choice for CTEPH is pulmonary thromboendarterectomy, which involves the dissection of endothelialized thrombi under cardiopulmonary bypass and deep hypothermia.[149] For the majority of patients, successful pulmonary thromboendarterectomy is considered curative. However, the hemodynamic outcome is incomplete in approximately 20% of patients. These patients have been successfully treated with medical therapies that are used in patients with idiopathic pulmonary arterial hypertension.[150] Indications for medical therapy in CTEPH include: (1) surgically accessible CTEPH in patients who elect not to undergo surgery for personal choice or where comorbidities are so substantial as to exclude the patient from consideration of thromboendarterectomy; (2) distal chronic thromboembolic disease or limited central disease that is so disproportionate to the severity of the pulmonary hypertension that the surgical mortality risk is prohibitive; (3) use as a preoperative therapeutic "bridge" to surgery in patients with severe right ventricular dysfunction; and (4) management of persistent pulmonary hypertension following pulmonary thromboendarterectomy. Patients with inoperable CTEPH or persistent pulmonary hypertension despite thromboendarterectomy may be considered for lung transplantation.

PROPHYLAXIS

The use of prophylactic strategies in hospitalized patients represents a major opportunity to prevent the morbidity and mortality associated with venous thromboembolism. Current data suggests, however that thrombosis prophylaxis is underutilized in patients at risk, especially medical patients whose risk approximates that of their moderate-risk surgical counterparts.[10,151,152]

Patients should be stratified according to DVT risk, and certain prophylactic measures are more appropriate for some patients than for others. The intensity of a prophylactic regimen should take into account the relative risk for thrombosis. Initial assessment should focus on the following questions: (1) What is the risk of venous thromboembolism in this patient? (2) What type(s) and intensity of prophylaxis should be used? (3) When is the best time to use prophylaxis? A patient's thrombotic risk may change over time and periodic assessment of the best prophylactic strategy should also be done. Most hospitalized patients are at risk of venous thromboembolism and should receive some form of prophylaxis unless its use is contraindicated. Prophylaxis may not be necessary in rare instances, as in the case of a young (less than 40 years) ambulatory patient who is admitted for a short (less than 48–72 hours) hospital stay without a history of prior venous thromboembolism history or recent surgery.

Four categories of drugs have been used successfully: unfractionated heparin, LMWH (enoxaparin, dalteparin), factor Xa inhibitors (fondaparinux, rivaroxaban), and the vitamin K antagonist warfarin. With the exception of warfarin, prophylactic dosing is subtherapeutic but sufficient to decrease the likelihood of thrombus formation. Recommended, evidence-based prophylactic strategies for a wide range of clinical circumstances in medical, surgical, and orthopedic patients have been published by the American College of Chest Physicians.[153–155]

When administered correctly in appropriate patients, prophylactic anticoagulation is safe and effective with an absolute reduction in the incidence of venous thromboembolism in the range of 40% to 60%. Major bleeding complications occur in less than 1% of patients.

Prevention of venous thromboembolism may also be achieved by the use of mechanical devices. These devices fall into two categories, graduated compression stockings and intermittent pneumatic compression stockings. Although studied less rigorously than pharmacologic methods of prophylaxis, the use of pneumatic compression has been shown in selected patients to be as effective as subcutaneous unfractionated heparin in preventing thrombosis. Mechanical methods of prophylaxis are especially useful in patients at bleeding risk and as an adjunct to pharmacologic methods in patients at high risk of thrombosis.[156]

Whatever form of prophylaxis is used, its intensity should be based on a patient's thrombotic risk determined by both individual and clinical circumstances. Prophylaxis adequate for a 41-year-old patient undergoing an elective appendectomy would be inadequate for a 70-year-old patient with cancer undergoing hip replacement surgery. Risk scores have been developed in an attempt to objectively and quantitatively describe the relative risk of venous thromboembolism in hospitalized patients and to help define the intensity of the prophylactic regimen.[157] The introduction of electronic medical records provides the opportunity to identify patients at risk, to alert the physician, and to develop decision-support, evidence-based recommendations for prophylaxis.

Thromboembolic risk does not necessarily end at the time of hospital discharge. The trend toward early hospital discharge has only served to transfer risk to the outpatient setting. Whether on an inpatient or outpatient basis, prophylaxis should continue until the thrombotic risk has resolved.[158]

The potential for bleeding complications associated with prophylaxis is a common dilemma in surgical or trauma patients, for whom bleeding may occur from the surgical site, especially in the immediate postoperative period. On the other hand, effective prophylaxis depends on timely administration of therapy before a thrombus develops. Recommendations can be drawn from multiple studies with regard to the appropriate timing for anticoagulation in different surgical settings. In cases in which anticoagulation may be delayed, it is customary to use either graduated compression stockings or pneumatic compression devices before surgery begins or as soon as surgery has been completed. Although evidence-based data are lacking, it may be reasonable to consider placement of a retrievable IVC filter in high-risk patients in whom pharmacologic prophylaxis is absolutely contraindicated.

OTHER VARIETIES OF EMBOLIC DISEASE

Because the lung receives all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a "sieve" for all particulate substances entering the venous blood and is the first

vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is, therefore, exposed to a wide variety of potentially obstructing and injurious agents.

VENOUS AIR EMBOLISM

An increasingly common form of nonthrombotic embolism in the United States is venous air embolism. The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma. The simple inadvertent transection or loss of closure of a large-bore intravenous catheter, particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, can enter the arterial system and are diffusely distributed throughout the body by way of either an intracardiac shunt (atrial septal defect, patent foramen ovale) or, more likely, through microvascular pulmonary shunts.

Physiologic consequences are related to the volume of air entrainment and rate of accumulation. An abrupt rise in pulmonary artery pressure and noncardiogenic pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of venous air embolism are variable and nonspecific, and may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom.[159] These and other consequences appear to be due to two phenomena: actual lodgment of the bubbles in capillary beds that interfere with nutrient supply to the affected organs, and the formation of platelet–fibrin aggregates, creating diffuse microthrombi. Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, the severity of the consequences depending upon the rate and volume of air gaining access to the circulation.

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore flow and promote reabsorption of the intravascular air.[160] Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and hyperbaric oxygen therapy. Using such aggressive measures, mortality from venous air embolism has been dramatically reduced.

FAT EMBOLISM

Fat embolism represents another form of nonthrombotic embolism.[161,162] In its full-blown form, a rather characteristic syndrome follows entry of neutral fat into the vascular system, consisting of dyspnea, hypoxemia, petechiae, and mental confusion. Seizures and focal neurologic deficits have been described. There is a variable lag time of 24 to 72 hours in the onset of the syndrome following the inciting event; rarely, cases occur within 12 hours or as late as 2 weeks after the event.

By far, the most common inciting event is traumatic fracture of long bones, with incidence rising with the number of fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally can lead to the same syndrome. Although considerably less common, fat embolism syndrome has been reported following both liposuction and lipoinjection procedures.

The basis for the variability in the incidence and severity of the syndrome after apparently comparable injuries has not been well defined, nor has the delay in clinical presentation. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat; and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat. The latter effect is probably the more important, causing diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds. The time necessary to produce toxic intermediaries may explain the delay from the inciting event to clinical presentation.

The diagnosis of fat embolism syndrome is a clinical one suggested by the constellation of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context. Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20% to 50% of cases. Therefore, their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome. Fat can be demonstrated in the serum of a majority of fracture patients with evidence of fat embolism syndrome. The finding of lipid-laden cells in bronchoalveolar lavage fluid appears to occur commonly in patients with traumatic injuries irrespective of the presence of fat embolism syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. The role of corticosteroid therapy to prevent the onset of fat embolism syndrome after an inciting event remains controversial.[163] Supportive treatment, including mechanical ventilatory support when necessary, is the primary approach, and survival is now the rule with meticulous support.

AMNIOTIC FLUID EMBOLISM

Another special form of embolism is amniotic fluid embolism, a rare, unpredictable and potentially catastrophic complication of pregnancy. Amniotic fluid embolism is reported to occur in approximately 2.0 per 100,000 deliveries and represents a leading cause of maternal mortality.[164] This disorder occurs during or after delivery when amniotic fluid gains access to uterine venous channels and, therefore, to the pulmonary and general circulations. The delivery may be either spontaneous or by Cesarean section and usually has been uneventful. Most cases occur during labor, but delayed onset of symptoms up to 48 hours after delivery can occur. Advanced maternal age, multiparity, premature placental separation, fetal death, and meconium staining of amniotic fluid have been associated with increased risk of amniotic fluid embolism.

Amniotic fluid embolism syndrome should be suspected with the sudden onset of severe respiratory distress, cyanosis, hypotension, cardiovascular collapse and, often, disseminated intravascular coagulation.[165] Occasionally, seizure activity occurs. It has been postulated that there is a biphasic pattern of hemodynamic disturbance: an initial period of pulmonary hypertension, commonly seen in animal models, followed by left ventricular dysfunction and cardiogenic shock. Patients who survive the first several hours develop noncardiogenic pulmonary edema coincident with improvement in left ventricular dysfunction.[166]

Amniotic fluid contains particulate materials that can cause pulmonary vascular obstruction, but the major pathogenetic mechanism of the syndrome remains uncertain. Amniotic fluid has thromboplastic activity that leads to extensive fibrin deposition in the pulmonary vasculature and, occasionally, other organs. As a consequence of fibrin deposition, severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. Following the acute event, an enhanced fibrinolytic state often occurs.

The diagnosis of amniotic fluid embolism is based on a compatible clinical picture, often enhanced by finding amniotic fluid components in the pulmonary circulation. The presence of squamous cells in pulmonary arterial blood, once considered pathognomonic, has proved to be a nonspecific finding. Serologic assays and immunohistochemical staining techniques have been described as having high sensitivity for amniotic fluid embolism.

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate), the best approach is supportive. Pulmonary artery catheterization is useful to monitor left ventricular function and volume status and to guide the appropriate use of inotropic and vasoactive agents. Even in the setting of aggressive supportive measures, however, maternal mortality has approached 80%.

SEPTIC EMBOLISM

Septic embolism is another special disorder that, unfortunately, is increasing in frequency owing to widespread intravenous drug abuse and the expanding use of indwelling intravenous devices. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis due to either septic abortion or postpuerperal uterine infection.[167] However, almost any venous structure can be involved, either as a focus of primary infection or from intravascular or contiguous spread: septic cavernous sinus thrombosis resulting from meningitis, sinusitis, or facial cellulitis; septic portal venous thrombosis resulting from diverticulitis or liver abscess; septic tonsillar or internal jugular venous thrombosis (Lemmiere syndrome) resulting from oropharyngeal infection. Increasingly common causes are those related to intravenous drug use and those that are iatrogenic; namely, infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.[168–170]

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization from such material does occur and can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, the chest roentgenogram displays scattered pulmonary infiltrates that undergo cavitation. An increasing number of such infiltrates develop over periods of hours to a few days. Symptoms and signs include fever, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antibiotics. If an indwelling catheter is the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis, or mimic it, particularly in drug addicts.

TUMOR EMBOLISM

Involvement of the pulmonary vascular bed by tumor cells is not unusual given the frequency with which circulating tumor cells can be identified in patients with a wide range of malignancies and the frequency with which tumor emboli are discovered as an incidental finding at autopsy.[171] Tumor embolism becomes clinically apparent, however, in only a minority of patients with malignancy.

Microvascular tumor embolism is associated with a wide range of malignancies, the most common of which are breast, lung, prostate, stomach, and liver cancer. Tumor embolism of large fragments occurs rarely and may mimic acute thromboembolic disease. In this setting, survival following tumor embolectomy has been reported.

The clinical presentation of microvascular tumor embolism is typically subacute and involves progressive dyspnea, tachycardia, and tachypnea. Jugular venous distention, a prominent P2, tricuspid regurgitation or a right-sided S3 may be present on physical examination if the extent of pulmonary vascular obstruction is sufficient to cause pulmonary hypertension.

The development of pulmonary hypertension is a common accompaniment of symptomatic, microvascular tumor embolism and remains a major cause of mortality. Pulmonary hypertension appears to result from an obliteration of the pulmonary vascular bed by an admixture of tumor cells and thrombus as well as the development of medial hypertrophy, intimal fibrosis, and fibrinoid necrosis encountered in other etiologies of pulmonary hypertension.

Hypoxemia and a compensated respiratory alkalosis are commonly present. The chest radiograph is most often normal but focal or diffuse infiltrates, which may be fleeting, have been described. V/Q scanning most commonly demonstrates a mottled appearance or peripheral, subsegmental defects; segmental or larger defects, indistinguishable from those associated with thromboembolic embolism, may occur in those rare instances of large-vessel involvement. CT may demonstrate peripheral, wedge-shaped defects consistent with infarcts; a pattern of multifocal dilatation and beading of the peripheral pulmonary arteries has been described.[172]

Pulmonary angiographic findings may include delayed vascular filling, pruning, and tortuosity, similar to that seen in other forms of small-vessel pulmonary hypertension. The angiographic findings in large fragment tumor embolism may be indistinguishable from those seen in acute thromboembolic disease.

Pulmonary microvascular cytology on specimens aspirated through a wedged pulmonary artery catheter may demonstrate malignant cells. Positive cytologies, however, can also be obtained in the setting of lymphangitic carcinomatosis. The misidentification of megakaryocytes as tumor cells obtained in this manner has been reported to lead to false-positive results.

Although diagnosis by transbronchial biopsy has been reported, diagnostic confirmation may require surgical lung biopsy. Before proceeding to that step, however, it must be stressed that the impact of early diagnosis on outcome is uncertain. This intervention should only be considered in the setting of a primary malignancy for which effective chemotherapeutic options are available.

The differential diagnosis of tumor embolism includes thrombotic embolism, parenchymal metastasis, lymphangitic carcinomatosis, malignant pericardial effusion, and chemotherapy-related lung toxicity. The premortem diagnosis is often one of exclusion. Parenchymal metastasis, lymphangitic carcinomatosis and chemotherapy-related lung toxicity can be differentiated from tumor embolism by findings on high-resolution CT. Differentiation of tumor embolism from thrombotic embolism may be somewhat more problematic, especially if there is large-vessel involvement.

SICKLE CELL DISEASE

Sickle cell disease affects the lungs by causing local thrombosis and occasionally by embolization of bone marrow elements. Small pulmonary arteries, arterioles, and capillaries are generally affected.[173,174] Thrombosis in the pulmonary circulation is part of the general proclivity of red blood cells containing S hemoglobin to sickle under appropriate circumstances, particularly hypoxia; stagnation and clotting follow sickling. In some instances, the thrombus organizes, the vascular lumen is obliterated, and perivascular fibrosis ensues in the adjacent lung; in others, the thrombus recanalizes. Occasionally, infarction occurs.

Of the factors that predispose to thrombosis in the lungs in sickle cell disease, the most important is the low oxygen saturation of mixed venous blood. Not only is the mixed venous oxygen inordinately low but also the O_2 dissociation curve is shifted to the right, thereby handicapping O_2 uptake in the lungs. Patients with sickle cell disease are prone to develop pneumonia, which, in turn, can lead to local areas of hypoxia favoring sickling and thrombosis in the lung. Patients with severe sickle cell anemia and large fractions of hemoglobin S in their red blood cells are particularly susceptible to intense sickling and thrombosis anywhere, including the lungs. However, vulnerability is not restricted to states of hemoglobin S. In some heterozygous sickle states – for example, hemoglobin SC, S-thalassemia, and hemoglobin SA – enough hemoglobin S is present to cause extensive thrombosis and infarction during an episode of severe hypoxemia, acidosis, or septicemia associated with fever and leukocytosis.

The clinical picture of pulmonary infarction in patients with sickle cell disease can mimic or coexist with bronchopneumonia. An

episode often begins with chest pain, fever, and sputum that is blood streaked but fails to disclose any specific bacterial cause. A fleeting episode of breathlessness is usually overlooked. The subsequent course is characterized by an unconvincing response to antibiotics and slow clearing; often a linear scar in the lungs remains as a residue of the infarction.

Distinguishing between in situ thrombosis and thromboembolism can be difficult clinically and even with invasive procedures such as angiography, although in situ thrombosis tends to be in small, distal vessels. Moreover, because radiographic contrast materials may promote sickling, they have to be used cautiously. To complicate matters, some patients with sickle cell disease are also at increased risk of thromboembolism because of predisposing factors, such as bed rest, congestive heart failure, and dehydration.

Sometimes, occlusive disease is sufficiently extensive to cause pulmonary hypertension and cor pulmonale. For this sequence to evolve, many severe episodes of sickling are required. The cor pulmonale that results is unusual because of its association with a high cardiac output (due to anemia) and with the intrinsic myocardial damage that generally complicates sickle cell disease.[175]

Management of the patient with pulmonary thrombosis and infarction in sickle cell disease is largely supportive and includes supplemental oxygen, intravenous hydration, and pain control.

Simple or exchange transfusions are recommended for patients with significant hypoxemia and pulmonary infiltrates (i.e., acute chest syndrome). Anticoagulants are generally not used in sickle cell crisis. Their utility in larger-vessel pulmonary artery thrombosis is uncertain since there are no data to substantiate their effectiveness. Because it implicates large vessels' occlusion, pulmonary artery thrombosis during acute chest syndrome should be amenable to the same therapeutic approach as currently used for venous thromboembolic disease.[174]

■ OTHER EMBOLI

Because of its sieve function, the lung may also be the target of embolization by a wide variety of other materials.[176–179] Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during pregnancy. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and bone marrow after cardiopulmonary resuscitation.

Finally, noninfectious vasculitic–thrombotic complications are seen in association with the intravenous use of drugs intended for oral use. Medications associated with pulmonary complications include methylphenidate hydrochloride, oral opiates (pentazocine, meperidine), and antihistamines. Particulate and irritant drug carriers (e.g., talc, cellulose) and occasionally the drugs themselves may cause vascular inflammation and secondary thrombosis. The clinical presentation may be diverse and includes lower lobe emphysema, diffuse interstitial fibrosis, and progressive massive fibrosis. Repetitive insults may lead to severe and irreversible pulmonary hypertension. In many intravenous drug users, perfusion scans demonstrate segmental or smaller defects. Distinguishing these defects from those due to venous thromboembolism may be difficult.

The diagnosis is often suggested by the clinical history. Radiographic findings include small, diffuse, well-defined nodular densities. These nodules can progress and massive fibrosis may ensue. Lower lobe emphysematous changes may also be present. Diagnostic confirmation often requires transbronchial or surgical lung biopsy. Occasionally, fine crystalline deposits may be seen in the retinal microvasculature on funduscopic examination, confirming the diagnosis noninvasively. The prognosis is generally poor with most patients experiencing progressive pulmonary disease.

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CHAPTER 74 Pulmonary Vasculitis

Ulrich Specks

NOMENCLATURE AND DEFINITIONS

Pulmonary vasculitis is usually a manifestation of a systemic disorder leading to inflammation of vessels of different sizes by a variety of immunological mechanisms. Vasculitis can be categorized into primary vasculitis and secondary vasculitis. The primary systemic vasculitides are a heterogeneous group of syndromes of unknown etiology, which share a clinical response to immunosuppressive therapy (Table 74-1). Their wide spectrum of frequently overlapping clinical manifestations is defined by the size and location of the affected vessels as well as the nature of the inflammatory infiltrate. Secondary vasculitis may represent significant management problems in the context of a well-defined underlying disorder, such as diffuse alveolar hemorrhage caused by systemic lupus erythematosus (SLE). Alternatively, secondary vasculitis may be an incidental histopathological finding, for instance, in the context of an infection or necrotizing sarcoid granulomatosis.

Classification schemes and definitions of the various forms of vasculitis have evolved over the past decades. Historically, the classification of the vasculitis has been based on the size of the most prominently affected vessels. The primary purpose of classification and nomenclature is to standardize communication between clinicians and investigators and to facilitate more uniform treatment approaches. Ideally, they reflect the current understanding of pathogenesis. The first international consensus conference on the nomenclature of systemic vasculitides held in 1992 in Chapel Hill aimed to reconcile definitions and classification schemes used by European and American investigators. The resulting nomenclature and definitions were based mainly on histopathological criteria, particularly the size of the vessels involved, but allowed for radiographic and clinical surrogates to fulfill the definitions. These definitions, nomenclature, and classification found wide acceptance. The terminology was recently revised and updated at the second 2012 Chapel Hill International Consensus Conference so that it reflects novel insights into the pathogenesis of various vasculitides while avoiding the use of eponyms as much as possible.[1] In this chapter, the specific definition of each form of vasculitis is discussed in detail as part of the description of the clinical manifestations and differential diagnosis of each entity.

TABLE 74-1 Chapel Hill Consensus Nomenclature of the Primary Systemic Vasculitides

Name	Respiratory Manifestations	Presence of ANCA
Large vessel vasculitis		
Giant cell arteritis	Rare	No
Takayasu arteritis	Frequent	No
Medium-sized vessel vasculitis		
Polyarteritis nodosa	Rare	No
Kawasaki disease	No	No
Small vessel vasculitis *ANCA-associated vasculitis*		
Granulomatosis with polyangiitis (formerly Wegener's)	Frequent	>80%
Microscopic polyangiitis	Frequent	>80%
Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome)	Frequent	>50%
Immune complex small vessel vasculitis		
Anti-GBM disease	Frequent	No
IgA vasculitis	Rare	IgA-ANCA reported
Cryoglobulinemic vasculitis	No	No
Hypocomplementemic urticarial vasculitis	Frequent	No
Variable vessel vasculitis		
Behçet disease	Rare	No

The 2012 Chapel Hill nomenclature is clinically very useful to pulmonologists as it reflects the clinical and histopathological pulmonary features and facilitates the therapeutic approach to individual patients. The three small vessel vasculitides that present most often with respiratory symptoms are granulomatosis with polyangiitis (GPA [formerly Wegener granulomatosis]), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA [formerly Churg–Strauss syndrome]). Most patients with these syndromes have antineutrophil cytoplasmic autoantibodies (ANCA) detectable in the serum at the time of initial presentation.[2] Consequently, this group of small vessel vasculitides is referred to *in cumulo* as "ANCA-associated vasculitis." In patients with vasculitis, two types of ANCA are of clinical significance. In more than 80% of patients with GPA (Fig. 74-1), ANCA occur and are associated with a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed neutrophils that react with the neutrophil granule enzyme, proteinase 3 (PR3-ANCA). In contrast, ANCA that cause a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils and react with myeloperoxidase (MPO-ANCA) occur in fewer than 10% of patients with GPA but in the majority of patients with MPA (Fig. 74-2). MPO-ANCA are also the predominant type of ANCA encountered in patients with EGPA, in which PR3-ANCA are the exception. Despite these circulating autoantibodies, hardly any immunoglobulin deposits can be detected in the tissue lesions of ANCA-associated vasculitis, and they are consequently called "pauci-immune" lesions.

EPIDEMIOLOGY

The primary systemic vasculitides are rare and few epidemiological studies have been conducted, mostly in ethnically homogeneous populations.[3] Giant cell arteritis is the most frequent form of systemic vasculitis with an annual incidence of 13 per million adults (40 per million over the age of 60). It appears to be increasing in frequency and becoming cyclical over time. The latter observation has been interpreted as possibly suggesting a relationship with

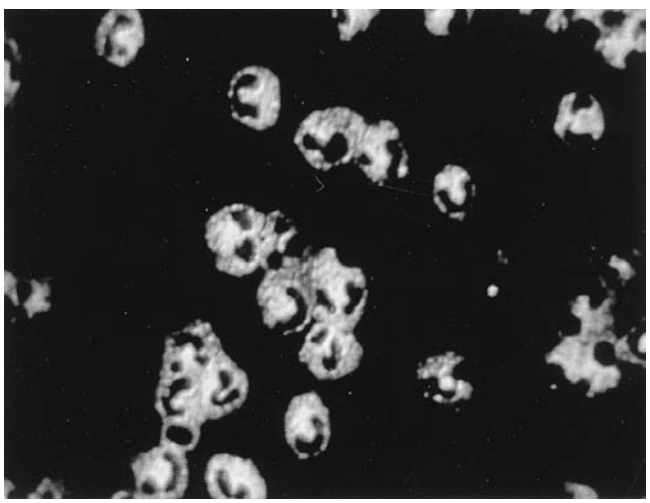


Figure 74-1 Cytoplasmic indirect immunofluorescence (C-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with PR3.

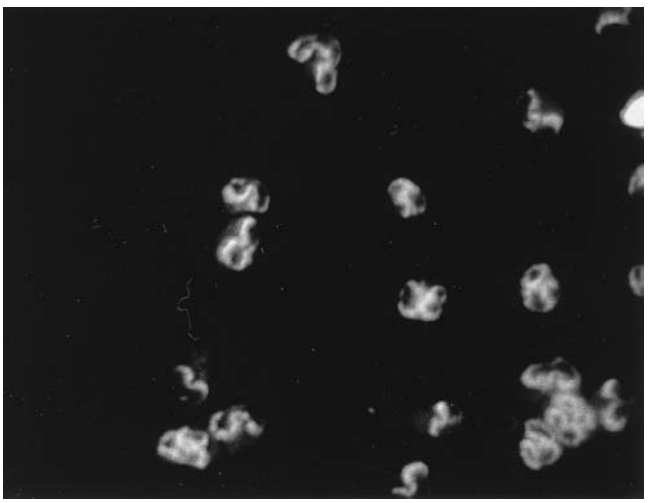


Figure 74-2 Perinuclear indirect immunofluorescence (P-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with MPO.

TABLE 74-2 Organ Systems Affected by ANCA-Associated Vasculitis

Feature	Granulomatosis with Polyangiitis (formerly Wegener's)	Microscopic Polyangiitis	Eosinophilic Granulomatosis with Polyangiitis (formerly Churg–Strauss)
Upper airway disease	90–95%	No	50–60%
Pulmonary parenchymal disease	54–85%	20%	30%
Alveolar hemorrhage	5–15%	10–50%	<3%
Glomerulonephritis	51–80%	60–90%	10%–25%
Gastrointestinal tract	<5%	30%	30–50%
Eyes	35–52%	<5%	<5%
Nervous system	20–50%	60–70%	70%–80%
Heart	8–16%	10–15%	10–15%
Skin	33–46%	62%	50–60%
Eosinophilia	Rare	Rare	Yes
Asthma	No[a]	No[a]	Yes
Granulomatous inflammation	Yes	No	Yes

[a]*Not more than general population.*

infections. Respiratory manifestations rarely represent significant management problems in these patients. Various studies from different regions of the world report a fairly uniform annual incidence of one to two cases per million for Takayasu arteritis. Pulmonary vascular complications occur in about half of the afflicted patients. The estimated annual incidence of GPA has been rising over the decades from 0.5 to 0.7 per million during the 1970s and early 1980s to current estimates of about 10 to 12 per million. Similar increases in annual incidence have been observed for MPA and EGPA. The average frequency of MPA is similar to that of GPA; for EGPA it is estimated to be of the order of one to three per million. The ANCA-associated vasculitides have different ethnic predilections: GPA affects predominantly whites, and northern Europeans appear more prone to develop GPA. In contrast, individuals of southern European and Mediterranean descent appear to be relatively more apt to develop MPA. GPA and MPA can affect individuals of any age. However, the incidence of GPA plateaus after age 50, whereas the likelihood of developing MPA continues to increase with age.

The annual incidence of the secondary vasculitides varies widely. The reported frequencies for rheumatoid vasculitis and vasculitis in SLE are 12.5 per million and 3.6 per million, respectively. Behçet disease has a peculiar geographic distribution along the old Silk Road, with the highest prevalence being reported from Turkey, Central and far eastern Asia, where the frequencies range from 100 to 380 per 100,000, compared with only 1 per 100,000 in western Europe.

The available population-based studies need to be interpreted with some caution because they do not distinguish between whether the observed increased incidence of systemic vasculitis is true, or the result of more frequent recognition of the disease. Moreover, whether individual diagnoses are accurate and consistent is challenged by the changing definitions of the syndromes over time.

ANCA-ASSOCIATED VASCULITIS

The ANCA-associated vasculitides include granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. The clinical presentation, diagnosis, pathophysiology, and treatment of these entities are discussed below.

GRANULOMATOSIS WITH POLYANGIITIS: CLINICAL PRESENTATION AND DIAGNOSIS

GPA is the most common form of vasculitis to involve the lung. The Chapel Hill Consensus Conference defined GPA as "necrotizing granulomatous inflammation usually involving the respiratory tract, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels."[1] However, it is important to recognize that GPA is a systemic disease that can affect almost any organ (Table 74-2). The most frequently involved sites are the upper airways, lungs, and kidneys.[4] Symptoms and clinical disease manifestations are the result of necrotizing granulomatous inflammation and small vessel vasculitis that occur in variable degrees of combination.

In the 1960s the term "limited Wegener granulomatosis" was introduced to indicate patients with GPA who lacked renal disease. The use of this term and its implications have evolved over the last two decades. Even in the absence of renal involvement, patients may have life-threatening pulmonary or neurological disease requiring aggressive immunosuppressive treatment. For instance, a patient who "only" has alveolar hemorrhage in the absence of glomerulonephritis should never be classified as having "limited" GPA. Consequently, today, the use of the term "limited GPA" implies that (a) the pathology is predominantly a necrotizing granulomatous inflammation, and the vasculitis seen on biopsy is of lesser clinical significance; and (b) there is no immediate threat either to the patient's life or that the affected organ is at risk for irreversible damage. In this sense, the terms "limited" or "nonsevere" GPA are now used interchangeably as distinction from "severe" GPA, which by definition either threatens the patient's life (alveolar hemorrhage) or a vital organ with the risk of irreversible damage (rapidly progressive glomerulonephritis, scleritis, or mononeuritis multiplex). These definitions and distinctions form the basis for stratification of current standard therapy.

Over 90% of patients with GPA first seek medical attention for symptoms arising from either the upper and/or lower airway. Nasal and sinus disease is characterized by congestion and epistaxis due to mucosal friability, ulceration, and thickening. Patients may also have features of chronic sinusitis and recurrent or chronic serous otitis. Perforation of the nasal septum and/or saddle nose deformity may result from ischemia of the nasal cartilage (Fig. 74-3). Oral manifestations include gingival hyperplasia (Fig. 74-4) and oropharyngeal ulcerations. Subglottic stenosis occurs in approximately 20% of patients and can cause life-threatening compromise of the airway. Subglottic stenosis may occur in the absence of other features of active GPA, and its symptoms may be nonspecific, for example, dyspnea, hoarseness, cough or stridor; the latter is occasionally mistaken for wheezing.

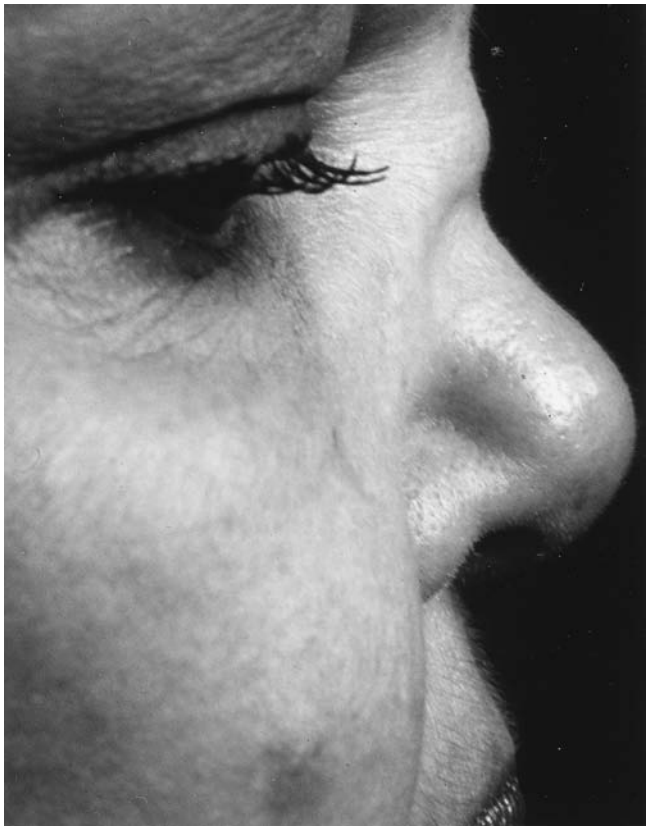


Figure 74-3 Saddle nose deformity of granulomatosis with polyangiitis.

GPA involving the lower airways can affect the pulmonary parenchyma, the bronchi, and rarely the pleura. Presenting features of parenchymal involvement may include cough, dyspnea, chest pain, or hemoptysis. However, some patients may be completely asymptomatic. Patients with diffuse alveolar hemorrhage usually present with progressive dyspnea and anemia (Fig. 74-5). Hemoptysis is absent in about one-third of patients. Patients with diffuse alveolar hemorrhage may deteriorate rapidly and experience respiratory failure, which has a mortality rate up to 50%.

The clinical presentation of alveolar hemorrhage is caused by pulmonary capillaritis (Fig. 74-6). The predominant inflammatory cells are neutrophils. However, eosinophils or monocytes may also be present. Capillaritis usually causes fibrinoid necrosis of alveolar and vessel walls and may culminate in the destruction of the underlying architecture of the lung. An important hallmark of capillaritis is the presence of pyknotic cells and nuclear fragments from

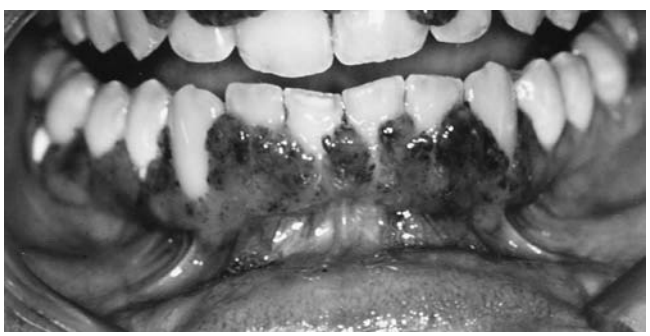


Figure 74-4 Strawberry or mulberry gums in a patient with granulomatosis with polyangiitis.

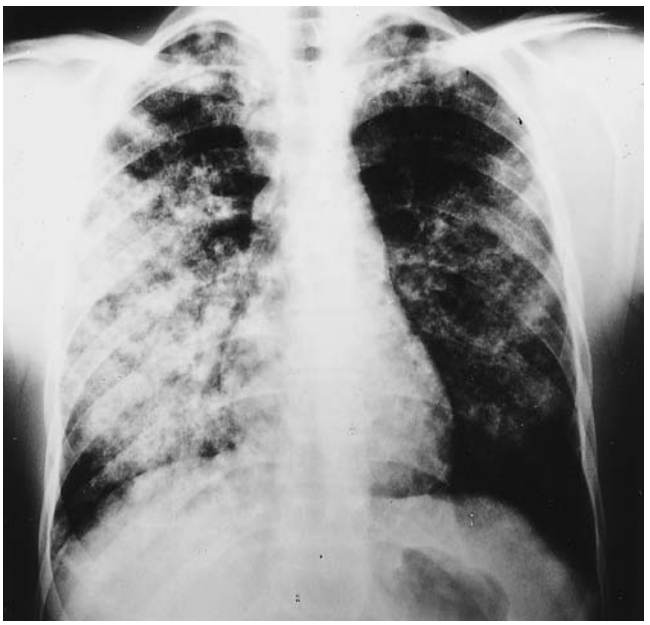


Figure 74-5 Chest radiograph of a patient with granulomatosis with polyangiitis displaying an alveolar filling pattern indicative of diffuse alveolar hemorrhage.

neutrophils undergoing apoptosis, a feature called leukocytoclasis. This hallmark enables distinction between true capillaritis and margination of neutrophils related to surgical trauma. Depending on the acuteness and duration of alveolar hemorrhage, hemosiderin-laden macrophages and interstitial hemosiderin deposits may be present.

The most common form of pulmonary involvement in GPA is caused by necrotizing granulomatous inflammation and presents radiographically as nodules or mass lesions, which may cavitate (Figs. 74-7–74-9). These lesions may be incidental findings on thoracic imaging studies as they cause little symptoms and do not result in significant abnormalities of pulmonary function. Prominent air–fluid levels can be seen when the necrotic center of the inflammatory lesion gets superinfected (Fig. 74-8). These necrotizing granulomatous lesions are a disease-defining feature of GPA. Their presence easily separates GPA from MPA. In the absence of other features of small vessel vasculitis in other organs, the differential diagnosis of these lesions consists primarily of infections, particularly caused by fungal or mycobacterial organisms, and less likely of malignancies or necrotizing sarcoid granulomatosis.

The lung nodules of GPA have very characteristic histopathological features. Small necrotizing microabscesses appear to be the earliest lesion. They enlarge and coalesce until the typical geographic and basophilic appearance of the necrosis has developed (Fig. 74-10). The necrotic center is surrounded by palisading histiocytes and scattered giant cells. Occasionally the necrosis may be bronchocentric. When this type of necrotizing granulomatous inflammation extends into the walls of small vessels it is referred to as granulomatous vasculitis (Fig. 74-11). In contrast to capillaritis, this type of vasculitis seems to be a secondary phenomenon of the necrotizing granulomatous inflammation affecting the lung parenchyma. The inflammatory background of the granulomatous necrosis and vasculitis consists of a mixed cellular infiltrate containing lymphocytes, plasma cells, scattered giant cells, and eosinophils. It may cause extensive parenchymal consolidation mimicking organizing pneumonia. Well-defined sarcoid-like nonnecrotizing granulomas are not found in GPA.

Inflammation and stenosis of the tracheobronchial tree occur in at least 15% of patients with lung involvement.[5,6] Endobronchial disease may be an incidental finding on bronchoscopy or present

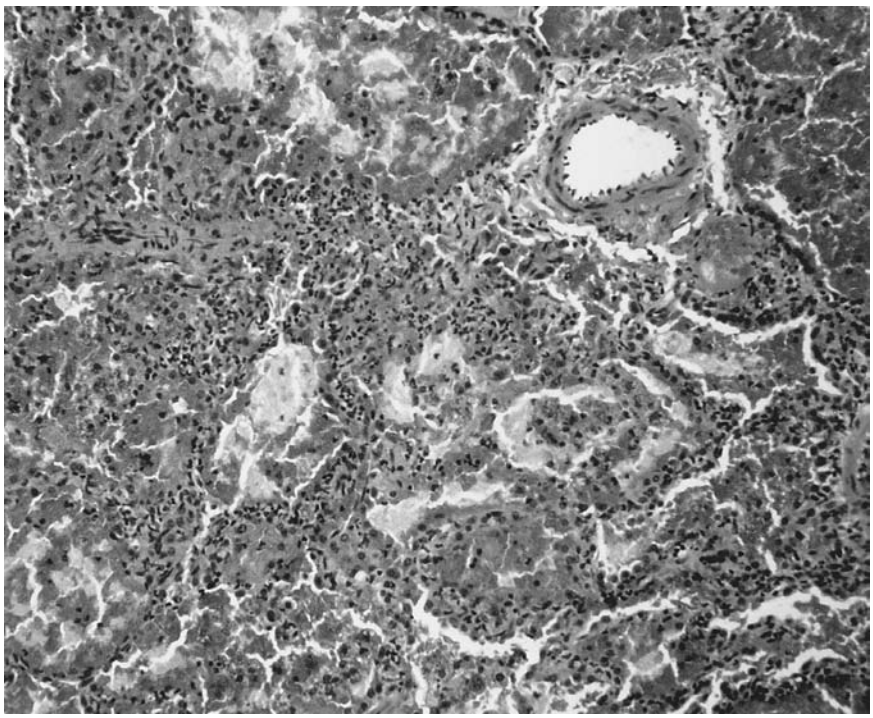


Figure 74-6 Alveolar capillaritis causing pulmonary hemorrhage in granulomatosis with polyangiitis.

with cough, hemoptysis, wheezing, dyspnea, or symptoms related to parenchymal collapse or postobstructive infection. Spirometry including inspiratory and expiratory flow–volume loops may show characteristic abnormalities indicative of degree and location of airway narrowing. Subglottic stenosis represents a fixed airway obstruction resulting in flattening of both the inspiratory and expiratory loops. If the intrathoracic trachea, or more commonly, one or both mainstem bronchi are affected, flattening of the expiratory curve can be found. Pleural effusions may occur, but are usually small, asymptomatic, and incidental findings (Fig. 74-9). Other thoracic manifestations of GPA include inflammatory pleural pseudotumors or hilar adenopathy. The latter should raise the suspicion of infection, sarcoidosis, or lymphoma.

Glomerulonephritis is among the most concerning disease manifestations of GPA as it can progress to complete renal failure in the absence of symptoms. It is usually detected by the presence of abnormal laboratory results such as active urine sediment with microscopic hematuria and red cell casts, proteinuria, and declining renal function. Continued vigilance for glomerulonephritis is essential as it is present at diagnosis in less than half of all patients. However, over the course of their disease, the kidneys are affected in 80% of patients.

A renal biopsy is useful to establish a diagnosis of ANCA-associated vasculitis and to determine the renal prognosis. The glomeruli are not affected uniformly (focal) by segmental, necrotizing inflammation (Fig. 74-12), and cellular crescents (Fig. 74-13) are frequently found. The number of glomeruli affected, degree of crescent formation, and destruction of individual glomeruli as well as the amount of sclerosis found determine the chance of recovery of renal function. In addition, tubular fibrosis and atrophy affect renal outcomes. Direct immunofluorescence reveals no or only scant immune deposits (pauci-immune glomerulonephritis). Granulomatous inflammation affecting the renal parenchyma and tubulointerstitial nephritis can also be found rarely.

A wide spectrum of ocular manifestations has been observed in GPA, which may threaten vision by affecting the eye directly or involving its contiguous structures. Manifestations may include conjunctivitis, episcleritis, scleritis, keratitis, corneal ulceration, uveitis, and retinal vasculitis. Involvement of the lacrimal system

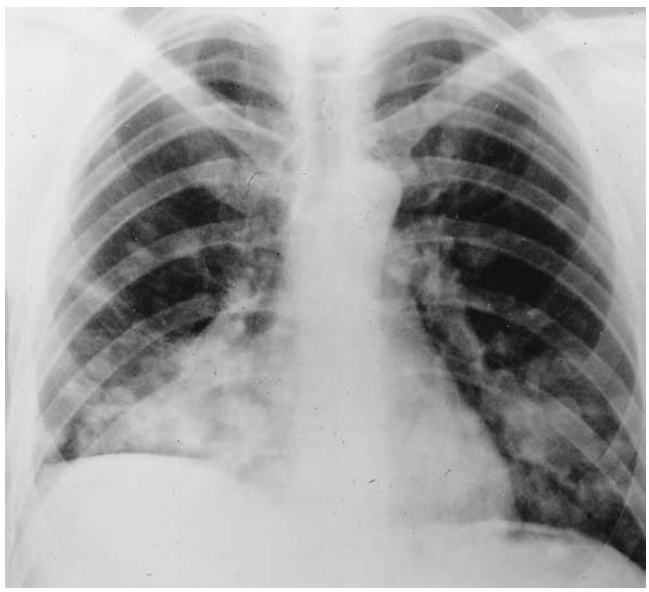


Figure 74-7 Chest radiograph of a patient with granulomatosis with polyangiitis displaying multiple nodules with and without cavitation.

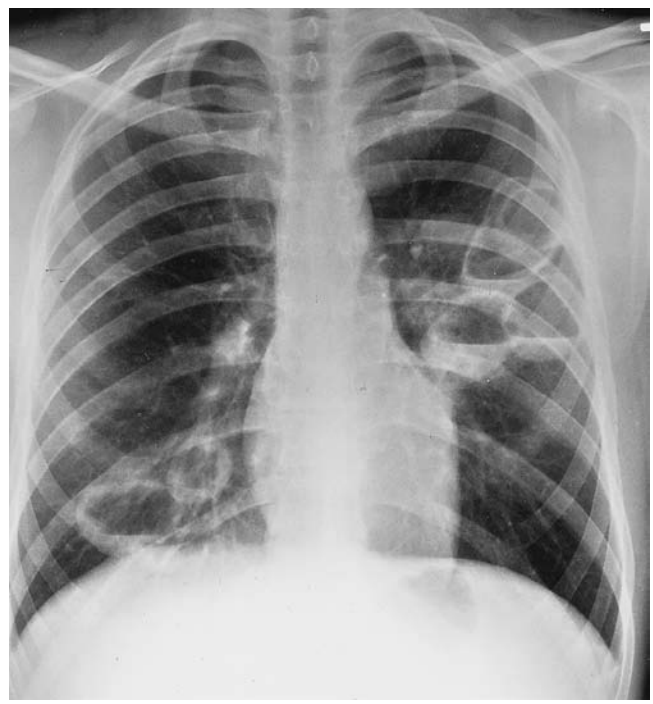


Figure 74-8 Chest radiograph of a patient with granulomatosis with polyangiitis showing multiple large cavities, some with air–fluid levels.

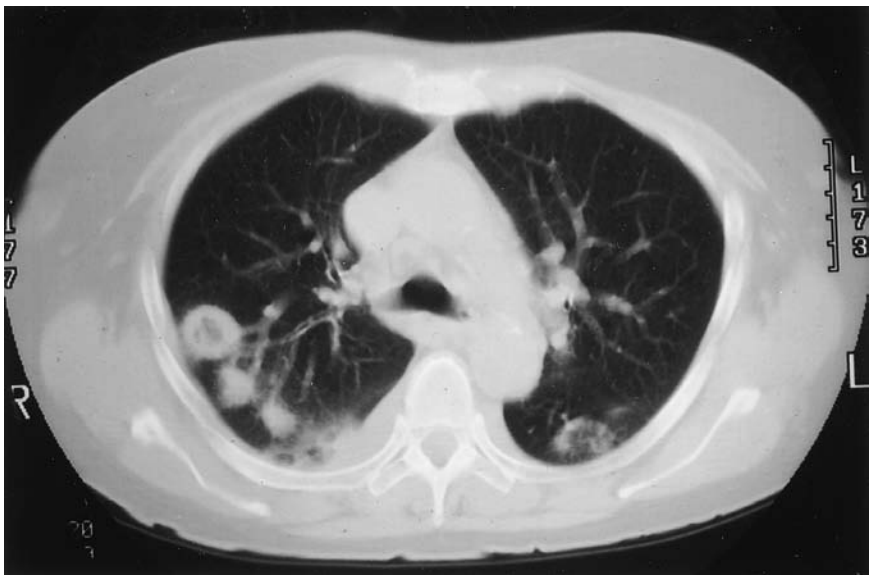


Figure 74-9 Computed tomography scan of a patient with granulomatosis with polyangiitis showing multiple nodules, some with cavitation. There are also small bilateral pleural effusions.

may result in epiphora, dacryocystitis, and fistula. Retro-orbital inflammatory pseudotumors may affect one or both the eyes, threaten the vision, and represent the most difficult challenge in the management of GPA (Figs. 74-14 and 74-15). Any patient with GPA who presents with eye pain or redness, proptosis, change in visual acuity, diplopia, or loss of visual field should be referred for emergent ophthalmological consultation.

Nervous system involvement may occur in up to one-third of patients. Mononeuritis multiplex of the peripheral nervous system caused by inflammation of the vasa nervorum as well as central nervous system vasculitis and pachymeningitis represent severe disease manifestations with substantial risk of irreversible damage, persisting even after the acute inflammation is adequately controlled.

Cardiac involvement may be occult. Regional wall motion abnormalities with a noncoronary distribution pattern are frequent echocardiographic findings.[7] It is unclear whether this type of cardiomyopathy is the result of small vessel disease or inflammatory infiltration of the cardiac muscle. Pericarditis, valvulitis, and inflammatory pseudotumor have also been described.

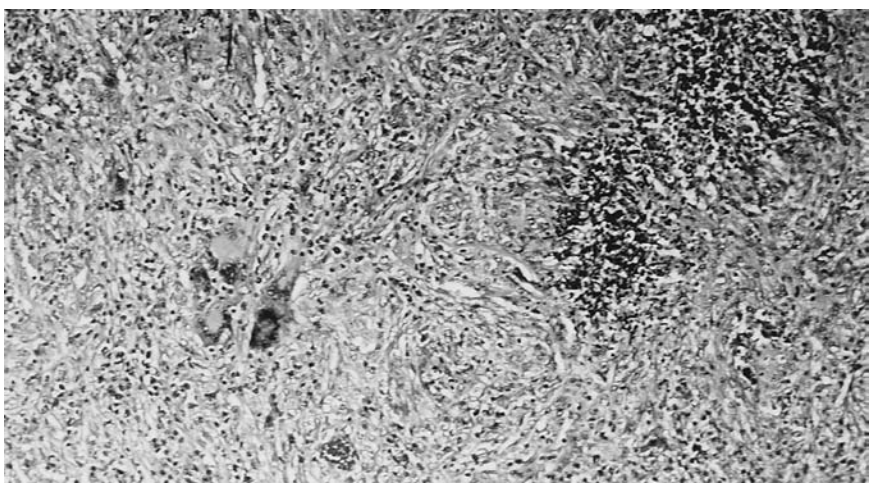


Figure 74-10 Geographic basophilic necrosis with palisading histiocytes and giant cells from a lung nodule in a patient with granulomatosis with polyangiitis.

A wide spectrum of cutaneous manifestations may be observed in GPA. Leukocytoclastic vasculitis presenting as palpable purpura is most common, followed by pyoderma gangrenosum–like lesions (Fig. 74-16) and so-called Churg–Strauss granulomas.

■ MICROSCOPIC POLYANGIITIS: CLINICAL PRESENTATION AND DIAGNOSIS

Histopathologically, the necrotizing small vessel vasculitis of MPA causing necrotizing crescentic glomerulonephritis and pulmonary capillaritis is indistinguishable from that encountered in GPA.[8] Consequently, there is substantial overlap in organ manifestations and symptoms between the two syndromes (Table 74-2). A timely diagnosis of MPA may be delayed by a gradual onset or the nonspecific nature of symptoms such as fever, malaise, and weight loss. All organ systems may be involved. The kidneys are most commonly affected in up to 80% of patients. Other commonly encountered disease manifestations include diffuse alveolar hemorrhage due to pulmonary capillaritis affecting 10% to 30% of patients. MPA is the most frequent cause of pulmonary renal syndrome. Several cases of MPA in association with severe obstructive airway disease or bronchiectasis have also been described. More recently, several case series have highlighted an association between usual interstitial pneumonia and MPO-ANCA–positive MPA. In these cases, the fibrotic changes either precede the development of MPA or are already present at the time of diagnosis of MPA.

Palpable purpura caused by leukocytoclastic vasculitis of the skin, and musculoskeletal complaints, such as arthralgias and myalgias, are also common. Gastrointestinal involvement occurs in about one-third of patients. This is in contrast to GPA, in which gastrointestinal involvement is very rare. Visceral angiography is generally not helpful for the evaluation of abdominal symptoms as the vessels involved are too small to be visualized. CT with or without contrast injection may be more helpful if gastrointestinal involvement is suspected. However, the use of contrast is relatively contraindicated in patients with active renal involvement. Sinusitis and asthma are rarely found in MPA, and should lead to the consideration of an alternative diagnosis.

Most patients with MPA have ANCA, and in 40% to 80% they are of the P-ANCA variety, reacting with MPO. C-ANCA reacting with PR3 is seen less frequently. Occasionally patients with MPA later develop granulomatous inflammation and are reclassified as having GPA; this is more likely to occur in patients with C-ANCA.

As in GPA, a histopathological diagnosis may be necessary to confirm the diagnosis before the patient is committed to prolonged immunosuppressive therapy. The biopsy specimen should be sought from the most accessible site. Renal biopsy shows pauci-immune focal segmental–necrotizing glomerulonephritis, with extracapillary proliferation forming crescents. In contrast to GPA, granulomatous inflammation is not a feature of MPA. All other histopathological features are indistinguishable from those of

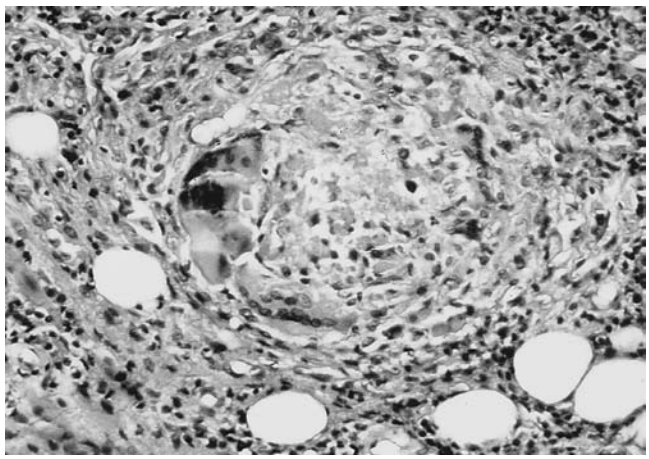


Figure 74-11 Granulomatous vasculitis with giant cells in a lung biopsy of a patient with granulomatosis with polyangiitis.

GPA. Treatment of MPA should follow the principles applied to the management of GPA. Consequently, most cases of MPA require immunosuppressive therapy used for patients with severe GPA.

■ EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: CLINICAL PRESENTATION AND DIAGNOSIS

EGPA is the third type of vasculitis that commonly affects the lung. The 2012 Chapel Hill Consensus definition for the disease is "eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory, and necrotizing vasculitis predominantly affecting small- to medium-sized vessels, and associated with asthma and eosinophilia."[1] EGPA is included among the ANCA-associated vasculitides even though only 40% to 70% of patients with active EGPA are ANCA positive.[9–11] EGPA is primarily distinguished from GPA and MPA by a high prevalence of asthma and peripheral blood and tissue eosinophilia. Three distinct phases of the disease have been described. The first is a prodromal allergic phase with asthma. This phase may last for a number of years. The second is an eosinophilic phase with prominent peripheral and tissue eosinophilia. This phase may also last a number of years and the manifestations may remit and recur over this time period. The differential diagnosis for patients in this phase of the disease includes parasitic infection and chronic eosinophilic pneumonia. The third vasculitic phase consists of systemic vasculitis and may be life threatening. The three phases are not seen in all patients and do not necessarily occur in this order; they may even concur. However, asthma usually predates vasculitic symptoms by a mean of 7 years (range 0–61). Formes frustes of EGPA have also been described with eosinophilic vasculitis and/or eosinophilic granulomas in isolated organs without evidence of systemic disease.

Pulmonary parenchymal involvement occurs in 38% of patients. Transient alveolar-type infiltrates are most common (Fig. 74-17). These have a predominantly peripheral distribution and are indistinguishable from infiltrates seen in chronic eosinophilic pneumonia. Occasionally, nodular lesions may be seen in EGPA. In contrast

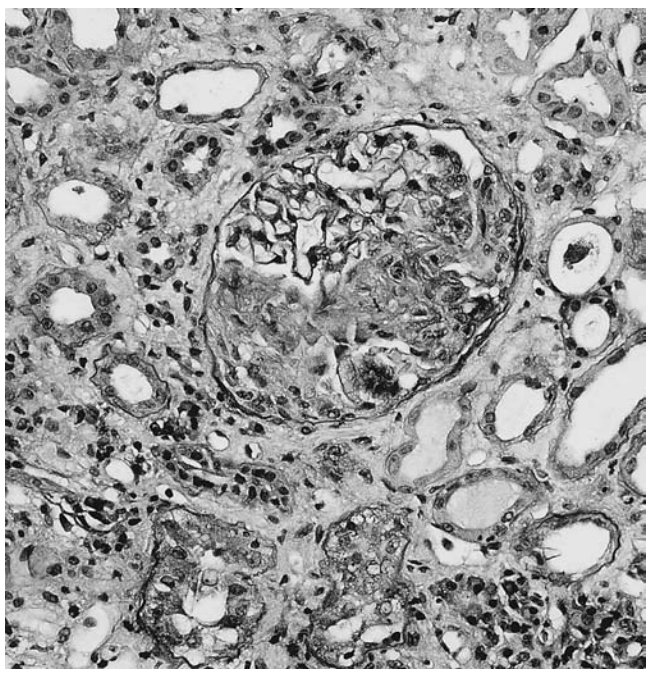


Figure 74-12 Focal necrotizing glomerulitis of granulomatosis with polyangiitis.

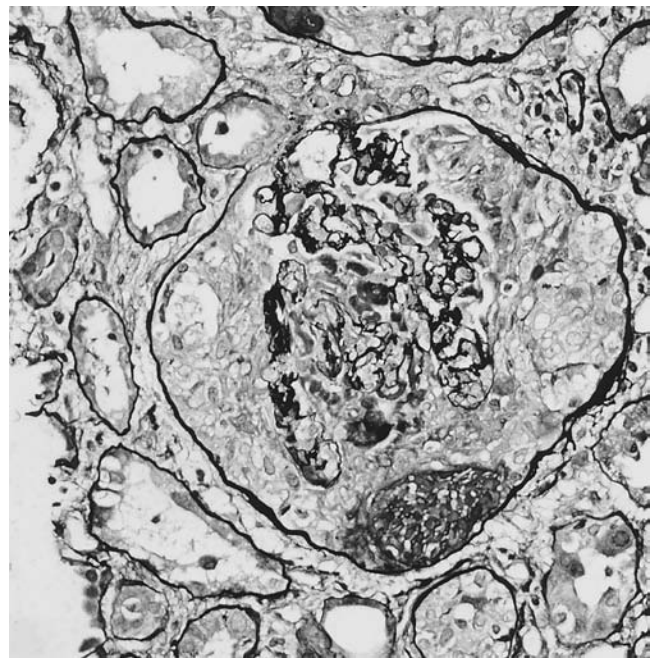


Figure 74-13 Rapidly progressive crescentic glomerulonephritis in granulomatosis with polyangiitis.

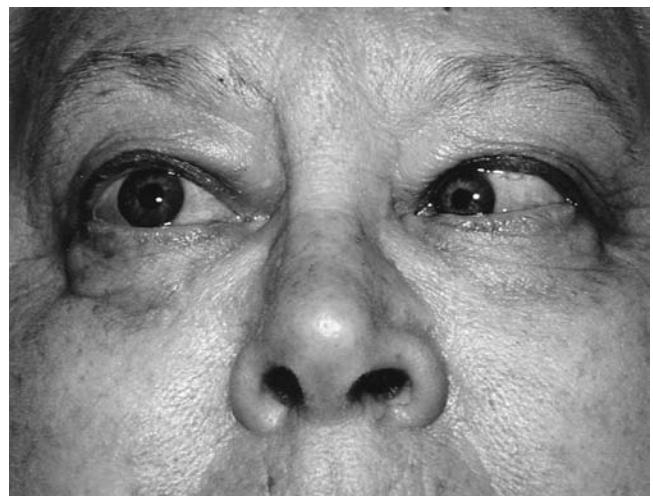


Figure 74-14 External ophthalmoplegia of the left eye due to orbital involvement with granulomatosis with polyangiitis.

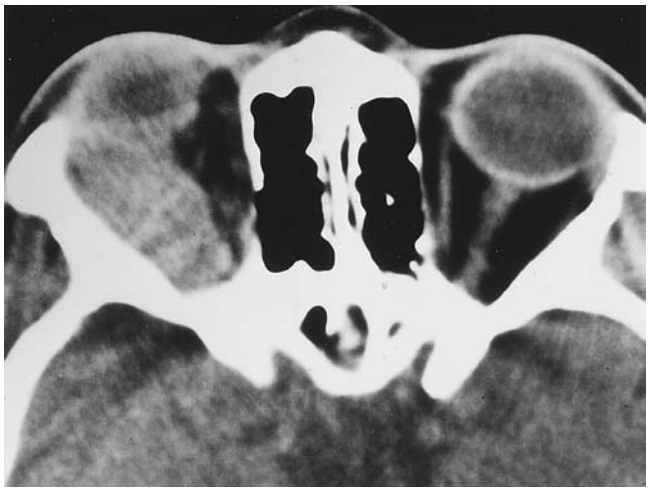


Figure 74-15 Computed tomography scan of the orbits in a patient with granulomatosis with polyangiitis showing a mass in the right orbit causing external ophthalmoplegia.

to GPA and MPA, alveolar hemorrhage is exceedingly rare. Renal involvement in EGPA is less prominent than in GPA and MPA and does not generally lead to renal failure. In contrast, peripheral nerve involvement, typically in the form of mononeuritis multiplex, is more frequent. The peripheral nerve involvement can result from both capillaritis and direct toxicity from eosinophil granule proteins. Skin, heart, central nervous system, and abdominal viscera may also be involved.

The classic histopathological picture consists of necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. However, not all features are found in every case, and they are not pathognomonic of the condition. Particularly the finding of a "Churg–Strauss granuloma" on skin biopsy should not be confused with the diagnosis of EGPA. While this type of necrotizing extravascular granuloma may be seen in EGPA, it may occur in other systemic autoimmune diseases, including GPA and rheumatoid arthritis.

If ANCA are present, they are usually P-ANCA reacting with MPO. The ANCA status appears to correlate with disease activity. Recent studies suggest a more vasculitic disease phenotype in the presence of ANCA, with ANCA being particularly frequent among patients with glomerulonephritis. Patients with heart involvement are less likely to be ANCA positive. However, not all studies have found this consistently, and there remains substantial overlap of

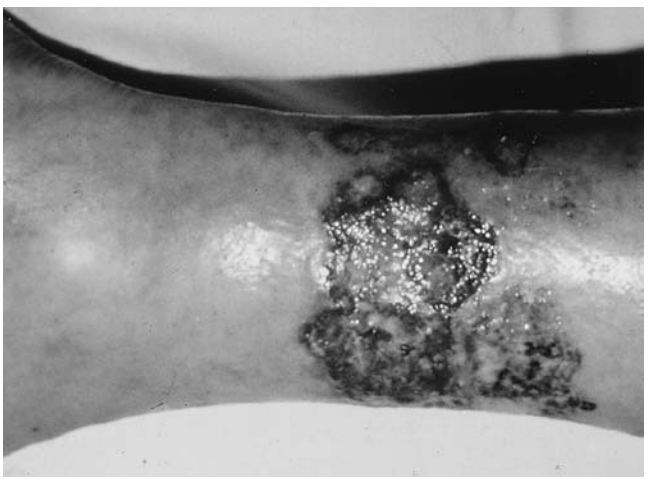
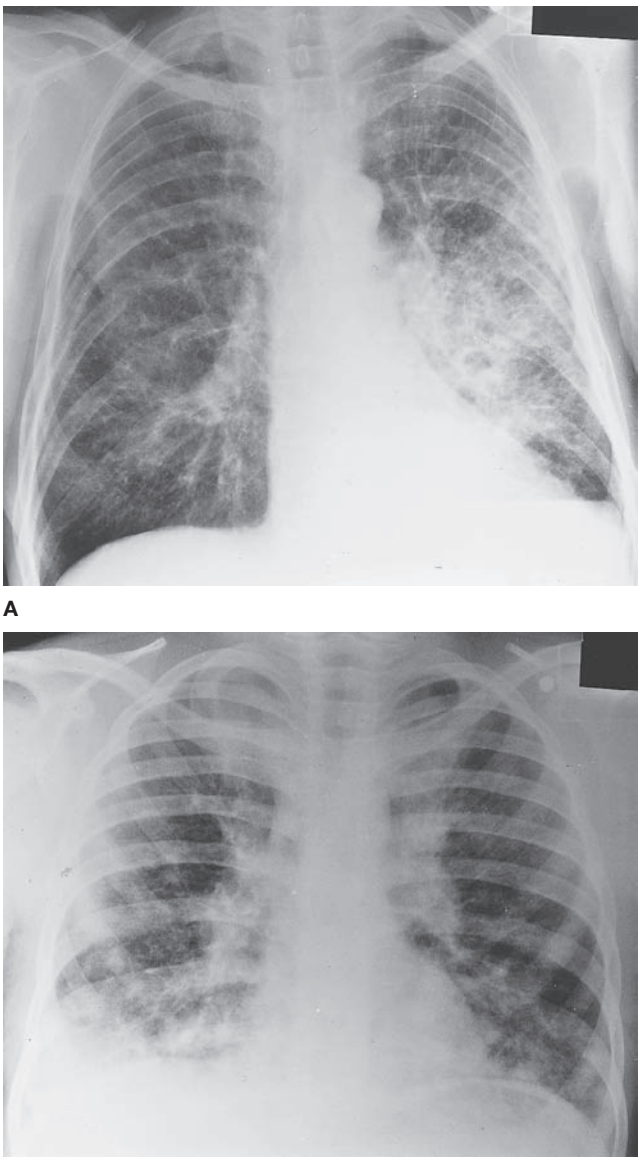


Figure 74-16 Pyoderma gangrenosum of the leg in a patient with granulomatosis with polyangiitis.



A

B

Figure 74-17 Chest radiographs of patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss): (**A**) Nonspecific gnomonic infiltrates; (**B**) Multiple vague, patchy infiltrates. *(Reproduced with permission from Chumbley LC, Harrison EG, DeRemee RA. Allergic Granulomatosis and angiitis (Churg-Strauss syndrome): report and analysis of 30 cases. Mayo Clin Proc. 1977;52(8):477–484.)*

organ manifestations between patients with EGPA who are ANCA positive and those who are ANCA negative.

In recent years significant attention has been devoted to EGPA detected in patients using leukotriene receptor antagonists. Available case studies and limited population-based incidence estimates suggest that these agents may lead to unmasking of vasculitic symptoms in asthmatics, by allowing dose reductions or discontinuation of oral glucocorticoid therapy. There is no evidence suggesting that these agents cause EGPA.

The prognosis of EGPA is better than that of GPA and MPA, as the overall mortality is lower and not significantly different from the normal population. Most deaths are secondary to cardiac involvement.

■ PATHOPHYSIOLOGY OF ANCA-ASSOCIATED VASCULITIS

The etiology of ANCA-associated vasculitis remains unknown. Several different pathways and mechanisms have been proposed

for the pathogenesis.[12] A genetic predisposition for autoimmunity, epigenetic factors and environmental triggers seem to play a role in the development of ANCA-associated vasculitis. Currently available clinical and experimental evidence support that infections or other environmental exposures can lead to the loss of tolerance and an inflammatory environment that is conducive for the production of autoantibodies (ANCA) in predisposed patients. In the context of an inflammatory milieu, ANCA can cause specific tissue inflammation and injury by a variety of different mechanisms which involve direct interactions with PR3 or MPO.

Multiple studies have reported skewing in polymorphisms of a variety of immune response genes and genes encoding for ANCA-target antigens and α1-proteinase inhibitor with potential effects on disease outcome. A recent genome-wide association study found major histocompatibility complex (MHC) and non-MHC associations with GPA and MPA and that these syndromes are genetically distinct.[13] Moreover, the associations with the specific ANCA types (PR3-ANCA vs. MPO-ANCA) and the differences between them were stronger than those between patients diagnosed with GPA versus MPA. For PR3-ANCA–positive patients strong associations were found with *HLA-DP*, the serpin A1 gene (*SERPINA1*), which codes for the α1-antitrypsin, the major inhibitor of PR3, and with the *PRTN3* gene which encodes PR3. In patients with MPO-ANCA only an association with *HLA-DQ* was found.

The expression of ANCA-target antigens on the neutrophil surface, particularly PR3, is increased in patients with GPA and genetically determined. Moreover, epigenetic modifications that interfere with the normal silencing of genes coding for the ANCA autoantigens in mature neutrophils may also contribute to the observed inappropriately increased expression of PR3 or MPO by these cells in patients with GPA or MPA.

Many clinical observations suggest that the presence or absence of ANCA as well as the specific type of ANCA (PR3-ANCA vs. MPO-ANCA) defines the disease phenotype. Patients with limited GPA who remain ANCA negative rarely develop systemic vasculitic disease manifestations. Patients with glomerulonephritis and PR3-ANCA lose their renal function much more rapidly than patients with MPO-ANCA. Patients with PR3-ANCA also have a higher relapse rate than patients with MPO-ANCA. Experimental data and animal models support a pathogenic role of ANCA in the development of vasculitis. A couple of recent studies have also suggested a different clinical phenotype of ANCA-positive patients with Churg–Strauss syndrome compared with ANCA-negative patients.

In GPA, the presence of PR3-ANCA appears most closely related to the development of vasculitic complications. Furthermore, systemic vasculitic relapses without recurrence of ANCA are extremely rare. Yet, remission may be maintained for extended periods of time in up to one-half of the patients despite the presence of ANCA. These clinical observations suggest that ANCA alone are not sufficient to cause disease activity, but ANCA seem to be required for the development of vasculitic complications of GPA and systemic relapses.

Many in vitro studies have demonstrated proinflammatory effects of PR3-ANCA and MPO-ANCA on neutrophils, monocytes, and endothelial cells, which enhance and perpetuate endothelial cell and tissue damage. ANCA may increase the adhesion of neutrophils to endothelial cells by enhancing the expression of cell adhesion molecules on endothelial cells. ANCA can activate primed neutrophils, resulting in the release of oxygen radicals and proteolytic enzymes. The latter may in turn induce endothelial cell apoptosis. ANCA-mediated neutrophil activation involves both Fc-γ–receptor engagement and recognition of expressed target antigen on the surface of primed neutrophils. ANCA may also cause endothelial cell damage by direct cytotoxicity or localized immune complex formation with target antigens bound to the endothelial cell surface. The latter may initiate localized complement activation. Finally, ANCA are thought to contribute to the recruitment of more inflammatory cells to the area of tissue injury by stimulating the release of chemotactic chemokines and agents from neutrophils, monocytes, and endothelial cells. For a detailed description of pathways and mechanisms by which ANCA may directly and indirectly contribute to damage of the vascular endothelium, the reader is referred to other recent reviews.

Many patients with ANCA-associated vasculitis relate the onset or recurrence of their disease to preceding infectious episodes. The following link to infection has been hypothesized. Most ANCA-mediated effects on neutrophils and monocytes require priming of the cells. This cytokine-dependent process is not unique to vasculitis. Cytokine stimulation of neutrophils and monocytes, typically by tumor necrosis factor (TNF), with resulting increased surface expression of ANCA-target antigens, occurs normally in the context of infections. Patients with active vasculitis have indeed been shown to have both increased expression of ANCA-target antigens on the surface of their neutrophils and elevated levels of TNF. In combination, these observations allow the hypothesis that neutrophil priming, which occurs in response to cytokine stimulation during infection, enables ANCA to interact with their target antigen on the neutrophil surface. This in turn sets the documented proinflammatory effects of ANCA in motion, which aggravate and perpetuate the inflammatory reaction at the endothelial cell interphase.

Rodent models of MPO-ANCA–associated vasculitis support this hypothesis of a pathogenic role of ANCA. They clearly indicate that ANCA contribute directly to the development of vasculitis and glomerulonephritis, and that the interaction of ANCA with its target antigen is required for the development of lesions. Furthermore, the localization of lesions is determined by the site of this interaction. At the same time, animal models support the significance of genetic determinants for the development of autoimmunity, vasculitis, and a specific phenotype with characteristic organ involvement and histopathological features. Finally, animal model studies indicate that infections may be significant disease modifiers. Even though proinflammatory effects of murine PR3-ANCA could also be documented in vivo, the animals did not develop organ pathology typical for GPA or MPA, and good animal model for PR3-ANCA–associated vasculitis remains elusive. This may be due to substantial differences between human and murine PR3, as the latter behaves more like human elastase than human PR3.

To date, the causes of the production and persistence of ANCA remain poorly understood. Yet infections may be instrumental for the development of this specific type of autoimmunity. ANCA directed against a broad variety of target antigens have been documented in association with viral, fungal, bacterial, and protozoal infections. In the rare instances of C-ANCA/PR3-ANCA observed in infections, the ANCA disappeared with appropriate antimicrobial therapy. These observations may suggest that ANCA can occur transiently in the setting of infection, and that the persistent ANCA response in patients with vasculitis may be the result of molecular mimicry in susceptible hosts. Subsequent diversification of T- and B-cell responses ("epitope spreading") may lead to responses against different epitopes on the same target molecule (intramolecular spreading) or extend to other molecules (intermolecular spreading. Bacterial superantigens have also been implicated in the pathogenesis of ANCA-associated vasculitis. GPA patients colonized with superantigen-producing *Staphylococcus aureus* are at high risk for relapse. GPA patients had expansion of T-cell clones expressing Vβ genes specific for *S. aureus* superantigens more frequently than controls. This supports the theory that *S. aureus* contributes to the pathogenesis of vasculitis. By inducing potent T- and B-cell activity, superantigens produced during an *S. aureus* infection could initiate and maintain both ANCA production and cytokine release, thought to be required for the cascade that results in necrotizing granulomatous inflammation and vasculitis.

■ TREATMENT OF ANCA-ASSOCIATED VASCULITIS

Treatment of granulomatosis with polyangiitis and microscopic polyangiitis, including management of patients who are refractory to standard therapy, is described below. In addition, treatment of eosinophilic granulomatosis with polyangiitis is considered.

Treatment of Granulomatosis with Polyangiitis and Microscopic Polyangiitis

The first goal of therapy for patients with ANCA-associated vasculitis is to induce a remission as quickly as possible, so that irreversible organ damage is minimized. To this end, early diagnosis and prompt application of an appropriate immunosuppressive regimen are crucial. At the same time the treatment plan needs to include the prevention of treatment-related toxicity. Once remission has been induced, the second goal of therapy is to maintain remission with as few side effects as possible. Finally, once the patient has enjoyed a stable remission, surgical interventions aiming to repair damage may proceed as necessary. These overarching principles apply to the therapy of both GPA and MPA.

Remission Induction Therapy

Remission induction therapy is best tailored to the patient's degree of disease severity, extent, and acuity. Patients who present with indolent GPA localized to the upper and/or lower airways and who are ANCA negative can be treated with trimethoprim/sulfamethoxazole (T/S) at a dose of 160/800 mg twice daily. The mechanism of action of T/S is unclear, but possibly related to antimicrobial effects on *S. aureus,* the organism most frequently cultured from the nostrils of patients with GPA. It is also possible that this agent has immune-modulatory effects not shared with other antibiotics. T/S monotherapy should not be used in ANCA-positive patients, in the setting of glomerulonephritis or any other severe disease manifestation, and patients treated with T/S need continued long-term observation, as some will later develop more severe disease manifestations requiring immunosuppressive therapy.

Standard remission induction therapy for most patients categorized as having "limited" or "nonsevere" or "early-systemic" GPA or MPA consists of oral prednisone at doses of 0.5 to 1 mg/kg per day (generally not to exceed 80 mg/d) in combination with methotrexate with a target dose of 20 to 25 mg once a week.[14,15] This dose can be applied orally or subcutaneously. To minimize toxicity and the risk of *Pneumocystis* pneumonia (PCP), this immunosuppressive regimen should be supplemented by folic acid, 1 mg/d and standard PCP prophylaxis.

For the last four decades standard remission induction therapy for patients with severe disease (also called "generalized" or "organ-threatening" disease) has consisted of oral prednisone in combination with oral cyclophosphamide at a dose of 2 mg/kg daily for 3 to 6 months.[16] One randomized controlled trial has shown that intravenous pulse therapy with cyclophosphamide consisting of three pulses of 15 mg/kg given 2 weeks apart followed by 15 mg/kg pulses given every 3 weeks for 6 months, is equally effective to induce remission in severe GPA or MPA.[17] Based on results from a large multicenter randomized double-dummy–controlled trial that compared four once-weekly doses (375 mg/m^2 of body surface) of rituximab to standard oral cyclophosphamide for remission induction in severe ANCA-associated vasculitis, rituximab has now been approved for this indication by most regulatory agencies across the globe.[18] The long-term follow-up of this study has shown that the efficacy of a single course of four once-weekly doses of rituximab (375 mg/m^2 of body surface) remains equivalent to continued standard daily oral immunosuppressive therapy with cyclophosphamide followed by azathioprine for 18 months.[19] These three remission induction regimens have been shown to be equivalent for newly diagnosed patients with severe GPA or MPA. Remission can be achieved in up to 90% of patients with either of these regimens. For patients presenting with a severe disease relapse, rituximab was found to be superior to cyclophosphamide.[18,19] Rituximab is also the preferred agent for young patients in whom fertility needs to be preserved. If oral cyclophosphamide is used, patients need to be monitored carefully to minimize the risk of bone marrow toxicity. The dose of cyclophosphamide should be adjusted in patients with impaired renal function, and the patient's complete blood counts need to be monitored at least biweekly for the duration of therapy. Optimal dosing with oral cyclophosphamide is achieved when the lymphocyte count is reduced, but the total white blood count is maintained above 3500. To avoid bladder toxicity of cyclophosphamide, the entire dose is applied in the morning and patients are instructed to drink at least 3 L of fluid per day.

In patients with rapidly progressive fulminant disease, such as those presenting with alveolar hemorrhage or rapidly deteriorating renal function, intravenous methylprednisolone, 1000 mg per day for 3 to 5 days may be necessary for effective control of inflammation. If this therapy does not generate the desired effects, plasma exchange should be implemented.[20,21]

Remission Maintenance Therapy

Once remission has been induced the prednisone dose is tapered gradually over the course of 5 to 6 months with the goal of complete discontinuation. Patients with limited or "nonsevere" disease should be maintained on methotrexate for remission maintenance.[15] Patients treated with cyclophosphamide for remission induction should be switched to either methotrexate or azathioprine for remission maintenance.[22] Azathioprine is preferred in patients with any degree of renal insufficiency. Mycophenolate mofetil is an alternative for patients who cannot tolerate either methotrexate or azathioprine for remission maintenance. However, mycophenolate mofetil appears less effective than azathioprine for remission maintenance. Remission maintenance therapy is continued for at least 12 months beyond achievement of remission, and longer in patients who have suffered relapses. Early discontinuation of immunosuppressive therapy is associated with an unduly high relapse rate. The need for remission maintenance therapy following remission induction with rituximab in newly diagnosed patients remains unclear. Over 18 months a single remission induction course of rituximab is as effective as oral cyclophosphamide followed by azathioprine, but PR3-ANCA–positive patients with GPA are at risk for relapse once peripheral blood B lymphocytes are reconstituted (after 6–12 months) and may benefit from long-term remission maintenance therapy.[23]

Long-term remission maintenance therapy with T/S beyond immunosuppression may also be beneficial. In one study, patients who received T/S at a dose of 160/800 mg twice daily had a lower rate of disease relapse than those who received placebo.[24]

Treatment of Patients Refractory to Standard Therapy

About 10% of patients do not respond adequately to therapy with cyclophosphamide and fail to achieve remission. These patients are particularly challenging. Anti–TNF-α agents have not been shown to be effective in such patients. One large multicenter, double-blind, placebo-controlled, randomized trial conducted in GPA, has shown no efficacy of etanercept when added to standard therapy.[25] Moreover, a higher frequency of malignancies was observed in the treatment arm compared with the control arm of that trial. All patients with malignancies had also received cyclophosphamide. For this reason, the use of etanercept in patients who have received cyclophosphamide is now strongly discouraged. Smaller, uncontrolled open-label studies with infliximab conducted in Europe have suggested some efficacy of that agent, but many complicated infections were observed in these patients. Over the last decade many cohort studies have found rituximab to be very effective in such patients, and rituximab has now become the *de facto* standard of care for refractory GPA.[26]

Supportive Therapy

PCP still carries a mortality of up to 35%. Therefore, PCP with T/S is recommended for all non–sulfa allergic patients with ANCA-associated vasculitis receiving immunosuppressive therapy including rituximab. Patients who have a sulfa allergy manifesting itself with a skin rash can be desensitized against the drug. Those who fail this approach or have other contraindications for the use of this drug should be given other agents for PCP prophylaxis. Patients receiving methotrexate for remission induction or maintenance should also receive PCP. This can be safely accomplished with T/S at recommended doses for this purpose, provided that folic acid, 1 mg daily, is also given. Patients undergoing intense immunosuppression during the remission induction phase may also benefit from prophylactic antifungal therapy. Finally, every patient treated with glucocorticoids for ANCA-associated vasculitis should receive osteoporosis prophylaxis with calcium and vitamin D supplements and possibly bisphosphonates.

■ TREATMENT OF EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Even though mortality of EGPA is lower than that of GPA or MPA, the management of EGPA remains a challenge. Systemic glucocorticoids are the cornerstone of therapy. There are no clinical trials that provide clear guidance. The reports from the French Vasculitis Study Group are difficult to interpret with respect to this disease, because patients with EGPA were not separated from those with polyarteritis nodosa and MPA, two diseases with distinct clinical manifestations, pathophysiology, and prognosis.[27,28] Yet, these studies suggest that it is appropriate to treat EGPA according to the principles applied to the management of GPA and MPA. Accordingly, cyclophosphamide should be added to glucocorticoids for remission induction in all patients with disease manifestations that threaten the patient's life or the function of a vital organ, that is, particularly those with central or peripheral nerve involvement, glomerulonephritis, heart involvement, or alveolar hemorrhage. Methotrexate, azathioprine, and mycophenolate mofetil have been used as glucocorticoid-sparing agents in less severe disease and for remission maintenance. Refractory disease and disease dominated by difficult-to-control eosinophilic inflammation may respond to interferon-α therapy.[29] However, continued long-term interferon-α therapy may be necessary, and this treatment carries the risk of substantial toxicity. More recently, small case series and a formal pilot trial have shown beneficial effects of rituximab, particularly in ANCA-positive patients with renal involvement.[30,31] Two pilot trials have documented substantial glucocorticoid-sparing effects of anti–interleukin-5 therapy with mepolizumab.[32,33]

OTHER DISORDERS PRESENTING WITH PULMONARY VASCULITIS

A broad spectrum of other disorders which may include pulmonary vasculitis is described below.

■ GIANT CELL ARTERITIS

Giant cell arteritis is a generalized inflammatory disorder involving large- and medium-sized arteries.[34] It is the most common form of vasculitis in the white population, and appears to affect predominantly elderly patients. Respiratory symptoms have been reported in up to 25% of patients. However, pulmonologists rarely see patients with giant cell arteritis for the management of its respiratory complications. Cough, hoarseness, and throat pain usually resolve promptly with prednisone therapy.[35] Chest roentgenograms and pulmonary function tests rarely show abnormalities attributable to the disease. Occasionally respiratory symptoms are the initial manifestations of giant cell arteritis. Therefore, this possibility should be considered in any elderly patient with new onset of cough, hoarseness, or throat pain without other identifiable cause, and it is reasonable to measure the erythrocyte sedimentation rate in such patients. Isolated cases with pleural effusion or multinodular pulmonary lesions have also been reported in giant cell arteritis. Such cases are difficult to interpret. Particularly in the latter situation, Wegener granulomatosis should be considered in the differential diagnosis, because it may also present with temporal arteritis.

■ TAKAYASU ARTERITIS

Takayasu arteritis is a large vessel vasculitis affecting predominantly the aorta and its major branches in young patients.[34] Pulmonary complications are the result of a unique arteriopathy predominantly of the large- and medium-sized pulmonary vessels. Progressive defects in the outer media of the arteries and ingrowth of granulation tissue–like capillaries associated with thickened intima and subendothelial smooth muscle proliferation lead to pulmonary artery stenoses and occlusion as well as pulmonary hypertension in up to one-half of all patients. The involvement of pulmonary arteries is common but often asymptomatic. It is detectable by conventional angiography, perfusion scan, or magnetic resonance angiography. CT may show areas of low attenuation as a result of regional hypoperfusion, subpleural reticulolinear changes, and pleural thickening. Fistula formation between pulmonary artery branches and bronchial arteries, as well as nonspecific inflammatory interstitial lung disease, has also been reported.

Therapy for Takayasu arteritis consists primarily of immunosuppression with glucocorticoids. Other immunosuppressive agents, including methotrexate are used as in conjunction with glucocorticoids for remission induction and as glucocorticoid-sparing agents for remission maintenance. Unfortunately, many patients relapse when the glucocorticoid dose is reduced below 15 mg daily. Most recently, the use of anti–TNF-α agents has been reported as beneficial in patients who are refractory to standard therapy. Vascular bypass or stenting procedures may be beneficial in severe disease, but their long-term benefits remain unclear.

■ CLASSIC POLYARTERITIS NODOSA

Since its formal separation from microscopic polyangiitis, this form of vasculitis affecting predominantly medium-sized vessels is diagnosed rarely. Because it does not affect capillaries, it does not cause either glomerulonephritis or alveolar hemorrhage. However, classic polyarteritis nodosa can affect the bronchial or bronchiolar arteries on rare occasions. Most cases of classic polyarteritis nodosa diagnosed today are associated with viral infections, specifically hepatitis B and C. Consequently, antiviral therapy plays a prominent role in the management of such cases in addition to immunosuppression. Classic polyarteritis nodosa is far less likely to relapse than microscopic polyangiitis, and therefore can generally be treated with a shorter course of immunosuppression.

■ BEHÇET DISEASE

Behçet disease is a rare chronically relapsing systemic inflammatory disorder characterized by aphthous oral ulcers and at least two or more of the following: aphthous genital ulcers, uveitis, cutaneous nodules or pustules, or meningoencephalitis. Respiratory manifestations are common in Behçet disease and include cough, hemoptysis, chest pain, and dyspnea.[36] Hemoptysis is often massive and fatal. The vasculitis of Behçet disease is immune complex mediated, and may affect vessels of all sizes. If the veins are affected secondary thrombosis with major venous occlusion can occur. This type of thrombosis may not be preventable by anticoagulation, but the use of aspirin 80 mg/d has been advocated. Massive hemoptysis is the result of destruction of the elastic lamina of pulmonary arteries leading to the characteristic aneurysm formation, secondary erosion of bronchi, and arterial–bronchial fistulae. Pulmonary artery aneurysms are detectable by CT or MR angiography, and pulmonary angiography is no longer

necessary. Recurrent pneumonia as well as bronchial obstruction as a consequence of mucosal inflammation has also been described.

Therapy of the underlying disease consists of immunosuppression. Prednisone alone may not be sufficient to control the vasculitis. The addition of other drugs, such as colchicine, chlorambucil, methotrexate, cyclosporin, or azathioprine is recommended. The addition of azathioprine or cyclophosphamide to glucocorticoids has resulted in resolution of pulmonary aneurysms. Once pulmonary arteritis has been identified in these patients, anticoagulation should be avoided. The prognosis of pulmonary involvement is poor. About one-third of patients die within 2 years of developing pulmonary involvement, most from fatal pulmonary hemorrhage. Embolization therapy may be used as treatment and prevention of hemorrhage from pulmonary artery aneurysms.

IDIOPATHIC PAUCI-IMMUNE PULMONARY CAPILLARITIS

Diffuse alveolar hemorrhage as a result of capillaritis in the absence of symptoms or serological evidence of any detectable underlying systemic disorder may occur rarely.[37] Direct immunofluorescence studies of the lung tissue did not reveal any immune deposits. This isolated pauci-immune pulmonary capillaritis is histopathologically indistinguishable from that of ANCA-associated vasculitis. It is a diagnosis of exclusion, and such patients are best treated with an immunosuppressive regimen according to the guidelines for severe Wegener granulomatosis or microscopic polyangiitis.

SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER COLLAGEN VASCULAR DISORDERS

The disease manifestations of SLE are highly variable. Pulmonary capillaritis leading to diffuse alveolar hemorrhage is rare in patients with SLE. However, it represents one of the most serious complications of the disease. In contrast to the pauci-immune pathology of ANCA-associated vasculitis, prominent immune complex deposits can be detected by direct immunofluorescence in the affected tissue of patients with SLE (Fig. 74-18). Hence, the development of pulmonary capillaritis in SLE is thought to be immune complex mediated. The onset of diffuse alveolar hemorrhage in patients with SLE is usually abrupt, and it is seldom the first sign of SLE. In the overwhelming majority of patients the rapid development of pulmonary infiltrates is associated with fever. Hemoptysis may be absent in up to one-half of the patients. Consequently, the differentiation of diffuse alveolar hemorrhage from infection may be difficult in patients with SLE, and may require a diagnostic bronchoalveolar lavage. Mechanical ventilation, infection, and cyclophosphamide therapy were identified as negative prognostic factors in one cohort.[38] However, no multivariate analysis was performed, and these factors may simply identify patients with more severe disease. The reported mortality from diffuse alveolar hemorrhage in SLE varies widely, between 0% and 90%. Treatment consists of glucocorticoids and cyclophosphamide.[39] The use of plasma exchange has been suggested, but its benefit remains unproved.

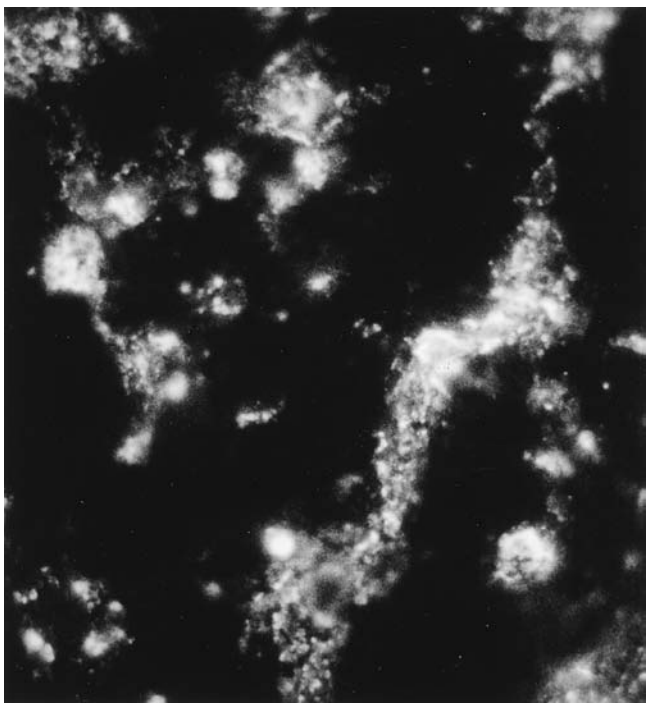


Figure 74-18 Lung biopsy of a patient with lupus erythematosus and alveolar hemorrhage showing so-called lumpy, bumpy deposition of immune complexes as demonstrated by direct immunofluorescence.

Respiratory complications are very common in all other types of collagen vascular or connective tissue disorders. However, pulmonary capillaritis presenting as diffuse alveolar hemorrhage is rare. Isolated cases have been reported with polymyositis, rheumatoid arthritis, and mixed connective tissue disease. Consequently, serological testing performed as part of an evaluation of diffuse alveolar hemorrhage should include studies aimed at the identification of these potential underlying disease entities.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is defined by arterial and venous thromboses, or recurrent miscarriages occurring in patients with antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant, or both). If antiphospholipid syndrome in the context of another autoimmune disease, malignancy, or drug exposure, it is labeled secondary antiphospholipid syndrome. In the absence of other coexisting disorders, it is considered primary. Hypercoagulability can cause pulmonary embolism and infarction, pulmonary microthrombosis, and pulmonary arterial thrombosis with secondary pulmonary hypertension as consequence. However, primary pulmonary hypertension has also been reported in antiphospholipid syndrome. Acute respiratory distress syndrome (ARDS) is another possible complication of antiphospholipid syndrome. Antiphospholipid syndrome can also be complicated by diffuse alveolar hemorrhage, presenting with cough, dyspnea, fever, and bilateral pulmonary infiltrates. Because of this nonspecific clinical presentation, the possible occurrence of diffuse alveolar hemorrhage in the context of ARDS, and the lack of hemoptysis in over one-half of the reported antiphospholipid syndrome patients with alveolar hemorrhage, and early bronchoalveolar lavage may help in the differential diagnosis. Tissue necrosis from microthrombosis as well as pulmonary capillaritis has been implicated as the cause of alveolar hemorrhage in antiphospholipid syndrome. As in SLE, the capillaritis of antiphospholipid syndrome appears to be immune complex mediated. Most patients respond to glucocorticoids.[40,41] Yet, the coexistence of thrombosis and capillaritis with alveolar hemorrhage represents a therapeutic dilemma, as anticoagulation may need to be interrupted to control the hemorrhage. Early plasma exchange in addition to immunosuppressive therapy should be considered in patients with antiphospholipid syndrome and alveolar hemorrhage.[42]

ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE

Historically, the syndrome of alveolar hemorrhage and glomerulonephritis has been called Goodpasture syndrome. Today's terminology restricts the use of the term Goodpasture disease to alveolar hemorrhage or necrotizing glomerulonephritis caused by autoantibodies directed against the NC1-domain of the α3 chain of basement membrane collagen type IV. This epitope is only accessible for autoantibodies in the basement membranes of kidneys and lungs. Diffuse alveolar hemorrhage is common in anti–glomerular basement membrane (anti-GBM) disease but is thought

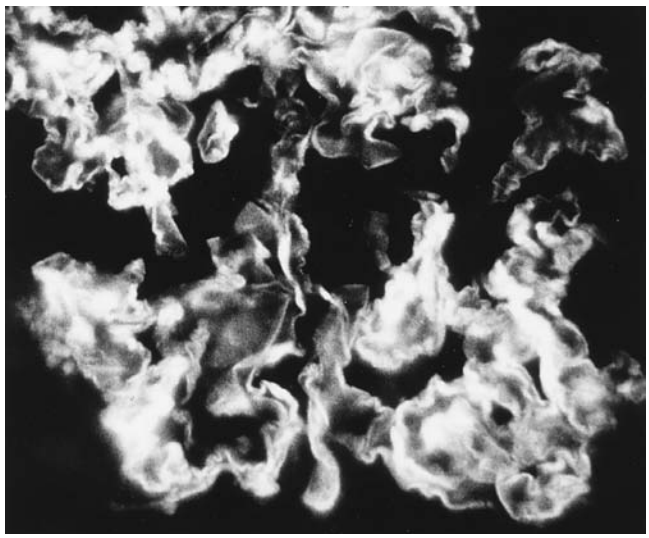


Figure 74-19 Kidney biopsy of a patient with anti–glomerular basement membrane (anti-GBM) disease showing linear immunofluorescence of the GBM due to fixation of IgG anti-GBM antibodies.

to require an additional inhalational injury, particularly smoking for the development of the pulmonary manifestation of this disease. Isolated alveolar hemorrhage in the absence of renal disease is rare in anti-GBM disease. The finding of circulating anti-GBM autoantibodies in the serum may facilitate the early implementation of appropriate therapy. However, methods used for their detection are of highly variable sensitivity and specificity, and a definitive diagnosis depends on the documentation of linear anti-GBM deposits in the kidney or lung (Fig. 74-19). In most patients, tissue from the kidney is more easily accessible for histopathological evaluation than lung tissue. Anti-GBM is arguably not a vasculitis. Bland pulmonary hemorrhage is the most frequently described histopathological pattern in diffuse alveolar hemorrhage associated with anti-GBM disease. However, capillaritis as a secondary histopathological feature has been encountered in some patients. Early implementation of immunosuppressive therapy in conjunction with plasma exchange is the key to a favorable outcome in patients with anti-GBM disease.[43]

IgA VASCULITIS (HENOCH–SCHÖNLEIN)

Henoch–Schönlein purpura has been renamed into IgA vasculitis (Henoch–Schönlein) as at the 2012 Chapel Hill Consensus Conference to reflect the evolving understanding of its pathogenesis. Pulmonary manifestations of IgA vasculitis are rare. Only 26 cases have been reported to date, and capillaritis has been documented histopathologically only in a minority of them.[44] IgA deposits along the pulmonary capillary walls, analogous to those found in vessels of the skin and glomeruli of affected kidneys are pathognomonic features of IgA vasculitis, detectable by direct immunofluorescence.

DRUG-INDUCED VASCULITIS

The list of drugs described in association with vasculitis includes a long list of therapeutic agents as well as drugs of abuse.[45] The clinical spectrum of drug-induced vasculitis ranges from isolated and mild vasculitis of the skin to severe multiorgan system disease. Small- to medium-sized vessels are usually affected. Based on clinical manifestations, drug-induced vasculitis cannot be distinguished from the primary vasculitis syndromes.

The following drug-induced syndromes merit special attention. First, a variety of drugs including propyl-thiouracil, D-penicillamine, hydralazine, sulfasalazine, minocycline, allopurinol, and others can induce an ANCA-associated vasculitis. Pulmonary capillaritis as a manifestation of an ANCA-associated vasculitis induced by these agents is well documented. Drug-induced ANCA-associated vasculitis should be treated with immunosuppression according to the principles for primary ANCA-associated vasculitis. However, once the offending drug has been eliminated, the likelihood of a relapse seems low.

The use of all-*trans*-retinoic acid in acute promyelocytic leukemia can cause a syndrome of fever, leukocytosis, fluid retention, hemorrhage, thrombosis, and organ failure. Pulmonary complications of this syndrome are frequent, and pulmonary capillaritis has been reported in this context.

Some chronic nasal cocaine abusers develop severe midline destructive lesions. In its early stage, such a lesion is clinically and histopathologically difficult to differentiate from limited Wegener granulomatosis, particularly in patients who do not volunteer the history of abuse.[46] The presence of ANCA reacting with human neutrophil elastase (HNE) appears to be an immunological marker separating patients with cocaine-induced midline destructive lesions from those with Wegener granulomatosis.[47]

More recently levamisole has become a common adulterant of cocaine.[48] Levamisole is a polyclonal B-cell–stimulating agent that can induce a variety of autoantibodies including antigranulocyte antibodies, antiphospholipid antibodies, and ANCA. The ANCA reactivity is directed against multiple target antigens including MPO, PR3, and HNE.[49] The clinical picture of patients exposed to levamisole can mimic systemic vasculitis.

PULMONARY CAPILLARITIS AFTER LUNG TRANSPLANTATION

Five cases of acute rejection after lung transplantation with prominent pulmonary capillaritis, histopathologically distinct from typical rejection, have been reported. In these cases, the capillaritis was

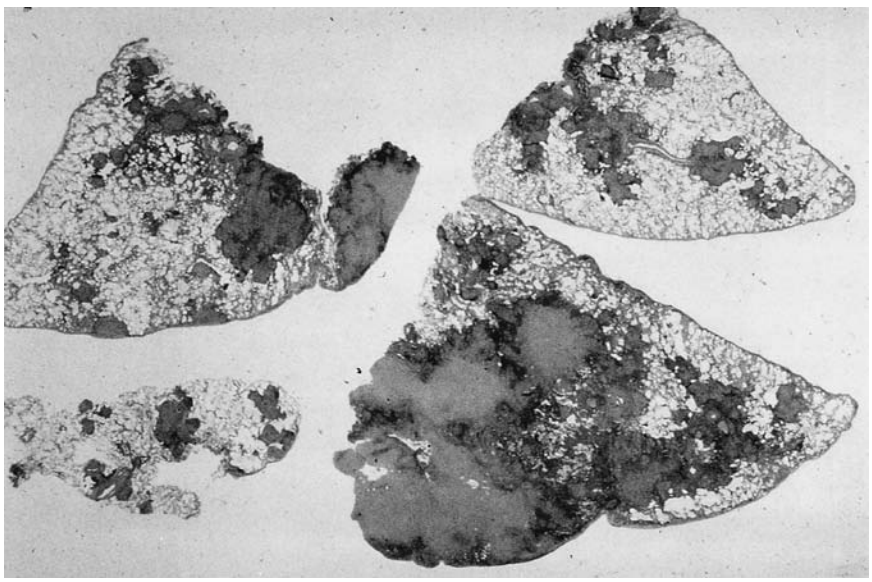


Figure 74-20 Low-power photomicrograph of lung revealing coalescing necrotizing granulomas in a patient with necrotizing sarcoid granulomatosis.

thought to represent a form of severe, acute vascular rejection. Early histological diagnosis and aggressive immunosuppression, possibly in conjunction with plasma exchange, was suggested to control the inflammatory activity and prevent relapses.

NECROTIZING SARCOID GRANULOMATOSIS

Vasculitis is a prominent histopathological feature of necrotizing sarcoid granulomatosis. The disease is usually limited to the lungs. The characteristic pulmonary nodules are bilateral, and may be an incidental finding in asymptomatic patients. Alternatively, patients may complain of cough, dyspnea, or phlegm production. Generalized constitutional symptoms occur rarely. The differential diagnosis of necrotizing sarcoid granulomatosis includes primarily infectious processes. Special sputum and tissue stains and cultures should always be obtained to exclude mycobacterial or fungal disease. Clinically, these patients are difficult to differentiate from limited Wegener granulomatosis. Histopathologically, there are characteristic necrotizing epithelioid granulomas that may form aggregates (Fig. 74-20). In contrast to Wegener granulomatosis, these granulomas are well circumscribed. Vasculitis is a central histopathological feature of necrotizing sarcoid granulomatosis. Liebow originally described three types of vasculitis: an epithelioid-granulomatous form, a form reminiscent of giant cell arteritis with prominent histiocytes and multinucleated giant cells in the inflammatory infiltrate of the vessel wall, and a lymphocytic form lacking granuloma formation and giant cells. The separation from sarcoidosis remains controversial. Yet, the extensive vasculitis and necrosis seen in necrotizing sarcoid granulomatosis are unusual for sarcoidosis. The chest roentgenographic appearance of pulmonary nodules, or masses and pleural involvement are also atypical for sarcoidosis. Finally, extrapulmonary involvement has only rarely been documented in necrotizing sarcoid granulomatosis.

It is debatable whether necrotizing sarcoid granulomatosis should be included with the systemic vasculitides. Most authors would argue against this inclusion because of its limitation to the lungs and good prognosis (spontaneous remission may occur). Therapeutically, necrotizing sarcoid granulomatosis can be approached as cases with chronic pulmonary sarcoidosis. Decisions about the use of oral glucocorticoid therapy should be individualized based on symptoms, pulmonary function data, and their evolution over time.

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CHAPTER 75

Pulmonary Arteriovenous Malformations

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Murali Chakinala

HISTORY

Pulmonary arteriovenous malformations (PAVMs) were first described in the late 19th century; Churton[1] reported the autopsy findings in a young boy with cyanosis in 1897. Based on the correlation of physical with postmortem findings, the triad of cyanosis, clubbing, and polycythemia was identified with PAVM in 1932.[2] Hereditary hemorrhagic telangiectasia (HHT) was first connected to PAVM in 1938.[3] As described below (Causes and Disease Associations), HHT is often intimately related to PAVMs—a fact that prompts the following discussion of the history of HHT.

Hereditary epistaxis was first described in 1864,[4] though neither that nor Babbington's description a year later report an association with telangiectasia.[5] These reports were not generally recognized; nor were subsequent descriptions of telangiectasia, hereditary transmission, and epistaxis by Legg[6] in 1876, or a similar kindred reported by Chiari in 1887.[7] The first widely recognized connection of epistaxis to telangiectasia was made by Rendu in 1896.[8] Osler[9] added three cases, and recognized familial occurrence in 1901. Weber[10] elucidated the familial nature and lack of coagulation abnormality, and thus earned his eponymic association. By precedence of description, this eponym should be Rendu–Osler–Weber, even though Osler–Weber–Rendu is the most common usage.

Hanes[11] was responsible for naming the syndrome HHT, the designation now most often preferred, in 1909.

GENETICS

The genetic basis, if any, of isolated PAVMs remains unknown. HHT is an autosomal dominant disease. Its frequency was believed until relatively recently to be less than 3 per 100,000 people.[12] Newer studies suggest a much higher prevalence. The highest frequency reported, 1:1331, occurs in the Afro-Caribbean population of the Netherlands Antilles, presumably due to a founder effect.[13] Other estimates vary geographically; 1:6410 in Denmark,[14] 1:8000 in Japan,[15] and 1:16,500 in Vermont.[16] Phenotypic variation is extreme, ranging from asymptomatic to severely symptomatic, and from cases with no or few mucocutaneous lesions to those with diffuse cutaneous telangiectasias. For many patients, the disease remains undiagnosed by their primary care physicians, suggesting that disease frequency may be greater than reported, and that some patients with "isolated" PAVMs may actually have HHT.

A gene for HHT was first localized to chromosome 9, region q^{33-34} ($9q^{33-34}$).[17–19] Investigation revealed the protein product to be endoglin, which associates with the transforming growth factor-beta (TGF-β) bone morphogenetic protein (BMP) receptor complex and binds TGF-β-1 and -3.[20] The same work showed the disease to be genetically heterogeneous, with multiple mutations in the responsible gene. It rapidly became clear that there were other chromosomal mutations resulting in the same syndrome, and the endoglin mutation disease was designated HHT-I; it was noted to be associated more often with PAVMs than were those with non-$9q^3$ mutations.[21,22] A haploinsufficient mouse model also demonstrated phenotypic heterogeneity which was very dependent on the genetic background.[23]

The activin receptor–like kinase 1 gene (ALK-1 or ACVRL1) on chromosome 12 is the second locus for HHT.[24,25] It produces a TGF-β superfamily type I receptor. Mice heterozygous for a loss-of-function mutation in ALK-1 develop age-dependent vascular lesions in the skin, extremities, oral cavity and in the lung, liver, intestine, spleen, and brain, similar to those seen in HHT patients.[26] Disease resulting from mutations in this gene has been designated HHT-2.

A small number of patients with juvenile polyposis also have HHT. This is due to mutations in MADH4 (encoding SMAD4); SMAD proteins influence the cellular response to TGF-β through interactions with other SMADs as transcription factors.[27,28]

A fourth gene abnormality producing clinical HHT in one family has been described on chromosome 5. The gene product is as yet unidentified.[29]

A fifth genetic abnormality in a family with HHT has been described on the short arm of chromosome 7.[30] The gene product of this mutation is also unknown at present.

Most HHT appears to be caused by mutations in endoglin and ALK-1. Mutations can be identified in up to 88% of affected individuals[31,32]; in one series, 61% were in endoglin, 37% in ALK-1, and 2% in MADH4.[33] ALK-1 mutations appear to be more common in France and Italy, with endoglin mutations more frequent in northern Europe and North America.[31,32,34] PAVMs are more frequent and on the average of larger size in HHT-1.[35]

Genetic testing for mutations in endoglin, ALK-1, and MADH-4 is currently available from six laboratories in North America, and a number of other laboratories in Europe. An up-to-date list with contact information is maintained at http://hht.org. The primary role for testing is to identify a mutation in an index case who meets criteria for a diagnosis of HHT. If this is possible, the index case's children and other first-degree relatives may be screened. Those with negative tests may be reassured, and those with positive tests may be evaluated for complications of HHT. On occasion, a diagnosis may be confirmed in an index case when clinical criteria are insufficient for clinical diagnosis. As with all genetic diseases, testing should be accompanied by genetic counseling.

PATHOPHYSIOLOGY

Important pathophysiologic considerations of PAVM are discussed below.

STRUCTURE

The three essential structural elements of PAVMs are the arterial supply ("feeder vessel"), a draining vein, and the intervening aneurysmal sac. Because of this simple relationship, the label of "AVM" is a bit of a misnomer as these malformations are more characteristic of a fistulous connection between arterial and venous branches without a customary intervening capillary network that is vital for gas exchange. PAVMs appear to develop between precapillary arterioles and venules, with intervening epithelial dysplasia.[36,37]

Approximately 80% of PAVMs have a single feeding and a single draining vessel; the remaining 20% are complex, with two or more of each.[38] By far the most common form of PAVM has a pulmonary arterial supply and pulmonary venous drainage.[39] In one series, 60 of 63 PAVMs had a pulmonary arterial blood supply[40] but arteries from the systemic circulation can also be involved, including arterial branches from the internal mammary artery, intercostal arteries, and subdiaphragmatic arteries. While systemic "feeders" are prone to develop as sequelae of chronic suppuration in the lung (e.g., sequestration), postpulmonary infarction after pulmonary embolism, or postembolization of pulmonary artery-to-vein malformations,[41] this chapter will focus on the classic form PAVMs involving the pulmonary arteries.

PATHOGENESIS

Our evolving understanding of PAVM development was summarized in a recent and thorough review of HHT.[42] Briefly, pathogenesis of PAVMs is presumed to initiate from periods of increased angiogenic activity, possibly triggered at sites of vascular injury,[43] and likely spurred on by an imbalance between proangiogenic signaling and reduced antiangiogenic activity. Angiogenesis is dysregulated due to altered expression of TGF-β–mediated pathways in endothelial cells of the pulmonary circulation, which plays a critical role in endothelial cell homeostasis. Mutations in one of the HHT-causative genes (described earlier) leads to either altered ligand-receptor interaction at the endothelial cell surface (ENG or ACVR1) or intracellular signaling (SMAD4) within endothelial cells. Downregulation of TGF-β expression is postulated to permit excessive endothelial cell proliferation and increase blood vessel formation[44] (under the influence of proangiogenic signals from molecules such as vascular endothelial growth factor [VEGF]), form persistent direct arteriovenous connections,[45] and destabilize vessels due to interactions between endothelial and mural cells (e.g., pericytes, smooth muscle cells).[46] The lack of a capillary network within a PAVM and the direct communication between arterioles and venules exposes thin-walled conduits to arterial blood flow and increased shear forces. Again, genetic defects and dysregulated angiogenesis lead to a muted compensatory response within these "arterialized" veins that must dilate. Furthering this concept, work in an animal model of HHT suggests a two-step dysregulatory sequence culminating in AVM formation, whereby the initial endothelial cell proliferation is mediated by HHT-causing mutations[44] and the subsequent dilation and persistence of downstream arteriovenous communications is independent of the mutations and, indeed, may be a homeostatic response to altered upstream blood flow pattern.[47] Over time, these initial microscopic communications grow into macroscopic communications[48] notable for relatively increased flow and passage of material normally sequestered or cleared in the pulmonary microcirculation (e.g., air bubbles, thrombi, bacteria). Further work in this area should clarify the molecular steps from altered gene expression to dysregulated

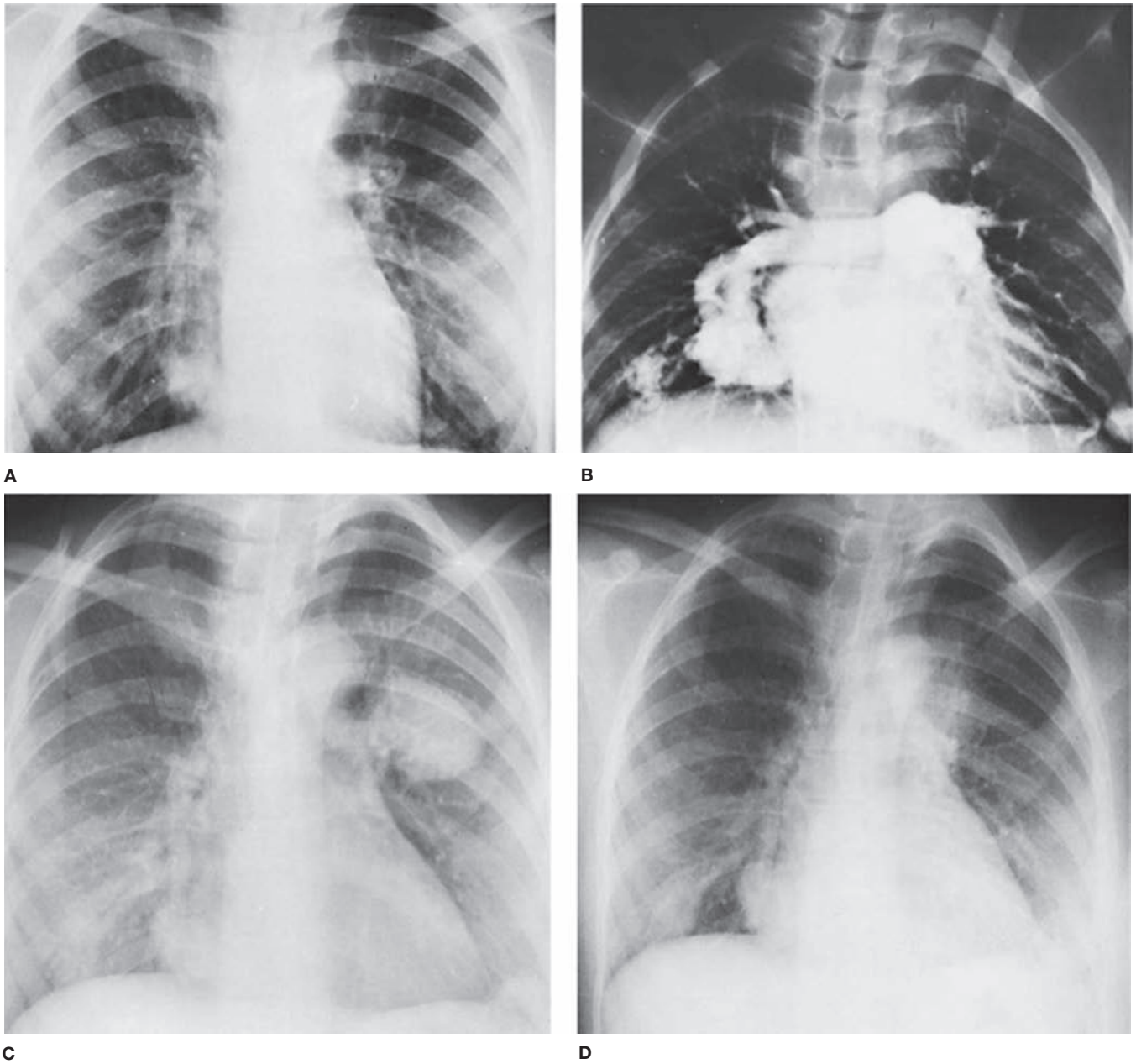


Figure 75-1 Pulmonary arteriovenous fistulas in a pregnant 24-year-old woman with hereditary hemorrhagic telangiectasia. **A.** Before pregnancy. Small nodular densities are seen at both bases and in the left hilus. The shunt was estimated to be 49% of the cardiac output. **B.** Arteriogram before pregnancy demonstrates arteriovenous fistulas of both lower lobes. **C.** Seven months pregnant, the patient was admitted to the hospital with hemoptysis and left hemothorax. The enlargement of the arteriovenous fistulas is striking. The pregnancy was terminated. **D.** Two weeks after termination of pregnancy, the nodular densities have decreased in size. *(Used with permission of Dr. M. Rossman.)*

multistep angiogenesis, discover precipitants of the dysregulated angiogenesis, and identify comediators, associated pathways, and environmental factors that influence angiogenesis.

Growth rates of AVMs remain unknown but is likely subject to intersubject variability and overall blood flow. One observed phenomenon of PAVM growth is accelerated growth during pregnancy leading to potential peripartum hemorrhagic complications,[49] which in part is theorized to occur due to increased blood flow and higher cardiac output of pregnancy but customary hormonal alterations of pregnancy could also be influential (Fig. 75-1).[50]

NUMBER

In one series, more than 60% of individuals present with more than one PAVM.[51] In general, multiple PAVMs correlate with HHT. A small percentage have diffuse, multilobar PAVMs that are typically bilateral and associated with marked hypoxemia.[52,53]

SIZE

PAVMs may vary from malformations too small to be seen by radiography or angiography[54,55] to those greater than 5 cm in diameter.[56]

LOCATION

Up to 65% of PAVMs are located in the lower lobes[55]—a phenomenon that may be due to the increased pulmonary blood flow and pressure, and subsequent "stretch" due to hydrodynamic forces. A recent small series noted less selectivity for the lower lobes in cases of "idiopathic" PAVMs.[57] The lower lobe location is the likely cause of the orthodeoxia (desaturation in an upright position) and platypnea (dyspnea in

an upright position) which are sometimes seen. These symptoms may also occur with cirrhosis, which has pulmonary vascular abnormalities see below "Other Associations". Location may also account for an increase in right-to-left shunt which occurs at total lung capacity.[58]

CAUSES AND DISEASE ASSOCIATIONS

Early observers thought that all PAVMs were due to HHT.[38] The estimates of frequency with which PAVMs are due to HHT have varied substantially, from 36% to 95%.[38,40,50,59,60] Most recent series report HHT in well over 90%.

Estimates of the percentage of patients with HHT who have associated PAVMs have varied widely. Different series have reported frequencies of 15%,[50] 20%,[61] 24%,[36] 33%,[62] 49%,[63] and 57%.[64] Frequency of PAVMs appears to be significantly greater in cases with ENG mutations, as opposed to ACVRL1 mutations.[65] Furthermore, overall PAVM detection rates are being influenced by improving imaging techniques that provide clearer resolution of the vasculature in the peripheral areas of the lung.

OTHER ASSOCIATIONS

Cirrhosis may result in diffuse small arteriovenous connections.[66] Nearly all such patients have cutaneous spider angiomas. The right-to-left shunt is probably due not to true PAVMs but, rather, to vasodilation of pleural vessels, which resemble cutaneous spiders, and increased numbers of peripheral small arteriolar branches with precapillary arteriole-to-venous connections in the peripheral respiratory lobule. As many as 44% to 60% may have positive contrast echocardiography indicative of intrapulmonary shunt;[67,68] many of these patients have shunt eliminated by liver transplantation. A PAVM of significant size, known as a Rasmussen aneurysm, may also develop as a result of tuberculosis.[69] Metastatic thyroid carcinoma, a highly vascular tumor, may mimic pulmonary arteriovenous fistula.[70] Cavopulmonary anastomosis, used in the palliation of functionally univentricular heart disease, results in pulmonary arteriovenous connections similar to those in cirrhosis, in approximately 10% of patients. The reasons are unclear.[71] Rarely, penetrating chest trauma may result in subsequent PAVM.[72]

PRESENTATION AND COMPLICATIONS

PRESENTATION

The occurrence and frequency of symptoms related to PAVMs depend on how the patients are found—that is, whether they present with manifestations of disease or whether they are discovered as a result of screening. When detection occurs as a result of screening in patients with HHT, between 25% and 59% are asymptomatic.[50,73–75]

The age at onset is usually in the third or fourth decade.[38] The mean age at detection in various series is remarkably constant at 38 to 40 years.[50,51,73,74] In one series, the patients ranged in age from 5 to 76 years, with a mean of 36; 26% presented at an age less than 21 years.[55] PAVMs are, however, uncommon in childhood; only 4% of affected persons are under 10.[78,79]

Pulmonary symptoms include dyspnea on exertion, with a frequency ranging from 27% to 71%.[21,40,55,80] Platypnea and orthodeoxia also may occur. Hemoptysis ranges in frequency from 4% to 18%.[21,51,55] Extrapulmonary symptoms include chest pain in 6%[81] and epistaxis (largely seen in HHT), ranging from 32% to 85%.[37,80,82] The mean age at onset of epistaxis in HHT is 12 years, with 54% of patients presenting by age 10. Severity of epistaxis ranges from mild to severe, with up to 45 episodes per month.[76] Headache is also remarkably common in HHT patients, occurring in 43%.[55] Transient ischemic attack (TIA) occurs in up to 57% of patients with PAVM, and symptomatic cerebrovascular accident in 18%.[55,76]

Physical signs due to the PAVM itself are relatively uncommon. As many as 25% of patients may exhibit no findings at all.[40] Hypoxemia, when present, is secondary to the right-to-left shunt, and may result in cyanosis and secondary polycythemia. This tends to occur in advanced disease, and has been reported in 9% to 73% (mean 30%).[40,59,76] The frequency of clubbing has been reported in an average of 32%[76]; it is much less common in our experience.[49,56] Clubbing is nearly always associated with cyanosis. Clubbing may resolve after the PAVM is removed[83] or occluded. A pulmonary bruit, which is often described, is also variable; its frequency, probably influenced by selection bias, ranges from less than 10% to 58%.[40,49,76,80]

Telangiectasia have been reported in up to 66% of patients with PAVM, depending on the frequency of HHT.[84] These small red vascular blemishes occur most frequently on the face, followed in descending order by the lips, nares, tongue, ears, hands, chest, and feet. They often increase in size and number with age, and cutaneous telangiectasias are seldom identifiable until the second or third decade.[37] We have been struck by the frequency with which classic tongue and lip telangiectasias have been passed off as nonspecific blemishes by primary care physicians.

Laboratory results are nonspecific. A complete blood count may show polycythemia, although in patients with HHT, this tendency may be overshadowed by iron deficiency anemia. Anemia was present in 94 of 292 (34%) in our series. This was more often due to GI bleeding when severe. GI blood loss of variable severity was present in 65 of 292 (22%).[56]

The severely affected person may have arterial hypoxemia at rest; those less severely affected may have orthodeoxia documented by supine and upright arterial blood gases.[85] Arterial blood gases, determined on blood samples drawn while the patient is breathing room air, followed by 100% oxygen, may reveal a significant right-to-left shunt.[86]

COMPLICATIONS

Pulmonary and neurologic complications of PAVMs are important considerations.

Pulmonary Complications

Significant hemoptysis occurs in fewer than 10% of patients; in our most recent series, it occurred in 5 of 142 (<4%). Two of five occurred during pregnancy.[56] It may be massive and life-threatening. Bronchial telangiectasias may be the cause,[62] but all cases in untreated patients in our experience have been due to PAVMs. An increasingly frequent problem in recent years is hemoptysis following extensive embolotherapy after a delay of months to years. This has generally been due to postembolization bronchial collateral formation.

Hemothorax has been reported in up to 9% of patients,[87] but is usually less than 2%.[76] Pregnancy has been associated with hemothorax on several occasions, perhaps related to PAVM enlargement.[88–90] Hemothorax may also occur without any other predisposing factors, presumably caused by rupture of large subpleural PAVMs into the pleural space.

Typically, PAVMs are associated with a normal or low pulmonary vascular resistance (PVR) as the direct arteriovenous communications are low-resistance circuits. However, pulmonary hypertension is encountered, albeit uncommonly, in the setting of PAVMs and HHT.[91] Pulmonary hypertension most often develops from increased pulmonary blood flow, which occurs in HHT because of massive hepatic arteriovenous malformations that rapidly return blood to the right side of the heart and lead to a high cardiac output state. The high output can be aggravated by concomitant chronic anemia from blood loss. In this situation, the PVR will be low as the entire pulmonary circuit, not just the PAVM, dilates to accommodate increased pulmonary blood flow; but the capacitance of the circuit has limits and additional blood flow will lead to mild pulmonary hypertension. In distinction, another more devastating

but rarer form of pulmonary hypertension can be seen in the setting of PAVMs, whereby the PVR is quite high due to a proliferative vasculopathy of small pulmonary arterioles.[92] In these rare cases, mutations occur primarily in ACVRL1 gene and represent a form of heritable pulmonary arterial hypertension (HPAH),[93] which is a form of Group I pulmonary hypertension in the Dana Point classification of pulmonary hypertension.[94] When PAH patients are discovered to have ACVRL1 or endoglin mutations during the genetic workup, PAVMs should be excluded as other clues for HHT can be subtle or absent in this rare population and PAH can be detected prior to a diagnosis of HHT being made.[95,96] When PAVMs coexist with significant PAH, caution must be exercised with PAVM embolization (see Treatment section) as sudden obliteration of the low-resistance circuit could significantly increase the PVR and unsettle an already fragile right ventricle or lead to other hemorrhagic complications[97,98]; these rare cases should be managed in a multidisciplinary fashion by individuals familiar with the management of PAVMs and PAH.

Central Nervous System Complications

The pulmonary capillary vascular bed appears to be an important filter for otherwise asymptomatic small emboli, and may also have a significant role in cleansing the bloodstream during transient bacteremia. Most neurologic complications, which occur in 8% to 12% of patients with HHT, are complications of PAVMs. In one series, 60% were due to PAVM, including brain abscess, paradoxical embolus, and hypoxemia.[37,99]

TIAs occur in approximately 37% of patients with PAVMs.[55] PAVMs can cause symptomatic cerebrovascular accidents (Fig. 75-2); the frequency of this complication ranges from 6% to 27%.[40,55,76] In our clinic, 28 of 132 patients screened by magnetic resonance imaging (MRI) had evidence of prior paradoxical embolic stroke.[56] Unfortunately, paradoxical embolization to the brain may be the first manifestation of an occult pulmonary venous malformation. This has been a particularly regrettable repetitive problem in young women who smoke and take oral contraceptives. Care should be taken to avoid air embolism; IV should be free of air and a micropore inline filter used.

Brain abscess occurs in 3% to 10% of patients with PAVMs.[37,76] In a series in our clinic, 5/132 (4%) had prior brain abscess.[56] Up to 1% of HHT patients may have brain abscesses (1000 times the incidence in the general population). In one series, 5 of 31 patients had recurrent abscess[100]; in another, 6 of 128.[101] Up to 8% of brain abscesses in the general population may be due to PAVMs.[102] Unfortunately, brain abscess may also be the first symptom of an occult PAVM (Fig. 75-3), and many years may elapse before diagnosis of PAVM (Fig. 75-4). Most occur following dental work. For that reason, antibiotic prophylaxis following the standard American Heart Association protocol for prevention of endocarditis is recommended.[103]

Migraine is more common in HHT than in the general population, and appears to be more common in those with PAVM. In one series, migraine occurred in 88 patients with HHT, a prevalence of 16.4%. The prevalence of migraine in patients with PAVM was 21.2%, which

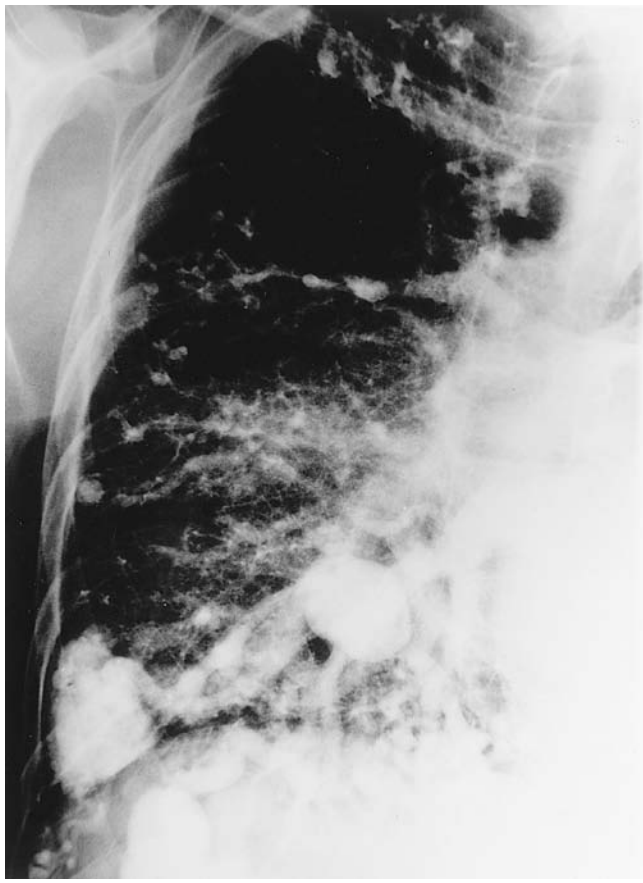


Figure 75-2 Right-sided pulmonary angiogram showing multiple PAVMs in a middle-aged man with clubbing, polycythemia, and CT evidence of several prior strokes.

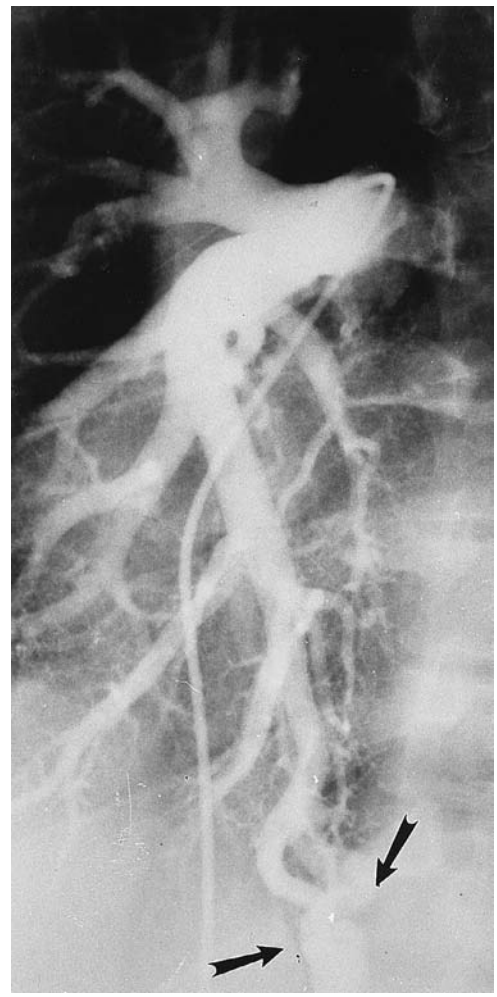


Figure 75-3 PAVM detected in patient with HHT after initial presentation with brain abscess. The PA and lateral chest radiographs were normal on several occasions. Right pulmonary angiogram with inferomedial PAVM *(arrows)*.

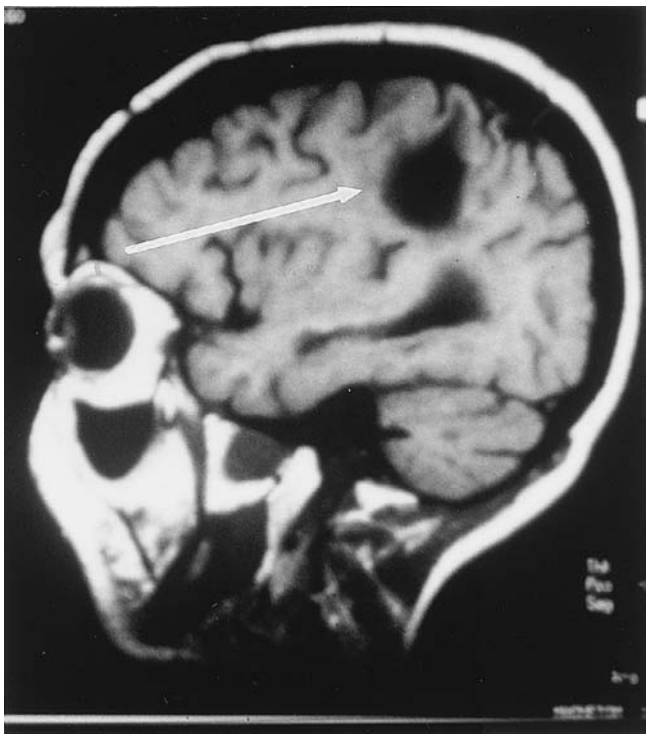


Figure 75-4 MRI showing brain abscess residua in patient whose brain abscess preceded diagnosis of pulmonary arteriovenous fistula by 17 years.

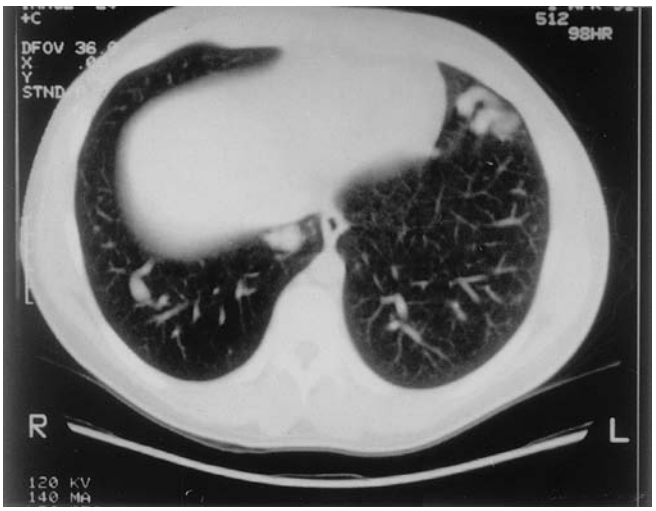


Figure 75-5 Characteristic CT image appearance of PAVM in left hemithorax. Portions of two PAVMs are seen in right hemithorax.

was significantly higher than in patients without PAVM (13.3%).[104] In our experience, migraines occurred in 74/292 (25%) with HHT.[56]

Cerebral arteriovenous malformations (CAVMs) occur in 4% to 8% of patients with HHT[55,105] and tend to run in families.[106] Although CAVMs are not complications of PAVMs, they occur more frequently in patients with endoglin mutations, as do PAVMs. In our series of 149 patients screened by MRI, 11 had CAVM (7%). An additional 16 (11%) had telangiectasia or venous angioma (11%).[56] It is recommended that individuals with HHT, including children, be screened for CAVM.[103] The hemorrhage rate in individuals with cerebral AV malformations appears to be 0.5% annually, less than that in the non-HHT population with cerebral AVMs.[107] Cerebral MRI is currently the most sensitive noninvasive test, although it will fail to detect a significant proportion of AVMs.[105] MRI may be performed in patients with pulmonary AVMs embolized with both stainless steel coils and platinum Nester coils in machine with fields up to 3.0 T[108]; we have performed many such cerebral MRI examinations without complications, although the MRI is not done for a minimum of 6 weeks after embolotherapy.

DIAGNOSIS

Diagnostic evaluation of suspected PAVMs includes assessment of chest radiographs and CT scans, supplemented by additional studies, as warranted.

EVALUATION OF A RADIOGRAPHIC ABNORMALITY

Discovery of a nodule on chest x-ray is typically followed by CT scan of the chest. This may show the typical lesion with feeding and draining veins (Fig. 75-5),[3] but vascular tumors may cause false-positive results. Evidence of intrapulmonary right-to-left shunt confirms the diagnosis. A perfusion lung scan may detect a right-to-left shunt. Ordinarily, 95% of the technetium-labeled macroaggregated albumin, with an average diameter of approximately 35 μ, is trapped in the pulmonary capillaries. When there is an intracardiac or intrapulmonary shunt, unusually large amounts may pass through the lung and travel to the brain and kidneys, resulting in excess radioactivity in those areas. However, this method cannot differentiate intracardiac from intrapulmonary shunt.

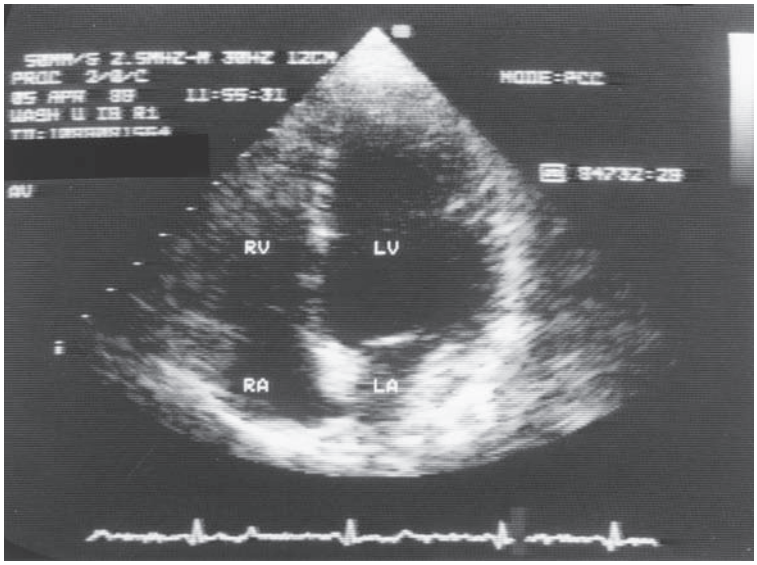
Echocardiography, using indocyanine green as a contrast material, was found to be effective in the diagnosis of intrapulmonary shunt, with delayed appearance of the contrast material in the left side of the heart.[109] This was simplified and improved by the use of agitated saline as contrast (Fig. 75-6) (Video 75-1).[110] The intrapulmonary nature of the shunt can be determined by the delay, averaging four to five cardiac cycles, of left heart contrast appearance. If contrast echocardiography is negative, a PAVM is very unlikely, and an alternative cause of the pulmonary nodule should be sought. On rare occasions, if the PAVM is fed by a systemic artery, the contrast echocardiogram will be negative, and bronchial and/or internal mammary angiography should be undertaken if suspicion is high.

SCREENING OF PROBANDS OR RELATIVES WITH HHT

Because the majority of PAVMs occur in HHT, it is important to evaluate individuals with PAVMs for HHT, and to screen individuals with HHT for PAVMs. Criteria for diagnosis of HHT include (1) spontaneous and recurrent epistaxis; (2) multiple characteristic telangiectasia (typically found on lips, tongue, malar eminence, pinnae, and digits); (3) visceral lesions (gastrointestinal telangiectasia with or without GI bleeding, PAVMs, hepatic arteriovenous malformations, CAVMs, and spinal AVMs); (4) family history with a first-degree relative with HHT.[111] In addition, relatives of patients with HHT should be evaluated for that diagnosis. Those found to have HHT should be screened for PAVMs. Consensus of an international panel was that screening should occur at the time of diagnosis, including children.[103]

The reported sensitivity of chest radiographs varies widely, depending on whether they are used for screening or in patients with symptomatic disease. Rates of abnormality on the chest radiograph range from 41%[75] to 100%.[40] In our experience, chest

Video 75-1 Saline contrast echocardiogram demonstrating characteristic delay of left-sided contrast in patient with intrapulmonary shunt. *(Used with permission of Dr. Daniel Goodenberger) Access at www.fishmansonline.com*



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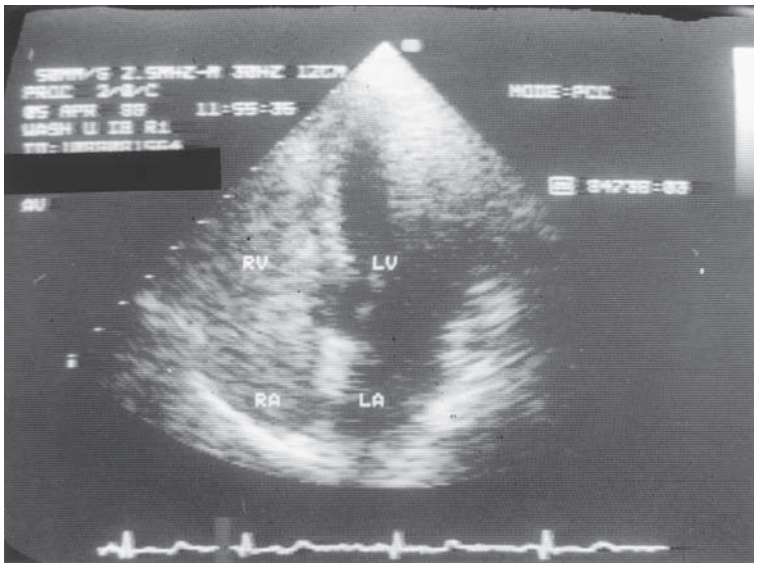

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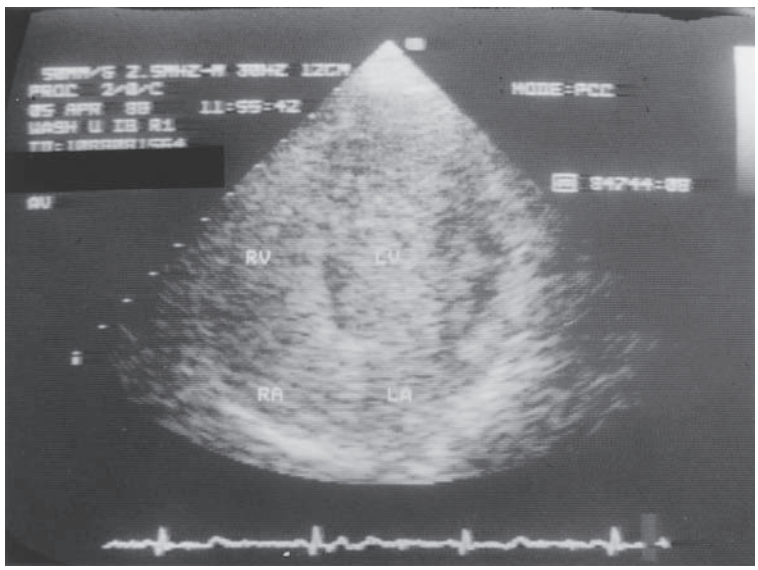


C

Figure 75-6 Echocardiographic images using saline contrast. **A.** Before contrast. **B.** Right-sided chamber opacification. **C.** Delayed high-degree left-sided chamber opacification indicative of large intrapulmonary shunt.

radiography does not reliably detect PAVMs less than 20 mm in size (Fig. 75-7), and it may miss larger PAVMs when they are located in radiographically inopportune places, such as the costophrenic sulci, the retrocardiac region, or the proximal hila (Fig. 75-8).[86]

Arterial blood gases, determined on samples drawn while the patient is supine and upright, have been advocated for screening.[85] However, this technique has not proved useful. Various combinations of shunt measurement utilizing albumin microspheres labeled with technetium-99m, Pa_{O_2} on room air, shunt measurement in subjects breathing 100% oxygen, and erect oxygen saturation measurement have been utilized, but all have insufficient sensitivity, specificity, or both.[14,78,112–114]

Contrast echocardiography is more sensitive than symptoms, plain radiography, measurements of Sa_{O_2}, Pa_{O_2} on room air, and Pa_{O_2} breathing 100% oxygen.[14,63] It is positive in 55% to 73% of those with HHT,[56,112] and may be the only positive screening study in 31% of patients.[113] Eighty percent or more will have persistently positive contrast echo findings after undergoing embolotherapy.[115] In patients with diffuse small PAVMs or telangiectasia, transesophageal contrast echocardiography may provide the definitive evidence.[116] On the basis of the preceding information, a screening algorithm based on contrast echocardiography and anteroposterior chest radiograph, followed by chest CT if either test is positive, is used in many centers.[63] This algorithm is based on studies in which CT without contrast was used as the "gold standard," with confirmatory pulmonary angiogram only if positive, and has been recommended by the international HHT working group.[103]

The sensitivity and specificity of chest CT are unknown, although this modality is significantly more sensitive than are chest radiographs.[85] One early study suggested that CT enabled identification more than 98% of PAVMs and was superior to pulmonary angiography.[117] CT has also been advocated for pretherapy planning.[118]

Our center for many years followed a scheme in which patients with HHT are screened with saline contrast echocardiography. Those with positive findings underwent pulmonary angiography. This approach identified PAVMs in 57% of patients screened. In combination with our observations regarding false-negative chest CT, we believed the frequency of PAVMs identified, greater than in any other series, justified this approach. In ~15% of patients with angiographically detectable PAVMs using this approach, no therapeutic embolization results. These PAVMs represent an opportunity to more fully understand the natural history and complication rates of PAVMs.[64]

Technology has an impact on this approach. Contrast-enhanced 64-row multidetector array chest CT with reconstruction is now used in our center as an alternative to diagnostic angiography (Video 75-2). Results to

Video 75-2 CT angiogram of right lower lobe pulmonary arteriovenous malformation in patient with hereditary hemorrhagic telangiectasia. *(Used with permission of Dr. Daniel Goodenberger) Access at www.fishmansonline.com*

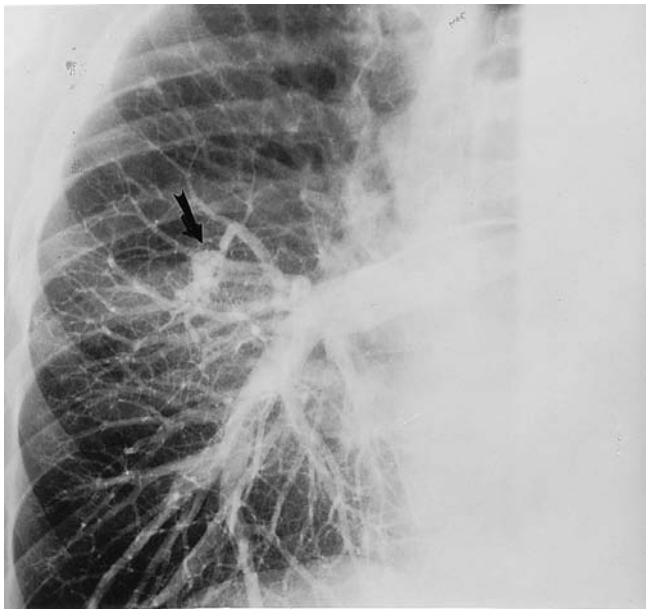


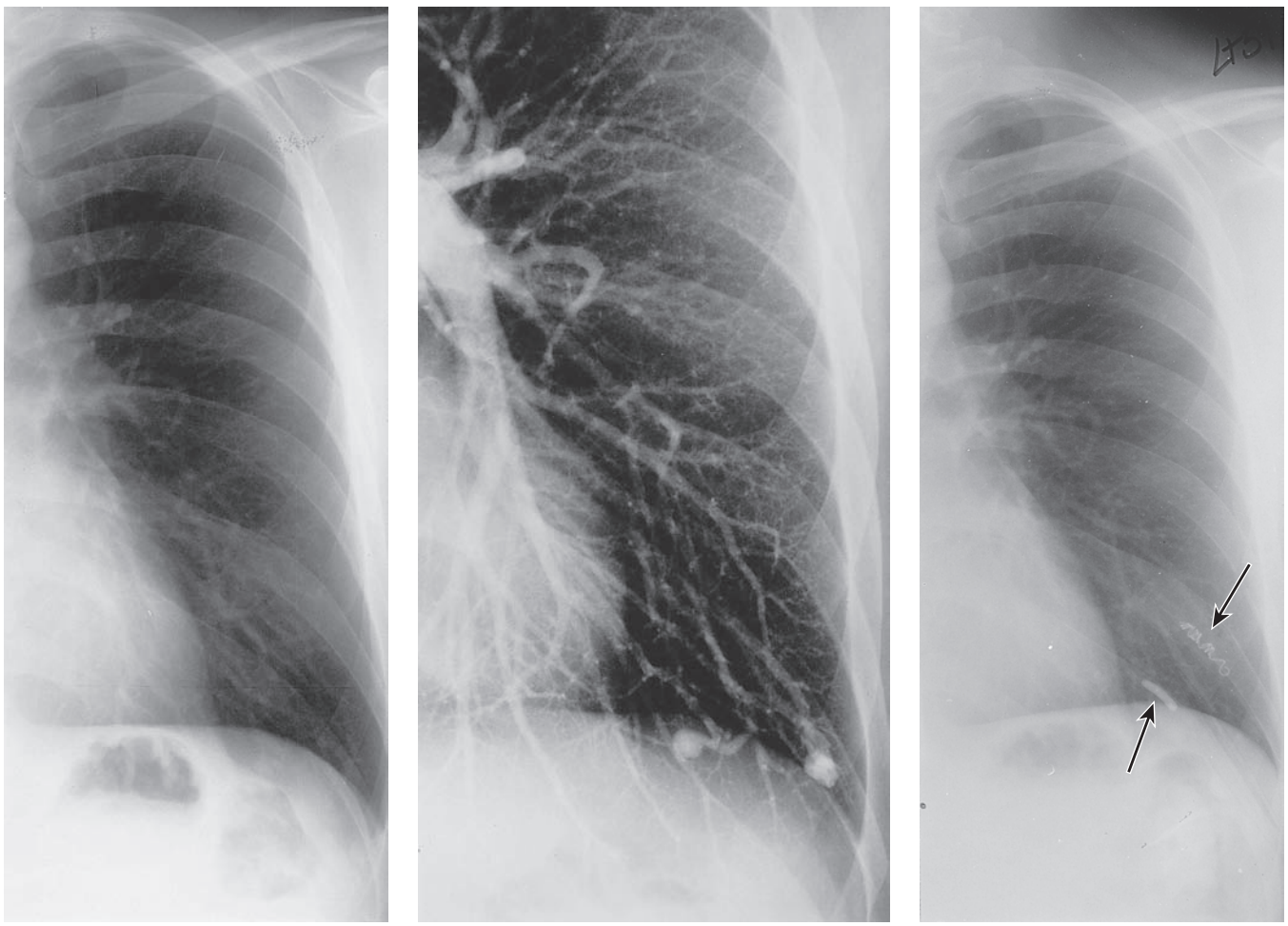
Figure 75-7 Example of PAVM not seen on standard chest radiography. Right pulmonary angiogram showing small PAVM *(arrow)*.

date suggest that this technique is at least equivalent to pulmonary angiography (Fig. 75-9).

TREATMENT

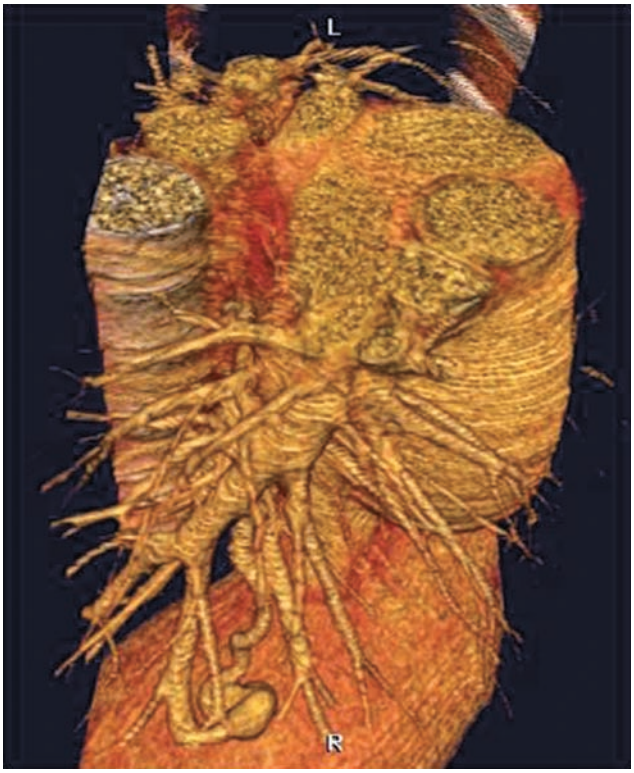
The earliest treatment of PAVMs was thoracotomy and resection. Pneumonectomy was the first successful surgical approach, reported in 1942.[119] As thoracic surgery improved, the extent of resections diminished; by 1959, local excision was the procedure of choice.[62] Surgical removal of a PAVM inevitably results in loss of viable lung tissue, a problem for patients with multiple PAVMs; the record is probably held by a patient who underwent staged bilateral thoracotomies with removal of 23 PAVMs, with substantial symptomatic improvement.[120] Thoracoscopic resection has more recently been described.[121] Although surgical mortality can be as low as 0%,[62] the general anesthesia, morbidity of thoracotomy, and loss of viable lung tissue made a new approach desirable.

Embolization of PAVMs has proved to be an excellent alternative. This procedure was first performed using homemade coils. The procedure was refined and perfected at Johns Hopkins by Terry et al.[122] The original procedure utilized silicone balloons unless the feeding vessel was larger than 9 mm in diameter, in which case embolization



A B C

Figure 75-8 Example of patient with PAVMs that were not seen on standard radiography but were detected by echocardiographic screening. **A.** Before embolization. **B.** Angiogram. **C.** After embolization, showing both coil and balloon emboli.



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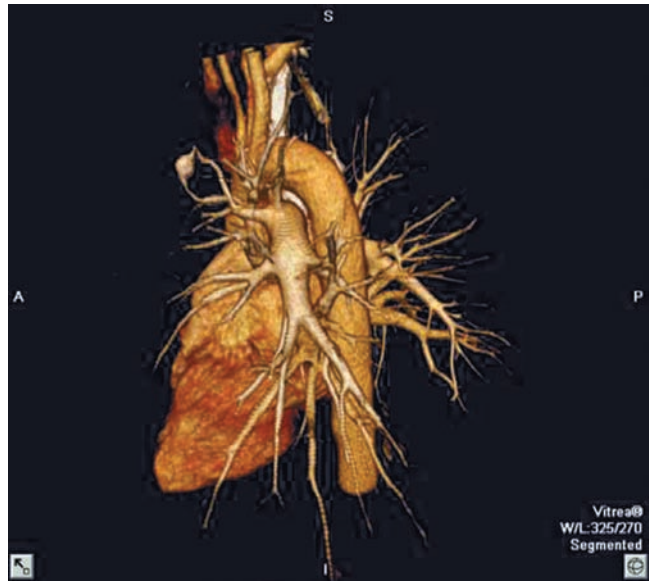

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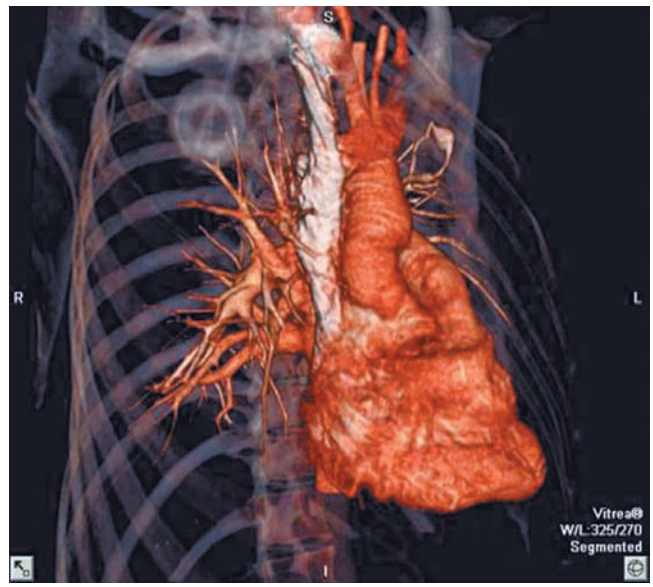


C

Figure 75-9 **A–C.** Three-dimensional reconstruction of PAVMs on 64-row multidetector array CT.

coils with thrombogenic Dacron tails were used (Fig. 75-10A–C).[55] Generally, all PAVMs with feeding vessel diameter of 3 mm or larger are embolized. Results have been very good, with success rates greater than 93%,[123] and embolization therapy is now the procedure of choice, with an apparent mortality of 0%, few serious complications, minimal loss of pulmonary parenchyma, and no exposure to anesthesia or thoracotomy. Silicone balloons are no longer available and are of historic interest only. Recently, many interventional radiologists have preferred using vascular plugs for larger feeding vessels, reserving coils for small or more tortuous vessels. Advantages include occlusion with a single device, allowing decreased operative time, and possible reduction in reperfusion (Fig. 75-11A–C).[124]

Pregnant women requiring urgent embolotherapy because of hemoptysis or hemothorax may safely undergo embolization, with radiation exposure to the fetus acceptable after 16 weeks of gestational age, with successful pregnancy outcome.[77] Absent those complications, embolotherapy may be deferred until the patient is postpartum.

Embolotherapy may also be performed safely and effectively in children.[125]

There are some limitations. The feeding vessel must be 2 to 3 mm in diameter or larger. It is technically feasible to embolize most PAVMs, but occasionally this is not possible. All but three patients in our 24-year experience have been able to be treated with embolotherapy (2/132 in the most recent series).[56] A majority will have persistent intrapulmonary shunt and should receive predental antibiotic prophylaxis.[115]

Reperfusion of the embolized vessel may occur in up to 15%.[80,126,127] This may require repeated embolotherapy. The current standard is follow-up by CT at 6 months, and if negative, every 3 years thereafter.[103]

While observations documenting serial growth of small PAVMs are somewhat limited, there is published evidence to support their growth with time.[12,40,60,80,128,129] Progression of PAVMs appears more likely in those with multiple PAVMs.[75] It has been suggested that patients with treated PAVM need follow-up every 5 years to detect growth of small PAVMs that could become large enough to cause paradoxical embolization and stroke.[103]

In general, successful embolization of most or all visible PAVMs results in abatement of hypoxemia and its complications,[128,130] but a

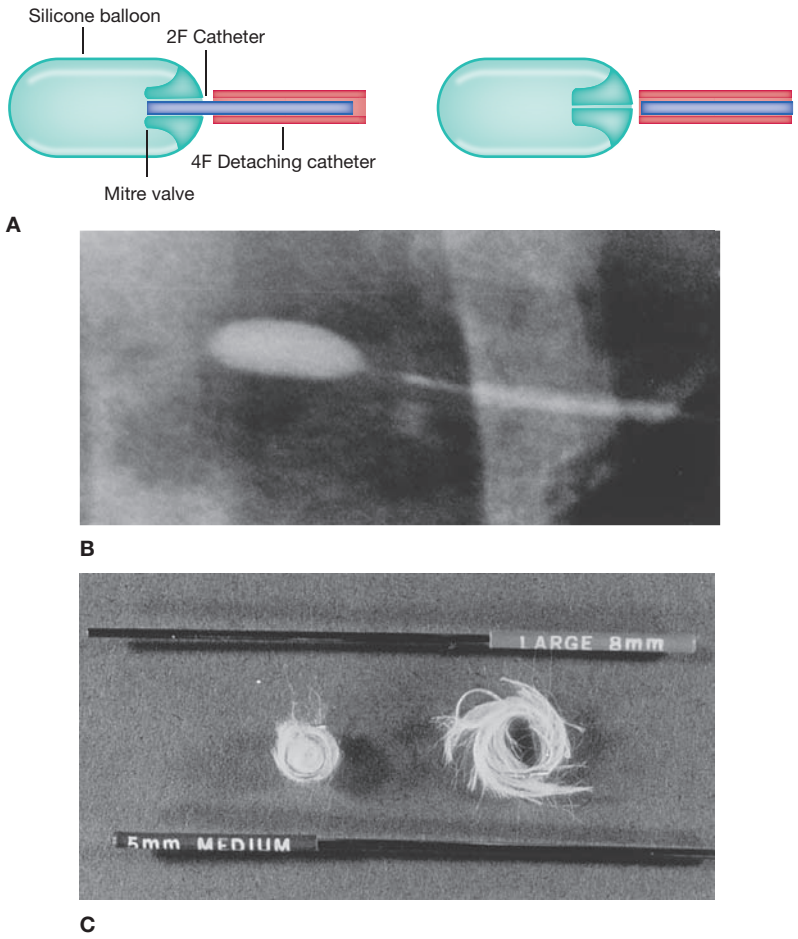


Figure 75-10 Embolotherapy devices. **A.** Detachable balloon mechanism from catheter. **B.** Fluoroscopic image of balloon in vivo. **C.** Embolization coils of two sizes.

small number of patients have diffuse small PAVMs not amenable to embolization.

Occlusion of all PAVMs with feeding vessels 3 mm or larger greatly reduces the risk of embolic stroke. Complex PAVMs must have all feeding vessels embolized for success. Embolotherapy may reduce the risk of brain abscess, but abscess may recur even after successful therapy.[129] Although no data regarding efficacy exist, standard American Heart Association endocarditis guidelines for antibiotic prophylaxis before embolotherapy is recommended.[103] Because of the frequent observation of small persistent left-to-right shunt demonstrated by echocardiography even after successful embolotherapy, antibiotic prophylaxis is recommended for dental and other surgical procedures.[103]

In general, those PAVMs which may feasibly be embolized should be occluded at or around the time of discovery, as immediate embolotherapy on detection results in improved life expectancy and quality-adjusted survival.[131]

Serious complications of embolotherapy are rare. Because of the potential for systemic air and particulate embolism, all intravenous tubing is equipped with micropore filters and embolization precautions are taken. Air embolism during the procedure is rare, occurring in less than 5% in one series. It is generally manifested by perioral paresthesias or angina without permanent effect.[55] The most common postembolization symptom is pleurisy, and has been reported at rates ranging from 10% to 31%.[55,80,132] The onset may be delayed for up to 17 days in our experience, and severity may range from mild pain to a level of discomfort requiring hospitalization. These episodes are sometimes accompanied by large pleural effusions. The effusions and resulting hypoxemia always resolve within several weeks. Other complications have included migration of an embolic device, PAVM perforation, TIA, early cerebral infarction after embolization, and paradoxical embolization of a device during deployment (4%).[128,129,132–134]

Diffuse PAVMs resulting in hypoxemia are difficult to treat with embolization therapy. Multiple embolizations tend to result in modest improvement at best, and posttherapy complications may be severe.[53,135] Those which are not amenable to embolotherapy represent a particularly difficult problem. A few such cases have been successfully treated with lung transplantation.[136,137]

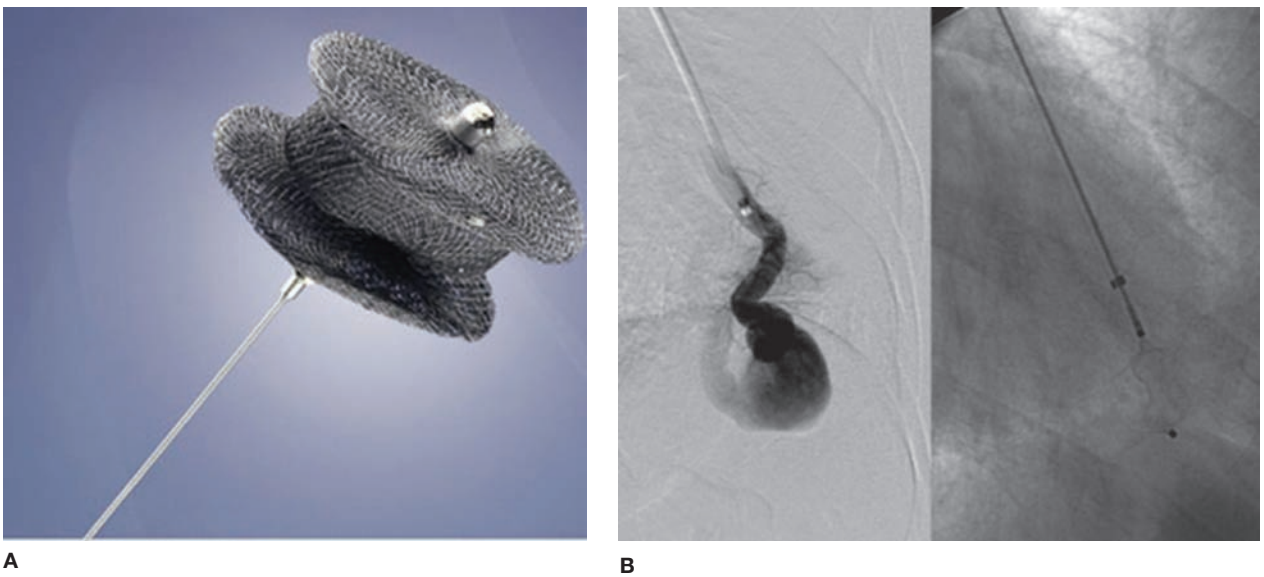
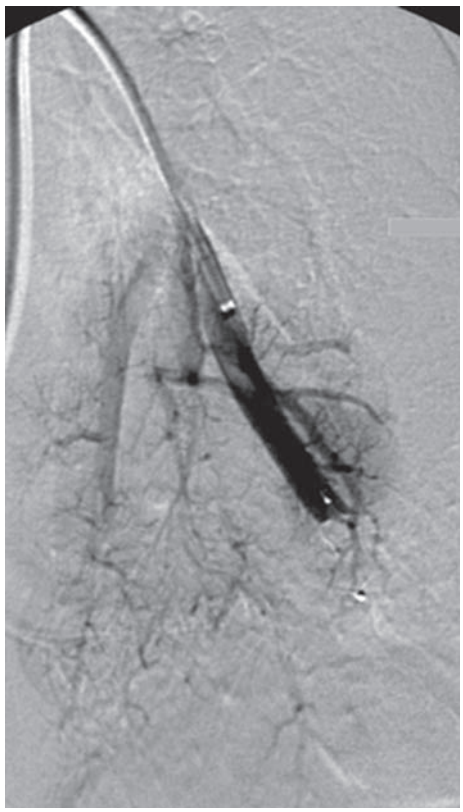


Figure 75-11 Vascular occlusion plugs. **A.** Amplatzer vascular occlusion plug. **B.** Pulmonary AVM before and after deployment. *(continued)*



C

Figure 75-11 *(Continued)* **C.** Pulmonary angiogram after deployment.

FOLLOW-UP AND PROGNOSIS

Patients with HHT and screening negative for PAVM should have repeat screening (a) after puberty; (b) after pregnancy; (c) within 5 years of planned pregnancy; and (d) every 5 to 10 years routinely.[103]

Early reports suggested a high mortality for patients who did not undergo treatment of PAVMs. Examination of family trees in older reports impresses one with the frequency of death from meningitis, brain abscess, and stroke. Some of this apparently high mortality may have been due to selection bias. More recent studies suggest that the prognosis may be more benign, and complications may be nonexistent when PAVMs are discovered by screening.[75] In one series, mortality was approximately 10%. Two-thirds of deaths were due to cerebrovascular accident, and all of these patients were cyanotic and polycythemic.[40]

In summary, patients with PAVM can be successfully treated, with resolution of essentially all symptoms and substantial reduction in risk of complications. Embolotherapy is the treatment of choice for most patients. The relatives of patients with PAVMs or HHT should be screened with contrast echocardiography to prevent central nervous system complications as the first manifestation of disease. Patients with PAVMs should be fully educated about their diagnosis, potential clinical complications, and the often hereditary nature of the problem. Educational materials for patients with HHT, and the location of specialized centers for managing HHT and PAVM are available from the HHT Foundation International at http://hht.org. Caregivers are also urged to consult the website for updated recommendations.

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PART 9

Disorders of the Pleural Space

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CHAPTER 76

Nonmalignant Pleural Effusions

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INTRODUCTION

Nonmalignant pleural effusions develop as a consequence of diverse extrapleural conditions that secondarily affect the pleural space. These disorders include systemic diseases (e.g., lupus), disorders of individual organ systems (e.g., chronic pancreatitis, congestive heart failure [CHF]), trauma and surgery, and iatrogenic interventions (e.g., drug related). Pleural fluid (PF) collects by one or more mechanisms: (1) pleural injury that causes increased pleural membrane permeability and protein-rich exudates, (2) increased intravascular hydrostatic forces and/or decreased oncotic forces that cause protein-poor transudates, and (3) extravasation of fluid from lymphatic or vascular structures or from an adjacent body compartment into the pleural space.[1]

Determining the etiology of a pleural effusion requires a sequential approach that begins with a detailed history and physical examination. Exposures and past occupations (e.g., tuberculosis, asbestos), underlying known conditions (e.g., rheumatoid arthritis [RA], CHF, pneumonia), and subtle symptoms related to a disorder not yet diagnosed (e.g., muscle weakness from myositis) may suggest the probable cause of an effusion. A thorough physical examination may detect abnormal nails with lymphedema suggesting yellow nail syndrome (YNS) or a malar rash indicating lupus pleuritis. Often the history and physical examination provide more diagnostic information than PF analysis or pleural biopsy, which may be nondiagnostic.

A differential diagnosis formulated from the history and physical examination guides a focused evaluation with imaging studies. Initial studies may examine nonpleural structures rather than the pleural space itself. Echocardiography, for instance, may establish CHF or pericarditis as the cause of a pleural effusion. Abdominal computerized tomography (CT) may detect hydronephrosis that underlies urinothorax. Among pleuropulmonary imaging studies, ultrasonography (US) and chest CT with pleural phase contrast enhancement provide detailed examinations of the pleural space, lung, diaphragm, and mediastinal structures that surpass the diagnostic value of standard chest radiography.

Portable US is highly sensitive and accurate for detecting and measuring the volume of PF.[2] It also gauges pleural thickness and defines pleural masses, loculations, and the viscosity of PF for diagnostic purposes, guiding thoracentesis and pleural biopsy. Chest CT allows imaging of interlobar and paramediastinal pleural surfaces beyond the reach of US in addition to associated lung abnormalities.[3] Like US, CT imaging can guide pleural biopsy and interventions to drain the pleural space. CT angiography allows the diagnosis of pulmonary embolism, which is increasingly recognized as a cause of exudative effusions.[4]

Thoracentesis is indicated for all patients with an undiagnosed pleural effusion in the presence of >1 to 2 cm of layering fluid detected by imaging studies unless CHF is the probable cause. Categorization of the fluid as a transudate or exudate simplifies the differential diagnosis, because conditions associated with PF formation tend to cause effusions of one of these types. Light's three-criteria rule has been the traditional approach for identifying exudative effusions (Table 76-1). Although the Light's criteria rule has a high sensitivity; it requires blood tests, suffers from mathematical coupling with two of its criteria, both using PF lactate dehydrogenase (LDH), and misclassifies with its modest specificity up to 30% of patients, when any one of the three test results return values close to its cutoff point (e.g., 15% of malignant effusions misclassified as transudates).[5] Alternative rules listed in Table 76-1 avoid some of these limitations and perform equally well as Light's criteria.[6–9] A battery of routine and specialized PF tests may be indicated depending on the pre-thoracentesis differential diagnosis (Table 76-2).

Pleural biopsy provides diagnostic value for patients with exudative effusions who remain undiagnosed after thoracentesis. Approaches to pleural biopsy include closed needle biopsy with an Abrams needle, which is indicated when tuberculous pleuritis is likely, image-guided percutaneous pleural biopsy, and biopsy by video-assisted thoracoscopic surgery (VATS), medical thoracoscopy, or pleuroscopy.[10,11]

CAUSES OF PLEURAL EFFUSIONS THAT ARE USUALLY TRANSUDATES

A number of causes of transudative pleural effusions have been recognized. Each is discussed below.

CONGESTIVE HEART FAILURE

CHF represents the most common cause of transudative effusions, present in 50% to 90% of patients hospitalized for CHF.[12,13] PF accumulates when elevated left atrial pressure generates pulmonary edema that provokes leakage of interstitial lung water down a hydrostatic pressure gradient into the pleural space.[14,15] Left ventricular failure has been considered an essential factor for producing CHF-related effusions.[16] However, small pleural transudative effusions may occur in ~20% of patients with pulmonary arterial hypertension and isolated right ventricular failure,[17] which may develop because raised systemic venous pressures increase fluid filtration from chest wall veins into the pleural space and/or impede egress of PF via parietal pleural lymphatics.

Pleural effusions due to CHF are usually bilateral (60%–85%); unilateral effusions are more commonly right sided in a 2-to-1 right-to-left ratio.[18] Although CHF is the most common cause of bilateral pleural effusions,[18] bilateral effusions in the absence of cardiomegaly suggest a malignant etiology. PF may collect in interlobar fissures and produce the imaging finding of a "pseudotumor."

Typical presentations of CHF warrant a trial of diuresis and monitoring for resolution of PF. Thoracentesis is indicated for evaluating atypical clinical presentations and failure of PF to resolve. PF

TABLE 76-1 Rules to Classified Pleural Fluid as Exudate Versus Transudate

Rule	Criteria
Light's criteria	PF/serum protein ratio >0.5, or PF/serum LDH ratio >0.6, or PF LDH > two-thirds upper limits of the laboratory's normal serum LDH
Rule that does not require serum tests	PF protein >2.9 g/dL, or PF cholesterol >45 mg/dL, or PF LDH >0.45 times upper limit of the laboratory's normal serum LDH

LDH, lactate dehydrogenase; PF, pleural fluid; S, serum.

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TABLE 76-2 Pleural Fluid Test Results and Commonly Associated Conditions

Test	Result	Most Common Suggested Conditions
Erythrocytes	PF/S HCT >0.5	Hemothorax
Neutrophils	>10,000/μL	Parapneumonic effusion, lupus pleuritis, acute pancreatitis
	>50,000/μL	Empyema
Lymphocytes	>85–95%	TB pleurisy, sarcoid, chronic rheumatoid pleurisy, yellow nail syndrome, chylothorax
Eosinophils	>10%	Hemothorax, pneumothorax, benign asbestos pleurisy, pulmonary infarction, coccidioidomycosis, paragonimiasis and other parasites, drug-induced pleurisy, duropleural fistula, Churg–Strauss syndrome, sarcoidosis, TB pleurisy
Protein	<1 g/dL	Peritoneal dialysis, CVC erosion, duropleural fistula
	>4 g/dL	TB pleurisy
LDH	>1000 IU/L	Bacterial empyema, paragonimiasis, amebic empyema, septic emboli, rheumatoid pleurisy
Glucose	PF/S <0.5	Complicated parapneumonic effusion, chronic rheumatoid pleurisy, paragonimiasis, amebic empyema, esophageal rupture, TB pleurisy, lupus pleuritis, urinothorax
	PF/S >1	Peritoneal dialysis, CVC erosion
pH	<7.30	Esophageal rupture, chronic rheumatoid pleurisy, complicated parapneumonic effusion, paragonimiasis, amebic empyema, TB pleurisy, lupus pleuritis, urinothorax, pancreaticopleural fistula
Amylase	Elevated	Esophageal rupture, acute pancreatitis, pancreaticopleural fistula
Cholesterol	>200 mg/dL	Cholesterol effusion
Creatinine	PF/S >1	Urinothorax
Beta 2 transferrin	Elevated	Duropleural fistula, ventriculoperitoneal shunt migration
Triglycerides	>110 mg/dL	Chylothorax, CVC erosion if lipids infused
Chylomicrons	Present	Chylothorax
Bilirubin	PF/S >1	Biliopleural fistula
Glycine	PF/S >1	Glycinothorax
ADA with lymphocytosis	>40 IU/dL	TB pleurisy

ADA, adenosine deaminase; CVC, central venous catheter; TB, tuberculous.

is characteristically a transudate. Up to 30% of effusions, however, fulfill Light's criteria for an exudate for several possible reasons.[19,20] Most commonly, a coexisting condition that causes exudative effusions, such as pneumonia or pulmonary embolism, is the actual cause of the effusion.[21] Less commonly, diuretic therapy for CHF promotes more rapid reabsorption of intrapleural fluid as compared with protein and LDH, which creates a concentrating effect on PF. Finally, some CHF-related effusions have PF erythrocyte count >10,000/μL, which causes sufficient release of LDH from red cell autolysis to fulfill Light's criteria for an exudate.[22] Several strategies exist to determine that an exudative effusion in the setting of CHF is due to heart failure rather than a comorbid condition (Table 76-3).

Pleural effusions due to CHF gradually resolve as cardiac performance improves with therapy. Patients with large, symptomatic effusions may benefit from therapeutic thoracentesis when a response to cardiac therapy is delayed. Rarely, effusions in patients with refractory heart failure may require pleurodesis to manage PF-related respiratory symptoms, but outcomes data for this approach are limited.[30] Placement of a tunneled catheter for intermittent drainage at home provides additional palliative support.[31–33]

HEPATIC HYDROTHORAX

Hepatic hydrothorax defines a transudative effusion in a patient with cirrhosis and portal hypertension in the absence of another explanation for the effusion.[34] Although only 6% of patients with cirrhosis and portal hypertension have clinically apparent hepatic hydrothorax,[35–37] 15% of cirrhotics have evidence of effusions when examined by CT or US.[38]

Hepatic hydrothorax develops when ascites accumulates, raising intraperitoneal pressure that herniates blebs of peritoneum into the

TABLE 76-3 Rules for Evaluating Heart Failure–Related Effusions Misclassified as Exudates

Test Results	Comments
• PF-to-S albumin gradient >1.2 g/dL • PF/S albumin ratio <0.6 • PF-to-S protein gradient >3.1 g/dL (less accurate than the albumin-based tests above)[20,23]	These three rules more accurately establish CHF as cause of an effusion for patients with a high pretest probability of CHF as compared with Light's criteria[20,24]
• Serum assay of amino terminal fragment of proBNP (NT-proBNP) >1500 pg/mL CHF-related <400 pg/mL CHF-unrelated	More accurate than protein or albumin-based testing rules[18,23,25–27]
• Pleural fluid assay of NT-proBNP >1500 pg/mL CHF-related <400 pg/mL CHF-unrelated[18]	High accuracy but no advantage over serum NT-proBNP[23,25–28]
• Pleural fluid BNP >400 pg/mL CHF-related <100 pg/mL CHF-unrelated	Lower discriminative properties as compared with NT-proBNP[29]

BNP, brain natriuretic peptide; PF, pleural fluid; S, serum.

chest through small diaphragmatic stomata. When these blebs burst, ascites flows from the relatively high-pressure peritoneal space into the lower-pressure pleural space.[39] Because stomata occur more commonly in the tendinous portion of the right hemidiaphragm as compared with the thicker and more muscular left hemidiaphragm, 80% of hydrothoraces are right sided, 18% left sided, and 2% bilateral.[40] Although 20% of patients will not have clinically apparent ascites because most of the ascites fluid has decompressed into the pleural space,[41] US or CT will demonstrate residual ascites in nearly all patients.[42]

The clinical presentation of hepatic hydrothorax ranges from an incidental radiographic finding to varying degrees of dyspnea, which depends on the volume of PF, the volume of ascites that stiffens the diaphragm, and presence of underlying cardiopulmonary disease. Rapid-onset respiratory failure may rarely occur when ascites suddenly ruptures into the pleural space.[43]

Diagnosis requires thoracentesis to profile PF as transudative and exclude other causes of pleural effusion. Thoracentesis presents a low risk of complications despite the presence of cirrhosis and coagulopathy.[44] PF is transudative by Light's criteria in 90% of patients,[19] although PF protein levels are usually higher than the concomitant protein concentration in the ascites fluid because of a concentrating effect.[45] Diuretic therapy may convert a transudative pleural effusion to an exudate akin to the diuretic effect in CHF.[19] Correct classification as a transudate may require calculation of protein and/or albumin gradients as commonly done for CHF patients (Table 76-3).[20] Any suspicion of a true exudate, however, warrants evaluation for an empyema or tuberculosis. Although injection of a radionuclide tracer into ascites fluid may detect tracer flow from the abdomen to the chest, scintigraphy confirmation of the diagnosis is usually unnecessary.

Treatment centers on limiting sodium retention and lowering portal vein pressures. Therapeutic thoracentesis provides only transient relief of dyspnea because effusions rapidly recur making paracentesis preferred initial management for symptomatic patients. Chest tube drainage is avoided because of risks of massive fluid loss and poor healing of the chest wall tract after chest tube removal.[46–48] Transjugular intrahepatic portosystemic shunts may decrease PF in 88% of patients, but the 1-year survival is only 50%.[49–55] Hepatic hydrothorax does not represent a contraindication for liver transplantation.[53] Failing other interventions, VATS for closure of diaphragmatic fenestrations and performing talc pleurodesis may benefit some patients, but the risks of this procedure are high.[56–58] Chemical pleurodesis by chest catheter or VATS is challenging because of the rapid reaccumulation of PF that prevents apposition of pleural membranes.[59–61] Tunneled pleural catheters may provide palliation.[62] Spontaneous infection of a hydrothorax represents an important complication being found in 15% of patients admitted with cirrhosis and pleural effusions.[38,42] PF features of this condition include a PF neutrophil count >250 cells/μL with a positive PF culture or a PF neutrophil count ≥500 cells/μL with a negative culture in the absence of pneumonia.[49]

■ CONSTRICTIVE PERICARDITIS

More than 50% of patients with constrictive pericarditis develop a pleural effusion that can be the presenting manifestation of pericardial disease.[63–65] The pathogenesis of the effusions is unknown but may relate to migration of coexisting ascites into the pleural space or compromised left ventricular function that causes a CHF-related effusion. Both of these mechanisms would cause a transudative effusion.[63] Exudative effusions[65] and chylothoraces,[66,67] however, can also occur. PF may be bilateral or unilateral, with equal side distribution when unilateral.[64]

■ RENAL

Nephrosis

A transudative pleural effusion may develop in patients with nephrotic syndrome because of severe hypoalbuminemia. The effusions are typically small and bilateral in distribution.[68] Larger effusions require the exclusion of pulmonary thromboembolism (PTE) because of the high risk of this condition in nephrosis.

Urinothorax

Urinothorax occurs when urine dissects from the retroperitoneal space into the pleural space most often as a consequence of obstructive uropathy at the level of the bladder or urethra. Obstruction at the renal or ureteral level may produce urinothorax in the presence of a nonfunctioning contralateral kidney.[69] Other causes include kidney biopsy, renal transplantation, lithotripsy, failed tube nephrostomy, urinary tract malignancies, retroperitoneal trauma, and surgical complications.[69,70] Patients present with mild to moderate respiratory symptoms due to the space occupying effects of the effusion, which are usually unilateral.[69,71]

PF looks and smells like urine and meets definitions of a transudate by a low protein concentration. The PF LDH, however, is often elevated into the exudative range.[70,72] The PF pH[73] and glucose[74] values may be low, making urinothorax the only cause of a low pH and low glucose transudate in the absence of systemic acidemia and hypoglycemia. The PF/serum creatinine ratio is greater than 1 (mean value >10 in reported cases) in all instances, although the specificity of this finding is less than 100%.[70] Elevated ratios in other conditions, however, are closer to 1. Renal scintigraphy can demonstrate tracer flow from the urinary tract to the pleural space to establish the diagnosis. Urinothoraces typically resolve with relief of urinary obstruction.

Peritoneal Dialysis

Pleural effusions develop as a consequence of peritoneal dialysis (PD) in 2% to 10% of patients[75,76] with 88% being right sided and a minority bilateral.[76] Effusions range in size from small to moderate with 75% of patients having dyspnea,[76] but effusions may be massive.[77] PF forms due to the migration of dialysate from the relatively high-pressure peritoneal cavity into the low-pressure pleural space.[78] Clinicians may note decreased effectiveness of ultrafiltration as the first sign of migration of dialysate into the pleural space.

PF is transudative with a PF protein <0.5 g/dL and glucose >200 to 2000 mg/dL.[79,80] PF-to-serum glucose gradients range from 1 mg/dL to 1885 mg/dL with 20% of patients having gradients <50 mg/dL.[81] The PF/serum glucose ratio is always >1.[81] Peritoneal scintigraphy using technetium-99 m tagged macroaggregated albumin (28–30) or Tc-99 m sulfur colloid detects the flow of dialysate into the pleural space.[75,77,82] Management begins with reduction of dialysate volume or temporary discontinuation of PD.[75,83,84] Discontinuation of PD for 4 to 6 weeks may allow diaphragmatic conduits to heal.[85] Up to 58% of patients may resume PD without recurrence of their effusions.[86,87]

■ CENTRAL NERVOUS SYSTEM

Cerebrospinal Fluid Leakage into the Pleural Space

Cerebrospinal fluid (CSF) can leak into the pleural space when a duropleural fistula forms from a malignancy or after spinal surgery (particularly cervical laminectomy),[88] thoracic surgery,[89] or blunt or penetrating trauma.[90] Symptoms include dyspnea, meningitis,[91] CSF pressure headaches,[91] and various neurologic symptoms.[89,91] PF appears as clear as CSF with essentially no cells and a PF protein <1 g/dL, low LDH, and glucose and pH values similar to serum. Beta-2 transferrin is a protein found in CSF and inner ear perilymph that has a sensitivity and specificity of 100% and 95%, respectively for establishing CSF-related effusions.[92] Duropleural fistulae rarely heal spontaneously and present risks for CNS infection and pneumocephalus. CT myelography can visualize the fistula tract in preparation for surgical repair.[89,93]

Ventriculoperitoneal Shunts

Pleural effusion is a rare complication of ventriculoperitoneal (VP) shunting that occurs most commonly in children but has been reported in adults.[94] PF accumulates either from migration of the shunt catheter into the thorax[94–100] or from flow of CSF ascites into the pleural space.[95,100–102] PF analysis demonstrates no cells, a low protein and LDH content, and presence of beta-2 transferrin.[102,103] A radionuclide shuntogram can confirm the diagnosis.[104] Reports also exist of fibrothorax,[105] tension hydrothorax,[106] bronchopleural fistulae,[107] and empyema[108] subsequent to migration of a VP shunt.

■ PLEURAL

Trapped Lung

Remote pleural inflammation that causes fibrotic membranes to form on the visceral pleura can prevent lung expansion and create negative intrathoracic pressures that cause a hydrostatic gradient for PF formation.[109,110] A trapped lung should be suspected when PF drains incompletely by thoracentesis or recurs quickly and when a hydropneumothorax forms after thoracentesis with a similar configuration of the lung margin as compared with the pre-thoracentesis chest radiograph. Because of the chronic nature of the effusion, most patients are asymptomatic. The PF is usually a transudate. If sampled during the early formation of a trapped lung when inflammation may be present, the effusion may be exudative.[111] Pleural manometry performed during thoracentesis demonstrates rapid drops in measured pleural pressure as fluid is removed with calculated lung elasticity values >14.5 cm H_2O/L. A CT scan shows thickened visceral pleural membranes.[110] For patients with dyspnea, surgical decortication can be considered to allow lung reexpansion. Patients must be evaluated thoroughly for other causes of dyspnea, considering the difficulty and risks of decortication for established trapped lungs.[109]

■ PROCEDURAL IATROGENOSIS

Central Venous Catheter Migration

Initial misplacement of central venous catheters into the mediastinum or subsequent erosion of catheters through vascular walls allows infusates to flow into the mediastinum and subsequently the pleural space.[112–117] The resulting unilateral or bilateral pleural effusions vary in size depending on the rate of fluid infusion. Unilateral effusions may be ipsilateral or contralateral to the catheter insertion site.[112] Various catheter configurations apparent on chest radiographs and CT studies may identify patients at risk for catheter erosion.[112,118,119] The PF profile reflects the nature of the infusate with glucose containing solutions having a PF/serum glucose ratio >1.[112] Infusion of lipid-containing formulations causes increased pleural triglyceride levels. Most infusates are low in protein so PF protein is <1.0 g/dL. Infusion of chemotherapeutic agents into the pleural space may cause an inflammatory exudate and acute chest pain.[120]

Glycinothorax

Right-sided pleural effusions may rarely occur in patients undergoing bladder instrumentation with bladder irrigation using glycine solutions.[121,122] Perforation of the bladder allows glycine solutions to pass through the peritoneal cavity into the pleural space. The PF is a sanguineous transudate with a high concentration of glycine.

■ VASCULAR

Pleural effusions may develop in 13% of patients with isolated right heart failure due to pulmonary arterial hypertension.[17] Most of the effusions are trace to small (63%) and right sided in 58% and bilateral in 26%. Of the four patients reported with thoracentesis, all of the effusions were transudates.

Pulmonary veno-occlusive disease is a rare condition associated with specific pathologic changes of the postcapillary (venous) pulmonary circulation that produce pulmonary arterial hypertension.[123] Chest CT commonly detects unilateral or bilateral pleural effusions in this condition.[123–127] The nature of the effusions is uncertain but presumed to be transudative because of the raised pulmonary venous hydrostatic forces. Pulmonary capillary hemangiomatosis has also been reported to cause pleural effusions and presumed to be transudative in nature.[124,128]

CAUSES OF PLEURAL EFFUSIONS THAT ARE USUALLY EXUDATES

A number of causes of exudative pleural effusions have been recognized. Each is discussed below.

■ PATHOGEN RELATED

Parapneumonic Effusions

Twenty to 57% of patients hospitalized for community-acquired pneumonia develop a parapneumonic effusion,[129,130] as defined by a pleural effusion caused by pneumonia. PF forms when inflammatory cells migrate to the pleural space from an adjacent zone of lung infection and release proinflammatory mediators that alter pleural membrane permeability and recruit additional inflammatory cells.[131–133] An influx of protein-rich fluid creates an initially sterile, free-flowing effusion. Subsequent invasion of bacteria promotes a procoagulant effect in PF, which generates fibrin[132–134] that deposits on pleural surfaces and begins the formation of intrapleural loculations and a pleural rind. Infected PF eventually evolves into pus and a frank empyema. Although the development of an empyema represents a continuous sequence of pathophysiologic events, it has been arbitrarily described as a three-stage process to assist management (Table 76-4).[135] Parapneumonic effusions have also been classified as "uncomplicated" (treatable by antibiotics alone) or "complicated" (pleural space drainage is required).[136,137]

The incidence of pleural infections has increased during the last several decades across all age groups[138–140] with 30-day mortality that ranges from 5% to 27% depending on the extent of intrapleural suppuration, patient age, and presence of comorbid conditions.[138,140–142]

TABLE 76-4 Stages of an Empyema

Exudative	Increased permeability of pleural membranes with influx of inflammatory cells and protein-rich exudate. Most patients will respond to antibiotics without pleural drainage.
Fibrinopurulent	
Early Fibrinopurulent	Increased procoagulant activity in the pleural space promotes deposition of fibrin with early septation of the effusion. Pleural fluid becomes more viscous with increasing LDH and decreasing glucose and pH. Some patients may respond to antibiotics alone but drainage becoming increasingly likely.
Late Fibrinopurulent	Extensive fibrin deposition on pleural membranes causing loculations and pleural rind. Viable bacteria present with markedly increase PF LDH and low glucose and pH. Pleural fluid appears macroscopically purulent. Pleural fluid drainage and, possibly decortication, required.
Organizing	Fibroblast proliferation generates a fibrous pleural peel that requires decortication. A trapped lung may occur if the empyema space is not obliterated.

Risk factors for parapneumonic effusions include diabetes, immunosuppression, alcoholism, cancer, poor dental hygiene, and increased severity of the index pneumonia.[130]

Signs and symptoms of a parapneumonic effusion merge with those of the underlying pneumonia with fever, productive cough, and dyspnea predominating. Pleuritic chest pain increases the probability of a parapneumonic effusion and, along with tachycardia and leukocytosis above 15,000/mm^3, increases risk that the effusion is complicated.[99] Subacute or chronic constitutional symptoms of malaise, anorexia, and weight loss with fetid breath represent characteristic findings of an anaerobic empyema. Failure of a patient with pneumonia to respond to antibiotics as expected suggests the possibility of a partially treated empyema.

Chest imaging identifies approximately 90% of clinically significant parapneumonic effusions.[143,144] Most effusions are apparent as a dependent fluid collection with a meniscus on standard two-view chest radiographs. The only radiographic sign of an effusion, however, may be obscuration of a diaphragm that may be incorrectly attributed to lower lobe consolidation.[144] Consequently, a parapneumonic effusion should be suspected and evaluated by US in the presence of a diaphragmatic silhouette sign. Presence of intrapleural air-fluid levels indicates a bronchopleural fistula with empyema. A loculated effusion in a nondependent location suggests a complicated parapneumonic effusion.

US has a higher sensitivity and specificity for detecting PF as compared with standard radiographs.[145–148] Echogenic PF and septations suggest the presence of a complicated parapneumonic effusion in the fibrinopurulent or organizing stage and thereby increasing the likelihood that drainage will be required.[149–152] Ultrasound also allows image-guidance for thoracentesis, which improves the success and safety of the procedure in the presence of pleural loculations.[153,154] Contrast-enhanced chest CT can establish the presence, location, and extent of parapneumonic effusions for patients with complex PF collections and uncertain radiographic and US findings.[3,143] Loculated empyemas with interlobar and paramediastinal fluid collections can only be imaged by chest CT. Characteristic CT findings include the "split pleura sign" (enhanced pleurae that surround a loculated effusion), pleural thickening, and increased attenuation of extrapleural subcostal fat.[143] Chest CT can also differentiate between an empyema and a peripheral lung abscess adjacent to the chest wall.[155] Ultrasound, however, is more sensitive as compared with chest CT for detecting septations.

Thoracentesis and PF analysis to provide diagnostic and therapeutic information are indicated when PF is greater than 1 to 2 cm in depth by US or decubitus radiographs.[156,157] PF may appear grossly turbid, serosanguineous, or frankly purulent. A fetid odor suggests an anaerobic empyema. Appropriate PF tests with their clinical implications are listed in Table 76-5. PF procalcitonin levels do not provide value in guiding drainage decisions.[158,159] Clinical practice guidelines recommend basing the decision to drain a parapneumonic effusion on a combination of clinical, imaging, and PF findings (see Chapter 127).[160,161]

Uncomplicated parapneumonic effusions resolve after effective antibiotic therapy for the underlying pneumonia. Although it is widely accepted that complicated parapneumonic effusions by definition require drainage of infected PF, consensus does not exist regarding the initial approach to drainage.[168] Insertion of an image-guided, small-bore (<15 Fr) intercostal catheter connected to suction and flushed with saline every 6 hours provides effective therapy for many patients.[169–171] Limited data indicate that viscous effusions that fail to drain after catheter insertion may subsequently drain with intrapleural instillation of tissue plasminogen activator (tPA) to lyse fibrin adhesions and deoxyribonuclease (DNase) to thin PF.[172–176] Up to 30% of complicated parapneumonic effusions, however, require surgical drainage either by VATS or thoracotomy, depending on the degree of loculation, extent of pleural peels and need for debridement or decortication, and operability of the patient.[177] Studies have not validated any clinical or imaging findings that reliably identify patients who are unlikely to respond to catheter drainage and should be triaged directly to surgical drainage.[163] Moreover, studies have not demonstrated advantages with surgery as a routine, first-line therapy for empyema.[178,179] Regardless of the drainage approach adopted, unnecessary delays in draining infected PF increase hospital stay, morbidity, and mortality.[180–183] Organized empyemas may require more extensive surgery to promote long-term open drainage and eventual closure of the empyema cavity.[184]

TABLE 76-5 Commonly Ordered Pleural Fluid Tests

Test	Clinical Significance
Cell count and differential	Leukocyte counts vary depending on the stage of empyema formation; frank empyemas may have low leukocyte counts because cells have undergone lysis. The effusions are neutrophil predominant although a mononuclear cell predominance may exist with partially treated parapneumonic effusions.
Protein	Defines an exudate when >3.0 g/dL. Tuberculous effusions almost invariably >4.0 g/dL. Values >7.0 g/dL suggest Waldenström macroglobulinemia, multiple myeloma, or a cholesterol effusion.
LDH	Defines an exudate in Light's criteria rule; usually >1000 IU/L in empyemas.
Microbiologic staining and culture	Microbiologic staining and culture with sensitivity blood culture bottles.[162] Cultures positive in ~60% of patients who have signs of pleural infection.[141,163]
pH and glucose	Pleural fluid pH and glucose decrease because of intrapleural bacterial metabolism and inflammatory cell activity that utilize glucose and release lactic acid.[164–166] A PF pH <7.20 and glucose <60 mg/dL suggest that a parapneumonic effusion is complicated and requires drainage.[167] The studies upon which these recommendations are based, however, have extensive limitations in design.[167]
Amylase (ordered in selected settings)	Elevated in patients with empyema secondary to esophageal rupture (elevated salivary isoenzyme of amylase); elevated in pancreaticopleural fistula (elevated pancreatic isoenzyme of amylase).

LDH, lactate dehydrogenase; PF, pleural fluid.

Tuberculous Pleurisy

Tuberculous pleurisy can occur with primary infection or as reactivation disease.[185] It accounts for 30% to 80% of all pleural effusions in developing countries and occurs in up to 30% of patients who present with pulmonary tuberculosis.[186,187] Its prevalence is lower in developed nations accounting for 1% of all pleural effusions and occurring with pulmonary tuberculosis in only 3% to 5% of patients.[186] HIV-positive patients, however, have a higher incidence of tuberculous pleurisy presenting with underlying pulmonary tuberculosis.[188] Patients with tuberculous pleurisy commonly resolve their effusions spontaneously but present within 2 years with pulmonary tuberculosis.[189,190]

PF develops from an intrapleural hypersensitivity response to mycobacterial antigens released by rupture into the pleural space of a subpleural caseous focus.[191,192] The number of viable acid-fast organisms in PF is insufficient to allow reliable diagnosis by standard PF staining and culture techniques. Patients present with

subacute symptoms characterized by cough, pleuritic chest pain, dyspnea, and fever; although some patients present more acutely simulating bacterial pneumonia and others more indolently with weight loss and fatigue. Purified protein derivative skin tests are positive in only 50% of patients but usually convert to positive within 2 months.[193,194] The effusion is usually unilateral encompassing less than two-thirds of the hemothorax.[194] Standard chest radiographs and chest CT scans detect active parenchymal tuberculosis in 20% and 80% of patients, respectively.[194,195]

Any undiagnosed exudative pleural effusion should prompt consideration of tuberculous pleurisy with highest suspicion for lymphocyte predominant effusions (>60% lymphocytes) with protein concentrations >5 g/dL.[196] Up to 17% of patients, however, have lymphocyte percentages <50%.[196] The PF cell differential may be neutrophil predominant within the first 2 weeks of symptom onset.[197] PF mesothelial cell percentages are nearly always <5%.[198] PF glucose and pH mirror serum levels although some patients have PD levels lower than serum.

PF staining for acid-fast organisms has a low yield except in the presence of HIV-infection wherein 20% may be smear positive.[199] Although PF culture has traditionally been reported to have a sensitivity <50%,[194,200,201] studies using liquid culture techniques report a sensitivity of 63% to 75%.[196,202] Sputum mycobacterial cultures may be positive in >50% of patients[196,203] with positivity of either sputum and/or PF cultures in 79%.[196]

Adenosine deaminase (ADA) is found in increased concentrations in tuberculous effusions and some other inflammatory and neoplastic pleural conditions. In regions with a high prevalence of tuberculosis, a PF ADA >40 IU/L in a lymphocyte predominant effusion confirms tuberculous pleurisy,[200,201,204–206] allowing a diagnosis for 90% of patients after a single thoracentesis.[10] An ADA value <40 IU/L adequately excludes the diagnosis in high prevalence settings.[207] In regions with low or intermediate prevalence of tuberculosis, PF ADA assay has insufficient sensitivity and specificity, and most patients with negative PF microbiologic evaluations require pleural biopsy.[10,208–210] Although elevated ADA concentrations in the pleural space represent the ADA2 isoform, ADA2-specific PF assays provide only negligible benefits over ADA.[211] Although several other biomarkers (interferon-gamma, interferon-gamma–induced protein of 10 kDa, and dipeptidyl peptidase [DPP] 4 levels in unstimulated PF) provide similar diagnostic value as compared with PF ADA,[212–216] none has comparable availability for routine use.[215,217,218] Commercially available T-cell interferon-gamma release assays performed on both blood and PF have inadequate diagnostic accuracy[219,220] as do PF nucleic acid amplification tests.[216,221,222]

Pleural biopsy may be required in complicated settings. Tuberculous granulomata are diffusely distributed over pleural surfaces, which allows up to 70% to 87% of patients to be diagnosed by closed (blind) needle biopsy using an image-guided Abrams needle technique.[194,200,200,223–226] This approach is appropriate when the pretest probability of tuberculosis is high for an undiagnosed exudative pleural effusion.[201] Six pleural biopsies are recommended.[201,224] For other patients, thoracoscopy provides a 100% diagnostic yield.[200,201,208] Biopsied pleural tissue must be cultured for acid-fast organisms and examined for organisms and granulomata. Microscopic-observation drug-susceptibility culture as compared with Lowenstein–Jensen culture has a higher diagnostic yield.[227]

Drug therapy for tuberculous pleurisy is the same as for pulmonary tuberculosis with a four-drug regimen for susceptible organisms.[228] Evidence does not support a role for adjunctive corticosteroids.[229] When examined with chest CT after chemotherapy, nearly 70% of patients will have some degree of residual pleural thickening that may contribute to measureable pulmonary restriction.[230] Some experts recommend therapeutic thoracentesis to prevent pleural fibrosis for moderate to large tuberculous effusions,[228] although evidence of benefit is uncertain.[231,232] Ultrasonographic detection of complex septated pleural space, CT evidence of extrapleural fat proliferation or loculated effusion, and long duration of symptoms at initiation of therapy may identify patients at greatest risk of pleural thickening 1 year later.[230,233]

Pleural Effusions Caused by Viral Infections

Acute viral respiratory infections may be associated with transient pleural effusions. The incidence of viral-related pleural effusions is unknown because most patients have a mild clinical course and do not undergo testing for viruses or imaging studies. Recent case series that review the chest studies of patients with documented viral pneumonias, however, demonstrate a low incidence of pleural effusions.[234–236] The presence of a pleural effusion in a patient suspected with viral pneumonia and sufficiently ill to require hospitalization, therefore, should prompt consideration of a bacterial coinfection and a parapneumonic effusion. Notably, pneumonia due to swine-origin influenza A (H1N1) is commonly associated with pleural effusions.[237,238]

Fungal and Parasitic-Related Pleural Effusions

A wide spectrum of fungal infections causes pleural effusions in diverse clinical settings. Immunocompromised hosts may develop fungal empyema secondary to pleural seeding from a fungal pneumonia or more distant sites of infection. Common pathogens include *Aspergillus*[239,240] and *Cryptococcus* species.[240,241] Cryptococcal pleuritis suggests the presence of disseminated disease.[241] In immunocompetent patients, chylothoraces may occur secondary to mediastinal granulomatous disease caused by *Histoplasma capsulatum*.[242] Patients with allergic bronchopulmonary aspergillosis may develop eosinophilic pleural effusions[242] or erosion of fungus balls into the pleural space.[243,244] Finally, pulmonary fungal infections may lead to pleural effusions, which may be sterile or infected with fungal elements. Coccidioidomycosis represents the most common and distinctive endemic fungus presenting in this manner.[245,246] Fifteen percent of patients hospitalized with acute pulmonary coccidioidomycosis have pleural effusions[247,248] with nearly a quarter of patients progressing to empyema.[248] PF is exudative with eosinophilia being commonly present.[248]

Anecdotal reports exist of a broad range of parasitic infestations associated with pleural effusions.[249–257] Among these, pleural effusions related to rupture of an amebic liver abscess across the diaphragm into the pleural space producing an empyema[258] and pulmonary infestation with *Paragonimus* (a genus of flatworms)[254,256,259,260] are the most common. Amebic empyema is most commonly right sided, with PF having an anchovy paste or chocolate-milk appearance. A reactive pleural effusion can also occur secondary to transdiaphragmatic inflammation.[257] Paragonimiasis produces pleural effusions and pulmonary parenchymal changes that may simulate malignancies or tuberculosis.[256] Chest CT series indicate that pleural effusions are the most common intrathoracic imaging findings of the North American form of paragonimiasis (*Paragonimus kellicotti*).[259] PF has a markedly increased LDH and may also assume characteristics of a chylothorax.[251] Blood or PF eosinophilia are variable findings. Pulmonary echinococcosis can produce pleural effusions, hydropneumothorax, and secondary pleural hydatidosis when pulmonary or hepatic echinococcal cysts rupture into the pleural space.[257,261] A reactive pleural effusion may also occur because lung echinococcal cysts are usually subpleural in location. PF may be an eosinophilic exudate[262] or empyema.[263] Other parasites rarely involve the pleural space.[257]

■ VASCULAR

Pulmonary Thromboembolism

Up to 40% of patients with PTE have associated pleural effusions when examined by standard radiographs with 47% having effusions on chest CT images.[264–268] Lung ischemia results in increased

pleural membrane permeability with an influx of protein-rich fluid into the pleural space; effusions related to PTE are almost always exudates.[265,269] Effusions are unilateral in 85% of patients with approximately equal distribution of right- versus left-sided locations occurring ipsilateral or contralateral to the site of the PTE.[265,269] Less than 20% of effusions occupy more than one-third of the hemithorax[264,265,269] with most only blunting the costophrenic angle. Delayed diagnosis may cause the effusions to loculate.[265,270]

PF findings are nonspecific with erythrocyte counts greater than 10,000/μL in 67% of patients, neutrophil predominance in 60%, and eosinophil counts >10% in 18%.[269] Only 57% have bloody PF.[269] Thoracentesis, therefore, has a limited role in evaluating PF for suspected PTE but has value for excluding other conditions, such as pleural infection or hemothorax. PF usually reabsorbs during anticoagulant therapy. The presence of a bloody effusion does not obviate systemic anticoagulation because hemothorax rarely occurs. When pleural bleeding does occur, it presents with sudden cardiopulmonary compromise usually during the first week of anticoagulation.[271–273]

Nonthrombotic Pulmonary Emboli

Septic Emboli Septic emboli typically lodge in lung periphery, which can cause sterile or infected pleural effusions. Common causes of septic emboli include infected venous catheters,[274] septic thrombophlebitis (e.g., Lemmiere syndrome),[275] and right-sided endocarditis. Patients with intravenous drug addiction may present with pyopneumothorax.[276,277] Common CT imaging findings include peripheral nodules with clearly identifiable feeding vessels and/or air bronchograms, metastatic lung abscesses, and subpleural, wedge-shaped densities with or without necrosis.[278–280] PF reflects acute sterile inflammation or evidence of an empyema.[281]

Hemothorax

Hemothorax is defined by the presence of bloody PF with a PF hematocrit (hct) >50% of the simultaneous blood hct value.[282] Because erythrocytes undergo spontaneous lysis in the pleural space, a PF hct between 25% and 50% measured a few days after the onset of pleural effusion supports the diagnosis. Hemothoraces result from blunt and penetrating chest trauma, procedures that damage vasculature in or near the pleural space, and underlying conditions that promote spontaneous intrapleural hemorrhage (Table 76-6). Hemothorax carries a potential for unabated hemorrhage, respiratory compromise, and shock. Principles of management include drainage of the pleural space by thoracentesis in the absence of ongoing bleeding, or by chest tube to monitor ongoing bleeding rates, removal of intrapleural blood, and prevention of a subsequent trapped lung or empyema. Pleural drainage also apposes pleural membranes to tamponade pleural-based bleeding sites. Patients may require emergency thoracotomy or VATS to control bleeding and evacuate intrapleural clots.[283]

Catamenial hemothorax represents a unique form of hemothorax occurring in young, multiparous, and menstruating women with pelvic endometriosis.[292,293] Two-thirds of patients have intrapleural endometriosis noted during VATS.[293] Unilateral and right sided in 80% of instances, bilateral pleural effusions occasionally occur.[293] Catamenial pneumothorax[294] and hemoptysis[293,295] may occur simultaneously with hemothorax. Intrapleural bleeding is usually mild and self-limited, which may delay diagnosis until the temporal relationship with menses is noted. Once diagnosed, most patients are sufficiently stable to allow medical management with hormonal therapies that provide only partial effectiveness.[282,296] Patients with recurrent hemothorax may require surgical resection of intrathoracic endometriomas, although relapse commonly occurs.[292]

Vasculitis

Pleural effusions can occur in granulomatous polyangiitis (GP, also termed Wegener granulomatosus) as a result of primary pleural involvement with necrotizing vasculitis or secondary to renal disease, pneumonia, or CHF as complications of vasculitis.[297–299] Small patient series indicate that 10% to 20% of patients with GP have pleural effusions usually as incidental findings.[298,300] Patients may rarely present, however, with a pleural effusion[301,302] and massive effusions with bronchopleural fistulae have been reported.[303] From the limited reports of PF analyses, the effusions are exudates with neutrophil predominance.[304,305] Pleural biopsy may detect evidence of granulomatous vasculitis or only nonspecific fibrosis.[306,307]

Up to 30% of patients in the vasculitic phase of Churg–Strauss syndrome have pleural effusions, although most are small and asymptomatic.[308,309] Massive effusions, however, have been reported.[310] Only rare reports exist of PF analysis, which characterize the fluid as having increased eosinophils.[310–312] One report noted a low pH and glucose.[312] Effusions may respond to corticosteroid therapy.[312]

Pleural effusions rarely occur in patients with giant cell arteritis[313–320] and may represent the presenting feature of the disease.[313,315,316,320] PF is exudative with neutrophil predominance and a normal glucose, although lymphocyte predominance[314] and transudative effusions have been reported.[315] Pleural biopsy is nonspecific.[317] The effusions respond to prednisone therapy.[313,319]

Behçet disease is a chronic, relapsing inflammatory disorder of unknown etiology. Vascular involvement represents the major risk for mortality with any sized vessel in the venous, arterial, or capillary circulation being potentially affected. Among a myriad of intrathoracic complications,[321] Behçet disease can cause abnormalities of

TABLE 76-6 Cases of Hemothorax

Condition	Comments
Coagulopathy and bleeding diatheses	Hemothorax due to primary coagulopathies, thrombocytopenia, anticoagulant therapy, or systemic and intrapleural fibrinolytic therapy rarely occur[284–286]
Pneumothorax and ruptured lung bullae	Hemothorax uncommon with spontaneous pneumothorax but can occur especially with ruptured lung bullae[282]
Neurofibromatosis	Rupture of friable vasculature in patients with neurofibromatosis may occur by vascular invasion or arterial dysplasia[287]
Arteriovenous malformations	Arteriovenous malformations rarely bleed into the pleural space with one-half of instances related to Osler–Weber–Rendu disease[282]
Aneurysms	Dissection or rupture of a major intrathoracic artery is a common and usually clinically apparent cause of hemothorax[288] Most commonly aortic but also pulmonary vasculature
Ehlers–Danlos disease	Associated with internal mammary artery rupture[289,290]
Connective tissue diseases	Rare reports
Extramedullary hematopoiesis	Rare reports
Endometriosis	Varying degrees of hemorrhagic effusions or hemothorax
Exostoses	Formation of new bone on the surface of existing bone creates sharp boney edges that can erode adjacent vascular structures and cause hemothorax[291]
Postpartum	Related to thoracic pressure changes during labor straining

pleural membranes and various types of pleural effusions. High-resolution CT scans commonly detect pleural thickening and nodularity that may represent resolved pulmonary infarctions, spread of subpleural pulmonary inflammation, and/or pleural vasculitis.[322–326] Pleural effusions commonly occur in patients with vascular obstruction and can be transudates in patients with superior vena cava (SVC) obstruction[327] or chylothoraces in patients with thrombosis of the SVC or other major intrathoracic vessels.[328–332] Effusions respond variably to corticosteroid therapy[330,331] and may require anticoagulation, immunosuppressive drug therapy,[333] and/or pleurodesis.[330]

Superior Vena Cava Syndrome

More than 60% of patients with SVC syndrome develop pleural effusions that are nearly always exudative in nature, with 18% being chylothoraces.[334] The etiology of the effusions is unknown, but increased resistance to lymphatic duct drainage into the brachiocephalic vein may contribute to chylothorax.[335] Effusions are equally right sided or left sided and most effusions occupy less than 50% of a hemithorax.[335] The effusions usually resolve with resolution of the SVC syndrome.

■ GASTROINTESTINAL AND INTRA-ABDOMINAL DISORDERS

Pancreatitis and Pancreatic Fistulae

Pleural effusions are apparent in 50% of patients hospitalized with acute pancreatitis.[336,337] Several potential mechanisms exist for PF formation, which include release of proinflammatory mediators from the pancreas into the circulation, transdiaphragmatic transit of parapancreatic inflammatory exudates, lipolysis of mediastinal fat, and early formation of pancreaticopleural fistulae.[338,339] Early onset of pleural effusions represents a negative prognosticator for acute pancreatitis.[337,340,341] The PF profile includes a neutrophil predominant exudate with an elevated amylase usually greater than twice the serum value.[342]

Predominantly left-sided effusions may develop in patients with chronic pancreatitis who develop a pseudocyst with a sinus tract through the retroperitoneum into the pleural space. Most patients are male (70%) with a history of chronic alcoholic pancreatitis (50%), but other causes of pancreatitis, such as choledocolithiasis, also occur.[343] Patients present with dyspnea (65%), abdominal pain (29%), cough (27%), and chest pain (23%).[344] PF pancreatic amylase is markedly elevated (>1000 IU/L). Visualization of the pancreaticopleural fistula with its drainage into the pleural space can be achieved by helical CT scanning, endoscopic retrograde cholangiopancreatography, or magnetic resonance cholangiopancreatography (MRCP) with MRCP being the most sensitive initial examination.[343–348]

No validated algorithm for treatment of pancreaticopleural fistula exists, but most centers initiate a sequential approach that begins with alimentary nutrition and observation supplemented with octreotide to suppress exocrine secretion.[345,347–349] Thirty-five percent of patients will fail conservative therapy and require endoscopic placement of a pancreatic stent followed by surgery, if the stent is unsuccessful.[343,344,346–348,350] Prolonged medical therapy only delays recovery, so patients should be evaluated for definitive operative intervention early in the course of treatment.[343]

Esophageal Perforation

Rupture or perforation of the esophagus with decompression of gastroesophageal contents into the pleural space represents a life-threatening condition. Esophageal disruption results from forceful vomiting (Boerhaave syndrome), esophageal lesions (retained foreign bodies or neoplasms), or esophageal instrumentation (endoscopy, gastric banding for weight loss).[351] Boerhaave syndrome presents with chest pain and signs of sepsis with a rapidly progressing, usually left-sided effusion. Meckler's triad of vomiting, chest pain, and subcutaneous emphysema suggests the diagnosis. Imaging studies demonstrate a rapidly progressing pleural effusion or hydropneumothorax often associated with mediastinal, paraesophageal, and/or subcutaneous emphysema.[352,353] PF findings include high salivary amylase, low pH, low glucose, high LDH, and evidence of pleural infection. Cytologic examination may identify food particles and/or squamous epithelial cells.[354] Gastrografin-contrasted chest CT or endoscopy may localize the esophageal injury and fistula tract, but negative studies do not exclude the diagnosis. Adequate surgical debridement with drainage of the mediastinum and pleural space within 24 hours of presentation improves outcome in Boerhaave syndrome.[355,356] Iatrogenic esophageal perforation may be managed more conservatively.[357]

Endometriosis

Endometriosis involving the peritoneum complicated by ascites may rarely cause a pleural effusion that is characteristically right sided with bloody or chocolate-brown appearing PF.[358,359] The effusions are linked temporally with menses and contain hemosiderin-laden macrophages. In contrast to catamenial hemothorax due to intrathoracic endometriosis, this condition is characterized by endometrial tissue that is confined to the abdominopelvic region with secondary flow of fluid into the pleural space.

Intra-Abdominal Diseases

Infradiaphragmatic abscesses and various ischemic and inflammatory lesions of abdominal organs (e.g., perihepititis[360] and splenic ischemia[361]) can cause exudative effusions that may become infected if intra-abdominal pathogens migrate into the pleural space. Depending on the location of the intra-abdominal locus of infection or inflammation, the effusions may be predominately right sided (e.g., hepatic abscess) or left sided (e.g., splenic abscess or infarction). CT scanning establishes the diagnosis in most instances and directs both pleural and abdominal drainage.

Biliothorax

Bile can flow into the pleural space causing a right-sided pleural effusion as a complication of percutaneous biliary drainage,[362–365] radiofrequency ablation or catheter embolization of liver lesions,[366–368] or spontaneous pancreaticopleural or cholecystopleural fistulae.[369,370] PF has a green tint with neutrophil predominance and a PF/serum bilirubin ratio >1.

■ SYSTEMIC DISEASES

Connective Tissue Diseases

As many as 30% of patients with systemic lupus erythematosus (SLE) experience pleuritis at some time during the course of their disease.[371,372] Pleuritis is an independent predictor of mortality in lupus.[371] Associated pleural effusions are usually small to moderate, but large effusions can occur. Usually bilateral, they have an equal side distribution when unilateral.[373] Concomitant anti-Sm and anti-RNP antibody seropositivity, greater severity and longer duration of lupus, and young age at SLE onset are associated with a higher rate of pleural disease.[371] Typical PF profiles are shown in Table 76-7.[374,375] Detection of a positive PF antinuclear antibody (ANA) does not provide incremental diagnostic value to a positive serum ANA.[376] Rarely, lupus pleuritis may progress to fibrothorax and trapped lung.[377] Effusions respond to nonsteroidal anti-inflammatory drugs as initial therapy, or corticosteroids if necessary, in most patients, but pleuritis tends to recur, often on the contralateral side. Refractory massive pleural effusions rarely occur and may require high-dose steroids and cyclophosphamide, intravenous immunoglobulins, and occasionally pleurodesis.[378]

Pleural involvement is the most frequent manifestation of RA in the chest and causes pleural effusions in up to 20% of patients.[373,379] As many as 11% of patients within the first year of RA diagnosis have evidence of pleural thickening or pleural effusions on high-resolution CT imaging.[380] Pleural effusions occur most often in

TABLE 76-7 Pleural Fluid Test Results in Common Autoimmune Causes of Pleuritis

Finding	Lupus Pleuritis	Rheumatoid Arthritis
Appearance	Clear	Variably serous, purulent, milky, hemorrhagic
Protein	Low in exudative range	High in exudative range
Glucose	Similar to serum	Often low <30 mg/dL
Leukocytes	3–5000/μL	Usually <10,000/μL
Complement	Low	Low
Immune complexes	High	High
PF ANA	Positive	Variable
LDH	Twice upper limits of normal for serum	High
Rheumatoid factor	Low	Elevated

PF, pleural fluid; LDH, lactate dehydrogenase; ANA, antinuclear antibody.

men who have active arthritis, subcutaneous rheumatoid nodules, elevated rheumatoid factors, and radiographic evidence of underlying rheumatoid lung lesions.[379] Patients with RA may rarely present with pleurisy.[381] Pleural effusions are small to moderate in size, more often left sided, and asymptomatic.[382] Symptomatic effusions warrant thoracentesis to exclude empyema that can occur spontaneously with RA pleural effusions.[379] Sterile RA effusions have the pleural profile listed in Table 76-7. Effusions have a neutrophil predominance at onset but may convert to lymphocytic predominance in 7 to 11 days.[383] PF cytology may demonstrate, elongated macrophages and multinucleated giant cells (tadpole cells), and granular debris.[383] Sterile RA effusions often have a low glucose (<30 mg/dL) and pH (<7.20) that complicates differentiation from pleural infection. Pleural biopsy may demonstrate replacement of parietal pleural mesothelial cells with a palisade of macrophage-derived cells,[383] but biopsy is usually not needed for diagnosis. Most effusions resolve spontaneously but some persist or progress to fibrothorax.[379] No therapy has demonstrated value for RA pleural effusions. RA may also cause cholesterol effusions[384] and bronchopleural fistulae.[385]

Although recurrent pleuritic chest pain commonly occurs in patients with Sjögren syndrome,[386] pleural effusions rarely develop. Among 343 patients reported with Sjögren syndrome, only 9% had pulmonary manifestations, of which 4 patients had pleural effusions.[386] Limited data indicate that the effusions associated with Sjögren syndrome are lymphocyte predominant exudates with high PF levels of anti–SS-A/SS-B antibodies.[387] An effusion should suggest lymphoma, which occurs with increased frequency in Sjögren syndrome.

Up to 7% of patients with systemic sclerosis may have a pleural effusion that can result from pleural involvement with sclerodermal tissue changes or secondary causes of pleural effusions associated with scleroderma, such as CHF.[388] PF is a lymphocyte predominant exudate unless it is a transudate due to associated CHF or renal failure.[388,389]

Mixed connective tissue disease (MCTD) has clinical features of SLE, scleroderma, and polymyositis–dermatomyositis and is defined by the presence of high serum titers of antibodies against uridine-rich RNA-small nuclear ribonucleoprotein (snRNP).[390] Pleuropulmonary complications commonly occur in up to 50% of patients having pleural effusions and 20% having symptoms of pleurisy.[391–393] Pleural effusions are usually incidental imaging findings, but may rarely be the presenting feature of the disease.[394] The PF profile is poorly defined, but a report exists of a granulocyte predominant exudate.[395]

Exudative effusions with normal PF glucose levels have been rarely reported in patients with ankylosing spondylitis.[396–399] Associated nonspecific pleuritis has been demonstrated on pleural biopsy specimens.[399] Effusions may be transient[399] or recurrent.[396]

Polymyositis and dermatomyositis cause interstitial lung disease in approximately 10% to 20% of patients and have the potential for provoking respiratory failure, especially in patients with the antisynthetase syndrome.[400] Although pleural irregularities are noted in a high proportion of patients,[401] pleural effusions rarely occur and, when present, invariably exist in association with interstitial lung disease and should prompt consideration of an alternative underlying diagnosis.[402–404] The PF profile has been reported to be lymphocyte predominant with rare reports of increased eosinophils.[402]

Sarcoidosis

Pleural effusions rarely occur in patients with sarcoidosis with a reported prevalence of 0.7% to 10%.[405–411] A large case series reported 1.1% prevalence of sarcoid-related effusions in asymptomatic ambulatory patients examined by US.[407] Thirty-three percent of patients examined by CT scanning have evidence of pleural thickening and subpleural nodules, which are assumed related to sarcoidosis.[412,413] Sarcoid effusions are usually small to moderate sized, unilateral, and asymptomatic although large, symptomatic effusions can occur. Only 20% of effusions are bilateral.[407] Most effusions are lymphocyte predominant exudates[407,414] with one report of the lymphocyte populations having a high CD4/CD8 ratio.[415] Chylothorax,[409] eosinophilic effusions,[416,417] trapped lung,[418] and hemorrhagic effusions[419] may occur. Pleural biopsy may demonstrate sarcoid granulomas.[405,408,410] Most sarcoid effusions resolve spontaneously.

Myedema

Both transudative and exudative effusions have been reported in patients with myxedema.[420–425] Most of these effusions respond to thyroid replacement therapy.

Amyloid

Exudative or transudative pleural effusions can develop from infiltration of amyloid into parietal pleural surfaces, increasing capillary permeability and blocking reabsorption of PF through lymphatic stomata.[426,427] Most effusions are associated with light chain amyloidosis. Pleural effusions can also occur through indirect mechanisms of amyloid-induced hypothyroidism, nephrosis, and CHF, the latter two of which may cause transudative effusions in this setting.[428] Amyloid-related exudative effusions rarely resolve spontaneously and may require repeated thoracentesis or pleurodesis.

Extramedullary Hematopoiesis

Extramedullary hematopoiesis involving the mediastinum and pleural membranes has been associated with exudative pleural effusions,[429–432] hemothorax,[433] and chylothorax.[434] Detection of normoblasts[435] and myeloblasts[432] in PF suggests the diagnosis. Symptomatic effusions have been successfully managed by low-dose thoracic radiotherapy, pleurodesis, and hydroxyurea.[429,430,434]

■ DRUG RELATED

A wide spectrum of drugs can cause pleural effusions through a variety of mechanisms. A listing of these drugs is available at http://pneumotox.com/indexf.php?fich=clin0&lg=en.

One unique form of drug-induced pleural effusions is represented by ovarian hyperstimulation syndrome (OHSS) that develops during induced ovulation with human chorionic gonadotropin hormone. This condition is characterized by massive increases in ovarian size, extravascular fluid shifts, and hemoconcentration that can result in shock and organ failure. Signaling by vasogenic molecules released from corpus lutae is thought to provoke increased epithelial

membrane permeability.[436,437] Unilateral and bilateral pleural effusions commonly occur during the full expression of the syndrome but also as isolated findings.[438–441] Limited data exist regarding the PF profile, which is considered exudative.[442] PF may contain high levels of cytokines.[443] In most instances, OHSS is self-limited and spontaneous regression occurs although chest catheters may be required initially for draining large volumes of PF.[444]

■ ENVIRONMENTAL—ASBESTOS

Up to 3% of patients with an occupational exposure to asbestos will develop transient exudative pleural effusions, [445–447] termed benign asbestos pleurisy.[446,448] Asbestos exposure may underlie many undiagnosed exudative pleural effusions.[447,449] The pathophysiology of benign asbestos pleurisy is uncertain, but asbestos fibers can provoke pleural inflammation both by direct toxicity to mesothelial cells and also by indirect effects through stimulating the release of growth factors and inflammatory cytokines from the lung.[450] Mean latency time from first asbestos exposure to pleural effusions is 30 years but ranges from 1 to 58 years.[451] Symptoms of dyspnea, chest pain, and/or fever develop in only 35% to 50% of patients.[447,451] Pleural effusions range from small to large and present most often as unilateral effusions with equal side distribution or as bilateral effusions in 15%.[446,451] PF appears hemorrhagic in 50% of patients, and 25% have increased numbers of eosinophils.[449,451] The effusions almost always follow a benign course with spontaneous resolution within 1 to 10 months (median 3 months),[451] but some effusions recur.[447] Patients with heavy asbestos exposure may have residual pleural thickening,[445–447,449,452] which may require decortication if lung restriction occurs.

■ LYMPHATICS AND LIPID-RELATED EFFUSIONS

Chylothorax

Chylothorax is defined by the presence of chyle in the pleural space,[453] which denotes a leakage of lymphatic fluid from the thoracic duct or its tributaries. Chyle contains lipids in transit from the digestive tract to the venous circulation via the cisterna chyli near the junction of the left jugular and subclavian veins. Disruption of these lymphatic channels anywhere along their course can result in a pleural effusion. Lymphatic fluid also contains a high content of lymphocytes and immunoglobulins. A classification of chylothorax and listing of common causes are shown in Table 76-8.

TABLE 76-8 Causes of Chylothorax

Classification	Comments
Traumatic	Account for 50% of chylothoraces with thoracic surgery most common cause.[454] Also occur after neck surgery, central venous catheter and pacemaker insertion, blunt chest injury, traction injuries to the chest and neck, and sudden pressure changes with sneezing, vomiting, or labor and delivery.
Nontraumatic	Lymphoma has decreased in incidence to 11% because of earlier lymphoma diagnosis.[453] Less common causes include congenital or acquired lymphatic disorders, constrictive pericarditis, SVC syndrome, lymphangiomatosis, lymphangiectasias, lymphangioleiomyomatosis, Noonan syndrome, yellow nail syndrome, Down syndrome, granulomatous infections, and thyroid goiter[453]
Idiopathic	Small number idiopathic despite a complete diagnostic evaluation

Chylothoraces usually present as unilateral effusions, but 20% may be bilateral. The thoracic duct ascends on the right side of the mediastinum crossing to the left side near the fifth thoracic vertebral body (T5). Consequently, a right- versus left-sided chylothorax suggests the presence of disruption to the thoracic duct below or above a T5 level, respectively. Because of the noninflammatory nature of chyle, patients do not experience pleuritic pain but present with dyspnea. The PF appears free flowing and nonloculated without pleural thickening on imaging studies. PF is grossly white, milky, and opalescent in 50% of patients but may be serous or serosanguineous when patients are fasting. PF analysis demonstrates a lymphocyte predominant exudate with an elevated protein but not LDH. A transudate may occur in 14% to 32% of patients,[455] which suggests a coexisting condition such as CHF or hepatic hydrothorax.[456] PF triglyceride concentration is usually above 110 mg/dL but 15% of patients have lower values that may be <50 mg/dL.[455] PF triglyceride testing, therefore, has a high positive but low negative predictive value for chylothorax.[455] In the absence of elevated triglyceride levels, analysis of PF for chylomicrons is indicated.

With an established diagnosis, some centers perform conventional lymphangiography or lymphoscintigraphy imaging studies to visualize thoracic lymphatics and identify the anatomical site of chyle leakage. The value of these studies for directing therapy, however, has not been established. No evidence-based algorithm exists for managing patients with chylothorax, and extensive practice variation exists. Generally accepted principles of care, however, encourage identification of the underlying etiology; guidance of therapy in a stepwise manner based on the severity of symptoms, size of the effusion, rate of fluid reaccumulation after thoracentesis, and the patient's overall clinical condition, comorbidities, and ability to tolerate invasive procedures; and avoidance of prolonged PF drainage by chest tube, which results in nutritional depletion and immunosuppression.[457]

Observation may suffice for stable and small to moderate effusions with mild symptoms. Nonsurgical, conservative measures resolve 50% of traumatic chylothoraces but prove less successful for nontraumatic forms of the disease, which usually require surgery.[458] Only two-thirds of patients with nontraumatic chylothoraces, however, respond to surgical interventions. Most patients with traumatic chylothorax respond to surgical interventions, if required.[458] Dietary measures include restriction of fat except for medium chain triglycerides that are absorbed directly into the portal circulation. Available surgical interventions include pleurodesis, pleurectomy, thoracic duct repair or ligation, lymphovenous anastomosis, and pleuroperitoneal shunting. VATS for localizing and managing thoracic duct disruptions has improved outcomes as compared with open thoracotomy.[459–461] Recent interest in percutaneous transabdominal embolization of the thoracic duct has developed.[462,463] Patients nonresponsive to therapy or patients with terminal conditions may benefit from placement of a pleuroperitoneal shunt.[464,465]

Cholesterol Effusions

Cholesterol pleural effusions, also termed *pseudochylous* or *chyliform* effusions, usually present as unilateral effusions with 30% of patients being asymptomatic.[459] PF appears grossly turbid or milky due to high lipid content, largely composed of cholesterol and lecithin–globulin complexes. The pathogenesis of cholesterol effusions is unknown. Because they most often develop in patients with chronic (>5 years) exudative effusions and thickened pleural membranes, they have been considered a form of "trapped lung" wherein erythrocytes and neutrophils lyse and release their intracellular lipids that cannot be reabsorbed across thickened pleural membranes.[459] Reports exist, however, of cholesterol effusions after shorter intervals of exudative effusions without pleural membrane thickening.[384] The most common underlying conditions associated with cholesterol effusions include tuberculous pleurisy, chronic pneumothorax,

chronic hemothorax, and chronic rheumatoid pleuritis.[466] Less commonly associated conditions include pleural echinococcosis, paragonimiasis, and malignancies.

PF analysis demonstrates a cholesterol concentration >200 mg/dL and usually a neutrophil predominant exudate. The triglyceride concentration is usually but not always <110 mg/dL. If the triglyceride level is elevated, the PF cholesterol/triglyceride ratio is >1.0.[459] Some PF samples demonstrate cholesterol crystals but chylomicrons are not present. Pleural biopsy may assist in diagnosing an underlying etiologic condition although biopsy samples are diagnostic in only 17%.[467] Most patients with cholesterol effusions do not require therapy directed at the pleural space. Symptomatic effusions, however, may benefit from periodic therapeutic thoracentesis, pleurodesis, or rarely decortication. Some effusions may stabilize or resolve with drug therapy for underlying RA if present.[384]

Lymphatic Abnormalities

Lymphangioleiomyomatosis Ten to 40% of patients with lymphangioleiomyomatosis develop pleural effusions that are almost always chylous.[468] Chylothorax occurs as a consequent of obstruction or disruption of the thoracic duct or its tributaries, generalized oozing from pleural lymphatics, and/or transdiaphragmatic flow of chylous ascites.[469] Effusions may be unilateral or bilateral,[469] and chyloptysis may also occur.

Chylous effusions follow a variable clinical course. They most often progress in size and recur after thoracentesis,[470] but may remain stable over years[471] or resolve spontaneously.[472] Symptomatic patients do not respond well to low-fat diets. Chemical or mechanical pleurodesis with or without thoracic duct ligation performed close to the diaphragm is successful in most patients, but pleurectomy with or without thoracic duct ligation may be required.[469]

Yellow Nail Syndrome The YNS is a rare, acquired disorder characterized by the triad of abnormal nails (yellowing, slow growth, ridging, onycholysis, excessive long-axis curvature, and/or diminished lunulae), lymphedema, and pleural effusions.[453] Some patients have associated bronchiectasis, recurrent lower respiratory tract infections, and chronic sinusitis. The diagnosis is suspected by the presence of two of the triad findings in the absence of another more likely explanation. The etiology is unknown, but both anatomic and functional abnormalities of lymphatic ducts have been proposed.[473–475] Histologic analyses of pleural membranes do not consistently detect lymphatic vessel abnormalities.[476,477]

Most (80%) patients have symmetric, lower extremity, nonpitting lymphedema, which is a finding in 30% of patients who present with pleural effusions. Lymphedema can also involve the face, arms, larynx, and peritoneal cavity producing ascites. Up to 40% of patients having pleural effusions are most often bilateral. The fluid is lymphocytic predominant with an elevated protein meeting exudative criteria, but often an LDH and cholesterol in the transudative range.[476,478] Up to 30% of effusions are chylothoraces.[476] Management is supportive with therapeutic thoracentesis for symptomatic effusions, pleurodesis or pleuroperitoneal shunting for recurrent effusions, and VATS with thoracic duct ligation for chylothoraces.[479]

KIDNEY RELATED

Pleural effusions occur for a variety of reasons in patients with end-stage renal disease undergoing long-term hemodialysis. Approximately 50% of hemodialysis patients with acute respiratory complaints have pleural effusions when evaluated by CT.[480] Although the most common etiologies of symptomatic effusions are cardiac failure, pneumonia, tuberculosis, malignancies, and volume overload;[480–482] pleural effusions can develop as a direct consequence of uremia (uremic pleuritis).[480]

The onset or size of effusions related to uremic pleuritis does not correlate with the severity of underlying uremia or timing of hemodialysis.[483] Most patients have chest pain, cough, dyspnea, and/or fever. PF is exudative with a predominance of lymphocytes. The diagnosis is one of the exclusion that requires careful consideration of alternative explanations, such as infection, heart failure, and malignancy. Most patients respond to continuation of hemodialysis, but some patients may develop pleural fibrosis with a trapped lung.[110]

EFFUSIONS AFTER CARDIAC SURGERY

Most patients develop exudative pleural effusions after cardiac surgery in the immediate postoperative period as a direct consequence of the surgery itself in the absence of complications of the procedure, such as hemothorax or chylothorax. Effusions after coronary artery bypass graft surgery (CABG-related effusions) have received the greatest attention,[484–487] but nonspecific exudative effusions also occur after cardiac valve replacement.[488] CABG-related effusions have been separated into early (within 30 days of surgery) and late onset (30 days after surgery).[489] The pathogenesis of these effusions is unknown but may relate to topical cardiac cooling, surgical interruption of lymphatic channels, direct surgical injury of the pleura, and/or pericarditis.[487,490–492]

Ninety percent of CABG-related effusions encompass <25% of a hemithorax and most are left sided and asymptomatic. Large effusions, however, may cause dyspnea, but chest pain and fever are uncommon.[484] Because these effusions resolve spontaneously, thoracentesis is indicated only in certain instances based on the timing of onset, progression, and persistence of the effusion and any associated cardiopulmonary symptoms. Small- to moderate-sized effusions, effusions that develop within days of surgery, asymptomatic effusions, and nonprogressive effusions may be observed for resolution. Symptomatic, large, or progressive pleural effusions require thoracentesis either to manage dyspnea or to evaluate patients for the alternative diagnoses. PTE should be considered with appropriate studies.

When thoracentesis is performed, effusions that occur within the first 30 days of surgery are typically bloody in appearance and may contain >10% eosinophils.[493,494] Late-onset effusions are nonbloody with lymphocyte predominance.[493,494]

Postcardiac injury syndrome (Dressler syndrome) develops 1 week or more after myocardial injury and is characterized by pericarditis, pulmonary infiltrates, and pleural effusions.[495] Patients commonly have pericardial chest pain, fever, leukocytosis, and pleuropericardial friction rubs. Pleural effusions occur in 60% to 80% of patients and are typically small and unilateral, most often left sided.[496,497] PF is hemorrhagic in 70% with a neutrophil predominant exudate during the acute presentation that evolves to lymphocyte predominance.[496] The effusion usually resolves with anti-inflammatory drug therapy.

IATROGENIC PROCEDURES AND TREATMENTS

Thoracic Irradiation

Small exudative pleural effusions may occur in 10% of patients with radiation pneumonitis after external beam radiotherapy, with higher incidences in patients with esophageal cancer treated with extensive mediastinal radiation.[498] In addition to direct effects on pleural membranes, lymphatic structures, and pulmonary parenchyma, radiotherapy can promote PF formation by causing constrictive pericarditis.[63] The differential diagnosis includes pneumonia with parapneumonic effusions, venous thromboembolism, malignant pleural effusion, drug-induced effusions, and pericarditis. In contrast to malignant effusions, postirradiation effusions do not progress and tend to resolve over time.

Feeding Tubes

Pleural effusions can occur after inadvertent transbronchial placement of a feeding tube into the pleural space.[499,500] Cardiopulmonary

collapse due to massive hydrothorax can occur if misplacement is not promptly recognized and infusates discontinued.[501]

■ OBSTETRICAL AND GYNECOLOGICAL

Postpartum Pleural Effusions

One case series demonstrated small, asymptomatic pleural effusions by chest radiographs in 46% of postpartum patients; the effusions had no relationship with method of delivery or antepartum complications.[502] A subsequent study using US did not confirm these observations finding pleural effusions in only one patient, who had severe preeclampsia.[503] Another study using US detected pleural effusions in 6 of 34 patients with moderate or severe preeclampsia.[504] Considering these observations in aggregate, detection of small, asymptomatic effusions in a healthy woman during antepartum or postpartum periods should not trigger a diagnostic evaluation unless respiratory symptoms exist or other clinical features suggest a pathologic etiology for the effusion.

Meigs Syndrome

Meigs syndrome is defined by the presence of pleural effusions and ascites in a patient with a benign ovarian fibroma or fibrothecoma. The effusions and ascites resolve with resection of the ovarian tumor. The tumors generate large volumes of fluid that flow transdiaphragmatically into the pleural space causing usually right sided, exudative effusions.[505] Meigs syndrome may be associated with marked elevations of serum CA125, which denotes ovarian cancer in other clinical settings.[506–508]

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CHAPTER 77
Malignant Pleural Effusions

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A malignant pleural effusion is diagnosed by detecting exfoliated malignant cells in pleural fluid or demonstrating these cells in pleural tissue obtained by percutaneous pleural biopsy, thoracoscopy, thoracotomy, or at autopsy. In a number of patients, even though the pleural effusion is caused by the malignancy, neoplastic cells cannot be detected in pleural fluid or pleural tissue and, in fact, probably are not present in these tissues. It is logical to categorize these pleural effusions associated with malignancy, in which there is no direct pleural involvement with tumor and no other cause for the effusion is found, as paramalignant effusions (Table 77-1). Lymphatic obstruction appears to be the most common mechanism for the development of a paramalignant effusion. Other local effects of the tumor causing a paramalignant effusion are bronchial obstruction resulting in pneumonia or atelectasis. Furthermore, it is important for the clinician to recognize that effusions can result from systemic effects of the tumor and adverse effects of therapy.

The presence of a malignant pleural effusion secondary to lung cancer portends a poor outcome.[1] Similarly, a malignant effusion secondary to a nonlung primary is a manifestation of far advanced disease and is associated with limited survival.

TABLE 77-1 Causes of Paramalignant Pleural Effusions

Cause	Comment
Local effects of tumor	
Lymphatic obstruction	Predominant mechanism for pleural fluid accumulation
Bronchial obstruction with pneumonia	Parapneumonic effusion; does not exclude operability in lung cancer
Bronchial obstruction with atelectasis	Transudate; does not exclude operability in lung cancer
Chylothorax	Disruption of thoracic duct or its major tributaries; lymphoma a common cause
Systemic effects of tumor	
Pulmonary embolism	Hypercoagulable state; adenocarcinomas
Hypoalbuminemia	Serum albumin <1.5 g/dL; anasarca typically present
Complications of therapy	
Radiation therapy	
Early	Pleuritis 6 wk to 6 mo following completion of radiation
Late	Mediastinal fibrosis
	Constrictive pericarditis
	Vena caval obstruction
Chemotherapy	
Methotrexate	Pleuritis or effusion ± blood eosinophilia
Procarbazine	Blood eosinophilia; fever and chills
Cyclophosphamide	Pleuropericarditis
Mitomycin	In association with interstitial disease
Bleomycin	In association with interstitial disease

MALIGNANCIES ASSOCIATED WITH PLEURAL EFFUSIONS

Carcinoma of any organ can metastasize to the pleura. However, carcinoma of the lung is the most common malignancy to invade the pleura and produce malignant and paramalignant effusions (Table 77-2). Carcinoma of the breast is second in incidence and, in some populations, exceeds lung cancer as a cause of malignant effusions. Together, both malignancies account for 65% of all malignant pleural effusions.[2] After lung and breast cancer, the frequency declines markedly, with ovarian and gastric cancer representing up to 5% of malignant pleural effusions. Lymphoma accounts for approximately 10% of all malignant pleural effusions and is a common cause of chylothorax. Carcinomas of the lung, breast, ovary, and stomach and lymphomas account for about 80% of all malignant pleural effusions. In approximately 7% of patients with malignant pleural effusions, the primary site is unknown when the diagnosis of a malignant pleural effusion is first established.[3]

A less common cause of a malignant pleural effusion, other than metastatic carcinoma and lymphoma, is a primary tumor of the pleura, malignant mesothelioma. The association of asbestos exposure and malignant mesothelioma was documented in the 1960s following an initial report from the North Western Cape Province of South Africa and a subsequent study of insulation workers in this country. Owing to the long latency period of 20 to 40 years between exposure and onset of disease, death due to a malignant mesothelioma is expected to reach 9000 annually in Europe and 2200 annually in the United States in 2020.

PATHOGENESIS

Lymphatics are situated beneath the parietal pleura over the intercostal spaces. An important feature of the parietal pleura is lymphatic stomata, 2- to 12-μm openings between parietal pleural mesothelial cells. The stomata and their associated lymphatic channels form lymphatic lacunae immediately beneath the mesothelial layer. These lacunae coalesce into collecting lymphatics, which join the intercostal trunk vessels with flow directed mainly toward the mediastinal lymph nodes. The lymphatic system of the parietal pleura plays a major role in the resorption of pleural liquid and protein. Interference with the integrity of the lymphatic system between the

TABLE 77-2 Causes of Malignant Pleural Effusion[a]

Tumor	*n*	Percent
Lung	641	36
Breast	449	25
Lymphoma	187	10
Ovary	88	5
Stomach	42	2
Unknown primary	129	7
All other malignancies	257	14

[a] *n = 1793. Combined data from nine series.*

parietal pleura and mediastinal lymph nodes can result in a pleural effusion.[4–7] Autopsy series have indicated that impaired lymphatic drainage from the pleural space is the predominant mechanism for the accumulation of fluid associated with malignancy: A strong relationship was found between carcinomatous infiltration of the mediastinal lymph nodes and the occurrence of pleural effusion. In contrast, no relationship was found between the extent of direct pleural involvement by metastasis and the occurrence of a pleural effusion. Further support for this mechanism is provided by the observation that pleural effusions generally do not develop when the pleura is involved by sarcoma because of the characteristic absence of lymphatic metastases.

When pleural metastases develop, tumor cells either "seed" the mesothelial surface or invade the subserous layer: When the mesothelial surface is involved, abundant tumor cells can be found in pleural fluid; with subserous involvement, a paucity of malignant cells are exfoliated into the pleural space. Tumor involvement of the pleura causes reactive changes in the mesothelium that may lead to mesothelial shedding, mesothelial thickening, and, on occasion, marked pleural fibrosis. Pleural fibrosis, usually observed in the more advanced stage of tumor involvement of the pleura, is at least partially responsible for the low concentrations of glucose and the low pH seen in some malignant pleural effusions and for the failure to achieve pleurodesis after instillation of chemical agents.

A bloody, malignant pleural effusion usually results from direct invasion of blood vessels, occlusion of venules, tumor-induced angiogenesis, or possibly increased capillary permeability due to vasoactive cytokines and chemokines. Malignant pleural effusions usually contain a large number of morphologically normal lymphocytes, usually in the 50% to 70% range, but typically less than that occurs with tuberculous pleurisy (usually ≥80%). Although the explanation for the lymphocytosis is unclear, these lymphocytes are predominantly T lymphocytes that appear to play a role in the local defense against tumor invasion of the pleural cavity. The percentage of mesothelial cells in malignant effusions is variable, ranging from few to a large percentage of the total cells. An abundance of mesothelial cells occur early in the course of pleural infiltration, before pleural fibrosis and marked infiltration with tumor; in more advanced stages of pleural metastasis, fewer mesothelial cells are generally seen because of pleural fibrosis.

Autopsy findings in patients with malignant effusions have provided valuable information about the pathogenesis of pleural metastases. When carcinoma of the lung metastasizes to the pleura, both the visceral and parietal pleural surfaces tend to be involved. The visceral pleural surface is rarely, and the parietal pleural surface is almost never, the sole site of involvement. Parietal pleural involvement in lung cancer most likely results from neoplastic spread across the pleural cavity from visceral pleural sites along pleural adhesions that are either preformed or secondary to the malignant process.[4–7] The pathogenesis of visceral pleural metastasis in lung cancer appears to be through pulmonary artery invasion and embolization.[5] The histological type of lung cancer does not appear to determine the propensity for pulmonary arterial invasion. Adenocarcinoma of the lung is the most common cell type to involve the pleura because of its peripheral location and spread by contiguity. Bilateral pleural metastases in lung cancer are almost always associated with hepatic involvement and parenchymal invasion of the contralateral lung.

Pleural metastases from primary sites below the diaphragm generally are a manifestation of tertiary spread from established liver metastases. The data with breast cancer are conflicting; some studies show a high incidence of ipsilateral pleural effusion, while others show no such predilection. Probably two mechanisms are operative, chest wall lymphatic invasion resulting in an ipsilateral effusion and hepatic spread with bilateral or contralateral disease.

At diagnosis, pleural effusions are rare in Hodgkin disease but not infrequent in non-Hodgkin lymphoma. Pleural effusions can be found in previously untreated patients with non-Hodgkin lymphoma, even in the absence of detectable intrathoracic lymphadenopathy; however, the pleural effusion is usually not an isolated manifestation of the disease. At autopsy in Hodgkin disease, lymphomatous infiltration of the lung rather than direct pleural invasion or mediastinal adenopathy has been found in association with the pleural effusion. Lymphomatous invasion of the pleura appears to be an uncommon and late finding in Hodgkin disease but is seen with increased frequency in non-Hodgkin lymphoma. As Hodgkin disease progresses, the incidence of pleural effusion increases and approaches 30%. At autopsy, a 30% to 60% incidence of pleural effusions and a 7% to 30% incidence of pleural nodular infiltrative lesions have been noted.[8]

While pleural effusion in lymphoma can be due to impaired lymphatic drainage secondary to mediastinal adenopathy, pleural or pulmonary infiltration, or thoracic duct obstruction, impaired lymphatic drainage appears to be the primary mechanism in Hodgkin disease and direct pleural infiltration the predominant cause in non-Hodgkin lymphoma.[9]

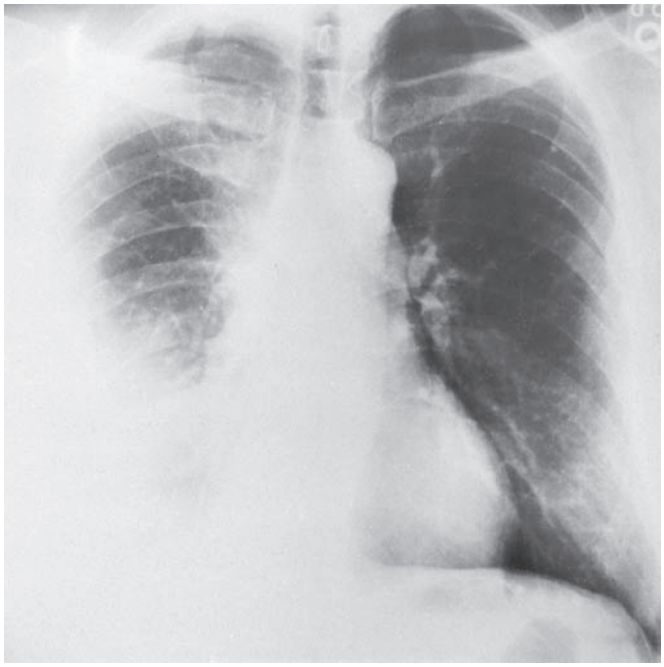
Malignant mesothelioma (see Chapter 79) is usually a unilateral disease (Fig. 77-1); bilateral tumors are present in less than 10% of patients. An early manifestation of the tumor is a pleural effusion that is reabsorbed or organized and then largely replaced by tumor and fibrosis. At autopsy, the lung is often encased in tumor that involves both visceral and parietal pleural surfaces. The pleural space is often obliterated, and the amount of pleural fluid is variable. The tumor seldom penetrates deeply into the lung parenchyma; instead, it extends into interlobar fissures. Hilar lymph nodes are involved by tumor in less than 50% of patients. Distant hematogenous metastases are unusual but have been described in liver, bone, adrenals, thyroid, and kidneys.[10–13]

The two distinct histological types of malignant mesothelioma (epithelial and sarcomatous) generally behave differently. Some patients have mixed tumors with both epithelioid and sarcomatous features. The clinical features of epithelial mesothelioma are similar to those of metastatic carcinoma of the pleura associated with tumor spread by direct extension, that is, a large pleural effusion and metastases to regional lymph nodes. In contrast, patients with sarcomatous mesotheliomas tend to have features characteristic of sarcomas, that is, distant metastases are common, whereas there is little or no pleural effusion. These data are consistent with the pathogenesis of pleural effusions in carcinoma of the pleura, that is, the pleural effusion is primarily due to invasion of the lymphatic system. Moreover, the large bulk of tumor on the pleural surface would be expected to interfere with the removal of pleural fluid by the parietal pleural lymphatics, even if the lymphatics were not directly involved with tumor.

Benign asbestos pleural effusion probably develops as a result of the pleural inflammation that occurs during the passage of asbestos fibers across the pleural space to the parietal pleural lymphatics.

CLINICAL PRESENTATION

Patients with carcinoma involving the pleura most often present with symptoms attributable to a large pleural effusion—dyspnea on exertion and cough. The presence and degree of dyspnea depends on the size of the effusion and the patient's underlying pulmonary function. A therapeutic thoracentesis results in relief of dyspnea in most patients.[14] However, the volume of pleural fluid removed at thoracentesis does not correlate with the change in lung volume. The increase in total lung capacity (TLC) approximates one-third of the volume of fluid removed, while the forced vital capacity (FVC) increases to about one-half of the TLC. Indeed, the mechanism of dyspnea caused by a large pleural effusion appears to be multifactorial in origin, probably entailing a decrease in the compliance of the chest wall, a contralateral shift of the mediastinum, inversion of the ipsilateral



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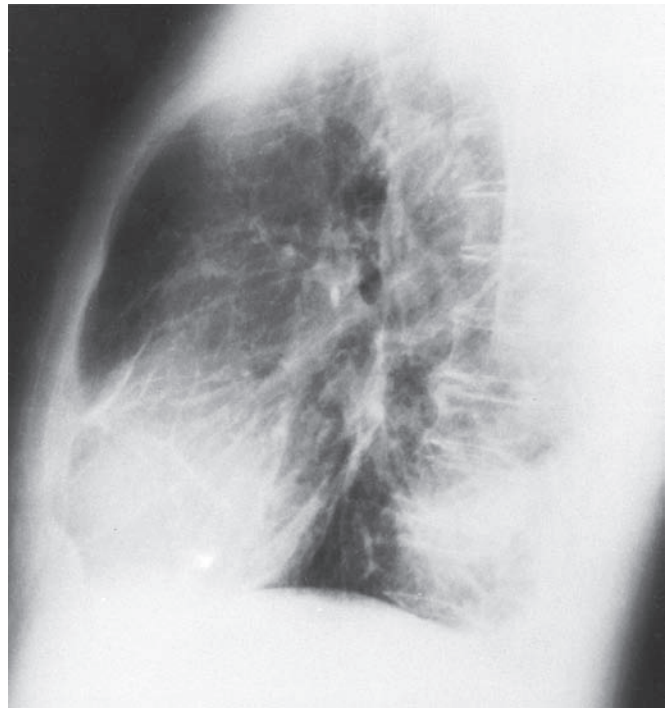
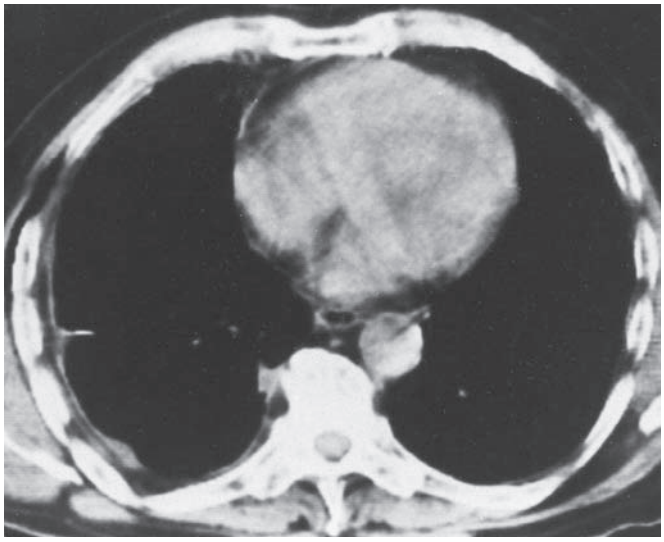


B



C

Figure 77-1 Malignant mesothelioma in a 64-year-old man. **A, B.** Diffuse, right-sided involvement. **C.** Computed tomography scan shows peripheral disposition of mesothelioma along right pleura. The radiodensity in the right hemithorax is a consequence primarily of pleural tumor with little pleural effusion, subsequently treated by right extrapleural pneumonectomy. *(Used with permission of Dr. David Murphy.)*

diaphragm, and a decrease in ipsilateral lung volume modulated by neurogenic reflexes from the lungs and chest wall. Other factors that may contribute to dyspnea and cough are postobstructive pneumonia or atelectasis due to a central bronchial lesion, or the presence of infiltrative malignant disease of the pulmonary parenchyma.[15]

Since malignant involvement of the pleura signifies far advanced disease, these patients commonly have substantial weight loss and appear chronically ill. Chest pain may be present because of involvement of the parietal pleura, ribs, or chest wall. However, in a large series of patients with metastatic carcinoma of the pleura, almost 25% were "asymptomatic" at the time of presentation. In these patients, the malignant pleural effusion was first suspected on physical examination or diagnosed on routine chest radiograph. In almost 50% of patients, the pleural effusion was the first indication of cancer.

The respiratory symptoms of patients with pleural effusion due to lymphoma are indistinguishable in nature and frequency from those due to carcinoma. About 20% of patients with lymphoma have no respiratory symptoms when the malignant pleural effusion is diagnosed.

Most patients with carcinoma of the pleura have evidence of a pleural effusion on physical examination when first seen by the physician. Physical signs of pleural effusion are to be expected, since the volume of pleural fluid in most malignant effusions is greater than 500 mL. Cachexia and lymphadenopathy are present in about one-third of patients on initial presentation. Ipsilateral chest wall tenderness and a pleural friction rub are rare.

In contrast to patients with carcinomatous involvement of the pleura, virtually all patients with malignant mesotheliomas are symptomatic when first seen by the physician. In six series of patients encompassing 160 cases of malignant mesothelioma, only one patient was asymptomatic at presentation.[10–12] Chest pain is the most common presenting symptom and occurs in 60% to 70% of patients. Dyspnea and cough are next in frequency and are present in about 25% and 20% of patients, respectively.

Benign pleural effusion due to asbestos exposure is a diagnosis of exclusion. Its frequency of occurrence in exposed workers is estimated to be up to 7%. Benign asbestos pleural effusion is the most common manifestation of asbestos-related pleuropulmonary

disease in the first 20 years after initial asbestos exposure. Two-thirds of patients with benign asbestos pleural effusions are asymptomatic at presentation, with the effusion diagnosed on a routine chest radiograph. Approximately 20% of patients present with pleuritic pain and 10% with dyspnea.[16] The effusion generally persists for several months and resolves within 1 year. Recurrent effusions, either on the ipsilateral or contralateral side, occur in approximately 25% of patients. The differential diagnosis centers around distinguishing benign asbestos pleural effusion from mesothelioma. Since benign asbestos pleural effusion occurs sooner after initial exposure than does mesothelioma (20 years being the rough dividing line), a pleural effusion in a young asbestos-exposed individual is more likely to represent a benign effusion than is an effusion that occurs 20 to 40 years after initial exposure.[16] Also, an asymptomatic pleural effusion is more apt to be benign. The absence of other radiographic manifestations of asbestos exposure is not helpful in distinguishing between a benign effusion and mesothelioma. Preoccupation with asbestos-related disease occasionally leads to overlooking treatable causes of pleural effusion, such as tuberculosis.

CHEST RADIOGRAPHY

A pleural effusion ipsilateral to the primary lesion is the rule in carcinoma of the lung. When the primary site of the cancer is elsewhere than the lung and with the possible exception of breast cancer, there seems to be no ipsilateral predilection and bilateral effusions are common.

In three of four patients who present with carcinomatous involvement of the pleura, the pleural effusion is moderate to large, with volumes ranging from 500 to 2000 mL of fluid. Approximately 10% present with effusions of less than 500 mL; another 10% present with massive pleural effusions (complete opacification of the hemithorax) (Fig. 77-2). Some 70% of patients with a massive pleural effusion have a malignancy.

The finding of bilateral effusions with a normal heart size also suggests a malignant etiology (Fig. 77-3). Approximately 50% of patients who present with this radiographic finding have a malignant effusion. However, lupus pleuritis, hypoalbuminemia, constrictive pericarditis, rheumatoid pleurisy, benign asbestos pleural effusions, and cirrhosis must also be considered in the differential diagnosis.

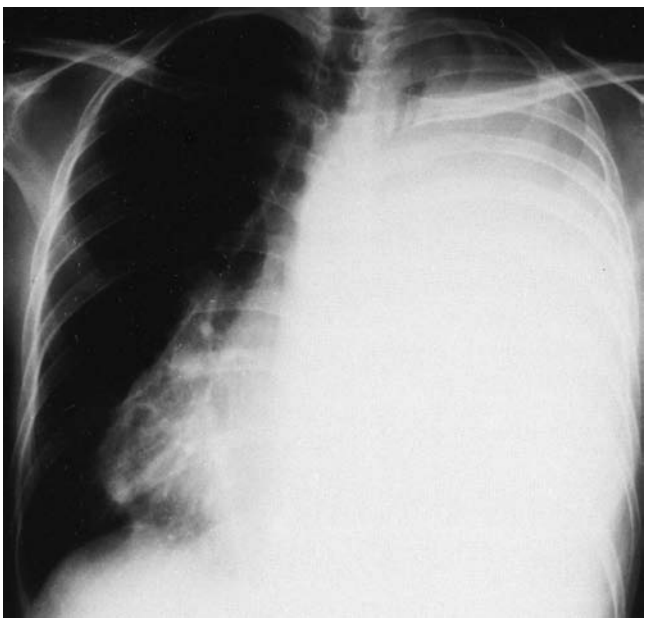


Figure 77-2 Carcinoma of the cervix metastatic to the left pleura and mediastinum. The massive pleural effusion is associated with a contralateral shift of the mediastinum.

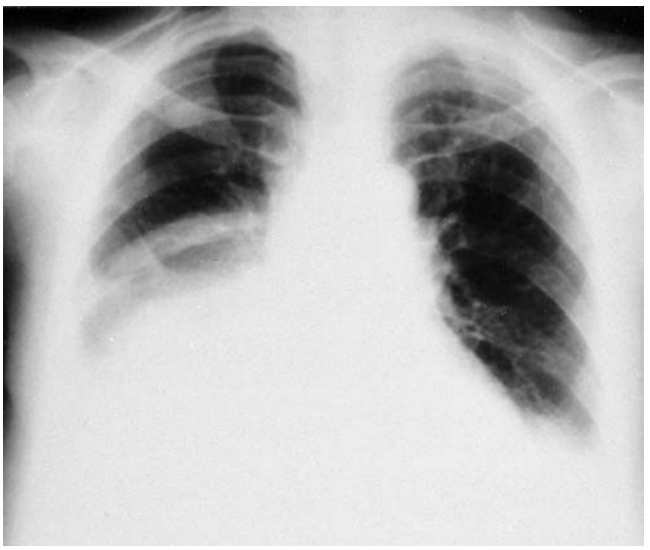


Figure 77-3 Carcinoma of the lung involving right lower lobe, with metastasis to right pleura and mediastinal lymph nodes. The pleural effusions are bilateral and the heart size is normal.

If the mediastinum does not shift contralaterally in the face of a large pleural effusion (>1500 mL), malignancy is highly likely. The following diagnoses are then considered: (1) Carcinoma of the ipsilateral mainstem bronchus resulting in atelectasis (Fig. 77-4); (2) a fixed mediastinum due to malignant lymph nodes; (3) malignant mesothelioma (the radiodensity represents predominantly tumor with only a small effusion); and (4) extensive tumor infiltration of the ipsilateral lung, radiographically mimicking a large effusion. Interstitial infiltrates with effusions (lymphangitic carcinomatosis) and multiple nodules with effusions also suggest malignant disease.

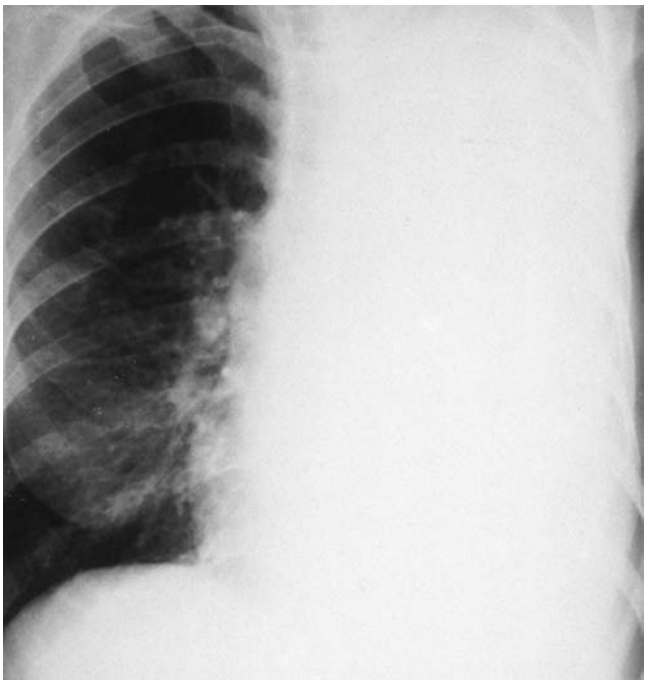


Figure 77-4 Carcinoma of the left mainstem bronchus resulting in complete atelectasis of the left lung. The left hemithorax is completely opacified, and the mediastinum has shifted to the side of the bronchial occlusion. The radiographic opacity represents a combination of collapsed lung and pleural fluid.

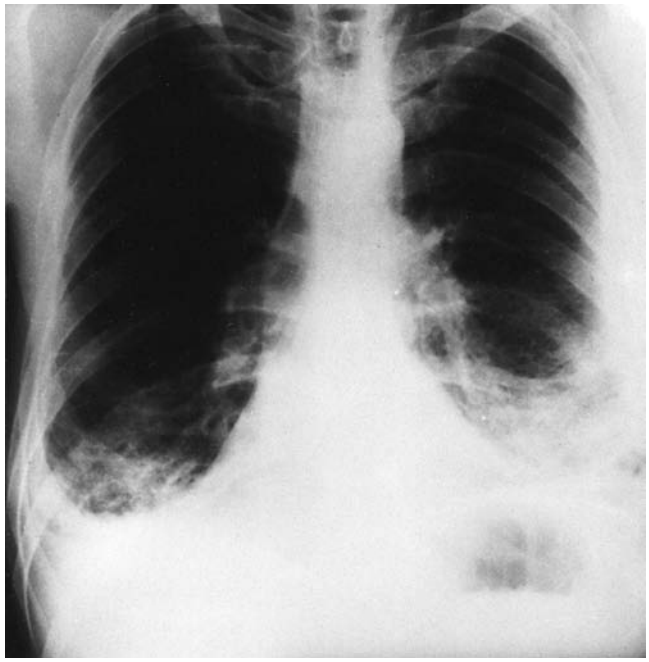


Figure 77-5 Bilateral pleural thickening in a 44-year-old man exposed to asbestos for 18 months 20 years ago. Bilateral pleural effusions were succeeded by progressive pleural thickening.

Depending on the stage of the mesothelioma at the time of presentation, the chest radiograph may show a moderate to large pleural effusion (early) or a nodular, thickened pleura with extension to the apex of the hemithorax (late). Contralateral mediastinal shift often occurs early, that is, when the pleural effusion is large; but, as fluid resorbs and is replaced by tumor, the ipsilateral hemithorax shrinks in size and the mediastinal structures either remain in the midline or shift ipsilaterally (Fig. 77-1).[10–12] Contralateral manifestations of asbestos-induced pleuropulmonary disease, such as pleural plaques with or without calcification and interstitial lung disease, often reinforce the diagnosis. In the more advanced stages of malignant mesothelioma, other radiographic findings are mediastinal widening due to lymph node involvement, an enlarged cardiac silhouette due to pericardial involvement with effusion, and extrapleural lesions, such as soft tissue masses or rib destruction.

Benign asbestos pleural effusions are small to moderate (<1000 mL) unilateral effusions with evidence of pleural plaques or asbestosis identifiable in less than 20% of patients.[16] Calcified pleural plaques are rare, since calcifications require 25 to 40 years from the time of initial asbestos exposure, whereas benign asbestos pleural effusion tends to be the earliest manifestation of asbestos pleuropulmonary disease. Some patients are left with normal chest radiographs, but most have residual abnormalities. These include a blunted costophrenic angle (most common), crow's feet (converging fibrous strands creating a likeness of a bird's foot), rounded atelectasis (in which a portion of the lung periphery has become atelectatic due to pleural adhesions that collapse small bronchi), and diffuse pleural thickening that is sometimes progressive (Fig. 77-5).

PLEURAL FLUID CHARACTERISTICS

Malignant pleural fluid may be serous, serosanguineous, or grossly bloody. The number of nucleated cells in the pleural fluid is modest (1500–4000/μL) and consists of lymphocytes, macrophages, and mesothelial cells. In about one-half of malignant pleural effusions, lymphocytes predominate (50% –70% of nucleated cells). Malignant cells in pleural fluid are rare in some patients; in others, they constitute virtually the complete population. Polymorphonuclear leukocytes usually represent less than 25% of the cell population; but, rarely, when pleural inflammation is active, they predominate. The reported prevalence of pleural eosinophilia in malignant effusions ranges from 8% to 12%.[17] However, malignancy was as frequent in eosinophilic as noneosinophilic pleural effusions. Therefore, the finding of pleural fluid eosinophilia should not be considered a predictor of benign disease.

The pleural fluid in patients with carcinoma of the pleura is typically an exudate with a protein concentration of about 4 g/dL. However, protein concentrations have been reported in the range of 1.5 to 8.0 g/dL. Often unappreciated is the fact that less than 5% of malignant pleural effusions can be transudates. These transudates are due either to concomitant congestive heart failure, atelectasis from tumor obstructing a major bronchus, or the early stages of lymphatic obstruction. Since protein can exit from the pleural space only by parietal pleural lymphatics, a few weeks are necessary for protein to accumulate (from the 1.5 g/dL of normal pleural liquid) to a level of greater than 50% of the serum concentration. Chronic pleural effusions and those with a low pleural fluid pH and glucose tend to have a higher total protein concentration and are virtually never transudates. Sometimes, the total protein pleural fluid to serum ratio may be low (<0.50), but the fluid would qualify as an exudate by lactate dehydrogenase (LDH) criterion alone.

In about one-third of patients with malignant pleural effusions at the time of diagnosis, the pleural fluid pH is low (<7.30), ranging from 6.95 to 7.29. In these low-pH effusions, the glucose concentration is also low (<60 mg/dL, or the ratio of pleural fluid to serum glucose is below 0.5), the lactate concentration is high, the P_{CO_2} is high, and the Po_2 is low.[1,18] As a rule, the glucose concentrations are in the range of 30 to 55 mg/dL though on rare occasions, the glucose is as low as 5 mg/dL. These low-pH, low-glucose effusions have usually been present for several months and are associated with a large tumor burden and fibrosis of the pleura. The markedly abnormal pleura interferes with glucose transport from blood to pleural fluid; the glucose that does enter is metabolized by normal and malignant pleural cells to form CO_2 and lactate. The abnormal pleura impairs the efflux of these end products of glucose metabolism from the pleural space, resulting in pleural fluid acidosis. About 10% of malignant pleural effusions have high amylase concentrations. The finding of a high level of salivary-like isoamylase in a patient without esophageal rupture essentially establishes the diagnosis of malignancy, most likely adenocarcinoma of the lung.

Early in the course of malignant mesothelioma, the pleural fluid may be serous; later, it tends to be hemorrhagic. The effusion associated with malignant mesothelioma is an exudate with a protein concentration in the range of 4 to 5 g/dL and a modest number of nucleated cells (<5000/μL), predominantly mononuclear. The LDH concentration tends to be higher than in the patient with carcinoma of the pleura; frequently the concentration exceeds 600 IU/L. In 60% of patients with malignant mesothelioma, at the time that the diagnosis is established, the pleural fluid pH is low (below 7.30) and the glucose concentration is also low (pleural fluid/serum ratio below 0.5); in contrast, the incidence of low pH and low glucose concentration in carcinoma of the pleura is about 30%. The natural progression of malignant mesothelioma, resulting in large tumor masses and concomitant fibrosis that obliterate the pleural membrane, provides a reasonable explanation for these biochemical findings. In some instances of malignant mesothelioma, the viscosity of pleural fluid is greatly increased because of a high concentration of hyaluronic acid. Although a high concentration of hyaluronic acid in pleural fluid does raise the question of malignant mesothelioma as the cause, this test is not specific and only moderately sensitive; thus, it is of no diagnostic value.

The pleural fluid in benign asbestos pleural effusions is a sanguineous, lymphocyte-predominant exudate, with pleural fluid eosinophilia

in 30% of cases. During the acute stage, there may be a moderate number of polymorphonuclear leukocytes. The pH and glucose are in the normal range (above 7.30 and 60 mg/dL, respectively).

DIAGNOSIS

A malignant pleural effusion can be diagnosed only by demonstrating malignant cells in pleural fluid or pleural tissue. Cytology is a more sensitive test for the diagnosis than percutaneous pleural biopsy, because pleural metastases tend to be focal and the latter is a blind sampling procedure. The yield of either procedure increases as the disease becomes more advanced. It appears, based on thoracoscopy, that initial pleural metastases originate near the mediastinum and diaphragm; as the disease progresses, tumor spreads cephalad and costally. The yield from pleural biopsy with a proven malignant effusion averages 50% to 60%. With improved techniques, the yield from exfoliative cytology now approaches 90% to 95%. If the clinician suspects a malignant effusion, several hundred milliliters of fluid should be removed at the initial diagnostic thoracentesis and at least 60 mL sent for cytological examination.[19] This maneuver will not improve the yield on the initial study but, if it is negative, a repeat procedure several days later may provide fluid with fewer degenerative mesothelial cells and freshly exfoliated malignant cells. Percutaneous pleural biopsy should be reserved for the second thoracentesis if the initial pleural fluid cytological examination is negative. If the second cytological examination and initial pleural biopsy are negative, a third cytological examination and second pleural biopsy soon after, usually is not diagnostic.

There are several options for the patient with suspected malignancy and a negative pleural fluid and pleural tissue examination. These include observation for a few weeks with repeat studies, thoracoscopy, or open pleural biopsy. Before proceeding to more invasive procedures, other causes of an exudative pleural effusion must be excluded. Tuberculous pleurisy should always be considered in the patient with a lymphocyte-predominant exudate with or without a positive tuberculin skin test. The yield from pleural biopsy culture and histology, in conjunction with pleural fluid culture, should provide a bacteriological diagnosis of tuberculous pleurisy in 90% to 95% of cases. Even if diagnostic studies are negative, patients with a positive purified protein derivative skin test or interferon-γ release assay and a lymphocyte-predominant exudate should be treated presumptively for tuberculous pleurisy because of the high risk (43%–65%) of developing active pulmonary or extrapulmonary tuberculosis within 5 years if untreated. Bronchoscopy has a low diagnostic yield for an idiopathic pleural effusion without parenchymal lesions on chest radiograph, ipsilateral mediastinal shift, or hemoptysis. The value of computed tomographic examination of the chest in an undiagnosed exudative effusion is unknown and probably not cost-effective. If observation is the course undertaken, the clinician would expect a malignant pleural effusion to be stable or progress and an effusion not due to malignancy to be stable or regress over time. Failure to identify a malignant pleural effusion for several weeks is rarely a disservice to the patient, who has incurable disease. Exceptions are those malignancies that tend to be responsive to therapy, such as breast cancer, prostate cancer, thyroid cancer, small-cell lung carcinoma, germ-cell neoplasms, and lymphomas.

The diagnostic utility of immunohistochemistry in the diagnosis of malignant pleural effusions secondary to adenocarcinoma, mesothelioma, and lymphoma has been established. Carcinoembryonic antigen (CEA), Leu-M1, B 72.3, Ber-EP4, and BG-8 are the best markers for the diagnosis of adenocarcinoma.[20] Calretinin and cytokeratin 5/6 are the best markers for mesothelioma.[11,20] Flow cytometry is useful in the evaluation of lymphocytic pleural effusions in which lymphoma is a possible diagnosis.[21] The ability of tumor markers to discriminate between benign and malignant pleural effusions is poor. Markers such as CEA, vascular endothelial growth factor (VEGF), carbohydrate antigens (e.g., CA 15-3, 19-9, and 72.4), cytokeratin 19, and enolase have significant overlap between benign and malignant pleural effusions. Hyaluronan does not appear to discriminate between pleural effusions from adenocarcinoma and mesothelioma.[22]

Inflammatory processes involving the pleura may mimic mesothelioma, and patients are often subjected to a battery of tests and consultations before the diagnosis is established. An accurate diagnosis is imperative for proper epidemiological records, appropriate therapeutic intervention, and litigation. Early in the course of a mesothelioma, establishing a definitive diagnosis may be problematic. Pleural fluid cytology and pleural biopsy may allow the diagnosis of malignancy but often cannot distinguish between mesothelioma and adenocarcinoma. Sarcomatous type mesothelioma can be confused with rare tumors, such as fibrosarcomas or hemangiopericytomas. Thoracoscopic biopsy or open thoracotomy is usually necessary to obtain adequate tissue to confirm the diagnosis. Thoracoscopic biopsy has a high diagnostic yield for mesothelioma, approaching 100% in some series, while the yield for pleural fluid cytology alone is 25% and that for combined pleural fluid cytology and closed pleural biopsy is 40%. Histochemical and immunochemical studies, in conjunction with electron microscopy, have improved the accuracy of the diagnosis of malignant mesothelioma.

PROGNOSIS

The diagnosis of a malignant pleural effusion signals a poor prognosis. Patients with carcinoma of the lung, stomach, and ovary tend to have a survival time of only a few months from the time that the malignant effusion is diagnosed; patients with breast cancer tend to survive longer, several months to years, depending on the response to chemotherapy. Patients with lymphomatous pleural effusions tend to have survival times intermediate between those of breast cancer and other carcinomas.

Several studies have suggested that when pH and glucose concentrations in the malignant pleural effusion are low (below 7.30 and 60 mg/dL, respectively), the survival time is less (average 2 months) than in those with a normal pH and glucose (average 10 months). However, in a systematic review of 433 patients with malignant effusions, pleural fluid pH was of marginal clinical utility in predicting survival less than 3 months.[1] Performance status at the time of diagnosis may be the only true predictive marker for mortality. A Karnofsky score less than 30 is associated with a median survival of 1.1 months compared to a median survival of 13.2 months in association with a Karnofsky score more than 70.

A pleural effusion in the setting of lung cancer usually excludes operability; however, approximately 5% of these patients have a paramalignant effusion or an effusion from another cause and may be operable and curable. Thus, it is essential to establish the cause of the pleural effusion before deciding that the patient is not a candidate for curative surgery.

Survival following the diagnosis of malignant mesothelioma is related to the stage of the disease at the time of presentation. Those patients with only ipsilateral involvement of the pleura and lung survive the longest, whereas those with distant hematogenous metastases have the shortest survival. Chest pain portends a worse prognosis than dyspnea, reflecting a more advanced stage of disease. Overall, the median survival in malignant mesothelioma is about 9 months. The epithelial type has a median survival approximately twice that of the sarcomatous type; long-term survivors of more than 3 years are seen almost exclusively with the epithelial type. As in metastatic carcinoma of the pleura, a low-pH effusion in malignant mesothelioma is also predictive of a short survival with one study reporting an association with increasing pH and survival.

Benign asbestos pleural effusions tend to resolve within 3 to 4 months, leaving some residual on the chest radiograph. Although

malignant mesothelioma occasionally develops in patients with benign asbestos effusions, it does not appear to be a harbinger of mesothelioma. Obviously, the risk of developing mesothelioma is greater in these asbestos-exposed individuals than in the general population.

TREATMENT

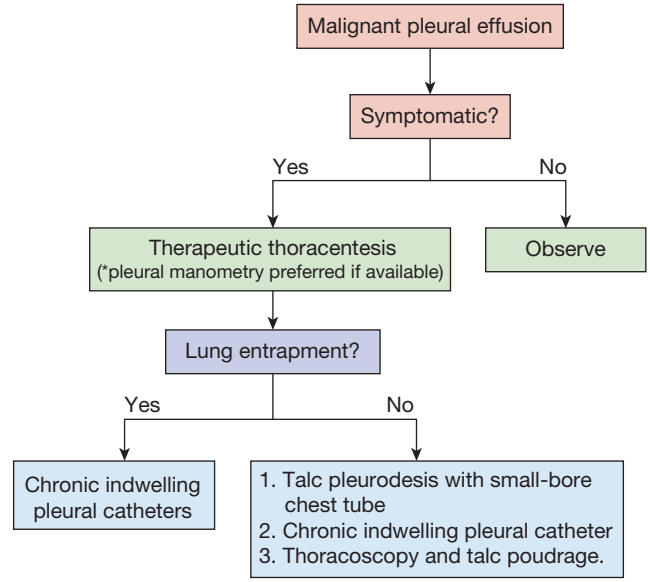
When the pleural effusion has been proved to be malignant or paramalignant and the patient is not a surgical candidate, the type of palliative therapy is weighed, taking into account the patient's general condition, symptoms, performance status, primary tumor type and expected response to therapy, expected survival, and degree of lung reexpansion following pleural fluid evacuation. Several management options are available (Table 77-3 and Fig. 77-6). Asymptomatic patients need not be treated; however, most will develop progressive pleural effusions that will evoke symptoms and require therapy, but some will reach a steady state of pleural fluid formation and removal and not progress to a symptomatic stage. In the debilitated patient in whom a short survival is expected based upon the general health, extent of disease, and biochemical characteristics of the pleural fluid, periodic therapeutic thoracentesis as an outpatient is often preferable to hospitalization for tube thoracostomy and intrapleural instillation of a chemical agent. However, outpatient pleurodesis using small-bore catheters can be accomplished successfully with decreased cost and morbidity.

The most important mechanical factor governing pleurodesis success is the degree of visceral and parietal pleural apposition. Lack of apposition following pleural fluid drainage will not allow for a successful pleurodesis. Current guidelines and treatment strategies rely on the postthoracentesis chest radiographs following thoracentesis to determine if lung reexpansion has occurred. The identification of a pneumothorax "ex vacuo" will typically preclude attempts at pleurodesis if less than 50% of pleural apposition is seen on the chest radiograph.

An unexpandable lung is characterized as the inability of the lung to expand to the chest wall allowing for normal visceral and parietal pleural apposition. Unexpandable lung is the direct result of either pleural disease, endobronchial obstruction resulting in lobar collapse,

TABLE 77-3 Management of Malignant and Paramalignant Pleural Effusions

Option	Comment
Observation	Small asymptomatic effusion; most will progress and require therapy
Therapeutic thoracentesis	Prompt relief of dyspnea; recurrence rate variable
Chemotherapy	May be effective in lymphoma, small-cell lung cancer, breast cancer
Radiotherapy	Mediastinal radiation may be effective in lymphoma and lymphomatous chylothorax
Indwelling catheter	Patient-controlled symptom relief; spontaneous pleurodesis in 50% by 2 mo. Effective for symptomatic relief with lung entrapment.
Chest tube drainage with talc slurry	Control of effusion in >90% of cases if lung entrapment not present
Thoracoscopy with talc poudrage	Control of effusion in >90% of cases if lung entrapment not present
Pleuroperitoneal shunt	When other options have failed or not indicated; may be useful for chylothorax
Pleural abrasion and partial pleurectomy	Virtually 100% effective; requires VATS or thoracotomy



*Pleural space elastance (PEL) > 19 cm H_2O/L with the first 500 mL of fluid removed was shown to have a complete pleurodesis failure at 1 month. PEL > 14.5 cm H_2O/L during the terminal stages of drainage probably have a high predictive pleurodesis failure and we would advocate the use of chronic indwelling pleural catheter in this group.

Figure 77-6 Management algorithm for malignant pleural effusions.

or chronic atelectasis.[23–25] Unexpandable lung occurring as a consequence of active or remote pleural disease may present as a postthoracentesis hydropneumothorax or inability to completely drain the effusion due to the development of anterior chest pain. We believe that pleural manometry is the gold standard for identifying an unexpandable lung during initial pleural drainage. Unexpandable lung occurring as a consequence of active or remote pleural disease has been separated into two distinct clinical entities termed trapped lung and lung entrapment. We define an unexpandable lung with a visceral pleural peel in the absence of malignancy or active pleural inflammation as a trapped lung. In contrast, an unexpandable lung resulting from a visceral pleural peel secondary to active pleural inflammation, infection, or malignancy is defined as lung entrapment.[23–26]

Abnormal lung expansion, detected with pleural manometry, is associated with pleurodesis failure. A pleural space elastance more than 19.0 cm H_2O/L during the first 500 mL of pleural fluid removed was predictive of a 100% pleurodesis failure at 1 month.[27] Abnormalities of lung expansion detected during later stages of pleural drainage are more common in malignant pleural effusions and may affect immediate or delayed pleurodesis outcomes. The frequency with which abnormalities of lung expansion occur in this setting is quite common and approaches 50% of our malignant pleural effusion cases at our institution.

The use of indwelling catheters (PleurX, Denver Biomaterials, Golden, Colorado) has gained popularity because it is an outpatient procedure, and the patient and family can manage the pleural effusion in a timely fashion at home. These catheters have become the mainstay of treatment for a symptomatic refractory or recurrent malignant pleural effusion in most centers in the United States, because they can successfully palliate the symptoms of dyspnea regardless of whether lung entrapment is present or not. Approximately 50% of patients develop spontaneous pleurodesis by 2 months.[28–30] The infection rate appears to be low. However, the expense of the drainage bottles can be prohibitive for some patients. An option with the indwelling catheter is to perform chemical pleurodesis through the catheter 1 or 2 weeks following insertion depending upon the clinical situation. In situations where the patient

with a malignant pleural effusion has lung entrapment, there are two mechanisms responsible for the accumulation of fluid. The patient is instructed to remove fluid when dyspnea occurs and stop drainage immediately when chest pain develops. The onset of substernal chest pain signals the point when the "malignant fluid" has been evacuated, leaving the unexpandable lung from tumor involvement of the visceral pleural surface. The remaining fluid simply represents hydrostatic equilibrium.

Pleural abrasion and/or pleurectomy are highly effective in obliterating the pleural space and controlling a malignant pleural effusion. Although mechanical abrasion can be performed thoracoscopically, pleurectomy is a major surgical procedure associated with considerable morbidity and some mortality.[31] Accordingly, this procedure is reserved for patients who are in good general condition and have a reasonably long expected survival or who have failed a sclerosing agent procedure.

In general, systemic chemotherapy is disappointing for the control of malignant pleural effusions. However, some patients with lymphoma, breast cancer, or small-cell carcinoma of the lung manifest a good response to chemotherapy. In patients with carcinoma of the breast, assessment of steroid receptor status from the malignant pleural fluid can provide valuable information relating to the potential response to hormonal manipulation.

As a rule, radiation of the hemithorax is contraindicated in malignant pleural effusions from lung cancer, since the adverse effects from radiation pneumonitis outweigh possible benefits of therapy. However, radiation may be helpful in patients with lymphoma and lymphomatous chylothorax when involvement of mediastinal nodes predominates.

Until recently, the most common method of controlling a malignant pleural effusion was chest tube drainage and intrapleural instillation of a chemical agent. A number of antineoplastic and nonantineoplastic chemical agents have been used for pleurodesis with variable success. Currently, the most widely used agents are talc, doxycycline, and bleomycin.[32–35] Talc pleurodesis, by either poudrage or slurry, has been shown by numerous investigators to have a success rate of about 90%. In head-to-head comparisons with tetracycline and bleomycin, talc has been shown to be more effective. Talc is available to administer as slurry or an aerosol. When used as slurry through a chest tube, talc is less expensive than doxycycline and substantially less expensive than bleomycin. The use of VATS to administer talc significantly increases the cost and usually requires a few days of hospitalization. The degree of pain associated with talc has been variously reported from nonexistent to severe. Fever following talc poudrage and slurry is common, occurring 16% to 69% of the time. Fever, occasionally as high as 102°F, characteristically occurs 4 to 12 hours after talc instillation and may last for 72 hours. Other complications that have been reported with talc include empyema, arrhythmia, and respiratory failure, including adult respiratory distress syndrome (ARDS) and pneumonitis. The method of administration (poudrage or slurry) does not appear to be associated with the development of respiratory failure, and both high (10 g) and low (2 g) doses have been implicated. The size of the talc particles may be the major risk factor for respiratory failure, with fewer episodes reported with large particle size. Patients with severe pulmonary impairment appear to be at greatest risk of developing acute respiratory failure.[31]

Before instituting chest tube drainage for intrapleural instillation of a chemical agent, it is necessary to demonstrate that fluid removal improves dyspnea. Determination of the FVC and P_{O_2} during the first 12 hours after therapeutic thoracentesis can be misleading. Some patients experience a transient decrease in P_{O_2} and minimal improvement in pulmonary function, despite relief of dyspnea, as dyspnea is largely related to decreased chest wall compliance and stimulation of the neurogenic receptors of the chest wall and lung.

Following the initial therapeutic thoracentesis, the recurrence rate and the interval for return of symptoms should be noted. If recurrence is rapid, with return of dyspnea, pleurodesis should be considered. If the expected survival is at least several weeks, the patient is not debilitated, and the pleural fluid pH is above 7.30, the patient is a suitable candidate for pleurodesis. However, it is fruitless to attempt pleurodesis if the lung cannot be expanded fully, as with bronchial occlusion or lung entrapment. Furthermore, demonstrating a low pleural fluid pH not only suggests a shorter survival but also predicts a lower likelihood of response to chemical pleurodesis. A large tumor bulk involving the pleural surfaces, seen with low-pH, low-glucose pleural effusions, is associated with diminished effectiveness of the chemical agent.

Ideally, when contemplating chemical pleurodesis the patient should undergo pleural manometry with therapeutic thoracentesis.[26] A simple water manometer connected to a digital analog system can determine whether the patient has lung entrapment. If lung entrapment is present, the pleurodesis procedure will not be completely successful. Pleural manometry measures elastance of the pleural space by evaluating the pressure change in relationship to the volume of fluid removed. Individuals with lung entrapment have a significant decrease in pleural pressure with removal of fluid. When the patient's pleural elastance is normal (<14.5 cm H_2O/L of fluid removed) there is a high likelihood of successful pleurodesis with proper technique.[26] The pleural space should be drained as completely as possible so that the pleural surfaces remain in close contact during the time of the initial inflammatory insult. This is best accomplished by tube thoracostomy. A small-bore chest tube, 14 to 16Fr, is as effective as a standard large-bore chest tube and causes less morbidity for the patient. When the follow-up chest radiograph demonstrates that the effusion has been drained and the lung is fully expanded, 5 g of talc slurry should be instilled into the pleural space. Following instillation, the tube should be clamped for 1 to 2 hours. It has been demonstrated that the instillation of radiolabeled tetracycline through a chest tube disperses rapidly and completely in the pleural space without patient repositioning. However, with talc slurry, it is currently recommended that the patient be rotated frequently during the period when the chest tube is clamped, including Trendelenburg and sitting upright. The chest tube should be removed when drainage is less than 150 mL in 24 hours. If a large volume of drainage persists, a repeat dose of talc should be instilled. With the properly selected candidate and rigorously applied technique, the malignant effusion is controlled with talc slurry in about 90% of cases.

A further option available for the patient with an intractable, symptomatic, malignant effusion, who cannot undergo pleurodesis, is a pleuroperitoneal shunt.[36] These shunts have been found to be safe and effective. The shunt may be particularly beneficial in refractory chylothorax, as it allows recirculation of chyle.[37,38] Few complications have been associated with shunt placement, and it can be inserted in patients who are poor surgical candidates. With experienced operators, palliation is obtained in 80% to 90% of properly selected patients. The major problem has been shunt failure, which is most commonly due to clotting of the catheter. It is unknown whether patients who have experienced shunt occlusion are at greater risk for occlusion after a new shunt is placed.

In general, there is a nihilistic attitude regarding the management of patients with malignant mesothelioma because of the tumor's poor response to chemotherapy and radiation therapy. Early in the course of some patients with a mesothelioma, a large unilateral pleural effusion can cause substantial dyspnea. Pleurodesis may be successful in some patients; however, in others, the procedure is unhelpful because of lung entrapment from the tumor burden in the pleural space.

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CHAPTER 78

Pneumothorax

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DEFINITION

The abnormal presence of air in the pleural cavity, separating the visceral from the parietal pleura, with subsequent collapse of the adjacent lung, is known as pneumothorax. Traditionally, pneumothorax has been classified as having occurred spontaneously or as a result of trauma. Spontaneous pneumothorax is then further subclassified as having occurred without an apparent cause, in a background of clinically normal lungs (primary spontaneous pneumothorax [PSP]) or having occurred in the setting, and as a consequence of, underlying lung disease (secondary spontaneous pneumothorax [SSP]). Although it is now believed that the majority of PSPs occur in the setting of occult lung disease with underlying anatomical abnormalities such as subpleural blebs, this method of classification is still in common practice.

Traumatic pneumothorax occurs as a result of either blunt or penetrating trauma to the chest with a subsequent disruption of the structural integrity of the lung, chest wall, esophagus, trachea, or bronchi. Iatrogenic pneumothorax is a subtype of traumatic pneumothorax resulting as a consequence of diagnostic or therapeutic procedures such as central-line insertions, thoracentesis, or mechanical ventilation.

PATHOPHYSIOLOGY

As alluded to above, air does not normally exist within the pleural space. The pressure within the pleural space is negative with respect to the alveolar pressure during the entire respiratory cycle. Despite this, air does not enter the pleural space from the alveoli. The reason for this lies in the fact that the partial pressure of all gases in the venous blood averages only 706 mm Hg, thereby driving the net movement of alveolar air (760 mm Hg at sea level during end-inspiration) into the capillaries and not into the pleural space, which would require a pleural pressure lower than 706 mm Hg to pull the air in. Under normal circumstances, most individuals do not generate a net negative inspiratory force of −54 mm Hg.[1]

The negative pressure in the pleural space results from the inherent tendency for the lung to collapse (elastic recoil) and of the chest wall to expand. The negative intrapleural pressure is not uniform throughout the pleural space; a gradient of 0.25 cm of water per centimeter of vertical distance can be measured between the apex and the base of the lung. At the apex, the pressure is more negative than at the base, and this pressure difference tends to favor a greater distention of the alveoli located in this region.

The presence of air in the pleural cavity is thought to occur by one of three events: a communication between the pleura and the alveolus, a communication between the atmosphere and the pleural space, or the presence of a gas-producing organism within the pleura.[1] When a communication develops between an alveolus and the pleural space, air will move from the alveolus into the pleural space until there is equalization of pressure or until the communication is sealed. The same happens with a communication between the chest wall and the pleural cavity. The greater the amount of air that enters the pleural cavity, the more the lung collapses. If unabated, enough air may enter the pleural space to cause a shift of the mediastinum and eventually lead to hemodynamic compromise, a condition referred to as tension pneumothorax.

Although the mechanism responsible for PSP is not completely understood, experimental overdistention of normal lungs results in rupture of subpleural alveoli.[2] Air can dissect along the bronchovascular sheath medially to produce pneumomediastinum, which may be accompanied by subcutaneous emphysema or pneumothorax (Fig. 78-1), or it can dissect to the peripheral portion of the lung.[3] Peripheral dissection of air may result in an air-containing space within or immediately beneath the visceral pleura. Pathologic studies of resected lungs from patients with PSP usually show one or both of these types of airspaces, a bleb or a bulla. A pneumothorax may occur when these peripheral bullae or blebs become distended and rupture into the pleural space.

Clinically, the results of a pneumothorax are dependent on the degree of lung collapse but the main physiologic consequences of a pneumothorax are a decrease in the vital capacity of the lung and a decrease in the Pa_{O_2}. The reduction in arterial Pa_{O_2} appears to be caused by low ventilation–perfusion (V/Q) ratios, anatomic shunts, and, occasionally, alveolar hypoventilation. Total lung capacity, functional residual capacity, and diffusing capacity are also reduced, though less than vital capacity. Air in the pleural space eliminates the gravitational gradients of pleural pressure and regional lung volume so that regional ventilation is more uniform and reduced. Anthonisen reported that lungs demonstrate airway closure at low lung volumes and suggested that airway closure is the main cause of V/Q imbalance in patients with pneumothorax.[4] If perfusion to the collapsed lung is preserved, there is an increase in pulmonary

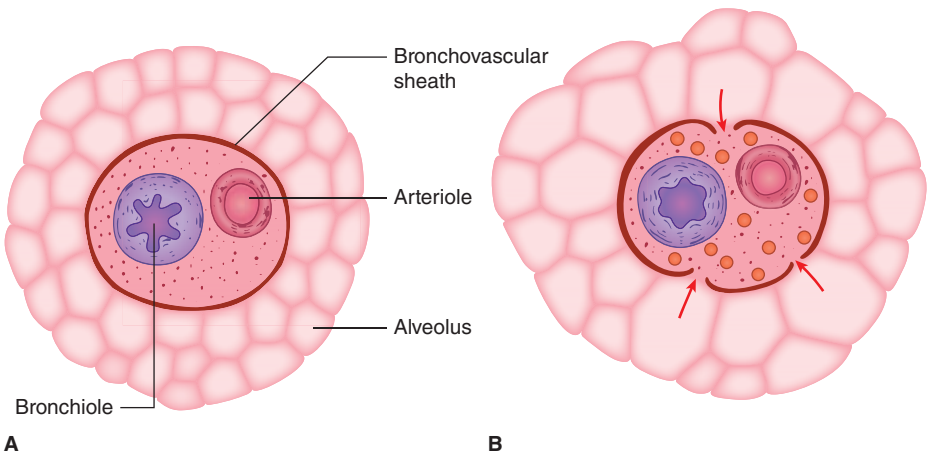

Figure 78-1 Proposed mechanism of alveolar rupture in spontaneous pneumothorax. **A.** Normal structures. **B.** Overdistention of marginal alveoli. Pressure in the adjacent bronchovascular sheath remains lower than in the overdistended alveoli. This pressure gradient may lead to rupture of the alveoli with dissection of air toward the pleura or mediastinum. *(Reproduced with permission from Maunder RJ, Pierson DJ, Hudson LD. Subcutaneous and mediastinal emphysema: pathophysiology, diagnosis, and management. Arch Intern Med. 1984;144(7):1447–1453.)*

shunt and substantial hypoxemia. If perfusion to the collapsed lung is reduced by hypoxic vasoconstriction, hypoxemia may be minimal. In general, pneumothoraces occupying less than 25% of the hemithorax are not usually associated with significant shunts.[5] Under normal circumstances, despite the degree of pneumothorax; hypoxemia tends to abate within 24 hours, presumably from redistribution of pulmonary blood flow.

In the healthy person, the decrease in vital capacity and Pa_{O_2} is typically well tolerated. In patients with compromised pulmonary function prior to pneumothorax, the decrease in vital capacity may result in significant hypoxemia, alveolar hypoventilation, and respiratory acidosis. Upon evacuation of air from the pleural space, the Pa_{O_2} usually improves. In animal studies, the Pa_{O_2} returns to baseline immediately after reexpansion of the lung.[6] In humans, normalization of the Pa_{O_2} takes longer and may occur over hours to several days. The delay in improvement may be related to the duration of the pneumothorax.

REABSORPTION OF PLEURAL GASES

The time required to absorb all gases in a pneumothorax is quite variable. It has been estimated that between 1% and 6% of a pneumothorax is absorbed in 24 hours.[7] Gas reabsorption from the pleural space is achieved by simple diffusion from the pleural space into the venous blood. The rate of gas reabsorption depends on four variables: (1) the pressure gradient for the gases between the pleural space in relation to the venous blood, (2) the diffusion properties for the gases present in the pleural space, (3) the area of contact between the pleural gas and the pleura, and (4) the permeability of the pleural surface. (i.e., a thickened, fibrotic pleura will absorb less than normal pleura.)

The solubility and diffusion properties of different gases vary considerably, and the speed of reabsorption will depend on the type of gas. Oxygen will be absorbed 62 times faster than nitrogen, the slowest gas to be reabsorbed. Carbon dioxide will be absorbed 23 times faster than oxygen, and carbon dioxide and water vapor will equilibrate almost instantaneously. Under normal circumstances, the total gas pressure in the pneumothorax is within a few millimeters of mercury of that of the atmosphere, or 760 mm Hg. Tissue gas tensions are close to those of systemic venous blood: typically pCO_2 = 46 mm Hg, pO_2 = 40 mm Hg, pH_2O = 47 mm Hg, and pN_2 = 569 mm Hg, giving a total pressure of 702 mm Hg as mentioned above. This positive-pressure gradient between the pneumothorax and the venous blood constitutes the driving force responsible for gas reabsorption from a pneumothorax.

When breathing room air, this driving force is only 58 mm Hg (760–702 mm Hg) and this limits the rate of resorption (Fig. 78-2). During inhalation of 100% oxygen, the total gas pressure is about 146 mm Hg. This difference is due to the reduction in partial pressure of nitrogen from 569 to zero mm Hg. Though this is associated with an increase in oxygen in arterial blood from 100 to 640 mm Hg, oxygen consumption in the tissues ensures that the partial pressure in the end-capillary blood rises only slightly (from 40 mm Hg to about 54 mm Hg). The results of one, small prospective human trial and one experimental, animal model trial suggest that administration of high-flow oxygen can expedite resolution of a pneumothorax.[8,9]

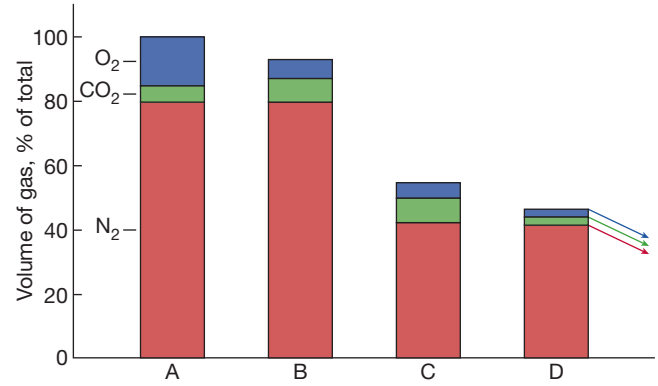

Figure 78-2 Hypothetical representation of the resorption of a spontaneous pneumothorax. **A.** Closed pleural space after leak has stopped. The alveolar gas in the space contains 15% O_2, 5% CO_2, and 80% N_2. **B.** CO_2 and O_2 have quickly equilibrated with the surrounding tissues; the amount of N_2 in the pneumothorax is unchanged. The pneumothorax is already decreased by about 10%. **C.** The number of N_2 molecules is unchanged, but the total volume of the pneumothorax has decreased (see **B**). Therefore, the outward diffusion of N_2 increases because pN_2 in the pleural space is greater than pN_2 in the tissues. As N_2 diffuses out, the total volume of gas in the pleural space decreases and concentrations of O_2 and CO_2 increase. As a result, O_2 and CO_2 diffuse out of the pleural space. **D.** The high N_2 concentration promotes the exit of N_2 from the pleural space and continues the cycle by which the pneumothorax grows smaller. *(Reproduced with permission from Farhi LE. Atmospheric nitrogen and it's role in modern medicine. JAMA. 1964;188:984–993.)*

SYNDROMES

■ PRIMARY SPONTANEOUS PNEUMOTHORAX

Epidemiology

The age-adjusted annual incidence of PSP ranges from 7.4 to 18 cases per 100,000 population in males and 1.2 to 6 cases per 100,000 in females. The male-to-female ratio ranges from 3:1 to as high as 6:1 and the characteristic patient is a tall, thin male in the third to fifth decade of life.[1,10]

Patients with PSP tend to be taller and thinner than control populations. A study of military recruits who developed spontaneous pneumothorax found subjects to be, on average, 2 in taller and 25 lb lighter than the typical military recruit.[11] In another study, the frequency of PSP rose with increasing stature and reached an incidence of 200 per 100,000 person-years for subjects at least 76 in tall.[10]

In addition to stature and male sex, tobacco smoking significantly increases the risk of spontaneous pneumothorax and has been associated with a ninefold or greater risk of developing a first PSP.[12] The relative risk of PSP has been shown to exhibit a dose–response relationship with the quantity of cigarettes per day and the length of exposure, increasing more than 20 times in men who smoke one-half pack per day and 100 times in men who smoke one pack per day compared to nonsmokers. The lifetime risk in healthy smoking men may be as high as 12%, as opposed to 0.1% in nonsmokers.[12] One review of 402 patients with spontaneous primary pneumothorax reported that 92% of the patients were smokers or ex-smokers.[5] Another study showed that patients who had stopped smoking more than 1 year before their first spontaneous pneumothorax had no recurrence during a follow-up of 5.2 years.[13]

Etiology

Although the diagnosis of PSP is restricted to patients without primary lung disease, it is likely that many of these patients do in fact have underlying lung pathology. Thus, a more accurate description of PSP is pneumothorax occurring in patients with no *obvious* lung disease.[14] While the exact mechanism by which a spontaneous communication between the alveolar space and the pleura has not been elucidated, most authors believe that rupture of a previously unidentified bleb or bulla adjacent to the pleura is to blame for the development of PSP.[15] These subpleural blebs and bullae are typically referred to as emphysema-like changes (ELCs) when seen on CT scan and, although it has been shown that the majority of patients with PSP have ELC, no causal relationship has clearly been established. These blebs are demonstrated by chest radiograph in only 20% of cases of PSP, but can be seen in approximately 80% of affected patients by both CT imaging and by surgical evaluation.[16,17]

In two studies, ELCs were found in 89% on the ipsilateral side and up to 80% bilaterally, while only 20% of those without PSP had these changes.[18,19] Another study showed that 81% of nonsmokers with healed PSP had ELCs while those nonsmokers without PSP had none.[20] Despite this clear association, a causative relationship is still debated. In part, this is due to the observation that only a minority of blebs are observed to be ruptured at the time of surgery, and other lesions, termed pleural porosity, are observed.[1] Pleural porosity is believed to predispose the pleura to air leakage by disruption or replacement of the mesothelial cells of the visceral pleura with inflammatory cells that increase pleural permeability.[17]

The pathogenesis of these bullae, blebs, and pleural porosity is not definitively known but has been associated with a variety of elements, most commonly with airway inflammation.[21,22]

Airway inflammation secondary to cigarette smoking may be associated with or contribute to the development of these blebs. Respiratory bronchiolitis in smokers may be an important element in the development of PSP.[23] Pathologic evidence of respiratory bronchiolitis was found in more than 88% of smokers undergoing surgery for PSP.[24]

In addition to airway inflammation, other factors have been linked to ELC and pleural porosity, including connective tissue abnormalities, hereditary influences, increased negative pressure at the apices associated with ectomorphic body habitus, anatomical bronchial abnormalities, and overdistention of alveoli with poor collateral ventilation. Pleural pressure is most negative at the apices, and the degree of negativity relates to the height of the lungs. The alveoli of taller persons are subjected to greater mean distending pressures. Over a long period, this phenomenon could lead to the formation of subpleural blebs in a taller population genetically predisposed to bleb formation.

There are multiple reports of genetic associations or patterns of PSP. Some reports suggest that PSP is inherited through an autosomal dominant gene with variable penetrance[25] while others report an associated autosomal recessive[26] or an X-linked recessive inheritance pattern.[25] Genetic risk factors that have been associated to PSP include the HLA haplotype $A_2B_{40,}$[27] the α_1-antitrypsin phenotypes M_1M_2, and the FBN1 gene mutations.[28]

The rate of recurrence after a PSP is approximately 25% (range: 23%–52%) and recurrence usually occurs within 1 to 2 years after the first episode.[29] The rate of recurrence may increase with each successive pneumothorax. In one study, the risk of recurrence increased to more than 60% after the second pneumothorax and to 83% after the third.[30] Although there is no predilection for the right or left hemithorax with the initial episode, more than 75% of recurrences occur on the same side as the first pneumothorax. Despite the documentation that pleural blebs occur bilaterally in many patients with PSP, the risk of contralateral pneumothorax is only 5% to 10%. Risk factors for recurrence that have been identified include greater height, lower weight, and smoking status.[31]

Death rarely occurs after PSP.[32] In a study of spontaneous pneumothorax in which patient ages ranged from 15 to 34 years (most likely representing patients with PSP) the mortality rate was reported to be 0.09% for men and 0.06% for women.[33]

■ SECONDARY SPONTANEOUS PNEUMOTHORAX

Epidemiology

SSP is a more serious event than PSP because, by definition, the patient has underlying lung disease. A pneumothorax in a patient with already diminished pulmonary reserve can be life-threatening and requires more immediate medical attention and intervention.

The incidence of SSP is similar to that of PSP. An epidemiologic study in Olmsted County, Minnesota, documented an incidence of SSP of 6.3/100,000 year for males and 2/100,000 year for females.[10] On average, patients with SSP are 15 to 20 years older than patients with PSP due largely to the older age of patients with emphysematous lung disease. The risk of recurrence for SSP is somewhat higher than for PSP and ranges from 40% to 80%, again, likely due to the underlying lung pathology.

Etiology

A variety of pulmonary diseases have been associated with spontaneous pneumothorax, but chronic obstructive pulmonary disease (COPD) is the most common. The Veterans Administration Cooperative Study on Pneumothorax noted that pneumothorax tended to occur in patients with moderately severe COPD, with a quarter of the participants having an FEV_1 below 1 L and a mean FEV_1/FVC ratio of 57%.[34] Persistent bronchopleural fistula was also noted to be common in patients with obstructive lung disease, and 35% of patients had an air leak for more than 5 days.

Although airway diseases (COPD, cystic fibrosis [CF], and severe asthma) are the most common underlying lung disorders, a wide spectrum of pulmonary diseases has been associated with SSP (Table 78-1).[35]

In contrast to the low mortality rate associated with PSP, patients with SSP have a much higher risk of death. The VA Cooperative study reports an analysis of three papers that combined, reveal a

TABLE 78-1 Etiology of Secondary Spontaneous Pneumothorax

Obstructive Lung Disease
Chronic obstructive pulmonary disease (COPD)
Asthma
Interstitial Lung Disease
Idiopathic pulmonary fibrosis (usual interstitial pneumonitis [UIP])
Nonspecific interstitial pneumonitis
Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Sarcoidosis
Radiation pneumonitis or fibrosis
Infection
P. jiroveci pneumonia
Tuberculosis
Coccidioidomycosis
Acute bacterial pneumonia (i.e., *Staphylococcus*)
Malignancy
Primary lung carcinoma
Pulmonary metastasis (especially sarcomas)
Complications of chemotherapy
Connective Tissue Disease
Rheumatoid arthritis
Ankylosing spondylitis
Marfan syndrome
Ehlers–Danlos syndrome
Polymyositis/dermatomyositis
Scleroderma
Other
Catamenial pneumothorax
Pulmonary infarction
Pulmonary alveolar proteinosis
von Recklinghausen disease
Granulomatosis with polyangiitis (Wegener)

mortality of 16% for SSP.[34] Videm et al.[36] showed that SSP increased the mortality of age-matched COPD patients by 3.5 times.

Cystic Fibrosis

Pneumothorax is a common and potentially serious complication of CF lung disease. It occurs more frequently in CF than in the general population and results in significant morbidity and mortality, typically occurring with more advanced disease. Approximately 3.5% of patients with CF will suffer this complication at some point in their lives. The majority occur in adulthood, with a median age of 21 years.[37] Pneumothorax may also be a marker of poor prognosis with one study showing the median survival after the first spontaneous pneumothorax to be only 29.9 months.[38]

The pathophysiology of spontaneous pneumothorax in CF is likely related to chronic airway inflammation that eventually leads to structural changes with severe airflow obstruction; inflammation with poor clearance of thick, inspissated secretions; air trapping in the distal airways; and eventual rupture of the pleural surface with rising alveolar pressures.[37]

The risk of developing pneumothorax increases with age and with declining pulmonary function (FEV_1). A recent study of pneumothorax in CF demonstrated that the risk of pneumothorax increased by 50% when FEV_1 was <30% predicted.[39] Other important risk factors for the development of pneumothorax include the presence of *Pseudomonas aeruginosa, Burkholderia cepacia,* or *Aspergillus* in the airways, and the use of Dornase alfa. The presence of these airway pathogens may increase inflammation and secretions leading to obstruction and the use of inhaled Dornase alfa may cause bronchospasm leading to acute decline in FEV_1 with inhalation.[40]

CF-specific recommendations exist regarding the management of pneumothorax.[41] A full discussion of these is beyond the scope of this chapter but several points regarding airway clearance in the setting of pneumothorax are of particular importance. With small pneumothoraces it is recommended that most airway clearance modalities could be continued, with the exception of those providing positive-pressure or percussive ventilation, which could further increase the size of pneumothorax. With large pneumothorax, it is recommended that airway clearance modalities should be held. Though the use of inhaled medications could provoke coughing, it is not recommended that these be held.

Recurrence of pneumothorax is more frequent in this population. An estimated failure rate of 37% with tube thoracostomy alone has been reported, but up to 70% of all patients have either an initial treatment failure, or an ipsilateral recurrence, ultimately needing more definitive treatment.[42] Despite the recurrence rate being so high, the guidelines recommend reserving pleurodesis for large recurrent pneumothoraces.[41] However, because the recurrence rate in CF is high, many CF centers still consider pleurodesis after the first episode. In the past, there was concern that pleurodesis would preclude patients from lung transplantation. However, recent studies have shown that pleurodesis does not add appreciably to complications during lung transplantation.[43–45] Although center-dependent, pleurodesis is no longer considered a contraindication to transplantation.[43]

Catamenial Pneumothorax

Catamenial pneumothorax is a rare condition that occurs in women and is defined as recurrent pneumothoraces occurring within 72 hours of onset of menses. One study reported a mean of 3.17 episodes (range: 2–10) in a population of women prior to surgical treatment.[46] This syndrome, by designation, occurs during the reproductive years, usually in the third or fourth decade of life; however, cases associated with hormone replacement have been reported.[47] Though initially felt to be extremely rare, the condition is becoming increasingly recognized. A series from the Mayo Clinic found the condition in 5.6% of women with spontaneous pneumothorax over a 21-year period; however, more recent studies suggest the incidence of this disorder may actually be much higher.[48,49]

There is no single, definitive etiology for the development of catamenial pneumothorax. One theory suggests pleural and/or diaphragmatic endometriosis as the basis for this disorder; yet, only a fraction of women is found to have endometrial deposits at the time of surgical exploration. Alternative mechanisms that have been proposed include peritoneal air entering the thoracic cavity through diaphragmatic defects during menstruation or intercourse, endometrial implants in the terminal bronchioles causing obstruction, and increased circulating levels of prostaglandin $F_{2\alpha}$ during menstruation resulting in bronchospasm and vasospasm.[47] It is possible that various pathogenic mechanisms are at work.

The diagnosis, as mentioned above, is based on *recurrent* pneumothorax occurring within 72 hours of the onset of menses. Onset is typically heralded by chest pain and dyspnea. Over 90% of catamenial pneumothoraces affect the right hemithorax, but isolated left-side or bilateral pneumothoraces have been reported.

Given the unacceptably high recurrence rate of 50% to 100% with medical treatment alone, management with surgery followed by medical/hormonal therapy is typically indicated.[47,49,50] Surgical treatment, which can be accomplished with video-assisted thoracoscopy, involves excision of endometrial implants, closure of any diaphragmatic defects, stapling of any blebs, and pleurodesis. Medical treatment is aimed at suppressing the ectopic endometrium and ovulation and at preventing further seeding. This is typically accomplished by using oral contraceptives, danazol, or gonadotropin-releasing hormone agonists. No controlled trials have examined the efficacy of one medication over another. If menses is not suppressed, there is a risk of recurrence, even after surgical treatment. Hysterectomy with bilateral oophorectomy will induce surgical menopause and has been employed to prevent pneumothorax.[47]

Pneumothorax in Acquired Immunodeficiency Syndrome

Patients with acquired immunodeficiency syndrome (AIDS) have a significantly increased risk of developing pneumothorax. Roughly 2% to 5% of AIDS patients experience spontaneous pneumothorax. In one study, pneumothorax complicated 1.2% of 599 HIV patient admissions over 3 years.[51] Mortality was significantly higher (30.8%) in patients with pneumothorax than in those without (5.8%).

Pneumothorax in AIDS patients is associated with multiple infectious etiologies. *Pneumocystis jiroveci,* bacterial infections, Kaposi sarcoma, cytomegalovirus, pulmonary Cryptococcus, coccidiomycosis, and mycobacterial disease have all been associated with spontaneous pneumothoraces. Other risk factors for the development of pneumothorax in HIV include tobacco use, treatment with inhaled pentamidine, and the presence of a pneumatocele on chest radiograph.

Most studies have shown *Pneumocystis jiroveci* pneumonia (PCP) to be the primary etiology. However, a recent observational study of 105 HIV patients with spontaneous pneumothoraces found bacterial pneumonia to be the major underlying etiology (34.3%) followed by PCP (29.5%) and pulmonary tuberculosis (15.2%).[52] In addition, the authors noted that bacterial pneumonia was a more common cause among drug users and those with CD4+ count over 200 cells/mL whereas PCP was a more common cause among patients with sexually transmitted HIV and CD4+ counts less than 200 cells/mL. Bilateral pneumothoraces were more commonly associated with PCP. Given the strong association with PCP, evaluation and treatment for PCP is recommended in any patient with

AIDS who presents with an otherwise unexplained spontaneous pneumothorax.

The high frequency of pneumothoraces seen in patients with PCP is thought to be secondary to the presence of subpleural cysts and subpleural necrosis associated with this entity. Extensive tissue invasion within the alveolar interstitium is common in severe PCP and may result in subpleural necrosis. These cystic changes are thought to be due to repeated episodes of inflammation and cytotoxic effects of HIV on pulmonary macrophages with elastase production and necrosis of lung tissue.[44,53] These lesions occur most frequently at the apices of the lungs and consist of necrotic alveoli filled with *P. jiroveci* organisms, macrophages, eosinophilic exudate, and fibrinous material.[54] Histologic examination of patients who have recovered from PCP demonstrates subpleural blebs and bullae as well as pneumatoceles. Because of the necrotizing nature of the pneumonia, spontaneous pneumothorax from PCP is notoriously difficult to treat. Persistent air leaks often require tube thoracostomy for several weeks, and up to one-quarter of patients require surgical intervention. Some authors recommend early thoracoscopic therapy in good surgical candidates to avoid prolonged hospitalization.

The incidence of bilateral cystic disease in these patients is extremely high, and the incidence of contralateral pneumothorax was about 50% in one study.[55] Therefore, if surgical intervention is planned, some authors recommend preoperative CT scan of the chest and median sternotomy in patients with significant bilateral disease to facilitate bilateral pleurodesis.

With the rise of AIDS, the frequency of pulmonary tuberculosis has increased. Pneumothorax has been reported in approximately 7% of HIV patients with pulmonary tuberculosis.[56] All pneumothoraces associated with tuberculosis should be treated and often require prolonged periods of chest tube drainage. In cases of tuberculosis, it has been suggested that thoracotomy should not be considered until the patient has received antituberculous therapy for at least 6 weeks; however, objective evidence that this affects outcome is lacking.

TRAUMATIC PNEUMOTHORAX

Trauma is the most common cause of pneumothorax. Patients who have either polytrauma or trauma to the thorax are at risk for pneumothorax. In one study of over 300 pneumothoraces, trauma was responsible for 56% of cases, the majority of which were iatrogenic.[10] Noniatrogenic, traumatic pneumothorax can result from either penetrating or nonpenetrating chest injury. The diagnosis needs to be considered in any patient who is evaluated for significant trauma.

Penetrating chest trauma produces a pneumothorax by allowing air to enter the pleural cavity directly through the chest wall. In addition, if the visceral pleural is penetrated, air may leak from the tracheobronchial tree. If the continuity of the chest wall is disrupted, an open pneumothorax is produced. If the opening in the chest wall is larger than the diameter of the trachea (1.2–1.5 cm in an adult), air movement occurs through the pathway of least resistance, and air is preferentially inspired into the thoracic cavity through the open chest wound. Any open chest wound must be occluded to assure adequate ventilation of the patient.

Pneumothorax is also a frequent finding in patients with blunt trauma to the chest. The visceral pleura may be lacerated secondary to a rib fracture or dislocation; however, in almost one-half of patients with pneumothorax secondary to blunt trauma, there are no associated rib fractures. This is especially common with blunt trauma to the chest secondary to blast injuries and high-altitude falls into water. In such incidents, the abrupt increase in the pressure gradient between the alveolus and the adjacent bronchovascular sheath causes disruption of the alveolar membrane. Dissection of air through the interstitial space results in either pneumothorax or pneumomediastinum.

Occasionally, patients with traumatic pneumothorax have coexisting injuries of the tracheobronchial tree or of the esophagus. In a patient with a traumatic pneumothorax, fiberoptic bronchoscopy should be performed in the presence of hemoptysis or a persistent air leak. Eighty percent of injuries to the tracheobronchial tree are within 2.5 cm of the carina, most commonly on the right side at the membranous–cartilaginous interface. The main lobar bronchi and the cervical trachea are the next most common sites of injury.

Traumatic rupture of the esophagus usually produces a hydropneumothorax. Therefore, if a patient with a traumatic pneumothorax also has a pleural effusion, the possibility of esophageal rupture should be entertained. Almost all patients with perforation of the thoracic esophagus also have dysphagia and pneumomediastinum. An elevated pleural fluid amylase concentration is a reliable screening procedure for esophageal rupture. Once the diagnosis is suspected, contrast radiographic studies of the esophagus should be performed as soon as possible. Untreated, esophageal rupture results in mediastinitis and septic shock; therefore, a high index of suspicion is essential in making an early diagnosis.

Increasing utilization of invasive diagnostic and therapeutic interventions has significantly increased the rate of iatrogenic pneumothorax. These cases may result in considerable morbidity, prolonged hospitalization, and even death, for the affected patient.[57] Iatrogenic pneumothorax can occur as a complication of multiple procedures, but the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration followed by subclavian vein catheter insertion, thoracentesis, transbronchial biopsy, pleural biopsy, and positive-pressure ventilation.[58] The incidence ranges between 20% to 40% with transthoracic needle aspiration; risk factors include COPD, depth of lesion within the lung, and lesions smaller than 2 cm.[59–61] Pneumothorax may also occur with transbronchial needle aspiration, liver biopsy, intercostal nerve block, mediastinoscopy, and tracheostomy among others.

Central venous catheterization carries the second highest risk of iatrogenic pneumothorax. The reported risk ranges from 2% to 12% when using anatomic landmarks for guidance. Subclavian catheterization carries a higher risk than internal jugular catheterization. The increasing use of real-time sonographic guidance for central venous catheterization has significantly decreased this risk for both internal jugular and subclavian approaches.[62,63] Similarly, the routine use of real-time ultrasound guidance for localization of needle puncture site during thoracentesis may decrease the risk of pneumothorax, which develops in approximately 5% of cases.[64]

Another cause of pneumothorax that is frequently overlooked is chest tube malfunction. Common causes of chest tube malfunction include inadequately securing the chest tube to the drainage system, failing to fill the U-tube manometer in the water seal chamber, failing to refill the water in the suction control chamber, and permitting intermittent disconnection of the system during diagnostic or therapeutic studies.

Mechanical ventilation is a frequent, potentially lethal cause of iatrogenic pneumothorax. The overall incidence of pneumothorax during mechanical ventilation ranges from 4% to 15%, but may be significantly higher in patients with underlying inflammatory diseases such as aspiration pneumonia.[65] The incidence of pneumothorax is also increased during mechanical ventilation if patients have chronic pulmonary disease, are on increased amounts of positive end-expiratory pressure, or have right mainstem intubation.[65] The incidence of pneumothorax has been reported to be 6.9% to 14% of patients with acute respiratory distress syndrome (ARDS).[66,67]

Another study reported a 48.8% incidence of pneumothorax in patients with severe ARDS requiring extracorporeal support.[68]

A pneumothorax should be suspected in any patient whose clinical status acutely decompensates on the ventilator. Bedside clues include a sudden increase in respiratory rate or appearance of patient-ventilator dyssynchrony. An increase in the peak and plateau pressures on the ventilator can be a sensitive indicator if the patient is on volume-cycled ventilation. The peak inspiratory pressure often rises suddenly as the lung compliance falls. If the patient is on pressure control ventilation, decreased tidal volumes will be a sign of pneumothorax.

Radiographs of critically ill, mechanically ventilated patients are frequently obtained only in the supine or semisupine position. In one study, supine and semierect radiographs were obtained in 88 critically ill patients with 112 cases of pneumothorax.[69] The radiologist initially failed to detect the pneumothorax in 30% of the cases. Patients with extensive infiltrates, such as in the setting of ARDS, may have no suggestion of lung collapse on chest radiograph. In these patients, the only radiologic sign that may be evident is that of a deep sulcus on the side of the pneumothorax. This finding, as well as any increased lucency on a supine film, should raise suspicion of a pneumothorax and be evaluated by either erect or decubitus views, or ultrasound. If erect or decubitus films cannot be obtained or ultrasound is unavailable, CT scans of the chest may be necessary.

It should be noted that recipients of bilateral lung transplants and patients who have had a "clamshell" thoracotomy do not have an intact mediastinum. Because of this, the normally separate pleural spaces may be in direct communication with each other. Physicians performing procedures on these patients need to be aware that the patient can develop bilateral pneumothoraces because of this anomaly.[70]

CLINICAL FEATURES

The main symptoms with the development of a pneumothorax are chest pain and dyspnea, which occur in 95% of patients. The pain is usually acute, localized to the side of the pneumothorax, and typically pleuritic. Cough, hemoptysis, orthopnea, and Horner syndrome are uncommon manifestations of a pneumothorax.[5,71] A small percentage of patients are asymptomatic or complain only of generalized malaise.

Spontaneous pneumothorax usually occurs at rest, and fewer than 10% occur during strenuous exercise. In PSP, both the dyspnea and chest pain may subsequently abate over the first 24 hours. This may explain why nearly half of patients have symptoms for 2 days before seeking medical attention and why 18% wait for more than a week.[5] Most patients with SSP have more severe symptoms than patients with PSP, and dyspnea frequently seems out of proportion to the size of the pneumothorax.[72]

Small pneumothoraces (<20%) are usually not detectable on physical examination. In patients with obstructive lung disease, even larger pneumothoraces may be difficult to detect since decreased breath sounds and hyperresonance may already be present.[73] On physical examination, vital signs are usually normal, with the exception of moderate tachycardia. Examination of the chest may reveal the affected side to be larger and move less during respiration. Tactile fremitus is absent, the percussion note is hyperresonant, and breath sounds are absent or reduced on the side with the pneumothorax. Hamman sign may be detected. This sign, also heard with pneumomediastinum, has been described as crunching or clicking noises synchronous with the heartbeat but influenced by respiration and body position. Severe tachycardia, with a heart rate above 140 beats a minute, hypotension, cyanosis, or tracheal deviation, suggests the possibility of a tension pneumothorax.

Arterial blood gases often show hypoxemia and perhaps hypocarbia from hyperventilation. Hypoxemia is usually mild in PSP when less than 25% of the lung is affected. When more than 25% of the lung is involved, pulmonary shunts occur more frequently and hypoxemia may be severe. In patients with SSP, pulmonary reserve is already diminished and life-threatening hypoxemia and hypercapnea may be present. In one study, the mean Pa_{O_2} was 48 mm Hg and the mean pCO_2 was 58 mm Hg when patients with emphysema presented with a spontaneous pneumothorax.[73]

Patients with a left pneumothorax may show changes on EKG suggesting an anterolateral myocardial infarction. A rightward shift of the frontal QRS axis and clockwise rotation of the heart result in a diminution of precordial R-wave voltage, a decrease in the QRS amplitude, and precordial T-wave inversion.[74] These electrocardiographic features differ from a transmural myocardial infarction because of the absence of ST-segment elevation or significant Q waves. An anterior subendocardial infarction may present with T-wave inversion but without the rightward shift in the frontal axis. The electrocardiographic changes with a left pneumothorax may normalize when the patient is in the upright or right lateral decubitus position.

RADIOGRAPHIC APPEARANCE

Below are considered the radiographic (plain radiography and CT) and ultrasound findings in pneumothorax.

PLAIN RADIOGRAPHY

Classically, the diagnosis of pneumothorax is established by demonstrating the outer margin of the visceral pleura (and lung) separated from the parietal pleura (and chest wall) by a lucent space devoid of pulmonary vessels (Fig. 78-3) on chest radiograph,

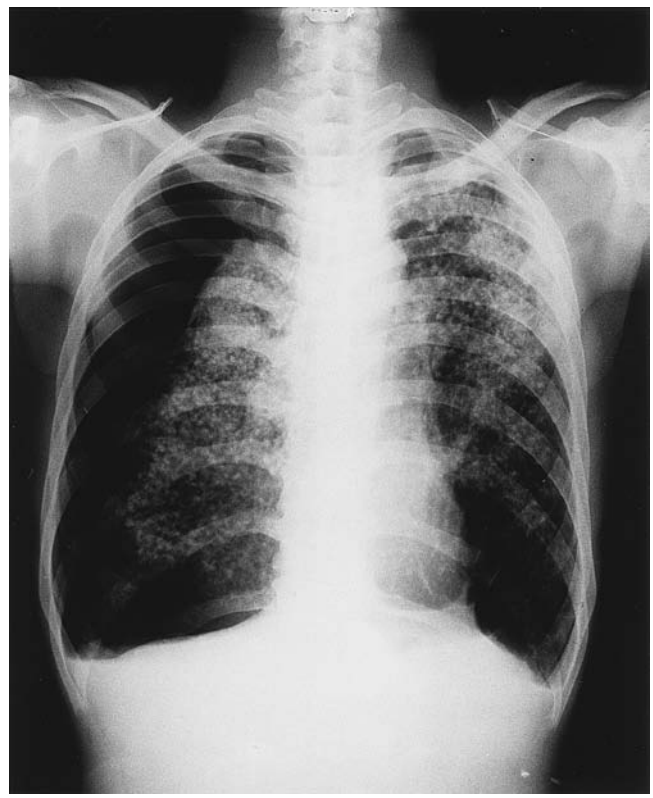

Figure 78-3 A patient with nodular silicosis and a spontaneous secondary pneumothorax. The visceral pleural line is clearly seen with the absence of vascular workings beyond the pleural line. There are cicatricial bullae in both bases.

ultrasound, or CT scan. The pleural line may be difficult to detect with a small pneumothorax unless high-quality upright films are obtained. In erect patients, pleural gas collects over the apex, and the space between the lung and chest wall is most notable there. In the supine position, gas migrates along the broad ventral surface of the lung, making detection on a frontal radiograph difficult. In the supine position, the juxtacardiac area, the lateral chest wall, and the subpulmonic region are the best areas to search for evidence of pneumothorax. Lateral decubitus studies of the appropriate side may be helpful; however, several studies have shown that expiratory films have little or no advantage over upright inspiratory films in the diagnosis of pneumothorax.[75–77] The most recent British Thoracic Society guidelines do not recommend the routine use of expiratory chest films in the evaluation of suspected pneumothorax.[78]

It is very important to differentiate the pleural line of a pneumothorax on chest radiographs from that of a skinfold, clothing, tubing, or chest wall artifact. Careful inspection of the film may show that the artifact extends beyond the thorax, or that lung markings are visible beyond the apparent pleural line. In the absence of underlying lung disease, the pleural line of a pneumothorax usually parallels the shape of the chest wall. Artifactual densities generally do not parallel the course of the chest wall over their entire length. Avascular bullae or thin-walled cysts can be mistaken for a pneumothorax. The pleural line caused by a pneumothorax is usually bowed at its center toward the lateral chest wall. As opposed to a pneumothorax, the inner margins of bullae or cysts are, in general, concave rather than convex and do not exactly conform to the contour of the costophrenic sulcus. A pneumothorax with a pleural adhesion may also simulate bullae or lung cysts. An adhesion tends to form a straight line connecting the lung to the parietal pleura; bullae or cysts have rounded edges. Such features are not 100% specific, and if there is any doubt as to whether the patient has a bulla or cyst or a pneumothorax, a CT scan should be obtained as CT can usually differentiate the two.[79] Pleural effusions may occur coincident with pneumothorax in up to 20% to 25% of cases. Hemopneumothorax occurs in 2% to 3% of cases of spontaneous pneumothorax. Bleeding is believed to represent rupture or tearing of vascular adhesions between the visceral and parietal pleura as the lung collapses.

Quantification of the size of a pneumothorax on chest radiographs is helpful but the methods for quantifying lack uniformity and are by no means precise. Light suggested measuring the average diameters of the collapsed lung and of the affected hemithorax, then cubing these diameters to estimate the percentage of collapsed lung by the following equation: $100 \times (1 - \text{diameter of collapsed lung}^3/\text{diameter of hemithorax}^3)$.[71] For example, if the diameter of the collapsed lung is 6 cm and the diameter of the hemithorax is 10 cm, the collapsed lung is estimated by the formula $100 \times (1 - 6^3/10^3)$. Thus, the estimated size of the pneumothorax is 78%.[71] Rhea et al.[80] proposed the use of a nomogram to calculate the size of the pneumothorax. With this method, the average intrapleural distance is calculated by measuring the interpleural distance at the apex and at the midpoints of both the upper and lower lungs. These three values are then averaged, and the number is reported on a nomogram, which gives an estimated size of the pneumothorax. An example of these calculations is shown in Figure 78-4.

The most common radiographic manifestations of tension pneumothorax are mediastinal shift, diaphragmatic depression, and rib cage expansion (Fig. 78-5). Any significant degree of displacement of the mediastinum from the midline position on maximum inspiration, or any depression of the diaphragm, should be taken as evidence of tension. The degree of lung collapse is an unreliable sign for or against the presence of a tension pneumothorax, since underlying lung disease may prevent collapse even in the presence of tension.

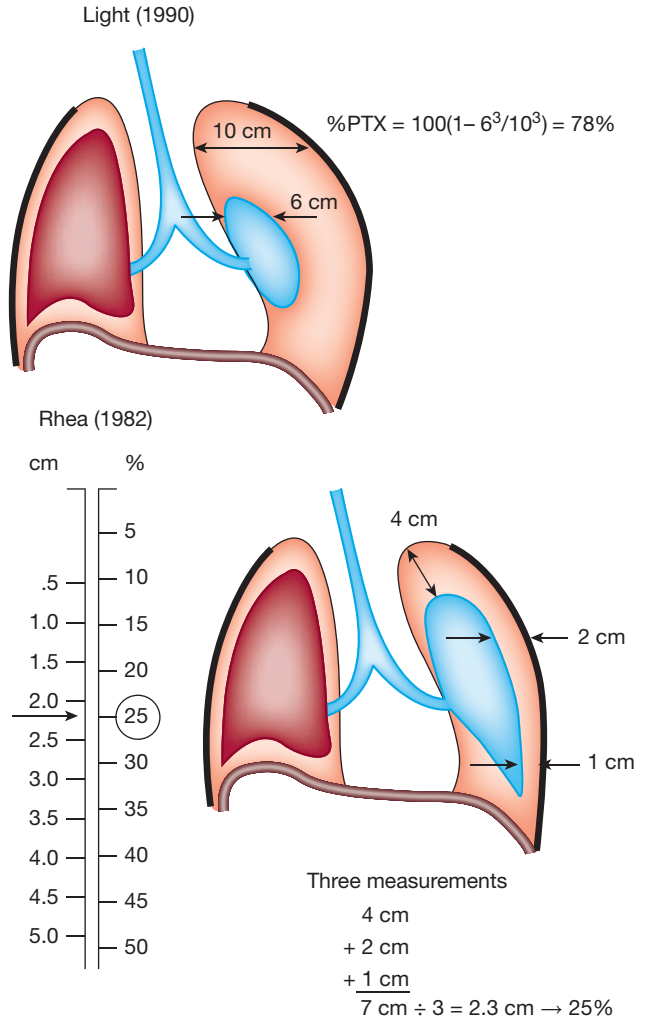

Figure 78-4 Estimation of the size of the pneumothorax according to the method described by Light[32] and Rhea et al.[49] *(Reproduced with permission from Beauchchamp. In: Pearson, ed. Textbook of Thoracic Surgery; 1995.)*

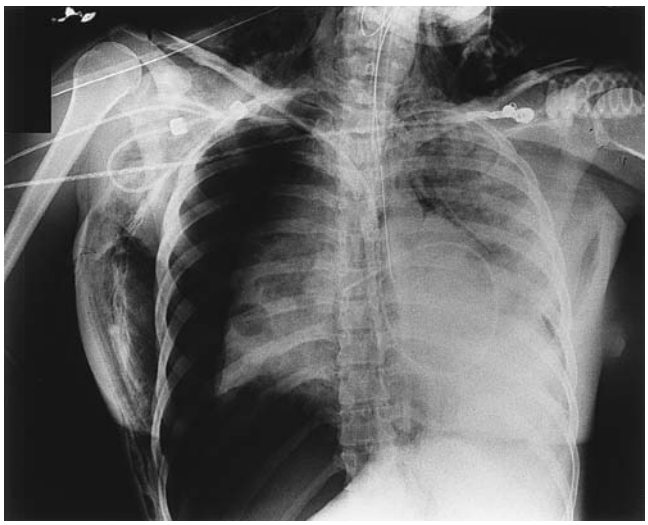

Figure 78-5 Right tension pneumothorax in a young patient with staphylococcal endocarditis and septic emboli. There is marked depression of the right hemidiaphragm, shift of the mediastinum, and subcutaneous emphysema. *Note:* The pulmonary artery catheter, endotracheal tube, and nasogastric tube (midchest) are all displaced to the left.

Video 78-1 Normal lung sliding. This sagittal view using two-dimensional ultrasound shows normal lung sliding through an anterior chest interspace. Two ribs that cast shadows are seen on the left and right edges of the image. The pleural surface is seen below the ribs. The visceral and parietal pleura are apposed giving a shimmering, glistening appearance as the visceral pleura slides back and forth against the parietal pleura with respirations (See also Video 31-9). *Access at www.fishmansonline.com*

LUNG ULTRASOUND

Ultrasound has evolved to become an indispensable bedside tool for rapid diagnosis of pneumothorax. Since the early 1990s, our understanding of lung and pleural ultrasonography has continued to mature as new research has emerged and more clinicians have integrated point-of-care ultrasound into clinical practice. In an observational study of 260 consecutive patients admitted to an intensive care unit (ICU) with acute respiratory failure, experienced physicians performing lung ultrasound alone without additional clinical information were able to correctly diagnose the cause of acute respiratory failure in 90.5% of patients.[81] An observational study of critically ill patients demonstrated that lung ultrasound facilitated diagnosis in 66% and guided management in 47% of patients.[82] A similar more recent observational study in mechanically ventilated patients demonstrated that lung ultrasound changed management in 41% and revealed diagnoses not suspected by the treating physician in 21% of patients.[83]

Lung ultrasound is more sensitive than chest x-ray for detection of pneumothorax when using chest CT as the gold standard. Early studies by Lichtenstein et al. established superiority of lung ultrasound compared to chest x-ray to detect pneumothorax, with sensitivities and specificities ranging from 66% to 100% and 91% to 100%, respectively.[84–87] Meta-analyses (13–21 studies) report a pooled sensitivity of 79% to 95% and specificity of 98% to 99% for lung ultrasound in detecting pneumothorax. Pooled sensitivity and specificity for chest radiography have been reported at 40% to 52% and 99% to 100%, respectively.[88–90]

Normal lung and pleura are characterized by two ultrasound findings: lung sliding and A-lines. By conventional two-dimensional ultrasonography, normal visceral and parietal pleura appear as a bright white (hyperechoic) line that glistens with respirations as the visceral pleura slides back and forth against the parietal pleura (Video 78-1). A principal finding to diagnose pneumothorax is absence of lung sliding (Video 78-2). The presence of air in between the visceral and parietal pleura in pneumothorax prevents propagation of ultrasound waves beyond the parietal pleura, and the sliding, shimmering appearance created by apposed pleura is not seen.[91,92] Presence of lung sliding definitively rules out pneumothorax with a negative predictive value of 100%[84]; however, absence of lung sliding is not specific to pneumothorax and can be seen with any cause of pleural symphysis (chemical pleurodesis, infectious/inflammatory adhesions, fibrosis) or lung volume loss (mainstem intubation, massive atelectasis, mucus plug, pneumonectomy, apnea).[91] If lung sliding is absent, identification of the lung point, a specific sign of pneumothorax, can confirm the diagnosis. The lung point is the edge of a pneumothorax, or boundary between collapsed and aerated lung, and a lung point is 100% specific to rule in pneumothorax.[87] The defining feature of lung point sign is visualization of aerated lung sliding into the field of view next to collapsed lung (Videos 78-3 and 78-4). The lung point can be found anteriorly when the pneumothorax is small, and laterally when it is large.[92]

Evaluation of lung sliding should be confirmed using M-mode, or motion mode. M-mode displays movement of tissues over time. The normal M-mode pattern of lungs includes: horizontal, linear lines at the top, corresponding to the chest wall; a hyperechoic line corresponding to the pleura; and a granular pattern at the bottom corresponding to aerated lung parenchyma. The normal M-mode pattern is called "seashore" sign with the lung parenchyma representing the beach and the chest wall representing the ocean (Fig. 78-6). In pneumothorax, the granular pattern of lung parenchyma is lost, and horizontal, linear lines are seen throughout the display. The M-mode pattern of pneumothorax is often called "stratosphere" or "barcode" sign (Fig. 78-7).[91] The lung point will display a distinct M-mode pattern with alternating segments of "seashore" and "barcode" patterns (Fig. 78-8).

A-lines are ultrasound image artifacts due to repeated reflections, or reverberations, between the highly reflective pleura and transducer. A-lines are seen as a series of equidistant horizontal white lines deep to the pleura (Fig. 78-9). A-lines are seen in normal lungs but also in pneumothorax, pulmonary embolism, COPD, or asthma. Therefore, presence of A-lines supports a diagnosis of pneumothorax but is not specific for pneumothorax. In contrast, the presence of B-lines, an artifact arising from the pleura, rules out pneumothorax with a negative predictive value of 100% (Video 78-5).[86]

A focused lung ultrasound examination to evaluate for pneumothorax can be performed rapidly—in less than 1 minute in one study by experienced clinicians.[87] A phased array, linear array, or microconvex transducer is required. Specifically for evaluation of pneumothorax, a high-frequency (5–10 MHz), linear array transducer is preferred because of its higher resolution and sensitivity (82% vs. 76%) compared to convex array transducers.[90] Air in the pleural space accumulates in the least dependent parts of the chest, which are anterior and inferior in supine patients. In a longitudinal plane with the transducer marker oriented cephalad, place the transducer in the midclavicular line, and scan each interspace sequentially evaluating for lung sliding. If absence of lung sliding is detected, move the transducer laterally in search of the lung point and to qualitatively assess the size of the pneumothorax. Use M-mode to confirm the presence or absence of lung sliding.[92]

Video 78-2 Absence of lung sliding due to pneumothorax. Using two-dimensional ultrasound in a sagittal plane, the absence of lung sliding can be appreciated as the shimmering, glistening appearance of the pleura is not seen below the ribs (See also Video 31-10). *Access at www.fishmansonline.com*

Video 78-3 Lung point sign (lateral chest wall). The edge of a pneumothorax, or lung point, can be seen on the curvature of the lateral chest of a mechanically ventilated patient with a large, postprocedural pneumothorax. Aerated lung superiorly *(left)* slides into the field of view next to the collapsed, nonsliding portion of lung *(right)*. *Access at www.fishmansonline.com*

Video 78-4 Lung point sign (anterior chest wall). The edge of a pneumothorax, or lung point, can be seen on the anterior, inferior chest wall of a patient with a small, spontaneous pneumothorax. Aerated lung slides in and out of the field of view next to the collapsed, nonsliding portion of lung (See also Video 31-11). *Access at www.fishmansonline.com*

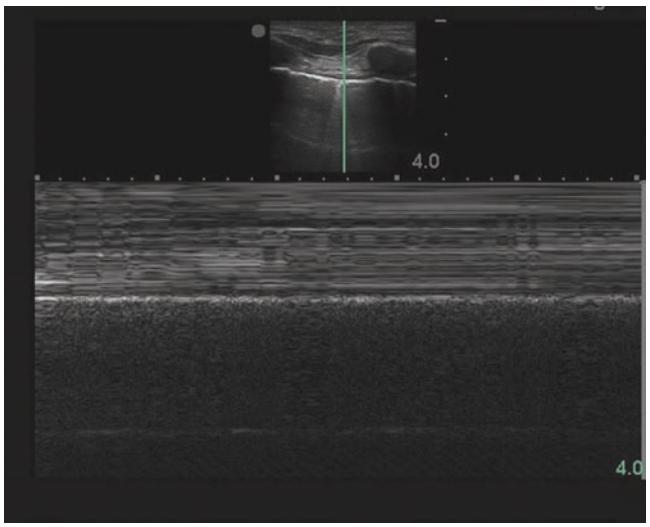

Figure 78-6 Normal lung in M-mode. A two-dimensional ultrasound image at the top shows the sample line along which the movement of all tissues is recorded and displayed below. The chest wall creates a series of horizontal lines. Also noted are the hyperechoic line of the pleura and a granular pattern created by aerated lung.

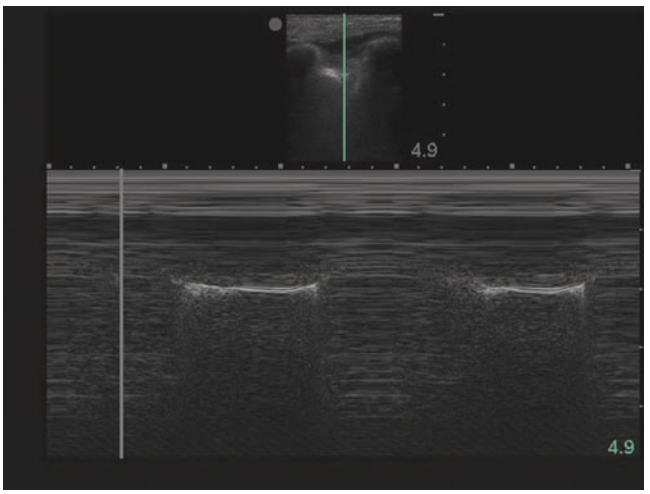

Figure 78-8 Lung point in M-mode. This M-mode image displays alternating patterns of normal lung and pneumothorax as normal, aerated lung slides over the area of collapsed lung.

■ COMPUTED TOMOGRAPHY

CT scans of the chest are being used with increasing frequency in patients with pneumothorax. CT scans may be necessary to diagnose pneumothorax in critically ill patients when upright or decubitus films are not possible. CT scans may also prove helpful in predicting the rate of recurrence in patients with spontaneous pneumothorax. One study demonstrated that patients who have larger or more numerous blebs on thoracic CT scans are more likely to have recurrence.[93]

Traumatic pneumothoraces, if large, can be detected both clinically and with chest radiography. However, a small, posttraumatic pneumothorax may be easily missed by both physical examination and chest radiograph. One prospective series revealed that 51% of trauma patients presented with an occult pneumothorax that was not seen on initial chest radiograph, but identified on CT imaging.[94] In another large series looking at multiple trauma patients, 4.4% had a pneumothorax and 38.8% of these were detected only by CT scan.[95] Early incorporation of a routine CT scan in all patients with chest trauma or multiple traumatic injuries may be required to successfully diagnose traumatic pneumothoraces.

Given the difficulties associated with diagnosing small pneumothoraces by plain chest radiograph, as well as the cost and delay of CT scans, thoracic ultrasound is quickly emerging as a valuable tool for the diagnosis of occult pneumothorax. The small size and portability of newer machines, as well as the advantage of immediate bedside interpretation, make ultrasound especially helpful in the management of critically ill and hemodynamically unstable patients. Most data has come from trauma literature

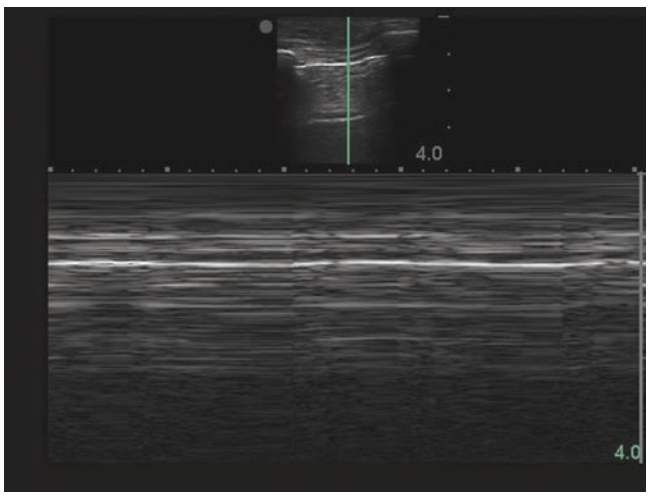

Figure 78-7 Pneumothorax in M-mode. The separation of visceral and parietal pleura by air from a pneumothorax prevents ultrasound waves from reaching the visceral pleura resulting in loss of the granular pattern of normal lung at the bottom of the M-mode image. A series of horizontal lines is seen throughout the M-mode image and is often called "stratosphere sign" or "bar code sign."

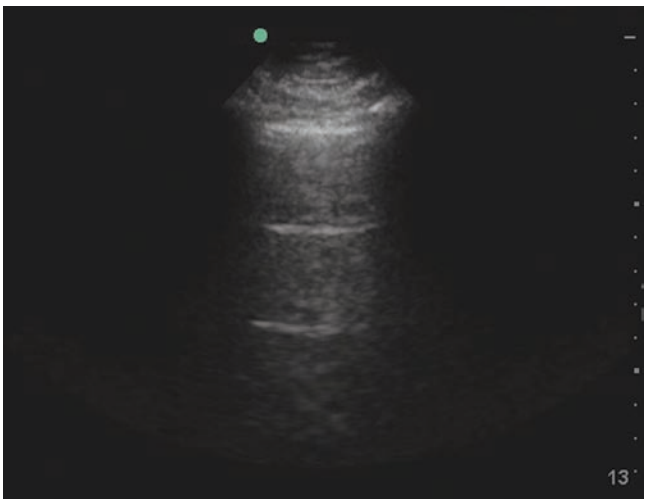

Figure 78-9 A-lines. A-lines are a type of reverberation artifact seen as equidistant horizontal lines that are generated from reflections of the pleura. A-lines are seen in normal, aerated lungs, but are also seen in pneumothorax, pulmonary embolism, chronic obstructive pulmonary disease, and asthma.

Video 78-5 B-lines. B-lines are a type of reverberation artifact, also known as comet-tail artifacts, that arise from the pleural surface and extend vertically to the bottom of the screen as discrete, hyperechoic rays that slide with pleural movement. Presence of B-lines rules out pneumothorax (See also Video 31-12). *Access at www.fishmansonline.com*

where ultrasound has a more well-established role. Hand-held ultrasonography was shown to have better sensitivity (48.8 vs. 20.9%) and similar specificity compared with chest radiograph for detection of traumatic pneumothorax using CT as the gold standard.[96] A review of ultrasound specifically in ICU patients concluded that ultrasound had a sensitivity of 95% and specificity of 94% compared to CT for the detection of pneumothorax.[97] Ultrasound has the additional advantage of serving as a guide to direct the site of drainage.[98]

THERAPEUTIC OPTIONS

Therapy for pneumothorax is dependent on the size of the pneumothorax, symptomatology, and etiology. The basic tenets of therapy are to evacuate the space, achieve closure of the leak, and either prevent or reduce the risk of recurrence. A variety of treatment methods and adjuncts exist. The choice of therapy depends on many factors, including the clinical status of the patient, the cause of the pneumothorax, evidence for concomitant lung disease, prior history of pneumothorax, risk of recurrence, and, finally, the experience and preferred techniques of the physicians caring for the patient as well as the availability of specific therapeutic options.[99] Major categories of treatment methods are listed below, followed by suggested guidelines for their application.

OBSERVATION

Simple observation of the patient with a pneumothorax requires evidence that the air leak is sealed (i.e., that there is no further progression of the pneumothorax). This form of management is generally reserved for asymptomatic patients with a small (<20%) unilateral pneumothorax.

A suggested protocol is the performance of serial chest radiographs over the initial 24 hours to assess for further progression of the pneumothorax. Some have suggested that this approach could be performed safely on an outpatient basis with close observation and limited patient activity. This form of management is risky because complications may occur rapidly, with potential morbidity. In one study of observation, 5% mortality was reported owing to the development of tension pneumothorax from an unrecognized pleural leak.[29] Inpatient monitoring during the initial phase of therapy also allows the use of adjunct measures such as supplemental oxygen, which increases the rate of absorption of pleural gas. Depending on the circumstances and level of patient compliance, continued follow-up may be done on an outpatient basis.

ASPIRATION

Aspiration of pneumothorax has been advocated by some but has shown varied levels of success and there is poor consensus between guidelines as to which patients warrant this approach.[100] The British Thoracic Society guidelines recommend simple aspiration as first-line therapy for all clinically stable patients with "large" first-time spontaneous pneumothorax.[78] This is in contrast to the American College of Chest Physicians Delphi Consensus Statement on this issue, which advocates placement of a pleural catheter and drainage.[101] The differences between selected guidelines are highlighted in Table 78-2.[78,101–103]

TABLE 78-2 Comparison of Management Techniques by Society Guidelines

Society	Management Technique	Indication
ACCP	Catheter drainage	>3 cm interpleural distance at apex
BSP	Aspiration or catheter drainage	Pleural gap along entire lateral chest wall
BTS	Simple aspiration	>2 cm interpleural distance anywhere
SEPAR	Aspiration or catheter drainage	Pleural gap along entire lateral chest wall

ACCP, American College of Chest Physicians; BSP, Belgian Society of Pulmonology; BTS, British Thoracic Society; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery.

A meta-analysis of randomized controlled trials of simple aspiration versus chest tube insertion concluded that simple aspiration was advantageous because of shorter hospitalization times and no significant difference in recurrence rates at 1 year.[104] In these studies, approximately 66% of patients had resolution of their pneumothorax. Patients with secondary or a recurrence of spontaneous pneumothorax generally do not have good results with simple aspiration.[100,105–107]

The procedure consists of insertion of a 16- or 18-gauge plastic catheter under local anesthesia using sterile technique. The recommended point of insertion is the second anterior intercostal space in the midclavicular line. The catheter is connected to a three-way stopcock and a large-volume syringe. Aspiration is performed until no further gas can be withdrawn. Follow-up chest radiographs are performed. Again controversy exists regarding a second attempt at aspiration if the first attempt is unsuccessful. If large volumes are aspirated without resolution or the second attempt is unsuccessful, a tube thoracostomy should be performed.

TUBE THORACOSTOMY

This entails the placement of an indwelling catheter into the pleural space for continual removal of the intrapleural gas. The classic method is the use of standard tube thoracostomy. For uncomplicated pneumothorax without evidence of significant amounts of fluid or blood, one may use standard thoracostomy tubes ranging from 20 to 24 French to minimize the discomfort of a larger tube in the intercostal space. Generally, a safe site for a chest tube or pleural catheter placement is the lateral chest wall above the fourth to sixth ribs in the mid- to anterior axillary line. If possible, tube placement in the back to posterior axillary line should be avoided because patients will tend to lie on them, increasing the risk of tube kinking and patient discomfort.

The tube is then connected to a pleural drainage system. Commercial systems commonly employ variations on the three-chamber system (Fig. 78-10). The three-chamber system consists of a fluid collection chamber attached to a water seal chamber to allow egress of gas from the pleural space, but in a one-way fashion. The final connection is to a manometer bottle, which regulates the degree of suction being applied to the system. After placement of tube thoracostomy, care should be taken with regard to immediate placement to suction because of the potential for reexpansion pulmonary edema (REPE) (see below). In many cases it may be prudent to leave the tube to water seal and allow the lung to expand gradually. Once the majority of the pneumothorax is evacuated, suction is applied for the next 24 hours. If an air leak exists, as evidenced by

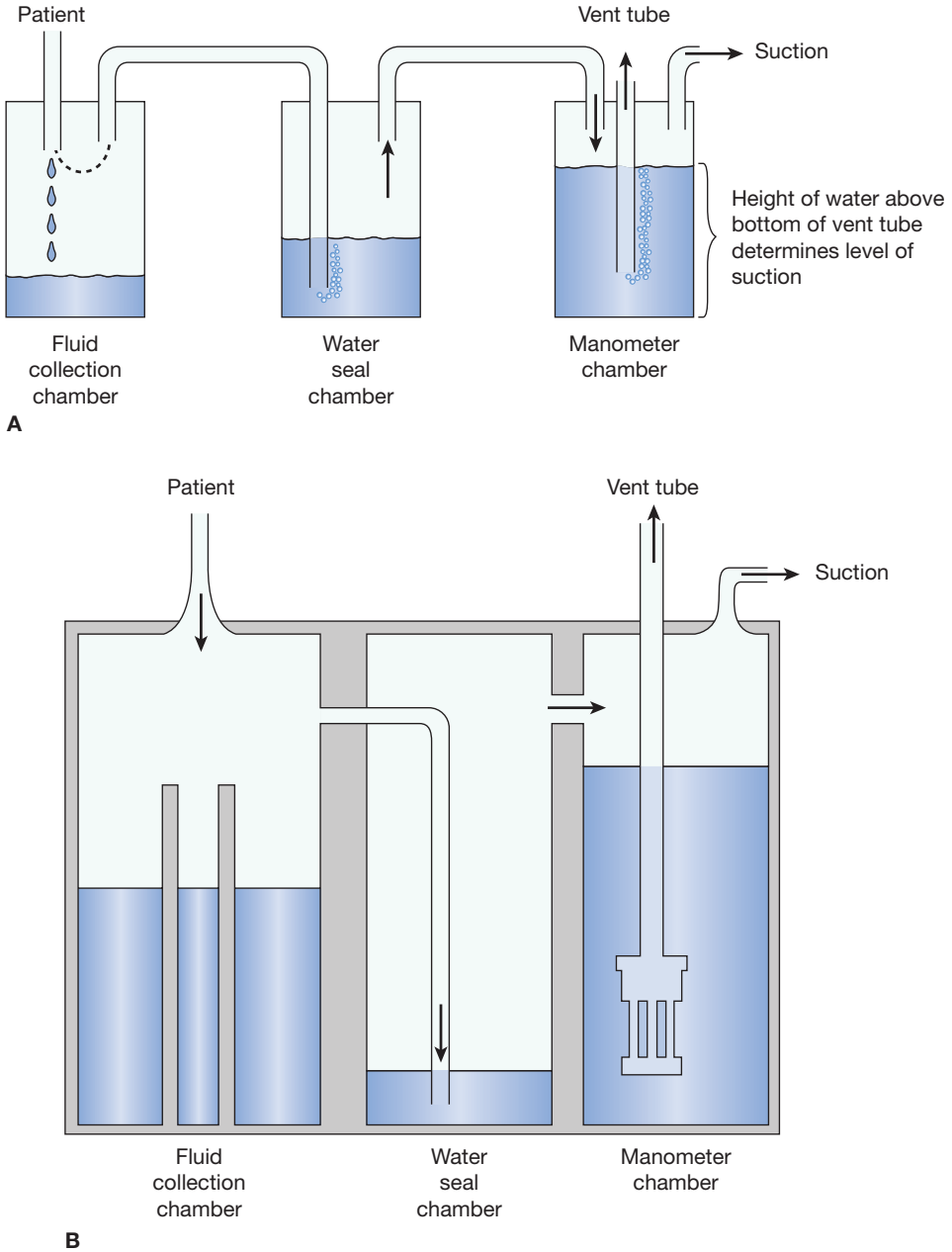

Figure 78-10 **A.** Three-bottle chest tube drainage system. The system consists of a collection bottle, a water-seal bottle, and a suction-control bottle. The collection bottle allows sterile drainage from the pleural spaces. The water-seal bottle acts as a one-way valve in the absence of suction, and the suction bottle allows for the regulation of negative pressure applied to the pleural space. **B.** Commercially available, compartmentalized plastic drainage system.

continual or intermittent egress of gas through the water seal chamber, suction is maintained. Once there is no evidence of an active air leak, the tube may be placed to water seal. After an additional period of observation of 12 to 24 hours, the chest tube may be removed if the pneumothorax does not recur.[108] Tube thoracostomy alone will result in closure of an air leak in most cases by complete evacuation of the pleural space and apposition of the visceral and parietal pleura. Persistence of an air leak for more than 72 to 96 hours generally presages a leak that will not close by this regimen and should prompt consideration of more aggressive therapy, usually surgical with or without some form of pleurodesis.[109]

To have a less traumatic method of placement of an indwelling tube, as well as to minimize the discomfort from a large-bore tube in the intercostal space, a variety of smaller catheters have been suggested for use as an interpleural drain.[110] The method of placement is similar to needle aspiration in terms of preparation and location of entry. Once the pleural space is entered with the needle, the Seldinger technique is used to pass a soft tip wire. The 8-French pigtail catheter is then placed over the wire into the pleural space and the wire withdrawn. The catheter is left in place and attached to pleural drainage system as described above. Potential problems with smaller catheters relate to a greater propensity for blockage of the tube. Also, the smaller size makes them more prone to kinking, clotting from blood or fluid, and sealing around the tube by the lung, resulting in a loculated pneumothorax. In cases in which the pneumothorax is associated with significant amounts of blood or fluid, tube thoracostomy using a larger-bore chest tube (26–32 French) is recommended.[111]

Use of these types of catheters has created the possibility of a form of hybrid therapy in which these catheters are placed and simple aspiration performed as noted. If the lung fails to reexpand or the volume of air obtained excessively large suggesting a continued air leak, the catheter may be left in and connected to longer-term drainage.

A variation on the use of pleural drainage systems is the substitution of a one-way valve to permit greater mobility by the patient.[112] The most common is the Heimlich flutter valve, which is useful in cases in which long-term indwelling catheterization is required but surgical therapy is declined or not possible. This valve is not widely recommended; however, owing to a potential for problems

with blockage, which may not be immediately recognized on an outpatient basis.

PLEURODESIS

Pleurodesis is an adjunct to the other forms of therapy. The goal is to achieve pleural symphysis, or adhesion of the visceral and parietal pleura to obliterate the pleural space. Sealing the visceral and parietal pleura together will prevent future air leaks and prohibit the lung from "falling away" from the chest wall. The basic mechanism entails chemical or physical irritation of the pleural surface to promote an inflammatory response and subsequent adhesion formation.

The goal of pleurodesis is to prevent recurrence in both PSP and SSP. There is good consensus for the use of pleurodesis in both; however, when and how to achieve pleurodesis depends on both the kind of pneumothorax as well as if there has been a recurrence.

Chemical pleurodesis may be used in combination with tube thoracostomy or surgical therapy. In patients who are unable to undergo a surgical procedure (e.g., severe comorbidity), pleurodesis can be achieved by administering the sclerosing agent through a chest tube. The success of the antibiotics (tetracycline, doxycycline, minocycline) and talc by slurry have been shown to be superior to chest tube drainage alone, but not as good as thoracoscopic treatment.[13]

As an adjunct to tube thoracostomy, the chemical of choice is suspended in fluid and instilled through the tube. The tube is clamped for 6 to 8 hours, then placed back to either suction or water seal. Periodically changing patient position during this period has not been shown to improve outcome.[113,114] Success is largely dependent on apposition of the visceral and parietal pleura during the period of inflammation while the tube is clamped. Excessive pleural fluid will dilute the sclerosing agent, and an air leak will allow the lung to separate from the chest wall. Doxycycline pleurodesis in the face of an air leak has been tried,[115–117] but in our experience it has a significantly reduced success rate.

The ideal agent should be effective, safe, easy to administer, and widely available and affordable. A number of pleural irritants have been suggested, including quinacrine, silver nitrate, bleomycin, autologous blood, antibiotics (doxycycline), and talc. Minor side effects of pleurodesis with a sclerosing agent include chest pain and low-grade fevers.

Tetracycline was shown to be very effective in creating sufficient pleural fibrosis formation when compared to hydrochloric acid, quinacrine, nitrogen mustard, bleomycin, or sodium hydroxide.[2] A randomized study comparing the recurrence rates in PSP after drainage alone with that of drainage plus tetracycline or talc found recurrence rates of 36, 13, and 8%, respectively.[116] Tetracycline, however, is no longer commercially available. Minocycline and doxycycline have been suggested as a replacement for tetracycline with experimental data that suggests equal efficacy.[101,118,119] Typical doses of these antibiotics are 0.5 to 1 g of doxycycline in 50 to 100 mL normal saline and 600 mg of minocycline in 50 to 100 mL of normal saline.

Talc has also been shown to be a very effective sclerosing agent when applied as slurry via a chest tube or by talc poudrage during thoracoscopy. In an experimental study, talc was noted to be as efficacious as mechanical abrasion.[120] In a meta-analysis, talc achieved a success rate of 91%.[121] Doses between 2 to 10 g of talc in 100 to 200 mL of normal saline have been reported. There is no standardized practice when using talc administered by chest tube. The drawbacks of talc slurry are prolonged pleural drainage and inhomogeneity of deposition. The distribution of talc may lead to loculation and incomplete symphysis. The advantages are it can be performed easily at the bedside. There are data, however, that suggest an increased incidence of adult respiratory distress syndrome associated with the use of talc as a sclerosant. The size of the talc particles (<15 μm) and the dose (>5 g) may be associated with a higher incidence of ARDS. In a comprehensive literature review, Sahn et al.[122] found acute respiratory failure in 0.15% of patients treated with talc poudrage.

As an adjunct to surgical therapy, the most commonly described material is talc. Sterile, asbestos-free talc is insufflated during thoracoscopy or thoracotomy to coat the visceral pleural surface. Typically, 2 to 10 g are used.[121,123]

Mechanical pleurodesis is performed as part of a surgical procedure. It may consist of simple abrasion of the parietal pleural surface or may entail stripping of the parietal pleura (pleurectomy). The second method has a greater potential for complications, including injury to an intercostal neurovascular bundle or excessive bleeding from the large raw surface area. Also considered in this category is the use of an Nd:YAG laser or an argon beam coagulator, which essentially cauterizes the pleural surface.[124] Experimental studies have not borne out their effectiveness.[120]

The performance of pleurodesis in someone who may need future thoracic surgery is somewhat debatable and relates to the degree of pleural symphysis that can be obtained and the method utilized. Currently, guidelines suggest evaluation for pleurodesis in patients with prolonged air leaks for greater than 4 days, recurrent pneumothorax, and as part of the treatment of catamenial pneumothorax and pneumothorax associated with HIV.[78,101] Either chemical or mechanical pleurodesis, may result in rather significant adhesion formation. Clearly there is a significant reduction in the incidence of recurrence. However, in some cases, there are concerns that future surgical procedures, such as pulmonary resection, open lung biopsy, and lung transplantation, may be hampered by this degree of pleural symphysis. The application of pleurodesis thus depends on an assessment of the risk of recurrent pneumothorax and the potential morbidity to the patient should a recurrence occur versus the potential for later operative procedures in the thorax. One suggested compromise is limitation of the pleurodesis to the apical area, as this is the most common location for air leaks to occur. Later thoracic procedures may be done, albeit with more difficulty, by entrance inferior to the area of pleurodesis and subsequent adhesion lysis apically. Localized pleurodesis is not possible when it is performed as an adjunct to tube thoracostomy. A second potential compromise is the use of tetracycline analogs such as doxycycline or minocycline. Experimental studies and anecdotal reports indicate that with the use of tetracycline, the degree of pleural symphysis and density of adhesions are not as great as with talc or mechanical pleurodesis.[116–120]

OPERATIVE THERAPY

Operative treatment (mechanical pleurodesis with or without stapling of blebs or pleurectomy) is generally thought to be the most effective in assuring expansion of the lung, with complete evacuation of the pleural space, and providing for the best means of reducing the risk of recurrence. In addition, it provides a means of potentially identifying an air leak and closing it. However, increased patient discomfort, risks of general anesthesia, and greater costs of the procedures, combined with moderate success of the less invasive methods, result in restricted application of surgery for pneumothorax.

Operative therapy is indicated in cases in which the above-mentioned, less invasive techniques have failed, with persistence or recurrence of the pneumothorax, or in cases of initial presentation of patients with limited pulmonary reserve. This risk of recurrence should include an assessment of the potential morbidity or mortality to the patient should another pneumothorax occur.

Longitudinal studies have indicated that the recurrence rate is approximately 30% after tube thoracostomy alone for treatment of a spontaneous pneumothorax. Among patients in whom the disease recurs once, the subsequent recurrence rate continues to increase.[125]

Evidence suggests that a more definitive procedure – namely surgery – is indicated with the first recurrence. In patients with localized lung disease, such as congenital lobar emphysema or a single large bulla, surgery may be indicated for the initial episode of pneumothorax. Patients who have high-risk lifestyles, such as pilots or scuba divers, or patients who may not have ready access to medical care may possess a relative indication for surgical treatment of a first occurrence of spontaneous pneumothorax because of the risk to the patient should a pneumothorax occur. Patients who present with bilateral or tension pneumothorax may also fall in this category of morbidity assessment.

Patients with a pneumothorax from any cause who have a persistent air leak despite prolonged chest tube drainage should also be considered for operative therapy. An air leak that fails to close after 72 to 96 hours of suction has a very low chance of closing spontaneously. This is the recommended time for surgical referral.[109] Finally, patients in whom the previous forms of therapy result in incomplete reexpansion of the lung should be considered for surgery. This situation may reflect loculation of the pneumothorax or trapping of the lung by a fibrotic "peel," which will require surgery to be released.

■ VIDEO-ASSISTED THORACOSCOPIC SURGERY

In recent years, video-assisted thoracoscopic surgery (VATS) has emerged as the preferred surgical approach when surgical intervention for pneumothorax is required. It is associated with less postoperative discomfort and decreased length of hospital stay compared to standard thoracotomy. The decreased morbidity is the result of the ability to examine the pleural space and manipulate the lung without significant muscle division or rib spreading.[123]

In most cases, the technique requires general anesthesia with double-lumen endotracheal ventilation (single lung ventilation). Those patients who are at high risk (elderly or significant underlying lung disease) can undergo this procedure under local and epidural anesthesia.[126] Up to three separate ports are placed in the intercostal spaces to effect installation of the camera as well as manipulating devices. The entire lung can be inspected and a search for the air leak carried out. Generally speaking, the apical area is the location, and this area can then be closed with the use of a stapler. In patients with concomitant lung disease, particularly COPD, the staple line can be reinforced with the aid of bovine pericardium to minimize persistence of air leaks.[127] The pleural surface can then be abraded or talc insufflated, as mentioned above, to achieve some degree of pleural adhesion following reexpansion of the lung. Long-term follow-up of recurrence rates has shown results similar to those for open thoracotomy. Stapled resection of bullae and talc poudrage can be performed safely.

The less invasive nature of VATS compared to open thoracotomy has prompted earlier and more frequent surgical referral. While the risks associated with general anesthesia remain, overall costs are generally less than thoracotomy owing to shorter hospital stay. The cost of VATS as an initial procedure for spontaneous pneumothoraces may be less in the course of the treatment of the disease as compared to more conservative therapies for both PSP and SSP.[128] These conclusions, however, are not based on prospective randomized trials and should be verified in larger prospective studies.

■ OPEN THORACOTOMY

Classically, thoracotomy was believed to be the ultimate and most effective form of therapy for pneumothorax. Recurrence rates are generally less than 2%.[129] Thoracotomy allows examination of the lung for the site of an air leak, enables lysis of previous adhesions that may lead to a loculated pneumothorax, and enables the release of a fibrotic peel that occasionally forms, leading to incomplete reexpansion of the lung. Drawbacks include the potential risks associated with general anesthesia, increased costs, and the significant amount of patient discomfort. Discomfort is generally most severe with a standard lateral or posterolateral thoracotomy with muscle division and rib spreading.

In an effort to minimize the level of discomfort, variations have been developed, including the use of smaller incisions, the so-called muscle-sparing thoracotomies, and the axillary thoracotomy. Lung examination and air leak closure and possible pleurodesis or pleurectomy can then still be performed.[129]

While VATS has supplanted thoracotomy as the surgical treatment of pneumothorax in many institutions, open thoracotomy remains a valuable option in the treatment of complicated cases.

SUGGESTED GUIDELINES FOR MANAGEMENT

Based on the relative efficacy of the various forms of therapy combined with relative risks for the major categories of pneumothorax, the following guidelines are suggested.

■ PRIMARY PNEUMOTHORAX

Patients with a first-time PSP who are asymptomatic and whose pneumothorax is thought to be less than 20% may be treated with observation and sometimes adjunct measures, including the use of supplemental oxygen. Patients with PSP who are symptomatic or whose pneumothorax is greater than 20% should undergo an attempt at catheter aspiration or insertion of a small 8- to 10-French pneumothorax catheter. Subsequent small- or large-tube thoracostomy is indicated for failure of simple aspiration.

Patients who undergo successful tube thoracostomy with complete lung reexpansion and absence of an air leak may opt for a chemical pleurodesis while the chest tube is in place. Since the risk of recurrence is low (approximately one in five), most physicians recommend patients in good general health defer this procedure until a second pneumothorax occurs. Patients with persistent air leaks for more than 72 to 96 hours after insertion of a chest tube should be referred for surgical therapy. Because of the progressive increase in risk of recurrence, patients with their first recurrence of a primary pneumothorax should undergo chemical pleurodesis or be referred for surgical therapy, preferably VATS, with stapling of any air leak and pleural abrasion or chemical pleurodesis.

■ SECONDARY PNEUMOTHORAX

In general, therapy for secondary pneumothorax should be more aggressive because of the higher rate of recurrence due to the underlying lung pathology. Specific conditions with pneumothorax as a common occurrence are as listed below.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Most cases of pneumothorax in patients with COPD should be treated with some form of long-term aspiration, typically tube thoracostomy. In patients who are not good surgical candidates, chemical pleurodesis with doxycycline or talc should be performed once there is complete reexpansion and absence of an air leak. In COPD patients who are good surgical candidates or in patients with a persistent air leak longer than 72 hours, more aggressive therapy should be considered.[36] Recommended therapy includes VATS or thoracotomy with talc insufflation, mechanical pleurodesis, stapling resection, and/or pleurectomy. This approach provides a more effective way of achieving a lower risk of recurrent pneumothorax.

CYSTIC FIBROSIS

Although there are no clinical trials to guide therapy in patients with CF and pneumothorax, retrospective reports offer suggestions for management. Clinically stable patients with small pneumothoraces may be followed with observation. Clinical instability or large pneumothorax requires chest tube placement. Pleurodesis should be considered after recurrence of a large pneumothorax. Surgical

pleurodesis is associated with fewer recurrences in the CF population and is the preferred modality. Noninvasive positive-pressure ventilation, positive expiratory pressure devices, and intrapulmonary percussive ventilation should be stopped until the pneumothorax has resolved but aerosols need not be held. Because of the growing application of lung transplantation to patients with CF, localized pleurodesis is recommended as an adjunct to surgical closure of the air leak.[39,41]

AIDS

For most AIDS patients presenting with a pneumothorax, tube thoracostomy is the primary mode of initial treatment. Because of the high primary and secondary treatment failure rates, patients who have no air leak with complete lung reexpansion should undergo talc slurry pleurodesis. For patients with a persistent air leak who are felt to be poor surgical risks because of severe debilitation, a Heimlich valve may be utilized. For patients who are deemed good risks for surgery, thoracoscopy with talc insufflation is recommended.[44]

OTHER CONDITIONS

While there are insufficient data to make firm recommendations for all situations, some suggestions are offered. Patients with pneumothorax secondary to iatrogenic causes may be treated with observation or aspiration according to the guidelines previously listed. In patients who have a pneumothorax secondary to trauma, we suggest large-bore tube thoracostomy, because there is a high association with hemothorax and the patient's physiologic reserve and ability to tolerate the pneumothorax may be decreased owing to other injury. However, recent publications question the need for large-bore chest tubes.[130]

Patients who experience a pneumothorax while on positive-pressure ventilation should have tube thoracostomy placement to avoid progression to a tension pneumothorax.[130] Patients who present with bilateral pneumothoraces or a tension pneumothorax, but who are not on positive-pressure ventilation, should have placement of tube thoracostomy. Further therapy with regard to chemical pleurodesis versus surgery is dependent on underlying lung pathology.

COMPLICATIONS

TENSION PNEUMOTHORAX

A tension pneumothorax is present when the intrapleural pressure is greater than atmospheric throughout expiration and often during inspiration as well. The term *expiratory tension pneumothorax* has been proposed to highlight the fact that in a spontaneously breathing person, pleural pressure must be negative in relation to atmospheric pressure during part of the respiratory cycle for air to enter the pleural space. The mechanism responsible for tension pneumothorax relates to the disruption of the visceral or parietal pleura in such a manner that a one-way valve develops. During inspiration, the respiratory muscles contract and create negative intrapleural pressure, allowing for air movement into the pleural space. Then, during expiration, when the expiratory muscles relax, the pleural pressure becomes positive and the one-way valve prevents the egress of air from the pleural space. As tension pneumothorax progresses, the pleural pressure remains positive during a greater portion of the inspiratory cycle. If the patient is on mechanical ventilation, the alveolar pressure remains positive throughout inspiration and expiration.

A tension pneumothorax can occur after any type of pneumothorax; it is independent of the etiology. It can sometimes occur after a spontaneous pneumothorax but is more common after a traumatic pneumothorax, with mechanical ventilation, or during cardiopulmonary resuscitation.

The clinical picture associated with the development of a tension pneumothorax is striking. The patient will appear acutely ill, develop severe dyspnea, marked tachycardia, profuse diaphoresis, and cyanosis. On physical examination, the patient may demonstrate profound hypotension and hypoxemia, distended neck veins, tracheal deviation to the side opposite the pneumothorax, subcutaneous emphysema, and unilateral chest hyperinflation. The involved hemithorax can enlarge, with widened interspaces. Arterial blood gases reveal severe hypoxemia and can show a severe respiratory acidosis. Chest radiographs may show mediastinal shift to the contralateral side of the pneumothorax. Patients receiving mechanical ventilation often develop a sudden increase in their peak and plateau pressures, with an associated decrease in the oxygen saturation. If the patient is on pressure control ventilation and is paralyzed, arterial blood gases will show a respiratory acidosis, as the patient is unable to increase his respiratory rate.

The development of a tension pneumothorax is a medical emergency requiring immediate chest drainage to relieve the intrapleural pressure. It should be suspected in any patient with a pneumothorax whose condition deteriorates acutely or in any patient with cardiopulmonary collapse after a procedure known to cause a pneumothorax, or with mechanical ventilation. One should also suspect a tension pneumothorax in any patient undergoing cardiopulmonary resuscitation who is difficult to ventilate or develops electromechanical dissociation. A tension pneumothorax may also develop because of improper connection of a one-way flutter valve to the chest tube. It can occur even if there is a chest tube in place, due to either malpositioning of the tube or disconnection at the site of tube or the site of the pleurevac container.

When the diagnosis of a tension pneumothorax is considered, the patient should be given a high concentration of oxygen to alleviate the extreme hypoxemia seen with this syndrome. Radiographic documentation may not be possible in an emergency situation. Tension pneumothorax is a clinical diagnosis and therapy should not be held up by confirmation of the chest radiograph. A large-bore needle should be inserted into the second anterior intercostal space. Optimally, the needle should be connected to a syringe partly filled with sterile saline. Air bubbling outward through the fluid confirms the diagnosis. The needle or its plastic outer sheath should be left in place, and the patient should be prepared for immediate tube thoracostomy.

Cardiopulmonary decompensation in patients with tension pneumothorax is usually attributed to diminished venous return and marked decrease in the cardiac output. Animal studies demonstrate that cardiac output is maintained by tachycardia and the increase in negative intrathoracic pressure during inspiration.[131] The importance of negative intrathoracic pressure swings in maintaining cardiac output was demonstrated by the precipitous fall in cardiac output when mechanical ventilation was initiated.[132] Deterioration has been shown to be related to severe hypoxemia, probably because of increased shunting and V/Q mismatch in the compressed lung. Preterminally, CO_2 retention and respiratory acidosis are noted.

BRONCHOPLEURAL FISTULA

A bronchopleural fistula is a communication between the pleural space and the bronchial tree. It is a rare, but serious complication associated with several pulmonary conditions. In the setting of a pneumothorax, it is manifested by a prolonged air leak.

Most air leaks seal within 24 to 48 hours after tube thoracoscopy. Only 3% to 5% of patients with pneumothorax have a persisting air leak.[133] Few air leaks that persist for more than 48 hours will seal over the next 7 to 10 days with continuous suction alone.[134] Current guidelines recommend that patients with air leaks persisting over 3 to 4 days should be evaluated for surgery to close the air leak and perform a pleurodesis procedure to prevent recurrence.[78] VATS is the preferred procedure for managing bronchopleural fistulas. Use of an additional chest tube may occasionally help, but surgery should be considered after 3 to 4 days of tube drainage.[109]

Patients with CF or COPD are at increased risk for the development of persistent bronchopleural fistula. For those who are not candidates for surgical intervention, the fistula may be localized by bronchoscopic balloon catheter occlusion and subsequently injected with a variety of substances to promote sealing of the air leak. Fibrin glue, liquid bioadhesive (isobutyl 2-cyanocrylate), sterile gelatin sponge, and even lead shot have been used for this purpose.[127] In addition, after localization by balloon catheter occlusion, one-way endobronchial valves have been placed bronchoscopically as a nonoperative therapy for persistent air leaks.[135] Autologous "blood patch" pleurodesis has also been accomplished, using 50 to 120 mL of the patient's blood and injecting it into the chest tube. While high success rates have been reported in postoperative patients, we have observed limited success in patients with spontaneous pneumothorax.[136,137]

REEXPANSION PULMONARY EDEMA

REPE is a rare but potentially lethal condition that can occur with the rapid reexpansion of a collapsed lung after tube thoracostomy is used to drain air (pneumothorax) or fluid (pleural effusion) from the pleural space.[138] The incidence of this complication is uncertain. There were no cases reported in the Veterans Administrative Cooperative study of more than 200 patients with spontaneous pneumothoraces. The single largest retrospective study ($n = 21$) reported an incidence of 14%.[139]

The pulmonary edema is most commonly unilateral (involving the reexpanded lung), but on occasion, can become bilateral. Occasionally, associated hypoxemia and respiratory distress is sufficiently severe to require intubation and mechanical ventilation. Although the mortality rate is not well defined, one older study reported that 11/53 cases (21%) resulted in death.

The pathogenesis of REPE is not completely understood. A number of mechanisms have been suggested. It appears that, at least to some degree, REPE is due to increased permeability of pulmonary capillaries that are damaged by mechanical stress during reexpansion of the lung. Reperfusion injury due to free radicals may also be responsible for increased capillary permeability. Other theories include decreased surfactant, airway obstruction, and decreased lymphatic flow.[140]

The duration of pneumothorax prior to drainage has been shown to be significant risk factor for development of REPE. Animal models demonstrate that REPE occurs when a pneumothorax has been present for 3 days or more and the lung has been expanded with more than −20 cm H_2O pleural pressure. The severity of the pneumothorax may also be predictive of developing REPE. In one series, no patient with a pneumothorax less than 30% of the lung field developed this complication compared to 17% of patients with total collapse and 44% of patients with tension pneumothorax. Finally, use of suction and rapid rate of expansion have been implicated as potential risk factors.

The clinical presentation of REPE can be relatively benign or present as a life-threatening event. When serious, its onset is sudden and dramatic. The majority of patients presenting with symptoms do so within 1 hour of reexpansion and all are symptomatic within 24 hours. Symptoms include severe persistent cough and chest pain. In more severe cases, patients develop hypoxemia, tachypnea, tachycardia, and hypotension. Symptoms may worsen for 24 to 48 hours. Chest radiographs demonstrate patchy or diffuse alveolar infiltrates in the reexpanded lung. If the patient survives the first 48 hours, recovery is usually complete.

Treatment is supportive and, in severe cases, includes mechanical ventilation. The best strategy is prevention, though there are no randomized trials to guide practice. It is recommended that when tube thoracostomy is performed for a spontaneous pneumothorax of unknown duration, the tube should initially be connected to water seal rather than to negative pressure. If the lung fails to fully expand after 12 to 24 hours, negative pressure can be applied to the pleural space.

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PART 10

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CHAPTER 79

Malignant Mesothelioma and Other Primary Pleural Tumors

Edmund K. Moon
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The pleura is a membranous structure covering the entire surface of the lung and lining the inside of the chest cavity. It is composed of a thin mesothelial layer with underlying fibroblasts and varying amounts of collagenous fibrous tissue with interdigitating capillaries and venules. The most common tumors of the pleura are metastatic neoplasms, predominantly of lung, breast, or colonic origin. Tumors arising primarily from the pleura are rare, but still constitute a variety of benign and malignant lesions from several different cells of origin, some of which have yet to be identified.

MALIGNANT MESOTHELIOMA

The most common primary malignant tumor of the pleura is malignant mesothelioma, an insidious neoplasm with a generally dismal prognosis arising from the mesothelial surfaces of the pleural and peritoneal cavities, as well as from the tunica vaginalis and pericardium. Eighty percent of all cases of mesothelioma are pleural in origin.

EPIDEMIOLOGY

The incidence of mesothelioma in the United States is estimated to be 3300 cases per year.[1] The incidence within the United States peaked in the year 2000 and is now declining, secondary to control of asbestos exposure.[2] However, incidence is increasing in other parts of the world, such as Europe, Japan, and Australia. In Great Britain, mesothelioma death rates rose from 153 per year in 1968 to 1848 per year in 2001. Similar numbers of deaths are expected annually until the year 2015 when a peak of up to 2450 deaths per year is expected.[3] After that time, mesothelioma rates are expected to drop in England and other developed countries because of legislation aimed at reducing asbestos exposure in the workplace and the general environment. In contrast, mesothelioma incidence rates are predicted to escalate for much longer times in the Third World because of poor regulation of asbestos mining and widespread industrial and household utilization of asbestos.[3–5]

ETIOLOGY

Inhalational exposure to asbestos has been clearly established as the predominant cause of malignant mesothelioma in humans. Approximately 70% of cases of pleural mesothelioma are associated with documented asbestos exposure. In ancient Greece, the philosopher Pliny first established the association between asbestos exposure and lung disease by making the observation that slaves working in asbestos mines were less healthy than other slaves. It was not until 1960, with the publication by Wagner et al.[6] of a series of 33 mesothelioma cases occurring in a crocidolite mining community in South Africa, that the etiologic connection between asbestos and mesothelioma was established. Wagner's study was soon followed by several other accounts of mesothelioma afflicting asbestos workers at locations around the world. In addition to asbestos miners and workers, other occupations at especially high risk include plumbers/pipefitters, mechanical engineers, ship and boat building and repairing.[4]

The lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 8% to 13%.[7] There is a latency period of approximately 30 to 40 years from the time of asbestos exposure to the development of mesothelioma. It remains unclear whether there is a dose–response relationship between asbestos exposure and development of mesothelioma. The possibility of a dose–response relationship was demonstrated in a cohort study of over 4500 people who resided in an Australian city that produced crocidolite asbestos but who did not directly participate in its mining or milling. In this study, the incidence of mesothelioma increased significantly with greater environmental exposure, based upon the neighborhood and duration of residence. In a cohort of textile workers with heavy exposure to asbestos, the risk of pleural mesothelioma was increased and was proportional to the latency period. In contrast, many well-documented cases of mesothelioma occur after brief, but intense, or longer-term low-level exposures to asbestos (i.e., spouses of asbestos workers exposed by washing clothes).[8]

Asbestos is not a specific compound, but the commercial name for a group of hydrated magnesium silicate fibrous minerals divided into two major types: the serpentines and the amphiboles. Serpentine chrysotile fibers, which account for more than 95% of the asbestos previously used for industrial purposes in the United States, are spiral-shaped, pliable, easily breakable, and soluble in tissues, whereas the amphiboles (crocidolite, amosite, tremolite, anthophyllite, actinolite) are rigid, long and needle-like, with a longer biologic persistence than the serpentine fibers. The carcinogenicity of asbestos is thought to depend on dose, biodurability, surface reactivity, and the physical properties of the fibers. Fibers with a high length-to-width ratio, such as crocidolite, which are able to more readily penetrate through the lung to the pleural surface, are considered more carcinogenic. Among the remaining asbestos fibers, amosite has an intermediate carcinogenic risk, chrysotile the lowest. It is unclear whether the cases of mesothelioma attributed to chrysotile exposure are caused primarily by the chrysotile itself or by contamination with tremolite fibers. All asbestos fiber types, however, have carcinogenic potential.[3,4]

The development of malignant pleural mesothelioma has also been associated in rare cases with other etiologic factors, including therapeutic ionizing irradiation to supradiaphragmatic fields,[9–13] intrapleural thorium dioxide (Thorotrast), and inhalation of other fibrous silicates such as erionite. Epidemiologic studies of a region in central Anatolia (Turkey) with an abnormally high incidence of pleural mesothelioma (22 per 10,000 individuals over 25 years old) implicated routine household use of a locally ubiquitous silicate, erionite, as a potential etiologic agent. However, it appears that only specific families (who appear to have as yet to be defined genetic abnormality) are susceptible to erionite-induced mesothelioma.[14]

MOLECULAR PATHOGENESIS

The latency period from asbestos exposure to the development of mesothelioma ranges from approximately 20 to 50 years, suggesting the necessity of multiple genetic alterations for eventual malignant transformation of the mesothelium. Despite extensive

investigation, the exact mechanisms of asbestos carcinogenesis have not yet been fully elucidated. In rodent model systems, asbestos fibers act like tumor promoters in combination with a carcinogen, eliciting proliferation of mesothelial cells. Asbestos fibers can also interact with the mitotic spindle to cause missegregation of chromosomes and aneuploidy. In rat pleural mesothelial cells, asbestos fibers and erionite have been shown to induce the protooncogenes c-fos and c-jun in a prolonged and dose–responsive manner. Several growth factors, secreted by mesothelial/mesothelioma cells in an autocrine fashion, have been implicated in various stages of mesothelioma tumorigenesis. Platelet-derived growth factors A and B (PDGF A and B), insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor, transforming growth factor-β1, 2, and 3 (TGF-β1, 2, and 3) constitute a complex mixture of autocrine and paracrine stimuli for mesothelioma cell proliferation as well as initiation of tumor angiogenesis. More recently, asbestos has been shown to induce necrotic cell death with resultant release of high mobility group protein B1 (HMGB-1) in the extracellular space, which leads to a chronic inflammatory response involving macrophage accumulation and secretion of tumor necrosis factor α (TNFα). This in turn activates NF-κB leading to survival of human primary mesothelial cells that have accumulated genetic damage from asbestos exposure. There is also evidence implicating aberrant activation of the Wnt signaling pathway in mesothelioma.[15,16]

It has been well established that chronic inflammation predisposes to cancer development. Asbestos fibers appear to stimulate the production of chronic oxidative stress in lung macrophages and other cells for many years. In animal models, crocidolite fibers clearly induce specific DNA adducts (8-hydroxydeoxyguanosine, 8-OHdG) associated with oxidative damage in the DNA from peritoneal cells and macrophages of asbestos-exposed animals. These same type of 8-OHd DNA adducts have been observed in the blood lymphocytes of asbestos-exposed individuals decades after exposure suggesting chronic exposure to oxidant stress.[17]

The pathogenesis of malignant mesothelioma involves molecular changes such as chromosomal alterations in tumor suppressor genes, allele loss, gene silencing by DNA methylation in specific chromosomal regions, epigenetic dysregulation of tumor suppressor genes by histone acetyltransferase and histone deacetylase (HDAC) chromatin condensation/decondensation balance, and gene mutations. Analysis of explanted human mesotheliomas and cultured human mesothelioma cell lines has revealed a number of cytogenetic aberrations that may predispose to the development of the malignant phenotype. Partial or total loss of chromosomes 1, 3, and 4, deletions of 9p, and monosomy of chromosome 22 are the most common abnormalities seen. For mesotheliomas, 9p deletions have been associated with the loss of function of the $p16^{INK4}$ cdk inhibitor, a putative tumor suppressor gene, engendering unchecked cdk4-mediated phosphorylation of the retinoblastoma 1 (Rb1) gene product and leading to loss of regulation of cell division. Monosomy 22, the most frequent numerical cytogenetic abnormality in mesothelioma, has recently been correlated with mutations in the neurofibromatosis 2 (NF2) tumor suppresser gene mutations more commonly associated with acoustic neuromas, schwannomas, and meningiomas. The product of NF2, Merlin, appears to inhibit cell proliferation and cell cycle progression by repressing cyclin D1 expression as well as inhibiting invasiveness. The presence of the Wilms tumor suppresser gene (WT1) in human mesotheliomas raises the possibility that alterations in this gene or binding of the WT1 gene product to the p53 tumor suppressor may predispose to mesothelial cell carcinogenesis.[15,16,18]

VIRAL ONCOGENES

Simian virus-40 (SV-40) is a polyoma virus with oncogenic potential in humans. Its actions are thought to result from inactivation of tumor suppressor genes such as the retinoblastoma gene (Rb) and wild-type p53 (wt p53) by a peptide known as the SV-40 large T-antigen (Tag). SV-40 is a potent oncogenic virus in human and rodent cells; SV-40 DNA sequences have been identified in brain tumors, osteosarcomas, and lymphomas.[19] SV-40 is the only agent known to cause malignant transformation of human primary mesothelial cell in vitro.[20] When cell lines are exposed to both SV-40 and asbestos fibers, the rate of transformation increases significantly. Animal studies have also shown that crocidolite asbestos and SV-40 can act as cocarcinogens.[21] Several studies have documented the presence of SV-40 in patients with mesothelioma (some of whom did not have obvious asbestos exposure), as well as in cases of atypical mesothelial proliferation.[22–26] As an example, one report examined 35 archival mesothelioma specimens and found that SV-40–like sequences were present in 86% of cases.[23] However, the possibility that technical factors can produce false-positive results suggestive of SV-40 infection also has been raised.[27,28] Despite the fact that there was worldwide dissemination of SV-40 contaminated polio vaccines in the 1950s and 1960s, there is no convincing epidemiologic evidence linking SV-40 exposure to the development of malignant mesothelioma.

Nonetheless, it is possible that Tag interference with Rb and wt p53 may play an accessory role in the carcinogenesis of malignant mesothelioma.[29] If this hypothesis is validated, novel strategies of vaccination to prevent mesothelioma or molecular techniques to improve early diagnosis may become possible.

GENETIC PREDISPOSITION

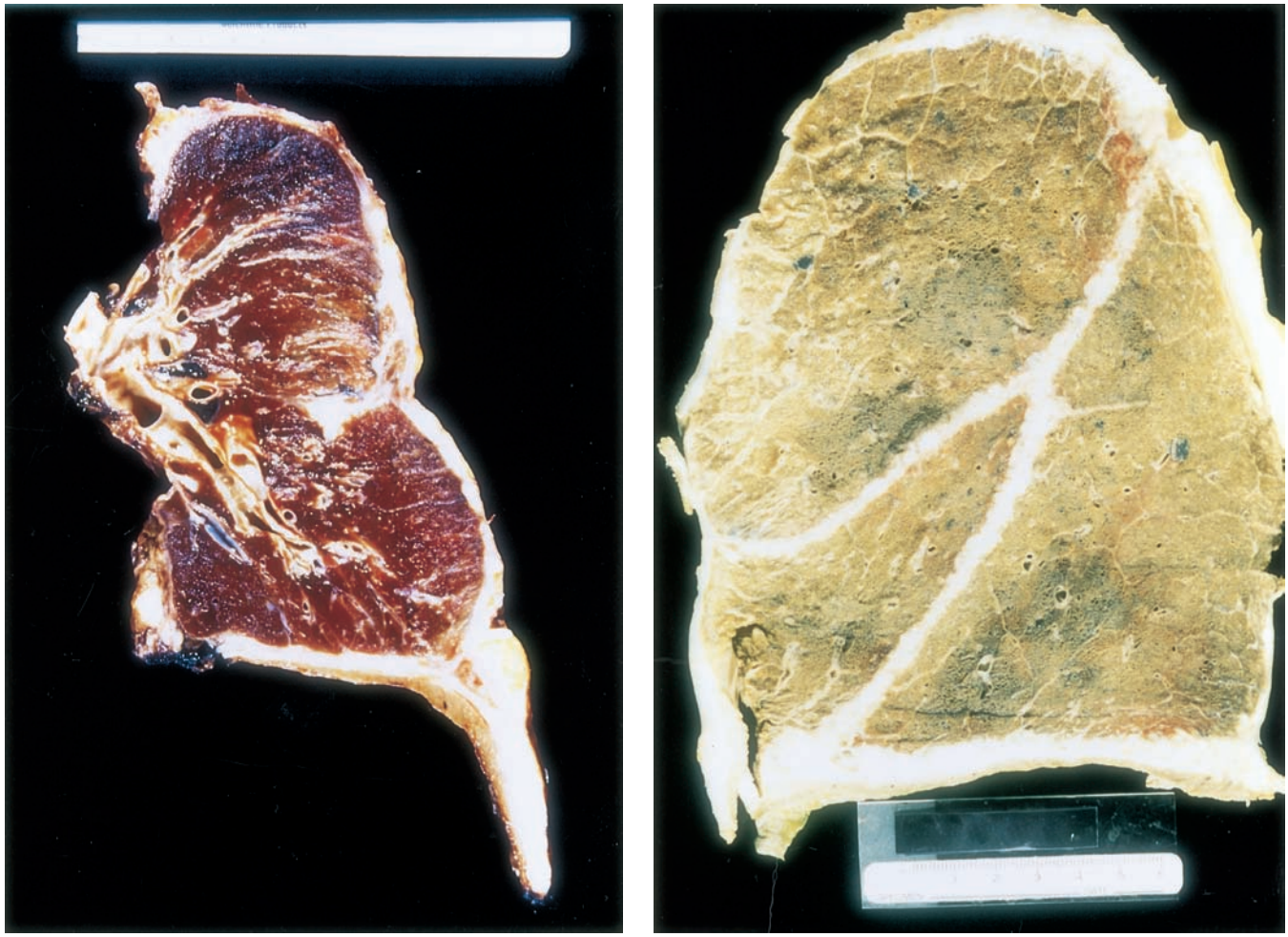
Gene polymorphism studies are in their early stages in asbestos-exposed populations. Some suggestive associations in DNA repair genes with mesothelioma development have been reported, but need validation. One study reported an increased incidence of mesothelioma among asbestos-exposed individuals in Finland found to be lacking the glutathione-S-transferase M1 (GSTM1) gene and carrying the "slow-acetylator" type of the *N*-acetyltransferase 2 (NAT-2) gene.[30] The GSTM1 gene is important in the detoxification of several carcinogens, including polycyclic aromatic hydrocarbons; NAT-2 is associated with the biotransformation of aromatic amines. Some genetically predisposed families have been identified, but without identification of a specific "mesothelioma" gene. An increased frequency of polymorphisms in the nod-like receptor pyrin domain (NLRP) inflammasome complex among a cohort of Italians with mesothelioma has also been described.[31] Inactivation of the nuclear deubiquitinase BAP1, which appears to regulate key histones and transcription factors related to the development of tumors, is associated with malignant pleural mesothelioma.[32] A so-called BAP1 "syndrome" has been described in some families bearing this gene mutation, in which there is higher frequency of mesothelioma, ocular melanoma, and melanocytic lesions of the skin, sometimes even occurring simultaneously in the same individual.[33]

PATHOLOGY

Gross and microscopic pathologic findings in malignant mesothelioma are discussed below.

Gross Pathology

The vast majority of malignant mesotheliomas involving the pleura are those tumors that diffusely involve the pleura and are properly termed "diffuse malignant mesothelioma." A rare localized gross



A B

Figure 79-1 **A.** Transverse section of an extrapleural pneumonectomy surgical specimen with the entire right lung, parietal and visceral pleurae, portions of pericardium, and the majority of the right hemidiaphragm. Note the thick rind of tumor along the pleural surface encasing the lung and invading the diaphragm. **B.** Postmortem mesothelioma specimen with overnight formalin inflation and fixation. The right lung pictured is covered by a thick, whitish rind of tumor involving the entire pleural surface, which has also infiltrated and demarcated the interlobar fissures.

variant of malignant mesothelioma that forms a single mass arising in the pleura but is otherwise microscopically identical to diffuse malignant mesothelioma has been described and termed "localized malignant mesothelioma." Diffuse malignant mesothelioma begins as multiple discrete nodules that, in earlier stages, tend to preferentially involve the parietal pleura over the visceral pleura. In time, these nodules tend to coalesce on the visceral and parietal pleural surfaces with subsequent fusion of the pleurae. Progressive tumor growth typically leads to partial or complete encasement of the lung with rinds of pleural tumor that can be several centimeters in thickness, but may show only minimal penetration of the underlying lung parenchyma (Fig. 79-1). Advanced cases show more extensive spread along interlobar fissures, deeper invasion into the underlying lung parenchyma and through the diaphragm, as well as contiguous involvement of the chest wall, pericardium, and mediastinum. Although it is rare for patients with mesothelioma to present clinically with metastatic disease, peribronchial lymphovascular spread, regional lymph node metastases, and extrathoracic hematogenous metastases become increasingly common over the course of the disease. Seventy percent of patients have mediastinal lymph node involvement at autopsy. Hematogenous metastases follow the exact same pattern of spread as non–small cell lung carcinomas with involvement of the contralateral lung and pleura, liver, adrenals, bone, brain, and kidney.

Histology

The 2004 revision of the WHO classification of pleural tumors recognizes four major histologic subtypes—epithelioid, sarcomatoid, desmoplastic, and biphasic. In the 2004 WHO classification, the use of the term "well-differentiated papillary mesothelioma" is restricted to an exceptionally rare and distinctive mesothelial tumor that has bland cytologic features, stout papillary architecture, and a tendency toward superficial spread without invasion. Part of the diagnostic utility of the WHO classification is that each subtype is associated with a particular differential diagnosis that guides the pathology workup. This workup requires additional time and expense. Multiple sections may be taken and ancillary studies are usually required for definitive diagnosis. From a prognostic perspective, most studies have shown that the purely epithelioid subtype has the longest survival but these differences in survival, on the basis of histologic subtype, are within the range of only a few months. It should be recognized that the larger the tissue sample, the more frequent the histologic variation and the higher the incidence of biphasic tumors.

The epithelioid variant is the most common with a wide range and mix of histologic patterns. Typical histologic appearances of this subtype include tubulopapillary, glandular/microglandular, and solid sheet-like patterns (Fig. 79-2A). A myxoid matrix may be prominent and may be mistaken for mucin, but this matrix is

actually hyaluronate and shows hyaluronidase-sensitive staining with Alcian blue.

Sarcomatoid mesotheliomas can also have a wide variety of histologic patterns. The most frequently encountered pattern is that of fibroblastic-like spindle cells arranged in storiform, fascicular, or haphazard patterns that mimic a fibrosarcoma (Fig. 79-2B). Other variants include a malignant fibrous histiocytoma-like tumor and malignant mesotheliomas with malignant smooth muscle, chrondroid, osseous, or rhabdomyoblastic differentiation.

Desmoplastic mesotheliomas, by definition, have areas of densely collagenized tissue with atypical cells arranged in a storiform or "patternless" pattern. This pattern should comprise at least 50% of the tumor. The deceptively bland appearance of the tumor makes its separation from fibrous pleuritis exceedingly difficult, particularly with limited sampling. Studies that have examined the criteria used for diagnosis have highlighted the importance of "interface biopsies" in which unequivocal evidence of invasion into the underlying adipose tissue, skeletal muscle, or lung may be demonstrated. Other criteria, which may require multiple tissue sections to detect,

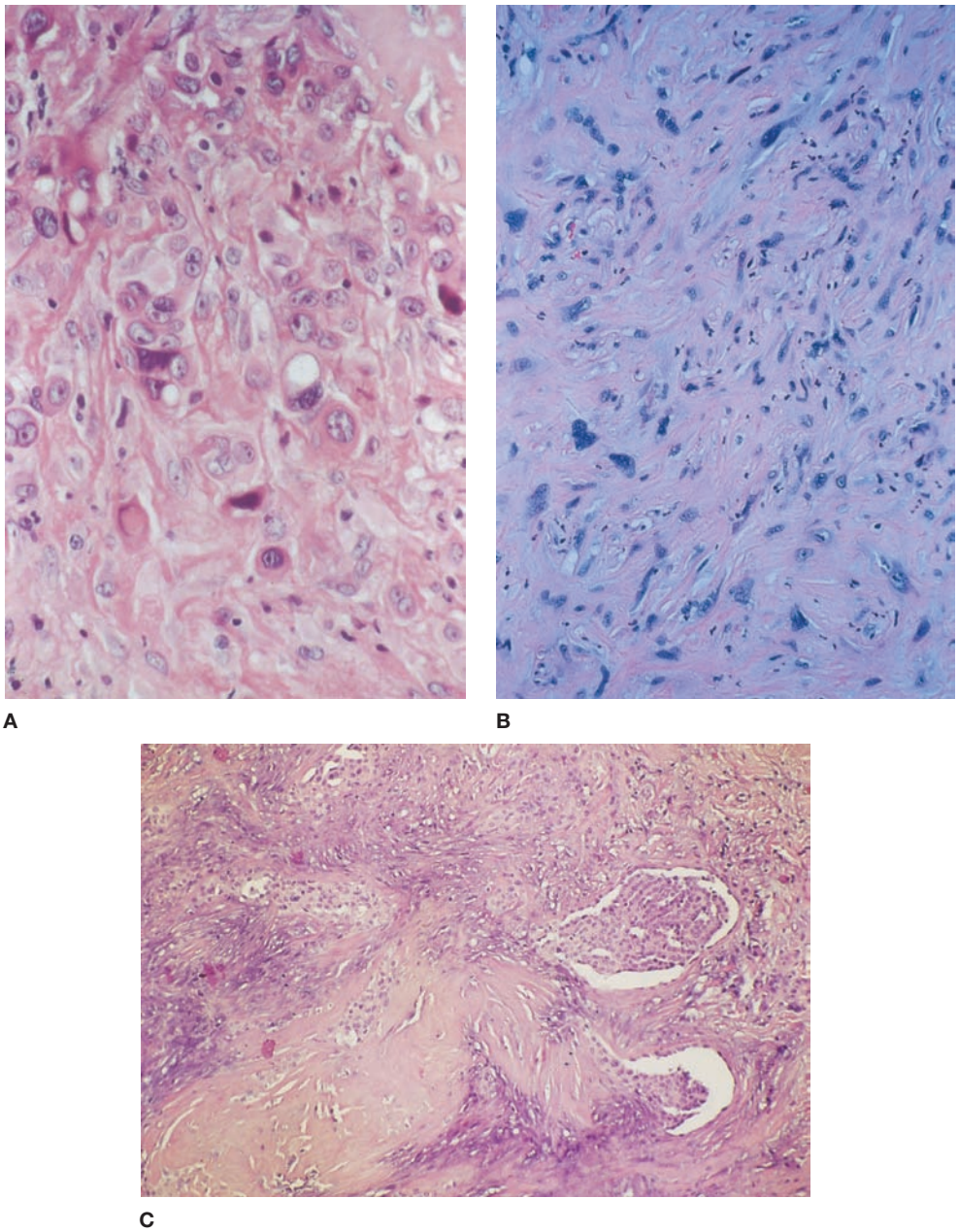


Figure 79-2 **A.** Photomicrograph of an epithelial malignant mesothelioma. These sheets of pleomorphic cells are epithelial in appearance, with eosinophilic cytoplasm and fairly well-defined cell borders. Note the cytoplasmic vacuoles, which can lead to confusion with a signet ring type of adenocarcinoma. By electron microscopy, these vacuoles can be shown to contain crystallized hyaluronic acid (H&E, ×400). **B.** Photomicrograph of a sarcomatoid malignant mesothelioma. This tumor has a malignant mesenchymal appearance with bizarre spindled cells and a growth pattern resembling that of a sarcoma. These cells demonstrated strong cytokeratin positivity on immunohistochemical staining, distinguishing this tumor from a sarcoma (H&E, ×400). **C.** Photomicrograph of a biphasic malignant mesothelioma. This tumor demonstrates several areas of epithelioid histology with a papillary growth pattern seen against a background of spindled and more poorly differentiated epithelioid cells (H&E, ×200).

include obvious sarcomatoid areas, foci of necrosis, and distant metastases. Bone metastases similarly may be deceptively bland and confused with a primary benign fibrous tumor of bone.[34,35]

Biphasic mesotheliomas have both epithelioid and sarcomatoid components (Fig. 79-2C). Each component should represent at least 10% of the tumor for the designation of biphasic. Biphasic mesotheliomas represent about 30% of cases. As previously noted, the percentage of biphasic tumors, which have a prognosis that is intermediate between the epithelioid and sarcomatoid subtypes, increase with larger tumor samples. In recent years, the percentage of sarcomatoid component within biphasic mesotheliomas has been shown to be prognostic factor, with greater than 50% sarcomatoid elements corresponding to decreased overall patient survival.[34]

Immunohistochemistry

Immunohistochemistry (IHC) has largely replaced electron microscopy as the gold standard for diagnosis. This is because of the comparative low cost, ease, and greater availability of IHC, as well as the expanded array of commercially available antibodies that are reliable markers of mesothelial differentiation. Because there is no single marker with sufficiently high sensitivity and specificity for malignant mesothelioma, it is standard practice for pathologists to employ a panel of markers (both positive and negative) to confirm the diagnosis of malignant mesothelioma. Institutions will vary somewhat in their selection of which markers to include and these panels are typically refined as publications appear with comparative utility studies. As in any instance in which IHC is used as an adjunct in tumor diagnosis, careful consideration must be given to the tumor's histologic appearance as well as the clinical-radiographic context and the differential diagnosis that is generated from this information.[36]

Broad-spectrum cytokeratin (CK) antibody cocktails are essential in the diagnosis of malignant mesothelioma. In epithelioid tumors, strong and diffuse CK positivity can be used to exclude the rare case of large cell lymphoma, epithelioid vascular tumors, or melanoma involving the pleura. CK reactivity usually differentiates malignant mesotheliomas from many sarcomas, although there are occasional CK-negative sarcomatoid mesotheliomas as well as focally CK-positive sarcomas. Although CK positivity does not distinguish malignant mesothelioma from reactive lesions, positive CK staining may help to highlight invasion into adjacent structures.

Common affirmative immunohistochemical markers, which, if positive, can be used to support a diagnosis of malignant mesothelioma include calretinin, CK5/6, the Wilms tumor I (WT1) antigen, and D2-40 (Fig. 79-3).[36] These markers are most useful in the narrow differential diagnosis of malignant epithelioid mesothelioma versus primary pulmonary adenocarcinoma. It should be noted that these markers do not invariably exclude other tumors, including metastases from nonpulmonary primary sites. A wide variety of markers can be used to support a diagnosis of adenocarcinoma, as opposed to malignant mesothelioma. Markers such as CEA, Leu-M1 (CD15), thyroid transcription factor-1 (TTF-1),

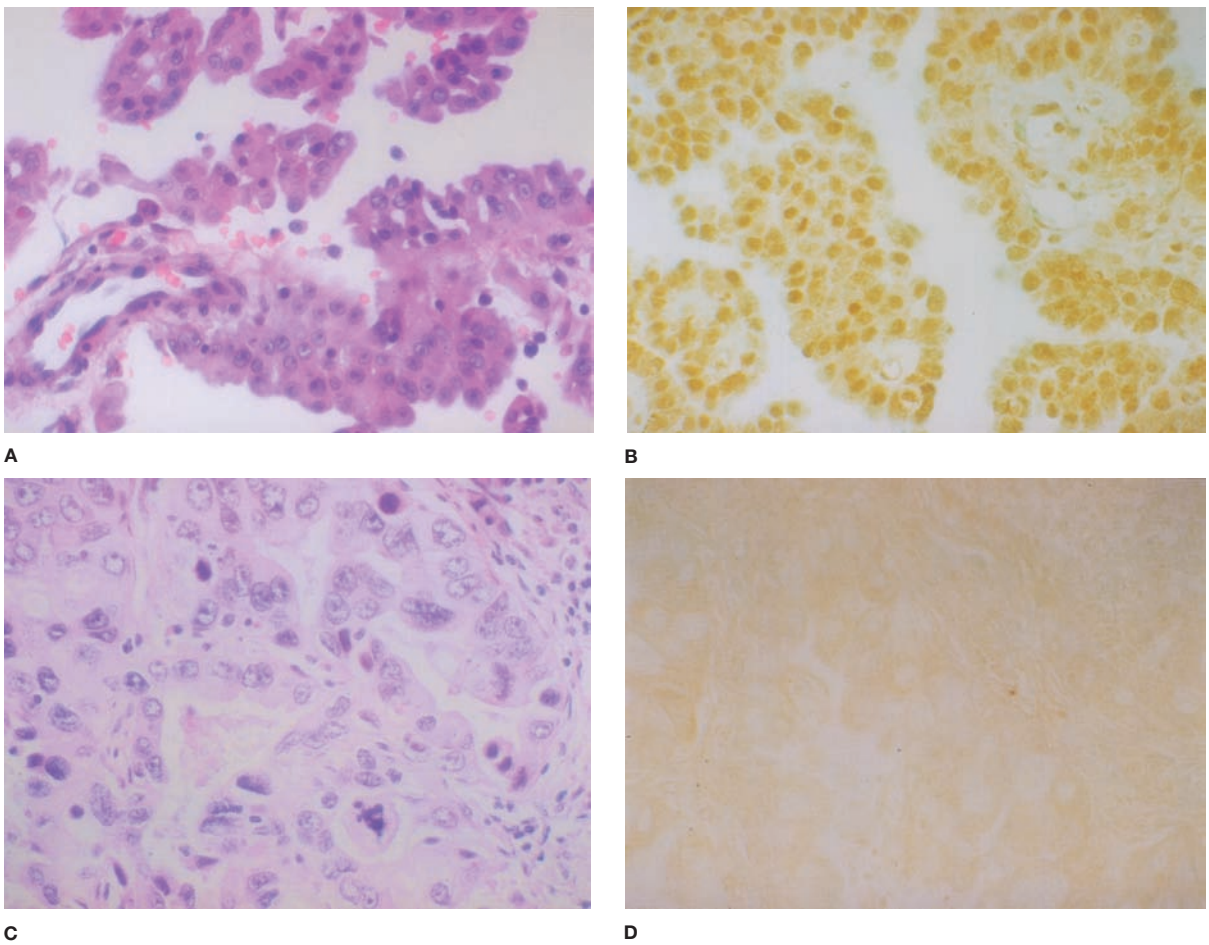


Figure 79-3 **A.** Photomicrograph of an epithelial mesothelioma (H&E, ×400). **B.** Photomicrograph of epithelial mesothelioma demonstrating positive nuclear staining with an antibody to the Wilms tumor 1 (WT1) gene product (×400). **C.** Photomicrograph of an adenocarcinoma metastatic to the pleura (H&E, ×400). **D.** Photomicrograph of pleural adenocarcinoma stained with an anti-WT1 antibody (×400). Only minimal background staining is present.

Ber-EP4, B72.3, Bg8, and MOC 31 are commonly included in such panels.[36] The sensitivity and specificity of both the affirmative mesothelioma markers as well as the adenocarcinoma markers vary greatly when the differential diagnosis is broadened to include other subtypes of primary pulmonary carcinoma such as squamous cell carcinoma or metastases from extrapulmonary sites such as the kidney and ovary. Both categories of markers are generally less reliable in the differential diagnosis of sarcomatoid lesions. The immunohistochemical panel that is recommended for the initial evaluation of a sarcomatoid tumor involving the pleura includes CKs (including AE1/3, CAM5.2, CK18, and CK7), calretinin, and D2-40.[37–39] If other types of sarcomas are being considered, then the marker panel should be expanded accordingly to include antibodies such as CD31, CD34, desmin, myoglobin, and S-100.

OTHER ANCILLARY STUDIES

Histochemical stains for the presence of intracytoplasmic mucin are still commonly used as a means of differentiating adenocarcinomas from epithelioid malignant mesotheliomas. Mucicarmine and periodic acid-Schiff (PAS) with diastase are the two most frequently used. These stains are technically easy to perform, inexpensive, and rapid. Care must be taken to exclude the possibility of false-positive staining that can be seen with hyaluronate. The use of histochemical staining (Alcian blue with hyaluronidase) to detect the high levels of hyaluronic acid in mesothelioma cells was used far more frequently before the widespread use of IHC.

Electron microscopy had traditionally been considered the gold standard for the diagnosis of malignant mesothelioma and ultrastructural analysis can still be useful in occasional problematic cases. The predominant epithelioid form is composed of polygonal cells with numerous long surface microvilli, prominent desmosomes, and abundant tonofilaments (Fig. 79-4). Electron microscopy of the sarcomatoid variant reveals the presence of elongated nuclei, CK and vimentin filaments, as well as copious rough endoplasmic reticulum, some intracellular attachments, and rare microvilli. Electron microscopic studies may be inconclusive in poorly differentiated tumors of either subtype and have no utility in the diagnosis of desmoplastic malignant mesothelioma. Molecular analysis can be performed on formalin-fixed, paraffin-embedded tissue to demonstrate the X:18 translocation characteristic of synovial sarcoma—a biphasic or monophasic sarcomatoid tumor that can involve the pleura. As discussed at the end of the chapter, synovial sarcoma should be considered in the differential diagnosis of a pleural tumor with a biphasic or monophasic spindle cell appearance.[40,41]

MOLECULAR PROFILING

As compared with routine histologic evaluation and classification, the examination of multiple expressed genes and/or proteins within individual tumors may be more informative for making diagnoses, estimating prognosis, and response to therapy. The development of microarray methodology, which permits the expression of thousands of genes to be assayed simultaneously, represents a powerful technique to read the "molecular signature" of an individual patient's tumor, a process termed gene expression profiling. Gene expression profiling studies have been used to identify genes with potential pathogenic significance, such as aurora kinases or key inhibitors of apoptosis proteins. Profiles have also been identified that help to reliably differentiate different subtypes of mesothelioma. By using gene expression ratios, it is possible to reliably distinguish between epithelioid mesothelioma and lung adenocarcinoma or ovarian carcinomas from peritoneal mesotheliomas.[42,43] An area of active investigation is the use of expression profiles as a means of predicting outcome and clustering groups of patients with pleural mesothelioma into those with good risk (i.e., more likely to be cured using aggressive therapy) and poor risk disease (i.e., with a low cure rate despite aggressive therapy). Some groups have found this approach to be highly predictive, whereas others suggest the accuracy has been overestimated.[44]

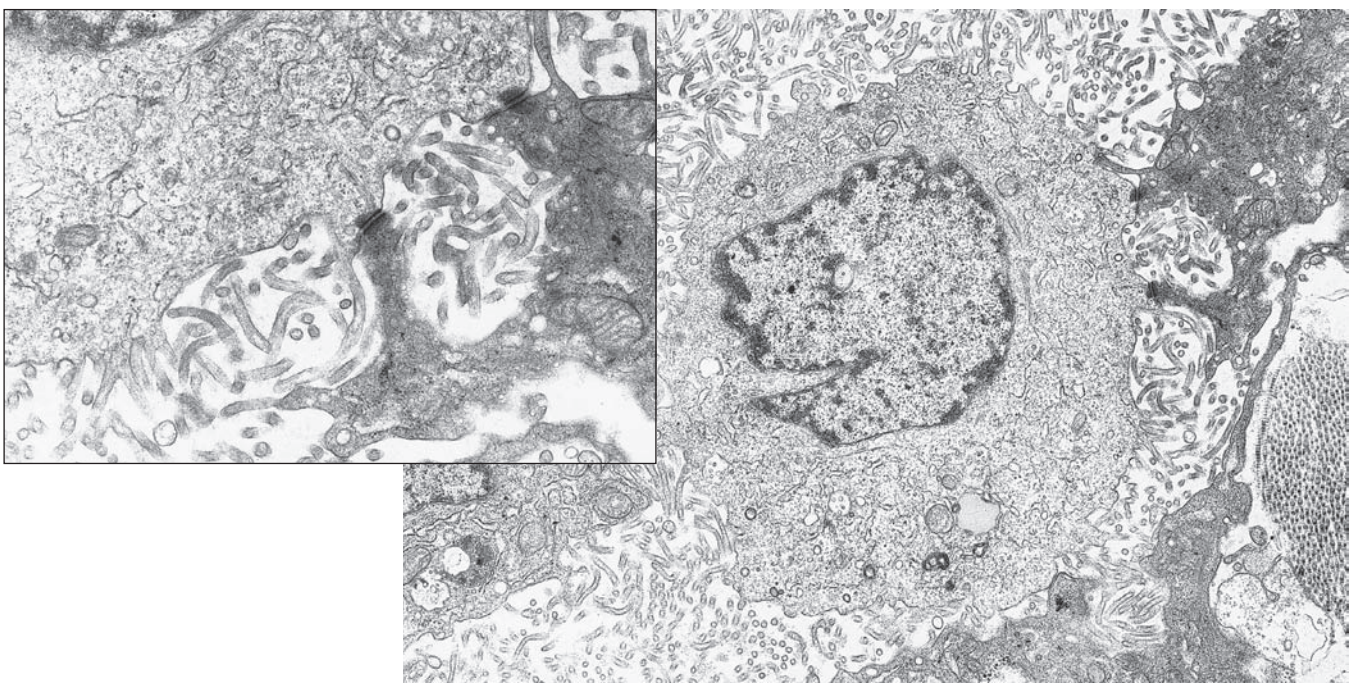


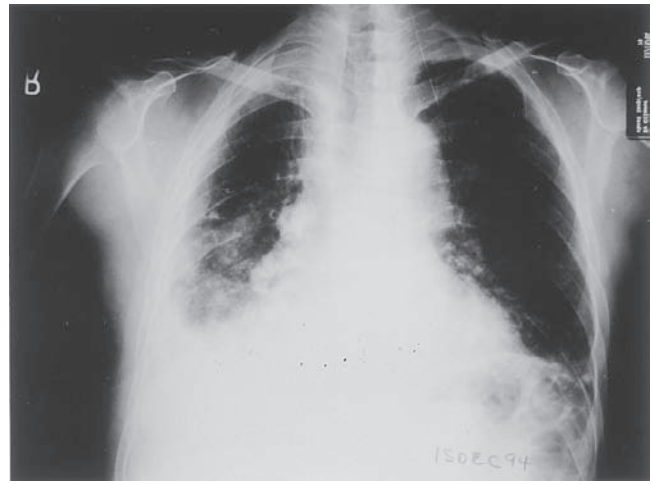
Figure 79-4 Electron micrograph of a human mesothelioma cell showing abundant microvilli arising from the cell surface and prominent desmosomes (×10,500; inset, ×30,000). *(Used with permission of Dr. Giuseppe G. Pietra, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.)*

CLINICAL PRESENTATION

Malignant pleural mesothelioma most commonly presents in the fifth to seventh decades of life. Most patients diagnosed with mesothelioma earlier in life have a history of childhood asbestos exposure. The most frequent presenting symptoms of pleural mesothelioma, which are caused by the presence of extensive intrathoracic disease, are nonpleuritic chest pain (60%–70% of patients), dyspnea (25%), and cough (20%). Some patients are asymptomatic at diagnosis, with unilateral pleural effusions found incidentally on routine chest radiographs. Mesothelioma is typically a unilateral disease—only 10% of patients with mesothelioma have bilateral involvement at presentation. In more advanced stages of disease, physical findings may include unilateral dullness to percussion and decreased air movement throughout the hemithorax, asymmetric chest wall expansion during respiration, palpable chest wall masses, and scoliosis toward the side of the malignancy.

RADIOGRAPHIC PRESENTATION

The most common initial radiographic manifestation of pleural mesothelioma is a large unilateral pleural effusion, often with contralateral mediastinal shift (Fig. 79-5A). Sixty percent of patients have right-sided lesions, putatively related to the gravitational predilection for inhaled asbestos fibers and dusts to travel directly to the right lower lobe airways. Occasionally, mesothelioma can present as unilateral, concentric, plaque-like, or nodular pleural thickening, but effusions may obscure the presence of the underlying pleural thickening. The tumor frequently extends into the fissures, which become thickened and irregular in contour. Only 20% of patients with pleural mesothelioma have radiographic signs of asbestosis (i.e., bibasilar interstitial fibrosis), although many have evidence of pleural plaques and/or calcifications. In later stages of disease, ipsilateral mediastinal shift is seen secondary to encasement of the lung by a thick rind of tumor and resultant significant unilateral loss of lung volume. Patients with advanced mesothelioma may also have other radiographic signs of volume loss: diaphragm elevation and intercostal space narrowing. They may also have mediastinal widening owing to direct tumor invasion or lymph node involvement, enlargement of the cardiac margins secondary to pericardial invasion with effusion, and evidence of rib destruction or soft tissue masses extending from the chest wall.[45] Chest computed tomography (CT) is important in detecting invasion of chest wall, ribs, and mediastinal structures, as well as extension along the pleural surfaces and diaphragm (Fig. 79-5B). Furthermore, CT scans can distinguish between pleural thickening and effusion.[46] Coronal magnetic resonance imaging (MRI) is helpful in discerning the extent of disease, particularly invasion of the chest wall, endothoracic fascial involvement, and extension of pleural mesothelioma through the diaphragm into the peritoneal cavity.[47] In one study of 95 patients with pleural mesothelioma, MRI was directly compared with CT scan. The overall diagnostic accuracy for mediastinal nodal disease was approximately 50% for both modalities, but MRI outperformed CT for detection of diaphragmatic invasion (82% vs. 55% accuracy, respectively), and for detecting invasion of endothoracic fascia or chest wall (69% vs. 46%).[48]



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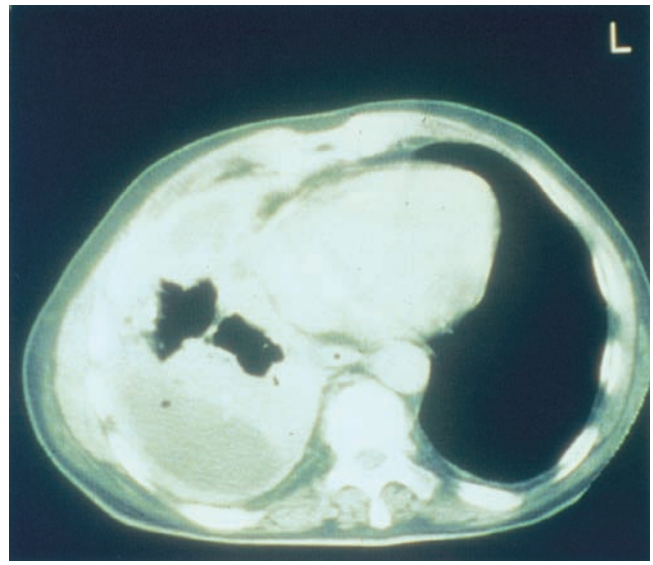


B

Figure 79-5 **A.** Posteroanterior chest radiograph in a patient with malignant pleural mesothelioma demonstrating significant right-sided pleural effusion and diffuse pleural thickening associated with marked volume loss of the right hemithorax. No definite calcified pleural plaques are seen. **B.** Computed axial tomographic image from a patient with pleural mesothelioma, illustrating complete encasement of the ipsilateral lung with a thick rind of tumor, neoplastic invasion of the interlobar fissures, small residual pleural effusion, and marked unilateral volume loss.

POSITRON EMISSION TOMOGRAPHY

The role of positron emission tomography (PET) imaging, particularly PET/CT, in the care of patients with mesothelioma is multifold. It can be used in diagnosis and staging by evaluating the extent of pleural disease, establishing mediastinal lymph node involvement, evaluating tumor invasion into the lung and thoracic wall, and detecting extrathoracic metastases. It is becoming particularly useful to assess the treatment response to chemotherapy and radiotherapy and also plays an important role in the planning of radiation therapy.

The role of PET scans with 18-fluorodeoxyglucose (FDG) in staging and preoperative evaluation is evolving. In a small study of 28 patients with suspected pleural mesothelioma who underwent 18-FDG PET scanning followed by thoracoscopic or open surgical biopsy, PET was shown to be better than CT for differentiating malignant from benign pleural processes. Uptake of FDG was significantly higher in malignant lesions, and an overall sensitivity and specificity of 91% and 100% could be achieved with PET scanning for the detection of malignant as compared with benign disease. However, hypermetabolic lymph nodes were detected in 12 patients (of whom nine had a normal CT scan), and only five had histologically proven malignant nodal disease.[49]

In another small study, PET assessment demonstrated pleural lesions in 12 of 13 patients with malignant pleural disease (malignant pleural mesothelioma in ten patients, adenocarcinoma in two and liposarcoma in one), also revealing distant metastases in two patients. A patient with an epithelial mesothelioma had a false-negative result. In a study of 16 patients with pleural changes, PET correctly identified all 12 malignant cases; conversely, the four

patients (4/4) who had no FDG uptake all had benign pleural disease (fibroma, tuberculous pleurisy, empyema, and pleural fibrosis).[50]

PET scan appears more sensitive than CT for finding extrathoracic disease, but has limited sensitivity for locoregional staging (i.e., determining potential resectability). In one retrospective study, 60 patients with malignant pleural mesothelioma were identified who had undergone PET scans preoperatively and the results of clinical staging were compared with surgical and pathologic results. FDG uptake was detected in 59, and the one false-negative case had disease limited to the parietal pleura (stage IA). The sensitivity of PET scans for determining the presence of T4 (unresectable) disease was only 19% (7 of 21 patients). Among the 31 patients whose nodal status was assessed pathologically, only one of nine patients with N2 disease was correctly identified by PET scan, and the overall sensitivity for nodal disease was only 11%.[51]

PET scanning may help differentiate between benign and malignant pathology when patients present with a chest radiograph demonstrating pleural abnormalities. One study demonstrated that dual timepoint FDG PET scanning, which measures uptake of (18)F-FDG over time, could distinguish between benign and malignant pleural diseases among 55 suspected cases.[52]

One of the potential future uses of PET that needs to be further evaluated is its utilization in the screening of patients with a history of significant asbestos exposure. These patients may potentially harbor microscopic disease, not apparent on CT or MRI, which may be amenable to early aggressive therapy. Because of the limits of detection of current 18-FDG PET technology, the use of PET for screening for pleural mesothelioma must await the development of novel radiopharmaceuticals.

PET scans can also be used to predict survival and response to therapy. One study involving 177 patients with mesothelioma found that patients with tumors demonstrating intense FDG avidity (standardized uptake value >5) had a far worse prognosis. Another study showed that decreased radiopharmaceutical uptake on follow-up PET scans performed early after treatment may be an excellent predictor of overall clinical response.[53] Furthermore, there is evidence supporting the use of PET scans after neoadjuvant chemotherapy to determine those who will benefit most from moving onto surgical resection.[54]

LABORATORY STUDIES

Although there are no specific pleural fluid biomarkers for malignant mesothelioma, evaluation of pleural fluid chemistries may still be beneficial. Effusions associated with mesothelioma are strongly exudative, with elevated protein concentrations in the range of 4 to 5 g/dL and a lymphocytic predominance. Pleural fluid lactate dehydrogenase (LDH) concentrations often exceed those of patients with carcinomatous pleural effusions, with levels greater than 600 IU/L. In patients with advanced disease and extensive involvement of visceral and parietal pleura, pleural fluid pH and glucose are commonly low. In patients with mesothelioma, the presence of a low pleural fluid pH denotes both a poor overall prognosis and refractoriness to achieving successful palliative pleurodesis. In addition, the pleural effusion associated with mesothelioma is characteristically highly viscus, presumably because of elevated concentrations of hyaluronic acid.[55] An increased pleural fluid hyaluronidase level is suggestive but not diagnostic of mesothelioma.[56] The cytokine profile of pleural effusions related to mesothelioma is somewhat unique in that the tumor constitutively produces high concentrations of interleukin-6 (IL-6) and transforming growth factor-β (TGF-β), but relatively low levels of IL-1β and TNFα. These elevated intrapleural levels of IL-6 in patients with malignant mesothelioma are postulated to induce systemic manifestations such as fever, cachexia, and thrombocytosis.[57,58]

Pulmonary function testing typically demonstrates a restrictive pattern resulting from pleural effusions, tumor encasement of the lung, or chest wall involvement.

MESOTHELIN AND OTHER NOVEL SERUM MARKERS

There is increasing evidence supporting the clinical utility of a monoclonal antibody–based serum assay for a soluble form of the protein mesothelin (soluble mesothelin–related peptide [SMRP]). Mesothelin is a 40-kDa glycoprotein that is found in low levels on the cell surface of normal mesothelial cells (lining the pleura, peritoneum, pericardium, and tunica vaginalis), but is highly expressed on mesothelioma, pancreatic cancer, and ovarian cancer cells.[59,60] Multiple studies have observed that SMRP can be elevated in serum and pleural fluid of patients with mesothelioma.[61] Increased levels of SMRP were found in serum samples from 37 of 44 patients with mesothelioma (87%), compared with 3 of 160 patients with other cancers or inflammatory lung or pleural diseases (2%), and none of 28 controls without a past asbestos exposure.[62] At the present time, SMRP levels play an adjunctive role in the diagnosis of patients with mesothelioma. A meta-analysis of 16 diagnostic studies found that the sensitivity ranged widely from 19% to 68%, depending on the specific criterion for positivity.[61] SMRP has also been measured in pleural fluid. In a retrospective study of 52 patients with malignant mesothelioma, the assay had a sensitivity of 67% with a specificity of 98% in 84 patients with benign pleural effusions.[63] It is intriguing to posit that SMRP may also play a role in screening of high-risk patients for incipient mesothelioma. In one report, 7 of 40 asbestos-exposed individuals had elevated levels and 4 of these 7 subsequently developed mesothelioma or lung cancer within 1 to 5 years.[62] However, measurement of SMRP is indicated currently only for monitoring patients in whom the diagnosis has already been established.

Osteopontin, a glycoprotein that mediates cell–matrix interactions and is overexpressed in several types of cancer, was higher in patients with malignant mesothelioma than in patients with asbestos-related nonmalignant pleural disease or no prior asbestos exposure in a study of 190 patients.[64]

Fibulin-3 is an extracellular glycoprotein that is encoded by the epidermal growth factor–containing fibulin-like extracellular matrix protein 1 (EFEMP1) gene. Initial studies found that elevated levels of fibulin-3 in the plasma had high sensitivity and specificity (97% and 96%, respectively) in distinguishing patients with pleural mesothelioma from those with a history of asbestos exposure but without mesothelioma and from those with other malignancies or benign causes of pleural effusion. Levels of fibulin-3 decreased in patient with mesothelioma who underwent surgical resection. Additional studies will be required to determine its role as a biomarker for early diagnosis and monitoring of patients who have undergone therapy.[65]

DIAGNOSIS

The differential diagnosis of malignant pleural mesothelioma includes both benign and malignant processes. Inflammatory reactions such as chronic, organized empyema can mimic the dense pleural thickening and large, viscous pleural effusions characteristic of mesothelioma. As discussed, epithelial mesotheliomas can be extremely difficult to distinguish grossly and histologically from metastatic adenocarcinoma to the pleura from any number of primary sources, including lung, breast, stomach, kidney, ovary, and prostate. Sarcomas such as fibrosarcoma can present in similar fashion and infiltrate-like sarcomatoid mesotheliomas. The mixed-cellular (biphasic) subtype of mesothelioma can bear a significant histologic resemblance to sarcomatoid carcinomas and synovial sarcoma.

Thoracentesis or closed pleural biopsy can often establish the diagnosis of pleural malignancy, but may not provide enough diagnostic material to determine the specific diagnosis of mesothelioma. Immunohistochemical markers and monoclonal antibodies may aid in differentiating mesothelioma from other carcinomas on cytology specimens. In addition, certain cytopathologic features of cells obtained from pleural fluid have been found to correlate well with the presence of mesothelioma, including papillary aggregates, multinucleation with atypia, cell-to-cell apposition, nuclear pleomorphism,

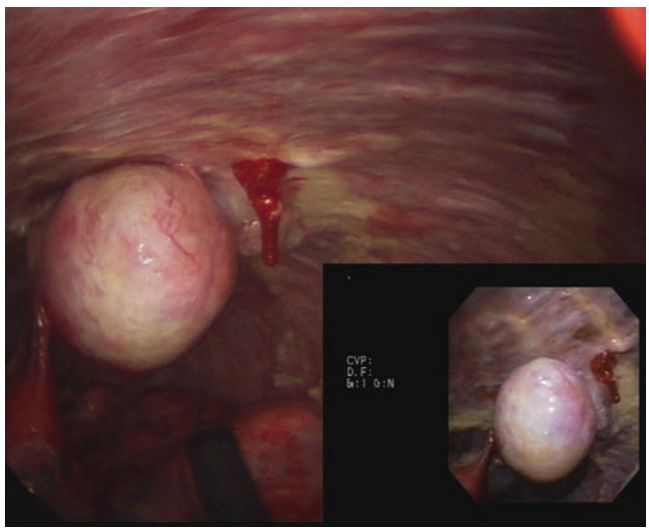
and macronucleoli. Gene expression ratios may also be increasingly helpful in this regard. Negative results from thoracentesis and/or pleural biopsy do not exclude the diagnosis of mesothelioma and therefore surgical biopsy, which has a higher diagnostic yield, should be pursued in patients with high clinical suspicion.

Surgical intervention, via video-assisted thoracoscopic surgery (VATS) or open thoracotomy, is often necessary to firmly establish the diagnosis. Boutin et al. from Marseille prospectively evaluated VATS for the diagnosis of malignant pleural mesothelioma in 188 consecutive patients from 1973 to 1990 and found that thoracoscopic biopsy was diagnostic in 98% of cases, compared with only 26% for thoracentesis alone, and 39% for fluid cytology and closed pleural biopsy. These thoracoscopic procedures were performed under local anesthesia in an endoscopy suite with minimal morbidity or complications.[66] It is important to note that approximately 10% of patients who undergo a transthoracic diagnostic procedure for mesothelioma may seed the biopsy site with tumor cells, later developing chest wall recurrences. This complication can potentially be prevented by prophylactic radiation therapy to the surgical incision or thoracentesis sites (Fig. 79-6).

Concurrent bronchoscopy may be important in distinguishing between mesothelioma and metastatic adenocarcinoma of the lung, as endobronchial lesions are rarely seen in mesothelioma. In addition, both endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy play important roles in the diagnosis and staging of mesothelioma, as several studies have documented the significant negative prognostic implications of mediastinal nodal invasion in this disease. In comparative trials, EBUS-TBNA may actually have a higher sensitivity and specificity for determining mediastinal nodal involvement than mediastinoscopy.[67,68]

STAGING

The staging of malignant mesothelioma has proved to be more controversial than that of many other tumors. The most commonly used schema was devised by Butchart in 1976 (Table 79-1). Although useful, its ability to predict survival is weakened by lack of inclusion of lymph node involvement and chest wall invasion. For this reason, the Union Internationale Contre le Cancer (UICC) in 1990 first proposed a staging system based on the TNM (tumor/node/metastasis) standard used for many other tumors. In the TNM staging system, stages I and II disease have pleural involvement, potentially including diaphragmatic muscle or pulmonary parenchyma, but no evidence of lymph node involvement, distant metastases, or locally advanced, unresectable disease. Stage III mesothelioma includes those cases with regional lymph node involvement. Stage IV includes those with locally advanced and unresectable disease, contralateral lymph node involvement, supraclavicular lymph node involvement, and/or distant metastases.[69] More recently, Rusch et al. from the International Mesothelioma Interest Group (IMIG) proposed an updated staging system based upon tumor descriptors, providing precise anatomic definitions of the local extent of the primary tumor. This staging system (Table 79-2) was designed to provide the framework for proper analysis of prospective clinical trials of new treatment modalities.[70]



A B

Figure 79-6 **A.** View of a mesothelioma tumor in the pleural cavity attached to the visceral pleura through surgical thoracoscope. **B.** View of the same tumor through a flexible medical pleuroscope.

TABLE 79-1 Butchart Staging System

Stage I	Tumor confined within the "capsule" of the parietal pleura
Stage II	Tumor invading chest wall or involving mediastinal structures
Stage III	Tumor penetrating diaphragm to involve peritoneum; involvement of opposite pleura; lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

CLINICAL COURSE AND COMPLICATIONS

The morbidity and mortality associated with mesothelioma is chiefly related to inexorable local invasion. Patients typically develop dyspnea and chest pain as tumor and fibrosis gradually obliterate the pleural space and replace any pleural fluid. As the tumor spreads, it covers both visceral and parietal pleural surfaces, encasing the

TABLE 79-2 International Mesothelioma Interest Group (IMIG) Staging System

T1	T1a: Tumor limited to ipsilateral parietal pleura T1b: Tumor involving ipsilateral parietal pleura, with scattered foci of tumor on visceral pleural surface
T2	Tumor involving all ipsilateral pleural surfaces with diaphragmatic invasion or extension into underlying pulmonary parenchyma
T3	Involvement of the endothoracic fascia; mediastinal fat; solitary, resectable chest wall focus; or nontransmural pericardial invasion
T4	Diffuse extension into chest wall, peritoneum, spine, mediastinal organs, contralateral pleura, internal surface of pericardium or myocardium
NO	No regional lymph nodes metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes
N3	Metastases in the contralateral mediastinal or internal mammary lymph nodes or any supraclavicular node metastasis
Staging	
Stage I	Ia: T1aN0M0 Ib: T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0, any N1M0, any N2M0
Stage IV	Any T4, any N3, any M1

ipsilateral lung with a thick, fibrous peel that extends into interlobar fissures and occasionally into lung parenchyma. Deoxygenated blood is shunted through the trapped lung, leading to significant dyspnea and to hypoxemia that is often refractory to supplemental oxygen. Dyspnea also results from abnormal chest wall mechanics secondary to tumor invasion into ribs as well as intercostal nerves and muscles. Local invasion of crucial thoracic structures can result in dysphagia, hoarseness, cord compression, brachial plexopathy, paralysis, Horner syndrome, and superior vena cava syndrome. Hilar and mediastinal lymph node involvement occurs at diagnosis in less than 50% of patients, but is a harbinger of poor prognosis. Transdiaphragmatic spread into the abdominal cavity rapidly leads to intraperitoneal dissemination, with encasement of the mesentery and small and large bowel. Local invasion into the pericardial space can lead to pericardial effusion and tamponade. Distant metastatic disease by hematogenous spread, is unusual early in the course of mesothelioma but may present in liver, bone, brain, adrenals, thyroid, and kidney. Widespread metastatic disease is more often a manifestation of end-stage malignant mesothelioma.[5,71–74]

MORTALITY

Median survival of patients with mesothelioma is between 8 and 14 months and varies depending on stage, histologic subtype, and concomitant medical problems. Patients with pleural mesothelioma most commonly die from local extension and respiratory failure, primarily related to spread to the contralateral hemithorax. As mentioned, tumor extension below the diaphragm may result in death from small bowel obstruction. Patients may also die from arrhythmias, heart failure, or stroke caused by tumor invasion of the heart or pericardium.[5,71–74]

PARANEOPLASTIC SYNDROMES

Disseminated intravascular coagulation, migratory thrombophlebitis, thrombocytosis, Coombs-positive hemolytic anemia, hypoglycemia, and hypercalcemia associated with secretion of a parathyroid hormone–like peptide have all been described in the setting of mesothelioma.[74]

PROGNOSTIC FACTORS

Poor prognosis at the time of presentation is indicated by the presence of thrombocytosis, leukocytosis, low hemoglobin, fever of unknown origin, sarcomatoid or mixed histology, age greater than 65 to 75 years, poor performance status, and male gender. Good prognosis at presentation is associated with epithelial histology; stage I disease; age under 65 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; absence of chest pain; and the presence of symptoms for more than 6 months prior to diagnosis.[75–79]

The prognostic scoring systems derived by the Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC) are the most useful clinical prognostic scoring schemes available. They incorporate both the extent of disease, as well as systemic factors. The CALGB evaluated the impact of clinical characteristics on the survival of 337 patients treated with chemotherapy for advanced mesothelioma in sequential phase II treatment studies over a 10-year period. In multivariate analysis, serum LDH greater than 500 IU/L, poor performance status, chest pain, platelet count over 400,000/μL, nonepithelial histology, and age older than 75 years jointly predicted poor survival. Six distinct prognostic subgroups were generated with median survival times ranging from 1.4 to 13.9 months. The median survival overall was 7 months. This prognostic schema was subsequently validated in an American phase II trial evaluating the investigational agent ranpirnase, and in an independent European data set.[78]

The EORTC Prognostic scoring system was derived from an analysis of data from 204 adults who were entered into five consecutive phase II trials over 9 years. When five factors were taken into consideration (poor performance status, high WBC count, male gender, sarcomatoid cell type, and the certainty of the diagnosis), favorable and poor prognostic groups could be delineated, with 1-year survival rates of 40% and 12%, respectively. Median survival from the date of study entry was 8.4 months.[80,81] The relevance of these earlier prognostic indicators is somewhat limited given that the study was performed in the pre-pemetrexed era. However, the prognostic significance of the EORTC index has subsequently been confirmed in a multivariate analysis of a phase III trial assessing cisplatin plus raltitrexed.

CURRENT APPROACHES TO THE TREATMENT OF PLEURAL MESOTHELIOMA

Over the past decade, advances have been made that have improved our ability to treat malignant pleural mesothelioma and, possibly, the quality and quantity of life for patients with mesothelioma. Multimodality treatment programs that combine surgical cytoreduction with novel forms of radiation therapy and more effective chemotherapy combinations may offer significant increases in survival for certain subgroups of mesothelioma patients. Innovative palliative approaches have proved successful in alleviation of the symptoms experienced by many mesothelioma patients. Experimental treatments such as immunotherapy and gene therapy present a window of hope for all mesothelioma patients, and in the future, may be combined with "standard therapy" in multimodality protocols.

Chemotherapy

Over the past 20 years, several phase II single-agent and combination chemotherapy studies have been performed in mesothelioma. These studies have demonstrated evidence of antitumor activity with anthracyclines, platinum derivatives, and antimetabolites. Combination chemotherapy has been associated with higher overall response rates but not, until recently, longer median survivals.[82]

The current standard of care for first-line chemotherapy in good performance status patients with unresectable mesothelioma is combination treatment with cisplatin and pemetrexed. Pemetrexed (Alimta®, Eli Lilly and Company, Indianapolis, IN) is an antifolate compound that targets multiple enzymes in the folate metabolism pathway. Pemetrexed is a potent inhibitor of thymidilate synthase, the rate-limiting step in the synthesis of thymidilate, which is required for DNA synthesis. Thymidilate synthase is also the enzyme inhibited by the cytotoxic agents, 5-fluorouracil and raltitrexed.

In 2003, Vogelzang et al. reported the results of a phase III randomized clinical trial in chemotherapy-naive mesothelioma patients comparing treatment with pemetrexed and cisplatin with cisplatin monotherapy. A total of 456 patients were randomized: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the combination pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the cisplatin-only arm ($p = 0.02$). The hazard ratio for death of patients in the combination arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months ($p = 0.001$). Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm ($p < 0.0001$). The addition of folic acid and vitamin B12 to chemotherapy resulted in reduction in the severity and frequency of hematologic and nonhematologic toxicities in the pemetrexed/cisplatin arm.[83] Another randomized phase III study of cisplatin with a newer-generation antifolate, raltitrexed showed similar increases in survival.[84] Pemetrexed plus carboplatin may be an alternative regimen if cisplatin toxicity is a particular concern, particularly in elderly patients or those with compromised renal function.[85]

The combination of gemcitabine and cisplatin or carboplatin is also a valid first-line option in the treatment of mesothelioma owing to its acceptable toxicity profile, good response rate, and palliative effects.

A Northern Italian phase II study of gemcitabine and carboplatin in patients with pleural mesothelioma reported a 26% partial response rate and a median response duration of 55 weeks. There were also significant palliative benefits, decreased dyspnea in 46% of patients, weight gain in 40%, and pain reduction in 26%. Median survival for patients in this study was 66 weeks.[86] The potential value of the gemcitabine plus cisplatin regimen was also demonstrated in a second multicenter phase II trial, in which 106 previously untreated patients were treated with gemcitabine plus cisplatin and randomly assigned to receive either bevacizumab or placebo. The median survival was approximately 15 months in both treatment arms, consistent with the results seen with cisplatin plus pemetrexed. The trial showed no benefit from the addition of bevacizumab to the regimen.[87] An ongoing randomized clinical trial in Europe is evaluating the benefit of bevacizumab in combination with standard front-line pemetrexed-based chemotherapy.

There is no current standard of care for second-line chemotherapy in mesothelioma following treatment with cisplatin and pemetrexed. The most commonly used second-line regimens include gemcitabine, or other drugs with single-agent activity such as vinorelbine. A large, double-blinded, randomized clinical trial of the HDAC inhibitor vorinostat in second-line therapy for mesothelioma showed no survival benefit for study drug over placebo.[88] There exists insufficient evidence to recommend second-line chemotherapy as a standard treatment. Patients with adequate performance status should be enrolled onto clinical trials of second-line experimental therapies.

Radiation Therapy

Contrary to the prevailing wisdom that malignant pleural mesothelioma is a radioresistant neoplasm, it has been demonstrated that mesothelioma cell lines are actually more responsive to ionizing radiation in vitro than non–small cell lung cancer cell lines. External beam radiation therapy for mesothelioma is, however, somewhat limited by the large treatment volumes required and the radiation sensitivity of the surrounding organs (heart, lung, esophagus, spinal cord). Although palliative radiotherapy with an attempt to treat the entire involved pleural surface is technically challenging, and associated with a high risk of radiation pneumonitis, myelitis, hepatitis, and myocarditis, it can provide effective local palliation in up to 50% of patients.[89]

There are anecdotal reports of long-term survivors following high-dose external beam irradiation, and even after intrapleural administration of radioactive isotopes. However, most studies have shown no significant effect upon overall survival in patients with mesothelioma.[90]

Radiation therapy may play a role by preventing chest wall recurrences after invasive procedures, and in improving local control after pleurectomy or extrapleural pneumonectomy (EPP).[4,90–92] Mesothelioma frequently implants along the tracts of biopsies, chest tubes, thoracoscopy trocars, and surgical incisions, producing uncomfortable subcutaneous nodules. This can be prevented with prophylactic radiotherapy. In a small randomized trial, Boutin et al. demonstrated that 21 Gy administered in three daily fractions, 10 to 15 days after thoracoscopy, decreased local recurrence from 40% to 0%.[93] These findings have been confirmed by other investigators as well.

Multimodality approaches commonly include adjuvant radiation following surgery, although there are no randomized trials that demonstrate its efficacy. Because the lung remains in place after pleurectomy, radiotherapy doses must be lower than when EPP is performed. The Radiation Oncology group at The University of Texas MD Anderson Cancer Center reported encouraging results using intensity-modulated radiotherapy (IMRT) following extrapleural pneumonectomy.[94,95] Employing careful treatment planning and IMRT, radiation doses of up to 50 to 60 Gy were possible without severe toxicity. With the combination of EPP and IMRT, local recurrences after surgery were virtually eliminated; however, novel distant disease patterns have begun to emerge. These data suggest that the combination of EPP and IMRT requires an additional treatment modality (i.e., chemotherapy or immunotherapy) to limit distant tumor growth. Although IMRT following EPP appeared to be more effective for local disease control in this initial series, a second series from the Dana-Farber Cancer Center suggested there was a significant increase in severe toxicity. In that report, 6 of 13 patients developed fatal pneumonitis in the contralateral lung.[96] More recent studies have demonstrated safety and efficacy of IMRT, either after EPP or in the adjuvant setting post–radical pleurectomy (RP) in the presence of an intact lung.[97–99] Novel forms of radiation therapy, including proton beam therapy, are currently under investigation for treatment of mesothelioma.[100,101]

Surgical Approaches

Although associated with substantial morbidity, surgical management of mesothelioma has made significant strides in palliating the major symptoms of the disease, as well as potentially offering some improvement in survival for highly selected patients. The increased use of VATS, in conjunction with novel biomarkers, has facilitated early diagnosis of mesothelioma in more patients, at which point they may be candidates for more aggressive attempts at "definitive" surgical treatment (along with neoadjuvant/adjuvant therapies). However, definitive surgical intervention is only possible in a small percentage of patients. Furthermore, fewer than 25% of those who undergo aggressive surgical intervention will be alive at 5 years, and even fewer will be disease free at that timepoint.[102] The vast majority of pleural mesothelioma patients have locally advanced disease at the time of presentation, which, along with advanced age and/or other comorbid medical illnesses, often precludes aggressive surgical intervention.

EPP is a radical surgical procedure involving complete removal of the ipsilateral lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm (Fig. 79-7 and Video 79-1). EPP achieves the greatest degree of cytoreduction, and, because the lung has been removed, allows higher radiation doses to be delivered to the ipsilateral hemithorax. It is the only debulking procedure possible when a thick tumor rind obliterates the pleural space. There is a small group of long-term survivors following EPP when it is a component of a multimodality treatment program, suggesting that this procedure may alter the natural history of the disease in appropriately selected patients with early-stage disease.[103] Unfortunately, the benefits of EPP with adjuvant chemotherapy +/– local radiotherapy are limited to otherwise healthy patients with early-stage disease, epithelial histology, and no mediastinal lymph node involvement. Patients with

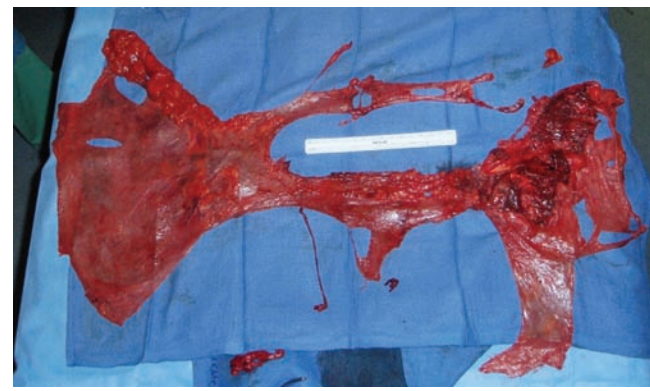


Figure 79-7 Gross photograph of a surgically resected pleurectomy/decortication specimen from a patient with malignant pleural mesothelioma. This involves the removal of the diseased pleura as an attempt to free the underlying lung to allow it to expand more freely. The steps involved are usually (1) incision and exposure of the parietal pleura, (2) dissection of parietal pleura from endothoracic fascia, diaphragm, and mediastinum, (3) incision of the parietal pleura and exposure of the visceral pleura, (4) decortication of the visceral pleura, and (5) reconstruction.

Video 79-1 Video recording from intraoperative thoracoscopic view of radical pleurectomy for malignant pleural mesothelioma performed through a thoracotomy incision. This surgical therapy for MPM is an alternative to extrapleural pneumonectomy. The procedure often takes up to several hours and involves extrapleural dissection, dissection of the diaphragm and pericardium, visceral pleurectomy, and lymph node dissection. *Access at www.fishmansonline.com*

biphasic or sarcomatoid histology and/or mediastinal or hilar node positivity have an ominous prognosis.[92,104]

EPP alone is an excellent means of palliating the profound dyspnea and orthopnea associated with the severe ventilation/perfusion mismatch resulting from lung encasement by mesothelioma. However, EPP alone has no influence on survival in the absence of adjuvant therapy.[105,106] In most EPP series, median survival from surgical debulking alone is less than 2 years, and 10% to 20% of patients are 5-year survivors. Biphasic/sarcomatoid histology and/or involvement of mediastinal lymph nodes confer a poorer prognosis and lack of demonstrable survival benefit from surgical intervention.

Several approaches for adjuvant therapy in conjunction with EPP have been studied. Investigators at Brigham and Women's Hospital have combined EPP with sequential postoperative chemotherapy and up to 55 Gy of adjuvant radiation therapy to the postoperative hemithorax.[107] More recently, the Brigham Thoracic Program has been investigating the role of hyperthermic intracavitary chemotherapy as an adjuvant to maximal cytoreductive surgery, in combination with hemithoracic irradiation and systemic chemotherapy.[108,109] In addition, several investigators have evaluated the utility of postresectional photodynamic therapy (PDT) with or without adjuvant chemotherapy or immunotherapy.[110] One randomized trial conducted by Pass et al.[111,112] at the National Cancer Institute failed to confirm any benefit for adjuvant PDT compared with surgery alone. Novel photosensitizers are currently under study that may provide better local control, decreased photosensitivity, and perhaps improved induction of systemic antitumor immune responses. Other novel multicenter clinical trials combine maximal surgical debulking with adjuvant IMRT or alternatively assess the role of neoadjuvant chemotherapy prior to cytoreductive surgery to improve long-term outcomes. EPP in these contexts is designed as a cytoreductive, not a curative procedure.[113–115]

Parietal pleurectomy, that is, open surgical stripping of the pleura from the apex of the lung to the diaphragm, is more successful than talc pleurodesis in reducing the recurrence of pleural effusion in mesothelioma. (Fig. 79-8) Thoracoscopic pleurectomy has been employed to achieve similar results as the open procedure, but with less morbidity.[91,116]

Complete parietal and visceral pleurectomy (pleurectomy/decortication or RP), has not been shown by itself to prolong survival in patients with mesothelioma.[117]

Investigators have evaluated the combination of pleurectomy/decortication with postoperative intrapleural radiation therapy, external beam irradiation, and/or systemic chemotherapy.[90,118–121] One single institution study reported a median survival of 22.5 months and a 2-year survival rate of 41% in a group of 27 patients, predominantly with the epithelial subtype.[118,120] There is some evidence in retrospective studies for better survival for mesothelioma patients who underwent pleurectomy/decortication compared with those treated with EPP despite a higher rate of local recurrence.[122,123]

RP is a recent modification of pleurectomy or pleurectomy decortication in which a maximal cytoreduction is achieved while leaving the ipsilateral lung intact. There have been several recent reports describing cytoreductive RP as the mainstay of multimodality treatment for both early-stage and locally advanced malignant pleural

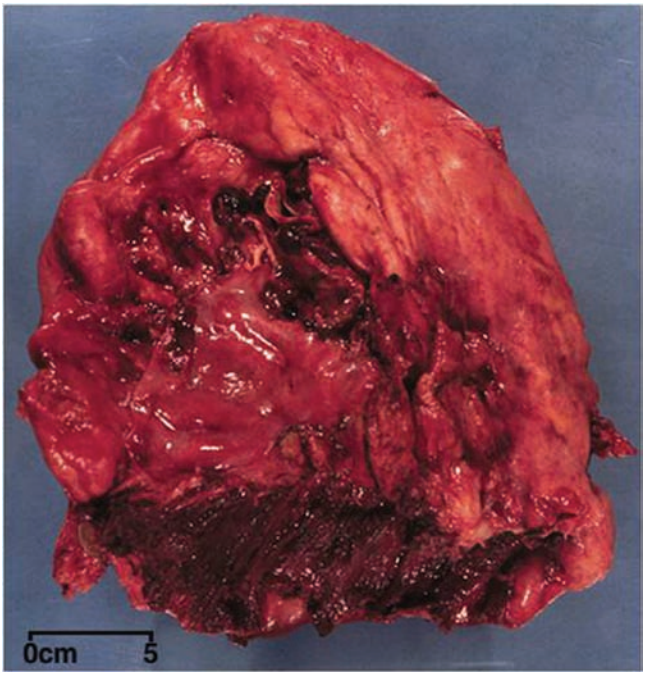


Figure 79-8 Gross photograph of a surgically resected extrapleural pneumonectomy specimen from a patient with malignant pleural mesothelioma. The specimen includes the completely removed lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm.

mesothelioma with various adjuvant intraoperative therapies such as intrapleural PDT,[124] intrapleural hyperthermic chemotherapy (cisplatin, gemcitabine),[125] and hyperthermic perfusion with povidone-iodine.[126] These have also been administered in association with IMRT in the presence of intact lung with demonstration of preserved/improved pulmonary function. In all cases, adjuvant chemotherapy was administered, unless patients had received preoperative chemotherapy (neoadjuvant).

Management of Pleural Effusions

The most common and discomforting symptom in mesothelioma is debilitating dyspnea from large, unilateral pleural effusions. A reasonable palliative approach is complete drainage of the pleural effusion (by tube thoracostomy or VATS) and instillation or insufflation of a sclerosing agent into the pleural space to induce pleurodesis. At present, the most widely used compound for pleurodesis is sterile, asbestos-free talc, administered either as a powder or slurry.[127,128] Thoracoscopic application (poudrage) may be more successful than other methods of pleurodesis (e.g., by tube thoracostomy). The effect of talc may be enhanced by an ability to induce apoptosis in some mesothelioma cell lines in vitro.[129] Interestingly, there have been reports of prolonged survival in mesothelioma patients after talc pleurodesis with no other active therapy for the disease.[130]

Entrapment of the lung by a thick visceral pleural peel of tumor compromises the efficacy of pleurodesis in patients with pleural mesothelioma. In the setting of trapped lung, the use of a semipermanent tunneled intrapleural catheter for intermittent drainage of recurrent effusions provides excellent palliation of dyspnea.[131,132] Pleuroperitoneal shunting, an alternative approach for dealing with lung entrapment in pleura mesothelioma, carries the overt risk of malignant seeding of the peritoneal cavity. The primary concerns regarding the use of tunneled pleural catheters in mesothelioma are the development of tumor implants at the insertion site or along the subcutaneous tunnel, as well as the risk of chest wall and/or intrapleural infections with long-term use of the catheter. Recent reports of tunneled catheters for mesothelioma

show equivalent results for the control of effusions compared with talc slurry pleurodesis.[133,134] Therefore, these catheters should be considered for management of symptomatic effusions in patients with mesothelioma, even in those whose lungs are able to expand.

Treatment of Nonpleural Forms of Mesothelioma

In patients with peritoneal mesothelioma, the second most common form of mesothelioma after the pleural form, most often present with abdominal pain, distention, and ascites. In addition, peritoneal mesothelioma can be associated with hypoalbuminemia, night sweats, inguinal and umbilical hernias, and hypercoagulability. Laboratory investigation shows an increased platelet count in about 50% of patients and many patients also have elevation of the tumor marker CA-125. As with pleural mesothelioma, single-agent chemotherapy for the peritoneal variant has a response rate of 10% to 15%, whereas combination chemotherapies, such as cisplatin plus pemetrexed, improve the response rate to about 25%. Immunotherapeutic agents such as interferons and various cytokines may have a role in treating this disease, especially when the extent of disease is minimal.[135–137]

Patients diagnosed with peritoneal mesothelioma appear to have a better overall prognosis relative to the pleural form. This may reflect the technical ease of delivery of intraperitoneal chemotherapy as well as the capacity for multiple resections/debulking of peritoneal masses. One-third of patients with peritoneal mesothelioma in a Dana-Farber phase II series of 25 patients remained disease free at 2 to 3 years after treatment.[136] Multimodality treatment protocol includes surgical debulking followed by intraperitoneal administration of cisplatin, doxorubicin, and interferon-gamma, second laparotomy with attempted resection of any residual disease and intraoperative hyperthermic perfusion with cisplatin and mitomycin followed subsequently by whole abdominal radiotherapy. In one study, the median overall survival of the 27 patients treated in this study was 68 months.[138]

Pericardial mesothelioma is quite rare, but characteristically presents with pericardial effusion and, often, tamponade physiology. Mesotheliomas of the tunica vaginalis are even less common than the pericardial variant, but typically present with a bloody hydrocele. There is no effective therapy for mesothelioma of the pericardium or tunica vaginalis other than palliation; these neoplasms share the dismal prognosis of the pleural form of the disease.

Novel and Evolving Therapeutic Approaches

Despite the small but significant improvement in survival achieved with intensive multimodality therapy for mesothelioma, it is obvious that less morbid, more effective interventions are needed. Many investigators, focusing on the hemithorax as the primary site of disease, have attempted to treat this disease primarily by direct instillation of chemotherapeutic and other compounds into the pleural space, but with minimal success. Based on anecdotal reports that mesothelioma patients with greater amounts of intratumoral lymphocytic infiltration had improved median survival rates, several groups have looked at immunotherapy as an alternative means of achieving better tumor response rates.

Immunotherapy The use of compounds to stimulate an antitumor immune response against pleural malignancy stemmed from the observation that patients who developed empyemas postthoracotomy for primary lung carcinoma had improved survival rates.[139,140] Subsequently, intrapleural bacille Calmette-Guérin (BCG) was studied as a surgical adjuvant, but no significant benefit was seen.[141] Several systemic immunotherapies have been administered to patients with mesothelioma, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ), both of which demonstrated limited efficacy and significant side effects. Subcutaneous IFN-α-2a was found to have some efficacy; one complete response and three partial responses were documented in one study of 25 patients and the therapy was well tolerated.[142] One European phase I/II study of intrapleural IL-2 administered by continuous infusion via an intrapleural catheter revealed a 19% partial response rate with marked dose-related toxicity, primarily the development of ipsilateral empyemas. Of note were the high ratios of intrapleural/systemic IL-2 levels approaching 1000:1, particularly in the highest doses.[143]

Boutin et al. in Marseilles, France pioneered the intrapleural administration of immunostimulants to treat mesothelioma, and demonstrated significant local tumor responses with both intrapleural IL-2 and IFN-γ. Most impressive were the results of intrapleural IFN-γ in patients with early-stage mesothelioma (Butchart stages I and II). A total of 89 patients were treated over 46 months with an overall response rate of 20%. Eight patients had histologically confirmed complete responses and nine had partial responses with greater than 50% reduction in tumor volume. Overall, patients with stage I disease had a response rate of 45%. The effectiveness of IFN-γ against mesothelioma was thought to be mediated in part by direct inhibitory effects on mesothelioma cell growth as well as by decreased intrapleural IL-6 production, with resultant activation of tumor-directed macrophages and cytotoxic T-lymphocytes.[144,145] Other groups have demonstrated only limited activity with the combination of intrapleurally administered autologous-activated macrophages and IFN-γ. The overall response rate was 11% in a trial of 19 patients, with one patient having a partial response that lasted for 30 months.[146]

Immunotherapy trials in Australia demonstrated tumor regression with repeated intralesional injection of granulocyte macrophage colony–stimulating factor (GM-CSF), but with substantial complications related to the catheters used for cytokine instillation.[147–149]

"Targeted" Therapy The presence of platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) pathways in some mesothelioma cell lines in vitro suggested that novel inhibitors of these pathways might prove useful clinically, either as monotherapy, or in combination with chemotherapy. Unfortunately, early-phase clinical trials in mesothelioma of imatinib mesylate and gefitinib (and erlotinib), inhibitors of the tyrosine kinases essential to PDGF and EGF signaling, respectively, failed to demonstrate any significant clinical benefits.[150–152] Clinical trials have been conducted with other novel targeted agents, such as the antiangiogenic agents, bevacizumab and thalidomide, and the copper-chelating agent, tetrathiomolybdate, which depletes copper, a key cofactor in tumor angiogenesis. Only the latter compound has demonstrated any demonstrable benefit to date in human trials.[153–155] Currently, there are several clinical trials of combinations of targeted agents to see if they may have synergistic effects upon growth of mesothelioma in patients with advanced disease.

Gene Therapy In the absence of other effective, nontoxic therapies for malignant mesothelioma, several groups of investigators have looked to the newly evolving technologies of gene therapy for new treatment modalities.[156] Gene therapy is attractive because mesothelioma remains localized initially and pleural access to the tumor is easy and safe. A large number of approaches have been used in cell culture and in animal models. Gene therapy vectors have included liposomal/DNA complexes and modified herpes, vaccinia, and adenoviruses. Transgenes have included suicide genes, cytokines, tumor suppressor genes (i.e., p53), and proapoptotic genes. Studies have also been done using replication-restricted, tumor selective adenoviruses and herpes viruses as well as carrier cells, such as modified ovarian carcinoma cells.[156,157]

Some phase I clinical trials have been performed. These include a "suicide" gene therapy strategy employing the instillation of recombinant adenovirus (rAd) genetically engineered to contain the herpes simplex virus thymidine kinase "suicide gene" (HSVtk).[158,159] The rationale for the suicide gene approach for mesothelioma was that

administration of rAd.HSVtk into the pleural cavity would sensitize the cells to the normally nontoxic antiviral agent ganciclovir. The vector was well tolerated, gene transfer was seen at higher doses, and a number of patients had clinical responses, including patients with minimal radiographic evidence of disease 7 years after treatment, with no other intervening antineoplastic therapy. The HSVtk gene was also introduced into patients using an irradiated allogeneic ovarian cancer cell line. No information on clinical responses has been reported. A few early phase trials have recently completed using adenoviral-mediated immunogene therapy delivering the cytokines interferon-alpha and beta (IFN-α, IFN-β), which have a number of antitumor immune effects. The vector was well tolerated (most common adverse events were lymphopenia, hypoalbuminemia, hypotension, anemia, hypocalcemia, and mild cytokine release syndrome), resulted in detectable intrapleural levels of the interferon proteins in most patients, and was accompanied by antitumor immune responses in multiple patients. A number of patients with low tumor burdens had disease stability or clinical responses.[160–162] Currently a phase I/II clinical trial testing first-line standard chemotherapy with intrapleural Ad-IFN-α is nearing completion.

Other gene therapy approaches have been studied by various groups attempting to achieve high-level expression of other immunostimulatory cytokines like IL-2, IL-12, tumor necrosis factor (TNF), and GM-CSF. In addition, there are ongoing phase I trials of intrapleural delivery of oncolytic viruses, including measles, herpes simplex, and vaccinia viruses, all of which have shown significant antitumor activity against mesothelioma in vitro and in preclinical models.[156]

Adoptive Cellular Therapy Adoptive transfer of T cells and other immune cells into patients after ex vivo expansion has demonstrated very promising results in diseases like malignant melanoma and leukemias. Groups have attempted to acquire tumor-reactive tumor-infiltrating lymphocytes (TILs) from mesothelioma samples, expanding them ex vivo, then reinfusing them back into the host with minimal success. Researchers at the University of Pennsylvania have successfully genetically modified T cells to express a chimeric antigen receptor (CAR) that recognizes the tumor antigen mesothelin through the variable chain of an antimesothelin antibody that activates the T cell through the internal signaling domains of the T cell receptor.[163,164] The mesothelin CAR T cells were able to eradicate large mesothelioma tumors in mice, and a phase I clinical trial has begun testing the feasibility and safety of multiple doses of CAR T cells reactive to mesothelin.

Other cellular therapies that are being investigated are injection of mesothelioma tumor lysate-pulsed dendritic cells and lymphokine-activated killer cells.[165,166]

SOLITARY FIBROUS TUMOR OF THE PLEURA

Solitary fibrous tumors of the pleura had been previously referred to in the literature as "benign mesothelioma." This is an inappropriate expression, both in terms of histogenesis and the potential for confusion with malignant mesothelioma. Solitary fibrous tumors have also been called localized fibrous tumor because of the occasional incidence of multiple masses. Solitary fibrous tumor is a mesenchymal tumor of probable fibroblastic origin and similar tumors have been described in other extrathoracic sites.[167] It is important to note that there is no significant association of solitary fibrous tumors with asbestos exposure or other environmental agents.[168,169] Although the peak age range of affected patients is similar to that of mesothelioma (40–70 years), solitary fibrous tumors can affect patients of all ages, including children as young as 5 years old.

CLINICAL PRESENTATION

Patients with solitary fibrous tumors of the pleura are usually asymptomatic and are diagnosed incidentally by routine chest radiography, but they can present with nonpleuritic chest pain, dyspnea, cough, or pleural effusion. A significant proportion (up to 40%) of patients present with symptomatic hypoglycemia, thought to be secondary to elaboration of insulin-like growth factors. Clubbing of fingers and toes is common, as are diffuse arthralgias, but the incidence of pulmonary hypertrophic osteoarthropathy is controversial.[168–171]

RADIOGRAPHY

Solitary fibrous tumors typically present radiographically as large, rounded, well-circumscribed pleura-based masses, but occasionally they can appear to be intraparenchymal. Some of these masses can be very large (over 30 cm in diameter) and can cause clinically significant compression of the lung. About 17% present with an ipsilateral pleural effusion.[169,172]

GROSS PATHOLOGY

The typical solitary fibrous tumor of the pleura arises from a pedicle off of the visceral pleura surface and rarely invades beyond the visceral pleura itself (Fig. 79-9A). The tumors are usually well-circumscribed, firm, often pedunculated masses that vary in size from 1 cm to more than 30 cm in diameter. When sectioned, the cut surface has a whorled appearance. Attention should be paid to areas of hemorrhage or necrosis. Malignant solitary fibrous tumors have been described, although they are less frequent.[167,173,174]

MICROSCOPIC PATHOLOGY

Histologically, solitary fibrous tumors have what has been described as a "patternless pattern" (Fig. 79-9B). Sections typically show alternating areas of hypocellularity and hypercellularity with short fascicles of interlacing spindle cells, creating a storiform pattern. These fascicles are interspersed between areas of variably collagenized tissue. A hemangiopericytoma-like branching vascular pattern is also quite typical. Histologic criteria that may predict a malignant course include high cellularity, infiltrative growth, moderate to marked cytologic atypia, and high mitotic rate (>4 mitoses per 10 high-power fields). Immunohistochemical stains confirm the diagnosis. These tumors are CD34 (Fig. 79-9C) and bcl-2 positive but CK negative. Malignant solitary fibrous tumors are not always positive for CD34 and bcl-2; therefore, the diagnosis requires the exclusion of other malignant tumors such as malignant mesothelioma, monophasic synovial sarcoma, and peripheral nerve sheath tumors.[173,174]

TREATMENT

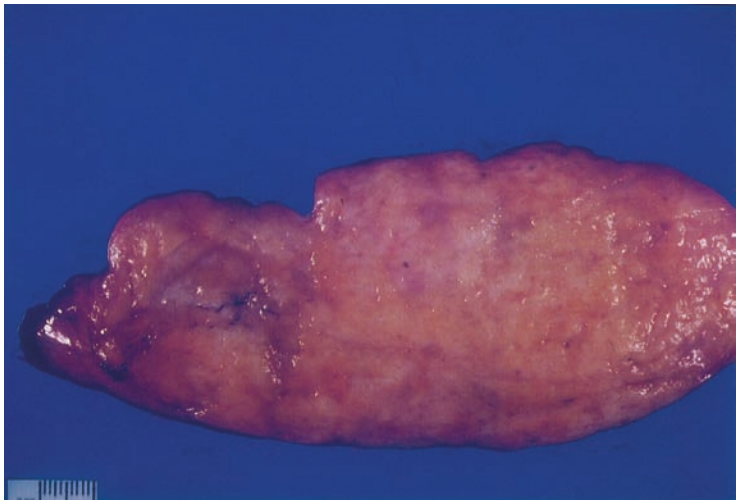
Surgical resection of solitary fibrous tumors of the pleura is curative with little risk of recurrence. There is typically a discrete separation between the tumor and underlying compressed lung, so extensive pulmonary resection is usually unnecessary. Some tumors may require a limited chest wall resection. A small percentage of patients develop recurrences several decades after surgical resection and may die from extensive local disease. Some of these recurrent fibrous tumors of the pleura demonstrate more aggressive histologic features but are often successfully cured by surgical excision, in particular the pedunculated lesions.[169–171]

Even with malignant solitary fibrous tumors of the pleura, complete resection portends a favorable prognosis in most patients. In one series, complete resection was achieved in over 90% of patients with disease-free survival rates of 72% and 61% at 5 and 10 years, respectively.[171]

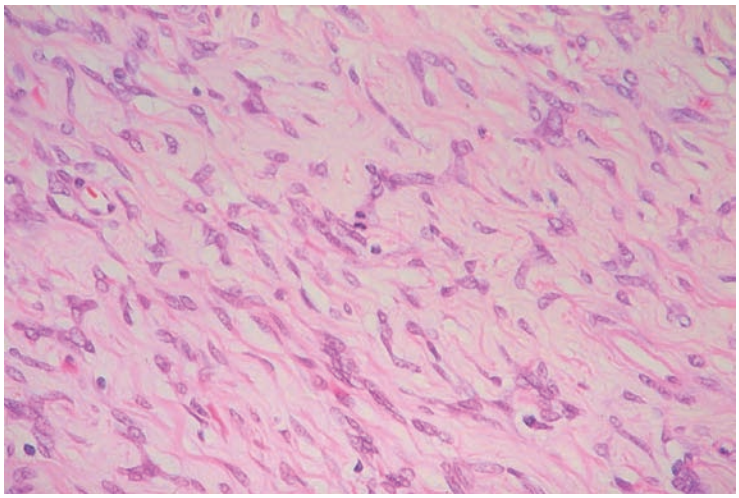
OTHER PRIMARY PLEURAL TUMORS

As discussed in the differential diagnosis of sarcomatoid mesotheliomas, there are other relatively rare malignant mesenchymal tumors that can be primary within the pleura. These tumors include vascular tumors (pleural epithelioid hemangioendothelioma/angiosarcoma) and synovial sarcoma.

Pleural epithelioid hemangioendothelioma is a low- to intermediate-grade vascular tumor. High-grade epithelioid vascular tumors



A



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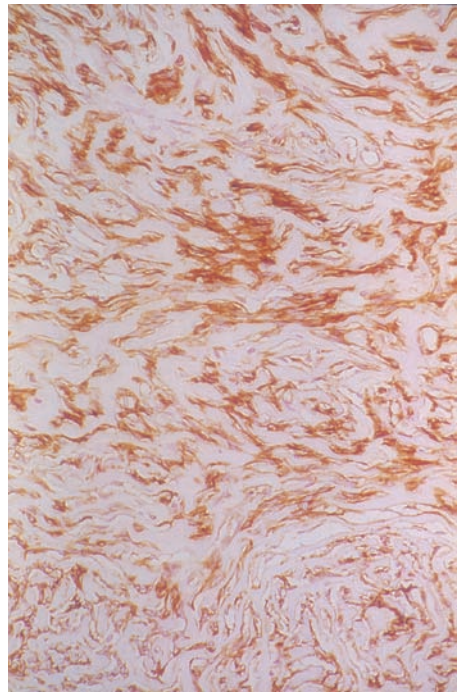

C

Figure 79-9 **A.** Gross photograph of a surgically resected, solitary, benign pleural fibrous tumor. Note the well-circumscribed nature of this firm, slightly lobulated mass with its smooth-cut surface and punctate areas of hemorrhage and necrosis. **B.** Photomicrograph of a typical solitary fibrous tumor demonstrating the "patternless-pattern" (H&E, ×400). **C.** Photomicrograph of a section of solitary fibrous tumor stained with an antibody directed against CD34, a cell surface marker found commonly on endothelial cells and some smooth muscle and vascular tumors (×400). Positive staining for CD34 helps distinguish these lesions from mesotheliomas and other pleural neoplasms. *(Used with permission of Dr. Matt van de Rijn, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.)*

are termed epithelioid angiosarcoma. The clinical presentation of patients with these tumors, as well as the radiographic features and gross appearance, are essentially identical to malignant mesothelioma. Patients present with diffuse pleural thickening, pleural effusion, and/or chest pain. Microscopic examination with the ancillary use of IHC is required for diagnosis. These tumors usually have a biphasic pattern with nests of epithelioid cells embedded within a spindle cell stroma. The epithelioid cells characteristically have intracytoplasmic vacuoles and the associated stroma typically has a distinctive myxohyaline or chondroid appearance. As with malignant mesotheliomas, a tubopapillary pattern may also be present. Vascular differentiation is demonstrated by strong positive staining with one or more endothelial markers (CD31, CD34, Fli1, or factor VIII). CK positivity may also be present and can be misleading if the diagnosis of a vascular tumor is not considered. These tumors behave aggressively and there is, at the current time, no effective therapy.[175–178]

The diagnosis of pleural synovial sarcoma has improved with increased awareness and the greater availability of molecular testing for its distinctive X:18 translocation that now can be demonstrated in formalin-fixed paraffin-embedded tissue. Synovial sarcomas present as either a biphasic epithelioid and spindled cell tumor or as a monophasic spindle cell tumor. In either instance, synovial sarcoma can be mistaken for malignant mesothelioma or a pulmonary sarcomatoid carcinoma. On average, patients tend to be younger than those with malignant mesothelioma but there is a wide reported age range that encompasses older patients into their eighth decade. There is a similar overlap in clinical presentation with malignant mesothelioma that includes chest pain, pleural effusions, dyspnea, and pneumothorax. Although pleural synovial sarcoma is more commonly a localized, solid tumor, diffuse pleural thickening does occur. The tumors can be quite large (mean size of 13 cm) and can have areas of necrosis and cystic degeneration. There are some histologic features that are suggestive of synovial sarcoma, in particular its long interweaving fascicles, but the immunohistochemical profile of these tumors is not distinctive. The epithelioid component may show focal positive staining for CK, EMA, CEA, or BER-EP4. The spindled cell component may express calretinin. Confirmation of the diagnosis requires molecular testing for the X:18 translocation. Pleural synovial sarcoma is an aggressive disease with a generally poor prognosis.[179–184]

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CHAPTER 80

Nonneoplastic Disorders of the Mediastinum

Cameron D. Wright

ANATOMY

The boundaries defining the mediastinum, as well as its subdivisions or compartments, and important anatomical considerations regarding mediastinal lymphatics are discussed below.

BOUNDARIES

The mediastinum is defined as the potential space between the two pleural cavities bounded by the sternum anteriorly, the vertebral column posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly (Fig. 80-1).[1] The major mediastinal structures are the heart and great vessels, the trachea and main bronchi, and the esophagus, all closely related to one another and connected by loose connective tissue. Also present are the thymus, lymph nodes, and fat. Hence, air or infection can disseminate widely throughout the mediastinal space, contained laterally only by the mediastinal pleural reflections. The mediastinum communicates with both the neck and the retroperitoneum, and these portals can also serve as routes of egress from the mediastinum. Fascial planes connect the neck, mediastinum, and retroperitoneum and thus facilitate movement of air or infection from one location to another.

COMPARTMENTS

Several subdivisions of the mediastinum have been emphasized in the surgical and radiologic literature but there is no consensus. Most often, three compartments are proposed: anterior, middle (visceral), and posterior (paravertebral sulcus) (Fig. 80-2).[2] The boundaries of these divisions are not agreed upon, further emphasizing their nonanatomic origins. Shields proposed a simple three-compartment subdivision in 1972 that makes both anatomic and surgical sense. The anterior compartment is bounded by the sternum and the anterior surface of the pericardium and great vessels. The middle (visceral) compartment extends from the posterior limit of the anterior compartment to the anterior surface of the vertebral columns and then to the thoracic inlet. The posterior compartment (paravertebral sulcus) extends from the anterior surface of the vertebral column to the anterior surface of the paravertebral ribs. The structures in these compartments are listed in (Table 80-1). The pericardial sac is the only true compartment of the mediastinum and it provides a strong barrier to infection. Subdividing the mediastinum into compartments proves most helpful when one is interpreting a plain radiograph that shows a mediastinal mass. Knowledge of the contents of the involved compartment facilitates arriving at a proper diagnosis.

LYMPHATICS

The mediastinal lymphatic system is quite complex and variable. Mediastinal lymph nodes are interconnected; thus, involvement of one group of lymph nodes in a pathologic process frequently leads to involvement of other groups. Similar to subdividing the mediastinum into compartments, naming individual nodal stations is somewhat arbitrary and leads to the mistaken notion that these nodal stations are discrete. To the contrary, the mediastinum is covered in a dense network of lymphatic vessels and

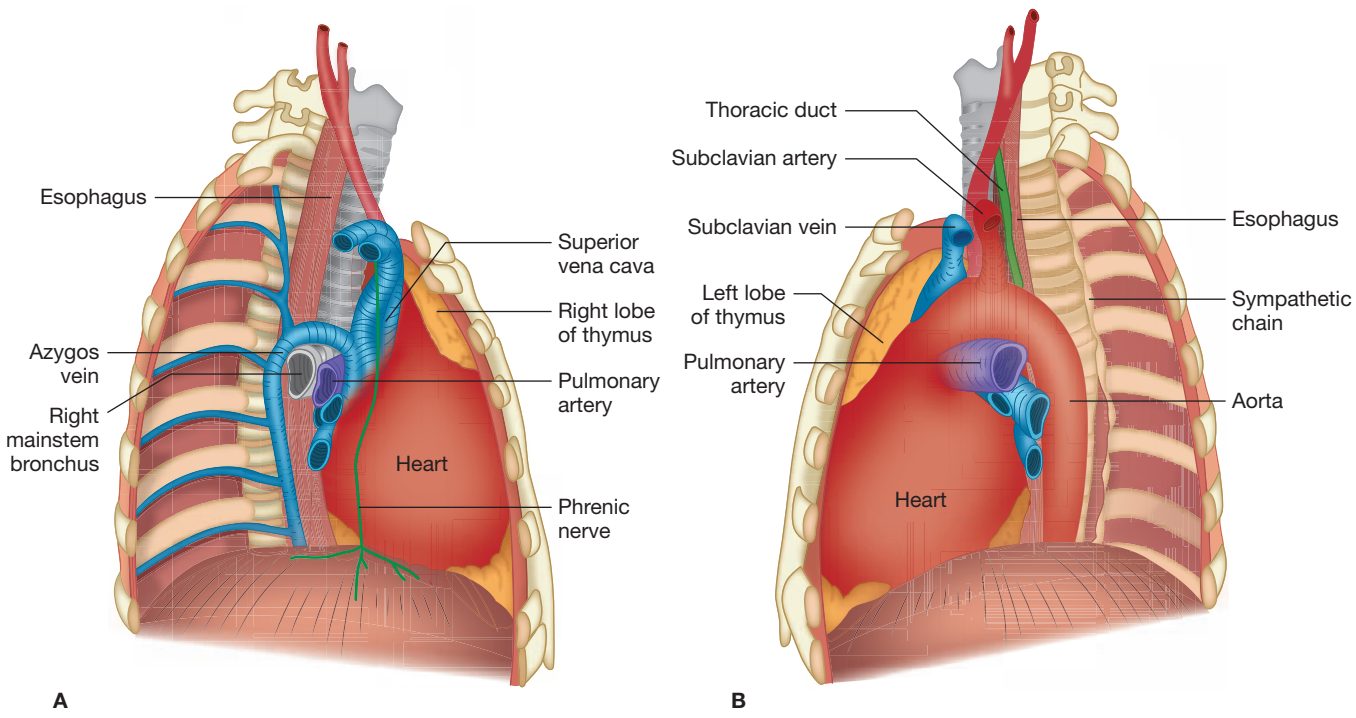


Figure 80-1 **A.** Lateral view of the mediastinum as seen through a right thoracotomy. **B.** Lateral view of the mediastinum as seen through a left thoracotomy. *(Reproduced with permission from LoCicero J. Median sternotomy and thoracotomy. In: Shields TW, ed. Mediastinal Surgery. Philadelphia, PA. Lea & Febiger; 1991.)*

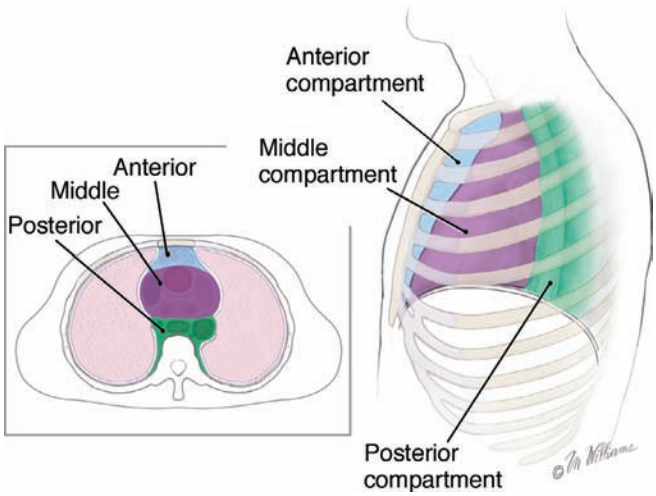


Figure 80-2 Mediastinal tumors are divided for the convenience of diagnosis and surgical approach into three compartments: anterior, middle, and posterior. *(Used with permission of Marcia Williams.)*

lymph nodes with no predictable boundaries. Nonetheless, there are commonly accepted nodal stations that have clinical importance, especially in the staging of lung cancer. The lymph node map proposed by Naruke in 1978 has been widely accepted and serves as a standard for communication of lymph node involvement (Fig. 80-3).[3]

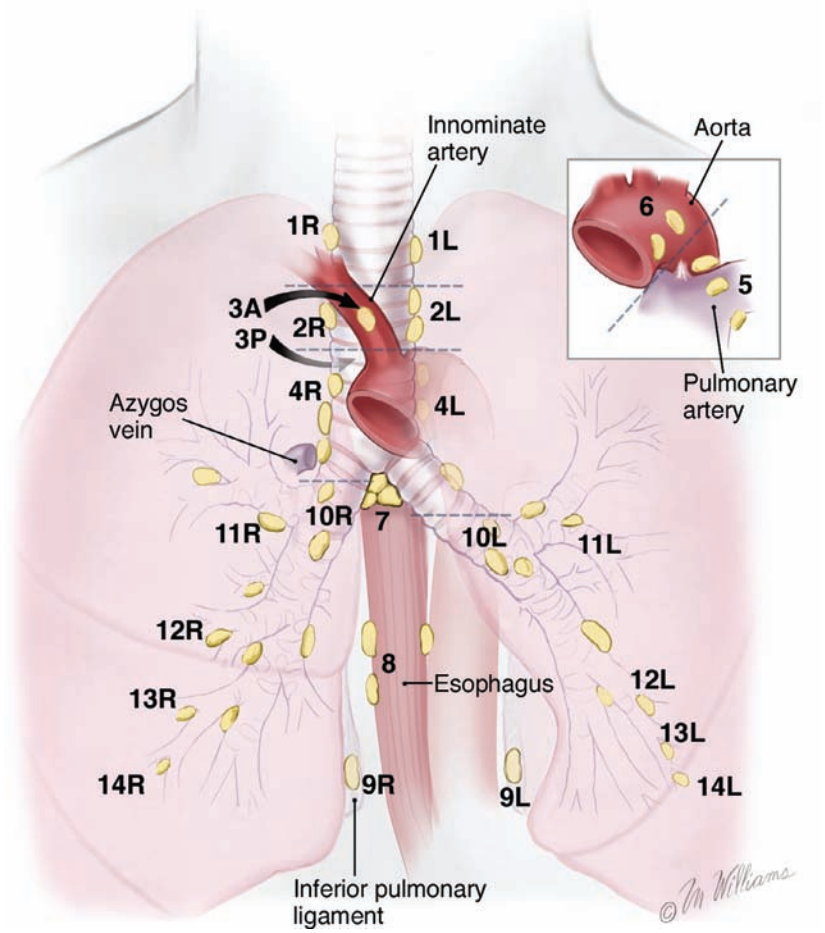


Figure 80-3 Lung cancer lymph node stations map. Note that any double-digit numeral is considered N_1 disease. L = left; R = right; A = anterior; P = posterior. *(Used with permission of Marcia Williams.)*

TABLE 80-1 Contents of Mediastinal Compartments

Anterior	Middle	Posterior
Thymus gland	Pericardium	Azygos and hemiazygos veins
Pericardial fat	Heart	
Lymph nodes	Trachea and main bronchus	Thoracic duct
	Esophagus	Sympathetic trunk
	Aorta	
	Phrenic and vagus nerves	Intercostal nerves
	Lymph nodes	

PNEUMOMEDIASTINUM

Pneumomediastinum (mediastinal emphysema) is an uncommon condition characterized by the accumulation of air or gas in the mediastinum. Depending on the cause, management may be expectant or may involve specific treatment directed at the underlying abnormality.

ANATOMIC CONSIDERATIONS

Pneumomediastinum is frequently associated with other forms of extra-alveolar air, including pulmonary interstitial emphysema, pneumopericardium, pneumothorax, subcutaneous emphysema, pneumoretroperitoneum, and pneumoperitoneum. The key to understanding the distribution of extra-alveolar air lies in the recognition of the common fascial planes that unite these areas. In the neck, the deep layer of the deep cervical fascia ensheaths the trachea and esophagus as they descend into the mediastinum. The trachea and esophagus are thus enclosed in this visceral space; therefore, air or infection can readily travel from the mediastinum to the neck or retroperitoneum (Fig. 80-4).[4] This fascial plane extends into the hilum of the lung and merges with the bronchovascular sheaths that surround the terminal bronchioles, arteries, and veins. The bronchovascular sheath also merges with and is continuous with the pericardium. After alveolar rupture, air enters the perivascular interstitium and dissects proximally within the bronchovascular sheath toward the mediastinum (Fig. 80-5). Air can then enter the pericardial space, resulting in pneumopericardium, or it may dissect along the adventitia of the great vessels (Fig. 80-6). More commonly, mediastinal air can decompress by extension into the cervical, subcutaneous, and retroperitoneal spaces. A pneumomediastinum that ruptures into the free pleural space results in a pneumothorax. Pneumothorax may also result from air dissecting out toward the visceral pleural surface of the lung and rupturing. Macklin, in 1944, in an elegant experimental cat model, confirmed this theory of progression of extra-alveolar air following alveolar rupture.[5] Pneumomediastinum usually results from a ruptured alveolus due to a Valsalva maneuver or mechanical ventilation. There are many other

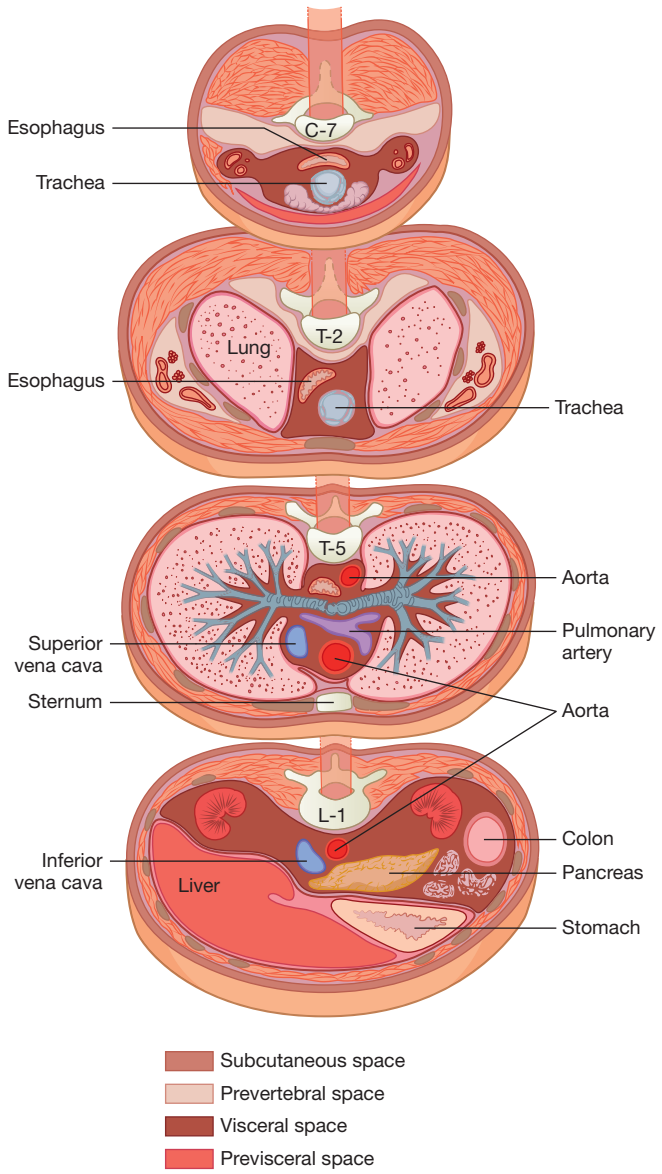


Figure 80-4 Soft tissue compartments of the neck, thorax, and abdomen demonstrating continuity of visceral space between regions. *(Reproduced with permission from Maunder RJ, Pierson DJ, Hudson LD. Subcutaneous and mediastinal emphysema: pathophysiology, diagnosis, and management. Arch Intern Med. 1984;144(7):1447–1453.)*

possible sources, however, that must be considered when the physician has to manage a patient with pneumomediastinum (Table 80-2). Dental procedures, especially those on the mandible with the addition of compressed air to maintain a clear field, are an occasional cause of mediastinal emphysema.

■ SPONTANEOUS PNEUMOMEDIASTINUM

Idiopathic spontaneous pneumomediastinum is a rare self-limited condition that most commonly affects young adult men. Hamman[6] is credited with the original description of this entity in 1939, including the characteristic crepitation synchronous with the heartbeat heard in these patients (Hamman sign). The majority of patients with spontaneous pneumomediastinum have predisposing factors that cause increase in airway pressure, which leads to alveolar rupture.[7,8] Most commonly, this results from straining against a closed glottis (i.e., the Valsalva maneuver) as during vomiting, coughing, or exercising. Other mechanisms include

TABLE 80-2 Etiology of Pneumomediastinum

Upper respiratory tract
Head and neck infection
Fracture of facial bones
Trauma to hypopharynx and larynx (especially intubation)
Dental procedures (especially mandibular)
Lower respiratory tract
Trauma
Bronchoscopy, especially therapeutic bronchoscopy (i.e., YAG laser, rigid core-out, dilation, and transbronchial biopsy)
Lung
Trauma
Surgery
Spontaneous alveolar rupture
Straining and Valsalva maneuver
Local airway obstruction
Scuba diving
Mechanical ventilation
Gastrointestinal tract
Esophageal perforation
Perforated viscus
Infection
Acute mediastinitis
Descending necrotizing mediastinitis
Air from outside the body
Trauma
Surgery (especially mediastinoscopy, tracheostomy, and sternotomy)
Pneumoperitoneum (especially with laparoscopic hiatus hernia repair)

sudden and/or severe increases in lung volume, as occur during marijuana smoking, inhaling of cocaine, or during a seizure. Localized airway obstruction from tumor, foreign bodies, asthma, or parenchymal lung disease can also cause alveolar rupture. An accurate history is most important to define the mechanism in a particular patient.

Spontaneous pneumomediastinum almost always presents with substernal pain, often pleuritic, which may radiate to the neck or back. Additional symptoms that may occur, either separately or in combination, include dyspnea, dysphagia, odynophagia, and dysphonia. Air in the subcutaneous tissues of the neck produces a characteristic change in voice quality, a higher-pitched nasal tone that the experienced clinician easily recognizes. Examination often reveals palpable subcutaneous emphysema in the neck. Auscultation of the chest may reveal a crunching or clicking sound heard over the pericardium, synchronous with the heartbeat (Hamman sign). Low-grade fever is present in about one-third of cases and mild leukocytosis in about one-half. Nonspecific electrocardiographic changes, such as ST-T wave changes and ST elevation, may also be present. A chest radiograph usually demonstrates a thin radiolucent strip along a mediastinal fascial plane, most commonly along the left heart border. The aortic knob may be highlighted as well (see Fig. 80-6). Computed tomography (CT) is more sensitive in detecting air than are plain radiographs (Fig. 80-7). Air may be evident deep in the neck as well as in the subcutaneous tissue.

The differential diagnosis is broad and includes musculoskeletal, pleural, pulmonary, cardiac, and esophageal causes. Although most

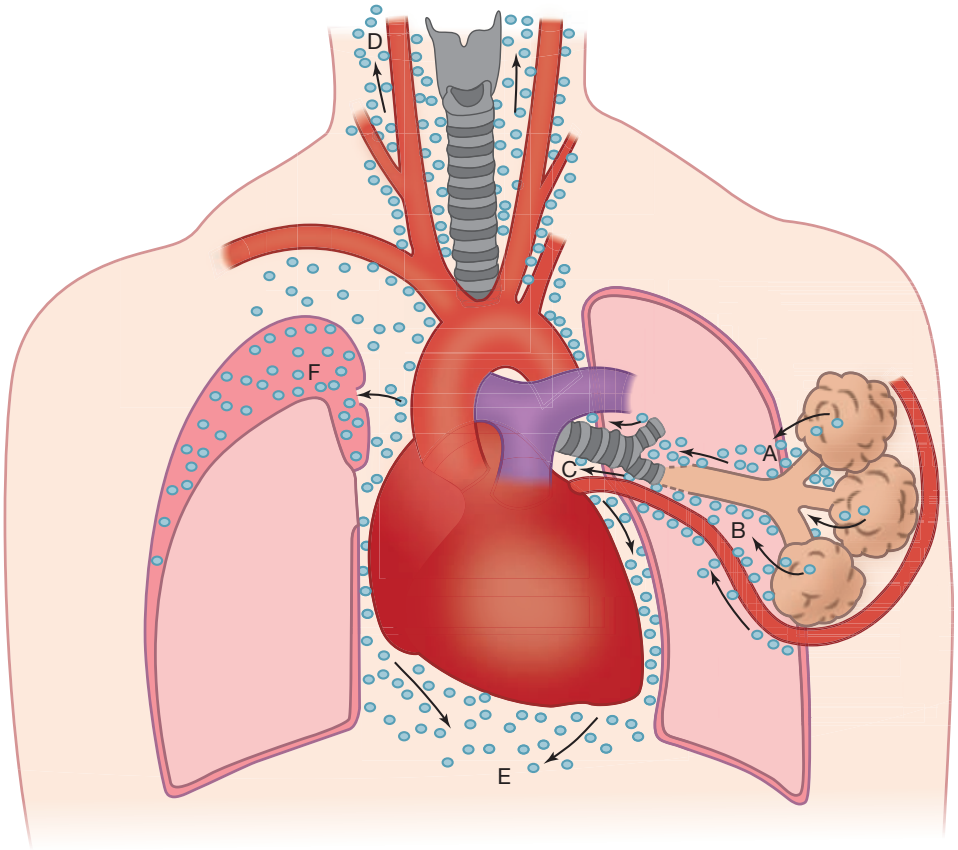


Figure 80-5 Possible routes of air following alveolar disruption. Air from the alveolus (**A**), enters perivascular interstitium (**B**), dissecting proximally within bronchovascular sheath toward mediastinum (**C**), as mediastinal pressure rises, decompression occurs in cervical (**D**), subcutaneous, and retroperitoneal (**E**), soft tissue spaces. A pneumothorax is possible if the pleura (**F**) is ruptured. *(Reproduced with permission from Cooley JC, Gillespie JB. Mediastinal emphysema: pathogenesis and management. Report of a case. Dis Chest. 1966;49(1):104–108.)*

patients who present are not acutely ill, an occasional patient may suffer an acute, catastrophic onset with hypotension and hemodynamic compromise. Esophageal perforation is the condition most likely to be confused with spontaneous mediastinal emphysema. Worrisome features suggestive of esophageal perforation include recent esophageal instrumentation, a history of esophageal problems, severe retching, the presence of a pleural effusion, or shock. A contrast esophagogram should be obtained immediately if there is any question of an esophageal perforation, since a delay in making this diagnosis often proves fatal. A high index of suspicion regarding esophageal perforation should always be present whenever a patient presents with mediastinal emphysema.

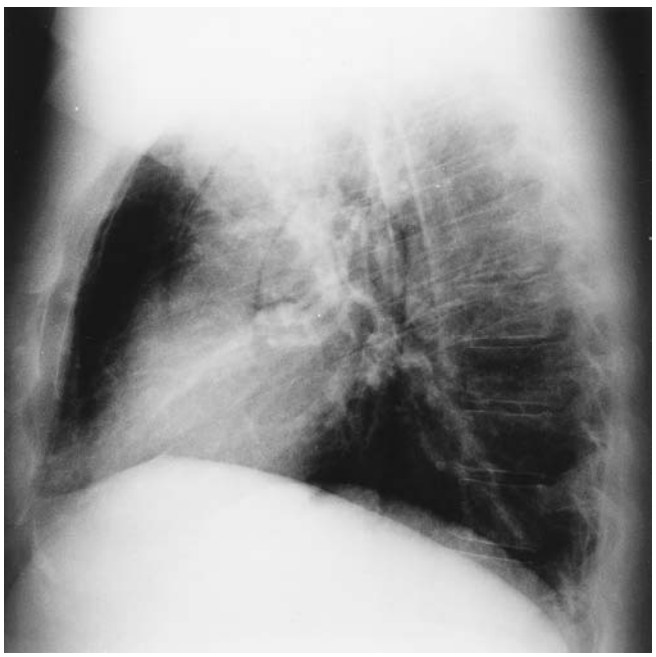


Figure 80-6 Lateral radiograph of a middle-aged patient with an acute asthma attack causing pneumomediastinum requiring hospital admission. Mediastinal air is seen outlining the aorta and esophagus. This resolved spontaneously.

Treatment of spontaneous mediastinal emphysema is supportive and is primarily directed at pain relief and reassurance. Appropriate management of contributing causes such as foreign bodies, asthma, and parenchymal lung disorders should be instituted. The patient should be followed both clinically and radiographically to exclude another cause for mediastinal emphysema and detect a possible pneumothorax. Prompt resolution is the rule. Supplemental oxygen to hasten reabsorption (similar to that proposed for pneumothorax) has been reported but is probably not necessary. Needle aspiration or skin incision to relieve subcutaneous emphysema is almost never necessary. Prophylactic tube thoracostomy is unnecessary. For patients who present with minimal findings and a clear inciting factor (such as coughing), only a short period of observation in the emergency department is required. Most patients require admission for a short period of pain control and observation. Recurrence is rare.

A recent large case series reinforces these principles. Macia et al.[8] reported on 41 patients over a 16-year period. The incidence of spontaneous pneumomediastinum was 22 cases per 1,000,000 emergency department visits. The mean age was 21 and 83% were men. Asthma and illicit drug use were the most common predisposing factors and exercise, vomiting, and coughing were the most common precipitating factors. Common symptoms included chest pain (85%), dyspnea (49%), neck pain (44%), odynophagia (37%), cough (24%), and dysphonia (12%). Common signs included subcutaneous emphysema of the neck (66%) and chest (29%) and Hamman sign (12%). All chest radiographs demonstrated pneumomediastinum and 66% revealed subcutaneous air in the neck. An elevated WBC was seen in 42% of patients. The mean length of stay was 5 days and all were treated with just supportive care.

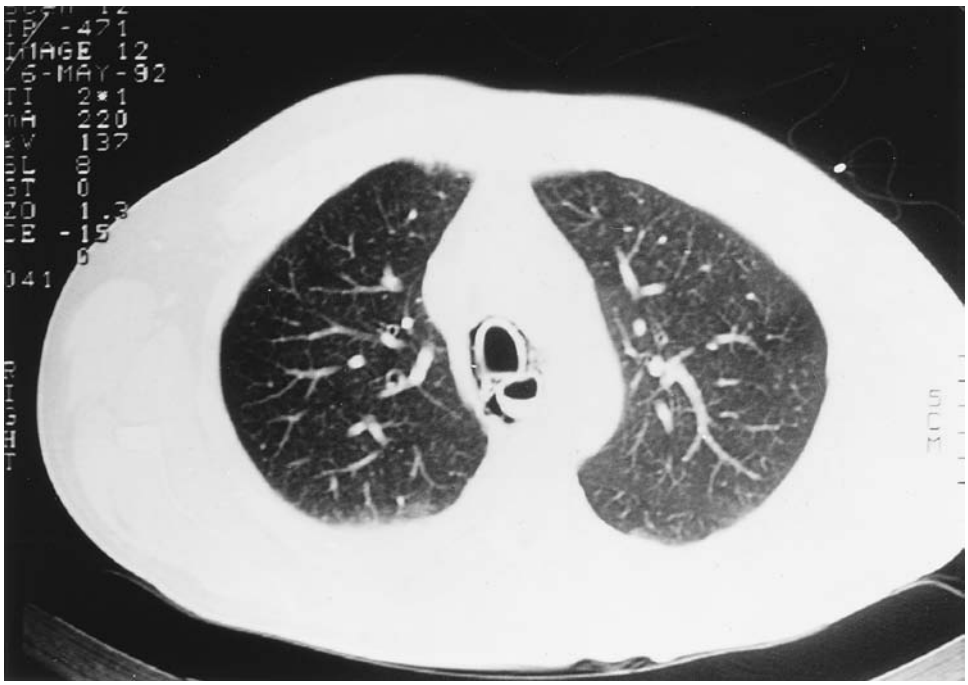


Figure 80-7 Computed tomography of a man with an 8-hour-old postemetic esophageal rupture. Posteroanterior radiograph was normal. Mediastinal air is seen outlining trachea and esophagus.

■ PNEUMOMEDIASTINUM ASSOCIATED WITH MECHANICAL VENTILATION

Mechanical ventilation is commonly associated with pneumomediastinum and may often lead to life-threatening tension pneumothorax. Alveolar rupture results from high peak inspiratory pressures, which increases alveolar pressures in patients with abnormal airways or parenchyma (decreased compliance). Classic predisposing factors include high tidal volumes, high levels of positive end-expiratory pressure (PEEP), and "fighting" the ventilator. Air trapping with occult positive end-expiratory pressure (auto-PEEP) is an underrecognized cause of barotrauma. It is not clear if one mode of ventilation (pressure-controlled vs. volume-limited) is associated with a decreased incidence of barotrauma.

Unlike spontaneous mediastinal emphysema, pneumomediastinum occurring in a patient on mechanical ventilation is potentially catastrophic because of its frequent association with tension pneumothorax. The chest radiograph should be closely examined to detect even a small pneumothorax and, if such is present, tube thoracostomy should be promptly performed. Obviously, a sudden deterioration marked by hypotension and increased pulmonary pressures should prompt immediate attention with insertion of unilateral or bilateral chest tubes, depending on the clinical examination. The issue of inserting a tube prophylactically is controversial if pneumomediastinum without pneumothorax is identified. At a minimum, a thoracostomy tray should be kept at the patient's bedside and the nursing staff reminded of the signs of a pneumothorax in a mechanically ventilated patient. If a physician is not readily available around the clock, it may be advisable to perform bilateral prophylactic tube thoracostomy in certain patients. Removing the patient from mechanical ventilation as soon as possible is appropriate. Since this is seldom possible, efforts should be directed at minimizing alveolar distention. These efforts include relief of bronchospasm, minimizing "fighting" the ventilator, reducing tidal volume and PEEP, and manipulation of inspiratory flow and timing to reduce auto-PEEP.

■ PNEUMOPERICARDIUM

Pneumopericardium as a form of barotrauma is much more frequent in neonates, presumably due to immature fascial planes. Hemodynamically significant tamponade is also much more likely to occur in infants rather than adults and has resulted in collapse and death. Pericardial drainage with a subxyphoid tube should be performed promptly in the neonate. In the adult, drainage should be performed only if there is hemodynamic embarrassment.

ACUTE MEDIASTINITIS

Acute mediastinitis is a life-threatening disorder that causes severe morbidity in the afflicted patient. All three mediastinal compartments can be affected; the anterior compartment most commonly after sternotomy for cardiac surgery, the middle compartment usually from esophageal perforation, and the posterior compartment from direct extension from the neck, lung, or spine. Instrumental perforation of the esophagus is the most common cause of acute mediastinitis in the United States.

■ MEDIASTINITIS FROM ESOPHAGEAL PERFORATION

Instrumental perforation of the esophagus now accounts for almost one-half of all esophageal perforations.[9] Perforation is more common after rigid esophagoscopy, dilation of a stricture, and pneumatic dilation for achalasia, but it also occurs after variceal sclerosis, esophageal tube placement (nasogastric, Sengstaken–Blakemore, and salivary bypass tubes), and simple flexible esophagoscopy. Boerhaave syndrome (postemetic rupture) was described in 1724 but still represents a diagnostic challenge and remains a major consideration in patients with otherwise unexplained mediastinitis (Fig. 80-8). Patients usually present with the abrupt onset of severe substernal chest pain, which is pleuritic after forceful vomiting or retching. Dyspnea is common even in the absence of pneumothorax. Shock develops quickly and the patient usually appears gravely ill. Examination reveals tachypnea, tachycardia, fever, hypotension, splinting of the chest and abdomen, and cervical emphysema. Radiographic findings include cervical or mediastinal emphysema, pneumothorax, and pleural effusion. A contrast esophagogram (usually with water-soluble contrast) should be performed immediately when the diagnosis is suspected, but one should be aware that this study has a false-negative rate of 10%. A chest CT scan is the next best study in a patient in whom esophageal perforation is suspected but who has a negative esophagogram. Prompt diagnosis and, therefore, a high index of suspicion are essential, as the frequency of

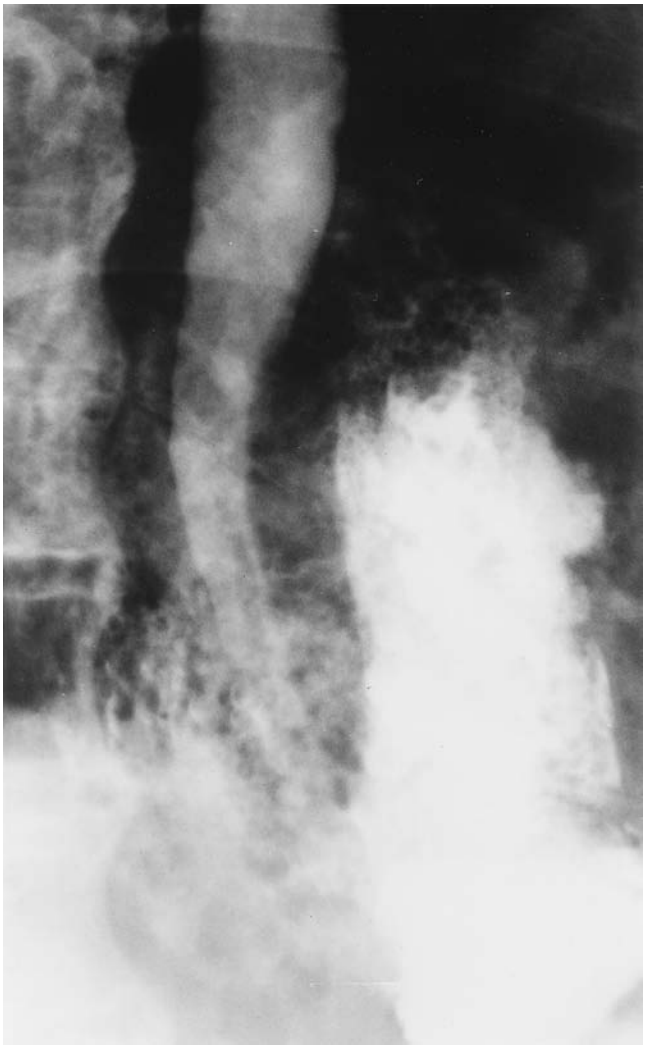


Figure 80-8 Water-contrast esophagogram of a patient with Boerhaave syndrome. Note extensive extravasation of contrast and mediastinal emphysema.

complications and the mortality rate are directly dependent on the time elapsed between perforation and treatment. The differential diagnosis is broad and includes perforated ulcer, acute pancreatitis, myocardial infarction, pneumonia, aortic dissection, and pulmonary embolism.

Treatment should be instituted urgently and involves surgical debridement of necrotic tissue, secure closure of the perforation, correction of any distal obstruction, and wide drainage, usually performed through a left thoracotomy.[10] Recent reports suggest favorable results in appropriately selected patients' management with covered esophageal stents and image-directed drainage.[11] Appropriate broad-spectrum antibiotics with anaerobic coverage and the maintenance of proper nutrition are also integral components of the management plan. Esophagectomy is occasionally required in the presence of a perforated, nondilatable stricture, a destroyed esophagus in which direct repair is not possible, or cancer. Nonoperative treatment is rarely appropriate but may be instituted in highly selected cases (i.e., contained, asymptomatic instrumental perforations) in which a significant interval has passed and the patient is clinically stable. Mortality is less than 10% if the perforation is recognized and repaired within 24 hours, whereas mortality increases to 30% to 40% if more than 24 hours have elapsed between perforation and repair. The mortality rises even higher with advanced age of the patient.

TRACHEOBRONCHIAL PERFORATION

Tracheobronchial perforation is rare and is most commonly seen following trauma or instrumentation. Less common causes include anastomotic dehiscence after lung transplantation or airway surgery and necrotizing infections involving the airway. Severe mediastinitis is rare after tracheobronchial disruption, presumably due to the less noxious nature of its contents and better containment. Intubation is now the most frequent cause of tracheobronchial injury, but injury can be avoidable with gentle and proper technique. Blood in the airway, airway obstruction (infrequent), subcutaneous and mediastinal emphysema, and pneumothorax are the common presenting signs. Prompt recognition and operative repair are necessary and yield excellent results, although small tears in the cervical trachea may often be managed with antibiotics alone, without operation.

DESCENDING NECROTIZING MEDIASTINITIS

Mediastinitis occasionally develops after severe deep head and neck infections that originate from the oropharynx or hypopharynx.[12–18] Most patients present with a mixed aerobic and anaerobic infection. Previously these infections had a fulminant, often lethal course with mortality as high as 40%. Extension of the cervical infection down the layers of the deep cervical fascia into the mediastinum leads to this syndrome of descending necrotizing mediastinitis. Downward spread is aided by gravity, negative intrapleural pressure, and lytic dissolution of fascia and fat. The deep cervical fascia consists of three layers: the superficial (buccopharyngeal) layer, the middle (visceral) layer, and the deep layer that is further subdivided into the alar and prevertebral layers. All layers originate from the base of the skull. The superficial layer terminates at the superior chest. The visceral layer terminates as a continuation of the pericardium. The potential space between the superficial and middle layers, called the retropharyngeal space, allows infection to descend to the middle of the chest. The alar layer terminates at the diaphragm. The potential space between the middle and the alar layer confines infection above the diaphragm. Rare infections between the alar and prevertebral layers may allow the spread of infection below the diaphragm. Endo et al.[15] classified descending necrotizing mediastinitis according to the extent of the infection to guide the surgical management according to this classification: Type 1, infection above the carina, Type IIA, infection to the level of the lower anterior mediastinum, and Type IIB, infection involving the lower anterior and posterior mediastinum.

The criteria for diagnosing descending necrotizing mediastinitis were established by Wheatley et al.[14] in 1990 and include (1) severe head and/or neck infection, (2) radiographic evidence of mediastinitis, (3) evidence of necrotizing infection, and (4) establishment of a relationship between the cervical infection and necrotizing mediastinitis. Ridder et al.[13] recently reported a large series and performed an updated meta-analysis of collected series that illustrate the cardinal features of this important clinical problem. Patients present with odyophagia (66%), neck swelling (41%), neck pain (21%), dyspnea (21%), and chest pain (5%). Signs include fever (100%) and swelling and redness of the oropharynx (69%). About 2/3 of patients have comorbidities that are associated with immunosuppression or chronic illnesses. Common causes include tooth abscesses, pharyngitis, peritonsillar abscess, epiglottis, and perforation of the pharynx. A period of delay of either presentation or diagnosis is common.

CT with intravenous contrast should be performed on all severe neck infections and suspected cases of descending necrotizing mediastinitis to identify radiologic signs of mediastinitis that may not be clinically apparent (Fig. 80-9). *Streptococcus* species are the most common aerobic organisms and *Bacteroides* species are the most common anaerobic organisms isolated. Antibiotics should be started upon clinical suspicion of this diagnosis. All patients require cervical incision, exploration, drainage, and treatment of the underlying condition. Many patients also require transthoracic drainage by a variety

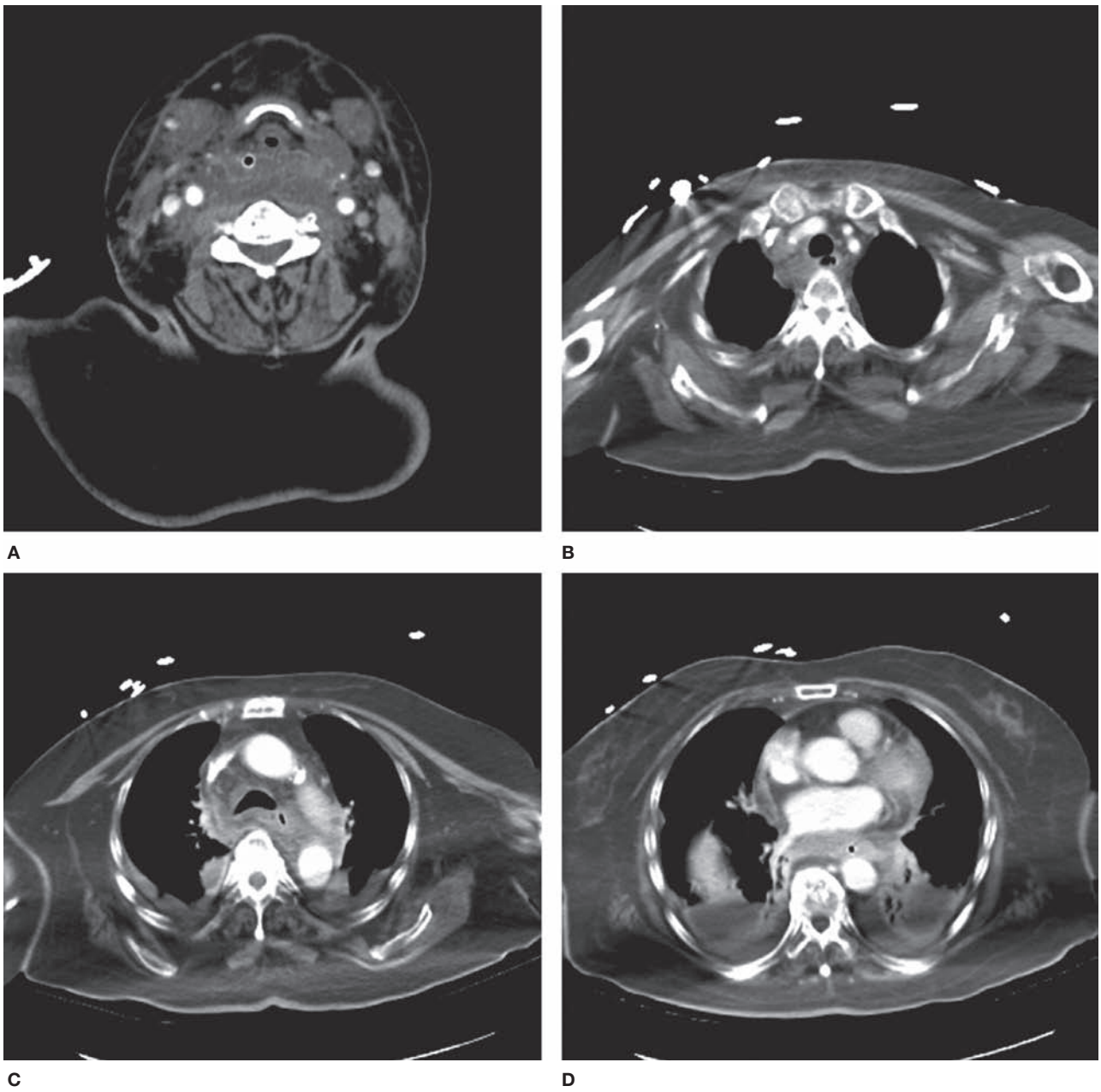


Figure 80-9 Representative CT images from a patient with descending necrotizing mediastinitis from a retropharyngeal abscess. **A.** Low-density collection surrounding the trachea and retropharyngeal space. **B.** Right paratracheal collection. **C.** Collection surrounding the airway and esophagus with small loculated empyemas. **D.** Bilateral empyemas. This patient required transcervical and transthoracic drainage. *(Reproduced with permission from Chen KC, Chen JS, Kuo SW. Descending necrotizing mediastinitis: a 10-year surgical experience in a single institution. J Thorac Cardiovasc Surg. 2008;136(1):191–198.)*

of routes, including thoracotomy, videothoracoscopy, transmediastinal, and subxyphoid. Many patients require several trips to the operating room for repeat debridements and drainage procedures. Tracheostomy is often required due to the severity of upper airway swelling. The mean length of stay is 36 days reflecting the severity of this illness. Recent series report an average mortality of 11%.

■ MEDIASTINITIS FROM DIRECT EXTENSION

Necrotizing pneumonias may cause mediastinitis by direct extension, most often in immunocompromised patients. Aspergillosis of the posterior mediastinum has been reported with increasing frequency and is highly lethal. Treatment involves reversal of immunosuppression (if possible), appropriate antibiotic therapy, and surgical drainage and debridement.

Pancreatitis can extend from the retroperitoneum into the mediastinum and may present as a mediastinal process with evidence of mediastinitis. Pancreatic pseudocysts can also erode into the mediastinum and cause pleural effusions with increased levels of amylase. Treatment is directed at providing adequate drainage of the pseudocyst, usually by internal drainage into the stomach. The pleural effusion(s) may require tube thoracostomy drainage.

■ POSTSTERNOTOMY MEDIASTINITIS

Sternal wound infection with resulting mediastinitis is a relatively new entity, which emerged in the era of modern cardiac surgery. The incidence remains low at 0.5% to 1% of all sternotomies, but such infection is a source of major morbidity, prolonged hospital stay, and significant mortality (0%–30%; average, 15%). Multivariate analysis

has demonstrated that prolonged preoperative stay, advanced age, BMI >30 kg/m^2, chronic obstructive pulmonary disease, diabetes, reoperation, blood transfusions, and reexploration for bleeding are significant risk factors.[19,20] *Staphylococcus aureus* is the most common causative organism. Other organisms commonly isolated include *Staphylococcus epidermidis*, various gram-negative organisms, as well as Candida species and atypical mycobacteria. The etiology appears to be a combination of intraoperative contamination and hematogenous seeding of mediastinal clot in the early postoperative period. Most patients with poststernotomy mediastinitis have an insidious presentation with low-grade fever and leukocytosis, wound problems (erythema, drainage, sternal instability), and eventually bacteremia. Infections caused by gram-negative organisms tend to become manifest earlier than those caused by gram-positive organisms. Most infections occur within the first or second week following the operative procedure. A high index of suspicion must be maintained so that an early diagnosis can be made and appropriate treatment instituted. Wound aspiration, local wound exploration, and CT imaging aid in making the diagnosis. Exploration in the operating room remains the definitive diagnostic maneuver and material should be obtained for culture at that time if it has not been obtained before or has been unrevealing.

If the infection is relatively early and the bony sternum appears viable, debridement, drainage, and saline (or antibiotic) irrigation with reclosure are indicated.[20] Although it may seemingly violate time-honored surgical principles (leaving contaminated wounds open, to close by secondary intention), primary closure of the early, infected sternum yields excellent results in many patients if adequate debridement is carried out. Of course, proper and prolonged antibiotic therapy is necessary. Reported mortality rates approach zero for these early infections if managed appropriately. Late sternal wound infections with mediastinitis present a more formidable challenge, in part due to the extensive sternal osteomyelitis and necrotic soft tissue which, when debrided, result in significant dead space, thereby creating a favorable environment for continued bacterial proliferation and persistent infection. The presence of prosthetic material, such as sutures, Teflon pledgets, or prosthetic grafts further complicates the problem and may lead to catastrophic hemorrhage with a fatal outcome. Mediastinitis in the presence of a prosthetic aortic graft is a particularly disastrous complication. Most surgeons favor extensive sternal debridement, usually with total sternal excision and rotation of pectoralis muscle flaps (bilateral) or transposition of gastrocolic omentum to fill the dead space with viable tissue. More recently successful outcomes have been reported with the use of negative pressure wound therapy (vacuum-assisted closure [VAC]).[21] Caution is required to protect the right ventricle when using negative pressure wound therapy to prevent erosion of the ventricle against the sternum.[22]

■ ANTHRAX MEDIASTINITIS

Anthrax, caused by *Bacillus anthracis*, was previously found primarily in the Middle East, with farm animals as the primary reservoir.[23,24] Following the advent of substantial immigration and bioterrorism, anthrax has been diagnosed in the United States and has been prominent in the mainstream media. An index case of fatal inhalational anthrax complicated by hemorrhagic mediastinitis due to bioterrorism in the United States has been reported in detail.[25] The inhalation of anthrax spores allows entry into the lungs with subsequent transport to the mediastinal lymph nodes by alveolar macrophages. A hemorrhagic mediastinitis typically quickly ensues and death is common. Gram-positive bacilli are present in tissue specimens. The initial treatment involves the initial use of either ciprofloxacin or doxycycline plus one or two additional antimicrobial agents with activity against *B. anthracis*.

CHRONIC MEDIASTINITIS

Several important clinical entities within the spectrum of chronic mediastinits, including mediastinal granuloma, fibrosing mediastinitis, and compression syndromes arising from fibrosing mediastinitis, are presented below.

■ MEDIASTINAL GRANULOMA

Granulomatous mediastinitis is a disease of the mediastinal lymph nodes usually resulting from infection by *Histoplasma capsulatum* and occasionally from tuberculosis, other fungi, and sarcoidosis. In certain areas of the country (e.g., Mississippi river valley) where *Histoplasma* is endemic, this disease is fairly common. Coalescence of caseous mediastinal lymph nodes can result in a single large mass that incites a considerable fibrotic response, which can result in encapsulation and produce a mediastinal granuloma.[26] The right paratracheal area is the most common site for development of an encapsulated mass. When calcification is absent and the patient presents with what appears to be mediastinal adenopathy, a tissue diagnosis is required to exclude malignancy. With progressive increase in the size of this "benign" mass, compression of the trachea, superior vena cava, or esophagus can occur. In a report from the Mayo Clinic, 34% of patients with mediastinal granuloma went on to develop mediastinal fibrosis over a 2-year period.[27] Based on such reports, most authors suggest that there exists a spectrum of diseases ranging from mediastinal granuloma to fibrosing mediastinitis. Caseating lymph nodes can also erode into and rupture in the esophagus, be associated with esophageal diverticula (Fig. 80-10), and erode into the airway, causing obstruction or bleeding.

Mediastinal granulomas should be excised if symptomatic. Although complete excision is sometimes possible, the intense

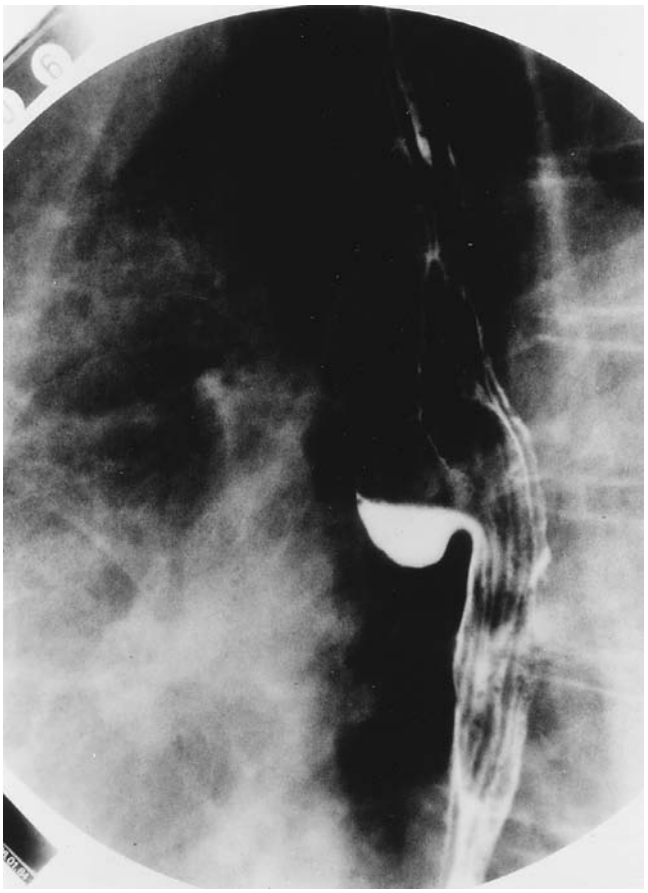


Figure 80-10 Barium swallow of an elderly woman with a history of treated tuberculosis with symptomatic diverticulum of midesophagus adjacent to the subcarinal lymph nodes.

surrounding fibrosis places important structures at risk for operative injury. Evacuation of the granulomatous mass is usually a safer option. Specimens for culture and special stains should be obtained at the time of operation, but organisms can rarely be identified or grown in culture.

Mediastinal lymph nodes involved by the granulomatous process may become calcified as individual masses and – because of the proximity of lymph nodes to the tracheobronchial tree – ultimately erode into the airway. The presence of calcified lymph node masses within the bronchi is referred to as *broncholithiasis.* Erosion into the airway, if it occurs, does so over a prolonged period of time and may remain clinically silent, only to be noted if a bronchoscopy is performed for some other indication. Broncholithiasis may also present with symptoms of cough, obstruction, or bleeding. Symptomatic broncholithiasis should prompt bronchoscopy for documentation of findings. Rarely, if ever, should broncholiths be removed bronchoscopically, the exception being the occasional "stone" that is completely free within the bronchus. An effort to remove a broncholith that is not completely detached from the wall of the bronchus may be accompanied by catastrophic hemorrhage due to the close proximity of pulmonary artery branches to the bronchus. Most symptomatic broncholiths should be removed at thoracotomy, where the pulmonary artery may be managed. These can be extremely difficult and hazardous operations and should be carried out by thoracic surgeons experienced in the management of granulomatous disease. Usually lobectomy or segmentectomy is required, since removal of the calcified mass will almost certainly take a portion of the bronchial wall.

Fistulas occurring between the trachea and esophagus or esophagus and mediastinum as a result of granulomatous lymphadenitis should be closed and reinforced with viable tissue.[28] There is no consensus regarding management of large asymptomatic mediastinal granulomas but some have recommended excision to forestall the development of compression syndromes or fibrosing mediastinitis.

FIBROSING MEDIASTINITIS

Fibrosing mediastinitis may cause a variety of clinical syndromes due to the compression and/or obstruction of vital mediastinal structures by the dense fibrous tissue reaction that is present.[29] In North America fibrosing mediastinits is most commonly associated with *Histoplasma capsulatum* infection. Other rare causes include other fungi, tuberculosis, silicosis, sarcoidosis, the drug methysergide, autoimmune disorders, and familial multifocal fibrosclerosis.[30–32] Fibrosing mediastinitis is labeled as idiopathic if there is no identifiable cause. Goodwin proposed the most widely accepted hypothesis that fibrosing mediastinitis results from a delayed hypersensitivity reaction to fungal, mycobacterial, or other antigens. Pathologic features include the presence of dense fibrotic tissue surrounding the trachea and hila of the lungs, often extending into contiguous structures. Compression of the airway, esophagus, pulmonary arteries, or pulmonary veins may occur because of this process. Histologic features include dense hyalinized collagenous tissue, aggregates of plasma cells and lymphocytes, and occasionally granulomas. Cultures are almost always negative, as are special stains for organisms. Some cases present with radiographic features that suggest malignancy, particularly if calcification is minimal, leading to surgical biopsies for diagnosis.

Symptoms are primarily caused by compression of vital mediastinal structures. Fibrosis around the right peritracheal area commonly causes superior vena cava syndrome. Subcarinal fibrosis can extend posteriorly to encase the esophagus or extend laterally to involve the pulmonary veins. Hilar fibrosis can obstruct either the tracheobronchial tree or pulmonary arteries (Fig. 80-12). Rarely, constrictive pericarditis or obstruction of the trachea or proximal main bronchi can also occur. The signs and symptoms may progress over a period of time.

The optimal treatment of fibrosing mediastinitis remains unknown. Case reports have suggested that antifungal, anti-inflammatory, or antifibrotic treatment may have some benefit, but large case series mostly refute these observations. Interventions to relieve compression of mediastinal structures have been reported with moderate success, but sometimes with relatively high periprocedure morbidity.

Peikert et al.[29] from the Mayo Clinic recently reviewed a large series of patients with fibrosing mediastinitis that nicely summarizes our current limited understanding of this disease. Their clinical definition of fibrosing mediastinitis was radiographic evidence of an infiltrative mediastinal process with associated vascular, airway, or esophageal compression. The pathologic definition was that of a predominance of extensive pauci-cellular fibrotic tissue infiltrating and obliterating adipose tissue with or without patchy infiltration of mononuclear cells. The median age of their patients was 42 years with an equal gender distribution. There was evidence of histoplasmosis (by culture, fungal stains, or positive serologic titer) in 83% of patients. The involved mediastinal organs that were compressed were vascular (48%), bronchial (27%), superior vena cava only (20%), and esophagus (3%). Only 5% of patients were asymptomatic at presentation. Presenting symptoms included dyspnea (47%), cough (21%), symptoms compatible with the superior vena cava syndrome (21%), chest pain (20%), and hemoptysis (20%). Focal mediastinal imaging findings were seen in 95% of patients while only 5% had diffuse infiltration. Calcifications were seen in 73% of patients. PET scans, when obtained for the suspicion of malignancy, were uniformly positive. Medical therapy with antifungal treatment in 28 patients was minimally effective with only an 18% rate of a partial response. Endovascular interventions were successful in 4 of 15 patients but the majority required repeat interventions. Bronchoscopic interventions were not successful. Surgical interventions were successful in 95% of patients. There were no periprocedural deaths. Long-term survival of these patients was identical to age-matched controls.

McNeeley et al. recently reported a review of imaging of fibrosing mediastinitis.[33] The chest radiograph is usually abnormal in fibrosing mediastinitis but findings are usually nonspecific. The most common findings include mediastinal widening, lymphadenopathy, and calcified nodes. Contrast-enhanced CT is the imaging modality of choice and shows fibrotic tissue with variable enhancement. Multiplanar reformatted views are especially helpful in demonstrating compression of vessels and airways and for planning an intervention. A practical differential diagnosis for granulomatous fibrosing mediastinitis includes lung cancer, mediastinal nodal metastases (especially sclerosing adenocarcinomas), sclerosing non-Hodgkin lymphoma, nodular sclerosing Hodgkin lymphoma, and tuberculosis.

COMPRESSION SYNDROMES ASSOCIATED WITH FIBROSING MEDIASTINITIS

The most common mediastinal compression syndrome seen in fibrosing mediastinitis is the superior vena cava syndrome, which occurs in 20% to 50% of patients.[29] In the vast majority of patients, the superior vena cava syndrome is due to malignant disease; fibrosing mediastinitis is the most common benign cause. Patients present with distention of the veins in the neck; edema and plethora of the face, neck, and arms; and central nervous system complaints such as headache and visual disturbances. Men often note as a first sign an increase in collar size; and symptoms become worse upon bending over. Because this syndrome is usually of gradual onset, venous collaterals develop over the anterior chest wall and, in many patients, provide adequate decompression (Fig. 80-11). Confirmation of the diagnosis of superior vena cava syndrome is easily made with contrast CT or venography, which demonstrate blockage of contrast at the thoracic inlet and the presence of collateral vessels. Bilateral upper extremity venograms demonstrate the precise anatomy of the involved veins and are helpful if surgical decompression is

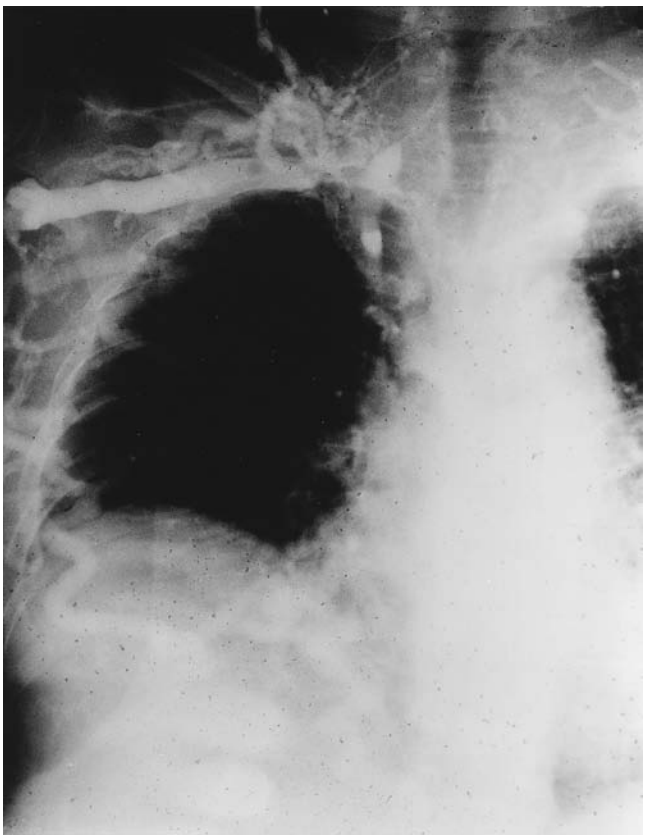
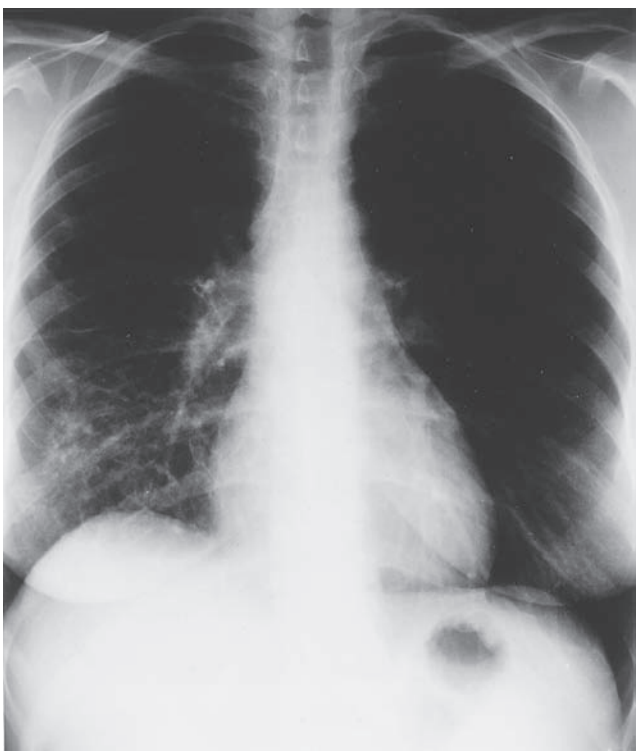


Figure 80-11 Patient with SVC syndrome secondary to mediastinal fibrosis due to histoplasmosis. Numerous dilated and tortuous collateral veins present on the chest wall are characteristic of chronic SVC obstruction.

contemplated. Surgical bypass is reserved for patients with intractable symptoms and is performed by connecting an unobstructed large brachiocephalic vein to the right atrial appendage with a graft of either a saphenous vein or an externally supported polytetrafluoroethylene graft. Favorable long-term results have been reported. Percutaneous angioplasty and stenting of a stenotic superior vena cava has been reported, but long-term follow-up is limited.

Tracheobronchial compression is also common and leads to dyspnea, obstructive pneumonias, wheezing, hemoptysis, cough, and the middle lobe syndrome (see Fig. 80–12). A localized stenotic area sometimes can be dilated, but often pulmonary resection is required. Resection is the procedure of choice if chronic infection has been present. Bronchoscopic interventions are appropriate if lung parenchyma remains normal. The bronchoscopic placement of stents into the trachea and/or mainstem bronchi may allow for adequate management of a compressed airway. A Y-bifurcation stent and individual self-expanding stents placed in the trachea or bronchi are available. Airway management must be individualized based on findings at bronchoscopy. Often the airway strictures are so fibrotic that they are not amenable to stenting.[28]

Complete or partial unilateral or bilateral pulmonary artery obstruction can result from fibrosing mediastinitis (see Fig. 80-12).[28,31,32] Dyspnea and signs of right heart failure can be present. The differential diagnosis should include chronic pulmonary thromboembolism. The fibrosis may also extend to involve the pulmonary veins, producing a syndrome mimicking pulmonary venoocclusive disease. Some patients present with complaints similar to those of patients presenting with mitral stenosis: dyspnea, cough, and hemoptysis. Surgical correction of these disorders is rarely possible due to the extreme fibrosis present around the vessels. Angioplasty and/or stenting of the pulmonary veins has been reported. If the situation is unilateral with associated airway obstruction a pneumonectomy may be an alternative.



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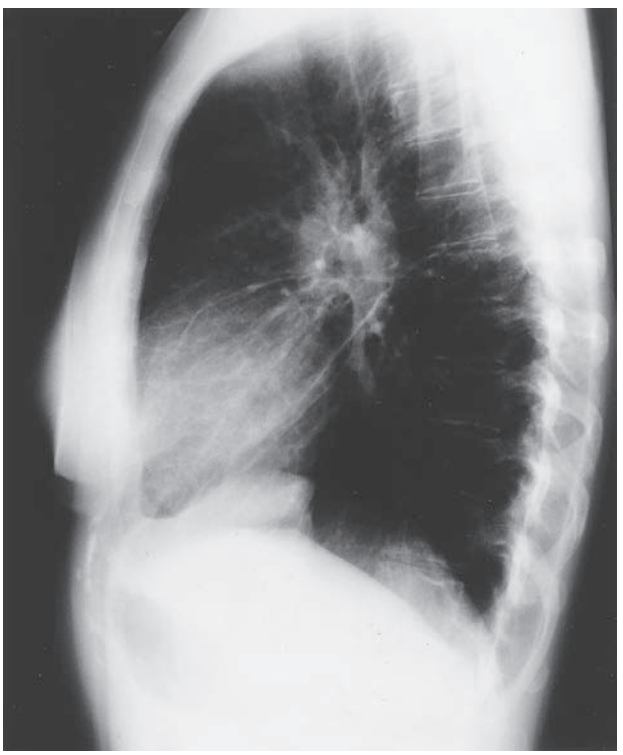

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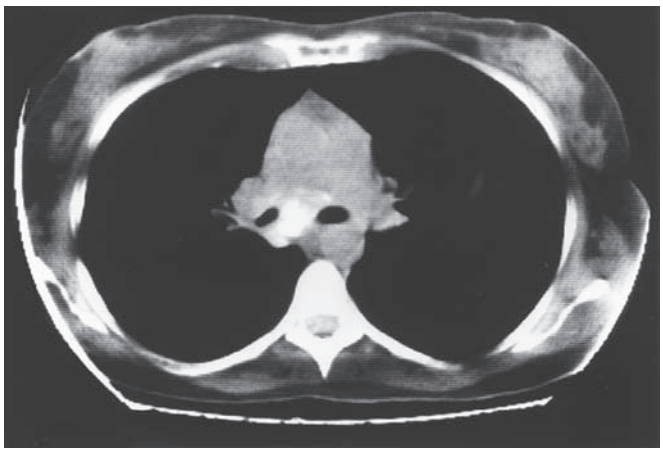
Figure 80-12 Mediastinal fibrosis due to histoplasmosis in a middle-aged nurse with narrowing of the trachea and main bronchi as well as occlusion of the right pulmonary artery. **A.** Posteroanterior radiograph demonstrating focal infiltrate in right lower zone with right hilar fullness. **B.** Lateral radiograph demonstrating a mass centered around the carina with mild narrowing of the distal trachea. *(continued)*



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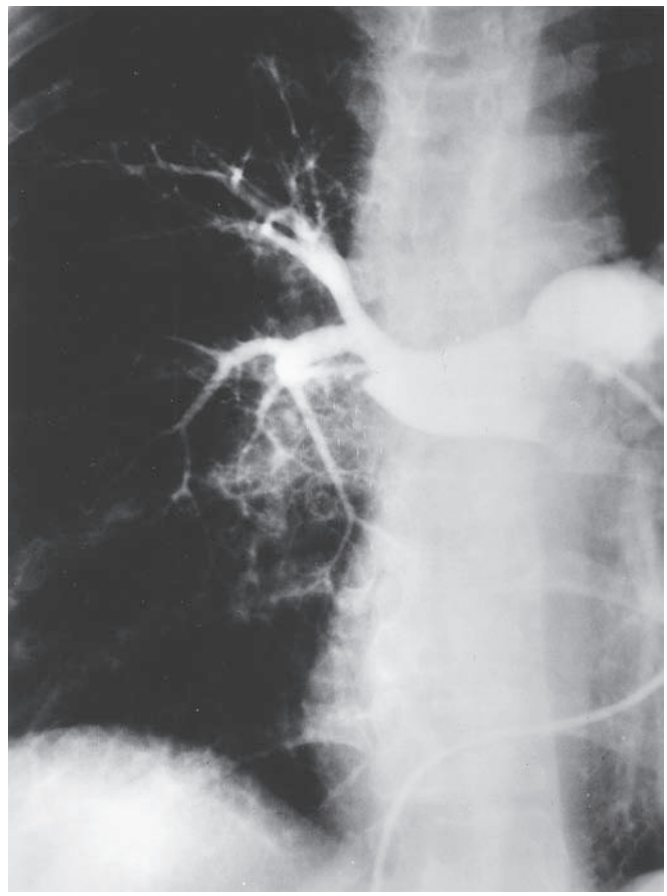

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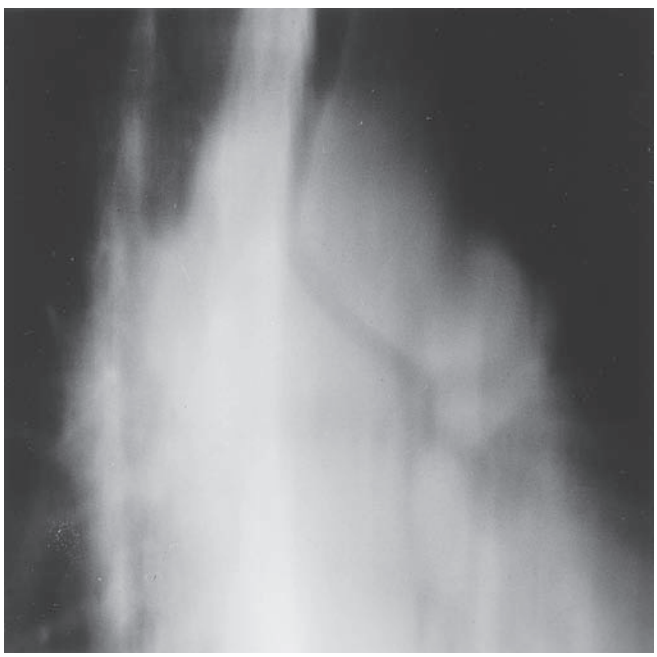

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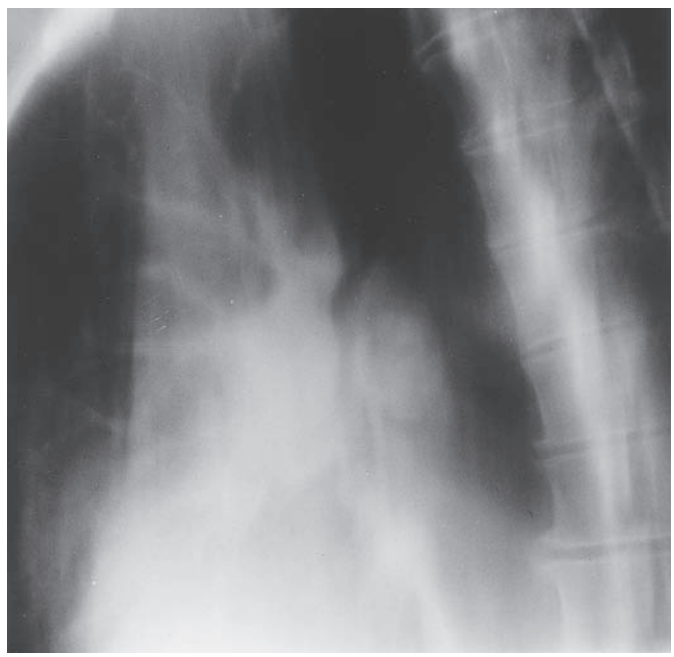

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Figure 80-12 *(Continued)* **C.** Computed tomography shows calcified mass around bronchus intermedius with mild compression of bronchus. **D.** Pulmonary angiogram demonstrates complete occlusion of right pulmonary artery beyond the anterior trunk due to mediastinal fibrosis. The left pulmonary artery was moderately narrowed. **E.** Oblique tomogram demonstrating narrowing of distal trachea and left main bronchus. **F.** Oblique tomogram demonstrating narrowing of right bronchus intermedius with large mass of lymph nodes anterior and posterior to the airway.

Esophageal obstruction resulting from fibrosing mediastinitis most frequently involves the middle third of the esophagus because of its relationship to the subcarinal space. Dilation, enucleation of scar, and resection are therapeutic options. Fistulas may also occur between the subcarinal lymph nodes and the esophagus or into the tracheobronchial tree. Operative treatment for fistula formation is directed at closing the fistula and separating the airway and esophagus using viable tissue such as muscle. An esophageal diverticulum may form from inflammatory adherence to the subcarinal lymph nodes but is usually asymptomatic (see Fig. 80-10).

MISCELLANEOUS MEDIASTINAL PATHOLOGY: SPONTANEOUS MEDIASTINAL HEMORRHAGE

Spontaneous mediastinal hemorrhage is quite rare. Mediastinal hemorrhage due to aortic dissection, contained rupture of a thoracic aortic aneurysm, or iatrogenic injury is much more common. Symptoms are usually of sudden onset and consist of substernal pain, dyspnea, and, rarely, hemodynamic compromise. The hemorrhage is usually brief and self-limited. Treatment is supportive, and secondary causes of mediastinal hemorrhage must be excluded. Mediastinal fibrosis has rarely been reported following mediastinal hemorrhage.

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CHAPTER 81

Congenital Cysts of the Mediastinum: Bronchopulmonary Foregut Anomalies

Alberto de Hoyos
Malcolm M. DeCamp Jr.

Mediastinal masses represent a diverse collection of tumors, vascular abnormalities, and cysts arising from and associated with each of the organs and structures found within the thorax.[1–4] Cystic lesions account for up to 25% of reported mediastinal masses.[1,3–5] These cysts may be congenital or acquired or may represent cystic degeneration of a previously solid tumor. In this chapter, we focus on congenital cystic lesions within the mediastinum, specifically addressing the spectrum of foregut cysts including bronchogenic cysts, esophageal duplication cysts, and neurenteric cysts. Together they constitute up to 9% of all primary mediastinal masses. In addition, we briefly consider simple cysts arising from the thymus, pericardium, and thoracic duct. Many other solid mediastinal neoplasms (dermoids, teratomas, thymomas, parathyroid adenomas, and thyroid goiters) may present with cystic components. These lesions are discussed in Chapter 82.

ANATOMY

Cysts arise in each of the three distinct anatomic regions of the mediastinum:

- The *anterosuperior compartment* extends from the manubrium of the sternum and the first rib to the diaphragm. The anterior border of this region is the posterior sternal table, while the posterior margin includes the pericardium and the innominate vessels. Thymic cysts and endocrine lesions, such as thyroid goiters and cystic adenomas of the parathyroid gland, are found in this compartment.[6]
- The *middle mediastinum* is the site of origin of most bronchopulmonary foregut cysts. The boundaries of the middle mediastinum include the pericardial reflections superiorly and anteriorly and the diaphragm inferiorly. The posterior margin of the middle mediastinum is the anterior border of the spine. Pericardial cysts, as well as bronchogenic cysts, are found in this compartment.[7]
- The *posterior mediastinum* extends from the superior aspect of the first thoracic vertebral body to the diaphragm. Its anterior border is the ventral aspect of the vertebral bodies and it extends posteriorly to the articulation of the vertebral transverse process with each rib. The posterior mediastinum includes both costovertebral sulci and segmental nerve roots as well as the sympathetic chain. Other structures found within the posterior compartment include the esophagus, vagus nerves, the thoracic duct, the azygos vein, as well as the descending aorta. Neurenteric cysts, thoracic duct cysts, as well as some esophageal duplication cysts, and occasional bronchogenic cysts are found in this compartment.[7,8]

Lesions that arise primarily within the mediastinum may extend above the chest into the neck or below the diaphragm into the retroperitoneum, where they present as extrathoracic mass lesions. In addition, cysts within one mediastinal compartment may also extend into the adjacent compartment since there are no strict anatomic barriers.

EPIDEMIOLOGY

In reported series of mediastinal masses, the prevalence of primary cysts ranges from 10% to 25% and has remained steady for the past six decades (Table 81-1) with relatively similar incidences in males and females. Some minor heterogeneity over this time span is accounted for by variations in the ages of patients reported in each series.[1,3–5,9,10]

Bronchogenic cysts account for approximately 40% of mediastinal cysts, while pericardial cysts account for 35%, enteric for 10%, and nonspecific cysts for 15%. The etiology and distribution of cystic mediastinal masses are different in children and adults. Cysts of foregut origin account for only half of the lesions found in adults, whereas they constitute nearly 90% of cystic lesions reported in pediatric series (Table 81-2). Conversely, pericardial cysts account for up to one-third of all cystic lesions in adults, whereas true pericardial cysts are exceedingly rare in children. Among congenital lesions of the foregut and tracheobronchial tree seen in children – including pulmonary sequestrations, congenital lobar emphysema, cystic adenomatoid malformations, arteriovenous malformations, and bronchial atresias – simple foregut cysts (bronchogenic, enterogenous, and neurenteric) comprise between 13% and 29% of reported cases.[4,5,9–11]

Although the relative frequencies of cystic and solid mediastinal masses have remained fairly constant, the advent of cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), has increased the detection of all mediastinal lesions.[12–16]

Multidetector computed tomography (MDCT) with volumetric acquisition provides fast acquisition of high-resolution images and multiplanar reconstruction. Both 2D and 3D imaging may help with improving diagnostic accuracy, surgical planning, and in assessing resectability. In most cases, CT imaging provides enough information to make accurate diagnostic and therapeutic decisions without further testing. In selected cases, MRI may offer advantages over other modalities for detecting and identifying cystic, or fluid-filled mediastinal masses because of the intrinsic high soft tissue contrast and direct multiplanar imaging capabilities. In addition, sagittal or coronal CT and MRI reformations can provide additional anatomic information that the transaxial images cannot.

TABLE 81-1 Prevalence of Primary Cysts in Reported Series of Mediastinal Tumors over Six Decades

Year	*n*	Mediastinal Cysts (%)	Reference
1952	101	20	Sabiston & Scott[64]
1963	92	24	Heimberger et al.[5]
1972	209	9	Benjamin et al.[2]
1987	400	25	Davis et al.[4]
1993	257	18	Azarow et al.[1]
1999	124	4	Whooley et al.[8]
2003	806	13	Takeda et al.[9]

TABLE 81-2 Origin of Mediastinal Cysts

Cyst Type	All Ages ($n = 419$) (%)	Pediatric Only ($n = 70$) (%)
Bronchogenic	36	53
Enteric	12	35
Pericardial	29	1
Other	23	11

Sources: Data from Azarow KS, Pearl RH, Zurcher R, Edwards FH, Cohen AJ. Primary mediastinal masses: a comparison of adult and pediatric populations. J Thorac Cardiovasc Surg. 1993;106:67–72; Benjamin SP, McCormack LJ, Effer DB, Grover LK. Primary tumors of the mediastinum. Chest. 1972;62:297–303; Bower RJ, Kiesewetter WB. Mediastinal masses in infants and children. Arch Surg. 1977;112:1003–1009; Whooley BP, Urschel JD, Antkowiak JG, Takita H. Primary tumors of the mediastinum. J Surg Oncol. 1999;70(2):95–99; Takeda S, Miyoshi S, Minami M, Ohta M, Masaoka A, Matsuda H. Clinical spectrum of mediastinal cysts. Chest. 2003;124(1):125–132.

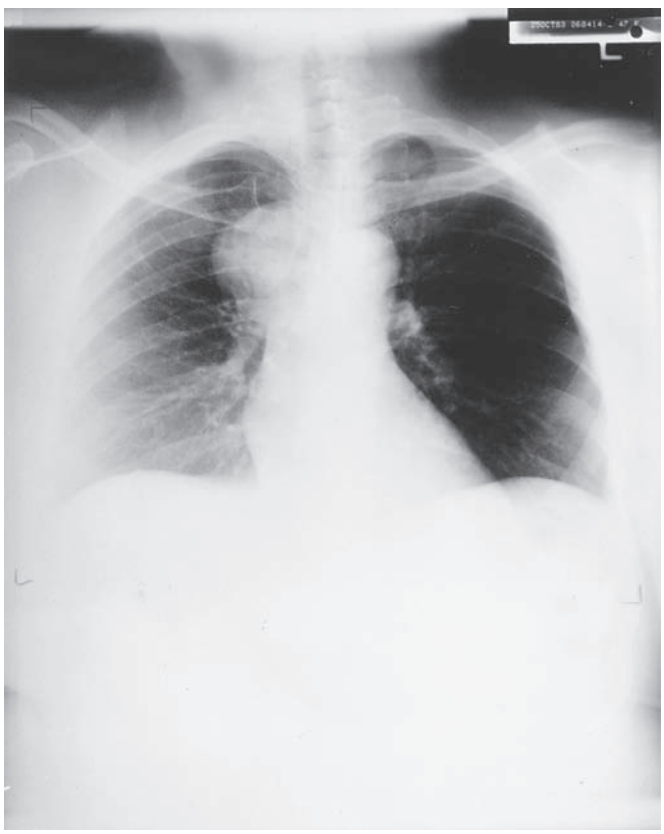
BRONCHOGENIC CYSTS

The embryology, clinical presentation, diagnosis, and management of bronchogenic cysts are discussed below.

EMBRYOLOGY AND TERMINOLOGY

The primitive respiratory and upper gastrointestinal systems have a common embryologic endodermal origin. The primitive foregut gives rise to a variety of aerodigestive organs and tissues, beginning with the pharynx and subsequently giving rise to the larynx, upper and lower respiratory tracts, esophagus, stomach, proximal duodenum, liver, pancreas, and associated ducts.[17] Cystic malformations of foregut origin may have a variety of epithelial linings that reflect the embryologic tissues from which they are derived. The lung bud develops caudally from the laryngotracheal tube, beginning in the fourth week of gestation. By the fifth week, the single bud has divided into right and left main bronchi, which grow into the surrounding splanchnic mesenchyme that is destined to become bronchial cartilage and smooth muscle as well as visceral pleura. Dichotomous branching of the primitive bronchi continues until about the 24th week, when the terminal bronchioles begin to give rise to primitive alveoli.

Throughout this period of embryogenesis, abnormal bronchi and bronchioles may form larger saccular structures, which are clinically recognized as bronchogenic cysts. Such saccular malformations may be invested by their own splanchnic mesenchyme (neopleura). Abnormal bud separation may lead to cyst formation lined with respiratory epithelium. Some investigators believe that mediastinal bronchogenic cysts arise early in the cycle of bronchial branching, whereas intrapulmonary bronchogenic cysts represent derangements later in fetal development. If the separation occurs early, the cyst is associated with the large airways within the mediastinum. Delayed bud separation may lead to cyst formation more distally within the lung parenchyma. Approximately three-quarters of bronchogenic cysts are within the mediastinum and associated with the large airways and one-quarter are intraparenchymal.[16] Cysts abutting the trachea, carina, or hilum, are termed *mediastinal bronchogenic cysts* and they rarely maintain communication with the respiratory tract (Figs. 81-1 and 81-2). Less frequently, these lesions are contained within the pulmonary parenchyma, most commonly in the lower lobes and are termed *intrapulmonary bronchogenic cysts* (Fig. 81-3). Other locations include the neck, esophageal wall, pleura and diaphragm, and, rarely, in the skin. Bronchogenic cysts are lined by respiratory epithelium and may contain cartilage within their walls. Because they uniformly arise before alveoli form (at 28 weeks), bronchogenic cysts have no gas



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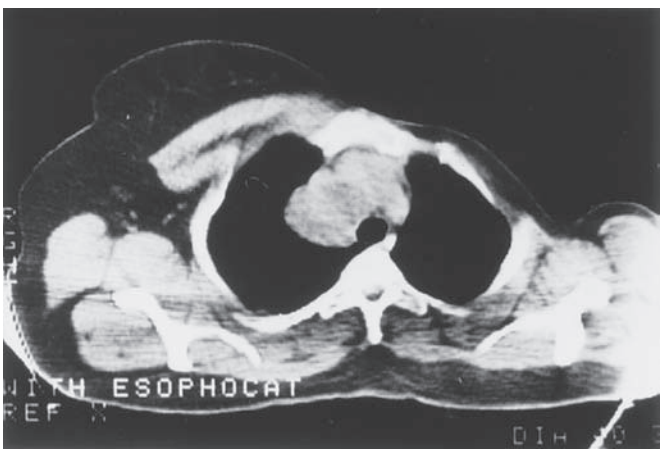
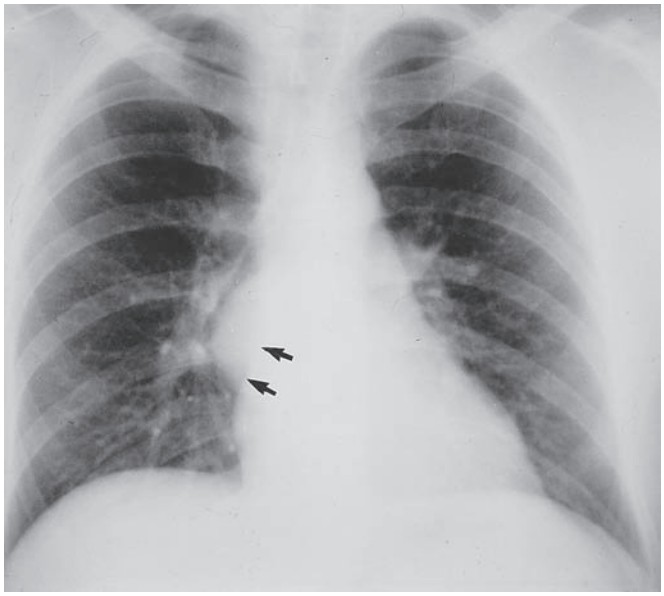


B

Figure 81-1 **A.** Posteroanterior radiograph of a smooth-walled paratracheal bronchogenic cyst. **B.** Computed tomogram of the same paratracheal bronchogenic cyst. Note that the cyst contents are somewhat heterogeneous but generally of lower density than the surrounding mediastinal structures.



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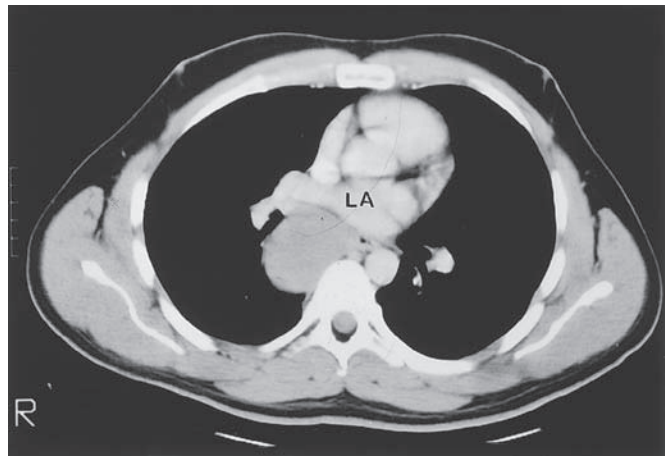

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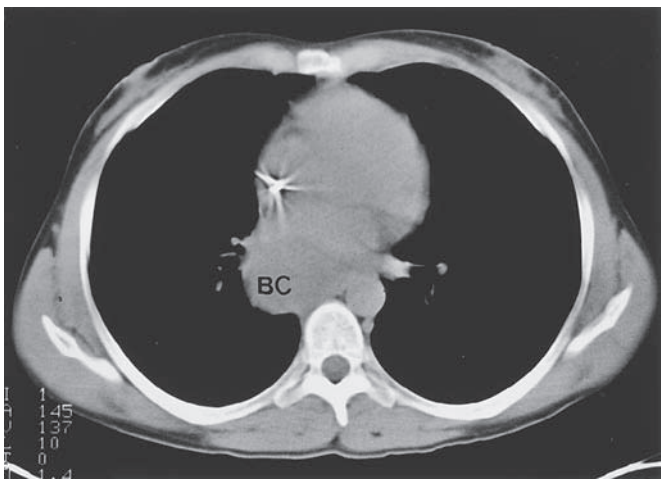
Figure 81-2 **A.** Posteroanterior radiograph of a smooth-walled subcarinal bronchogenic cyst. Note that the cyst is distinct from the right heart border *(arrows)*. **B.** Contrast-enhanced axial CT image of the homogeneous, subcarinal bronchogenic cyst. This patient presented with atrial dysrhythmia attributed to left atrial (LA) compression by the cyst. *(Reproduced with permission from DeCamp MM Jr, Swanson SJ, Sugarbaker DJ. The mediastinum, in Baue AE, Geha AS, Hammond GL, et al (eds). Glenn's Thoracic and Cardiovascular Surgery, 6th ed. Stamford, CT: Appleton & Lange; 1996.)*



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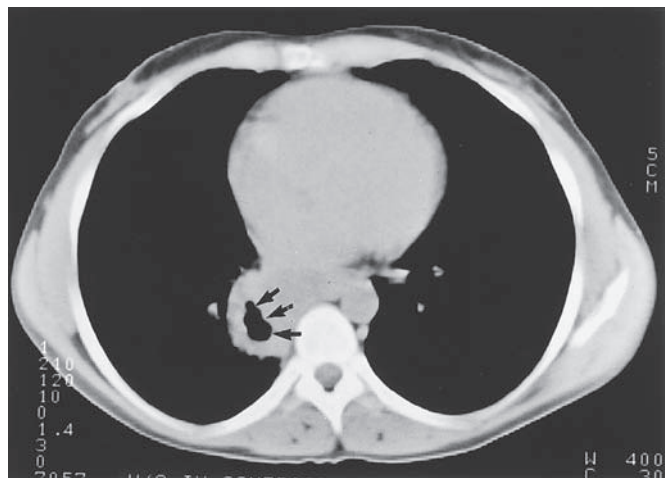

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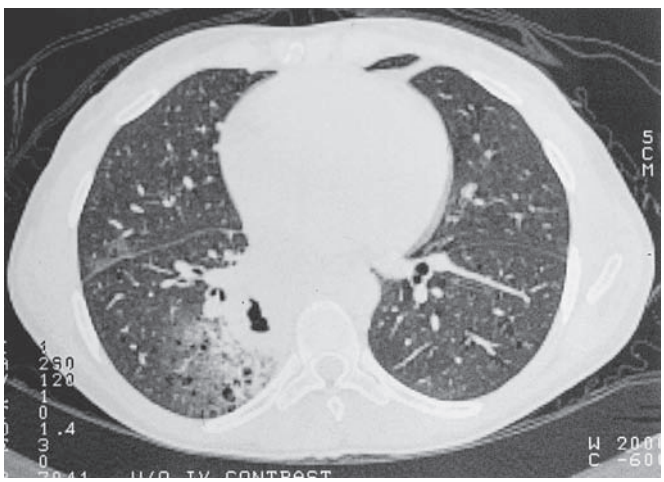


C

Figure 81-3 **A.** Nonenhanced CT image of an asymptomatic bronchogenic cyst (BC). **B.** Nonenhanced CT image of the same cyst after 6 months of expectant management. The cyst has "cavitated" *(arrows)* indicative of secondary infection. **C.** Axial CT image with "lung windows" of the infected, intraparenchymal bronchogenic cyst. Note the associated right lower lobe pneumonitis surrounding the cyst, not appreciated by the "mediastinal" window in image (**B**).

TABLE 81-3 Clinical Characteristics of Cysts in the Mediastinum (Symptoms and Signs)[a]

Characteristics	Bronchogenic $n = 47$	Esophageal $n = 4$	Thymic $n = 30$	Pericardial $n = 12$	Pleural $n = 7$	Others $n = 5$	Total $n = 105$
Asymptomatic	28	3	18	10	6	2	67 (63.8)
Chest pain	6	0	6	2	0	1[b]	15 (14.3)
Dyspnea	3	1	3	0	1	0	8 (7.6)
Cough	5	0	2	0	0	0	7 (6.7)
Fever	5	0	1	0	0	0	6 (5.7)
Hoarseness	1	0	4	0	0	0	5 (4.8)
Sputum	3	0	0	0	0	0	3 (2.9)
Dysphagia	1	1	1	0	0	0	3 (2.9)
Cyanosis	0	0	0	0	1	0	1
Hemoptysis	1	0	0	0	0	0	1
Others	1	0	1	0	0	2[c]	4

[a]*Data are presented as No. or No. (%).*
[b]*Chest pain associated with thoracic duct cyst.*
[c]*Neurofibromatosis associated with meningocele.*
Source: Reproduced with permission from Takeda S, Miyoshi S, Minami M, Ohta M, Masaoka A, Matsuda H. Clinical spectrum of mediastinal cysts. Chest. 2003;124(1):125–132.

exchange potential even if their bronchial communications persist, an extremely rare event.

PRESENTATION AND DIAGNOSIS

Bronchogenic cysts represent the most frequent cystic lesions found in the mediastinum and represent up to 15% to 20% of all mediastinal masses. The majority of the mediastinal bronchogenic cysts are located below the carina (77%), while the remainder occur above the carina (23%). Most young patients with bronchogenic cysts have symptoms at the time of diagnosis (Table 81-3), although in a significant minority of patients (20%–30%), the cysts may be identified incidentally on CT scans performed for other reasons. The pediatric population is particularly predisposed to symptomatic cysts due to the smaller size of their thorax and more malleable airways.[1,5,9,11] Eraklis et al.[18] noted life-threatening respiratory compromise in 70% of infants with foregut cysts. Mass effects from the cysts, which caused compression, "ball valving," or differential ventilation, were the predominant causes of respiratory distress. These neonates were often cyanotic, with wheezing or stridor, and their radiographs demonstrated inhomogeneous aeration, lobar collapse, and/or mediastinal shift. In series of nonneonatal children, up to 95% had symptoms. Signs and symptoms of infection may be present, especially in the older children population.

In adults, symptomatic bronchogenic cysts are less common.[1,4,10,19,20] In a large series, symptoms were present in about one-third of patients and included chest pain, cough, wheezing, stridor, dyspnea, dysphagia, cyanotic spells, and pneumonia. Other manifestations include compression of the superior vena cava or left atrium, or evidence of infection such as pneumonia or empyema (Fig. 81-3C). In more recent series, 75% to 95% of patients were asymptomatic when the lesions were detected.[20–24] With long-term follow-up, however, two-thirds of patients who were initially asymptomatic eventually developed symptoms.

The presence of a bronchogenic cyst is suggested by plain chest radiographs in up to two-thirds of cases in any age group. The usual appearance is that of a 2- to 10-cm ovoid, smooth, homogeneous mass that abuts the mediastinum or hilum or splays the carina.[25] An air–fluid level connotes either persistent bronchial communication or secondary infection of the cyst (Fig. 81-3). As mentioned earlier, some cysts (especially in infants) may exert a mass effect, causing airway compression, parenchymal atelectasis, or cardiovascular compression (Fig. 81-2B). In 60% to 65% of patients, posteroanterior and lateral plain chest radiographs make it possible to diagnose these lesions and to document their precise location.

Ultrasonography is helpful in confirming the cystic nature of mediastinal lesions in infants and children. Prenatal diagnosis is also feasible. Such forewarning allows for the expeditious management of these infants antenatally or at the time of delivery, when most affected infants quickly develop symptoms coincident with inflation of the lungs. In the adult, surface ultrasonography has little to offer in the acoustic visualization of suspected bronchogenic cysts because air within the lungs is a poor conductor of sound. Esophageal ultrasound can be useful in the diagnosis of mediastinal bronchogenic cysts due to the proximity of the endoscopic probe to the cyst. However, needle aspiration through the esophagus should not be performed due to the possibility of infection and sepsis.[26,27]

Cross-sectional imaging techniques, using either CT or MRI, have become the diagnostic procedures of choice for investigating mediastinal masses. These methods provide helpful details of cyst structure, including the density and type of cyst fluid, amount of calcium in the cyst wall, vascularity of the cyst, and the relationships of the cyst to adjacent mediastinal structures. MRI and CT are probably equally useful in the diagnosis of mediastinal-based cysts, although in most situations, a CT scan will provide all the necessary information. CT is superior for the examination of intrapulmonary cysts because of its ability to delineate more sharply the cystic lesion from the surrounding air-filled parenchyma (Figs. 81-1–81-3). On CT, bronchogenic cysts appear as a single, smooth, round, or elliptic mass with a well-defined, thin, smooth wall and nonenhancing homogeneous cyst mass. Half of these lesions have the same density as water with attenuation values in a range consistent with serous fluid (0–20 Hounsfield units [HUs]) and others have a CT density that varies depending on the cyst's protein content.[15,16,25] Higher attenuation in the range of 30 to 130 HU is the result of the presence of calcium, proteinaceous fluid, mucus, and/or blood within the cyst. The presence of especially high attenuation fluid within the cyst on CT scan suggests a high calcium content (milk of calcium).[16] On MRI, bronchogenic cysts frequently show signal intensity higher than that of muscle on T1-weighted images. Variable signal intensity may be due to variable cystic

components and presence of protein, blood, or mucoid material. On T2-weighted images, cysts show high signal intensity.

Bronchoscopy is normal in the majority of cases, but abnormalities include extrinsic compression of the airways, secretions from infected cysts, and rarely, direct communication with the cyst cavity. Rupture into the airway, esophagus, or pericardium has been documented.

THERAPY

The treatment options for bronchogenic cysts include observation, resection, and aspiration. In the absence of definitive diagnosis, surgical exploration is recommended for nearly all patients with an abnormal mediastinal mass. Bronchogenic cysts are the most commonly treated mediastinal foregut anomaly and account for 60% of all mediastinal masses. Once a bronchogenic cyst is diagnosed, surgical excision is indicated to relieve clinical symptoms, to address enlarging cysts, or to prevent possible complications such as infection, malignant transformation, tracheal or vascular compression, or hemoptysis.[28–30] Complete excision of the cyst should be performed, thus minimizing the chance of recurrence and the potential for complications. Traditionally, a thoracotomy was necessary. Since most cysts are located in the subcarinal area, a right fifth interspace thoracotomy is usually recommended. With the right lung mobilized anteriorly, access is gained to the area below the azygos vein. The mediastinal pleura is incised and the cyst is meticulously dissected from the surrounding structures, paying particular attention to the areas of attachment to the airway, esophagus, and pericardium. Video-assisted thoracoscopic surgery (VATS) is being utilized with increasing frequency to resect mediastinal cysts with excellent results, low conversion rates to open procedure (7%–30%), and no significant increases in recurrence rates.[31–34] A standard three-port technique is typically utilized. Large bronchogenic cysts located in the subcarinal area may extend to the mid or distal left main bronchus and may be densely adherent to the airway or esophagus, making thoracoscopic dissection difficult or even risky with potential for injury to the adjacent structures. Decompression of the cyst by aspiration of its content may make handling and dissection somewhat easier.[33]

Urschel and Horan[35] described piecemeal resection of a mediastinal bronchogenic cyst using a Carlens mediastinoscope introduced through a small suprasternal incision. This may be particularly helpful in the treatment of recurrent subcarinal cysts previously approached through a thoracotomy. Partial resection of a bronchogenic cyst may occasionally be necessary, if the cyst is found to be densely adherent to and inseparable from the membranous airway, main pulmonary vessels, esophagus, phrenic nerve, or aorta. In these cases, the majority of the wall of the cyst should be excised and the mucosa lining the remaining cyst wall should be ablated with electrocautery in an effort to prevent recurrences. When subtotal excision is necessary, symptomatic recurrences requiring re-excision have been reported.

Aspiration of a cyst to confirm a benign diagnosis and to instill a sclerosing agent (ethanol or bleomycin) has been used to manage some cysts. The advent of endobronchial ultrasonography with transbronchial intervention has resulted in an even less invasive management option. However, the fluid is almost always thick and viscous and unlikely to be drained through a long, small needle. Reports of long-term follow-up for this approach to both the diagnosis and therapy of bronchogenic cysts are scant. However, it may represent a useful form of therapy for inoperable patients.

Whatever the operative approach, the goal of surgery should be complete excision of all elements of the cyst. Occasional case reports of malignancy arising from the cyst mucosa support the general concept of complete resection for any bronchogenic cyst.[36] A variety of tumors have been associated with bronchogenic cysts including adenocarcinoma, squamous cell carcinoma, carcinoid tumors, anaplastic carcinoma, and leiomyosarcoma in both children and adults.

Treatment of asymptomatic cysts remains controversial.[37] A conservative approach can be considered for small, asymptomatic cysts that do not compress adjacent structures, do not enlarge over time, do not display atypical characteristics, or arouse suspicion of malignancy.

ENTEROGENOUS CYSTS

The embryology, clinical presentation, diagnosis, and management of enterogenous cysts are discussed below.

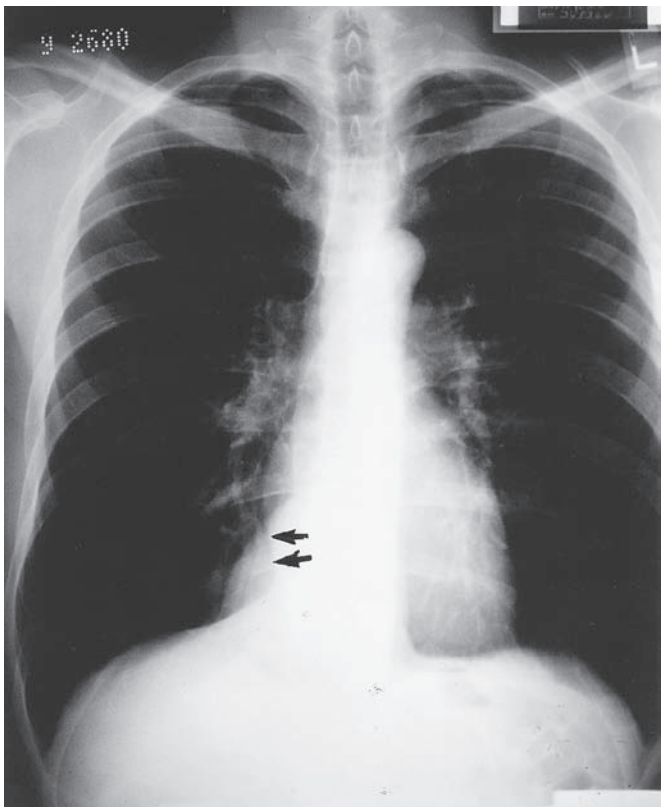
EMBRYOLOGY AND TERMINOLOGY

Enterogenous cysts are also termed *esophageal duplications*. They arise from the elongating esophagus, which separates from the respiratory tract at about the fifth week of gestation (see Chapter 4). As with most intestinal duplications, enterogenous cysts represent failure of normal recanalization during embryogenesis.[38] Most esophageal duplications are of the closed and cystic type. Rarely are they tubular or demonstrate preserved communication with the alimentary tract.

PRESENTATION AND DIAGNOSIS

After leiomyomas and benign polyps, esophageal cysts are the third most common esophageal mass, although they remain much less common than bronchogenic cysts. Of all mediastinal cysts, only 5% to 15% are esophageal in origin. The majority of esophageal duplication cysts occur in infants or children and nearly 75% of esophageal duplication cysts are recognized before 16 years of age.[39–41] In up to 60% of patients they are located adjacent to or within the lower one-third of the esophageal wall in the lower posterior mediastinum with a two-to-one predilection for cysts to be on the right side. Most adults are asymptomatic, with cysts incidentally identified on chest CT.[42] The natural history of esophageal cysts is variable, but if left untreated most will become symptomatic. Symptoms are usually due to compression of the airways resulting in cough, dyspnea, and occasionally stridor.[43–45] Dysphagia is surprisingly infrequent. In asymptomatic patients, the most common clue leading to this diagnosis is the coexistence of other gastrointestinal duplication(s). Associated conditions include other intestinal cysts, esophageal atresia, tracheoesophageal fistula, and spinal abnormalities. Unlike bronchogenic cysts, which are always lined with respiratory mucosa, enterogenous cysts may have a variety of epithelial linings, including the squamous epithelium native to the esophagus. From 50% to 60% of esophageal cysts contain ectopic gastric mucosa, with some containing pancreatic tissue. The presence of gastric mucosa containing parietal cells capable of acid secretion may explain events such as spontaneous hemorrhage and perforation.[44]

Esophageal duplications usually present radiographically as smooth-walled, posterior mediastinal lesions at the base of the right hemithorax (Fig. 81-4A). A barium swallow demonstrates deviation of the lumen around the cyst, but rarely shows communication with it (Fig. 81-4B). Proximal esophageal dilatation is not common because the cysts usually are not obstructive. In patients with suspected duplication, a technetium pertechnetate nuclear scan may suggest the presence of ectopic gastric mucosa within the chest. Cross-sectional imaging (CT or MRI) is almost routinely employed to characterize the contents of a cyst and to define the relationship of the cyst to contiguous structures (Fig. 81-4C). The characteristic CT and MRI findings are identical to those of bronchogenic cysts, except that the wall may be thicker and in closer contact with the esophagus. Endoesophageal ultrasound has provided a useful, minimally invasive tool to investigate these lesions and to allow sampling of cyst



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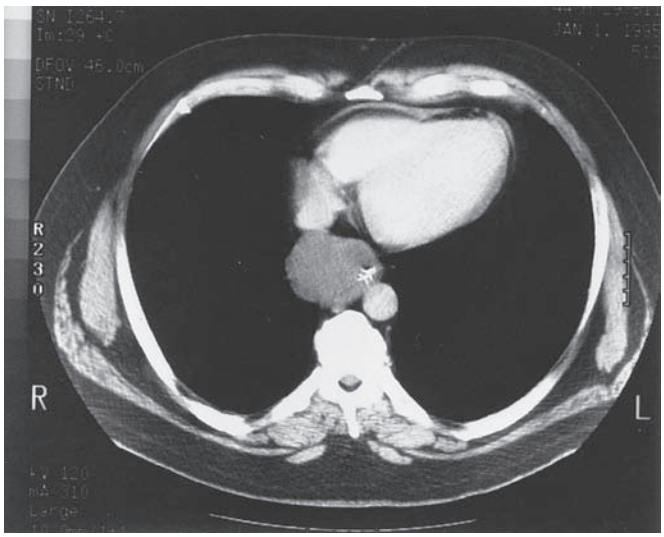

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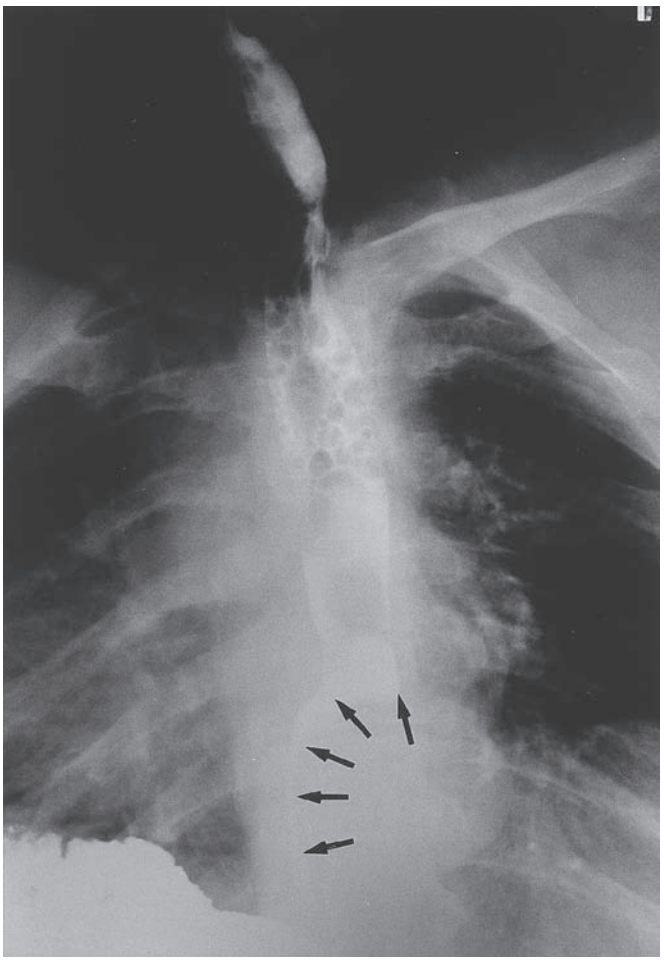


B

Figure 81-4 **A.** Frontal radiograph demonstrating smooth-walled posterior mediastinal mass consistent with an enterogenous cyst. The lesion is easily separable from the right heart border *(arrows)*. **B.** Barium esophagogram of the same patient demonstrating deviation of the true esophageal lumen around the smooth extramucosal lesion *(arrows)*, found at resection to be an enterogenous cyst (esophageal duplication). **C.** Oral and intravenous contrast-enhanced CT image of the enterogenous cyst. The lesion is radiographically inseparable from the esophagus but free of all cardiac structures.

contents to confirm that the lesion, in an otherwise asymptomatic patient, is benign.[26,46] There is however, potential risk of infection and aspiration should be avoided if the echo characteristics suggest a simple cyst. Esophagoscopy, when performed, will demonstrate a smooth, soft, compressible mass without mucosal abnormality or communication with the extraluminal mass.

THERAPY

As in the case of bronchogenic cysts, esophageal duplications are likely to become larger or infected over time. Thus, resection is recommended for all enterogenous cysts, whether for current symptoms or for the high likelihood of future complications. Esophageal duplication cysts can be approached through a standard thoracotomy, VATS, or robotic techniques.[47–53] Regardless of the approach, the following steps should be emphasized: (1) Preservation of the muscular layer for repair, (2) identification and preservation of the vagus nerves, and (3) assessment of mucosal integrity via air insufflation under water. In most cases a plane of dissection in the submucosa can be achieved to complete the resection. Despite the lack of communication with the esophageal lumen, cyst resection may leave defects in the esophageal wall that must be meticulously repaired. If the mucosa is breached, the esophagus should be closed primarily in layers, and the repair should be reinforced with a locally procured flap of vascularized tissue. Options for buttressing include the pericardial fat pad, pleura, intercostal muscle, pericardium, or omentum. Case reports documenting the occurrence of an adenocarcinoma in esophageal duplication cysts underscore the need for resection at the time of diagnosis.

NEURENTERIC CYSTS

The embryology, clinical presentation, diagnosis, and management of neurenteric cysts are discussed below.

■ EMBRYOLOGY AND TERMINOLOGY

During the third week of normal embryogenesis, the notochord should separate from the primitive foregut (see Chapter 4). If this separation is incomplete, the mesodermal masses, which normally encircle the neural tube, cannot enclose it and vertebral anomalies arise. The attached foregut often spawns an associated mediastinal enteric cyst. This form of congenital cyst accounts for only 5% to 10% of all foregut lesions and is consistently associated with bony anomalies of the spine.[54] The spectrum of vertebral anomalies includes butterfly vertebrae, hemivertebrae, and anterior spina bifida. They occur primarily in the lower cervical and upper thoracic regions and are usually cephalad to the cystic lesion, since the esophagus descends (or the pharynx ascends) during fetal development. The fluid within the cyst may be nearly identical to CSF or may be milky, cream-colored, yellowish, or xanthochromic. Neurenteric cysts may be intradural, extramedullary, and situated ventral or ventrolateral to the spinal cord.[55]

■ PRESENTATION AND DIAGNOSIS

Neurenteric cysts are exceedingly rare; virtually all present within the first year of life.[56] More than half of afflicted children have neurologic complaints or findings. These include back pain, motor deficits of a lower extremity, and gait disturbance, especially if there is communication with the spinal canal. Often times the triad of a mediastinal mass, airway symptoms, and a vertebral anomaly will be present. The diagnosis is often made after detection of vertebral anomalies on the chest radiograph. CT scans show vertebral abnormalities in 50% of affected patients and can define bony abnormalities and demonstrate extension of the cystic lesion into the spinal canal. MRI has supplanted CT myelography and provides a complete, noninvasive assessment of the bony abnormality, the intraspinal extent of the cyst, and the degree of spinal cord or nerve root compression associated with a neurenteric cyst.[57]

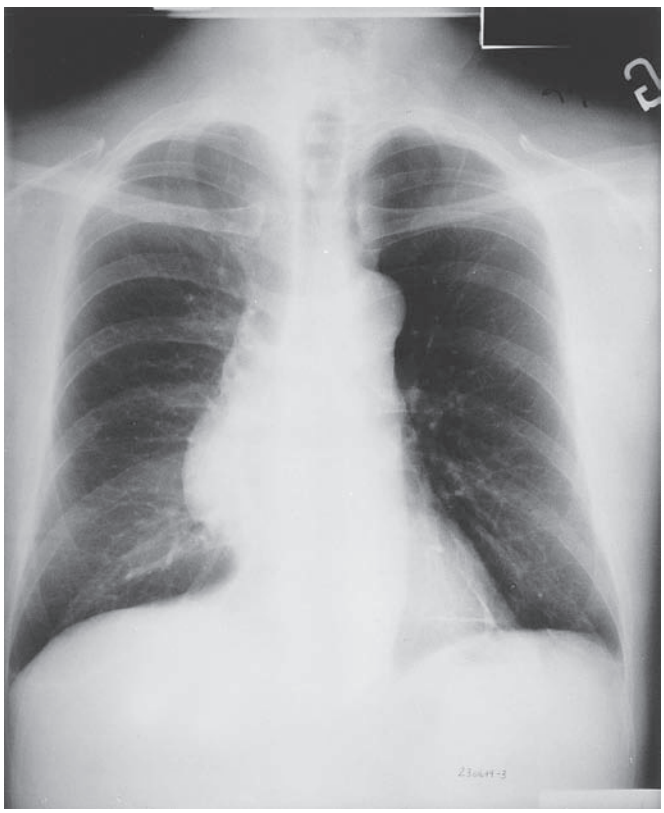
■ THERAPY

Careful imaging of suspected neurenteric cysts is paramount for successful extirpation. MRI is useful to exclude extension of the cystic component into a neural foramen or the spinal canal proper and to exclude an associated meningocele. Such findings would require a staged resection employing a posterior neurosurgical approach first, to decompress the cord or its nerve roots, followed by resection of the mediastinal component by standard thoracotomy or VATS.[57–60] Complete cyst excision is the treatment of choice. When preoperative diagnostic imaging shows no intraspinal extension of the cyst, thoracoscopic excision may be possible. When there is only minimal involvement of the vertebral body, resection can be accomplished with VATS or more commonly a posterolateral thoracotomy. If the spinal abnormality is severe a combined neurosurgical and thoracic approach is recommended.

THYMIC CYSTS

The thymus is derived from the third pharyngeal pouch. Its development is incomplete at birth, and the gland continues to grow throughout childhood into adolescence. Cysts within the gland are thought to occur during adulthood, when gland architecture involutes and central cells degenerate and are replaced by fat.

Thymic cysts are rare congenital or acquired lesions embryologically derived from the pharyngeal pouches. They account for only 3% to 5% of all anterior mediastinal masses.[4–6,9,11,16] Most thymic cysts are asymptomatic and discovered incidentally on imaging studies performed for other reasons. Although thymic cysts are benign, they must be distinguished from thymomas, germ cell tumors, and lymphomas—all of which may have areas of cystic degeneration. These cysts arise in the anterior mediastinum (Fig. 81-5) and may extend to the middle mediastinal compartment, especially in the



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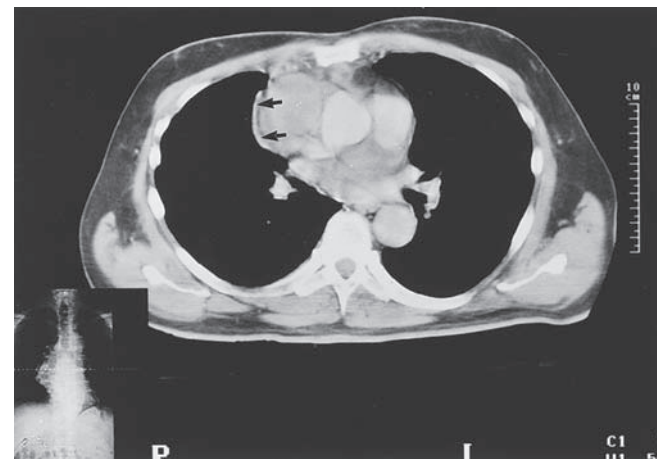
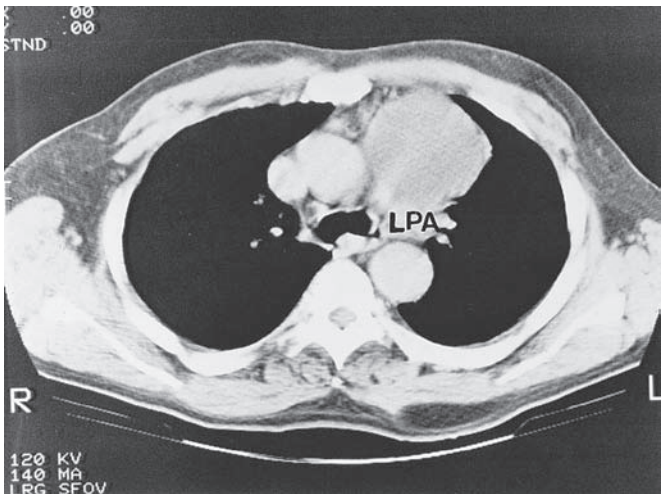


B

Figure 81-5 **A.** Frontal radiograph of an anterior mediastinal mass inseparable from the right heart border. **B.** Axial CT image of this mass demonstrates its thick, focally calcified *(arrows)* wall containing homogeneous nonenhancing fluid. At resection what was feared to be a teratoma was found to be a thymic cyst. *(Reproduced with permission from DeCamp MM Jr, Swanson SJ, Sugarbaker DJ. The mediastinum, in Baue AE, Geha AS, Hammond GL, et al (eds). Glenn's Thoracic and Cardiovascular Surgery, 6th ed. Stamford, CT: Appleton & Lange; 1996.)*



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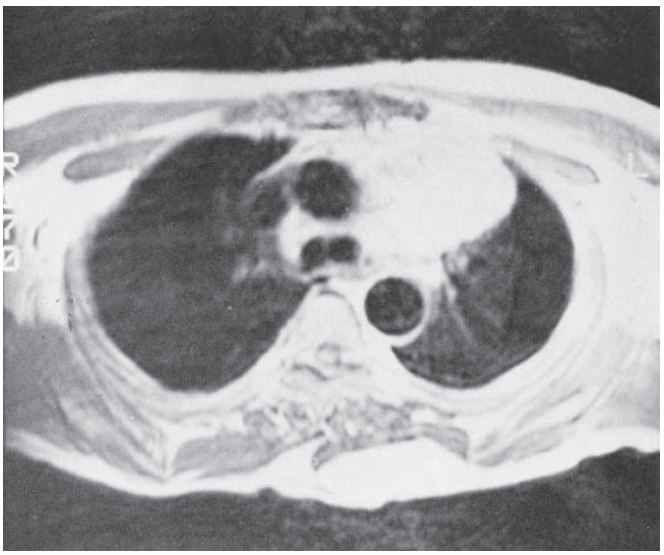

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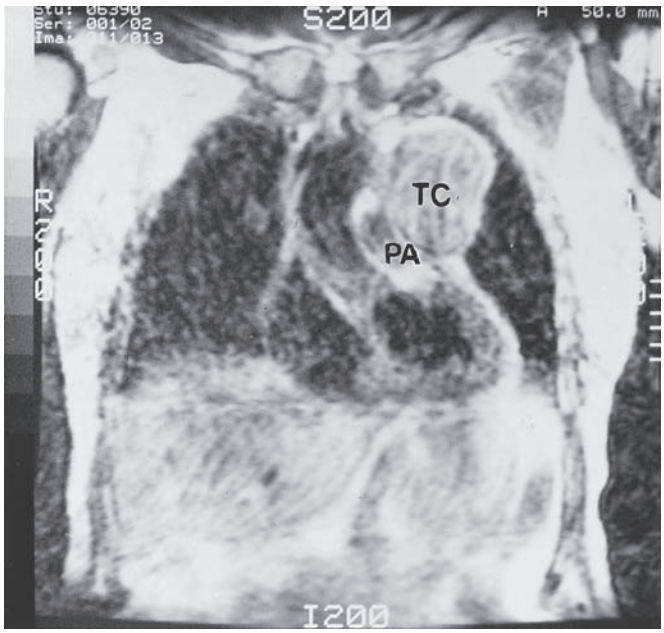

C

Figure 81-6 Equivalent axial-enhanced CT (**A**) and axial MRI (**B**) images of an aortopulmonary window mass that appears to compress if not invade the left pulmonary artery (LPA). Coronal MR image (**C**) of the same lesion demonstrating an intact tissue plane separating the benign thymic cyst (TC) from the pulmonary artery (PA).

aortopulmonary window (Fig. 81-6).[61] Congenital cysts are typically unilocular and contain clear fluid and an imperceptibly thin wall. Multilocular thymic cysts are usually acquired lesions. Plain radiographs do not differentiate thymic cysts from other nonlobulated thymic masses, therefore CT and MRI are employed for diagnosis. Both CT and MRI demonstrate clear tissue planes separating the cyst from other vital structures (Figs. 81-5 and 81-6). If hemorrhage or infection occurs, the cyst may show high signal intensity. In older patients, benign cysts may degenerate and present as a complex, thickened cystic mass with calcified walls that contain heterogeneous fluid (Fig. 81-5). Such lesions are easily confused with a mediastinal teratoma. Multiloculated thymic cysts can occur in association with thymic neoplasms, including thymoma and thymic carcinoma. Complete thymic excision can be accomplished through sternotomy, thoracotomy, VATS, or robotically.[33,34,51–53]

PERICARDIAL CYSTS

Pericardial diverticula and pericardial cysts represent slightly different stages of a lesion that has a common embryogenesis. When a communication exists between the pericardial sac and the extrapericardial fluid collection, the lesion is a diverticulum. Absence of communication defines a pericardial cyst.[62] Both diverticula and cysts derive from the ventral recess of the pericardial celom, rather than from the pericardial lacunae. The discovery that a diverticulum-like structure in the ventral recess of the pericardial celom occurred during development of the pericardium at the site where so many of these lesions were found led to speculation as to their possible relationship. Persistence of the recess results in formation of a diverticulum, while constriction of the proximal part of the persistent recess accounts for either a diverticulum with a narrow neck or a cyst in communication with the pericardial cavity. If the proximal portion of the recess is completely pinched off, an isolated pericardial cyst occurs in the cardiophrenic angle.

Pericardial cysts are simple, smooth-walled cystic lesions (Fig. 81-7) that are commonly located at the lateral basal edge of the pericardium, where it fuses with the diaphragm at the right cardiophrenic angle.[63] They can be mistaken for foramen of Morgagni hernias or prominent pericardial fat pads. They can be differentiated from more solid mediastinal tumors by CT or MRI. Pericardial cysts characteristically contain clear, low-density serous fluid. The appearance of these thin-walled, translucent cysts containing crystal-clear fluid gave rise to the term "spring water cysts."[62] They have no malignant potential and rarely get infected. Potential complications include hemorrhage or spontaneous rupture. Needle aspiration is

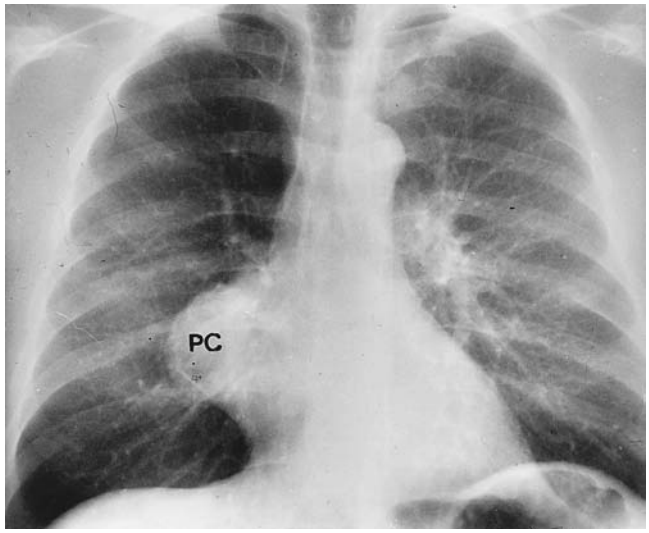

Figure 81-7 Frontal radiograph of a mediastinal mass, isodense with and inseparable from the right heart border. Thoracoscopy showed this to be a broadly based pericardial cyst (PC).

often followed by reaccumulation of fluid, and is not generally recommended. Surgery for pericardial cysts or diverticula is not indicated in the majority of cases because these lesions are always benign and most are asymptomatic. Resection should be reserved for cysts that cause symptoms (hemodynamic compromise, arrhythmia, chest discomfort, substernal pain, atelectasis) or for those demonstrating significant enlargement over time.[63] The operative approach, whether endoscopic or open is dependent upon the location, size, and proximity of the cyst to vital structures. Most often, a right VATS approach is successful in excising the cyst. In most cases, standard two or three incision technique is utilized. Because pericardial cysts often overlie the right phrenic nerve, an unroofing procedure or subtotal resection is acceptable therapy if total excision would jeopardize diaphragmatic function.

THORACIC DUCT CYSTS

Lymphatic channels develop from the lateral plate mesoderm, either as outgrowths of the venous system or by the fusion of mesenchymal clefts into vessels. The lymphatic sacs, which develop by the second month of gestation, are connected by these primitive lymphatic channels. It is these channels that unite the jugular lymph sacs to the cisterna chyli to form the thoracic duct. A congenital weakening of the thoracic duct wall is postulated to be responsible for some thoracic duct cysts.[64] These cysts are exceedingly rare; less than 40 cases have been reported in the literature. Histologically, they are similar to the thoracic duct, with the presence of occasional endothelial cells lining the cyst. They occur anywhere along the course of the duct from the cisterna chyli to the supraclavicular area.[65–67] Age at detection varies widely, and up to half of all patients are asymptomatic. Symptoms arise from compression of adjacent structures resulting in dyspnea, cough, chest pain, dysphonia, or dysphagia.[67–69] Plain films may demonstrate a middle or posterior mediastinal mass, with CT demonstrating a smooth, homogeneous cystic mass (Fig. 81-8).[12] MRI is superior to CT for evaluation, permitting superior delineation of the cyst boundaries (Fig. 81-9). As thoracic duct cysts can contain varying degrees of lipids and proteins, their MRI characteristics may vary accordingly. Contiguity with the thoracic duct and dilation of the thoracic duct aid the radiologist in making the correct diagnosis.[70] Confirmatory diagnosis may be made using lymphangiography or the presence of high triglyceride content in aspirated fluid, but these techniques are not commonly employed.

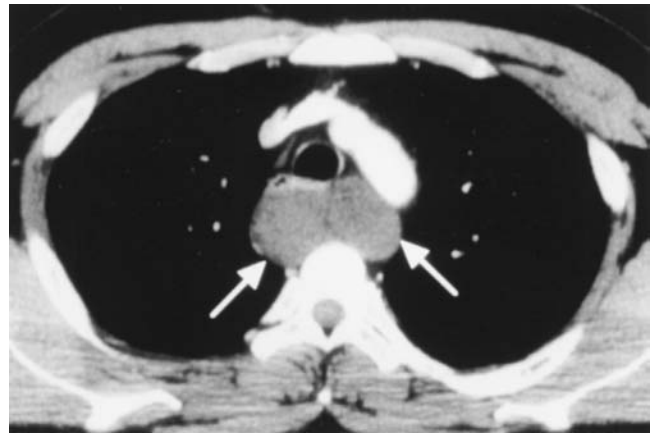

Figure 81-8 Axial contrast-enhanced CT scan of the chest revealed a large cystic mass measuring 3 × 5 × 15 cm *(arrows)* in the posterior mediastinum, displacing the esophagus and trachea anteriorly. *(Reproduced with permission from Chen F, Bando T, et al. Mediastinal Thoracic Duct Cyst. Chest. 1999;115(2):584–584.)*

Endobronchial ultrasound with transbronchial needle aspiration can also lead to the correct diagnosis.[71] Small cysts are generally observed whereas symptomatic and larger cysts should be resected. Successful surgical management is contingent upon appropriate control of both

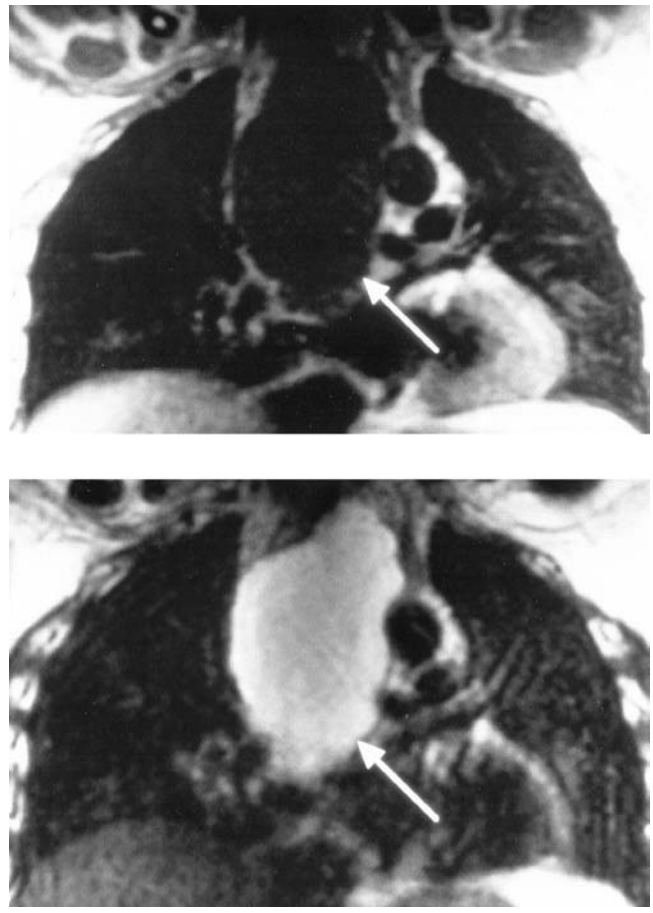

Figure 81-9 MRI scan. Top: Coronal T1-weighted imaging showing a low-intensity mass with a well-circumscribed margin *(arrow)*. Bottom: Coronal T2-weighted imaging showed a high-intensity mass *(arrow)*. *(Reproduced with permission from Chen F, Bando T, et al. Mediastinal Thoracic Duct Cyst. Chest. 1999;115(2):584–584.)*

afferent and efferent thoracic duct pedicles to avoid postoperative chylothorax. Excision can be accomplished through thoracotomy or VATS with application of clips or energy devices that fuse the vessel walls to control the afferent and efferent lymphatic channels.[65,71,72]

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CHAPTER 82

Benign and Malignant Neoplasms of the Mediastinum

Bryan M. Burt
Joseph B. Shrager

INTRODUCTION

Primary lesions of the mediastinum are less common than lesions that secondarily involve the mediastinum. Overall, the majority of masses discovered in the mediastinum will be found to be metastases from a primary lung cancer. Neoplasms that arise primarily in the mediastinum, however, are often encountered in the clinic and are represented by a variety of lesions. This chapter first reviews the anatomy of the mediastinum and then focuses on the benign and malignant neoplasms that arise within each of the anatomic regions of the mediastinum. Covered elsewhere in this textbook (see Chapter 80) are nonneoplastic disorders of the mediastinum that include pneumomediastinum, acute mediastinitis, chronic mediastinitis, and other miscellaneous disorders. Likewise, congenital lesions of the mediastinum, such as bronchogenic, enterogenous, neurogenic, thymic, pericardial, and thoracic duct cysts, are also covered elsewhere (see Chapter 81).

ANATOMY OF THE MEDIASTINUM

The mediastinum comprises an anatomic space located between the thoracic inlet and the diaphragm, and bordered on the left and right sides by the pleural cavities. This central anatomic location houses or borders vital structures of almost every major organ system including the heart and great vessels of the circulatory system, the esophagus, and major airways of the aerodigestive tract, the thymus of the immune system, and important nerves such as the phrenic and vagus nerves. Further, various endocrine organs may project into it, distant malignancies may metastasize to it, and infectious processes can manifest themselves within it.

The mediastinum is compartmentalized based upon the borders of anatomic structures as seen on a lateral chest radiograph (Fig. 82-1). We believe that the most anatomically appropriate and clinically useful model of the mediastinum is the three-compartment model.[1] The three-compartment scheme divides the mediastinum into anterior, middle, and posterior compartments. Here, the anterior mediastinum extends from the thoracic inlet superiorly to the diaphragm inferiorly and is bounded anteriorly by the posterior table of the sternum, and posteriorly by the anterior pericardium and the aorta, innominate vein, and brachiocephalic vessels. The content of the anterior compartment includes the thymus, variable amounts of fat and lymphatic tissues, and the internal mammary arteries and veins. The middle compartment of the mediastinum is bounded anteriorly by the pericardium and posteriorly by the pericardium and posterior wall of the trachea, extending only as high as the pericardial reflection. The middle mediastinum contains the heart, pericardium, superior and inferior vena cava, ascending and transverse aorta, trachea and mainstem bronchi, and lymphatic tissues. The posterior mediastinum extends from the thoracic inlet to the diaphragm, and in this "three-compartment scheme," lies posterior to the posterior pericardium and airway. It includes the descending aorta, thoracic duct, esophagus, vagus nerves, and lymph nodes, as well as structures emerging from the spinal canal such as intercostal nerves.

One of the main advantages of categorizing the anatomy of the mediastinum is the ability it confers to generate a differential diagnosis for a mediastinal mass based on the structures naturally contained within the compartment in which it arises (Table 82-1). Such a classification scheme allows a clinician to proceed systematically to determine the appropriate diagnostic or therapeutic approach depending on the differential diagnosis.

EPIDEMIOLOGY AND INCIDENCE

The incidence and type of primary mediastinal neoplasms varies with patient age. In combined series totaling 3017 mostly adult patients, the incidence of mediastinal masses in decreasing frequency were thymomas and thymic cysts (26.5%), neurogenic tumors (20.2%), germ cell tumors (GCTs) (13.8%), lymphomas (12.7%), foregut cysts (10.3%), and pleuropericardial cysts (6.6%). In children, combined series totaling 718 patients demonstrated that neurogenic tumors were most common (41.6%), followed by GCTs (13.5%), foregut cysts (13.4%), lymphomas (13.4%), angiomas and lymphangiomas (6.1%), and thymic tumors or cysts (4.9%).[2] In general, the incidence of anterior lesions is higher in adults, and posterior lesions predominate in children. Further, the incidence of malignancy differs among primary mediastinal masses arising in each of the different compartments. In one of the largest series, Davis and colleagues demonstrated that among patients with mediastinal masses, malignancy was found in 59% of those in the anterior mediastinum, 29% of those in the middle mediastinum, and 16% of those in the posterior mediastinum.[3]

As discussed below, mediastinal masses are often incidentally detected on imaging studies obtained for other reasons. An estimate of the frequency of "incidental" mediastinal masses has been provided by a large lung cancer screening study. In 9263 individuals at high risk for lung cancer who underwent a computed tomography (CT) screening examination, a mediastinal mass was found in 71 patients (0.77%). The majority of these incidental masses were thymic and most were treated successfully with a conservative approach.[4]

SIGNS AND SYMPTOMS

Signs and symptoms of mediastinal tumors can vary widely at presentation and usually offer only nonspecific clues to the nature of the underlying disease process. While over 60% of patients do present with symptoms, it is also quite common for an asymptomatic mass to be detected on a routine screening examination. Most asymptomatic patients with a mediastinal mass will have a benign lesion, while the majority of patients that present with symptoms have an underlying malignant process. In Davis' series of 400 patients with mediastinal masses, 83% of the lesions found on routine chest radiographs were benign, whereas 57% of lesions in symptomatic patients were malignant.[3]

The presenting symptoms of a mediastinal mass vary widely and are influenced by anatomic location and the presence of malignant invasion or mass effect. Dyspnea or cough may result from airway invasion or abutment, tamponade, or the presence of a pleural effusion. Dysphagia is seen with esophageal compression, and chest pain may represent chest wall or neural invasion or abutment. Invasion of the airway may result in hemoptysis, invasion of the recurrent laryngeal nerve may present as hoarseness, and invasion of the superior vena cava can present with facial swelling and superior vena cava syndrome. Constitutional symptoms such as fever

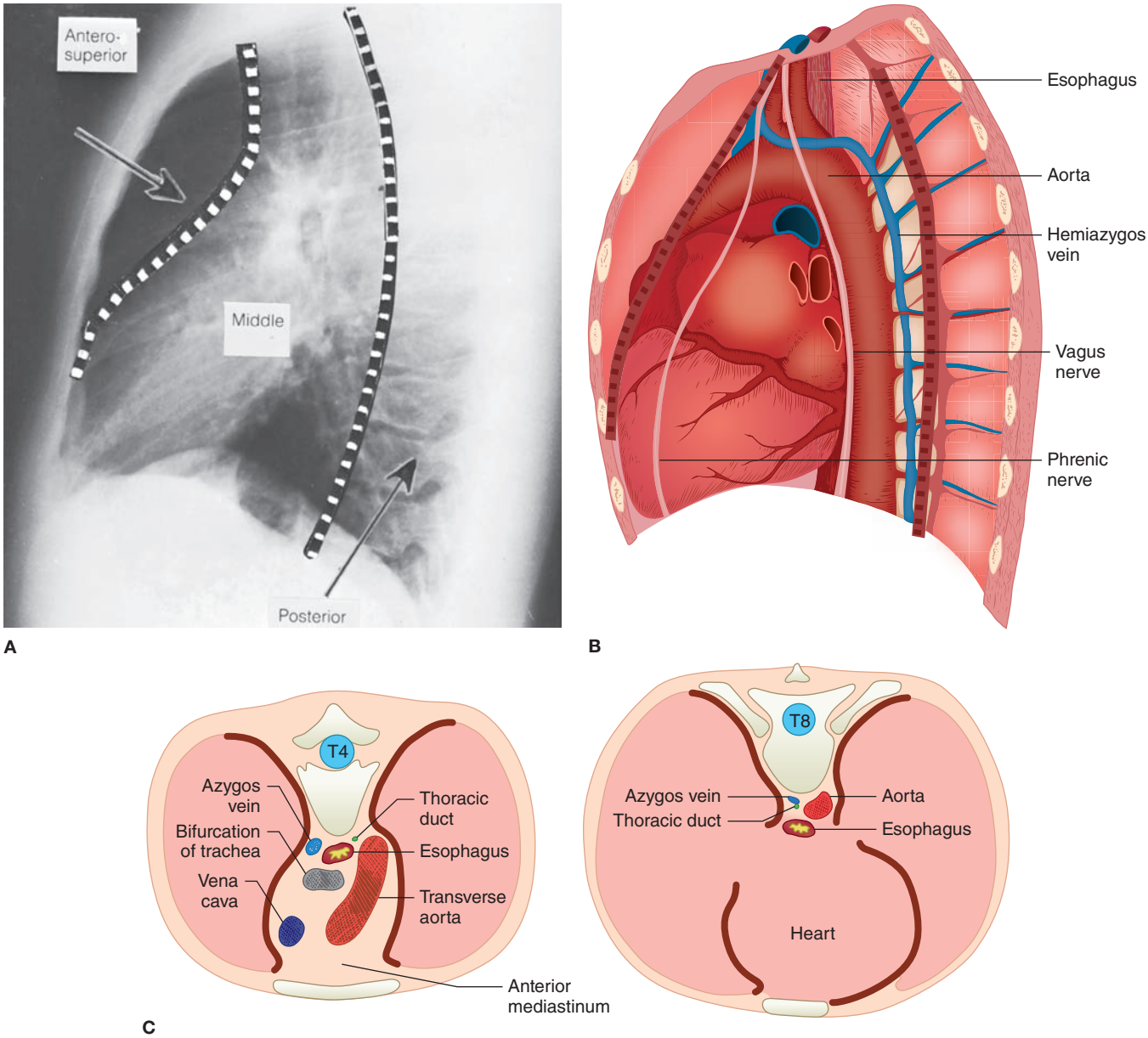


Figure 82-1 Three-compartment model of the mediastinum. **A.** Lateral radiograph of the chest. **B.** Schematic representation of the contents of the three compartments of the mediastinum. **C.** Cross sections of the thorax at T4 (left) and T8 (right) to show relative positions of mediastinal structures.

and night sweats are often associated with mediastinal lymphoma, and myasthenic symptoms may be suggestive of thymoma.

ANTERIOR MEDIASTINAL NEOPLASMS

Neoplasms of the anterior mediastinum are discussed below.

■ EVALUATION OF THE ANTERIOR MEDIASTINAL MASS

In a patient with an anterior mediastinal mass, it is often possible to make a strong provisional diagnosis based upon clinical evaluation and imaging data.[5] Whereas specific workup for common anterior mediastinal mass lesions is described in the following sections, some general principles are reviewed here.

History and Examination

In an individual younger than 40 years, lymphoma is the most likely diagnosis and the presence of International Working Formulation (IWF) group B symptoms or palpable lymphadenopathy further increases the level of suspicion. In contrast to lymphoma, thymic neoplasms are very uncommon before the fourth decade of life. The presence of a paraneoplastic syndrome associated with an anterior mediastinal mass essentially clinches the diagnosis of thymoma. The majority of GCTs (benign or malignant) are diagnosed in the second or third decade of life. Whereas patients with a thymoma often have an indolent presentation, patients with a lymphoma or a malignant GCT often have a rapid onset of symptoms. Workup must include examination of the testes to rule out a testicular primary GCT.

Serum Studies

Autoantibodies to the acetylcholine receptor (anti-AChR) should be measured as their presence is virtually diagnostic of myasthenia gravis, even if the patient is without obvious symptoms. Characteristic serum tumor markers such as beta-human chorionic gonadotropin (β-HCG) and alpha-fetoprotein (AFP) are elaborated by most malignant GCTs but not by benign GCTs.[6] Elevated

TABLE 82-1 Structures and Primary Neoplasms in the Three-Compartment Model of the Mediastinum

Structures	Common Lesions	Rare Lesions
Anterior compartment		
Thymus	Thymomas	Thymic carcinoma; benign thymic tumors
Fat and lymphatics	Lymphomas	Vascular lesions
Internal mammary vessels	Germ cell tumors	Mesenchymal tumors
Thyroid (occasional)		Endocrine tumors (e.g., ectopic parathyroid, goiter)
		Castleman's disease
Middle compartment		
Heart	Foregut cysts	Pleural and pericardial cysts
Pericardium	Lymphoma	Castleman disease
Aorta		
Superior and inferior vena cava		
Trachea and main bronchi		
Lymph nodes		
Posterior compartment		
Descending aorta	Nerve sheath tumors	Vascular tumors
Esophagus	Neurogenic tumors	Mesenchymal tumors
Vagus nerves		Lymphatic lesions
Thoracic duct		Neurenteric cysts
Sympathetic chain		
Lymph nodes		

serum LDH is suggestive of lymphoma. Evidence of hypo- or hyperthyroidism, as measured by thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4), suggests mediastinal goiter, though goiter is not invariably associated with abnormal hormone production.

Imaging Studies

CT provides valuable data about the anatomic location of the tumor, its physical characteristics (fatty, solid, or cystic) and degree of invasiveness. Occasionally, magnetic resonance imaging (MRI) provides useful additional information concerning obliteration of normal tissue planes and vascular invasion. Although imaging is most often not diagnostic of the specific type of tumor, some imaging features can be pathognomonic. For example, the finding of a well-encapsulated lesion in the anterior mediastinum containing several tissue elements – calcium, fat, fluid – is essentially diagnostic of a mature teratoma.

Need for Biopsy

The decision whether to perform a biopsy of an anterior mediastinal mass is not simple. Routine biopsy should not be endorsed, not only because of the unnecessary morbidity and costs associated with the procedure, but also because of the potential risk of tumor spread. Well-encapsulated lesions believed not to be lymphoma are often resected for both diagnosis and treatment, without a preceding biopsy. Conversely, for locally invasive or frankly unresectable anterior mediastinal masses, a biopsy should often be performed as such lesions may represent lymphoma, aggressive thymomas that could benefit from neoadjuvant treatment, malignant GCTs, or other rare diseases.

Once a clinical diagnosis of thymoma is made, the goal is to proceed directly to resection without preliminary biopsy, as these tumors have a predilection for local recurrence once the thymic capsule has been violated. When palpable peripheral nodes are present, the diagnosis of lymphoma is often most easily obtained by excision of one of them. Patients with suspected lymphoma and an isolated anterior mediastinal mass should undergo either a CT-guided core needle biopsy or a Chamberlain procedure (anterior mediastinotomy) for diagnosis, depending upon the pathologist's level of comfort in classifying lymphoma on the basis of specimen size at one's institution. Resection of lymphoma is not indicated and can almost always be avoided by performing a diagnostic biopsy when lymphoma is suspected. Surgical extirpation is the mainstay of treatment for mature GCTs, and biopsy is not indicated for these lesions if they have the characteristic imaging characteristics. Malignant GCTs, on the other hand, are treated primarily with chemotherapy, radiotherapy, or both. In situations where these lesions are suspected but tumor markers (AFP and β-HCG) are not markedly elevated, biopsy should be performed.

■ THYMOMA

Clinical assessment and management of thymoma are discussed below.

Presentation

The age distribution of patients with a thymoma is represented by a broad peak between approximately 35 and 70 years with a median age of about 54 years.[7] The ratio of men to women with this disease is about equal. Approximately one-third of patients with a thymoma will not report significant symptoms and an additional one-third will report symptoms of cough, dyspnea, or chest pain reflective of compression or invasion of adjacent structures. Patients may also present with symptoms of an associated paraneoplastic syndrome. Forty to 45% of patients with a thymoma will present with myasthenia gravis and, conversely, 5% to 15% of patients with myasthenia gravis will be found to have a thymoma.[8,9] Notably, myasthenia gravis can develop some time after diagnosis of thymoma, and occasionally following resection, highlighting the necessity of complete resection of both the thymoma and the entire thymus gland. Thymomas may also be associated with pure red cell aplasia, agammaglobulinemia, systemic lupus erythematosus, and other autoimmune disorders.

Diagnosis

A clinical diagnosis of thymoma is often sufficient to proceed to resection without biopsy. The presence of a paraneoplastic syndrome associated with an anterior mediastinal mass essentially clinches the diagnosis of thymoma. Autoantibodies to the acetylcholine (Ach) receptor should be measured, and their presence is virtually diagnostic of myasthenia gravis and also clinches the diagnosis of thymoma. Interestingly, Ach receptor antibodies are demonstrated in approximately 60% of patients who have thymoma without neurologic symptoms.[10] It is not necessary to obtain a preoperative tissue biopsy for a small, resectable anterior mediastinal tumor whose radiographic features are typical of thymoma in an asymptomatic patient. Although there are no pathognomonic imaging features that differentiate thymoma from several other mediastinal tumors, in a patient without B-symptoms to suggest lymphoma, the diagnosis of thymoma is strongly suggested by a CT scan demonstrating a well-circumscribed, solid anterior mediastinal mass without

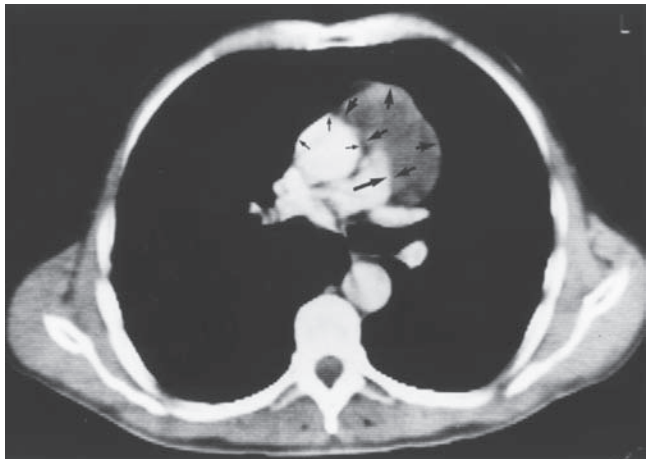


Figure 82-2 Thymoma. Axial section from a CT scan demonstrates a 4-cm mass abutting the thoracic aorta without any evidence of invasion *(arrows)*.

the low-density areas that would suggest the cystic and fatty components of a teratoma (Fig. 82-2). Most thymomas are solid tumors, but up to a third may have components that are necrotic, hemorrhagic, or cystic. Several small studies have investigated the utility of PET in evaluation of thymoma and have suggested that FDG uptake is greater in thymoma than in thymic hyperplasia, and that thymic carcinomas demonstrate the highest FDG avidity.[11] However, PET is not required to stage a thymoma preoperatively when it appears noninvasive/nonmalignant on CT.

Once a diagnosis of thymoma is suggested, the goal is to proceed directly to resection without preliminary biopsy, as these tumors have a predilection for local recurrence once the capsule has been violated. A definitive tissue diagnosis is needed primarily when a presumed thymoma is so advanced that it would be best treated either nonoperatively or with neoadjuvant chemotherapy or chemoradiotherapy, or in instances where there is a strong possibility of lymphoma. If required, the pathologic diagnosis of thymoma can usually be achieved by image-guided core needle biopsy, or if that fails, through open surgical biopsy. The success rate of needle biopsy in establishing the diagnosis of thymoma is approximately 60% and the success rate of surgical biopsy is approximately 90%.[12] In our opinion, video-assisted thoracoscopic surgical (VATS) biopsy of an anterior mediastinal mass in which thymoma is in the differential should be assiduously avoided, due to the great potential of spread into the pleural space. If core needle biopsy fails and a diagnosis is required, a Chamberlain procedure (anterior mediastinotomy) should be performed.

All patients with suspected thymoma should be evaluated for myasthenia gravis. This evaluation usually begins with a careful assessment for the presence of ocular, bulbar, and limb muscle weakness. The diagnosis of myasthenia gravis in a patient with a characteristic history and physical examination requires two positive confirmatory tests among pharmacologic (Tensilon test), serologic (anti-AChR antibodies), and electrodiagnostic (EMG) studies. If there is any suggestion of myasthenia gravis on initial presentation, the patient should undergo preoperative evaluation by a neurologist. Medical optimization prior to surgery using some combination of cholinesterase inhibitors, intravenous immunoglobulin, plasmapheresis, and occasionally steroids, can help avoid respiratory failure in the perioperative period. Other paraneoplastic syndromes are also associated with thymoma, including hypogammaglobulinemia in 10% of patients, and pure red cell aplasia in 5% of patients.

TABLE 82-2 Staging of Thymic Malignancies

Stage	Description	10-y Survival (%)
I	Encapsulated tumors without gross or microscopic invasion	90 (75–100)
II	Transcapsular invasion	75 (42–100)
IIA	Microscopic invasion	
IIB	Macroscopic invasion	
III	Macroscopic invasion of surrounding tissues (lung, pericardium, vena cava, or aorta)	56 (26–84)
IVA	Disseminated disease within the chest	38 (22–47)
IVB	Distant metastases	Unknown

Source: Data from Detterbeck FC. Evaluation and treatment of stage I and II thymoma. J Thorac Oncol. 2010;5(10 Suppl 4):S318–S322.

Staging

The most widely utilized classification scheme for thymoma was proposed by Masaoka in 1981 and is based on the local invasiveness of the tumor (Table 82-2).[13] The Masaoka classification system has prognostic value[14] and permits stratification for adjuvant therapy. One difficulty with this system is that it is based upon the findings at the time of surgical resection, thus precluding its use for triaging some patients to neoadjuvant therapy.

Thymomas are also classified histologically. A thymoma is composed of a mixture of thymic epithelial cells with bland features as well as lymphocytes in various stages of development. The neoplastic cell of origin is believed to be the thymic epithelial cell and not the lymphocyte,[15] and thymomas appear histologically benign even when they are invasive. In 1985, Müller-Hermelink proposed a novel histologic classification system to separate all thymomas into categories of cortical, medullary, or mixed, based on the histologic appearance of the thymic epithelial cells.[16] Cortical thymomas are composed of large, round, or polygonal epithelial cells and medullary thymomas contain smaller, spindle cell–shaped epithelial cells with irregular nuclei. This histologic classification system was found to reliably predict tumor behavior and prognosis, with medullary thymomas behaving in an essentially benign fashion and cortical thymomas more frequently demonstrating evidence of invasive and malignant disease.[17] Later studies have demonstrated that both the Masaoka staging and Müller-Hermelink grading systems are strong and independent prognostic indicators of both overall as well as disease-free survival.[14,18,19]

More recently, the World Health Organization (WHO) proposed a histologic classification system (resembling the Müller-Hermelink system) that has become the histologic grading system of choice in the current era and is useful to distinguish between thymoma, thymic carcinoma, and thymic carcinoids (Table 82-3).[20] It is now accepted that the Masaoka staging criteria used in combination with the WHO grading criteria provide the most accurate prognostic information for survival and recurrence in thymoma.[21,22]

Treatment

Surgical resection is the mainstay of treatment of Masaoka stage I–III thymoma while the treatment of stage IVa thymoma is controversial. Resection of even a small, stage I thymoma without myasthenia gravis should include removal of the entire thymus en bloc along with the tumor because (1) myasthenia gravis can potentially develop postoperatively (and total thymectomy is an appropriate treatment for myasthenia gravis), and (2) a second focus of tumor within the thymus is occasionally found. The gold standard surgical approach to thymoma remains median sternotomy but minimally

TABLE 82-3 World Health Organization (WHO) Histologic Classification System

Type	Description
A	Tumor in which foci having features of type A thymoma are admixed with foci rich in lymphocytes
B1	Tumor resembles normal functional thymus; combines large expanses having an appearance practically indistinguishable from that of normal thymic cortex with areas resembling thymic medulla
B2	Tumor in which neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; perivascular spaces are common and sometimes very prominent; a perivascular arrangement of tumor cells resulting in a palisading effect may be seen
B3	Thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia; they are admixed with a mild component of lymphocytes, resulting in a sheet-like growth of the neoplastic epithelial cells
C	Thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of the other organs; type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells

invasive approaches including VATS and robotic techniques are likely equally effective for smaller tumors in experienced hands. Certainly if there is suspicion of invasion into adjacent structures, sternotomy is the preferred approach as it is critical that the involved portions of these structures are resected en bloc with the thymus gland and tumor. This can require resection of lung, pericardium, innominate vein, superior vena cava, phrenic nerve, and even aorta.

Stage I thymomas are treated adequately with complete resection alone. Although in the past adjuvant radiotherapy was frequently administered to patients with stage II thymoma, accumulated data suggest that adjuvant radiotherapy is of little additional benefit following complete resection.[23–25] Thymoma is a radiosensitive tumor however, and for patients who have incomplete resection, postoperative radiotherapy is recommended. For patients with advanced disease (stage III or IV thymoma), chemotherapy is recommended and is often followed by radiation for patients with incompletely resected disease. For thymoma that is initially considered unresectable, induction chemotherapy followed by surgical resection can result in favorable rates of overall and disease-free survival.[26,27] Further, surgical resection plays an important role in the management of recurrences and complete resection of a recurrence can result in improved overall survival.[28]

Outcome

Although thymomas are generally indolent tumors, they should be considered a malignant neoplasm as they have the ability to metastasize to the pleura, pericardium, and (less commonly) distant sites. One study reported that 4% of 207 patients evaluated for surgical resection of a thymoma had lymph node or distant metastases at presentation, and another 16% developed nodal or distant metastases at some point in their course.[29] Others have shown that distant metastases can occur with any stage or histology.[30,31] Detterbeck reviewed overall survival in compiled surgical series of at least 100 patients (2437 patients total) and demonstrated favorable 10-year survival rates of approximately 90% and 70% for stage I and II, and 55% and 35% for stage III and IVa thymoma, respectively.[12] Completeness of resection is the most important predictor of recurrence and survival; significantly better survival is demonstrated when resection is complete in all large studies examining this issue.

Locoregional recurrence is far more common than distant recurrence, and about half of all local recurrences involve the pleural space or the lung. The average recurrence rate for stage I tumors is 3% but increases to 11% and 30% for stage II and III tumors, respectively.[7] The relatively indolent nature of a thymoma is reflected by an average time to recurrence of 5 years, with rare recurrences seen as far out as 20 years. The presence of myasthenia gravis is no longer considered a negative prognostic factor, as it was in older studies, and over 30% of patients with myasthenia and thymoma ultimately achieve a complete remission of the myasthenia following thymectomy.[32] Similarly, approximately one-third of patients with associated red cell aplasia experience improvement following thymectomy. In contrast, hypogammaglobulinemia associated with thymoma generally does not respond to thymectomy.

■ THYMIC CARCINOMA

Clinical assessment and management of thymic carcinoma are discussed below.

Presentation

Thymic carcinomas (WHO type C) are highly aggressive neoplasms of thymic epithelial origin and are very different from thymomas (WHO types A, AB, and B). Thymic carcinomas are rare, constituting approximately 10% of all thymic neoplasms.[28] They can occur at any age but are most frequently observed in persons between 30 and 60 years of age. The majority of patients with thymic carcinoma present with symptoms of local invasion or compression such as cough, chest pain, or superior vena cava syndrome. Pericardial and/or pleural effusions are often seen. Thymic carcinoma is typically not associated with myasthenia gravis. Unlike thymomas, thymic carcinomas frequently metastasize to lymph nodes and distant sites. Eighty percent of patients have local invasion of contiguous mediastinal structures at the time of presentation, and 40% of cases have metastatic spread to bones, lung, pleura, liver, or lymph nodes.[33] Over half of the patients will present with locally advanced, although potentially resectable, disease.[34,35]

Diagnosis

Thymic carcinomas can be distinguished from thymomas based on their malignant histologic features and different immunohistochemical and genetic characteristics. Imaging studies often reveal an invasive presentation, and for this reason, percutaneous needle biopsy should generally be undertaken.

Staging

The Masaoka staging system and WHO histologic classification system are used to stage thymic carcinoma. In the WHO system, thymic carcinomas are type C lesions. These tumors are distinct from thymoma and should not be considered in the same light as a thymoma with local invasion. Histologically, thymic carcinoma contains a number of different cell types, but they are unified by their unequivocal malignant appearance on light microscopy. Division of patients into those with low-grade histology and those with high-grade histology has prognostic significance. The median survival for patients with low-grade histology (squamous, mucoepidermoid, and basiloid thymic carcinomas) is 29 months, as compared to 11 months for patients with high-grade histology (sarcomatoid and clear cell thymic carcinoma).[36]

Treatment

While there is no standard-of-care approach to patients with thymic carcinoma, a multidisciplinary strategy is recommended. The prevailing practice is that patients with stage I–III and some IVa patients should be treated with some combination of surgical resection plus chemotherapy and/or radiotherapy.[37] Although thymic carcinomas generally respond poorly to chemotherapy, carboplatin and paclitaxel are recommended because this combination has shown the highest response rates in clinical trials. For the rare thymic carcinoma patients with clearly resectable disease, surgery is considered the primary therapeutic modality. For those with disease thought to be initially unresectable or disease that appears clearly to be invading one or more surrounding organs or major vascular structures, neoadjuvant chemotherapy and/or radiation may improve operability and permit subsequent resection.[36,38,39]

Outcome

The prognosis for patients with thymic carcinoma is much worse than for patients with thymoma, with 5-year overall survival rates for thymic carcinomas in the range of 30% to 50%.[35,40,41] A more recent clinicopathologic study of 65 cases of primary thymic carcinoma, however, reported a more favorable 5-year survival rate of 66%. In this study, 63% of the patients received additional therapy in the form of chemotherapy or radiation.[34] Similar to thymoma, patients with completely resected thymic carcinomas have longer overall and progression-free survival rates than those who undergo incomplete resection or are unresectable. In a recent series of 60 patients with thymic carcinoma (40 treated surgically), completely resected lesions and early Masaoka stages are the most important factors associated with successful disease control and long-term survival. Five-year survival of 85% was obtained after complete resection, compared with 29% in those with incomplete resection.[42] In another series of 16 patients, a multimodality approach that included surgery resulted in complete resection in 88% of the patients and a mean survival of 4.2 years for the entire group.[43]

■ OTHER THYMIC NEOPLASMS

Clinical assessment and management of a variety of other thymic neoplasms are considered below.

Thymic Hyperplasia

Thymic hyperplasia is a term used to describe either a histologically normal thymus that is enlarged for the patient's age, or a thymus that histologically shows cellular hyperplasia, which is also generally associated with gross enlargement of the gland. This condition can present as a spectrum of disease ranging from respiratory compromise due to impingement on the airway (almost always in the pediatric population) to the more common situation of an incidental finding on an unrelated imaging study. Many of the thymus glands removed from patients with myasthenia gravis demonstrate "true thymic hyperplasia" (cellular hyperplasia), and this is thought to contribute to the pathogenesis of myasthenia gravis. In addition to myasthenia gravis, thymic hyperplasia can be seen following severe or chronic illness, the so-called "thymic rebound." Steroid use will also generally lead to substantial thymic hyperplasia. Practically speaking, when a diffusely enlarged thymus without a discrete mass is discovered in an otherwise asymptomatic patient, this can be followed expectantly, as these glands have a negligible incidence of harboring significant thymic disease.[44]

Thymolipoma

Thymolipomas are distinguished from simple mediastinal lipomas by their location within the thymic capsule. Histologically, these neoplasms composed of mature adipocytes as well as normal thymic components.[45] Thymolipomas, like thymomas, can be associated with thymic paraneoplastic syndromes such as red cell aplasia, hypogammaglobulinemia, and aplastic anemia. These lesions can grow to significant size and result in compressive and obstructive symptoms. The treatment of thyolipomas is surgical excision.

Thymic Carcinoid

Thymic carcinoids are very rare neoplasms of the thymus that are classified as neuroendocrine carcinomas. They have a strong association with endocrinopathies such as multiple endocrine neoplasia type I. Unlike other carcinoids, they rarely present with carcinoid syndrome, but many do secrete ACTH resulting in Cushing syndrome. Thymic carcinoids tend to be very aggressive tumors. Upon presentation, the majority of thymic carcinoids are locally invasive and approximately half of all patients will have metastatic disease.[46] Surgery is the therapy of choice for resectable neuroendocrine carcinomas of the thymus and should include aggressive local resection. The prognosis is poor despite aggressive therapy, and most patients present with local recurrence or metastases within 5 years of surgery and will die within 10 years.[47]

■ GERM CELL TUMORS

GCTs comprise a group of neoplasms that arise from gonadal tissue. The anterior mediastinum is the most common location for occurrence of extragonadal GCTs. GCTs account for 15% of all anterior mediastinal masses in adults (85% of which are benign mature GCTs) and 25% of anterior mediastinal masses in children (essentially all of which are benign).[48] GCTs typically occur in young adults in the second to fourth decades of life with no gender predilection.

While previously thought to be metastatic from a gonadal primary, it is now accepted that these neoplasms are primary mediastinal tumors. The precise origin of the germ cells that form these tumors in sites heterotopic to the gonads is still not completely clear, but this may result from aberrant migration of germ cells during embryonic development or as a part of normal embryogenesis. Because primordial germ cells are undifferentiated cells from which a variety of different tumors can arise, there have been numerous overlapping and sometimes confusing classification and grading systems proposed for these tumors. Even more confusing for classifying GCTs is that it is common to see two or more GCT histologies arising from within a single mass. Based on the need for standard classification, investigators from the Armed Forces Institute of Pathology developed a reproducible histologic classification system (Table 82-4) and clinical staging system (Table 82-5) based on review of more than 300 cases.[49]

TABLE 82-4 Classification of Mediastinal Germ Cell Tumors (GCTs)

Mature teratoma
Immature teratoma
Teratomas with malignant component: Type I: with an associated GCT (seminoma, etc.) Type II: with another epithelial malignancy (squamous, adenocarcinoma, etc.) Type III: with sarcomatous component (rhabdomyosarcoma, osteosarcoma, etc.) Type IV: a combination of any of the above
Seminoma
Yolk sac tumor (endodermal sinus tumor)
Embryonal carcinoma
Choriocarcinoma
Combined GCT without teratomatous component

TABLE 82-5 Clinical Staging of Mediastinal Germ Tumors

Stage	Characteristics
I	Well-circumscribed tumor with or without focal adhesions to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures
II	Tumor confined to the mediastinum with macroscopic and/or microscopic evidence of infiltration into adjacent structures (pleura, pericardium, great vessels)
III	Tumor with metastases
IIIA	With metastases to intrathoracic organs (lymph nodes, lung, etc.)
IIIB	With extrathoracic metastases

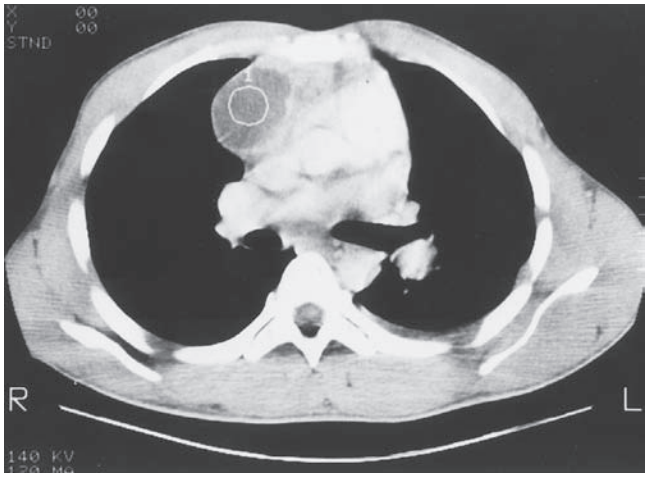


Figure 82-3 Mediastinal seminoma. Axial section from a CT reveals a homogeneous mass within the anterior mediastinum.

Mediastinal GCTs are composed of benign and malignant neoplasms that for descriptive purposes can be simplified into three categories. Benign mediastinal GCTs are composed primarily of benign mediastinal teratomas, which account for 60% of all mediastinal GCTs. Malignant tumors are divided into seminomatous GCTs, which account for 40% of malignant mediastinal GCTs, and nonseminomatous GCTs (NSGCTs) which account for 60% of malignant mediastinal germ tumors. NSGCTs include embryonal cell carcinomas, choriocarcinomas, yolk sac tumors, and malignant teratomas.

Mediastinal Teratomas

Teratomas are defined by the presence of tissue from more than one of the three primitive germ cell layers. Mature (benign) teratomas are composed of well-differentiated elements such as fat, muscle, and cartilage (mesoderm); hair, skin, and teeth (ectoderm); and intestinal tissue (endoderm). Mature teratomas can be symptomatic or asymptomatic upon presentation. Symptoms include chest pain, dyspnea, cough, or fever (if they become infected). Occasionally the tumor may erode into an airway and a patient may cough up hair (trichophytosis) or oily sebum that is pathognomonic of a benign mediastinal teratoma.

CT with contrast is the diagnostic procedure of choice and usually demonstrates a thick-walled cystic mass. Calcification is often present and when intermixed with areas of fat and/or fluid density, the diagnosis is made with a high degree of certainty.[50] Benign teratomas can also be primarily solid, and in these cases the diagnosis is more challenging. Tumor markers such as β-HCG and AFP should be measured and will not be elevated in benign teratoma. Needle biopsy of a mass that is highly suspected to be a benign teratoma based on imaging is not necessary. Such a patient should go directly to surgical resection.

The treatment for benign GCTs is total resection before the development of complications. Even benign teratomas are frequently adherent to adjacent structures such as lung, blood vessels, and pericardium; en bloc resection of involved structures is sometimes required. Radiation and chemotherapy play no therapeutic role, unless concurrent malignant disease is present. Outcome after resection of a benign teratoma is excellent, on the order of 93% 10-year survival.[51] Occasionally, teratomas will contain less well-differentiated tissues and behave more aggressively, resembling malignant teratomas (see below).

Malignant Seminomatous Germ Cell Tumors

Malignant GCTs, both seminomatous and nonseminomatous, are almost exclusively diseases of men. Seminoma usually presents in men during the third or fourth decade of life as a large anterior mediastinal mass, although it rarely occurs in the middle and posterior mediastinum. Most patients are symptomatic upon presentation; symptoms are variable and most commonly include chest pain and dyspnea.[52]

Careful bimanual examination and ultrasound of the testicles should be performed to rule out a testicular primary tumor, and a thorough staging workup should be performed including CT scan of the abdomen along with the chest. Measurement of serum tumor markers is critical to the diagnosis and follow-up of patients with mediastinal seminomas. Patients with mediastinal seminomas will demonstrate mild elevation of β-HCG (<100 mIU/mL), whereas higher levels than this should raise the suspicion of a mixed tumor or a NSGCT.[53] An elevated AFP level excludes the diagnosis of seminomatous tumor and defines the tumor as a NSGCT or mixed GCT. Chest CT is the most useful imaging modality for a seminoma, which typically appears as a large, bulky homogeneous mass that may obscure tissue planes or invade adjacent structures, and is often surrounded by bulky lymphadenopathy (Fig. 82-3). These tumors are frequently FDG-avid and PET may be useful in monitoring response to therapy. A biopsy is usually necessary to secure the diagnosis and percutaneous core needle biopsy is the preferred initial approach, saving open surgical biopsies for cases where percutaneous sampling is inconclusive.

Sixty to 70% of patients with mediastinal seminoma will present with metastatic disease, primarily to intrathoracic organs, although distant metastases can also be found. The treatment of primary mediastinal seminomatous tumors has evolved over the past 20 years from a primarily surgical approach to a chiefly nonsurgical approach. It has become clear that the first line of treatment in all cases of mediastinal seminoma should be chemotherapy, and 5-year survival rates upward 90% are achieved with cisplatin-based chemotherapy regimens.[54,55] As is the case with testicular seminomas, pure mediastinal germ cell seminomas are radiosensitive. Whereas radiotherapy alone may achieve complete remission in only about 65% of patients,[56] the addition of radiotherapy to chemotherapy appears to enhance the benefit of chemotherapy alone. The role of surgical resection in this disease remains controversial. Surgery is generally reserved for patients with residual mediastinal masses following chemotherapy and radiation when residual active disease is a concern (e.g., with persistently elevated or rising markers, or increasing FDG avidity on PET). The benefits of surgical resection in this setting would be to document if there is residual malignant seminomatous tumor (as opposed to necrotic debris) and to completely resect it; in addition, occasional patients are identified who

have a previously unrecognized nonseminomatous malignant component of the tumor.

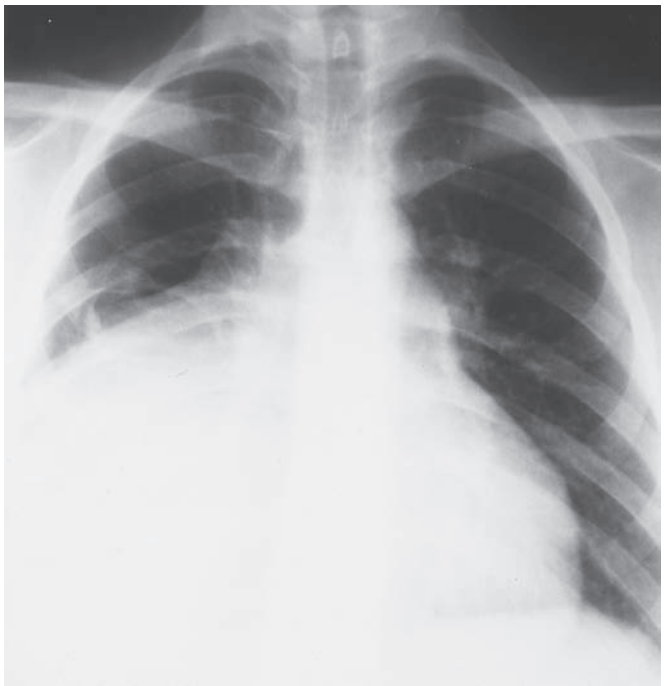
Nonseminomatous Germ Cell Tumors

NSGCTs are malignant tumors that are seen almost exclusively in men and there is a particular propensity for men with Klinefelter syndrome to develop these tumors. A variety of nonseminomatous histologies have been categorized and their incidence is best gathered from the largest series of 229 cases.[49] NSGCTs are composed of teratocarcinoma (41%), endodermal sinus (yolk sac) tumor (35%), choriocarcinoma (7%), embryonal carcinoma (6%), and mixed histologies (11%). Further, non–germ cell components including sarcoma or epithelial carcinoma were found in 58% of teratocarcinomas.

Mediastinal NSGCTs are characterized by rapid local growth and early distant metastases, and patients often present with advanced disease. Most patients will have symptoms caused by compression or invasion of adjacent structures, and constitutional symptoms including weight loss, fever, and weakness are more common in patients with NSGCT compared with pure seminoma. Like seminoma, sites of metastases in NSGCT include the lung, pleura, lymph nodes, and liver; 85% to 95% of patients with an NSGCT will have at least one site of metastases.[57,58]

Workup should include CT of the chest and abdomen and measurement of serum tumor markers. Chest CT will typically reveal a large, irregular anterior mediastinal mass with poorly defined margins and multiple areas of necrosis and hemorrhage (Fig. 82-4). Unlike seminoma, over 90% of patients with NSGCT will have an elevation of either β-HCG (30%–35% of patients) or AFP (80% of patients), and an AFP level greater than 500 ng/mL is essentially diagnostic of NSGCT.[53,59] NSGCTs, especially those with yolk sac histology, are associated with a variety of hematologic malignancies including leukemia, and these occur independently of the chemotherapy used to treat the tumor.[60]

As most patients present with bulky or metastatic disease, surgical resection is not the first line of treatment. Historically, patients with NSGCT had an exceedingly poor prognosis, but this has dramatically improved with the implementation of intensive cisplatin-based chemotherapy protocols. A summary of studies of patients treated with first-line cisplatin-based combination chemotherapy



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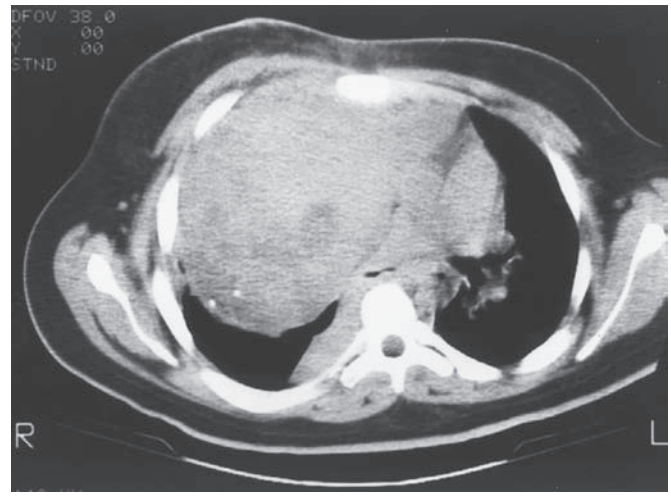

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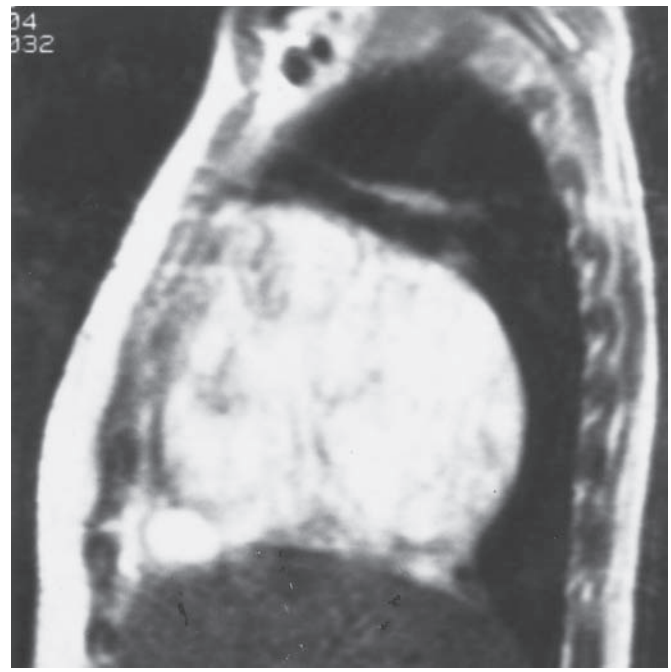


C

Figure 82-4 Nonseminomatous germ cell tumor. A 19-year-old male presented with a 1-month history of fever, heaviness in the chest, and cough. Examination revealed a tall, thin male with dystrophic testes (habitus consistent with Klinefelter syndrome). Serum AFP was 32,000 and β-HCG was 25,000. **A.** PA radiograph of the chest reveals a large mediastinal mass projecting into the right hemithorax. **B.** Axial section from a CT at the level of the diaphragm demonstrates an inhomogeneous mass; diaphragmatic invasion could not be assessed. **C.** Sagittal view of an MRI demonstrates that the mass is contained above the diaphragm. Biopsy revealed embryonal cell carcinoma.

regimens showed an overall long-term survival rate of 42%.[61] After completion of chemotherapy, patients should be restaged with a CT of the chest and abdomen and serum tumor markers should be remeasured. The majority of patients will be found to have residual masses or radiographic abnormalities after completing chemotherapy. Regardless of whether tumor markers are elevated or not, these patients should undergo surgical resection of residual masses if technically feasible because salvage chemotherapy is usually ineffective,[62] and surgical resection is curative in a substantial portion of patients.[63] In addition, occasional patients will be found to have a previously unrecognized mature (benign) teratoma component, which can only be cured by resection.

LYMPHOMA

Both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) can present as anterior mediastinal masses. HL accounts for approximately 50% to 70% of mediastinal lymphomas. The three most common types of lymphoma found in the mediastinum are nodular sclerosing HL, large cell lymphoma, and lymphoblastic lymphoma.[64] In general, these are systemic diseases that also involve the mediastinum, although some patients do present with disease limited to the mediastinum alone. Due to the generally widespread nature of these diseases, treatment is centered on systemic chemotherapy and radiation is the primary modality used for local control. Surgery is not typically utilized as a therapeutic option but may be required to make a histologic diagnosis.

Hodgkin Lymphoma

HL has a bimodal age distribution with its incidence peaking in young adulthood and again after 50 years of age. HL is divided into four subtypes: nodular sclerosing (most common), lymphocyte-rich, mixed cellularity, and lymphocyte-depleted. Most patients present with asymptomatic lymphadenopathy, but up to 25% of patients will experience B symptoms consisting of fever, night sweats, and weight loss.[65] Over half of all patients with HL will have involvement of the mediastinum, almost always in the anterior mediastinum or involving paratracheal lymph nodes (Fig. 82-5). Suspicion for HL warrants a tissue biopsy and the presence of Reed–Sternberg cells is pathognomonic. Because the tumors tend to be quite fibrotic, with only scattered malignant cells, surgical biopsy is often required to establish a diagnosis—either by cervical mediastinoscopy (for paratracheal nodes) or by anterior mediastinotomy (for anterior mediastinal masses). PET generally demonstrates high FDG avidity in lymphomas, and therefore PET/CT may be useful in guiding sites for biopsy. The Ann Arbor staging system (Table 82-6) is still widely used for staging HL and invasive staging (laparotomy and splenectomy) has fallen out of favor.

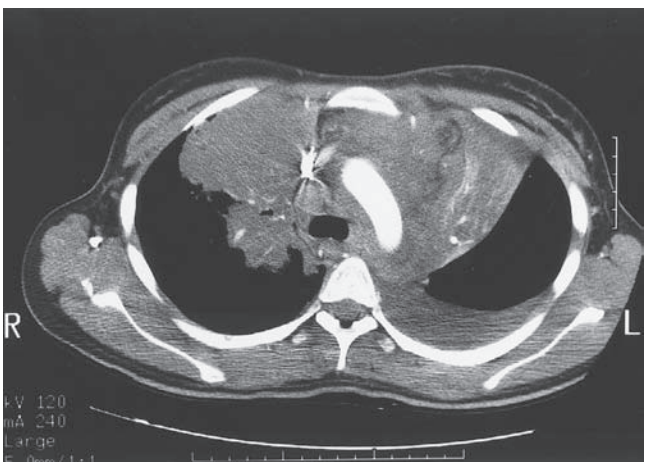


Figure 82-5 Hodgkin Disease. Axial section from a CT shows a bulky mediastinal mass and pleural effusion.

TABLE 82-6 Ann Arbor Staging System with Cotswolds Modification For Hodgkin Disease

Stage	Characteristics
I	Involvement of one lymph node region or lymphoid structure
II	Two or more lymph node regions on the same side of the diaphragm
III	Lymph nodes on both sides of the diaphragm
IV	Involvement of extranodal sites
Modifications	
A	No symptoms
B	Fever, night sweats, weight loss >10% in 6 mo
X	Bulky disease (greater than 1/3 widening of the mediastinum or >10 cm diameter of nodal mass
E	Involvement of single, contiguous, or extranodal site

Treatment approaches to HL are separated into those for early-stage disease (stage I and II) and advanced stage disease (stage III and IV). Modern treatment protocols most often involve chemotherapy regimens combined with limited (involved field) radiation. Patients with advanced stage disease as well as patients with B symptoms are treated with chemotherapy regimens such as ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Radiation is sometimes additionally employed in cases of bulky disease and patients who relapse may benefit from a hematopoietic stem cell transplant. Cure rates are greater than 90% for stage I and II HL, 30% to 90% for stage IIIA, 60% to 70% for stage IIIB, and 50% to 60% for stage IV.[64,65]

Non-Hodgkin Lymphomas

NHL is a heterogeneous group of systemic diseases that are categorized into many classes and grades. Mediastinal tumor burden in NHL is more likely to be part of the generalized disease process than the main focus of disease, and only 20% of patients with NHL will have involvement of the mediastinum at the time of presentation. This disease is not limited to the anterior mediastinum and can occur in the middle and posterior mediastinal compartments. Of patients with primarily mediastinal disease, the majority will have either lymphoblastic lymphoma or large B-cell lymphoma. The mean age of presentation for these patients is between 28 and 35 years.

Lymphoblastic lymphomas are highly aggressive tumors, and invasive symptoms including cough, wheezing, dyspnea, and manifestations of superior vena cava syndrome, cardiac tamponade, or tracheal obstruction are common. The central nervous system, skin, and gonads may be involved and bone marrow involvement with blasts is relatively common.[64] Primary mediastinal B-cell lymphoma is composed histologically of large cells with expression of the B-cell–associated antigen CD20; immunohistochemistry and/or flow cytometry are critical to the diagnosis. Presentation with symptoms related to invasion or obstruction of adjacent structures is common, but there is less involvement of extrathoracic sites and bone marrow than in lymphoblastic lymphoma. Staging of NHL is also performed according to the Ann Arbor staging system, and CT scan of the chest, abdomen, and pelvis is the initial and often only necessary imaging (Fig. 82-6).

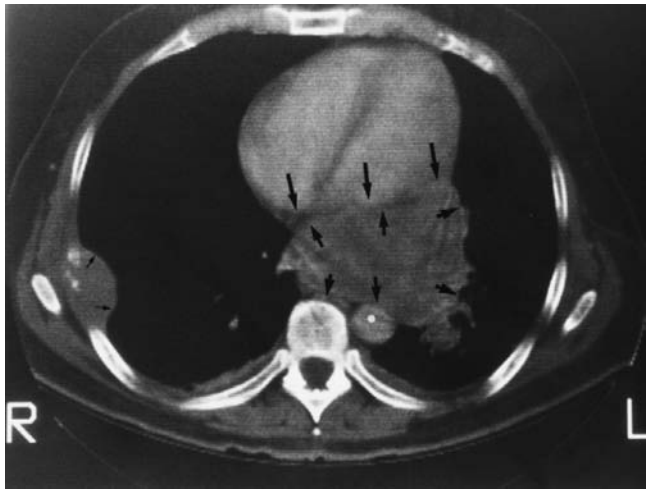


Figure 82-6 Non-Hodgkin lymphoma. Axial section from a CT demonstrates a large middle and posterior mediastinal mass with distant metastasis to a rib in the contralateral chest. This skip involvement is typical of non-Hodgkin lymphoma.

Treatment regimens for mediastinal NHL are dependent upon stage and histologic subtype. Due to its propensity to involve the bone marrow, lymphoblastic lymphoma commonly employs a treatment regimen similar to that for acute lymphoblastic leukemia, often including intrathecal chemotherapy and bone marrow transplantation. Patients with primary mediastinal B-cell lymphoma can be treated with conventional chemotherapy regimens, but high-dose chemotherapy and "involved field" radiotherapy are sometimes employed. In general, relapses in NHL are common and the long-term prognosis is worse than for HL.

■ OTHER ANTERIOR MEDIASTINAL NEOPLASMS

Other anterior mediastinal neoplasms include substernal thyroid and parathyroid adenoma.

Substernal Thyroid

Substernal and ectopic thyroid tissue can present as an anterior mediastinal mass and may involve the middle mediastinum, if the thyroid tissue descends more caudally into the paratracheal space. In the majority of cases, the substernal thyroid is a euthyroid goiter and an enlarged thyroid gland will be palpable in the neck. We have found that a noncontrast CT is the single most useful test in differentiating substernal thyroid from other mediastinal masses. Because of its iodine content, substernal thyroid tissue shows enhancement on a noncontrast CT scan and this usually confirms the diagnosis. Surgical resection is recommended, as needle biopsy cannot rule out malignancy in such a large lesion and substernal goiters will often cause symptoms of airway compression as they continue to grow. Nearly all substernal goiters can be removed by cervical incision.

Parathyroid Adenoma

The anterior mediastinum is the most common location for an ectopic parathyroid tumor. Often, ectopic parathyroid glands will present as persistent primary hyperparathyroidism after an unsuccessful neck exploration. Before proceeding with mediastinal exploration, localizing studies such as Technetium-99m-sestamibi scintigraphy and CT are recommended. MRI may be useful to reveal a well-defined mass, however they are usually small (<3 cm). The adenoma is typically embedded in the thymus gland. Surgical resection of the adenoma, typically requiring resection of the thymus itself, is curative. We find the surgical technique of transcervical thymectomy, performed via the neck with a retractor lifting the sternum anteriorly, is ideal for this disease process and can be performed on an outpatient basis.

MIDDLE MEDIASTINAL NEOPLASMS

Metastatic bronchogenic carcinoma is the most common etiology of middle mediastinal masses, as the mediastinal lymph nodes in the middle mediastinal compartment are a frequent site of lung cancer metastases. The most common primary masses of the middle mediastinum are lymphoma (described above) and benign cysts. Cysts comprise 12% to 20% of all primary mediastinal masses and are found chiefly in the middle compartment of the mediastinum. These cysts comprise congenital foregut cysts, bronchogenic cysts, neurenteric cysts, and pericardial cysts and are reviewed in Chapter 81.

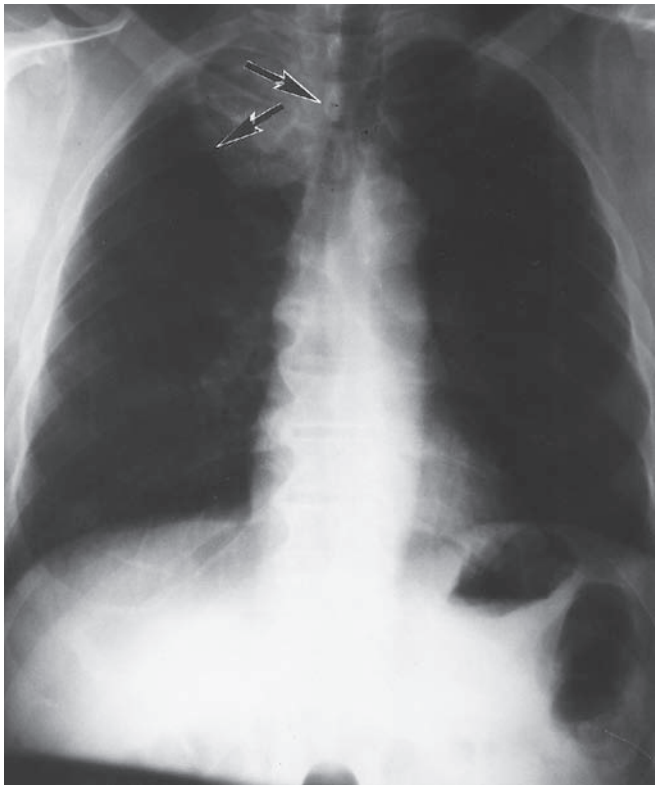
POSTERIOR MEDIASTINAL NEOPLASMS

Neurogenic tumors are the most common neoplasms of the posterior mediastinum, collectively representing 12% to 21% of all mediastinal masses and occurring almost exclusively (95%) in the posterior compartment.[66] Neurogenic tumors are categorized into three groups based on the neurogenic tissue of origin. Neoplasms arising from the nerve sheath include schwannoma, neurofibroma, and malignant nerve sheath tumors. Nerve sheath tumors are the most common neurogenic tumors found in the adult. Neoplasms arising from the sympathetic ganglion include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma and these tumors are more commonly found in children. Neoplasms arising in parasympathetic ganglia include paraganglioma and chemodectoma, both of which occur in the posterior mediastinum and are exceedingly rare. Approximately 98% of neurogenic mediastinal tumors in adults are benign, whereas it is estimated that more than 50% of neurogenic tumors in children are malignant.

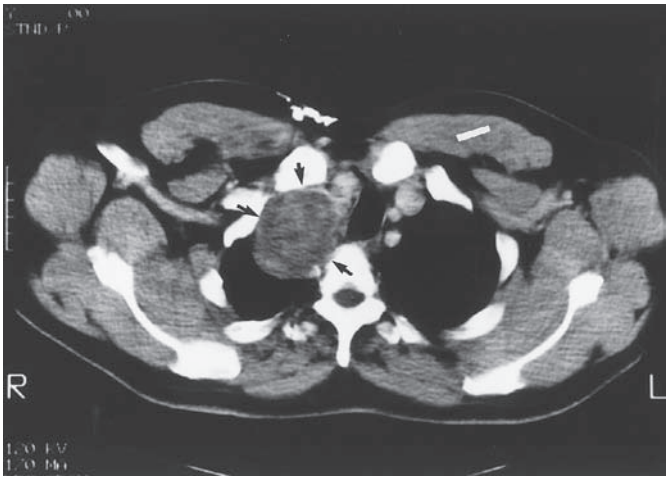
■ NERVE SHEATH TUMORS

Schwannoma (neurilemmoma) and *neurofibroma* are the most common mediastinal neurogenic tumors.[67] Both of these lesions are benign, slow-growing tumors. Most commonly, they appear as encapsulated and well-marginated masses found in the costovertebral sulci where they arise from intercostal nerve rami. Less frequently they can be found in the middle mediastinal compartment when they occur as tumors of the vagus or phrenic nerves. CT typically reveals a solitary, smoothly rounded mass in the upper half of either paravertebral sulcus abutting the vertebra (Fig. 82-7). An MRI should be employed to rule out intraspinal extension, if there is any possibility of this on CT. Upon presentation, most patients are asymptomatic, although neurologic symptoms from intercostal nerve involvement or intraforaminal extension can be present.[68] Thus, many of these are identified as incidental findings on scans performed for other reasons. Over one-third of patients with neurofibromas will have neurofibromatosis (von Recklinghausen disease), and these patients tend to present at an earlier age and may have café au lait spots suggesting the diagnosis.[68,69]

Surgical resection is the definitive treatment for these benign nerve sheath tumors, commonly performed via VATS with favorable results.[70,71] There may be a role for chemotherapy and radiation when complete resection is not possible. Excellent long-term survival is obtained with complete surgical excision of the tumors and recurrence is uncommon.[66,70] However, additional neurofibromas or schwannomas may develop in patients with neurofibromatosis. Ten percent of these tumors extend through the intervertebral foramen and create a "dumbbell" appearance on imaging studies. For these lesions, combined thoracic and neurosurgical *en bloc* resection can be achieved with low morbidity.[72] Typically this is accomplished with a posterior laminectomy followed by an anterior thoracoscopic approach.



A



B

Figure 82-7 Schwannoma. A 67-year-old man who had undergone a total thyroidectomy 20 years earlier presented with chronic cough. **A.** PA chest radiograph demonstrates a superior mediastinal mass projecting into the right hemithorax. **B.** Axial section from a CT demonstrates this neurogenic tumor high in thoracic inlet.

Malignant nerve sheath tumors are essentially spindle cell sarcomas of the mediastinum and include malignant schwannoma, neurofibrosarcoma, and malignant neurofibroma. These tumors are rare, affect men and women equally in the third to fifth decades of life, and are closely associated with neurofibromatosis. Malignant schwannomas remain one of the most poorly characterized of all soft tissue sarcomas. In general, patients with malignant schwannomas present with large invasive tumors and have a poor prognosis. Complete surgical resection is rarely possible, and even when accomplished, local recurrence is common. Neurofibrosarcoma likely evolves from the malignant degeneration of a neurofibroma. Unlike benign nerve sheath tumors, patients with neurofibrosarcoma generally have symptoms of pain and nerve impingement.[73] On CT imaging, these tumors often appear as round masses with central areas of necrosis and hemorrhage. Radical surgical excision provides the only hope of cure; however, the 5-year overall survival rates are low (16% in patients with neurofibromatosis) and no survival benefit is gained by adjuvant chemotherapy.[73,74] Chemotherapy and radiotherapy are options for unresectable tumors.

■ SYMPATHETIC GANGLION TUMORS

Tumors of the sympathetic ganglia likely represent malignant degeneration of the nerve cell rather than the nerve sheath. These tumors are represented by the spectrum of ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Mature tumors such as ganglioneuroma occur in older children (median age of ~7 years) and tend to behave in a benign fashion, whereas immature tumors such as neuroblastoma tend to occur in younger patients (median age under 2 years) and behave aggressively.[75]

Ganglioneuromas are the most benign type of sympathetic ganglion tumor. They are typically diagnosed in the second or third decade of life and are the most common neurogenic tumors occurring in childhood. Most patients with ganglioneuroma are asymptomatic upon presentation, although larger tumors may result in symptoms such as cough, dyspnea, dysphagia, chest pain, and Horner syndrome, and symptoms related to the secretion of catecholamines have been reported. Ganglioneuromas are generally large, well-circumscribed, and encapsulated tumors located in the paravertebral sulci. Surgical resection is a highly successful treatment for ganglioneuromas.[76]

Ganglioneuroblastoma is a tumor that demonstrates histologic elements similar to the well-differentiated ganglion cells seen in a ganglioneuroma as well as less-differentiated neuroblastoma-like features, and the degree of malignant behavior is related to the extent of the latter. Presentation is in the first decade of life and both sexes are equally affected. Approximately half of patients will present with symptoms. Most children present with a solitary mass that is amenable to complete surgical resection. The treatment of ganglioneuroblastoma is primarily surgical although chemotherapy is indicated in intermediate and high-risk groups. Overall these tumors are associated with relatively high 5-year survival rates, reported to be 88% in one large series.[77]

Neuroblastomas are the most malignant of the sympathetic ganglion tumors. These highly aggressive and readily metastasizing tumors are found almost exclusively in children, with 95% occurring in patients less than 5 years old.[78] Most patients present with symptoms that include chest pain, dyspnea, myelopathy from spinal canal involvement, and symptoms of excess catecholamine production. Distant metastases are common.[79] On CT, mediastinal neuroblastomas appear as elongated paraspinous masses often impinging on adjacent structures and causing bony destruction. Eighty percent of tumors demonstrate calcification.[80] MRI is useful for determining nodal, chest wall, and intraspinal involvement. The International Neuroblastoma Staging System (INSS) is the most commonly used staging system for this disease. It includes factors such as tumor size, lymph node metastases, and extent of unresectable disease and can be used to predict survival.[81] Amplification of the oncogene N-myc has additionally been shown to correlate with worse prognosis.[82] The treatment of neuroblastoma depends primarily on stage. For patients with stage I disease, resection alone is usually curative.[83,84]

For patients with partially resectable stage II and III diseases, surgical resection is followed by postoperative multiagent chemotherapy. Patients with stage IV disease are generally treated with chemotherapy and radiation, and the role of surgery is more controversial.

NEOPLASMS ARISING IN PARASYMPATHETIC GANGLION

Paragangliomas are rare tumors that arise from specialized neural crest cells associated with autonomic ganglia, called paraganglia. Paragangliomas can be categorized into two groups based upon association with either the parasympathetic system or the sympathetic system. Parasympathetic paragangliomas do not secrete catecholamines and are termed *chemodectomas*. Chemodectomas may arise from mediastinal chemoreceptors including the aortopulmonary glomulus or anywhere along the vagus nerve and are chromaffin-negative tumors. Tumors connected with the sympathetic nervous system are divided into functional paragangliomas and nonfunctional paragangliomas based on their ability to secrete catecholamines. These tumors have been previously referred to as extra-adrenal pheochromocytomas.

Both genders are equally affected by mediastinal paragangliomas, usually in the third or fourth decade of life. The clinical presentation includes symptoms of local mass effect as well as varying degrees of hypertension and hypermetabolism secondary to the production of epinephrine and norepinephrine. Excess plasma and urinary levels of catecholamines can often be detected. Preoperative localization is essential. CT, MRI, and echocardiography can be useful for anatomic imaging and functional imaging studies such as ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy can be used to localize lesions not seen on other scans. Treatment requires surgical excision, and presurgical conditioning with alpha and then beta blockade is usually necessary for functional lesions to prevent severe hypertension intraoperatively.

OTHER MEDIASTINAL TUMORS

Additional neoplasms of the mediastinum include those seen in Castleman's Disease and a variety of mesenchymal tumors.

CASTLEMAN'S DISEASE

Castleman's disease is a rare lymphoproliferative disorder that can involve enlargement of one (unicentric Castleman's disease) or multiple (multicentric Castleman's disease) lymph nodes. Most adults with unicentric disease are asymptomatic. The mediastinum is the most common location of unicentric disease and lesions most frequently occur in the anterior and middle compartments.[85,86] Multicentric Castleman's disease is characterized by peripheral lymphadenopathy and hepatosplenomegaly; a subset of patients also demonstrate mediastinal and intra-abdominal adenopathy. Human herpesvirus 8 infection has been implicated in the pathogenesis of multicentric but not unicentric disease.

Castleman's disease is categorized into two histologic types (hyaline vascular and plasma cell), but it appears that centricity rather than histology is more important in predicting long-term outcome in this disease. Complete surgical resection should be performed in unicentric disease and is associated with greater than 95% overall survival and greater than 80% disease-free survival at 5 years.[86] Multicentric Castleman's disease can be rapidly progressive and often fatal and the role of surgery other than to obtain tissue to establish a diagnosis is uncertain.

MESENCHYMAL TUMORS

Mesenchymal tumors constitute approximately 6% of all tumors that occur in the mediastinum.[3] More than half of these lesions turn out to be malignant. A large variety of categories exist for mesenchymal tumors of the mediastinum and their spectrum runs the entire gamut of soft tissue tumors, including but not limited to adipocytic tumors (lipoma, lipomatosis, liposarcoma), vascular tumors (hemangioma, lymphangioma), fibroblastic tumors (fibrous tumors), smooth muscle tumors (leiomyoma, leiomyosarcoma), skeletal muscle tumors (rhabdomyoma, rhabdomyosarcoma), and chondroosseous tumors (chondrosarcoma, osteosarcoma). Their management is similar to extrathoracic soft tissue tumors, with resection indicated if possible.

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PART 11

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CHAPTER 83

Nonmuscular Diseases of the Chest Wall

George E. Tzelepis
F. Dennis McCool

INTRODUCTION

The chest wall is a major component of the respiratory pump and consists of the rib cage and abdomen. It is inflated by the inspiratory muscles of the rib cage and the diaphragm and its integrity is key to sustaining ventilation. Disorders affecting the nonmuscular structures of the chest wall (the thoracic spine, ribs, costovertebral joints, abdominal wall, and sternum) may lead to respiratory dysfunction. When the integrity of these nonmuscular components is severely compromised, respiratory failure may ensue. The pathophysiology of disorders affecting these nonmuscular components is generally related to the imposition of excessive elastic loads placed on the respiratory muscles. In some disorders, such as kyphoscoliosis (KS) and obesity, the load on the respiratory muscles is chronic and progressive. By contrast, with flail chest, the load on the respiratory muscles is acute. If the respiratory muscles had not adapted or had little time to adapt to loads that increase the work of breathing, respiratory failure may quickly ensue. Other disorders, such as ankylosing spondylitis (AS) and pectus excavatum, have a minimal impact on respiratory function. Diseases directly affecting the respiratory muscles are discussed in Chapter 84.

KYPHOSCOLIOSIS

Important physiologic and clinical considerations in kyphoscoliosis are discussed below.

ETIOLOGY AND DIAGNOSIS

KS comprises a group of spinal disorders that are characterized by curvature of the spine in the lateral direction (scoliosis) and sagittal plane (kyphosis) as well as by spinal axis rotation. It is a common spinal abnormality, with estimates of prevalence in the United States ranging from 1 in 10,000 people for severe deformities to 1 in 1000 people for mild deformities.[1] The etiology of KS is unknown for the vast majority of cases (85% classified as idiopathic). With the remainder, KS is due to either neuromuscular disease (paralytic or secondary KS) or is congenital (Table 83-1).[2–4]

Idiopathic KS usually manifests in late childhood or early adolescence and involves primarily females (ratio of 4:1).[5] Individuals with idiopathic KS may complain of back pain or may have psychological problems.[5] When KS is severe, complaints include dyspnea with exertion and constitutional symptoms related to nocturnal hypoventilation. Respiratory failure also may develop.[6] Paralytic or secondary KS may be due to a number of neuromuscular disorders including polio, muscular dystrophy, cerebral palsy, and spinal bifida.[4] With these diseases, KS typically occurs when the individuals become nonambulatory. Congenital KS results from developmental vertebral anomalies that are usually present at birth.[3] Although uncommon, it can lead to serious neurological complications such as paraplegia.

The diagnosis of KS is made by physical examination and radiological assessment. In severe KS, physical examination reveals a dorsal hump involving the rib cage. This is due to angulated ribs and shoulder asymmetry. In addition, there is "hip tilt" that is related to spinal rotation (Fig. 83-1). With mild spinal deformity, kyphosis and scoliosis are less apparent when inspecting the spine and the rib cage. In this context, subtle changes in spinal curvature may be elicited by performing the Adam's forward bend test. With this test, the patient bends forward at the waist with feet together and knees straight, until the spine becomes parallel to the floor. The observer, then, examines for thoracic or lumbar region asymmetry.

Radiographic studies (upright PA and lateral views of the spine) are used to confirm the diagnosis, and to assess severity by measuring the Cobb angle.[7] This angle is formed by the intersection of two lines, each of which is parallel to the top and bottom vertebrae of the scoliotic or kyphotic curves (Fig. 83-2). A spinal deformity with a Cobb angle greater than 10 degrees is considered scoliosis.[5] The greater the Cobb angle, the more severe the deformity. Cobb angles less than 60 degrees are usually not associated with ventilatory impairment, those greater than 100 degrees are invariably associated with respiratory symptoms, and those greater than 120 degrees with respiratory failure.[5,8,9] Sequential radiographic studies are useful in evaluating progression of the spinal deformity.

RESPIRATORY MECHANICS

The pathophysiological hallmark of KS is reduced chest wall distensibility.[10] Namely, chest wall compliance is reduced and the pressure required to inflate the chest wall at any given lung volume is greater than in a healthy individual. Consequently, functional residual capacity (FRC) is invariably decreased, the elastic load placed on the respiratory muscles is increased, and the work of breathing is significantly increased. In idiopathic KS, the compliance of the chest wall and respiratory system both decrease as the Cobb angle increases (Fig. 83-3 A,B) with the most pronounced reductions in chest wall compliance seen in individuals with Cobb angles greater

TABLE 83-1 Causes of Kyphoscoliosis

Congenital
Paralytic or secondary
Neuromuscular
Poliomyelitis
Muscular dystrophy
Cerebral palsy
Friedreich ataxia
Charcot–Marie–Tooth disease
Neurofibromatosis
Syringomyelia
Disorders of connective tissue
Marfan syndrome
Ehlers–Danlos syndrome
Morquio syndrome
Vertebral disease
Osteoporosis
Osteomalacia
Vitamin D-resistant rickets
Tuberculous spondylitis
Spina bifida
Postthoracoplasty
Idiopathic

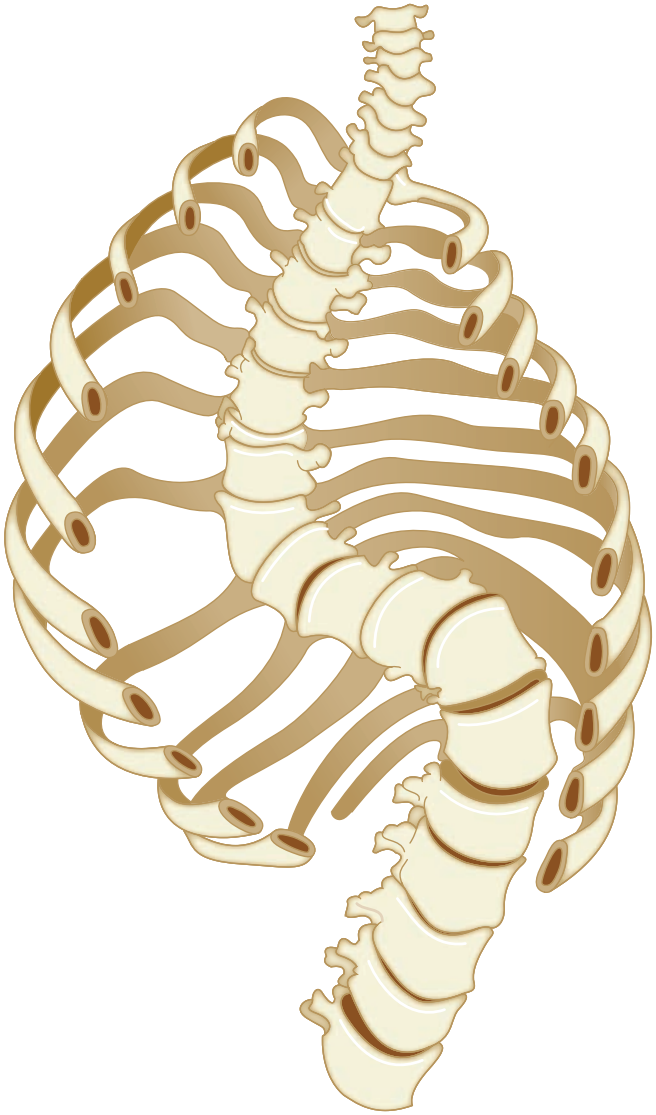

Figure 83-1 Schematic representation of the rotation of the spine and the rib cage seen with scoliosis. *(Data from Bergofsky et al. Medicine (Baltimore). 1959;38:263.)*

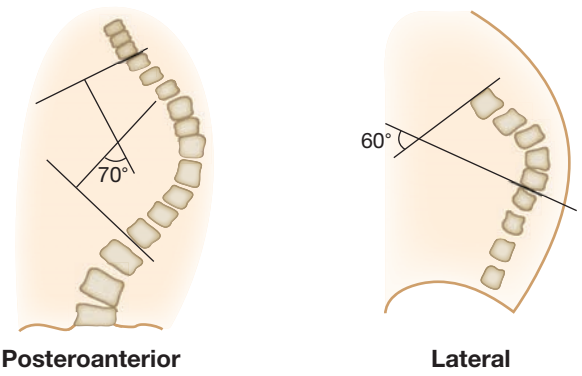

Figure 83-2 Schematic of the posteroanterior radiograph depicting the lines constructed to measure the Cobb angle of scoliosis and the lines drawn on the lateral radiograph to measure the Cobb angle of kyphosis. *(Data of Rochester, Findley, in Murray and Nadel editors, Textbook of Respiratory Medicine. Philadelphia: WB Saunders; 1988.)*

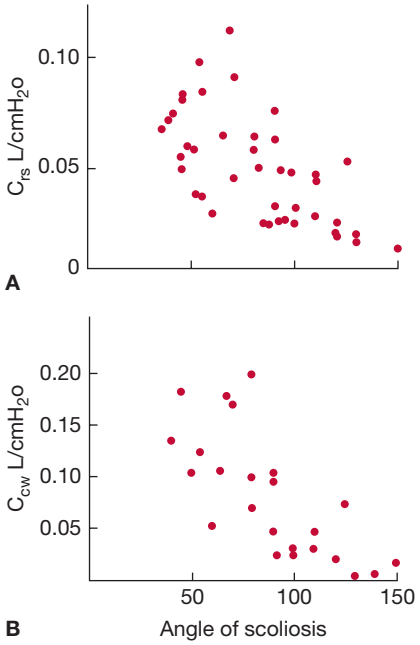

Figure 83-3 Relationship between (**A**) the angle of scoliosis and compliance of the total respiratory system and (**B**) the angle of scoliosis and compliance of the chest wall in patients with idiopathic scoliosis. *(Reproduced with permission from Kafer ER. Mechanical properties of the respiratory system and the ventilatory response to carbon dioxide. J Clin Invest. 1975;55(6):1153–1163.)*

than 100 degrees.[10] Cobb angles up to 50 degrees do not significantly decrease respiratory system compliance.[10]

The reduction in chest wall compliance promotes breathing with shallow tidal breaths and the reduction in FRC leads to breathing at low lung volumes. Both factors predispose to the development of atelectasis. Consequently, lung compliance may be reduced in the absence of any intrinsic lung disease. Although lung compliance may be diminished, it is not as severely affected as the chest wall. Since chest wall compliance decreases with age, respiratory mechanics invariably deteriorate with age even though the spinal deformity may not worsen over time.[11]

Respiratory muscle strength, as reflected in measurements of maximal static inspiratory (PI_{max}) and expiratory pressures (PE_{max}), is usually normal in individuals with idiopathic KS and Cobb angles of less than 50 degrees. With Cobb angles greater than 50 degrees, there may be mild to moderate reductions in PI_{max} and PE_{max} accompanied by only mild reductions in vital capacity (VC).[12,13] The reductions in PI_{max} with idiopathic KS may be due to mechanical disadvantage of the respiratory muscles coupled to a distorted rib cage.[14] However, in patients with secondary KS, reductions in PI_{max} are related to intrinsic muscle weakness.[15] In these individuals, the combination of weakened inspiratory muscles and a stiff, poorly compliant, respiratory system will lead to profound decrements in VC and predispose these individuals to respiratory failure.[16]

The reductions in VC in idiopathic KS are typically seen in patients with severe spinal deformities (Cobb angles greater than 100 degrees). Total lung capacity (TLC) and VC may be reduced to 30% of predicted.[2,8] Forced vital capacity (FVC) decreases in proportion to the reduction in TLC in the absence of obstructive airway disease. Residual volume (RV) may be normal or slightly increased. This is in contrast to the reduction in RV that occurs in restriction due to interstitial lung disease. The disproportionate reduction in TLC relative to RV in KS produces a relatively high RV/TLC ratio.[2] In individuals with mild and moderate degrees of kyphosis and scoliosis (i.e., Cobb angles less than 60 degrees) VC and TLC may be

only mildly reduced. Although uncommon, obstructive dysfunction in nonsmokers has been described.[17] This includes reductions in midexpiratory flow rates or FEV_1 resulting from tracheal displacement or torsion of major bronchi.[18]

Factors other than Cobb angle can contribute to the reduction in TLC and VC. These factors include the location of the spinal curve (thoracic vs. lumbar), number of vertebrae involved, patient's age, degree of spinal rotation, and, most importantly, the presence or absence of inspiratory muscle weakness. Concomitant respiratory muscle weakness will significantly affect the severity of restriction. In patients with paralytic KS (spinal deformity secondary to neuromuscular disease), the degree of lung restriction is primarily determined by the magnitude of respiratory muscle weakness rather than by the degree of spinal curvature.[15,19] Thus, for a similar Cobb angle, patients with paralytic KS are likely to have greater pulmonary function impairment than patients with idiopathic KS.[15,19] In patients with congenital KS, coexisting rib deformities or underlying lung abnormalities similarly lead to a greater loss in VC for a given degree of spinal deformity than seen in patients with idiopathic KS.[20]

The work of breathing is increased in KS because of the elastic load related to the stiff chest wall.[10] Consequently, the oxygen cost of breathing may be three to five times of that seen in healthy subjects. Concomitant inspiratory muscle weakness decreases ventilatory reserve and predisposes the respiratory muscles to fatigue and contributes to respiratory failure in these patients.[16]

EXERCISE CAPACITY

Exercise capacity may be severely limited in KS, especially when the Cobb angle is greater than 60 degrees. Cardiorespiratory dysfunction related to restrictive pulmonary function, reduced respiratory system compliance, increased work of breathing, and respiratory muscle weakness contribute to poor exercise capacity.[21,22] Typically, maximal oxygen consumption is reduced to about 60% to 80% of predicted, heart rate is higher per work load, the ratio of tidal volume to vital capacity (VT/VC) is greater than 0.5, and the ratio of maximum exercise ventilation to maximum voluntary ventilation (VE_{max}/MVV) can reach 0.7. Concomitant pulmonary hypertension in those with Cobb angles greater than 100 degrees may independently contribute to exercise limitation.

Kyphoscoliotic individuals with mild to moderate spinal curves (Cobb angles 20–45 degrees), also may have poor exercise tolerance but any reduction in $\dot{V}O_{2max}$ more likely is due to limb muscle deconditioning rather than ventilatory constraints.[23] In support of this notion, there is recent data reporting weakness of the quadriceps muscle, reduced Type I myosin, and presence of oxidative stress in the quadriceps muscle of these patients.[24]

CONTROL OF BREATHING

Advanced KS is associated with significant alterations in breathing pattern. Typically, individuals with severe KS adopt a rapid shallow breathing pattern consisting of low tidal volumes, shortened inspiratory time (T_I), and an increased respiratory rate (i.e., reduced total breath time, T_{TOT}).[16,25] In young patients with KS and normal blood gases, T_I and duty cycle (T_I/T_{TOT}) correlate negatively with the angle of scoliosis.[25] These changes in breathing pattern likely represent an adaptation to chest wall restriction. The benefit of using this breathing pattern is twofold. First, the work per breath is decreased. Second, the ratio of the pressure needed to inhale (P_{breath}) to PI_{max} is reduced. In theory, reducing P_{breath}/PI_{max} lessens the likelihood of developing inspiratory muscle fatigue and respiratory failure. The disadvantage of a rapid shallow breathing pattern is that it promotes atelectasis, causes hypoxemia, and may lead to a further reduction of lung compliance.

A second means of adapting to the added elastic load of the stiffened chest wall is to increase respiratory drive.[25] Indirect measurements of the neural drive to the respiratory muscles, such as mouth occlusion pressure at 100 ms (P0.1) are usually elevated in these individuals and correlate positively with the degree of scoliosis.[25] The increase in neural drive is not necessarily associated with increased alveolar ventilation as the stiff chest wall and the weak respiratory muscles will limit any augmentation in alveolar ventilation.

SLEEP DISORDERED BREATHING

Nocturnal hypoventilation may occur in severe KS and typically predates the development of chronic hypercapnia.[9,26] While awake, individuals with Cobb angles greater than 100 degrees can maintain adequate alveolar ventilation by increasing respiratory drive to the diaphragm and recruiting accessory inspiratory muscles.[16,25] However, during sleep, neural drive to all the inspiratory muscles is diminished, especially during REM sleep.[27] Since these patients are dependent exclusively on the diaphragm to maintain alveolar ventilation in REM sleep, they are at risk for becoming hypercapnic and hypoxemic. The risk of hypoventilation is amplified if there is any underlying diaphragm dysfunction. Of interest, the magnitude of nocturnal hypoventilation may not correlate with the degree of thoracic deformity.[28] This observation suggests that inspiratory muscle weakness may be a more important factor for developing nocturnal hypoventilation. The presence of sustained nocturnal desaturation and hypercapnia may further weaken the respiratory muscles, compound the hypoxemia, lead to pulmonary hypertension and eventually cor pulmonale. Obstructive sleep apnea, which has a similar prevalence in KS to that of the general population, also may complicate nocturnal hypoventilation.[29] Since nocturnal hypoventilation occurs before development of the typical symptoms and signs of cardiorespiratory failure, the clinician must be alert to sleep-related breathing abnormalities in these patients and promptly diagnose them with overnight polysomnography.[29]

GAS EXCHANGE

Abnormalities in gas exchange are frequently found in patients with KS; normocapnic hypoxemia being the most common abnormality. In nonsmokers with idiopathic KS, Pa_{O_2} correlates directly with VC and inversely with the angle of scoliosis. The age-dependent decrease in Pa_{O_2} is greater than that of normal individuals and oxyhemoglobin desaturation can occur with minimal activity.[11,30] Hypoxemia is primarily due to ventilation–perfusion mismatch and less often to intrapulmonary shunt associated with atelectasis.[30] In severe KS with chronic hypercapnia, hypoventilation also contributes to hypoxemia. Hypercapnia is initially detected only during sleep or with exercise.[26] With aging or as the disease progresses, hypercapnia is seen at rest while awake.

CLINICAL COURSE

Individuals with congenital KS and severe spinal deformities may exhibit a rapidly deteriorating clinical course resulting in pronounced restrictive dysfunction, *cor pulmonale*, and early death.[6,31] Those with secondary KS associated with neuromuscular disease may similarly progress to develop severe restrictive dysfunction and cardiorespiratory failure.[32] In general, when KS manifests early in life (age 0–8 years) there is a greater risk for rapid progression of the spinal deformity during growth, continued progression of the deformity after skeletal maturity, and a greater likelihood of developing respiratory failure.[31]

Individuals with idiopathic KS typically have a more benign course. If the spinal deformity at skeletal maturity is mild, they have an excellent prognosis with little respiratory impairment, and an overall good quality of life.[5] In individuals with idiopathic KS and moderate or severe deformity at presentation (age 12–16 years), the risk of deformity progression and development of respiratory impairment increases significantly.[5] Progressive curvature of the spinal deformity is, in general, greater in skeletally immature individuals, in those with large deformities at presentation, and in those whose curves have a thoracic apex.[5] By rough estimates, individuals

with thoracic deformities greater than 50 degrees at skeletal maturity are at risk for a progressive increase in the spinal curve at a rate of about 1 degree annually.[33]

Most young individuals with idiopathic KS are asymptomatic. As they age, many will develop back pain and dyspnea. Initially dyspnea may only be problematic with activities and eventually may be present at rest if the spinal deformity progresses.[11] Consequently, individuals with severe idiopathic KS, especially those with a Cobb angle greater than 110 degrees and VC of less than 45% of predicted, should be monitored for respiratory compromise as they age.[11] Once cardiorespiratory failure develops, the prognosis is poor; without supplemental oxygen or ventilatory support death may occur within 1 year. The risk of respiratory failure is even greater in patients with inspiratory muscle weakness, sleep disordered breathing, obesity, or concomitant obstructive airway disease. Pregnancy poses no added risk for respiratory failure; however, women with idiopathic KS and a VC reduced to less than 1 L may develop respiratory problems during pregnancy.

TREATMENT

General supportive measures for adults with KS include smoking cessation, maintenance of body weight within a desirable range, engaging in frequent physical activity to improve exercise capacity and minimize deconditioning, immunization against influenza and pneumococci, prompt treatment of respiratory infections, and psychological support for those with diminished self-esteem. Supplemental oxygen may be needed with activity or during sleep if there is evidence of oxyhemoglobin desaturation with exertion or with sleep. Treatment with supplemental oxygen alone may be sufficient if it corrects nocturnal hypoxemia without inducing hypercapnia.[34] However, the development of hypercapnia needs to be closely monitored, especially in individuals with a VC of less than 50% of predicted. If hypercapnia is present, nocturnal noninvasive ventilatory support should be initiated. Dyspnea, morning headaches, poor sleep quality, fatigue, and the presence of *cor pulmonale* are symptoms and signs that should alert the clinician to the presence of nocturnal hypoventilation.[35] Long-term, nocturnal noninvasive ventilation should be offered to all patients with KS and chronic hypercapnic respiratory failure as it reduces mortality (Canadian Thoracic Society, grade 1B).[34,36]

Noninvasive positive pressure ventilation can be delivered via a nasal mask or full-face mask, with or without supplemental oxygen. When prescribing a positive pressure device, either a pressure- or volume-preset ventilator can be used.[9] Apart from the potential for greater leakage with the pressure mode, pressure or volume ventilation has equivalent beneficial effects on physiological and clinical parameters as well as overall health status. Contraindications to noninvasive ventilation include the inability to protect the upper airway due to impaired cough, excessive airway secretions, or inability to cooperate.[35] When noninvasive ventilation has failed or is contraindicated, invasive ventilation should be considered.

Benefits of noninvasive ventilation include improvements in quality of life, gas exchange, sleep efficiency, pulmonary hemodynamics, respiratory drive, and survival (Table 83-2).[9,37] By contrast, measurements of VC, PI_{max}, twitch transdiaphragmatic pressure and respiratory muscle endurance are not improved by noninvasive ventilation.[38] Accordingly, the lower incidence of respiratory failure in patients undergoing positive pressure ventilation may be attributed to improvements in respiratory control rather than improvement of respiratory muscle contractility.[38] Long-term noninvasive ventilation considerably reduces the number of hospitalizations for respiratory failure and the length of hospital stay.[9] Survival benefit of KS patients treated with noninvasive ventilation and supplemental oxygen over those patients treated with just oxygen has been demonstrated by comparative and observational studies (Fig. 83-4).[36]

TABLE 83-2 Therapeutic Benefits of Noninvasive Mechanical Ventilation in Patients with Kyphoscoliosis

Gas Exchange Indices	
Pa_{O_2}	Increase
Pa_{CO_2}	Decrease
Bicarbonate	Decrease
Pulmonary Function Tests	
FVC	No change
FEV_1	No change
TLC	No change
FRC	No change
Respiratory Mechanics	
PI_{max}, PE_{max}	No change or slight increase
Twitch P_{di}	No change
Chest wall compliance	No change
Lung compliance	No change
Hemodynamic Parameters	
PAP	Decrease
Ventilatory Control	
Hypercapnic ventilatory	Improved response
Sleep	
Epworth sleepiness scale	Decrease
Quality of life	Improvement
Survival	Increase

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; FRC. functional residual capacity; PI_{max}, maximum inspiratory pressure; PE_{max}, maximum expiratory pressure; P_{di}, transdiaphragmatic pressure; PAP, pulmonary artery pressure.

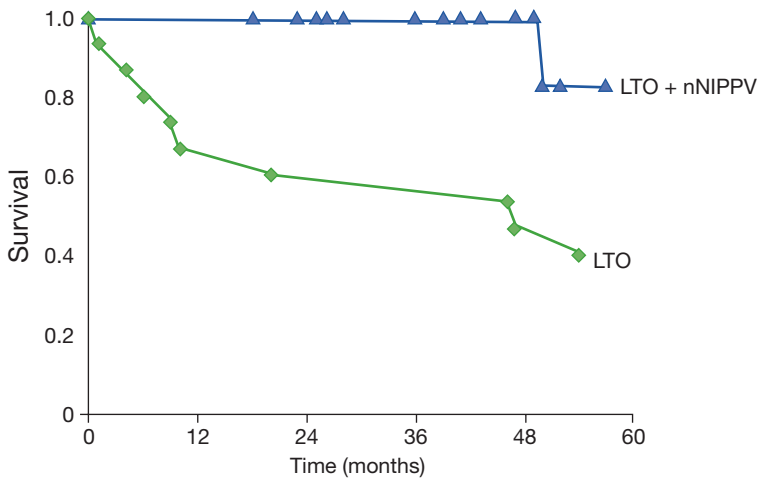

Figure 83-4 Survival curves of kyphoscoliotic patients treated with long-term oxygen therapy (LTO) and nocturnal nasal intermittent positive pressure ventilation (nNIPPV). *(Reproduced with permission from Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? Eur Respir J. 2003;22(3):525–528.)*

Traditional surgical approaches to correct spinal deformities in skeletally immature children have included spinal fusion and/or implantation of rods. Spinal fusion has considerable disadvantages as it has been associated with restrictive respiratory defects, decreased ability to carry out daily activities, and poor cosmetic results.[39] In young children (age <10 years), severe restrictive respiratory disease (VC <50% of predicted) may occur in roughly 50% of patients undergoing spinal fusion, especially in those with extensive thoracic fusions or in those with fusions of the proximal thoracic spine.[39] Surgical fusion of the spine may have a role in children with congenital spinal deformities or in children with KS secondary to neurological defects. A nonfusion approach includes implantation of growth-friendly rods such as expandable spinal rods, titanium rib implants, or remotely distractible magnetically controlled rods.[40] These newer techniques permit control of spinal deformity while allowing continued spinal growth and pulmonary development.[40]

THORACOPLASTY

In the pre-antituberculous chemotherapy era, thoracoplasty was the standard surgical approach to control pulmonary tuberculosis. The surgery consisted of different combinations of rib removal, rib fracture, phrenic nerve resection, or lung compression by filling the pleural space with foreign material (i.e., ping pong balls) (Fig. 83-5). Since the procedure was primarily performed in the 1940s and 1950s, very few people who had undergone the procedure are still alive.[41,42] Historically, these individuals commonly developed dyspnea, severe restrictive dysfunction, and chronic hypercapnic respiratory failure as they aged.[41,42] The severity of the restrictive defect was often comparable to that seen in KS (Tables 83-3 and 83-4) and was related to the number of ribs removed, presence of fibrothorax, lung fibrosis secondary to underlying granulomatous disease, prior lung resection, or intentional phrenic nerve damage.[41,42] As in most restrictive chest wall diseases, these patients had impaired gas exchange, limited exercise tolerance, an increased oxygen cost of breathing, and eventually would develop *cor pulmonale*. Progressive scoliosis with aging further impaired respiratory function. Although this procedure is of historical interest, the purpose of reviewing thoracoplasty in this chapter is that the procedure is still occasionally performed. Currently, thoracoplasty is indicated for treatment of bronchopleural fistulae that have failed to close following decortication or for treatment of persistent empyema in which decortication is not feasible or has failed to eradicate the infection.[43] Treatment of individuals who are postthoracoplasty and have developed restrictive disease consists of supplemental oxygen, antibiotics for respiratory infections, and noninvasive ventilatory support.

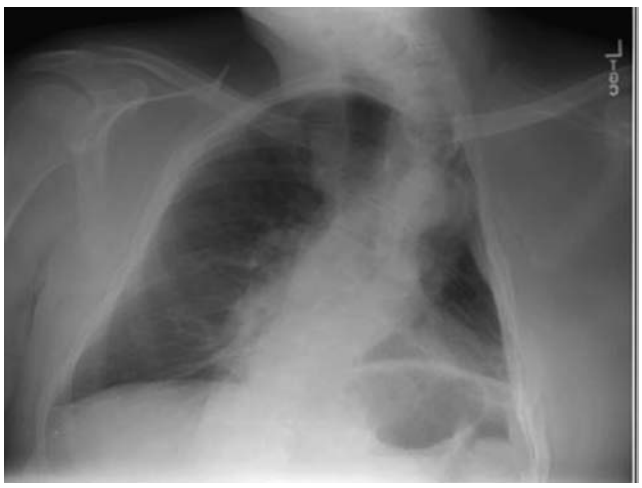

Figure 83-5 Chest radiograph of a patient with a history of *Mycobacterium tuberculosis*, demonstrating marked deformity of the left hemithorax consistent with prior thoracoplasty.

TABLE 83-3 Pulmonary Function in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
TLC (% predicted)	44	64	90	85
VC (% predicted)	30	49	90	79
RV (% predicted)	94	91	100	97
FEV_1 (% predicted)	40	41	93	81
FEV_1/FVC	80	57	81	74

KS, kyphoscoliosis; Post-THOR, post-thoracoplasty; AS, ankylosing spondylitis; PE, pectus excavatum; TLC, total lung capacity; VC, vital capacity; RV, residual volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

PECTUS EXCAVATUM

Clinical considerations in pectus excavatum are discussed below.

■ ETIOLOGY AND CLINICAL FEATURES

Pectus excavatum, also known as funnel chest, refers to a congenital chest wall deformity characterized by excessive depression of the sternum and the adjacent ribs producing a caved-in appearance to the rib cage.[44] It is the most common congenital deformity of the chest wall, with a prevalence of about 1 in 1000 live births and a male to female ratio of 3 to 1.[45] A family history may be present in 15% to 40% of cases.[46] It is believed to result from an abnormal growth of cartilage around the sternum due to a defect in collagen formation.[44] In support of this mechanism, is the higher prevalence of pectus excavatum in Marfan syndrome.[47] However, the pathogenesis of pectus excavatum in the majority of cases is unknown.

The sternal depression may be minimal or prominent. In extreme cases, it is usually apparent at birth and progresses as the child grows. The most frequent complaints of individuals with pectus excavatum are cosmetic. The psychological impact of the pectus deformity becomes more troublesome during the teenage years when body image becomes more important. Exertional dyspnea and exercise intolerance may occur in 30% to 70% of patients.[44] However, these symptoms cannot be entirely explained by the mild restrictive pattern, which is sometimes seen (Table 83-3) or by limitations in cardiac output.

The degree of sternal depression is best assessed with a chest CT scan. The ratio of the transverse to anterior–posterior (AP) diameters of the rib cage at the level of the deepest sternal depression (Haller index) can easily be measured using this technique

TABLE 83-4 Respiratory Mechanics in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
CRS (% predicted)	50	50	—	70
CCW (% predicted)	30	40	—	60
CL (% predicted)	60	50	80	80
PI_{max} (cmH_2O)	37	50	90	56
MVV (L/min)	37	37	107	80

KS, kyphoscoliosis; Post-THOR, post-thoracoplasty; AS, ankylosing spondylitis; PE, pectus excavatum; CRS, compliance of respiratory system; CCW, compliance of chest wall; CL, compliance of lungs; PI_{max}, maximum inspiratory pressure; MVV, maximum voluntary ventilation.

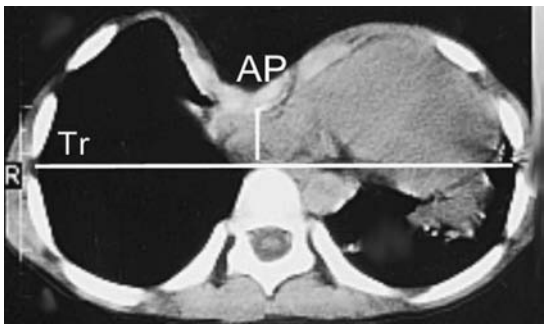

Figure 83-6 Chest computed tomography of a patient with pectus excavatum. The distance between the anterior aspect of the vertebral body and the posterior aspect of the sternum (AP) is decreased. The Haller index is calculated as the ratio of the internal transverse diameter (Tr) to AP distance.

(Fig. 83-6).[44] In normal individuals this ratio is about 2.5. A ratio greater than 3.25 is considered significant sternal depression.[44]

■ PATHOPHYSIOLOGY

Severe pectus deformities may be associated with mild restriction on pulmonary function tests. A Haller index of 5 or higher can be associated with mild reductions in TLC and VC. The restriction may be more pronounced if there is concomitant scoliosis.[48] Although obstructive defects are infrequent (approximately 2% of cases)[48] RV and the RV/TLC ratio are commonly increased. The elevated RV and RV/TLC may be due to stiffness of the rib cage resulting in reduced chest wall compliance in these young individuals rather than air trapping or expiratory muscle weakness. In most cases there is no underlying lung disease, and lung compliance is normal. Unlike AS, the mobility of the rib cage is not impaired at rest or during exercise in pectus excavatum.[49,50]

Cardiopulmonary exercise testing is usually normal in individuals with pectus excavatum. Indices such as maximal work rate, maximum oxygen consumption, and maximal oxygen pulse are not different from those of healthy individuals. In severe deformities, limited exercise capacity with reductions in maximal work rate or oxygen consumption at a given work rate may occur and often are out of proportion to the mild restrictive respiratory impairment found in these patients.[51] The explanation for the limited exercise capacity in this group of patients may be a reduction in venous return to heart associated with right ventricular compression due to sternal depression. Distortion of right ventricular geometry may be detected by echocardiographic or cardiac magnetic resonance imaging studies.[52] However, the role of these findings in limiting exercise capacity is not entirely known.

■ TREATMENT

Although surgery is most often performed for cosmetic reasons, it is clearly indicated when the deformity has significant physiological and psychological repercussions for the individual.[45,53] The optimal timing for repair is around 10 to 14 years of age or at a younger age if there is significant cardiopulmonary compromise. Individuals selected for repair typically have a Haller index greater than 3.25.[45,53]

The most common surgical approaches include modifications of the open-resection method originally described by Ravitch or the minimally invasive approach described by Nuss.[44] The first method involves resection of costal cartilage and a sternal osteotomy, with or without fixation of the sternum by external or internal supports. This procedure may be complicated by sternal necrosis, infection, or recurrence of the deformity. Recurrence may arise in younger children in whom sternal supports are not used. The invasive approach is best suited for individuals with combined pectus excavatum and carinatum, marked asymmetry, or extensive defects involving the upper ribs.[44]

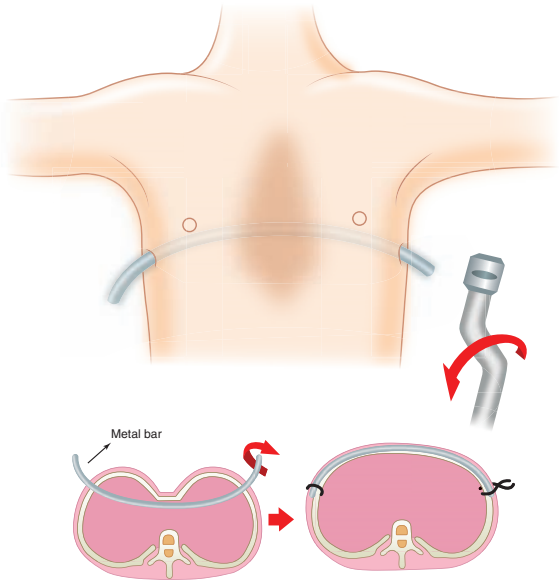

Figure 83-7 Schematic depicting the Nuss procedure in a patient with pectus excavatum. A curved bar is inserted behind the sternum and then rotated to displace the depressed sternum ventrally.

The Nuss procedure, developed in the 1990s, provides a minimally invasive alternative to reconstructing the deformity.[54] It consists of placing a curved metal bar under the sternum at the point of deepest depression through small incisions made on each side of the rib cage. The sternum is then pushed forward and stabilized by the metal bar (Fig. 83-7). With this procedure, the costal cartilage is not resected. The bar is generally left in place for 2 to 4 years, resulting in permanent chest wall remodeling. Complications of this approach include bar displacement or rotation that would require reoperation, as well as pneumothorax, pericarditis, and infection. The use of thoracoscopic techniques has minimized associated complications. Overall, the rate of complications does not differ significantly between the two surgical approaches.[55] Deformity repair with either procedure impacts positively on the psychosocial well-being of the individual.[55]

Improvements in cardiopulmonary function with invasive or minimally invasive procedures remain controversial.[56] If there is improvement, it is mostly modest and clinically insignificant. Improvements in exercise tolerance, cardiac output, and $\dot{V}O_{2max}$ after surgical correction have been described in some but not all studies.[56,57] Discrepancies among studies may be due to differences in patient populations (younger vs. older patients), surgical techniques, the interval at which tests are performed following the operation, or the effects of growth on pulmonary function. One year following surgery, any improvement in pulmonary function is independent of which surgical procedure was performed.

ANKYLOSING SPONDYLITIS

Important physiologic and clinical considerations in ankylosing spondylitis are described below.

■ ETIOLOGY AND CLINICAL FEATURES

AS is a chronic multisystem disease characterized by inflammation of the spine, sacroiliac and peripheral joints as well as involvement of extra-articular organs including the lungs and the heart.[58] Chronic inflammation of the spinal structures, costovertebral, apophyseal, and sacroiliac joints leads to fibrosis and ossification of these structures.[59] Consequently, spinal mobility is reduced and there is considerable limitation of rib cage expansion.[60]

AS affects approximately 0.1% of the general population and is more common in men than in women, with a ratio of 16:1. Its

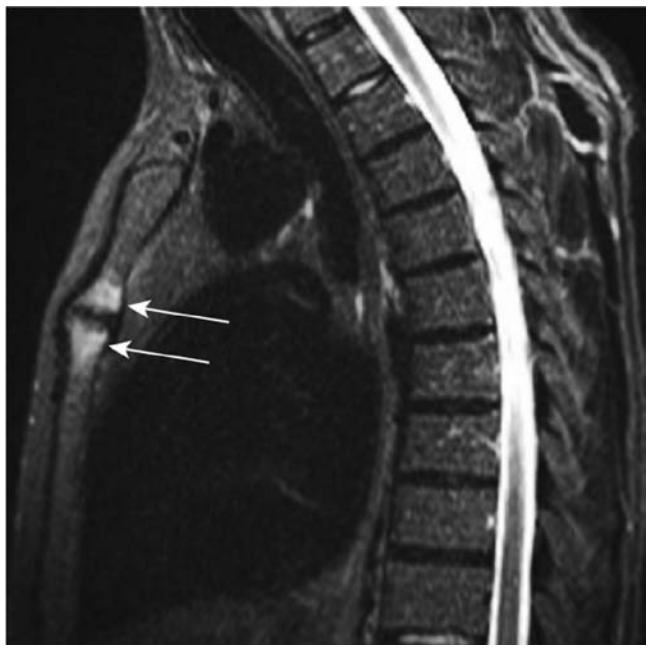

Figure 83-8 Inflammatory lesions of the anterior chest wall displayed by whole-body MRI in an ankylosing spondylitis patient complaining of anterior chest wall pain. *Arrows* point to bone marrow edema in both parts of the manubriosternal joint. *(Modified with permission from Weber U, Lambert RGW, Rufibach K et al. Anterior chest wall inflammation by whole-body magnetic resonance imaging in patients with spondyloarthritis: lack of association between clinical and imaging findings in a cross-sectional study. Arthritis Research & Therapy. 2012;14(1):R3.)*

etiology is unclear. There is a genetic predisposition for AS, as 95% of whites with AS have the HLA-B27 antigen.[58] Clinically, patients in late adolescence or early adulthood, present with back pain or morning stiffness due to involvement of sacroiliac joints. Onset of symptoms after the age of 45 is rare. Typically, the symptoms are worse in the morning or after prolonged rest. About 30% of individuals with AS have involvement of a peripheral joint or non-granulomatous anterior uveitis. Aortitis and dilatation of the aortic root may occur in up to 25% of patients.

Chest pain due to inflammation of manubriosternal junction and/or the sternoclavicular joints with inability to fully expand the chest on inspiration can occasionally occur (Fig. 83-8).[61] On physical examination, there may be tenderness of the anterior chest wall, the costochondral region, or the manubriosternal junction. Chronic back pain may cause sleep fragmentation resulting in difficulties with daytime somnolence and fatigue.[62] Upper airway obstruction due to cricoarytenoid cartilage involvement is a rare complication.[63]

Individuals with advanced AS have very limited rib cage motion and are more dependent on diaphragmatic breathing. Prominent abdominal excursion during inspiration may be apparent in supine or upright individuals. The degree of rib cage immobility can be assessed by measuring the change in rib cage circumference at the level of the fourth intercostal space between a full inspiration and full expiration. Rib cage expansion less than 2.5 cm should raise the possibility of AS in young patients with chronic low back pain.

■ RESPIRATORY PATHOPHYSIOLOGY

Limited rib cage expansion is the pathophysiological hallmark of AS.[59,64,65] This limitation results from fusion of the costovertebral and sternoclavicular joints and possibly leads to intercostal muscle atrophy.[59] Rib cage motion is similar to that in healthy individuals in terms of direction, but the extent of movement is diminished.[60] Rib

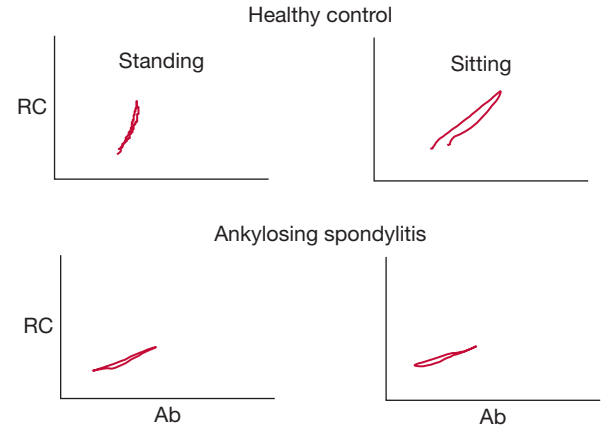

Figure 83-9 Changes in anteroposterior dimensions of the rib cage (RC) and abdomen (Ab) in a healthy individual and one with ankylosing spondylitis (AS). There is limited mobility of the rib cage in all positions resulting in greater motion of the abdomen relative to the rib cage.

cage immobility leads to a reduction in chest wall and total respiratory system compliance but lung compliance is generally normal (Table 83-4).[65]

Only mild reductions in VC or TLC (75%–80% of predicted) may be present despite moderately severe reductions in rib cage mobility (Table 83-3).[66] The restrictive impairment is associated with disease activity, disease duration, and spinal mobility.[66,67] Mild reductions of respiratory muscle strength (PI_{max}, and PE_{max}) may be recorded in individuals with severely limited rib cage expansion. However, diaphragmatic strength is typically intact in these patients.[59] Since rib cage expansion is severely limited in advanced AS, chest wall inflation is primarily accomplished through diaphragmatic displacement of the abdomen (Fig. 83-9). This pathway accounts for most of the change in tidal volume during quiet breathing, speech, or exercise.[68] In this setting, the increased diaphragm shortening and the relatively greater transdiaphragmatic pressure required to inflate a stiff rib cage[59] may potentially provide a training stimulus to the diaphragm.

In the absence of parenchymal lung disease, Pa_{O_2} is either in the normal range or mildly reduced.[66] Exercise capacity may be mildly decreased in patients with AS, especially in those with marked rib cage restriction.[69] The mechanism of limited exercise is most likely related to peripheral deconditioning rather than ventilatory constraints.[69]

■ PLEUROPULMONARY ABNORMALITIES

Upper lobe fibrobullous disease occurs in a small percentage (up to 4%) of individuals with AS.[70,71] It is more common in males with long-standing disease and may manifest as interstitial infiltrates, fibrosis with honeycombing, or cavitation that may mimic tuberculosis.[70,71] The pathogenesis of upper lobe fibrobullous disease is unknown. Possible mechanisms include decreased upper lobe ventilation, mechanical stress due to rib cage rigidity, and recurrent lung infection due to impaired cough. Individuals with fibrobullous disease have an increased propensity for spontaneous pneumothorax and infections with *Aspergillus* or atypical mycobacteria.[71] Fibrobullous disease tends to be progressive and its course is not altered by steroid treatment. Because resection of the lung segment with fibrobullous disease can be complicated by bronchopleural fistula in 50% to 60% of patients, surgery is reserved for treatment of massive hemoptysis.[71] Additional pleuropulmonary abnormalities that can be detected by chest CT include interstitial lung disease, pleural thickening, parenchymal bands, and bronchial wall thickening.[70] These abnormalities are subtle and do not correlate with clinical or functional impairment.

■ SLEEP DISORDERED BREATHING

An increased prevalence of obstructive sleep apnea in AS has been reported, especially in patients with long-standing disease (>5 years).[72,73] Because fatigue is a common complaint in AS, clinicians should have a high index of suspicion for concomitant sleep disordered breathing contributing to excessive daytime sleepiness and screen these patients with polysomnography.[72,73]

■ TREATMENT

Treatment of individuals with AS should incorporate pain relief, physical therapy, and measures to maintain posture. Physical therapy exercises that promote rib cage expansion have beneficial effects on pain and spinal mobility. Smoking should be avoided and baseline chest radiographs and spirometry obtained.

Over the past decade, the use of antagonists of tumor necrosis factor (TNF) has had a dramatic effect on pain control, fatigue, spinal flexibility, and quality of life in these patients.[74] Rib cage expansion is also improved following treatment with biological agents. The effectiveness of TNF-blockade can be maintained for several years with continued treatment. Since anti-TNF agents do not prevent new bone formation in AS patients, their overall effects on the natural history of the disease await further assessment.[75] An adverse effect of the anti-TNF therapy is reactivation of tuberculosis. Therefore, AS patients who are candidates for anti-TNF therapy should be screened for latent tuberculosis and receive prophylactic treatment with isoniazid before starting treatment.[76] Additional rare adverse pulmonary complications of anti-TNF blockade include interstitial lung disease and development of a sarcoid-like disorder.[76]

OBESITY

Obesity is a prevalent problem. Important clinical considerations are discussed below.

■ CLINICAL FEATURES

Obesity has reached an alarming prevalence throughout the world. It is estimated that about two-thirds of adults in the United States are either overweight or obese and 20% of children are obese.[77] The World Health Organization has declared obesity one of the top ten risk conditions worldwide and one of the top five in developed countries.[78] Obesity is associated directly or indirectly with several comorbidities, increased disability and decreased life expectancy.[79] It is a significant contributor to escalating healthcare costs.

Severity of obesity is commonly assessed by calculating the body mass index (BMI), defined as body weight (BW) in kilograms divided by the square of height (Ht) in meters (BW/Ht^2).[80] An individual with a BMI between 18.5 and 24.9 kg/m^2 is normal; a BMI between 25 and 29.9 kg/m^2 is overweight, and a BMI greater than 30 kg/m^2 is considered obese; BMI greater than 40 kg/m^2 is considered morbid obesity. Morbidity and premature mortality usually begin to increase at a BMI of 25 to 29.9 kg/m^2 and further increase with a BMI greater than 30 kg/m^2.

Obesity-associated respiratory morbidity results primarily from derangements in chest wall mechanics and the control of breathing.[81,82] Obesity may decrease lung volumes, decrease respiratory muscle strength, increase the work of breathing and reduce respiratory drive.[81,82] Despite these limitations, most morbidly obese patients remain eucapnic; referred to as simple obesity (SO). However, a subgroup of morbidly obese individuals develops hypercapnia.[81] These individuals have obesity hypoventilation syndrome (OHS) (Table 83-5).

■ PULMONARY FUNCTION AND CHEST WALL MECHANICS

In SO, the most common impairments in pulmonary function include a decrease in expiratory reserve volume (ERV) and FRC.[83] In contrast, TLC is normal or only mildly reduced (Table 83-6).[83] The lower than normal FRC is due to the increased volume of abdominal and thoracic fat that makes pleural pressure less subatmospheric and may decrease chest wall compliance.[82,84,85] Both factors lower resting end-expiratory relaxation volume (FRC). RV may be normal or even slightly increased in SO.[83] As a result, ERV which is the difference between FRC and RV is reduced.[83] Expiratory flow rates and the FEV_1/FVC ratio are usually normal in SO except for modest reductions in FVC when the BMI exceeds 45 kg/m^2.[82]

In OHS, FRC and ERV are more severely reduced than they are in individuals with SO and a comparable BMI (Table 83-6). In OHS, TLC is reduced but to a lesser extent than FRC and ERV.[81,86] These differences in pulmonary function between SO and OHS may be explained by differences in the distribution of adipose tissue. Individuals with OHS, typically have a central pattern of fat distribution. For a given BMI, a central pattern of fat distribution (measured as the waist:hip circumference ratio) is associated with greater impairment in lung function than a peripheral (around the hips) fat distribution.[87,88] This pattern is seen more commonly in men than in women.[89]

Respiratory system compliance is invariably decreased in obese individuals.[84,90,91] In morbidly obese patients, respiratory system compliance decreases exponentially as BMI increases. The reduction in respiratory system compliance can be primarily attributed to a decrease in lung compliance.[85] When FRC is reduced with obesity, lung compliance decreases due to airway closure and the

TABLE 83-5 Diagnostic Criteria for Obesity Hypoventilation Syndrome

BMI >30 kg/m^2
Daytime Pa_{CO_2} >45 mm Hg
Rise in Pa_{CO_2} of >5 mm Hg during sleep
Sleep disordered breathing
Absence of other known causes of hypoventilation

TABLE 83-6 Pulmonary Function, Gas Exchange, and Respiratory Mechanics in Simple Obesity (SO) and Obesity Hypoventilation Syndrome (OHS)

	Normal	SO	OHS
BW (% ideal)	105	195	201
BMI (kg/m^2)	24	45	46
FVC (% predicted)	95	88	70
FEV_1 (% predicted)	100	85	70
FRC (% predicted)	100	83	80
ERV (% predicted)	96	52	32
TLC (% predicted)	100	95	83
MVV (% predicted)	159	129	89
Pa_{O_2} (mm Hg)	90	83	58
Pa_{CO_2} (mm Hg)	37	38	55
CRS (L/cmH_2O)	0.11	0.05	0.06
RRS ($cmH_2O\ L^{-1}\cdot s$)	1.2	4.0	7.8
PI_{max} (cmH_2O)	100	95	60
Work (J/L)	0.43	0.74	1.64

BW, Body weight; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; ERV, expiratory reserve volume; TLC, total lung capacity; MVV, maximum voluntary ventilation; CRS, compliance of respiratory system; RRS, resistance of respiratory system; PI_{max}, maximum inspiratory pressure.

development of atelectasis. Whether a stiffened chest wall contributes to the reduction in respiratory system compliance remains controversial. Differences among studies reporting either normal or reduced chest wall compliance may be due to difficulties measuring chest wall compliance when the respiratory muscles are not fully relaxed.[90–93] To circumvent this issue, chest wall compliance has been measured in anesthetized, paralyzed obese individuals and found to be normal.[90,94] In this setting, the chest wall pressure–volume curve has the same slope as a nonobese individual but is shifted rightward. This rightward shift is consistent with mass loading of the thorax. Mechanistically, the excess chest wall adipose represents an inspiratory threshold load. Once the threshold load is overcome, the chest wall inflates similar to the normal chest wall.[82,90]

Morbidly obese individuals may have increased airway resistance,[95] exhibit expiratory flow limitation[96] and develop intrinsic positive end-expiratory pressure (PEEP).[96–98] The increase in airway resistance has been attributed to breathing at low lung volumes.[99,100] However, even when correcting for low lung volume, specific airway resistance remains elevated. Thus additional factors must be contributing to increased airway resistance.[95,101] Expiratory flow limitation has been described in obese individuals during tidal breathing, especially in the supine position.[96,97] Flow limitation may be primarily related to shifting FRC to a region on the flow–volume curve where tidal breathing encroaches on the maximal flow–volume envelope.[82] In the supine position, further reductions in FRC[95,100] increase the likelihood that expiration will be flow-limited. Intrinsic PEEP develops as a consequence of expiratory flow limitation especially in circumstances where expiratory time is reduced or tidal volume increased (i.e., exercise). Intrinsic PEEP also may develop in the supine position when FRC is further reduced. Consequently, obese individuals may complain of orthopnea.[96–98]

Respiratory muscle strength, as measured by PI_{max} and PE_{max}, as well as respiratory muscle endurance, as measured by MVV, are generally preserved in SO.[98,100,102] In contrast, individuals with OHS often have a reduction in MVV and exhibit respiratory muscle weakness, with strength diminished to approximately 40% of predicted.[81,102] Mechanisms that potentially explain respiratory muscle weakness in OHS include respiratory acidosis and mechanical disadvantage of the diaphragm related to its rostral displacement by adipose tissue.[81,102] The combination of weakened inspiratory muscles and altered chest wall mechanics contribute to the reduction in TLC in OHS (Fig. 83-10).[95]

CONTROL OF BREATHING

In nonobese individuals, added elastic or threshold inspiratory loads increase neural drive to the respiratory muscles.[103] Likewise, in eucapnic morbidly obese individuals the added elastic and threshold loads increase respiratory drive; usually two to three times that of nonobese subjects.[104] Changing from the sitting to supine position increases further the respiratory drive in obese but not in nonobese individuals.[98] The augmented respiratory drive is strongly associated with BMI and is important for maintaining normocapnia in obesity.[98] Patients with OHS do not exhibit increased respiratory drive in response to loads placed on the respiratory muscles.[105]

Respiratory drive can be assessed by measuring either the ventilatory or mouth occlusion pressure (P0.1) responses to hypercapnia or hypoxia. The ventilatory response to hypercapnia is mildly reduced in SO compared to normal weight individuals.[104,105] The inability of individuals with SO to appropriately increase ventilation in response to CO_2, however, may reflect disordered chest wall mechanics limiting ventilation rather than a true reduction in central respiratory drive. When compared to SO, individuals with OHS have an even lower ventilatory response to hypercapnia and hypoxia, with the response to hypoxia blunted to a greater extent than the response to hypercapnia.[105] As with SO, altered respiratory system mechanics contribute to the inability to appropriately increase ventilation. However, with OHS, other indices of central respiratory drive, such as P0.1 and diaphragmatic EMG, are reduced. Factors that may reduce chemosensitivity in OHS include the presence of sleep apnea, persistent hypoxia, or hormonal mediators such as adipokines.[81] High serum levels of leptin, a hormone produced by adipose tissue, are associated with reduced respiratory drive in severely obese individuals (Fig. 83-11).[81,106]

Basal O_2 consumption and CO_2 production are increased in morbid obesity.[91] Therefore, these individuals require higher levels of alveolar ventilation to maintain eucapnia.[82] In addition, the work of breathing is increased in morbid obesity.[107,108] To attain the requisite levels of ventilation and minimize the work per breath, obese individuals adopt a rapid shallow breathing pattern with breathing frequency about 40% higher than that of nonobese individuals.[103] The increase in breathing frequency is accomplished by shortening both inspiratory and expiratory time while the ratio of inspiration to total breath time (T_I/T_{TOT}) remains normal.[103,107,109] A rapid shallow breathing pattern allows them to minimize the elastic and resistive work per breath. This pattern is amplified in OHS.[104,109] These individuals have a breathing frequency that is higher and a tidal volume that is about 25% lower than individuals with SO.[104,109]

Exercise capacity is near normal in SO.[110] During treadmill exercise, minute ventilation, respiratory rate, heart rate, and oxygen consumption are generally higher in obese individuals than in

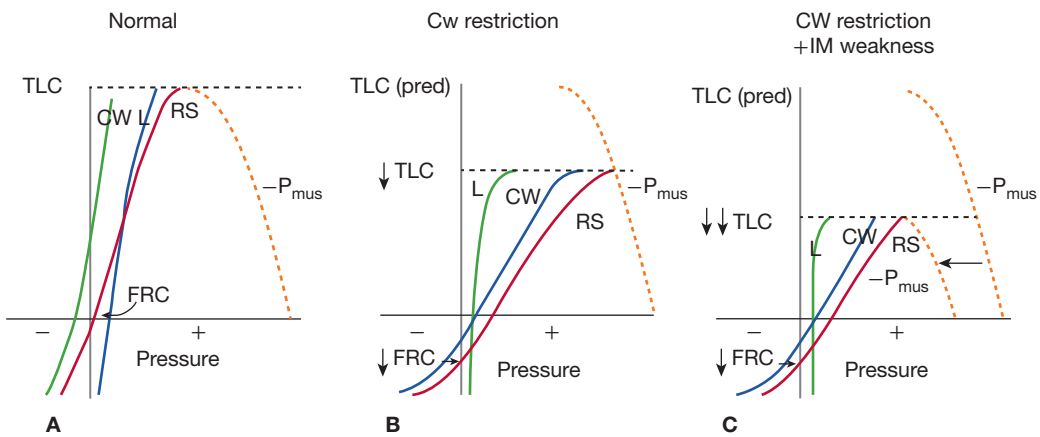

Figure 83-10 Schematic showing the volume–pressure relationships of the chest wall *(dashed line)*, lung *(dot and dashed lines)*, and respiratory system *(solid line)* for (**A**) healthy individuals, (**B**) individuals with chest wall restriction, and (**C**) individuals with chest wall restriction complicated by inspiratory muscle (IM) weakness. In panel B, the reduced chest wall compliance lowers respiratory system compliance, FRC, and TLC. In panel C, maximal inspiratory muscle pressures (P_{mus}) are half of predicted and the restriction is amplified by the presence of IM weakness.

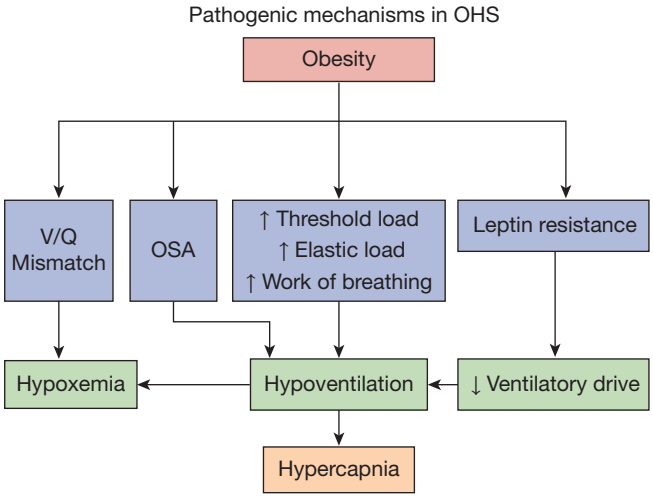

Figure 83-11 Factors involved in the pathophysiology of obesity hypoventilation syndrome.

normal weight individuals.[110,111] However, the anaerobic threshold is lower than in normal weight individuals.[110,111] With weight loss, the metabolic demands are reduced and carbon dioxide production and alveolar ventilation are reduced by approximately 20%.[112]

GAS EXCHANGE

Hypoxemia is either mild or absent in SO whereas it is usually present in OHS.[82] Hypercapnia during wakefulness, the defining characteristic of OHS, rarely occurs in obese individuals with a BMI less than 30 kg/m^2.[82,113] In obese individuals with a BMI greater than 30 kg/m^2, Pa_{O_2} is negatively and Pa_{CO_2} is positively related with BMI (Fig. 83-12).[82,113] In OHS, gas exchange abnormalities are primarily due to hypoventilation, which lowers the partial pressure of O_2 and increases the partial pressure of CO_2 in the alveoli. In addition, venous admixture due to ventilation–perfusion mismatch widens the alveolar–arterial oxygen gradient and worsens hypoxemia.[114] Mismatch of ventilation and perfusion is likely to occur at the lung bases, which are generally well perfused in obesity but poorly ventilated due to airway closure or atelectasis.[94,114] Gas exchange abnormalities are amplified when obese individuals assume the supine position.[115] This can be a major concern during induction of anesthesia as these individuals may become profoundly hypoxemic.[116]

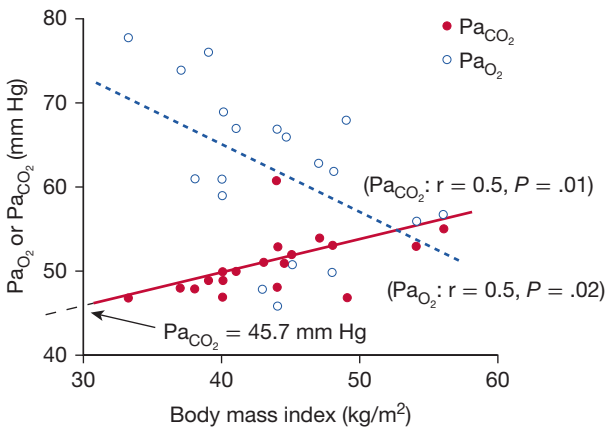

Figure 83-12 Relationship between Pa_{CO_2} and Pa_{O_2} with body mass index in patients with obesity hypoventilation syndrome. *(Reproduced with permission from Mokhlesi B. Obesity Hypoventilation Syndrome: A State-of-the-Art Review, Respir Care. 2010;55(10):1347–1362.)*

TREATMENT

Although difficult, dietary changes combined with exercise and behavioral modifications can lead to weight loss in some obese individuals. However, these modalities are usually not successful in maintaining long-term weight loss.[117] Bariatric surgery has evolved into a relatively common intervention that can produce not only weight loss but also long-term maintenance of weight loss.[118] In patients with OHS and acute or chronic hypercapnic respiratory failure, intermittent noninvasive ventilation may improve gas exchange, daytime somnolence, and quality of life.

Weight loss, induced either by diet or surgical intervention, has beneficial effects on pulmonary function, gas exchange, and ventilatory control in both OS and OHS.[81,119] A weight loss of about 40 kg leads to a significant increase in ERV and, to a lesser extent, increases in FRC, VC, and TLC.[81,119] The Pa_{O_2} increases by about 4 to 8 mm Hg due to improved ventilation of the lung bases. In OHS, the effects of weight loss on ERV and FRC are more pronounced than in SO, with VC increasing as well.[37,114] Similarly, Pa_{O_2} and Pa_{O_2} are significantly improved in OHS.[37,114] Following weight loss, ventilatory drive trends toward normal in both SO and OHS; namely it decreases in SO and increases in OHS.[81,120] The oxygen cost for a given level of exercise is also diminished after weight loss in OHS.[121]

FLAIL CHEST

Flail chest refers to a condition in which multiple rib fractures produce a segment of the rib cage that deforms markedly during breathing. According to a classic definition, double fractures of three or more adjacent ribs or the combination of sternal and rib fractures are required to produce a flail segment of the rib cage and lead to respiratory failure.[122] The flail segment is displaced inward rather that outward during inspiration However, clinical observations suggest that multiple single rib fractures in a single plane can also lead to respiratory failure. In this instance, the term "nonintegrated chest wall" rather than "flail chest" has been used.[123] Flail chest can occur in up to 15% of adults with chest wall trauma[124] The most common cause of flail chest is trauma related to automobile accidents or falls.[124,125] Other causes include rib fractures after aggressive cardiopulmonary resuscitation and rarely pathological rib fractures (i.e., multiple myeloma, other metastases).[126]

The diagnosis of flail chest can readily be made in spontaneously breathing individuals by inspecting the chest wall and observing the paradoxical motion of the flail segment of the rib cage. In fully sedated mechanically ventilated patients the diagnosis may be delayed until patients resume spontaneous breathing.[127] Chest radiographs showing multiple rib fractures confirm the diagnosis but usually miss 50% of rib fractures, especially those at the costochondral junction.[128] Chest CT with reconstruction of the rib cage is the best imaging modality to visualize rib fractures and to demonstrate the extent of injuries to the pleura and pulmonary parenchyma (Fig. 83-13).[129]

The mortality of chest wall trauma with no flail present ranges between 7% and 14%. When chest wall trauma is complicated by flail chest, the mortality rate further increases.[130] This can be attributed to pulmonary complications, such as pulmonary contusion, hemothorax, or pneumothorax, which can occur in up to 60% of patients with flail chest.[130] In addition, trauma sufficient to cause flail chest is often accompanied by extrathoracic injuries such as head trauma, rupture of the aortic arch or other arteries, laceration of the spleen or liver, and fractures of the long bones, all of which increase morbidity and mortality. Patients with multiple trauma and lung contusion complicating flail chest have mortality as great as 56%. Age is another factor strongly associated with mortality in patients with flail chest.[131] In one study, patients with flail chest over the age of 80 had a mortality of 86%.[132] In survivors of flail chest, long-term disability consisting of chest tightness, chest pain, or exertional dyspnea may occur.[133]

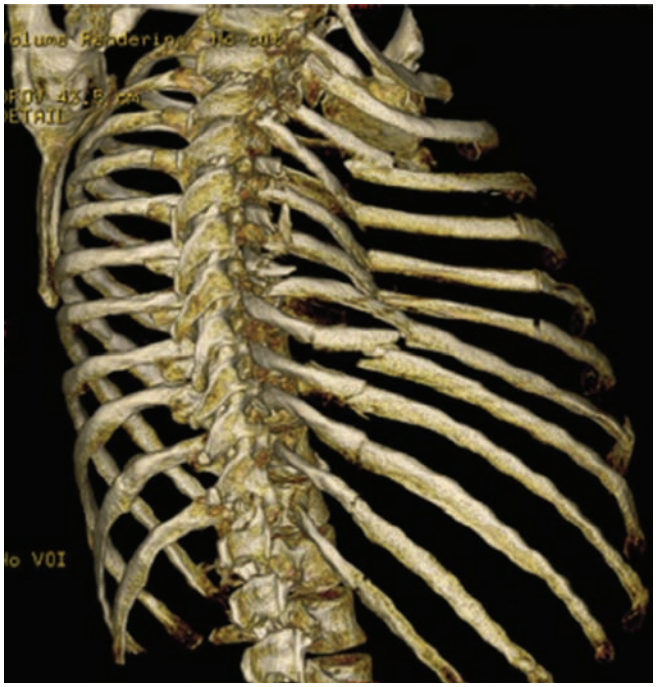

Figure 83-13 Posterior view of a reconstructed three-dimensional computed tomographic scan depicting a massive flail chest. *(Reproduced with permission from Pacheco PE, Orem AR, Vegunta RK, et al. The novel use of Nuss bars for reconstruction of a massive flail chest. J Thorac Cardiovasc Surg. 2009;138(5):1239–1240.)*

■ RESPIRATORY FUNCTION AND RESPIRATORY MECHANICS

Disruption of rib cage integrity in flail chest renders motion of the flail segment entirely dependent on pleural pressure changes during breathing. Normally, rib cage expansion is accomplished by (a) the inflationary action of the contracting diaphragm on the lower rib cage; (b) the actions of the intercostal muscles on the upper rib cage; (c) positive intra-abdominal pressure in the zone of apposition of the diaphragm to the rib cage; and (d) the passive outward recoil of the rib cage at low lung volumes. During inspiration, pleural pressure becomes subatmospheric, which is inflationary to the lung and deflationary to the rib cage. When multiple rib fractures uncouple a segment of the rib cage from the remainder of the chest wall, the deflationary effect of subatmospheric pleural pressure is unopposed by the factors that promote rib cage expansion (Fig. 83-14).[64] Consequently, the flail segment moves inward rather than outward during inspiration. During expiration, pleural pressure becomes more positive and the flail segment moves outward. This paradoxical motion of the flail segment is augmented by conditions that load the respiratory system thereby amplifying pleural pressure swings. Specifically, conditions such as a reduction in lung compliance (pulmonary contusion or edema) or increases in airway resistance (bronchial secretions, bronchospasm) will make movement of the flail segment more pronounced.[64]

The most common anatomical location for flail chest is the lateral rib cage. Anterior flail chest occurs when there are separations between the sternum and the ribs.[130] Posterior flail chest is associated with less severe clinical derangements due to splinting provided by the paravertebral muscles. The pattern of paradoxical rib cage and abdominal motion is not unique to the location of the flail segment. Paradoxical chest wall motion may occur within the rib cage itself (i.e., between the upper and lower rib cage), or between the rib cage and abdomen (i.e., lower rib cage and anterior abdominal wall).[64] These different patterns of motion of flail chest may reflect different respiratory muscle recruitment patterns.[64] Supporting evidence for alteration in the pattern of respiratory muscle action is the

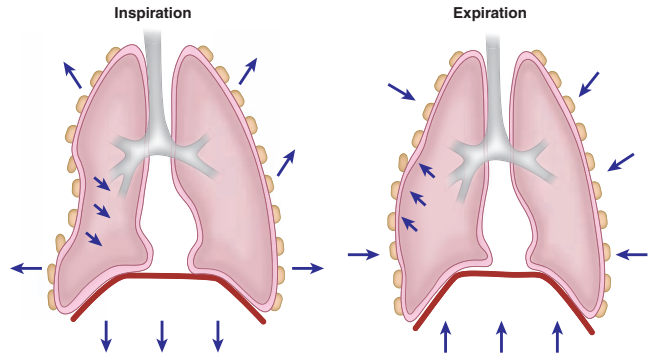

Figure 83-14 During inspiration, pleural pressure becomes more negative causing the flail segment to move paradoxically inward as the remainder of the chest wall is moving outward. During expiration, pleural pressure increases, causing the flail segment to move outward as the remainder of the chest wall becomes smaller.

observation that EMG activity of the external intercostal muscles increases more than threefold in the flail region.[134]

VC and FRC can be reduced to as much as 50% of predicted in patients with flail chest.[127] Paradoxical movement of the flail segment and coexisting pulmonary contusion contribute to reductions in VC. With surgical stabilization of the flail segment, VC usually returns to normal range in about 3 months. In patients with pulmonary contusion complicating flail chest, VC and FRC may remain reduced for up to 4 years due to fibrous changes in the contused area.[127,133,135]

The pathogenesis of respiratory failure in flail chest is complex. The notion that the paradoxical motion of a flail segment contributes to respiratory failure through a pendelluft-like movement of gas from the normal hemithorax to the flail hemithorax is not valid. Rather, factors related to flail-induced changes in lung and respiratory muscle function likely contribute to respiratory failure. Specifically, flail chest is accompanied by considerable pain, which can impair cough effectiveness, cause regional atelectasis, rib cage muscle spasm, and alter the pattern of respiratory muscle activation and recruitment. In addition, flail chest may increase the elastic load imposed on the respiratory muscles through development of regional (near the flail segment) or generalized atelectasis (due to splinting and pain). Associated pulmonary contusion also would increase the elastic load and work of breathing. In addition, the work of breathing is increased because the inspiratory muscles have to shorten more for a given tidal volume. The excessive muscle shortening represents extra work that is not measured using standard calculations of work per breath (the muscles shorten but do not produce measurable flow at the mouth).[64] Another adverse consequence of excessive inspiratory muscle shortening is a reduction in the mean operating length of the inspiratory muscles. When the inspiratory muscles are activated at a shorter than optimal length, inspiratory muscle efficiency is reduced, thereby adding to the oxygen cost of breathing.[64] The combination of added work of breathing, respiratory muscle inefficiency, hypoxemia due to atelectasis, and pulmonary contusion all combine to predispose these patients to respiratory muscle fatigue and respiratory failure (Fig. 83-15).

■ TREATMENT

The basic objective of treatment is to control pain and minimize atelectasis. Improved pain control also would enhance cough efficiency and allow for larger tidal volumes and reduce dead space ventilation. Pain control can be accomplished by use of oral or intravenous narcotics, intercostal nerve blocks, or epidural anesthesia. Adequate pain relief in combination with supplemental oxygen, frequent tracheal bronchial toilet, and cautious fluid replacement

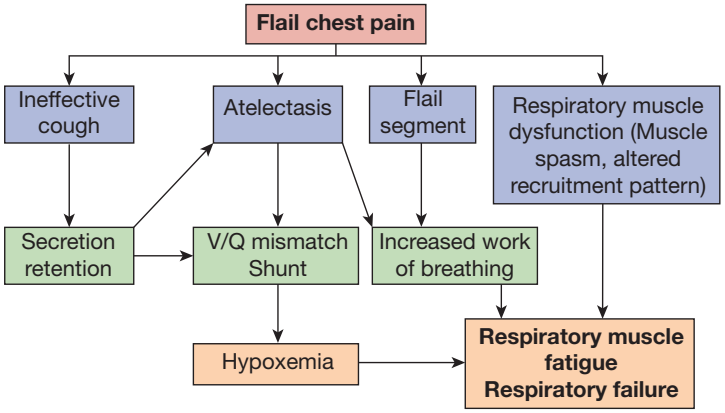

Figure 83-15 Factors involved in the pathophysiology of flail chest.

often prevents development of respiratory failure and leads to successful treatment of flail chest. Stability of the flail chest can be accomplished with the use of positive pressure mechanical ventilation or surgical fixation in selected individuals.

Mechanical ventilation with positive pressure breathing can stabilize the flail segment by eliminating the subatmospheric changes of pleural pressure that occur during spontaneous breathing. Prolonged mechanical ventilation as a means of treating flail chest was proposed in the 1960s and was initially accomplished through tracheostomy. However, complications related to mechanical ventilation, such as pneumonia, increased morbidity and mortality led to abandoning this modality as a primary means of stabilizing the chest wall. Currently, mechanical ventilation is indicated when there is respiratory failure, concomitant central nervous system or intra-abdominal injuries, shock, or the need to operate for other injuries. If mechanical ventilation delivered via an endotracheal tube is instituted, ventilator modes that minimize patient effort and the generation of subatmospheric pleural pressure should be employed. For example, low impedance modes of mechanical ventilation (i.e., high-flow continuous positive airway pressure [CPAP]) are associated with less chest wall distortion during inspiration.[64]

Noninvasive positive pressure ventilation may provide an alternative means of stabilizing the flail segment in selected patients who are breathing spontaneously.[136–138] This modality in conjunction with regional anesthesia can improve gas exchange and enable physiotherapy and early patient mobilization. In selected patients with flail chest, noninvasive ventilation may significantly reduce morbidity and length of hospitalization.[136–138] A randomized control trial comparing patients with mask CPAP versus assist control ventilation found that patients treated with mask CPAP had fewer complications, a shorter hospital and intensive care unit length of stay, and less ventilator time than patients with similar degrees of blunt thoracic trauma treated with assist control ventilation.[136] Larger trials evaluating noninvasive positive pressure ventilation are needed for further validation.

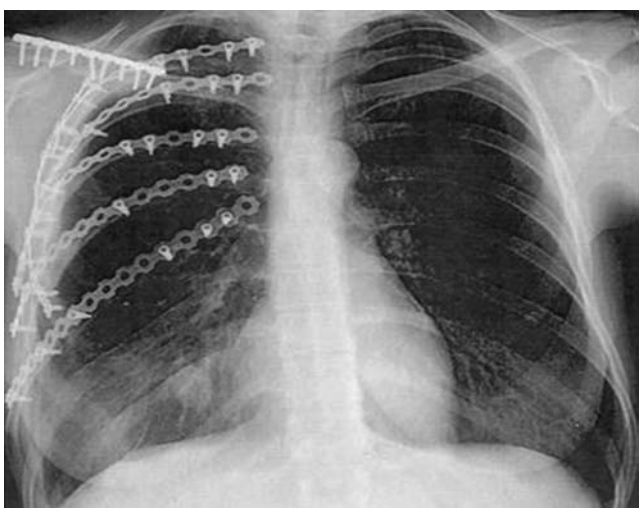

Figure 83-16 Chest radiograph depicting osteosynthesis plates in an individual who has undergone operative chest wall fixation for flail chest. *(Reproduced with permission from Engel C, Krieg JC, Madey SM et al. Operative chest wall fixation with osteosynthesis plates. J Trauma. 2005;58(1):181–186.)*

Surgical fixation of the flail chest can potentially provide substantial benefits to mechanically ventilated patients. In selected patients with flail chest, fixation of the chest wall with wires, steel plates, and splints improves respiratory mechanics and reduces the duration of mechanical ventilation as well as hospital stay (Fig. 83-16).[139–141] Operative fixation will likely benefit patients who are ventilator dependent and able to protect their upper airways. Other potential candidates may be patients undergoing thoracotomy for intrathoracic injuries, young patients with severe chest deformation, or patients with large unstable segments and borderline pulmonary function. The indications for operative fixation remain controversial largely due to the lack of studies comparing operative and nonoperative treatment.[139–141]

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CHAPTER 84

Effects of Neuromuscular Diseases on Ventilation

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INTRODUCTION

Neuromuscular diseases comprise a diverse group of disorders that vary markedly in etiology, rate of progression, pattern of respiratory involvement, prognosis, and therapy. Neuromuscular disorders impair the respiratory system as a vital pump; however, depending on the particular disease, the respiratory pump may be impaired at the level of the central nervous system (e.g., cerebral cortex or brainstem), spinal cord, peripheral nerve, neuromuscular junction, or respiratory muscle (Table 84-1).

The pattern of ventilatory impairment among these disorders is highly dependent on the specific neuromuscular disease. For example, some disorders may impair ventilation at only one level (e.g., isolated diaphragm paralysis) or simultaneously affect it at different levels (e.g., multiple sclerosis [MS]). In addition, the severity of impairment may be minimal and totally resolve with time and proper treatment (e.g., Guillain–Barré syndrome [GBS]) or is characterized by relentless progression to eventual respiratory death (e.g., amyotrophic lateral sclerosis [ALS]). Moreover, some neuromuscular diseases concomitantly affect several structures (e.g., swallowing dysfunction in poliomyelitis, interstitial lung disease in polymyositis), increasing ventilatory workload in patients who already have diminished ventilatory reserve.

This chapter describes the etiology, pathophysiology, and treatment of ventilatory dysfunction in neuromuscular diseases.

TABLE 84-1 Levels of Respiratory System Dysfunction Induced by Neuromuscular Diseases and Conditions

Level	Disease or Condition
Upper motor neuron	Parkinson disease
Cerebral	Vascular accidents Cerebellar atrophy Trauma
Spinal cord	Trauma Tumor Syringomyelia Multiple sclerosis
Lower motor neuron	
Anterior horn cells	Poliomyelitis Spinal muscle atrophy Amyotrophic lateral sclerosis
Motor nerves	Cardiac surgery Charcot–Marie–Tooth disease Diabetes Polyneuropathy Toxins Guillain–Barré syndrome
Neuromuscular junction	Neuralgia amyotrophy Critical illness polyneuropathy Myasthenia gravis Eaton–Lambert syndrome
Muscle	Botulism Organophosphate poisoning Drugs Dystrophy Acid maltase deficiency Malnutrition Corticosteroids Polymyositis

RESPIRATORY PATHOPHYSIOLOGY

Substantial information exists concerning the ventilatory function of patients with neuromuscular disease at rest and during sleep, as well as the effects on maximum static inspiratory and expiratory efforts and responses associated with these disorders to hypoxic and hypercapnic challenges. In general, the response of the respiratory system to moderate or severe neuromuscular disease is relatively stereotyped. The typical features are a reduced forced vital capacity (VC), reduced respiratory muscle strength, and, in some cases, malfunction of the neurons that control breathing.

CONTROL OF BREATHING

The breathing pattern is often abnormal in patients with neuromuscular disease. In comparison with healthy subjects, patients with respiratory muscle weakness have a low tidal volume and a high respiratory rate that persists in response even to hypoxic or hypercapnic challenge. Moreover, this rapid, shallow breathing pattern is not due to abnormalities in gas exchange (i.e., hypoxemia or hypercapnia) but is more likely to be due to severe muscle weakness and/or disordered afferent and efferent output in motor neurons impaired by the underlying neuromuscular disease.[1]

Changes in ventilation can be used to evaluate ventilatory drive in subjects with normal lung and respiratory muscle mechanics. However, ventilation is not a good index of respiratory motor activity in subjects with significant respiratory muscle weakness because the thoracic bellows cannot perform increased work of breathing. Decreased ventilatory response to hypoxic or hypercapnic challenge in these patients could indicate abnormalities in afferent information from diseased respiratory muscles, abnormal lung or chest wall mechanics, or upper motor neuron dysfunction, rather than an abnormality in the central control of breathing. In some neuromuscular diseases, degenerative changes in the muscle spindle, impaired afferent stimulation from abnormal stretch reflexes in the muscle spindles, or decreased mechanoreceptor output from tendons may explain the altered breathing pattern.[1]

Measurement of mouth occlusion pressure generated during the first 100 ms of inspiration ($P_{0.1}$) is relatively independent of inspiratory effort and therefore is a more reliable estimate of central ventilatory drive independent of respiratory muscle mechanics.[2] $P_{0.1}$ is maintained or increased in patients with neuromuscular disease despite substantial muscle weakness. The relationship between respiratory mechanics, respiratory muscle strength, and control of ventilation has been examined in patients with neuromuscular diseases in comparison with healthy control subjects. Although patients had 37% and 52% reductions in maximum inspiratory and expiratory mouth pressures, respectively, their $P_{0.1}$ was 66% greater than that of controls.[1]

Similar findings were encountered when normal subjects had acute muscle weakness induced by curarization. After severe muscle weakness was induced, significant increases in $P_{0.1}$ were observed

during hypercapnic challenge.[3] Partial curarization of spontaneously breathing cats also produced a marked increase in phrenic nerve discharge despite a substantial decrease in minute ventilation.[4] These studies indicate that under conditions of substantial respiratory muscle weakness, ventilation is not a reliable measure of central respiratory drive, and that central respiratory drive, at least when measured by $P_{0.1}$, is usually well preserved.

RESPIRATORY MUSCLE FUNCTION

Patients with neuromuscular disease who develop significant respiratory muscle weakness may experience fatigue, dyspnea and impaired control of secretions, recurrent lower respiratory tract infections, acute or chronic presentations of respiratory failure, pulmonary hypertension, and cor pulmonale.

The pattern, prognosis, and degree of respiratory muscle weakness attributable to a neuromuscular disorder are varied. They depend on the level of neuromuscular system impairment, the prognosis of the underlying disorder, and whether therapy is available. Patients with neuropathy, such as GBS, tend to have less severe respiratory muscle weakness than patients with lower motor neuron lesions or neuromuscular junction disorders, such as myasthenia gravis. Even when respiratory muscle dysfunction is observed, not all respiratory muscles are equally impaired, and the course of the underlying neuromuscular disease and degree of respiratory and nonrespiratory muscle impairment can be very different between patients with the same disease. In some neuromuscular disorders, respiratory muscle weakness is the only presentation of an underlying disease (i.e., neuralgia amyotrophy of the diaphragm); in the case of muscular dystrophy, significant respiratory muscle weakness may occur only late in the disease course. Severe, relentless, progressive dysfunction of the respiratory muscles may occur, as in ALS, or be characterized by exacerbations and relapses (e.g., MS). Finally, respiratory muscle weakness may completely reverse with time (phrenic nerve injury after open heart surgery) or with therapy (plasmapheresis in myasthenia gravis).

A significant proportion of patients with severe respiratory muscle weakness were also found in 50% of 30 asymptomatic patients with stable chronic neuromuscular disease. Reductions in inspiratory and expiratory mouth pressures did not correlate with general muscle strength assessment; however, the type of neuromuscular disease and distribution of general muscle weakness both correlated with respiratory muscle impairment.[5] Patients with myopathy, rather than polyneuropathy, whose involvement produced proximal rather than distal limb muscle weakness, were more likely to have significant respiratory muscle weakness. Pulmonary symptoms correlated poorly with evidence of respiratory muscle weakness.

Explanations for the lack of pulmonary complaints in these two studies despite significant muscle weakness are not clear. Patients with chronic and severe neuromuscular disease are usually sedentary and incapable of exertion and, therefore, seldom stress the respiratory system, which may explain their lack of symptoms.

The rapid, shallow breathing pattern found in patients with respiratory muscle weakness may be due to decreased respiratory muscle force generation, but it may also be due to changes in lung and chest wall elastic recoil. A decrease in inspiratory muscle tone may lead to unopposed lung elastic recoil, which reduces lung volume and produces chronic changes in chest wall tone and distensibility. Once inspiratory muscle strength decreases to approximately 30% of normal, abnormalities in gas exchange (manifested primarily by hypercapnia) commonly occur.

Expiratory muscle weakness is also commonly observed in patients with neuromuscular disease. It causes ineffectual cough and impaired secretion clearance, which in some patients lead to recurrent lower respiratory tract infections. In normal persons, dynamic compression of the central intrathoracic airways by large changes in pleural pressure generated by forceful contraction of the expiratory muscles acts to propel secretions proximally, where they can be expectorated. As expiratory muscle weakness progresses, pleural pressures generated during coughing efforts are reduced and airway clearance is impaired.

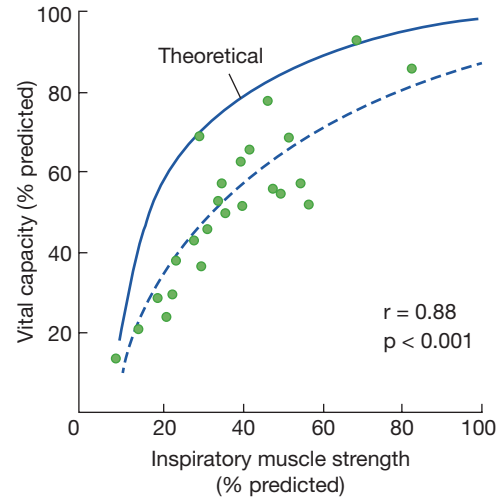


Figure 84-1 The *solid curve* represents the theoretic effect of respiratory muscle weakness on vital capacity (VC) on the assumption that the relaxation pressure–volume characteristic of the lung and chest wall are normal and that the inspiratory and expiratory muscles are uniformly involved. *Dashed curve* is the logarithmic regression calculated in 25 patients with neuromuscular disease *(closed circles)*. Data suggest that loss of lung volume is out of proportion to the degree of inspiratory muscle weakness. *(Data from De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax. 1980;35:603–610.)*

LUNG AND CHEST WALL MECHANICS

A characteristic hallmark of chronic neuromuscular disease is a decreased VC. The VC is reduced because of respiratory muscle weakness, and the decrease in VC parallels the progression of the underlying disease, but the magnitude of the reduction in VC is greater than expected solely based on the reduction in respiratory muscle force. The sigmoidal shape of the pressure–volume curve would suggest that large reductions in pressure initially produce only small reductions in lung volume. In 25 patients with a variety of neuromuscular diseases, De Troyer et al.[6] found that reductions in VC were much greater than expected, solely based on the reductions in inspiratory muscle strength (Fig. 84-1).

It appears that in addition to muscle weakness, alterations in the mechanical properties of the lung and chest wall contribute to the reduced VC. Using the mean deflationary pressure–volume curve of the lung in 25 patients with moderate-to-severe neuromuscular disease, De Troyer et al.[6] found, on average, a 40% decrease in lung compliance (Fig. 84-2). Furthermore, measurements of static lung compliance measured during inspiration in patients with neuromuscular diseases also show marked reductions, suggesting that chronic respiratory muscle weakness changes the elastic properties of the lung itself.[7]

The cause of reduced lung distensibility in patients with neuromuscular disease is unknown. Several causes such as failed maturation of normal lung tissue during childhood or congenital neuromuscular diseases, the presence of micro- or macroatelectasis, increased alveolar surface tension caused by breathing chronically at low tidal volumes, and alteration in lung tissue elasticity have been proposed.

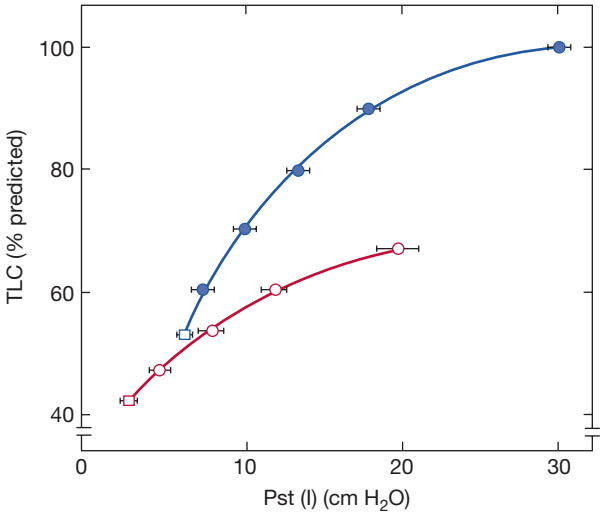


Figure 84-2 Static expiratory pressure–volume curve in patients with neuromuscular disease and respiratory muscle weakness. *Open circles* represent average data in 25 patients. Volume is displayed on the Y-axis as a percentage of predicted total lung capacity (TLC). *Closed circles* represent mean predicted values. In patients, absolute lung volume was decreased for any given transpulmonary pressure. *(Data from De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax. 1980;35:603–610.)*

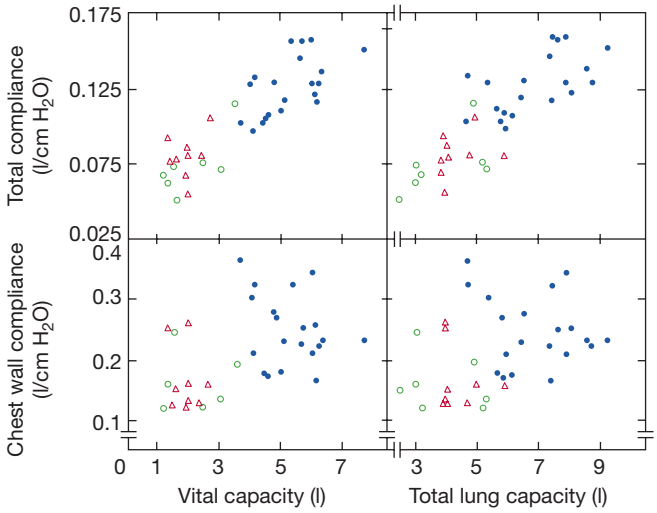


Figure 84-3 Relationships between total respiratory system compliance and VC and TLC (upper panels) and between chest wall compliance and VC and TLC (lower panels) in 16 patients with chronic neuromuscular diseases *(open symbols)* compared to 20 healthy controls *(closed circles)*. *Triangles* symbolize patients who are quadriplegic, *squares* symbolize patients who are paraplegic and four patients had generalized neuromuscular diseases *(circles)*. Compared to healthy controls *(closed circles)*, those with neuromuscular disease had significant reductions in both total respiratory system and chest wall compliance. *(Data from Estenne A, Heliporn A, Dellez L, et al. Chest wall stiffness in patients with chronic respiratory muscle weakness. Am Rev Respir Dis. 1983;128:1002–1007.)*

Impaired lung maturation is unlikely, since patients who develop neuromuscular disease in adulthood also have a reduction in VC that is disproportionate to the magnitude of respiratory muscle weakness. The presence of micro- and macroatelectasis also appears untenable, because most patients who have significant reductions in VC typically do not have alveolar collapse on radiographic imaging. Although rapid and shallow breathing patterns are encountered in patients with chronic severe neuromuscular disease, mechanical hyperinflation of the lung does not restore lung distensibility. Therefore, increased alveolar surface tension is not considered the principal cause of reduced lung compliance in patients with chronic neuromuscular disease.

Theoretically, a reduction in lung tissue elasticity may also contribute to a reduction in lung compliance in patients with neuromuscular disease, but there is no evidence that lung collagen, elastin, and other matrix proteins change in these diseases. Currently, the reason for the reduction in lung compliance in patients with chronic neuromuscular disease is unknown and awaits further study.

Many studies indicate that chest wall compliance is decreased by approximately 30% in patients with chronic neuromuscular disorder. In 16 patients with chronic neuromuscular diseases (e.g., spinal cord injury, Duchenne muscular dystrophy [DMD], and myasthenia gravis), the weighted spirometer technique was used to examine chest wall compliance in comparison with that of 20 healthy control subjects. The weighted spirometer technique delivers an airway pressure that causes an increment in thoracic volumes so as to construct the pressure–volume relationship. In 12 of these patients, chest wall compliance was reduced (Fig. 84-3).[8] Based on the contour of the pressure–volume curve of the normal relaxed chest wall at lower lung volumes, a reduction in functional residual capacity (FRC), as seen in patients with chronic neuromuscular diseases, may in itself reduce static chest wall compliance. However, in other disorders in which FRC is decreased owing to parenchymal lung disease (i.e., pulmonary fibrosis), a reduction in chest wall compliance has not been demonstrated. The mechanism for the reduction in chest wall compliance in patients with chronic neuromuscular disease has not been definitely established, but limitations in respiratory excursions have been proposed to lead to increased rib cage stiffness by decreasing the viscoelasticity of chest wall structures. Regardless of the mechanism, it appears that a reduction in chest wall compliance, along with a decrease in lung compliance, contributes to the marked decrease in VC observation in patients with neuromuscular disease.

Although reductions in VC appear to be clearly established in patients with chronic neuromuscular disease, the effect of chronic neuromuscular disease on FRC and residual volume (RV) are contradictory. FRC and RV have been reported to be unchanged, decreased, or mildly increased. Discrepancies between these studies could be explained by differences in the type of severity, and stages of neuromuscular diseases studied or body positions in which testing were performed. However, in two separate studies, patients with a wide variety of chronic neuromuscular diseases, all studied in a similar seated position, were found to have approximately 20% reductions in FRC but normally predicted values of RV.[9,10] Furthermore, confirmation of these findings was demonstrated in eight patients with myasthenia gravis given pyridostigmine, which acutely decreased FRC by approximately 15% without any significant change in RV.[11] On the basis of the previously mentioned data, it appears that patients with chronic neuromuscular disease have moderate reductions in VC and total lung capacity (TLC) that are associated with a moderate decrease in FRC and a normal RV. The decrease in VC not only is due to respiratory muscle weakness but also appears to result from decreased lung and chest wall compliance. Table 84-2 summarizes the effect of neuromuscular diseases on both lung volumes and central respiratory drive.

SLEEP-RELATED BREATHING DISTURBANCES

Breathing during sleep is often abnormal in patients with neuromuscular disease. Impaired sleep quality and hypopnea and hypercapnia

TABLE 84-2 Characteristic Changes in Respiratory Mechanics in Patients with Neuromuscular Disease

Central drive	Rapid shallow breathing pattern
	Decreased ventilatory response to hypoxic or hypercapnic challenge
	Normal or increased $P_{0.1}$ to hypoxic or hypercapnic challenge
Lung volumes	Decreased vital capacity (VC)
	Decreased inspiratory capacity (IC)
	Decreased functional residual capacity (FRC)
	Decreased expiratory reserve volume (ERV)
	Maintained residual volume (RV)

related to rapid eye movement (REM) sleep are frequent. Patients with chronic neuromuscular disease of various causes have significant and numerous episodes of nocturnal desaturation, which are most prevalent during REM sleep and are characterized by hypoventilation rather than upper airway obstruction (Fig. 84-4).[12] Of six patients, 16 to 22 years of age, with advanced DMD, randomized to breathing either air or oxygen on two consecutive nights, five demonstrated significant oxygen desaturation during REM sleep and approximately 35% reductions in minute ventilation compared to their baseline awake values. Furthermore, the severity of diaphragmatic dysfunction was related to the degree of oxygen desaturation.[13]

Several hypotheses have been proposed to explain nocturnal desaturation. Patients with chronic neuromuscular diseases develop an even more rapid and shallow breathing pattern during REM sleep. A rapid and shallow breathing pattern leads to increased dead space ventilation, which promotes hypercapnia and worsened oxygenation. Reductions in ventilatory drive may be accentuated during sleep in patients with underlying neuromuscular disease, especially in those who have pre-existing abnormalities of ventilatory control, which may further contribute to worsened nocturnal hypoventilation.

It has been hypothesized that patients with neuromuscular disease, especially with diaphragmatic dysfunction, may be more prone to nocturnal desaturation during REM sleep. Intercostal muscle and accessory respiratory muscle activity during REM sleep are depressed, with a greater contribution of the diaphragm required for maintenance of eucapnia and oxygenation. Support for this hypothesis comes from studies that have found diaphragm dysfunction to be highly correlated with the presence and magnitude of REM-related oxygen desaturation. A direct relation has been found between the lowest Sa_{O_2} value measured during REM sleep and the percentage fall in VC measured between the erect and supine positions, using the latter measurements as an index of diaphragm weakness. Similarly, among patients who have paradoxical abdominal movement, signifying a decrease in diaphragmatic contribution to ventilation, a greater oxygen desaturation in both REM and non-REM sleep is observed.[14] In contrast, patients with isolated diaphragmatic dysfunction with intact accessory muscle function are not predisposed to severe nocturnal hypoventilation.[15] Accordingly, severe hypoventilation may become evident only when diaphragmatic weakness is found in the background of global accessory and intercostal muscle weakness, or when ventilatory reserve is severely reduced for other reasons, such as asthma or chronic obstructive pulmonary disease (COPD).

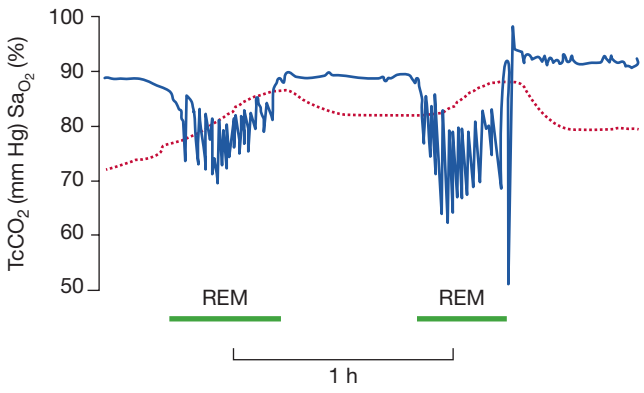


Figure 84-4 Oxygen desaturation and hypercapnia in REM sleep shown from a recording of an all-night sleep study. Transcutaneous carbon dioxide ($TcCO_2$) is shown as the *dashed line*; arterial hemoglobin oxygen saturation (Sa_{O_2}) is shown in the line with sharp deflections. Patients with neuromuscular diseases are often at risk for hypoventilation during REM sleep resulting in a decrease in Sa_{O_2} and increase in TcO_2. *(Data from Bye PT, Ellis ER, Issa FG, et al. Respiratory failure and sleep in neuromuscular disease. Thorax. 1990;45:241–247.)*

Abnormalities in nocturnal gas exchange are harbingers of problems in daytime gas exchange. Hypoventilation during sleep precedes the appearance of daytime hypercapnia, and patients with the most impaired gas exchange during REM sleep have the greatest degree of daytime hypercapnia. Moreover, patients with normal nocturnal gas exchange are unlikely to have abnormal daytime values. Noninvasive (e.g., nasal positive-pressure ventilation, external negative-pressure ventilation) or invasive (e.g., positive-pressure ventilation by tracheostomy) mechanical ventilation improves nocturnal gas exchange and sleep quality, with simultaneous improvement in daytime gas exchange.

Two theories have been proposed to explain the sustained improvements in gas exchange during daytime spontaneous breathing in patients with chronic neuromuscular disease who receive nocturnal ventilatory support. One theory states that nocturnal ventilation rests chronically fatigued respiratory muscles, thereby permitting improved spontaneous ventilation and gas exchange. Although several studies have demonstrated that noninvasive ventilation provides inspiratory muscle fatigue in patients with neuromuscular disease, or that mechanical ventilation consistently increases respiratory muscle strength. However, evidence that inspiratory muscle fatigue is commonly present in patients with neuromuscular disease or that mechanical ventilation consistently increases respiratory muscle strength is lacking. An alternative hypothesis suggests that nocturnal ventilatory support lowers the central respiratory center CO_2 set point and, thereby, sets the central controller to maintain a lower spontaneous daytime CO_2 level. This hypothesis is supported by studies showing that after several weeks of chronic nocturnal ventilation, hypoventilation was less severe in nocturnal studies without ventilation than it had been on baseline nights before chronic intermittent ventilation. Moreover, interruption of successful nocturnal noninvasive ventilation in patients with neuromuscular disease and chronic respiratory failure results in a return of nocturnal hypoventilation and symptoms of impaired gas exchange without evidence of respiratory muscle dysfunction. To date, neither of the previously mentioned theories has been established conclusively, and further investigation is warranted, as one or the other, or both, may be valid in different patients.

ASSESSMENT OF RESPIRATORY FUNCTION

Patients with significant respiratory muscle impairment may range from being totally asymptomatic to having moderate dyspnea at rest or, in some cases, overt respiratory failure. Some patients with neuromuscular disease may have significant weakness of the respiratory muscles and be asymptomatic,[16] whereas others may present with ventilatory failure without an established history of a neuromuscular

TABLE 84-3 Innervation of the Respiratory Muscles

Muscle Group	Innervation	
	Level	Nerve
Upper airway		
Palate, pharynx	IX, X, XI	Glossopharyngeal, vagus, spinal accessory
Genioglossus	XII	Hypoglossal
Inspiratory		
Diaphragm	C3–C5	Phrenic
Scalenes	C4–C8	
Parasternal intercostals	T1–T7	Intercostal
Sternocleidomastoid	X1, C1, C2	Spinal accessory
Lateral external intercostals	T1–T12	Intercostal
Expiratory		
Abdominal	T7–L1	Lumbar
Internal intercostals	T1–T12	Intercostal

disease. In the latter patients, the diagnosis of neuromuscular disease may initially be entertained only after difficulty is encountered in weaning the patient from mechanical ventilation. A detailed history and physical examination, coupled with appropriate diagnostic tests, enable the physician to diagnose the presence and type of neuromuscular disease and its effect on the respiratory system. The following section reviews features of the history and physical examination and the diagnostic studies considered useful in the assessment of respiratory function in patients with neuromuscular disease.

In order to provide an organized approach to direct the clinical history taking and physical examination of patients with neuromuscular disease, Table 84-1 characterizes the types of neuromuscular diseases that present at different levels of the neuromuscular system, and Table 84-3 describes the innervation of the different groups of respiratory muscles.

CLINICAL HISTORY

The signs and symptoms of respiratory muscle weakness due to a neuromuscular disease are usually nonspecific and of limited value. Moreover, the clinical manifestations of respiratory muscle dysfunction depend on the specific muscle or muscles affected and the extent of their impairment. In conditions of mild weakness, or in the early stages of neuromuscular disease, the patient may be totally asymptomatic.[16] As respiratory muscle weakness progresses, however, dyspnea on exertion, followed by dyspnea at rest occurs. Disturbances in sleep and daytime hypersomnolence resulting from nocturnal hypoventilation may occur, and if the expiratory muscles are affected, patients may have impaired cough and repeated lower respiratory tract infections. As respiratory muscle weakness becomes more severe, hypercapnia or hypoxemia becomes evident and respiratory failure may ensue, requiring ventilatory support.

The clinical history is invaluable in that it may be the first clue that a neuromuscular disease is the cause of the patient's pulmonary dysfunction. A history is also useful in characterizing the type of neuromuscular disease that is present. Dyspnea and impaired cough with or without recurrent lower respiratory tract infections may be the first clinical clues that a neuromuscular disease is present. Impaired swallowing due to bulbar symptoms and the presence of peripheral limb muscle weakness are indications that one is dealing with generalized neuromuscular disease.

PHYSICAL EXAMINATION

Although the physical examination may yield normal results in patients with early or mild impairment of the respiratory system, patients with more established disease often demonstrate tachypnea at rest. Further clinical information on the nature of the underlying disease and the extent of underlying muscle impairment can be gleaned from the pattern of respiratory muscle contraction in both seated and supine positions. Respiratory rate should be recorded along with any evidence of nasal flaring, intercostal muscle retraction, or palpable evidence of contraction of the sternocleidomastoid and scalene muscles. Furthermore, inward paradoxical motion of the rib cage or abdomen should be sought, as its presence may indicate a respiratory workload that is greater than the patient's respiratory muscle strength, or evidence of severe weakness of the diaphragm as a result of the underlying neuromuscular disease. Besides gross paradoxical movement of the rib cage or abdominal compartments, asynchronous compartmental movements (e.g., one compartment moving faster than the other) may be early evidence of impaired respiratory pump performance.

The hallmark finding of severe diaphragm weakness or paralysis is paradoxical inward movement of the abdomen with inspiration. In the presence of severe diaphragm weakness, the upper abdomen moves inward when the upper rib cage moves outward in stark contrast to the normal pattern of synchronized outward movements of the rib cage and abdominal compartments. Besides paradoxical movement of the upper abdomen, a marked increase in respiratory rate, accompanied by progressive accessory muscle use, and increased dyspnea occur when patients assume the recumbent position due to hypoxemia, hypercapnia, and placing the accessory inspiratory muscles at mechanical disadvantage. Upon reassuming the upright posture, patients may have palpable phasic contractions of the abdominal expiratory muscles. Physiologically, this inward movement of the abdomen on expiration enables passive outward movement of the upper abdomen and diaphragm descent during expiratory muscle relaxation in early inspiration.

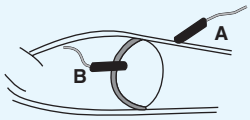
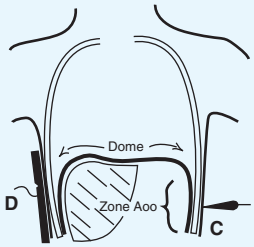
Besides a detailed examination of the respiratory musculature and breathing pattern, the physical examination should include a complete neuromuscular examination to exclude systemic involvement. Inspection for atrophy or fasciculations of respiratory and nonrespiratory muscles may point to a lower motor neuron disease. The presence of scoliosis may contribute to the development of restrictive ventilatory pattern.

RADIOGRAPHIC ASSESSMENT

In patients with severe inspiratory muscle weakness or bilateral diaphragm paralysis, maximum inspiration is limited and lung volume appears reduced on chest radiograph. Unilateral hemidiaphragm paralysis produces an elevated hemidiaphragm on the affected side.[17]

Fluoroscopy is often used in the assessment of diaphragm paralysis with the patient making a forceful sniff in the supine position.[17] In unilateral diaphragm paralysis, a positive "sniff" test may demonstrate paradoxical upward movement of the affected hemidiaphragm. However, "sniff" tests have a false-positive rate as high as 6% in normal persons. The use of the "sniff" test to diagnose bilateral diaphragm paralysis is limited by compensatory abdominal muscle contraction. With abrupt cessation of abdominal muscle contraction during early inspiration, the abdominal contents descend caudally. The abdominal wall moves outward and the diaphragm will then appear to descend caudally, at least radiographically. Besides the fact that passive diaphragm descent due to active abdominal muscle contraction is a limitation during fluoroscopy, the fluoroscopic observational field used to examine the diaphragm is limited because of the small visual band that encompasses only the diaphragmatic dome and adjacent ribs. If rib cage rostral movement exceeds diaphragm ascent, the diaphragm will appear to descend lower than the thorax that may falsely suggest the presence of diaphragm shortening.[18]

TABLE 84-4 Two Approaches to Ultrasound of Diaphragm. Taken from the American Thoracic Society Consensus Statement on Respiratory Muscle Testing

Name of Test	Information Provided	Diagnostic Purposes	How to Perform
		Diaphragm	
Dome ultrasound 	Movement of right (or left) dome	Unilateral or bilateral diaphragm paralysis	Ultrasound probes with sufficient penetration (3 or 3.5 MHz) placed over abdomen (A) or over lateral rib cage (B). M-mode
Zone of apposition ultrasound 	Thickness at different lung volumes, relaxed or contracted	Detect contraction during tidal breathing or inspiratory effects Effects of pulmonary or neuromuscular disease, training, and disuse Placement of intramuscular electrodes	High-resolution probe with less penetration (7.5 MHz) over intercostal space, usually in anterior axillary line. B- or M-mode (C) Linear probe in craniocaudal plane over lateral rib cage. B-mode (D)
	Length at different lung volumes	Estimates of diaphragm length and swept volume	Both measurements are usually made on the right side

Source: Reproduced with permission from ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518–624.

Although the diaphragm itself is poorly echogenic, ultrasound can be used to assess its function because the parietal pleura and peritoneal membranes lining the diaphragm are brightly echogenic. The two approaches used are the visualization of the dome or measurement of the muscle thickness at the zone of apposition.[2] Craniocaudal movement of the dome of the diaphragm can be measured by placing an ultrasound probe on the upper abdomen or on the lateral chest as shown in Table 84-4. This technique has compared favorably to the traditional fluoroscopic procedures used to assess diaphragm movement. Because the costal portion of the diaphragm is close to the skin, the zone of apposition (Table 84-4) is an ideal area to use ultrasound for assessment of the diaphragm thickness and estimation of length. The thickness of the diaphragm increases with increasing lung volumes and is inversely proportional to its length. Measurement of the zone of apposition will permit the detection of diaphragm contraction during inspiratory efforts when trying to diagnose diaphragm paralysis. As the subject with diaphragm paralysis makes an inspiratory effort there will not be thickening of the diaphragm at the zone of apposition. Measurement of the thickness also allows for the assessment of atrophy or the effect of neuromuscular diseases.

■ ARTERIAL BLOOD GAS ANALYSIS

Arterial blood gas abnormalities usually occur only in patients with severe respiratory muscle weakness. Hypoxemia is usually mild and may occur as a result of macroatelectasis and subsequent intrapulmonary shunting or ventilation–perfusion mismatch. In addition, patients with impaired muscle strength have impaired cough and may retain secretions that further contribute to the development of hypoxemia. Measurement of arterial oxyhemoglobin saturation by pulse oximetry, which has become an extremely common laboratory test for oxygenation, is an insensitive indicator of hypoventilation. In patients with mild-to-moderate respiratory muscle weakness, the value of solely measuring the level of oxygenation is limited and may be misleading.

Hypercarbia is an insensitive measure of respiratory muscle strength. The Pa_{CO_2} does not increase until respiratory muscle strength (measured by maximum inspiratory and expiratory mouth pressures) is less than 50% of predicted. In patients with severe respiratory muscle weakness, however, an elevation in Pa_{CO_2} may be evident. Serum bicarbonate and arterial pH values may help determine whether an acute or chronic respiratory acidosis is present. Because daytime hypercapnia is usually followed by nocturnal hypoventilation, the presence of daytime hypercapnia should prompt investigation of the breathing pattern and gas exchange during sleep, so that appropriate therapy (e.g., nocturnal supplemental oxygen or noninvasive ventilation) can be implemented.

RESPIRATORY MUSCLE STRENGTH

A variety of techniques have been used to assess respiratory muscle strength. Each is discussed below.

■ MAXIMUM MOUTH PRESSURES

Maximum static inspiratory and expiratory mouth pressures, measured at the airway opening during a voluntary contraction against an occluded airway, are the simplest and most commonly performed tests of respiratory muscle strength. Although several methods exist, the technique of Black and Hyatt is still the most widely used.[19] In this technique, mouth pressures are measured using a handheld manometer with the patient seated upright with a nose clip on. During these maneuvers, the patient purses the lips inside a circular wide-bore rubber mouthpiece, which prevents perioral air leakage. This small orifice (2 mm in diameter, 15 mm in length) is placed in the circuit to minimize the contribution of the facial muscles to airway pressure and to keep the glottis open. Maximum inspiratory pressures (PI_{max}) are measured near RV after maximal expiration, while maximal expiratory pressures (PE_{max}) are measured at or near TLC. In each case, efforts are maintained for at least 1 second. Maximum inspiratory and expiratory mouth pressures in normal males and females are listed in Table 84-5. Reported values in normal subjects vary widely and may be due to differences in techniques between different studies or a learning effect in subjects who perform these maneuvers.[20–25]

A major factor affecting PI_{max} is lung volume. PI_{max} is greatest at RV, whereby the inspiratory muscles are at greatest mechanical advantage and the outward elastic recoil of the respiratory system is maximum. On the other hand, measurement of PE_{max} is greatest at TLC because expiratory muscles are at greatest mechanical advantage and inward elastic recoil of the respiratory system is greatest (Fig. 84-5). Only at FRC, where the respiratory system recoil pressures measured at the airway opening are zero, are maximum inspiratory and expiratory mouth pressures solely a function of the pressure generated by actively contracting respiratory muscles (P_{mus}).

TABLE 84-5 Reported Values for Maximum Static Airway Pressures in Normal Adults

Study	Sex	No. of Subjects	Age Range (Years)	PI_{max} (cm H_2O)	PE_{max} (cm H_2O)
Black and Hyatt[20]	Males	60	20–54	124 ± 22	233 ± 42
	Females	60	20–54	87 ± 16	152 ± 27
Ringqvist[25]	Males	100	18–83	130 ± 32	237 ± 46
	Females	100	18–83	98 ± 25	165 ± 30
Leech et al.[22]	Males	325	17–35	114 ± 36	154 ± 82
	Females	480	15–35	71 ± 27	94 ± 33
Rochester Arora[21]	Males	80	19–49	127 ± 28	216 ± 41
	Females	121	19–49	91 ± 25	138 ± 39
Vincken et al.[24]	Males	46	16–79	105 ± 25	140 ± 38
	Females	60	16–79	71 ± 23	89 ± 24
Wilson et al.[23]	Males	48	19–65	106 ± 31	148 ± 34
	Females	87	18–65	73 ± 22	93 ± 17

Values are mean ± standard deviation.

Changes in lung volume due to chest wall or lung pathology may have important effects on the generation of maximum respiratory pressures in patients. For example, patients with COPD and significant hyperinflation have a larger FRC and RV than normal subjects; therefore, PI_{max} performed at FRC or RV usually results in lower values than in age- and sex-matched normal subjects. Likewise, a reduction in TLC due to restrictive ventilatory diseases may result in a reduction in measured values for PE_{max}. Therefore, it is important to realize that in patients with pathologically altered lung volumes, all or part of the reduction in mouth pressures may be due to inspiratory muscle mechanical disadvantage.

Maximum inspiratory and expiratory mouth pressures in patients with neuromuscular diseases range from normal to severely reduced. Patients may have significant respiratory muscle weakness without any pulmonary complaints, and no correlation exists between respiratory muscle strength and the presence of generalized nonrespiratory muscle weakness.[16] When PI_{max} falls below 30 cm H_2O, ventilatory failure commonly ensues.

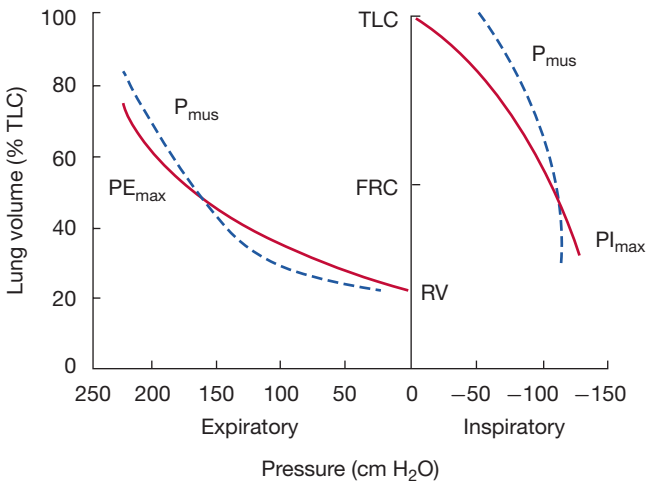


Figure 84-5 The effect of lung volume on maximum respiratory pressures (PI_{max} and PE_{max}) measured at the airway opening displayed by *solid lines*. Both PI_{max} and PE_{max} are made up of two components: the pressure generated by the respiratory muscles (P_{mus}, *dashed lines*) and the recoil pressure of the respiratory system. Only at FRC when recoil pressures are zero are PE_{max} and PI_{max} solely due to P_{mus}.

The assessment of a patient's ability to generate an effective cough is extremely important when managing the pulmonary effects of neuromuscular diseases. Nearly all of these disorders result in weak cough, which puts the individual at risk for aspiration and pneumonia. While a normal PE_{max} ensures that the patient has adequate cough, a low PE_{max} could result from poor effort, bulbar weakness not allowing a tight seal around the mouthpiece or true expiratory muscle weakness. Therefore there is interest in developing a test that will allow the assessment of cough strength in a nonvolitional manner. Measurement of positive pleural pressures with an esophageal balloon during a forceful cough (P_{es} cough) has also been proposed as a measure of expiratory muscle strength. P_{es} cough has been shown to decrease in parallel with PE_{max} when expiratory muscle weakness is induced by progressive curarization. A study examined the use of measurement of gastric pressures during cough (P_{ga} cough) in a group of normal subjects and in those with suspected respiratory muscle weakness from pulmonary and neuromuscular disease. The measurement of P_{ga} cough is theoretically better because it takes into account the abdominal musculature, eliminates the problem of leak around the mouthpiece, and a cough maneuver is easier to perform than the PE_{max} maneuver. In 122 patients with a normal PE_{max}, more than 95% also had a normal P_{ga} cough, but in 171 patients with a low PE_{max} 72 had a normal P_{ga} cough suggesting a high false-positive rate of a low PE_{max}. Conversely, in 105 patients with a low P_{ga} cough only 6 had a normal PE_{max} suggesting a low false-positive rate for a low P_{ga} cough.[31]

Transdiaphragmatic Pressure Measurement

While maximum static airway pressures are useful measures of global respiratory muscle strength, they fail to assess individual respiratory muscle function. Since the diaphragm is the primary muscle of inspiration, and may be susceptible to isolated disease (e.g., phrenic nerve paralysis after open heart surgery or idiopathic diaphragm paralysis), specific testing of diaphragm strength is desirable in some patients. Assessment of diaphragm strength is made by measuring gastric (P_{ga}) and endoesophageal (P_{es}) pressures with balloon-tipped catheters placed in the stomach and midesophagus, respectively. Transdiaphragmatic pressure (P_{di}) is then calculated as the algebraic subtraction of P_{es} from P_{ga} ($P_{di} = P_{ga} - P_{es}$).[2]

Maneuvers to elicit maximum transdiaphragmatic pressures ($P_{di,max}$) have been the subject of intensive study. Earlier studies measured P_{di} during maximum static inspiratory efforts against a closed airway (e.g., Muller maneuver) at FRC or RV. However, this maneuver results in submaximal diaphragm activation, with the degree of activation varying widely from subject to subject. Several studies have demonstrated significant intraindividual variability, with a coefficient of variation as high as 40% in measurement of $P_{di,max}$ during Muller maneuver. When five maneuvers to measure $P_{di,max}$ in 35 subjects (10 normal, 13 with restrictive lung disease, and 12 with COPD) were compared, a combined maneuver of active expulsion with superimposed Muller maneuver yielded the most reproducible and maximal transdiaphragmatic pressure.[32]

Phrenic Nerve Stimulation

A crucial factor in the measurement of diaphragm strength is the ability to consistently obtain maximal activation of the diaphragm during volitional efforts. Electrophrenic stimulation is a method that has been utilized to consistently activate the diaphragm. Besides assessing diaphragm strength, this technique has the added advantage of assessing phrenic nerve conduction and excluding the possibility of phrenic nerve injury in patients with diaphragm weakness of unknown origin.[2]

The phrenic nerve is stimulated in the neck near the posterior border of the sternocleidomastoid muscle, at the level of the cricoid

cartilage, where the phrenic nerves are most superficial. Stimulation may be performed either transcutaneously with surface electrodes (electrical stimulation electrodes), magnetic coil, or percutaneously with needle or wire electrodes. The percutaneous method is rarely used now. Stimulation of the phrenic nerves must be supramaximal with regard to voltage and current. Supramaximal conditions are ensured by increasing the stimulus intensity until maximum diaphragm muscle action potential (DMAP) or P_{di} is achieved. The DMAP is measured by surface electromyography (EMG) electrodes, and the P_{di} is measured by measuring the esophageal and gastric pressures via two pressure transducers as described earlier. The DMAP is then checked periodically throughout the study to ensure that consistent stimulation is maintained.[2,33]

The most commonly used technique of electrophrenic stimulation now employs a frequency of one pulse per second to measure P_{di} during a single unfused twitch contraction (e.g., $P_{di,tw}$). $P_{di,tw}$ has also been used to assess maximal static P_{di} indirectly by the twitch occlusion technique.[2,34] In this method, single twitches are superimposed on progressively stronger voluntary P_{di} contractions. As voluntary effort and P_{di} increase, the increment in P_{di} produced during the twitch (the twitch deflection superimposed on the P_{di}) decreases (Fig. 84-6A). When there is no discernible $P_{di,tw}$ deflection, it is assumed that the diaphragm is maximally activated and voluntary efforts from the inverse linear relationship between the amplitude of the superimposed twitch and P_{di} measured during volitional effort. The extrapolation of the line of this relationship to the X-axis has been interpreted as representing maximum static P_{di} (Fig. 84-6B).

An alternate way to perform phrenic nerve stimulation is via magnetic stimulation.[2,35] In this technique, an electric current is run through a coil thereby producing a magnetic field. The coil is placed over the spinous process of the seventh cervical vertebral body (cervical magnetic stimulation) stimulating the C3 to C5 cervical roots of the phrenic nerve causing the diaphragm to contract. Magnetic stimulation of this area will also stimulate contraction of neck and upper rib cage muscles as well. The advantages of this technique are that it is less painful than the electrical stimulation method, and it is easier to evoke diaphragm contractions. Also it is possible to perform magnetic stimulation of the phrenic nerve while the patient is in the supine position by placing the magnetic coil anterior to the sternum. This would allow for hospitalized bed-bound patients to be evaluated for diaphragm weakness via phrenic nerve stimulation. One of the disadvantages of magnetic stimulation is that it lacks the specificity that electrophrenic stimulation has for the diaphragm and obtaining an EMG_{di} signal can be more difficult with magnetic stimulation. When comparing magnetic stimulation $P_{di,tw}$ to electrophrenic $P_{di,tw}$, the $P_{di,tw}$ tends to be 20% to 25% higher with magnetic stimulation.

In addition to assessing diaphragm strength, phrenic nerve stimulation can be used to assess phrenic nerve function. The EMG_{di} is measured via surface or esophageal electrodes during electric or magnetic phrenic nerve stimulation and the phrenic nerve conduction time can be measured.[2] This measurement is useful when assessing possible injury to the phrenic nerve from thoracic surgery, trauma, or neuropathies (i.e., critical illness polyneuropathy [CIP] or GBS). The normal conduction time via electrical stimulation is 7.5 to 9 ms, but the normal conduction time via magnetic stimulation has not been well defined because activation of the brachial plexus affects the phrenic nerve conduction time. However, Luo et al. demonstrated that if the magnetic coil is placed anteriorly to the cricoid cartilage then the phrenic nerve conduction time was very similar to that obtained by electric stimulation. The authors believe that this occurred because there was more brachial plexus activation in the lower position compared to the higher position.[36]

Because of the relative invasiveness of electrophrenic stimulation of the diaphragm, and the large coefficient of variation in some studies when P_{di} was measured during maximal volitional efforts,

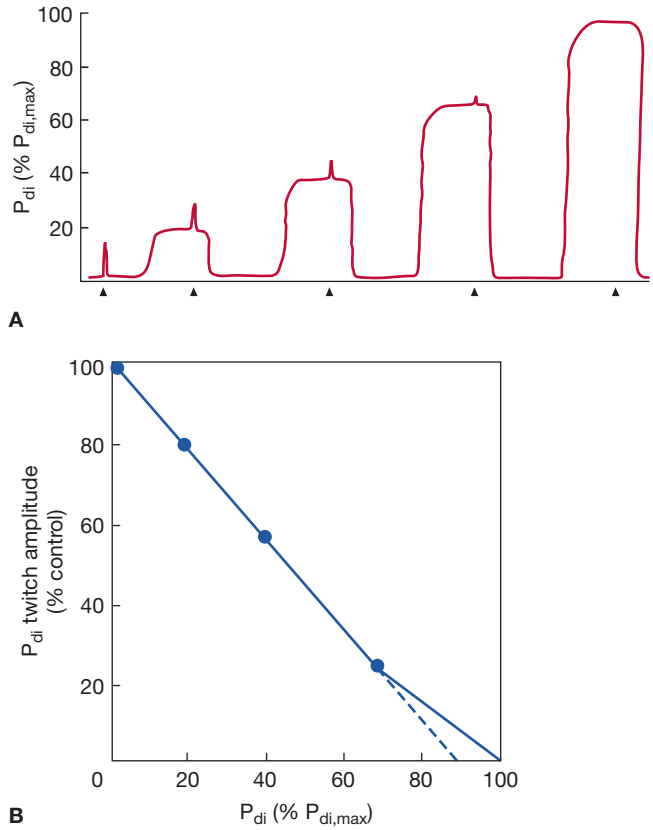


Figure 84-6 **A.** Illustration of a typical P_{di} tracing during twitch occlusion study. As the P_{di} increases during volitional efforts, the superimposed P_{di} deflection during phrenic nerve 1-Hz stimulation (twitch) decreases. At 100% of $P_{di,max}$, the diaphragm is maximally activated and no superimposed twitch is seen. *Arrows* on the horizontal axis mark indicate the phrenic nerve twitches. **B.** Data from A plotted as $P_{di,tw}$ amplitude versus voluntary P_{di}. Using linear regression, $P_{di,max}$ can be extrapolated from results obtained during submaximal efforts. It has been suggested that extrapolation performed from P_{di} values below 70% of maximum may underestimate $P_{di,max}$ by approximately 10% *(dashed line)*.

some investigators prefer measuring maximum inspiratory pressures during a sniff maneuver (Fig. 84-7). In this technique, the subject performs a vigorous sniff against an unoccluded airway. During such an effort, the nose acts as a Starling resistor, thereby generating intrathoracic pressures against an occluded airway. Some investigators argue that this maneuver approaches a more natural respiratory

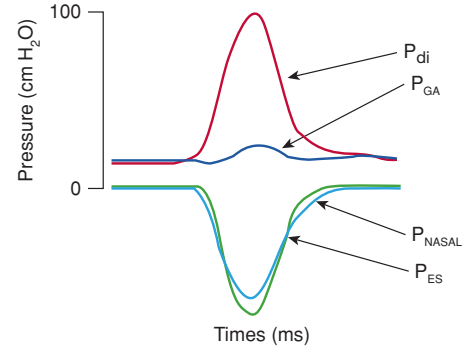


Figure 84-7 Pressure tracing produced utilizing sniff maneuver in a normal individual with gastric and esophageal balloon manometry in place. The noninvasive P_{NASAL} pressure closely mirrors that of the invasive P_{ES}. P_{GA}, gastric pressure; P_{di}, transdiaphragmatic pressure; P_{ES}, esophageal pressure; P_{NASAL}, nasal pressure during sniff maneuver.

effort than other types of maneuvers used to measure maximum inspiratory pressures and thus should be easily mastered by patients and more reproducibly performed by technicians.[37]

Analysis of Rib Cage and Abdominal Motion

During normal tidal breathing, the chest and abdominal compartments move synchronously in an outward direction, owing to diaphragm contraction decreasing pleural pressure and increasing abdominal pressure. In situations where the diaphragm is severely paretic or paralyzed, however, the flaccid diaphragm cannot counterbalance the negative changes in pleural pressure generated by contraction of the inspiratory muscles of the neck and rib cage. Instead of moving normally in a caudad direction the flaccid diaphragm moves paradoxically cephalad into the thorax. This change in diaphragm motion gives rise to a paradoxical inward motion of the upper abdomen indicative of severe diaphragm weakness or paralysis.

Changes in rib cage and abdominal pressure, or volume displacement during respiration, can provide important information about diaphragm strength. Partitioning of respiration can be examined from changes in abdominal and pleural pressures, as proposed by Macklem et al.[38] Changes in abdominal and pleural pressures during inspiration, expressed as the ratio of delta P_{ab}:delta P_{PL} are normally negative as pleural pressure becomes more negative and abdominal pressure becomes more positive. This ratio has a maximum value of +1 when the diaphragm does not contribute to inspiration and is valid only if the expiratory muscles do not contribute significantly to the pressures being generated. Alternatively, the partitioning of ventilation can be noninvasively measured by compartmental changes in rib cage and abdominal volume by respiratory inductance plethysmography or magnetometry. Optoelectronic plethysmography (OEP) is a technique that allows for measurement of chest wall and abdominal motion as well as lung volumes. A series of 89 retroreflective markers are placed on the thorax and abdomen that are monitored by a series of six to eight cameras (Fig. 84-8). The cameras record the distance the markers move in space and using Gauss' theorem the total thoracoabdominal lung volume can be calculated. OEP can differentiate between volume generated by the rib cage (rib cage musculature) and volume generated by the abdomen (diaphragm).[39] OEP can also be used to measure flow and is a nonvolitional test that can be done in any spontaneously breathing individual without regard to the degree of muscle weakness.[39] This technique has been used in patients with DMD to show that with disease progression the proportion of the tidal volume attributable to the abdomen decreases while the tidal volume attributable to the rib cage increases. Furthermore those that had this change in breathing pattern were more likely to have nocturnal desaturation.[40]

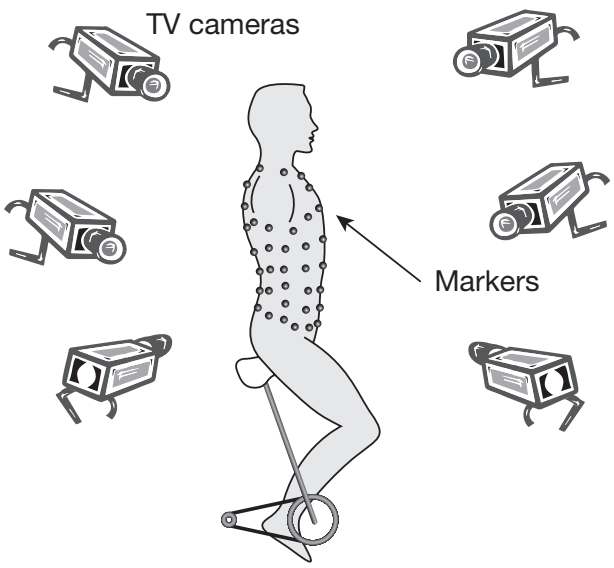


Figure 84-8 An example of optoelectronic plethysmography. A series of markers are placed on the subject's thorax and abdomen. A group of cameras record the distance the markers move in all planes thus permitting calculation of lung volumes during the breathing cycle. *(Reproduced with permission from Vogiatzis et al. Eur J Appl Physiol. 2005; 93(5–6):581–587.)*

SPIROMETRY

Respiratory muscle weakness induced by neuromuscular disease produces a restrictive pattern on spirometric testing with a reduction in VC.[6] As previously mentioned, the reduced VC is commonly out of proportion to the reduction in maximal respiratory muscle force. Reductions in lung and chest wall compliance also probably contribute. Moreover, because of the contour of the pressure–volume curve, large reductions in the respiratory muscle forces have to occur before VC is significantly reduced. A decrease in VC greater than 25% on moving from the upright to supine postures has been used as a sign of diaphragmatic weakness and a greater likelihood of sleep-related hypoventilation.[14,41]

Forced expiratory volume in 1 second (FEV_1) and measurements of midexpiratory flow rates ($FEF_{25–75}$ or FEF_{50}) are often greater than normal predicted values in patients with neuromuscular disease. Further increases in expiratory flow may occur in patients with neuromuscular disease due to increased lung recoil. Two independent studies have shown that partial curarization in normal subjects produces a decrease in peak expiratory flow with an increase in midexpiratory flow rates compared to baseline.[3,42] Moreover, myasthenia gravis patients at their baseline weakness prior to the administration of pyridostigmine have increased midexpiratory flow rates over the range of VC when referenced to absolute lung volumes (Fig. 84-9).[6]

FLOW–VOLUME LOOPS

Changes in the configuration of the flow–volume loop occur in various neuromuscular diseases.[2,43,44] These changes reflect respiratory

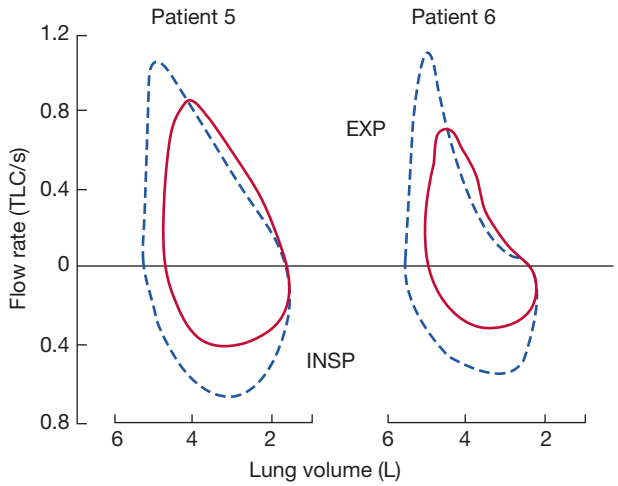


Figure 84-9 Two representative patients with myasthenia gravis and respiratory muscle weakness illustrating the effect of anticholinesterase therapy on maximum flow–volume curves. *Solid curves* represent pretreatment data; dashed curves were obtained following the injection of pyridostigmine. Prior to administration of pyridostigmine the midexpiratory flow rates were greater even though respiratory muscles were weaker and lung volumes were lower. *(Reproduced with permission from DeTroyer A, Borenstien S. Acute changes in respiratory mechanics after pyridostigmine injection in patients with myasthenia gravis. Am Rev Respir Dis. 1980;121(4):629–638.)*

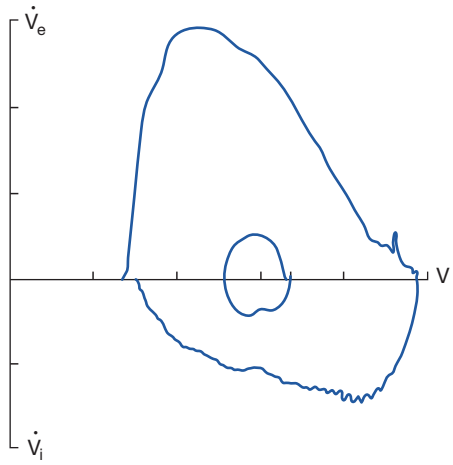


Figure 84-10 Flow–volume loop in a patient with motor neuron disease, showing inspiratory flow oscillation and inspiratory flow limitation. Subdivisions on volume and flow axis represents 1 L, flow axis 1 L/s. *(Data from Vincken W, Elleker MG, Cosio MG. Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. Am J Med. 1987;82:53–58.)*

muscle weakness or malfunction of upper airway muscles. "Sawtoothing" of the flow contour is seen in extrapyramidal disorders affecting upper airway muscles.[45] Similarly, plateauing of the inspiratory flow waveform indicative of extrathoracic airway obstruction has been described in vocal cord paralysis caused by extrapyramidal neuromuscular disorders. An abnormal flow–volume curve is significantly more common in patients with clinically apparent bulbar muscle involvement (90% vs. 15%, respectively), and the presence of an abnormal, flow–volume loop predicted bulbar and upper muscle involvement by a neuromuscular disease with a high sensitivity and specificity.[46] A characteristic flow–volume contour showing involvement of the upper airway muscles by motor neuron disease is shown in Figure 84-10.

Among patients with stable, chronic neuromuscular disease, the flow–volume loop is significantly more disturbed in those with respiratory muscle weakness, and these abnormalities correlate with reduced mouth pressures. Several features of flow–volume loop configuration correlate with reduced maximum static inspiratory and expiratory mouth pressures; a reduced peak expiratory flow, decreased slope of the ascending limb of the maximum expiratory curve, a drop-off of forced expiratory flow near RV, and a reduction in forced inspiratory flow at 50% of VC (Fig. 84-11). A flow–volume loop score composed of the aforementioned parameters has a high degree of specificity and 90% sensitivity in predicting respiratory muscle weakness.[46]

LUNG VOLUMES

A restrictive ventilatory pattern is demonstrated in patients with neuromuscular disease. A reduced TLC and a normal or reduced FRC are common. The RV is usually elevated and is a sign of expiratory muscle weakness.

MAXIMUM VOLUNTARY VENTILATION

Maximum voluntary ventilation (MVV) is an index of respiratory muscle endurance in the presence of normal expiratory flow rates. This appears to be appropriate in patients with neuromuscular disease, since airway resistance and FRC are usually within the normal range. Values for MVV correlate with respiratory muscle strength and may be even more sensitive than VC in detecting respiratory muscle weakness.[2]

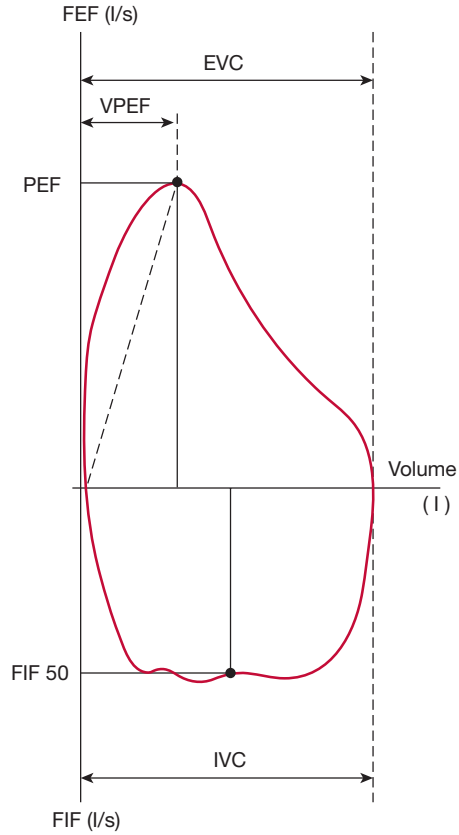


Figure 84-11 Representative flow–volume loop of a patient with chronic neuromuscular disease, showing different volume loop parameters indicative of respiratory muscle weakness. These parameters quantify the effects of respiratory muscle strength on the effort-dependent portions of the flow–volume loop. These four parameters are peak expiratory flow (PEF); ratio of PEF to the exhaled volume at which PEF was achieved, rapid vertical drop of forced expiratory flow at residual volume, and forced midinspiratory flow. *(Data from Vincken W, Elleker MG, Cosio MG. Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. Am J Med. 1987;82:53–58.)*

SELECTED NEUROMUSCULAR DISEASES

A helpful approach toward understanding how specific neuromuscular diseases affect the respiratory system is to localize the anatomic involvement of the respiratory system. A detailed description of the neuroanatomy of respiration is outside the scope of this chapter and is covered elsewhere in this text. In general, however, neuromuscular disorders can be broken down into disorders that involve the upper motor neuron, the lower motor neuron, or the muscle itself.

Lesions that arise in the cerebral cortex, brainstem, or spinal cord are classified as upper motor neuron lesions and are characterized by an increase in muscle tone or spasticity, the presence of an extensor plantar response, and increased reflex activity. Lesions in the lower motor neuron system demonstrate flaccidity, depressed reflexes, muscular fasciculations, and atrophy. The location and character of the patient's weakness may enable one to identify the exact site of the lesion in the lower motor neuron system (i.e., the anterior horn cell, the peripheral nerve, the neuromuscular junction, or the muscle itself).

The following describes the effect of specific neuromuscular disease on the respiratory system and makes recommendations for treatment.

■ UPPER MOTOR NEURON LESIONS

A variety of disorders in which the primary pathology is centered on upper motor neurons have significant respiratory consequences. Each is discussed below.

Stroke

Hemispheric ischemic strokes reduce chest wall and diaphragm movement on the side contralateral to the cerebral insult. Decreased diaphragm excursion with stroke correlates with diaphragmatic cortical representation identified by transcranial magnetic stimulation. Bilateral hemispheric strokes are also associated with Cheyne–Stokes respiration, which is progressive hyperventilation alternating with hypoventilation and ending in apnea. This breathing pattern may result from increased responsiveness to carbon dioxide as result of interruption of normal cortical inhibition. The significance of Cheyne–Stokes respiration to stroke remains unclear but appears to be more common with bilateral than unilateral insults. Besides its effects on an alteration of breathing pattern, up to 50% of patients with strokes may have signs of pulmonary aspiration due to dysfunction of upper airway muscles that protect the airway.

Spinal cord injury

The degree of respiratory impairment depends on the level and extent of the spinal cord injury. High cervical cord lesions (C1–C3) cause paralysis of the diaphragmatic, intercostal, scalene, and abdominal muscles. Because all respiratory muscle activity is lost except for accessory and bulbar muscle function, high cervical cord injuries almost always require ventilatory assistance. In some patients, spontaneous breathing can be accomplished by glossopharyngeal breathing or diaphragmatic pacing because the phrenic nerve motor neurons (C3–C5) remain intact.

Middle cervical cord (C3–C5) lesions destroy the phrenic motor neurons and prohibit the use of phrenic nerve pacing. Patients with more caudal lesions (i.e., C4–C5 level) have an improved chance to wean from ventilator support compared to those with more cranial lesions (40% of patients with C3 lesions remain ventilator dependent.). Patients with lower cervical (C6–C8) and upper thoracic (T1–T6) cord lesions have intact diaphragm and neck accessory muscle action, but have denervated intercostal and abdominal muscles. These patients usually require ventilatory support only during the period immediately after the injury and rarely require long-term ventilation. Despite this these patients still have increased mortality. In a group of spinal cord injury patients not requiring mechanical ventilation or tracheostomy followed prospectively for a median of 4.5 years, predictors of death included age, cardiac disease, diabetes, smoking history, and lower FEV_1.[47] The decline in FEV_1 and FVC in these patients is related to aging, increasing BMI, smoking, persistent wheeze, and lower MIP.[48] These data suggest that there are modifiable risk factors that can be altered to improve outcomes in those with spinal cord injuries that do not require mechanical ventilation.

In a study of C5 or lower spinal cord–injured patients, inspiratory muscle strength was reduced to approximately 60% of predicted but was dependent on the level of cord injury. In this study, PI_{max} values in low cervical, midthoracic, and lower thoracic–upper lumbar lesions were 61%, 69%, and 75% of predicted, respectively, whereas PE_{max} values were 30%, 32%, and 54% of predicted, respectively. The lower PE_{max} values were explained by a paralysis of abdominal and intercostal muscles resulting in reduced cough and decreased clearance of bronchial secretions. Abdominal muscle paralysis probably accounts for an abnormally compliant abdomen in patients with lower spinal cord injury, which is in stark contrast to the 30% reduction in chest wall compliance believed due to abnormal rib cage stiffness.[8]

Patients with spinal cord injuries also have alterations in thoracoabdominal motion during tidal breathing that is further accentuated by changing from the erect to supine position. In quadriplegic patients with relatively intact diaphragm function, the distribution of respiratory muscle weakness results in paradoxical inward motion of the upper rib cage during inspiration owing to weakness of the parasternal and scalene muscles. This pattern of abnormal thoracoabdominal movement is more marked in the supine than in the upright position. Patients with high quadriplegia (above C3–C5) may be able to sustain short periods of spontaneous respiration because of inspiratory activity of the sternocleidomastoid and trapezius muscles. Phasic inspiratory EMG activity has been observed in the platysma, mylohyoid, and sternohyoid muscles. Analysis of ribcage motion in these patients shows increased upper rib cage diameter, due to the inspiratory action of the neck accessory muscles pulling the sternum cranially and expanding the upper rib cage.

The distribution of muscle paralysis in low cervical cord spinal patients also has a profound effect on the performance of forced expiratory maneuvers. In contrast to healthy normal subjects, in whom VC is moderately decreased on assuming the supine position, in quadriplegic patients there is a paradoxical increase in VC in the supine compared to seated position without a significant increase in TLC. In 14 quadriplegic patients (C4–C7), there was a 16% increase in VC on changing from the upright to supine position and a reduction in RV (29%) and TLC (on average, 6%).[27] The mechanism believed to be responsible for the increase in VC in supine quadriplegic patients is the hydrostatic effect of abdominal contents, causing cephalad displacement and diaphragm lengthening and thereby placing the diaphragm on a more favorable portion of its length–tension curve. The use of elastic binders when quadriplegics assume upright posture has been advocated to prevent the increase in abdominal compliance. Abdominal binding may have physiologic benefit by maintaining diaphragm precontraction length in a more optimum position on its length–tension curve.[49]

It was previously believed that all expiratory muscles were paralyzed in lower cervical cord injuries. However, studies of C5 to C8 quadriplegics indicate that phasic EMG activity of the clavicular portion of the pectoralis major is associated with a marked decrease in the anteroposterior diameter of the upper rib cage.[50] This portion of the pectoralis muscle receives innervation from the C5 to C6 cord level. With the arms placed at the subject's side, contraction of the caudate head of the pectoralis major causes caudal displacement of the manubrium sterni and upper rib cage. This expiratory action has been shown to decrease expiratory reserve volume (ERV) by 60% when the shoulders are held in abduction. After 6 weeks of pectoralis muscle isometric training, patients with low quadriplegia can have a marked increase in maximum pectoralis muscle isometric strength and a significant reduction in ERV.[51] Conceivably, therefore, training of this muscle could improve the effectiveness of cough in patients with low spinal cord injury.

In the months following spinal cord injury, pulmonary function typically improves. In patients with spinal injuries below the C5 level, VC is approximately 30% of predicted in the first week after injury, but increases to 45% of predicted by the fifth week and by the fifth month to approximately 60% of predicted.[52] Improvements in VC have been attributed to spasticity developing in previously flaccid intercostal and abdominal muscles thereby increasing the rigidity of the thorax and abdomen and improving diaphragm force generation.

There is a role for corticosteroid use in the acute management of spinal cord injury. Methylprednisolone given as a bolus 30 mg/kg followed by a 24-hour infusion at 5.4 mg/kg/h has been shown to improve motor function at 6 weeks, 6 months, and 1 year, but only in those received the drug within 8 hours of injury.[53] A subsequent study compared methylprednisolone infusion (5.4 mg/kg/h) for 48 hours to 24 hours after the administration of a bolus (30 mg/kg).[54] There was no difference in functional outcome between the two infusion periods except in those where the bolus dose was given between 3 to 8 hours after the injury. If the methylprednisolone was started between 3 to 8 hours after the injury, then those that received the infusion for 48 hours did have improved motor function at 6 weeks and 6 months.

There were higher rates of pneumonia and sepsis in the 48-hour infusion group but mortality was not different.[54] No trial has shown a mortality benefit, and it should be recognized that the outcome measured was an improvement in the functional independence measure (FIM) score and not a return to normal motor function.

Parkinson Disease

Parkinson disease is due to degeneration of neurons in the substantia nigra and has a prevalence in the United States of approximately 200 cases per 100,000 people. Parkinson disease can be either primary (e.g., idiopathic) or secondary, as in postencephalitic parkinsonism associated with the influenza pandemic, or part of a more generalized disorder, such as multiple system atrophy or drug abuse with MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine).

Parkinson disease has been thought to be a purely motor disorder but recently non-motor findings are being associated with Parkinson disease, which can predate motor symptoms.[55] These findings have led to speculation that Parkinson disease could alter respiratory control at the level of the brainstem. A study in 15 subjects with early Parkinson disease and normal respiratory flow and volumes found that 7/15 had an abnormal ventilatory response while 11/15 has an abnormal occlusion pressure response ($P_{0.1}$) to hypercapnic challenge testing suggesting abnormal respiratory control.[56]

Respiratory abnormalities are common in Parkinson disease, with pneumonia being the most common cause of death. A substantial problem with Parkinson disease is glottic muscle dysfunction.[57] An abnormal flow–volume loop contour showing flow oscillations commonly occurs. On direct fiberoptic visualization of the upper airway, these oscillations correspond to rhythmic involuntary movements of glottic and subglottic structures. Physiologic evidence of upper airway obstruction may be present. In addition to the presence of oscillations in flow, a rounding off of the peak of the midexpiratory flow–volume curve, a lowered peak expiratory flow rate, and a delayed appearance of peak expiratory flow have been observed in Parkinson patients. These results have been interpreted as evidence for less coordinated or less "explosive" respiratory muscle contractions.[43,45]

Patients with mild-to-moderate Parkinson disease are able to perform simple single respiratory efforts (e.g., measurements of lung volume and maximum static inspiratory pressures) but have difficulty performing more complex, repetitive ventilatory efforts (i.e., sustaining inspiratory resistive loads to exhaustion and performing maximum unloaded breathing efforts). Performance of repetitive respiratory tasks is associated with an increased work of breathing when compared to that of an age-matched control group. These findings are similar to derangements in task performance exhibited by peripheral skeletal muscle groups in Parkinson patients.[26]

Treatment significantly improves neurologic scores, maximum expiratory pressures, and peak inspiratory flow. A recent meta-analysis has demonstrated that levodopa improves peak expiratory flow and FVC in Parkinson disease.[28] Deep brain stimulation by stereotactically placing electrodes into the suprathalamic nucleus or the globus pallidus nucleus has been shown to be equally effective when treating medically resistant patients.[58] The electrodes produce a low-voltage high-frequency stimulation that results in inhibition of the neurons in the nucleus. Although the effect on respiratory function has not been directly studied, this procedure has been shown to improve motor function and quality of life.[59]

Multiple Sclerosis

MS is a demyelinating disorder of the central nervous system, characterized clinically by remissions and relapses of clinical symptoms due to disseminating CNS lesions. MS is the most common neurologic disease afflicting young adults, with an estimated prevalence of 250,000 to 300,000 cases in the United States in 1990. The cause of the disease is unknown, although epidemiologic evidence points to genetic and environmental factors. Classic clinical symptoms include paresthesia, motor weakness, diplopia, blurred vision, dysarthria, bladder incontinence, and ataxia.

Because MS can cause focal lesions anywhere in the central nervous system, different patterns of respiratory impairment can occur. Impairment of the respiratory centers and the medulla can cause failure of automatic breathing (Ondine's curse), apneustic or neurogenic pulmonary edema. The three most common respiratory manifestations of MS are respiratory muscle weakness, bulbar dysfunction, and abnormalities in respiratory control.

Acute respiratory failure rarely occurs in this disease, but it can occur because of severe demyelination of the cervical cord. Diaphragmatic paralysis resulting in respiratory insufficiency has also been reported. Even with severe disability and impaired respiratory muscle strength, patients with MS seldom complain of dyspnea. This paucity of respiratory complaints may be due to restricted motor activities and greater expiratory than inspiratory muscle dysfunction. Clinical signs that may be helpful in predicting respiratory muscle impairment are weak cough and inability to clear secretions, limited ability to count on a single exhalation, and upper extremity involvement. Advanced MS is frequently complicated by aspiration, atelectasis, and pneumonia.

In a group of 38 patients that were not bedridden or wheelchair bound without bulbar involvement and a diagnosis of MS for 9.2 years, there was a significant decrease in the maximal inspiratory pressure (MIP) and the maximal expiratory pressure (MEP) to 77% and 60% predicted respectively.[60] In a group of 21 ambulatory stable MS patients, the percent predicted MEP was significantly reduced when compared to age-matched healthy controls (69.4% vs. 85.6%, $p = 0.03$). Furthermore, these patients had a greater change in the upright versus supine FVC compared to healthy controls (262 vs. 98 mL, $p = 0.001$).[61] Not surprisingly the MEP had an inverse correlation ($r = -0.47$; $p = 0.04$) with MS functional scores. These data suggest that even in ambulatory MS patients without respiratory symptoms respiratory muscle weakness is present, and should be monitored periodically (particularly MEP). In 60 bedridden MS patients, pulmonary function studies revealed severely decreased MIP (47% predicted), MEP (30% predicted), and VC that was 80% of predicted. In those with a VC below 80% predicted, the MIP and MEP were significantly lower than those with a normal VC.[62] In all of these studies the MEP was more affected than the MIP, and the respiratory muscle weakness directly correlated with the severity of the subject's overall neurologic function. Smeltzer et al. developed a pulmonary dysfunction index for patients with MS and found that it is correlated with MEP measurements. The score assesses the patient's assessment of cough and ability to handle secretions, the examiner's assessment of cough, and how high the patient can count on a single exhalation (Table 84-6). A subject with normal cough efficacy would have a score of 4 while an individual with the most impairment would have a score of 11.[63] Gosselink et al.[29] examined the effect of respiratory muscle training (e.g., three sets of 15 expiratory contractions at 60% of MEP twice daily) on respiratory muscle strength and the subject's pulmonary index score in a group of severe MS patients. At 3 months there was a statistically significant improvement in MIP, and although the MEP improved the p value was 0.07 compared to control patients. The pulmonary index was statistically better at 3 months and 6 months following expiratory muscle training but the FVC was not.[29] A subsequent study in 17 ambulatory MS patients who underwent expiratory muscle training was able to statistically improve MEP but this did not improve pulmonary function or markers of cough effectiveness.[64]

Treatment of MS has traditionally included the use of immunosuppressive agents such as high-dose corticosteroids, cyclophosphamide, and azathioprine. Other treatments have included intravenous immunoglobulin (IVIG), plasmapheresis, and recently medications such as glatiramer, mitoxantrone, and interferon beta (INFβ-1a).[65]

TABLE 84-6 Pulmonary Dysfunction Index for Multiple Sclerosis Patients

Clinical Signs		Score
Patient rating		
1. History of difficulty handling secretions	No	1
	Yes	2
2. Cough	Normal	1
	Weak	2
Examiner rating		
3. Strength of cough when asked to cough voluntarily as hard as possible	Normal	1
	Weak	2
	Very weak/inaudible	3
4. Value reached when patient counts aloud on a single exhalation after a maximal inspiratory effort	>30	1
	20–29	2
	10–19	3
	<9	4

Source: Data from Smeltzer SC, Skurnick JH, Troiano R, Cook SD, Duran W, Lavietes MH. Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function. Chest. 1992;101(2):479–484.

The choice of therapy depends on the clinical situation and whether relapsing–remitting or secondary progressive disease is being treated.

Most of the available data has focused on treating the acute attacks of the relapsing–remitting form of the disease. In one randomized placebo-controlled study, treatment with 10 days of high-dose oral methylprednisolone resulted in improved neurologic function, but there was no difference in the reoccurrence of future acute exacerbations.[30] INFβ-1a has been shown in a multicenter, double-blind placebo-controlled study to decrease the relapse rate after 1 and 2 years of therapy.[66] Both the American Academy of Neurology and the MS Council for Clinical Practice Guidelines recommend the use of INFb for the treatment of acute attacks in relapsing–remitting MS.[65] The use of IVIG has been controversial due to a lack of randomized controlled trials, but it does appear that IVIG can both delay and prevent the occurrences of acute attacks in the relapsing and remitting form of the disease in some patients.[67] Achiron et al.[68] has shown that in patients given IVIG within the first 6 weeks of neurologic symptoms there was a significant reduction in disease activity as measured by MRI imaging and neurologic symptoms. However, there was no significant additional benefit to adding IVIG to methylprednisolone therapy, and a recent study looking at the effect of IVIG use for 27 months in secondary progressive MS failed to show any difference in progression of disability.[69]

■ LOWER MOTOR NEURON LESIONS

The spectrum of disorders of lower motor neurons affecting respiration is considered below.

Poliomyelitis

In the early part of the 20th century, poliomyelitis was the most common cause of lower motor neuron disease in the United States. Paralytic poliomyelitis is the most devastating respiratory presentation of poliomyelitis infection and is preceded by a period of fever and mild illness. After several days of mild fever and myalgia, symptoms disappear; then, 5 to 10 days later, fever reoccurs with signs of meningeal irritation and asymmetric flaccid paralysis. Respiratory motor nuclei may be directly involved, resulting in diaphragmatic or other respiratory muscle dysfunction. In 6% to 25% of paralytic cases, bulbar symptoms may arise, increasing the risk of upper airway obstruction, pooling of pharyngeal secretions, and pulmonary aspiration. Moreover, the central respiratory centers can be directly affected, resulting in irregular respirations.[70]

In contrast to GBS, sensation is intact. Tendon reflexes are significantly diminished or absent. Cerebrospinal fluid analysis shows a pleocytosis associated with mild protein elevation, and electroneuromyography shows widespread patchy denervation.

Fifteen to 30% of adults with paralyzing infection die and treatment overall is supportive. Many patients require aggressive ventilatory and hemodynamic support during the acute phases of their illness. As temporarily damaged nerve cells regain function, recovery begins and may continue for as long 6 months. Paralysis persisting beyond that point is permanent, however, and may be associated with complaints of severe pain, which sometimes recurs years after the illness.

Some patients develop progressive muscle weakness 20 to 30 years after the initial infection. This has been termed "postpolio syndrome."[70] Symptoms vary from mild-to-moderate deterioration of function, with fatigue, joint pain, or weakness that may progress to muscle atrophy. The most common symptom is muscle pain, (typically after exertion) which occurs in 36% to 86% of the patients. The weakness tends to progress slowly, with an average decline in muscle strength of approximately 1% per year. The pathogenesis appears to be due to dysfunction of surviving motor neurons, with slow disintegration of axonal terminals eventually leading to muscle denervation. Although respiratory complaints are common in this disorder, significant hypoventilation with elevated Pa_{CO_2} rarely occurs.[71] Respiratory failure is more common in those that required mechanical ventilation during the acute poliomyelitis phase.

Amyotrophic Lateral Sclerosis

ALS is a chronic, degenerative neurologic disorder characterized by death of motor neurons in the cerebral cortex and spinal cord. The result is a combination of upper and lower motor neuron dysfunction, manifested by spasticity and hyperreflexia muscle wasting, weakness, and fasciculations. It has an incidence of approximately 1 to 2 cases per 100,000 people. Males are more commonly affected than females—by a 2:1 ratio. Most cases are sporadic, but approximately 10% of cases are familial, and there is no difference in response to therapy in those with familial ALS (FALS) or sporadic cases.[72] ALS is now recognized as a multisystem disorder that can initially present as cognitive defects prior to the development of motor symptoms and is known as ALS with frontotemporal degeneration (FTLD). Additionally, some FTLD patients go on to develop motor symptoms consistent with ALS. The main pathologic finding is abnormal accumulation of insoluble proteins in the cytoplasm of motor neurons.[73] Recently, it was discovered that two of these proteins are TAR DNA–binding protein 43 (TDP-43), and fused in sarcoma/translated in liposarcoma (FUS/TLS). Mutations in the genes encoding for these proteins have been found in FALS, SALS, and FTLD, but not in ALS associated with mutations in the superoxide dismutase-1 (SOD-1) gene on chromosome 21.[73] Even in FALS genetic mutations have been discovered in only about 30% of the cases and most remain unexplained.[73]

The usual clinical presentation is progressive weakness of the distal extremities, although severe respiratory muscle weakness, particularly intercostal muscle and diaphragm weakness, has resulted in some ALS patients presenting with respiratory insufficiency as the initial symptom. Respiratory muscle impairment is more evident in the advanced stages of the disease. Abnormalities in pulmonary function are apparent, even in patients with mild extremity weakness. Progression of respiratory impairment is much faster in ALS than in other chronic neuromuscular disorders, and serial lung function studies in ALS patients show progressive reduction in FVC and MVV. In contrast to patients with other neurologic disorders, however, patients with ALS usually have a normal or slightly elevated transpulmonary pressures at FRC, and RV is usually increased

and continues to rise as the disease progresses with maintenance of a normal TLC.[74] These changes are thought to be due to earlier involvement of the abdominal musculature, with preservation of intercostal and diaphragm function. Support for these physiologic findings comes from pathologic studies that show a more pronounced loss of motor neurons in the lumbosacral and lower thoracic spinal segments than in the upper and midthoracic regions.

The use of respiratory muscle testing has been used to help determine the prognosis and help clinicians decide when to initiate ventilatory assistance. The sniff nasal inspiratory pressure (SNIP) test is theoretically easier than the FVC maneuver for the ALS patient, because a tight seal around a mouthpiece is not required. A sniff is a short voluntary inspiratory maneuver, which has been shown to correlate with invasive nonvolitional tests of diaphragm strength. A SNIP <40 cm H_2O was found to predict nocturnal hypoxemia better than FVC. More importantly, a SNIP <40 cm H_2O was associated with a hazard risk for death of 9.1 with a median 6-month survival of 50%. Surprisingly, in those with SNIF <40 cm H_2O 66% had an FVC above 50% and the hazard risk for death was 13.6 in this group.[75] When comparing the two techniques for the ability to predict 6-month mortality, the SNIP test had a sensitivity of 97% and specificity of 79% while the FVC was 58% sensitive and 96% specific.[75] A separate study also has shown that in ALS patients without bulbar involvement SNIP was superior to both VC and MIP in predicting the development of respiratory failure as defined by hypercapnia (Pa_{CO_2} >45 mm Hg) with a specificity of 85% and sensitivity of 81%.[76] In patients with significant bulbar involvement, there was no single test of respiratory muscle function that reliably predicted the development of respiratory failure.[76]

The shape of the flow–volume curve may also pinpoint the subgroup of ALS patients with greater weakness of the expiratory muscles. In patients with severe expiratory muscle weakness, the flow–volume curve near RV shows a sharp drop in flow such that the maximum expiratory curve has a concave appearance. This group of ALS patients usually has lower maximum expiratory pressures, smaller VC, reduced expiratory reserve volume, and a higher RV than do ALS patients with more-normal–appearing flow–volume curves.[74] A prospective study of 55 ALS patients demonstrated that the peak expiratory flow time increased over baseline at a rate of 4.7% per month while the decline in the FVC was only 1.2% per month. The authors concluded that the peak expiratory flow rate can be used as an earlier marker of pulmonary involvement from ALS.[44]

ALS is a progressive and uniformly fatal neuromuscular disease and all patients will eventually develop respiratory failure, which will necessitate the discussion of mechanical ventilation (see Chapter 85). Currently, guidelines from the American Academy of Neurology recommend treatment with noninvasive mechanical ventilation once the FVC is below 50% of predicted, MIP <−60 cm H_2O, SNIP <40 cm H_2O, or have orthopnea.[77] Ventilation with bilevel positive airway pressure has been shown to increase both survival and quality of life in patients with ALS, while those with orthopnea seemed to derive the most benefit.[78–81] A randomized controlled trial of noninvasive ventilation compared to standard of care in 41 patients with ALS that had orthopnea with PI_{max} <60% predicted or symptomatic daytime hypercapnia confirmed these findings. The investigators found that overall survival was prolonged in the noninvasive ventilation group (219 [75–1382] vs. 171 [1–878]) days; $p = 0.006$], with the greatest benefit in those without severe bulbar symptoms.[80] There was also improved quality of life in the noninvasive ventilation group overall but the effect was seen only in those without severe bulbar symptoms.[80]

Due to weakness of both inspiratory and expiratory muscles, ALS patients have diminished cough reflex. Impaired cough becomes even more important when airway secretions are increased during respiratory infections or in those with bulbar symptoms. One group of investigators prospectively followed 53 patients with ALS for 1 year and found that peak cough flow (PCF), peak cough flow/peak velocity time (PCF/PVT), and severity of bulbar symptoms were most predictive of ineffective cough during a respiratory infection.[82] A mechanical insufflation–exsufflation (MI-E) device can be used to augment cough in patients by providing positive airway pressure at 40 to 45 cm (insufflation) for a few seconds and then suddenly switching to 40 to 45 cm of negative pressure (exsufflation). This creates high volume expiratory airflow that can be timed with coughing during exsufflation. MI-E increased PCF by 19% in ALS subjects with bulbar symptoms and 21% in those without bulbar symptoms. Treatment of the other respiratory complications of ALS includes a high index of suspicion for impaired swallowing due to bulbar involvement. Difficulty in swallowing food or even saliva predisposes ALS patients to a markedly high risk for pulmonary aspiration. Special swallowing precautions, earlier placement of enteral feeding tubes, or antisialogues may be required.

Currently, the antiglutamate drug riluzole is the only pharmacologic agent approved for use in ALS. This drug has been shown to induce a significant improvement in median survival from 11.8 to 14.8 months and decrease the rate of deterioration in muscle strength in comparison to a placebo.[83,84]

However, despite any pharmacologic interventions, ALS is a progressive and fatal neuromuscular disease and all patients will eventually develop respiratory failure and ventilatory assistance will therefore need to be considered. In those without bulbar involvement, noninvasive forms of ventilatory support are clearly indicated and will provide both a survival and quality-of-life benefit. Airway intubation may be required because of bulbar dysfunction further impairing cough and the inability to clear secretions. Long-term invasive ventilatory support is infrequently applied in ALS patients, but decisions must be made on an individual basis.

■ DISORDERS OF PERIPHERAL NERVES

Phrenic nerve dysfunction can be a significant cause of respiratory weakness in patients with neuromuscular diseases due to a variety of causes.

Diaphragm Paralysis

Unilateral or bilateral diaphragm paralysis following phrenic nerve injury can result from cardiac surgery, trauma, mediastinal tumors, infections of the pleural space, or forceful manipulation of the neck. Phrenic nerve injury during open-heart surgery is one of the most common causes of unilateral and bilateral diaphragm paralysis and is due either to cold exposure during cardioplegia or to mechanical stretching of the phrenic nerve during surgery. Diaphragm paralysis may also be seen with a variety of motor neuron diseases, myelopathies, neuropathies, and myopathies.

Bilateral diaphragm paralysis is characterized by a severe restrictive ventilatory impairment, with VC being frequently less than 50% of predicted in the upright position and a further reduction of 25% or more in VC in the supine position. TLC is also markedly decreased, as well as FRC and static pulmonary compliance. In most patients with nontraumatic bilateral diaphragm paralysis, the most important clinical feature is orthopnea out of proportion to the severity of the underlying cardiopulmonary disease.[15]

In patients with nontraumatic bilateral diaphragm paralysis, the diaphragm usually goes unrecognized until they present with cor pulmonale or cardiorespiratory failure. A chest radiograph showing elevation of both hemidiaphragms with volume loss and/or atelectasis at the lung bases is common. The diagnosis of bilateral diaphragm paralysis should be considered when any of the following four abnormalities is present: (1) a 40% or greater reduction in VC in the supine compared to upright position; (2) fluoroscopically observed paradoxical movements of both hemidiaphragms during a "sniff" test; (3)

absence of phrenic latency or phrenic nerve conduction velocity tests or lack of EMG evidence of spontaneous diaphragm activity; and (4) transdiaphragmatic pressure two standard deviations below the expected mean for normal subjects with paradoxical inward abdominal motion during maximum inspiratory efforts.[2,17,18,85]

Because in most patients, bilateral diaphragm paralysis occurs in the context of global respiratory muscle impairment, measurements of PI_{max} and PE_{max} may be sufficient to arouse suspicion of diaphragm paralysis as a cause of the patient's complaints. With diaphragm paralysis, a marked reduction in PI_{max} with preservation of PE_{max} should be found, and in general, there is a correlation between maximum inspiratory pressures and $P_{diSNIFF}$. Reductions in $P_{diSNIFF}$ to less than 30 cm H_2O are accompanied by orthopnea, a supine decrease in VC, and the presence of abdominal paradox. In most cases, the presence of severe bilateral diaphragm weakness can be diagnosed from physical examination, measurements of VC in the upright and supine positions, and PI_{max} and PE_{max}. In cases where the diagnosis is uncertain, or when definite documentation is desired, measurement of transdiaphragmatic pressures, phrenic nerve conduction times, EMG activity, transdiaphragmatic pressures during phrenic nerve stimulation, or ultrasound imaging of the diaphragm may be performed.[2] An elevation in Pa_{CO_2}, particularly in the supine position in patients with diaphragm paralysis, has been reported, but is not consistent.

Hemidiaphragm paralysis is more common than bilateral paralysis and is usually diagnosed from unilateral elevation of the hemidiaphragm on chest radiograph. Ultrasound of the diaphragm can be performed to confirm the diagnosis as well.[2] Most disorders reported as causing bilateral diaphragm paralysis have also been reported as causes of unilateral paralysis (e.g., cervical spondylosis, spine cord injury, poliomyelitis, and muscular dystrophy). Other, more specific causes of unilateral diaphragm paralysis are pneumonia, trauma from central vein cannulation, and viral infections of the cervical nerve roots.

Patient complaints and physical examination abnormalities in unilateral diaphragm paralysis are usually the same as with bilateral diaphragm paralysis but are less striking. Orthopnea is a frequent complaint, but it is less dramatic than in patients with bilateral paralysis. Moreover, physical examination findings are nonspecific, but occasionally may show paradoxical inward motion of the paralyzed hemidiaphragm with a reduction in breath sounds at the affected lung base and an increase in percussible dullness. The alveolar–arterial oxygen gradient may be increased with mild hypoxemia due to the reduction in ventilation and perfusion of the lower lobe on the affected side.

Tests of diaphragm function are intermediate between those in patients with bilateral diaphragm paralysis and normal predicted values. VC in the upright posture may be reduced to 74% to 81% of predicted, with a fall in VC also present in the supine compared to erect position, but of lesser magnitude than in patients with bilateral diaphragm paralysis. In patients with right hemidiaphragm paralysis, the fall in VC may be almost twice as great (19% vs. 10%) in comparison with left-sided paralysis, owing to the weight of the liver further encroaching on lung volume. Maximum inspiratory mouth pressures are frequently reduced to approximately 50% to 62% of normal. Similar reductions are also found in maximum P_{di} measured during maximum static voluntary efforts and during maximum sniff.

Treatment of patients with bilateral diaphragm paralysis is similar to that of other patients with chronic neuromuscular diseases. Eliminating nocturnal hypoventilation, especially during REM sleep is warranted, and the implementation of noninvasive ventilation, especially positive-pressure ventilation, may be indicated. In some cases of symptomatic unilateral hemidiaphragm elevation, surgical plication of the affected hemidiaphragm may relieve symptoms and improve FVC and transdiaphragmatic pressure. A series of 22 patients that underwent diaphragmatic plication were followed for an average of 4.9 years, and the investigators found that the percent decline in FVC from seated to supine position improved from 34% (range 10%–47%) preoperatively to 9% (range 0%–21%) postoperatively ($p = 0.004$). There also was an improvement in the transitional dyspnea index (TDI) postoperatively but the TDI did not correlate with the improvement in spirometry.[86] Surgical plication is achieved by placing a series of 6 to 8 U-shaped sutures in the diaphragm, which results in the diaphragm becoming fixed and immovable. This prevents excursion of the diaphragm into the thoracic cavity during inspiration, and permits the accessory muscles of respiration to generate negative intrathoracic pressure.

Guillain–Barré Syndrome

GBS precipitates respiratory failure more often than any other peripheral neuropathy. It is an acute idiopathic polyneuritis with an annual incidence of 0.89 to 1.99 cases per 100,000 people.[87] It usually presents as paresthesia and ascending paralysis of the lower extremities with absent deep tendon reflexes in a symmetrical distribution. Objective findings of sensory loss are variable, and the degree of motor weakness can range from mild paresis to complete paralysis. Maximum weakness of the lower extremities occurs within 2 weeks in 50% of cases, and 90% of cases reach their nadir in weakness by 4 weeks. After the nadir is reached, patients remain at that level for an additional 1 to 4 weeks before recovery begins. Facial, ocular, and oropharyngeal muscles may be impaired as well as the respiratory muscles. Respiratory muscle weakness and, specifically, severe diaphragm weakness may be found in patients with GBS.[87]

The distribution of muscle weakness between respiratory and nonrespiratory muscles is not uniform in GBS, and peripheral muscle strength does not correlate with the presence or absence of respiratory muscle weakness. However, ventilatory failure correlates with diaphragmatic weakness.

The impairment on respiratory tests in GBS is similar to that for other generalized neuromuscular diseases. A decline in FVC and maximum inspiratory and expiratory mouth pressures, impairment in nocturnal gas exchange during REM sleep, and the onset of hypercapnia detected by arterial blood gas analysis have all been reported in symptomatic GBS patients. An FVC of 15 cc/kg is a sign of imminent respiratory failure in GBS.[87,88] Hypercapnia is a late sign of respiratory failure, with the average Pa_{CO_2} at the time of intubation 43 mm Hg when FVC is less than 12 cc/kg.

Respiratory treatment of GBS patients is mainly supportive. Since bulbar involvement, leading to swallowing dysfunction, increases the propensity for pulmonary aspiration, special precautions for feeding and control of upper airway secretions may be required. Primarily because of bulbar dysfunction in those with respiratory failure, noninvasive ventilation has not been used outside of a few case reports. Individual cases without bulbar dysfunction merit special consideration and the use of noninvasive ventilation may be appropriate. Approximately 20% to 30% of GBS patients will require mechanical ventilation. Airway intubation and mechanical ventilation should be initiated when one major criterion or two minor criteria are present (Table 84-7).[87] Earlier intubation and assisted ventilation may be

TABLE 84-7 Criteria for Airway Intubation and Mechanical Ventilation in Guillain–Barré Syndrome

Major Criteria	Minor Criteria
Hypercarbia ($Pa_{CO_2} \geq 48$ mm Hg)	Ineffective cough
Hypoxemia ($Pa_{O_2} \leq 56$ mm Hg)	Impaired swallowing
Vital capacity < 15 cc/kg	Atelectasis

TABLE 84-8 Erasmus GBS Respiratory Insufficiency Score (EGRIS) for Predicting Respiratory Failure in the First 7 Days of Hospitalization

Measure	Categories	Score
Days between onset of weakness and hospitalization	>7 d	0
	4–7 d	1
	≤3 d	2
Facial and/or bulbar weakness on hospitalization	Absent	0
	Present	1
MRC sum score at hospitalization	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤20	4
EGRIS	**Risk of Intubation (%)**	
Low (0–2)	4	
Intermediate (3–4)	24	
High (5–7)	65	

GBS, Guillain–Barré syndrome; MRC, medical research council.

indicated to avoid complications that arise from progressive respiratory failure, overwhelming pulmonary infections, or both. When indicated, intubation and mechanical ventilation should be initiated early because emergent intubations have been associated with worse outcomes. It is well established that mechanical ventilation is indicated when the VC falls below 15 cc/kg. However, it would be ideal to predict the need for mechanical ventilation at an earlier time. A Dutch group of investigators demonstrated that the most important factors in predicting respiratory failure in the first week of hospitalization were Medical Research Council (MRC) sum score (a muscle strength score), days between onset of weakness and hospitalization, and the presence of facial and/or bulbar weakness at hospitalization.[89] Based on their model the Erasmus GBS Respiratory Insufficiency Score (EGRIS) was made and is shown in Table 84-8. Patients at highest risk for intubation (EGRIS 5–7) should be admitted to the ICU for close observation and timely intubation if required. Evaluation for discontinuation of mechanical ventilation is not different in individuals with GBS, but if the presence of dysautonomia is present at the time of extubation then reintubation rates are exceeding high (73% vs. 26.7%; $p = 0.008$)[90] while an improvement of >4 mL/kg in VC was associated with a 90% positive predictive value for extubation.[90] Aggressive pulmonary toilet, including repeated bronchoscopy, may be needed to decrease atelectasis and the incidence of nosocomial pneumonia.

In a multicenter trial, plasmapheresis (total of four treatments), using either albumin or fresh frozen plasma as replacement fluids, produced short-term benefits in earlier motor recovery, ambulation, reduction in number of patients who required assisted ventilation, and shortened the duration of mechanical ventilation.[91] A subsequent study from the same group showed that two plasmapheresis treatments were better than none in mild disease, but four were better than two in moderate and severe diseases. Giving more than four treatments was not beneficial, even in severe disease. IVIG, given within 2 weeks after the onset of GBS, may also be effective therapy.[92] IVIG has been compared to plasmapheresis and recovery was as effective as plasmapheresis and may have been slightly better. In a study of 150 patients with GBS, 53% of the group treated with IVIG had an improvement of one grade (on a seven point scale) in muscle strength compared to 34% of those treated with plasmapheresis after 4 weeks of therapy.[93] Currently, there is no evidence from randomized controlled trials to support the use of corticosteroids in the treatment of GBS.

Critical Illness Polyneuropathy

CIP was initially described in five patients that had survived sepsis and multisystem organ failure, and the entity is now recognized as a serious complication of critical illness that contributes significantly to morbidity and mortality.[94,95] The disease is common with as many as 68% of patients with sepsis and multisystem organ failure requiring mechanical ventilation having evidence of CIP on EMG/nerve conduction studies. Patients affected by this disorder typically exhibit varying degrees of musculoskeletal weakness, which ranges from mild weakness to near total paralysis with hyporeflexive deep tendon reflexes. Unfortunately, physical examination is unreliable as the sole means of diagnosis, and EMG with nerve conduction studies (EMG/NCS) are required to confirm the diagnosis. EMG studies in these patients show a reduction in the amplitude of the compound muscle action potential without significant prolongation of stimulus latency, suggesting primarily axonal nerve damage rather than a demyelinating process.

Recognition of CIP is important because the disease affects patient management and the prognosis of recovery from the critical illness. Patients that develop CIP tend to require a longer period of mechanical ventilation and longer hospital stays compared to those without CIP. Garnacho-Montero et al. found that in a group of patients with sepsis and prolonged mechanical ventilation that those with CIP required 34 days of mechanical ventilation versus only 14 days for those without CIP. Additionally, the weakness associated with CIP results in an extended rehabilitation period, and there is evidence of persistent neuropathy on EMG/NCS as long as 5 years after discharge from the ICU. Patients that develop CIP appear to have a higher mortality with one study showing a 3.5-fold increase in ICU mortality, and another with significantly higher in hospital mortality.[96]

Although the exact mechanism for axonal damage in this syndrome is unknown, several risk factors for the development of CIP have been described. Two of the most important risk factors are the presence of the systemic inflammatory response syndrome (SIRS) and the APACHE III score. One study looked at 98 patients prospectively and found that 72% of patients with SIRS and an APACHE III score above 85 will develop CIP. Multivariate analysis of associated risk factors from another study found that hyperosmolality, parenteral nutrition, the use of neuromuscular blocking agents, and neurologic failure (GCS <10) were associated with an increased risk of developing CIP.[97] Exactly how these risk factors lead to the development of CIP is not known, but possibilities include nerve toxins released during episodes of multiple system organ failure, antibiotics impairing neuromuscular transmission, protracted use of neuromuscular blocking agents, and hyperglycemia causing nerve ischemia by endovascular shunting.

Because no specific therapy for CIP exists, treatment is purely supportive and includes aggressive rehabilitation, nutrition support and treatment of any medical complications. It should be emphasized to both patient and family that recovery may be prolonged (as long as 5 years).[98]

■ DISORDERS OF THE NEUROMUSCULAR JUNCTION

Disorders of the neuromuscular junction, including myasthenia gravis, Eaton-Lambert syndrome, and botulism, may have profound effects on respiration. Each is discussed below.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder characterized by impaired transmission of neural impulses across the neuromuscular junction due to the production of antibodies directed against the

acetylcholine receptor. The prevalence of myasthenia gravis is estimated to be approximately 1 in 10,000 people with 2-to-1 female-to-male predominance. It occurs more often in younger than older adults. The typical myasthenic patient presents with fluctuating muscular weakness, with improvement after rest and the administration of anticholinesterase agents (e.g., edrophonium chloride). Ocular, facial, and neck muscles are commonly affected, but patients who have the most severe respiratory involvement have either acute fulminating or late severe classifications of myasthenia gravis.

In 17 patients with moderate, generalized myasthenia gravis, pulmonary function studies before the administration of edrophonium chloride reveal a mild reduction in VC and moderate reductions in both maximum inspiratory (~54% of predicted) and expiratory (reduced to ~52% of predicted) mouth pressures.[99] Because of increased lung recoil pressure, normal or supranormal values of maximal expiratory flow are seen in relation to lung recoil pressure or absolute lung volume. Although upper airway obstruction due to bulbar muscle involvement is theoretically possible, it has rarely been reported. However, Putman and Wise examined flow–volume loops in myasthenia gravis patients that were adequate for interpretation. They found that in 12/61 patients with myasthenia gravis with reproducible flow–volume loops 7 had either a variable extrathoracic or fixed upper airway obstruction suggesting that upper airway obstruction may be more common than previously thought.[100]

Acute respiratory failure usually occurs in the setting of a myasthenic crisis or cholinergic crisis or as the initial presentation of the disease. A myasthenic crisis refers to worsening of the basic underlying disease, usually precipitated by decreased anticholinesterase medication, surgery, or administration of neuromuscular blocking medication. Clinical parameters useful in predicting the development of postoperative respiratory failure include the severity of the disease (e.g., acute fulminating or late severe categories of myasthenia gravis), a low preoperative VC, and bulbar symptoms.[101] The most common complications of myasthenic crisis are respiratory failure and recurrent pneumonias due to aspiration from bulbar involvement and impaired cough. The mean duration of mechanical ventilation in myasthenia gravis in a series of 22 patients was 8 days, with six patients (32%) requiring tracheostomy for prolonged mechanical ventilation. Of the 22 patients 21 survived and were totally weaned from ventilatory support over 1 to 32 days.[102] Noninvasive bilevel (BiPAP) positive-pressure ventilation is a viable option to treat respiratory failure during a myasthenic crisis until effective therapy is delivered. BiPAP was used in a series of 11 myasthenic crisis events in nine patients. The mean pressures used were 13/5 cm H_2O, and endotracheal intubation was avoided in all but four instances. The only predictor for failure of BiPAP was a Pa_{CO_2} above 50 mm Hg.[103] A subsequent study in 24 patients treated with BiPAP (mean pressure 14/6 mm Hg) had similar findings in that 58% of myasthenia crisis patients avoided intubation, and the best predictor of BiPAP failure was a Pa_{CO_2} >45 mm Hg. Although there was no difference in mortality, those treated with BiPAP had a shorter ICU length of stay (7 vs. 13 days, $p = 0.002$).[104] These data suggest that the use of early noninvasive ventilation prior to the development of severe hypercapnia can reduce intubation rates and ICU length of stay.

The treatment of myasthenia gravis includes anticholinesterase agents, high-dose corticosteroids, thymectomy, and plasmapheresis in patients' refractory to steroid or immunosuppressive therapy. Anticholinesterase agents are the first line of treatment. Most patients improve significantly with anticholinesterase agents, but only a few regain normal function. Remissions can be induced in up to 80% of patients with the use of corticosteroids. However, corticosteroids may cause temporary worsening of muscle weakness, usually on the sixth to tenth day of therapy, and close observation for signs of respiratory insufficiency is advisable.[101] Other immunosuppressive agents (e.g., cyclosporine and azathioprine) may be useful with or without concomitant corticosteroids.

In retrospective studies, thymectomy improves survival and relieves clinical symptoms, even in the absence of thymoma. In patients with thymoma, thymectomy is also indicated because the risk for malignant transformation is high in patients less than 55 years of age. In up to 80% of myasthenia gravis patients without thymoma, clinical improvement after thymectomy occurs during prolonged follow-up.

Plasmapheresis and the use of IVIG produce a temporary reduction in acetylcholine receptor antibody level and may be helpful in patients with respiratory failure not responding to anticholinesterase and immunosuppressive agents. Plasmapheresis and IVIG have been compared and both are equally efficacious. However, IVIG was associated with less severe adverse reactions and therefore is the preferred initial agent in the treatment of myasthenic crisis.

Eaton–Lambert Syndrome

Eaton–Lambert syndrome is a rare myasthenia disorder resulting from a reduction in neurotransmitter release from presynaptic terminals that develops in association with tumors (especially small cell lung carcinoma). Although patients may respond weakly to administration of edrophonium chloride, the disease is differentiated from myasthenia gravis by the predominant involvement of limb and girdle muscles compared to the ocular and bulbar muscle involvement in myasthenia gravis. Respiratory muscle weakness is often detected on pulmonary function tests, but respiratory failure is infrequent.

Botulism

Botulism is a rare disorder caused by the *Clostridium botulinum* toxin. It occurs as a result of eating improperly cooked food, wound contamination by the organism, or, especially in infants, the absorption of toxin from the GI tract. There are eight types of toxins, although human diseases are usually caused by type A, B, or E.

Botulinum toxin binds to the calcium channel in presynaptic terminals, impairing neuromuscular transmission of acetylcholine. GI symptoms predominate early in the disease, followed by neurologic impairment, including descending paralysis of the neck, trunk, and limb muscles. Weakness of the respiratory muscles requiring mechanical ventilation is frequent, especially with botulinum type A toxins. Spirometry usually reveals a restrictive ventilatory defect, and recovery from respiratory muscle weakness may take months, often requiring prolonged mechanical ventilation. The average duration of ventilatory support for type A poisoning is 58 days, in contrast to 26 days for type B botulism. Exertional dyspnea and poor exercise tolerance may persist, even with normal lung function.

■ INHERITED AND ACQUIRED MYOPATHIES

Respiratory function may be significantly affected by a variety of inherited muscle disorders and acquired myopathies (Table 84-9). The inherited muscular dystrophies refer to a heterogeneous group of progressive, degenerative, hereditary skeletal muscle diseases that cause severe muscle weakness, eventually resulting in repeated pneumonias, respiratory failure, and, in some cases, death. Respiratory failure, often accompanied by pneumonia, contributes to death in more than 75% of patients with DMD.

Inherited Myopathies

Duchenne Muscular Dystrophy DMD is the best characterized of these heredofamilial muscle diseases. This disease is transmitted by an X-linked recessive gene, although approximately one-third of cases arise from spontaneous mutation. The disease is due to the mutation of the gene for skeletal protein dystrophin, a subsarcolemma

TABLE 84-9 Myopathies Likely to Produce Respiratory Abnormalities

Inherited Myopathies	Acquired Myopathies
Muscular Dystrophies	Inflammatory (dermatomyositis, polymyositis)
Duchenne	Systemic lupus erythematosus
Myotonic	Endocrine myopathies
Fascioscapulohumeral	Thyroid dysfunction
Limb–girdle	Hyperadrenocorticism
Oculopharyngeal	Acute steroid myopathy
Congenital myopathies	Electrolyte disorders
Nemaline myopathy	Rhabdomyolysis
Centronuclear myopathy	
Metabolic myopathies	
Acid maltase deficiency	
Mitochondrial myopathies	

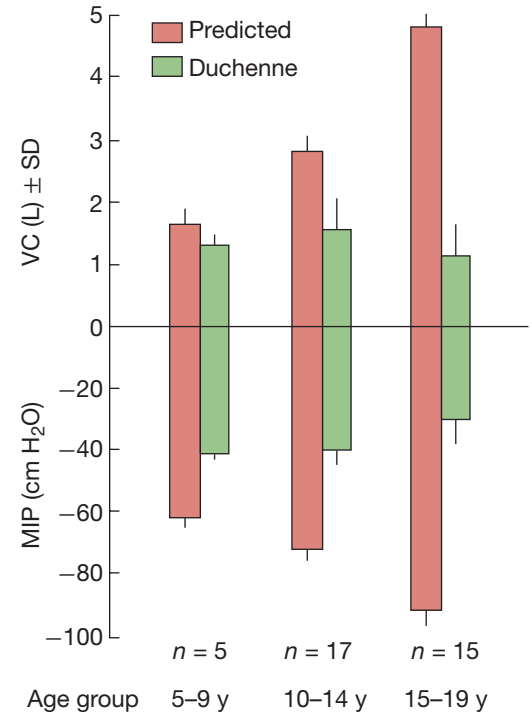


Figure 84-12 Mean vital capacity (VC) and maximum static inspiratory pressures (MIP) in 37 DMD patients in three age groups *(shaded bars)* in comparison to normal predicted values *(unshaded bars)*. MIP decreases gradually as DMD progresses, despite body growth, whereas VC increases until patients reach their early teens. *(Data from Smith PEM, Edwards RHT, Evans GA, et al. Practical problems in the respiratory care of patients with muscular dystrophy. New Engl J Med. 1987;316:1197–1205.)*

protein believed to play a major role in providing structural integrity in the muscle cell surface membrane. Lack of dystrophin leads to a weaker cell membrane that becomes further impaired with muscle contraction. Muscle inflammation, necrosis, and fibrosis subsequently lead to severe atrophy and loss of function. Approximately 30% to 40% of the normal amount of dystrophin must be expressed in order to prevent major myopathic symptoms. The diagnosis is confirmed by demonstrating mutation of the dystrophin gene in DNA from peripheral leukocytes, or an absence or abnormality in dystrophin in muscle biopsy samples.

Symptoms usually present in early childhood. Gait disturbances and delayed motor development are common manifestations, with proximal weakness resulting in an exaggerated lumbar lordosis. Most patients are wheelchair bound by the age of 12 to 15 years, with death occurring around the age of 20 years as a result of progressive respiratory failure and pneumonia. Kyphoscoliosis commonly develops as a result of severe muscle weakness and further contributes to a restrictive ventilatory deficit. Pulmonary symptoms are often minimal early on, despite significant weakness of the respiratory muscles. Maximum inspiratory pressure is reduced at all lung volumes in patients with DMD and declines with time. FVC increases with growth during the first decade and may mask early respiratory muscle dysfunction before it plateaus and progressively decreases about 5% to 6% per year after 12 years of age (Fig. 84-12).[105] Reductions in maximum inspiratory pressure, therefore, occur early in the clinical course of DMD and may precede the reduction observed in VC. In a series of 58 DMD patients, the median decline in FVC was 0.18 L (0.04–0.74 L) per year and once the FVC fell below 1 L the median survival was 3.1 years with a 5-year survival of 8%.[106] Inspiratory muscle weakness does not necessarily parallel the development of expiratory muscle weakness. Maximum expiratory mouth pressures are substantially lower than maximum inspiratory mouth pressures, possibly leading to a marked decrease in the effectiveness of cough. FVC should be measured annually in patients that are able to ambulate and every 6 months in nonambulatory DMD patients. Additionally, PCF, MIP, and MEP should be measured every 6 months in nonambulatory patients.[107,108]

Despite severe and progressive muscle weakness, hypercapnia is uncommon in patients with DMD in the absence of pulmonary infections. The absence of hypercapnia despite severe muscle weakness is believed to be due to relative preservation of diaphragm function until very late in the illness. Once hypercapnia occurs, however, the course is rapidly progressive and mean survival is approximately 10 months.

Since ventilation is heavily dependent on diaphragmatic function in DMD patients, severe nocturnal hypoventilation may occur during REM sleep, when activity of chest wall and neck muscles is markedly attenuated. Indeed, hypoventilation may occur during REM sleep, when activity of chest wall and neck muscles is markedly attenuated, and has been documented in DMD patients with normal daytime gas exchange. The American Thoracic Society has recommended that an annual sleep study be performed when the patient becomes nonambulatory unless symptoms of nocturnal hypoventilation are present.[109] Sleep-related hypoxemia may contribute to respiratory insufficiency and the development of cor pulmonale.

Management of patients with DMD is mainly supportive. Ambulation should be maintained and encouraged as long as possible to retard the development of scoliosis. Surgical correction may attenuate the scoliotic contribution to the fall in VC and improve patient morale and quality of life overall. While the decline in FVC will continue postoperatively, it may be slowed somewhat. In a group of 56 DMD patients that underwent posterior spinal fusion for scoliosis, the decline in FVC decreased from 4% per year preoperatively to 1.75% per year postoperatively ($p < 0.0001$).[110] General physiotherapy may be helpful in preventing contractures. Maintenance of proper nutrition, with an emphasis on weight control, is important. Patients with DMD have a propensity to become overweight through a combination of inactivity, reduced energy requirements, and a misguided desire to improve muscle bulk by overeating. Some authors have emphasized a high-protein (more than 80 g protein daily), low-calorie diet, aiming to achieve a body weight somewhat lower than the ideal weight in patients of a similar height and normal muscle mass.

Inspiratory muscle training (IMT) has been examined as a tool to prevent further decrease in respiratory muscle function in those with DMD, but its routine use remains controversial. Because there is loss of the protective mechanism of nitric oxide release in children with DMD, IMT could potentially be detrimental. Koessler et al.[111] studied the effect of 2 years of IMT on a group of 27 patients with neuromuscular disease (18 DMD and 9 spinal atrophy), and showed a clear increase in PI_{max} and MVV. There was a plateau reached after 10 months of training. Because there is potential for harm and no long-term studies to support its use, ATS guidelines do not suggest the use of routine IMT in this group of patients.[109]

Maintenance of cough and adequate airway clearance is extremely important in attempting to prevent atelectasis and pneumonia in this patient population. A PE_{max} of at least 60 cm H_2O has been shown to be adequate to generate an effective cough in patients with DMD, while a drop below 45 cm H_2O has been associated with ineffective cough.[109,112] Once an ineffective cough is recognized there are multiple treatment modalities. The most studied technique is the use of a manual insuffator–exsufflator, which stimulates cough by providing a positive pressure breath immediately followed by a negative pressure exsufflation. The technique can be used on patients with or without a tracheotomy, and is generally well tolerated. It has been shown to be effective in generating cough and clearing airways in children with DMD, especially once scoliosis has developed.[109] Respiratory tract infections are a serious complication in DMD patients, and must be treated aggressively with physiotherapy, postural drainage, assisted cough techniques, and appropriate antibiotics. All patients, regardless of cough status, should receive vaccination against pneumococcal pneumonia and influenza.

In some patients, assisted ventilation is required once respiratory insufficiency or symptoms of sleep-related breathing disorders are present. Intermittent noninvasive positive-pressure ventilation (NPPV) prolongs survival, improves quality of life, and may attenuate the decline in FVC and MVV. Longer-term follow-up of DMD patients treated with noninvasive ventilation demonstrates that pulmonary function continues to deteriorate 3–4 years after the initiation of noninvasive ventilation, with patients requiring longer periods of ventilation and/or transition to tracheostomy with positive-pressure ventilation.[113] Once patients require the use of NPPV, the pressure should be titrated in the sleep laboratory to eliminate nocturnal apneas and hypopneas. Generally, BiPAP should be used in those with significant daytime or nocturnal hypoventilation, and CPAP should be used primarily in those with obstructive sleep apnea without evidence of hypoventilation.

DMD is a relentlessly progressive disease that eventually will lead to respiratory failure requiring invasive mechanical ventilation (see Chapter 85). End-of-life care and plans for the use of invasive mechanical ventilation should be discussed with the family and the patient well in advance if at all possible. While the institution of mechanical ventilation has been shown to prolong life in the appropriate setting, little is known on the effect on quality of life, and decisions must be made on an individual basis.

There is evidence to suggest that prednisone treatment is beneficial. In a randomized, double-blind controlled 6-month trial of prednisone in 103 boys with DMD, patients were assigned to low-dose prednisone (0.75 mg/kg per day), high-dose prednisone (1.5 mg/kg per day), or placebo. Both prednisone groups showed significant improvements in muscle strength, functional scores, and FVC at 6 months compared to placebo, but there was no difference between low- or high-dose prednisone.[114] A subsequent study found that muscle strength was greater in DMD patients taking 0.75 m/kg compared to 0.3 mg/kg of prednisone for 6 months.[115] The effect of prednisone therapy on respiratory muscle function has been less clear but a case-control study found that steroid therapy for a mean duration of 8.2 years resulted in improved FVC, MIP, MEP, PCF, and FVC compared to those not treated with prednisone.[116] Based on these data expert panels have recommended that corticosteroid therapy be used in DMD patients.[107]

While steroid therapy may improve muscle strength it has not led to improved survival, and most experts believe that gene therapy will be applicable to DMD in the future as a potential cure for the disease. A newer method of gene therapy known as exon skipping is an attractive approach because some DMD mutations result in mRNA, which causes a premature stop in translation of the dystrophin protein. Small oligonucleotides can be developed to bind exons and block them from being incorporated into mRNA which then will allow for translation of a truncated dystrophin protein that will result in some function of the native protein.[117] Traditional gene therapy is limited in DMD by the large amount of skeletal muscle, the large size of the dysmorphin gene, and patient immunity against viral vectors.[118]

Myotonic Dystrophy Myotonic dystrophy is the most common form of hereditary muscular dystrophy in adults, with an estimated incidence of 1 in 8000 people. The gene responsible for the disease is located on the long arm of chromosome 19 and demonstrates an autosomal dominant inheritance pattern. Symptoms usually present during adolescence and in early adulthood, although the syndrome may be recognized as early as infancy.

Respiratory muscle weakness is common and can be severe, despite mild limb muscle weakness. Myotonia of the respiratory muscles contributes to an increased work of breathing by increasing inspiratory impedance. Studies have suggested that the presence of a chaotic breathing pattern may explain the higher prevalence of chronic hypercapnia in patients with myotonic dystrophy than in patients with other forms of muscular dystrophy. Support for these findings came from studies that showed abnormal ventilatory responses to hypercapnic challenges in patients with myotonic dystrophy. However, studies that have used mouth occlusion pressures ($P_{0.1}$) have revealed normal or supranormal responses in $P_{0.1}$ in patients with myotonic dystrophy compared to controls. These data seem to suggest that prior studies showing hypercapnia in patients with myotonic dystrophy underestimated the severity of respiratory muscle weakness by itself as a limitation in the ability to mount a normal ventilatory response. The chaotic breathing pattern observed in some patients with myotonic dystrophy has been suggested to be related to disordered afferent information from diseased muscle spindles.

Patients with myotonic dystrophy are particularly susceptible to development of respiratory failure with general anesthesia and sedatives. Postoperative respiratory monitoring is essential if surgery or the use of these agents is required. Pharyngeal and laryngeal dysfunction increases the risk of aspiration. Sleep-related breathing disturbances are common and may include both central and obstructive forms of sleep apnea. Nocturnal positive-pressure ventilation should be tried when hypercapnia and hypoxemia are present.

Facioscapulohumeral Dystrophy Other inherited adult muscular dystrophies are facioscapulohumeral dystrophy (FSH) and limb–girdle dystrophy. FSH is an autosomal dominant dystrophy that primarily affects muscles of the face and the proximal portion of the upper extremities. FVC is significantly reduced in patients with FSH, although facial weakness complicates spirometric assessment. In 20% of patients with FSH, the disease affects pelvic girdle and trunk muscles, sometimes impairing respiratory function.

Limb–Girdle Dystrophy Limb–girdle dystrophy is a heterogeneous group of autosomal dominant recessive disorders. The disease usually becomes evident in the second or third decade of life. Several case reports have documented the development of chronic hypercapnia

in patients with limb–girdle dystrophy who have severe diaphragm weakness or bilateral diaphragm paralysis as the basis for hypercapnia. However, not all patients with limb–girdle dystrophy develop hypercapnia. Most patients have moderate respiratory muscle weakness with normal gas exchange.

Acid Maltase Deficiency (Pompe Disease) Two metabolic myopathies, acid maltase deficiency and mitochondrial myopathy, have received attention as potential causes of respiratory failure. Acid maltase deficiency is a type I glycogen storage disease due to the deficiency of the lysosomal enzyme responsible for hydrolysis of both the α1 to 4 and α1 to 6 linkages of glycogen. The disease presents in three clinical forms: infantile, childhood, and adult. In adult-onset disease, onset usually occurs after 20 years of age and presents with progressive proximal muscle weakness. The diagnosis may be difficult to establish in some patients, as respiratory failure or sleep-related complaints, secondary to respiratory deterioration during REM sleep, may be the initial presentation. Diagnostic studies include elevated serum muscle enzymes; myopathic changes on EMG, and vacuoles filled with lysosomal breakdown products on muscle biopsy. Enzyme replacement therapy with recombinant human acid maltase, alglucosidase alfa, is now available for both early- and late-onset disease. In a study of 99 patients with late-onset Pompe disease, treated for 78 weeks with biweekly infusions of alglucosidase, the investigators found an improvement in FVC and 6-minute walk distance.[119]

Mitochondrial Myopathy Mitochondrial myopathy represents a heterogeneous group of disorders that affect mitochondrial function and may present as complex multisystem disorders with brain and striated skeletal muscle being the predominant organs affected; (1) Kearns–Sayre syndrome; (2) myoclonic epilepsy, "ragged red fibers," and mitochondrial myopathy; and (3) encephalopathy, lactic acidosis, and stroke-like episodes. The clinical manifestations may be broad and include myalgia and exercise intolerance, proximal muscle weakness, and external ophthalmoplegia with unexplained respiratory failure. All three disorders are characterized by hypoventilation and depressed responses to hypoxia and hypercapnia and, in some cases, unexplained respiratory failure. Skeletal muscle biopsy establishes the diagnosis of mitochondrial myopathy by showing "ragged red fibers," which are accumulations of mitochondria identified with modified trichrome staining. Treatment is supportive. Once identified, patients should be cautioned regarding the use of sedatives, and special attention is required when sedation or surgery is planned.

Acquired Myopathies

A variety of acquired myopathies, outlined in Table 84-9, may affect respiratory muscles. The reader is referred to other sources for detailed discussion.

TREATMENT

Principles in management of respiratory dysfunction in patient with neuromuscular disease include (1) preventative therapies designed to minimize the impact of impaired secretion clearance, alveolar hypoventilation on gas exchange and lower respiratory tract infections and (2) stabilization of patients who develop acute or chronic respiratory failure. Because patients with neuromuscular disease usually have nonpulmonary symptoms and signs before the onset of respiratory problems, preventive actions can be taken to preserve their respiratory status. In neuromuscular disorders causing bulbar dysfunction, swallowing precautions and airway control measures are required. With advanced bulbar symptoms, upper airway control with a cuffed tracheostomy tube may be needed to protect the airway and facilitate suction of lower respiratory track secretions, averting atelectasis and pneumonia. In patients with impaired cough, assisted coughing (e.g., ancillary hand thrust in the substernal location to increase intrathoracic pressure and expel secretions mouthward) may be helpful, along with posture drainage and the use of incentive spirometry. Treatment modalities used for treating pulmonary complications of neuromuscular disease include respiratory muscle training, mechanical ventilation (invasive and noninvasive), and glossopharyngeal breathing, which are all covered extensively in Chapter 85.

DIAPHRAGMATIC PACING

To increase independence from mechanical ventilation, diaphragmatic pacing may be a treatment option in selected patients. Although phrenic nerve pacing by external stimulation has been well documented since the late 1940s, long-term phrenic nerve stimulation did not become a reality until a small implantable electrode and receiver were developed in the late 1960s. Diaphragmatic pacing consists of a radiofrequency transmitter and an antenna that discharges stimulatory signals to a receiver that when activated by radiofrequency waves, transmits electrical impulses in an electrode placed over the phrenic nerve. Surgery is required to implant the electrodes and receiver. Electrode implantation around the phrenic nerves can be achieved by a cervical or thoracic approach; however, the thoracic approach is preferred, to ensure stimulation of all phrenic nerve roots while avoiding the brachial plexus. The subcutaneous receiver is usually placed in the lower anterolateral rib cage to allow it to be superficial, but in an area where soft tissue movement is limited.[120–122] The subject must have intact phrenic nerves in order for the procedure to be successful, and the phrenic nerve is typically assessed by measuring conduction times along the nerve. Electric stimulation is applied transcutaneously in the neck region and surface diaphragm EMG is monitored. The nerve conduction time can then be calculated with normal being around 7.5 to 9 msec.

Diaphragmatic pacing has a number of potential limitations, including its high cost, the potential to fail abruptly, the development of upper airway obstruction, and the induction of diaphragm fatigue. On the other hand, successful implantation allows patients to be independent from ventilatory support for prolonged periods, and to speak more freely.

While implantation of phrenic nerve electrodes has become an accepted procedure, there is ongoing research into placing diaphragmatic electrodes laproscopically, and the technique has been performed successfully in a few centers.[123] This approach would be less invasive, more cost efficient, and have less morbidity than the current approach. Two electrodes are placed on each hemidiaphragm near the motor points of the phrenic nerve. Initially, removable suction electrodes are placed until a location is found that induces maximal contraction of the diaphragm and a large intra-abdominal pressure change both by twitch and high-frequency stimulation. The wires are then brought through the skin and connected to the stimulator. Because patients on chronic mechanical ventilation develop diaphragm atrophy,[124] a reconditioning period is required before the restoration of maximal diaphragm function. Figure 84-13 shows the tidal volume generated gradually increased with time as the muscle is reconditioned and the tidal volume is greatest with bilateral stimulation. In a case series using this technique, 3 of 5 subjects achieved independence from mechanical ventilation. One other was free of mechanical ventilation for 20 hours per day, and the other did not have activation of the diaphragm. This individual most likely did not have intact phrenic nerves.[121] Intact phrenic nerves are required for successful intramuscular diaphragm pacing as evidenced by animal studies showing no diaphragm activation with intramuscular pacing after transection of the phrenic nerves. This probably occurs because the mechanism of intramuscular pacing is by stimulation of phrenic nerve roots in the diaphragm.

Because the intercostal muscles are capable of contributing up to 35% to 40% of the VC they should be able to liberate a subject from

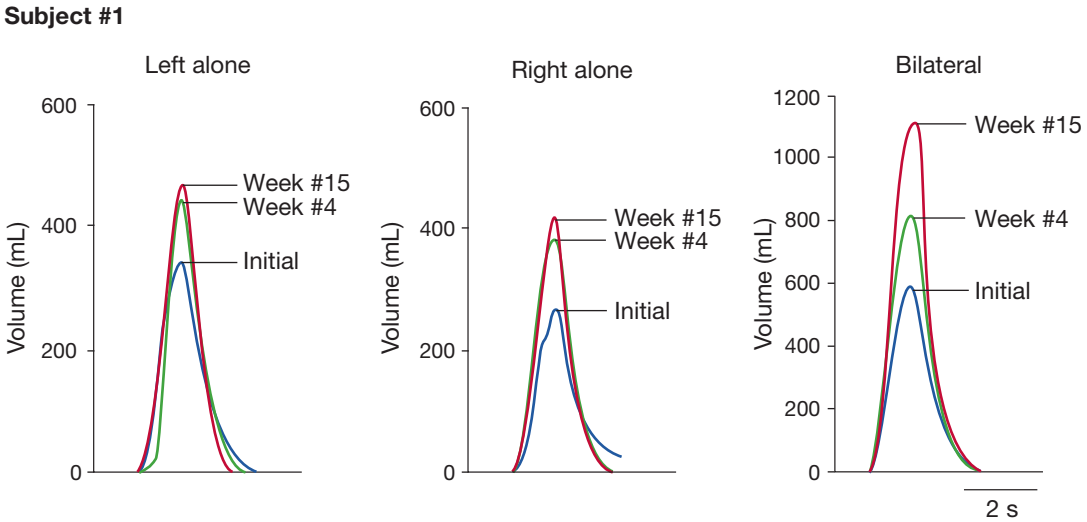


Figure 84-13 Reconditioning of the diaphragm as evidenced by increased inspired volumes initially, at 4, and 15 weeks postoperatively after left and right hemidiaphragm and bilateral diaphragm contraction via diaphragmatic electrode pacing. *(Data from DiMarco AF, Onder BP, Ignagni A, et al. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest. 2005;127:671–678.)*

mechanical ventilation if stimulated through pacing. In animal models, stimulation of the ventral surface of T1 to T3 resulted in maximal inspired volumes, and when combined with bilateral phrenic nerve pacing results in tidal volumes that approach the inspiratory capacity. However, when applied to a group of spinal cord injury patients with phrenic nerve damage, very little volumes were generated with stimulation of ventral aspect of T1 to T3, and subjects were unable to breathe without mechanical ventilation for short time periods (20 minutes to 2.45 hours). This discrepancy between animal and human studies may be secondary to the different shape of the human thoracic cage or the reduction in rib cage and lung compliance in those with tetraplegia. Additionally stimulation of T1 to T3 resulted in the movement of several nonrespiratory muscles, which led to hypertrophy of the upper trunk musculature.[121] A follow-up trial combined intercostal pacing with unilateral diaphragm pacing in a small group of patients that had unilateral phrenic nerve injuries in addition to spinal cord injury. All of these patients were able to have significant periods of time free from mechanical ventilation.[125] The main limitation to this approach remains contraction of nonrespiratory muscles, which makes the process metabolically inefficient and can lead to uncontrollable muscle activity.

Patients who appear to benefit from diaphragmatic pacing are ventilator-dependent patients following high cervical cord injury. Approximately one-third of patients with high cervical spinal cord injuries may be suitable for this type of treatment. Although short-term improvements are noted in terms of ventilator independence and improvement in functional status, no long-term studies demonstrating efficacy have been published to date.

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CHAPTER 85

Management of Neuromuscular Respiratory Muscle Dysfunction

John R. Bach

INTRODUCTION

Patients with ventilatory impairment due to ventilatory muscle dysfunction are often evaluated and managed according to practices developed for patients with chronic lung diseases. However, pulmonary function laboratories, designed primarily for assessment of lung diseases, do not evaluate lung volume recruitment capacities or cough flows that are important in the assessment of patients with inspiratory and expiratory muscle dysfunction. In the setting of ventilatory muscle dysfunction polysomnograms may be misinterpreted as central or obstructive apneas and hypopneas rather than hypoventilation due to inspiratory muscle dysfunction, and continuous positive airway pressure (CPAP) or nocturnal bilevel positive airway pressure (BiPAP) prescribed. In the context of ventilatory muscle dysfunction CPAP does not increase tidal volumes, and may actually reduce them by causing them to approach maximum lung capacity for these patients with severe pulmonary restriction while BiPAP is often used at pressures inadequate to support alveolar ventilation, provide inspiratory muscle rest, or assist in coughing.[1] In addition, the patients are often treated with supplemental oxygen to correct hypoxemia when efforts to improve oxygenation should be directed at normalizing alveolar ventilation and clearing airway secretions. With advancing inspiratory and expiratory muscle weakness, the common scenario is that respiratory failure ensues and is treated by mechanical ventilation via endotracheal intubation. When ventilator weaning fails, a tracheostomy is performed and mechanical ventilation is continued indefinitely, often in an institution.

Therapeutic modalities commonly used for respiratory diseases can have adverse effects in patients with neuromuscular disorders. Bronchodilator therapy can augment the anxiety and tachycardia that are common in myopathic patients, many of whom have cardiomyopathies. Oxygen therapy increases the risk of pulmonary morbidity, rate of hospitalizations, and mortality by comparison with the use of ventilator assistance or with no treatment at all.[2] As noted earlier, oxygen therapy may obscure recognition of mucus plugging because it alleviates oxyhemoglobin desaturation without attention to the expulsion of airway mucus. Oxygen therapy may also prolong hypopneas and apneas during rapid eye movement (REM) sleep,[3] and it appears to suppress the reflex muscular activity needed for effective noninvasive intermittent positive pressure ventilation (IPPV) during sleep.[4] Translaryngeal intubation, tracheostomy, and tracheal suctioning continue to be used for patients with neuromuscular diseases even though noninvasive IPPV, noninvasive suctioning, and mechanically assisted coughing (MAC) can be more effective and comfortable.

Despite the proven effectiveness of measures to support ventilation noninvasively for long periods even in the absence of respiratory muscle function, these therapeutic modalities have yet to be adopted by many physicians. In Great Britain, 82% of patients with amyotrophic lateral sclerosis (ALS) die receiving morphine and 64% receive benzodiazepines, while few are provided with respiratory muscle aids to prevent respiratory failure.[5] This approach both smoothes and hastens passage to the grave by leading to CO_2 narcosis.[6,7] Often, without consulting the patient, the physician judges the patient's quality of life to be unacceptable and the disease terminal, ignores options that prevent respiratory complications, renders the patient and family hopeless, and biases the family against ventilator use which the physician associates with tracheostomy. Proclaimed as "palliation," the results of this professional point of view are anguish and hopelessness and not infrequently lead patients to seek quack therapies and assisted suicide. Over a recent 5-year period, 12 publications in the New England Journal of Medicine concerned clinical management and assisted suicide for patients with ALS. In none of these reports was prevention of respiratory complications or ventilator assistance by invasive or noninvasive means considered. Failure to consider noninvasive IPPV for full ventilator support continues.[8,9]

PATHOPHYSIOLOGY

Patients with neuromuscular disorders can develop respiratory failure because of some combination of respiratory muscle dysfunction (Table 85-1), that is, dysfunction of inspiratory, expiratory, and bulbar-innervated muscles. These muscle groups will be considered here and the reader is referred to Chapters 84 and 143 for detailed discussions of the physiological disturbances associated with chest wall and neuromuscular disorders that affect ventilation.

Autonomously breathing patients with advanced ventilatory muscle dysfunction develop a rapid, shallow breathing pattern with inability to take deep breaths. If untreated, this can lead to chronic microatelectasis and decreased lung and chest wall compliance.[10,11] Acute respiratory tract infections with pulmonary scarring and the kyphosis and scoliosis that are common in these patients can cause further loss of lung compliance.

In the context of neuromuscular disorders, hypercapnia develops insidiously as a consequence of shallow breathing as respiratory control centers reset and increasing central nervous system bicarbonate levels accommodate and permit it to worsen. Hypercapnia, itself, can decrease respiratory muscle strength,[4] and decreases the effectiveness of its treatment by the nocturnal use of BiPAP or noninvasive IPPV.[4] The risk of pulmonary morbidity and mortality from acute respiratory failure correlates with increasing hypercapnia.[2,4]

Inspiratory muscle weakness, mechanical dysfunction of the chest wall and lungs associated with thoracic deformities, hypopharyngeal collapse or other upper airway narrowing, extreme obesity, abdominal distension, use of improperly fitting thoracolumbar orthoses as well as narcotic and sedative medications, supplemental oxygen, malnutrition and deconditioning, infection, and fatigue can all either cause or exacerbate alveolar hypoventilation and lead to respiratory failure. Oxygen therapy often results in CO_2 narcosis, otherwise hypoventilation is usually first recognized during an intercurrent respiratory infection when bronchial mucus plugging triggers pneumonia and acute respiratory failure due to an ineffective cough and fatigue during acute respiratory infections.[2,7] Ventilatory failure can also develop suddenly or over a period of hours or days in patients with acute cervical myelopathies, Guillain–Barré syndrome, myasthenia gravis, acute poliomyelitis, or exacerbations of multiple sclerosis.

Patients with generalized muscle dysfunction usually also have concomitant expiratory and oropharyngeal (bulbar) muscle weakness that decreases cough peak flows (CPF). When CPF do not exceed 2.7 L/s, cough may be completely ineffective.[12] CPF are

TABLE 85-1 Physical Medicine Respiratory Interventions Benefit Patients with the Following Conditions

Critical care neuromyopathies/deconditioning
Myopathies
Muscular dystrophies
Dystrophinopathies—Duchenne and Becker dystrophies
Other muscular dystrophies—limb-girdle, Emery–Dreifuss, facioscapulohumeral, congenital, childhood autosomal recessive, and myotonic dystrophy
Non-Duchenne myopathies
Congenital and metabolic myopathies like acid maltase deficiency
Inflammatory myopathies such as polymyositis
Diseases of the myoneural junction such as myasthenia gravis, mixed connective tissue disease
Myopathies of systemic disease such as carcinomatous myopathy, cachexia/anorexia nervosa, medication associated
Neurological Disorders
Spinal muscular atrophies
Motor neuron diseases
Spinal cord injuries
Poliomyelitis
Neuropathies
Hereditary sensory motor neuropathies
Phrenic neuropathies–associated with cardiac hypothermia, surgical or other trauma, radiation, phrenic electrostimulation, familial, paraneoplastic or infectious etiology, and with lupus erythematosus
Guillain–Barré Syndrome
Multiple sclerosis
Disorders of supraspinal tone such as Friedreich ataxia
Myelopathies of rheumatoid, infectious, spondylitic, vascular, traumatic, or idiopathic etiology
Tetraplegia associated with pancuronium bromide, botulism
Sleep-disordered breathing including obesity hypoventilation, central and congenital hypoventilation syndromes, and hypoventilation associated with diabetic microangiopathy, or familial dysautonomia
Skeletal pathology such as kyphoscoliosis, osteogenesis imperfecta, and rigid spine syndrome

reduced by airway obstruction caused by tracheal stenosis, laryngeal incompetence, postintubation vocal cord adhesions or paralysis, hypopharyngeal collapse due to bulbar-innervated muscle weakness or spasticity, airway granulation tissue, and obstructive pulmonary disease. The CPF are reduced further when patients cannot take or receive a breath greater than 1.5 L.[13] Thus, the airway secretions that develop during upper respiratory tract infections and after surgical anesthesia often result in pneumonia and acute respiratory failure. Smoking, the presence of an endotracheal cannula that causes bronchorrhea, or bronchorrhea for any other reason increases the tendency to develop mucus plugging that is all too frequently managed by repeated bronchoscopies, intubation, and tracheotomy without trying MAC. Intubation, however, results in a burden of pathogenic bacteria that, even when not causing ventilator-associated pneumonia, exceeds the commonly accepted threshold for diagnosing it.[14]

For patients with ventilatory muscle dysfunction, arterial hypoxemia and hypercapnia occur initially during REM sleep and later extend throughout sleep and eventually throughout the awake hours. Cough reflex is also suppressed during sleep, which is when mucus plugs are most likely to cause sudden and severe hypoxemia. Normocapnic arterial hypoxemia is also common during sleep, most likely reflecting ventilation/perfusion mismatches associated with microatelectasis, scoliosis, airway mucus congestion, and pulmonary scarring.

THE RESPIRATORY MUSCLE GROUPS

The diaphragm is the principal muscle of inspiration. The abdominal muscles are the principal muscles of expiration or coughing. The bulbar-innervated muscles are the muscles of the upper airway. They include the muscles of the mouth, uvula and palate, tongue, and larynx. While these muscles do not have a direct action on the chest wall, they are essential for keeping the upper airway patent; they affect airway resistance and airflow; and they permit glossopharyngeal breathing (GPB).

Decreased inspiratory muscle function results in decreased vital capacity (VC), atelectasis, increased relative work of breathing, and eventually in hypoventilation. Expiratory, inspiratory, and bulbar-innervated muscle dysfunctions result in an ineffective cough. The latter can also affect speech, swallowing, and safe food and saliva management. Fortunately, the inspiratory and expiratory muscles can be substituted for by physical medicine interventions. Indeed, numerous patients with no muscle function below the neck and no measurable VC for over 50 years do not need tracheostomy tubes or develop hypercapnic respiratory failure.

INSPIRATORY AND EXPIRATORY MUSCLE AIDS

Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or pressure changes to the airway to assist or substitute for inspiratory or expiratory muscle function. Negative pressure applied to the airway during expiration assists the expiratory muscles for coughing, just as positive pressure applied to the airway during inhalation (noninvasive IPPV) assists inspiratory function.

A manual thrust applied to the abdomen during expiration, especially when in combination with mild chest compression, assists expiratory muscle function and increases cough flows.[13] The devices that act on the body to enhance inspiratory and expiratory muscle function include body ventilators. The intermittent abdominal pressure ventilator (IAPV) involves the intermittent inflation of an elastic air sac that is contained in a corset or belt worn beneath the patient's outer clothing (Fig. 85-1). The sac is inflated by a positive pressure ventilator. Bladder action against the abdominal wall moves the diaphragm upward, causing a forced exsufflation. During bladder deflation, the abdominal contents and diaphragm return to the resting position, and inspiration occurs passively. A trunk angle of 70 to 80 degrees from the horizontal is ideal for use. The patient who has any inspiratory capacity or is capable of GPB can add autonomous volumes to the mechanical insufflations. The IAPV generally augments tidal volumes by about 300 mL, but volumes as high as 1200 mL have been reported when there is no scoliosis or obesity.[15] Patients with less than 1 hour of ventilator-free breathing ability tend to prefer to use the IAPV rather than use noninvasive IPPV during daytime hours.[15]

Note, CPAP does not assist inspiratory or expiratory muscles and should rarely if ever be used for these patients whose symptoms of sleep disordered breathing are associated with muscle weakness rather than central or obstructive sleep apneas.

CLINICAL GOALS

The goals of management are to optimally inflate the lungs and chest wall to maintain pulmonary compliance, to maintain normal alveolar ventilation around-the-clock, and to maximize CPF.

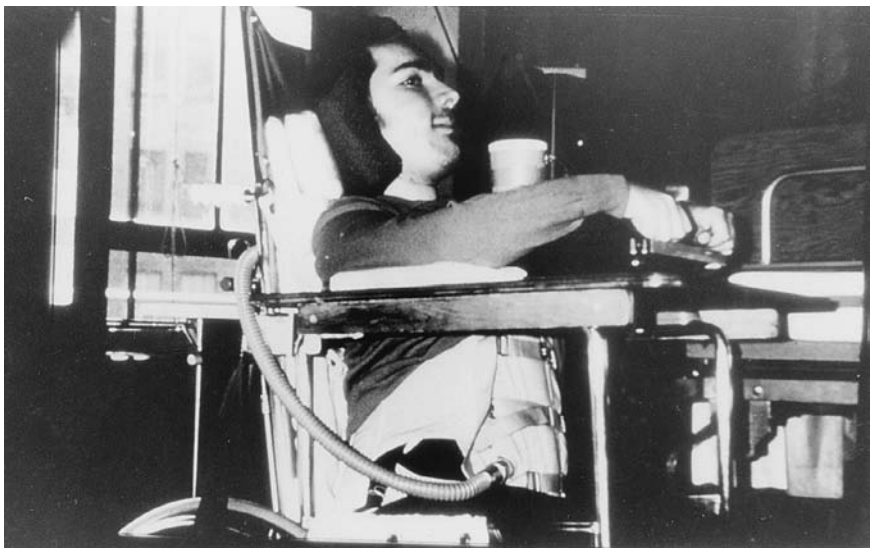

Figure 85-1 The girdle of the intermittent abdominal pressure ventilator (IAPV) with its air sac connected to the tubing of a volume-cycled ventilator. This DMD patient with no measurable vital capacity used the IAPV for daytime ventilator support for 15 years.

MAINTAIN PULMONARY COMPLIANCE AND CHEST WALL MOBILITY

Incentive spirometry can expand the lungs no greater than the VC so it is ineffective as a tool for lung volume recruitment. Like limb articulations, the lungs and chest wall too require regular mobilization.[11] This can be achieved actively by air stacking (Video 85-1),[16] passively by providing deep insufflations for those with an incompetent glottis, or by nocturnal noninvasive ventilation for infants who cannot cooperate with air stacking or passive deep insufflations.[17]

A patient's maximum insufflation capacity (MIC) is the largest volume of air that can be held with a closed glottis. The patient "air stacks" consecutively delivered volumes from a volume-cycled ventilator or a manual resuscitator, holding these volumes with a closed glottis to maximally expand the lungs. The air is delivered via a mouth piece (Video 85-1), nasal or oronasal interface if the lips are too weak to retain the air. This is performed multiple times in three daily sessions. Patients who learn GPB can often air stack consecutive gulps to or beyond the MIC. The difference between the MIC and the VC is a function of bulbar-innervated muscle integrity (force of glottic closure).[13] If the bulbar muscles are too weak for deep active air stacking, single deep insufflations are provided via a mechanical insufflator–exsufflator at 40 to 70 cm H_2O in three daily sessions. Deep insufflations can also be delivered via manual resuscitator with the expiratory valve blocked.

The primary objectives of lung recruitment therapy are to increase voice volume and MIC, maximize CPF, improve pulmonary compliance, prevent atelectasis, and master noninvasive IPPV. Occasionally the VC also increases with increases in MIC. Should the situation arise, the ability to air stack facilitates extubation to noninvasive IPPV (Video 85-1). This is extremely important for avoiding tracheotomy because such patients can be safely extubated without being ventilator weaned.[18]

Video 85-1 A ventilator-dependent patient with amyotrophic lateral sclerosis who failed all spontaneous breathing trials, extubated to full-support noninvasive intermittent positive pressure ventilation via a 15-mm angled mouth piece. He demonstrates lung volume recruitment and increased voice volume by air stacking. *Access at www.fishmansonline.com*

Lung volume recruitment also promotes lung growth and chest wall development in children. While infants cannot air stack, nocturnal use of high span (IPAP [inspiratory positive airway pressures] – EPAP [expiratory positive airway pressures] >10 cm H_2O) BiPAP or a pressure-cycling portable ventilator set at pressures over 16 cm H_2O has been demonstrated to prevent pectus excavatum and promote lung and chest wall growth for infants with spinal muscular atrophy (SMA), all of whom have paradoxical breathing when not using it.[19,20]

MAINTAIN NORMAL ALVEOLAR VENTILATION

Noninvasive Ventilation

BiPAP is not optimal for patients with neuromuscular disorders because one cannot air stack using pressure-cycled ventilators or fully expand the lungs with the machines currently on the market. IPPV from volume-cycled machines can be delivered via lip seals, nasal, or oral–nasal interfaces for ventilator support during sleep. The patients can be trained and equipped in the outpatient and home settings. While inpatient polysomnography can be helpful for adjusting ventilator settings to optimize sleep quality, we have managed over 1500 patients on noninvasive ventilation, many of whom eventually requiring it around-the-clock, without using this expensive intervention.

Patients requiring around-the-clock support use simple 15- or 22-mm angled mouth pieces that are grabbed with the teeth for IPPVs (Fig. 85-2) during the day. To use mouthpiece IPPV, adequate neck

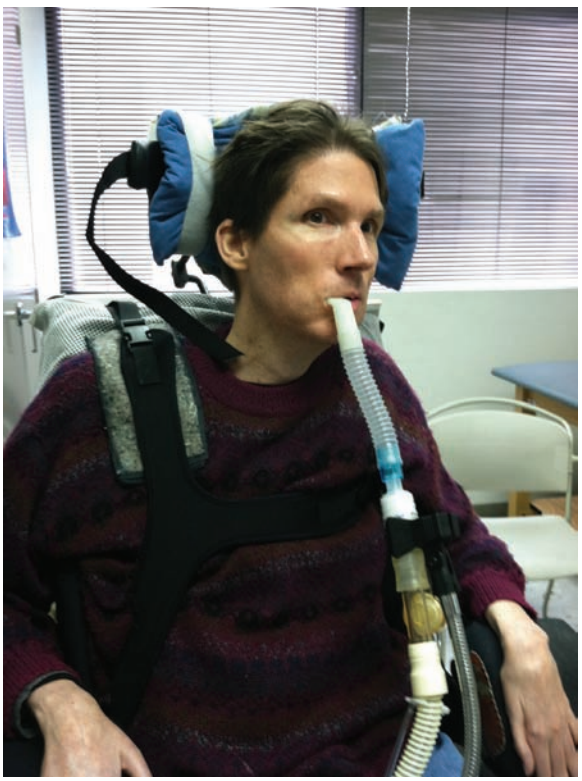

Figure 85-2 A 48-year old with Duchenne muscular dystrophy, continuously dependent on noninvasive intermittent positive pressure ventilation (IPPV) since 23 years of age, seen here using IPPV via a 15-mm angled mouth piece for daytime ventilator support.

Figure 85-3 Brothers with spinal muscular atrophy type 1 (Werdnig–Hoffman disease) who have been continuously noninvasive intermittent positive pressure dependent since 4 months of age using a nasal prongs interface during daytime hours that permits the use of eye glasses. These patients' lips are too weak to use mouth piece; they have had nasogastric tube feedings since infancy; and their vital capacities have been 0 to 10 mL for more than 10 years but they are managed noninvasively.

rotation and oral motor function are necessary to grab the mouth piece and receive IPPV without insufflation leakage out of the mouth or nose. In addition, the patient must open the glottis and vocal cords, dilate the hypopharynx, and maintain airway patency to receive the air.

When the lips are too weak to grab a mouthpiece, the patient can use an IAPV[15] or continue nocturnal nasal IPPV into daytime hours (Fig. 85-3). In the latter case, nasal interfaces are alternated to vary skin pressure. Inconspicuous nasal interfaces that permit the use of eye glasses can also be used.

Although the use of oronasal interfaces is popular in some centers, we have rarely found them to be necessary. Even patients with little or no measurable VC can be safely ventilated day and night by open systems of nasal or oral ventilation. Closed systems are unnecessary provided that ventilatory drive is not blunted by oxygen therapy, sedative medications, or excessive daytime hypercapnia, all of which can result in excessive air leakage out of the nose or mouth when using the open systems of mouth piece/lip seal or nasal ventilation for sleep.[4] If necessary, one can provide an essentially closed system of ventilatory support by using a lip seal device and placing cotton pledgets in the nostrils and sealing the nostrils with a band-aid, or more commonly today, by using a nasal prong system that extends down over the lips, for example, the Hybrid Universal Interface™ (Innomed Technologies, Savannah, Georgia) and the Mirage Liberty™ interface (ResMed Inc., Duncan, South Carolina).

The benefits derived from the part-time, usually nocturnal, use of noninvasive ventilation, appear to be due to some combination of respiratory muscle rest, increasing tidal volumes and alveolar ventilation, and improving blood gases, lung compliance, chemotaxic sensitivity, and possibly ventilation/perfusion matching by reducing atelectasis and small airway closure.[4] To accomplish optimal rest, high volumes or pressure spans are used, that is, assist-control mode at volumes of 800 to 1500 mL or pressures of 18 to 20 cm H_2O for adults and inspiratory-to-expiratory positive airway pressure spans of 13 to 18 cm H_2O for BiPAP users. Patients vary the volume of air taken in from ventilator cycle to ventilator cycle to vary tidal volume, speech volume, and cough flows, as well as to air stack and provide lung expansion.

Complications of noninvasive IPPV include claustrophobia, skin discomfort, abdominal distension, occasional allergy to the plastic or silicone interfaces, mouth dryness, eye irritation from air leakage, nasal congestion and dripping, sinusitis and nose bleeds, gum discomfort and receding, maxillary flattening in children, aerophagia,[21,22] and, as for invasive ventilation, barotrauma. Switching to lip-delivered IPPV can relieve most of the difficulties associated with nasal IPPV, however, it is more difficult to speak when using lip-delivery devices. Abdominal distention can be alleviated by switching to pressure cycling. Distension is often relieved as the air passes as flatus once the patient sits up in the morning or by "burping" of a gastrostomy tube if present. Barotrauma can occur with invasive or noninvasive ventilation but is rare with the latter for patients with neuromuscular disorders.

FACILITATE CLEARANCE OF AIRWAY SECRETIONS

Chest percussion and vibration can help mobilize deep airway secretions, but they are not substitutes for coughing. Cough can be assisted manually or by mechanical means.

Manually Assisted Coughing

Manually assisted coughing requires substantial lung inflation by air stacking or a deep passive lung insufflation especially if the VC is less than 1.5 L.[13] This is followed by an abdominal thrust applied as the glottis opens. Whereas all three respiratory muscle groups are needed for spontaneous coughing, only bulbar-innervated muscle function is required for assisted coughing. This is because airway pressure changes and abdominal thrusts substitute for inspiratory and expiratory muscles but there is nothing noninvasive that can substitute for the function of the glottis.

Manually assisted coughing requires a cooperative patient, good coordination between the patient and care giver, and adequate physical effort and often frequent application by the care giver. When inadequate, and especially when inadequacy is due to difficulty air stacking or diminished strength of the glottis, MAC is required.

Mechanically Assisted Coughing

MAC combines passive mechanical insufflation–exsufflation with an abdominal thrust. Mechanical insufflator–exsufflators deliver deep insufflations followed immediately by deep exsufflations. The MAC cough volumes normally exceed 2 L at flows of 10 L/s. Insufflation to exsufflation pressures of +50 to −50 cm H_2O delivered via oronasal interface or adult tracheostomy or translaryngeal tubes with the cuff inflated are most effective. Machine pressures, however, are secondary. What is important is to fully expand and then fully and rapidly empty the lungs.

Whether via the upper airway or via indwelling airway tubes, routine airway suctioning misses the left main stem bronchus about 90% of the time. This explains high rates of left lower lobe pneumonia. MAC, on the other hand, provides the same exsufflation flows in both left and right airways without discomfort, fatigue, or airway trauma and it can be effective when suctioning is not.

MAC supports or takes the place of the inspiratory and expiratory muscles. Thus, the patients who need it are those whose inspiratory and expiratory muscles are too weak for effective coughing but whose bulbar-innervated muscle function can maintain adequate airway patency but not air stack effectively for assisted CPF over 5 L/s. This is typical of most patients with neuromuscular disease. On the other hand, MAC is usually unnecessary for patients with intact bulbar-innervated muscle function such as those with spinal cord injury, as they can usually air stack sufficiently such that with a properly applied abdominal thrust (assisted) CPF can exceed 6 L/s. MAC becomes ineffective if bulbar-innervated muscle function cannot maintain airway patency during the mechanical exsufflation or if saliva is continually aspirated as often happens in advanced bulbar ALS.

THE OXIMETRY FEEDBACK—RESPIRATORY AID PROTOCOL

This protocol consists of using inspiratory (noninvasive IPPV) and/or expiratory (MAC) aids in combination with pulse oximetry

Video 85-2 This video demonstrates postextubation airway secretion expulsion by mechanical insufflation–exsufflation (MIE) applied via an oronasal interface. A large bolus of mucopurulent material can be seen entering the interface during the exsufflation phase of MIE. *Access at www.fishmansonline.com*

feedback to maintain patients' room air Sa_{O_2} ≥95%. The protocol is most important during respiratory tract infections and when extubating patients with little or no VC (Video 85-2). Noninvasive IPPV and MAC with oximetry feedback has averted hundreds of hospitalizations for patients with Duchenne muscular dystrophy (DMD),[23] SMA,[17] ALS,[24] and other neuromuscular conditions.[25] On the other hand, tracheostomy is indicated when saliva is continuously aspirated and the Sa_{O_2} remains below 95% despite optimal use of noninvasive IPPV and MAC. This essentially only occurs in advanced bulbar ALS. Ninety percent (33 of 35) of these ALS patients whose Sa_{O_2} baseline has decreased below 95% despite noninvasive IPPV and MAC were reported to have been deceased within 2 months unless undergoing tracheotomy.[15,23,24]

NONINVASIVE VERSUS TRACHEOSTOMY IPPV OUTCOMES

In a controlled study in which over a 7-year period all continuously ventilator-dependent DMD patients underwent tracheostomy, 21 survived to a mean age of 28.1 ± 8.3 years of age with 3 still alive. Over the next 21-year period 88 consecutive continuously ventilator-dependent DMD patients used only continuous noninvasive IPPV with none undergoing tracheostomy. These 88 had a 50% survival by Kaplan–Meier analysis to 39.6 years of age ($p < 0.001$).[26] We, too, have reported DMD survival by continuous noninvasive IPPV dependence for 101 DMD with 5 now over age 40 and having required continuous support for over 20 years,[27] and including one to age 48 having used continuous noninvasive support for 25 years.[28] Twenty-two DMD patients unable to pass spontaneous breathing trials were extubated and 8 decannulated to continue full-time noninvasive IPPV.[18]

Considering ALS, although it appears that all patients would eventually lose sufficient bulbar-innervated muscle function to satisfy the Sa_{O_2} criterion for tracheotomy,[24] in one study 22 patients (25%)[29] and in another 41 (42%)[24] became dependent on continuous noninvasive IPPV for means of 8 and 12 months (range to 8 years), respectively, before requiring tracheotomy. In the latter study, 13 became continuously ventilator dependent without developing acute respiratory failure or requiring hospitalization. The difference between the patients who could be spared respiratory failure from those who could not was that the latter had stridor and upper airway spasticity as well as no ability to generate measurable CPF.[24] We have extubated 16 and decannulated 5 ALS patients who could not pass spontaneous breathing trials and who subsequently survived as long as 8 years using continuous noninvasive IPPV before requiring tracheotomy. Once bulbar ALS patients undergo tracheostomy for ventilatory support, survival has been reported to be about 5 years before most patients die from complications related to their tracheostomies.[30]

Infants with SMA type 1 have 70% mortality by 6 months of age and 90% by 24 months of age from respiratory failure unless undergoing tracheotomy. In a recent study of 80 nasal noninvasive ventilation users, all of whom continuously ventilator dependent before 24 months of age, the protocol extubation (Table 85-2) success rate was 87% by comparison to 6% by conventional extubation approaches. Hospitalization rates for the noninvasively managed patients fell from 1.6 per year up to age 3 to 0.04 per year after age 5.[17] Fourteen such typical and severe SMA type 1 patients are currently over 15 years of age, with the oldest being 22 years of age, using nasal ventilation 24 hours a day in some cases since 4 months of age (Video 85-3).[31] Sixty of 63 typical and severe SMA type 1 patients who required intubation for intercurrent chest infections were successfully extubated to continuous noninvasive support despite being unable to pass spontaneous breathing trials.[31] SMA type 1 patients who undergo tracheotomy have also been described to survive into adolescence but tend to die from complications of the tracheostomy tube.[17]

TABLE 85-2 Criteria for Successful Use of Noninvasive Ventilatory Support for Neuromusculoskeletal Disorders

Patient cooperative and no use of heavy sedation or narcotics
No substance abuse or convulsions
Cough flows (with or without manual or mechanical assistance) sufficient to eliminate airway debris and maintain baseline Sa_{O_2} >94%
No mechanical obstacles to using IPPV interfaces (e.g., facial fractures or interfering devices)

Noninvasive IPPV is overwhelmingly preferred by patients over tracheostomy IPPV for speech, sleep, swallowing, comfort, appearance, security, use of GPB, and overall.[32] One study also demonstrated 200% cost savings by using noninvasive support by facilitating community management rather than institutionalization.[33] Despite the benefits of noninvasive management, few clinicians are aware that they can be used instead of tracheostomy IPPV and even fewer are familiar with all of the techniques available.[1] A review of the criteria for successful noninvasive management can be found in Table 85-2.

GLOSSOPHARYNGEAL BREATHING

Both inspiratory and, indirectly, expiratory muscle activity can be assisted by GPB. This technique involves the glottis capturing air and propelling it into the lungs. One breath usually consists of 6 to 9 gulps of 60 to 100 mL each. GPB can permit lung volume recruitment by using the glottis rather than a manual resuscitator or volume cycling ventilator for air stacking (Fig. 85-4). It can provide individuals with no inspiratory muscle function to have normal ventilation throughout daytime hours without using a ventilator and safety in the event of ventilator failure during sleep.[34] The safety and versatility afforded by GPB are key to avoiding tracheostomy or removing one in favor of using noninvasive aids for neuromuscular ventilatory failure. About 65% of patients with functional bulbar-innervated musculature but inadequate respiratory muscle function to sustain respiration have been reported to be able to use GPB instead of respirators in some cases throughout daytime hours.[34,35]

EXTUBATION AND DECANNULATION

Patients in acute distress can be relieved and intubation avoided when Sa_{O_2} can be maintained ≥95% in ambient air by using noninvasive IPPV and MAC. When needed, however, intubation is often

Video 85-3 This video demonstrates postextubation management of a 19-year old with spinal muscular atrophy type 1 who has been continuously dependent on full-support noninvasive intermittent positive pressure ventilation via nasal interface since 2 years of age. Her mother applies the nasal interface and mechanical insufflation–exsufflation. *Access at www.fishmansonline.com*

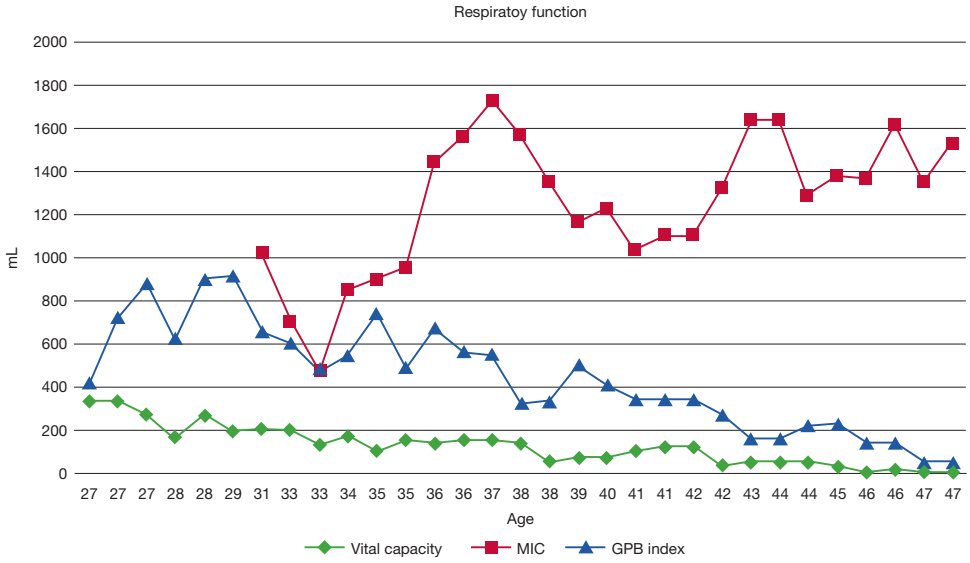

Figure 85-4 A graph of vital capacity (VC), glossopharyngeal maximum single breath capacity (GPmaxSBC), and maximum insufflation capacity (MIC) for the 48-year old with Duchenne muscular dystrophy in Figure 85-2. At age 37, despite having a VC of only 100 mL, he could air stack to 1700 mL to maintain pulmonary compliance and cough effectiveness and his GPmaxSBC was sufficient to permit him ventilator-free breathing.

delayed for fear of inability to ultimately successfully extubate. As for any patient presenting with respiratory distress, patients with neuromuscular disorders conventionally receive supplemental oxygen along with bronchodilators, mucolytics, CPAP, BiPAP, chest physical therapy, and possibly, sedation, but not noninvasive IPPV or MAC. Oxygen therapy, sedation, and BiPAP when used at low spans rather than noninvasive IPPV and MAC, often result in respiratory arrest.

Once intubated, ventilator weaning attempts are conventionally done at the cost of hypercapnia. Because an Sa_{O_2} of 90% to 95% is acceptable for most lung disease patients, patients with neuromuscular disorders are often extubated without concern for their ability to maintain normal Sa_{O_2} in ambient air. An Sa_{O_2} in ambient air less than 95% signals hypoventilation, airway mucus, or residual lung disease and extubation should be avoided. The conventional ventilator weaning parameters including resting minute ventilation, maximum voluntary ventilation, tidal volume, VC, maximum inspiratory pressure, arterial-alveolar oxygen gradient on 100% oxygen, and ratio of dead space to tidal volume, correlate with ability to breathe ("wean") and clear airway secretions and are unnecessary for neuromuscular disease patients who can be safely extubated without functioning respiratory muscles. "Weaning schedules" can cause anxiety when the patient is too weak to breathe or the schedule may be too conservative, delaying respiratory muscle reconditioning. Patients are often extubated to CPAP or inappropriately low span BiPAP and cough aids are not used. However, for these patients the extent of hypercapnia is directly associated with subsequent pulmonary complications and death.[2] Once extubation fails, the clinician feels justified in recommending tracheotomy.

A more appropriate approach for patients with primarily ventilatory impairment is presented in Table 85-3. The strategy is to remove the invasive tube and let the patient "wean" him/herself by using full-setting noninvasive IPPV via a mouth piece and grabbing it less and less as needed (Video 85-1). Thus, "weaning" is done by the patient after extubation when possible or the patient is discharged using continuous noninvasive ventilatory support. It is because of this that tracheotomy can be averted for patients with neuromuscular disease other than advanced bulbar-ALS.[23,34] Postextubation, manually assisted CPF >160 L/min are a sensitive parameter to predict its success because they reflect (glottis) bulbar-innervated muscle integrity and, therefore, the ability to maintain airway patency for effective noninvasive IPPV and MAC (Video 85-2).[12,13]

TABLE 85-3 Protocol for Extubation in Neuromuscular Diseases

Oxygen administration limited to achieve Sa_{O_2} of ~95%, no higher.
Mechanically assisted coughing used via the endotracheal tube up to every few minutes as needed to fully expand and quickly empty the lungs to reverse oxyhemoglobin desaturations due to airway mucus accumulation, when there is auscultatory evidence of secretion accumulation, and on patient demand. Tube and upper airway are suctioned following use of expiratory aids.
Ventilator weaning attempted without permitting hypercapnia.
Extubation whether or not the patient is ventilator weaned when meeting the following criteria:
Afebrile and normal white blood cell count
No supplemental oxygen required to maintain Sa_{O_2} >94% for >24 h
Chest radiograph abnormalities cleared or clearing
Respiratory depressants discontinued with no residual effects from them
Airway secretions normal and suctioning required <1-2×/8 h
Coryza diminished sufficiently to permit use of nasal ventilation
Extubation to continuous high span BiPAP or noninvasive IPPV via mouth/nasal interface, no supplemental oxygen.
Oximetry feedback used to guide the use of MAC, postural drainage, and chest physical therapy to reverse desaturations below 95% due to airway mucus.
With CO_2 retention or ventilator synchronization difficulties, nasal interface leaks are eliminated. For small children with rapid breathing rates who are using high span BiPAP, the inspiratory ramp may need to be shortened or the IPAP decreased. Backup BiPAP rates may need to be set at one-half the child's breathing rate to capture every other breath. Synchrony may also improve by switching to using a more trigger-sensitive volume cycle ventilator. Persistent oxyhemoglobin desaturation despite eucapnia and aggressive MAC can indicate impending severe respiratory distress and need to reintubate.
Following reintubation the protocol is used for a second trial of extubation to nasal IPPV or high span nasal BiPAP. Once extubation is successful and Sa_{O_2} remains >94% in ambient air, the patient weans him/herself to the preintubation regime of ventilator use by taking fewer and fewer mouth piece IPPVs as tolerated and as presented in Figure 85-2.

INSPIRATORY AND EXPIRATORY AIDS AND SURGICAL ANESTHESIA

Prevention or correction of spinal deformities is crucial to maintain quality of life for patients with neuromuscular disorders. Surveys of neuromuscular disease clinics indicated that most children with neuromuscular scoliosis were not undergoing spinal instrumentation and fusion for fear of respiratory complications.[1] As a result, the ability to sit or use an IAPV is often lost. However, respiratory complications are preventable when patients are trained in noninvasive IPPV and MAC pre-op and are extubated to them as described in Table 85-3. We have extubated 17 consecutive pediatric neuromuscular scoliosis patients with pre-op vital capacities less than 40% of normal including those with post-op vital capacities as low as 2% of predicted normal, none of whom could pass spontaneous breathing trials either before or after extubation, to full-setting noninvasive IPPV and MAC with no complications as described.[18] Two of the patients were continuously noninvasive IPPV dependent for several years even before the surgery.

In summary, wider use of noninvasive respiratory muscle aids and approaches would avoid the complications inherent in invasive management and facilitate community disposition rather than lifetime institutionalization and quality of life while greatly diminishing cost.

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PART 12

Occupational and Environmental Disorders

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CHAPTER 86

Asbestos-Related Lung Disease

William N. Rom

INTRODUCTION

Asbestos is a fibrous hydrated magnesium silicate with commercial use due to its indestructible nature, fire resistance, and easy transformability into industrial products from yarn to insulation block to brakes. Asbestos fibers are generally defined as long, thin fibers with a length to width ratio (aspect ratio) of 3:1. There are six commercial forms of asbestos: chrysotile, crocidolite, amosite, anthophyllite, actinolite, and tremolite. Most of the asbestos used in the United States has been chrysotile, a serpentine form of asbestos. Other asbestos types are the amphiboles—notably amosite, mined in South Africa, and crocidolite, mined in the Cape Province of South Africa and in Western Australia. These asbestos fiber types have strikingly different physical characteristics: chrysotile tends to be wavy and long, and occurs in bundles; crocidolite is needle-shaped with many long fibers; and amosite is similar to crocidolite but generally thicker. Asbestos fibers accumulate in the interstitium of the lung and are coated by iron and hemosiderin in a beaded, clubbed fashion referred to as ferruginous or asbestos bodies.

Initially, asbestos was widely used in fireproof textiles and later as insulation for boilers and pipes. Thereafter, asbestos was used in yarn, felt, paper, millboard, shingles, paints, cloth, tape, filters, wire insulation, cement pipes for potable water, gaskets, and in friction materials, including brake linings, and roofing and floor products. Asbestos was extensively used for ship construction during World War II. Occupational exposure to asbestos in the United States now primarily occurs during maintenance activities or remediation of buildings containing asbestos. The Occupational Safety and Health Administration (OSHA) has estimated that 1.3 million workers in general industry continue to be exposed to asbestos, and the National Institute for Occupational Safety and Health (NIOSH) estimates that 44,000 mine workers might be exposed to asbestos fibers or amphibole cleavage fragments, especially tremolite. Although the European Union has banned imports and use of asbestos, approximately 2 million tons are used worldwide. Asbestos is mined in Eastern Europe and Asia where asbestos products are manufactured for use in insulation, roofing, and construction. Globalization has resulted in export of asbestos to developing countries for manufacture and export to other developing countries with concomitant increase in asbestosis and mesothelioma.[1]

TYPES OF EXPOSURE

Primary asbestos exposures occurred in miners and millers. Secondary exposures occurred in manufacturing plants using asbestos in the production of textiles, friction materials, tiles, and insulation materials. Epidemiological studies focused on cohorts in these plants, since asbestos fiber type was often specified and dust measurements were obtained. These studies demonstrated that intensity and duration of exposure play an important role in the prevalence of asbestos-related disease. Common trades with asbestos exposure include sheet metal work, plumbing, pipefitting, insulation, railroad and utility work, and school or building custodians. Prevalence of radiographic opacities in asbestos insulation workers exposed prior to the 1970s reached 50% in long-term workers and was approximately 15% in sheet metal workers. There is a long latency period between exposure and manifestation of asbestos-related disease making identification and intervention difficult.

Although measurements of airborne asbestos fibers were seldom made, the most significant exposures appear to have occurred in the construction trades. These trades included asbestos insulators (called "laggers" in the United Kingdom), who mixed asbestos cement on site to insulate joints and elbows on pipes; boilermakers and sheet metal workers, who worked adjacent to the asbestos workers; and electricians, carpenters, plumbers, and others who worked in the vicinity of work requiring asbestos exposure. These exposures were mainly to chrysotile asbestos, since practically no crocidolite was imported into the United States, and only small amounts of amosite were admixed. Asbestos workers and other construction workers wore their asbestos-covered clothes home, exposing their wives and children when greeting them or while washing their garments. These household contact exposures are often referred to as *indirect exposures,* and those exposed while working near asbestos workers are called *bystander exposures.*

Projected lung cancer deaths range from 55,000 to 76,700 for the 30-year period due to asbestos exposure over 1980 to 2009. The National Occupational Respiratory Mortality System has tracked asbestosis deaths since 1968, peaking at 1400/y since 2004 and mesothelioma deaths peaking at 2700/y since 2005. Asbestosis is the cause of about 11% of deaths in asbestos workers; interestingly, the most important determinant is radiographic profusion score with rates increasing from 2.4% to 10.98% and 35.4% with profusion category increasing from 1 to 3. Profusion of irregular opacities is categorized into four levels ranging from 0 to 3, with 12 subcategories 0/0 to 0/1 to 1/0 up to 3/4 for the most dense fibrosis according to a scale agreed to by the International Labor Organization. Dyspnea, a low FVC, and/or physical examination findings typical of interstitial fibrosis (rales, clubbing or cyanosis) raise the risk of death from asbestosis from two- to sixfold.[2]

NONMALIGNANT PLEURAL MANIFESTATIONS

Pleural disease is the most common manifestation of asbestos exposure. The nonmalignant manifestations of asbestos exposure in the pleural space include circumscribed pleural plaques, diffuse pleural thickening, rounded atelectasis, and asbestos-related pleural effusions.[3]

■ PLEURAL PLAQUES

Important pathogenetic and clinical features of pleural plaques are discussed below.

Pathology

Pleural plaques are the most common manifestation of asbestos exposure. They are focal, irregular, raised white lesions found on the parietal and, rarely, the visceral pleura. The plaques may be small or extensive; commonly they occur in the lateral and posterior midlung zones, where they may follow rib contours and the diaphragm. They commonly enter lobar fissures and can invade the mediastinum or pericardium; rarely do they invade the apices or costophrenic sulci. Histologically, asbestos-related pleural plaques are characterized by a paucity of cells, extensive collagen fibrils arranged in a basket-weave pattern, and a thin covering of mesothelial cells. The parietal pleura is uniformly involved, with minimal thickening of the visceral pleura. The two pleural surfaces are free of adhesions. Pleural calcifications

frequently develop in these fibrohyaline lesions as the length of time from exposure increases. Exposure to asbestos is the most frequent cause of pleural plaques.

Pathogenesis

Two theories have been proposed for the pathogenesis of pleural plaques. The most plausible is based on the direct effects of fibers that reach the pleural space. Asbestos fibers – the short, thin ones in particular – have been shown to be transported by subpleural lymphatics to the pleural space. In the pleural space, it is believed that they scratch, injure, and irritate the pleural surface, leading to hemorrhage, inflammation, and eventually fibrosis. The plaques are submesothelial. Mesothelial cells appear to play an important role in the pathogenesis of these lesions: they internalize asbestos fibers via an integrin receptor that recognizes vitronectin; in vitro pleural mesothelial cells also can synthesize collagens (types I, III, and IV), elastin, laminin, and fibronectin. In keeping with the submesothelial location of the plaques, cultured mesothelial cells can organize these macromolecular connective tissue components into an assemblage of extracellular matrix that is limited to the base of the cell.

Epidemiology and Natural History

Hyaline and calcified pleural plaques have been noted to be an index of exposure to asbestos. In shipyard workers, the frequency of pleural abnormalities was approximately 10 times that of parenchymal disease. The greater the exposure, the more likely the worker was to have extensive calcified pleural plaques as well as parenchymal fibrosis. The intensity of the exposure has been noted to be an important determinant of the prevalence of these abnormalities. For example, among British shipyard workers, 36% of those with continuous exposure as "laggers" developed pleural plaques, while extensive pleural thickening and pulmonary fibrosis were seen in 5% and 7%, respectively. In contrast, those with intermittent exposure had a 6% prevalence of plaques and no pulmonary fibrosis. On average, the latency time for the appearance of plaques is 30 years, but the time can vary greatly. This variation can also be appreciated from studies of British shipyard workers in whom the prevalence of pleural plaques increased from 17% at 10 years after the first exposure to 70% at 30 years among those with continuous exposure; for those with intermittent exposures, the prevalence increased from 1% at 10 years to 16% at 30 years.

All asbestos fibers are equally capable of inducing pleural plaques: Pleural plaques are found in US insulators or shipyard workers exposed to chrysotile or amosite, as well as miners in Western Australia who were exposed to crocidolite.

In addition to occupational exposures, environmental, domestic and residential exposures have been implicated in the production of pleural plaques. Evidence for the latter is the remarkably high rates of pleural calcification (up to 45%) in some rural areas of Greece, Corsica, Cyprus, and Turkey where outcroppings of tremolite asbestos have been used to whitewash houses. Pleural plaques have been noted from environmental exposure to tremolite asbestos fibers contaminating vermiculite mining and milling in Libby, Montana.

Clinical and Physiological Features

In the absence of concomitant asbestosis or obliteration of the costophrenic angle, pleural plaques are usually asymptomatic. Most often they are incidental findings on chest radiographs. In addition, they do not cause significant abnormalities such as pleural rubs, rales, or rhonchi on auscultation of the chest.

Pleural disease has been recognized as a cause of reduced pulmonary function since the 1970s. Among 998 shipyard workers in Groton, Connecticut, who had 15 or more years of asbestos exposure, 17% of those with pleural changes had a forced vital capacity (FVC) under 80% of predicted; for those with normal chest radiographs, 9% had decreased vital capacities. In those with normal chest radiographs, the values were significantly reduced only among smokers and ex-smokers. Recent studies that have applied stepwise regression analysis to data from insulation workers have disclosed a significant inverse relationship between FVC and an integrative pleural index for patients with circumscribed pleural plaques.[4] Even among those with pleuroparenchymal abnormalities, the pleural index was found to make a significant contribution to decrements in FVC, independent of that due to parenchymal abnormalities.

In nonsmoking asbestos workers with circumscribed or diaphragmatic pleural plaques, flow rates (FEV_1, $FEF_{25–75\%}$) have been reported to be reduced. In an epidemiological study of 1211 sheet metal workers, pleural fibrosis was detected in 334 and was related to age, duration of exposure, more pack-years of smoking, and the presence and degree of interstitial fibrosis. After controlling for these confounders, multivariate regression analysis found that both plaques and diffuse thickening were independently associated with decrements in FVC, but not with decrements in the FEV_1/FVC ratio. Furthermore, diffuse pleural thickening was associated with a decrement in FVC twice as great as that seen with circumscribed pleural plaques. After confounding variables such as age, height, smoking status, and the presence of parenchymal abnormality as assessed by chest radiography and gallium scintigraphy were taken into account, there was a significant decrease in FEV_1 and FVC (222 and 402 mL, respectively) among workers who had pleural plaques or diffuse pleural fibrosis.

Radiographic Features

The visualization of plaques on digital chest radiography depends on their thickness, location, and the orientation of the radiographic beam.[5] As a result, they can be viewed in profile along the lateral chest wall or on en face with a rolled or holly-leaf pattern, especially if calcified (Fig. 86-1). Only a modest proportion of plaques detected

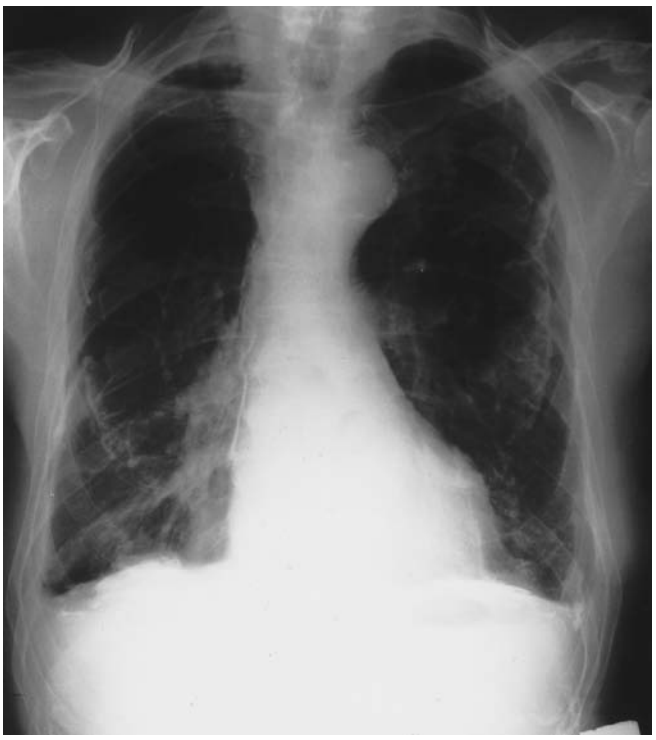


Figure 86-1 Posteroanterior (PA) chest radiograph of a 75-year-old man who worked in a shipyard during World War II insulating ships. The radiograph shows bilateral calcified pleural plaques en face and on top of the diaphragm. The pleura is diffusely thickened bilaterally and the costophrenic angles are blunted. Mediastinal pleural calcification is present on the right. *(Used with permission of Dr. Timothy Harkin.)*

at autopsy can be seen on digital chest radiography. Computed tomographic (CT) scanning increases plaque detection (increase in sensitivity and specificity).

The CT scan can recognize plaques at a much earlier and less well-defined state than digital chest radiography. The CT scan is particularly useful for perivertebral and pericardiac plaques, and high-resolution CT scanning (HRCT) helps to establish the presence of diaphragmatic lesions. In all cases, the CT scan can help to differentiate plaques from extrapleural fat pads and can detect concomitant parenchymal abnormalities that may be difficult or impossible to see on the PA chest radiograph.

Diagnosis

Pleural plaques due to asbestos exposure are usually bilateral (80% of the time), whereas unilateral pleural plaques may be due to trauma, previous tuberculosis, or, rarely, other causes, such as collagen vascular disease. The lesions are usually stable and remain the same size for months. This helps to differentiate plaques from pleural tumors. Histological tissue examination is not necessary for diagnosis the vast majority of the time.

Treatment

No specific treatment is required for asbestos pleural plaques. Since they are markers of asbestos exposure and identify patients at risk for other asbestos-related disorders, medical surveillance, including periodic CT scans and blood biomarkers, are recommended.[6]

■ DIFFUSE PLEURAL THICKENING

Pleural thickening, another common manifestation of asbestos exposure, is discussed below.

Pathology

Pleural fibrosis in persons who have been exposed to asbestos has been well described. The fibrotic responses can be localized or diffuse and either unilateral or bilateral. Macroscopically, the lesions vary in thickness from a whitish discoloration of the lung surface to a thick white peel that can encase significant pulmonary structures. Diffuse pleural thickening is most often seen as a continuous sheet that is 5 to 10 cm in craniocaudal extent, and in 90% of patients it affects the costophrenic angle. Interlobar and interlobular fissures are commonly involved. Whereas pleural plaques predominantly affect the parietal pleura, diffuse pleural fibrosis occurs most commonly as part of a fibrotic process of the visceral pleura and subadjacent interstitium.

Pathogenesis

Diffuse pleural thickening has been proposed to result from three different mechanisms. The first is the confluence of large pleural plaques. This is believed to account for 10% to 20% of the cases. The second is the extension of subpleural fibrosis to the visceral pleura. This probably accounts for 10% to 30% of cases. The most common pathogenic mechanism is thought to be the fibrotic resolution of a benign pleural effusion, producing diffuse pleural thickening. The importance of this mechanism is highlighted by the finding that about one-third of patients with diffuse pleural thickening have had a prior benign asbestos-related pleural effusion diagnosed by thoracentesis or on serial chest radiographs. The pathogenic mechanisms differentiating diffuse pleural thickening from circumscribed pleural plaques are not well defined. However, the fundamental mechanism of asbestos fibers activating macrophages and mesothelial cells to release growth factors and stimulate collagen formation is likely to be important in both. In the case of diffuse pleural responses, these fibers are deposited mainly in the parenchymal subpleural areas of the lung.

Clinical and Physiological Manifestations

Diffuse pleural fibrosis most often occurs long after short-term heavy exposure to asbestos. When mild, diffuse pleural fibrosis can be asymptomatic and discovered as an incidental finding on a chest radiograph obtained for another reason. The diffuse nature of the lesion, however, often leads to pulmonary symptoms, including dyspnea on exertion, chronic dry cough, and chest pain. As noted earlier, diffuse pleural thickening can cause a restrictive physiological abnormality. The degree of physiological abnormality varies with the degree of fibrotic response. On rare occasions, in patients with severe bilateral disease, respiratory insufficiency has occurred. Diffuse pleural fibrosis can increase in severity over time.

Radiographic Features

On the routine chest radiograph, diffuse pleural fibrosis presents as a continuous pleural opacity extending over more than 25% of the pleural surface of a lung, often blunting the costophrenic angle. It can be unilateral or bilateral and seen in the presence or absence of concomitant asbestosis and pleural calcifications. Rarely, the pleural fibrosis will produce a fibrotic pseudotumor with a pleural basis (rounded atelectasis) (see below). CT scanning is particularly useful in delineating the relationship between diffuse fibrosis and other pleural abnormalities and differentiating pleural fibrosis from fat deposits.

Diagnosis

The diagnosis of diffuse pleural fibrosis is usually based on the clinical presentation and chest radiograph. The lesions of diffuse pleural fibrosis are not unique to asbestos-exposed persons and can represent old inflammatory reactions from tuberculosis, thoracic surgery, or hemorrhagic chest trauma. Differentiation among these causes is frequently based on a careful clinical history. Radiographic patterns are also helpful, since bilateral interstitial changes in the lower lung zones in association with pleural plaques or calcifications strongly support a diagnosis of asbestos exposure. A biopsy may be required when the thoracic lesion is progressing or when malignancy is in the differential.

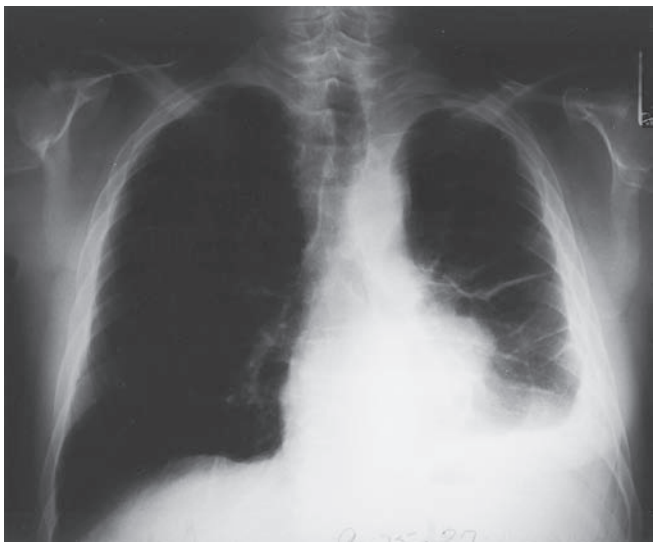
Treatment

As seen with circumscribed pleural plaques, there are no specific therapies for asbestos-related diffuse pleural fibrosis. Medical surveillance is required to detect disease progression, lung cancer, and mesothelioma.

■ ROUNDED ATELECTASIS

Rounded atelectasis is a rare complication of asbestos-induced pleural disease. It is caused by scarring of the visceral and pari etal pleura and the adjacent lung, with the pleural reaction folding over on itself. The pleural surfaces then fuse to one another, trapping the underlying lung and leading to atelectasis. As a result of this alteration, a mass lesion that mimics lung cancer can be seen on the PA chest radiograph (Fig. 86-2). This lesion is most easily appreciated to be a pseudotumor with use of CT scanning. HRCT can noninvasively demonstrate continuity to areas of diffuse pleural thickening, evidence of volume loss in the adjacent lung, or a characteristic comet tail of vessels and bronchi sweeping into a wedge-shaped mass (Fig. 86-2).

CT scanning can also demonstrate stability over time (from months to years), which supports the diagnosis of a benign lesion, and pleural plaques or parenchymal changes, which support a diagnosis of asbestos exposure. In one clinical series of 74 patients with rounded atelectasis, 64 had significant asbestos exposure, and the lingula or right middle lobe was affected in 49 of the patients.[7] HRCT scans localized most cases of rounded atelectasis to the lower, posterior portion of the lung; moreover, in one-third of the patients, the lesions were multiple. In most patients, rounded atelectasis occurs suddenly on a background of only plaques or a normal chest radiograph. In others, a slowly increasing pleural effusion may precede its appearance.



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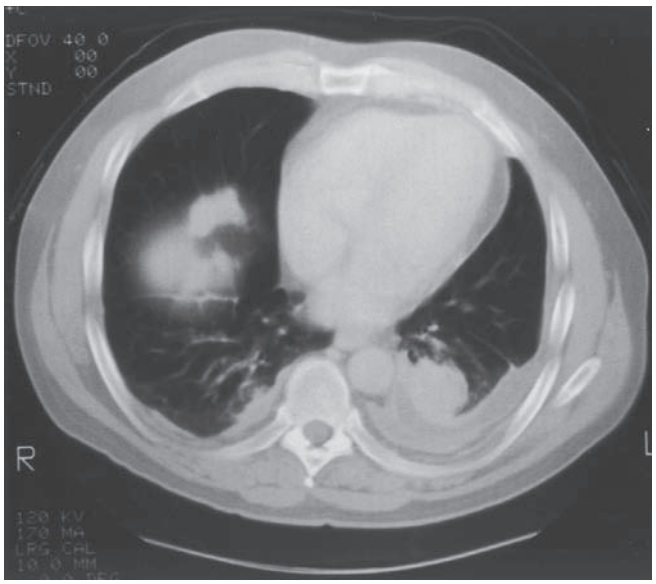

B

Figure 86-2 Rounded atelectasis and other pleural abnormalities in an asbestos worker. The chest radiograph (**A**) shows a left-sided pleural effusion, bilateral pleural thickening, greater on the left than on the right, and a mass in the left midlung field. HRCT (**B**) demonstrates the mass to be rounded atelectasis, with bronchovascular structures entering the trapped lung. It also reveals the pleural effusion, bilateral pleural thickening, and pleural plaques, one of which is on the right hemidiaphragm. *(Used with permission of William M. Rom, MD, MPH.)*

■ ACUTE BENIGN PLEURAL EFFUSIONS

Acute benign pleural effusions are common pleural manifestations in asbestos-exposed persons between 20 and 40 years of age. The latency period for these effusions is shorter than for pleural plaques, malignant mesotheliomas, or pulmonary malignancies. Benign pleural effusions generally occur earlier after exposure than do other asbestos-related processes; the latency is shorter, for example, 12 to 15 years rather than >20 years after the first asbestos exposure compared to pleural plaques or asbestosis.

About 50% of the patients with acute benign pleural effusions are asymptomatic. When patients are symptomatic, the manifestations may be those of a pleurisy (chest pain, chest tightness, dyspnea, cough, and fever). Physical examination reveals the signs of a pleural effusion; a pleural friction rub may be heard. The effusions are exudative and often bloody; glucose concentrations are normal. Mesothelial cells in effusions are found in about 50% of patients. In about 25% of patients, the fluid is eosinophilic. Rarely are asbestos bodies found even though they may be present in underlying lung tissue.

The designation "benign" refers to the lack of evidence of malignancy. The collections may persist for 6 months or more. They frequently clear spontaneously, only to recur on the contralateral side. However, a benign asbestos pleural effusion is a risk factor for the development of pleural thickening, especially diffuse pleural fibrosis. The diagnosis of acute benign pleural effusions is one of exclusion. Thoracentesis is essential. Pleural biopsy is frequently required to rule out other causes of pleural effusions, including mesothelioma. The usual pathological findings are a chronic fibrous pleurisy with minimal cellularity. Diffuse malignant pleural mesothelioma invariably presents as a pleural effusion, but pleural mass lesions are usually seen on CT scan, which are absent in benign asbestos effusions.

ASBESTOSIS

Important pathologic and clinical aspects of asbestosis are discussed below.

■ PATHOLOGY

Asbestosis is the interstitial pneumonitis and fibrosis caused by exposure to asbestos fibers.[3] Early lesions are characterized by discrete areas of fibrosis in the walls of respiratory bronchioles. The septi adjacent to the respiratory bronchioles are often thickened, and the fibrosis sometimes appears to spread outward from the bronchioles. In addition to the peribronchiolar fibrosis, there is an intense peribronchiolar cellular reaction that may narrow and obstruct the airway lumen. Macrophage accumulation is a prominent feature of this cellularity. Proliferation of type II alveolar epithelial cells is enhanced. The interstitium may contain collections of lymphocytes; smooth muscle proliferation may be prominent in areas of remodeling; and buds of loose connective tissue may be seen within the alveoli (Fig. 86-3).[8] Initially, the disease usually involves first-order bronchioles; subsequently, second- and third-order bronchioles are affected. As the disease progresses, the fibrosis becomes diffuse, the architecture of the lung undergoes extensive remodeling, and

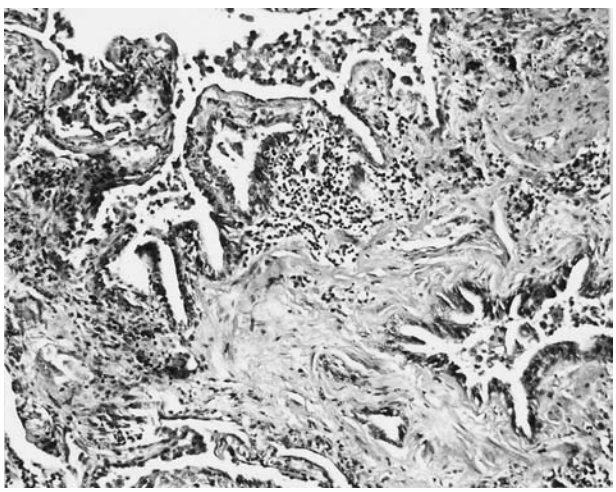

Figure 86-3 Lung tissue from a 64-year-old asbestos insulator with 46 years of exposure to asbestos while insulating pipes. His chest radiograph revealed extensive irregular opacities and bilateral pleural thickening. The figure illustrates peribronchiolar fibrosis, interstitial chronic inflammation, accumulation of macrophages in the airspaces, and proliferation of type II pneumocytes. *(Reproduced with permission from Rom WN, Travis WD, Brody AR. Cellular and molecular basis of the asbestos-related diseases: State of the art. Am Rev Respir Dis.1991;143(2):408–422.)*

honeycombing supervenes. In contrast to other pneumoconioses, lymph node enlargement and progressive massive fibrosis do not occur. Pathologically, the alterations seen in asbestosis cannot be differentiated from many other interstitial fibrotic disorders except for the presence of asbestos bodies and uncoated asbestos fibers.

PATHOGENESIS

Asbestos fibers are deposited at airway bifurcations and in respiratory bronchioles and alveoli by impaction, sedimentation, and interception. Fibers then migrate into the interstitium, in part via an uptake process involving type I alveolar epithelial cells. This causes alveolar macrophages to accumulate in the alveolar ducts, peribronchiolar interstitium, and alveolar spaces, constituting an alveolar macrophage alveolitis. Following this initial macrophage alveolitis, most fibers are cleared, leaving the lungs unscarred. If clearance is incomplete, fibrosis can ensue. The degree of fibrosis in asbestosis relates, in general, to the lung dust burden. If the dust load is small, the tissue reaction may be limited and the disease may be mild and not progress. If the retained dust load is great, tissue reaction and macrophage alveolitis are proportionately more intense, greater injury occurs, and chronic and progressive lung disease can develop.

The macrophage alveolitis that is seen in early stages of asbestosis results from monocyte recruitment from the blood and in situ macrophage replication. These cells appear to play an important role in the pathogenesis of the inflammation and fibrosis seen in this disorder. Morphologically, they express an activated phenotype characterized by cellular multinucleation and a striking increase in membrane ruffling, surface blebbing, and lysosomes and phagolysosomes.[9] These macrophages are presumably attempting to engulf and clear the asbestos fibers. This process is not uniformly successful, however. First, the fibers induce apoptosis in the cells. Although the coating of asbestos fibers to form asbestos bodies makes them less toxic, the vast majority of fibers in the lung remain uncoated. Second, the long fibers cannot be completely phagocytosed. Finally, chrysotile asbestos fibers tend to split longitudinally. This generates additional fibers that can multiply the asbestos effect even after exposure has ceased. As a result, asbestos has a prolonged residence, surprising mobility, and penetrates the interstitium of the distal lung.

These characteristics probably contribute to the pathogenesis of the disease, since – in contrast to inert particles, which can be ingested by macrophages and cleared without generating a significant response – asbestos fibers stimulate macrophages to produce a variety of important cytokines and growth factors. Both asbestos and silica are phagocytosed by alveolar macrophages, which then activates them to release cytokines, growth factors, and oxidants. These include platelet-derived growth factor (PDGF), and insulin-like growth factor-1 (IGF-1), transforming growth factor-β, and cytokines interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-8, the matrix molecule fibronectin, oxygen free radicals, and matrix metalloproteinases.[10–12] The oxygen radicals contribute to tissue injury via direct cell cytotoxicity and lipid peroxidation of membrane components. The IL-8 recruits neutrophils to sites of disease activity. The PDGF, IGF-1, IL-1, TNF-α, and fibronectin contribute to tissue fibrosis by stimulating fibroblast proliferation and chemotaxis and collagen biosynthesis.[8] In vitro exposure of mononuclear phagocytes to silica, asbestos, or coal activates transcription factors including AP-1 and NF-κB with subsequent release of cytokines and growth factors.

Bronchoalveolar lavage (BAL) in asbestosis has demonstrated an alveolar macrophage alveolitis with a modest increase in neutrophils.[11] This neutrophilia correlates with the finding of rales on physical examination and oxygenation parameters and is apt to be more pronounced in patients with advanced disease. In patients with asbestosis, ^{67}gallium lung scans may also be positive. Clinically apparent asbestosis occurs only after a significant latent period. However, studies using BAL, CT scanning, and ^{67}gallium scanning have demonstrated that inflammatory events occur well before the onset of clinical disease. Thus, it is likely that the initial exposure induces inflammation and injury that persist through the latent or subclinical phase and develops into the clinical disease diagnosed by classic radiography and other techniques. Current concepts of the pathogenesis of the disease link inflammation and fibrosis in a causal fashion.

EPIDEMIOLOGY

The prevalence of parenchymal asbestosis among asbestos workers increases as the length of employment increases. This is illustrated in an early report in which investigators analyzed the chest radiographs of 1117 New York and New Jersey asbestos insulation workers. They found asbestosis in 10% of the workers who had been employed for 10 to 19 years, in 73% of those who had worked for 20 to 29 years, and in 92% of those who had worked 40 or more years.[13] A similar dose–response relationship was found in the asbestos cement industry. Among "bystanders" (i.e., among sheet metal workers who worked in close proximity to insulation workers) the overall prevalence of asbestos-related changes was 31%, including 9% who had only pleural abnormalities and 12% who had parenchymal abnormalities.[14] Among those who had been in the trade for 40 years or more, 41.5% had radiographic signs of asbestos-related disease.

Cigarette smoking can affect the expression of asbestosis.[15] Smokers without dust exposure may have a few irregular radiographic opacities, probably representing acute or chronic bronchitis or bronchiectatic changes in the lung parenchyma. Both smokers and ex-smokers have a higher frequency of asbestos-related irregular opacities on their chest radiographs than do their nonsmoking colleagues. Smoking does not alter the expression of asbestos-induced pleural fibrosis. However, cigarette smoking may interfere with the clearance of inhaled asbestos, thereby potentiating the effects of the dust in the lung.

NATURAL HISTORY

Following asbestos exposure, asbestosis becomes evident only after an appreciable latent period. The duration of exposure and its intensity influence the prevalence of radiographically evident parenchymal pulmonary fibrosis. Because work sites around the world increasingly meet recommended control levels, high-level exposure to asbestos is now uncommon and clinical asbestosis is becoming a less severe disease that manifests after a longer latent interval. In Western Australian crocidolite workers, a median of 14 years elapsed before asbestosis was detectable radiographically (range, 2–34 years). In retired Quebec chrysotile miners and millers, the frequency of pleuroparenchymal lesions was 31%, and progression of parenchymal opacities occurred in 9.3%; progression was confined to the more heavily exposed group.[16]

One approach to the study of low-level exposure is to evaluate the outcome from short-term exposure. In such a study in an amosite asbestos factory, employment for even as little as 1 month resulted in a 20% prevalence of parenchymal opacities: one-third of the participants had pleural abnormalities after 20 years of follow-up; it is significant that both "first attacks" and progression of established radiographic abnormalities occurred 20 and more years after exposure had ceased.[17]

Radiographic asbestosis, once established, may remain static or progress. Rarely has regression been recorded. The factors that determine the outcome are poorly understood. The level and duration of exposure (i.e., cumulative exposure) appear to be prognostic factors. Progression is also considerably more common in persons who already have radiographic abnormalities. This fact provides the basis for the advice that further exposure is to be avoided once the diagnosis of parenchymal asbestosis has been made.

CLINICAL AND PHYSIOLOGICAL FEATURES

Dyspnea on exertion is the earliest, most consistently reported, and frequently the most distressing symptom of asbestosis. Often

dyspnea is accompanied by a persistent cough, which can be spasmodic, with sputum production. Chest tightness is not uncommon, and wheezing also can occur. In a cross-sectional survey of 816 asbestos-exposed workers using a respiratory symptoms questionnaire, cough, phlegm, wheeze, and dyspnea were inversely related to pulmonary function.[18] Cough, phlegm, and chronic bronchitis were associated with a 2% to 8% reduction in FVC and FEV_1; the reduction in these measurements was more significant with wheeze and dyspnea, which caused an 11% to 17% reduction. Similarly, the prevalence of dyspnea on the level less than one block among asbestos insulators increased in stepwise fashion from 19% in patients with category 1 chest radiographic abnormalities to 35% in patients with category 2 chest radiographs and to 49% in patients with category 3 radiographic abnormalities.[19]

Rales are a distinctive feature of asbestosis. They are usually bilateral, late to paninspiratory in timing, heard best at the posterior lung bases, and not cleared by coughing. They differ in quality and timing from the crackles of bronchitis, which tend to be fewer and earlier. The crackles of asbestosis appear first at the bases in the midaxillary line and tend to spread toward the posterior bases. In prevalence surveys, approximately 83% of patients with higher radiographic categories of asbestosis had bilateral rales. In a study of 42 patients with a clinical diagnosis of asbestosis, in 40 the chest radiograph showed at least 1/0 profusion of irregular opacities, 36 had rales, 36 had dyspnea, and 22 had digital clubbing.[20]

The characteristic pulmonary function changes of asbestosis are a restrictive impairment with a reduction in lung volumes (especially FVC and total lung capacity), decreased lung diffusing capacity (D_{LCO}), and arterial hypoxemia.[21] Large-airway function, as reflected in the FEV_1/FVC ratio, is generally well preserved. In one of the earliest studies, approximately 50% of asbestos workers had a reduced FVC and the vital capacity was decreased, on average, by 18% as predicted over the next 10 years. Among the 1117 asbestos insulators in New York and New Jersey, the frequency of an abnormal FVC increased to more than 50% as follow-up was prolonged. In a larger cohort of 2611 asbestos insulators, the FVC percent predicted decreased as the profusion of irregular opacities on the chest radiograph increased; pleural thickening exaggerated the decrease for each category of profusion. For each category of profusion, diffuse pleural thickening caused a further decrease (at least 10%) in FVC percent predicted compared to circumscribed plaques.[22]

Mild airway obstruction can also be seen in nonsmokers with asbestosis.[23] These patients usually have a restrictive pattern of lung function, increased isoflow volume, and increased upstream resistance at low lung volumes. Open lung biopsies from a limited number of these patients suggest that these obstructive findings may be due to peribronchiolar fibrosis, since they revealed peribronchiolar infiltrates with macrophages and fibrosis that extended into the adjacent interstitium. Therefore, it is not surprising that lesser grades of asbestosis can show a mixed restrictive and obstructive abnormality.

Long-term medical surveillance is recommended for all asbestos-exposed persons, especially those with radiographic abnormalities. Periodic physiological assessments play an important role in these evaluations. Prospective assessments of asbestosis should include spirometry as most useful, and diffusing capacity to assess alveolo–capillary function.

■ RADIOGRAPHIC FEATURES

In asbestosis, digital radiography reveals bilateral diffuse reticulonodular opacities, predominantly in the lower lung zones.[5] The International Classification of the Radiographs of the Pneumoconioses uses the term *small irregular opacities* to describe the irregular linear shadows that develop in the lung parenchyma and obscure the normal bronchovascular branching pattern seen in disease-free lungs. This schema categorized the irregular or rounded opacities found on conventional PA chest radiographs according to size and expressed them on a 12-point scale. Category 0 was defined as a normal radiograph and category 1 as mild asbestosis. Typically, a profusion of irregular opacities at the level of 1/0 is taken as the break point between normal and abnormal. Moderate asbestosis and advanced asbestosis were defined as category 2 and 3 chest radiographs, respectively. As duration from onset and intensity of exposure increase, there is an increase in prevalence and severity of asbestosis as reflected in the chest radiograph.

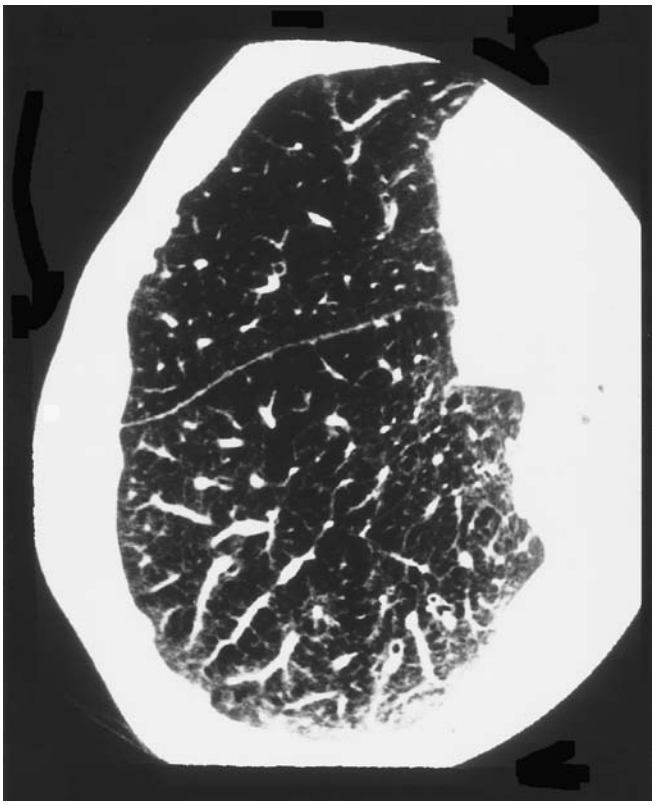

Figure 86-4 HRCT scan with irregular opacities of the lung parenchyma and interlobar structure. The PA chest radiograph was graded 2/1 on the ILO International Classification of the Radiographs of the Pneumoconioses. *(Used with permission of Dr. David Naidich.)*

CT scanning has improved the sensitivity for detecting asbestos-related lesions (Fig. 86-4). It eliminates a common problem with digital chest radiographs—that is, the superimposition of pleural abnormalities over parenchymal lesions. It also enhances the attenuation discrimination for parenchymal opacities. As a result of more than 300 HRCT evaluations of persons with asbestos exposure, five HRCT features of asbestosis have been identified: (1) Curvilinear subpleural lines, (2) increased intralobular septa, (3) dependent opacities, (4) parenchymal bands and interlobular core structures, and (5) honeycombing. These changes have been corroborated by histological examination.[24] In asbestos-exposed workers, abnormal HRCT has been shown to correlate with restrictive physiological abnormalities and abnormal diffusing capacities. HRCT is also extremely sensitive in documenting the asbestos-related pleural abnormalities discussed earlier. The presence of pleural plaques (particularly if they are bilateral) provides useful evidence that the parenchymal process is asbestos-related. Hilar node enlargement is not a feature of asbestosis, and progressive massive fibrosis is also uncommon.

■ DIAGNOSIS

Asbestosis is defined as parenchymal fibrosis, with or without pleural thickening, usually associated with dyspnea, bibasilar rales, and

pulmonary function changes. To diagnose this disorder, one must establish the presence of pulmonary fibrosis and determine whether exposure has occurred of a duration and intensity sufficient to put the person at risk. A profusion of irregular opacities at the level of 1/0 is used as the break point between normal and abnormal in the evaluation of lung fields on the chest radiographs of asbestos-exposed persons. When radiographic or lung function changes are marginal, CT scanning often reveals characteristic parenchymal abnormalities as well as pleural plaques and/or pleural fibrosis. These lesions, particularly when bilateral, are strongly suggestive of asbestosis. The diagnosis of asbestosis must always be based on the chronological occupational history with potential exposures. The features of the history that need to be defined include the duration, onset, type, and intensity of exposure. In taking the occupational history, it is important to keep in mind that intensity of exposure can be heavy even if duration of exposure is short. For example, heavy exposures were experienced by shipyard workers engaged in insulation application or removal in contained areas for brief periods aboard ship and by asbestos insulators during their apprenticeship when they unloaded asbestos sacks into troughs and mixed asbestos cement. Short, intense exposures of this sort, which lasted from several months to 1 or 2 years, can be sufficient to cause asbestosis. Exposures over 10 to 20 years are, however, usually necessary. The timing of the exposure is also relevant. Industrial hygiene controls in the 1960s and 1970s, especially in the construction trades, were not widely applied or enforced. Cohort studies have identified latency to be an important factor, with the prevalence of asbestosis increasing with time since the onset of exposure.

The specificity of the diagnosis of asbestosis increases with the number of consistent findings on chest film, the number of clinical features present (e.g., symptoms, signs, and pulmonary function changes), and the significance and strength of the history of exposure. The more significant the asbestos exposure the greater accuracy is the diagnosis. The more trivial the asbestos exposure, the less likely it is to be causal. Misclassification and diagnostic difficulty occur in patients with a heavy cigarette smoking history and concurrent emphysema (which also reduces the diffusing capacity). Patients with idiopathic pulmonary fibrosis (IPF) may have a history of asbestos exposure. These patients tend to be younger, however, and their asbestos exposure is usually casual, brief, and recent and can often be discounted. If an open lung biopsy is available one or more asbestos bodies per high power field (Fig. 86-5) or an asbestos fiber count per milligram of dry lung can be helpful to distinguish from IPF. In the absence of an adequate exposure history or in the presence of a confusing clinical presentation, biopsy material may be helpful in identifying the nature of the disease. It allows the pulmonary interstitial process to be compared to the known features of asbestosis and other interstitial disorders. Uncoated asbestos fibers are much more common than asbestos bodies, exceeding the frequency of coated fibers by anything from 5- to 10,000-fold. Although other inhaled particles may also become coated, most coated fibers found in human lungs have an asbestos core. Thus, the presence of asbestos bodies or asbestos fibers is considered the hallmark of exposure, past or current. Asbestos bodies can also be detected in BAL samples. Asbestos bodies in BAL correlate with heavy exposure, reduced lung function consistent with interstitial lung disease, and asbestosis.[25] This is illustrated in a large series of 563 patients: Those with asbestosis had a mean of 120 asbestos bodies per milliliter; those with pleural disease, 5 asbestos bodies per milliliter; and those with malignant mesothelioma or lung cancer, 8 asbestos bodies per milliliter of lavage fluid. Of 49 patients with more than 100 asbestos bodies per milliliter of lavage fluid, 30 had asbestosis, 8 had pleural disease, 13 had mesothelioma or lung cancer, and 3 had an exposure history only. Others have estimated that one asbestos body per milliliter of BAL fluid correlates with 1000 to 3000 asbestos bodies per gram of dry lung tissue.

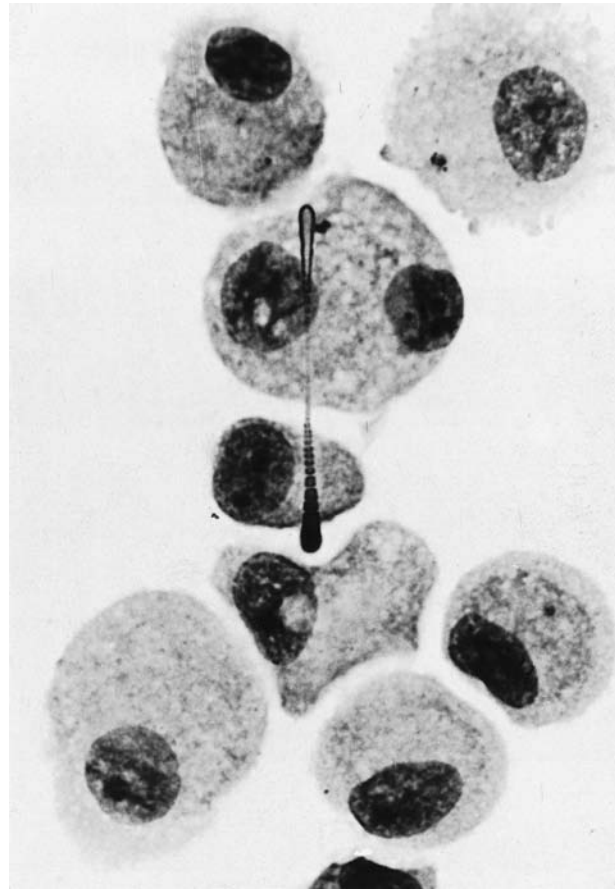

Figure 86-5 Light microscopic appearance of an asbestos body in a cytocentrifuged preparation of alveolar macrophages lavaged from a nonsmoking asbestos insulator (Wright–Giemsa stain, ×400). *(Used with permission of William M. Rom, MD, MPH.)*

■ TREATMENT AND PROGNOSIS

Major causes of morbidity and mortality in patients with asbestosis include the progression of the underlying lung disease and the development of lung cancer and malignant mesothelioma. Longitudinal observations of asbestos-exposed trade workers have demonstrated accelerated declines in pulmonary function. In a study of 77 workers with a mean of 31 ± 1 years of occupational exposure, linear regression demonstrated a mean annual decline of 92 ± 28 mL/y in FVC, 66 ± 22 mL/y in FEV_1, and 14 ± 53 mL/y in total lung capacity.[26] At present, there is no established treatment for this disorder. Because of the risk of lung cancer and mesothelioma, medical surveillance with CT scans for those who also smoke >30 pack-years and age >55 years on an annual basis is recommended.[27] Blood biomarkers for proteins or autoantibodies may assist in distinguishing benign nodules from malignant.

MALIGNANT MESOTHELIOMA

Malignant mesothelioma is an important complication of asbestos exposure, as discussed below.

■ PATHOLOGY

Malignant pleural mesothelioma occurs in persons who have an exposure history to asbestos fibers, with 85% of men having an occupational history and 50% of women. In its early stage, the mesothelioma appears as multiple, small, grayish nodules on the visceral and parietal pleura that evolve to coalesce and form larger masses of tumors. These tumors then invade thoracic and other structures by direct extension. Fewer than 25% of malignant mesotheliomas are peritoneal in origin.

Mesotheliomas are conventionally classified into three histological patterns: Epithelial, sarcomatous, and mixed or biphasic; these patterns account for 50%, 20%, and 30%, respectively. The epithelial variant – in which neoplastic cells are arranged in papillary, tubular, or solid nest configurations – is most easily confused with metastatic adenocarcinoma. The sarcomatous variant has spindle-shaped cells that may be pleomorphic, with considerable mitotic activity.

The pathological diagnosis of malignant mesothelioma may be difficult. In particular, the differentiation of malignant mesotheliomas, adenocarcinomas, and other tumors may be problematic. Histochemistry and immunohistochemistry may be helpful in making the distinction. Thus, in contrast to mesotheliomas, adenocarcinomas contain neutral mucin that stains positive with the periodic acid–Schiff stain and is often resistant to diastase. Hyaluronic acid, the major acid mucopolysaccharide in mesotheliomas, can be identified with the Alcian blue or colloidal iron stain. Removal by prior digestion with hyaluronidase increases the specificity of the reaction. In contrast, adenocarcinomas are negative for Alcian blue and colloidal iron. Mesothelial cells contain cytoskeletal filaments, including cytokeratin and vimentin; staining for these structures is not specific, since other tumor types are also positive. Carcinoembryonic antigen is absent in malignant mesothelioma but is present in up to 90% of adenocarcinomas. Similarly, the monoclonal antibody B72.3, generated against a membrane fraction of human metastatic breast cancer, was positive in 19 of 22 pulmonary adenocarcinomas but none of 20 mesotheliomas. Monoclonal antibody Leu MI is frequently positive in lung carcinomas and nonreactive with mesotheliomas.[28]

The ultrastructural features of malignant mesotheliomas are also noteworthy. Malignant mesotheliomas contain abundant tonofilaments, often organized into perinuclear bundles, and long, sinuous, slender surface microvilli. The microvilli sometimes show secondary and tertiary branching and may interdigitate with stromal collagen. Malignant mesothelial cells produce collagen, a prominent feature of the sarcomatous variant.

Malignant mesotheliomas are locally invasive, spreading along the pleural wall and invading the lung, mediastinal lymph nodes, and other thoracic and nearby structures. At autopsy, tumor may be found in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract serosa, bone, pancreas, and kidneys. Between 50% and 80% of patients also have metastases.

About 10% of patients with a malignant mesothelioma are alive at 24 months. Survival is significantly longer for patients with an epithelial subtype or with a pleural rather than a peritoneal mesothelioma, and for those under 65 years of age.

The incidence of mesothelioma is increasing because of the cohort exposed to asbestos between 1940 and 1970. Incidence rates vary from a low of 11 to 13 per million per year in the United States to 33 per million per year in South Africa and to 66 per million per year in Western Australia.[29] These rates reflect mining and manufacturing industries and the location of crocidolite mines. Although the peak incidence in the United States may have passed since imports decreased after 1945, imports of asbestos in the United Kingdom reached their peak in the 1960s to 1970s. Thus, the peak of mesothelioma deaths in the United Kingdom is expected to occur in 2020, when up to 1% of men may die of the disease. Chrysotile was the major asbestos import to the United Kingdom, and half of this material went into the construction industry. Amosite was the leading amphibole import, and most of it went into insulation board. Thus, workers in the construction industry in the United Kingdom seem to be at greatest risk.

EPIDEMIOLOGY

In 1960, Wagner et al.[30] published a landmark paper demonstrating an association between malignant mesothelioma and asbestos exposure. They reported on 33 patients from South Africa, 28 of whom were exposed in the crocidolite mining region and 4 of whom were exposed in asbestos factories. They observed that mesotheliomas occurred 20 to 40 years after exposure to asbestos dust and found asbestos bodies in lung tissue from 8 of 10 patients from whom lung tissue was available for study. Subsequently, the importance of direct asbestos exposure was confirmed and the potential importance of indirect exposure to asbestos was recognized.

Evaluations of asbestos fiber content have shown a clear association between asbestos exposure and the occurrence of mesothelioma.[31] Epidemiological studies have shown crocidolite to be a potent fiber type among South African and Western Australian asbestos miners and millers. Most mesotheliomas have occurred from chrysotile–amphibole mixtures, since chrysotile is the most common fiber in commercial use. The incidence of malignant mesotheliomas among chrysotile workers who came before the Workers' Compensation Board of Quebec was similar to that in western Australian crocidolite miners. Studies of Canadian cohorts have also indicated that high concentrations of chrysotile, or tremolite, are required to cause mesothelioma, and further suggest that chrysotile has weaker biopersistence than does tremolite, which is merely a contaminant in most ores. In the United States, amosite is the predominant amphibole found in lung tissue: In one study it was identified in 81% of 90 patients with mesothelioma; in this population, it accounted for 58% of all fibers at least 5 μm in length. Finally, there is no association between smoking and malignant mesothelioma.

An epidemic of mesothelioma was reported in the Cappadocia region of Turkey where 40% of deaths were caused by the disease in several villages.[32] The exposure was to erionite, an aluminum silicate fibrous zeolite, and villagers used the stone to build their homes, whitewash their walls, and carved rooms in the soft volcanic tuff. There also appeared to be a family concordance beyond the household exposure.[33] Evaluation of some mesotheliomas has also found evidence of simian virus 40. SV40 is a DNA tumor virus that causes mesothelioma in hamsters and has been detected in several human mesotheliomas. Asbestos fibers appear to increase SV40-mediated transformation of human mesothelial cells in vitro. In an in vivo demonstration of cocarcinogenicity of SV40 and asbestos fibers, mice containing high copy numbers of SV40 viral oncogene rapidly developed fast-growing mesothelioma following asbestos challenge. This virus can bind the retinoblastoma transcription factor that could inhibit p53 function, and promote carcinogenesis.

PATHOGENESIS

Insight into the pathogenesis of malignant mesothelioma has come from experiments in which asbestos fibers were introduced into the pleural space of animals. These studies have demonstrated that amosite, anthophyllite, crocidolite, and Canadian chrysotile can all cause these pleural malignancies. Studies of fiber size in animals have shown that the most carcinogenic fibers are biopersistent, 0.1 to 1.0 μm in diameter and more than 8 μm in length. Inspection of electron micrographs of asbestos fibers has shown that crocidolite and amosite possess needlelike characteristics, whereas anthophyllite has a more boxlike appearance and chrysotile has a long, curly appearance. These variations in size are also consistent with epidemiological studies indicating that crocidolite and amosite may have greater risk for mesothelioma than do other types of asbestos.

One theory concerning the mechanism of asbestos-induced carcinogenesis focuses on the observation that asbestos fibers become entangled in the mitotic spindle during interphase, thereby causing chromosomal abnormalities. Electron microscopic evaluations have shown fibers penetrating between multiple lobes of the nucleus and associating, along their length, with the outer surface of the nuclear envelope. Structural chromosomal abnormalities in mesothelioma are clonal and complex, and include both chromosomal gains (chromosome 22) and losses (chromosome 7). Deletions of the short arm of chromosome 3, the break point 1p11 to p22, chromosome 17,

and structural and numeric changes in chromosome 7 have been described. In asbestos insulators, sister chromatid exchanges in circulating lymphocytes are increased: Larger chromosomes are more susceptible, and in the largest chromosome group, there is a significant interactive effect between asbestos exposure and cigarette smoking.

Cell lines established from malignant mesotheliomas have been shown to constitutively upregulate the PDGF B-chain gene and, to a lesser extent, the PDGF A-chain gene. High levels of transforming growth factor and IGF-1 bioactivity have been reported for cell lines derived from malignant mesotheliomas. These growth factors contribute to the considerable matrix formation that accompanies mesothelial tumors and promote mesothelioma cell proliferation.

CLINICAL AND RADIOGRAPHIC FEATURES

Pleural mesotheliomas are found mainly in males (ratio, between 3 and 4 to 1) and are most commonly diagnosed in patients between 50 and 70 years of age. Chest pain is the most common symptom experienced by patients with mesotheliomas. Dyspnea is next in frequency. Less common symptoms are cough, weight loss, and fever. A pleural effusion is usually present and can be massive. The effusion is an exudate, can be hemorrhagic, and may have high levels of hyaluronic acid (Fig. 86-6). Malignant mesothelioma is locally invasive, spreading along the pleural wall and invading the lung and nearby structures. Metastases are less common but can give rise to symptoms due to tumor in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract, bone, pancreas, and kidneys. The paraneoplastic syndromes of inappropriate antidiuretic hormone secretion, clubbing, or hypoglycemia are reported. Thrombocytosis is common (90% in one series) and thromboembolic complications can occur. Ascites and weight loss are characteristic features of peritoneal mesothelioma.

A variety of radiographic abnormalities are found in malignant mesothelioma. They include a thick pleural peel along the lateral chest wall that can extend to the apex with an irregular nodular surface, multiple pleural nodules or masses, plaque-like opacities, and pleural effusion(s). As the disease progresses, the lung parenchyma may be involved, the affected hemithorax may decrease in size, and the mediastinal or hilar nodes may be invaded. Pericardial thickening or effusion, abdominal extension, and chest wall invasion are common. The HRCT can help in differentiating pleural effusion from tumor and in determining the extent of tumor progression. The presence of asbestosis or of pleural plaques on the opposite side can assist in establishing the diagnosis of malignant mesothelioma.

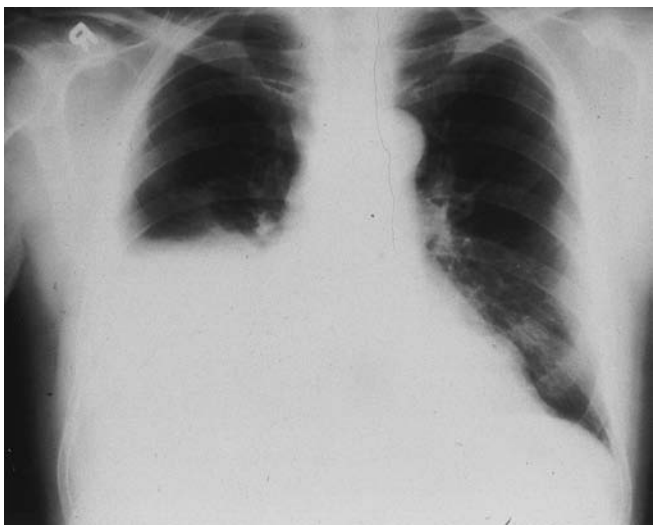

Figure 86-6 Large pleural effusion in an asbestos-exposed worker with an underlying malignant mesothelioma. *(Used with permission of Dr. J. Elias.)*

DIAGNOSIS

The diagnosis of malignant mesothelioma requires cytological and immunohistological validation. Calretinin, cytokeratin 5/6, and WT1 are the best positive markers for differentiating mesothelioma from pulmonary adenocarcinoma, and the best negative markers are CEA, MOC-31, and B72.3.[34] Obtaining a cytological diagnosis from the pleural exudate is difficult because reactive mesothelial cells and malignant cells are not easy to distinguish. Biopsy is required. Because mesothelioma has been shown to invade the needle track, open biopsy is preferable. Thoracoscopy is the procedure of choice in establishing the diagnosis of mesothelioma.

Noninvasive biomarkers include plasma soluble mesothelin, osteopontin, and fibulin-3.[35,36,28] The receiver operating curve (ROC) for plasma fibulin-3 levels had a sensitivity of 96.7% and a specificity of 95.5% at a cutoff value of 52.8 ng of fibulin-3 per milliliter and blinded validation revealed an area under the curve (AUC) of 0.87 for plasma specimens from 96 asbestos-exposed persons as compared with 48 patients with mesothelioma.[35] An AUC of 0.5 is no different between the groups and an increased AUC greater than 0.7 is increasingly more sensitive toward 1.0, which is perfect sensitivity and specificity for the test in question. These blood tests can distinguish patients with malignant mesothelioma from asbestosis and pleural plaques as well as other causes of malignant pleural effusion such as lung and breast cancer.

TREATMENT AND PROGNOSIS

Median survival time is approximately 8 to 12 months for all patients with malignant mesothelioma. Overall, fewer than 10% of patients are alive at 5 years. Extrapleural pneumonectomy, combined with radiation therapy, may result in improved survival. Chemotherapy with gemcitabine and carboplatin or pemetrexed and cisplatin may improve survival. Immunotherapy with intrapleural or gene therapy with interferons has produced occasional complete or partial responses.

Interventions, such as gene therapy or the use of cytokines, for the treatment of malignant mesothelioma are currently being investigated.[37,38] In 89 patients, the intrapleural instillation of γ-interferon twice weekly for 8 weeks resulted in 8 histologically confirmed complete responses and 9 partial responses, with at least a 50% reduction in tumor size.[39] The overall response rate was 20%, increasing to 45% in stage I disease. In 23 patients, a phase I clinical trial of continuous infusion into the pleural space of recombinant IL-2, revealed two partial and seven stable disease out of 21 evaluable patients.[40] Gene therapy using a replication-defective adenovirus carrying the herpes simplex–thymidine kinase (HSV*tk*) gene followed by the antiviral drug ganciclovir, was used successfully in a phase I clinical trial to treat malignant mesothelioma.[41] There was HSV*tk* gene transfer in 11 of 20 evaluable individuals in a dose-related fashion using RT-PCR, in situ hybridization, immunohistochemistry, and immunoblotting.[41] However, humoral and cell-mediated immune responses that developed against viral surface proteins and gene transfer were noted only in superficial cells compromised the therapeutic effectiveness of this approach.[42] Also, the thymidine kinase gene in vivo had no effect on promoting regression of the tumor. Another promising area of research is intrapleural administration of adenoviral interferon-α2b, which resulted in tumor regression in five patients including one dramatic example of partial tumor regression at sites not in contiguity with vector infusion.[43]

LUNG CANCER

In addition to mesothelioma, lung cancer is another well recognized malignant complication of asbestos exposure.

EPIDEMIOLOGY

The association between asbestos exposure and the development of lung cancer was highlighted by Sir Richard Doll's 1955 epidemiological cohort study of 113 men exposed to asbestos for 20 years reported 11 deaths due to lung cancer (compared with 0.8 expected).[44] All of

the individuals who died of lung cancer had evidence of asbestosis. In 1965, a retrospective cohort study in two asbestos insulator unions in the United States reported that deaths from lung cancer were 6.8 times the expected rate and that the incidence of lung cancer increased with time after exposure. In 1968, a follow-up of men in this cohort demonstrated an important synergy between asbestos exposure and cigarette smoking, since the risk of lung cancer was almost entirely borne by those who had a history of cigarette smoking.[45]

The largest survey of asbestos-related deaths evaluated a North American asbestos insulator cohort that reported a threefold excess of lung cancer deaths.[46] Comparatively few of these excess deaths were observed among those less than 25 years after the start of exposure. Lung cancer peaked at 30 years from exposure and mesothelioma at 45 years. In contrast, death rates from asbestosis increased progressively with time. This study confirmed the multiplicative effect of smoking plus asbestos exposure on the risk of lung cancer. Moreover, it showed that deaths from lung cancer dropped by almost two-thirds for asbestos insulators who subsequently stopped smoking. A recent follow-up of the North American insulator cohort from 1981 to 2008 found the following: 19% of the deaths were caused by lung cancer; the rate ratio of lung cancer in nonsmokers was 3.6 (95% Confidence Interval [CI] 1.7–7.6) and by asbestosis in nonsmokers was 7.40 (95% CI 4.0–13.7); the joint effect of smoking and asbestos alone was additive (rate ratio 14.4) and with asbestosis, supra-additive (rate ratio 36.8).[47] Insulator lung cancer mortality halved within 10 years of smoking cessation and converged with that of never-smokers 30 years after smoking cessation.

Additional insights were provided by a study of amosite workers who were exposed to concentrations of 50 fibers per milliliter.[48] These patients experienced a fivefold increase in lung cancer. Long-term follow-up showed: (1) a latency period of about 20 years before the increase in cancer occurred; (2) the greater the dose or the longer the exposure, the greater risk of developing lung cancer; and (3) the greater the dose or exposure time, the shorter the latency period before the tumor developed. Malignancies were also noted in the wives and children of these workers who were exposed to asbestos in the household, primarily on work clothes. In addition, men employed for less than 1 month between 1941 and 1945 developed lung cancer at an increased rate. Studies of a variety of other cohorts have confirmed the increased incidence of lung cancer in asbestos-exposed populations. They have also demonstrated an increased frequency of cancer of the larynx; in the latter, asbestos has been found in laryngeal tissue. As in the case of cancer of the lung, cigarette smoking has a strong association with the occurrence of these laryngeal malignancies.

Epidemiological studies have also provided information about dose–response relationships and about the importance of asbestos-processing techniques and fiber type in the pathogenesis of pulmonary malignancies. A number of investigators have observed linear dose–response relationships for lung cancer. Different dose–response relationships have, however, been found in other studies. These differences may be the result of differences in processing techniques. For example, studies in a South Carolina plant demonstrated that the steeper dose–response relationship of miners versus textile weavers was probably due to the manufacturing process, which resulted in high levels of brief exposure during the opening of asbestos bags and the sudden separation of the asbestos fibers.[49] Similarly, differences in lung cancer mortality in asbestos cement product plants in Louisiana were found to be associated with the addition, in one of these plants, of crocidolite to the asbestos cement pipe mixture. The risk of lung cancer increases most clearly with cumulative asbestos exposure.

PATHOLOGY

Asbestos-related lung cancers are not distinct from lung cancers that occur in cigarette smokers and otherwise normal persons in type, nature, or location. All histological types of lung cancer occur with increased frequency, but adenocarcinoma has the highest incidence. In the vast majority of patients, there is histological evidence of asbestosis and asbestos bodies are frequently found. Asbestos-related lung cancer can occur in the absence of asbestosis.

PATHOGENESIS

Animal experiments using several types of asbestos have succeeded in reproducing pulmonary malignancies. In one study, approximately one-third of rats exposed by inhalation to asbestos (amosite, anthophyllite, crocidolite, Canadian chrysotile, or Rhodesian chrysotile) for periods ranging from 1 day to 24 months developed adenocarcinomas or squamous cell carcinomas of the lung.[50] In these experiments, a clear dose–response relationship existed between asbestos dose and the occurrence of tumors. The mechanisms responsible for the induction of these malignancies are poorly understood. However, DNA injury and activation of nuclear transcription factors may play an important role. The former appears to relate to the physical properties of the asbestos fibers, which enable DNA, RNA, and chromatin to bind to asbestos. Crocidolite asbestos causes double-strand DNA breaks in small airway epithelial cells, which is the site for asbestos-induced fibrosis and carcinogenesis.[51] Reactive oxygen species may also play an important role in this process, since chrysotile asbestos, along with cigarette smoke, synergistically increases the number of breaks in DNA strands, and oxidant scavengers—such as mannitol, catalase, iron chelators, and dimethylsulfoxide prevent this DNA damage. Asbestos also induces nuclear factor-κB DNA binding in tracheal epithelial cells in vitro. NF-κB is an important transcription factor for cytokines, growth factors, and protooncogenes that could contribute in a variety of ways to malignant transformation. Alveolar macrophages also release TNF-α after phagocytosis of asbestos fibers, and TNF-α induces NF-κB in human mesothelial cells leading to increased survival (antiapoptosis).[52] These mesothelial cells exhibit increased mitotic index and metaphases have prematurely separated chromatids or other chromatid abnormalities in vitro cell culture.

CLINICAL FEATURES

The patterns of presentation of lung cancer among asbestos workers are similar to those of high-risk patients: cough, chest pain, dyspnea, hemoptysis, recurrent bouts of pneumonia, and localized wheezing. However, patients can also be asymptomatic at the time of initial discovery, the abnormality being noted on a routine or screening CT scan. Other manifestations of carcinoma – such as rib invasion, shoulder–arm pain, and paraneoplastic syndromes – can also occur in asbestos-related malignancies.

Individuals with asbestosis have an increased risk of lung cancer.[53] Most patients with lung cancer in the Quebec asbestos mining district had small parenchymal opacities on the chest radiograph before death. In amphibole miners from South Africa with carcinoma of the lung who were evaluated by stepwise regression analysis for exposure variables, asbestosis was by far the most striking variable. Moreover, a dose–response relationship was found between the severity of asbestosis and the frequency of lung cancer.[54] In the North American insulator cohort, 18% of the patients who died of lung cancer did not have radiographic evidence of parenchymal fibrosis.[54] Similarly, in a case control study of 271 patients with lung cancer, a small but definite increase in cancer risk was noted in patients whose chest radiographs were not definitely abnormal (0/1 or less).[55] This study indicated that asbestos exposures that do not cause small opacities on the chest radiograph may nevertheless increase the risk of lung cancer.

RADIOGRAPHIC FEATURES

The radiographic manifestations of asbestos-induced lung cancers do not differ, per se, from those of lung cancers associated with other carcinogens. Mass lesions, atelectasis, postobstructive pneumonia, and pleural effusions are all seen. As noted earlier, these lesions are

frequently superimposed on a background of asbestosis or asbestos-induced pleural abnormalities. Confusion with lung cancer may arise from en face pleural plaques or rounded atelectasis. In contrast to lung cancer, however, these abnormalities are stable over time. The helical CT scan, which can evaluate the chest in a single breath, can increase the early detection rate of lung cancer in this high-risk patient population.[27]

DIAGNOSIS

The principles employed in the diagnosis of lung cancer in asbestos workers are identical to those in the diagnosis of pulmonary malignancies in patients exposed to other carcinogenic agents. Appropriate cytological or histological specimens are required. This can be accomplished by sputum analysis or by bronchoscopy with brushings, biopsy, or lavage. Transthoracic needle aspirates, thoracoscopic parenchymal biopsies, or open lung biopsies may be required for definitive diagnosis.

TREATMENT AND PROGNOSIS

The therapeutic approaches utilized for asbestos-related lung cancers are similar to those employed for lung cancers induced under other circumstances. When one is dealing with non–small-cell malignancies, patient operability and resectability need to be evaluated and, if appropriate, surgical extirpation undertaken. The impact of other asbestos-related pulmonary processes must always be taken into account. For example, severe asbestosis may limit operability, and diffuse pleural thickening may make surgical intervention problematic.

EFFORTS AT ASBESTOS CONTROL

In order to control the risk of exposure to asbestos, the Occupational Safety and Health Administration's Permissible Exposure Level not to be exceeded is 0.1 fiber/mL over an 8-hour time-weighted–average.

Industrial hygiene efforts to control exposure have focused on engineering controls, including enclosure of the process lines, especially all sites where asbestos is introduced into a system, increasing ventilation, and the use of wet manufacturing methods. Personal respirators are used as a last resort in achieving control of exposure in the workplace. Most of the insulation-manufacturing industry has switched to alternative materials, especially fibrous glass, rock and slag wool, and refractory ceramic fibers. Animal experiments have generally shown these asbestos substitutes to be safe, except that refractory ceramic fibers were able to produce mesotheliomas in hamsters.

CONCLUSIONS

The asbestos-related diseases should be confined to history with the banning of asbestos in many countries and substitution of other insulating products. However, we have the legacy of past exposures and the continuation of exposures during renovation and destruction of asbestos-containing buildings and products. It continues to be an important area of compensation for workers developing mesothelioma, and for continued research on the mechanisms of fibrosis and carcinogenesis. Biomarkers for detection of lung cancer and mesothelioma are important for early diagnosis. Finally, the global control of asbestos should be a priority for international organizations since there is no further reason for asbestos to remain in commerce.

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CHAPTER 87

Chronic Beryllium Disease and Hard-Metal Lung Diseases

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CHRONIC BERYLLIUM DISEASE

Beryllium is the lightest metal and has an atomic number 4. Gem stones, such as aquamarine, emerald, and beryl contain beryllium and have been recognized since ancient times. But beryllium, as an element, was first discovered in 1798 by the French chemist, Vauquelin and reduced to its metallic form; subsequently, it was named beryllium in 1828 by the German metallurgist, Wohler. Beryllium became a commercial product when it was used as an alloy first with aluminum and later with copper, nickel, and cobalt after World War I. The industry grew in the 1930s due to the increased use of beryllium–copper products during World War II and the use of beryllium oxide in the refractory and fluorescent lamp industries. During and after World War II, beryllium was used in the nuclear industry because of its ability to function as a neutron multiplier. Beryllium was used for both civilian nuclear reactors and for military weapons.

With an increased industrial need for beryllium, acute chemical pneumonitis was first described by Weber and Engelhardt[1] in Germany in 1933 and in the United States by van Ordstrand et al. in 1943.[2] This condition was usually limited to the upper respiratory tract, though it could extend to the bronchi, bronchioli, and alveoli if there was sufficient exposure. This condition peaked in the 1940s and will not only be seen if there are plant explosions or other serious lapses in procedures.[3] The last reported possible case in the United States occurred in the early 1980s.

A second pulmonary complication of beryllium exposure was first described by Hardy and Tabershaw[4] in 1946. This disease differed from the acute chemical pneumonitis because of the delayed onset, granulomatous response, and chronic course. Now known as chronic beryllium disease (CBD), this condition is a hypersensitivity reaction to beryllium and is the major hazard facing beryllium workers today.

CLINICAL PRESENTATION

CBD is primarily a pulmonary granulomatous disorder. Although involvement of other organ systems has been reported (e.g., lymph node, skin, and liver), the lungs are the principal organ affected and account for the morbidity and mortality of this disease.[5,6] In the early stages, CBD may be asymptomatic. A positive blood proliferative response to beryllium (evidence for beryllium hypersensitivity) may be the earliest sign of CBD.[7,8] Radiologic changes can also be detected on routine chest radiographs. Symptomatic disease usually begins with nonspecific respiratory complaints, such as dyspnea and cough. Early in the disease process, routine chest radiography may not be helpful. Pulmonary function testing early in the disease may be normal or have an isolated abnormality of the diffusing capacity (D_{LCO}).[9] As the disease progresses, symptoms become more characteristic for chronic interstitial lung disease (ILD) with a nonproductive cough, substernal burning pain, and progressive exertional dyspnea. At this stage dry bibasilar crackles are observed on physical examination. A rare patient may have asthmatic-type complaints and physical findings. With advanced disease progressive weakness, easy fatigability, dyspnea at rest, anorexia, and weight loss may occur and acrocyanosis and clubbing may be observed. As cor pulmonale develops, peripheral edema, hepatomegaly, and distended neck veins are seen.[10] Fever is unusual but can be seen. Hypercalcemia and nephrocalcinosis, hyperuricemia, joint pains, and severe cachexia have been described. Severe liver involvement has not been seen, but liver granulomas with mild elevation of the liver function tests occur. Skin involvement may occur in 10% to 30% of cases and frequently involves small granulomatous nodules on the hands, arms, and chest.[5]

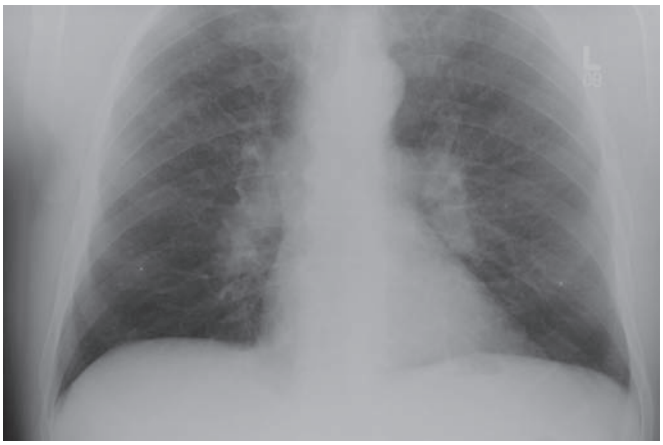
RADIOGRAPHY

Radiographic changes in CBD are nonspecific and cannot be differentiated from sarcoidosis (Fig. 87-1). The most common radiographic abnormalities are diffuse round and reticular abnormalities.[11,12] While most patients have both round and reticular nodules, opacities may be only round or only reticular. These opacities are usually present diffusely throughout the lungs but may be confined to the upper lobes. Hilar adenopathy similar to what is commonly observed in sarcoidosis may also be seen in up to 50% of cases. However, the large "potato type" node involvement is not seen. As the disease advances, radiologic evidence of scarring and retraction can be seen. The hila are retracted upward and conglomerate mass and emphysematous bullae may be present. Gross architectural distortion can occur from severe fibrosis. Pleural thickening can be seen in the presence of long-standing disease. In early disease, complete resolution of radiographic abnormalities can occur secondary to corticosteroid therapy and may recur as the corticosteroids are tapered.[13] Complete spontaneous disappearance of the radiographic lesions has not been observed. The computed tomographic appearance of CBD includes upper lobe or diffuse fibrosis, pulmonary nodularity, and hilar and mediastinal adenopathy. However, in biopsy-proven CBD the computed tomographic findings may be normal or demonstrate ground-glass changes.

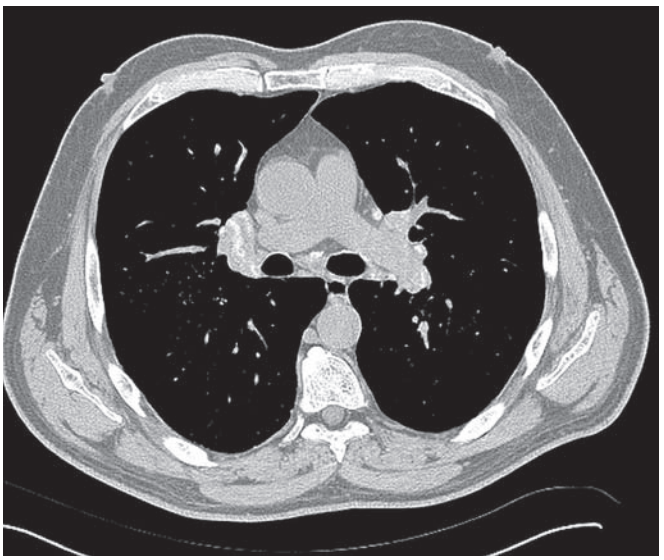
IMMUNOPATHOGENESIS

There are three important characteristics of CBD. First, this disease is usually associated with industrial exposure to beryllium. The only cases that have been described in nonindustrial workers have been in individuals who lived near beryllium plants and were either exposed to the airborne emissions from the plant or from family members who brought contaminated work clothes into the home.[14,15] All other cases have been described in individuals who have been involved in the heating, grinding, abrading, or handling of beryllium metals, alloys, salts, or oxides. In addition, workers not directly handling beryllium may be exposed from processes occurring near them. Industrial hygienic practices today include efforts to remove potential airborne beryllium at the source to prevent beryllium from becoming airborne, limiting the number of workers with potential exposure to beryllium, limiting skin exposure, and trying to keep the airborne levels as low as possible.[16] Recently, the Department of Energy has used 0.2 $\mu g/m^3$ as an action level because of the repeated reports of CBD with possible exposure below the Occupational Safety and Health Administration (OSHA) recommended threshold level of 2 $\mu g/m^3$/8 h shift.[17]

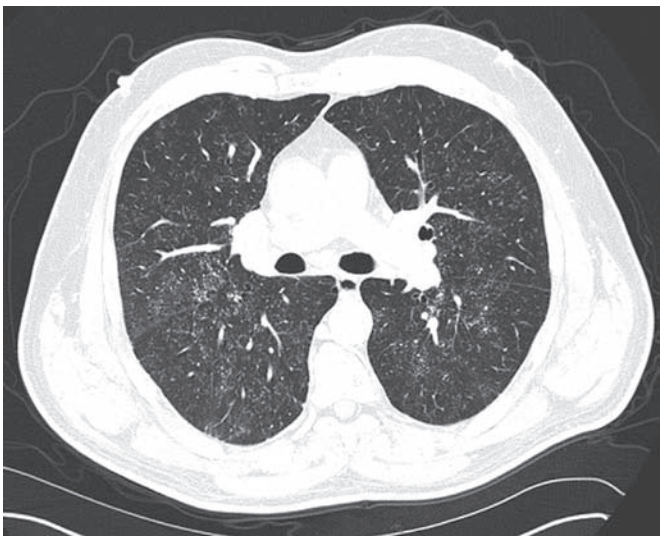
A second important characteristic of CBD is the long time interval or latency that occurs between initial exposure and the onset of disease.[14] The average time to the onset of clinical symptoms is 10 years. This fact combined with the lack of a clear-cut



A



B



C

Figure 87-1 A 61-year-old male smoker who had worked at a beryllium processing facility for 20 years. He had a productive cough for 10 years but denied any shortness of breath. He had a positive response of both his blood and BAL cells to beryllium (stimulation index [SI] for blood beryllium lymphocyte proliferation test [BeLPT] = 13.8 [NI < 3.0], SI for BAL BeLPT = 306 [NI < 5.0]). His BAL also demonstrated a marked lymphocytosis (cell yield = 6 × 105 cells/mL [NI < 3.0 × 105 cells/mL], lymphocytes = 55.2% [NI <20%]). **A.** Chest radiograph demonstrating nodular interstitial disease with adenopathy. **B.** Chest CT mediastinal window demonstrating calcified bilateral hilar and mediastinal lymph nodes. **C.** Chest CT lung window demonstrating a diffuse fine nodular pattern of interstitial lung disease that was most prominent in the mid and upper lung zones.

dose–response relationship to CBD has hampered efforts to determine a safe level of beryllium. Thus, it is uncertain whether a peak exposure level or a total accumulated dose is more important for the development of CBD. Individuals have been described (i.e., secretaries with apparently little exposure) who have worked in industry for less than 1 year and yet still develop disease years to decades later.

A third important characteristic of CBD is that not all exposed workers will develop the disease. Only 1% to 8% of exposed workers will ever develop the disease.[14] This percentage appears to have remained the same despite dramatic efforts by industry to reduce the potential exposure in their workers. This last characteristic of CBD is most likely due to a genetic predisposition.

The suspicion that an immunologic reaction to beryllium caused CBD was based on the following observations: (1) Beryllium painted on the skin (patch testing) could elicit delayed-type hypersensitivity reactions in patients with CBD.[18] However, because of the concern that patch testing could sensitize individuals to beryllium, skin testing has not been widely used. (2) CBD was associated with "immunologic granuloma." (3) Finally, animal studies demonstrated that a hypersensitivity could be demonstrated in animals and that this could be passed with cells.[19]

In vitro studies that simulated patch testing were developed in the 1970s and applied to patients with CBD.[20,21] The blood cells from a large percent of patients with CBD had positive proliferative responses to beryllium. In addition, after stimulation with beryllium, blood cells from many patients with CBD could release the lymphokine, macrophage inhibition factor. However, all patients with CBD did not have positive responses with their blood cells.[22]

The confirmation that CBD was due to a cell-mediated response to beryllium came in the 1980s when cells harvested from the bronchoalveolar lavage fluid (BALF) from patients with CBD were examined.[23] Not only was a marked increase in the number and percent of CD4+ T lymphocytes in the BALF noted, but also a positive proliferative response of bronchoalveolar lymphocytes to beryllium was observed. Positive proliferative responses to beryllium were observed in all cases of CBD and negative responses were noted in beryllium workers with biopsy-proven, non-beryllium lung disease, patients with sarcoidosis and no history of beryllium exposure, and normal volunteers.[24,25] Not only did all patients with CBD have a positive proliferative response of their bronchoalveolar cells to beryllium, but this response was more pronounced in their lung cells than their blood cells. The accumulation of beryllium-specific cells in the

lungs of patients with CBD has been confirmed and shown to be due to effector memory T cells[26] that produce TH1 cytokines (IL-2, γ-interferon, TNFα).[27,28] The T-cell response to beryllium is oligoclonal[29] and the response can be blocked by anti-HLA DP antibodies and requires the presence of HLA-DP2 antigen presenting cells.[30]

The CD4+ T-cell response to beryllium suggested that specific HLA class II molecules might be involved in CBD, since HLA class II molecules present antigenic peptides to CD4+ T cells. A strong association of CBD with the marker HLA DPB1-glu 69 was first shown by Richeldi et al.[31] and subsequently confirmed in three other laboratories.[32–34] However, rather than just a marker for CBD, this marker appears to be associated with the ability to develop an immune response to beryllium. The less frequent alleles that code for DPB1-glu 69 appear to be more associated with beryllium sensitization and disease than the more common alleles.[35,36] The crystal structure of HLA-DP2 has been solved[37] and helps to explain the association with beryllium disease. βGlu 69 lies in a pocket that is accessible to beryllium. In addition, two additional acidic amino acids, βGlu 26 and βGlu 69, lie in this pocket. Mutation of any one of these three amino acids eliminated the ability of the molecule to present beryllium to sensitized T cells. A similar molecule on DR may be responsible for the development of beryllium sensitization in those who do not have HLA DPB1-glu 69.[35] Additional genes probably account for the progression from beryllium sensitization to disease. Polymorphisms on a number of genes including IL-1 A,[38] CC chemokine receptor 5,[39] BTNL2 in DP glu 69 negative individuals,[40] and TGFb1[41] have been identified as a possibility progression factor for the development of CBD. No association has been found with TNFα promoter regions[42] or the TNFα gene.[43]

The previously mentioned studies suggest the following model for the pathogenesis of CBD. Beryllium is inhaled and deposited in the periphery of the lung. Beryllium, either alone as a crystal or combined with a normal lung protein(s), is bound by glu 69–containing DPB1 molecules and presented to beryllium-specific T cells. The beryllium protein or beryllium crystal is poorly digestible and cannot be removed by the immune response. Persistent inflammation leads to granuloma formation. The cells of the granuloma secrete enzymes that cause tissue destruction and fibrosis.

DIAGNOSIS

Because of the frequent need for corticosteroid treatment of patients with CBD, all patients should have tissue confirmation of their diagnosis. A confirmed diagnosis of CBD requires demonstration of a granulomatous reaction secondary to beryllium hypersensitivity. The former requires biopsy material. The latter can be most convincingly demonstrated by testing the proliferative response of bronchoalveolar cells to beryllium. If bronchoalveolar lavage (BAL) cells cannot be easily or safely obtained, testing of blood proliferative responses to beryllium is a reasonable alternative. Laboratories performing these tests are listed in Table 87-1. In cases where biopsy demonstration of granulomatous inflammation is not possible, radiologic evidence of granulomatous inflammation may substitute.

Because immunologic tests of beryllium hypersensitivity have been available only since the late 1980s, their use for screening worker populations is not clear. However, studies to date indicate that blood proliferative response to beryllium is the most sensitive screening test for CBD. The major difficulty with using the blood proliferative response to beryllium as a screening tool is that not all individuals with beryllium sensitization will go on to develop CBD. In addition, the number of workers with beryllium sensitization that ultimately develop symptomatic CBD that requires treatment is unknown but may be relatively low[8] and is probably less than 10%.

In addition, the justification for a screening test requires that there must be some action that will alter the course of the disease.

TABLE 87-1 Laboratories Performing Beryllium Proliferation Testing

Immunopathology Laboratory
Cleveland Clinic Foundation
Cleveland, OH
National Jewish Center for Immunology and Respiratory Medicine
Denver, CO
Oak Ridge Institute for Science and Education
Oak Ridge, TN

Although it is generally believed that early treatment of CBD will alter the natural course of this condition, this is not certain.[44] In addition, removal from further exposure, a prudent but unproven practice, is possible for current workers but would not be applicable to former workers. Thus, the strongest recommendation for use of the beryllium lymphocyte proliferation test as a screening test can be made for current workers. Recommendations for screening former workers and residents of communities with past beryllium exposure from the ambient air are less certain. Nevertheless, because the risk of developing CBD is lifelong, the question of appropriate screening for exposed individuals' remains.

DIFFERENTIAL DIAGNOSIS

The major challenge to making the diagnosis of CBD is to think of the possibility of beryllium exposure. Most cases of CBD that are misdiagnosed are diagnosed as sarcoidosis because either the exposure to beryllium was not known by the patient or the physician failed to elicit an occupational history. In 84 cases of sarcoidosis with a history of possible beryllium exposure, a final diagnosis of CBD was made in 34 with a mean delay from the diagnosis of sarcoidosis of 4 years.[45] A similar search for cases of beryllium disease in a cohort of sarcoidosis patients, failed to identify any cases of beryllium disease.[46] Because the radiographic and clinical presentation of CBD (Table 87-2) is similar to sarcoidosis,[47] the differential diagnosis includes upper-lobe fibrotic processes (Table 87-3). In addition, as for sarcoidosis, other causes of granulomatous disease must be searched for and eliminated. The differential between

TABLE 87-2 Comparison of Chronic Beryllium Disease and Sarcoidosis

Manifestations	Sarcoidosis	Chronic Beryllium Disease
Erythema nodosum	10–20%	Absent
Hilar adenopathy	50–75%	<50%
Peripheral adenopathy	Occasional	Rare
Hypercalcemia	Occasional	Rare
Nephrocalcinosis	Rare	Rare
Bone changes	In chronic disease	Absent
Parotid involvement	Occasional	Absent
Posterior uveitis	Occasional	Absent
Liver involvement	Common	Frequent
Splenomegaly	Rare	Rare
Skin	Uncommon	Unusual
CNS	Occasional	Absent
Response to steroids	Only active disease	Only active disease

TABLE 87-3 Differential Diagnosis of Chronic Beryllium Disease

Sarcoidosis
Hypersensitivity pneumonitis
Tuberculosis
Histoplasmosis
Silicosis
Talc granulomatosis
Eosinophilic granuloma
Idiopathic pulmonary fibrosis

sarcoidosis and CBD depends upon the result of the proliferation test to beryllium. Patients with sarcoidosis do not respond to blood proliferation to beryllium, while CBD patients do. Cases of sarcoidosis among beryllium workers can be diagnosed in this manner. However, caution should always be used and repeatedly negative blood and lung tests should be determined before accepting a case of granulomatous lung disease in a beryllium worker as sarcoidosis.

TREATMENT

No standard approach to the use of corticosteroids has been adopted in the treatment of CBD.[48–50] Because of the side effects, corticosteroids should be reserved for patients with documented pulmonary impairment or those with progressive deterioration. Doses of corticosteroids should be tapered to the lowest dose that controls signs of active disease. Monitoring of patients with chest radiographs, pulmonary function tests, and exercise tests may be useful. Most cases of CBD will be arrested with corticosteroid treatment. In cases of corticosteroid resistance or end-stage disease discovered at initial diagnosis, lung transplantation may be a reasonable approach.

Little data are available on the use of steroid sparing medications.[51] A recent trial of the anti-TNFα antibody showed no significant clinical response in a very small cohort.[52]

The long-term prognosis for CBD is uncertain. Follow-up of cases that were diagnosed in the 1940s and 1950s suggest that the mortality of the disease might be as high as 30%.[5] Whether a similar mortality will be present in patients with disease diagnosed since the 1990s is not certain. Newer techniques to diagnose CBD (immunologic testing) enable the disease to be detected earlier. The natural history of this condition detected at the presymptomatic stage is unknown. The two major questions are whether or not the disease detected early is inevitably progressive and whether the disease will be more responsive to corticosteroid therapy.

BERYLLIUM AND LUNG CANCER

Animal studies have clearly indicated that beryllium is carcinogenic. Whether beryllium is carcinogenic in humans is not clear. A National Institute for Occupational Safety and Health (NIOSH) study suggests that a small increase in lung cancer (SMR = 1.17)[53] may occur in beryllium workers. However, this finding has been challenged because of the poor data with regard to cigarette smoking.[54] This issue will remain controversial, as additional studies are not currently planned. Whatever the risk of cancer is in beryllium workers, the more significant medical concern is CBD.

HARD-METAL LUNG DISEASE

Hard metal is an alloy of tungsten carbide in a matrix of cobalt into which smaller amounts of chromium, molybdenum, nickel, niobium, tantalum, titanium, and/or vanadium may be added. These components are milled to a fine powder, mixed together, pressed into the desired shape, and heated under pressure between 800° and 1000°C, yielding a product with a chalk-like consistency. The material may then undergo additional machining before being baked at 1500°C, which is above the melting point of cobalt and leads to the formation of an alloy that is 90% to 95% as hard as a diamond.[55] Because of this property, hard metal is an important component in cutting tools, drill bits, armor plate, and jet engine parts.

Hard metal was developed in the 1920s, and ILD was first reported in hard-metal workers in 1940.[56] Lung disease has been noted to occur in those working in both the initial production of hard metal and the machining and maintenance of hard-metal tool components. In addition, although hard metal is not used in the diamond-polishing industry, a similar spectrum of disease has been reported in diamond polishers using steel polishing disks whose cutting surfaces consist of microdiamonds cemented into a fine cobalt mesh.[57] In contrast, workers in the cobalt-producing industry, who are more likely to be exposed to cobalt alone, may develop occupational asthma but appear to be much less likely to develop ILD.

The industrial processes associated with hard-metal lung disease produce respirable fine metallic dust particles. They also produce metallic ions that accumulate in the coolants used in the metalworking procedure and are absorbed through the skin or inhaled in vaporized coolant fluids. To counteract these exposures, the American Conference of Government Industrial Hygienists (ACGIH) have established current permissible exposure limits for cobalt metal, dust, and fumes at an 8-hour threshold-weighted average (TWA) of 0.02 mg/m^3. NIOSH recommends an exposure limit of 0.05 mg/m^3 as a TWA for a 10-hour workday and a 40-hour workweek and OSHA requires an 8-hour TWA of 0.1 mg/m^3.[58]

CLINICAL MANIFESTATIONS IN HARD METAL—AND COBALT—EXPOSED PERSONS

A variety of respiratory syndromes have been associated with exposure to hard metal, most commonly: (1) asthmatic reactions; (2) a form of hypersensitivity lung disease; and (3) interstitial pulmonary fibrosis. The last two forms may be a continuum of the same process with subclinical or unrecognized hypersensitivity alveolitis proceeding to the development of fibrotic lung disease. Hard-metal disease (HMD) has been used to describe all types of lung disease but is most often used to reference the parenchymal or ILD rather than the airway-related manifestations of hard-metal inhalations.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) has been seen in hard-metal workers and diamond polishers. Studies have attempted to determine the prevalence of ILD among hard-metal workers. The studies have been frequently limited by lack of appropriate control groups, loss of former workers who may have left the plant due to illness, inconsistent disease detection/definitions, and small numbers. However, despite these limitations it is clear that ILD develops in a small minority of exposed workers. Estimates range from 0.7% to 12.9% in cross-sectional studies.[59–64] A more recent longitudinal study found no ILD in its cohort but it was a small study with more recent exposure and may represent the effects of limiting exposure levels.[65] Reports of exposure intensity, duration, and immediacy have varied a great deal. For instance, in one review of 100 cases of HMD the duration of exposure varied from 1 to 30 years and 1 case was diagnosed 40 years after a 3-year exposure had ceased.[66] Nonsmokers and former smokers also appear to be at higher risk.[67] Interestingly, most studies suggest that workers exposed to cobalt alone without tungsten and other metals do not appear to develop ILD. A few cases of diamond polishers exposed to cobalt alone who have developed ILD have been reported, but this appears to be fairly rare.[68]

In some patients, HMD presents as a hypersensitivity pneumonitis, or allergic alveolitis. These patients manifest fever, anorexia, cough, dyspnea, inspiratory crackles, and fine reticulonodular infiltrates on chest radiograph. Pulmonary function testing typically shows a restrictive pattern, with a reduced D_{LCO}. Symptoms may resolve when exposure is discontinued but may recur with reexposure.[69] Over time, progressive dyspnea, lung function impairment, and interstitial fibrosis may develop. Fibrosis may also occur in the absence of antecedent symptoms. Patients with advanced disease exhibit weight loss, hypoxemia, digital clubbing, pulmonary hypertension, and cor pulmonale.

The histopathologic manifestations of the interstitial disease in these patients can be varied with findings consistent with bronchiolitis, desquamative interstitial pneumonitis, usual interstitial fibrosis, and giant-cell interstitial pneumonitis (GIP). Granuloma formation is infrequent. Lung biopsies may show heterogeneous patchy involvement with foci of active alveolitis, fibrosis, and normal parenchyma. Bronchiolitis may be seen in areas with and without active alveolitis. GIP is characterized by lymphoplasmacytic infiltration, epithelial desquamation, and the presence of numerous multinucleated giant cells in the alveolar spaces.[70] These giant cells are formed by both actively phagocytic alveolar macrophages and type II pneumocytes. Infiltration with eosinophils has also been described. Analysis of BALF may demonstrate hypercellularity with increased numbers of macrophages and giant cells. A relative or absolute increase in the number of lymphocytes with a reduced CD4/CD8 ratio as well as increased numbers of neutrophils, eosinophils, and mast cells, may also be seen. In addition, the multinucleated giant cells can also be found in the BALF, which can be diagnostic of hard-metal lung disease without requiring a surgical lung biopsy.[71,72] One study found that a high number of eosinophils in the BAL that persisted after cessation of exposure and on therapy was associated with a poorer outcome.[72] Electron microscopy with energy dispersive X-ray analysis (EDAX) of the particulate material present in biopsy specimens may demonstrate the presence of the elements used to form hard metal. Because of its high solubility, significant amounts of cobalt is often not present.[66]

Naqvi et al.[66] reviewed 100 cases of HMD identified either by the histologic presence of GIP or with a quantitative EDAX analysis containing tungsten at concentrations greater than 2×10^6 particles per cm^3 of lung tissues. Of these, 59 had changes diagnostic of GIP. In more advanced cases, there were changes of end-stage fibrosis and honeycombing with or without characteristic GIP lesions. Only four cases demonstrated granulomas and of those two also had changes of GIP. They examined 746 cases of ILDs examined by EDAX and found a striking correlation of tungsten with the finding of GIP with higher levels of tungsten being more likely to have GIP. Cobalt was detected in only 36 patients in the larger cohort. Only those who had tungsten present in addition to the cobalt had GIP findings on pathology. They concluded that the presence or absence of cobalt was not useful in diagnosing or excluding HMD. Few studies have looked at the radiography of HMD. Many of the screening studies of cobalt workers rely on plain chest radiographs and use the profusion score of the International Labour Office (ILO). However, a consistent description of the typical findings has not been offered. More recently, with the advent of computed tomography (CT) scans a few case reports have described the CT findings of patients with HMD. Like the pathology, these findings show a wide variability and can include end-stage honeycombing with cystic changes and traction bronchiectasis, to less impressive reticulation and even areas of ground-glass opacities.[73] No pathognomonic finding has been described.

Treatment for this disease consists of discontinuation of exposure and administration of systemic corticosteroids. There is a case report of a patient responding to high dose of inhaled corticosteroids alone.[74] Although no clinical trials have been performed, dosage and duration of treatment similar to those used in other forms of active alveolitis or fibrosis should be considered. Patients with active alveolitis may show a dramatic response to steroids, whereas patients with more prominent fibrosis may show minimal response despite prolonged steroid treatment.[55] Fibrosis can also progress despite cessation of exposure. GIP has been observed to recur after lung transplantation despite cessation of occupational exposure.[66,75]

OCCUPATIONAL ASTHMA

In contradistinction from ILD, asthma can occur in workers exposed to cobalt alone without tungsten.[76,77] The reported prevalence of asthma or wheezing related to cobalt or hard-metal exposure is also low and ranges from 6.6% to 10.9%.[64,76,78] This variation may be attributed to different levels of exposure and the criteria used by various authors to define occupational asthma. As with other forms of occupational asthma, patients may note cough, wheezing, dyspnea, chest tightness, conjunctivitis, and rhinitis. Throughout the workday, symptoms may increase in severity and a progressive decline in peak flow may be demonstrated. Symptoms usually abate during weekends or vacations and often resolve when exposure is discontinued. Upper-airway symptoms may result from either direct airway irritation or atopic responses.

In addition to demonstrating an association between workplace exposure and symptoms, the diagnosis may be confirmed by bronchoprovocation testing (BPT) with cobalt or cobalt salts. Testing with cobalt salts is preferable, as it is much easier to control dosage and delivery of soluble ion solutions than those of particulate substances. Immediate or delayed airway reactivity to cobalt chloride may be observed after BPT.[79] Tungsten carbide has not been shown to produce bronchoconstriction. A positive radioimmunosorbent test (RAST) to cobalt-conjugated human serum albumin has also been reported in some patients, suggesting a type I allergic response. Skin patch testing with cobalt salts does not appear to be of use in diagnosing hard-metal asthma.[79]

Some studies have suggested a dose–response relationship between higher levels of cobalt exposures and lower forced expiratory volume in 1 second (FEV_1) on spirometry and symptoms of asthma.[64,77,80] A twofold increase in the relative odds ratio for work-related wheezing was noted when cobalt exposure exceeded 0.05 mg/m^3.[64] However, asthma and reductions in FEV_1 have been seen at levels below the allowable limit of 0.05 mg/m^3.[81,82] This suggests that the current permissible exposure limit may not protect all workers against the development of cobalt-induced asthma. Because of findings of this sort, baseline evaluations and employee screenings should be performed in workers exposed to hard-metal dust. A reasonable strategy would include assessments for symptoms of rhinitis, conjunctivitis, wheezing, dyspnea, or chest tightness; the relationship of symptoms to work hours; smoking history; physical examination; pulmonary function testing; and chest radiography. In patients with symptoms or findings suggestive of occupational asthma, peak flow monitoring during working and nonworking hours should be performed and other causes of pulmonary function deterioration ruled out. Specific BPT and RAST results may provide additional positive criteria for diagnosis. Personal employee air sampling and measurement of urinary cobalt levels can provide information about ongoing exposure.[83] The workplace should also be examined for levels of cobalt exposure and employee protective practices. However, there may also be long-term respiratory health effects independent of the development of asthma. One recent longitudinal study found that those smokers with higher exposure had a greater fall in their FEV_1 over 10 years than those with less exposure. However, the contribution of the cobalt exposure to the overall expected decline was relatively modest (103 mL in addition to a 518 mL from smoking alone in the highest exposure group).[65]

Treatment for occupational asthma related to cobalt includes control of exposure as well as medical therapy with bronchodilators

and inhaled corticosteroids. Systemic corticosteroid treatment is usually not required.[55]

LUNG CANCER

Cobalt and cobalt-containing compounds have been shown to cause cancer in rats after local injection and intratracheal instillation.[84] The International Agency for Research on Cancer reviewed the evidence for the carcinogenicity of cobalt in 1991 and concluded that although there was sufficient evidence for the carcinogenicity of cobalt metal powder and cobalt oxide in experimental animals, there was inadequate evidence for the carcinogenicity of cobalt and cobalt compounds in humans.[84] Since that publication, however, there have been studies suggesting a relationship. One study of 709 French hard-metal workers found an excess of lung cancer mortality in their workers and the excess was greater in workers with the highest levels of exposures though no relationship with duration of exposure was found.[85] However, this study was not powered to examine the effect of smoking as well so firm conclusions could not be drawn. A second study by the same group of researchers found a twofold higher risk of lung cancer among subjects exposed to both tungsten and cobalt and the odds ratio increased with cumulative exposure.[86] This study was able to adjust for smoking and found the relationship between hard metal and lung cancer held. A more recent study of one of the same plants was published in 2000 and examined mortality again from lung cancer with greater adjustment for smoking and exposure by job matrix.[87] They found an elevated standardized mortality rate that increased with increasing duration, intensity, and cumulative dose of exposure to hard-metal dust. The excess was almost exclusively in subjects exposed to unsintered hard-metal dust.

MECHANISMS OF INJURY

The pathogenesis of the hard-metal–associated lung diseases is poorly understood. There are two predominant hypotheses for the pathogenesis of hard-metal lung toxicity: (1) hypersensitivity with lymphocyte-driven toxicity; and (2) free-radical and cytokine-mediated injury.

Several authors point out the similarities of hard-metal lung disease and hypersensitivity lung disease including the ability of cobalt to function as a hapten in complex with albumin and cause a contact dermatitis.[88] BAL studies of both exposed workers and those with HMD have shown increased lymphocytes with reduction of the helper/suppressor T-cell ratios.[89] In addition, in at least one subject with HMD, a lymphocyte transformation test was found to be positive in the presence of cobalt.[90] Finally, a recent report suggests an association between a glutamic acid residue in position 69 of the HLA-DP beta chain and susceptibility to HMD.[91] This is similar to CBD, a known hypersensitivity disorder.

However, there are features of this disease that do not suggest a hypersensitivity reaction as the mechanism for the disease. Perhaps most obviously is the fact that granulomas, the hallmark of chronic hypersensitivity pneumonitis, are not typically found on biopsy. In addition, the finding that both cobalt and tungsten are required for most (though not all) cases of hard-metal lung disease requires explanation. In vitro studies using peritoneal and alveolar macrophages from rats and mice have demonstrated that the combination of tungsten carbide and cobalt is highly cytotoxic, while cobalt and tungsten carbide alone produce minimal or no cytotoxicity.[92] In addition, the acute lung toxicity of tungsten carbide plus cobalt is much higher than that of each component after intratracheal instillation in rats.[93]

Lison[88] has proposed a mechanism that might explain this interaction. He suggests that tungsten carbide can act as an electron carrier to transfer electrons from cobalt to oxygen. This then leads to the production of free radicals and reactive oxygen species, which, in turn, causes pulmonary damage. Differences in susceptibility to disease would therefore be due to differences in subjects' antioxidant defenses. Further research is required to elucidate the pathophysiology behind hard-metal lung disease.

SUMMARY

This chapter addresses, two metals that cause lung injury. Both beryllium and hard metal can cause interstitial pulmonary inflammation that is immune mediated. Beryllium results in a chronic cell–mediated response that is mediated by CD4+ T cells and results in granuloma formation. The mechanism of hard metal's interstitial inflammatory response is less clear but results in a giant-cell interstitial pneumonia. However, both metals have also been implicated in lung cancer and acute toxicity and hard metal has been associated with an asthmatic reaction. Improved diagnostic approaches to these conditions have resulted in earlier diagnosis and recognition of harmful workplace exposures.

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CHAPTER 88

Coal Workers' Lung Diseases and Silicosis

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COAL WORKERS' LUNG DISEASES

Coal miners are at risk for developing several distinct clinical illnesses in relation to their occupational exposures. Historically, some names applied to these conditions were miners' asthma, phthisis, anthracosis, and in Scotland, miners' black lung. It was recognized early that these afflictions were related to the occupation of mining; however, it was not until the development of specialized techniques such as chest radiography, pulmonary function testing, the discovery of the tubercle bacillus, and sophisticated histologic examination of tissue that respiratory diseases affecting miners could be separated and defined. Recent advances in the understanding of respiratory health issues in coal miners have focused on the spectrum of disease caused by inhalation of coal mine dust, termed coal mine dust lung disease (CMDLD).[1]

CMDLD includes the classic occupational interstitial lung diseases, such as coal worker's pneumoconiosis (CWP), silicosis, and mixed dust pneumoconiosis, but also includes the more recently described entity labeled dust-related diffuse fibrosis (DDF).[1] CMDLD is a preventable occupational disease that results from inhalation of coal mine dust into the lungs leading to parenchymal and airway damage, not only from the foreign material itself but also the tissue's reaction to the dust.[1,2] This disease process was identified as early as the 1800s, but became much more prevalent as coal production increased during the industrial revolution. Unfortunately, disability from coal mine dust exposure went mostly unrecognized by medical authorities in the United States through the first part of the 20th century. Congress finally passed comprehensive legislation with the Federal Coal Mine Health and Safety Act of 1969. This Act went above and beyond previous legislation by providing for the first mandatory standards for working conditions in US mines, a system for enforcement, and ongoing monitoring of miner health, as well as a mechanism for seeking financial compensation for coal miners who could demonstrate total disability arising from their dust exposure (aka "black lung").[3]

Since the time of this landmark legislation further acts by Congress and enforcement agencies have improved miners' working conditions, which now fall under the purview of the Mine Safety and Health Administration (MSHA). Much of our improved understanding of the nature and extent of lung disease associated with mining coal in the United States over the past half century comes from the large number of studies performed by the National Institute for Occupational Safety and Health (NIOSH). Despite increased understanding of CWP and reports of stable or improved dust levels in mines, dust-related respiratory disease remains a significant burden. Most worrisome are recent data suggesting that contemporary dust exposure is leading to rapidly progressive pneumoconiosis particularly in young miners, with a significant impact on pulmonary function and premature death.[4]

COAL AND COAL MINING

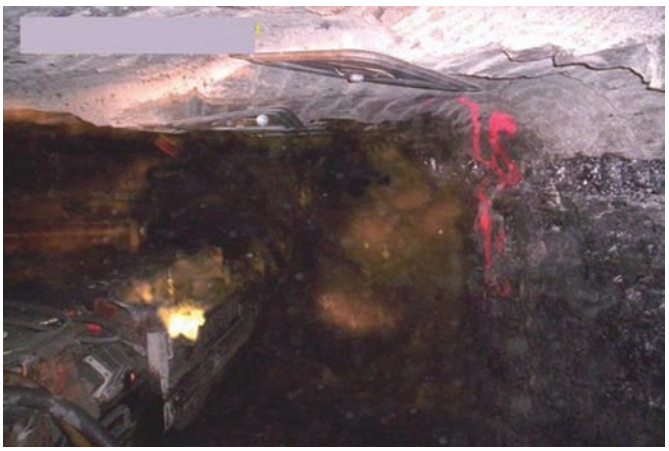
Coal is not a pure mineral. It is a spectrum of carbonaceous rocks derived from the accumulation of vegetation sedimented under swampy conditions and subjected to extreme pressure over long periods of time. Coals are characterized by rank, which relates to geologic age, hardness, carbon content, and the amount of heat released (BTUs) when they are burned. Thus, peat is the lowest rank (softest) coal, being geologically the newest, and anthracite is the highest rank (hardest) and oldest type of coal.

Coal may be found in outcroppings and in seams that vary from a few feet to several thousand feet below the surface. Surface or strip mining, which currently accounts for the majority of US coal production, involves removal of the overburden and mining the coal seams with large earth-moving equipment. In some areas of the eastern United States, mountaintop removal mining has become a dominant form of mining. Mountaintop mining involves first removal of all vegetation and soil, and then drilling and blasting through hundreds of feet of strata to access the coal seam. The excess rock and soil is placed in the steep stream beds along the mountainsides, creating areas called valley fills. Occasionally, surface mining is also performed by boring into coal outcrops with an auger. Dust levels measured in the air at surface mines have generally been lower than in underground mines, with a few notable exceptions, but miners who work exclusively at surface operations may still develop advanced forms of pneumoconiosis (discussed below).[5,6] Coal outcrops of sufficient size can be mined deep into the hillsides. Deep seams are accessed through vertical shafts drilled from the surface to the coal seam where the mining process then follows the seam through a series of more or less horizontal tunnels. Shaft drilling, which is frequently performed under contract for mine operators, may present an important silicosis hazard. A majority of the approximately 92,000 coal miners in the US work at underground mines,[3] although deep mines produce somewhat less than half of the coal mined; in China, there are about six million underground miners.[1]

Respirable dust concentration, coal rank, types of mining work, mining category, and duration of exposure are known risk factors for the development of pneumoconiosis.[7] Dust exposure varies significantly between specific tasks within the mines. In underground mining, airborne dust is generally highest during work at the coal-cutting face, where coal is removed from intact seams. Miners involved in roof support (termed roof bolters; see Fig. 88-1), miners who do not use protective respiratory equipment, workers exposed to explosive blasting fumes, and those who use stored mine water for dust suppression spray are all at increased risk for accelerated loss of lung function.[8]

Many miners also have exposure to respirable crystalline silica, placing them at risk for silicosis and or concurrent CWP/silicosis.[9] In particular, silicosis has been recognized among miners performing roof bolting, and drilling operations, as well as motormen who operate underground coal trains and use sand for traction on the rails.[10,11] Workers in some aboveground coal mining operations also may have important exposure to dusts.[5,12] These include workers at tipples and preparation plants, where crushing, sizing, washing, and blending of coal is done, and coal is stored or loaded onto ships, railroad cars, or river barges. At surface coal mines, drilling rigs are used to bore holes in which explosives are placed. Equipment operators may be exposed to silica and silicate dusts from the rock strata, representing a risk for silicosis or mixed dust pneumoconiosis, rather than CWP (Fig. 88-1).

A



B

Figure 88-1 Photographs illustrating underground coal mining. In (**A**), miner is engaged in drilling before placing a roof bolt. In (**B**), the gray area above the black coal seam indicates where the mining equipment has pulverized a layer of silica-bearing rock. *(Used with permission of Anita Wolfe, National Institute for Occupational Safety and Health, Morgantown, WV.)*

EPIDEMIOLOGY OF LUNG DISEASES IN US COAL MINERS

The first major survey of the health of American coal workers was conducted by the US Public Health Service from 1969 to 1971, evaluating symptoms, lung function, and chest radiographic findings. This study included over 9000 miners at 31 underground mines (2 were anthracite mines; 29 were bituminous mines). Participation in the survey was over 90%. The mines were chosen to represent different geographic areas, coal seams, and mining methods. After this initial study, three subsequent surveys have been conducted to evaluate miners at these and other US mines.

Results of radiographic surveillance from the 1970s through the mid-1990s showed a marked decline in the prevalence of CMDLD.[13,14] The decreased prevalence was a source of great optimism that government regulations and oversight was resulting in improvement in miners' respiratory health. Unfortunately the decline has not continued. Since about 1995, the observed prevalence of CMDLD among miners who participate in health surveillance has been increasing (see Fig. 88-2).[15] In response to this troubling finding, availability of health surveillance for miners was increased. When data from underground miner health surveillance are compared to reported dust measurements, CWP prevalence is less than expected in some regions but substantially greater than expected in others, with some miners experiencing rapid progression of disease.[16]

RADIOGRAPHIC FINDINGS

Radiographic epidemiologic studies and surveillance findings for underground coal miners have been reported over the last four decades. As part of these activities, each miner's chest radiograph is independently interpreted by at least two qualified physicians, using the International Labour Office (ILO) pneumoconiosis classification system (see Table 88-1 for the definition of ILO terminology).[17] Radiographic data from the initial health surveys showed an overall prevalence of simple and complicated CWP of nearly 30%. There was variation in prevalence by region of the country and the type (rank) of coal mined.[18] Enforcement of dust control measures in the United States, fully enacted in 1973, resulted in a declining pneumoconiosis attack rate. This decreased prevalence was confirmed

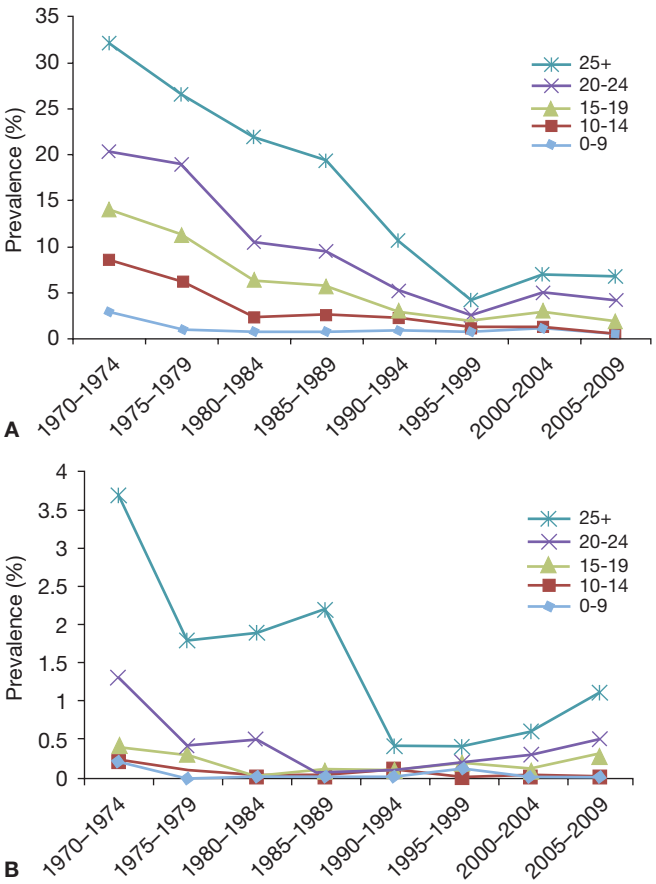


Figure 88-2 Proportion of miners examined in the NIOSH Coal Workers' X-ray Surveillance Program from 1970–2009 with Coal Workers' Pneumoconiosis category 1 or greater (**A**) or progressive massive fibrosis (**B**), by tenure in underground coal mining. *(Adapted with permission from Attfield MD. Centers for Disease Control and Prevention: Current Intelligence Bulletin 64: Coal Mine Dust Exposures and Associated Health Outcomes—A Review of Information Published Since 1995. DHHS(NIOSH) Publication No. 2011–172; 2011. Available from: http://www.cdc.gov/niosh/docs/2011–172.)*

TABLE 88-1 Definitions of Terminology Used by the International Labour Office Classification to Describe Pneumoconiotic Opacities

ILO Term	Opacity Width	Opacity Type
P	≤1.5 mm	Small rounded
Q	1.5–3 mm	Small rounded
R	≥3–10 mm	Small rounded
S	≤1.5 mm	Linear/irregular
T	1.5–3 mm	Linear/irregular
U	≥3–10 mm	Linear/irregular
A	≥10–50 mm	Large
B	≥50–RUZ mm	Large
C	≥RUZ	Large

RUZ, Right upper (lung) zone.
Source: Data from International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconiosis. Revised edition 2011. Geneva, Switzerland: International Labour Office; 2011.

through the federally mandated chest radiographic surveillance program for underground US miners.[13,14] Between 1973 and 1978, CWP was found in about one-third of the miners who participated in the program and had worked 25 years or more underground.[14] By 1995 to 1999, only 1 in 25 (4.2%) of these miners showed radiographic evidence of CWP (Table 2011 to 2012 in reference 14).

Regrettably, continued surveillance by NIOSH has revealed a significant increase in the prevalence of radiographic pneumoconiosis (to 7%) in 2005 to 2009 for miners with more than 25 years tenure, since hitting its nadir in the late 1990s.[14] The rate of progressive massive fibrosis (PMF) has also tripled to 1.1% after reaching its low point over a decade ago.[18] Also of interest is the elevated disease prevalence among workers at smaller mines.[19]

Perhaps the most concerning findings of ongoing surveillance studies have been the frequency of rapidly progressive radiographic disease in certain mining populations. During their 2005 analysis, Antao et al. found that in miners with pneumoconiosis, about 35% had rapidly progressive disease. This rapid progression was defined as an increase of greater than one ILO subcategory over 5 years.[16] More worrisome is the fact that 15% developed PMF, the most advanced and debilitating form of the disease. Current studies are now underway to assess the reason(s) for this rapidly progressive form of CMDLD.

Radiographic analysis has been complemented by ventilatory lung function testing as an integral component of respiratory health studies of the mining population. Early reports strived to identify a relationship between radiographic disease and spirometry results. Multiple studies in the United States and abroad have subsequently evaluated the relationship between radiographically evident CMDLD and lung function.[20–22] Although several earlier studies did not associate lung function impairment with uncomplicated CWP, recent analysis has identified significant ventilatory deficits among coal miners with small radiographic opacities, in addition to the important decrements in lung function that have been observed in miners with the large radiographic shadows (>10 mm) of PMF.[4,22,23]

Studies in the United States and Great Britain evaluated lung function with respect to the miners' cumulative dust exposure, and have helped to clarify the adverse effect of dust on coal miners' lung function.[24–26] Miners show a progressively greater risk of lung function loss with increasing cumulative dust exposure, independent of the chest radiographic findings of CWP. The forced expiratory volume in 1 second (FEV_1) loss is most severe in those who work for many years at the dustiest jobs. Among smoking miners, the effects of tobacco smoke appear to be additive and of similar magnitude to the dust effect. Studies of FEV_1 decline have demonstrated essential equivalence between 1 year of work in a job at the coal face and 1 year of cigarette smoking: no disproportionate dust effect has been noted in relation to tobacco use. Also, there is evidence that miners experience a more rapid loss in spirometric function parameters during their first few years of mining, with slower dust-related declines after that time.[27]

In summary, the epidemiologic evidence has shown that coal miners experience ventilatory lung function loss with increasing exposure to dust, either in the presence or absence of radiographic CWP. Among smoking miners, the effects of tobacco and dust appear to be additive. Although, on average, the functional losses associated with either dust or smoking are small, it is estimated that after 35 years of work at the current permissible limit, dust exposures will cause a clinically important FEV_1 loss in 8 out of 100 nonsmoking coal miners. Higher exposures result in greater losses. When chronic bronchitis is present, there is an additional FEV_1 reduction averaging 200 to 250 mL.[7,27] With simple CWP, and especially when PMF is present, an additional ventilatory deficit is likely.

Investigations into miner mortality have been completed in both the United States and Britain. Findings from both countries have been generally consistent, and reveal that the miners experience increased mortality attributable to pneumoconiosis, emphysema, chronic bronchitis, and ischemic heart disease.[28–33] Radiographic findings of advanced CWP (PMF) consistently affect mortality, especially in categories B and C (see Table 88-1 for definition of ILO terminology) whereas among miners with simple CWP, decreases in survival were smaller. Accelerated FEV_1 decline is also associated with increased mortality from both cardiovascular and respiratory causes.[30] Miners' risks of dying from the obstructive airway diseases of emphysema and chronic bronchitis exhibit a different geographic pattern than the mortality from CWP, suggesting that these dust effects have different mechanisms.[31] Attfield and Kuempel[32] analyzed the mortality experience over 22 to 24 years among 8899 working coal miners. Their results revealed increased mortality from nonviolent causes, nonmalignant respiratory disease, and accidents, and confirmed previous results indicating that exposure to coal mine dust leads to increased mortality in the absence of tobacco smoke exposure.

Troubling recent data regarding miners with both rapidly declining lung function and rapid progression of radiographic disease seem to have also had mortality implications. A NIOSH report from 2009 revealed a substantial increase after 2006 in years of potential life lost (YPLL) before age 65 years associated with CWP.[2] A recent study looked at data over the past decade (at current exposure levels). Investigators found rapidly progressive pneumoconiosis and massive fibrosis in relatively young West Virginia coal miners that led not only to important lung dysfunction but also premature death.[4] More documentation for the high risk of contemporary coal mine exposures comes from investigations into mining accidents. Lung tissue analysis was performed on 24 victims of a recent mine explosion. Seventy-one percent (17/24) had autopsy evidence of CMDLD and 16 of the 17 miners with CWP had started working after the modern dust limits were put into effect.[34] The implications of these new studies are incompletely understood, but it is obvious that contemporary miners are still developing severe and fatal CMDLD.

PATHOLOGY OF COAL MINERS' LUNG DISEASES

Heppleston[35] identified the coal macule as a fundamental histopathologic finding in CMDLD in 1953 (Fig. 88-3). In his discussion he described the macule as consisting of a focal collection of coal dust

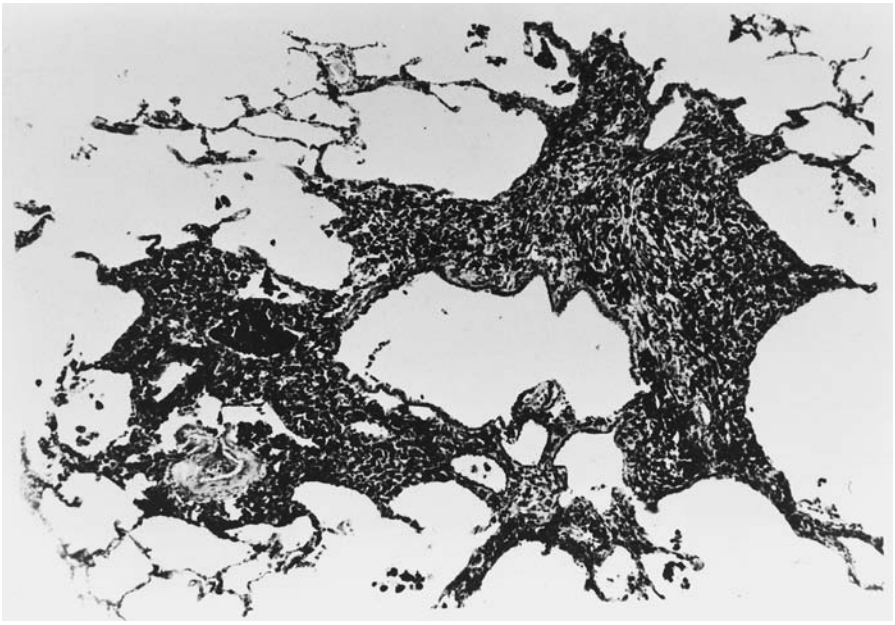


Figure 88-3 A coal macule, microscopic section. *(Used with permission of Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

in pigment-laden macrophages around the respiratory bronchioles and tapering off toward the alveolar duct. A fine network of reticulin is present in the early stages and may include a small amount of collagen depending upon the character of the dust.[36] Centriacinar emphysema, the dilation and injury of lung gas exchange units, is observed with increased prevalence in the lungs of coal miners. Focal emphysema is the form of centriacinar emphysema that is seen as an integral part of the lesion of simple CWP. It is characterized by enlargement of the airspaces immediately adjacent to the dust macule. The pathologic severity of the emphysema is proportional to the miner's cumulative dust exposure and increases with increasing lung dust retention.[37–39] Muscular thickening of pulmonary arteries, in conjunction with hypertrophy of the right ventricle, can be observed with both simple and complicated CWP, and is increasingly prominent when CWP is associated with other lung disorders.[40] The development of pulmonary hypertension secondary to these changes may have a profound adverse effect on miner mortality.[41] Pathologic changes in the airways consistent with chronic bronchitis, including enlargement of mucus glands, have also been documented in miners' lungs.[42]

Central to the biology of CMDLD (discussed below) is the alveolar macrophage.[43–45] Dust particles that travel to the distal airways (beyond the mucociliary escalator) are engulfed by alveolar macrophages and removed from the airways and lung parenchyma via lymphatics. With extended excessive dust exposure, this system is overwhelmed and coal mine dusts as well as dust-laden macrophages begin to accumulate in the airway walls and interstitium. Recent evidence suggests that important lung functional losses observed during coal mining work may at least in part be related to this dust reaction in the small airways.[46] With ongoing dust deposition and inadequate clearance mechanisms, these lung lesions increase in size and number. These larger fibrotic lesions are called coal nodules and are palpable in lung specimens, whereas coal macules are not. Palpable coal nodules are classified as micronodular up to 7 mm in diameter and macronodular from 7 mm and larger.[47]

A less common form of CMDLD and silicosis labeled DDF has been increasingly recognized. This finding had previously been interpreted as representing the development of usual interstitial pneumonitis (UIP) in miners. Recognition of a pulmonary fibrosis pattern related to CMDLD has been supported by case reports and several studies.[48–50] In their position paper the Industrial Injuries Advisory Council (IIAC) found "there is good evidence for a form of interstitial fibrosis which is really part of the disease process of CWP and is not typical of cases of interstitial fibrosis in noncoal workers." DDF has been described in pathologic terms as a bridging fibrosis connecting various stages of CMDLD lesions and/or lesions of silicosis, and has been found in approximately 12% of coal miners at autopsy.[50] An occupational history is of utmost importance to the proper clinical recognition of DDF as opposed to UIP.[1] This distinction is of importance both from a prognostic and management standpoint.

At autopsy, complicated CWP (PMF) is confirmed when one or more nodules in a lung specimen are noted to attain a size of 2 cm or greater in diameter.[47] The 2 cm is an arbitrary choice of a minimal diameter that permits better correlation with clinical and radiographic measurements. (In fact, when radiographic pneumoconiotic shadows are >1 cm, PMF is said to be present.) Lesions are solid, heavily pigmented, and rubbery to hard. They tend to occur symmetrically, but may be asymmetrical, and may cavitate.[51,52] Airways and vessels adjacent to the lesions may be distorted, and within the lesions, they are destroyed. PMF generally occurs in association with background pathologic changes of simple CWP.[53]

BIOLOGY OF COAL WORKERS' PNEUMOCONIOSIS

Numerous studies have evaluated the relationship of coal mine dust exposure and activation of immunologic and inflammatory mechanisms. Soutar et al.[54] reported a study of serum antinuclear antibodies (ANA) and rheumatoid factor (RF) among 109 miners with radiographic evidence of pneumoconiosis attending the London Pneumoconiosis Panel. They reported positive ANA in 17% and RF in 10% of the miners whereas about 2% to 3% positive ANA was expected in a healthy male population. The prevalence of ANA was 9% in simple CWP and 27% in those with category C (PMF). A similar trend was seen with RF, ranging from 6% in simple CWP to 18% in category C. Combining both ANA and RF resulted in prevalences of positive results in 13% of the miners with simple CWP and 45% of those with category C CWP.

Studies of serum immunoglobulins were conducted by Hahon et al.[55] among 155 US coal miners with chest radiographs demonstrating simple CWP, Caplan syndrome (an atypical clinical presentation of pneumoconiosis associated with features of rheumatoid arthritis), or PMF. Among miners with PMF, those mining anthracite coal had

significantly higher serum concentrations of C3, α1-antitrypsin, IgA, and IgG compared to miners from bituminous regions. Compared to normal controls, the miners had elevated C3, α1-antitrypsin, and IgG values. There were few differences in these serum proteins among the miners with simple CWP. The authors did not find any association between the elevated immunoglobulins and FEV_1.

Over the past decade much research has been undertaken to understand the mechanism(s) of coal mine dust–induced inflammation. Compared to controls, miners with CMDLD have been shown to have elevations in both serum and bronchoalveolar lavage (BAL) of several cytokines, which play an important role in lung inflammation and fibrosis, including IL-1β, IL-6, and TNF-α.[56,57] Inflammation resulting from oxidative stress has also been suggested in both human and animal data.[58,59] One potential contributor to miners' increased oxidative stress is the level of bioavailable iron. Iron has the known potential to catalyze oxidant formation through its interaction with oxygen or hydrogen peroxide. The potential of bioavailable iron to induce oxidative stress has been associated ecologically with regional variations of CMDLD prevalence.[60]

Although immunomodulation and inflammation play an important role in the development of CMDLD, the underlying host susceptibilities that lead one miner to develop severe disease in a given environment while another miner may have a relatively minimal disease burden remain elusive. Genetic studies have been unable to identify specific markers of susceptibility to CMDLD, although one study suggested certain polymorphisms of IL-18 may be protective.[61–63] Continued studies on the mechanisms of CMDLD and understanding of disease susceptibility are important, given recent trends in CMDLD epidemiology.

CLINICAL FEATURES OF COAL WORKERS' LUNG DISEASES

Reflecting the diverse lung pathology associated with coal mine dust exposure, it is not surprising that the clinical presentation of the disease may be quite variable. Miners with simple CWP, perhaps detected through a screening radiograph, may deny significant respiratory symptoms. With increased dust exposures, chronic cough and sputum production are more common, regardless of the presence or absence of simple pneumoconiosis.[64] These symptoms are likely related to bronchitic changes in the large airways, including thickening of the airway wall with mucus gland enlargement and hypersecretion that result from continued inhalation of dust particles presenting a chronic burden to the mucociliary escalator.[42,65] A study by Henneberger and Attfield[66] reported symptoms of chronic bronchitis in 35% of seasoned US miners.

Emphysema has been shown to be more common in miners than nonminers, even after controlling for smoking status, and increases with increasing cumulative dust exposure.[37] As would be expected, with more severe airflow obstruction or advanced pneumoconiosis, dyspnea, cough, and sputum production are frequent. The physiologic importance of the small airway lesions from dust exposure has been debated. A pathologic label of mineral dust-related airway disease has been used to describe a lesion of pigmentation and fibrosis specific to walls of the respiratory bronchioles among workers exposed to mineral dusts.[67]

Less commonly, edema of the lower extremities, and findings consistent with cor pulmonale/pulmonary hypertension may occur.[40,41,68] An exceedingly rare but unique clinical manifestation of CMDLD is melanoptysis (expectoration of black sputum). Melanoptysis may be a very worrisome symptom for patients, but is the harmless result of excavation and liquefaction of a PMF lesion.[69]

Clubbing and crackles have not generally been considered features of coal miners' lung diseases, and if noted, should prompt further studies. However, a series of 38 cases of a chronic interstitial pneumonia among coal miners has recently been reported. The clinical findings in these atypical cases included crackles, finger clubbing, restrictive impairment, diffusion block, and neutrophilic BAL.[70] Studies have not associated CWP with an increased risk for development of coexisting mycobacterial infection, in contrast to silicosis, where the risk is well documented. However, in a minority of coal miners, the lungs show classic silicotic nodules.[71] Certainly, coal miners with progressive infiltrates or cavitary lesions in PMF should undergo thorough sputum examination for typical and atypical mycobacteria.[72]

RADIOLOGY OF COAL WORKERS' PNEUMOCONIOSIS

The diagnosis of CWP can be made with confidence based on the classic radiographic findings and the presence of an adequate history (at least 10 years) of coal mine dust exposure without the need for histological confirmation.[1] The radiographic opacities of CMDLD have been well described and are classified according to the ILO system.[17] This system includes a set of standard radiographs, which can facilitate an accurate and consistent approach to recognizing and categorizing the radiographic changes associated with dust exposure. Traditionally analog chest films were used in the classification scheme. This practice changed in 2011 to include classification of digitally acquired images on a high-resolution medical viewing system.[73] Digital systems can provide equivalent results in the recognition and classification of the pneumoconioses, when applied according to professional recommendations.[73,74] The radiograph in simple pneumoconiosis shows small pneumoconiotic opacities, ranging in size from pinhead up to 9 mm in diameter. In a study of working US coal miners with radiographic small opacities, 62% showed mainly rounded small opacities while 38% had predominantly irregular opacities.[75] Irregular opacities were more common in lower lung zones. PMF is characterized by one or more opacities in the lung fields greater than 1 cm. Complicated pneumoconiosis is more commonly seen in the upper lung zones, but is confined to the middle and/or lower zones in about one-fourth of cases.[76,77] Although there are some limitations to the use of standard posteroanterior CXR in the diagnosis of simple CWP and of PMF, standard radiographic evaluation of CMDLD remains important for diagnosis, surveillance, compensation, and disease prevention.[78]

Computed tomography (CT) scanning in coal miners may reveal parenchymal nodules and emphysema when standard radiographs are normal.[79,80] In atypical cases, CT scans may show ground-glass opacities and honeycombing, at times without nodular findings typical of CWP.[70] Radiographic evidence of bronchiectasis has also been reported in coal miners, particularly among those with CWP.[81] CT scanning is currently not recommended in the surveillance of exposed miners, but is likely of use in symptomatic miners with normal plain chest radiography or in miners where alternate diagnoses are being considered.[82] A proposed pneumoconiosis classification scheme for CT has shown good reliability, but has yet to be widely adopted.[83]

Several schemes have been used for classifying the radiographic shadows of pneumoconiosis in epidemiologic studies; currently the ILO 2011 Classification of Radiographs of the Pneumoconioses is the most widely accepted (Table 88-1).[17] When using the ILO system, simple pneumoconiosis is divided into major categories 0, 1, 2, and 3 according to the profusion of small opacities (number per unit area) in the lung fields. Each major category, including 0, is subdivided into 3 subcategories, providing a full range of 12 categories of simple CWP. A reading of category 1/0 indicates the definite presence of opacities consistent with pneumoconiosis. Complicated pneumoconiosis (PMF) is divided into categories A, B, and C, based on the size of the large opacities. The classification also permits documentations of other findings that may be associated with the shadows of simple or complicated pneumoconiosis, such as tuberculosis, cor pulmonale, collapse, consolidation, and emphysema. A system of training and examinations (http://www.cdc.gov/niosh/topics/chestradiography/breader-info.html) is available for physicians who wish to document competence in application of the ILO Classification.

TABLE 88-2 Top 10 Industries and Occupations with Significantly Elevated Proportionate Mortality Ratios for Silicosis, 26 States, 1985–1999. CDC/NIOSH National Occupational Respiratory Mortality System

Industries	Occupations
Metal mining	Miscellaneous metal and plastic-processing machine operators
Miscellaneous nonmetallic mineral and stone products	Hand molders and shapers, except jewelers
Pottery and related products	Hand molding, casting, and forming occupations
Nonmetallic mining and quarrying, except fuel	Crushing and grinding machine operators
Iron and steel foundries	Molding and casting machine operators
Structural clay products	Mining engineers
Coal mining	Mining machine operators
Miscellaneous fabricated metal products	Mining occupations, not elsewhere classified
Miscellaneous retail stores	Supervisors, extractive occupations
Blast furnaces, steelworks, rolling, and finishing mills	Construction trades, not elsewhere classified

Source: Adapted with permission from Centers for Disease Control and Prevention: Silicosis mortality, prevention, and control—United States, 1968–2002. MMWR—Morbidity Mortality Weekly Report. 2005;54(16);401–405.

The clinician may be presented with the diagnostic dilemma of distinguishing primary or metastatic lung neoplasia from an unusual presentation of PMF or Caplan syndrome. When typical large opacities of PMF occur symmetrically and bilaterally on a background of simple CWP, one can be confident that the lesions are unlikely to represent neoplastic disease. Prior radiographs from medical screening programs are often obtainable, and can help confirm stability or progression over a long time interval. Positron emission tomography with fluorodeoxyglucose (FDG-PET) scanning may be useful in differentiating PMF lesions from malignancy when the mass lesion has a low level of glucose metabolism, although some massive pneumoconiotic lesions may demonstrate an uptake of fluorodeoxyglucose similar to neoplasms.[84] On magnetic resonance imaging (MRI) with contrast enhancement, the pattern of change over time in signal intensity has been reported to be a differential criterion in this setting.[84,85] When the imaging workup is equivocal, the differentiation of PMF from neoplasm may be impossible without a biopsy. In this case, patients with CMDLD who are deemed potential candidates for therapy should undergo biopsy of the suspicious lesion. Hemorrhagic complications may occur during biopsy of PMF lesions due to their vascular nature.

■ LUNG FUNCTION AND RESPIRATORY IMPAIRMENT IN COAL MINERS

As discussed earlier, CMDLD encompasses a spectrum of diseases caused by inhalation of coal mine dust that results in several pathologic processes (simple and complicated CWP, silicosis, DDF, chronic bronchitis, mineral dust airway disease, emphysema, and dust-related airflow limitation), each of which may contribute to adverse physiologic consequences. In an individual miner, the pattern and severity of impairment found will be related to such recognized factors as the intensity and duration of respirable dust exposure, geologic factors (e.g., coal rank, silica content), residence time of dust in the lung, and exposure to other respiratory hazards (e.g., tobacco smoke).[7,8,20–27,31] In miners with airway hyperresponsiveness, greater functional deficits and an increased risk of symptoms may be expected.[86,87] Several other mining exposures may also contribute to lung function loss in coal miners, including gases from underground explosive blasting and aerosols of potentially contaminated water used for dust control.[8] Additional factors implicated in underground coal miners' accelerated lung function declines include weight gain, childhood pneumonia, and childhood environmental smoke exposures.[8]

Ventilatory Function

As CMDLD can manifest pathologically as disease of the lung parenchyma, small airways, and/or large airways, the corresponding physiologic defects appreciated on lung function testing may include obstructive, restrictive, or mixed defects.[46,88] The predominant functional abnormality in a given exposed miner will depend on the relative contribution of emphysema, airway disease, and fibrosis in the individual. Epidemiologic studies, as discussed earlier, have extensively documented the occurrence of exposure-related deficits in FEV_1 and forced vital capacity (FVC) in coal miners.[7,24–27,89,90] Although the magnitude of dust-related decline has varied between studies, an important subgroup of miners with accelerated decrements in lung function (FEV_1 decrease of >60 mL/y) has been identified. These miners were found to have more chest illnesses, respiratory symptoms, and a greater risk of death from cardiovascular or nonmalignant respiratory disease than were their cohorts with more stable lung function.[30] Airflow obstruction developing during coal mining has been associated with physiologic evidence of increased resistance to airflow in small (<2 mm internal diameter) airways, including abnormal airflow at low lung volumes and reduced density dependence of maximum expiratory flows.[46] Not surprisingly, deficits in lung function have also been documented in US surface coal miners.[15]

Gas Exchange

Diffusing capacity has been studied in relation to radiographic changes of coal worker's pneumoconiosis.[90–92] The small rounded opacities seen in miners with simple CWP have not generally been associated with measurable reductions in diffusion capacity, and large opacities of complicated CWP are not predictably associated with decreased diffusion. In contrast, miners with irregular opacities may have significant impairment in diffusion capacity, and abnormalities of gas exchange have been associated with increasing coal mine dust exposure independent of radiographic changes. Investigators have demonstrated a significant correlation between subjective measures of breathlessness and measurements of diffusion capacity, which may not be consistently observed with other pulmonary function parameters including FEV_1.[91] Gas exchange on exercise has also been investigated in coal miners.[40,41,93–95] Many reports have been based on patients referred for disability evaluations, and thus suffer from ill-defined selection biases. Exposure–response relationships are also unclear with respect to findings in these series. Exertional hypoxia, pulmonary arterial hypertension,

and excess ventilation have frequently been observed in miners, particularly those with complicated CWP or airflow obstruction.[1] However, the proportion of miners who show exertional gas exchange abnormalities in the absence of either PMF or clinically important airflow obstruction is still a topic of investigation.

SPECIAL STUDIES

BAL has been used in studying pathogenetic mechanisms in the pulmonary pathology in CWP. Rom et al.[96] reported BAL results for 15 symptomatic, nonsmoking coal miners with simple CWP. They found no significant difference between miners and controls in the number of cells recovered, the percentage distribution, and in the release of superoxide anion or hydrogen peroxide. This contrasted with the findings in subjects with asbestosis and silicosis, whose values for spontaneous release of superoxide and hydrogen peroxide were significantly higher than controls. With regard to fibronectin and alveolar macrophage–derived growth factor, the miners with CWP had values that were elevated above controls and not different from the values obtained in subjects with asbestosis and silicosis.

Wallaert et al.[44] demonstrated significantly increased total number of lung cells recovered from 25 miners with simple and complicated CWP, as well as increased percentages of alveolar macrophages, lymphocytes, and neutrophils. Alveolar cells from miners with simple and complicated CWP spontaneously released significantly more superoxide, demonstrated by chemiluminescence, than controls.

MANAGEMENT OF COAL WORKERS' LUNG DISEASES

There is no specific therapy for CMDLD. Whole lung lavage has been evaluated, but studies to date have not adequately defined the risks, benefits, and role in CMDLD management.[97] Thus, the crux of management is directed toward prevention, early recognition, and treatment of complications. The major clinical challenges are the recognition and management of airflow obstruction, respiratory infection, hypoxemia, respiratory failure, cor pulmonale, arrhythmias, and pneumothorax.

After implementation of the current mandated permissible exposure limit (PEL) of 2 milligrams per cubic meter (mg/m^3) of respirable coal mine dust and improvements in mine dust control methods, the prevalence of CMDLD appeared to have been decreasing.[14] The recent epidemiologic findings of significantly increasing prevalence and rapid progression to severe disease in CMDLD should motivate workers to assure continuous control of dust, participate in medical surveillance programs, and exercise their rights to frequent dust measurements and job transfer when necessary. Previous surveillance programs have monitored worker lung health with chest radiographs every 5 years. The current health risks for coal workers necessitate not only chest imaging but also spirometry (every 1–3 years), to provide an opportunity to protect lung health through early detection of rapid functional declines.[98] Identification of rapidly declining lung function or worsening radiographic disease should prompt strict dust controls and transfer to low dust jobs when available. These workers should also be carefully advised about the risks of further dust exposures. Mine management and workers must assure that ventilation systems, water sprays, and other dust capture devices that are mandated by federal law are operating throughout the workshift and their effectiveness is continuously monitored.

Workers presenting with respiratory symptoms should have careful evaluation. Initial history and examination should be supplemented by a chest radiograph, spirometry with bronchodilators, diffusing capacity, electrocardiogram, and resting arterial blood-gas measurement as indicated.[99] A comprehensive initial evaluation of the pulmonary system allows accurate assessment of the worker's respiratory health status, and serves as a starting point for documenting the response to therapy or progression of disease. For miners who smoke, cessation is important regardless of symptoms, radiographic abnormalities, or functional status. Physician encouragement to stop smoking should be supplemented by support from smoking cessation groups, use of nicotine replacement, pharmacologic aids, and behavior modification techniques.[99]

Symptomatic reversible airflow obstruction may benefit from treatment with inhaled and oral bronchodilators. Patients with severe obstruction and inadequate improvement from the usual measures should be considered for a monitored trial of corticosteroids. If improvement is objectively documented, continuation of inhaled and, rarely, oral steroids may be of benefit. Hypoxemia can be a serious complication in advanced pneumoconiosis. It may be present at rest, with exercise, or during sleep. Chronic hypoxemia can lead to additional complications including polycythemia, pulmonary hypertension, cor pulmonale, and cerebral dysfunction. Therapy with low-flow oxygen is indicated when arterial oxygen tension is 55 torr or less. Oxygen therapy in this setting may improve exercise tolerance, reduce dyspnea, and prevent arrhythmias, polycythemia, and heart failure.[100] Patients with functional abnormalities and/or radiographic CWP should receive appropriate immunization with influenza and pneumococcal vaccines.[101] Bacterial and viral episodes of bronchitis or pneumonia should be promptly recognized and appropriately treated.

Patients with complicated pneumoconiosis, especially those who have been exposed to silica as well as coal mine dust, deserve special attention with regard to mycobacterial infection.[72] These patients are considered at higher risk of TB than the general US population; thus a purified protein derivative test with >10 mm of induration is considered positive.[102] Patients with a history of weight loss, fever, sweats, or malaise should be promptly investigated with chest radiographs and sputum examination for acid-fast bacilli stains and cultures. Occasionally, the sputum may be negative and mycobacterial infection can only be documented by fiberoptic bronchoscopy with brushings and washings. Active tuberculosis in patients with CWP can, in general, be successfully treated with the usual drug regimens provided rifampin is one of the drugs used. However, some authorities would recommend that in coal miners with a significant history of concurrent silica exposure (such as motormen, roof bolters, drillers, and shaft development workers), the treatment regimens for tuberculosis should be more prolonged, and long-term follow-up is indicated in view of several reports of recurrent pulmonary tuberculosis in patients with PMF after completion of apparently adequate therapy.[103]

Respiratory failure may complicate advanced disease in coal miners, as it does in other chronic respiratory diseases. Ventilatory support measures are indicated when the failure is precipitated by a treatable complication. The application of ventilatory support measures should be clarified in advanced directives before the need arises.

Clinicians need to assess the contribution of occupational dust exposures to ventilatory impairments in their patients with a history of coal mine exposure. Factors that can assist in this include a careful work history with documentation of the mining region, duration and categories of coal mine employment, as well as the duration and intensity of any tobacco smoking. Factors associated with an increased risk of a clinically important dust effect are a history of prolonged exposures in dusty jobs, exposures to higher rank coals, a younger age at first employment, and the finding of radiographic changes of CWP. Physicians should assist their patients with job-related impairments in obtaining appropriate compensation through state and national programs.[104]

SILICOSIS

Silicosis is a fibrosing disease of the lungs caused by the inhalation, retention, and pulmonary reaction to crystalline silica.[105] Despite knowledge of the cause of this disorder (inhalation of

dust-containing respirable crystalline silica), this serious and potentially fatal occupational lung disease remains prevalent throughout the world.[106] Silica, or silicon dioxide, is the predominant component of the Earth's crust.[105] Occupational exposure to silica particles of respirable size (aerodynamic diameter of 0.5 to 5 μ) has classically been associated with mining, quarrying, drilling, tunneling, and abrasive blasting with quartz-containing materials (sandblasting).[107–109] Many other occupations (Table 88-1) have potential for silica exposure and development of disease.[105] Because silica sand is inexpensive, accessible, and versatile, millions of workers throughout the world are at risk of disease. Occasionally, silicosis is reported from nonoccupational environmental exposures.[110] The disease is often unrecognized and underreported, and thus its true prevalence is substantially underestimated.[106] Fatal cases of silicosis and multiple cases from the same worksite continue to be recognized.[110,111]

DEFINITION

Silicosis is an occupational lung disease attributable to the inhalation of silicon dioxide, commonly known as silica, in crystalline forms, usually as quartz, but also as other important crystalline forms of silica (i.e., cristobalite and tridymite).[112] These forms are also called "free silica" to distinguish them from the silicates. The silica content in different rock formations, such as sandstone, granite, and slate, varies from 20% to nearly 100%.

WORKERS IN HIGH-RISK OCCUPATIONS AND INDUSTRIES

Silicosis is considered the oldest occupational lung disease (alluded to by Hippocrates and Pliny), while new cases are still reported in both the developed and developing world.[113–117] Workers' respiratory health is at risk whenever the Earth's crust is disturbed, or silica-containing rock or sand is used or processed. Without adequate dust controls, silica exposures in many mechanized industrial processes can be a major cause of morbidity and mortality.[117,118] For instance, after introduction of pneumatic tools in the early 1900s, Vermont granite workers experienced "appallingly high mortality from silicosis and silicotuberculosis," which prompted the state government to enforce dust exposure limits in this industry.[119,120] The type of silica exposure appears to affect the risk of disease—processes such as drilling or sandblasting represent an increased risk of silicosis.[121,122] Even brief periods of exposure to high levels of freshly fractured silica can result in a lifetime increased risk for disease.[123,124] Silicosis frequently develops or progresses after exposures have ceased.[124] In both developed and developing nations, workers in mining, quarrying, tunneling, abrasive blasting, construction, and foundry work continue to develop silicosis.[105] Silicosis also continues to be diagnosed among workers from industries and work settings not previously recognized to offer a risk, reflecting the nearly ubiquitous presence of silica.[111,125]

FORMS OF SILICOSIS: EXPOSURE HISTORY AND CLINICOPATHOLOGIC DESCRIPTIONS

Chronic, accelerated, and acute forms of silicosis have been well characterized.[126] These clinical and pathologic expressions of the disease reflect differing exposure intensities, latency periods, and natural histories. The chronic or classic form usually follows 15 or more years of exposure to respirable dust-containing quartz.[127] Accelerated silicosis results from heavier exposures and develops more rapidly than the chronic form, often with a latency of 5 to 10 years.[127] It generally progresses inexorably even after exposure is interrupted. The acute form of silicosis is a consequence of exposures to high levels of respirable dust which contain silica.[128] The exposure period is usually from several months up to about 5 years, and the clinical course one of rapid progression.

Chronic (or classic) silicosis may be asymptomatic or result in insidiously progressive exertional dyspnea or cough (often mistakenly attributed to the aging process).[113,126] Radiographs show small (<10 mm) rounded opacities predominantly in the upper lung zones.[17,84] The pathologic hallmark in the lungs of patients with the chronic form is the silicotic nodule. The lesion is characterized by a cell-free central area of concentrically arranged, whorled hyalinized collagen fibers, surrounded by cellular connective tissue with reticulin fibers (Fig. 88-4).[129] When examined under polarized light, the silicotic nodule shows birefringent particles, most

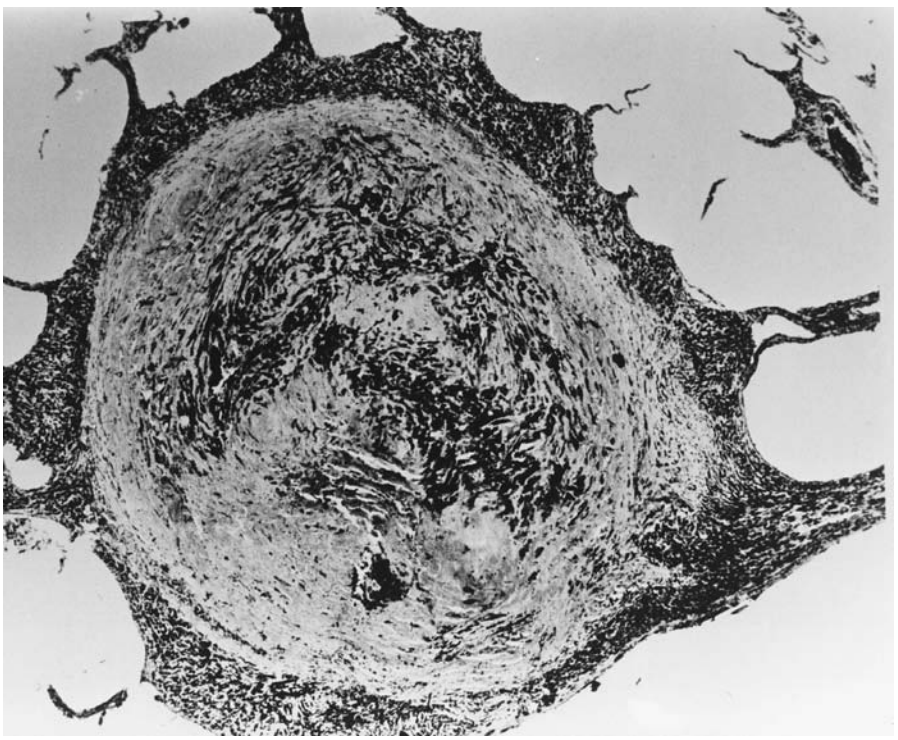


Figure 88-4 Lung pathology showing a classic silicotic nodule. (See text for description.) *(Used with permission of Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

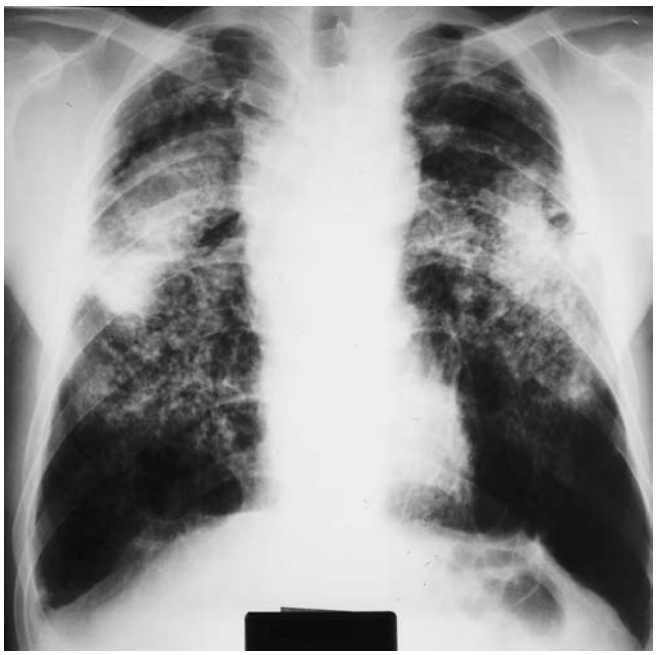


Figure 88-5 Radiographic changes of progressive massive fibrosis in a worker with complicated silicosis.

prominent in the periphery.[130] Electron microscopy using specialized techniques can identify the specific mineral content of the particles, but is rarely needed for routine diagnostic purposes.[131] Silicotic nodules in the visceral pleura, regional lymph nodes, and occasionally in other organs, may also result from exposure.[132] The small lung nodules of chronic silicosis may coalesce and result in larger shadows on the chest radiograph (>10 mm), heralding the onset of complicated or conglomerate silicosis (often referred to as PMF) (Fig. 88-5).[17,133] This progressive illness may begin after dust exposure has ceased.[134]

PMF is frequently associated with a clinically important compromise of lung structure and function, and as a consequence, symptoms of exertional dyspnea and reduced functional status.[135,136] Common laboratory findings include a diminished carbon monoxide diffusing capacity, reduced arterial oxygen tension at rest or with exercise, and classically a restrictive pattern on spirometry and lung volume measurement.[105,137,138] Concomitant dust-induced bronchitis or distortion of the bronchial tree may also result in productive cough and multiple studies have now confirmed the presence of airflow obstruction in many patients with silica exposure with or without radiographic silicosis.[137–140] Recurrent bacterial infections may occur.[141] Weight loss and cavitation of the large opacities may herald tuberculosis or other mycobacterial infection.[105] Pneumothorax may be a life-threatening complication, since the lung may be difficult to reexpand.[142] Hypoxemic respiratory failure, cor pulmonale, and congestive heart failure are common late findings.

Accelerated silicosis results from exposures that are more intense and of shorter (5–10 years) duration than in the chronic form, while symptoms, radiographic findings, physiologic measurements, and lung pathology are similar.[143] Deterioration in lung function is more rapid, and mycobacterial infection more common. Findings consistent with autoimmune diseases, including scleroderma, rheumatoid arthritis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, autoimmune hemolytic anemia, dermatopolymyositis, or systemic lupus, may be seen in association with silicosis, more often in the accelerated type.[144–147] The progression of radiographic abnormalities and functional impairment can be very rapid when autoimmune disease occurs with silicosis.[141]

Acute silicosis develops within a few months up to about 5 years after a massive inhalation of silica.[145] Dramatic dyspnea, weakness, and weight loss are often presenting symptoms.[143] Unlike chronic forms of silicosis, chest radiographs show diffuse alveolar filling, with a lower lung zone predominance.[148,149] Air bronchograms may be present. Histology resembles pulmonary alveolar proteinosis, with occasional extrapulmonary (renal and hepatic) abnormalities.[145,150–152] The usual clinical course is rapid progression to severe hypoxemic respiratory failure and death.

Tuberculosis may complicate silica exposure alone, and all forms of silicosis, but risk is greatest with acute and accelerated disease.[153,154] Both tuberculosis and nontuberculous (atypical) mycobacterial infections are seen.[127,155]

Even in the absence of radiographic silicosis, silica-exposed workers may also develop other diseases associated with occupational dust exposure, such as chronic bronchitis and the associated emphysema. Progressive declines in lung function have been documented in workers from inhalation of silica and other occupational mineral dust exposures.[139]

PATHOGENESIS AND THE ASSOCIATION WITH TUBERCULOSIS

The precise mechanism of silica toxicity is uncertain, but it is thought to be mediated by generation of reactive oxygen species, both by the surface of silica particles themselves and by activation of alveolar macrophages.[122,156–158] Disease risk is related to the intensity and duration of the exposure; however, there is growing evidence that freshly fractured silica is more toxic than aged silica-containing dusts, perhaps related to reactive groups on the surface cleavage plane.[159] An abundance of evidence implicates the interaction between the pulmonary alveolar macrophage and silica particles deposited in the lung. Release of chemotactic factors (particularly the IL-1 signaling pathway) and inflammatory mediators, such as tumor necrosis factor, result in recruitment of polymorphonuclear leukocytes, lymphocytes, and additional macrophages.[105,112,160,161] The result of this cascade is chronic lung inflammation and eventually fibrosis. The central acellular zone of the silicotic nodule is surrounded by whorls of collagen and fibroblasts, and an active peripheral zone composed of macrophages, fibroblasts, plasma cells, and silica particles (Fig. 88-5).[145] Silica induces macrophage apoptosis, allowing the phagocytosed silica particle to be reintroduced into lung tissues and generate another cycle of phagocytosis and inflammation.[112,162] A large number of mediators have been implicated in the ongoing inflammation and fibrosis associated with silica exposure. These include IL-1B, TNF-α, TGF-β, fibronectin, and a family of inflammatory cytokines known as chemokines.[163–169] A recent study by Sellamuthu et al.[169] investigated mechanisms of crystalline silica–induced pulmonary toxicity by evaluating global gene expression in a human alveolar basal carcinoma epithelial cell line. Their results confirmed the involvement of previously identified molecular targets involved in silica toxicity, but also identified novel molecular pathways likely involved in toxicity. Upregulation of genes that encode for inflammatory cytokines/chemokines that function as chemoattractants, recruit inflammatory cells, especially PMNs, into the lungs, appear to provide mechanisms for propagation and acceleration of initial silica-induced tissue damage.

In acute silicosis, in contrast to the chronic forms, the alveolar space is filled with amorphous lipoproteinaceous material that stains with periodic acid-Schiff (PAS) regent,[151,152] possibly related to abnormal handling and accumulation of pulmonary surfactant.[170–172]

As mentioned earlier among coal miners, DDF has been described in pathologic terms as a bridging fibrosis connecting various lesions of silicosis. This interstitial fibrosis appears to be a unique response in some silica-exposed individuals and is not thought to represent the concurrent development of UIP.

Immune system dysfunction is well described in association with silicosis, including increased prevalence of circulating immune complexes as well as increased production of serum autoantibodies, such as antinuclear antibody and RF.[173,174] The susceptibility of silicotic workers to infections, including tuberculosis and Nocardia asteroides, is likely related to the toxic effect of silica on pulmonary macrophages.[141,175] Thus, silica appears to activate humoral immunity (in a dysregulated manner), while impairing cell-mediated immunity.

Chen et al.[176] studied three cohorts of miners in different industries all with silica exposure. These researchers observed differences in the exposure-related risk of silicosis across the three cohorts. This epidemiologic finding lends support to the basic science literature suggesting that silica dust characteristics, in addition to cumulative respirable silica dust exposure, may affect the risk of silicosis.

CLINICAL PICTURE OF SILICOSIS

When silicosis is symptomatic, the primary symptom is usually dyspnea, first noted with activity or exercise and later, also at rest. However, in the absence of other respiratory disease, shortness of breath may be absent and the presentation may be an asymptomatic worker with an abnormal chest radiograph. The radiograph may at times show quite advanced disease with only minimal symptoms. The appearance or progression of dyspnea may herald the development of complications including tuberculosis, airway obstruction, PMF, or cor pulmonale. Productive cough is often present, secondary to chronic bronchitis from occupational dust exposure, tobacco use, or both. Cough may at times also be attributed to pressure on the trachea or mainstem bronchi from large masses of silicotic lymph nodes.

Other chest symptoms are less common. Hemoptysis is rare and should raise concern for complicating disorders, such as pulmonary neoplasms or mycobacterial infection. Wheeze and chest tightness may occur in silicosis, but usually associated with bronchitis or airflow obstruction. Chest pain and finger clubbing are not typically features of silicosis. Systemic symptoms, such as fever and weight loss, suggest complicating infection or neoplastic disease. Advanced forms of silicosis are associated with progressive respiratory failure with or without cor pulmonale. Few physical signs may be noted unless complications are present; inspiratory crackles are often absent.

RADIOGRAPHIC PATTERNS IN SILICOSIS

The earliest radiographic signs of uncomplicated silicosis are generally small, rounded opacities. These can be categorized using the ILO International Classification of Radiographs of Pneumoconioses by size, shape, and profusion category.[17] In silicosis, rounded opacities of the "q" and "r" type dominate (see Table 88-1 above). Other patterns have also been described, including linear or irregular shadows. The opacities seen on the radiograph represent the summation of pathologic silicotic nodules and associated changes. They are usually found to predominate initially in the upper lung zones and may progress to involve other zones.[84] Hilar lymphadenopathy is also noted, sometimes before nodular parenchymal shadows.[84] Eggshell calcification of the lymph nodes is strongly suggestive of silicosis in the appropriate clinical context, although this feature is uncommon.[177] The development of PMF is indicated by large radiographic opacities, which are categorized by size as A, B, or C (see Table 88-1), using the ILO classification.[17] PMF lesions tend to contract to the upper lung zones, leaving areas of compensatory emphysema at their margins and in the lung bases.[84] The contraction process causes small pneumoconiotic opacities that previously were evident on the radiograph to become less visible or at times disappear. Pleural abnormalities are occasionally observed on routine chest radiographs with silicosis; however, CT scanning often documents localized pleural thickening, particularly in association with conglomerate lesions.[178] Pleural effusions are less frequently noted. The radiographic distinction between large pneumoconiotic lesions and lung malignancies may be difficult, particularly if no earlier radiographs are available. As in complicated CWP, FDG-PET scanning may sometimes be helpful in this distinction, but false positives occur.[179–181] Cavitation or a rapid change in the radiographic appearance of a large silicotic lesion may be due to ischemic necrosis, but should always prompt a vigorous search for mycobacterial disease. Acute silicosis may present with an alveolar filling pattern and rapid development of complicated mass lesions.[148]

LUNG FUNCTIONAL ABNORMALITIES IN SILICOSIS

Pulmonary function tests, including spirometry and diffusing capacity, are helpful in the clinical evaluation of individuals with suspected silicosis. Spirometry may also be of value in early recognition of the health effects from occupational dust exposures, as it may detect physiologic abnormalities that may precede radiographic changes.[182] No specific or characteristic pattern of ventilatory impairment is present in silicosis. Spirometry may be normal, or when abnormal, the tracings may show obstruction, restriction, or a mixed pattern.[182] Numerous studies have investigated the impact of silica dust exposure and lung function.[182–185] These data suggest that obstruction may indeed be the more common finding. Silica and mixed dust exposures may lead to clinically important airflow limitation independent of radiographic abnormality; however there is some evidence that lung function deficits are more associated with silica-related emphysema than nodularity on imaging.[135] Functional changes tend to be more marked with advanced radiologic categories.[135] However, no good correlation exists between radiographic abnormalities and ventilatory impairment, and workers experience lung function loss proportionate to the duration and intensity of silica dust exposure.[137] Diffusing impairment may also occur in the absence of ventilatory impairment. In acute and accelerated silicosis, functional changes generally occur earlier, are more marked, and progress more rapidly.[149,186–188] In acute silicosis, radiographic progression is accompanied by increasing ventilatory impairment and gas exchange abnormalities, which leads to respiratory failure and eventually to death from intractable hypoxemia.[141]

COMPLICATIONS AND SPECIAL DIAGNOSTIC ISSUES IN SILICOSIS

With a history of sufficient exposure and a characteristic radiograph, the diagnosis of silicosis is generally not difficult to establish. Challenges arise when the radiologic features are unusual or the history of exposure is not recognized. Lung biopsy is rarely required to establish the diagnosis. However, tissue samples may be helpful in some clinical settings when complications are present or the differential diagnosis includes tuberculosis, neoplasm, or PMF. Biopsy material should be sent for culture, and in research settings, dust analysis may be a useful additional measure. When tissue is required, open or thoracoscopic lung biopsies are generally necessary for adequate material for examination, to assure satisfactory hemostasis, and due to concern about life-threatening pneumothorax in the fibrotic lung.[189] Some evidence suggests BAL and transbronchial biopsy may be of diagnostic aid in some cases where the diagnosis of silicosis is not straight forward.[189]

Vigilance for infectious complications, especially tuberculosis and other mycobacteria, cannot be overemphasized. Any fever, weight loss, worsening symptoms, or radiographic changes should trigger a workup to exclude this treatable problem. In acute silicosis, Nocardia and fungal infections must be considered.[141]

In 1997, the International Agency for Research on Cancer (IARC) reclassified crystalline silica as a Group I carcinogen. This new designation indicates IARC found "sufficient data" to determine

that crystalline silica in the form of quartz or cristobalite dust is carcinogenic to humans.[190] Uncertainty remains over the pathogenic mechanisms for the development of lung cancer in silica-exposed populations, and the relationship between silicosis (or lung fibrosis) and cancer continues to be studied. IARC noted that a link to carcinogenicity was not detected in every type of industrial exposure, and may be related to an interaction between the silica dust and other environmental factors.[190] Regardless of the mechanism, there is ample evidence confirming a causal link between occupational exposure to silica and lung cancer.

A relationship between renal complications and silica exposure has been suspected since the early 20th century.[191] A 2002 study reported a 5.1% excess risk of end-stage renal disease (ESRD) and a 1.8% excess risk of death from kidney disease in individuals exposed to silica.[192] Glomerulonephritis and nephrotic syndrome have been described in association with silica exposure.[144,193–195] The specific mechanism(s) of renal injury is not completely understood, but evidence suggests injury may occur by both direct (silica particulate in the kidney) and indirect insults (immunologic injury by immune complex formation).[144,195]

Several autoimmune diseases are clearly linked with silica dust exposure.[196,200] Perhaps the most well known of these is scleroderma, first reported in the 1910s and subsequently described by Erasmus (sometimes referred to as Erasmus syndrome) in 1957 from investigations into South African gold miners.[197,198] A study analyzing the prevalence of connective tissue disease in silicosis between 1985 to 2006 reported a 24-fold risk of developing scleroderma among silicotics compared to the general population.[144] This study also found two- to eightfold risks for rheumatoid arthritis and systemic lupus erythematosus, as well as a striking increased prevalence of ANCA-associated vasculitis. A Finnish study also suggested a strong association between silica exposure and rheumatoid arthritis.[199] An earlier NIOSH review of the health implications of silica exposure cited the most commonly associated autoimmune diseases to be scleroderma, systemic lupus erythematosus (lupus), rheumatoid arthritis, autoimmune hemolytic anemia, and dermatomyositis or dermatopolymyositis.[143]

PREVENTION OF SILICOSIS

Prevention remains the principal goal in dealing with this occupational lung disease. Despite the current OSHA PEL for respirable crystalline silica of 100 $\mu g/m^3$ as an 8-hour time-weighted average, silica-exposed workers continue to develop disease.[200,201] NIOSH since 1974 has recommended the PEL be reduced to 50 $\mu g/m^3$ as a time-weighted average for up to 10 hours/d.[200] Effective exposure controls are available for most processes, and include process enclosure, wet abrasive techniques, and local exhaust ventilation, combined with a comprehensive approach to personal protection. Where possible, less hazardous agents should be substituted for silica. Unfortunately, noncompliance with the current permissive exposure limit appears common in many work environments.[202,203] Both employers and workers must remain vigilant regarding the hazards of silica dust exposure and control measures.

If silicosis is recognized in a worker, termination of any continuing exposures is advisable. Unfortunately, the disease often will progress even without further silica exposure. The finding of a case of silicosis is a "sentinel health event" and should prompt a thorough evaluation of workplace exposures and control measures by a competent authority, with the goal of recognizing the sources of the hazard and protecting other workers who may continue to be at risk.

MEDICAL SCREENING AND SURVEILLANCE IN SILICOSIS

Workers exposed to silica and other mineral dusts should be monitored on a regular basis for adverse health effects as a supplement to, but not a substitute for, exposure monitoring and control. Health screening commonly includes periodic evaluation of respiratory symptoms, spirometric abnormalities, and radiographic changes. There is evidence that, if silicosis subsequently develops, workers who have participated in periodic health monitoring experience reduced severity of disease.[204] Evaluation for tuberculosis infection should also be performed. Historically, this was done using intradermal skin testing, although new diagnostic techniques useful in the screening and diagnosis of TB termed interferon gamma release assays (IGRAs) have come to market. While not specifically studied in the silica-exposed population, studies in general populations suggest equal if not great specificity and sensitivity in comparison to standard dermal screening for TB. The advantages offered by these tests include: (1) no interference with the BCG vaccine, (2) subjective interpretation is avoided, (3) a second appointment for reading the results is avoided, (4) the test incorporates a positive control that provides valuable information for interpreting an apparently negative test as either a true negative or indeterminate as a result of technical errors or immunosuppression.[205] In addition to reporting of health surveillance results to the individual workers, health data from all workers at a plant or operation should be periodically analyzed (e.g., every 1–3 years) to assess the adequacy of prevention activities.

THERAPY, MANAGEMENT OF COMPLICATIONS, AND CONTROL OF SILICOSIS

When prevention has been unsuccessful and silicosis has developed, therapy is directed largely at detecting and treating complications. Therapeutic measures are similar to those commonly used in the management of airflow obstruction, infection, pneumothorax, hypoxemia, and respiratory failure complicating other pulmonary disease. Historically, there have been a number of unsuccessful attempts to find a drug treatment that can reverse silicosis.[206,207] Whole lung lavage has been attempted with the hope of removing dust, inflammatory cells, and other mediators to potentially ameliorate disease progression.[97] Currently, there are no data to confirm that this or any other therapy alters the natural progression of human silicosis. Because of the high prevalence of disease in some countries, investigations of combinations of drugs and other interventions continue.

For workers with a diagnosis of silicosis, further exposure to silica-containing dusts is undesirable. If the disease is advanced, or has occurred after a relatively short exposure (i.e., <15 years), then further dust exposure should be assiduously avoided. Advice on job reassignment should be considered in the context of the worker's age, symptoms, functional status, and the current working conditions and measured silica exposures. Patients with silicosis may have few symptoms or findings early in the disease; however, physicians should be aware that many states have a strict time limit, dating from the physician's recognition of findings of silicosis, regarding application for workers' compensation and reimbursement of medical costs.

In the medical management of silicosis, vigilance for complicating infection, especially tuberculosis, is critical. The use of bacillus Calmette-Guérin (BCG) vaccine in the tuberculin-negative silicotic patient is not recommended, but the use of preventive isoniazid (INH) therapy in the tuberculin-positive silicotic patient is advised.[208] The diagnosis of active tuberculosis infection in patients with silicosis can be difficult. Clinical symptoms of weight loss, fever, sweats, and malaise should prompt radiographic evaluation and sputum acid-fast bacilli stains and cultures.[209] Radiographic changes with infection may be subtle and atypical. Enlargement or cavitation in conglomerate lesions or nodular opacities is of particular concern. Bacteriologic studies on expectorated sputum are indicated, but may not be reliable in silicotuberculosis because expectoration may produce only scant numbers of active organisms. Fiberoptic bronchoscopy for additional specimens for culture and

study may be helpful in establishing a diagnosis of active disease. The use of multidrug therapy for suspected active disease is justified at a lower level of suspicion in silicotics, compared to the non-silicotic patient, due to the difficulty in firmly establishing evidence for active infection. To obtain satisfactory results in the presence of silicosis, antituberculous treatment must be more prolonged, with regimens lasting at least 8 months.[103] A multiplicative increase in risk of mycobacterial infection is associated with the combination of silicosis and human immunodeficiency virus (HIV) infection, as has been encountered in South African gold miners.[210] Coinfection with HIV and tuberculosis may also have an adverse impact on progression of silicosis and lung function decline.[211] These infections represent major clinical and public health challenges.[212] Prolonged treatment is essential, and there is potential for both adverse drug reactions and interactions between antiretroviral and antituberculous therapy. Recommended approaches continue to evolve, and clinicians should consult the latest authoritative recommendations.

Ventilatory support for respiratory failure may be indicated when precipitated by a treatable complication. Pneumothorax, spontaneous and ventilator related, is usually treated by chest tube insertion. Bronchopleural fistula may develop, and surgical consultation and management should be considered.

Acute silicosis may rapidly progress to respiratory failure. When this disease resembles pulmonary alveolar proteinosis and severe hypoxemia is present, aggressive therapy has included massive whole lung lavage with the patient under general anesthesia in an attempt to improve gas exchange and remove alveolar debris. Although appealing in concept, the efficacy of whole lung lavage has not been established.[213] Glucocorticoid therapy has also been used for acute silicosis; however, it is also of unproven benefit.[214,215]

Some younger patients with end-stage silicosis may be considered candidates for lung or heart–lung transplantation by centers experienced with this expensive and high-risk procedure.[216] Early referral and evaluation for this intervention may be offered to selected patients.

The discussion of an aggressive and high-technology therapeutic intervention such as transplantation serves to dramatically underscore the serious and potentially fatal nature of silicosis, as well as emphasize the crucial role for primary prevention. The control of silicosis ultimately depends upon the control of workplace dust exposures. This is accomplished by rigorous and conscientious application of fundamental occupational hygiene and engineering principles, with a commitment to the preservation of worker health.

PREVENTION STRATEGIES FOR COAL WORKERS' LUNG DISEASES AND SILICOSIS

The control of coal workers' lung diseases and silicosis in both the developed and developing world requires comprehensive prevention strategies, including exposure control, medical surveillance, research, and education. Example approaches include the following:

- Major efforts must be directed to installation of effective engineering controls and improvements in work practices to progressively reduce dust exposures to recommended levels. These efforts are labeled primary prevention. In selected situations, personal respiratory protection can also play a role, particularly during short-term operations or unusual/emergency conditions, and while engineering controls are being modified or improved. The use of respirators will only be effective when part of a professionally managed comprehensive respiratory protection program, and should never be relied upon outside of such a program.
- Primary prevention should involve ongoing dust exposure monitoring, and include mechanisms for feedback to modify and improve working conditions if exposures are measured above recommended levels. Even exposure at currently permissible levels has been recognized to represent a risk of disease.
- Secondary prevention through medical screening and surveillance should be designed to benefit the individual worker and other potentially exposed workers. Illness identified through medical screening represents a failure of primary prevention, and thus should trigger feedback to those responsible for environmental monitoring, exposure controls, and work practice evaluations.
- Education about the respiratory health hazards from uncontrolled exposures to silica and coal mine dust must be available to workers, employers, managers, and healthcare providers.
- Information on the cumulative burden of disease should be monitored over time for both silica and coal mine dust.
- Research into mining-related lung diseases should be encouraged, to improve recognition, monitoring, exposure reduction, and therapy, and to increase understanding of pathogenesis. Research efforts should supplement, not displace, attention to dust control.
- Clinicians who recognize coal-related diseases or silicosis in their patients should attempt to determine whether ongoing workplace exposures present a continuing risk to current workers, while maintaining the confidentiality of the patient–physician relationship. Assistance in this can often be obtained through local or state health departments, occupational medicine groups, and federal agencies. Reporting of occupational diseases is required in many states.

CONCLUSIONS

Although much is known about the causes, pathogenesis, natural history, and prevention of dust-related respiratory diseases, the pneumoconioses remain important causes of morbidity and mortality in the United States and throughout the world. Healthcare providers need to maintain medical vigilance and familiarity with the clinical features and management of these disorders, especially those whose clinical practice includes persons with significant mining or industrial employment. When patients are exposed to occupational lung hazards, they should be provided effective workplace protections, respiratory health monitoring, timely and accurate recognition and management of dust diseases and their complications, and referrals for public health evaluations and equitable compensation whenever appropriate.

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CHAPTER 89

Occupational Asthma, Byssinosis, and Industrial Bronchitis

J. Allen D. Cooper

Inhalation of dusts, fumes, and organic substances at the workplace can cause a number of pulmonary syndromes.[1–4] The lung parenchyma and airways, as well as the pleura, can be affected by inhalation of foreign substances. This chapter discusses reactions of the large airways to inhalation of toxic substances present in the workplace. Lung parenchymal and pleural reactions, as well as obliterative bronchiolitis in response to inhaled materials, are discussed elsewhere in this text. Occupational airway disease can manifest itself as chronic bronchitis with variable airway hyperreactivity (industrial bronchitis or asthma-like syndrome), or with asthma accompanied by persistent hyperreactivity of the airways (occupational asthma). Some occupational exposures can cause both industrial bronchitis and asthma whereas others cause only one or the other. Cotton dust is the most common cause of industrial bronchitis without occupational asthma. Grain dust can cause both industrial bronchitis and asthma. In this chapter, general and specific issues regarding industrial bronchitis and occupational asthma are discussed.

INDUSTRIAL BRONCHITIS

Two important causes of industrial bronchitis - byssinosis and grain dust exposure - are discussed below.

BYSSINOSIS

Adverse pulmonary reactions in cotton workers have been recognized for more than 100 years. In 1831, Kay[5] described chest tightness and fever that commonly occurred on Monday after workers had been off work over the weekend. It was because of this observation that the term *Monday morning fever* was coined. The term *byssinosis* was proposed by the French physician Proust[6] and is derived from the Greek word meaning linen or fine flax. Over the years, as cotton mills appeared in more and more countries, the association of chronic bronchitis with cotton dust exposure was confirmed.

Epidemiology

There is no doubt that recurrent exposure to cotton dust causes acute and chronic bronchitis. In a prospective study, 16% of cotton mill workers in South Carolina developed symptoms of chronic bronchitis,[7] as compared to only 1% of appropriate controls in the region. A very recent study[8] of textile workers in Pakistan confirmed this finding; 16.7% of workers complained of frequent cough and 26.6% of workers had frequent phlegm production. Another recent study of cotton textile workers in China[9] found that the frequency of symptoms of byssinosis increased from 7.6% at baseline to 15.3% after 15 years of working in the textile mill. In this latter study, airway flow rates decreased significantly over time in textile workers when compared to silk workers. The appearance of symptoms during work or worsening of pulmonary function tests during the work shift predicted this accelerated loss of pulmonary function. The association between the length of time working in a textile mill and the onset of symptoms was also confirmed in the study from Pakistan.

Overall textile employment has dropped over the past few years but there are still over 200,000 employed in this industry in the United States.[10] These individuals are at risk for the developing symptoms due to inhalation of cotton dust. Flax and hemp workers are also at risk for developing the disease. Clinical studies suggest that approximately 65% of the general population will react significantly to de novo inhalation of components of cotton dust. Therefore, the majority of individuals who begin employment that entails the processing of cotton, flax, or hemp are at risk for developing respiratory symptoms. Why some individuals are more susceptible than others to the respiratory effects of cotton dust is unclear.

Certain jobs in the textile mill are associated with a higher risk for the development of bronchitis. Ginning, opening, or carding work carries a higher degree of risk. In addition, workers who clean out or maintain the various machines that divide up and clean the cotton are especially prone to developing symptoms. These are particularly high-risk jobs because of the high levels of cotton dust generated during the cleaning procedures. Strippers and grinders, who maintain the carding machinery that cleans and aligns the cotton, are also at risk for the development of symptoms. Indeed, in the past, byssinosis was called "strippers' asthma." In the recent study out of Pakistan, the job of spinning carried a higher risk for the development of respiratory symptoms than weaving.[8]

Clinical Presentation, Risk Factors, and Stages of Byssinosis

Shortness of breath often occurs on the day back to work at the textile mill after several days off, such as on a Monday after being off over the weekend. Overtime workers can develop more persistent symptoms. Schilling[11] has graded byssinosis (Table 89-1) to allow comparison of symptomatology with physiological parameters. Using this grading system, it has been established that workers with a higher grade of symptoms tend to have a more rapid decline in pulmonary function. Risk factors for developing higher grades of byssinosis include length of employment in a cotton mill and level of cotton dust exposure. Tobacco smoking has been shown to be synergistic with exposure to cotton dust in producing chronic bronchitis. There is evidence that exposure to cotton dust without cigarette smoking causes chronic pulmonary disability, approximately 7% of exposed individuals will develop irreversible airway obstruction that cannot be explained by smoking.[10] The degree of decrease in flow rates in function tests before and after work predicts chronic effects.[9]

Pulmonary Function Test Abnormalities

Characteristically,[10] byssinosis is associated with a reduction in the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) on the day of return to work after an absence. The degree of reduction in these parameters increases over the workday. This change is generally more severe on the first day of work after an absence and attenuates on subsequent continuous workdays. The

TABLE 89-1 Clinical Grading of Byssinosis as Proposed by Schilling

Grade 0	No symptoms on first day of work
Grade 1/2	Occasional chest tightness or irritation of respiratory tract on the first workday of week
Grade 1	Chest tightness on every first day of work week
Grade 2	Chest tightness on first and other days of work week
Grade 3	Chest tightness on first and other days of work week and physiological evidence of permanent disability

TABLE 89-2 Evidence that Bacterial Endotoxin is the Causative Agent in Byssinosis

1. Measurable levels of endotoxin can be detected in cotton dust.
2. Inhaled endotoxin can induce airway inflammation in animals and humans.
3. In a controlled setting, ambient levels of endotoxin correlate with degree of airflow reduction occurring in a simulated carding room.
4. Repeated inhalation of endotoxin results in an attenuation of the airway response similar to that noted in patients with byssinosis.
5. Measures that reduce levels of ambient endotoxin reduce the incidence of byssinosis.

mechanism by which this developed tolerance occurs is unknown although there are studies demonstrating that the inflammatory effects of endotoxin, the purported causative agent of byssinosis, attenuate with repeat exposure.

Pathology and Pathogenesis of Byssinosis

The histopathology of byssinosis[12] is similar to that of the bronchitis that is induced by tobacco smoke—with hyperplasia of mucus glands and infiltration of the bronchi with polymorphonuclear neutrophils. Several animal studies have demonstrated that different components of cotton dust can recruit neutrophils into bronchi. In addition, components of cotton dust can also stimulate resident pulmonary cells, such as mast cells and macrophages, to release molecules that attract neutrophils.

There is now a large amount of information that points to a lipopolysaccharide (endotoxin) produced by bacterial contaminants of cotton as the causative agent of byssinosis. The evidence for this is listed in Table 89-2. The most compelling study that examines this issue was presented by Castellan et al.,[13] who demonstrated that ambient concentrations of endotoxin in a simulated carding room correlated with reduction in airway flow rates in a time frame similar to that which occurs after exposure to cotton dust in the workplace. An interesting related finding is that byssinosis is less prevalent in Australia, probably because of the lower level of endotoxin in cotton grown in this drier climate.[10] The acquired tolerance during the work week displayed by patients with byssinosis can be simulated by administration of multiple aerosols of endotoxin in animals.[10,13]

Treatment and Prevention

The most important interventions for byssinosis are removal of the symptomatic individual from the offending work environment and reduction in cotton dust as a preventative measure.[10] Screening pulmonary function testing at the workplace is important to identify susceptible individuals who exhibit airflow abnormalities. In addition, since the 1970s, measures have been taken in developed countries to control cotton dust levels in textile mills. One measure has been to steam-clean cotton while it is still in the bale. In 1970, Burlington Industries began a program for dust control and annual medical surveillance. With this program, the incidence of symptoms of byssinosis dropped from 4.5% in 1970 to 0.6% in 1979. In addition, the number of employees who had a significant decrease in FEV_1 over the work shift decreased from 18% in 1971 to 3.5% in 1979. Similar measures have been taken in other textile plants, with good success in controlling byssinosis. Unfortunately these measures have not been implemented worldwide, and there remains a significant prevalence of byssinosis outside of the United States.

GRAIN DUST–INDUCED INDUSTRIAL BRONCHITIS

Exposure to grain dust can also result in the development of chronic bronchitis.[14] This can occur in conjunction with development of organic dust toxic syndrome, a term recently proposed to describe a noninfectious febrile illness associated with chills, malaise, myalgia, dry cough, dyspnea, headache, and nausea that occurs after organic dust exposure. Not only grain workers, but farmers are susceptible to development of this syndrome. Between 4% and 11% of grain workers show a reduction in FEV_1 of 10% or greater over the work shift. This reduction in flow rates is directly related to the amount of dust in the air. Studies have suggested that the component of grain dust responsible for causing airway symptoms is also endotoxin, the apparent active component of cotton dust. Grain dust extract, possibly its endotoxin contaminant, can activate complement, and this may be a mechanism by which grain dust induces inflammation in bronchi. However, in contrast to cotton dust, grain dust can, in sensitive individuals, also precipitate an acute drop in airway flow rates[14] rather than the slow reduction in flow rates similar to that precipitated by cotton dust. This finding suggests that airway reactions to grain dust may be heterogeneous. Grain dust also tends to produce skin abnormalities in affected individuals, in contrast to cotton dust, which generally does not cause skin reactions.[14]

OCCUPATIONAL ASTHMA

Below are considered the definition of occupational asthma, its risk factors, clinical presentation, mechanisms, diagnosis, and management. In addition, multiple specific examples of occupational asthma are discussed.

DEFINITION AND LIST OF OFFENDING AGENTS

Occupational asthma is characterized by variable airway obstruction resulting from exposure to ambient dusts, vapors, gases, or fumes incidentally present at a workplace.[15] Bronchial hyperresponsiveness to nonspecific agents, such as methacholine or histamine, is usually present in these patients. An important differentiation is between the true occupational asthma caused de novo by the offending agent and underlying asthma exacerbated by the offending agent (work exacerbated asthma [WEA]). The 1995 American College of Chest Physicians (ACCP)[4] consensus statement for the diagnosis of occupational asthma includes several criteria that can be used for the definitive or probable diagnosis of the disease (Table 89-3). A more recent (2007)[16] consensus statement further defines steps in

TABLE 89-3 ACCP Case Definition of Occupational Asthma

A. Physician diagnosis of asthma
B. Onset of asthma after entering workplace
C. Association between symptoms of asthma and work
D. One of the following:
1. Workplace exposure to agent known to cause occupational asthma
2. Work-related changes in FEV_1 or PEF
3. Work-related changes in bronchial responsiveness
4. Positive response to specific inhalation challenge test
5. Onset of asthma with a clear association with a symptomatic exposure to an inhaled irritant agent in the workplace
Definite occupational asthma requires A, B, C, and D(2) or D(3) or D(4) or D(5)
Likely occupational asthma requires A, B, C, and D(1)

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow.

TABLE 89-4 ACCP Consensus Statement Regarding Diagnosis and Management of Work-Related Asthma

1.	In all individuals with new-onset or worsening asthma, take a history to screen for work-related asthma (WRA), occupational asthma (OA), and work-exacerbated asthma (WEA).
2.	Obtain a history of job duties, exposures, industry, use of protective devices/equipment, and the presence of respiratory disease in coworkers; and consult material safety data sheets (MSDS) that list many recognized hazardous agents. Document the onset and timing of symptoms, medication use, and lung function, and their temporal relationship to periods at and away from work.
3.	Perform additional objective tests when feasible (e.g., serial peak-flow recordings, serial methacholine challenges, immunologic assessments, induced sputum testing, and SICs) to improve the diagnostic probability.
4.	In individuals with suspected WRA who are currently working at the job in question, record serial measurements of peak flow as part of the diagnostic evaluation and ask the patient to record these optimally a minimum of four times daily, for at least 2 wk at work and 2 wk off work.
5.	In individuals with OA, working at the job in question, perform a methacholine challenge test or obtain comparable measurements of nonspecific airway responsiveness during a working period, and repeat it during a period (optimally, at least 2 wk) away from the work exposure to identify work-related changes.
6.	In individuals with OA, perform immunologic tests (skin prick testing or in vitro specific IgE assays) to identify sensitization to specific work allergens when these tests are technically reliable and available.
7.	For all individuals with WRA, attempt better control of exposures. Remove patients from further exposure to the causative agent in addition to providing other asthma management.
8.	For workers who are potentially exposed to sensitizers or uncontrolled levels of irritants, the panel advises primary prevention through the control of exposures (e.g., elimination, substitution, process modification, respirator use, and engineering control).
9.	An individual diagnosis of OA represents a potential sentinel health event. Evaluate the workplace to identify and prevent other cases of OA.

Source: Data from Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. Chest. 2008;134(3 Suppl);1S–41S.

diagnosis and management of work-related asthma (occupational asthma and work exacerbated asthma) (Table 89-4).

Several hundred agents[17] have been reported to cause occupational asthma. Agents that have been associated with induction of occupational asthma can be conveniently grouped into categories of high- and low–molecular-weight (MW) compounds (Table 89-5). All of these agents tend to sensitize the individual, so that low ambient concentrations of the substance can ultimately cause significant bronchoconstriction. In addition, certain agents can cause direct irritant-related bronchoconstriction and airway hyperreactivity. Because the number of agents associated with occupational asthma is large and expanding, several websites have been established to allow health-care providers to obtain up-to-date information on agents that induce occupational disorders. One of these is www.occupationalasthma.com

RISK FACTORS

Atopy appears to be the major risk factor for developing occupational asthma, particularly when the inciting agent is a high-MW compound that induces an antibody response. Family or personal history of atopy appears to put the subject at risk. Because low-MW agents can induce asthma through nonallergic as well as allergic mechanisms, atopy may not be as important with these agents. Smoking is also a risk factor for the development of occupational asthma, particularly in workers exposed to platinum salts and anhydride compounds.[3] There have been several studies documenting that workers who smoke have a higher incidence of asthmatic reactions to specific airborne agents, possibly due to overall higher immunoglobulin E (IgE) levels in smokers as compared with nonsmokers.[3] There may also be genetic factors that predispose to occupational asthma. Major histocompatibility complex class II proteins are important for development of occupational asthma due to acid anhydrides, diisocyanates, western red cedar, platinum salts, latex, and animal proteins.[18] Certain glutathione S-transferase and N-acetyltransferase genotypes also predict development of occupational asthma in certain settings.[18]

CLINICAL PRESENTATIONS

Occupational asthma presents in a similar manner as other forms of asthma. If the physician does not maintain a high index of suspicion, symptoms will be treated but the inciting agent will not be identified. Two general forms of occupational asthma have been identified: one in which symptoms occur after a period of exposure to the inciting agent (occupational asthma with latency) and another in which symptoms develop immediately with exposure to the agent (occupational asthma without latency or irritant-induced asthma or reactive airway dysfunction syndrome). In general, the former syndrome is associated with a true allergic reaction to the offending agent while the latter is generally mediated nonimmunologically.

Occupational Asthma with Latency

Most commonly patients who develop occupational asthma do so after a period of exposure to the inciting agent. Agents that induce this sort of pattern include high- and low-MW molecules. Individuals are usually exposed to the agent for weeks to months before developing symptoms. With the appearance of symptoms, nonspecific airway hyperreactivity, determined by methacholine or histamine challenge, is present. Also with appearance of symptoms, the individual develops airway reactivity to low ambient concentrations of the offending agent. Therefore, exposure to very low concentrations of the material in the workplace precipitates severe bronchoconstriction in these patients. Controlled simulated exposure with the offending agent will elicit bronchoconstriction in patients with this syndrome, especially when asthma is due to a high-MW molecule.[16,19]

Occupational Asthma without Latency (Irritant-Induced Asthma, Reactive Airway Dysfunction Syndrome)

This syndrome[20] is less common but can be devastating. Symptoms develop within hours of exposure. Pathological changes are generally similar to those occurring in the syndrome of occupational asthma with latency, although epithelial changes such as desquamation and subepithelial fibrosis may be more prominent. Agents that commonly cause this syndrome are irritant gases or fumes such as chlorine or ammonia (see Chapter 90). In addition, certain agents such as acid anhydrides and isocyanates can cause occupational asthma with and without latency. Reactive airway dysfunction syndrome is a form of occupational asthma without latency. The criteria for diagnosis of this syndrome are listed in Table 89-6.

TABLE 89-5 Causes of Occupational Asthma

Categories	Occupations at Risk	Major Putative Component
High–molecular-weight compounds		
Animal products	Animal handlers Veterinarians	Pelt or urinary proteins
Seafoods	Crab or prawn processors Oyster farmers	Water-extractable proteins
Insects	Entomologists Grain workers Laboratory workers River workers Flight crews	Insect proteins
Plants	Grain handlers Bakers Tea workers Brewery chemists Tobacco manufacturers	Extractable plant proteins
Biologic enzymes	Detergent industry workers Bakers Pharmaceutical workers	*Bacillus subtilis*, trypsin, pancreatin, papain, pepsin
Latex	Health care workers Doll manufacturers Glove makers	Latex rubber extract
Gums	Printers Gum manufacturers	Gum acacia Gum tragacanth
Low–molecular-weight compounds		
Diisocyanates	Polyurethane workers Plastic workers Foundry workers Spray painters	Isocyanate-protein complex
Anhydrides	Epoxy resin workers Plastics workers	Phthalic anhydride-protein complexes
Wood dust	Carpenters Sawmill workers	Plicatic acid (western red cedar) Wood dust extracts
Fluxes	Aluminum solderers Electronics workers	Aminoethylethanolamine
Pharmaceuticals	Pharmaceutical manufacturers	Antibiotics, psyllium, piperazine
Fixatives	Hospital workers	Formaldehyde, glutaraldehyde
Diesel exhaust	Farmers, diesel mechanics	Nitrogen oxides, sulfur dioxide, particulates

TABLE 89-6 Diagnostic Criteria for Reactive Airway Dysfunction Syndrome (RADS)

1. There is an absence of pre-existing respiratory disorder, asthma symptomatology, or a history of asthma in remission and an exclusion of conditions that can simulate asthma.
2. The onset of asthma occurs after a single exposure or an accident.
3. The exposure is to an irritant vapor, gas, fumes, or smoke in very high concentrations.
4. The onset of asthma symptoms develops within minutes to hours and less than 24 h after the exposure.
5. There is a positive methacholine challenge test finding or equivalent test, which signifies hyperreactive airways, following the exposure.
6. There may or may not be airflow obstruction confirmed with pulmonary function testing.
7. There is exclusion of another pulmonary disorder that explains the symptoms and findings.

Source: Data from Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. Chest. 2008;134(3 Suppl);1S–41S.

MECHANISMS AND PATHOLOGY

Both high- and low- molecular weight compounds may promote development of occupational asthma.

High–Molecular-Weight Compounds

Most commonly, high-MW compounds, usually proteins produced at the workplace, induce asthma through IgE-dependent classic immediate hypersensitivity reactions. Specific serum IgE antibodies to the protein can usually be demonstrated and skin tests using extracts of the substance show positive results. Atopic individuals are more at risk for developing the syndrome. Because specific IgE antibodies must be produced in this setting, the latent period for developing the reaction can be long, sometimes several months or years. Pathologically, asthma due to high-MW compounds is associated with bronchial infiltration of lymphocytes and eosinophils, indistinguishable from other forms of allergic asthma. Specific IgE antibodies to occupation-related allergens trigger mast cell degranulation in a similar manner as in the nonoccupational setting. In severe cases, bronchial epithelial desquamation and subepithelial fibrosis are exhibited pathologically.[18]

Low–Molecular-Weight Compound

These agents also tend to cause IgE-dependent bronchoconstriction. However, in contrast to higher-MW agents, specific IgE or IgG antibodies produced in these individuals are directed at the low-MW compound coupled to a protein within the serum.[16,18] There is also some evidence that low-MW compounds induce asthma through IgE-independent mechanisms, possibly by affecting T lymphocytes directly, as shown for cobalt and nickel salts as well as isocyanates.[18] Interestingly, the bronchial pathology is similar whether or not the response is an IgE-dependent reaction.[18] In addition, certain low-MW compounds can directly affect chemical pathways that are involved in airway tone. For example, organophosphates have been shown to induce bronchoconstriction through anticholinergic effects.[16] Other agents may cause asthma simply through irritation of the airways.[18]

DIAGNOSIS

Key components in the evaluation of suspected occupational asthma are discussed below.

History

A high index of suspicion for occupational causes must always be present when patients with new-onset asthma are being evaluated. Because asthma can be induced by remote exposure to a substance, the current and previous occupational history is very important. Computerized lists of exposures that occur at various workplaces are available (www.occupationalasthma.com), and these facilitate this process. Included in the history should be the documentation of specific jobs of the individual at the specific workplace as well as potential exposures during performance of those jobs. The history can be verified through the use of material safety data sheets (MSDS), forms that contain information about a particular agent, including identification, hazard(s) identification, composition/information on ingredients, first-aid measures, fire-fighting measures, accidental release measures, handling and storage, exposure controls/personal protection, physical and chemical properties, stability and reactivity, toxicological information, ecological information, disposal considerations, transport information, and regulatory information, as well as industrial hygiene data and employee health records from the workplace. Once suspect agents are identified, any previous reports of their association with work-related asthma can be searched on available websites such as www.occupationalasthma.com. Clinical history that suggests occupation-related asthma includes symptoms that occur at work and improves when the patient is away from work for a period of time, as during vacations. The duration of symptoms prior to removal from the offending environment is important for predicting prognosis. Those individuals who have had symptoms for a longer period of time are more likely to develop chronic symptoms that do not remit after exposure has been discontinued.[21] It should be noted that many compounds induce a late reaction, several hours after exposure. Therefore, the relationship between exposure and symptoms may not be entirely apparent to the patient. Questions should also be asked regarding other causes of obstructive pulmonary disease. Questions regarding a history of tobacco use are important. A past history or family history of asthma may suggest that the patient's symptoms are not occupation related. Therefore, questions to establish the degree of respiratory symptomatology before beginning a particular job are important. Questions aimed at assessing cardiac or upper-airway abnormalities are also very important.

Physical Examination

Signs of atopy should be assessed. As in cases of asthma due to other causes, the pulmonary examination may be entirely normal when the patient is seen outside of the workplace. However, wheezing, either during quiet respiration or on a forced maneuver, suggests airflow obstruction. Signs of dermatitis particularly in the case of latex sensitivity may support the diagnosis of work-related disease.[3,22]

Skin and Immunologic Tests

General atopy is a risk factor for developing certain forms of occupational asthma when it is due to high-MW compounds. Therefore, routine skin testing, using a panel of allergens, for wheal-and-flare reactions can be useful. In addition, extracts of a compound that is suspected to cause occupational asthma in a particular patient can be used for skin testing. Extracts from flour, animal by-products, coffee, and other sources have been used for skin testing in various studies.[3,18] Specific IgE antibodies to extracts that contain high-MW compounds or to low-MW compounds coupled to a serum protein, such as albumin, can also be detected by the radioallergosorbent test (RAST) or enzyme-linked immunoadsorbent assay (ELISA).[3,18] In addition, specific IgE antibodies to low-MW compounds have been detected in patients with asthma due to these compounds.[3,18] However, positive results in all of these tests do not necessarily indicate that disease is due to the specific agent; they simply suggest sensitization. Results of all of these tests must be evaluated in the context of the individual patient.

Pulmonary Function Tests

Patients with workplace-induced asthma may present with normal pulmonary function tests when they are away from the inciting agent. For this reason, pulmonary function tests should be assessed in the light of the time that has elapsed since the patient was exposed to a suspected agent. Pulmonary function tests pre- and postwork can be very helpful in objectively evaluating respiratory function in relation to work.

Peak-flow monitors are useful in the assessment of workplace-related symptoms because they can be used in a job. Initially, peak-flow measurements should be determined at least four times per day: on awakening, at the beginning and end of work, and before bed. Similarly, timed measurements should also be performed on days that the subject is off work. Three measurements at each time period should be made and recorded; two of these should be within 20 L/min of each other to demonstrate reproducibility. Measurements should be performed each day over at least 4 weeks. In addition to this regimen, a more intense regimen of peak-flow measurements every 2 hours has been proposed by Burge et al.,[23] but this schedule may be too cumbersome to be practical, and studies have suggested that a protocol using measurements performed four times a day is as predictive.[16]

Because peak-flow measurements are very effort dependent, they should be supplemented by other methods for assessing the degree of impairment. It is always important to document that patients who

are being evaluated for occupational asthma are not malingering in order to obtain compensation. When pulmonary function is assessed in these patients, technicians should be alerted that a work-related disorder is suspected, so that they can evaluate the patient's effort. In addition, reproducibility of the repeated maneuvers can be useful in determining the degree of effort. If peak-flow measurements suggest that there is an airway reaction to a substance at the workplace, a technician with a portable spirometer can be sent to the workplace to measure FVC and FEV_1 at hourly intervals during work.

Bronchial Provocation Tests

Patients who develop occupational asthma invariably develop bronchial hyperreactivity to nonspecific agents such as methacholine and histamine. An arbitrary cutoff of a provocative concentration producing a 20% decline in FEV_1 (PC_{20}) of 8 to 16 mg/mL of methacholine has been chosen.[24] In patients with normal spirograms at presentation, a bronchial challenge with either of these agents may be necessary for diagnosis. Such a challenge can also be used to choose the concentration(s) of specific allergen that should be employed in a specific bronchial provocation test, since studies have shown a good correlation between the degree of nonspecific bronchial reactivity and responses to specific allergens.[16]

Specific simulated bronchoprovocation can be a valuable tool to determine whether a patient's symptoms are due to a particular agent. This maneuver should be performed only by an experienced physician because it carries some risks, particularly prolonged bronchospasm that requires therapy. Bronchodilator and anti-inflammatory medication should be withheld prior to the exposure, which should be performed in a whole-body chamber that allows more reproducibility of the work situation. Exposure levels should start low and gradually increase to levels that are consistent with ambient levels in the subject's workplace.[19]

Patterns of bronchoconstriction after exposure to specific agents can differ.[19] The two most common patterns are an immediate reaction, occurring within a few minutes of challenge and peaking at 10 to 15 minutes after challenge, and a late reaction, occurring several hours after challenge and peaking at 5 to 8 hours (Fig. 89-1). These responses can be seen individually or together in a given patient. Less frequent patterns have also been noted. One of these involves a reduction in flow rates 1 hour after challenge, with resolution 3 to 4 hours after exposure.[19] In another, a reduction in flow rates occurs much later, the day after the exposure, and occasionally recurrent abnormalities can be manifest for several days.[19] Recurrent symptoms of nocturnal asthma for several days have also been reported after exposure to a number of agents.[19]

MANAGEMENT

Once it has been determined that an individual has developed asthma due to exposure in the workplace, he or she should be removed from the offending environment. In some instances, reduction in exposure at the workplace can allow the worker to continue gainful employment without having progressive respiratory symptoms. Although some studies[25] have suggested the use of certain therapeutic agents, such as inhaled cromolyn for bakers' asthma, which can inhibit physiological changes triggered by the offending agent, protection is not complete. Because it is sometimes difficult to convince the patient to change jobs, an alternative to this is the use of a protective mask to prevent airway exposure to the offending agent. The inciting agent dictates the type of protective headgear employed. For example, subjects working with low-MW compounds require helmet respirators with an isolated air source to prevent exposure while exposure to high-MW compounds can generally be avoided with simple high-efficiency particulate air mask. If the subject continues to work in the implicated environment, pulmonary function tests should be done frequently to rule out progressive physiological impairment. Unfortunately as few as 33% of patients with occupational asthma recover even with complete avoidance from the offending substance.[3] In addition, data that protective masks/respirators can prevent the problem are sparse.

DISABILITY DETERMINATION

Documentation of impairment associated with objective physiological changes that occur predominantly in the workplace suggests an occupation-related disorder. Patients with asthma due to an occupational exposure should be referred to the appropriate compensation or review board. The American Thoracic Society[26] and the American Medical Association[27] have developed guidelines for the evaluation of impairment and disability due to this disorder. Determination of initial impairment should be made after optimal treatment of the asthma has been delivered. Impairment should be assessed using lung function tests, or measurements of airway hyperresponsiveness using: methacholine or histamine; documentation of the type and amount of medication required to treat the patient; and observation of the effect of the disease on the patient's life-style.

SPECIFIC EXAMPLES

Multiple examples of occupational asthma are described below.

Animal Handlers' and Pet Shop Workers' Asthma

For several years it has been known that there is a high incidence of asthma and rhinitis among workers in animal-care facilities.[28–30] There is also expanding information that up to 22% of pet shop workers develop respiratory symptoms at work. Development of symptoms in animal handlers tends to occur following months or years of exposure. Symptoms of asthma are often preceded by rhinitis, conjunctivitis, or urticaria that occur primarily at work. In one study, 56% of individuals who had been exposed to laboratory animals for 3 months or more complained of respiratory symptoms.[28,29] Skin testing with animal-associated allergens may be helpful in determining individuals at risk for developing this syndrome. In addition, a prior history of atopy, elevated serum IgE levels, and positive skin tests against nonanimal environmental allergens also predict the development of asthma in animal

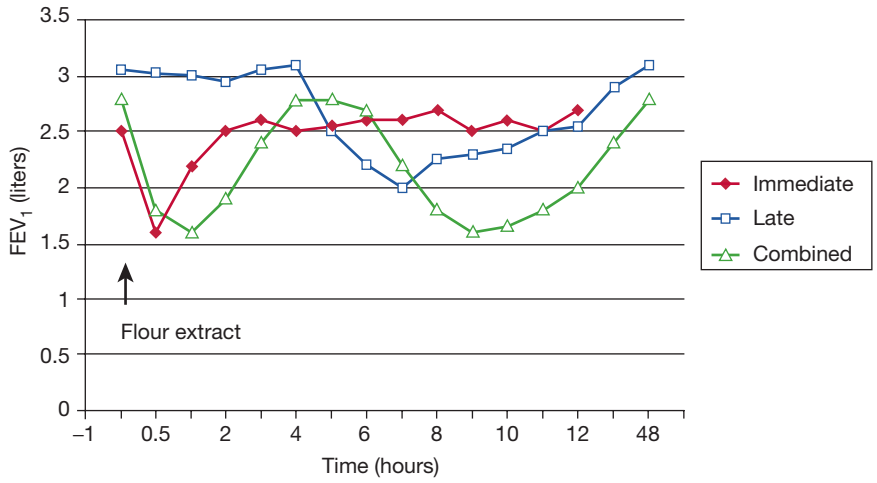

Figure 89-1 Examples of early, late, and combined reactions to inhalation of a specific agent (in this case, flour extract) implicated in causing occupational asthma. Flow rates are plotted versus time after inhalational exposure.

handlers. Approximately one-third of individuals with a history of atopy develop asthma when exposed to laboratory animals for more than 3 months. Although multiple allergens – including molecules found in the pelt, serum, and urine of the animal – may be involved, a major allergen is the rat urinary allergen. In one study, specific IgE antibody to this protein correlated very well with reported asthmatic symptoms in animal handlers.[28,29] Serum IgG antibody to this protein was also present in animal handlers with symptoms, but it was additionally present in a significant number of asymptomatic subjects as well.[28,29] Anti-rat urinary protein IgG antibody appeared to be simply a marker of exposure, while IgE antibody was integrally associated with onset of asthma.[28,29]

Avoidance of exposure to laboratory or pet shop animals is the best treatment for this condition. Although one study has documented that airway reactivity in animal handlers does not tend to worsen in these individuals even if they remain on the job,[29] chronic exposure probably perpetuates airway inflammation. If the individual cannot avoid the exposure, use of a helmet respirator, enabling him or her to completely avoid inhalation of the protein allergen, can prevent symptoms. Worker education regarding avoidance of airborne allergens can also be useful in controlling symptoms.

Bakers' Asthma

Cereal flours induce a specific IgE reaction in a high percentage of exposed subjects.[31] Epidemiological studies of bakers' asthma have been most complete in Germany, where it has been shown that IgE-mediated immediate skin test reactivity in bakers is directly related to their time in service. One study has shown that 20% of bakers' apprentices develop positive skin tests after 5 years of service.[31] However, exposed individuals can develop specific IgE antibodies and skin test reactivity to flour antigens without developing asthma, suggesting these tests are mainly a parameter of exposure.[31] In one study, however, the percentage of bakers with documented occupation-related airway disease had a much higher concentration of IgE antibody than did unselected bakers who had been employed for a similar period of time.[31] Overall, 7% to 20% of bakers develop allergic symptoms, including asthma, that occur predominantly in the workplace.[31] Symptoms can be minimized by using properly occlusive masks, although most subjects find these devices difficult to wear during the entire work shift. Airway reactions to inhaled flour dust allergens can also be reduced by pretreatment with cromolyn sodium. However, no studies have documented that cromolyn can reduce symptoms at the workplace or prevent chronic respiratory abnormalities from developing.

Asthma due to Latex

Urticaria and asthma occur in a small number of individuals who are exposed to rubber latex by wearing gloves or working in doll factories.[22,32,33] Risk factors for developing sensitization to latex are frequent use of disposable gloves, the presence of prior atopic disease, and prior or current hand dermatitis. Approximately 80% of patients with asthma due to latex develop contact urticaria upon wearing gloves, a large percentage of patients also report rhinitis and conjunctivitis upon exposure to latex.[22,32,33] Skin tests using extracts of latex are usually positive in affected individuals.[22,32,33] Treatment is limited to avoidance of latex-based products. One study has shown that measures implemented to reduce exposure while working, such as use of powder-free gloves, can allow a sensitized individual to continue to remain on the job.[22,32,33] In fact, with institution of the general use of powder-free latex gloves and use of latex gloves only if necessary for dexterity, the incidence of latex-associated asthma has diminished.

Asthma due to Acid Anhydrides

These low-MW compounds are used in numerous industries,[34,35] including the curing of epoxy and alkyl resins, production of plasticizers and adhesives, and the manufacture of drugs. Specific acid anhydride compounds used include trimellitic acid (TMA), phthalic acid (PA), tetrachlorophthalic acid (TCPA), and malic acid (MA). All of these compounds have been associated with induction of asthma.[35] TMA exposure has been associated with several different syndromes: an irritant syndrome, early asthma and rhinitis, late-onset dyspnea with systemic symptoms (TMA flu), and pulmonary infiltrates with hemoptysis.[35] The irritant syndrome does not require a latency period, whereas the other three syndromes require a period of exposure to the acid anhydride prior to development. Asthma caused by these compounds appears to be due to the development of specific antibodies to the acid anhydride coupled to a body protein. Specific IgE and IgG antibodies to TMA coupled to human serum albumin have been noted.[35] In one study, total IgE levels were a good parameter of exposure, whereas specific IgE levels correlated with symptoms of asthma and skin test positivity.[36] The absence of a specific IgE antibody to TMA strongly argues against TMA as the cause of asthma in a particular patient. Another study has shown that IgG in serum from sensitized patients can trigger histamine release by basophils.[18] In contrast to asthma caused by high-MW compounds, atopy does not appear to be a definite risk factor for development of asthma due to acid anhydrides. However, a history of smoking may be a risk for the development of asthma due to these agents. Removal of the employee from the environment is the best form of therapy for the disorder. Employee education regarding exposure can also be useful. Even with removal from the offending environment, affected subjects may continue to have symptoms for as many as 5 years after changing work. Specific IgE antibody may also be detected several years after discontinuation of exposure.

Isocyanate-Induced Asthma

Isocyanates are highly reactive chemicals used in a number of industries.[17] Prominent in this regard is their use in the production of polyurethane, which is found in paints, varnishes, flexible foams, and adhesives. Major forms of isocyanates include toluene diisocyanate (TDI), diphenyl methane diisocyanate (MDI), and hexamethylene diisocyanate (HDI). Exposure to TDI has been most often associated with the development of asthma, and TDI is also the most chemically reactive isocyanate.[37–39] Overall 5% to 30% of workers exposed to TDI develop airway symptoms.[34,37–41] There is some evidence that human leukocyte antigen (HLA) class II alleles are associated with increased risk for the development of isocyanate-induced asthma.[37] In addition, asthma due to TDI is associated with the Ile^{105}/Ile^{105} phenotype of glutathione-S-transferase enzyme protein, whereas the Val^{105}/Val^{105} protects against asthma in this setting.[38] Also, slow acetylator genotypes of the N-acetyltransferase gene have an increased risk of diisocyanate-induced asthma.[18]

Isocyanates can also cause an airway irritation syndrome similar to that due to acid anhydrides, occurring without significant time latency.[39] In one reported case, a patient was exposed to large concentrations of TDI and developed airway symptoms within hours of the exposure. Twelve years after exposure, the patient continued to manifest hyperactivity to TDI as nonspecific airway hyperreactivity.[40] More commonly, isocyanates induce an asthma syndrome that develops after exposure to the substance for weeks to years.[39] When subjects develop asthma due to these agents, they also manifest bronchoconstriction after exposure to the substances in a controlled setting, such as an exposure chamber; usually these individuals will also manifest nonspecific airway reactivity to methacholine or histamine.[39] Isocyanates may also induce chronic airway abnormalities in the absence of symptoms. One study, which examined the decremental fall in flow rates in workers exposed to TDI, predicted a 2-L greater loss in FEV_1 over 40 years in these workers as compared with controls.[39,40]

Isocyanates cause asthma by inducing intense airway inflammation.[39] Bronchoalveolar lavage studies have demonstrated increased numbers of neutrophils and eosinophils in the airways of subjects

with asthma due to isocyanates, particularly those who manifest a late airway reaction upon controlled exposure. Bronchial biopsies of affected patients also show intense inflammation, much of which is lymphocytic.[39] Why inflammation is induced by these agents is controversial as there are studies suggesting that isocyanates may interact directly with elements that modulate inflammation, but because of the latency period that is commonly required prior to the development of isocyanate-induced asthma, an immunologic mechanism is likely. Lymphocyte-mediated and humoral responses have been proposed.[39] One study has demonstrated specific IgE and IgG antibodies to isocyanates coupled to human serum albumin in sera of individuals with symptoms and positive inhalation challenge tests with isocyanates.[18] Although the levels of both of these subclasses of immunoglobulins tend to correlate with airway responsiveness to the isocyanate, the IgG level tends to be more predictive.[41]

As with other forms of occupational asthma, the most efficacious treatment for individuals affected with isocyanate-induced asthma is removal from the offending environment. Once the individual has become sensitized, very low concentrations of the particular agent can induce bronchospasm, so that transfer of the individual to an area that is in close proximity to an area of isocyanate use is not an effective management. Bronchoconstriction following controlled isocyanate exposure can be attenuated by inhaled or oral corticosteroids. However, use of these agents should not replace removal of the patient from exposure at work. Use of respirators prophylactically in areas with high concentrations of isocyanates is important to prevent the development of asthma. There have been reports of persistent isocyanate-induced asthma even after removal of the subject from the offending environment. One study reported persistent respiratory symptoms in 83% of workers who had been away from isocyanate exposure for 4 years.[39,40] Another study demonstrated that 7 of 12 subjects with TDI-induced asthma continued to have nonspecific airway hyperreactivity 2 years after removal from the work environment.[40]

Asthma in Emergency Responders at the World Trade Center

Approximately 25% of firefighters who responded to the World Trade Center collapse developed airway hyperreactivity to methacholine from exposure to respirable particles, possibly because of high alkalinity of the dust.[21] The predominant symptom associated with this exposure was cough. One study showed that airway hyperreactivity shortly after the disaster predicted airway hyperreactivity 6 months later.[21]

Asthma due to Western Red Cedar Wood Dust

Asthma can occur due to chronic wood dust exposure.[17,42] Although a number of woods are associated with this problem, the syndrome due to western red cedar is best characterized and the causative agent within the dust has been identified.[42] Overall 5% of workers who are exposed to western red cedar dust develop symptoms of wheezing and cough after a latency period of months to years.[42] The mean latency period prior to the development of symptoms is 50 months. Workers who develop the syndrome usually have nonspecific airway hyperreactivity to methacholine or histamine. In addition, a specific airway reaction to plicatic acid, a component of the wood dust, is usually present and manifested by an early or late reduction in flow rates after exposure.[42]

Mechanisms of western red cedar-induced asthma are not totally defined. Plicatic acid, which makes up approximately 50% of the total extractable fraction of the wood dust, induces bronchoconstriction in affected subjects.[42] Subjects who manifest an early and late airway response to inhalation of plicatic acid generally have had a longer exposure to the western red cedar dust. Specific IgE antibodies to plicatic acid coupled with human serum albumin have also been detected in 28% to 40% of subjects with the syndrome.[42]

Like other forms of occupational asthma due to low-MW compounds, subjects with asthma due to western red cedar can continue to have symptoms even when they are removed from the offending environment. In one study, 60% of affected individuals continued to have symptoms after leaving the industry.[3] For this reason, the identification of individuals and specific jobs that place individuals at risk is important. Use of protective devices may reduce exposure and subsequent development of asthma due to this dust, but this has not been systematically addressed.

Asthma due to Metal Salts

Platinum used in electroplating, platinum refinery, and jewelry making has been noted to cause asthma.[17] Smoking is a risk factor for the development of asthma due to this metal. Airway responses to preparations of complex salts of platinum have been documented in affected workers. In addition, positive skin-prick tests and specific IgE antibodies to platinum conjugated to albumin have been found.[43] Exposure to nickel, chromium, cobalt, vanadium, and tungsten carbide has also been associated with the development of asthma.[43] Welders are commonly exposed to nickel fumes while welding stainless steel.

Soldering Flux Asthma

Various fluxes – including aluminum solder flux, which contains aminoethylethanolamine and colophony[17] – have been associated with, and thought to cause asthma. One study documented occupational asthma in 21% of workers in the plant of a manufacturer of consumer electronics.[44] Colophony fumes can also induce bronchoconstriction in affected individuals when given as a controlled exposure.[17] Mechanism of airway reactivity to colophony fumes may be irritant properties of the fumes or a specific immunologic reaction to pine resin.[44]

Diesel Exhaust Exposure

Mounting evidence suggests that air pollution contributes to the rising incidence of asthma.[45] Certain occupations place workers in environments of higher diesel exhaust,[46,47] one component of air pollution that causes asthma, and there is some evidence that this is associated with induction of asthma. One study examined specific exposures in farmers and found that diesel exhaust and solvent exposure correlated with onset of asthma.[47] Another study from England showed a relationship between diesel exhaust exposure at work and asthma.[46]

SUMMARY

Since the beginning of the Industrial Age, workplace exposures have adversely affected human beings. Effects of substances inhaled at the workplace are becoming increasingly apparent with marked expansion of agents that have been associated with lung damage. Exposures that affect the airways with subsequent development of bronchitis or asthma cause a large degree of disability and subsequent cost to society through increased health-care costs and inability to work. This chapter describes major causes of these airway syndromes in the hope that treating clinicians can recognize them early and improve outcomes.

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CHAPTER 90

Acute and Chronic Responses to Toxic Inhalations

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INTRODUCTION

The lungs and airways are in constant contact with the outside world and thus, are especially vulnerable to toxic substances present in the environment. Within seconds of exposure to an inhaled toxin, pathologic events occur that may cause immediate distress, systemic illness lasting days, or even lead to the development of chronic lung disease. This chapter discusses the pathology and pathophysiology that can result from various inhaled toxins, and also highlights the role of several common and medically significant toxic inhalants that are known to cause acute and chronic pathophysiologic responses in the lung. The chapter also discusses several systemic syndromes caused by acute toxic inhalations. The scope of this chapter does not include chronic exposure to low levels of toxins.

DETERMINANTS AND MECHANISMS OF IRRITANT-INDUCED PULMONARY INJURY

Inhaled toxins exist in many forms and may be categorized by taking into account their physical properties. General categories include gases, vapors, fumes, aerosols, and smoke. A variety of factors determine the pathologic results of a toxic inhalation: the size of inhaled particles, the solubility of the inhaled substance in water, the concentration of the inhalant in ambient air, the duration of exposure, the presence or absence of ventilation, and a variety of host factors (age, smoking status, comorbid diseases, use of respiratory protection, and perhaps even genetic susceptibility). While toxic inhalants provoke a broad range of chemical and biologic activities that contribute to pathogenesis, their physical properties, namely their particle size and water solubility, are of fundamental importance in determining the site and severity of pulmonary injury. Tables 90-1 to 90-3 summarizes the physical properties of the discussed inhalants that substantially affect the resulting pathogenesis of these agents.

The size of aerosolized particles is of critical importance in inhaled toxin pathogenesis. In general, larger aerosolized particles are more likely to deposit on the nasopharynx via impaction and not gain access to the lower airways, while smaller particles are able to penetrate smaller airways and effect toxicity at the level of the alveolus. Aerosolized particles larger than 30 to 80 μm are not inhalable through the nose,[1] and particles larger than 5 μm typically do not reach the alveoli.[2] Ultrafine particles (those <0.1 μm) have been specifically implicated in the toxicity due to the agents of polymer fume fever.[3] Inhaled particles may have direct toxic effects themselves, or they may function as vehicles for adsorbed gaseous agents that are toxic to terminal bronchioles and alveolar cells.

In addition to particle size, the relative solubility of an inhalant in water determines where along the respiratory tract toxicity will occur. Substances with high water solubility, such as ammonia, sulfur dioxide, and hydrochloric acid, provoke immediate and evident injury to the conjunctiva and mucosal surfaces of the upper airways; they are largely absorbed by the mucus lining the pharynx and larynx and often react there to form caustic acids and alkalis. The provoked symptoms quickly prompt exposed individuals to flee the area or contain the source of exposure, reducing the duration of exposure. These compounds can also activate irritant receptors in the upper airways, provoking a bronchoconstrictor reflex that may further limit access of the inhalant to lower airways.[4] In contrast, compounds like phosgene and ozone have low water solubility and thus fail to cause immediate irritation, promoting longer exposure to the

TABLE 90-1 Definitions of Types of Inhaled Substances

Gas: a formless state of matter in which molecules move freely about and completely occupy the space of enclosure
Aerosol: a relatively stable suspension of liquid droplets or solid particles in a gaseous medium
Coarse particles: particles between 1 and 10 μm
Fine particles: particles between 0.1 and 1 μm
Ultrafine particles: particles less than 0.1 μm
Vapor: the gaseous form of a substance that normally exists as a liquid or solid and that generally can be changed back to a liquid or solid by either increasing ambient pressure or decreasing the temperature.
Fume: an aerosol of solid particles generally less than 0.1 μm in size that arises from a chemical reaction or condensation of vapors, usually after volatilization from molten materials.
Smoke: the volatilized gaseous and particulate products of combustion; the particles are generally less than 0.5 μm in size and do not settle readily.

Source: Adapted with permission from Kizer KW. Toxic inhalations. Emerg Med Clin North Am. 1984;2(3):649–666.

TABLE 90-2 Water Solubility and Mechanisms of Lung Injury of Gaseous Respiratory Irritants

Irritant Gas	Water Solubility	Mechanism of Injury
Ammonia	High	Alkali burns
Chlorine	Intermediate	Acid burns, reactive oxygen species, reactive nitrogen species
Hydrogen chloride	High	Acid burns
Oxides of nitrogen	Low	Acid burns, reactive oxygen species, reactive nitrogen species
Ozone	Low	Reactive oxygen species, reactive nitrogen species
Phosgene	Low	Acid burns, reactive oxygen species, protein acetylation
Sulfur dioxide	High	Acid burns, reactive oxygen species

Source: Reproduced with permission from Schwartz DA. Acute inhalational injury. In: Rosenstock L, ed. Occupational medicine: Occupational Pulmonary Disease. Vol 2. Philadelphia: Hanley and Belfus; 1987.

TABLE 90-3 Water Solubility and Site of Initial Impact of Toxic Irritants

Water Solubility	Initial Level of Impact	Inhalant
High	Nose	Ammonia
	Pharynx	Chlorine
	Larynx	Sulfur dioxide
Medium	Trachea	Ozone
	Bronchi	
Low	Bronchioles	Nitrogen dioxide
	Alveoli	Phosgene

Source: Reproduced with permission from US Department of Health and Human Services, Surgeon General's Office: The Health Consequences of Involuntary Smoking. 1986.

inhalant and deeper penetration of the lower airways. Compounds of intermediate solubility, for example, chlorine gas, typically have pathologic effects throughout the respiratory tract. These differences in solubility can be overcome by differences in concentration and duration of inhalant exposure: virtually any inhaled toxin (even the most soluble agents) can cause diffuse damage of the respiratory tract by overwhelming the absorptive capacity of the upper respiratory tract. Furthermore, adsorption of a toxic gas on particulate matter may permit a toxin access to otherwise unreachable airways.

Host factors also play a significant role in predicting an individual's response to a toxic inhalation. Underlying pulmonary or extrapulmonary disease may worsen a patient's response to an exposure. Children deposit a smaller fraction of inhaled particles in their nasopharynx than adults and thus may be at elevated risk of lower airway exposure and pathology[5]; moreover, as some gases (such as chlorine and sulfur dioxide) are heavier than air, children may be subjected to a longer duration and higher concentration of gas than adults near the same site of toxin release. With particles greater than 0.5 μm, breathing through one's nose increases upper airway particle deposition compared to mouth-breathing; this difference is absent with particles less than 0.5 μm.[6] Tobacco smoking impairs ciliary clearance and cellular defense, limiting the exposed patient's ability to clear inhaled particles and prolonging exposure. Patients with increased minute ventilation (such as those panicking at the scene of an irritant gas release) are at elevated risk of increased exposure and toxicity. An emerging literature in experiments with inbred strains of mice suggests that genetic variants may alter the risk of responding to various inhaled toxins.[7]

Injury from toxic inhalation may occur via a number of mechanisms. If the concentration of the inhalant is high enough and if ventilation is inadequate, simple asphyxiation due to displacement of atmospheric oxygen may occur. The reflex bronchoconstriction triggered by upper airway irritant receptor activation may itself cause inadequate oxygen inhalation. Cell injury from acute toxin exposure typically occurs via nonimmunologic mechanisms of injury and inflammation, generally via formation of an acid (chlorine, oxides of nitrogen, phosgene, and sulfur dioxide), an alkali (ammonia), or reactive oxygen or nitrogen species (ozone, oxides of nitrogen and chlorine). Acid formation results in coagulation of underlying tissue, while alkali exposure causes a liquefaction of mucosa and characteristically deep lesions within the airways. Reactive oxygen and nitrogen species and their derivatives achieve local tissue damage via lipid peroxidation and protein oxidation, and may cause similar toxicity systemically.[8] Free radicals may be direct derivatives of inhaled substances, or they may be released by alveolar macrophages that are activated by inhalant exposure.[9] All three types of tissue damage generally lead to an increase in expression of proinflammatory cytokines that can perpetuate the acute injury and may be responsible for the development of later sequelae. Disruption and repair of injured airway epithelial tissue may compromise the host's defenses against further infectious or irritant substances. A role played by the innate immune system in disease progression is evident in the case of endotoxin exposure in organic dust toxin syndrome (ODTS, below), and may be a host factor in the response to ozone and nitrogen dioxide.[7,10]

PATHOGENESIS AND CLINICAL PRESENTATION OF TOXIC INHALATION INJURY

Mechanisms of disease and clinical manifestations based on respiratory site exposure are considered below.

UPPER AIRWAY

Effects of toxins on the upper airways are typically sudden and short-lived compared to those more distal along the respiratory tract; chronic pathology in this region is unusual. Compounds that provoke a response in the nose, pharynx, and larynx tend to be particulate with relatively large average particle size or gases with high water solubility. Acids, alkalis, and reactive oxygen and nitrogen species may all cause tissue injury in this region depending on the inhaled compound and its reactions along airway epithelium. Characteristic tissue injury depends on dosage and ranges from slight edema of the nasopharynx and larynx to epithelial ulceration and frank hemorrhage. Once the airway epithelia are compromised, it fails to function as a protective barrier against the environment. Underlying inflammatory cells, nerves, muscles, and blood vessels become exposed, which may further the inflammatory response. An obstructive response to some irritants starts to occur at concentrations only barely perceivable as irritating.[11]

The typical presentation of patients with acute exposure of irritant substances to the upper airways includes burning sensations of the nasal passages and throat, copious sputum production, coughing, and sneezing. Extrapulmonary manifestations include burning of the eyes, profuse lacrimation, headache, and dizziness. The most serious risk in the exposed patient is airway obstruction due to reflex bronchospasm or laryngospasm, mucosal edema, increased secretions, and sloughed epithelial cells. Patients presenting with hoarseness or stridor should be carefully observed for further evidence of airway compromise. Though inhalational injury confined to the upper airways tends to be self-limited with no or few long-term sequelae, a chronic rhinitis following irritant exposure, *reactive upper airway dysfunction syndrome* (RUDS) has been described[12] and was observed among World Trade Center rescue workers following the attacks of September 11, 2001.[13]

Patients with acute toxic exposure to the upper airways should be immediately removed from the source, which may require removal of the patient's clothes. The patient's airway should be secured and monitored; racemic epinephrine may be used, but it should not delay endotracheal intubation if necessary. Frequent suction may be required. Profuse amounts of water should be irrigated over exposed surfaces. Supplemental oxygen should be provided if appropriate. Patients with extensive upper airway edema may benefit from corticosteroids,[14] though this is unsupported by clinical trials. Ophthalmologic consultation should be sought for management of eye exposure.

CONDUCTING AIRWAYS

Acute or chronic effects on the airways may be observed.

Acute Injury

As is the case with the upper airways, the conducting airways protect their submucosal structures with epithelium that may be compromised by acute inhalational injury. The resulting edema, inflammation, and bronchoconstriction may be life-threatening if it results in

an obstructed airway, and without its epithelial barrier the airway is vulnerable to infections and other environmental pathologies. This damage to the epithelium appears to occur at the tight junction interface between cells,[15–17] resulting in increased epithelial permeability to other irritants, which gain direct access to effector cells within the subepithelial mucosa. Resulting bronchospasm may cause ventilation–perfusion mismatch. The smooth muscle of the airways can be hyperresponsive in the hours and days following irritant exposure, an effect probably mediated by the neutrophilic and eosinophilic inflammatory response inhalational injury provokes.[18,19]

Conducting airway injury may manifest as intrathoracic airflow obstruction hours after the initial insult. Patients with histories of exposure who present with any evidence of respiratory compromise should be hospitalized for observation, even if asymptomatic. Findings of concern include expiratory wheezing, decreased airflow on peak expiratory flow measurement or spirometry, abnormalities of gas exchange or an abnormal chest X-ray. Likewise, patients with complaints of dyspnea or chest tightness should be observed carefully and treated symptomatically with inhaled steroids and bronchodilators, even in the absence of objective findings. When significant airflow obstruction is present, systemic steroids may be of some utility.

Chronic Injury

Two forms of chronic injury include reactive airways dysfunction syndrome and vocal cord dysfunction.

Reactive Airway Dysfunction Syndrome A persistent asthma-like disease following acute exposure to an irritant inhalant, known as *reactive airway dysfunction syndrome* (RADS, or "Brooks syndrome") was named in 1985[20] but observed among World War I soldiers exposed to war gases.[21] Investigation and diagnosis of the disease is generally limited by the absence of spirometry results in patients prior to exposure and the presence of confounding factors (e.g., cigarette smoking), but numerous reports exist of previously asymptomatic patients experiencing hyperreactive airway disease presenting soon after a single toxic exposure and persisting for months or years.[20,22–29] RADS is distinguished from immunologic occupational asthma in that it follows a single exposure and does not follow a latency period of sensitization to the offending substance.

The pathogenesis of RADS likely begins with the initial injury to and desquamation of the epithelium, which results in hemorrhage and edema followed by inflammatory changes, and finally long-term structural changes of the airways involving epithelial regeneration and fibrosis.[30,31] Ensuing airway narrowing may be due to mucosal edema, inflammation, or structural changes to the architecture of the bronchial wall.[32]

RADS typically presents abruptly within 24 hours following exposure with the classic symptoms of obstructive airway disease: wheezing, chest tightness, dyspnea, and cough. The symptoms and obstructive findings on examination and spirometry are relieved by bronchodilators, though not as effectively as in other types of reactive airway disease (perhaps due to chronic fibrotic remodeling of the conducting airways). The disease can persist for months and, may, in some instances, be permanent.[33] A recent case report shows that a patient with severe unremitting symptoms of RADS for 5 years following an ammonia exposure responded to high-dose oral vitamin D supplements.[34] Anecdotally, inhaled corticosteroids have shown benefit in relieving airflow obstruction.[30] Systemic corticosteroids have been proven beneficial in an animal model of RADS.[35]

Vocal Cord Dysfunction Vocal cord dysfunction may also follow a single acute irritant exposure and may be confused with RADS.[36,37] The disorder may be caused by reflex response to nerve stimulation by irritants.[38] Patients suspected of having RADS who do not respond appropriately to bronchodilators should be evaluated for vocal cord dysfunction; direct laryngoscopy is the gold standard for diagnosis.[37]

■ LOWER AIRWAYS AND PULMONARY PARENCHYMA

The lower airways and lung parenchyma are primary sites for inhalational injury. Effects may be acute or chronic.

Acute Injury

Though all toxic inhalants are capable of producing distal airway disease at extreme concentrations and durations, the gases most likely to do so are those with low water solubility like phosgene and nitrogen dioxide, which bypass reflex bronchoconstriction and absorption by upper airway mucus (Fig. 90-1). The initial pathologic events in distal airways are caused by the cellular toxicity of the inhaled agent and its derivatives, which compromise the impermeability of the alveolar–capillary interface.[39] Some of this cytotoxicity may be derived indirectly from reactive oxygen species released from activated inflammatory cells.[9] In the absence of an intact alveolar–capillary interface, profound pulmonary edema may develop that impairs gas exchange and can prove fatal. The severity of this pulmonary edema, which typically presents after a latent period of several hours following the initial insult, is likely dose-related. This process may cause no more than slight dyspnea and cough with a mild alveolar infiltrate, or it may progress via diffuse alveolar damage to acute respiratory distress syndrome (ARDS). For this reason, patients with exposure to gases capable of causing distal airway disease should be hospitalized and monitored for symptoms of respiratory distress and with serial chest X-rays for at least 24 hours following exposure. Development of ARDS from toxin exposure likely shares a common pathway with other causes of acute lung injury, and management is similar: supportive care with mechanical ventilation, careful control of blood glucose, surveillance for infection, and deep vein thrombosis prophylaxis. Diuresis, intravenous corticosteroids, prone positioning, nitric oxide inhalation, and exogenous surfactant are all unsupported by clinical trials but potentially of some benefit. Diffuse bronchiolitis has also been reported following acute exposure.[40]

Chronic Injury

Two forms of chronic injury include bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia.

Bronchiolitis Obliterans Bronchiolitis obliterans (BO) is a well-documented but infrequent long-term sequela of toxic gas exposure, especially of nitrogen dioxide (Refer to Chapter 54)[41,42] but also to ammonia,[43] mercury,[44] and sulfur dioxide.[45,46] The disease typically presents 1 to 3 weeks following the initial lung injury and pulmonary edema (Fig. 90-2). The interim is often free of symptoms. When BO does develop, patients may present with dyspnea on exertion or obstructive findings on spirometry. Physical examination may be either unremarkable or remarkable only for early inspiratory crackles. Chest X-ray will either be normal or demonstrate hyperinflation. Pulmonary function tests typically demonstrate airflow obstruction that may in some cases also be associated with restrictive defects. On biopsy, granulation tissue will be seen in the lumen of small airways and bronchiole walls may be obliterated by fibrous scarring. Corticosteroids may be of benefit in preventing or alleviating BO if administered early in the course of the disease,[47] though this is controversial.

BO Organizing Pneumonia BO organizing pneumonia (BOOP) is another observed delayed sequela of toxic inhalation.[48,49] Patients present in the weeks following exposure with fever, a persistent and nonproductive cough, sore throat, and malaise. Late inspiratory crackles may be observed. Chest X-ray may reveal bilateral patchy "ground-glass" densities that start as focal lesions but may coalesce with time. Pulmonary function tests generally reveal a restrictive process with decreased diffusion capacity. Histologically, granulation tissue extends past the terminal bronchioles and into the alveolar spaces, sometimes with interstitial scarring. BOOP and BO are probably both chronic results of the initial inflammatory response

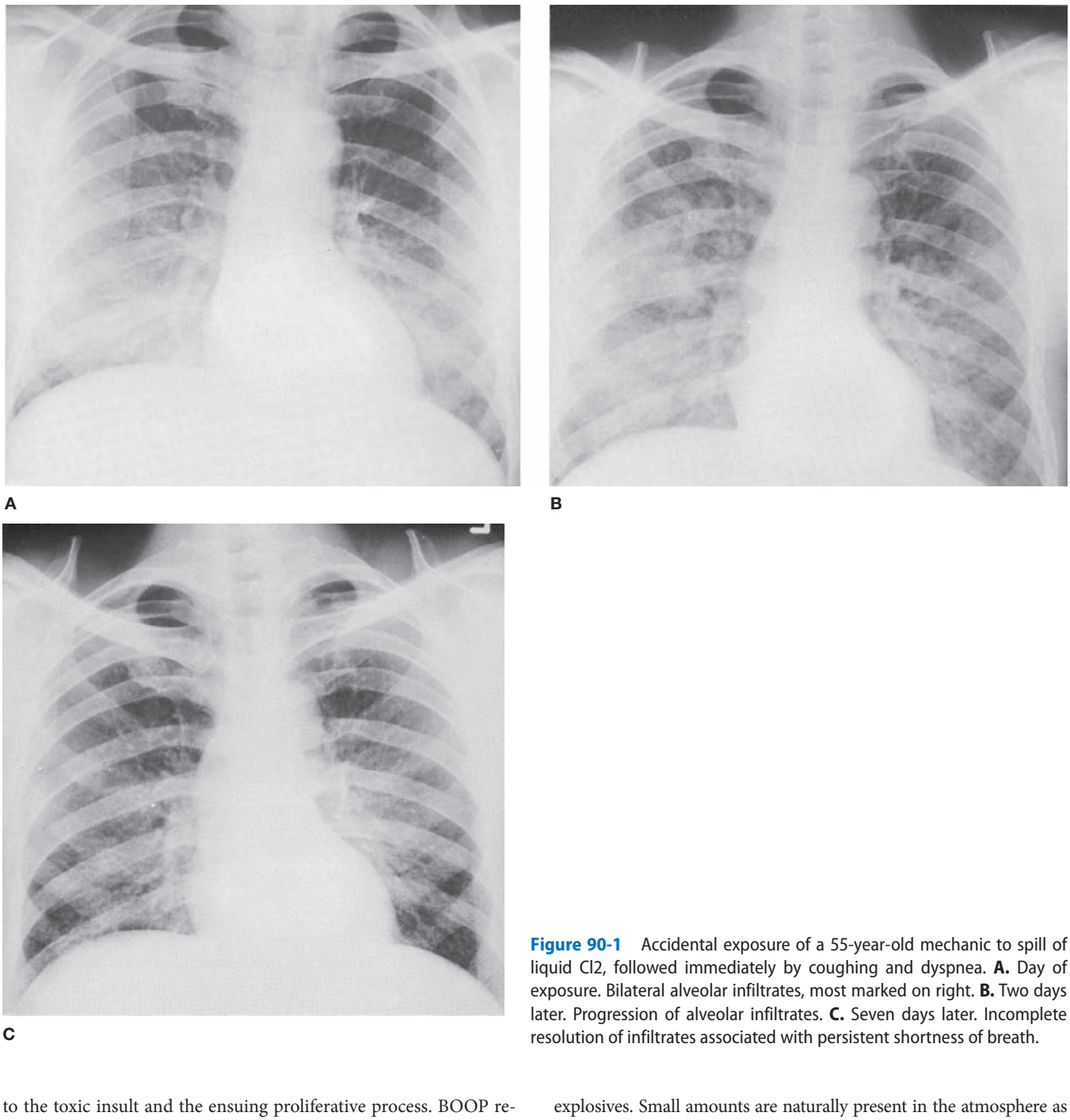


Figure 90-1 Accidental exposure of a 55-year-old mechanic to spill of liquid Cl2, followed immediately by coughing and dyspnea. **A.** Day of exposure. Bilateral alveolar infiltrates, most marked on right. **B.** Two days later. Progression of alveolar infiltrates. **C.** Seven days later. Incomplete resolution of infiltrates associated with persistent shortness of breath.

to the toxic insult and the ensuing proliferative process. BOOP responds well to corticosteroids,[50] though a small number of patients may develop progressive fibrosis. Duration of therapy should be guided by the patient's clinical status.

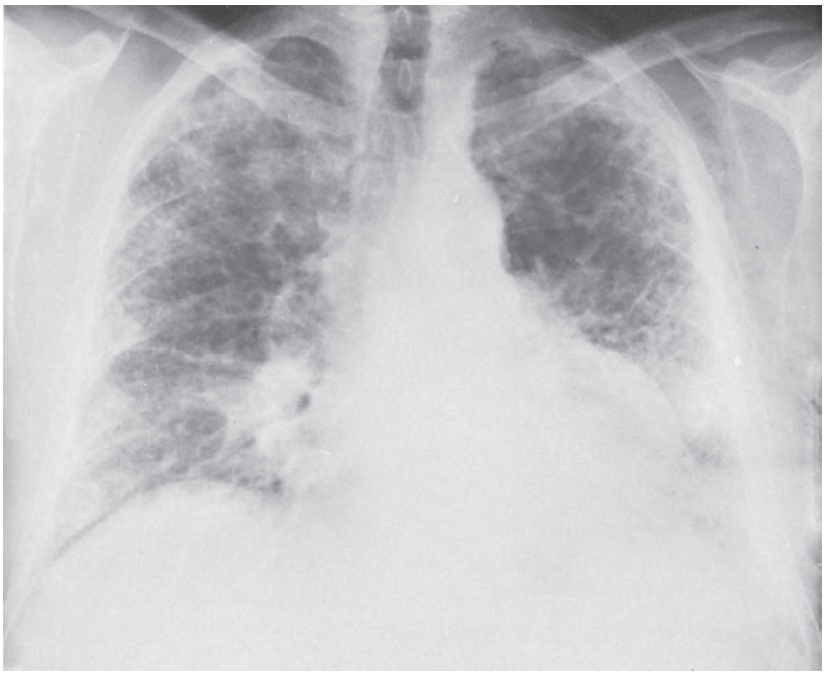
EFFECTS OF SPECIFIC INHALED TOXINS ON THE RESPIRATORY SYSTEM

The respiratory consequences of inhalation of commonly encountered toxins are discussed individually below.

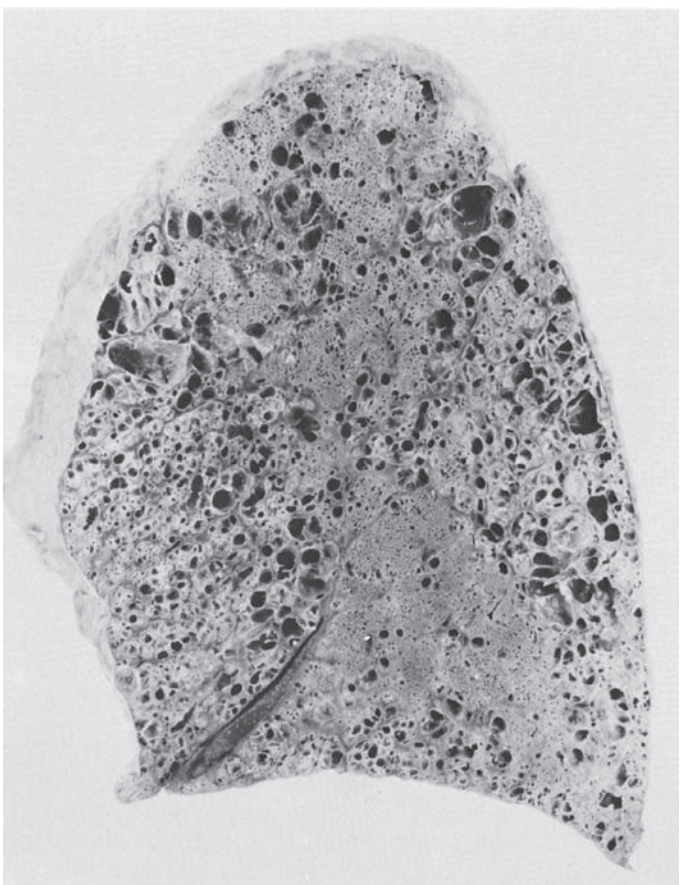
AMMONIA

Ammonia (NH_3) is a stable colorless gas at room temperature and a water-soluble nitrogen-containing compound that ranks among the most commonly spilled hazardous substances (Table 90-4).[51] Familiar to all as a household cleaner, it also has countless uses in industry: as a chemical coolant used for refrigeration, as a fertilizer, as a fixative in photocopiers, and in the manufacture of polymers and explosives. Small amounts are naturally present in the atmosphere as products of the putrefaction of vegetable and animal proteins. The smell of concentrated ammonia (as low as 5 ppm) is immediately recognizable. Due to the prevalence of ammonia in household cleaners and to its use in smelling salts (which exploit the noxious effect of ammonia on nasal membranes to arouse consciousness), the odor threshold may extend to over 50 ppm because of the olfactory fatigue and adaption.[52,53] Ammonia is frequently dissolved into water for storage and transportation, and vaporizes readily on exposure to air. Most inhalation exposures are the result of accidental releases, including tank leaks and transportation mishaps,[54–56] and most exposures occur in the industrial workplace.[57] A recently reported source of exposure is via fumes produced in clandestine methamphetamine laboratories.[58]

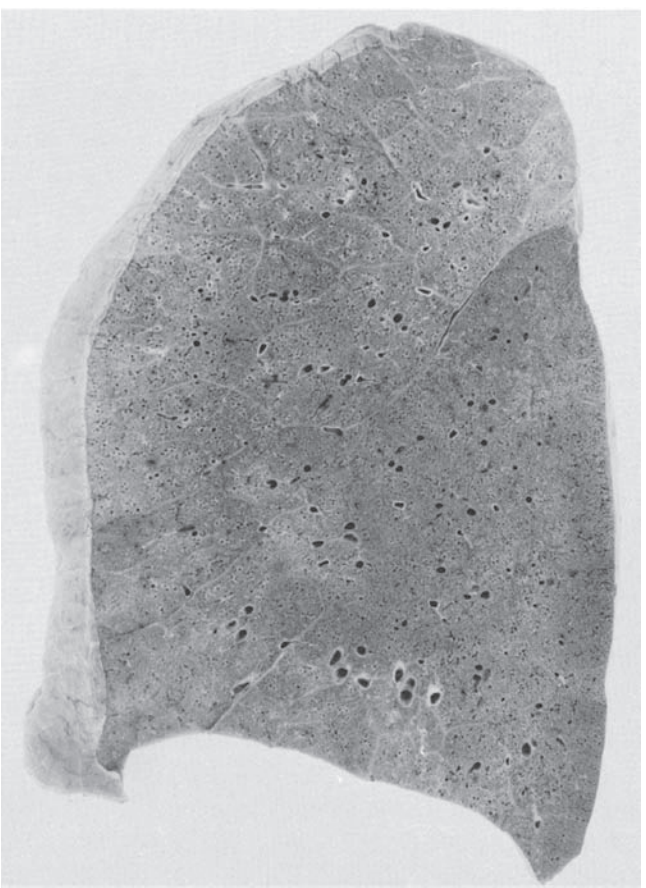
The mechanisms of toxicity to the respiratory system involve both direct irritation and alkaline chemical burns. Ammonia tends to affect the proximal airways, where it reacts rapidly with the water present on mucosal surfaces to form ammonium hydroxide, causing tissue liquefaction. This necrosis liberates formerly intracellular



A



B



C

Figure 90-2 Bronchiolitis obliterans in a 63-year-old man who had been exposed to a wide variety of unidentified fumes in his jobs, which included welding. **A.** Chest radiograph. Diffuse pulmonary fibrosis and honeycombing, most marked in the peripheral portions of the lungs. **B.** Sagittal section of lung from same patient showing markedly dilated airspaces. Microscopic sections revealed bronchiolitis obliterans and chronic interstitial pulmonary fibrosis. **C.** Normal lung from a 43-year-old man who died suddenly. The difference between (**B**) and (**C**) in the alveolar portions of the lungs is striking. *(Used with permission of Dr. R. Ochs.)*

TABLE 90-4 Pulmonary Manifestations of Toxin Inhalation

		Acute Clinical Manifestations		Chronic Clinical Manifestations	
Substance	Onset	Upper airway irritation	Pneumonitis, ARDS	Bronchiolitis obliterans, BOOP	RADS
Irritant gases					
Ammonia	Minutes	Severe	+	+	+
Chlorine	Minutes to hours	Moderate	+	–	+
Hydrogen chloride	Minutes	Severe	+	–	+
Oxides of nitrogen	Hours	Mild	+	+	+
Ozone	Minutes to hours	Mild	+	–	–
Phosgene	Hours	Mild	+	–	+
Sulfur dioxide	Minutes	Severe	+	+	+
Metals					
Cadmium	Hours	Mild	+	–	–
Mercury	Hours	Mild	+	+	–
Zinc chloride	Minutes	Mild	+	–	+
Zinc oxide	Hours	Mild	+	–	–

+, exposure reported to be associated with clinical entity; –, exposure as yet not reported to be associated with clinical entity.

water, which serves as further reactant for ammonia, perpetuating the reaction. In addition to the alkali burns caused by the generated ammonium hydroxide, thermal burns can result from the heat generated by this exothermic reaction. The resulting injury, typical of alkali burns, penetrates deeply. The initial injury to the mucosa of the oropharynx can cause edema, hemorrhage, sloughing of tissue, and increased secretions that can bring about fatal upper airway obstruction. Ammonia is directly caustic to airways at concentrations of 1000 ppm and higher.

Though concentrated at the proximal airways, the effects of ammonia have been observed at all levels of the respiratory tract. The penetration of the gas to the smaller airways and alveoli is a function of its concentration and the duration of exposure. Reported acute conditions associated with ammonia exposure include pulmonary edema, laryngitis/tracheobronchitis, bronchiolitis, and bronchopneumonia; reported chronic sequelae include bronchiectasis, bronchospasm/asthma (termed RADS), and chronic obstructive pulmonary disease.[59] There are several reports of interstitial lung disease following a single exposure to ammonia.[57] A biphasic pattern of pulmonary response to ammonia inhalation has been reported, characterized by initial, acute pneumonitis that may clear over the next 2 to 3 days, followed in some individuals by the gradual development of airway obstruction and respiratory failure.[54] There may be a correlation between the development of a bacterial superinfection after exposure with the ensuing emergence of bronchiectasis.[60] In one review of published case reports, 21% of patients with acute ammonia inhalation died within 60 days of exposure.[59] The most common causes of death were laryngeal edema and obstruction, noncardiogenic pulmonary edema, and extensive pneumonic complications.

Management of a patient who has experienced ammonia inhalation requires removing him or her from the source of the irritant, securing the airway, and immediately irrigating all exposed surfaces (especially the eyes) with copious amounts of water. Humidified oxygen should be administered early. Airway management aggressiveness depends on the extent of complications such as laryngeal edema, pulmonary edema, hemoptysis, or respiratory failure that occur.[61] Rales detected on physical examination are predictive of the subsequent hospital course, even in the absence of hypoxemia and chest X-ray abnormalities.[54] Medical management is largely supportive. Aerosolized bronchodilators together with corticosteroids can be administered to treat bronchospasm. Corticosteroids and antibiotics are both frequently used, but both are unproven in human trials.

CHLORINE, CHLORAMINES, AND HYDROCHLORIC ACID

Chlorine (Cl_2) is a common gas of intermediate water solubility. The first reports of its toxicity followed its use as an agent of chemical warfare in World War I, and war gassings remain the largest historical source of chlorine gas exposure.[62] Most exposures since then have occurred in the industrial setting, where chlorine is used in the manufacture of paper, cloth, antiseptics, and other products.[63] More common in the household is the liberation of chloramines and other toxic chlorine derivatives from the reaction of chlorine-containing products (such as hypochlorite bleach) with ammonia or products containing hydrochloric or phosphoric acid. Numerous exposures to chlorine gas have occurred near swimming pools, where chlorine-releasing agents (e.g., calcium hypochlorite and chlorinated isocyanuritic acids) are used in water purification.[40] Chlorine gas is greenish-yellow in color and is heavier than air; though its odor is distinct, patient exposure to it may be prolonged compared to other toxic gases due to its delayed irritation of mucosal surfaces and its high density, which keeps it low to the ground.

The pathogenicity of chlorine gas derives directly from elemental chlorine's effects on the respiratory tract and indirectly from its reaction with water to form hydrochloric acid (HCl) and hypochlorous acid (HOCl). The character and distribution of injury from chlorine exposure varies according to duration of exposure and the relative concentrations of elemental chlorine and its derivative compounds. HCl and HOCl possess considerable water solubility and are responsible for the tissue damage sustained by the upper airways and ocular conjunctivae. Irritation to trigeminal nerve endings caused by these compounds can cause a reflex bronchoconstriction that may contribute to compromise airway diameter.[64] In addition to causing the tissue coagulation typical of acid exposures (described above), these compounds ionize and enter cells, where they may form reactive oxygen species. HOCl has been shown to react with nitrite (NO_2^-) to produce reactive nitrogen-containing compounds able to nitrate, chlorinate, and dimerize phenolic amino acids.[65] As nitrite and nitric oxide (its parent compound) levels are elevated at sites of tissue inflammation, this potentially is another mechanism of injury.[66] Though lower

respiratory tract irritation has been reported following high-level exposures, less than 5% of inhaled chlorine gas penetrates beyond the upper airways.[67] Fatal dosages from chlorine inhalation have ranged from 50 to 2000 ppm.[40]

The immediate clinical manifestations of acute chlorine exposure are typical of irritants of its solubility: rhinitis, cough, dyspnea, wheezing, and chest tightness, along with conjunctivitis and skin irritation.[68] When chlorine gas exposure has resulted acutely in death, autopsies have revealed diffuse ulcerative tracheobronchitis, pulmonary edema, thrombi within pulmonary vessels, and denudation of respiratory tract epithelium.[69] Acute respiratory symptoms are more prevalent and severe among patients who already have chronic respiratory disease. In 2005, a derailment train released 40 to 60 tons of chlorine gas near a small town in South Carolina. Nine people died and 71 were hospitalized. The majority of people (>90%) had respiratory symptoms including wheezing, rales/crackles, cough, decreased breathing sound, rhonchi, and labored breathing. Autopsy findings revealed the causes of death included asphyxia, lactic acidosis, and acute respiratory failure.[70]

The lasting respiratory sequelae of chlorine gas exposure have been described since the years following use of the gas in World War I.[71] Reported long-term pulmonary diseases following exposure have included both restrictive and obstructive processes, frequently resolving to normal function within a month and almost always before 2 years following exposure. RADS may be an infrequent sequela of high-level exposures to chlorine.[22,72]

Patients who have been exposed to chlorine gas should be managed according to the severity of their presenting symptoms similarly to other victims of irritant inhalation. The treatment for lung injury is primarily supportive care including humidified oxygen administration, lung protective mechanical ventilation, and pharmacologic therapy. Nebulized sodium bicarbonate has shown promise as a useful treatment,[73] but lacks supporting clinical trials and showed no outcome benefit in a relatively large observational study of chloramine gas exposure.[74] Beta-agonist bronchodilators and corticosteroid are frequently used and are probably of benefit. The reported benefit of corticosteroid administration is anecdotal[69] and unconfirmed by clinical trial.

SULFUR DIOXIDE

Sulfur dioxide is a heavy, colorless, and highly water-soluble gas that has the distinct, pungent odor of burnt matches. It is generated in the combustion of coal and petroleum and is often used as a preservative in alcoholic beverages and fruit. Industrial exposures have occurred around ore smelting, metal smelting, oil refining, sugar refining, and the bleaching of wool and wood pulp. In 1930, 63 people died and thousands became ill in the narrow Meuse River Valley of Belgium due to the trapped high concentrations of sulfur dioxide from the waste products of industry resources (United States Environmental Protection Agency). Sulfur dioxide is among the most harmful gases released to the atmosphere during volcanic eruptions[75]; in 1986 the gases emitted from one eruption killed nearly 2000 people in Cameroon.[76] Sulfur dioxide's great density keeps it low to the ground and slow to dissipate from sites of release; thus children may be at an increased risk of exposure.

Sulfur dioxide reacts with water present on mucus membrane to form sulfuric acid, which causes tissue coagulation underlying exposed surfaces. Sulfuric acid also further dissociates into hydrogen ions, sulfite, and bisulfite,[77] which can then react with oxygen to produce reactive oxygen species; ensuing lipid peroxidation may be a contributing mechanism of injury to immediate tissues and elsewhere.[8,78]

Sulfur dioxide is detectible to humans at 3 to 5 ppm and is lethal at levels exceeding 400 ppm for 1 minute.[79] High water solubility makes sulfur dioxide primarily an upper airway irritant. The direct irritant of bisulfate iron inhibits mucociliary transport.[80] The irritation-induced parasympathetic stimulation leads to smooth muscle contraction and mucosal secretion. Exposures of high enough intensity can irritate both upper and lower airways. Patients exposed typically present with dyspnea, burning of the nose and throat, rhinorrhea, cough, and airway obstruction.[81] Proximal airway injury is characterized by acute denudation of the airway mucosa without inflammatory cell infiltrates. When lower airways are exposed, alveoli fill with fluid due to noncardiogenic pulmonary edema and the clinical picture is consistent with ARDS. Alveolar architecture is generally preserved. Extremely high-intensity acute exposures can lead within minutes to death from respiratory failure due to a combination of alveolar hemorrhage and edema, possible reflex vagal stimulation, and the asphyxiating effect of high concentrations of sulfur dioxide.[82] RADS has been reported following single sulfur dioxide exposure[29]; bronchitis has also been observed.[83] One pattern of postexposure progression reported is a rapid recovery followed several weeks later by the onset of irreversible airflow obstruction due to BO.[82] Care for patients who have been exposed to sulfur dioxide is supportive: humidified supplemental oxygen, bronchodilators, and intubation and ventilation if necessary. The use of corticosteroids in the setting of ARDS following sulfur dioxide exposure has not been shown to be of benefit, but a trial is not unreasonable. Antibiotics may be reserved for use upon evidence of infectious complications.

NITROGEN OXIDES

Nitrogen oxides are ubiquitous air pollutants, released from automobile engines and the combustion of coal and petroleum, and are present in cigarette smoke. High-level acute exposure is most likely to occur in industrial settings, including mining, acetylene welding, and explosives manufacturing. A well-known form of exposure occurs in "Silo-filler's disease," in which farmers inhale concentrated nitrogen dioxide gas released within silos by decomposing nitrogenous biomaterial.[41,84] Exposures to high levels of nitrogen dioxide have been attributed to blast furnaces,[40] anesthetic gases,[85] military incidents,[86,87] and ice-hockey arenas (secondary to combustion byproducts from ice-resurfacing machines).[88–91] Nitrogen dioxide is a liquid at room temperature and a reddish-brown gas above 70°F. The acrid smell of nitrogen dioxide makes the inhalation exposure to be avoided at low concentration. Thus, short-term (1 hour peak) nitrogen dioxide concentration outdoor is unlikely to exceed 0.2 ppm.[92] However, low concentrations at 4 ppm may anesthetize the nose, resulting in overexposure.

Nitrogen dioxide is hydrolyzed by the water on mucosal surfaces to form nitric and nitrous acids, though much of its toxicity is explained via the free radical activity of nitrogen dioxide itself and the nitrites and nitrates that derive from it.[93] Though the predominant site of toxicity from nitrogen dioxide exposure is the interface of the terminal bronchioles and alveolar membranes,[94] the relative insolubility of nitrogen dioxide in water ensures that enough gas penetrates the upper airways such that injury can occur virtually anywhere along the respiratory tract.[95] Nitrogen dioxide itself is a reactive nitrogen species that, along with other reactive derivatives, is capable of lipid peroxidation and protein oxidation,[96] both of which may be significant contributors to the gas toxicity via disruption of the cell membrane. Mice with defective toll-like receptor 4 expression exhibit a lessened response to nitrogen dioxide exposure compared to normal strains,[10] suggesting that the patient's innate immunity may play a role in disease development. There is also evidence that nitrogen dioxide exposure is mutagenic to lung cells.[97]

The initial effects of nitrogen dioxide exposure are relatively benign at all but very elevated concentrations, that is, cough, fatigue, and, occasionally, nausea. Recent studies suggest that exposure of nitrogen dioxide in the first year of life increase the risk of persistent cough and developing asthma.[98,99] With high-intensity exposure, patients may also experience headache and chest tightness, though

even these symptoms tend to resolve promptly. Nitrogen dioxide is less irritating to mucosal surfaces than other toxic inhalants. Symptoms typically abate for a period of hours before an intense pulmonary edema consistent with ARDS occurs due to increased capillary permeability following extensive damage to vascular and airway epithelia. Patients who survive this are at risk for the development of BO and BOOP 1 to 4 weeks following exposure.[42]

This clinical course of nitrogen dioxide toxicity demands vigilant monitoring on the part of medical personnel. Patients who are relatively asymptomatic following exposure may rapidly progress to ARDS within hours or severe obstructive BO within weeks. Treatment is largely supportive. In animal studies, antioxidant administration has proven protective against lung injury following nitrogen dioxide exposure,[100] suggesting that aerosolized antioxidant medications are potentially of some utility in humans. Interestingly, nitric oxide (NO) has been used successfully as a pulmonary vasodilator in the treatment of ARDS following acute nitrogen dioxide toxicity.[84] Individuals who survive the initial lung injury still require close following with serial assessment of pulmonary mechanics and gas exchange over the ensuing several weeks. Patients exhibiting evidence of progressive airflow obstruction may benefit from corticosteroids to prevent or decrease the severity of BO.

PHOSGENE

Phosgene (carbonyl chloride, $COCl_2$), like nitrogen dioxide, has relatively low water solubility and penetrates deeply to the alveolar spaces. It is colorless, lacks a strong odor (in high concentrations it is reported to smell like moldy hay) and is not irritating to the nasal and oral mucosa. These traits were notoriously exploited in World War I, when phosgene was used by both sides of the conflict as a weapon, resulting in tens of thousands of fatalities. Modern uses include the production of pesticides, polyurethane resin, toluene diisocyanate, pharmaceutical products, and dyes. It can also be produced accidentally via the heat decomposition of various solvents, paint removers, dry-cleaning fluids, and methylene chloride.[101,102] Small amounts can naturally occur from the breakdown and combustion of organochlorine compounds, such as those used in refrigeration systems.

Phosgene reacts with water to form hydrochloric acid and carbon dioxide, but its limited solubility results in little hydrolysis in the upper airways. In the relatively moist alveolar air spaces, however, the resulting acid is destructive of alveolar walls and small vessels, resulting in epithelial necrosis. Phosgene's lack of irritability in the upper airways precludes the reflex bronchoconstriction provoked by other toxic gases, ensuring open passage of the gas to the alveoli. Phosgene also causes tissue damage by rapidly acetylating the amino, hydroxyl, and sulfhydryl groups of proteins, resulting in protein denaturation and structural compromise of cell membranes,[103] leading to a breakdown of the blood–air interface. Lipid peroxidation has also been shown to occur, and antioxidant therapy has been shown to attenuate phosgene's effects in animal models.[104]

On exposure to phosgene, patients may experience chest tightness, wheezing, or cough; some victims experience no immediate symptoms. Following exposure, the patient experiences a latent period of 30 minutes to 8 hours before the onset of symptoms. The duration of this latent period is thought to be inversely proportional to both the severity of exposure and the ensuing severity of disease.[103] The latent period is typically followed by pulmonary edema: the patient experiences dyspnea, cough and respiratory distress, and rales and cyanosis are appreciable on physical examination. Though survival for patients with acute phosgene exposure is good, numerous long-term sequelae have been reported, including prolonged exertional dyspnea, chronic bronchitis, and emphysema.[105]

During the latent period following exposure, numerous therapeutic options exist that may prevent or lessen the severity of pulmonary edema. Early intervention with antioxidant (N-acetylcysteine) has been shown to be beneficial in animal models by reducing free radical species and preventing biologic mediator–induced inflammation.[104] Ibuprofen, aminophylline, and isoproterenol have all proven beneficial in animal models.[106] Corticosteroids are frequently used but of unproven benefit.[107] There is no benefit from nebulized steroid when administered 1 hour after exposure, or methylprednisolone if administered intravenously ≥6 hours after exposure. Intravenous bolus of high-dose corticosteroid (e.g., methylprednisolone 1 g) may be considered if presentation is <6 hours, although no experimental data are available.[108] The experiments from animal models suggested nebulized furosemide for pulmonary edema should be avoided following phosgene exposure.[109] Nebulized salbutamol treatment following phosgene is also not recommended.[110]

OZONE

Ozone (O_3) is a colorless, odorless gas of low water solubility. It is found throughout the atmosphere and occurs in greatest concentrations in the stratosphere, where it is protective against ultraviolet radiation. It is the main oxidant pollutant in smog and can reach hazardous levels at ground levels on days with elevated atmospheric temperature. Atmospheric levels are known to aggravate chronic lung diseases such as asthma[111] and chronic obstructive pulmonary disease.[112] Acute toxic exposures are associated with its uses in industry, including bleaching of fabrics, disinfecting water and surfaces, and the manufacture of plastics. Reports of acute ozone exposure have been reported in an airplane cabin on a high-altitude flight.[113]

Ozone is extremely reactive, and is almost entirely consumed before crossing a single bilayer membrane.[114] It results in the formation of reactive nitrogen species[115,116] and probably causes toxicity via the oxidation of membrane lipids.[117] Pre-exposure to ozone resulted in enhanced airway hyperresponsiveness (AHR), increased concentrations of total protein and proinflammatory cytokines in whole-lung lavage, and reduced inflammatory cell recruitment to the lower airways. Molecular mechanisms include enhancement of LPS- and LTA-mediated signaling in lung tissue.[118,119] Studies in humans have shown that exposure to ambient levels of ozone can selectively impair epithelial permeability,[120] and that this loss of epithelial integrity is parallel to, but not necessarily coupled with, increased inflammation in the lower respiratory tract.[121,122] Ozone induces epithelial necrosis and airway inflammation[122] and in severe exposures can cause dyspnea, cyanosis, and pulmonary edema. A genetic component to the response to ozone through innate immune signaling has been reported.[123] Treatment is supportive and no specific therapies have been shown to be beneficial.

CADMIUM

Cadmium is a highly corrosion-resistant metal with many industrial applications. Most cadmium is used in nickel–cadmium batteries, though it is also found in alkaline accumulators, electroplating, bearings, solder, and as a barrier around nuclear fission generators. It is present in many metal ores, and cadmium-containing pigments are used in paints, artists' colors, rubber, plastics, printing inks, wallpaper, leather, glass, and enamels. Most inhalations occur in workers who are involved with soldering, brazing, smelting, and refining.[124] The heating of sheet metal electroplated in a cadmium cyanide bath has been reported to cause cadmium toxicity.[125]

The mechanisms involved with the acute lung injury due to cadmium inhalation are not well defined. Some studies suggested that cadmium-induced alveolar cell apoptosis is mediated by FasL and caspase-dependent mitochondrial apoptosis pathways in animal models.[126] Decreased adhesion molecular E-cadherin in epithelial cells of the alveoli and small bronchioles and of VE-cadherin in vascular endothelial cells were found in mouse models post

exposure to cadmium.[127] Postmortem examinations of individuals who died after accidental acute inhalation exposure have revealed tracheobronchitis, consolidated lungs, denuded bronchial epithelium, intra-alveolar hemorrhage, and the presence of macrophages in the alveolar spaces.[128] It is known that cadmium inhibits the synthesis of plasma alpha 1-antitrypsin,[129] which may explain the correlation between cadmium exposure and the later development of emphysema.[130] Rats exposed to cadmium fumes and cadmium chloride aerosols develop pulmonary edema and on necropsy show increased numbers of alveolar type II cells.[124]

When cadmium-containing materials are heated, cadmium vapors and cadmium oxide fumes are released. Patients who are exposed initially present similarly to those with metal fume fever (see below): They are asymptomatic for several hours before developing fever, malaise, and myalgias.[124] These constitutional symptoms are often accompanied by, or shortly followed by, respiratory distress, including cough, chest tightness, and dyspnea. Cadmium may be detected in the urine if the identity of the toxin is uncertain.[131] Fatal cases have been remarkable for initial pneumonitis that relentlessly progresses to ARDS and eventual death from respiratory failure.[128] Management is supportive; there are no specific treatments for cadmium inhalation. Formoterol and ipratropium bromide have been shown to partially protect the lungs against inflammation by reducing neutrophilic infiltration in rats.[132]

MERCURY

Though mercury has a low solubility in distilled water, its solubility increases in contact with plasma or whole blood, as at the blood–air interface. Sources of mercury gas exposure are primarily industrial and include ore smelting, cement production, fur and felt hat manufacture, fossil fuel combustion, and gold extraction. Mercury is found within the silver amalgam used by dentists, and a number of exposures, including several with fatal outcomes, have occurred in the home during amateur attempts to extract precious metals from amalgams that also contain mercury.[133,134]

Like phosgene and cadmium, mercury vapor has little or no immediate upper airway or mucosal surface irritant effects, and as a result exposed individuals may inadvertently remain in an area where the harmful vapors are present. The fatal level of mercury vapor to humans is not known. An exposure to more than 1 to 2 mg/m^3 of elemental mercury vapor for a few hours causes acute chemical bronchiolitis and pneumonitis.[130] Typical clinical presentations include symptoms of cough, dyspnea, and respiratory distress that develop 12 to 24 hours post exposure. These initial symptoms are sometimes accompanied by fever, nausea, vomiting, diarrhea, and a metallic taste in the mouth, similar to what is often experienced by individuals with metal fume fever and associated transient pneumonitis. In fact, mercury vapor inhalation can be mistaken for metal fume fever or influenza. Symptoms of mercury vapor inhalation do not, however, spontaneously resolve as with metal fume fever. Instead, the pneumonitis may progress to ARDS; death has been preceded in several reports by tension pneumothorax.[134,135] The toxicity of mercury vapors within the lung is thought to be due in part to the irritant effects of oxidized mercurous and mercuric ions[136] and to the disruption of enzyme systems containing sulfhydryl groups.[134] Mercury coagulates protein, blocks cellular metabolism of carbohydrates at the pyruvic oxidase level, and as a result produces a metabolic acidosis.[133] Lung pathology following acute exposure reveals pulmonary edema, capillary damage, and the desquamation and proliferation of airway epithelium followed by an obliteration of airspaces.[137] Early CT imaging in patients with acute mercury poisoning reveal ground-glass opacification, alveolar consolidation, and ill-defined nodules. These abnormalities were resolved in follow-up CT scans 30 days after exposure.[138] Inhaled mercury vapor is absorbed rapidly into the blood, where it can achieve systemic toxicity; renal, hepatic, and nervous system pathology have been reported.[139,140] Patients surviving the acute injury typically experience resolution of their symptoms within a week following onset, but have also progressed to develop interstitial fibrosis.[141,142] Mortality due to exposure may be increased in children.[143]

Blood levels of mercury may reflect acute uptake, and urine levels can monitor chronic stores. Treatment of mercury inhalation is supportive and addresses the acute lung injury. Mechanical ventilation, including positive pressure and high frequency oscillating ventilation, may be beneficial in the treatment of mercury-induced ARDS.[143] Early vigorous administration of steroids can decrease the inflammation and delay or prevent the progression to severe interstitial pulmonary fibrosis in mildly affected patients.[144] Chelating agents, such as dimercaprol and d-penicillamine, are frequently used to increase the rate of mercury excretion after ingestion, but have not been shown to affect the outcome of the acute lung injury.[134,144]

ZINC CHLORIDE

Zinc chloride ($ZnCl_2$, or hexite) is odorless, a major ingredient of smoke bombs and smoke-generating devices, and has been responsible for numerous toxic and fatal exposures.[145–148] The compound forms when zinc oxide is ignited with hexachlorethane. Toxic inhalations have occurred in settings in which individuals have inhaled smoke in confined spaces, in most instances without functional protective breathing apparatus (Fig. 90-3). The smoke effect tends to contribute to the duration of exposure by obscuring vision, sometimes resulting in directional disorientation and the inability to quickly escape the area of exposure.

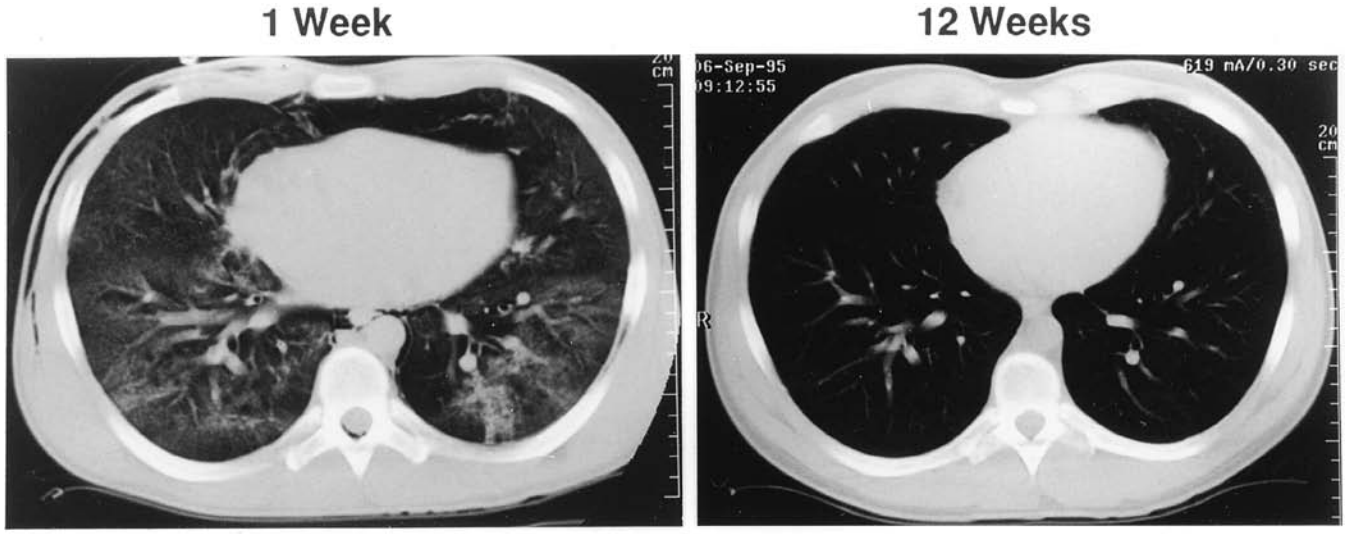
When inhaled, zinc chloride is in particulate form with an average particle size of 0.1 μm, small enough to allow large amounts of it to penetrate through to the lower respiratory tract. After depositing on the airway and alveolar surfaces, zinc chloride reacts with water to form hydrochloric acid and zinc oxychloride. This directly causes irritation of exposed mucosal surfaces and is the probable mechanism behind the diffuse lung injury observed on exposure.[149] The irritation of the mucus membrane of the respiratory tract leads to symptoms, which include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting.

Zinc chloride inhalation is commonly followed by tracheobronchitis and pneumonitis, reflecting the sites of particle deposition. Patients experience cough, dyspnea, and chest tightness followed by a period of relative stabilization before progressing to ARDS.[146–148] Chest imaging may be initially normal but can reveal pleural effusions, pneumomediastinum, and bilateral infiltrates consistent with pneumonitis. There is evidence that prominence of ground-glass opacities observed on high-resolution CT imaging is predictive of both severity of exposure and length of hospital stay.[148]

A urine zinc level may confirm the diagnosis of zinc inhalation toxicity. Patients should be monitored for progression to ARDS and treated with supplemental oxygen and mechanical ventilation if indicated. The administration of high doses of N-acetylcysteine may accelerate systemic zinc clearance[150] and thereby spare some oxidant-induced lung injury, though this is unsupported by clinical experience.[146] Since zinc inhalation is locally deposited in the respiratory tract rather than in systemic zinc overdose, the effect of N-acetylcysteine is questionable.[150] Corticosteroid use is similarly controversial. The aim to reduce overwhelming inflammation by early administration of intravenous steroid was offset by the risk of ARDS in patients with sepsis.[151]

MACE AND TEAR GAS

"Tear gas" is actually not gas but a compound of toxic chemical irritants collectively given the names chloroacetophenone (CN or "chemical mace"), *ortho*-chlorobenzylidene malonitrile (CS) and



	1 week	3 weeks	12 weeks
FVC	2.5 (54%)	3.2 (68%)	5.7 (119%)
FEV_1	2.2 (52%)	3.0 (69%)	4.7 (107%)
FEV_1/FVC	88%	75%	83%
TLC	3.6 (61%)	4.9 (82%)	6.9 (114%)
RV	1.1 (90%)	1.3 (106%)	1.2 (94%)
DLCO	14 (44%)	19.1 (58%)	48.7 (141%)

Figure 90-3 Chest computed tomography (CT) scan and pulmonary function tests obtained on a person with inhalation injury after a smoke bomb was ignited in an underground cave. The CT scans were obtained 1 week and 12 weeks after the accident and demonstrated extensive interstitial lung disease, which resolved on radiographs. The pulmonary function tests obtained 1, 3, and 12 weeks after the exposure demonstrated marked restrictive lung function and abnormal gas exchange, which also resolved within 3 months of exposure.

oleoresin capsicum (OC or "pepper spray"). All three agents are used by military and law enforcement agencies to control crowds and individuals, making use of their intense and immediate irritant effects on mucus membranes and lacrimal glands. Exposure to any of them results in immediate rhinorrhea, mucositis, chemical conjunctivitis, and profuse lacrimation.[152,153] Immediate pulmonary effects include an intense burning sensation in the upper airways, reflex airway constriction, chest tightness, dyspnea, and cough. Exposure may also provoke nausea, headache, and photophobia. Delayed contact allergy, leukodermia, or exacerbation of pre-existing dermatitis has also been described in case reports.[154] Severity of response depends on the concentration of the agent used, the duration of exposure and the presence or absence of ventilation and protective breathing apparatus.

The effects of tear gas are predominantly due to its upper airway irritant effects, and thus lower airway injury and parenchymal disease are rarely observed. Auscultation of the chest is typically clear, and the chest radiograph is usually without abnormality. Case reports of severe pulmonary disease exist, describing pneumonitis, pulmonary edema, RADS, and acute bronchospasm in an asthmatic.[155–158] These cases have in common prolonged periods of exposure with poor ventilation. A fatal hypersensitivity reaction to CS has been reported.[159]

Due to the possible secondary contamination of healthcare staff, the initial medical management of patients exposed to tear gases consist primarily of nonspecific chemical decontamination and symptomatic therapy.[160] The most immediate concern in the treatment of tear gas exposure is maintenance of a patent airway. Mucosal surfaces should be irrigated profusely, and suction may be useful in clearing the copious oral and nasal secretions that may compromise the airway. Humidified O_2 should be administered. Beta-agonists and ipratropium aerosols should be used in the presence of bronchospasm[161,162]; no benefit from corticosteroids has been observed. Patients with prolonged or intense exposure should be monitored carefully for evidence of progression to significant respiratory disease.

SYSTEMIC ILLNESS FROM INHALED TOXINS

Systemic, flu-like illness lasting under 2 days has been observed in patients exposed to organic dusts and fumes of heated metals and fluorocarbons. The disease course is self-limited and in all cases appears to be cytokine mediated.

METAL FUME FEVER

Since its first description by Potissier in 1822,[163] metal fume fever has been known by a number of other names: brazier's disease, spelter shakes, brass chills, zinc chills, welder's ague, copper fever, foundry fever, and Monday morning fever. It is a self-limited syndrome characterized by the delayed onset of fever, chills, myalgias, and generalized malaise following exposure to fumes that contain

metal oxides. Specific fumes that have been blamed include those of beryllium, cadmium, copper, magnesium, nickel, silver, and zinc. Welders are at the highest risk for developing metal fume fever, though it has been reported in other metalworking occupations including soldering, brazing, cutting, metallizing, forging, melting, and casting. Episodes of varying severity of metal fume fever may be experienced by between 20% and 35% of all welders.[164,165] Exposure is typically associated with confined spaces and poor ventilation. An estimated 2000 cases of metal fume fever are reported each year in the United States.[166]

The typical course of metal fume fever begins with sensations of dry throat and a sweet or metallic taste. Fever, chills, and myalgias develop from 4 to 8 hours after exposure and spontaneously resolve within 48 hours. Respiratory-related symptoms of chest tightness, nonproductive cough, and dyspnea are sometimes observed. Laboratory findings are remarkable for transient leukocytosis; chest X-ray is typically normal, though findings consistent with pneumonitis have been observed. Pulmonary function tests are usually normal, though obstructive and restrictive deficits, as well as abnormalities of diffusion, have been reported. Repeated exposure appears to lead to tachyphylaxis; however, this tolerance is transient and only persists through the work week. The name "Monday morning fever" refers to the recurrence of acute disease on return to exposure following a short period of absence.[167] A proposed mechanism of the observed tolerance to metal fumes involves the increased synthesis of toxic metal–binding protein metallothionein in exposed patients.[168] The disease has been mistaken for influenza, atypical or community-acquired pneumonia, and a malaria-like illness because of overlapping presenting symptoms. The diagnosis is based primarily upon a history of exposure to metal oxide fumes. Metal fume fever is generally thought to have no long-term sequelae. An association between it and the later development of occupational asthma has been observed,[165] but a prospective study failed to show that a history of metal fume fever is predictive of later bronchial hyperresponsiveness.[169]

The pathogenesis of metal fume fever appears to involve an increase in proinflammatory cytokine activity in the lung; increased bronchoalveolar lavage fluid concentrations of tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8) have been reported in subjects exposed to zinc oxide fumes,[170] probably produced by pulmonary macrophages.[171] Following exposure, bronchoalveolar lavage TNF-alpha levels peak earlier than other cytokines, suggesting that its role may be central to disease progression.[170] Of the numerous components of metal fumes, it appears to be the soluble transition metal particles, which generate reactive oxygen species and deplete glutathione stores, that are responsible for the fumes' cytotoxicity.[172] Gene expression profiling of lung injury following welding fume exposure in a monkey model has been reported to aid in understanding the inflammatory response of lung tissues.[173]

The treatment of metal fume fever is supportive, including bedrest, antipyretics, and analgesics. Metal fume fever must be distinguished from acute metal fume toxicity, as with cadmium or mercury, which can present similarly to metal fume fever but fails to resolve and instead progresses to respiratory distress. Prevention of metal fume fever involves provision of adequate ventilation, fume removal devices, and respiratory protection for workers in environments where metal oxide fumes are generated.

POLYMER FUME FEVER

A syndrome similar to but less common than metal fume fever, polymer fume fever was first reported in 1951.[174] Fluorocarbon polymers are a class of compounds that are commonly used as nonstick coatings on cooking equipment (polytetrafluoroethylene [PTFE, or Teflon®] is a famous example) but are also used as mold-release sprays, lubricants, and fabric or leather treatments.[175] When fluorocarbon polymers are heated to over 300°C, fumes are produced that include carbonyl fluoride, perfluorinated alkanes, hydrofluoric acid, and carbon dioxide.[175] Extremely small particles capable of reaching alveolar sacs may also contribute to disease progression.[176]

Polymer fume fever presents similarly to metal fume fever: Initial symptoms include dry throat, rhinitis, chest tightness, and conjunctivitis. Constitutional symptoms (fever, chills, myalgias) typically follow exposure by about 4 to 8 hours and spontaneously resolve within 1 day. As with metal fume fever, a leukocytosis is observed concurrent with the patient's constitutional symptoms. Individuals with pre-existing obstructive lung disease may experience worsening obstruction after recurrent exposures to polymer fumes.[177] Pneumonitis is more frequently observed than with metal fume fever, perhaps due to release of hydrofluoric acid. Tachyphylaxis, a hallmark observation of metal fume fever, is not observed in polymer fume fever, suggesting that different mechanisms are responsible for the two diseases.[177] As with metal fume fever, the systemic response to particle inhalation appears to be cytokine mediated.[178]

Though exposure to pyrolized fluoropolymers occurs in industrial settings where it may be immediately suspected in the context of respiratory complaints, it also occurs in homes and via less obvious means of exposure. In one report, within an hour of an empty PTFE-coated pan being heated on a stove, five exposed pet birds died and their owner contracted polymer fume fever.[179] Numerous reports have suggested that workers with skin exposed to fluoropolymers may have contracted polymer fume fever via smoking their self-contaminated tobacco.[180–182] Others may have contracted the disease via igniting their marijuana with cotton that had previously been impregnated with hairspray.[183] Several recent episodes of polymer fume fever have occurred following exposure via the waterproofing spray used on horse rugs.[184]

Treatment of polymer fume fever is supportive. Workers exposed to fluoropolymers should both be provided adequate ventilation and also instructed of the risk of indirect exposure via skin contamination. Strict hand-washing should be required and tobacco smoking should be especially discouraged after exposure.

ORGANIC DUST TOXIC SYNDROME

Another systemic illness caused by inhalational exposure is organic dust toxic syndrome (ODTS), also known as silo unloader's syndrome, atypical farmer's lung, pulmonary mycotoxicosis, and toxic pneumonitis. As with metal fume fever and polymer fume fever, ODTS is a self-limited disease that presents with fever, chills, and myalgias several hours after exposure to the offending agent, in this case organic dusts.[185,186] As with the other systemic diseases discussed, ODTS typically resolves spontaneously within 48 hours following exposure. However, patients with underlying lung conditions may lead to incomplete or delayed recovery.[187]

Agricultural workers are at the highest risk for contracting ODTS, as it commonly follows exposure to hay or corn silage–containing silos, spoiled animal feed, and swine confinement facilities. Other settings of ODTS have included a college fraternity party in which hay was laid on the floor,[188] a storehouse containing moldy oranges,[189] a waste-sorting plant,[190] a print-shop in which an air humidifier was colonized with gram-negative bacteria, fungi, and amoebae,[191] and following exposure to woodchip mulch.[192] Lifetime risk of contracting ODTS may be around 19% for farmers with exposure to organic dust.[193]

The specific agent or agents within organic dust responsible for ODTS have not been fully characterized. An epidemiologic study in 2007 suggested contaminated mulch was implicated as the source of presumed ODTS among urban landscape workers, highlighting that ODTS is not limited to rural agricultural settings.[194]

Bacterial cell wall components, endotoxin and peptidoglycan, are thought to play prominent roles.[195,196] Workers handling grass, cereal, or vegetable seeds are at risk of exposure to high levels of endotoxin-containing seed dust.[197] Fungal spores and actinomyces also are likely contributors to pathogenicity,[198] and an ODTS-like response can be provoked with endotoxin-free grain extracts.[199] The disease process is likely initiated or provoked by activation of the patient's innate immune system by organic dust components, such as endotoxin's activation of toll-like receptor 4. Cytokine expression increases following organic dust exposure, especially of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6),[200] suggesting a means by which local activation of innate immunity may provoke the observed systemic manifestations. Interleukin-1 (IL-1) is also thought to play a critical role in ODTS development.[201] An intriguing correlation has been observed between patients with celiac disease and the development of ODTS,[202] suggesting that some underlying disorder, perhaps a hyperactivity of innate immunity, may increase a patient's susceptibility to both.

Patients with ODTS frequently present with no findings on chest examination, though bibasilar crackles and scattered wheezes may be appreciated. A neutrophil-predominant leukocytosis is frequently found, and mild hypoxemia and bilateral infiltrates on chest X-ray have been reported. Though bronchoalveolar lavage may initially reveal a predominance of neutrophils, a lymphocytic response may come to dominate the BAL cellular population.[186]

ODTS needs to be clinically distinguished from hypersensitivity pneumonitis (HP), which is also provoked by inhaled organic dust. HP typically follows low levels of exposure after a period of sensitization, while ODTS is an acute reaction to high levels of organic dust, potentially on first exposure. HP is a restrictive process detectable by pulmonary function testing, while ODTS sometimes presents with transient airflow obstruction and often with no appreciable functional abnormality. The early BAL findings in ODTS are overwhelmingly neutrophilic, unlike the lymphocytic findings in HP.

Treatment of ODTS is symptomatic. Unlike with HP, corticosteroids appear to be of only marginal benefit in the treatment of ODTS.[203]

SUMMARY

Toxic inhalations may be due to numerous agents and produce a broad spectrum of pulmonary and systemic injuries.[204–205] Treatment is largely supportive and should be guided by the patient's clinical status. Specific attention should be paid to the patency of the airway following acute upper airway exposures, and providers should be aware of the risk of the development of severe pulmonary disease following an asymptomatic latent period. Given the unpredictable clinical course of these exposures, cautious monitoring of exposed patients is prudent. Materials safety data sheets and the National Library of Medicine's TOXNET (http://toxnet.nlm.nih.gov/) are excellent information resources for specific toxins.

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CHAPTER 91

Indoor and Outdoor Air Pollution

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Both indoor and outdoor air pollution are of concern to pulmonary physicians. Exposures to indoor and outdoor air pollutants may both exacerbate and cause respiratory diseases and also increase the population's risk for morbidity and mortality from malignant and nonmalignant diseases. This chapter provides a broad introduction to indoor and outdoor air pollution. It begins with a brief review of the emergence of indoor and outdoor air pollution as clinical and public health issues. The chapter then considers general principles and concepts related to inhalation injury, exposure, and health outcomes. The health consequences of indoor and outdoor air pollution are covered separately, although this distinction is artificial, given the penetration of outdoor pollutants into indoor environments and the overlap between the pollutants found in indoor and outdoor locations. The chapter concludes by considering two issues of direct concern to clinicians: susceptible populations and control strategies, both at the public health and individual levels. Pulmonary physicians have a key role in advising their patients and in carrying out research relevant to air quality management.

OVERVIEW

Air pollution has probably had adverse effects on health throughout history. The use of fire for heating and cooking brought exposure to smoke, a problem that persists today for the billions who still use biomass fuels, and the rise of cities concentrated the emissions of pollutants from dwellings and manufacturing facilities within restricted locales. Industrialization and electric power generation brought new point sources of pollution; that is, localized sources such as power plants, and sometimes immense emissions of combustion by-products, particles, nitrogen oxides (NOx), and sulfur oxides into areas where people lived and worked. During the twentieth century, mobile sources, including cars, trucks, and other fossil fuel–powered vehicles, created a new type of pollution – photochemical pollution, or "smog" – first recognized in the Los Angeles air basin in the 1940s. The unprecedented growth of some urban areas to form "megacities," such as Mexico City, São Paulo, and Shanghai, has led to unrelenting air pollution from massive vehicle fleets, snarled traffic, and polluting industries and power plants. During the twentieth century, there was increasing recognition that the air pollution problem extends into indoor environments. In less-developed countries, exposure to smoke from biomass fuel combustion (e.g., open burning of wood for heating and cooking inside the home) is widespread, as it was in past centuries. In the more developed countries, indoor pollutants are generated by human activities (e.g., cooking, personal care products, etc.) and released from the materials used for construction and in furnishings, and often maintained at unhealthy concentrations by building designs that seal pollutants within.

Health effects of air pollution have long been of concern. During the reign of Edward I (1272–1307), the pollution of London by coal smoke prompted a royal proclamation banning burning of "sea coal" in open furnaces.[1] In 1661, John Evelyn published *Fumifugium or the Aer and Smoake of London Dissipated*, describing an approach to the control of air pollution in London. However, air pollution was not regulated in England until approximately two centuries later with the passage of the Smoke Nuisance Abatement Act and the Alkali Act, directed at industrial pollution. In the United States, recognition of the public health dimensions of air pollution began in the middle of the twentieth century, driven by the rising problem of smog in southern California and the 1948 air pollution episode in Donora, Pennsylvania, which caused 20 excess deaths and thousands of illnesses.[2] The first national legislation, the Air Pollution Control Act, was passed in the mid-1950s; the original Clean Air Act was passed in 1963[3] and most recently revised in 1990.[4] It provides a comprehensive structure for air quality management in the United States.

The modern era of air pollution research and control dates to the episodes in Donora and other cities, during which extremely high levels of pollution caused clearly evident excess deaths. The most dramatic episode was the London Fog of 1952, which caused thousands of excess deaths.[5] These catastrophic episodes led to regulations for the control of outdoor air pollution and to the conduct of research designed to develop evidence on the health effects of outdoor air pollution as a foundation for control measures. The research included characterization of the pollutants in outdoor air as to their sources, concentrations, and chemical and physical properties; toxicological investigation on the injury caused by air pollutants and the underlying mechanisms; and epidemiological studies of the health effects of air pollution in the community. These approaches remain fundamental to research on air pollution. We now have a large body of evidence on the health effects of air pollution gained over more than a half-century of investigation and complex regulations that limit emissions and control concentrations of key pollutants in outdoor air. These evidence-driven regulations have had substantial impact on air quality in the United States, driving down levels of the most prominent pollutants (Fig. 91-1).[6]

In spite of these improvements in air quality, as indexed by specific pollutants, air pollution remains a significant public health concern. Epidemiological studies show that adverse health effects still occur at concentrations frequently observed and at the upper end of the range of the National Ambient Air Quality Standards (NAAQS). In addition, the approach of regulating concentrations of individual pollutants has left the problem of air pollution mixtures unsolved. One mixture of particular concern is that associated with high-density traffic.[7] Studies conducted over the last two decades have linked this mixture to diverse adverse health effects, including lung cancer, allergies and asthma, respiratory symptoms, reduced lung function, and a variety of cardiovascular consequences. Global warming, a consequence of massive pollution of the atmosphere by "greenhouse" gases, has direct and indirect health consequences.[8]

The health effects of indoor air pollution are a more recent concern.[9] Only limited measurements were made of indoor air contaminant levels before the 1970s, and the findings of the first large-scale studies of the health effects of indoor air pollution were not reported until the late 1960s and early 1970s. Pollutants of initial interest included secondhand smoke (SHS) or environmental tobacco smoke (ETS), the mixture of sidestream smoke and exhaled mainstream smoke inhaled involuntarily by nonsmokers, and nitrogen dioxide (NO_2) generated by gas cooking stoves and

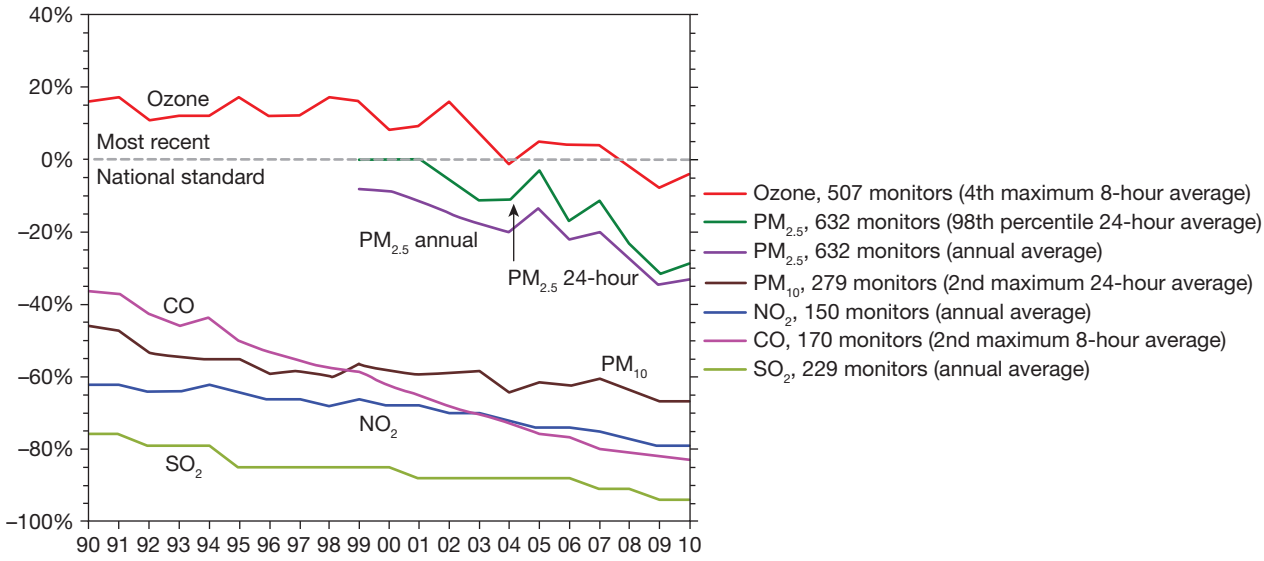

Figure 91-1 Comparison of national levels of the six common pollutants to the most recent National Ambient Air Quality Standards, 1990–2010. National levels are averaged across all monitors with complete data for the time period.

ranges and by space heaters. Research soon broadened to biological agents, volatile organic compounds (VOCs), and two respiratory carcinogens—radon and asbestos (for further discussion on asbestos, see Chapter 86). Concern about the potential health effects of indoor air pollution was heightened by the design and construction of buildings with reduced exchange of indoor with outdoor air for the purpose of energy conservation; the reduction of air exchange was anticipated to diminish dilution and thereby increase indoor air pollutant concentrations. Beginning in the 1970s, outbreaks of nonspecific complaints started to occur among workers, who attributed their symptoms to the indoor environments in which they worked. Now referred to as *sick building syndrome (SBS)*, these outbreaks continue but seemingly in smaller numbers than 10 years ago. Another syndrome, *multiple chemical sensitivity*, has also been linked to indoor air pollution; persons with this controversial syndrome, who may obtain consultation from pulmonary specialists, often report debilitating symptoms after exposure to indoor air contaminants, even at levels that may be considered generally safe. Another concern is disease resulting from potential exposure to mold in homes, particularly following water damage. The flooding of many homes in the Gulf States and New Jersey and New York by catastrophic hurricanes has served to reinforce the potential for chronic exposure to mold.

Control of indoor air pollution has been enacted primarily through nonregulatory approaches,[9] as the Environmental Protection Agency (EPA) does not directly regulate the levels of pollutants in indoor air. The cornerstone of the control of indoor air pollution has been education of the public, manufacturers, and employers on approaches for reducing exposures and for reducing emissions from indoor sources. The EPA has given a guideline value for an acceptable indoor radon concentration; it has also proposed that all homes be tested for radon and the homes modified if the concentration is above the guideline.[10] The handling of asbestos in schools was regulated under the Asbestos Hazard Emergency Reduction Act, and the agency has classified ETS as a class A carcinogen. A rising number of states and municipalities have banned smoking in public places and workplaces. For the majority of households with one or more smokers, some sort of policy is in place to address smoking, either by limiting it to specific locations or not allowing it indoors.

The literature on air pollution is now voluminous and has been published in a broad array of journals and technical reports. Of necessity, this chapter is selective in its review; emphasis has been placed on the most relevant findings for clinicians and on the newer literature. The documents prepared by the EPA on the six "criteria" pollutants (sulfur dioxide [SO_2], particulate matter, NO_2, carbon monoxide [CO], ozone [O_3], and lead) offer encyclopedic reviews that are updated periodically (Table 91-1). Key documents on specific pollutants are cited within the appropriate sections of this chapter.

TABLE 91-1 Criteria Pollutants, Sources, and National Ambient Air Quality Standards (NAAQS)

Pollutant	Sources	Primary Standards	Averaging Time[a]
Sulfur dioxide	Coal and petroleum combustion, smelting, and other manufacturing	75 ppb	1 h
PM_{10}	Coal and petroleum combustion, vehicles, industry, surface dust	150 μg/m^3	24 h
$PM_{2.5}$	Fuel combustion from automobiles, power plants, wood burning, industrial processes, and diesel-powered vehicles	12.0 μg/m^3	Annual (arithmetic mean)
Nitrogen dioxide	Coal and petroleum combustion, vehicles, industry	100 ppb	1 h
Carbon monoxide	Coal and petroleum combustion, vehicles	35 ppm (40 μg/m^3) 9 ppm (10 μg/m^3)	1 h 8 h
Ozone	Secondary formation from NO_2 and hydrocarbons	0.075 ppm	8 h
Lead	Gasoline, lead-containing dust	0.15 μg/m^3	Rolling 3-mo average

[a]*Averaging time denotes the defined time period over which concentration is measured and averaged.*

GENERAL PRINCIPLES AND CONCEPTS

Adverse responses to air pollutants reflect exposure and the delivery of the dose of the injurious agent to the target site within the respiratory tract. Air pollutants cause disease through various mechanisms. This section of the chapter covers principles of inhalation injury and the related spectrum of adverse health effects; it also covers principles of exposure assessment. The research methods used to characterize the effects of air pollutants are also detailed.

PRINCIPLES OF INHALATION INJURY

Atmospheric pollutants, whether indoors or outdoors, exist in both gaseous and particulate forms. In evaluating clinical consequences of specific exposures, the clinician should recognize that penetration into and retention within the respiratory tract of toxic gases can vary widely, depending on the physical properties of the gas (e.g., solubility), the concentration of the gas in the inspired air, the rate and depth of ventilation, and the extent to which the material is reactive. Gases that are highly water soluble, such as SO_2, are almost completely extracted by the upper airways of healthy subjects during brief exposures at rest. In contrast, removal of less water-soluble gases, such as NO_2 or O_3, is much less complete, and these gases may penetrate to the airways and alveoli of the respiratory tract. CO is poorly soluble in water and is not removed in the upper airways. On reaching the lung, CO diffuses across the alveolar–capillary membrane and then binds avidly to hemoglobin.

Exercise greatly augments penetration of gases into the deep lung and, thus, the total dose of pollutants delivered to targets in the airways. Exercise increases the dose directly by increasing minute ventilation; also, because many people switch from the nasal to the oral breathing route during moderate to heavy exercise, the more efficient pollutant removal in the nasal passages is replaced by the less efficient removal in the oral airway.

Particulate pollutants usually occur in nature as aerosols. Small liquid droplets or solid particles are dispersed in the atmosphere with sufficient stability to remain in an aerosol suspension. Examples of common aerosols are sulfuric acid mists and sulfate and nitrate salts formed from SO_2 and NO_2, respectively. Deposition of inhaled particles depends on many factors, including the aerodynamic properties of the particle (primarily size), airway anatomy, and breathing pattern. Particles greater than 10 μm are effectively filtered out in the nose and nasopharynx, where these relatively large particles are deposited efficiently because of impaction against surfaces and gravitational forces. Particles trapped in the nose and nasopharynx are cleared in secretions and coughed out or swallowed. Particles less than 10 μm in aerodynamic diameter (PM_{10}) may be deposited in the tracheobronchial tree; deposition in the lung's alveoli is maximal for particles less than 1 to 2 μm in diameter. Particles less than 0.5 μm move by diffusion to the alveolar level, where they collide with gas molecules by brownian movement and are impacted on alveolar surfaces. Recent interest has focused on both environmental and artificial particles in the so-called "ultrafine" range, that is, particles less than 100 nm in size; despite their extremely small size, high deposition has been found in the respiratory tract and total deposition increases as the particles get smaller. Removal of particles from the larger airways by the mucociliary apparatus is efficient and occurs within hours of deposition; clearance from the deep lung by alveolar macrophages is much slower, requiring days to months. Although particulate matter toxicity has been primarily linked with fine particles, recent studies have indicated that both the ultrafine[11] and the coarse fractions[12] are associated with adverse cardiopulmonary effects.

The mechanisms by which inhaled gases and particles injure the lung are diverse and not yet fully understood. Oxidant gases, O_3 and NO_2, cause inflammation of the respiratory epithelium, presumably through the production of toxic oxidant species and release of potent mediators. SO_2 is also an irritant gas. The response to particles likely depends on the chemical and physical nature of the particles. Oxidizing compounds on particles may dissolve into tissue fluids and induce an inflammatory response. Organic materials on particles may also produce inflammation or act as initiators or promoters of cancer. Particles, once thought to only adversely affect the lungs, may also trigger acute cardiovascular events, in part through effects on pulmonary inflammation and on pulmonary reflexes, via oxidative stress, endothelial dysfunction, autonomic dysfunction, platelet activation, coagulation, etc. A recent review by the American Heart Association discusses these mechanisms and studies of air pollution effects on them in greater detail.[13] The respiratory track, of course, is exposed to multiple pollutants, and interactions among them may synergistically increase effects. Exposure to oxidant gases, for example, enhances responses to inhaled allergens.

ADVERSE HEALTH EFFECTS OF AIR POLLUTION: CLINICAL AND PUBLIC HEALTH CONCERNS

The spectrum of adverse effects of air pollution is broad, ranging from the consequences of acute and dramatic exposures, which may cause death, to far more subtle and chronic effects on disease risk and well-being. This spectrum has been conceptualized as a pyramid with mortality at its tip and an increasingly common set of morbidities as the base. Perhaps the most common "adverse" effect is a loss of well-being from the diminished aesthetic value of a polluted environment. Clinicians are more likely to be concerned with the less common, more acute effects with clinical consequences—acute responses, often in asthmatics, for which a link to air pollution exposure may be made by history or challenge testing; the more subtle and long-term consequences are typically a focus for public health researchers and regulators. Nevertheless, clinicians may be asked to assess risks of long-term exposures or to estimate the contribution of exposures to disease causation in a particular patient. They may also be asked to guide their communities in evaluating air pollution as a local public health problem.

To interpret the scientific evidence on the effects of air pollution, clinicians need a framework for determining whether an effect is "adverse." Judgment on the adversity of responses is societal and reflective of prevalent valuations and perceptions of risk. The Clean Air Act uses the term "adverse" without definition. If a broad construct of health is used that includes a state of well-being as a component, adverse effects of air pollution include not only clinically evident disease but also more subtle symptom responses and physiological effects that may compromise well-being or increase the risk of disease. In a report issued in 2000, a committee of the American Thoracic Society (ATS) offered guidelines for defining adverse respiratory health effects in epidemiological studies of outdoor air pollution.[14] The committee turned to a medical basis for this determination, defining adverse respiratory health effects as medically significant physiological or pathological changes. Increasingly, research focuses on preclinical markers and whether acute changes in panels of markers constitute an adverse health impact remain uncertain.

Indoor air pollution has a broad range of effects as well (Table 91-2).[15] Cases of clinically evident disease caused by indoor air pollution occur, and an unquestionable causal link can often be established for specific persons from a careful history or appropriate diagnostic testing, as with hypersensitivity pneumonitis. Indoor air pollution can also exacerbate chronic respiratory diseases—for example, house dust mite antigen and asthma in house dust mite-allergic persons. More subtle effects have become an increasing concern as we have learned that indoor air pollution can adversely affect comfort and increase risk for future disease; consequently, even the perception of exposure to indoor pollutants may adversely affect well-being. Radon and asbestos, for example, are respiratory carcinogens, which are presumed to increase risk of lung cancer.

TABLE 91-2 A Classification of the Adverse Effects of Indoor Air Pollution

Clinically evident diseases: Diseases for which the usual methods of clinical evaluation can establish a causal link to an indoor air pollutant
Exacerbation of disease: The clinical status of already established disease is exacerbated by indoor air pollution
Increased risk for diseases: Diseases for which epidemiological or other evidence establishes increased risk in exposed persons; however, the usual clinical methods indicative of injury typically cannot establish the causal link in an individual patient
Physiological impairment: Transient or persistent effects on a measure of physiological functioning that are of insufficient magnitude to cause clinical disease
Symptom responses: Subjectively reported responses that can be linked to indoor pollutants or are attributed to indoor pollutants
Perception of unacceptable indoor air quality: Sensing of indoor air quality as uncomfortable to an unacceptable degree
Perception of exposure to indoor air pollutants: Awareness of exposure to one or more pollutants with an unacceptable level of concern about exposure

Source: Data from Samet JM. Indoor air pollution: A public health perspective. Indoor Air. 1993;3:219–226.

CONCEPTS OF TIME–ACTIVITY AND TOTAL PERSONAL EXPOSURE

Definitions of concentration, exposure, and dose are fundamental to considering the health effects of air pollution and steps to reduce risk.[16] *Concentration* refers to the amount of material present in air. *Exposure* constitutes contact with a material at a portal of entry into the body—the respiratory tract, gastrointestinal tract, and skin. For the lung, exposure would constitute the time spent in contaminated air. Exposure is calculated as the unit of concentration multiplied by time. *Dose* refers to the amount of material that enters the body; *biologically effective dose* is the amount of material reaching target sites for injury—for example, the mass of respirable particles delivered to the small airways. For example, the concentration of particles less than 10 μm in aerodynamic diameter (PM_{10}) might be 100 $\mu g/m^3$. A person spending 10 hours at this concentration would have an exposure of 10-hour times 100 $\mu g/m^3$, or 1000 $\mu g/m^3 \times h$. Assuming lung deposition to be 50% of the total mass and a minute volume of 10 L/min, the deposited dose of PM_{10} would be 300 μg (0.5 × 100 $\mu g/m^3$ × 10 L/min × 600 min × 0.001 L/m^3). For most inhaled pollutants, dose will vary with activity level which drives ventilation rate.

With regard to impact on health, *total personal exposure* to a pollutant is the relevant index of exposure, not the exposures received separately within indoor and outdoor environments. The total personal exposure of a person to a pollutant can be conceptualized as the time-weighted average pollutant concentration in the "microenvironments" in which the person spends time (Fig. 91-2).[17] The microenvironments are locations having relatively constant concentration of the pollutant during the time spent there. The principal microenvironments contributing to total personal exposure are those with relatively high concentrations or in which relatively large amounts of time are spent. For example, for exposure to particles, key microenvironments might include an office in which smoking is allowed and an urban environment in which a home is located and time is spent outdoors and indoors. New sensing approaches are facilitating more refined studies of activity levels and air pollution and will sharpen understanding of where and when the most risky exposures take place.

Studies of time–activity patterns indicate that residents of more developed countries spend most of their time indoors and, consequently, personal exposures to many pollutants take place largely in indoor microenvironments. However, pollutants generated by outdoor sources do penetrate indoors, so indoor microenvironments can contribute to exposures to pollutants typically considered outdoor pollutants, such as particles and CO. Data on time use in a number of countries showed that people spend an average of 65% to 75% of their time inside their residences and more than 90% of time indoors, counting time at home, work, and elsewhere. Data from a 1987 to 1988 survey of Californians show a similar pattern, with employed adults averaging 15 hours per day indoors at home and 6 hours per day in other indoor settings. In the California study, school-age children spent an average of 18 hours indoors at home.[18] National data from 1992 to 1994 were very similar.[19] While these data emphasize the predominance of indoor microenvironments in determining exposures to many pollutants, exposure outdoors may be the predominant determinant of dose for some pollutants. For example, the dose of O_3 (which generally has low indoor levels) received by the lung's airways may be dominated by exposure received outdoors, particularly for people exercising or working outdoors.

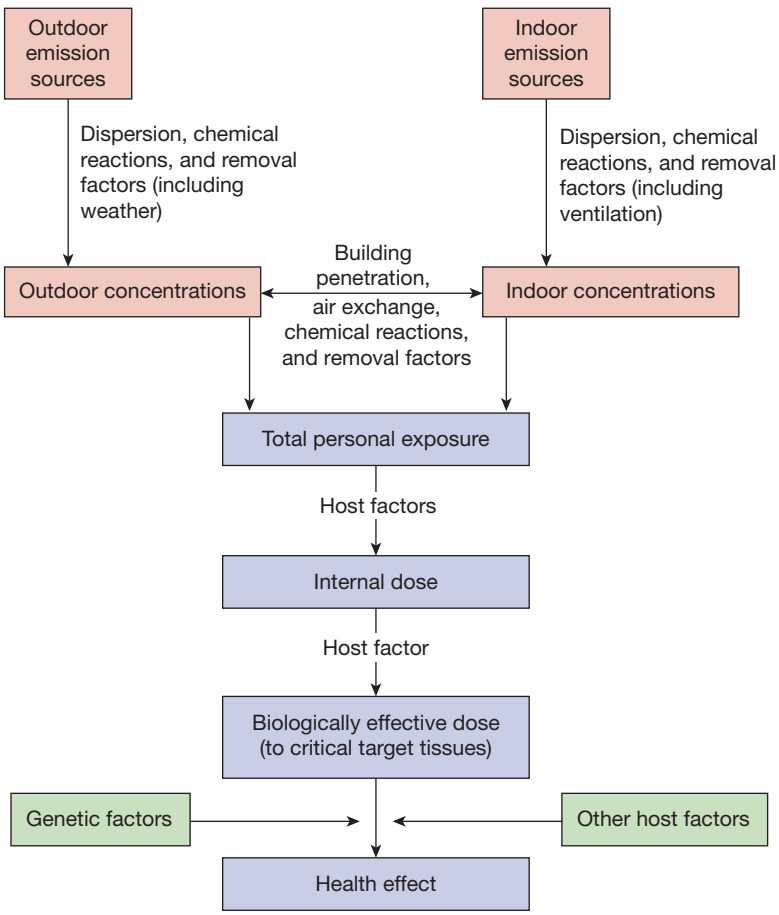

Figure 91-2 Framework for conceptualizing exposure, dose, and health effects from outdoor and indoor air pollution. *(Based on National Research Council data.)*

RESEARCH APPROACHES TO AIR POLLUTION

Our understanding of the health effects of air pollution derives from a tripartite research approach: characterization of atmospheric pollutants and exposures, toxicological studies, and epidemiological studies. These approaches are complementary. There has long been research on the physical and chemical properties of air pollutants, and more recently, exposure assessment has emerged as a separate research discipline. The tools of the exposure assessor include questionnaires that capture activities and time use, personal and area monitoring of air pollution levels, statistical models using these data to estimate exposures, and increasingly sophisticated biomarkers of exposure and dose.[16] There is anticipation that new high-throughput technologies will facilitate data-rich measurement of "the exposome," a variety of biomarkers that will complement the existing approaches.

Toxicological studies are often conducted to characterize the hazards of air pollutants; research may entail exposures of animals to one or more pollutants to assess patterns of injury and disease risk. Increasingly, toxicological approaches are used to characterize the relationship between exposure and dose and the mechanisms underlying injury. This mechanistic information addresses the appropriateness of extrapolating from animal studies to humans, particularly if parallel data from humans are available on dosimetry and mechanisms. Toxicological studies in which volunteers are exposed to pollutants in a controlled setting (e.g., exposure chamber or exposure room sealed off), often referred to as *clinical studies,* have proved to be an informative approach for investigating the acute consequences of pollution exposure. Such studies have been carried out using gases, for example, NO_2 and SO_2, and particles, including concentrated ambient particles and ultrafine particles (UFPs). In addition to healthy volunteers, groups in the population considered susceptible to the effects of the pollutant(s) of concern may be selected for investigation—for example, persons with asthma, chronic obstructive pulmonary disease (COPD), or coronary artery disease. Of necessity, exposures in clinical studies are of brief duration and ethically limited to levels that will have limited, transient effects. In addition to monitoring symptoms and physiological measures, clinical studies may be strengthened by a more invasive collection of biological specimens, using phlebotomy, nasal lavage, or fiberoptic bronchoscopy with biopsy of the mucosa or bronchoalveolar lavage (BAL), to elucidate mechanisms of injury. Molecular approaches using microarrays to analyze changes in gene expression are now being applied to cells (e.g., macrophages and blood monocytes) removed from humans following controlled exposure to pollutants. Clinical studies are also incorporating analyses to identify genetic polymorphisms that determine susceptibility to air pollutants.

There is also growing expectation for using high-throughput testing for assessing the toxicity of various chemicals including air pollutants. Various types of assays are being developed for this purpose; such testing is considered the cornerstone for future predictive toxicology. These approaches envision increased efficiency in toxicity testing and decreased animal usage by transitioning from lengthy in vivo testing to in vitro toxicity assays on human cells or cell lines with mechanistic quantitative parameters. Risk assessment in the exposed human population would focus on avoiding significant perturbations in these toxicity pathways.[20]

Epidemiological studies provide an assessment of the adverse effects of pollution exposures under the circumstances of "real world" exposure.[17] The principal epidemiological study designs used for air pollution research include the following: cross-sectional studies or surveys; short-term cohort studies with intensive measurements of exposures and outcomes (i.e., panel studies); longer-term cohort studies directed at mortality and chronic disease risk[21]; time-series studies that assess short-term changes in outcomes (e.g., daily mortality counts) in relation to changes in daily air pollution levels[22]; and case-crossover studies that contrast the pollution exposure for an individual subject right before he or she had a health event to air pollution exposures of that same subject at other times when that person did not have that health event.[23] There have been several landmark cohort studies, such as the Six Cities Study[24] and the Children's Health Study,[25] but few studies of this design are likely to be implemented in the future, at least in countries like the United States where air pollution levels have declined substantially in recent decades. In part because of feasibility, time-series studies of morbidity and mortality are the most frequent.

The findings of epidemiological studies of air pollution have direct public health and regulatory relevance. The exposures are inherently representative of those received in the community, and the pollutants are inhaled in the form of the complex mixtures that actually exist in indoor and outdoor air. In addition, the community members in a study can be selected from the full spectrum of potentially susceptible subjects. There are, however, weaknesses to the epidemiological approach. Exposures to pollutants may be difficult to measure accurately, particularly past exposures that are used to study current health status. Hence, exposure estimates in epidemiological studies are subject to substantial error, both random and systematic. Generally such errors are likely to lead to underestimation of risk but overestimation is also possible. The effects of other exposures that are correlated with the air pollution exposure of interest and are themselves a predictor of the health outcome of interest, termed *confounding factors,* may not be sufficiently controlled, and thus when not accounted for in the analysis, may artefactually increase or decrease the apparent effect of air pollution exposure. Epidemiological studies having inadequate sample size and, therefore, limited statistical power may supply imprecise and uninformative estimates of risk and not precisely answer public health questions.

The technique of quantitative risk assessment has been increasingly applied to estimate the burden of disease associated with air pollution, particularly carcinogens.[26] The 1990 Clean Air Act amendments include specific provisions on the use of risk assessment, particularly in regard to the hazardous air pollutants regulated under Section 112 of the Act. This process integrates the information on exposure and dose response to provide a characterization of the impact of an environmental agent on the population's health; as the evidence is systematically reviewed in the conduct of a risk assessment, gaps in the evidence and attendant uncertainties are identified, and assumptions are made to fill the gaps.[26] The approach was also used by the World Health Organization in its Global Burden of Disease estimates, which covered indoor and outdoor air pollution.

Risk assessment can be conceptualized as comprising the four steps outlined in the seminal 1983 report of the National Research Council (Table 91-3).[27] A full risk assessment can be a large undertaking, requiring review of all relevant data and mathematical modeling to characterize the risk. It should be undertaken with a clear framing of the questions to be addressed. In a risk assessment, gaps in the scientific evidence, which are sources of uncertainty, are

TABLE 91-3 Steps in Risk Assessment

Hazard identification: The determination of whether an agent is causally linked to the health effect of concern
Dose–response assessment: The determination of the relation between level of exposure and risk of the health effect
Exposure assessment: Description of the extent of human exposure
Risk characterization: Description of the human risk, including uncertainties

Source: Data from National Research Council (NRC), Committee on the Institutional Means for Assessment of Risks to Public Health. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press; 1983.

catalogued and used to estimate the level of confidence to attach to the risk characterization. The findings of risk assessment guide *risk management*, the process by which decisions are made about the need for risk reduction and the approaches to be implemented to reduce risks. Risk management means choosing among the options to control risk and balancing risk reduction, costs, and technological capability for reducing exposure. Uncertainties in the scientific information that have been catalogued in the risk assessment process may cloud risk management and introduce ambiguity regarding the optimum strategy. Nevertheless, risk managers need to make decisions in the face of uncertainty.

Understanding the effects of complex mixtures of pollutants in indoor and outdoor air has proved particularly daunting for researchers. Exposures to pollutants rarely occur singly, without simultaneous exposures to other pollutants in the relevant microenvironments. Many outdoor sources inherently produce complex pollutant mixtures; for example, power plants release particles, NOx, and sulfur oxides, and vehicle exhaust contains CO, NOx, particles, and hydrocarbons. Indoor air is inevitably contaminated by complex mixtures, reflecting the multiplicity of sources in indoor environments. Synergistic or antagonistic interactions between components of complex pollutant mixtures could produce unanticipated effects, based on the toxicity of individual components.

OUTDOOR AIR POLLUTION

Outdoor air pollutants have diverse sources, both artificial and natural. This section begins with a review of the sources and then considers the effects of the principal artificial outdoor pollutants. The pollutants are grouped according to their designation by the EPA.

OVERVIEW: SOURCES AND CLASSIFICATION OF OUTDOOR AIR POLLUTION

Many pollutants, from both artificial and natural sources, can be found in outdoor air. Some naturally occurring pollutants in outdoor air are well documented as causing or exacerbating pulmonary diseases—for example, pollens and fungi. This chapter does not address these biological agents but considers the artificial pollutants. Researchers have focused more attention on the effects of artificial pollutants, which may reach potentially hazardous levels in urban areas or near-point sources, such as power plants, smelters, or manufacturing facilities. In the United States, the principal outdoor pollutants are generally classified within the framework provided by the Clean Air Act, which identifies two sets of air pollutants, "criteria" pollutants (Table 91-1) and "toxic" air pollutants. The term *criteria* refers to the standard-setting process for these pollutants, which requires preparation of a criteria document reviewing all relevant evidence every 5 years. The criteria pollutants include primarily combustion-related pollutants (SO_2, NO_2, CO, and particles), the secondary pollutant O_3, and lead. The toxic pollutants are predominantly carcinogens, such as asbestos and radionuclides, and irritants. The sources are diverse but principally comprise industrial emissions and waste products. Examples of these pollutants are benzene, chlordane, ethylene oxide, hydrochloric acid, methane, parathion, propylene oxide, toluene, and vinyl chloride.

These two groups of pollutants are regulated through different mechanisms. For the criteria pollutants, NAAQS are set after extensive review of all relevant evidence. The standards must afford protection to the entire population, including those with heightened susceptibility, and offer an "adequate margin of safety." For the hazardous pollutants, standards for maximum concentrations are intended to provide a margin of safety. The Clean Air Act includes mechanisms for achieving levels within the standards and enforcement. In spite of existing federal standards for ambient air quality, excesses are common in many areas of the country, most often for O_3. Although the pollutants are considered in the following section on an individual basis, it should be re-emphasized that exposures of the population occur most often to mixtures, and synergism among individual pollutants may increase the effects of the mixture beyond the expected effect based on the components.

OUTDOOR AIR POLLUTANTS: EXPOSURES AND HEALTH EFFECTS

The pollutants covered in this section are of public health significance throughout the world. Sulfur oxides, particles, NOx, and CO are generated by combustion and are typically found together in the complex air pollutant mixtures in outdoor environments. O_3 is a secondary pollutant. While the pollutants are considered individually, exposures to them typically occur in the form of inhaled mixtures.

Sulfur Dioxide

Sulfur oxides are produced by combustion of fuels containing sulfur, such as coal from the Eastern United States and crude petroleum. Because of changing patterns of fuel use, reduction of acid emissions to control acid rain, and various other control strategies, pollution with sulfur oxides is far less prevalent nationally, while remaining important in some locales with point sources. Smelting of ores containing sulfur is also a prominent source in some regions, such as the southwestern United States. In the past, scientific research and regulatory concern in relation to the sulfur oxides were directed primarily at the health effects of SO_2, the criteria pollutant regulated by the EPA. SO_2 is a water-soluble gas that is effectively scrubbed from inspired air by the upper airway. Exercise, however, may increase the inhaled dose by its effect on minute ventilation and the switch to the oral breathing route. This pollutant has been shown to have adverse effects without concomitant exposures to other pollutants.[28,29] In fact, exposures of volunteers to SO_2 alone show that the gas may have adverse respiratory effects. Asthmatics are particularly sensitive, with some asthmatics having more severe health responses at a particular concentration than others with asthma (see below for specific examples). Significant exposures to SO_2 alone might result from plumes released by smelters processing sulfur-containing ores or from other industrial processes.

Exposures to SO_2 in outdoor air occur primarily with simultaneous exposures to other combustion-related pollutants, including NOx and particles. Heavy industry and coal-burning power plants are predominant sources for this type of pollutant mixture. Tall smokestacks for power plants, used to control local pollutant concentrations, release sulfur oxides and NOx high into the atmosphere, where residence time is prolonged. Through a series of chemical reactions, the sulfur oxides and NOx form acidic sulfate and nitrate particles, which may undergo long-range transport.[30] These acidic particles represent a regional air pollution problem—blanketing, for example, the Central and Northeastern United States and portions of Canada. Fortunately, concentrations of SO_2 have fallen in the United States, in part due to controls implemented under the Environmental Protection Agency's Acid Rain Program, and from changing patterns of fuel use and energy generation. From 1983 to 2002, the average annual concentration fell about 50%. The effects of particulate air pollution and acidic aerosols are considered separately below. This section considers the effects of gaseous SO_2.

Asthmatics are particularly susceptible to SO_2, responding to exposure in chambers with increased airway resistance and reduced levels of lung function. With exercise and hyperventilation, which increase the dose delivered to the respiratory tract, some asthmatics are adversely affected at levels common in ambient air and well below those that might occur transiently with direct exposure to the plume from a power plant or factory. Inhalation of SO_2 produces an immediate response within minutes and does not provoke delayed reactions several hours later or repetitive nocturnal attacks. The decrements in lung function on breathing of SO_2 may be sufficient to produce symptoms of dyspnea, wheezing, and chest tightness. The

bronchoconstriction resolves within an hour of exposure, and peak bronchoconstrictor responses may lessen on repeated challenge after a short recovery period. Responses to SO_2 can be partly blocked by pretreatment with cromolyn sodium and anticholinergics and can be reversed by β-adrenergic agonists. Sequential exposures to SO_2 and oxidant gases (O_3 and NO_2) have been performed in asthmatics; these clinical studies have provided little evidence of synergistic interactions in reducing airway function. Although some asthmatics have been shown to be affected by SO_2 with exposure at low concentrations in the laboratory,[31] complementary epidemiological data have not been reported that document parallel community morbidity.

Epidemiological studies from Hong Kong have examined the consequences of a major reduction in sulfur content in fuels over a very short period of time.[32] The investigators found an associated substantial reduction in health effects (childhood respiratory disease and all age mortality outcomes). Daily SO_2 was significantly associated with daily mortality in 12 Canadian cities with an average concentration of only 5 μg/m^3.[33] Nevertheless, there is still considerable uncertainty as to whether SO_2 is the pollutant responsible for the observed adverse effects or, rather, a surrogate indicator for UFPs or some other correlated substance. For example, in Germany[34] and the Netherlands[35] a strong reduction of SO_2 concentrations occurred over a decade. Although mortality decreased with time, the association of SO_2 and mortality was judged as noncausal and attributed to a similar time trend of particulate matter. Wichmann et al. [34] in Germany considered the persistence of the SO_2 effect as artifact because the SO_2 concentration was much below levels at which effects were usually expected. Furthermore, the results for SO_2 were inconsistent with those from earlier studies conducted in Erfurt. They concluded that both fine particles (represented by particle mass) and UFPs (represented by particle number) showed independent effects on mortality at ambient concentrations. Comparable associations for gaseous pollutants were interpreted as artifacts of collinearity with particles from the same sources.

Nitrogen Dioxide

NOx, like sulfur oxides, are produced by combustion processes (i.e., primary pollutants) and contribute to the formation of aerosols.[28–30] Even though NO_2 is regulated by the EPA as a criteria pollutant, substantial personal exposure in the United States occurs in indoor microenvironments contaminated by unvented gas stoves and space heaters. The principal source of NO_2 in outdoor air is motor vehicle emissions, but power plants and industrial sources may also contribute. There have been few locations where point sources were strong enough to make NO_2 alone a source of concern. The health effects of NO_2 released into outdoor air probably arise principally from the formation of secondary pollutants. NO_2 is an essential precursor of O_3, and one of the principal pathways by which NO_2 in outdoor air adversely affects respiratory health may be through the formation of O_3. The NOx also secondarily form acidic nitrate particles.

NO_2 is an oxidant gas of low solubility that penetrates to the small airways and alveoli of the lung. The toxicological evidence at exposures far greater than typically sustained in indoor and outdoor environments suggests that NO_2 exposure can impair lung defenses against respiratory pathogens and cause airway inflammation, with associated effects on lung function and respiratory symptoms. In animal models, exposure to NO_2 increases mortality after challenge with bacterial respiratory pathogens. Therefore, a wide range of health effects are of concern, including increased risk for respiratory infections, respiratory symptoms, reduced lung function, exacerbation of chronic respiratory diseases as well as acute cardiovascular responses including myocardial infarction. These studies and other evidence on indoor exposures are considered separately in the section on indoor air pollution. Several more recent studies link NO_2 to indicators of morbidity, but the findings are inconsistent and are unlikely to reflect NO_2 acting by itself. Interpretation of findings related to NO_2 is complicated by its role in the formation of O_3 and the importance of vehicular emissions as a source in most locations, making NO_2 concentration a surrogate for the mixture of traffic-related pollutants.

A number of clinical studies have been performed to investigate the acute effects of NO_2 by itself on persons with asthma.[36] These studies were performed to assess the need for a short-term standard for outdoor NO_2 concentration, as the present NAAQS provide only an annual standard for NO_2. NO_2 could plausibly affect airway responsiveness by causing airway inflammation. The findings of the clinical studies have been inconsistent, and the discrepancies between the "positive" and "negative" studies have not been readily explained. The EPA published its most recent assessment of the evidence in the form of an Integrated Science Assessment in 2008.[37] That review concluded that NO_2 is associated with increased airway responsiveness, citing the findings of epidemiological studies. As a result, NO_2 exposure is thought to increase respiratory symptoms on a short-term basis and to contribute to respiratory morbidity. Persons with asthma or COPD may represent groups with increased susceptibility to short-term outdoor exposure to NO_2.

Particles

Particles in outdoor air have numerous natural and artificial sources, including the same combustion processes that produce SO_2 and NO_2. Particles are suspended in air by the action of wind on crustal material and road dust. The artificial sources are diverse and include power plants, industry, and motor vehicles, including diesel-powered vehicles that emit particles in the inhalable size range. Particles, of course, are present in indoor and outdoor air. Consequently, personal exposures to particles reflect both indoor and outdoor microenvironments. In addition, outdoor particles, particularly those of smaller size, penetrate indoors.

The artificial particles are primary (i.e., emitted directly by combustion or other processes), or secondary (i.e., formed through chemical and physical transformation of gaseous pollutants, such as NO_2 and SO_2). Because of the diversity of sources, particles have a rich mixture/composition that may be quite variable, spatially and temporally. The toxicity of particles in a particular place thus reflects the source mix, which includes both local sources and those contributing to the regional background pollution (i.e., pollution generated elsewhere but transported to this and other locations via prevailing winds). In the Eastern United States, for example, much of the regional background of $PM_{2.5}$ comes from transport of power plant emissions from the central portion of the country. Hypotheses proposed on the determinants of particle toxicity have focused on issues related to particle acidity, particle content of transition metals,[38] organic compounds on particles (e.g., diesel particles), bioaerosols, and particle size (e.g., UFPs: particles less than 100 nm in aerodynamic diameter[39]; coarse particles [$PM_{10-2.5}$]: particles between 2.5 and 10 μm in mass). Metals associated with particulate matter are capable of causing pulmonary inflammation and injury and the same chemical properties that allow metals to function as catalysts in reactions with molecular oxygen can generate oxygen-based free radicals and cause oxidative stress. UFPs have a high specific surface area and carry an increased burden of reactive oxygen species. They may be particularly important with regard to cardiovascular effects because of their potential for evading clearance mechanisms, and for entering the lung interstitium and vascular space. Coarse particles, by virtue of their size, are less likely to reach the alveoli. However, they have been associated with increased cardiovascular emergency department visits, and increased respiratory emergency department visits, with the most consistent evidence shown in children. Some, but not all, clinical studies and toxicological studies have also provided evidence for respiratory effects, including pulmonary inflammation and decreased pulmonary function.

Historically, particle concentrations in outdoor air have been measured with several different techniques and over recent decades these technologies have been refined and directed at biologically relevant size fractions. Until 1987, the EPA specified the measurement of total suspended particulates (TSPs), which included particles well above the inhalable size range. In 1987, the reference method for the NAAQS was changed to particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), and in 1997 24-hour and annual standards were added for $PM_{2.5}$. The PM_{10} standard, challenged in court, was set aside in a Supreme Court decision, and in 2005, the EPA proposed a standard for coarse mixes in urban areas, $PM_{10-2.5}$. This set of standards makes no provision with regard to the chemical composition of the particles. Equivalent mass concentrations of particles are hypothesized to have differing toxicity, depending on acidity, content of metals, or carcinogenic potency. The characteristics of particles that determine their toxicity are a focus of current research. The size distribution below the 10 and 2.5 μm cutoffs may also affect toxicity through its consequence for sites of deposition. In addition, the ultrafine component contributes little to the mass and the number count or surface area, but may turn out to be an important metric.

Nationally PM_{10} concentrations have decreased 31% since 1988, mainly in regions of the country that had higher concentrations such as the Northwest (39%), the Southwest (33%), and Southern California (35%). Since 1999, $PM_{2.5}$ concentrations have decreased 10% nationally. $PM_{2.5}$ has decreased the most in regions with the highest concentrations to start with, such as the Southeast (20%), Southern California (16%), and the industrial Midwest (9%). Except for the Northeast, most regions of the country have had at least modest declines from 1999 to 2003. Nationally these declines in PM_{10} and $PM_{2.5}$ have continued through 2010 **(Fig. 91-1)**.

A recent paper has suggested that these reductions in particulate air pollution during the 1980s and 1990s have led to measurable improvements in life expectancy in the United States.[40] They estimated that for each 10 $\mu g/m^3$ reduction in air pollution seen during this time in the United States (many areas in the country saw substantially larger reductions than this, and some regions smaller changes), the average gain in life expectancy was 0.61 years (7.3 months). This gain in life expectancy was independent of changes in socioeconomic status and other lifestyle factors. Further, they concluded that as much as 15% of the total life expectancy increase seen during this time in these areas, was attributable to the air pollution reductions.

There have been extensive epidemiological and toxicological investigations of the effects of particles on health since the air pollution disasters of mid-century.[28,29] The toxicological studies have used a range of approaches, from exposing volunteers to generated particles or concentrated air particles, to animal exposures, and to diverse in vitro assays. This extensive body of evidence shows that particles are injurious and indicates mechanisms by which particles could cause adverse effects on the respiratory and cardiovascular systems.

The epidemiological studies have addressed the relationship between exposures to particles and short- and long-term variations in mortality, both from all causes and from cardiovascular and respiratory causes. The studies have also addressed the relationship between exposures to particles and diverse indicators of respiratory morbidity, including the frequency of respiratory symptoms and illnesses, level of lung function and rates of lung function growth and decline, and outpatient visits and inpatient admissions. More recently, studies have examined if and by what mechanisms particles may trigger acute cardiovascular and cerebrovascular events (e.g., myocardial infarction, ventricular arrhythmia, and stroke) in both epidemiology studies using outdoor particle concentrations (e.g., PM_{10} or $PM_{2.5}$)[41–43] and clinical studies using controlled particle exposures (e.g., concentrated UFP and concentrated $PM_{2.5}$).[44,45] These studies have identified numerous biomarkers of interacting mechanisms responding to short-term increases in ambient and controlled air pollution exposures including systemic and pulmonary inflammation, oxidative stress, coagulation, vascular dysfunction, and autonomic dysfunction to name a few. A more complete discussion of studies examining these and other mechanisms is provided in two recent American Heart Association statements on air pollution and cardiovascular disease.[13,46] In the studies of particulate air pollution during the 1950s and 1960s, the measures of exposure were general. Some studies included only surrogate measures of exposure, such as location of the place of residence. In spite of such crude exposure measures, these studies found adverse effects of exposure to particulate air pollution and became the basis for establishing air quality standards for particles. The standards were generally considered to be sufficiently protective of public health. Studies linked particulate air pollution to a number of adverse health effects including total, cardiovascular, and respiratory mortality, exacerbation of asthma, hospital admissions, impaired lung function, and upper and lower respiratory symptoms.[47]

As levels of air pollution were reduced in the United States and other Western countries, excess mortality at times of higher concentrations was not readily evident and, since the 1970s, the focus of research and of public health concern has generally shifted to morbidity. However, studies of air pollution and daily variations in mortality, facilitated by new techniques for longitudinal data analysis, have shown statistically significant, positive associations between measures of particle concentration and daily mortality counts for cities in the United States and elsewhere. Several analyses have combined data for multiple cities in the United States, Europe, and Asia including studies in China.[48–57] These analyses pool the information from many locations to estimate precisely the effect of particulate matter and also to examine the variations in risk among the contributing locations. These analyses show a statistically significant effect of airborne particles on mortality, independent of the possible contributions of other pollutants or weather. In interpreting these findings, the extent to which life is lost from these short-term effects is critical. Several prospective studies indicate that life shortening from air pollution may be substantial.

Many complementary studies of morbidity have also been reported. These studies have been directed at clinical indicators, such as hospitalization or the triggering of arrhythmias, myocardial infarction, or sudden death. They have also examined biomarkers and electrocardiographic parameters. A review in 2004,[46] and an update in 2010,[13] both by the American Heart Association, detailed a substantial body of evidence linking particulate air pollution to adverse cardiovascular effects. In addition, in some studies, airborne particles have been shown to adversely affect persons with asthma and COPD. These findings suggest that the present NAAQS for particulate matter may not protect against adverse health effects with the "adequate margin of safety" mandated by the Clean Air Act. They also call into question other national and international standards and have led to tightening of the standards, most recently in 2012 when the $PM_{2.5}$ annual concentration standard was reduced to 12 $\mu g/m^3$.

Guidance to patients related to ambient particulate air pollution calls for tracking when pollution levels are high, either by weather forecasts, EPA alerts, or visible haze and reduced visibility. At such times, it is reasonable to advise patients to reduce outdoor activity, particularly with exercise, and avoid locations where pollution levels may be particularly high, for example, adjacent to busy roadways. Such guidance is particularly appropriate for people susceptible to health effects of air pollution (e.g., people with asthma, COPD, coronary artery disease, and/or hypertension). Although mechanisms of toxicity are not completely understood, avoiding air pollution exposure can only help reduce air pollution-mediated cardiorespiratory morbidity and mortality.

Carbon Monoxide

CO is an invisible gas formed by incomplete combustion of fossil fuels and other organic materials. The most prominent outdoor source is vehicle exhaust; consequently, outdoor concentrations are highly variable in place and time, changing with vehicle density and traffic patterns. Urban locations with high traffic density tend to have the highest concentrations. CO also has indoor sources, such as cooking stoves and tobacco smoke. Exposures to CO can be conveniently assessed by using the level of carboxyhemoglobin (COHb) as a biomarker of exposure or by measuring the concentration of CO in an end-tidal breath sample, following a breath hold.

With the passage of the Clean Air Act, significant reductions in outdoor CO have occurred, reflecting emissions control particularly on vehicles. Between 1980 and 2010, there has been an 82% decrease in ambient CO levels. From 2000 to 2010, CO decreased 54%.[58] In regard to outdoor air, acute effects of CO on susceptible persons have been of particular concern, and the current US standard is intended to protect susceptible persons with coronary artery disease. Inhaled CO binds to hemoglobin with high affinity (more than 200 times greater than for oxygen) to form COHb. The COHb complex is very stable; depending on ambient levels of CO, level of activity, and lung function, the half-life of CO in the body ranges from about 2.5 to 4 hours. The rate of accumulation of ambient CO in the body above endogenous levels is affected by ambient CO concentrations, alveolar ventilation, lung diffusivity, total hemoglobin mass, and COHb level.[59] People with impaired gas exchange (e.g., persons with COPD) have compromised ability to excrete CO.

The binding of CO to hemoglobin reduces oxygen transport by red blood cells to tissues. The binding also displaces oxygen and causes an allosteric change in the hemoglobin molecule, which increases the affinity of heme groups for oxygen. Persons with cardiovascular disease are considered to be at greatest risk from CO exposure. Standard exercise tests on subjects with ischemic heart disease have demonstrated a decreased time interval to the onset of angina at COHb levels ranging from 2% to 6%.[60] The 1-hour 35-ppm and 8-hour 9-ppm federal standards for outdoor air (Table 91-1) were selected to prevent COHb levels from rising above 1.5%, thereby protecting persons with ischemic heart disease from aggravation of myocardial ischemia with onset of angina and attendant loss of exercise capacity. Recent evidence indicates that controlled CO exposure during exercise of patients with stable coronary artery disease can induce subjective and objective evidence of myocardial ischemia earlier in the exposure than during exercise without CO. This effect can be induced at COHb levels as low as 2% to 4%. These studies are relevant to the urban environment, where people may be exposed to sufficient CO to reach blood COHb levels in this range. Furthermore, moderate exercise results in even greater CO uptake. In addition, at a COHb level of 6%, patients with coronary artery disease have an increased frequency of arrhythmias.[61] Fetuses, as well as persons with COPD, may also be harmed by CO, and normal persons may have reduced oxygen uptake during exercise at low levels of CO exposure.[61]

The recent studies from the 2008 Beijing Olympics (discussed below) demonstrated a potential role of CO and perhaps other pollutants in inducing adverse changes in cardiorespiratory biomarkers in a panel of healthy young people. CO levels decreased 48% (together with similar-sized reductions in $PM_{2.5}$, SO_2, NO_2, and other pollutants) from before to during the Olympic Games. These pollutant changes were associated with significant reductions in coagulation biomarkers suggesting a role in thrombosis endothelial dysfunction mechanisms[43] as well as in exhaled breath biomarkers suggesting pollution-induced pulmonary inflammation along with signs of respiratory and systemic oxidative stress.[62] A more recent study[63] from Hong Kong found that lower CO levels were associated with a reduced risk of hospital admissions for respiratory tract infections. It is unclear whether pollutant-related CO exposure causes noncardiac toxicity independently or whether it plays a role in health effects elicited by the air pollution mixture.

Ozone

Photochemical pollution, or "smog," is a complex oxidant mixture produced by the action of sunlight on hydrocarbons and NOx in vehicle exhaust.[28,29] O_3, a secondary pollutant, is invariably present in photochemical pollution, and its concentration serves as an index of the level of this mixture. The problem of tropospheric O_3 pollution, that is, ground level, is distinct from the problem of depletion of the stratospheric ozone layer. Photochemical pollution was first recognized over 50 years ago in southern California, where the combination of sunlight and heavy vehicle travel promotes its formation. O_3 has now become a problem in many other locations, including Western cities with similar sprawling growth and heavy vehicle traffic and the Eastern United States during the summer. O_3 is also produced naturally, but the exposure of concern for health almost exclusively reflects the O_3 created by human activities.

Since 1990, NOx emissions have decreased approximately 25% and VOCs emissions have dropped by about 35%. National ozone levels in 2004 were 11% lower than in 1990 and 21% lower than in 1980 for the 8-hour standard (3-year average of the annual fourth highest daily maximum 8-hour average concentration is less than 0.08 ppm). Between 1990 and 2004 the most significant improvements in air quality were in the Northeast (17% decrease) and Southwest (16% decrease) regions of the country.[64] This decline has continued through 2010 for most of the country, with the larger declines in the Northeast (Fig. 91-3).

The toxicology of O_3 has been extensively investigated. Low-level exposures cause damage to the small airways of experimental animals; the demonstration of subtle fibrosis in one animal model has raised concern about permanent structural alteration in exposed populations. Volunteers exposed to O_3 at concentrations in the range of the present standard – which are often present during pollution episodes – experience transient reductions in lung function; normal subjects have a range of responsiveness that is broad but repeatable for individuals. Evidence of an inflammatory response and biochemical changes in BAL fluid has been detected 18 hours after an experimental exposure to O_3 at levels that are commonly found. Taken together, the progressive decrements in pulmonary mechanics during exposure, coupled with the persistent biochemical changes many hours after cessation of exposure, indicate the potential for chronic effects from repeated inhalation. Surprisingly, in clinical studies, asthmatics have not been shown to have increased susceptibility to O_3 compared with nonasthmatics. The evidence for short-term effects of O_3 exposure on the lung function of normal volunteers has raised concern about possible long-term effects of living in Southern California and other locations with sustained photochemical pollution. Relevant epidemiological data suggest that O_3 may have chronic effects, but these data are not definitive, and a long-term study of southern California children found that O_3 specifically was not associated with reduced lung function growth, although other measures of the air pollution mixture were.[25,65] The same study found evidence that O_3 might contribute to the onset of asthma. Some time-series studies have linked short-term exposure to O_3 to increased risk of mortality.[66]

Although there is some evidence that long-term O_3 exposure is associated with increased respiratory and cardiovascular mortality, less is known about if and how O_3 may impact cardiovascular morbidity. Epidemiology studies have provided inconsistent evidence, with one study reporting increased risk of paroxysmal atrial fibrillation associated with increased O_3 concentrations[67] while several studies of myocardial infarction find no such associations with increased O_3 concentrations.[68] There have been few clinical studies of cardiovascular health effects of O_3 exposure or concentrations.

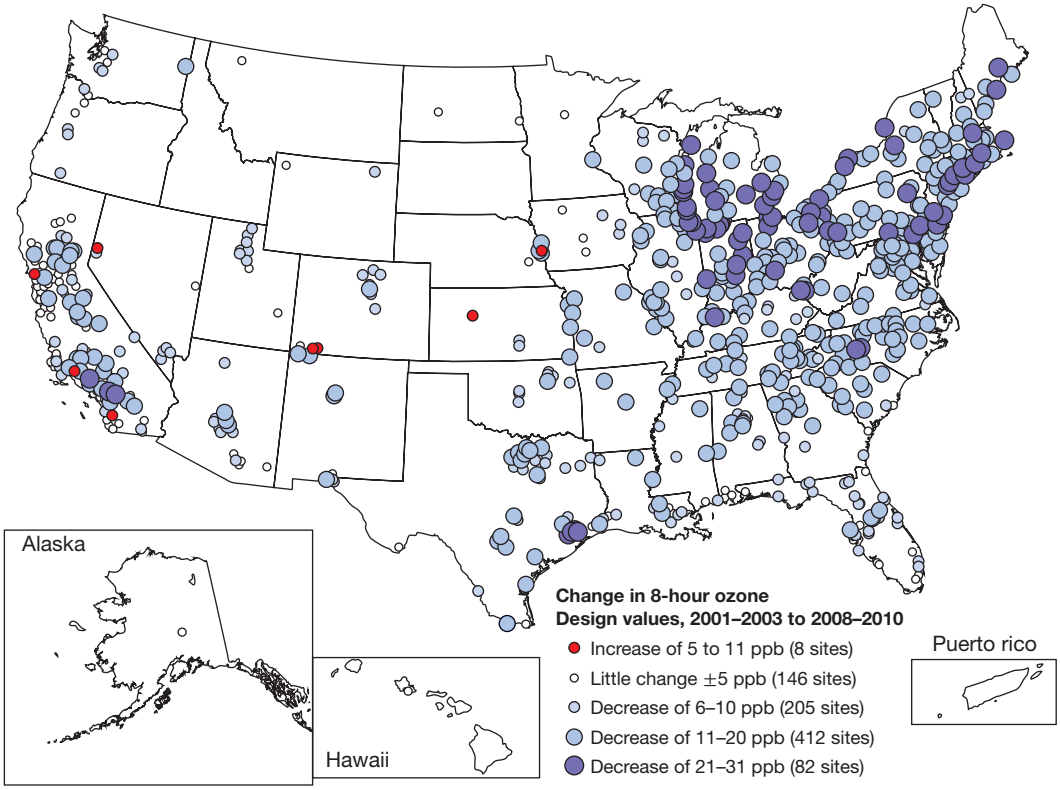

Figure 91-3 Individual monitor 8-hour daily maximum ozone design values, displayed as change from 2001–2003 to 2008–2010.

Recently, a clinical study using "low levels" of O_3 (0.06 and 0.07 ppm for 6.6 hours with exercise) found possible lung function declines following O_3 exposure.[69] A second study with the same two levels of O_3 exposure reported decreased lung function at 0.07 ppm, but not at 0.06 ppm.[70] Based in part on these studies, the 8-hour O_3 standard was reduced to 0.075 ppm. However, there are no studies of cardiovascular responses at these low levels.

Mixtures—Traffic and Diesel Pollution

Much of the health effects research that we discuss in this chapter is based on studies examining individual pollutants, one at a time. For example, in the clinical studies, investigators contrast two exposures (e.g., UFPs at a high concentration with no other pollutants vs. clean air with no UFP or other pollutants) so as to isolate health effects of UFP exposure. In epidemiology studies, researchers typically estimate the risk of a health event associated with an increase in the concentration of one pollutant, even though it is part of a complex mixture. However, none of these pollutants exist in the natural world in isolation. Each day, we are exposed to mixtures of pollutants in various places (at home while cooking food, in a car on the highway, at work in an office or manufacturing facility, etc.). Recently, researchers have begun to look at these air pollution mixtures, both in controlled exposure and epidemiology studies. A review of traffic pollution and related health effects has recently been published.[7]

For example, researchers have studied whether traffic pollution exposure (i.e., gasoline engine emissions, resuspended road dust, tire wear, brake wear) is associated with cardiovascular and respiratory morbidity. One approach for investigating such health effects of traffic pollution is a panel study of people who commute, with health measurements (e.g., blood sample, ECG recording) before, during, and after the time a subject is in the car. Simultaneously, the air pollution levels in the car can be measured, and in statistical analyses, one can determine if the in-vehicle air pollutant levels, which the subject presumably inhaled, were associated with adverse changes in markers measured in the blood and on the ECG. In these panel studies, increased in-vehicle pollution has been associated with adverse changes in numerous cardiovascular biomarkers of inflammation, vascular function, and autonomic function.[71–74] In epidemiological studies, an increased risk of myocardial infarction or ventricular arrhythmias has been associated with being in a car in the previous few hours[75] or even the previous 30 minutes,[76] and with residential distance to major roadways[77] (with people living closer to highways assume to have higher traffic pollution exposure than people living farther from highways). Individual pollutants thought to be markers of traffic pollution (e.g., NO_2, CO, and black carbon) have repeatedly been associated with both cardiovascular and respiratory events, and also with adverse changes in these biomarkers of mechanisms thought to underlie the cardiorespiratory response to pollution. Clinically controlled exposure studies presumably provide the cleanest assessment of health effects of traffic pollution. Evidence clearly suggests that traffic pollution has adverse health effects. However, there is concern that stress and road noise, which may occur at the same time as traffic pollution exposure, may confound these associations.

The impact of diesel exhaust exposure remains another area of concern for adverse cardiopulmonary effects including lung cancer, asthma, and respiratory infections. Several research groups have conducted controlled exposure studies of diesel exhaust, with mixed results. Diesel exhaust is an irritant to which some people are highly sensitive. It has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC), which has concluded that it causes lung cancer. The recently reported Advanced Collaborative Emissions Study (ACES) investigated the cancer and noncancer health effects of subchronic exposures to rats and mice for up to 12 months to diesel exhaust emissions from a heavy-duty diesel engine system compliant with 2007 EPA regulations.[78] In brief, only mild exposure-related effects from detailed histology, pulmonary function, and blood biomarker studies were found. In contrast to the pollutant levels in the "traditional diesel,"

the levels of PM, SO_2, and VOCs in the "new" diesel engines were quite low. A future report on exposures up to 24 months should provide additional insight regarding toxicity of diesel exhaust.

In summary, research methods to study the health effects of these traffic pollutant mixtures, in animal, clinical, and population settings, are being refined. As such, our ability to understand if and how these mixtures impact our health will be greatly improved in the years to come. More work is needed to confirm these adverse effects of traffic, but clearly reducing time exposed to vehicle exhaust would be beneficial.

Lead

Exposure to lead may occur through many environmental media, including ambient air. At present, ingestion is the principal pathway of concern in the United States. Fortunately, in the United States the importance of ambient air as a source of exposure of the population to lead has diminished with the removal of lead from gasoline. Children are particularly vulnerable to lead exposure. Even levels previously considered safe have been associated with adverse neurological effects, and there has been a progressive tightening of recommendations of blood lead levels by the Centers for Disease Control and Prevention. More recent data have linked lead exposure with osteoporosis and possible arthritis.[79] In adults, bone mineral density has shown an inverse association with blood lead levels.[80]

Toxic Air Pollutants

The toxic air pollutants are predominantly carcinogens, but they also include a variety of other toxins. Approximately 200 "hazardous pollutants" are listed as air toxins in the 1990 Clean Air Act amendments. Examples of the hazardous pollutants are asbestos, benzene, cadmium compounds, chlorine, formaldehyde, and nickel. Although the sources are diverse, emission releases tend to be localized, often at industrial sites, or from municipal incinerators or waste sites. The health consequences of these agents are diverse, and include cancer and noncancer effects. Formaldehyde, a ubiquitous pollutant in urban areas, causes cancer of the nasopharynx, exacerbates asthma, and is an irritant to the eyes and upper airway.

Only a small proportion of lung cancers can be attributed to air pollution, even though carcinogens are found widely in outdoor air. For example, polycyclic aromatic hydrocarbons (PAHs), in diesel exhaust, are widely dispersed and present in urban air throughout the world. The PAHs possess mutagenic and carcinogenic activity. But, to date, only limited epidemiological data on risks in humans are available. Analyses of occupational cohorts exposed to diesel exhaust for years are suggestive of a small excess risk of lung cancer.[81] The IARC of the World Health Organization has classified diesel particles as a human carcinogen.[82] Given the difficulties of measuring or estimating exposure, confounding by cigarette smoke and by other occupations, and the small excess numbers of lung cancers, it is difficult to quantify the risk of lung cancer associated with diesel exhaust exposure with a high degree of certainty. Nevertheless, as the percentage of light-duty vehicles powered by diesel fuel in the United States increases, there will be an increasing imperative to determine the carcinogenicity of the PAHs and diesel exhaust. There is also current concern that new types of fuels may introduce additional carcinogens into outdoor air. However, on the more positive side, the ACES discussed earlier has demonstrated the potential with engineering controls to dramatically reduce emissions even from the heavy-duty diesel engines and their potential adverse health effects.[78]

INDOOR AIR POLLUTANTS AND HEALTH EFFECTS

Indoor environments are contaminated by numerous air pollutants, including outdoor air pollutants that have penetrated indoors and indoor air pollutants generated by the numerous indoor sources. This section reviews exposures and health effects of the principal indoor pollutants. The organic compounds and biological agents include myriad individual agents that may adversely affect health. As for outdoor air pollution, clinicians should consider that exposures to indoor air pollutants typically occur as exposures to mixtures, rather than as single agents.

OVERVIEW: SOURCES AND CLASSIFICATION OF INDOOR AIR POLLUTION

Indoor air pollution has myriad sources, including the materials from which the space is constructed, its furnishings, processes operating within the environment, biological agents, and even the occupants. Outdoor air pollutants can also penetrate indoors, as can soil gas, which may contain radon and termiticides. The broad source headings are combustion, evaporation, abrasion, biological, and radon (Table 91-4). The principal combustion sources are gas cooking stoves, burning cigarettes, fireplaces and wood stoves, and unvented space heaters. Evaporation of VOCs from materials and products leads to ubiquitous contamination by these agents. Abrasion of friable asbestos is a principal source of this indoor contaminant. The biological agents are heterogeneous, extending from infectious organisms to pets and the occupants themselves. Radon comes primarily from soil gas.

The concentration of an indoor contaminant depends on the strength of its source, the rate of removal, the volume of the space, and the rate of exchange of air between the space and outdoors. This *mass-balance* formulation indicates that the concentration of a contaminant might be reduced by limiting source strength, increasing removal rate, or increasing exchange between indoor and outdoor air.

In the typical modern building, the exchange of indoor with outdoor air is accomplished by a central heating, ventilating, and air-conditioning (HVAC) system. These systems are diverse, although all have the same purpose: the delivery of air of acceptable quality to building occupants.[83] The volume of air to be delivered follows the recommendation of standards set by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers. In most new high-rise buildings, occupants can no longer control the temperature of the work environment and cannot open windows to increase air exchange. Most residences, however, still rely on natural ventilation.

Carbon Monoxide

CO, a by-product of combustion of fuels, is released indoors by cooking and heating devices and also by smoking. Surveys conducted several decades ago of urban population exposures in Denver, Colorado, and Washington, DC, indicate that residential concentrations of CO are typically low, ranging from 2 to 4 ppm during the winter, when windows of homes are generally closed and the homes heated.[59] People living in homes with gas cooking ranges and those living with smokers have slightly higher levels of personal exposure. Measurements in the surveys of CO in commercial and institutional buildings showed concentrations in the same range as in residences. The CO in residences and public buildings without combustion sources primarily reflects entry of motor vehicle exhaust from outdoor air into buildings through natural and mechanical ventilation. Intake vents at street level bring co-contaminated air into buildings. Elevated levels have been measured in commercial buildings with drive-in window operations (e.g., banks), buildings with underground parking garages, and enclosed ice rinks with ice-resurfacing machines without emission controls.

Acute and chronic health effects may be caused by CO exposure. About 500 accidental deaths in the United States are attributed annually to asphyxiation by CO inhalation and approximately 15,000 people are treated each year in emergency departments for CO exposure. The majority of the nonfatal cases occur in residences, with about 20% associated with faulty furnaces. A small proportion of cases occur in public buildings having faulty, unvented, or

TABLE 91-4 Sources of Common Air Contaminants

Contaminant	Source
Asbestos	
Chrysotile	Some wall and ceiling insulation installed between 1930 and 1950
Crocidolite	Old insulation on heating pipes and equipment
Amosite	Old wood stove door gaskets
Tremolite	Some vinyl floor tiles
	Drywall joint-finishing material and textured paint purchased before 1977
	Cement–asbestos millboard and exterior wall shingles
	Some sprayed and troweled ceiling-finishing plaster installed between 1945 and 1973
	Sprayed onto some structural steel beams as fire retardant
Combustion by-products	
Carbon monoxide	Gas ranges
Nitrogen dioxide	Wood and coal stoves
Sulfur dioxide	Gas and propane engines
Particulate soot	Fireplaces
Nitrogenated compounds	Backdrafting of exhaust flues
	Candles and incense
Tobacco smoke	
Carbon monoxide	Cigarettes
Nitrogen dioxide	Pipes
Carbon dioxide	Cigars
Hydrogen cyanide	
Nitrosamines	
Aromatic hydrocarbons	
Benzo(a)pyrene	
Particles	
Benzene	
Formaldehyde	
Nicotine	
Formaldehyde	Some particle board, plywood, pressed board, paneling
	Some carpeting and carpet backing
	Some furniture and dyed materials
	Urea-formaldehyde insulating foam
	Some household cleaners and deodorizers
	Combustion (gas, tobacco, wood)
	Some glues and resins
	Tobacco smoke
	Cosmetics
	Permanent-press textiles

Contaminant	Source
Biological organisms	
Fungal spores	Mold, mildew, and other fungi
Bacteria	Humidifiers with stagnant water
Virus	Water-damaged surfaces and materials
Pollens	Condensing coils and drip pans in HVAC systems
Arthropods	Drainage pans in refrigerators
Protozoa	Some thermophiles on dirty heating coils
	Animals
	Rodents
	Insects
	Humans
Radon	
Radon gas and radon progeny	Radon gas emanating from soil, rocks, and water that diffuses through cracks and holes in the foundation and floor
	Radon in well water
	Radon in natural gas used near the source wells
	Some building materials such as granite
Volatile organic compounds	
Alkanes	Solvents and cleaning compounds
Aromatic hydrocarbons	Paints
Esters	Glues and resins
Alcohols	Spray propellants
Aldehydes	Fabric softeners and deodorizers
Ketones	Combustion
	Dry-cleaning fluids
	Some fabrics and furnishings
	Stored gasoline
	Outgassing from water
	Some building materials
	Waxes and polishing compounds
	Pens and markers
	Binders and plasticizers

Source: Data from Turner WA, Bearg DW, Brennan T. Ventilation. In: Seltzer JM (ed). Effects of the Indoor Environment on Health. Philadelphia, PA: Hanley & Belfus; 1995:41–58.

improperly ventilated combustion sources, such as charcoal stoves.[84] The most common symptoms are nonspecific and include headache, nausea, and dizziness.

The level of CO in the blood is a useful biomarker of dose, and the health effects of exposure to CO can be related to COHb levels. In nonsmokers who are not exposed to CO in the environment, COHb levels are approximately 0.5%. This endogenous COHb comes from catabolism of hemoglobin and heme-containing enzymes of the liver. In comparison, COHb levels of cigarette smokers average about 4% and may be much higher. Frank CO poisoning, as

manifest in headache, loss of motor control, and coma, generally occurs with COHb levels above 20%. Clinicians have proposed the concept of "occult" CO poisoning, arising from persistent exposure to low levels of CO in indoor environments. Headache and dizziness, early symptoms of CO poisoning, have been associated with COHb levels greater than 10%. Increased levels of COHb resulting from indoor exposures may, at times, extend to values at which clinical testing has demonstrated cardiovascular and neurobehavioral effects. The Centers for Disease Control and Prevention recommend use of battery-powered CO detectors in homes to avoid CO exposure.

Nitrogen Dioxide

In the United States, with the exception of a few urban areas where outdoor NO_2 levels are high, indoor environments are the predominant determinant of total individual exposure.[85] Residential exposures from unvented gas cooking stoves and kerosene space heaters are the major sources contributing to total individual exposure. Although vented to the outside by building codes, gas furnaces and water heaters may pollute residences because of flue gas spillage and backdrafting caused by improper installation, maintenance, and weather conditions.

Levels in residences and the determinants of these levels have been characterized in many regions of the United States. Indoor NO_2 levels are generally increased during the winter, when homes are closed; they may also be high in the summer, when homes are closed for air conditioning. During cooking, concentrations may reach 1000 ppb while the stove is in use, resulting in substantial, but brief, exposures for persons near the stove. High indoor NO_2 concentrations have been documented in small inner-city apartments and when an oven is used for heating. Data on NO_2 levels in commercial and institutional buildings are very limited, but they generally show low levels consistent with the lack of indoor sources. High concentrations of NO_2 have been measured in ice-skating rinks, contaminated by emissions from resurfacing machines without emissions controls.

Oxidant injury has been postulated to be the principal mechanism by which NO_2 damages the lung. Inhaled NO_2 is thought to combine with water in the lung to form nitric acid (HNO_3) and nitrous acid (HNO_2). At high concentrations, NO_2 causes extensive lung injury in animals and humans. Fatal pulmonary edema and bronchopneumonia have been reported at extremely high concentrations; lower concentrations are associated with bronchitis, bronchiolitis, and pneumonia.

Experimental evidence indicates that NO_2 exposure adversely affects lung defense mechanisms.[36,85] In experimental models, NO_2 affects mucociliary clearance, the alveolar macrophage, and the immune system. In animal experiments employing challenge with respiratory pathogens, exposure to NO_2 reduces clearance of infecting organisms and increases the mortality of the experimental animals.[6] Adverse effects in these animal experiments have been demonstrated at concentrations that are an order of magnitude greater than those typically found in indoor environments.[36,37]

The health effects of indoor NO_2 have been investigated primarily in studies directed at the consequences of indoor exposures for children.[36,85] The toxicology of NO_2 implies that a wide variety of health effects are of potential concern, including reduced efficacy of host defenses against infectious organisms and the consequent increased risk of infection, exacerbation of asthma and COPD, and respiratory tract inflammation with respiratory symptoms and a reduction in lung function. In spite of extensive investigation using laboratory and epidemiological approaches, the evidence still remains inconclusive with respect to each of these health outcomes.

The hypothesis that NO_2 increases the risk for respiratory infection has received the most intensive investigation. A number of epidemiological studies have compared the occurrence of respiratory infections in children in homes having gas stoves and higher concentrations of NO_2 with the occurrence in children in homes with electric stoves and lower concentrations of NO_2. In a cohort study of infants at risk for asthma, NO_2 exposure during the first year of life was associated with respiratory symptoms including wheeze, cough, and shortness of breath.[86] The findings of these studies have been inconsistent, largely because of the methodological complexities of investigating this association. Experimental exposures also have failed to provide consistent evidence that NO_2 increases infectivity in humans.[87]

Inflammation of the airways by NO_2 could plausibly be associated with increased respiratory symptoms and reduced lung function. These potential adverse effects of NO_2 have been examined using data from epidemiological studies of children and adults. Many of these studies have included large numbers of participants studied cross-sectionally. The health outcome measures (e.g., reports of symptoms and levels of spirometric lung function) have been compared for participants living in homes with NO_2 sources, such as gas stoves and space heaters, and participants living in homes without such sources. Despite the number of such studies, there is no clear pattern of results. A meta-analysis using data from 11 studies found that a long-term increase in NO_2 exposure of approximately 15 ppb, consistent with the presence of a gas stove in the home, is associated with a 20% increase in the risk of respiratory illness in children.[88]

Inflammation of airways would be expected to worsen the health status of persons with asthma. Short-term effects of NO_2 exposures on asthmatics have been studied by exposing volunteers and following the level of pulmonary function and nonspecific airway responsiveness. The evidence has been conflicting,[36] and the findings are of limited generality because of the inclusion of relatively mild asthmatics in most studies.

The NO_2 exposures typically found in indoor and outdoor environments are not likely to cause clinically relevant effects for most persons with asthma. However, recent studies indicate that exposure to NO_2, in combination with allergens, may adversely affect persons with asthma. Studies have shown that exposure to NO_2 increases the response to challenge with specific allergen at levels as low as 0.40 ppm.[89] A study of asthmatic children in the United Kingdom showed that exposure to NO_2 increased the severity of virus-caused exacerbations.[90] An experimental study in Australia of reduction of NO_2 exposures in schools showed that symptom rates in asthmatic children dropped following reduction of NO_2 concentration in the classroom.[91] Thus, for persons with asthma, indoor NO_2 from unvented combustion sources could increase the adverse effects of exposure to common indoor allergens, such as those associated with house dust mites, cats, and cockroaches, and to viral pathogens. Little information is available on the effects of NO_2 exposure on persons with COPD.

Secondhand Smoke

Although the prevalence of smoking in the United States has decreased among adults to 19% in 2011,[92] smoking remains common in public places and homes. *Secondhand smoke* (SHS) is a term now widely used to refer to the combination of sidestream smoke that is released from the cigarette's burning end and the mainstream smoke exhaled by the smoker. Survey and biomarkers data on SHS exposure for nonsmokers and children have documented widespread exposures, but the most recent evidence shows substantial declines in exposure to SHS. Blood levels of cotinine, the nicotine biomarker, dropped sharply from years 1999–2000 to 2007–2008 among nonsmoking participants in the National Health and Nutrition Examination Survey (NHANES).[93] In the first survey, most participants had a detectable cotinine value, but a majority did not in the more recent report. If smokers are present, exposure received indoors at home may dominate total personal exposures of involuntary smokers for particles and some gaseous pollutants, such as benzene.[94]

TABLE 91-5 Established Health Effects of Involuntary Exposure to Tobacco Smoke

Decrement in pulmonary function growth in childhood
Increased frequency of acute lower respiratory illness in early childhood
Increase in respiratory illness in children
Increased frequency of middle-ear disease
Increased severity of asthma episodes and symptoms
Onset of asthma
Sudden infant death syndrome
Lung cancer in nonsmokers
Coronary heart disease
Reduced birth weight

Hundreds of chemical compounds have been identified in cigarette smoke; the indicators most often used to quantify its presence in the environment are respirable suspended particles (RSP), particles of mean aerodynamic diameter of less than 2.5 μm, CO, and nicotine, which is in the vapor phase of SHS.[95] Nicotine is a highly specific marker for the presence of tobacco smoke; it can be monitored with both active and passive techniques. Largely because RSP can be readily monitored with area and personal sampling methods, levels of RSP have been widely used as a marker for SHS. The data show that smoking in the home approximately doubles the 24-hour average indoor RSP concentration. Much higher short-term exposures, not reflected in these longer-term integrated measurements, must occur in homes when smoking is actually taking place. Data on SHS levels in public buildings have shown high short-term measurements in bowling alleys, at cocktail parties, in bars, and in other locations with a high density of smokers.

The adverse effects of SHS have been assessed in the context of the voluminous evidence on active smoking and health and of the detailed characterizations that have been made of the composition and toxicology of mainstream and sidestream cigarette smoke. Associations of SHS with disease and other adverse outcomes have been demonstrated (Table 91-5).[95] The evidence has been reviewed by a number of expert panels, with the repeated conclusion that SHS causes both malignant and nonmalignant diseases in nonsmokers.

Studies of children of smoking parents provided the first warning of the adverse effects of SHS on nonsmokers. Maternal smoking was found to increase risk of infants for lower respiratory tract illnesses, and smoking by household members, particularly the mother, was shown to increase the incidence of chronic respiratory symptoms and reduce the rate of lung growth in children.[95] Children with asthma whose parents smoke have heightened airway responsiveness and increased morbidity, as documented by indexes of medical care utilization. Exposure to SHS is also a suspected cause of asthma, and infants of smoking parents have increased airway responsiveness shortly after birth. Epidemiological studies show that parental smoking is associated with persistent middle-ear effusions and other ear problems.[95]

Exposure to SHS was first linked to lung cancer in never smokers in two reports published in 1981.[96,97] Numerous epidemiological studies have addressed this association, and the weight of the evidence shows a consistent positive association between living with a smoker and the risk of lung cancer. By 1986, the evidence led to conclusions of the IARC,[98] the US Surgeon General,[99] and the US National Research Council[100] that SHS causes lung cancer in never smokers. The risk of lung cancer is increased by approximately 20% for never-smoking women married to smokers. Based on review of the epidemiological evidence, as well as the supporting toxicological data, the EPA classified SHS as a class A carcinogen, a designation applied to agents causally linked to cancer.

Additional health effects of SHS have now been identified. A number of epidemiological studies have shown that marriage to a smoker increases risk for ischemic heart disease.[95] Although the evidence is not as extensive as for the respiratory consequences of SHS exposure, the American Heart Association, the United Kingdom's Scientific Committee on Tobacco, and the EPA of the State of California have concluded that SHS exposure is a cause of cardiovascular disease and death. Estimates have been made that SHS causes between 23,000 and 70,000 cardiovascular disease–related deaths annually. Cited mechanisms include promotion of atherosclerosis, increased platelet aggregation, endothelial cell damage, and the consequences of CO exposure. SHS exposure at home and in the workplace has been linked to reduced lung function in some studies.

Recently, research has been published on "thirdhand smoke," referring to surface-deposited components (e.g., on clothing, furniture, and other surfaces) of tobacco smoke and metabolic byproducts of these components.[101] Thirdhand smoke is neither smoke nor a pollutant present in the air, rather, it is composed of various compounds, many that are volatile or semivolatile, that may have a long-lived presence following deposition. Experimental research and field specimens show that these compounds may be long lived and undergo chemical transformations. Thirdhand smoke components may be absorbed via the skin or through ingestion of components on the hands or on contaminated objects that young children put into their mouths.[101]

Wood Smoke

The presence of wood smoke indoors can be assessed by measurements of particles, organic compounds, and CO. Available data for developed countries suggest that the routine operation of a properly installed and maintained wood stove does not greatly affect indoor air quality, and outdoor air contaminated with wood smoke of neighbors can enter and pollute the interior air of homes without wood stoves. By contrast, in developing countries, biomass fuel combustion for cooking and space heating leads to very high exposures for large numbers of households around the world and also contributes to outdoor air pollution.

Wood smoke is a complex mixture, both in its physical and chemical characteristics and in its toxicological properties. The toxicology of some components of wood smoke, such as benzo(*a*)pyrene, other polycyclic organic compounds, and NOx, has been extensively studied. Little research, however, has addressed the toxicology of wood smoke as a complex mixture.

Some of the epidemiological evidence on the health effects of wood smoke is derived from investigations in developing countries, where intense smoke exposure results from the use of cooking fires in poorly ventilated dwellings. Studies from less developed countries suggest that smoke exposure adversely affects children and adults, increasing the occurrence of acute respiratory illness in children and chronic respiratory morbidity in children and adults. The occurrence of COPD in never-smoking women exposed to wood smoke has been described as well.

In developed countries (e.g., northern states of the United States), wood burning is becoming more prevalent as a heating source due to the improvement in home wood burning technologies and the need for less expensive and renewable alternative fuels. Recreational wood burning (e.g., open outdoor fire pits, bonfires, etc.) also remains prevalent. In the winter during cold periods, when there are more often stagnant air masses and temperature inversions, outdoor wood smoke particulate matter concentrations may remain elevated

TABLE 91-6 Common Organic Chemicals and Their Sources

Chemicals	Measured Peak Nonoccupational Exposure (μg/m^3)	Major Sources of Exposure
Volatile chemicals		
Benzene	1000	Smoking, auto exhaust, passive smoking, driving, pumping gas
Tetrachloroethylene	1000	Wearing or storing dry-cleaned clothes, visiting dry cleaners
p-Dichlorobenzene	1000	Room deodorizers, moth cakes
Chloroform	250	Showering (10-min average)
	50	Washing clothes, dishes
Methylene chloride	500,000	Paint stripping, solvent usage
1,1,1-Trichloroethane	1000	Wearing or storing dry-cleaned clothes, aerosol sprays, fabric protectors
Trichloroethylene	100	Unknown (cosmetics, electronic parts)
Carbon tetrachloride	100	Industrial strength cleansers
Aromatic hydrocarbons	1000	Paints, adhesives, gasoline, combustion sources
Toluene, xylenes, ethylbenzene, trimethylbenzenes		
Aliphatic hydrocarbons	1000	Paints, adhesives, gasoline, combustion sources
Octane, decane, undecane		
Terpenes	1000	Scented deodorizers, polishes, fabrics, fabric softeners, cigarettes, food, and beverages
Limonene, *a*-pinene		
Semivolatile chemicals		
Chlorpyrifos (Dursban)	10	Insecticide
Chlordane, heptachlor	100	Termiticide
Diazinon	100	Insecticide
Polychlorinated biphenyls (PCBs)		Transformers, fluorescent ballasts, ceiling tiles
Polycyclic aromatic hydrocarbons (PAHs)	1	Combustion products (smoking, wood burning, kerosene heaters)

Source: Data from Wallace LA. The Total Exposure Assessment Methodology (TEAM) Study: Summary and Analysis. Washington, DC: US Environmental Protection Agency. Office of Research and Development; 1987.

for extended time periods. Further, indoor wood smoke exposure may be quite high if proper ventilation is not used. Data from health effect studies suggest that increased particulate air pollutant concentrations from wood smoke are associated with respiratory health effects, but a recent review concluded there was no evidence that wood smoke particles infer more or less toxicity than particles from other sources.[102]

There has been limited work examining cardiovascular health effects of wood smoke exposure. Studies done in occupationally exposed firefighters and studies using controlled wood smoke exposures have had mixed results, with some, but not all, reporting increased pulmonary and systemic inflammation and hemostatic responses.[103–108] However, studies have generally not reported increases in acute cardiovascular events in populations exposed to forest fire smoke.[109–112] In cities where wood smoke particle concentrations are a large component of particulate air pollution in the winter (likely from wood being burned for indoor heating), increased concentrations have been associated with increased cardiorespiratory hospital admissions.[113–115] Other community-wide and in-home intervention studies have examined whether efforts to reduce pollution levels improve health. These studies have generally reported improved levels of inflammatory, endothelial function, blood pressure, and myocardial ischemia biomarkers, as well as reduced cardiorespiratory mortality associated with reduced wood smoke exposures and concentrations.[116–119] Although these studies suggest that wood smoke may impact cardiovascular outcomes, the evidence is not conclusive. But again, reducing exposure to wood smoke is likely beneficial.

Organic Compounds

Organic compounds are ubiquitous indoors, where they are released from furnishings and equipment, construction materials, and consumer and office products (Table 91-6).[94] The organic compounds found in indoor air can be grouped by boiling point range as volatile (0–240 °C), semivolatile (240–380°C), and particulate (greater than 380°C). The volatile and semivolatile organic compounds are most relevant to human health. VOCs exist as vapors over the normal range of air temperatures and pressures, whereas semivolatile organic compounds are liquids or solids but also evaporate.

Hundreds of organic compounds have been identified in indoor air.[94] Although many of these agents are also released by outdoor sources such as chemical plants, indoor concentrations and sources have been shown to determine personal exposures to most of the organic compounds. The Total Exposure Assessment Methodology (TEAM) study conducted by the EPA showed the dominant contributions of indoor sources to personal exposures, even in locations with outdoor air polluted by industry.[120] For example, benzene, a human carcinogen, may be emitted into outdoor air by industry and from gasoline. Among cigarette smokers in the TEAM study, however, the main source of personal exposure was benzene in mainstream cigarette smoke; passive smokers are also exposed to benzene.

Formaldehyde, used in hundreds of products, is one of the most ubiquitous indoor organic compounds. The largest use of formaldehyde is in preparation of urea and phenol-formaldehyde resins, which are used to bond laminated wood products and to bind the wood chips in particle board. Formaldehyde-containing

wood products are used as shelving, counters, bookcases, cabinets, floors, and wall coverings in homes, offices, and public buildings. Formaldehyde resins are also used to treat paper products and fabrics and are constituents of numerous other consumer products. Formaldehyde is an irritant to which some people are highly sensitive. Formaldehyde has been classified as a human carcinogen by the IARC, which concluded that formaldehyde causes nasopharyngeal cancer and also leukemia.[121]

The health risks of the organic compounds are diverse; the organics found in indoor air include several dozen carcinogens and mutagens (e.g., benzene), irritants (e.g., formaldehyde and terpenes), and neurotoxins (e.g., aromatic compounds). Despite the potential risks of the organic compounds in indoor air, few studies have shown specific exposure–disease associations, largely because of the difficulty of characterizing exposures and identifying effects of components of complex mixtures in indoor air. Indoor exposures to organics may contribute to the risks for several cancers, although few epidemiological studies have been directed specifically at assessing cancer risk in relation to indoor exposures to organics.

Radon

Radon-222, a noble gas, is in the decay chain of naturally occurring uranium-238. It decays with a half-life of 3.8 days into a series of short-lived progeny: polonium-218, lead-214, bismuth-214, and polonium-214. Irradiation of respiratory epithelial cells by alpha particles released by polonium-218 and polonium-214 damages cellular DNA and causes lung cancer. The principal source of radon in buildings is naturally occurring gas in soil.[122] The driving pressure for entry of soil gas into a building is the pressure gradient established by a structure across the soil. The soil gas enters through openings, such as sump pump wells, drains, cracks, and utility access holes. In most locales, building materials and water used in the home do not contribute significantly to concentrations of radon indoors. Because radium, the parent radioisotope for radon, is ubiquitous, radon is present in outdoor air and in higher concentrations in indoor environments.

Extensive data on radon concentrations in homes in the United States show that the average value is about 1.5 picocuries per liter (pCi/L). Homes with high concentrations have been identified in all states, although the proportion exceeding the EPA's action guideline of 4 pCi/L is variable among the states. In a national survey conducted from 1988 to 1991, the EPA measured radon concentration in 6000 randomly selected homes in the United States. About 4% of homes were estimated to exceed the guideline of 4 pCi/L annual average.

Exposure to radon progeny, the short-lived decay products of radon, has been causally linked to increased risk of lung cancer in uranium miners and other underground workers.[123] Measurements made since the 1970s in the United States and elsewhere have shown that radon is present in most homes and can reach high concentrations – as high as those in underground mines – with a documented excess of lung cancer. Current risk models that assume that the risk follows a linear nonthreshold relationship imply that even values under current guidelines cause a significant number of lung cancer cases. Thus, any exposure is assumed to convey some risk, an assumption supported by experimental data. In addition, epidemiological studies of indoor radon confirm that indoor radon concentration is positively associated with radon risk.[124,125]

The hazard posed by exposure to radon progeny in indoor air has been characterized primarily through risk estimation procedures. In the most widely applied risk assessment approach, the risks for the general population are projected by extrapolating risks observed in the studies of miners to the general population. The risk of radon indoors has also been directly estimated by carrying out case-control studies in the general populations. Estimates obtained by pooling the results of these studies are consistent with the extrapolated risks from studies in miners. Use of such models leads to the conclusion that radon contributes significantly to the incidence of lung cancer in the population. The burden of radon-related lung cancer in the general population reflects, in part, the synergism between radon and cigarette smoking assumed in the models.

One risk model is based on a pooled analysis of data from 11 epidemiological studies of male miners, including 68,000 who accounted for more than 2700 cancer deaths.[123] The analysis showed a positive linear relationship between the risk of lung cancer and occupational radon exposure, down to exposures only a fewfold greater than average lifetime exposure from indoor radon. Lung cancer risk was found to decline with increasing age and time since exposure; the risk was also found to increase as the rate of exposure decreased—the so-called inverse dose-rate effect. When the model was applied to the US population, indoor exposure to radon at home was estimated to be responsible for about 12% of lung cancer deaths in the United States. Of the 15,000 to 22,000 lung cancer deaths attributed to radon in 1995, about 85% were assigned to smokers and 15% to never smokers.

The substantial lung cancer burden attributed to indoor radon has led to programs for reduction of exposure. The program in the United States, conducted by the EPA, calls for voluntary measurement of radon levels in single-family homes and modification if the annual concentration exceeds the agency's guideline level of 4 pCi/L.[126] Two types of passive measurement devices are available: short-term devices, which make measurements for a few days, and long-term devices, which make measurements for periods of months up to a year. The short-term devices, primarily charcoal canisters, are often used when a measurement is quickly needed during a real estate transaction; the longer-term devices incorporate a piece of plastic that is etched by alpha particles released by progeny.

Fortunately, increased radon concentrations can be lowered, often by such simple measures as sealing basement cracks and sump holes. Approaches also include ventilating the basement to the outside and, for homes built on concrete slabs, by providing a system to exhaust the soil gas from beneath the slab. In areas having a high potential for indoor radon problems, radon-resistant construction techniques can be applied in anticipation of high levels.

The success of the EPA's program for managing the indoor radon problem rests on voluntary action by the public. To engage the public, the Agency has developed a risk communication strategy that uses the media, voluntary health agencies (e.g., the American Lung Association), and healthcare providers. Its pamphlet, "A Citizen's Guide to Radon," informs readers about the risks and the recommended approaches for managing them.[126]

Asbestos and Artificial Fibers

Asbestos, comprising several fibrous inorganic materials characterized by chemical formulation and crystalline structure, has been used extensively in building materials since the beginning of the last century because of its high tensile strength and thermal properties (see also Chapter 86). The broad categories of use are thermal and acoustic insulation, fire protection, and reinforcement of building products. In addition to its use in acoustic ceiling tiles and vinyl floor tiles, asbestos has been used in paints and wall and ceiling plaster; until banned in the late 1970s, asbestos materials were used to coat pipes, boilers, and steel structural beams.

Asbestos-containing materials are present in homes, offices, and schools. The EPA has estimated that 20% of the nation's buildings, or about 733,000 buildings (not including schools and residential dwellings with fewer than 10 units), contain some asbestos materials.[127]

Asbestos had been used widely in ceiling tiles, pipe wrap, plaster, floor tiles, shingles, and sprayed-on insulation, among other applications. Release of fibers from these materials may result from impact, abrasion, fallout, vibration, air erosion, and fire damage.[127] Water damage and the normal aging of binders, leading to the friability of the material, increase the likelihood of release.

Asbestos-contaminated surface dust may contribute to airborne concentrations in buildings.

Artificial mineral fibers are now used increasingly as substitutes for asbestos in building materials. These are fibrous inorganic substances made primarily from rock, clay, slag, or glass; the principal types are glass fibers (comprising glass wool and glass filaments), rock wool, slag wool, and ceramic fibers. Fiberglass and glass wool refer to silica-based vitreous fibers manufactured by a number of different processes. The different types of fibers vary in their chemistry and dimensions, as well as in their durability in vivo. Because they are physically fibrous, there is concern about the same health effects as for asbestos.

An enlarging database on airborne asbestos concentrations in buildings demonstrates extremely low average values under the conditions of normal building use.[127,128] Occupant risk is determined by exposures to airborne fibers, rather than the presence of asbestos-containing materials in the building. Surveys of asbestos concentrations in commercial buildings demonstrate very low fiber concentrations under normal conditions. The Literature Review Panel Report published by the Health Effects Institute, Asbestos Research Committee, compiled all published data, as well as previously unpublished information, on buildings sampled for litigation and for other purposes. The total data set included 1377 measurements made by transmission electron microscopy in 198 buildings. For fibers greater than 5 mm in length, which are considered most relevant to disease risk,[129] the mean and median concentrations were low, at approximately 0.001 fiber per milliliter, or three or more orders of magnitude lower than concentrations in the occupational settings of the past. Individual buildings with levels much higher than the typical values in the data assembled by the Health Effects Institute, Asbestos Research Committee, have been reported.

For office workers, visitors to buildings, and schoolchildren and teachers, mesothelioma and lung cancer are the principal health effects of concern; asbestosis would not be expected at usual exposures for these building occupants. The risks of indoor asbestos for the general population have been estimated by extrapolation of risks for occupationally exposed persons. Uncertainty is inherent in this approach, but the risks cannot be directly investigated by epidemiological methods. The Literature Review Panel Report of the Health Effects Institute, Asbestos Research Committee, has estimated risks for various scenarios of exposure (Table 91-7).

Custodial and maintenance workers in buildings with asbestos-containing materials may be exposed to higher levels of asbestos than other building occupants, since their activities disturb the materials and release fibers. These workers may be at particular risk if they are unaware that asbestos-containing materials are present or are untrained in dealing with these materials. Several studies have shown that custodial and maintenance workers may have pleural plaques and possibly asbestosis, causing concern that a "third wave" of asbestos-caused disease could occur in such workers.

Because of the morphological and toxicological comparability of asbestos and artificial mineral fibers, there has been concern that exposure to artificial mineral fibers could produce the same diseases caused by asbestos. The relevant epidemiological data from exposed workers are less extensive than for asbestos. Animal studies have shown the fibers that are long and thin to be carcinogenic. The health risk of artificial mineral fibers for exposures of building occupants remains uncertain.

In 2002, IARC re-evaluated the carcinogenic risk of airborne artificial vitreous fibers.[130] Epidemiological studies as well as research conducted on newer fibers, were evaluated. Pulmonary morbidity studies among production workers in the United States and Europe have demonstrated an absence of interstitial fibrosis. IARC concluded that only the more biopersistent materials, such as refractory ceramic fiber (RCF), remain classified as possible human carcinogens. Continuous glass filaments and the more commonly used vitreous fiber wools, such as insulation glass wool, rock wool, and slag wool, are now considered not classifiable as to their carcinogenicity to humans. Nevertheless, to date, no data are available linking RCF with tumors in humans. The one mortality study of RCF workers showed no excess mortality for all deaths, all cancers, or malignancies or diseases of the respiratory system including mesothelioma.[131]

TABLE 91-7 Estimated Lifetime Cancer Risks for Different Scenarios of Exposure to Airborne Asbestos Fibers[a]

Conditions	Premature Cancer Deaths (Lifetime Risks) per Million Exposed Persons
Lifetime, continuous outdoor exposure	
0.00001 fiber/mL from birth (rural)	4
0.00001 fiber/mL (high urban)	40
Exposure in a school containing ACM, from age 5 to 18 y (180 d/y, 5 h/d)	
0.0005 fiber/mL (average)[b]	6
0.005 fiber/mL (high)[b]	60
Exposure in a public building containing ACM, from age 25 to 45 y (240 d/y, 8 h/d)	
0.0002 fiber/mL (average)[b]	4
0.002 fiber/mL (high)[b]	40
Occupational exposure from age 25 to 45 y	
0.1 fiber/mL (current occupational levels)[c]	2000
10 fiber/mL (historical industrial exposures)	200,000

ACM, asbestos-containing material.

[a]This table represents the combined risk (average for males and females) estimated for lung cancer and mesothelioma for building occupants exposed to airborne asbestos fibers under the circumstances specified. These estimates should be interpreted with caution because of the reservations concerning the reliability of the estimates of average levels and of the risk assessment models.

[b]The "average" levels for the sampled schools and buildings represent the means of building averages for the buildings reviewed herein. The "high" levels for schools and public buildings, shown as 10 times the average, are approximately equal to the average airborne levels of asbestos recorded in approximately 5% of schools and buildings with asbestos-containing materials. If the single highest sample value is excluded from calculation of the average indoor asbestos concentration in public and commercial buildings, the average value is reduced from 0.00021 to 0.00008 fiber/mL, and the lifetime risk is approximately halved.

[c]The concentration shown (0.1 fiber/mL) represents the permissible exposure limit proposed by the U.S. Occupational Safety and Health Administration. Actual worker exposure, expected to be lower, will depend on a variety of factors, including work practices and use and efficiency of respiratory protective equipment.

Source: Data from Health Effects Institute, Asbestos Research Committee, Literature Review Panel. Asbestos in Public and Commercial Buildings: A Literature Review and a Synthesis of Current Knowledge. Cambridge, MA: Health Effects Institute; 1991.

Biological Agents

Indoor allergens and microbes – the principal biological agents in indoor air relevant to human health – have diverse sources, both indoors and outdoors (Table 91-8). Indoor levels of allergens and microbes may be increased by accumulation of materials indoors, such as human and animal dander, and growth of fungi and bacteria

TABLE 91-8 Sources of Biological Air Pollutants

Acarids
Dust mites and spiders
Insects
Cockroaches, crickets, beetles, fleas, moths, flies, and midges
Domestic animals
Cats, dogs, other mammals, and birds
Rodents
Wild
Mice and rats
Pets
Mice, gerbils, and guinea pigs
Fungi
Indoors (growing on interior surfaces or in air-conditioning systems)
Penicillium, Aspergillus, Rhizopus, and *Cladosporium*
Outdoors
Numerous species entering with incoming air
Pollens
Derived from outdoor plants or plant materials brought inside
Bacteria
Legionella (introduced into ventilation systems by cooling towers and standing water reservoirs)

on interior surfaces or in air-conditioning systems. Indoor pollen is derived almost entirely from outdoor plants, and fungal spores from outdoors may also enter the indoor environment on air infiltration or inadvertently on people, animals, or objects.

Some of the most severe and prevalent indoor biological pollution problems result from the growth of microorganisms on interior surfaces that are wet and moist. Substrates which provide a source of both carbon and water can support the growth of microorganisms. High relative humidity, in excess of 70%, promotes condensation on interior surfaces (e.g., cool exterior walls or windowsills). Leaks from water pipes and roofs can also provide consistent sources of moisture. Other moisture sources are humidifiers, vaporizers, and air conditioners; once contaminated, these devices can distribute fungal fragments, spores, and dissolved allergens into room air. Mold has been a problem in homes flooded by storms.

In recent years, the growth of molds in home, school, and office environments has been cited as the cause of a wide variety of human ailments and disabilities. So-called "toxic mold" has become a prominent topic in the lay press and is increasingly the basis for litigation when individuals, families, or building occupants believe they have been harmed by exposure to indoor molds.

Molds and other fungi may adversely affect human health through allergy or infection. Some species of fungi, including some molds, are known to be capable of producing secondary metabolites, or mycotoxins and, possibly, of causing respiratory disease via a toxic syndrome. A controversial issue regarding mold in the home is that of "idiopathic pulmonary hemorrhage" associated with *Stachybotrys chartarum*. Following an initial report of 10 cases in Cleveland in 1994,[132] additional case reports followed, linking mold exposure or mycotoxins with pulmonary hemorrhage in infants. Recent critical reviews of the literature have concluded that indoor airborne levels of microorganisms are only weakly correlated with human disease or building-related symptoms and that a causal relationship has not been established between these complaints and indoor exposures to *S. chartarum*.[133]

Limited information exists on levels of microbial particles in air. Indoor levels and, hence, personal exposure are highly variable and are probably affected by activities such as vacuuming, sweeping, dusting, making beds, scrubbing contaminated surfaces, and using electric fans. Further, airborne and dust concentrations of allergens probably have limited value for assessing the contribution of a particular allergen in causing disease. Factors such as aerodynamic behavior, respirability, solubility, and cross-reactivity with other allergens are also important in the process of immunological sensitization and the development of allergic disease.[134]

Dust mites (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*, and *Euroglyphus maynei*) are commonly found in houses and are important sources of allergens, particularly for persons with asthma.[134] These mites are approximately 0.3 mm in length and live in carpets, upholstered furniture, mattresses, and bedding, where they eat skin scales. Two major dust mite allergens have been identified, *Der p* I and *Der p* II. These proteins are derived from digestive enzymes in the gut of the mite and are found in high concentrations in the fecal pellets. Vacuum sampling and immunological assays indicate that in the home, the highest levels of allergen occur in the bedroom in carpeting, mattresses, and bedding.

Domestic cockroaches, including the German cockroach, *Blattella germanica*, are commonly found indoors and represent another source of allergen in residences, particularly in infested inner-city housing. Fecal material and saliva contain large amounts of the allergens *Bla g* I and *Bla g* II. In inner-city homes, mice infestations may contaminate residences with the mUS antigen.

Cats and dogs are prevalent sources of allergen exposures. *Fel d* I is the most significant allergen associated with cats, and high levels of this protein are found in cat dander and fur and also in saliva and urine. The median level of *Fel d* I in samples of settled household dust in homes with a cat are reported to range from 6 to 130,000 ng/g of dust, with a median level of 31,000 ng of *Fel d* I/g of dust.[135] In homes without a cat, much lower levels are observed, ranging from 2 to 7500 ng (median 63 ng) of *Fel d* I/g of dust; the antigen is persistent in indoor environments for long periods after a cat is no longer indoors.[135] The presence of the allergen in the dust of homes and buildings in which cats are not kept suggests that the allergen can be transported on clothing. The major dog allergen, *Can f* I, is present in dog fur and saliva and is a relatively stable protein that may persist in dust for a long time. The content of *Can f* I in household dust from homes with a dog ranges from 10 to 10,000 μg/g of dust, compared with <0.3 to 23 μg/g of dust in homes without a dog.[136]

Mouse allergen, a cause of asthma in laboratory workers, is prevalent in homes. A national study of inner-city childhood asthma found widespread contamination with this allergen and frequent positivity to the allergen on skin testing.[137]

Fungi are present in the air of virtually all homes and public buildings. Commonly isolated genera include *Cladosporium, Penicillium, Alternaria, Epicoccum, Aspergillus,* and *Drechslera.*

Biological agents in indoor air may cause disease through various mechanisms, including direct toxicity, infections, and immune hyperresponsiveness. A complete review of these diverse effects is beyond the scope of this chapter. Selected examples of diseases caused by biological agents are given; more extensive information is available in published reviews.[138]

The presence of dampness and mold, determined by questionnaire, has been associated with upper respiratory symptoms and eye irritation in large studies of children in the United States and elsewhere. These associations were adjusted for known determinants of respiratory symptoms, including maternal smoking, city, child's age and sex, and parent education. There are also similar findings in adults. A systematic review concluded that dampness in buildings contributes to adverse health effects in persons with and without

atopy, but a specific causal agent cannot be identified.[139] The evidence on dampness was reviewed by an Institute of Medicine committee which did not find the evidence to be sufficient to conclude that dampness causes respiratory symptoms or asthma.[140]

Allergic rhinitis, or "hay fever," is common, affecting approximately 20% or more adults in the United States. Identification of the specific indoor allergen associated with the symptoms may be accomplished by skin testing and in vitro measurement of antibody (radioallergosorbent test [RAST]). Many persons with asthma are sensitive to specific antigens from pollens, animal fur, fungi spores, and house dust. The risk of acute or severe attacks of asthma is increased in residences with levels of *Der p* I in excess of 10 μg/g of house dust, and asthmatic patients have been reported to show a 25% prevalence of skin test positively to cat or dog allergen extracts. Building-related allergic respiratory disease and epidemic asthma have been reported in office buildings in association with air-handling systems and humidifiers contaminated with bacteria and fungi.

Avian proteins are present in bird excreta (e.g., the droppings of pet birds such as parakeets), and fungal spores of thermophilic actinomycetes, *Aspergillus* species, *Penicillium* species, and *Aureobasidium* species may contaminate the indoor environment and cause hypersensitivity pneumonitis. A careful review of symptom pattern in relation to home and work environments and site evaluation may be needed to identify the source of exposure.

The bacterium *Legionella pneumophila,* the agent of Legionnaires' disease, causes an often fatal pneumonia associated with exposure to the bacterium in aerosols of cooling towers and air-handling systems and in humidifiers and spas.[141] It exemplifies a respiratory pathogen associated primarily with indoor environments, in both source and transmission. Of course, indoor environments are the locus of transmission of many infectious respiratory diseases, including influenza and tuberculosis. The risk of diseases depends on the strength of sources and the level of ventilation. A low air exchange rate increased the risk for pneumococcal infection among inmates in a large county jail.

CLINICAL SYNDROMES ASSOCIATED WITH INDOOR ENVIRONMENTS

During the last 20 years, complaints attributable to indoor environments have generally been classified into one of two broad groups: specific building-related illnesses and SBS.

Building-related illnesses have a number of etiologies, but the specific agent responsible for causing the disease is present in the indoor environment, for example, hypersensitivity pneumonitis caused by fungi in the ventilation system or Legionnaires' disease resulting from transmission of the organism that grows in cooling tower water.

SBS refers to nonspecific health problems related to indoor air quality in nonindustrial buildings. Irritation of mucosal surfaces and neurotoxic effects may contribute to the nonspecific symptom complex that often include headache, fatigue, and difficulty concentrating. Atopic individuals have been shown to have lower irritant thresholds than nonatopics. Multiple factors, including specific exposures, inadequate ventilation, and poor building maintenance have been linked to SBS. Panel studies in Denmark have found that complaints were most often attributed to the ventilation system, SHS, office machines, and other sources.[142]

SUSCEPTIBLE POPULATIONS

To fully protect public health, we need to characterize variation in risk associated with pollution exposure across the population along with the determinants of that variation. Vulnerability refers to factors that increase potential for exposure. Susceptibility refers to individual factors that increase risk at any given level of exposure. Increased susceptibility implies a greater health response at any given level of exposure. Factors associated with increased susceptibility include certain chronic diseases and selected genotypes. The concept of environmental justice is linked to vulnerability, as disadvantaged groups are more likely to have higher exposures.

The legislative history of the Clean Air Act mandated that the primary NAAQS were to be set low enough to protect the health of all susceptible groups within the population except those requiring life-support systems. Only two diseases, asthma and emphysema, were specifically identified in the Clean Air Act as associated with increased susceptibility. Other groups in the population, accounting for large numbers of people, are also considered to be at increased risk from air pollutants: persons with coronary artery disease and, possibly, peripheral vascular disease; infants and the elderly in general; and children with chronic pulmonary ailments such as cystic fibrosis and bronchopulmonary dysplasia.

In this section, we consider the evidence concerning these susceptible groups (Table 91-9). Pulmonologists are likely to be asked about the consequences of pollution exposures by persons with chronic lung diseases. Patients may report being adversely affected by exposures and may request guidance concerning control measures—for example, purchase of an air-cleaning device or additional medication use when exposed.

CLINICAL STUDIES IN ASTHMA AND COPD

Clinical studies have provided much of the evidence on the acute effects of pollutants on persons with chronic respiratory diseases. Controlled laboratory studies of volunteers have attempted to identify specific effects of individual pollutants, as assessed primarily by

TABLE 91-9 Populations Considered Susceptible to Air Pollution

Population	Potential Mechanism	Consequences
Asthmatics	Increased airway responsiveness	Increased risk for exacerbation and respiratory symptoms
Cigarette smokers	Impaired defense and clearance, lung injury	Increased damage through synergism
Elderly	Impaired respiratory defenses	Increased risk for respiratory infection
	Reduced functional reserve	Increased risk for clinically significant effects on function
Infants	Immature defense mechanisms of the lung	Increased risk for respiratory infection
Persons with coronary heart disease	Impaired myocardial oxygenation	Increased risk for myocardial ischemia
Persons with chronic obstructive pulmonary disease	Reduced level of lung function	Increased risk for clinically significant effects on function
	Increased pulmonary and systemic inflammation	Increased risk for myocardial ischemia

pulmonary mechanics; however, other end points, including symptoms, have been assessed.

The most striking effect of acute exposure to SO_2 at concentrations less than 1.0 ppm is the induction of bronchoconstriction in asthmatics after exposures lasting only 5 minutes. In contrast, inhalation of concentrations of SO_2 in excess of 5 ppm causes only small decrements in airway function in normal subjects. Lung function responses to SO_2 in asthmatics are greater when SO_2 exposure is accompanied by increased ventilation, usually stimulated by exercise. SO_2-induced bronchoconstriction can be exacerbated by breathing cold or dry air and oral (vs. nasal) breathing. The SO_2 bronchoconstrictor response can be reduced or inhibited in asthmatics by anticholinergic agents, mast cell stabilizers, or β-agonist bronchodilators.

Inhalation of acidic aerosols generally produces little alteration in pulmonary function in normal subjects, even permissible exposure limit of 1 mg/m^3 in the workplace. As with SO_2, asthmatic subjects have been found to be susceptible to the effects of acidic aerosol exposure, although different laboratories have found differing concentrations for threshold exposure. Adult asthmatics exposed to aerosols of 450 and 1000 μg/m^3 of H_2SO_4 demonstrate decrements in specific airway conductance. Adolescent asthmatics appear to be more sensitive to the effects of acidic aerosols than adult asthmatics. Decrements of lung function have been observed in adolescents at levels as low as 70 μg/m^3, concentrations occasionally noted in outdoor air and an order of magnitude lower than the level at which effects are observed in normal subjects. The apparent difference in sensitivity of adult and adolescent asthmatics may also be due to differences in the research protocols. In these studies, young asthmatics showed functional decrements at exposure levels that corresponded to near-peak outdoor levels in the northeastern United States. Field studies in summer camps of both normal and asthmatic children reported decrements in pulmonary function during pollution episodes that included exposure to increased levels of acidic aerosols, supporting the concern that children and adolescents may be particularly susceptible to effects of acidic atmospheres.

Although several controlled human studies have found asthmatics to be responsive to low levels of NO_2, the findings have not been consistent. The conflicting results among these studies are probably related to the differences in subject selection and exposure protocols. Persons with COPD may represent a group with increased susceptibility to short-term exposure to NO_2. Further study of the issue is needed.

Consonant with the provisions of the Clean Air Act and with its legislative history, a group that appears to be at potential risk from exposure to O_3 consists of those characterized as having pre-existing respiratory disease. In the case of asthmatics, however, emerging data from controlled studies indicate no greater responsiveness to O_3 in mild asthmatics than in normal, healthy populations. Pretreatment of healthy volunteers with β-adrenergic agents before O_3 exposure and exercise does not prevent bronchoconstriction, whereas pretreatment with atropine or indomethacin reduces the decrement in lung function. Since exercise greatly potentiates the response to O_3, the best strategy for clinical management includes avoiding outdoor exercise during periods of high O_3 pollution.

CLINICAL AND EPIDEMIOLOGICAL STUDIES IN HEART DISEASE

Persons with coronary heart disease have also been identified as a group at risk from increased levels of air pollution. In the presence of coronary artery disease, there is limited ability to increase coronary blood flow in response to increased myocardial oxygen consumption during exercise. When myocardial blood flow is not sufficient to meet oxygen demand, the myocardium becomes ischemic, resulting in angina pectoris, ECG changes, or both. Several recent studies conducted at relatively low COHb levels have investigated the effects of CO exposure on exercise capacity and the occurrence of myocardial ischemia. These studies found a decrease in the time to the occurrence of myocardial ischemia in persons with coronary artery disease during exercise after CO exposure. The lowest CO dose to produce a decrease in time to the onset of angina was associated with a 2% COHb level. In this study, there was a mean decrease of 4.2% in the time to angina and a mean decrease of 5.1% in the time to ECG changes, indicative of myocardial ischemia at 2% COHb compared to control (air exposure) days; greater effects were noted at 3.9% COHb.[60] Clinical studies have shown a significant dose–response relationship for the individual differences in time to the onset of ECG changes at increasing COHb levels. In addition, at a COHb level of 6%, patients with coronary artery disease experience an increase in the frequency of arrhythmias. Of note, at the same low levels of COHb, adverse effects have been observed in humans but not in animals.[61] Older people and very young individuals may also be at a heightened susceptibility to air pollution–mediated cardiovascular effects due to weakened defense mechanisms, existing comorbid conditions, or growth and development in the case of infants and children and diminished reserves in the case of older adults. Epidemiological studies examining associations between outdoor air pollution levels and cardiovascular morbidity and mortality have examined whether patients with other comorbid conditions are more susceptible to air pollution effects than patients without these conditions.[143] For example, although it has been hypothesized that patients with type 2 diabetes, with its underlying vascular dysfunction, are more susceptible to air pollution health effects, the evidence is not conclusive.[144,145] However as another example, several studies have documented that patients with COPD may be more susceptible to cardiovascular effects (e.g., myocardial infarction) of air pollution, perhaps due to a heightened inflammatory state. For example, one study found that the risk of a myocardial infarction associated with increased fine particle concentrations was four times higher in people who had COPD compared to people without COPD.[146]

Although mostly done to investigate mechanisms by which air pollution exposure may cause a health effect, studies have also examined whether several genetic polymorphisms either protect or give an individual increased susceptibility to these cardiorespiratory health effects. For example, individuals without a polymorphism to protect against oxidative stress (e.g., glutathione S-transferase mu 1 [GSTM1] null) may be more responsive to air pollution health effects than individuals with wild type GSTM1.[147] More work is needed, however, before we understand these as generic markers of susceptibility. In summary, existing respiratory and cardiovascular conditions may make a patient susceptible to air pollution–mediated health effects, as several mechanisms thought to be involved in mediating a cardiovascular health response to air pollution may already be activated.

CONTROL STRATEGIES

Controlling the health effects of indoor and outdoor air pollution requires strategies oriented toward populations and toward individual patients. Clinicians can make practical recommendations to their patients to reduce risk for disease and for exacerbation of established disease. Clinicians may serve as consultants or as advocates in seeking to reduce the effects of indoor and outdoor air pollutants through population-oriented control approaches.

PATIENT-ORIENTED STRATEGIES

Approaches for limiting the health risks of breathing polluted ambient air have received little investigation. Present understanding of the determinants of exposure suggests that modifying time–activity patterns to limit time outside during episodes of pollution represents the most effective strategy. The levels of some reactive

TABLE 91-10 Questions and Answers About Indoor Air Pollution

Question	Answer
Do air cleaners work?	Air cleaners have not yet been shown to have direct health benefits.
Should the radon concentration in my home be measured?	Yes, radon can be readily measured at relatively low cost, and mitigation is feasible.
Should the air ducts in my home be cleaned?	There is no evidence on health benefits of cleaning air ducts.
Will controlling mites be beneficial?	Controlling mite levels is beneficial for persons with mite-sensitive asthma.
Should my home be humidified?	Humidification may increase allergen levels.

pollutants tend to be lower indoors than outdoors. O_3 levels in buildings are lower than outdoor levels, but they can be driven upward by increasing the rate of exchange of indoor with outdoor air. There is potential for O_3 oxidation products in indoor environments to increase toxicity but few data are available to support the hypothesis. Fine acid aerosols can penetrate indoors, but neutralization by ammonia produced by occupants, pets, and household products may reduce concentrations. Other types of particles in outdoor air may also enter indoor air, but concentrations of particles of outdoor origin, measured indoors, are generally lower indoors. Nevertheless, healthcare providers can reasonably advise patients to stay indoors during pollution episodes. Vigorous exercise outdoors, which increases the dose of pollution delivered to the respiratory tract, should also be avoided at such times.

Susceptible patients should be counseled concerning the nature and degree of their susceptibility. The use of medication should follow the usual clinical indications, and therapeutic regimens should not be adjusted because of the occurrence of a pollution episode without evidence of an adverse effect on symptoms or function. In the laboratory, inhalation of cromolyn sodium and bronchodilating agents blocks the response to some pollutants, but use of these drugs solely because of exposure to air pollution cannot be advised.

Respiratory protective equipment has been developed for use in the workplace to minimize exposure to toxic gases and particles. Many of these devices, particularly those likely to be most effective, add to the work of breathing and cannot be tolerated by persons with respiratory disease. Under most circumstances, healthcare providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution. Similarly, air cleaners have not been shown to have health benefits, whether directed at indoor pollutants generated by indoor sources or at those brought in with outside air.

Pulmonologists may be concerned with diverse issues related to the control of indoor air pollution, ranging from answering patients' questions about pollutant health effects and control, to management of complex problems in large buildings. Some commonly asked questions and answers that reasonably reflect the state of the evidence are provided in (Table 91-10). The clinically relevant microenvironments are numerous, including the home, the workplace, public buildings, and places where leisure time is spent.

Workplace problems, such as the "SBS," may be particularly challenging. The healthcare provider needs to establish the connection between the workplace and the occurrence of symptoms and then seek a solution that includes identifying and remediating the responsible factors in the workplace. The diagnostic task requires a sufficient awareness of the possible causal role of the indoor environment (Fig. 91-4). Resolution may require an evaluation and intervention by indoor air quality professionals. The physician may be unable to resolve the patient's symptoms without motivating a building evaluation and resolution of underlying problems. Guidance for the clinician has been offered by the ATS.[148–150]

COMMUNITY-ORIENTED STRATEGIES

Frequently, communities become concerned about the effect of particular local sources—for example, a power plant or manufacturing facility or vehicle depot. In Beijing, China, during the 2008 Summer Olympics, the air pollution concentrations, normally much higher than in the United States and other western European countries, were drastically reduced during the Olympic and Paralympic Games, by restricting automobile use, and shutting down construction and industrial emissions in Beijing and the surrounding provinces. These air pollution reductions were associated with improved levels of biomarkers of inflammation, coagulation, vascular function, pulmonary inflammation, and function in a panel of otherwise healthy, young, medical residents living in central Beijing.[43,62] Thus, community strategies to reduce pollution can have a beneficial health impact.

Exposures to air pollutants and other environmental contaminants may disproportionately affect disadvantaged communities. The term "environmental justice" is used in addressing inequities between poorer and more well-to-do communities. Concern about the health risks may quickly lead to controversy and litigation. Thus, understanding the health risks posed by local sources may be difficult and may require skills in community health, as well as in epidemiology and toxicology. Local physicians may become active through concerns about the health of their patients or as advocates for the community's environment or for the polluting facility. Most often the dimensions of such complex problems exceed the skills of local physicians. Involvement may be appropriate, but guidance should be obtained from appropriate public health and environmental agencies.

In 1976, the EPA proposed cautionary statements for public reporting of outdoor air quality – the Pollutant Standards Index – for criteria pollutants. In the 1999 revision, the name was changed to the air quality index (AQI). The index provides AQI levels, descriptors of air quality, and guidelines for cautionary statements, based on levels of air pollution in comparison to the NAAQS. The AQI is color coded into six categories of decreasing air quality: green (good), yellow (moderate), orange (unhealthy for sensitive groups), red (unhealthy), purple (very unhealthy), and maroon (hazardous). Air pollution forecasts are now widely available on local or national TV, radio or newspaper reports, and on the Weather Channel and EPA websites (http://www.weather.com/) and (http://airnow.gov/), respectively. Notification by email is available through www.enviroflash.info. The actions taken when "alert levels" are reached or expected to be reached include the issuance of health advisories (or cautionary statements) to the public. The EPA's advice is intended to be applied by local air pollution agencies in preparing daily air quality summaries for dissemination to the media and in providing useful guidelines for physicians and public health officials.

With the amendments to the Clean Air Act in 1970 enhancing the regulatory role of the legislation, we have witnessed a remarkable increase in our understanding of the sources, dosimetry,

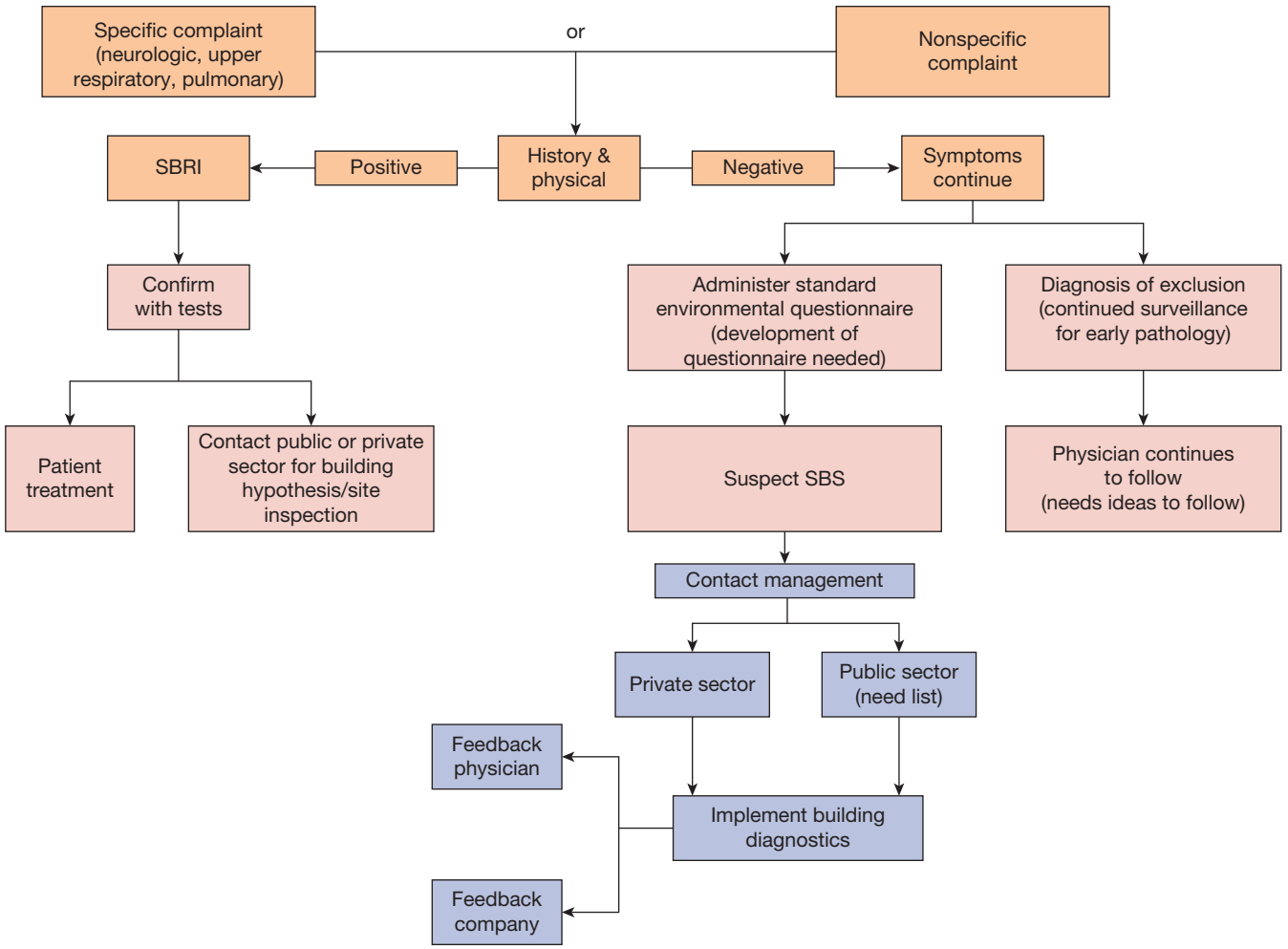

Figure 91-4 Medical approach to patient with complaints possibly related to indoor air pollution without an antecedent diagnosis. SBRI, specific building-related illnesses; SBS, sick building syndrome. *(Based on American Thoracic Society data.)*

pharmacokinetics, and health effects of not only the critical air pollutants but also a large number of indoor and other unregulated pollutants. Reductions in auto emissions and more efficient engines, cleaner fuels, removal of lead from gasoline, and smoking bans in indoor environments are just a few of the interventions, together with tighter standards, that have resulted in improved air quality. For the future, a multipollutant approach to controlling air pollution, rather than a pollutant by pollutant approach, is anticipated. The interplay between science and policy continues to play in protecting the public health from a variety of toxic indoor and outdoor pollutants.

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CHAPTER 92

High-Altitude Physiology and Clinical Disorders

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INTRODUCTION

Altitude physiology typically focuses on people above 2500 m; ~8000 ft. Altitudes above that are sometimes subdivided into very high (3500–5500 m; ~11,500–18,000 ft) and extreme (>5500 m; >18,000 ft). An estimated 40 million people travel each year to altitudes >2500 m (~8000 ft),[1] and as many or more travel to altitude for leisure and sports, and work in mines, military or border operations, and the like. Altitude medicine considers the clinical disorders associated with acclimatization by the travelers, workers and migrants, and with adaptation by people with lifetimes or populations with millennia of residence (an estimated 83 million people).[2]

With a hurried ascent, many (~80%) will report a transient headache (high-altitude headache or [HAH]), and some will develop one of three forms of acute high-altitude illness: acute mountain sickness (AMS) and HAH, high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).[3,4] AMS (see Table 92-1) and HAH are annoying and interfere with activity and work, however, HACE and HAPE can be fatal with mortality rates approaching 30%.[5–7] Among some residents, chronic mountain sickness (CMS) and right ventricular hypertrophy develop over months to years of residence at altitude. Birth weights are generally lower and the rate of small-for-gestational-age babies and congenital heart defects are higher than that in lowland populations.[4]

Hypoxemia (FIO_2 equivalent to ~17% O_2 at 2500 m, down to ~8% O_2 at the summit of Everest) causes the physiologic responses and illnesses. Altitude-related exposure to cold and extreme exercise may also contribute to illness. Other environmental features may include UV radiation, trauma, and infection that are not covered in this chapter. Finally, dealing with illness in a remote area can be challenging. For example, facilities for management of clinical disorders in remote areas or evacuation to a lower altitude may be limited.

CONSIDERATIONS OF EXPOSURE AND TIMECOURSE

Individual responses to hypobaric hypoxia may be conceptualized along a time continuum of interrelated phases: acute (immediate to 3–5 days in which acute illnesses present), subacute (over weeks leading toward acclimatization), chronic (years), and lifelong residence (Fig. 92-1). The reduction in environmental oxygen as a result of altitude exposure lowers the oxygen available for gas exchange in the lungs (PA_{O_2}), arterial oxygen (Pa_{O_2}), and cellular oxidative phosphorylation for adenosine triphosphate (ATP) production.

Oxygen levels in the atmosphere were extremely low; rose about 2.5 million years ago in the Great Oxidation event and then rose sharply.[8] Over the past 600 million years, oxygen levels have varied from as low as ~12% to as high as ~30%.[8,10] All multicellular animals[11] have genetically encoded oxygen homeostasis pathways. We have a common ancestry and therefore share many elements of the response to hypoxia. People moved to live at high altitudes in the past 100,000 years and evolutionary forces have resulted in different strategies of adaptation in different populations.[12]

RESPONSES TO HYPOBARIC HYPOXIA

Important adaptations to hypobaric hypoxia are considered below.

Ventilatory Adaptations

An increase in ventilation is an immediate vital, mammalian response. It results in a decrease in alveolar CO_2 in order to increase PA_{O_2}, thus mitigating decreases in vascular oxygen delivery at altitude compared to sea level (Fig. 92-2).

The sensor initiating the acute response is the carotid body at the bifurcation of the internal and external carotid arteries. Ablation of the carotid body attenuates the acute response to altitude exposure.[13]

Blood flowing through the carotid body comes from the lungs via the carotid artery, where the oxygen pressure is typically 80 to 100 mm Hg. Carotid body afferent activity rises significantly as arterial oxygen pressure falls below 60 mm Hg.[13] However, oxygen pressure in the mitochondria is much lower, as oxygen has to diffuse across vessels and interstitial spaces and is extracted by cells for a number of metabolic processes. In the microvessels of the carotid body, the average oxygen pressure is about 50 mm Hg with minimal values likely near 20 mm Hg. It is reasonable to expect an average mitochondrial oxygen pressure of about 40 mm Hg and a minimum

TABLE 92-1 Lake Louise Symptom Score Self-Report Questionnaire. Fill Out Before and Each Morning Upon Exposure to Altitude or on a Trek

Symptoms	Severity	Points
Headache	No headache	0
	Mild headache	1
	Moderate headache	2
	Severe headache, incapacitating	3
Gastrointestinal	No gastrointestinal symptoms	0
	Poor appetite or nausea	1
	Moderate nausea or vomiting	2
	Severe nausea or vomiting, incapacitating	3
Fatigue and/or weakness	Not tired or weak	0
	Mild fatigue/weakness	1
	Moderate fatigue/weakness	2
	Severe fatigue/weakness, incapacitating	3
Dizziness/ lightheadedness	Not dizzy	0
	Mild dizziness	1
	Moderate dizziness	2
	Severe dizziness, incapacitating	3
Difficulty of sleeping	Slept as well as usual	0
	Did not sleep as well as usual	1
	Woke up many times, poor night's sleep	2
	Unable to sleep	3

Add up the responses to each of the questions of the self-report score. A diagnosis of AMS is based on a recent rise in altitude, the presence of a headache with the presence of at least one other symptom, and a total score of >3 with no evidence for other reason of symptoms.

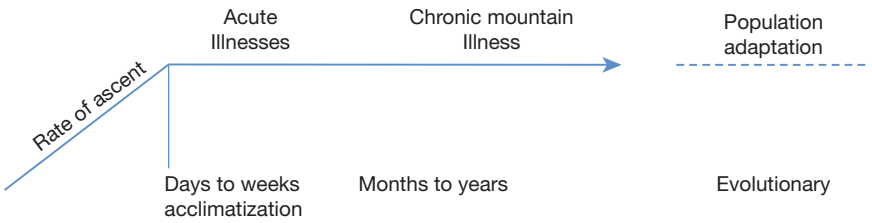

Figure 92-1 Individuals respond to altitude with time-dependent acclimatization and illness expression, and populations living at altitude exhibit adaptations that differ according to population ancestry.

of about 15 mm Hg. If this seems low, in the liver and spleen average tissue values are measured at less than 12 to 15 mm Hg.[14] Thus, tissue in the carotid body may be exposed to oxygen pressure significantly less than typical levels of arterial oxygen pressure ~80 mm Hg.

Oxygen level is major driver of carotid body response although carotid body afferent activity can also be stimulated, at least transiently, by changes in carbon dioxide or hydrogen ion concentrations. Respiration is stimulated by decreasing the [ATP]/[ADP][Pi] ratio and, as a result, the rate of respiration does not decrease until oxygen deprivation is severe enough to cripple metabolism.[14] Decreased availability of oxygen first affects the ability of mitochondria to maintain the [ATP]/[ADP][Pi] ratio, a measure of energy available when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Mitochondrial ATP synthesis is tightly coupled to oxygen consumption; that is, mitochondria respire only fast enough to replenish ATP as it is used. However, other responses to lowered oxygen levels are engaged depending on the duration and severity of the oxygen deprivation. Cellular oxygen–sensor responses activate short- and long-term energy savings and cellular protection mechanisms.[15]

In the first few minutes of exposure, as $P_{A_{O_2}}$ decreases to below ~60 mm Hg, ventilation increases, resulting in a decrease in $P_{A_{CO_2}}$.[13,16] In the carotid body, low O_2 and high CO_2 interact synergistically to depolarize glomus cells and produce an action potential; the ventilatory effects of concurrent hypoxia and hypercapnia are greater than the sum of the two stimuli applied separately. As the $P_{A_{O_2}}$ level declines, the relationship between the sensory afferent nerve activity and $P_{A_{CO_2}}$ becomes increasingly steeper, leading to higher ventilatory drive. The physiologic response to acute exposure is an abrupt increase in ventilation (Fig. 92-3), which continues to increase over days. After a few days adaptations take place in the brainstem controller through circuit adaptations so that ventilation is increased with reductions in $P_{A_{CO_2}}$ at all levels of $P_{A_{O_2}}$, and the afferent responses from the carotid body also reflect this change in responsiveness to chemoreception even when there is a near restoration of pH. Even though this organ's response is pathognomonic of the acclimatization process in response to altitude-associated chronic hypoxia, there is bidirectional, efferent as well as afferent, communication so that attributing the entire physiologic response to the carotid body is problematic.

Hypoxic chemotransduction in the carotid body requires release of excitatory transmitters that activate afferent sensory neurons.[17] Cellular events including bioenergetic, biosynthetic, and conformational cause the chemotransduction.[18] Mechanisms implicated include oxygen-sensitive ion channels, reactive oxygen species and the "redox" state of the cell, and direct effect of oxygen to alter the conformation of a protein, such as NADPH oxidase 4, an enzyme encoded by the NOX4 gene. This phagocyte-type oxidase has been postulated as an oxygen sensor of sorts because its activation is linearly and steeply dependent on oxygen availability. A cascade of immediate intracellular effects will initiate changes in afferent information from the carotid body to the medulla that will lead to the increased tidal volume and respiratory frequency.[19]

A physical remodeling of ventilatory control begins soon after exposure through changes in gene expression. In blood vessels this includes growth factors such as vascular endothelial growth factor *(VEGF)*. The main pathway for such hypoxic responses is mediated by the hypoxia-inducible transcription factor 1 alpha (HIF-1α).[15] HIF-1α is the oxygen-dependent subunit of the HIF-1 heterodimer, considered the master regulator of oxygen homeostasis that initiates transcription of over 100 hypoxia-inducible genes, that have hypoxia response elements. Under normoxia, HIF-1α is formed continuously and degraded in the cytoplasm. HIF-1α is hydroxylated by the enzyme prolyl hydroxylases prior to its degradation. The prolyl hydroxylases have a relatively high Km for oxygen; hydroxylation leads to degradation under physiologic conditions. Decreased oxygen pressure results in significant accumulation of HIF-1α in less than 2 minutes; HIF-1α is rapidly degraded upon reoxygenation.

Central controllers can be affected directly and indirectly by oxygen availability, but over time neurotransmitter expression correlates with changes in gain and changes in gene expression with some additive epigenetic changes.[20] Within days of exposure, there is a progressive increase in sensitivity but a downregulation of the magnitude of the ventilatory response by the brainstem networks that integrate afferent information.[21] At 4300 m, hyperventilation increases over the first few days and then over 1 to 2 weeks despite metabolic compensation to the respiratory alkalosis.[22] The acclimatized person will continue to hyperventilate when returned to normoxia, a phenomenon not observed during the very first hour of hypoxic exposure. pH compensation to hypocapnia occurs in 2 to 4 days and a mild alkalinity persists over the following weeks. The ventilatory response to chronic hypoxia consists of both

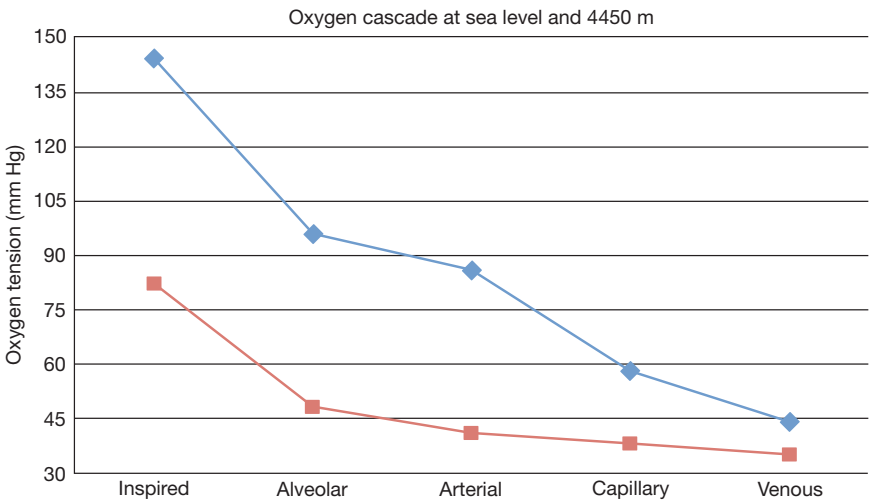

Figure 92-2 Oxygen tension is lower along the axis of oxygen delivery at 4540 m or ~15,000 ft *(red line)* as compared with sea level *(blue line)*. *(Adapted from Hurtado A. Animals in high altitudes: resident man. In: Dill DB, ed. Handbook of Physiology. Section 4: adaptation to the Environment. Washington, D.C.: American Physiological Society;1964:843–859.)*

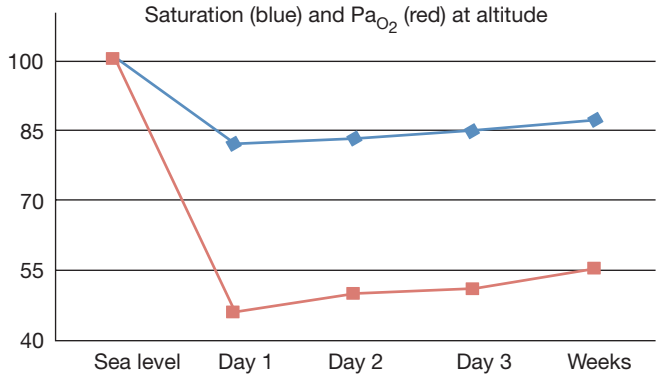

Figure 92-3 The figure illustrates the problem with hypoxemia encountered with acute altitude exposure. Values of arterial oxygen saturation (*blue*, % O_2 saturation) and arterial oxygen tension (Pa_{O_2}) before, during the first few days at altitude, and after weeks of residence.

frequency and tidal volume changes. Acclimatized individuals will return to nearly normal control arterial acid–base status within 24 to 48 hours of normoxia, following acclimatization to 4300 m.

Thus, the transition points from acute to subacute to full acclimatization in the ventilatory domain blend from one to another.[23] Acclimatization results from cellular and system responses that improve oxygen delivery. Ventilatory responses are complemented by systemic ones, including erythrocytosis and new blood vessel formation that further assist in increasing oxygen delivery to peripheral tissues. For instance, HIF-1α affects a variety of "hypoxic response elements" with downstream effects on many hypoxic response proteins including erythropoietin.[24] Some actions of erythropoietin result in increases in hemoglobin levels, and thus will affect oxygen carrying capacity in the blood and an improvement in oxygen delivery, lasting weeks to months. People with a mutation limiting HIF-1 degradation have high baseline ventilation and exaggerated ventilatory response to hypoxia, as well as chronic polycythemia under nomroxia.[25]

SLEEP AND PERIODIC BREATHING

Healthy people at altitude may develop a pattern of regularly recurring periods of hyperpnea and apnea. This phenomenon results from a dynamic interaction among elements in two separate feedback loops, one through peripheral and the other through central chemoreceptor reflexes, with contributions by cardiac output and brain blood flow.[26] Periodic breathing occurs during wakefulness but is especially evident in sleep, and apneas and hypopneas of the nonobstructive type are reported as occurring almost equally in non-REM and REM sleep in health subjects.[27] Recurrent central apneas will occur during sleep at modest altitude (>2500 m), and is a manifestation of increased alveolar ventilation (hyperpnea) from hypoxia producing hypocapnia competing with a normal elevation in the apneic (carbon dioxide) threshold with sleep.[28] The apneas or hypopneas produce a fall in arterial oxygen and a rise in carbon dioxide and lead to arousals from sleep during the hyperpneic phase.[29] The alternating hyperpnea and apnea produce an oscillatory pattern of oxygen saturation, with the nadir of oxygen saturation playing some role in susceptibility to HAPE and HACE.[30]

At altitudes above 3000 m, the quality of both REM and non-REM sleep is impaired by arousals often associated with periodic breathing;[31] at extreme altitude (above 5500 m) length of and number of apneas decrease due to a high frequency of breathing. The reason for this phenomenon could represent a greater relative influence of central oxygen–chemosensitive sites over afferent information on peripheral hypoxia and hypocapnia.[32,33] With acclimatization, the sleep pattern tends to become more normal; however, periodic breathing during non-REM sleep may persist over a week or more.[30]

THE PULMONARY CIRCULATION

Moderate-to-severe pulmonary hypertension (both systolic and diastolic) is a common finding in all the altitude-related diseases.[4] Although pulmonary blood vessels are extensively supplied with sympathetic (vasoconstrictor) and parasympathetic (vasodilator) fibers, regulation of vasomotor tone is largely due to the local effects of oxygen and carbon dioxide. At altitude the entire lung is hypoxic and CO_2 levels are low as a consequence of hyperventilation; as a result, altitude is a model of whole lung hypoxic, hypocapnic pulmonary vascular vasoconstrictive responses.[4] Acute vasoconstriction over a few hours is a physiologic response and can be reversed as soon as the hypoxia is lifted. With days to weeks of hypoxic exposure there occurs a structural remodeling of pulmonary arterioles and an increase in resting pulmonary arterial pressure and pulmonary vascular resistance; hence pulmonary artery pressure does not decline immediately with restoration of normoxia. With return to sea level after weeks to months, right ventricular hypertrophy and pulmonary vascular pressures will return to normal over several weeks.[4]

Andean highlanders have high pulmonary artery pressures and do not restore pulmonary artery pressure or right ventricular hypertrophy to normal levels after returning to sea level or normal oxygen tensions. In contrast, Tibetan highlanders have minimal elevation of pulmonary artery pressure and do not exhibit the vesicular changes of the Andean highlanders.[34]

The pulmonary circulation is a high-flow, low-pressure system.[35] Based upon a balance of hydrostatic and oncotic pressure gradients across pulmonary capillary microvessels, and by Na^+ pumps, the pulmonary interstitium and alveolar spaces are maintained in a "dry" state. At high altitude, while respiratory mechanics do not change appreciably, changes in hemodynamics due to vasoconstriction and high shear stress are dramatic and in certain individuals lead to acute presentations of pulmonary edema.[4]

FLUID HOMEOSTASIS

Dermal edema is seen in faces of many, but not all mountaineers at high altitude[36] and in the retinal vessels of almost all individuals.[37] Lung edema, cerebral edema, and peripheral edema are the hallmarks of disease. Extravasation may also result from loss of tight channels due to oxidative stress and free radicals or a direct effect of hypoxia on ion channels.[38] Local dysregulation of the renin–angiotensin–aldosterone system is proposed to play a role in this generalized response.[39,40]

ERYTHROPOIESIS AND HEMOGLOBIN AFFINITY

An increase in the number of red blood cells occurs with acute exposure owing to an increase in EPO synthesis in response to HIF-1 and HIF-2.[41,42] This acclimatization response takes a week or so and is reversible upon return to low altitudes. With chronic hypoxia, there are an increased number of erythrocytes and an increase in oxygen content among upward migrants such as Colorado residents and among Andean highlanders. Tibetan highlanders have minimal or no erythrocytosis owing to the high frequencies of variants in EPAS1 (HIF-2α) associating with lower hemoglobin concentration.[43]

Several studies have considered the potential for a change in oxygen affinity. The increase in ventilation results in decreases in alveolar and arterial P_{CO_2} and arterial $[H^+]$; concomitantly, serum levels of 2,3-diphosphoglycerate (2,3-DPG) are increased. While the reductions in Pa_{CO_2} and $[H^+]$ increase hemoglobin affinity for O_2, increases in 2,3-DPG diminish the affinity; loading and unloading of O_2 from hemoglobin depends upon the balance of these factors.[44] Humans, native to the Andes or Himalayan mountains, also can increase $O(_2)$ affinity, not because of a fundamental difference in hemoglobin structure or function, but because of extreme hyperventilation and alkalosis.[45]

COMMON CLINICAL DISORDERS OF HIGH ALTITUDE

Altitude-related clinical disorders are well recognized. They may be observed occasionally at altitudes as low as 8000 ft (2500 m), however their frequency increases with increasing altitude. A recent clinical practice review is available from the Medical Commission of International Mountaineering and Climbing Federation (UIAA).[46] Information about high-altitude travel for those with pulmonary disease is also available.[47]

HIGH-ALTITUDE HEADACHE

High-altitude headache (HAH) is very common, and is exacerbated by insufficient hydration in the setting of increased water loss with hyperventilation, overexertion, and insufficient energy intake, particularly in those who have experienced HAH on a previous visit to altitude. Vasodilation from hypocapnia may also contribute, but there is little evidence for brain edema in those without neurologic symptoms.[48,49] Acetaminophen or ibuprofen with hydration will improve this symptom.[50]

ACUTE MOUNTAIN SICKNESS

Acute mountain sickness (AMS) occurs after 4 to 36 hours of altitude exposure. Symptoms are headache (usually frontal), nausea, vomiting, irritability, malaise, insomnia, and poor climbing performance. Symptoms frequently occur first or are more severe the morning after the first night at altitude. Sleep-disordered breathing contributes to the severity of AMS in the morning after the first night at high altitude.[51] AMS is usually self-limited, but can be ameliorated by drug therapy.

Many mechanisms have been proposed (Fig. 92-4). Studies target one or another potentially identifying marker or therapeutic pathway, but few believe that only one factor produces one or more of the altitude illnesses.

Incidence

The incidence of AMS is altitude- and time-dependent.[52] The incidence is ~30% on same-day, several-hour car trips to the Hawaiian or Colorado mountains (3000–4300 m).[7,53] It occurs in 10% of those at 2500 m and 51% at 4500 to 5000 m on multiday trips.[7] A survey of Alpine walkers at overnight huts noted an incidence of 9% at 2850 m, 13% at 3050 m, 34% at 3650 m, and 53% at 4559 m.[54] Among trekkers en route to an Everest base camp, the incidence was 43% at 4300 m, and higher in those who had flown into an airstrip at 2800 m (49%) than those who had walked in all the way (31%).[55]

The Lake Louise Symptom Score Questionnaire (Table 92-1) is the most common and useful self-administered tool to determine the severity of AMS and provides a score for the five signature symptoms rating them from 1 (mild) to 4 (severe). A score of 4 and more is considered AMS, a score of 10 and more is considered severe and requires immediate intervention.[56,57] Copies should be included as equipment of any trekking group to high altitude.[58] Confounders affect such scoring systems; for instance, a hangover will give a positive AMS score even at sea level. So there is a need for context and allowance for confounding factors. On the other hand, day-trippers, trekkers, and physicians unaware of the high prevalence of AMS may mistake symptoms for signs of viral illness, food intolerance, poor sleep, intense exercise, or jet lag.

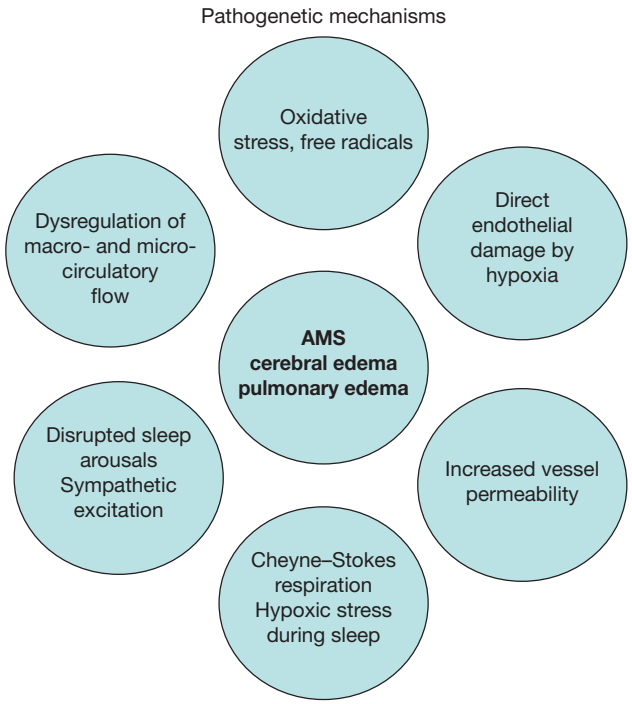

Figure 92-4 Evidence for several mechanisms for AMS, HACE, and HAPE.

Risk Factors

For novices, the altitude and speed of ascent on a previous trip should be considered, as rapid ascent to altitude appears to affect everybody.[4,58] Women may be less likely to get AMS than men,[59] and there are hints that teenagers and young adults have a higher incidence of AMS than adults.[60] Other clinical features reported in the literature include history of migraine, persistence of a patent foramen ovale, Down syndrome, congenital pulmonary abnormalities, perinatal pulmonary vascular insult, and Holmes–Adie syndrome, a rare disorder of autonomic control.[61]

Response to challenge with hypoxia improves risk assessment but is not routine.[62] A recent report on a fairly large cohort found factors independently associated with severe high-altitude illness were a previous history of acute illness, ascent greater than 400 m/d, history of migraine, ventilatory response to hypoxia at exercise less than 0.78 L/min, and desaturation at exercise in hypoxia equal to or greater than 22%.[63] Chemosensitivity parameters (high desaturation and low ventilatory response to hypoxia at exercise) improved the discrimination ability in this prediction model.

While AMS is an environmentally mediated disorder, there are individual differences in risk. The concept is that AMS is a polygenic disorder in which genotype contributes to capacity to rapidly and efficiently acclimatize to altitude; nevertheless, the mechanisms by which this occurs have yet to be elucidated.[64]

Preventive Medicine

The most common internal medicine diseases like diabetes, arterial hypertension, WHO Class II COPD, elevated lipid profiles, mild coronary artery disease, renal insufficiency, etc. are no reason to cancel a trip to high altitude if the same preventive and treatment measures are taken during the travel as they are at home and the traveler is aware of his/her symptoms and how they might change during the trip.[46] Exercise-induced asthma can be exacerbated at altitude due to increased ventilation (increased heat exchange). Known disease of more than mild severity (COPD, sleep apnea, heart failure, etc.) may be a relative contraindication for travel for pleasure,[47] although there are reports of the successful use of supplemental oxygen. The arterial hypoxemia at high altitude poses a risk of faster disease progression in those with pre-existing kidney disease. An inability to diurese increases the risk of developing acute altitude illness in patients with chronic kidney disease.[65]

Drug interactions require consideration.[50] Acetazolamide is the most widely used drug intervention against AMS or HACE.[1] It can cause problems for patients with renal failure (reduced elimination and increasing metabolic acidosis), hepatic insufficiency (ammonium ion toxicity), COPD (dyspnea), and pregnant women (accumulating effect with natural higher progesterone levels followed by

dyspnea). Patients taking aspirin (acetylsalicylic acid) on a regular basis have reduced acetazolamide elimination and increased central nervous system penetration with toxicity. Phosphodiesterase inhibitors sildenafil and tadalafil use should be accompanied with the usual caution about a danger of serious hypotension in those also treated with nitrates.[38] One study that patients on β-blockers had significantly reduced oxygen saturation and increased heart work with a reduced exercise tolerance in hypoxia compared to control.[66] The mechanisms were not explored but the recommendation was made to consider a switch in the antihypertensive drug regimen.

Preacclimatization in hypobaric chambers and normobaric hypoxic rooms reduces the risk of acquiring altitude illness on site, if it happens within a week before the trip.[67] If more facilities become available, preacclimatization could become a method of prevention for the leisure traveler or businessman, especially those who reach high altitude by plane.

However, the *key element* is to limit the elevation change per day to less than 400 m/d.[63,68] A slow rate of ascent is the best way to prevent AMS. A suggested rule is that above 3000 m (10,000 ft), ascent should be at a rate less than 300 m (1000 ft) per day, with a "rest" day (i.e., no additional ascent) every 3 days. This rate will be too fast for some and unnecessarily slow for others.[58] For direct travel to an altitude between 2500 m and 3000 m, stay at that altitude for two days and then ascend with a speed of 300 m per day.[38] Well-trained people ascend too fast and are more vulnerable. This need for acclimatization also implies that those in a "Kilimanjaro in 5 days tour" have no chance for safe acclimatization and are at a high risk for acute altitude illnesses.

An additional rule is, "If symptoms of AMS develop, go no higher. If they become severe, go down." Individuals who ascend to high altitude should be advised to limit their activity for the first few days upon ascent. Adequate hydration should be encouraged, and 2 L of extra fluid per day is a common rule of thumb.

Prophylactic administration of acetazolamide is advisable for anyone with a prior history of AMS. Use of acetazolamide (250 mg at bedtime or 125 mg bid) for several days after arrival may improve sleep and ability to function during the day. Some suggest starting the drug 2 to 3 days before arrival.[46] Corticosteroids (e.g., dexamethasone at a dose of 4 mg every 6 hours) is recommended as an alternative for individuals unable to take acetazolamide (e.g., those with sulfa allergy).[46] The drug is continued for a few days at altitude.

Treatment

Mild AMS is self-limiting and usually lasts about 3 days, so treatment is not mandatory. A placebo-controlled trial found ibuprofen was useful, while the information on aspirin or acetaminophen is anecdotal.[46] If the symptoms progress, the patient should descend (Fig. 92-5). If descent is delayed, acetazolamide is generally considered first-line treatment; dexamethasone can be used in sulfa-allergic individuals. A combination of the two agents can be used for rapidly evolving symptoms. For sleep disturbances, temazepam is effective in reducing recurrent central apnea and arousals, and appears safe to use, without any measurable adverse effects the next day.[69] Based on the ability of iron to influence cellular oxygen sensing pathways, one randomized, double-blind, placebo-controlled trial found that intravenous iron supplementation protected against the symptoms of AMS in healthy volunteers.[70] This is however impractical for common use.

HIGH-ALTITUDE CEREBRAL EDEMA

If the "mild" edema in the brain worsens toward compression of brain structure, the status of high-altitude cerebral edema (HACE) is reached. HACE can occur even in the relative absence of AMS symptoms. Signature symptoms are dizziness, severe almost unbearable headache, and vomiting. Ataxia is common, and some propose that a positive Romberg sign, the inability to stand straight with the feet together and the eyes closed, is an essential feature.[71] Somnolence, stupor, and changes in pupillary responsiveness mark the onset of a fatal stage. Concurrent signs of pulmonary edema may also be noted. In the absence of treatment, the condition will progress to coma and mortality will be high.

Descent is critical. While awaiting evacuation, supplemental oxygen should be given. Every 1% increase in oxygen concentration above 21% reduces the equivalent altitude by about 300 m. Several hours in a portable hyperbaric chamber may buy time and be potentially useful as a life-saving measure while descent is arranged;[61] however, the beneficial effects of the portable chamber (Fig. 92-6) may develop more slowly in HACE than in HAPE, especially in severe cases.[6] Administration of dexamethasone (4–8 mg), intramuscularly in severe cases, or orally in less severe cases, helps reduce cerebral edema and should be given while awaiting evacuation; doses can be repeated every 6 hours.[3]

HIGH-ALTITUDE PULMONARY EDEMA

A typical patient is a fit young man who has climbed rapidly and is energetic on arrival.[72] Moderate symptoms of AMS may be present initially as the individual becomes more breathless (Fig. 92-5). A cough develops, which is initially dry, then productive of frothy white sputum, later becoming blood tinged. The climber may complain of chest discomfort. The pulse and respiratory rate are increased, and auscultation of the chest reveals crackles at the bases. An elevated jugular venous pressure and peripheral edema may be seen, and a right ventricular heave and accentuated pulmonary component of the second heart sound may be detected. Over a few hours, the patient's condition may deteriorate further, with additional increases in pulse and respiratory rate. As breathing becomes "bubbly" due to pulmonary edema, cyanosis develops. In the absence of definitive treatment, hypoxemia progresses to respiratory failure, and coma and death ensue.

High-altitude pulmonary edema (HAPE) may occur independently of AMS. The symptoms are like those of pulmonary edema at sea level. HAPE requires a substantial medical intervention. Prevalence estimates are 0.5% to 2.0% of those rapidly ascending to altitude. Individuals with a previous history of HAPE are at greater risk of all altitude-related disorders.[3,4] Some demonstrate a "threshold" effect in which repeated ascents to a particular altitude are

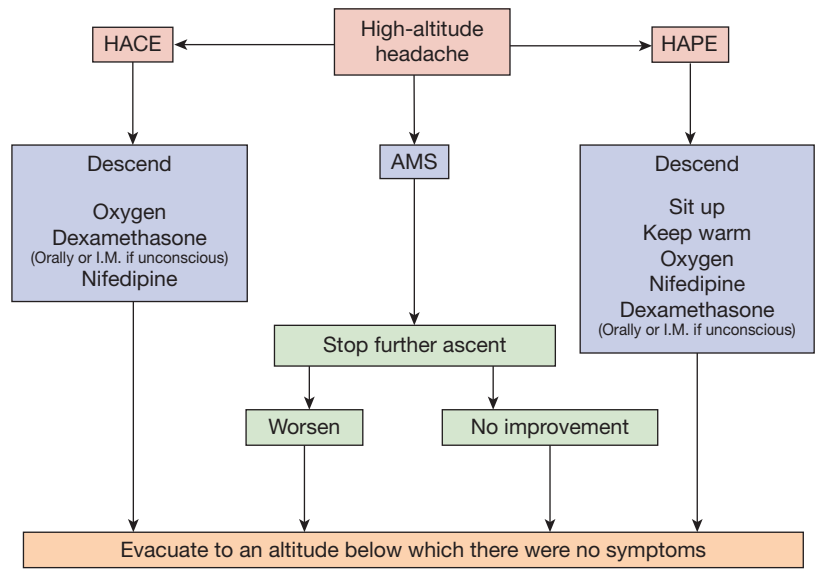

Figure 92-5 Pathway for management of acute altitude illnesses.

Figure 92-6 Shown is a portable hyperbaric chamber, in which higher oxygen concentrations are reached through inflation of the chamber to a higher barometric pressure. It has demonstrated utility for acute intervention of AMS and HAPE, until rapid descent by helicopter or porter is possible. The use of these chambers requires a nonclaustrophobic patient, fit comrades, and a flat surface. *(© N. Netzer, MD.)*

associated with development of HAPE, but lower altitudes are not. Individuals residing at high altitude who descend and then return to high altitude are susceptible.

Mechanism

HAPE is caused by migration of fluid into extravasal space through endothelial damage along with shear stresses produced by increased cardiac output and pulmonary artery pressure. The most popular hypothesis is that susceptible subjects experience the hypoxic pulmonary artery vasoconstrictor response that is uneven throughout the lung.[3] In some areas, where there is a greater degree of vasoconstriction, blood flow is reduced and the areas are protected from development of pulmonary edema. In those areas in which vasoconstriction is less marked, increased blood flow is associated with edema formation, perhaps through flow-related capillary damage, or sheer stress on vessel walls, or increased intracapillary pressure. In addition, various kinins that have been identified in the edema fluid are likely to increase permeability and to recruit leukocytes.[47]

Prevention

In those who have experienced HAPE before, use of nifedipine prophylactically (slow-release formulation, 20 mg twice daily prior to ascent, then three times daily) appears to lower significantly the incidence of HAPE.[3,61] Mean systolic pulmonary artery pressure is lowered with this approach suggesting effects on smooth muscle relaxation. The drug appears to be ineffective in preventing AMS. Prophylactic use of an inhaled β-agonist may reduce the risk of HAPE.[46,47]

Treatment

Descent is critical for survival. Initial medical treatment while the subject awaits descent includes strict rest and supplemental oxygen (Fig. 92-4). Although not yet studied in a well-controlled trial, nifedipine (10 mg sublingually) may be used. If clinically significant hypotension does not occur with the first dose of nifedipine, its administration can be repeated every 15 to 30 minutes.[3,61] Phosphodiesterase inhibitors sildenafil and tadalafil are becoming fashionable drugs in the treatment of HAPE,[39] but a consensus of evidence is not available.[3,61] Anecdotally there are beneficial effects of a portable hyperbaric chamber (Fig. 92-6),[6] again a temporary measure while descent is arranged.

■ CHRONIC MOUNTAIN SICKNESS

In the 1920s, Carlos Monge reported cases of polycythemia in high-altitude residents of the Andes (Monge disease), and in 1942, Hurtado published detailed observations of eight cases, including symptomatology and hematologic changes.[73] The defining feature is extreme polycythemia, with hemoglobin concentrations as high as 23 g/dL and hematocrits as high as 83%. Patients may have vague neuropsychological complaints, including headache, dizziness, somnolence, fatigue, difficulty in concentration, and loss of mental acuity. Irritability, depression, and even hallucinations are reported. Dyspnea on exertion is not common, but poor exercise tolerance is. The condition of CMS is quite different from AMS.[74] Excessive erythrocytosis associated with a lower oxygen saturation and hypoxic ventilatory response with relative hypercapnia are the main features of CMS, followed by right ventricular enlargement, pulmonary hypertension, and remodeling of pulmonary arterioles.

Risk Factors

Age, sex, and obesity are risk factors in Andean but not Tibetan populations. In an ecologic study of 108 Chinese highland military units stationed in Tibet for months to years, the rate of CMS ranged from ~1% to ~37% and was higher among rural construction units or those with poorer medical facilities.[75] CMS is more common in males, and in civilian populations may develop in middle and later life.[73] There may be some risk to children born at altitude but with a low birth weight for age or whose mothers had problematic pregnancies.[76]

Descent to sea level is the definitive treatment. However, for those who wish to remain at altitude for family or economic reasons, phlebotomy and administration of supplemental oxygen are beneficial.[73] Phlebotomy improves many of the neuropsychological symptoms, and in some patients pulmonary gas exchange and exercise performance are also improved.

The foundation underlying therapeutic agents for CMS, as well as the clinical evidence existing so far on their usefulness in the treatment of CMS, is sparse, compared to the work on acute illness.[73] In the Andean ACE inhibition can effectively and safely ameliorate altitude polycythemia while also reducing proteinuria.[77] There is a literature on respiratory stimulants but these studies are less rigorous. Medroxyprogesterone has been employed with some success; side effects, including loss of libido, limit its use.[73] Although acetazolamide has been used in prevention of AMS, trials addressing its use in CMS are lacking. However, the drug may be useful in improving oxygen saturation during sleep and by this mechanism reducing hematocrit. Further studies are necessary in establishing the role, if any, of sildenafil and related compounds used in acute illnesses in patients with CMS.

■ OTHER DISORDERS OF ALTITUDE RESIDENCE

Pulmonary arterial hypertension may develop over months to years of residence at altitude. There is an interesting literature on susceptibility factors.[78] One line of research has identified genetic polymorphisms in the ACE pathway associated with increased hypoxic responses and/or development of pulmonary hypertension.[79] Another line of work has focused on receptor functions, in particular a downregulation in the function of the β-adrenergic receptor system, found in altitude populations but not at sea level, for instance the pulmonary hypertension in the setting of mitral

stenosis.[80] A third may involve a perinatal predisposition for development of high-altitude chronic illnesses, in a way that some adult chronic diseases at sea level also have perinatal origins. An intriguing publication suggested that gestational age, preterm birth, preeclampsia in the mother, or a diagnosis of neonatal hypoxia, and impaired growth in utero raises susceptibility to adult disease through a reduced fetal growth of pulmonary vessels and/or an epigenetic effect of perinatal hypoxia.[76] Medications (phosphodiesterase inhibitors and prostaglandin agents) have been shown to alter pulmonary artery pressures in those born at high altitude and susceptible to pulmonary hypertension, but most of these studies are in smaller groups in a single population.[81–84]

Studies in permanent residents suggest that altitude may aggravate complications of pregnancy and prenatal life. Examples include fetal growth retardation and an increased incidence of the complications of preeclampsia and neonatal hyperbilirubinemia.[85] Mechanisms are not well understood and interventions in this population have not been performed.[86] Presumably measures such as prenatal care, vitamin supplements, and identification of known risk factors can be implemented in these populations, which often do not have the public health systems seen in Western lowland populations.

CONCLUSIONS

Altitude physiology encompasses the responses to acute and chronic residence above 2500 m. With a hurried ascent, many healthy people will report a transient headache (HAH), and some will develop one of three forms of acute high-altitude illness: AMS with or without HAH, HACE, and HAPE. In some residents, CMS and right ventricular hypertrophy develop over months to years of residence at altitude. While altitude-related exposure to cold and UV radiation, and exercise, trauma and infection are present and could contribute, in the main hypoxemia causes these physiologic responses and illnesses. Rapid descent is the optimal treatment, although there are some medications that could be considered. Oxygen is a cue to which many proteins in the cell and physiologic systems respond. These elements and their biologic pathways account for actions of drugs that have evidence for efficacy or empiric use; however, major gaps in understanding remain.

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CHAPTER 93

Diving Injuries and Air Embolism

Christopher Logue

During the winter of 1942–1943, Jacques Cousteau and Emile Gagnan collaborated to develop and patent the first commercially successful open-circuit self-contained underwater breathing apparatus (SCUBA), which was later named the Aqua Lung. The apparatus consisted of a demand valve regulator that could be attached to a portable cylinder containing stored compressed breathing gas. The regulator reduced the relatively high pressure of the stored gas to ambient pressure, which could then be breathed by a diver submersed in water. Prior to the development of reliable SCUBA equipment, divers were limited by surface supplied breathing gas requiring direct and continuous surface support.

The mass production of SCUBA diving equipment revolutionized underwater exploration. While this was a significant development for the military and commercial diving communities, it marks the beginning of the sport diving era. SCUBA diving has since evolved into a popular recreational activity.

Although diving-related injuries were described prior to the development of modern-day SCUBA equipment, their relative importance increased as more divers became equipped to explore the underwater world. The most accurate available statistics of diving-related injuries are published online by the Divers Alert Network (DAN) in an Annual Review of Recreational Scuba Diving Injuries and Fatalities.

A recent detailed and thorough analysis of 947 recreational SCUBA diving fatalities from 1992 to 2003 identified the cause of death (COD) along with triggers, disabling agents, and disabling injuries that contributed to the COD.[1] The leading COD was drowning (70%), but the identifiable disabling injuries that contributed to the COD told a more useful story. The most common disabling injuries included: asphyxia with no preceding disabling injury (33%), arterial gas embolism (AGE) (29%), cardiac events (26%), trauma (5%), decompression sickness (DCS) (3%), unexplained loss of consciousness (2%), and inappropriate gas mixture (2%). In addition, risk factors associated with each disabling injury were identified (Table 93-1).

Of all the possible causes of diving-related injuries, this chapter focuses only on those caused by dissolved or embolic gas. In addition, this chapter includes a discussion of nondiving-related gas embolism. A number of excellent sources for review of diving-related injuries are available.[2–7]

FUNDAMENTAL CONCEPTS

Before presenting individual clinical entities, fundamental concepts related to pressure and the behavior of gases are reviewed.

PRESSURE

Pressure is defined as force per unit area. The air-containing atmosphere of the earth applies pressure to any object within it. At sea level this pressure is defined as one atmosphere (1 ATM). One atmosphere is equivalent to 760 torr (mm Hg), 29.92 in Hg, 14.7 psi, 101.3 kPa, or 1.013 bar. Most of the world's population lives at or near sea level and rarely experiences significant changes in

TABLE 93-1 Disabling Injuries and Associated Risk Factors Contributing to the Cause of Death in Recreational Diving Fatalities

Disabling Injuries	Risk Factors (Odds Ratio)
Asphyxia	• Entrapment (>30) • Running out of gas (15.9) • Buoyancy/equipment problems (4.5)
Arterial gas embolism	• Emergency ascent (>30)
Cardiac events	• Previous cardiovascular disease (10.5) • Older than 40 y (5.9)
Trauma	• Rough water (2.6)
Decompression sickness	• Diving deeper than 180 fsw (>30) • Diving alone (17.2) • Emergency ascent with omitted decompression (16.0)
Unexplained loss of consciousness	• Diabetes (12.0)

ambient pressure. Divers are unique in that they experience significant increases in ambient pressure as they descend through the water column. Every 33 ft of sea water (fsw) through which a diver descends adds an additional 1 ATM of pressure. By the time a diver reaches a depth of 99 fsw, he or she has added an additional 3 ATM to the earth's atmospheric pressure. The diver experiences a pressure of 4 atmospheres absolute (4 ATA) at this depth. The pressure subsequently decreases as the diver ascends back to the surface.

BOYLE'S LAW

Originally described by Sir Robert Boyle in 1662, Boyle's Law describes the relationship between pressure and volume of a fixed amount of an ideal gas given that the temperature of the system remains constant (Video 93-1), stating that pressure and volume are inversely proportional. It is important to note that because the relationship is exponential, larger changes in volume occur with changes in pressure over a range of lower pressure values.

BAROTRAUMA

Barotrauma is physical damage to tissues within the body that occurs as a result of changing ambient pressure. Tissues that contain air spaces are at risk. Barotrauma can be considered a physiological ramification of Boyle's Law.

Middle ear barotrauma (MEB) is the most common diving-related injury. As a diver descends in the water column he or she must be able to equalize the pressure within the air-containing middle ear space to the surrounding increasing ambient pressure. If the pressure cannot be equalized by adding gas to the space during descent, the volume within the middle ear space will contract according to Boyle's Law. Proper eustachian tube function is critically important in the prevention of MEB; divers can utilize different maneuvers to assist in the equalization of middle ear pressures.

Video 93-1 This animation demonstrates the inverse relationship between pressure and volume of an ideal gas given a fixed mass and constant temperature. Note from the graph that the relationship is exponential. Larger changes in volume are noted with pressure changes at the smaller pressure values. Also, note that the density of the gas increases with increased pressure. *Access at www.fishmansonline.com*

The most common manifestation of MEB is ear pain experienced during descent. Other manifestations include changes in the appearance of the tympanic membrane with possible rupture, the evolution of a middle ear effusion (with or without blood), decreased hearing, and mild vertigo. Injuries associated with MEB are usually transient and reversible. Treatment is supportive and may include the use of decongestants, along with avoiding further changes in ambient pressure.

Other less frequent forms of barotrauma include situations where gas becomes trapped in the sinuses, gastrointestinal tract, and within a tooth filling. Pulmonary barotrauma is discussed later in the chapter.

DALTON'S LAW OF PARTIAL PRESSURES

Originally described by John Dalton in 1801, Dalton's Law states that the total pressure exerted by a gas mixture is equal to the sum of the partial pressures of each individual gas component.

$$P_{absolute} = pN_2 + pO_2 + pCO_2 + \ldots$$

The partial pressure of a gas component within the mixture can be determined by multiplying the fraction of the component gas by the absolute pressure. For example:

$$pN_2 = F_iN_2 \times P_{absolute}$$

It is important to note that as absolute pressure increases, so does the partial pressure of each individual gas component within the gas mixture. A SCUBA diver breathing air (78% N_2, 21% O_2) descending to a depth of 99 fsw (4 ATA) is exposed to elevated partial pressures of each of the component gases within the mixture. The partial pressure of nitrogen in the inspired air at this depth is significantly increased (~3.1 ATM).

There are physiological ramifications of exposure to elevated partial pressures of specific gases. Exposure to elevated partial pressures of nitrogen causes nitrogen narcosis and provides a pressure gradient, driving dissolved nitrogen into tissues of the body. Exposure to elevated partial pressures of oxygen causes oxygen toxicity, which can manifest as seizure activity and loss of consciousness without warning. This becomes a significant concern for divers breathing mixtures with increased F_iO_2 or those who dive to extreme depth.

HENRY'S LAW

Originally described by William Henry in 1803, Henry's Law states that the amount of a given gas that dissolves in a liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid given at constant temperature. An alternative explanation is that the solubility of a gas in a liquid is directly proportional to the partial pressure of the gas above the liquid.

An air-breathing diver descending in the water column experiences a pressure gradient which drives dissolved nitrogen into the tissues based on Dalton's Law; in addition, the solubility of nitrogen within the tissues also increases according to Henry's Law. During decompression the amount of nitrogen that can remain dissolved decreases, favoring transition to gas phase and the evolution of gas bubbles.

An understanding of both Dalton's Law and Henry's Law is important because these laws contribute to inert gas (i.e., nitrogen) exchange. The tissues of a diver will load or "on-gas" inert gas during compression and with time at depth. Unloading or "off-gassing" occurs during decompression and with time once the diver has reached the surface again.

Physiological ramifications of Henry's Law include DCS, which is discussed later in the chapter.

DECOMPRESSION ILLNESS

The term decompression illness (DCI) refers to disease processes caused by gas bubbles that result from a reduction in ambient pressure. The term includes both dysbaric AGE and DCS.

PULMONARY BAROTRAUMA

If a diver were to descend while holding his or her breath, the gas within the lungs would be compressed progressively while maintaining a volume that is inversely proportional to the increasing pressure. In order to prevent collapse of the lung to less than residual volume, with tearing of pulmonary parenchyma and blood vessels, the diver is obliged to breathe an oxygen-containing gas mixture at a pressure equal to that of the surrounding water. During return to normal atmospheric pressure, compressed gas within the lungs expands exponentially and must be exhaled if alveolar rupture is to be avoided.

The greatest danger of alveolar bursting occurs during ascent in the shallowest depth range because of the exponential inverse relationship between pressure and volume according to Boyle's Law. Fatal AGE associated with breathing compressed gas has been reported following ascent from a depth of only 4 fsw.[8]

POSSIBLE SEQUELAE OF ALVEOLAR RUPTURE DURING DECOMPRESSION

The sequelae of pulmonary overpressure accidents are determined by the nature and severity of associated tissue trauma as well as by the volume of expanding extra-alveolar gas. Following rupture of alveolar septa, expanding gas enters the interstitial spaces and dissects along perivascular sheaths to enter the mediastinum. Mediastinal gas may further dissect into the pericardial sac, the retroperitoneal space, or the subcutaneous tissues of the neck. Gas also may enter the pleural space to cause a pneumothorax.

Mediastinal emphysema is often associated with mild substernal discomfort that may be described as a dull ache or a feeling of tightness. Deep inspiration, coughing, or swallowing may exacerbate symptoms, and pain may radiate to the shoulders, neck, or back. Unless extensive, mediastinal emphysema is rarely associated with dyspnea, tachypnea, or other signs of respiratory distress. Gas volumes within the pericardial sac or retroperitoneal space are seldom large enough to be clinically significant.

Subcutaneous emphysema from pulmonary barotrauma causes swelling and crepitance in the neck and supraclavicular fossae. These signs may be associated with sore throat, dysphagia, or a change in voice tone. Subcutaneous gas can be demonstrated radiographically (Fig. 93-1). If symptoms of mediastinal or subcutaneous emphysema are bothersome, resolution of gas can be hastened by breathing 100% oxygen at normal atmospheric pressure. Recompression therapy is not recommended as it may exacerbate the underlying lung injury and add compressed gas to the spaces followed by expansion during decompression from treatment.

Surprisingly, pneumothorax is not a frequent complication of diving-related pulmonary barotrauma. In one series of submarine escape ascents, pneumothorax occurred in only 5% to 10% of the divers who had lung overinflation syndromes and suffered cerebral AGE.[9] Recompression of an individual who is known to have a pneumothorax should be avoided if possible. However, it may be necessary if neurological symptoms or other manifestations of AGE are present. Insertion of a thoracostomy tube prior to recompression treatment is recommended.

Conversion from an untreated simple pneumothorax to a tension pneumothorax can occur during recompression therapy in a hyperbaric chamber. This will occur if a tear in the visceral pleura remains open during compression, thereby allowing compressed gas to enter the pleural space. If the air in the pleural space becomes effectively sealed prior to or during decompression, the gas will expand to compress the lung and interfere with venous return. Severe dyspnea, cyanosis, and hypotension may occur. This is an emergency that requires immediate recompression to relieve symptoms and insertion of a chest tube before decompression is resumed. Alternatively, a pneumothorax can be managed by needle decompression and the use of a flutter (one-way) valve.

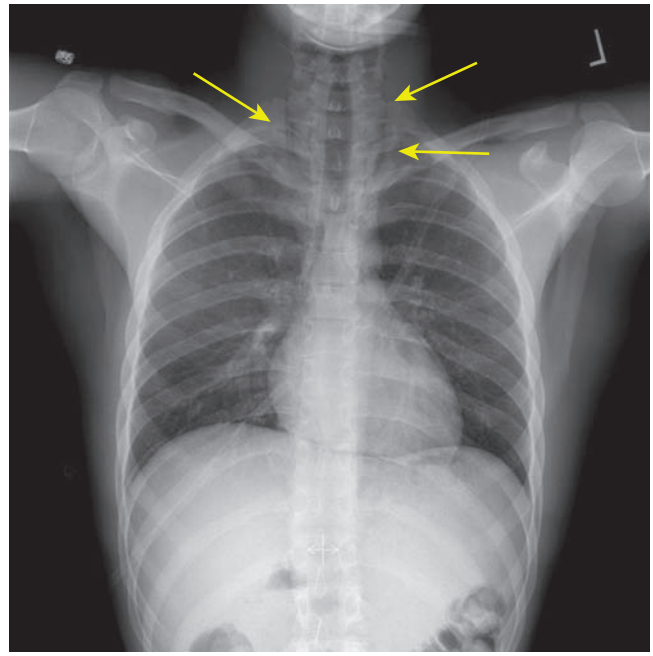

Figure 93-1 Subcutaneous emphysema *(arrows)* secondary to pulmonary barotrauma is demonstrated radiographically. This novice diver, participating in his initial training dives, was attempting to equalize his middle ear pressures using a forced valsalva maneuver during ascent.

DYSBARIC ARTERIAL GAS EMBOLISM

When expanding extra-alveolar gas is forced down a pressure gradient into torn septal vessels, it traverses the pulmonary veins to the left atrium and left ventricle, from which it is ejected into the systemic circulation as foamy particles or discrete bubbles. Distribution of the gas emboli is determined by their buoyancy relative to blood and orientation of the body with respect to gravity. It may also be influenced by local factors such as blood flow and vessel size. With the body in the head-up, erect position, most of the embolic gas travels to the brain.

Although the precipitating event for dysbaric AGE is presumed to be due to pulmonary overinflation injury, demonstrable radiographic evidence of pulmonary barotrauma is not always seen. In one series of divers suffering symptomatic AGE, radiographic evidence of pulmonary barotrauma was demonstrated in only 42% of cases.[10]

Clinical manifestations of dysbaric AGE have been grouped into two categories based on the initial presentation and response to treatment. About 5% of the divers who experience AGE are critically injured and often die even when recompression is initiated within minutes.[11] These individuals develop apnea, unconsciousness, and cardiac arrest during ascent or immediately after surfacing from a dive. The most likely cause of this frequently lethal condition is massive volumes of gas in the central circulation.

The majority of patients with dysbaric AGE present with neurological signs and symptoms, but spontaneous respiration and heart rate are maintained. Just as in the more seriously injured divers, onset of symptoms occurs during ascent or within minutes after surfacing. The clinical spectrum of neurological disturbances ranges from focal signs such as monoparesis or discrete sensory deficits to diffuse brain dysfunction, as manifested by confusion, stupor, or coma. In response to prompt recompression and hyperbaric oxygenation, most patients have complete resolution of all neurological deficits.

For reasons that are not well understood, a subgroup of these patients will fail to respond completely or will experience initial improvement followed by recurrence of the presenting signs and symptoms secondary to delayed cerebral edema.[12] The probability of

incomplete response or recurrence is increased as the time between onset of symptoms and initiation of definitive therapy is prolonged.

The true incidence of cerebral AGE may be higher than that established on the basis of historical and physical findings alone, as electroencephalographic evidence of abnormal neuronal activity has been demonstrated after submarine escape training ascents in the absence of associated clinical manifestations.[13]

IATROGENIC AND ACCIDENTAL ARTERIAL GAS EMBOLISM

Accidental AGE is a serious and sometimes lethal complication of many procedures that are widely used in modern medicine.[14] It is often misdiagnosed or recognized only after a delay of several hours. Most cases of AGE present with focal or diffuse manifestations of brain ischemia. Management is often made more difficult by the existence of concurrent medical or surgical complications. In many patients, hyperbaric oxygen therapy, if administered promptly, completely reverses all neurological deficits. It is generally remarkably efficacious even when initiated after a delay of several hours. For a list of surgical procedures that have been associated with iatrogenic AGE, see Table 93-2.

AGE has also been reported in association with penetrating chest trauma and blast injuries.[15] Other accidental causes of AGE reported in the literature include inhalation of pressurized helium,[16] ingestion of hydrogen peroxide,[17] oral sex during pregnancy,[18] and sexual intercourse after vaginal delivery.[19]

TABLE 93-2 Procedures Associated with Iatrogenic Gas Embolism

Neurosurgical
• Craniotomy in the sitting position
• Procedures involving the posterior fossa
• Spinal surgery (fusion and laminectomy)
Cardiovascular
• Cardiac surgery (including CABG and angioplasty)
• Carotid endarterectomy
• Cardiopulmonary resuscitation
Pulmonary
• Lung biopsy
• Thoracentesis
• Thoracotomy
• Mechanical ventilation after endotracheal intubation
Orthopedic
• Total hip arthroplasty
• Arthroscopy
Gastrointestinal
• Laparoscopy (including laparoscopic cholecystectomy)
• ERCP
• Liver transplantation
• Percutaneous liver puncture
Gynecological
• Therapeutic (or criminal) abortion
• Hysteroscopy
• Cesarean section
Urologic
• Transurethral prostatectomy
Vascular access
• Central venous catheter placement and removal
• Hemodialysis
• CT auto-injector

DECOMPRESSION SICKNESS

DCS occurs when ambient pressure is reduced too rapidly to allow the inert gas dissolved in blood and body tissues to remain in physical solution. It usually occurs in the diver after inadequate decompression from prolonged exposure to increased ambient pressures, but it can also occur in the aviator or astronaut who is exposed to high altitude or space with blood and body tissues that are saturated with inert gas at normal atmospheric pressure. The minimum depth necessary to produce DCS in an air breathing diver with a prolonged exposure time (saturation dive) is between 20 and 25 fsw. Dive tables or dive computers are routinely used to lower risk of DCS. Time limits based upon depth for a single (nonrepetitive) air dive without the requirement of staged decompression according to the US Navy are shown in Table 93-3.

Although the precipitating cause of DCS seems to be the evolution of dissolved inert gas from body fluids, neither the physical mechanisms nor the locations of bubble formation are completely understood. Both intravascular and extravascular bubbles have been found in animals exposed to severe decompression stress. Intravascular bubbles are more likely formed in veins than in arteries, due to the greater hydrostatic pressure in the latter vessels. Primary effects caused by the physical presence of undissolved gas in vivo include the obstruction of blood vessels and the mechanical disruption of tissue. In addition, there are secondary effects, caused by tissue reactions to intravascular or extravascular bubbles, which include the concurrent activations of cellular components, such as leukocytes and platelets, and biochemical pathways, such as the complement, coagulation, and kinin systems.[20] Recent literature has demonstrated that circulating levels of microparticles significantly increase after decompression stress and may play a significant role in the pathophysiological process.[21]

It is also possible during or after decompression from a dive to have circulating venous bubbles, as detected by Doppler ultrasonography, without precipitating the onset of DCS (Audio 93-1).[22] Right to left shunting of venous gas emboli through a patent foramen ovale or other anatomic anomaly may increase risk of DCS.

Musculoskeletal pain in one or more extremities is the most common symptom of DCS especially in military divers, commercial divers, and caisson workers. Sport divers more commonly present with neurological symptoms or signs as the chief complaint. These apparent patterns may reflect both the reluctance of professional divers to report neurological symptoms due to the related occupational penalties and the tendency of many recreational divers to delay seeking medical assistance until neurological symptoms occur.

Neurological and pain-only manifestations of DCS appear to have different latencies. Among divers who present with neurological involvement, about 50% become symptomatic within 10 minutes of surfacing, and over 90% are symptomatic within 3 hours.[23] In about 90% of divers who present with musculoskeletal pain only, symptoms occur within 6 hours after the dive.[24] Onset of symptoms 36 hours or more after the dive has been reported, but delays

Audio 93-1 Doppler ultrasonic recordings of venous gas bubbles detected in divers following decompression. **A.** Demonstrates a low bubble score detected in the subclavian vein. **B.** Demonstrates a high bubble score also detected in the subclavian vein. The divers in these examples did not suffer clinical signs or symptoms of decompression sickness. *Access at www.fishmansonline.com*

TABLE 93-3 US Navy Dive Table 9-7. No-Decompression Limits and Repetitive Group Designators for No-Decompression Air Dives

Depth (fsw)	No-Stop Limit	Repetitive Group Designation															
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Z
10	Unlimited	57	101	158	245	426	*										
15	Unlimited	38	60	88	121	163	217	297	449	*							
20	Unlimited	26	43	61	82	106	133	165	205	258	330	461	*				
25	595	20	33	47	62	78	97	117	140	166	198	236	285	354	469	595	
30	371	17	27	38	50	62	76	91	107	125	145	167	193	223	260	307	371
35	232	14	23	32	42	52	63	74	87	100	115	131	148	168	190	215	232
40	163	12	20	27	36	44	53	63	73	84	95	108	121	135	151	163	
45	125	11	17	24	31	39	46	55	63	72	82	92	102	114	125		
50	92	9	15	21	28	34	41	48	56	63	71	80	89	92			
55	74	8	14	19	25	31	37	43	50	56	63	71	74				
60	60	7	12	17	22	28	33	39	45	51	57	60					
70	48	6	10	14	19	23	28	32	37	42	47	48					
80	39	5	9	12	16	20	24	28	32	36	39						
90	30	4	7	11	14	17	21	24	28	30							
100	25	4	6	9	12	15	18	21	25								
110	20	3	6	8	11	14	16	19	20								
120	15	3	5	7	10	12	15										
130	10	2	4	6	9	10											
140	10	2	4	6	8	10											
150	5	2	3	5													
160	5		3	5													
170	5			4	5												
180	5			4	5												
190	5			3	5												

**The letter group designation to be used for repetitive diving if your dive time is beyond than the times listed in the table for that depth.*
Recommended time limits for each depth without requiring stage decompression are shown. Repetitive group designation is used if repetitive diving is planned.

exceeding 24 hours are extremely rare. Delayed symptom onset sometimes occurs during flight in commercial aircraft that may have cabin altitude exposures in the range of 5000 to 8000 ft too soon after diving. It is generally recommended that flying should be delayed for at least 24 hours after diving.

Clinical manifestations of neurological DCS usually reflect involvement of the spinal cord at the lower thoracic or upper lumbar levels. Paresthesias and sensory deficits may occur with or without associated weakness or paralysis. Transient or persistent abdominal pain may be present. Bladder or bowel dysfunction may occur alone or with associated signs.

DCS may also manifest with cutaneous changes sometimes referred to as skin bends. The most common type is a nonspecific erythematous, macular rash involving the trunk. Urticaria can also occur. As a general rule, these forms of skin bends are considered mild manifestations of decompression stress, resolve with normobaric oxygen, and do not require recompression therapy in the absence of other signs or symptoms. However, cutis marmorata, a rash with a reticulated, marbled appearance is almost pathognomonic for DCS and is frequently associated with the development of neurological DCS (Fig. 93-2).

A less common form of DCS that is characterized by vestibular involvement may present with the sudden onset of vertigo and severe impairment of balance. Associated symptoms often include nausea, vomiting, nystagmus, tinnitus, and sensorineural hearing loss. Vestibular DCS can be unusually difficult to treat, as manifested by a slow or incomplete response to aggressive hyperbaric oxygen therapy.

EVALUATION AND MANAGEMENT OF DECOMPRESSION ILLNESS

Obtaining an adequate history is critically important when evaluating an injured diver, as DCS and AGE are clinical diagnoses.

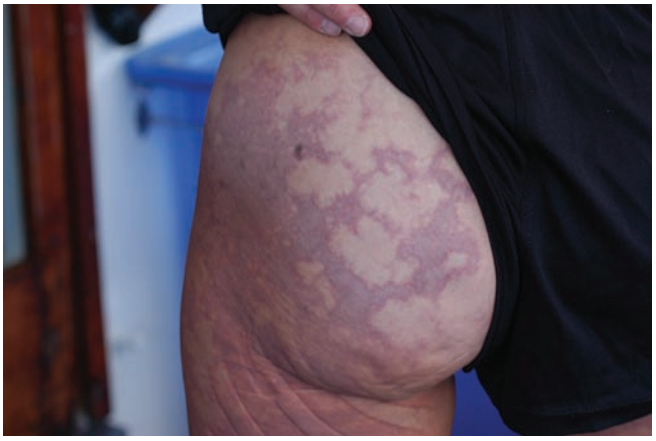

Figure 93-2 Cutis marmorata in a diver suffering from decompression sickness.

Determining the nature, frequency, gas mixtures used, and profiles of the dives leading up to the injury will be helpful. In addition, one must be alert for a history that includes omitted decompression or an uncontrolled, rapid, or emergency ascent. Most modern-day SCUBA divers utilize dive computers, which, when interrogated, will reveal dive profiles and rates of ascent.

The physical examination should be thorough and includes otoscopy to screen for MEB, a skin examination for signs of cutaneous DCS, and a complete neurological examination. Subtle neurological abnormalities are often seen in DCS including an abnormal mini-mental status examination and problems with gait and balance.

Common laboratory abnormalities seen in DCS and AGE include leukocytosis and hemoconcentration. Creatine kinase is frequently elevated in cases of cerebral AGE and correlates well with neurological outcome.[25] A chest radiograph or noncontrast CT scan of the chest should be performed to screen for pulmonary barotrauma especially prior to recompression therapy.

Other than standard ACLS protocols, the mainstay of treatment for both AGE and DCS is supplemental oxygen. The goal should be F_iO_2 as close to 100% as possible. This will improve oxygenation to tissues and provide a gradient diving inert gas out of bubbles and tissues. Unless contraindicated, oral or isotonic intravenous fluids should be administered to replace lost intravascular volume.

Nonsteroidal anti-inflammatory medications may be useful in the management of DCS. A recent randomized trial examining the adjunctive administration of tenoxicam to divers suffering DCS demonstrated a statistically significant reduction in the number of hyperbaric oxygen treatments required to alleviate symptoms.[26]

Lidocaine is a class 1b antiarrhythmic agent and local anesthetic that has been shown to have cerebroprotective effects. Animal models have demonstrated efficacy in both the prevention and treatment of experimental AGE. The successful use of lidocaine along with hyperbaric oxygen therapy as treatment for nondiving-related cerebral arterial gas embolism (CAGE) has been reported.[16] Although more research is needed, current evidence supports the use of lidocaine as an adjunct to recompression therapy for the treatment of CAGE. An appropriate bolus and infusion should be initiated with infusion rates eventually adjusted based on serum concentrations.

HYPERBARIC OXYGEN THERAPY FOR DECOMPRESSION ILLNESS

Hyperbaric oxygen therapy (HBOT) involves the inhalation of 100% oxygen at a pressure greater than 1 ATA. The typical treatment pressure range is 2.0 to 3.0 ATA. Higher treatment pressures are sometimes used when treating severely injured divers or critically ill patients with CAGE. At pressures higher than 3.0 ATA, mixed treatment gases must be utilized including nitrogen–oxygen or helium–oxygen mixtures allowing for adequate hyperoxia while mitigating the risk of oxygen toxicity. HBOT allows for dramatic increases in both arterial (~2000 mm Hg) and tissue (~200–400 mm Hg) oxygen tensions.

Hyperbaric chambers are generally classified as either multiplace or monoplace chambers. Multiplace chambers are compressed with air and capable of treating multiple patients at the same time along with one or more medical attendants who accompany the patient(s) (Fig. 93-3). The patient breathes oxygen through a tightly sealed mask, hood, or endotracheal tube. Monoplace chambers can be compressed with air or oxygen and the patient treated in isolation. Monoplace chambers typically have pressure limitations of 3.0 ATA.

AGE and DCS have different etiologies and clinical presentations; however, similar therapeutic principles are applied in both conditions. Primary aims of therapy in both cases are reduction in bubble volume, acceleration of bubble resolution, and maintenance of tissue oxygenation. Resolution of bubbles in DCS and AGE is

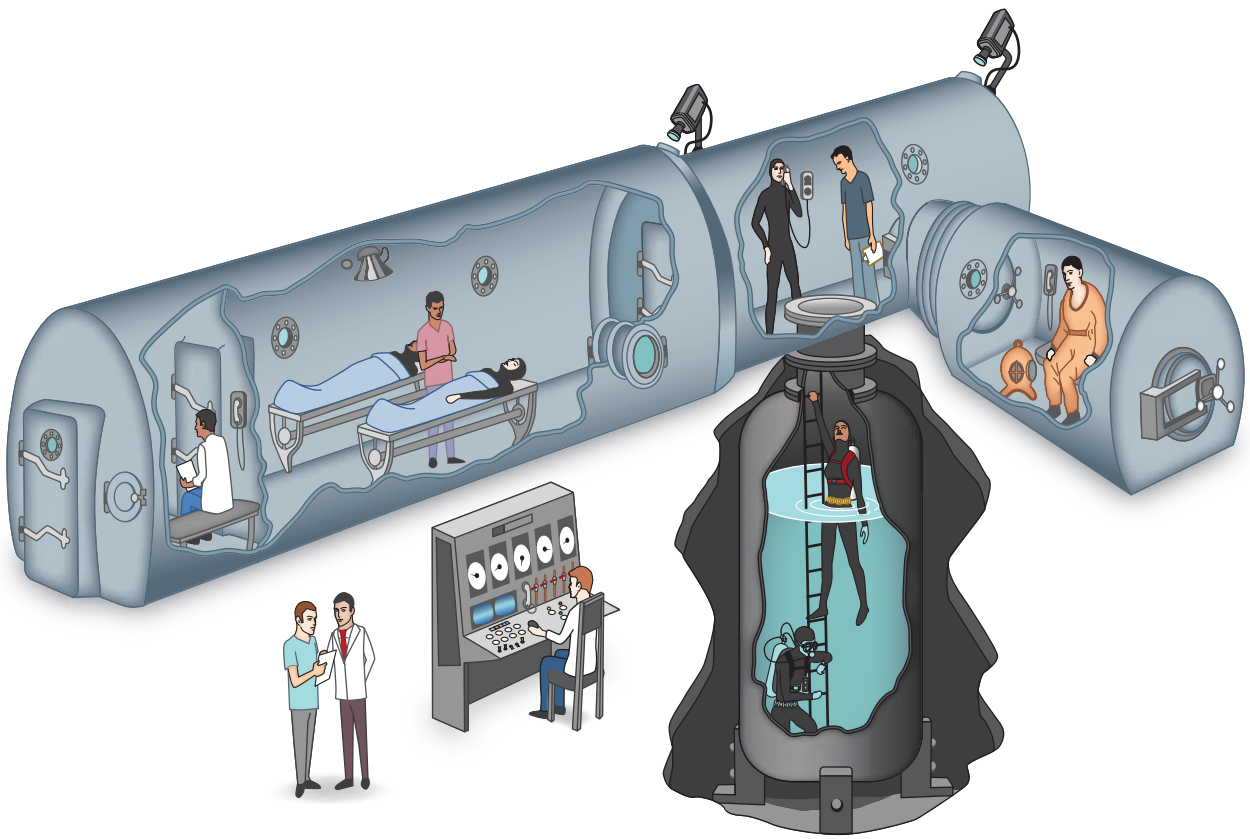

Figure 93-3 A diagram of the multiplace hyperbaric chamber complex at the University of Pennsylvania.

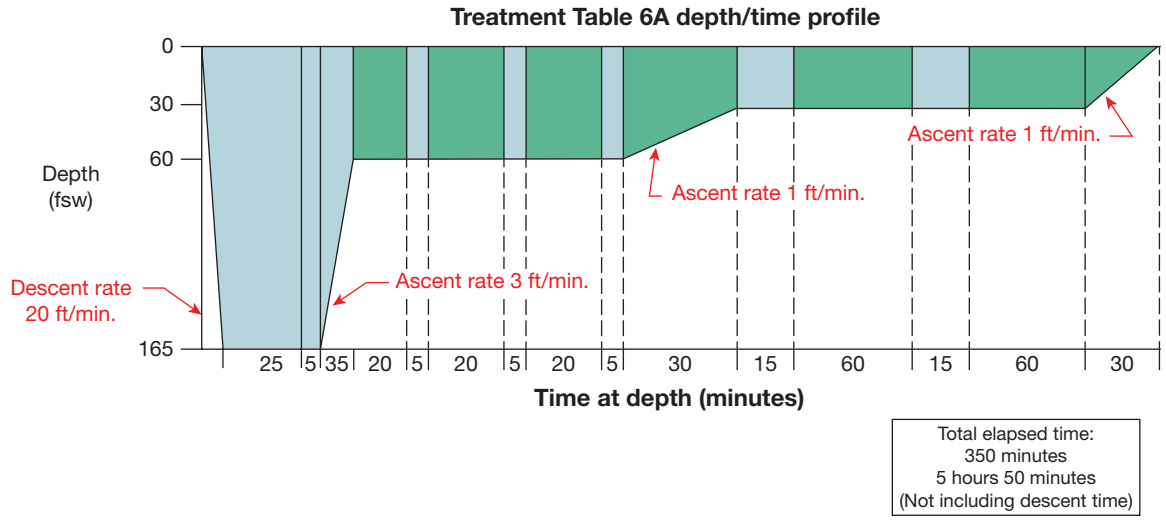

Figure 93-4 US Navy Treatment Table 6A historically used for the treatment of cerebral AGE. Initial compression is to 165 fsw (6.0 ATA). A 50% oxygen mixture is typically administered at this depth. One-hundred percent of oxygen with intermittent air breaks is administered upon arrival at 60 fsw.

greatly hastened by breathing oxygen at increased pressure because the associated elimination of nitrogen from all body tissues and concurrent bubble compression combine to maximize the outward diffusion gradient for bubble nitrogen. The pressure–oxygenation profile historically used to accomplish these aims in CAGE is shown in Figure 93-4.

The rationale for initial compression to 165 fsw (6.0 ATA) is that reduction in bubble sizes to one-sixth of their original volume allows at least some bubbles to traverse capillaries, enter the venous circulation, and be trapped in the lung. Since the patient cannot safely breathe 100% oxygen at 165 fsw, administration of 50% oxygen throughout this phase provides hyperoxygenation at a level slightly greater than that afforded by breathing 100% oxygen at 60 fsw (2.8 ATA). Oxygen is administered with intermittent air breaks throughout the remainder of the therapy to accelerate bubble resolution and maintain tissue oxygenation, while avoiding harmful effects of oxygen toxicity by allowing partial recovery during the air intervals. The profile may be extended in severe cases by adding oxygen intervals at 60 fsw (2.8 ATA) and 30 fsw (1.9 ATA).

The theoretical benefits of compression to pressures beyond 3.0 ATA for the treatment of cerebral AGE have been questioned.[27] In addition, therapeutic mechanisms of HBOT extend beyond the reduction of bubble volume and elimination of inert gas from bubbles and tissues. These beneficial effects are specific to hyperoxia and include the controlled production of reactive oxygen and nitrogen species. In modern times, the most common treatment profile used for treatment of both cerebral AGE and DCS is shown in Figure 93-5. The treatment does not involve compression beyond 2.8 ATA and does not require the use of a multiplace chamber or mixed gas capabilities. This profile may also be extended by adding additional oxygen breathing periods at both 60 and 30 fsw in cases where symptoms are severe or response to treatment is not complete.

LIMITATIONS IMPOSED BY OXYGEN TOXICITY

During oxygen breathing at increased ambient pressures, the rate of intoxication increases progressively in proportion to inspired pO_2 elevation. Duration of oxygen exposure at 1.0 to 2.0 ATA is limited primarily by pulmonary effects of oxygen toxicity. At oxygen pressures of 3.0 ATA or higher, visual impairment and convulsions usually occur before the development of prominent pulmonary toxicity.

Although the toxic effects of oxygen are numerous and varied, they can be avoided by appropriate administration of HBOT. Early stages

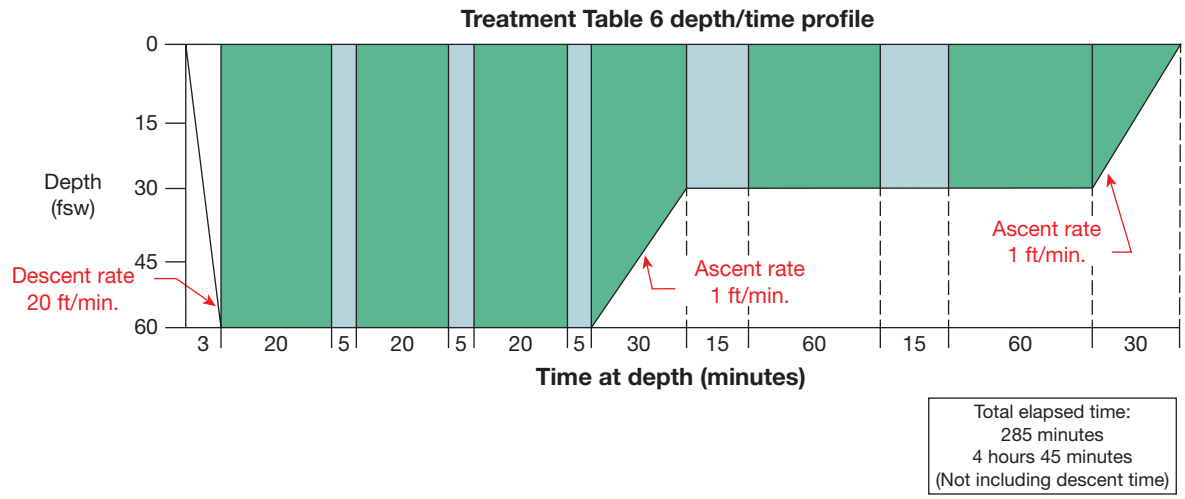

Figure 93-5 US Navy Treatment Table 6 is used for the treatment of DCS and is generally preferred for the treatment of AGE in modern times. The treatment gas is 100% oxygen and air breaks are intermittently provided.

of intoxication, even when associated with symptoms and detectable functional alterations, are fully reversible upon termination of exposure. The onset of toxic effects is delayed effectively by periodic interruption of oxygen exposure with scheduled air breathing periods during HBOT. Supplemental oxygen, unless necessary, should be avoided between hyperbaric oxygen treatments, as it can lead to accelerated pulmonary oxygen toxicity and excessive oxidative stress.

CONCLUSION

Diving injuries, including DCS and dysbaric gas embolism, are pathophysiological processes that occur as a result of changes in ambient pressure. A basic understanding of a few fundamental concepts of applied physics will aid the medical professional during the evaluation and treatment of the injured diver. Iatrogenic gas embolism may occur in association with certain modern-day medical procedures, and early diagnosis and treatment can greatly minimize associated morbidity and mortality.

Administration of supplemental oxygen with referral for HBOT is recommended as the primary treatment option for patients suffering from DCS and AGE. The mechanisms of action of HBOT are complex. Oxygen toxicity can be avoided if the treatment is carefully applied.

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CHAPTER 94

Thermal Lung Injury and Acute Smoke Inhalation

Perenlei Enkhbaatar

INTRODUCTION AND EPIDEMIOLOGY

Smoke inhalation is a serious medical problem and continues to have a significant impact on the morbidity and mortality of patients with flame burns. According to the American Burn Association Repository (2012), inhalation injury is present in 17% of patients with flame burns and increases the overall mortality rate of these patients up to 24%, while the mortality of burn patients without inhalation injury is 3%.[1] The presence of smoke inhalation injury prolongs the length of hospital stay 2.5-fold compared to those without smoke inhalation injury (24 days vs. 10 days).[1]

Similar percentages of fire victims who have sustained smoke inhalation appear in several other countries.[2–5] In patients with combined injury, the lung is the critical organ and the progressive respiratory failure associated with pulmonary edema is a pivotal determinant of mortality.[6–8] Although not as lethal, smoke inhalation alone is a serious problem. It is estimated by the World Health Organization that there are over one billion people who develop airway and pulmonary inflammation as a result of inhaling smoke from indoor cooking fires, forest fires, and burning of crops.[9,10]

The inhalation of smoke has been of interest for a number of years, especially as a result of the use of gas warfare. In the 1940s there were two very large fires that focused interest on the inhalation of smoke in fire victims. The first was a fire at a nightclub in Boston called the Cocoanut Grove, where a large number of people were trapped in a burning building and consequently sustained severe inhalation injury.[11,12] It is interesting that in recent times a similar fire occurred in a nightclub near Boston in Rhode Island. The second occurred in Texas City across the bay from Galveston, Texas.[13] Here a ship exploded in a harbor and set off a chain of explosions and fires among some 50 refineries and chemical plants, resulting in over 2,000 hospital admissions of patients with smoke inhalation alone, those with burn injuries, many of whom who had simultaneously inhaled smoke as well. At any rate these two disasters led to the establishments of centers for the care of burn victims and to research into the pathophysiology of burn injury. In many ways the burn victims of the 9/11 disaster were similar to these individuals since the burns and inhalation involved combustion of petroleum products.[14,15] Approximately half (49%) of 790 victims who survived the World Trade Center attack had an inhalation injury.[15,16]

TOXIC SMOKE COMPOUNDS

The fire environment contains a number of toxic compounds, each of which is discussed in this section.

Inhalation injury is caused by steam or toxic inhalants such as fumes, gases, and mists. Fumes consist of small particles dispersed in air with various irritants or cytotoxic chemicals adherent to the particles. Mists consist of aerosolized irritant or cytotoxic liquids. Smoke consists of a combination of fumes, gases, mists, and hot air. Heat, toxic gases, and low oxygen levels are most common causes of death in a fire scene. A large variety of toxic gases and chemicals can be generated depending on the fire environment (Table 94-1).

TABLE 94-1 Origin of Selected Toxic Compounds[17]

Gases and Chemicals	Material	Source
Carbon monoxide	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
	Cellulose	Clothing, fabric
		Wood, paper, cotton
Cyanide	Wool, silk	Clothing, fabric, blankets, furniture
	Polyurethane	Insulation, upholstery material
	Polyacrylonitrile	Appliances, engineering, plastics
	Polyamide	Carpeting, clothing
	Melamine resins	Household and kitchen goods
Hydrogen chloride	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
	Polyester	Clothing, fabric
Phosgene	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
Ammonia	Wool, silk	Clothing, fabric, blankets, furniture
	Polyurethane	Insulation, upholstery material
	Polyamide	Carpeting, clothing
	Melamine resins	Household and kitchen goods
Sulfur dioxide	Rubber	Tires
Hydrogen sulfide	Wool, silk	Clothing, fabric, blankets, furniture
Acrolein	Cellulose	Wood, paper, cotton, jute
	Polypropylene	Upholstery, carpeting
	Acrylics	Aircraft windows, textiles, wall coverings
Formaldehyde	Melamine resins	Household and kitchen goods
Isocyanates	Polyurethane	Insulation, upholstery material
Acrylonitriles	Polyurethane	Insulation, upholstery material

Source: Modified with permission from Prien T, Traber DL. Toxic smoke compounds and inhalation injury–a review. Burns Incl Therm Inj. 1988;14(6):451–460.

Many of these compounds may act together to increase mortality, especially carbon monoxide and hydrogen cyanide[17,18] in which a synergism has been found to increase tissue hypoxia and acidosis[18] and perhaps also decrease cerebral oxygen consumption and metabolism.[19,20] Hydrogen sulfide would also be predicted to synergize with carbon monoxide since both cyanide and hydrogen sulfide are inhibitors of mitochondrial cytochrome oxidase. Victims may be incapacitated by the blinding and irritating effects of smoke, as well as the decreasing oxygen concentration that occurs with combustion and results in progressive hypoxia.

Inhalation injury can be classified as (1) upper airway injury, (2) lower airways and pulmonary parenchymal injury, and (3) systemic toxicity. The extent of inhalation damage depends on fire environment: the ignition source, temperature, concentration, and solubility of the toxic gases generated. For instance, thermal and chemical compounds usually cause upper airway injury. The water-soluble materials such as acrolein and the other aldehydes damage the proximal airways and set off reactions that are inflammatory to the bronchi and parenchyma, whereas agents with lower water solubility such as chlorine, phosgene, nitrogen oxide, and nitrogen dioxide or N_2O_3 or even N_2O_4 are more likely to cause insidious injury.[21] Toxic gases such as carbon monoxide and cyanide rarely damage the airway but affect gas exchange, producing more systemic effects. Thus, it is important to obtain information relative to the source of the fire and the combustion products generated when treating a fire victim (see Table 94-1). It is also important to know the duration of exposure and the extent to which the fire victim was in an enclosed area because this relates to the dose of toxic materials presented.

CARBON MONOXIDE

Carbon monoxide (CO) is an odorless, colorless gas that is produced by incomplete combustion of many fuels, especially cellulolytic (cellulose products) such as wood, paper, and cotton.[22] Carbon monoxide toxicity remains one of the most frequent immediate causes of death following smoke-induced inhalation injury. There are 50,000 estimated annual visits to emergency department in the United States as a result of CO poisoning.[23] The predominant toxic effect of CO is its binding to hemoglobin to form carboxyhemoglobin (COHb). The affinity of CO for hemoglobin is ~200 to 250 times higher than that of oxygen.[24] Inhalation of a 0.1% CO mixture may result in generation of a COHb level as high as 50%. The correlation of inhaled CO and COHb levels is summarized in Table 94-2.

The competitive binding of CO to hemoglobin reduces delivery of oxygen to tissues leading to severe hypoxia, especially of most vulnerable organs such as brain and heart. The oxygen–hemoglobin dissociation curve loses its sigmoid shape and is shifted to the left, thus further impairing tissue oxygen availability.[17] In addition, ability of CO to bind to intracellular cytochromes and to other metalloproteins contributes to CO toxicity. This competitive inhibition with cytochrome oxidase enzyme systems (most notably cytochromes a and P-450) results in an inability of cellular systems to use oxygen.[27] Shimazu et al. have shown that extravascular binding of CO to cytochromes and other structures accounts for 10% to 15% of total-body CO stores, which explains the two-compartment elimination of CO from the circulation.[28] CO also inhibits cytochrome c oxidase activity in lymphocytes. The electron chain dysfunction by CO may cause electron leakage, leading to superoxide production and mitochondrial oxidative stress. Additionally, the excessive nitric oxide and its byproduct peroxynitrite, lipid peroxidation, apoptosis, and delayed inflammation[29–32] contribute to the CO toxicity at both systemic and cellular levels.

Symptoms and Diagnosis

The symptoms predominantly manifest in organs and systems with high oxygen utilization. The severity of clinical manifestations is varied depending on the concentration of CO. For instance, the central nervous system symptoms such as headache, confusion, and collapse may occur when the blood COHb level is from 40% to 50%. Symptoms such as unconsciousness, intermittent convulsions, and respiratory failure may occur if COHb level exceeds 60%, and eventually leading to death if exposure continues. The cardiovascular manifestations result in tachycardia, increase in cardiac output, dysrhythmias, myocardial ischemia, and hypotension depending on the severity of poisoning. The correlations of clinical manifestations and severity of CO poisoning are summarized in Table 94-3.

Blumenthal[35] correlated the clinical signs and symptoms of CO poisoning to the concentration of the inhaled CO: headache and dizziness—up to 100 ppm, 0.01% air concentration, loss of judgment, confusion, and disorientation—up to 200 ppm, 0.02%, and nausea, vomiting, fatigue, confusion, disorientation, visual disturbance, syncope, up to the onset of coma—800 ppm, 0.08% to 12,800 ppm, 1.28%.

Diagnosis should be based on direct measurement of COHb levels in arterial or venous blood by co-oximetry. Portable breath analyzers may be used at the scene. Inability to differentiate oxyhemoglobin from COHb limits the use of pulse oximeters. Although there are some controversies on its reliability, the fingertip pulse co-oximetry, a new technology available since 2005, can be used at the scene of the fire for measurement of COHb.[36] The use of blood gas analyzers that estimate SO_2 based on measurement of dissolved

TABLE 94-2 COHb Levels at Various Concentrations of Inhaled CO[25,26]

CO in Atmosphere		Estimated Carboxyhemoglobin in Blood (%)
%	ppm	
0.001	10	2
0.007	70	10
0.012	120	20
0.022	220	30
0.035–0.052	350–520	40–50
0.08–0.122	800–1220	60–70
0.195	1950	80

TABLE 94-3 Symptoms and Signs at Various Concentrations of COHb[33,34]

COHb%	Symptoms
0–10	None
10–20	Tightness over forehead, slight headache dilation of cutaneous blood vessels
20–30	Headache and throbbing in the temples
30–40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting
40–50	As above; greater possibility of syncope, increased pulse and respiratory rate
50–60	Syncope, increased pulse and respiratory rate, coma, intermittent convulsions, Cheyne–Stokes respirations
60–70	Coma, intermittent convulsions, depressed cardiac and respiratory function, possible death
70–80	Weak pulse, slow respirations, death within hours
80–90	Death in less than 1 h
90–100	Death within minutes

Source: Reproduced with permission from Einhorn IN. Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect. 1975;11:163–189.

PO_2 should be avoided. The measurements of acid–base balance, plasma lactate levels, and bicarbonate are helpful in management of CO poisoning with accompanying lactic or metabolic acidosis. It is important to note that high oxygen concentrations are usually administered to the victim in transit to the hospital, and some delay from cessation of exposure to measurement of CO may limit evaluation of the true extent of exposure.[37] A nomogram has been developed that can relate the COHb levels of a patient to the values that may have been present at the time of smoke inhalation; this can be used to estimate the true degree of inhalation injury.[38]

Treatment

The half-life of COHb is 320 minutes (adult male) in room air and ~74 minutes in a person breathing normobaric 100% oxygen at 1 atmosphere.[39,40] Those values are 30% less in females.[41] Therefore, all fire victims should be isolated from fire site and given 100% oxygen on route to the hospital. This allows delivery of an inspired oxygen concentration of 50% to 60%, which is usually adequate. To adequately treat a CO poisoning it is also important to establish COHb level as early as it is possible. In patients with loss of consciousness, cyanosis, or an inability to maintain the airway, 100% oxygen should be delivered via mechanical ventilation through endotracheal tube until COHb levels drop below 10% to 15%. The alternative method to rapidly decrease COHb is hyperbaric oxygen therapy (HBOT) (see Chapter 93). The HBOT allows CO to dissociate from cytochromes a and a3, and to increase PO_2 despite impaired hemoglobin function.[42,43] Chou et al. reported that children with CO poisoning alone who are treated with HBOT are at low risk for dying regardless of initial COHb level.[44] However, there is some debate on use of HBOT especially in patients with burn injury. Because of difficulty of physiological monitoring and providing emergency procedures in small chambers, unstable hemodynamic conditions and other complications such as seizures, or aspiration of severely burned patients limit the use of HBOT.[45]

■ HYDROGEN CYANIDE

Hydrogen cyanide is a colorless gas with the odor of bitter almonds. However, it is difficult to detect it at the site of the fire. Cyanide is a likely weapon for terrorists because of its notoriety, lethality, and availability. Hydrogen cyanide is produced in fires involving nitrogen-containing polymers (upholstery, furniture, nylon, wool, silk, and acrylics) and may produce rapid and lethal incapacitation of a victim at the fire source.[46] Toxicity of cyanide is produced by inhibition of cellular oxygenation with resultant tissue anoxia, which is caused by reversible inhibition of cytochrome c oxidase.[37] It is toxic to a number of enzyme systems. The mechanism includes combination with essential metal ions, formation of cyanohydrins with carbonyl compounds, and the sequestration of sulfur as thiocyanate. However, the main target enzyme is cytochrome c oxidase, the terminal oxidase of the respiratory chain, and involves interaction with the ferric ion of cytochrome a_3.[47]

Symptoms and Diagnosis

Diagnosis at the fire scene may be difficult. Poisoning leads to central nervous system, respiratory, and cardiovascular dysfunction resulting from inhibition of oxidative phosphorylation. It may result in dyspnea, tachypnea, vomiting, bradycardia, hypotension, coma, and seizures. Electrocardiographic S-T segment elevation, which mimics an acute myocardial infarction, may be suggestive.[48] Laboratory findings of anion gap metabolic acidosis and lacticacidemia aid in confirming the diagnosis.[47] The lactic acidosis that is not rapidly responsive to oxygen therapy may be a good indicator of cyanide poisoning.[38,49] Also, an elevated mixed venous saturation is suggestive of cyanide toxicity. Cyanide increases ventilation through the carotid body with peripheral chemoreceptor stimulation. Increasing ventilation may augment toxicity in the early stages. Correlations of blood cyanide concentrations with clinical symptoms are summarized in Table 94-4.

TABLE 94-4 Hydrogen Cyanide Concentrations in Air and Associated Symptoms in Humans[33,50]

HCN Concentration (ppm)	Symptoms
0.2–5.0	Threshold of odor
10 (maximum allowed concentration)	Mild irritation of mucus membranes
18–36	Slight symptoms (headache) after several hours, irritation of throat
45-54	Tolerated for 1/2–1 h without difficulty of breathing
100	Death in 1 h
110–135	Fatal in 1/2–1 h
181	Fatal in 10 min
280	Immediately fatal

Source: Data from Einhorn IN. Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect. 1975;11:163–189. Kimmerle G: Aspects and methodology for the evaluation of toxicological parameters during fire exposure, in Polymer Conference Series: Flammability Characteristics of Materials. Salt Lake City, University of Utah, 1973.

Hydrogen cyanide is found routinely in low levels in the blood of healthy individuals at levels of 0.02 μg/mL in nonsmokers and 0.04 μg/mL in smokers. Toxicity at a level of 0.1 μg/mL and at 1.0 μg/mL death is likely.[51]

Treatment

Fire victims suspected to have cyanide poisoning should be removed from exposure and fully decontaminated. All victims should be given pure oxygen (100%) and resuscitated properly if cardiopulmonary failure is present. Oxygen therapy appears to have strong positive effect; however, HBOT is not recommended for the reasons previously mentioned.[47,51] Cyanide is metabolized by hepatic rhodanese, which catalyzes the donation of sulfur from the sulfane pool to cyanide to form nontoxic thiocyanate. The half-life time of cyanide is approximately 1 to 3 hours in humans.[49,52] Although there is still controversy surrounding the treatment of cyanide poisoning, there are few antidotes available that can be used by first responders. Kelocyanor (dicobalt edetate) may be useful, but is dangerous, and requires experts to administer it.[53] The following agents may be considered in an intensive care setting.

■ METHEMOGLOBIN GENERATORS

The therapeutic goal is to convert the ferrous ion of hemoglobin to ferric ion. The resultant methemoglobin chelates cyanide to form cyanmethemoglobin (cyanide has a greater affinity for binding with methemoglobin and thus, is displaced from cytochrome oxidase). The drugs of choice in this group are sodium nitrite (intravenously) and amyl nitrite (inhaled). These drugs reduce oxygen-carrying capacity; therefore, they should be used with caution especially in patients with concomitant CO poisoning, which induces COHb that may further compromise oxygen transport. These drugs should be also used with precautions in patients with burn shock, because they are also vasodilators and can cause hypotension. In addition, there is little evidence to suggest these measures are effective, and cardiac toxicity in people with heart disease may be problematic.[54] Thus, the methemoglobin generators should be used with extra precautions, carefully weighing patient conditions and comorbidities.

■ SULFUR DONORS

The therapeutic goal is to convert cyanide to thiocyanate. The drug of choice in this group is sodium thiosulfate (intravenously). Toxicity is minimal other than an osmotic diuretic action, which

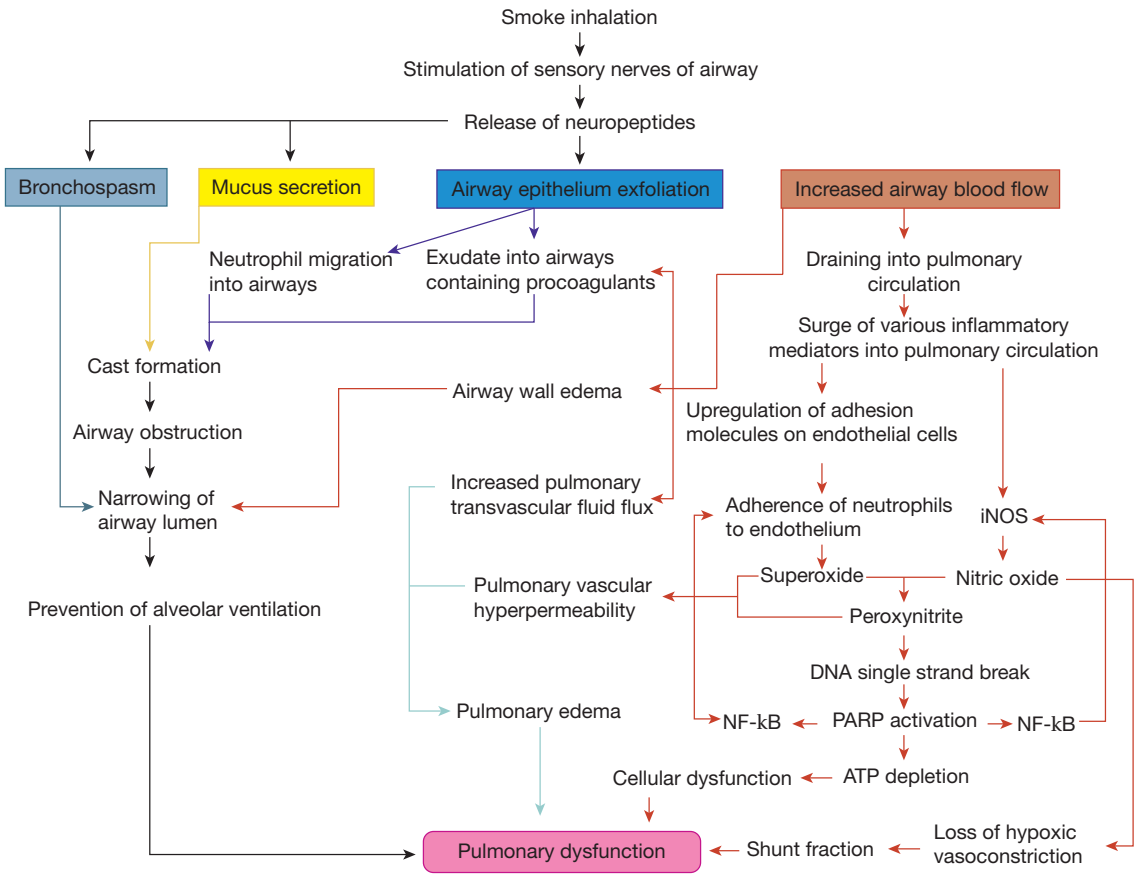


Figure 94-1 The mechanisms of lung parenchyma damage and role of airway changes following smoke inhalation injury. iNOS, inducible nitric oxide; NF-κB, nuclear factor kappa B; PARP, poly(ADP-ribose) polymerase; ATP, adenosine triphosphate.

may be beneficial. However, the onset of action is quite slow. Therefore, it should be used as a second-line therapy.[17,55]

■ DIRECT BINDING AGENTS

These are based on cobalt chemistry and chelate the cyanide ion directly. Hydroxocobalamin is the precursor of vitamin B_{12} and has very little toxicity.[17,51] Minor adverse effects include transient chromaturia, alterations in renal function, reddish skin discoloration, hypertension, and rarely allergic reactions.[56,57] It detoxifies cyanide by binding with it and forming cyanocobalamin, which is then excreted in the urine. The drug is currently approved for use in the United States by the Food and Drug Administration (FDA). However, there is a controversy around its efficacy.

PATHOPHYSIOLOGY

The pathophysiologic consequences of smoke inhalation on the tracheobronchial tree and lung parenchyma are discussed below.

■ TRACHEOBRONCHIAL TREE

In normal conditions, the airway provides a protective barrier against toxic agents and bacteria, maintaining a sterile lung environment. It also facilitates airflow within the lung to ensure efficient gas exchange. Following smoke inhalation, the normal function of the airway is compromised. With rare exceptions such as inhalation of steam, injury to the airway is usually from the chemicals in smoke. The heat capacity of air is low and the bronchial circulation is very efficient in warming or cooling the airway gases so that most gases are at body temperature as they pass the glottis.[58] Flames must be in almost direct contact with the airway to induce thermal injury.[59] The chemicals in smoke are dependent on the materials that are being burned; however, for the most part the host response is similar. In most instances biological materials such as cotton fabric, wood, grass, or products of these such as cattle feces (commonly used as fuel in third world countries) are the fuel for the fire. These contain caustic materials such as reactive oxygen (ROS) and nitrogen species (RNS) as well as organic acids and aldehydes.[60] These chemicals interact with the airway to induce an initial response to trigger an inflammatory response.

Although the degree of airway dysfunction may vary depending on the severity of inhalation injury, it can generally be characterized by few major pathologic alterations that lead to the narrowing/occlusion of the airway lumen reducing or preventing the normal alveolar gas exchange. The factors leading to the airway lumen narrowing are (1) airway hyperemia; (2) formation of an airway obstructive cast; (3) increased mucus secretion; and (4) bronchospasm (see Fig. 94-1). Airway inflammation plays a major role in the overall response to inhalation injury.

Hyperemia of the airway is such a consistent bronchoscopic finding in smoke inhalation that it is used to diagnose the injury.[61,62] Other variables that are used include injury in an enclosed space, singed nasal hair, and soot in sputum. However, these latter injuries may be present but the subject may still not develop the signs of pulmonary edema characteristic of inhalation injury.

The normal bronchial blood circulation is about 1% of cardiac output. Following the smoke inhalation, the airway blood flow rapidly increases resulting in airway wall edema and protein rich plasma leak into the airways. The data presented in Figure 94-2 confirm the dramatic (10–15 fold) increase in tracheal (A) and bronchial (B) blood flow following smoke inhalation that leads to the airway wall edema as confirmed by the macroscopic picture, which clearly illustrates the severe edema formation in the tracheal soft tissue compared to the trachea of an uninjured sheep (C). Many of the studies concerning bronchial circulation following smoke inhalation injury have been performed in sheep, because these animals have a

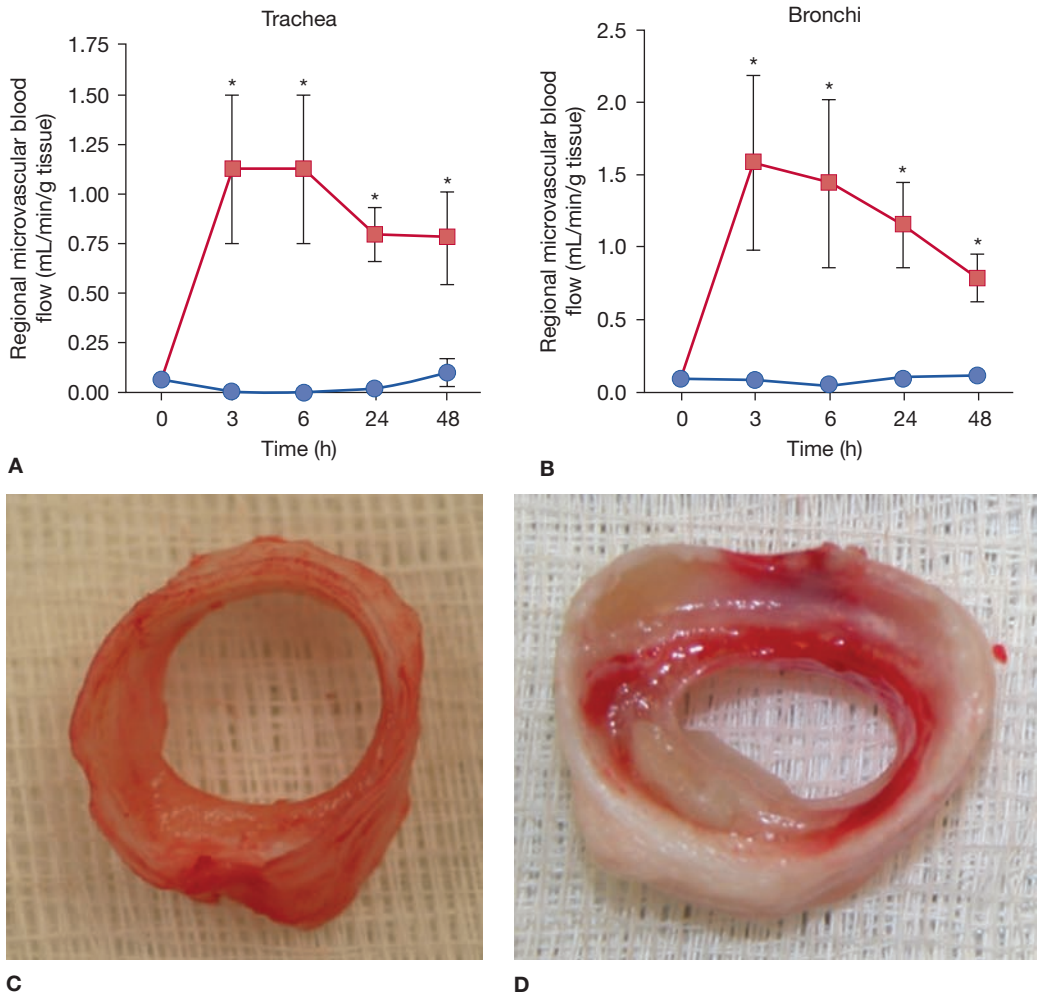
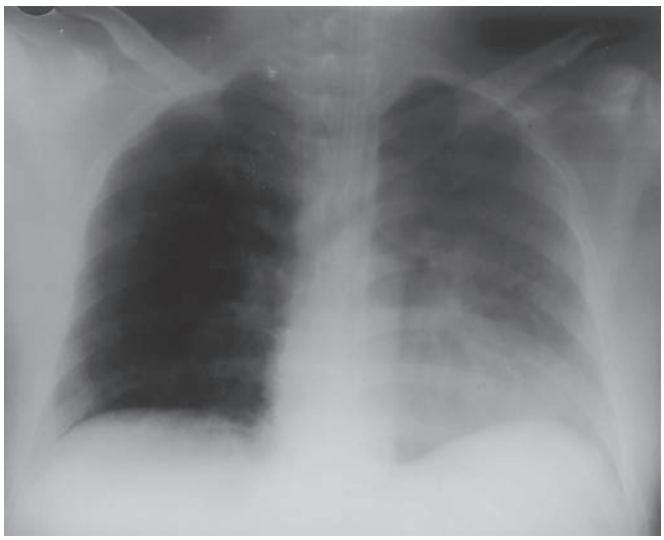


Figure 94-2 Time changes in trachea (**A**) and bronchial (**B**) blood flow in sheep following cotton smoke inhalation (48 breaths) injury. Blood flow was determined by microsphere injection technique. Data are expressed as ±SEM. *$p < 0.05$ versus sham. *Closed circles* represent sheep without injury (sham smoke), and *closed squares* represent sheep with smoke inhalation. **C, D.** Macroscopic pictures of trachea taken 48 hours after sham smoke (**C**) and smoke inhalation (**D**) in sheep.

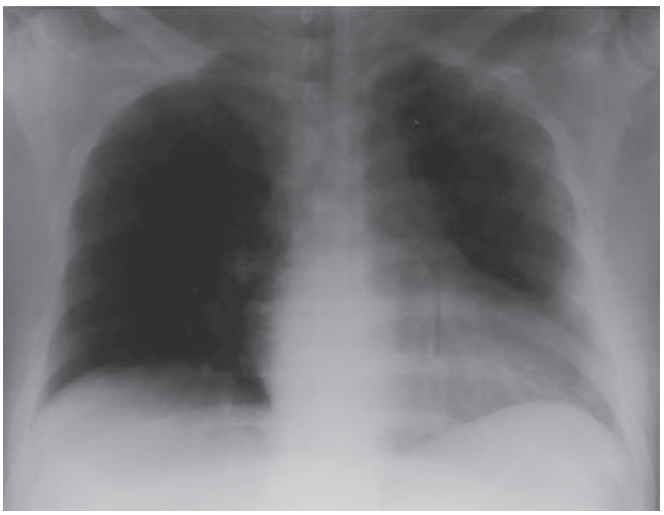
single bronchial artery[63] and a single lymphatic draining the lung that allows the measure of pulmonary transvascular fluid flux.[64] Abdi et al. reported a 10-fold increase in bronchial blood flow within 20 minutes of smoke inhalation in sheep.[65] These same animals demonstrate a sixfold increase in pulmonary transvascular fluid flux and a fall in $Pa_{O_2}/FI_{O_2} \leq 300$ but these were delayed to 24 hours. Similar findings have been reported in patients with smoke inhalation alone or the combination of a large cutaneous thermal injury and smoke inhalation.[66] A few investigators have also demonstrated ~10- to 20-fold increases of airway blood flow depending on the anatomical localization of the airways using the same model.[67–69] These changes in blood flow are associated with increased bronchial microvascular permeability to protein and small particles[70] and increased pressure.[71] The ablation of the bronchial blood flow either by a ligation of the bronchial artery or the nebulization of adrenergic agonist epinephrine significantly improved the pulmonary gas exchange in the sheep smoke inhalation and burn injury model.[67,69,72,73] Simultaneous with the changes in the function of the bronchial microvasculature, there is a loss or shedding of the bronchial columnar epithelium.[74,75] As noted, these changes result in a perfuse transudate with a protein content similar to an ultrafiltrate of the plasma.[76]

The augmented airway circulation not only leads to the airway wall edema, but also contributes to the formation of airway obstructive casts. In conditions where the basement membrane is impaired due to smoke inhalation, the increased airway blood flow leads to the massive airway transudation. This transudate, containing procoagulants combines with copious secretions from the goblet cells and leukocytes[77] to form a solid airway obstructive cast. Airway obstructive casts not only reduce/prevent normal air passage, but also become a perfect culture media for bacterial growth. In Figure 94-3, massive airway obstructive casts from human following smoke inhalation injury are shown. The airway obstructive casts, positive for submucosal gland mucus 5B (MUC5B), occupy most of the airway lumen and prevents the normal aeration of the alveoli (Fig. 4A and B).

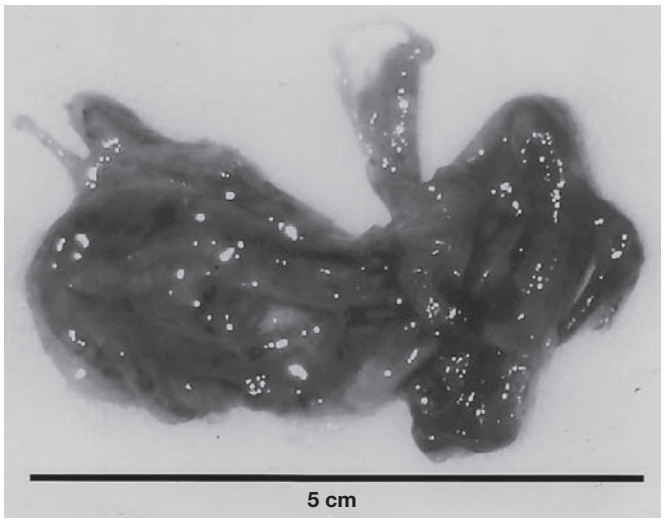
Early in the response these secretions are fluid and form a foamy material in the airway that many mistake for severe pulmonary edema in human patients.[78] After several hours, this transudate/exudate solidifies or clots in the presence of fibrin, forming firm obstructive materials in the airways. Figure 94-4C shows a presence of fibrin in the airway as a part of the obstructive cast. The mechanism of airway obstructive cast formation is illustrated in Figure 94-5 (cartoon on obstruction). These obstructive materials formed in the upper airway may migrate to the lower airways and alveoli.[77] This obstructive material is problematic from several standpoints. In some rare instances of severe airway injury these materials can induce total obstruction causing a life-threatening problem (Fig. 94-3). The presence of fibrin makes the removal of airway obstructive cast extremely difficult. Occlusion of some of the bronchi



A



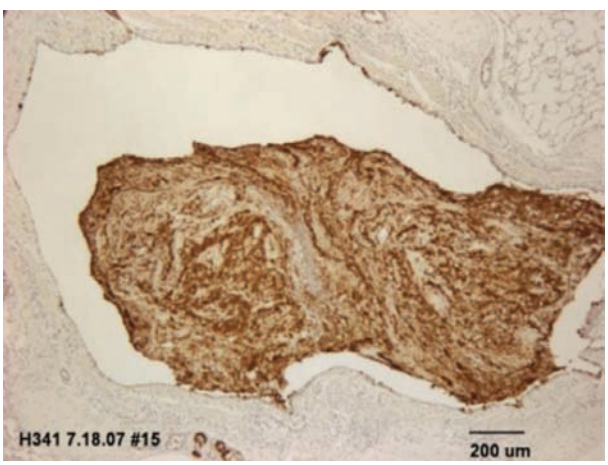
B



C

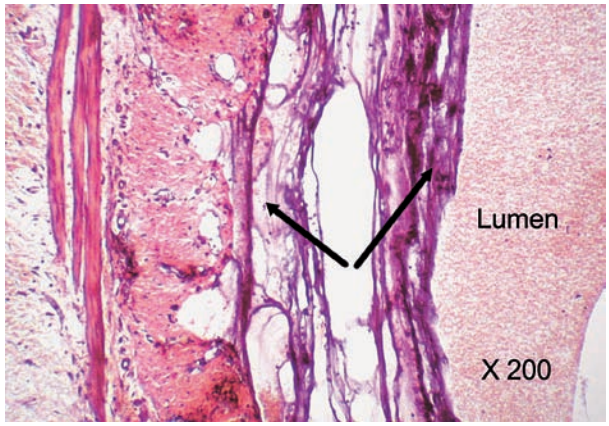
Figure 94-3 A chest X-ray of patients suffering from smoke inhalation taken at the time of admission and after removal of solid airway obstructive cast. **A.** On physical examination there was decreased transmission of breath sounds over the entire left chest; the chest radiograph shows obscuration of the left heart border and elevation of the left hemidiaphragm before removal of the cast. **B.** Radiograph taken 30 minutes after removal shows improved aeration; in addition, the left heart border is now visible. **C.** The cast was removed with basket forceps from the main left bronchus to the bifurcation of the upper and lower lobe bronchi. *(Reproduced with permission from Nakae H, Tanaka H, Inaba H. Failure to clear casts and secretions following inhalation injury can be dangerous: Report of case. Burns. 2001;27(2):189–191.)*

A



B

Figure 94-4 **A.** A macroscopic picture of airway obstructive cast taken 48 hours after burn and smoke inhalation injury in sheep; **B.** Brown spots within the cast material indicate presence of MUC5B, an index of mucus secretion in sheep after burn and smoke inhalation injury; *(continued)*



C

Figure 94-4 *(Continued)* **C.** Light micrograph showing the presence of fibrin *(arrows)* lining the lumen of bronchus in sheep subjected to combined burn and cotton smoke inhalation. Lung tissue for histological analysis (formalin fixation, Zenker postfixation), modified Masson trichrome stain) was taken 48 hours after the injury.

or bronchioles in association with high production of NO can lead to a loss of hypoxic pulmonary vasoconstriction and thus increased shunt fraction. Loss of hypoxic pulmonary vasoconstriction with inhalation injury has been reported.[79] Finally, if single bronchi are occluded while the patient is on a volume limited-ventilated ventilator, there could be overstretch and barotrauma to the alveoli of the nonoccluded portion of the lung. In Figure 94-6, high-resolution computed tomographic (upper panel) and magnetic resonance (lower panel) images illustrate massive airway obstructive casts and edema surrounding the trachea, main bronchi, and great vessels.

The airway is also richly innervated with vasomotor and sensory nerve endings.[80] It is known that these fibers release neuropeptides in response to caustic materials.[81] Neuropeptide release can cause activation of nitric oxide synthase, stimulate chemokine activity, and change microvascular permeability.[82] The resultant activities lead to the formation of reactive oxygen and nitrogen species. Some of the latter are very potent oxidants that can damage DNA. Damage

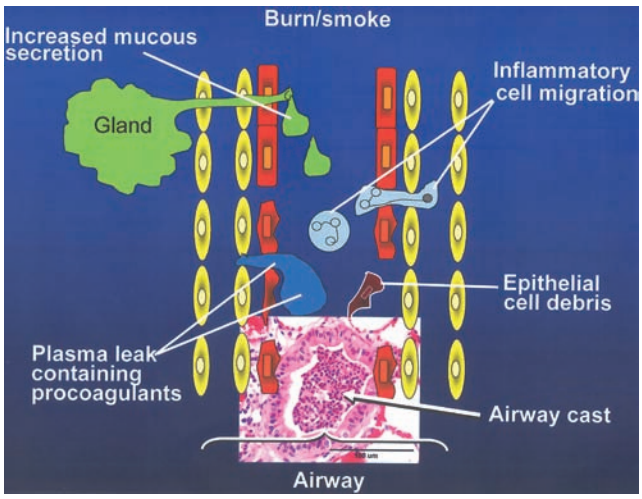


Figure 94-5 The pathophysiological process involved in the formation of the airway obstructive material following injury. At the bottom is a microscopic picture of a bronchiole almost completely blocked by airway obstructive material containing mostly mucus/fibrin and inflammatory cells. Sheep lung tissue was taken for histological analysis 48 hours after combined burn and smoke inhalation injury.

to DNA causes the activation of a repair enzyme poly(ADP-ribose) polymerase (PARP). This enzyme depletes the cell of high-energy phosphates and causes the activation of nuclear factor–kappaB (NF-κB). Activation of the nuclear factor causes the upregulation of iNOS and IL-8, thus creating accelerated production of reactive oxygen and nitrogen species (Fig. 94-1).[43] NO and 3-nitrotyrosine, an index of reactive nitrogen species, and iNOS mRNA and protein have been reported to be elevated in the airway after smoke inhalation.[83] Poly(ADP-ribose) [PAR], the product of the constitutive enzyme PAR polymerase, was identified in the lung tissues following smoke inhalation combined with burn[84] and pneumonia.[85] Inhibition of PARP prevented the formation of PAR, the upregulation of NF-κB and the formation of 3-nitrotyrosine.[84] Airway inflammation is not seen in a typical asthma model in the presence of a PARP inhibitor or in mice lacking the PARP gene.[86]

LUNG PARENCHYMA

As noted earlier the lung parenchyma changes, as reflected by reduced Pa_{O_2}/FI_{O_2}, reduced compliance, and increased edema formation are delayed. The delay is dependent on the severity of airway injury. Lung injury is associated with an increased pulmonary transvascular fluid flux.[83] The degree of transvascular fluid is proportional to the duration of smoke exposure[67] and is independent of the levels of CO in the inhalant gas.[87] The factors responsible for fluid leak are codified in the Starling–Landis equation.[88,89] The variables of this equation relate fluid movement to pressure and permeability variations. With inhalation of smoke there is a reduction in refection coefficient (permeability to protein), an increase in filtration coefficient (permeability to small particles), and an increase in pulmonary microvascular pressure.[90–92] Figure 94-7 demonstrates that pulmonary transvascular fluid flux in sheep following smoke inhalation is due to changes in both microvascular permeability and pressure. It appears that microvascular changes are responsible for early event.

Animals that had been exposed to smoke inhalation injury were also noted to have reduced Pa_{O_2}/FI_{O_2}. The change in this variable showed a good relationship to the histologic injury scores and the changes in transvascular fluid flux.[84] In addition, there was a loss of hypoxic pulmonary vasoconstriction in the injured animals that would help to explain the poor oxygenation.[85]

As in the airway the injury is markedly reduced by the administration of an iNOS or PARP inhibitors and is associated with the reduction of PAR and 3-nitrotyrosine.[68,83,93]

The venous outflow of the bronchial circulation drains into the pulmonary microcirculation at the precapillary level.[94] The fact that initial damage to the airway appeared to drive the pathophysiology of the parenchyma led investigators to hypothesize that the bronchial blood might deliver cytotoxic materials or cells into the pulmonary microcirculation. To test this hypothesis, several investigators have tied off the bronchial artery of sheep and then exposed the animals to smoke.[70,67,95] The hypothesis was affirmed in these studies; lung parenchymal changes were reduced. Recently, Lange et al. demonstrated that nebulized epinephrine attenuated smoke inhalation–induced increases in both tracheal and bronchial blood flow and improved pulmonary gas exchange.[69]

What could be the linkage among the airway, the bronchial venous drainage, and parenchymal injury to the lung? Neutrophils activated in the bronchial circulation flow out into the bronchial venous drainage. Activated polymorphonuclear cells (PMN) especially neutrophils are stiff. The diameter of neutrophils that have been fixed is approximately 7 μm.[96] Since these cells have been dehydrated in alcohol as part of the fixation process, unfixed cells are much larger, on the order of 12 μm. The pulmonary capillary is small with an average diameter of 6 μm.[96] Normally, the large neutrophil can traverse the pulmonary capillary by changing the

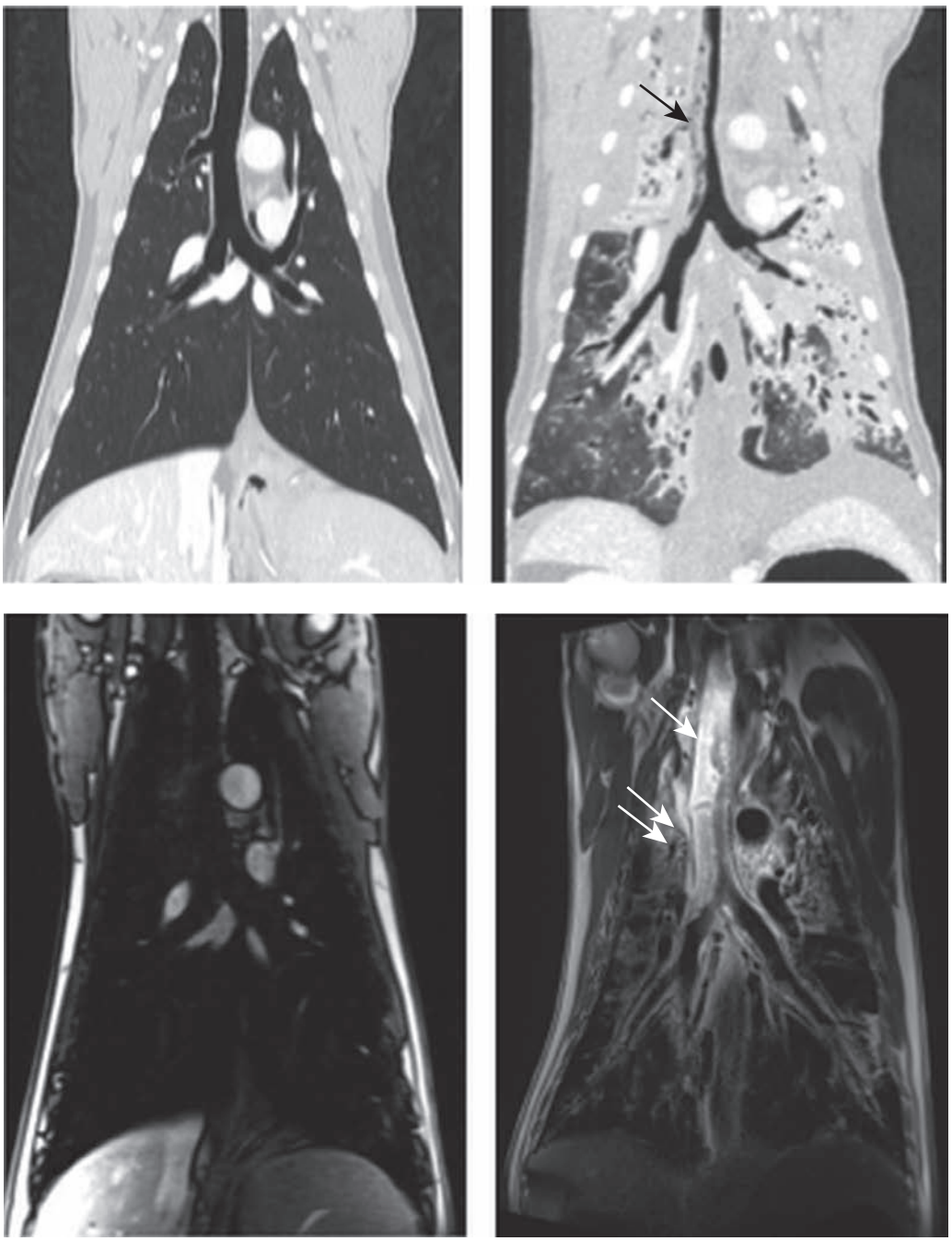


Figure 94-6 Coronal reformatted computed tomographic *(upper panels)* and magnetic resonance *(lower panels)* images before (images on left) and after (24 hours) (images on the right) the cotton smoke inhalation in sheep show casts in the upper airway *(single black arrow)*, including accessory right upper lobe causing its collapse. Severe edema surrounding the trachea, main bronchi, and great vessels is present with a cranio-caudal gradient. *Double white arrows* indicate consolidative collapse of the right upper lobe.

shape. However, when many neutrophils have been activated in the bronchial areas, their F-actin is activated and the cells are stiff and cannot deform. These stiff cells are carried to the pulmonary microvasculature, where they are impaled by the narrow pulmonary capillaries. The activated neutrophils release ROS and proteases that damage the parenchyma. The following evidence supports this concept of neutrophil cytotoxicity. Oxidative processes are well known following inhalation injury. There is lipid peroxidation and release of proteolytic enzymes following injury.[97–99] Administration of protease inhibitors or scavengers of ROS reduces the response to smoke inhalation[97,100–102] when activated PMNs lose the L-selectin on their surface. This L-selectin shedding is prevented by the treatment with an L-selectin antibody.[103] Treatment of the cells with an antibody to L-selectin prevents the changes in transvascular fluid flux and other aspects of parenchymal damage.[104] The final proof of this hypothesis was to deplete the animals of their neutrophils and determine how this affected the response to inhalation injury. In these studies of sheep depleted of their leukocytes, a high percentage of the parenchymal response to smoke inhalation was blocked.[105]

In addition to the depletion of antioxidants, it has also been reported that burned patients are depleted of arginine.[106] When arginine levels are low nitric oxide synthase produces superoxide rather than nitric oxide.[107] Administration of arginine may assist in reducing the oxidation that occurs with inhalation injury. However, the necessity of administering the arginine as arginine hydrochloride (because of solubility) limits the amount that may be given

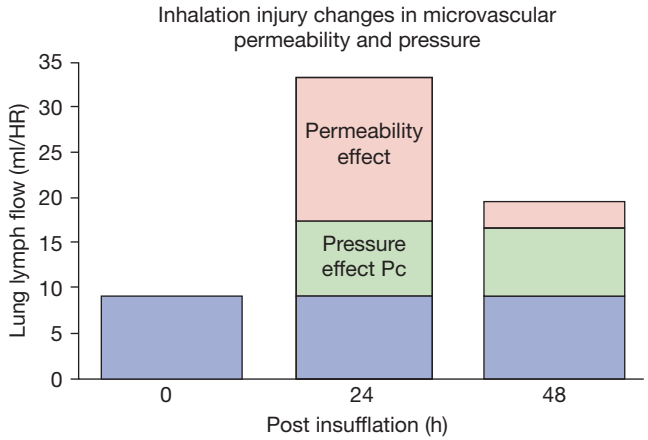


Figure 94-7 Diagram showing portion of edema resulting from either changes in pulmonary microvascular permeability or pressure at 24 and 48 hours after inhalation injury. *(Data from Isago T, Fujioka K, Traber LD, et al. Derived pulmonary capillary pressure changes after smoke inhalation in sheep. Crit Care Med. 1991;19(11):1407–1413.)*

intravenously without producing acidosis. Efficacy of arginine supplementation was demonstrated only in animal models of burn and smoke inhalation injury.[108]

Smoke inhalation injury, especially when it is combined with cutaneous burns, causes both local airway and systemic coagulopathy.[109,110–112] The hypercoagulable state in burn patients during the initial 24 hours is associated with high levels of activated factor VII (FVIIa), thrombin–antithrombin complex (TAT), PAI-1, and low levels of antithrombin.[113] Taken together the results of the previously mentioned studies could suggest, that a high rate of fibrin or thrombin formation and their diffuse deposition in the microvasculature during the first days following injury, accompanied by a relatively ineffective fibrinolysis due to excess PAI-1 could play an important pathophysiological role in the development of organ dysfunction.

TREATMENT

The treatment of smoke inhalation is complex. There is no defined and uniformly accepted standard treatment for smoke inhalation injury. The airway is a major concern immediately after the inhalation injury. The airway management is very difficult in patients with combined burn and inhalation injuries. Intubation of patients with burns of soft tissues of the face, oral pharynx, and neck is challenging. Burn injury to these soft tissues results in an almost immediate and severe edema and swelling.[114] Intubation in such an individual requires great skill. Securing the tube is also difficult. Accidental removal of the endotracheal tube can easily happen and is lethal. Often burns and/or the chemicals in smoke can damage the larynx, and placement of the tube can cause damage and delay healing of such a wound. Tracheostomy is sometimes performed, but also can be difficult if it has to be placed through burned skin on the neck. For information on this, the reader is referred to the chapters of Fitzpatrick and Cioffi as well as Mlcak and Herndon, in Herndon's *Total Burn Care*.[115,116]

To counter obstruction, vigorous airway toilet should be performed. The airway cast material contains fibrin. Experimentally, the use of heparin has been reported to be effective in reducing airway obstruction.[117] Many burn units nebulize heparin into the airway of their patients with inhalation injury.[118] Of note, heparin requires the presence of antithrombin to be effective, and this factor has been reported to be deficient following burn injury.[111,119] Consequently, antithrombin has been reported to be effective in these situations in animal studies.[111,112,120,121–123] Intravenous administration of antithrombin has also been shown to reduce mortality and morbidity of burn patients.[124] Antithrombin may also act as an anti-inflammatory agent.[125] Because the concomitant heparin prevents antithrombin's anti-inflammatory effects, administration of these compounds by different routes was suggested in translational large animal studies, that is, heparin via nebulization and systemic administration of antithrombin, to achieve maximum local (airway) anticoagulant and systemic anti-inflammatory effects.[111,126] Tasaki et al. also reported beneficial effects of nebulized heparin combined with intravenous infusion of anti-inflammatory agents.[127]

Once obstructive materials have formed in the airway anticoagulant therapy (heparin and antithrombin) is ineffective in removing them. Animal studies have demonstrated that tissue plasminogen activator could be effective in removing these materials.[110] Aerosolized tissue plasminogen activator has also been reported to be effective in removing bronchial obstructive material in patients who have had Fontan procedures (surgical procedures for complex congenital heart diseases named after Dr. Fontan).[128,129]

To alleviate airway smooth muscle spasm, nebulized albuterol as a bronchodilator was successfully used in both an animal model of smoke inhalation and burn patients with concomitant smoke inhalation.[130,131] Other bronchodilators such as nebulized tiotropium bromide and epinephrine were shown to be beneficial in the animal model of inhalation injury.[69,132]

Because of almost immediate airway hyperemia following smoke inhalation, the use of nebulized agents that modulate augmented airway blood flow may be of particular importance. Lange et al. recently reported that nebulized epinephrine, a nonspecific adrenergic agonist reduced both trachea and bronchi blood flow and improved arterial oxygenation in a sheep model of cotton smoke injury.[69] Nebulized epinephrine may be of particular interest in management of inhalation injury, since it has both alpha (vasoconstriction) and beta (bronchodilation) effects. However, further studies are needed for the safety of such a therapy minimizing its systemic effects to be established. The importance of reducing airway hyperemia has been repeatedly shown in animal models by ablating the bronchial artery.[67,70,72,73,133] The local administration of the various compounds to the bronchial artery that attenuate augmented bronchial circulation and inflammation prevents many pathological changes following smoke and burn injury in sheep.[134–136] Although such therapies (ligation and cannulation of bronchial artery for drug infusion) are not feasible in clinical practice, these findings strongly suggest the critical role of airway dysfunction (hyperemia, inflammation) in the pathophysiology of lung injury after smoke inhalation. These findings also suggest the crucial importance of efficient airway management in alleviating severe lung injury following smoke inhalation.

Many other drugs have also proved effective in reducing the injury to the lung parenchyma of animal models of inhalation injury, including cyclooxygenase inhibitors,[137] iNOS inhibitors,[68] PARP inhibitors[84] and free radical scavengers,[100] as well as the anticoagulant factors[111,126] mentioned earlier. However, only the latter are in clinical use and/or have been studied in clinical trials.[124,138]

Mechanical ventilation should be indicated in case of respiratory failure. However, in many instances conventional methods of ventilation can no longer sustain the pulmonary function of burned patients. Extracorporeal membrane oxygenation has been used in these patients with some success.[139] Techniques have now been developed in animal models of inhalation injury that involve a unique form of CO_2 removal called arterial venous CO_2 removal or AVCOR. Off the shelf CO_2 removal devices, used in extracorporal bypass and cardiopulmonary bypass, have been modified to be driven by the subject's own arterial pressure.[140] These were tested in animal models and shown to be very successful in reducing pathophysiology, morbidity, mortality, and days of ventilatory support of models of inhalation injury.[141–143]

Finally, some pretreatment for smoke inhalation can be accomplished. People who are chronically exposed to smoke such as farmers who burn crops, individuals with fires in their huts, and fire fighters may benefit from pretreatment. There are reports that individuals who are chronically exposed to smoke are depleted of their antioxidants.[144] Consequently, supplementation of antioxidants should be considered.[144]

CONCLUSION

The diagnosis and treatment of smoke inhalation injury are complex. There are neither existing standardized criteria for the diagnosis of smoke inhalation injury nor specific pharmacological agents developed against this malady. Multicenter, prospective, randomized, and large scale clinical trials are needed to test the efficacy and safety of promising pharmacological agents from basic science and translational studies—nebulized fibrinolytics, anticoagulants, beta or mixed beta and alpha-adrenergic agonists, and antioxidants. These multicenter clinical trials may also help scientists and clinicians reach concurrence upon the uniformly characterized diagnostic standard.

ACKNOLWEDGMENTS

Dedicated to the memory of Dr. Daniel L. Traber who was my mentor and the coauthor of this chapter in the previous edition.

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PART 13

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CHAPTER 95

Noninfectious Pulmonary Complications of Hematopoietic Stem Cell and Solid Organ Transplantation

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Steve G. Peters
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HEMATOPOIETIC STEM CELL TRANSPLANTATION

Following a brief overview of the topic, we present a discussion on the frequency of noninfectious complications, associated risk factors, and the impact of noninfectious complications on outcome.

OVERVIEW

Important considerations in hematopoietic stem cell transplantation are discussed below. Subsequently, solid organ transplantation is discussed in a separate section.

Hematopoietic stem cell transplantation (HSCT) primarily is used to treat hematological and lymphoid cancers, selected solid tumors, and nonneoplastic diseases including autoimmune disorders, amyloidosis, and aplastic anemia.[1] Over 30,000 autologous and 25,000 allogeneic HSCTs are performed annually worldwide.[2] The most common graft source is peripheral blood.[2] Other graft sources include bone marrow and cord blood. A total of 7892 allogeneic and 12047 autologous HSCTs were performed in 2011 in the United States.[2] The main indications for autologous transplant include multiple myeloma and lymphomas, and allogeneic transplant is most commonly performed for acute and chronic leukemia, lymphoma, and myelodysplastic syndrome. A conditioning regimen is employed before transplantation to eradicate malignant cells and, in allogeneic transplantation, to induce immunosuppression that permits engraftment.[1] Some patients are also given total-body irradiation for myeloablation and immunosuppression. The conditioning regimen can be termed myeloablative, reduced intensity, or nonmyeloablative.[3]

Following HSCT, the immune system recovers along predictable patterns depending on the underlying disorder, stem cell source, and complications such as graft versus host disease (GVHD).[4] Recovery occurs faster in autologous recipients, in those who receive peripheral blood stem cell grafts, and after nonmyeloablative conditioning. The posttransplant period is divided into three phases: Pre-engraftment, early posttransplant, and late posttransplant.[5] The pre-engraftment phase (0–30 days) is characterized by neutropenia and breaks in the mucocutaneous barriers. The early post-engraftment phase (30–100 days) is dominated by impaired cell-mediated immunity. The impact of this cell-mediated defect is determined by the development of GVHD and the corresponding immunosuppressant medications. The late posttransplant phase (>100 days) is characterized by defects in cell-mediated and humoral immunity, as well as function of the reticuloendothelial system in allogeneic transplant recipients. The development of noninfectious pulmonary complications follows characteristic temporal patterns.[6] Pulmonary edema, diffuse alveolar hemorrhage (DAH), and peri-engraftment respiratory distress syndrome (PERDS) usually occur during the first 30 days posttransplant (Fig. 95-1). Idiopathic pneumonia syndrome (IPS) can occur at any time following transplant.

The mortality of patients following HSCT is high and depends on the underlying disease and type of transplant.[2] Patients receiving human leukocyte antigen (HLA)-identical sibling transplants for acute myelogenous leukemia (AML) in remission have a 100-day mortality rate of 7% to 9%, compared with 22% for patients with active leukemia at the time of transplantation. Early mortality after an unrelated donor transplant is higher than after an HLA-identical sibling transplant, but the rate also depends on the disease and stage. The causes of death in the first 100 days posttransplant mainly relate to the primary disease, GVHD, infection, and end-organ damage. IPS accounts for 1% to 5% of deaths. After an autologous transplant, recurrence or progression of primary disease is the most commonly reported cause of death. Among allogeneic transplant recipients, unrelated donor transplants have fewer deaths related to the primary disease; however, deaths related to organ failure and infections are more frequent.

FREQUENCY OF NONINFECTIOUS PULMONARY COMPLICATIONS

Many pulmonary complications occur in HSCT recipients (Table 95-1). Earlier reports identified pulmonary complications in 30%

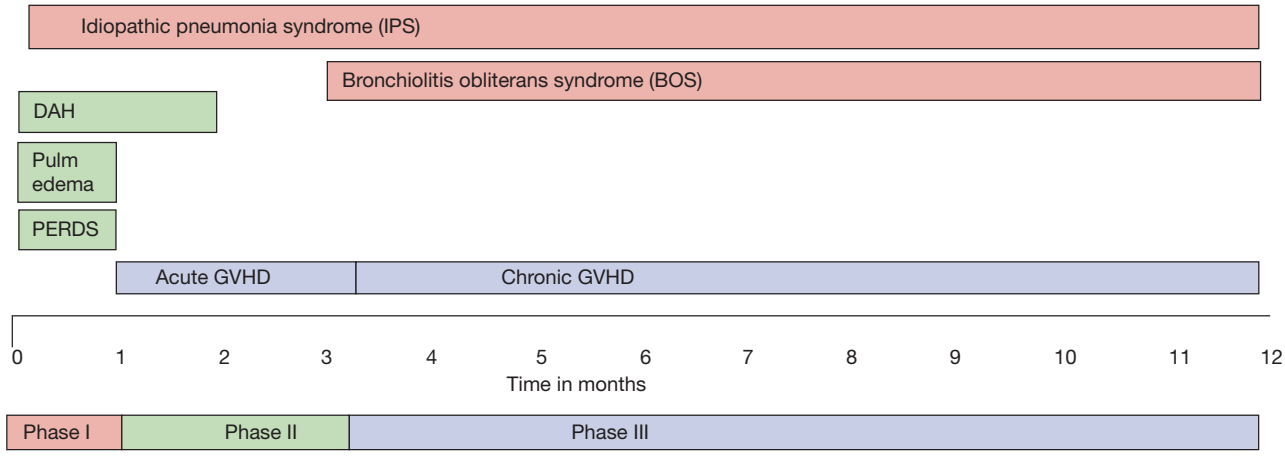

Figure 95-1 The temporal pattern of major noninfectious pulmonary complications following hematopoietic stem cell transplantation.

TABLE 95-1 Noninfectious Pulmonary Complications in the HSCT Recipient

Isolated abnormality in pulmonary function
Bronchiolitis obliterans syndrome
Bronchiolitis obliterans organizing pneumonia
Idiopathic pulmonary syndrome
Delayed pulmonary toxicity syndrome
Diffuse alveolar hemorrhage
Peri-engraftment respiratory distress syndrome
Pulmonary cytolytic thrombotic syndrome
Pulmonary venoocclusive disease
Progressive pulmonary fibrosis
Pulmonary hypertension
Hepatopulmonary syndrome
Pulmonary alveolar proteinosis
Eosinophilic pneumonia

TABLE 95-2 Risk Factors for Pulmonary Complications in HSCT Recipients

Pre-existing lung disease
Older age
Underlying disease leading to transplant
Type of stem cell transplant (autologous vs. allogeneic)
Previous infections
Cytomegalovirus serology positive in recipient or donor
Current and prior immunosuppressant medications
Pretransplant conditioning regimen
Total-body irradiation
Time interval between underlying diagnosis and transplant
Time elapsed since transplant
Graft vs. host disease

to 60% of HSCT recipients.[7–9] Recent publications suggest changes in the pattern and frequency. In a study of 70 patients, pulmonary complications developed in 18 (25.7%), of whom only 2 had noninfectious pulmonary complications, one cryptogenic organizing pneumonia (COP), and another IPS.[10] In a study of T-cell–depleted HSCT recipients, pulmonary complications developed in 16.5%.[11] In a more recent report of autologous HSCT recipients, pulmonary complications developed in 27.6%, with noninfectious diagnoses in 10.2%.[12] The reported rates of respiratory failure in allogeneic HSCT recipients also have declined over time.[13]

In a group of pediatric HSCT recipients, pulmonary complications were found in 90 of 363 (25%).[14] In a study of pediatric allogeneic HSCT recipients, late-onset noninfectious pulmonary complications developed in 10 of 97 (10.3%), including 8 COP and 2 IPS.[15] In autopsy series, the rate of pulmonary complications exceeds 80%.[16,17]

RISK FACTORS FOR NONINFECTIOUS PULMONARY COMPLICATIONS

Several factors have been implicated as risk factors for pulmonary complication in HSCT recipients (Table 95-2).[5,11,14,15,18–23] It is controversial whether impaired pulmonary function before stem cell transplant is a risk factor for the development of early posttransplant respiratory failure and mortality. Studies that have examined the predictive value of pretransplant pulmonary function tests suggest that poor lung function before transplant increases the risk for posttransplant pulmonary complications[24–28] and mortality.[25,29,30] These findings were not confirmed in a large study.[31] In addition, these analyses disagreed on which pretransplant lung function parameters were the strongest predictors of pulmonary complications and mortality, and they were limited by relatively small cohorts. A retrospective analysis of 2852 HSCT recipients assessed the association of pretransplant FEV_1, FVC, total lung capacity (TLC), diffusing capacity for carbon monoxide (D_{LCO}), and the development of early respiratory failure and mortality.[32] Patients who developed early respiratory failure were more likely to have impaired lung function prior to transplant. Univariate analysis demonstrated that pretransplant FEV_1, FVC, TLC, and D_{LCO} were more likely to be reduced among patients who developed early respiratory failure.[32] In a recent report of 1243 autologous HSCT recipients, pretransplant D_{LCO} and underlying disease were the only independent risk factors for the development of pulmonary complications.[12] In a study of 307 autologous and allogeneic HSCT recipients, 170 developed venoocclusive disease of the liver, and this was associated with reduced pretransplant D_{LCO}.[33] Advanced stage of the underlying disease at transplant is associated with the development of late-onset noninfectious pulmonary complications.[22] Nonmyeloablative conditioning is associated with reduced pulmonary complications.[34] Also, the incidence of pulmonary complications is low after T-cell–depleted stem cell transplant.[11] Due to the absence of GVHD and the infrequent use of immunosuppressant medications and radiation therapy, noninfectious complications are less common in the autologous HSCT recipient.

IMPACT OF PULMONARY COMPLICATIONS ON PATIENT OUTCOME

The mortality rate of allogeneic HSCT recipients has declined over time.[13] A 2006 report found median survival of 41 weeks for patients with pulmonary complications compared with 350 weeks for those without complications.[11] In patients who survived beyond 2 years after transplant, pulmonary complications accounted for 5% of the subsequent deaths, and patients with pulmonary complications had a 15-fold increased risk of death.[35] In a study of pediatric allogeneic HSCT recipients, the 5-year posttransplant survival of patients with noninfectious pulmonary complications was 28.0% compared with 87.2% of those without complications.[15] In an autopsy study of HSCT recipients, pulmonary complications were the only cause of death in 64% and one of multiple causes in 10%.[16] There is controversy in the provision of intensive care for severe pulmonary complications. Respiratory failure accounts for about one-third of ICU admissions following HSCT, and early reports observed nearly 100% short-term mortality for HSCT recipients requiring ventilator support. More recent series report improving outcomes, with overall hospital mortality approximately 50% after ICU admission, and mortality 75% to 85% following mechanical ventilation.[36–38] Worse outcomes are associated with advanced underlying disease, GVHD, multiple organ failure, and the need for vasopressors. Intensive care and aggressive management are usually warranted in the acute situation, especially during the engraftment period, to assess for potentially reversible conditions.

APPROACH TO THE DIAGNOSIS OF NONINFECTIOUS PULMONARY COMPLICATIONS

The diagnostic approach to HSCT recipient with suspected noninfectious pulmonary complications should follow a systematic approach.[6] Recipients with respiratory symptoms and signs usually

are evaluated with a chest radiograph followed by high-resolution computed tomography (HRCT). If the radiographic evaluation fails to reveal pulmonary infiltrates, especially in allogeneic recipients, PFT should be performed to assess for bronchiolitis obliterans syndrome (BOS). For patients with pulmonary infiltrates, noninvasive tests should be performed for infections and other causes. Noninvasive approaches include sputum for microbiology studies, blood culture, blood aspergillus assay, cytomegalovirus (CMV) viral load testing, and urine antigen for *Legionella pneumophila* and *Pneumococcus pneumonia*.[39] If noninvasive testing is nondiagnostic, invasive techniques should be considered, balancing the risk–benefit ratio. The invasive approach usually relies on fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and occasionally transbronchial lung biopsy. Other invasive procedures such as image-guided transthoracic needle aspiration and video-assisted thoracoscopic biopsy rarely may be needed.[40]

PULMONARY FUNCTION ABNORMALITIES FOLLOWING HSCT

Although the value of pretransplant PFT in predicting posttransplant outcome is somewhat controversial, many institutions perform pretransplant PFT as a baseline reference on all recipients, and posttransplant testing for allogeneic recipients.[26,41,42] Some patients develop PFT abnormalities in the absence of respiratory symptoms.[43] Restrictive and obstructive ventilatory defects, and gas transfer abnormalities are frequent long-term sequelae following allogeneic transplantation. A systematic review of data regarding allogeneic HSCT recipients reported decreased D_{LCO} in 83%, restriction in 35%, and obstruction in 23%.[44] A more recent study of over 500 allogeneic HSCT recipients documented somewhat lower frequencies: Impaired D_{LCO} in 35%, restriction in 12%, and obstruction in only 6% of long-term survivors.[45] While the frequency of restrictive defect and of impaired D_{LCO} appeared constant over time, this study suggested a declining frequency of airflow obstruction. HSCT recipients with IPS and COP present with restrictive pulmonary function impairment, and those with BOS demonstrate airflow obstruction.[46] The development of any posttransplant PFT abnormality is associated with increased risk of death.[24,25,45,47]

Risk factors for the development of PFT abnormalities following HSCT include smoking history, pretransplant pulmonary infection, viral infection in the early posttransplant period, older age, underlying disease, pretransplant chemotherapy and conditioning regimen, GVHD, and HLA mismatch.[29,48–50] Respiratory muscle weakness, an alternative cause of restrictive PFT abnormalities, was reported in 52% of allogeneic HSCT recipients in a retrospective study.[51] Risk factors for respiratory muscle weakness include chemotherapy, total-body irradiation, high-dose corticosteroids, immobility, and GVHD.[51]

UPPER AIRWAY COMPLICATIONS

Significant injury to the mucosal barrier occurs in about 75% of HSCT recipients.[52] Total-body irradiation, allogeneic transplant, leukemia, and delayed neutrophil engraftment are risk factors for mucositis.[53] Upper airway inflammation due to mucositis may lead to laryngeal edema, dysphagia, and aspiration pneumonia. Life-threatening upper airway complications are more common in children.[54,55] More severe mucositis is associated with an increased risk of secondary infection, requirement for narcotics, longer duration of parenteral nutrition and hospital length of stay, and increased overall mortality.[53,56] Upper airway injury in HSCT recipients is usually managed with supportive care, including local symptomatic therapy and endotracheal intubation in severe cases.

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans (BO) is an inflammatory and fibroproliferative process primarily affecting the small airways that leads to the presence of airflow limitation.[57] Although BO can be idiopathic, it is more often associated with connective tissue disease, inhaled toxins, infections, drugs, chronic rejection following lung transplantation, and chronic GVHD.[57–59] GVHD is a frequent complication of allogeneic HSCT, and is commonly associated with lung disease.[48,59–61] The pulmonary manifestations of GVHD include diffuse alveolar damage, lymphocytic bronchitis/bronchiolitis with interstitial pneumonitis, COP, and BO.[62] BO has only rarely been reported in autologous HSCT recipients.[63]

Frequency

The rate of BO varies among studies, depending on patient population. The lack of precise definition and uniform diagnostic criteria contribute to these variations. Although some studies have included pathological findings, most of the reported cases of the syndrome in HSCT recipients were defined by the presence of airflow limitation in the appropriate clinical setting.[48]

In a previous review of nine studies including 2152 allogeneic HSCT recipients, BO was reported in 8.3%, with a range of 6% to 20% in long-term survivors.[58] In seven more recent studies, including 5543 allogeneic HSCT recipients, the average BO rate was 3.7%, with range of 2.6% to 10.3%.[11,22,60,61,64–66]

Risk Factors

Several factors are implicated as risks for BO.[58] The most common is GVHD.[25,61,64,65,67,68] In one study of allogeneic HSCT recipients, 6% of those with chronic GVHD developed BO compared to none without GVHD.[69] Data from the International Bone Marrow Registry of 6275 adults with leukemia who received HLA-matched sibling transplant from 1989 to 1997, and survived at least for 100 days, showed that BO was associated with busulfan-based conditioning, time from disease diagnosis to transplant of 14 months or longer, peripheral blood stem cell source, transplant from female donor to male recipient, acute GVHD, and interstitial pneumonia.[67] Older recipient or donor age, methotrexate use, and serum immunoglobulin deficiency are also implicated to be risk factors for BO.[25,61,69–72] While pulmonary infections are common in patients with BO, it is not clear whether they are causally related or result from associated immunodeficiency.

Pathogenesis

Little is known about the pathogenesis of BO. Early in the syndrome, bronchiolar inflammation has been identified.[62,73] The histopathology begins with lymphocyte inflammation around small vessels and the respiratory epithelial lining of the small airways, followed by epithelial cell necrosis and mucosal denudation.[68] Two different forms of BO have been described, distinguished by their response to azithromycin: A responsive, neutrophilic, partially reversible form and a nonresponsive fibroproliferative variant.[74,75] The association between BO and chronic GVHD has led to the hypothesis that host bronchiolar epithelial cells serve as target for donor cytotoxic T lymphocytes.[76] Alternative explanations include recurrent aspiration of oral material due to esophagitis associated with GVHD, abnormal local immunoglobulin secretory function in the lungs, or unrecognized infection.[69,76] The variations in histopathology, bronchoalveolar cell differential, clinical course, and the frequency of associated pulmonary infection suggest that the pathogenesis is multifactorial.[76,77] BO in HSCT recipients resembles chronic allograft rejection in lung transplant recipients at immunological, pathological, and physiological levels.[78] T-cell–mediated recognition of alloantigens expressed in the lung tissue plays a central role.[68] In one study, none of the HSCT recipients with T-cell depletion developed BO.[79]

Clinical Findings

From several reports, the onset of BO occurs at a median 328 to 335 days and range 48 to 1690 days following HSCT.[60,64,65,70,72,79] In

the International Bone Marrow Registry of 6275 allogeneic HSCT recipients with leukemia, median time (range) from transplant to BO is 431 (65–2244) days.[67] Twenty percent of the patients with BO had no respiratory symptoms at the time of the first abnormal pulmonary test. The absence of symptoms has been observed during the mild stage of BO.[80] Typical respiratory symptoms include dry cough, dyspnea and exercise intolerance.[70,72,81] The physical finding of wheezing may be detected in about 40%.[70] Unlike COP, fever is absent in BO. Since these symptoms are nonspecific, a complete history, including prior medications and infections, and thorough physical examination focusing on signs of chronic GVHD should be obtained.

Diagnosis

The clinical criteria that have been most widely used for the diagnosis of BO in the HSCT population include $FEV_1/FVC < 0.7$ and $FEV_1 < 75\%$ of predicted; evidence of air trapping, small airway thickening, or bronchiectasis on HRCT of the chest (with inspiratory and expiratory cuts); residual volume >120% of predicted; and absence of infection in the respiratory tract.[46,82] While definitive diagnosis ideally would include demonstration of histological evidence of BO, this almost always would require a surgical lung biopsy since the yield of transbronchial biopsy for this entity is extremely low. Because it is difficult to establish a histological diagnosis of BO by minimally invasive means, a surrogate functional diagnostic schema based on FEV_1 decline was developed, referred to as BOS. BOS is defined as the presence of airflow limitation leading to a decline in FEV_1 of at least 20% compared to baseline, in the absence of identifiable causes (e.g., infection). Based on the magnitude of decline in FEV_1, BOS is classified into stages as follows: stage 1 (FEV_1 66%–80% of peak posttransplant baseline), stage 2 (FEV_1 51%–65% of baseline), and stage 3 (FEV_1 <50% of baseline).[83] This classification scheme was initially devised exclusively for lung transplant recipients and has not yet been widely applied to the HSCT population. Thus, its utility in defining severity or prognosis in this population remains to be established.

In HSCT recipients with suspected BO, laboratory evaluation should be undertaken to exclude infection and complications of GVHD. Complete blood count with differential, blood urea nitrogen, creatinine, total bilirubin, hepatic transaminases, immunoglobulin levels and subclasses, and urinalysis are recommended.[76] Chest radiograph is usually normal or may show hyperinflation.[70,78,84–86] Inspiratory and expiratory HRCT of the chest should be included as part of BO evaluation.[80] HRCT of the chest typically shows mosaic attenuation due to air trapping (most pronounced on expiratory images), often accompanied by vascular attenuation, bronchiectasis, and bronchiolectasis (Fig. 95-2).[78,85,87–89] GVHD is a risk factor for sinusitis in HSCT recipients.[90] Since timely treatment of the sinusitis may lead to clinical improvement, radiological investigation including CT of the sinuses is recommended.[76,90–93]

BAL is used in suspected BO to exclude infection and to assess the patterns of lung inflammation. In one study of seven HSCT patients with airflow obstruction, BAL showed predominantly neutrophilic inflammation in four, lymphocytic in two, and a mixed pattern in one.[77] Because BO involves respiratory and membranous bronchioles, transbronchial lung biopsy is usually inadequate for diagnosis. Video-assisted thoracoscopic lung biopsy is a gold standard for definitive diagnosis, but is rarely pursued if other typical clinical–radiographic features are present.[80] The pathology shows damage to the bronchiolar epithelium, fibrinous obliteration of bronchiolar lumen, inflammation between epithelium and smooth muscle, and pulmonary fibrosis (Fig. 95-3).[78,81,94,95] Peribronchiolar inflammatory cellular infiltrates consisting of neutrophils and lymphocytes may be present.[96]

Treatment

There is insufficient evidence to support specific recommendations for the treatment of BO.[68] First-line treatment usually involves corticosteroids.[46] Prednisone 1 to 1.5 mg/kg/d, or its equivalent, is given for 4 to 6 weeks and if respiratory status remains stable, therapy is tapered and discontinued in 6 to 12 months. However, clinical responses are observed in only about 20% of patients and treatment success often does not persist.[63,68,70,78,85,89,97] Immunosuppressive drugs used to treat BO associated with GVHD include cyclosporine, azathioprine, tacrolimus, and mycophenolate.[46,76] The typical dose of azathioprine is 2 to 3 mg/kg/d, not to exceed 200 mg. Cyclosporine or tacrolimus dose is adjusted according to serum levels.[58]

Inhaled corticosteroids are used commonly to treat BO, but data are limited. A study comparing a combination of inhaled fluticasone, oral azithromycin, and montelukast in 9 patients with BOS against a historical control of 14 patients treated with high-dose corticosteroids showed no difference between the groups.[98] Another study of 13 HSCT recipients with BO showed improvement in lung function and symptoms.[99] These encouraging results provide potential for less toxic therapeutic options, but require confirmation in a larger group of patients with a longer follow-up period.

Macrolides have immunomodulatory effects that may halt disease progression in BO.[100] Although the mechanism of action is not fully understood, it seems that it not only leads to a reduction of neutrophil inflammation,[74,101] but also has prokinetic properties on the upper gastrointestinal tract, reducing gastroesophageal

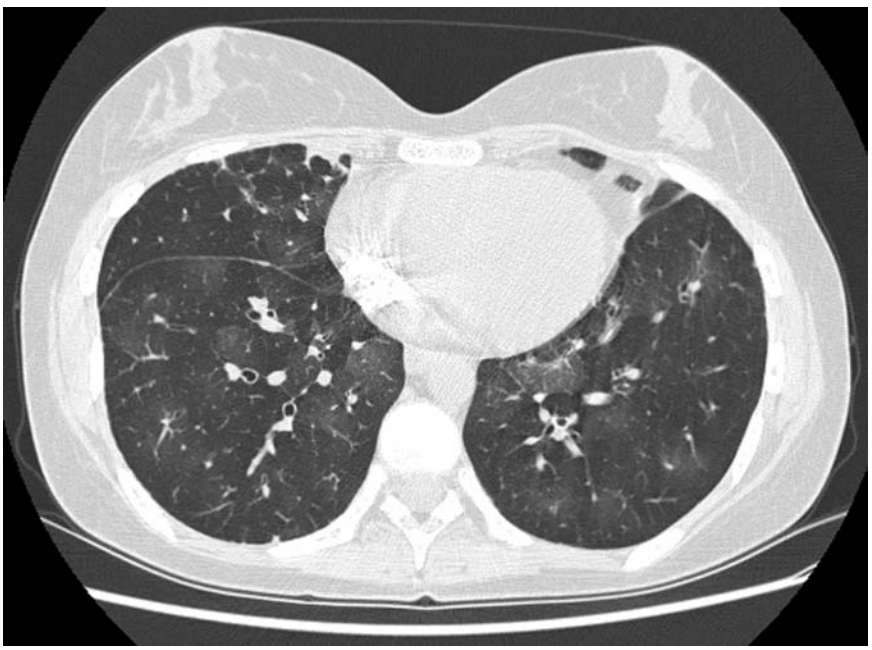

Figure 95-2 Computed tomography scan expiratory views of a patient with bronchiolitis obliterans following HSCT, showing mosaic attenuation associated with air trapping *(darker areas)*, bronchial thickening, and mild bronchiectasis.

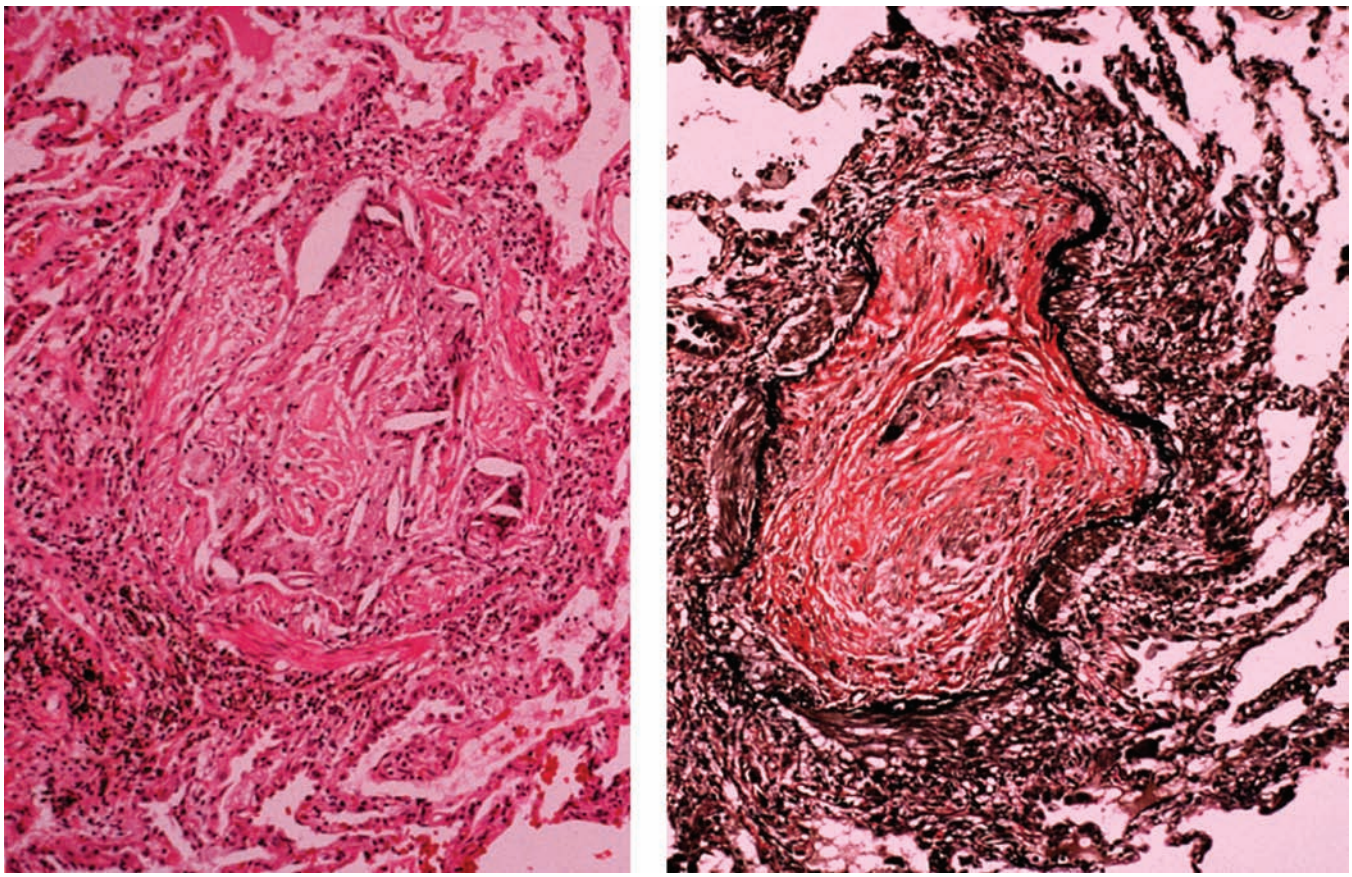

Figure 95-3 Lung pathology in bronchiolitis obliterans, showing inflammation and obliteration of the airway lumen, associated with fibrous connective tissue (hematoxylin and eosin stain, left; Verhoeff–Van Gieson elastic stain, right).

reflux, another risk factor for BO.[102] Macrolides are commonly used to treat diffuse panbronchiolitis.[103–107] There are case series documenting the beneficial role of macrolides for the treatment of BOS in lung transplant recipients.[108] There are even less data addressing the role of macrolides in HSCT recipients with BO. In a series of eight patients treated with azithromycin 500 mg daily for 3 days, followed by 250 mg three times each week for 12 weeks, clinical improvement was achieved in seven patients.[109] In a report of 10 HSCT recipients with BOS, azithromycin was not associated with improvement in lung function.[110] Treatment of BOS in eight HSCT recipients with formoterol, azithromycin, and montelukast showed that this regimen may spare the use of high-dose systemic steroids.[98] In a recent randomized double-blinded placebo-controlled trial of HSCT recipients with BOS, 10 were treated with oral azithromycin 250 mg daily while 12 were treated with placebo for 12 weeks.[111] There were no significant differences in outcome between the two groups. Overall, there is insufficient evidence to substantiate the use of macrolides in the treatment of HSCT patients with BO.

Leukotrienes are eicosanoid lipid mediators that contribute to the inflammatory processes in the development of asthma, alveolitis, pulmonary fibrosis, and BO following lung transplantation, and promote bronchoconstriction, as well as eosinophil and neutrophil recruitment.[112] There are limited data addressing the role of the leukotriene receptor antagonist montelukast in the treatment of BO. In a pilot study of 19 patients with refractory chronic GVHD, montelukast 10 mg daily was administered for a mean of 10 months.[112] Overall improvement was observed in 15 of the 19 patients. In a prospective study comparing the combination of fluticasone, azithromycin, and montelukast against high-dose corticosteroids, there was no difference in lung function between the groups.[98] However, with the montelukast combination, it was possible to taper systemic corticosteroids rapidly.

There are limited data regarding tumor necrosis factor (TNF) blockade in the treatment of BO. There is a case report of biopsy-proven BO after HSCT in a child who was treated with infliximab after failed corticosteroid therapy.[113] The pulmonary symptoms and spirometric abnormalities resolved and the patient remained asymptomatic for several months.

The anti-CD4 monoclonal antibody, rituximab, has been used in refractory chronic GVHD. In one study, rituximab resulted in reduced systemic corticosteroid use.[114] Improvement in lung function was noted in three of eight patients. In a phase II prospective multicenter study of HSCT recipients with steroid-refractory chronic GVHD, 37 patients were treated with weekly infusion of rituximab for 4 weeks followed by monthly infusion for 4 months.[115] The treatment was complicated by infections and relapse. Only one of 11 patients showed partial response in the lung.

Extracorporeal photochemotherapy (ECP), or photopheresis, an immunomodulatory therapy developed for treating cutaneous T-cell lymphoma, has shown promise in treating chronic GVHD in uncontrolled studies.[116] In this procedure, white blood cells are removed and exposed to ultraviolet radiation after pretreatment with a psoralen derivative, leading to cell death. In a retrospective study of 14 allogeneic HSCT recipients with extensive chronic GVHD, ECP was administered three times weekly on alternating days.[116] Improvement in the pulmonary manifestations was noted in 1 of the 3 patients and systemic corticosteroid was tapered in 11 of the 14. In another study, nine allogeneic HSCT recipients with BO were treated with ECP.[117] Six of nine (67%) patients responded

after a median of 25 days. No ECP-related complications occurred. ECP stabilized rapidly declining pulmonary function tests in about two-thirds of patients with severe and refractory BO.

If otherwise successful HSCT is complicated by end-stage lung disease from BO, lung transplantation may be considered. There are insufficient data addressing this issue, with several single case reports.[118–124] In a cross-sectional study of 313 lung transplant recipients, 3 were performed for BO in allogeneic HSCT recipients.[123] Lung transplants from living donors have also been reported in this setting.[121,124,125]

Prognosis

The prognosis of BO in HSCT recipients is poor. Fewer than 20% improve and 65% die within 3 years of diagnosis.[61,64,80,97,113] The rate of decline in FEV_1 is widely variable and rapid deterioration is associated with increased mortality.[70] Despite treatment, improvement in lung function is noted in only 8% to 20%.[58] The reported case fatality rates vary widely, ranging from 14% to 100% with a mean of 61%.[58] In one study of allogeneic HSCT recipients with GVHD, the 3-year mortality rate of those with BO was 65% compared to 44% of those without BO.[70] In a more recent study, the 5-year survival of HSCT recipients with BO from the time of diagnosis was 45.4%, significantly less than those without (77.5%, $p < 0.001$).[65] The mortality of BO has not improved over the last two decades.[80]

■ PERI-ENGRAFTMENT RESPIRATORY DISTRESS SYNDROME

PERDS is the pulmonary manifestation of engraftment syndrome in HSCT recipients.[126] The engraftment syndrome is characterized by skin rash, noninfectious pulmonary infiltrates, fever, diarrhea, and capillary leak during the peri-engraftment period.[127–129] Engraftment syndrome develops in 7% to 53% of HSCT recipients.[127,128,130,131] Among 152 autologous HSCT recipients supported by either granulocyte or granulocyte macrophage colony–stimulating factors, engraftment syndrome developed in 20 (13%).[132] Although most of the studies reporting engraftment syndrome are in autologous HSCT recipients, it also occurs after allogeneic transplantation.[133,134] In two recent studies, pulmonary manifestations were reported in 18 of 61 (30%) patients with engraftment syndrome.[127,131]

Frequency, Risk Factors, and Pathogenesis

There is only one study that addressed PERDS specifically and reported an occurrence in 4.6% of 416 autologous HSCT recipients.[126] Using similar criteria in the same institution, a recent study reported PERDS in 52 of 1243 (4.2%) autologous HSCT recipients.[12]

Earlier studies of the engraftment syndrome noted possible relationships with the underlying disease, therapies prior to transplant, stem cell dose and source, growth factor use, amphotericin administration, and rate of engraftment.[130,133,135] In one study focusing specifically on PERDS, there was no association with demographics, type and stage of underlying disease, conditioning regimen, graft source, use of cytokines either for stem cell mobilization or after transplant, viral serologies, pretransplant pulmonary function, or laboratory values.[126]

The pathogenesis of PERDS is not well defined, but is believed to represent a complex interaction between conditioning-related endothelial damage and the cytokine release associated with neutrophil and lymphocyte recovery.[126] Tissue infiltration by neutrophils has been shown to occur earlier than their appearance in the peripheral blood.[136]

Clinical Findings

In 19 patients with PERDS, median duration from transplant to onset of symptoms or radiographic pulmonary infiltrates was 11 days (range, 4–25).[126] The median duration to neutrophil engraftment was also 11 days after transplant (range, 8–25). Symptoms and signs occurred within 5 days of neutrophil engraftment. Dyspnea was the initial symptom in all patients, and fever was present in 12 patients (63%).

Diagnostic Evaluation

PERDS is considered in the presence of fever (>38.3°C) and pulmonary injury with evidence of hypoxemia (Sa_{O_2} <90%) and/or pulmonary infiltrates on chest radiograph, in the absence of clinical cardiac dysfunction or infection, all occurring within 5 days of neutrophil engraftment (defined as absolute neutrophil count of more than 500/mL on consecutive days).[126] The median white blood cell count at the time of symptom onset is 1.3×10^9/L (range, 0.2–29.6) and the median neutrophil count is 0.7×10^9/L (range, 0.1–28.6). Chest radiographs show bilateral infiltrates in the majority. In one study, BAL was performed to exclude pulmonary infections, but in a more recent study, BAL was not performed if noninvasive evaluation was considered adequate.[12] Transbronchial lung biopsy cannot be performed safely in most HSCT recipients during the peri-engraftment period because of thrombocytopenia. Surgical lung biopsy may show diffuse alveolar damage, but is rarely necessary.[126]

Treatment

In the only study focusing on PERDS, 11 patients received high-dose corticosteroid therapy, including 5 of the 6 who required mechanical ventilation.[126] Ten patients experienced clinical improvement, which occurred within 24 hours in five cases, and over 2 to 4 days in the remainder. The rapid response to corticosteroid treatment and the fact that such a therapy was delayed until after intubation in all the mechanically ventilated patients suggested a therapeutic benefit. Among the eight patients who did not receive steroids, one required mechanical ventilation at the onset of symptoms, and subsequently died.[126] The other seven patients recovered and were discharged from the hospital. There was no correlation between gender, age, source of stem cells, mononuclear cell count of the graft, use of posttransplant growth factors, WBC at the onset of symptoms, rate of rise in WBC, amphotericin use, or the need for mechanical ventilation and posttransplant mortality.[126] The mean absolute neutrophil count was significantly higher among patients with evidence of alveolar hemorrhage by BAL. Unlike DAH and IPS, only about one-third of HSCT recipients with PERDS require ICU admission and mechanical ventilation.

■ ACUTE PULMONARY EDEMA

Acute pulmonary edema is common during the neutropenic phase and likely represents a combination of cardiogenic and noncardiogenic factors. Noncardiogenic pulmonary edema has many contributory factors including total-body radiation, induction drugs, and septic episodes. These factors likely damage the capillary endothelium, leading to radiographic findings similar to hydrostatic edema. Patients with hydrostatic pulmonary edema have often received high volumes of fluid for medications, total parenteral nutrition, and multiple blood product transfusions. The heart may also be compromised by chemotherapeutic agents such as Adriamycin and high-dose cyclophosphamide used during induction. In a recent study of 1243 autologous HSCT recipients, acute pulmonary edema was reported in 4.7%.[12] Patients develop weight gain and dyspnea, and bibasilar crackles. Radiographic findings of vascular and hilar indistinctness, symmetric ground-glass/consolidative opacities, enlarged heart, small pleural effusions, and subfissural thickening are typically seen. While pulmonary edema is usually diagnosed by plain chest radiograph, CT findings include prominent pulmonary vessels, interlobular septal thickening, ground-glass attenuation, and pleural effusions. Acute pulmonary edema usually can be prevented and treated with fluid restriction and diuretics.

IDIOPATHIC PNEUMONIA SYNDROME

Important aspects of the idiopathic pneumonia syndrome are considered below, including frequency, risk factors, clinical findings, treatment, and prognosis.

Frequency

The term IPS has been used for many years to describe lung injury without infectious etiology in HSCT recipients. In a 1985 review of pulmonary complications in 4500 HSCT recipients, Krowka et al. reported a 35% frequency of idiopathic pneumonia.[12,137] Another study from a major HSCT center found a rate of 7.3%.[138] The wide variation in the reported incidence of IPS was partly due to the lack of uniform definition and diagnostic criteria. Diagnostic criteria were addressed in 1993 by a workshop sponsored by the National Heart, Lung, and Blood Institute.[139] This workshop defined IPS as widespread alveolar injury in the absence of lower respiratory tract infection.[139] The definition has been updated recently.[140] The current criteria for IPS include evidence of widespread of alveolar injury, absence of active lower respiratory tract infection, and exclusion of cardiac dysfunction, renal failure, or fluid overload.[140] Based on data compiled from several studies of 4496 HSCT recipients, 449 cases of IPS (10%; range 2%–17%) were reported.[138,140–149]

Risk Factors

The probability of developing IPS increases with the number of risk factors.[148] Patients transplanted for aplastic anemia have low risk for IPS.[150] With the advent of prophylaxis for CMV infection, IPS has become a relatively more frequent cause of interstitial pneumonia.[151] Using multiple logistic regression analysis, Kantrow et al.[138] did not find significant difference in the rate of IPS between autologous and allogeneic HSCT recipients. However, a review of selected studies showed 36 of 617 autologous HSCT recipients (5.8%) developed IPS compared to 380 of 3569 allogeneic HSCT recipients (10.6%), a significant difference.[58]

Pathogenesis

Although the pathogenesis of IPS is not well defined, lung injury, inflammation, and cytokine release are implicated.[58] Pulmonary vascular endothelial cell damage, mediated by TNF-α, is linked to the development of experimental IPS.[140,152] Another potential mechanism is parenchymal damage from previous chemoradiation therapy, GVHD, undiagnosed infection, and excessive recruitment and activation of inflammatory cells.[138] The occurrence of IPS after autologous BMT suggests that the pretransplant conditioning regimens, rather than GVHD and CMV infection, are likely to be culprits.[153] Latent and unrecognized infections such as human herpes virus-6 (HHV-6) and systemic activation of inflammatory cytokines during sepsis may also be responsible for lung injury.[138,154–157] Cell-mediated immune injury during GVHD reactions is another possible mechanism.[138] Further, IPS may be the result of persistent proinflammatory events and oxidant responses.[158,159]

Clinical Findings

The median time of onset of IPS is 19 days, range 4 to 106 days, after transplant.[140] Despite the variable onset, the majority of patients present within the first 120 days following HSCT.[138,144] The clinical presentation of IPS includes dyspnea, dry cough, hypoxemia, and nonlobar radiographic infiltrates.[139] The spectrum is broad, ranging from acute respiratory failure to incidental radiographic abnormalities. Because IPS mimics infectious pneumonia, the majority of patients are on antibiotics at the time of diagnosis.

Diagnostic Evaluation

Clinical presentation and radiographic findings cannot be used to differentiate between patients with infectious and idiopathic pneumonia. Pulmonary function testing and computed tomography (CT) of the chest are also nonspecific.[138] More than 90% of patients with IPS have diffuse infiltrates on chest radiograph.[160] Based on the IPS criteria, PERDS and DAH are considered to be subsets of IPS. There is overlap between PERDS and DAH; however, the clinical course and response to corticosteroid therapy differ between these conditions.

Infection should be excluded before the diagnosis of IPS is made. In earlier studies, IPS was diagnosed histologically when biopsy or autopsy of lung tissue showed inflammation without any histological or microbiological evidence of infection.[144,149,150] In a study from Fred Hutchinson Cancer Research Center, 80% of IPS cases were diagnosed without tissue and with infection excluded by BAL, 4% required lung biopsy, and 16% were diagnosed at autopsy.[138] Although the NHLBI workshop accepted BAL as the main method for the exclusion of infection and the diagnosis of IPS, the limitations of this approach in excluding invasive fungus, neoplasms, and other abnormalities of potential therapeutic or prognostic importance are well recognized.[138] When pursued, lung biopsies of patients with IPS show diffuse alveolar damage, organizing or acute pneumonia, and interstitial lymphocytic inflammation.[138,143]

Treatment

There are scarce data addressing the treatment of IPS in HSCT recipients. One study reported three patients with IPS who responded to treatment, which included corticosteroids.[138,143] Despite treatment with methylprednisolone at 1 to 2 mg/kg/d, studies with larger sample sizes have not shown any outcome benefit.[138,160] There are reports of IPS responding to etanercept.[161–163] Currently, the only accepted treatments are supportive care, and prevention and treatment of infection. Lung transplant offers a potential therapeutic option for patients who develop respiratory failure despite treatment, but this option is limited to the rare circumstances of a patient without other comorbidities and for whom the transplant was considered curative to have definitively eradicated the underlying disease process.[120]

Prognosis

The clinical course of IPS is commonly complicated by infections, including viral and fungal pneumonias.[138,160] Other complications include pneumothorax, pneumomediastinum, subcutaneous emphysema, and pulmonary fibrosis. Autoimmune polyserositis involving the pleura and pericardium has also been reported.[164]

Patients often develop severe hypoxemia and require assisted ventilation.[165] In a review of selected studies, the overall mortality of 388 HSCT recipients with IPS was 74%, with a range of 60% to 86%.[138,144,148–150,160] The 1-year survival rate is less than 15%.[138,160] Infectious complications and nonpulmonary organ failure contribute to the high mortality rate.[138,160] For those who require mechanical ventilation, the hospital mortality may exceed 95%.[138]

DIFFUSE ALVEOLAR HEMORRHAGE

Although pulmonary infections can cause alveolar hemorrhage, the term DAH in the HSCT recipient is reserved for alveolar hemorrhage of noninfectious etiology.

Frequency

The frequency of DAH has varied among reported series because of differences in patient mix and diagnostic criteria.[166] Factors that influence the incidence of DAH have changed over time and among HSCT centers. In a review of several studies that included 3806 HSCT recipients, the cumulative frequency of DAH was 5%, ranging from 2% to 14% in the individual series.[166] Among 692 HSCT recipients who underwent bronchoscopy, DAH was reported in 97 (14%), with a range between 1% and 23%.[126,167–173] In patients admitted to the intensive care unit for respiratory failure, the prevalence of DAH may exceed 40%.[174,175] DAH has been reported in approximately 10% of autopsies of HSCT recipients.[16,17]

Risk Factors

Pretransplant chemotherapy and conditioning regimen, total-body irradiation, thoracic irradiation, and older age are associated with DAH.[9,153,176–179] There are conflicting data regarding solid tumors as a risk factor for DAH.[166,180,181] Although DAH occurs in both autologous and allogeneic HSCT recipients, the initial studies included mostly autologous recipients.[153] In data from several reports, however, no significant difference was found in the incidence of DAH between autologous and allogeneic HSCT recipients.[166] Pulmonary function tests have shown no association between the development of DAH and pretransplant PFTs.[153] Pretransplant bronchoscopy has shown a higher number of bronchial neutrophils and eosinophils in patients who develop DAH after HSCT compared with those who do not.[182] White blood cell recovery and renal insufficiency, but not prolonged prothrombin, partial thromboplastin time, or low platelets, are associated with the development of DAH.[9,153] Although most patients with DAH have thrombocytopenia, DAH is not corrected by platelet transfusion.[153]

Pathogenesis

Various conditions, including infections, mitral valve disease, systemic vasculitides, collagen vascular diseases, drugs, and anticoagulation have been implicated as causing alveolar hemorrhage in non-HSCT recipients. The etiology and pathogenesis of DAH in the HSCT recipient have not been clearly established. Lung tissue injury, inflammation, and cytokine release are implicated.[166]

Pretransplant high-dose chemotherapy, thoracic or total-body radiation, and undocumented infections may be responsible for the initial injury to lung tissue. Vascular endothelial swelling and thrombi are found in the autopsies of HSCT recipients with acute hemorrhagic pulmonary edema.[183] The incidence of pulmonary hemorrhage is high in HSCT recipients with GVHD.[179] In addition to the toxicity from therapy for GVHD, antigen-specific injury to endothelium may be a contributing factor to the development of DAH.[184]

Vasculopathy of small muscular arteries and thrombotic microangiopathy have been reported in HSCT recipients with DAH.[185] The vasculopathy manifests as concentric intimal or medial hyperplasia with luminal narrowing, prominent myxoid change, extravasated red blood cells, and the presence of foamy histiocytes. Thrombotic microangiopathy has also been associated with DAH, characterized by fragmented erythrocytes on peripheral smears, decreased hemoglobin and platelet counts, refractoriness to platelet transfusions, and the absence of disseminated intravascular coagulation.[185]

Inflammatory cells are likely to play a role in the development of DAH, and models are characterized by increase in the alveolar leukocytes, platelet microthrombi, damage of alveolar endothelial and epithelial cells, increased turnover rate of alveolar cells, and an increase in the cell number and protein content of the BAL.[186] Pretransplant bronchoscopy has shown increased bronchial inflammatory cells in patients who develop DAH after HSCT, suggesting that bronchial inflammation precedes alveolar inflammation.[182,187] The initial injury is compounded by damage related to the return of inflammatory cells to the lung coincident with marrow recovery.[188] Even in the presence of peripheral leukopenia, neutrophils are seen in the lower respiratory tract of HSCT recipients at the time of DAH.[166] One-third of autologous HSCT recipients with PERDS have DAH.[126] Among the patients with PERDS, those with DAH have higher absolute neutrophil counts than those without DAH.

In allogeneic transplants, donor T cells react to host alloantigens, proliferate, and secrete inflammatory mediators. This response may be amplified by the release of endotoxin from the gut after injury from mucositis or GVHD. It is suggested that the pathophysiology of acute GVHD is a cytokine storm of inflammatory mediators.[189] In autologous HSCT recipients, the generation of cytokines is self-limited and resolves in 7 to 10 days.[189] Despite the more profound release of cytokines in allogeneic HSCT recipients, the frequency of DAH is similar between allogeneic and autologous groups. This may be due to the protective effect of the immunosuppressive agents used for prophylaxis of GVHD in the allogeneic group.

Clinical Findings

The onset of DAH is usually within the first 30 (median between 11 and 19) days after HSCT.[166] However, cases of DAH after the first month of transplant are not uncommon.[179] HSCT recipients with DAH often have dyspnea and dry cough.[153] Although coexistent sepsis and mucositis may obscure the clinical picture, fever is a common finding.[166] Hemoptysis is relatively rare.[9,190] None of 29 patients had hemoptysis in the study by Robbins et al.[153]

Diagnostic Evaluation

DAH is a syndrome with nonspecific clinical and radiological features. Although pulmonary infections can cause alveolar hemorrhage, the term DAH in the HSCT recipient is reserved for alveolar hemorrhage of noninfectious etiology. DAH should be distinguished from localized bleeding caused by bronchitis, bronchiectasis, tumors, or infections. The diagnostic criteria of DAH in the HSCT recipient are (1) evidence of widespread alveolar injury manifested by multilobar pulmonary infiltrates, symptoms and signs of pneumonia, and abnormal pulmonary physiology with increased alveolar to arterial oxygen gradient and restrictive ventilatory defect; (2) absence of infection compatible with the diagnosis; and (3) BAL showing progressively bloodier return from three separate subsegmental bronchi, the presence of 20% or more hemosiderin-laden macrophages in BAL, or the presence of blood in at least 30% of the alveolar surfaces of lung tissue.[166]

Chest radiograph shows diffuse interstitial and alveolar infiltrates, primarily central, and involving predominantly lower and middle lung zones.[191] The earliest radiographic manifestation is the presence of bilateral fine reticular opacities. In the later phase of DAH, 70% of patients develop an alveolar pattern, and the interstitial pattern persists in 30%. Although chest CT may be helpful in patients in whom a focal source of bleeding is suspected, chest CT has a limited role in DAH. The most common CT finding is bilateral ground-glass attenuation or consolidation.[192]

Treatment

Because the pathogenesis of DAH is considered to be an inflammatory response, and based on anecdotal and retrospective studies, HSCT recipients with DAH are treated with systemic corticosteroids.[178,188,193] There are no prospective, randomized clinical trials addressing the treatment of DAH in HSCT recipients. In a retrospective study, Metcalf et al.[188] compared three groups: No corticosteroids, daily methylprednisolone of 30 mg or less, and daily methylprednisolone of more than 30 mg. The mortality rate was lower and fewer patients required invasive mechanical ventilation in the high-dose methylprednisolone group. The high-dose methylprednisolone group received 125 to 250 mg every 6 hours for the first 4 to 5 days, tapered over 2 to 4 weeks. Low-dose methylprednisolone was similar to no steroid therapy. In another study of 15 HSCT recipients with DAH treated with 250 mg to 2 g/d of methylprednisolone, transient clinical improvement was seen in 10 patients; however, the overall mortality of 74% was not significantly different from previous reports.[194]

Although many HSCT recipients may die from other complications, most patients with DAH improve in response to corticosteroid therapy.[166] The dose and duration of corticosteroids are not well standardized. Although immunosuppressive therapy, plasma exchange, and plasmapheresis have been tried in other populations,

there is no evidence to justify their use in HSCT recipients. Fresh frozen plasma transfusion and plasmapheresis yielded inconclusive results in one study.[185] There are reports of allogeneic HSCT recipients with DAH successfully treated with recombinant factor VIIa.[195–197]

Prognosis

DAH is a major complication of HSCT, contributing significantly to morbidity and mortality. The majority of HSCT recipients with DAH require mechanical ventilator support for respiratory failure.[166] HSCT recipients with DAH are at high risk for infectious complications. The reported mortality rate of DAH in HSCT recipients is approximately 80%, with a range between 64% and 100%.[166] Although the initial presentation of DAH in HSCT recipients may be respiratory failure, the most common causes of death are multiple organ failure and sepsis. Respiratory failure with active pulmonary hemorrhage is responsible for fewer than 15% of the deaths. Despite the high mortality rate, long-term survivors of HSCT recipients with DAH can manifest normal pulmonary function.

■ CRYPTOGENIC ORGANIZING PNEUMONIA

Idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) had been widely recognized since Epler introduced the term in 1985.[198] The American Thoracic Society/European Respiratory Society recommended replacing BOOP with COP since it better describes the essential features of the syndrome.[199] COP is characterized by organizing pneumonia in the alveolar ducts and alveoli, with or without bronchiolar involvement.[199] It has clinical features more consistent with pneumonia than airway disease. COP in HSCT patients was first reported in the early 1990s.[200,201] The literature in HSCT recipients is limited to case series, with a maximum of seven patients.[10–12,22,62,85,200–209] Risk factors for COP are not well described, although GVHD may play a role.[202,206,208]

Pathogenesis

The occurrence of COP almost exclusively in allogeneic HSCT recipients with GVHD suggests that it may represent alloimmune-mediated injury to the lung by the transplanted stem cell.[202] In one study of three HSCT recipients with COP, the exhaled nitric oxide level was increased and then declined following improvement.[210] There is also a report suggesting that HLA-B35 may be an important host factor.[211]

Clinical Findings

Most HSCT recipients with COP have GVHD.[85,202,209] However, COP has been reported in allogeneic HSCT recipients in the absence of clinical GVHD.[200,212] The presenting symptoms include dry cough, dyspnea, and fever.[200–202,206] Some patients may present with respiratory failure.[208] The reported onset of COP is between 1 and 13 months following transplant.[85,200–202,205,207,209,212,213] One allogeneic recipient with asymptomatic COP was reported.[85] Physical examination may reveal inspiratory crackles.

Diagnostic Evaluation

COP should be included in the differential diagnosis of bilateral airspace disease in HSCT recipients, especially if they do not respond to antibiotics for presumed pneumonia. Pulmonary function tests usually show restrictive defect, decreased D_{LCO}, and normal airflow.[198,201,202] Arterial blood gases show mild hypoxemia.[202] Chest radiographs and CT show patchy air space consolidation, ground-glass attenuation, and nodular opacities.[86,192,200–203,214] The radiographic abnormalities usually have peripheral distribution.[215] In the appropriate clinical setting, chest CT findings may suggest the diagnosis of COP. However, confirmation requires lung biopsy. Although the diagnosis of COP in the HSCT recipient can be made with transbronchial lung biopsy, about 85% of cases require surgical lung biopsy.[202] Histological confirmation of the diagnosis is desirable as therapy with corticosteroids is usually needed for several months. The histological hallmark of COP is the presence of patchy intraluminal fibrosis, consisting of polypoid plugs of immature fibroblast tissue resembling granulation tissue.[216]

Treatment

Corticosteroid therapy is typically given to HSCT recipients with COP, and about 80% respond favorably.[85,200–202,205,207,209,213] The duration and dosage of corticosteroid therapy have not been clearly defined, but radiographic abnormalities usually clear within 1 to 3 months of initiating corticosteroids.[200,202,207] Based on the experience from non-HSCT recipients with COP, the initial dose of corticosteroid therapy is prednisone 0.75 to 1.5 mg/kg/d, up to 100 mg, or its equivalent, for 1 to 3 months, followed by lower doses for a total duration of 6 to 12 months.[217] There is a report of erythromycin in conjunction with corticosteroid used successfully to treat COP in HSCT recipients.[205]

Prognosis

COP in HSCT recipients appears to have a worse prognosis than idiopathic COP. Alasaly et al.[202] found a case fatality rate of 40% in allogeneic HSCT recipients compared to 21% in idiopathic COP. Among 19 reported HSCT recipients with COP, the overall case fatality was 21%.[85,200–202,205,207,209,212,213]

■ DELAYED PULMONARY TOXICITY SYNDROME

Delayed pulmonary toxicity syndrome (DPTS), characterized by interstitial pneumonitis and fibrosis, with clinical presentation delayed for months to years, was described in autologous HSCT recipients with breast cancer who had received high-dose chemotherapy.[218,219] Glutathione depletion with impaired antioxidant defense due to cyclophosphamide and carmustine (BCNU) was implicated in the pathogenesis.[220] The high incidence, low mortality, and good response to corticosteroid treatment distinguish this syndrome from IPS.[219] It developed in about 72% of autologous HSCT recipients who received high-dose chemotherapy for breast cancer.[218] Presentation with cough, dyspnea, fever, and hypoxemia occurred at a median of 45 days after high-dose chemotherapy.[218–221] The D_{LCO} declined to a nadir 15 to 18 weeks following the chemotherapy/transplant.[219] CT scans of 13 patients demonstrated scattered, predominantly peripheral ground-glass or consolidated opacities that occasionally looked nodular or mass-like.[222] Treatment with corticosteroid usually improves lung function in DPTS, and no death has been attributed directly to the syndrome.[218,219] Interferon-γ has been used with improvement in one patient refractory to corticosteroid therapy.[223] Prophylactic treatment with inhaled fluticasone propionate, 880 mg every 24 hours for 12 weeks beginning on the day of starting BCNU-containing conditioning regimen, decreased the incidence of DPTS compared to historical controls.[224] Since the abandonment of HSCT for breast cancer, the frequency of DPTS has declined.

■ PULMONARY CYTOLYTIC THROMBI

Pulmonary cytolytic thrombi (PCT) is a recently described noninfectious pulmonary complication of HSCT recipients.[225,226] PCT occurs almost exclusively in children with acute or chronic GVHD and is characterized by fever and pulmonary nodules. The time of onset ranges from 8 to 343 days (median 72) after transplant.[226] Patients are febrile and some have cough at presentation, but dyspnea has not been noted. Chest radiographs may be normal in 25%. Abnormal chest radiographic findings include nodules, interstitial prominence and atelectasis. Chest CT shows multiple peripheral

pulmonary nodules, ranging from a few millimeters to 4 cm in size.[225–228] BAL is used to exclude infection. Because of the peripheral and intravascular location of the nodules, transbronchial lung biopsy is unlikely to yield a diagnosis. Among 33 HSCT recipients who underwent open lung biopsy for nodular pulmonary lesions, 15 (45%) had PCT.[228] Biopsy of the pulmonary nodules shows a unique pattern of necrotic, basophilic thromboemboli with amorphous material suggestive of cellular breakdown products.[227,229] Most of the patients with PCT improve clinically within 1 to 2 weeks, and radiographically over weeks to months.[226] There have been no reported deaths attributed to PCT. In one study, 9 of the 13 HSCT recipients with PCT were alive at a median follow-up of 1.5 years.[226] All patients received broad-spectrum antibiotics and nine were treated with systemic corticosteroids.[226]

■ OTHER CONDITIONS

Several additional important noninfectious disorders in HSCT are described below.

Pulmonary Venoocclusive Disease

Pulmonary venoocclusive disease (PVOD) is clinically suspected by the presence of pulmonary arterial hypertension, radiographic evidence of pulmonary edema, and normal pulmonary artery occlusion pressure. However, a definite diagnosis requires lung biopsy. The incidence of PVOD in HSCT recipients is not known. In one study, PVOD was reported in one of five HSCT recipients at autopsy.[230] However, no case of PVOD was identified in a recent autopsy of 71 adult HSCT recipients.[17] Approximately 29 HSCT recipients with PVOD have been reported in the literature.[48,231] Most underwent transplant for hematological malignancy, and only two of the 29 patients with PVOD had autologous grafts. Endothelial damage may be responsible for the pathophysiology of PVOD.[232] There is no proven therapy for PVOD; vasodilator agents may be introduced with caution but carry an associated risk of precipitating pulmonary edema.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis is characterized by excessive accumulation of surfactant lipoprotein in the alveoli, leading to abnormal gas exchange.[233] It is diagnosed by the presence of periodic acid-Schiff proteinaceous material in BAL fluid. Pulmonary alveolar proteinosis in HSCT recipients is limited to case reports.[17,234–236] Chest radiographs show diffuse infiltrates. The roles of whole lung lavage and aerosolized granulocyte macrophage colony–stimulating factor, therapies employed in the primary form of pulmonary alveolar proteinosis, are unknown in the secondary form seen in HSCT recipients.

Chronic Eosinophilic Pneumonia

There are fewer than 10 case reports of chronic eosinophilic pneumonia in HSCT recipients.[237–240] It occurs in both allogeneic and autologous recipients. Despite good response to steroid therapy in most, one patient had a fatal course.[239]

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a clinical syndrome characterized by bilateral noncardiogenic pulmonary edema in association with transfusions of blood products. It has been reported following the infusion of allogeneic hematopoietic stem cells during HSCT.[241–243]

Sarcoidosis

Sarcoidosis is uncommon in HSCT recipients. The first reported HSCT recipients with sarcoidosis received stem cells from donors with sarcoidosis.[244] One study reported sarcoidosis in autologous HSCT recipients and allogeneic recipients who received stem cells from donors without sarcoidosis.[245]

SOLID ORGAN TRANSPLANTATION

The era of human solid organ transplantation was inaugurated a half century ago when a kidney harvested from a healthy donor was implanted into the body of his identical twin brother suffering from renal failure. Over the ensuing decades, organ transplantation has evolved to include not only kidney but also heart, liver, lung, intestine, and pancreas replacement. While offering extended survival and enhanced quality of life to many patients with lethal or debilitating conditions, these procedures are accompanied by a multitude of complications. The lungs are particularly vulnerable, subject to the immediate effects of the transplant surgery as well as the infectious, neoplastic, and toxic consequences of the immunosuppressive agents required to maintain the health of the allograft.

This section will focus on noninfectious complications associated with the three most commonly performed solid organ transplant procedures—heart, kidney, and liver transplantation. Noninfectious complications in lung transplant recipients are discussed in Chapter 107 (Lung Transplantation) and infectious complications in immunocompromised hosts, including solid organ transplant recipients, are discussed in Chapter 123 (Pulmonary Infections in the Immunocompromised Host).

■ PERIOPERATIVE COMPLICATIONS

Important perioperative complications seen in liver, heart, and kidney transplantation are considered below.

Liver Transplantation

Ventilatory support beyond 24 hours is required by approximately 10% of recipients immediately following liver transplantation.[246] For those who are successfully extubated, reintubation at some point in the perioperative period occurs in one-third of patients who had initially required greater than 24 hours of ventilatory support and 10% of those initially ventilated for less than 24 hours.[246,247] Both postoperative respiratory failure and the need for reintubation are associated with significantly poorer survival.[247,248]

A number of factors contribute to respiratory failure, including impaired respiratory muscle function from extensive upper abdominal surgery, malnutrition, and debility; marked intravascular volume shifts and volume overload; aggressive blood product support; and a relatively high frequency of postoperative pneumonia. In addition, patients undergoing liver transplantation are often critically ill at the time of transplantation and it is not unusual for patients to have been supported on mechanical ventilation for varying periods of time prior to transplantation. In one study employing multivariate analysis, preoperative risk factors independently associated with an increased risk of postoperative respiratory failure following liver transplantation were diabetes mellitus, impaired renal function, preoperative ventilator support, use of a molecular adsorbent recycling system as an artificial liver support strategy, and deceased donor liver transplantation.[248]

Acute respiratory distress syndrome (ARDS) is a particularly lethal cause of postoperative respiratory failure following liver transplantation. The reported incidence ranges from 4% to 16%, with a mortality rate as high as 80% to 100%.[249] Sepsis is the most common risk factor reported but other potential risk factors include massive blood transfusions, TRALI, aspiration, and the use of OKT3 antilymphocyte therapy. Recipients with fulminant hepatic failure prior to transplantation are predisposed to noncardiogenic pulmonary edema as a component of their liver failure.

Hepatopulmonary syndrome and portopulmonary hypertension are two pulmonary complications of advanced liver disease. Although their onset precedes liver transplantation, these disorders do not immediately or invariably correct following this intervention and they can therefore contribute significantly to morbidity and mortality intraoperatively and in the early postoperative period.

Hepatopulmonary syndrome is defined as the triad of liver disease, arterial hypoxemia, and abnormal intrapulmonary vascular dilatation. The vast majority of cases involve diffuse dilatation of the pulmonary microvasculature at the precapillary and capillary levels. Rarely, discrete macroscopic arteriovenous communications are present. Proof of the presence of intrapulmonary vascular abnormalities is provided by demonstration of systemic uptake of technetium-labeled macroaggregated albumin on radionuclide perfusion imaging or the delayed appearance of bubbles in the left atrium by contrast echocardiography. Diffuse microvascular dilatation is postulated to cause hypoxemia by increasing the distance through which oxygen must diffuse and thereby creating a central stream of inadequately oxygenated red cells. Unlike a true shunt, this process can be partially corrected with administration of 100% oxygen, which serves to increase the pressure gradient favoring transfer of oxygen from the alveolus to the bloodstream. An unusual feature of hepatopulmonary syndrome is the tendency for oxygenation to worsen in the erect as opposed to supine position (orthodeoxia), presumably due to basilar predominance of the vascular abnormalities.

Although hepatopulmonary syndrome was once considered an absolute contraindication to liver transplantation, subsequent demonstration of its resolution following transplantation led to the reversal of this stance. Indeed, liver transplant candidates with severe hepatopulmonary syndrome (Pa_{O_2} <60 mm Hg on room air) are granted additional model for end-stage liver disease (MELD) points and thus receive enhanced priority with regard to organ allocation. Nonetheless, because hypoxemia often does not correct immediately and may in fact dramatically worsen in the early postoperative period, excessive morbidity and mortality was observed among these patients. In a review of 13 published reports encompassing 81 patients with hepatopulmonary syndrome who underwent liver transplantation prior to 1997, refractory hypoxemia contributed significantly to the observed 16% perioperative mortality, and 21% of survivors required prolonged mechanical ventilatory support.[250] In contrast, a more recent report of 21 patients with hepatopulmonary syndrome who underwent liver transplantation between 2002 and 2008 documented a perioperative survival rate of 100% and 1-year survival rate of 93%.[251] Notably, 5 of the 21 patients required prolonged postoperative administration of 100% inspired oxygen for persistent severe hypoxemia. The vast majority of patients who survive to hospital discharge ultimately achieve normal room air oxygen levels, most by 6 months following transplantation.[251] Late recurrence of hepatopulmonary syndrome coincident with deteriorating allograft function has been reported.[250]

Attempts to identify factors predictive of posttransplantation outcome in patients with hepatopulmonary syndrome have yielded conflicting results. Arguedas et al.[252] found that a preoperative arterial oxygen tension on room air of less than or equal to 50 mm Hg and an extrapulmonary shunt fraction of greater than or equal to 20% (calculated based on uptake of tracer in the brain on macroaggregated albumin scintigraphy), each were strong predictors of posttransplant mortality, with positive predictive values of 67% and 64% and negative predictive values of 93% and 100%, respectively. In contrast, Taille et al.[253] were unable to discern any significant relationship between these parameters and postoperative mortality, though they did find a correlation between the magnitude of preoperative hypoxemia and the length of time to achieve a normal oxygen level posttransplantation.

Postoperative care of the patient with persistent hypoxemia due to hepatopulmonary syndrome centers on the administration of supplemental oxygen while awaiting resolution of the disorder. Based on the positional nature of hypoxemia discussed earlier, one group reported improvement in oxygenation in a patient with use of the Trendelenburg position.[254] With the demonstration that nitric oxide is an important mediator of the abnormal vascular dilatation that characterizes hepatopulmonary syndrome, attention has turned to the potential therapeutic role of inhibitors of nitric oxide in treating hypoxemia.[255] Schenk et al.[256] described significant improvement in oxygenation and shunt fraction for up to 10 hours after administration of a single dose of methylene blue to seven patients with advanced cirrhosis and hepatopulmonary syndrome. Brussino et al.[257] administered nebulized N(G)-nitro-L-arginine methyl ester – an inhibitor of nitric oxide synthesis – to a single patient with hepatopulmonary syndrome and demonstrated a marked rise in arterial oxygen tension and a dramatic reduction in the magnitude of bubbles appearing in the left atrium on contrast echocardiography. Although these preliminary observations are promising, additional corroborating studies are necessary before the widespread clinical use of these agents can be recommended. In the rare instances in which discrete arteriovenous malformations are present, coil embolization can be an effective treatment strategy.[258]

Portopulmonary hypertension describes the development of pulmonary hypertension in patients with advanced liver disease and portal hypertension. The diagnosis rests on demonstration of a mean pulmonary artery pressure exceeding 25 mm Hg and a normal pulmonary capillary wedge pressure. Some authors also include the criterion of a pulmonary vascular resistance exceeding 120 dyn • sec/cm^5 to distinguish this syndrome from the more benign and common finding of elevated pulmonary pressures due solely to increased cardiac output. Histologically, the abnormalities in the pulmonary vascular bed are identical to those seen in primary pulmonary hypertension: Medial hypertrophy, intimal fibrosis, and plexiform lesions. While a mechanistic link has yet to be defined, the observation that the prevalence of pulmonary hypertension in patients with liver disease exceeds that of the general population suggests that there is a connection. Portopulmonary hypertension is encountered in 1% to 2% of patients with chronic liver disease and in up to 12.5% of patients referred for liver transplant evaluation.[259]

Although mild pulmonary hypertension does not appear to adversely impact liver transplantation, more significant elevations in pressure are associated with excessive posttransplantation mortality. A retrospective review from the Mayo Clinic and a subsequent multicenter database documented perioperative mortality rates of 0% to 17% among liver transplant recipients with a preoperative mean pulmonary artery pressure below 35 mm Hg. In contrast, perioperative mortality rates were 35% to 40% for patients with a mean pulmonary artery pressure of 35 to 50 mm Hg and 40% to 100% for those with a mean pulmonary artery pressure exceeding 50 mm Hg.[260,261] Most deaths occur intraoperatively or in the immediate postoperative period and are largely attributable to progressive right heart failure and hemodynamic collapse.

Several case series document successful transplantation of patients with severe portopulmonary hypertension who responded favorably to the preoperative initiation of vasodilator agents.[262–264] For such patients, intravenous or inhaled epoprostenol should be employed in the perioperative period. Since pulmonary hypertension tends to persist despite transplantation, these patients frequently require long-term therapy but can often be transitioned to oral vasodilator agents.

Heart Transplantation

Heart transplant recipients are subject to the same generic perioperative pulmonary complications encountered in the general cardiac surgical population. These include atelectasis, pulmonary edema, pleural effusions, and mediastinitis. The risk of respiratory failure and acute lung injury following heart transplantation is relatively low. In a series of 157 consecutive heart transplant procedures, prolonged respiratory failure requiring tracheostomy was reported

in only 7 cases (4.4%); 5 of the 7 cases occurred within the first 6 months following transplantation.[265]

Kidney Transplantation

Kidney transplantation is carried out with relatively few perioperative pulmonary complications, reflecting the use of a lower abdominal incision and the comparatively good health of the recipients. The vast majority of patients are extubated in the operating room. Perioperative respiratory failure was documented in 4% of 178 kidney transplant recipients from the University of Pittsburgh.[266] The most common noninfectious pulmonary complication is hydrostatic pulmonary edema due to impaired salt and water excretion in the setting of early allograft dysfunction or rejection. ARDS, on the other hand, occurs infrequently. In a retrospective review of a national kidney transplant database encompassing over 42,000 transplants, ARDS was documented in only 86 patients (0.2%) and only 1 of these cases occurred within the perioperative period.[267]

■ PLEURAL EFFUSIONS IN LIVER TRANSPLANTATION

Postoperative pleural effusions are present in 40% to 100% of liver transplant recipients.[268,269] Effusions are transudative and are typically right-sided or bilateral but are rarely exclusively on the left. Disruption of diaphragmatic lymphatics during hepatectomy is postulated to be the principal mechanism of fluid accumulation. Other contributing mechanisms include volume overload, hypoalbuminemia, and atelectasis. Effusions may enlarge over the first postoperative week but typically resolve by the third week. The need for drainage because of perceived respiratory compromise has been reported in up to 31% of patients.[249,268,269] Effusions that continue to enlarge beyond the first week, persist beyond 3 weeks, or involve only the left hemithorax should be sampled to rule out other causes. Persistent or enlarging effusions should also prompt consideration of subdiaphragmatic processes including hematoma, biloma, or subphrenic abscess.

■ DIAPHRAGMATIC DISORDERS

Disorders of the diaphragm may be seen following liver or heart transplantation. They are discussed briefly below.

Liver Transplantation

Right-sided diaphragmatic dysfunction following liver transplantation is postulated to result from crush injury to the right phrenic nerve by the suprahepatic vena caval clamp placed during surgery. In one older series of 48 patients, evidence of delayed or absent right-sided phrenic nerve conduction was found in 79% of patients while the left phrenic conducted normally in all cases.[270] In 38% of patients, there was associated right diaphragmatic paralysis documented by ultrasound. Phrenic nerve injury was not associated with increased duration of mechanical ventilatory support or hospital stay. In a subset of patients followed with serial testing, abnormalities in phrenic nerve conduction and diaphragmatic excursion normalized by 9 months after surgery. Newer surgical approaches have been introduced that preserve the suprahepatic inferior vena cava, thereby minimizing the risk of phrenic nerve injury.

Heart Transplantation

Diaphragmatic dysfunction due to phrenic nerve injury occurs in up to 12% of heart transplant recipients.[271] The right phrenic nerve is most prone to injury. Diaphragmatic dysfunction has been associated with an increased risk of postoperative pneumonia and a trend toward increased length of intubation.

Diaphragmatic hernias have been reported in heart transplant recipients who had left ventricular assist devices (LVADs) implanted prior to transplantation. These devices are placed either preperitoneally or intraperitoneally in the left upper quadrant. The inflow cannula penetrates the left hemidiaphragm and attaches to the left ventricle while the outflow cannula emerges from the ascending aorta and crosses anterior to the diaphragm near the midline. At the time of heart transplantation, the LVAD is explanted and the left-sided diaphragmatic defect is routinely repaired. However, repair of the anterior diaphragmatic defect is not necessarily standard practice, as it has been reasoned this would add to the operative time and that midline scarring would naturally close the rent. The incidence of diaphragmatic hernias has been reported to be as high as 16% among heart transplant recipients in whom closure of the anterior midline diaphragmatic defect was not performed, and in all cases the hernia arose at the site of the unrepaired midline defect.[272] In contrast, only 4% to 5% of patients experienced this complication when the surgical procedure was modified to include routine closure of the anterior defect at the time of LVAD explantation.[272,273] Patients with diaphragmatic hernias can be entirely asymptomatic, experience subacute gastrointestinal symptoms (abdominal pain, nausea, vomiting), or present emergently with colonic incarceration. Chest radiographs can be nonspecific, demonstrating only an ill-defined opacity at the base of the right or left lung. More suggestive findings include the presence of air within the opacity or actual visualization of colonic haustra. The diagnosis can usually be established definitively with CT of the chest and abdomen, after administration of oral contrast. Surgical repair, either via conventional laparotomy or performed laparoscopically, is indicated even in asymptomatic cases because of risk of incarceration.

■ NEOPLASTIC DISORDERS

Posttransplant lymphoproliferative disorder (PTLD) is second only to nonmelanoma skin cancers as a leading neoplastic complication of organ transplantation. PTLD encompasses a spectrum of abnormal B-cell–proliferative responses ranging from benign polyclonal hyperplasia to malignant lymphomas. Epstein–Barr virus (EBV) has been identified as the stimulus for B-cell proliferation, which proceeds in an unchecked fashion due to the inadequate cytotoxic T-cell response in the immunosuppressed host. EBV-naïve recipients who acquire primary infection at the time of organ transplantation are at greatest risk of developing PTLD. A higher intensity of immunosuppression and, in particular, the use of antilymphocyte antibody preparations have also been implicated as risk factors. Likely reflecting differences in the magnitude of immunosuppression employed, the incidence of PTLD is only 1% to 2% among kidney and liver transplant recipients but is in the range of 5% to 7% among heart transplant recipients.[274,275] The incidence is greatest within the first year posttransplantation. Among the nonlung organ transplant populations, heart transplant recipients are the most likely to present with intrathoracic involvement, which typically assumes the form of one or multiple pulmonary nodules occasionally accompanied by regional adenopathy or pleural effusions.

Initial treatment involves reduction in the level of immunosuppression to permit partial restoration of host cellular immunity. Such a strategy can lead to regression of tumor in up to two-thirds of solid organ recipients but carries the risk of precipitating acute or chronic allograft rejection.[276] For patients who fail to achieve a complete remission, cannot tolerate reduced immunosuppression, or have widespread disease, immunotherapy with anti-CD20 monoclonal antibodies (rituximab) is the preferred option. Experience with standard chemotherapy has been poor due to the high risk of infection during periods of neutropenia.

The mortality rate attributable to PTLD is not well defined. In multivariate analysis, increased age, elevated lactate dehydrogenase levels, severe organ dysfunction, presence of B symptoms, and multiorgan involvement are independent markers of poor prognosis.[276]

Other malignancies occasionally present in the lungs following transplantation. Bronchogenic carcinoma develops in 2% to 4% of heart transplant recipients.[277] It is unclear whether the development of

lung cancer in the heart transplant population reflects an increased risk or simply represents the expected occurrence rate in a population with a high prevalence of cigarette smoking. Among liver transplant recipients with a pretransplantation history of hepatocellular carcinoma, the lung is the most common site of recurrence. Recurrence usually occurs within 2 years of transplantation and appears radiographically as single or multiple lung nodules. An elevated α-fetoprotein level provides an important clue to the possibility of recurrent disease.

DRUG-INDUCED LUNG DISEASE

Sirolimus, also known as rapamycin, is a potent immunosuppressive agent recently introduced into clinical practice. Since its release, numerous cases of interstitial pneumonitis developing in association with sirolimus administration have been reported.[278,279] The incidence of this complication remains unknown. Initial reports suggested that interstitial pneumonitis was largely a result of excessive sirolimus blood concentrations but more recent reports describe this complication in the setting of therapeutic drug levels.[279,280] Patients typically present with dry cough, progressive dyspnea, fatigue, and weakness; fever and hemoptysis are less commonly present. Radiographic abnormalities include interstitial infiltrates, alveolar consolidation, and nodular opacities. BAL reveals evidence of a lymphocytic alveolitis and, less commonly, of alveolar hemorrhage. Reported findings on transbronchial lung biopsies include bronchiolitis obliterans with organizing pneumonia, interstitial lymphocytic infiltrates, and nonnecrotizing granulomas. Discontinuation of the drug may be sufficient treatment in many cases; corticosteroids have been given to hasten resolution but support for this approach is anecdotal. Conversion from sirolimus to everolimus, an agent that shares similar biochemical features and mechanism of action, has led to resolution of pneumonitis in some cases[281,282] but reports of everolimus-induced pneumonitis have also recently appeared.[283–285]

The murine monoclonal anti-CD3 antibody OKT3 was commonly used in the past for induction immunosuppression and treatment of refractory acute rejection. This agent is associated with a "cytokine release syndrome" that is most pronounced with the first dose and that clinically presents with fever, rigors, nausea, hypotension, and dyspnea. A small number of patients have been reported to develop noncardiogenic pulmonary edema, which rarely can be fatal. Because of its toxicity and the availability of alternative agents, the use of OKT3 has diminished in recent years. The interleukin-2 receptor antagonists basiliximab and daclizumab are being used with increasing frequency as induction agents, in part because of a generally favorable side-effect profile. However, several cases of noncardiogenic pulmonary edema in renal transplant recipients have been reported in association with basiliximab infusion.[286]

PULMONARY METASTATIC CALCIFICATION

Deposition of calcium in the lung parenchyma and other organs is a well-documented complication of chronic renal failure and is postulated to relate to alterations in calcium and phosphate balance and parathyroid hormone secretion.[287] Although renal transplantation should have a mitigating effect, pulmonary metastatic calcification rarely may progress despite successful transplantation[288,289] and may accelerate in association with graft failure.[290,291] Pulmonary metastatic calcification has also been described in liver transplant recipients, with a reported incidence in two series of 5.2% and 47%.[292,293] Renal insufficiency was a common but not universal feature in these patients. Secondary hyperparathyroidism, due to transient hypocalcemia induced by large volume infusion of citrate-containing blood products and, when present, to renal insufficiency, has been offered as a possible mechanism.[293]

Metastatic pulmonary calcification is most often clinically silent but rarely may lead to restrictive lung disease or fulminant respiratory failure.[290,291,294] The major import of this disorder lies in its ability to radiographically mimic more ominous processes such as infection or malignancy. Single or multiple nodular opacities or areas of alveolar consolidation are seen on plain chest radiographs but calcification of these lesions may not be apparent. CT findings include multiple diffuse calcified nodules, diffuse or patchy areas of ground-glass opacity or consolidation, and confluent high-attenuation parenchymal consolidation.[295] The abnormalities are typically most pronounced in the upper lung zones. Calcification is evident by CT in approximately 60% of cases. In the absence of calcification, the demonstration of high-attenuation (>100 HU) parenchymal opacities by CT scan or of increased uptake of tracer in the lung by technetium bone scintigraphy is helpful in establishing a diagnosis. In instances of diagnostic uncertainty, transbronchial or surgical lung biopsy may be necessary. There is no established treatment for pulmonary metastatic calcification but, given the overall favorable prognosis, this is rarely a consideration.

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CHAPTER 96

Pulmonary Complications of Sickle Cell Disease

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INTRODUCTION

Sickle cell disease (SCD) is one of the most common monogenetic diseases in the world. Sickle cell anemia, the most common and most severe form of SCD, occurs in individuals who are homozygous for a single GAG α GTG substitution in the β-globin gene, resulting in the production of hemoglobin S (HbS). Patients with other types of SCD are compound heterozygotes, having one copy of HbS and one copy of another β-globin mutation, such as hemoglobin SC or HbS-β thalassemia.[1] The presence of concurrent α-thalassemia, which will reduce the intracellular concentration of hemoglobin, also modulates disease severity and accounts for some of the variability in the clinical presentation of patients with SCD.[2] It is estimated that approximately 250,000 children worldwide are born with homozygous sickle cell (HbSS) anemia every year.[3] Approximately 0.15% of African Americans are homozygous for SCD, and 8% have sickle cell trait. In sub-Saharan Africa, up to 40% of the population carry sickle cell trait, and up to 1% of children are born with SCD.[4]

Despite significant improvements in the life expectancy of patients with SCD, estimates of the median age at death range from 42 to 53 years for men and 48 to 58.5 years for women.[5,6] Within this context, pulmonary complications of SCD are common and a major threat to the well-being of patients with SCD, accounting for a large proportion of deaths among these patients.[5,7–9] According to the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective multicenter study of 3764 patients, over 20% of adults likely had fatal pulmonary complications of SCD.[5] Among the 299 patients enrolled in the long-term follow-up study of patients who participated in the Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia, pulmonary disease was the most common cause of mortality, accounting for 28% of all deaths.[10] The numbers likely underestimate the importance of pulmonary disease in risk of death, as pulmonary hypertension (PH) was not diagnosed in these cohorts. Indeed, retrospective evaluation of banked plasma samples from the studies using N-terminal probrain natriuretic peptide (NT-proBNP) as a surrogate for the presence of PH suggested that PH was a major risk factor for death in both the CSSCD and MSH cohorts.[11,12]

When deoxygenated, HbS is much less soluble than normal hemoglobin (HbA).[13,14] Deoxygenated HbS polymerizes and aggregates inside sickle erythrocytes as they traverse the microcirculation. Rigid, dense, and sickled cells can become physically entrapped in the microcirculation, a process that is enhanced by inflammation and integrin molecule expression, causing red cell and leukocyte adhesion to endothelium. Mechanistic studies in transgenic mice expressing exclusively human HbS suggests that microvascular occlusion results in episodic interruption in blood flow, ischemia, and reperfusion injury, with secondary inflammatory, thrombotic, and oxidant stress.[15–22]

In patients, vasoocclusion leads to the frequent episodes of bone pain and acute chest syndrome (ACS) that complicate SCD. Furthermore, the membrane of erythrocytes containing intracellular HbS polymer is constantly exposed to mechanical and oxidant injury as the red cells traverse the microcirculation. Ultimately, cumulative membrane damage shortens red cell life span, so that SCD is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges nitric oxide (NO) and releases red blood cell arginase-1 into the plasma, which, in turn, catabolizes arginine, the substrate for NO synthesis.[23–25] Hence, intravascular hemolysis produces a state of endothelial dysfunction and vascular proliferation, along with prooxidant and proinflammatory stress.[26–28] In effect, intraerthrocytic HbS polymerization leads to downstream vascular inflammation, hemolysis-related vasculopathy, and ischemia–reperfusion organ injury.

Anemia, per se, should also be considered in the evaluation of the cardiopulmonary effects of SCD, since decreasing oxygen

carrying capacity of the blood related to severe anemia can impair cardiopulmonary function. The signs and symptoms induced by anemia depend on the degree of anemia, the rate at which it evolves, the oxygen demands of the patient, and the presence of chronic cardiopulmonary disease. For instance, in resting adults subjected to acute isovolemic anemia, oxygen delivery can be maintained at hemoglobin concentrations as low as 5 g/dL,[29] a finding also noted in individuals with chronic severe anemia.[30,31] Thus, anemia, even when severe, rarely causes heart failure; when it does, it is likely that the high-output failure is superimposed upon an underlying cardiac abnormality.

From the hemodynamic standpoint, as hemoglobin level decreases (particularly with hemoglobin values <7 g/dL), blood viscosity decreases, cardiac output increases, cardiac filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease substantially. Such abnormalities are readily reversible with red blood cell transfusions.[30–32] Finally, in severe cases, especially in patients with cardiopulmonary disease, anemic hypoxia can also occur as a consequence of reduced ability of blood to participate in gas exchange and oxygen transport. Interestingly, the severity of hemolytic anemia in patients with SCD is strongly correlated with systemic hypoxemia and decreasing arterial hemoglobin oxygen saturation, a finding that is likely related to both increased cardiac output and altered pulmonary vascular perfusion. Alterations in pulmonary vascular perfusion result in impaired ventilation–perfusion matching.[33,34]

ACUTE CHEST SYNDROME

The ACS in SCD is defined as a lung injury syndrome characterized by a new pulmonary infiltrate that (1) is consistent with alveolar consolidation, rather than atelectasis; (2) involves at least one complete lung segment; and (3) is accompanied by chest pain, fever, tachypnea, wheezing, or cough.[35]

EPIDEMIOLOGY

ACS is the second most common cause of hospitalization in patients with SCD, the leading cause of admission to an intensive care unit, and, together with PH, a leading cause of premature death, accounting for 25% of SCD-related mortality in earlier cohorts.[5,8] More recently, increased awareness, the chronic use of hydroxyurea, and the early and aggressive use of transfusion therapy have led to a decrease in ACS-related mortality.[36] For example, in a multicenter trial of inhaled NO for vasoocclusive crisis, only 10% of patients in the study developed ACS, and none required mechanical ventilation or died.[36]

ACS can occur in any of the sickle hemoglobinopathies but it is more common in individuals with HbSS disease. In the CSSCD, a 29% incidence of the ACS was noted in 3751 subjects over a 2-year period, representing an attack rate of 12.8 episodes per 100 patient-years for homozygous HbS disease.[5] The incidence is higher in children than in adults (24.5 events vs. 8.8 events per 100 patient-years). As many as half of episodes of ACS occur in association with vasoocclusive pain crises, and a significant proportion of patients will have a painful event within 2 weeks of the diagnosis of ACS.[37,38] Ten to twenty percent of patients admitted with an acute vasoocclusive pain crisis develop ACS within the first 3 days of hospitalization. Recent studies suggest a much higher rate of ACS following influenza infection.[39–41]

Clinical parameters that appear to increase risk for, or are associated with, development of ACS include: young age, active smoking, environmental smoke exposure,[42] major surgical procedures, acute rib infarcts, avascular necrosis of the hips, pregnancy, use of narcotics, acute anemic events, nocturnal or daytime hypoxemia, and previous pulmonary events.[37,38] In children, a number of studies suggest that asthma is a risk factor for the development of ACS.[43–45] Laboratory parameters in steady state associated with an increased risk for the development of ACS include an elevated white blood cell count, higher steady-state level of hemoglobin, and lower steady-state level of fetal hemoglobin.[37,38]

While a high steady-state level of hemoglobin is a risk factor for ACS, during acute hospitalization for a vasoocclusive crisis, development of the ACS is often preceded by an abrupt drop in hemoglobin (mean decrease of 0.78 g/dL) and increases in markers of hemolysis, for example, lactate dehydrogenase. The platelet count may also fall prior to ACS, and platelet levels lower than 200,000 cells per mL constitute an independent risk factor for the severity of ACS, an increased risk of neurological complications, and the need for mechanical ventilation.

A limited number of studies have addressed the role of candidate gene polymorphisms in patients with ACS. In a small cohort of 134 pediatric patients with SCD, *NOS1* AAT repeat polymorphism in intron 13 was associated with increased risk of ACS.[46] Similarly, in a study of 173 pediatric patients with SCD, individuals homozygous for a *ET-1* T8002 C polymorphism had higher rates of ACS, while those homozygous for a *NOS3* T-786 C polymorphism had lower rates.[47] Finally, in a cohort of 942 children with SCD, a highly polymorphic (GT)n dinucleotide repeat located in the promoter region of *HMOX1*, with long repeat lengths linked to decreased activity and inducibility, was evaluated. After adjusting for sex, age, asthma, percentage of fetal hemoglobin, and α-globin gene deletion, children with two shorter alleles had lower rates of hospitalization for ACS compared with children with longer allele lengths.[48]

PATHOGENESIS

The etiology of ACS is multifactorial. Although a specific cause is not identified in a substantial proportion of patients, three major pathogenetic mechanisms are involved, including infection, bone marrow fat embolization, and direct red cell intravascular sequestration, which cause lung injury and infarction (Table 96-1, Fig. 96-1).

The most common etiology of ACS in both children and adults is infection by a community-acquired pathogen. It has been proposed that community-acquired respiratory infection induces an excessive inflammatory lung injury response in patients with SCD, as SCD mice that express only human HbS show increased susceptibility to inflammatory triggers (lipopolysaccharide and bacteria) and development of lung injury at lower levels of endotoxin that do not adversely affect wild-type mice.[49,50] In addition, more than 80% of adults with SCD report a history of having been admitted to the hospital for "pneumonia."[26]

The National ACS Study Group analyzed 671 episodes of ACS in 538 patients with SCD. Respiratory samples obtained from sputum and BAL were analyzed for viral and bacterial infections.[35] Among the infectious agents identified most commonly (Table 96-1) were atypical bacteria and viruses, including *Chlamydia pneumonia* (29%), *Mycoplasma pneumonia* (20%), *Legionella pneumophila* (2%), respiratory syncytial virus (10%), parvovirus (4%), rhinovirus (3%), parainfluenza virus (2%), influenza A virus (2%), cytomegalovirus (2%), Epstein–Barr virus (1%), and herpes simplex virus (1%). Community-acquired encapsulated bacteria were rarely isolated, despite the fact that patients with homozygous HbS disease rarely have normal splenic function. *Staphylococcus aureus* was isolated in 5% of cases and *Streptococcus pneumonia* in only 4% of cases. Cases of severe ACS related to seasonal influenza have also been described.[39–41]

Fat embolization syndrome occurs as a complication of vasoocclusive pain crisis involving multiple bones, resulting in bone marrow edema, infarction, and necrosis. Fat embolism was identified by the National ACS Study Group as the cause of ACS in 16% of patients. During fat embolization, bone marrow contents are released into the systemic circulation and are trapped in the

TABLE 96-1 Causes of the Acute Chest Syndrome[a]

Cause	All Episodes ($n = 670$)	Age at Episode of Acute Chest Syndrome		
		No. of Episodes (%)		
		0–9 y ($n = 329$)	10–19 y ($n = 188$)	≥20 y ($n = 153$)
Fat embolism, with or without infection[b]	59 (8.8)	24	16	19
Chlamydia[c]	48 (7.2)	19	15	14
Mycoplasma[d]	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	15	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections[e]	3 (0.4)	0	3	0
Infarction[f]	108 (16.1)	50	43	15
Unknown[g]	306 (45.7)	139	88	79

[a]*Data on one episode were excluded because the patient's birth date was not known.*
[b]*Nineteen of the episodes of pulmonary fat embolism were associated with infectious pathogens.*
[c]*This category included episodes in which Chlamydia alone was identified, but not episodes involving mixed infections or pulmonary fat embolism.*
[d]*This category included only episodes in which only Mycoplasma pneumoniae or Mycoplasma hominis was identified, but not episodes involving mixed infections, Mycobacterium tuberculosis or pulmonary fat embolism.*
[e]*This category included two cases of tuberculosis and one case of Mycobacterium avium complex infection.*
[f]*A pulmonary infarction was presumed to have occurred when the results of the analysis for pulmonary fat embolism, bacterial studies, viral isolation studies, and serological tests were complete and were all negative.*
[g]*The cause of episodes for which some or all of the diagnostic data were incomplete and no etiological agent was identified was considered to be unknown.*
Source: Reproduced with permission from Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855–1865.

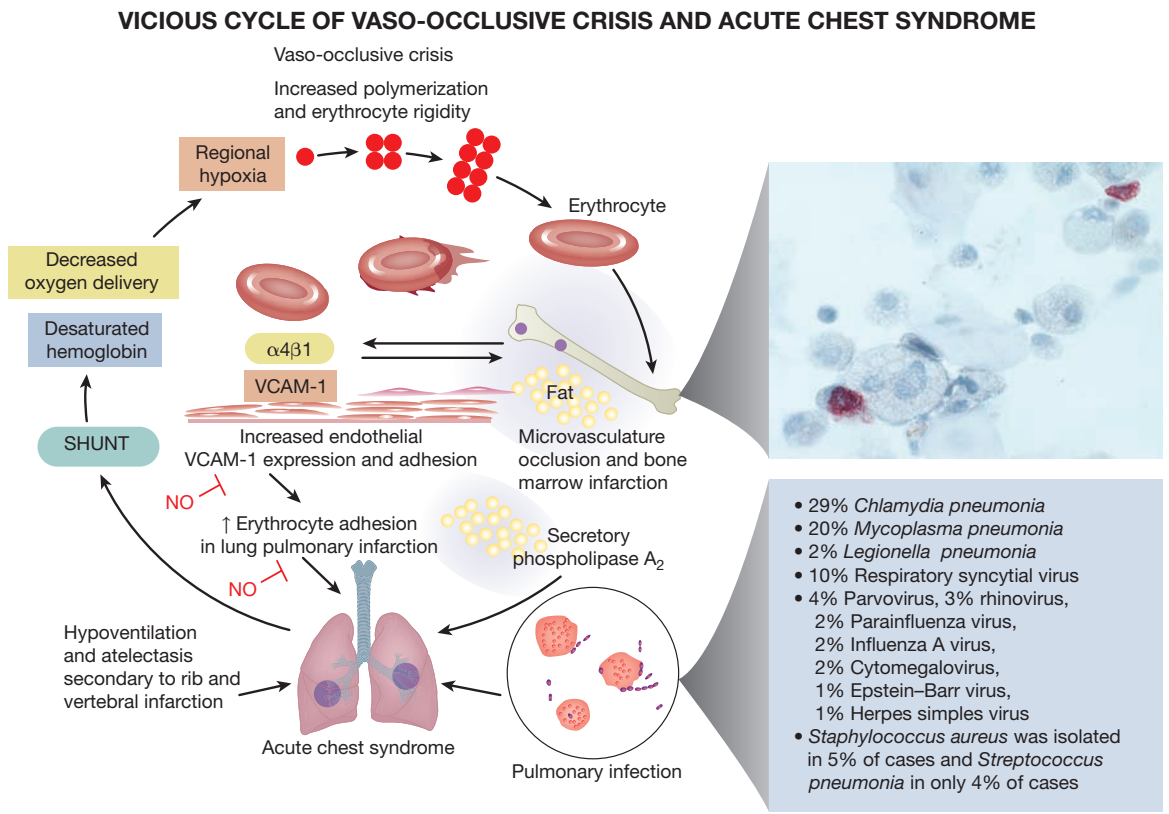
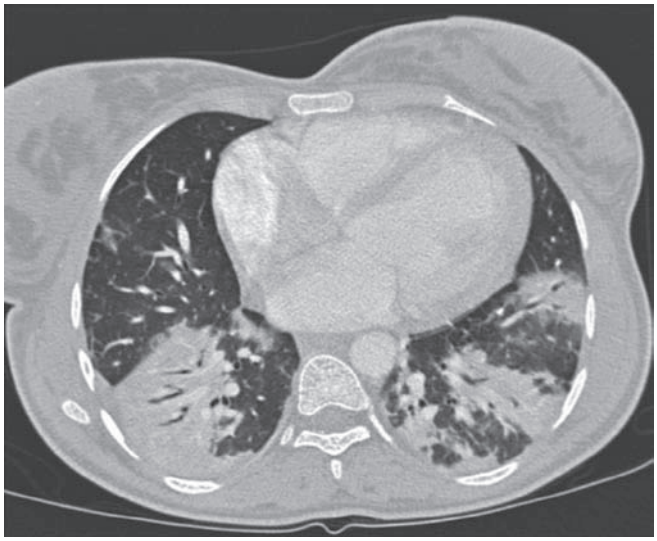


Figure 96-1 Pathogenesis of the acute chest syndrome. Three major mechanisms are associated with the development of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction. Lung injury results in ventilation–perfusion mismatch and hypoxemia, which leads to increased hemoglobin S polymerization, and erythrocyte vasoocclusion. This worsens bone marrow infarction and pulmonary vasoocclusion to promote a vicious cycle. Fat embolization can be diagnosed by Oil Red O staining of pulmonary alveolar macrophages, revealing the characteristic red lipid inclusions. Common infectious organisms identified in cases of ACS are listed. *(Reproduced with permission from Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med. 2008;359(21):2254–2265.)*



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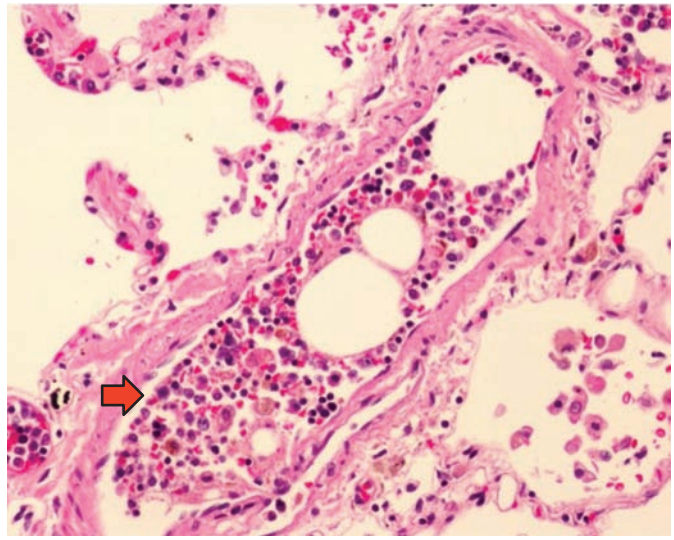


B

Figure 96-2 Fat embolization in acute chest syndrome. **A.** Chest CT scan of a patient with acute chest syndrome and fat embolization syndrome. **B.** Postmortem examination specimen of a patient who died suddenly during an episode of vasoocclusive crisis and acute chest syndrome demonstrating bone marrow elements lodged in the small pulmonary artery *(arrow)*. (*Reproduced with permission from Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. Chest. 2010;138(4):973–983.)*

pulmonary circulation, producing acute PH, severe lung inflammation, and hypoxemia (Fig. 96-2).[51–53] Bone marrow fat released into the bloodstream is also converted to free fatty acids by secretory phospholipase A_2, producing direct inflammatory lung injury.[54]

In approximately 20% of patients, direct adhesion of sickled cells in the pulmonary vasculature arising during lung infarction or lung vasoocclusion is associated with the development of ACS; a small fraction of patients develop wedge-shaped infarctions, sometimes followed by central cavitation.[55] In situ pulmonary arterial thrombosis and cellular occlusion also appear to be common in patients with ACS. In a study of 144 episodes of ACS in 125 consecutive patients evaluated using CT angiography, a 17% prevalence of subsegmental thromboembolism was noted; there was no evidence of peripheral venous thrombosis.[56]

A potential role for hemolysis-derived plasma-free hemoglobin and its by-products, such as free heme, has been suggested in the pathogenesis of ACS. Administration of lysed red blood cells into the circulation of sickle cell mice has been shown to increase vascular permeability in the lung without impacting permeability in other organs.[57] Furthermore, preliminary studies have demonstrated that intravenous administration of heme to sickle cell mice induces severe and lethal acute lung injury.[58] In aggregate, these data suggest that plasma-free hemoglobin or heme specifically may directly contribute to lung injury in the context of vasoocclusive crisis and ACS. The relationship between increased intravascular hemolysis and thrombocytopenia (see below) suggests that a possible thrombotic thrombocytopenic purpura–like mechanism may occur in a subset of patients with ACS. In fact, studies have demonstrated that hemoglobin produced during hemolysis may inhibit ADAMTS13 activity.[59–61]

■ CLINICAL FEATURES AND EVALUATION

Eighty percent of patients with ACS present with fever and 62% with cough; approximately 40% have chest pain, tachypnea, dyspnea, and abdominal, arm, leg, rib, or sternal pain.[35] Some of the clinical features of ACS are age dependent, which likely reflects the different disease etiologies in different age groups. Children have a higher proportion of infectious etiologies in comparison to adults, who have fat embolization as a major cause. Most adult patients present with severe extremity or chest pain and develop ACS 24 to 72 hours later. Reactive airway disease is observed in 13% of cases and is much more common in children.[35]

ACS is associated with signs of systemic inflammation. Mean peak temperature is 38.9°C and mean white blood cell count is 23,000 cells per mL. In addition, a drop in hemoglobin level (mean decrease of 0.78 g/dL from steady-state level) and an increase in markers of hemolysis are noted.[35] Thrombocytopenia may also occur; platelet counts less than 200,000 cells per mL appear to be a marker of more severe ACS and are associated with increased risk of neurological complications and need for mechanical ventilation.[35] Secretory phospholipase A_2 levels, that are elevated early in the course of ACS, even before development of radiographic changes, have been used to predict onset of the syndrome.[62]

Some patients manifest evidence of systemic fat embolization. In these cases, ACS is part of the spectrum of the systemic fat emboli syndrome, evident as acute multiorgan system failure (MOSF) (Chapter 142). Patients with MOSF experience acute hypoxic respiratory failure, acute cor pulmonale, renal and hepatic dysfunction, alterations in mental status, seizures, thrombocytopenia, and coagulopathy.[63,64]

The diagnosis of pulmonary fat embolization syndrome is based on identification of Oil Red O–positive lipid accumulations within alveolar macrophages, as the clinical manifestations can be indistinguishable from other causes of ACS (Fig. 96-2). Bronchoscopy has been used as the diagnostic modality of choice for the diagnosis of pulmonary fat embolization syndrome. Interestingly, a study comparing the diagnostic utility of induced sputum sampling of alveolar macrophages with specimens obtained from bronchoalveolar lavage found a significant, albeit modest, correlation between the two ($R = 0.65$).[65] Patients with ACS who have lipid-laden macrophages detected in induced sputum have significantly more extrathoracic pain than those without evidence of fat emboli, more neurological symptoms, a lower platelet count, and higher serum transaminase levels.[65]

The mean length of hospitalization for ACS is 10.5 days, compared with 3 to 4 days for uncomplicated vasoocclusive painful crisis. Large registry studies suggest that 13% of patients require mechanical ventilation. The overall mortality is 3% for all patients and 9% for adults, however, as noted previously, these rates may be

lower in experienced medical centers employing more aggressive and earlier transfusion therapy.

Risk factors for mechanical ventilation and poor outcome include a platelet count less than 200,000 per μL (likely indicative of the fat emboli syndrome), a greater number of lobes involved on the chest radiograph, and a self-reported or medical record–based history of cardiac disease.

Acute cor pulmonale can also complicate the course of ACS. In a study of 84 consecutive patients hospitalized with ACS, 13% manifested right heart failure. This subgroup had significant elevations in B-type natriuretic peptide and troponin I levels and the highest risk for needing mechanical ventilation and death.[66] PH and right heart dysfunction appear to represent major comorbidities in ACS; right heart failure should be considered in those patients presenting with shock or severe hypoxia.

TREATMENT

Since the triggers and risk factors for ACS are well known, preventive strategies in the outpatient setting, clinical surveillance, and aggressive and early therapy are likely to improve prognosis.

Patients with multiple episodes of vasoocclusive crises or a previous history of ACS should be treated with hydroxyurea in the outpatient setting, since its use has been shown to reduce the risk of developing ACS by approximately 50%.[67,68] A chronic transfusion regimen is also effective in reducing the incidence of ACS,[69] as is preoperative blood transfusion in patients undergoing surgical procedures.[70]

In acutely ill patients, specific strategies, such as aggressive pain management and incentive spirometry, can minimize chest wall splinting, mitigating development of atelectasis and alveolar hypoxia. The use of incentive spirometry has been shown to decrease the incidence of new pulmonary infiltrates in patients admitted with vasoocclusive pain affecting the chest wall.[55]

In one small study evaluating the efficacy of prophylactic blood transfusions in patients with serum phospholipase A_2 elevations during vasoocclusive crisis,[71] transfusion eliminated ACS in the study cohort. Larger confirmatory trials are indicated.

We recommend use of empiric antimicrobial therapy in all patients with ACS, given the high prevalence of infectious etiologies. Coverage should include agents effective against atypical bacteria and encapsulated organisms. Important to consider are alternative organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and influenza viruses, especially in patients who do not respond to therapy or who develop ACS during influenza season.

Although not demonstrated in randomized trials, blood transfusion remains the mainstay of ACS therapy and is considered standard of care. Acute red cell transfusion increases Pa_{O_2} and hemoglobin oxygen saturation and may rapidly resolve the pulmonary event.[35,72] In the DeNOVO trial,[36] no episodes of ventilator-dependent respiratory failure and no deaths were noted in 30 patients with ACS receiving the current practice of early transfusion therapy. The improved outcomes compare favorably with historical data from the National ACS Study Group.

To avoid the adverse effects of increased blood viscosity and the consequent risk of vasoocclusion, the hemoglobin level should not be raised higher than 11 g/dL with simple transfusion therapy. The National Acute Chest Syndrome Study Group found no significant differences in outcomes between patients treated with simple transfusion or red cell exchange (erythrocytapheresis), suggesting that the former approach is preferred as initial therapy.[35] Patients with high initial hemoglobin concentrations (≥9 g/dL) or patients with severe or rapidly progressive disease should receive erythrocytapheresis. Most importantly, to decrease the risk of delayed hemolytic transfusion reactions related to alloimmunization against minor red blood cell antigens, all transfused blood should be matched to Rh, C, E, and Kell antigens.

Treatment with corticosteroids has been shown to reduce the severity of pain and length of hospitalization, but this therapy is complicated by a high rate of rebound pain and readmission.[73,74] An investigation of the use of a slow, tapering protocol corticosteroids to maintain their beneficial effects while limiting rebound pain and readmission was terminated early because of slow accrual of study patients.[75]

Noninvasive mechanical ventilation (NIMV) has been studied in the setting of ACS. In a prospective, randomized, open single-center study of 67 adult patients with ACS, use of NIMV improved respiratory rate and gas exchange but failed to significantly reduce the number of patients remaining hypoxemic by day 3 of hospitalization; in addition, use of NIMV was associated with greater patient discomfort.[76] In addition, NIMV did not change transfusion rates, pain scores, narcotic dose, or hospital length of stay. In fact, its use prolonged length of stay in the step-down unit.[76]

The DeNOVO trial explored use of inhaled NO for patients with SCD presenting in vasoocclusive crisis. Despite two prior positive small phase II trials,[77,78] the DeNOVO study did not demonstrate an effect of inhaled NO therapy compared with placebo on the duration of pain crisis, narcotic use, pain scores, or development of ACS.[36]

ASTHMA AND AIRWAY REACTIVITY

Asthma is common among patients with SCD, particularly in children. In a prospective study of 291 African-American children with SCD, 17% received a clinical diagnosis of asthma.[43] Interestingly, the reported incidence of airway hyperresponsiveness in children with SCD is much higher, ranging from 40% to 77%, as measured by methacholine, exercise, or cold air challenge tests.[79–81]

Asthma has been associated with multiple complications of SCD, including ACS. Children with SCD and asthma experience almost twice as many episodes of ACS as their counterparts without asthma, even after matching for age, sex, fetal hemoglobin percentage, and lifetime average hematocrit.[43–45,82–85] Several mechanisms have been proposed for this association, including ventilation–perfusion mismatch leading to hypoxemia and sickling, and inflammation causing increased erythrocyte adhesion to vascular endothelium.[86] Asthma is an independent risk factor for mortality in children with SCD, conferring a twofold higher risk of death (hazard ratio, 2.36; confidence interval [CI], 1.21–4.62; $p = 0.01$).[87] The reasons for increased mortality remain unclear, but are likely related to the higher risk of vasoocclusive crises and ACS.

Data on asthma in adults with SCD are scarce. The diagnostic and prognostic significance of the disease in adults is less clear than in children. A study of 31 adults with SCD without a clinical diagnosis of asthma showed an average TLC of 73% predicted, FVC of 79% predicted, and FEV_1 of 75% predicted.[85] Fifteen patients demonstrated bronchial hyperreactivity on methacholine provocation testing; there was evidence of a correlation between bronchial hyperreactivity and previous episodes of ACS. Another cohort study evaluated physician-diagnosed asthma and a history of wheezing in 114 adults with SCD.[88] Although self-reported severe and recurrent wheezing was associated with increased rates of pain, ACS, and risk of death, no relationship was found between a physician-established diagnosis of asthma and these complications.

Although there are no controlled trials of asthma therapy in the SCD population, most experts recommend treatment following generally established guidelines for asthmatics in general.[89] Systemic corticosteroids must be used with caution, however, as corticosteroids appear to induce vasoocclusive crises and ACS in patients with SCD. In fact, the use of corticosteroids in pediatric patients with SCD has been shown to worsen outcomes.

PULMONARY HYPERTENSION

Among the chronic cardiopulmonary complications of SCD, PH, defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg, has emerged as the major threat to the well-being and longevity of patients. A number of studies have added significantly to our understanding of the prevalence, underlying pathogenetic mechanisms, and clinical phenotype of patients with PH and SCD. Several screening cohort studies have focused on the prevalence, risk factors, and mortality rate of patients with SCD and PH diagnosed by right heart catheterization.

EPIDEMIOLOGY

Retrospective studies using Doppler echocardiography have demonstrated that 20% to 30% of patients with SCD have an elevated estimated pulmonary artery systolic pressure (PASP) that is two standard deviations above the normal mean value (tricuspid regurgitant jet velocity [TRV] ≥ 2.5 m/s). Approximately 8% to 10% have values three standard deviations above the normal mean (≥3.0 m/s).[64,90] These findings have been corroborated in several prospective studies.

In one study using echocardiographic screening, 23% of patients with SCD had borderline or mild elevations in PASP (defined by a TRV ≥2.5–2.9 m/s and corresponding to a PASP of approximately 30–39 mm Hg), and 9% had moderately to severely elevated pressures (defined by TRV ≥3.0 m/s, corresponding to a PASP of approximately 40–45 mm Hg).[26] Similar rates were found in other studies.[91–94]

In a study of patients enrolled in the MSH, plasma NT-proBNP, a prohormone released by right and left ventricular myocardium under pressure stress, was elevated in 30%, suggesting the presence of elevated pulmonary pressures and right heart strain.[11] Similarly, measurements of NT-proBNP in banked plasma from patients enrolled in the CSSCD from 1978 to 1988 revealed that 27.6% of adults had elevated levels.[12] In both studies, elevated study entry levels of NT-proBNP were independently associated with a higher risk of death in prospective follow-up.

Epidemiological risk factors associated with an elevated TRV include a history of renal or cardiovascular complications, increased systemic systolic blood pressure, abnormalities in markers of hemolytic anemia (anemia; reticulocytosis; and increased lactate dehydrogenase, aspartate aminotransferase, and bilirubin levels), iron overload, cholestatic liver dysfunction (elevations in alkaline phosphatase), renal insufficiency, a history of cutaneous leg ulceration, and, in men, a history of priapism.[11,26] These risk factors have also been observed in more recently published studies using right heart catheterization to diagnose PH.[93,95,96] Surprisingly, in these studies development of an elevated TRV was not associated with the number of vasoocclusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts.[11,26] PH determined by right heart catheterization has also been shown not to correlate with episodes of vasoocclusive crisis or ACS, suggesting that this complication arises secondary to hemolytic anemia, rather than recurrent episodes of vasoocclusion. A large screening study of 483 patients with homozygous SS disease conducted in the United States and England reproduced these associations[97]; patients with elevations in Doppler-estimated PASP had more severe hemolytic anemia and renal insufficiency. These patients also had lower arterial oxygen saturation, higher levels of NT-proBNP, and lower 6-minute walk distances. A high Doppler-estimated pulmonary artery pressure was also independent of rates of vasoocclusive disease or ACS, providing further support to the hypothesis that this complication arises secondary to chronic hemolytic anemia and end-organ dysfunction (renal and liver disease), rather than episodes of ACS and related pulmonary fibrosis.

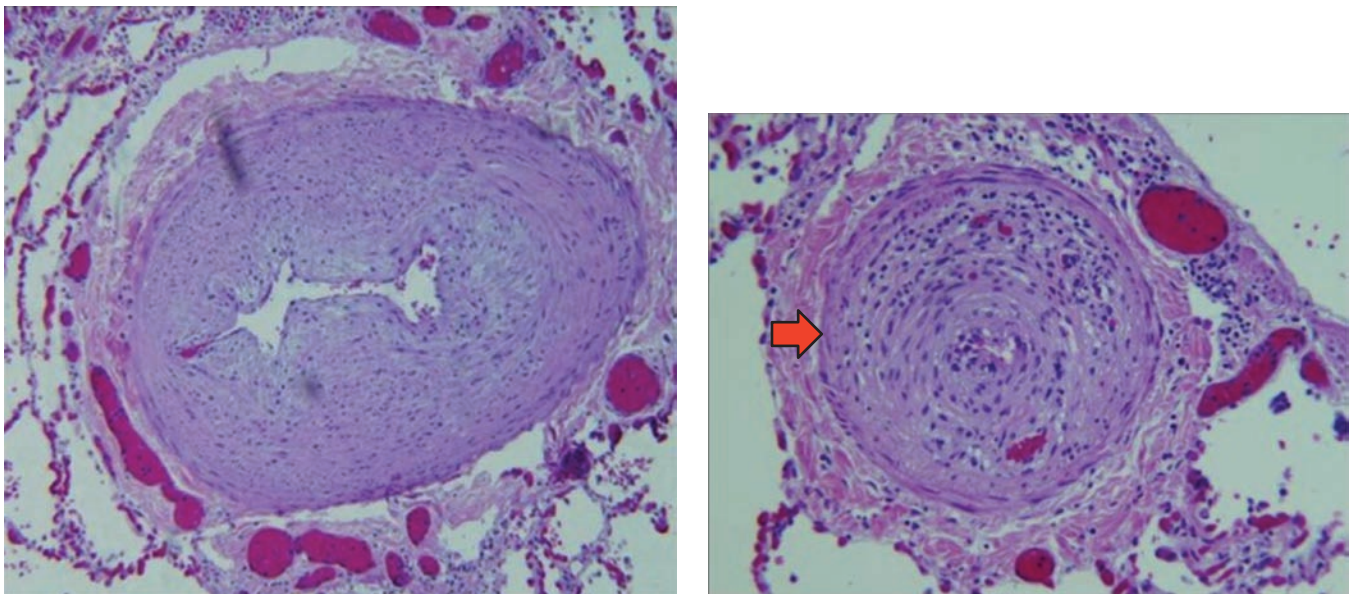
An elevated estimated PASP by Doppler-echocardiographic screening or right heart catheterization is a significant risk factor for death in patients with SCD. The risk appears to be linearly related to the elevation in PASP.[26] In one study, a 14% mortality rate over 2 years was reported in patients with an elevated TRV versus a 3% mortality rate in those with normal TRV.[92] Similarly, in another study, the mortality rate over 2.5 years was 25% in patients with an elevated TRV and less than 2% in those with a normal TRV.[91] Consistent with these data, in a cohort of 632 patients with SCD from the United States and England, 11.2% had TRV ≥3.0 m/sec and 24.1% had NT-proBNP level ≥160 pg/mL. Of 22 deaths during follow-up, 50% had a TRV ≥3.0 m/sec. At 24 months the cumulative survival was 83% with TRV ≥3.0 m/sec and 98% with TRV <3.0 m/sec. The hazard ratios for death were 11.1 (95% CI 4.1–30.1; p <0.0001) for TRV ≥3.0 m/sec, 4.6 (1.8–11.3; p = 0.001) for NT-proBNP ≥160 pg/mL, and 14.9 (5.5–39.9; p <0.0001) for both TRV ≥3.0 m/sec and NT-proBNP ≥160 pg/mL.[98]

Several studies have provided new insights into PH in SCD using the gold standard diagnostic test for the disease—right heart catheterization (Table 96-2).

TABLE 96-2 Right Heart Catheterization–based Pulmonary Hypertension Screening Studies in Sickle Cell Disease

	Parent[94]	Fonseca[93]	Mehari[95]
Subjects screened (*N*)	398	80	531
Number of subjects with PH	24	8	55
Percent of screened population	6	10	10.5
mPAP, mm Hg	30 ± 6	33 ± 9	36 ± 9
CO, l/min	9 ± 2	5 ± 2[a]	9 ± 2
PVR, dyn-s/cm^5	138 ± 58	179 ± 120[b]	227 ± 149
6MWD, m	404 ± 94	460 ± 152	358 ± 115
Number of subjects with PAH	11	3	31
Percent of screened population	2.7	3.75	6.0
Number of subjects with PVH	13	5	24
Percent of screened population	3.3	6.25	4.5
Mortality in PH group	23%	38%	36%

PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance.
[a]*Cardiac index (l/min/m2).*
[b]*Converted mean value: PVR measured in Wood units.*



A B

Figure 96-3 Pulmonary arteriopathy in sickle cell-related pulmonary hypertension. **A.** Low power photomicrograph demonstrating intimal and pulmonary arterial smooth muscle hypertrophy (H&E stain). **B.** Plexiform lesion (*arrow*, H&E stain).

In a screening study of over 500 patients followed for up to 9 years (median duration of follow-up, 4.4 years),[96] 86 patients underwent right heart catheterization; 56 were diagnosed with PH (10.5%). Similar findings were observed in another screening study of 80 patients (10% prevalence of PH using right heart catheterization).[93] A large screening study of nearly 400 patients with SCD in France[94] demonstrated a prevalence of PH (determined by right heart catheterization) of 6%.

The presence of PH, as documented by right heart catheterization, is a major risk factor for death in patients with SCD, with mortality rates ranging from 23% to 38%.[93,94,96] In one study, a 50% 2-year mortality rate was reported in patients with PH and SCD.[99] Each increase of 10 mm Hg in mean PAP was associated with a 1.7-fold increase in death rate. Autopsy studies suggest that up to 75% of patients with SCD have histological evidence of pulmonary arterial hypertension at the time of death (Fig. 96-3).[100]

Finally, specific hemodynamic predictors of mortality independently associated with mortality include increases in mean PAP, diastolic PAP, diastolic PAP–pulmonary capillary wedge pressure gradient, transpulmonary gradient, and pulmonary vascular resistance. These data strongly suggest that mortality in adults with SCD and PH is proportional to the severity of precapillary PH.[95]

PATHOGENESIS

An association between the development of PH and the intensity of hemolytic anemia has been observed in prospective screening studies of adult patients with SCD,[26,91,92,94,96,97] and in an expanding number of pediatric studies.[101–105] The association suggests that hemolysis is related mechanistically to PH.

Hemolysis releases plasma-free hemoglobin that inactivates the intrinsic vasodilator, NO,[24,25] and arginase-1, which depletes L-arginine, the substrate for NO synthesis.[23] The result of these combined pathological processes is decreased NO bioavailability and "resistance" to NO-dependent vasodilation.[25] In addition, the accumulation of redox-active heme and iron from lysed red blood cells contributes to the generation of reactive oxygen species that can exacerbate thrombosis and vascular proliferative responses.[106]

In situ thrombosis is well documented in patients with pulmonary arterial hypertension and chronic thromboembolism causes chronic thromboembolic PH. A correlation exists between the rate of hemolysis and levels of procoagulant factors in blood in patients with SCD.[107–109] In addition, hemolysis and decreased NO bioavailability induce platelet activation,[110] thrombin generation, and tissue factor activation, which would induce a procoagulant state.[111] Hemolysis is also associated with the formation of red blood cell microvesicles expressing phosphatidylserine, which activate tissue factor, a procoagulant mediator.[109,112]

Splenectomy has been reported to be a risk factor for development of PH,[113] particularly in patients with hemolytic disorders.[114–116] Thus, functional or surgical asplenia may contribute to development of PH in patients with SCD. In addition, loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[117] Patients with SCD also have increased levels of cell-free hemoglobin and red cell prothrombotic microvesicles. Following splenectomy, the rate of intravascular hemolysis increases.[109]

Additional mechanisms in the pathogenesis of PH in SCD may be operative. In patients with SCD at clinical baseline or during vaso-occlusive pain crises, plasma endothelin-1 levels are increased.[118] In vitro, sickled erythrocytes increase endothelin-1 production by cultured human endothelial cells. In addition, endothelin receptor A antagonism abolishes the vasoconstrictive effects of media obtained from pulmonary endothelial cells exposed to sickled erythrocytes on aortic rings.[118]

Finally, in theory, a high pulmonary artery pressure may result from the high cardiac output state associated with chronic anemia in SCD. However, this hyperdynamic state does not appear to be a major contributor to significant elevations in pulmonary artery pressure, as reports of PH associated with nonhemolytic anemias are lacking. Conceivably, a high cardiac output state, combined with hemolytic anemia and other risk factors, such as renal insufficiency and iron overload, conspire to drive pathological pulmonary vascular remodeling.

CLINICAL FEATURES AND EVALUATION

The diagnostic evaluation of patients with SCD suspected of having PH should follow the same guidelines established for other causes of PH.[119,120] Given the high prevalence of PH in this population and the associated high mortality, we recommend universal noninvasive screening of all adults using Doppler echocardiography,

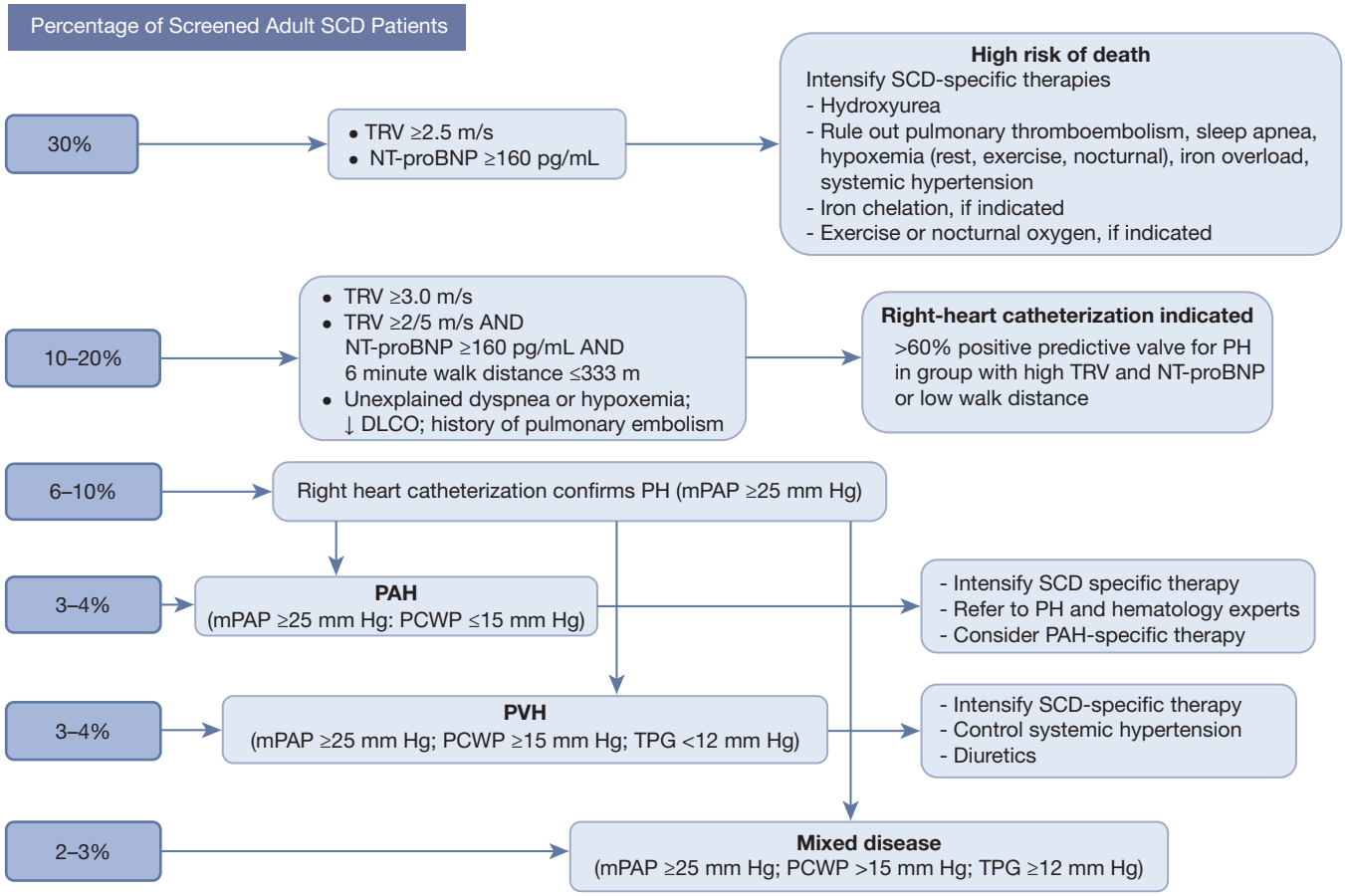


Figure 96-4 Pulmonary hypertension diagnostic algorithm. TPG, transpulmonary gradient; PCWP, pulmonary capillary wedge pressure. *(Reproduced with permission from Miller AC, Gladwin MT: Pulmonary complications of sickle cell disease, Am J Respir Crit Care Med. 2012;185(11):1154–1165.)*

measurement of steady-state plasma NT-proBNP levels, and assessment of functional capacity. In patients with SCD, the echocardiographic estimation of PASP (PASP = 4 × TRV^2 + estimate of the central venous pressure) correlates well with measured PASP by right heart catheterization.[26] While no prospective data on prevalence and risk of PH are available for children, we currently recommend that children with hypoxemia, high hemolytic rate (hemoglobin values <7 g/dL and high LDH), or recurrent ACS, be screened. Importantly, screening should be performed in the steady state, as pulmonary artery pressures rise during vasoocclusive painful crises.[121]

The Doppler echocardiogram is an important tool for population screening and estimation of pulmonary artery pressure, but it cannot be used to diagnose or define PH, which is based on measurement of mPAP via right heart catheterization. A TRV ≥2.5 m/s is associated with a very low specificity for the diagnosis of PH; only 25% of patients with a value greater than 2.5 m/s have PH.[94] A TRV ≥2.9 m/s is associated with a fairly high positive predictive value of 64%, but an unacceptably high false-negative rate of 42%. The positive predictive value for PH for a combination of a TRV ≥2.5 m/s, a high NT-proBNP level (>164.5 pg/mL), and a 6-minute walk distance <333 m is 62%; the false-negative rate is 7%. Based on these data, we propose a PH-screening algorithm for adult patients with SCD (Fig. 96-4).

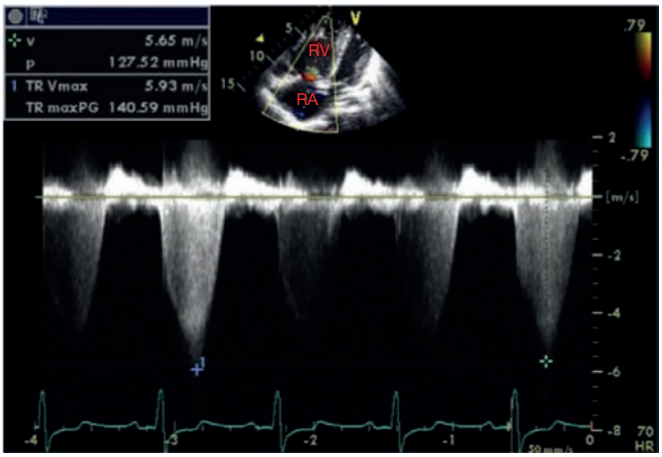
The diagnosis of PH in patients with SCD may be challenging (Fig. 96-5). Exertional dyspnea, the most typical presentation of PH, is also a cardinal symptom of chronic anemia and other conditions commonly present in patients with SCD, such as left ventricular dysfunction, pulmonary fibrosis, and cirrhosis. Therefore, a high index of suspicion for diagnosis is necessary.

Patients with SCD and PH tend to be older, have higher systolic arterial blood pressure, lower hemoglobin levels, higher indices of hemolysis, lower hemoglobin–oxygen saturation, greater degrees of renal and liver dysfunction, and higher numbers of lifetime red blood cell transfusions.[26] Diagnostic evaluation should also include an aggressive search for other conditions that might contribute to PH, such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and pulmonary thromboembolism. A diagnostic right heart catheterization is essential to confirm the diagnosis and to exclude diastolic dysfunction.[119] The 6-minute walk test is a useful surrogate for assessing functional capacity in this patient population and inversely correlates with the severity of PH.[122] In spite of this correlation, important to note is that in patients with SCD, noncardiopulmonary factors, such as concurrent pain and avascular necrosis of the hip, can interfere with test performance.

Measurement of NT-proBNP levels may be used as a PH biomarker for diagnosis and risk stratification in patients with SCD.[11] NT-proBNP levels are higher in patients with sickle cell–associated PH and correlate directly with the severity of PH and degree of functional impairment. An NT-proBNP level of 160 pg/mL or greater is associated with PH and is an independent predictor of mortality (risk ratio, 5.1; 95% CI, 2.1–12.5; $p < 0.001$).[11]

Most adult patients with SCD develop abnormal pulmonary function characterized by mild restriction (mean TLC approximately 79% of predicted), abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis.[8,123–127] The severity of the defects seems to be slightly greater in those patients with PH.[122] However, in these patients, the degree of pulmonary function abnormalities is rarely severe enough to be a major contributor to the etiology of the PH.

A ventilation–perfusion scan is an indispensable component of the evaluation, since chronic pulmonary thromboembolic disease, if amenable to pulmonary endarterectomy is a potentially curable



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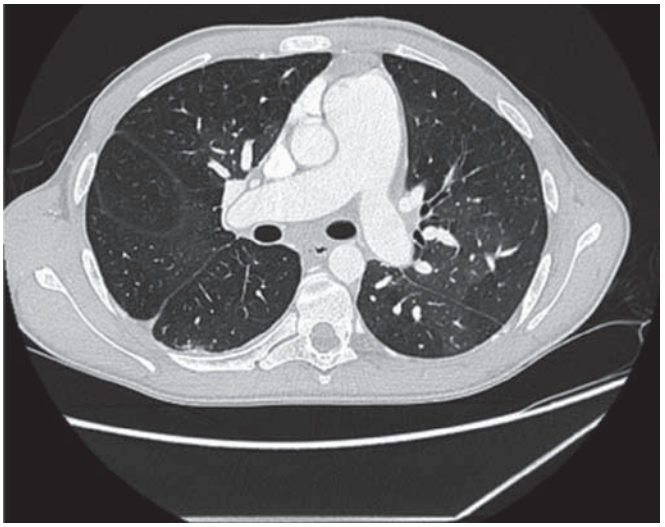

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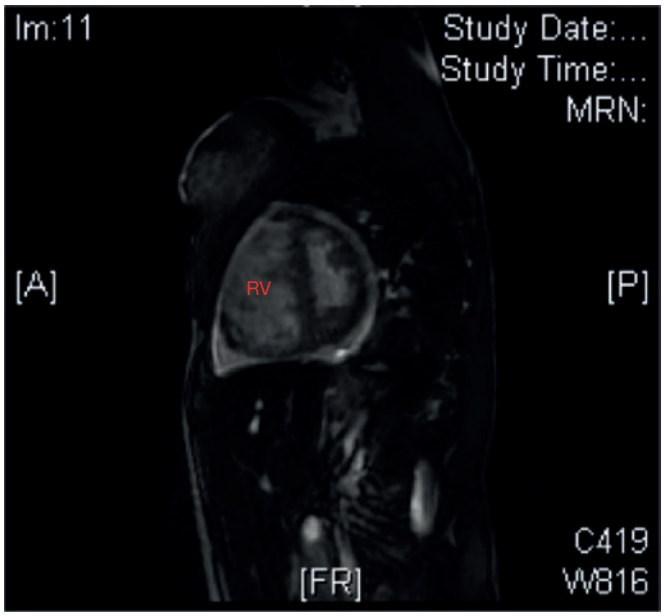

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Figure 96-5 Imaging features of sickle cell disease and pulmonary hypertension. **A.** Echocardiographic four-chamber view of the heart, illustrating severe right ventricular (RV) and right atrial (RA) dilation. Doppler tracing from a patient with severe pulmonary hypertension reveals a jet velocity of more than 5 m/s. **B.** Enlargement of pulmonary arteries in severe pulmonary hypertension. **C.** Cardiac resonance imaging showing right ventricular (RV) dilatation in severe pulmonary hypertension.

form of PH in patients with chronic hemolytic disorders. In the majority of cases, observed scintigraphic evidence of thromboembolic disease is uncommon; the most commonly seen abnormalities are patchy areas of abnormal perfusion, similar to findings described in other forms of PH.[122,128] However, scintigraphic evidence suggestive of chronic thromboembolic PH occurs in approximately 5% of patients with SCD and severe PH,[121] and the PH has been successfully treated surgically in two patients (Fig. 96-6).[129] Consequently, patients should undergo imaging studies, and if findings are suggestive of chronic thromboembolic PH, additional invasive studies (i.e., angiography) are warranted to exclude a potentially surgically treatable condition.

HEMODYNAMIC PROFILES AND ETIOLOGY OF PULMONARY HYPERTENSION IN SICKLE CELL DISEASE

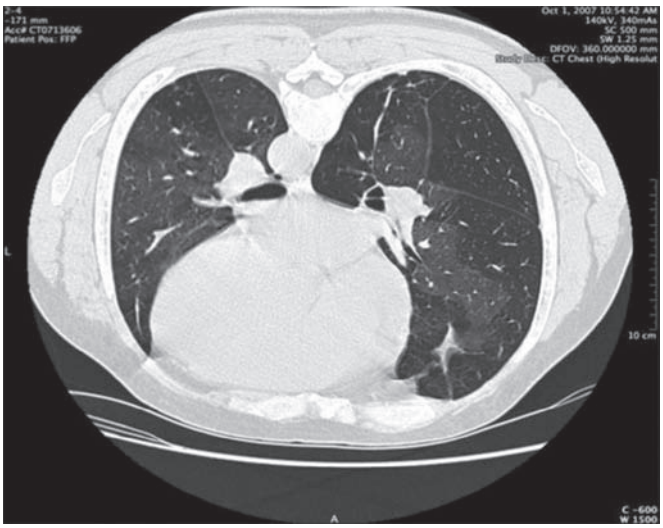
As previously discussed, as hemoglobin level decreases cardiac output increases, filling pressures tend to decrease and systemic and pulmonary vascular resistances decrease. In studies of patients with SCD undergoing right heart catheterization, the mean cardiac output and pulmonary vascular resistance for patients without PH were 10 L/min and 59 dyn s/cm^5, respectively.[31,99,122] It is within the context of these data that one must consider the impact of PH in chronically anemic patients with hemolytic disorders. As such, we believe that it is appropriate to consider a lower upper limit of "normal" pulmonary vascular resistance (such as <160 dyn-s/cm^5) in these patients.

In contrast to patients with traditional forms of pulmonary arterial hypertension (e.g., idiopathic, scleroderma associated), who are symptomatic with mean pulmonary arterial pressures in the range of 50 to 60 mm Hg, in patients with SCD the degree of elevation in mean pulmonary pressures is mild to moderate, in the range of 30 to 40 mm Hg, with mild elevations in pulmonary vascular resistance.[31,93,94,96,99,122] These patients also have coexistent mild elevation in pulmonary capillary wedge pressure, suggesting left heart failure.[31,93,94,96,99,122]

Right heart catheterization data from these multiple studies show that the hemodynamic etiology of the PH in patients with SCD is multifactorial: Pulmonary arterial hypertension (PAH: defined by an mPAP ≥25 mm Hg and a wedge pressure ≤15 mm Hg) is present in 50% of catheterized patients, while pulmonary venous hypertension secondary to left ventricular diastolic dysfunction (PVH: defined by an mPAP ≥25 mm Hg, a wedge pressure >15 mm Hg) is present in 50%.

DIASTOLIC DYSFUNCTION

In response to chronic anemia the left ventricle responds with an increase in stroke volume and chamber dilation. This response leads to increased wall stress and an increase in left ventricular



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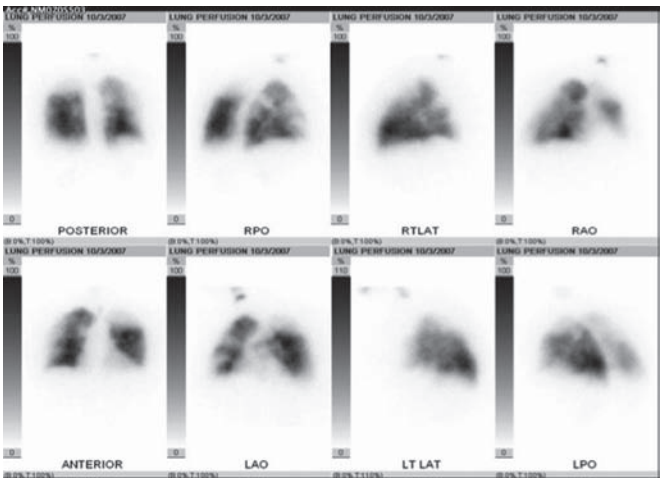

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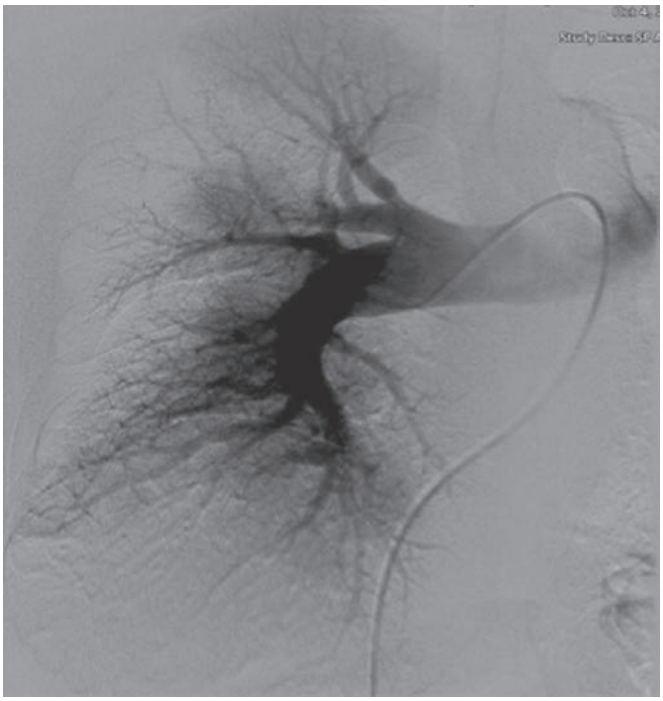

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Figure 96-6 Chronic thromboembolic pulmonary hypertension in a patient with sickle cell disease. **A.** HRCT demonstrating mosaic pattern of attenuation. **B.** Perfusion scan demonstrating multiple unmatched perfusion defects. **C.** Digital subtraction pulmonary angiogram demonstrating peripheral filling defects in the pulmonary arteries. *(Reproduced with permission from Mason RJ. Murray and Nadel's Textbook of Respiratory Medicine, 5th Edition. Philadelphia, PA: Elsevier; 2010.)*

mass which, in turn, leads to impaired filling, which characterizes diastolic dysfunction. Using echocardiography in a cohort of 141 patients, Sachdev, et al. found that 47% had a high TRV, diastolic dysfunction, or both (29% had a high TRV alone, 11% had diastolic dysfunction and a high TRV, and 7% had diastolic dysfunction alone). An elevated TRV and diastolic dysfunction were associated with a relative risk of death of 5.1 (95% CI, 2.0–13.3) and 4.8 (95% CI, 1.9–12.1), respectively, while the relative risk of death when both were present was 12.0 (95% CI, 3.8–38.1), suggesting that both PH and diastolic dysfunction independently carry additive mortality risk.[130] In addition, in a series of 483 patients with homozygous SCD, markers of diastolic dysfunction were independently associated with a low 6-minute walk distance.[97]

EFFECTS OF PULMONARY HYPERTENSION ON EXERCISE CAPACITY

Patients with SCD appear to be poorly tolerant of even small additional increases in pulmonary artery pressure and pulmonary vascular resistance. When compared to age, gender, and hemoglobin-matched patients with SCD without PH, individuals with PH and mPAP of 36 mm Hg exhibit lower 6-minute walk distance (435 ± 31 vs. 320 ± 20 m; $p = 0.002$) and peak oxygen consumption (50 ± 3% vs. 41 ± 2% of predicted; $p = 0.02$) and higher ventilatory equivalent for CO_2 at anaerobic threshold (31.6 ± 1.5% vs. 39.2 ± 1.6; $p = 0.035$) on cardiopulmonary exercise testing (see Chapter 34).[122] In that study, the 6-minute walk distance was inversely correlated with pulmonary vascular resistance and mPAP, and directly correlated with maximal oxygen consumption, supporting the contribution of increasing pulmonary artery pressures to loss of exercise capacity. A lower exercise capacity (assessed by the 6-minute walk test) in patients with PH has also been demonstrated in larger cohorts of patients with SCD.[93,94,96,97] In addition, in patients with SCD, pulmonary artery pressure and pulmonary vascular resistance sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional limitation in these patients.[121] In aggregate, these data suggest that in patients with chronic anemia, mild-to-moderate PH has a severe adverse impact on functional and aerobic exercise capacity.

TREATMENT

There are limited data on the specific management of patients with SCD and PH, and most treatment recommendations are based on expert opinion or extrapolated from data derived from other forms of PH.[131] The general approach should include maximization of SCD-specific therapy (i.e., treatment of primary hemoglobinopathy), treatment of hypoxia with chronic oxygen therapy, treatment of associated cardiopulmonary conditions (such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, thromboembolic disorders, left ventricular disease). In patients with SCD with PAH (mean PAP ≥25 mm Hg and wedge pressures <15 mm Hg, with a relatively high pulmonary vascular resistance, e.g., >160 dyn-s/cm^5), PAH-specific therapy can be considered. There are no long-term data on the specific treatment of PH in SCD and the choice of agents is largely empirical and based on the safety profile of the drugs and physician preference. Therapy should be initiated and monitored by a team composed of a PAH specialist and a hematologist specializing in SCD care.

Hydroxyurea has been shown to decrease the incidence of pain episodes and ACS, to reduce the need for transfusions, and to lower overall mortality.[10,67] It is possible that some of the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in PH. However, these considerations have to be balanced with the lack of association between fetal hemoglobin levels and the use of hydroxyurea, and protection against the development of PH.[26] For patients with creatinine levels less than 1 mg/dL hydroxyurea is started at a dose of 15 mg/kg/d and titrated up to a maximum of 35 mg/kg/d. Recent detailed treatment guidelines have been published.[68,132] Patients with renal dysfunction tend not to tolerate the myelosuppressant effects of hydroxyurea and in those cases, we recommend the addition of erythropoietin to the regimen. Long-term transfusion therapy lowers the risks of most complications of the disease, including the risks of pulmonary events and central nervous system vasculopathy[133–135]; and might improve cardiopulmonary function and prevent the progression of PH.

The potential benefits of warfarin therapy observed in patients with idiopathic pulmonary arterial hypertension[136] have to be weighed against the risk of hemorrhagic stroke in adults with SCD or hemorrhage in chronically anemic individuals. We believe that the relatively low risk of hemorrhagic stroke (0.21 events per 100 patient-years[137]) compared with the high risk of death in patients with severe PH supports anticoagulation in patients with hemodynamic evidence of pulmonary arterial hypertension or chronic thromboembolic PH and without a specific contraindication.

Sildenafil functions by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. In a series of seven patients with either thalassemia or sickle thalassemia and severe PH treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6-minute walk distance.[138] In another case series, twelve patients with SCD were treated with sildenafil for a mean of 6 months. Mean PASP decreased by 9 mm Hg (95% CI, 0·3–17; $p = 0·047$), 6-minute walk distance improved by 78 m (95% CI, 40–117; $p = 0·003$), mean BNP decreased by 448 pg/mL ($p = 0·002$).[139] These preliminary data were not supported by the results of the Walk-PHaSST study.[140] This 16-week, NIH-sponsored multicenter double-blind placebo-controlled trial of sildenafil in 74 patients with SCD with increased TRV and a low exercise capacity was stopped early, before enrollment of the planned 132 patients, due to a higher percentage of subjects experiencing serious adverse events in the sildenafil arm (45% of sildenafil, 22% placebo, $p = 0.022$). Subject hospitalization for pain was the predominant cause for this difference: 35% sildenafil versus 14% placebo ($p = 0.029$). Although the study was underpowered at the time it was stopped, there was no evidence of a treatment effect on 6MWD (placebo-corrected effect, −9 m; 95% CI, −56 to 38; $p = 0.703$), TRV ($p = 0.503$), or NT-proBNP ($p = 0.410$). Based on these findings, sildenafil and the other PDE5 inhibitors should not be used as first-line agents in patients with SCD and PAH. If used, it should only be in patients on chronic transfusion therapy or very well controlled with hydroxyurea, to limit the apparent effects of these agents on increasing pain.

The published experience with endothelin receptor antagonists in the treatment of PH is also very limited. Minniti, et al.[141] reported on the use of bosentan and ambrisentan in a cohort of 14 patients with SCD and PH documented by heart catheterization. Endothelin antagonist therapy either as monotherapy or in combination with sildenafil resulted in a modest improvement in 6-minute walk distance (baseline 357 ± 22 vs. 398 ± 18 m 6 months posttherapy, $p < 0.05$) as well as lowered NT-proBNP levels and estimated PASP. Adverse events while on therapy occurred in 7 of 14 patients, including increased serum alanine aminotransferase (2), increased peripheral edema (4), rash (1), headache (1), and decreased hemoglobin (2). Only two patients required treatment discontinuation, and few patients experienced multiple side effects. Two randomized multicenter placebo-controlled studies evaluating the role of endothelin receptor antagonism in patients with SCD have been conducted. The ASSET-1 and ASSET-2 studies enrolled patients with pulmonary arterial hypertension and pulmonary venous hypertension, respectively who were randomized to bosentan or placebo. After enrollment of 26 subjects the studies were terminated due to slow site activation and withdrawal of support by the sponsor. In that limited sample of patients bosentan was well tolerated with no significant differences in serious averse events or laboratory tests between patients receiving study drug or placebo but efficacy endpoints could not be formally analyzed.[142]

Prostanoid analogs are the most effective agents for the treatment of pulmonary arterial hypertension. Acute administration of epoprostenol decreases pulmonary artery pressure and pulmonary vascular resistance, and increases cardiac output in patients with PH and SCD,[99] but chronic therapy with these agents has not been described in the literature.

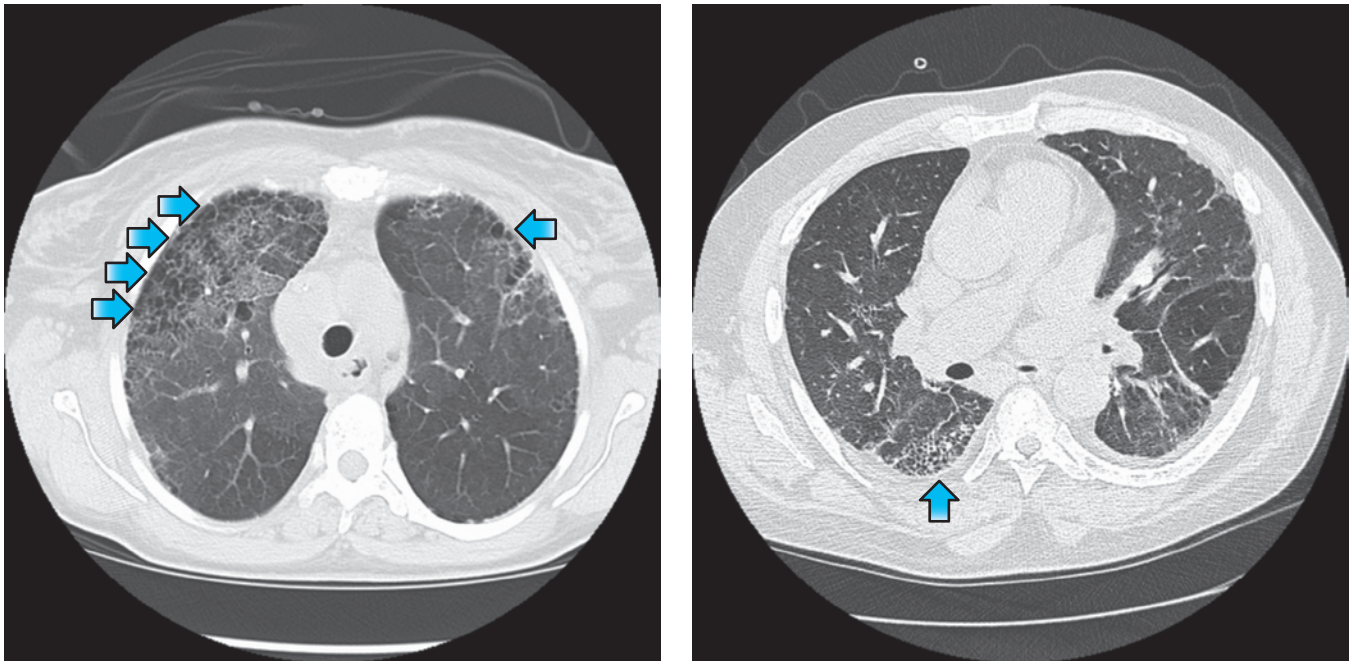
A case of severe pulmonary arterial hypertension related to pulmonary veno-occlusive disease has been reported in a patient with SCD. This patient failed medical therapy and underwent a successful bilateral lung transplantation.[143]

RESTRICTIVE LUNG DISEASE

Repetitive episodes of acute lung injury related to the ACS can result in parenchymal damage and restrictive lung disease (Fig. 96-7). In a study of 310 patients with homozygous SCD, pulmonary function was abnormal in 90% of adult patients.[144] The most common abnormal pattern was a mild restrictive pattern, found in 74% of those patients (TLC of 70 ± 15% predicted). An isolated decreased D_{LCO} was found in 13% (57 ± 20% predicted), persisted when corrected for hemoglobin, and negatively correlated with age. Evidence of obstructive lung disease occurred in only 3% of those studied. Although patients may present with advanced interstitial lung disease, these findings suggest that pulmonary fibrosis secondary to recurrent episodes of ACS tends to be mild in most cases.

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing has been reported in both children and adults with SCD.[145–147] In children, sleep-related upper airway obstruction and hypoxemia are the most common disturbances. In an uncontrolled study, adenotonsillectomy led to symptomatic improvement and amelioration of oxygen desaturation.[148,149] A small study of autoadjusting continuous positive airway pressure (auto-CPAP) with supplemental oxygen also suggests that this therapeutic modality is well tolerated, safe, and effective in pediatric patients with SCD.[150]



A B

Figure 96-7 Pulmonary fibrosis *(blue arrows)* complicating multiple episodes of acute chest syndrome. **A.** Cystic changes in areas of fibrosis. **B.** Subpleural fibrosis with honeycombing. *(Reproduced with permission from Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med. 2012;185(11):1154–1165.)*

Several lines of evidence suggest that nocturnal hypoxemia contributes to the development of neurological events and vasoocclusive crisis via mechanisms that could involve upregulation of several inflammatory endothelial adhesion molecules.[151–153] In addition, nighttime oxygen desaturation is associated with an increase in left ventricular mass and impaired diastolic function as evidenced by a study of 44 children with SCD.[154]

SUMMARY AND CONCLUSIONS

Pulmonary complications are a major cause of morbidity and mortality in patients with SCD and the burden of these complications are likely to become more prevalent as the life expectancy of these patients continues to increase.

Among the acute complications, ACS, which is often complicated by right heart failure, remains a major cause of death in children and adults with SCD. Fortunately, current strategies of early aggressive supportive therapy with antibiotics and red blood cell transfusion appear to have improved outcomes when compared with historical data.

PH is common and the most significant cause of death in adults with SCD. Although the etiology of PH is multifactorial in these patients, pulmonary arterial hypertension appears to be the main driver of morbidity and mortality. Additional studies evaluating pulmonary arterial hypertension–targeted therapy are needed in this complex and high-risk population.

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CHAPTER 97

Pulmonary Disorders and Pregnancy

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INTRODUCTION

Nearly six million pregnancies are reported in the United States every year. A number of characteristics of the pregnant population appear to be changing over time. For example, women are becoming pregnant later in their reproductive lives. In addition, with advances in medicine and assisted reproductive technology, women with chronic medical conditions are now able to become pregnant. Consequently, pregnant women are now older and have more comorbid conditions than in past generations. Given the physiologic changes that occur during gestation, pregnancy can be an important stressor to chronic medical conditions. Notably, the health of the pregnancy may be a window into the mother's long-term health.

Labor and delivery constitute a major hemodynamic and respiratory challenge; hence, women with both acute and chronic conditions need to be managed by a multidisciplinary healthcare team, which may include a pulmonologist. This multidisciplinary team should address medical and obstetrical concerns, along with risks and benefits of anesthesia and analgesia, thereby ensuring appropriate management and anticipation of potential complications.

This chapter addresses core pulmonary and cardiovascular physiologic concepts before consideration of important, common clinical entities related to diagnosis and management in pregnancy.

THE PHYSIOLOGY OF PREGNANCY

While the normal physiologic changes of pregnancy are extensive, several areas are of central importance and are considered below. These include changes in respiratory and cardiovascular physiology, normal physiologic developments during labor and delivery, and determinants of fetal oxygenation and ventilation.

RESPIRATORY PHYSIOLOGY

During pregnancy, the respiratory system undergoes changes which range anatomically from the nasopharynx to the lungs.

The effects of increasing levels of estrogen on the nasal mucosa include edema, hyperemia, and glandular hypersecretion. The result is gestational rhinitis, which typically occurs in the last few weeks of pregnancy.

The subcostal angle of the rib cage and the circumference of the chest wall increase due to the effects of relaxin.[1] The diaphragm moves cranially about 4 to 5 cm.[2] These changes occur to accommodate the growing uterus. Diaphragm excursion does not decrease in pregnancy, despite the changes in chest wall configuration. However, due to the higher resting position of the diaphragm, the decreased downward pull of the abdomen, and the aforementioned chest wall changes, functional residual capacity (FRC) decreases by 20% to 30% by late gestation[3] and declines further in the supine position (Table 97-1).[4] The reduction in FRC may be somewhat attenuated when measured using body plethysmography,[5] likely due to the effect of early airway closure during tidal breathing and air trapping.[6] Inspiratory capacity increases and, therefore total lung capacity (TLC) is not significantly changed (Fig. 97-1).[7]

Despite a reduction in FRC and reduced nasopharyngeal caliber, air flow rates and airway resistance do not change in pregnancy, since pregnancy is associated with bronchial smooth muscle relaxation.[8] While the increased cardiac output of pregnancy (see Section "Cardiac Physiology") may increase diffusion capacity, the associated anemia of pregnancy offsets the effect. D_{LCO} is higher in the first trimester (after correcting for alveolar volume and hemoglobin), but it may decline later in pregnancy, reaching a nadir at about 24 to 27 weeks of gestation.[9]

Progesterone is a respiratory stimulant; consequently, minute ventilation in pregnancy increases by about 50% due to an increase in

TABLE 97-1 Physiologic Changes in Pregnancy

Respiratory Parameter	Change	Normal Range in Pregnancy
Arterial blood gas values		
pH	↑	Mild respiratory alkalosis
Pa_{O_2}	↑	Average 100–105
Pa_{CO_2}	↓	Average 28–32
HCO_3	↓	18–22 mEq/L
Alveolar–arterial O_2 gradient	↑	Increase in late gestation to approximately 20 mm Hg
Oxygen consumption	↑	20% increase, further increase during labor and delivery
Minute ventilation	↑	50% increase
Respiratory rate	↔	No change
Tidal volume	↑	40–50% increase
Total lung capacity	↓	4–5% decrease
Functional residual capacity	↓	20% decrease by term
Residual volume	↓	
Vital capacity	↔	
Diffusion capacity	↔	Minimal change
Forced expiratory volume in 1 s	↔	
Peak expiratory flow rate	↔	
Cardiac	**Change**	**Normal Range in Pregnancy**
Blood pressure	↓	10–15 mm Hg decrease in first two trimesters
Blood volume	↑	30–50% increase
Cardiac output	↑↑	5–7 $L/m^2/min$ (40% increase)
Central venous pressure	↔	<13 mm Hg
Colloid oncotic pressure	↓	10–15% decrease
Ejection fraction	↔	70%
Heart rate	↑	Increases by 10–20 bpm
Pulmonary artery pressure	↔	≤25 mm Hg
Pulmonary capillary wedge pressure	↔	<13 mm Hg
Stroke volume	↑	70–100 mL/beat
Systemic vascular resistance	↓	25–30% decrease

↑ Increase, ↓ Decrease, ↔ No change.
Source: Modified with permission from Miller M, Bourjeily G. Management of the critically ill pregnant patient. Volume 23 (Lesson 8). Pulmonary and Critical Care Update (PCCSU); 2014.

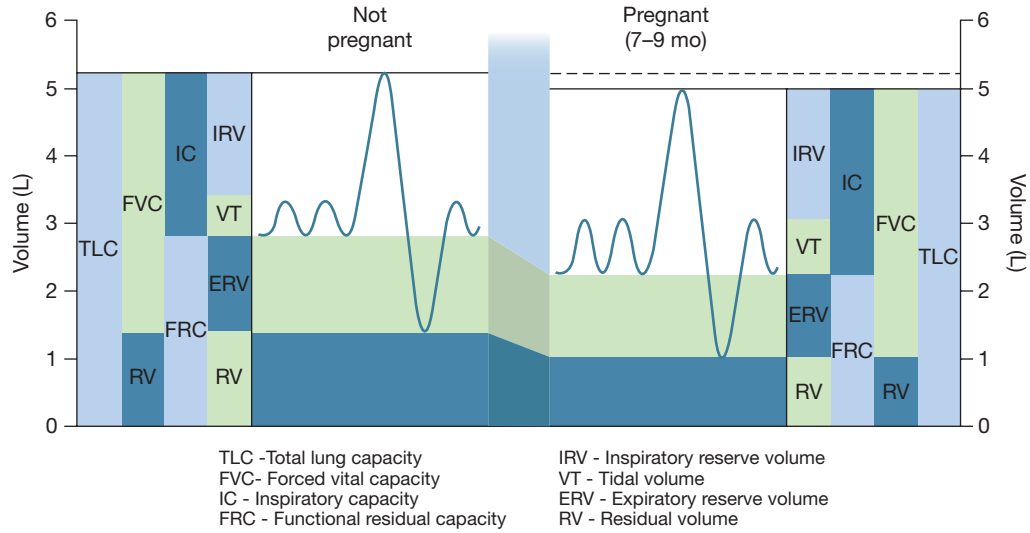

Figure 97-1 Changes in lung volumes in pregnancy. *(Reproduced with permission from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011;32(1):1–13.)*

tidal volume. Although some studies suggest a progressive increase in minute ventilation during the course of pregnancy,[3] most studies show a sharp increase in the first trimester, with minimal rise after that.[10,11] The ratio of dead space to tidal volume (V_D/V_T) is unchanged in pregnancy, suggesting that dead space is actually also increased. Although the increase in cardiac output seen in pregnancy, coupled with resulting improved perfusion of the lung apices, would suggest that a reduction in dead space should occur, many studies suggest the opposite effect.[12,13]

Arterial oxygen tension increases in pregnancy to about 100 to 105 mm Hg, thereby facilitating oxygen transfer across the placenta.[13] Carbon dioxide tension decreases in pregnancy to 27 to 32 mm Hg, with a resultant increase in bicarbonate excretion and elevation in arterial pH to approximately 7.42 to 7.46. Both Pa_{CO_2} and HCO_3 are mildly lower in the third trimester compared to the first trimester.[14] The chronic respiratory alkalosis of pregnancy causes a rightward shift of the oxyhemoglobin dissociation curve, facilitating oxygen transfer across the placenta.

CARDIAC PHYSIOLOGY

In parallel with growth of the fetus and the accompanying increase in maternal oxygen consumption, pregnancy is accompanied by profound cardiovascular changes. Plasma volume and cardiac output progressively increase throughout gestation and are approximately 30% to 50% higher[15] at term (Fig. 97-2).[16] Heart rate also increases by 20 to 30 beats per minute. Systemic vascular resistance decreases, with a resultant drop in blood pressure in the first half of pregnancy. Despite the increase in cardiac output, pulmonary artery pressures do not change significantly[17] due to a decrease in pulmonary vascular resistance (PVR). Oxygen consumption is increased approximately 20% above prepregnancy levels; the rate of increase in oxygen consumption is faster in pregnant women compared to nonpregnant women performing weight-bearing exercises.[18]

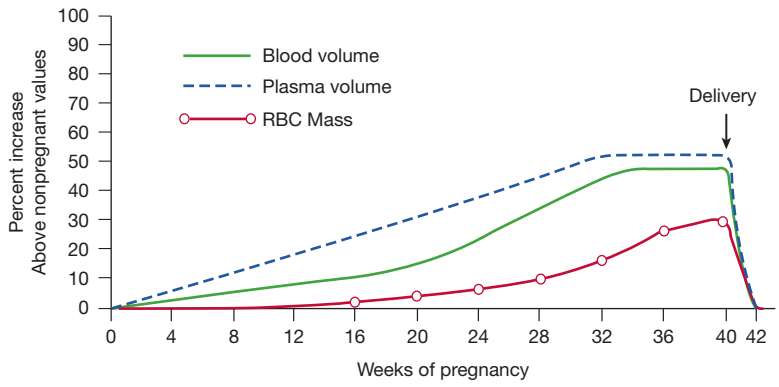

Figure 97-2 Physiologic changes in blood volume, plasma volume, and erythrocyte mass in pregnancy.

LABOR AND DELIVERY

Labor and delivery are associated with additional respiratory and cardiac physiologic changes. Pain, due to contractions and anxiety, leads to increases in oxygen consumption and minute ventilation. Increased minute ventilation leads to further reduction in Pa_{CO_2} which, in cases of tenuous placental reserve, may reduce placental perfusion. In addition, in women with poor respiratory reserve, such as those with poorly controlled asthma or restrictive pulmonary physiology, the additional increase in minute ventilation may lead to respiratory decompensation and respiratory failure. Pain control may help minimize these effects. However, the use of systemic opiates can lead to respiratory depression, whereas targeted regional anesthesia – thereby avoiding an effect on respiratory muscles – may prevent these adverse effects. Physiologic changes occurring in pregnancy quickly reverse in the postpartum period.

Cardiovascular changes in labor, delivery, and the postpartum period include an additional 10% to 15% increase in cardiac output in early labor, with further increases of up to 50% in the second stage of labor.[19] The changes are mediated by autotransfusion, in which 300 to 500 mL of blood is shunted into the systemic maternal circulation with every uterine contraction,[20] and by pain and anxiety.[21,22] Analgesia attenuates the changes. In addition, in the postpartum period, relief of aortocaval compression by the uterus results in an increase in venous return; autotransfusion from the contracting uterus further increases cardiac output. Women with underlying cardiac or pulmonary vascular disease may not tolerate the physiologic changes of labor and delivery. Although scheduled Cesarean-section deliveries may appear to be an attractive option for women with chronic pulmonary or cardiac disease (since they may eliminate the pain and anxiety of contractions), Cesarean-section

deliveries are unlikely to improve outcomes, since autotransfusion occurs with both vaginal and operative deliveries. Furthermore, the immediate fluid shifts that occur in the postpartum period are similar with both vaginal and Cesarean-section deliveries. In addition, operative deliveries are associated with higher rates of surgical and medical complications compared with vaginal deliveries.

FETAL OXYGENATION AND VENTILATION

Uterine blood flow constitutes about 17% of the total cardiac output.[23] The placental vessels are low-resistance, high-capacitance vessels that function at maximal capacity at baseline. Therefore, when a hemodynamic insult occurs, the placental circulation cannot further vasodilate.

Supine positioning in late pregnancy may be associated with significant reduction in cardiac output and may alter the uterine circulation. Fetal oxygenation, like oxygenation of maternal organs, depends on maternal cardiac output, maternal oxygenation, and the fetal oxyhemoglobin dissociation curve. In addition, characteristics of the placenta affect diffusion of oxygen across this organ.

The fetus displays many protective mechanisms for maintaining adequate oxygenation. For example, fetal hemoglobin, which lacks beta chains, is less sensitive to the effects of 2,3-DPG than is adult hemoglobin. Consequently, the fetal oxyhemoglobin dissociation curve is shifted to the left, reflecting an increased oxygen affinity. The fetus also appears to have the ability to shunt blood to vital organs and to decrease oxygen consumption during periods of hypoxia. Despite these protective mechanisms, placental health has an important role in effecting oxygen transport to the fetus.[24]

Clinical conditions that cause a reduction in cardiac output or uterine blood flow (e.g., shock, use of vasoconstricting drugs), oxygen content (e.g., anemia, hypoxemia), oxyhemoglobin saturation (e.g., severe alkalosis, presence of carboxyhemoglobin), or placental perfusion may result in poor fetal oxygenation. Human studies on the optimal maternal oxygen level needed to achieve favorable fetal oxygenation are scarce. Based on available animal data, experts recommend that maternal oxygenation be maintained above a Pa_{O_2} of 70 mm Hg and an oxygen saturation of greater than 95%.

Finally, a gradient for CO_2 of approximately 10 mm Hg between fetal and maternal circulations exists (higher level in the fetus), facilitating CO_2 clearance from the fetal circulation. This fact may influence how best to use permissive hypercapnia in patients who might benefit from this ventilatory strategy. Fetal hypercapnia results in rapid fetal acidemia, increases in intracranial pressure, and a rightward shift of the oxyhemoglobin dissociation curve.

DIAGNOSTIC IMAGING OF THE PREGNANT WOMAN

Use of ionizing radiation is a major concern for most clinicians evaluating a pregnant patient. Risks that need to be considered when ordering an imaging study that involves the use of ionizing radiation are the risk of malignancy and the risk of teratogenicity.

The risk of oncogenicity follows a stochastic effect (nonthreshold effect), suggesting that the risk of malignancy may occur even at low levels of exposure. Based on atomic bomb survivor data, the risk of malignancy following high-dose exposures is indisputable; however, the risk following low doses associated with diagnostic testing is more controversial. This risk is not evenly distributed, as recent data suggest a lower risk of cancer when exposure occurs in utero compared to exposure in childhood.[25]

The risk of teratogenicity, however, does follow a threshold effect. Based on animal and human studies of radiation exposure, a threshold has been determined for congenital malformations and miscarriage. For diagnostic tests resulting in a fetal exposure of 10 cGy or less, the risk of radiation to the embryo is very small when compared to the spontaneous risk. More conservative opinions suggest aiming for a maximum exposure of 5 cGy. With the exception of computed tomography venography, radiation exposure from imaging procedures used for the workup of a patient with a suspected or diagnosed respiratory disorder does not exceed 5 cGy (Table 97-2).[26] As the risk of radiation below 10 cGy is miniscule, medical care of the mother takes priority over the risks of diagnostic radiation exposure to the fetus.[27]

TABLE 97-2 Radiation Exposure to the Fetus Associated with Various Diagnostic Procedures

Diagnostic Test	Radiation Dose (cGy)
Chest radiography	<0.001
Ventilation scintigraphy[28]	0.028–0.051[a]
Perfusion scintigraphy[28] (half dose)	0.014–0.025
CT pulmonary angiography[29]	0.0003–0.0131
Conventional pulmonary angiography	<0.05 via brachial route 0.2–0.3 via femoral route
CT venography	>5
Conventional venography	0.6
Chest Fluoroscopy[27]	<0.01 cGy/min
IR abdominal fluoroscopy[27]	0.6 cGy/min
PET[27]	0.8–1.6

CT, computed tomography; PET, positron emission tomography.
[a]Dependent on agent used.
Source: Modified with permission from Bourjeily G. et al. Pulmonary embolism in pregnancy. Lancet. 2010;375(9713):500–512.

Another consideration in diagnostic imaging studies includes use of contrast agents. Iodinated contrast media are small molecules that are known to cross the placenta and carry a potential risk of thyroid dysfunction in utero. However, in a study of 350 women who received iodinated contrast in pregnancy, none of the babies born had any significant thyroid dysfunction.[30] The study was, however, performed in the northeast United States, an area where iodine deficiency is rare. Use of iodinated contrast is, therefore, certainly justifiable. However, iodine reserve, timing of the study in pregnancy, and maternal renal function should be considered. Gadolinium is usually used with nonionizing radiation imaging studies and is known to cross the placenta.[31] The effect of gadolinium on the growing fetus is unknown, as human safety data are not available. Hence, use of gadolinium should be reserved for cases where benefit outweighs the potential unknown risk of gadolinium exposure.

Diagnostic studies involving radionuclides expose the fetus to radiation differently than external radiation. Given that radionuclides are excreted by the kidneys and may pool in the bladder, continuous exposure to the fetus may occur after the study has been completed.

PHARMACOTHERAPY CONSIDERATIONS IN THE PREGNANT PATIENT

Over-the-counter drugs and prescription medications are frequently used during pregnancy. Although a number of drugs have been clearly shown to be either teratogenic or safe in pregnancy, insufficient safety data exists for most. Most data on safety for a given drug in pregnancy are based on animal studies, case reports or series, case-control studies, or pregnancy registries. Prospective studies evaluating safety are scarce. Establishing risk is challenging, since a baseline risk of malformation exists for any pregnancy. To clearly define a teratogenic risk, a recurrent syndrome of abnormalities needs to be demonstrated. In addition, in many cases it may be hard to tease out the effect of the medication from the effect of

the disease. Justification of randomization to treatment or placebo groups during pregnancy is challenging. An informed decision by the patient, formulated in the context of discussion with the physician, is key. Integral to the discussion is the patient's understanding of the limitations of the available data and the intricacies of pharmacotherapy in pregnancy.

Placental transfer of medications and their risks depend on maternal drug metabolism, drug molecular size, drug ionization, the agent's lipid solubility, and maturity of the fetal target organ. As a general rule, most drugs cross the placenta. Although most consider the period beyond embryogenesis a safe timeframe to use medication, it is important to recall that the fetal nervous system continues to develop throughout gestation. For this reason, fetal neurologic and behavioral development and function of various organs, such as thyroid or kidney, may be affected by medications administered after the first trimester. Physiologic changes of pregnancy, such as increased plasma volume, increased glomerular filtration rate, and hypoproteinemia may affect medication bioavailability.

The categories of drug safety in pregnancy used by the US Food and Drug Administration (FDA) have several well-established shortcomings. For example, since teratogenicity is not species specific, supportive evidence from human and animal data should not be given equal weight. The risk of drugs in a given category may not be comparable. For instance, drugs in category C either have been shown to demonstrate evidence of adverse effects in animals or lack available animal data. In addition, adverse fetal effects are not all equal, and a mild reduction in fetal weight should not be considered equivalent to a major congenital anomaly. Finally, the FDA categorization does not take into account the risk of the untreated disease. Therefore, the decision for using a drug should be based on principles of efficacy and safety and should encompass consideration of medication risk versus risk of untreated disease. For example, use of a category C drug in a life-threatening situation may be reasonable, whereas use of a category B drug for a self-limited condition, such as an upper respiratory infection, may not.

Breastfeeding is associated with significant benefits to newborns, such as a lower risk of obesity, diabetes, and cardiovascular disease, among others,[32–34] and consideration of drug passage into breast milk is an important consideration. A variety of factors influence drug passage to the neonate. For example, drugs with no oral absorption by the neonate are unlikely to cause systemic effects. Drug levels in breast milk are proportional to those in the maternal serum. Hence, breast milk drug levels vary with timing of maternal drug intake. Drugs with the highest protein binding and lowest lipid solubility are preferable for breastfeeding women.[35] Table 97-3 summarizes data on commonly used drugs in pregnancy and lactation.

INTERVENTIONAL PROCEDURES IN PREGNANCY

Indications for interventional procedures in pregnancy are no different than in the nonpregnant population. In the general population, most interventional procedures are not delayed if they are anticipated to be of clinical importance in patient management. Similar logic should be applied in pregnancy. As with any intervention, the risk of the intervention should be weighed against the risk of an inappropriate diagnosis or untreated disease. For example, the risk of bronchoscopy in pregnancy may be related to the procedure itself, as well as to the sedatives used during the procedure. Medication effects may be even more pronounced in the pregnant patient, given the altered physiology of pregnancy, including drug distribution, response to sedatives, and decreased airway patency. However, the risk is usually minimal.

In pregnant women, an upper airway evaluation should be performed prior to every procedure, given the higher risk of intubation failure in pregnancy. Risk of aspiration may also be increased because of a decrease in lower esophageal and increase in intra-abdominal pressures. To minimize the risk of hypotension and hemodynamic instability during procedures performed in the second half of pregnancy, patients should be positioned supine with a left tilt to relieve the compression of the inferior vena cava by the gravid uterus.

Given the risk of hypoxemia with bronchoscopy,[41] especially when bronchoalveolar lavage is performed,[42] oxygenation should be monitored routinely and supplemental oxygen administered as needed to keep oxygen saturation above 95%. Fetal monitoring should be discussed with the obstetric team; however, in general, fetal monitoring prior to 28 weeks of gestation can be unreliable and difficult to interpret, while monitoring prior to 24 weeks is likely unnecessary.[43] Since pregnant women may more quickly develop hypercapnia and hypoxemia than nonpregnant women,[44] smaller doses of sedation might be considered. Midazolam, meperidine, fentanyl, and lidocaine have not been reported to be associated with congenital malformations.[45]

Fluoroscopy during bronchoscopy can be used in pregnancy, given the low dose of radiation associated with its use (Table 97-2)[26] and the fact that the fetus is not in the radiation field. A discussion with the institution's medical physicist can help keep radiation exposure to a minimum.

Pleural procedures can also be performed in pregnancy, but providers should keep in mind the potential 4 to 5 cm cranial displacement of the diaphragm during pregnancy. Ultrasound guidance may help minimize risks of the procedure.

SMOKING DURING PREGNANCY

Estimates are that 22% of women of reproductive age in the United States smoke. Data from Europe and the United States show that 10.7% to 13.1% of fetuses are exposed to maternal smoking. Although about half of women smokers quit during pregnancy, many start smoking again after delivery. In 1993, the estimated annual cost of maternal conditions attributable to smoking in pregnancy, including the protective effect against preeclampsia, was between $135 and $167 million.[46,47]

Smoking is associated with adverse fetal outcomes. Various mechanisms may be responsible. Placentas from smokers have reduced capillary volume and increased thickness of villous membranes.[48–50] Carboxyhemoglobin is cleared slowly from the fetal circulation and competes with fetal oxyhemoglobin. Amniocytes from smokers have an increased incidence of structural chromosomal abnormalities compared with nonsmokers.[51] In addition, nicotine promotes platelet activation, impairs estrogen synthesis, and can directly impair lung development due to interaction with nicotinic acetylcholine receptors.

Smoking is associated with placental abnormalities, premature rupture of membranes, decreased thyroid function, psychiatric illness, reduced fertility, and conception delay,[52–56] as well as decreased production of milk volume, and lower rates and shorter duration of breastfeeding.[57] Prospective[58] and retrospective studies[59] confirm an association of fetal growth restriction with smoking during pregnancy, even in the first trimester.[60] Both active and secondhand smoke exposures are associated with increased risk of first trimester pregnancy loss.[61]

Babies born to pregnant smokers are also at risk for preterm birth.[62] The association of smoking with a risk of congenital anomalies[63] is a complex issue and may be closely related to maternal genotype. Maternal smoking during pregnancy is also associated with adverse cognitive and behavioral outcomes in the offspring, such as low scholastic achievement, attention deficit and hyperactivity disorder, conduct disorder, regular smoking,[64] wheezing, and asthma.[65] Childhood exposure to secondhand smoke is associated with upper and lower respiratory tract infections, ear infections, sudden infant death syndrome (SIDS), and asthma.[66–68]

Smoking cessation at any point during pregnancy is likely associated with some benefit.[69] Pregnancy offers a unique opportunity for smoking cessation, given the mother's motivation for fetal

well-being and her frequent contact with healthcare providers. Women should be screened for secondhand smoking exposure, as well as potential abuse of other substances and comorbid psychiatric illness. Women should also be followed for smoking abstinence into the postpartum period, given the high rate of smoking relapse.

Pharmacotherapy can be used in pregnancy, but data regarding efficacy and safety are scarce. The US Preventive Services Task Force states that the use of pharmaceuticals has not been sufficiently evaluated to determine their safety or efficacy in pregnancy.[70] Data on nicotine replacement therapy shows conflicting evidence with regard to safety.[71,72] Many trials have been halted in the United States because of either adverse effects or failure to demonstrate effectiveness.[73,74] The Danish National Birth Cohort of 72,761 women showed no significant association between type or duration of nicotine product use and birth weight.[75] Overall, the risk from various chemicals in cigarette smoke likely outweighs the small risk of possible weight reduction from nicotine pharmaceuticals.

Although animal data on the safety of use of varenicline in pregnancy are available, human data are lacking. Varenicline is likely transferred through breast milk; however, data are not available. Bupropion has not been associated with an increase in congenital defects in experimental animal studies. However, pregnancy registry data for bupropion calls attention to a possible association with congenital heart defects.[76] Although bupropion is passed to the fetus in breast milk, based on measurement of infant plasma levels, the dose transmitted is unlikely to be clinically significant.

MANAGEMENT OF ASTHMA DURING PREGNANCY

Asthma is the most common respiratory disease of pregnancy, affecting 4% to 8% of all pregnancies in the United States and almost 12% of pregnancies in the United Kingdom and Australia. Asthma may improve, worsen, or remain unchanged in pregnancy.[77] Predictors of disease course include prepregnancy asthma severity, race, presence of obesity, compliance with medication use, and patient difficulties in accessing antenatal care. Factors contributing to modifications of disease severity include a number of pregnancy-associated conditions: higher prevalence of gastroesophageal reflux disease,[78] nasal congestion,[79] alterations in immunity, and hormonal factors.[80] The rate of asthma exacerbations is increased between 17 and 32 weeks of gestation.[77,81] Improvement in the last few weeks of pregnancy may be related to significantly higher cortisol levels compared with preconception levels.

Poorly controlled asthma may negatively impact some maternal and fetal outcomes. In the largest study performed to date, asthmatic women were more likely to have pregnancies complicated by miscarriage, antepartum and postpartum hemorrhage, anemia, or depression.[82] In a retrospective cohort study performed in 12 clinical centers in the United States, asthmatics experienced increased risk of preeclampsia; gestational diabetes; preterm births, including spontaneous preterm birth; and induced preterm birth.[83] A systematic review of nine studies has shown an increased risk of preterm birth, small for gestational age and low birth weight if the mother has asthma.[84] Babies born to asthmatic mothers may be more likely to have congenital anomalies.[85,86]

Since pregnancy does not affect air flow rates, reductions in peak expiratory flow rate (PEFR) should prompt quick medical evaluation. In a multi-institutional prospective study, lower forced expiratory volume in 1 second (FEV_1), but not symptom control, was associated with adverse perinatal outcomes.[87] These data may be related to the fact that, given the high prevalence of physiologic dyspnea in pregnancy, symptom interpretation both by providers and patients may be difficult without objective measures; hence, the need for close physiologic monitoring is apparent.

Most medications used to treat asthma are safe for use in pregnancy (Table 97-3). An important message to patients is that good asthma control is the main goal, and the risk of medication use is lower than the risk of adverse outcomes from untreated or poorly treated disease. Recent evidence from a double-blind, randomized, controlled trial suggests that pregnant women managed according to a validated treatment algorithm based on measurements of exhaled nitric oxide (FeNO) had fewer exacerbations compared with those treated according to a symptom-based approach.[88]

Patients with more severe disease, or those who suffer an exacerbation close to term, require a detailed labor and delivery plan. Stress dosing with corticosteroids during labor should be considered in patients who have been on prolonged courses of systemic steroids during the pregnancy. Patients with active symptoms or more severe asthma may benefit from regional anesthesia aimed at reducing minute ventilation and oxygen consumption and preventing hyperinflation. If general anesthesia is considered, ketamine and halogenated anesthetics are preferred. Oxytocin and prostaglandin E2 are safe to use. However, other prostaglandins used for induction of labor and morphine and meperidine should be avoided, since they may cause worsening bronchospasm.

CYSTIC FIBROSIS AND PREGNANCY

Cystic fibrosis (CF) impacts fertility in both men and women. Women with CF have various reproductive system abnormalities. Since the CF transmembrane conductance regulator (CFTR) is present in reproductive organs, cervical mucus is thicker and more tenacious, leading to obstruction of the cervical os and impaired sperm penetration. Despite these changes, fertility occurs in women with CF, and affected women should be counseled regarding contraception. Women with higher body weight and higher FEV_1 are more likely to desire and achieve pregnancy.[89] Genetic screening of both mother and father can help assess the risk of CF in the offspring. Preimplantation genetic diagnosis can be performed during assisted reproduction and may help detect embryos affected by the disorder.

In two series reporting on 72 and 90 pregnancies in patients with CF, the need for intravenous antibiotic therapy was 65% to 77%, and higher rates of hospitalization compared to nonpregnant patients were reported.[90,91] FEV_1 may decline during pregnancy in CF, and then improve in some patients following delivery.[92] However, in larger case-controlled series, the FEV_1 decline appears similar to that experienced by nonpregnant patients with CF.[90,93] Reduced FEV_1 appears to be a predictor of adverse outcomes in pregnancy in CF,[91] including early mortality following delivery. Other predictors of decreased survival include maternal colonization with *Burkholderia cepacia* and pancreatic insufficiency.

Increased energy expenditure in pregnancy makes weight gain more challenging. Glucose intolerance and gestational diabetes occur as a result of decreased insulin production, impaired insulin sensitivity, and increased hepatic glucose production.[93,94] Multiple studies have shown an increased risk of preterm delivery,[90,95] possibly related to altered lung function. The risks of fetal demise and birth defects are likely similar to controls.[90,91,93]

Azithromycin, penicillins, and cephalosporins are safe to use in pregnancy. In animal studies, use of fluoroquinolones may be associated with increased risk of abnormal cartilage development; similar effects have not been observed in human studies.[96] Use of tetracyclines is hard to justify in pregnancy, since they result in tooth and bone discoloration. Rifamycins are associated with an increased risk of fetal damage and bleeding in both mother and neonate.[97] Dornase use has been described in pregnancy,[98] but safety data are limited. Safety data on use of pancreatic enzyme replacement therapy are limited,[99,100] but use is likely justifiable. Vitamin replacement can be used in pregnancy; however, vitamin A supplementation should not exceed 10,000 U daily because of teratogenic effects. Although sulfonylureas are likely safe in pregnancy, they are associated with an increased risk of fetal hypoglycemia. Insulin is the preferred glucose-lowering drug.

TABLE 97-3 Drug Safety in Pregnancy and Lactation

	Pregnancy	Lactation
Ambrisentan	Ambrisentan is expected to be teratogenic, given its mechanism of action and known teratogenicity in animal studies. No human data.	Infant risk cannot be ruled out. It is not known whether ambrisentan is excreted into human milk. **AAP:** Not reviewed
Amoxicillin/ Clavulanate	Amoxicillin/clavulanate is acceptable for use during pregnancy. Penicillins are generally considered to be safe for use in nonallergic patients during pregnancy.	No harmful effects have been reported. **AAP:** Maternal Medication Usually Compatible with breastfeeding **Lactation Risk Category:** L1
Azathioprine	Based on human case series, azathioprine is unlikely to increase the risk of congenital anomalies.	Caution is recommended. Monitor the infant closely for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis, and other symptoms of 6-mercaptopurine exposure. The risks to the infant are probably low. Recent long-term data suggest that the rate of infections in treated groups is no different from nontreated controls. **Lactation Risk Category:** L3
Beta agonists	Albuterol is listed as preferred beta agonist in 2004 NIH report on treatment of asthma in pregnancy. High doses (32 mg/d) of oral albuterol appeared to prolong gestation in a population of 132 pregnancies.[36] Various birth defects were described in association with albuterol and may have been due to chance. Salmeterol is not expected to increase the risk of congenital malformations. Formoterol is not expected to increase the risk of malformations, but human data are inadequate.	Safe to use in breastfeeding mothers. Use via inhalation is recommended. **AAP:** Not reviewed **Lactation Risk Category:** L1 Safe to use in breastfeeding women. Levels in breast milk very low to undetectable. **AAP:** Not reviewed **Lactation Risk Category:** L2
Bosentan	Bosentan is believed by its manufacturer to increase the risk for congenital anomalies in humans, based on rodent studies and the known mechanism of action of the medication.	No data are available on the transfer into human milk, but based on its structure, bosentan levels in the milk compartment would probably be very low. However given 50% oral bioavailability and high incidence of liver toxicity, great caution is recommended with this product in breastfeeding mothers until we have published milk levels. **Pediatric Concerns:** No data are available. May be dosed down to children weighing at least 22 lb. **Lactation Risk Category:** L4
Budesonide Inhaler	No association with congenital birth defects. Children exposed to inhaled steroids are more likely to develop endocrine, metabolic, and nutritional disorders.	Unlikely clinically relevant concentrations of budesonide reach breast milk. **Lactation Risk Category:** L1
Bupropion (Wellbutrin)	Bupropion has not been associated with an increased risk of congenital defects; however, pregnancy registry data have called attention to a possible weak association with congenital heart defects (not confirmed in other studies).	Bupropion may, in some women, suppress milk production. Some caution is recommended concerning changes to milk supply. **AAP:** Drugs whose effect on nursing infants is unknown but may be of concern
Cephalosporins	Cephalosporins may cross into the fetal circulation in small amounts, but teratogenicity has not been attributed to these agents.	As a highly protein-bound group, the cephalosporins do not pose a significant risk to the nursing infant.
Cyclosporin	Experimental animal studies do not predict an increase in congenital anomalies after pregnancy exposure to cyclosporines. A limited number of human cases are also reassuring.	Cytotoxic drug that may interfere with cellular metabolism of the nursing infant. Close observation of the infant including monitoring of the infants' plasma levels. **AAP:** Possible immune suppression; unknown effect on growth or association with carcinogenesis **Lactation Risk Category:** L3
Epoprostenol sodium	It is unknown if epoprostenol shares any of the abortifacient properties of other prostaglandins. Should it be determined that it does, its use in pregnant women would be strictly contraindicated; therefore, use should be avoided if possible.	Unknown **AAP:** Not reviewed **Lactation Risk Category:** L3
Gentamicin	Ototoxicity and nephrotoxicity in the fetus are theoretical possibilities that have not been confirmed clinically. This agent is known to cross the human placenta at term, but its use is likely justifiable in certain conditions.	**AAP:** Compatible with breastfeeding **Lactation Risk Category:** L2
Iloprost (Ventavis)	No epidemiologic studies of congenital anomalies among infants born to women who were treated with iloprost during pregnancy have been reported. Iloprost has been shown to be teratogenic in rats due to its systemic circulatory effects.	It is not known whether iloprost appears in milk. Increased mortality of nursed rat pups was reported and manufacturer recommends discontinuing nursing in women being treated with iloprost.

TABLE 97-3 Drug Safety in Pregnancy and Lactation *(Continued)*

	Pregnancy	Lactation
Ipratropium bromide	Based on animal studies, ipratropium is not expected to increase the risk of congenital malformations.	Transfer into breast milk in exceedingly small and clinically insignificant levels. **Lactation Risk Category:** L2
Linezolid	Linezolid does not cause congenital malformations in mice and rats, even at high doses. There are no human data.	Minimal human data available. Linezolid is transferred to breast milk with a likely maximal dose of 2 mg/kg daily (with maximal dose for infants being 30 mg/kg daily). **Lactation Risk Category:** L3
Macrolide antibiotics	*Erythromycin* use during pregnancy is unlikely to increase teratogenic risk to the infant, including cardiac and gastrointestinal defects. *Clarithromycin* may increase the risk of adverse pregnancy outcome. In a series of observational studies, *azithromycin* did not cause an increased rate of congenital anomalies when used during pregnancy.	Pyloric stenosis has been reported associated with the use of erythromycin early postpartum. **AAP:** Usually Compatible with breastfeeding **Lactation Risk Category:** L3
Methotrexate	Methotrexate increases the incidence of congenital anomalies in experimental animals and appears to do so in humans as well. Methotrexate is used clinically as an abortifacient[37–39] and in the treatment of ectopic pregnancy. One study indicates a higher risk of fetal malformation in mothers who received methotrexate months prior to becoming pregnant.[40] Therefore, pregnancy should be delayed for at least 3 mo following therapy if either partner is receiving methotrexate.	Methotrexate is believed to be retained in human tissues (particularly neonatal gastrointestinal cells and ovarian cells) for long periods (months). It is apparent that the concentration of methotrexate in human milk is minimal, although due to the toxicity of this agent, it is probably wise to pump and discard the mother's milk for a minimum of 2–4 d. **AAP:** Possible immune suppression; unknown effect on growth or association with carcinogenesis; neutropenia. **Lactation Risk Category:** L3
Nicotine replacement	Nicotine therapy may decrease fetal growth similar to smoking. Some types are however beneficial regarding cigarette consumption, gestational age, and birth weight.	Nicotine is secreted into human milk. Use of replacement products is compatible with breastfeeding. **AAP:** Not reviewed **Lactation Risk Category:** L2
Omalizumab	Data in monkeys are reassuring, but currently, there are no human data. Pregnancy registry exists.	Omalizumab may be secreted into human milk but levels likely very low. Oral bioavailability extremely low. **AAP:** Not reviewed **Lactation Risk Category:** L3
Penicillin	Penicillins are not believed to increase adverse pregnancy outcome. Penicillins accumulate in amniotic fluid during maternal ingestion. No adverse fetal effects have been associated with this process.	Usually compatible with breastfeeding Penicillins are excreted into human milk in small amounts with possible alterations in bowel flora and potential risk of allergic sensitization in the infant.
Prednisone	Prednisone and other glucocorticoids are associated with fetal growth impairment in humans. Prednisone is metabolized by the placenta to a large extent, and minimal doses reach the fetus. Other steroids, such as betamethasone, are less well metabolized by the placenta and are used to enhance lung maturity in pregnancies expected to end preterm. These medications increase oral clefting in experimental animals and may do so in humans in early pregnancy exposure.	Small amounts of most corticosteroids are secreted into breast milk. With prolonged high dose therapy, the infant should be closely monitored for growth and development. **AAP:** Usually Compatible with breastfeeding **Lactation Risk Category:** L2
Quinolones	Quinolones are avoided during pregnancy due to cartilage toxicity demonstrated in experimental animals. Human data are not supportive.	Quinolones are secreted in milk. Infants should be observed for changes in gut flora, Candida overgrowth, or diarrhea. The use of quinolones in the pediatric population is increasing due to minimal evidence of cartilage toxicity. **AAP:** Not reviewed **Lactation Risk Category:** L2
Sildenafil	Based on experimental animal studies, sildenafil does not appear to increase the risk of congenital malformations in exposed pregnancies.	There is insufficient data to determine the safety of sildenafil in human lactation.
Tacrolimus	Based on experimental animal studies and human case reports, tacrolimus is not expected to increase the risk of congenital anomalies. Hypertension, prematurity, and neonatal hyperkalemia have been suggested by case reports as possible adverse effects.	According to the manufacturer, tacrolimus is excreted in breast milk and should be avoided during lactation. However, studies in lactating mothers suggest the exclusively breastfed infant would receive less than 0.2% of the pediatric dosage for organ transplant rejection. **AAP:** Not reviewed **Lactation Risk Category:** L3

(continued)

TABLE 97-3 Drug Safety in Pregnancy and Lactation *(Continued)*

	Pregnancy	Lactation
Treprostinil	Based on experimental animal studies with subcutaneous treprostinil, adverse effects in pregnancy are not anticipated. Human data and data on drug inhalation are lacking.	Manufacturer states that no reports describing the use of treprostinil during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown
Vancomycin	Based on experimental animal studies, vancomycin is not expected to increase the risk of congenital malformations. Theoretical concern exists regarding ototoxicity and nephrotoxicity, but supportive evidence in humans is not available.	Only low levels are secreted into human milk. Its poor absorption from the infant's gastrointestinal tract would limit its systemic absorption. Low levels in infant could provide alterations of gastrointestinal flora. **AAP:** Not reviewed **Lactation Risk Category:** L1
Varenicline (Chantix)	Based on experimental animal studies, use of varenicline during pregnancy is not expected to increase the risk of congenital malformations. Human data are not available.	There have been no studies performed on the transfer of varenicline into human milk. **Lactation Risk Category:** L4

Vaginal delivery is the expected mode of delivery in CF unless other indications for Cesarean section exist. Epidural anesthesia may help with minimizing minute ventilation and oxygen consumption in patients with reduced lung function. Breastfeeding may not be advisable for women with poor nutritional status.

PNEUMONIA IN THE PREGNANT WOMAN

Pneumonia is one of the leading causes of nonobstetric maternal death in the United States.[101] The risk of pneumonia is increased in pregnant women with comorbid conditions, such as asthma, anemia, HIV infection, and tobacco or substance abuse.[102] Pregnant women may be more susceptible than nonpregnant women to contracting viral infections, and they usually have more severe disease than those who are not pregnant. Immune alterations associated with normal pregnancy may impair the response to infection and increase the risk of certain infections.

Preterm delivery appears to be the most common complication associated with pneumonia. Other potential complications include low birth weight, intrauterine growth restriction, a fetus that is small for gestational age, placental abruption, preeclampsia or eclampsia, and low Apgar scores.[103–105] Varicella infection increases morbidity and mortality in pregnancy and is associated with congenital abnormalities and poor fetal outcomes. Congenital varicella syndrome is associated with high mortality in the first 30 days of life and severe impairment related to neurologic, cardiac, gastrointestinal, and developmental delays in survivors.

In the pregnant patient with pneumonia, antibiotic therapy should be initiated empirically while awaiting confirmatory tests that may aid in narrowing the antimicrobial coverage. During influenza season, antivirals (usually oseltamivir) should be started empirically, as well. Extensive use of oseltamivir during the 2009 H1N1 epidemic was thought not to be associated with any adverse fetal effects. Acyclovir or valacyclovir should be used in patients with a suspicion of varicella pneumonia; those suspected of varicella infection should be admitted for observation. Antibiotic use in the pregnant patient with CF has been discussed previously; Table 97-3 provides additional details. Although use of aminoglycosides or vancomycin theoretically may be associated with hearing and renal dysfunction in the fetus, in most circumstances where there is an indication for one or the other agent, its benefit likely outweighs its risk.

In pregnant women with acute respiratory failure from pneumonia or other causes, decisions regarding oxygenation and ventilation should be predicated on the previously discussed physiology. Airway intubation should be anticipated and performed by the most experienced personnel available, using advanced airway devices and readily accessible equipment, given the high risk of intubation failures in pregnant women.

TUBERCULOSIS: CLINICAL COURSE AND MANAGEMENT DURING PREGNANCY

Tuberculosis (TB) is an important infection of pregnant woman. In the United States, a steady overall decline in the incidence of TB has been observed, but a rise in incidence has been seen in the 15-45 year old age group. As a result, an increase in the prevalence of TB among pregnant woman in certain communities, for example, New York City, has been reported.[106] In sub-Saharan Africa, TB is the third leading cause of maternal death, following sepsis and hypertensive disorders of pregnancy.[107]

Pregnancy was originally believed to worsen the course of TB infection, but this has been shown not to be the case. The risks of TB to the mother and unborn child include intrauterine growth restriction, prematurity, and an increased risk for both maternal and fetal mortality. Transmission of TB to the fetus is also well documented[108–110] and may occur through hematogenous spread, by contiguous spread from endometrial TB, or via aspiration of TB-infected amniotic fluid. If neonatal TB is suspected, placental and endometrial tissue can be examined at the time of delivery; however, a workup of suspected active maternal TB should never be delayed until delivery. The diagnosis of TB in pregnancy often requires a high level of suspicion, since fatigue and malaise can be confused with symptoms of pregnancy.

Pulmonary TB is the most common form of TB in pregnancy, accounting for up to 85% of all cases. Consequently, a chest radiograph can be essential in making the diagnosis. Tuberculin skin testing (TST) is the gold standard for screening during pregnancy[111] studies on use of Quantiferon testing in this population are limited.[112,113] Pregnancy may be an excellent opportunity to screen for latent TB, given patients' frequent contact with healthcare providers and the added motivation for fetal well-being.

Treatment of latent TB infection (LTBI) in pregnancy may be delayed until the postpartum period in pregnant women at low risk for reactivation.[114] This recommendation is based on a study showing a higher risk of INH-induced hepatitis in pregnant women compared with non-concurrent controls.[115] However, in the study noted, the risk of INH-induced fatal hepatitis in both the active treatment and the control group was quite low. Conversion to active TB infection in patients coinfected with HIV is significant; therefore, immediate treatment should be initiated in coinfected patients to avoid placing the neonate, mother, and community at risk.

Active, untreated TB infection in a pregnant woman is more of a hazard than the treatment. When active TB is confirmed, treatment should not be delayed. Treatment is similar to that in the absence of pregnancy. First-line therapies for TB, including rifampin, INH, and ethambutol, have been shown to be safe in pregnancy and unassociated with human fetal malformations.[116,117] INH does carry a risk of acute hepatitis, especially if the patient is treated concomitantly with rifampin. Pyrazinamide is less well studied. Although the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease note that the use of pyrazinamide is justifiable in pregnancy, the Center for Disease Control (CDC) does not recommend it in pregnancy. When drug resistance is suspected, addition of pyrazinamide may be justified. Second-line agents are considered more toxic than first-line agents, and clinical experience to guide their use and safety is lacking. Streptomycin should be avoided because of its fetal ototoxicity, while amikacin and kanamycin carry known fetal nephrotoxicity. Para-aminosalicylic acid (PAS) has been used with INH in the past; there has been no indication of teratogenicity among babies whose mothers received the drug.[112,113,118]

Breastfeeding should not be discouraged in women being treated for TB, unless the mother is thought to be infectious. Since anti-TB drugs are secreted in small concentrations in breast milk, caution should be exercised when breastfeeding newborns that are also being treated for TB, since that may increase the risk of drug toxicity. Transmission via breast milk is, however, quite unlikely, except for rare cases of TB mastitis.

VENOUS THROMBOEMBOLISM: DIAGNOSIS AND MANAGEMENT DURING PREGNANCY

Diagnostic and management approaches for thromboembolic disease, including pulmonary embolism (PE), in the pregnant woman merit special considerations.

DIAGNOSIS OF VENOUS THROMBOEMBOLISM AND PULMONARY EMBOLISM

Venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the developed world and, as such, when suspicion for disease is high, early implementation of therapeutic anticoagulation is important. In pregnancy, the risk of VTE is as high as 7 to 10 times that of nonpregnant, age-matched controls.[119] The risk is disproportionately higher in the postpartum period. In pregnancy, 70% to 85% of deep venous thromboses (DVT) occur in the left leg.[120,121] This is thought to be due to compression of the left iliac vein by the right iliac artery and the gravid uterus. Isolated pelvic DVT is more prevalent in pregnancy compared with the nonpregnant population,[121,122] possibly suggesting a different pathogenesis for the disorder.

The increased risk of VTE during pregnancy is due to stasis, hypercoagulability, and vascular damage. Venous stasis in the lower extremity is secondary to the gravid uterus, as well as hormonally mediated venodilation.[123] Pregnancy is marked by many changes in the coagulation cascade, which lead to a hypercoagulable state.[124] Finally, vascular injury occurs with delivery, thereby augmenting risk in the postpartum period.

Existing clinical pretest probability tools are not validated in pregnancy, and their utility is limited by the physiologic changes of pregnancy.[125] D-Dimer performance characteristics are different in pregnant women, and its measurement in pregnancy without concomitant diagnostic imaging to exclude VTE is unreliable.[126,127]

Testing for symptomatic DVT in pregnant and nonpregnant individuals is similar: Compression ultrasonography (CUS) is the standard of care.[128] In pregnancy, the sensitivity of CUS may not be as high, given the increased risk of pelvic vein thrombosis in pregnant patients.[121] Absence of flow or need for increased pressure during CUS may be suggestive of pelvic vein thrombosis. However, the low sensitivity of CUS in detecting iliac thrombi necessitates use of other imaging studies, such as nonenhanced magnetic resonance venography.

In pregnant women suspected of PE who also have lower extremity symptoms, CUS is the recommended initial test in those who are hemodynamically stable. In women without lower extremity symptoms, American Thoracic Society/Society of Thoracic Radiology guidelines recommend a chest X-ray (CXR) as the next diagnostic step.[129] A CXR may provide an alternative diagnosis and also determine the utility of a perfusion scan. Using the proposed diagnostic algorithm, patients with a normal CXR are next evaluated with a ventilation–perfusion lung scan, whereas those who have an abnormal CXR undergo a multidetector computed tomography-pulmonary angiogram (MDCT-PA).[129] The main advantage of MDCT-PA over a ventilation–perfusion scan is that it provides an alternative diagnosis in 17% to 19% of pregnant women suspected of having a PE.[130] MDCT-PA may be technically limited in up to 20% of pregnant women[131] due to physiologic changes of pregnancy, including a higher plasma volume and heart rate, which affect vascular enhancement. These effects may be more pronounced in obese women and those with multiple gestations. Imaging protocol modifications may help reduce technical limitations of the technique.[132]

MANAGEMENT OF THROMBOEMBOLIC DISEASE IN PREGNANCY

Since the interval between diagnosis of PE and institution of therapeutic anticoagulation has been shown to be an independent predictor of death, early and appropriate treatment is essential. In pregnancy, prognostic assessment tools, such as brain (B-type) natriuretic peptide (BNP), or cardiac echocardiography for evaluation of right ventricular dysfunction, are not well validated. Furthermore, their interpretations are limited by the physiologic changes of pregnancy.[133–135] Additional work in deriving prognostic indictors for thromboembolic disease in pregnancy is needed.

Both unfractionated heparin (UFH) and low–molecular-weight heparin (LMWH) are safe during pregnancy, as they do not cross the placenta. LMWH is superior to UFH for all measured outcomes of VTE—risk of recurrent thrombosis, bleeding, and death.[136,137] Other advantages of LMWH over UFH include a lower risk of heparin-induced thrombocytopenia and thrombosis (HIT) and bone demineralization with subsequent fractures.[138–140]

UFH may still play a role in pregnancy, particularly around labor and delivery, given its shorter duration of action and easy reversibility. Given UFH's increased clearance and volume of distribution (and, therefore, bioavailability), its use in pregnancy should be monitored using measurements of aPTT or, preferably, heparin anti-Xa levels.[141] UFH administered intravenously is the treatment of choice for patients with acute renal failure or if urgent need for drug reversal may be required for delivery.

Dosing and monitoring of LMWH is controversial. Twice-daily dosing is preferred by many experts, guided by weekly anti-Xa levels obtained 3 to 6 hours after a dose. The goal for anti-Xa levels is 0.5 to 1.1 units/mL. LMWH does not appear to increase the risk of peripartum bleeding over UFH. The incidence of peripartum hemorrhage is approximately 0.9% to 1.8%, whereas the risk of antenatal hemorrhage and wound hematoma is less than 1%.[142] Although most available data were derived from the study of enoxaparin, tinzaparin likely has a similar side-effect profile.[143]

The duration of treatment for VTE in pregnancy is not well defined; consequently, recommendations for management are similar to those in the nonpregnant patient. Consensus suggests that therapy for VTE should extend for 6 weeks into the postpartum treatment, since this is a high-risk time for thromboembolism. The total duration beyond that is unclear, but a minimum of 3 months is probably warranted and should be based upon careful assessment of the risk of recurrence.[144,145]

Data on use of thrombolytics in pregnancy are available. The main risk of thrombolysis is maternal bleeding, which is reported to occur in as many as 8.1% of patients treated; no cases of intracranial hemorrhage have been reported.[146] In one series on the use of thrombolytics in pregnancy, although no maternal bleeding was reported, the rate of fetal mortality was 8%.[147] Fetal complications may be related to thromboembolic disease severity, as well as the choice of thrombolytic agent. Alteplase (rt-TPA) does not cross the placenta and carries no risk for teratogenicity. In patients with PE who are hemodynamically stable, use of thrombolytics is controversial (even in the absence of pregnancy) and is generally discouraged. In patients who are hemodynamically unstable, but who cannot undergo systemic thrombolysis, surgical or percutaneous embolectomy are potential therapeutic options when clinical expertise for these procedures is available.[148]

Management of VTE in the peripartum period is complex and requires a detailed labor and delivery plan. The plan should take into consideration the risk of bleeding with full anticoagulation and the risk of recurrent VTE when anticoagulation is withheld. In addition, the need for regional anesthesia should be evaluated. A planned transition from LMWH to UFH near term may be considered, since UFH is more predictably reversed, has a shorter half-life, and easily monitored.[149] A planned induction can ensure a controlled environment for delivery. However, given the unpredictable nature of labor, patients should be instructed to stop their injections at the first sign of labor and to contact their provider for further instructions.

Since a new VTE without treatment during the first month carries a 40% risk of recurrence, patients who are within 2 weeks of expected delivery should be considered for placement of an IVC filter.[150,151] Patients developing a clot between weeks 2 and 4 prior to delivery may be treated with intravenous UFH[152] or an IVC filter. Removable IVC filters can be placed in pregnancy, but they are usually placed above the renal veins. Intravenous UFH should be restarted postpartum as soon as possible.

Warfarin, an oral vitamin K agonist, crosses the placenta, is known to be teratogenic, and increases the risk of intracranial bleeding.[153] Use of warfarin for the treatment of VTE in pregnancy cannot be justified, given the availability of drugs with similar efficacy and better safety.[26] Warfarin is detectable in breast milk, but in clinically insignificant amounts; hence, its use is considered safe in breastfeeding mothers.[154] Use of postpartum intravenous UFH or subcutaneous LMWH as a bridge to warfarin is warranted. It has been shown that use of warfarin alone, without antecedent use of heparin carries about a threefold risk of recurrent VTE.[155]

PULMONARY ARTERIAL HYPERTENSION AND PREGNANCY

Pulmonary arterial hypertension (PAH) is an uncommon disorder that may affect women of childbearing age. PAH may present, or significantly worsen, during pregnancy. The hallmark of PAH is an increase in PVR. The increase in blood volume, cardiac output, and oxygen consumption, and the decrease in systemic vascular resistance seen in pregnancy are poorly tolerated in patients with fixed PVR. These hemodynamic challenges are exacerbated at the time of delivery as a result of uterine contractions, autotransfusion, and increased sympathetic tone, as well as by large fluid shifts in the postpartum period. In affected patients, the normal physiologic changes of pregnancy may lead to right ventricular volume overload and, eventually, right ventricular failure and death.

Two large reviews of a total of 198 pregnancies in women with PAH revealed a mortality range from 17% in patients with idiopathic pulmonary arterial hypertension (iPAH) to 56% in women with other causes of pulmonary hypertension.[156,157] In contemporary case series in which patients were managed with pulmonary-specific vasodilators, substantially better outcomes have been reported. However, these reports may be limited due to publication biases.[158,159] Nearly all fatalities occur in the peripartum period as a result of heart failure, VTE, or sudden death. Due to the limited data and nature of the publications in this field, it remains uncertain if patients with less severe disease (i.e., lower mPAP or PVR) are at lower risk for death than are those with more severe disease, although this has been suggested in a number of reported series.[160,161] Currently, the recommendation remains that patients with even mild PAH should avoid pregnancy.[162] A decision to terminate a pregnancy or to induce delivery in the setting of PAH depends on the timing of diagnosis in gestation and the anticipated physiologic changes. In more advanced pregnancies, termination may not lessen risk of mortality or morbidity.

Given the risk both to mother and baby, contraception is essential in patients with PAH. Options for contraception should be discussed in collaboration with a specialist familiar with both PAH and contraception. As patients with PAH are prothrombotic, estrogen-based contraception should be avoided. Similarly, intrauterine device placement carries a 5% risk of a vasovagal event, which may be fatal in patients with PAH. Thus, device implantation may require hospital admission.[163] In all patients starting treatment with endothelin receptor antagonists (e.g., bosentan, ambrisentan) two forms of contraception are recommended, since these agents are considered teratogenic.

A multidisciplinary team that includes a PAH specialist should manage the patient throughout pregnancy and in the peripartum period. Carefully planned regional anesthesia may carry less risk than general anesthesia.[156,159] Cesarean-section delivery is unlikely to reduce anesthesia risk in women with PAH; in fact, Cesarean section may be associated with a higher risk of medical complications in PAH, including VTE and atelectasis. Throughout pregnancy, close monitoring for worsening right heart failure is essential. Its development may herald the need for hospitalization, institution of bed rest, augmentation of therapy for PAH, emergent delivery, or termination of pregnancy.

Use of medications for PAH in pregnancy is not well studied. Calcium channel blockers have been used successfully and are relatively safe in pregnant patients who have a vasodilator response demonstrated during right heart catheterization.[161] Unfortunately, loss of efficacy of calcium channel blockers over the long-term limits their use, so pulmonary-specific vasodilators may be needed.[164] Pulmonary-specific vasodilators that have been used successfully during pregnancy include prostacyclins (treprostinil or epoprostenol) and phosphodiesterase (PDE) inhibitors (sildenafil and tadalafil).[165,166] Iloprost is teratogenic in animals, although there are reports of its use in pregnancy without teratogenicity.[167,168] Case reports describe successful use of inhaled nitric oxide (iNO) at the time of delivery, but risks to fetus and neonate remain unclear. Since pregnancy is a prothrombotic state, anticoagulation for PAH should be used when indicated, including in those women with PAH who are on prolonged bed rest. LMWH is the preferred agent and should be continued in the postpartum period.

INFILTRATIVE LUNG DISEASES IN PREGNANCY

Only a minority of infiltrative lung diseases (ILD) occur in women of childbearing age. In chronic ILD, preconception counseling is crucial to ensure appropriate disease control at the time of conception and use of medications with good efficacy and good safety profiles.[169] A multidisciplinary approach to these disorders is crucial to achieving improved outcomes.

Patients with a restrictive physiology may develop worsening symptoms in pregnancy due to a number of changes, including, for example, a significant increase in tidal volume. Experts believe that a vital capacity greater than 1 L is associated with a favorable outcome in pregnancy, despite limited supporting evidence. Outcome often depends on the cause of restriction and disease progression during the course of the pregnancy. Patients should be assessed by an expert in obstetric anesthesiology prior to delivery, and a plan developed to avoid both high levels of anesthesia and use of the Trendelenburg position, when possible.

A number of systemic diseases may affect the lungs, producing pulmonary parenchymal and other respiratory and manifestations that may profoundly impact pregnancy.

Rheumatoid arthritis (RA) usually improves in the second and third trimesters[170] and flares in the postpartum period.[171] Convincing evidence that RA results in adverse pregnancy outcomes is lacking.

Systemic lupus erythematosus (SLE) is likely to flare in pregnancy, especially in women with renal involvement and those with poor disease control at the time of conception. The postpartum period confers a particularly high risk of lupus pneumonitis.[172] SLE increases the risk of complications of pregnancy and adverse fetal outcomes, including preeclampsia, spontaneous abortion, growth restriction, and preterm birth.[173–175]

Systemic sclerosis may have devastating consequences in pregnancy. Pregnancy planning and close monitoring can improve maternal and fetal outcomes. Renal crisis is a feared complication that is usually treated with angiotensin converting enzyme (ACE) inhibitors. Given the high morbidity of this condition and the clear advantage of using ACE inhibitors over any other antihypertensive agents, use of these drugs can be justified, despite their known teratogenicity and the risk of neonatal renal dysfunction at birth. Pulmonary hypertension, another complication of systemic sclerosis, should be evaluated prior to pregnancy, and affected patients advised to avoid pregnancy (see Pulmonary Arterial Hypertension, above).

Disease severity in polymyositis and dermatomyositis is likely a predictor of adverse fetal outcomes.[176] General anesthesia should be avoided in patients with polymyositis because of the risk of delayed muscle recovery, arrhythmias, heart failure, and aspiration.

The use of certain medications in pregnancy, such as corticosteroids, azathioprine, hydroxychloroquine, sulfasalazine, and intravenous immunoglobins, is justifiable. Use of tumor necrosis factor (TNF) antagonists is justifiable in rare circumstances. TNF antagonists have been implicated in cases of VATER (verterbral, anal, tracheal, esophageal, and radial anomalies) syndrome.[177] Cyclosporin A is unlikely to have teratogenic effects. Use of methotrexate, cyclophosphamide, mycophenolate mofetil, rituximab, leflunomide, and D-penicillamine should be avoided in pregnancy and alternative agents employed in women planning a pregnancy.

Stable sarcoidosis likely has no significant effects on pregnancy outcomes. However, patients with pulmonary parenchymal disease, extrapulmonary sarcoidosis, or PAH, and those requiring drugs other than corticosteroids for disease suppression tend to have more complicated pregnancies.[178]

Lymphangioleiomyomatosis (LAM) is a rare disorder that affects women of childbearing age. LAM is likely accelerated by exogenous hormones and pregnancy. Pregnancy in LAM is associated with a high incidence of pneumothorax and chylous effusion.[179] It is possible that LAM diagnosed during pregnancy may be a marker of disease severity.[180] The European Respiratory Society guidelines suggest that patients be informed of the risk of complications of LAM, for example, pneumothorax and chylous effusions, prior to pregnancy.[181] Women with more severe disease are less likely to tolerate these complications.

PULMONARY EDEMA

Pulmonary edema during pregnancy is not uncommon, despite the young age of the patients.[182] Plasma oncotic pressures decrease as gestation duration increases and decrease further in the postpartum period. Consequently, pulmonary edema may occur at lower-than-usual hydrostatic pressures during pregnancy. Given the profound hemodynamic changes at the time of labor and delivery and the postpartum period, the vast majority of peripartum cases of pulmonary edema are reported postpartum. Intravenous fluid administration used to counteract the effect of vasodilation caused by regional anesthesia may contribute to its development.

Additional causes of pregnancy-related pulmonary edema include preeclampsia, which may be associated with left ventricular dysfunction; lower oncotic pressure; possible capillary endothelial dysfunction. Tocoltic agents have also been associated with pulmonary edema. Treatment of pulmonary edema in pregnancy is essentially the same as in the nonpregnant population; however, pregnant women are typically responsive to low doses of diuretics (e.g., 10 mg of furosemide administered intravenously). ACE inhibitors are known teratogens and should be avoided. Nitroglycerine and hydralazine may be used.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism (AFE), also known as anaphylactoid syndrome of pregnancy is a rare, but potentially catastrophic condition characterized by cardiopulmonary collapse and multiorgan dysfunction. Mortality rates between 20% and 90% have been reported. Proposed risk factors for the development of AFE include advanced maternal age, complicated labor and delivery, obstetric interventions, uterine trauma, placental pathologies, and fetal distress.[183] The pathogenesis of AFE remains a subject of debate.

AFE presents as sudden hemodynamic instability, respiratory failure (cardiogenic or noncardiogenic pulmonary edema), disseminated intravascular coagulation, encephalopathy, and seizures. Detection of fetal squamous cells in the pulmonary vasculature is not a specific finding in AFE; it has been reported in asymptomatic women at term.

Treatment of AFE focuses on supportive measures and correction of the initial hemodynamic instability. Immediate Cesarean section, which should be considered in cases of severe, refractory shock, should be promptly performed in hope of improving maternal and fetal outcomes.[184] Use of recombinant factor VII,[185] iNO and other pulmonary vasodilators, exchange transfusion, extracorporeal membrane oxygenation (ECMO), and continuous venovenous hemofiltration (CVVH)[186,187] have been described. However, little supportive evidence is available.

OVARIAN HYPERSTIMULATION SYNDROME

Severe ovarian hyperstimulation syndrome (OHSS) is an uncommon iatrogenic complication of exogenous gonadotropins used in assisted reproduction. Pulmonary complications include pleural effusions and VTE. In the severe stages, massive ovaries and ascites, large pleural effusions, oliguria, hemoconcentration, and VTE can be life-threatening. Risk factors for OHSS include age older than 30 years, high serum estradiol, multiple ovarian follicles, and pregnancy.[188] Research suggests that vascular endothelial growth factor (VEGF), angiotensin-II, and insulin-like growth factor play important roles in the pathogenesis of OHSS by increasing vascular permeability, leading to vascular leakage of albumin, electrolyte imbalances, and rapid accumulation of extravascular fluid, including pleural effusions and ascites. Patients with OHSS are also at a higher risk for VTE and, in particular, a higher prevalence of upper extremity DVT, since estradiol-rich fluid drains through the thoracic duct into upper extremity veins.

Patients with severe symptoms of OHSS should have intravascular volume expansion; the possibility of worsening intra-abdominal hypertension should be kept in mind. Repeated large-volume paracenteses may improve renal perfusion by decreasing abdominal hypertension. Therapeutic thoracenteses may also be needed. Close monitoring for early signs of acute respiratory distress syndrome (ARDS), thromboembolism, and advanced renal failure is recommended. Thromboprophylaxis using UFH or LMWH should be initiated as soon as possible due to the high incidence of thromboembolic complications.[189]

SLEEP-DISORDERED BREATHING AND PREGNANCY

Sleep disruption and sleep disorders are common in pregnancy. This section focuses on sleep-disordered breathing (SDB) and its implications in pregnancy.

Central sleep apnea (CSA) is quite uncommon in pregnant women suspected of SDB, likely because the majority of these women are younger than the typical population with CSA. The prevalence of hypoventilation syndromes in pregnancy compared with the nonpregnant population is not well established.

Pregnancy appears to confer an increased risk for obstructive sleep apnea (OSA). Mallampati scores [190] increase as pregnancy progresses.[191] Due to the effect of estrogens and increased plasma volume, nasal patency is reduced. Upper airway size is smaller in pregnant women with[192] and without preeclampsia[193] compared with nonpregnant controls. The reduction in FRC likely results in a tendency for upper airway collapse.[194] The effects of progesterone on minute ventilation may lead to a more negative inspiratory pressure, resulting in a vacuum effect on the upper airway. On the other hand, progesterone increases the electromyographic activity of the upper airway dilator muscles[195] and enhances their responsiveness to chemical stimuli.[196] In addition, reduced REM sleep,[197] preference for assuming a lateral sleeping position in late gestation,[198] and increased minute ventilation may play protective roles. The balance of these factors favors an increased risk for SDB in pregnancy. Notably, snoring occurs in approximately 35% of pregnant women.[199]

OSA may actually improve in untreated women 3 months after delivery.[200] Most available data on SDB in pregnancy are cross-sectional, primarily because pregnancy is unplanned in about 50% of subjects. Availability of longitudinal data would help clarify whether pregestational and gestational OSA does, in fact, have different clinical consequences.

Lack of significant effort by obstetric providers in screening for SDB, even in obese patients, has been reported.[201] The Berlin questionnaire, a widely used tool in screening the nonpregnant population, appears to have poor positive and negative predictive values in pregnancy.[202] Excessive daytime sleepiness correlates with other symptoms of SDB, such as snoring and witnessed apneas.[203] Chronic hypertension, increased age, obesity, and snoring appear to have good predictive value for diagnosing OSA in high-risk populations.[204] Further validation of a potential predictive model in pregnant populations is needed.

SDB is associated with a variety of medical disorders, which may have a major influence on pregnancy and its course. Gestational hypertension and gestational diabetes are associated with short-term maternal, fetal, and neonatal complications,[205–207] as well as long-term cardiovascular[208] and metabolic outcomes.[209] Hence, the association of these disorders with a modifiable disorder holds the promise of potentially preventing long-term, highly morbid outcomes.

Snoring and OSA have been shown to be associated with a variety of adverse pregnancy outcomes, including gestational hypertension,[199,210–212] gestational diabetes,[199,213–215] and Cesarean deliveries.[199,216,217] Abnormalities in glucose metabolism, longer labor, and Cesarean deliveries are also associated with short sleep duration.[199,214] Mechanistic studies are lacking, and the directionality of the association is not well clarified. The association of SDB with adverse fetal outcomes may be mediated by associated comorbidities. Growth restriction[211] and preterm birth[199,217,218] have been reported in association with snoring, OSA, or poor sleep in some studies. Case reports and case series suggest that fetal decelerations secondary to sleep apnea occur, but a recent study evaluating synchronized limited sleep studies and fetal monitors failed to show a significantly higher prevalence of late decelerations with obstructive events.[202]

Once diagnosed, treatment of OSA is recommended for patients with an apnea–hypopnea index (AHI) >15 or those with AHI >5, who have symptoms that respond to therapy, such as daytime sleepiness. For multiple reasons, specific guidelines on initiation of therapy in pregnancy are not available. To date, no trials have shown that treatment of OSA in pregnancy improves pregnancy or fetal outcomes. This likely contributes to underscreening and underdiagnosis in this population.[201] More so, it is possible that, with weight loss and reversal of pregnancy physiology, the disorder may resolve, or at least improve, in the postpartum period.[200]

Alcohol and cigarette smoking avoidance carry additional pregnancy-specific benefits. Observational studies of positive airway pressure (PAP) therapy have shown improvement in daytime fatigue and daytime somnolence in pregnant women with OSA treated with CPAP and retitrated around midpregnancy.[219] Auto-PAP may circumvent the need for repeat titration with pregnancy progression. In women with preeclampsia, small, randomized trials have shown that in-laboratory PAP therapy improves hemodynamics, uric acid, and cardiac output compared with untreated women.[220,221] Trials evaluating the effect of PAP therapy on pregnancy-specific outcomes are sorely needed to help determine the "urgency" of starting PAP therapy in pregnancy.

SUMMARY

Pregnancy constitutes a distinctive state in a woman's life that presents a number of unique physiologic, diagnostic, and therapeutic challenges. Pregnancy also offers an opportunity for many women to have meaningful interactions with the healthcare system and providers, including those focused on lung health. Prompt diagnostic and therapeutic interventions and close patient monitoring are warranted to help the pregnant woman tolerate the physiologic demands of pregnancy and the hemodynamic and respiratory stressors associated with labor and delivery. Deliberate postponement of a warranted clinical evaluation or intervention until after delivery is rarely the right approach.

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CHAPTER 98

Pulmonary Complications of Intra-abdominal Disease

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INTRODUCTION

Intra-abdominal pathology may have distant effects on the pulmonary vascular bed, the pulmonary parenchyma, or the pleural space. This chapter reviews the pulmonary complications of intra-abdominal disease, focusing on the pathology, epidemiology, clinical features, and management. Topics are organized according to the primary abdominal organ system in which the disease is centered.

PULMONARY COMPLICATIONS OF HEPATIC DISEASE

A number of respiratory complications of hepatic disease are well recognized, including portopulmonary hypertension (POPH), hepatopulmonary syndrome (HPS), hepatic hydrothorax (HH), and spontaneous bacterial empyema (SBEM). Each is discussed in the subsequent sections.

PORTOPULMONARY HYPERTENSION

POPH is defined as pulmonary hypertension (PH) occurring in the setting of liver disease, or more specifically, in the setting of portal hypertension.

Epidemiology And Pathogenesis

Approximately 2% to 6% of patients with decompensated liver disease develop POPH.[1–3] Based on multicenter, case-control studies, autoimmune hepatitis and female gender are identified risk factors for the development of POPH; therefore, the role of hormonal and immunologic influences in the pathogenesis of POPH is a focus of investigation.[4,5]

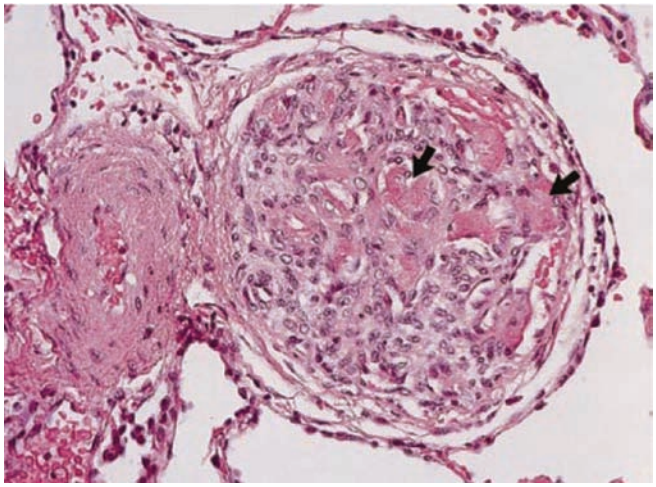

Figure 98-1 Autopsy specimen from a 55-year-old female with cryptogenic cirrhosis and portopulmonary hypertension, showing the plexiform lesion common in pulmonary arterial hypertension. The *arrows* show acute platelet-fibrin thrombi within the plexiform lesion. *(Reproduced with permission from Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. Liver Transpl. 2000;6(2):241–242.)*

Patients with POPH have measurable alterations in levels of pulmonary vasoactive substances. For example, prostacyclin is a potent pulmonary vasodilator that also has antithrombotic and antiproliferative properties; levels of prostacyclin are decreased in the lungs of patients with PH. In patients with POPH, loss of endothelial prostacyclin synthase expression compared with normal controls has been demonstrated.[6] Endothelin-1 (ET-1), a pro-proliferative and vasoconstrictive agent implicated in the pathophysiology of other types of PH, has also been shown to be increased in the circulation of patients with POPH.[7]

Histologically, POPH appears to be very similar to other types of PH. POPH is a precapillary pulmonary arteriopathy involving multiple layers of the vessel; specifically, POPH is characterized by smooth muscle hypertrophy, adventitial proliferation, and endothelial cell proliferation. In addition, the plexiform lesions characteristic of other types of PH have been demonstrated in patients with POPH (Fig. 98-1).[8]

The microvascular changes in POPH result in a pulmonary circulation characterized by increased resistance and low capacitance—the antithesis of the normal pulmonary vascular physiology, which is characterized by a low-pressure and high-flow state. The altered physiology constitutes an increased workload to the right ventricle (RV). Early in the disease process, the RV hypertrophies and increases its stroke volume. Over time, these changes become maladaptive, and the RV dilates and becomes dysfunctional. At this stage, the patient demonstrates progressive right ventricular failure. The clinical course of POPH is similar to that seen in other types of PH (see Chapter 72), justifying its placement in Group 1 of the World Health Organization (WHO) Classification (Table 98-1).[9] However, the concomitant presence of end-stage liver disease, with accompanying fluid retention, hypoalbuminemia, coagulopathy, renal dysfunction, and gastrointestinal bleeding, complicates the clinical management of patients.

Clinical Features

Patients with POPH may present with complaints of fatigue and dyspnea with exertion, which are later accompanied by signs and symptoms of right ventricular failure, such as jugular venous distension, lower extremity edema, presyncope, and syncope.[10] The diagnosis can be particularly elusive in the cirrhotic patient, who may have edema from portal hypertension and a spectrum of hemodynamic disturbances. Consequently, the diagnostic workup must be performed carefully to avoid a misdiagnosis of POPH.

TABLE 98-1 Updated Dana Point WHO Classification of PH

Group I, pulmonary arterial hypertension
Idiopathic
Hereditary
Associated with:
Collagen vascular disease
Congenital heart disease
Human immunodeficiency virus
Drugs or toxins
Portal hypertension
Chronic hemolytic anemia
Schistosomiasis
Group II, pulmonary venous hypertension
Systolic dysfunction
Diastolic dysfunction
Valvular disease
Group III, PH associated with respiratory disease/hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Group IV, chronic thromboembolic PH
Group V, PH with unclear/multifactorial mechanism

Source: Adapted with permission from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. Journal of the American College of Cardiology. 2009;54(1 Suppl):S43–S54.

The most common hemodynamic derangement in patients with liver disease is not PH, but rather, a state of systemic vasodilation and high cardiac output (CO) induced by splanchnic vasodilation.[3] In these patients, hemodynamics are characterized by increased mean pulmonary artery pressure (mPAP), high CO, low pulmonary capillary wedge pressure (PCWP), and reduced pulmonary vascular resistance (PVR). Affected patients do not have small vessel arteriopathy, but rather, increased pressure resulting from high flow through the pulmonary circulation. This hemodynamic pattern is evident in approximately 35% of liver transplant candidates and is not associated with a poor outcome.[3]

A second abnormal hemodynamic profile present in patients with liver disease reflects volume overload or diastolic dysfunction. With this profile, pulmonary pressures may be elevated, but CO and PCWP are also increased; in addition, PVR is low, indicating pulmonary *venous* hypertension from elevated left heart filling pressures, rather than small vessel pulmonary arteriopathy.

Finally, a third hemodynamic profile that may be seen in POPH is an elevated pulmonary artery pressure, normal PCWP, high PVR, and high, normal, or low CO—depending on the degree of resultant right ventricular failure and liver disease (Table 98-2).

Not infrequently, patients may present with a *combination* of these hemodynamic profiles, for example, POPH with volume overload. In this case, an increased transpulmonary gradient (TPG) >12 mm Hg (TPG = mPAP − PCWP) may suggest existence of combined volume overload and pulmonary arteriopathy. To characterize such complexity, many have suggested that the hemodynamic definition of POPH be expanded to include mPAP >25, TPG >12, and PVR >3 Wood units.

TABLE 98-2 Hemodynamic Patterns in Patients with Liver Disease

	mPAP	CO	PCWP	PVR	TPG
High cardiac output and vasodilated	↑	↑↑	↓	↓↓	N↑
Fluid overload or diastolic dysfunction	↑	N↑	↑↑	N	N
POPH	↑	↑↓	N	↑	↑

mPAP, mean pulmonary artery pressure (normal, <25 mm Hg); PCWP, pulmonary capillary wedge pressure (normal, <15 mm Hg); CO, cardiac output (normal, 4–6 L/min); PVR, pulmonary vascular resistance (normal, <3 Wood units: ([mPAP–PWCP]/CO); TPG, transpulmonary gradient (normal, <12: mPAP-PCWP); N, normal.

Diagnosis

To establish a diagnosis of POPH, objective evidence (increased hepatic vein-free pressure to wedge pressure gradient) or clinical evidence of portal hypertension must be present. The diagnosis of POPH is often first suggested by an echocardiogram, but echocardiography is confounded by the previously noted hemodynamic changes seen in cirrhosis.[11] Therefore, an echocardiographically estimated peak PA pressure >50 mm Hg or signs of significant right ventricular dysfunction should trigger confirmatory right heart catheterization (RHC). A screening series at the Mayo Clinic determined that this threshold for PA pressure was 100% sensitive in diagnosing POPH, and it minimized unnecessary invasive testing in patients with cirrhosis, who often have a hyperdynamic circulation.[3]

Clinical Course

Patients with POPH appear to have worse clinical outcomes than patients with other types of PH. The French registry recorded the outcomes of 154 patients with POPH and included both treated and untreated subjects. Five-year survival was reported in 68% of patients. Multivariate analysis identified advanced Childs–Pugh Scores (B and C) and lower cardiac index as independent risk factors for mortality.[12]

The REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) registry for PH is an ongoing, multicenter, observational study that has recorded the outcomes of 174 patients with POPH—the largest cohort to date. The data show that patients with POPH have poorer survival and higher all-cause hospitalization rates compared with patients with idiopathic or familial PH, despite the group with POPH having a more favorable initial hemodynamic profile than the others (Fig. 98-2).[13] Furthermore, when data were analyzed to derive a risk score for 1-year mortality for all patients presenting with PH, POPH demonstrated a hazard ratio of 3.6 compared to other etiologies.[14]

Management

POPH is classified as WHO Group I PH, and, therefore, is a treatable category of PH using FDA-approved drugs. However, POPH was excluded from clinical trials assessing use of these agents. Specific data on treatment of POPH are derived from case series and single-center studies, as summarized in the following sections.

Endothelin Antagonists The endothelin antagonists, bosentan and ambrisentan, are established treatments in WHO Group I PAH. Endothelin is a pulmonary vasoconstrictor and pro-proliferative agent, and its antagonism has been shown to improve exercise capacity and hemodynamics in patients with PH. Data on use of these agents specifically in POPH are limited.

Bosentan is a dual endothelin receptor antagonist (ET_A and ET_B). In small, single-center, uncontrolled, observational trials, patients with POPH treated with bosentan have shown improvements in exercise capacity and survival.[15,16] Use of bosentan has been limited in this group due to its well-described hepatotoxicity occurring in a minority of patients (approximately 10%) with PH, but no underlying liver disease. The hepatotoxicity is likely related to the agent's inhibition of a bile salt transporter; the toxicity is reversible with drug discontinuation.[17]

Ambrisentan is a selective ET_A antagonist and is also FDA approved for the treatment of WHO Group I PAH. Hepatotoxicity has not been reported with this agent. A single-center, uncontrolled, observational trial of ambrisentan in POPH from the Mayo Clinic reported a significant improvement in mPAP and PVR with treatment and no hepatotoxic events.[18]

Phosphodiesterase Type 5 Inhibitors Two phosphodiesterase type 5 inhibitors, sildenafil and tadalafil, are currently FDA approved for the treatment of WHO Group I PH. The agents vasodilate the pulmonary vascular bed by inhibiting breakdown of cyclic GMP and work within the nitric oxide pathway. Small, uncontrolled, observational trials reveal that sildenafil in POPH increases 6-minute walk test distance and lowers levels of N-terminal prohormone-brain natriuretic peptide, both of which correlate with a better prognosis in patients with PH.[19] The reported hemodynamic response has been mixed, with one observational trial reporting an improved PVR in three of five patients at 1 year,[20] and another showing improved PVR in all nine patients studied at follow-up, which ranged from 95 to 282 days.[21]

Prostacyclins Prostacyclin analogs are key agents in the treatment of PAH, and they are considered by many to be the agents of choice for the "sickest" patients. These drugs must be given continuously via subcutaneous or intravenous routes, or intermittently in inhaled form. Current FDA-approved prostacyclins for intravenous use are epoprostenol and treprostinil. Treprostinil is also available for subcutaneous or inhalational administration. In the United States, iloprost is available only in the inhaled form, although it is given intravenously in Europe.

Uncontrolled, single-center series have consistently demonstrated that prostacyclin infusions result in significant improvements in mean PAP, CO, and PVR in patients with POPH.[22–24] Furthermore, prostacyclin

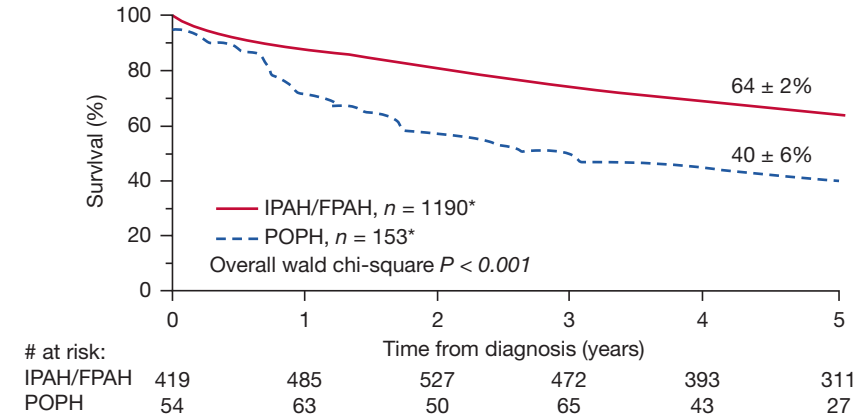

Figure 98-2 Five-year survival from the time of diagnosis of POPH versus IPAH/FPAH. *(Data from REVEAL registry. Only patients enrolled within 5 years of diagnosis were included in the 5 years survival from diagnosis curve. Chest. 2012;141(4):905–915.)*

infusions have been used successfully to improve hemodynamics in patients with POPH in advance of safe pursuit of liver transplantation.[24–27] Limited data are available to support the use of inhalational prostacyclins for POPH. Although iloprost has been shown to improve hemodynamics acutely, long-term effects are less certain.[28]

Liver Transplantation The history of liver transplantation in the setting of POPH is controversial. Early in the history of liver transplantation, the diagnosis of POPH was made in the operating room at the time of the procedure. Patients were neither previously treated for the disease, nor under the care of a medical team familiar with critical care of patients with POPH. Not surprisingly, intraoperative mortality from decompensated right ventricular failure was high.[29] Long-term outcome was also adversely affected. Those with severe PH (sPAP >60 mm Hg) had a 9-month posttransplant survival rate of 58%.[30] Consequently, severe POPH was considered a contraindication to liver transplantation.

With increasing clinical experience and the advent of new treatments for PH, transplant centers began to report both successful liver transplants in patients with POPH, and, in some, regression of the POPH following surgery.[31,32] In 2006, a case series of eight sequential patients with POPH were treated with IV epoprostenol. Of the eight, seven had significant hemodynamic improvement. Six of the seven were listed for liver transplantation, and four of those listed were successfully transplanted. Of those transplanted, survival was 100% at 5 years.[26,32] Furthermore, in a retrospective study based on screening of patients with POPH with RHC, 5-year survival for those not transplanted or treated for PH was 15%, whereas 5-year survival for those who were treated for PH and transplanted was 64%.[33]

Because of the initial poor experiences with POPH patients undergoing liver transplantation, retrospective studies sought to identify risk factors for perioperative mortality. These series have suggested that if a patient has a mean PAP <35 mm Hg and normal right ventricular function, perioperative mortality approaches that of patients without POPH. However, if mean PAP is >50 mm Hg at the time of transplant, mortality approaches 100%.[29,31,34]

Because there is a role for liver transplantation in selected patients with POPH, the United Network for Organ Sharing (UNOS) allows for upgrade points in the model for end-stage liver disease (MELD) score, facilitating liver transplantation. The MELD system prioritizes liver transplantation for the sickest patients, and the exception system allows extra points for those whose mortality risk is not reflected in their MELD score. Currently, the guidelines indicate that if a patient has a confirmed diagnosis of POPH (using mPAP, PVR, and TPG), and they are treated with pulmonary vasodilator therapy to attain an mPAP <35 and a PVR <5 Wood units, they are eligible for a MELD exception to 22 points, with an increase in their MELD by 10% every 3 months, until they are transplanted.

Liver transplantation in these patients should be performed at a center experienced in pulmonary vascular disease, as the perioperative course may be complicated. Even in patients without POPH, a well-described "reperfusion syndrome" may occur at the time of allograft reperfusion. Reperfusion syndrome may cause acute elevations in PAP and may induce acute, decompensated right ventricular failure in patients with POPH.[35,36] The use of intraoperative prostacyclin infusion, inhaled nitric oxide, or intravenous milrinone has been described in this emergent setting; results have been mixed.[37,38]

Limited data exist regarding the clinical course of POPH after liver transplantation. POPH progression, stability, improvement, and resolution have all been reported. In most of the cases, patients are able to wean from their prostacyclin infusion over a period of months, but some remain on oral pulmonary vasodilators. Available data suggest that 40% to 50% of patients may be able to be weaned from all pulmonary vasodilators, given enough time.[24–26]

Summary

POPH is an uncommon complication of liver disease, which is characterized by a progressive pulmonary arteriopathy, and which may result in right ventricular failure and death. Patients with POPH appear to have an increased mortality compared with those with similar levels of liver disease or with other types of PH. Specific protocols for optimal use of, pulmonary vasomodulators for POPH are under investigation. However, patients exhibit improved hemodynamics and exercise capacity when receiving therapy for PH. The role of liver transplantation in this setting is arguable, but transplantation may be performed in carefully selected patients and may cure not only their liver disease, but also their POPH.

■ HEPATOPULMONARY SYNDROME

HPS is a liver-induced pulmonary vascular disorder characterized by a widened alveolar–arterial oxygen gradient. The widened gradient is the result of intrapulmonary vasodilation (IPVD) in the presence of hepatic disease or portal hypertension. Clinically, IPVD may occur with or without overt hypoxemia, depending on the severity of the disease. HPS increases mortality in patients with liver disease, is without specific therapy, and is completely curable with liver transplantation. Therefore, unlike POPH, the presence of significant HPS is considered an indication for liver transplantation.

Epidemiology and Pathogenesis

The prevalence of HPS is reported as 4% to 32% in cohorts of cirrhotic patients undergoing liver transplant evaluation.[39,40] The pathogenesis is poorly understood, but is thought to involve angiogenesis, as well as inadequate synthesis or metabolism by the impaired liver of pulmonary vasoactive substances, such as nitric oxide, prostaglandins, vasoactive intestinal peptide, endothelin, calcitonin, glucagon, substance P, and atrial natriuretic factor.[41–43] Nitric oxide has long been implicated in the pathophysiology of HPS, given its known pulmonary vasodilatory effects.[44–48] Endothelin has also been implicated in the pathophysiology of HPS. Although endothelin is often thought of as a vasoconstricting agent, and its inhibition is a common therapy for PH, endothelin's actions vary widely by the receptor to which it attaches. When ET-1 binds to the ET_A receptor, the effect is pulmonary vasoconstriction. However, when ET-1 attaches to the ET_B receptor, it enhances the activity of endothelial nitric oxide synthase and causes pulmonary vasodilation. In experimental models of HPS, the ET_B receptor has been demonstrated to be upregulated; in these animal models, the experimental HPS was reversed by ET_B receptor blockade.[49,50]

Whatever the underlying mechanism of HPS, patients develop IPVD that causes a ventilation–perfusion mismatch and diffusion limitation to oxygenation because of an increase in vascular diameter. The normal pulmonary capillary is 8 to 15 μm in diameter, but in HPS capillaries may dilate to 15 to 100 μm in diameter. Because of this alteration in the normal structure of the alveolar–capillary units, inhaled oxygen does not reach the center of the blood vessel, and some blood returns to the left heart still deoxygenated. In a very rare subset of patients the hypoxemia is the result of true shunt, and AVMs occur with no communication with alveoli.

Clinical Features

Most patients with HPS present with symptoms of chronic liver disease, and a minority (18% in one trial) present with dyspnea as their primary symptom.[48] Therefore, a high index of suspicion should be maintained to make a timely diagnosis. Patients may complain of platypnea (dyspnea with standing) or have the physical examination finding of orthodeoxia, which is defined as a Pa_{O_2} decrease of 5% or 4 mm Hg upon standing. This combination of findings is attributed to the increases in IPVD in the lung bases, and, therefore, increased ventilation–perfusion mismatch in the standing position. Although

the combination of findings is well described in HPS, it is neither common (occurs in 25% of patients) nor pathognomonic; it also has been noted in patients with atrial septal defects, following pneumonectomy, and post-pulmonary emboli.[51]

On physical examination, patients with HPS may present with spider angiomata, digital clubbing, and peripheral cyanosis.[39] The chest radiograph is often normal, but it may reveal bibasilar increased interstitial markings, which may reflect vascular dilation in the bases.[52] Pulmonary function testing often reveals reduced diffusion capacity for carbon monoxide, which is out of proportion to other pulmonary function abnormalities.[53]

HPS has been reported in patients with both acute and chronic liver diseases. Most commonly, it is described in cirrhotics, but HPS has also been documented in the setting of noncirrhotic portal hypertension and acute and chronic hepatitis.[48,54] The severity of HPS does not correlate with the severity of the underlying liver disease.

Diagnosis

The diagnosis of HPS requires the presence of (1) cirrhosis or portal hypertension, (2) a widened age-corrected alveolar–arterial oxygen gradient (>15 mm Hg), and (3) demonstration of IVPD on a bubble contrast–enhanced transthoracic echocardiogram (TTE).

Bubble contrast–enhanced TTE is the most sensitive test for the detection of IPVD. However, TTE is a qualitative examination in which saline is agitated and then injected into a peripheral vein. The agitation causes formation of microbubbles that are at least 15 μm in diameter. In normals, the microbubbles are trapped within the pulmonary capillary bed and absorbed. However, if IPVD is present, the bubbles traverse the pulmonary capillaries and appear in the left atrium approximately three to six cardiac cycles after their injection. TTE can also identify an intracardiac shunt, in which case, the bubbles appear in the left atrium within the three cardiac cycles.[55]

IPVD may also be detected by technetium-labeled macroaggregated albumin lung perfusion scanning (^{99m}TcMAA). In this examination, ^{99m}TcMAA is injected intravenously and uptake detected in the lungs and brain. In the absence of intrapulmonary or intracardiac shunt, the tracer is trapped within the pulmonary circulation and very little is observed on brain imaging. A fractional uptake >5% is considered abnormal. Although MAA scanning allows quantification of the shunt, it cannot differentiate between intracardiac shunt and IPVD. One additional advantage of the ^{99m}TcMAA scan is that it is specific for HPS, even in the presence of intrinsic lung disease. Therefore, it may help to distinguish hypoxemia from HPS from that due to pulmonary parenchymal disease if both are present. ^{99m}TcMAA scanning is less sensitive than TTE for detecting the presence of HPS, and, as demonstrated in several clinical trials, the magnitude of the shunt detected correlates poorly with the degree of hypoxemia.[55]

Arterial blood gases that quantify Pa_{O_2} and the alveolar–arteriolar oxygen gradient for HPS should be obtained with the patient seated at rest and breathing room air. Due to disease-associated alterations in ventilation–perfusion matching with positional changes, along with a propensity for increased IPVD in the lung bases, hypoxemia may worsen with standing and improve in the supine position. Guidelines published in 2004 by the European Respiratory Society Task Force suggest subclassification of HPS according to level of hypoxemia: Pa_{O_2} >80 mm Hg is considered mild; Pa_{O_2} <80 mm Hg but ≥60 mm Hg is considered moderate; Pa_{O_2} <60 mm Hg but ≥50 mm Hg is considered severe, and Pa_{O_2} <50 mm Hg is considered very severe.[56]

Pulse oximetry is a noninvasive screening method for HPS, which may prompt arterial blood gas analysis. A prospective study of pulse oximetry in cirrhotic patients demonstrated that a threshold Sp_{O_2} <96% was 100% sensitive and 88% specific in detecting patients with HPS and a Pa_{O_2} <70 mm Hg. Application of this threshold cut-point resulted in arterial blood gas testing in 14% of the cohort studied.[57]

Clinical Course

The presence of significant HPS decreases exercise capacity, impairs quality of life, and increases mortality compared with patients without HPS who have a similar severity of liver disease.[58] Furthermore, the majority of patients with HPS progress over time; the average rate of decline in resting Pa_{O_2} is 5 mm Hg/y.[59] In one multicenter, prospective study, patients with HPS had a doubling in risk of death compared with patients without HPS, despite no differences in rates of listing for liver transplantation, performance of liver transplantation, age, sex, or race.[58] A number of centers have implemented screening programs for HPS at the time of liver transplant evaluation. Consequently, a population of patients with IPVD has been identified using screening contrast-enhanced echocardiography without hypoxemia. These patients may not share the poor prognosis of the hypoxemic patients described earlier.[60]

Management

No medical therapy has been shown to improve patients with HPS. Many agents have been tried unsuccessfully, including norfloxacin, β-blockade, nitric oxide inhibitors, nitric oxide, glucocorticoids, cyclooxygenase inhibitors, indomethacin, somatostatin, cyclophosphamide, and plasma exchange.[61] Pentoxifylline, a phosphodiesterase-4 inhibitor that interferes with tumor necrosis factor (TNFα) synthesis, has been demonstrated to have some success in animal models of HPS. In a pilot study of 10 children, 3 months of treatment was associated with a significant increase in Pa_{O_2} (>10 mm Hg in all patients); however, the treatment effect disappeared 3 months after drug discontinuation. In addition, the rate of drug discontinuation was 40% due to side effects.[62] A pilot study of pentoxifylline in adults showed no significant change in Pa_{O_2}. The drug was poorly tolerated due to gastrointestinal toxicity.[63] Supplemental oxygen is often administered in HPS and may ameliorate the symptoms of hypoxemia.

Liver Transplantation Liver transplantation is the only therapy proved to resolve HPS. Long-term follow-up reveals significant improvement or resolution of HPS in 85% of patients who undergo liver transplantation.[64–66] The time required for improvement in oxygenation is variable and may take up to 1 year, or longer.

Hypoxemia due to HPS may complicate the postoperative course in liver transplantation. In one prospective study, the finding of a preoperative Pa_{O_2} <50 and an MAA shunt fraction ≥20% was associated with increased postoperative mortality.[67] However, other reports suggest that liver transplantation may be safely performed in patients with HPS, including those with severe hypoxemia.[68,69]

Because of the increased mortality associated with HPS and the favorable outcome for liver transplantation, the UNOS has instituted a MELD exception guideline for affected patients: If the diagnosis of HPS is confirmed with bubble contrast echocardiography and the patient's Pa_{O_2} is <60 mm Hg, an application for MELD upgrade may be submitted. The upgrade increases the patient's MELD score to 22, regardless of the level of liver disease, with an increase by 10% every 3 months until liver transplantation.[70]

Summary

HPS is a liver-induced pulmonary vascular disorder characterized by intrapulmonary vascular dilation resulting in ventilation–perfusion mismatch and a diffusion limitation for oxygenation. No known medical treatment for HPS exists, and patients with HPS have a poorer prognosis than for patients with liver disease without HPS. HPS is an indication for, and is curable by, liver transplantation.

■ HEPATIC HYDROTHORAX

HH is defined as pleural fluid (>500 mL) occurring in a patient with liver disease in the absence of cardiac or pulmonary dysfunction. HH may complicate management cirrhosis, and it may contribute to morbidity.

Epidemiology and Pathophysiology

HH occurs in 6% to 10% of patients with end-stage liver disease. Its development is related to anatomic defects in the diaphragm, which allow fluid migration down a pressure gradient from the peritoneum into the negative pressure environment of the pleural space.[71,72] It is postulated that as ascites develops, intra-abdominal pressure increases and strains diaphragmatic tissue, which then weakens. Eventually, pleuroperitoneal blebs form and then rupture, creating a communication between the abdominal and pleural cavities. In general, these blebs are <1 cm in diameter and are more common in the right hemidiaphragm, perhaps as a consequence of the more muscular construct of the left hemidiaphragm.[73] Although HH usually occurs in the setting of ascites, HH may be present even when clinically apparent ascites is absent, making the diagnosis more challenging.[74,75]

Clinical Features

HH is right sided in 85% of patients, left sided in 13%, and bilateral in 2%.[75] Pleural fluid analysis generally reveals characteristics consistent with ascitic fluid, with slight alterations due to the increased ability of the pleura to absorb free water. HH is transudative, with a total protein level <2.5 g/dL, lactate dehydrogenase fluid-to-serum ratio <0.5, and a total protein fluid-to-serum ratio <2.5. The serum-to-fluid albumin gradient is generally >1.1 g/dL.[71,75,76] Occasionally, patients present with hepatic chylothorax. In these cases, the fluid is also transudative, but the fluid-to-serum triglyceride level exceeds 1; in addition, the fluid-to-serum cholesterol ratio is high. Hepatic chylothorax is thought to arise from chylous ascites entering the pleural space through the previously described mechanism.[77]

Diagnosis

Diagnostic thoracentesis should be performed in the setting of hepatocellular carcinoma, fever, or pain. A prospective series investigating the clinical utility and risks of thoracentesis in the cirrhotic population demonstrated that 30% of patients have an alternative diagnosis to uncomplicated HH. The most common alternative diagnoses are SBEM (see below), pleural tuberculosis, or adenocarcinoma.[66] In another large prospective series, thoracentesis was safely performed in cirrhotic patients with mild coagulopathy (PT or PTT ≤ 2× normal, platelet count of 50–99,000[per μL]) without prophylactic plasma or platelet transfusion. Hence, the presence of a mild coagulopathy should not delay diagnostic evaluation.[78]

■ SPONTANEOUS BACTERIAL EMPYEMA

SBEM occurs when a previously existing HH becomes infected. The empyema portion of this term is a misnomer, because diagnosis does not require purulent material in the pleural cavity, but rather, refers to an infection diagnosed by pleural fluid cell count analysis. The diagnosis is made if the pleural fluid has a positive culture and the polymorphonuclear neutrophil (PMN) count is >250 cells/mm^3, or, if the culture is negative, the fluid contains >500 PMNs/mm^3. The sensitivity of the culture increases from 33% to 77% if blood culture bottles are directly inoculated at the bedside during the procedure.[79] The incidence of SBEM has been reported as 13% in hospitalized patients with cirrhosis and a pleural effusion. Simultaneous SBP is a risk factor for the development of SBEM; however, up to 40% of cases are not associated with SBP.[79,80] Mortality has been reported as high as 20%. Therefore, clinicians should maintain a high index of suspicion to ensure the diagnosis is made in a timely manner.[81]

The most commonly identified bacterial pathogens in SBEM are *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus* species, and *Enterococcus* species. Third-generation cephalosporins are the empiric treatment of choice until culture data are obtained.[82] Chest tube insertion is not recommended unless frank pus is present in the pleural cavity, given the risks of complications from the procedure in this patient population.

Management

Medical and surgical interventions are employed in the management of HH. Each is described briefly in the subsequent sections.

Diuretics As is the case in management of ascites, the mainstay of treatment of HH is the establishment of negative sodium balance. Current guidelines for management of ascites call for a diet that entails 2 g/d sodium restriction, along with the administration of furosemide and spironolactone in a ratio of 40 mg of furosemide to 100 mg of spironolactone daily. Despite aggressive medical management, 20% to 26% of cirrhotics with ascites are refractory to medical treatment.[83]

Thoracentesis Thoracentesis can be performed safely in patients with cirrhosis, even in the face of mild coagulopathy. Therefore, therapeutic thoracentesis may be performed to relieve dyspnea in patients with HH that is refractory to dietary sodium restriction and diuretics. Traditionally, removal of no more than 2 L of fluid is recommended at one time because of the risk of reexpansion pulmonary edema and hypotension. However, whether the risks of large-volume thoracenteses apply to this population of patients is unclear.[84] Large-volume thoracenteses have been performed safely with close patient monitoring and measurement of end-expiratory pleural pressure. The recommended goal for end-expiratory pleural pressure is >−20 cm H_2O.[85] Data in support of use of intravenous infusion of albumin to avoid hypotension during thoracentesis are lacking.

Large-volume paracentesis may also be considered for patients in respiratory distress in patients due to ascites or HH. Paracentesis improves dyspnea and lung function within 2 hours of fluid removal. The procedure may provide symptomatic relief for patients with HH and a lower risk than thoracentesis.[86]

Tube Thoracostomy Although tube thoracostomy may seem an attractive option in patients with recurrent HH, multiple reports have confirmed a high complication rate. Specifically, pneumothorax, hemothorax, empyema, electrolyte abnormalities, and hepatorenal syndrome have all been reported. In one series of 59 patients with cirrhosis and chest tube placement, a complication rate of 80% and mortality rate of 27% were reported. Therefore, this intervention should be avoided.[87]

Transjugular Intrahepatic Portosystemic Shunt Transjugular intrahepatic portosystemic shunt (TIPS) reduces portal pressure by creating a shunt between the portal and hepatic veins. TIPS placement is the treatment of choice for a refractory HH. In a series of 73 patients with refractory HH who underwent TIPS placement, 79% had a complete or partial response to the procedure; long-term survival rates were consistent with the severity of liver disease.[88]

TIPS placement is not appropriate for all patients, despite its success in patients with HH and ascites. Patients with severely decompensated liver disease may decompensate further following the procedure because of the shunt's negative effect on hepatic blood flow. In addition, shunting blood from the portal to hepatic vein increases right atrial and pulmonary artery pressure and may further compromise patients with right-sided heart failure or PH.[89] Therefore, MELD >18, PH, large portal vein thrombus, significant hepatic encephalopathy, advanced age (>70 years), or right-sided heart dysfunction are considered relative contraindications for TIPS placement.[90] In a high-risk patient, the option of liver transplantation should be discussed before proceeding with TIPS, since transplantation can be used as a "safety net" for clinical decompensation. In a carefully selected population with refractory HH, TIPS is the standard of care.

Surgical Intervention Small case series have documented success in treating HH using open thoracotomy or video-assisted thoracoscopy (VATS).[91–94] The procedures are based on identification of

diaphragmatic defects and their closure with subsequent pleurodesis. Surgical pleurodesis has a documented success rate of 73% to 100% in preventing recurrence of HH; however, high complication rates have been noted. In one series of 18 patients, a success rate of 48% was noted, but 3-month mortality was 38.9%.[95] Therefore, although VATS with pleurodesis may be an option for patients with refractory HH, larger trials are needed to assess safety before this procedure is considered a standard recommendation.

Liver Transplantation Liver transplantation is curative for HH and should be the primary intervention for patients with refractory disease. The presence of HH does not affect ventilator days in the immediate postoperative period, nor does it increase long- or short-term posttransplant mortality.[96]

Summary

HH may complicate the clinical course of a patient with cirrhosis. A high index of suspicion is needed to diagnose SBEM and to avoid the high mortality rate associated with this condition. Dietary sodium restriction and diuretic use are the mainstays of therapy for pleural effusion, but refractory patients may require therapeutic thoracentesis or TIPS for control. Ultimately, liver transplantation is curative for refractory HH.

PULMONARY COMPLICATIONS OF GASTROINTESTINAL DISEASE

In addition to the aforementioned pulmonary complications of liver disease, diseases of other intra-abdominal organs may have significant effects on the lungs. These include disorders of the esophagus, bowel, and pancreas. Pulmonary complications of renal disease are discussed separately, below.

■ GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) affects up to 20% of the population.[97] GERD is characterized by reflux of gastric contents into the esophagus due to failure of the protective mechanisms of the upper gastrointestinal tract (see below) and produces symptoms of mucosal damage. In addition to the common symptom of "heartburn," reflux may be associated with a range of extraesophageal symptoms, including chronic cough, asthma, IPF, bronchiectasis, aspiration pneumonia, and COPD.[98]

Pathophysiology

Normally, several antireflux mechanisms protect the esophagus and airways from gastric contents: (1) Esophageal peristalsis allows clearance of regurgitated materials; dysmotility is associated with GERD. Abnormal peristalsis is reported in 40% to 50% of affected patients.[99] (2) The lower esophageal sphincter (LES) creates a barrier between the esophagus and the stomach. An incompetent LES is associated with reflux. (3) The diaphragm helps prevent reflux through external compression of the lower esophagus. Maintenance of a low thoracoabdominal pressure gradient may be important in minimizing reflux. Obese patients have higher incidence of GERD, which may be a reflection of the increase in intra-abdominal pressure that occurs with obesity.[100,101]

GERD-related pulmonary disease occurs with gross aspiration of large volumes of gastric contents, recurrent microaspiration, or, possibly, a GERD-induced reflex that causes an increase in vagal tone and resultant bronchospasm.[102–104]

Diagnosis

Diagnostic testing includes ambulatory esophageal pH monitoring and esophageal impedance testing.

Ambulatory Esophageal pH Monitoring Twenty-four hour ambulatory pH monitoring is considered the "gold-standard" diagnostic maneuver.[105] Until recently, this procedure required a catheter-based system, inserted through the nose and placed near the squamocolumnar junction in the esophagus. Various symptom scoring techniques allow linking of patient symptoms and reflux events to determine an association between the two and potential therapeutic intervention. However, the catheters employed are uncomfortable and external, and data suggest that the catheter, itself, may alter patient activity enough to impede the diagnostic accuracy. Recently, a capsule-based system with wireless data transmission has been developed, allowing increased patient comfort and incremental data collection to aid in the diagnosis of GERD. Currently, the American College of Gastroenterology recommends ambulatory pH monitoring for patients with negative findings on esophagogastroduodenoscopy (EGD) who are being considered for an antireflux procedure, and for those failing therapy with a proton pump inhibitor (PPI). Symptom correlation during the procedure is recommended, although its diagnostic role is unproven for extraesophageal symptoms other than chest pain.

Esophageal Impedance Testing Esophageal impedance testing measures changes in tissue resistance to electrical current generated in adjacent electrodes encompassed within an esophageal catheter assembly. The setup allows for identification of retrograde or anterograde food bolus movement along the esophagus. It does not differentiate between acidic, weakly acidic, or alkaline material and, therefore, the technique is often combined with pH monitoring. Impedance testing is more sensitive than pH monitoring alone for detecting the presence of GERD, although it has not been validated for the evaluation of extraesophageal manifestations of GERD.

Clinical Features

Several potential pulmonary associations of underlying GERD should be considered, including asthma, IPF, and chronic cough.

GERD and Asthma The nature of the relationship between GERD and asthma is a subject of controversy, but GERD is present in 15% to 83% of asthmatics.[106–108] Several mechanisms by which acid reflux may be related to bronchoconstriction have been described in the literature. Acid reflux into the distal esophagus is postulated to cause bronchoconstriction through vagal stimulation.[109,110]

Declines in esophageal and tracheal pH coincide with reduced airflow, suggesting that microaspiration of gastric acid may lead to bronchoconstriction.[111] Interestingly, some studies have actually suggested the converse—that asthma exacerbations promote GERD by increasing the pleural-peritoneal pressure gradient by lowering pleural pressure,[112] by promoting LES relaxation,[113] or, perhaps, by a direct effect of bronchodilators on the LES.[114–116]

Asthma guidelines suggest that GERD be treated in asthmatics who have complaints of heartburn or frequent night-time symptoms. However, in a study of over 400 patients with poorly controlled asthma who received a PPI, treatment had no effect on respiratory exacerbations compared with those who received placebo.[117] Current NIH guidelines suggest that treatment of GERD may improve asthma control, citing grade B evidence.[118]

GERD and Idiopathic Pulmonary Fibrosis Recently, a clinical association has been noted between GERD and IPF; the estimated prevalence of GERD in the IPF population is 90%. This association coincides with a recent shift in thought regarding the etiology of IPF, away from one of active inflammation, and toward one of alveolar injury and maladaptive repair, resulting in fibroblast proliferation and, ultimately, lung fibrosis.[119] A strong association between IPF and GERD has been documented in recent clinical trials.[120–122] In addition, one retrospective review of 14 patients awaiting lung transplantation for IPF-reported stabilization, but not improvement, of lung function with laparoscopic Nissen fundoplication.[123] The mechanistic relationship between IPF and GERD, the best diagnostic modality for assessment, and the optimal treatment algorithm are areas of active investigation. No established guidelines have yet been created.

GERD and Chronic Cough GERD is a well-known cause of chronic cough, and treatment of GERD is considered a mainstay in initial therapy for chronic cough. GERD was identified as a cause of chronic cough in 1981, and since then data have emerged ranking it as the second most common cause.[124,125] Twenty-eight percent of patients with chronic cough that improves with GERD therapy deny typical symptoms of GERD.[126] Although 24-hour esophageal pH monitoring is considered the most sensitive test for GERD in chronic cough, it is expensive and has limitations. Therefore, the most recent American College of Chest Physicians guidelines on the treatment of cough recommend empiric therapy for GERD in patients whose cough is plausibly related to reflux.[127]

Treatment

The three main treatments for GERD are antacids, histamine-2 receptor antagonists (H2RA), and PPIs. PPIs have established efficacy over other options and are now the mainstay of therapy. Surgical therapy using Nissen fundoplication is reserved for refractory cases; it may be performed through an open incision or laparoscopically. Finally, new, less invasive procedures to improve the function of the LES are under investigation.

Summary

GERD is a common condition, affecting up to 20% of the population. The reflux of gastric contents into the esophagus may exacerbate pulmonary conditions such as IPF, asthma, and COPD, but neither a causal relationship nor a significant response to therapy has been documented in any of these conditions. GERD is a frequent cause of chronic cough; treatment with a PPI may ameliorate symptoms in affected patients.

■ INFLAMMATORY BOWEL DISEASE

Pulmonary complications associated with inflammatory bowel disease (IBD) were first described in 1976 in a small series of patients who had both IBD and chronic bronchitis.[128] Since that time, a connection between IBD and pulmonary disease has been increasingly recognized, but the pathophysiology of the relationship remains unclear. Both Crohn's disease and ulcerative colitis (UC) have been associated with a variety of respiratory problems: airway disease, parenchymal lung disease, serositis, and pulmonary vascular disease.

Airway involvement, the most common pulmonary disorder in IBD, may present as bronchiectasis, chronic bronchitis, tracheitis, subglottic stenosis, or, rarely, small airway disease.[129–131] Pulmonary parenchymal involvement is less common, but cryptogenic organizing pneumonia, eosinophilic pneumonia, nonspecific interstitial pneumonitis, necrobiotic nodules, and sarcoidosis have been described in IBD.[129,132,133] In addition, an exudative pleuritis that does not relate to IBD disease activity has been reported.[129] The association between the gastrointestinal and pulmonary "inflammation" is unclear, but the majority of these pulmonary complications appear to be steroid-responsive.[132] Finally, patients with IBD have a higher incidence of thromboembolic events than do age-matched controls; the risk of pulmonary embolism does not appear to be related to disease activity.[134]

PULMONARY COMPLICATIONS OF ACUTE PANCREATITIS

Acute pancreatitis (AP) is an acute inflammation of the pancreas, which may cause both systemic inflammatory response syndrome (SIRS) and multisystem organ dysfunction syndrome (MODS) (see Chapter 142). When MODS accompanies pancreatitis, mortality is reported at 15% to 20%.[135,136] Pulmonary complications of pancreatitis are reported in 75% of cases. The most common presentations are hypoxemia without radiologic abnormalities, pleural effusions or, in the sickest patients, acute respiratory distress syndrome (ARDS).[137,138]

■ HYPOXEMIA

Hypoxemia occurring early in the course of pancreatitis, even prior to development of radiological abnormalities, is well documented and a risk factor for ARDS and increased mortality.[137,139,140] Consequently, hypoxemia is included in the pancreatitis severity scores of both Ranson and Imrie.[141,142]

Several inflammatory mechanisms are implicated in development of the early lung injury of pancreatitis. Increased permeability at the microvasculature leads to alveolar filling and decreased lung compliance. In addition, nitric oxide–related endothelial cell damage occurs, with leukocyte activation and adhesion at the level of the pulmonary microvasculature. Furthermore, the systemic release of pancreatic elastase may contribute to inflammation in the lung parenchyma, and fibrinogen metabolism may allow fibrin deposition in alveoli. Collectively, these processes transform the relatively benign environment of the alveolus into an inflammatory milieu and profoundly affect gas exchange. Early hypoxemia is an independent predictor of poor outcome in AP.[140]

■ PLEURAL EFFUSION

The presence of a pleural effusion is a marker of the severity of pancreatitis and occurs in 84% of patients with severe disease, but in only 8.6% of patients with mild disease.[143] Approximately two-thirds of the effusions are left sided, but they may be bilateral or right sided.[144] The effusion is usually small and may be hemorrhagic. Analysis of pleural fluid reveals a very high amylase and elevations in protein and LDH levels when compared with serum.[145] Pleural effusions in AP may be caused by transdiaphragmatic lymphatic blockage or arise as a sympathetic effusion due to associated inflammation. A rare complication is a pancreaticopleural fistula, in which the pancreatic duct or a pseudocyst empties posteriorly into the retroperitoneum, tracking up the mediastinum and rupturing into the pleural cavity. The resulting effusions are generally massive and require evacuation and correction of the anatomic defect.[146,147] When less than massive, the effusions are treated conservatively and typically resolve with resolution of the pancreatitis.

■ ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS develops in approximately 15% to 20% of patients with AP. When present, mortality rises >50%.[148] The pathophysiologic basis of ARDS in AP is poorly understood, but inflammatory cytokines have been implicated (see Chapter 140). Specifically, trypsin injures the pulmonary vasculature and promotes leukostasis and increased vascular permeability.[149,150] Phospholipase A2 (PLA2), which removes fatty acids from phospholipids, may act on surfactant, contributing to respiratory failure.[151,152] Multiple other mediators have been implicated, including IL-6, IL-8, NO, TNFα, and substance P. Whatever the underlying mechanism, ARDS is the basis for 50% to 90% of deaths in AP.[153] Treatment is supportive and incorporates an alveolar protective ventilator strategy (see Chapter 141).

Summary

AP may cause a SIRS and MODS. One of the early signs of ensuing MODS may be hypoxemia, which is a risk factor for the later development of ARDS and early mortality. Pancreatitis is often accompanied by a pleural effusion, which is exudative and characterized by a high amylase level. In general, these effusions may be handled conservatively. ARDS occurs in 15% to 20% of patients with pancreatitis and is the cause of death in most who do not survive the bout of pancreatitis.

PULMONARY COMPLICATIONS OF RENAL FAILURE

Several notable associations exist between respiratory disease and renal failure, including PH and metastatic pulmonary calcification.

TABLE 98-3 Common Hemodynamic Profiles in Patients with CKD

CKD Associated Condition	mPAP	CO	PCWP	PVR
Chronic volume overload	↑	N	↑↑	N
Anemia	↑	↑	N	N
Increased cardiac output due to AV fistula	↑	↑	N	N↓
Left ventricular dysfunction (usually diastolic)	↑	N	↑	N↑

mPAP, mean pulmonary artery pressure (normal, <25 mm Hg); CO, cardiac output (normal, 4–6 L/min); PCWP, pulmonary capillary wedge pressure (normal, <15 mm Hg); PVR, pulmonary vascular resistance (normal, <3 Wood units: ([MPAP–PWCP]/CO); N, normal.

PULMONARY HYPERTENSION AND RENAL FAILURE

PH associated with chronic kidney disease (CKD) is encompassed within Group 5 of the WHO classification of PH (PH with unclear or multifactorial causes).[154] CKD is defined by a reduced glomerular filtration rate (GFR) <60/mL/min/1/73 m^2) for ≥3 months. Screening for PH in CKD is accomplished using TTE and estimation of right ventricular systolic pressure (RVSP). Generally, RVSP >35 mm Hg is considered "abnormal" in patients with CKD.[154] Subsequent to screening, accurate characterization and definitive diagnosis of PH in CKD requires RHC. Patients with CKD are complex with respect to the many factors, acting individually or in combination, that may increase RVSP (Table 98-3).[155,156]

The frequency of PH in CKD has been reviewed extensively; findings depend on the stage of CKD, dialysis methods and duration, and method of assessment for PH (i.e., TTE vs. RHC).[154] The incidence of PH in CKD varies from 9% to 39% in nondialysis-dependent patients and up to 82% for those on hemodialysis (HD). Patients undergoing peritoneal dialysis appear to have a lower incidence of PH than do patients on HD. WHO Group I Pulmonary artery hypertension (↑MPAP, normal PCWP, ↑PVR) complicating CKD is uncommon (13%) and may only be unmasked by RHC postdialysis.[155] Often, other comorbidities exist, such COPD or sleep apnea, which may contribute to PH.

The finding of PH on TTE in dialysis patients has ranged from 29% to 47% and is associated with increased all-cause mortality.[157,158] In addition, in a study of kidney transplant candidates, 32% of whom had an RVSP >35 mm Hg, pretransplant severity of PH (which was related to time on dialysis) correlated significantly with worsening posttransplant survival at 3 years.[159]

Summary

The pathogenesis of, and optimal treatment regimen for, PH in CKD is poorly understood. The presence of PH is associated with a poor outcome in patients on dialysis and in those who undergo renal transplantation.

METASTATIC PULMONARY CALCIFICATION

Metastatic calcification in the lung is a well-documented complication of CKD that requires HD. It is fairly common, with 60% to 75% of autopsy specimens of patients on HD patients exhibiting disease.[160,161] Despite this common pathologic finding, patients are generally asymptomatic, and only a minority have disease visible on the chest radiograph.[160]

Metastatic calcification in patients with chronic renal failure (CRF) is thought to arise from several mechanisms. Chronic metabolic acidosis from renal failure leaches calcium and phosphate from bone. In addition, when bicarbonate is used for HD, a transient alkalosis may predispose to calcium deposition in tissue.[161,162] Secondary hyperparathyroidism, which is common in CKD, results in increased calcium and phosphate release from bone. Finally, decreased clearance of phosphate due to CKD results in an increased calcium-phosphate product and further salt deposition.[163] Deposition of calcium phosphate, the primary salt, is generally benign. However, the radiographic finding may result in a workup for pulmonary infiltrates. In difficult cases, differentiating metastatic calcification from pneumonia or edema is most definitively done using ^{99m}Tc-MDP bone scintigraphy, which identifies a calcified focus in the lungs.[164] Treatment is centered on lowering the patient's calcium-phosphate product with medication and dialysis. Although the majority of cases are benign in course, some are associated with progressive dyspnea, restrictive physiology, low diffusing capacity, hypoxemia, respiratory failure, and death.[165,166]

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CHAPTER 99

Sleep Apnea Syndromes: Central and Obstructive

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HISTORY OF SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (SDB) is an extremely common medical disorder associated with important morbidity. Recognition of its relevance in medicine is relatively recent, although clinical reports of SDB were first made in the 19th century.[1] Likely influenced by such observations, descriptions of an entity constituting obesity and extreme somnolence were highlighted in the character narratives of the "fat boy" in Charles Dickens' series, *Posthumous Papers of the Pickwick Club,* first published in 1837.[2] Dickens described Joe, the fat boy, as a loud snorer who was obese and excessively somnolent—the classical description of Pickwickian syndrome. Sir William Osler in 1918 was credited with first linking the relationship between obesity and Pickwickian syndrome.[3] In the mid-20th century, further work led to the association of Pickwickian syndrome with alveolar hypoventilation by Burwell et al. in 1956, and periodic cessation of respiration by Drachman and Gumnit in 1962.[4,5]

Over the last 40 years, we have begun to understand the pathogenesis of sleep apnea and have developed effective diagnostic and treatment modalities for this common disorder. Gastaut et al.[6] in 1965 showed that cessation of respiration was due to obstruction of the upper airway, and obstructive sleep apnea (OSA) was recognized. In 1972, a conference organized by Lugaresi and his Bologna (Italy) group entitled "Hypersomnia and Periodic Breathing," served as a springboard for the growth of interest and research in SDB.[7] Guilleminault et al.[8] coined the terms sleep apnea syndrome and obstructive sleep apnea syndrome (OSAS) in 1976 to underscore that airway obstruction during sleep was not restricted to obese subjects.

As the understanding of the etiology of OSA increased, treatment options began to emerge. In 1969, a case report describing treatment of OSA in a patient with tracheostomy was published.[9] The first reports demonstrating reversal of OSA with positive airway pressure (PAP) did not occur until more than 10 years later.[10,11] The role of weight loss and its shortcomings in resolution of OSA was noted by Fishman in 1972.[12]

SLEEP APNEA DEFINITIONS

Adult SDB is present when repetitive apneas (episodes of breathing cessation) and hypopneas (episodes of decrement in airflow) occur during sleep, usually associated with sleep fragmentation, arousals, and reductions in oxygen saturation. Apneas are generally defined as an episode of breathing cessation lasting at least 10 seconds in duration, and can be classified as obstructive (in which there is no airflow despite continued respiratory effort), central (no airflow and no respiratory effort), or mixed (events initially appear central in origin, with respiratory effort occurring during the latter portion of the same episode). Hypopneas are SDB events during which decrements in airflow are observed and can also be obstructive or central in origin. In practice, hypopnea definitions vary substantially according to the degree of airflow limitation expected, the magnitude of oxygen desaturation needed, and by whether the definition includes events associated with arousal but not oxygen desaturation.[13,14] In addition, the term "respiratory effort–related arousal" (RERA) is sometimes used to designate a series of breaths characterized by increasing effort leading to an arousal from sleep that does not meet the criteria for apnea or hypopnea.[15] Although both physiologic and epidemiologic studies have demonstrated that hypopneas produce the same clinical consequences as apneas, evolving hypopnea definitions can make it challenging to compare sleep apnea severity and associated consequences across different study populations.

Currently, the apnea–hypopnea index (AHI, number of apneas and hypopneas per hour of sleep) is the standard metric used to describe the severity of sleep apnea.[13] In older papers, the term respiratory disturbance index (RDI) was often used interchangeably with AHI. More recently, some authors have included the number of RERAs per hour of sleep in the RDI definition, that is, number of apneas, hypopneas, and RERAs per hour of sleep. Nevertheless, neither AHI nor RDI take into consideration other characteristics of SDB such as the magnitude of oxygen desaturation or duration of hypoxia.

OBSTRUCTIVE SLEEP APNEA

OSA is defined by the presence of repetitive episodes of upper airway obstruction during sleep. An AHI of equal to or greater than 5 events/h is commonly used to define OSA, with obstructive or mixed (rather than central) events comprising more than 50% of the total.[14] The OSAS is usually defined by an AHI equal to or greater than 5 events/h and persistent complaints of excessive daytime somnolence, unrefreshing sleep, or fatigue.[16] Other OSA definitions suggest that OSA be recognized if the AHI is at least 10 to 14 events/h, or in cases in which the AHI is between 5 and 14 events/h and documented hypertension, ischemic heart disease, history of stroke, or symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, or insomnia exist.[17,18]

OSA is often classified as mild, moderate, or severe according to the AHI. A common scheme is 5 to 15 (mild), 15 to 30 (moderate), >30 events/h (severe).[14] Some authors have suggested that severity should be defined by associations with adverse clinical outcomes rather than the event index.[19,20] Recent changes in clinical hypopnea definitions by organizing bodies such as the American Academy of Sleep Medicine (AASM) have also provoked debate over parameters of disease severity.[14,21,22]

In the past, the term upper airway resistance syndrome (UARS) has been used to describe symptoms of sleepiness and fatigue in the setting of milder SDB not meeting criteria for apneas and hypopneas.[23] Advances in detection of SDB events (e.g., with nasal pressure) and the inclusion of events associated with arousals in the hypopnea definition have likely eliminated the need to designate UARS as a separate entity.[14,24] These individuals are now likely to be diagnosed with OSA. Debate continues as to whether some nonobese individuals may have a hypersensitive arousal response to repetitive increased respiratory effort that is distinct from OSA.[25,26]

CENTRAL SLEEP APNEA

Central sleep apnea (CSA) is much less common than OSA and is characterized by a transient cessation of rhythmic breathing. It is defined as repeated episodes of apnea in the absence of respiratory muscle effort and is observed on the polysomnogram as an absence of both nasal–oral airflow and thoracoabdominal excursion.[27] A number of etiologies for CSA have been recognized, among which congestive heart failure (CHF) and stroke are the most common. Patients with CSA experience sleep fragmentation and can report similar daytime symptoms to OSA patients.

OBESITY HYPOVENTILATION SYNDROME

Obesity hypoventilation syndrome (OHS), or the Pickwickian syndrome, is defined by obesity, SDB, and hypoventilation with daytime hypercapnia in the absence of other causes for hypoventilation. Thus, OHS should be regarded as a diagnosis of exclusion. Seventy to 90% of patients with OHS have been estimated to have OSA.[28,29] Conversely, 10% to 15% of sleep apnea patients have been noted to have daytime hypercapnia and can be classified as having concomitant OHS.[30] OHS is discussed more fully in Chapter 100.

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA

The pathogenesis of OSA involves both anatomic and neurologic components. The upper airway is a complicated structure that performs multiple physiologic functions, including vocalization, respiration, and deglutition. The upper airway extends from the posterior margin of the nasal septum to the larynx and has a paucity of rigid bony support. It is divided into four anatomic regions (Fig. 99-1):

- Nasopharynx: between the nares and the hard palate
- Retropalatal oropharynx: between the hard palate and the caudal margin of the soft palate
- Retroglossal oropharynx: between the caudal margin of the soft palate and the base of the epiglottis
- Hypopharynx: from the base of the tongue to the larynx

The major contributors to the airway boundaries include the soft palate and tongue anteriorly; the pharyngeal constrictor muscles, lymphoid tissue, parapharyngeal fat pads, and mandibular rami laterally; and the pharyngeal constrictor muscles posteriorly.[31,32] The soft tissue and craniofacial (bony) structures in the retropalatal and retroglossal regions contribute to the specific morphology of the airway of a given individual.[32] Collapse of the upper airway reduces its airway intraluminal diameter and increases airway resistance, leading to the apneas and hypopneas that characterize OSA.[33,34] Figure 99-1 displays a midsagittal magnetic resonance image in a normal individual in which the retropalatal and retroglossal regions are outlined. This midsagittal image also highlights the airway, tongue, soft palate, mandible, and subcutaneous fat. The lateral upper airway soft tissue structures of the retropalatal region, that is, the lateral pharyngeal walls and lateral parapharyngeal fat pads, are depicted in Figure 99-2.

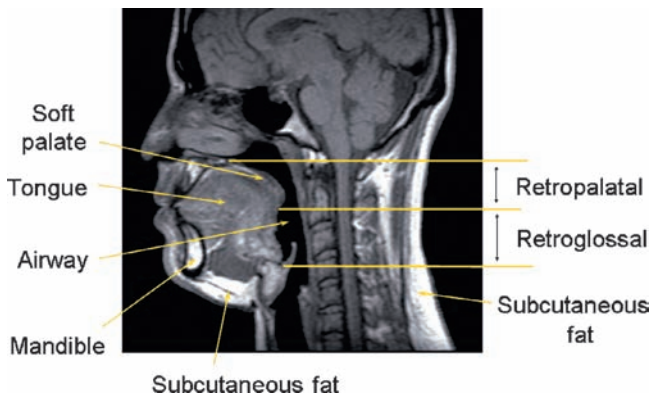

Figure 99-1 Midsagittal magnetic resonance image in a normal individual demonstrating the anatomic regions of the upper airway and relevant craniofacial and soft tissue structures. The retropalatal (RP) region is defined from the level of the hard palate to the distal margin of the soft palate; the retroglossal (RG) region is defined from the distal margin of the soft palate to the base of the epiglottis. In patients with OSA, obstruction usually occurs in the retropalatal or retroglossal levels or at both locations. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1673–1689.)*

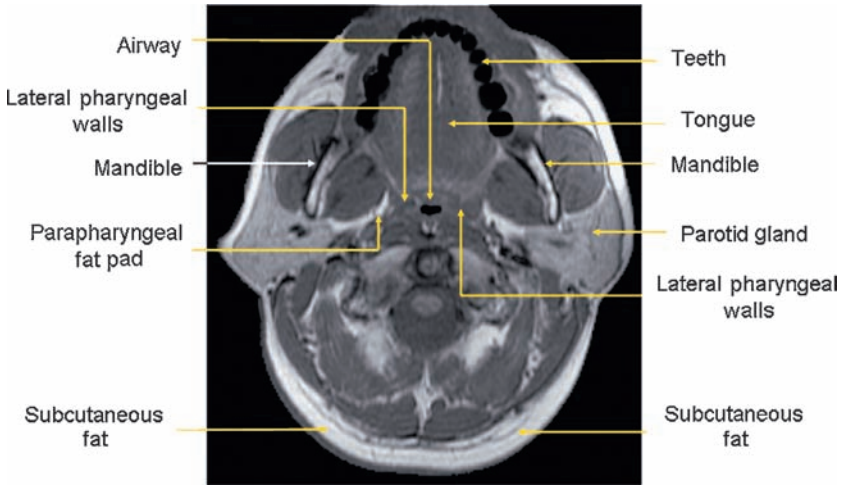

Figure 99-2 Axial MR image at the retropalatal level in a normal subject. The relevant soft tissue and bony structures surrounding the upper airway are highlighted. The tissues immediately lateral to the airway are the lateral pharyngeal walls and the parapharyngeal fat pads. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1): 1673–1689.)*

Anatomical factors are clearly a major contributor to the propensity for airway collapse during sleep. In addition, the critical role of neuromechanical control of the upper airway in the pathophysiology of OSA is becoming increasingly well understood.

ANATOMIC FEATURES THAT PREDISPOSE TO OBSTRUCTIVE SLEEP APNEA

The extrathoracic upper airway lacks a robust support framework of cartilaginous rings and therefore is at risk for collapse due to extraluminal tissue pressure exerted by circumferential craniofacial and soft tissue structures and negative pressure associated with inspiration. Changes in pharyngeal transmural pressure, defined as the difference between the pressure in the airway lumen and the pressure exerted by tissues surrounding the site of collapse, modulate upper airway size. Activity of the pharyngeal dilator muscles offsets extraluminal tissue pressure to help maintain upper airway patency.[35]

Among individuals with sleep apnea, upper airway collapse occurs most commonly in the retropalatal and retroglossal regions, reducing airway intraluminal diameter and increasing airway resistance, which leads to apneas and hypopneas.[36] Multiple potential sites of upper airway collapse have been visualized in many patients with OSA and tend to be reproducible from episode to episode.[37] During wakefulness, upper airway caliber is smaller in patients with sleep apnea compared to normal individuals.[38] Habitual snorers also have generalized narrowing of the pharyngeal lumen compared to normal subjects, regardless of whether they are obese.[32] Nevertheless, smaller upper airway caliber does not entirely explain OSA risk: Men have larger pharyngeal airway cross-sectional area and airway volumes than

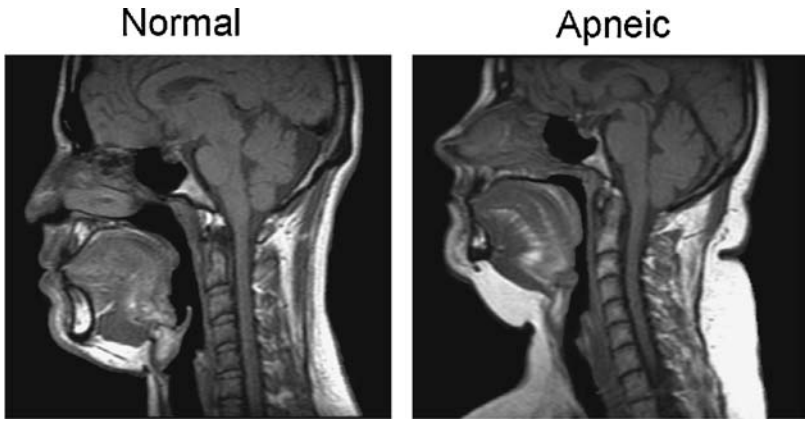

Figure 99-3 Midsagittal magnetic resonance imaging (MRI) of a normal subject on the left and a patient with sleep apnea on the right. The upper airway is smaller in both the retropalatal and retroglossal region in the apneic patient. The soft palate is longer in the apneic patient. The tongue is bigger in the retroglossal region in the patient with sleep apnea. The amount of subcutaneous fat (*white area* at the back of the neck) is greater in the apneic. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1673–1689.)*

women, but are more likely to develop sleep apnea. Recently, attention has focused on the role of airway length to explain gender disparity in OSA risk, given observations that men have longer, and thus more collapsible, pharyngeal airways compared to women.[39] A reduction in the lateral diameter of the airway in individuals with OSA, with relative preservation of the anterior–posterior diameter, may also promote upper airway dysfunction.[40]

In population studies, neck circumference is a strong predictor of OSA.[41] Consistent with this observation, individuals with OSA demonstrate an excess of upper airway soft tissue for the space within the craniofacial structures that envelop the pharyngeal lumen. Patients with sleep apnea have larger tongues and longer soft palates than normal subjects (Fig. 99-3).[39,42–44] The larger the volume of the lateral pharyngeal walls, tongue, and total upper airway soft tissue (Fig. 99-4), the greater the likelihood of having OSA; specifically, increased thickness of the lateral pharyngeal walls may contribute to narrowing of the apneic airway.[42] Imaging studies have demonstrated that the total volume of fat surrounding the airway is also greater in apneic individuals compared to BMI-matched normal subjects.[45] These findings suggest that fat deposition in the neck—in the parapharyngeal fat pads, under the mandible, and particularly in the tongue—may similarly reduce upper airway caliber. Increased soft tissue mass may increase tissue pressure, resulting in airway collapse and decreased airway volume.[35]

Variations in craniofacial morphology also influence upper airway configuration. For example, retroposed mandible and increased hyoid–mandibular plane distance have been associated with higher risks of apnea.[46–48]

Changes in upper airway anatomy during the respiratory cycle can influence the propensity for airway collapse during both inspiration and expiration. Using dynamic upper airway imaging with CT, MRI, and nasopharyngoscopy, the airway's geometrical changes have been

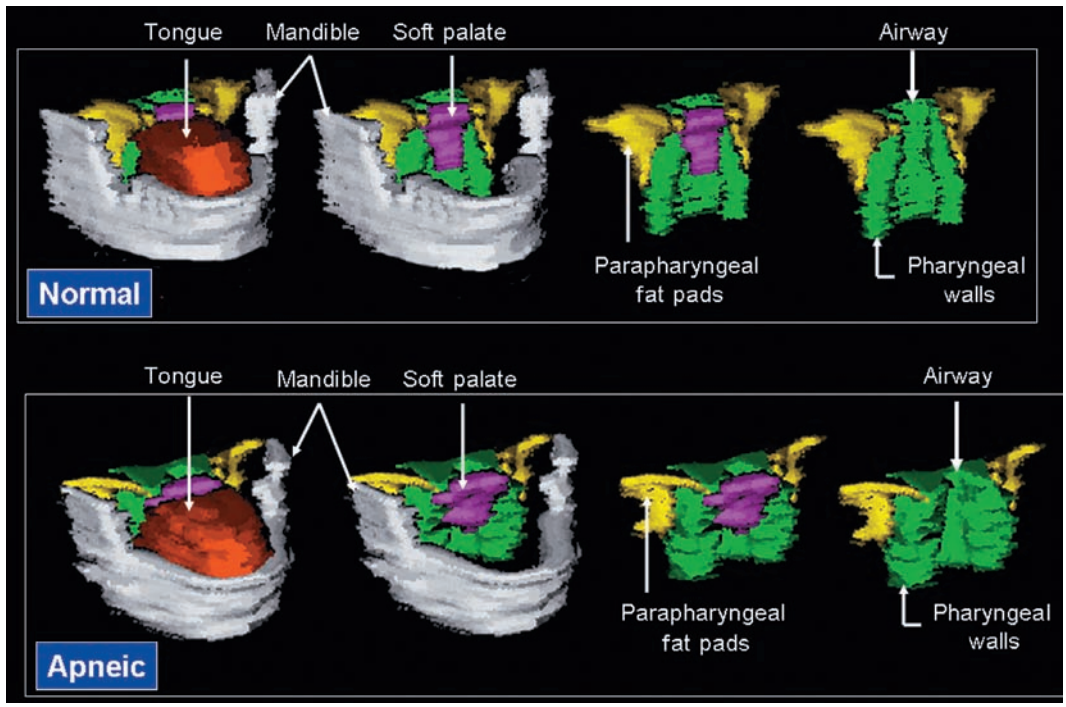

Figure 99-4 Volumetric reconstruction of axial magnetic resonance (MR) images in a normal subject (top panel) and a patient with sleep apnea (bottom panel). The mandible is depicted in *gray*, the tongue in *orange/rust*, the soft palate in *purple*, the lateral parapharyngeal fat pads in *yellow,* and the lateral/posterior pharyngeal walls in *green*. Both subjects had an equivalent body mass index (32.5 kg/m^2). Upper airway caliber is greater in the normal subject than in the patient with sleep apnea. The tongue, soft palate, and lateral pharyngeal walls are all larger in the patient with sleep apnea than in the normal subject. *(Reproduced with permission from Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med. 2003;168(5):522–530.)*

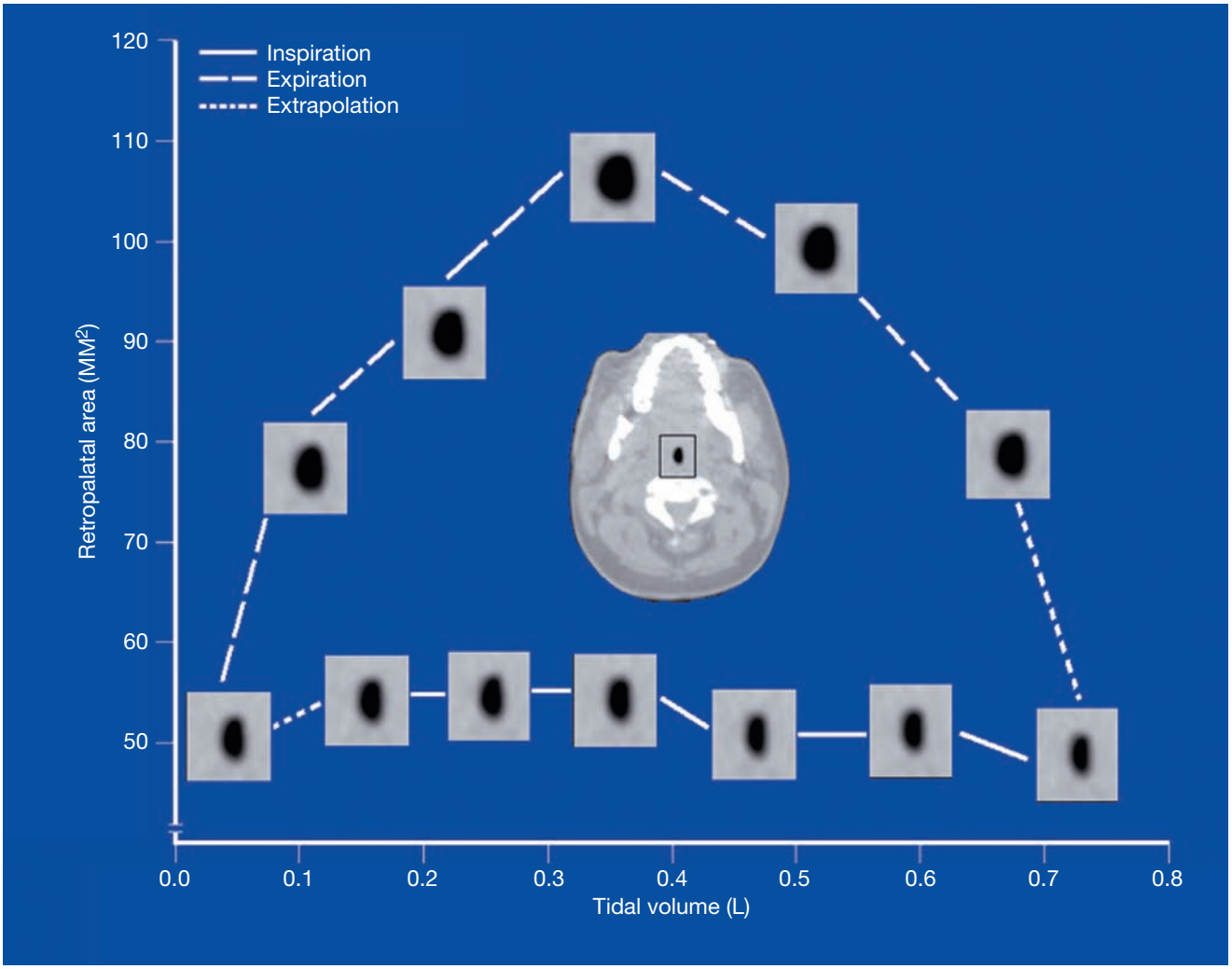

Figure 99-5 Changes in upper airway area as a function of tidal volume during the respiratory cycle using cine CT (computed tomography). Airway caliber is relatively constant in inspiration. Airway size increases in early expiration and decreases in late expiration. *(Reproduced with permission from Schwab RJ, Gefter WB, Hoffman EA, et al. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep-disordered breathing. Am Rev Respir Dis. 1993;148(5):1385–1400.)*

partitioned into three phases (Fig. 99-5). During inspiration, upper airway area is relatively constant, implying a balance between muscle dilator activity and negative airway lumen pressure. In early expiration, the activity of airway dilator muscles decreases, intraluminal pressure rises, and the airway widens maximally. At end expiration, upper airway dimensions decrease. Patients with OSA have more narrowing during end expiration compared to normal controls.[40,49,50]

A number of recent studies have also demonstrated that redistribution of extracellular fluid can occur during sleep and in the supine position, leading to significant increases in neck circumference and airway collapsibility, and a reduction in upper airway cross-sectional area.[51–53] The magnitude of fluid redistribution is associated with the degree of SDB, suggesting a contributory role for this mechanism in the development of OSA. However, absolute AHI fell only modestly in a small crossover study in which patients wore compression stockings during the daytime to reduce nocturnal fluid shifts, suggesting that this mechanism does not play a major role in OSA pathogenesis.[54]

■ NEURAL MODULATION OF UPPER AIRWAY PATENCY

During sleep, the balance in transpharyngeal pressure shifts toward upper airway collapse due to reduced upper airway dilator muscle activity. MR images suggest that even among normal individuals, the retropalatal upper airway narrows during sleep (Fig. 99-6). The neural control of the upper airway muscles is complex and involves several neurotransmitters (serotonin, norepinephrine, orexin–acetylcholine, and gamma-aminobutyric acid) that are influenced by sleep itself.[55–57] The most widely studied upper airway muscle is the genioglossus.

Three neural mechanisms have been shown to be operative with regard to genioglossus muscle activity and vulnerability to obstructive apneic events. First, negative airway pressure detected by laryngeal mechanoreceptors activates the genioglossus via increased hypoglossal nerve discharge. This reflex is diminished during non-REM sleep compared to wakefulness, and is further reduced during REM sleep, placing the airway at risk for collapse.[58–61] Recently, a novel, state-sensitive motor inhibitory cholinergic channel that operates at the hypoglossal motor pool has been identified as the principal mechanism of REM sleep pharyngeal motor inhibition.[62] Furthermore, patients with OSA have reduced upper airway reflexes during sleep compared to normal individuals.[63] Whether these differences occur due to individual variability in neuromuscular responses placing some individuals at increased risk for OSA, or whether repetitive injury from snoring vibration or oxidative stress leads to neural or muscular damage have been debated.[64–66]

Second, the upper airway muscles respond to input from the respiratory control center in the medulla, with increases and decreases in activity in proportion to respiratory drive. In situations of ventilatory

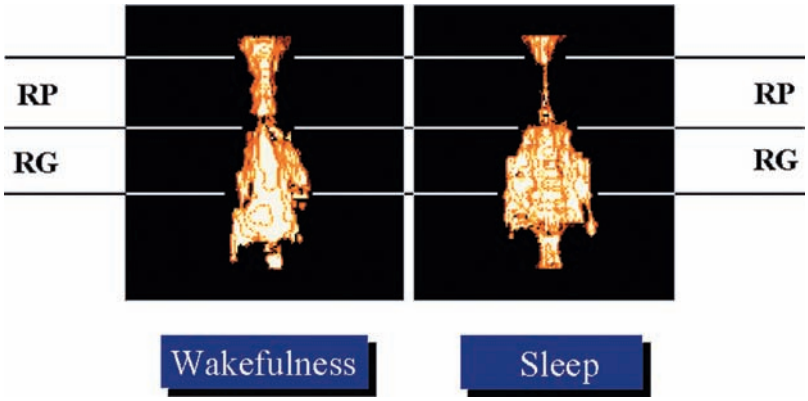

Figure 99-6 Volumetric state–dependent airway imaging in a normal subject using magnetic resonance imaging (MRI). Airway volume during sleep is smaller in the retropalatal (RP) region but not the retroglossal (RG) region. Such images suggest that the upper airway during sleep does not narrow as a homogeneous tube. Nonetheless such images indicate that the upper airway of subjects without sleep apnea narrows during sleep. *(Reproduced with permission from Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med. 2003;168(5):522–530.)*

control instability in which respiratory drive waxes and wanes, diminished upper airway muscle activity can precipitate airway collapse, that is, obstructive apnea.[67,68] Third, neural mechanisms modulating arousal (serotonergic and noradrenergic neurons) have a tonic excitatory influence on genioglossus activity. With the onset of sleep, there is a reduction in arousal-modulated excitatory output to the upper airway musculature.[69,70] During episodes of upper airway collapse, arousal from sleep in response to respiratory activation helps to restore airway patency.[71,72] Although arousals are not always necessary for recovery from upper airway obstruction, patients with OSA have a diminished ability to restore ventilation without cortical arousal compared to nonsnorers.[73]

THE APNEIC EVENT

Occlusion of the airway results in a range of immediate physiologic disturbances. Episodic reductions or cessations in ventilation despite continued respiratory efforts, recurrent episodes of intermittent hypoxemia, and frequent arousals from sleep form the basis for a cascade of downstream perturbations. During obstructive apneas, breathing efforts create abrupt reductions in intrathoracic pressure that can increase atrial natriuretic peptide (ANP) release and left ventricular (LV) transmural pressure, compromise LV filling and increase both preload and afterload.[74–78] Myocardial oxygen demand increases despite reduced coronary blood flow and decreased oxygen delivery due to apnea-related hypoxia.[79] Surges in sympathetic nervous system activity that occur due to apnea, hypoxia, hypercapnia, and arousal result in increased peripheral resistance and cardiac stimulation, which in turn lead to postapneic increases in blood pressure (BP) and heart rate.[80–83] These elevations in sympathetic activity persist during the day in individuals with OSA.[84] Intermittent hypoxemia is associated with increased production of reactive oxygen species and oxidative stress, which can impair endothelially mediated vasodilation, contributing to BP elevation.[85,86] Reactive oxygen species also increase activity of the transcription factor nuclear factor kappa B (NF-κβ), a key component of the inflammatory response.[87] NF-κβ stimulates the production of inflammatory mediators (e.g., C-reactive protein, tumor necrosis factor-α, and interleukins 6 and 8) and adhesion molecules (platelet endothelial adhesion molecule, intercellular adhesion molecules [ICAMs]).[88–92] These effects of intermittent hypoxia are likely to promote endothelial damage and atherosclerosis.[93,94]

Termination of obstructive apneas usually occurs with a transient arousal or awakening from sleep. Arousals are coupled with respiratory effort and involve both chemical (hypoxia) and mechanical (increased respiratory effort against an occluded airway) stimuli.[95,96] Arousal mechanisms can be adversely affected by alterations in chemosensitive systems, ingestion of alcohol, or use of sedatives and hypnotics, leading to prolongation of apneic events.

EPIDEMIOLOGY AND RISK FACTORS FOR OSA

The section focuses on the epidemiology of obstructive sleep apnea and the many risk factor for the disorder.

EPIDEMIOLOGY OF OSA

Estimates of the prevalence of OSA in the general population are variable and dependent on several factors, including the characteristics of the population studied (e.g., obesity, ethnicity), methods used to measure SDB, disease definitions (e.g., hypopnea definition), and the AHI threshold used to define OSA.[17,97,98] In the United States, a landmark community-based population study (the Wisconsin Sleep Cohort Study) published in 1993 reported the prevalence of OSA with daytime sleepiness (i.e., OSAS) to be 4% in men and 2% in women between the ages of 30 and 60.[99] Subsequently, additional epidemiologic studies from a diverse array of countries including Australia, the United States, China, India, Korea, Spain, and Brazil have estimated the prevalence of symptomatic OSA to be between 3% and 8% in men and 1% and 5% in women.[17,99–107] In fact, current prevalence is likely to be substantially higher, given rising rates of obesity and the aging of the population worldwide.[108]

The prevalence of OSA defined by the presence of SDB events alone, without daytime symptoms, is also considerably higher than the prevalence of symptomatic OSA.[17,99,106] For instance, 24% of men and 9% of women in the Wisconsin Sleep Cohort Study had an AHI of at least 5 events/h.[99] However, the impact of milder, asymptomatic OSA on adverse health outcomes remains an area of active debate.

Age

The effect of age on the prevalence of OSA is complex. Population studies have demonstrated that the prevalence of OSA increases through midlife, but then plateaus after age 60 to 65.[109] Furthermore, after controlling for obesity, mean OSA severity may decline with age.[17] Nevertheless, individuals between ages 65 and 100 are more than six times more likely to have OSA compared to men and women 20 to 44 years of age.[17,101] Several studies have observed that the prevalence of SDB is greater than 50% in those at least 65 years of age.[97,106,109,110] These findings have raised questions about whether there is a "survivor effect" for OSA among older adults (i.e., whereby those with OSA who survive to old age are relatively resistant to its adverse effects). Thus, the clinical significance of OSA in the elderly is debated, as is whether a higher threshold should be used to define OSA in this age group.[111]

Gender

Epidemiologic studies demonstrate that the prevalence of OSA is two to three times higher in men than women and that postmenopausal women are at an approximately threefold higher risk for OSA compared to premenopausal women.[17,99,105,112] The lower risk among premenopausal women appears to be related to the effects of reproductive hormones; however, data describing how hormone levels affect upper airway anatomy and function or the control of breathing leading to SDB remain limited.[113–115]

Gender differences in the prevalence of OSA may also be related to differences in body fat distribution. Men exhibit a more central fat distribution, including the neck, thereby increasing the risk for narrowing

and closure of the upper airway.[116–118] Among women, pregnancy poses an additional period of vulnerability for SDB, with important potential consequences for maternal and fetal well-being.[119,120] The prevalence of self-reported snoring increases with advancing pregnancy and has been estimated to be between 14% and 46%.[121,122] Further work is needed to define the incidence, prevalence, and impact of gestational sleep apnea.

Ethnicity

While the majority of population-based prevalence estimates for OSA are derived from Caucasian populations, several recent studies have sought to characterize the burden of OSA in several Asian countries, in South America (Brazil), and among African-Americans and Hispanics in the United States.[102–105,107] In Hong Kong, India, and Korea, the prevalence of OSA is similar to Caucasian population samples, despite the lower prevalence of obesity among Asians. In fact, after controlling the effects of age and obesity, OSA severity appears to be higher among Asians, perhaps due in part to craniofacial characteristics.[123–126]

Among middle-aged African-Americans, the prevalence of OSA is comparable to Caucasians.[109,127] A higher prevalence of OSA has been observed, however, among young African-Americans (<25 years of age) compared to either Caucasians or African-Americans in other age groups.[127,128] Among Hispanics in the United States, snoring is more common than among Caucasians.[129,130] Emerging data suggest that the prevalence of OSA may be higher among Hispanics compared to non-Hispanic whites.[131–133] Data on OSA prevalence in other ethnic groups and countries are relatively sparse at present.

■ RISK FACTORS FOR SLEEP APNEA

Risk factors for OSA are summarized in Table 99-1.

Obesity

After rising dramatically during the last decades of the 20th century, the rate at which obesity is increasing in the United States appears to be slowing or reaching a plateau.[134–137] Worldwide, the prevalence of obesity has nearly doubled since 1980.[138] The increase in obesity prevalence is important because numerous epidemiologic studies have shown that obesity is the strongest risk factor for OSA in adults, and that a dose–response relationship exists between excess body weight and sleep apnea prevalence, such that the prevalence of OSA is greatest among individuals in the highest BMI categories.[17,100–106] Although the majority of these investigations were cross-sectional, several longitudinal studies have demonstrated that weight gain accelerates disease progression. Interestingly, among the elderly, the influence of obesity is diminished compared to its effect in younger adults,[109] which may be due to accelerated mortality among obese individuals with OSA (i.e., survivorship bias) and the greater role of other age-related risk factors for OSA.

Individuals with OSA have been observed to have larger neck circumferences than those without.[41] Imaging studies have demonstrated that obese individuals with OSA have larger soft tissue structures compared to normal individuals, and BMI has been shown to correlate with the percentage of fat deposition within the tongue.[42,139] As noted earlier, the larger size of the soft tissue structures may promote pharyngeal collapse during sleep by increasing tissue pressure on the pharyngeal wall.[43,45,140] In addition to biomechanical effects associated with larger soft tissue structures, obesity is also likely to have important interactions with other risk factors, such as craniofacial characteristics.

Anatomical factors alone, however, do not appear to fully explain the relationship between obesity and the development of OSA. Recent experiments have demonstrated that mice deficient in leptin, a hormone produced by adipocyte tissue that plays a major role in regulating appetite and metabolism, have more collapsible airways independent of weight.[141] Furthermore, leptin replacement can mitigate upper airway obstruction through a combination of peripheral mechanical and central neuromuscular actions. Obese humans, however, are generally leptin resistant and have high circulating levels of leptin, rather than leptin deficiency.[142] Other pathways via which obesity may increase the propensity for OSA include effects on ventilatory control mechanisms; neural compensatory mechanisms that maintain airway patency; and changes in lung volumes. Nonanatomic phenotypic traits such as genioglossus muscle responsiveness, arousal threshold, respiratory control stability, and loop gain appear to be particularly important in determining whether individuals with less collapsible airways manifest OSA.[143]

TABLE 99-1 Risk Factors for Obstructive Sleep Apnea

Obesity (BMI > 30 kg/m^2)
Neck size (collar size >17 inches in males, >16 inches in females)
Gender (male/female 2–3:1)
Genetic factors/family history
Upper airway and craniofacial anatomy
Macroglossia
Lateral peritonsillar narrowing
Elongation/enlargement of the soft palate
Tonsillar hypertrophy
Nasal septal deviation
Retrognathia, micrognathia
Narrowing of the hard palate
Class III/IV modified Mallampati airway
Specific genetic disorders, e.g., Treacher Collins, Down syndrome, Apert syndrome, etc.
Endocrine disorders, i.e., hypothyroidism, polycystic ovarian syndrome, acromegaly
Alcohol, sedative, or hypnotic use

Genetic Factors

Evidence that genetic factors are involved in the pathogenesis of sleep apnea continues to accumulate. A number of studies initially demonstrated the tendency for OSA to aggregate in families.[144,145] More recently, studies utilizing evolving genetic epidemiology techniques have demonstrated increased risk for OSA, independent of obesity, among first-degree relatives in geographically diverse populations in Iceland, Israel, Scotland, and Cleveland (USA).[46,146–148] A recent review documented 50 associations between genetic polymorphisms and OSA that have been identified in over 31 published candidate gene studies (for details, see Varvarigou et al, SLEEP 2011).[149] The majority of these candidate gene studies had inadequate sample sizes. Among these, four of the polymorphisms were observed in at least three separate studies. However, only one gene variant (TNFA rs1800629) remained significantly associated with OSA using meta-analysis techniques.[149] A genome-wide association study in OSA has not yet been published. Ultimately, given the complexity of SDB, many different genes are likely to contribute.

Craniofacial Anatomy

A proportion of patients with OSA are not obese. In nonobese individuals, craniofacial features such as retroposed mandible, micrognathia, and narrowing of the hard palate are the primary risk factors for apnea.[46–48] Furthermore, heritability of craniofacial abnormalities (retroposed mandible, inferior displaced hyoid bone) and upper airway soft tissue structures (tongue volume, lateral pharyngeal walls, and total soft tissue) has been demonstrated in first-degree

relatives and siblings.[46,150,151] These factors may operate in concert or alone to increase the risk of apnea. Genetic disorders associated with craniofacial and/or upper airway soft tissue abnormalities, including Treacher Collins syndrome, Down syndrome, Apert syndrome, and Pierre Robin syndrome, also confer increased risk of SDB.[152]

Endocrine Abnormalities

Individuals with specific endocrine conditions are at risk for OSA. Hypothyroidism, especially when accompanied by myxedema, is associated with both obstructive and CSA due to alterations in muscle function and blunted ventilatory response.[153,154] The presence of a goiter may place the patient at risk for OSA[155]; and thyroid surgery (lobectomy or total thyroidectomy) can improve OSA symptoms including snoring and excessive somnolence.[156] Macroglossia associated with hypothyroidism also contributes to the development of OSA. OSA is common and often severe in patients with acromegaly, presumably related to both osseous and soft tissue changes narrowing the upper airway.[157]

Given the low prevalence of OSA among premenopausal women compared to postmenopausal women and men, the female reproductive hormones appear to have a protective effect on OSA risk. Interestingly, among women with polycystic ovarian syndrome, which is characterized by hyperandrogenism, obesity, and cardiometabolic dysfunction, OSA risk is markedly higher compared to weight-matched controls.[158,159] OSA risk among postmenopausal users of hormone replacement therapy is similar to that of premenopausal women and lower compared to nonhormone users.[17,112] However, due to increased risk of cardiovascular disease and breast cancer and equivocal data from small treatment trials, hormone replacement therapy is not recommended as a treatment for OSA.[160–164]

Other Considerations

Alcohol, which reduces upper airway tone, and sedatives or hypnotics, which reduce the arousal mechanism, can also worsen OSA.[165,166] Each potential risk factor should be considered in the patient evaluation, as it is important to address why an individual has developed sleep apnea.

CLINICAL PRESENTATION AND SCREENING FOR OSA

Elements in the history and physical examination, as well as screening tools useful in establishing a diagnosis of OSA, are discussed below.

■ CLINICAL PRESENTATION

History

The diagnosis of OSA is frequently suggested by the history. Patients with sleep apnea often complain of both daytime and nighttime symptoms (Table 99-2). Bed partners are crucial informants of nocturnal events, and when available, a detailed history from the bed partner is imperative in cases of suspected OSA. Snoring is the cardinal complaint reported by the bed partner. Typically, the snoring is loud, nightly, and has existed for many years. Snoring may be so disruptive that the bed partner can be driven to sleep in another room.[167] A bed partner may report a witnessed apnea that is followed by a loud snort or gasp at the end of the apneic episode. This can be extremely concerning to the partner and serve as the trigger for seeking medical attention.

TABLE 99-2 Clinical Presentation of Obstructive Sleep Apnea

Loud, habitual snoring
Witnessed apneas
Nocturnal awakening
Gasping or choking episodes during sleep
Nocturia
Nocturnal sweating
Unrefreshing sleep, morning headaches
Excessive daytime sleepiness
Automobile or work-related accidents
Irritability, memory loss, personality change
Decreased libido
Impotence

Individuals with OSA may also report snorting or gasping, choking, nocturnal diaphoresis, and restlessness related to airway obstruction.[168,169] A sensation of choking or dyspnea is reported in up to 30% of patients. Frequent nocturnal awakenings related to repetitive airway obstruction lead to sleep fragmentation. Nocturia is fairly common and has been attributed to ANP release in response to apnea-related right atrial stretch.[78] However, while a large community-based epidemiologic study recently found a dose–response relationship between the severity of sleep apnea and levels of brain natriuretic peptide (BNP), this relationship was not observed in a similar analysis performed in a subset of participants from the Sleep Heart Health Study.[170,171]

Repetitive apneic events are not conducive to restorative sleep. Some studies have shown that untreated OSA patients have decreased slow wave sleep (non-REM stage 3) and REM sleep and more sleep stage transitions.[172,173] Thus, individuals with OSA are frequently unrefreshed upon awakening in the morning. Morning headaches are a less common manifestation of sleep apnea. When reported, the possibility of hypercapnia due to OHS should be considered.[174]

Excessive daytime sleepiness is a chief clinical consequence among patients with OSA.[175] Less commonly, patients may report insomnia, with difficulties initiating and maintaining sleep.[176,177] Interestingly, although the proportion of individuals who endorse daytime sleepiness increases with OSA severity, disease severity has proven to correlate only modestly with the degree of excessive somnolence.[178,179] Typically, the excessive daytime sleepiness of individuals with OSA occurs in sedentary situations, for example, following meals, watching television, reading, and during conversation. Driving is particularly problematic in patients with sleep apnea.[180,181] Patients may report falling asleep at red lights or stop signs, drowsiness while driving, and in extreme cases, motor vehicle accidents.[182] Thus, it is imperative to inquire about drowsy driving, which is risky not only to the patient but also to others on the road. The Epworth Sleepiness Scale (Table 99-3), a questionnaire for assessing the degree of subjective sleepiness, is usually elevated in sleep apnea patients (scored 0–24, with >10 considered abnormal) and can be a useful tool for assessing sleepiness in clinical settings.[178] Nevertheless, it is important to appreciate that the presence of excessive daytime somnolence is neither a necessary nor a sufficient condition to make the diagnosis of OSA: Many individuals with an elevated AHI do not report daytime sleepiness and others report sleepiness in the absence of sleep apnea (often due to insufficient sleep).

OSA can also cause symptoms related to cognitive impairment.[183–186] Inattention and deficits in memory and concentration often affect the ability to function at work. Fear of falling asleep inappropriately may limit an individual's willingness to integrate socially.[187] Moreover, patients with sleep apnea and/or their spouses can report irritability, depressive symptoms, and personality change.[188,189] Sexual dysfunction, that is, either decreased libido or impotence, is another common complaint among men with OSA.[190]

Physical Examination

The examination of the patient with suspected OSAS should focus on careful inspection of the head and neck, determination of the presence of obesity (BMI > 30 kg/m^2), and measurement of BP. Neck circumference greater than 17 in (43.2 cm) in men or 16 in (40.6 cm) in women suggests an increased risk for OSA.[191] The evaluation should also include assessment for abnormalities of the shape and size of the

TABLE 99-3 Epworth Sleepiness Scale

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? (This refers to your usual life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you.) Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of Dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (i.e., a theater or a meeting)	_____
As a passenger in a car for an hour without break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopping for a few minutes in traffic	_____

Source: Reproduced with permission from Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep. 1991;14(6):540–545.

craniofacial structures (e.g., mandibular retrognathia, micrognathia, crossbite, narrowing of the hard palate, and dental malocclusion); evaluation for factors contributing to nasal obstruction including nasal asymmetry, polyps, septal deviation, and hypertrophy of the turbinates; and visualization of the pharynx to assess crowding and soft tissue dimensions (macroglossia, tonsillar hypertrophy, lateral peritonsillar wall narrowing, enlarged/elongated uvula, or a narrow, high-arched hard palate). The modified Mallampati classification is often used to describe the patency of the upper airway, with increased risk for sleep apnea observed among individuals with class III or IV airways.[192]

TABLE 99-4 Conditions in which Evaluation for Obstructive Sleep Apnea Should be Considered

Obesity
Systemic hypertension
Myocardial infarction
Cerebrovascular accident
Type 2 diabetes mellitus
Pulmonary hypertension
Polycystic ovarian syndrome
Atrial fibrillation
Driver involved in a sleep-related automobile crash
Preoperative anesthesia evaluation

■ SCREENING FOR SLEEP APNEA

Inexpensive tools have been developed to assess the likelihood of apnea. The ability of a number of standardized instruments, such as the Multivariable Apnea Prediction (MAP) Index and the Berlin questionnaire, to identify individuals at risk for sleep apnea have been evaluated.[168,193] The sensitivity and specificity of these questionnaires tend to vary depending on the population studied, the specific cutoffs chosen and the severity of OSA to be identified.[194] Recently, in the surgical preoperative setting, an 8-item questionnaire (STOP-BANG) has been shown to have good predictive value for identifying severe OSA.[195] Other clinical situations in which sleep apnea should be considered in evaluating patients are outlined in Table 99-4.

In the past, overnight pulse oximetry (Fig. 99-7) has been used to screen for OSA.[196,197] Typically, patients with OSA manifest a sawtooth pattern on nocturnal oximetry. However, overnight oximetry does not detect apneas or hypopneas or arousals in the absence of significant oxygen desaturation, rendering the sensitivity of the test suboptimal. Furthermore, abnormal ambulatory overnight oximetry results obtained by general internists based on their initial clinical suspicion for OSA frequently fail to lead to further sleep evaluation.[198]

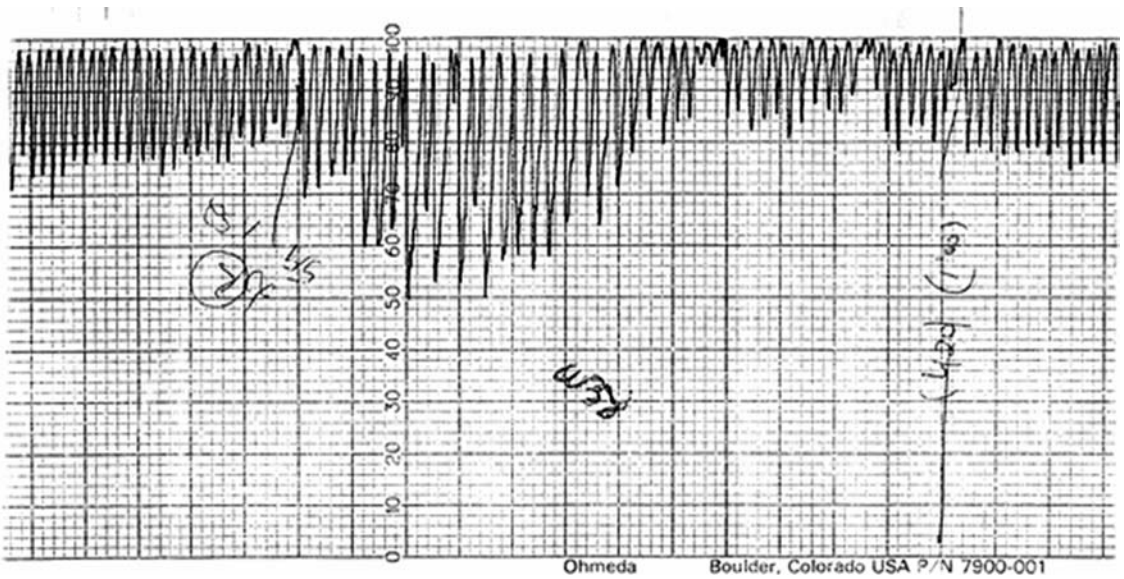

Figure 99-7 Nocturnal oximetry pattern in a patient with obstructive sleep apnea. This patient manifests recurrent oxyhemoglobin desaturations ("sawtooth pattern") that are most severe in REM sleep. Oximetry calibrated from 0% to 100%. Paper speed each small line 1 minute; each *dark black line* 5 minutes.

DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

While questionnaires and prediction models (i.e., Epworth Sleepiness Scale, MAP) can assist in OSA risk stratification, objective sleep testing is required to confirm the diagnosis and determine disease severity.[199] Polysomnography (PSG), the gold standard sleep study, records many parameters while the patient sleeps: Electroencephalogram (EEG) to indicate sleep state, electrooculogram (EOG) to monitor eye movements, electromyogram (EMG) to measure muscle activity, oronasal thermistor and nasal pressure sensors to indicate respiratory airflow, chest and waist bands to measure respiratory effort and arterial oxygen saturation (Fig. 99-8) (Video 99-1). These measurements are integrated to provide sleep staging and to indicate apneas, hypopneas, and arousals as depicted in Figures 99-9 and 99-10.

Stratifying disease severity through the AHI is important, given demonstrated linearity between AHI elevations and likelihood of adverse outcomes (e.g., hypertension, cardiovascular mortality, stroke).[200–202] However, despite the ubiquitous use of AHI in OSA diagnosis, the index has some limitations. First, AHI elevations often fail to correlate with sleep quality measures and clinical outcomes.[203] In addition, it does not capture other significant aspects of the disorder, such as the degree of oxyhemoglobin desaturation, nocturnal hypoxemia, hypoventilation (i.e., hypercapnia), or associated sleep disruption. Furthermore, variance in hypopnea definitions has led to substantial disparities in measured severity of SDB.[14,21] Despite these shortcomings, the AHI remains the primary determinant of OSA diagnosis and severity.[199]

While in-laboratory PSG remains the gold standard to establish AHI, limited patient access and relatively high cost have led to increasing use of out-of-center sleep testing—also known as portable or unattended sleep testing (Video 99-2). Typically performed in patients' homes, these sleep studies offer greater convenience at lower cost, and ideally replicate a usual night of sleep. The amount of data procured ranges widely, depending on the AASM-designated type of sleep testing performed (Table 99-5). An in-laboratory PSG as described earlier is designated a Type I study. Overall, Type II and III studies are differentiated by the number of variables measured. The former is a complete unattended home study and measures the same parameters as a Type I study (PSG). The latter typically includes measurement of airflow, respiratory effort, pulse, and sleep position. Since EEG is not obtained, sleep stage information and stage-related events (e.g., arousals) are undetectable. Type IV studies are limited to only one or two parameters, such as pulse rate and oximetry. The United States Centers for Medicare and Medicaid Services outlined guidelines for use of portable sleep testing for OSA diagnosis and treatment initiation in 2009.[18] Portable monitors' accuracy and precision relative to PSG have been easier to question than to demonstrate. Significant differences among monitor brands of the same type, inherent night-to-night variability of AHI which is also noted on in-laboratory PSG, and difficulties keeping pace with emerging technologies have all

Video 99-1 Description and demonstration of In-Laboratory Polysomnography (PSG). *Access at www.fishmansonline.com*

Video 99-2 Description and demonstration of Out-of-Center Sleep Testing (OCST). *Access at www.fishmansonline.com*

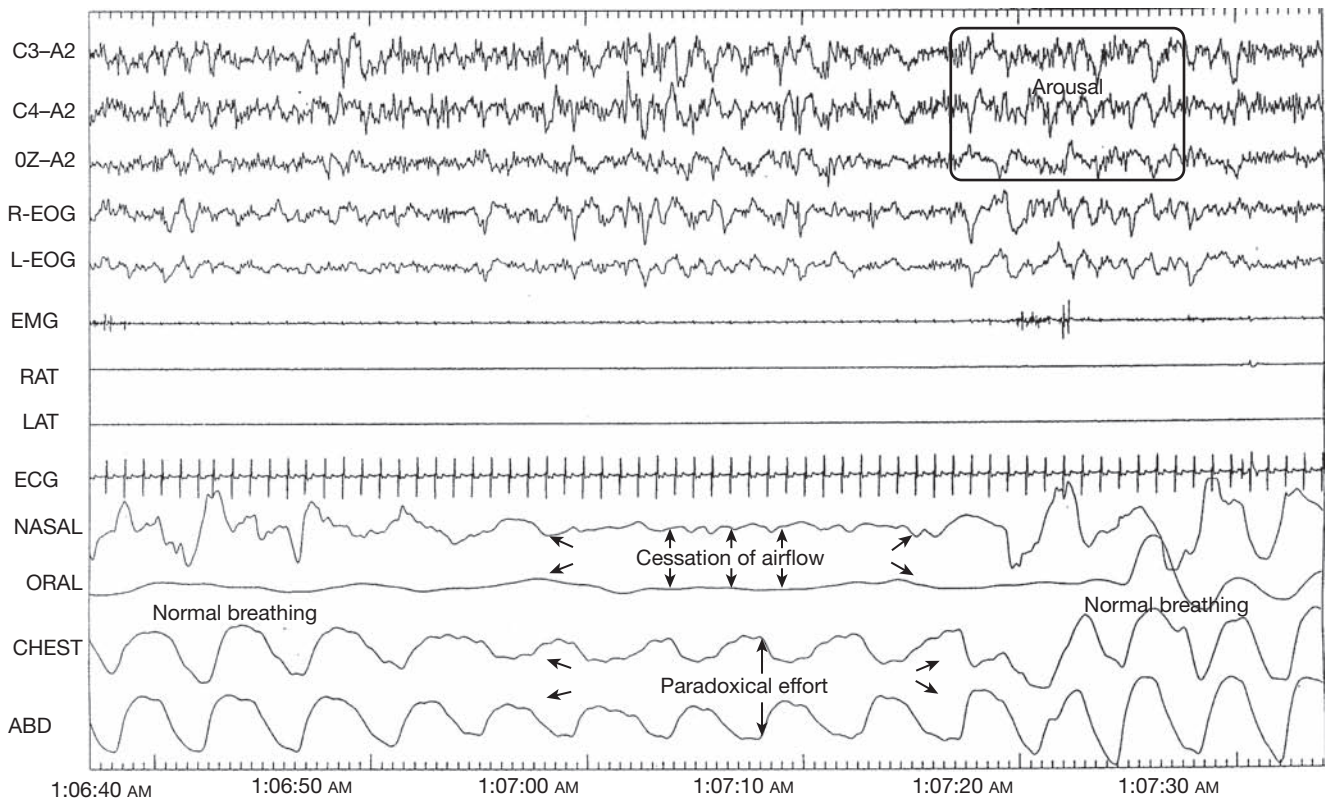

Figure 99-8 Example of an obstructive apnea in a patient with sleep apnea syndrome in stage 2 sleep. The polysomnography traces from the top down are as follows: Three EEG channels (C3–A2, C4–A2, OZ–A2); two EOG channels (R and L); submental electromyogram (EMG); right and left anterior tibialis EMG (RAT, LAT), electrocardiogram (ECG); nasal and oral airflow; chest and abdominal motion (chest & abd). During the apneic episodes, there is abnormal airflow (both oral and nasal) with paradoxical motion of the rib cage and abdomen. At the end of the apneic episode there is a burst of EMG activity at the arousal. Following the arousal, respiration resumes with synchronous movements of the rib cage and abdomen.

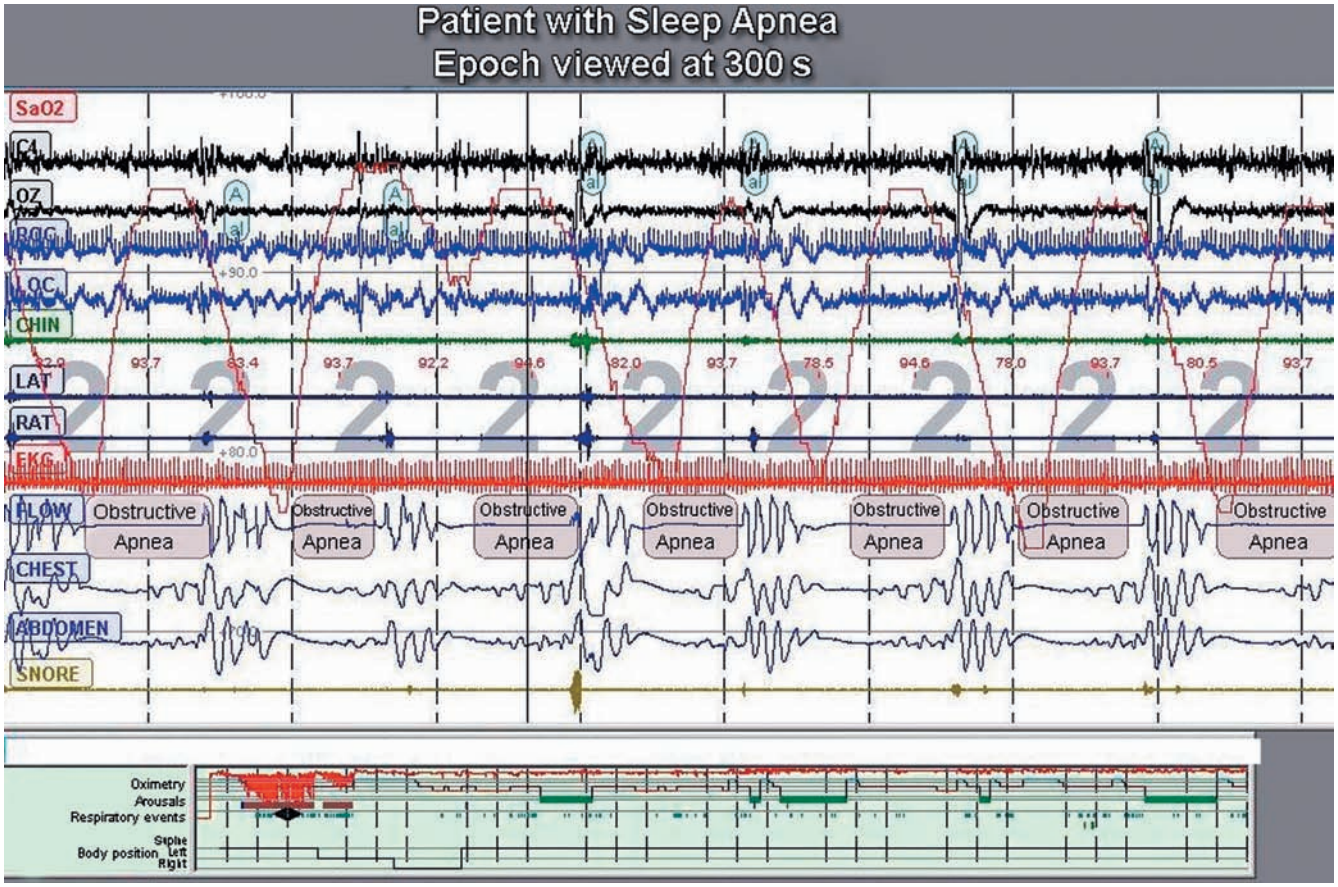

Figure 99-9 Example of a sleep study epoch from a split night sleep study in a patient with severe apnea. The epoch is viewed at 300 seconds. This patient has recurrent apneic events associated with oxyhemoglobin desaturations (recurrent dips in the *red line*). At the bottom of the figure is a hypnogram displaying the sleep data from the entire night. The *black diamond* in the hypnogram shows the time frame for the specific epoch displayed in the top portion of the figure. Later on in the night the patient is started on CPAP and the recurrent apneas and oxyhemoglobin desaturations are abolished (the recurrent desaturations: *red lines* noted in the hypnogram resolve). C4 and OZ are EEG leads; ROC and LOC are the right and left ocular leads; RAT and LAT are the right and left anterior tibialis electromyograms; Sa_{O_2} is the oximetry lead.

TABLE 99-5 Diagnostic Testing Options for Sleep-Disordered Breathing

	Type	Parameters Measured
	I	EEG, EOG, EMG, ECG, airflow, respiratory effort, O_2 saturation, usually video (all conducted in a sleep laboratory with a sleep professional present)
Out-of-center testing	II	Minimum of seven channels including EEG, EOG, chin EMG, ECG/HR, airflow, respiratory effort, and O_2 saturation
	III	Minimum of four channels including ECG/HR, O_2 saturation and at least two channels of respiratory movement or respiratory movement and airflow
	IV	Airflow and/or O_2 saturation[a]

[a]*Centers for Medicare and Medicaid Services require measuring a minimum of three channels, at least one of which is airflow.*

EEG, electroencephalogram; EOG, electrooculogram; EMG, electromyogram; ECG, electrocardiogram, HR, heart rate.

Source: Adapted with permission from Chesson AL, Berry RB, Pack A. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep. 2003;26(7):907–913.

limited research in the field. AHIs determined from Type III studies tend to underestimate PSG indices largely due to absence of EEG leads; PSG AHI is calculated as the number of respiratory events per hour of *sleep*, while Type III monitor AHI is based on hours of *use*. In addition, hypopneas can be underdiagnosed in the absence of EEG (arousals used to score hypopneas cannot be reliably determined). Therefore, portable monitors may have reduced sensitivity to detect OSA, especially in patients with mild disease.[204]

Once the diagnosis is made, treatment decisions among providers (CPAP or no CPAP) are more heterogeneous for patients with portable monitor-diagnosed mild-to-moderate OSA compared to patients diagnosed with OSA of the same severity through PSG.[205] Nevertheless, functional outcomes after treatment have not differed in patients with a high pretest probability for OSA diagnosed using portable monitors, compared to in-laboratory PSG.[206,207]

Guidelines for portable sleep testing were updated in 2007.[208] They recommend that out-of-center sleep testing with a portable monitor be performed only in patients: with high pretest probability of moderate-to-severe OSA without significant comorbidities including CHF, severe COPD, and neuromuscular disease, risk of CSA, or other sleep disorders such as parasomnias or narcolepsy; in whom in-laboratory PSG is not feasible due to immobility, safety, or critical illness; or who need noncontinuous positive airway pressure (non-CPAP) treatment (i.e., oral appliance, upper airway surgery, weight loss) response monitoring.

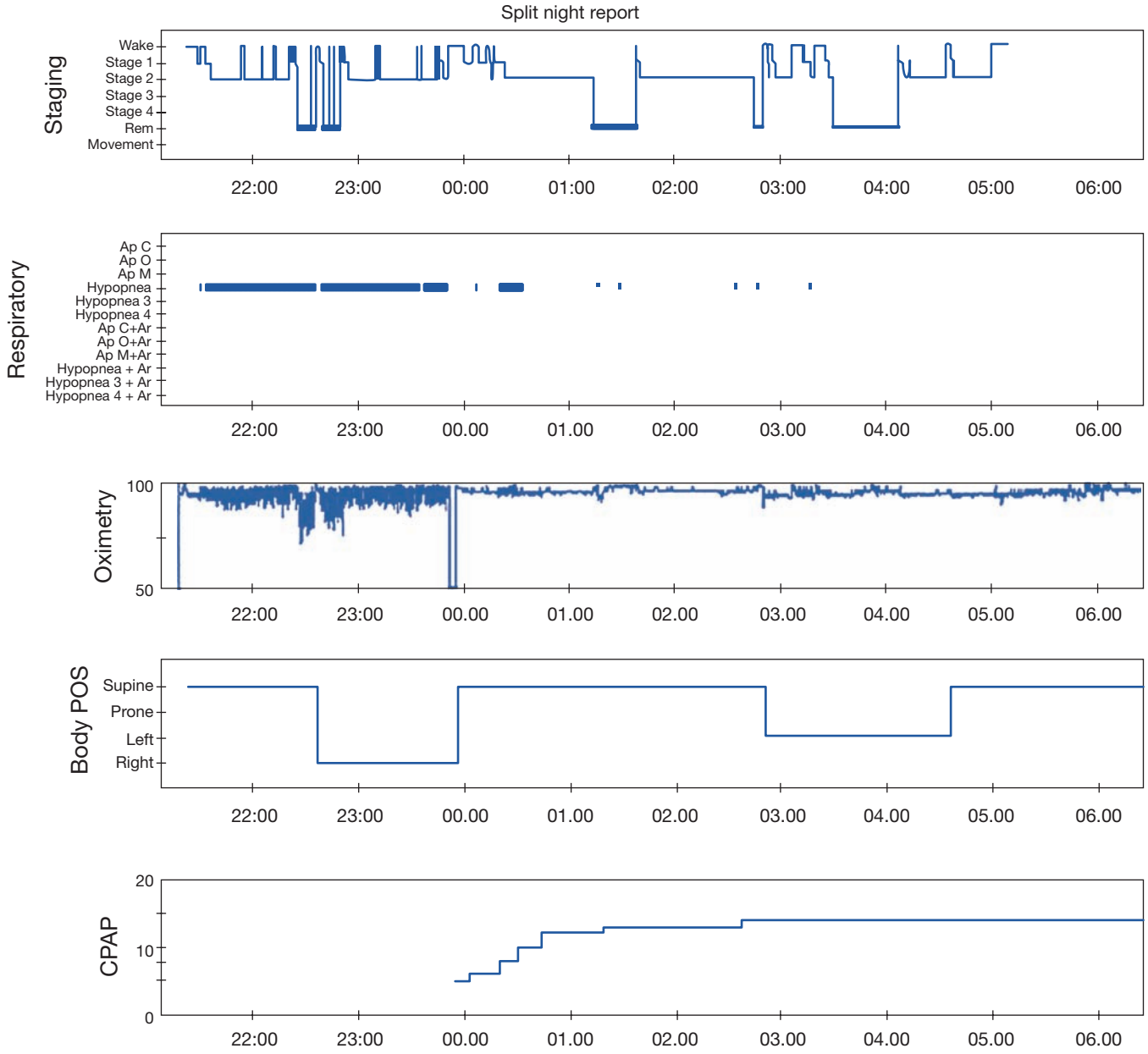

Figure 99-10 Split night hypnogram in a patient with obstructive sleep apnea. The patient has frequent hypopneas with recurrent oxyhemoglobin desaturations until he is started on CPAP at midnight. The CPAP was titrated to 14 cm H_2O, which abolished the hypopneas and oxyhemoglobin desaturations.

Despite these guidelines, portable sleep monitor utilization varies widely due to a number of factors, including local availability of in-laboratory PSG and the burgeoning number of insurers now mandating portable testing in lieu of PSG.[209] An algorithm for appropriate testing modalities for SDB can be seen in Figure 99-11.

In summary, in-laboratory PSG represents the gold standard for diagnosing sleep apnea. Technologic advancements in portable monitors and acceptance of out-of-center sleep testing by third party payers has led to increased access to diagnostic testing. However, excessive focus on the significance of absolute elevations in AHI can hamper the diagnosis and treatment of SDB. Patients may exhibit similar AHI, but experience dramatically different quality of sleep and outcomes. Important variables such as oxygen desaturation, number of arousals, and apnea/hypopnea length are not reflected by the AHI. Furthermore, it is not the AHI itself but the consequences (hypertension, myocardial infarction [MI], stroke, cardiac arrhythmias, excessive daytime sleepiness) of sleep apnea that are of paramount importance.

CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

The number of recognized associations with sleep apnea has increased considerably. Figure 99-12 is a simplified representation of three principal disturbances associated with apnea during sleep, the proposed downstream pathophysiologic mechanisms, and reported clinical consequences. This is not a complete depiction of all that is known, and many factors operate in a complex interplay that can jointly augment health risk. Nevertheless, OSA sequelae can be broadly categorized by their neurocognitive, cardiovascular, and metabolic effects. OSA should be seen as a systemic disorder with effects on multiple organ systems.

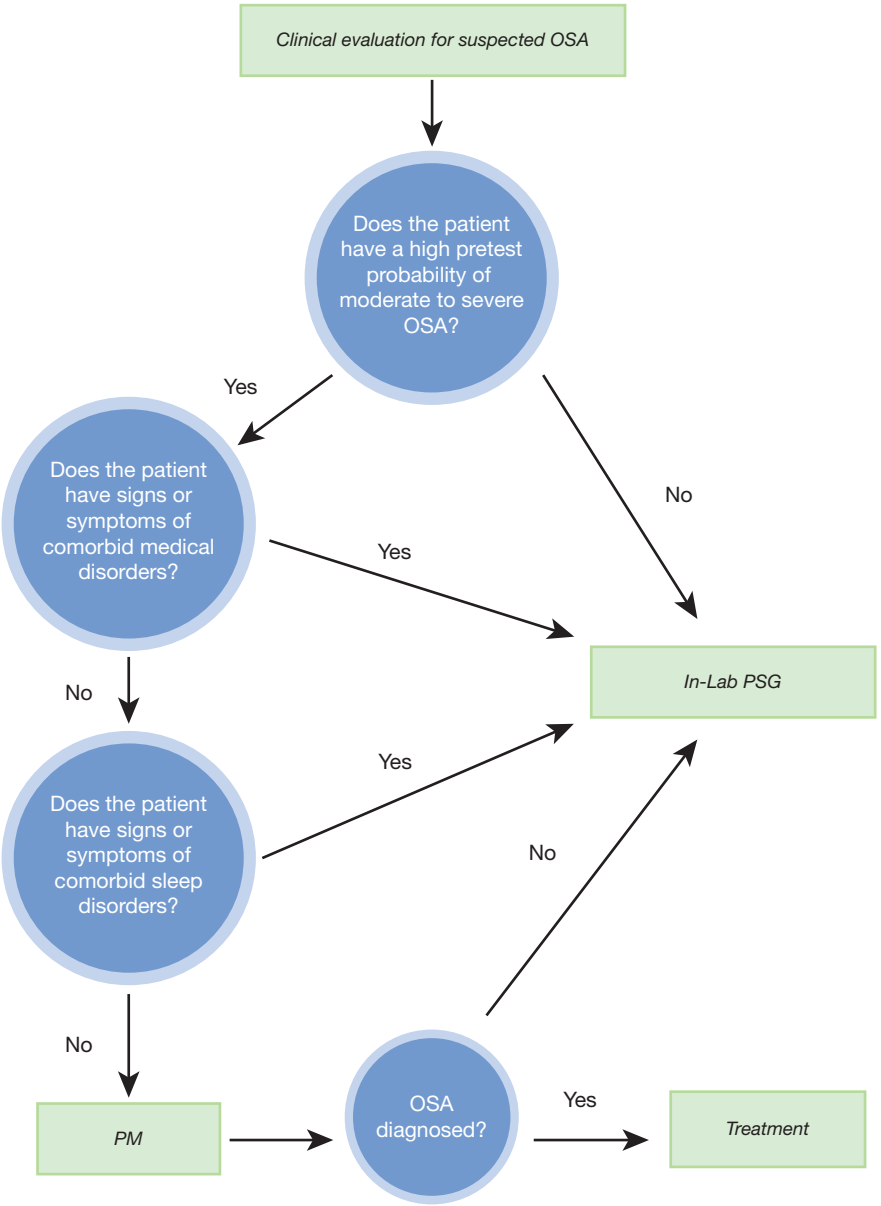

Figure 99-11 Out-of-center testing decision tree. OSA, Obstructive sleep apnea; PSG, polysomnography; PM, portable monitor (out-of-center sleep testing). *(Data from Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. J Clin Sleep Med. 2007;15:737–747.)*

■ NEUROCOGNITIVE CONSEQUENCES OF OSA

OSA-associated neurocognitive dysfunction may occur via a hypoxia/reperfusion injury mechanism whereby increased lipid peroxidation induces oxidative stress within neural tissue.[210,211] Neurovascular endothelial dysfunction has also been demonstrated in OSA patients, leading to an imbalance between vasodilation and vasoconstriction imbalance; lower nitric oxide levels in OSA patients appear to be a key mediator.[212] Dysregulated endothelium can also lead to hypercoagulability and atherosclerosis, potentially placing these patients at higher risk of vascular dementia.[213] Indeed, severe OSA has also been linked to increased risk of developing dementia in elderly patients.[214,215]

Excessive daytime sleepiness and sleep fragmentation associated with sleep apnea can lead to diminished cognitive function, affecting attention, memory, vigilance, and executive function.[216–219] While motor speed appears to be spared, fine motor coordination is impaired in OSA patients.[183,219,220] Despite these associations, recently published data from the Apnea Positive Pressure Long-term Efficacy Study (APPLES) failed to show correlation between AHI and neurocognitive performance after adjusting for ethnicity, educational level, and gender in a cross-sectional cohort.[221] Modest relationships between oxygen desaturation and neurocognitive performance were observed in this study and in the Sleep Heart Health Study.[222,223] Although the APPLES study's methodology has been questioned, these studies demonstrate inherent difficulties in establishing neurocognitive sequelae prevalence among OSA patients.[224]

OSA-related daytime sleepiness, attention lapses, and reduced vigilance are particularly salient when considering motor vehicle crashes. Several studies and a meta-analysis have shown these patients have at least a twofold increase in relative risk of automobile accidents; up to 20% of crashes are due to sleepiness, with OSA as the most common contributing medical cause.[180,225,226] When treated with CPAP, accident rates return to those of the general population.[227] This creates an intriguing medicolegal quandary for physicians treating nonadherent OSA patients who are known to drive drowsy. Practicing physicians should understand the relevant laws in their own state for guiding decisions regarding monitoring of drivers and reporting to appropriate agencies. The American Thoracic Society has published new guidelines regarding OSA and driving.[226] These support expedited diagnosis using PSG and/or out-of-center testing and rapid treatment

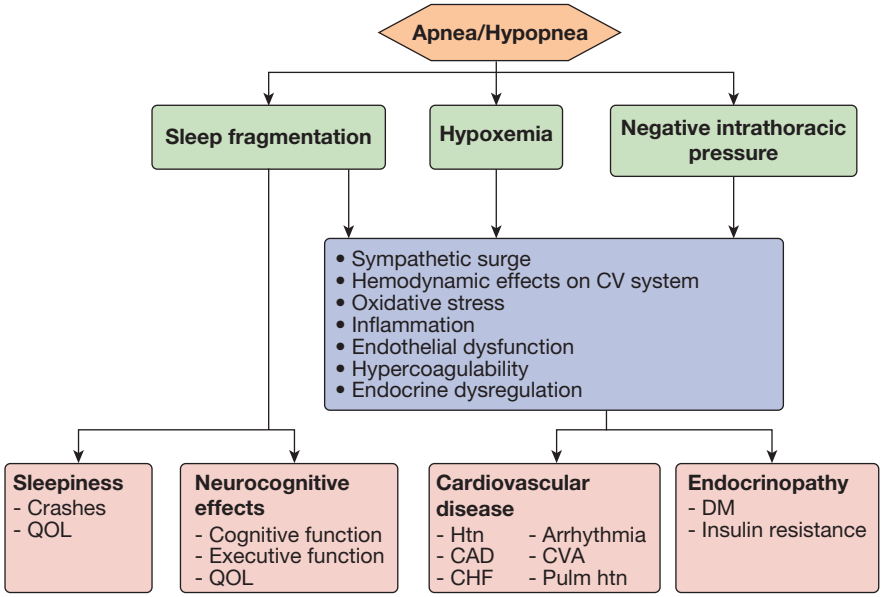

Figure 99-12 Flow chart of the proposed pathophysiologic mechanisms and consequences of obstructive sleep apnea. CV, cardiovascular; QOL, quality of life; Htn, hypertension; CHF, congestive heart failure; CVA, cerebrovascular accident; Pulm htn, pulmonary hypertension; DM, diabetes mellitus.

with PAP therapy. Clinicians should also consider implementation of a practice-based plan for patient education regarding drowsy driving risks and countermeasures.[226] Special consideration should be given to commercial drivers with OSA given the increased risk of fatality in large truck crashes.[228–231]

Untreated OSA has also been independently associated with depression.[188] SDB should be considered in anyone suffering from this mood disorder. Beyond depressive symptoms per se, OSA also impacts quality of life as measures by the Functional Outcomes of Sleepiness Questionnaire (FOSQ) and the Sleep Apnea Quality of Life Instrument (SAQLI).[232,233] CPAP therapy has been shown to improve these measures.[234]

■ CARDIOVASCULAR CONSEQUENCES OF OSA

A number of cardiovascular consequences of sleep apnea have been reported. While each is discussed individually, they share common and complex pathophysiology. Obstructive apneas result in recurrent hypoxia, repetitive arousals, and large swings in intrathoracic pressure.[235] These processes lead to an array of maladaptive mechanisms: Sympathetic surges, oxidative stress, inflammation, vascular endothelial dysfunction, metabolic dysregulation, hypercoagulability, and mechanical effects on the heart and vessels.[211,236–250] Each of these physiologic responses to apnea has been the focus of detailed research and requires further reading beyond the scope of this chapter. Overall, it is evident that sleep apnea induces physiologic processes conducive to the development of cardiovascular disease; results from a 10-year nonrandomized controlled observational study of patients with and without OSA showed untreated severe OSA patients had a 2.9-fold increased rate of fatal cardiovascular events after adjusting for confounding variables (Fig. 99-13).[200]

Hypertension

There are growing data that link OSA with systemic hypertension. About half of patients with known OSA have coexisting hypertension, and 30% to 40% of patients with hypertension have OSA.[251–253] The prevalence of OSA in patients with resistant hypertension is even higher; Logan et al.[254] studied subjects with hypertension who were all taking optimal doses of at least three antihypertensive agents and found an OSA (AHI ≥ 10 events/h) prevalence of 83% with a mean AHI of 25 events/h.

A canine model of sleep apnea demonstrated that recurrent occlusion of a tracheostomy each time when the animal fell asleep leads to the development of hypertension, both acutely during the sleeping period and subsequently chronically during the wake period even though the airway was no longer occluded.[255] In humans, OSA has ranked among the main causes of secondary hypertension, with several large cross-sectional studies demonstrating this relationship.[256] In the Sleep Heart Health Study, the odds ratio for the presence of hypertension in the highest category of AHI (≥30 events/h) was 1.37 compared with the lowest category AHI (<1.5 events/h).[257] The Wisconsin Sleep Cohort Study, a prospective population-based study, demonstrated an increased risk of incident hypertension in patients with even mild OSA (AHI = 5–15 events/h). Independent of BMI, the odds ratio was 2.0 for mild (AHI = 5–15 events/h) and 2.9 for moderate or severe sleep apnea (AHI ≥ 15 events/h) over a 4- to 8-year follow-up period.[258]

In several randomized trials, treatment of OSA with continuous positive airway pressure (CPAP) has been shown to reduce BP, particularly if OSA is severe.[259–261] In these studies, BP was significantly lowered not only in patients with resistant hypertension, but also in patients with relatively mild hypertension. One randomized controlled trial demonstrated that several weeks to months of CPAP resulted in a significant reduction in daytime BP up to 5.1 mm Hg compared to treatment with subtherapeutic CPAP.[262] A meta-analysis of 16 randomized trials comparing CPAP users to OSA-positive nonusers found a mean net decrease in systolic pressure of 2.46 mm Hg in the former group compared to the latter.[263] This effect may appear modest, but antihypertensive mediation literature shows a 41% decline in stroke and a 22% decline in coronary artery disease (CAD) from just a 5 mm Hg decline in diastolic BP; even a 2 mm Hg diastolic BP drop may decrease risk by 15% and 6%, respectively.[264,265]

CPAP appears to impact BP elevation most in patients with resistant hypertension. One study found a mean arterial pressure drop of 5.6 mm Hg in CPAP-adherent, resistant hypertension

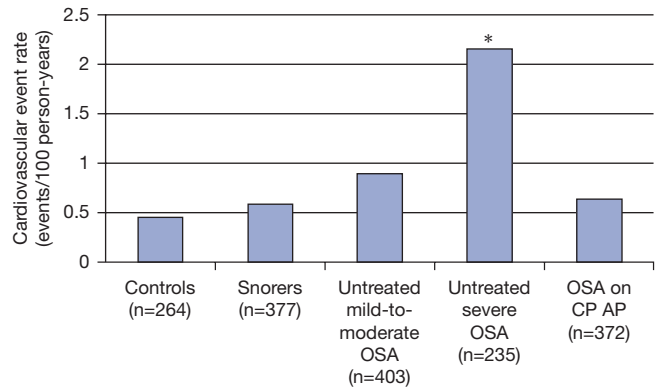

Figure 99-13 Cardiovascular event incidence during 10-year follow-up in healthy men (controls), snorers, and treated and untreated OSA patients. *p<0.0001 vs. healthy men. *(Data from Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. Lancet. 2005;365:1046–1053.)*

patients versus a drop of 0.8 mm Hg in CPAP-adherent patients with controlled hypertension. Nearly 71% of these resistant hypertensive patients had their antihypertension regimen simplified after CPAP.[266] Other work has shown up to a 7.3 mm Hg drop in nocturnal systolic pressure in similar resistant hypertension patients using CPAP, with resumption of normal nocturnal BP dipping observed in 27% of their 33-person cohort.[267] These beneficial effects of CPAP on hypertension, however, should not detract from emphasis on conventional pharmacologic methods of lowering BP.

Myocardial and Cerebrovascular Events

OSA has been associated with MI and stroke in cross-sectional studies, with a large longitudinal follow-up study confirming increased rates of cardiovascular events and cardiovascular mortality in patients with untreated severe OSA (Fig. 99-13).[200,268,269] One study showed increased cardiovascular event rates even in patients with moderate OSA.[270]

Specifically considering the stroke literature, OSA prevalence among these patients ranges from 50% to 70%.[271] Therefore, all stroke patients should be screened for OSA. Recent results from the Sleep Heart Health Study reveal that men with moderately severe OSA have an almost threefold increased risk of ischemic stroke compared to men without OSA. In fact, risk of stroke in men increased 6% with every unit increase in AHI between 5 and 25 events/h. The effect does not seem as strong in women, with risk of stroke only significantly increased at AHI >25 events/h.[202]

OSA likely leads to MI and cerebrovascular events in a variety of ways. Hypoxic events during sleep may trigger them; individuals with OSA who suffered an MI are more likely to have had their acute event between the hours of midnight and 6:00 AM than OSA-free individuals.[272] Another contributor could be OSA-related oxidative stress and proinflammatory state, leading to atherosclerosis. This has been demonstrated in a mouse model.[273] In addition, research reveals that snoring is associated with plaques in the carotid arteries but not the femoral arteries, even in patients with few apneas.[274] Since rat tail vibration has been previously shown to induce blood vessel endothelial damage, snoring-related vibration may have a similar effect on the carotid arteries, increasing risk of stroke.[275] Should this concept be demonstrated in humans, treating any patient who snores – regardless of OSA status – could become the norm.

Other Cardiovascular Consequences of Sleep Apnea

OSA adversely impacts a number of other cardiovascular outcomes including CAD and CHF. The Sleep Heart Health Study studied men and women ≥40 years old who were free of CAD and CHF at baseline.[276] After a median 8.7-year follow-up and adjusting for multiple risk factors, they found OSA to be a significant predictor of CAD in men (but not women) ≤70 years of age. Men aged 40 to 70 were 68% more likely to develop CAD if they had severe OSA than no OSA. Men were also 58% more likely to develop incident CHF when comparing these two groups. Explanations for the observed sex differences are unclear, but may include less exposure to OSA in women due to their tendency to develop the disorder after menopause, and possible sex differences in physiologic response to OSA.[276]

There are several pathophysiologic explanations for higher rates of CHF in OSA patients.[277] Generation of negative intrathoracic pressure resulting from obstructive apneic events can increase the difference between extracardiac and intracardiac forces, increasing LV transmural pressure and leading to LV hypertrophy.[278] Apneic events can also distend the right ventricle, as increased filling (due to negative intrathoracic pressure) and pulmonary vasoconstriction (due to hypoxia) occur simultaneously. Leftward shifting of the intraventricular septum can occur, resulting in reduced LV filling and stroke volume.[279] OSA-associated hypoxia has also been shown to decrease systolic contractility directly while impairing diastolic relaxation.[280,281]

Cardiac arrhythmias have also been associated with OSA. Relatively benign arrhythmias (i.e., bradycardia/tachycardia [bradycardia during the apnea and tachycardia during the arousal], atrial premature contractions, and ventricular ectopy) have long been observed, but recent attention has focused on atrial fibrillation.[235] Data from the Sleep Heart Health Study have shown that atrial fibrillation is more common in patients with severe OSA than in those without OSA.[282] Patients with untreated OSA whose atrial fibrillation converts to sinus rhythm after cardioversion are more likely than other patients to relapse into atrial fibrillation.[283] In addition, OSA is felt to be a risk factor for recurrent atrial fibrillation after radiofrequency catheter ablation.[284–286]

METABOLIC CONSEQUENCES OF OSA

OSA has been proposed as an additional component of the metabolic syndrome, a multisystem disorder currently characterized by obesity, impaired fasting glucose, hypertriglyceridemia, and reduced high-density lipoprotein (HDL). In fact, OSA has been independently associated with each component of this syndrome; individuals with OSA (AHI ≥ 15 events/h) have about 5.9 to 9 times the likelihood of having the metabolic syndrome compared to individuals without it.[287–289] Specifically considering glucose tolerance, up to 86% of type 2 diabetes patients have at least mild OSA (AHI ≥ 5 events/h).[290] A recent study that followed diabetes-free men for 10 years showed that development of the disease was independently associated with presence of OSA at baseline.[291]

There is evidence of OSA as an independent risk factor for insulin resistance (controlling for obesity) in general population and sleep center cohort studies.[244,292] Results from intervention studies has been mixed, with CPAP therapy leading to improved glycemic control in one study, but having no significant impact in another.[293,294]

Assessing causality between OSA and the metabolic syndrome has been difficult, and there is likely synergy between the two disorders. Mechanisms underlying this link are likely complex and remain to be fully elucidated. Chronic intermittent hypoxia exposure and sleep fragmentation are key mediators that may trigger a systemic inflammatory response.[295] At a minimum, patients with OSA should be assessed for the presence of relevant metabolic disturbances and the metabolic syndrome. Obese patients with type 2 diabetes mellitus should be screened for OSA.

MORTALITY

Several cohort studies, including the Wisconsin Sleep Cohort, Busselton Health Study, and the Sleep Heart Health Study demonstrate an association between untreated OSA and increased mortality.[201,296,297] This relationship is strongest when considering cardiovascular mortality and individuals with severe OSA.[297] A recent study of patients with ischemic heart disease showed a dose–response relationship between OSA severity and mortality, reinforcing the importance of OSA screening in this population.[298] In addition, survival curves for patients with severe OSA are identical whether or not they complain of sleepiness, supporting treatment for nonsomnolent patients with OSA.[201,299]

The association between OSA and mortality is more questionable for individuals over the age of 65 years.[300] Indeed, Lavie et al. showed a survival *advantage* in elderly patients (≥65 years) with RDIs (similar to AHI) between 20 and 40 events/h; OSA may be protective in this group due to ischemic preconditioning, leading to increased vascular endothelial growth factor (VEGF) and collateral coronary vessels.[301,302] Nevertheless, a more recent study showed that mortality rates are significantly increased among elderly people with severe OSA (AHI ≥ 30 events/h), and that those rates return to normal with CPAP treatment.[303] Therefore, there is no consensus that modifying OSA evaluation and treatment for elderly patients leads to any mortality benefit.

ECONOMIC CONSEQUENCES OF OSA

Because it is so common, sleep apnea poses a sizeable economic burden on society. OSA subjects have been demonstrated to utilize healthcare resources at approximately 1.5 to 2 times the rate of controls as far back as 10 years prior to diagnosis.[304–307] Estimates of the total economic cost that sleep apnea confers upon society are sparse. However, the financial burden of moderate-to-severe OSA in the United States is $65 to $165 billion/y, which is greater than asthma, stroke, heart failure, and hypertensive disease ($20–$80 billion).[308,309]

Limited numbers of sleep laboratories, sleep physicians, and sleep technologists coupled with cost of equipment and reimbursement issues have created a "bottleneck" effect in which global demand for sleep medicine services exceeds capacity. Nevertheless, economic analyses have shown that addressing diagnosis and treatment of moderate-to-severe sleep apnea, particularly with CPAP, is economically attractive and supports the value to society relative to other accepted treatment for other common conditions such as hypertension control, breast cancer screening, and comprehensive diabetes care.[310–314]

TREATMENT OF OSA

The decision to treat OSA should be based on its severity, related symptoms, and medical comorbidities. Treating moderate-to-severe disease (defined as AHI ≥15), particularly with PAP therapy, reduces cardiovascular risk, improves neurobehavioral performance, and enhances quality of life.[315,316] The AASM currently considers PAP as *standard* therapy for this group regardless of symptoms or comorbidities.[317] The same Practice Guidelines suggest PAP as an *option* for mild OSA, given conflicting data on its medical, behavioral, and functional sequelae.[318] In addition to OSA severity, disease-related sleepiness (or lack thereof) has been identified as a treatment determinant. Only sleepy patients with mild-to-moderate OSA show functional improvement using PAP, though the effect may be small.[319,320] Moreover, nonsleepy patients may not experience significant BP or cardiovascular event rate reduction on PAP, regardless of OSA severity.[321,322]

Third party payers have utilized these data in creating treatment coverage structures. The Centers for Medicare and Medicaid Services cover at least the initial 12 weeks of PAP therapy in patients whose AHI or RDI is ≥15 events/h. Patients with indices ≥5 events/h but ≤14 events/h must have documented excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, hypertension, ischemic heart disease, or history of stroke to qualify for PAP coverage.[323] Ultimately, provider expertise should dovetail with patient preference to guide treatment choice and modality.

Options for the treatment of OSA include PAP therapy, behavioral therapies, mandibular repositioning devices, surgical treatments, and adjunctive therapies.[199] First-line therapy for sleep apnea syndrome remains medical.

POSITIVE AIRWAY PRESSURE THERAPIES

Colin Sullivan et al.[10] first described the use of nasal CPAP to treat OSA in 1981 (see examples of subjects wearing CPAP in Fig. 99-14). Today, CPAP remains the mainstay of therapy for most patients with OSA. CPAP delivers a fixed pressure continuously throughout inspiration and expiration, providing a pneumatic splint for the airway that prevents airway collapse during sleep, when upper airway muscle dilator activity is reduced. CPAP therapy increases airway caliber in the retropalatal and retroglossal regions (Fig. 99-15); in particular, it increases the lateral dimensions of the airway and thins the lateral pharyngeal walls.[324]

CPAP usually reduces the number of apneic episodes during sleep to the normal range and has the advantage of being noninvasive. It clearly improves daytime sleepiness in patients with OSA in numerous studies including those in which patients were randomized to CPAP or sham (subtherapeutic) CPAP therapy, with greater improvements in daytime sleepiness among those with the highest AHIs.[320,325–330] A number of studies have demonstrated that CPAP use is associated with a modest reduction in BP among patients with hypertension and OSA.[259–261] In addition, drivers with OSA who are treated with CPAP have a reduced risk of motor vehicle crashes.[331]

CPAP therapy is indicated in all patients with moderate or severe sleep apnea (i.e., an AHI ≥15 events/h) and in those patients with mild OSA who have associated symptoms, as noted previously.[317] The optimal pressure can be determined during a titration polysomnogram or using out-of-laboratory treatment algorithms in conjunction with portable monitoring for OSA diagnosis.[332,333] Typically, pressures of 5 to 20 cm H_2O are needed to abolish apneic events, snoring, and oxyhemoglobin desaturation in all positions and during REM sleep.

CPAP can be delivered using a variety of interfaces (Fig. 99-14) including nasal masks, nasal inserts, or full-face masks (which cover the nose and mouth). It is important to ensure that the patient has a well-fitting interface with the CPAP machine absent of air leaks. Mouth leaks, which often result from mouth breathing while using a nasal mask, can render CPAP ineffective, since the positive pressure generated by the CPAP unit escapes. Use of heated humidity with CPAP therapy has been shown to successfully ameliorate some of the side effects listed in Table 99-6. Some but not all studies have demonstrated improvements in CPAP adherence with the use of heated humidification.[334–336]

Over the last two decades, CPAP machines and masks have become increasingly user friendly. CPAP masks have improved profoundly so the prospect of using CPAP has become much less daunting. Some institutions operate "mask clinics" concomitantly with sleep clinics so that patients with OSA can be fitted for a CPAP mask immediately after the sleep specialist consultation. CPAP units are also smaller, portable, and quieter, and they now nearly universally provide data

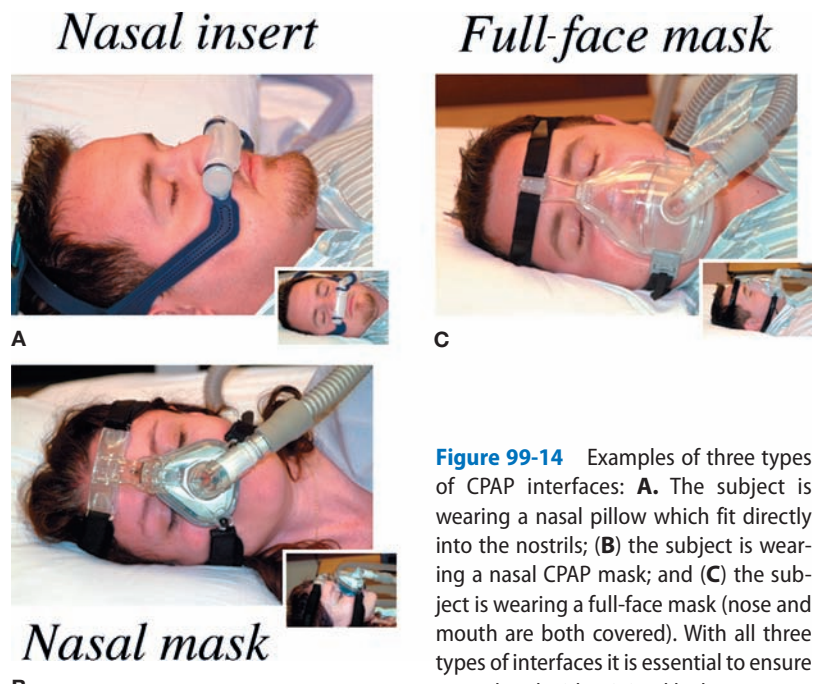

Figure 99-14 Examples of three types of CPAP interfaces: **A.** The subject is wearing a nasal pillow which fit directly into the nostrils; (**B**) the subject is wearing a nasal CPAP mask; and (**C**) the subject is wearing a full-face mask (nose and mouth are both covered). With all three types of interfaces it is essential to ensure a good seal with minimal leaks.

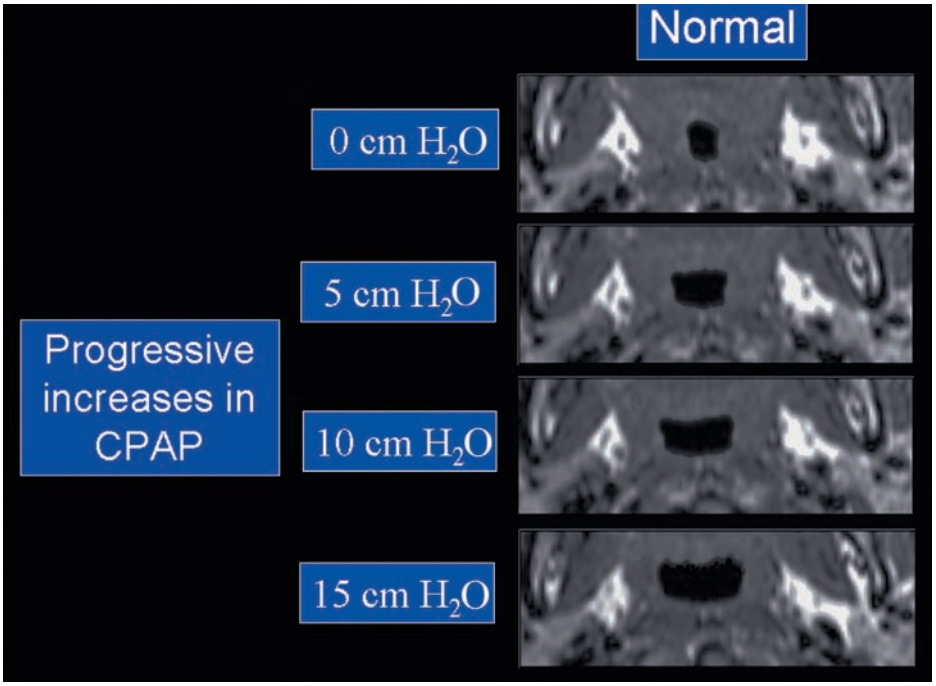

Figure 99-15 Axial retropalatal magnetic resonance imaging (MRI) in a normal individual with continuous positive airway pressure (CPAP) ranging from 0 to 15 cm H_2O. With increasing CPAP there is a progressive increase in the size of the upper airway, particularly in the lateral dimension (the anterior–posterior dimensions of the airway do not change significantly with CPAP). There is little movement of the parapharyngeal fat pads (*white structures* lateral to the airway) but progressive thinning of the lateral pharyngeal walls. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med. 1996;154(4 Pt 1):1106–1116.)*

on patient adherence patterns, mask leaks, and the effectiveness of the delivered CPAP pressure (i.e., residual SDB events with use of CPAP). These data provide critical clinical information and are also being used by insurers to make coverage decisions (i.e., poor adherence to CPAP can lead to denials of equipment coverage). For instance, for continuing coverage, Medicare currently requires documentation of use of PAP ≥4 hours per night on 70% of nights during a consecutive 30-day period during the first 3 months of initial usage.[337]

CPAP use is associated with few serious side effects.[338–341] Common side effects are listed in Table 99-6. Nasal irritation and rhinitis are treated with heated humidification and consideration of a nasal steroid spray. Claustrophobia may be relieved in some cases by changing the type of mask. Aerophagia can be ameliorated by altering body position or mask type. Serious adverse effects are uncommon but include very rare reports of severe epistaxis, meningitis, and pneumocephalus.[342–344]

Adherence to CPAP therapy is variable and ranges in most studies from 60% to 85%.[345] Although estimates suggest that patients use CPAP treatment, on average, for only 4 to 5 hours per night, a dose–response relationship has been observed between longer durations of nightly use and greater likelihood of achieving normal daytime alertness and functional status.[346,347] Patterns of CPAP usage have been reported to declare themselves within the first weeks of therapy.[348,349] Groups of "consistent users" (CPAP >90% of nights per week) and "intermittent users" (skipped CPAP use one or more nights per week) remain stable at 1 to 3 months. Thus, initiatives to enhance CPAP adherence are likely to be more effective during the period immediately following initiation of CPAP therapy. Intervention studies have tested educational, technologic, psychosocial, pharmacologic, and multidimensional strategies.[345] Practices that may promote CPAP adherence include involving the bed partner, promoting positive initial experiences with CPAP, and anticipatory support for side effects and troubleshooting. Applications that allow OSA patients to access and track their own CPAP adherence data on computers and smartphones are also becoming available (e.g., SleepMapper from Respironics). Reported predictors of adherence to CPAP therapy include race/ethnicity, socioeconomic status, AHI, and Epworth Sleepiness Score.[341,345,350–353]

In addition to fixed CPAP, PAP can be delivered via bilevel systems and automatically titrating systems. Bilevel systems deliver higher pressures during inspiration and lower pressures during expiration, and may be used when patients report difficulty with exhaling against PAP. However, bilevel systems are more expensive and evidence is lacking in terms of better adherence and treatment outcomes when compared with CPAP.[354,355] Limited evidence suggests that patients with coexisting lung disease or respiratory acidosis demonstrate improved gas exchange with the use of bilevel PAP compared with CPAP.

Autotitrating CPAP, or auto-CPAP, adjusts CPAP during use by detecting airway flow, snoring, apneas, and inspiratory flow limitation (Fig. 99-16). The specific algorithm used depends on the individual device. Each auto-CPAP unit uses a different algorithm for abolishing apneas. These units can be utilized in several ways: For chronic treatment of OSA (e.g., for patients with difficulty tolerating fixed CPAP and evidence of variable positive pressure needs due to REM-related or positional sleep apnea); or for use in the laboratory or at home to determine the optimal setting for conventional fixed CPAP after a trial period.[356] Patient adherence does not appear to be significantly improved with chronic use of auto-CPAP compared to fixed CPAP therapy.[357] The use of auto-CPAP for OSA titration is associated with substantially lower costs compared to in-laboratory CPAP titration, and a number of studies have shown that auto-CPAP can be successfully incorporated into algorithms for diagnosis and treatment of OSA. Furthermore, with the greater implementation of out-of-laboratory treatment algorithms in which

TABLE 99-6 Complications Associated with CPAP

Nocturnal arousals
Rhinitis, nasal irritation, and dryness
Aerophagia
Mask and mouth leaks (dry mouth in morning)
Facial rash or irritation
Difficulty with exhalation
Claustrophobia

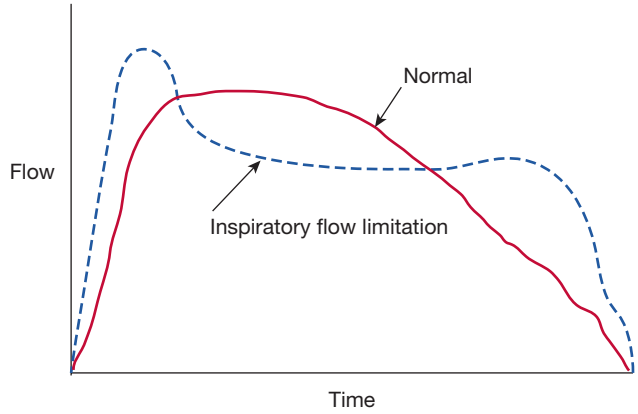

Figure 99-16 Schematic diagram showing the normal pattern of airflow during inspiration and that which occurs when there is inspiratory flow limitation. In the latter the flow quickly reaches a level that is maintained relatively constant throughout inspiration. This pattern of airflow can be detected by processors built into auto-CPAP units.

patients undergo portable monitoring for OSA diagnosis and are then started and maintained on auto-CPAP therapy, utilization of auto-CPAP has become increasingly common.[333,358,359] Studies to date have not demonstrated significant differences between the effects of auto-CPAP and fixed pressure CPAP on BP.[360–363]

GENERAL MEASURES

Patients with sleep apnea should avoid alcohol, sedative hypnotics, and opioids.[364] These commonly used substances are generally thought to reduce upper airway muscle tone and increase the severity of snoring and apneas.[365–370] They may also depress arousal mechanisms, thereby prolonging apneas and causing greater oxygen desaturations.[367,368,370]

Adherence to good sleep hygiene practices so as to maintain adequate sleep amounts also is important in sleep apnea patients. Sleep deprivation can reduce hypoxic and hypercapnic respiratory drive and prolong apnea duration.[371–374]

WEIGHT LOSS

Excess weight theoretically increases the propensity for upper airway collapse due to higher extraluminal pressures associated with excess soft tissue/fat and the encroachment of the tongue and soft palate.[42,375] Truncal obesity may also play a role by reducing chest compliance and functional residual capacity; this leads to increased oxygen demand.[376] Weight loss via dietary modification has been associated with significant reductions in SDB.[377,378] The extent of weight loss and degree of improvement are not always directly related, although it has been shown on average that a 1% change in weight is associated with a 3% change in AHI.[379] More specifically, weight loss in obese patients with type 2 diabetes mellitus is associated with a significant reduction in the AHI.[380] Interestingly, AHI changes associated with weight loss (or weight gain) are stronger in men than women.[381] Weight loss effects on OSA can be beneficial well into the weight maintenance phase.[382–384]

Over the past several years, there has been progressive interest in the use of bariatric surgery to treat extreme obesity. Interestingly, the effect of bariatric surgery as a treatment for OSA is unclear. In a recent randomized control trial, laparoscopic adjustable gastric bypass, although associated with major differences in weight loss over conventional therapy with dietary modification, was not associated with significantly greater reduction in SDB.[385] The Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention Study (MOBIL-study) demonstrated that patients undergoing Roux-en-Y gastric bypass had a greater reduction in the prevalence and severity of SDB compared to intensive lifestyle intervention. Of note, adjusting for degree of BMI change in this nonrandomized trial negated the effect on AHI.[386] These findings suggest that improvements in SDB are likely driven by weight loss more than the method of weight loss. Not surprisingly, short-term (30-day) complications were higher in individuals undergoing bariatric surgery (either Roux-en-Y or adjustable laparoscopic banding) who had a diagnosis of OSA as well as a history of thromboembolic disease and impaired functional status compared to those who were undergoing those surgeries without these comorbidities.[387] A recent meta-analysis demonstrated that bariatric surgery patients were unlikely to experience enough of a reduction in the AHI to obviate the need for continued treatment of OSA with CPAP despite significant surgical weight loss.[388] Given the available data, individuals who undergo bariatric surgery and experience a significant amount of weight loss should be formally reassessed for the presence of apnea after maximal weight loss has been achieved. The use of autoadjusting CPAP should be considered during the postoperative period to accommodate changes in SDB during this time. Of note, exercise appears to have a beneficial effect on the incidence of mild-to-moderate OSA; this effect appears to be related to changes in body habitus.[389] It should be noted that SDB can, in turn, promote obesity via several mechanisms including physical inactivity due to sleepiness, poor dietary habits related to abnormalities in leptin, a satiety hormone, insulin resistance, and systemic inflammation.[240,244,292,390–401] Given these findings, weight loss should be recommended in all overweight patients with OSA.

Of interest, a recent secondary analysis of data from the APPLES revealed that individuals using CPAP experienced modest weight gain compared to those using sham CPAP. Those who were the most adherent to CPAP (i.e., using CPAP for more than 4 hours for 70% of the nights) had the greatest amount of weight gain compared with nonadherent subjects.[402] While the reason for the weight gain is unclear, suggestions include a loss of increased sympathetic tone and/or a loss of a high energy cost of breathing overnight. Hypothetically, these lower energy states in conjunction with a continued level of caloric intake may lead to a net weight gain.

INTRAORAL DEVICES

Although CPAP represents the gold standard for treating OSA, adherence can be challenging for many patients.[339,341,348,403,404] Given this, increasing attention has focused on the intraoral devices, also known as oral appliances, as an alternative treatment to CPAP.

Oral devices aim to alter the position of the upper airway structures, thereby enlarging airway caliber or reducing airway collapsibility during sleep. The oral appliances have undergone considerable evolution in their design, comfort, and effect on airway structures in the past three decades. The tongue retaining device (TRD) developed in the 1980s by Samelson was designed to maintain the tongue in a forward position during sleep.[405] Two other types of devices are palatal lifting devices and mandibular advancing devices, the latter being the most studied (see example of mandibular advancing device, Fig. 99-17). The mandibular advancement devices produce downward rotation and advancement of the lower jaw during sleep.[406] These devices are fashioned out of a wide variety of materials and are available with various device features. Many mandibular advancement devices are custom-made for the client following a dental or maxillofacial surgery consultation. In choosing an oral device, attention to its adjustability (modifiability over time) and titratability (ability to alter jaw position by adjusting the appliance) are important. In addition, provisions for temporomandibular joint support, tooth coverage, and jaw mobility are important as side effects of the oral devices include excessive salivation, dry mouth, tooth or jaw discomfort, occlusive changes, and temporomandibular joint pain.[407]

A recent Cochrane review of the effect of oral appliances in the treatment of OSA in adults found that CPAP was more effective

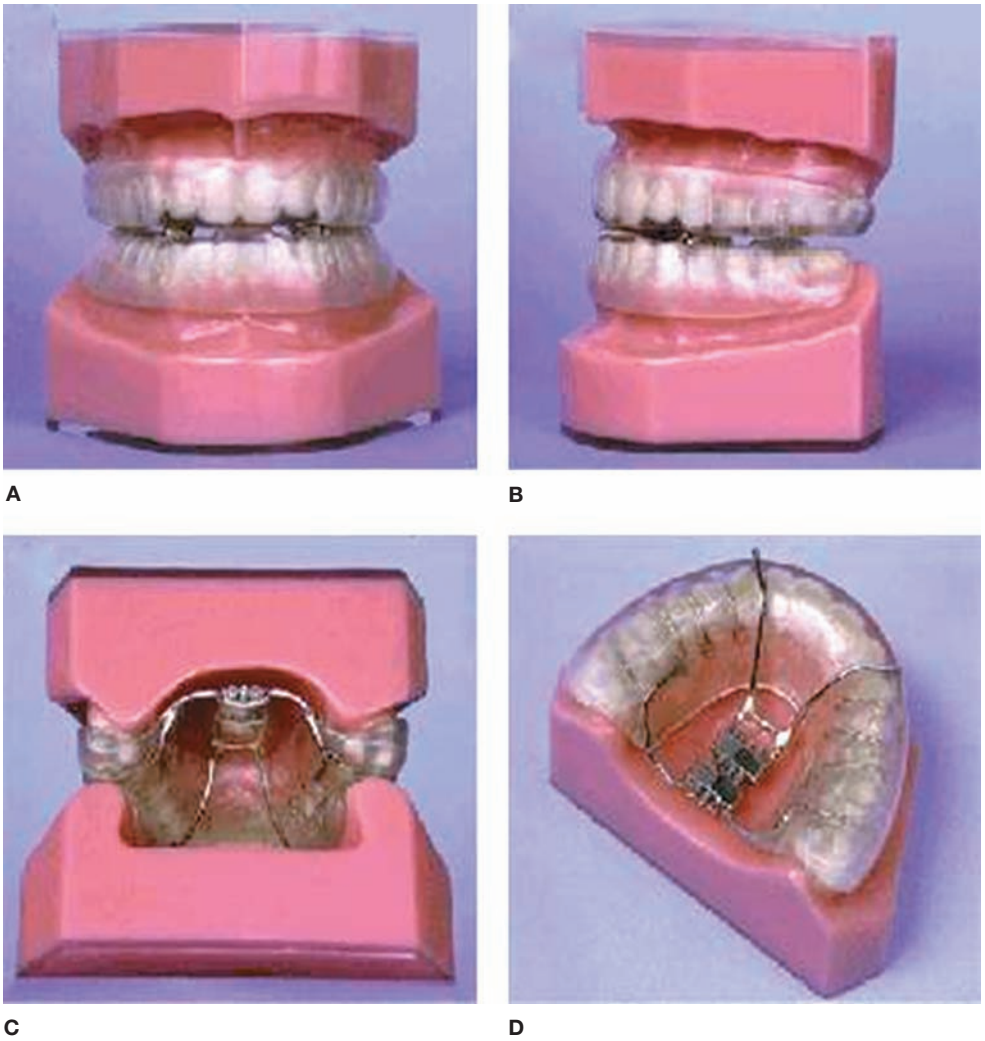

Figure 99-17 Anterior (**A**), lateral (**B**), posterior (**C**), and superior (**D**) views of an adjustable mandibular repositioning device (Klearway appliance, University of British Columbia, Vancouver, Canada). This device fits on the upper and lower teeth; it is worn during sleep and results in anterior motion of the mandible with consequent enlargement of the airway. The appliance is adjusted until the sleep-disordered breathing improves.

in reducing sleep disruption and AHI and was associated with an increase in the minimum oxygen saturation during sleep.[408] However, these benefits might be offset by increased patient adherence in those who used an oral appliance.[316] Based on randomized trials, the oral appliance is a reasonable alternative to CPAP, particularly for patients with mild-to-moderate OSA.[330,409–411]

At present, oral appliances/mandibular reposition devices are indicated for patients with primary snoring, or mild-to-moderate OSA who prefer them to CPAP or do not respond to, are not appropriate candidates for, or who fail treatment attempts with CPAP.[412] Patients with severe OSA should have a trial of CPAP first based on lower success rates with oral appliances.[317] Patients treated with an intraoral device are recommended to have follow-up PSG to verify efficacy, as some patients show no improvement. Importantly, the ability of oral appliances to reduce the severity of SDB to less than 10 events/h has been estimated to be approximately 50%.[407] Thus, there should be close monitoring by the treating physician to monitor for signs and symptoms of worsening OSA. In addition, regular follow-up with the dental specialist who fashioned the device is an important component of ongoing care in the patient who utilizes an oral appliance.

Recently, a novel treatment modality was introduced involving application of intraoral negative pressure via an oral interface connected to a vacuum pump in an attempt to stabilize upper airway tissue in patients with OSA.[413] A 4-week, multicenter, open-label, single-arm, randomized crossover trial was conducted on 63 subjects who used the oral pressure therapy (OPT device) and revealed improvement in the median AHI of 47% on the first treatment night and improvement in the 28-day median AHI of 43%. Thirty-one percent of the subjects saw a clinically significant response denoted as an AHI ≤10 events/h and ≤50% of control values. In addition, improvements in sleep quality (e.g., increased REM sleep and decreased arousals), sleepiness, and oxyhemoglobin desaturation index were noted. No significant adverse events were reported and nightly usage was high. Preliminary data suggest that OPT targets retropalatal collapse.[413] More studies including randomized controlled trials will be needed to determine the role OPT will play in the treatment of OSA.

■ POSITION THERAPY

It seems intuitive that body position during sleep would have an effect on respiratory mechanics.[414–416] Sleep in the supine position would seem to be more conducive to airway obstruction by virtue of gravity's effect on the tongue. Raising the head of bed angle to between 30 and 60 degrees has been studied; however, it is unclear if its effects reach beyond promoting airway stability to actually reducing AHI.[414,415,417] In 1984, Cartwright[418] defined positional-dependent sleep apnea as SDB in which the AHI while asleep in the supine position was at least twice as high as in the lateral position. The prevalence of position-dependent sleep apnea using this definition may be as high as 50% to 70% and may be of particular significance in patients with mild OSA.[419–423] For patients with position-dependent sleep apnea, symptoms may be alleviated by promoting sleep in the lateral decubitus position.[421,424–429] The lateral position is associated with increased maximum cross-sectional upper airway area and lower closing

pressure of the passive pharyngeal airway compared to the supine position.[416] Lateral positioning during sleep can be accomplished by sewing pockets for tennis balls to the back of sleep attire.[430] Devices to train people to sleep in the lateral position with the use of an alarm have been described.[424] Various other mechanisms have been suggested including a backpack and ball, a thoracic antisupine band, and a Zzoma positional sleeper.[421,431,432] Several studies have suggested that positional therapy is equivalent to CPAP in the treatment of positional-dependent sleep apnea.[421,432] However, a recent meta-analysis concluded that in terms of reducing the AHI and increasing oxyhemoglobin saturation, positional therapy was inferior to CPAP therapy.[433] In addition, long-term compliance for positional therapy appears to be mediocre at best; nonetheless it is better than adherence to CPAP therapy.[434] Interestingly, use of positional therapy in combination with other therapies for position-dependent OSA such as nasal expiratory PAP and mandibular repositioning devices may be associated with greater reductions in AHI.[435,436] Given all that is known about positional therapy, a relatively simple and inexpensive technique, consideration of its use to treat mild OSA with a positional component or as an additive measure to improve the efficacy of other treatment measures is warranted.

NASAL EXPIRATORY POSITIVE AIRWAY PRESSURE

Nasal expiratory positive airway pressure (EPAP) is delivered via a novel device with a one-way mechanical valve that provides high expiratory resistance in the setting of very low inspiratory resistance. The nasal EPAP device is applied to each nostril using adhesive and is designed for one-time use. Positive pressure resulting from the high expiratory resistance during exhalation stents open the upper airway, rendering it less likely to collapse on subsequent inhalation and increases end-expiratory lung volumes.[437,438] Nasal EPAP appears to reduce AHI and improve subjective sleepiness in patients with mild-to-moderate OSA.[439–441] Nasal EPAP has not yet been compared to CPAP directly in this population. A recent study assessing the utility of nasal EPAP as an alternative short-term therapy for patients with moderate-to-severe OSA already on therapeutic CPAP was unable to show a beneficial effect of nasal EPAP.[442] Given our current knowledge, nasal EPAP can be considered as an alternative therapy in individuals with mild-to-moderate SDB who are unable to tolerate CPAP therapy.

PHARYNGEAL MUSCLE STIMULATION

The genioglossus muscle is the largest airway dilator muscle. Electrical stimulation causes tongue protusion and stiffening of the anterior pharyngeal wall.[443] Attempts at muscle stimulation have enlarged upper airway diameter and reduced apneas and hypopneas during sleep in patients with SDB.[444–449] However, use of this technique has been limited by arousals associated with tongue protrusion.[449–451] An alternative strategy is to electrically stimulate the hypoglossal nerve to cause contraction of the genioglossus muscle, thereby increasing airway patency during sleep. The branches of the hypoglossal nerve that innervate the genioglossus consist mostly of efferent (motor) fibers that activate the genioglossus muscle with minimal sensory feedback.[443] Chronic stimulation of the hypoglossal nerve as a possible treatment for OSA was initially considered more than 20 years ago, but several technical limitations led to a 10-year hiatus before enthusiasm for hypoglossal nerve stimulation resurfaced.[443,452–455] Several recent open-label studies have demonstrated efficacy, including improved airflow, reduced AHI, and improved symptoms, as well as safety and compliance with the use of newer implantable hypoglossal nerve stimulators.[443,456–459] Preliminary data also suggest that there may be a beneficial residual effect after 1 year of therapy with hypoglossal nerve stimulation.[459] Although the recent data using new devices seem promising, more studies need to be performed with this modality.[460] A randomized clinical trial is presently underway that will hopefully provide additional information as to the role of hypoglossal nerve stimulation in patients with OSA.[461]

TABLE 99-7 Surgery for Obstructive Sleep Apnea

Nasal surgery (septoplasty, sinus surgery, and others)
Tonsillectomy ± adenoidectomy
Uvulopalatopharyngoplasty (UPPP)
Laser-assisted uvulopalatoplasty (LAUP)
Radiofrequency volumetric tissue reduction
Lingular tonsillectomy
Genioglossus and hyoid advancement (GAHM)
Sliding genioplasty
Maxillomandibular advancement osteotomy
Tracheostomy

SURGICAL TREATMENT OF OSA

A variety of surgical options are available to correct abnormalities in the upper airway that lead to obstruction during sleep (Table 99-7). However, the success of these treatments, aside from tracheostomy, is less well established and generally less effective than PAP therapy.[298] The leading objective for presurgical evaluation is to identify the primary site(s) of obstruction. The level of obstructive site influences the type of surgical procedure to be performed. Fiberoptic laryngoscopy, drug-induced sleep endoscopy, or imaging can be used to classify the obstruction of the airway at the nasal, oropharyngeal, and/or hypopharyngeal level.[462,463] Surgeries aimed at reducing obstruction at the nasal, palatal, and lingual levels are referred to as Phase 1 surgeries. They are typically performed first with subsequent use of a Phase 2 surgery such as maxillomandibular advancement (MMA) if needed.[298]

Tracheostomy is virtually 100% effective in eliminating obstructive apneas.[464] Despite its high efficacy, it requires changes in lifestyle and is associated with negative impact on patients' quality of life. Tracheostomy is generally reserved for patients with severe OSA who have failed medical or surgical therapy and who manifest severe complications such as malignant arrhythmias without treatment.[465] Tonsillectomy and adenoidectomy is the primary therapy for children with OSA; however, it is not usually successful in adults.[466]

There is a paucity of high-level published data on the efficacy of the various surgical options for SDB.[467,468] When change in the AHI is used as the primary measure of efficacy, MMA emerges as a procedure with substantial reduction in AHI (87%).[468] The studies consisted of nine case series, which included 234 subjects.[469–477] All but two of the studies had a residual postoperative AHI <10 events/h.[468] Nevertheless, because of low-quality studies, the reliable reduction in AHI seen with PAP therapy and lack of data regarding the effect of MMA on sleepiness and quality of life, MMA should be considered only in patients with severe OSA in whom PAP therapy and oral appliance are ineffective.[465] In addition, a recent systematic review noted that uvulopalatopharyngoplasty (UPPP) with or without tonsillectomy as a sole surgical procedure does not have a consistent effect on the AHI, and therefore cannot be recommended as a stand-alone treatment for OSA.[468] However, there is some evidence to suggest that use of a multilevel surgical approach involving UPPP and MMA may be beneficial to some patients; additional research, including clinical trials, is much needed.[465]

The role of other Phase 1 therapies remains unclear. Currently, laser-assisted uvulopalatoplasty (LAUP), a procedure involving removal of the uvula and a part of the soft palate with a carbon dioxide laser, is not recommended as a treatment option for OSA

by the AASM.[465] Radiofrequency volumetric tissue reduction (i.e., radiofrequency ablation [RFA]), a minimally invasive technique, has been employed to treat turbinate hypertrophy and reduce the size of the base of the tongue. Palatal implants are intended to stiffen the soft palate and protect against upper airway collapse. Only modest improvements in symptoms and AHI were noted in one randomized controlled trial.[478] In part because of their relatively low surgical risk, RFA and soft palatal implants can be considered in individuals with mild-to-moderate OSA who have found CPAP and oral appliance therapy ineffective and/or undesirable.[465]

Genioglossus advancement with hyoid myotomy involves movement of the tongue forward without moving the mandible, with the leading aim of achieving a larger-caliber airway. The success of such combinations has been variable ranging from 23% to 77%.[479–482] Because of inconsistent results in the setting of increased surgical risks, genioglossus advancement and related surgeries are presently not recommended therapies for SDB.

The value of performing UPPP in combination with robot-assisted lingual tonsillectomy was assessed in a recent prospective, nonrandomized trial compared with historical controls.[483] In this case series of candidates who were selected via drug-induced sleep endoscopy, 20 patients underwent transoral robot-assisted lingual tonsillectomy with UPPP as well as pre- and postoperative PSG. The mean AHI of 56 events/h decreased by 57% to a mean AHI of 24 ($p < 0.001$). The minimal arterial oxygen saturation and subjective measure of sleepiness improved as well. Minimal surgical complications were noted.

Other procedures listed in Table 99-7 are designed to increase airway caliber or to improve CPAP compliance. Treatment of nasal obstruction by surgical means has proved helpful in some patients, especially by allowing the patient to better tolerate CPAP. The most common nasal surgical procedure is septoplasty and turbinate reduction. These procedures can lead to subjective improvement in nasal patency and a reduction in nasal CPAP pressure requirement.

Surgery represents a viable therapeutic option for carefully selected OSA patients who cannot tolerate PAP therapy or an oral appliance. Meticulous preoperative assessment by examination, nasopharyngoscopy, and radiologic imaging can help to identify the likely area of upper airway obstruction. If a surgical procedure is performed, close follow-up in the immediate postoperative period to assess treatment response as well as long-term follow-up to monitor for recurrence of disease are warranted.[465]

OXYGEN THERAPY

Oxygen may have a limited role in the treatment of sleep apnea syndrome. Chronic hypoxemia is associated with reduced hypoxic and hypercapnic ventilatory drives.[484] This may worsen the severity and duration of SDB events. Although oxygen desaturation may be mitigated by the delivery of oxygen, there is some evidence that administration of supplemental oxygen may delay the arousal threshold and thereby prolong apneic events.[485] In this same study of three patients, use of supplemental oxygen was also associated with worsening respiratory acidosis.[485] However, subsequent studies with larger numbers of subjects demonstrated that the use of supplemental oxygen reduced the degree of oxyhemoglobin desaturation and improved or did not worsen apnea frequency or duration.[484,486–489] Among patients with a relatively unstable ventilatory control system, supplemental oxygen may stabilize ventilation, thus reducing AHI.[490,491] The role of supplemental oxygen alone in the treatment of OSA remains unclear; at a minimum it improves nocturnal oxygen saturation during use without significant adverse consequences.

MEDICATIONS

Several pharmacologic agents have been investigated as possible therapies for primary treatment of OSA. Unfortunately, none have demonstrated significant effectiveness for treatment of OSA.[492] Specifically, selective serotonergic reuptake inhibitors, protriptyline, methylxanthine derivatives (e.g., theophylline), and estrogen therapy are not recommended.[199,493–495] Of notable exception, patients with hypothyroidism and acromegaly should be treated with thyroid replacement and somatostatin analogs, respectively, as such treatment can improve AHI.[199,493]

While short-acting nasal decongestants have no effect on airway patency in sleep apnea, topical nasal corticosteroids may be useful as adjunctive therapy to treat concurrent rhinitis.[199,494,495] Such treatment may be particularly helpful if rhinitis is exacerbated by PAP therapy despite the use of heated humidification. In addition, there are conflicting data regarding the use of sedative-hypnotics at the time of CPAP initiation.[496–499]

Stimulants, such as modafinil, can also be utilized as adjunctive therapy for residual sleepiness in patients who remain symptomatic despite adequate treatment for SDB.[494] Doses ranging from 200 to 400 mg daily have been shown to be effective in improving excessive daytime sleepiness in several randomized trials.[500–504] Treatment with modafinil should only be undertaken after a careful search for alternative causes of residual sleepiness has been performed.[199]

CENTRAL SLEEP APNEA SYNDROMES

CSA, in which repetitive episodes of breathing cessation occur in the absence of respiratory effort, is characterized by an altered ventilatory motor output (Fig. 99-18). CSA is much less common than OSA, with one study estimating the prevalence in the general population to be <1%. Even in the clinical sleep laboratory setting, CSA is relatively uncommon.[101,505] However, small disruptions within a number of complex feedback loops in the ventilatory control system can lead to and then sustain CSA. CSA has been described as a physiologic process in normal individuals in response to an arousal (especially children and the elderly), as a manifestation of breathing instability in a number of medical conditions (e.g., Cheyne–Stokes respiration [CSR] in CHF and high altitude), or in association with neurologic diseases such as Shy–Drager syndrome, stroke, myasthenia gravis, neuromuscular disease, bulbar poliomyelitis, brainstem infarction, and encephalitis.[506–510] It is often divided into hypocapnic and hypercapnic types.

The following discussion will focus on hypocapnic CSA, as the hypercapnic CSA syndromes (e.g., OHS and congenital central hypoventilation syndrome) are discussed elsewhere (Chapter 100). Note is made, however, of the fact that a majority of patients with OHS have concomitant OSA.[28,29] Characteristic findings observed with OHS include awake resting hypoxemia, hypersomnolence, signs of cor pulmonale (right-sided heart failure and lower extremity edema), and nocturnal hypoventilation. In general, the hypocapnic CSA syndromes are associated with increased chemoresponsiveness of the ventilatory control system and are seen most commonly in individuals with heart failure and at altitude.

During wakefulness, there is an endogenous drive to breathe that arises from the brainstem reticular formation and has been termed the wakefulness stimulus. With the onset of sleep, withdrawal of the wakefulness stimulus occurs and the chemical drive to breathe predominates.[511] Minute ventilation falls by 10% to 15% and P_{CO_2} levels rise approximately 2 to 6 Torr.[512–514] Central apneas occur if the arterial P_{CO_2} falls below the "apneic threshold," or P_{CO_2} level necessary to maintain rhythmic breathing, resulting in reduced ventilatory motor output.[515] Causes of hypocapnia include sleep-state changes, hypoxia, and fluctuations in minute ventilation related to heart failure.

Other features of the ventilatory control system can promote and sustain recurring central apneas. If the magnitude of the increase in ventilation that occurs in response to changes in P_{CO_2} is larger than is needed to achieve eupnea, self-sustaining oscillations in ventilation in which P_{CO_2} is repeatedly driven to the apneic threshold can occur and manifest as periodic breathing.[516–518] Such oscillations in ventilation can also occur when there is a lag between changes in

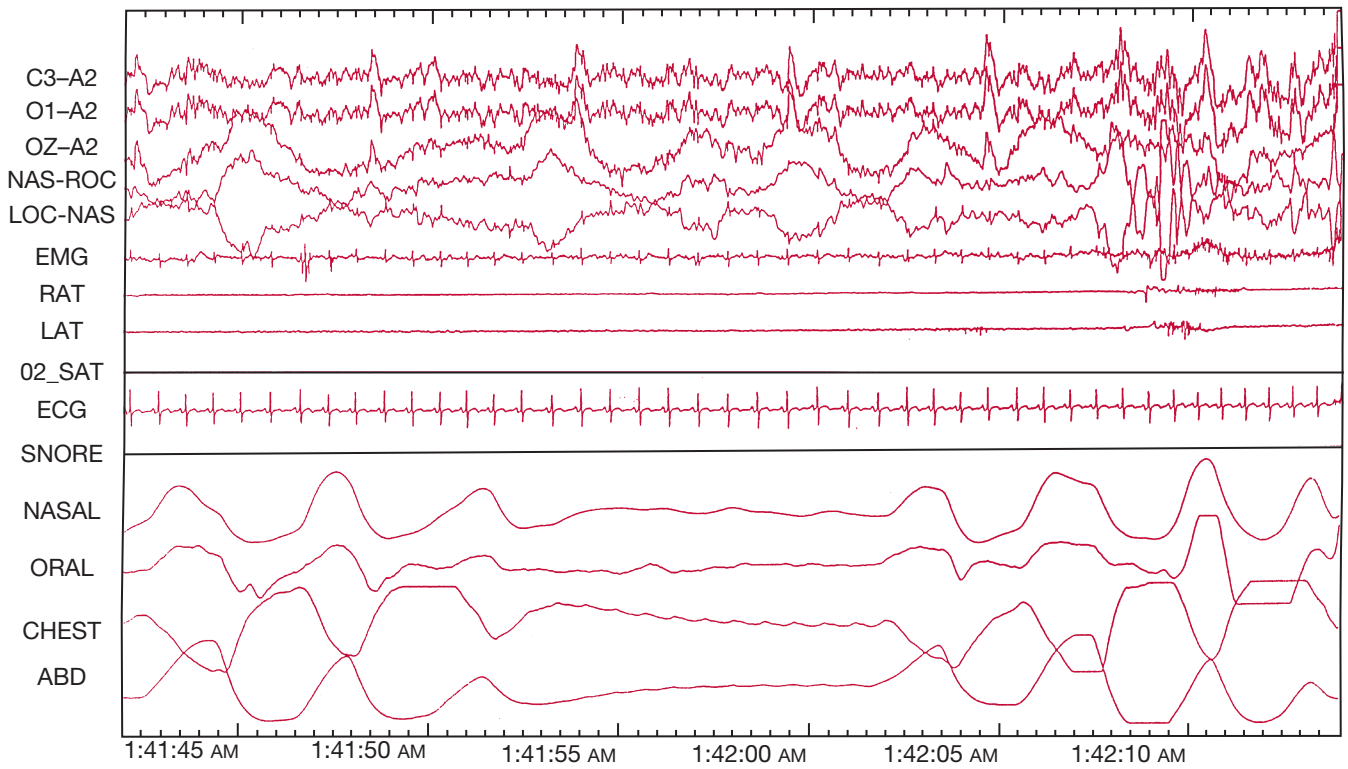

Figure 99-18 Example of central apneas. The polysomnography traces from the top down are as follows: Three EEG channels (C3, C4, O1); two EOG channels (ROC and LOC); submental electromyogram (EMG)); right and left anterior tibialis EMG (RAT and LAT), oxyhemoglobin saturation (SaO2); electrocardiogram (ECG); snoring channel (SNORE); nasal airflow (NASAL); oral thermistor (ORAL); and chest and abdominal motion (CHEST and ABD). During the apneic episodes, there is lack of airflow without rib cage or abdominal motion. At the end of each apneic episode there is a burst of EEG activity consistent with an arousal.

ventilation and detection of the ensuing effects on P_{CO_2} and P_{O_2} by the central and peripheral chemoreceptors, as occurs when arterial circulation time increases.[519] Recurrent arousals from sleep can also play an important role in initiating and maintaining central apneas as the state change from sleep to wakefulness re-engages the neurogenic drive to breathe.[515,520] This can provoke ventilatory overshoot as P_{CO_2} is driven to the lower P_{CO_2} set point of wakefulness, especially in the setting of continued sleep–wake instability.

■ HIGH ALTITUDE PERIODIC BREATHING

Periodic breathing with hypocapnic central apnea occurs in many healthy individuals at high altitude. At altitude, the peripheral chemoreceptors in the carotid body that sense hypoxia increase ventilatory drive.[521] As P_{CO_2} falls in response, the apneic threshold is reached, precipitating central apneas and creating a cycle of periodic breathing. Because the delay between changes in P_{O_2} and P_{CO_2} levels and detection by peripheral and central chemoreceptors is brief, the cycle time of periodic breathing at altitude tends to be short (12–34 seconds).[522] Poor sleep quality is a frequent complaint at altitude and is likely to be related to hypoxemia and periodic breathing with frequent arousals.[523,524] Although it seems intuitive that periodic breathing would resolve as individuals acclimate to altitude, observations of decreases, increases, and lack of change in periodic breathing have all been reported.[525–528] High altitude periodic breathing can be treated using acetazolamide, which increases the magnitude of the change in P_{CO_2} required to produce central apneas.[529] Use of supplemental oxygen improves high altitude periodic breathing and sleep quality and thus should also be considered.[530,531]

■ CHEYNE–STOKES RESPIRATION

CSR is most commonly seen in individuals with systolic heart failure and, especially when present during wakefulness, is a risk factor for higher mortality in this population.[532–534] CSR is also observed in individuals with encephalopathies, stroke, and other conditions.[535–537] Among individuals with systolic heart failure, male gender, age >65, atrial fibrillation, and hypocapnia all increase the risk for CSR.[538] Despite speculation that the prevalence of CSR has declined with the use of beta blockers for treatment of CHF in recent years, two recent studies indicate that the prevalence of SDB in general, and CSR in particular, remains high in this population.[539–541]

CSR is characterized by prolonged hyperpneas with a waxing and waning respiratory pattern and prolonged cycle duration (Fig. 99-19). Although CSR can occur during wakefulness, it is much more common during sleep, especially during non-REM sleep, when ventilation is predominantly under metabolic control and thus particularly sensitive to the apneic threshold and changes in P_{CO_2}.[542,543] Greater peripheral and central chemoresponsiveness among individuals with heart failure and CSR promotes hyperventilation and hypocapnia.[518,544] The timing and role of arousals associated with CSR, which tend to occur at the peak of ventilation, distinguish them from arousals associated with obstructive events, which occur at apnea termination. Thus, arousals during CSR provoke ventilatory overshoot and help to sustain oscillations in respiration, rather than fostering upper airway muscle activation and the resumption of airflow as occurs in obstructive apneas.[545] The cycle length in CSR generally ranges from 40 to 90 seconds, due at least in part to prolonged transit time between the lungs and chemoreceptors in the setting of reduced cardiac output and increased circulation time.[515]

The clinical presentation of patients with CSR is variable. Although some patients with heart failure and CSR complain of sleep fragmentation, daytime sleepiness, and poor nocturnal sleep, many do not.[546] The diagnosis of CSR is established by PSG demonstrating repetitive

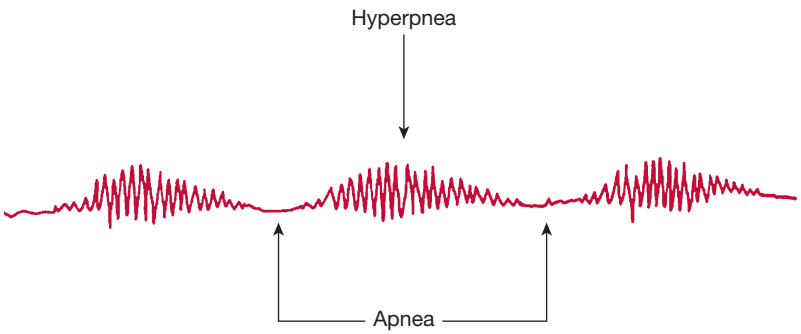

Figure 99-19 Example of Cheyne–Stokes respiration, a pattern of periodic breathing in which intervals of hyperpnea alternate with intervals of apnea. Respiration waxes and wanes in a crescendo–decrescendo pattern. Arousals during CSR tend to occur during the peak of ventilation, that is, during the hyperpneic phase rather than at the termination of the apnea. The duration of the hyperpneic phase of Cheyne–Stokes respiration correlates with the degree of circulatory delay.

apneas in the absence of thoracic–abdominal excursion.[14] Not infrequently, a combination of obstructive and mixed apneas may be seen; central SDB events must comprise >50% of total events to make the diagnosis of CSA.[545]

CSR can be treated in several ways. Aggressive pharmacologic management of heart failure, including beta blockade and angiotensin-converting enzyme inhibitors, improves heart failure status and may reduce CSA.[547,548] The use of supplemental oxygen can help to stabilize oscillations in ventilation but generally does not normalize the AHI.[549] Data demonstrating improved long-term outcomes with use of supplemental oxygen are lacking. However, given results from several recent trials demonstrating improvements in LV ejection fraction among patients with heart failure and CSA who received oxygen, supplemental oxygen has been recommended for this patient population.[550–553] Likewise, administering a small amount of CO_2 to patients with CSR dramatically reduces central apneas, though this intervention has not been implemented clinically.[554]

Although a number of initial reports demonstrated that CPAP therapy lowers AHI, reduces systolic BP, and improves LV systolic function, this treatment has proven disappointing.[533,555,556] A large, randomized trial in individuals with heart failure and CSA failed to demonstrate mortality benefit after use of CPAP for 2 years, despite improvements in the severity of CSA, nocturnal oxygenation, ejection fraction, and other physiologic measurements.[557] Furthermore, early survival was lower among those receiving CPAP, though ultimately, mortality was not significantly different between the groups. Post hoc analyses demonstrated that among those individuals receiving CPAP whose CSA was reduced to <15 events/h, survival was improved.[558] Whether these findings represent benefit from CPAP use in this subgroup, however, or whether the reduction in AHI to <15 events/h identified individuals with a better overall prognosis is unclear.

More recently, a mode of PAP therapy termed adaptive servo-ventilation has been developed for use in patients with CSR and other forms of hypocapnic CSA.[559] ASV provides bilevel PAP with a fixed expiratory pressure and variable inspiratory pressure that responds to changes in the ventilatory pattern while maintaining a target ventilation based on a continuous moving window of the patient's recent average ventilation. Thus, proportionate increases and decreases in inspiratory pressure occur that help to stabilize ventilation. To date, a number of randomized trials and other studies have shown that ASV improves CSA associated with CSR due to heart failure, as well as LV ejection fraction, sleep disruption, and exercise capacity.[560–565] While the ability of ASV to improve mortality in this population has not yet been demonstrated, a multinational, multicenter, randomized trial of ASV in patients with symptomatic chronic heart failure with depressed LV ejection fraction and predominant CSA is currently in progress and is expected to be completed in 2015.[566] After assessing the available current data, the AASM has recently recommended the use of CPAP, oxygen, or ASV for first-line treatment of CSR related to heart failure.[553]

IDIOPATHIC CENTRAL SLEEP APNEA

An idiopathic form of CSA similar to CSR has occasionally been described in individuals with normal cardiac function. Presenting symptoms can include snoring, witnessed apneas, insomnia, and excessive sleepiness.[567–569] These individuals have an increased ventilatory response to CO_2 during sleep and wakefulness. There is no standardized treatment. While CPAP therapy has proven effective for some patients, other reported treatments have included respiratory stimulants such as acetazolamide, and use of benzodiazepine and hypnotic medications to improve sleep continuity and reduce sleep state instability.[570–573]

COMPLEX SLEEP APNEA

In recent years, the term "complex sleep apnea" has been applied to the emergence of central apneas during CPAP titration for treatment of OSA.[505] The prevalence of complex sleep apnea has been estimated to be between 5% and 15% of patients undergoing CPAP titration.[505,574–577] Individuals who manifest CPAP-emergent central apneas have been described in some studies to be more likely to be male, to be more obese, and to be more likely to have a history of cardiac disease compared to individuals without complex sleep apnea.

The clinical relevance of complex sleep apnea has been vigorously debated, given evidence that CPAP-emergent central apneas may be associated primarily with CPAP initiation and are likely to resolve over time.[578,579] Two recent studies have observed that among patients who were initially diagnosed with complex sleep apnea, only 20% to 25% of patients who returned for PSG after using CPAP for 1 to 3 months had persistent central apneas >5/h.[574,577] Other explanations for CPAP-emergent central apneas include over- and undertitration of CPAP therapy, the presence of occult heart failure, and use of respiratory-depressant medications such as opioids and benzodiazepines.[579] Use of chronic opioid medications, which has become much more common in the past several decades, also places patients at risk for sustained complex apnea during sleep.[166,580,581]

The results of several studies that have examined the use of PAP devices for treatment of complex sleep apnea suggest that adaptive servo-ventilation appears to most effectively reduce AHI.[560,582,583] However, given evidence that complex apnea resolves in the majority of patients, it seems reasonable to initiate a trial of CPAP therapy and to reserve ASV for the relatively few individuals who exhibit persistent apnea.

EFFECT OF SLEEP IN PATIENTS WITH PULMONARY DISORDERS

Normal sleep is associated with hypoventilation and hypoxemia. This may occur via a variety of mechanisms. Sleep onset has been associated with a 2 to 6 mm Hg increase in the P_{CO_2} set point for ventilation.[584,585] Hypoxic ventilatory responses can be reduced such that normal subjects may experience a decrement in up to 10 mm Hg of Pa_{O_2} during sleep; this response may be more pronounced in men as compared to women.[113,586,587] Sleep is also associated with changes in respiratory mechanics, the most obvious of which is the posture adopted during sleep. The supine position, in particular, is associated with an additional

load on inspiratory muscles due to a shifting of abdominal contents.[588] REM sleep is associated with atonia, which spares the diaphragm, but not the accessory muscles of respiration and can reduce functional residual capacity.[589,590] Upper airway patency is dependent on muscle activity, which can be reduced or absent in NREM versus REM sleep and by an increase in supraglottic resistance.[591]

Pulmonary disorders can deteriorate during normal sleep and especially in patients with concomitant sleep apnea. SDB is associated with exaggeration of the normal circadian changes that elicit increases in bronchial hyperresponsiveness, vagal tone, and airway inflammation, which can contribute to asthma.[592–604] The sleep disruptions and hypoxia associated with SDB can also promote insulin resistance and glucose intolerance that, coupled with daytime sleepiness and reduction in general activity, ultimately lead to weight gain.[232,244,292,394,604–606] Obesity, in turn, is a significant risk factor for asthma.[604,607–613] Furthermore, snoring or apnea is likely to worsen gastroesophageal reflux, which in turn, is known to exacerbate asthma.[614–617] Studies addressing nocturnal asthma and OSA have shown symptom improvement with CPAP use.[618–621] Given these interactions, asthmatic patients who fail to improve with optimal medical therapy or who manifest primarily nocturnal asthma should be considered for evaluation of sleep apnea, particularly if snoring is present.[604,618]

In obstructive lung diseases such as COPD, those patients who exhibit daytime hypoxemia also experience profound declines in Pa_{O_2}, especially during REM sleep.[622,623] Hypoxemia is multifactorial, and mechanisms include exaggerated normal sleep respiratory physiology including reduced functional residual capacity (which decreases oxygen reserve), increased airway resistance, decreased respiratory muscle function, altered chemosensitivity, alveolar hypoventilation, and ventilation–perfusion mismatch.[624] The coexistence of COPD and OSA is relatively frequent because both disorders are so common.[625,626] In this so-called overlap syndrome, patients are at increased risk of pulmonary hypertension and respiratory failure related to progressive nocturnal hypoxemia.[569,626–628] Patients are also at increased risk of death and hospitalization due to COPD exacerbation.[629]

While oxygen is the therapy of choice in COPD patients with daytime hypoxia, its chronic use in patients with isolated nocturnal hypoxia without SDB is without clear benefit.[588,630–634] Oxygen therapy is unlikely to be sufficient in patients who suffer the overlap syndrome. In patients with COPD and chronic hypercapnia, the use of nocturnal noninvasive positive pressure ventilation is unlikely to be of added benefit.[635–637] Conversely, patients with the overlap syndrome (i.e., concomitant OSA and COPD) who are treated with CPAP have improved survival and decreased hospitalizations due to fewer COPD exacerbations.[629] Given this observation, screening of COPD patients for clinical features indicative of coexistent OSA is warranted.[629]

It is important to recognize that a wide variety of other lung diseases, including both parenchymal lung disease and neuromuscular disease, can place patients at risk for hypoxemia during sleep. This is related to operating on the steep segment of the sigmoid-shaped oxygen dissociation curve while awake.[634] As with patients with COPD, the benefit of oxygen therapy during sleep in patients with isolated nocturnal oxygen desaturations is not clearly established; clinical judgment should be exercised before instituting such therapy, and reassessment is advised.[634] Furthermore, it is likely that OSA is common in other types of lung diseases such as idiopathic pulmonary fibrosis and sickle cell disease.[638,639] The role of CPAP has yet to be defined in these non-COPD overlap syndromes.

CONCLUSION

The past several decades have brought major advances in our understanding of normal and disordered breathing during sleep. Results from a growing number of epidemiologic studies from around the world continue to illuminate our understanding of the consequences of OSA, which extend far beyond excessive daytime sleepiness to include cardiometabolic morbidity and increased mortality. Advances in basic and translational research are revealing that the effects of obesity on OSA risk may occur not only via anatomical and functional effects but also through effects on ventilation and neuromuscular control of the upper airway. Evidence that effective treatment of OSA can reduce morbidity and mortality continues to accumulate. And as we learn more about the genotypic and phenotypic expression of sleep apnea, we are likely to be able to better tailor individualized therapies for patients.

These advances are occurring against a backdrop of greater demand for sleep medicine services and reforms in health care that have generated growing pressure to streamline the diagnosis and management of sleep apnea patients with an emphasis on out-of-laboratory, portable testing. In response, new treatments for SDB continue to be developed and new technologies are helping providers to better understand and motivate adherence to PAP therapies. As algorithms for effective management within these systemic constraints are being developed and implemented, the intensifying focus within healthcare on patient-centered, outcomes-based care demands that these principles be incorporated into successful models of care for sleep disorders. Meeting this challenge is imperative to our ability to provide optimal patient care and to make continued advances in our understanding of SDB.

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CHAPTER 100

Sleep-Related Hypoventilation Syndromes

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Sleep can have profound changes on the respiratory system (see Chapter 96) especially in patients with underlying cardiopulmonary disorders. Sleep-related hypoventilation syndromes are characterized by an abnormal increase in partial pressure of carbon dioxide (Pa_{CO_2}) and a decrease in Pa_{O_2} during sleep. In an attempt to standardize definitions and facilitate research, in 1999 the American Academy of Sleep Medicine (AASM) included an arterial Pa_{CO_2} >45 Torr during wakefulness and a greater than 10 Torr increase in Pa_{CO_2} during sleep from awake supine values in the definition of sleep hypoventilation syndromes.[1] Similarly, the 2005 International Classification of Sleep Disorders (ICSD-2) incorporated a Pa_{CO_2} during sleep greater than 45 mm Hg or disproportionately increased relative to levels during wakefulness in the diagnostic criteria for sleep-related hypoxemia/hypoventilation syndromes.[2] More recently, the AASM Sleep Apnea Definitions Task Force revised scoring of sleep hypoventilation in 2012 to include a Pa_{CO_2} increase >55 mm Hg for ≥10 minutes or a ≥10 mm Hg increase in Pa_{CO_2} during sleep in comparison to awake supine values to a value exceeding 50 mm Hg for ≥10 minutes.[3] While based on data that normal individuals rarely have a Pa_{CO_2} >55 mm Hg during sleep, the precise Pa_{CO_2} level demarcating the transition from physiologic hypercapnia to pathologic hypoventilation remains unclear. The duration of 10 minutes decided by the AASM Task Force was arbitrary and based on consensus with a lack of normative data on the amount of total sleep time at different Pa_{CO_2} values in sleeping adults.[3] Sleep is associated with stage-specific changes in ventilation covered in Chapter 96. Loss of the wakefulness drive to breathe, altered ventilatory response to hypoxia and hypercapnia and increased upper airway resistance result in a decrease in ventilation in both nonrapid eye movement (NREM) and rapid eye movement (REM) sleep when compared to wakefulness. Consequently there is a small normal physiologic increase in the Pa_{CO_2} of 4 to 6 mm Hg during sleep.

The small decrease in ventilation and increase in Pa_{CO_2} during sleep is usually of little clinical consequence in normal individuals but in patients with respiratory muscle weakness, altered respiratory mechanics, impaired gas exchange and/or abnormal ventilatory drive, sleep is a vulnerable time. Nocturnal hypoventilation often precedes chronic daytime hypoventilation but the extent to which sleep can elicit and exacerbate chronic hypoventilation is often under appreciated. A high index of clinical suspicion for nocturnal hypoventilation is necessary especially with the availability of effective treatment, and this chapter aims to review some of the common causes of sleep-related hypoventilation.

CAUSES OF SLEEP-RELATED HYPOVENTILATION

The Pa_{CO_2} is determined by CO_2 production divided by alveolar ventilation (minute ventilation [the product of tidal volume and respiratory rate] minus dead space ventilation). Hypercapnia results when alveolar ventilation is insufficient to meet metabolic needs and is caused by a decrease in minute ventilation, an increase in dead space ventilation, or rarely an increase in CO_2 production. The causes of sleep-related hypoventilation can be thought of as disorders of ventilatory drive, that is, "won't breathe," or disorders of respiratory mechanics and/or impaired gas exchange, that is, "can't breathe" (Table 100-1).[4] The ICSD-2 classified sleep-related hypoventilation/hypoxemic syndromes by etiology (Table 100-2).

DISORDERS OF VENTILATORY CONTROL

Disorders of ventilatory drive can result in central apnea and nocturnal hypoventilation. These disorders can be primary including congenital central hypoventilation syndrome (CCHS) and primary idiopathic alveolar hypoventilation where no other cause for central hypoventilation is found. Alternatively these disorders can be acquired, usually following neurologic disorders that affect the brain stem and spinal cord and opiate medications.

CONGENITAL CENTRAL ALVEOLAR HYPOVENTILATION SYNDROME

Congenital central hypoventilation syndrome (CCHS) is a rare cause of central hypoventilation first described in 1970 by Mellins et al.[5] CCHS is characterized by hypoventilation and diffuse autonomic nervous system dysregulation (ANSD) but the exact underlying mechanism is uncertain. Studies suggest abnormal brainstem integration of chemoreceptor afferent pathways for ventilation with demonstration of some, albeit blunted, physiologic response of both central and peripheral chemoreceptors. Abnormal central integration of chemoreceptor afferents is also thought to be responsible for the autonomic nervous system dysfunction seen in CCHS. Traditionally considered a disorder of infants and children, with advancements in knowledge and treatment, patients are now surviving into adulthood. Nonetheless, this lifelong disorder is rare. The exact incidence is unknown but a French CCHS registry reported a prevalence in 2005 of 1 in 200,000 live births.[6]

CCHS is caused by a mutation in the paired-like homeobox 2B (PHOX2B) gene.[7,8] The PHOX2B gene on chromosome 4p12 encodes for a transcription factor that plays a role in the development of the autonomic nervous system and regulation of neural crest cell migration. Approximately 90% of PHOX2B mutations involve polyalanine repeat expansion mutations (PARMs) producing genotypes of 20/24 to 20/33 whereas the normal genotype is

TABLE 100-1 The 2005 International Classification of Sleep Disorders

ISCD-2 Classification of Sleep-related Hypoventilation/Hypoxemic Syndrome

- Sleep-related hypoventilation/hypoxemic syndromes
  - Sleep-related nonobstructive alveolar hypoventilation, idiopathic
  - Congenital central alveolar hypoventilation syndrome
- Sleep-related hypoventilation/hypoxemia due to medical condition
  - Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
  - Sleep-related hypoventilation/hypoxemia due to lower airway obstruction
  - Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders

Source: Data from Medicine AAoS. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL, 2005.

TABLE 100-2 Disorders Associated with Sleep-Related Hypoventilation

- Disorders of ventilatory control, i.e., "won't breathe": congenital central hypoventilation syndrome, brainstem injuries (stroke, infection, tumor), medications, idiopathic alveolar hypoventilation
- Disorders of respiratory mechanics and/or impaired gas exchange, i.e., "can't breathe"
  - Neuromuscular disorders: amyotrophic lateral sclerosis, spinal cord injury, poliomyelitis, Guillain–Barré syndrome, myasthenia gravis, spinal muscular atrophy, myotonic dystrophy, congenital myopathy, metabolic myopathies
  - Chest wall disorders: kyphoscoliosis, thorocoplasty, posttuberculosis, fibrothorax, obesity hypoventilation syndrome
  - Pulmonary disorders: chronic obstructive pulmonary disease, overlap syndrome, cystic fibrosis

20/20. The remaining 10% are heterozygous for nonpolyalanine repeat mutations (NPARMs) and include missense, nonsense, or frameshift mutations. Most expansion mutations occur de novo but in 5% to 10% parents will be mosaic for the PHOX2B mutation, with a 50% chance of transmitting the mutation in all.[9]

CCHS is a clinically heterogeneous disorder. Studies have demonstrated a relationship between the PHOX2B genotype and CCHS phenotype. A spectrum of hypoventilation severity is seen, and patients with 20/27 to 20/33 genotype and NPARMs typically require 24-hour continuous ventilatory support.[10] The syndrome is typically diagnosed in newborns with episodes of cyanosis and apnea usually requiring mechanical ventilation. After maturation of the respiratory and central nervous systems, many patients with CCHS eventually breathe adequately while awake but CCHS does not resolve spontaneously. Hypoventilation in CCHS is most apparent in NREM compared to REM sleep. This is unique from other sleep-related breathing disorders and is thought to be due to intrinsic REM-related ventilatory drive.[11] Moreover CCHS children lack perception of dyspnea, do not manifest signs of respiratory distress, and are unable to augment ventilation when faced with a respiratory challenge like an infection or anesthesia; therefore these patients can develop sudden decompensated respiratory failure. Unrecognized, children with CCHS present with complications of chronic hypoventilation including pulmonary hypertension, cor pulmonale, seizures, or developmental delay. While patients can present outside the newborn period with late-onset central hypoventilation syndrome (LO-CCHS), reported as late as 35 years,[12] careful review of the medical history typically reveals signs and symptoms compatible with hypoventilation and autonomic dysregulation from the newborn period. It is thought to reflect the variable penetrance of PHOX2B mutations and should be distinguished from rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD). ROHHAD is not associated with PHOX2B mutations. Patients typically present after the age of 2 years with hyperphagic obesity followed by hypothalamic and autonomic dysregulation, central hypoventilation and behavioral changes, and the syndrome is now considered distinct from CCHS.[9,13]

ANSD and disorders of neural crest origin are common in CCHS. Hirschsprung disease (a congenital malformation of the enteric nervous system) has been reported in approximately 16% of patients with CCHS and is often of greater severity than the general population with Hirschsprung disease while neural crest tumors including neuroblastoma or ganglioneuroma have been described in 5%.[14,15] Other symptoms of autonomic dysfunction described in CCHS patients include diminished pupillary light response, temperature instability, sporadic profuse sweating, altered perception of discomfort and anxiety, and esophageal dysmotility. Cardiac arrhythmias including decreased beat-to-beat heart rate variability, reduced respiratory sinus arrhythmia, and asystoles have been observed.[9,16] Children with CCHS may have a characteristic box-shaped facies that is shorter and flatter with a lip trait (Fig. 100-1).[17] PHOX2B genotype–CCHS phenotype relationships have also been demonstrated for the more severe CCHS phenotypes that manifest Hirschsprung disease, tumors of neural crest origin, cardiac asystole, ANSD, and facial dysmorphology.[9,10] For example, Hirschsprung disease has been reported in 87% to 100% of NPARMs compared to 13% to 30% of PARMs, while neural crest tumors have been described in 50% of NPARMs compared to 1% with PARMs.[9]

Diagnosis of CCHS relies on genetic testing after excluding other causes of central hypoventilation including pulmonary, neurologic, and metabolic etiologies. Genetic testing with PHOX2B Screening Test will identify mutations in 95% of cases. If the PHOX2B Screening Test is negative but there remains a high clinical suspicion the PHOX2B Sequencing Test can be performed to detect NPARM mutations. A sleep study with continuous monitoring of end-tidal CO_2 or transcutaneous P_{CO_2} is recommended to assess ventilatory requirements in all stages of sleep. Further diagnostic studies are guided by the clinical evaluation and include but are not limited to screening for other autonomic dysfunction including Hirschsprung with a barium enema or manometry, cardiac arrhythmias with 72-hour Holter monitoring, neural crest tumors with serial chest and abdominal imaging, pupillary function with a comprehensive ophthalmologic examination and neurocognitive testing.

Treatment for CCHS is directed at ensuring adequate ventilation both during sleep and wakefulness ideally with an experienced multidisciplinary team. Chronic ventilatory support is required and in 6% to 33% of patients ventilatory support during both wakefulness and sleep is needed.[14] Respiratory stimulants have not been shown to improve ventilatory drive in CCHS. Ventilatory support can be provided by various modalities including positive pressure ventilation via tracheostomy, bilevel positive airway pressure (BPAP) via nasal or full face mask, negative pressure ventilators, and diaphragmatic pacing. The mode of ventilatory support should be guided by the needs of the patient. In infants and younger children positive pressure ventilation via tracheostomy is preferred. When only nocturnal ventilatory support is required, BPAP via a mask interface is commonly used but in patients unable to generate adequate spontaneous breaths to trigger the ventilator, only the timed or spontaneous timed (setting a backup rate) modes guarantee breath delivery. Regardless of the mode of ventilatory support, close monitoring is necessary usually with continuous pulse oximeters and end-tidal CO_2 monitors. Apnea/bradycardia monitors will not detect hypoventilation or sinus pauses in CCHS and have no role. With early diagnosis, close monitoring and support, children with CCHS can be expected to function well in society and have a good quality of life but mortality rates of 8% to 38% have been reported.[14] Genetic counseling is essential for individuals diagnosed with CCHS.

OBESITY HYPOVENTILATION SYNDROME

The obesity hypoventilation syndrome (OHS) is defined by the presence of obesity (body mass index, BMI $\geq$30 kg/m^2), chronic alveolar hypoventilation with daytime hypercapnia (awake Pa_{CO_2} $\geq$45 mm Hg), and sleep-related breathing disorder in the absence of any other causes of hypoventilation. While first described in ancient Greek literature it was not until the 1950s following case descriptions by Auchincloss and later Burwell that the syndrome gained attention and the term, the "Pickwickian syndrome," from the character of Joe in The Posthumous Papers of the Pickwick Club by Charles Dickens emerged.[18–20]

The risk of OHS increases as BMI increases and in the United States it is now estimated that more than one-third of adults are

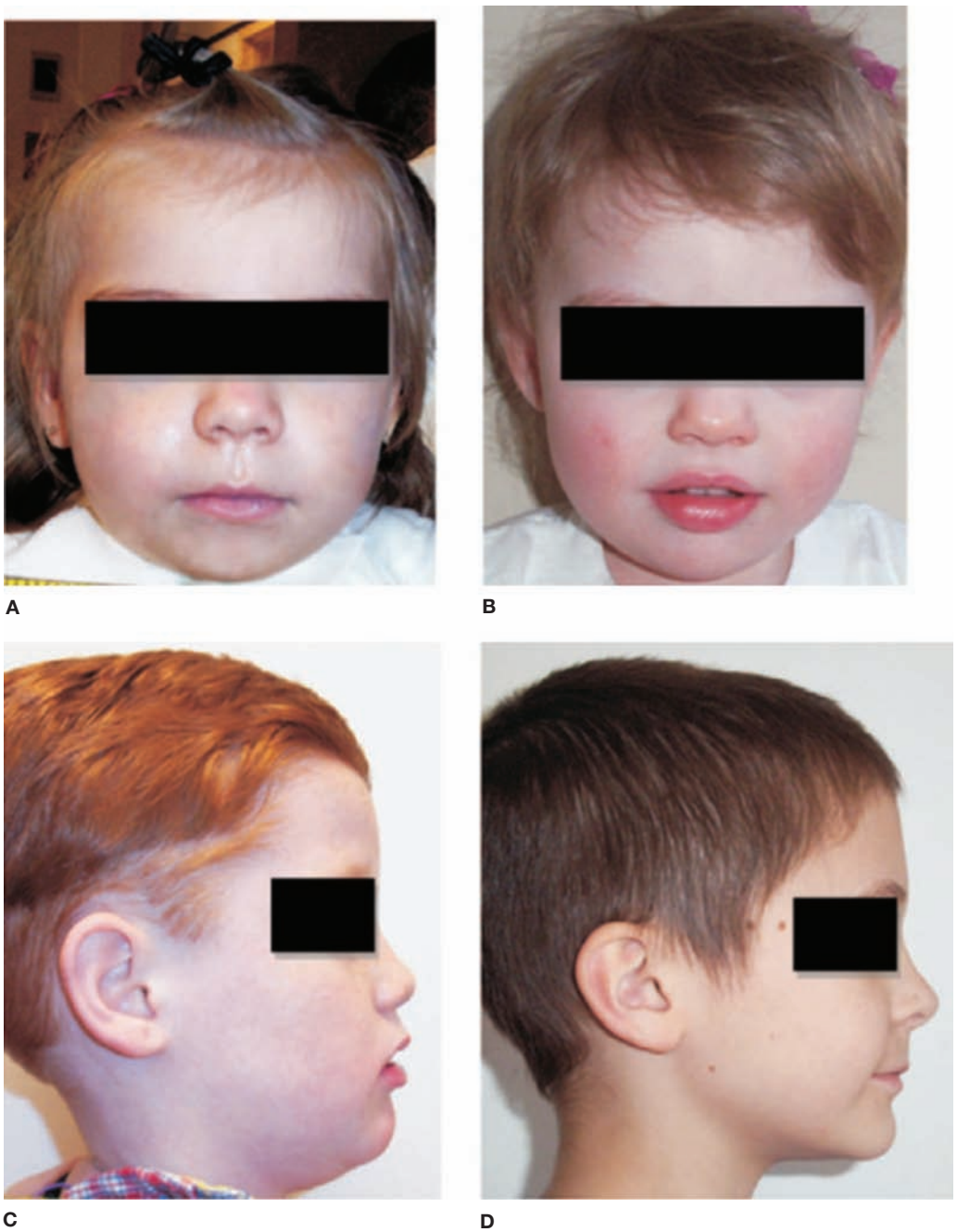

Figure 100-1 Photographs of representative congenital central hypoventilation syndrome (**A** and **C**) and control (**B** and **D**) subjects showing representative box-shaped facies of CCHS with decreases in the slope of the forehead, upper face height, upper facial inclination, nasolabial angle, upper and lower lip heights, and inferior inflection of the lateral vermillion border of the upper lip. *(Reproduced with permission from Todd ES, Weinberg SM, Berry-Kravis EM, et al. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. Pediatr Res. 2006;59(1):39–45.)*

obese.[21] As obesity and in particular super obesity (BMI $\geq$50 kg/m^2) increases exponentially, OHS is emerging as a leading cause of sleep-related hypoventilation. A prevalence of 10% to 20% has been reported in obese patients with obstructive sleep apnea (OSA), almost 50% in hospitalized patients with a BMI $\geq$50 kg/m^2, while a conservative prevalence of 0.3% has been estimated in the general US adult population.[22–24]

■ PATHOPHYSIOLOGY

The precise mechanism by which obesity leads to hypoventilation remains incompletely understood. A complex interaction between (1) abnormal respiratory system mechanics and increased work of breathing due to obesity (reduced chest wall and respiratory system compliance, increased airway resistance, expiratory flow limitation, intrinsic positive end-expiratory pressure, reduced respiratory muscle efficiency); (2) sleep-related breathing disorder; and (3) blunted central hypercapnic and hypoxic ventilatory drive, including "resistance" to leptin (a protein produced mainly by adipose tissue that stimulates ventilation) likely exists (Fig. 100-2).[23]

In approximately 90% of OHS patients the sleep-related breathing disorder is OSA. In the remaining 10% the sleep-related breathing disorder is nonobstructive sleep hypoventilation characterized by sustained hypoxia and an increase in Pa_{CO_2} by 10 mm Hg above wakefulness in the absence of significant obstructive apneas or hypopneas.

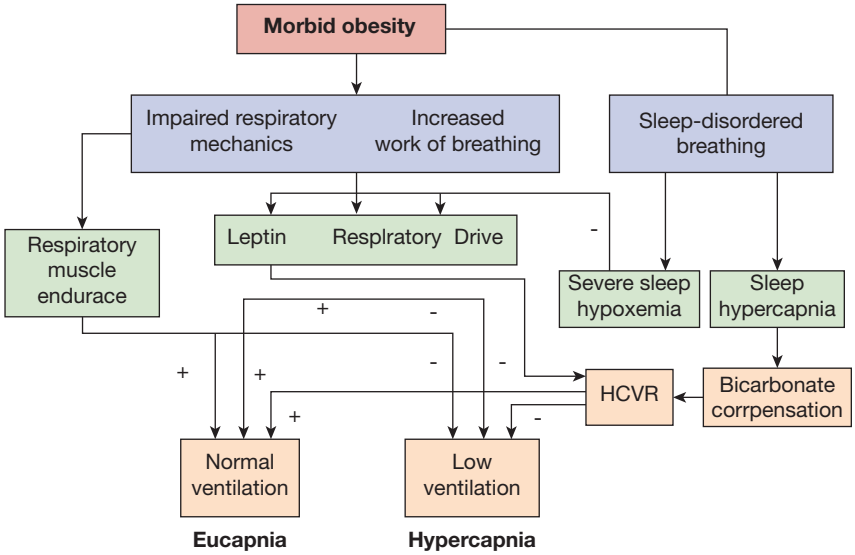

Figure 100-2 Interaction of the various pathophysiologic mechanisms implicated in the development of hypercapnia in the obesity hypoventilation syndrome. (+), positive influence on maintaining ventilation if normal or increased; (–), negative influence on maintaining ventilation if reduced or blunted; HCVR, hypercapnic ventilator response. *(Reproduced with permission from Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. J Appl Physiol. 2010;108(1):199–205.)*

More recently, OHS has been suggested to result from an inadequate compensatory ventilatory response to offload the CO_2 that accumulates during apneic and hypopneic events in sleep.[26] In addition, if the bicarbonate retained by the kidneys to buffer this transient decrease in pH is slowly eliminated, there is further blunting of the ventilatory responsiveness to CO_2, causing progressive hypercapnia (Fig. 100-3).[27]

CLINICAL PRESENTATION

OHS is associated with increased morbidity and mortality, higher rates of hospitalization and ICU admissions, increased healthcare utilization, and reduced quality of life.[22–24,28] Timely diagnosis is essential given higher rates of systemic hypertension, angina, congestive heart failure, and cor pulmonale reported in OHS compared to eucapnic obese individuals.[23,28] Yet despite the clinical consequences of OHS the diagnosis of OHS is often overlooked and a high index of clinical suspicion is required.[24]

Typical symptoms of OSA (see Chapter 97) are commonly reported by OHS patients but additional symptoms of hypercapnia including morning headaches may be present. Dyspnea is more frequently reported than eucapnic OSA patients. Pulmonary hypertension, cor pulmonale, and polycythemia are also more common in patients with OHS compared to patients with OSA alone. Not infrequently, OHS patients can present

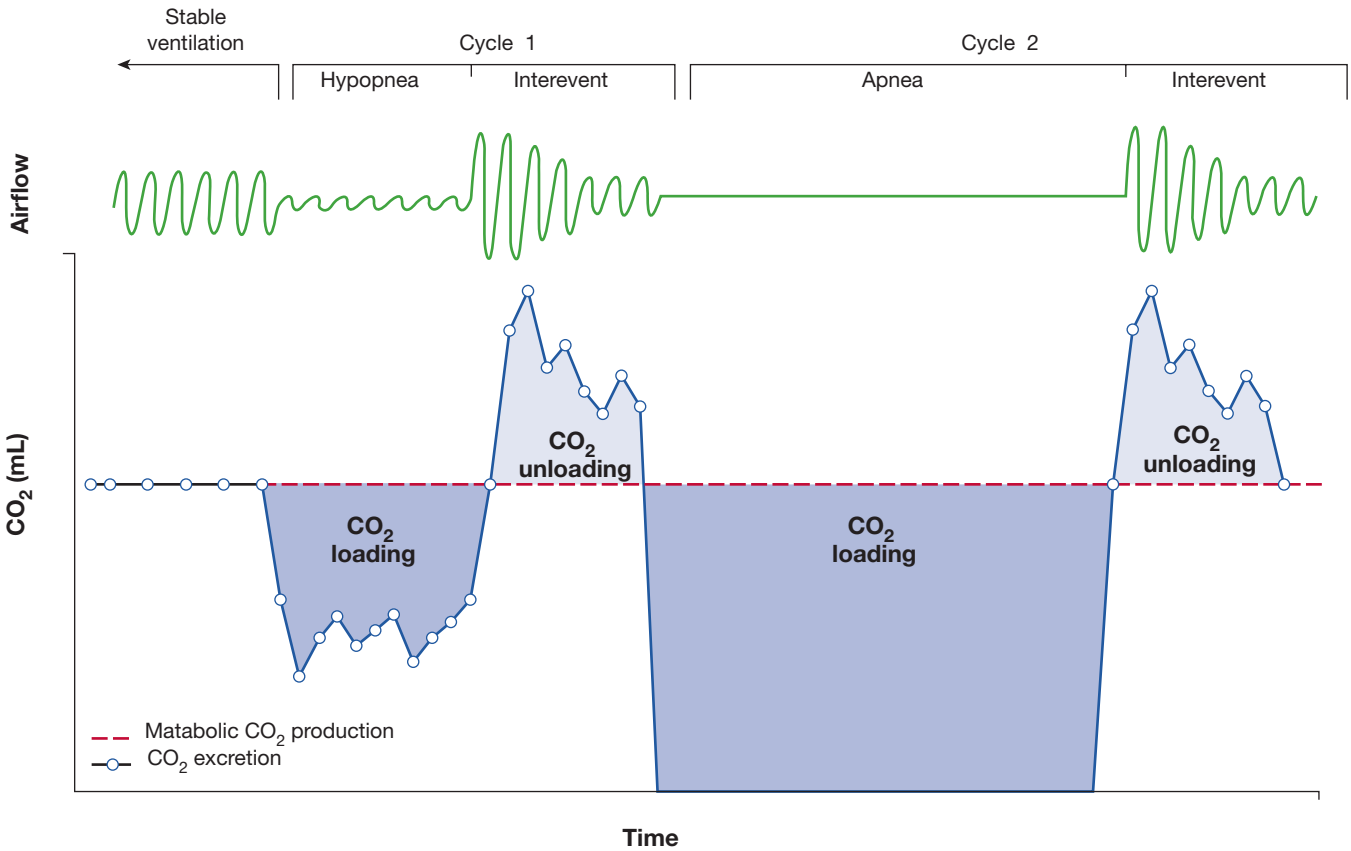

Figure 100-3 Schema depicting a proposed inadequate compensatory ventilatory response to CO_2 loading during obstructive respiratory events in the obesity hypoventilation syndrome. The dark-shaded areas depict CO_2 loading due to reduced CO_2 excretion during respiratory events while the light-shaded areas depict CO_2 unloading due to compensatory hyperventilation between respiratory events. *(Reproduced with permission from Berger KI, Goldring RM, Rapoport DM. Obesity hypoventilation syndrome. Semin Respir Crit Care Med. 2009;30(3):253–261.)*

decompensated in acute hypercapnic respiratory failure requiring the ICU.

Physical examination may reveal facial plethora, injected sclera, a prominent pulmonic component of the second heart sound and signs of right heart failure including lower extremity edema in addition to signs suggestive of OSA. Compared to eucapnic OSA patients, OHS patients commonly have awake hypoxemia typically with a Pa_{O_2} less than 70 mm Hg. Awake hypoxemia is uncommon in eucapnic OSA patients and a pulse oximetry recording of <94% should prompt consideration of an arterial blood gas measurement.[23]

DIAGNOSTIC APPROACH

The diagnosis of OHS relies on demonstration of awake hypercapnia and an arterial blood gas on room air is necessary. Chronic hypercapnia may be suggested by an elevated serum bicarbonate and a serum bicarbonate of 27 mEq/L or greater has been shown to be highly sensitive (92%) but not specific (50%) for hypercapnia.[23,29] Typically patients manifest a >10 Torr increase in their Pa_{CO_2} during sleep.

OHS is a diagnosis of exclusion. Other causes of chronic hypoventilation including significant pulmonary disease, chest wall disorders, neuromuscular disease, severe hypothyroidism, and central hypoventilation syndromes must be excluded, but in reality it is likely that the pathophysiologic mechanisms underlying OHS can coexist with these disorders. Further diagnostic testing should be guided by the clinical history and physical examination but should include pulmonary function testing, chest imaging, electrocardiography, thyroid function testing, and a sleep study, where a characteristic pattern is often seen including increased sleep time with Sp_{O_2} <90% as outlined in Figure 100-4.[23,30,31]

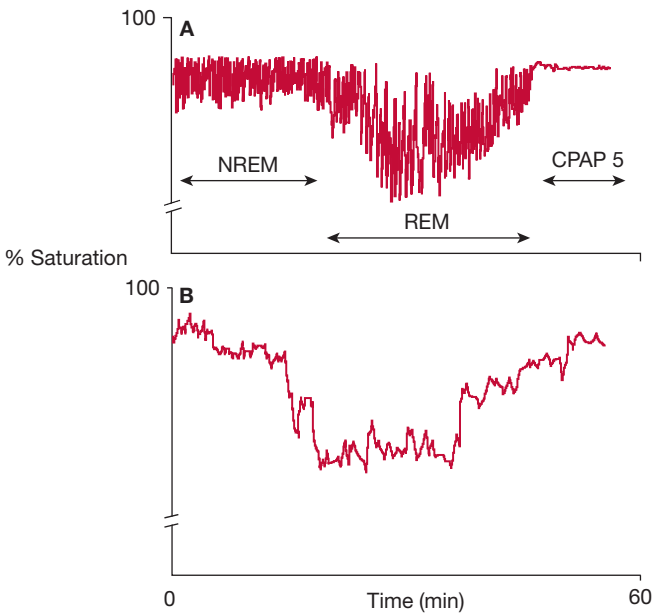

Figure 100-4 **A.** Nocturnal oximetry in a patient with severe obstructive sleep apnea demonstrating recurrent desaturations in nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. Each apneic event results in an oxyhemoglobin desaturation that improves as the apnea is terminated. The degree of desaturation is greater in REM sleep and resolves when continuous positive airway pressure (CPAP) of 5 cm H_2O is applied. **B.** In contrast to **A**, this nocturnal oximetry demonstrates prolonged desaturation in a patient with obesity hypoventilation syndrome (OHS). The desaturation corresponds to periods of prolonged hypoventilation. Although not diagnostic, this pattern is highly suggestive of OHS.

TREATMENT

Nocturnal positive airway pressure (PAP) is currently the mainstay of treatment. PAP has been shown to improve hypercapnia and hypoxemia, symptoms, pulmonary hypertension, and quality of life.[22,32–35] Despite the widespread adoption of PAP the best modality remains unknown. Continuous positive airway pressure (CPAP) relieves upper airway obstruction and concomitant OSA. Since OSA is present in over 90% of OHS patients it is not surprising that CPAP alone has been shown to be effective in treating of the order of 60% to 80% of patients with OHS.[29,31,36] A sleep laboratory titration is recommended to determine optimal pressures to eliminate respiratory flow limitations and correct hypoxemia. While autoadjusting CPAP units are gaining increasing popularity, the technology as of yet does not recognize hypoventilation and cannot be routinely recommended. Serial ABG monitoring is suggested to ensure delivery of adequate ventilation. PAP adherence must be encouraged with the degree of improvement in hypercapnia shown to correlate with PAP adherence.[37]

Despite excellent adherence, hypercapnia and hypoxemia persist in 20% to 50% of OHS patients on CPAP.[23] BPAP is generally considered the next step but few studies to date have compared BPAP to CPAP, further complicated by the development of increasingly sophisticated home PAP units. Piper et al. randomized 36 OHS patients to either BPAP or CPAP and after 3 months observed no difference in CO_2 or O_2 levels or adherence between the two groups. The study, however, excluded 20% of subjects who had persistent hypoxemia defined arbitrarily as 10 continuous minutes of Sp_{O_2} <80% without apnea or an acute rise in transcutaneous carbon dioxide pressure during REM sleep (during a full night of CPAP titration), which limits the generalizability of the study.[36] In general, BPAP is recommended for decompensated acute hypercapnic respiratory failure, the small number of OHS patients without OSA, patients intolerant of CPAP especially at the higher pressures often required, and patients with persistent hypercapnia and hypoxemia despite 3 months of CPAP treatment. There are, however, no established guidelines regarding the optimal PAP modality in these patients.

Similarly no standard guidelines exist for BPAP titration in OHS. Frequently the expiratory positive airway pressure (EPAP) is increased until flow limitation is eliminated followed by the addition of inspiratory positive airway pressure (IPAP) to improve alveolar ventilation. Typically an EPAP of 6 to 10 cm H_2O, an IPAP of 16 to 20 cm H_2O, and a difference between IPAP and EPAP of at least 8 to 10 cm H_2O is required.[22,32,35,38] The role of a backup rate is unknown but should be used given the ventilatory control abnormalities in these patients. A newer hybrid mode of ventilator known as average volume assured pressure support (AVAPS) aims to maintain a target tidal volume by means of an algorithm estimating the patient's tidal volume over several breaths and adjusting IPAP to achieve that target tidal volume. For example, if patient effort and tidal volume decreases, AVAPS automatically increases IPAP to maintain the target tidal volume. Successful application of AVAPS in OHS has been described but few studies have compared it to more conventional BPAP modes.[39] In up to half of OHS patients, supplemental oxygen is needed in addition to PAP therapy to keep Sp_{O_2} >90%, although the need for supplemental oxygen may abate with continued PAP usage.[37] Oxygen therapy alone is inappropriate for OHS and may prolong apnea and worsen hypercapnia.[40] Oxygen should only be given in conjunction with PAP.

Weight loss should be encouraged in all patients but significant weight loss is often difficult to achieve and maintain medically. Bariatric surgery is an effective approach to sustained weight loss and should be considered in all patients with OHS. Hypercapnia can improve following bariatric surgery but a recent meta-analysis of 342 patients found 62% had residual OSA with a mean residual apnea–hypopnea index (AHI) of 16 events per hour following maximum weight loss after bariatric surgery.[41] Close clinical monitoring and a repeat sleep study are suggested following surgery. Worsening hypercapnia was reported

by Sugerman et al.[42] 1 to 5 years following surgery despite only a small increase in BMI, thought to be due to recurrence of sleep-related breathing disorder. While bariatric surgery is to be considered in all OHS patients it is important to recognize that the surgery is associated with postoperative risks with a reported perioperative mortality between 0.5% to 1.5%.[43,44] Tracheostomy was available long before PAP therapy but there are very few large studies evaluating long-term outcomes. A tracheostomy bypasses the upper airway and has been shown to improve OSA but correction of daytime hypercapnia is neither universal nor complete and ongoing monitoring is necessary.[45,46] Tracheostomy is now generally reserved for those who have failed all other PAP modalities, which is becoming increasingly uncommon with the technologic advances in PAP units and evolution of more comfortable and varied interfaces. In addition, tracheostomy is often challenging in this population given the excessive neck adipose tissue in most patients with OHS. If a tracheostomy is performed ventilation through the trachea will still be necessary to increase minute ventilation.

Finally, while there has been interest in the use of various pharmacologic respiratory stimulants including medroxyprogesterone and acetazolamide, a carbonic anhydrase inhibitor that induces metabolic acidosis thereby increasing minute ventilation, studies are few and small.[22] These medications should not be used in patients with OHS because of frequent side effects and a lack of demonstrated long-term benefits.

SLEEP-RELATED HYPOVENTILATION IN PULMONARY DISORDERS

Sleep-related hypoventilation occurring in chronic obstructive pulmonary disease and in the so-called "overlap syndrome" are discussed below.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (COPD) are particularly susceptible to nocturnal hypoventilation especially during REM sleep (Fig. 100-5).[47] Becker et al.[48] demonstrated an approximate 16% decrease in ventilation from wakefulness to NREM sleep and an almost 32% decrease during REM compared to wakefulness in COPD patients. The greater fall in minute ventilation in COPD patients during sleep is largely due to a decrease in tidal volume. Patients with COPD are often hyperinflated reducing diaphragmatic efficiency, which results in increased reliance on use of accessory muscles. During REM sleep there is muscle atonia with loss of this accessory muscle contribution such that ventilation is further reduced. Hypoventilation is further augmented by a decreased ventilatory responsiveness to CO_2 during sleep. Nocturnal hypoventilation results in nocturnal oxygen desaturation and nocturnal oxygen desaturation is a marker of increased mortality in COPD patients.[47,49] The oxygen desaturation nadir during sleep in patients with COPD has been shown to be greater than during exercise, with Sp_{O_2} falling an average of 12.9+10.5% during sleep compared to 4.5+3.7% during maximum treadmill exercise testing.[50]

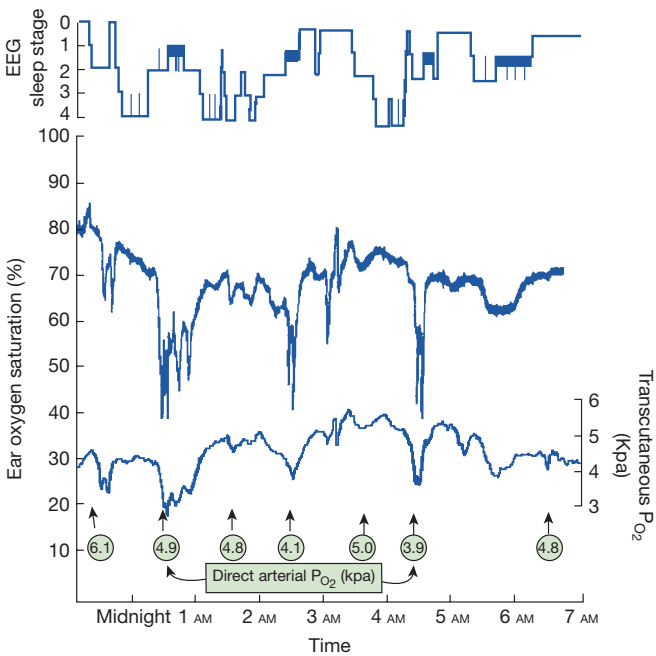

Figure 100-5 EEG sleep stage (*closed bars*, rapid eye movement [REM] sleep), ear oxygen saturation and transcutaneous P_{O_2} in a "blue bloater" during sleep on room air depicting susceptibility to nocturnal hypoventilation, particularly during REM sleep. 1 kPa = 7.501 Torr. *(Reproduced with permission from Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med. 1985;6(4):651–661.)*

While alveolar hypoventilation likely accounts for most of the oxygen desaturation in COPD, changes in ventilation–perfusion matching and decreased end-expiratory lung volumes have also been described.[51,52] Ventilation–perfusion mismatching is suggested by discordance between a decreased Sa_{O_2} and a stable or slightly increased Pa_{CO_2}.[53] Changes in lung volumes including a reduction in functional residual capacity leading to closure of small airways have been suggested but studies are conflicting.[52] In addition, as patients with COPD typically have lower wakefulness Pa_{O_2} and lie closer to the steep portion of the oxyhemoglobin dissociation curve they are more susceptible to significant nocturnal oxygen desaturation. This is particularly relevant in the presence of coexisting OSA, as discussed below.

Nocturnal oxygen desaturation has been associated with pulmonary hypertension, cardiac arrhythmias, and impaired sleep quality.[51,53] Poor sleep has been both subjectively reported and objectively demonstrated in COPD patients with reduced sleep efficiency, delayed sleep onset, reduced total sleep time, sleep fragmentation, and a decrease in slow-wave and REM sleep.[54,55]

Long-term oxygen therapy worn ≥15 hours per day has been shown to improve mortality and quality of life in COPD patients with chronic resting hypoxemia.[56,57] However, correction of nocturnal hypoxemia in COPD patients with only nocturnal oxygen desaturation has not been shown to consistently improve outcomes.[12,58–60] There has been significant interest in the use of noninvasive ventilation (NIV) in stable hypercapnic COPD but studies are conflicting as to whether it is beneficial.[61–64] Currently the Centers for Medicare and Medicaid Services require a Pa_{CO_2} >52 mm Hg on an ABG drawn while awake (breathing the patient's prescribed FI_{O_2}) and sleep oximetry (performed while breathing supplemental oxygen at 2 L/min or the patient's usual prescribed FI_{O_2}) demonstrating an Sp_{O_2} <88% for >5 minutes for reimbursement of NIV in patients with stable COPD.[61]

THE OVERLAP SYNDROME

The term overlap syndrome was coined by Dr. David Flenley in 1985 to describe the coexistence of COPD and OSA although his original description alludes to a broader definition of coexisting hypoxemic lung disease and OSA.[51] It is of particular clinical relevance given its association with greater sleep-related hypoventilation than either COPD or OSA alone.

The prevalence of the overlap syndrome is estimated at 1% of adults but prevalence data varies with the definitions used for both COPD and OSA. There is a lack of a standardized definition for the overlap syndrome.[65] Using an OSA definition of AHI ≥5 events/h and a COPD definition of Global Initiative for Chronic Obstructive Lung Disease Stage I (FEV_1 >80%), a prevalence of 4% of males has been suggested based on an OSA prevalence of 24% of males in the Wisconsin Sleep Apnea Study and a COPD prevalence of 16.8% in

the National Health and Nutrition Examination Survey III (NHANES III).[65] Evidence suggests a similar prevalence of OSA in patients with COPD as in the general population with no increased association between at least mild COPD and OSA.[52,66,67]

Patients with the overlap syndrome have more significant nocturnal hypoventilation with greater hypoxemia and hypercapnia than COPD or OSA alone.[54,66,68,69] A decreased hypercapnic ventilatory response has been shown in these patients.[70] Pulmonary hypertension is more common and more severe than in either patients with COPD or OSA alone where typically severe pulmonary hypertension is uncommon.[71] Consequently, the overlap syndrome should be considered in patients with either COPD or OSA with significant hypoxemia, hypercapnia, or pulmonary hypertension disproportionate to the severity of their disease. What remains unclear, however, is if the degree of severity of the combined diseases has additive or synergistic clinical relevance. That is, it is unknown whether patients with severe COPD and mild OSA have the same clinical consequences as those with mild COPD and severe OSA.[52]

The diagnosis of the overlap syndrome is important given the increased morbidity and mortality compared to either COPD or OSA alone.[52] Marin et al.[72] in an observational study compared 213 patients with untreated overlap syndrome to 210 patients with COPD alone and demonstrated increased mortality (relative risk 1.79, confidence interval 1.16–2.77) in the overlap group over a median follow-up of 9.4 years. COPD has been shown to be a marker of increased mortality in OSA[73] and more recently there have been emerging data examining the potential overlap of systemic inflammation, oxidative stress, and leukocyte dysfunction implicated in both COPD and OSA and cardiovascular disease.[65]

Given the clinical implications of the overlap syndrome, the symptoms and signs suggestive of OSA should be included in the evaluation of all COPD patients. If there is any clinical suspicion a full in-laboratory sleep study should be performed. Unattended portable sleep studies have not yet been validated in the COPD population.[74] Similarly nocturnal oximetry alone cannot reliably discriminate nocturnal oxygen desaturation secondary to COPD alone, OSA or some combination of the two, and given differences in treatment based on the underlying pathophysiology it is not recommended currently for diagnosis.

Treatment of the overlap syndrome is directed at the constituent disorders. Recent studies have suggested a survival benefit in patients with the overlap syndrome with CPAP[72,75] but these studies were not randomized. Nevertheless, CPAP is currently the accepted standard for the treatment of the overlap syndrome. CPAP in addition to relieving upper airway obstruction has been suggested to off-load the respiratory muscles reducing hypoventilation, oxygen consumption or CO_2 production by respiratory muscles, and may offset intrinsic PEEP in severe COPD patients.[52] CPAP alone may not fully correct hypoxemia requiring addition of supplemental oxygen but oxygen alone is not recommended for the overlap syndrome because it can potentially worsen hypercapnia.[76] The role of BPAP in the treatment of the overlap syndrome has not yet been explored and it remains uncertain whether it offers additional benefits over CPAP. NIV may be beneficial in this population but further research on the long-term effects of NIV compared to CPAP with or without supplemental oxygen is required.[52]

SLEEP-RELATED HYPOVENTILATION IN NEUROMUSCULAR DISORDERS

Sleep-related hypoventilation is common in neuromuscular disorders[77] including but not limited to amyotrophic lateral sclerosis (ALS), spinal muscle atrophies, postpolio syndrome, muscular dystrophies, congenital muscular dystrophy, myotonic dystrophy, metabolic myopathies, Guillain–Barré syndrome, and myasthenia gravis. The effects of neuromuscular disorders on ventilation are covered in Chapter 84. Sleep-related breathing disorders generally precede daytime ventilatory failure and the full spectrum from obstructive and central respiratory events to hypoventilation are found.

The mechanisms for sleep-related hypoventilation in neuromuscular disorders are multifactorial. Respiratory muscle weakness plays a central role. The type and severity of sleep-related breathing disorders usually parallel the extent and distribution of respiratory muscle weakness. Sleep hypoventilation often develops when supine vital capacity is <60% of the predicted value or maximal inspiratory pressure not as negative than –34 cm H_2O.[78] Patients with diaphragmatic weakness depend on recruitment of accessory inspiratory muscles and expiratory abdominal muscles and are particularly susceptible to significant hypoventilation during REM sleep where there is relative atonia of these skeletal muscles.

Weakness of the upper airway musculature can cause obstructive events, further exacerbated by an imbalance between the inspiratory force generated by the inspiratory muscles and activity of the muscles responsible for stabilizing the upper airway.[79] With progressive respiratory muscle weakness the number of respiratory events and the AHI may decline in ALS.[80] This may reflect an inability of the inspiratory respiratory muscles to generate pressures above the closing pressure of the upper airway resulting in fewer recorded respiratory events. In addition, bulbar muscle dysfunction and aspiration risk have not been shown to be significantly associated with severity or type of sleep-related breathing disorders in ALS.[79,81,82]

Abnormalities of ventilatory control have been also described in certain neuromuscular disorders, including myotonic dystrophy and congenital myopathy.[79] The hypercapnia and bicarbonate retention caused by nocturnal hypoventilation can further depress respiratory drive exacerbating sleep-related hypoventilation. Consequently, sleep fragmentation with shorter total sleep time, frequent arousals, and a reduction in or complete suppression of REM sleep have been described in neuromuscular disorders.[83] This sleep fragmentation and sleep debt may further suppress the arousal response and worsen hypoventilation.

Given the pervasiveness of sleep-related hypoventilation in neuromuscular disorders a detailed sleep history is an essential component of any clinical evaluation. Early in-laboratory polysomnography with continuous CO_2 monitoring is indicated in this patient population as sleep-related hypoventilation may long precede diurnal hypoventilation. NIV has been shown to improve sleep quality, quality of life and mortality in various neuromuscular disorders, and management of neuromuscular respiratory muscle dysfunction is covered in Chapter 84.[62,63,83–85] However, the optimal criteria for initiation of NIV for sleep-related hypoventilation in neuromuscular disorders remain uncertain.

SLEEP-RELATED HYPOVENTILATION IN RESTRICTIVE CHEST WALL DISORDERS

Chest wall deformities, in particular scoliosis, often accompany neuromuscular disorders, and can contribute to sleep-related hypoventilation. Nonmuscular diseases of the chest wall are reviewed in Chapter 83.

Patients with scoliosis, a rotational deformity of the spine, have reduced chest wall and lung compliance, increased work of breathing, respiratory muscle weakness, ventilation–perfusion mismatching, and reduced respiratory drive. The degree of respiratory impairment is associated with severity of spinal deformity accordingly, and respiratory failure is uncommon if the Cobb angle (a radiographic measure of spinal curvature in the coronal plane, calculated from two lines drawn perpendicular to lines drawn through the middle of the two vertebrae at the top and bottom of the curved segment) is less than 100 degrees.[86] Sleep is a vulnerable period and as with neuromuscular disorders gas exchange is worst during REM sleep.[87–90] While central hypoventilation is more common,

airway obstruction can also occur. Patients with scoliosis breathe at low lung volumes and lower airway caliber is proportional to lung volumes. In addition, secondary cervical curvature can displace the intrathoracic trachea to cause significant upper airway obstruction. Therefore clinical evaluation for sleep-related hypoventilation is necessary in this population, followed by polysomnography when sleep-related breathing disorder is suspected. NIV has been shown in small studies to improve gas change in restrictive chest wall disorders including scoliosis and posttuberculosis but results on sleep architecture and sleep quality have been mixed.[90–94]

CONCLUSION

An understanding of normal sleep–associated changes in ventilation is essential in identifying sleep-related hypoventilation syndromes and appreciating the potential vulnerability of the sleep period for patients with underlying cardiopulmonary disorders, neuromuscular disease, and restrictive chest wall disorders. Consequently, a comprehensive sleep evaluation should be incorporated in the clinical evaluation of each of these high-risk patient populations. This is particularly relevant given the recent advances in NIV treatment.

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CHAPTER 101

Changes in the Cardiorespiratory System During Sleep

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As outlined in Chapter 12, sleep occurs in distinct states classified broadly as non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These occur in a temporally organized fashion across the sleep period, with NREM dominating during the early hours of sleep and REM during the final hours of sleep. Myocardial infarction and ischemic stroke occur at a higher frequency during early morning hours,[1–3] when REM sleep predominates. This temporal distribution of events may be explained at least in part by specific alterations in autonomic regulation during sleep. This chapter presents additional information on alterations in cardiopulmonary function during sleep.

CHANGES IN CARDIOVASCULAR CONTROL DURING SLEEP

During NREM sleep, heart rate slows by 5% to 10%,[4] and blood pressure drops by about 10%.[4] These changes are most prominent in the deepest stage of NREM sleep,[4] that is, stage 4 (now known as N3[5] or slow-wave sleep[4]). The mechanism for this decline was elucidated by the seminal studies of Somers et al.[4] using microneurography to record sympathetic bursts in the peroneal nerve in healthy humans during wake and in the different stages of sleep (Fig. 101-1). These studies confirmed a fall in sympathetic activity during NREM sleep, which is responsible for the drop in blood pressure, cardiac output, and systemic vascular resistance.[4] This fall is accompanied by an increase in parasympathetic (vagal nerve) activity that is believed to be responsible for the bradycardia of NREM sleep.[6] Thus, the balance of parasympathetic/sympathetic activity is altered during NREM sleep, with the parasympathetic being dominant. This also results in alteration in heart rate variability during sleep. The high-frequency component of this heart rate variability is said to reflect parasympathetic activity, while the low-frequency component is related to sympathetic activity.[4] Thus, during NREM sleep there is an increase in the high-frequency component compared with wakefulness and a quite marked reduction in the low-frequency component of heart rate variability.[4]

Changes in REM sleep differ from those that occur during NREM sleep. During REM sleep, which occurs at approximately 90-minute intervals, there is a return of sympathetic activity such that heart rate and blood pressure return to wakefulness levels.[4] This has been shown directly by recording sympathetic nerve activity (SNA) in humans (Figs. 101-1 and 101-2).[4] Thus, during REM sleep the high- and low-frequency components of heart rate variability are the same as in wakefulness.[4]

During REM sleep there is also phasic activity that occurs in bursts. These phasic bursts of activity result in REMs and hence the name for the state. Phasic bursts of activity can lead to both brief, sudden increases in heart rate and blood pressure that are mediated by increases in sympathetic activity,[4,6–8] which are similar to waking levels,[4] and by sudden, baroreflex-mediated periods of decrease.[6] These changes have pathophysiological significance. During surges of heart rate, there are also increases in coronary blood flow.[7,8] But these can be mismatched such that the increased delivery of blood flow is insufficient to meet the extra myocardial demands consequent to the increase in heart rate. Moreover, in animal models of severe coronary stenosis, phasic decreases in coronary arterial blood flow are found when heart rate increases.[7] Such changes may play a role in the known diurnal rhythm of timing of reported acute cardiac events in humans.[1–3]

Episodes of abrupt slowing of heart rate can also occur during REM sleep. In addition to baroreceptor-mediated decelerations, sudden slowing of the heart rate may be a result of reduction in central autonomic input to the heart, an increase in vagal tone, or both.[9] At the extreme, brief episodes of asystole in phasic REM sleep have been described in otherwise healthy adults.[10]

CHANGES IN VENTILATION AND ITS CONTROL WITH SLEEP

As with the cardiovascular system, there are important changes in ventilation during sleep.[11] These, too, are different in NREM and REM sleep.[11,12] During NREM sleep ventilation declines. The various studies in this area have been summarized by Krieger et al.[13] All studies have reported this decrease, although the magnitude of change varies from study to study (see summary in Fig. 101-3). In general, there is a decline in tidal volume while the change in respiratory rate is more variable (see Table 1 in Krieger J et al., 1990).[13] Ventilation in

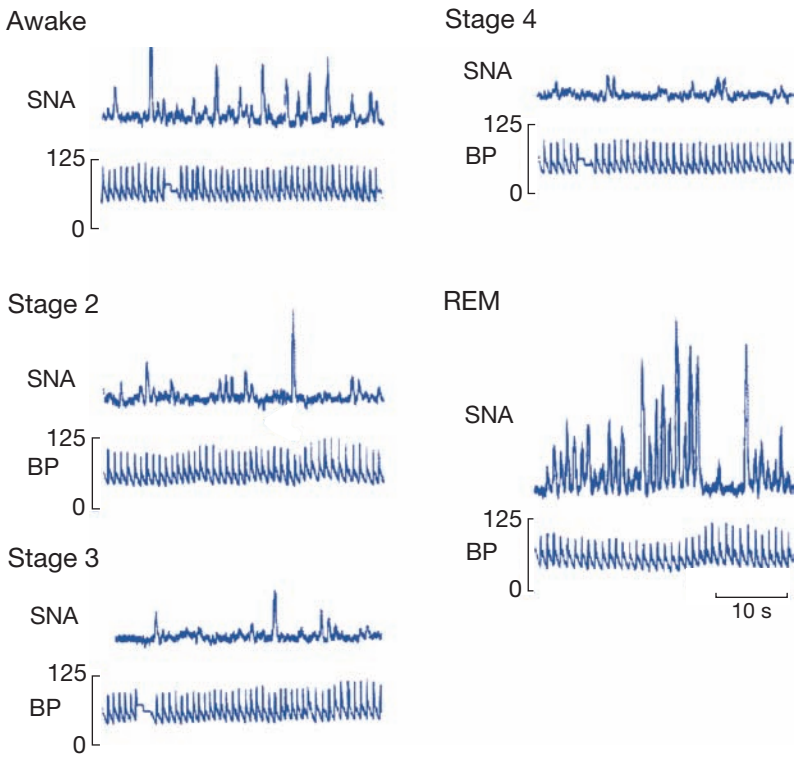

Figure 101-1 Alterations in recorded bursts of sympathetic nerve activity (SNA) and blood pressure in wakefulness, different stages of non-rapid eye movement sleep (NREM) (stages 2–4), and rapid eye movement (REM). With deepening of NREM sleep, there is progressive loss of sympathetic activity, which is virtually absent in slow-wave sleep (stage 4). Sympathetic activity returns in REM but is highly variable. *(Reproduced with permission from Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303–307.)*

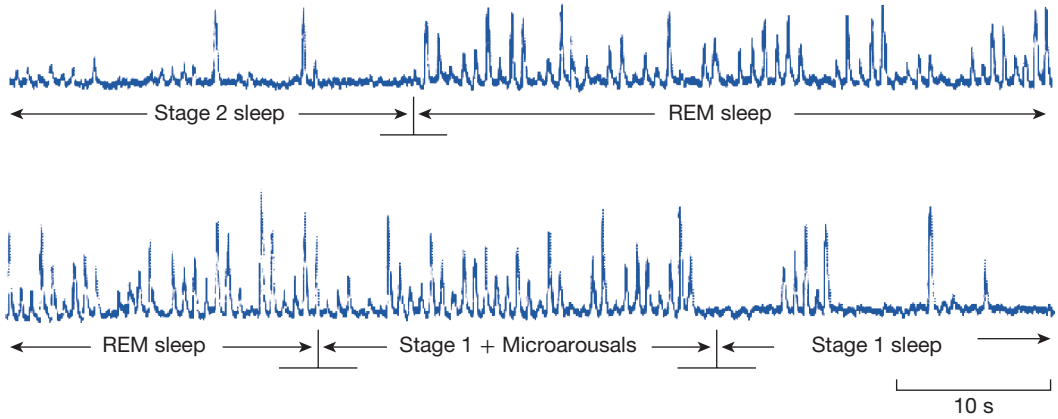

Figure 101-2 Changes in recorded sympathetic nerve bursts in a healthy human during transitions between different sleep stages. There are more bursts, that is, more sympathetic activity, in REM sleep compared with stage 2 NREM sleep (top panel) and more activity in stage 2 sleep when it is transitional with many microarousals than when fully established (bottom panel). *(Reproduced with permission from Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328:303–307.)*

REM sleep is also consistently less than in wakefulness; some studies report a small increase in ventilation in REM compared with NREM sleep (0.9%–7.1%), whereas other studies report a further decrease (−1.1% to −10.8%).[13] This variability is likely related to the variability of ventilation in REM sleep itself. As in the cardiovascular system, there are changes in ventilation in association with the phasic events of REM sleep.[14] Both acceleration and slowing of respiratory rate are found as are declines in ventilation. These effects seem to vary between subjects (Fig. 101-4),[14] with some subjects showing large reductions in inspiratory flow and increased respiratory frequency during REMs and others showing only subtle changes.[14]

The changes in NREM sleep in normal humans are largely the result of increases in upper airway resistance.[15] This resistance progressively increases going from stage N1 to stage N3 NREM sleep (Fig. 101-5). This increase in resistance is associated with decrease in upper airway muscle activity in muscles such as the genioglossus[16–20] and tensor palatini[15] in the soft palate. During REM sleep, pharyngeal muscle activity is shut down via sleep-specific motor inhibition,[18] predisposing individuals to obstructive sleep apnea.

The neural control of upper airway motoneurons is complex and involves inputs from many premotor neurons originating in the forebrain, midbrain, pons, and medulla,[21] which communicate with upper airway motoneurons via a diverse group of neurotransmitters. It has always been the hope that identification of the neurochemical change that is responsible for reduced upper airway motor tone would elucidate promising pharmacologic targets for obstructive sleep apnea. It is now clear that neurochemical drive to upper airway motoneurons varies with behavioral state and in fact is quite distinct in NREM sleep relative to REM sleep. In NREM sleep, reduced noradrenergic input from the pons[16,19,20] contributes to reduced upper airway tone. Noradrenaline as a neuromodulator may play this role by potentiating glutamatergic excitation,[16] rather than via direct excitation, as measured by masseter muscle activity. Muscarinic inhibition of the hypoglossal motor pool prevents the inhibition of genioglossus activity throughout REM sleep.[18] During REM sleep, muscarinic receptors for acetylcholine linked to G-protein coupled, inwardly rectifying potassium (GIRK) channels have been shown to be important.[18] Thus, preventing apneas in both NREM and REM sleep will likely require modulation of both noradrenergic and cholinergic neurotransmitters as well as potentially specific GIRK channels.

Individuals without upper airway obstruction as well as those with sleep-disordered breathing demonstrate increased Pa_{CO_2} in sleep. These findings support the concept that central ventilatory drive is also altered by sleep state. Although an increase in upper airway resistance is the major mechanism, it is, however, not the only mechanism, since even in laryngotomized subjects with tracheostomies, which bypass the upper airway, P_{CO_2} increases in NREM sleep compared to wakefulness.[22] Of interest, the effects of sleep on ventilatory drive are in part gender-specific. The relative importance of the increase in upper airway resistance reflects different neural control of upper airway muscles[18–20,23,24] and the respiratory pump muscles such as the diaphragm. The former is much more coupled to state, that is, wake and sleep, while the latter, the diaphragm, is more affected by chemical control rather than variations in state (Fig. 101-6). This is why obstructive sleep apnea occurs commonly, whereas central sleep apnea is relatively rare. Sleep also alters the ventilatory response to hypoxia and hypercapnia. The ventilatory response to hypoxia declines in NREM sleep compared to wakefulness in men,[25,26] but appears to remain the same in wakefulness and NREM sleep in women.[27] This

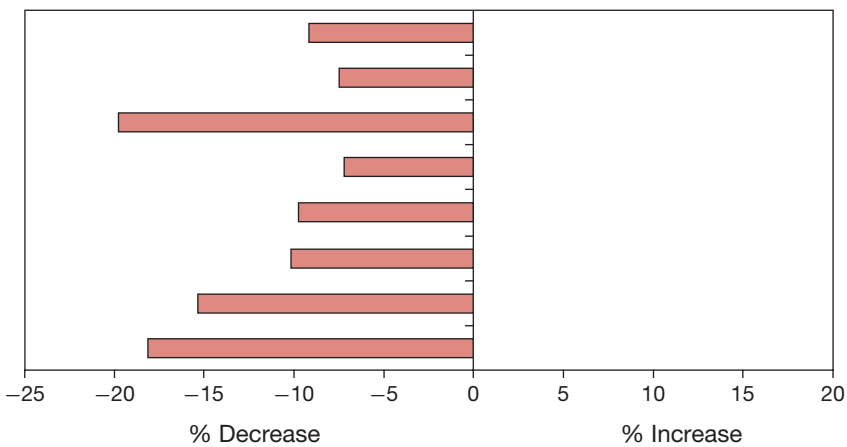

Figure 101-3 Percentage change in minute ventilation from wakefulness to NREM sleep in several different studies. There is some variation among studies in the magnitude of the drop in ventilation in NREM sleep, but all studies show a decline. *(Data from Krieger J, Maglasiu N, Sforza E, et al. Breathing during sleep in normal middle-aged subjects. Sleep. 1990;13:143–154.)*

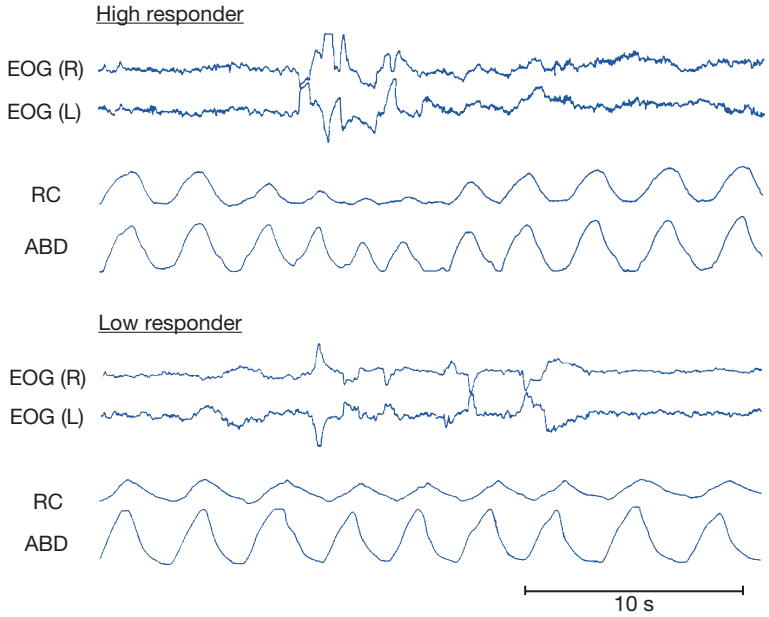

Figure 101-4 Changes in respiration during REM sleep. The data shown are for two normal healthy adults. The top traces are right and left electrooculogram [EOG(R) and EOG(L)] that show phasic eye movements during REM sleep. The bottom traces are ribcage (RC) and abdominal (ABD) motion. The subject in the top panel (labeled High Responder) has a marked fall in ribcage and to a lesser extent abdominal motion in association with the eye movements. The subject in the bottom panel (labeled Low Responder) has little alteration in ventilatory movements during these phasic eye movements. *(Reproduced with permission from Neilly JB, Gaipa EA, Maislin G, et al. Ventilation during early and late rapid-eye-movement sleep in normal humans. J Appl Physiol. 1991;71(4):1201–1215.)*

difference was attributed to higher rates of ventilation during wakefulness in men, with comparable rates in NREM sleep in men and women.[27] The ventilatory response to hypoxia is lower in REM sleep than NREM in both men and women.[25–27] Likewise, the slope of the ventilatory response to carbon dioxide is reduced in NREM sleep by as much as 50%,[28] compared to wakefulness and further reduced in REM sleep. However, there is no compelling evidence that there is alteration in central neural response to chemical stimuli since there is, as outlined, a change in upper airway resistance that will alter the increase in ventilation produced by increases in the neural output to the diaphragm.

As a consequence of these changes in ventilation and its control, Pa_{CO_2} rises typically from its normal value of 40 mm Hg by a few mm Hg in NREM sleep.[29] The magnitude of this increase in Pa_{CO_2} is a function of the responsiveness of the system to CO_2 during wakefulness; subjects with low ventilatory responses to CO_2 have larger increases in Pa_{CO_2} during NREM sleep than do subjects with high responsivity (Fig. 101-7).[29]

Parallel to this increase in Pa_{CO_2}, the Pa_{O_2} can fall in sleep. In healthy individuals living at sea level, the Pa_{O_2} does not fall to a level where significant desaturations occur. However, in persons with low Pa_{O_2} during wakefulness, who operate closer to the "knee" of the oxygen saturation curve, this fall in Pa_{O_2} during sleep may lead to a significant hypoxemia. For example, patients with chronic obstructive pulmonary disease may require supplemental oxygen during sleep but not during wakefulness. The severity of sleep-related hypoxemia will also vary with sleep-state–dependent functional residual capacity. When this is low as a consequence of obesity or intrinsic lung disease, the drops in Pa_{O_2} will be greater than expected for the increase in Pa_{CO_2}.

Another major change that occurs during NREM sleep is an increase in the CO_2 apnea threshold. This apnea threshold is the Pa_{CO_2} at which there is insufficient chemical drive and ventilation ceases. During wakefulness, Pa_{CO_2} can be reduced by assisted ventilation to values as low as 20 mm Hg and rhythmic ventilation will be maintained[12]; thus, the CO_2 apnea threshold during wakefulness is extremely low. In contrast, during NREM sleep, the Pa_{CO_2} needs be reduced only to values close to the normal awake Pa_{CO_2} (from 42–45 to 38–40 mm Hg) and ventilation will cease.[12] Indeed, the normal increase in Pa_{CO_2} that occurs during NREM sleep is often necessary to maintain rhythmic ventilation.

This NREM sleep–related increase in apnea threshold has profound implications. In situations in which ventilation is stimulated – for example, by hypoxia – Pa_{CO_2} may be reduced below the apnea threshold typical for normoxic conditions, creating a state of increased vulnerability to central apneas.[12,30] It is likely that unexplained central apnea during sleep occurs in association with hypocapnia.[30,31] This hypocapnia may be the result of chronic hyperventilation, which is probably related to augmented central and peripheral respiratory drive, which predisposes to respiratory control system instability.[30] If this is the mechanism for these apneas, increase in the Pa_{CO_2} should abolish them. This has been demonstrated in idiopathic central apnea.[12] Relative hypocapnia is also a risk factor for the development of Cheyne–Stokes respiration in patients with congestive heart failure.[30,31]

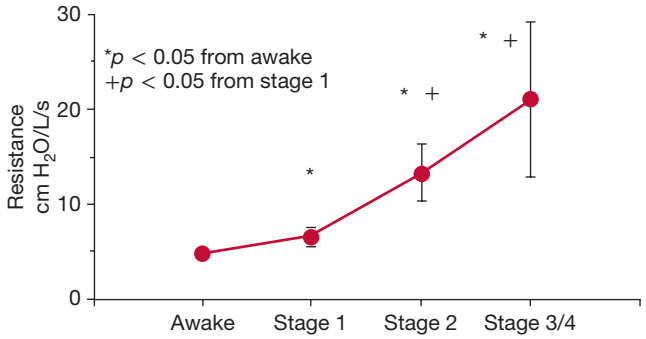

Figure 101-5 Upper airway resistance increases progressively on going from wakefulness to the deeper stages of NREM sleep. *(Data from Tangel DJ, Mezzanotte WS, White DP. Influence of sleep on tensor palatini EMG and upper airway resistance in normal men. J Appl Physiol. 1991;70:2574–2581.)*

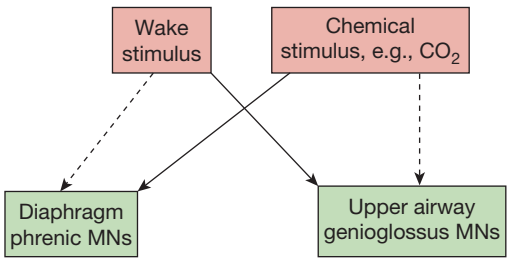

Figure 101-6 Schematic diagram illustrating the relative role of the "wakefulness drive" to breathe and that related to the chemical control system determined by Pa_{CO_2} and Pa_{O_2}. The diaphragm is only little affected by the wakefulness drive *(dashed line)* and is predominantly responding to chemical stimuli *(thick line)*. In contrast, upper airway motoneurons, such as genioglossus, are more affected by the "wakefulness stimulus" coupled to sleep state. MN, Motorneurons.

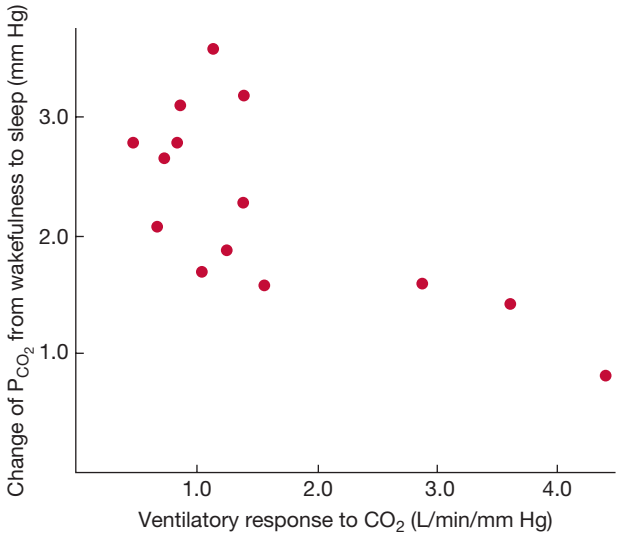

Figure 101-7 Relationship between the increase in Pa_{CO_2} that occurs in normal subjects in going from wakefulness to stages 1 and 2 NREM sleep and the CO_2 ventilatory response in wakefulness. Persons with the lowest ventilatory responses show the largest change in Pa_{CO_2} in going to sleep. *(Adapted with permission from Gothe B, Altose MD, Goldman MD, et al. Effect of quiet sleep on resting and CO_2-stimulated breathing in humans. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(4):724–730.)*

The specific cellular and neurochemical mechanisms for this NREM sleep–related change in the apnea threshold are currently unknown. Conceptually, however, it may be considered within the same category as the so-called wakefulness stimulus for breathing. Brain stem neuronal groups, such as the locus coeruleus and raphe nuclei in which the major transmitters are norepinephrine and serotonin, respectively, decrease their activity with sleep.[32] Since both these transmitters have important excitatory effects at various levels of the central respiratory control system, these neuronal groups likely represent major components of the wakefulness stimulus.

AROUSAL DURING SLEEP

During sleep various sensory stimuli, including auditory and tactile,[33] can lead to a sudden change in sleep state to a lighter stage of sleep or complete wakefulness. Arousal can be detected with abrupt changes in the electroencephalogram.[34] Arousal also results in an increase in heart rate and blood pressure as well as an increase in ventilation,[35] a response that is independent of CO_2[36] and which decreases with age.[37] So-called subcortical or brain stem arousals can arise, including in patients with obstructive sleep apnea,[38] that is, when there is an abrupt change in cardiopulmonary variables but no change in the electroencephalogram. As would be anticipated from the discussion of the wakefulness stimulus, arousals produce much more marked increases in activity of the upper airway muscles than in the diaphragm,[39] but it is also critical to appreciate that an arousal response is akin to accentuated wakefulness and therefore can produce an overshoot.

Respiratory stimuli can also lead to arousal during sleep.[33,38] Such stimuli include airway occlusion, increased upper airway resistance, hypoxia, and hypercapnia.[33] Isocapnic hypoxia is, however, a poor stimulus to arousal. Subjects can remain asleep without interruption even with Sa_{O_2} values as low as 70%.[38] It appears that the major respiratory stimulus to arousal is the degree of respiratory effort.[38] Arousal occurs at a relatively constant increased respiratory neural output, that is, respiratory effort that is independent of the causes of this increased effort.[33,38]

PERIODICITIES OF VENTILATION IN LIGHT NREM SLEEP

Periodic (oscillatory) ventilation is more likely to occur during light NREM sleep (stages N1 and N2) than in slow-wave sleep (stage N3).[40–42] This is highly relevant to the problem of obstructive sleep apnea[42] (see further, Chapter 99); most apneas occur in stages N1 and N2 sleep.[42] If a subject with sleep apnea is able to enter stage N3 NREM sleep, regular ventilation resumes and apneas are less likely to occur.[42] Oscillatory ventilation is also typically observed during hypoxia, as in lung disease or at high altitude, and in certain cardiovascular diseases.[43]

Ventilation may be periodic because of particular dynamic properties of the chemical feedback system that controls respiration.[41,44,45] As in any feedback system, the critical determinants of this unstable (oscillatory) behavior are the overall response (gain) of the control system and the time delay (phase lag) between the plant and the controller. For the respiratory system, the plant is the gas exchange apparatus in the lung; the controllers are the chemoreceptors, peripheral and central; and the controlled variables are the arterial blood-gas tensions, Pa_{CO_2} and Pa_{O_2}. Thus, in the case of the respiratory control system, this time delay is that between the lung and the sensors, the peripheral and central chemoreceptors.[44]

The importance of this delay is illustrated in Figure 101-8 for a situation in which a disturbance to the ventilatory control system leads to a change in Pa_{CO_2}. If there is no delay, the control system responds immediately to this perturbation by adjusting ventilation to correct the change in Pa_{CO_2} (Fig. 101-8A). In contrast, if there is a delay in the feedback loop, the controller may act to sustain the cyclical disturbance (Fig. 101-8B); this is because during the time it takes the altered Pa_{CO_2} level to reach the sensor, the controller may make an inappropriate correction. For example, when the Pa_{CO_2} in the blood leaving the lung is low, the controller should respond by reducing ventilation, returning the Pa_{CO_2} to the regulated value. If, however, the delay is such that by the time the low Pa_{CO_2} signal reaches the sensor, the Pa_{CO_2} of the blood leaving the lung is already higher (e.g., due to the presence of an external perturbation or already existing oscillations, as in Fig. 101-8B), the controller will act incorrectly to reduce ventilation and further increase the Pa_{CO_2}. Such a situation promotes self-sustaining periodic ventilation. Thus, the time delay determines not only whether periodic ventilation will or will not occur, but also the period of this oscillation.

Periodic ventilation would not occur if the control system failed to respond, or responded weakly, to these perturbations. Thus, the gain of the response of the system is as important as the magnitude of the delay in determining whether unstable operation of the ventilatory control system will occur. This gain is usually defined as the product of the response of the controller (the change in ventilation per unit change in Pa_{CO_2}, i.e., CO_2 sensitivity) and the gain of the plant (the change in Pa_{CO_2} per unit change in ventilation, i.e., the plant gain). Overall loop gain is the product of these.[44]

Periodic breathing occurs in clinical situations, particularly in hypoxic subjects (e.g., patients with lung disease) and normal sojourners at high altitude.[46] Hypoxia increases the gain of the response of the controller, making the system more unstable. The period of the oscillations in ventilation induced by hypoxia is on the order of 20 seconds, that is, much shorter than those typically seen in patients with obstructive sleep apnea or in Cheyne–Stokes respiration. Abnormally increased circulatory time, which prolongs the delay between the lung and chemoreceptors, can also produce an unstable system and ventilatory periodicities. This mechanism is likely to be responsible, at least in part, for the ventilatory oscillations that occur during sleep in patients with severe congestive heart failure (Cheyne–Stokes respiration).[47,48]

In addition to these mechanisms that are related to instability of the chemical control system for ventilation, state instability can produce sleep-related oscillations in ventilation[12,14,25–28,44]; state

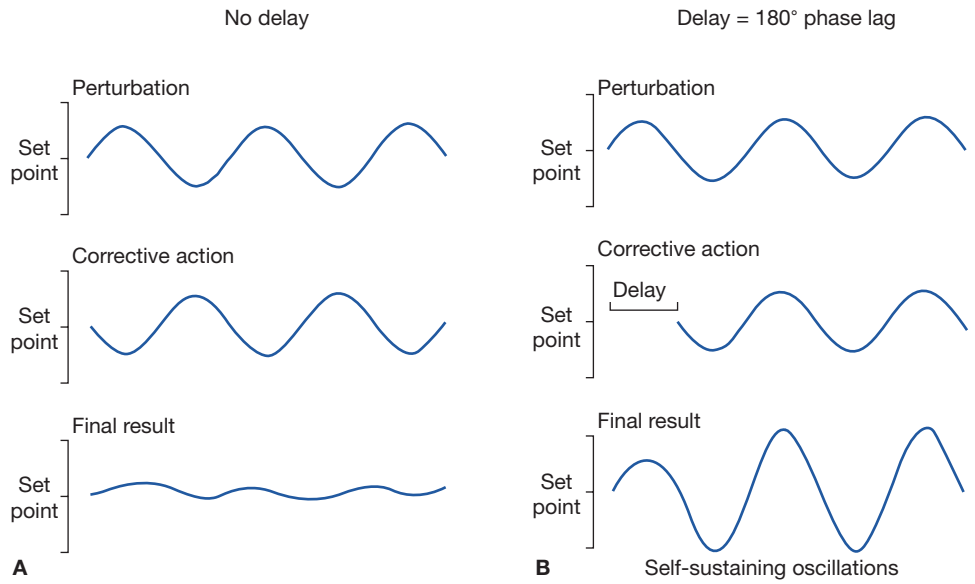

Figure 101-8 Implications for a control system with a delay between the plant and the control system. The left panel (**A**) shows how a control system will respond to a sinusoidal perturbation when there is no delay. The perturbation is essentially neutralized. The right panel (**B**) shows how a control system acts if it has a delay that results in the corrective action being 180 degrees out of phase with the perturbation. In this case, the controller's action acts to sustain, and not to neutralize, the original sinusoidal perturbation.

instability is defined as periodic changes in the stages of sleep that cause discrete and periodic changes in the level of the wakefulness stimulus to ventilation. As discussed in the preceding section, at the onset of sleep, there are decreases in ventilation[11,13,29] and increases in upper airway resistance[15] that cause an increase in Pa_{CO_2}; the increase in Pa_{CO_2} may, in turn, directly or indirectly interfere with the normal progression of the sleep cycle. For example, an abrupt change in sleep state may occur as a result of airflow limitation and increased respiratory effort, leading to an awakening to a lighter stage of sleep, that is, to an arousal. Upon arousal, ventilation increases, upper airway resistance decreases, and Pa_{CO_2} drops. The subject returns to sleep, and the whole cycle may repeat itself. This state instability is more likely to arise if the ventilatory response to CO_2 is low, since the Pa_{CO_2} increases more at sleep onset and is more apt to drive the level of respiratory effort to a point at which an arousal from sleep occurs. The period of ventilatory oscillation caused by this mechanism is longer than that seen with chemical instability, that is, around 60 to 90 seconds. This mechanism likely predominates in producing the sleep apnea syndrome and periodic breathing in patients with low ventilatory responses to CO_2 (e.g., patients with hypothyroidism, in whom central and obstructive apneas are common).[40,44]

CIRCADIAN CLOCKS IN THE CARDIOVASCULAR SYSTEM AND LUNG

While much is known about the physiology of cardiopulmonary changes during sleep, recently attention has turned to changes in molecular mechanisms. In the late 1990s the discovery of the molecular components that produce circadian clocks led to the study of expression of circadian clock genes in many different organs.[49] Surprisingly, functioning clocks were not only found where they were expected, that is, in the suprachiasmatic nucleus of the hypothalamus – the site of the master circadian clock – but also in many organs. In particular, functioning clocks have been demonstrated in the lung and cardiovascular system.[50,51] In cardiac myocytes and vascular smooth muscle cells, the clocks are intrinsic to these cells since they maintain a circadian rhythm even when the cells are isolated and in culture. This work has been described elsewhere.[51] Many other cell types have not been as extensively tested to date, but peripheral clocks including those in the liver, kidney, heart, and adipose tissue[52,53] have been described. These clocks likely alter the temporal pattern of expression of genes in the relevant organs. Microarray studies indicate that about 10% to 15% of all genes have a diurnal variation in their expression levels. In heart, there is, for example, diurnal variation of genes promoting fatty acid oxidation. Expression of these genes in rats peaks during the dark phase, that is, their active period.[51] Expression of genes for K+ channels also exhibits diurnal variation in the heart and likely contributes to the altered excitability of the cardiac myocyte across the day.[50]

These observations indicate that at a fundamental molecular level the heart and lung at night are not the same as during the day. Emerging data indicate that molecular processes in peripheral organs will also be affected by sleep and sleep deprivation,[54] and this is an area that is likely to be a fruitful area of inquiry. The molecular basis of circadian rhythms and molecular functions of sleep are discussed in more detail in Chapter 12.

CONCLUSION

In conclusion, there are major changes in cardiopulmonary function during sleep as compared with wakefulness. These changes are sleep-state specific, being different between NREM and REM sleep. The changes have important pathogenetic significance. This significance includes the following: the timing across the day of acute cardiovascular events; the periodic breathing that occurs during sleep at high altitude; the neuronal changes that lead to obstructive apnea during sleep; and the pathogenesis of Cheyne–Stokes respiration. Currently, a new window on changes in the cardiopulmonary system with sleep is opening, that is, changes at the molecular level. This is likely to lead to new insights that will also have implications for the pathogenesis of disease and treatment.

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CHAPTER 102

Differential Diagnosis and Evaluation of Sleepiness

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Excessive daytime sleepiness (EDS) is a common problem affecting large segments of the general population. Although estimates depend on how sleepiness is defined (i.e., sleeping too much vs. falling asleep in the daytime), about 16% of adults experience sleepiness that affects their daytime function, and there is increasing evidence that sleepiness plays a part in both industrial and road traffic accidents. The National Highway Traffic Safety Administration estimates that more than 100,000 automotive crashes per year are fatigue related. These sleepiness-related accidents contribute to 40,000 injuries and 1550 deaths per year.[1] Over the past two decades, research has provided increased understanding of obstructive sleep apnea (OSA), among other sleep disorders.[2]

The current prevalence estimates of moderate to severe sleep-disordered breathing with an apnea–hypopnea index, measured as events/h, ≥15 are thought to be higher, with contributing factors such as obesity increasing the prevalence. These estimated prevalence rates represent substantial increases over the last 20 years (relative increases of between 14% and 55% depending on the subgroup). Specifically, the prevalence is 10% (95% confidence interval [CI]: 7, 12) among 30- to 49-year-old men; 17% (95% CI: 15, 21) among 50- to 70-year-old men; 3% (95% CI: 2, 4) among 30- to 49-year-old women; and 9% (95% CI: 7, 11) among 50- to 70-year-old women.[3]

There is increasing awareness of sleep disorders by the general public and respiratory physicians, by necessity, are dealing more and more with sleep apnea and other sleep disorders. In recognition of the need for training pulmonary physicians in sleep disorders, in 1994 the American Thoracic Society (ATS) published recommendations for training in sleep medicine that has grown to include not only the ATS, but also the AASM, ACCP, AASM,[4] and ABIM.[5] There is also significant impact on future training in medicine and surgery based on the sleepiness of the learner. Restriction of duty hours has been reviewed in many countries including ACGME in the US and the RCPSC in Canada. The IOM Report Sleep Supervision and Safety reviewed the potential impact of sleep in training and recommendations made in 2008 were implemented by ACGME including:

The new ACGME standards require residency programs to:

1. Tailor supervision standards for different levels of training, particularly greater supervision for first-year residents.
2. Ensure competence in structured handover processes.
3. Incorporate clinical quality improvement and patient safety into resident learning.
4. Provide safe transportation and/or sleeping facilities for fatigued residents.
5. Adjust workload according to patient severity and resident training.
6. Improve oversight of compliance with duty hour limits.

Specific duty hour recommendations from the IOM include:

1. The maximum number of work hours remains at 80 hours per week, averaged over 4 weeks;
2. Moonlighting, now both internal and external, is counted against the 80-hour weekly limit; and
3. Duty periods are limited to 16 hours (although only for first-year residents by ACGME).

In Canada, the author (MS) was a member of the Medical Education Working Group and contributing author of Fatigue, Risk, Excellence: Towards a Pan-Canadian Consensus on Resident Duty Hours (June 2013). The recommendations from this report suggest each training program is unique and therefore deserves unique solutions for managing sleep schedules to optimize learning. The National Steering Committee published five recommendations for Canadian training programs:

1. Recognizing that there are many factors that contribute to resident fatigue, a comprehensive approach to minimize fatigue and fatigue-related risks should be developed and implemented in residency training in all jurisdictions in Canada.

2. Educational approaches should be redesigned to leverage innovations and new approaches, to ensure appropriate training and acquisition of competencies in an era of increasing resident duty hour regulations.
3. Accreditation standards must be adapted to support planned modifications of the content and duration of resident duty, through the enforcement of fatigue risk management activities.
4. An inventory of alternate models of scheduling and after-hours care provision should be created and disseminated to provide alternatives and benchmarks of scheduling and service delivery.
5. An independent, pan-Canadian consortium devoted to the evaluation of resident duty hours in Canada should be created.

These organizations are looking to guidance from physicians with sleep training to help mitigate sleepiness to optimize learning. There are many additional public health issues including patient safety that require physicians to understand sleepiness.[6] It is clear, therefore, that pulmonary physicians need to better understand and be able to treat EDS, regardless of the etiology.

THE PHENOMENON OF SLEEPINESS

Sleepiness is both a subjective and an objective phenomenon, a constellation of sensations and a physiological state with stereotypical behaviors. As such, it is sometimes difficult to define, and its measurement (see Section on Quantifying Sleepiness) depends on the circumstances. Sleepiness may be expressed as feeling sleepy, fatigued, or tired; sleeping too much; or fighting to maintain alertness. Sleepiness can be reflected by any or all of the following: heaviness of the eyelids, mild burning or itching of the eyes, difficulty keeping the eyes open, heaviness in the arms or legs, reluctance to move, loss of initiative, loss of interest in surroundings, and difficulty with concentration or memory. These sensations are accompanied by behavioral changes such as rubbing the eyes, yawning and stretching, and nodding the head, and by generally reduced motor functions such as speech, facial expression, and body movement. Literature shows that sleep-deprived healthy individuals demonstrate attenuated facial expressions to stimuli.[7]

Sleepiness may also be considered a physiological state like hunger or thirst. Just as hunger and thirst are physiological states that occur with fasting and are satisfied by eating and drinking, sleepiness in individuals without a specific sleep disorder is produced by sleep restriction or deprivation and is reversed or satisfied by sleep. However, a difference between sleep and other physiological factors is that food may satisfy hunger but the sleep quality along with quantity is necessary to satiate sleep loss. Sleep quality is impaired in individuals with specific sleep disorders such as sleep apnea. The factors that produce and influence sleepiness are detailed below; they include such obvious factors as time since last asleep, previous amount of sleep, continuity of sleep, and normal 24-hour circadian influences. Environmental stimuli influence this state and can determine, up to a point, whether or not this sleepy tendency will be manifested. For example, heavy meals, warm rooms, boring lectures, or monotonous tasks are usually considered soporific activities or situations. In these situations, a person might feel sleepy and, might fall asleep. Yet the environmental factors themselves do not cause the sleepiness; they only allow it to be expressed. Equally, the same degree of physiological sleep tendency might go unnoticed when environmental stimulation occurs in the form of a life-threatening situation. In other words, the degree to which sleepiness is experienced or evident in behavior is determined by the underlying physiological sleep tendency (or the need for sleep) and environmental factors, which interact to manifest the sleep tendency or sleep propensity.[8]

While it is accepted that sleepiness is a physiological state, the physiological substrates of this state have not been identified. Neurotransmitters such as serotonin, acetylcholine, histamine, and the catecholamines have been implicated in the sleep/wake mechanism along with a variety of other sleep-inducing substances, including adenosine through its inhibition of wakefulness-promoting neurons. While much research is ongoing, the understanding of the neurochemicals responsible for sleep, sleepiness, and loss of alertness are still far from clear.[9–13]

QUANTIFYING SLEEPINESS

The sensation of sleepiness is often difficult to quantify, as are other subjective symptoms, such as pain or shortness of breath. All of these subjective sensations may mean different things to different people, and are modified by factors including motivation, external stimulation, and competing needs. What constitutes extreme sleepiness for one person may be only mild sleepiness for another and depends on the situation in which it occurs. An approach is outlined in Table 102-1. Sleepiness has different dimensions with both feelings of perceived sleepiness as well as self-estimates of sleepy behavior, which are different in passive versus active situations. The notion of a sleepiness trait, a composite of sleep need and sleepability, which is the ability to transition into sleep.[14]

Other individual difference factors have been proposed to explain individual dissimilarities in sleepiness.[8] Sleep drive is an inherited trait.[15]

SUBJECTIVE MEASURES OF SLEEPINESS

Subjective reports may be used to quantify sleepiness, but statements such as "I feel sleepy" and "I feel very sleepy" often do not distinguish between feelings caused by a high physiological sleep tendency and those resulting from muscular fatigue, depressed mood, or a general lack of energy. Thus, several subjective sleepiness scales have been developed. The Stanford Sleepiness Scale (SSS), the first to receive widespread use, is a seven-point self-rating scale ranging from 1 (alert, wide awake) to 7 (almost in reverie, sleep onset soon).[16] It is brief, simple to use and measures current degree of sleepiness. It has been shown to correlate with the performance of mental tasks and demonstrate changes in sleepiness with sleep loss. However, there are no normative data and results often depend on the duration of prior sleepiness. For example, unlike normal persons who are experimentally sleep deprived, patients with more chronic sleep deprivation (i.e., sleep apnea) cannot be accurately tested with the SSS. Some patients who have an obvious overwhelming physiological sleep tendency may claim to be only mildly sleepy, yet fall asleep before your eyes. This was first observed in the early 1970s, and was a stimulus

TABLE 102-1 An Approach to Sleepiness

I.	The Phenomenon of Sleepiness
II.	Quantifying Sleepiness
	Subjective measures of sleepiness
	Objective measures of sleepiness
	Performance and vigilance tests
III.	Factors Affecting Sleepiness
	Sleep quantity
	Sleep quality
	Circadian rhythms
	Medications
IV	Prevalence of Excessive Daytime Sleepiness
V.	Evaluating the Sleepy Patient
	Approach and differential diagnosis

for Stanford investigator group to develop more objective measures of sleepiness.[16] Studies have shown that with continued increases in lapses in performance over several days of sleep restriction but the self-reported sleepiness does not continue to get worse.[17]

It is clear that over a period of months or years, many sleep apnea patients lose their frame of reference with regard to normal alertness and cannot distinguish major changes in sleepiness. Thus, the subjective report of sleepiness (using the SSS) by people who are chronically and severely sleep deprived is not reliable.[16]

The Karolinska Sleepiness Scale (KSS) is a nine-point scale ranging from 1 (very alert) to 9 (very sleepy, fighting sleep, making an effort to keep awake), with verbal descriptions of every second point.[18] Like the SSS,[16] the KSS requires the subject to integrate and translate a number of sensations to a continuum that is fairly abstract despite the verbal description. Ratings obtained with these scales may be affected by the situation in which the scale is presented (at rest or during performing a task) and how the subject relates his or her perception to that particular time or place. These scales reflect current sleepiness. Nonetheless, both the SSS and KSS show high correlations with performance. The KSS was also found to be strongly related to EEG and electrooculographic signs of sleepiness.[18]

The Epworth Sleepiness Scale (ESS; Table 102-2) was designed to measure sleep propensity in a single, standardized way and is based on questions relating to eight situations, some known to be very soporific.[19] The ESS, in contrary to the KSS and SSS, assesses symptoms of chronic sleep deprivation. The questions are self-administered, and subjects are asked to rate on a 0 to 3 scale how likely they are to doze off in the situation based on their usual habits over recent weeks to months. The ESS tries to overcome the fact that people have different daily routines, some facilitating and others preventing daytime sleep. An ESS of 10 or below is considered normal. Scores above this are considered indicative of excessive sleepiness. ESS scores have shown significant correlations with mean sleep latency in the multiple sleep latency test (MSLT, see further below) and have distinguished groups of patients with disorders of excessive sleepiness such as narcolepsy, OSA, and idiopathic hypersomnolence. The ESS score has been validated against the MSLT in sleep disorder patient population, specifically narcolepsy patients, to show a 95% sensitivity and 73% specificity in comparison to the MSLT.[20] The ESS has high test–retest reliability and a high level of internal reliability in normals and patients with sleep apnea.[21] Further work examining the utility of measuring sleepiness in

TABLE 102-2 Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **would never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g., a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

THANK YOU FOR YOUR COOPERATION

Source: © M.W. Johns 1990–1997. Reprinted from http://epworthsleepinessscale.com/1997-version-ess/.

different situations using the ESS suggests that individual measurements of sleep propensity (i.e., sleepiness) entail three components of variation: a general characteristic of the subject (the average sleep propensity), a general characteristic of the situation in which the sleepiness or sleep propensity is measured (its soporific nature), and a third component that is specific for both subjects and situation.

OBJECTIVE MEASURES OF SLEEPINESS

MSLT[20] has been developed and standardized as an objective, reliable, and reproducible measure of physiological sleep tendency.[20] Performed at intervals throughout the day the MSLT measures the time to sleep onset, as determined by the EEG. This test is based on the assumption that, given the proper surroundings, physiological sleep tendency will be expressed; it has an intuitive appeal in that if one patient is more sleepy than the other, the sleepier patient should fall asleep more quickly. Patients are instrumented to record the EEG, electrooculogram (EOG), and electromyogram (EMG); they are put in a quiet, darkened, temperature-controlled room, and are asked to lie quietly, close their eyes, and try to fall asleep. Naps are scheduled at 2-hour intervals, with 20 minutes allowed for sleep to occur. If an individual initiates sleep, a mean sleep onset latency (SOL) can be measured and can support excessive daytime somnolence or a diagnosis of narcolepsy, as explained below. Thus, the average SOL of the naps represents the result of the MSLT. Both clinical and research protocols exist for conducting the MSLT.[20]

Since sleepiness follows a circadian rhythm (see Section on Circadian Rhythms), one nap is insufficient to document and quantify daytime sleepiness. Accordingly, a minimum of four and a maximum of six naps are recommended. The MSLT is a reliable, reproducible test that has been validated in a number of sleep deprivation experiments in normal subjects and a variety of clinical conditions with patients who have disorders such as narcolepsy and sleep apnea and may be useful for documenting treatment response to the sleep disorder, such as medications in narcolepsy or CPAP in sleep apnea.[20] An important advantage of the MSLT is that patient motivation cannot counteract the effects of previous sleep loss on sleep latency. That is, while most people can be motivated to compensate for reduced performance after sleep deprivation, motivation cannot overcome an increased pressure for sleep, particularly when the patient is in bed in a darkened room.

The Maintenance of Wakefulness Test (MWT) is an alternative to the MSLT. This is a variation on a theme in which subjects sit in a chair in a darkened room and are requested to remain awake for 20 (or 40) minutes. This test was developed on the assumption that the ability to fall asleep and the ability to stay awake are two separate phenomena. The MWT has undergone further tests of validity, but has been criticized for lack of a standardized protocol with 20-, 30-, and 40-minute tests being reported. Recent practice parameters suggest using a 20-minute four-trial protocol opportunities for the patient to initiate a nap.[20] The naps are separated by 2 hours.

This is a relevant question when assessing whether or not a patient can stay awake in a situation of personal or public safety. The physiological ability to fall asleep is measured by any naps initiated during the 20-minute period. Any sleep onset REM (SOREM) is closely observed as it can signify a diagnosis of narcolepsy.

While both MSLT and MWT require observer recognition of EEG changes, quantitative computerized analysis *of EEG* has been proposed as an alternate and perhaps more sensitive objective measure of sleepiness. Increased EEG delta activity with sleep deprivation and decreased alpha activity just before sleep onset are two possible metrics. However, these have yet to be translated into clinically useful tests. The Alpha Attenuation Test (AAT) has been validated in sleep-restricted normals and in patients with narcolepsy and correlates strongly with the MSLT.[20]

Oxford SLEep Resistance Test (OSLER test) was designed as a low-cost alternative designed to reproduce many of the features of the MWT, but without the labor-intensive, continuous technician monitoring of EEG.[22]

In the OSLER tests, subjects respond to a visual stimulus. A light-emitting diode mounted on the wall, which flashes for 1 second every 3 seconds in fixed intervals. If there is no response after seven consecutive stimuli, the subject is deemed to be asleep and the test is ended. The original study compared OSLER sleep latency with MWT latency in 10 OSA patients and 10 control subjects, done on separate days, and showed that OSLER could be validated against the MWT in this patient population. Two other studies involving small numbers of sleep disorders center patients and/or normal subjects before and after sleep deprivation have demonstrated excellent agreement between the two measures and suggest that the OSLER could be an alternative to measuring sleepiness.[23] In a study of heart failure patients receiving adaptive ventilation for treatment of Cheyne–Stokes respiration, improvement in OSLER scores followed improvement in nighttime sleep.[24] Despite these promising results, there are no large-scale studies using the OSLER, and the main limitation of this test is its dependence on patient cooperation.[25,26]

PERFORMANCE AND VIGILANCE TESTS

Measurements of performance after sleep loss reflect daytime sleepiness, since most people report decreased performance after a sleepless night. Previously it was felt that only performance tests that were prolonged and monotonous were sensitive to sleep loss. However, the work of Dinges et al. (using his Psychomotor Vigilance Task [PVT]) demonstrates that if the signal rate is high and the response measure sufficiently sensitive, repetitive tasks of only 10-minutes duration will expose the limits of performance in sleepy persons.[27,28] Performance decrements resulting from sleep deprivation (or sleep disorders such as sleep apnea) can be observed in such a task if results are analyzed over time. This time-on-task or vigilance decrement may be observed as evidence of fatigue even in well-motivated subjects with adequate prior sleep, and it manifests itself as a shallow decline in performance as time-on-task increases. When the subject is sleep deprived, it is impossible to sustain attention long enough to maintain peak performance throughout the entire task and lapses in performance occur. Sleep loss increases the rate of decline in performance. The number of interrupted episodes also contribute to performance decline. The Psychomotor Vigilance Test (PVT) has become the most widely used measure of neurobehavioral performance. It has been validated with the SSS and MSLT. Recent work using this test has demonstrated consistent individual differences in neurobehavioral deficits from sleep loss when repeated in the same subject, which indicate differential trait vulnerability to sleepiness.[29]

While the MSLT and MWT can provide helpful information, they require repeated testing every 2 hours and a whole day of tests. Data published recently suggest that a single administration of objective tests, in particular the PVT, can help assess sleepiness in controlled conditions that may be applied clinically.[30]

Other tests of sustained attention and performance have been developed, many to assess simulated driving performance. Using a divided attention task, where individuals are required to pay attention to more than one aspect of the task, such as a driving task, sleep apnea patients have been shown to perform poorly, and in some cases, equal to or worse than normals impaired by alcohol.[31] Nonetheless sleepiness as measured by MSLT accounts for less than 25% of the variance in tracking performance. Thus, while the effects of sleepiness on performance may occur in a dose-dependent fashion in normals, performance decrements in patients who are sleepy because of an underlying sleep disorder may be accounted for by factors other than sleepiness.

Mitigating subjective "sleepiness" in patients with mild to moderate OSA, untreated with CPAP, has been shown with modafinil. The effect size was clinically important as was the improvement on the driving simulator performance and reaction time.[32]

FACTORS AFFECTING SLEEPINESS

Sleepiness is determined by the quantity of sleep and the quality and type of sleep, interacting with circadian rhythms or drugs that patients may be taking.

SLEEP QUANTITY

The amount of nocturnal sleep has a strong relationship to the degree of daytime sleepiness. Partial or total sleep deprivation is followed by increased daytime sleepiness in normal persons. Furthermore, sleep restriction will become cumulative over time and lead to increasing daytime sleepiness.[28]

The effect of sleep restriction on SOL is shown in Figure 102-1. When the sleep of young adults was reduced by 2 hours a night on consecutive nights, sleepiness (as measured by the MSLT) progressively increased over 7 days. Even as little as 1 hour per night of sleep loss will accumulate over time and lead to daytime sleepiness—a fact generally not appreciated. Each person has a certain biological sleep need, and the specific amount varies from one subject to the next. Regardless of cultural or environmental factors, most adults sleep 7 to 8 hours per day, but the old adage that we must sleep 8 hours each night is not true for everyone. Some people require more than 8 hours, and others less. There may be many contributors to the amount of sleep an individual requires including a genetic contribution. Recent data support a genetic variant (hDEC2-P385R) contributing to individuals who only need a short sleep time.[33] Individual differences in required sleep time is also evident in conjoined twins who show an independence of sleep needs. In the absence of pathology, normal human sleep length varies between 6 and 9 hours, although some people require less. It would be ideal to require a minimum amount of sleep to allow maximum productivity in work and adequate time for social pursuits. Indeed, some investigators believe that Western society predisposes to sleep deprivation.[34] With economic and social constraints – the latter leading to voluntary sleep restriction – the sleep period is the time most encroached on, potentially leading to daytime sleepiness.[35] There has been progressive reduction in sleep duration over many age ranges that is more commonly found in the United States. There are multiple etiologies for this including work intruding into sleep period. Thus, there is a national agenda for 2020 (Healthy People 2020) in the United States to understand the implications and associations of this more comprehensively.[36] Overall, it appears short sleep duration is increasing in prevalence, which may be associated with adverse health outcomes, such as weight gain and associated morbidities of obesity.[37] In addition, the prevalence of short sleep (<6 hours) has increased in individuals who are employed full time.[38]

Voluntary sleep restriction or insufficient sleep causes daytime sleepiness. Among all prominent features differentiating this group of patients with insufficient sleep from those with narcolepsy is the report, obtained from the sleep history, of a disparity between the amount of sleep on weekdays and that on weekends. People with insufficient sleep typically have a much longer sleep period on weekends (by 2 hours or more).

Most patients consider their weekly sleep loss trivial and assume that it is recovered on weekends. However, while recovery from a single experimental sleep restriction occurs in a couple of nights, it is not likely that repeated episodes of sleep deprivation can be compensated for in just one night. A study of a large group of normal subjects without complaints of daytime sleepiness has shown that young subjects (particularly college students) had shorter sleep latencies than did older subjects. Within the group of 120 young subjects, 12 healthy, nonsmoking men aged 21 to 35 years, had a mean sleep latency of less than 6 minutes on MSLT testing, whereas another 12 had an MSLT of greater than 16 minutes.[20] These subjects had baseline testing and then extended their sleep period time from 8 to 10 hours over 6 days. Repeat testing on days 1, 3, and 6 showed stepwise increases in MSLT and performance testing for both subgroups. These data support the notion that chronic voluntary sleep restriction in real life produces objective sleepiness that may or may not be perceived by the subject.

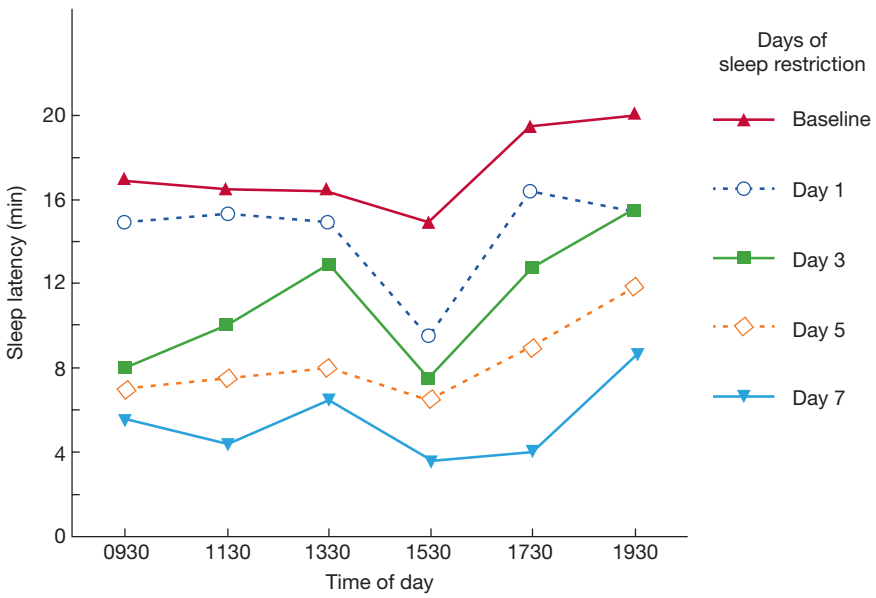

Figure 102-1 Average daily sleep latency test scores for young adults when nighttime sleep was reduced by 2 hours a night for 7 consecutive nights. *(Adapted with permission from Dement WC, Carskadon MA. An essay on sleepiness, in Boldy-Moulinier M (ed). Actualitiés en Médécine Expérimentale, en Hommage au Prof D Passouant. Montpellier, Euromed; 1981.)*

SLEEP QUALITY

Sleep quality is perceived to be abnormal when sleep is decreased or discontinuous. Disrupting sleep continuity – that is, causing arousal from sleep, either experimentally or by sleep disorders – affects the quality of sleep and results in increased physiological sleep tendency. An arousal can be defined as a brief (3–15 seconds) speeding up of the EEG, or as a burst of alpha activity occasionally accompanied by transient increases in skeletal muscle tone.[11,12] These typically do not result in awakening as defined by standard sleep staging criteria or behavioral indicators. Sleep studies can identify various causes of arousal, such as recurrent obstructive apnea, periodic leg movements, or chronic pain, in some but not all cases. A common exception is the patient with chronic obstructive pulmonary disease (COPD) who has frequent arousals from sleep in the absence of obstructive apnea or leg movements.[39] Patients with COPD often experience oxygen desaturation during sleep, and this is a potential stimulus for arousal. Nonetheless, compared with age-matched controls, COPD patients have discontinuous sleep and poor sleep efficiency (defined as percentage of time actually asleep in bed).

Auditory stimuli presented externally to normal subjects during sleep can produce arousal; repetitive presentation of such

stimuli can produce daytime sleepiness. Several studies have shown decreased performance and increased sleepiness the day after repetitive arousal, with the degree of daytime sleepiness related to the frequency of nocturnal sleep disruption. Not surprisingly, the shortest sleep latency occurred after the most fragmented nocturnal sleep. This increased sleepiness will result even if the stimulus is only sufficient to produce EEG signs of arousal, without full wakefulness. The importance of sleep disturbance from environmental noise has been reported by Basner et al.[40] There are both auditory effects such as EEG arousals, impaired daytime alertness from lack of sleep quality and quantity as well as quality of life and nonauditory effects, such as increased catecholamine release and association with cardiovascular disease. Environmental noise exposure, such as from airports and other urban environmental areas, can cause lasting damage resulting in hearing loss. Noise-induced hearing loss and tinnitus may not always be recognized in our society but the effects on the affected individuals' quality of life can be tremendous.[40]

CIRCADIAN RHYTHMS

If sleep latency is measured every 2 hours over a complete 24-hour day, a biphasic pattern of sleep tendency becomes obvious (Fig. 102-2). This demonstrates that there are two peaks and troughs of sleepiness over a 24-hour period. Not surprisingly, the times of increased sleepiness are during the nocturnal hours and during the daytime hours (in the midafternoon between 2 and 4 PM). This circadian rhythm of sleepiness is present in all age groups, although the time of the peak rhythm may vary. The circadian rhythm of sleepiness is similar to other circadian rhythms in that it possesses an endogenous periodicity that can be affected by environmental influences that fine tune or entrain the rhythm. Even in the absence of these environmental cues (i.e., awakening time, alarm clock, degree of light or darkness, food and stimulants, and social contact), rhythms show a persistent periodicity. The circadian rhythm of temperature is extremely stable. Temperatures fall in the late afternoon, are lowest during the middle of the sleep period, and rise before morning awakening. The temperature rhythm synchronizes most closely with sleepiness. Although the amplitude of body temperature and sleep latency rhythms differs considerably, no other biological rhythms correlate so well in time. Circadian rhythm is discussed more extensively in Chapter 12.

Two other examples of the influence of circadian rhythms on sleepiness are obvious. The first is that associated with shift work, and the second is due to transcontinental travel (jet lag). Workers with a normal nocturnal sleep period and a previously stable circadian sleepiness rhythm suddenly will have a trough of sleepiness during the middle of their night work period. They will attempt to stay awake, while the circadian influences will promote sleep.[27,41] Jet lag is similar, in that the body's circadian rhythm is out of synchrony with the destination clock time. As a result, performance may suffer.

MEDICATIONS

Drug effects on sleep can be significant and can either promote sleep and sleepiness or increase wakefulness and alertness. When assessing subjective or objective sleepiness, it is important to know whether the patient is taking a medication that may affect the degree of sleepiness, that is, sleepiness is a side effect of this medication.

Not surprisingly, sedative drugs increase sleepiness. Benzodiazepine hypnotics have been used to help people get to sleep at night however nonbenzodiazepine hypnotics are also used. Many objective studies confirm the ability of hypnotics to shorten sleep latency at bedtime through $GABA_A$ receptor stimulation. When given during the day, they will promote sleep. However, the daytime carryover effect of nocturnal sedation is not always recognized. This effect occurs most commonly with long-acting benzodiazepines, but it may occur with other medications as well. Recently, warnings have been issued from the FDA about potential sleepiness the morning after taking these medications, especially in women, and have recommended reduction in zolpidem dosages to half to increase patient safety. Second-generation antiepileptics (i.e., gabapentin, pregabalin, vigabatrin) also act as GABA agonists without interacting with the $GABA_A$ or $GABA_B$ receptors. Alcohol consistently shortens sleep onset and produces sedation, whether given at night or during the day. It, however, also alters sleep architecture by suppressing REM sleep and contributing to sleep fragmentation through the latter portions of the night.[42]

Drugs that produce sleepiness include antihistamines, which are used in allergy and pulmonary practice. Many of the early H_1 antihistamines, such as diphenhydramine and chlorpheniramine, have been shown to reduce the MSLT. Some newer antihistamines, such as terfenadine and astemizole, do not produce objective sleepiness. The more lipid-soluble drugs (i.e., diphenhydramine and chlorpheniramine) penetrate the central nervous system more easily and therefore are more likely than less lipid-soluble drugs to produce sedation. Other medications with high lipid solubility have been reported to produce daytime sedation; the most common of these are the beta-blocker drugs. There are no controlled, objective studies of sleep latency with this type of drug, and sleepiness from these medications is based on reports of side effects or subjective questionnaires, such as Pittsburg Sleep Quality Index (PSQI).[43]

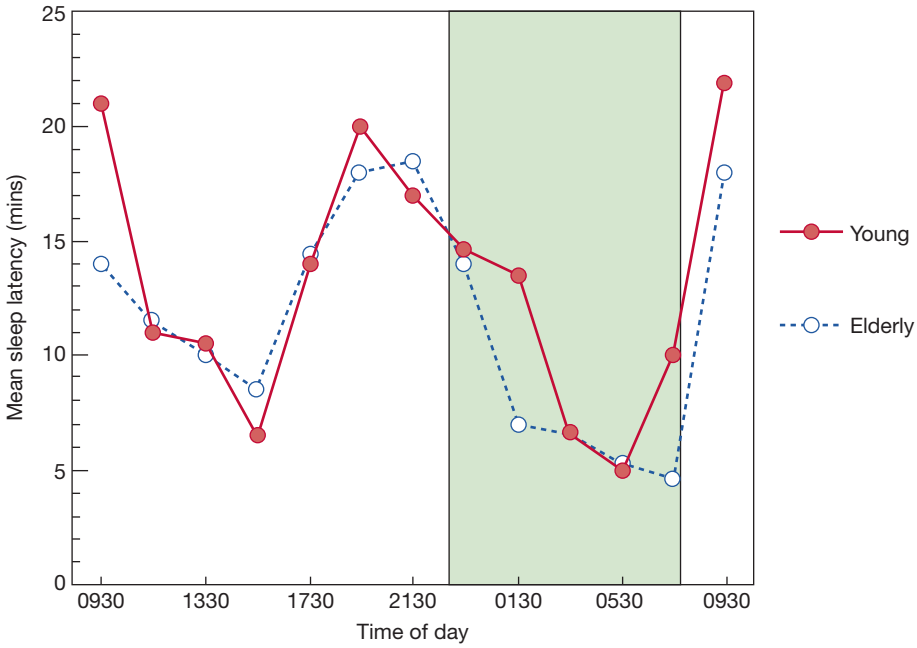

Figure 102-2 Sleep latency (mean) as a function of time of day for young subjects (*filled circles*) and elderly subjects (*open circles*). *Stippled area* denotes nighttime sleep period. *(Adapted with permission from Richardson GS, Carskadon MA, Orav EJ, et al. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep. 1982;5(Suppl 2):S82–S94.)*

The effect of a particular drug in producing sleepiness also depends on the background level of sleepiness or alertness. When ethanol or caffeine is given to normal-sleeping young men in the morning, one might expect ethanol to produce daytime sleepiness and caffeine to increase sleep latency during the day. Subjects are consistently sleepier after ethanol than after caffeine ingestion, but fully rested subjects (those having spent 11 hours in bed) do not show sleepiness after taking ethanol. In other words, the sedative effects of drugs such as alcohol can be enhanced by increased background sleepiness. Thus, a driver who is sleepy to start with may be as vulnerable after just one or two drinks as a previously alert driver who has become legally intoxicated.[42]

Drugs that increase wakefulness or alertness include stimulants such as amphetamine, methylphenidate, modafinil, and armodafinil. These are most often used in the treatment of narcolepsy but may be used to stay awake for long periods of time. Caffeine, probably the most widely used stimulant, can reduce daytime sleepiness and transiently increase alertness. Excessive caffeine intake also paradoxically may cause a degree of daytime sleepiness. This occurs when caffeine levels persist into nocturnal hours and promote difficulties with sleep onset and increased awakenings during sleep.

In patients with narcolepsy, another agent, sodium oxybate (Xyrem) is used to treat EDS and cataplexy through action of $GABA_B$ and gamma-hydroxybutyrate (GHB) receptors.[44] While its mechanism of action is not completely clear, it has been shown to dramatically increase the amount and duration of slow-wave sleep in patients. While it is only given at night, due to its rapid onset of sedation, interestingly, the medication promotes alertness through the day shown in randomized trials.[45]

PREVALENCE OF EXCESSIVE DAYTIME SLEEPINESS

Prevalence rates for sleepiness depend greatly on the type of questions addressing sleepiness. Are you sleeping too much versus are you falling asleep during the daytime versus does your sense of sleepiness impair your daytime activities all result in widely different prevalence rates. Also men tend to report sleepy behavior whereas women report feelings of EDS, again contributing to variable prevalence. Prevalence of sleepiness also varies with the population examined.

There are many socioeconomic and demographic factors that may contribute to sleep disorders or poor sleep quality or quantity in the population. Specific associations with long SOL include being female, having black/African American heritage, lower education, lack of private health insurance, as well as food insecurity. The demographics were most associated, not only with prolonged SOL but with nonrestorative sleep as well as sleep maintenance difficulties, including early morning awakenings. EDS occurred more frequently in female gender and in divorced individuals.[46]

The Wisconsin Sleep Cohort study[47] was the first to formally determine the prevalence of sleepiness as a function of sleep apnea. This landmark study demonstrated that at least 2% of middle-aged women and 4% of middle-aged men had OSA and symptoms of EDS. More recent literature suggests 14% to 55% of the population has Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS).[3] While there may have been other causes for the daytime sleepiness besides OSA, it is clear that sleep apnea is responsible for a great deal of the daytime sleepiness in North America.

EVALUATING THE SLEEPY PATIENT

Keeping in mind the factors that determine daytime sleepiness, the sleep history can be individualized and can be very helpful in narrowing the differential diagnosis (Table 102-3). One should always question the patient about his or her nocturnal sleep, looking specifically at sleep onset time, sleep period time, number of awakenings, and time of rising in the morning. One should also ask about when the change in sleep occurred as well as questions about sleep hygiene (i.e., when awake, reading book in dim light vs. playing games on an electronic device with bright light). Sleep onset phenomena such as sleep paralysis and hypnagogic hallucinations often suggest a diagnosis of narcolepsy although these sometimes occur in apneics who are severely sleep deprived.[48] A history of loud snoring or stopping breathing during sleep is suggestive of sleep apnea hypopnea syndrome, particularly if the snoring is "cyclical" rather than continuous, with periods of loud snoring or snorting alternating with quiet intervals. Since insufficient sleep may be the cause of sleepiness, it is important to ask if there is any difference in the amount of sleep required during the week compared with that on weekends. Equally important is whether the patient has any changes in subjective sleepiness on weekends or holidays compared with weekdays.

TABLE 102-3 Common Causes of Persistent Daytime Sleepiness

Obstructive sleep apnea and other sleep-disordered breathing conditions (e.g., neuromuscular weakness with nocturnal respiratory failure)
Narcolepsy/cataplexy syndrome
Sleep-related movement disorders (e.g., periodic limb movement disorder, bruxism, etc.)
Depression
Postviral fatigue
Head injury
Metabolic, toxic, and drug-induced hypersomnolence
Idiopathic hypersomnolence
Insufficient sleep
Circadian rhythm sleep disorders

In some instances, more information will be obtained from the spouse (or bed partner) or from a sleep/wake diary, since not all people are aware of the severity of their sleepiness. Moreover, patients may not understand the importance of good sleep hygiene; the diary can serve as a reminder for patients to be diligent about it.

In estimating the degree of daytime sleepiness, it is useful to ask when and during what activities the patient experiences sleepiness. Is the patient sleepy on awakening in the morning, or is it only by midday? Does the patient fall asleep while doing things or only when inactive? Driving to and from work are important times when sleepiness may become obvious, particularly while the person is waiting at a railroad crossing or stoplight. Episodes of automatic behavior, related to "microsleeps," often occur while one is driving. Do patients nap during the day, and if so, is the nap refreshing? Many patients with sleep apnea are still sleepy or foggy after a nap, whereas patients with narcolepsy most often feel refreshed immediately upon awakening.[26,29,49,50]

Since drugs can have a profound effect on sleep and sleepiness, a careful drug history is mandatory in the assessment of sleepiness. The clinician must remember to include queries not only about drugs that specifically affect sleep (hypnotics, sedatives, or other psychoactive medications) but also about substances that may not be considered to have any effect on sleep or waking. In particular, alcohol is a known precipitant or exaggerating factor for sleep apnea; patients will often report that they feel much worse the day after ingesting alcohol despite having had a nonintoxicating dose.[51]

It is important to remember that CNS pathology can independently contribute to EDS. While narcolepsy or idiopathic hypersomnia fall within the realm of sleep medicine, in other neurological

diseases (e.g., Parkinson disease) or neuromuscular diseases (e.g., myotonic dystrophy), EDS can be a presenting symptom that the pulmonologist should keep in the differential diagnosis. Apart from a general physical examination, one should pay particular attention to the size of the jaw, face, and upper airway, looking for obvious skeletal abnormalities—particularly retrognathia or micrognathia. One then carefully examines the upper airway, looking for nasal obstructions such as a deviated nasal septum or inflammatory allergic polyps; then, one examines the oropharynx, looking at the size of the tongue, the position of the soft palate, and the size of the uvula; finally one examines the larynx to rule out upper airway tumors or other obstructing lesions. While the typical sleep apnea patient will be the obese plethoric man with a thick neck, it is important to remember that examination of the awake, upright airway may bear no relationship to what happens when the patient is supine and asleep. Thus, the diagnosis of sleep apnea usually is confirmed by nocturnal polysomnography or a more limited home study (see further, Chapter 99).

The patient who has a history of snoring and daytime sleepiness but has no flow limitation, or sleep apnea or hypopnea during his or her nocturnal study must undergo an objective measure of daytime sleepiness, because some patients who claim to have substantial daytime somnolence are simply looking for compensation.[52] Also, some OSA patients will remain sleepy despite adequate treatment of their apnea and an additional sleep disorder may coexist. There may also be residual sleepiness in patients with mild to moderate OSA.[32] Again, daytime quantification of sleepiness will be necessary. The only disadvantage of the MSLT is that it is an inefficient test. Compared with objective measurements of airflow (i.e., an FEV_1), which take seconds to perform and interpret, the MSLT takes almost a whole day and provides only one piece of information. Until better tests are developed and validated, however, the MSLT will continue as a standard, albeit time-inefficient, objective measure of daytime sleepiness.

CONCLUSION

Sleep is important in health and wellness. Excessive sleepiness is a very common symptom. In patients with respiratory disease, a sleep disorder may be the presenting disease or may coexist with other disorders. Given the increasing prevalence of sleep disorders and their impact on health, it is imperative that there be a sound understanding of sleep medicine by practicing respirologists who are able to develop a relevant differential diagnosis for patients with excessive sleepiness and a management plan for their patients.

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CHAPTER 103

Perioperative Respiratory Considerations in the Surgical Patient

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Postoperative pulmonary complications constitute a significant cause of morbidity and mortality following surgery. Managing patients at risk for postoperative pulmonary problems requires an understanding of the predictable changes in pulmonary physiology that occur with surgery and anesthesia, as well as knowledge of factors associated with development of postsurgical respiratory compromise. Despite the availability of several screening tests, a careful history and physical examination continue to be the cornerstone of preoperative pulmonary evaluation. Although a number of measures can be employed before and after surgery to minimize the risk of respiratory complications, close patient monitoring and early detection are essential.

This chapter focuses initially on changes in pulmonary function with surgery. Pulmonary risk factors before, during, and after surgery are reviewed prior to discussion of preoperative evaluation of the patient for surgery, including lung resectional surgery. Finally, recommendations are made regarding preoperative preparation and postoperative prophylactic measures. A more detailed discussion of the perioperative care of the patient undergoing resectional lung surgery is provided in Chapter 105 and development of acute respiratory failure in the surgical patient is addressed in Chapter 104.

CHANGES IN PULMONARY FUNCTION WITH SURGERY

Many postoperative respiratory complications relate to exaggerations of the expected postoperative changes in pulmonary function that occur as a result of the surgery itself, anesthesia, or various pharmacologic interventions.[1,2] Hence, an appreciation of normal postoperative pulmonary physiology is useful in understanding a number of pulmonary problems seen following surgery. Five principal categories of change in pulmonary function with surgery may be considered: (1) lung volumes, (2) diaphragm function, (3) gas exchange, (4) control of breathing, and (5) lung defense mechanisms (Table 103-1).

TABLE 103-1 Changes in Pulmonary Function with Surgery

Reduction in lung volumes
Diaphragm dysfunction
Impaired gas exchange
Respiratory depression due to residual effects of anesthesia or postoperative narcotics
Impaired cough and mucociliary clearance

Source: Reproduced with permission from Goldmann DR, Brown FH, Guarnieri DM (eds). Perioperative Medicine. New York, McGraw-Hill; 1994.

LUNG VOLUMES

The pattern of pulmonary function abnormalities following thoracic and abdominal surgery is restrictive, characterized by moderate-to-severe reductions in vital capacity (VC) and smaller, but more important, reductions in functional residual capacity (FRC). The degree of impairment is similar after upper abdominal and thoracic surgery[3–5] and is less for laparoscopic procedures compared with open abdominal procedures.[6] Smaller changes in VC and FRC are noted with lower abdominal surgery; superficial or extremity surgery is usually not associated with any significant or persistent changes in lung volumes.[7,8] During the first 24 hours following upper abdominal surgery, VC and FRC may be reduced by more than 70% and 50%, respectively, and they may remain depressed for more than a week.[7–9] Consequently, it is not surprising that pulmonary complications are seen more often with thoracic and upper abdominal procedures than with surgery involving the lower abdomen or extremities (see discussion of intraoperative risk factors, below).

Reductions in other lung volumes, including total lung capacity (TLC), inspiratory capacity (IC), expiratory reserve volume (ERV), and residual volume (RV) have been noted. While the forced expiratory volume in 1 second (FEV_1) is decreased, the ratio of FEV_1 to the forced vital capacity (FEV_1/FVC%) remains unchanged, indicating that major airway obstruction does not occur.[4]

Since patients undergoing superficial or extremity surgery do not experience major changes in lung volumes, residual or carryover effects from general anesthesia do not appear to play a primary role in this regard. In fact, studies have shown that in many patients, FRC in the early postoperative period is unchanged from baseline. An alternative proposal for the reduction in FRC is that postsurgical pain and associated muscle splinting impair lung mechanics. However, while processes other than pain may be operative, based on the finding that effective pain control using epidural analgesia or intercostal nerve block fails to fully restore VC or FRC to preoperative levels,[10–12] this notion has been challenged.[13] The established consensus is that diaphragm dysfunction is an important contributing factor (see below).[2]

The postoperative reduction in FRC is of major physiologic significance. Its importance can be understood when the phenomenon of airway closure and the concept of closing capacity (CC) are considered.[4]

FRC is the lung volume at the end of a normal tidal expiration. CC is the lung volume at which small airways in the lung bases begin to close during expiration because of a reduction in airway radial traction. The relationship between the two is a key factor in the development of postoperative changes in lung function (Fig. 130-1). In a normal lung, FRC is always greater than CC, and the airways remain open throughout a tidal breath. However, when CC is greater than FRC, lung volume fails to increase sufficiently during tidal breathing to open all the airways and, consequently, some alveolar units remain closed during a breath. Such regions constitute areas of atelectasis. An intermediate state exists when CC exceeds lung volume for part of the time during each tidal breath. Under these circumstances, the airways open for only a portion of the respiratory cycle, creating areas of low ventilation relative to perfusion. In summary, any circumstance that reduces FRC below CC or that increases CC above FRC produces regions of reduced ventilation and atelectasis (Table 103-2).

DIAPHRAGM FUNCTION

Diaphragm dysfunction has been recognized as an important factor contributing to the postoperative reduction in lung volumes.[6,11–16] In patients undergoing cholecystectomy, the diaphragm's contribution

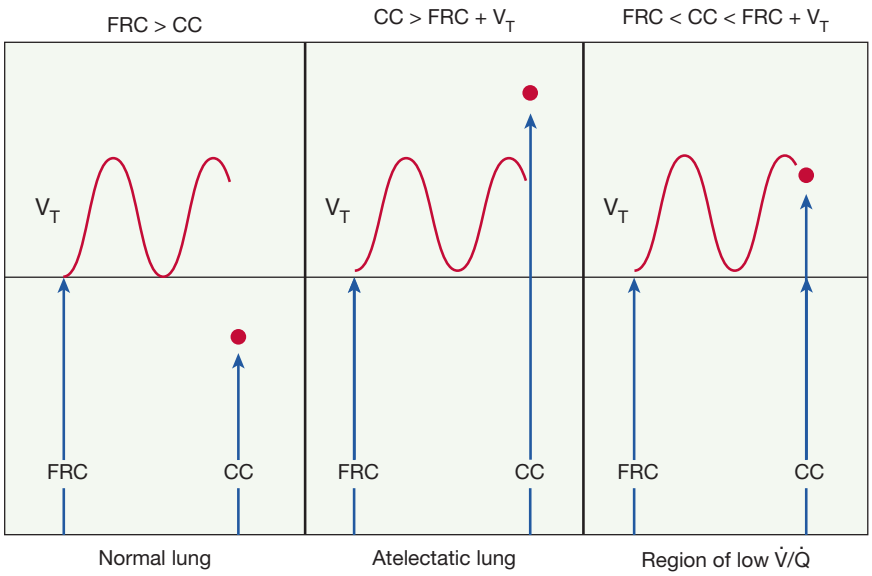

Figure 103-1 The relationship between functional residual capacity (FRC) and closing capacity (CC). V_T = Tidal volume. See text. *(Reproduced with permission from Goldmann DR, Brown FH, Guarnieri DM (eds). Perioperative Medicine. New York, McGraw-Hill; 1994.)*

to quiet tidal breathing after surgery is reduced.[14] Measurements of transdiaphragmatic pressure during maximal phrenic nerve stimulation following upper abdominal surgery indicate that decreased central nervous system output to the phrenic nerves, possibly as a result of inhibitory reflexes arising from sympathetic, vagal, or splanchnic receptors, may be the important etiologic factor.[15] Studies of the role of pain in this impairment have yielded conflicting results, pointing to either a limited[10–12] or significant[13] role for pain, depending on the procedures used for analgesia.

GAS EXCHANGE

Postoperative arterial hypoxemia occurs commonly, and two phases in its development may be described.[17,18]

The initial phase occurs in the first several hours following anesthesia and surgery. The underlying mechanisms are related largely to the residual effects of the anesthesia and include ventilation–perfusion mismatch, anesthetic-induced inhibition of hypoxic pulmonary vasoconstriction, right-to-left shunting, alveolar hypoventilation, depressed cardiac output, and increased oxygen consumption by peripheral muscles. This phase resolves within 24 hours following superficial surgery.

A second phase of hypoxemia, which may persist for several days or weeks, is seen after thoracic and upper abdominal surgery. This phase correlates with reductions in FRC and changes in the FRC–CC relationship. Although alterations in the FRC–CC relationship predominate, other processes may contribute to late postoperative hypoxemia: (1) alveolar hypoventilation (see discussion of control of breathing below); (2) increased dead space ventilation due to rapid, shallow breathing; and (3) decreased mixed venous oxygen tension due to increased oxygen consumption, impaired cardiac output, and reduced oxygen carrying capacity.

TABLE 103-2 Conditions that Alter the Relationship between Functional Residual Capacity (FRC) and Closing Capacity (CC)

Decrease FRC	Increase CC
Supine position	Advanced age
Obesity	Smoking
Pregnancy	COPD
General anesthesia	Pulmonary edema
Abdominal pain	

Source: Reproduced with permission from Goldmann DR, Brown FH, Guarnieri DM (eds). Perioperative Medicine. New York, McGraw-Hill; 1994.

CONTROL OF BREATHING

Respiratory depression is a common feature of the postoperative period. Two factors are responsible. First, residual effects of preanesthetic or anesthetic agents inhibit respiratory drive and reduce the ventilatory response to hypercapnia, hypoxia, and acidosis.[19] Second, narcotics given for postoperative analgesia depress both hypercapnic and hypoxic ventilatory drives, resulting in decreased tidal volume, reduced minute ventilation, and increased Pa_{CO_2}.[20] Narcotics also alter the pattern of breathing, reducing the frequency of sighs or eliminating them entirely; in susceptible patients, narcotics may precipitate sleep apnea.

LUNG DEFENSE MECHANISMS

Several mechanisms protect the lung from environmental and infectious insults. Two of the most important – cough and mucociliary transport – are compromised after surgery, contributing to an increased risk of pulmonary infection.[4,21] Postoperative pain or excessive use of narcotics may inhibit coughing; in addition, altered lung mechanics decrease the expulsive force generated with each cough. Mucociliary clearance is impaired for up to a week following upper abdominal surgery. Although an ineffective cough reflex contributes significantly to reduced mucociliary clearance, several additional mechanisms are involved. These include (1) cilia damage from endotracheal intubation and inhalation of dry, hyperoxic gas mixtures; (2) reduced tracheal mucus velocity due to the presence of an endotracheal tube; (3) anesthetic-induced inhibition of mucociliary transport; and (4) atelectasis.

PULMONARY COMPLICATIONS

The criteria used for defining postoperative pulmonary morbidity have varied considerably in published reports,[22,23] although it is clear that, from a broad perspective, five major categories of complications may be considered: (1) atelectasis; (2) infection, including acute tracheobronchitis and pneumonia; (3) exacerbation of underlying chronic lung disease; (4) prolonged mechanical ventilation and respiratory failure; and (5) thromboembolic disease. With thoracic surgery, several additional problems may occur,[24–36] which are summarized in Table 103-3.

The variability in defining postoperative pulmonary complications has resulted in reported incidences that have ranged widely in the literature, depending on the patient population sampled and the procedures studied. In general, a healthy, young nonsmoker of normal weight has a very low risk of postoperative pulmonary complications (1% or less).[37] However, a number of factors have been identified that are associated with the development of postoperative pulmonary complications (Table 103-4).[22,23,38–41] They include preoperative factors (chronic lung disease, smoking, general state of health, age, obesity, nutritional status, and antecedent respiratory

TABLE 103-3 Pulmonary Complications Associated with Thoracic Surgery

Procedure	Complication	Incidence (%)	References
Coronary artery bypass grafting	Phrenic nerve damage[a]	10–20	24–26
	Pleural effusions (postpericardiotomy syndrome)	10–15	27
Lung resection surgery	Pleural space complications (bronchopleural fistula, prolonged air leaks, or empyema[b])	5–20	28–32
Median sternotomy	Sternal wound infection (mediastinitis or osteomyelitis)	1–4	33,34
Esophagectomy	Anastomotic leak	3–12	35,36

[a]*Incidence for clinically significant injury with prolonged mechanical ventilation is 1% to 2%.*
[b]*Rates higher for patients undergoing resection for aspergilloma.*

tract infection), intraoperative factors (the emergent nature of the procedure, type and duration of anesthesia, location of surgical site, and type of surgical incision), and postoperative factors (inadequate pain control and immobilization). Tables 103-5 and 103-6 list, respectively, the relative strengths of preoperative and intraoperative factors associated with development of postoperative pulmonary complications based on odds ratios.[23,42]

PREOPERATIVE RISK FACTORS

A number of patient-related factors have been implicated in the development of postoperative respiratory complications.[23] They include the presence of chronic lung disease (particularly obstructive airway disease); the patient's overall state of health, age, and history of cigarette smoking; and the presence of comorbid conditions, including malnutrition, congestive heart failure, alcohol use, functional dependence, and impaired sensorium. The precise risk associated with recent respiratory viral infections is unknown. Obesity appears not to increase the risk for major postoperative pulmonary complications.

■ CHRONIC LUNG DISEASE

The following discussion focuses on the operative risks in patients who have one of four common categories of chronic lung disease: (1) chronic obstructive pulmonary disease (COPD), (2) restrictive lung diseases, (3) obstructive sleep apnea (OSA), and (4) pulmonary vascular diseases.

Chronic Obstructive Pulmonary Disease

Most studies addressing the impact of pre-existing lung disease on surgical risk have focused on COPD, which has been identified as a significant risk for development of postoperative pulmonary complications.[38,39,43–53] The reported incidence of postoperative pulmonary complications in patients with COPD varies from 10% to greater than 50% and is influenced by type of surgery, magnitude of pre-existing respiratory impairment, and criteria used to define complications. Although not precisely quantified in the literature, the risk for postoperative respiratory complications appears to increase significantly when the FEV_1 is below 65% of predicted. Evidence exists that the risk for postoperative respiratory complications in COPD may be raised further by the concomitant presence of resting hypoxemia.[54] Although an increased risk has been suggested for patients who are hypercapnic at rest,[43,55] whether hypercapnia is, in fact, an independent predictor of pulmonary complications after surgery is unclear.[56]

In patients with severe disease, an important issue is whether a critical level of lung function exists below which the risk of developing a major, potentially life-threatening pulmonary complication is so high as to make anesthesia and surgery too dangerous. In the past, such a prohibitive threshold or level was proposed. Subsequent studies, however, have failed to support this hypothesis.[57] Patients with an FEV_1 as low as 450 mL have been found to tolerate surgery safely.[55] Hence, patients should not be denied necessary operative procedures solely on the basis of marginal lung function. As with all medical interventions, the potential benefits of the operative procedure must be weighed against the operative risk.

TABLE 103-4 Factors Associated with Development of Postoperative Pulmonary Complications

Preoperative	Intraoperative	Postoperative
Chronic lung disease	Type of anesthesia	Immobilization
Smoking	Duration of anesthesia	Inadequate pain control
General state of health	Surgical site	
Age	Type of surgical incision	
Obesity		
Nutritional status	Emergent nature of the procedure	
Antecedent respiratory tract infection		

TABLE 103-5 Relative Strength of Preoperative Risk Factors Associated with the Development of Postoperative Pulmonary Complications

Factor	Odds Ratio
General state of health (ASA Class >II)	2.55–4.87
Congestive heart failure	2.93
Albumin <3.5 g/L	2.53
Age >60 y	2.09–3.04
COPD	1.79
Functional dependence	1.65–2.51
Weight loss	1.62
Impaired sensorium	1.39
Cigarette smoking	1.26
Alcohol use	1.21
Antecedent respiratory tract infection	Risk not known
Obesity	No increased risk for major morbidity

Source: Adapted with permission from Sweitzer BJ, Smetana GW. Identification and evaluation of the patient with lung disease. Med Clin N Am. 2009;93(5):1017–1030.

TABLE 103-6 Relative Strength of Intraoperative Risk Factors Associated with the Development of Postoperative Pulmonary Complications

Factor	Odds Ratio
Surgical Site	
Aortic aneurysm repair	6.90
Thoracic surgery	4.24
Abdominal surgery	3.01
Neurosurgery	2.53
Head and neck surgery	2.21
Vascular surgery	2.10
Gynecologic or urologic surgery	Not a risk factor
Hip surgery	Not a risk factor
Procedure-Related Issues	
Duration of surgery >2.5–4.0 h	2.26
Emergency surgery	2.21
General anesthesia	1.83

Source: Adapted with permission from Sweitzer BJ, Smetana GW. Identification and evaluation of the patient with lung disease. Med Clin N Am. 2009;93(5):1017–1030.

The increased incidence of postoperative pulmonary complications in patients with COPD is due, in part, to an increase in the CC, favoring development of areas of low ventilation-to-perfusion ratios and atelectasis. In addition, in patients who continue to smoke, impaired ciliary function and chronic tracheobronchitis may be contributing factors.

Restrictive Lung Diseases

The risk of pulmonary complications in patients with restrictive lung diseases who undergo surgery is unknown. Although some experience has been reported with patients having thoracic or corrective orthopedic surgery (see below), very little data exist with regard to abdominal and extremity surgery. One might expect a higher incidence of postoperative respiratory complications in these patients for two reasons: (1) FRC is reduced, favoring the formation of areas of poor ventilation and atelectasis; (2) coughing and the ability to clear respiratory secretions are impaired.

Experience with postoperative pulmonary complications has been reported in three relatively common situations for patients with restrictive disorders: (1) sarcoidosis complicated by aspergilloma and hemoptysis, (2) corrective surgery for kyphoscoliosis, and (3) myasthenia gravis with associated thymoma.

Sarcoidosis may progress to diffuse interstitial fibrosis and cavitary changes, primarily involving the upper lobes (see Chapter 55, Moller). The cavities are prone to infection with *Aspergillus* species and aspergilloma formation, with subsequent development of recurrent and, at times, life-threatening, hemoptysis. Affected patients generally have very poor lung function and, hence, are managed conservatively. However, if supportive medical therapy fails, patients may require thoracotomy and lung resection. These procedures can be done with low mortality, but they may be complicated by empyema, chylothorax, prolonged pulmonary parenchymal air leaks, or bronchopleural fistulae.[30–32]

Corrective surgery in patients with kyphoscoliosis may involve anterior or posterior spinal fusion procedures or a combination of the two.[58,59] In addition to correction of the primary orthopedic abnormality, an important indication for performing these procedures is progressive deterioration of pulmonary function. Postoperative respiratory complications have been reported in up to 20% of patients, including pleural space–related processes (e.g., pneumothorax, pleural effusion, bronchopleural fistula, and empyema) and lobar or total lung atelectasis.[59–61] Important risk factors include (1) nonidiopathic scoliosis, (2) open anterior spinal fusion procedures, (3) age greater than 20 years, (4) mental retardation, (5) preoperative hypoxemia, and (6) obstructive pulmonary function tests.[60] Thoracotomy has been associated with a significant decrease in pulmonary function for up to 2 years after surgery.[59,62] Video-assisted thoracoscopic surgery (VATS) has emerged as an alternative to open thoracotomy; the outcomes of anterior fusion via VATS and thoracotomy are similar.[63,64]

The majority of patients with myasthenia gravis will, during the course of their disease, undergo thymectomy, which appears to improve long-term outcomes.[65] Surgical options for thymectomy include the long-established method of transsternal resection, a transcervical approach, a combined transsternal–transcervical procedure, and, more recently, VATS.[66,67]

Historically, up to 30% of patients undergoing thymectomy required mechanical ventilation for more than 3 days following the transsternal approach.[68,69] Reported risk factors for postoperative pulmonary complications following transsternal resection include chronic myasthenia gravis (>6 years), severe bulbar weakness, preexisting respiratory illness, need for large doses of pyridostigmine, and reduced maximal static expiratory pressure (<50 cm H_2O or 66% of predicted).[68–70] Preoperative VC has not proved a consistent predictor of respiratory morbidity following thymectomy. More recent routine use of plasma exchange in patients with bulbar or generalized myasthenia gravis has significantly reduced the duration of postoperative ventilatory support and time in the intensive care unit following transsternal thymectomy.[66]

Video-assisted thoracoscopic thymectomy is an increasingly common approach, with outcomes equivalent or superior to more invasive procedures.[67]

Virtually all patients with myasthenia gravis are treated with anticholinesterases, which are usually discontinued prior to surgery to minimize tracheobronchial secretions. Controversy exists, however, regarding whether these agents should be restarted immediately after surgery or withheld for 24 to 48 hours following thymectomy.

Obstructive Sleep Apnea

OSA is common, with a prevalence of 5% or higher, depending on the population studied (see Chapter 99, Pien and Rosen). For many of these patients, the diagnosis of OSA is not established preoperatively.[71] Unrecognized OSA is significant, because both anesthesia and surgery affect sleep architecture; in addition, use of postoperative narcotics for analgesia may further blunt ventilatory chemosensitivity, suggesting that postoperative respiratory morbidity is likely higher in patients with OSA than in the general population. Although initial studies were consistent with this expectation,[72] subsequent reports have failed to show that OSA is significant risk factor for development of major postoperative pulmonary complications.[73–75] Thus, while it is prudent and in the patient's best interest to use the preoperative evaluation as an opportunity to screen for OSA, the value of preoperative screening for OSA as a means of decreasing postoperative pulmonary complications has not been established.

Pulmonary Vascular Diseases

The risk of postoperative pulmonary complications in patients with underlying pulmonary vascular disease and intact respiratory mechanics is not known. However, one might anticipate an exaggeration of, or prolongation in, the hypoxemia seen postoperatively

(see discussion of gas exchange, above). In addition, pulmonary reserve in these patients is usually reduced; hence, additional pulmonary insults are less likely to be tolerated.

SMOKING HISTORY

That smoking increases the risk of postoperative respiratory complications, even among those without COPD, has long been recognized.[44,76] Given the well-documented adverse effects of smoking on respiratory epithelium and pulmonary function, the magnitudes of which correlate with the degree of tobacco consumption, such an association is not surprising.

In individuals undergoing coronary artery bypass graft surgery, the risk of smoking becomes significant when tobacco use exceeds 20 pack-years.[77] A statistically significant reduction in complications occurs only when patients discontinue smoking for at least 8 weeks prior to surgery. This finding is consistent with studies showing that abnormalities in pulmonary function may persist up to several months after smoking cessation.[78,79] Although smoking cessation of more than 2 months is associated with a decreased risk of postoperative respiratory complications, early retrospective studies actually showed a paradoxical *increase* in pulmonary complications in patients who stopped smoking only a few weeks or days prior to surgery.[80] However, more recent studies[81] and analyses[82] have failed to demonstrate increased pulmonary complications in patients who quit smoking within 2 months of surgery.

GENERAL STATE OF HEALTH

Overall clinical status, as categorized by the American Society of Anesthesiologists' (ASA) classification (Table 103-7), correlates with development of postoperative pulmonary complications.[50,83–85] Specifically, an ASA classification of II or higher is a powerful predictor of increased risk for respiratory problems after surgery.[23]

AGE

Although increased age was previously thought to be a minor risk factor for postoperative respiratory complications,[86] more recent analyses indicate that increasing age is, in fact, a significant independent predictor, even after accounting for comorbid conditions associated with aging.[23] Advanced age, however, should not be the sole reason for withholding surgery, particularly lung resection.

In one important study, despite the finding of a higher 30-day postoperative mortality in patients over age 70 years who underwent resectional lung surgery, the incidence of postoperative pulmonary complications and hospital stay were not increased, and survival was not decreased, in the older group.[87] More recently, in a nested, case-control study of patients greater than age 70 years who underwent lung resection, no significant differences were found between the elderly and younger controls in length of stay, major morbidity, or operative mortality.[88] These findings, along with other published results,[89] indicate that treatment decisions should be individualized for each patient.

TABLE 103-7 American Society of Anesthesiologists' (ASA) Clinical Classification

ASA I	Otherwise healthy patient undergoing elective surgery
ASA II	Patient with single system or well-controlled disease that does not affect daily life
ASA III	Patient with multisystem or well-controlled major system disease that limits daily activity
ASA IV	Patient with severe, incapacitating disease that is poorly controlled or end stage
ASA V	Patient who is in imminent danger of death and is not expected to survive 24 h

OBESITY

A number of changes in respiratory mechanics and pulmonary function occur with obesity.[90–93] The accumulation of fat in the chest wall, diaphragm, and abdomen may reduce total respiratory compliance by more than 60%—a change that is amplified when the patient assumes the supine position.[94] The reduced compliance, in turn, increases the work of breathing.[90,91] Consequently, minute ventilation, oxygen consumption, and carbon dioxide production are further increased beyond baseline values, which are already elevated as a result of increased metabolic demands imposed by the obese state. In terms of gas exchange, modest effects at rest are observed only in morbidly obese individuals: lower than predicted Pa_{O_2}, higher than predicted alveolar-to-arterial oxygen pressure difference, normal blood oxygen saturation, and normal Pa_{CO_2}.[95]

Typically, spirometry in obese patients does not indicate airway obstruction. However, a reduction in ERV is found consistently. The magnitude of the reduction correlates with the degree of obesity. Areas of low ventilation relative to perfusion and atelectasis are seen (see discussion of lung volumes, above). In addition to these changes, obese patients appear to have a larger gastric volume and lower gastric pH than do nonobese patients and may be predisposed to aspiration.[96]

Morbidly obese patients may be at an increased risk for development of atelectasis, as noted on chest radiographs.[97,98] However, when bacterial pneumonia, acute respiratory failure, or prolonged mechanical ventilation are considered, and confounding factors are excluded, obese patients undergoing abdominal surgery do not show an increased incidence of clinically significant postoperative pulmonary complications compared with nonobese patients.[37,99–101] Major respiratory complications occur in only 4% to 7% of morbidly obese patients undergoing gastric bypass surgery; therefore, in the absence of concurrent cardiopulmonary disease, the risk of postoperative pulmonary complications associated with obesity appears not to be excessive.[102] However, as noted previously, obesity is clearly a risk factor for OSA syndrome, which may be unmasked or exacerbated because of use of postoperative analgesics or narcotics.[103]

NUTRITIONAL STATUS

The effects of malnutrition and severe starvation on the respiratory system include a reduced ventilatory response to hypoxia, decreased diaphragmatic muscle function, impaired cell-mediated and humoral immunity, and alterations in the elastic properties of the lung. Depending on the clinical metrics examined (e.g., weight loss >10% over the previous 6 months, BMI <20 kg/m^2), the screening procedures utilized (e.g., Mini Nutritional Assessment (MNA) score <17), and the laboratory tests employed (e.g., serum albumin <36 g/L), malnutrition may be found in 50% or more of hospitalized patients.[104,105] Evidence exists that these levels of malnutrition are associated with expiratory muscle weakness (despite preservation of pulmonary function)[106] and an increased incidence of postoperative respiratory complications.[38,99,107,108] However, aggressive preoperative nutritional support has not been shown to decrease postsurgical pulmonary morbidity.[109]

ANTECEDENT RESPIRATORY TRACT INFECTION

The effects of an antecedent respiratory tract infection on the incidence of respiratory complications following surgery are difficult to predict. With respiratory syncytial virus (RSV) infections, symptoms typically resolve in 7 to 10 days; viral shedding averages 10 to 13 days, but it may persist beyond 20 days.[110,111] Furthermore,

enhanced airway reactivity and increased airway resistance associated with this and other viral infections may persist for weeks beyond resolution of acute symptoms.[112,113] In addition, diaphragmatic function may be impaired during viral infections.[114]

In pediatric patients, perioperative, nonlife-threatening, adverse respiratory events are more common in patients with recent (within 4 weeks) upper respiratory tract infections compared with those without infections.[115,116] In an adult population, history of an acute respiratory infection in the month preceding surgery is an independent risk factor for development of a postoperative pulmonary complication.[41] Therefore, in the setting of an active or recent respiratory tract infection (in the previous 2 weeks), a 2- to 4-week delay in elective surgery is generally advised.

OTHER PATIENT-RELATED FACTORS

Other factors have been reported to be associated with an increased incidence of postoperative pulmonary complications.[23] These include congestive heart failure,[41,117,118] preoperative functional dependence, impaired sensorium (acute confusion or delirium), and active alcohol use (>2 drinks per day in the past 2 weeks).[38,39]

INTRAOPERATIVE RISK FACTORS

Several operative factors have been associated with development of pulmonary complications after surgery. These include whether the surgery is emergent or nonemergent, type of anesthesia used, length of the procedure (as determined by the duration of anesthesia), surgical site, and type of surgical incision.

EMERGENT NATURE OF THE PROCEDURE

Postoperative pulmonary complication rates are higher for surgeries done on an emergent basis.[38,39,41,47,48,117] The increased risk of emergency surgery may be significant[23] and may be related to loss of the ability to implement some of the preventative measures outlined subsequently or to deliberately plan the anesthetic strategy.

TYPE OF ANESTHESIA

The pulmonary effects of general anesthesia have been implicated in the development of postoperative pulmonary complications.[38,39,50,51] They include impairment of oxygenation and carbon dioxide elimination. These effects result from anesthetic-induced changes in the shape and motion of the chest wall and diaphragm, which, in turn, lead to increases in alveolar dead space, shunt fraction, and ventilation–perfusion mismatching. Alterations in lung function may contribute to pulmonary morbidity.

Because of the effects of general anesthesia on gas exchange, regional anesthesia (spinal or epidural anesthesia) or local anesthesia with monitored anesthesia care (MAC) has been used as alternatives, particularly in patients with underlying pulmonary disease. Indeed, epidural anesthesia to a T4 sensory level does not appear to alter FRC, VC, FEV_1, the alveolar–arterial oxygen gradient, shunt fraction, or cardiac output.[119] Overall, regional anesthesia, as compared to general anesthesia, decreases the risk of postoperative respiratory complications, particularly deep vein thrombosis.[120,121] These beneficial effects, however, appear to be most significant for abdominal and thoracic procedures[122,123] and less so for nonthoracoabdominal procedures, such as carotid endarterectomy[124,125] and hip fracture surgery.[126,127]

DURATION OF ANESTHESIA

The incidence of pulmonary complications increases significantly for procedures lasting longer than 2 to 4 hours.[41,44,45,69,84] Patients whose procedures last 4 hours or more are five times more likely to experience postoperative pneumonia than those whose procedures last less than 2 hours.[99]

SURGICAL SITE

Development of postoperative pulmonary complications has long been recognized to correlate strongly with the anatomic site of operation.[41,44,45,69,84] The complication rate (excluding thromboembolic disease) is less than 5% for gynecologic and urologic procedures, 5% to 10% for lower abdominal and head and neck surgeries, and 10% to 20% for upper abdominal surgeries. Abdominal aortic surgery is associated with a pulmonary complication rate of 25% or more.[23]

Reported postoperative complication rates for thoracic surgery involving lung resection vary from under 10% to 40% or higher.[128–133] Postoperative respiratory morbidity following lung resection surgery (in addition to all the factors cited earlier) also depends on a number of other issues, including (1) the presence of underlying lung disease, (2) the amount of functional lung removed, and (3) the extent to which the "bellows" function of the lung is impaired (see discussion of evaluation for lung resection below). Furthermore, the potentially higher incidence of postoperative respiratory complications after lung resection surgery relative to other procedures also reflects the occurrence of specific problems related to entering the pleural space or resection of lung tissue (e.g., development of pleural effusion, empyema, pneumothorax, or persistent pulmonary parenchymal air leak).

TYPE OF SURGICAL INCISION

For abdominal procedures, vertical laparotomy incisions may carry a higher incidence of postoperative complications than do horizontal incisions,[134] although this finding has been questioned.[135] Abdominal laparoscopic procedures and thoracoscopic lung resection have gained widespread acceptance because of reduced patient discomfort, shortened length of hospitalization, and faster patient return to full activity. Since the magnitude of incisional pain is usually less, and since patients typically ambulate sooner, the incidence of postoperative respiratory complications with these less invasive procedures is likely to be lower. Laparoscopic cholecystectomy, when compared with open cholecystectomy, demonstrates better preservation and faster recovery of lung volumes, higher arterial oxygen saturations, less postoperative pain and analgesia use, and a lower incidence of postoperative pulmonary complications.[136–138] Comparable findings have been noted for minimally invasive esophagectomies compared with open procedures, and for video-assisted thoracic surgery versus open thoracotomy.[29]

POSTOPERATIVE RISK FACTORS

Inadequate pain control, prolonged bed rest, and patient inactivity contribute to development of postoperative respiratory complications.

INADEQUATE POSTOPERATIVE ANALGESIA

Effective pain control is vital in the early postoperative period, since pain inhibits coughing and deep breathing and discourages early mobilization—factors that contribute to an increased risk of pulmonary complications. More importantly, there is evidence that effective analgesia after thoracic or abdominal surgery reduces the occurrences of postoperative pulmonary complications.[139–142] Obstacles to good postoperative analgesia include hesitancy of the patient to report pain for fear of being labeled a "bad" patient and anxiety of caregivers in administering narcotics because of side effects.

IMMOBILIZATION

Prolonged bed rest and inactivity following surgery impact the risk of postoperative respiratory complications in several ways. FRC decreases by 500 to 1000 mL in moving from the upright to the supine position, favoring development of atelectasis.[18] Increased ambulation is associated with better clearance of respiratory secretions. Postoperative immobilization is a major risk factor for development of deep venous thrombosis and pulmonary embolism.

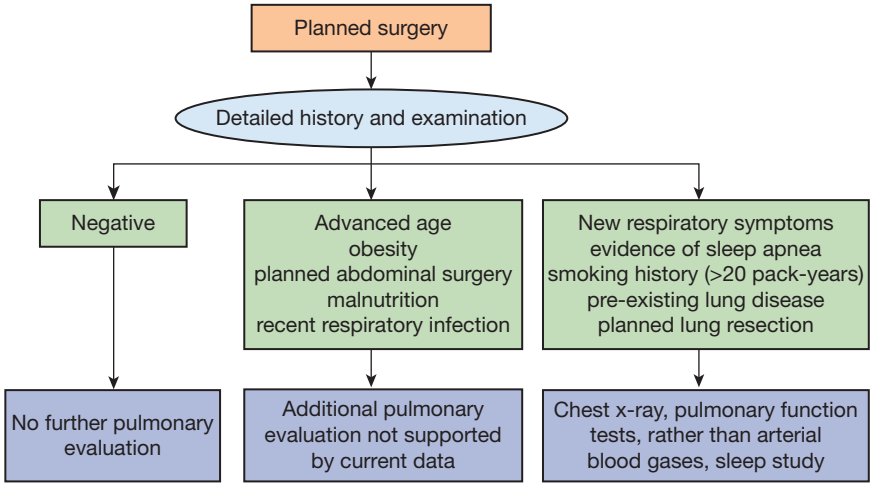

Figure 103-2 Algorithm for preoperative pulmonary evaluation. See text for discussion.

PREOPERATIVE EVALUATION

The principal elements in preoperative evaluation of the surgical patient are (1) the history and physical examination, (2) the chest radiograph, (3) arterial blood gas analysis, and (4) pulmonary function tests (Fig. 103-2).

HISTORY AND PHYSICAL EXAMINATION

A careful history is an essential component of preoperative evaluation. The following issues should be reviewed: (1) smoking history; (2) history of respiratory symptoms (e.g., cough, chest pain, dyspnea), including symptoms of sleep apnea; (3) extent of preexisting lung disease; and (4) history of recent respiratory tract infection. The physical examination is rarely helpful in identifying pulmonary risk factors. When the history is negative, the physical examination is typically unremarkable. However, the initial physical examination supplements the history and provides a baseline for future comparisons.

CHEST RADIOGRAPH

The preoperative chest radiograph is usually unrevealing if risk factors and abnormal physical findings are absent.[143,144] Although the admission or screening chest radiograph is more likely to show an abnormality in individuals with known cardiopulmonary disease, the study usually simply confirms the presence of previously known abnormalities; only occasionally does it result in an alteration in management. Thus, a preoperative chest radiograph is indicated when there are new or unexplained symptoms or signs, when there is a history of underlying lung disease and no recent chest radiograph, or when thoracic surgery is planned.

ARTERIAL BLOOD GAS ANALYSIS

Since an elevated Pa_{CO_2} is associated with an increased incidence of postoperative respiratory morbidity in patients with significant chronic lung disease, an arterial blood gas analysis should be done preoperatively in these patients.[54] Although supportive data are lacking, it is common practice to obtain an arterial blood gas sample in all patients undergoing lung resection surgery, even those without significant underlying lung disease. The determination serves as a basis for comparison with subsequent intra- and postoperative measurements. It is also recommended that an arterial blood gas specimen be obtained in patients who, by either history or physical examination, have a new significant pulmonary process. Data do not support the use of arterial blood gas analysis as a routine preoperative screening test.[145]

PULMONARY FUNCTION TESTS

An increased risk of postoperative respiratory complications has been demonstrated only with obstructive pulmonary disorders. Although theoretical reasons may prompt expectation of a higher incidence of postoperative respiratory problems in patients with restrictive lung diseases (see discussion of preoperative risk factors, above), currently, data demonstrating a correlation between the degree of restriction (as assessed by lung volumes) and postoperative pulmonary morbidity are lacking. Hence, although a complete battery of pulmonary function tests is useful in evaluating suspected restrictive lung disease, spirometry to evaluate for airway obstruction is all that is required to screen patients at risk for postoperative pulmonary complications.

Indications for preoperative pulmonary function testing include the presence of cough or unexplained dyspnea, a history of chronic lung disease, a history of cigarette smoking (>20 pack-years), or planned lung resection (see below). Current data do not support the routine use of these studies to evaluate the pulmonary risks of advanced age, obesity, malnutrition, or abdominal surgery.[146–149] Finally, normal pulmonary function tests obviously do not guarantee a complication-free postoperative course and do not lessen the need for diligent respiratory care following surgery.

EVALUATION FOR LUNG RESECTION

In evaluating patients for lung resection, the clinician must consider two broad issues: (1) What is the surgical morbidity and mortality for the patient with significant underlying chronic lung disease? (2) Will postoperative lung function be adequate to support a reasonable quality of life? Pulmonary function testing, supplemented by exercise testing in selected cases, provides the basis for answering these questions.[150,151]

PULMONARY FUNCTION TESTING

Studies dating back to the 1950s have shown that the risk of postoperative respiratory complications following pneumonectomy increases significantly when the FEV_1 is less than 2 L or 80% of predicted normal, or when the maximal voluntary ventilation (MVV) is less than 50% of predicted.[152] For a lobectomy, an FEV_1 of 1.5 L appears to be the critical threshold. The diffusion capacity for carbon monoxide (D_{LCO}) has also been identified as a predictor of postoperative complications.[153,154] Increased risk is associated with a D_{LCO} of less than 60% to 80% of predicted and appears to be independent from FEV_1 as a predictor of complications, morbidity, and death.[155–157] Therefore, predictive postoperative lung function should be estimated for patients with an FEV_1 or D_{LCO} less than 80% of predicted.[150,151]

PREDICTION OF POSTOPERATIVE FEV_1 OR D_{LCO}

Ventilation–perfusion lung scans measure the relative blood flow or ventilation to one lung or lung region and can be used to predict postoperative FEV_1 or D_{LCO} using the following equation:

$$\text{Predicted postoperative } FEV_1 \text{ or } D_{LCO} = \text{Preoperative } FEV_1 \text{ or } D_{LCO} \times (\text{lung function remaining after resection, as determined by radionuclide imaging}) \quad (1)$$

An alternative approach to estimating the predicted postoperative pulmonary function involves a calculation based on the number segments of the lung (10 on the right and nine on the left)[158] as follows:

Predicted postoperative FEV_1 or D_{LCO} = Preoperative FEV_1 or D_{LCO} × (lung function remaining after resection, as determined by radionuclide imaging) (2)

Studies comparing the radionuclide imaging-based technique versus the segment-based method suggest that perfusion imaging, overall, provides a better prediction of postoperative lung function, as the segment method underestimates lung function after pneumonectomy.[159,160]

In addition to the two methods noted earlier, other approaches have been employed to predict postresection lung function. However, procedures such as quantitative computed tomographic imaging,[161] have failed to gain wide acceptance, and oxygen-enhanced MRI,[162] although promising, awaits further development.

A number of studies have demonstrated that the perioperative risk for lung resection increases significantly when the predicted postoperative FEV_1 or D_{LCO} has <40% of predicted.[153,163–166] Therefore, a predicted postoperative FEV_1 or D_{LCO} ≥40% predicted has been proposed as useful criteria for undertaking "safe" pulmonary resection.[150,167] Finally, with recognition that most patients who undergo resectional lung surgery have lung cancer, and that this malignancy has virtually a 100% mortality without surgery (for nonsmall cell tumors), caution must be exercised in applying exclusionary criteria for surgery.

EXERCISE TESTING

A number of investigators have found measurement of maximal oxygen consumption (V_{O_2max}) during cardiopulmonary exercise testing to be useful in predicting postoperative morbidity and mortality.[168–172] Specifically, a $\dot{V}_{O_2\ max}$ of less than 15 to 20 mL/kg/min is associated with an increased incidence of postoperative complications. Cardiopulmonary exercise testing is, therefore, used to further assess the operability of patients of who would be at high risk for surgery based on determination of predicted postoperative pulmonary function.[150]

If cardiopulmonary exercise testing is unavailable, two technologically simpler approaches, stair climbing and a walking test, can be used to assess a patient's fitness for lung resection. Although standardization of the stair climbing test may be problematic, demonstration of a patient's ability to climb five flights of stairs predicts a $\dot{V}_{O_2\ max}$ >20 mL/kg/min; patients who are unable to climb one flight of stairs have a $\dot{V}_{O_2\ max}$ <10 mL/kg/min.[173] Furthermore, an ability to climb three flights of stairs reliably identifies patients who are likely to do well after a lobectomy, despite having a predicted postoperative FEV_1 or D_{LCO} that is <40% of predicted.[174,175]

The shuttle walk and 6-minute walk tests have also been investigated as alternatives to cardiopulmonary exercise testing. For the shuttle walk, the patient walks back and forth over a distance of 25 m at a progressively faster rate. Inability to complete 25 shuttles approximates a $\dot{V}_{O_2\ max}$ <10 mL/kg/min.[176,177] A 6-minute walk distance >1000 ft has been reported as predictive of successful surgical outcome.[164]

RECOMMENDED APPROACH

Summarized in Fig. 103-3 is a recommended sequence for evaluating patients for lung resection. The approach is adapted from

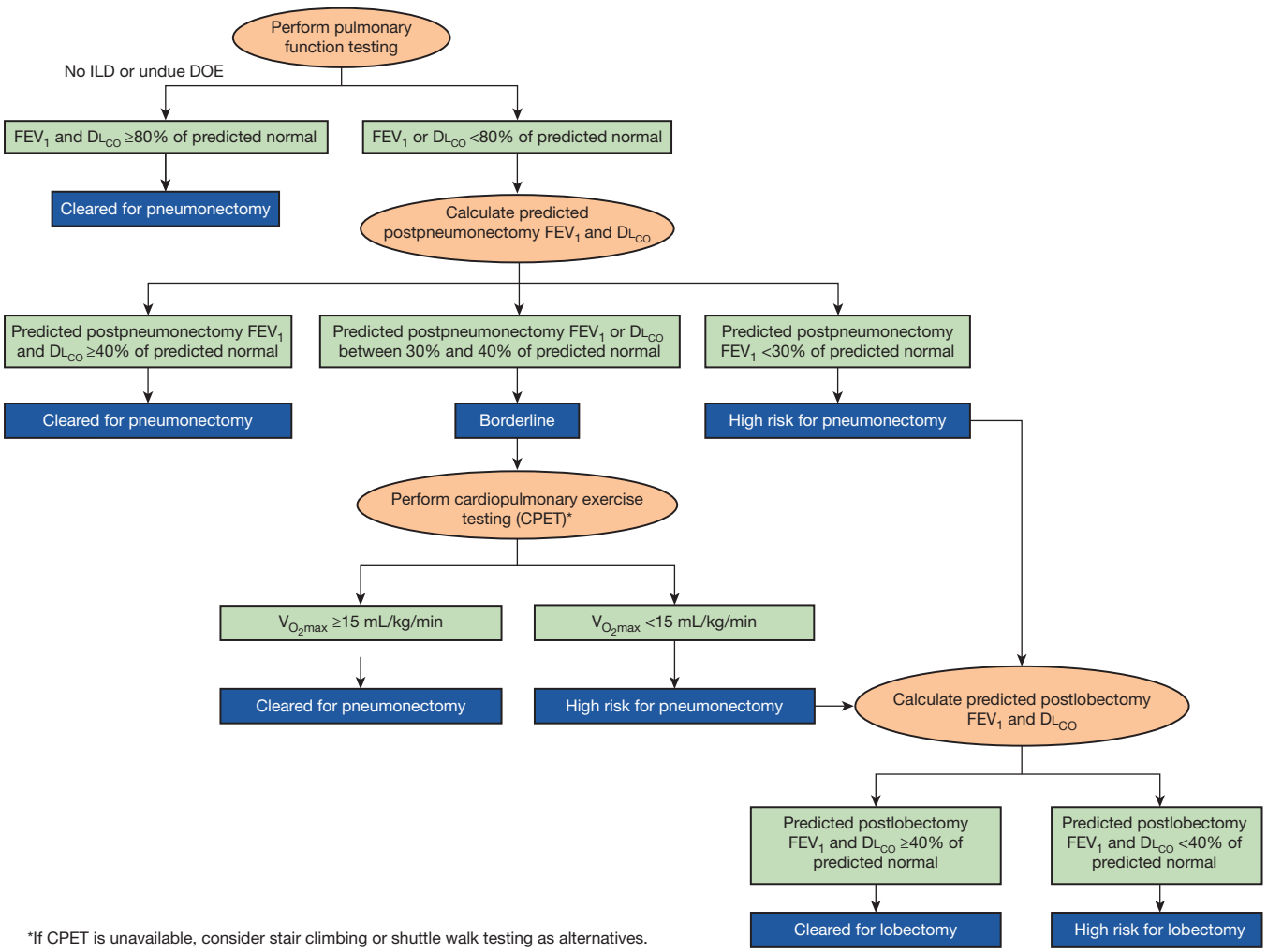

Figure 103-3 Algorithm for preoperative evaluation for lung resection. See text for discussion. ILD, interstitial lung disease; DOE, dyspnea on exertion.

recommendations of the American College of Chest Physicians (ACCP),[150] which, despite some differences, is also consistent with guidelines from several European professional societies.[151,167] The approach is predicated on determining the patient's operability for pneumonectomy, should this procedure be deemed necessary at the time of surgery (e.g., to permit complete removal of a tumor or to deal with an unanticipated intraoperative complication):

- If the preoperative FEV_1 and the D_{LCO} are ≥80% predicted normal and the patient has no dyspnea on exertion or interstitial lung disease, the patient is cleared for pneumonectomy; no further testing is required.
- If the preoperative FEV_1 or the D_{LCO} are <80% predicted normal, the predicted postpneumonectomy FEV_1 and D_{LCO} should be estimated.
- If the predicted postpneumonectomy FEV_1 and D_{LCO} are ≥40% of predicted normal, the patient is cleared for pneumonectomy and no further testing is required.
- If the predicted postpneumonectomy FEV_1 is <30% predicted normal, the patient is considered at high risk for a pneumonectomy.
- If the patient is considered at borderline risk for pneumonectomy (the predicted postoperative FEV_1 or D_{LCO} is <40% but ≥30 predicted normal), exercise testing should be done. Borderline patients with a $\dot{V}_{O_2\ max}$ ≥15 mL/kg/min are cleared for pneumonectomy (no further testing is required), while patients with $\dot{V}_{O_2\ max}$ <15 mL/kg/min are considered at high risk for a pneumonectomy.
- If the patient is determined to be at high risk for pneumonectomy, the predicted postlobectomy FEV_1 and D_{LCO} should be determined to inform conversations about the risks and benefits of more limited surgical resections or nonoperative treatment options.

For selected, high-risk patients with emphysema and potentially resectable lung cancer, consideration should be given for a segmental resection[178] or combined cancer resection and lung volume reduction.[179] The latter is particularly worth considering if the emphysema is heterogeneous and primarily involves the lobe to be resected.

PREOPERATIVE PREPARATION

Relatively few studies have specifically addressed the question of whether aggressive, preoperative pulmonary preparation decreases postoperative pulmonary morbidity and mortality.[180] Although data on preoperative preparation are limited, for patients with active obstructive airway disease, intensive preoperative respiratory therapy (bronchodilators, corticosteroids, antibiotics, and chest physiotherapy) does appear to reduce the incidence of postoperative respiratory complications by more than 50%.[84,181–183]

Several preoperative prophylactic measures should be considered in patients undergoing elective surgery (Table 103-8).

Pulmonary function in patients with obstructive airway disease should be optimized. Therapy may include any or all of the following: bronchodilators, corticosteroids, antibiotics (when there is evidence of infection), and chest physiotherapy (if excessive secretions are present). When possible, these interventions should be implemented 48 to 72 hours prior to surgery.

Ideally, for at least 8 weeks prior to surgery, smoking should be discontinued. As noted previously, recent data indicate that complication rates are not increased by shorter periods of abstinence; therefore, even when 8 weeks of abstinence is not possible, patients should still be advised to quit smoking prior to surgery.[81,82]

A program of inspiratory muscle training for at least 2 weeks prior to surgery may reduce the incidence of postoperative pulmonary complications in patients at high risk for their development.[184]

Finally, patient education on the importance of postoperative coughing and pain control, proper use of an incentive spirometer, and deep breathing exercises should take place preoperatively.

POSTOPERATIVE PROPHYLACTIC MEASURES

Several postoperative measures may be employed in an attempt to prevent respiratory complications (Table 103-9).

Early patient mobilization and ambulation should be encouraged. As noted previously, these measures are important postoperatively in reducing the incidence of atelectasis, in promoting the clearance of secretions, and in decreasing the risk of thromboembolic disease.

Prophylactic lung expansion maneuvers should be initiated.[185] Two equally effective measures are deep breathing exercises and incentive spirometry.[186,187] Intermittent positive pressure breathing (IPPB) is generally ineffective and costly and is associated with several adverse effects.[185] Reports of intermittent continuous positive airway pressure (CPAP) applied by face mask indicate that it is at least equivalent to deep breathing exercises and incentive spirometry in preventing atelectasis and pneumonia.[188]However, while CPAP may be useful in the patient who cannot cooperate with inspiratory maneuvers, its role in the management of patients capable of taking deep breaths is unclear.

Adequate analgesia should be provided, particularly for patients undergoing major, open surgery. Traditionally, parenteral narcotics have been used for postoperative analgesia, despite the risk of respiratory depression. Unfortunately, concerns over adverse respiratory effects may lead to inadequate dosing and inadequate pain relief. To overcome this problem, alternative approaches, including use of epidural analgesia, peripheral nerve blockade, paravertebral block, and wound catheter infiltration may be employed as alternatives to the use of systemic opioids.[189] These alternative techniques provide analgesia equivalent or superior to parenteral narcotics; however, whether they are effective in reducing postoperative pulmonary complications remains unclear.

Prophylaxis for thromboembolism is an important consideration,[190] and careful monitoring for other postoperative complications constitutes a key element in all surgical patients.

TABLE 103-8 Preoperative Pulmonary Preparation

Optimization of airway function in patients with obstructive lung disease (bronchodilators; corticosteroids, antibiotics, and chest physiotherapy, when indicated)
Smoking cessation (ideally, a minimum of 8 wk prior to surgery)
Patient education (deep breathing exercises, importance of coughing and pain control, use of incentive spirometry)
Consider inspiratory muscle training

Source: Adapted with permission from Goldmann DR, Brown FH, Guarnieri DM (eds). Perioperative Medicine. New York, McGraw-Hill; 1994.

TABLE 103-9 Postoperative Measures for the Prevention of Respiratory Complications

Early patient mobilization and ambulation
Prophylactic lung expansion maneuvers (incentive spirometry, deep breathing exercises, CPAP)
Provision of adequate analgesia
Prophylaxis against thromboembolism

Source: Adapted with permission from Goldmann DR, Brown FH, Guarnieri DM (eds). Perioperative Medicine. New York, McGraw-Hill; 1994.

Finally, several postoperative interventions have been shown to be ineffective, including chest physiotherapy in the absence of excessive secretions or sputum production,[191] and routine application of positive end-expiratory pressure in mechanically ventilated patients.[192]

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CHAPTER 104

Acute Respiratory Failure in the Surgical Patient

Robert M. Kotloff

INTRODUCTION

Advances in surgical technique, anesthesia and analgesia, and postoperative supportive care have emboldened surgeons to consider an expanding spectrum of patients for surgical interventions. In most instances, the success or failure of the surgery is defined not in the operating room, but postoperatively, when the adverse effects of surgery may first become apparent and when intercurrent complications may jeopardize the patient's recovery. The respiratory system is particularly vulnerable to the effects of general anesthesia and surgery, and postoperative respiratory impairment is common. While generally mild and well tolerated in otherwise healthy, young patients, postoperative respiratory compromise may have serious consequences in the elderly and in patients with pre-existing lung disease. A number of postoperative complications, such as pneumonia, aspiration pneumonitis, and acute respiratory distress syndrome (ARDS) may lead to respiratory compromise independent of the patient's presurgical status.

This chapter focuses on the most serious consequence of perioperative respiratory compromise—acute respiratory failure. This complication is associated with a 30-day mortality rate in the range of 25% following major surgical procedures, compared to approximately 1% for unaffected patients.[1] In addition to its adverse impact on survival, respiratory failure prolongs intensive care and hospital stay, delays convalescence, and increases healthcare costs among survivors. Clinicians who provide preoperative evaluation and postoperative care must be able to identify high-risk patients who require a greater degree of vigilance, and to rapidly recognize and appropriately treat the complications that result in postoperative respiratory failure.

IDENTIFICATION OF THE HIGH-RISK PATIENT

There have been several published studies using large databases that have provided insight into the incidence of postoperative respiratory failure, its impact on survival, and factors associated with increased risk. In one of the earliest surveys involving over 7000 patients undergoing various gastrointestinal, urological, gynecological, and orthopedic procedures, respiratory failure requiring mechanical ventilation beyond 24 hours occurred in only 0.8%.[2] More recently, analysis of a database of 180,359 patients undergoing major general or vascular surgical procedures at 128 Veterans Affairs hospitals and 14 private sector hospitals documented a 3% incidence of postoperative respiratory failure (defined as mechanical ventilation beyond 48 hours after surgery or need for reintubation).[1] Thirty-day mortality was 27% for the group with respiratory failure compared to only 1.4% for those without. Twenty-eight variables were identified that were independently associated with increased risk. These included higher American Society of Anesthesiologists (ASA) class, preoperative sepsis, emergency as opposed to elective procedure, impaired preoperative renal function, history of smoking or COPD, and older age. The type of procedure also impacted risk (Table 104-1), with the greatest incidence of respiratory failure associated with upper aerodigestive tract surgery, thoracic or thoracoabdominal aneurysm repair, thoracic surgery, and gastrointestinal and hepatobiliary surgery. The investigators incorporated the 28 variables (Table 104-2) into a respiratory risk index (Table 104-3) to predict the likelihood that a patient will develop respiratory failure and validated it using a second patient cohort. Unfortunately, the complexity of the model renders it unwieldy and has limited its widespread acceptance.

In the largest study of this nature to date, investigators used the 2007 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database of over 210,000 patients who underwent a broad array of surgical procedures to identify risk factors and derive a predictive model for assessing risk of postoperative respiratory failure.[3] Respiratory failure developed in 3.1% of patients, with an associated 30-day mortality rate of 26% compared to 0.98% for patients not experiencing this complication. On multivariate logistic regression analysis, five preoperative predictors of postoperative respiratory failure were identified: type of surgery (highest risk with brain, abdominal, aortic surgery), emergency cases, poor preoperative functional status, preoperative sepsis, and higher ASA class. These variables were incorporated into a predictive model that was validated in a second cohort of over 250,000 patients from the 2008 NSQIP database. An interactive risk calculator, available online at http://www.surgicalriskcalculator.com/prf-risk-calculator, was then developed that estimates the likelihood of respiratory failure for a given patient.

Pulmonary consultants providing preoperative assessment are commonly asked to specifically comment on the risk posed by a patient's history of COPD. COPD has been identified as an

TABLE 104-1 Incidence of Respiratory Failure Following Various Surgical Procedures

Procedure	Incidence of Postoperative Respiratory Failure (%)
Mouth, palate, salivary glands, pharynx, adenoids, and esophagus	6.9
Thoracic and thoracoabdominal aneurysms, embolectomy/ thrombectomy, venous reconstruction, and endovascular repair	6.6
Stomach, intestines, appendix and mesentery, rectum and anus, liver, biliary tract, pancreas, abdomen, peritoneum, and omentum (nonhernia)	4.3
Respiratory system, hemic and lymphatic systems, mediastinum, and diaphragm	4.3
Aneurysm, blood vessel repair, thromboendarterectomy, angioscopy, angioplasty and atherectomy, bypass and composite grafts, other artery, and vein	4.2
Integumentary and musculoskeletal system	1.9
Hernioplasty, herniorrhaphy, herniotomy	0.4

Source: Adapted with permission from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1198.

TABLE 104-2 Scoring System for Estimating Risk of Postoperative Respiratory Failure: Parameters Used and Score Assigned

Parameter Set	Description	Score
1	ASA class 3	3
1	ASA class 4–5	5
2	Emergency	2
3	Work RVU 10–17	2
3	Work RVU >17	4
4	Preoperative albumin ≤3.5	1
5	Procedure: integumentary	1
5	Procedure: respiratory and hemic	3
5	Procedure: heart	2
5	Procedure: aneurysm	2
5	Procedure: mouth, palate	7
5	Procedure: stomach, intestines	2
5	Procedure: endocrine	2
6	Preoperative sepsis	2
7	Preoperative creatinine ≥1.5	2
8	History of severe COPD	2
9	Ascites	2
10	Dyspnea	1
11	Impaired sensorium	1
12	Preoperative bilirubin >1.0	1
13	>2 alcoholic drinks/d in 2 wk before admission	1
14	Bleeding disorders	1
15	Age >40 y	2
16	Preoperative white blood count <2.5 or >10	1
17	Preoperative serum sodium >145	2
18	Weight loss >10%	1
19	Preoperative acute renal failure	2
20	Male gender	1
21	Congestive heart failure <30 d before operation	1
22	Smoker	1
23	Preoperative platelet count ≤150	1
24	CVA/stroke with neurological deficit	1
25	Wound class (clean/contaminated)	1
25	Wound class (contaminated)	1
25	Wound class (infected)	1
26	Preoperative AST >40	1
27	Preoperative hematocrit ≤38	1
28	CVA/stroke without neurological deficit	1

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; RVU, relative value unit.
Source: Adapted with permission from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1198.

independent predictor of postoperative respiratory failure in numerous studies.[1,4–7] The largest and most comprehensive study utilized the NSQIP database containing over 460,000 patients who underwent a variety of surgical procedures. COPD was independently associated with an increased risk of ventilator dependence for more than 48 hours following surgery (odds ratio 1.45) and reintubation (odds ratio 1.54). Notably, neither this study nor the others referenced earlier categorized patients according to preoperative pulmonary function parameters, precluding conclusions about the relationship between severity of COPD and risk of postoperative respiratory failure.

The use of preoperative pulmonary function testing to assess risk of postoperative respiratory failure in COPD patients has been most closely examined in the context of lung resection surgery for lung cancer. Studies of patients undergoing standard thoracotomy and either pneumonectomy or lobectomy have used preoperative spirometry in conjunction with quantitative ventilation/perfusion lung scans to estimate postresection FEV_1 and diffusing capacity. While the study populations are small, published case series suggest that a predicted postresection FEV_1 or diffusing capacity less than 40% of normal is associated with a high risk for postoperative respiratory failure and death.[8–11] In one study that examined the performance characteristics of these parameters, the probability of respiratory failure or death was 33% for those patients with an FEV_1 <40% while the probability of avoiding these complications was 90% for those with an FEV_1 ≥40%.[10] Coupling pulmonary function testing with cardiopulmonary exercise testing allows for more precise risk stratification. Those patient with peak oxygen consumption of ≥10 to 15 mL/kg/min despite predicted postresection FEV_1 or diffusing capacity <40% appear to have a low risk of respiratory failure and death following thoracotomy and definitive lung resection procedures.[9,12] The use of video-assisted thoracoscopic surgery (VATS) in combination with lobectomy, segmentectomy, or wedge resection appears to be well tolerated by patients with severe lung disease, with only a 4% incidence of respiratory failure and a 1% mortality rate documented in one study of 100 consecutive patients with an FEV_1 <35% predicted.[13]

TABLE 104-3 Scoring System for Estimating Risk of Postoperative Respiratory Failure: Respiratory Risk Index

Score Range	Risk Level	Predicted Probability of PRF (%)
<8	Low	0.2
8–12	Medium	1.0
>12	High	6.5

Source: Adapted with permission from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1198.

Studies using preoperative spirometry to assess severity of COPD in patients undergoing cardiac surgery have provided conflicting results with respect to the risk of respiratory failure. One study found that an FEV_1 <70% was an independent predictor of post-CABG respiratory failure but the rather broad nature of the spirometric threshold used limits the utility of this finding.[4] A study of 1412 patients found that the combined incidence of prolonged postoperative mechanical ventilation (>48 hours) and reintubation increased with increasing severity of COPD: 2.3% in patients without COPD compared to 0%, 13%, and 77% in patients with FEV_1 60% to 80%, 40% to 59%, and <40%, respectively. In contrast, the largest study to date utilizing a database of over 11,000 patients did not detect an association between COPD severity and risk of prolonged postoperative mechanical ventilation even among patients with the most severe disease (FEV_1 <50%), though there was an increased risk of early mortality in this group.[14]

Data related to the use of preoperative pulmonary function parameters to stratify risk of postoperative respiratory failure in relation to noncardiothoracic surgical procedures are scant and conflicting. These data are summarized in a recent guidelines statement issued by the American College of Physicians, which concludes that for noncardiothoracic surgery, "insufficient evidence supports preoperative spirometry as a tool to stratify risk."[15] The guideline authors caution that available studies do not define a spirometric threshold below which the risk for noncardiothoracic surgery is prohibitive.

MEASURES TO REDUCE RISK

A number of the factors associated with an increased risk of postoperative respiratory failure can potentially be addressed to mitigate the risk. In some cases, the surgical approach can be modified. For example, use of a transverse abdominal incision appears to carry less risk than a vertical midline incision. Cholecystectomy performed by laparoscopic technique is associated with significantly less compromise in postoperative FEV_1 and FVC and more rapid recovery of lung function compared with the conventional open approach.[16] For thoracic procedures, median sternotomy and muscle-sparing lateral thoracotomy are better tolerated than posterolateral thoracotomy. However, these approaches provide more limited access to the thorax than does the standard thoracotomy incision and they are generally inadequate for resection of the left lower lobe or for tumors involving the posterior chest wall, diaphragm, or superior sulcus. In addition, removal of bulky tumors via the muscle-sparing approach may be problematic. VATS offers a minimally invasive alternative that is associated with a less severe decrement in respiratory muscle strength and lung function in the immediate perioperative period compared to thoracotomy.[17] A propensity-matched analysis of patients undergoing lobectomy by means of VATS versus open thoracotomy demonstrated a significantly lower rate of postoperative reintubation in the VATS cohort (1.4% vs. 3.1%).

Patients with COPD scheduled for surgery should undergo a preparatory pulmonary regimen intended to optimize lung function and minimize airway secretions. This regimen should include smoking cessation, institution or intensification of inhaled bronchodilator and inhaled corticosteroid therapy, and use of oral antibiotics in the presence of purulent secretions or a "loose" cough. Patients should be instructed on the use of incentive spirometry or cough and deep breathing techniques prior to surgery. A short course of oral corticosteroids should be considered in patients who have a significant bronchospastic component to their disease. Other than the assurance of strict compliance with the regimen, there is no reason to believe that hospitalization is superior to outpatient preparation of the patient.

Smoking has been shown to be a risk factor for postoperative pulmonary complications in general and for prolonged ventilatory support in particular.[1] Smoking does not appear simply to be a surrogate marker of COPD; rather it poses risk that is independent of the magnitude of pulmonary impairment. Detrimental effects of smoking include bronchial irritation with resultant excessive airway secretions, impairment in mucociliary clearance, and elevation of carboxyhemoglobin levels with consequent impairment in oxygen uptake and tissue oxygen utilization. Observational studies suggest that preoperative smoking cessation is associated with a reduction in pulmonary complications but these studies do not address the specific question of whether abstinence reduces the risk of respiratory failure.[18] A prospective, randomized trial investigated the impact of a preoperative smoking cessation program (counseling and nicotine replacement patch) on a number of postoperative complications including respiratory failure, following elective hip and knee replacement. Complete abstinence from smoking was achieved in 60% of the patients in the intervention arm compared to only 7% in the control arm. Despite this marked difference, only one patient in each group experienced postoperative respiratory failure. The obvious limitation of this trial relates to the choice of a surgical population at minimal risk for the complication under investigation. Pending additional studies, it would appear prudent to initiate smoking cessation measures in preparing patients for surgery, though the full benefit with respect to global reduction in pulmonary complications may require a minimum of 8 weeks of abstinence.[19]

IMPACT OF ANESTHESIA AND POSTOPERATIVE ANALGESIA ON PULMONARY FUNCTION

The potential impact of anesthesia and postoperative analgesia on pulmonary function is related to the form of anesthesia or analgesia employed.

GENERAL ANESTHESIA

Use of general anesthetic agents is associated with a number of well-characterized alterations in pulmonary mechanics, gas exchange, and respiratory drive.[20,21] In the controlled environment of the operating room, these physiological derangements are clinically inconsequential and easily overcome by simple adjustments of the ventilator. However, lingering effects of general anesthesia after completion of surgery may impede efforts to extubate the patient or may precipitate respiratory failure in the recovery room.

Administration of general anesthesia, whether by the inhaled or intravenous route, results in an almost immediate loss of diaphragmatic and intercostal muscle tone, a cephalad shift of the diaphragm, and a decrease in the transverse thoracic diameter. These dimensional alterations in thoracic volume result in a 20% reduction in functional residual capacity (FRC) and in the development of compressive atelectasis. As demonstrated using computerized tomography during and after general anesthesia, patients develop crescent-shaped areas of atelectasis in dependent areas of lung within 10 minutes of induction.[22] Atelectatic areas comprise approximately 2% to 10% of total lung volume and disappear

with the application of positive end-expiratory pressure (PEEP). Dependent atelectasis develops after administration of either inhalational or intravenous anesthetics. A notable exception is ketamine, a drug that is unique in its maintenance of respiratory muscle tone. The degree of atelectasis appears unaffected by whether the patient is breathing spontaneously or is mechanically ventilated.

Areas of dependent atelectasis perturb the normal balance of ventilation and perfusion in the lung. Persistent perfusion of nonventilated atelectatic areas results in an increase in the shunt fraction, which may approach 15%. The magnitude of shunt correlates directly with the volume of atelectatic lung and may be further magnified by impairment of hypoxic pulmonary vasoconstriction induced by certain inhalational anesthetics. Elderly patients, those who are obese, and patients with underlying COPD are most likely to develop clinically apparent hypoxemia in response to general anesthesia; the effect may persist into the early postoperative period.

The inhaled anesthetic agents in common usage are respiratory depressants that blunt the response to both hypoxemia and hypercapnia. These agents depress the ventilatory response to CO_2 in a dose-dependent fashion. They have a negligible effect on the hypercapnic response at the low concentrations encountered during emergence from anesthesia. In contrast, hypoxemic drive is markedly attenuated even at very low, subanesthetic concentrations of the volatile agents. As a result of deposition of these agents in muscle and fat, concentrations sufficient to depress hypoxic drive persist for several hours after termination of anesthesia. This can result in significant postoperative respiratory depression in patients with chronic hypercapnia who are dependent on hypoxic ventilatory drive to breathe.

NEURAXIAL ANESTHESIA

It is common practice for those providing preoperative assessment of high-risk patients to recommend the use of neuraxial (i.e., spinal or epidural) anesthesia, predicated on the impression that this route of administration lessens the adverse impact of anesthesia on the respiratory system. Neuraxial anesthesia does possess a number of favorable physiological features. In contrast to the effects of general anesthesia, neuraxial anesthesia preserves diaphragmatic innervation and function. External intercostal muscle paralysis is induced by thoracic levels of neuraxial anesthesia, but the level is generally two dermatomes below the sensory level because of the lesser sensitivity of motor neurons to the effects of the anesthetic agent. Hypoxic pulmonary vasoconstriction is unaffected by neuraxial anesthesia, and the ventilatory response to CO_2 is unimpaired; indeed the CO_2 response may be heightened. A meta-analysis of trials comparing general to neuraxial anesthesia detected a significant reduction in 30-day mortality, venous thromboembolism, pneumonia, and respiratory depression.[23] Another meta-analysis restricted to patients undergoing hip fracture surgery also detected a reduction in 30-day mortality as well as a trend toward a lower incidence of postoperative hypoxemia associated with neuraxial anesthesia.[24] While these analyses suggest significant advantages associated with use of neuraxial anesthesia, they have been criticized because of the heterogeneous nature of the surgical populations and the use of older anesthetic techniques and older anesthetic agents.[25] Pending further studies, neuraxial anesthesia should not necessarily be viewed as the strategy of choice in more tenuous surgical candidates.

POSTOPERATIVE ANALGESIA

Postoperative analgesia is an essential component of the care of the surgical patient. Analgesia is important not only in ensuring patient comfort, but also in mitigating the adverse effects of pain on respiratory function and airway clearance. Inadequate pain relief can lead to splinting and patient reluctance to cough and deep breathe; the end result is promotion of retained secretions, atelectasis, hypoxemia, and, possibly, pneumonia. For major surgical procedures, particularly those involving the chest and upper abdomen, administration of opiates via the parenteral or epidural route has become the analgesic method of choice.

The use of narcotic analgesia in the postoperative period is associated with a small, but not insignificant, risk of precipitating respiratory depression. The reported incidence of respiratory depression varies based on the criteria employed. A meta-analysis of published studies revealed an incidence of 0.3% defined by the need to administer naloxone, 3.3% defined by the presence of hypercapnia, and 17% defined by oxygen desaturation.[26] The risk may be slightly lower in association with the epidural as opposed to parenteral route of administration. When administered epidurally, hydrophilic narcotics (e.g., morphine) have a greater tendency than lipophilic compounds (e.g., fentanyl) to remain in the cerebrospinal fluid and to spread rostrally to the respiratory center located in the floor of the fourth ventricle. Elderly patients are particularly susceptible to the respiratory depressant effects of opiates, likely reflecting an impaired ability to metabolize these agents. Respiratory depression in the postoperative patient is most likely to occur during the initial 24 hours following surgery. It is typically accompanied by a decreased level of consciousness and a slow respiratory rate. Treatment consists of administration of naloxone in 0.1 to 0.4 mg aliquots. Ventilation should be supported with a face mask and Ambu bag, reserving intubation for the failure of naloxone to swiftly rectify the problem.

Prospective, randomized trials examining pulmonary complications associated with epidural versus intravenous administration of perioperative analgesia following major abdominal surgical procedures have provided somewhat conflicting results. One study of 168 patients found no difference in rates of prolonged intubation or reintubation between groups receiving epidural versus intravenous postoperative analgesia.[27] A small trial involving 70 elderly patients reported no difference in duration of postoperative mechanical ventilation or major pulmonary complications (including reintubation).[28] In contrast, a larger study of 915 patients with at least one comorbidity defining them as "high-risk" surgical candidates found that epidural analgesia was associated with a significant reduction (23% with epidural vs. 30% with intravenous route) in postoperative respiratory failure, defined rather broadly as need for prolonged ventilation or reintubation or $Pa_{O_2} \leq 50$ mm Hg or $Pa_{CO_2} \geq 50$ mm Hg on room air.[29] Finally, a trial of over 1000 patients demonstrated a significant reduction in postoperative respiratory failure (defined as the need for intubation and mechanical ventilation for >24 hours postoperatively or reintubation) with the use of epidural analgesia in the subset of patients undergoing aortic surgery, but not those undergoing nonaortic abdominal surgery.[30]

IMPACT OF SURGERY ON POSTOPERATIVE PULMONARY FUNCTION

Surgery involving the upper abdomen and thorax results in a pronounced impairment in pulmonary function in the postoperative period. The impairment is more severe and prolonged than that due to administration of general anesthesia alone. Typically, upper abdominal and thoracic procedures are associated with a fall in lung volumes, development of atelectasis, and hypoxemia. These adverse effects commonly necessitate short-term administration of low-flow, supplemental oxygen, but when severe, or when accompanied by underlying lung disease, may precipitate respiratory failure.

UPPER ABDOMINAL SURGERY

Within 24 hours following upper abdominal surgery, vital capacity declines by 50%.[31] Although the vital capacity improves with time, marked impairment persists for as long as 7 days after the surgery. In contrast, vital capacity falls by only 25% following lower abdominal procedures; it returns to normal by the third postoperative day.[31]

Underlying these profound changes after upper abdominal surgery is the development of diaphragmatic dysfunction, as reflected in a reduction in transdiaphragmatic pressure with tidal respirations and in a shift from abdominal to rib cage breathing.[32,33]

Two main theories have been proposed to explain the observed impairment in diaphragmatic function. One theory is that there is a primary alteration in diaphragmatic contractility induced by local irritation, inflammation, surgical trauma, or pain. This theory has been rendered improbable with the demonstration that external stimulation of the phrenic nerves produces normal peak transdiaphragmatic pressure in patients recovering from upper abdominal surgery.[32] In other words, when maximally stimulated the diaphragm functions in a normal fashion.

The alternative, and currently favored, theory proposes that diaphragmatic dysfunction results from diminished phrenic nerve output. The basis for the attenuation in neural drive remains a matter of speculation, although several putative pathways can be rationally eliminated. For example, general anesthesia is known to depress output from the central respiratory centers, as well as to inhibit synaptic transmission. However, as noted previously, the effects of general anesthesia on diaphragmatic tone are transient and modest. In addition, the degree of dysfunction observed after upper abdominal procedures is not seen following general anesthesia for procedures on the lower abdomen and extremities. An inhibitory arc initiated by abdominal nociceptors for pain is unlikely, given that achievement of adequate pain control by epidural opiates fails to consistently improve pulmonary function or to normalize diaphragmatic performance. In contrast, the epidural administration of anesthetic agents such as bupivacaine does ameliorate diaphragmatic dysfunction following upper abdominal surgery. Since these agents produce sympathetic blockade in addition to pain control, it has been argued that visceral sympathetic afferents are responsible for providing an inhibitory signal that downgrades central neural drive and phrenic nerve activity, thereby leading to impaired diaphragmatic function. Supporting the notion of a reflex inhibitory arc mediated by visceral afferents is the demonstration in experimental animals that mechanical gall bladder stimulation strongly inhibits electromyographic activity and motion of the diaphragm.[34]

CARDIAC SURGERY

Although CABG – the most commonly performed cardiac surgical procedure – has been most intensively scrutinized with respect to its impact on the respiratory system, other related cardiac procedures (e.g., valve replacement) are likely to have similar effects. Lung volumes decrease by approximately 30% after CABG; the return to preoperative values may take several months.[35–37] Lung function may decline to a greater degree when internal mammary harvesting and grafting are employed.[35] Gas exchange is also impaired after CABG, as evident in the development of hypoxemia and significant widening of the alveolar–arterial oxygen gradient. In 125 patients who had daily room air arterial blood gas determinations prior to and following CABG, Pa_{O_2} fell from approximately 75 mm Hg preoperatively to a nadir of 55 mm Hg on postoperative day 2.[38] The Pa_{O_2} improved but remained below preoperative values at the end of the first postoperative week. A similar pattern and magnitude of decline in oxygenation have been demonstrated in other studies, with the development of hypoxemia associated with an increase in calculated shunt fraction from 3% preoperatively to a peak of 19% postoperatively.[37] The increase in shunt fraction is readily accounted for on the basis of atelectasis, which is invariably present postoperatively, especially on the left side.

A number of factors have been implicated in the development of post-CABG pulmonary dysfunction and atelectasis. Alterations in chest wall compliance and motion may result from division of the sternum, harvesting of the internal mammary artery, and traumatic injury to the costovertebral joints and first rib induced by retraction. Intraoperative lung retraction may directly injure the left lower lobe, leading to contusion and atelectasis, and, perhaps, accounting for the predilection for radiographic infiltrates on the left side. An alternative explanation for post-CABG left lower lobe atelectasis is intraoperative injury to the left phrenic nerve and consequent diaphragmatic paralysis or paresis. The phrenic nerve is vulnerable to stretch and ischemic injury during sternal retraction, dissection of the left internal mammary artery, or prolonged distention of the pericardium. In addition, thermal injury to the nerve may occur with the cardioplegic technique of instilling iced slush into the open pericardial sac. The actual incidence of phrenic nerve dysfunction after CABG is best defined in studies employing electrophysiological techniques, which have documented evidence of phrenic nerve injury in 10% to 16% of patients.[39–41] This suggests that phrenic nerve injury accounts for only a minority of the observed cases of left lower lobe atelectasis.

Finally, cardiopulmonary bypass (CPB) may contribute to pulmonary impairment after cardiac surgery. The duration of CPB has been linked to the severity of postoperative atelectasis; whether this relationship is causal is unclear.[40] It has been hypothesized that the use of CPB leads to abnormal surfactant production – possibly due to ischemic, thermal, or toxic injury to the alveolar epithelium – predisposing to the development of atelectasis. More clearly established is the ability of the bypass pump to induce a capillary leak syndrome, marked by extravasation of fluid into the alveolar interstitium and, rarely, into the airspaces. This process is thought to result from exposure of blood to nonendothelial surfaces, resultant activation of neutrophils, complement, and other inflammatory cascades, and sequestration of neutrophils within the microvasculature. While this rarely may lead to full-blown ARDS (see discussion below), the consequences are usually more subtle, manifesting as a widened arterial–alveolar oxygen gradient and diminished lung compliance. The recent introduction of "off-pump" CABG has permitted a greater appreciation of the adverse impact of CPB on postoperative lung function. For example, a recent large multicenter comparative analysis from the United Kingdom of CABG with or without CPB demonstrated significant reductions in the rates of prolonged mechanical ventilation (>24 hours), reintubation/tracheostomy, and ARDS/pulmonary edema/pneumonia among the group that underwent off-pump CABG.[42]

LUNG RESECTION

Unique to lung resection surgery is the immediate loss of lung function due to removal of lung parenchyma. The magnitude of the loss can be estimated reliably from preoperative quantitative lung scanning in conjunction with standard spirometry. The impact of lung resection on pulmonary function is further magnified in the perioperative period by other factors. For example, the standard posterolateral thoracotomy incision represents significant chest wall trauma, with rib retraction and resection, and transection of intercostal, latissimus dorsi, trapezius, and serratus anterior muscles. As a result, total respiratory compliance may fall by as much as 75%; work of breathing increases; and lung volumes decline dramatically, out of proportion to the surgical loss of functional lung. Following standard thoracotomy and lung resection (either lobectomy or wedge resection), FEV_1 and FVC fall to 25% of preoperative values at 1 hour, and to 30% at 24 hours. When a more limited, muscle-sparing incision is used, the impact on pulmonary function is markedly attenuated.[43] Lung resection via VATS is also associated with less severe impairment in lung function.[17]

As with cardiac and upper abdominal surgery, atelectasis is frequently present after lung surgery and results in impaired oxygenation. Phrenic nerve activity remains normal and diaphragmatic

TABLE 104-4 Causes of Postoperative Respiratory Failure

Factors extrinsic to the lung
• Depression of central respiratory drive (anesthetics, opioids, sedatives)
• Phrenic nerve injury/diaphragmatic dysfunction
• Obstructive sleep apnea
Factors intrinsic to the lung
• Atelectasis
• Pneumonia
• Aspiration of gastric contents
• Acute respiratory distress syndrome
• Volume overload/congestive heart failure
• Pulmonary embolism
• Bronchospasm/COPD

function during tidal breathing is preserved, although maximal diaphragmatic strength may be reduced.

CAUSES OF POSTOPERATIVE RESPIRATORY FAILURE

The development of acute respiratory failure in the surgical patient should prompt a systematic assessment of the likely causes (Table 104-4). In approaching this life-threatening problem, one must consider the nature and magnitude of pre-existing pulmonary disease, type of surgery performed, drugs administered intra- and postoperatively, and predominant derangement in gas exchange (i.e., hypoxemia or hypercapnia). In conjunction with important information derived from the physical examination and chest radiograph, the analysis should readily identify factors responsible for or contributing to respiratory failure. The following discussion focuses on the more common or unique causes of postoperative respiratory failure in the surgical setting.

■ ATELECTASIS

Atelectasis is the most common pulmonary complication encountered in the surgical patient, particularly following thoracic and upper abdominal procedures. As discussed previously, anesthesia and surgical manipulation act in concert to produce regional atelectasis through incompletely defined mechanisms, including diaphragmatic dysfunction and diminished surfactant activity. The atelectasis is typically basilar and segmental in distribution, obscuring the hemidiaphragms radiographically. A distinct and less common cause of postoperative atelectasis is plugging of central airways by retained secretions. This problem is encountered in the surgical patient whose efforts to clear secretions are compromised by depressed consciousness, inadequate pain control, or a weak, ineffective cough. When situated in a main stem bronchus, mucus plugs can result in collapse of an entire lung; more distal obstruction leads to lobar collapse. An abrupt termination of the proximal bronchial air shadow and the absence of air bronchograms within the atelectatic portion of lung are clues to the possible presence of mucus plugging.

While often clinically insignificant, postoperative atelectasis may lead to severe hypoxemia and respiratory distress. The magnitude of hypoxemia is dictated by the extent of atelectasis, the presence and severity of underlying lung disease, and the integrity of the hypoxemic pulmonary vasoconstrictive response. Impairment of hypoxemic pulmonary vasoconstriction by vasodilatory drugs, commonly administered to surgical patients for treatment of underlying hypertension or ischemic heart disease, prevents the compensatory diversion of blood flow away from nonventilated areas of lung and magnifies the shunt fraction.

Respiratory distress due to atelectasis usually evolves insidiously over the first several postoperative days. Supplemental oxygen requirements increase in association with worsening basilar infiltrates noted on the chest radiograph. The clinicoradiographic picture may be indistinguishable from that of pneumonia. While fever and leukocytosis suggest infection, these signs are common and nonspecific. When atelectasis is due to central airway occlusion by mucus plugs, hypoxemia and respiratory distress may develop quickly. A chest radiograph obtained immediately after the onset of symptoms may be surprisingly unrevealing if sufficient time has not passed to permit resorption of gas from the airspaces of the nonventilated lung. Careful examination of the patient, however, will reveal an absence of breath sounds over the involved lung, providing an important clue to the presence of central airway obstruction and obviating pursuit of other considerations, such as pulmonary embolism (PE).

Treatment of respiratory failure due to atelectasis is directed toward the combined goals of adequate oxygenation and re-expansion of lung segments. Supplemental oxygen should be titrated to achieve an arterial oxyhemoglobin saturation of at least 90%. Refractory hypoxemia, severe respiratory distress, progressive hypercapnia, or inability of the patient to clear copious airway secretions should prompt immediate intubation and mechanical ventilatory support. This lifesaving intervention permits more efficient delivery of oxygen, secures access for suctioning of the airways, and facilitates performance of bronchoscopy should it be necessary. Moreover, the positive pressure and large tidal volumes delivered by the ventilator are often effective in rapidly re-expanding collapsed lung segments. In less dire circumstances, noninvasive ventilation may be equally effective.

Fiberoptic bronchoscopy is commonly employed in the treatment of serious atelectasis but evidence suggests that it may be no more effective than standard chest physiotherapy. In the only randomized study directly comparing these strategies, immediate fiberoptic bronchoscopy did not result in more rapid or complete resolution of acute lobar atelectasis when compared with a regimen of deep breathing, coughing, suctioning of the intubated patient, aerosolized bronchodilator treatments, chest percussion, and postural drainage.[44] Resolution of atelectasis was dictated not by the treatment modality employed, but by radiographic evidence of central airway patency. In this regard, both chest physiotherapy and bronchoscopy were highly effective in the absence of an air bronchogram. In contrast, the presence of an air bronchogram, which indicates that the atelectasis is not due to proximal airway obstruction, was associated with minimal response to either modality. Based on this, standard respiratory therapy techniques applied to either the spontaneously or mechanically ventilated patient should be considered the mainstay of treatment for lobar atelectasis. Fiberoptic bronchoscopy should be reserved for those situations where chest physiotherapy is contraindicated (e.g., chest trauma, immobilized patient), poorly tolerated, or unsuccessful, or in the setting of life-threatening hypoxemia.

A number of other measures are commonly employed in the treatment of atelectasis. Judicious use of analgesia is an essential adjunct, permitting the patient to breathe deeply, cough forcefully, and comfortably participate in chest physiotherapy maneuvers. Care must be taken to avoid excessive sedation, which will offset the beneficial effects of pain control. In the setting of marked hypoxemia, attempts should be made to discontinue vasoactive drugs with the potential to influence the pulmonary vascular bed; examples include nitrates, nitroprusside, calcium channel blockers, angiotensin-converting enzyme inhibitors, and hydralazine. Mucolytics, such as N-acetyl cysteine, are commonly administered in an effort to promote clearance of tenacious secretions; however, their efficacy in this setting has not been well documented. Some clinicians and

respiratory therapists advocate the use of nasotracheal suctioning of the nonintubated patient with a weak and ineffective cough. However, this technique is associated with considerable discomfort and is an inefficient and highly transient means of clearing secretions from the tracheobronchial tree.

Maneuvers to promote periodic full lung expansion, including intermittent positive pressure breathing (IPPB), cough and deep breathing exercises, and incentive spirometry, have been developed in an attempt to prevent or mitigate the severity of atelectasis. Early trials suggested that all three techniques were equally efficacious and superior to no therapy in the prevention of postoperative pulmonary complications following abdominal surgery.[45] IPPB has largely been abandoned due to its expense, need for specially trained personnel and close patient supervision, and tendency to produce abdominal distention. While incentive spirometry is universally employed in the care of the postoperative patient, two recent Cochrane Reviews challenge the deeply ingrained view that this is an essential measure. These reviews, focusing on upper abdominal surgery[46] and CABG,[47] respectively, conclude that there is no evidence of benefit from incentive spirometry in reducing pulmonary complications and, in the case of CABG, in decreasing the negative effects on pulmonary function. Both reviews caution that there are extensive methodological shortcomings of available studies that limit their interpretation. Given that incentive spirometry is inexpensive and simple to perform, it seems prudent to continue this practice despite the absence of rigorous proof of efficacy.

PNEUMONIA

Pneumonia is the third most common postoperative infection and the most lethal, with an associated mortality rate of 20% to 50%.[48] Pneumonia represents a principal cause of postoperative respiratory compromise and may precipitate acute respiratory failure, as well as complicate respiratory failure in the patient who is ventilator-dependent for other reasons. The type of surgery heavily influences the risk of developing pneumonia in the postoperative period. In particular, the risk is greatest following abdominal aortic aneurysm repair, thoracic and upper abdominal procedures, head and neck surgery, and neurosurgical procedures.[48] Patient-specific risk factors that have been identified include advanced age, chronic steroid use, current or recent smoking, COPD, low serum albumin level, impaired sensorium, and dependent preoperative functional status.[48,49] The presence of a nasogastric tube and the use of gastric acid–suppressive medications, commonly employed interventions in postoperative patients, have been cited as risk factors for nosocomial pneumonia in general.[50] A multifactorial model, employing a number of these patient-related and procedure-related factors, has been developed and validated that predicts the risk of pneumonia in nonintubated patients following major noncardiac surgery.[48] Perhaps the most important risk factor, not addressed in this predictive model, is the need for postoperative mechanical ventilatory support. Overall, mechanically ventilated patients have a 6- to 21-fold increased risk of pneumonia compared with nonventilated patients.[51]

While organisms may reach the lower respiratory tract by several routes, microaspiration of oropharyngeal secretions appears to be the predominant mechanism in the pathogenesis of nosocomial pneumonia. A critical initiating event in this pathway is colonization of the oropharynx with gram-negative aerobic bacilli, a process that characteristically occurs in response to serious illness or surgical stress. Clinically occult aspiration of these virulent organisms is facilitated by a number of iatrogenic measures imposed upon the surgical patient. Paramount among these is the placement of an endotracheal tube, which impairs swallowing, stents open the glottis, and permits pooling of secretions above the tube cuff. The inflated cuff is an imperfect barrier and allows intermittent seepage of secretions into the lower airways. Prolonged intubation has also been associated with postextubation swallowing dysfunction. Depressed consciousness as a consequence of general anesthesia and postoperative analgesia further contributes to the risk of aspiration.

Recent attention has focused on the stomach as an additional source of bacteria in the development of nosocomial pneumonia. While the acidic milieu of the stomach normally inhibits bacterial growth, the common use of H2-blockers and antacids as stress ulcer prophylaxis overrides this natural barrier and promotes gastric colonization with gram-negative enteric organisms. Gastroesophageal reflux, a common feature of the critically ill patient, permits bacteria-laden gastric contents to enter the respiratory tract either directly or by first colonizing the oropharynx. This route of migration has been confirmed by recovery of technetium-99m-labeled gastric contents in endobronchial secretions and by the demonstration in some patients that organisms cultured from the airways first appeared in the stomach.[52] Perhaps the most compelling, albeit circumstantial, evidence derives from studies that have shown a higher incidence of nosocomial pneumonia in patients receiving H2-blockers or proton-pump inhibitors.[50]

The fate of organisms introduced into the lower respiratory tract is dependent upon the integrity of mechanical and immunological pulmonary defense mechanisms. Impairment of the mucociliary escalator (e.g., due to recent cigarette smoking or underlying COPD), weak and ineffective cough, and use of immunosuppressive medications (e.g., corticosteroids) favor the proliferation of organisms and the development of pneumonia. It is widely held that postoperative atelectasis predisposes to pneumonia by entrapping bacteria. However, studies demonstrating a lack of concordance between the degree of atelectasis and the subsequent risk of pneumonia challenge this contention.[53]

The constellation of fever, leukocytosis, purulent sputum, and radiographic infiltrates has traditionally defined the presence of pneumonia. While these diagnostic criteria are reasonably accurate in the previously healthy outpatient, they are notoriously nonspecific in the setting of recent surgery, particularly with prolonged use of mechanical ventilation. In one autopsy series, traditional clinical and radiographic criteria provided the correct antemortem diagnosis in only 70% of cases.[54] Alternative etiologies of radiographic infiltrates include atelectasis, pulmonary edema, infarction or hemorrhage due to pulmonary emboli, pulmonary contusion, and chemical pneumonitis. Cultures of sputum and tracheal aspirates are poorly reflective of the bacterial flora of the distal airways, since these specimens are contaminated by colonizing organisms in the oropharynx and upper respiratory tract. In an attempt to enhance diagnostic certainty, bronchoscopic sampling of the distal airways using a sterile sheathed brush or bronchoalveolar lavage has been advocated. While the absence of a "gold standard" for the diagnosis of pneumonia has complicated attempts to define the accuracy of these techniques, rates of false-positive and false-negative results have generally fallen in the range of 30%. It is questionable, therefore, whether the performance of bronchoscopy actually contributes significantly to a reduction in the degree of diagnostic uncertainty.

The most common organisms isolated in cases of postoperative pneumonia are gram-negative bacteria and *Staphylococcus aureus*.[55] Polymicrobial infections are common, occurring in approximately one-third of cases. The emergence of highly resistant organisms, such as methicillin-resistant *S. aureus* and multidrug resistant *Acinetobacter* species poses a particular challenge in selecting empiric antibiotics and in definitively treating these infections. In one large study of postoperative pneumonia, the initial antibiotic regimen had to be modified in 47% of cases because of antibiotic resistance or clinical failure.[55]

Preventative strategies intended to diminish the risk of pneumonia are an important consideration in the care of the surgical patient. Prevention begins in the preoperative phase with emphasis

on abstinence from cigarette smoking for a minimum of 8 weeks prior to elective surgery. Following surgery, nasogastric and endotracheal tubes should be removed as soon as possible. Postoperative analgesia must be titrated to permit the patient to comfortably and vigorously cough, but excessive sedation impairing protection of the airway and enhancing the risk of aspiration must be avoided. For the high-risk ventilator-dependent patient, maintenance of a semierect position has been shown to diminish the magnitude of clinically occult aspiration of gastric contents and the incidence of pneumonia. More controversial in this high-risk population is the use of selective digestive decontamination (SDD), intended to prevent or diminish the magnitude of gram-negative colonization of the aerodigestive tract. Regimens have varied among studies, but they typically consist of some combination of antibiotics applied topically to the oropharynx, instilled into the stomach as a slurry, and/or administered systemically. Several prospective randomized trials and meta-analyses demonstrated that SDD reduced the incidence of pneumonia among critically ill patients.[56,57] Despite the suggested efficacy of this approach, SDD is not widely utilized, in part because of lingering concerns that this strategy will lead to emergence of increasingly resistant bacterial strains.

■ ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is defined by the constellation of hypoxemic respiratory failure, diffuse pulmonary infiltrates, and the absence of clinical evidence of elevated left atrial pressure (see Chapter 141). The histological hallmark of ARDS is diffuse alveolar damage, a widespread injury to the alveolar–capillary membrane that leads to increased capillary permeability and development of noncardiogenic pulmonary edema. ARDS represents the end result of a variety of insults that either involve the lung directly (e.g., aspiration of gastric contents) or trigger pulmonary inflammation as part of a systemic process (e.g., sepsis). Many of the risk factors associated with development of ARDS are commonly encountered in surgical patients. In decreasing order of risk, these include sepsis, massive blood transfusion, pulmonary contusion, aspiration of gastric contents, and multiple fractures.[58] Causes of ARDS of particular relevance to the surgical patient, and, in some cases, unique to this population, are described in greater detail below.

■ ASPIRATION OF GASTRIC CONTENTS

Aspiration of gastric contents can rapidly lead to widespread acute lung injury and is an important cause of ARDS in the surgical patient. It is the third leading cause of anesthesia-related deaths, accounting for 10% to 30% of fatal outcomes. Aspiration typically occurs when the mechanisms of glottic closure and cough, which normally protect the airway, are compromised. In the surgical patient, the period of maximal vulnerability for aspiration spans from the induction of general anesthesia to full return of consciousness postoperatively. A number of factors combine to enhance the risk of aspiration during this period. Most important is the blunting of consciousness that accompanies induction and administration of general anesthesia. Insufflation of air into the stomach during induction may cause gastric distention and promote vomiting. Vomiting may also be provoked by noxious stimulation of the posterior oropharynx during intubation or extubation. Reflux of gastric contents is facilitated by medication-induced relaxation of the lower esophageal sphincter, placement of the patient in a supine position, and manipulation of the bowel during abdominal procedures. At the completion of surgery, extubation is commonly performed at a time when the patient, while able to ventilate adequately, may not yet be capable of fully protecting the airway. Indeed, upper airway reflexes remain significantly impaired for up to 2 hours after recovery from anesthesia, even at a time when mental alertness has returned. Moreover, translaryngeal intubation, even when brief, may cause residual glottic dysfunction for up to 8 hours following removal of the tube. While the risk of aspiration diminishes beyond the immediate perioperative period, it remains a concern in the patient receiving narcotic analgesia, which may not only induce vomiting, but also depress consciousness.

The risk of aspiration during the immediate perioperative period was delineated in a survey of over 215,000 general anesthetic procedures performed at the Mayo Clinic.[59] Aspiration was defined as the presence of bilious or particulate matter in the airways or the development of a new infiltrate on the immediate postoperative chest radiograph. The overall incidence of aspiration was only 0.03%, but the incidence was nearly fourfold higher (0.11%) in the setting of emergency surgery. In addition to the use of general anesthesia, other predisposing factors were present in over half of the patients who aspirated. These included gastrointestinal obstruction, swallowing dysfunction, altered sensorium, previous esophageal surgery, and a recent meal. The majority of events occurred during laryngoscopy (in preparation for insertion of the endotracheal tube) and during tracheal extubation. Twenty percent of patients who aspirated required postoperative mechanical ventilation in excess of 6 hours; 5% died as a direct result of this complication. The use of laryngeal mask airway devices does not appear to be associated with an increased risk of aspiration despite the fact that these devices do not isolate the larynx from the gastrointestinal tract.[60]

Acidic gastric contents introduced into the airways are rapidly disseminated throughout the bronchial tree and lung parenchyma, producing an almost instantaneous chemical burn. In addition, acid aspiration triggers a more delayed inflammatory response, with release of inflammatory cytokines and recruitment of neutrophils into the lung. The result is injury to the alveolar–capillary membrane, with flooding of the interstitium and airspaces by proteinaceous edema fluid. Surfactant levels drop precipitously due to both direct acid denaturation and diminished production, leading to alveolar instability and atelectasis. The magnitude of lung injury is directly related to the pH and volume of aspirated material. Initial studies in animals suggested that a pH of less than 2.5 and a volume in excess of 0.4 mL/kg are critical threshold values for the induction of lung injury.[61] While these values are now often quoted in the literature, their validity has been challenged by more recent studies demonstrating significant injury in association with lower volumes and higher pH. In particular, aspiration of bile is capable of inducing widespread injury even at a pH as high as 7.19. The presence of large food particles may further exacerbate the problem by causing airway obstruction and atelectasis. Notably, infection does not normally play a significant role in the initial lung injury from aspiration of acidic gastric contents, as the low pH serves to maintain relative sterility of the inoculum. However, gastric colonization with bacteria can occur in patients maintained on acid-suppressive agents, those receiving enteral feeds, and those with gastroparesis or small bowel obstruction.

The diagnosis of aspiration is most firmly established in the setting of witnessed vomiting or recovery of gastric contents from the airways. More often, the diagnosis is suspected circumstantially in a patient with risk factors and a compatible clinicoradiographic picture. Massive aspiration presents with fever, tachypnea, and diffuse rales developing within several hours of the event. Wheezing is appreciated in approximately one-third of patients and may be due either to obstruction of airways by particulate matter or, more commonly, to reflex bronchospasm. Hypoxemia is universally present with massive aspiration and is sufficiently severe in the majority of patients to mandate use of mechanical ventilation. The initial presence of apnea or shock is particularly ominous and portends a high risk of subsequent death. Initial radiographic patterns vary, depending upon the volume, causticity, and distribution of the aspirated material. However, three general patterns have been described:

(1) extensive bilateral consolidation resembling diffuse pulmonary edema; (2) widespread, but discrete, patchy infiltrates involving dependent areas of lung; and (3) focal consolidation usually localized to one or both lung bases.

The clinical course following massive aspiration is variable, but it typically diverges along one of several pathways. A minority of patients follow a fulminant course leading quickly to hypoxemic respiratory failure. More commonly, patients demonstrate progressive radiographic and clinical improvement over the first several days. Although most of these patients will go on to full recovery, a subset demonstrates secondary deterioration due to the development of nosocomial pneumonia. The overall mortality rate associated with massive aspiration is approximately 30% and exceeds 50% in those patients with initial shock or apnea, secondary pneumonia, or ARDS.

The treatment of respiratory failure secondary to aspiration is supportive and includes mechanical ventilatory strategies common to other forms of ARDS (Chapter 141). Bronchoscopy is indicated only when large airway obstruction by particulate matter is suspected on the basis of a localized wheeze or lobar atelectasis. Because acid is disseminated and endogenously neutralized within seconds, large-volume bronchoalveolar lavage is ineffective in attenuating the degree of injury and is not recommended. Studies of the administration of systemic corticosteroids in the treatment of aspiration pneumonitis have been inconclusive and do not currently justify their use. Similarly, use of prophylactic antibiotics is generally discouraged in the absence of supportive data and because of fear that this practice will preferentially select more highly resistant organisms. Some authors do advocate use of empiric antibiotics for that subset of patients at risk for gastric colonization with bacteria, as described above. In addition, up to 40% of patients will develop a superimposed bacterial pneumonia within several days of the aspiration event, often heralded by a new fever, new or progressive infiltrates, and purulent sputum. Broad-spectrum antibiotic therapy is indicated at that time.

The high morbidity and mortality associated with aspiration and the lack of effective therapy once the event has occurred have focused attention on measures to prevent this complication. The most straightforward and widely utilized measure is the convention of overnight fasting prior to elective surgery. However, despite prolonged fasting, up to one-third of patients will maintain a gastric volume in excess of 0.4 mL/kg (approximately 25–30 mL in the average adult), and up to three-quarters will have a gastric pH below 2.5. Administration of H2-blockers and proton-pump inhibitors can effectively raise the pH and reduce the volume of gastric contents, suggesting a potentially appealing strategy.[60] However, evidence suggesting that preoperative administration of these agents decreases the incidence or severity of aspiration is notably absent and their routine use in the preoperative setting is not currently recommended. In high-risk patients, rapid sequence induction of anesthesia should be employed to shorten the time between loss of consciousness and tracheal intubation. During induction, manual pressure should be applied to the cricoid cartilage (Sellick maneuver) and maintained until the endotracheal tube is in proper position and the cuff is inflated. Postoperatively, extubation should be performed only when consciousness and the gag reflex have returned to a level sufficient to permit adequate protection of the airway.

■ POSTPNEUMONECTOMY PULMONARY EDEMA

Postpneumonectomy pulmonary edema describes the development of diffuse pulmonary edema in the remaining lung, in the absence of identifiable causes. While some authors apply this term exclusively in the setting of pneumonectomy, others have reported similar cases following lobectomy. Demonstration of normal pulmonary artery occlusion pressures and of protein-rich edema fluid in a small number of patients suggests that an increase in vascular permeability rather than hydrostatic pressure underlies the edema formation.[62] However, the exact mechanism responsible for lung injury remains a matter of conjecture. Mechanisms that have been advanced include hyperinflation and volutrauma resulting from single lung ventilation, endothelial injury due to hyperperfusion of the remaining lung, disruption of lymphatic drainage, and ischemia-reperfusion injury.[63]

The incidence of postpneumonectomy pulmonary edema ranges between 4% and 7%, in part reflecting variable definitions.[63] For unclear reasons, the complication is encountered more frequently following right pneumonectomy. The majority of cases develop by postoperative day 3. The observed mortality rate is in the range of 50% to 100%. Treatment is supportive, centering on lung-protective ventilator strategies. A nonrandomized trial suggested that the intraoperative administration of Solu-Medrol was associated with a decreased incidence of postpneumonectomy pulmonary edema but this is not considered standard of care.[64]

■ CARDIOPULMONARY BYPASS

ARDS develops immediately following use of CPB in approximately 1% of cases.[65] While factors unrelated to the use of CPB may be at play, there is evidence from both animal models and clinical studies to suggest that CPB activates a number of inflammatory pathways that could lead to acute lung injury. It is well established, for example, that CPB results in neutrophil activation, likely through mechanical shear stress and exposure to the artificial surfaces of the bypass circuit. In addition, an increased expression of cell surface adhesion molecules has been demonstrated, which may promote neutrophil binding to pulmonary endothelium and release of proteolytic enzymes and reactive oxygen species. The central role played by neutrophils in causing acute lung injury following CPB is supported by several lines of evidence: (1) bronchoalveolar lavage fluid from patients undergoing CPB contains an increased number of neutrophils; (2) plasma levels of neutrophil elastase and myeloperoxidase are increased; and (3) inhibition of neutrophil activation with pentoxiphylline as well as neutrophil depletion attenuate the degree of pulmonary dysfunction. A number of other inflammatory mediators are released in association with CPB, including complement, proinflammatory cytokines, and prostaglandins. Perhaps the most compelling, albeit circumstantial, evidence implicating CPB as a cause of postoperative pulmonary dysfunction is the demonstration in multiple studies of a significant reduction in the incidence of prolonged postoperative ventilator dependence associated with CABG when performed off-pump.[42,66,67]

■ AMIODARONE

Amiodarone-induced pulmonary toxicity usually presents as a subacute illness characterized by cough, dyspnea, fever, and patchy pulmonary infiltrates. Less commonly, the use of amiodarone has been linked to the development of ARDS immediately following cardiac and thoracic surgery. In most of the reported cases, amiodarone was administered preoperatively for varying periods of time for control of arrhythmias.[68] The majority of patients had no evidence prior to surgery of the more indolent form of amiodarone pulmonary toxicity. Development of ARDS also has been described in patients whose only exposure to amiodarone occurred in the postoperative period, when the drug was initiated as prophylaxis or treatment for atrial arrhythmias. In one report, postoperative ARDS developed in 11% of patients receiving amiodarone and in only 1.8% of untreated patients.[69] The specific perioperative factors that act in concert with amiodarone to produce acute lung injury remain to be defined.

Some authors have suggested that exposure to high levels of supplemental oxygen may be a contributing factor. The diagnosis rests on exclusion of other causes rather than on specific diagnostic tests or histology. In addition to stopping the drug, high doses of corticosteroids are often given, though support for this is anecdotal at best.

TRANSFUSION-RELATED ACUTE LUNG INJURY

The transfusion of blood and blood products has been linked to the development of acute lung injury in two ways. An association between massive blood transfusion (>15 units/24 hours) and ARDS has been noted in epidemiological studies, but it remains unclear whether this link is truly causal or is indirect and reflective only of the critically ill nature of the patient requiring such massive transfusion support.[58] Acute lung injury can also be associated with the transfusion of a single unit of blood or blood components, an entity known as "transfusion-related acute lung injury" (TRALI). TRALI is operationally defined as the acute development of hypoxemia and bilateral radiographic opacities during or within 6 hours of a completed transfusion, in the absence of evidence of circulatory overload or alternative etiologies of acute lung injury.[70]

The mechanism underlying TRALI was initially determined to involve passive infusion via transfused blood products of donor-derived antibodies directed against recipient leukocytes. These antibodies are typically contained in blood products obtained from multiparous female donors, whose exposure to foreign human leukocyte antigen (HLA) or neutrophil antigens occurred during prior pregnancies. When transfused into a recipient with cognate antigens, these antibodies result in leukoagglutination and activation of recipient granulocytes or monocytes within the pulmonary microvasculature, triggering increased capillary permeability and the development of noncardiogenic pulmonary edema. Less commonly, the leukoagglutinating process can be triggered by an interaction between recipient anti-HLA or antineutrophil antibodies and donor-derived leukocytes contained in the transfused blood products.[71]

While ample clinical and animal model evidence exists to support the antibody hypothesis,[70,72] several lines of evidence suggest that other factors may also be involved. First, not all patients who receive blood products containing recipient-specific anti-HLA or antineutrophil antibodies develop TRALI. Second, in a significant minority of cases, leukoagglutinating antibodies cannot be detected in either the donor or recipient. This has prompted the proposal of an alternative "two hit" mechanism, whereby an initial event is required to prime recipient neutrophils and a second event leads to activation of primed neutrophils.[70,72] Priming events that have been associated with an increased risk of TRALI include recent surgery, active infection, sepsis, and chronic alcohol abuse.[73,74] The second event involves transfusion of substances that trigger neutrophil activation: either antileukocyte antibodies or biologically active lipids resulting from breakdown of stored blood products.

The true incidence of TRALI is difficult to determine due to underrecognition of the entity and a tendency to attribute the findings to other causes of acute lung injury. Although virtually all blood products have been implicated, the risk of TRALI is highest in association with fresh-frozen plasma and platelets.[71,72] Many cases are detected in surgical patients in the immediate postoperative period, a fact that likely reflects the frequent need for transfusions in this setting and the close monitoring of cardiopulmonary function in the postanesthesia recovery area.[75,76]

Clinically, TRALI is characterized by the abrupt onset of dyspnea and hypoxemia during or shortly following transfusion of blood products. Accompanying features include fever, chills, and hypotension. Respiratory distress and hypoxemia are of sufficient magnitude to require mechanical ventilatory support in up to 45% of cases.[71] The differential diagnosis includes volume overload, congestive heart failure, myocardial infarction, and aspiration. Although many cases are self-limited, with clearing of infiltrates and improved oxygenation over several days, mortality rates of 5% to 20% have been reported.[71]

When TRALI is suspected, the blood bank should be notified. Ideally, this should trigger testing of all donor specimens (typically retained by the blood bank) for the presence of anti-HLA and antineutrophil antibodies. However, the expense and time required often prevent blood banks from performing these studies.

ACUTE EXACERBATIONS OF PULMONARY FIBROSIS

Patients with idiopathic pulmonary fibrosis (IPF) can experience sudden and dramatic respiratory decompensation in the absence of identifiable precipitants. Referred to as an exacerbation of IPF, this phenomenon is characterized by acutely worsening hypoxemia in association with new bilateral ground-glass opacities or consolidation on chest CT.[77] The histological hallmark is diffuse alveolar damage, superimposed on underlying usual interstitial pneumonia. IPF exacerbation is a diagnosis of exclusion, established only after infection, heart failure, PE, and identifiable causes of acute lung injury have been ruled out.

The immediate postoperative period following lung surgery is one of the settings in which acute exacerbations of IPF have been reported to occur.[78–80] Most cases have occurred following either lung resection for lung cancer or lung biopsy for diagnosis of IPF. The reported incidence ranges from 2% to 7%. The mechanism by which surgical manipulation of the lung could cause an exacerbation is currently speculative. Mortality associated with postoperative acute exacerbations is high, ranging from 50% to 100%. Steroids and other immunosuppressive agents are commonly initiated but there is no compelling evidence for efficacy. Lung transplantation may be an option in selected cases.

PHRENIC NERVE INJURY AND DIAPHRAGMATIC DYSFUNCTION

Phrenic nerve injury is a well-described complication of CABG. In the past, this complication arose chiefly from the use of iced saline slush placed in the pericardium for topical cooling of the heart. Thermal injury causes both demyelination and axonal degeneration of the nerve, with slowing of conduction and impaired activation of the diaphragm. The use of topical cooling techniques has fallen out of favor largely because of this potential complication. However, the phrenic nerves can also be injured by traction, ischemia, use of diathermy, or transection during sternal retraction and harvesting of the internal mammary arteries. Unilateral phrenic nerve injury, typically involving the left phrenic, has been reported in approximately 10% of patients undergoing CABG.[41,81] Bilateral phrenic nerve injury was reported to occur in 1% to 3% of cases in the era of widespread topical cardioplegia usage but is now a rare event. Phrenic nerve injury is not restricted to CABG but is also seen in association with other cardiac procedures, thoracic surgery, neck surgery, and liver transplantation.

Although typically inconsequential in the otherwise healthy patient, unilateral diaphragmatic paralysis can lead to significant respiratory compromise in patients with underlying chronic lung disease or those who are otherwise marginal. In patients with COPD, for example, the duration of postoperative mechanical ventilation and the rate of reintubation are higher for those with versus without unilateral phrenic nerve injury following CABG.[82] Bilateral diaphragmatic paralysis results in marked impairment in pulmonary function and frequently leads to respiratory failure. In the proper setting, phrenic nerve injury should be suspected when attempts to wean a postoperative patient from mechanical

ventilation result in progressive hypercapnia or atelectasis. The spontaneously breathing patient will often complain of orthopnea, which may be misinterpreted by the unsuspecting clinician as indicative of congestive heart failure. However, orthopnea is actually due to further impairment in diaphragmatic function resulting from loss of gravitational assistance in the supine position. The detection of inspiratory thoracoabdominal paradox – an inward movement of the abdominal wall with simultaneous expansion of the thorax – is an important bedside clue to the presence of bilateral diaphragmatic paralysis and is best evoked in the supine position. The chest radiograph may also hold important clues, demonstrating either unilateral or bilateral elevation of the diaphragms and accompanying basilar atelectasis. However, these findings are not specific for phrenic nerve injury and may also be due to splinting or abdominal distention. A reduced maximum inspiratory pressure recorded at the mouth is another sensitive but nonspecific indication of significant diaphragmatic dysfunction.

Unilateral diaphragmatic paralysis can be readily diagnosed by fluoroscopic inspection, which reveals paradoxical upward movement of the affected hemidiaphragm with a maximal inspiratory effort ("sniff"). The situation is more problematic with bilateral diaphragmatic dysfunction. In this setting, patients often assume an altered breathing pattern marked by active contraction of the abdominal muscles during expiration, forcing the flaccid hemidiaphragms upward. With subsequent inspiration, the abdominal muscles relax and the hemidiaphragms descend briefly, potentially creating the false impression that they are functional. Because of this, fluoroscopy may not be confirmatory in these patients. Ultrasound has emerged as a simple bedside test for assessing diaphragmatic function. Thickening of the diaphragm with inspiration reflects diaphragmatic shortening and failure to observe this sign is indicative of diaphragmatic paralysis. Ultrasound can thus be used to diagnose both unilateral and bilateral paralysis and can be performed serially to assess for recovery of function.[83]

The gold standard for confirmation of phrenic nerve injury is electrophysiological testing, although even this methodology is occasionally flawed. The phrenic nerve is stimulated transcutaneously in the neck, and the diaphragmatic electromyogram (EMG) is recorded by surface electrodes placed in the seventh intercostal space at the costochondral junction. Demonstration of a prolonged latency between nerve stimulation and diaphragmatic action potential confirms a diagnosis of demyelinating injury. It is more difficult to interpret the significance of diminished amplitude or complete absence of the surface recording of the diaphragmatic EMG. This finding could represent either phrenic nerve injury/transection or failure to properly localize the diaphragm, which is typically shifted caudally in the postoperative patient and, therefore, away from the surface electrodes. Direct puncture of the diaphragm with a recording electrode may be employed to clarify this issue, but the technique requires a high level of expertise and carries a risk of pneumothorax.

Nontraumatic causes of phrenic nerve injury and diaphragmatic dysfunction can also lead to prolonged respiratory failure and delayed weaning in the surgical patient. Phrenic neuropathy can be a component of a more generalized polyneuropathy of critical illness, commonly encountered in the wake of an episode of severe sepsis or systemic inflammatory response syndrome. A critical illness myopathy affecting the diaphragms and other muscles of respiration can be encountered under the same circumstances. Finally, diaphragmatic dysfunction can arise as a component of a myopathy induced by the concurrent use of high-dose systemic corticosteroids and neuromuscular blocking agents.

Patients with diaphragmatic dysfunction are generally well suited for noninvasive positive pressure ventilatory support if they are awake and able to effectively handle respiratory secretions. Tracheostomy is indicated for patients with ineffective cough and those who cannot be weaned from conventional mechanical ventilation. The prognosis for patients with thermal or traction injury of the phrenic nerve is favorable; recovery is typically complete, but often protracted. In symptomatic patients with unilateral diaphragmatic paralysis due to transection of the phrenic nerve, surgical placation of the flaccid hemidiaphragm may lead to improved pulmonary function and successful liberation from mechanical ventilation.[84]

PULMONARY EMBOLISM

An increased risk of PE accompanies a number of surgical procedures, including upper abdominal, neurosurgical, cardiac, major urological, and lower extremity orthopedic procedures. Other, nonsurgical risk factors that predispose the patient to PE may also be present, including obesity, immobility, and underlying malignancy.

While alterations in gas exchange typify PE, frank hypoxemic respiratory failure is relatively uncommon and suggests massive clot burden. Lesser degrees of clot burden may produce equally devastating physiological impairment in patients with underlying pulmonary disease. In the presence of severe hypoxemia, there is little remaining cardiopulmonary reserve. Failure to establish a correct diagnosis and to swiftly and appropriately intervene can prove lethal.

Unfortunately, little information pointing specifically to a diagnosis of PE is easily gleaned at the bedside. The patient is often dyspneic, and tachypnea and tachycardia are observed on physical examination. However, these features are common in many postoperative patients because of pain and atelectasis. More informative, but infrequently detected, is evidence of acute cor pulmonale: distended neck veins, a parasternal heave, right-sided third heart sound, and accentuation of the pulmonic component of the second heart sound. An electrocardiogram may also demonstrate evidence of right heart strain, with an "S1Q3T3" pattern or new right bundle branch block. The chest radiograph is most suggestive of PE when it is normal in the face of severe hypoxemia. When abnormal, the greatest utility of the chest radiograph is in identifying other causes of hypoxemia such as pneumonia, pneumothorax, or ARDS. Echocardiography is commonly performed in the setting of hypotension; evidence of a dilated right ventricle in the face of a normal or underfilled left ventricle should raise suspicion for massive PE.

CT angiography has emerged as the imaging procedure of choice, assuming the patient is sufficiently stable to be safely transported for the study. The accuracy of CT angiography in diagnosing acute PE was most comprehensively assessed in the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial.[85] The positive predictive values of this technique were documented to be 96% and 92% when coupled with a high or intermediate clinical suspicion for PE, respectively, as assessed by use of the Wells Score. Conversely, the negative predictive value was 96% when coupled with a low clinical suspicion. Notably, discordance of radiographic results with clinical assessment significantly compromised the performance of CT angiography. For example, 42% of CT angiography readings were falsely positive among patients with a low clinical probability of PE. Conventional pulmonary angiography represents an alternative diagnostic modality in situations where CT angiography is not definitive.

While anticoagulation with heparin forms the mainstay of therapy for the otherwise stable patient, the presence of life-threatening hypoxemia and/or hemodynamic instability should prompt consideration of alternative or additional interventions. Since additional clot burden could be fatal, insertion of an inferior vena cava filter is generally advised in this setting and should be considered mandatory when anticoagulation is contraindicated. Thrombolytic therapy should also be considered in the critically ill patient, but its use in the postoperative period is limited by the risk of precipitating bleeding at the site of recent surgery. This risk appears to fall to an acceptable level beyond the seventh postoperative day; the exception is intracranial surgery, which contraindicates use of lytic agents for at least

2 months. Several interventional radiological techniques – thrombus fragmentation, suction embolectomy, and intraembolic infusion of low-dose thrombolytics – as well as surgical embolectomy are alternative considerations in the deteriorating patient for whom systemic thrombolytics are either contraindicated or unsuccessful.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is highly prevalent within surgical populations, affecting approximately 25% of adults undergoing elective general surgical procedures,[86] over 30% of neurosurgical patients,[87] and greater than 70% of morbidly obese patients undergoing bariatric surgery.[88] It is characterized by repetitive upper airway obstruction during sleep, resulting in arterial desaturation, hypercapnia, and arrhythmias. The perioperative period is a particularly precarious time for patients with this disorder. Because of alterations in oropharyngeal anatomy that commonly accompany obesity and OSA, orotracheal intubation at the time of induction may be difficult. The use of anesthetics, opioids, and sedatives diminishes the activity of the upper airway dilator musculature and concurrently dampens respiratory arousal mechanisms that can terminate obstructive apneas. These effects lead to an increase in the frequency and duration of obstructive apneas that, in turn, can place the surgical patient at significant risk for serious respiratory complications. A recent meta-analysis demonstrated that the incidence of postoperative respiratory failure was significantly higher among patients with OSA compared to those without.[87] Similarly, analysis of a national database of approximately 6 million surgical patients demonstrated that OSA increased the risk of postoperative intubation and mechanical ventilation fivefold after orthopedic procedures and twofold after general surgical procedures.[89]

As many as 80% of patients with OSA are undiagnosed at the time of surgery.[86] Identification of high-risk candidates with OSA prior to surgery is thus an essential strategy in minimizing the adverse impact of OSA on postoperative outcomes. Several easily administered screening tools have been developed and validated that can be incorporated into the preoperative assessment of surgical candidates. For example, the STOP-Bang tool uses a self-administered four-item questionnaire in conjunction with assessment of four patient characteristics (Table 104-5). It has positive predictive and negative predictive values of 52% and 90%, respectively, in identifying surgical candidates with moderate-to-severe OSA (apnea–hypopnea index >15).[90]

TABLE 104-5 STOP-Bang Scoring Model for Preoperative Assessment of OSA Risk[a]

Snoring: Do you snore loudly?
Tired: Do you often feel tired, fatigued, or sleepy during daytime?
Observed: Has anyone observed you stop breathing during your sleep?
Pressure: Do you have or are you being treated for high blood pressure?
BMI: BMI more than 35?
Age: Age over 50 y?
Neck circumference: Neck circumference greater than 40 cm?
Gender: Male?

[a]*High risk of OSA, answering yes to three or more items. Low risk of OSA, answering yes to less than three items.*

Source: Adapted with permission from Chung F, Elsaid H. Screening for obstructive sleep apnea before surgery: why is it important? Curr Opin Anaesthesiol. 2009;22(3):405–411.

A number of measures can be employed in an attempt to reduce the risk of serious pulmonary complications in surgical patients with OSA.[88] The anesthesiologist should be made aware of the potential for a difficult intubation and emergency airway devices should be readily available. Ideally, shorter acting anesthetic agents should be employed. Intraoperative use of opioids should be minimized; if deemed necessary, use of ultrashort-acting agents such as remifentanil is preferable. Extubation following completion of surgery should be carried out only after the patient is fully awake. Application of continuous positive airway pressure (CPAP) immediately after extubation should be considered, particularly if apneic episodes are noted in the recovery area. Nonopioid analgesics should be used in an attempt to avoid or minimize use of opioids in the postoperative period.

USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION

For patients with respiratory failure refractory to conservative measures, endotracheal intubation is the standard means to facilitate mechanical ventilatory support. However, in recent years, a greater appreciation for the untoward effects of endotracheal intubation has emerged. In addition to airway trauma, these include an increased risk of nosocomial pneumonia and sinusitis and the frequent need for heavy sedation that, while addressing patient discomfort, often prolongs the process of weaning and extubation. The desire to avoid endotracheal intubation has prompted interest in the use of noninvasive positive pressure ventilation (NIPPV), employing a tight-fitting nasal or full face mask as the interface between patient and ventilator.

There is ample evidence supporting the benefits of NIPPV in the treatment of a variety of causes of respiratory failure in the medical patient but only recently have data emerged confirming its safety and efficacy in the postoperative setting. The most compelling study randomized patients with hypoxic respiratory failure following lung resection surgery to standard therapy (supplemental oxygen, bronchodilators, chest physiotherapy) with or without NIPPV. Compared to the control group, the use of NIPPV was associated with a marked reduction in the need for endotracheal intubation (20.8% vs. 50%) and in mortality at 3 months (12.5% vs. 37.5%).[91] While there has been a concern about using NIPPV following esophageal or gastric surgery, recent experience suggests that this can be accomplished safely.[92] In this setting, care must be taken to avoid gastric distention, using a nasogastric tube for decompression if necessary, and the magnitude of positive pressure ventilation employed should be limited to <20 cm H_2O. Since NIPPV often requires a period of acclimation, it should not be used in unstable patients. Other contraindications to its use include depressed or agitated mental status, inability to protect the airway, compromised airway clearance due to copious secretions or weak cough.

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CHAPTER 105

Perioperative Care of the Patient Undergoing Lung Resection

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Ayesha S. Bryant

The postoperative care of any patient who undergoes pulmonary resection starts long before the incision is made and comprises three main areas. The first is patient selection, the second is the actual operation itself, and the third is postoperative care. This chapter briefly reviews some of the specifics that go into these three areas. In addition, it discusses the incidence, prevention, and treatment of some of the most common postoperative problems that continue to vex thoracic surgeons around the world.

PATIENT SELECTION

Perhaps the best way to minimize postoperative complications is to operate only on young healthy patients. Unfortunately, thoracic surgeons, like most other surgeons, are now presented with older and sicker patients with increasing comorbidities. The median age of our society has increased and so has obesity and patients with chronic pain syndromes. We are increasingly challenged with larger tumors in older patients with smaller pulmonary reserve. As the bar for the upper age limit has been raised, the threshold for the acceptable FEV_1% and D_{LCO} % has fallen. Currently there are few, if any, absolute contraindications to pulmonary resection based on chronological age or pulmonary function.

MORBIDITY AND MORTALITY

During the perioperative period, many factors contribute to pulmonary compromise. Estimates of the overall surgical mortality for pulmonary resection range in large series from 2% to 4%. The estimated mortality increases with the size of the resection—from less than 1% for a wedge resection of the lung, to 2% to 3% for a lobectomy, and 6% to 8% for a pneumonectomy.

The morbidity associated with elective pulmonary resection is also high. Complications have been reported to occur in 36% to 75% of patients undergoing pneumonectomy and 41% to 50% of patients after lobectomy. Most complications are minor and include air leak, atrial fibrillation, and atelectasis. However, a significant number are major; these most commonly include pneumonia, aspiration, respiratory failure, myocardial infarction, bronchopleural fistula (BPF), and pulmonary embolus.

PREOPERATIVE ASSESSMENT AND OPTIMIZATION

Preoperative evaluation focuses on assessment of pulmonary function and its optimization, evaluation of cardiac status, and careful consideration of issues related to quality of life.

LUNG FUNCTION

Assessment of the patient's risk for pulmonary resection starts preoperatively in the clinic. One important but difficult factor to quantify is the patient's desire to undergo the work required to recuperate from a thoracic surgical procedure. The importance of walking and

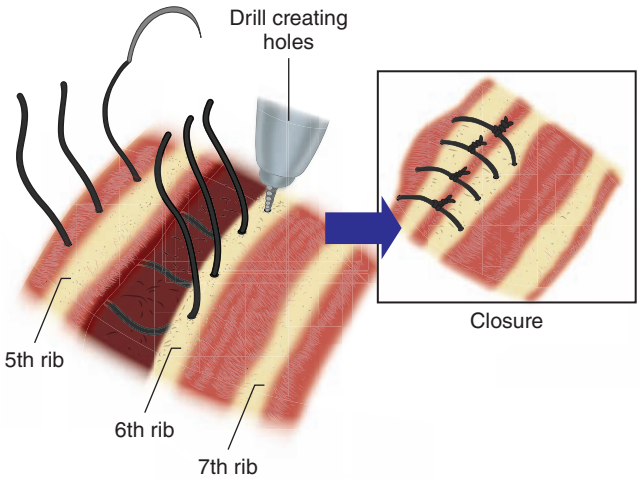

Figure 105-1 Drilling holes in the bottom rib, thus enabling sutures to be placed through it.

deep breathing after lung resection cannot be overstated. A study performed by the Lung Cancer Study Group suggested that the patient's attitude toward his or her malignancy was the best indicator of long-term survival.[1] A patient who appears to be unwilling to participate in his recovery should be allowed ample opportunity to explore reasonable alternative therapies, such as radiation. Moreover, if this attitude persists, it may be best not to operate at all.

A large number of studies have examined preoperative factors that predict postoperative risk to a patient. In a study of 476 patients operated on over 12 years, only 3 of 7 preoperative risk factors for morbidity and mortality were found to carry a significant association with mortality.[1] These risks were age older than 60 years, pneumonectomy, and the presence of ventricular premature contractions on the preoperative electrocardiogram. All risk factors analyzed together accounted for only 12% of the risk of mortality. At the time of the initial visit, an attempt to establish the amount and character of sputum production, the presence or absence of an effective cough, and a patient's ability to climb a flight of stairs of fixed height help provide an idea of a patient's ability to undergo surgery. Patients with preoperative arterial hypercapnia are apt to have pulmonary hypertension and are poor candidates for pneumonectomy, but they may be able to tolerate a lobectomy. Pulmonary function tests, in particular the FEV_1% and the D_{LCO} %, in combination with lobar perfusion scans, allow prediction of the postoperative predicted or postresectional FEV_1% (Fig. 105-1). A postresectional FEV_1% less than 40% of predicted is a cause for concern. A study of the D_{LCO} % in 165 patients who underwent lung resection identified it as the most important indicator of postoperative pulmonary complications or death.[2] Another study focused on the maximal oxygen consumption (MVO_2). An MVO_2 of 20 mL/kg/min was associated with the fewest chance of complications, whereas an MVO_2 less than 15 mL/kg/min was associated with a 75% postoperative morbidity rate.[3]

CARDIAC STRESS TEST

Since many patients are smokers and elderly, we prefer to perform a preoperative stress test in most patients prior to thoracotomy. Previously undiscovered or unsuspected coronary artery disease should be determined, anatomically identified, and corrected prior to elective thoracotomy.

QUALITY OF LIFE CONSIDERATIONS

Quality of life (QOL) is an important metric by which to assess all types of medical and surgical treatments. This is no different for patients who undergo pulmonary resection. In fact, QOL is becoming an increasingly important part of the preoperative conversation between patients and surgeons in planning out the procedure.[4] For this reason smaller resections such as segmentectomy are becoming more common especially for tumors that are less than 2 cm in size. Similarly, pneumonectomy is less commonly performed. Recently we evaluated the long-term QOL in 110 patients who underwent a pneumonectomy and found that their overall physical scores were quite low but their mental well-being scores were high.[5]

OPTIMIZATION OF PREOPERATIVE PULMONARY FUNCTION

A variety of medical therapies are designed to improve pulmonary function. Many patients who are to undergo elective pulmonary resection are current smokers. Optimization of pulmonary function begins first and foremost with smoking cessation. Even a short period of abstinence from cigarettes can improve the effectiveness of mucociliary transport. Heavy smokers also maintain high levels of carboxyhemoglobin that interfere with oxygen transport and delivery to peripheral tissues. However, the optimal time after smoking cessation for elective thoracotomy is still unknown. In patients with evidence of reversible airway obstruction on pulmonary function tests, or symptoms suggestive of airflow obstruction, nebulized albuterol appears to be of benefit. Mucostasis, if present, may warrant the addition of mucolytics such as N-acetylcysteine. However, this medication may also lead to certain side effects, such as increased mucus production and bronchoconstriction. Similarly, although the condition of patients with reversible airflow obstruction generally improves with corticosteroids, these agents should be added cautiously because of their adverse effects on wound healing and the increased risk of wound infection. If steroids are necessary, the dosage in the postoperative period should be minimized. Patients who produce purulent sputum should be treated with oral antibiotics directed at the organism identified and surgery delayed until the infection is eradicated.

PERIOPERATIVE FACTORS REDUCING CARDIOPULMONARY FUNCTION

Despite the wide variety of pathologies and types of operative procedures performed by thoracic surgeons, the postoperative course is often quite predictable. We have published the techniques and specific steps that enable patients to be "fast-tracked" after both elective pulmonary resection and esophageal resection.[6,7] These clinical pathways and/or computerized algorithms lead most importantly to safe results, high patient satisfaction, and only a 3- to 4-day length of stay after pulmonary resection. Early ambulation and aggressive pulmonary rehabilitation are cornerstones for successful fast-tracking. The physiological consequences of decreased activity and lack of changes in posture form a background for the pathophysiological processes caused by the underlying illness and the surgical procedure.

It is interesting that these changes might be less in patients with chronic pulmonary disease. Thus, in patients with chronic airflow obstruction, a decrease in FRC of only 3.5% accompanies a move from the upright to supine position and a decrease of only 1.9% accompanies the move from the supine to lateral decubitus position.[8] Finally, although arterial oxygen saturation decreases significantly in supine normal subjects, it does not do so in patients with significant airflow obstruction.

The degree to which the described changes affect gas exchange has been only partly studied. In normal young males after 10 days of bed rest, Pa_{O_2} decreased by 9 mm Hg and the alveolar–arterial difference in Po_2 by 10 mm Hg, without change in Pa_{CO_2}. Such changes, which would probably not be important in normal young people, might take on greater significance in a patient with chronic obstructive pulmonary disease (COPD).

BED REST AND CARDIAC FUNCTION

Upon standing, approximately 500 mL of blood shifts from the upper to the lower body. When lying down, the central venous

return increases, resulting in a decrease in heart rate, peripheral vasodilation, increased renal blood flow, and diuresis. Within an average of 24 hours the diuresis causes a 5% decrease in plasma volume, which continues to fall by 10% in 6 days and 20% in 14 days.

A wide variety of experimental subjects and protocols have been used to examine the cardiovascular effects of prolonged immobilization. Orthostatic intolerance is common after prolonged bed rest. This is attributable, at least in part, to the depletion in intravascular volume. This may be compounded by an increase in venous pooling in the lower extremities because of an increase in venous compliance after bed rest. Prolonged recumbency also blunts cardiac responsiveness to rapid changes in posture. Bed rest increases the resting heart rate by 4 to 15 beats per minute. After prolonged bed rest, the increase in heart rate during exercise is more pronounced. For example, normal volunteers experienced an increase in heart rate to approximately 129 beats per minute during submaximal exercise; after bed rest, the same exercise drove the heart rate to approximately 165 beats per minute.

■ ALTERATIONS IN LUNG FUNCTION SECONDARY TO SURGERY

In addition to the physiological consequences of inactivity described in the preceding section, the thoracic surgery patient also experiences major alterations in chest wall compliance. The pain and discomfort of deep breathing also lead to an increase in the work of breathing that is independent of the amount of resected lung. Manipulation of the lung and re-expansion of the lung lead to pulmonary "bruising." Microscopic or even macroscopic areas of atelectasis persist. Fluid or blood clots in the pleural cavity may compress the lung parenchyma. Inhalational anesthesia depresses mucociliary transport. Mechanical changes alter the work of breathing. Thoracotomy alone was found to decrease chest wall compliance to 47% of preoperative levels and to increase the work of breathing to 143% of preoperative levels.[9] As a result, vital capacity and oxygen saturation fall significantly in the first few postoperative days. Pain, among other factors, leads to diminished cough. Cough pressures were found to decrease to 29% of preoperative levels after surgery and to increase only to 50% of preoperative levels by the seventh postoperative day.

ROUTINE POSTOPERATIVE CARE

Routine post-operative care focuses on decisions regarding timing of extubation, use of supplemental oxygen, judicious use of antibiotics, and fluid and electrolyte management. Additionally, radiographic evaluation and decisions regarding use and removal of chest tubes are important considerations.

■ EXTUBATION AND POSTOPERATIVE SUPPLEMENTAL OXYGEN

Almost every patient undergoing lung resection should be extubated in the operating room and brought to the recovery room breathing spontaneously. Reintubation in the immediate postoperative period is rare. If prolonged intubation is anticipated, however, the double-lumen endotracheal tube should be replaced by a single-lumen endotracheal tube of sufficient size to permit the introduction of an adult bronchoscope. For extubation, standard criteria are followed: vital capacity more than 10 mL/kg, respiratory rate less than 30 breaths per minute, and acceptable arterial blood gases.

Supplemental oxygen is supplied in the postoperative period if the patient's arterial oxygen saturation, measured by pulse oximetry, is less than 90%, either at rest or during exercise. We prefer sending patients directly to the floor and have not used the intensive care unit after lobectomy for over a decade. Many centers have adopted a similar practice; however, patients must have 24-hour telemetry and pulse oximetry monitoring in these specialized units. Nurses need to have chest tube training. These types of floors allow the patient's family to stay in close proximity at all times. This offers significant psychological support to most patients; if the family is attentive and intelligent, they also can act as an invaluable part of the patient's care and add another level of patient protection.

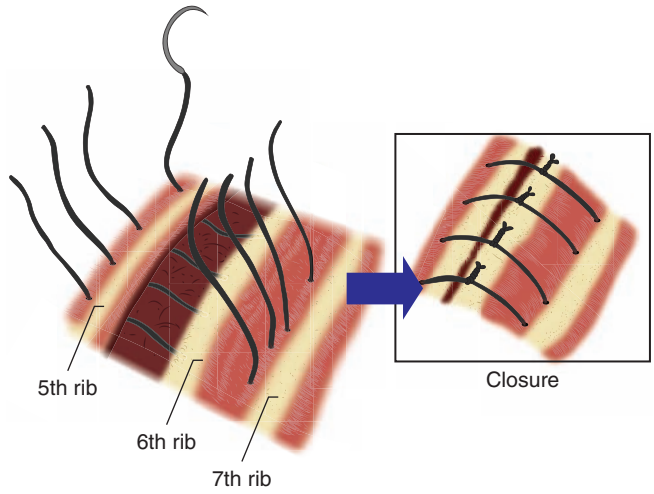

Figure 105-2 Standard pericostal sutures.

■ PAIN CONTROL

Adequate pain control in the postoperative state is critically important. The choice of surgical procedure and analgesic strategy to be employed are discussed below.

Impact of Surgical Techniques on Postoperative Pain

A thoracotomy is a painful procedure, in part related to trauma and/or compression of the intercostal nerve. We have evaluated ways to reduce the pain of thoracotomy using prospective randomized studies. One study showed that drilling holes in the bottom rib, thus enabling sutures to be placed through it rather than around the ribs, helps avoid entrapment of the lower intercostal nerve (Fig. 105-1) and this simple technique reduces the pain compared with the standard pericostal sutures (Fig. 105-2).[10] Another study examined the use of an intercostal muscle flap.[11] This flap is harvested prior to rib retraction (Fig. 105-3) so as to avoid retractor injury to the intercostal nerve, which runs in the muscle flap. Both of these studies showed reduction in postoperative pain in the hospital and a lessening of a decrease in the tidal volume immediately postoperatively. In addition, there was less pain at 3 months, both early and up to 12 weeks postoperatively. Simple techniques such as these, as well as video-assisted procedures that help prevent or limit the amount of pain are important.

Postoperative pain is reduced through minimally invasive surgical approaches such as the use of video-assisted thoracoscopic surgery (VATS) and thoracic robotic surgery. Advantages of the robot in comparison to VATS include easier operations in the mediastinum, such as a thymectomy or a resection of an esophageal leiomyoma. Other potential advantages are improved lymph node resection and the dissection of enlarged or metastatic N1 lymph nodes off the pulmonary artery. However, there are significant limitations and concerns to the implementation of a robotic approach including the high cost, the lack of consistent platform availability, the lack of tactile feedback, the fact that several countries cannot afford the current robotic system, the need for the bedside assistant to fire the stapler on pulmonary vessels, and the lack of standardized credentials and training programs for the surgeons and technical assistants.

Analgesic Strategies

Postoperative pain that is not controlled early reduces the ability to breathe and cough and increases respiratory complications.

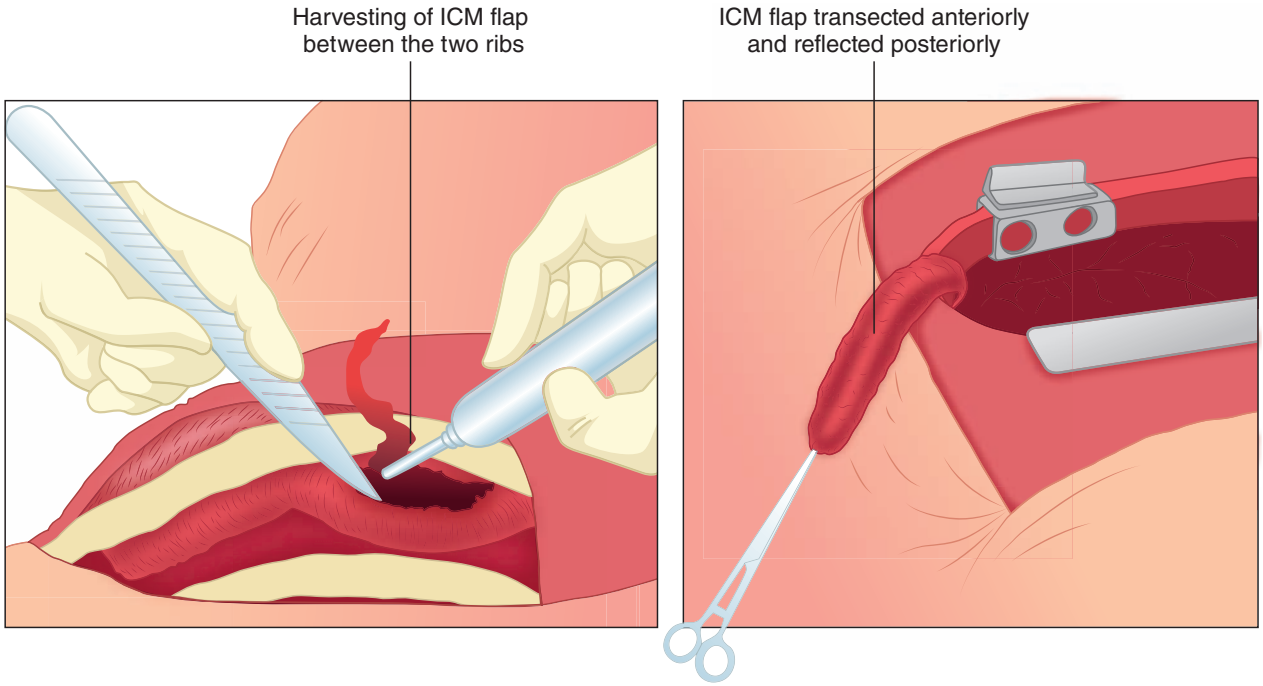

Figure 105-3 Muscle flap harvested prior to rib retraction.

Moreover, the best way to reduce late or chronic pain is to aggressively treat early pain. Most patients should receive a thoracic epidural prior to thoracotomy and/or a patient-controlled analgesic (PCA) intravenous device. Recently, some surgeons have tried subpleural catheter systems that infuse local anesthetics in the paravertebral area as well. The complications associated with epidural opiates are numerous and include pruritus, ileus, urinary retention, and respiratory depression. Epidural analgesia is most useful in the young patient with poor pulmonary function. We have avoided it in elderly patients, those who become somnolent, or those who have a rising carbon dioxide level on arterial blood gas. The use of nonsteroidal agents such as oral ketorolac in addition to narcotics is helpful as well and should be given immediately in the operating room and continued for a few days to help prevent pain. It should be avoided in those with marginal renal function. After postoperative day 2 or 3, the epidural should be removed and oral opioids should be added. Treating pain using a combination of different classes of agents is helpful.

■ ANTIBIOTICS

Wound infection following thoracotomy is rare. This may be due to the large amount of musculature contained in the chest wall. In addition, prophylactic antibiotics are often given in an attempt to reduce the incidence of wound infection. Currently, it is recommended that a broad-spectrum antibiotic, such as cefazolin, be administered within 1 hour of the skin incision. Subsequent antibiotic administration should be based on clinical factors such as fever, radiographic pulmonary infiltrates, leukocytosis, and sputum Gram stain and culture results. There is no need to provide antibiotic coverage simply because a chest tube is in place.

A study that examined the relationship between pulmonary flora and postoperative infections found that *Haemophilus influenzae* was the most common organism identified from sputum at the time of surgery and that the risk of pneumonia in culture-positive patients was 10-fold that of patients with culture-negative secretions.[12] However, the cultured organisms were sensitive to the antibiotic that was administered, suggesting that the administration of antibiotics may be less important than careful pulmonary toilet in preventing postoperative pneumonia.

■ FLUIDS, ELECTROLYTES, AND ORAL INTAKE

A routine lung resection is not associated with large fluid losses intraoperatively or sequestration of volume in the third space postoperatively. Most patients should leave the operating room relatively euvolemic. Administration of intravenous fluids consisting of 5% dextrose and 0.45% normal saline at 50 to 75 mL/h until the patient begins to take oral fluids is usually adequate to maintain intravascular fluid volume. Oral intake should be resumed as soon as the patient is able to take fluids by mouth, but strict aspiration precautions cannot be overemphasized. Urine output should be maintained at 0.5 to 1 mL/kg of body weight an hour to preserve renal function. Oliguria, which is often overtreated by surgical residents, should be tolerated in patients who have undergone elective pulmonary resection. Some surgeons practice aggressive diuresis with the goal of reducing secretions. However, it is not clear that a lower volume of thick, tenacious secretions is preferable to a higher volume of thin secretions that are more readily cleared. Ideally, diuresis should be guided by measurements of intravascular volume. Measurements of central venous pressure correlate poorly with intravascular volume. Many surgeons are reluctant to insert Swan–Ganz catheters into patients after lung resection, particularly after pneumonectomy, because of the possibility of disruption of a pulmonary artery closure. Even if a Swan–Ganz balloon-tipped catheter has been safely introduced into a patient postoperatively, the data should be interpreted with caution because the inflated balloon may have occluded a significant portion of the remaining pulmonary vascular bed, thereby artificially increasing right ventricular afterload and decreasing cardiac output. In our practice the measurement of central venous pressure is rarely if ever used and a Swan is reserved for a patient in the intensive care unit that is hypotensive, oliguric, and hypoxic.

Blood transfusion is not necessary unless the patient's hemodynamics and overall clinical scenario call for it. Some believe that a hematocrit less than 24% is an indication for transfusion, but we prefer to use the hemoglobin level, which is less affected by dilution. A decision should be made on each individual patient's situation and a knee-jerk reaction to any specific level should be avoided.

Transfusion of 250 mL of packed red blood cells increases the intravascular volume by 750 to 1000 mL, because of the movement of extravascular volume into the intravascular space due to plasma oncotic forces. The increase in intravascular volume may be more dangerous than low hemoglobin. Furthermore, the intraoperative administration of blood is probably immunosuppressive and may be associated with a decrease in frequency of 5-year disease-free intervals.

ROUTINE CHEST X-RAYS

We have studied the use of daily chest radiographs, which most surgeons perform to ensure the effective removal of air and fluid from the pleural space.[13] These films, which are labor intensive, costly, and wake the patient in the early morning hours, are not needed if the patient does not have an air leak or other clinical problems. If the postoperative chest roentgenogram in the recovery room after surgery has no significant pathology and the patient is not hypoxic, a daily chest X-ray is not needed. If a patient develops subcutaneous emphysema and hypoxemia and there is a pneumothorax, then suction should be added.

CHEST TUBES

Chest tubes are commonly placed after thoracotomy to drain blood, serum, and air from the pleural space. The ideal number, type, or size of a chest tube to place after elective pulmonary resection is controversial. There are little data to suggest that one practice is better than another; however, recently several prospective randomized studies have shown that one chest tube works as well as two.[14] After routine lobectomy we have changed our practice based on these studies and now only use one chest tube in patients who do not have a large untre atable air leak or a large fixed pleural space deficit after lobectomy. We use a 24-French soft catheter that is difficult to kink. The advantage of one tube is that it may cause less pain and morbidity, but this advantage is theoretical.

For resections other than pneumonectomy, chest tubes are removed when there is no air leak and fluid output has decreased. The maximum amount of drainage per day has not been studied. Many surgeon use less than 200 mL a day, but there are no data that higher volumes cannot be accepted. We currently remove tubes with 450 cc per day and this has been a safe cutoff value in more than 4000 thoracotomies. One needs to ensure there is no blood, chyle, or cerebrospinal fluid prior to removal of the tube. Removal is performed while the patient executes a Valsalva maneuver. Some argue that it may be best to remove the tube when the patient takes a deep breath out and holds it, as opposed to a deep breath in and holds it. An occlusive dressing is maintained over the site for 24 hours. Patients should be advised that it is not uncommon to have additional drainage after tube removal.

If the chest tube output in the first several hours after surgery is greater than 200 cc/h for more than a few hours or if clinically suspected, bleeding must be ruled out. Early surgical re-exploration, before the patient leaves the recovery room, is our preference if the patient's coagulogram (INR, PTT, and platelet count) is normal. Each individual patient's clinical scenario should be considered. Confirmation that the drainage is blood can be obtained by simple visual inspection of the effluent or, if needed, the effluent can be sent for a confirmatory hemoglobin and/or hematocrit level.

Postpneumonectomy space drainage is managed differently from postlobectomy drainage. After pneumonectomy, the position of the mediastinum is a major concern. Shift of the mediastinal structures either into the pneumonectomy cavity or toward the residual lung can lead to either hemodynamic or respiratory compromise. To allow "balancing" of the mediastinum after a pneumonectomy, most surgeons leave a single chest tube in the pleural cavity. This tube can be removed in the operating room after the patient has been returned to the supine position and is hemodynamically stable. We prefer to leave the tube in overnight attached to a special pneumonectomy-balanced drainage system. The tube can be removed the morning of postoperative day 1 if there is no bleeding.

COMPLICATIONS AFTER LUNG RESECTION

The spectrum of potential complications following lung resection is broad. Important examples are discussed below.

AIR LEAK

An alveolar pleural fistula (APF), more commonly known as an air leak, is probably the most common complication after elective pulmonary resection. It is defined as a communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space. Factors that increase the incidence of air leak include emphysema, steroids or other medical conditions that slow wound healing, bilobectomy compared with lobectomy, and poor chest tube placement. Operative techniques that help prevent air leaks include pleural tents, pericardial buttressed staple lines, fissure-less surgery, and checking for air leaks before closing.

Recently, a great deal of scientific research has been devoted to the best management of chest tubes after pulmonary resection. Until 1998 there were few if any objective data concerning the best setting (i.e., suction or water seal) for chest tubes after lung surgery and most practices were opinion driven rather than evidence based. We and others have studied this process using prospective randomized studies.[15–17] We have developed a classification system for air leaks so as to be able to study air leaks objectively with scientific rigor. The summary of our work is that we prefer to connect the tubes to suction for the night of surgery and then convert to water seal the next morning, especially in patients who have an air leak. If patients have no leak but have a pneumothorax, we prefer suction. In patients with an air leak, we prefer water seal unless there is a pneumothorax, in which case we prefer −10 cm H_2O of suction (instead of −20 cm H_2O). However, Brunelli, who has carefully and critically studied the problems of air leaks after the pulmonary resection process, prefers water seal during the day and some suction at night. Brunelli did not find a statistical advantage for water seal; however, he did identify a trend in patients who did not undergo pleural tenting favoring water seal over suction.[20] Marshall has corroborated our findings in a prospective randomized study of her own and found that air leaks are best treated by placing chest tubes on water seal instead of suction in the postoperative setting.[21] Thus, the best treatment of most air leaks appears to be water seal in most patients so long as they do not develop a pneumothorax or subcutaneous air on seal.

We have also studied the problem of air leaks in patients with a concomitant pneumothorax and found that the least amount of suction (usually −10 cm H_2O) needed to alleviate the pneumothorax or subcutaneous air is best. Other daily management techniques should include "stripping" the tubes in the attempt to remove clots, examining all connections to ensure their integrity, and maintaining appropriate water levels in all drainage bottles. If the leak continues after postoperative day 4, then the patient may be discharged home on a Heimlich valve or a similar device such as an Atrium Express (Atrium USA, Hudson, NH). The chest tube can be removed after 2 weeks even if the air leak remains. A discharge PA and lateral X-ray should be performed before leaving, which serves as an important baseline film for later comparisons.

Occasionally, massive subcutaneous emphysema may occur if either the loss of air from the lung into the pleural cavity exceeds the drainage capacities of the chest tube or the tube is positioned away from the site of the air leak (Fig. 105-4). The latter condition is much more common than the former. If this occurs, chest tubes should be examined for patency. Occasionally, a tube will be found to be clamped or twisted by the bed or IV pole, at the skin level or in the subcutaneous fat. If a tube is occluded because of a plug, the

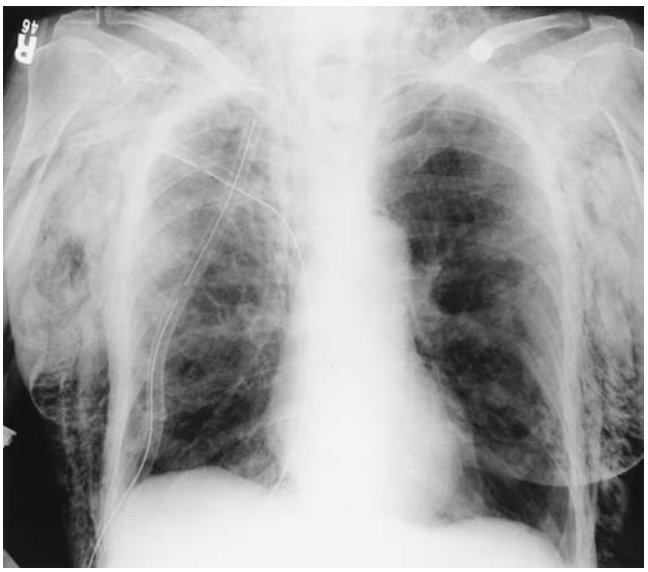

Figure 105-4 Massive subcutaneous emphysema following a pulmonary resection.

tube should be stripped; if this fails to re-establish patency, the tube should be opened and suctioned, using sterile technique, with a nasotracheal suction catheter. Some surgeons irrigate an occluded tube with sterile saline, but because of the possibility of infectious contamination this should only be used as a last resort. If all methods fail to re-establish patency of a chest tube, the tube should be removed and a new one inserted.

Although uncomfortable and disfiguring, massive subcutaneous emphysema is rarely life threatening. However, two dangerous situations can arise. First, in patients with tracheostomies, the tube can be displaced into the subcutaneous tissues if the skin is elevated up and away from the tracheal opening. Second, circumferential massive lifting of the skin around the thorax can lead to restriction of normal outward excursions of the rib cage excursion, limiting tidal volume—as in the case of limitation imposed by circumferential eschar in a burn patient. Such emergency situations may require the placement of small skin incisions, usually in an infraclavicular location. This technique should be reserved for the scenario when the chest tube is in good position, on high (−40 cm H_2O) suction and patent, and the subcutaneous air is not decreasing.

Until recently air leaks have been reported using an analog system only. Recently a few companies have developed systems that quantify the air leaks digitally (in mL/min). Digital air leak meters allow clinicians to quantify the size of air leaks objectively. It almost eliminates the subjectivity to air leaks and may allow for more uniform chest tube management. This may shorten the length of stay as well as the number of patients that are discharged home with chest tubes. Some of the newer digital chest tube devices allow a recording of air leak history. Limitations include the high cost of these systems and training of the hospital personnel.[18,19]

■ HIGH-OUTPUT CHEST TUBE STATES (CHYLOTHORAX, SUBARACHNOID–PLEURAL FISTULA)

A chylothorax is diagnosed when milky white chylous drainage is observed from the chest tube in a patient after enteral intake. It consists of intestinal lymphatic fluid (lymphocytes, immunoglobulins, and enzymes) and fat (fat-soluble vitamins, chylomicrons, and triglycerides). Once the patient starts to eat, the diagnosis is obvious. However, the diagnosis should be suspected in a patient who is not eating, has a stable hemoglobin and hematocrit, and whose chest tube output is high but the cause is unexplained. The diagnosis is made by sending the effluent for analysis. A triglyceride level greater than 110 mg/dL or a positive Sudan fat stain helps secure the diagnosis, with the caveat that these studies can be negative if the patient is not eating. The incidence of a chylothorax has been reported to be about 1% to 2.4% after lobectomy, and 0.7% to 1% after pneumonectomy.

The treatment of a chylothorax depends on the level of the injury. Most commonly after pulmonary resection, a chylothorax occurs from engorged lymphatics in patients with positive mediastinal (N2) nodal disease who have undergone an aggressive nodal dissection. It is also seen in patients who have received neoadjuvant therapy for N2 nodal disease and have undergone a complete thoracic lymphadenectomy. The best treatment for most patients is to make them NPO and ensure the chest tube volume decreases. A medium-chain triglyceride (MCT) diet should then be instituted as well. In this situation reoperation is less helpful, even if fibrin glue is applied to the draining nodal basins, because the lymphatic channels are engorged with obstructed lymphatics from cancer. Radiation has been used successfully in this situation. The patient may be discharged home with the tube in place on the MCT diet for 2 weeks. Finally, we challenge the patient with fatty meals for 2 days. If chest tube output is decreased, the chest tube is removed. However, if the output volume remains high despite compliance on an MCT diet, then complete cessation of all oral intake is needed and total parental nutrient is required. Nutritional parameters should be tested and the white blood cell count monitored. Persistent chylothorax can lead to neutropenia, infection, and malnutrition. Surgical intervention is rarely needed.[20] Less frequently, a chylothorax following pulmonary resection occurs due to injury to the main thoracic duct. If there is an injury to the main thoracic duct (best determined from a lymphangiogram), then early reoperation with duct ligation and pleurodesis is best. Alternatively, percutaneous thoracic duct embolization performed by an interventional radiologist has been successful in addressing postoperative chylous effusions.

Subarachnoid–pleural fistulas are an unusual cause of high-output chest tube drainage. The incidence of a subarachnoid–pleural fistula after thoracic surgery is very low, but several cases have been reported. They occur most often after trauma but may also complicate thoracic surgical procedures if dissection in the costovertebral angle or excessive traction avulses a thoracic nerve root from its dural sleeve. The most common setting for this to occur is during resection of malignancies invading either the posterior chest wall or vertebral column. However, retraction of the ribs for exposure during a standard posterolateral thoracotomy may generate sufficient traction to avulse a nerve root. The presence of a communication between the subarachnoid and pleural spaces allows for the bidirectional movement of cerebrospinal fluid and pleural fluid: During inspiration, low intrathoracic pressure draws cerebrospinal fluid into the thorax; during expiration, the elevated thoracic pressure forces air and potentially contaminated material outward into the subarachnoid space. A chest tube placed next to the fistulous tract may increase loss of cerebrospinal fluid. As a result, patients may develop headaches, meningismus, paresis, seizures, hemorrhagic infarcts, and obtundation leading to death. Cerebrospinal fluid analysis may be bizarre, owing to the entry of serosanguineous fluid into the subarachnoid space.

The diagnosis of a communication between the subarachnoid and pleural spaces is suggested by visualization of a pneumocephalus on skull radiographs. More specifically, the fistulous communication may be delineated by contrast CT myelography. The time between thoracotomy and clinical diagnosis of the fistula ranges from 5 to 8 weeks. The unpredictable nature of the neurological sequelae mandates that surgical closure of the dura be carried out as soon as the diagnosis is confirmed via reoperation and application of glues and a muscle flap.

ATRIAL FIBRILLATION

Atrial fibrillation is another very common complication after pulmonary resection. The incidence varies due to inconsistent definitions. Its incidence ranged from 12% to 20% in several large series, with over 500 patients each, with a peak onset on postoperative day 2.

Risk factors for postoperative atrial fibrillation include advanced age (greatest for those older than 70 years old), amount of lung resected, clamshell incision, and history of congestive heart failure. The incidence is also dependent on the extent of pulmonary resection performed. Other identified risk factors for the development of postoperative atrial fibrillation include male gender, previous cardiac arrhythmia, and intraoperative blood transfusions.

The ideal treatment of atrial fibrillation is prevention. A prospective randomized trial from Sloan Kettering showed that prophylactic diltiazem reduced the overall incidence of atrial fibrillation after standard and intrapericardial pneumonectomy.[21] The treatment of postoperative atrial fibrillation depends on the patient's ventricular rate and hemodynamic status. If the patient is unstable, electrical cardioversion may be needed. However, the vast majority of patients are hemodynamically stable despite a rapid ventricular rate. These patients are best treated with a calcium channel blocker or beta blocker. Often a drip can be used while the blood pressure is carefully monitored. The use of digitalis has fallen out of favor, but this safe and time-tested drug slows the ventricular rate, although it may not restore normal sinus rhythm. More recently, amiodarone has been shown to be effective in the treatment of supraventricular arrhythmias; it is safe even in elderly patients and often restores normal sinus rhythm.

ATELECTASIS

Atelectasis is a common complication after pulmonary surgery. Fortunately, most atelectasis is plate-like, discoid, or linear and is subsegmental and has little clinical consequence in the patient with adequate pulmonary reserve. However, atelectasis that is segmental or greater may cause clinical deterioration and may require bronchoscopy. Risk factors for this type of atelectasis are poor cough, impaired pulmonary function, inadequate pain control, diaphragmatic dysfunction, chest wall instability, and sleeve resection. The clinical sequela of this type of atelectasis is ventilation–perfusion mismatch that leads to hypoxemia, impaired alveolar macrophage function, and often pneumonia.

Again, prevention is the best treatment. Chest physiotherapy with vibratory percussion, incentive spirometry, ambulation at least three to four times daily, and secretion control is the mainstay of prevention. Ambulation redirects pulmonary blood flow and helps improve areas of ventilation–perfusion mismatch. Respiratory treatments entail nebulized bronchodilators and chest percussion with postural drainage. Pain control allows for deep cough and facilitates adequate mobilization of secretions.

PNEUMONIA

Pneumonia remains a vexing problem following pulmonary resection. Although the incidence at our institution has been reported to be as low (2.2%) in one series, we have also seen much higher rates (7%–9%) reported in other series. When pneumonia occurs, it wreaks significant morbidity. Risk factors include longer preoperative hospital stay, immunocompromised state, procedure type (pneumonectomy > lobectomy), compromised pulmonary reserve, smoking, and atelectasis.

With the development of fever and a new infiltrate on chest X-ray, sputum cultures should be obtained and broad-spectrum antibiotics started. Although Tobin and Grenvik[22] showed that up to 30% of new infiltrates in the intensive care unit prove not to be pneumonia, a missed pneumonia in a postoperative patient has high morbidity. Once the culture results are available with a sensitivity panel, the antibiotics should be narrowed to treat the offending organism. Often there is no evidence of an infiltrate but the patient develops a productive cough, fever, and/or elevated white count. Since the radiological findings of an infiltrate often lag behind a clinical pneumonia, especially in the dehydrated patient, broad-spectrum antibiotics should be started. If all the cultures are negative, then the antibiotics can be stopped. However, if an infiltrate develops or worsens or if the patient's clinical course deteriorates, consideration should be given to performance of bronchoalveolar lavage to help identify the pathogen and direct antibiotic coverage.

POSTOPERATIVE SOMNOLENCE FROM EPIDURAL ANALGESIA

Epidural analgesia has been one of the most important advances in general thoracic surgery in the last several decades. It reduces respiratory complications by allowing patients to breathe deeper, walk sooner, and better mobilize secretions.

While beneficial, epidural analgesia is associated with a number of complications, including accidental entry into the subarachnoid space, hematoma, urinary retention, itching, nausea, and respiratory depression. A "wet tap" can occur when the needle or catheter accidentally enters the subarachnoid space. The former should be immediately recognized by the one placing the epidural. The latter is recognized when the test dose given after insertion results in numbness in the chest area. The most significant and common complication from epidural analgesia is the over-narcotized patient. This is not uncommon and needs to be swiftly recognized and treated. New-onset somnolence may have several etiologies (stoke, intracranial abnormalities, electrolyte imbalances, sundowning, etc.); however, the epidural should not be overlooked as a potential cause. Often, a patient's family members aggressively deliver the analgesia. Clinical staff should discourage this practice. If the patient cannot deliver his or her own pain medicines or does not understand how to use the machine, he or she is a poor candidate for PCA units and should not have one. In this case, traditional pain medicines should be delivered by the nursing staff.

If the patient is somnolent from excessive narcotic analgesia, we prefer to arouse her or him with external stimuli. A chest rub or aggressive bedside maneuvers can quickly wake a patient up, and this helps establish the diagnosis and can eliminate other potential causes. A reliable calm family member in the room can also be helpful, and often one-on-one nursing may be needed. If external stimulation fails, if the patient's oxygen saturations remain low or an arterial blood gas continues to show hypercapnia despite aggressive pulmonary toilet and incentive spirometry, then we prefer to give one-fourth amp of intravenous naloxone. A higher dose can result in too much rebound pain. If the patient does not awaken after this, a higher dose can be administered after other causes of the new-onset somnolence have been ruled out. This patient is best transferred to the intensive care unit. If the patient arouses with naloxone, the epidural basal rate should be eliminated and/or the catheter removed, depending on the situation and postoperative day.

ASPIRATION

Aspiration is a devastating complication after thoracic surgery. The incidence is often underestimated because pneumonia may be caused by silent (unsuspected) aspiration. Risk factors for an acute aspiration event include age (the incidence is greater in elderly patients), altered mental status, and weak and/or somnolent patients. It can also occur in a healthy patient who is preparing to go home following an uncomplicated postoperative course. In its most full-blown form, it can lead to sepsis syndrome, multiorgan

system failure, and death. Therefore, one's guard against aspiration can never be lowered; its occurrence must be aggressively avoided. Patients should be instructed to eat only when fully awake and sitting upright at 90 degrees in bed or a chair. Family members should be discouraged from "helping feed the patient to get him or her stronger," especially if the patient is sleepy.

Once aspiration occurs, patients quickly desaturate. Continuous pulse oximetry monitoring until discharge helps signal this event and leads to a quick diagnosis. The diagnosis can be made by history if the patient is still alert or by a family member if he or she was present at the time of the aspiration event. Treatment depends on the patient's clinical status. Most patients should have a nasogastric tube placed, a chest radiograph taken, an arterial blood gas drawn, and other laboratory work performed. If the patient is in extreme respiratory distress, immediate intubation should be performed. Broad-spectrum antibiotics should be employed if aspiration pneumonia rather than pneumonitis is suspected, hemodynamics maximized to help perfuse and protect end-organs, and the patient should be transferred to the intensive care unit.

PULMONARY EDEMA

Patients undergoing thoracic surgery do not typically require aggressive intravenous fluid resuscitation that many other postsurgical patients need. Pulmonary surgery does not cause large fluid shifts, as does intraperitoneal surgery. Moreover, expansion and deflation of the lung secondary to double-lumen tube anesthesia, intraoperative barotrauma and volutrauma to the alveoli, and surgical manipulation of the lung all lead to pulmonary damage and edema. Therefore, the guiding standard to treat pulmonary edema is the principle of prevention. The true incidence is difficult to gauge because of the different etiologies and definitions. The tendency to give the patient large volumes of fluids after the epidural placement because of hypotension from the sympathectomy effect must be avoided. This difficult task is only accomplished by continued communication among the surgeons; the rest of the surgical service; and the pain and anesthesia nurses and residents who continually rotate through these services. We prefer the use of alpha agonists such as phenylephrine if mean arterial blood pressure falls after epidural dosing in the patient who is to undergo pulmonary resection after one 250-cc bolus of fluids.

However, despite "running the patient dry," some patients still develop pulmonary edema. Obviously, one needs to ensure that the cause is not cardiac insufficiency. Diuretics remain the mainstay of treatment. Other factors that need to be considered include the patient's weight gain since surgery, the chloride level, and the urinary osmolarity if diuretics have not been given yet. The more commonly used central venous pressure and/or pulmonary capillary pressure are not needed in most patients unless they are "wet" on chest roentgenogram, hypoxic, hypotensive, and oliguric. If the patient continues to deteriorate, echocardiography should be performed to assess both right and left ventricular function and the patient should be transferred to the intensive care unit for placement of a Swan–Ganz catheter. Blood cultures and appropriate scans should be performed to rule out occult infection and noncardiogenic pulmonary edema from sepsis. If high-dose diuretics are not successful, the patient may have acute respiratory distress syndrome. Management of this complication is discussed elsewhere in this volume.

RIGHT VENTRICULAR FAILURE

Some patients with postoperative complications after lung resection experience an acute worsening of pulmonary arterial hypertension that leads to right ventricular failure and a decrease in cardiac output. Several reports suggest this possibility. One study, based on the use of thermodilution catheters, found that the right ventricular end-diastolic volume increased from 153 to 177 mL, and that the right ventricular ejection fraction decreased from 45% to 36% in the first few postoperative days.[23] Another, using echocardiography, found that patients who developed supraventricular arrhythmias after lung resection had a significant increase in the velocity of the tricuspid regurgitant jet, whereas those who underwent lung resection without arrhythmias did not.[24] A third study of patients undergoing pneumonectomy was unable to find any hemodynamic variable or pulmonary function test that augured early morbidity.[25] It did, however, indicate that a right ventricular ejection fraction of less than 35%, pulmonary vascular resistance greater than 200 dyne s/cm^5, and a pulmonary vascular resistance/right ventricular ejection fraction ratio equal to or greater than 5.0 indicated long-term cardiopulmonary disability. No studies have been reported of patients suffering severe complications, such as pneumonia, in the remaining lung after pneumonectomy to determine whether right ventricular failure is a component of cardiopulmonary dysfunction.

A better understanding of the alterations in right ventricular function might lead to modification in patient management. For example, the anesthetic technique might be altered. In a recent study concerning ventilation of one lung, the administration of propofol was associated with sustained decrease in right ventricular ejection fraction and mean cardiac output as compared with the administration of isoflurane.[26] The use of proper anesthetic agents might minimize the additive effects of hypoxic pulmonary vasoconstriction and surgical resection of the pulmonary vascular bed. In principle, numerous therapies are available to lessen the burden on the right ventricle in the postoperative period. Among the agents proposed are nitric oxide, adenosine, calcium channel blockers, dopamine, and mechanical devices. However, none of these has yet been put to the test.

EARLY BRONCHOPLEURAL FISTULA

BPF is defined as a communication between a lobar or segmental pulmonary bronchus and the pleural space. It is different from an APF. This difference is not just one of semantics, but also centers around treatment since an APF almost never requires a reoperation, whereas a BPF almost always does. A BPF can present as an early complication but more commonly is a late one. The incidence of a BPF has been reported to be 4.5% to 7% after a pneumonectomy (8.6% if right pneumonectomy and 2.3% if left pneumonectomy), about 1% after a lobectomy, and 0.3% after a segmentectomy.[27] However, a BPF after lobectomy that was performed for cancer is very rare. Risk factors for a BPF are divided into patient characteristics and intraoperative techniques. The former include infectious etiology, preoperative radiation, type of procedure (right pneumonectomies have the greatest incidence), immunocompromised state such as history of solid-organ transplant, and comorbidities such as diabetes. Intraoperative technique risk factors include surgeon inexperience, a long stump, leaving lymph nodes on the bronchus, and injuring the arterial blood supply to the bronchus.

When a BPF presents as an early complication, it is signaled by the development of a new large air leak.[28] It usually is a continuous leak as described by the RDC classification system of air leaks.[29] Immediate recognition is essential and requires a high index of suspicion any time the air leak suddenly increases. Usually the diagnosis can be confirmed with bronchoscopy; however, this test can be falsely negative, as a small BPF can be missed. If the diagnosis remains in question, a xenon ventilation scan can be performed, though this is difficult if the patient is intubated. The xenon gas can be seen escaping the airway, traversing the pleural space, and going into the chest tube and drainage system. This secures the diagnosis. Once diagnosed, the BPF should be treated with reoperation using muscle flaps or omentum.

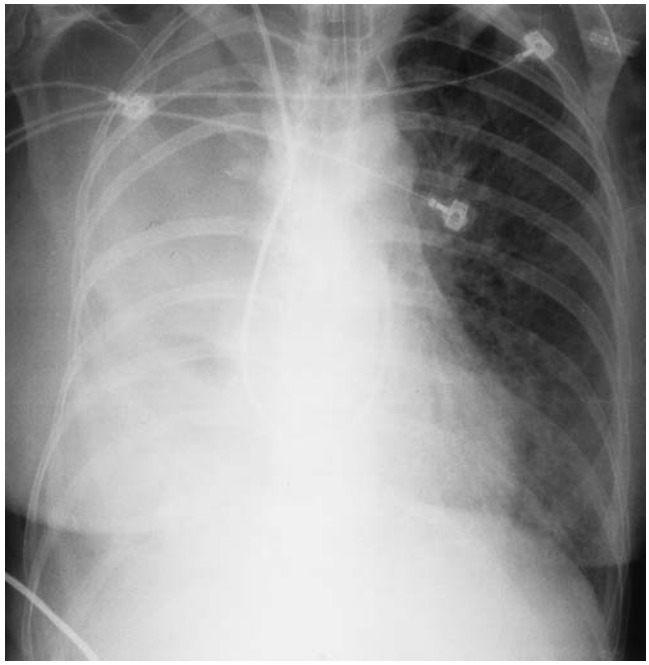

Figure 105-5 Postpneumonectomy pulmonary edema with onset 48 hours after extrapleural pneumonectomy. There is a diffuse interstitial infiltrate present that was heralded by the insidious development of hypoxemia in this otherwise healthy 60-year-old woman.

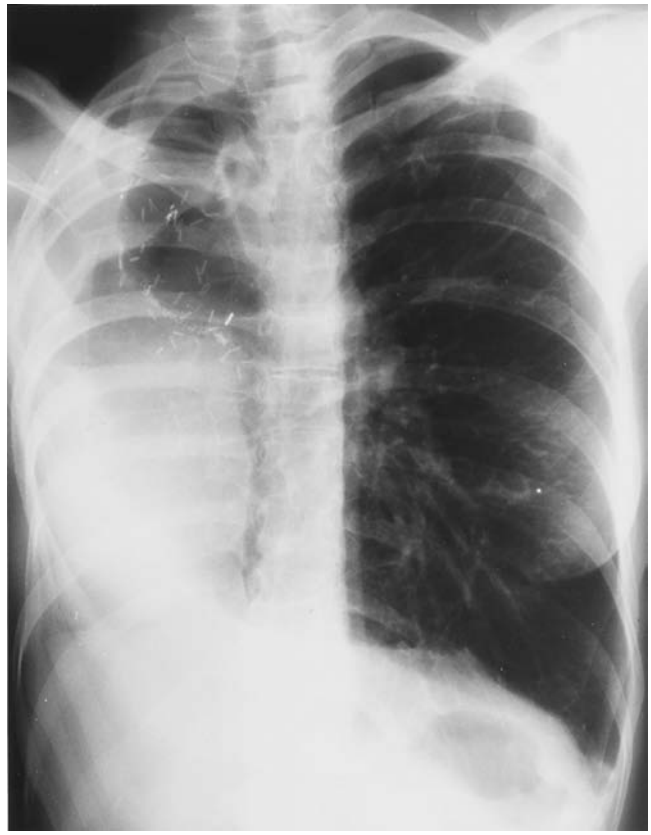

Figure 105-6 Marked shift of the mediastinum with hyperinflation of the left lung and tethering of the left mainstem bronchus over the vertebral column, characteristic of postpneumonectomy syndrome.

■ POSTPNEUMONECTOMY PULMONARY EDEMA

Postpneumonectomy pulmonary edema is a rare but potentially lethal complication of pneumonectomy. For several reasons, the patient who has undergone pneumonectomy is thought to be at increased risk of pulmonary edema. First, although the removal of one lung is well tolerated if the pulmonary vasculature is normal, if pre-existing pulmonary vascular disease is present, the reduced pulmonary vascular bed may be unable to accommodate the cardiac output without an inordinate increase in pulmonary arterial pressure. Second, disruption of lymphatics associated with mediastinal lymph node dissection may interfere significantly with the clearance of fluid from the lung. In the presence of these two predisposing factors, overzealous administration of fluid may lead to the formation of lethal pulmonary edema.

The clinical presentation of postpneumonectomy pulmonary edema is that of a relatively uneventful initial 24- to 48-hour postoperative period, followed by a relentlessly increasing need for respiratory support, usually culminating in death within 24 to 48 hours. The pulmonary edema progresses despite aggressive efforts to effect diuresis and other supportive measures (Fig. 105-5). Current therapy is directed at limiting the administration of fluids perioperatively and providing supportive measures if the complication should arise.

■ POSTPNEUMONECTOMY SYNDROME

Postpneumonectomy syndrome is a rare complication manifested by cough and dyspnea on exertion that usually follows right pneumonectomy. It is due to progressive mediastinal shift with compression of the left mainstem bronchus by the vertebral column. The underlying cause of this complication of pneumonectomy is herniation of the contralateral lung into the vacant pleural space, causing compression of the mainstem bronchus between the aorta, pulmonary artery, or vertebral column (Fig. 105-6). Repair is directed toward repositioning and stabilizing the mediastinum in the midline by a combined procedure of cardiopexy and placement of pliable, variable-volume tissue expanders into the empty pleural space. Cardiopexy alone probably provides insufficient protection against recurrence. Before surgical repositioning, it can be difficult to assess whether significant tracheomalacia is present in the compressed segment. Persistent airway narrowing and symptoms of obstruction following correction of mediastinal shift may require placement of an airway stent or reoperation for resection of the affected bronchial segment. Some surgeons have had success with minimally invasive repair of postpneumonectomy syndrome.[30]

■ EMPYEMA

Empyema is an uncommon complication after pulmonary resection; however, when it occurs, it is associated with high morbidity. It is most often seen in patients who have undergone pneumonectomy. It is estimated to occur in about 2% to 16% of postpneumonectomy patients. In a study by Varela et al.,[31] empyema was the most common cause of readmission after pulmonary resection, involving 18 of 727 patients (2.5%). The primary risk factor has been cited to be pneumonectomy with an associated BPF. Less commonly cited risk factors include anatomic extent of disease (no association with stage I cancer, some association with stages II and III cancer), degree of surgical manipulation, and an immunocompromised host.

The treatment centers on drainage of the pleural space. This can be established by chest tube placement, video-assisted thoracoscopic approach, or most commonly a redo thoracotomy with a muscle flap. If there is any question that an early BPF is the cause of the early empyema, then redo thoracotomy with muscle or omental harvesting is mandatory to not only drain the empyema and decorticate the lung, but to also buttress the open bronchus.

POSTOPERATIVE RESPIRATORY FAILURE

Despite preoperative tests and pulmonary preserving techniques, respiratory failure can still occur after pulmonary resection. The inability to extubate a patient immediately after the operation (which should be extremely rare) is a poor prognostic sign. The difficulty usually arises on postoperative day 2 or 3 secondary to pneumonia, poor cough effort, or pulmonary edema. The patient often begins to develop signs of respiratory distress even before an opacity appears on the chest radiograph. Sputum cultures should be obtained and broad-spectrum antibiotics should be started immediately. These should be tailored to the particular sensitivities of the organism reported later. Pulmonary mechanics must be maximized; this includes minimal intravenous fluids, aggressive chest physiotherapy, continuous respiratory treatments with bronchodilators, incentive spirometry, frequent ambulation with physical therapy, control of secretions, and nutritional support. If the patient cannot clear his or her own secretions, then nasal tracheal suction should be used to "encourage" coughing. Nasal tracheal suctioning via a nasal trumpet or even minitracheostomy affords the surgeon other methods to help clear the airway and avoid recurrent atelectasis and pneumonia. If the patient is somnolent, she or he needs to be aroused and treated as described in the preceding section "Postoperative solnolence from epidural analgesia". Arterial blood gases should be performed to rule out hypercapnia.

RENAL INSUFFICIENCY

It is not uncommon for patients to have an increase in their creatinine level after pulmonary resection. Most patients are elderly and thus have reduced renal reserve, and many are hypotensive due to effects of the epidural and the low amount of fluids administered. Thus, early recognition of this problem entails checking the creatinine level in all patients who produce less than 0.5 mg/kg per hour of urine. Treatment is early recognition, the removal of renal toxic agents, and the gentle rehydration of the patient.

POSTOPERATIVE HEMORRHAGE

The incidence of postoperative hemorrhage after elective general thoracic surgical procedures in a noncoagulopathic patient is extremely low. In our experience, re-exploration for bleeding occurred in 7 patients in our last 2400 thoracotomies (0.3%). In all cases, bleeding was from a small vessel (or the bronchial artery in one patient). The pulmonary artery should be handled with meticulous care, and it should be carefully dissected. We prefer double ligation or stapling. The vein can be safely handled with a stapler as well. Prior to chest closure, the major vascular structures in addition to all other sites of surgical dissection should also be re-examined to ensure hemostasis. The inferior pulmonary ligament, which usually contains a small artery, should be checked. We perform a complete lymph node resection in all patients with bronchogenic carcinoma; therefore, all lymph node stations are potential sites of postoperative bleeding. This is especially true of the #7, subcarinal area. There is a large artery that feeds the subcarinal lymph nodes that comes off the carina. It should be visualized and ligated. This is often difficult to do, especially on the left side. Excessive cauterization should be avoided, especially in the aorta–pulmonary window lymph node area on the left and the paratracheal area on the right, to avoid injury to the recurrent laryngeal nerves. Bleeding can also occur from the pulmonary parenchyma, especially after wedge resection. This area needs to be re-evaluated prior to chest closure. The surface of the undercut rib both anteriorly and posteriorly should be carefully examined also. Finally, the chest tube sites and pericostal sutures sites (if used instead of the preferred intracostal sutures) should be examined from inside the chest before closure. The branches of the bronchial artery that can spasm and later bleed should be identified and clipped or tied if dissected.

If a patient is having excessive postoperative bleeding of greater than 200 cc/h (i.e., blood loss alone; not chyle, cerebrospinal fluid, or transudative effusion) for 2 to 4 consecutive hours, INR, PTT, and platelet count should be checked. Any abnormalities should be corrected. If the mediastinum and/or pleural space do not have retained clots, and the coagulogram is abnormal, reoperation can be avoided if the underlying problem is corrected and the bleeding slows down. However, if there is residual clot in either space, this often leads to a local consumptive coagulopathy and the patient will continue to hemorrhage until the clot is fully evacuated, either via the chest tubes or usually by reoperation.

PULMONARY TORSION

During a pulmonary resection, an extensive dissection is usually performed around the hilum for division of the pulmonary vessels. In addition, after an upper lobectomy, the inferior pulmonary ligament is divided to allow the lower lobe to rise within the pleural space to obliterate the residual apical space and to remove the #9 inferior pulmonary ligament lymph node. Unfortunately, on rare occasions the increased mobility of these structures can lead to torsion of all or part of the residual lung, causing venous outflow obstruction and, possibly pulmonary gangrene. The right middle lobe is at greatest risk, especially after a right upper lobectomy, since the right middle lobe fissure-like connection to the right lower lobe is often diminutive. This complication is preventable by the surgeon. Some prefer to prevent it by tacking the middle to the lower lobe before closing the chest. However, we simply ensure that the right middle lobe inflates correctly without a twist after a right upper lobectomy has been performed and before closing the chest. We watch the middle and lower lobe inflated with the robotic camera, VATS camera, or under direct vision if a thoracotomy has been performed. However, it can still occur and any portion of residual lung can be affected (Fig. 105-7).

Pulmonary torsion may be suggested by the radiographic finding of consolidated lung, in association with fever, leukocytosis,

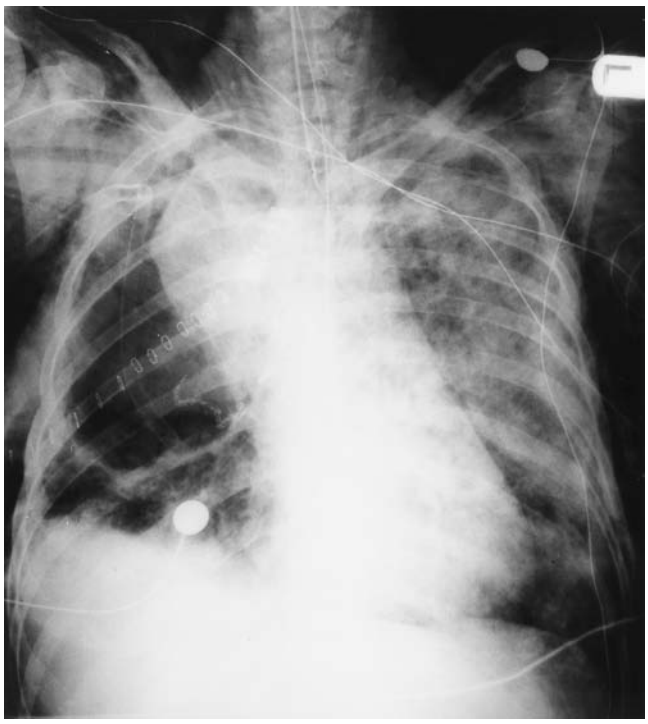

Figure 105-7 Consolidation of the right middle lobe caused by torsion following right upper lobectomy.

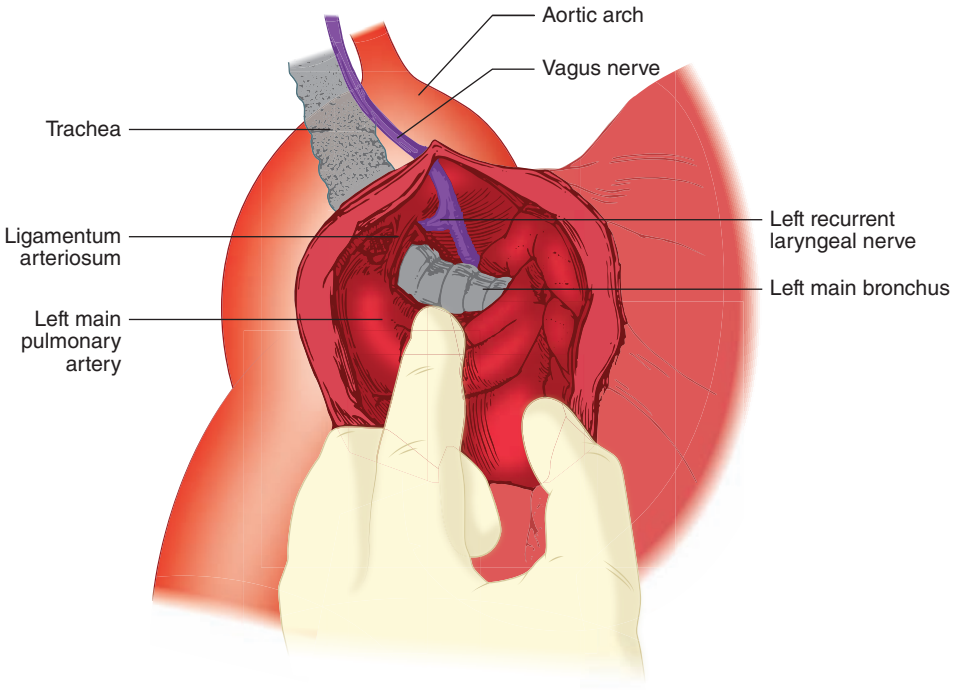

Figure 105-8 Location of the left recurrent laryngeal nerve as it takes its origin from the vagus nerve at the level of the aortic arch. Note its position relative to the ligamentum arteriosum.

and purulent, occasionally bloody, sputum. Bronchoscopy may be helpful if a twisted bronchus can be demonstrated. The treatment is immediate surgical exploration with rerotation of the affected lung, followed by fixation to surrounding structures. If the lung is not viable, lobectomy or complete pneumonectomy may be required. Sometimes if caught early, a bronchoscope can be used to untwist the right middle lobe bronchus and prevent the need for re-exploration, but this is uncommon.

RECURRENT LARYNGEAL NERVE INJURY

In a patient with lung cancer, the recurrent laryngeal nerves are vulnerable to injury because of either direct invasion by malignancy or injury during surgical dissection. The left vagus nerve is at greater risk than the right because of its course from the neck down into the left aspect of the mediastinum and across the aortic arch before giving off the left recurrent laryngeal nerve at the level of the inferior border of the aortic arch (Fig. 105-8). The nerve passes around the ligamentum arteriosum and "recurs" along the left tracheoesophageal groove. If either nerve is injured, unilateral vocal cord dysfunction results in hoarseness, an increased risk of aspiration, and marked decrease in the effectiveness of cough and the ability to clear secretions. Neurapraxia may resolve within weeks or last for 6 to 9 months. For the patient with limited pulmonary reserve who has undergone surgery with its attendant postoperative transient decrease in pulmonary function, vocal cord paralysis can be a devastating problem and may mean the difference between recovery and respiratory failure secondary to aspiration.

Surgical correction of unilateral vocal cord paralysis is becoming increasingly popular. Techniques include injection of Gelfoam for temporary medialization, Teflon for permanent medialization, or surgical placement of a hand-crafted silicone elastomer implant. The success rate, as measured by symptomatic improvement in dysphonia, aspiration, or incidence of pneumonia, exceeds 90%.

PULMONARY HERNIATION

Herniation of the lung outside of the chest is uncommon but can occur in immunocompromised thin patients. The patient complains of a bulge with coughing or sneezing and a CT scan demonstrates the pulmonary parenchyma in an extrathoracic position. Treatment is surgical reclosure and approximation of the ribs.

CONCLUSION

The key to the management of postoperative complications is thoughtful patient selection and meticulous intraoperative technique. Despite these caveats and hypervigilant postoperative care, many of the complications described earlier occur. Complications are a part of surgery. A full understanding of the cardiopulmonary physiological changes that occur after pulmonary resection, either after thoracotomy, video-assisted thoracoscopy, or a completely portal robotic approach is required for the proper management of complications. Early recognition secondary to a high index of suspicion along with prompt treatment leads to the minimization of the morbidity of these unwanted postoperative events.

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CHAPTER 106

Thoracic Trauma

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J. Wayne Meredith

EMERGENT INTERVENTIONS

Thoracic injuries are common, with up to one of five trauma patients presenting with injuries involving the chest. Thoracic injury and the ensuing complications are responsible for as much as 25% of the blunt trauma mortality.[1] Motor vehicle accidents (MVA) are the most common cause of blunt thoracic injuries, followed by falls, with injury resulting from the transmission of energy to the chest wall and underlying structures. The size and location of the chest make it vulnerable to penetrating mechanisms, such as gunshot and stab wounds. Early identification and intervention can lead to significant impact on mortality in the trauma population.

Many injuries to the thorax require immediate intervention during the primary survey to support cardiopulmonary function. Establishment of a secure airway and ventilatory assistance should occur immediately in patients with respiratory compromise. Evidence of reduced respiratory compliance measured on mechanical ventilation (i.e., elevated peak and plateau airway pressures) and decreased breath sounds may indicate a tension pneumothorax, which requires urgent intervention. External bleeding should be controlled with direct pressure while resuscitation with crystalloid solution and blood products is initiated. Hemodynamic instability may signal injuries that need to be addressed during the primary surgery such as tension pneumothorax requiring decompression, hypovolemia requiring hemorrhage control and resuscitation, or cardiac dysfunction secondary to pericardial tamponade. Evaluation for sources of bleeding should commence after addressing airway and breathing issues. This should include a chest X-ray as well as a bedside ultrasound looking for the presence of a pericardial effusion, especially in the setting of penetrating trauma. Based on these initial interventions, decisions regarding subsequent management such as immediate operation can be determined. In the event of cardiac arrest, especially in the setting of penetrating mechanisms, a resuscitative thoracotomy can be considered but carries with it an extremely high mortality. The chance of a salvageable patient is even less in blunt trauma and resuscitative thoracotomy should be reserved for circumstances where there is a witnessed cardiac arrest.

EVALUATION

Most thoracic injuries can be identified with a physical examination and plain chest radiography. Physical examination will reveal superficial injuries, including chest wall defects and penetrating wounds. Deviation of the trachea at the sternal notch may reveal intrathoracic tension on the side opposite the trachea. Distended neck veins indicate heart failure or impaired venous return, which requires further evaluation. Chest radiography is performed on all significantly injured patients at risk for thoracic injuries. This study can be obtained rapidly in the trauma bay, with the results quickly revealed. The chest radiograph identifies the presence of a pneumothorax or hemothorax, as well as rib and sternal fractures. The appearance of a widened mediastinum may suggest a thoracic aortic injury (Fig. 106-1). An ultrasound of the pericardium, which may reveal pericardial blood, is a component of the focused abdominal sonography for trauma (FAST) examination. In recent years, thoracic CT angiography has emerged as a valuable tool in the evaluation of blunt thoracic trauma. CT provides visualization of the chest wall and hemithoraces, allowing determination of rib fractures, pneumothoraces, and hemothoraces, and pulmonary contusion. Of great value has been the ability to evaluate the thoracic aorta for injury that historically required standard angiography when suggested by a chest radiograph. Chest CT angiography is able to identify transection of the aortic wall, as well as lower-grade injuries that involve only the aortic intima. Many thoracic surgeons have modified their approach and now proceed with operative intervention based on the chest CT alone, without formal angiography.

Penetrating injuries to the chest that cross the mediastinum or are in the vicinity of the heart and mediastinal structures require a methodical evaluation. Penetrating wounds in "the box," an area defined by the sternal notch superiorly, the costal margin inferiorly, and the nipples laterally, are in this group requiring further evaluation. This includes an assessment of the cardiovascular and aerodigestive structures of the mediastinum. Immediate ultrasound is performed to evaluate the pericardium for effusion. In the setting of an associated hemothorax, ultrasound may yield false-negative results due to decompression of a cardiac injury into the pleural cavity. In stable patients further evaluation has historically included an angiogram of the chest, which has now been replaced by CT angiography in most of the situations. The heart and great vessels are evaluated for injury, although this can be impeded by the presence of retained missile fragments that cause scatter on CT. In this setting, standard angiography may be necessary. Depending on the trajectory of the penetrating object, the trachea and proximal airways may require evaluation with bronchoscopy. If injury is suspected, the esophagus should be assessed with a combination of esophagoscopy and contrast esophagography. Frequently, thoracic CT will accurately identify the trajectory of the wound and thus guide the need for further evaluation.

MANAGEMENT

Up to 85% of all thoracic injuries can be managed with nothing more than a tube thoracostomy. In most cases, the placement of a chest tube is urgent but should still be performed in a controlled

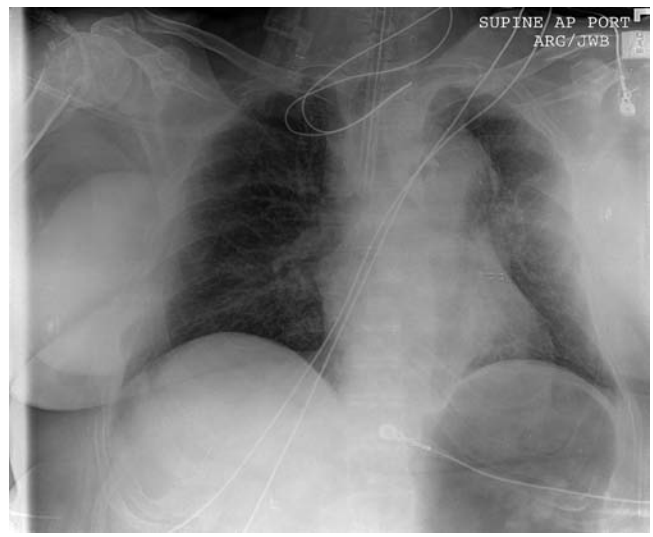

Figure 106-1 Widened mediastinum suspicious for thoracic aorta injury.

manner that includes strict sterile preparation and excellent surgical technique. This is very important given the morbidity associated with an empyema that can result from improper chest tube placement. The chest should be prepared appropriately with a formal skin preparation as well as wide draping to maintain the sterility of the field and the tube to be placed. The skin incision should be in the fourth to fifth intercostal space usually identified as the level of the nipple to stay superior enough to avoid the highest reach of the diaphragm. A tunnel is created in a superior direction and the chest is entered bluntly in an interspace above the skin incision. The lung is palpated to confirm chest entry and evaluate for intrathoracic adhesions. A tube large enough to drain blood (typically 32–36 Fr) is then advanced superiorly through the incision and posterior to the lung. Chest tubes that are being placed only for a pneumothorax can be positioned in the anterior hemithorax. The thoracostomy is then connected to an underwater drainage device providing 20 cm H_2O suction.

Tube thoracostomies that drain large amounts of blood on initial placement or demonstrate ongoing output may indicate active intrathoracic bleeding that requires thoracotomy. Other indications for immediate thoracotomy include a massive air leak with associated pneumothorax or drainage of esophageal or gastric contents from the chest tube. The choice of thoracic approach depends on the presumed injured structures. Access to the lungs, pulmonary vasculature, and hemidiaphragm is through a posterolateral thoracotomy that is best performed through the fifth interspace, with or without removal of the fifth rib. The decision of which side to approach the injury depends on the target organ and which portion of the organ needs to be exposed. A median sternotomy can be a highly versatile approach, allowing exposure of the right heart, ascending aorta, aortic arch with right-sided arch vessels, and pulmonary vasculature.

■ CHEST WALL AND PLEURAL SPACE INJURIES

During the trauma evaluation, chest wall injuries are commonly recognized. Chest wall tenderness and changes in chest wall motion are suggestive. Some patients require immediate intervention for chest injuries, but most will subsequently undergo further evaluation. Injuries involving the chest wall or pleural space can frequently be identified on chest radiographs (Fig. 106-2). Chest CT is a common part of the evaluation for thoracic injuries at many centers. CT identifies rib and sternal fractures, as well as pleural air and blood with high sensitivity.

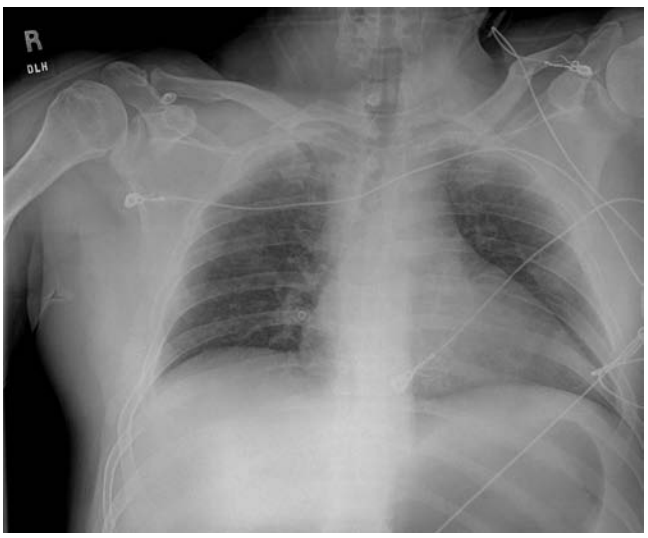

Figure 106-2 Multiple left-sided rib fractures on a plain chest radiography.

Rib Fractures

Fractures of the ribs are the most common thoracic injury following blunt trauma, with almost 80% of patients with chest injuries sustaining one or more fractures. Rib fractures typically occur secondary to compression of the thoracic cage in an anteroposterior or lateral direction that often will dictate the location of the cortical disruption along the rib. Steering wheels and seatbelts are commonly identified as the impinging structure resulting in a fracture.

Rib fractures can vary greatly in severity, depending on the number present and patient characteristics. Associated pain can be severe and the resultant splinting can lead to the development of atelectasis and pneumonia. Aggressive analgesia should be provided to allow adequate pulmonary toilet and promote comfort. Adequate analgesia can be achieved with IV narcotics in mild cases but, in more severe cases, patients benefit greatly from the provision of epidural analgesia. Epidural analgesia after chest wall injuries has been associated with fewer ventilator days, shorter intensive care unit (ICU) length of stay, and fewer hospital days. Furthermore, one study demonstrated fewer pulmonary infections and decreased duration of mechanical ventilation with the use of epidural analgesia in patients with three or more rib fractures.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are also beneficial in conjunction with narcotics. Aggressive pulmonary toilet, including deep breathing, frequent coughing, and incentive spirometry, should be highly encouraged. Chest physiotherapy and positive expiratory pressure exercises may also be beneficial. Severe chest wall injuries with respiratory failure may require mechanical ventilation.

There has been renewed interest in the operative fixation of rib fractures, although the optimal indications for these procedures and their associated benefit remain incompletely defined. Tanaka et al.[3] performed the only randomized, controlled study of operative fixation versus internal pneumatic stabilization. Groups were well matched in terms of injury severity, criteria for ventilatory support, and ventilator management. The incidence of pneumonia was lower in the surgical group (22% vs. 90%) as was the length of ventilation and length of ICU stay. The investigators reported improved lung volumes, decreased pain and dyspnea and higher return-to-work at 1 year with surgical fixation. The investigators concluded that surgical stabilization may be preferable for severe flail chest patients when prolonged ventilatory support would otherwise be expected. Other studies have yielded less supportive data. Ventilated patients who fail to demonstrate progress in moving toward extubation or patients with alternative indications for surgical intervention (e.g., retained hemothorax) should be strongly considered for chest wall stabilization.

Flail Chest

In its most severe form, large amounts of energy transferred to the chest wall can result in the creation of a flail segment, defined as two or more adjacent ribs that are each fractured in two or more locations. This results in a separation of a segment of the chest wall. Although pulmonary mechanics can be disrupted by the presence of a flail segment, the greatest physiologic insult is caused by the underlying pulmonary contusion that almost invariably occurs. As mentioned earlier, fixation of the chest wall is an attractive option but it does nothing to address the underlying contusion. Most current ongoing trials examining fixation exclude patients with large contusions, making further study of operative intervention in this population a challenge.

Pneumothorax

Simple pneumothorax is created when a tear in the pleura allows entry of air into the pleural space with resultant loss of negative intrathoracic pressure. If an injury to the lung parenchyma produces an air leak, the air accumulates in the pleural space with each breath, markedly increasing intrathoracic pressure and thereby shifting the

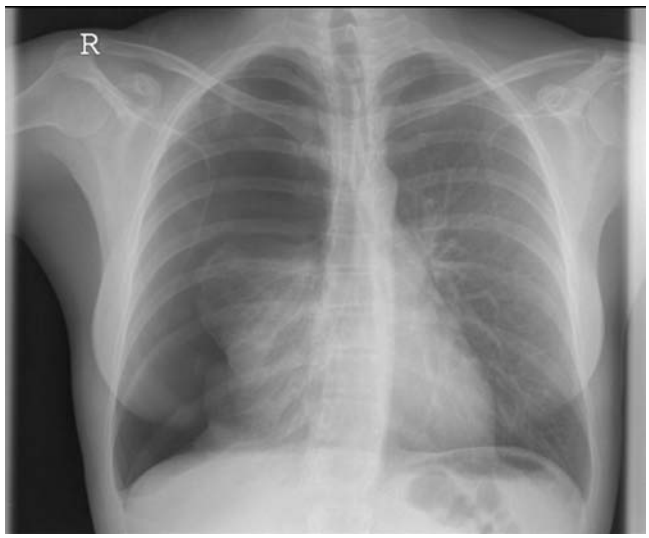

Figure 106-3 Tension pneumothorax on the right.

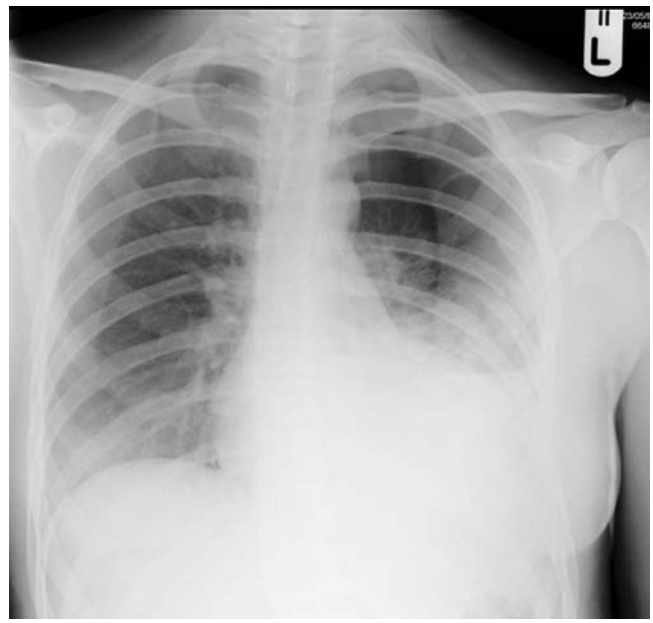

Figure 106-4 Left-sided hemothorax seen on plain chest radiography.

mediastinum toward the opposite hemithorax (Fig. 106-3). This so-called tension pneumothorax is immediately life-threatening because of the limitation of vena caval blood flow causing decreased venous return, which results in hypotension, tachycardia, and cardiac arrest. Once the diagnosis of tension pneumothorax is suspected, treatment should be initiated immediately without waiting for chest radiograph confirmation. This is most rapidly done by placing a large-bore needle into the second intercostal space. This is then followed by a formal tube thoracostomy under sterile precautions.

Pneumothorax that is visible on a chest radiograph requires performance of a tube thoracostomy. Chest tube drainage should continue until any pulmonary air leak has resolved and pleural fluid drainage is not excessive (<150 cc/d). As CT scan is being performed more commonly in the evaluation of trauma patients, many injuries are now identified that had previously not been detected. Occult pneumothorax, defined as a pneumothorax that is seen on chest CT but not on plain films, is being diagnosed more frequently.[4] Retrospective data in these cases suggests that placing a chest tube will lead to longer ICU and hospital stays.[5] Most occult pneumothoraces can be safely observed but enlargement of the pneumothorax on follow-up imaging necessitates a chest tube. Another key question has been the factor of positive pressure ventilation. Several investigators have tried to answer the effect that positive pressure has on occult pneumothorax, with conflicting results. In a prospective study, Enderson et al.[6] found that patients with pneumothoraces treated with observation who underwent positive pressure ventilation experienced an unacceptable rate of complications, with 3 of the 15 patients developing a tension pneumothorax. In contrast, in a prospective randomized study Brasel et al.[7] found no increase in complications regardless of whether chest tube or observation was chosen. Both studies suffered from low numbers but suggested that the majority of patients with occult pneumothoraces will not have progression regardless of the presence of positive pressure ventilation. Patients who demonstrate a large amount of subcutaneous air without significant pneumothorax should be followed closely, with a low threshold for placing a chest tube, because a pulmonary air leak may still be present.

Pneumothorax and Open Chest Wound When a pneumothorax is associated with an open chest wound after penetrating trauma, initial management is designed to restore a seal to the thoracic cavity. This is accomplished by applying a sterile occlusive dressing to the wound, taped on three sides. The dressing allows air to escape from the pleural space but does not allow air from the outside to enter. This should be immediately followed by placement of a chest tube at a different location.

Hemothorax

It is estimated that the occurrence of hemothorax related to trauma in the United States approaches 300,000 cases per year.[8] Hemothoraces should be drained if visible on plain films (Fig. 106-4) due to the concern that this quantity of blood in the pleural space could result in lung entrapment as the hematoma matures.[9,10] The presence of retained hemothorax after chest tube placement has been shown to be an independent predictor of the development of an empyema in 33% of patients.[10] Hemothoraces that do not resolve after insertion of a tube thoracostomy should be evaluated with a CT scan. Significant residual collections may benefit from drainage via video-assisted thoracoscopic surgery (VATS).[11] Surgical intervention is favored over placement of a second chest tube as it has been shown to decrease the duration of tube drainage, the length of hospital stay, and hospital cost.[12] The timing of VATS is also important. Early VATS (before day 3) results in statistically significant reduction in operative difficulty, contamination/infection of clot, and hospital length of stay, compared to those performed later.[13] There appears to be no absolute contraindication to attempting VATS in a delayed fashion as successful procedures have been performed as far out as 14 days.[14] The surgeon should anticipate that conversion to thoracotomy is more likely after 5 days, and should counsel the patient accordingly.[13,15]

Historically, immediate thoracotomy is indicated for more than 1500 mL of blood drained on chest tube insertion or more than 200 mL/h for 3 hours. These figures were based on Vietnam military data that suggested increased mortality in patients who reached these thresholds.[16] Although these values clearly may be associated with ongoing intrathoracic bleeding, the decision to operate should be carefully considered, especially with regard to the immediate output. In a hemodynamically stable patient, chest tubes that initially drain 1500 mL may indicate bleeding from a lung laceration that ceased with lung reexpansion and may not require or benefit from thoracotomy.

Sternal Fractures

Sternal fractures are managed similar to rib fractures, with emphasis on analgesia and pulmonary toilet. Occasionally, sternal fractures

result in the development of a mediastinal hematoma. Although these typically do not require specific treatment, the presence of active bleeding from the adjacent internal mammary artery may require angioembolization or open ligation in the setting of hemodynamic instability. The relationship of sternal fractures and cardiac contusions is weak enough that the injuries should be approached independently. In the absence of symptoms of cardiac contusion patients with a sternal fracture do not need an automatic evaluation for cardiac injury.

■ PULMONARY INJURIES

The lungs are susceptible to injury during blunt and penetrating mechanisms. Pulmonary contusion is the most common injury identified in the setting of blunt thoracic trauma, occurring in 30% to 70% of all cases. Pneumonia and acute respiratory distress syndrome are frequently encountered and mortality rates ranging from 10% to 25% have been reported. Pulmonary contusion results from energy transfer through the chest wall to the pulmonary parenchyma, resulting in tissue damage, as well as hemorrhage into the alveolar and interstitial spaces. The result is the development of physiologic shunt with hypoxemia. These injuries are also associated with a profound inflammatory response that can lead to further respiratory dysfunction and systemic inflammation.[17] Frequently, pulmonary contusion is identified in the presence of a flail segment and is the major cause of associated morbidity and mortality. Penetrating mechanisms can result in lung contusions or laceration of the pulmonary parenchyma.

Chest radiographs obtained shortly after patient arrival may demonstrate pneumothorax or hemothorax indicative of an underlying pulmonary injury. Lung contusions may be present on the initial chest radiograph but typically require time to become evident on plain film. Pulmonary contusions identified early on chest film are frequently severe and rapidly progressive to respiratory failure. A pulmonary contusion is easily identified by thoracic CT, although at times it can be challenging to differentiate contusion from atelectasis. A basic rule of thumb is that atelectasis does not cross pulmonary fissures, whereas contusions are not limited by anatomic segments (Fig. 106-5). Also, higher-density pulmonary tissue in the vicinity of chest wall injuries, especially when not in dependent areas, is highly suggestive of pulmonary contusion.

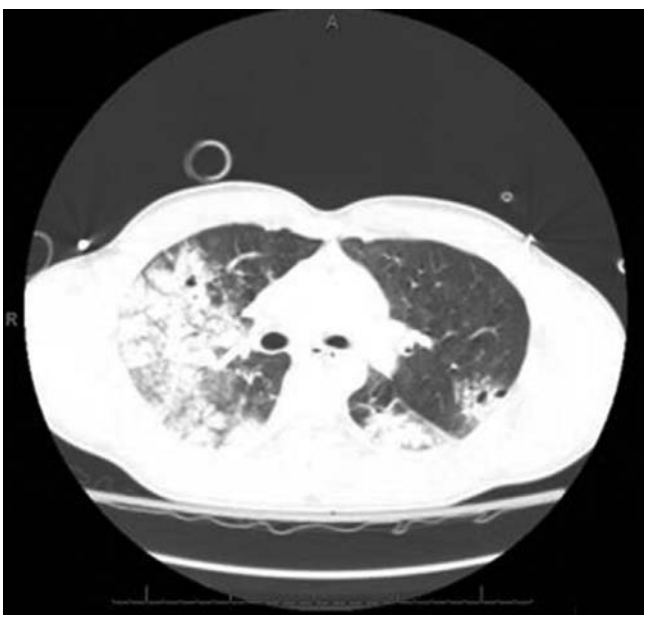

Figure 106-5 Pulmonary contusion crossing lobes of the right lung on axial CT scan.

The management of pulmonary contusion is largely supportive. Patients should be monitored for indications of respiratory decompensation such as hypoxemia, increased work of breathing, and agitation, which mandate intubation and mechanical ventilation. Pulmonary function is supported until the physiologic insult related to the contusion resolves. The mode of ventilation used does not impact overall outcome and the mode most familiar to the practitioner or most comfortable for the patient should be employed.[18] Efforts to prevent ventilator-associated pneumonia are valuable because of a significantly increased risk. Intubation should be guided by the patient's observed respiratory status and should not be performed prophylactically simply on recognition of pulmonary contusion. Similarly, the presence of a pulmonary contusion or flail chest does not require mandatory chest tube placement in the absence of a pneumothorax or hemothorax. It is a common misconception that patients with pulmonary contusion should be managed with fluid restriction.[19] Rather, appropriate resuscitation to maintain acceptable vital organ perfusion should be provided as for other severely injured patients. Excessive volume expansion should be avoided. Placement of a pulmonary artery catheter may be of value to guide fluid administration, especially when the respiratory status is tenuous and could suffer significantly from overvigorous fluid resuscitation. Aggressive pulmonary toilet can be beneficial, as well as adequate pain control, when concomitant chest wall injuries are present.

■ CARDIAC INJURIES

Sequelae from cardiac injuries range from the benign to catastrophic. It has been estimated that in the prehospital setting, 20% of traumatic deaths are caused by cardiac-related injuries.[20] These numbers likely underestimate the true incidence of cardiac injuries because many are immediately lethal and never present to a hospital.

Penetrating cardiac injuries will frequently be evident on initial examination. A significant number of patients will present in extremis with pericardial tamponade or bleeding into one of the hemithoraces. Diagnosis may then be made during resuscitative thoracotomy in agonal patients. In others, indicators of pericardial tamponade (Beck triad) may be present, including hypotension with distended neck veins and muffled heart sounds, although their presence can be highly variable. Ultrasound is a valuable tool for quickly assessing the pericardium for fluid and should be performed in all patients with hemodynamic instability. A subxiphoid pericardial window is a valuable means of evaluating for cardiac injury and should be used in cases for which ultrasound is not available or the results are inconclusive.

Rarely, blunt thoracic trauma can cause blunt cardiac injury (BCI) otherwise known as cardiac contusion, which is usually self-limited but can lead to arrhythmias. In rare cases, BCI can lead to more severe consequences such as septal defects, valvular damage, heart failure, or cardiogenic shock.

Diagnosis of BCI consists of recognizing a clinical pattern in the context of thoracic trauma. Since arrhythmias are the most common complication of BCI (up to 70% of the patients) documentation of their occurrence should prompt evaluation for BCI. Patients without EKG changes or arrhythmias on initial evaluation do not need further evaluation. Cardiac enzymes do not reliably predict which patients need intervention or will develop complications and are therefore of little clinical use in stable patients.[21,22] Most arrhythmias demonstrated on initial assessment do not require medical treatment and resolve quickly during the course of monitoring. Those with more severe electrocardiographic (EKG) changes or arrhythmias on admission require telemetry for 24 to 48 hours and therapy initiated for the specific electrical abnormality. The presence of hemodynamic instability with evidence of heart failure should prompt an echocardiogram (EKG) to assess cardiac wall and septal motion, as well as valvular function, which in rare cases can be compromised during blunt thoracic trauma. Heart failure may

require treatment with inotropic support and right ventricular afterload reduction, given the frequent involvement of the right heart. Patients who demonstrate structural abnormalities on echocardiography may require urgent operation to repair cardiac injuries.

THORACIC AORTIC INJURIES

Injuries to the thoracic aorta are life-threatening but fortunately not common. Only 0.3% of patients sustaining blunt trauma in the National Trauma Database sustained an aortic injury, although the associated mortality rate exceeded 47%.[23] As with cardiac injuries, this likely underestimates the true incidence because aortic transection is a common cause of immediate death in blunt trauma patients who never present to the emergency department. In 3.8% of cases, the aorta is involved in penetrating thoracic trauma; almost all these injuries are fatal (mortality = 86.1%).[24] Blunt aortic injuries have traditionally been believed to be a result of rapid deceleration, which tears the aortic wall in the vicinity of the ligamentum arteriosum, where it is fixed to the thorax. Lateral mechanisms may also contribute, during which the aortic arch acts as a lever and causes torque to develop at the aortic isthmus. These mechanisms can result in injuries that range from a tear in the aortic intima to full-thickness transection of the wall. Regardless of the degree of injury it must be a contained rupture for the patient to survive to presentation. A free rupture of a thoracic aorta would lead to death within moments.

Penetrating aortic injury may be discovered at the time of thoracotomy or sternotomy, performed because the patient was in extremis. Blunt aortic injury may be suggested by a chest radiograph that demonstrates a widened mediastinum, apical capping, loss of the aortic knob, or deviation of the left mainstem bronchus. Because of a high rate of missed injuries by plain radiograph, most patients involved in high-energy injury mechanisms undergo helical CT angiography of the chest to evaluate for aortic injury. Injuries to the thoracic aorta can be identified on CT as a disruption in the intima or as a pseudoaneurysm with a mediastinal hematoma, which appears as contrast contained outside the aortic lumen. Usually, this study alone is sufficient to plan operative repair, although standard angiography is necessary in some cases, usually at the discretion of the thoracic surgeon.

The treatment of patients who present with a contained blunt thoracic aortic rupture is evolving. Until recently, surgical repair was required in all of these cases because the natural history of these injuries is slow expansion, which ultimately culminates in free aortic rupture. To prevent that occurrence, medical therapy with beta antagonists aimed at controlling aortic wall stress is often initiated at the time of diagnosis. It has been recognized that there is usually a delay in progression of this injury that allows other more urgent issues, such as acute hemorrhage, to be addressed. Small penetrating injuries to the aorta can be closed primarily if exposed prior to exsanguination. Larger penetrating injuries and blunt transection require replacement of a segment of the aorta with a prosthetic graft. This is most commonly performed with the assistance of cardiopulmonary bypass, with full bypass through a femoral–femoral approach or with a centrifugal pump and left heart bypass. The use of cardiopulmonary bypass has been associated with a decreased incidence of paraplegia, which can result from cessation of aortic blood flow during the clamp and sew technique.[25]

More recently, there has been a great deal of interest in the use of endovascular stent grafts to repair the injured thoracic aorta. This is particularly appealing for those patients at high operative risk and with favorable vascular anatomy. In many centers, this approach is becoming a mainstay of treatment for managing these injuries. Described advantages associated with the endovascular repair of aortic injury include a reduction in the incidence of paraplegia and a potential improvement in mortality. Although rare, patients with an intimal tear only may be candidates for nonoperative management because many of these injuries will heal without intervention. Patients should be treated with beta blocker therapy and undergo follow-up imaging to ensure the absence of expansion and ultimately the resolution of the injury.

TRACHEOBRONCHIAL INJURIES

Injuries to the tracheobronchial tree are uncommon but are associated with significant morbidity and mortality. A mortality rate of 6% has been reported but it is believed that many patients with these injuries succumb prior to the arrival of prehospital personnel.[26] Approximately 50% of these injuries involved the right mainstem bronchus within 2 cm of the carina. It is thought that these injuries result from the application of a large amount of kinetic energy to the anterior chest, this force pulls the lungs laterally and avulses the bronchi from the fixed carina. Another proposed mechanism is a rupture caused by rapid compression of the lungs and airways against a closed glottis, which perforates the trachea along the membranous portion. Penetrating injuries, mainly secondary to gunshot wounds, can also result in injuries to the tracheobronchial tree.

Identification of tracheobronchial injuries depends somewhat on the location of airway disruption. Significant subcutaneous air may be present on physical examination. Injuries that involve the thoracic trachea and proximal bronchi may result in significant pneumomediastinum identified by chest radiography or chest CT. More distal airway injuries will typically cause a pneumothorax requiring insertion of a tube thoracostomy. A continuous air leak with persistent pneumothorax is highly suggestive of an injury to a bronchus. Diagnosis is made with fiberoptic bronchoscopy, which allows for the identification of the injury and a detailed characterization, such as the location and severity of the disruption.

Initial management of tracheobronchial injuries includes careful airway management. With the placement of any airway, avoiding any further disruption is vital and may benefit from bronchoscopic guidance under direct visualization. Injuries that occupy less than one-third of the luminal circumference may be considered for nonoperative management if any pneumothorax and associated air leak that were present resolve after insertion of a chest tube and the lung expands completely. Management includes antibiotics, humidified oxygen, careful suctioning, and close observation to be sure that infectious sequelae do not develop. Repair includes debridement of devitalized tissue or segmental resection with closure, using absorbable sutures. The repair then benefits from coverage with a tissue pedicle, such as a previously preserved intercostal muscle flap. Patients requiring ongoing ventilation may benefit from passage of the endotracheal tube distal to the repair to provide protection. Other options include dual-lung ventilation and extracorporeal life support during the immediate postoperative time period.

ESOPHAGEAL INJURIES

Injuries to the thoracic esophagus occur predominantly after penetrating trauma but remain uncommon from any cause. Most of these are caused by gunshot wounds, followed by stab wounds in fewer than 20% of cases. Penetrating esophageal injuries may be suggested by the trajectory of a missile or weapon. Injuries in the vicinity of the mediastinum require consideration of possible esophageal injury. The mortality associated with these injuries is significant (39%) because of the severe consequences of esophageal perforation and because the adjacent vital structures can also be injured along with the esophagus.[27] Blunt esophageal injury is exceedingly rare. Twenty-five percent of patients, with this injury die, largely because of the significant energy required to rupture the thoracic esophagus. Blunt esophageal injury is believed to be caused by a rapid elevation in intraluminal pressure during compression of the chest or abdomen. An impact to the upper abdomen can compress the distended stomach, leading to transmission of air and fluid up the esophagus and resulting in a perforation of the wall, usually in the distal segment.

The esophagus is best evaluated through a combination of contrast esophagography and esophagoscopy. Individually, these studies each have an approximate 20% false-negative rate, but their combined sensitivity approaches 100%.[28,29] Findings include extravasation of contrast from the esophageal lumen or a disruption of the mucosa visualized on endoscopy. These studies should also be used to determine the location of the injury along the esophagus to assist in operative planning. Chest CT may reveal air adjacent to the esophagus but outside the lumen, as well as surrounding soft tissue inflammation. At times, the defect itself can be visualized on CT. Esophageal injuries at the gastroesophageal junction may result in abdominal pain and tenderness.

The rapid identification and management of esophageal injuries are paramount because delays are associated with worse outcomes. Clinical evaluation and studies that reveal an esophageal injury should prompt immediate operative repair. Chest and mediastinal drains should be placed in the vicinity of the repair to control any leak that may develop. A gastrostomy and feeding jejunostomy are frequently advisable to allow gastric decompression and early nutritional support. Esophageal injuries that are identified late may not allow primary repair because of the massive amounts of inflammation that can develop. In some situations, esophagectomy is the only option to allow recovery from the associated inflammatory insult, followed by planned elective reconstruction.

DIAPHRAGMATIC INJURIES

Injuries to the diaphragm can be a diagnostic challenge. They are often first identified at the time of laparotomy for penetrating injury or late following blunt trauma. Approximately 3% of patients with trauma to the torso have a diaphragmatic injury identified, with approximately two-thirds of them secondary to penetrating trauma.[30,31] Mortality is secondary to injuries involving adjacent vital organs because diaphragmatic injuries themselves are usually of limited threat to life. Blunt diaphragmatic injuries are believed to be a result of a rapid increase in intra-abdominal pressure during an anterior impact that causes a blowout of the diaphragmatic tissue. Injuries are most commonly recognized on the left side, with only 25% occurring adjacent to the liver or in the central portion of the diaphragm. Because of the high energy required to create a blunt diaphragmatic rupture, there is a significant associated mortality, approximately 29%.[32]

Diagnosis requires a high index of suspicion when confronted with even the most subtle indicators of injury to the diaphragm. Frequently, penetrating diaphragmatic injuries are discovered on operative exploration of the chest or abdomen. Identifying the trajectory of the injury will usually allow recognition of the diaphragmatic defect. Blunt injuries can be more elusive. The chest radiograph may identify injuries to the diaphragm by demonstrating the presence of abdominal viscera, most commonly the stomach, within the chest (Fig. 106-6), although this finding may be absent in a significant number of injuries. Passage of a nasogastric tube can be of assistance if the tube is identified in the lower left hemithorax; the administration of gastric contrast may add to the detection. Chest and abdominal CT scans may demonstrate the presence of abdominal viscera in the chest or an abnormality of the diaphragm itself, such as discontinuity, thickening, or elevation. Given the challenge of diagnosis, operative exploration may be required when imaging is suggestive.

Repair of diaphragmatic injuries includes debridement of nonviable tissue and closure of the defect. Typically, the diaphragm exhibits enough redundancy to close all but the largest defects primarily. Large areas of tissue loss are rare in traumatic rupture but, when present, may require reconstruction with a prosthetic. When the diaphragm has been traumatically detached from the periphery, it may be reinserted to the chest wall one or two interspaces superior.

In cases where the diaphragmatic perforation was not initially recognized and repaired, the injury may only come to light months to years later. The natural history of these injuries includes progressive enlargement with herniation of abdominal viscera into the chest, which is commonly the identified abnormality on radiographic evaluation.

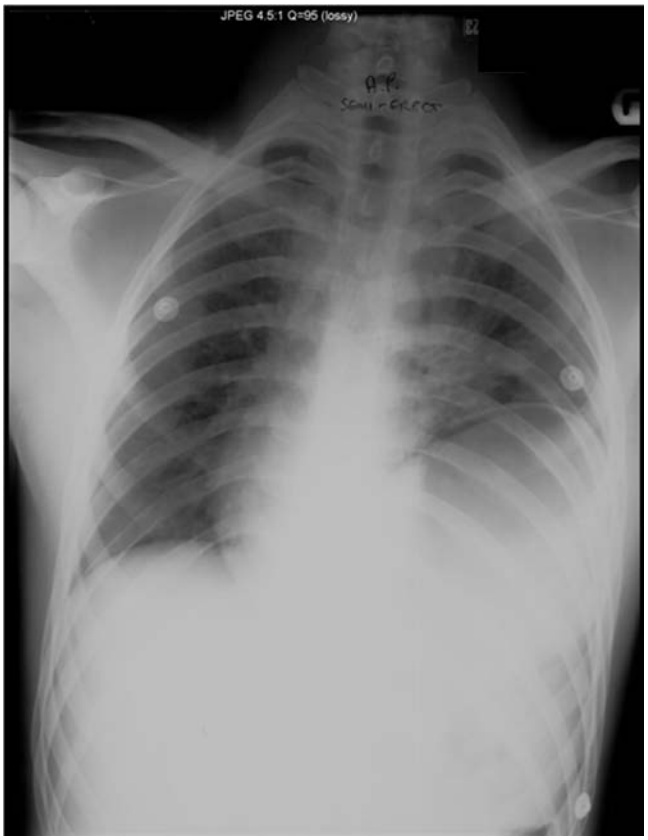

Figure 106-6 Left-sided diaphragmatic injury on a plain chest radiograph. The gas-filled stomach can be visualized in the left chest; this was caused by herniation through a large diaphragmatic laceration.

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CHAPTER 107 Lung Transplantation

Allan R. Glanville

The last 30 years have seen the development and promulgation of lung transplantation as a robust therapy for advanced lung diseases for which no other medical therapy is effective. At best lung transplantation is immediately lifesaving and capable of offering selected recipients extended and good quality survival. However, there are many problems that beset the graft and may lead to chronic lung allograft dysfunction (CLAD). Principal among these is chronic rejection (CR), manifest as fibrotic luminal occlusion of small airways (bronchiolitis obliterans) for which the term bronchiolitis obliterans syndrome (BOS) was coined to allow a uniformity of description and grading of severity throughout the world.[1,2] As the field of lung transplantation has matured, a community of dedicated lung transplant clinicians and scientists has formed, working together to develop a number of position papers, guidelines and clinical trials to guide practice. Lung transplantation has expanded its reach in dramatic fashion, with the edge of the diaspora that commenced in the modern era at Stanford University Medical Center touching most nations and many conditions once thought unsuitable for transplantation. It has been used as a successful therapeutic intervention for a wide variety of end-stage pulmonary parenchymal and vascular diseases. There is no doubt that advances in recipient and donor selection, surgical technique, and postoperative management have improved early survival as documented in serial iterations of the annual registry of the International Society for Heart and Lung Transplantation (ISHLT); late survival is slowly improving as well.[4]

Novel areas of interest in the lung transplantation world include the use of so-called marginal donors to assist in overcoming the relative shortage of donor organs and the development of donation after circulatory death protocols that hold great promise to provide outcomes at least equivalent if not better than donation

after brain death.[5] *Ex vivo* lung perfusion may facilitate organ salvage and promote optimal outcomes.[6,7] So may our increasing understanding of antibody-mediated rejection (AMR), another area where knowledge is changing rapidly, generate superior outcomes in the future.[8,9]

HISTORY

Pioneering efforts in experimental lung transplantation were undertaken in the 1940s and 1950s. In Russia in 1946, Demikhov, working without the benefit of cardiopulmonary bypass, performed a variety of experiments involving transplantation of pulmonary lobes and heart–lung blocs in dogs.[10] These experiments demonstrated the technical feasibility of such procedures but warned of the physiologic challenges of the control of breathing reflexes. Dogs have a well-developed Hering–Breuer inflation inhibition reflex, so they fail to breathe adequately after reimplantation of the heart–lung bloc. Demikhov's first heart–lung transplant survived 2 hours and only 2 of the 67 transplants he performed over the next 5 years survived more than 5 days. Nakae subsequently demonstrated the fallacy of assuming the homogeneity of pulmonary neural control between species and showed how this reflex was developed differentially between species in an elegant series of experiments in cats, dogs, and monkeys.[11] This opened the way for further work on subhuman primates by Shumway and Reitz, who were able to demonstrate extended survival after heart–lung transplantation.[12] Subhuman primates were able to override the Hering–Breuer reflex and breathe so the hope of human lung transplantation was rekindled. This physiologic quirk excited a number of the early researchers who studied the physiology of the transplanted lung devoid of neural control mechanisms, cough reflexes, antegrade bronchial blood supply, and normal mucociliary clearance mechanisms.[13–20] In addition, an early observation was that in heart–lung transplantation, the heart and the lung individually pursued different functional courses, foreshadowing the differing rates of rejection of the heart and lungs that were seen in human combined heart–lung transplantation performed more than three decades later.[21]

Human lung transplantation was undertaken first by Hardy[22,23] in 1963. The procedure consisted of a left single-lung transplant performed for a carcinoma of the left lung that involved the hilum. The patient survived for 18 days, dying of renal failure and malnutrition. This effort demonstrated that a transplanted lung could function for the short term in a patient and stimulated further clinical and experimental efforts. Between 1963 and 1978, however, at least 38 attempts were made at isolated lung transplantation and only 1 patient survived to hospital discharge, succumbing to sepsis and CR 8 months after transplantation. The remaining patients in this 15-year experience all died postoperatively. The major cause of mortality beyond the first postoperative week in these patients was bronchial dehiscence. In addition, most of the patients were greatly debilitated at the time of the procedure, frequently ventilator dependent or in a state of multisystem and multiorgan failure, hindering their ability to survive. It was appreciated that in many of these patients, the available immunosuppressive regimens, which relied on high-dose corticosteroids, significantly compromised postoperative healing of the bronchus and further potentiated the adverse effects of preexisting conditions.

The problem of bronchial healing was related to the relative ischemia of the donor bronchus, which followed revascularization of the lung graft without reestablishment of the bronchial circulation. One technical approach to this problem was the development of a procedure for combined heart–lung transplantation, allowing for maintenance of collateral circulation from the coronary circulation to the tracheal anastomosis and mediastinal tissues as well as retrograde perfusion from the pulmonary arterial circulation. Although the operation was performed primarily for patients with end-stage cardiac failure due to pulmonary hypertension, the initial report of successful heart–lung transplantation demonstrated the feasibility of this approach in obtaining healing of the airway and confirmed the ability of the transplanted lung to provide long-term respiratory function. The world's first recipient of a combined heart–lung transplant died 5 years post transplant from trauma. Postmortem examination revealed no complications of rejection or infection in the transplanted heart or lungs. Subsequently, heart–lung transplantation has been performed for numerous pulmonary parenchymal diseases, including emphysema and bilateral septic lung disease, such as cystic fibrosis, but is now only performed for conditions that cannot be serviced by single- or bilateral-lung transplantation such as some forms of congenital heart disease.

An alternative technique for improving bronchial healing was to optimize the bronchial–pulmonary collateral circulation by limiting the length of the donor bronchus and by providing an alternative vascular supply by extrinsically wrapping the anastomosis with omentum. In addition to these technical measures, the avoidance of high-dose steroid immunosuppressive regimens, made possible by the use of cyclosporine, was shown to improve bronchial anastomotic healing. These advances, combined with the selection of well-conditioned recipients with pulmonary fibrosis, whose pathophysiology favored preferential perfusion and ventilation of the allograft, culminated in the initial clinical success of single-lung transplantation. Further efforts were made to perfect a technique for double-lung transplantation to expand this approach to patients with bilateral septic lung disease. The initial clinical success of an en bloc double-lung transplant procedure was tempered by a significant incidence of tracheal anastomotic complications. However, further modification of the technique, by either direct bronchial revascularization or performance of two sequential single-lung transplantations at the same operative sitting (i.e., bilateral sequential single-lung transplantation), has provided satisfactory results.

It has since been shown that despite initial concerns about the physiology of allograft ventilation, single-lung transplantation is also appropriate for patients with end-stage chronic obstructive pulmonary disease (COPD). Single- and bilateral-lung transplantation have also been successfully applied to patients with primary pulmonary hypertension or Eisenmenger syndrome (with correction of the congenital shunt), for whom combined heart–lung transplantation was initially devised. As the utility of lung transplantation for these pulmonary diseases has been demonstrated, the need for heart–lung transplantation has diminished. There are now relatively few surgeons who have extensive experience with combined heart–lung transplantation while experience with bilateral-lung transplantation continues to grow, driven by demonstrable superior outcomes for most indications.[4]

RECIPIENT SELECTION

Selection of appropriate candidates is critical to the success of lung transplantation. The numerous factors that are considered when selecting candidates are discussed in detail in the following sections.

GENERAL CONSIDERATIONS

Recipient selection is one area where a remarkable international consensus has been achieved among key societies dedicated to the investigation and management of advanced respiratory diseases.[24,25] The current published guidelines represent a conjoint effort of members of the ISHLT, American Thoracic Society, European Respiratory Society, American Society of Transplant Physicians, and

TABLE 107-1 Recipient Evaluation for Lung Transplantation

Hematology
Complete blood count with differential, platelet count, PT, PTT, ESR
Chemistry
Na, K, Cl, CO_2, BUN, Cr, glucose, uric acid, Ca, P, Mg, total protein, albumin, globulin, bilirubin (direct, indirect), alkaline phosphatase, SGOT, LDH, CPK, triglycerides, cholesterol, HDL/LDL
Renal function
Urinalysis, 24 h for calcium and creatinine
Endocrine
TSH, LH, FSH, vitamin D, testosterone (males), estradiol (females)
Infectious disease
Sputum (Gram stain, C + S, fungal smear and culture, AFB smear and culture), CMV (IgG and IgM), hepatitis B (antigen/antibody), hepatitis C, herpes, Varicella, EBV, HIV, toxoplasma PPD
Immunology
ABO blood type and cross match, MHC typing, HLA antibody screen), vasculitic screen for interstitial lung disease, pulmonary hypertension
Radiology
Chest radiograph (AP, lateral), high-resolution chest CT scan, quantitative V/Q scan, quantitative bone density, abdominal ultrasonography, sinus CT[a]
Cardiology
ECG, echocardiogram with pulse Doppler imaging, right heart catheterization, left heart catheterization[b]
Pulmonary
Pulmonary function tests (spirometry, lung volumes, $D_{L_{CO}}$), arterial blood gases, cardiopulmonary exercise test[c]

[a] *Septic lung disease.*
[b] *If >50 years of age, coronary artery disease or LVEF <45%.*
[c] *Excluding patients with pulmonary hypertension.*

the Thoracic Society of Australia and New Zealand.[25] Published first in 1998 and revised in 2006, the guidelines are now under further revision as there have been major changes in acceptance of candidates, especially those needing advanced life support and those of more mature age.

In brief, the evaluation of a potential candidate for lung transplantation should include a complete assessment of cardiopulmonary function and the patient's general health in addition to a thorough evaluation of psychosocial status. A battery of screening tests is required, as well as evaluation by members of the transplant team, including pulmonologists, cardiologists, thoracic surgeons, psychiatrists, and social workers (Table 107-1). Contingent on the patient's status, this evaluation can be completed in many instances on an outpatient basis. A coordinated review of the results of these studies by the multidisciplinary transplant team serves to assure that the best candidates are accepted as potential transplant recipients. The so-called "best candidates" are those who are deemed to have a superior chance of obtaining both an immediate survival benefit and an enduring quality-of-life benefit. The introduction of the Lung Allocation Score (LAS) within the United States has been an attempt to provide potential lung transplant recipients with a uniform lung donor allocation system designed to achieve at least the first of these broad goals.[26] One iconoclastic action of the LAS has been to abolish the "time-accrued" principle of determining who received the next lung transplant. The "time-accrued" principle valued the serendipity of time of listing greater than the acuity of the disease and led directly to an excess mortality on the waiting list and indirectly to overly large waiting lists at some institutions. Within a month of introducing the LAS the number of patients waiting for lung transplantation within the United States halved due to the acknowledgment by transplant centers that many on the list were there simply to accrue time but were not in immediate need of transplantation.

INDICATIONS

Lung transplantation is a treatment of last resort. Potential recipients should be patients with end-stage pulmonary parenchymal, airways, or vascular disease who have a limited life expectancy and for whom no effective alternative therapy is available. Additional considerations include the degree of reduction in activities of daily living resulting from the disease and the patient's quality of life. The variable rates of progression of the diseases for which lung transplantation is performed and the variety of supportive therapies available dictate the use of disease-specific criteria in assessing the appropriate timing of listing a given patient.

Immunologic study of potential transplant candidates includes assessment of ABO status and preformed anti-HLA antibodies. All patients are currently matched to donors by ABO status, most commonly with ABO-identical donors and less commonly with ABO-compatible donors (this situation arises commonly for blood type AB candidates). Screening for sensitization to HLA antigens is now routine and will be further discussed under the section on AMR. Pregnancy, blood transfusion, or prior transplantation can lead to HLA sensitization.[27]

CONTRAINDICATIONS

There are few absolute contraindications to lung transplantation. Over the years the impetus has swung from focusing on which patients should be excluded to how to reasonably include patients after appropriate evaluation and management. With newer support technologies, a number of the original exclusion criteria have been relaxed. Absolute contraindications include bone marrow failure and hepatic cirrhosis, the latter to be distinguished from reversible hepatic dysfunction due to right heart failure, which resolves following lung transplantation (Table 107-2). In exceptional circumstances, combined liver and lung transplantation may be contemplated, and in experienced hands this procedure has acceptable long-term outcomes. Active malignancy precluding long-term survival is also an absolute contraindication. One consideration that impacts the determination of who may receive a transplant is the current limited supply of donor lungs. Hence, other significant life-limiting comorbidities also stand as a proscription against lung transplantation.

A host of additional factors may be considered relative contraindications to lung transplantation (Table 107-2). The age of the recipient may be a significant factor in view of the limited number of donor organs and the presumed subclinical organ dysfunction associated with the aging process that increases the potential for postoperative complications. As the latter factor is variable, a "physiologic age" rather than a strict chronologic criterion is appropriate. The type of transplant procedure also influences the significance of age as a contraindication. Many centers consider single-lung transplantation as more suitable for older patients because of its lower risk. Nevertheless, there is a definite creep toward offering transplantation to the well-chosen older recipient for whom it may be the best palliative option. In fact, according to the OPTN/SRTR 2011 report, the largest expansion in the waiting list population for lung transplantation in the United States was over the 65 age group.[28] Other contraindications are evidence of

TABLE 107-2 Absolute and Relative Contraindications for Lung Transplantation

Absolute Contraindications for Lung Transplantation	Relative Contraindications for Lung Transplantation
• Malignancy in the last 2 y, with the exception of cutaneous squamous and basal cell tumors. In general, a 5-y disease-free interval is prudent. The role of lung transplantation for localized bronchioalveolar cell carcinoma remains controversial • Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney). Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart–lung transplantation could be considered in highly selected cases • Noncurable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus • Significant chest wall/spinal deformity • Documented nonadherence or inability to follow through with medical therapy or office follow-up, or both • Untreatable psychiatric or psychologic condition associated with the inability to cooperate or comply with medical therapy • Absence of a consistent or reliable social support system • Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 mo	• Age older than 65 y. Older patients have less optimal survival, likely due to comorbidities, and therefore, recipient age should be a factor in candidate selection. Although there cannot be endorsement of an upper age limit as an absolute contraindication (recognizing that advancing age alone in an otherwise acceptable candidate with few comorbidities does not necessarily compromise successful transplant outcomes), the presence of several relative contraindications can combine to increase the risks of transplantation above a safe threshold • Critical or unstable clinical condition (e.g., shock, mechanical ventilation or extracorporeal membrane oxygenation) • Severely limited functional status with poor rehabilitation potential • Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria • Severe obesity defined as a body mass index (BMI) exceeding 30 kg/m^2 • Severe or symptomatic osteoporosis • Mechanical ventilation. Carefully selected candidates on mechanical ventilation without other acute or chronic organ dysfunction, who are able to actively participate in a meaningful rehabilitation program, may be successfully transplanted • Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux should be optimally treated before transplantation. Patients with coronary artery disease may undergo percutaneous intervention before transplantation or coronary artery bypass grafting concurrent with the procedure

Source: Reproduced with permission from Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates. J Heart Lung Transplant. 2006;25(7):745–755.

psychosocial instability that would preclude compliance with the necessary posttransplant regimens and active use of tobacco products or other substances of addiction during the wait for transplantation. Obesity or cachexia can increase the risk for perioperative morbidity.[29–32] The same is true of the continued need for high doses of corticosteroid therapy (more than 20 mg of prednisone, or equivalent dose of another agent, per day).

Respiratory failure requiring mechanical ventilation before transplantation also increases the likelihood of complications.[33] Some centers will not consider a new patient for evaluation who is completely ventilator dependent or who has acutely deteriorated and become ventilator dependent. However, this stance is definitely changing and many centers, particularly those in Europe and Australia, have championed the use of a high-urgency status to allow successful transplantation of patients on extracorporeal membrane oxygenation (ECMO).[34] Patients who have a chronic need for partial ventilatory assistance or those who have been accepted as transplant candidates and require assisted ventilation because of progression of their native disease are often still considered potential recipients unless multiorgan failure intervenes.[35] Prolonged mechanical ventilation results in colonization of the lower respiratory tract with significant microbiologic pathogens and a degree of deconditioning and protein wasting that significantly increases the perioperative risk of transplantation. Nevertheless, despite these theoretical concerns recent outcomes have improved significantly for well-selected patients needing assisted ventilation.

Chronic kidney disease may affect eligibility for lung transplantation. The calcineurin inhibitors (CNIs) universally used as part of posttransplant immunosuppressive regimens are nephrotoxic and invariably cause some degree of renal insufficiency as a complication of therapy. As with irreversible hepatic dysfunction, combined renal and lung transplantation may be considered, but the potential risks of the procedure, particularly in the context of the shortage of donor lungs, require careful consideration. In most patients, severe pre-existing renal insufficiency is a contraindication for lung transplantation.

Severe peripheral vascular disease may be a limiting factor in selecting candidates for a number of reasons including the occasional need for cardiopulmonary support in the perioperative period by either partial cardiopulmonary bypass or ECMO via the femoral or subclavian routes. Peripheral vascular disease is also frequently associated with occult significant coronary or aortic disease, which may greatly increase the morbidity and mortality of the lung transplant procedure and limit quality long-term survival. Finally, transplantation is contraindicated in patients with gangrenous changes in the extremities due to peripheral vascular disease because of the potential for systemic spread of the infectious process during immunosuppression.

Careful consideration is required before patients with pre-existing osteoporosis are accepted for transplantation. In addition, chronic steroid immunosuppressive therapy causes bone loss in all patients and exacerbates the complications of prior osteoporosis. Post operative rib fractures or compression fractures of the vertebrae not only cause severe pain requiring the use of narcotic analgesia but limit cough, mobility, and rehabilitation and can lead directly to sputum retention, pneumonia, and death.

Infectious diseases have a profound effect on the morbidity and mortality of lung transplantation. Colonization of the respiratory tract with potential pathogens in patients with end-stage pulmonary disease requires careful assessment. Most bacterial flora in transplant candidates have a pattern of antibiotic sensitivity that can be identified preoperatively to select an appropriate perioperative antibiotic regimen. For example, lung transplant patients harboring gram-negative bacilli preoperatively were found to be at risk for posttransplant pneumonia, demonstrating the importance of preoperative identification and a plan for eradication of potential pathogens. However, *Burkholderia cenocepacia (BCC),* a pathogen found in up to 15% of patients with cystic fibrosis in some geographic regions, is often highly resistant to antimicrobials and is a relative contraindication to transplantation unless a suitable pattern of antibiotic sensitivity can be identified before transplantation. Irrespective of the precise genomovar, it is the biologic behavior of the organism within a particular host that determines outcome.[36,37] *Aspergillus fumigatus* and other *Aspergillus* species are also common pathogens in the sputum of patients with bronchiectasis, sarcoidosis, or COPD and, while not a contraindication to transplant, these organisms can occasionally lead to life-threatening posttransplant infections.[38–41] Other pathogens such as *Scedosporium species* may be associated with fatal dissemination post transplant.[38–41] *Scedosporium prolificans* in particular may be difficult to control and is hard to eradicate.[42,43] Lifelong therapy with voriconazole and terbinafine may be effective but carries the risk of accelerated development of skin cancers especially squamous cell cancer of the lip.[44] Interestingly, the presence of organisms in donor lungs is not always a predictor of post–lung transplant pneumonia, perhaps reflecting the efficacy of targeted antibiotic therapies or the successful eradication with removal of the diseased lungs.

Viral diseases in a potential lung transplant recipient can also have a significant impact on the outcome of transplantation. Active hepatitis B or C in the lung transplant candidate is associated with increased early and late mortality because of the effect of hepatic dysfunction on perioperative complications and the accelerated progression of these diseases in patients requiring chronic immunosuppression. However, successful lung transplantation has been reported in patients in whom therapy for hepatitis C has been effective.[45] Cytomegalovirus (CMV), a DNA-type virus that is incorporated into the host genome, can cause both systemic illness and pneumonitis in immunosuppressed patients. Therefore, the serologic CMV status of the recipient is an important determination to make before transplantation. An early publication in the preprophylaxis era found that CMV infection developed in 54% (32/59) of patients who underwent heart–lung or lung transplantation and survived for more than 30 days, and that CMV infection was more common in patients who had been CMV seropositive prior to transplant (95%) than those who had been seronegative preoperatively (38%).[46] While some centers still prefer to match CMV-negative recipients with CMV-negative donors as a strategy for reducing the chance of primary CMV infection, the widespread use of prophylactic ganciclovir and valganciclovir therapy has been shown to significantly reduce the risk of CMV disease in transplant patients. Extended prophylaxis with valganciclovir appears both safe and effective.[47–51] However, some strains of CMV are resistant to ganciclovir, hence ongoing surveillance for CMV using PCR assays and transbronchial lung biopsy is advised.[52]

SPECIFIC DISEASE STATES

In addition to general selection criteria, there are disease-specific considerations that impact decisions about candidate selection and timing of listing.

■ CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The rate of progression of the underlying disease is an important factor in the timing of the evaluation and selection of potential transplant recipients (Table 107-3). The most common indication for lung transplantation is obstructive lung disease, with COPD accounting for more than one-third of all lung transplants and emphysema due to α_1-antitrypsin deficiency accounting for 8% of all lung transplants. Patients with these diseases tend to remain relatively stable for long periods, albeit with a reduced quality of life. It is now apparent that lung transplantation not only provides marked symptomatic and functional palliation for these patients but improved survival as well, depending on the severity of disease at the time of transplant.[53] The recently devised BODE index (Table 107-4) that incorporates multiple factors (B, body mass index; O, obstruction as indicated by the FEV_1 as % predicted; D, degree of dyspnea; and E, exercise capacity) is a validated survival measure that is more accurate in predicting survival in individuals with COPD than the FEV_1 alone.[54–56] Accordingly, calculation of the BODE index is now included in the international guidelines for referral and transplantation for COPD (Table 107-3). Prior to the introduction of the LAS, death during the wait for transplantation was rare in these patients, occurring in less than 5% of cases. In addition to reflecting the slow progression of COPD, two additional factors may contribute to their low mortality: their participation in a graduated rehabilitation program while they await transplantation, which may maintain or even increase their functional capacity, and the institution of oxygen therapy, which improves survival in patients with obstructive lung disease.

■ INTERSTITIAL LUNG DISEASES

Interstitial lung diseases are the indication for lung transplantation in 24% of patients who undergo lung transplantation. The most common cause is idiopathic pulmonary fibrosis (IPF), whereas a variety of interstitial lung diseases including sarcoidosis, collagen vascular disease–associated interstitial lung disease, and drug-induced lung disease account for the remainder.

The end-stage fibrotic lung is characterized by severe destruction of gas exchange units, secondary distortion and dilatation of the airways with development of cystic lesions, and replacement of the lung with nondistensible fibrous tissue. The work of breathing in these patients may be increased five times above normal because of the increased elastic load. The vital capacity in patients with pulmonary fibrosis is severely reduced, as is the functional residual capacity and total lung capacity. Dead-space ventilation is increased, and may actually increase further during exercise. A marked reduction in diffusing capacity is invariably present. Although some degree of alveolar hyperventilation is common early in the course of disease, hypercapnia during exercise and later at rest is encountered in the advanced stages. Extensive intrapulmonary shunting of blood flow is seen, resulting in hypoxemia and, in later stages, pulmonary hypertension. Progression of the disease may be variable, but patients often deteriorate precipitously, developing progressive hypoxemia and pulmonary hypertension. Acute exacerbations of IPF are associated with mortality exceeding 50% irrespective of therapy. As a result, the mortality of these patients while they await transplantation is more than 20%. Criteria for considering IPF patients for transplantation include severe dyspnea, forced vital capacity less than 50% of predicted, resting arterial hypoxemia or hypercapnia, and pulmonary hypertension. However, a downhill clinical course is the best individual indication for transplantation. It must be emphasized that there is currently no proven therapy that reverses established IPF.[57–59]

Two other factors in patients with interstitial lung disease are also important. First, many of these diseases are systemic, and the effects

TABLE 107-3 Disease-Specific Considerations for Lung Transplantation

Chronic Obstructive Pulmonary Disease (COPD)	Cystic Fibrosis/Bronchiectasis	Idiopathic Pulmonary Fibrosis/Nonspecific Interstitial Pneumonia (NSIP)
Guidelines for referral BODE index exceeding 5 **Guidelines for transplantation** Patients with a BODE index of 7–10 with at least one of the following: History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} exceeding 50 mm Hg) Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy FEV_1 of less than 20% and either $D_{L_{CO}}$ of less than 20% or homogeneous distribution of emphysema	**Guidelines for referral** FEV_1 below 30% predicted or a rapid decline in FEV_1—in particular in young female patients Exacerbation of pulmonary disease requiring ICU stay Increasing frequency of exacerbations requiring antibiotic therapy Refractory and/or recurrent pneumothorax Recurrent hemoptysis not controlled by embolization **Guidelines for transplantation** Oxygen-dependent respiratory failure Hypercapnia Pulmonary hypertension	**Guidelines for referral** Histologic or radiographic evidence of UIP irrespective of vital capacity Histologic evidence of fibrotic NSIP **Guidelines for transplantation** Histologic or radiographic evidence of UIP and any of the following: $D_{L_{CO}}$ less than 39% predicted 10% or greater decrement in FVC during 6 mo of follow-up Decrease in pulse oximetry below 88% during a 6-MWT Honeycombing on HRCT (fibrosis score of >2) Histologic evidence of NSIP and any of the following: $D_{L_{CO}}$ less than 35% predicted 10% or greater decrement in FVC or 15% decrease in $D_{L_{CO}}$ during 6 mo of follow-up
Pulmonary Arterial Hypertension	**Sarcoidosis**	**Lymphangioleiomyomatosis (LAM)/Pulmonary Langerhans Cell Histiocytosis (eosinophilic granuloma)**
Guidelines for referral NYHA functional class III or IV, irrespective of ongoing therapy Rapidly progressive disease **Guidelines for transplantation** Persistent NYHA class III or IV on maximal medical therapy Low (<350 m) or declining 6-MWT Falling therapy with intravenous epoprostenol, or equivalent Cardiac index of less than 2 L/min/m^2 Right atrial pressure exceeding 15 mm Hg	**Guidelines for referral** NYHA functional class III or IV **Guidelines for transplantation** Impairment of exercise tolerance (NYHA functional class III or IV) and any of the following: Hypoxemia at rest Pulmonary hypertension Elevated right atrial pressure exceeding 15 mm Hg	**Guidelines for referral** NYHA functional class III or IV **Guidelines for transplantation** Severe impairment in lung function and exercise capacity (e.g., $\dot{V}_{O_{2max}}$ <50% predicted) Hypoxemia at rest

Source: Reproduced with permission from Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates. J Heart Lung Transplant. 2006;25(7):745–755.

TABLE 107-4 The BODE Index for COPD

Variable	Points on BODE Index[a] 0	1	2	3
FEV_1(%) of predicted)[b]	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale[c]	0–1	2	3	4
Body mass index[d]	>21	≤21		

[a]The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV1 denotes forced expiratory volume in 1 second.
[b]The FEV_1 categories are based on stages identified by the American Thoracic Society.
[c]Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
[d]The values for body mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body mass index at a value of 21.
Source: Reproduced with permission from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–1012.

of the disease on extrapulmonary organs may result in a sufficient number of relative contraindications to exclude the patient from consideration for transplantation. The presence of an underlying connective tissue disease should be investigated in appropriate cases, and an individual determination made about the possibility of an enduring benefit from lung transplantation. Second, a number of these diseases, including sarcoidosis and lymphangiomyomatosis, may recur in the lung graft, but typically do not impact posttransplant survival.

■ SEPTIC LUNG DISEASE

Septic lung disease, including cystic fibrosis and other types of bronchiectasis, accounts for approximately 20% of patients undergoing lung transplantation. Candidates with focal or unilateral disease can sometimes be managed with medical treatment or surgical resection of the affected area. In most patients, however, the disease is bilateral or systemic, and the natural history is one of recurrent infection and progressive respiratory failure. It is important to attempt to establish a cause of the bronchiectasis before transplant evaluation, because of the impact of systemic

diseases on management before and after transplantation. Cystic fibrosis can be diagnosed with a sweat test or from genotyping. Serum immunoglobulin levels should be measured and a careful assessment for evidence for a systemic illness – such as rheumatoid arthritis, ulcerative colitis, or immotile cilia syndrome – should be undertaken. Primary infectious causes, such as tuberculosis and allergic bronchopulmonary aspergillosis, should be identified and treated appropriately before consideration of the potential benefit of transplantation can be evaluated fully. Finally, any suggestion of aspiration as a primary or secondary factor demands further investigation, including a barium swallow and esophageal manometry testing to rule out gastroesophageal reflux.

Many of these patients demonstrate significant short-term improvement in response to optimum medical therapy, which includes postural drainage, intravenous and/or inhaled antibiotics, and nutritional supplementation. Once medical therapy has been optimized, however, a pattern of more frequent hospitalizations for exacerbations, continued weight loss, and progressive functional impairment is indicative of a patient who has a limited life span and should be given priority for transplantation. Cystic fibrosis patients with an FEV_1 under 30% of the predicted value, a Pa_{O_2} under 55 mm Hg, or a Pa_{CO_2} greater than 50 mm Hg have a 2-year mortality of 50%; the FEV_1 appears to be the most sensitive predictive factor. Any patient with septic lung disease who manifests these criteria should be further evaluated as a potential transplant recipient.

While the patient is awaiting transplantation, close medical follow-up is required, and all components of the patient's therapeutic regimen should be continued. Serial study of sputum microbiology is important for assessing changes in flora. Aerosolized broad-spectrum antibiotic therapy may reduce the colonizing bacterial load while minimizing the potential for renal toxicity and in some cases it may transiently improve functional capacity. In the event of progressive hemoptysis, bronchial artery embolization can provide adequate short-term control of the bleeding without significantly compromising technical aspects of the transplant procedure. Finally, institution of noninvasive positive pressure ventilation in the patient who is approaching respiratory failure has been shown to stabilize lung function without adversely affecting the outcome of transplantation. Because of the shortage of donor organs and the variability in the progression of the disease some programs had previously developed the approach of live donor lobar transplantation of the lung. This uses bilateral lobar transplants from two live donors, often parents or close relatives, particularly for small recipients with cystic fibrosis. It has proven to achieve outcomes comparable to cadaveric donor transplantation without donor mortality or significant morbidity.[60] The use of this procedure in the United States has largely been abandoned as the implementation of the LAS system has provided an alternative means of expediting transplantation for severely ill patients but the procedure has now gained popularity in Japan.[61–65]

■ PULMONARY VASCULAR DISEASE

Pulmonary vascular disease, either idiopathic pulmonary arterial hypertension (IPAH) or secondary pulmonary arterial hypertension due to Eisenmenger syndrome, accounts for 4% to 5% of patients requiring lung transplantation and approximately 25% of patients requiring heart–lung transplantation. The criteria for identifying patients who may require transplantation relate to the risks of death due to the underlying disease. On the basis of data from the National Heart, Lung, and Blood Institute registry, it is apparent that an NYHA class III or IV functional status, an elevated central venous pressure, a decreased cardiac index, and an elevated mean pulmonary artery pressure correlate with a poor prognosis. Episodes of near-syncope or syncope, which tend to occur later in the course of the disease, are also associated with mortality. The changing landscape of medical therapy for pulmonary arterial hypertension has had a major impact on the survival of these patient populations and the timing of referral and listing for lung transplantation. A wide variety of effective therapies are now available, including traditional therapies with anticoagulation and high-dose calcium channel blockers as well as newer vasodilator drugs such as sildenafil, endothelin receptor antagonists, and inhaled, subcutaneous and intravenous prostanoids.[66] These therapies may significantly modify the natural history of the disease. Therefore, symptomatic patients with pulmonary arterial hypertension who do not respond to medical therapy are the ones best considered for transplantation. Early referral before the development of end-stage organ system failure is critical to success. Although the vast majority of data concerning the natural history of patients with pulmonary arterial hypertension is derived from the IPAH population, similar clinical criteria are applied to those with Eisenmenger syndrome in deciding when to list for lung transplantation. Notably, however, many patients with Eisenmenger physiology are well compensated for many years and transplantation can often be delayed much longer than for patients with IPAH.

The decision as to what procedure a patient with pulmonary vascular disease should undergo has evolved over time. The relative shortage of suitable heart–lung donor blocs combined with a mortality of 20% to 25% among patients with significant pulmonary hypertension awaiting heart–lung transplantation, has led to a shift away from this procedure in favor of bilateral-lung transplantation. The results with bilateral-lung transplantation are similar to those with heart–lung transplantation for pulmonary vascular disease provided that there is no significant left ventricular dysfunction. Of interest, the presence of severe right ventricular systolic dysfunction does not appear to affect the results of lung transplantation; the severe tricuspid regurgitation and pulmonary valvular regurgitation that are present in virtually all patients preoperatively resolve almost immediately and right ventricular function normalizes over a period of weeks to months. Patients with Eisenmenger syndrome who have a shunt defect that can be corrected at the time of transplantation are also candidates for lung transplantation. Thus, heart–lung transplantation is primarily limited to patients with either significant biventricular dysfunction or uncorrectable congenital heart defects.

TRANSPLANT PROCEDURE SELECTION

Except for patients with bilateral septic lung disease or severe pulmonary arterial hypertension, single-lung transplantation is potentially suitable for the majority of end-stage pulmonary diseases that require transplantation (Table 107-5). However, there has been a very definite swing away from single-lung transplantation and toward bilateral-lung transplantation worldwide, based in part on the lower long-term survival outcomes associated with the former procedure, particularly when applied to the COPD population.[4,67] The argument that single-lung transplantation is associated with a shorter wait for donor lungs and a lower morbidity and mortality rate after transplantation than other lung transplant procedures performed for the same recipient diagnoses is no longer tenable given improvements in surgical experience and techniques combined with the ramifications of the LAS. The surgical mortality for single-lung transplantation ranges from 3% to 10%, relating to the specific transplant indication, the presence or absence of pulmonary hypertension, and the intraoperative need for cardiopulmonary bypass. The incidence of graft failure within the first 6 weeks following single-lung transplantation approximates 5%.[28]

TABLE 107-5 Indications for Lung Transplant Procedures

Single-lung transplantation
Obstructive lung disease
Restrictive lung disease
Idiopathic pulmonary arterial hypertension (rarely)
Eisenmenger syndrome with a correctable shunt defect (rarely)
Bilateral-lung transplantation
Obstructive lung disease (patient <60 y old)
Septic lung disease
Idiopathic pulmonary arterial hypertension
Eisenmenger syndrome with a correctable shunt defect
Combined heart–lung transplantation
Significant intrinsic left ventricular dysfunction (LVEF <45%)
Significant coronary artery disease, not amenable to nonsurgical interventions
Eisenmenger syndrome with an irreparable shunt defect

Bilateral-lung transplantation is the procedure of choice for patients with septic lung disease, such as cystic fibrosis, and for patients with severe pulmonary arterial hypertension from either primary or secondary causes. Many centers also favor bilateral-lung transplantation for patients with emphysema who are less than 60 to 65 years of age.[67] More controversial is the preferential use of bilateral-lung transplantation for patients with fibrotic lung disease in the absence of severe secondary pulmonary hypertension. As currently performed, each lung is sequentially resected and the donor lung implanted; that is, two single-lung transplants are performed sequentially at the same operative sitting. This is in distinction to the original double-lung transplant, which used a double-lung bloc and a tracheal anastomosis. Bilateral-lung transplantation is performed via a bilateral thoracosternotomy incision, median sternotomy, or bilateral anterior thoracotomy incisions. The latter has the decided advantage of avoiding transection of the sternum and thereby preventing any chance of sternal infection and dehiscence, a major complication that can be associated with significant morbidity and occasional mortality. Surgical mortality is now equivalent for bilateral- and single-lung transplantation. Similarly, at most large centers, perioperative rates of acute graft failure and bronchial dehiscence are similar.

Combined heart–lung transplantation has been used successfully for virtually all end-stage pulmonary diseases. However, with the perfection of the techniques of single and bilateral transplantation, and in light of the significant limitations in supply of donor organs, the use of heart–lung transplantation has focused on patients with significant intrinsic left ventricular dysfunction or Eisenmenger syndrome and surgically irreparable shunt defects. The surgical mortality for heart–lung transplantation at large centers is about 10%; typically, it is higher than the surgical mortality for single or bilateral transplantation for similar disease states. Notably, the number of procedures performed worldwide has fallen with the realization that most recipients can be well serviced with lung transplantation alone.

DONOR SELECTION

The most significant factor limiting wider application of lung transplantation is the supply of donor organs.[68] Unlike other solid organs used for transplantation, the lung is exposed before brain death to environmental contamination, including both microbiologic pathogens and toxic substances, which may significantly impair its functional capabilities. The microbiologic aspects of this exposure are accentuated by the endotracheal intubation that is a necessary aspect of donor management. In addition, aspiration of oropharyngeal or gastric contents is a common occurrence during the events preceding brain death. Nearly half of all comatose patients develop pneumonia within 1 week of intubation, probably owing to a combination of these factors. Brain death itself may also lead to neurogenic pulmonary edema. In cases of trauma that lead to brain death, significant injury to the thorax may occur, or the volume replacement required for the resuscitation of these patients may limit the suitability of the lungs for subsequent transplantation. In addition to these immediate insults, a history of significant cigarette smoking raises concerns about more chronic damage to donor lungs.

As a result of these factors, only about 25% of cadaveric organ donors have historically proven to be potential lung donors. In recent years concerted efforts to improve donor supply and optimize donor utilization worldwide have proved fruitful, pushing the lung recovery rate up to approximately 50% in some centers. In part, this has been facilitated by an increasing willingness to use donors that were formerly called "marginal donors," a practice that has proven to be safe in most circumstances. The advent of *ex vivo* lung perfusion to "recondition" lungs following recovery heralds a most exciting phase in the development of the science of lung transplantation and holds great promise of optimizing donor lungs and allowing salvage of lungs that formerly would not have been considered suitable for organ donation.[6,7,69,70]

Criteria for lung donation are meant to identify donors with evidence of acceptable gas exchange in the absence of infection of the airways or parenchyma (Table 107-6). A donor age of less than 60 years and a history of smoking for less than 20 to 30 pack-years are important. Both increasing age and prolonged tobacco use are known to correlate directly with anatomic alterations in the pulmonary parenchyma, which, despite preservation of gas exchange function in the donor, may result in impaired graft function in the recipient. Despite these theoretical considerations the ultimate decision to use or not use a particular donor often depends on the status of the potential recipient. It is argued that it is preferable to use a donor that has smoked than miss a transplant opportunity that may equate to a death on the waiting list.

The chest radiograph should reveal normal lung on the side(s) of the lung(s) considered for donation. Unilateral pneumonia or parenchymal trauma does not preclude use of the contralateral lung

TABLE 107-6 Traditional Characteristics of a Suitable Lung Donor

Age <60 y
Cigarette smoking <20-30 pack-years
No significant prior thoracic surgery on the side of the donor lung
Normal chest radiograph of the donor lung
Adequate gas exchange of the donor lung
Pa_{O_2} > 300 mm Hg on $F_{I_{O_2}}$ 1.0, PEEP ≥5 cm
Pv_{O_2} > 450 mm Hg on $F_{I_{O_2}}$ 1.0, PEEP ≥5 cm
Bronchoscopic evaluation demonstrating absence of mucosal inflammation or aspiration
No significant pulmonary trauma or anatomic abnormalities

for transplantation in most circumstances. No major thoracic surgery should have been performed on the side of proposed donation, not only because of potential technical limitations but also because such a history usually suggests either a major anatomic abnormality (e.g., prior lobectomy) or pathology (e.g., malignant neoplasm), which would preclude donation.

Finally, the size of the donor lungs, based on direct measurement or correlated to predicted total lung capacity – as estimated by donor height, age, and gender – is a useful parameter to use when selecting lungs for a particular recipient. The simple expediency of measuring lung heights (apex to base) and transthoracic diameter correlates well with predicted total lung capacity and is a time-honored method of determining lung size. Generally, the donor lungs should be within 25% of the *predicted* size of the recipient's lungs. Donor lungs larger than these measurements can be volume reduced at the time of transplantation, whereas donor lungs considerably smaller than these measurements usually should be avoided. As a rule of thumb, donor organs should be smaller than the actual size of the hyperinflated native lungs of the recipient with emphysema so that the optimal length–tension relationships of the respiratory muscles can be reestablished. Conversely the donor for a patient with restrictive physiology should be larger than the actual size of the recipient native lungs so that after remodeling of the chest cavity the new total lung capacity approximates normal.

Adequate oxygenation has been defined as a Pa_{O_2} greater than 300 mm Hg on mechanical ventilation, with an $F_{I_{O_2}}$ of 1.0 and positive end-expiratory pressure (PEEP) of at least 5 cm H_2O. However, this is both arbitrary and dynamic. It is the trend that is most important and lungs with initial poor gas exchange due to a host of factors such as edema or atelectasis may well be suitable. It is the challenge of the donor retrieval team to analyze closely the operational factors to determine how to maximize the function of any potential donor organ. A "low stretch" ventilator protocol (i.e., tidal volume 6 mL/kg) should be utilized and recruitment maneuvers should be employed to maximize oxygenation. If a unilateral pulmonary process is present, a lower Pa_{O_2} may be acceptable because of the possibility of mixing of venous blood from the two lungs at the level of the left atrium. In this circumstance, intraoperative evaluation of unilateral gas exchange by sampling from the ipsilateral pulmonary vein for determination of P_{O_2} can be used to determine that the prospective donor lung is satisfactory.

All lung donors have some evidence of colonization of the lower respiratory tract by potential pathogens owing to the requisite endotracheal intubation, which bypasses the defense mechanisms of the upper airway. A distal tracheitis is uniformly present after 72 hours of intubation. Therefore, a sputum Gram's stain revealing polymorphonuclear leukocytes or multiple bacterial forms does not necessarily imply invasive infection. For this reason, bronchoscopy is a critical step in the evaluation of any potential lung donor. Bronchoscopy allows inspection of the large airways for the presence of aspirated debris as well as assessment of the character of the secretions and status of the bronchial mucosa. A finding of diffuse bronchial mucosal inflammation is significant, even if only a limited amount of aspirated debris or secretions are present. However, purulent secretions without significant mucosal inflammation in the presence of a clear chest radiograph and preserved gas exchange generally indicate a suitable lung for donation. A potassium hydroxide smear for fungal organisms is also a part of the routine evaluation of the lung donor, although as with the Gram's stain, the mere presence of fungal organisms, particularly Candida species, does not preclude lung donation. In most cases, the presence of potential pathogens in the donor sputum by either Gram's stain or fungal smear requires preemptive modification of the recipient's antimicrobial regimen if such lungs are used for transplantation. At some centers, this treatment is begun by the administration of intravenous or aerosolized antimicrobial therapy to the donor before retrieval of the donor lungs. Prophylaxis for Candida and fungal organisms found in the donor swabs should be prolonged to prevent dehiscence of vascular and airway anastomoses.

The donor evaluation is completed by intraoperative inspection of the pleural space and lung. Occasionally, unsuspected parenchymal trauma is evident in the form of a bloody pleural effusion or pulmonary contusion. The donor lung also should be studied for evidence of unsuspected bullous disease or mass lesions. Excisional biopsy and intraoperative pathologic evaluation of any parenchymal mass lesion should be carried out. Finally, the anesthesiologist should be directed to maintain adequate tidal volumes and PEEP during intraoperative ventilation to preserve optimal function of the donor lung before its removal.

The appropriateness of a potential lung donor always should be interpreted in the context of the recipient's disease and clinical status. Older patients and patients with a sudden clinical deterioration, such as those who have recently been placed on mechanical ventilation, may all benefit from transplantation with a lung that does not fulfill all the criteria of an optimal donor lung. Most frequently, the criteria relating to cigarette smoking and Pa_{O_2} are breached in these circumstances. The results have generally been satisfactory in such recipients, suggesting that the use of "marginal" lung donors may partly address the problem of donor organ shortage.[71] It has also been shown that the effect of the functional status of the donor lung is most significant in the first 24 hours after transplantation, and that subsequent graft function depends primarily on factors related to the recipient. In addition, these studies have underscored that patients with pulmonary hypertension, who are the most difficult to manage postoperatively, are best served by transplantation with lungs from optimal donors.

LUNG PRESERVATION

The ideal method of pulmonary preservation has not yet been identified. With current techniques, however, satisfactory graft function can be obtained after ischemic intervals as long as 6 to 8 hours. As with other vascular solid organs used for transplantation, the lung consists of a heterogeneous population of cells, of which the vascular endothelial cell appears to be the most sensitive to ischemia. Ischemic injury to the pulmonary vascular endothelium increases its permeability and results in pulmonary edema, the common end point for assessment of injury in models of pulmonary preservation techniques. Hypothermia is the major method used clinically to limit ischemic injury to these cells. The lung also has some unique biologic and physical characteristics that distinguish it from other solid organ transplants. Although it has an absolute requirement for aerobic metabolism, the lung is capable of using ambient oxygen for the metabolism of glucose, even during the ischemic state. In addition, the effective size of the pulmonary vascular bed and thermal conductivity of the lung can be manipulated by the degree of lung inflation. Current clinical methods of lung preservation make use of these characteristics to optimize graft function following an ischemic interval.

Two techniques are currently being used for lung preservation, core cooling and hypothermic flush perfusion. *Extracorporeal core cooling* (ECC) is a technique that has been used primarily for procurement of heart–lung donor blocs, commonly in conjunction with multiorgan procurement at abdominal sites. ECC consists of systemic heparinization of the donor and institution of full cardiopulmonary bypass (CPB) by means of a transpericardial approach. The donor is cooled to 15°C (rectal temperature). Ventricular fibrillation typically develops during this maneuver, and the heart

is decompressed through the left ventricle. CPB is then discontinued, and the heart–lung bloc is harvested and transported in a cold ischemic state with the lungs inflated. No flush solutions are used, although the lungs are essentially being flushed by cooled autologous blood during the time of CPB. Safe ischemic times of 6 hours or more have been reported with adequate pulmonary function. It is of interest that while oxygenation in lungs preserved by ECC appears to be somewhat less optimal than in those preserved by hypothermic flush techniques, the pulmonary vascular resistance (PVR) upon reperfusion of the lungs following ECC is generally lower than that seen upon reperfusion of lungs obtained by flush techniques.

Hypothermic flush perfusion is the method most commonly used for pulmonary preservation in clinical practice. This technique consists of flushing the pulmonary vasculature with a cold solution after systemic heparinization of the donor, followed by extraction and transport of the lungs inflated with 100% oxygen. Flushing can be performed in antegrade fashion via the pulmonary artery or retrograde fashion via the left atrium or pulmonary veins. Many centers favor the retrograde technique as it appears to be more effective in flushing out clots from the pulmonary arterial circulation thereby improving gas exchange by enhancing ventilation and perfusion matching. A low-potassium dextran solution is used. The ideal pulmonary preservation solution is a topic of much debate.

The state of inflation of the lungs is important in obtaining optimal perfusion of the pulmonary vasculature by the flush solution, to achieve both rapid cooling and direct cellular preservation by the solution itself. Intraoperatively, maintaining a tidal volume similar to that used during the initial donor assessment is important. The addition of PEEP during the procurement procedure maintains functional residual capacity and the desired state of inflation of the donor lungs. PEEP also increases the intra-alveolar release of surfactant, minimizing pulmonary compliance abnormalities after implantation of the donor lungs. Ventilation is continued throughout the period of lung perfusion to maintain the effective size of the pulmonary vascular bed. Although it was once thought that the maintenance of an $F_{I_{O_2}}$ of 1.0 during the procurement was useful, particularly at the time of lung extraction, to provide an oxygen-rich ambient environment for metabolic activity of the lung during the ischemic interval, new information suggests that use of high $F_{I_{O_2}}$ is associated with a higher risk of primary graft dysfunction (PGD). The lungs are extracted and transported in a state of inflation that approximates end-tidal inspiration. Some consideration should be given to the fact that the donor lungs may be transported by aircraft, in which a fall in atmospheric pressure may result in further inflation of the lungs. Overinflation of the donor lungs is to be avoided, as this leads to increased capillary permeability and postimplantation pulmonary edema.

The administration of prostanoids, either prostaglandin E_1 (PgE_1) or prostacyclin, into the pulmonary circulation before flush perfusion has been shown to improve lung preservation. The mechanism of action of prostanoids includes dilation of the pulmonary vasculature, allowing for better distribution of the flush solution, and decreased leukocyte adhesiveness, which can abrogate the initial events of reperfusion injury. Most commonly in North America, PgE_1 is used as a bolus (500 μg) into the pulmonary circulation, with or without the addition of similar amounts of PgE_1 directly to the flush solution. The use of prostanoids in combination with intracellular flush solutions has been shown to provide pulmonary preservation equivalent, if not superior, to that with the use of extracellular-type flush solutions alone.

Most flush solutions are administered at a temperature of 4°C, while topical cooling is carried out by filling of the pleural cavity with iced crystalloid solution. After extraction, the lungs are immersed in crystalloid and packed in ice, resulting in a transport temperature of 1° to 4°C. Some studies have shown that lung preservation is superior when a more moderate hypothermia with a temperature of 10°C is used. However, because of the concerns regarding the deleterious effects of flush and storage temperatures greater than 10°C, and the difficulties in maintaining this temperature during the procurement procedure, clinical flush perfusion continues to be performed at the lower temperature ranges.

Experimental work has identified numerous adjuncts to the techniques currently used for pulmonary preservation that have the potential for prolonging ischemic intervals. A significant part of the lung injury seen after ischemia has been shown to be due to the phenomenon of reperfusion, which is initiated by leukocyte adhesion to endothelial cells and the production of oxygen-derived free radicals and peroxides. Measures that diminish this response, in addition to the use of prostanoids, include donor leukocyte depletion, the administration of antibodies to block adhesion molecules, the use of inhaled nitric oxide, and the inclusion of oxygen radical scavengers, such as superoxide dismutase or catalase, to the flush solution. In addition, methods of increasing the resistance of cells to ischemic injury, such as the induction of heat shock proteins, have been shown to be beneficial in other organs and may be of some use in lung preservation. Evidence of the effect of these manipulations on tolerable ischemic intervals in clinical lung transplantation awaits additional study.

TECHNIQUES OF LUNG TRANSPLANTATION

Technical aspects of lung transplantation include both anesthetic and surgical considerations. Single lung, bilateral lung, and heart-lung transplantation are the surgical options currently utilized.

ANESTHETIC MANAGEMENT

Proper perioperative management of the recipient is crucial to obtain the best outcome following lung transplantation.[72] Close cooperation and understanding between the anesthesiology and surgical teams are essential. An appreciation of the unique aspects of the physiology of the various types of lung transplant recipient is also important. Patients with COPD have reduced expiratory flow rates, air trapping, and increased lung volumes. Following endotracheal intubation, extreme care should be taken to allow adequate expiratory time for emptying of the lungs, avoiding the cardiovascular instability caused by "pulmonary tamponade" due to progressive air trapping in the lungs and reduction of ventricular filling. Tension pneumothorax due to rupture of bullae can also occur but is relatively uncommon. Pneumothorax is particularly difficult to diagnose in the supine patient and may be missed on fluoroscopy especially if there is an anterior air collection. Patients with restrictive lung disease have progressive fibrosis of the lung tissue, with secondary hypoxemia and progressive pulmonary hypertension. Patients with these diseases have an increased work of breathing and are oxygen dependent and extremely dyspneic before transplantation. Many of these patients have evidence of cor pulmonale at the time of transplantation and cannot tolerate occlusion of the pulmonary artery during implantation of the donor lung without the support of cardiopulmonary bypass. Careful and repeated assessment of filling pressures and cardiac output is required to allow prompt interventions in such patients. Patients with septic lung disease demonstrate primarily the abnormalities in pulmonary function seen in patients with obstructive airway disease. However, these recipients have excessive copious purulent secretions, which can exacerbate air trapping and also contribute to marked V/Q abnormalities – particularly during single-lung ventilation. Careful management

of double-lumen endotracheal tubes to avoid contamination of the contralateral lung graft and attention to bronchopulmonary hygiene to avoid obstruction of the lumens of these tubes are needed in these patients. Finally, recipients with pulmonary vascular disease who present for transplantation have marginally compensated cor pulmonale and are extremely dyspneic and anxious. Patients with IPAH become oxygen dependent late in the course of their disease, although oxygen is commonly administered to these patients to lessen the hypoxic contribution to their pulmonary hypertension. For this reason, oxygen therapy should be continued throughout the time of preoperative preparation and line placement to avoid abrupt right heart dysfunction. Because these patients have normal pulmonary mechanics, they generally tolerate mechanical ventilation well. Patients with Eisenmenger syndrome are well adapted to chronic hypoxemia. In these patients, supplemental oxygen does not reverse the hypoxemia and may even worsen arterial hypoxemia by eliciting systemic vasodilatation and increasing right-to-left shunting.

All lung transplant procedures should be performed with CPB available on standby, if not utilized by surgeon choice. There is an argument to avoid CPB in cases of septic lung disease or other situations where there are known extensive intrapleural adhesions, to avoid excessive bleeding complications, but as always it is a balance of experience and safety. No specific preoperative factors can be used to predict the need for CPB—with the exception of severe pulmonary arterial hypertension, for which CPB is requisite for the procedure. For other lung transplant recipients, assessment of the need for CPB is best made intraoperatively by trial clamping of the pulmonary artery, followed by assessment of hemodynamic parameters, oximetry, and if available, ventricular function testing by transesophageal echocardiography. Progressive deterioration in these parameters requires unclamping of the pulmonary artery and an attempt to optimize factors such as preload, inotropic support, Pa_{O_2}, Pa_{CO_2}, and PVR. If repeat trial clamping of the pulmonary artery is still not tolerated, plans for CPB are made. Typically, cannulation after systemic heparinization is via the femoral vessels for single-lung transplantation and via a transpericardial approach for patients undergoing bilateral-lung or heart–lung transplantation.

SINGLE-LUNG TRANSPLANTATION

The approach to single-lung transplantation requires an initial decision regarding the side of implantation. Most commonly, the native lung with the least pulmonary function based on preoperative V/Q scans is excised. In some patients, however, specific technical factors, such as a prior pleurodesis, may override this factor. When the function of the two lungs is equal or when the need for CPB is anticipated, the right side is preferred because of the greater ease of surgical exposure and the institution of CPB via the ascending aorta and right atrium. A right-sided approach also facilitates exposure for closure of intracardiac defects in patients with Eisenmenger syndrome. Despite the potential differences in size of the right and left hemithorax, there does not appear to be any long-term difference in outcome following right or left single-lung transplantation.

Most often, exposure for single-lung transplantation is via a generous posterolateral thoracotomy through the fifth intercostal space or the bed of the excised fifth rib. When elective CPB via the right hemithorax is planned, the use of a fourth interspace may facilitate placement of the cannulae. The ipsilateral groin is included in the surgical field in the event that cannulation of the femoral vessels is required for partial CPB. Although the use of femoral sites for cannulation requires repair of the vessels after removal of the cannulae, it does provide a site for additional venous drainage with use of intrathoracic cannulation sites. Femoral cannulation sites also provide access for conversion to ECMO support if acute graft failure occurs immediately after implantation. Occasionally, when the repair of an associated intracardiac defect requires an anterior approach, a median sternotomy may be used for right single-lung transplantation in patients with Eisenmenger syndrome (though single-lung transplantation is rarely used for this indication).

The donor lung is prepared for implantation and then wrapped in sponges soaked with cold crystalloid solution and placed into the hemithorax. The bronchial anastomosis is performed first. Although a variety of techniques have been described, the essential points are to minimize the length of both the donor and recipient bronchi to preserve collateral blood supply and achieve some degree of anastomotic overlap. An end-to-end anastomosis is preferred (Fig. 107-1). Occasionally, it is necessary to telescope the smaller bronchus, most commonly the donor bronchus, into the larger bronchus with either a technique of interrupted sutures or a combination of running sutures on the membranous wall and interrupted sutures on the anterior wall in a figure-eight or horizontal mattress fashion. Polyfilament absorbable suture (e.g., 4-0 polyglactin) or monofilament suture, either absorbable (e.g., polydioxanone) or nonabsorbable (e.g., polypropylene), may be used. The anastomosis is then covered by either local peribronchial tissue or local pedicled flaps of thymic tissue or pericardial fat.

The order of the vascular anastomoses can vary even though the pulmonary artery anastomosis is frequently the more technically difficult to perform. A continuous 5-0 polypropylene suture is used for each anastomosis, leaving the ends untied for deairing upon reperfusion of the lung. For the pulmonary artery anastomosis, the length of the donor and recipient vessels requires careful assessment to avoid kinking. For the left atrial anastomosis, the confluence of the recipient pulmonary veins is incised to create a left atrial cuff. Occasionally, dissection in the interatrial groove is required to allow more proximal placement of the vascular clamp on the recipient left atrium

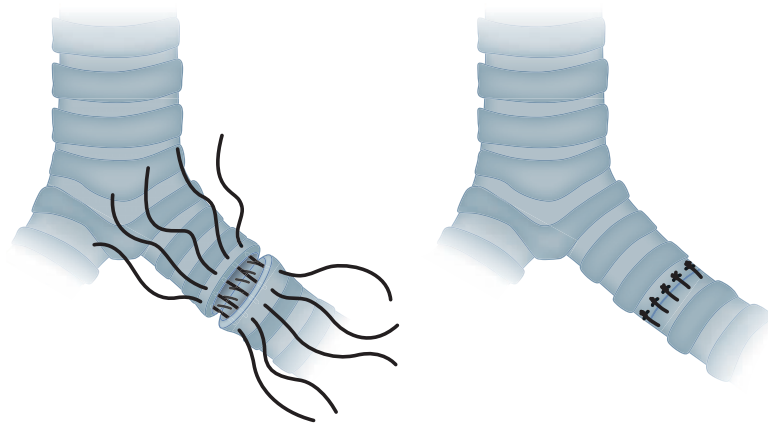

Figure 107-1 Bronchial anastomosis for lung transplantation. A technique of approximation using stay sutures at the junction of the cartilaginous and membranous walls is shown. If the donor and recipient bronchi are size matched a continuous monofilament suture can be utilized. If there is a significant size mismatch alternative techniques are employed to minimize puckering. A running suture is used for the membranous wall, followed by an interrupted suture technique of horizontal mattress sutures on the cartilaginous wall to achieve an end to end anastomosis. Additional anastomotic coverage may be obtained by approximation of peribronchial and mediastinal tissues about the site.

(Fig. 107-2). After completion of these anastomoses, the lung is gently reinflated. Perfusion of the lung graft is then reestablished, initially in an antegrade fashion, evacuating air via the left atrial suture line. The atrial clamp is removed, with the atrial suture line under a fluid level to prevent entrainment of air into the left heart. Ventilation of the donor lung is resumed, and after a few minutes to allow the vascular suture lines to adapt to the distention caused by increased flow, these suture lines are secured. Hemostasis is then obtained, two chest tubes are placed, and the chest is closed in a standard fashion. Following reintubation with a single-lumen tube, flexible bronchoscopy is completed to inspect the bronchial anastomosis and clear the airway of blood or residual secretions.

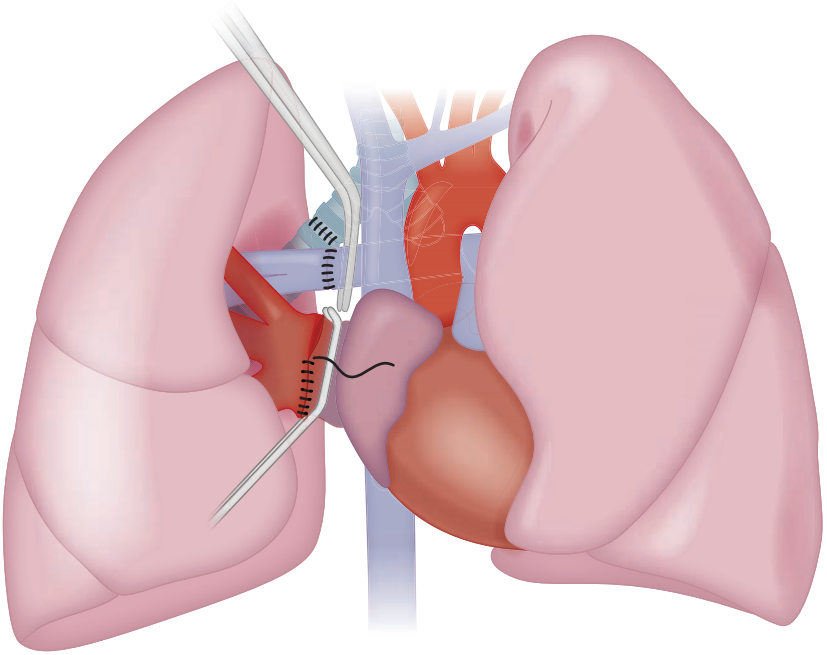

Figure 107-2 Implantation of the donor lung at the right hilum. The bronchial anastomosis is performed first, followed by the venous then arterial anastomoses. A clamp is placed on the left atrium within the pericardium. After excision of the pulmonary vein stumps, the confluence of the pulmonary veins is incised to create a cuff of left atrium. The atrial anastomosis is performed with a running monofilament suture following approximation with stay sutures superiorly and inferiorly. The pulmonary arterial anastomosis is performed last. A clamp is placed on the proximal pulmonary artery. Usually the anastomosis is proximal to the upper lobe pulmonary artery branch on the right side however if there is a size mismatch the anastomosis may be distal to this branch. On completion of the anastomosis, the sutures are left untied until lung reinflation and antegrade reperfusion is completed to evacuate air from the donor vasculature.

■ BILATERAL-LUNG TRANSPLANTATION

Although most commonly referred to as bilateral-lung transplantation in the medical literature, the most frequently performed bilateral procedure is more accurately described as bilateral sequential single-lung transplantation. This procedure has a significantly lower incidence of anastomotic complications than the en bloc double-lung procedure that it replaced, and is technically less difficult to perform than en bloc double lung with simultaneous bronchial artery revascularization. The exposure for bilateral-lung transplantation has traditionally been via bilateral anterolateral thoracotomies through the fourth or fifth intercostal space, connected by a transverse sternotomy—the so-called clamshell incision (Fig. 107-3). The incision provides adequate exposure for mobilization of intrapleural adhesions, even after previous pulmonary resections or pleurodesis, and also provides excellent access for institution of CPB and correction of intracardiac defects. In most patients, the entire incision is made at the beginning of the procedure, and both lungs are completely mobilized. For patients with emphysema who undergo bilateral-lung transplantation, however, the contralateral hemithorax may be left closed until after the first lung graft is implanted; this sequence minimizes the tendency to overinflation of the native lung that may occur during the initial implantation procedure. As mentioned above, a number of centers now prefer bilateral anterior thoracotomy incisions for bilateral-lung transplantation, which provides a superior cosmetic result as well as avoiding the risk of sternal dehiscence or infection. The mobilization and pneumonectomy of the native lung and the implantation of the lung graft are conducted in the same manner as described for single-lung transplantation. Thymic and anterior mediastinal tissue on a superiorly based vascular pedicle may be mobilized for coverage of the bronchial anastomoses. Finally, some centers utilize a median sternotomy approach.

Living-related lung transplantation is most commonly performed as a bilateral sequential transplant procedure using the clamshell incision. Cardiopulmonary bypass is instituted electively after the recipient native lungs are mobilized. Each of the donor lobes is implanted at the recipient hilum. Typically, there is little discrepancy in size between the lobar bronchus and pulmonary vein of the donor (usually an adult) and the main bronchus and left atrium of the typical pediatric recipient. The order of the anastomoses (bronchus first) and the technique are the same as for cadaveric single- and bilateral-lung transplantation. Overinflation of the lobar graft is more likely than with a cadaveric allograft and may contribute to postoperative pulmonary edema. A marked size discrepancy between the lobar allograft and the

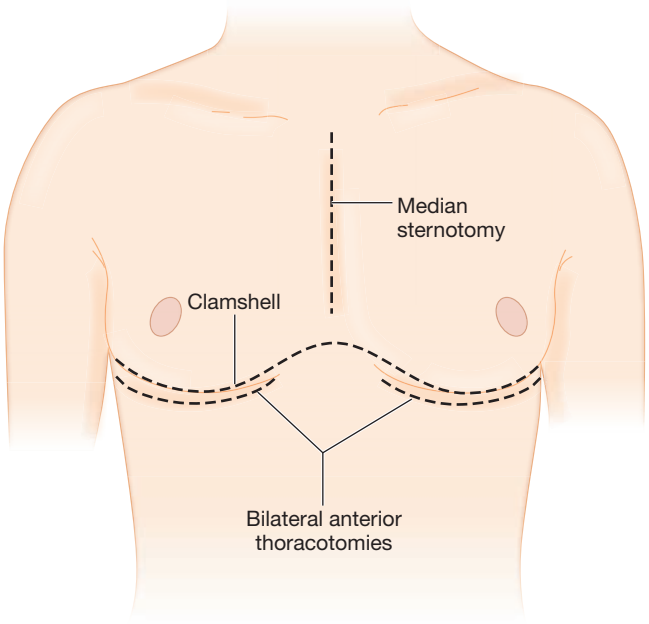

Figure 107-3 Approaches to bilateral lung transplantation. Bilateral anterior thoracotomy is now used commonly. Bilateral thoracosternotomy or "clam shell" incision is an alternative, consisting of bilateral anterior thoracotomy with transverse sternotomy, defined by the line of the inframammary crease. Entrance into the chest cavity is via either the fourth or fifth intercostal space, followed by placement of bilateral rib retractors. Occasionally a midline sternotomy is performed.

recipient hemithorax is uncommon; if present, the discrepancy should be treated conservatively (e.g., by avoiding chest tube suction rather than by aggressive surgical measures such as thoracoplasty). In all cases, sufficient remodeling of the thorax or hyperinflation of the lobar grafts will occur to obliterate any residual pleural space.

HEART–LUNG TRANSPLANTATION

Either a standard median sternotomy or a clamshell incision may be used for heart–lung transplantation. The latter provides better access for mobilization of intrapleural incisions and is particularly useful for recipients with septic lung disease or prior pulmonary procedures. Following institution of CPB, the lungs are removed by an extrapericardial approach using successive stapling of the bronchovascular structures at the pulmonary hila. The donor right atrium is incised from the inferior vena cava to the right atrial appendage. Inspection is made for the presence of an atrial septal defect and adequate closure of the superior vena cava. The donor bloc is positioned by passing the lungs into the pleural spaces via the retrophrenic pedicles. If a tracheal anastomosis is used, the posterior pericardium is incised between the ascending aorta and superior vena cava to expose the distal trachea and, after the donor and recipient tracheas have been trimmed, a distal tracheal anastomosis is performed. Some centers prefer bilateral bronchial anastomoses at the mediastinal pleural reflection, using the same technique employed for single-lung transplantation. This approach obviates dissection in the posterior mediastinum and may be associated with fewer anastomotic complications. The right atrial anastomosis is completed, followed by the aortic anastomosis. The aortic cross clamp is removed, and after reinflation of the lungs, the heart is deaired via the pulmonary artery and left ventricle. After defibrillation, the patient is weaned from CPB.

POSTOPERATIVE MANAGEMENT

Care of the lung transplant recipient in the immediate postoperative period is multifaceted and includes respiratory and hemodynamic management and initiation of antimicrobial prophylaxis and immunosuppressive agents.

VENTILATION

In most cases, ventilatory management follows standard criteria. The $F_{I_{O_2}}$ is adjusted to maintain a Pa_{O_2} greater than 65 mm Hg. Standard volume ventilation is used, and many centers are now using lower tidal volume of 6 mL/kg and PEEP of 5 to 7.5 cm H_2O. Transition from volume ventilation to pressure support ventilation is commonly performed once the patient is awake and spontaneously breathing. Appropriate management of postoperative pain is also helpful in weaning patients from the ventilator. Extubation is performed when the patient is awake and responsive to command and the patient has achieved a reasonable rate of ventilation and spontaneous tidal volume, typically 12 to 72 hours after the procedure. Maintaining good bronchopulmonary hygiene, with an early bronchoscopic inspection of the anastomoses and distal airways coupled with physiotherapy, is important in achieving and maintaining extubation in these patients.

Patients with emphysema who undergo single-lung transplantation are an exception to the guidelines mentioned earlier. These patients require particular attention to airway pressures and to the compliance difference between the allograft and the native lung. Hyperinflation of the native lung may not only result in compromise of cardiac filling but also interferes progressively with ventilation of the allograft. Efforts to control hyperinflation of the native lung include use of lower tidal volumes and respiratory rates and higher inspiratory flow rates to allow for more prolonged expiratory times. In rare circumstances, when significant edema has occurred in the allograft, independent lung ventilation using a double-lumen endotracheal tube may be needed.

In patients with significant pulmonary hypertension who undergo lung transplantation, the postoperative pulmonary hemodynamics are unique. In these patients, the right ventricle has been conditioned to generate peak systolic pressures against a markedly elevated PVR. Following lung transplantation, the PVR abruptly decreases to near-normal levels, accompanied by improved ventricular hemodynamics. Minimal catecholamine stimulation occurs when the patient awakens from anesthesia or is weaned from a ventilator, causing the right ventricle to respond by generating peak systolic pressures similar to those that existed preoperatively. The resultant abrupt increase in pulmonary artery pressure, in combination with increased capillary permeability due to ischemia and reperfusion injury and the absence of lymphatic continuity, causes fluid to accumulate rapidly in the donor lung. Typically, this pulmonary edema is very rapid in onset and results in hypoxia that elicits additional increase in pulmonary artery pressure. Preemptive treatment for this condition is necessary and requires maintenance of a high degree of sedation in the first 3 to 5 days after surgery. Following this period, patients can be awakened cautiously and weaned from the ventilator with standard methods while cardiac output, blood gases, and pulmonary artery pressures are closely monitored.

FLUID MANAGEMENT

The goal of fluid management after lung transplantation is to minimize the accumulation of edema fluid in the allograft(s) while maintaining optimal cardiac function. As previously noted, the effects of ischemia, reperfusion injury, and lymphatic discontinuity all contribute to a tendency to develop pulmonary edema in the lung graft. Pulmonary artery pressures and pulmonary capillary wedge pressures need to be kept as low as possible after surgery without compromising ventricular preload. For most patients, a reduction in PVR almost immediately after lung transplantation results in improved right ventricular and, secondarily, left ventricular performance. However, some inotropic support may be required in patients who have pre-existing right ventricular systolic dysfunction. Systolic vascular resistance may be low in the postoperative period, due to a systemic inflammatory response to surgery and to use of epidural analgesics, and this may necessitate the use of pressors to address hypotension.

ANTIMICROBIAL THERAPY

Bacterial prophylaxis entails the use of agents for prophylaxis against gram-positive, gram-negative, and anaerobic organisms in combination with targeted antibiotics to provide appropriate coverage for organisms identified preoperatively from the sputum of the recipient. Recipients who have been hospitalized recently, and therefore exposed to respiratory therapy equipment, or those with cystic fibrosis, require specific antibiotic coverage against *Pseudomonas* species, based on susceptibility data. Bear in mind that in vitro sensitivity does not always predict the in vivo response to antibiotics, which may show the effect of in vivo synergy and high-concentration gradients within the lung especially for quinolones and macrolides. For cystic fibrosis patients, ongoing surveillance of sputum flora and determination of antibiotic sensitivities are important in the waiting period before transplantation so that an appropriate multidrug antimicrobial regimen can be developed for perioperative use. The addition of antimicrobial inhalation therapy, using either tobramycin or Colistin, can have additive effects in reducing the colonizing load of organisms. Postoperative antibacterial coverage should be modified if pathogens not already covered by the recipient-specific regimen are found in the sputum or bronchoscopic specimens of the donor.

Routine prophylaxis for fungal organisms is useful when preoperative recipient sputum cultures have demonstrated the presence of *Aspergillus* species at any time before the transplant procedure or when there has been evidence of heavy overgrowth of yeast (e.g., *Candida*) in the donor sputum culture. In the case of *Aspergillus,*

most units employ prophylactic therapy with the use of either nebulized amphotericin B or azole therapy with voriconazole or itraconazole. Some centers employ a hybrid strategy of initial universal fungal prophylaxis with inhaled therapies followed by preemptive therapy for any organisms detected on surveillance cultures.

The occurrence of herpes simplex virus (HSV) infection, including mucosal ulceration, esophagitis, and pneumonitis, has been virtually eliminated by the routine use of antiviral prophylaxis after lung transplantation but significant infections can still occur and may impact both survival and quality of life.[73–75] Valganciclovir used to prevent CMV has cross reactivity for herpes simplex but it is important not to forget to institute prophylaxis in CMV donor-negative/CMV recipient–negative patients who may not be allocated valganciclovir.[47,51] In such cases, acyclovir or valacyclovir should be administered for a minimum of 6 months. CMV infection is still a significant problem following lung transplantation.[50,74–78] The incidence of CMV infection after lung transplantation is related to the preoperative CMV status of both the donor and the recipient. Recipients with prior exposure to CMV are at risk for reactivation of infection and, if they receive an organ from a CMV-positive donor, for reinfection. The greatest risk occurs when a CMV-negative recipient receives a lung from a CMV-positive donor; the primary infection of the recipient that can ensue tends to be more severe than either reactivation or reinfection. For this reason, some centers prefer to avoid mismatching a CMV-positive donor with a CMV-negative recipient. However, the use of antiviral prophylaxis with ganciclovir or valganciclovir prophylaxis has significantly reduced the incidence of primary disease.

The incidence of *Pneumocystis jiroveci* infection in lung transplant patients has also been significantly reduced by the routine use of trimethoprim–sulfamethoxazole.[79] If this drug is not tolerated alternatives such as dapsone (watch for Coombs-positive hemolytic anemia) or inhaled pentamidine should be entertained.

IMMUNOSUPPRESSION

The induction of a state of relatively nonspecific immune suppression by pharmacologic means has been the key to successful clinical lung transplantation. While the ideal method would be to achieve specific, permanent tolerance of the allograft without the need for chronic medication, this is not possible at present. As a result, although the current regimens lead to satisfactory control of most acute rejection (AR) processes, the combined side effects of these medications and their incomplete ability to control CR in the lung account for the major long-term morbidity and mortality associated with lung transplantation. It is always a balance of efficacy versus toxicity and the transplanted lung has one risk factor that no other solid organ faces, namely it is exposed to the ambient environment with every breath.[80,81]

The immunosuppressive regimens used for lung transplantation are based on the successful protocols that have evolved for renal and heart transplantation. Recent trials have supported similar regimes in lung transplantation.[82–89] Virtually all centers use a three-drug regimen for immunosuppression comprising a CNI, a cell-cycle inhibitor and a corticosteroid, with the hope of obtaining additive effects in terms of immune suppression while limiting drug toxicities. Most lung transplant programs use steroids as part of the regimen for the induction of immunosuppression. However, some centers have used cytolytic therapies such as daclizumab, basiliximab, alemtuzumab, OKT3, and antithymocyte globulin for this purpose. These therapies are typically initiated within 24 hours of transplantation, and are typically combined with the usual triple-drug regimen of steroids, a CNI, and a cell-cycle inhibitor.

Tacrolimus has now overtaken cyclosporine as the mainstay of immunosuppression for lung transplantation and there is a growing evidential base to support this policy.[4,89] Tacrolimus (FK-506) is a macrolide compound with a mechanism of action similar to that of cyclosporine mediated through an immunophilin protein called the FK-binding protein (FKBP). Toxicity is similar to that of cyclosporine and includes renal dysfunction, hypertension, and neurotoxicity. New-onset diabetes mellitus has also been reported. In contrast to cyclosporine, hirsuitism and gingival hyperplasia have not been seen with tacrolimus. In a randomized trial in lung-transplant patients of three-drug regimens containing either cyclosporine or tacrolimus, the incidence of postoperative fungal infections was higher in patients receiving tacrolimus. A large 3-year study recently reported a significant reduction in the rate of BOS at 3 years in the arm taking tacrolimus but this was not associated with a difference in 3-year mortality.[89]

Intravenous or sublingual administration of tacrolimus is usually begun before the graft is implanted and continued postoperatively, provided renal function remains satisfactory. Subsequent conversion to oral dosing is completed when gastrointestinal function is normal. Blood levels of both tacrolimus and cyclosporine correlate with immunosuppressive effects and toxicity but there is still some debate regarding the optimum method of performing therapeutic drug monitoring. For cyclosporine there is good evidence that the best single-point surrogate measure of the area under the time–concentration curve is the value taken at 2 hours post dose.[90–93] Less data are available for tacrolimus but it is clear that like cyclosporine, trough levels may both overestimate and underestimate total drug exposure, which may lead to risk of rejection and nephrotoxicity respectively. Nephrotoxicity, the major side effect of both cyclosporine and tacrolimus, results in part from vasoconstriction of the afferent glomerular arteriole and may be ameliorated by the concomitant use of diltiazem. However, chronic CNI toxicity is common and results in granular contracted kidneys with permanent renal failure.

Azathioprine, a purine analog, is converted to several purine metabolites, including 6-mercaptopurine, in red cells and hepatocytes. These purine metabolites have a variety of inhibitory effects on hematologic cell proliferation, with a somewhat greater effect on T cells than B cells. Azathioprine is begun at a dosage of 2 to 2.5 mg/kg per day and adjusted downward to maintain a white blood cell count of more than 4000 cells/mL. The dosage is the same for both the intravenous and oral routes. If necessary, azathioprine may be omitted for several days without significant compromise of its immunosuppressive effect.

Mycophenolate preparations subserve a similar role as cell-cycle inhibitors but despite demonstrable efficacy after heart transplantation in particular, trials after lung transplantation have not shown convincing evidence of superior efficacy or tolerability compared to azathioprine. The largest study to date was an open label study that may have been underpowered by the presentation of 1-year data that was favorable in the mycophenolate arm, perhaps leading to a large number of patients in the azathioprine arm switching to mycophenolate.[88] Mycophenolic acid inhibits de novo purine synthesis by inhibiting the conversion of inosine monophosphate to xanthine monophosphate. Since lymphocytes depend almost exclusively on de novo purine synthesis, mycophenolic acid selectively inhibits their replication, including the formation of cytotoxic lymphocytes and both primary and secondary antibody formation. Mycophenolic acid has been shown to reverse AR that is resistant to both corticosteroids and OKT3. Side effects include nausea, gastritis, ileus, and myelosuppression.[88]

Corticosteroids have a variety of effects on the immune response, mediated by the interaction of the steroid with a high-affinity cytoplasmic receptor. Steroids affect both inflammation and immunity, and modulate lymphocyte-, mononuclear phagocyte–, and antigen-presenting cell functions. Prednisone, prednisolone, and methylprednisolone are all synthetic derivatives of cortisol that are used clinically for transplant patients.[94] Intraoperatively, methylprednisolone is administered before reperfusion of the lung graft. Postoperatively, in the absence of cytolytic induction therapy,

moderate-dose corticosteroid therapy is used in combination with a CNI and cell-cycle inhibitor for induction immunosuppression. Oral corticosteroids (0.5–1.0 mg/kg/d) are usually begun after the postoperative intravenous steroids and when oral therapies are commenced. Although corticosteroids have profound inhibitory effects on wound healing, their use in this fashion in the immediate postoperative period has not adversely affected the outcomes of lung transplantation.

Various antilymphocyte antibody preparations, the so-called cytolytic therapies, have been used in clinical lung transplantation. Both polyclonal preparations, such as antilymphocyte globulin and antithymocyte globulin (ATG), and a murine monoclonal antibody to the CD3 complex of human lymphocytes (OKT3) have been used. Initially, it was believed that strict avoidance of corticosteroids was needed in the early postoperative period to assure satisfactory healing of the bronchial anastomosis. As a result, cytolytic therapy was thought to be necessary to induce immunosuppression before the initiation of steroid therapy in the second postoperative week. The subsequent demonstration that moderate-dose corticosteroid therapy was well tolerated immediately after lung transplantation, as described, as well as concerns regarding the risks of cytolytic therapy, resulted in many centers reserving the use of these agents for the treatment of refractory AR. However, data from the ISHLT Registry suggest the majority of centers now use some form of cytolytic induction based on the belief that the benefit of a reduced rate of BOS so engendered is worth the risk.[4]

The two most significant concerns regarding the use of cytolytic therapy have been the increased incidence of CMV disease and of posttransplant lymphoproliferative disorder (PTLD).[95–97]

The mammalian target of rapamycin inhibitors sirolimus (rapamycin) and everolimus inhibit the response of T lymphocytes to IL-2 and other cytokines but do not inhibit IL-2 production. Sirolimus has been shown to reverse rejection and prolong graft survival in animal models. However, sirolimus has been associated with lethal airway anastomotic dehiscence when used for immunosuppression early posttransplantation.[98] Recent reports also warn of an excess rate of venous thrombosis with sirolimus.[99] Concurrent cyclosporine administration increases the potency of rapamycin, suggesting that it may be used in combination with cyclosporine to lower the overall toxicity of a multidrug immunosuppressive regimen. Importantly, rapamycin increases the AUC of cyclosporine by more than 150%, which may lead to CNI-induced nephrotoxicity and possibly hemolytic uremic syndrome.[100]

COMPLICATIONS

Lung transplant recipients are at risk for a number of complications that can adversely impact allograft function as well as posttransplant survival. These include technical, infectious, immune-mediated, and neoplastic complications.

SURGICAL COMPLICATIONS

Major technical complications following lung transplantation have become increasingly rare with improvements in surgical technique and perioperative management. Postoperative hemorrhage requiring exploration is very uncommon with the use of the clamshell incision to improve operative exposure for patients requiring bilateral-lung transplantation or heart lung transplantation. Patients with extensive pleural adhesions from their underlying disease or from prior thoracic surgery or pleurodesis are at greatest risk for intraoperative and postoperative bleeding. Pulmonary artery obstruction can occur as a result of anastomotic stenosis, kinking, or extrinsic compression. In these patients, persistent pulmonary hypertension and unexplained hypoxemia may be evident. Attention to anatomic factors, such as the length of donor and recipient pulmonary arteries and division of the pericardial attachments surrounding the donor pulmonary artery, as well as awareness of the potential for a flap wrapping the bronchial anastomosis to compress the adjacent anastomosis, helps to avoid these problems. Pulmonary venous or left atrial anastomotic obstruction can also occur because of faulty anastomotic technique, kinking upon closure of the chest, or thrombus. This problem results in more severe abnormalities than pulmonary artery obstruction, including marked pulmonary hypertension and ipsilateral pulmonary edema. Diagnostic methods for these vascular anastomotic complications include routine intraoperative measurement of anastomotic gradients and transesophageal echocardiography, which is particularly helpful in assessing the left atrial anastomosis. Postoperatively, diagnostic measures include contrast angiography and ventilation/perfusion scanning. Urgent reoperation and correction of the anastomosis are indicated if clinical compromise is apparent, which is particularly likely if there is significant left atrial anastomotic obstruction. The clinical clue is a diffuse infiltrate within the transplanted lung with evidence of suffusion of the bronchial mucosa at bronchoscopy with or without blood-stained secretions, that may mimic frank pulmonary edema fluid.

About 20% of patients have PGD, characterized by severe early abnormalities of lung function, with rapidly progressive pulmonary edema, persistent pulmonary hypertension, and markedly diminished pulmonary compliance that occurs rapidly after graft implantation (Table 107-7).[101] PGD is the most common cause of early mortality after lung transplantation and is associated with long-term sequelae including BOS and increased mortality.[101]

In some patients, acute graft dysfunction is due to unsuspected abnormalities in the donor lung, such as aspiration or contusion, volume overload, or venous outflow obstruction.

Management of PGD includes evaluation of the venous anastomoses with transesophageal echocardiography to rule out a potentially correctable technical complication, and maintenance of oxygenation using mechanical ventilation and PEEP. In severe cases associated with profound hypoxemia and/or hypercapnia, ECMO should be considered early in the perioperative period. In most patients, regardless of the supportive measure required, the process resolves over several days.

Pleural space complications are not uncommon after lung transplantation, although they are usually of minor significance. Pneumothorax may occur on either the side of a lung graft or on the side of a native lung. Pneumothoraces that arise from the lung graft are of greatest concern because of the possibility that airway dehiscence communicates with the pleural space. Fortunately, this is a rare occurrence. Nonetheless, flexible bronchoscopy is always indicated for diagnostic purposes in patients presenting with this problem. In most patients, placement of a chest tube with expansion of the lung limits the process acutely. More commonly, pneumothorax is the result of rupture of a bullous lesion in an emphysematous native lung after single-lung transplantation. Conservative management with chest tube drainage is indicated. Occasionally,

TABLE 107-7 Recommended Grading System for Primary Graft Dysfunction (PGD)

Grade	Pa_{O_2}/FI_{O_2}	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Source: Reproduced with permission from Christie JD, Carby M, Bag R, et al. Report of the ISHLT Working Group on Primary Lung Dysfunction, part II: Definition. J Heart Lung Transplant. 2005;24(10):1454–1459.

pneumothoraces are noted after bilateral-lung transplantation when a significant size discrepancy exists between the donor lungs and recipient thorax. In these patients, the space resolves spontaneously in a short time and specific interventions are not required.

Pleural effusions are common after lung transplantation, particularly when a significant size disparity exists between the donor lungs and the thorax. Management of these effusions is best done conservatively, with diuretic therapy and dietary salt restriction. Invasive measures, such as thoracentesis and tube drainage, are indicated only for enlarging effusions, particularly those that impact ventilatory function, and for large effusions that persist for more than 4 weeks after surgery.

The frequency of airway complications following lung transplantation has diminished in recent years. Bronchial ischemia is the most common cause of postoperative airway complications. The most common methods of lung transplantation do not provide direct revascularization of the bronchial arterial circulation, and the donor bronchus must rely entirely on collateral perfusion from the pulmonary circulation in the initial postimplantation period. Airway ischemia at this time may lead to mucosal ulceration followed by progressive mural necrosis. Localized bronchomalacia is frequently present adjacent to this region. A spectrum of abnormalities, ranging from anastomotic dehiscence to submucosal fibrosis, may occur as a result. Most commonly, partial anastomotic dehiscence occurs, followed by formation of granulation tissue and eventually some degree of anastomotic stenosis.

The reduced incidence of these complications has been attributed to methods of surgical anastomosis that limit the length of the donor bronchus, minimizing the amount of airway for which collateral perfusion is required. Most anastomotic techniques emphasize trimming the donor bronchus to within two rings of the upper-lobe orifice and the preservation of peribronchial tissues containing the collateral circulation. Telescoping the bronchi and covering the anastomosis with vascular tissue may be useful adjunctive measures. The effect of improved methods of lung preservation and of more specific immunosuppression on the decrease in airway complications is difficult to quantitate, but these factors are probably of some importance in the reduced incidence of this problem.

The overall incidence of airway complications in all lung transplant patients is 5% to 15%. In approximately half of these patients, the diagnosis is made from endoscopic surveillance alone, and healing occurs without further treatment or secondary complication. In the rest, the airway complication requires more specific management and may lead to secondary complications. Of these patients, 70% require anastomotic dilatation or stent placement and 20% develop a bronchopleural fistula that requires a chest tube and perhaps reoperation. Death due to extensive airway necrosis or secondary infectious complications occurs in about 10% of patients who develop symptomatic airway complications. Successful management of early strictures does not limit survival.

Atrial dysrhythmias are common in the early postoperative period, as with other types of cardiothoracic surgery, and are managed in a similar fashion. Transplant patients are also prone to significant gastrointestinal complications, whose manifestations may be obscured by the anti-inflammatory effects of immunosuppressive therapy. Hepatobiliary and pancreatic complications are especially common after intrathoracic transplantation, particularly when CPB has been required. Postoperatively, continued surveillance of pancreatic exocrine function, bilirubin, and liver function tests is indicated to allow prompt diagnosis and intervention for specific abnormalities. In view of the surgical stress and use of corticosteroids in these patients, all patients should receive H_2-blocking agents or proton pump inhibitors postoperatively to prevent upper gastrointestinal hemorrhage. Gastroparesis and pseudo-obstruction are common complications as is distal intestinal obstruction syndrome (DIOS) in patients with cystic fibrosis. Preventative strategies designed to promote bowel function are critical in this group. A prior history of DIOS is the greatest risk factor for the development of this complication post transplantation.

INFECTIOUS COMPLICATIONS

Lung transplant patients have several unique attributes that account for a rate of infectious complications that is higher than the rate for other transplant recipients. Before implantation, the donor lung may contain significant pathogens, owing to the changes in lung defense mechanisms that follow intubation and brain death. After the transplant, the lung allograft continues to be exposed both to the external environment and sites in the upper respiratory tract, such as the sinuses, that may contain significant pulmonary pathogens. Finally, the lack of a cough reflex and a disturbed pattern of mucociliary clearance in the donor lung after the transplant predispose to pulmonary infection. An aggressive approach to the evaluation of all new pulmonary infiltrates is required in these patients. Flexible bronchoscopy is often helpful for proper diagnosis of pulmonary infections after lung transplantation.

Bacterial pneumonia is the most commonly acquired infection after lung transplantation. It occurs most frequently within 2 months of transplantation and is usually due to gram-negative bacilli. Potential native sources of contamination of the respiratory tract should be evaluated, particularly in patients with cystic fibrosis or recurrent pneumonia. Chronic sinusitis is common in cystic fibrosis patients and may act as a source of contamination of the lower respiratory tract. Careful otolaryngologic evaluation and sinus drainage are indicated in selected patients. Gastroesophageal reflux (GERD) is common in lung transplant recipients and can lead to recurrent aspiration pneumonia in dependent regions of the lungs.[102–109] In most patients, conservative treatment with elevation of the head of the bed and the administration of promotility agents, in addition to the H_2-blocking agents or proton pump inhibitors taken by most transplant recipients, control the reflux. Reflux of pH-neutral or alkaline gastric contents may not be detected by standard esophageal pH probe monitoring and requires impedance monitoring. Early laparoscopic Nissan fundoplication seems to have an acceptable risk–benefit for selected patients with GERD not controlled by medical means and in certain series has been shown to reduce the risk of BOS.[110–113] The mechanism may relate to prevention of direct graft damage from bile acids or by preventing exposure of cryptic antigens that may elicit an autoimmune response.[114,115] In patients who have undergone single-lung transplantation, the native lung may occasionally be a site of graft contamination or, more commonly, may become the site of pneumonia or a lung abscess. Standard therapy is recommended for such cases, although a localized area of anatomic abnormality in the native lung (e.g., focal bronchiectasis) may require surgical excision if it proves to be the source of recurrent infection.

Viral infections can be a major source of morbidity or mortality for lung transplant patients. Previously, HSV infection was an occasional cause of tracheobronchitis or pneumonitis following lung transplantation. As stated above, the use of prophylactic acyclovir, ganciclovir, or more recently valganciclovir has substantially reduced the incidence of these infections. Community-acquired respiratory viruses represent a clear and present danger to the survival and quality of life of lung transplant recipients. Influenza in particular may carry an excess mortality so yearly vaccination is recommended despite the acknowledgment that seroconversion may only occur in 60% to 70% of subjects.[116–120] Other community-acquired respiratory viruses include the family of paramyxoviruses comprising respiratory syncytial virus (RSV), Parainfluenza 1,2,3, and the newly described human metapneumovirus, all of which can cause pneumonitis and bronchiolitis. RSV, human metapneumovirus, and influenza are more frequently identified in lung

transplant patients during the winter and early spring months but parainfluenza can occur all year round. Treatment of RSV has evolved at some centers to include both intravenous and oral ribavirin.[121–123] Although successful treatment of the acute disease has been reported, a major issue remains regarding the potential for later development of obliterative bronchiolitis following RSV as well as other viral respiratory tract infections.[124] The cost, complication rate, and cumbersome nature of RSV therapies have stimulated a search for alternative measures such as the recently described use of an inhaled small mRNAi molecule.[125]

CMV, a member of the human herpes virus family, is the second most frequent cause of infection in the lung transplant patient and the most important opportunistic infection that occurs in these patients.[46,74,76,126,127] Following infection with CMV, the virus remains in a latent state in the body; evidence of the infection can be identified from a positive serologic assay demonstrating anti-CMV antibodies. Approximately, 80% of adults are seropositive for CMV. Immunosuppression can cause reactivation of the latent virus and shedding of CMV into both the urine and sputum. Viremia may also be detected. CMV infection of a lung transplant recipient can occur either from reactivation of a recipient's latent virus or direct transmission to the patient of latent virus in the donor lung. Direct transmission, which occurs by the transfusion of blood products obtained from seropositive donors into seronegative recipients, has been essentially eliminated by administration of blood products only from seronegative donors to seronegative recipients.

The incidence of CMV infection in the lung transplant recipient is related to the serologic status of both the donor and recipient.[128] Recipients who are seronegative for CMV and receive seronegative lungs should not develop CMV infection, provided they are protected from transmission of the virus by blood transfusion. Conversely, seronegative recipients who receive lungs from a seropositive donor are at high risk for primary infection, which in the absence of preventive measures can lead to life-threatening pneumonitis and systemic disease. Recipients who are seropositive for CMV are at lower risk for serious CMV disease in the posttransplant period because of their preoperative immunity; nonetheless, they are at risk for both infection by the donor strain (if the donor is seropositive) and reactivation of their own latent strain.

The most serious form of CMV disease that threatens the lung transplant recipient is pneumonitis in the lung graft. This is an invasive infection, with evidence of viral-induced cytotrophic changes in the pulmonary parenchyma in addition to the presence of CMV in serum (Fig. 107-4). Other manifestations of CMV disease include hepatitis, encephalitis, retinitis, and enterocolitis as well as CMV syndrome (fever, malaise, and viremia without organ-specific signs or symptoms). The treatment of choice for CMV disease is ganciclovir 5 mg/kg intravenously twice a day, titrated for renal function. A viable alternative for milder presentations is oral valganciclovir at a dose of 900 mg daily titrated for renal function. Treatment with these agents is continued until CMV is shown to clear from the serum by PCR. However, CMV can be compartmentalized so that clearance from the lung may be delayed. Some centers use CMV hyperimmune globulin in conjunction with ganciclovir for severe infections but evidence documenting the benefits of combined therapy over ganciclovir alone is anecdotal. In addition to its acute impact, CMV pneumonitis in some series appears to be a risk factor for the subsequent development of BOS.

A major advance in the management of CMV has been the widespread implementation of viral prophylaxis with valganciclovir, for all patients who are at risk for CMV disease.[126] This approach has led to a marked decrease in the incidence of serious CMV disease, particularly for patients with disparate donor–recipient CMV status. Prolonged prophylaxis with valganciclovir appears to have an acceptable risk–benefit ratio but is associated with significant cost and the risk of selecting strains of resistant viruses.[48] Donor-positive/recipient-negative patients typically receive at least a year of prophylaxis while recipient-positive patients (independent of donor serologic status) typically receive a 6- to 12-month course.

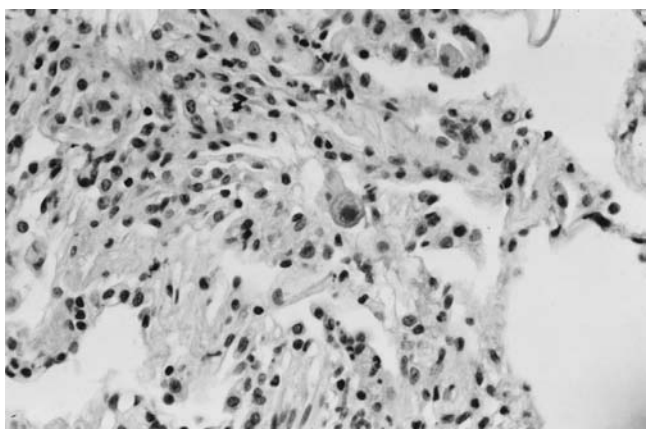

Figure 107-4 Cytomegalovirus (CMV) pneumonitis. A characteristic cytotrophic change in the pulmonary parenchyma is seen with invasive CMV infection.

■ REJECTION

Lung grafts contain a large population of immunocompetent cells, including lymphocytes and macrophages within the parenchyma, hilar and pulmonary lymph nodes, and bronchus-associated lymphoid tissue. Most of these cells are memory T cells. A prominent interaction occurs between donor and recipient immune cells during the early period after implantation. Analysis of cells obtained by BAL during the first month after transplant demonstrates donor-specific lymphocyte proliferation, suggesting in vivo mixed lymphocyte reactivity at a time when both donor and recipient immune-competent cells are present. Subsequently, rapid replacement of donor lymphocytes and macrophages occurs. By 90 days after transplantation, most of the parenchymal cells are of recipient origin and bronchus-associated lymphoid tissue has been markedly depleted.

In view of these rapid and profound changes in immune cell populations, it is not surprising that rejection is common in lung allografts and that, in the case of heart–lung grafts, lung rejection may occur more frequently than, and independent of, rejection of the heart. A protocol of routine transbronchial biopsy of the lung for identification of histologic evidence of lung rejection is usually recommended for both heart–lung and isolated-lung transplant recipients because of the likelihood of rejection that may occur with minimal clinical symptoms.[129–141] The frequency with which surveillance biopsies are performed is center dependent, and many centers stop this practice after the first year in patients who have not had significant episodes of rejection. Bronchoscopy and biopsy are, of course, also performed for clinical symptoms or for changes in spirometry.

AR is characterized by perivascular and subendothelial mononuclear cellular infiltrates (Fig. 107-5). Airway inflammation, particularly lymphocytic bronchiolitis, may also be seen as a component of AR.[142–145] Clinically, patients may manifest dyspnea, low-grade fever, hypoxemia, and pulmonary infiltrates on chest radiograph. More commonly, however, the patient is asymptomatic. Flexible bronchoscopy with BAL and transbronchial biopsy is the most useful method of differentiating AR from infection. BAL is most useful in excluding infection and is not generally helpful in confirming rejection. The transbronchial biopsy is assessed with a

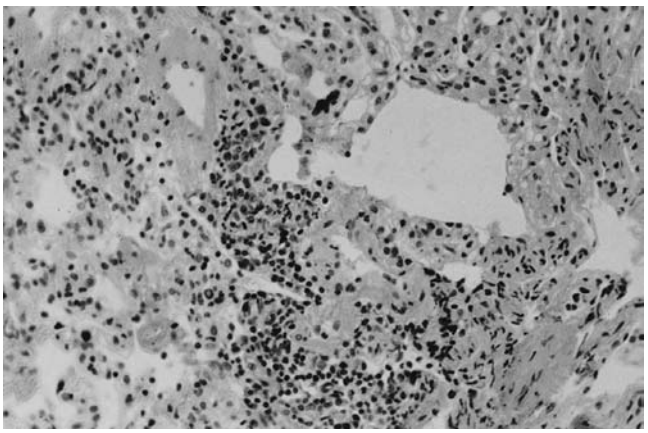

Figure 107-5 Lung allograft rejection–acute rejection, grade A2. Acute rejection is characterized by lymphocytic infiltration about pulmonary vessels. Grading of the rejection process is based on the extent of the lymphocytic infiltration into the surrounding lung parenchyma.

standard histologic grading of AR based on the degree of perivascular infiltrate, with an additional category for assessing the degree of airway inflammation (Table 107-8). Efforts are being made to improve kappa scores between pathologists grading rejection by the use of web-based digitized images based on the recognition that between pathologist grading was highly variable when compared with a central panel.[146] The severity of the perivascular process and the bronchiolar process determine the grade of AR and both processes have been identified as independent risk factors for the later development of BOS.[143]

The initial treatment of AR is administration of a brief course of high-dose corticosteroids (e.g., methylprednisolone 500–1000 mg intravenously every day for 3 days). CMV prophylaxis using oral valganciclovir is advisable for all mismatched and recipient-positive patients when antirejection therapy is initiated. In most patients, symptomatic and radiographic improvement is seen within 48 hours. Thereafter, the maintenance dose of steroids is usually increased for several weeks and then slowly reduced to maintenance levels. Repeat transbronchial biopsy to confirm resolution of the AR also allows the detection of other secondary infections or other unsuspected pathologies.[147] Occasionally, some patients with persistent findings require a second course of steroids, either as previously administered or as a slightly longer course of oral therapy. If persistent AR is identified, cytolytic therapy with OKT3 or antithymocyte globulin should be considered.

AMR is now recognized to play a significant role after lung transplantation. The ISHLT Pathology Council Working Group has outlined the histologic criteria for the determination of pulmonary AMR that are suggestive, if not wholly diagnostic of AMR.[148] Immunologic and clinical features of allograft dysfunction are needed to secure the diagnosis. The four diagnostic pillars that comprise AMR are histopathology (neutrophilic capillaritis or neutrophilic margination), C4d immunostaining involving 50% or greater interstitial capillaries, the presence of circulating donor-specific antibodies, and allograft dysfunction. Capillaritis is now the preferred term rather than the somewhat vague "capillary injury."

An important and not uncommon clinical question is how to manage the patient in whom there is discordance between the four pillars of the diagnostic criteria. Donor-specific antibodies are commonly present without demonstrable histologic change or C4d staining. Histologic change and C4d staining may be present without donor-specific antibodies raising the proposition of whether low-level phasic release of donor-specific antibodies is responsible, whether the antibodies are all tissue bound or indeed whether the presence of IgM is causing a false-negative donor-specific antibody assay. The possibility of non-HLA targets is not discounted.[149] Indeed, a number of authors have postulated that BOS is the result of humoral and cellular immune responses developed against non-major histocompatibility complex molecules expressed by airway epithelial cells of the lung allograft.[150] Irrespective of the type of antibody, allograft specificity is important and this raises the vexing question of how often to monitor for the presence of donor-specific antibodies and what the threshold for commencing treatment should be. The development of donor-specific antibodies has been shown to be associated with an inferior outcome due to the development of BOS. This has prompted some centers to initiate therapy intended to remove these circulating antibodies. There is preliminary evidence that therapy with intravenous gamma globulin combined with therapeutic plasma exchange with or without rituximab or bortezomib may be beneficial but further corroboration is required before this approach can be considered to be standard of care.[151–157]

CR in the lung may affect either the pulmonary vasculature or the airway.[158–160] Occasionally, accelerated sclerosis of the pulmonary arteries and veins may be encountered in lung allografts. These changes are analogous to the CR identified in many isolated cardiac allograft recipients. In fact, when this type of CR is identified in the lungs of heart–lung transplant recipients, it appears to correlate with similar changes in the coronary arteries of these patients.

More typically, CR in the lung is manifested histologically by obliterative bronchiolitis and consists of dense eosinophilic scarring of the membranous and respiratory bronchioles (Fig. 107-6). This is accompanied physiologically by evidence of airflow obstruction as assessed by simple spirometry. Clinically, progressive dyspnea occurs, although a gradual decline in FEV_1 or in expiratory flow rates often precedes symptoms. The lung has a great deal of physiologic reserve so that by the time the patient is symptomatic the process is usually far advanced. Further progression of this process leads to worsening dyspnea and bronchiectasis with secondary

TABLE 107-8 Working Formulation for Classification and Grading of Pulmonary Allograft Rejection

A. Acute rejection—(with/without [B])
Grade A0, none
Grade A1, minimal
Grade A2, mild
Grade A3, moderate
Grade A4, severe
Grade AX, ungradable because of insufficient tissue, sampling problem, infection, tangential cutting, etc.
B. Airway inflammation—lymphocytic bronchitis/bronchiolitis
B0, no airway inflammation
B1R, minimal–mild airway inflammation
B2R, moderate–severe airway inflammation
BX, ungradable because of insufficient tissue, sampling problem, infection, tangential cutting, etc.
C. Chronic airway rejection—bronchiolitis obliterans
D. Chronic vascular rejection—accelerated graft vascular sclerosis

Source: Reproduced with permission from Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007;26 (12):1229–1242.

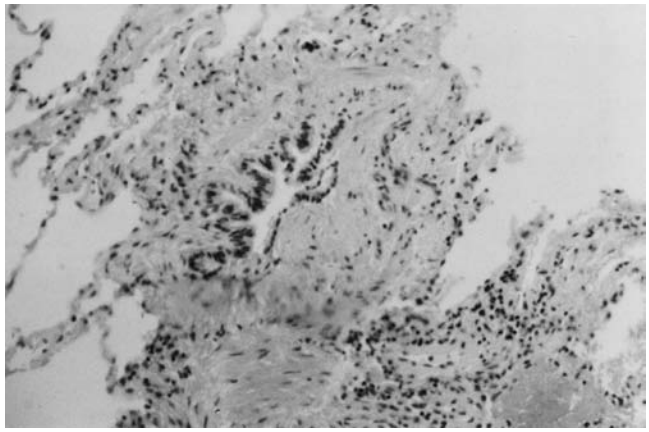

Figure 107-6 Lung allograft rejection–obliterative bronchiolitis. Chronic rejection in the lung most commonly involves the small airways, resulting in obliterative bronchiolitis. Dense submucosal scarring occurs and may completely obstruct the lumen of small airways. The process may be categorized as active or inactive, depending on the degree of associated inflammation.

infection. Although this form of CR is uncommon in the first 3 months after lung transplantation, up to 50% of patients develop it within 5 years and the mortality at 3 years after diagnosis is 40% or higher. Risk factors for the development of this process include episodes of severe AR, three or more episodes of mild AR, and, in some centers, the occurrence of CMV pneumonitis.[161–165] Lymphocytic bronchiolitis appears to be the most important risk factor, which makes sense as this process targets the same airways involved with scar tissue in established obliterative bronchiolitis.[143]

The term *BOS* has been introduced as a noninvasive means to identify patients thought to have CR of the lung involving the airways.[1] Sampling limitations of transbronchial biopsy and the risk of surgical lung biopsy result in many patients with CR not having histologic proof of obliterative bronchiolitis despite a course of progressive deterioration. Therefore, the diagnosis of BOS is based on objective changes in pulmonary function and does not require histologic evidence of obliterative bronchiolitis. The severity of BOS is graded on a scale from 0 to 3 (Table 107-9) depending on the magnitude of the fall in FEV_1 from a baseline determined as the mean of the two best FEV_1 value measures (without the use of a bronchodilator) taken at least 3 weeks apart.[2] In brief, the assignation of a particular grade of BOS is made retrospectively at the time of the first of two FEV_1 measurements at least 3 weeks apart, both of which show a percentage fall in FEV_1 from the baseline value. Although some patients with BOS will remain stable within a given grade, most demonstrate evidence of disease progression. Some evidence suggests that augmented immunosuppression may stabilize the BOS process, particularly if initiated early in its evolution. Augmented corticosteroid therapy (including inhaled steroids), cytolytic agents, tacrolimus, and sirolimus have been used for this purpose but the level of evidence supporting efficacy of these strategies is low. The lack of a uniformly accepted therapy for BOS speaks to the lack of proven benefit of therapies. Azithromycin has shown great promise in a number of studies for patients with BOS associated with BAL neutrophilia, although at least one study found patients without a predominant neutrophil population on BAL also responded.[166–172] Azithromycin has multiple sites of action including as a prokinetic agent and anti-inflammatory agent, but it also has significant antimicrobial activity, particularly against *Chlamydia pneumonia*, which has been associated with graft dysfunction and rejection.[173–175]

Management of progressive BOS in its later stages is mostly palliative unless retransplantation is possible. At its most advanced stage, BOS may have similar features of an acquired form of septic lung disease, including the development of bronchiectasis and recurrent airway infections with *Pseudomonas aeruginosa*. Management is similar to that required for other patients with septic lung disease. Salvage therapies such as total lymphoid irradiation and extracorporeal photopheresis have met with some success but must be commenced prior to the development of terminal respiratory failure, for which only redo lung transplantation has been shown effective.[176,177] Retransplantation has been performed for a number of patients with BOS.[178] The results demonstrate significantly increased perioperative mortality for such patients. One-year survival is approximately 60% to 70% in well-chosen subjects, a rate lower than that associated with primary lung transplantation. Approximately 30% of patients surviving retransplantation develop recurrent BOS by 3 years—an incidence similar to that following primary lung transplantation.

TABLE 107-9 Staging Classification of Bronchiolitis Obliterans Syndrome

Stage	Severity	FEV_1 (% baseline)
0	Nil	>80
1	Mild	66–80
2	Moderate	51–65
3	Severe	≤50

■ NEOPLASTIC COMPLICATIONS

Immunosuppression increases the risk of development of neoplasms after lung transplantation.[179,180] The risk applies to a specific group of solid tumors, including squamous cell cancers of the lip and skin, Kaposi sarcoma, soft tissue sarcomas, carcinomas of the vulva and perineum, and hepatobiliary tumors.[181,182] Colon cancer appears to be more common in cystic fibrosis patients after transplant.[179] Transplant recipients are not at increased risk for developing the more common cancers encountered in the general population, such as carcinoma of the lung, breast, or prostate, and some of the newer agents, such as mycophenolate mofetil and sirolimus may have antitumor properties, although they have yet to be studied long term to determine whether they will reduce malignancy-related mortality.

The most common malignancy seen after lung transplantation is a type of B-cell lymphoid proliferation known as PTLD. PTLD represents a morphologically diverse group of polyclonal lymphoid proliferations. The pathogenesis of PTLD appears to be related to EBV infection of B lymphocytes that are free to proliferate as a result of the recipient's immunosuppression.[97,183] Clinically, a distinction can be made between patients presenting with PTLD within 1 year after transplantation and those presenting with PTLD at later times. Patients presenting early tend to have disease localized to the allograft that responds to a temporary reduction in immunosuppression; their long-term prognosis is excellent. Patients who present after 1 year often have extrapulmonary or disseminated disease that does not respond to reduced immunosuppression and requires tumor-specific therapies to control. The mortality from lymphoma in these patients is 50% to 60%. Epstein–Barr virus seronegative recipients, particularly those treated with cytolytic induction therapy, are at highest risk for developing PTLD.[95] Of interest is that the use of valganciclovir and ganciclovir for prophylaxis against CMV disease in lung transplant patients may also help to control the incidence of PTLD, since these agents also have significant activity against EBV. Rituximab and chemotherapy have been shown to be effective in EBV-positive patients with PTLD who fail or do not tolerate reduction in immunosuppression. Rituximab is well tolerated

and is considered first-line therapy for CD-20 positive tumors. In contrast, chemotherapy is associated with marked toxicity and appreciable mortality but may induce an enduring remission.

RESULTS

The success of lung transplantation is assessed by both survival and functional metrics, as discussed below.

SURVIVAL

Early mortality following lung transplantation has decreased significantly over the past decade. The cause of this reduction is probably multifactorial—that is, the result of technical improvements in the procedure, of improved recipient selection and preoperative management, and increasing experience in perioperative management of these patients. In the ISHLT database, 90-day mortality following lung transplantation is 10%. Short-term mortality after heart–lung transplantation is usually slightly higher. PGD is the major cause of early mortality followed by infection.[101,184,185]

Longer-term survival data indicate a cumulative survival rate above 80% at 1 year. Survival curves vary significantly at 1 year, depending on the disease for which transplantation was performed.[4] Patients with emphysema and those with cystic fibrosis appear to have a survival advantage over patients with pulmonary fibrosis at this time point. Beyond the first year, BOS begins to have a significant impact on survival, leading to an overall survival rate of only approximately 65% at 5 years.[4] Causes of death in this period include infection and BOS, which can be identified in up to half of the patients who survive to 5 years. Malignancy, usually PTLD, is the third most common cause of late mortality following lung transplantation.

FUNCTIONAL RESULTS

Most patients surviving lung transplantation experience a highly significant improvement in their functional capability over their preoperative state. Typically, patients can resume an exercise program without oxygen supplementation by 6 weeks after transplantation. However, the occurrence of severe PGD may delay full recovery for 2 to 3 months. Survivors of severe PGD are frequently left with significant functional deficits, though recovery of normal allograft function is possible.

Improvements occur regardless of the native disease that led to transplantation. Unless BOS occurs, functional capacity based on the standards of reproducible exercise testing remains stable for at least 3 years. Controversy exists over the potential functional benefit of single-lung transplantation as compared to the bilateral procedure for younger patients with emphysema and most centers now offer bilateral transplantation to this group.[53,186,187] Although the results of spirometry are obviously better in bilateral recipients, exercise tolerance is similar in the two groups.

RETRANSPLANTATION

Pulmonary retransplantation has been undertaken with increasing frequency in recent years.[188] Retransplantation has been used either as a method to correct an acute complication, such as graft failure or severe bronchial dehiscence, or as a treatment for a chronic process in the graft, such as BOS or airway stenosis. The benefits of emergent retransplantation for early, acute complications appear very limited while patients transplanted for BOS generally do well, albeit with slightly lower survival rates compared to primary transplantation. At the present time, BOS is the most common indication for retransplantation. Novick described the largest pooled data series but many centers have reported individual results with variable success rates.[189–203] Ipsilateral single-, contralateral single-, and bilateral-lung transplantation all have been used for retransplantation following initial single or bilateral transplantation; the superiority of one approach over another has not been demonstrated. These are technically challenging procedures, with a surgical mortality of nearly 20%. Factors contributing to a more favorable outcome include retransplantation beyond the first 30 days, an ambulatory status before retransplantation and prior institutional experience with retransplantation. In the early days of retransplantation, the long-term results of retransplantation were far worse than those of initial lung transplantation. However, results have improved so that 1-year survival is now about 70%.

SUMMARY

Lung transplantation is now an established therapy for advanced lung diseases for which no other therapy is applicable. A shortage of donor organs, however, remains the most significant obstacle to wider use of this method of treatment. Nevertheless, there are now almost 10,000 living recipients within the United States alone, which is a testament to the growth of the discipline and the durability of the outcome in selected recipients. There are now a number of long-term survivors who continue to enjoy good health and an excellent quality of life, which no other therapy could have provided. Techniques of donor lung preservation and implantation allow ischemic intervals of 6–8 hours for reasonable postoperative function, with the hope of extended periods afforded by the newly developed technique of ex vivo lung perfusion. Surgical mortality has declined considerably over the years. Functional results in survivors of the operation are excellent. PGD and infection remain significant causes of morbidity and mortality in both the early and late postoperative periods. The most significant impediment to long-term survival is the development of chronic allograft dysfunction, often manifested as BOS, in almost half of the patients by 5 years after transplantation. Further measures to prevent and manage BOS and other forms of CR are critical to improving long-term survival rates following lung transplantation.

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PART 16

Neoplasms of the Lungs

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CHAPTER 108

Genetic and Molecular Changes in Lung Cancer: Prospects for a Personalized Pharmacological Approach to Treatment

Howard Li
Jeffrey A. Kern

INTRODUCTION

Lung cancer is the most common cause of cancer-related death in men and women worldwide, responsible for over 1 million deaths annually.[1] Each year, more people die of lung cancer than of the next three leading causes of cancer death combined: breast, colon, and prostate cancer. Despite advances in surgical techniques and combined therapies, lung cancer remains a disease with a dismal prognosis. Although 1-year survival has improved over the past few decades, overall 5-year survival has remained relatively unchanged at 12% to 16% over the past 30 years.[2] These data underscore the need to develop new diagnostic modalities and therapeutic approaches to target lung cancer.

Lung cancer therapy is in the midst of a revolution toward personalized therapy. A key discovery in the past decade has been that some lung cancers harbor specific mutations that are essential for malignant growth (i.e., "driver mutations"), which lead to gain of function of oncogenes or loss of function of tumor suppressor genes (TSGs). In contrast, lung cancers also harbor mutations that are functionally insignificant (i.e., "passenger mutations"). While clearly promoting the oncogenic state, driver mutations are also commonly associated with "oncogene addiction," or dependency of some cancers on one gene for the maintenance of the malignant phenotype. These dependencies, which are specific to an individual's cancer, are absent in normal cells. Inhibition of "druggable" proteins coded for by driver mutations, such as the BCR-ABL fusion protein with imatinib in chronic myelogenous leukemia or human epidermal growth factor receptor 2 (HER2)/Neu with trastuzumab in breast cancer, are prime examples of successful therapeutic targeting of critical signaling nodes in cancer.

Historically, nonsmall cell lung cancer (NSCLC) has been classified histologically as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, and various chemotherapeutic regimens have been used to treat different histological subtypes. But with the realization that NSCLC is a collection of diseases that are identifiable by specific molecular abnormalities, personalized therapy became a goal – and now a reality – for patients with NSCLC. Between 1980 and 2000, NSCLC driver lesions that were investigated included mutations in the Kirsten rat sarcoma viral oncogene homolog *(KRAS)* and protein 53 *(p53)* genes, loss of specific chromosomal loci, loss of heterozygosity, and DNA methylation of TSGs. In 2004, driver mutations in the epidermal growth factor receptor *(EGFR)* gene, a membrane-bound receptor tyrosine kinase (RTK) that regulates cell growth, were discovered in NSCLC, especially in adenocarcinomas.[3–5] These *EGFR* driver mutations resulted in a receptor with deregulated signaling driving cell growth and the oncogenic phenotype, but also led to a cellular dependence on EGFR RTK signaling. Thus, these mutations were strongly associated with therapeutic sensitivity to tyrosine kinase inhibitor (TKI) drugs that inhibited the tyrosine kinase (TK) function of EGFR. In 2007, the existence of the echinoderm microtubule-associated protein-like 4 *(EML4)* translocation to the anaplastic lymphoma kinase *(ALK)* gene resulting in an *EML4-ALK* fusion gene was discovered in NSCLC.[6] As with EGFR, this translocation resulted in deregulated TK signaling by ALK, again driving cell growth and the oncogenic phenotype, as well as a cellular dependence on EML4-ALK signaling. Targeting the TK domain of ALK with ALK inhibitors has been found to be highly effective in lung cancers that have this translocation.

The observation that the response rates with EGFR TKIs are higher in never smokers than in smokers with advanced NSCLC led to the realization that lung cancer in never smokers is a distinct disease from tobacco-associated lung cancer, with unique molecular and biological characteristics. Tobacco components promote lung carcinogenesis through the accumulation of mutations in key genes in the growth regulatory pathways, leading to uncontrolled cellular proliferation and tumorigenesis. Although tobacco use is the oldest and the most well-established risk factor for lung cancer, lung cancer can also occur in patients who have no history of smoking. A "never smoker" is commonly defined as an individual who has smoked less than 100 cigarettes over his or her lifetime.[7] The World Health Organization estimates that 25% of lung cancer worldwide occurs in never smokers,[8] but in Western countries this percentage is closer to 10% to 15%.[7,9–11] Histologically, the most frequent type of lung cancer in never smokers is adenocarcinoma.[7] In all series of never smokers, lung cancer is much more frequent in women than in men, and generally occurs at an earlier age.[7,9,12–14] Although lung cancer in never smokers occurs worldwide, geographic and ethnic variation is striking, with 30% to 40% of Asian patients with lung cancer having never smoked, compared with 10% to 20% of Caucasians.[7,15–17] In the United States, African American never smokers have greater incidence and mortality rates of lung cancer compared with Caucasian never smokers.[15,18] As the molecular drivers in lung cancer have been identified, it has become clear that driver mutations in never smokers are distinct from those in smokers. For example, patients with lung cancer who have never smoked are more likely to have *EGFR* gene mutations and *EML4-ALK* gene fusions, and have better response to inhibitors of these pathways than do patients with tobacco-associated lung cancer. Moreover, in patients with NSCLC, the average mutation frequency is more than 10-fold higher in smokers than in never smokers.[19] Thus, it is clear that lung cancer in never smokers is a very different disease than that seen in tobacco-associated lung cancer (Table 108-1).

These discoveries illustrate that molecular biological findings can be directly linked to the development of novel chemotherapies and thereby improve the survival rates of lung cancer patients. As new pathways and mechanisms that drive lung cancer are identified, existing agents that have not been previously considered for lung cancer can now be tested, or new drugs targeting the affected pathways can be developed. These discoveries allow a patient's therapy to be individualized to the molecular elements that drive their disease

TABLE 108-1 Clinical and Molecular Characteristics of Lung Cancer in Smokers and Never Smokers

	Smokers	Never Smokers/ Light Smokers
Age	Older (>60)	Younger (<60)
Gender	Male > Female	Female > Male
Ethnicity	Caucasian predominant	East Asian > Caucasian
Histological subtype	All	Adenocarcinoma
Associated mutations/ alterations	KRAS, PIK3CA, RB, p53	EGFR, EML4-ALK

and treatment with agents that best target the characteristics of their cancer, potentially offering higher response rates and improvements in survival. Because these therapies are targeted to mutations that are only present in cancer cells, normal tissues are relatively unaffected, resulting in fewer side effects. However, hundreds of mutations occur in a cancer cell and not all of them are functionally important or suitable targets for personalized therapy. To improve the chances of success in the development of personalized medicine for lung cancer, we need to identify a functionally important target or pathway, a biomarker to identify and follow therapeutic response, the appropriate therapeutic end point, and the mechanisms of resistance to personalized therapy, both primary and acquired.

REGULATION OF CELL GROWTH AND SURVIVAL

Lung cancer results from the deregulation of cellular processes that control cell cycling and death, allowing unrestricted cell growth. Dysfunctional signaling pathways and proteins that promote carcinogenesis include membrane-bound RTKs such as EGFR, guanosine triphosphatases (GTPases) such as RAS, and nuclear proteins that contribute to cell mitosis and abrogate the appropriate apoptotic (programmed cell death) pathway such as Myc and p53, respectively.

MEMBRANE-BOUND RECEPTOR TYROSINE KINASES

Membrane-bound RTKs share a common general structure composed of an extracellular region that contains a ligand-binding domain, an extracellular juxtamembrane region, a hydrophobic transmembrane domain, a cytoplasmic TK domain, and a cytoplasmic tail with tyrosine residues that serve as sites for receptor phosphorylation (Fig. 108-1). Ligand-binding results in activation of the receptor's TK domain, leading to phosphorylation of the receptor's tyrosine residues. This, in turn, results in recruitment of signaling molecules to the phosphorylated tyrosine residues and coupling to downstream effectors, eventually leading to biological responses. RTK activity in nonmalignant cells is normally under tight temporal and spatial regulation by the receptor and its ligand, which act as safeguards against unwanted activation. Driver lesions in the membrane-bound RTKs result in deregulated signaling or in a receptor that cannot be shut off. RTK activation in cancer may occur via overexpression of wild-type receptor due to gene amplification (resulting in excess signaling), excess ligand production, ligand overstimulation, activating mutations, translocations resulting in activated fusion proteins, or reduced receptor downregulation.

The prototypical RTKs involved in lung cancer are members of the ErbB family. The ErbB family of RTKs includes ErbB1 (EGFR; HER1), ErbB2 (HER2/Neu), ErbB3 (HER3), and ErbB4 (HER4). In the lung, these RTKs are expressed by the pulmonary epithelium (e.g., alveolar type II cells and bronchial cells) and fibroblasts. Members of the epidermal growth factor (EGF) family of peptide hormones serve as ligands for ErbB RTKs, and include EGF, transforming growth factor-α, betacellulin, and epiregulin for ErbB1; and the neuregulins for ErbB3 and ErbB4. Ligand-binding activates the receptor and multiple intracellular signaling pathways that govern fundamental cellular processes including proliferation, cell migration, metabolism, and survival. For example, phosphorylation of ErbB RTKs results in activation of growth factor receptor–bound protein 2 (Grb2) and Son of Sevenless (SOS), which ultimately leads to phosphorylation and activation of RAS. Activation of the RAS/RAF/MEK/extracellular signal–regulated kinase (ERK) pathway leads to cell proliferation. In contrast, activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway by ErbB RTK signaling results in prolonged cell survival via the expression of mitochondrial antiapoptotic proteins. Thus, deregulation in an RTK pathway can give a selective growth and survival advantage to a cell, resulting in clonal expansion and tumorigenesis. Sequencing a patient's lung cancer for *EGFR* or *ErbB2* gene mutations can identify specific alterations in this pathway, allowing the use of targeted chemotherapy agents.

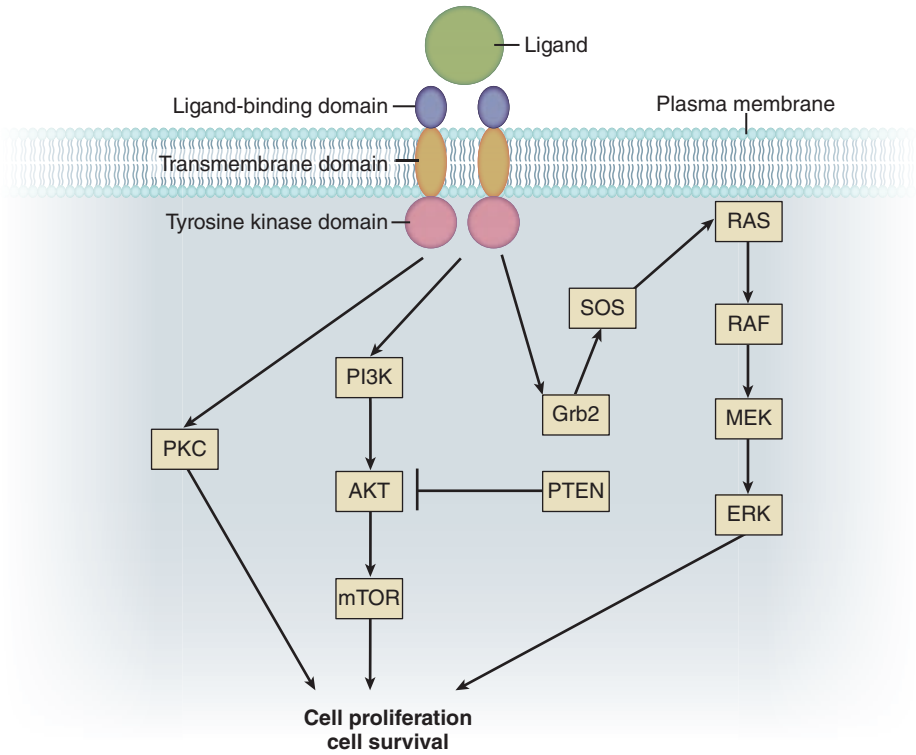

Figure 108-1 Simplified schematic of receptor tyrosine kinase (RTK) and downstream signaling pathways. Binding of ligand to the RTK leads to activation of the RAS/RAF/MEK/ERK signaling cascade, which is involved in cell proliferation. Similarly, RTK phosphorylation can also signal through the PI3K/AKT/mTOR pathway, which is involved in cell survival.

■ INTRACELLULAR KINASES AND TARGETS: RAS/RAF/MEK/ERK PATHWAY

Downstream of membrane-bound RTKs is the RAS/RAF/MEK/ERK pathway, which is a pivotal intracellular signaling pathway that transmits RTK signals to the nucleus via a cascade of specific protein phosphorylation (Fig. 108-1). When activated, ERK translocates to the nucleus, where it induces regulatory proteins such as the nuclear transcription factors Elk-1, Fos, Jun, activator protein 1 (AP-1), and Myc, which regulate genes that play key roles in proliferation, angiogenesis, metastasis, and chemotherapy resistance.

RAS

The *RAS* family of oncogenes includes neuroblastoma RAS viral oncogene homolog *(NRAS)*, *KRAS*, and Harvey rat sarcoma viral oncogene homolog *(HRAS)*. *KRAS* is the gene that is most commonly involved in lung cancer. *RAS* genes encode a family of membrane-bound GTPases, or G proteins, whose signaling regulates cell growth, differentiation, and apoptosis. Similar to RTKs, G proteins can be thought of as "on/off switches" for signaling (Fig. 108-2). In the "off" state RAS is bound to the nucleotide guanosine diphosphate (GDP), while in the "on" state it is bound to guanosine triphosphate (GTP). A phosphate group is then transferred from GTP to a RAS effector molecule, activating the downstream signaling process. The remaining GDP is incapable of signaling, and thus puts the RAS complex in an "off" state. Activation and deactivation of RAS and other small G proteins are thus controlled by cycling between the active GTP-bound and inactive GDP-bound forms. Activated RAS stimulates RAF protein kinases, which in turn initiates the MEK cascade leading to ERK activation and ultimately activation of transcription factors that regulate cell cycle progression. Other effectors of activated RAS include signal transducer and activator of transcription (STAT) and PI3K signaling cascades.

Approximately 20% to 30% of NSCLC harbor activating point mutations in *RAS* genes.[20–23] Mutations occur most frequently in the *KRAS* gene (90%), specifically in codons 12, 13, and 61.[24] These mutations result in compromised GTPase activity, causing mutant RAS protein to favor its active GTP-bound state. Therefore, mutant RAS protein results in continuous signaling even in the absence of growth factor stimulation, conferring a proliferative advantage to tumor cells.

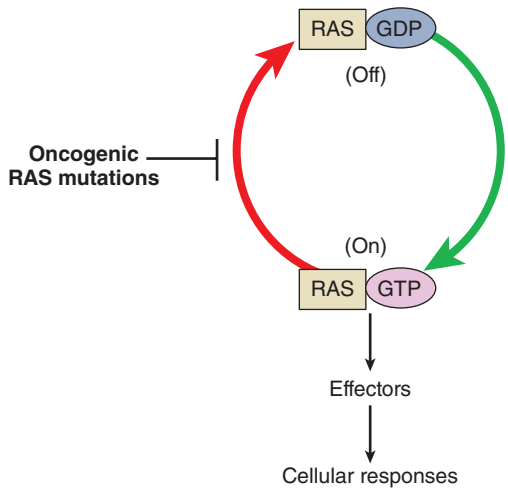

Figure 108-2 Activation cycle of Ras proteins. Growth factor stimulation leads to activation of RTKs, which causes the adaptor protein growth factor receptor–bound protein 2 (Grb2) to bind to Ras and recruit Son of Sevenless (SOS), which stimulates the conversion of Ras from the inactive guanosine diphosphate (GDP)-bound form to the active guanosine triphosphate (GTP)-bound form. Stimulation of Ras activates a mitogen-activated protein kinase cascade, leading to cell growth and differentiation. Oncogenic Ras mutations result in compromised GTPase activity, causing mutant RAS to favor its active GTP-bound state. Therefore, mutant RAS results in continuous signaling even in the absence of growth factor stimulation, conferring a proliferative advantage to tumor cells.

RAF

Next in the RAS signaling cascade is RAF, which is a family of serine–threonine kinases that includes A-RAF, B-RAF, and RAF-1 (also known as C-RAF). Although RAF is activated by RAS, activation can also occur independently of RAS through other activators such as Src, c-Jun NH2-terminal kinase, interferon-β, protein kinase C-α (PKC-α), or through dimerization between RAF isoforms. Activating mutations of the *B-RAF* gene have been reported in up to 3% of NSCLC tumors, most of which are adenocarcinoma.[25,26]

ERK/MEK

To date, no activating mutations have been identified in *ERK* or *MEK* genes. However, activation of ERK/MEK signaling is a result of upstream pathway activation, and tumor cells often have coactivation of ERK/MEK and either RAS or RAF.[27]

■ SERINE–THREONINE KINASES

Membrane-bound RTKs also couple to serine–threonine kinases, which are a second class of regulatory molecules (Fig. 108-1). These enzymes also function through phosphorylation and subsequent activation of their substrate, but unlike RTKs, they phosphorylate serine and threonine residues instead of tyrosine.

Protein Kinase C

Protein kinase C (PKC) is a major component of downstream signaling pathways activated by various RTKs, including VEGF receptor (VEGFR), EGFR, and c-MET. PKC transduces signals that initiate cellular events important for carcinogenesis, including cell growth, cell cycle progression, drug efflux, apoptosis, and angiogenesis. PKC-α and PKC-β isoforms are highly expressed in approximately 20% of NSCLC tumors.[28,29]

PI3K/AKT/mTOR

The PI3K pathway is a complex pathway with numerous feedback loops that is fundamental for cell development, growth, and survival. Activation of the PI3K pathway is also important in the development of lung cancer. Many cell surface receptors activate second messengers that in turn activate PI3K. In addition, activation of the PI3K pathway can occur through loss of phosphatase and tensin homolog (PTEN), a lipid phosphatase that inactivates phosphatidylinositol (3,4,5)-triphosphate (PIP3). Loss of PTEN expression by immunohistochemistry or quantitative real-time polymerase chain reaction (PCR) occurs in up to 73% of NSCLC patients.[30–33] PI3K generates phosphorylated phosphatidylinositides (e.g., PIP3) that bind to phosphoinositide-dependent kinase, which subsequently phosphorylates AKT at the threonine 308 residue. The resultant activation of AKT in this pathway promotes cell survival through inhibition of apoptosis and promotion of cell cycle progression, and leads to phosphorylation of mammalian target of rapamycin (mTOR), which is a serine–threonine kinase that mediates cell growth and proliferation.

By sequencing *RAS*, *RAF*, *PI3K*, *mTOR*, and *PTEN* genes, a specific mutation in this signaling pathway can be identified, leading to tumor-specific targets for personalized therapy. In addition, knowledge of where driver mutations occur in a signaling pathway is critical to define appropriate therapy. For example, identification of a *KRAS* driver mutation would suggest that therapy targeted to

molecules upstream of KRAS, such as EGFR, HER2, or c-MET, would be ineffective. Clinically, this has been well confirmed.

CELL CYCLE REGULATION

In nontransformed pulmonary epithelial cells, cell division is a tightly regulated process with multiple checkpoints that assess extracellular growth signals, cell size, and DNA integrity (Fig. 108-3). Cyclins and their associated cyclin-dependent kinases (CDKs) are the central machinery that control cell cycle progression. Alterations in these proteins may lead to a bypass of the checkpoints that assess a cell's readiness to divide. These are critical checkpoints, because any mutation that is not identified and corrected by DNA repair mechanisms will be incorporated into the genome through DNA replication during S (synthesis) phase. At the next replication cycle, the cell will "read" this mutation as normal and it is subsequently fixed into the cell's genome.

Rb

The product of the retinoblastoma susceptibility gene, Rb, plays a central role in the G_1-S transition, and *Rb* is considered a tumor suppressor gene. Therefore, loss of normal function of this gene removes its suppressor effect leading to cellular transformation. In its unphosphorylated state, Rb protein prevents progression from G_1 to S phase by binding the key transcription factor E2F/DP-1. Once the Rb protein is phosphorylated by the cyclin D/CDK complex, E2F is released allowing transcription of a battery of genes that regulate DNA metabolism. Mutation of the *Rb* gene can result in a protein that does not require phosphorylation and is constitutively activated. In this case, cell cycle arrest does not occur at the G_1-S transition. Alternatively, alterations in the mechanisms that phosphorylate Rb can inappropriately activate Rb, again leading to loss of the G_1-S restriction point. For example, the cyclin E/CDK2 complex is an important regulator of entry into the S phase through Rb phosphorylation. Disruption of this complex regulation by increased cyclin production or loss of endogenous cell CDK inhibitors, such as the Cip/Kip family (p21, p27, p57) and the INK4 family (p16, p18, p19), can result in unregulated progression through the G_1-S checkpoint.

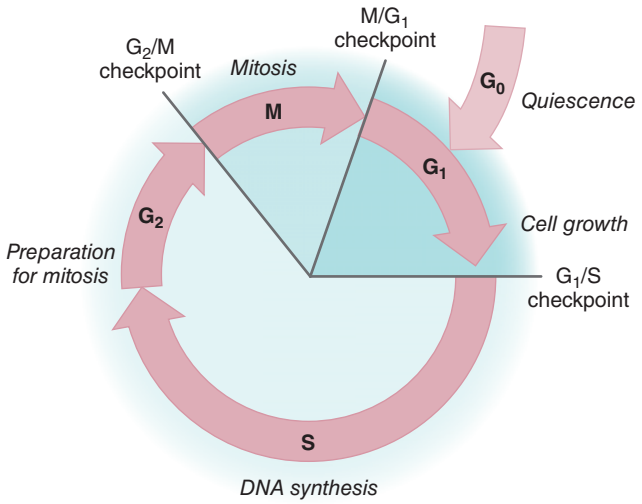

Figure 108-3 Cell cycle regulation. The cell cycle is an ordered process of events that occurs in four stages. During the two gap phases, G_1 and G_2, the cell is actively metabolizing but not dividing. In S (synthesis) phase, the chromosomes duplicate as a result of DNA replication. During the M (mitosis) phase, the chromosomes separate in the nucleus and the division of cytoplasm occurs. There are checkpoints in the cycle at the end of G_1 and G_2 that can prevent the cell from entering the S or M phases of the cycle. Cells that are not in the process of dividing are in the G_0 stage.

p53

p53 is a transcription factor that can activate the transcription of numerous genes, including the CDK inhibitor p21. Under normal conditions, p53 is rapidly degraded and therefore not detectable within the cell. Mutation of the *p53* gene results in a protein that fails to bind DNA effectively. Therefore, expression of the CDK inhibitor *p21* gene is decreased, and p21 protein production is decreased. p21 protein is not available to stop the entry of the cell into S phase, again resulting in unregulated cell cycle progression. Mutations of the *p53* gene occur in nearly 50% of NSCLC,[34,35] and abnormalities of p53 protein may play an important role in the tumorigenesis of lung epithelial cells.

Disruption of the normal regulation of cell growth lies at the heart of the events leading to lung cancer. Complex networks of regulatory factors dictate whether lung cancer cells proliferate or die. Knowledge of these regulatory networks has led to identification of key pathways involved in the development of lung cancer. A detailed understanding of the molecular changes underlying lung cancer offers the prospect of specifically targeting malfunctioning pathways to achieve more rational lung cancer therapy.

PERSONALIZED THERAPY IN LUNG CANCER

EGFR

Small-molecule agents have been developed to inhibit EGFR kinase signaling by blocking the intracellular TK domain (Table 108-2). The first of these EGFR TKIs, gefitinib and erlotinib, began testing in clinical trials in the early 2000s. Both gefitinib and erlotinib are orally administered agents that bind at the catalytic cleft of EGFR in competition with ATP, suppressing EGFR phosphorylation and downstream signaling.[36–38] Initial randomized studies in NSCLC with EGFR TKIs in combination with standard first-line platinum-based chemotherapy were all negative. However, in the TRIBUTE trial of carboplatin and paclitaxel with erlotinib or placebo, 116 patients who reported that they had never smoked had a prolongation in survival with erlotinib treatment (22.5 months) compared to placebo treatment (10.1 months, $p = 0.01$), suggesting treatment with erlotinib improved survival in never smokers.[39]

In 2004, as a result of basic research to understand the dramatically different response rates to EGFR TKI therapy, several academic groups reported the discovery of a collection of activating mutations in the TK domain of EGFR that correlated with a high likelihood of response to EGFR TKIs.[3–5] Many of the patients harboring these mutations demonstrated rapid, nearly complete reduction of their cancers that persisted for up to several years. *EGFR* gene mutations were much more commonly found in female never smokers of East

TABLE 108-2 Targeted Therapies Against Oncogenic Pathways in Lung Cancer

Gene	Drug
ALK	Crizotinib
EGFR	EGFR TKIs: erlotinib, gefitinib, afatinib
	EGFR monoclonal antibodies: cetuximab, matuzumab, necitumumab, panitumumab
MEK	AZD6244
MET	Tivantinib, cabozantinib, foretinib, crizotinib, MetMAb
mTOR	Everolimus
RAF	Sorafenib

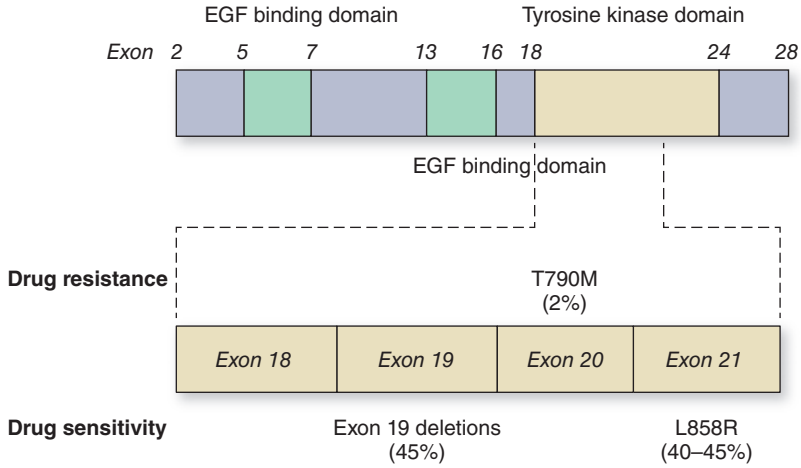

Figure 108-4 Epidermal growth factor receptor (EGFR) mutations in NSCLC. A cartoon representation of EGFR showing the distribution of exons in the epidermal growth factor (EGF) binding and tyrosine kinase domains. Exons 18 to 21 in the tyrosine kinase region where the relevant mutations are located are expanded and the most common mutations associated with drug sensitivity and drug resistance are shown.

Asian origin with adenocarcinoma histology. Whereas the incidence of *EGFR* mutations in Asians is 25% to 35%, the incidence in North American and Western European patients is approximately 15%. However, the strongest predictor of *EGFR* mutation status appears to be absent or low smoking history.[40,41]

Approximately 90% of observed *EGFR* gene mutations are either small in-frame deletions in exon 19 clustered around the catalytic site of the receptor, or an amino acid substitution from a leucine to an arginine at position 858 in EGFR (L858R), which lies within the TK activation loop in exon 21 (Fig. 108-4).[3–5,42–45] In cells harboring *EGFR* gene mutations, the mutated receptor leads to enhanced AKT signaling and downstream activation of antiapoptotic and prosurvival signals. The location of *EGFR* gene mutations within critical residues of the catalytic domain leads to altered physical structure, enhanced drug binding, and sensitivity to EGFR TKIs.[46] Other types of *EGFR* TK domain mutations have been reported. In contrast to the more common exon 19 deletions and L858R mutation, some of these minor mutations are associated with resistance to EGFR TKIs.[47–49]

The rapid and dramatic clinical responses to EGFR TKI therapy seen in patients with *EGFR* gene mutations have led to the "oncogene addiction" hypothesis,[50,51] which states that because EGFR-mutant lung cancers develop in a setting in which the mutated receptor is constantly transducing high levels of antiapoptotic signals, the cancer cells are "addicted" to EGFR kinase prosurvival signaling. As a result, sudden interruption of EGFR signaling by EGFR TKIs causes massive cell death. Another hypothesis, termed the "oncogenic shock" hypothesis,[52] states that proapoptotic signals are still present in EGFR-mutant lung cancer cells. When receptor signaling is inhibited by EGFR TKIs, both antiapoptotic and proapoptotic signals are blocked. However, antiapoptotic signals decay much more rapidly than proapoptotic signals, leading to a temporary predominance in proapoptotic signaling and cell death.

A large number of retrospective series have demonstrated that the response rate of *EGFR* mutation-positive patients to EGFR TKIs exceeds 60%,[5] which is markedly higher than the typical 20% response rate to combination chemotherapy in NSCLC.[53] Several studies have also shown that NSCLC patients harboring *EGFR* mutations survive longer with EGFR TKI therapy than wild-type EGFR patients, with median survivals of 11 to 30 months.[43,54–60] Thus, personalized therapy targeting the specific genetic changes in a patient's lung cancer is critical for improving response rates and overall survival.

Several randomized phase III trials comparing gefitinib to platinum-based chemotherapy in patients with advanced NSCLC have been reported. Although participants were not selected based on *EGFR* gene mutation status, the IPASS trial enriched its study population for subjects with *EGFR* mutations by selecting patients according to clinical factors known to be associated with higher prevalence of *EGFR* mutation: East Asian patients, adenocarcinomas, and never smokers or former light smokers.[61] The IPASS trial was designed with progression-free survival (PFS) as the primary end point to assess the noninferiority of gefitinib compared with carboplatin/paclitaxel. The study met its primary objective demonstrating noninferiority and showed superiority of gefitinib for PFS, objective response rate (ORR), and quality of life for the entire cohort. However, results depended upon the *EGFR* mutation status. For patients whose tumors contained an *EGFR* mutation, PFS was significantly prolonged with gefitinib (9.5 months) in contrast to carboplatin/paclitaxel (6.3 months). In comparison, for those without an *EGFR* mutation, PFS was significantly shorter with gefitinib (1.5 vs. 6.5 months). Two additional randomized phase III trials of patients with advanced NSCLC selected for *EGFR* mutations (either the exon 19 deletion or L858R point mutation) also demonstrated a significant increase in PFS with gefitinib compared to platinum-based chemotherapy as first-line treatment.[62,63] Similarly, a multicenter, open-label, randomized phase III trial of erlotinib versus standard chemotherapy as first-line treatment for Caucasian patients with advanced *EGFR* mutation-positive NSCLC (EURTAC) reported a median PFS of 9.7 months in the erlotinib group, compared with 5.2 months in the standard chemotherapy group.[64] These studies confirm that treatment of *EGFR* mutation-positive patients with first-line EGFR TKI therapy is superior to standard chemotherapy and represents one of the most promising advances in the field of lung cancer in recent years.

Another strategy to block EGFR kinase function in patients with NSCLC focuses on the use of monoclonal antibodies directed against EGFR. Cetuximab, a chimeric anti-EGFR monoclonal antibody, has been studied in combination with different chemotherapy protocols in both phase II and phase III trials in patients with advanced NSCLC. In the phase III FLEX trial, cetuximab added to cisplatin and vinorelbine in patients with advanced *EGFR* mutation-positive NSCLC resulted in an absolute overall survival benefit of 1.2 months.[65] Additional anti-EGFR monoclonal antibodies under study include matuzumab and panitumumab, which have been evaluated in phase II trials, and necitumumab, which is currently being evaluated in combination with chemotherapy in phase III trials.

Unfortunately, virtually all patients who initially respond to EGFR TKI therapy will develop resistance and suffer a clinical relapse. Approximately 50% of the cases of acquired TKI resistance are attributed to a secondary *EGFR* gene mutation, the threonine to methionine point mutation at amino acid 790 (T790M) in exon 20 (Fig. 108-4).[49] The threonine residue at position 790 is highly conserved across the oncogenic RTKs EGFR, ABL, and KIT, and mutations of this residue often lead to resistance to kinase-targeted drugs.[66] The T790M mutation in EGFR kinase causes drug resistance by increasing the receptor's affinity for ATP at the ATP-binding pocket, thereby minimizing the effects of EGFR TKIs.

Several second-generation EGFR TKIs have been developed with a specific focus on the T790M mutation. Typically, these are small molecules that covalently bind to the intracellular kinase domain of the EGFR protein. In addition to binding irreversibly to wild-type

EGFR, HER2, and HER4, these novel agents also bind to receptors carrying the T790M mutation. The LUX-Lung 1 trial[67] studied 585 patients with lung adenocarcinoma who had progressed after treatment with a platinum-based regimen followed by at least 12 weeks of erlotinib or gefitinib, which are criteria for acquired resistance proposed by Jackman et al.[68] Treatment with the second-generation TKI afatinib tripled PFS from 1.1 to 3.3 months, suggesting afatinib may have a role in the treatment of NSCLC patients with *EGFR* gene mutations who acquire resistance to EGFR TKIs. The LUX-Lung 3 trial investigated the efficacy and safety of afatinib compared with pemetrexed/cisplatin in patients with *EGFR* mutation-positive stage IIIB/IV lung adenocarcinoma.[69] Treatment with afatinib led to a significantly prolonged PFS versus pemetrexed/cisplatin (median 11.1 vs. 6.9 months) and significantly higher ORR (56% vs. 23%), indicating afatinib may also be a first-line treatment option in NSCLC patients with *EGFR* gene mutations.

Blocking both the intracellular and extracellular domains of the EGFR kinase ("vertical blockade") by combining a TKI and an EGFR antibody concurrently may offer an additional strategy to overcome TKI resistance. Vertical blockade of the EGFR receptor with the combination of the dual EGFR/HER2 inhibitor lapatinib and the monoclonal antibody trastuzumab has been shown to significantly improve PFS and disease control rate in HER2-positive metastatic breast cancer patients.[70] In preclinical studies, dual targeting with the EGFR TKI afatinib and the anti-EGFR monoclonal antibody cetuximab was able to induce near complete responses in T790M transgenic mouse models.[71] A phase 1 trial of afatinib and cetuximab in NSCLC patients with clinically defined acquired EGFR TKI resistance is currently ongoing. Further studies are underway to clarify the roles of second-generation TKIs and vertical inhibition in the treatment of EGFR TKI-resistant patients.

In addition to secondary resistances caused by T790M, several other mechanisms of resistance to EGFR TKIs have been described. MET protein overexpression or *MET* gene amplification was observed in up to 20% of tumor samples after treatment with EGFR TKI.[72] Cells with *MET* gene amplification are capable of maintaining AKT activation in the presence of EGFR TKIs. In these cases, inhibition of signaling by a TKI may result in the cell switching to an alternate signal pathway, undergoing a "kinase switch" to ensure their survival. In theory, kinase switching might be counteracted by concurrent blockade of EGFR and MET kinase signaling.

EML4-ALK

In 2007, Soda et al.[6] reported a new molecular abnormality involving the fusion of ALK with EML4 in lung adenocarcinoma. The fusion protein results from an inversion in the short arm of chromosome 2 that fuses the N-terminal domain of EML4 to the intracellular kinase domain of ALK, leading to constitutive activation of the ALK kinase (Fig. 108-5). In the original report by Soda and colleagues, 6.7% of unselected NSCLC patients had the EML4-ALK fusion protein. Similar to the clinical phenotype seen in patients with *EGFR* mutations, the EML4-ALK fusion protein occurs more commonly in younger patients who are never or former smokers and is predominantly associated with adenocarcinoma.[73,74] However, patients with *EML4-ALK* translocation have characteristics that distinguish them from patients with *EGFR* mutations. EML4-ALK-positive patients are younger than patients with *EGFR* mutations, with a median age of 52 years compared to 66 years.[74,75] Most reports show that *EML4-ALK* translocations are mutually exclusive of *EGFR* and *KRAS* mutations.[75–79]

In preclinical studies, the ALK kinase inhibitor TAE684 was shown to inhibit the growth of an EML4-ALK containing NSCLC cell line, both in vitro and in vivo.[6,80–83] These findings led to the testing of crizotinib, a small-molecule competitive inhibitor targeted to the ATP-binding pocket of the ALK TK. A phase 1 study of patients with EML4-ALK-positive stage III or IV NSCLC treated with crizotinib demonstrated an overall response rate of 60.8%, including three complete responses.[74] Median time to first documented objective response was 7.9 weeks. Median PFS was 9.7 months, and estimated overall survival at 6 and 12 months was 87.9% and 74.8%, respectively. These data show convincingly that ALK inhibition is effective in patients with NSCLC carrying an ALK rearrangement.

Similar to EGFR-targeted therapy, resistance to crizotinib in EML4-ALK-positive NSCLC has been reported. A patient on the original phase 1 study of crizotinib developed resistance after 5 months of therapy.[84] Deep sequencing of complementary DNA comparing *EML4-ALK* translocation before and after resistance identified two independent events in the resistant cancers: point mutation of residue 1156 from cytosine to tyrosine (C1156Y) and at residue 1196 from leucine to methionine (L1196M). In vitro, these new mutations decreased the fusion protein's sensitivity to crizotinib. Structural analysis of these mutants showed that C1156Y was close to the edge of the ATP-binding pocket. Interestingly, L1196M corresponds to the T790M gatekeeper mutation in EGFR, suggesting a common mechanism for the development of resistance in TKs. Doebele et al.[85] analyzed tissue obtained from patients with *ALK* gene rearranged NSCLC who showed radiological progression while on crizotinib, and found that mechanisms of resistance to crizotinib included secondary mutations in the TK domain of *ALK*, new onset *ALK* copy number gain, and outgrowth of either *EGFR*- or *KRAS*-mutant NSCLC. Novel inhibitors of ALK kinase are in development that can decrease ALK protein phosphorylation, induce apoptosis, and reduce cell survival in crizotinib-resistant EML4-ALK-mutant cell lines. These inhibitors represent potentially novel treatment options for patients with EML4-ALK fusion proteins that develop crizotinib resistance.

KRAS

In 1984, a human lung cancer specimen was found to contain an activating *KRAS* mutation that was not found in corresponding normal tissue.[86] Subsequently, investigators have found that 20% to 40% of NSCLC tumors harbor somatic *KRAS* mutations.[87–89] *RAS* gene mutations are found in approximately one-third of all human malignancies, with *KRAS* accounting for the majority of *RAS* mutations.[90] Whereas *KRAS* accounts for 90% of *RAS* mutations in lung adenocarcinomas, *KRAS* mutations are uncommon in lung squamous cell carcinomas.[20,21] *KRAS* mutations are more common in NSCLC tumors from smokers than from never smokers.[91] A meta-analysis of 53 studies on lung cancer assessing prognostic value of *RAS* mutation on survival found a worse survival for NSCLC with *KRAS* mutations, particularly in adenocarcinomas.[23] Because the RAS protein is a downstream effector of EGFR, *KRAS* mutations have been assessed as a primary mechanism of resistance to EGFR TKIs, and the presence of *KRAS* mutations predicts that a patient will not respond to EGFR TKIs.[92,93]

Due to the frequency of *KRAS* mutations in NSCLC, development of agents to inhibit mutated RAS proteins has been widely pursued. However, the search for RAS inhibitors has proven challenging. Whereas RAS binds GTP with picomolar affinities, the concentration of GTP in cells approaches micromolar levels.[94] Thus, targeting mutant RAS with nucleotide analogs is unlikely to be successful. Moreover, RAS does not have an accessible active site or pocket to which molecules are likely to bind, and the search for small molecules that bind to the surface of RAS has been unsuccessful. Current therapeutic approaches targeting RAS fall into three major categories: inhibition of RAS protein synthesis, alteration of RAS membrane localization, or inhibition of effector molecules downstream of mutant RAS. Although *RAS* antisense oligonucleotides can block protein synthesis in vitro, drug delivery issues have led to difficulty developing effective agents for use in humans. Considerable

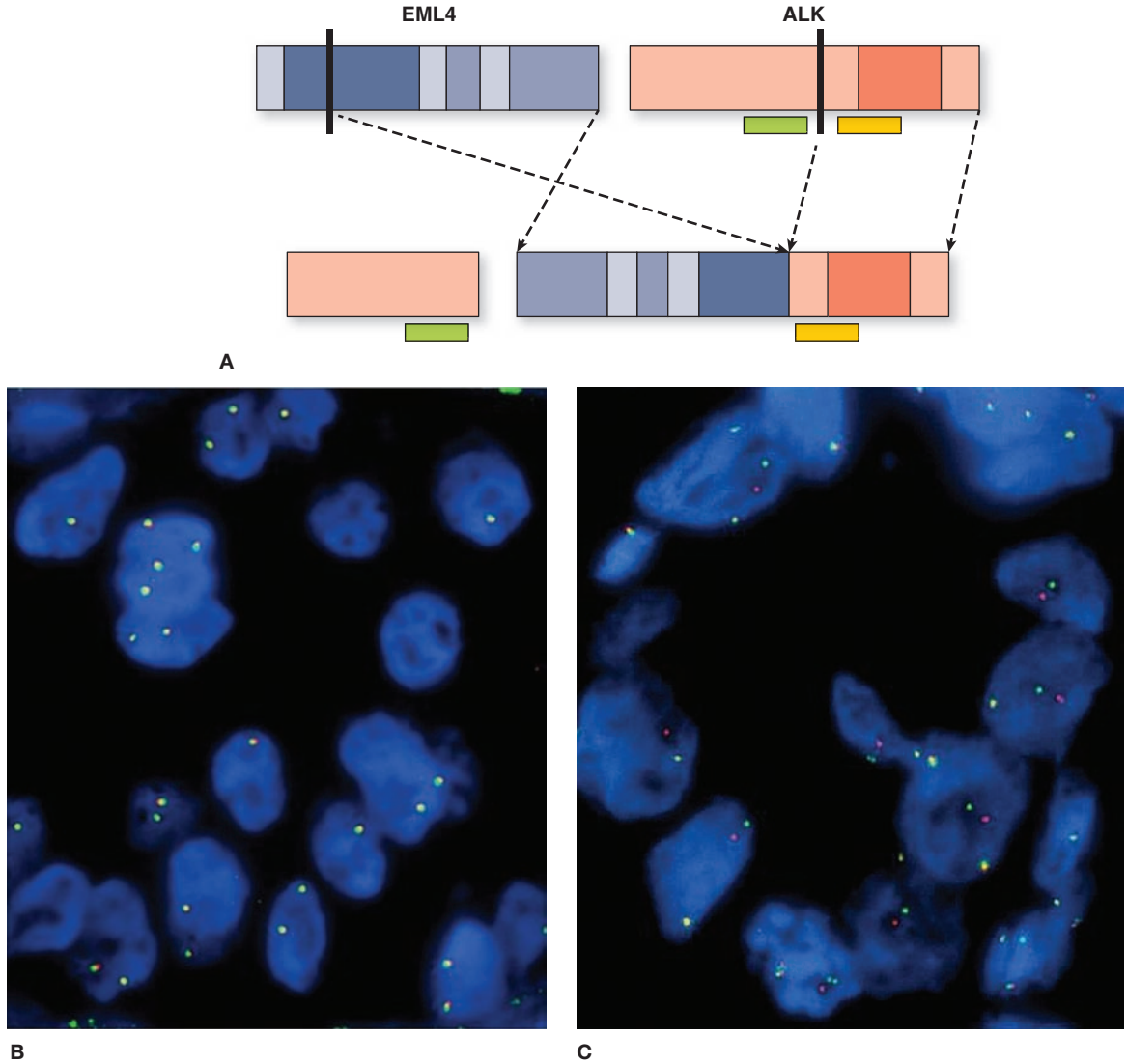

Figure 108-5 Schematic of echinoderm microtubule–associated protein-like 4 (EML4) translocation to the anaplastic lymphoma kinase (ALK) and its detection by fluorescence in situ hybridization (FISH). **A.** Both *EML4* (depicted in *blue*) and *ALK* (depicted in *red*) genes are located on the short arm of chromosome 2. A chromosomal inversion leads to *EML4-ALK* rearrangement and generation of a fusion protein. Green and orange bars represent DNA probes corresponding to the 5′ and 3′ fragments of the *ALK* gene. FISH detection of *EML4-ALK* rearrangement uses break-apart technology (ALK Break Apart FISH Probe, Abbott Molecular), which detects the adjacently located *EML4* and *ALK* genes in wild-type signals (**B,** adjacent green–orange probes) and break-apart signals caused by chromosomal inversion (**C,** separated green–orange). *(FISH images used with permission of Dr. Marileila Garcia, University of Colorado Anschutz Medical Campus.)*

research went into the development of farnesyl transferase inhibitors to alter RAS membrane localization such as farnesylthiosalicylic acid (Salirasib), which mimics the carboxy terminal amino acid of RAS and dislodges activated RAS from the membrane. However, farnesyl transferase inhibitors failed to demonstrate efficacy in clinical trials against tumors containing mutant KRAS, likely due to alternative pathways for farnesyl modification of KRAS. Two promising approaches to inhibiting KRAS that are currently under investigation involve the inhibition of downstream proteins RAF kinase and MEK. For example, sorafenib is a multikinase inhibitor of RAF, inhibiting wild-type B-RAF, oncogenic B-RAF, C-RAF, VEGF receptors 1 to 3, platelet-derived growth factor receptor-β, c-Kit, Fms-like TK 3, and rearranged during transfection protein (RET).[95] Unfortunately, clinical trials of sorafenib in unselected NSCLC patients have shown no clinical efficacy. However, in the BATTLE trial, sorafenib was active against tumors with mutated or wild-type KRAS, but had a worse disease control rate (compared with other study agents) in patients with *EGFR* mutations. MEK inhibitors are also being tested. A selective MEK inhibitor, AZD6244, showed clinical activity as second- or third-line therapy for patients with advanced NSCLC.[96] Based on preclinical data and clinical observations, multiple clinical trials are ongoing of AZD6244 for the treatment of *KRAS* and *B-RAF*-mutant NSCLC.

PI3K/AKT/mTOR

Investigators have hypothesized that PI3K signaling activity is induced by cigarette smoking before the development of lung cancer. In vitro, activation of the PI3K/AKT pathway by nicotine and a tobacco carcinogen in normal human bronchial and small airway epithelial cells has been shown to be an early event promoting cell survival.[97] Similarly, PI3K pathway activation has been identified in normal and premalignant bronchial airway epithelial cells of smokers with airway lesions.[98] Finally, inhibition of the PI3K/AKT pathway abrogates nicotine-triggered antiapoptotic

signals and blocks human lung cancer cell growth, suggesting that the PI3K/AKT pathway mediates the antiapoptotic effects of nicotine.[99,100]

AKT can be activated by amplification of upstream molecules of the PI3K pathway, directly through AKT overexpression, or overactivation of the AKT protein itself. Overexpression of PI3K and AKT has been demonstrated in primary NSCLC lung tumors and their metastases.[101] Moreover, genomic amplification of *PIK3CA* has been shown to occur in NSCLC tumors and preinvasive lesions.[102,103] However, mutations in the *PIK3CA* gene are rare in NSCLC.[103]

Targeting PI3K signaling with pharmacological inhibitors has become an important experimental therapeutic approach, and several direct PI3K inhibitors are under development. In phase I trials of patients with advanced solid tumors (including patients with advanced lung cancer), PI3K inhibitors decreased levels of phosphorylated AKT, MEK, and ERK in tumor biopsies.[104] Clinical trials of PI3K inhibitors in combination with platinum-based chemotherapy or with EGFR inhibitors are currently underway.

Another approach to targeting PI3K signaling has focused on inhibitors of its downstream target mTOR. In preclinical studies, the orally available mTOR inhibitor everolimus has been shown to have antitumor activity in both in vitro and in vivo models of NSCLC.[105] Upregulation of the PI3K/AKT/mTOR pathway is an important mechanism for resistance to chemotherapy targeting RTKs, such as EGFR TKI resistance in EGFR-mutant lung cancer and resistance to crizotinib in EML4-ALK-positive lung cancer. Thus, mTOR inhibition by everolimus is currently being studied as a therapeutic approach to overcome acquired resistance to RTK TKIs in patients with NSCLC.

MET

The MET pathway is activated in a number of human malignancies, including lung cancer. MET receptor overexpression by immunohistochemistry has been reported in NSCLC, in particular lung adenocarcinoma.[106,107] Using fluorescence in situ hybridization (FISH), the Lung Cancer Mutation Consortium reported that 4.1% of lung adenocarcinomas have *MET* gene amplification.[108] *MET* gene mutations have also been reported in human lung cancer, mainly clustered in the juxtamembrane domain, which enhance oncogenic signaling, tumorigenicity, cell motility, and migration.[109,110] MET kinase domain mutations are also somatically selected in metastatic tumors compared with the primary tumors.[111]

In preclinical studies, small-molecule MET inhibitors decrease cell viability and growth, and induce apoptosis in NSCLC cells via inhibition of MET/hepatocyte growth factor (HGF) signaling.[112–115] Although there are many MET-targeting agents under development, only one, tivantinib, is currently in phase 3 testing for advanced nonsquamous NSCLC. Tivantinib targets the MET RTK by locking the kinase in an inactive conformation. The combination of erlotinib and tivantinib prolonged PFS compared to erlotinib alone in a phase II trial of advanced NSCLC patients.[116] Interestingly, tivantinib combined with erlotinib inhibited tumor metastases in this phase II study, supporting the concept that the MET pathway plays an important role in human lung cancer metastasis.

Other MET agents include the multitargeted small-molecule kinase inhibitors cabozantinib, foretinib, and crizotinib. Since these agents also target kinases other than MET, it is difficult to determine the degree to which their efficacy is due to MET inhibition alone in lung cancer therapy. A recombinant, humanized, monoclonal antibody antagonist of the MET receptor (MetMAb) that inhibits HGF-induced MET signaling has been tested in a phase II study (ClinicalTrials.gov NCT00854308). The combination of erlotinib and MetMAb resulted in a statistically and clinically significant improvement in both PFS and overall survival compared to erlotinib alone in NSCLC patients with high MET protein expression by immunohistochemistry. Although MET-targeting agents show promise for the treatment of lung cancer, analysis of MET expression and amplification needs to be optimized and standardized.

Rb

Impairment of the Rb pathway has been shown to occur in almost all lung tumors.[117] Deregulation at any level of the Rb pathway mimics loss of Rb, leading to failure of cell cycle arrest and uncontrolled cellular proliferation. Rb protein expression varies with different lung cancer types. Whereas small cell lung cancer and large cell neuroendocrine carcinomas are characterized by loss of Rb expression, NSCLC is typically characterized by loss of p16 (an endogenous CDK inhibitor that prevents entry to cell cycle) or overexpression of CCND1 (an activator of CDK kinases that promotes entry into cell cycle), both of which lead to inactivation of the Rb pathway.[118–122]

In vitro, forced expression of p16 or constitutive activation of Rb potently inhibits cellular proliferation and can induce persistent cell cycle arrest in cancer cells.[123,124] However, reactivation of compromised tumor suppressors in the clinical setting has proven challenging. Inhibitors of DNA methylation or histone deacetylases can lead to activation of epigenetically silenced *p16*.[125] Unfortunately, these agents are cytotoxic and can lead to numerous other end points. CDK inhibitors, which prevent Rb phosphorylation, have also been studied as a way to reactivate Rb function in tumor cells, thereby inhibiting cell cycle entry.[126–128] However, these compounds are also relatively toxic due to effects on CDKs involved in normal transcriptional regulation. Finally, the optimal method to evaluate Rb pathway activity in biopsy specimens has not been standardized.

p53

Loss of heterozygosity in lung cancer cell lines and tumor samples at the location of the *p53* gene on chromosome 17p13 suggested that *p53* was likely to be involved in the pathogenesis of lung cancer. Genetic abnormality of the *p53* gene in lung cancers has been shown to be associated with poor prognosis and increased resistance to chemotherapy.[129,130] Among NSCLC tumor samples, the frequency of *p53* gene mutations is higher in squamous cell carcinomas than in adenocarcinomas.[131,132] Patients with tobacco-associated lung cancer have a higher frequency of *p53* gene mutations than patients who never smoked.[133–135] Lung cancer from smokers also shows a specific spectrum of *p53* gene mutations that is rarely observed in never smokers.[136] Although *p53* has been extensively studied as a prognostic marker in NSCLC, there is no evidence that *p53* status plays a role in the management of patients with NSCLC.

Aberrant p53 protein expression predicts clinical resistance to cisplatin-based chemotherapy in locally advanced NSCLC.[137] Similarly, tumors containing *p53* gene mutations are more resistant to ionizing radiation than those with wild-type *p53*. One strategy for therapeutic targeting of the p53 pathway is use of adenovirus-based gene therapy to introduce a copy of wild-type *p53* complementary DNA into tumor cells with mutant *p53*. In preclinical studies with lung cancer cell lines expressing mutant *p53*, *p53* replacement therapy improved responses to chemotherapy and radiotherapy.[138,139] *p53* gene therapy via bronchoscopic intratumoral injection is also being evaluated in clinical trials of patients with NSCLC.

FUTURE DIRECTIONS: EMERGING MOLECULAR MARKERS

Novel molecular alterations have been identified in a subset of NSCLC patients involving other RTKs, including ROS1, fibroblast growth factor receptor 1 (FGFR1), HER2, RET, and discoidin domain receptor 2

(DDR2).[23,140–155] These RTK mutations and gene amplifications represent excellent therapeutic targets. Inhibition of these pathways with a number of agents is being actively investigated, such as the use of the ALK inhibitor crizotinib for treatment of patients with advanced-stage NSCLC harboring *ROS1* gene rearrangements. Interestingly, *ROS1* gene fusions, *FGFR1* gene amplification, and *DDR2* gene mutations have been identified in squamous cell lung carcinomas, and kinase inhibitors directed against these molecules may represent targeted therapy for patients with squamous cell lung cancer.

Loss of heterozygosity involving several chromosome 3p regions accompanied by chromosome 3p deletions is frequently detected in NSCLC. These changes appear early in the pathogenesis of lung cancer and are found as clonal lesions in respiratory epithelium damaged by smoking. These 3p genetic alterations led to the discovery that the short arm of human chromosome 3 contains several TSGs. It has become apparent that genetic and epigenetic abnormalities of several genes residing in chromosome region 3p are important for the development of lung cancer. Tumor-acquired promoter DNA methylation is an important epigenetic mechanism for inactivation of these TSGs in lung cancer. However, which of the numerous candidate TSGs on chromosome 3p that have been identified play a key role in lung cancer pathogenesis remains unclear. Since epigenetic changes in chromosome 3p are early events in the development of lung cancer, improvements in the ability to detect acquired abnormalities of gene-specific methylation could lead to earlier diagnosis of lung cancer. Reversal of tumor-acquired promoter methylation of chromosome 3p TSGs with demethylating agents may also prove promising for the treatment of lung cancer.

MicroRNAs (miRNAs) are small noncoding, endogenous, single-stranded RNAs that regulate gene expression.[156] By regulating gene expression at the posttranscriptional level, miRNAs influence a wide variety of oncogenic pathways. Human miRNA genes are frequently located within or near chromosomal fragile sites, common breakpoints, minimal regions of loss of heterozygosity or amplification, and other genomic regions involved in cancers.[157] Accumulating evidence shows that miRNAs are profoundly deregulated in human NSCLC, and may serve as either oncogenes or tumor suppressors. These properties make miRNAs attractive targets in lung cancer therapy. However, one miRNA may target hundreds of messenger RNAs, which could lead to unpredictable side effects. Emerging data suggest that in addition to their potential use in NSCLC therapy, miRNAs may also be useful for classification and risk stratification of patients with NSCLC.[158–161] In the future, miRNAs may assist in patient selection for targeted therapy and form the basis for the development of novel therapeutics and/or early disease biomarkers.

CLINICAL PERSPECTIVE

Below are considered several important clinical aspects of molecular testing, including methods employed, the importance of adequate tissue sampling, initial studies, and acquired resistance to targeted therapy.

MOLECULAR TESTING METHODS

The identification of new genetic changes in patients with NSCLC signals a new era of personalized medicine for patients with lung cancer, in which it will be imperative to match the specific mutations of a patient's tumor with a specific therapy. An important issue to consider is which method will be used for molecular testing. Direct sequencing of PCR-amplified regions is the most common method of identifying *EGFR* and *KRAS* gene mutations. Testing for rearrangements and amplification is typically performed using FISH, but other approaches are possible, including chromogenic in situ hybridization and real-time quantitative PCR. In the future, as the cost of genome-wide screening decreases, methods such as comparative genomic hybridization and nucleic acid microarrays are likely to become commonly used techniques for molecular testing of lung cancer.

IMPORTANCE OF SATISFACTORY BIOPSIES FOR MOLECULAR TESTING OF LUNG CANCER

A satisfactory biopsy that allows for both histological characterization and mutation analysis is becoming increasingly important, both for the diagnosis of lung cancer and for molecular testing. The analytic sensitivity of an assay dictates the quantity of tumor that must be present in the tested sample. For FISH and immunohistochemical analysis, the Molecular Assays in NSCLC Working Group has recommended that a tumor tissue section should contain at least 1 to 2 mm^2 of tumor area to provide enough tumor cells for reliable interpretation.[162] FISH results should include hybridization signal counts from at least 100 to 200 tumor cells. Larger amounts of tissue may be required to ensure that sufficient DNA is obtained for mutational analysis. However, the minimum number of cells needed for mutational analysis by direct sequencing has not been determined.

Although surgical resection remains the gold standard, the techniques most commonly used for the diagnosis of lung cancer are fiberoptic bronchoscopy and CT-guided transthoracic needle aspiration. Because the majority of patients with NSCLC have advanced disease and are not candidates for surgery, nonsurgical biopsy procedures are preferable. For endobronchial tumors, four specimens have been shown to be adequate for optimal diagnostic yield.[163] However, biopsy specimens are generally small, averaging approximately 300 malignant cells in aggregate biopsies. In addition, not every biopsy contains tumor cells. Although four specimens may be sufficient to make a diagnosis of lung cancer, they may not provide enough tissue to perform a more detailed molecular analysis. Thus, some authors have recommended that six specimens be obtained from central, endobronchial lesions.[164]

Transbronchial needle aspiration (TBNA) of intrathoracic lymph nodes under endobronchial ultrasound (EBUS) has an increasingly important role in the diagnosis and staging of lung cancer. Several authors have described the successful use of EBUS-TBNA specimens for molecular analysis for *EGFR*, *EML4-ALK*, and *KRAS* gene mutations.[165–167] The concordance rate of mutation analysis between EBUS-TBNA cytological aspirates and histological samples obtained by surgical resection have been compared, and all mutations detected in the histological material of primary tumors were also identified in the cytological samples.[168] Three needle aspirates from each lymph node stage has been recommended for optimal diagnostic yield. However, the number of needle aspirates needed to obtain sufficient cellular material for molecular analysis has not been determined. Although bronchial washes and bronchial brushes can be useful for the diagnosis of lung cancer, they often will not provide enough tumor cells for molecular testing.

For patients with peripheral lung nodules or masses, transthoracic needle aspiration and biopsy are useful procedures. Core-needle biopsy specimens usually contain enough cellular material for molecular analysis (approximately 500 cells per core biopsy). In comparison, a transthoracic needle aspirate obtained using a 21-gauge needle yields approximately 100 cells.[169] Discordance between transthoracic needle aspiration and surgical pathology may be as high as 39%.[170]

INITIAL MOLECULAR TESTING

As we evolve toward a personalized pharmacological approach to the treatment of lung cancer, it will be necessary to determine the situations in which molecular testing of tumor specimens should be prioritized in addition to standard histological examination. At this time, molecular testing is not recommended for small cell or neuroendocrine lung cancers. However, all adenocarcinomas should undergo molecular testing when chemotherapy is being considered. Although mutation rates for driver mutations with

effective therapy are low in squamous cell carcinoma, there have been reports describing *EGFR* gene mutations in squamous cell carcinoma.[171–174] Automatically excluding all lesions classified as squamous cell carcinoma from molecular testing would potentially prevent these patients from receiving beneficial targeted therapies. Moreover, a small biopsy sample showing squamous morphology does not exclude the possibility of an adenocarcinomatous component elsewhere in the lesion. We therefore favor molecular testing of squamous cell carcinoma when chemotherapy is being considered, especially in younger patients with little or no smoking history. At a minimum, testing for *EGFR* mutation, *EML4-ALK* rearrangement, and *KRAS* mutation should be performed. Many argue that it is more cost effective to test only the patients most likely to have a specific mutation, such as *EGFR* in never smokers, and *KRAS* in patients being considered for EGFR TKI therapy, because the presence of *KRAS* mutations predicts lack of response to these agents. However, serial analysis for each mutation will take longer to define the cancer's mutational profile, thereby delaying treatment or potentially starting a harmful therapy. Thus, another challenge will be to develop testing platforms to simultaneously detect multiple somatic mutations. Newer technologies such as SNaPshot (Life Technologies, Carlsbad, CA) and MassARRAY (Sequenom, San Diego, CA) allow testing of multiple mutations at the same time and with little additional expense compared to testing for a single mutation. As more driver mutations are identified, we can expect overlapping mutations to be identified. In the future, it is likely that routine simultaneous testing of multiple markers will be conducted on all patients before initiation of therapy, irrespective of their clinical features.

■ ACQUIRED RESISTANCE TO TARGETED THERAPY

As described above, although most NSCLC patients with *EGFR* mutations or *ALK* rearrangements respond clinically and radiologically to targeted therapy, the disease always progresses due to acquired resistance. Thus, defining resistance to targeted therapy will be critical for determining whether treatment should be terminated. Jackman et al. proposed four criteria for the clinical definition of acquired resistance to EGFR TKIs: clinical exposure to an EGFR TKI, benefit from an EGFR TKI, evidence of disease progression by the RECIST criteria (an increase of 30% in summed maximum diameter or occurrence of new metastatic lesions), and lack of exposure to other drugs.[68] In patients who develop a growing lesion or new metastatic lesion on targeted therapy, we recommend that biopsies be obtained to confirm the presence of disease. Molecular testing should be repeated on these biopsy specimens to identify mechanisms of resistance, such as T790M mutations in the *EGFR* gene, and to direct further therapy. As we learn more about the mechanisms of resistance to targeted therapy, we will be able to provide alternative therapies to patients who have disease progression.

CONCLUSIONS

The past decade has witnessed dramatic success with personalized cancer therapy, and this paradigm shift has led to tremendous improvements in clinical outcomes in patients with molecularly defined subsets of lung tumors. Notably, the identification of a variety of molecular and genetic alternations in NSCLC has provided the opportunity for targeted therapy, such as EGFR TKIs for activating *EGFR* mutations in NSCLC, and the ALK inhibitor crizotinib for NSCLC harboring *ALK* fusions. The discovery of novel "druggable" driver mutations can lead to swift development of inhibitors of these targets and improved rational combinations of drugs. Despite initial responses to molecular-targeted therapy, however, the development of secondary resistance inevitably leads to treatment failure. Irreversible TKIs, combined approaches using multiple kinase inhibition, and vertical inhibition by combination of small molecules and antibodies are promising approaches to overcoming secondary drug resistance. A greater understanding of tumor resistance mechanisms will also provide additional therapeutic opportunities, leading to improved responses with targeted therapy.

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CHAPTER 109

Epidemiology of Lung Cancer

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THE EPIDEMIOLOGY OF LUNG CANCER

Lung cancer is the leading cause of cancer death in the United States and worldwide. Siegel et al.[1] estimated a total of 246,210 new lung cancer cases and 163,890 deaths from lung cancer in the United States in 2013.[1,2] These statistics reflect data ending in 2009, and likely underestimate the current lung cancer burden.

In the United States, more Americans die of lung cancer every year than from prostate, breast, and colon cancer combined.[1] Cancer of the lung and bronchus ranked second in cancer incidence in both sexes, with an estimated 118,080 new cases in males (14% of all new cancers) and 110,110 in females (14% of all new cancers).[1] The age-adjusted incidence rate of lung cancer was 62 per 100,000 men and women per year in the United States, with the incidence rate much higher in men than in women (75.2 vs. 52.3 per 100,000).[3] Lung cancer ranked first in both sexes in the number of estimated deaths yearly[1] (87,260 or 28% of all cancer deaths for males and 72,220 or 26% of all cancer deaths for females) (Fig. 109-1). The current 5-year survival rate in the United States for lung cancer is 17%; while this rate has actually increased over the past few decades, it lags behind survival advances in other common malignancies.[1]

Globally, lung cancer has been the most common cancer since 1985, both in terms of incidence and mortality rate. Worldwide, lung cancer is the largest contributor to new cancer diagnoses (1,350,000 new cases; 12.4% of total new cancer cases) and to death from cancer (1,180,000 deaths; 17.6% of total cancer deaths).[2] Worldwide, it was also the most commonly diagnosed cancer and

Estimated new cases

Males				Females		
Prostate	238,590	28%		Breast	232,340	29%
Lung & bronchus	118,080	14%		Lung & bronchus	110,110	14%
Colorectum	73,680	9%		Colorectum	69,140	9%
Urinary bladder	54,610	6%		Uterine corpus	49,560	6%
Melanoma of the skin	45,060	5%		Thyroid	45,310	6%
Kidney & renal pelvis	40,430	5%		Non-Hodgkin lymphoma	32,140	4%
Non-Hodgkin lymphoma	37,600	4%		Melanoma of the skin	31,630	4%
Oral cavity & pharynx	29,620	3%		Kidney & renal pelvis	24,720	3%
Leukemia	27,880	3%		Pancreas	22,480	3%
Pancreas	22,740	3%		Ovary	22,240	3%
All sites	**854,790**	**100%**		**All sites**	**805,500**	**100%**

Estimated deaths

Males				Females		
Lung & bronchus	87,260	28%		Lung & bronchus	72,220	26%
Prostate	29,720	10%		Breast	39,620	14%
Colorectum	26,300	9%		Colorectum	24,530	9%
Pancreas	19,480	6%		Pancreas	18,980	7%
Liver & intrahepatic bile duct	14,890	5%		Ovary	14,030	5%
Leukemia	13,660	4%		Leukemia	10,060	4%
Esophagus	12,220	4%		Non-Hodgkin lymphoma	8430	3%
Urinary bladder	10,820	4%		Uterine corpus	8190	3%
Non-Hodgkin lymphoma	10,590	3%		Liver & intrahepatic bile duct	6780	2%
Kidney & renal pelvis	8780	3%		Brain & other nervous system	6150	2%
All sites	**306,920**	**100%**		**All sites**	**273,430**	**100%**

Figure 109-1 Ten leading cancer types for the estimated new cancer cases and deaths categorized by sex. *(Reproduced with permission from Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.)*

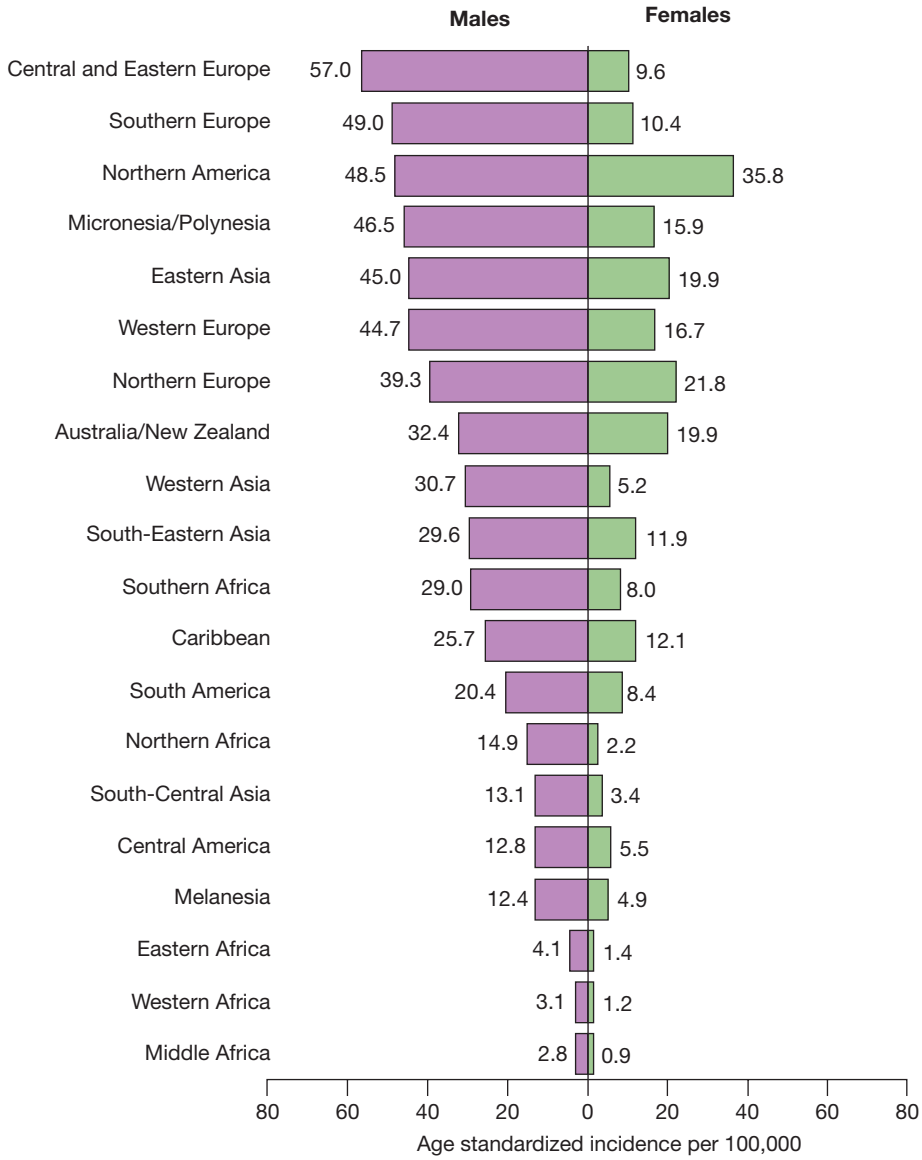

Figure 109-2 Age-standardized lung cancer incidence and mortality rates by sex and world area. Lung cancer incidence by sex and world area. Rates are standardized to the world standard population, in 2008. *(Adapted with permission from Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.)*

the leading cause of cancer death in males in 2008.[2] For females, lung cancer was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Lung cancer incidence and mortality rates are highest in the United States and the developed countries, and relatively lower in Central America and most of Africa (Fig. 109-2). However, there has been a large relative increase in the numbers of cases of lung cancer in developing countries. Almost half (49.9%) of the cases now occur in developing countries, whereas in 1980, 69% of cases were in developed countries. The estimated numbers of lung cancer cases worldwide has increased by 51% since 1985 (a 44% increase in men and a 76% increase in women).[2] The World Health Organization estimates that lung cancer deaths worldwide will continue to rise, largely as a result of an increase in global tobacco use, especially in Asia.[2]

Lung cancer incidence in males in the United States has been decreasing since the early 1980s (Fig. 109-3). The incidence and mortality rates for lung cancer tend to mirror one another because most patients diagnosed with lung cancer eventually die of the disease. Siegel et al.[4] noted decreases in death rates from lung cancer in men by 2.0% per year from 1994 to 2006 (Fig. 109-4). In women, lung cancer death rates instead increased by 0.3% per year from 1995 to 2005; however, more recent data from 2003 to 2006 show a decline of 0.9% per year (Fig. 109-4). Because of the change in lung cancer incidence in women, recent figures show that lung cancer death rates have decreased in women for the first time, more than a decade after the beginning of the decreasing trend in men.[5] The difference between the sexes in the onset of decline in lung cancer may be attributable to the fact that cigarette smoking in women peaked two decades later than in men. Lung cancer mortality rates thus appear to be reaching a plateau for women, which is an encouraging change from the steep rise in the 1970s.

The Surveillance, Epidemiology, and End Results (SEER) data from 2004 to 2008 report the median age at diagnosis for cancer of the lung and bronchus to be 71 years. No cases were diagnosed in patients younger than 20 years.[3] Approximately 0.2% of cases were diagnosed in patients between age 20 and 34 years; 1.5% between 35 and 44 years; 8.8% between 45 and 54 years; 20.9% between 55 and 64 years; 31.1% between 65 and 74 years; 29% between 75 and 84 years; and 8.3% at 85 years and older.

There are two broad categories of lung cancer: small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC). SCLC, which is a highly malignant tumor derived from cells exhibiting neuroendocrine characteristics, accounts for 15% of lung cancer cases. NSCLC, which accounts for the remaining 85% of cases, is further divided into three major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma by itself accounts for 38.5% of all lung cancer cases, with squamous cell carcinoma accounting for 20%, and large cell carcinoma accounting for 2.9%.[3,6] In the past several decades, the incidence of adenocarcinoma has increased greatly, and it has replaced squamous cell carcinoma as the most prevalent type of NSCLC.

Despite the availability of new diagnostic and genetic technologies, advancements in surgical techniques, and the development of new biologic treatments, the overall 5-year survival rate for lung cancer in the United States remains at a dismal 17%.[7] The 5-year survival rate in Europe, China, and developing countries is estimated at only 8.9%.[2] Lung cancer stage is often advanced at the time of diagnosis; 30% to 40% of cases of NSCLC and 60% of SCLC are stage IV at presentation. Patients with stage I disease at diagnosis have a 5-year survival rate of approximately 50%. In stark contrast, patients with advanced stage disease and distant metastasis at diagnosis have a dismal 5-year survival rate of 1% to 2%, which argues strongly for the need for better screening methods to detect early stage cancers.[8,9]

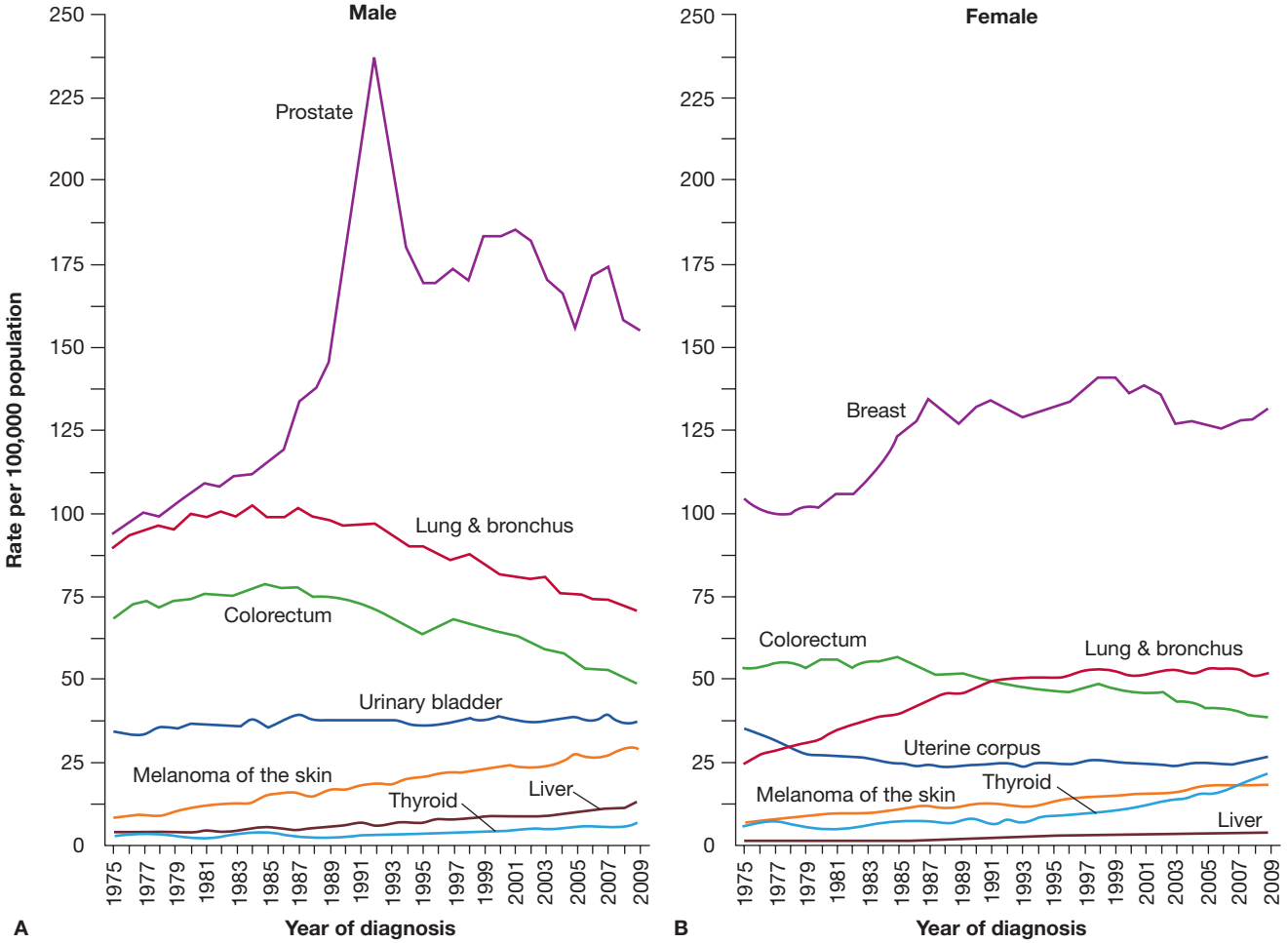

Figure 109-3 Trends in incidence rates for cancer of the lung and bronchus among (**A**) males and (**B**) females in the United States, 1975–2009. *(Reproduced with permission from Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.)*

ETIOLOGY OF LUNG CANCER —TOBACCO SMOKING AND LUNG CANCER

Tobacco smoking is the most important modifiable risk factor for lung cancer. It has been estimated that up to 20% of all cancer deaths worldwide could be prevented by the elimination of tobacco smoking.[10] More than 80% of lung cancers develop in smokers, and one in nine smokers develops lung cancer.[11] The cumulative lung cancer risk among lifelong heavy smokers can be as high as 30% compared with a lifetime risk of less than 1% in nonsmokers.[12,13] Smoking cessation, especially at a younger age, is associated with many health benefits including lowering the risk of lung cancer; cessation before the age of 40 years reduces the risk of death associated with continued smoking by about 90%.[14] Lung cancer risk is proportional to the magnitude of cigarette consumption, as factors such as the number of packs per day smoking, the age of onset of smoking, the degree of inhalation, the tar and nicotine content of cigarettes, and use of unfiltered cigarettes are important.[15,16] Individual susceptibility, which is a function of environmental factors and genetic predisposition, is a factor in carcinogenesis.

In 1912, Adler in an extensive review of autopsy reports from hospitals in the United States and western Europe identified 374 cases of primary lung cancer, representing <0.5% of all cancer cases.[17] He concluded at the time that "primary malignant neoplasms of the lung are among the rarest forms of disease." In 1920, lung cancer constituted only 1% of all malignancies in the United States, but over the next several decades, the incidence of lung cancer increased disproportionately to the incidence of all other cancers.[18] The first report linking cigarette smoking with an increased risk of premature death was in 1938 when Pearl showed that cigarette smoking had a dose-related adverse effect on longevity.[19] The finding that tar (the total particulate matter in cigarette smoke after water and nicotine are removed) applied to the skin of animals produced skin cancer raised concern that inhalation of tar products could be an important etiologic factor in lung cancer. Subsequent studies in patients and experimental animals demonstrated that tar from the burning of tobacco was carcinogenic.[20] Ochsner and DeBakey[21] stated in their 1941 review of lung carcinoma that "it is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking."

In 1950, two large landmark epidemiologic studies established the causal role of tobacco smoking in bronchogenic carcinoma.[22,23] In the United Kingdom, Doll and Hill described an association between carcinoma of the lung and cigarette smoking, and the effect of the number of cigarettes smoked on the development of lung cancer.[19,22,24] In the United States, Wynder and Graham examined 605 cases of lung cancer in men and found that 96.5% of lung cancers were in men who were moderate to heavy smokers for many years.[19] They concluded that (1) the excessive and prolonged use of tobacco was an important etiologic factor in lung cancer; (2) lung cancer in nonsmokers was rare; and (3) the onset of carcinoma could occur 10 years or more after the cessation of smoking.

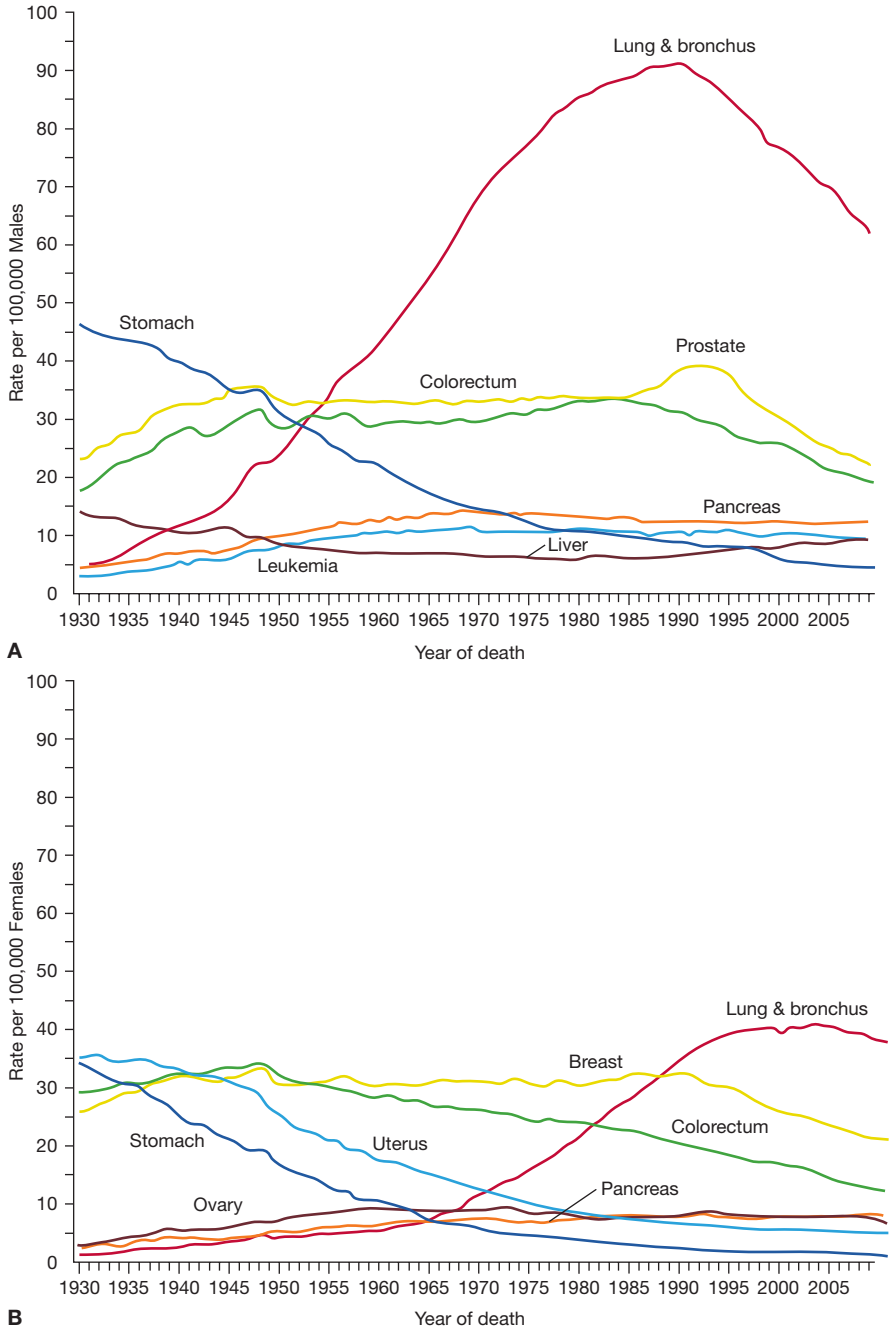

Figure 109-4 Death rates trend for selected cancers including cancer of the lung and bronchus in the United States. Rates are age adjusted to the 2000 US standard population with data from 1930 to 2009 for (**A**) males and (**B**) females. *(Reproduced with permission from Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.)*

In 1964, the United States Surgeon General issued a landmark report on smoking and its effects on health that included a number of key observations and conclusions. First, cigarette smoking was associated with a 70% increase in the age-specific death rates of men and a lesser increase in the death rates of women. Second, cigarette smoking was causally related to lung cancer in men. The magnitude of the effect of cigarette smoking far outweighed all other factors leading to lung cancer. The risk for lung cancer increased with the duration of smoking and the number of cigarettes smoked per day. The report estimated that the average male smoker had an approximately 10-fold risk for lung cancer, whereas heavy smokers had at least a 20-fold risk. At that time, the relative risk for lung cancer death among smokers was five times as high for men than for women; however, these differences between men and women are no longer as evident.[25] Third, cigarette smoking was believed to be much more important than occupational exposures in the causation of lung cancer in the general population. Fourth, cigarette smoking was the most important cause of chronic bronchitis in the United States. Finally, male cigarette smokers had a higher death rate from coronary artery disease than male nonsmokers. The report concluded that: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action." Despite efforts to curb tobacco smoking, there are approximately 1.1 billion smokers worldwide, and if the current trends continue, that number will increase to 1.9 billion by the year of 2025.[26] Wynder and Graham estimated that the average American adult smoked fewer than 100 cigarettes per year in 1900.[27] Fifty years later, the number smoked had risen to approximately 3500 cigarettes per person per year and reached a maximum of approximately 4400 cigarettes per person per year in the mid-1960s (Fig. 109-5).[28] Since the 1964 publication of the Surgeon General's first report on the health consequences of smoking, yearly per capita consumption of cigarettes has been declining in the United States (Fig. 109-5).[28] As of 2008, it is estimated that 20.6% of American adults over age 18 years old (46.0 million) are habitual smokers, an improvement from 24.1% a decade previously.[29,30] Of these, 79.8% (36.7 million) smoke every day and 20.2% (9.3 million) smoke some days. Unfortunately, the rate of decline in smoking prevalence has slowed recently, with 19.5% of American adults habitually smoking in 2009.[31] More than 80% of adult smokers begin before the age of 18 years. In 2009, one in five American high school students reported smoking cigarettes in the preceding 30 days.[32] Several factors identify populations more likely to smoke. Prevalence is higher in men (23.5%) than in women (17.9%). Socioeconomic influences contribute. Among persons below the federal poverty level, the prevalence of smoking is 31.1%. In the population of adults older than 25 years, the prevalence of smoking among persons with educational status less than a high school diploma is 28.5% compared with 5.6% among persons with a graduate degree.[30] There are also regional differences in the United States, with lowest smoking prevalence in western states (16.4%) compared to southern (21.8%) and midwest states (23.1%).[29]

Cigarette smoke is a complex aerosol composed of more than 4000 gaseous and particulate compounds. *Mainstream smoke* is produced by inhalation of air through the cigarette and is the primary source of smoke exposure for the smoker. *Sidestream smoke* is produced from smoldering of the cigarette between puffs and is the major source of environmental tobacco smoke (ETS). The primary determinant of tobacco addiction is nicotine; exposure to tar appears to be a major

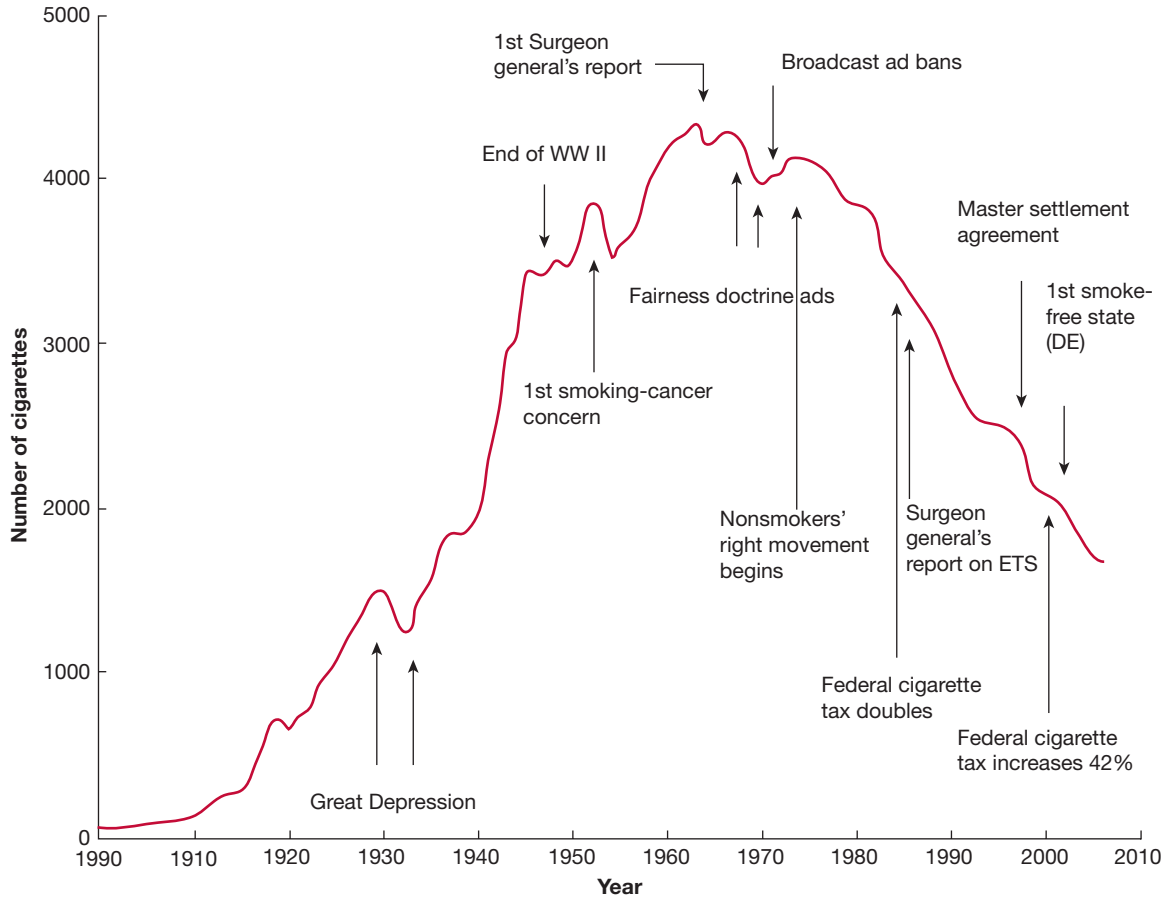

Figure 109-5 The adult per capita cigarette consumption in the United States, 1900 to 2006, with historical highlights. *(Adapted with permission from Warner KE, Mendez D. Tobacco control policy in developed countries: yesterday, today, and tomorrow. Nicotine Tob Res. 2010;12(9):876–887.)*

component of lung cancer risk. The nicotine and tar composition of mainstream smoke can vary greatly depending on the intensity of inhalation by the smoker. Although the use of filter tips decreases the amount of nicotine and tar in mainstream smoke, the effect of filter tips also varies in relation to differences in the compression of the filter tips by lips or fingers and the depth of inhalation of the smoker.

The primary factor determining intensity of cigarette use is the nicotine dependence of the smoker, and although cigarettes now contain less nicotine and tar than in the past, smokers tend to take more puffs per minute and inhale more deeply to satisfy their nicotine need. Low-yield filtered cigarettes have been hypothesized to contribute to the increase in the incidence of adenocarcinoma of the lung.[33] The nicotine-addicted smoker smokes low-yield cigarettes far more intensively than nonfiltered higher-yield cigarettes. With deeper inhalation, higher-order bronchi in the peripheral lung, which lack protective epithelium, are exposed to carcinogen-containing smoke, rather than simply the major bronchi.

The International Agency for Research on Cancer (IARC) has identified at least 50 carcinogens in tobacco smoke.[34,35] The agents that appear to be of particular concern in lung carcinoma are the tobacco-specific N-nitrosamines (TSNAs) formed by nitrosation of nicotine during tobacco processing and during smoking. Eight TSNAs have been described, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which is known to be an important inducer of lung cancer. Mainstream smoke contains other potential carcinogens, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and other organic and inorganic compounds such as benzene, vinyl chloride, arsenic, and chromium. The PAHs and TSNAs require metabolic activation to become carcinogenic. Metabolic detoxification of these compounds can also occur, and the balance between activation and detoxification likely affects individual cancer risk.

Tobacco carcinogens such as NNK can bind to DNA and form DNA adducts. Failure of the normal DNA repair mechanisms to remove DNA adducts can lead to permanent mutations. NNK can mediate signaling pathway activation that includes modulation of critical oncogenes and tumor-suppressor genes that promote uncontrolled cellular proliferation and tumorigenesis.[36] NNK is associated with DNA mutations resulting in the activation of K-*ras* oncogenes.[37,38] K-*ras* oncogene activation has been detected in 24% of human lung adenocarcinomas,[39] and is present in adenocarcinoma of the lung in ex-smokers, suggesting that such mutations persist even after smoking cessation.[40] This finding may explain the persistent elevation in lung cancer risk in ex-smokers even years after discontinuing cigarette use. Similarly, benzo(a)pyrene metabolite, a specific chemical constituent of tobacco smoke, can damage various *p53* tumor-suppressor gene loci that are known to be abnormal in approximately 60% of primary lung cancer cases.[41] Related PAHs in tobacco smoke can also target other lung cancer mutational hot spots.[42]

OTHER TYPES OF SMOKING

Cigar smoking and pipe smoking have been associated with increased risk for lung cancer, although seemingly not as great a risk as with cigarette smoking. The tobacco content of cigars can vary from 1 g to 20 g. Smoking five cigars a day on average is equivalent to smoking one pack of cigarettes a day. Cigar smokers have a

relative risk of lung cancer of 2.1 to 5.1 compared to nonsmokers; men who smoked five or more cigars a day have the greatest risk.[43] The risk for lung cancer in pipe smokers is similar to that in cigar smokers.[44,45] The effects of smoking marijuana and cocaine have not been extensively studied, and an association has not been fully established between such inhalant drug use and lung cancer. There have, however, been reports of increased risk for lung cancer in marijuana smokers; and metaplastic, histologic, and molecular changes similar to premalignant alterations have been detected in the bronchial epithelium in habitual smokers of marijuana or cocaine.[46,47]

NEVER SMOKERS

Never smokers are defined as persons who have smoked fewer than 100 cigarettes in their lifetime, including lifetime nonsmokers. An estimated 15% of lung cancers in men and up to 53% in women worldwide occur in never smokers, accounting for 25% of all lung cancer cases.[48] Lung cancer in never smokers considered as a distinct group would rank as the seventh most common cause of cancer death worldwide, ahead of cervical, pancreatic, and prostate cancer.[49] In countries in South Asia, up to 80% of women with lung cancer are never smokers.[50] In the United States, one study estimated that 19% of lung cancers in women and 9% in men occur in never smokers.[51] The age-adjusted rate for lung cancer in never smokers (aged 40–79 years) ranges from 11.2 to 13.7 per 100,000 person-years for men and from 15.2 to 20.8 per 100,000 person-years for women. The rates are 12 to 30 times higher in current smokers of the same age group.[52]

Adenocarcinoma of the lung is more common than squamous cell carcinoma in never smokers,[50] and recent data suggests that adenocarcinoma is also becoming more common in smokers.[53,54] Risk factors considered to be important for never smokers include environmental tobacco exposure ("secondhand smoke"); environmental exposures to carcinogens such as radon, outdoor and indoor air pollution, asbestos, and arsenic; a history of lung disease including interstitial lung disease; and genetic factors.[55] A population-based case-control study in Canada found that occupational exposures, history of lung disease, and family history of early-onset cancer were important risk factors for lung cancer among never smokers.[56] In this study, potential environmental sources of increased risk included exposure to solvents, paints or thinners, welding equipment, and smoke, soot, or exhaust. Other studies have implicated a genetic role in lung cancer in light of associations between lung cancer in never smokers and a family history of lung cancer.[57–59] Genes implicated include the epidermal growth factor receptor (EGFR) gene, the human repair gene (*hMSH2*), and various cytochrome P450, and glutathione-*S*-transferase (GST) enzymes. A case-control study following 2400 relatives of 316 never smokers with lung cancer cases showed a 25% excess risk for cancer in first-degree relatives.[58]

The investigation threshold in symptomatic never smokers might be higher than in smokers, leading to diagnosis at later stages in never smokers.[60] Despite this potential delayed diagnosis and later presentation of lung cancer in never smokers, the survival rate for never smokers is better than for smokers, independent of stage of disease, treatment received, and presence of comorbidities.[61–63] A multivariate analysis of lung adenocarcinoma found that never smoking status was an independent predictor of improved survival (23% overall 5-year survival rate for never smokers; 16% for current smokers).[61] Such findings have suggested that the cancer in never smokers may display a distinct biologic behavior and natural history. Microarray gene profiling studies have found that lung adenocarcinomas are heterogeneous, and the profiles of cancer in smokers and never smokers are quite different.[64,65] In 2010, the first genome-wide association study (GWAS) reported genetic variations in never smoking females in chromosome 13q31.3 that altered the expression of glypican 5 (*GPC5*), a heparin sulfate proteoglycan with many known functions involving cell growth and differentiation and tissue responses.[66] Another GWAS, focusing on lung adenocarcinomas in female Han Chinese never smokers in Taiwan, identified genetic variation in the *CLPTM1L-TERT* locus of chromosome 5p15.33 to be associated with risk for lung cancer in this population.[67] This 5p15.33 chromosome contains two genes implicated in carcinogenesis, telomerase reverse transcriptase (*TERT*) and cleft lip and palate transmembrane 1-like (*CLPTM1L*).

GENETIC FACTORS

The genetic component of lung cancer relates to host susceptibility with or without exposure to cigarette smoke, the development of certain types of lung cancer, and the patient's responsiveness to biologic therapies. A lung cancer risk prediction model developed by Spitz et al. incorporated such variables as smoking history, exposure to ETS, occupational exposures to dusts and to asbestos, and family history of cancer.[68,69] Their analysis showed the influence of family history of cancer on the risk for lung cancer in never smokers, former smokers, and current smokers (Table 109-1). Cassidy et al.[70] also highlighted a significantly increased risk for lung cancer specifically for persons with a family history of early-onset lung cancer (<60 years of age) (Table 109-2).

TABLE 109-1 Multivariable Logistic Model for Lung Cancer by Smoking Status

Risk Factor	*P* Value	OR (95% CI)
Never smoker		
ETS (yes vs. no)	0.0042	1.80 (1.20–2.89)
Family history (≥2 vs. <2)[a]	<0.001	2.00 (1.39–2.90)
Former smoker		
Emphysema (yes vs. no)	<0.001	2.65 (1.95–3.60)
Dust exposure (yes vs. no)	<0.001	1.59 (1.29–1.97)
Family history (≥2 vs. <2)[a]	<0.001	1.59 (1.28–1.98)
Age stopped smoking		
<42 y	Reference	
42–54 y	0.1110	1.24 (0.95–1.61)
≥54 y	0.0018 (*P* for trend = 0.017)	1.50 (1.16–1.94)
Current smoker		
Emphysema (yes)	<0.001	2.13 (1.58–2.88)
Pack-years		
<28	Reference	
28–41.9	0.1932	1.25 (0.89–1.74)
42–57.4	0.0241	1.45 (1.05–2.01)
≥57.5	<0.001 (*P* for trend <0.001)	1.85 (1.35–2.53)
Dust exposure (yes vs. no)	0.0075	1.36 (1.09–1.70)
Asbestos exposure (yes vs. no)	0.0127	1.51 (1.09–2.08)
Family history[b]		
0	Reference	
≥1	0.0021	1.47 (1.15–1.88)

ETS, environmental tobacco smoke.
[a]Number of first-degree relatives with any cancer.
[b]Number of first-degree relatives with smoking-related cancers such as lung cancers, renal cancer, cancers of upper digestive tract, esophagus, pancreas, bladder, and cervix.
Source: Reproduced with permission from Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst. 2007;99(9):715–726.

TABLE 109-2 Liverpool Lung Project – Multivariable Risk Model Lung Cancer

Risk Factor	*P* Value	OR (95% CI)
Smoking duration	<0.001	
Never		1.00 Reference
1–20 y		2.16 (1.21–3.85)
21–40 y		4.27 (2.62–6.94)
41–60 y		12.27 (7.41–20.30)
>60 y		15.25 (5.71–40.65)
Prior diagnosis of pneumonia	0.002	
No		1.00 Reference
Yes		1.83 (1.26–2.64)
Occupational exposure to asbestos	<0.001	
No		1.00 Reference
Yes		1.89 (1.35–2.62)
Prior diagnosis of malignant tumor	0.005	
No		1.00 Reference
Yes		1.96 (1.22–3.14)
Family history of lung cancer	0.01	
No		1.00 Reference
Early onset (<60 y)		2.02 (1.18–3.45)
Late onset (≥60 y)		1.18 (0.79–1.76)

Source: Reproduced with permission from Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer. 2008;98(2):270–276.

Recent reviews have examined the molecular epidemiology and biology of lung cancer, focusing on genetic markers of host susceptibility to lung carcinogens and their clinical implications.[71,72] The susceptibility genetic factors include high-penetrance low-frequency genes, low-penetrance high-frequency genes, and acquired epigenetic polymorphisms. There are associations of lung cancer with rare Mendelian cancer syndromes such as Bloom and Werner syndromes. Familial aggregation studies have demonstrated a hereditary component to the risk for lung cancer and have been used to discover high-penetrance, low-frequency genes. There is a twofold increased risk for lung cancer in persons with a family history of lung cancer, with an increased risk also present in nonsmokers.[73] There have also been numerous studies on candidate susceptibility genes that are of low penetrance and high frequency. The approach has been to target genes known to be involved in the absorption, metabolism, and accumulation of tobacco or other carcinogens in lung tissue. For example, genetic polymorphisms encoding enzymes involved in the activation and conjugation of tobacco smoke compounds, including PAHs, TSNAs, and aromatic amines have been widely studied. Some of the frequently studied enzymes in this system include CYP1A1, the GSTs, microsomal epoxide hydrolase 1 (mEH/EPHX1), myeloperoxidase (MPO), and NAD(P)H quinine oxidoreductase 1 (NQO1). A GWAS of tagged single nucleotide polymorphisms (SNPs) in histologically confirmed NSCLC was recently performed to identify common low-penetrance alleles that influence lung cancer risk. This study identified a susceptibility locus that contains the nicotinic acetylcholine receptor genes.[74] Polymorphisms in genes involved in DNA repair enzymes active in base excision repair (XRCC1, OGG1), nucleotide excision repair (ERCC1, XPD, XPA), and double-strand break repair (XRCC3) and different mismatch repair pathways have been studied as they relate to lung cancer risks.[75,76] Chronic inflammation in response to repetitive tobacco exposure has been theorized to be involved in lung tumorigenesis.[77] Genes encoding for the interleukins (IL-1, IL-6, IL-8) or the cyclooxygenase enzymes (COX2) involved in inflammation, or the metalloproteases (MMP-1, -2, -3, -12) involved in repair during inflammation, and more recently NFKB1 have been associated with lung cancer risk.[78] Various cell cycle–related genes have also been implicated in lung cancer susceptibility, including the tumor-suppressor genes *p53* and *p73*, mouse double minute 2 (*MDM2*), and the apoptosis genes encoding FAS and FASL.[79,80] Acquired or epigenetic changes to DNA chromosome can also lead to increased lung cancer susceptibility. These events include changes such as DNA methylation, histone deacetylation, and phosphorylation, all of which can affect gene expression.[81] Despite numerous genetic association studies, the specific genes responsible for the enhanced risk for lung cancer have not been identified. Collaborative efforts such as the Genetic Susceptibility to Environmental Carcinogens and the International Lung Cancer Consortium are attempting to pool findings to achieve greater study sample sizes.[82]

GENDER

In the late 1980s, lung cancer surpassed breast cancer as the leading cause of cancer death in women in the United States. At present, nearly twice as many American women die annually of lung cancer than succumb to breast cancer.[4] Since 1950 there has been a more than 600% increase in the lung cancer mortality rate in women. In the United States, the cigarette smoking rate for women increased during the period from 1930 to 1960; this increase was followed by an increase in lung cancer in women starting around 1960.[83,84] Smoking prevalence is higher among men (23.1%) than women (18.3%), but the difference is narrowing.[29] In 2009, lung cancer death rates for women declined for the first time in four decades, along with a decrease in the overall cancer death rate.[5] This trend varies geographically; for example, the rate of lung cancer is increasing among women in southern and midwestern states.[85]

Whether women are more or less susceptible than men to the carcinogenic effects of cigarette smoke is controversial. While lung cancer in never smoking women is more common than in never smoking men, up to 80% of lung cancer cases in women are related to smoking.[82] A recent study from the U.S. National Health Interview Survey showed a staggeringly high hazard ratio for lung cancer mortality of 17.8 for female smokers, compared to 14.6 for male smokers.[14] Recent analysis of the SEER data from 1997 to 2006 showed that the lung cancer mortality rate is 74.08 per 100,000 man-years compared to 40.81 per 100,000 woman-years.[86] However, other studies have suggested that women may be actually more vulnerable to carcinogens in tobacco smoke than men.[87–90] A study using the American Health Foundation data found that the odds ratio for the major lung cancer types has been consistently higher for women than for men at every level of exposure to cigarette smoke.[90] The dose-response odds ratios for lung cancer in women were 1.2- to 1.7-fold higher than in men. A Canadian case-control study of male–female differences in lung cancer covering the period 1981 to 1985 showed that with a history of 40 pack-years of cigarette smoking relative to lifelong nonsmoking, the odds ratio for women developing lung cancer was 27.9 versus 9.6 in men. The gender differences in susceptibility may be related to differences in nicotine metabolism and in metabolic activation or detoxification of lung carcinogens; women have higher levels of DNA adducts than men, which may result in greater susceptibility to carcinogens.[91] Hormonal factors may also play a role in susceptibility. A case-control study showed that estrogen replacement therapy was significantly associated with an increased risk for adenocarcinoma (odds ratio 1.7), and the combination of cigarette smoking and estrogen replacement increased that risk substantially (odds ratio

32.4).[92] Conversely, early menopause (age 40 years or younger) was associated with a decreased risk for adenocarcinoma (odds ratio 0.3). More recent large randomized studies suggest that the use of hormonal therapies such as estrogen and progestin may be associated with an increased risk of lung cancer in women.[93]

A separate but related issue is whether cigarette smoking may be associated with a higher risk of nonmalignant lung disease in women than in men. Neither the British Physicians Study in the United Kingdom[94,95] nor the Lung Health Study in the United States[96] found gender differences in mortality from smoking-related chronic obstructive pulmonary disease (COPD). However, other studies, including a report by Chen et al.,[97] suggest that cigarette smoking may be more harmful to pulmonary function in women compared with men. In this study, changes in forced expiratory volume in 1 second (FEV_1) and maximal midexpiratory flow rate increased with increasing pack-years more rapidly in women smokers than in their male counterparts. These changes were independent of age, height, and weight. Beck and colleagues in a study of 4690 Caucasians found that for a given level of smoking, women had greater decline in FEV_1 and maximal expiratory flow at 25% and 50% of vital capacity at a younger age (15–24 years) than men (40–45 years).[98] Because smokers with spirometric evidence of airway obstruction are at higher risk for lung cancer, the suggestion that women have increased susceptibility to smoking-induced airway disease may be important in the consideration of their risk for lung cancer.[98]

Finally, it also appears that lung cancer is more common in nonsmoking women than in nonsmoking men. For example, in never smokers, the age-adjusted incidence rate of lung cancer is much higher for women than men (14.4–20.8 per 100,000 person-years for women, compared with 4.8–13.7 per 100,000 person-years for men).[51] The proportion of never smoking lung cancer patients was more than twice as high for women than for men in a case-control study.[90]

RACE AND ETHNICITY

Race is a complex variable that often has a strong socioeconomic association. However, notable racial differences in disease states can shed light on the specific issues of a particular subpopulation. In general, the incidence of lung cancer is substantially higher among blacks, Native Hawaiians, and other Polynesians, and lower among Japanese Americans and Hispanics than among whites in the United States.[99] These differences initially have been attributed to the variations in cigarette smoking pattern among the different ethnic and racial groups. Recent smoking data show that among the different groups, Asians (9.9%) had the lowest smoking prevalence in the United States, whereas American Indians and Alaska Natives (32.4%) had significantly higher prevalence than the other groups.[29] Smoking prevalence among whites (22%) and blacks (21.3%) was significantly higher than among Hispanics (15.8%). Black smokers have higher rates of lung cancer than white smokers, even though only 8% of black smokers smoked at least 25 cigarettes per day compared with 28% of white smokers.[29] Native Hawaiians had higher rates of lung cancer than whites and Asians despite having similar smoking habits.[29] The relative risk for lung cancer among subjects smoking less than 20 cigarettes per day were 0.21 to 0.39 for Japanese Americans and Latinos, and 0.45 to 0.57 for whites as compared with black Americans.[29] However, the differences in lung cancer risks were not significant among all racial groups who exceeded 30 cigarettes per day of smoking. A recent SEER report specifically showed that black men, but not black women, in the United States had a higher age-adjusted incidence of lung cancer than their white counterparts at all age groups. Hispanics in the United States have lower incidence and death rates than non-Hispanic whites for lung cancer; however, they have higher rates for other organ cancers.[100] Further, first-degree relatives of black persons with early-onset lung cancer have a much greater risk of lung cancer than their white counterparts (25.1% vs. 17.1%, respectively).[101]

The explanation for these racial or ethnic variations in risk for lung cancer is not known. Black Americans also have higher mortality rates from lung cancer than white Americans.[29] This difference in mortality rates has been attributed not only to the higher incidence rates but also to the poorer survival of black patients with lung cancer than white patients. For example, the 5-year survival rate was 14.3% lower in black Americans compared to white Americans.[29] The reasons for these racial differences are not known. Some have hypothesized a potential role for greater use of menthol cigarettes among black Americans than among white Americans (69% vs. 22%), or the deeper inhalation of menthol cigarettes compared to nonmenthol cigarettes.[102]

AGE

Although smoking prevalence is lowest among persons aged 65 years and older (9.3%) compared to persons aged 18 to 24 years (21.4%), 25 to 44 years (23.7%), and 45 to 64 years (22.6%),[29] more than 65% of patients with lung cancer are older than 65 years.[3] Specifically, 31.1% of patients with lung cancer are between 65 and 74 years; 29% between 75 and 84 years; and 8.3% are 85 years old and older.[3] The mean age at the time of diagnosis is 71 years old. This difference between relatively lower current smoking prevalence and the higher cancer rate in the elderly population likely reflects the effects of prior smoking. In the past decade, the incidence and mortality from lung cancer have decreased among persons aged 50 years and younger, but have increased among persons aged 70 years and older.[103] The 5-year survival rate for lung cancer decreases incrementally with age for both sexes. Patients older than 80 years constitute 14% of all patients with lung cancer in the United States but account for almost a quarter of all lung cancer deaths.[103] It has been estimated that the number of lung cancer patients aged 85 years and older will quadruple by 2050.[104]

DIET AND OBESITY

It has been suggested that diet is responsible for approximately 30% of all cancers.[105] For example, low serum concentrations of antioxidants, such as vitamins A, C, and E, have been associated with the development of lung cancer.[106,107] The carotenoid component of vitamin A, in particular β-carotene, has been shown to have protective effects against lung cancer in dietary studies. Vitamins C and E (α-tocopherol) have also been shown to have some protective effect.[108,109] Based on those observations, several large intervention trials have been conducted to examine the relationship between vitamin supplementation and lung cancer. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (daily supplementation of a-tocopherol, β-carotene, or both) and the Beta-Carotene and Retinol Efficacy Trial (CARET) (β-carotene, vitamin A, or both) found that vitamin supplementation did not reduce lung cancer risk, and in some circumstances, actually increased the incidence of lung cancer.[110,111] Therefore, the use of supplemental β-carotene and vitamin A is discouraged. There have also been suggestions that low dietary intake of certain minerals, including magnesium, zinc, copper, and iron, is associated with increased lung cancer risk; however, a prospective cohort study observed no significant associations between total mineral intake and lung cancer risk.[112,113]

A diet rich in fruits and vegetables has been linked to decreased cancer incidence, and the protective effects are stronger in current than in former smokers.[114] Although no specific type of vegetable or fruit has been shown to be particularly responsible for the effect, consumption of cruciferous vegetables, such as broccoli and cabbage that are rich in isothiocyanates, has some protective effect against lung cancer.[115] Low or no intake of fruits or vegetables has

been associated with up to threefold risk for lung cancer.[116] It has been also further suggested that consuming fruits or vegetables raw rather than cooked is associated with a further reduction in risk for lung cancer because important carotenoids can be destroyed with cooking.[117] A large prospective NIH-AARP Diet and Health Study showed no relation between total intake of fruit and vegetables with lung cancer risk.[118] However, the study showed that higher consumption of several botanical groups such as rosaceae (apples, peaches, strawberries), convolvulaceas (sweet potatoes and yams), and umbelliferae (carrots), was significantly and inversely associated with lung cancer risk in men and in former smokers.[118] Flavonoid plant metabolites have antioxidant and antiproliferative properties and can be found in food such as berries, citrus fruits, tea, dark chocolate, and red wine. A prospective study showed that the risk for lung cancer was lower in men with the highest total flavonoid intake compared to those with the lowest intake.[119] Certain dietary items including red meat, dairy products, saturated fats, and lipids, have been reported to be associated with an increased risk of lung cancer.[120–123] Other foods found to have an adverse effect on lung cancer risk include items that contain nitrosodimethylamines and nitrites, such as those found in salami and salted and smoked meat products.[124,125]

In the United States, 35.1% of adults are classified as obese.[126] Excessive body weight has been associated with increased risk for endometrial, breast, and colorectal cancers but not for lung cancer. A meta-analysis reported that an inverse association between body mass index (BMI) and lung cancer risk, and obesity may even have a protective role.[127] However, in the absence of cigarette smoking, the association between BMI and lung cancer was not significant. It has been proposed that the observed BMI and cancer association may be related to residual strong confounding effects of smoking itself.[128] For example, smokers tend to have lower mean BMI than age- and sex-matched nonsmokers.[129] Smokers have a notably lower BMI than nonsmokers, and they gain weight when they quit smoking. More recent studies that adjusted for pack-years of smoking and other relevant covariates in a female cohort showed an inverse association of BMI and lung cancer risk in current and former smokers, whereas BMI was positively associated with lung cancer in never smokers.[130] Other studies have shown that waist circumference was positively associated with lung cancer risk in smokers.[131]

OTHER LUNG DISEASES AND AIRWAYS OBSTRUCTION

Some nonmalignant lung diseases have been associated with an increased risk for lung cancer, the strongest association being with COPD. Cigarette smoking is the primary cause of both lung cancer and COPD. COPD affects an estimated 40% to 70% of patients with lung cancer, a finding that reflects a common smoking history. Some evidence suggests an association between the presence of airflow obstruction and the development of lung cancer.[132] A recent study evaluated 602 patients with lung cancer and found that 50% of them had prebronchodilator pulmonary function test results consistent with a diagnosis of COPD GOLD stage 2 and higher, independent of age, sex, and smoking history, with an odds ratio of 11.6.[133] The prevalence of COPD in patients with newly diagnosed lung cancer was sixfold greater than matched smokers, suggesting that COPD itself is an important independent risk factor with potential relationship to the pathogenesis of lung cancer.

COPD is characterized by chronic inflammation, which, in turn, has been suggested as a risk factor for lung cancer. A Dutch study found that the likelihood of developing lung cancer was increased in patients with an elevated serum C-reactive protein, a marker of generalized inflammation. A large retrospective study of patients with COPD found that the risk for lung cancer was lower in patients who took high-dose inhaled corticosteroids than in patients taking lower doses or none at all.[134] These results suggest that inhaled corticosteroids may have a chemoprotective role in lung cancer in patients with COPD. A study of α_1-antitrypsin deficiency carriers found that they have an approximately twofold higher risk for lung cancer, after adjusting for the effects of tobacco smoke exposure and COPD.[135]

The incidence of lung cancer has been demonstrated to be increased in patients with pulmonary fibrosis, even after adjustment for smoking.[136] In a population-based cohort study, patients with pulmonary fibrosis had an odds ratio for lung cancer of 8.25 compared with control subjects. Other fibrosing diseases, including asbestosis and scleroderma-related lung disease, also appear to be associated with an increased risk of lung cancer.[136,137] The mechanism by which pulmonary fibrosis may predispose to pulmonary malignancy is not clear.

INFECTIONS

Oncogenic viruses have been proposed as a cause of lung cancer. The possible involvement of human papillomavirus (HPV), which is known to cause carcinoma in other tissues, in bronchial squamous cell lesions was first suggested because the epithelial changes in bronchial carcinomas resemble those of established HPV condylomatous lesions in the female genital tract.[138] HPV DNA has been detected in lung squamous cell carcinoma tissues.[139] However, there is inconsistency in the reported prevalence of HPV infection in patients with lung cancer in different countries, with racial and geographic variations. Studies to date testing lung cancer specimens for HPV have yielded mixed results because of variability in genetic susceptibility, method of HPV detection, and environmental and high-risk behavior variables. Epstein–Barr virus (EBV), which is associated with Burkitt lymphoma and nasopharyngeal carcinoma, has been strongly associated with lymphoepithelioma-like carcinoma (LELC), a rare form of lung cancer in Asian patients, but this association has not been observed in the Western population.[140] Other viruses suggested as etiologic for lung cancer include BK virus, JC virus, the human cytomegalovirus, simian virus 40 (SV40), and measles virus; however, the evidence of causality is inconclusive.[141–144] More recently, DNA from Torque teno virus (TTV), a relatively new virus, has been detected at high levels in idiopathic pulmonary fibrosis patients with lung cancer, but more studies are needed to confirm these findings and determine their clinical significance.[145] It has also been suggested that *Chlamydia pneumoniae*, a common cause of acute respiratory infection, especially in patients who smoke cigarettes, might be involved in lung carcinogenesis.[146] If such an association were established, it could have profound implications, particularly for lung cancer prevention. *Chlamydia* is not a known oncogenic pathogen, but some have hypothesized that the inflammation resulting from the infection can lead to reactive oxygen species that damage DNA and cause cell injury, resulting in mutations that may lead to an increased risk of tumorigenesis.

Some studies have also reported an association of pulmonary tuberculosis with lung cancer.[147,148] A cohort study showed an increased risk for lung cancer in tuberculosis patients with hazard ratio of 3.3 after adjusting for confounding factors such as COPD and smoking-related cancers other than lung cancer. The effect of tuberculosis was even greater when combined with COPD or with other smoking-related cancers.[148] Some have speculated that tuberculosis-related inflammation and scarring contribute to lung cancer pathogenesis.[147]

AIDS-related mortality has dramatically decreased since the advent of highly active antiretroviral therapy; however, this decrease has been accompanied by an increase in the proportion of deaths attributable to non-AIDS defining tumors, especially lung cancer.[149,150] The increased risk of lung cancer relative to the general population of the same age seems to be due in part to the higher

prevalence of smoking among HIV-infected patients. HIV was associated with a hazard ratio of 3.6 for lung cancer after controlling for smoking status.[151] Although smoking is a key risk factor for lung cancer in HIV-infected patients, several other factors may contribute to the higher incidence of lung cancer. These include greater prevalence of coinfection with oncogenic viruses such as human herpesvirus 8, HPV, and EBV and the potential direct effects of the HIV virus and the consequences of long-term immunosuppression.[152] For example, the HIV tat protein can transactivate cellular genes or proto-oncogenes, while other HIV genes inhibit tumor-suppressor genes.[153] HIV-infected patients with lung cancer have a worse prognosis than similarly staged non–HIV-infected patients.[154] They are also more likely to have more advanced stage lung cancer at diagnosis.[155] Studies have reported that HIV-infected patients were much younger, were more likely to be smokers, and had significantly reduced median survival.[155,156]

ENVIRONMENTAL TOBACCO SMOKE

ETS, also referred to as "secondhand smoke," contributes to an increased risk for lung cancer with a notable dose-dependent relationship.[157] ETS consists of both mainstream (exhaled) smoke and sidestream smoke. In one study, household exposure of 25 or more smoker-years before adulthood doubled the risk for lung cancer; exposure of less than 25 smoker-years did not increase risk.[158] At least 17% of lung cancers in nonsmokers are thought to be attributable to exposure to high levels of ETS during childhood and adolescence.[158] The Surgeon General's 1976 report raised concerns about hazards relating to such environmental smoke exposure.[159] Nonsmokers exposed to ETS have an increased rate of smoke-related problems, including upper respiratory symptoms and eye irritation, and exposed children have an increased frequency of respiratory illnesses. Therefore, the report suggested that the acknowledged carcinogenic effect of active tobacco smoking might also be present in those involuntarily exposed. The risk for lung cancer is increased in nonsmoking women married to men who smoke.[160,161]

The risk of lung cancer related to ETS has been studied, though quantification of the magnitude of exposure is problematic. In an analysis of 37 epidemiologic studies of the risk of lung cancer in nonsmokers who did or did not live with a smoker, encompassing 4626 cases, a lifetime nonsmoker had an estimated 24% greater risk of lung cancer if he/she lived with a smoker.[157] It is important to note that this should be interpreted from the perspective that the background risk for lung cancer in a nonsmoker is very low, and so a 24% increase will not substantively change that risk.[157] Similarly, in 1986, the National Research Council commissioned a review of the effects of ETS as a potential causal agent of lung cancer in nonsmokers exposed to household cigarette smoke.[162] Review of all the available evidence yielded an overall odds ratio of 1.34 in lung cancer risk associated with ETS. In nonsmokers, this translates into an approximately 30% increase of risk for lung cancer, which, as already noted, should be interpreted in the context of a low background risk.[162]

Many government agencies, including the U.S. Department of Health and Human Services, Environmental Protection Agency, and the IARC, classify ETS as containing lung carcinogens. The presence of ETS is pervasive and harmful. There are reports that suggest as many as 88% of nontobacco users have detectable levels of serum cotinine, a metabolite of nicotine, presumably from exposure to ETS.[163] Therefore, efforts to limit public smoking will be of great benefit in this regard. Given that 20.6% of the American adult population still smoke, ETS will continue to be a major public health issue until cigarette smoking altogether is eliminated.[164]

ENVIRONMENTAL POLLUTION

Outdoor air pollution has long been thought to increase the risk for lung cancer. Advances in analytical methods used to detect specific pollutants have helped investigators study the effects of airborne particulates. Early studies involving urban–rural comparisons have shown that an "urban factor" is associated with a 10% to 40% increase in lung cancer deaths.[165] Two large US cohort studies suggest that there is an excess risk for lung cancer of about 19% per 10 $\mu g/m^3$ increment in the long-term average exposure to fine particulates, after adjustments for multiple confounding factors. The Cancer Prevention II study found that fine particulate and sulfur oxide–related pollution were associated with 8% increased risk for lung cancer mortality for each 10 $\mu g/m^3$ elevation in long-term average ambient concentration of fine particles less than 2.5 μm in diameter.[166]

However, it is difficult to determine the carcinogenicity of single constituents of air pollution. Other sources of fossil fuel combustion products can also have potential carcinogenic components. Estimates of relative risks for lung cancer associated with exposure to combustion products range from 7.0 to 22.0 in cigarette smokers, 2.5 to 10.0 in coke oven workers, and 1.0 to 1.6 in residents of areas with high levels of air pollution.[167] Diesel exhaust, which is composed of a complex mixture of gases and fine particles, is also an important component of air pollution. Some of the gaseous components of diesel exhaust, including benzene, formaldehyde, and 1,3-butadiene, are suspected of causing or known to cause cancer in humans. There is strong support that occupational exposure to diesel exhaust, particularly in persons in the trucking industry, is associated with an approximately 30% to 50% increase in the relative risk for lung cancer.[168] Data linking gasoline engine exhaust and lung cancer are less compelling. In many parts of the world, solid fuels such as wood are burned as primary sources of domestic energy for cooking and heating. Incomplete combustion of coal in homes in China has been linked with lung cancer.[169] The IARC has classified indoor emission from household coal combustion as a human carcinogen and emissions from biomass fuel, primarily from wood, as a probable human carcinogen.

OCCUPATIONAL CARCINOGENS

The IARC has identified arsenic, asbestos, beryllium, cadmium, chloromethyl ethers, chromium, nickel, radon, silica, and vinyl chloride as carcinogens. The occupations associated with exposure to these agents are shown in Table 109-3. It has been estimated that 10% of lung cancer deaths in men and 5% in women worldwide could be attributable to exposure to eight occupational lung carcinogens, namely asbestos, arsenic, beryllium, cadmium, chromium, nickel, silica, and diesel fumes.[170,171] Worldwide, lung cancer related to occupational carcinogen exposures is estimated to be responsible for 152,000 deaths, and a loss of nearly 1.6 million disability-adjusted life years (DALYS).[170] The National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 9000 to 10,000 men and 900 to 1900 women per year in the United States develop lung cancer from exposure to occupational carcinogens.[172]

Asbestos is the most common occupational cause of lung cancer. Asbestos, a naturally occurring fibrous mineral, can be classified as serpentine (chrysotile) or amphibole (amosite, crocidolite, tremolite). Asbestos has been used in construction and as insulating material for its fire-retarding qualities and strength since the 1800s, but its role as lung carcinogen was not known until the 1940s. Fortunately, asbestos use has precipitously declined in the United States since the 1970s.[173,174]

Asbestos exposure has been reported to be associated with a relative risk of lung cancer of 3.5 after adjusting for age, smoking, and vitamin intake.[175] Risk may be dose dependent, as well as influenced by the type of asbestos fiber. For example, the risk of lung cancer appears to be higher for workers exposed to amphibole fibers than for those exposed to chrysotile fibers, after adjusting for similar exposure level.[176] Notably, it remains unclear whether asbestos exposure alone or asbestosis in particular is the actual risk factor

TABLE 109-3 Occupational Carcinogens and Associated Occupational Exposures

Known Carcinogen	Occupational Exposure	Suspected Carcinogens	Occupational Exposures
Arsenic	Copper, lead, or zinc ore smelting	Acrylonitrile	Textile manufacture
	Manufacture of insecticides		Plastics, petrochemical manufacture
	Mining		
Asbestos	Asbestos mining	Cadmium	Electroplating
	Asbestos textile production		Pigment production
	Brake lining work		Plastics industry
	Cement production		
	Construction work		
	Insulation work		
	Shipyard work		
Beryllium	Ceramic manufacture	Formaldehyde	Formaldehyde
	Electronic and aerospace equipment		Resin production
	Mining		Synthetic fibers
			Insulation work
			Insulation production
Chloromethyl ethers	Chemical manufacturing	Vinyl chloride	Plastic production
			Polyvinyl chloride production
Chromium	Chromate production		
	Chromium electroplating		
	Leather tanning		
	Pigment production		
Nickel	Nickel mining, refining, electroplating		
	Production of stainless and heat-resistant steel		
	Polycyclic aromatics		
	Aluminum production		
	Hydrocarbon compounds		
	Coke production		
	Ferrochromium alloy production		
	Nickel-containing ore smelting		
	Roofing		
Radon	Mining		
Silica	Ceramics and glass industry		
	Foundry industry		
	Granite industry		
	Metal ore smelting		
	Mining and quarrying		

for lung cancer. Two reviews discussing the extensive available epidemiologic data illustrate this controversy.[173,177] First, it is widely recognized that lung fibrosis of many causes, including idiopathic pulmonary fibrosis and interstitial disease associated with connective tissue disease, is associated with an increased risk for lung cancer.[171] Second, asbestos-exposed animals developed lung cancer only when they also developed pulmonary fibrosis.[178,179] Third, pleural plaques have not proved to be a reliable marker for increased risk for lung cancer. Fourth, the presence of asbestosis is associated with increased likelihood of lung cancer compared to patients with asbestos exposure without associated fibrosis.[175] Nonetheless, at present the issue of whether asbestosis is a necessary precursor to asbestos-attributable lung cancer is not definitively settled.[173,180] The risk for lung cancer from nonoccupational asbestos exposure in the general environment is extremely low.[181]

It is important to recognize that cigarette smoking contributes significantly to the lung cancer risk profile in asbestos-exposed individuals. Smoking cessation is especially important for cancer prevention programs in workers exposed to asbestos, and probably even more important for workers with asbestosis. In a study of 17,800 individuals with more than 20 years of occupational asbestos exposure, Hammond et al. obtained information on the combined effects of cigarette smoking and asbestos dust exposure on lung cancer mortality. The risk for death from lung cancer increased by 16-fold in asbestos workers who smoked more than one pack of cigarettes per day and by ninefold in workers who smoked less than one pack per day, compared to asbestos workers without significant smoking history.[182] The relative risk for lung cancer with asbestos exposure alone is sixfold, with cigarette smoking alone 11-fold, but with exposure to both asbestos and cigarette smoke, the increase

may be as high as 59-fold.[182] This study did not distinguish individuals with asbestos exposure alone from those who also had asbestosis and thus was unable to identify the contribution of the latter factor to lung cancer risk and mortality.[182]

Radon and its decay products are carcinogens associated with one of the world's oldest occupation, mining. Initially known as a wasting pulmonary disease of miners and metal smelters, radon-induced lung cancer was first attributed to dust or metal exposure, or infections such as tuberculosis, but later linked to radioactive materials.[183] Radon is a natural decay product of radium 226, itself a decay product of uranium 238. Ultimately, radon decay produces lead 210, which has a half-life of 22 years. Both uranium and radium are ubiquitous in soil and rock, though in highly variable concentration. At usual temperatures, radon is released as an inert radioactive gas. Radon has a half-life of 3.82 days and decays into radioisotopes known as radon decay products (or radon daughters) that have half-lives measured in seconds to minutes. These products include polonium 218 and polonium 214, which emit α particles. It is the α radiation that is highly damaging to tissues including the respiratory epithelium. Inhalation of these radon decay products and subsequent α-particle emission in the lung can cause damage to cells and genetic material. Evidence from epidemiologic studies of underground miners shows a linear relationship between radon exposure and lung cancer risk.[184,185] Uranium miners exposed to radon and its decay products have an increased risk for lung cancer, peaking 15 to 24 years after exposure.[186] Lubin et al.[187] pooled 11 cohort studies, examining 2700 lung cancer deaths occurring in 65,000 miners. They concluded that the relative risk for lung cancer was linearly related to cumulative radon progeny exposure, and that 40% of all lung cancer deaths in their cohort might be due to such exposure.[187] There is an increased risk of lung cancer in uranium miners who smoke, with smoking and uranium exposure acting in at least an additive fashion.[188,189] In addition, there appears to be an increased risk of lung cancer in nonsmoking uranium miners who have higher levels of uranium exposures.[190] In the study by Lubin et al.,[187] 70% of lung cancer deaths in never smokers were thought attributable to radon progeny exposure.

Uranium mining has ceased in the United States. However, radon exposure continues to be an occupational concern in nonuranium mining and underground work as well as in uranium and nonuranium mines around the world.[191] In the United States, occupational exposure to radon is legislatively controlled. It has been estimated that a 40-year radon exposure at the maximum allowed level by occupational standards would increase a person's lifetime risk for lung cancer twofold.[192] Continued longitudinal evaluation of occupationally exposed persons is needed to improve our understanding of the carcinogenic effects of radon.

There is legitimate concern about the possible risk for lung cancer in the general population associated with domestic radon exposure. The National Council on Radiation Protection and Measurements has identified radon and its decay products as the largest component of environmental radiation to persons living in the United States.[185] Radon is a ubiquitous indoor domestic air pollutant. The concentration of radon gas in an environment depends on the richness of the source of radium and the degree to which the air around that source is ventilated. The primary factor determining radon gas concentration in homes is the concentration of radium in the soil and rock beneath those structures.[188] Building materials, well water, and natural gas are less common sources, usually contributing only minimally to indoor radon concentrations.

It has been proposed that radon is the second leading attributable cause of lung cancer after smoking.[193] Smokers and nonsmoking residents of smoking households are at potentially increased risk for lung cancer even when radon levels are low.[191] However, the potential for mutagenic and carcinogenic effects of low-level radon has been an area of controversy, and the risk associated with exposure to radon in the home remains uncertain. One meta-analysis concluded that greater residential exposure levels were associated with a relative risk of lung cancer of 1.14, a number consistent with extrapolation of risk from studies performed in miners as well as with actual calculated risks in miners with low cumulative radon exposure.[191] However, other studies have demonstrated no increased risk even with high indoor domestic radon levels.[193–195] It has been pointed out that the effects of low-dose, low-level radiation have never been adequately evaluated, which contests the assumptions inherent in extrapolation of high radon exposure in miners to domestic situations. However, even low-dose α radiation from domestic radon exposure could very conceivably lead to cellular genetic mutation, an early step in the induction of cancer. From a practical standpoint, radon can usually be readily eliminated from domestic sites, and so testing and abatement should be encouraged. Environmental and indoor radon exposure should continue to be carefully assessed as a public health problem.

CONCLUSIONS

Most lung cancer deaths are attributable to cigarette smoking, and curtailing the rates of cigarette smoking continues to be an important global imperative. Insights into the epidemiology and causal factors of lung cancer provide additional foundation for disease prevention. Likewise, ionizing radiation and certain occupational exposures have been recognized as carcinogenic. At present, the 5-year survival rate for lung cancer is only 17%.[1] This is in stark contrast to the 5-year survival rates for the other leading causes of cancer death in the United States.[4] The absolute number of lung cancer cases continues to be alarming, with the incidence of lung cancer in women only now beginning to decline. The challenge in the future will be to modify the impact of identified external sources of risk while continuing to expand our knowledge of the genetic and molecular basis of lung carcinogenesis. With one-fifth of the American population still smoking cigarettes, continued efforts must be directed at smoking cessation and at preventing persons from becoming addicted to smoking. Although work in advancing the field of lung cancer treatment is critically important, the dismal survival rate associated with this disease demands that the medical profession contribute to efforts aimed at limiting its primary cause. If tobacco smoking could be eliminated, and if we address some of the other known exposure risks of lung cancer, then might we be able to return lung cancer to its designation by Adler at the turn of the 20th century as "among the rarest forms of disease."

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CHAPTER 110

Approach to the Patient with Pulmonary Nodules

David Ost

INTRODUCTION

The radiographic finding of a pulmonary nodule, formerly known as a *coin lesion,* has long challenged the clinician. At the heart of the dilemma, the question remains unchanged: "Is it malignant or benign?" When faced with a pulmonary nodule, the clinician and the patient usually have one of three choices: (1) observe it with serial chest computed tomography (CT), (2) perform additional diagnostic tests (imaging and/or a biopsy), or (3) remove it surgically.

The proper choice depends on epidemiology, radiographic appearance, assessment of surgical risk, and patient preferences. For malignant lesions, early surgical resection still represents the best chance for cure. On the other hand, unnecessary resection of benign nodules exposes patients to the morbidity and mortality of a surgical procedure. The aim of this chapter is to review what is known about the pulmonary nodule to formulate a diagnostic approach to this often controversial problem. The goal will be to arrive at a systematic approach that will promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules. To do this we need to have a clear definition of pulmonary nodules, information on their incidence and prevalence, the causes of malignant and benign nodules, the available imaging techniques, a method of estimating the probability of cancer, the strengths and weakness of serial CT imaging versus different biopsy techniques, and the impact of surgical risk and comorbidities on diagnostic strategies. These various considerations can then be integrated into an algorithm providing a unified approach to diagnosis and management.

DEFINITION

Pulmonary nodules should be characterized on the basis of number, size, and density as determined by CT. A solitary pulmonary nodule is defined as a single discrete pulmonary opacity that is surrounded by normal lung tissue that is not associated with adenopathy or atelectasis.[1,2] Previously there was controversy as to what constituted the upper size limit for defining a solitary pulmonary nodule. Some early series included lesions up to 6 cm in size.[3,4] However, it is now recognized that lesions larger than 3 cm are almost always malignant, so current convention is that solitary pulmonary nodules must be 3 cm or less in diameter.[5,6] Larger lesions should be referred to as pulmonary masses and should be managed with the understanding that they are most likely malignant; prompt diagnosis and resection is usually advisable.[7]

The term "solitary pulmonary nodule" was originally used when most nodules were detected incidentally by chest radiography. Today, most nodules are detected by CT, which greatly enhances nodule detection and characterization. However, we now recognize that many nodules that would have been characterized previously as "solitary" by chest radiograph are actually not solitary, since there may be other small nodules present. Thus, the classical definition of pulmonary nodules needs to be revised to take into account data from more recent CT-based studies.[1,7] As such, the term "solitary" should not be used for nodules accompanied by additional nodules or associated findings, or for nodules not completely surrounded by aerated lung.

CT has also increased awareness of subcentimeter nodules, which are defined as those ≤8 mm in diameter.[1,8–10] Subcentimeter nodules may be spherical or nonspherical, and malignant nodules may have either shape.[10] CT has also led to a more precise and nuanced classification of nodules according to their density. Nodules may have a pure solid appearance, a pure ground-glass appearance, or a mixed ground-glass and solid appearance. These characteristics can be used to help estimate the probability of cancer in the nodule.

INCIDENCE AND PREVALENCE

The incidence of pulmonary nodules and the probability of malignancy in those nodules vary widely, depending on the patient population; thus, many case series may not be directly comparable. This is a critical distinction when reviewing the literature. So the clinical context that led to nodule detection is a key factor to consider. Surgical case series, in which the denominator consists entirely of resected lung nodules, have a much higher prevalence of malignancy as compared to studies that use all nodules detected by chest radiograph or CT. Note that the prevalence of cancer seen in these surgical case series is not the same as the pretest probability of cancer for a newly identified lung nodule. Cancer prevalence in surgical series is high because the population being studied consists entirely of patients in whom the clinical suspicion of cancer based on prior testing has been deemed high enough to warrant the risk of surgery. Nodules unlikely to be malignant tend to be excluded from surgical case series. Given these limitations, surgical case series data can still be useful to gain insight into the factors that impact the probability of cancer, but the prevalence of cancer will be higher than in other clinical situations.

The frequency with which a pulmonary nodule is identified on chest radiography is on the order of 1 to 2 per 1000 chest radiographs.[11] Most of these are clinically silent, and about 90% are noted as an incidental finding on radiographic examination. Younger patients from areas where granulomatous diseases such as tuberculosis, histoplasmosis, and coccidioidomycosis are endemic can be expected to have a lower malignancy rate. In an Air Force Medical Center study from Illinois of 137 patients, only 22 (16%) had a malignancy.[12] Granulomas were diagnosed in 103 (75%) patients; 53 of them were attributable to histoplasmosis endemic to the area. Most of these patients (77%) were under age 45, and no malignant nodules were diagnosed in patients less than 35 years of age. This series predated the use of chest CT.

Importantly, the incidence of nodules and the probability of malignancy in the nodules are very different in more recent studies of low-dose CT screening for lung cancer among high-risk patients than in surgical case series. The prevalence of noncalcified nodules in observational studies of low-dose CT screening ranges from 13% to51%.[13–15] Among nodules that are identified on the first screening study, the prevalence of cancer ranges from 3% to 12%.[16] On follow-up CT imaging of the same population (i.e., incidence screens), the probability of new noncalcified nodules has varied widely, from 2.5% to 13%. The probability of cancer in these incidence nodules has varied from 5% to 23%.

MALIGNANT PULMONARY NODULES

Risk factors for malignancy have been identified from studies of pulmonary nodules and include patient age, smoking history, nodule size, and prior history of malignancy. Age is one of the most consistent risk factors. In a series of 370 resected indeterminate solitary pulmonary nodules, the incidence of malignancy increased from 63% for patients age 45 to 54 to 74% for ages 54 to 64 and continued to rise with age to 96% for those above the age of 75.[17] Since this was a surgical case series, in which the denominator consists of

resected lung nodules, the prevalence of malignancy is much higher as compared to studies of nodules detected by chest radiograph or during lung cancer screening, in which the denominator consists of all nodules detected. These findings correlate with those of previous studies, which also show that malignancy is very rarely found in patients under the age of 35.[12,18,19]

Smoking is closely correlated with the development of lung cancer, particularly squamous and small cell carcinoma. The Surgeon General's report of 1964 and subsequent studies have demonstrated that the risk of lung cancer increases with the duration of smoking and the number of cigarettes smoked. Average smokers have about a 10-fold risk and heavy smokers a 20-fold risk of developing lung cancer when compared to nonsmokers. Smoking is responsible for about 85% of the cases of bronchogenic carcinoma. Cessation of smoking will reduce this risk after 10 to 20 years, but it now appears that former smokers have a slightly higher risk of cancer throughout their lifetimes.

Nodule size is closely correlated to risk of malignancy. Several series have demonstrated an increased incidence of malignancy with increasing nodule size. Nodules larger than 3 cm will be malignant 80% to 99% of the time. In seven studies of nodules detected in lung cancer screening trials, the prevalence of malignancy was 0% to 1% in patients with nodules <5 mm in diameter, 6% to 28% for 5- to 10-mm nodules, 33% to 64% for 11- to 20-mm nodules, and 64% to 82% for nodules measuring >20 mm.[12,17,20–23]

Primary bronchogenic carcinoma is the most common malignant tumor that presents as a pulmonary nodule.[5,17,21,24] Histologically, adenocarcinoma and squamous cell carcinoma make up the majority; of the two, adenocarcinoma is the more common (Table 110-1). Of note, tumors that used to be called bronchioloalveolar cell carcinoma (BAC) have now been reclassified and the term adenocarcinoma in situ is used for BAC tumors once they have been confirmed by surgical resection. Small cell carcinoma presenting as a solitary pulmonary nodule is rare. Other rare primary lung tumors that may present as solitary pulmonary nodules are bronchial carcinoids, lymphomas, hemangioendotheliomas, and sarcomas.

Metastases may present as solitary pulmonary nodules in patients who have known primary malignancies or in whom the presence of primary malignancy is unknown. In up to 40% of such patients, who manifest only a single nodule on chest radiograph, CT scan may show other nodules that are not disclosed by plain chest radiograph.[25,26] Even though a lesion is solitary, 33% to 95% of nodules in patients with an established diagnosis of cancer will be malignant.[27–31] The most common histologic types of metastatic nodules are adenocarcinomas of the colon, breast, and kidney; head and neck tumors; sarcoma; and melanoma. Because of the high likelihood of malignancy, a nodule in a patient with an established diagnosis of cancer should be treated differently from other solitary nodules. Assuming no other obvious metastatic spread, one should consider proceeding directly to biopsy. Even in the presence of a known lung cancer, some of these nodules may represent a second primary pulmonary malignancy that is similar in histologic appearance. Immunohistochemistry and other confirmatory marker studies may be indicated to determine the nature of the nodule. A solitary pulmonary nodule in a patient with a history of malignant disease should be resected as long as there is no other evidence of recurrent or metastatic disease.

BENIGN PULMONARY NODULES

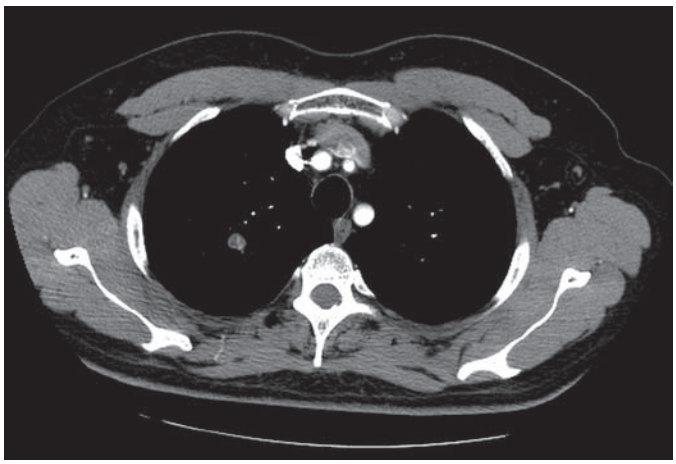
Benign solitary pulmonary nodules are more common in the young and in nonsmokers. Causes include benign tumors such as hamartomas, both infectious and noninfectious granulomas, vascular lesions, and rare miscellaneous conditions (Table 110-1).

Hamartomas are the most common benign tumors presenting as solitary pulmonary nodules. They are believed to be developmental malformations composed mainly of cartilage, fibromyxoid stroma, and adipose tissue. A review of six series with 3802 resected solitary pulmonary nodules found that 5% were hamartomas.[12,17,19,32–34] In a series of 215 hamartomas resected at the Mayo Clinic, the peak incidence was in the seventh decade of life; male-to-female ratio was 1:1; and the average size was 1.5 cm, although some were as big as 6 cm.[35] Most hamartomas were asymptomatic (97%), and 17% were noted to grow slowly on serial radiographic examination. They may be identified radiographically by a pattern of "popcorn" calcification, which is often intermixed with areas of low attenuation on CT scan representing fat deposits within the nodule. CT appearance will be diagnostic in about 50% of hamartomas (Fig. 110-1).[36]

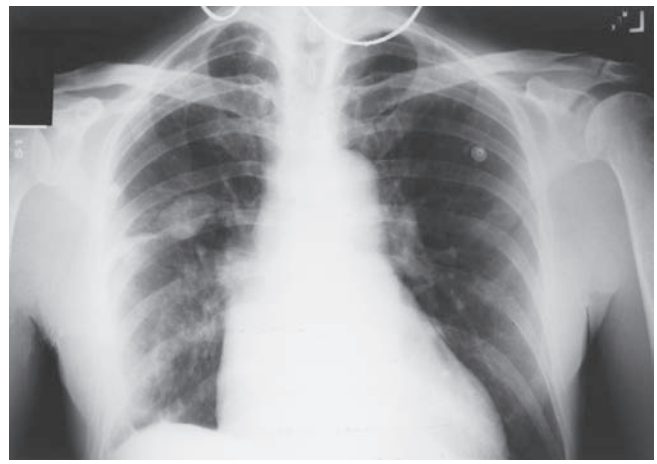
Infectious granulomas make up more than 90% of all benign nodules. They arise as a result of healing after infection from a variety of organisms. The offending agents will vary, depending on geographic

TABLE 110-1 Differential Diagnosis of Solitary Pulmonary Nodules

Malignant Tumors
Bronchogenic carcinoma (adenocarcinoma, large cell, squamous, small cell)
Carcinoid
Pulmonary lymphoma
Pulmonary sarcoma
Plasmacytoma
Solitary metastases (colon, breast, kidney, head and neck, germ cell, sarcoma, thyroid, melanoma, others)
Benign Tumors
Hamartoma
Adenoma
Lipoma
Infectious Granulomas
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Mycetoma
Ascaris
Echinococcal cyst
Dirofilariasis (dog heartworm)
Noninfectious Granulomas
Rheumatoid arthritis
Wegener granulomatosis
Sarcoidosis
Paraffinoma
Others
Miscellaneous
Bronchiolitis obliterans organizing pneumonia
Abscess
Silicosis
Fibrosis/scar
Hematoma
Pseudotumor
Spherical pneumonia
Pulmonary infarction
Arteriovenous malformation
Bronchogenic cyst
Amyloidoma



A



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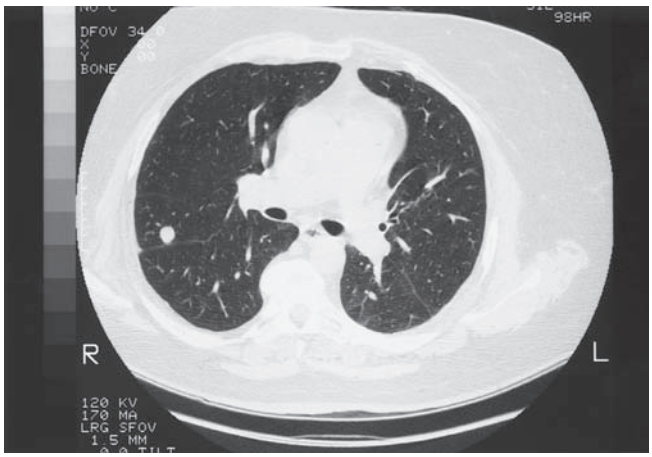

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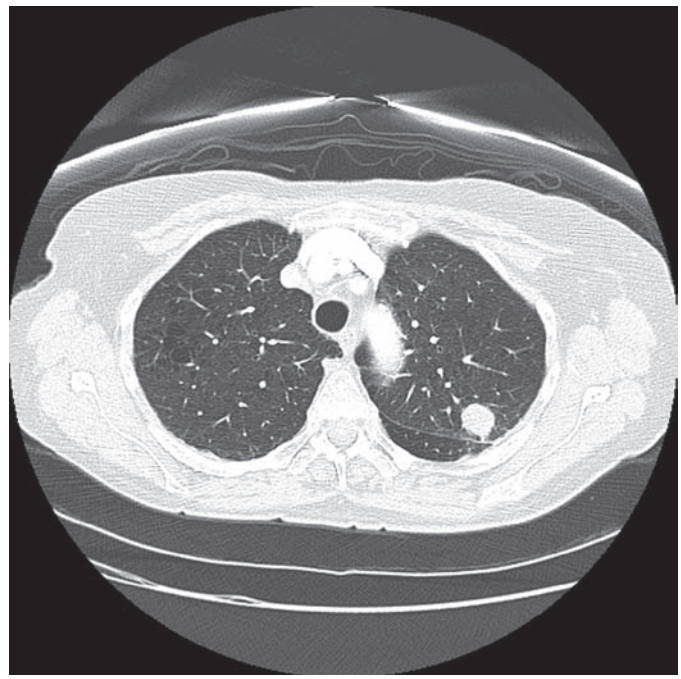


D

Figure 110-1 Benign pulmonary nodules and their radiographic patterns: **A.** Hamartoma with fat density within the nodule. **B.** Pseudotumor due to fluid in a fissure, the result of both pleural disease and fluid overload, has the appearance of a pulmonary mass. **C.** Noncontrast CT shows a round 1-cm nodule, with relatively high radiographic density, proven on resection to be a granuloma. **D.** Nodule with smooth border, diagnosis histoplasmosis.

location. Among the most common causes are histoplasmosis, coccidioidomycosis, and tuberculosis. Other, less common causes are dirofilariasis (dog heartworm), mycetoma, echinococcal cyst, and ascariasis. A history of exposure is important in establishing a possible infectious origin. Clues such as tuberculosis exposure history and skin test results, prior travel history, places of residence, occupation, and pets may be invaluable in some instances.

A variety of inflammatory diseases can also cause benign pulmonary nodules. Noninfectious granulomas sometimes present as pulmonary nodules in systemic diseases such as sarcoidosis, in which nodules are not invariably accompanied by hilar adenopathy. Rheumatoid arthritis may also be associated with pulmonary nodules, usually in patients with active rheumatoid disease who will also have subcutaneous nodules. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis) can also present with pulmonary nodules, which are often cavitary. In such cases there are usually multiple nodules and there may be concurrent renal disease.

Miscellaneous causes of benign pulmonary nodules have been described. Some of the more common conditions are lung abscess; rounded or spherical pneumonia; pseudotumor, which represents fluid in an interlobar fissure (Fig. 110-1); hematomas after thoracic trauma or surgery; and fibrosis or scars resulting from the resolution of infectious or inflammatory process. Rarer conditions presenting as pulmonary nodules include silicosis, bronchogenic cyst, amyloidosis, pulmonary infarct, and vascular anomalies. Arteriovenous malformations may also present as pulmonary nodules. They may grow slowly, and have a characteristic appearance on contrast-enhanced CT scan, with identification of afferent and efferent vessels emanating from and heading toward the hilum, respectively.

IMAGING TECHNIQUES

Imaging techniques are often helpful in distinguishing benign from malignant causes of pulmonary nodules, and as such they play a key role in their evaluation and management. During the last decade,

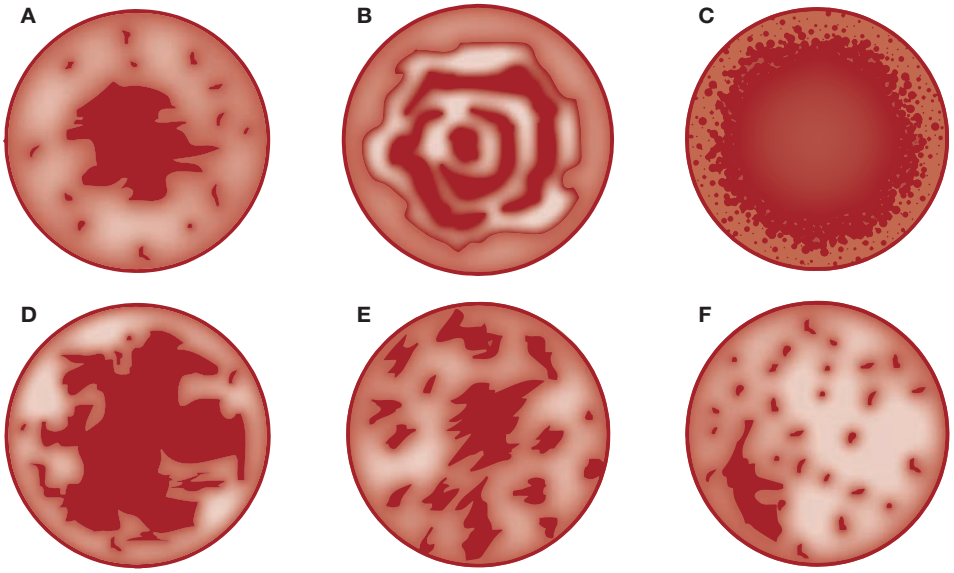


Figure 110-2 Patterns of calcification in nodules. **A.** Central. **B.** Laminated. **C.** Diffuse. **D.** Popcorn. **E.** Stippled. **F.** Eccentric. Patterns A, B, C, and D generally indicate a benign process; E and F suggest malignancy. *(Data from Lillington GA. Management of solitary pulmonary nodules. Dis Mon. 1991;37(5):271–318.)*

rapid advances in both CT and positron emission tomography (PET) have dramatically changed the diagnostic approach to pulmonary nodules. However, this does not mean that these techniques should be used indiscriminately. Cost-effective strategies to manage pulmonary nodules require that we understand the performance characteristics (sensitivity, specificity), strengths, and weaknesses of each of these technologies, so that they can be applied properly.[37] The primary technologies that need to be considered are plain chest radiography, CT, and PET.

■ PLAIN CHEST RADIOGRAPHY

Many pulmonary nodules are discovered on routine plain chest radiograph while asymptomatic. Nodules are usually identifiable on chest radiograph by the time they are 0.8 to 1 cm in diameter, although nodules 0.5 to 0.6 cm can occasionally be seen.[11] Most will be identified on posteroanterior (PA) projection, but some will be seen only on lateral projection, so standard PA and lateral chest radiography should be obtained whenever possible. When a nodule can be seen only on one projection, the clinician should question whether it is truly in the lung parenchyma. Structures overlying the lungs, such as leads used for cardiac monitoring, nipple shadows, skin lesions, and rib lesions can all mimic a pulmonary nodule, as can pulmonary vessels viewed end on. If in doubt, a CT should be done. Once it has been ascertained that a true nodule exists, the first step is to make every effort to obtain previous radiographs for comparison. A solid nodule that has remained stable with no increase in size for 2 years by CT is very likely benign and warrants no further investigation. Conversely, a nodule that was not present on a comparable radiograph within the past 2 months is unlikely to be malignant, having grown so rapidly.

■ COMPUTED TOMOGRAPHY

Chest CT should be part of the evaluation of all lung nodules, either alone or as part of a combined PET-CT. As with chest radiography, comparison with old films is critical, since it can provide an estimate of the growth rate over time. CT can pinpoint the exact location of the nodule and provide three-dimensional images of the lesion. Thin-section high-resolution CT can better define the borders and the nodule's relation to adjacent structures, such as vessels and the pleura.[23,38] CT is also more sensitive than standard chest radiographs in detecting calcifications and can quantify calcification in nodules even when they are not readily visible to the naked eye.[23,39] Nodules with higher radiographic density are more likely to be benign (Fig. 110-1).

Calcification is generally an indication of benignity in a pulmonary nodule. Infectious granulomas tend to calcify with central, diffuse, or stippled patterns (Fig. 110-2). Laminar or concentric calcification is characteristic of granulomas caused by histoplasmosis. A popcorn calcification pattern is typically seen in hamartomas and when coupled with fat density within the same nodule is highly specific. Eccentric calcification patterns should make one suspicious for malignancy. It should be noted that, in general, 6% to 14% of malignant nodules exhibit calcification. When calcifications are present in malignant lesions, they are usually eccentric and few. Benign patterns of calcification (central, diffuse, laminar, or popcorn) are very rare in malignant nodules. In one study of 1267 solitary pulmonary nodules, only seven malignant nodules (0.6%) had a benign calcification pattern.[40] Most nodules with a benign calcification pattern can be observed with serial CT scans.

The edge characteristics of nodules can also offer insight into whether or not a lesion is malignant. Benign lesions are often well circumscribed with a round appearance whereas malignant nodules tend to have irregular or lobulated borders (Fig. 110-3). CT imaging characteristics that suggest malignancy include spiculated margins (likelihood ratio [LR] 5.5),[23,24,38] pleural retraction (LR 1.9), and a vessel sign (LR 1.7). The feeding vessel sign consists of a vessel leading directly to a nodule. This is often associated with septic embolism but also occurs with metastasis, arteriovenous fistulas, and rarely in lung cancer. Lobulated margins (LR 1.1) are associated with malignancy but the predictive value is low.[41] Other patterns that have been reported to be associated with malignancy include vascular convergence (which suggests vascular and/or lymphatic invasion),[42] a dilated bronchus leading into the nodule,[43] pseudocavitation ("bubbly" appearance thought to represent air bronchiolograms),[38] and true cavitation when it is associated with a thick and irregular wall.[44] However, none of these radiographic signs is entirely specific for malignancy. Malignancy is somewhat less likely if a bronchus sign is present although its predictive value is low. An air-bronchus sign can be seen in primary pulmonary lymphoma, but this is a very rare disease, accounting for less than 1% of all lung cancers. Malignancy is much less likely if a nodule has smooth or polygonal margins (LR 0.2).

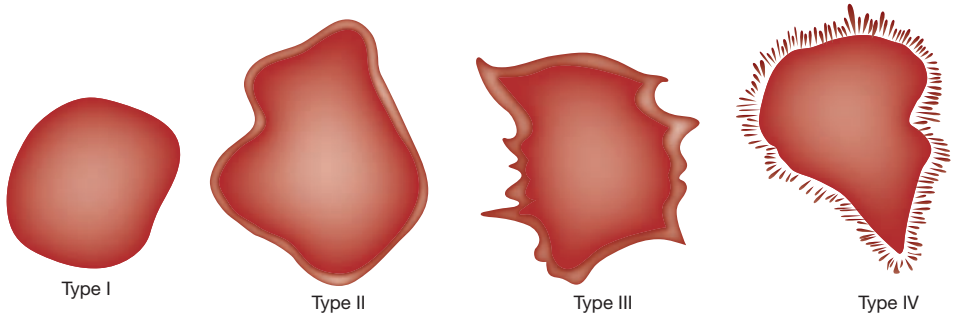


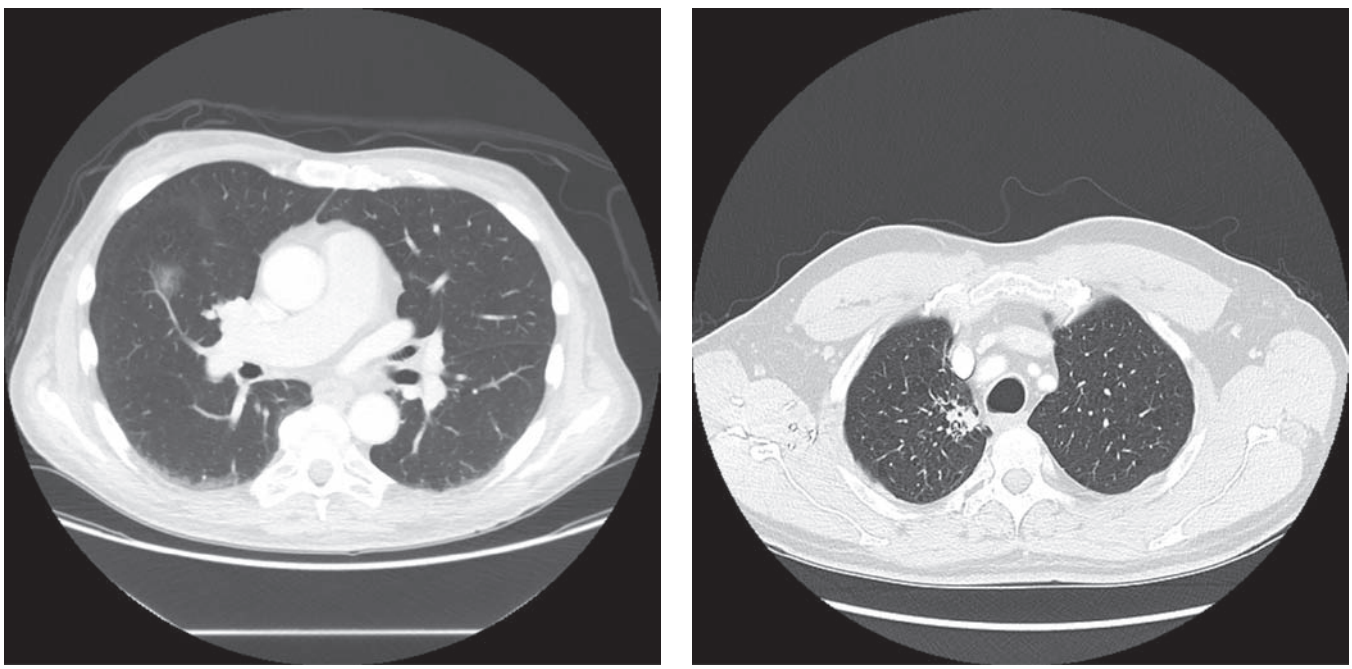
Figure 110-3 Characteristic appearance of nodule edges. Type I is sharp and smooth, type II is lobulated, type III has irregular undulations, and type IV is grossly irregular with many spiculations. *(Data from Siegelman SS, Khouri NF, Leo FP, Fishman EK, Braverman RM, Zerhouni EA. Solitary pulmonary nodules: CT assessment. Radiology. 1986;160(2):307–312.)*

Rapid advances in CT technology have also led to more precise characterization of the density of lung nodules. It is now appreciated that nodules may be characterized as solid, partly solid, or pure ground-glass opacities (defined as focal densities in which underlying lung morphology is preserved) (Fig. 110-4). This is particularly useful for categorizing small nodules (<1 cm) since these categories can help to distinguish benign from malignant nodules. The percentage of pure ground-glass opacities that are malignant varies significantly in the literature, from 18% to almost 60%.[45–47] For subcentimeter nodules, the likelihood of malignancy is similarly high in partly solid lesions, but much lower (<10%) in solid nodules.[45,47]

Ground-glass nodules may represent either atypical adenomatous hyperplasia (AAH) or adenocarcinoma in situ (formerly BAC).[42,48–55] In contrast, partly solid or solid nodules usually represent adenocarcinoma, but can also be caused by squamous cell carcinoma or small cell carcinoma. When pure ground-glass opacities start to grow and become more solid, demonstrating a replacement growth pattern, this should be considered highly suspicious for adenocarcinoma.[1,56,57] Of note, observed growth rates are often very slow for malignant ground-glass opacities, intermediate for partly solid nodules, and relatively fast for solid nodules.[58]

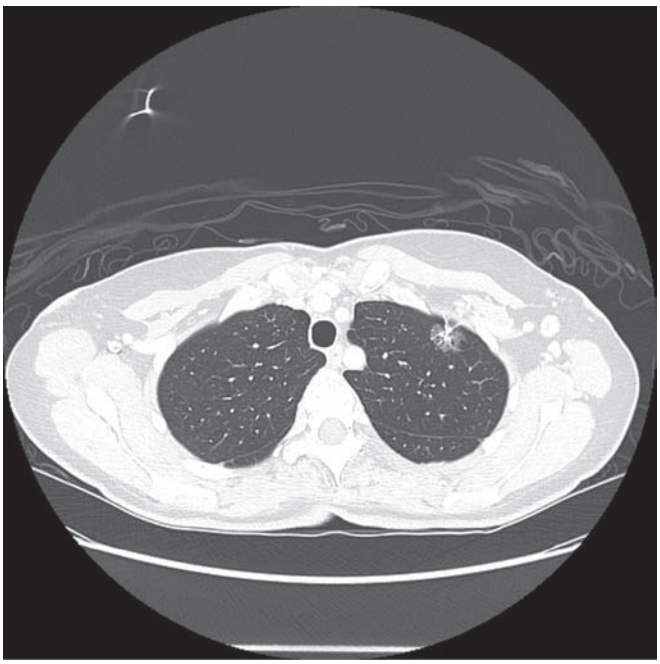
The superior resolution of multidetector scanners has also facilitated the development of volumetric CT. Volumetric CT may allow growing lesions to be identified earlier than conventional transverse CT. Preliminary studies demonstrated that three-dimensional volume analysis enabled tumor growth to be detected in 5-mm diameter nodules as early as 30 days after the initial CT.[59,60] Volumetric CT was successfully used to guide evaluation of small lung nodules in the NELSON trial.[8,61] In that trial, the investigators used serial volumetric CT measurements to calculate the doubling time of indeterminate lung nodules. CT volume doubling time of <400 days or a new solid component in a previously nonsolid nodule was defined as positive.[8] Follow-up imaging could detect growth as early as 6 weeks after imaging of an indeterminate nodule. The second round screening in this study had a sensitivity of 96.4%, specificity of 99.0%, positive predictive value of 42.2%, and a negative predictive value of 99.9%.

A complementary technique is dynamic CT, which uses iodinated IV contrast to look for enhancement of nodules.[62] Although malignant nodules enhance more than benign ones, benign lesions, such as

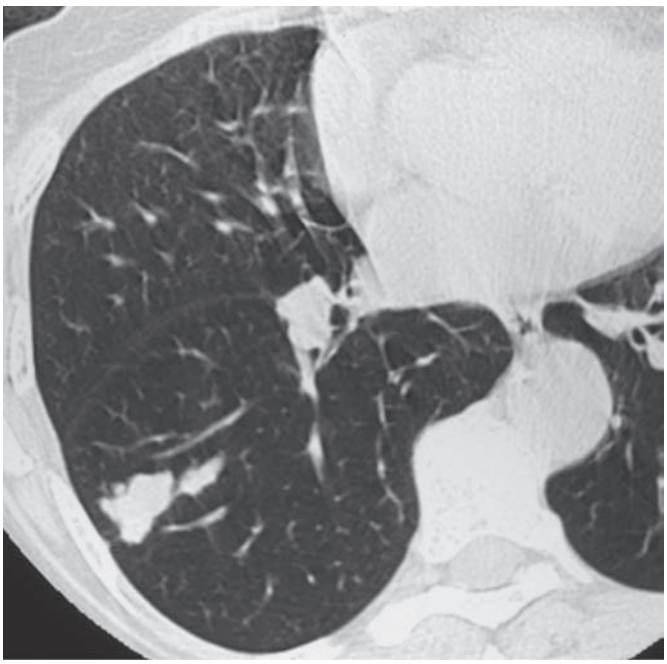


A B

Figure 110-4 Malignant nodules with different densities and borders: **A.** Ground-glass nodule, right middle lobe, diagnosis adenocarcinoma in situ. **B.** Air bronchogram with semisolid nodule, diagnosis adenocarcinoma. *(continued)*



C



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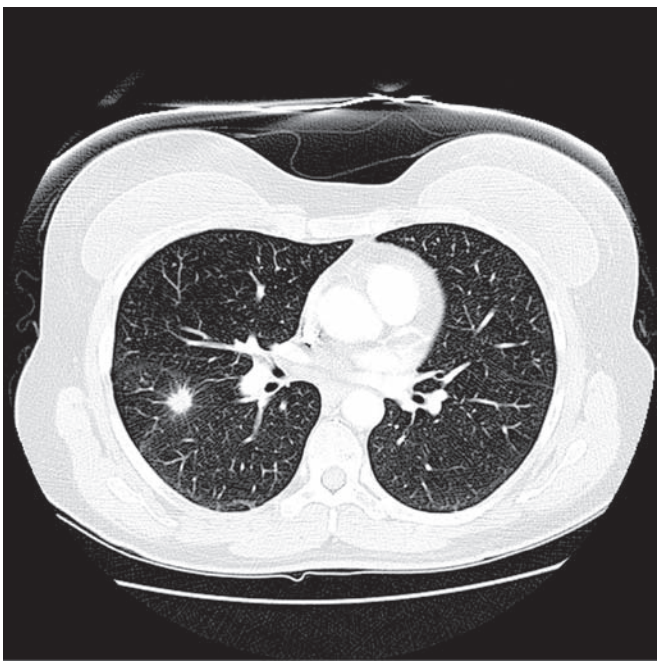

E

Figure 110-4 *(Continued)* **C.** Semisolid nodule **D.** Solid lung nodule, lobulated margin. **E.** Solid lung nodule, spiculated margin.

hamartomas and tuberculomas, may also enhance. Median sensitivity and specificity in seven studies from a systematic review were 96% and 75%, respectively.[20,62–68] In a multicenter trial using dynamic CT the negative predictive value was 97%. However, lack of specificity has limited the utility of this test, since it cannot reliably distinguish between malignant and active inflammatory or infectious nodules.[2] As a result few centers at the present time are using this approach.

■ POSITRON EMISSION TOMOGRAPHY

PET can be used to help differentiate noninvasively between malignant and benign nodules. PET takes advantage of the fact that tumor cells have increased glucose uptake and metabolism. A D-glucose analog labeled with a positron-emitting fluorine-18 radioisotope (FDG) is injected into the patient, and uptake by the nodule is then measured. Malignant nodules have a higher uptake of FDG. Sensitivity of PET in systematic reviews has ranged from 87% to 95%.[2,20,69] Integrated PET-CT scanners combine the CT and FDG imaging gantry, allowing more precise anatomic localization of areas of FDG uptake than dedicated PET imaging alone.[70–72] PET imaging also provides useful information regarding lung cancer staging, since it will occasionally detect unsuspected distant metastases.[73]

It is important to recognize that most studies of PET have used a single threshold level for discriminating malignant from benign nodules, typically a standard uptake value (SUV) of 2.5.[2,73] However, PET images actually provide a range of possible results, depending on the amount of uptake in the nodule as compared to that of the mediastinal blood pool. In a study of 344 patients undergoing PET-CT, the likelihood ratios (LRs) for benign, probably benign, indeterminate, probably malignant, and definitely malignant were 0.03, 0.15, 1.01, 3.2, and 9.9, respectively.[74] When FDG uptake was slightly greater than the mediastinal blood pool, this was considered as probably malignant. Substantially greater uptake was considered

as definitely malignant. Indeterminate readings were rare (1%). This study suggests that greater FDG uptake is more strongly associated with malignancy. Clinically, the implication is that physicians should consider not only whether a PET scan is positive, but should also consider the degree of FDG uptake when estimating the posterior probability of disease after PET imaging.

However, PET appears to be less sensitive for lesions less than 8 mm in size, so its use should be limited to those lesions ≥8 mm in size.[2,75] While there is limited preliminary evidence that PET may be useful for lesions as small as 8 to 10 mm in size, there are still too many false negatives reported to make PET useful for smaller lesions outside of a clinical trial at the current time.[76–78] False-negative findings have also been seen in patients with lepidic predominant adenocarcinomas (formerly BAC, also minimally invasive or adenocarcinoma in situ), carcinoids, and mucinous adenocarcinomas.[78,79] False positives have been seen in patients with granulomatous infections, such as tuberculosis, atypical mycobacterial disease, and endemic mycoses, as well as in patients with inflammatory conditions, such as rheumatoid arthritis and sarcoidosis.[80,81] Theoretically, false-positive results can also be caused by uncontrolled hyperglycemia.[82]

DISTINGUISHING BETWEEN BENIGN AND MALIGNANT NODULES

ESTIMATING PROBABILITY OF MALIGNANCY

Epidemiology, knowledge of the different causes of malignant and benign nodules, and the imaging characteristics of the nodule all serve to inform the physician as to the probability of malignancy in a given nodule. While physicians often estimate pretest probability of cancer intuitively, several investigators have attempted to develop mathematical models to estimate the probability of malignancy of indeterminate pulmonary nodules.[83–86] Using clinical and radiographic characteristics of malignancy derived from the literature, these authors have analyzed some combination of the following risk factors by Bayesian, neural network, and other methods to obtain a mathematical estimate of the probability of malignancy: nodule size, location, growth rate, margin characteristics, age of the patient, smoking history, prevalence of malignancy in the community, and occult calcification on CT densitometry.[83–85,87–90]

For example, in the Bayesian approach, each risk factor for a particular patient and nodule is assigned a LR of malignancy derived from published data. In one model, overall prevalence of malignancy, diameter of the nodule, patient's age, and smoking history were considered.[84] The LRs for malignancy of each of these factors were then multiplied to provide odds of malignancy, which are then converted into a percent probability of cancer. In a computerized neural network model that utilizes nonlinear mathematics to analyze input data, risk factors for malignancy were used and compared to the results of Bayesian analysis.[85] The authors found that their neural network was not as accurate as Bayesian analysis in predicting malignancy.

One of the problems with these and other methods is the quality of the input data (i.e., the LRs), which may not be representative of all patient populations. In addition, Bayesian analysis presupposes that the LRs for a particular risk factor are not affected by the presence or absence of any other factor. It is not clear that this is true of the LRs. Therefore, although mathematical models to predict probability of malignancy may seem attractive, the complexity of the issue once again leaves us with an uncertain answer. This may explain why the previously described methods are not in widespread clinical use. It is worth noting that the accuracy of models for predicting malignancy appears to be similar to that of expert physicians, although the correlation is poor, which suggests that models may provide additional insights.[87]

However, assessment of the pretest probability of malignancy is central to optimal strategy selection when managing pulmonary nodules.[1,2,37,56,91] While these formulas and neural networks may lack precision on an individual patient level, they can serve to inform decision making as to what risk factors to pay attention to and how important they are relative to each other.[5] Risk factors associated with a low probability of malignancy include diameter less than 1.5 cm, age less than 45 years, absence of tobacco use, having quit for 7 or more years, and a smooth appearance on radiographic imaging. Risk factors associated with a moderately increased risk of malignancy include diameter 1.5 to 2.2 cm, age 45 to 59, smoking up to 20 cigarettes per day or being a former smoker within the last 7 years, and a scalloped edge appearance on radiography. Risk factors associated with a high risk of malignancy include a diameter of 2.3 cm or greater, age greater than 60 years, being a current smoker of more than 20 cigarettes per day, a history of prior cancer, and a corona radiata or spiculated appearance on radiography.[4,5,87,92–94]

After consideration of these risk factors and possibly using one of the validated models to arrive at an estimate of the pretest probability of malignancy, physicians must then choose between alternative strategies. The main alternatives are (1) careful observation with serial CT imaging; (2) nonsurgical biopsy using CT guidance or bronchoscopy; or (3) surgery. The results of each strategy help to further refine the probability of malignancy, either up or down. As such, it is important to consider the strengths and weaknesses of each of these approaches.

CAREFUL OBSERVATION WITH SERIAL CT IMAGING

Careful observation with serial CT is predicated on the ability of the imaging technology to detect nodule growth. The fundamental assumption is that by comparing serial images over time a nodule's growth rate can be determined and this in turn can be used to help distinguish between benign and malignant nodules. Squamous and large cell tumors have an average doubling time (i.e., the time for a nodule to double in volume) of 60 to 80 days. Adenocarcinomas double at about 120 days, and the rare small cell carcinoma that presents as a solitary pulmonary nodule can have a doubling time of less than 30 days.[27] A nodule that has doubled in weeks to months is probably malignant and should be removed when possible.[5] Benign nodules have doubling times of less than 20 days or more than 400 days. A nodule that doubles in size in less than 20 days is usually the result of an acute infectious or inflammatory process, while those that grow very slowly are usually chronic granulomatous reactions or hamartomas. Nodules with doubling times over 400 days can be observed with serial radiographs.[1,2,5] This is the basis for the clinical axiom that 2-year radiographic stability is strong presumptive evidence that a nodule is benign.

It should be noted that controversy remains regarding how long follow-up should be continued. While traditional teaching has recommended observing lesions for a maximum of 2 years, it is now recognized that for some lesions longer follow-up may be warranted. Long doubling times have been observed in malignant lesions that presented as ground-glass nodules or as partially solid nodules.[48,54,58] As a consequence, longer follow-up extending over years may be appropriate in patients with pure ground-glass nodules, especially if there is an antecedent history of lung cancer.[95] However, for most solid nodules, 2 years of follow-up without evidence of growth is sufficiently long to warrant discontinuation of CT imaging.

Determination of nodule growth is based on the assumption that nodules are more or less spherical. Growth of a sphere must be considered in three-dimensional volume, not in two-dimensional diameter. The formula for volume of a sphere is $4/3(\pi)r^3$, or $1/6(\pi)d^3$, where r = radius and d = diameter. A nodule originally 1 cm in diameter whose diameter is now 1.3 cm has actually more than doubled in volume. Similarly, a 2-cm nodule has doubled in volume by the time its diameter reaches 2.5 cm. A nodule that has doubled in diameter has undergone an eightfold increase in volume. When

old radiographs are available, growth rate and nodule doubling time can be estimated. If the diameter of a nodule is measured at two different points in time (first t1 and later at t2), then doubling time in days = (t × log 2)/[3 × log (d2/d1)]. In this formula t is the number of days between t2 and t1; d1 and d2 are the diameters of the nodule at times t1 and t2, respectively. It is therefore critical that old radiographs and CT scans be obtained for comparison when evaluating pulmonary nodules, since they can provide valuable insights into the doubling time and natural history of the nodule.

Accepting the assumption that a tumor arises from serial doublings of a single cancerous cell, we can estimate that it will take 27 doublings for it to reach 0.5 cm. By the time a nodule is 1 cm in diameter, it represents 30 doubling times and about 1 billion tumor cells. Depending on the exact growth rate, this theoretical 1-cm nodule has probably existed for years before it is detected, as malignant bronchogenic tumors have doubling times estimated at between 20 and 400 days. The natural history of a tumor usually spans about 40 doublings, whereupon the tumor is 10 cm in diameter and the patient has usually died.[96]

Nodule growth rate and doubling times become clinically relevant when deciding how often to order follow-up imaging when observing a pulmonary nodule. The question often arises whether observing a pulmonary nodule for an extra 3 to 6 months increases the likelihood of metastatic disease, since that nodule has probably been growing for years. There is no convincing empiric evidence to support this hypothesis. Whether delays longer than 3 to 6 months are safe is unknown. However, estimating this hazard of delay is clinically relevant, since the optimal frequency of serial CT follow-up imaging to monitor nodules for growth is predicated on limiting this hazard of delay. The question is, how frequently do follow-up scans need to be done to minimize the hazard of delay while containing costs and avoiding excessive radiation exposure?

Traditional practice, based on little empiric evidence, recommended that when a careful observation strategy was warranted, repeat CT scans be done at 3, 6, 12, and 24 months.[5] However, more recent data from lung cancer screening trials using CT imaging suggests that a less aggressive practice may be reasonable in some patients with very small nodules.[1,2,8,92,97–99] Therefore, decisions about the frequency and duration of follow-up for patients with pulmonary nodules need to consider multiple dimensions of the problem, including clinical risk factors, nodule size, radiation dose, surgical risks, patient preferences, cost, and the limits of imaging technology resolution (especially at sizes less than 5 mm).[100–102] All of these can affect the optimal frequency of CT follow-up.

The ability to detect nodule growth is a function of image resolution. CT imaging greatly improved the ability to detect nodule growth as compared to conventional chest radiographs. This has made the careful observation strategy with serial imaging more effective, since it limits the hazard of delay by allowing earlier detection of growth. However, the accuracy of size measurements is still a problem when nodules are small. There is poor inter- and intraobserver variability when size differences of <1.5 mm are being assessed with two-dimensional (2D) CT.[103,104] As a result, 2D measurements of small nodules may not always be reliable. The presence of growth was incorrectly assessed in 27% to 37% of CT scan pairs when diameters or cross-sectional areas were used as compared to a reference standard of volumetric measurement.[2,101,105,106] Limited data suggests that volumetric measurements may provide a better alternative. When evaluated retrospectively, volumetric measurements using two CT scans performed a median of 3.7 months apart with a threshold volume doubling time >500 days was found to be 91% sensitive and 90% specific for malignancy. Another small study of predominantly solid nodules found that volumetric imaging changed management strategy in 10% of cases.[107] Volumetric imaging and doubling times were also used successfully to guide management in the NELSON lung cancer screening trial.[8] Unfortunately, volumetric measurement is time consuming and labor intensive and therefore has not yet become the standard of care.

TABLE 110-2 Schedule for Conducting Serial CT Imaging on Solid Nodules

Nodule Size	Solid Nodule and No Lung Cancer Risk Factors	Solid Nodule with Lung Cancer Risk Factors
≤4 mm	No follow-up needed	• CT in 12 mo • No additional imaging if there is no change
>4–6 mm	• CT in 12 mo • If no change then no additional follow-up	• CT at 6–12 mo • Repeat CT at 18–24 mo provided there is no change
>6–8 mm	• CT in 6–12 mo • Repeat CT at 18–24 mo provided there is no change	• CT at 3–6 mo • Repeat CT at 9–12 mo and 24 mo provided there is no change
>8 mm	• CT imaging at 3–6 mo • Repeat CT at 9–12 and 18–24 mo provided there is no change	• CT at 3 mo • Repeat CT at 6 mo, 12 mo, and 24 mo provided there is no change

Source: Data from Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S–e120S.

Given this framework, it is reasonable to apply more recent expert consensus-based guidelines to help guide the frequency of follow-up CT imaging for the pulmonary nodule.[2,95,108] For follow-up studies, imaging should be performed without contrast with thin sections using low-dose techniques.[2] Where available, volumetric CT may further facilitate growth detection and limit the hazard of delay. In all cases patients should be informed about the potential benefits and harms including the hazard of delay versus the risks of unnecessary testing. The frequency and duration of CT imaging for solid nodules in patients who are potentially treatable is shown in Table 110-2. For patients with indeterminate pure ground-glass nodules and patients with part-solid nodules the frequency and duration of surveillance is different (Table 110-3).

Patients with a solid indeterminate nodule or a part-solid, part ground-glass nodule that shows evidence of growth on serial imaging should have a nonsurgical biopsy or surgical resection. Similarly, any patient with a pure ground-glass nodule that develops a solid

TABLE 110-3 Schedule for Conducting Serial CT Imaging on Non-Solid Nodules

Pure Ground-glass Nodules	Part-solid, Part Ground-glass Nodules
Nodule size ≤5 mm: no follow-up needed	Nodule size ≤8 mm: CT imaging at 3, 12, and 24 mo with follow-up annual CT for 1–3 additional years
Nodule size >5 mm: re-evaluate at 3 mo. If there is no change then follow-up annually for 3–5 y	Nodule size >8 mm: CT imaging at 3 mo followed by PET and/or biopsy if nodules persist

component should have a nonsurgical biopsy or surgical resection. If a nonsurgical biopsy is chosen, then either a specific benign diagnosis (e.g., hamartoma) or a diagnosis of malignancy must be made. If the biopsy is nonspecific (e.g., inflammation) then surgical resection should be considered.

NONSURGICAL BIOPSY TECHNIQUES: CT-GUIDED TRANSTHORACIC NEEDLE BIOPSY

CT-guided transthoracic needle biopsy is most useful for peripheral lesions in the outer third of the lung, and in lesions under 2 cm in diameter. The sensitivity of CT-guided transthoracic needle biopsy for malignancy is 90%.[109] The major limitation of CT-guided transthoracic needle biopsy is its high rate of pneumothorax, with reported rates ranging from 10% to 35% overall.[42,110] In a recent cross-sectional analysis of 15,865 patients, the rate of any pneumothorax was 15% and the rate of pneumothorax requiring a chest tube was 7%.[111] Risk factors associated with pneumothorax include older age, smoking, emphysema, smaller lesions, deeper locations, lateral puncture site, proximity to fissures, and low entry angle to the pleura.[1,112,113] Because of the high rate of pneumothorax and its possible complications, the following patients should not undergo percutaneous needle aspiration: those with severely limited pulmonary reserve, those with bullous emphysema or blebs in the needle path, and postpneumonectomy patients. Other relative contraindications are bleeding diathesis, inability to hold breath, and severe pulmonary hypertension. Bronchoscopy can sometimes be used when percutaneous needle aspiration is contraindicated.

Importantly, CT-guided transthoracic needle biopsy does not always provide a specific benign or malignant diagnosis. Such nondiagnostic results occur in 4% to 41% of cases.[2] Because of this, if the pretest probability of cancer is high, then a nondiagnostic result does not necessarily rule out malignancy and additional testing or observation with serial CT may be warranted.

NONSURGICAL BIOPSY TECHNIQUES: BRONCHOSCOPY

Traditionally, bronchoscopy has been regarded as a procedure of limited usefulness in the evaluation of solitary pulmonary nodules.[114,115] Studies have shown variable success rates, with an overall diagnostic yield of 36% to 68% in nodules greater than 2 cm with bronchoscopic biopsy, brushings, and washings.[116,117] In general, the yield for specific benign diagnoses has ranged from 12% to 41%.[32,116] Complication rates are low at about 1% to 2%, with most of the risk being associated with the transbronchial biopsy component of the bronchoscopy.[118,119]

Factors to consider when deciding on the suitability of bronchoscopy for diagnosis of a pulmonary nodule include the size of the nodule, its location, the presence of air bronchograms, and the availability of new bronchoscopic technologies. In terms of nodule size, the sensitivity of conventional bronchoscopy is significantly worse for smaller lesions. The overall sensitivity when combining cytology brushing, transbronchial biopsy, and bronchoalveolar lavage was 34% for lesions <2 cm in diameter and 63% for lesions >2 cm.[109,120] Location also matters: nodules located in the inner or middle one-third of the lung have the best diagnostic yield; nodules in the outer one-third have a much lower diagnostic yield and as such are often best approached with CT-guided transthoracic needle aspiration if biopsy is needed. Another characteristic of pulmonary nodules to consider when deciding on the role of bronchoscopy is the relation of the nodule to neighboring bronchi.[109,121] Tsuboi et al. described four types of tumor–bronchus relationships: (1) the bronchial lumen is patent up to the tumor; (2) the bronchus is contained in the tumor mass; (3) the bronchus is compressed and narrowed by the tumor, but the bronchial mucosa is intact; and (4) the proximal bronchial tree is narrowed by peribronchial or submucosal spread of the tumor or by enlarged lymph nodes (Fig. 110-5). The presence of types I and II, a bronchus leading to or contained within the body of a nodule or mass on CT, has subsequently been termed a positive bronchus sign. When a bronchus sign is present on CT, the diagnostic yield of bronchoscopy can be as high as 60% to 90%.[109,122,123] With a negative bronchus sign, the yield drops to 14% to 30%. Signs and symptoms of airway involvement (cough, hemoptysis, localized wheezing), although rare in solitary pulmonary nodules, will increase diagnostic yield when present.

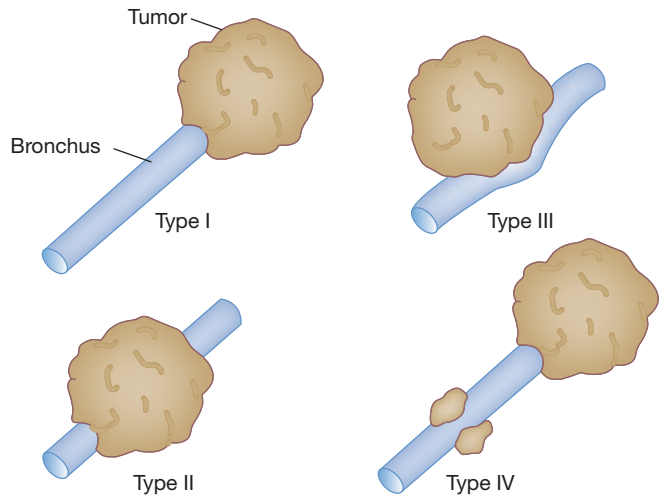

Figure 110-5 Schematic illustration of tumor–bronchus relationships (see text). *(Data from Tsuboi E, Ikeda S, Tajima M, Shimosato Y, Ishikawa S. Transbronchial biopsy smear for diagnosis of peripheral pulmonary carcinomas. Cancer. 1967;20(5):687–698.)*

New bronchoscopic technologies include electromagnetic navigation and guidance (EMN), radial endobronchial ultrasound (EBUS), ultrathin bronchoscopy, guide sheath techniques, and virtual bronchoscopic navigation. Importantly, many of these techniques can be used together. A systematic review of radial EBUS with transbronchial biopsy demonstrated 73% sensitivity for all lesions and 71% sensitivity for nodules <25 mm in size.[124] EMN with transbronchial biopsy for peripheral lesions has been reported to have a sensitivity ranging from 44% to 75%.[2,125–127] In a systematic review the diagnostic yield of EMN was 67%, radial EBUS was 71%, ultrathin bronchoscopy was 70%, guide sheath techniques was 73%, and virtual bronchoscopy 72%.[118] Note that in many of the studies cited, investigators would use multiple modalities concurrently—for example, a study using radial EBUS with a guide sheath and virtual bronchoscopy would be included in all three categories. As such, it is difficult to tell the contribution of individual system components, since what is truly relevant is overall aggregate system performance. In addition, many of the studies did not report on the method of patient selection, but it is clear that proper patient selection is vital if high diagnostic yields are to be obtained with these technologies, since they are not suitable for all patients. The presence of an air-bronchus sign significantly increases the yield of these technologies and is probably among the best predictors of success.[127]

On balance, EMN, EBUS, and VB appear to increase the diagnostic yield of bronchoscopy in select centers with the appropriate expertise, although the magnitude of the benefit for each of these technologies is difficult to quantify and there is a paucity of randomized controlled data. In cases in which there is an air-bronchus sign, or in cases in which there are very central lesions abutting the large airways, bronchoscopy may be of use. Similarly, if there is a suspicion for unusual infections (e.g., tuberculosis or fungal infections), then bronchoscopy may be warranted. The complication rate of bronchoscopy is also significantly lower than that of CT-guided biopsy.

As with CT-guided biopsy, bronchoscopy does not always provide a specific benign or malignant diagnosis. Because of this, if the pretest probability of cancer is high, a nondiagnostic bronchoscopy result does not necessarily rule out malignancy and additional testing or observation with serial CT may be warranted. It should also be mentioned that routine preoperative staging bronchoscopy is of no value in asymptomatic patients with a solitary pulmonary nodule smaller than 3 cm because it has not been shown to alter management decisions.[114,115] For most patients with pulmonary nodules without mediastinal adenopathy bronchoscopy will not play a major role since the sensitivity of CT-guided biopsy is considerably higher.

SURGERY: THORACOTOMY AND THORACOSCOPY

Surgical biopsy can be achieved with video-assisted thoracoscopic surgery (VATS), traditional thoracotomy, or a combination of both. If the frozen section demonstrates a benign lesion, then only a wedge resection may be required and if that is the case then operative mortality will be low (~0.5%).[56] Conversely, if the lesion is malignant and the patient has sufficient pulmonary reserve a lobectomy using either open thoracotomy or VATS with systematic lymph node sampling remains the standard of care.

Lobectomy mortality is 1% to 4%.[1] Mortality is higher in patients over age 70 and in patients with malignancy. These patients will often have other coexisting illness, such as chronic obstructive pulmonary disease (COPD) or coronary artery disease. The mortality risk increases with the extent of the procedure. In one series by Ginsberg et al.,[128] the mortality was 1.4% for wedge resection, 2.9% for lobectomy, and 6.2% for pneumonectomy. A more recent observational study of lung cancer surgery reported similar 30-day mortality rates.[129] Of note, this study indicated that there may be a relationship between volume of surgeries performed and outcome. Hospitals that performed the highest volume of lung cancer surgeries had lower 30-day mortality than those that had the lowest volume (3% vs. 6%).

VATS uses fiberoptic telescopes and miniaturized video cameras to facilitate biopsies and resection. VATS represents a complementary approach to traditional thoracotomy and can be very useful in some patients. This approach still requires general anesthesia but does not require a full thoracotomy incision or spreading of the ribs. VATS allows the experienced surgeon to identify and wedge out peripheral nodules in many cases with minimal morbidity and mortality. In a series by Mack et al.,[130] 242 nodules were resected with no mortality and minimal morbidity. Average hospital stay was 2.4 days. VATS can spare some patients with benign nodules the risks of open thoracotomy and can be useful for wedging out nodules in patients who have limited pulmonary reserve who cannot otherwise tolerate a lobectomy. However, in up to 12% of cases conversion from VATS to a minithoracotomy will still be required.[131–135]

Whether resection is performed by VATS or by thoracotomy, lobectomy with systematic lymph node sampling remains the procedure of choice for malignant solitary pulmonary nodules.[136] Wedge excisions or segmental resections for smaller cancers have been evaluated, but the role of these limited pulmonary resections in the management of lung cancer remains controversial. The Lung Cancer Study Group evaluated this in a study of 276 patients with T1N0 lesions that were strictly staged to prove N0 status. Patients were randomized to lobectomy or limited resection.[137] In patients undergoing limited resection, there was an observed 75% increase in recurrence rates ($p = 0.02$) attributable to an observed tripling of the local recurrence rate ($p = 0.008$), an observed 30% increase in overall death rate ($p = 0.08$), and an observed 50% increase in death with cancer rate ($p = 0.09$) compared to patients undergoing lobectomy. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy has been recommended as the surgical procedure of choice for patients with peripheral T1N0 nonsmall cell lung cancer.

For patients with insufficient pulmonary reserve to tolerate a lobectomy, segmentectomy or wedge resection remains a viable alternative. In addition, whether or not very small malignant lesions, less than 2 cm in size, can be managed with segmentectomy, radiation, or some combination thereof, remains controversial and is the subject of ongoing research. The original randomized trial used both wedge resections and segmentectomy, but more recent data suggests that segmentectomy is superior to wedge resection for tumors <2 cm in size.[138–140] At the present time, it is reasonable to recommend lobectomy with systematic lymph node dissection for all patients with malignant solitary pulmonary nodules who have sufficient pulmonary reserve to tolerate the procedure, with consideration of segmentectomy for those patients with inadequate pulmonary function to tolerate a lobectomy.

THE IMPACT OF SURGICAL RISK ASSESSMENT ON DIAGNOSTIC STRATEGY

For patients with pulmonary nodules, optimal management strategy depends on both probability and consequences. Factors to consider when calculating the probability of cancer have been reviewed earlier. If the probability of cancer is very close to 0, then a careful observation strategy with serial CT imaging will be superior. At the other extreme, if the probability of cancer is very close to 1, proceeding directly to surgery after an appropriate staging work-up will be best. When the probability of cancer is in the intermediate range, a nonsurgical biopsy will be warranted.

Clearly there must be some probability threshold at which the optimal strategy changes from one option to another (i.e., going from careful observation with serial CT scanning to nonsurgical biopsy to surgical biopsy). These probabilities are called decision thresholds.[1] The lower probability, when strategy changes from careful observation to nonsurgical biopsy we will call the "observation threshold." If the probability of cancer is below the observation threshold, careful observation will be warranted. The upper probability, when strategy changes from nonsurgical biopsy to surgical biopsy, we will call the "surgical threshold." If the probability of cancer is above this probability, then surgical biopsy with frozen section, usually followed by lobectomy if malignant, is warranted.

The factors that determine these decision thresholds are treatment consequences, specifically the relative potential for benefit and harm.[1,141] The benefit of treatment is defined as the difference in outcome between *patients with the disease* who receive treatment and similar patients who do not receive treatment. Harm is defined as the difference in outcome between patients *without the disease* who receive no treatment and similar patients who receive treatment. The treatment threshold probability is defined as the probability of disease at which the expected outcome of treatment and no treatment are exactly equal. As applied to pulmonary nodules, treatment usually refers to surgery and no treatment refers to careful observation with serial CT scans. The treatment threshold probability is equal to harm/(harm + benefit) which is the same as 1/(1 + [benefit/harm]).[141]

A useful way to conceptualize the treatment threshold is to imagine that there are no diagnostic tests available. At what probability of disease would empiric treatment be warranted? If a disease can be effectively treated (i.e., high benefit) and the impact of accidentally treating a patient without disease is minimal (i.e., low harm) then the treatment threshold will be low. An example would be using antibiotics to treat suspected meningitis. Conversely, if the treatment is not that effective (i.e., low benefit) and the consequences of accidentally treating a patient without disease are very bad (i.e., high harm) then the treatment threshold will be very high. A high burden of proof would be warranted in this case, for example, when using chemotherapy for cancer.

Once the treatment threshold has been determined the decision thresholds, including both the observation threshold and the

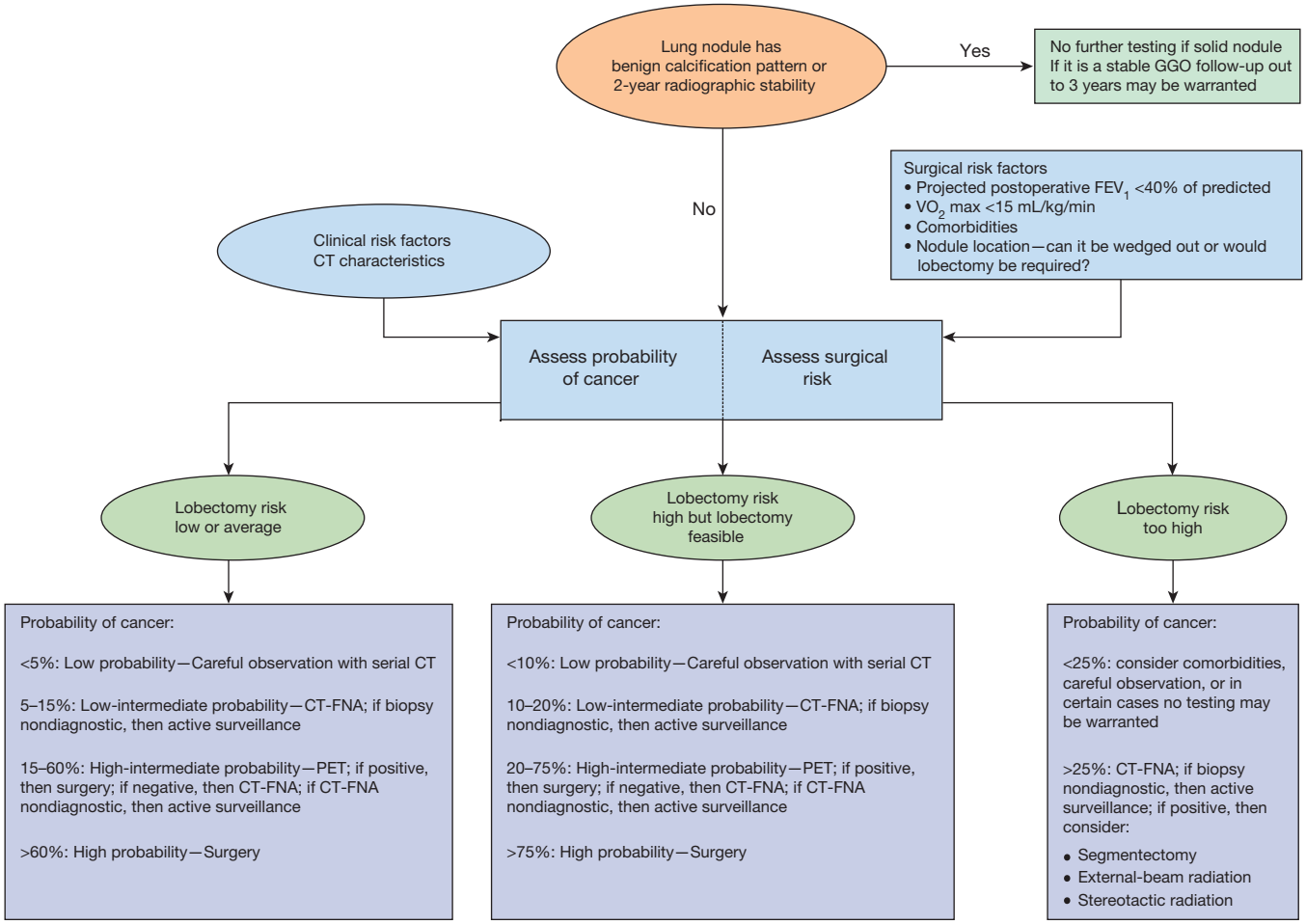

Figure 110-6 Systematic approach to the pulmonary nodule.

surgical threshold, can be calculated.[1,141] While the derivation of these thresholds is complex and has been published elsewhere,[1] it is conceptually easier to grasp the concept of decision thresholds by asking this question: Is there any test result that would shift the pretest probability of cancer from one side of the decision threshold to the other? For patients with a pretest probability that is above the treatment threshold, one possible strategy is to select a test (or tests) that if negative would result in a posttest probability of cancer below the treatment threshold. Alternatively, for patients with a pretest probability below the treatment threshold, a test(s) could be selected that if positive resulted in a posttest probability above the treatment threshold. Note that in the absence of perfect tests, there are some instances in which the pretest probability of cancer is so high that even if all tests were negative the resulting posttest probability would be greater than the treatment threshold. However, as the pretest probability decreases, it must reach some point at which a negative test result would indeed lower the posttest probability below the treatment threshold. For pulmonary nodules this is the surgical threshold. The opposite scenario is when the pretest probability of disease is exceedingly close to 0 such that even a positive test will yield a posttest probability less than the treatment threshold. As the pretest probability increases, there must be some point at which a positive test will indeed result in a posttest probability greater than the treatment threshold. This is the observation threshold.

Importantly the treatment threshold varies not only by disease, but also among patients with the same disease. Imagine two patients with the same probability of cancer with the same exact lung nodule in the same location. If one patient has normal pulmonary function and no comorbidities, the treatment threshold will be low. This is because the harms of accidentally doing surgery if he does not have cancer are relatively low. Conversely, if a patient has very limited pulmonary reserve and is much more likely to have complications, then the treatment threshold will be higher, because the potential for harm is higher. Note that we are not dealing with the probability of cancer here, but rather the severity of the consequences of treating or not treating. Of course, since the treatment threshold varies between patients, so too must the observation and surgical decision thresholds.

When we apply this to the pulmonary nodule, it becomes apparent that in addition to considerations about the probability of cancer, we must also consider the consequences of surgery and coexisting comorbidities. Assessing surgical risk is critical because it determines the benefits and harms, which will in turn determine the treatment threshold, the observation threshold, and the decision threshold. Patients with severe comorbidities (e.g., severe COPD, severe heart disease) will have higher treatment thresholds than patients who have good pulmonary reserve with little comorbidity. Differences in treatment thresholds will in turn change what constitutes optimal diagnostic strategy (Fig. 110-6).

SYSTEMATIC APPROACH TO THE PULMONARY NODULE

The goal is to promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules. Based on the previous discussion, the systematic approach to the pulmonary nodule should begin with a history and physical. The history and physical should focus on addressing the following questions: (1) What is the pretest probability of cancer? (2) What is the patient's surgical risk? This should include a detailed history of relevant comorbidities. These include

comorbidities that impact on surgical risk as well as severe competing diseases (e.g., severe Alzheimer's) that significantly limit life expectancy independent of cancer and surgical risk.

Surgical risk assessment should include spirometry and diffusion capacity for carbon monoxide (D_{LCO}). If pulmonary function is not normal, then quantitative perfusion scans may be warranted to calculate the projected postoperative FEV1 and D_{LCO}. If the projected postoperative FEV_1 and D_{LCO} are ≥40% of predicted the risk of pulmonary complications following surgery is acceptable. If one of the two measures is <40% while the other is ≥40%, pulmonary exercise testing may be useful to further risk stratify the patient. A $VO_{2\ max}$ ≥15 mL/kg/min is associated with a low risk of pulmonary complications following lobectomy. Other factors to consider include the location of the nodule. If the nodule is very peripheral and easily reached by VATS and wedge resection is feasible, then the potential harm of resecting a benign lesion will be relatively low. Conversely, if the nodule is very central, such that the only way to obtain a surgical biopsy is to do a lobectomy, then the potential harm of resecting a benign lesion will be high. These considerations in turn will impact the treatment threshold and hence optimal strategy.

A chest CT should be ordered if not already available and compared to all old chest radiographs and CT images (if available). A pretest probability of cancer should be estimated, based on clinical and radiographic features. If the lesion is a solid nodule and has demonstrated radiographic stability for 2 or more years no additional evaluation is warranted. If the lesion is a pure ground-glass nodule and has been unchanged for 2 years or less, serial CT may still be warranted.

At this point the physician should integrate the probability of cancer with the relative consequences of treatment. Treatment consequences should be considered by comparing the benefits of surgery if the patient has cancer with the potential harm of surgery if the patient does not have cancer. This determines the treatment threshold, which is the point around which the decision centers. These thresholds vary significantly between patients depending on their cardiopulmonary reserve, comorbidities, and individual preferences. Patient preferences for certain outcomes can play an important role in strategy selection, so physicians should discuss the risks and benefits of alternative strategies and elicit patient preferences.[2,37,88,142]

Management strategies can then be selected based upon the patient's surgical risk, probability of disease, and patient preferences (Fig. 110-6). Since individual patients vary widely, the probability thresholds provided are only estimates of a typical case – they represent an "average" case drawn from the body of evidence and derived from decision analysis studies.[37,88,143,144] However, it is important to remember that the median and mean are characteristics of populations, not individuals. The probability threshold for a given individual patient may be very different from those shown.

This is not to say that the probability thresholds are arbitrary but rather that for a given patient they are determined by multiple factors, including the individual patient's preferences, estimates of the effectiveness of surgery, the risks of surgery, the long-term consequences of surgery, estimates of the hazard of delay, the patient's comorbidities, the range of alternative diagnostic tests and their performance characteristics (sensitivity and specificity), and the range of alternative treatments.[145] The value of probability thresholds lies not in their precision, but in the underlying systematic approach that they represent and the recognition that careful assessment of the probability of cancer as well as the relative consequences of treatment is critical to determining optimal strategy.

Indeed there have been many decision analysis studies of solitary pulmonary nodules published over time, and the probability of cancer that defines low, intermediate, and high probability risk groups vary between studies.[37,88,143,144] In part, this is because diagnostic tests and treatments have changed over time so the underlying probability thresholds will of course vary over time. As new diagnostic and treatment alternatives become available, these thresholds need to be periodically reassessed.[145] However, even if technology were unchanging, patient preferences vary significantly, so defining a single "optimal answer" for all patients is not feasible. Given these constraints, all of the decision analyses published are fairly consistent, with low probability being approximately 5% to 12% or less, and high probability being approximately 60% to 72%.[37,88,143,144]

Keeping this in mind, we can gain some useful insights of a more general nature from a careful examination of Figure 110-6. While decision thresholds for individual patients vary because of the surgical risk, and hence the potential benefit and harm of surgery vary, the order of the preferred strategies is the same when going from lowest to highest pretest probability of cancer: careful observation with serial CT, then CT-FNA, then PET with possible CT-FNA, and then surgery. This is a consequence of the sensitivity and specificity of CT-FNA and PET as well as the risks associated with them.

The reason is as follows: Imagine the pretest probability is just above the observation threshold in the low-intermediate range. If a CT-FNA is done and it is nondiagnostic, the posttest probability of cancer will be somewhat lower, so careful observation will be warranted. The finding of a specific benign diagnosis (e.g., endemic mycosis) would lead to appropriate treatment. Because CT-FNA has close to 100% specificity for cancer, a positive result will raise the posttest probability of cancer high enough to warrant surgery.[20] In contrast, when the pretest probability is low, a PET will not be as useful because the specificity of PET is only 83%.[20,56] A positive PET scan increases the posttest probability of cancer, but the posttest probability of cancer will not be above the surgical threshold so it is not high enough to make a definitive treatment decision.

We can use the same approach to understand why PET is preferred when the pretest probability is in the high-intermediate range. Imagine that the pretest probability is just below the surgical threshold. The pretest probability is so high that any single negative test will not result in a posttest probability below the observation threshold. Thus a second negative test would be needed to lower the probability below the observation threshold. However, PET carries much less risk to the patient than CT-FNA. If PET is performed first when the pretest probability of cancer is high the posttest probability will be high enough to warrant surgery and the risks of CT-FNA will be avoided.

SUMMARY

Providing cost-effective, patient-centered care for patients with pulmonary nodules can be challenging because many factors must be considered simultaneously and technologies are constantly developing. Integrating current evidence with fundamental concepts from decision theory suggests that management of pulmonary nodules should begin with estimating the pretest probability of cancer. The consequences of treatment should be considered by comparing the benefits of surgery if the patient has cancer with the potential harms of surgery if the patient does not have cancer. This determines the treatment threshold. These thresholds vary widely among patients depending on their cardiopulmonary reserve, comorbidities, and individual preferences. For patients with a very low probability of cancer, careful observation with serial CT is warranted. For those with a very high probability of cancer, surgery is preferred. For patients with an intermediate probability of cancer, either CT-FNA or PET possibly followed by CT-FNA is best. Patient preferences should be considered because the absolute difference in outcomes between strategies may not be large. [2,88] Although the specific algorithms may change as technologies develop, the underlying principles remain the same. No set of guidelines can encompass all possible scenarios that occur in day-to-day clinical practice. It is important to recognize that the body of evidence is based on studies of populations, but that individual patients vary significantly in terms of their risks, potential

for benefit, and preferences. Applying these first principles in a systematic fashion will be useful for physicians, especially in challenging cases. Understanding the underlying concepts allows physicians to view the patient management process as a unified whole – a system of principles rather than a multitude of isolated facts.[1,145] Guidelines and algorithms are useful and provide a conceptual framework, but rote memorization and dogmatic adherence need to be avoided. Individualization of guidelines and application of their underlying principles to particular patients is the goal.

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CHAPTER 111

The Pathology of Bronchogenic Carcinoma

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There have been profound and fundamental changes in the significance of the histologic classification of bronchogenic carcinoma since the previous edition of this book. The past practice of simply dividing lung tumors into non–small-cell and small-cell lung carcinoma, particularly when evaluating small specimens in patients with advanced disease, was nearly always sufficient for providing the clinically relevant pathologic information that was necessary for treatment purposes. The development of new classes of drugs and targeted therapy for lung cancer has not only prompted an extensive reevaluation of the pathologic classification but has also affected strategies for tissue acquisition and routine processing. Rather than diminishing the traditional role of the pathologist in lung cancer treatment, the advent of what has been termed "personalized" or "precision" medicine has only made pathologic assessment more crucial to patient management.[1,2] This chapter focuses on the major histologic subtypes of malignant pulmonary epithelial tumors and includes carcinoid tumors, sarcomatoid carcinoma, and salivary gland tumors. Other unusual tumors, both benign and malignant, are covered in a separate chapter and there is a separate chapter on the genetic and molecular changes in lung cancer. The extremely rapid pace of developments in molecular diagnostics and therapy makes it quite difficult to make enduring summary statements about the prognostic and therapeutic implications for specific histologic subtypes. The overall intent of the chapter is to provide a broad overview of the current histologic classification with its controversies and to provide a deeper understanding of the current issues regarding the preanalytic steps of sampling, processing, and evaluating lung cancer specimens for molecular analysis.

GENERAL CONSIDERATIONS IN HISTOLOGIC CLASSIFICATION AND THE CURRENT CLASSIFICATION OF LUNG TUMORS

Pathologic assessments are continually refined to reflect changes in surgical and medical management, as well as to incorporate an improved understanding of basic tumor biology. Once the diagnosis of malignancy has been made, the pathologic evaluation of lung cancer has traditionally focused on histologic subtyping and, for the minority of patients undergoing surgical resection, determining the extent of disease. Histologic classification is essentially predicated on the assumption that the quantitative predominance of a particular histologic pattern reflects distinctive biologic characteristics. It has been gratifying to note that concurrent developments in other disciplines such as molecular biology have substantiated many aspects of the currently accepted framework for histologic classification. The 2004 World Health Organization (WHO) classification of lung tumors was the first edition to extensively summarize the molecular biology of different tumor subtypes.[3] Nevertheless, the main purpose of the 2004 WHO classification was to provide reproducible criteria to pathologists worldwide by using recognizable architectural patterns and individual cellular features that can be appreciated by routine light microscopy and standard hematoxylin- and eosin-stained slides. The use of ancillary techniques, such as immunohistochemistry or molecular biology, is not required in most instances, thereby making the classification accessible to all pathologists for diagnosis and fostering consistency in treatment and research protocols. Although this approach might seem antiquated, it should be noted that the incorporation of data from ancillary studies such as immunohistochemistry or molecular analysis has broad implications, not the least of which is the expense of the laboratory tests, which require additional time, special equipment, technical expertise, and the possibility of exhaustion of small tumor samples that are then no longer available for future testing. Criteria for the interpretation of some of these emerging molecular tests have yet to be well defined and the clinical significance addressed within the confines of prospectively designed, large clinical studies with standardized laboratory analysis.

The 1999 WHO classification introduced significant changes in the classification and nomenclature of malignant epithelial lung tumors from the previous 1982 WHO classification.[4] These changes reflected the substantial amount of pathologic observation and translational research that had ensued in the intervening 17 years. The 2004 revision made some minor changes in nomenclature but preserved the overall classification scheme that had been established in 1999. Major changes in the 1999 revision included the introduction of new variants of squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma, as well as new or refined definitions for bronchioloalveolar carcinoma (BAC) and solid adenocarcinoma. The 1999 revisions also incorporated consensus criteria for neuroendocrine tumors and biphasic or pleomorphic tumors. Although it is beyond the scope of this chapter to discuss in detail, it is worth noting that 1999 WHO revisions also added and defined two other preneoplastic processes – atypical adenomatous hyperplasia (AAH) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) – to the previously recognized squamous dysplasia/carcinoma in situ.

Tumor classification and associated generalizations pertaining to tumor type are often made to seem relatively straightforward but, in practice, it is always a challenge for any proposed scheme of histopathologic classification to ensure the reproducible recognition of tumor subtypes. One of the major criticisms of the current WHO classification is that the classification of lung cancer cell types is based on a detailed histologic examination of resection specimens despite the unfortunate fact that the majority of lung cancer patients present with advanced disease and never undergo resection. The 1999 and then the 2004 WHO classifications also had attempted

to reconcile the often bewildering heterogeneity of pulmonary adenocarcinomas by introducing the term "mixed" type. In practice this term ended up obscuring major differences between minimally and predominantly invasive adenocarcinomas and the potential prognostic significance of different histologic patterns in adenocarcinomas. The 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) International Multidisciplinary Classification of Lung Adenocarcinoma addressed these two major issues by proposing terminology for small biopsies/cytology specimens and by proposing a new classification for adenocarcinomas.[5] The overall framework of this classification has been generally accepted and adopted but with some criticism, particularly in regard to the new category of "lepidic predominant adenocarcinoma."[6] Despite these refinements, the degree to which histologic heterogeneity is recognized and tumors classified depends to some extent on sampling techniques, and that may, in turn, have implications for protocol design and data evaluation. The effects of prior therapy must also be considered in subsequent biopsies.

Lung carcinomas are classified according to the best differentiated component and pathologists assign a degree of differentiation to tumors that show differentiation, such as squamous cell carcinoma and adenocarcinoma. This is also known as histologic grading and it is used in tumor pathology as a way of attributing prognostic significance to a specific histologic pattern. It is an assessment as to how much the tumor cells phenotypically resemble a normal cell type, such as a squamous cell or a glandular cell. Histologic grading should not be viewed as a histogenetic determination, that is, that a tumor is derived from a specific cell of origin, such as a squamous cell, or that the tumor cell has "dedifferentiated" from a cell of origin. There are three histologic degrees of differentiation: well differentiated, moderately differentiated, and poorly differentiated. Many lung tumors show a wide variation in differentiation. If a tumor is largely undifferentiated but contains recognizable foci of squamous cell carcinoma or adenocarcinoma, it is classified as a poorly differentiated squamous cell carcinoma or adenocarcinoma, respectively. Some tumors, such as small-cell carcinoma or sarcomatoid carcinoma are, by definition, poorly differentiated. In recent years, the most intense focus has been on developing a standardized histologic grading system for pulmonary adenocarcinomas and these efforts will be summarized in the subsequent section on adenocarcinoma.

Only one study to date has provided data on the interobserver reproducibility for non–small-cell lung carcinomas with routine hematoxylin–eosin slides for the current 2004 WHO classification.[7] In this study, which included both community pathologists and expert pulmonary pathologists, overall interobserver reproducibility was only fair ($\kappa = 0.25$) when using all 44 diagnostic categories of malignant epithelial tumors, with improvement following consolidation into 10 diagnostic categories ($\kappa = 0.48$) or the therapeutically relevant small-cell/non–small-cell distinction ($\kappa = 0.55$). Not surprisingly, the study identified better differentiation, in addition to slide quality and pathologist expertise, as important predictive factors for increased interobserver reproducibility. The results help to define a baseline diagnostic agreement that might be used in the validation of other ancillary techniques such as immunohistochemistry or molecular analysis that are proposed to further refine diagnostic criteria.

The histologic subtyping of pulmonary carcinomas on the basis of morphology alone is even more challenging in small samples. With the advent of targeted therapies for non–small-cell carcinoma, further pathologic subclassification beyond the traditional distinction between small-cell carcinoma and non–small-cell carcinoma is now considered critical for selecting appropriate treatment for patients.[1] Subsequent sections will address the expanded use of immunohistochemical stains for further histologic subclassification as well as the competing priority of preserving sufficient tumor for molecular analysis.

INVASIVE ADENOCARCINOMA, INCLUDING ADENOCARCINOMA IN SITU AND MINIMALLY INVASIVE ADENOCARCINOMA

Adenocarcinoma is the most common histologic subtype in the United States and in most countries.[8] Adenocarcinoma is also the most frequently diagnosed subtype in nonsmokers.[9] The classification of pulmonary adenocarcinoma has long been a source of controversy—not only because of its diversity in histologic appearance but also because of a wide spectrum of clinical behavior, radiographic findings, and molecular characteristics associated with the entity. It is worth reviewing a concise history of the revisions in lung adenocarcinoma classification to understand the conceptual framework of 2011 IASLC/ATS/ERS multidisciplinary classification and current unsettled issues. The inherent histologic heterogeneity of many primary pulmonary adenocarcinomas has always made reproducible subclassification difficult and even small adenocarcinomas (<2 cm) can contain more than one histologic pattern.[10] This practical problem was addressed by the 1999 WHO revision, which introduced for the first time a *mixed* subtype to the four previously recognized subtypes of *acinar, papillary, bronchioloalveolar,* and *solid*.[4] In addition, a strict definition for BAC was adopted in the 1999 revision and retained in the 2004 classification. The definition required that the tumor have a pure lepidic growth pattern without evidence of stromal, vascular, or pleural invasion.[3,4] The term "lepidic" means that the proliferation of tumor cells should line the alveolar walls in a uniform manner, using the alveolar walls as a supporting scaffold. It should be noted that prior to the 1999 revision, pathologists widely varied in their assessments. Adenocarcinomas with a minor, usually central, and often more poorly differentiated invasive glandular component along with a peripheral bronchioloalveolar pattern are frequently encountered. In instances in which the peripheral BAC component predominated, it had been a common practice to designate the tumor either as a BAC or an "adenocarcinoma with a BAC pattern/features." The stricter definition of BAC prevailed in the revisions because of evidence demonstrating that small (<2 cm) solitary tumors with a pure lepidic growth pattern had a 100% 5-year survival.[11] Histologically, BACs were divided into two major subtypes, *nonmucinous* and *mucinous,* and were grouped together because of a similar "lepidic" growth pattern along alveolar septa. The more common nonmucinous type consists of cuboidal, columnar, or so-called "hobnail" cells with apical nuclei. The mucinous type consists of tall columnar cells with abundant apical pale mucinous cytoplasm and basally located nuclei, sometimes resembling goblet cells. A rare *mixed nonmucinous and mucinous* or *indeterminate* subtype was also recognized in the 1999/2004 revisions.

While this classification of BAC made sense from a histologic pattern perspective, it did not really encompass the variability in clinical presentation, radiographic features, or prognosis. Although practice patterns changed somewhat after these revisions, the diagnosis of BAC continued to be used for both small and well-differentiated adenocarcinomas as well as for more advanced stage tumors with obvious diffuse pneumonic spread or lymph node involvement. Moreover, in the years following the publication of the 2004 WHO classification, it became increasingly apparent that the nonmucinous and mucinous cell types have distinctive clinical, radiographic, immunophenotypic, and molecular correlations.[12,13] In 1995, Noguchi et al. had suggested that even small foci of invasion in what would otherwise be a pure BAC were associated with a 100% disease-free survival and, following the publication of the 2004 WHO classification, there were a number of other studies that similarly supported quantitation of the lepidic growth pattern and the area of invasion within these "mixed" type adenocarcinomas. These studies focused on a cutoff of 5 mm or less of

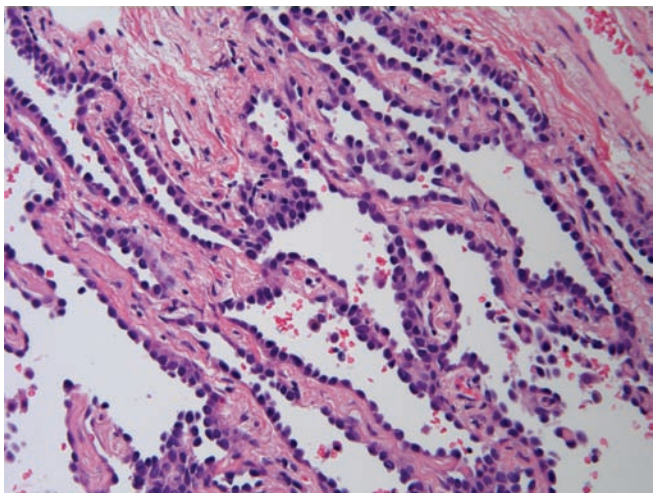


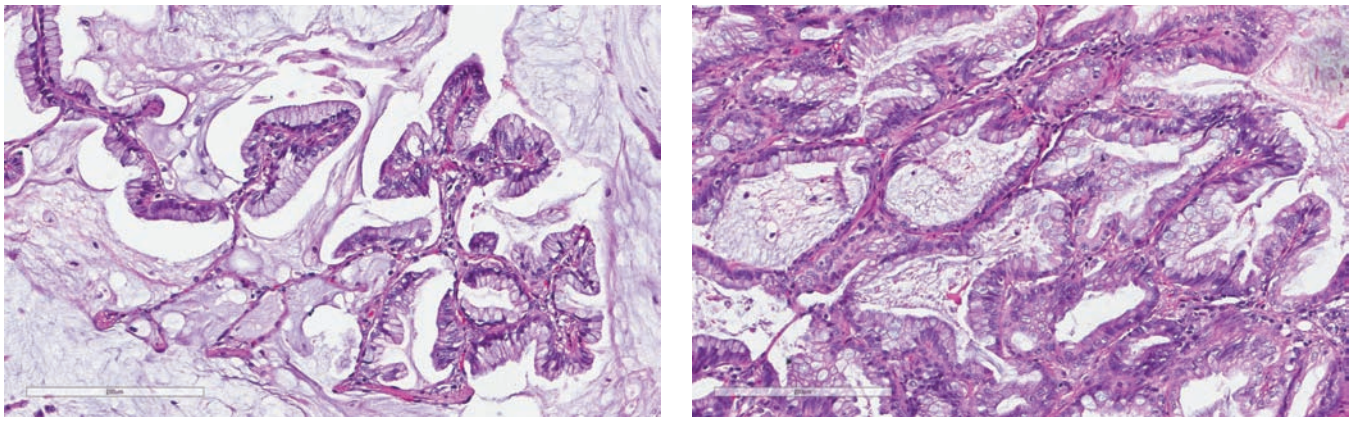
Figure 111-1 Adenocarcinoma in situ, nonmucinous. Uniform proliferation of atypical nonciliated columnar cells with apical nuclei. The tumor cells are growing along the alveolar septa without invasion. (H&E, 200×).

invasion as a way of defining a "minimally invasive adenocarcinoma" (MIA) with an excellent survival.[14,15]

The evidence from these and other studies culminated in the comprehensive 2011 IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma.[5] The 2011 classification completely discards the term BAC in favor of "adenocarcinoma in situ" (AIS). For small (≤3 cm) solitary adenocarcinomas with predominant lepidic growth and small foci of invasion measuring ≤0.5 cm, the term "minimally invasive adenocarcinoma" is recommended. By definition, MIA, can only be applied to a solitary and discrete lesion unless it is clear, in the instance of multiple tumors, that they are synchronous primaries.[5] Although the new terminology is a bit unsettling to pathologists and clinicians who have long been used to the entity of BAC, the terms AIS and MIA were favored because they more accurately reflect both the histologic growth pattern and survival statistics. AIS and MIA will typically present as pure ground-glass opacities without a solid component on computed tomography (CT) scans.[16] The majority of AIS and MIA cases are nonmucinous, although some cases of mixed nonmucinous and mucinous MIA have been reported (Fig. 111-1).[17] Most lesions with a mucinous "BAC" histologic pattern, if carefully examined and sampled, will have invasive foci and, therefore, are classified as "invasive mucinous adenocarcinoma" (Fig. 111-2A,B).

The IASLC/ATS/ERS consensus panel further proposed that invasive adenocarcinomas be characterized by a predominant subtype and recognized five patterns: Lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, and solid predominant with mucin production. The introduction of a "predominant" pattern was intended as a practical way to evaluate the characteristic heterogeneity of many adenocarcinomas and to allow for better stratification than the "mixed subtype."[5] The recommendation was based on studies in stage I tumors that had suggested that these different histologic patterns had prognostic value in a grading system and that these different patterns can be reproducibly recognized.[17–19] Other studies have further validated the prognostic significance of the predominant histologic pattern using this classification system or have evaluated other potential parameters for a grading system including mitotic rate and high thyroid transcription factor-1 (TTF-1) expression within this framework.[20–23] *Lepidic predominant adenocarcinoma* consists mainly of tumor cells growing along alveolar septa (previously referred to as a nonmucinous BAC pattern) but with greater than 5 mm invasion. *Acinar predominant adenocarcinoma* consists of irregularly contoured but nonetheless recognizable glandular structures and is often associated with a desmoplastic stroma (Fig. 111-3A). *Papillary predominant adenocarcinoma* consists of malignant cuboidal or columnar cells that line the surface of fibrovascular cores (Fig. 111-3B). *Micropapillary predominant adenocarcinoma* consists of small papillary clusters of glandular cells growing within airspaces (Fig. 111-3C). The micropapillary pattern was not recognized as a formal histologic subtype in the 2004 WHO classification but has since been recognized in IASLC/ATS/ERS adenocarcinoma classification.[5] *Solid predominant adenocarcinoma with mucin* consists of sheets of tumor cells without an acinar, papillary, or lepidic growth pattern (Fig. 111-3D). The tumor cells have abundant cytoplasmic and mostly vesicular nuclei with prominent nucleoli. Multiple tumor cells have basophilic cytoplasmic vacuoles that suggest intracytoplasmic mucin, which then may be confirmed by a special stain for mucin. The 2004 WHO classification requires that be there five or more mucin-positive cells in at least two high power fields for the diagnosis of *solid adenocarcinoma with mucin production*. This criterion was adopted because it is not uncommon for squamous cell or large-cell carcinomas to have rare mucin droplets and this is retained in 2011 IASLC/ATS/ERS classification. By definition, given the solid pattern of the tumor, solid adenocarcinomas are poorly differentiated.

The variants of invasive adenocarcinoma that were defined in the 1999/2004 WHO classifications were reconsidered in the 2011 update and four variants are now recognized: *invasive mucinous*



A **B**

Figure 111-2 Invasive mucinous adenocarcinoma. **A.** Tall columnar cells with abundant mucinous cytoplasm line the alveolar septa (former mucinous bronchiolalveolar carcinoma). **B.** Invasive pattern in same tumor. (H&E, 200×).

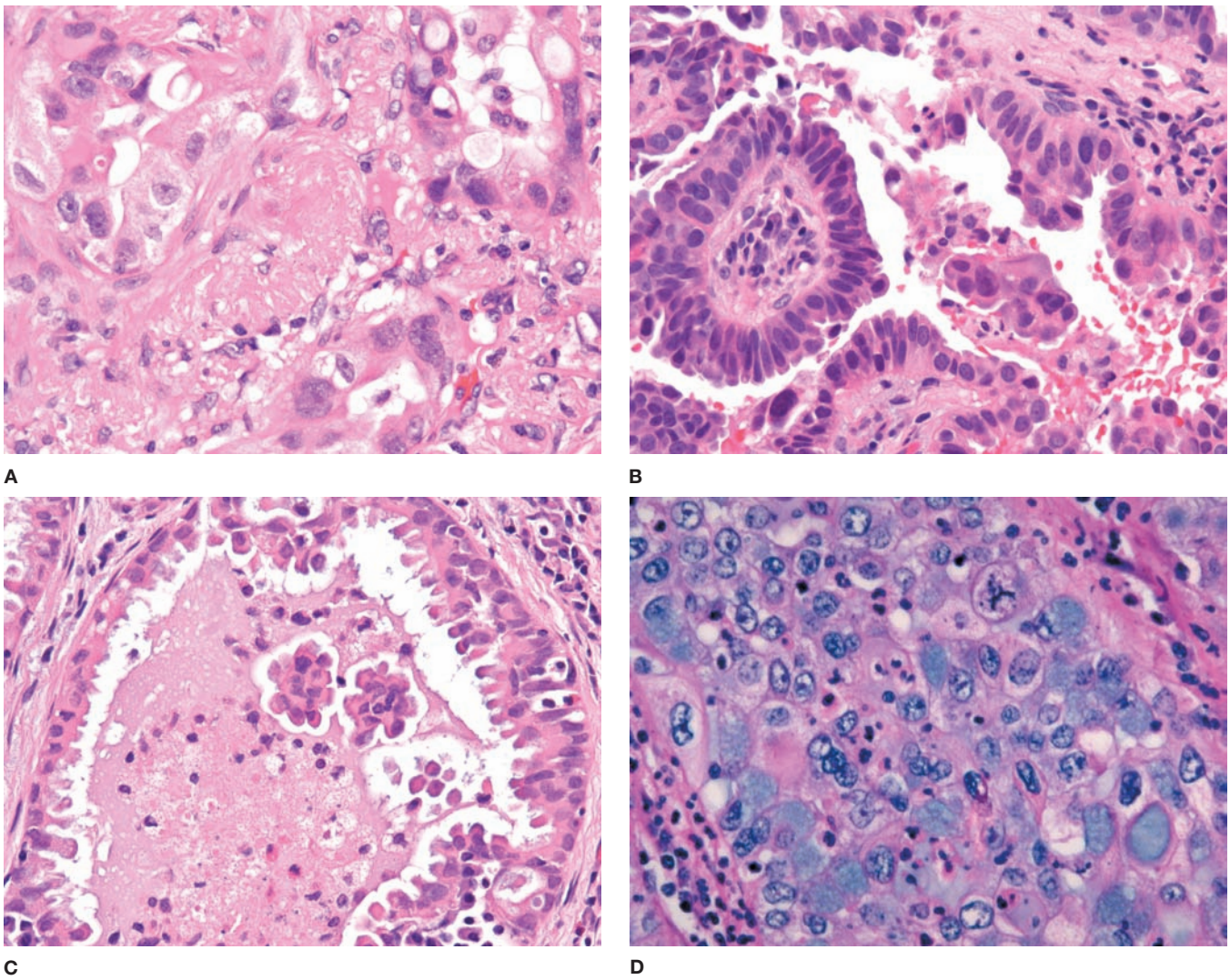


Figure 111-3 **A.** Invasive pulmonary adenocarcinoma, acinar predominant. Small, irregularly shaped glands within a desmoplastic stroma (H&E, 400×). **B.** Invasive pulmonary adenocarcinoma, papillary predominant. Malignant cells are arranged on the surface of fibrovascular cores (H&E, 400×). **C.** Invasive pulmonary adenocarcinoma, micropapillary predominant. Small papillary clusters without fibrovascular cores (H&E, 400×). **D.** Invasive pulmonary adenocarcinoma, solid predominant. Solid nests of cells with mucin (H&E, 400×).

adenocarcinoma (formerly mucinous BAC), *colloid adenocarcinoma*, *fetal adenocarcinoma* (low and high grade), and *enteric adenocarcinoma*.[5] The previously recognized variants of *signet-ring adenocarcinoma,* and *clear cell adenocarcinoma* were discarded as discrete entities and are now viewed as cytologic changes that can occur in association with multiple histologic patterns. Although echinoderm microtubule–associated protein-like 4 and anaplastic lymphoma gene fusions (*EML4-ALK*) may be seen in other histologic subtypes, a significant number of patients with this fusion will demonstrate a solid signet-ring cell pattern (Fig. 111-4).[24,25] *Enteric adenocarcinoma* was added because of its morphologic and immunohistochemical overlap with colorectal adenocarcinomas, thereby necessitating a clinical evaluation to exclude a gastrointestinal primary.[5]

The reproducibility of histopathologic subtype and invasion in pulmonary adenocarcinomas has been studied.[26] In pulmonary adenocarcinomas with classic morphology, there is good reproducibility in identifying a predominant pattern but only fair reproducibility in distinguishing invasion from in situ (wholly lepidic) patterns. Specifically recognizing stromal invasion is still somewhat problematic in practice, even among expert thoracic pathologists. Many adenocarcinomas have areas of fibrosis due to alveolar wall collapse or septal fibrosis with some observers interpreting an individual case as tumor-related stroma with fibroblasts (desmoplastic stroma) and others interpreting as benign fibroelastotic scarring. Histologic criteria for true invasion include single cell infiltration, a fibromyxoid stromal response, high-grade cytology, and a cribriform

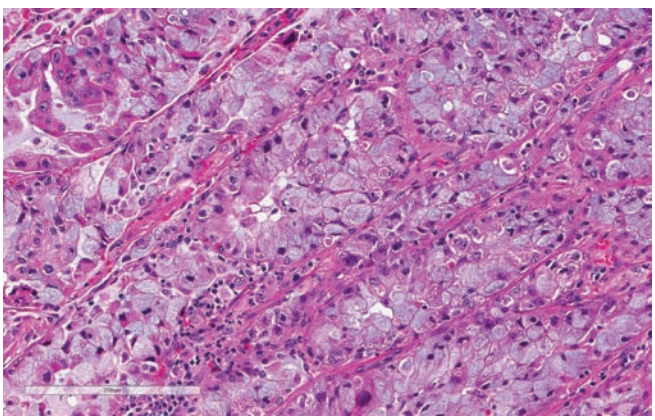


Figure 111-4 Numerous tumor cells with abundant intracellular mucin (signet-ring cells) that can be seen in association with *EML4-ALK* fusion. (H&E, 200×).

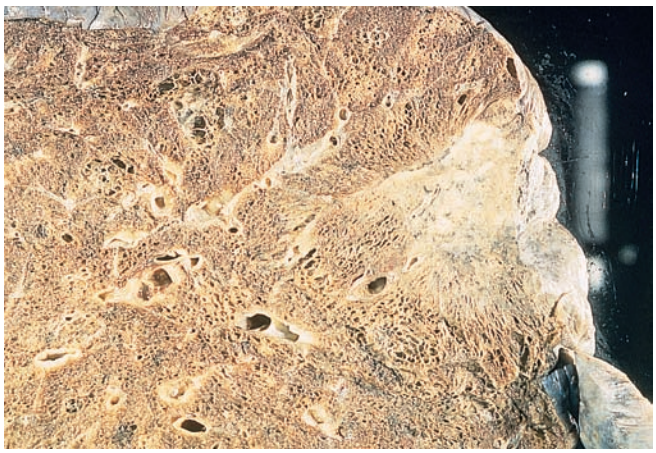


Figure 111-5 Peripheral adenocarcinoma of the lung with pleural puckering.

or acinar growth pattern. This lack of clarity and reproducibility in defining what constitutes invasion in well-differentiated adenocarcinomas makes the subtype of "lepidic predominant adenocarcinoma" the most controversial and there remains some work to be done in terms of refining, standardizing, and improving the recognition of purely in situ disease.[6,26]

The majority of adenocarcinomas arise in the periphery of the lung and are often associated with parenchymal scarring or puckering of the overlying pleura (Fig. 111-5). It is now a standard recommendation for accurate staging to use elastin stains in the evaluation of visceral pleura invasion in any lesion that approaches the visceral pleura (Fig. 111-6).[27,28] Although there are associations of specific subtypes of adenocarcinoma with, for example, *EGFR* mutations or the *EML4-ALK* fusion gene, histology is not robust enough to replace molecular analysis in predicting which lung cancers have mutations and are likely to respond to targeted therapy. However, the recognition of these subtypes by the pathologist may play a role in suggesting which molecular tests are most likely to yield positive results for a given cancer and this may be important if there are restrictions due to sample size, test availability, and turnaround time.[1]

The histologic heterogeneity of adenocarcinomas is such that the exclusion of metastatic disease or malignant mesothelioma is often an important consideration. As mentioned previously in the enteric variant of adenocarcinoma, the exclusion of a colorectal primary may be important. Other features such as signet-ring cytology raise

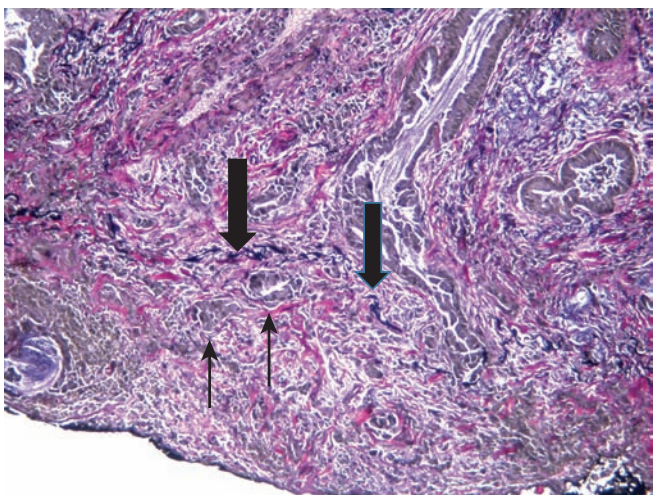


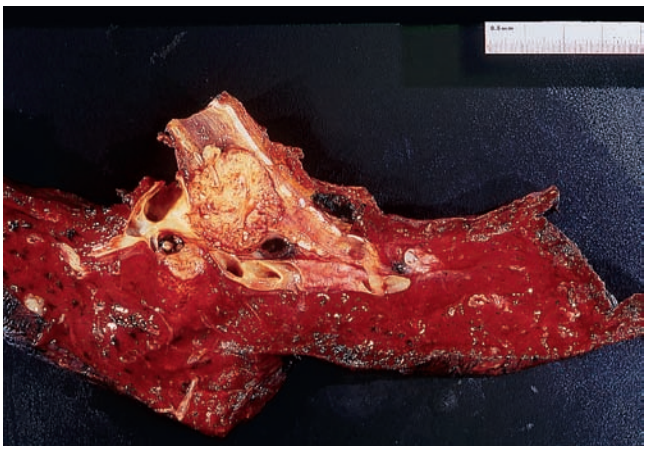
Figure 111-6 Visceral pleural invasion. Tumor cells *(thin black arrow)* are present beyond the black elastic layer of the visceral pleura *(thick black arrow)*. (Elastin, 100×).

the possibility of a gastric or appendiceal tumor as well as other primary sites. Mucinous carcinomas, particularly of pancreatic or ovarian origin, may metastasize to the lung and mimic a mucinous adenocarcinoma. All of the classic growth patterns – acinar, papillary, micropapillary, or solid – may be seen in any number of extrapulmonary primaries and clinicoradiologic correlation is always essential. The distinction between peripheral adenocarcinomas with extensive pleural involvement, diffuse carcinomatous involvement of the pleura by metastatic tumor, and malignant mesothelioma may be similarly problematic. Some carcinomas grow in a manner virtually identical to malignant mesothelioma, with extensive pleural involvement and limited parenchymal invasion.[29] Clinically, radiographically, and macroscopically, these tumors are indistinguishable from malignant pleural mesothelioma. The histologic appearance may be equally confusing, requiring the use of immunohistochemical stains. As will be discussed further in the general section on immunohistochemistry, there are multiple antibodies that will stain adenocarcinomas of the lung. Many of these antibodies (CEA, MOC31, B72.3, LeuM1, and BerEP4) recognize glycoproteins and are not specific for the lung. Surfactant protein A (SP-A), TTF-1, and Napsin A are the three commercially available markers that can be useful in the diagnosis of lung adenocarcinomas, with the latter two markers (TTF-1 and Napsin A) having higher sensitivity for lung adenocarcinomas.[30,31] It is important to recognize that neither TTF-1 nor Napsin A are entirely specific for lung adenocarcinomas and pathologists must still consider within the differential diagnosis a number of extrapulmonary tumors, depending on the clinical circumstances. The combined use of TFF-1 and Napsin A does result in improved sensitivity and specificity for identifying primary pulmonary adenocarcinomas.[32]

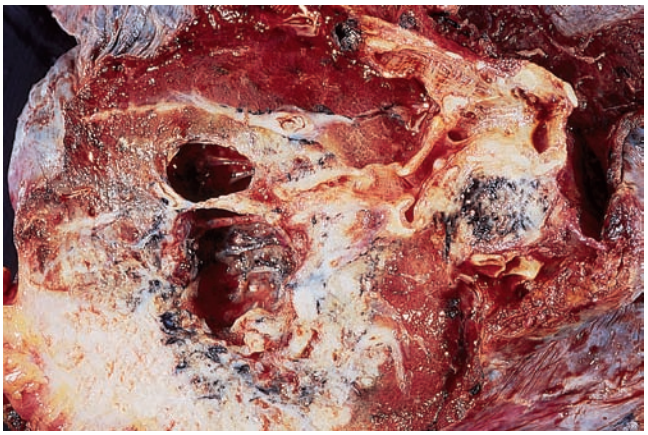
SQUAMOUS CELL CARCINOMA

Despite its replacement as the leading lung cancer cell type among both men and women in the United States and in many other countries, squamous cell carcinoma remains an important histologic subtype. Squamous cell carcinoma is seen more commonly in men and is still very strongly correlated with cigarette smoking.[33] About two-thirds of squamous cell carcinomas occur centrally, where involvement of a mainstem, lobar, or segmental bronchus may be demonstrated but squamous cell carcinoma may also present as a peripheral mass (Fig. 111-7A,C).[34] As would be expected from an endobronchial growth pattern, squamous cell carcinomas frequently are associated with bronchial obstruction and postobstructive pneumonia. Cavitation is seen more frequently in squamous cell carcinoma than in the other histologic subtypes (Fig. 111-7B).[3]

In the 2004 WHO classification, squamous cell carcinoma is defined as a malignant epithelial tumor showing keratinization and/or intercellular bridges. Keratinization may be in the form of squamous pearls or individual cells with dense eosinophilic cytoplasm. Intercellular "bridges" are seen in paraffin sections due to cell shrinkage caused by fixation and correspond to the desmosomal attachments that can be appreciated ultrastructurally (Fig. 111-8B,C). A desmoplastic (i.e., fibrotic) response is often associated with the invasive nests of tumor cells (Fig. 111-8A). As is true of other histologic types, squamous cell carcinomas often show areas of histologic heterogeneity. There are four histologic variants within the 2004 WHO classification of squamous cell carcinoma: papillary, clear cell, small cell, and basaloid patterns.[3] On occasion, a tumor may consist entirely of one of these variants, but it is far more common for these patterns to be focal. The *papillary variant* is characterized by an exophytic growth pattern and papillary cores. The classic tumor cells of a squamous cell carcinoma are large and polygonal with eosinophilic cytoplasm, but in the *clear cell variant*, as the name suggests, cells with clear cell cytoplasm can be seen (Fig. 111-8D). In the basaloid variant, the nests of tumor cells have prominent peripheral palisading and have less cytoplasm toward the



A



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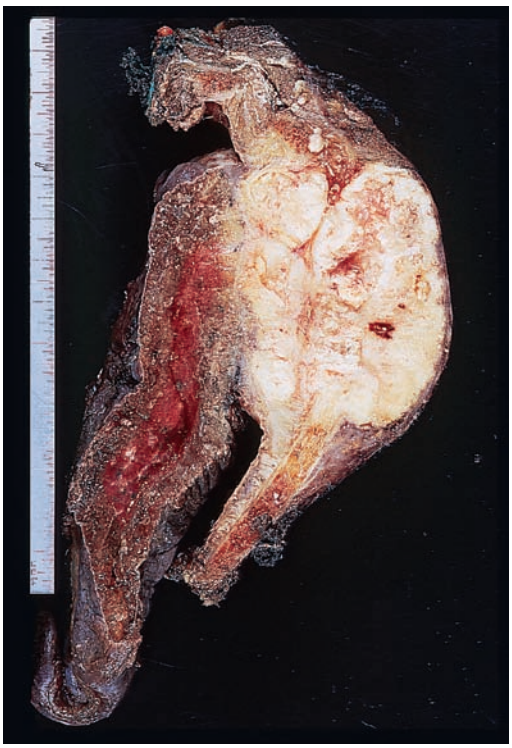


C

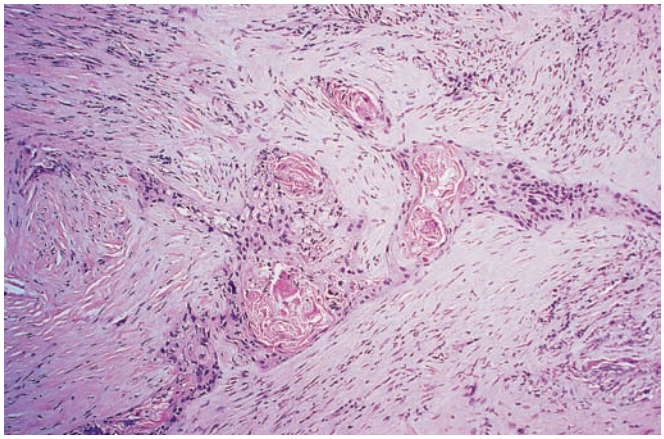
Figure 111-7 **A.** Large endobronchial squamous cell carcinoma with atelectasis and obstructive pneumonitis. **B.** Cavitation within a squamous cell carcinoma. **C.** Right upper lobectomy with chest wall resection for squamous cell carcinoma.

periphery, but the more centrally located cells have more obvious keratinization. In the *small-cell variant* of squamous cell carcinoma, the tumor cells are relatively smaller and can have granular nuclear chromatin, but there is some chromatin variation with more coarse or vesicular chromatin and prominent nucleoli. A careful search shows cytoplasmic evidence of squamous differentiation in the form of focal keratinization or intracellular bridges. A familiarity with these variant patterns is useful for the practicing pathologist, but at the current time there is no evidence that these variant patterns have any clinical significance. The basaloid and small-cell variants of squamous cell carcinoma can pose a diagnostic dilemma in small, poorly preserved biopsies when their relatively scant cytoplasm mimics small-cell carcinoma. In this instance, a panel of immunohistochemical stains that includes markers of squamous and neuroendocrine differentiation can be useful in interpretation.

Although not invariably demonstrated, it is easiest to identify a trend in tumor progression with the squamous cell histologic subtype. Sampling of a resected specimen may show changes in the adjacent bronchial mucosa ranging from squamous metaplasia to dysplasia to carcinoma in situ. If identified, the presence of an in situ component helps to differentiate a primary squamous cell carcinoma from a metastatic lesion. Aside from a clear-cut transition from in situ to invasive squamous cell carcinoma, there is no other conclusive morphologic means of differentiating a primary pulmonary squamous cell carcinoma from a metastasis. There is a tendency for metastatic tumors from the head and neck to be better differentiated (i.e., show more extensive keratinization) than their primary pulmonary counterparts, but reliably distinguishing a primary squamous cell carcinoma of the lung from other primary sites, particularly from the head and neck, continues to be an ongoing issue. There are studies that have used various molecular techniques to separate a primary squamous cell carcinoma of the lung from a metastasis from the head and neck or addressed these diagnostic issues within the broader context of synchronous or metachronous tumors and metastases.[35,36] It is anticipated that additional studies will further validate molecular techniques and facilitate their transition into routine clinical assays that can be used in equivocal clinicopathologic circumstances and when the distinction is critical for treatment or prognosis.

ADENOSQUAMOUS CARCINOMA

This tumor consists of well-defined squamous carcinoma and adenocarcinoma components, with each component comprising at least 10% of the whole tumor.[3] The areas of glandular and squamous differentiation may be located in different areas of the tumor or may be intimately admixed. In the past, different criteria had been used for this histologic subtype and these differences in definition, in addition to its low incidence, have made it extremely difficult to compare survival rates with other non–small-cell carcinomas. Prior to the widespread use of immunohistochemistry, the incidence of adenosquamous carcinoma was estimated at 1%.[37] It is unclear how the increasing use of immunohistochemistry for histologic subtyping will impact the incidence of this rare tumor. The 2004 WHO criterion of 10% was intended to foster more uniformity in clinical trials and research studies but there is still only a limited amount of data available on this histologic subtype. There are studies that have reported a worse prognosis with adenosquamous carcinoma when compared to other non–small-cell carcinomas of the lung.[38–40] The question as to whether adenosquamous carcinomas are a simple mix of adenocarcinoma and squamous cell carcinoma or whether they are more complex at a molecular level is an interesting one that may have a significant impact on targeted therapy selection. There is a limited amount of data that



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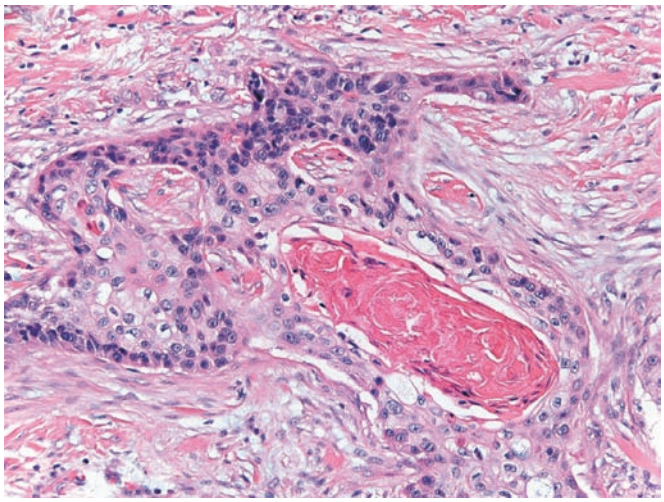

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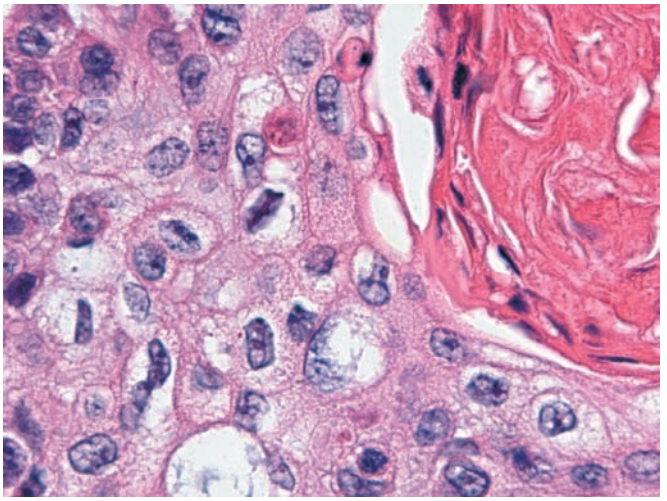

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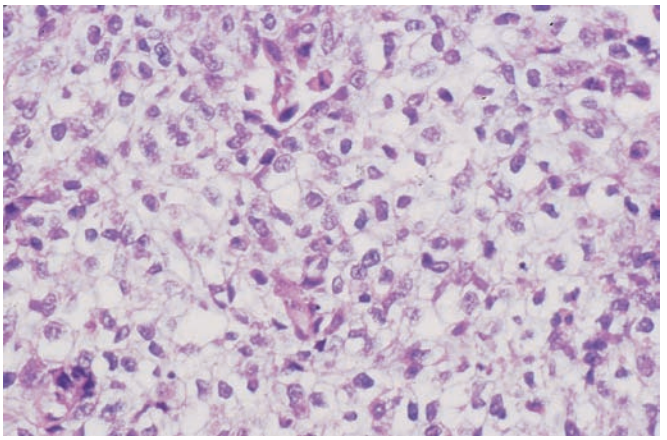


D

Figure 111-8 **A.** Desmoplastic response with nests of infiltrating squamous cell carcinoma (H&E, 200×). **B.** Squamous cell carcinoma with keratinization and intracellular bridges (H&E, 200×). **C.** High power view of keratinization and intercellular bridges (H&E, 400×). **D.** Tumor cells with clear cytoplasm from a squamous cell carcinoma (H&E, 400×).

suggests that these tumors are not simple mixtures of two histologic components but rather behave as their own unique entity.[41,42]

LARGE-CELL CARCINOMA

Large-cell carcinomas account for a little less than 10% of all lung cancers.[37] Large-cell undifferentiated carcinoma is defined in the 2004 WHO classification as "an undifferentiated malignant epithelial tumor that lacks the cytologic features of small-cell carcinoma and glandular or squamous differentiation."[3] The tumor cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm (Fig. 111-9). As is evident from this description, this tumor is defined more by what it is not than what it is. For practical purposes, it is a diagnosis of exclusion, and the diagnosis of large-cell carcinoma requires morphologic examination of the resected tumor to rule out areas of squamous or glandular differentiation. The WHO criteria for large-cell carcinoma are based on conventional microscopy, the occasional use of mucin stains, and the required use of immunohistochemistry for one variant (large-cell neuroendocrine carcinoma). Melanoma, malignant large-cell lymphomas, and epithelioid sarcomas also can mimic large-cell carcinoma, typically requiring the use of immunohistochemistry to exclude these diagnoses. The major change in the 1999/2004 WHO revisions was to expand the number of variants included within the category of large-cell carcinoma and transfer others, namely giant cell carcinoma and spindle cell carcinoma, into the sarcomatoid carcinoma category. The large-cell carcinoma variants now include *large-cell neuroendocrine carcinoma* and *combined large-cell neuroendocrine carcinoma* (to be covered in the section on neuroendocrine tumors) in addition to *basaloid carcinoma,*

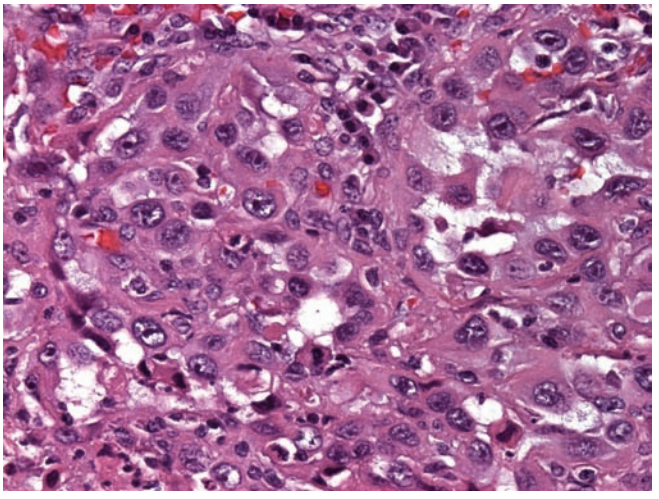


Figure 111-9 Large-cell carcinoma of the lung. There is no obvious squamous differentiation in the form of keratinization or intercellular bridges and a mucin stain was negative (H&E, 400×).

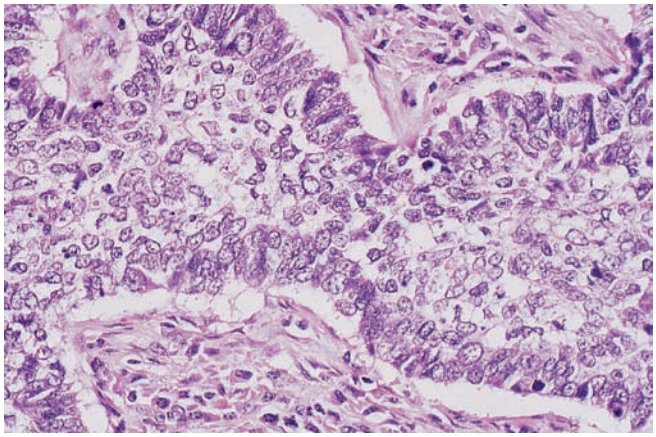


Figure 111-10 Basaloid carcinoma of the lung. The tumor cells are relatively small with hyperchromatic nuclei and scant cytoplasm. Note the tendency of the tumor cells to palisade at the periphery of the tumor nest (H&E, 400×).

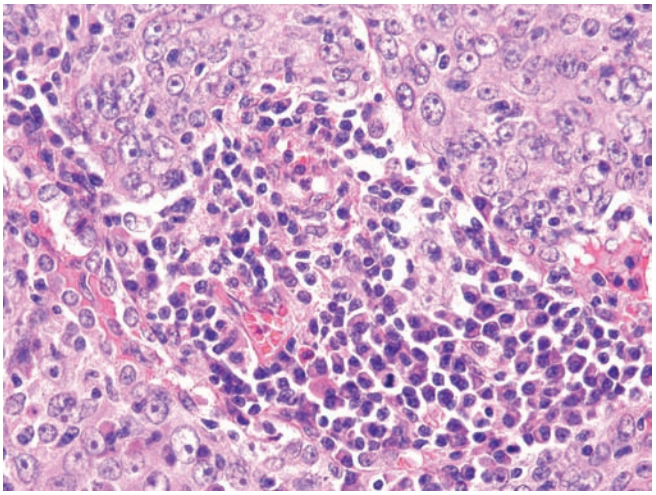


Figure 111-11 Lymphoepithelioma-like carcinoma. Large malignant cells with prominent nucleoli are arranged in nests within a lymphoid-rich stroma (H&E, 400×).

lymphoepithelioma-like carcinoma, clear cell carcinoma, and large-cell carcinoma with rhabdoid phenotype (discussed below).

Despite this definition of large-cell carcinoma based solely on morphology, it has long been known and generally acknowledged that the majority of these tumors represent either very poorly differentiated adenocarcinomas or squamous cell carcinomas. By electron microscopy, many large-cell carcinomas show focal ultrastructural features consistent with adenocarcinoma or a poorly differentiated squamous cell carcinoma.[43] Similar subsets within large-cell carcinoma can be defined using the same immunohistochemical stains that are routinely employed to distinguish between adenocarcinoma and squamous cell carcinoma and the distribution of targetable mutations can be generally correlated with the immunophenotyping profile.[44] The extent to which morphologically identifiable large-cell carcinomas with immunohistochemical marker profiles of adenocarcinoma or squamous cell carcinoma should be reclassified for prognostic and therapeutic purposes has not been resolved. It is nevertheless clear that there are therapeutically relevant genetic alterations within these "undifferentiated" carcinomas that have practical implications for predictive molecular testing strategies and individualized therapy.

■ OTHER VARIANTS OF LARGE-CELL CARCINOMA

In the 1999/2004 WHO revisions, *basaloid carcinoma of the lung* is considered to be a variant of large-cell carcinoma. The basaloid histologic features in lung carcinomas are similar to those also seen in other extrapulmonary sites such as the head and neck or cervix. Basaloid cells are typically described as relatively small monomorphic cuboidal to fusiform cells with moderately hyperchromatic nuclei, finely granular chromatin, absent or focal nucleoli, scant cytoplasm, and a high mitotic rate. Intercellular bridges and/or individual cell keratinization should not be present. The tumor cells are usually arranged in lobular, trabecular, or palisading growth patterns (Fig. 111-10). Since these types of histologic patterns can also be seen in neuroendocrine tumors, immunohistochemical stains for neuroendocrine markers should be negative or extremely focal. If the basaloid component is less than 50% and combined with a squamous cell carcinoma, the tumor is classified as squamous cell carcinoma (basaloid variant). One large series of basaloid carcinomas that included both tumors as a variant of large-cell carcinoma and those associated with a squamous cell component suggested that the basaloid pattern itself confers a poor prognosis.[45]

Lymphoepithelioma-like carcinomas are extremely rare in the Western population but are more frequently reported in Chinese patients.[46] This rare pulmonary tumor was first reported in the lung in 1987 and the morphologic features are identical to undifferentiated nasopharyngeal carcinoma of the head and neck.[47] Large malignant cells with prominent nucleoli are arranged in nests within a lymphoid-rich stroma (Fig. 111-11). In Eastern Asian patients, Epstein–Barr virus EBER-1 RNA has been demonstrated to be present in the large tumor cells.[46]

The *clear cell carcinoma variant* consists of a pure clear cell carcinoma without evidence of squamous or glandular differentiation. The tumor consists of large polygonal cells with clear or foamy cytoplasm.[3] In addition to other primary lung tumors, the differential diagnosis of a large-cell carcinoma with prominent clear cells should include tumors from other primary sites such as the kidney.

Large-cell carcinoma with rhabdoid phenotype, that is, a large-cell carcinoma with cells showing prominent eosinophilic cytoplasmic globules, is extremely rare. Although this variant is included under large-cell carcinoma, mixtures of rhabdoid tumor cells with other recognizable components such as adenocarcinoma have also been reported. In the limited number of cases that have been reported in the literature, this rhabdoid phenotype is associated with a poor prognosis.[48]

SARCOMATOID CARCINOMA

Tumors that have sarcoma-like elements such as malignant spindle or giant cells or have a sarcomatous component that consists of a neoplastic but differentiated connective tissue phenotype such as neoplastic bone, cartilage, and striated muscle have been described in many primary organ sites, including the lung. The proliferation of terms in past literature and even the variations in nomenclature that have characterized revisions in the WHO classification have generated a disproportionate degree of confusion when compared with the actual incidence of these relatively rare lung tumors. Various terms in the literature have included spindle cell carcinoma, sarcomatoid carcinoma, carcinosarcoma, pleomorphic carcinoma, giant cell carcinoma, and pulmonary blastoma. The 1999 revision established a minimum requirement of 10% for certain elements, such as spindle cells or giant cells, for a tumor to be appropriately classified.[4] The most recent 2004 WHO revision has settled on the term *sarcomatoid carcinoma* to categorize these tumors, which are by definition poorly differentiated non–small-cell carcinomas that have a histologic appearance that suggests mesenchymal differentiation. The current

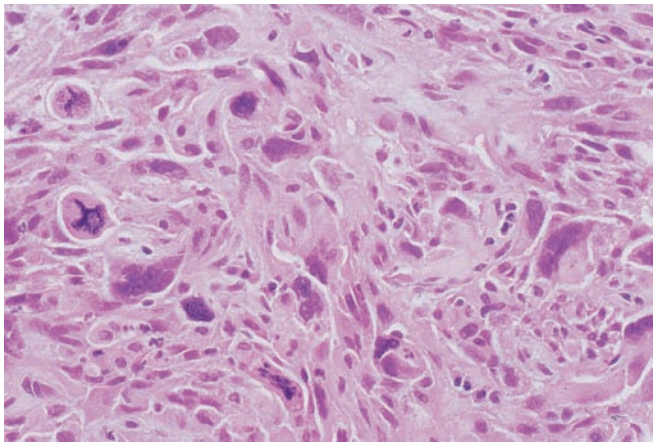


Figure 111-12 Pleomorphic carcinoma of the lung. The spindle cell and giant cell component in this large-cell carcinoma comprise at least 10% of the tumor (H&E, 400×).

variants of sarcomatoid carcinoma include *pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma,* and *pulmonary blastoma.*[3] It is now accepted that these variants are phenotypic variations that can occur within the spectrum of epithelial-derived lung tumors. Careful sampling of these tumors will often demonstrate an identifiable component of squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma. The rarity of these tumors (<2%) and previous confusion in terminology have made it difficult to characterize clinical characteristics and outcome.[49] These tumors have no distinguishing radiologic features and have been reported in both central and peripheral locations. With the exception of pulmonary blastoma, which appears to be most frequent in the fourth decade and occurs slightly more in women, the other variants occur primarily in men in the sixth and seventh decade and have the same general association with tobacco use as other more common lung tumors.[3] As with other entities in the WHO classification, the diagnosis of sarcomatoid carcinoma cannot be made on the basis of a cytology or small biopsy specimen. Features suggestive of the tumor in a small sampling may be mentioned on a descriptive basis, that is, poorly differentiated non–small-cell lung cancer with spindle and/or giant cell carcinoma.[5]

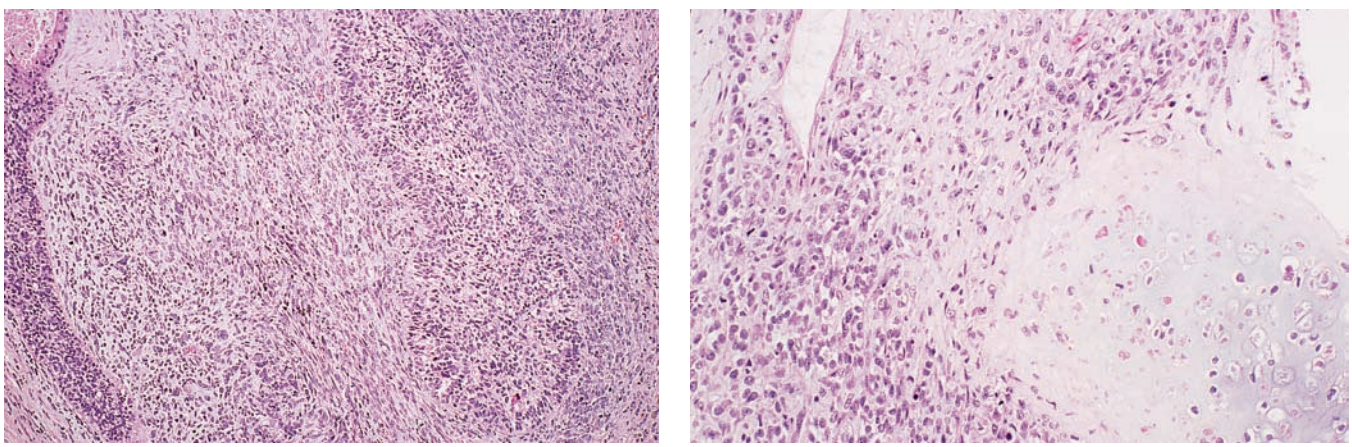
Pleomorphic carcinoma is defined as a poorly differentiated non–small-cell carcinoma containing spindle cells and/or giant cells. As mentioned, the spindle cell and/or giant cell component should comprise at least 10% of the tumor (Fig. 111-12). *Spindle cell carcinoma* and *giant cell carcinoma* are terms that are reserved for the extremely rare instance in which the tumor is shown to consist entirely of spindle cells or giant cells, respectively. The tumor giant cells are bizarre, dyscohesive, and multinucleated and often associated with an inflammatory infiltrate that includes increased numbers of neutrophils.

In the pathology literature, tumors that contain cells with a neoplastic but differentiated connective tissue phenotype are said to have "heterologous elements." *Carcinosarcoma* refers to a lung tumor that has recognizable heterologous elements such as rhabdomyosarcoma, osteosarcoma, or chondrosarcoma (Fig. 111-13). Rather than terminology, the more significant issues confronting the pathologist are exclusion of metastasis from another site and avoiding the misdiagnosis of a primary pulmonary sarcoma.

Pulmonary blastoma is a biphasic tumor that contains a primitive epithelial component that resembles well-differentiated fetal adenocarcinoma and a primitive mesenchymal stroma, which occasionally has foci of osteosarcoma, chondrosarcoma, or rhabdomyosarcoma.[3] The term pulmonary blastoma had been used historically to describe tumors that have been reported in all age groups. Manivel et al.[50] argued that the childhood intrathoracic tumor was a distinct clinicopathologic entity that differed from the adult type, particularly in the absence of a carcinomatous component and its variable anatomic location. They proposed the alternate nomenclature of *pleuropulmonary blastoma* for these pediatric tumors, which occur almost exclusively in children of 6 years of age or younger, and in the 2004 WHO classification, this tumor is recognized as a distinct entity in the mesenchymal tumor category.[3] *Pulmonary blastoma* mainly occurs in adults. Although uncommon, pulmonary blastomas composed exclusively of embryonal-like epithelial and mesenchymal elements do occur. Adult tumors consisting entirely of malignant primitive glandular epithelium have also been described and are termed *fetal adenocarcinomas,* now classified as a variant of adenocarcinoma. Pulmonary blastomas have a histologically distinct, malignant glandular component that resembles the developing fetal lung at an early gestational age and malignant cellular stroma with an embryonic appearance (Fig. 111-14). The treatment is surgical and there is no good data on adjuvant therapy.[51]

PULMONARY NEUROENDOCRINE TUMORS—OVERVIEW

The 2004 WHO classification includes four tumor subtypes with neuroendocrine differentiation: carcinoid tumor (typical), carcinoid tumor (atypical), large-cell neuroendocrine carcinoma, and small-cell carcinoma[3] Collectively, these neuroendocrine tumors



A B

Figure 111-13 **A.** Carcinosarcoma showing a mixture of sarcoma (center) and carcinoma (periphery) (H&E stain, 100×). **B.** Tumor includes a malignant cartilaginous component (H&E stain, 100×).

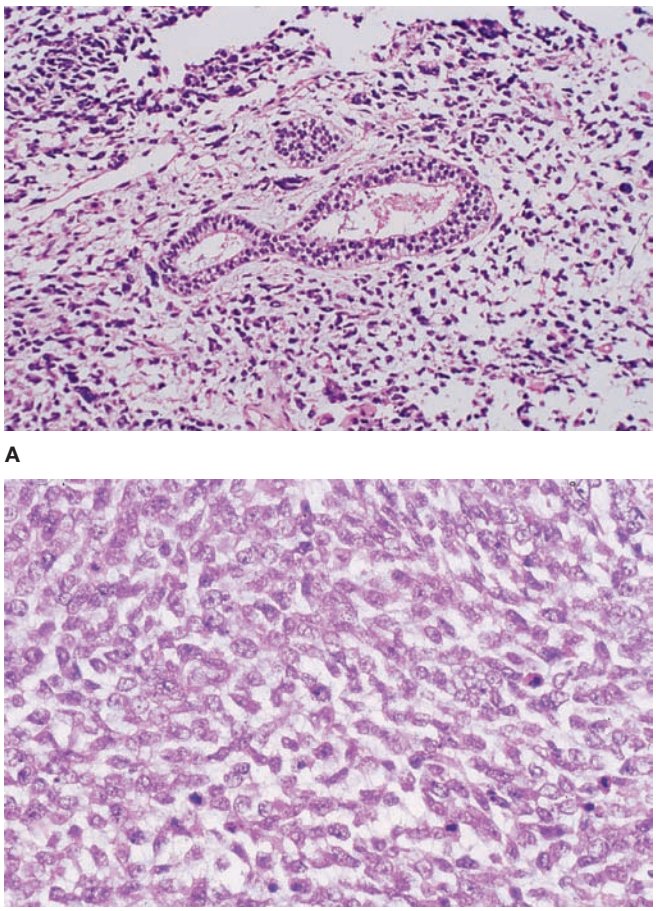


Figure 111-14 **A.** Pulmonary blastoma, showing a characteristic endometrioid-type gland, composed of cells with clear cytoplasm and basally oriented nuclei (H&E, 200×). **B.** Malignant stroma in a pulmonary blastoma (H&E, 400×).

represent about 25% of all primary pulmonary carcinomas with small-cell carcinoma being by far the most common. Typical carcinoid tumors are reasonably represented in surgical series but the relative rarity of atypical carcinoid tumors and the low incidence and controversies surrounding the definition of large-cell neuroendocrine carcinoma make it more difficult to establish treatment guidelines and prognosis for those entities. Historically, the recognition of "neuroendocrine differentiation" was based on morphologic characteristics as assessed by traditional light microscopy and hematoxylin and eosin sections. The subsequent introduction of electron microscopy and then the widespread use of immunohistochemistry (which has become the standard in routine clinical practice) led to a broader identification of "neuroendocrine differentiation" and, inevitably, debates about classification, therapeutic implications, and prognosis ensued. As is to be expected with any framework for classification, the WHO classification for neuroendocrine tumors is not without controversy and practical difficulties. Although it has been intellectually appealing to view the pulmonary neuroendocrine tumors along a continuous spectrum from low grade (typical carcinoid) to intermediate grade (atypical carcinoid) to high grade (large-cell neuroendocrine carcinoma and small-cell carcinoma), current epidemiologic, clinical, and molecular data suggest that this is not the case. Review of the data suggest a clear-cut separation of carcinoid tumors from the high-grade neuroendocrine carcinomas and anticipate that advances in molecular genetics may further impact the classification of the high-grade neuroendocrine tumors.[52] In the 2004 WHO classification, large-cell neuroendocrine carcinoma has been categorized as a non–small-cell carcinoma with a distinct morphologic appearance and immunohistochemical evidence of neuroendocrine differentiation. Some authors have challenged the reproducibility of this entity.[53] Other authors have suggested extrapolation from treatment paradigms for small-cell carcinoma in the management of large-cell neuroendocrine carcinoma, further blurring the clinical utility of the traditional separation of the two high-grade neuroendocrine tumors into small-cell carcinoma and non–small-cell carcinoma (large-cell neuroendocrine carcinoma).[54]

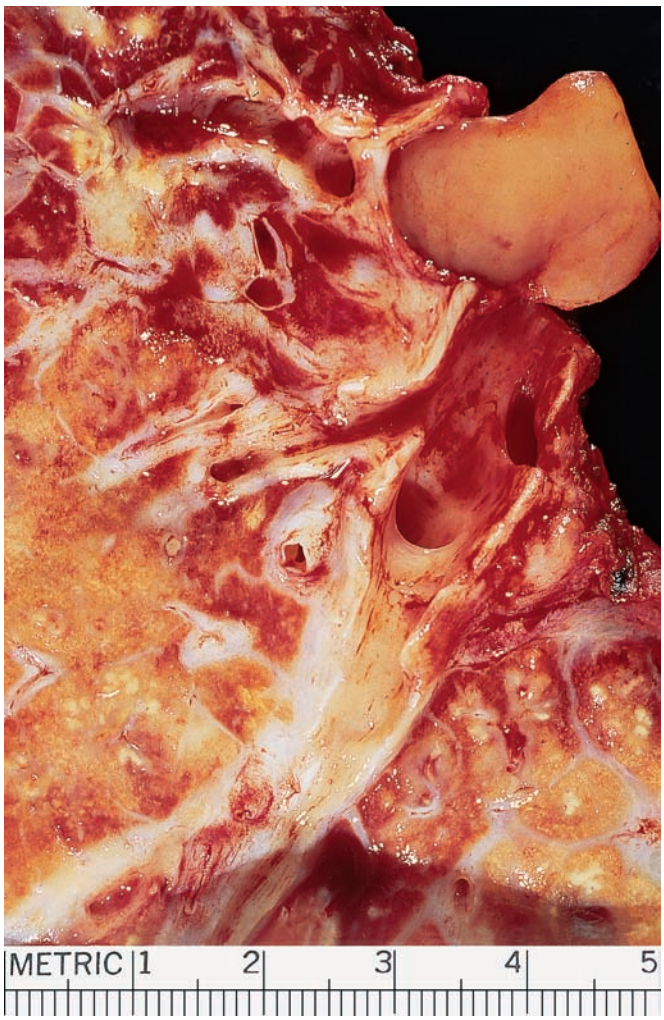
CARCINOID TUMORS

The 2004 WHO classification recognizes two distinct subtypes of carcinoid tumor—typical carcinoid tumor and atypical carcinoid tumor.[3] Both tumors are recognized by their low power architectural pattern and characteristic cytologic features that are familiar to pathologists and are similar in appearance to carcinoid tumors that occur in other primary sites such as the gastrointestinal tract. However, in contrast to the terms low grade or intermediate grade or well-differentiated neuroendocrine carcinoma that are now used in extrapulmonary sites, carcinoid tumor has been retained in the lung tumor nomenclature because of its familiarity to clinicians and because of the well-established clinical behavior associated with the terminology. In the intervening years between the 1981 WHO revisions and the 1999/2004 revisions, there was a significant amount of debate regarding the diagnostic criteria for these lesions, the most appropriate terminology, and their clinical behavior within the broader context of pulmonary neuroendocrine tumors. It should be noted that there is still no uniform agreement on one of the major criteria for separating typical from atypical carcinoid tumors – that of mitotic activity – usually expressed as the number of mitoses per 2 mm^2 or per 10 high power fields. Some authors have challenged the current WHO mitotic cutoff of <2 mitoses per 10 high power fields and have advocated a cutoff of <3 per 10 high power fields.[53] Even more problematic than mitotic counts is the fact that these criteria were established on resected specimens and therefore, it may be impossible to separate an atypical carcinoid from a typical carcinoid tumor on the basis of a small biopsy or to apply this criterion to a cytology specimen. The distinction may not affect initial surgical management but it may significantly impact subsequent prognosis.

TYPICAL CARCINOID

Typical carcinoid tumors can be divided into central and peripheral variants. Both variants can be asymptomatic but central carcinoids, which characteristically grow as an endobronchial mass, may present clinically with recurrent pneumonias or hemoptysis. Typical carcinoid tumors are not associated with tobacco use, but there is an association with multiple neuroendocrine neoplasia (MEN)1 syndrome in about 5% of cases and screening for pulmonary carcinoids with CT imaging is recommended in patients with MEN1.[55] The incidence of bronchial carcinoid tumors with carcinoid syndrome at presentation is low (1%–3%) and most typically occurs in the presence of metastatic liver disease.[56] Cushing syndrome due to ectopic production of ACTH is similarly rare.

Central carcinoids grossly appear as yellow or fleshy, polypoid masses (Fig. 111-15). The tumor usually has a significant exophytic endobronchial component but the tumor can infiltrate between cartilaginous rings to extensively involve the bronchial submucosa. The tumor cells form diverse patterns such as organoid nests, trabeculae, insular islands, ribbon, or rosette-like arrangements. Carcinoids can also have papillary, sclerosing, follicular, and glandular patterns. The tumor cells are generally uniform in appearance and have a low nuclear:cytoplasmic ratio with round to oval nuclei and eosinophilic



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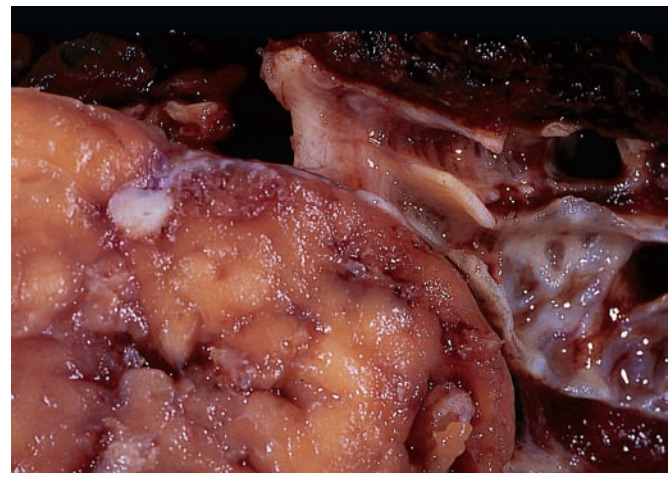

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Figure 111-15 **A.** Large endobronchial carcinoid. **B.** Endobronchial carcinoid. Grossly, the tumor is yellow, fleshy, and vascular.

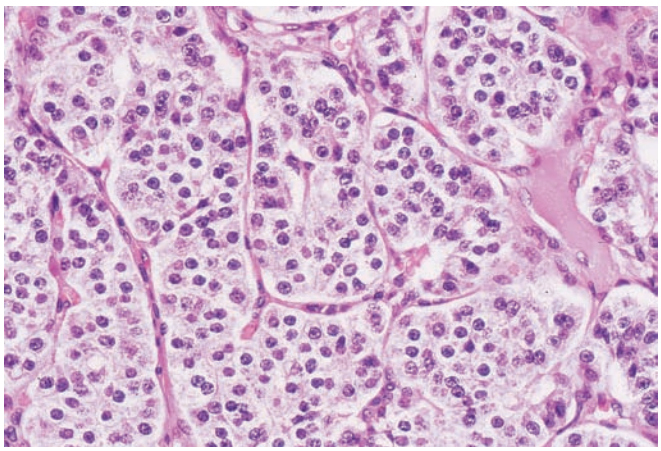
cytoplasm (Fig. 111-16). The tumor cells have characteristic neuroendocrine tumor chromatin that is finely granular or classically described as "salt and pepper."

Peripheral carcinoids are frequently subpleural and can be associated with a scar (Fig. 111-17A). Unlike the cells of central tumors, which are usually round or polygonal in shape, the tumor cells of peripheral carcinoids tend to have prominent spindle cell features (Fig. 111-17B). These fusiform cells have less cytoplasm than central tumors, but this feature should not be considered a sign of atypia. There is a subset of patients with one or more peripheral carcinoid tumors who have multiple tumorlets (defined as small neuroendocrine cell proliferations <0.5 cm) and DIPNECH. In these patients, it is believed that the neuroendocrine cell hyperplasia represents a preneoplastic condition. The most significant complication for this subset of patients is airway fibrosis, which can progress to severe obstructive lung disease.

The pathologic attributes of typical carcinoid tumors have been examined in numerous histologic, immunohistochemical, and molecular studies. The only consistent prognostic indicators have proved to be mitotic rate and necrosis—although as previously discussed there is still disagreement about what is the best prognostic cutoff for mitotic activity. The current 2004 WHO criteria for the diagnosis of carcinoid tumor require fewer than 2 mitoses per 10 high power fields of viable tumor and no necrosis. Cytologic atypia, increased cellularity, and lymphovascular invasion are not predictive features. Although carcinoid tumors have a generally excellent prognosis with reported 5-year survival rates of 87% to 100%, it is critical to understand that typical carcinoids are low-grade but malignant tumors. One large study and review of the literature reported a 5% to 15% incidence of lymph node metastasis and 3% incidence of distant metastasis at presentation.[57] The new seventh TNM classification is useful for staging bronchopulmonary carcinoid tumors.[58] There are currently no histologic characteristics that reliably predict which typical carcinoid tumors will behave more aggressively and go on to develop systemic disease.

■ ATYPICAL CARCINOID

The term "atypical carcinoid" was first introduced by Arrigoni et al.[59] in 1972. Twenty-three tumors were described that appeared to have a general resemblance to carcinoid tumors but that also had a focally disorganized growth pattern, areas of tumor necrosis, increased mitoses, and cellular pleomorphism. Dissension was immediately generated by the use of the word "atypical," given the aggressive biologic behavior in their series. Many other terms were introduced into the literature in the 1980s as more published reports detailing this entity appeared. The tumors described in these initial papers were a heterogeneous group, in part due to the subjective interpretation of features such as "architectural distortion." In defending atypical carcinoids as a distinct clinicopathologic entity, Travis et al.[60] emphasized that the overall architecture should be that of a recognizable carcinoid tumor with a predominantly organoid growth pattern. In the 2004 WHO classification, an atypical carcinoid tumor is defined as a carcinoid tumor with between 2 and 10 mitoses per 10 high power fields and/or with



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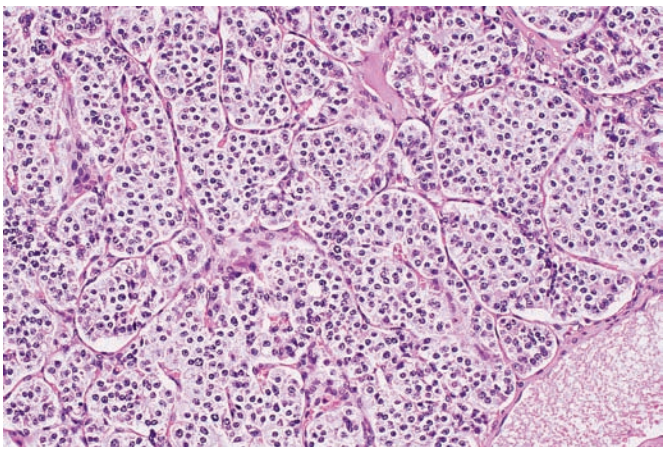

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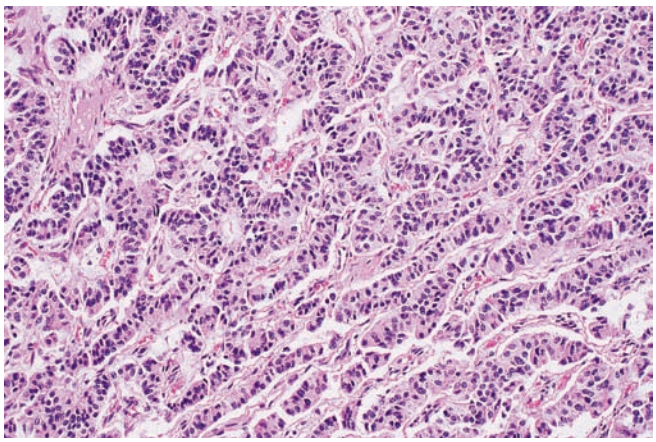
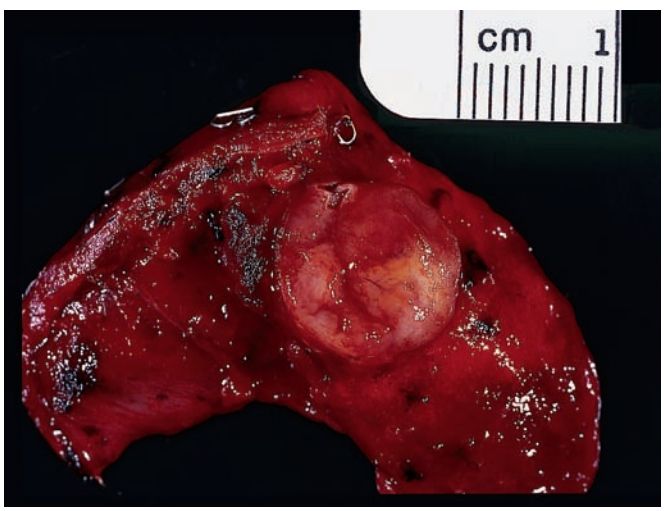


C

Figure 111-16 **A.** Cytologic features of carcinoid tumor with small, uniform cells. The nuclei are round to oval with a "salt and pepper" chromatin pattern (H&E, 400×). **B.** Carcinoid tumor, nested pattern of carcinoid tumor (H&E, 200×). **C.** Carcinoid tumor, ribboned pattern in carcinoid tumor (H&E, 200×).

foci of necrosis.[3] The necrosis in these tumors is usually punctate (Fig. 111-18) and one should be careful to exclude the possibility of a large area of necrosis that is secondary to a previous needle biopsy. Although cytologic atypia, lymphovascular invasion, nucleoli, increased cellularity, and disorganized architecture may be seen, these features are not a part of the classification system. Like typical carcinoid tumors, atypical carcinoid tumors can occur centrally as well as in the periphery. It is appropriate to consider atypical carcinoid tumors as an intermediate grade malignant tumor with an increased capacity for progression. Atypical carcinoids have a higher incidence of lymph node metastases at presentation (40%–50%) and of distant metastases at presentation (20%) than typical carcinoid tumors.[57] Stratified for stage, patients with tumors showing a higher mitotic rate (6–10 mitoses/2 mm^2) have a significantly worse survival rate than those patients with tumors with a lower mitotic rate (2–5/2 mm^2).[61]



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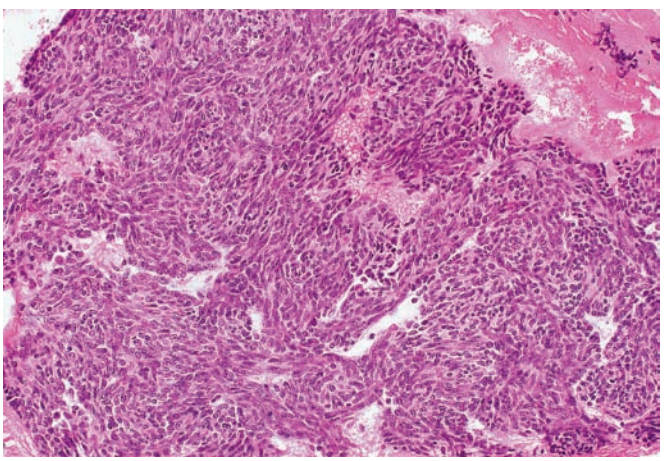

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Figure 111-17 **A.** Peripheral carcinoid. **B.** Peripheral carcinoid with prominent spindle cell features (H&E, 200×).

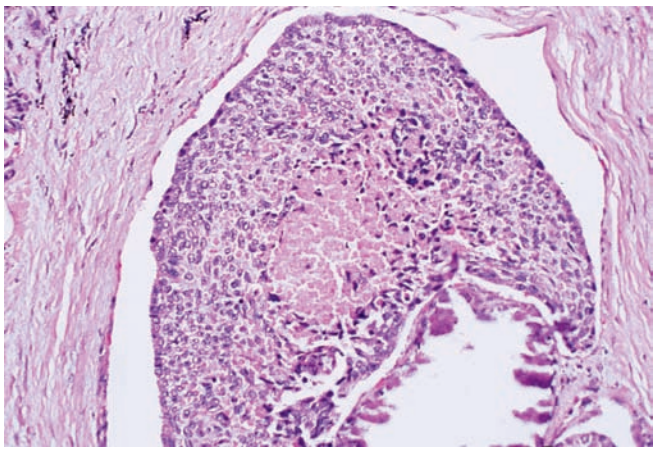


Figure 111-18 Central necrosis in an atypical carcinoid tumor (H&E, 200×).

SMALL-CELL CARCINOMA OF THE LUNG

The 2004 WHO classification defines small-cell carcinoma as a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.[3] The tumor cells can be round, oval, or spindle shaped. The criterion for cell size is given as "usually less than the size of three small resting lymphocytes" but there is no absolute criterion for cell size and cell size can vary from less than the diameter of three resting lymphocytes (10 μm) to that of a larger tumor cell (45 μm) depending on the type of specimen, the quality of fixation/processing, and inherent tumor heterogeneity.[62–64] Nuclear molding is commonly seen as is crush artifact with basophilic nuclear DNA encrustation of the vessel walls (Azzopardi effect). There is usually a high mitotic rate, averaging over 60 mitoses per 2 mm^2, but a significant mitotic rate may not be discernible in some small biopsy cases.[65] Extensive necrosis and numerous apoptotic cells are frequently seen but again may be absent in smaller biopsies (Fig. 111-19). While this definition can be simply summarized and the most classic appearance of small-cell carcinoma easily recognized with a high degree of interobserver agreement, diagnostic difficulties and issues of reproducibility do occur—even among experts.[66] Some of these difficulties are related to the sampling problems inherent in the small biopsies that are obtained by fiberoptic bronchoscopy and which are further discussed in the section on small biopsies. Some of these difficulties are related to the qualitative rather than quantitative criteria that have been set forth as distinguishing features between small-cell carcinoma and large-cell neuroendocrine carcinoma and which will be further discussed in the section on large-cell neuroendocrine carcinoma.

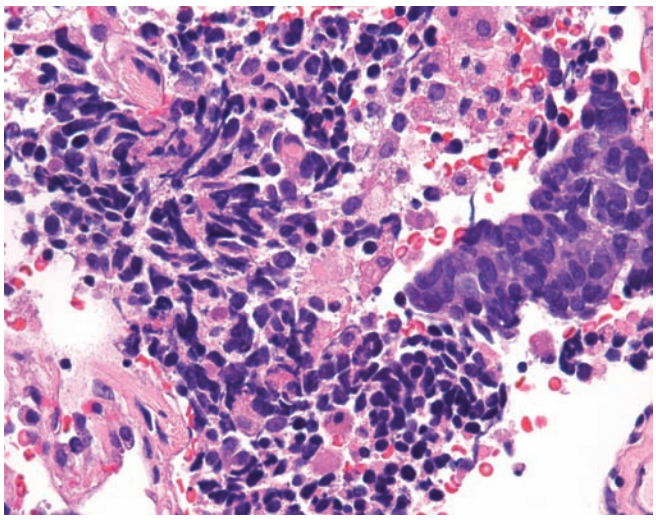


Figure 111-19 Small-cell carcinoma. Classic tumor cell appearance with scant amounts of cytoplasm, hyperchromatic nuclei, nuclear molding, crush artifact, and necrosis. (H&E, 400×).

Small-cell lung carcinoma has decreased in incidence in the United States where it now represents about 13% of all lung cancers but is still the most common of the pulmonary neuroendocrine tumors.[67] A significant smoking history is present in the vast majority of cases, such that the diagnosis of small-cell carcinoma should be seriously reconsidered in a patient without current or former heavy tobacco use. The current male:female ratio is about 2:1 and the average patient presents in their 60s. There are several different presentations that are familiar to most clinicians. Patients may present with pulmonary symptoms related to a large central mass that include cough, wheezing, dyspnea, and hemoptysis. Mediastinal extension may cause superior vena cava syndrome, recurrent laryngeal nerve paralysis, or dysphagia. Constitutional symptoms such as pain, decreased appetite, and weight loss are also common. A significant number of patients present with widespread metastases involving the liver, brain, bone, and adrenal glands. Paraneoplastic syndromes include the syndrome of inappropriate secretion of antidiuretic hormone, Eaton–Lambert syndrome, and ectopic Cushing syndrome. Despite the fact that less than 10% of patients with small-cell carcinoma limited to the lung are surgical candidates, the IASLC staging system is useful in predicting prognosis for small-cell carcinoma and the IASLC staging project has recommended the adoption of this staging system rather than the traditional limited versus extensive stage disease that has been used for staging small-cell carcinoma.[68] The 2009 College of American Pathologists (CAP) protocol for the examination of resected pulmonary specimens has been extended to include small-cell carcinoma and can be used as a template for pathologic evaluation as with non–small-cell carcinomas.[28]

Small-cell carcinoma can present as a solitary pulmonary nodule and early-stage small-cell carcinomas are occasionally resected. In the gross descriptions of surgically resected small-cell lung carcinomas, the gross appearance does not differ significantly from many other lung carcinomas.[64] The tumors are described as well circumscribed, often lobulated with others as endobronchial and some as subpleural. The cut surface is described as white to tan to yellow and gray with necrosis recorded in only a small number of cases.

In addition to other neuroendocrine tumors, the differential diagnosis of small-cell carcinoma might include nonspecific chronic inflammation, other small "round blue cell tumors" and poorly preserved, often necrotic non–small-cell lung carcinomas. The general use of immunohistochemistry in the differential diagnosis of lung tumors is discussed in a separate section, but two points deserved to be emphasized here. One point is that a positive TTF-1 stain cannot be used to support a diagnosis of a primary pulmonary small-cell carcinoma or to exclude a metastatic small-cell carcinoma from an extrapulmonary primary.[69] The second point is that it is a mistake to rely on neuroendocrine markers alone for the diagnosis of small-cell carcinoma. Not only are neuroendocrine markers negative in about 10% of small-cell carcinomas but other tumors within the differential diagnosis may be positive for neuroendocrine markers. The difficulties that can be encountered in separating out small-cell carcinoma from carcinoid tumors and other non–small-cell carcinomas in a small biopsy are discussed in greater detail in a separate section, as is the distinction from large-cell neuroendocrine carcinoma. But in general, it might be considered that the name itself, "small-cell" carcinoma, has led to a relative overemphasis on cell size in comparison to other criteria. From a therapeutic point of view, the recognition of any small-cell component has significant

clinical implications, but interpretative disagreements as to whether the tumor is a combined small-cell carcinoma or a pure small-cell carcinoma may not.

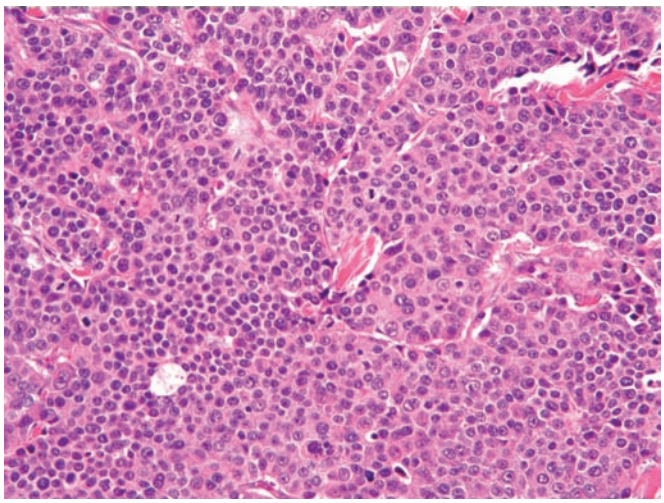
LARGE-CELL NEUROENDOCRINE CARCINOMA OF THE LUNG

In 1991, Travis et al.[70] first proposed criteria for this entity, which was considered to be histologically distinct from atypical carcinoid tumor or small-cell carcinoma. A great deal of controversy ensued over that following decade and continues to the current time. As mentioned in the introduction to this section on pulmonary neuroendocrine tumors, one controversy centers on the reproducibility of the diagnosis of large-cell neuroendocrine carcinoma. One study has demonstrated substantial agreement, at least among experienced lung pathologists.[66] In this study, a majority consensus diagnosis was achieved for 50% of the cases of large-cell neuroendocrine carcinoma, which is no worse than other categories of lung tumors. However, there are a number of other studies that question the reproducibility of the diagnosis and have highlighted the considerable overlap in cell size and the substantial degree of subjective interpretation that is required for categorization.[64,71–74] Also problematic, as it is for other WHO lung tumor entities, is that the definition of large-cell neuroendocrine carcinoma applies to resected tumors and not to smaller samples.

A third controversy has focused on the clinical significance of the diagnosis, particularly in relationship to small-cell carcinoma. From an epidemiologic perspective, both tumors are associated with heavy tobacco use and both tumors can occur in combination with other non–small-cell lung cancers.[63] Both tumors are aggressive high-grade neuroendocrine tumors and have a very poor prognosis.[75]

Large-cell neuroendocrine carcinoma is defined as "a large-cell carcinoma showing histologic features such as organoid nesting, trabecular, rosette-like and palisading patterns that suggest neuroendocrine differentiation and in which the latter can be confirmed by immunohistochemistry or electron microscopy."[3] The cells are relatively large in size, often polygonal in shape, with moderate to abundant cytoplasm. The nuclear chromatin ranges from vesicular to finely granular. Nucleoli are frequent and often prominent (Fig. 111-20A). The presence of nucleoli tends to be a critical feature in the separation from small-cell carcinoma (Fig. 111-20B) but some large-cell neuroendocrine carcinomas lack this criterion. Mitoses should be greater than 10 mitoses/10 high power fields. As mentioned previously, neuroendocrine differentiation must be demonstrated by ancillary techniques such as immunohistochemistry. Chromogranin and synaptophysin are the two stains that are most frequently used and are considered to be more specific than neuron-specific enolase. In order for a tumor to be designated as a large-cell neuroendocrine carcinoma, the tumor must have both neuroendocrine morphology and positive staining. Tumors that otherwise look like squamous cell carcinomas, adenocarcinomas, or large-cell carcinomas but have focal neuroendocrine staining have been termed "non–small-cell lung carcinoma with neuroendocrine differentiation." Although this designation appears in the literature, particularly in studies that have sought to determine whether non–small-cell lung carcinoma with neuroendocrine differentiation has a worse prognosis or differs in its response to chemotherapy, it is actually not formally part of the WHO classification. Similarly problematic are those tumors that show the histologic features of a large-cell neuroendocrine tumor but which fail to stain with neuroendocrine markers and have been classified as *large-cell carcinoma with neuroendocrine morphology or pattern,* with some authors suggesting that these are likely the same tumors as large-cell neuroendocrine carcinomas.[54] *Combined large-cell neuroendocrine carcinoma* refers to a large-cell neuroendocrine carcinoma with components of another non–small-cell carcinoma such as, for example, squamous cell carcinoma or adenocarcinoma.

The controversies in diagnosis and treatment of large-cell neuroendocrine carcinoma have been recently summarized.[54,75] The low incidence of the tumor (estimated as 2%–3% of non–small-cell carcinomas) combined with the limitations of the current WHO classification have resulted in a lack of robust evidence for stage-based treatment strategies. What can be concluded at this point in time is that the molecular genotype and phenotype of large-cell neuroendocrine carcinoma and small-cell carcinoma are similar enough to support at least some extrapolation from treatment paradigms for small-cell carcinoma and, as has been suggested, to include unresectable disease large-cell neuroendocrine carcinoma patients within clinical trials for small-cell carcinoma to obtain prospective data.[54] It is possible that in the future this data may demonstrate that the clinical and pathologic distinction between the two high-grade neuroendocrine carcinomas is of minimal significance.



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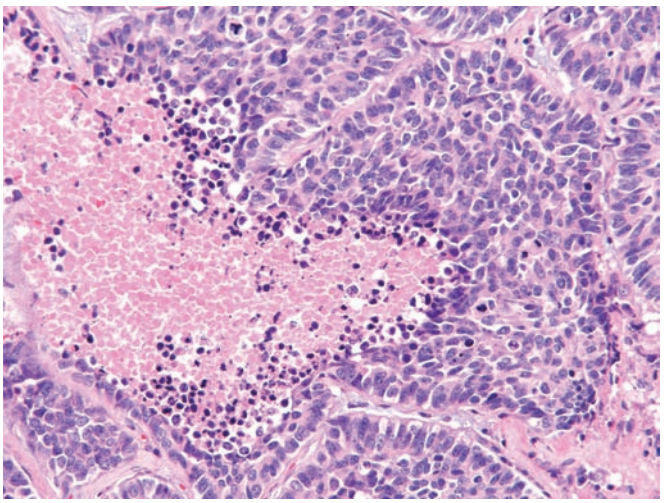


B

Figure 111-20 Side by side comparison of large-cell neuroendocrine carcinoma (**A**) with small-cell carcinoma (**B**). The large-cell neuroendocrine tumor cells have more cytoplasm and there are more prominent nucleoli. The small-cell carcinoma tumor cells have less cytoplasm and the nuclear chromatin is finely granular. (H&E, 200×).

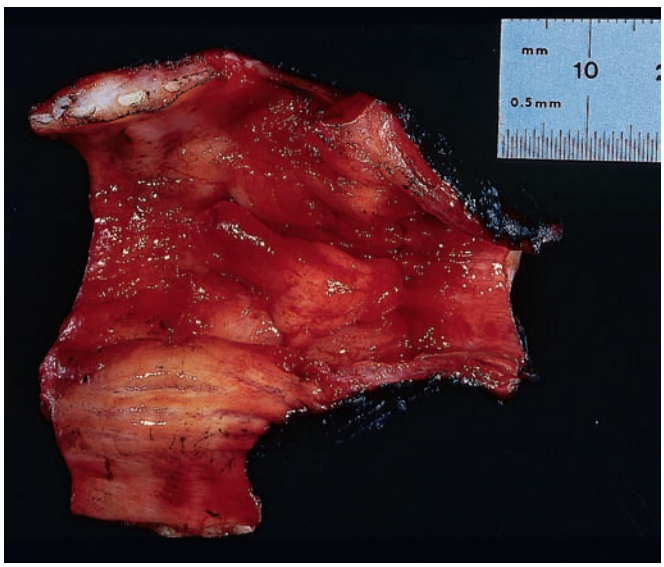
SALIVARY GLAND TUMORS

Mixed seromucinous glands are found in the tracheal and large bronchial submucosa and are believed to give rise to a variety of salivary gland–like tumors, histologically indistinguishable from their major salivary gland counterparts. The 2004 WHO revision recognizes three major subtypes of malignant salivary gland tumors: mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial–myoepithelial carcinoma.[3] Other salivary gland–like tumors such as acinic cell carcinoma or carcinoma ex pleomorphic–mixed tumor do occur in the lung but are exceptionally rare. Salivary gland carcinomas represent less than 1% of all lung carcinomas, with mucoepidermoid carcinoma and adenoid cystic carcinoma being the most common subtypes.[33] Although uncommon, their distinctive morphology, growth pattern, and clinical presentation make these salivary gland–type tumors of the lung an important subgroup of malignant epithelial tumors of the lung.

■ ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma is the most common of the tracheobronchial gland tumors but is still quite rare, representing less than 0.2% of all primary lung tumors.[33] There is a wide age range from young adults to older patients but the tumor tends to occur in the fourth and fifth decades of life.[76] The incidence is equal among men and women. The vast majority of cases originate intraluminally and the typical presenting symptoms such as wheezing, progressive dyspnea, stridor, cough, and hemoptysis reflect this intraluminal tumor growth. Unlike carcinoid tumors and mucoepidermoid carcinomas, which usually present as intraluminal endophytic masses, adenoid cystic carcinomas have a more variable growth pattern. Some tumors are grossly nodular with minimal invasion of the bronchus, whereas others have a mixed nodular/infiltrative or predominantly infiltrative growth pattern (Fig. 111-21A,B). More infiltrative tumors appear as small nodules within the airway or cause a generalized constriction of the airway. There may be lymph node involvement, usually by direct extension, and higher-grade tumors have a tendency to radially spread into the adjacent parenchyma rather than along the airways.

The microscopic level of invasion nearly always exceeds that which is grossly apparent. Negative resection margins often are difficult to achieve. Complete resection may be quite difficult and can require multiple frozen sections to confirm clear surgical margins. The tumor cells are small with a relatively high nuclear:cytoplasmic ratio but nuclear pleomorphism and mitoses are rare. Characteristic mucinous cysts of varying size are present within the tubular and cribriform patterns (Fig. 111-21C). Poorly differentiated tumors have a significant component of solid tumor nests. As is characteristic of their salivary gland counterparts, adenoid cystic carcinomas are notorious for perineural spread. Long-term survival can be achieved with adequate resection but local recurrence may occur even late (>10 years) following resection. The most common site of disseminated disease is the lung parenchyma, but extrathoracic metastases do occur.[77]



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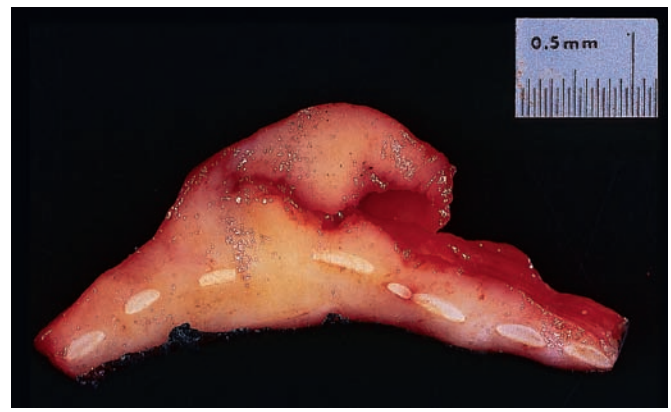

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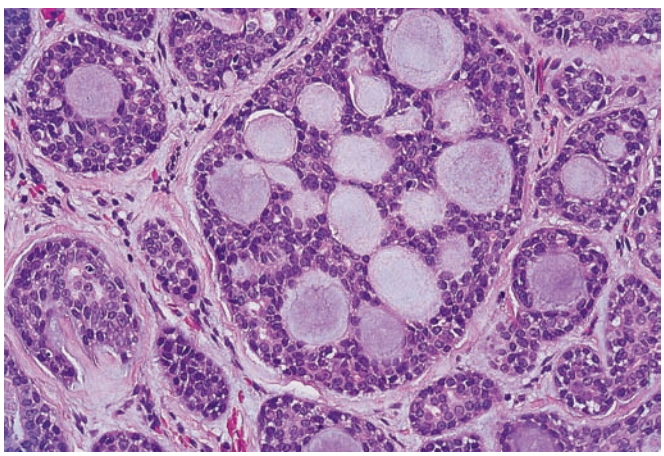


C

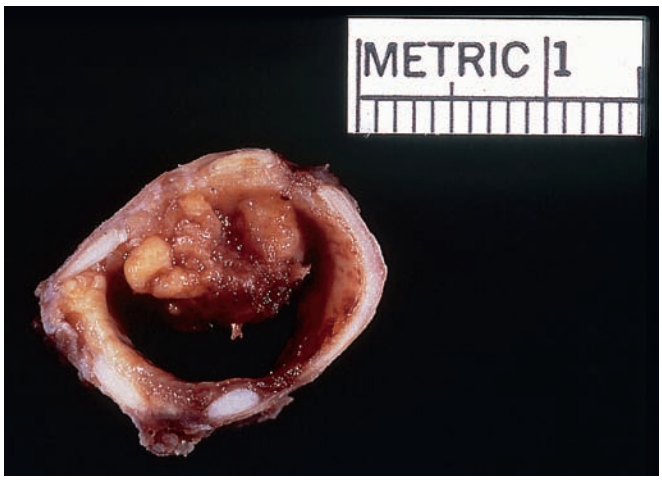
Figure 111-21 **A.** Carinal resection for adenoid cystic carcinoma with a mixed infiltrative and nodular pattern of growth within the submucosa. **B.** Same adenoid cystic carcinoma in cross section, illustrating the extensive diffuse involvement of the submucosa with infiltration beyond the cartilage. **C.** Cribriform growth pattern of adenoid cystic carcinoma (H&E, 200×).

■ MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinomas account for approximately 0.1% to 0.2% of lung cancers.[33] Patients with this tumor may be asymptomatic, but it is far more common for patients to present with symptoms of bronchial obstruction due to the tumor's characteristic endobronchial location.[78] These symptoms include wheezing, cough, and hemoptysis, and patients may present with postobstructive pneumonia. The age at presentation varies, but almost half of the cases of mucoepidermoid carcinoma occur in patients under 30 years of age and it is common in the pediatric population. There is no significant association with tobacco use. Although the radiographic findings may be subtle and identified in retrospect, a solitary, centrally located mass with distal pneumonia or atelectasis is typical.

Mucoepidermoid carcinomas usually arise from segmental and subsegmental bronchi, but can involve the trachea as well.[33] They range in size from a few millimeters to up to 6 cm and grow as polypoid masses with a tan or gray surface (Fig. 111-22A,B). On cross section, the tumor may appear more mucoid or cystic than the more common non–small-cell carcinomas of the lung. Histologically, mucoepidermoid tumors of the lung are separated into low- and high-grade tumors.[79,80] An "intermediate grade," which is used for tumors within the salivary gland, has not been formally recognized with the WHO classification but has been used.[77] The tumors are composed of a mixture of mucin-secreting cells, squamous cells, and what are termed "intermediate cells." The intermediate cells have a polygonal shape and eosinophilic cytoplasm, but lack obvious squamous or glandular differentiation. The mucinous component consists of well-differentiated glands, with both intracellular and extracellular mucin (Fig. 111-22C). Some tumors are associated with a prominent lymphocytic infiltrate.[81] Thus far, these tumors have been reported to be TTF-1 negative.[81] In low-grade tumors, the cells have minimal pleomorphism, rare mitoses, and minimal necrosis. Suggested criteria for high-grade tumors include an increased mitotic rate (average of 4 per 10 high power fields), necrosis, and nuclear pleomorphism. High-grade mucoepidermoid carcinomas may be difficult to distinguish from adenosquamous carcinomas. High-grade mucoepidermoid carcinomas still retain a characteristic admixture of mucin-containing cells, squamoid cells, a central endobronchial location, and transitional areas from low-grade mucoepidermoid carcinoma. There should be no keratinization, squamous pearl formation, or in situ squamous cell carcinoma. These features, if present, are more consistent with a diagnosis of squamous or adenosquamous carcinoma.

The clinical behavior of these neoplasms had been controversial, mainly due to past ambiguities regarding the definition of high-grade mucoepidermoid carcinomas and their distinction from adenosquamous carcinomas. Low-grade tumors, which are usually confined to the bronchus, have an excellent prognosis following complete excision. High-grade tumors, which tend to invade the adjacent lung parenchyma, carry a worse prognosis and tend to behave in a manner similar to more common non–small-cell carcinomas. The data suggest that long-term clinical follow-up is indicated for these patients. There is a low reported incidence of lymph node metastases and local recurrence has been reported with incomplete excision.



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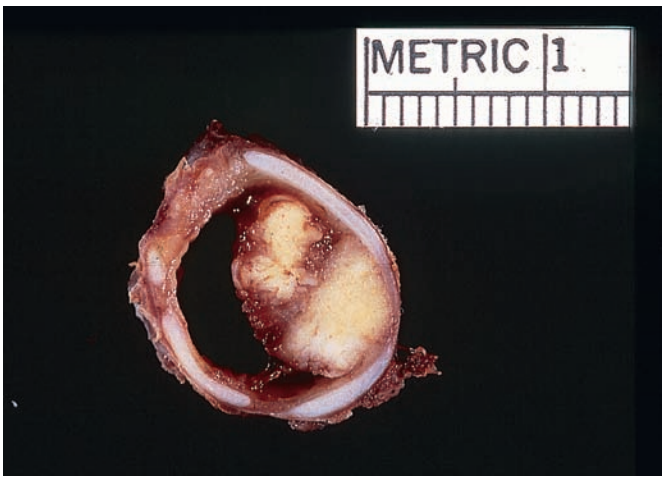

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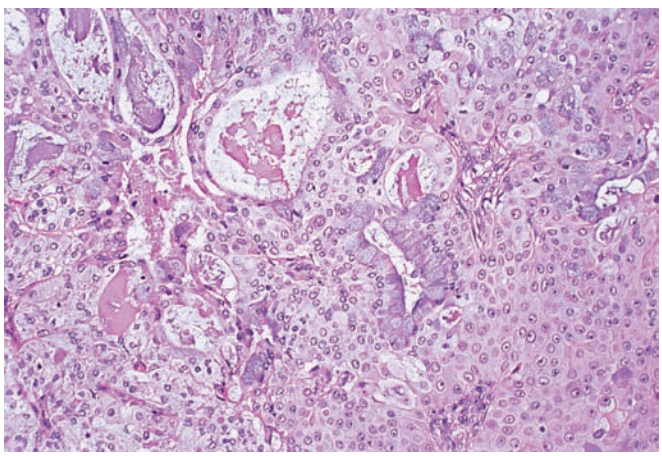

C

Figure 111-22 **A.** Left mainstem bronchus resection for endobronchial mucoepidermoid carcinoma. **B.** Same mucoepidermoid carcinoma tumor in cross section, demonstrating an attachment to the bronchus but invasion is limited to the superficial portion of the submucosa. **C.** Mucoepidermoid carcinoma. There are both well-differentiated mucinous glands *(left)* and intermediate cells *(right)* that have a polygonal shape and abundant eosinophilic cytoplasm (H&E, 200×).

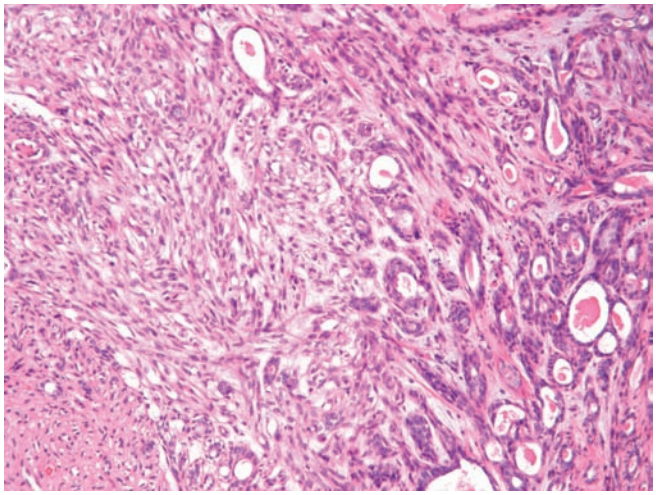

Figure 111-23 Epithelial–myoepithelial carcinoma. Tumor is composed of duct-forming epithelium and myoepithelial cells with a spindle cell morphology (100×).

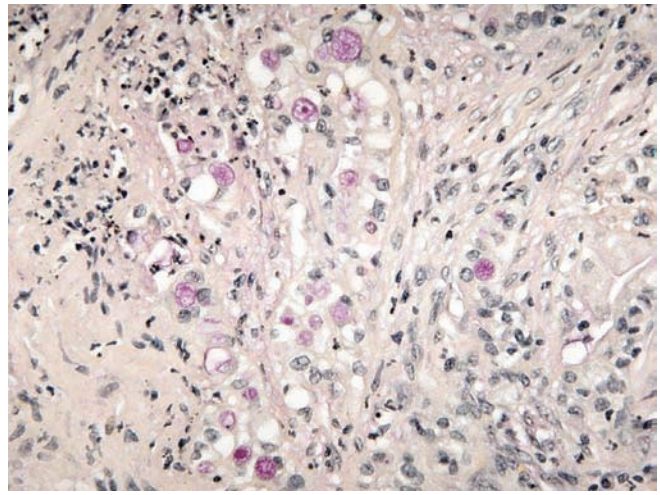

Figure 111-24 Positive mucin stain in a poorly differentiated non–small-cell carcinoma with clear cell change, supporting the diagnosis of adenocarcinoma (400×).

■ EPITHELIAL–MYOEPITHELIAL CARCINOMA

The 2004 WHO classification defines epithelial–myoepithelial carcinoma as a tumor that consists of "myoepithelial cells with spindle cell, clear cell or plasmacytoid morphology and varying amounts of duct-forming epithelium" (Fig. 111-23).[3] The tumor is extremely rare with 25 cases reported in the literature to date.[82] Nearly all of the tumors have been endobronchial and reported within the adult population with no known risk factors. There has been a wide range of terminology associated with this lesion in the literature including adenomyoepithelioma, myoepithelioma, epithelial–myoepithelial tumor of unproven malignant potential, and malignant mixed tumor comprising epithelial and myoepithelial cells. Grossly the tumor is well circumscribed but unencapsulated, with a size range of 1.2 to 5.0 cm. Microscopically, the tumor consists of duct-like structures that are lined by a double layer of cells with an inner layer of cuboidal cells with eosinophilic cytoplasm and an outer layer of cells with predominantly clear cell cytoplasm. There is often eosinophilic material in the luminal spaces. The outer layer of cells and more solid components typically stain positively for SMA, S-100, p63, and calponin, which is characteristic of myoepithelial cells. The inner layer of tumor cells stains positively with cytokeratins (CAM5.2, AE1/3, CK7, and CK903) as well as EMA and TTF-1.[83] The positive TTF-1 staining is of interest in that other salivary gland–type tumors such as adenoid cystic carcinoma and mucoepidermoid carcinoma are reported to be TTF-1 negative. Most of the cases reported (with limited follow-up) have been free of disease following complete surgical resection with a minority of cases showing lymph node involvement or recurrent disease.[82–84]

ANCILLARY STUDIES

The lung is a common site for both primary tumors and metastases and the pathologist must consider a broad differential diagnosis when analyzing a cytologic or tissue preparation. Ancillary studies typically are used to narrow the differential diagnosis or demonstrate differentiation. The appropriate use of ancillary studies is grounded in a well-formulated differential diagnosis based on the tumor's histologic appearance. The clinician contributes greatly by providing the details of a complete clinical history, thorough physical examination, and high-quality radiographic imaging. This helps direct the diagnostic workup and avoids unnecessary tests that will delay the diagnosis or exhaust the tumor contained in that specimen.

■ HISTOCHEMICAL STAINS

The most commonly used histochemical stains in tumor evaluation are those that demonstrate intracellular mucins – periodic acid-Schiff (PAS) after diastase and mucicarmine – characteristic of adenocarcinomas. Mucin stains are typically performed on poorly differentiated carcinomas that appear as solid carcinomas lacking glandular differentiation but prove to have numerous mucin-positive tumor cells and therefore would be best classified as adenocarcinomas, solid type (Fig. 111-24). While helpful in some instances, mucin stains have a low sensitivity for glandular differentiation (about 30%).[85] Although practice patterns vary somewhat, pathologists will often forego a mucin stain in small biopsies in an effort to preserve as much tissue as possible and do a limited panel of immunohistochemical stains instead. Stains for neutral mucins are still occasionally used to distinguish adenocarcinoma from epithelial mesothelioma. Alcian blue staining with hyaluronidase treatment can be used to distinguish the acid mucin of mesothelial cells from the epithelial mucin associated with adenocarcinomas, but its use has largely been supplanted by immunohistochemistry.

■ IMMUNOHISTOCHEMISTRY

Immunohistochemistry is based on a primary antigen–antibody reaction and a secondary antibody–enzyme complex that interacts with a chromogen for a microscopically visible color reaction. Since its introduction into diagnostic pathology in the early 1980s, immunohistochemistry has become an integral part of tumor diagnosis. Unfortunately, there are very few antibodies that approach 100% sensitivity and specificity. As experts on immunohistochemistry have emphasized, it is diagnostically irrelevant to speak of overall sensitivity and specificity for a particular antibody. Rather it is more appropriate to speak of relative sensitivity and specificity within a particular differential diagnosis. This requires clinical interaction and morphologic expertise in generating a differential diagnosis in addition to critical assessment of the immunohistochemical results with appropriate controls. New antibodies are developed, evaluated, and introduced at a fairly constant rate. The following summary remarks are meant only as broad overview of current practice with the understanding that the field is constantly evolving and that all of the markers mentioned have utility both in and outside of the lung.[86]

Immunohistochemistry is often used in the workup of an undifferentiated large-cell carcinoma, usually to exclude melanoma and lymphoma, which can mimic a highly pleomorphic epithelial

tumor. Within this differential diagnosis of an undifferentiated tumor comprised of large cells, cytokeratin antibodies such as AE1/3, CAM5.2, and pancytokeratin are used to support the diagnosis of carcinoma. Cytokeratin antibodies will at least focally stain most non–small-cell carcinomas of all histologic subtypes, in addition to a wide variety of carcinomas from other primary sites. There are, however, potential pitfalls. Cytokeratin antibodies stain benign bronchial and alveolar epithelia, which can be entrapped within tumors and lead to a false-positive interpretation. Reactive mesothelial cells and malignant mesotheliomas are cytokeratin positive as well. Cytokeratin positivity, usually focal, also has been demonstrated in sarcomas and melanomas. S100, HMB45, melan-A, MITF, and tyrosinase are markers of melanocytic differentiation; a panel using at least two or three of these is often employed when malignant melanoma is a strong consideration. Although sensitive, S100 is less specific for melanoma and stains other tumors, including those of neural origin and some adenocarcinomas of both primary pulmonary and extrapulmonary origin, such as the breast. The range of markers used to evaluate lymphoid neoplasms is extensive but include leukocyte common antigen (LCA), CD30, and B and T cell markers. There are antibodies to glycoproteins such as CEA, MOC31, B72.3, LeuM1, Bg8, and BerEP4, which stain a high percentage of adenocarcinomas, including adenocarcinomas of the lung. Recommended guidelines on the use of immunohistochemistry when the differential diagnosis includes malignant mesothelioma have been published and updated.[87] When the differential diagnosis centers on an epithelioid malignant mesothelioma versus adenocarcinoma, a panel of at least two affirmative markers for malignant mesothelioma and two affirmative markers for adenocarcinoma is recommended.

Immunohistochemistry is similarly used in the workup of an undifferentiated small-cell carcinoma, usually to exclude melanoma and other so-called "small round blue cell tumors" such as lymphoma, Merkel cell carcinoma, and other primitive neuroectodermal tumors. In this instance, attention to subtle differences in nuclear cytology, chromatin pattern, and mitotic activity is essential, as is a targeted immunohistochemical panel that might include (depending on the circumstances) pancytokeratin, synaptophysin, chromogranin, CD56, TTF-1, CK7, CK20, CD99, S-100, desmin, WT-1, LCA, myogenin, and TLE. Unusual clinical circumstances or radiographic imaging, particularly in a younger patient or a nonsmoker, should prompt consideration of a broad immunohistochemical workup as well as molecular tests for characteristic cytogenetic abnormalities for tumors such as a poorly differentiated synovial sarcoma, desmoplastic small round cell tumor, Ewing sarcoma, and rhabdomyosarcoma.

The use of immunohistochemistry has not eliminated the challenges of distinguishing a primary lung carcinoma from metastatic disease. There are only a limited number of instances in which immunohistochemical stains are useful in differentiating a pulmonary primary from a metastatic tumor. With the exception of thyroglobulin for the majority of thyroid tumors and prostate-specific antigen for the majority of prostatic adenocarcinomas, many other antibodies have too much overlap in specificity to be conclusive. There has been some qualified success in instances when the differential diagnosis includes other common solid organ malignancies such as breast or gastrointestinal carcinomas. Staining with a panel of antibodies to bolster one's diagnostic certainty in the differential diagnosis of primary lung carcinoma versus metastasis can certainly enhance diagnostic accuracy. Fundamentally, however, this type of immunohistochemical analysis remains an exercise in probabilities and may not be sufficient for certain clinical circumstances. It is most often the case that new markers are introduced into the literature with initial reports of high sensitivity and specificity. After a time, with additional studies and incorporation into daily practice, more exceptions appear. A good example is TTF-1. On average, TTF-1 stains about 75% of primary pulmonary adenocarcinomas, although the percentage is lower in more poorly differentiated tumors, some subtypes of adenocarcinoma, and better differentiated neuroendocrine tumors.[31] It was initially believed that the only extrapulmonary tumor that was as frequently positive for TTF-1 was thyroid carcinoma. Now there are reports of TTF-1 positivity in extrathoracic tumors that would not be expected – such as ovarian epithelial tumors – making the marker less specific than was initially asserted although often still useful.[31] The same can be said of gastrointestinal profile panels that use CK7, CK20, TTF-1, Napsin A, and CDX2 to support a luminal GI primary. Although many GI primaries will have a CK20, CDX2 positive and CK7, TTF-1, Napsin A negative staining pattern, a small subset of primary lung tumors with an "enteric" differentiation will show an overlapping staining pattern.[88] Whether "molecular profiles" will be able to improve diagnostic accuracy or supplant the relatively rapid turnaround time and low cost of immunohistochemistry remains to be seen.

As discussed in the section on pulmonary neuroendocrine tumors, the artifacts that are often present in small samples can make it difficult to separate out small-cell carcinoma from other non–small-cell carcinomas or to apply the criteria for separating out carcinoid tumors from the higher-grade neuroendocrine carcinomas. In addition to some of the other immunohistochemical stains mentioned for supporting neuroendocrine differentiation (synaptophysin, chromogranin, and CD56), an extended panel might also include CK5/6, p63 (or p40), and TTF-1 to exclude the possibility of a basaloid or small-cell variant of squamous cell carcinoma.[89] The proliferation marker, ki-67, is sometimes used in smaller specimens as a surrogate for identifying mitoses, which may be absent or infrequent. Although not completely standardized or reproducible, an increased proliferation index can be helpful in favoring a lower- or higher-grade neuroendocrine tumor.[65,90]

The need for a more precise classification of poorly differentiated non–small-cell carcinoma into squamous or nonsquamous histology has further expanded the use of immunohistochemistry within pulmonary pathology. A significant proportion of small biopsies (and some large resections) will not have obvious evidence of squamous differentiation, as defined by keratinization or intercellular bridges, or obvious features of adenocarcinoma, as defined by gland formation or intracellular mucin. In these instances when the tumor cells are arranged in solid nests and there is no specific evidence of differentiation, a panel of immunohistochemical stains can be used for further subclassification. There are numerous studies that have looked at the utility of immunohistochemistry in reducing the category of "non–small-cell lung carcinoma, not otherwise specified" and the minimum number of stains needed for evaluation. The latter point, of using the least number of stains with the most specificity and sensitivity, is not a trivial issue in the usual case of advanced disease patient who will have an initial biopsy that will likely be triaged for targeted therapy. At the current time, the data support at minimum a panel that includes TTF-1, CK5/6, and p63 (or p40), with addition of stains such as Napsin A or CK7 if there is sufficient tissue (Fig. 111-25A–D).[85,91–93] Beyond using evidence to construct the best limited immunohistochemical panel to determine differentiation, other techniques such as dual antibody staining cocktails can reduce the amount of tissue used (Fig. 111-26). As discussed in greater detail in the following section, processing decisions must be made up front to ensure that there is sufficient material for diagnosis, immunohistochemical stains if necessary, and residual tissue for molecular testing.

The increased use of immunohistochemistry for histologic subclassification has generated debate, particularly in the context of clinical trials for advanced disease patients, as to what exactly it means – biologically, therapeutically, and prognostically – for a tumor to only have immunohistochemical evidence of differentiation. These issues were further complicated by the conspicuous historic lack of any

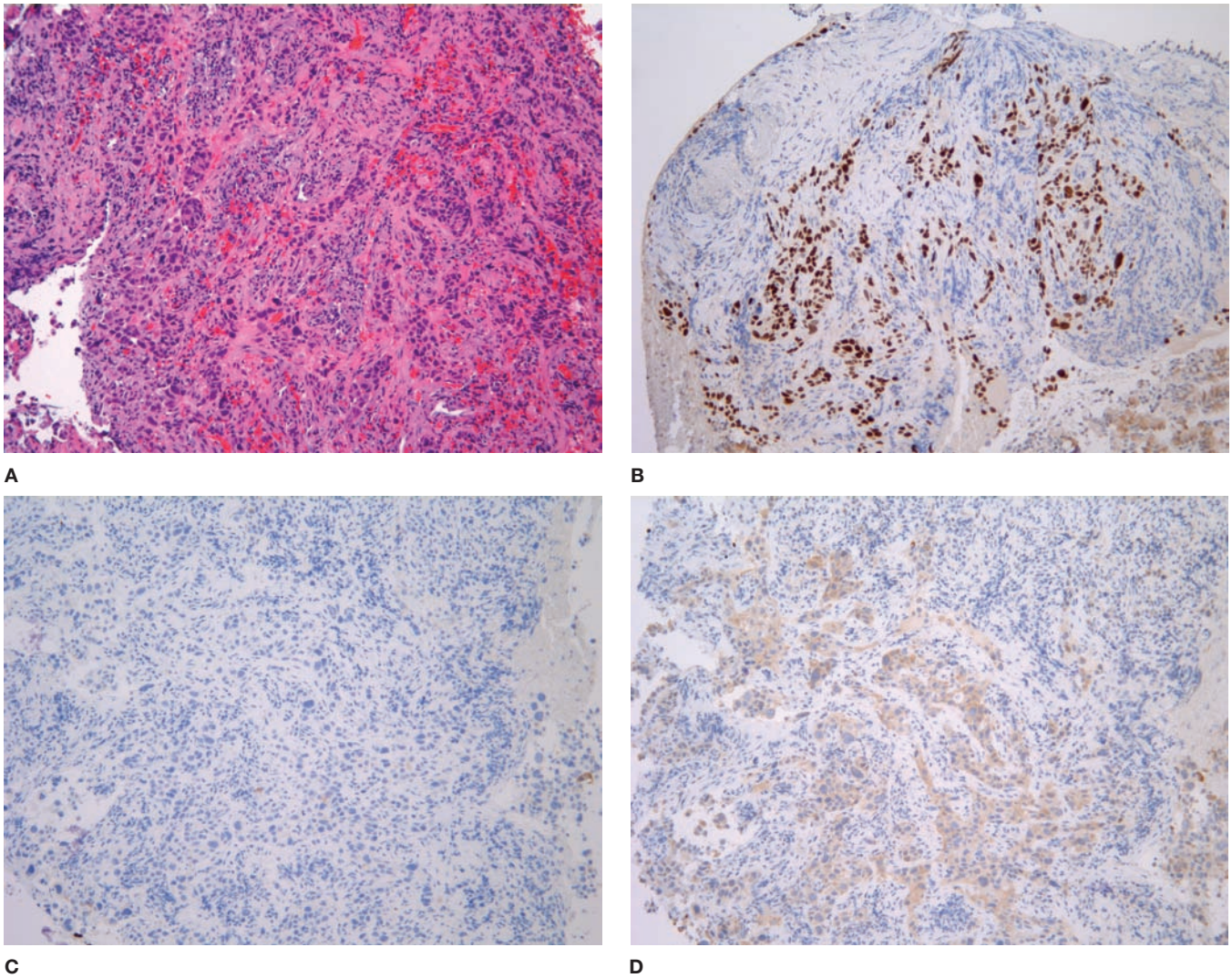

Figure 111-25 Small biopsy showing poorly differentiated non–small-cell carcinoma and immunohistochemical stains supporting the diagnosis of pulmonary adenocarcinoma. **A.** H&E (100×). **B.** TTF-1 antibody positive (100×). **C.** CK5/6 antibody negative (100×). **D.** p63 antibody negative in tumor nuclei (100×).

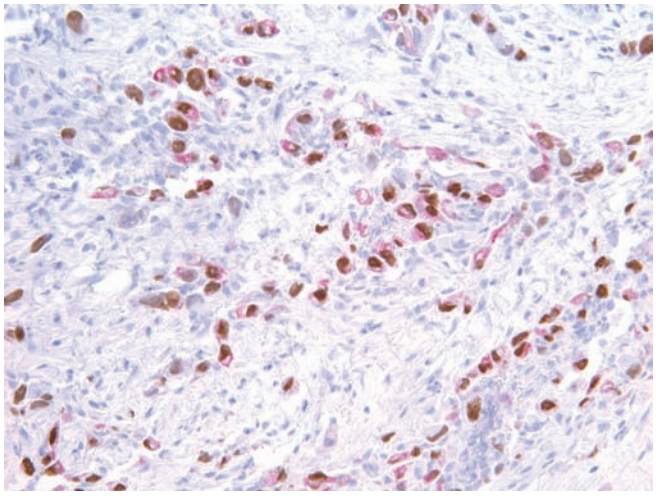

Figure 111-26 Poorly differentiated non–small-cell carcinoma with squamous differentiation demonstrated by positive dual antibody immunohistochemical staining for CK5/6 *(pink)* and p63 *(nuclear brown staining)* (200×).

standard nomenclature for small biopsies. The 2011 IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma proposed terminology for small biopsies/cytology specimens in these instances[5] although the adoption of this terminology in general practice and even within academic medical centers has been inconsistent.

ADEQUACY OF SMALL SPECIMENS FOR DIAGNOSIS, TREATMENT, AND MOLECULAR ANALYSIS

Small specimens occupy a central role in the majority of patients with lung cancer – often at multiple time points during the course of their disease – and the clinical relevance of these small specimens has led to a "paradigm shift" in the way these small specimens are processed and interpreted.[94] Bronchoscopic biopsies with or without endobronchial ultrasound guidance, fine-needle aspiration, or body fluid cytologic examination are all acceptable as minimally invasive procedures for the initial diagnosis of a primary lung carcinoma or to document metastasis. With the emerging emphasis on the importance of histologic subtyping in non–small-cell lung cancer and the need for molecular analysis for "personalized" or "precision" medicine, the debate in recent years had focused on whether small specimens are adequate for these purposes. Numerous studies have

now established that a variety of specimens, ranging from small biopsies to cytology cell blocks to cytology touch imprints or aspirates, are potentially suitable for molecular testing and the practical considerations for testing have been recently and comprehensively reviewed.[95] The essential point is that small diagnostic specimens must be handled carefully from the outset of any procedure with the understanding that the specimen may be the only specimen available for molecular analysis. Within each specific practice setting, an algorithm should be established that emphasizes the need for communication between the pathologist and the clinical care team *before* the specimen is processed.[96] This clinical information should include such information as whether the biopsy is for initial diagnosis, whether the patient is a candidate for surgical resection, whether the patient is a candidate for targeted therapy, whether the biopsy is for molecular prioritization in a patient with an established diagnosis of lung cancer, or whether the biopsy is a rebiopsy for resistance testing. All of this information will in turn allow the pathologist to communicate with molecular and histology laboratories to ensure that the specimen is appropriately triaged and that the optimal material is selected for diagnosis, ancillary immunohistochemical testing, and molecular prioritization.

CONCLUSION

In addition to the clinicopathologic features and histologic subtyping of primary pulmonary carcinomas, recent changes and current controversies in tumor classification have been reviewed. The pathologist makes a critical contribution to the management and treatment of lung carcinoma, but the final pathologic interpretation should not be rendered in a clinical vacuum. It is incumbent upon the clinician caring for the patient to be sure that the pathologist has the benefit of complete clinical information. Nowhere is this clinical information and communication more critical than in the processing of small specimens in this era of personalized medicine. The inclusion of the pathologist as an integral part of what is now a multidisciplinary evaluation team for a thoracic malignancy enhances the quality of care for the individual patient and refines the general practice of thoracic oncology.

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CHAPTER 112

Clinical Evaluation, Diagnosis, and Staging of Lung Cancer

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INTRODUCTION

Patients who present with suspected lung cancer require a detailed clinical evaluation followed by noninvasive testing and invasive procedures to establish both the histopathologic diagnosis as well as disease stage. Historically, great emphasis has been placed upon the differentiation of small-cell lung cancer (SCLC) from non–small-cell lung cancer (NSCLC). SCLC, which accounts for 14% of bronchogenic carcinomas, is histologically and clinically distinct from NSCLC.[1] NSCLCs have been traditionally regarded as a fairly uniform group of cancers. However, it has become increasingly evident that NSCLCs are comprised of clinically, pathologically, and molecularly diverse tumors that respond to different therapeutic agents based on specific histologic phenotypes and molecular characteristics.

The clinician evaluating the patient with suspected lung cancer must take into account several factors, including the likelihood of SCLC versus NSCLC, probability of metastatic disease, comorbid illness and functional status, presence of paraneoplastic syndromes, and treatment preferences of the patient. Good decision making regarding appropriate diagnostic test selection must incorporate: (1) careful assessment of pretest probabilities based upon clinical evaluation and initial radiographic features, and (2) understanding of specific test characteristics. The main objectives of the diagnostic and clinical staging evaluation are to obtain adequate tissue to establish the histopathologic diagnosis and, when indicated, molecular characterization of the tumor, and to ascertain the extent of disease to determine candidacy for specific therapies. These twinned goals should be accomplished in the safest, least invasive, and most cost-effective manner possible.

INITIAL CLINICAL EVALUATION

A detailed history and physical examination are of key importance in assessment of the patient's overall health status and medical appropriateness for specific therapies.[2] Certain comorbid conditions may reduce therapeutic options. Limited cardiopulmonary reserve may preclude surgical intervention. A thorough history can also assist a physician in determining overall extent of disease. At the time of presentation, it is most useful to consider the clinical stage using the International Association for the Study of Lung Cancer (IASLAC) 7th edition of the tumor, node, and metastasis (TNM) classification system (Table 112-1); pathologic stage is established only after surgical resection.[3]

Only 7% to 13% patients are asymptomatic at the time of initial diagnosis as lung cancer is usually a diagnosis made during its later stages.[4,5] A recent national cancer database survey of patients diagnosed from 1998 to 2006 demonstrates that the majority of patients have either locally advanced or metastatic disease at the time of diagnosis. Only 26% of patients have stage I disease and 8.3% have stage II, whereas 27.6% have stage III disease and 38.1% have metastatic disease (Fig. 112-1).[6]

Patients often have had symptoms for months prior to diagnosis.[7,8] Symptoms, particularly those associated with localized disease such as cough, wheezing, and dyspnea, are often attributed to comorbid illnesses by both patients and their physicians. In one study in the United Kingdom of newly diagnosed lung cancer patients, symptom duration ranged from 4 to 24 months with a median of 12 months.[9] In one of the earliest series describing the relationship of presenting symptoms to stage and prognosis, about a third of patients (27%) presented with symptoms related to primary tumor only (Table 112-2), another third (34%) presented with nonspecific symptoms concerning for metastatic disease, and the final third (32%) presented with symptoms attributable to a distant metastatic site.[10] Only 6% were asymptomatic.

TABLE 112-1 TNM Staging System for Lung Cancer

Primary tumor (T)	T1	Tumors ≤3 cm that do not invade the lobar bronchus and do not invade the visceral pleural
	T1a	Tumors ≤2 cm
	T2a	Tumors >2 cm but ≤3 cm
	T2	Tumors >3 cm but ≤7 cm OR invades the visceral pleural OR invades the mainstem bronchus OR associated with atelectasis or obstructive pneumonia extending from the hilum
	T2a	Tumor >3 cm but ≤5 cm
	T2b	Tumor >5 cm but ≤7 cm
	T3	Tumors >7 cm OR • Direct invasion of chest wall, diaphragm, phrenic nerve, mediastinal or parietal pleural, parietal pericardium, OR mainstem bronchus to within 2 cm carina OR • Atelectasis or obstructive pneumonia of whole lung OR • Satellite tumor nodules within same lobe
	T4	Direct invasion mediastinal structures OR trachea OR recurrent laryngeal nerve OR carina OR vertebral body OR Satellite tumor nodule within a different lobe of the ipsilateral lung
Regional lymph nodes (N)	N0	No regional lymph node metastases
	N1	Metastases or involvement by direct extension of ipsilateral peribronchial, intrapulmonary, or hilar nodes
	N2	Metastases to ipsilateral mediastinal or subcarinal lymph node
	N3	Metastases to any scalene or supraclavicular lymph node or to contralateral mediastinal or hilar nodes
Distant metastases (M)	M0	No distant metastases
	M1	Distant metastases present
	M1a	Satellite tumor nodule(s) in contralateral lung, pleural nodules, or malignant pleural or pericardial effusion
	M2a	Extrathoracic metastases

Source: Adapted with permission from Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. Journal of Thoracic Oncology. 2007;2(8):706–714.

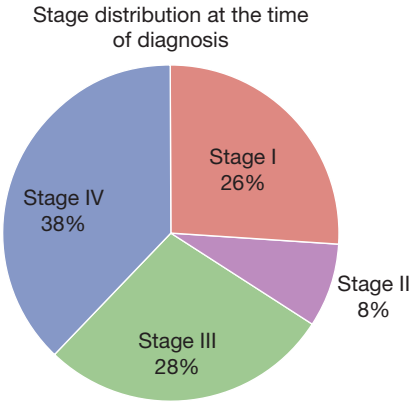

Figure 112-1 Stage distribution at the time of diagnosis.

Local symptoms can include cough, hemoptysis, dyspnea, chest pain, and wheezing.[5,11] Cough is the most frequently encountered presenting symptom and can be the result of endobronchial or parenchymal involvement by the primary tumor, regional lymph node enlargement, or postobstructive complications. Hemoptysis is the symptom that typically results in the most expeditious evaluation; about 5% of patients with hemoptysis and a normal chest x-ray will ultimately be diagnosed with lung cancer.[12] Chest discomfort and pain may indicate pleural involvement or direct tumor invasion of the chest wall or thoracic cage. Hoarseness, which can occur in up to 5% lung cancer patients at presentation, can be concerning for laryngeal nerve palsy, which can occur in 2% to 18% of lung cancer patients.[5] This is more commonly seen with left-sided tumors, which can involve the recurrent laryngeal nerve as it loops under the aortic arch.[11] Lung cancer accounts for up to 75% of all cases of superior vena cava (SVC) syndrome due to local compression or invasion.[13] Signs and symptoms of SVC syndrome include swelling of the face, neck, upper torso and arms, and dyspnea. Up to 4% of patients with NSCLC and 10% of patients with SCLC can develop SVC syndrome. Dysphagia can suggest extrinsic compression of the esophagus due to bulky mediastinal disease, particularly involving the subcarinal lymph node, or it can result from direct esophageal invasion. Central tumors such as squamous cell carcinoma may cause airway obstruction resulting in a localized or unilateral wheeze, atelectasis, or postobstructive pneumonia.[14,15] Cancers arising in the lung apex (superior sulcus tumors) can present with the Pancoast syndrome, an assortment of clinical manifestations due to invasion or compression of local structures. Characteristic signs and symptoms include shoulder pain due to invasion of the brachial plexus and/or ribs and vertebrae, upper extremity weakness and paresthesias, and Horner syndrome (unilateral ptosis, meiosis, and lack of facial sweating on the involved side) due to compression or invasion of the sympathetic chain.[16]

Focal symptoms of metastatic disease are fairly common at presentation: 25% of patients present with bone pain, 20% of patients present with symptoms associated with bulky mediastinal adenopathy such as cough and hoarseness, and 10% of patients have neurologic symptoms that may include headache, nausea and emesis, seizures and/or mental status changes at the time of diagnosis.[5,11] Lung cancer accounts for 70% of the cancers that first present as symptomatic brain metastases.[17] The presence of nonspecific constitutional symptoms (weakness, weight loss, fever, and anorexia) is worrisome for metastatic disease; often, patients with hepatic metastases present with symptoms of weakness and weight loss. Standard laboratory testing should include a complete blood count as well as chemistries that include liver function testing. Anemia (hematocrit less than 40% in men and less than 35% in women) can indicate higher likelihood of metastatic disease. Similarly, elevated liver function tests can be worrisome for hepatic metastases.

Hooper et al.[18] have enumerated a standard set of clinical features found to be associated with metastatic disease (Table 112-3). Systematic review suggests that absence of all of these features makes metastatic disease highly unlikely with a negative predictive value exceeding 90%.[19,20]

Initial clinical evaluation of the patient with suspected lung cancer should also include an assessment for paraneoplastic syndromes (Table 112-4), clinical disorders associated with malignant disease that are not directly attributable to the physical effects of the tumor. They may be seen in up to 10% patients with lung cancer.[5] The most commonly recognized paraneoplastic syndromes are hormonally mediated; tumor cells secrete hormones or hormonal analogs. The syndrome of

TABLE 112-2 Initial Signs and Symptoms of Lung Cancer[5]

Signs and Symptoms	Range of Reported Frequencies (%)
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–25
Bone pain	6–25
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing	0–2

Source: Data from Andersen HA, Prakash UBS. Diagnosis of symptomatic lung cancer. Semin Respir Med. 1982;3:165–175; Grippi MA. Clinical aspects of lung cancer, Semin Roentgenol. 1990:25:12–24; Hyde L, Hyde CI. Clinical manifestations of lung cancer. Chest. 1974;65:299–306; Cromartie RS III, Parker EF, May JE, et al. Carcinoma of the lung. Ann Thorac Surg. 1980;30:30–35; Karsell PR, McDougall JC. Diagnostic tests for lung cancer. Mayo Clin Proc. 1993;68:288–296; American Thoracic Society, European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. Am J Respir Crit Care Med. 1997;156:320–332.

TABLE 112-3 Features of a Standardized Evaluation for Metastatic Disease[5]

Symptoms	• Weight loss >10 lb • Focal skeletal pain • Neurologic symptoms: headaches, syncope, seizures, focal extremity weakness, altered mentation
Signs	• Palpable lymphadenopathy (>1 cm) • Hoarseness or SVC syndrome • Bone tenderness • Hepatomegaly (>13 cm) • Focal neurologic signs • Soft tissue mass
Laboratory testing	• Hematocrit <40% in men or <35% in women • Elevated alkaline phosphatase, liver function tests

Source: Data from Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine. 1990; 69:1–33; Hooper RG, Tenholder MF, Underwood GH, et al. Computed tomographic scanning of the brain in the initial staging of bronchogenic carcinoma. Chest. 1984;85:774–776.

TABLE 112-4 Paraneoplastic Syndromes Associated with Lung Cancer[5]

System	Syndrome
Endocrine	SIADH
	Hypercalcemia
	Cushing syndrome
	Gynecomastia
	Hypercalcitoninemia
	Elevated LH and FSH
	Hyperthyroidism
	Carcinoid syndrome
Neurologic	Subacute sensory neuropathy
	Mononeuritis multiplex
	LEMS
	Encephalomyelitis
	Necrotizing myelopathy
	Cancer-associated retinopathy
Skeletal	Hypertrophic osteoarthropathy
	Clubbing
Renal	Glomerulonephritis
	Nephrotic syndrome
Metabolic	Lactic acidosis
	Hypouricemia
Systemic	Anorexia
	Fever
Rheumatologic	Dermatomyositis and polymyositis
	Vasculitis
	SLE
Cutaneous	Acquired hypertrichosis lanuginosa
	Erythema multiforme
	Tylosis
	Erythroderma
	Exfoliative dermatitis
	Acanthosis nigricans
	Sweet syndrome
	Pruritus and urticaria
Hematologic	Anemia
	Leukocytosis and eosinophilia
	Thrombocytosis
	Thrombocytopenia purpura
	Thrombophlebitis
	Disseminated intravascular coagulation

Source: Data from Scagliotti G. Symptoms, signs and staging of lung cancer. Eur Respir Mon. 2001;17:86–119; Carbone PP, Frost JK, Feinstein AR, et al. Lung cancer: perspectives and prospects. Ann Intern Med. 1970;73:1003–1024.

inappropriate antidiuretic hormone (SIADH) is seen in 10% to 45% of patients with SCLC and 0.7% to 1% of patients with NSCLC (squamous cell and adenocarcinoma) although symptoms related to hyponatremia are present in just 1% to 5% of patients.[21,22] Hyponatremia is associated with decreased survival in SCLC.[23] Ectopic production of adrenocorticotropin hormone (ACTH) can be found in up to 50% of patients with lung cancer, but true Cushing syndrome is seen in only 1% to 5% of patients with SCLC.[5,21] Ectopic Cushing syndrome is also associated with a poor prognosis in SCLC, in part related to an increased susceptibility to opportunistic infection in patients given chemotherapy.[21,24–26]

Hypercalcemia is seen in 2% to 6% of all lung cancer patients at presentation, and in up to 10% to 25% during their clinical course.[5,21] Etiology of hypercalcemia can be due to direct tumor effect on local osteolytic activity when there are bony metastases. However, in a substantial fraction of patients, typically those with squamous cell histopathology and less commonly in SCLC, hypercalcemia is due to tumor cell–elaborated parathyroid hormone related peptide (PTHrP).

Digital clubbing and hypertrophic osteoarthropathy (HOA) are two paraneoplastic syndromes of the musculoskeletal system commonly associated with NSCLC. Clubbing manifests as enlargement of the terminal tufts of the fingers and toes. It results from the proliferation of connective tissue beneath the nail matrix and can be seen in up to 29% of patients with adenocarcinoma or squamous cell carcinoma histopathology.[27] HOA, which occurs in fewer patients (<4%), presents as painful symmetric arthropathy, usually involving the ankles, wrists, and knees, and is caused by new periosteal bone formation at the distal long bones, resulting in vascular hyperplasia and edema. It is postulated that HPO occurs due to overexpression of vascular endothelial growth factor (VEGF).[28]

Other paraneoplastic syndromes associated with lung cancer occur due to the development of autoantibodies that can cause neurologic disease or rheumatologic disease. Dermatomyositis and polymyositis are autoimmune inflammatory myopathies characterized by progressive symmetrical proximal muscle weakness associated with various malignancies. Patients with dermatomyositis additionally may have Gottron's papules, and a heliotrope rash with poikiloderma. In two series, lung cancer accounted for 17.4% and 18%, respectively, of new cancer diagnoses within the first year of diagnosis of dermatomyositis.[29,30] The diagnosis can be confirmed by muscle or skin biopsy. Polymyositis is similarly associated with an increased risk of malignancy, with lung cancer accounting for 20% of newly diagnosed cancers during 5-year follow-up.[29]

There are a large number and variety of paraneoplastic neurologic syndromes (Table 112-3).[31] Lambert Eaton myasthenic syndrome (LEMS) is one of the better defined; it occurs due to the development of autoantibodies against presynaptic voltage-gated calcium channels. These circulating autoantibodies can be found in up to 5% to 8% patients with SCLC although clinical LEMS occurs in only 1% to 3% of patients.[32–34] Other paraneoplastic neurologic syndromes occur due to the presence of circulating neuronal autoantibodies (including anti-Hu, anti-Yo, and anti-Ri antibodies) and have a myriad of clinical manifestations.[21] Up to 20% patients with SCLC have circulating anti-Hu antibodies although paraneoplastic syndromes do not occur in the majority.[35] The related syndromes can include autonomic overactivity, corticocerebellar degeneration, brainstem encephalitis, limbic encephalitis, myelopathy, and peripheral nerve palsies. Autopsy studies have revealed that patients suffering from these syndromes have lymphocytic inflammatory infiltration in areas of the nervous system corresponding to their neurologic deficits.

While paraneoplastic syndromes manifest systemically, they are not always indicative of advanced malignant disease. Indeed, syndromes may regress with appropriate treatment of the tumor. Approximately 70% of patients with neurologic paraneoplastic syndromes have limited stage SCLC.

IMAGING EVALUATION

Following the initial intake evaluation, further noninvasive and invasive work-up should be undertaken with paired goals of (1) definitive establishment of histopathologic diagnosis and, when indicated, molecular characterization of the tumor, and (2) determination of disease stage in the most cost effective and least invasive manner possible. Given the myriad of diagnostic modalities available, it is often advisable that patients suspected of having lung cancer undergo this phase of the evaluation at an established multidisciplinary lung cancer center.

Unless a patient is clearly not a candidate for any treatment, all patients should undergo a chest computed tomography (CT) scan appropriately modified for the purposes of lung cancer assessment. The lung cancer CT scan includes the chest and the upper abdomen such that the liver and the adrenal glands are visualized in their entirety. The administration of intravenous contrast facilitates better characterization of hilar and mediastinal lymph nodes by differentiating them from vascular structures and also helps to better characterize hepatic and adrenal lesions. CT is most useful in delineating the key features of the primary tumor (size, presence of satellite nodules, associated atelectasis and infection, and invasion of adjacent structures); these features are essential in establishing the clinical T stage.

Regional lymph node involvement can also be evaluated on chest CT. Lymph nodes are deemed to be enlarged when they measure greater than 1 cm in short-axis diameter on transverse images. Likelihood of metastatic involvement increases with the degree with mediastinal enlargement: 62% of lymph nodes measuring 10 to 15 mm are malignant versus 90% of nodes measuring >15 mm.[36] However, in most patients, lymph node staging cannot be accurately undertaken based upon CT findings alone. In a meta-analysis of 35 studies (5111 patients, 28% of whom had mediastinal metastases), the pooled sensitivity of CT scanning for mediastinal nodal metastases was found to be 51% and pooled specificity 86%.[37] About 20% of nodes deemed to be benign on chest CT were actually malignant and 40% of nodes deemed abnormal on chest CT were actually benign. On occasion, there are CT findings that demonstrate mediastinal tumor invasion convincingly enough that further staging is unnecessary. These findings include extensive infiltration of mediastinal structures such that discrete anatomic landmarks are lost, matting of nodal tissue such that boundaries become indistinct, and encircling of mediastinal structures by infiltrating tumor. In the absence of these findings, further studies need to be undertaken to adequately stage the mediastinum.

Chest CT can also often demonstrate findings that may be suggestive of metastatic disease. CT may better delineate pleural disease; the majority of these effusions are malignant. In addition, CT may reveal pericardial effusion, pleural nodularity, or nodules in the contralateral lung, all of which may indicate metastatic disease. Bony involvement of the thoracic cage may be seen. Adrenal lesions can be identified in up to 10% of patients, however, many of these are ultimately found to be benign.[38]

Positron emission tomography (PET) with 18-fluoro-2-deoxyglucose (FDG) has assumed an increasingly prominent role in the initial noninvasive evaluation of the patient with suspected lung cancer.[39] Metabolically active tissues take up FDG, a glucose analog, avidly and appear bright on PET scan. Strongly hypermetabolic activity raises suspicion of malignancy. However, hypermetabolic activity can also be seen in inflammatory processes related to infections or recent surgery, raising the specter of false positivity. False negatives can occur with low-grade malignancies or small foci of malignancy. Lesions less than 0.8 to 1.0 cm may be too small for accurate assessment. High-level physiologic uptake within the brain, heart, gastrointestinal, and genitourinary tracts may compromise precise evaluation of tumor invasion in these areas. In addition, the presence of hyperglycemia can interfere with the uptake of FDG and thus increase the likelihood of false-negative examinations. Integrated PET/CT allows more detailed evaluation of abnormal tissues and surrounding structures and it is more helpful than full-body PET, which has limited anatomic resolution, to elucidate specific tumor characteristics as well as surrounding structures.

The PET scan is more sensitive and specific than CT in regional lymph node assessment with a pooled sensitivity of 74% and specificity of 85% in the identification of mediastinal lymph node metastases.[37] In patients with enlarged mediastinal nodes, the sensitivity has been estimated to be as high as 100% with a specificity of 78%.[40] Thus the false-positive rate ranges between 13% and 25% in patients with nodal enlargement. In those with normal-sized nodes on CT, PET sensitivity is 82% but specificity is higher at 93%.[41] Approximately 20% of patients with normal mediastinal nodes on CT and PET will actually have malignant disease within the mediastinum.

PET scanning can disclose unsuspected metastatic disease (M1) in 6% to 37% of cases, depending on clinical pretest probability. Rates are lower in earlier-stage disease: 1% to 8% of patients with clinical stage I disease and 7% to 18% in patients with clinical stage II disease.[37] Liver metastases, adrenal metastases, and bone metastases can be diagnosed with good accuracy. A recent study of PET-CT in the evaluation of adrenal lesions detected in patients with lung cancers reported an overall sensitivity and specificity of 97% and 94%, respectively.[42] Two systematic reviews suggest that PET scanning has higher diagnostic value than bone scintigraphy for the detection of bone metastases from lung cancer, with >90% sensitivity and specificity for PET-CT.[40,43]

PET has been the most helpful in decreasing the frequency of understaging in patients at risk for advanced lung cancer. Clinical trials have suggested that addition of PET imaging to the evaluation results in a reduction of the rates of noncurative surgery for NSCLC from 40% down to 20%.[44,45] The frequency of understaging disease decreases from 30% to 15%. The beneficial impact of PET diminishes in patient with early-stage disease. In patients with clinical stage I disease, PET correctly detects N2, N3, or M1 disease in 7% to 10%.[46] However, this comes at a cost of increased false-positive rate of up to 14%. PET should not be used alone to confirm advanced stage disease as patients may be erroneously directed away from curative therapies.

MRI scanning is the test of choice when assessing for intracranial metastatic disease. It is more sensitive than CT scan of the brain.[47] Staging brain MRI should be considered in patients who present with locally advanced or advanced NSCLC on chest CT or PET scanning, patients with neurologic signs or symptoms, patients presenting with nonspecific constitutional symptoms of fevers, weight loss, anorexia, and weakness and in patients with SCLC. MRI scanning is also often the test of choice for focused examination for extent of chest wall invasion, diaphragmatic involvement, superior sulcus tumors, brachial plexus invasion, or invasion of the spine (T4 disease).

Any extrathoracic lesion detected on imaging studies in a patient suspected of having lung cancer should be biopsied first, if feasible. This will accomplish not only tissue diagnosis but also confirmation of advanced disease in both SCLC and NSCLC.

ESTABLISHING THE TISSUE DIAGNOSIS

Methods employed in establishing a tissue diagnosis SCLC and NSCLC are discussed below.

SCLC

Specific imaging characteristics on chest CT can be indicative of SCLC. In particular, the findings of massive lymphadenopathy, direct mediastinal invasion, or hilar masses can suggest SCLC. The suspicion should be raised if clinical evaluation is worrisome for SIADH, ectopic ACTH production, or neurologic paraneoplastic syndromes. If SCLC is suspected, then tissue diagnosis should be established utilizing the least invasive test feasible.

In 1989, the International Association for the Study of Lung Cancer modified the Veterans Administration Lung Study Group (VALSG) two-stage classification of SCLC; this modified classification system is currently the widely accepted clinical staging system for SCLC.[48] Patients with limited stage disease have disease confined to one hemithorax, the mediastinum, and ipsilateral supraclavicular lymph nodes. In other words, limited stage defines a primary tumor and regional nodes that can be incorporated into in a reasonably safe radiation port. Patients with extensive stage disease have malignant pleural and pericardial effusions, contralateral hilar or supraclavicular nodes, and/or distant metastases. Given the high likelihood of extensive disease at the time of presentation, all patients should undergo a full staging evaluation that

traditionally included a contrast-enhanced CT of the chest and abdomen, bone scan, and MRI or contrast-enhanced CT scan of the brain. MRI scanning, the preferred imaging modality, will detect brain metastasis in 10% to 15% of asymptomatic patients with SCLC at the time of diagnosis, and in 12% of patients with otherwise limited stage SCLC.[34,49] Routine bone marrow aspiration is not indicated. The use of PET scan in the initial stating of SCLC has been evaluated in several small studies.[50–54] Because SCLC is a highly metabolic malignancy, PET scan is 100% sensitive for the detection of primary tumor. In addition, PET is superior to standard imaging in both sensitivity and specificity for detection of non-CNS metastatic foci. In patients with radiographic evidence of extensive stage SCLC, tissue diagnosis, and stage confirmation should be accomplished by biopsy of a metastatic focus if feasible.

NSCLC

In the case of NSCLC, the primary goals in tissue sampling selection are more complicated. These goals are to (1) obtain a tissue specimen adequate for histopathology and genetic analysis and (2) establish the clinical stage of disease in the least invasive manner feasible. If imaging tests suggest a site of distant metastatic disease, then that site should be sampled first, if accessible.

Sputum cytology is the least invasive way of achieving a histologic diagnosis. However, yield is clearly center dependent and requires a highly trained respiratory cytologist to process and analyze specimens appropriately. Sensitivity of sputum cytology has been reported to be as low as 42% and as high as 97%.[55] Yield increases with number of specimens submitted: 68% for one specimen, 78% for two, and 86% when three or more specimens are submitted.[56] Diagnostic yield is higher in patients with central tumors, tumors >2.4 cm, squamous cell histopathology, and those with hemoptysis.[55] Diagnostic yield is lowest in patients with peripheral lesions.

Thoracentesis is indicated when a pleural effusion is present as a significant proportion of pleural effusions seen in patients with lung cancer are malignant. Positive pleural fluid cytology not only establishes the diagnosis but also establishes stage IV disease in NSCLC and extensive stage SCLC. Thoracentesis is best accomplished utilizing bedside ultrasound guidance, as this appears to improve the safety and yield of the procedure. Furthermore, ultrasound imaging can reveal findings that raise the suspicion for malignant disease, including pleural thickening and nodularity. A volume of at least 50 mL should be sent; diagnostic yield does not appear to increase with larger volume of fluid analyzed.[57] If the initial thoracentesis is negative, a second thoracentesis should be performed. A second thoracentesis has a diagnostic yield of 27% when the first is negative. Sensitivity of pleural fluid cytology can be as high as 72% when at least two separate specimens are sent.[55]

When pleural disease is present and thoracentesis is negative, additional diagnostic strategies include blind pleural biopsy, percutaneous image-guided biopsy, and thoracoscopic biopsy. Non-image guided closed pleural biopsy using an Abrams needle probably no longer has a role as it increases diagnostic yield over thoracentesis by only 7% to 27%.[55] Image-guided pleural biopsy has clear advantages in diagnostic yield, particularly when there are abnormal findings, with a sensitivity of 84%.[55] Thoracoscopy has a reported sensitivity of 80% to 99% in the diagnosis of malignant pleural disease.[55] However, when there is CT evidence of pleural thickening or nodules, the diagnostic yield of image-guided percutaneous biopsy is similar to thoracoscopy. Thus, medical or surgical thoracoscopy may be reserved for patients with pleural fluid but without a discrete target for CT-guided pleural biopsy.[58]

HISTOLOGIC SAMPLING OF THE PRIMARY TUMOR

There are numerous procedures presently utilized to sample the primary tumor with varying diagnostic yields depending on tumor characteristics and adjunct technologies (Table 112-5). Bronchoscopy enables sampling of the primary tumor as well as the mediastinum for regional lymph node staging. Overall sensitivity of endobronchial forceps biopsy of directly visualized central tumor is 74% with yield increasing with the number of biopsy passes.[55] It is recommended that at least three biopsies be taken. The yield of endobronchial washes and brushes is lower (sensitivity 47% and 61%, respectively) but may have additive benefit.[55] Endobronchial needle aspiration further increases yield as forceps biopsies of endobronchial lesions can sometimes sample areas of necrosis and may result in nondiagnostic biopsies.[59–61] When all techniques are utilized, reported yield of bronchoscopic sampling of endobronchial lesions can be as high as 91% to 96%. Bronchoscopic visualization of endobronchial disease is also the best way to estimate the extent of proximal tumor invasion, specifically if tumor invasion occurs proximal to a lobar bronchus (T2b lesion) or invades the mainstem bronchus to within 2 cm of the carina (T3 disease).

The utility of bronchoscopic sampling in patients with peripheral primary tumor is much lower. When lesions are sampled utilizing multiple techniques (transbronchial biopsy, transbronchial brush, lavage, and wash as well as transbronchial needle aspiration), the overall pooled sensitivity is 78% on recent comprehensive review of bronchoscopic techniques to diagnose lung cancer.[55] The sensitivity of transbronchial biopsy is 57% with the yield higher in larger lesions: 63% in lesions measuring at least 2 cm and only 34% in lesions measure <2 cm. When only one pass is made, the sensitivity is 45%. Sensitivity increased to 70% when at least six passes are made.

Adjunctive new technologies, including electromagnetic navigational (EMN) bronchoscopy and radial probe endobronchial ultrasound (R-EBUS), may also improve the yield of transbronchial biopsy of peripheral lesions. EMN bronchoscopic technology creates a real-time virtual thoracic map that helps the bronchoscopist steer an extended guidance sheath through subsegmental airways toward the target lesion. The utilization of this tool increases the diagnostic yield of bronchoscopic biopsy of peripheral lesions from 57% overall to 70%.[63] When CT scanning demonstrates that a subsegmental bronchus leads directly into the lesion, yield increases up to 79%.[63] One study suggests that the addition of needle aspiration further improves the yield.[64] R-EBUS permits direct real-time ultrasound imaging of target lesions; this can increase overall sensitivity of bronchoscopic biopsy of peripheral lesions up to 73%.[62] Lesion size, as with fluoroscopically guided procedures, continues to influence test performance, with a sensitivity of 56% for lesions measuring 2 cm or less and a much higher sensitivity of 78% for lesions measuring greater than 2 cm. Procedural complications are minimal with an overall rate of pneumothorax of 1% and pneumothorax requiring catheter drainage of 0.4%.[63] When R-EBUS is utilized in conjunction with EMN, reported diagnostic yield has been as high as 93%.[65]

Image-guided transthoracic needle aspiration has excellent sensitivity for peripheral lesions, with a pooled sensitivity of approximately 90%.[55] However, a negative biopsy does not rule out malignant disease. The false-negative rate can range between 20% and 30% depending on patient population and disease characteristics.[55] CT guidance is clearly superior to fluoroscopic guidance. The addition of transthoracic core biopsy does not increase sensitivity but can help establish specific histopathologic diagnosis by improving tissue acquisition for immunohistochemical staining and molecular characterization. In addition, a core biopsy may be helpful in ascertaining specific benign diagnoses.

The complication rate of transthoracic needle biopsy or aspiration is higher than that seen with bronchoscopy. The incidence of pneumothorax is 15% and the incidence of severe hemorrhage is 1%.[66] Risk factors for complications include tobacco use and underlying chronic obstructive pulmonary disease. Video-assisted thoracoscopic surgery (VATS) biopsy has the highest yield but also requires hospitalization and carries higher attendant risk. Therefore, despite overall lower yield, bronchoscopic sampling may be preferable, particularly in centers where advanced diagnostic technologies including R-EBUS and EMN are available. Furthermore, bronchoscopic techniques can also be utilized to stage the mediastinum.

TABLE 112-5 Sampling of Primary Tumor

Tumor Characteristics	Procedure	Sensitivity (%)	Comments
Directly visualized endobronchial tumor	Bronchoscopy with forceps biopsy	74[55]	
	Bronchoscopic washes	47[55]	
	Endobronchial brush	61[55]	
	Needle aspiration	75–96[59–61]	
Peripheral lesions	Transbronchial biopsy	57[55]	Yield increases with number of biopsy passes: 45% for one sample and 70% for six samples[55]
	Overall	34[55]	
	Lesions <2 cm	63[55]	
	Lesions >2 cm		
	Transbronchial brush	54[55]	
	Bronchoalveolar lavage/wash	43[55]	
	Transbronchial needle aspiration	65[55]	
	Combination of all modalities	78[55]	
	Radial EBUS	73[62]	Yield increases to 79% if subsegmental bronchus leads to lesion on chest CT[62]
	Overall	56[62]	
	Lesions ≤2 cm	78[62]	
	Lesions >2 cm		
	Transthoracic needle aspiration	90[55]	Pneumothorax rate 15%
	CT guided	92[55]	Use of core biopsy similar sensitivity to FNA for detection of malignancy but better able to determine specific benign diagnoses
	Fluoroscopically guided	88[55]	

Data from Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (3rd edition). Chest. 2013;143(5):e142S-e165S; Caglayan B, Akturk U, Fidan A, et al. Transbronchial Needl Aspiration in the Diagnosis of Endobronchial Malignant Lesions: a 3-Year Experience. Chest. 2005;128(2):704–708; Kacar N, Tuksavul F, Edipoglu O, Ermete S, Guclu S. Effectiveness of Transbronchial Needle Aspiration in the Diagnosis of Exophytic Endobronchial lesions and Submucosal/Peribronchial Diseases of the Lung. Lung Cnacer. 2005;50(2): 221–226; Dasgupta A, Jain P, Minae O, et al. Utility of Transbronchial Needle Aspiration in the Diagnosis of Endobronchial Lesions. Chest. 1999;115(5):1237–1241; Steinfort DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of pheripheral lung cancer: a systematic review and meta-analysis. European Respiratory Journal. 2011;37(4):902–910.

MEDIASTINAL STAGING

Lung cancer staging is based upon the tumor node metastasis (TNM) staging system last updated on January 1, 2010 (Table 112-1) by the International Association for the Study of Lung Cancer. Extent of disease is categorized by the characteristics of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of absence of distant metastases (M). Disease stage is the key determinant of candidacy for tumor resection. Patients with stage I and II diseases and otherwise adequate cardiopulmonary reserve should undergo surgery. Unfortunately, only 20% of patients are ultimately deemed operable after thorough clinical staging.

Nearly a third of patients with lung cancer have locally advanced disease with mediastinal involvement (N2 or N3) at the time of presentation.[4,6] Mediastinal staging is crucial in determining stage of disease and candidacy for surgical resection once metastatic disease has been ruled out. Tissue confirmation of mediastinal nodal metastasis becomes unnecessary only in situations where distant metastatic disease has already been confirmed or when the patient is clearly not a candidate for any treatment. Patients with NSCLC fall into four categories in regard to approach to clinical staging of the mediastinum based on the radiographic findings (Table 112-6).[67] Radiographic group A includes patients who have imaging characteristics that are unequivocally consistent with malignant invasion of the mediastinum (mediastinal infiltration with loss of normal tissue boundaries, nodal tissue is no longer discrete and can be matted together, and vascular structures are often encircled) (Fig. 112-2). In this group of patients, the goal is to obtain tissue by the least invasive procedure to establish the diagnosis. Group B includes patients with discrete lymph node enlargement (Fig. 112-3). Discrete enlargement of lymph nodes on a CT scan, even massive enlargement, is inadequate evidence for mediastinal metastases as up to 40% of these nodes are actually benign.[37] Conversely, group C includes patients with central lesions or N1 disease with radiographically normal mediastinal lymph nodes (Fig. 112-4). In this group, 20% to 25% are found to have nodal involvement.[37] Finally, the last group of patients, group D, includes those with peripheral clinical stage I lesions with radiographically normal mediastinal

TABLE 112-6 Classification of Mediastinal Disease by Radiographic Characteristics

Group	Description
A	Mediastinal infiltration: tumor invasion such that normal anatomic boundaries cannot be distinguished
B	Enlarged discrete mediastinal lymph nodes: lymph nodes measuring ≥1 cm in short-axis diameter on transverse CT scan
C	Clinical stage II or central stage I tumor: normal-sized mediastinal lymph nodes but enlarged N1 nodes or central tumor
D	Peripheral clinical stage I tumor: normal mediastinal and hilar nodes with a peripheral tumor

Source: Adapted with permission from Detterbeck F. Invasive mediastinal staging of lung cancer. Chest. 2007;132(3 Suppl):202S–220S.

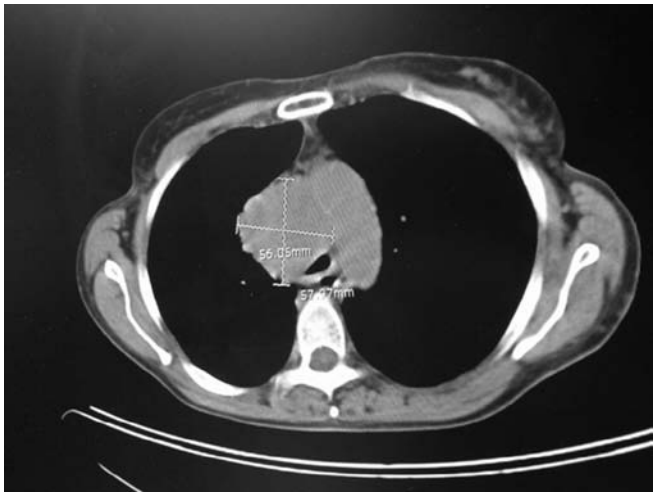

Figure 112-2 Example of radiographic group A disease: mediastinal infiltration with loss of normal anatomic boundaries.

and hilar lymph nodes. These patients have a sufficiently low pretest probability for mediastinal involvement that invasive mediastinal sampling becomes unnecessary. In patients with radiographic group B or C disease, adequate staging of the mediastinum is mandatory.

Mediastinal staging procedures include transthoracic needle aspiration (TTNA), transbronchial needle aspiration (TBNA) with or without endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS) needle aspiration, cervical mediastinoscopy, anterior mediastinoscopy, and thoracoscopy. Selection of appropriate procedure is made based upon nodal station (Table 112-7), pretest probability of disease, and medical appropriateness for surgical resection.[68] The diagnostic yield of each procedure (Table 112-8) should also be taken into account.

TTNA of mediastinal nodal tissue is possible when anterior mediastinal lymph nodes are enlarged. Recent systematic review reported a pooled sensitivity of 94%.[39] As with TTNA of peripheral lesions, the risk of pneumothorax is fairly high. In fact, chest tubes are required for evacuation of pneumothorax in 10% of procedures.[67] TTNA of the mediastinum is primarily utilized in patients with fairly bulky anterior mediastinal lymph node enlargement.

Bronchoscopic sampling with TBNA without image guidance is of variable yield. Nodal stations accessible to TBNA include stations 2, 4, 7, and 10. Sensitivity ranges from 14% to 100% in published studies, with an overall pooled sensitivity of 78%.[39,67] This technique is primarily

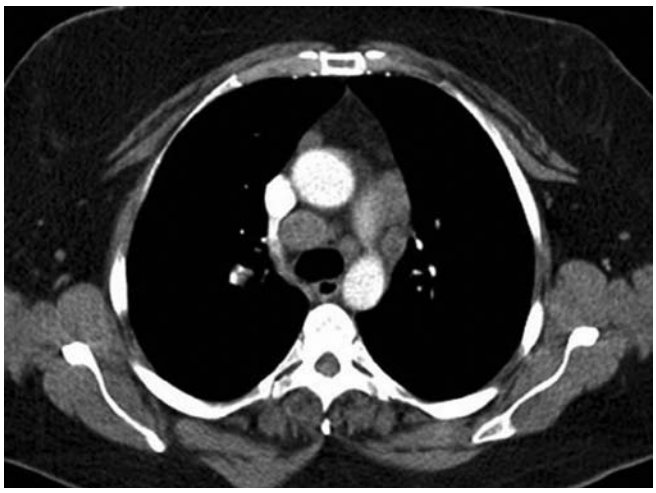

Figure 112-3 Example of radiographic Group B disease: discrete mediastinal (4R) nodal enlargement.

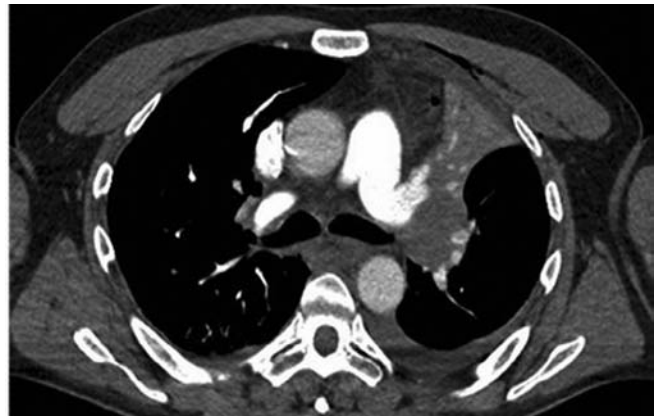

Figure 112-4 Example of radiographic group C disease: central lesion with N1 disease but no enlarged mediastinal lymphadenopathy.

utilized in patients with mediastinal lymph nodes large enough to be amenable to non–image-guided sampling. The availability of rapid on-site cytologic evaluation also improves diagnostic yield and decreases the number of biopsy passes needed.[72] The advent of convex probe EBUS has significantly improved the diagnostic yield of TBNA sampling of the mediastinum. EBUS allows for real-time visualization of the target nodal tissue with improved sensitivity to 88% to 93% on systematic review and it is recommended as the first procedure, if available, for sampling the hilar and mediastinal nodes. EBUS-FNA provides the ability to access nearly all lymph node stations, combine diagnosis and staging in a single procedure and results in equivalent if not better diagnostic yield when compared with mediastinoscopy.[39,69,70] Performance is best in patients with positive CT or PET results, with a sensitivity of

TABLE 112-7 Regional Lymph Node Stations (International Association for the Study of Lung Cancer)

Zone	Lymph Node Station	
Supraclavicular zone	1	Low cervical, supraclavicular, sternal notch
Superior mediastinal nodes	2R	Right upper paratracheal
	2L	Left upper paratracheal
	3a	Prevascular
	3p	Retrotracheal
	4R	Right lower paratracheal
	4L	Left lower paratracheal
Aortic nodes/aortopulmonary window nodes	5	Subaortic
	6	Para-aortic
Interior mediastinal nodes	7	Subcarinal
	8	Paraesophageal nodes
	9	Pulmonary ligament
Hilar nodes	10	Hilar nodes
	11	Interlobar nodes
Peripheral nodes	12	Lobar nodes
	13	Segmental nodes
	14	Subsegmental nodes

Source: Data from Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. Journal of Thoracic Oncology. 2009;4(5):568–577.

TABLE 112-8 Mediastinal Staging

Procedure	Lymph Node Stations	Sensitivity (%)	Comments
TBNA	Stations 4, 7, and 10	78[39]	
EBUS-TBNA	Stations 2, 4, 7, and 10	88–93[69,70]	Sensitivity 94% in PET positive lymph nodes[70]
EUS-FNA	Stations 5, 7–9	83, overall[71] 90, enlarged nodes[71] 58, normal-sized nodes[71]	
CT-guided TTNA		94[39]	
Mediastinoscopy	1, 2R, 2L, 3, 4R, 4L, anterior subcarinal (7)	81[39]	
Thoracoscopy	Stations 4, 7–10	99[39]	Typically only one side of the mediastinum is sampled. Right side is more easily accessible than the left

Data from Silvestri GA, Gonzales AV, Jantz MA, et al. Methods for Staging Non-small Cell Lung Cancer: Diagnosis and management of lung cancer, 3rd ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5):e211s–e250s; Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial utlrasound and transbronchial needle aspiratiopn biopsy for mediastinal staging in patients with lung cancer: a systematic review and meta-analysis. Thorax. 2009;64(9):757–762; Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. European Journal of Cancer. 2009;45(8):1389–1396; Micames CG. Endoscopic Ultrasound-Guided Fine-Needle Aspiration for Non-small Cell Lung Cancer Staging A Systematic Review and Metaanalysis. Chest. 2007.

94% in that population.[70] The false-negative rate remains substantial at 24%. Evaluation of tissue adequacy for immunohistochemical testing (IHC) and molecular characterization suggests that EBUS-TBNA can result in satisfactory sampling in up to 67% to 79% of cases. Diagnostic yield is clearly related to expertise of the bronchoscopist and there is significant heterogeneity in yield across hospitals.[73] Therefore, negative sampling should be followed by mediastinoscopy for patients who are candidates for surgical resection.

EUS-FNA can access the inferior mediastinal nodal stations as well as nodal tissue in the subaortic stations: 9, 8, 7, and 5 for fine-needle aspiration. Like bronchoscopy, EUS-FNA is minimally invasive and is an outpatient procedure. In addition, the left adrenal gland, celiac lymph nodes, and lesions involving the left lobe of the liver can be sampled utilizing this technique. The sensitivity for accessible mediastinal lymph nodes is excellent at 83% with an overall false-negative rate of 19%.[71] Yield is highest with enlarged nodes with a sensitivity of 90% and a false-negative rate of 22%.[71] In the hands of expert endoscopists, normal-sized nodes may also be sampled with a reported sensitivity of 58% for metastatic disease.[71] While a negative test impels further testing, a positive study obviates the need for more invasive evaluation.

When EUS is combined with EBUS, the mediastinum can be much more extensively sampled than with either modality alone. In the studies investigating this combined approach, sensitivity ranged between 72% and 100% with 98% to 100% specificity.[74–80] Negative predictive value ranged between 80% and 100%. This combined approach requires highly specialized expertise and is available only at selected centers.

Cervical mediastinoscopy is typically a same-day surgical procedure where an incision is made just above the suprasternal notch and a mediastinoscope inserted. It is a low morbidity procedure with complication rates of 2% and mortality of 0.08%.[67] The high and low paratracheal nodes (station 2R, 2L, 4R, and 4L), pretracheal (stations 1 and 3) and anterior subcarinal (station 7) nodal stations can be sampled. Mediastinoscopy is the procedure of choice to demonstrate node negativity prior to surgical resection of the primary tumor. Test sensitivity has been reported to be overall 80% with a false-negative rate as high as 10%.[67] The lymph nodes identified as false negatives are often located in nodal stations not accessible to the mediastinoscope. The addition of video mediastinoscopy may further improve test performance with sensitivity increasing to 80%.[67]

A Chamberlain procedure (i.e., anterior mediastinoscopy) can be performed to sample aortopulmonary and anterior mediastinal nodal stations (stations 5 and 6), commonly involved with left upper lobe cancers.

VATS can be utilized to sample multiple lymph node stations, including the right paratracheal (station 4R) nodes, stations 5 and 6 nodes, paraesophageal nodes, and stations 9 and 10 nodes. The left paratracheal lymph nodes are much more difficult to access. VATS sampling also provide the most reliable information short of full thoracotomy regarding extent of primary tumor invasion of the chest wall and mediastinal structures as well as pleural and pericardial involvement.

TISSUE ACQUISITION FOR HISTOPATHOLOGY AND GENETIC TESTING

It has become increasingly evident that NSCLCs encompass a heterogeneous group of cancers with not just different histologies but also different genetics. In addition, NSCLCs respond differently to therapeutic agents depending on histology and molecular characteristics. Significant positive outcomes have been reported when certain adenocarcinomas are combined with specific chemotherapy agents (pemetrexed) and tyrosine-kinase inhibitors (erlotinib), while patients with squamous cell histology are clearly at higher risk of toxicity from bevacizumab.[81–83]

The identification of specific driver mutations has provided new targets for molecular therapies. Epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors are now considered first-line therapy for patients with advanced NSCLC whose tumors have EGFR mutations. Testing for EGFR mutations in advanced NSCLC is now the standard of care.[84] Two other driver mutations, EML4 and anaplastic lymphoma kinase (EML4-ALK) oncogenic fusion gene, and ROS1 translocations are present in 7% and 2%, respectively, of adenocarcinomas of the lung. The use of crizotinib, an oral agent, in patients with either one of these genetic alterations has been shown to result in dramatic treatment response.[85,86]

The emergence of individually tailored therapy based on histology and molecular characteristics has served to emphasize how important adequate tissue acquisition is when diagnosing lung cancer. In patients who are candidates for treatment, it is no longer adequate to simply differentiate between SCLC and NSCLC. It has become incumbent upon clinicians who perform diagnostic studies to obtain sufficient tissue to perform IHC and molecular analysis in order to accurately ascertain the histologic subtype and molecular characterization of NSCLC. The impetus to obtain larger pieces of tissue can often seem discordant with the other objective of tissue acquisition, which is to achieve diagnosis and staging in the least invasive manner possible. In an era of minimally invasive procedures, several studies have reported high feasibility (range

67%–100%) of performing IHC and molecular analysis on specimens obtained via EBUS-TBNA.[84,87–94] Tissue adequacy depends on center expertise, and one study reported that IHC analysis was feasible in all studied specimens obtained by EBUS-TBNA from mediastinal nodes.[87]

Success rates in performing molecular testing for EGFR and Kras mutations on cytologic material obtained by EBUS-TBNA have been reported to be as high as 72% to 77%.[89,92] ALK fusion genes were detected in 6% of 109 samples obtained by EBUS-TBNA of lymph node metastases through IHC, fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR) in one published series.[94] DNA sequencing for EGFR and Kras mutations was demonstrated to be feasible in cytologic specimens acquired through a number of means, including body fluid aspiration, TTNA, and EBUS-TBNA, with a very low specimen insufficiency rate of only 6.2%; the lowest specimen insufficiency rates were seen in EBUS-TBNA (4%) and body fluid (3.7%).[93] Preservation of material from needle aspirates in cell block can store tumor cells for future IHC and molecular studies. How much tissue is needed to accurately diagnose the lung cancer histologic type and assess molecular markers has not been formally studied. It has been reported that one aspiration per lymph node station during EBUS-TBNA without rapid on-site cytology results in a sample adequacy of 90% compared to 100% for the three aspirations.[95]

SUMMARY

- Initial clinical evaluation of a patient with suspected lung cancer should focus upon presenting symptomatology as well as signs and symptoms suggestive of advanced stage disease. History and laboratory testing may also be revealing for paraneoplastic syndromes.
- Initial imaging evaluation should include a CT scan for all patients who may be candidates for treatment. PET scanning is indicated for the majority of patients, particularly for those who are at risk for mediastinal involvement as well as those patients with advanced thoracic disease and thus are at risk for distant metastatic disease. Integrated PET/CT scanning may be the initial study of choice at centers with available technology. CT with contrast or MRI of the brain should be performed to assess for intracranial metastases in those patient with neurologic symptoms or to screen for intracranial metastases in patients with locally advanced or advanced NSCLC, and in those with SCLC.
- When SCLC is suspected, tissue diagnosis should be obtained in the least invasive manner possible. Staging classification is either limited stage or extensive stage disease and if feasible, a suspicious metastatic lesion should be biopsied first to confirm diagnosis and stage. In selected cases, staging can be accomplished through imaging evaluation alone (patient with multiple brain lesions or multiple bone lesions).
- Multiple diagnostic modalities are available to establish tissue diagnosis and to confirm clinical stage. Selection should be based upon diagnostic yield, procedure safety, and ability to simultaneously establish stage. Thus, priority should be given to procedures that sample foci of metastatic disease detected on imaging evaluation (e.g., thoracentesis when pleural effusions are present, biopsy of PET avid adrenal, bone or hepatic lesions).
- Tissue sampling from the primary tumor can be accomplished percutaneously, bronchoscopically, and surgically. Yield of bronchoscopic biopsy for peripheral lung lesions is still not as high as that seen with TTNA. However, the advent of new techniques such as R-EBUS and EMN has improved test performance. Bronchoscopy remains the procedure with the lowest complication rate and should be strongly recommended as the procedure of choice in centers with local expertise.
- EBUS-FNA is the procedure of choice for sampling hilar and mediastinal lymph nodes.
- In the absence of M1 disease, clinical staging of the mediastinum becomes crucial unless the patients has radiographic findings of mediastinal invasion or the patient has a sufficiently low pretest probability of mediastinal metastasis (peripheral T1N0 lesion). Ultrasound-guided bronchoscopic and endoscopic techniques have resulted in much improved diagnostic yield with excellent procedural safety. However, negative results should prompt surgical mediastinal sampling.
- The emergence of therapies tailored to tumor histology and genetics has resulted in greater emphasis upon adequate tissue acquisition for molecular analysis.

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CHAPTER 113

Treatment of Non–Small-Cell Lung Cancer: Surgery

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Lung cancer represents the most common cause of cancer-related death in the world. It was considered a rare disease until the early part of the 20th century. In 1879, lung cancer represented only 1% of cancers identified at autopsy compared to 14% in 1927.[1] The famous surgeon, Alton Oschner reported that as a medical student in 1910, he was called to the autopsy suite to see a case of lung cancer, since it was so rare he was likely to never see another case. Seventeen years passed before he saw another case of lung cancer and then he saw 8 cases in 6 months.[2] The link between tobacco use and lung cancer has been common knowledge since the surgeon general's report in 1964, and despite that knowledge, the death rate continued to rise in men until 1991 and in women until 2003. The treatment of lung cancer has evolved from a single modality, surgery, to a multimodality approach that calls upon the skills of numerous specialists. Physicians, who diagnose and treat lung cancer, must work together to define the role that surgery plays in the modern management of lung cancer. Surgery, when appropriate remains the cornerstone of therapy, and surgeons play an integral role in the diagnosis and treatment of patients with lung cancer.

DIAGNOSIS

The diagnosis and staging of lung cancer is covered elsewhere in the text. It is illustrative to consider the route taken by most patients before being referred to a surgeon and the qualifications that the surgeon should ideally possess to contribute optimally to the management of the patient with lung cancer. Patients with lung cancer may present with obvious symptoms such as hemoptysis or chest wall pain. The most common presenting complaints are respiratory symptoms that prompt a chest radiograph. From the surgeon's viewpoint, the evaluation of patients with abnormal imaging studies depends on the likelihood of malignant disease. In patients with a history of smoking the level of suspicion is higher. Lung cancer is seen in nonsmokers, but the suspicion for cancer is significantly lower in this group than in smokers, in whom an abnormal chest radiograph is lung cancer until proved otherwise. If previous chest imaging is available those studies should be compared with the current imaging. A lesion that appears unchanged from older films, particularly those obtained more than 2 years previously, markedly diminishes, but does not eliminate, the probability that the current finding represents a lung cancer.

When a surgical referral is indicated, the surgical specialist should offer a complete armamentarium of surgical options and techniques as well as an understanding of the principles of lung cancer treatment. The technical ability to perform lung resection is the minimum requirement but by itself is not sufficient. There is an increasing trend toward thoracoscopic techniques such as video-assisted thoracic surgery (VATS) or robot-assisted surgery. At least 30% of lobectomies are performed using minimally invasive techniques but this proportion is rising rapidly.[3] Thoracoscopic lung resection has been shown to be associated with a decreased length of stay, decreased complication rate, and decreased need for blood transfusion.[4,5] The lymph node harvest is equivalent if not superior.[3] The thoracic surgical specialist should be proficient in staging procedures including mediastinoscopy and endobronchial ultrasound (EBUS) although in many hospitals, a pulmonologist performs this latter procedure. The critical element is the willingness of the surgical specialist to participate in coordinated multidisciplinary care. Patients with advanced disease, who may be candidates for resection after induction therapy, should be referred early in the process so that decisions about potential fitness for operation from oncologic, medical, and technical perspectives can be made.

As critical care and anesthetic techniques continue to improve and minimally invasive surgery advances, all patients with lung cancer should be considered for therapy by the treating specialists. Age bias against treatment including chemotherapy, radiation, and surgery has been documented across many fields of medicine.[6] Age alone should not be the basis for ruling out definitive treatment and each patient must be evaluated individually.

Patients may present with symptoms either referable to the chest or related to the presence of metastatic disease. The initial evaluation should be directed toward an explanation of the symptoms. A complete discussion of the clinical presentation is available in Chapter 112. Patients with evidence of metastatic disease still require a tissue diagnosis. The method employed to obtain the tissue diagnosis should have the highest probability of success. Whereas

bronchoscopy has a high likelihood of yielding a diagnosis in the patient who presents with cough or hemoptysis and a central lesion, it is less likely to be successful when the lung findings are confined to a peripheral small nodule. In these cases, transthoracic needle biopsy may have the highest yield. When a patient presents with presumed metastatic disease that is accessible, such as a palpable supraclavicular lymph node, a fine-needle aspirate, done in the office, may yield the diagnosis and obviate the need for mediastinal staging. Consideration must be given to tissue yield, since ideally a biopsy sample should have sufficient tissue to allow for the ever-expanding array of genetic testing such as for EGFR mutations or ALK gene rearrangements. Some patients with metastatic disease may require wedge resection or other excisional biopsy to obtain enough tissue to allow for extensive molecular testing. A percutaneous biopsy of an adrenal lesion may also provide both a diagnosis and stage; however, prior to biopsy, the likelihood of pheochromocytoma should be considered. Previously the only question of significance in the patient with metastatic disease was the differentiation between small cell and non–small-cell lung cancer (NSCLC). However, current adjuvant or definitive treatment algorithms differ considerably between the different histologic types of NSCLC. Occasionally mediastinoscopy may be required to obtain enough tissue and very rarely video thoracoscopic excision of a lung nodule may be needed. Exploratory thoracoscopy or thoracotomy has no place in the management of these patients.

For patients who present with a solitary pulmonary nodule, chest computed tomography (CT) should be performed to determine if the nodule is solitary as well as to assess the status of the mediastinum, liver, and adrenal glands. When the risk of malignancy is low, such as in nonsmokers with a small nodule, it is reasonable to follow the lesion over a period of time. A repeat chest CT in 3 to 12 months, depending on the size of the nodule, is the recommended approach in the low-risk candidate. If the lesion has increased in size, then excision is carried out. If there is no change in size continued observation with repeated chest imaging is warranted. Conversely, in a smoker in whom there is a high probability that the nodule is malignant, excision may be justified without a prior needle biopsy.

The role of percutaneous needle biopsy of the solitary pulmonary nodule remains controversial. Diagnostic accuracy of CT-guided biopsy has been reported as high as 93.5% but this is due largely to its ability to diagnose malignant as opposed to benign processes.[7] The accuracy can be improved with increasing use of core needles and on-site cytologic analysis. In a patient at high risk for cancer, a positive biopsy confirms what we already suspected; however, the patient has been exposed to the risk of the needle biopsy, namely, a 10% to 15% incidence of pneumothorax with a need for a chest tube in 2% to 5% of cases.[8] The National Lung Screening Trial reported a 21.2% complication rate of needle biopsy with one death.[9] A negative biopsy does not negate the fact that a suspicious nodule remains and is of little help. More definitive information has to be obtained, such as cartilage or fungal elements, for the biopsy to obviate the need for resection in a high-risk patient with a suspicious lesion. If biopsy is inconclusive or the patient has significant anxiety regarding the possibility of a pulmonary nodule being an occult cancer, then resection may be indicated. Most peripheral lesions can be resected thoracoscopically and sent for frozen section. If the nodule proves to be benign, then thoracoscopic excision both makes the diagnosis and completes the therapy. If the nodule is malignant, an anatomic or other therapeutic resection and lymph node sampling can be performed during the same operative session. A biopsy consistent with small cell cancer should not preclude resection if there is no mediastinal adenopathy. T1-2N0-1 small cell lung cancers are optimally treated with anatomic resection and mediastinal lymph node dissection or sampling.[10] Most thoracic surgeons would perform mediastinoscopy and/or EBUS prior to resection to confirm that the mediastinum is not involved with tumor. If the final pathology reveals small cell carcinoma, resection is followed by chemotherapy.

STAGING

A discussion of noninvasive staging is beyond the scope of this chapter and is dealt with elsewhere in this volume; however, the role of invasive staging and specific procedures utilized deserve mention. Staging determines the appropriate surgical and medical treatment plan. Therefore, thorough staging is mandated. In discussing stage, distinction must be made between *clinical* and *pathologic* stage. The former is based solely on noninvasive imaging studies, whereas the latter depends on actual histologic material obtained either by invasive staging studies or at the time of the surgical resection. The accuracy of clinical staging depends upon the accuracy of the study. A chest CT scan provides excellent visualization of the contents of the superior mediastinum. Typically, mediastinal lymph nodes are considered suspicious if they are greater than 1 cm in short axis. However the CT must always be considered in context of the remainder of the mediastinum. Volterrani et al.[11] have suggested creating size cutoffs for each of the mediastinal lymph node stations to improve diagnostic accuracy of CT alone. Fused CT-PET provides information on the metabolic activity of the primary lesion and the mediastinal lymph nodes and may detect occult distant metastases. A recent study in patients with clinical stage I NSCLC, who underwent staging with PET followed by resection and lymphadenectomy revealed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET to be 68%, 95%, 31%, 99%, and 94% respectively.[12] Thus PET is a highly specific test. However, a patient without obvious distant metastatic disease and a PET or CT that is concerning for mediastinal metastasis should not be deemed inoperable based on imaging alone. Patients with granulomatous lymphadenitis from sarcoidosis or histoplasmosis frequently have hypermetabolic lymph nodes not due to malignancy. These patients should undergo invasive mediastinal staging. In addition, patients with postobstructive pneumonia often have enlarged or hypermetabolic mediastinal lymph nodes as a reaction to infection. At our institution, in these cases, we perform EBUS and if negative for malignancy, we perform mediastinoscopy at the time of planned resection. EBUS followed by mediastinoscopy provides a greater sensitivity than either test alone and helps eliminate sampling error.[13] When performing EBUS for staging and diagnosis a logical progression from N3 to N2 to N1 nodes should be followed, minimizing the need for sampling nodal stations that would not affect the stage and preventing upstaging through needle contamination.[14]

With the constantly improving resolution of CT imaging and the increasing availability of EBUS, the need for routine mediastinoscopy for all patients with lung cancer must be questioned. While still considered a definitive staging technique, there are nodal stations that cannot be accessed by standard cervical mediastinoscopy. These include the subaortic nodes (level 5) and para-aortic nodes (level 6), both of which are located in the aortopulmonary window (Fig. 113-1). They are a common site for lymph node involvement in left upper lobe tumors but when involved in the absence of other lymph node disease, the prognosis is equivalent to N1 (hilar) disease. These nodes are not accessible through standard EBUS techniques and are difficult to access via the esophagus although transarterial sampling has been described but is rarely performed.[15]

Mediastinoscopy is performed through a small (2.5-cm) incision made in the neck 1 cm above the sternal notch. The area explored by mediastinoscopy, the superior mediastinum, is palpated first by inserting a finger along the anterior aspect of the trachea, which also serves to develop the space and facilitate insertion of the mediastinoscope (Figs. 113-2 and 113-3). Obviously involved lymph nodes often may be palpated, but palpation alone is insufficient,

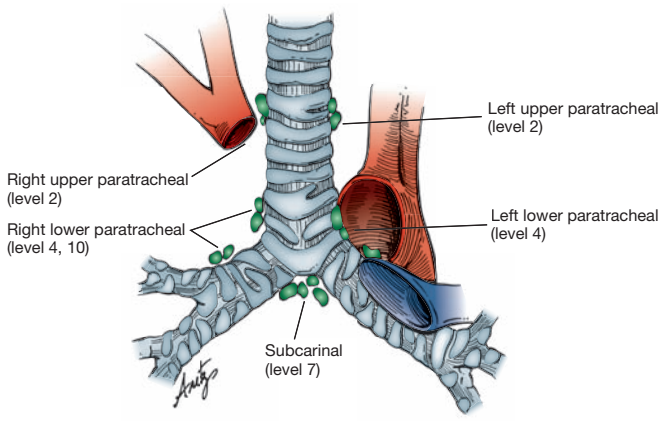


Figure 113-1 Lymph node stations accessible by cervical mediastinoscopy. For consistency the levels should be labeled with the appropriate number when submitted to surgical pathology.

since microscopic disease may be present that can only be identified if representative biopsies of the important nodal stations are taken following insertion of the mediastinoscope. Visual inspection without histologic confirmation is also to be scrupulously avoided. Of major importance are the ipsilateral nodes, but just as important is the status of the contralateral lymph nodes, especially in left lower lobe lesions, in which right paratracheal lymph nodes are commonly involved. Despite notions to the contrary, left-sided lymph nodes are readily accessible at mediastinoscopy but are somewhat more difficult to identify. In fact the left paratracheal lymph nodes are much more easily sampled at mediastinoscopy than at left thoracotomy because of the location of the aortic arch relative to the left mainstem bronchus. Because of this we have a much lower threshold for performing mediastinoscopy for left-sided lesions. Nodal stations most frequently sampled include levels 2 (upper paratracheal) and 4 (lower paratracheal) on the right, level 3 (pretracheal), level 7 (subcarinal), and level 4 on the left. Because the left level 4 lymph nodes occur at a slightly higher location, identifying separate level 2 nodes on the left can be difficult. It is not necessary always to sample all nodal stations; if there are nodes obviously involved, these, along with contralateral nodes, are all that are necessary to adequately stage the patient.

Mediastinoscopy is a technically demanding procedure that requires significant training to perform correctly. The close proximity of a number of major vascular structures makes it daunting even to the experienced practitioner. Major vessels within the operative field and therefore at risk include the innominate artery, aortic arch, superior vena cava, azygous vein, and right main pulmonary artery (Fig. 113-4). The left recurrent laryngeal nerve and esophagus are also subject to injury. A recent meta-analysis of the complications of mediastinoscopy reported a morbidity of 0% to 5.3% and a mortality of 0% to 0.05%.[16] Despite the stakes of the procedure, in experienced hands, the actual risk of the procedure is quite low and all but the most debilitated and infirm patients tolerate the procedure well. Inability or reluctance to adequately stage the mediastinum may result in unnecessary or unsuccessful thoracotomy or thoracoscopy.

Although mediastinoscopy is the mainstay of invasive staging for lung cancer, other procedures provide additional information that often complements that obtained at mediastinoscopy. The aortopulmonary window, a common site of nodal spread from tumors of the

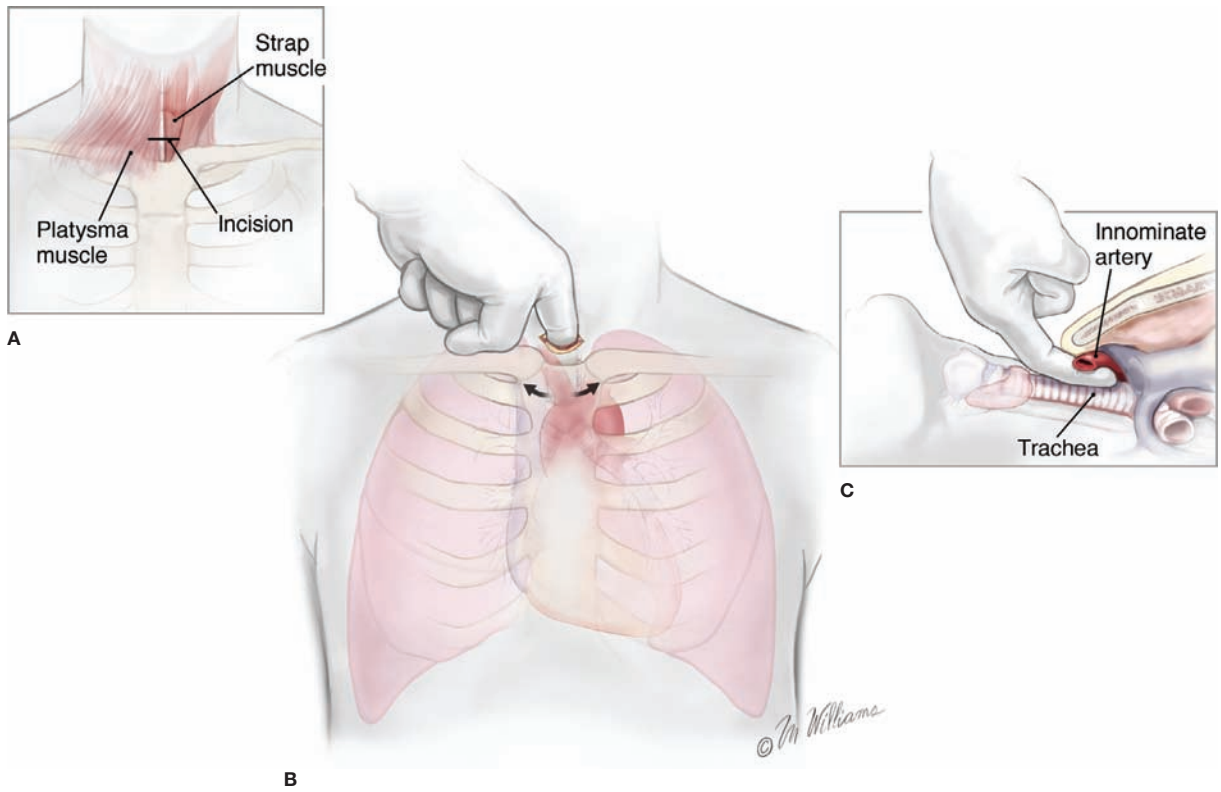


Figure 113-2 Technique of cervical mediastinoscopy. **A.** A 3-cm incision in the midline one fingerbreadth above the sternal notch. **B.** Pretracheal tunnel fashioned with blunt dissection using the index finger. **C.** Dorsal aspect of the finger remains on the trachea while the volar aspect comes in contact with the innominate artery. *(Used with permission of Marcia Williams.)*

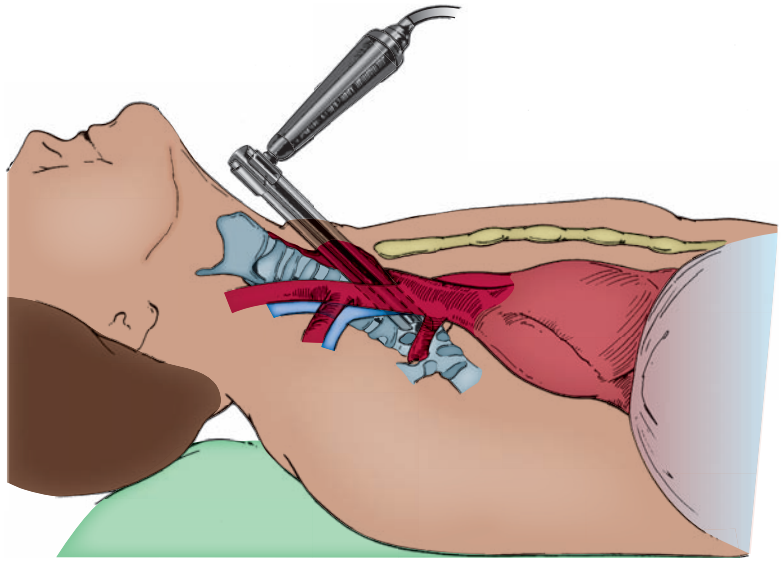


Figure 113-3 Mediastinoscope in place demonstrating the superior mediastinal plane.

left upper lobe, and one that cannot be reached with conventional mediastinoscopy or EBUS without traversing the left main pulmonary artery, may be reached with an anterior mediastinotomy, also known as the Chamberlain procedure. An incision is made over the left second costal cartilage, the cartilage is excised, and the pleural reflection is swept laterally to access the aortopulmonary window in an extrapleural plane. Typically, anterior mediastinotomy is performed in conjunction with cervical mediastinoscopy, and the mediastinoscope is used for visualization. Tube thoracostomy is rarely needed and this procedure can be performed as an outpatient. The involvement of lymph nodes at this level (level 5) in the absence of other nodal disease is associated with a 5-year survival that approaches 50% if the disease can be completely resected, a survival that is almost identical to that seen with N1 (hilar) disease. The rationale, then, behind performing parasternal mediastinotomy either is to assess resectability or document mediastinal nodal disease to justify placing the patient into an experimental protocol of neoadjuvant chemotherapy, radiation therapy, or both.

Similarly, video-assisted thoracoscopic surgery (VATS) aids in the staging of lung cancer, as an occasional adjunct to, but not in lieu of, mediastinoscopy. VATS offers an opportunity to sample nodes on the right and left through one incision and provides access to aortopulmonary window (level 5), ascending aortic (level 6), paraesophageal (level 8), and inferior pulmonary ligament (level 9) nodal stations. It is notable that levels 4R, 2R, 7, 8, and 9 nodes are often easily biopsied via esophageal endoscopic ultrasound. VATS also visualizes the pleural space, especially useful in the patient with a pleural effusion and negative fluid cytology, so as to rule out diffuse pleural involvement and prevent an unnecessary thoracotomy. Other nodules seen on CT scan that may have an impact on treatment planning also may be excised and defined histologically prior to formal thoracotomy.

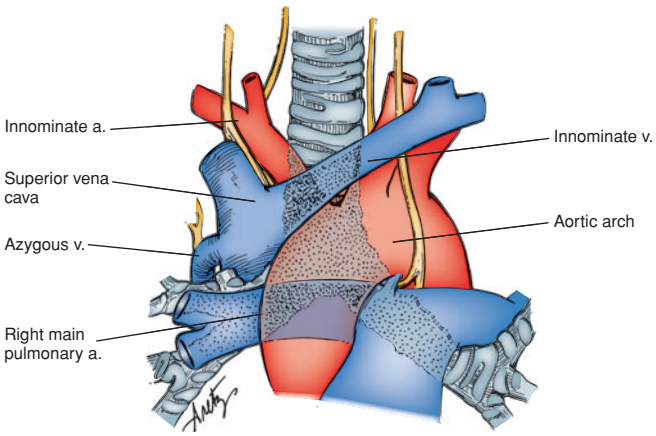


Figure 113-4 The relationship of major vascular structures potentially encountered during mediastinoscopy to the trachea and main bronchi.

Usually the ultimate decision regarding resectability of a locally invasive lesion must be made at the time of thoracotomy when the lesion itself may be palpated and the dissection conducted under greater control. Direct invasion into mediastinal structures including the superior vena cava or vertebral bodies is not a contraindication to resection. As imaging has evolved, the rate of exploratory thoracotomies has dropped. A logical progression from the less invasive to the more invasive procedures guided by the imaging studies often results in the patient being spared a procedure from which there will be no significant benefit.

SURGICAL TREATMENT OF LUNG CANCER

When evaluating a patient with lung cancer for possible resection there are three different criteria that must be satisfied: (1) Is resection oncologically beneficial, (2) is resection technically feasible, and (3) does the patient have the physiologic fitness to tolerate resection?

Staging studies and procedures determine the oncologic benefit of therapy. The feasibility of resection is typically a decision made by the operating surgeon. Involvement of ribs, vertebral bodies, or mainstem bronchi does not preclude resection. Extended resections are discussed later in this chapter. The final and often most difficult criterion to satisfy is the patient's physiologic fitness to undergo surgery. Factors that must be considered include pulmonary reserve, exercise capacity, heart disease, and other medical comorbidities. Frailty indices can be calculated and correlate with postoperative complications.[17] Cardiac risk factors should be identified and evaluated per published guidelines.[18] Often borderline patients benefit from functional testing such as stair climbing or shuttle walking. These tests are easily performed in the office and are associated with minimal cost. The height climbed or speed at which the patient climbs a set number of stairs can predict postoperative complications.[18,19] Formal exercise testing with measurement of oxygen consumption may help quantify the risk of lung resection in selected patients. Quantitative perfusion lung scans have allowed us to better select borderline patients for pulmonary resection, especially when pneumonectomy is a possibility. This information has all but eliminated the "pulmonary cripple" as a result of a lung resection. Quantitative split perfusion testing may identify poorly perfused lung tissue, especially in the setting of upper lobe tumors surrounded by severe upper lobe predominant emphysema. Those patients may tolerate resection because of a volume reduction effect. Experience with lung transplantation has shown that deconditioned patients benefit from at least a 6-week period of pulmonary rehabilitation, and selected patients with otherwise operable disease may be placed in a rehabilitation program before undergoing surgery.[20] Smoking cessation is of paramount importance.

Thoughtful and thorough evaluations combined with less invasive surgical approaches have allowed many patients who previously were not considered surgical candidates to undergo surgery. All but the frailest patients should be referred to a thoracic surgeon to allow this determination.

In spite of recent advances in nonoperative therapy, surgery remains the best treatment for early-stage disease. It is important that the

appropriate procedure be performed. The types of resection include anatomic resection such as segmentectomy, lobectomy, bilobectomy, and pneumonectomy; and nonanatomic wedge resections. Anatomic resections involve the individual ligation of the feeding pulmonary artery, vein, and bronchus to the region of the lung to be resected. Wedge resections are nonanatomic operations where lung parenchyma is divided without ligation of the feeding vasculature or bronchi. Extended resections include an anatomic resection with associated structures that are involved with the cancer. These can include portions of the chest wall resected *en bloc*, vertebral bodies, diaphragm, pericardium, left atrium, or superior vena cava. Also included in extended resections are bronchoplastic resections or pulmonary artery reconstruction procedures. The choice of resection is multifactorial based on the location and stage of the tumor and the patient's physiologic fitness.

OPEN VERSUS MINIMALLY INVASIVE TECHNIQUES

The role of minimally or less invasive surgical techniques in lung cancer resection continues to evolve. Currently most pulmonary resections are performed by thoracotomy but an increasing number of thoracic surgeons now perform these oncologic procedures using VATS or robotically assisted resections. VATS is analogous to laparoscopic surgery wherein operative visualization is provided by an endoscopic camera as opposed to direct visualization through the incision. Currently at least 30% of lobectomies for lung cancer are performed using VATS.[21] It should be emphasized that although the approach is different, the principles of anatomic lung resection should remain the same. Anatomic lung resections most typically performed by VATS include lobectomy and segmentectomy. Pneumonectomy has been reported as well as bronchoplastic procedures.[22,23] The key elements of these procedures involve the identification and individual ligation of the relevant branches of the pulmonary artery, pulmonary veins, and bronchi. A thorough mediastinal lymph node sampling should also be performed. In experienced hands, VATS lymph node harvest is equivalent when compared to thoracotomy.[24,25] The perioperative outcomes have been superior to thoracotomy for quality of life and pain.[26] Multiple studies have demonstrated oncologic equivalency, decreased complication rate, and decreased levels of inflammatory mediators.[27,28] Minimally invasive approaches to lobectomy are associated with decreased pain and length of stay.[28,29] There is increasing evidence that patients who undergo VATS lobectomy are better able to tolerate adjuvant chemotherapy and receive a greater proportion of the planned dose.[26,30] Robotic-assisted surgery continues to evolve; multiple case series have been reported and a retrospective multi-institutional review of robotic lobectomy revealed perioperative and long-term outcomes to be equivalent to VATS lobectomy.[31] Although VATS techniques are associated with improved outcomes in selected patients, many patients are best treated with open surgery. The decision of whether to employ a minimally invasive technique versus thoracotomy depends on many factors such as tumor size and location, extent of chest wall involvement, the presence of calcified lymphadenopathy, and surgeon experience.

TYPE OF RESECTION

Surgical considerations in management of lung cancer include lobectomy versus a lung-sparing resection.

Lobectomy

Lobectomy remains the definitive resection for most lung cancers, since it is an anatomic resection that removes the regional lymph nodes located along the lobar bronchus. Other choices include limited resections such as wedge resection, and segmentectomy. Some hilar tumors or those involving the chest wall or other structures may require pneumonectomy or extended resections. Doing less than a lobectomy may represent a compromise, although a nonanatomic wedge excision may be considered for small primary tumors. Tumors located within the center of the lobe or near the hilum typically require lobectomy.

Limited Resection: Wedge Resection and Segmentectomy

Smaller tumors that are peripherally situated may be candidates for lesser resections. Only patients with clinical stage I cancer (T1N0, T2N0) are possible candidates for a curative limited or sublobar resection. Tumor characteristics and location also play an important role in decision making. Pure ground-glass opacities on CT scan often are revealed to be adenocarcinoma in situ, adenocarcinoma with lepidic growth pattern, and minimally invasive adenocarcinoma with pure lepidic growth; this group of tumors was formerly known as bronchioloalveolar carcinoma (BAC). These lesions, if small, can be considered for limited resection, since resection yields almost 100% survival and may have equivalent survival after wedge resection.[32,33] Combining CT and PET characteristics such as percent ground-glass opacity and standardized uptake value (SUV) can aide in predicting who would benefit from limited resection.[34]

Wedge resection crosses lymphatic channels, does not remove the originating bronchus, and does not permit adequate regional lymph node resection, and parenchymal margins may be limited. These factors limit the value of wedge resection as a planned curative procedure for most primary lung cancers. Wedge resection is, at best, a compromise, and patients who otherwise could tolerate an anatomic resection are not well served by having less done. External beam radiation has been used in an attempt to augment the efficacy of wedge resection but it has been associated with increased pulmonary toxicity in a patient population that typically has compromised pulmonary function. Several groups have reported decreased local recurrence with adjuvant brachytherapy at the time of resection. ^{125}I seeds embedded in an absorbable mesh are applied to the line of resection.[35] A randomized phase III trial comparing sublobar resection with and without brachytherapy (ACOSOG Z4032) in high-risk patients has completed enrollment but the results are still maturing at the time of publication. Perioperative morbidity and mortality were not increased in patients receiving brachytherapy.[36]

Segmentectomy represents a more favorable option for limited resection than wedge resection. As an anatomic resection, segmentectomy provides a wider parenchymal margin and encompasses the regional lymphatics, which drain centrally, and permits regional lymph nodes to be evaluated during the resection. Parenchymal margins of resection are identified more clearly when an anatomic resection is accomplished and a longer length of bronchus is removed, minimizing the opportunity for local bronchial recurrence. Anatomic segmentectomy is the operation of choice in patients with marginal pulmonary function because mortality is lower, and long-term survival is almost comparable to lobectomy.

Segmentectomies are often more technically demanding to perform compared to lobectomy. Many surgeons who do not perform a high volume of pulmonary surgery may not possess the expertise required to perform this procedure. Segmentectomy can be performed by open or VATS techniques. The prototype segmental resection is the superior segment of the lower lobe, but any lung segment may be removed anatomically. Typically the basilar segments of either lower lobe are resected as a unit. The lingular segments or the upper division of the left upper lobe are often resected together. Segmentectomy of the middle lobe is rarely performed.

The key to segmental resection is the identification of the segmental artery, which, once ligated and divided, reveals the location of the segmental bronchus that is taken next. The segmental vein is divided last, and the parenchyma is divided with a stapler or stripped by dividing the lung parenchyma in the intersegmental plane using a combination of blunt and sharp dissection (Fig. 113-5). When properly performed, this technique is not associated with significant blood loss or air leak.

Most surgeons would consider limited resection only for tumors ≤2 cm. Tumors ≤2 cm and those presenting as ground-glass opacities offer better long-term prognosis in association with a limited

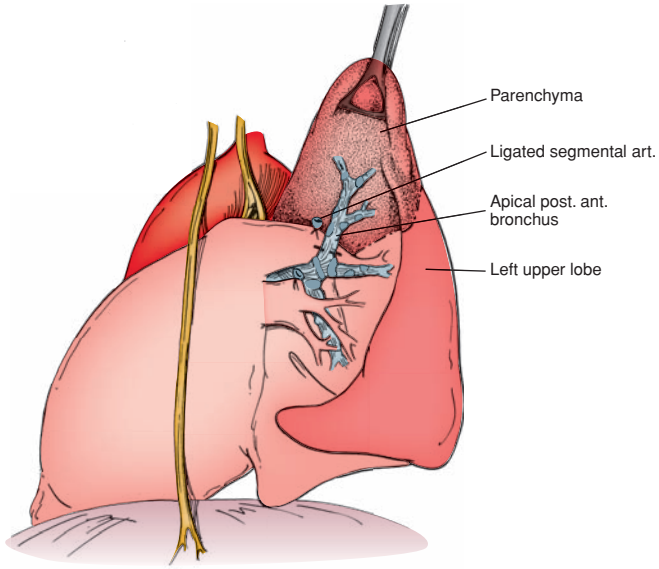


Figure 113-5 Segmental resection. The example shown here is the resection of the apical–posterior segment of the left upper lobe. The segmental pulmonary arterial branch is shown ligated and divided. The segmental bronchus has been dissected out and is the next structure to be divided.

resection. The perioperative risk needs to be balanced against the oncologic benefit of limited resection, especially wedge resection. Nonoperative therapy should be considered for any patient who is not a candidate for segmentectomy. A recent phase II trial of stereotactic body radiation therapy (SBRT) in medically inoperable early-stage cancers reported a 3-year locoregional control rate of 87% and overall a survival of 56%.[37] One drawback of nonoperative therapy is the lack of a pathologic sample, which may provide additional staging information such as pleural invasion, lymph node status, and more detailed histopathologic analysis. A prospective study of sublobar resection with or without brachytherapy versus SBRT is currently enrolling to evaluate these therapies in operable patients.

The Lung Cancer Study Group (LCSG) addressed the question of lobectomy versus limited resection for T1N0 lesions (tumor >3 cm, negative lymph nodes) in a prospective randomized trial.[38] The initial analysis of the data demonstrated an increased incidence of local recurrence in the limited resection group but no difference in survival. Subgroup analysis revealed superior survival for patients in the lobectomy group. This remains the only randomized prospective trial of lobectomy versus sublobar resection. The LCSG has been criticized extensively and many other studies have looked retrospectively at patients undergoing limited resection, which includes segmental resection, and have demonstrated long-term survivors. In a 2010 review of the SEER database of tumors ≤1 cm, Kates et al.[39] were not able to detect a survival difference in patients undergoing lobectomy versus sublobar resection. A new prospective randomized trial to address the issue of lobar versus sublobar resection for peripheral tumors ≤2 cm is currently accruing. The type of limited resection (wedge vs. segmentectomy) is at the surgeon's discretion. Most enrolling surgeons have opted to perform segmentectomy if possible.

In summary lobectomy remains the operation choice in most fit patients; in compromised patients, or those with peripheral tumors segmentectomy, when applicable, yields nearly equivalent results. Patients who are only candidates for wedge resection should be considered for nonoperative therapy such as SBRT.

Pneumonectomy and Extended Resections

Depending mainly on the location of the tumor, more extensive and complex resections than lobectomy may be required. The final determination to perform a pneumonectomy is made at the time of operation. Attempts should be made to perform parenchymal-sparing resections using bronchoplasty and arterioplasty if possible. Recognizing that even today pneumonectomy carries a perioperative mortality of at least 5%, most thoracic surgeons strive to avoid pneumonectomy. There are only a few absolute indications for performing pneumonectomy for the experienced surgeon. These include such proximal involvement of the main pulmonary artery that it is difficult to place a clamp on the artery, endobronchial tumor so extensive as to preclude sleeve resection, and involvement of the confluence of the pulmonary veins or of the left atrium. There is reason for concern if a surgeon is performing an abundance of pneumonectomies. A "difficult" fissure, unless tumor involves the artery in the fissure, is not an indication for pneumonectomy, nor is tumor crossing a fissure an absolute indication. Pneumonectomy, technically, is an easier operation to perform than lobectomy, requiring very little dissection and only several applications of the stapler.

Sleeve resections, or bronchoplastic procedures, are technically more demanding procedures that result in the same bronchial resection as a pneumonectomy, yet preserve lung tissue. The prototypical bronchoplastic procedure is the right upper lobe sleeve resection, in which the main bronchus is divided just proximal to the right upper lobe takeoff and the bronchus intermedius is divided just distal to the upper lobe bronchus (Fig. 113-6). The right upper lobe, with tumor present at the lobar orifice, is thus removed with a portion of the mainstem bronchus, and the bronchus intermedius is anastomosed to the mainstem bronchus. Thus the proximal bronchial

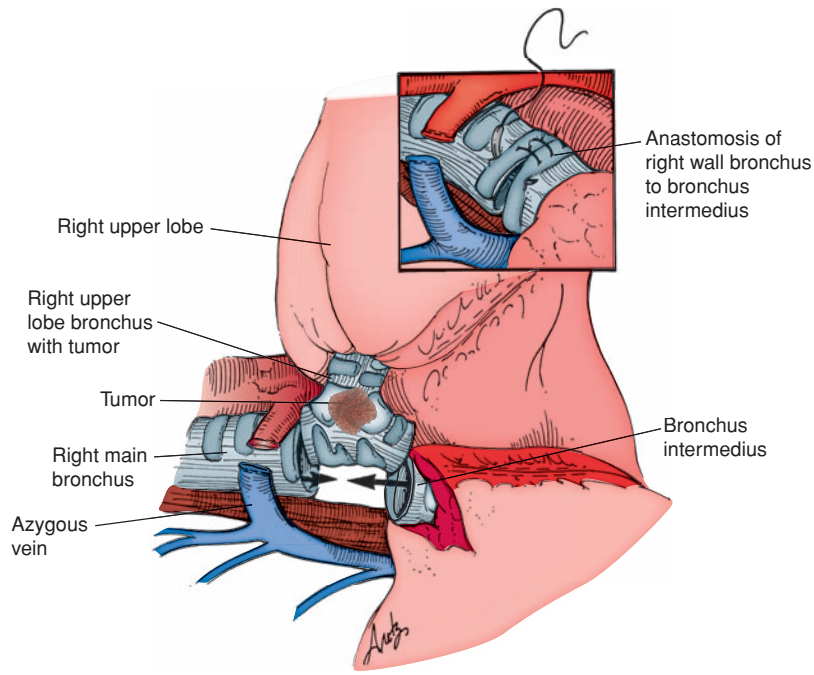


Figure 113-6 Right upper lobe sleeve resection. The right main bronchus has been divided just proximal to the right upper lobe takeoff where the tumor is located. The bronchus intermedius has been divided just distal to the right upper lobe bronchus. The bronchus intermedius is anastomosed to the right main bronchus *(inset)*.

division occurs essentially at the same site as if a pneumonectomy had been performed. Other sleeve resections are possible on both the right and the left side. All bronchoplastic resections result in lung conservation and are associated with long-term survival equivalent to pneumonectomy without the attendant morbidity of pneumonectomy and with the added bonus of preserved lung parenchyma. Even with proximal involvement of the pulmonary artery, partial resection or sleeve resection of the artery is possible to avoid removal of the entire lung. A patch angioplasty with pericardium may be utilized if a significant enough portion of the anterior wall of the artery is taken so as to narrow it. Alternatively a segment of the artery may be removed and an end-to-end anastomosis completed. Sometimes a pneumonectomy must be done, but the complete thoracic surgeon always looks to see if alternatives exist while preserving the principles of the cancer operation and not compromising margins. With any lung-conserving procedure, the margins of the resection should be sent for frozen section confirmation that no tumor is present.

The designation *locally advanced* includes a wide variety of lesions that extend outside of the lung parenchyma, whether by direct extension or nodal involvement to involve other structures within the hemithorax. Certain criteria need to be fulfilled before considering extending the indications for resection, since the intent is to maximize survival. The most obvious criterion is the exclusion of disseminated disease; thus, it is vital to complete an extent-of-disease evaluation before embarking upon a complex resection in which the indications for resection have been extended.

LYMPH NODE SAMPLING

A complete pulmonary resection requires more than simply excision of the tumor and the surrounding lung parenchyma, whether lobe or entire lung. The operation is incomplete without excision of lymph nodes to complete the staging assessment. The appropriate extent of lymph node harvest, ranging between systematic sampling and complete dissection, has been the subject of debate among thoracic surgeons. A randomized trial of over 1000 patients with T1 or T2 tumors was reported in 2011. There was no significant survival advantage to lymph node dissection as long as systematic and thorough lymph node sampling was performed. Systematic sampling included levels 2R, 4R, 7, and 10R for right-sided tumors and levels 5, 6, 7, and 10L for left-sided tumors. Mediastinoscopy was performed at the surgeon's discretion.[40] It is notable that this study was conducted in high-volume centers with dedicated general thoracic surgeons. Also these patients had relatively small tumors and underwent intraoperative frozen section analysis of N2 nodes, which is not common practice. Typically, most nodes are sent for routine pathologic analysis. Other groups continue to advocate formal lymph node dissection.[40,41] During anatomic resection, multiple inter- and intralobar lymph nodes are encountered, these N1 nodes are labeled by their anatomic location and sent for pathologic examination. Many surgeons perform frozen section on N1 nodes during segmentectomy and if positive for cancer, the operation is converted to lobectomy. Any sampling procedure of mediastinal lymph nodes depends on how the nodes to be sampled are chosen. The failure to include mediastinal lymph nodes as part of a resection results in incomplete information. More accurate staging through appropriate lymph node harvest improves prognostic accuracy and determines which patients should be considered for adjuvant treatment.

It is not uncommon to find microscopic disease in a node that grossly appears normal at the time of surgery. Finding tumor in mediastinal lymph nodes portends a significantly worse prognosis and at least prompts consideration of postoperative treatment. Postoperative adjuvant therapy, usually chemotherapy with or without radiation therapy, is now recommended for patients with positive lymph nodes.[42,43] This is in contrast to several previous studies and meta-analyses that did not show a survival benefit to adjuvant therapy.[44] All patients with pathologically determined stage II or III disease should be referred to a medical oncologist for evaluation for systemic therapy.

N2 DISEASE

Involvement of ipsilateral paratracheal or subcarinal lymph nodes classifies the patient as having N2 disease. Most experts believe that these patients are best treated with induction (neoadjuvent) therapy or definitive nonoperative therapy at the time of presentation since overall survival after primary resection is poor. Thorough evaluation of the mediastinum is mandatory to optimize the outcomes of patients with advanced disease. Contralateral or N3 disease, carries a significantly worse prognosis than ipsilateral disease, may also be detected at mediastinoscopy or EBUS and usually renders the patient inoperable, even if combined with neoadjuvant therapy.

Perhaps the first recognition that a subset of patients with mediastinal lymph node involvement could benefit from surgery came from the work of Martini, who was able to completely resect 151 patients out of approximately 500 with N2 disease. Many of these patients were treated with postoperative radiation therapy. For the group of completely resected patients he found a 28% 5-year actuarial survival and subsequently a 26% absolute survival. All the patients with N2 disease, resected or not, were identified at the time of thoracotomy, as mediastinoscopy was not performed.[45] Breaking the patients down into two groups yielded those staged as N0 or N1 preoperatively, and those with bulky disease, so-called clinical N2, noted either on preoperative chest radiograph or at bronchoscopy when carinal splaying was noted. Those patients thought to have N0 or N1 disease preoperatively had a 35% 5-year survival, and those with clinical N2 disease had 0% 5-year survival. Fewer than 10% of patients with clinical N2 disease could be completely resected.

In recognition that patients with bulky N2 disease not only had a low rate of resectability but also a poor long-term outlook, an attempt was made to improve the resectability rate and, it was hoped, survival in this patient group by employing preoperative (neoadjuvant) chemotherapy. In one study, there was a 77% response rate to the chemotherapy regimen of vinblastine and cisplatin with 10% complete responders.[45] Sixty-five percent of patients, who underwent surgery, after induction therapy, were able to have complete resection, a significant improvement over the rate of complete resection when no preoperative therapy was employed. All patients entered into this trial were those with bulky mediastinal disease. The overall survival was 28% at 3 years and 17% at 5 years, with a median survival of 19 months. Patients who were able to undergo a complete resection had a mean survival of 27 months and 3- and 5-year survival of 44% and 26%, respectively.[46] In another randomized trial of patients with N2 disease, 28 patients were randomized to receive three cycles of preoperative chemotherapy with cyclophosphamide, etoposide, and cisplatin followed by surgery, and 32 patients underwent operation without preoperative therapy.[47] Significant survival advantage was conferred upon those who received preoperative therapy. Median survival in the combined therapy group was 64 months compared to only 11 months for the surgery-only group, despite the fact that the percentage of patients able to have complete resection in each group was similar (39% vs. 31%). Although this trial clearly demonstrated an advantage to neoadjuvant therapy in a group of patients with locally advanced disease, survival in the surgery-only group was significantly shorter than expected, making the survival difference between the groups more striking. Excluded from the trial were patients with left lung tumors in conjunction with left paratracheal disease, as these patients were felt to be unresectable. A randomized trial of patients with stage IIIa disease included 25 patients with N2 disease who received chemotherapy followed by an operation and 19 patients with N2 disease who underwent operation as their only therapy. As in the other trials, there was a significant survival benefit in the group that received combination therapy (median, 26 vs. 8 months).[48]

In light of the previously mentioned studies, a phase III prospective, multicenter, randomized trial, Intergroup 0139 trial, compared induction chemoradiation followed by surgery with definitive chemoradiation.[49] Although overall survival was similar in the two groups, progression-free survival was significantly improved in association with the combined use of chemoradiation and surgery. Notably, perioperative mortality in the surgical patients who underwent pneumonectomy approached 26%. When the analysis was restricted to the subgroup of patients who underwent lobectomy, overall survival was improved compared to the group receiving definitive chemoradiation (Fig. 113-7). In an observational study of over 39,000 patients from the National Cancer Database of patients with clinical stage IIIa-N2 disease, Koshy et al.[50] reported improved survival in patients receiving neoadjuvant chemoradiation followed by lobectomy.

Subsequently, several groups have reported excellent results of patients undergoing pneumonectomy after induction therapy with perioperative mortality less than 5%.[50–53] Pneumonectomy can be considered in the setting of induction therapy in appropriate patients when performed in centers with experience in the management of these patients.

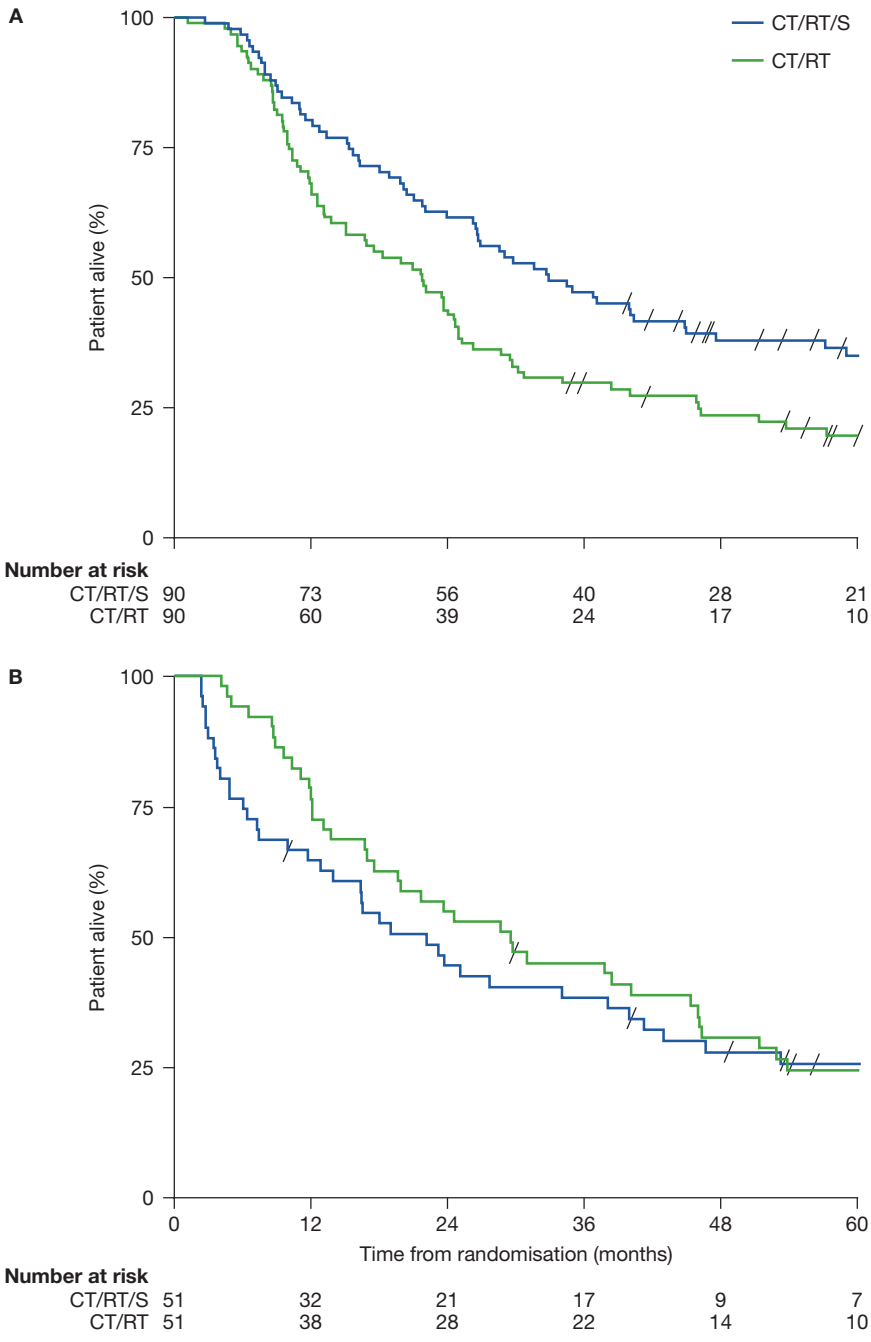


Figure 113-7 Overall survival of a subset of patients from Intergroup 0319 trial the intention-to-treat population given lobectomy (**A**) or pneumonectomy (**B**) in group 1 versus matched cohorts in group 2. *Slash marks* represent censored results. CT/RT/S, chemotherapy plus radiotherapy followed by surgery (group 1, $n = 202$). CT/RT, chemotherapy plus radiotherapy (group 2, $n = 194$). *(Reproduced with permission from Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–386.)*

Resections following preoperative therapy can be extremely difficult and hazardous because of the fibrosis that often results as a response to the therapy. This is especially significant when there has been a response in involved lymph nodes, since the nodes are intimately associated with the pulmonary artery and its branches, often making resection quite treacherous. It is particularly important to have proximal control of the pulmonary artery before undertaking a resection in a patient with N2 disease who has received preoperative therapy. Ideally, resections of this type should only be undertaken by a surgeon with experience in dealing with complex resections.

CHEST WALL RESECTION

Approximately 5% of lung cancers involve the chest wall by direct extension. This involvement may be limited to the parietal pleura or may invade the endothoracic fascia, intercostal muscle, or ribs. Chest wall involvement by direct extension is *not* a contraindication to resection unless vertebral bodies are invaded, and even then, under some circumstances, resection may still be completed. The optimal treatment for tumors involving the chest wall that do not involve the superior sulcus is resection followed by adjuvant therapy.[43,54] Chest wall pain is the most sensitive predictor of chest wall involvement in a patient with a peripheral lung lesion in which there is a question of chest wall invasion. Neither CT scan nor MRI can distinguish between abutment and invasion unless there is gross invasion of bone. PET or bone scan cannot absolutely predict chest wall involvement, especially if only the parietal pleura and muscle are involved. Lesions involving parietal pleura or other chest wall structures are clinically staged as T3 primary tumors, but definitive staging cannot be accomplished until the time of operation.

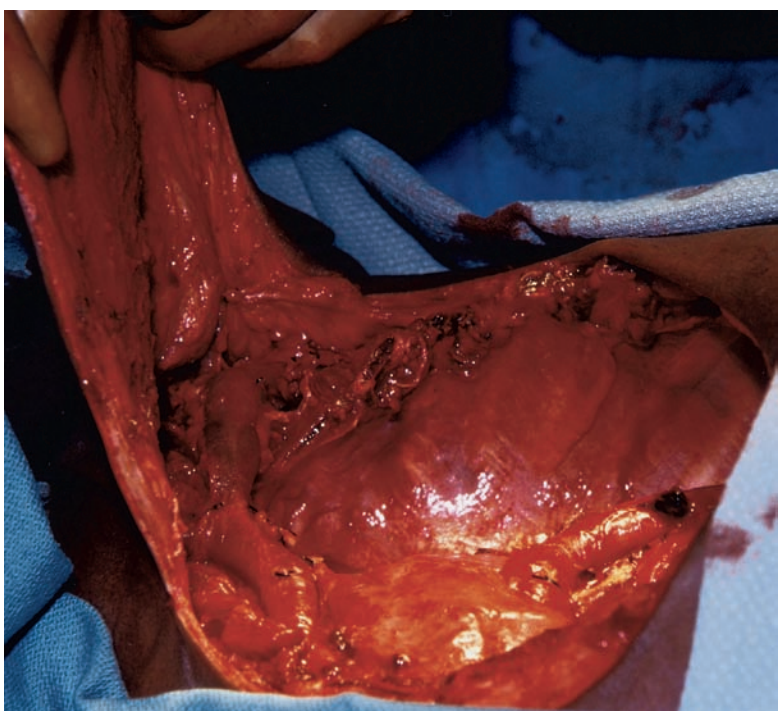
As with any lung cancer it is important to rule out disseminated disease before considering surgery in a patient with chest wall involvement. It is particularly important to assess the mediastinum in these patients, since mediastinal lymph node involvement is the single best prognostic indicator. Three-year survival approaches zero in patients with chest wall and mediastinal lymph node involvement, underscoring the importance of accurate mediastinal lymph node staging before considering thoracotomy in this

patient group. Conversely, greater than 50% 5-year survival can be expected in patients with chest wall involvement with negative mediastinal lymph nodes as long as the resection margins are negative.

The operation performed in a patient with suspected chest wall involvement begins by assessing the pleural space to rule out diffuse pleural disease and then defining whether the chest wall is invaded. Before beginning the chest wall resection it is important to assess the hilum of the lung to ensure that there is not such extensive disease as to preclude resection, though this should usually be apparent on a preoperative chest CT performed with contrast. Resection should begin in the extrapleural plane, thus separating the parietal pleura from the endothoracic fascia in the area of the lesion. If this plane is easily developed, it may be that the parietal pleura are not invaded but the adhesion is inflammatory. If there is any question at all about invasion when attempting to develop the extrapleural plane, then chest wall resection is performed (Fig. 113-8). Ideally the chest wall resection is performed in continuity with the parenchymal resection; the portion of chest wall resected remains attached to the underlying lung and the specimen is removed *en bloc*. The chest wall resection should include at least one rib and preferably two above and below the area of chest wall invasion. Three- to 5-cm margins should also be taken anteriorly and posteriorly. The intent is to achieve negative margins, so the resection margin should be wide; there is little if any additional morbidity to taking a somewhat larger piece of chest wall. For posteriorly based tumors the rib may be disarticulated and the nerve root ligated at its origin. Once the chest wall block is totally mobilized, the lobectomy and mediastinal lymph node dissection are completed. A mediastinoscopy should be performed prior to resection and a lymph node dissection should be completed with the anatomic resection. A posterior chest wall defect is reconstructed with polypropylene mesh or expanded polytetrafluoroethylene, and a defect in the anterior chest wall should be reconstructed. Many surgeons recommend a sandwich of methyl methacrylate cement and polypropylene mesh, which creates a rigid prosthesis. In posteriorly based tumors, the defect may be covered by the scapula, which obviates the need for reconstruction. Anterior rigid fixation provided by the methyl methacrylate and mesh eliminates any paradoxical motion that might interfere with mechanics of breathing. Interference with the mechanics of breathing is much less likely to occur with posterior defects. Chest wall resection, reconstruction, and anatomic resection can be accomplished in selected patients without formal thoracotomy, using VATS techniques and a variety of bone-cutting instruments.[55]

En bloc resection of the chest wall typically adds little, if any, additional morbidity to a pulmonary resection. Patients tend to have the chest tubes in a few days longer following chest wall resection because of increased fluid drainage. Pain in the early postoperative period is best controlled with a thoracic epidural catheter, which allows patients to be comfortable enough to maintain a good cough for clearance of secretions. There is no evidence that patients undergoing chest wall resection are subject to more pain than those who have a simple lobectomy. Many patients with bony erosion report a decrease in pain after resection. Aggressive pulmonary toilet is mandatory. If the cough is ineffective, and lobar collapse ensues, then bronchoscopy may be indicated.

Postoperative treatment for patients who have undergone chest wall resection with pulmonary resection includes adjuvant chemotherapy for margin-negative patient.[43] Currently no evidence exists that postoperative radiation therapy prolongs survival in patients with negative margins, but local recurrence may be problematic. Thus there may be a role for radiation therapy in some of these patients—in particular those with disease close to the spine, in whom local recurrence presents major management problems. If negative margins cannot be achieved, reresection or adjuvant radiation can be considered.[43] Anything less than a complete resection is associated with poor long-term survival.



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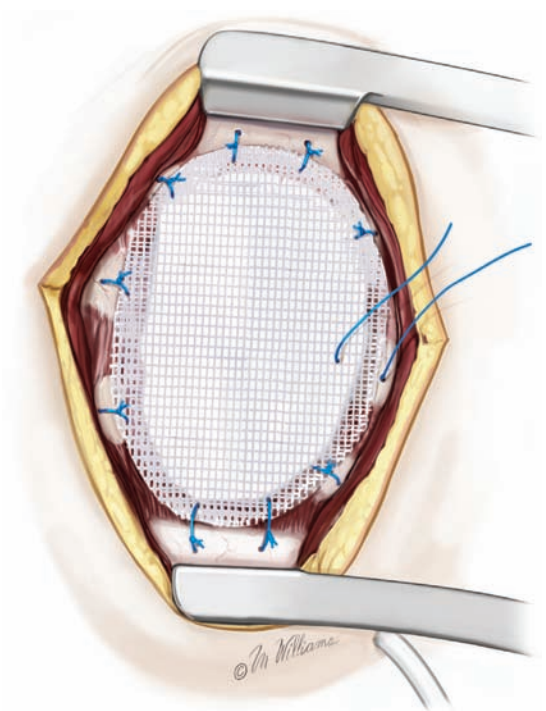

B

Figure 113-8 **A.** Operative photograph showing the defect left after resection of the left upper lobe in continuity with the anterior chest wall. **B.** This anterior defect requires reconstruction with prosthetic mesh and methyl methacrylate cement. *(**B.** Used with permission of Marcia Williams.)*

TUMORS OF THE SUPERIOR SULCUS

Tumors of the superior sulcus can represent an oncologic and surgical challenge. Therapy for these difficult tumors has evolved from palliative care to induction chemoradiation followed by surgery with curative intent.[56] Patients with superior sulcus tumors may present with the Pancoast syndrome, which includes pain, Horner syndrome, and neurologic deficits in the intrinsic muscles of the hand.[57] These patients should undergo extensive evaluation including MRI of the thoracic inlet, spinal imaging as appropriate, MRI of the brain, and invasive mediastinal staging. The presence of N2 disease generally remains a contraindication to surgery. Typical treatment regimens include induction chemoradiation with cisplatin and etoposide and 45 Gy of radiation followed by resection and planned follow-up chemotherapy.[58] These tumors may be approached using an anterior cervicothoracotomy, an extended posterolateral thoracotomy, or a combined anterior and posterior approach.[56,59] Involved vertebral bodies may be resected at the time of surgery.[60]

TUMORS INVOLVING THE MEDIASTINUM BY DIRECT EXTENSION

Some centrally located primary tumors may involve structures in the mediastinum by direct extension (Fig. 113-9). The assessment of this involvement, whether there is true invasion or just abutment and adherence, cannot be determined until the findings are seen intraoperatively and then often only as the dissection proceeds. The presence of a central tumor that appears on CT scan to be close to the mediastinum is not justification for ruling out resection. In the absence of frank invasion, this is a judgment that can only be made intraoperatively, since no imaging modality readily distinguishes abutment from invasion. There may be other reasons why the patient should not be operated on, but it is dangerous to simply assume that a lesion is unresectable. The distinction between a T3 tumor involving the mediastinum and a T4 tumor depends on the mediastinal structure invaded. Tumors invading structures such as the phrenic nerve, mediastinal pleura, the pericardium, or the diaphragm that may be readily removed are classified as T3 primary tumors and if N0 or N1 should be considered for primary resection. T4 primary tumors invade the mediastinum, heart, great vessels, esophagus, vertebral bodies, carina, and recurrent laryngeal nerve. There are occasions when tumors involving these structures are resected, most commonly with lesions involving the vena cava or left atrium. Rarely, if ever, is a portion of aorta resected for excision of a lung tumor, but a lesion may involve only the muscular wall of the esophagus and thus may be amenable to resection. T4N0-N1 tumors are staged as IIIa and should be evaluated and treated as such.[61] What is important to recognize is despite the seeming ability to remove some of these invasive lesions, the prognosis for long-term survival is dismal. For T4 lesions, fewer than 10% of patients are alive at 5 years.

Vertebral body invasion is not a contraindication to resection. Tumors that involve the transverse process or anterior aspect of the vertebral body can be approached with a partial resection of the vertebral body. If there is extensive involvement of one or more vertebral bodies or if resection could lead to spinal instability, a combined procedure with a neurosurgeon or orthopedic spine surgeon is planned in one or two stages. There are multiple reconstructive and stabilization techniques available. These complex procedures may be performed from a single approach or with posterior spinal stabilization either preceding or following en bloc resection of the lung parenchyma and involved vertebral bodies. These procedures can be performed primarily or preferably after induction therapy.[62] Excellent results have been reported in highly selected patients.[63]

Tumors preoperatively identified as involving the left recurrent laryngeal nerve are generally considered inoperable. This situation should be considered in any patient who presents with the new onset of hoarseness and is found to have paralysis of the left vocal cord. Almost always a tumor will be found in the left chest, usually the left upper lobe. The left recurrent nerve is in a position of great vulnerability, since it arises after the vagus nerve crosses the aortic arch and recurs around the ligamentum arteriosum (Fig. 113-10). The left recurrent nerve may be involved either by a primary tumor, which encases the vagus nerve as it crosses the aortic arch, or more commonly by lymph node disease in the aortopulmonary window. Because of the depth of the aortopulmonary window, there can be gross mediastinal lymph node involvement and a sheet of tumor despite minimal plain radiographic evidence, since tumor underneath the aortic arch is not easily seen. CT scan usually confirms extensive involvement. Involvement of the left recurrent laryngeal nerve represents a contraindication to operation, since these lesions are rarely able to be completely resected. Left recurrent laryngeal nerve involvement should exclude patients from participating in neoadjuvant trials as well. The only exception is the occasional situation in which the primary tumor involves the vagus nerve as it crosses the aortic arch, a situation that may prove to be resectable and justifies exploration. Rarely, if ever, does lung cancer involve the right recurrent laryngeal nerve, which "recurs" around the right subclavian artery above the apex of the chest.

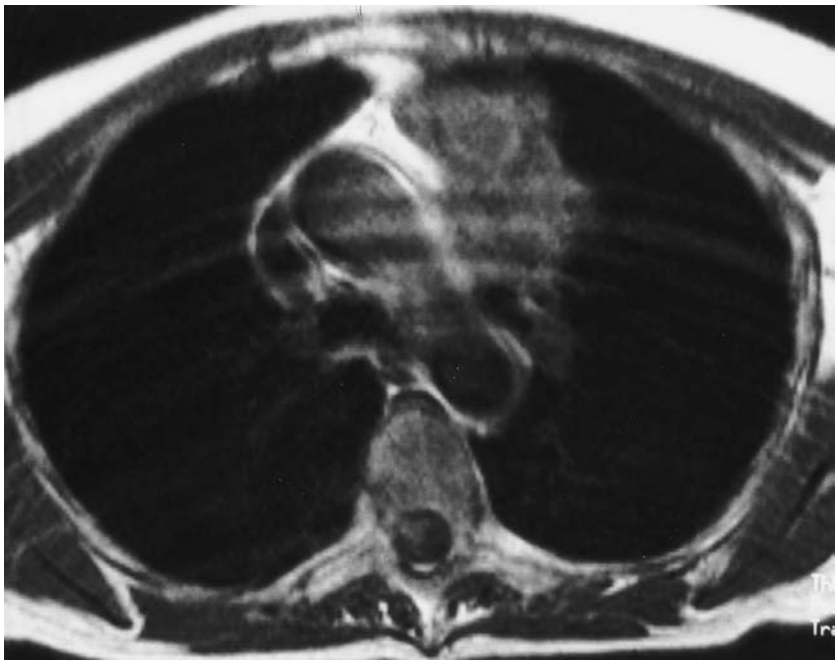

Figure 113-9 MRI scan showing a primary lung tumor involving the aorta by direct extension (T4 primary). The distinction between abutment and invasion often cannot be made until the findings are seen at operation. MRI is no better at delineating invasion than CT.

PALLIATIVE RESECTIONS

There is only a very limited role for palliative resections in the modern management of NSCLC; this is principally confined to select cases of massive hemoptysis or superinfection of necrotic tumors. Morbidity resulting from the primary tumor usually can be managed using

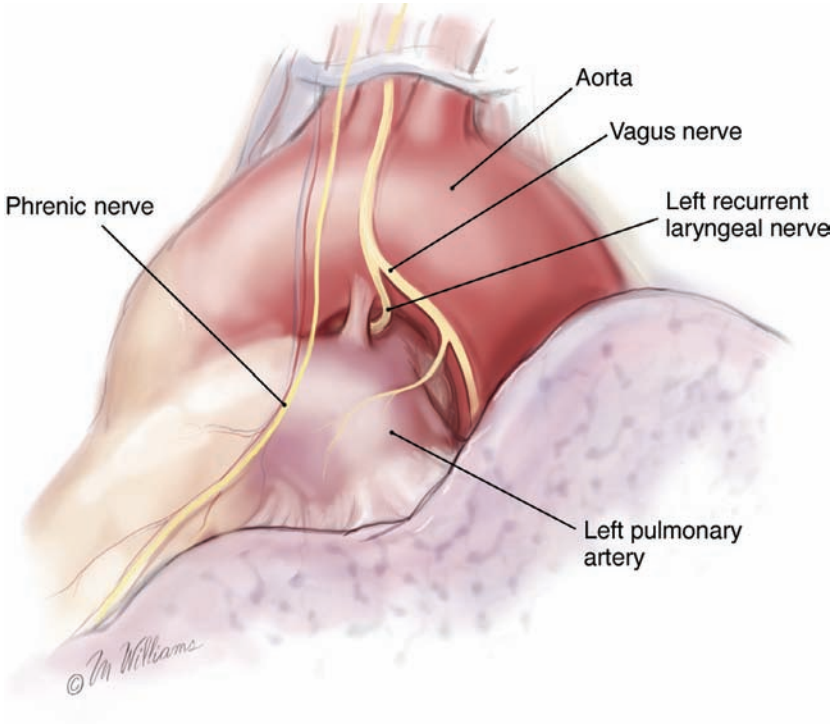

Figure 113-10 The anatomy of the aortopulmonary window showing the relationship of the left recurrent laryngeal nerve to the aortic arch and ligamentum arteriosum. The nerve is easily damaged in this location. Hoarseness may result from tumor involvement of the nerve in this location or from involvement of the vagus nerve at the level of the aortic arch proximal to the location where the recurrent laryngeal nerve originates. *(Used with permission of Marcia Williams.)*

modalities other than surgery. At the present time there is no role for surgical "debulking" in the management of the patient with unresectable disease. With the newer treatment planning modalities available, radiation therapy can be given accurately and in high doses to patients who are inoperable or unresectable. Patients with hemoptysis or postobstructive pneumonia may benefit from bronchoscopic debulking of endobronchial disease possibly combined with stent placement to maintain patency of the obstructed bronchus or trachea, followed by external beam radiation therapy or endobronchial brachytherapy. Chest wall pain usually is readily controlled by a course of radiation therapy.

RESULTS OF TREATMENT

Postoperative complications and morbidity, as well as prognosis, tumor recurrence, and post-operative follow-up are discussed below.

■ POSTOPERATIVE COMPLICATIONS

Major improvements in perioperative care of patients undergoing thoracic surgical procedures have led to decreased morbidity and mortality when compared with only 10 to 20 years ago. Improved preoperative evaluation of patients has allowed us to identify risk factors associated with morbidity and address these early on. The further refinement of lung-conserving procedures and the use of minimally invasive techniques such as VATS along with better perioperative pain management provided by continuous epidural administration of narcotic have provided the incentive to offer surgery to many patients previously thought not to be candidates because of poor pulmonary function. A greater recognition of the importance of preoperative teaching of postoperative maneuvers such as coughing and the use of chest physiotherapy given by expertly trained individuals also has contributed to decreasing respiratory complications. With the proliferation of general thoracic surgeons, dedicated service lines and inpatient units to care for patients undergoing pulmonary resections have emerged.

In spite of the advances in surgical and anesthetic techniques thoracic surgery remains a significant physiologic stress. Patients should be counseled that they may not achieve full physiologic and psychological recovery for several months. Serial quality-of-life measurements reveal progressive improvement at 3, 6, and 9 months after surgery.[64] Most patients have returned to baseline by 9 months.[65] Postthoracotomy pain, even in patients who underwent less invasive approaches, may persist for several weeks after surgery. For patients who still require narcotics beyond this point, referral back to the operating surgeon should be made to rule out postoperative problems. These patients often benefit from the use of nonnarcotic analgesics such as gabapentin. In addition, consideration should be given to referral to a pain specialist for comprehensive evaluation and treatment including epidural steroid injection and narcotic weaning.

■ POSTOPERATIVE MORTALITY

Recent analyses document that lobectomies and lesser resections have a mortality between 1% and 2%; notably, pneumonectomies still carry a mortality of 5% to 7%.[66,67] The mortality rate is directly proportional to increased age, associated diseases, and the extent of resection. Respiratory complications, not surprisingly, are the most common cause of postoperative mortality in patients undergoing pulmonary resection. Cardiac complications also account for a significant percentage of mortality, and technical problems such as hemorrhage, bronchopleural fistula, and empyema account for a small but significant percentage of complications leading to death.

■ POSTOPERATIVE MORBIDITY

Approximately 30% to 40% of patients undergoing pulmonary resection sustain a postoperative complication, of which approximately two-thirds are minor and the other one-third nonfatal major complications.[66] The most common complication is supraventricular arrhythmia, which occurs in up to 20% of patients, depending on how closely patients are monitored. Most of these respond to simple pharmacologic manipulation and rarely are hemodynamically significant at onset. With appropriate treatment the rhythm reverts to sinus rhythm quickly, and patients may be taken off the antiarrhythmic drugs usually after 1 month. Other minor complications include postoperative air leaks lasting greater than 7 days and atelectasis. Major nonfatal events most commonly are respiratory related, principally aspiration pneumonitis and nosocomial pneumonia. A small percentage of patients require reintubation in the postoperative period for respiratory failure. There are no definitive predictors for postoperative pulmonary complications, although significant risk factors for major complications include increasing age, FEV_1 less than 2 L, and diminished diffusing capacity (D_{LCO}).[68–70] Oxygen consumption less than 10 mL/kg/min on preoperative cardiopulmonary exercise testing is associated with an increased risk of major pulmonary complications. The use of VATS rather than standard thoracotomy may decrease the risk of pulmonary complications in patients with limited pulmonary reserve undergoing lobectomy.[71]

Pulmonary complications can be minimized with meticulous attention to postoperative respiratory maneuvers, including chest physiotherapy and preoperative teaching. Other complications of pulmonary resection include wound infections and disturbances in mental status, especially in older patients.

Complications specific to pneumonectomy include postpneumonectomy pulmonary edema and empyema with or without a bronchial stump leak. Postpneumonectomy edema is characterized by tachypnea, low-grade fever, and noncardiogenic pulmonary edema and hypoxemia in the absence of pneumonia. Supportive care, gentle diuresis, and protective ventilation strategies are the mainstays of care. The mortality can approach 50%.[72] Postpneumonectomy empyema is a devastating complication. In the early postoperative period it can be caused by contamination at the time of surgery or from a bronchial stump leak. A falling air–fluid level on chest radiograph and a cough productive of thin brownish sputum should trigger a prompt investigation.

PROGNOSIS FOLLOWING RESECTION

Outcomes following pulmonary resection for lung cancer have been well analyzed. Prognosis depends mainly on TNM stage, a classification that was revised as recently as 2009.[61] Short of disseminated disease, prognosis mainly depends on the status of the regional lymph nodes. Prognostic data are only as good as the sampling done at the time of operation, and lymph node dissection is the only sure way to ascertain definitively the status of the lymph nodes. Histologic type also has some prognostic significance but to a lesser extent, and histologic grade, according to present knowledge, has little prognostic significance. The presence of neuroendocrine features in what is otherwise an NSCLC, however, may have prognostic significance.

SITES OF RECURRENCE

Patients with lung cancer frequently die of disseminated disease, and it is a distant site that most commonly is the first site of recurrent disease. In a series from Memorial Sloan Kettering of patients who underwent resection for early-stage cancers, 44% of recurrences involved distant sites, 30% involved both distant and locoregional sites, and only 26% were locoregional.[73] Over 30% of patients with adenocarcinomas develop brain metastases, a percentage significantly higher than for patients with squamous carcinoma. Other common sites of metastatic disease include bone, lung, liver, and adrenals. Patients with higher-stage disease have a significantly greater likelihood of developing disseminated disease. This recognition has led to the development of neoadjuvant treatment regimens following surgical resection. As earlier, isolated local recurrence accounts for only a minority of events but sometimes is amenable to resection. This underscores the importance of a complete resection at the time of the initial operative procedure. Sites of local recurrence that may cause symptoms include the chest wall (pain), mediastinum (SVC syndrome, dysphagia), and involvement of the left recurrent laryngeal nerve (hoarseness). Symptomatic local recurrence is often treated with radiation therapy, and chemotherapy is employed for some patients who develop disseminated disease, while recognizing that cure is usually not possible in patients who have developed distant disease.

POSTSURGICAL FOLLOW-UP

Recognizing that essentially no patient is cured once distant disease is present might raise the question of why patients should be followed at all after pulmonary resection. Is there an advantage to recognizing the development of distant disease early rather than late? Actually there may be some advantage, especially when it comes to preventing some of the morbidity that may accompany disseminated disease if treatment begins early. Also the occasional patient presents with an isolated local recurrence that may be amenable to surgery. In addition, second primary cancers may be identified.

Current recommendations include a history and physical examination every 6 to 12 months with a chest CT with contrast for 2 years, followed by a yearly examination and noncontrast CT for an additional 2 years.[43] In light of the recent National Lung Screening trial results, the American Association for Thoracic Surgery recommends an annual low-dose screening CT for lung cancer survivors between the ages of 50 and 79 years who have completed 4 years of standard follow-up.[74,75] Additional studies such as PET and MRI are ordered based on patient symptoms or findings elicited by a careful history and physical examination.[74]

FUTURE DIRECTIONS

The role of surgery in the management of NSCLC has been well defined and remains the standard therapy for patients with localized disease. The challenge for all who deal with lung cancer is the problem of disseminated disease. Perhaps the better way to deal with the problem is to identify risk factors in addition to the already well-defined risk of cigarette smoking. Thus far a "lung cancer susceptibility" gene has not been demonstrated; however, based on the recent explosion of knowledge related to breast cancer, the identification of one or more genes involved in the genesis of certain lung cancers is at hand. Cigarette smoking has been identified as a major risk factor, yet only a small percentage of patients who smoke develop lung cancers. Efforts to identify such susceptibility genes have been hampered by the relative lack of families with a genetic predisposition. The issue of smoking as a risk factor only serves to confound the search.

Molecular markers to identify patients at increased risk of developing recurrent disease are also desperately needed. Once identified, these patients would begin adjuvant therapy designed to prevent recurrence in this high-risk group, sparing those patients who are at lower risk. This further underscores the need for better adjuvant therapy. Mutation-specific drugs and assays continue to proliferate and promise to achieve this goal. Major strides have been and continue to be made in the molecular biology and genetics of tumors, and we can expect lung cancer to be the beneficiary of some of these developments.

In the meantime, refinements in surgical techniques and perioperative management of patients with lung cancer have allowed greater numbers of patients with localized and locally advanced disease to benefit from operative intervention. Many patients with mediastinal lymph node disease previously thought not to be operative candidates now can be operated upon with improved survival after a course of neoadjuvant therapy. Many patients with severely compromised pulmonary function previously thought not to be surgical candidates may be considered for resection using minimally invasive techniques. In combination with advances in diagnosis and medical therapy, it is hoped that surgery will offer the promise of cure to an increasing number of patients with NSCLC.

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CHAPTER 114

Treatment of Non–Small-Cell Lung Cancer: Chemotherapy

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Historically, lung cancer is associated with high mortality rates and little effective therapy. Because this disease predominately affects those of advanced age with significant comorbidities, treatment can be difficult to deliver safely with manageable adverse effects. All of these factors can lead to a sense of futility among clinicians and patients when discussing lung cancer therapy. However, in the last several years novel therapies have emerged to make lung cancer therapy better tolerated and more effective, even among those with significant comorbidities. The introduction of better-tolerated cytotoxic chemotherapy and targeted agents has made lung cancer therapy tenable for many more patients. In addition, the improved response rates seen by matching targeted drugs to specific genetic alterations driving tumor growth have led to improved quality of life and survival among patients with these specific tumors. Thus, although the morbidity and mortality of lung cancer remain high, novel approaches to therapy and improved supportive care have begun to make a significant impact in the burden of this disease.

Chemotherapy, whether an oral targeted drug or an intravenous cytotoxic agent, is used for three main reasons in the treatment of non–small-cell lung cancer (NSCLC): (1) As adjuvant therapy in early-stage disease following potentially curable surgical resection to prevent disease recurrence, (2) as concurrent therapy with radiation in locally advanced disease to radiosensitize the tumor and prevent metastatic disease recurrence, and (3) as palliative therapy in the setting of advanced disease to ease symptoms and prolong survival. This chapter will focus on the role of systemic chemotherapy in the treatment of NSCLC in each of these settings.

EARLY-STAGE NON–SMALL-CELL LUNG CANCER

Surgery remains the standard of care for patients with early-stage disease who do not have medical contraindications. In this setting, surgery provides definitive treatment and allows for more accurate pathologic staging. Staging is central to the therapeutic approach to NSCLC. This entails determination of the extent of invasion of the mediastinal lymph nodes. Mediastinoscopy or fine-needle aspiration (FNA) of lymph nodes by endobronchial ultrasound (EBUS) can be used to sample mediastinal lymph nodes before a surgical resection. As for all surgical interventions for thoracic malignancy, complete nodal sampling or lymph node dissection is an integral part of the procedure. Reliance on noninvasive imaging alone may be inadequate for accurate assessment of the mediastinum (Fig. 114-1).

■ ADJUVANT CHEMOTHERAPY

It is well recognized that despite complete resection, most patients with locally advanced NSCLC will develop disseminated disease. The risk of developing disseminated disease can be predicted, with some accuracy, on the basis of the stage of the disease determined at the time of the initial resection. However, the value of the staging information depends on the completeness of the staging procedures carried out at the time of resection. Even with stage I disease, as many as 20% of patients die of disseminated disease within 5 years. With stage II disease, less than 50% of patients are alive at 5 years;

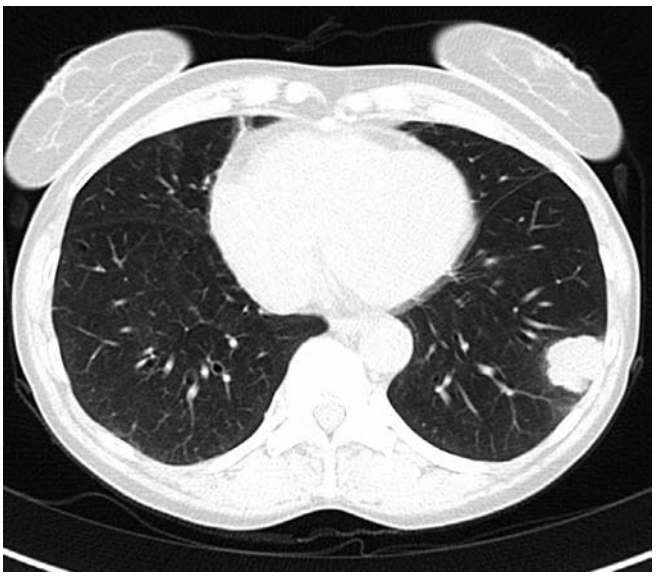

Figure 114-1 Computerized tomography (CT) scan of a 59-year-old female with ongoing smoking and chronic cough. The image shows a large nodule in the left lower lobe extending into the pleura. The patient underwent a mediastinal lymph node dissection and left lower lobectomy. She was found to have several hilar lymph nodes involved with tumor at the time of resection, (stage IIA). She received four cycles of cisplatin-based adjuvant chemotherapy following surgical resection.

TABLE 114-1 Randomized Trials for Adjuvant Chemotherapy

Trial	Number of Patients	Stage	Therapy	Overall Survival (mo)	Survival (%) 2 y	3 y	5 y
International Adjuvant Lung Cancer Trial[2,3]	1867	IA, IB, II, III	Observation	45	66.7		40.4
			Chemotherapy	54	70.3		44.5
CALGB 9633[4]	344	IB–T2N0	Observation	78[a]	84	73	58[a]
			Chemotherapy	95[a]	90	80	60[a]
NCIC JBR 10[5]	482	IB, II (no T3N0)	Observation	73			54
			Chemotherapy	94			69
ANITA[6]	840	IB, II, IIIA	Observation	43.7			
			Chemotherapy	65.7			
LACE Meta-analysis[7]	4584	IA, IB, II, III	Observation			Absolute improvement	
			Chemotherapy			3.9%	5.4%

[a]*Statistically insignificant*

CALGB, Cancer and Leukemia Group B; NCIC, National Cancer Institute of Canada; ANITA, Adjuvant Navelbine International Trialist Association; LACE, Lung Adjuvant Cisplatin Evaluation.

with stage IIIA (N2) disease, at best, 30% of patients are alive at 5 years. These numbers make clear the need for additional therapy to improve on the overall survival (OS) achieved by surgery.

To this end, there has been an emergence of a body of data to better define the role of chemotherapy in the adjuvant setting. The rationale behind this approach is to treat patients who are deemed to be at high risk for recurrence and dissemination of disease in the hope of eliminating micrometastatic disease. Early trials to study adjuvant chemotherapy were negative, possibly either due to the use of less effective chemotherapy regimens, the increased morbidity of treatment with fewer supportive care options, or the lack of statistical power. However, interest in studying adjuvant chemotherapy reemerged with presentation of a meta-analysis in 1995 in which 52 randomized trials were reviewed.[1] The authors concluded that the trials that compared cisplatin-based adjuvant chemotherapy to no further treatment favored the use of chemotherapy with an absolute survival benefit at 5 years of 5%. Since then, more homogeneous trials randomizing patients to surgery versus surgery followed by platinum-based chemotherapy have been conducted. These studies are outlined in Table 114-1.

International Adjuvant Lung Cancer Trial

The International Adjuvant Lung Cancer Trial (IALT) randomized 1867 patients with stage I, II, or III NSCLC to observation or chemotherapy after surgical resection.[2] The two groups were evenly matched with regard to age, sex, stage, performance status (PS), type of surgery, and histologic subtype. Due to the lack of consensus regarding the use of adjuvant radiotherapy, the choice of specific regimen was made by each participating institution at the time of protocol development. The chemotherapy regimens used consisted of cisplatin 80, 100, or 120 mg/m^2 offered on one of four different schedules with vindesine, vinblastine, vinorelbine, or etoposide. Patients were treated with three or four cycles. Of the various choices, the combination of cisplatin and etoposide was used to treat nearly 50% of the patients. When offered, radiation was given after chemotherapy in the group randomized to postoperative treatment. Radiation was planned for about 30% of the patients in the trial, with two-thirds of these having N2 disease. It was actually delivered to slightly more patients in the control group compared with the chemotherapy group (28% vs. 23%). Overall, the results favored the use of adjuvant chemotherapy, with a hazard ratio (HR) for death of 0.86 (0.76–0.98). At 5 years, the group that received chemotherapy had a statistically significant improvement in survival of 44.5% versus 40.4%. The toxicities associated with chemotherapy included the expected risks of neutropenia and nausea/vomiting. However, seven patients, (0.8%) died due to chemotherapy-related acute toxicities; this was predominately seen in those who received cisplatin at 120 mg/m^2. Long-term follow-up, (median 7.5 years) of this study was reported in 2009.[3] Although the benefit of cisplatin-based adjuvant chemotherapy on disease recurrence did not decrease with long-term follow-up, there was an increase in nonlung cancer–related death seen after 5 years in the treatment group. This positive trial demonstrated an absolute benefit at 5 years that was consistent with the previous meta-analysis and provided support for the use of cisplatin-based treatment in the adjuvant setting.

Retrospectively, tissue samples collected from patients participating in the IALT have been analyzed by immunohistochemistry to assess which biomarkers may predict a response to cisplatin therapy. Specifically, investigators have assayed for the enzyme excision repair cross-complementation group 1 (ERCC1).[8] Cisplatin acts by directly binding to DNA and forming platinum-DNA adducts, which prevents DNA replication. It is known that the presence of high levels of ERCC1 is associated with cisplatin resistance due to DNA repair of cisplatin adducts. To study this in the context of the IALT results, 761 tumor samples from that trial were assayed for ERCC1 expression by immunohistochemistry; half of these patients received chemotherapy and the remainder was in the control group. Of the tumors analyzed, 44% were ERCC1 positive. Expression was more common in patients over the age of 55 and those with squamous cell histology. Notably, there was a benefit from adjuvant chemotherapy in patients with ERCC1-negative tumors, with a statistically significant improvement in OS and disease-free survival due to chemotherapy (HR 0.65). In contrast, patients with ERCC1-positive tumors did not achieve a survival benefit from adjuvant chemotherapy compared with the control group. Among patients in the control group, those with ERCC1-positive tumors had an increased survival compared with patients with ERCC1-negative tumors. Although these results are intriguing, ERCC1 levels are difficult to quantify and it is currently not routinely tested in the clinical setting. Its use as a predictive marker for cisplatin-based adjuvant therapy needs to be validated in a prospective clinical trial.

CALGB 9633

The Cancer and Leukemia Group B (CALGB) conducted a trial to test the benefit of carboplatin-based adjuvant chemotherapy

exclusively in stage IB (T2N0) patients.[4] Other studies have included these patients along with those with more advanced disease, and in subset analyses the true benefit of chemotherapy after surgery in this population has been questioned. Originally, this study was intended to enroll 500 patients. However, due to poor accrual, this number was modified and in the final analysis, 344 patients were treated. Patients randomized to the chemotherapy arm received carboplatin dosed to a target area under the curve (AUC) of 6 mg/mL/min and paclitaxel 200 mg/m^2 every 3 weeks for four cycles. This study has been provocative in that it was initially reported in 2004 to be a positive trial with a statistically significant survival advantage, after a median follow-up of 34 months. This prompted the study to be terminated early, and the National Comprehensive Cancer Network (NCCN) practice guidelines adopted the use of adjuvant chemotherapy in stage IB patients. In 2008, when the results were updated after longer follow-up, (mean 74 months), the difference in 5-year survival between the chemotherapy and observation arms (59% vs. 57%, HR 0.83) was no longer statistically significant. However, the 3-year survival difference remained statistically significant, and there was a trend favoring a benefit in OS in the patients who received chemotherapy. Despite this, the routine practice of treating patients with stage IB disease is no longer recommended. In a subset analysis, there was a statistically significant benefit overall, (HR 0.69, $p = 0.43$), in patients with tumors over 4 cm in size who received chemotherapy. This benefit was not shared in those with tumors less than 4 cm in size. Therefore, in practice, many oncologists choose to treat patients with large-stage IB tumors, based on this subset analysis. The reason why the results are negative is not known and may be due to the population of patients being treated, the choice of a carboplatin-based regimen rather than cisplatin, or the abridged number of patients who were treated.

NCIC JBR 10

In this intergroup study, 482 patients with stage IB or II (excluding T3N0) NSCLC were randomized to either surgery or surgery followed by four cycles of chemotherapy.[5] Again, the treatment studied included cisplatin (50 mg/m^2 days 1 and 8) and vinorelbine (25 mg/m^2 weekly); one cycle was 4 weeks. This also was a positive study, with the 5-year survival favoring the chemotherapy group (69% vs. 54%), as well as a statistically significant improvement in disease-free and OS. Toxicity was associated with this regimen with two treatment-related deaths and over 70% of patients experiencing either grade 3 or 4 neutropenia. Other toxicities included fatigue, anorexia, and vomiting.

ANITA

The most recent study of interest is the Adjuvant Navelbine International Trialist Association (ANITA) study, in which 799 patients with stage IB, II, or IIIA NSCLC were randomized to four cycles of chemotherapy or observation after surgery.[6] Similar to the other trials, the chemotherapy regimen consisted of cisplatin (100 mg/m^2, day 1) and vinorelbine (30 mg/m^2, weekly) for a 4-week cycle. The choice of radiotherapy was left to the discretion of the treating physicians, and in the final analysis 24% of patients in the chemotherapy arm and 33% of patients in the observation arm received radiation. Patients who were randomized to chemotherapy had a significant improvement in median survival to 66 months, compared with 44 months in the control group. At 5 years, the absolute benefit in survival was 8.6%, and in a subset analysis this benefit seemed to be mainly noted in stage II and IIIA patients.

Lung Adjuvant Cisplatin Evaluation Meta-Analysis

In 2008, the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group published results of a pooled analysis of large trials (>300 subjects) investigating the use of cisplatin-based adjuvant chemotherapy versus no further therapy following complete resection of NSCLC.[7] The individual data from over 4500 subjects was analyzed with a median of 5.2 years follow-up. The investigators found an absolute benefit of 5.4% improvement in OS at 5 years in the treatment group. There was no interaction seen in regards to gender, age, histology, or type of surgery. However, the degree of benefit varied with stage; the HR for stage IB was 0.93 (95% CI: 0.78–1.10), for stage II HR = 0.83 (95% CI: 0.73–0.95), and for stage III, HR = 0.83 (95% CI: 0.72–0.94). In this analysis, a significant benefit from adjuvant chemotherapy was seen in those with better PS. In patients with Eastern Cooperative Oncology Group (ECOG) PS of 2 – defined as "ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours," – chemotherapy may be detrimental and is not recommended. This analysis confirmed the benefit of cisplatin-based adjuvant chemotherapy following complete resection in fit patients with stage II and III NSCLC. Currently the NCCN and American Society of Clinical Oncology (ASCO) guidelines recommend cisplatin-based adjuvant chemotherapy for stage II and IIIA NSCLC.

Future Directions

Adjuvant cisplatin doublet chemotherapy is currently the standard of care for stage II and IIIA patients. The role of adjuvant treatment of stage IB patients has yet to be defined more clearly, but based on subset analyses, it is possible that patients with tumors greater than 4 cm will benefit from chemotherapy. Given the now-negative results of the CALGB 9633 study, carboplatin cannot be recommended as a standard choice for adjuvant treatment. Hopefully future studies will provide further data to guide the therapy of stage IB patients. Also, although molecularly targeted agents have been studied in the advanced disease stage (as detailed in the following sections), the utility of these agents in the early-stage setting is unknown. To begin to answer this question, the current large intergroup effort that is underway will randomize patients with stage IB (tumor >4 cm), II, and IIIA NSCLC to a cisplatin-based doublet either with or without the antiangiogenesis agent bevacizumab. Adjuvant trials are also underway to assess the role of erlotinib in patients with a sensitizing mutation in EGFR.

LOCALLY ADVANCED NSCLC

The term *locally advanced* includes several different presentations of primary lung cancer, but all have in common the absence of disease outside of the chest. Included in this category are those with stage IIIA or IIIB disease. These tumors involve mediastinal lymph nodes, either ipsilateral (N2) or contralateral (N3), and/or large primary tumors that directly invade important thoracic structures. For example T3 tumors involve the chest wall, the main bronchus less than 2 cm from the carina, or are greater than 7 cm in size. T4 tumors invade the mediastinum and affect structures that are not usually considered resectable (e.g., aorta, esophagus, and vertebral bodies). Mediastinal lymph node invasion should be determined before surgical resection by way of mediastinoscopy or EBUS with FNA, which also allows contralateral mediastinal lymph nodes to be sampled.

About 40,000 cases of stage IIIA and IIIB disease occur per year in the United States. The best treatment approach to locally advanced disease has not yet been determined. A wide array of combined modality approaches have been used in stage IIIA patients (particularly those with N2 nodes). These include varying combinations of chemotherapy, radiation, and surgery. Many studies in which patients with locally advanced disease were treated with chemotherapy, radiotherapy, or a combination of the two have relied on noninvasive determination of the extent of the disease. Thus, on the basis of enlarged ipsilateral mediastinal lymph nodes seen on a computed tomographic (CT) scan, patients were assumed to have N2 disease and were treated without histologic documentation of mediastinal lymph node

TABLE 114-2 Randomized Trials in Stage III Disease: Radiation Alone Versus Radiation and Chemotherapy

		Median Survival				
Number of Patients	Therapy	Survival	1 y	2 y	3 y	Reference
155	RT	9.6	40	13	11	Dillman et al.[10]
	RT/CT	13.8	55	26	23	
353	RT	10	41	14	4	Le Chevalier et al.[9]
	RT/CT	12	51	21	12	
238	RT	10.2	41	17		Mattson et al.[12]
	RT/CT	10.9	42	19		
331	RT		46	13	2	Schaake-Koning et al.[13]
	RT/CT		54	26	16	
			44	19	13	
95	RT	11				Soresi et al.[14]
	RT/CT	16				
240	RT	46	45	13	2	Blanke et al.[15]
	RT/CT	43	43	18	5	

impairment. Such studies are seriously flawed. For meaningful interpretation, accurate histologic staging has to be included as an entry criterion for any study of locally advanced disease.

LOCALLY ADVANCED INOPERABLE OR UNRESECTABLE STAGE III NSCLC

Below are considered treatment approaches based on sequential or concurrent chemotherapy and radiation therapy in the management of locally advanced, inoperable or unresectable Stage III NSCLC.

Chemotherapy Followed by Radiation Therapy

Several prospective, randomized studies have compared radiation therapy alone and radiation therapy in sequence with chemotherapy in the setting of unresectable stage III disease. Le Chevalier et al.[9] randomized 353 patients to radiation alone (6500 cGy) or to cisplatin-based chemotherapy followed by radiation. One-, 2-, and 3-year survival rates all favored the combined therapy arm (51%, 21%, and 12% vs. 41%, 14%, and 4%, respectively). However, using repeat biopsies, the study found only a 17% incidence of local control in the radiation arm and a 15% incidence of local control in the chemotherapy and radiation arm.

In a trial conducted by CALGB, 155 patients were randomized to either radiation alone (6000 cGy) or a cisplatin-based regimen followed by radiation.[10] The median survival favored the combination therapy arm (13.8 vs. 9.7 months). The results at 1 and 2 years were so striking for the combined therapy group that the study was terminated early—a decision that subsequently prompted considerable criticism. The 3- and 5-year survival rates also favored the combination therapy (25% and 19%) over radiation therapy alone (11% and 7%). Unfortunately, the study was limited to patients with a high PS and less than 5% weight loss in the 6 months before enrollment in the trial. Limiting a study to the most favorable patients begs the question of the applicability of the results to the general group of patients with locally advanced lung cancer, many of whom have a decrease in their PS and have lost considerable weight.

A study seeking to confirm the CALGB report was initiated by the Radiation Therapy Oncology Group (RTOG), which randomized patients to the same two arms, in addition to a third arm using hyperfractionation radiation (69.6 cGy twice daily fractions) as the only treatment modality.[11] This study demonstrated that chemotherapy given prior to radiation was indeed superior to radiation alone in the patients with good PS (i.e., loss of weight of less than 5% in the previous 3 months). Analysis at 1 year showed the median survival to be statistically longer for those in the combined chemotherapy and radiation arm. At 3 years follow-up, however, no difference in survival (14%) was observed between the chemotherapy and radiation arm and the hyperfractionated arm. Both of these treatment regimens were better than standard radiation alone (Table 114-2).

Concurrent Chemotherapy and Radiation Therapy

The rationale for concurrent therapy, that is, chemotherapy given during a course of radiation therapy, is based on the concept that some drugs or drug combinations (notably cisplatin) may increase the radiosensitivity of tumor cells. The trade-off, however, is an increase in toxicity and a regimen that is not well tolerated by all potentially eligible patients. A meta-analysis of randomized trials directly comparing platinum-based chemotherapy given concurrently with thoracic radiation to chemotherapy given sequentially with thoracic radiation was performed in 2010.[16] Data from six trials (1205 individual patients) were analyzed. There was a significant benefit to concurrent therapy with an absolute OS benefit of 5.7% at 3 years (HR = 0.84, 95% CI: 0.74–0.95, $p = 0.004$). The primary effect was seen in control of locoregional disease, with no difference in risk of distant recurrence over sequential therapy. The risk of severe esophagitis was increased with concurrent therapy, although pulmonary toxicity was not different. Concurrent platinum chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced, inoperable disease, provided their PS and comorbidities do not limit their ability to withstand the toxicities associated with this approach. Based on small phase II trials conducted by the Southwest Oncology Group (SWOG), a favored regimen for concurrent therapy utilizes cisplatin (day 1, 8, 29, 36) and etoposide (days 1–5, 29–33) with conventional RT.[17–19] For those patients unable to receive cisplatin, due to renal insufficiency or hearing loss, weekly carboplatin and paclitaxel has demonstrated activity in this setting. The OS seen with carboplatin and paclitaxel treatment is less than the control arms of the cisplatin/etoposide studies, although these two chemotherapy regimens have not been directly compared in a randomized trial. For those unable to tolerate a concurrent approach, sequential chemotherapy followed by radiation is a reasonable alternative.

Induction or Consolidation Chemotherapy in Addition to Concurrent Chemoradiation

Although the addition of concurrent platinum-based chemotherapy to thoracic radiation for unresectable stage III NSCLC has been proven to improve local control and OS, disease recurrence at distant

sites remains high. With concurrent therapy, only two cycles of chemotherapy are given during the course of radiation. This is fewer than the four cycles of cisplatin-based chemotherapy that has proven benefit to lessen disease recurrence in the adjuvant setting. This has led to an interest in increasing the amount of chemotherapy given for patients receiving concurrent therapy in locally advanced disease by adding several additional cycles of chemotherapy either prior to (induction) or after (consolidation) the concurrent chemoradiation.

Multiple randomized clinical trials have studied each of these approaches. In a nonrandomized phase II study, concurrent chemoradiation was followed by two cycles of consolidation cisplatin and etoposide, resulting in a median survival of 15 months and a 5-year survival of 15%.[18] A subsequent trial used the same combined treatment regimen, but then switched to docetaxel for consolidation.[19] This yielded a median survival of 26 months and a 3-year survival of 37%. However, a randomized study performed by the Hoosier Oncology Group in which patients received cisplatin, etoposide, and radiation, either with or without consolidation docetaxel, failed to show a benefit from consolidation treatment.[20] This is the first and only randomized study of consolidation therapy after concurrent therapy and radiation. Another favored regimen utilizes low-dose carboplatin and paclitaxel with radiation, followed by consolidation therapy with the same agents. Noncomparative phase II studies of this regimen have demonstrated a median survival of 16 months.[21] CALGB published findings of a phase III randomized study of two cycles of induction chemotherapy with full-dose carboplatin and paclitaxel followed by concurrent weekly dosing with radiation versus concurrent therapy alone.[22] Overall survival was not significantly improved with induction therapy (14 vs. 12 months, $p = 0.3$). Multiple studies have attempted to integrate targeted agents into the treatment of patients with unresectable, locally advanced disease, as consolidation following chemotherapy and radiation, with disappointing outcomes to date.

New Approaches to Concurrent Chemoradiation

Novel approaches to the treatment of locally advanced, nonresectable NSCLC include addition of pemetrexed and/or the monoclonal antibody, cetuximab as radiosensitizers and increasing the dose of radiation to 74 Gy. In 2011, the results of CALGB Trial 30407, a phase II study of pemetrexed and carboplatin administered with concurrent radiation ± cetuximab, were reported.[23] The combination of pemetrexed, carboplatin, and concurrent radiation with an additional four cycles of pemetrexed alone as consolidation met the primary end point of an 18-month survival rate of 58% and was recommended for further study; the addition of cetuximab did not meet statistical significance. The results of PROCLAIM, a phase III study of pemetrexed, cisplatin, and concurrent radiation with pemetrexed consolidation versus cisplatin and etoposide with concurrent radiation and consolidation is awaited. This study will determine if pemetrexed improves outcomes in stage IIIB in those patients with predominately nonsquamous histology. Finally, results of the RTOG 0617 study randomizing patients to standard dose (60 Gy) versus high dose (74 Gy) of chemoradiation ± cetuximab are awaited. The initial planned interim analysis for OS was recently reported, with discontinuation of the high-dose radiation arm due to inferior survival.[23] The results of the addition of cetuximab are pending.

■ LOCALLY ADVANCED RESECTABLE NSCLC

The roles of sequential chemotherapy followed by surgery and concurrent chemoradiation followed by surgery in treating locally advanced, resectable NSCLC are described below.

Chemotherapy Followed by Surgery

Neoadjuvant therapy, also referred to as *induction therapy,* has been applied to the treatment of NSCLC. It entails treating patients with chemotherapy even though there is no clinical evidence that the primary cancer has spread. Lung cancers are particularly attractive targets for neoadjuvant therapy because even though many present as locally advanced disease confined to the chest, patients run a considerable risk of developing distant disease within a short time. Neoadjuvant therapy affords a unique opportunity to assess the sensitivity of the cancer to the drug regimen. This information may be useful in the postoperative period when the possibility of adjuvant therapy is under consideration. Moreover, preoperative neoadjuvant therapy may render resectable a tumor that would otherwise be regarded as unresectable. Another consideration is that the required dose-intensive regimens are apt to be tolerated better before than after surgery. Finally, neoadjuvant therapy may allow for improved drug delivery due to the preserved vasculature of the tumor, and thus may decrease the prospect of developing drug resistance. However, the possibility exists that delaying surgery may be disadvantageous. In patients with locally advanced disease who are at high risk for developing disseminated disease, the delay imposed by the administration of chemotherapy provides an additional period of observation during which a nonresponder may manifest distant disease, thereby precluding surgery.

There have been two phase III randomized trials of neoadjuvant chemotherapy in patients with locally advanced lung cancer (stage IIIA). Some patients had N2 disease alone, while others had T3N0 disease (now considered stage IIB by the 7th edition TNM staging).[24,25] In contrast to results in patients with disseminated NSCLC in whom the response to chemotherapy at best approaches 30%, 60% to 70% of patients with locally advanced disease responded favorably. Also, in both trials, the median survival was improved in the group of patients who received neoadjuvant treatment. The explanation for this difference in responsiveness may be the better overall status of patients who are regarded as candidates for surgery and the smaller tumor burden that these patients bear. Alternatively, qualities inherent in the primary tumor that differ from those in the tumor that has metastasized may contribute to a better response to chemotherapy. Currently, there is no way of assessing the response of micrometastatic disease other than the disease-free interval after resection and the OS.

Another experience with neoadjuvant chemotherapy for NSCLC was reported from the Memorial Sloan Kettering Cancer Center.[26] The study was prospective but nonrandomized. It included 41 patients with "clinical N2" disease defined as bulky mediastinal adenopathy that could be seen on the conventional chest radiograph or was manifested at bronchoscopy by widening of the carina. Patients received a cisplatin-based regimen plus mitomycin. The overall response rate was 77%; 19 of the patients achieved a complete response that was confirmed by histologic examination. Seventy-five percent of patients were able to undergo resection, even though resectability based on previous experience would have been anticipated to be about 10%. It must be emphasized that these patients had bulky mediastinal lymph node disease, not lymph nodes that appeared grossly normal but in whom disease was subsequently detected. The authors concluded that the results obtained paralleled those noted in neoadjuvant studies with other solid tumors in that response rates to chemotherapy were high, and complete resection rates were high after response to chemotherapy. They identified response to chemotherapy as a significant prognostic indicator for survival.

Concurrent Chemoradiation Followed by Surgery

Various theoretical considerations have led to trials of chemotherapy and radiation followed by surgery (trimodality therapy): (1) Tumor cell subpopulations in locally advanced NSCLC may respond differently to radiation and chemotherapy, and cells resistant to one treatment method may be sensitive to the other; (2) chemotherapy may promote the emergence of radiosensitive cells, thereby increasing the total number of cells killed by continued radiation treatments; and (3) induction of cell cycle synchronization by certain drugs may increase cell killing by radiation and induce recruitment of tumor cells in G_0.

SWOG conducted a trial using the cisplatin/etoposide regimen that they had developed with concurrent radiotherapy; the trial included both stage IIIA and IIIB patients.[17] All 126 patients underwent mediastinoscopy for histologic evaluation of mediastinal lymph nodes. The response rate to the preoperative therapy was 59%, with 29% having stable disease. The resection rate was 85% in the stage IIIA patients, and 80% in the stage IIIB patients. The 3-year survival was similar in both stage IIIA and IIIB patients at 27% and 24% respectively. The absence of tumor in the mediastinal nodes at the time of surgery was associated with improved survival. Failure was more common in distant, rather than locoregional, sites with relapse occurring in 26 patients.

It remains to be proven that surgery is a necessary part of the treatment of these patients. The high response rate to chemoradiotherapy in the high-performance patients entered into these clinical trials raises the question of whether chemotherapy and radiation might be able to achieve a similar end point with regard to local control. A large intergroup study addressed this question.[27] In this trial, 396 patients with stage IIIA pathologic N2 disease were randomized to either concurrent chemotherapy with cisplatin/etoposide and radiation to 4500 cGY followed by surgery or the same chemotherapy regimen with radiation to higher doses of 6100 cGy. The patients who were randomized to surgery had a statistically significant improvement in progression-free survival (12.8 vs. 10.5 months); while there was a trend toward an improvement in OS in the surgery group, this was not statistically significant. In an unplanned subset analysis, patients who seemed to do better were those who had a lobectomy rather than a pneumonectomy, as well as those who had obtained a pathologic response in the mediastinal nodes. Although there was no significant benefit in OS, surgery is still often offered to medically fit patients after induction chemoradiotherapy.

In summary, major issues remain concerning the sequence and type of treatment for locally advanced disease. Although some permutation of combined modality treatment is clearly needed in patients with locally advanced disease, we currently do not have data in the form of randomized control studies that compare the efficacy of the varying combinations of chemotherapy, radiation, and surgery. In patients who can tolerate the added toxicity, combined concurrent chemoradiotherapy is more effective than sequential therapy. Although it has not been proven that surgery after induction chemoradiotherapy confers a survival benefit compared to definitive chemoradiotherapy, surgery is still a preferred approach in many institutions if patients can tolerate trimodality treatment. It remains unclear how combined chemoradiotherapy compares to induction chemotherapy followed by surgery or chemoradiotherapy followed by surgery. At the present time, this is a matter of institutional preference as well as the particular characteristics of individual patients.

METASTATIC NSCLC

Cytotoxic chemotherapy remains the recommended first-line therapy for those with metastatic disease without activating mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) translocations, and for all patients as second-line therapy. Because the choice of treatment of metastatic NSCLC is based upon the presence of driver mutations, prompt molecular testing of the tumor biopsy material is of increasing importance. Currently the NCCN recommends the testing of all newly diagnosed nonsquamous cell NSCLC (and all cell types in never-smokers) for EGFR mutations and ALK translocations.[28] If these molecular targets are not identified, standard first-line therapy is a platinum (cisplatin or carboplatin)-based doublet with consideration for adding bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF). In metastatic lung cancer, the goals of chemotherapy are to improve the duration of survival and to palliate the symptoms of disease. The decision to use chemotherapy in the setting of incurable disease is based on patient preference, comorbidities, and PS and requires an ongoing dialogue between the patient and physician throughout the disease course.

FIRST-LINE CHEMOTHERAPY

For patients with adequate PS, the standard first-line chemotherapy recommendations currently consist of a platinum doublet, with several reasonable non-platinum combinations as an alternative. Numerous randomized studies have been conducted that compare the benefits of single-agent versus doublet regimens. A meta-analysis that reviewed 65 of these trials found a significant benefit in response and median survival with a cytotoxic doublet. There was no survival benefit with the addition of a third cytotoxic agent at the time of this analysis. Although there are several cisplatin or carboplatin backbone doublets to consider, carboplatin tends to be favored in the palliative setting due to its better toxicity profile. A large study that was conducted by the ECOG randomized 1207 patients with advanced disease to either cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, or carboplatin/paclitaxel.[29] The median survival among all four treatment groups was 7.9 months, with a 1-year survival of 33% and a 2-year survival of 11%. There was no clear survival benefit with any one regimen compared with the others. Carboplatin/paclitaxel did seem to have a slightly better toxicity profile. Hence, this is a common regimen in use, but the other doublets are acceptable as well.

Pemetrexed, an antifolate, is a relatively new addition to the available agents in the first-line setting. This cytotoxic agent is unique in that efficacy varies by the histology of the NSCLC and it is labeled by the FDA for use in nonsquamous cell NSCLC only. This labeling is based on a phase III trial in which newly diagnosed patients with advanced NSCLC were randomized to either cisplatin/gemcitabine or cisplatin/pemetrexed in the first-line setting.[30] This trial was designed as a noninferiority study and did demonstrate that the doublet cisplatin/pemetrexed was noninferior to a standard doublet with a median OS of 10.3 months. When given with the appropriate folic acid and B12 supplementation, the cisplatin/pemetrexed doublet was associated with less cytopenia and led to a decrease in the need for growth factors and blood transfusions. There was a prespecified histology stratification performed, nonsquamous NSCLC (including adenocarcinoma, large cell carcinoma, and others) versus squamous cell NSCLC. Median OS for the nonsquamous NSCLC histology was 11.0 months for those who received cisplatin/pemetrexed versus 10.1 months for cisplatin/gemcitabine (HR = 0.84, 95% CI: 0.74–0.96). Those with squamous cell histology had a median OS of 9.4 months with cisplatin/pemetrexed versus 10.8 months with cisplatin/gemcitabine (HR = 1.22, 95% CI: 0.99–1.5). As pemetrexed is well tolerated and not associated with alopecia, carboplatin with pemetrexed is a widely used first-line regimen in nonsquamous cell NSCLC.

Two randomized phase III studies have addressed the use of non–platinum-based regimens as first-line treatment. The first, by Kosmidis et al., randomized patients to paclitaxel and gemcitabine versus paclitaxel and carboplatin.[31] The study showed similar efficacy with respect to median survival, 1-year survival, and response rate. Both regimens were well tolerated. The largest study to address the role of non-platinum doublets randomly allocated 929 patients to carboplatin/paclitaxel, carboplatin/gemcitabine, or gemcitabine/paclitaxel.[32] Again, the results indicated similar efficacy in all three arms. There were differences in toxicities in that anemia and thrombocytopenia were more common in the carboplatin/gemcitabine arm, although peripheral neuropathy and alopecia were more common in the paclitaxel containing groups. For chemotherapy-naive patients, treatment choices tend to be heavily dependent on a patient's comorbidities and the toxicity profile of each regimen.

The monoclonal antibody bevacizumab, which targets the VEGF, is approved for first-line treatment of NSCLC when combined with cytotoxic chemotherapy. VEGF, a circulating ligand that promotes angiogenesis, is not mutated in NSCLC, and this therapy, though molecularly targeted, is not specific to the tumor. A large randomized phase III study published in 2006 demonstrated an improvement in OS, 12.3 versus 10.3 months (HR = 0.79, $p = 0.003$) for those patients who received bevacizumab in addition to carboplatin and paclitaxel for advanced NSCLC.[33] Due to the high risk of life-threatening hemoptysis seen in early clinical trials, patients with squamous cell lung cancer or a history of hemoptysis were excluded from this study. As an antiangiogenesis agent, bevacizumab has several unique adverse effects including hemoptysis, hypertension, and proteinuria.[34] When carefully used in patients with advanced lung cancer, bevacizumab is a novel targeted agent that can improve survival.

■ ELDERLY PATIENTS WITH ADVANCED NSCLC

The median age at diagnosis for patients with NSCLC is 65 years; therefore, a significant number of patients diagnosed with advanced disease are elderly (≥70 years). Chemotherapy has been demonstrated to improve survival in the elderly with advanced disease to the same extent as those who are young.[35] Although there is an increase in side effects, particularly cytopenias, advanced age is not a contraindication to chemotherapy. Randomized studies dedicated to the treatment of elderly patients with advanced NSCLC are few, but several have provided needed data for this group. In 1999 a randomized study of vinorelbine versus best supportive care in those ≥70 years demonstrated improved survival in those patients who received single-agent chemotherapy.[36] A follow-up study compared combined vinorelbine and gemcitabine to either agent alone.[37] The combination did not improve outcomes over using single-agent treatment. Due to these findings, national treatment guidelines recommended the use of single agents in the first-line treatment of elderly (70–89 years) with advanced disease. More recently, results of a randomized trial using a carboplatin-based doublet for elderly patients have changed this approach. This study randomized elderly patients to single-agent vinorelbine or gemcitabine versus carboplatin and weekly paclitaxel.[38] Those who received the platinum-based doublet had a higher response rate (27% vs. 10.2%, $p < 0.0001$) and better OS (10.3 vs. 6.2 months, $p < 0.001$). Higher rates of febrile neutropenia were seen with the doublet therapy. This study supports the use of carboplatin and weekly paclitaxel in elderly patients with good PS with close monitoring for associated cytopenia.

■ PATIENTS WITH POOR PERFORMANCE STATUS

Patients with poor PS represent another common group in need of treatment for advanced lung cancer, but underrepresented in randomized clinical trials. Patients with ECOG PS of 2 – defined as "ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours," – often are included in first-line trials, although they represent a small proportion of those enrolled. In 2012 data from a randomized clinical trial dedicated to first-line treatment of patients with ECOG PS 2 was presented.[39] In this study, patients were randomized to pemetrexed alone versus carboplatin and pemetrexed. Those who received the platinum-based doublet had an improved response rate (24% vs. 20%) and an improvement in median OS (9.1 vs. 5.6 months, $p = 0.001$). For those patients with ECOG PS 3 – "capable of only limited self-care, confined to bed or chair more than 50% of waking hours" – cytotoxic chemotherapy is of no known benefit, and best supportive care is recommended.

■ MOLECULAR TARGETED THERAPY

Advances in molecular biology have enabled the search for novel molecular abnormalities in lung cancer that provide insights into tumorigenesis as well as potential therapeutic targets. The identification of "driver mutations," those mutations that drive neoplastic transformation and contribute to tumor progression, has provided at least two clinically important targets to date. The epidermal growth factor receptor (EGFR) is a member of the human epidermal growth factor receptor (HER) family, a group of four transmembrane tyrosine kinase receptors expressed on epithelial cells of many organs, including the lung. In response to ligand binding, EGFR (HER1) forms a homodimer with another EGFR molecule or heterodimerizes with a different HER family receptor (HER 2, 3, or 4). This leads to tyrosine phosphorylation on the EGFR intracellular domain and activation of EGFR's kinase activity, resulting in phosphorylation of target proteins and initiation of downstream signaling. Normal functions of EGFR include epithelial growth and differentiation, cell–cell adhesion, and cell migration.[40]

Many NSCLCs harbor at least one EGFR mutation. Most EGFR mutations are in the tyrosine kinase domain and result in activation of EGFR and unregulated signaling.[41,42] The discovery of these mutations forms the basis for the use of erlotinib and gefitinib, EGFR tyrosine kinase inhibitors (TKI), as a treatment for lung cancer. Certain clinical characteristics are associated with EGFR mutation-positive lung cancer. Mutation-positive cancers are almost exclusively NSCLC, specifically adenocarcinoma.[41] EGFR mutations have been reported in 10% to 15% of Western and 25% to 30% of Asian lung cancer patients. EGFR mutations are significantly more common in women and nonsmokers. The presence of EGFR mutations strongly predicts a response to TKI therapy. One pooled analysis of three prior studies demonstrated a response rate to TKI treatment of 81% in mutation-positive cancers compared to <10% in mutation-negative cancers.[43] Given the poor response of mutation-negative cancers, therapy selection based on molecular characteristics is superior to using standard clinical criteria. However, further analyses have revealed growing complexity and certain EGFR mutations are associated with resistance to TKI treatment. In addition, over time almost all TKI-responsive lung cancers acquire secondary mutations rendering them resistant to further treatment and relapse is inevitable.[44]

The presence of driver mutations allows targeting of mutant proteins that are only present in the lung cancer, avoiding systemic toxicity seen in nontargeted therapy. An oral TKI, erlotinib, received FDA approval based on an improvement in OS seen in a randomized phase III trial of erlotinib versus best supportive care in heavily pretreated NSCLC patients.[45] The identification of specific activating mutations within EGFR that predict disease response to EGFR inhibitors has made routine genetic testing feasible.[46] Multiple randomized clinical trials have demonstrated that patients with activating mutations within EGFR have significant improvement in disease response with decreased toxicity when treated with erlotinib, compared to traditional chemotherapy, as first-line therapy.[47] Due to these findings, it is recommended that all patients with newly diagnosed advanced adenocarcinoma of the lung have their cancer tested for EGFR-activating mutations and treated with erlotinib if a mutation is identified.[48] The most common toxicities seen with EGFR inhibitors are acneform-type rash, diarrhea, and a small risk of interstitial lung disease (<1% in Caucasian patients). Patients treated with EGFR TKIs develop drug resistance on average about 1 year after treatment.[47] Mechanisms of resistance are being studied to provide future targeted therapy in this setting.

Another clinically relevant molecular subset of NSCLC is the one driven by the newly discovered echinoderm microtubule–associated protein-like 4 (EML4) and ALK translocation.[49] The EML4–ALK translocation in NSCLC leads to the constitutive activation of the ALK domain and promotes cell growth and survival. More recently additional fusion partners have been identified with ALK. ALK translocations are found in approximately 2% to 5% of NSCLC,

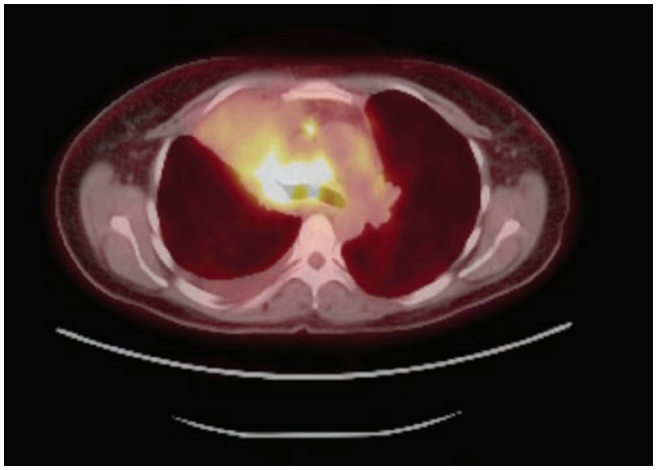

Figure 114-2 CT scan combined with fluorodeoxyglucose positron emission scan (FDG-PET) of a newly diagnosed metastatic lung adenocarcinoma in a never-smoker. This tumor was found to have an echinoderm microtubule–associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) translocation upon fluorescence in situ hybridization (FISH) analysis.

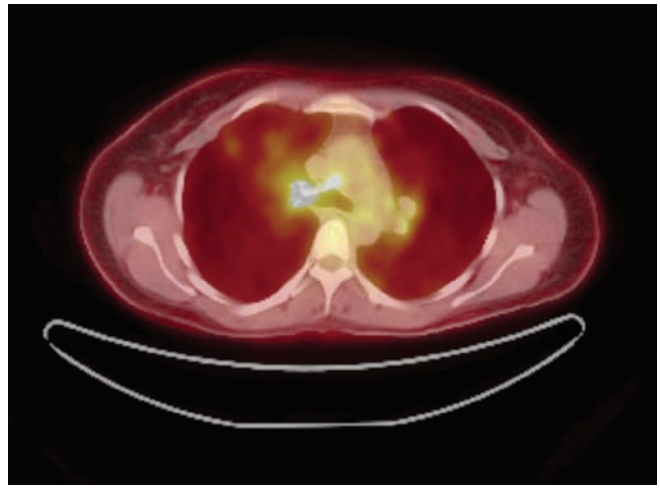

Figure 114-3 CT/FDG-PET scan of the same patient after 3 months of treatment with crizotinib, an oral tyrosine kinase inhibitor. The imaging shows marked disease response. The patient had progressive disease 9 months after starting crizotinib.

most commonly in never-smokers or light smokers with adenocarcinomas. These translocations are rarely found in tumors that harbor activating mutations in EGFR. A recently reported nonrandomized clinical trial of crizotinib, a TKI that targets the ALK kinase domain, demonstrated encouraging rates of disease control (90%) in patients with advanced lung cancer with EML4–ALK translocations.[50] In October 2011, the FDA gave crizotinib approval for treatment of NSCLC with ALK–EML4 translocations (Figs. 114-2 and 114-3).

■ MAINTENANCE THERAPY

Historically, first-line chemotherapy for NSCLC was given for four to six cycles then held, as there was no proven benefit to extending treatment with a doublet past six cycles. If the disease was under control (responded to therapy or stable), all treatment was held and the patient was followed clinically until disease progression. At that time, the patient would be considered for second-line chemotherapy. Over the past few years the availability of drugs that are better tolerated, such as pemetrexed and erlotinib, has enabled investigators to reevaluate this approach and consider maintenance therapy for those with disease control following first-line treatment. Maintenance therapy is given to keep cancer from progressing after response to initial treatment. In NSCLC, maintenance therapy has been divided into two general approaches: Switch maintenance and continuation maintenance. Recent clinical studies have demonstrated an OS benefit with use of maintenance therapy and it has become the standard of care in advanced NSCLC treatment (Table 114-3).

The NCCN defines switch maintenance as "the initiation of a different agent, not included as part of the first-line regimen, in that absence of disease progression, after 4 to 6 cycles of initial

TABLE 114-3 Randomized Trials of Maintenance Therapy in Advanced NSCLC

Trial	Therapy	Number of Patients	Progression-Free Survival (mo)	Median Overall Survival (mo)
Ciuleanu et al.[51]	Platinum doublet ×4, Pem	441	4.3 ($p < 0.0001$)	13.4 ($p = 0.012$)
	Platinum doublet ×4, placebo	222	2.6	10.6
SATURN[52]	Platinum doublet ×4, Erlotinib	438	12.3 wk ($p < 0.0001$)	
	Platinum doublet ×4, placebo	451	11.1 wk	
Fidias et al.[53]	GC ×4, Immediate Docetaxel	153	5.7 ($p = 0.0001$)	12.3 ($p = 0.0853$)
	GC ×4, Docetaxel upon progression	156	2.7	9.7
PARAMOUNT[54,55]	Cis/Pem ×4, Pem	359	4.1 ($p < 0.0001$)	13.9 ($p = 0.0195$)
	Cis/Pem ×4, placebo	180	2.8	11.0
AVAPERL[56]	Cis/Pem/B ×4, Pem/B	117	10.2	
	Cis/Pem/B ×4, B	110	6.6	
POINTBREAK[57]	C/Paclitaxel/B ×4, B	467	5.6 ($p = 0.012$)	13.4 ($p = 0.949$)
	C/Pem/B ×4, B/Pem	472	6.0	12.6
IFCT-GFPC 0502[58]	Cis/G ×4, G	154	3.8 ($p < 0.001$)	12.1 ($p = 0.387$)
	Cis/G ×4, Erlotinib	155	2.9 ($p = 0.003$)	11.4 ($p = 0.304$)
	Cis/G ×4, placebo	155	1.9	10.8

Pem, pemetrexed; G, gemcitabine; C, carboplatin; Cis, cisplatin; B, bevacizumab.

therapy."[28] Pemetrexed and erlotinib have been shown to improve progression-free survival and OS as maintenance therapy following disease control with platinum-based doublet chemotherapy. Ciuleanu et al.[51] investigated the use of pemetrexed as switch maintenance in nonsquamous NSCLC and reported an improvement in OS of 13.4 months versus 10.6 months ($p = 0.012$) in those who did not receive further treatment until disease progression. In a similar study design SATURN, a randomized placebo-controlled trial, demonstrated OS improvement in an unselected patient population that received erlotinib as switch maintenance following first-line chemotherapy.[52] For the overall patient population the progression-free survival in the erlotinib group was 12.3 weeks versus 11.1 weeks for the control group ($p < 0.0001$), with OS of 12 months versus 11 months ($p = 0.0088$). The improvement in progression-free survival, in a subgroup of those with an activating mutation in EGFR, was dramatic, 44.6 weeks versus 13 weeks ($p < 0.0001$). Overall survival benefit was not seen in this subgroup, presumably due to crossover to a TKI in the placebo arm upon progression.

Docetaxel has also been studied as a switch maintenance therapy compared to docetaxel upon disease progression.[53] This study essentially compared immediate versus delayed docetaxel and found an improvement in progression-free survival and OS for those who started docetaxel immediately following first-line treatment. However, the difference in outcome could be explained by the low number (60%) of patients in the delayed arm who actually received drug. When subjects who received docetaxel in the delayed arm were compared to those in the immediate docetaxel arm, no difference was seen. Careful monitoring of patients while on a treatment break following first-line therapy with prompt administration of second-line docetaxel is a reasonable alternative approach, particularly for patients with squamous cell cancer when pemetrexed is not a maintenance option.

Continuation maintenance is "the use of at least one of the agents given in the first line, beyond four to six cycles, in the absence of disease progression."[28] There are several agents that were originally approved for use in the first line that have been used in this fashion. For example, in ECOG 4599, bevacizumab is continued until disease progression even after the carboplatin and paclitaxel are held after four to six cycles. This is also true of the TKIs, erlotinib and crizotinib, when used as first-line treatment for those with target mutations. Pemetrexed has been studied as a single agent given as continuous maintenance when used as part of platinum-based doublet in the first line.[51] PARAMOUNT, a randomized trial of continuous maintenance pemetrexed following first-line treatment with cisplatin/pemetrexed, demonstrated an improvement in performance-free survival when compared with placebo: 4.1 months versus 2.8 months ($p < 0.001$) after randomization.[54] There is also preliminary data to suggest an OS advantage to the continuous use of pemetrexed (13.9 vs. 11.0 months).[54] As a result, the current recommendation is to continue pemetrexed until disease progression in those with disease control following cisplatin (or carboplatin) and pemetrexed. As many oncologists are now using carboplatin, pemetrexed, and bevacizumab as first-line treatment of nonsquamous NSCLC, studies are currently underway to determine the best continuous maintenance strategy in this setting. One of these studies, AVAPERL, randomized patients to bevacizumab/pemetrexed versus bevacizumab alone as continuous maintenance in this setting.[56] Preliminary data from this trial suggested that the use of pemetrexed and bevacizumab together in the maintenance setting was associated with superior progression-free survival (10.2 vs. 6.6 months). However POINTBREAK, an open-label, randomized, phase III study comparing carboplatin, paclitaxel and bevacizumab with bevacizumab as maintenance to carboplatin, pemetrexed and bevacizumab with bevacizumab and pemetrexed as maintenance found no difference in OS.[57] Finally, a recently published study investigated the use of gemcitabine as continuous maintenance following cisplatin/gemcitabine induction chemotherapy.[58] This study included a significant number of patients with squamous cell carcinoma. Progression-free survival was significantly improved in those who received gemcitabine versus placebo following induction chemotherapy. Overall survival benefit was seen in those who received gemcitabine after an objective response to induction therapy, but not those with stable disease. This suggests that gemcitabine is a reasonable agent to use as continuous maintenance in patients with squamous cell carcinoma with response to platinum-gemcitabine in the first line.

SECOND-LINE THERAPY

Ultimately, patients with advanced disease will progress after receiving first-line therapy, with or without maintenance treatment. There are several options to consider in the second-line setting, and selection of the appropriate agent depends on histology, ECOG PS, and previous treatment. Docetaxel was one of the first agents approved for this indication. In the first trial of interest, 104 previously treated patients were randomized to docetaxel every 3 weeks at 100 mg/m^2, 75 mg/m^2, or to supportive care.[59] Docetaxel therapy resulted in an improvement in median survival (7.5 vs. 4.6 months) and 1-year survival (37% vs. 11%). The lower dose of docetaxel was better tolerated. In another study, 373 patients who progressed after platinum therapy were randomized to docetaxel at one of two schedules, ifosfamide or vinorelbine. Treatment with docetaxel at 75 mg/m^2 was associated with a higher response rate as well as an improvement in 1-year survival.[60] Interestingly, there was no difference in OS between the four groups.

In a phase III trial of pemetrexed in NSCLC, 571 patients were randomized to docetaxel or pemetrexed in the second-line setting.[61] Survival was similar in each arm with a median survival of 8.3 and 7.9 months for pemetrexed and docetaxel, respectively. The 1-year survival was 29.7% in both groups. Although survival with pemetrexed was not improved compared to docetaxel, pemetrexed was better tolerated with a significant decrease in the incidence of grade 3 or 4 neutropenia and febrile neutropenia events.

Erlotinib has also proven to be beneficial in the second- and third-line setting and is the only agent with data to support its use in those with ECOG PS 3.[45] In a large multicenter trial, 731 patients with stage IIIB or IV disease who were previously treated with first- or second-line therapy were randomized to either erlotinib or placebo in a 2:1 randomization favoring erlotinib. Patients with an ECOG PS of 0, 1, 2, and 3 were eligible. The response rate to erlotinib was 8.9%, with an OS of 6.7 versus 4.7 months in the placebo arm. In addition, there was an improvement in cancer-related symptoms in patients who received erlotinib. This was a significant survival benefit, and based on this study, erlotinib obtained FDA approval in the second-line setting. A small percentage of patients required dose reductions or were taken off of therapy due to drug-related toxicity. This study was performed prior to routine molecular testing for activating mutations within EGFR. In a subgroup analysis of this study, patients who had an increased likelihood of a response included those who were never-smokers, of Asian origin, female, or who had the adenocarcinoma histology.

FUTURE DIRECTIONS IN THE TREATMENT OF METASTATIC NSCLC

The integration of agents that target signal transduction and other biologically relevant pathways are beginning to make an impact in the care of patients and in the design of future trials for NSCLC. Although responses and survival benefits are currently modest, one avenue of research is to combine multiple agents with nonoverlapping mechanisms of action and toxicity profiles to have obtained a

greater clinical benefit. Now that the number of biologic agents in development is increasing at a faster pace, future research will focus heavily on learning more about patterns of resistance and determining which biomarkers will predict responsiveness to each agent and regimen. In addition, unique immunotherapeutic agents that facilitate an autoimmune response to solid tumors are showing promise in NSCLC and further clinical studies are eagerly awaited with this novel class of drugs.

CONCLUSION

Chemotherapy has an established role in the adjuvant therapy of stage II and IIIA NSCLC. Randomized clinical trial data demonstrate improved median and long-term survival when antineoplastic agents are used as part of a multimodality approach. The next step in the development of adjuvant regimens will be to add molecular targeting agents; these trials are already underway.

Response rates to chemotherapy are higher in patients with localized disease than in those with disseminated disease. Some of these differences may be related to tumor burden or overall PS. Questions that need to be addressed in future and ongoing trials include the optimal sequence for various modalities and the best modalities for each situation in locally advanced disease. For advanced-stage NSCLC, there is now a growing list of active agents. However, especially for heavily pretreated patients and those with a poor PS, response rates and overall prognosis are still limited. There are data to suggest that cytotoxic and biologic agents can modestly increase survival and improve a patient's quality of life. However, even in the most recent phase III trial with bevacizumab in the advanced setting, the median survival barely increased over the 1-year mark. Thus, there is still considerable room for improvement. Cost/benefit analysis is another consideration, as the newer agents are especially expensive. With the development of molecular agents and the future potential to select treatment options based on genomic and proteomic profiles, there is cautious optimism that the treatment of NSCLC will continue to improve in the future.

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CHAPTER 115

Treatment of Non–Small-Cell Lung Cancer: Radiation Therapy

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Lung cancer is the second most common malignancy in the United States, after prostate cancer among men and breast cancer among women, but the number one cause of cancer-related mortality in both genders. Non–small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers.[1] Most patients with NSCLC receive radiotherapy as part of their treatment, either as initial management or later in the course of their disease. This may include thoracic radiotherapy and/or irradiation of sites of metastatic disease.

Thoracic radiotherapy for NSCLC can be categorized as follows:

- Neoadjuvant = preoperative
- Adjuvant = postoperative
- Definitive = cure without surgery as treatment goal; with or without chemotherapy
- Palliative = directed at relief of thoracic symptoms

There is some overlap in these categories with respect to the goals of treatment. For example, most patients treated with definitive intent are not cured but do achieve palliation of thoracic symptoms. Similarly, a few patients originally considered to be technically unresectable may have a dramatic response to irradiation and/or chemotherapy, and the goal of treatment may then change from palliative to neoadjuvant or definitive intent.

The size of the primary lesion, stage, and total dose of radiation are important factors in determining the likelihood of achieving local control. A summary of radiotherapy for lung cancer is provided in Table 115-1.

The decision to utilize thoracic radiotherapy as part of the therapeutic regimen, and the treatment goals of such therapy, depend not only on tumor-related factors such as stage but also on patient-related factors such as pulmonary reserve and performance status. All these factors need to be considered when deciding whether to irradiate. Although radiotherapy might be appropriate for a patient with a postoperative forced expiratory volume (FEV_1) of 2 L and pathologic stage T2N2M0 disease, the same treatment would be problematic in a patient with a postlobectomy FEV_1 of 1.1 L who has had a series of postoperative complications. Of course, such clear-cut cases usually are the exception rather than the rule in clinical oncology. Table 115-2 lists the relative contraindications to thoracic radiation for lung cancer.

Finally, it must be remembered that the prognosis for most patients with lung carcinoma remains poor with standard therapy, and a concerted effort should be made to enter patients into clinical trials that are investigating new treatments or combinations of treatments for this disease.

THORACIC RADIOTHERAPY MANAGEMENT STRATEGIES

Surgery, irradiation, and chemotherapy are all used in the treatment of NSCLC and are based on the stage of the disease at presentation. Staging for all patients should include PET-CT scan, and selected patients should have bronchoscopy with endobronchial ultrasound (EBUS)-guided sampling of intrathoracic lymph nodes

TABLE 115-1 Summary of Radiotherapy for Lung Cancer: Indications and Treatment

Type	Indication(s)	Dose[a]
Preoperative (with chemotherapy)	Pancoast tumor; clinical N2	45–50 Gy
Postoperative	N2 disease; T4 tumors; selected T3 and/or N1 disease; incomplete resection	50–66 Gy (depends on surgical pathology findings)
Definitive medically inoperable	T1–2N0–1 not surgical candidate or refuses surgery	60–74 Gy (conventional fractionation) or 40–60 Gy (accelerated hypofractionation with stereotactic techniques)
Definitive unresectable (with chemotherapy)	Selected stage III patients; performance status high	56–74 Gy
Palliative unresectable	Other stage III and IV patients with local symptoms	20–50 Gy with accelerated hypofractionation (2.5–4 Gy fraction size)
Small cell (with chemotherapy)	Limited stage with good performance status	45–55 Gy or in 1.5 Gy bid fractionation

[a] *1.8–2 Gy once daily fractionation unless otherwise indicated.*

or mediastinoscopy, and MRI of the brain. Surgical resection remains the primary curative modality and may be the only treatment required in early-stage disease. The local failure rate in stage I patients after lobectomy or pneumonectomy is less than 10%. With such a low incidence of local failure the addition of postoperative irradiation is unnecessary if resection margins are negative. Unfortunately, many patients present with locally advanced, unresectable, or marginally resectable disease. In marginally resectable NSCLC, the addition of radiation and chemotherapy is aimed at decreasing the high frequency of failure due to local and distant spread that occurs with surgery alone. However, progress has been slow, and the overall survival of patients with locally advanced lung cancer has only increased modestly over the past 20 years.

NEOADJUVANT THERAPY

The current use of preoperative radiotherapy in the management of NSCLC falls into two categories: (1) as part of neoadjuvant chemoradiotherapy for N2 (IIIA) disease; and (2) as part of neoadjuvant chemoradiotherapy for superior sulcus (Pancoast) tumors (T3-4NxM0). For patients who are otherwise surgical candidates but are found at mediastinoscopy to have positive mediastinal lymph nodes (N2 disease), it is not clear whether neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy; either is an acceptable option.

N2 Disease

Conceptually, it has become attractive to attempt to convert bulky mediastinal nodal disease to microscopic mediastinal nodal disease, thereby rendering the patient suitable for surgical resection. Two large randomized trials were conducted to compare surgical versus nonsurgical management for highly selected patients with stage III disease.[2,3] These studies demonstrated the safety and feasibility of the surgical approach, but no definitive improvement in survival by adding surgery to chemoradiotherapy. However, secondary analyses suggested a favorable outcome in patients who had a pathologic complete response after neoadjuvant therapy. Patients undergoing lobectomy after neoadjuvant therapy appear to have better outcomes than patients who require pneumonectomy. Despite several large phase III randomized trials, the optimal approach remains unclear. Options include chemotherapy followed by surgery, chemoradiotherapy followed by surgery, and definitive chemoradiotherapy alone. The median and 5-year survival rates for these three options appear to be similar. There is evidence that induction chemotherapy or chemoradiotherapy followed by pneumonectomy (particularly right pneumonectomy) may be excessively toxic, with the previously mentioned studies reporting treatment-related mortality rates above 20%. In contrast, induction therapy (chemotherapy or chemoradiotherapy) followed by lobectomy appears to be well tolerated.[2–4]

Chemoradiotherapy followed by thoracotomy is an intensive treatment with considerable morbidity and mortality. Its use should be limited to patients with excellent cardiac and pulmonary reserve and a high performance status. Preferably this combination should be used in the context of a prospective clinical trial. Only patients with reasonable expectation of benefit should receive this form of aggressive management; thorough staging workups for metastatic disease should be performed prior to the start of preoperative treatment and in the "window" period (i.e., after this therapy has been administered and before surgery). Lesions that are suspected of being distant metastases should be investigated by tissue biopsy. The radiotherapy dose should be moderate, approximately 45 to 50 Gy, with standard fractionation (1.8–2 Gy once daily). An interval of approximately 3 to 8 weeks between completion of irradiation and surgery is advised to minimize the risk of difficulties in wound healing. Bronchial stump reinforcement at the time of surgery is strongly encouraged. As noted, right pneumonectomy after neoadjuvant chemoradiotherapy has a high mortality rate and should be avoided.

Preoperative radiotherapy carries with it the potential disadvantage of limiting the ability to give additional radiotherapy if the tumor proves to be unresectable or if residual disease remains after resection. After 45 Gy preoperatively, only about 30 Gy of additional irradiation can be safely administered postoperatively. Thus, it may be preferable to defer additional radiotherapy unless or until there is clear evidence of local progression. Chemotherapy may be offered, although in general, the patient left with residual or unresectable

TABLE 115-2 Relative Contraindications to Thoracic Radiotherapy for Lung Cancer

Prior high-dose thoracic radiotherapy (RT)
Connective tissue disease
FEV_1 <800 cc
Tracheobronchial–esophageal fistula
Projected RT fields to include >35% of normal lung volume (i.e., >40% of normal lung volume is projected by three-dimensional treatment plan to receive >20 Gy)
Projected RT fields to include >50% of heart volume
Patient expected to be noncompliant with treatment or follow-up visits

disease after preoperative chemoradiotherapy has a low likelihood of achieving long-term disease-free survival.

Superior Sulcus (Pancoast) Tumor

Superior sulcus tumors are uncommon lung cancers and account for only 3% of all lung cancer cases. They deserve special consideration as they can invade blood vessels if located anteriorly, brachial plexus if located in the middle or the stellate ganglion, or vertebral bodies if located posteriorly. These syndromes can cause extremely debilitating symptoms that are difficult to manage. In addition to the routine staging workup, MRI scan of the chest and/or spine may be very valuable to rule out any brachial plexus or vertebral body invasion.

Treatment depends on the extent of the disease. Presence of hilar or mediastinal nodal involvement is associated with poorer outcome. Single center studies have reported improved outcome using preoperative radiotherapy with or without chemotherapy. A phase II study by SWOG (SWOG 9416/INT0160) showed 2-year overall survival of 55% in T3–4N0 superior sulcus tumors.[5] In most institutions, preoperative chemoradiotherapy is standard management for superior sulcus tumors, with excellent outcome. However, selected patients may undergo surgery first followed by adjuvant treatment. In patients who are not candidate for surgical resection, concurrent chemoradiation is the preferred treatment approach.

■ ADJUVANT THERAPY

The primary tumor-related factors considered in decisions about the need for postoperative radiotherapy (PORT) are the pathologic stage and the completeness of the surgical resection. PORT is generally considered to be the standard of care for patients with resected ipsilateral mediastinal node–positive (N2) NSCLC, based in part on a Lung Cancer Study Group Trial that demonstrated a longer relapse-free survival with PORT in this subgroup.[6] There is no role for PORT for T1-2N0 tumors completely resected by lobectomy or pneumonectomy. The role of PORT for T1-2N1 tumors is questionable; in fact, there is the suggestion of a slight detrimental effect of PORT on overall survival. It is less clear whether radiotherapy should be administered after a wedge resection, although in selected patients, the high local failure rate after this procedure suggests a possible role for adjuvant radiotherapy.[7] Phase II data suggest that the combination of wedge resection plus brachytherapy results in local failure rates below 5%, comparable to that of lobectomy, and this approach can be considered in this situation. A multicenter phase III trial suggested sublobar resection with brachytherapy is feasible without any increase in morbidity compared to sublobar resection alone, and with low mortality at 30 and 90 days in high-risk patients with NSCLC.[8]

Whether PORT for stage IIIA NSCLC (N2-positive disease) has any impact on survival is debatable. Although many retrospective studies have shown a survival benefit to PORT, prospective, randomized trials have not. In fact, a highly publicized meta-analysis of randomized trials of surgery alone versus surgery plus PORT showed a detrimental effect of PORT on survival for lower stage.[9] This negative effect of PORT was very strong for stage I disease and modest for stage II disease; there was no evidence of any detrimental effect of PORT in stage III disease. The reasons for excess deaths in the PORT arm were not addressed, though likely attributable to radiation-induced cardiopulmonary toxicity. It should be noted that the legacy randomized trials included in the PORT meta-analysis and also in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute all used radiotherapy techniques that would be considered outdated by modern standards.

A more recent study utilizing the SEER database looked at the role of PORT in resected NSCLC. There was no difference in survival for the overall group but a subgroup analysis suggested increased survival with PORT in the N2 subgroup and decreased survival in N0–1 subgroups.[10] Douillard et al.[11] retrospectively analyzed patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial, and found a benefit to PORT in patients with IIIA/N2 disease.

Future studies of PORT should focus on stage III disease and selected stage II disease, and on coordinating selective use of PORT with adjuvant chemotherapy. The majority of patients with node-positive resected NSCLC probably harbor micrometastatic disease outside of the thorax and thus adjuvant chemotherapy is appropriate. However, the risk for potentially morbid local–regional recurrence also exists in these patients. Further research is needed to better identify which patients are at very high risk for local–regional recurrence and thus most likely to benefit from PORT. If more effective therapy to prevent distant disease is developed, then the improvement in local control may lead to consistent significant increases in survival.

When employing PORT, meticulous radiotherapy treatment planning is essential to minimize risks of toxicity. Radiotherapy fields should be relatively modest in size, yet include the high-risk regions of the bronchial stump, ipsilateral hilum, and the portion(s) of the mediastinum considered high risk for regional recurrence. If resection margins are negative and if there is no chest wall invasion, there is no reason to irradiate the "tumor bed"; doing so would only increase toxicity by irradiating that portion of remaining lung that has filled into the space left by the lobectomy. A radiation dose of 50 to 55 Gy using a standard fractionation schedule (1.8–2 Gy per day) should provide excellent local and regional control. Higher doses may be reasonable if resection margins are compromised and the patient has excellent underlying cardiopulmonary function.

Patients who undergo incomplete resection (gross residual disease) or suffer local recurrence after surgery alone have a poor prognosis, although radiation is usually used in an attempt to maximize local control. These patients should be considered to have the equivalent of locally advanced, nonoperative NSCLC and treated accordingly, potentially with definitive intent (see the following).

■ DEFINITIVE THERAPY (LOCALLY ADVANCED, NONOPERATIVE NON–SMALL-CELL LUNG CANCER IIIA OR IIIB)

Patients who do not have demonstrable distant metastases but have locally advanced, unresectable disease are often referred for radiation therapy, with or without chemotherapy. For nonoperable (stage IIIA and IIIB) patients, combined chemotherapy and radiation therapy is often considered as the standard of care in patients with good performance status and no other significant medical comorbidities.[12] Because combined modality therapy has considerable toxicity and requires a high level of patient time, commitment, and expense, intensive chemoradiotherapy generally should be limited to patients whose Karnofsky scores are 70% or greater. Significant weight loss, defined in most cooperative group trials as greater than 5%, is also a relative contraindication to aggressive combined modality therapy as it carries a poor prognosis. Although age itself is not a contraindication to combination therapy, intensive regimens should be applied cautiously in patients more than 70 years old. Notably, the median age averaged 60 years in most of the trials utilizing chemoradiotherapy. Although large tumor size is not a contraindication to definitive treatment, larger tumors generally result in a larger portion of normal tissue (lung, heart, and esophagus) being included in a radiotherapy portal, and the resultant high-dose irradiation may carry an unacceptable risk of complications. The location of the tumor (e.g., proximity to the heart and/or extensive involvement of the right lower lobe of the lung) and the patient's pulmonary reserve may also influence the decision regarding definitive irradiation. Supraclavicular adenopathy (N3 disease) is not an absolute contraindication for definitive therapy, although its presence is a poor prognostic indicator.

There is now strong evidence that concurrent chemoradiotherapy is better than sequential induction chemotherapy followed by

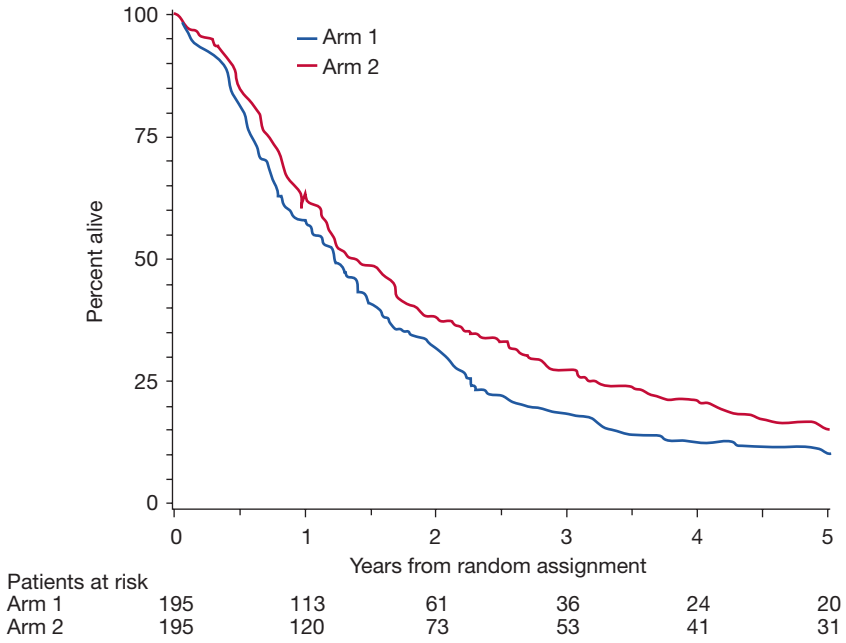


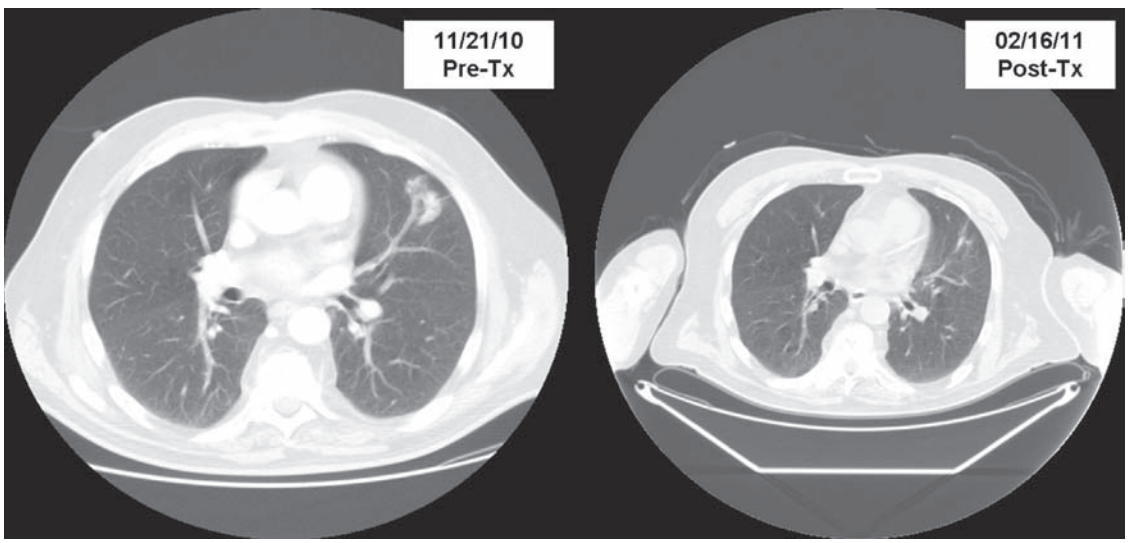
Figure 115-1 Five-year survival results for patients assigned to recrive standard radiation with concurrent chemotherapy compared with patients assigned to receive sequential chemotherapy and radiotherapy. Hazard ratio for death = 0.812, 95% confidence interval = 0.663 to 0.996, $P = .046$, two-sided log-rank test. Total dead at any time: Arm 1 = 189 and Arm 2 = 185. **Slash marks** indicate censored observations. *(Reproduced with permission from Curran WJ Jr1, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 941. J Natl Cancer Inst. 2011;103(19):1452–1460.)*

radiotherapy. Several randomized trials have addressed this topic, and most show a clear benefit in local–regional control, median survival, and 2- and 3-year survival in favor of concurrent therapy (Fig. 115-1).[13–15] A meta-analysis showed significant overall survival benefit with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years. The concomitant treatment also reduced locoregional progression significantly but there was no difference in distant progression between the sequential or concurrent treatment.[16] Long-term toxicity rates appear similar between sequential versus concurrent chemoradiotherapy; however acute toxicity with esophagitis is markedly increased with concurrent therapy without any increase in acute pulmonary toxicity.[16]

The conventional dose fractionation schedule used for definitive irradiation is 60 to 66 Gy in standard fractionation (1.8–2 Gy once daily). The maximum tolerated dose of irradiation is probably higher than that for small- to medium-sized tumors in which the amount of normal tissue in the field is low. However, preliminary results from a randomized trial did not show a benefit to 74 Gy as compared with 60 Gy.[17] The standard chemotherapy drugs are a platinum-based doublet regimen. Figures 115-2 and 115-3 show examples of radiographic response to combined chemoradiotherapy in two patients with NSCLC.

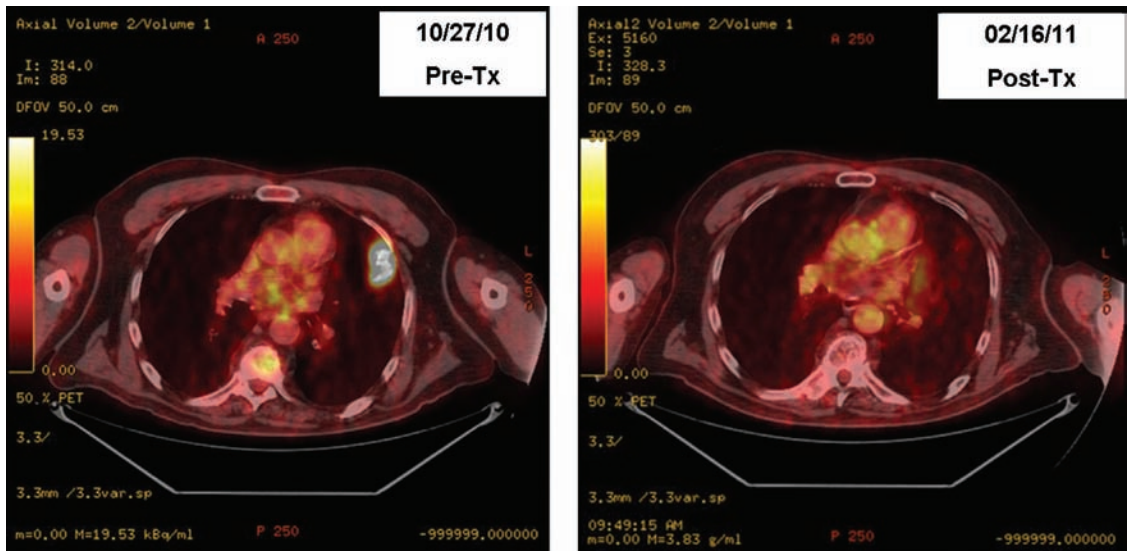
For many years, the fields to be treated in the definitive therapy of NSCLC have followed the Halsted principle of "radical en bloc" locoregional therapy (Fig. 115-4). The typical radiotherapy field encompassed the primary tumor (with approximately 2 cm margin), both the ipsilateral and contralateral hila, and the entire mediastinum from the thoracic inlet to a point at least 5 cm below the carina. Elective supraclavicular nodal irradiation was also typically used for upper lobe cancers. This usually results in a field size measuring approximately 16 ×20 cm, which incidentally irradiates a large amount of normal tissue. With this technique, it has been estimated that greater than 30% of a patient's normal lung tissue is exposed to a dose of irradiation expected to cause permanent fibrosis.

Because of these issues, in recent years there has been a trend toward smaller field size in definitive radiotherapy, encompassing gross disease with an appropriate margin and fewer areas of "prophylactic" nodal stations (Fig. 115-5). This evolution has been accelerated by improvements in preradiotherapy imaging (e.g., PET scan–based treatment planning) and the addition of chemotherapy to control microscopic disease).[18] Several studies have confirmed nodal failure to be 7% to 10% if prophylactic nodal irradiation has been omitted.[19,20] The use of smaller field sizes makes radiotherapy better tolerated and offers the possibility for higher doses of radiotherapy in



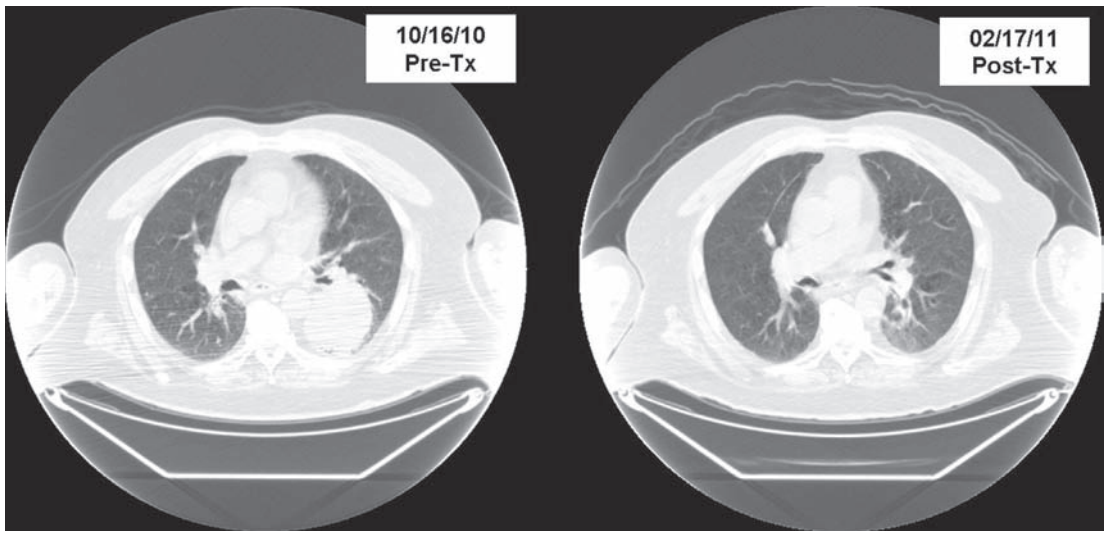
A

Figure 115-2 **A.** Pre- and postchemoradiotherapy CT scan of a patient with T1N2M0 non–small-cell lung carcinoma of the left upper lobe lung region. *(continued)*

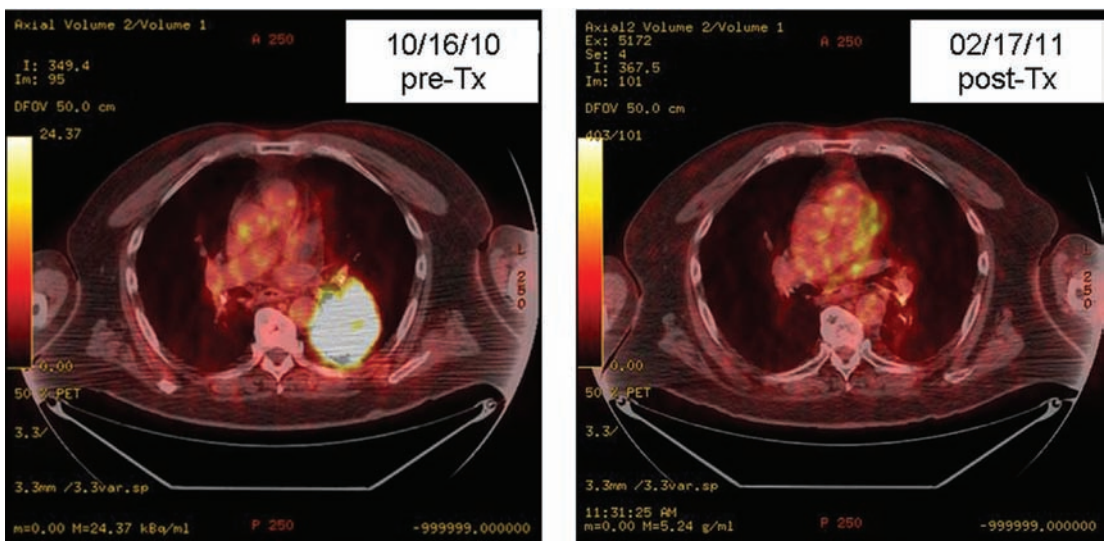


B

Figure 115-2 *(Continued)* **B.** Pre- and postchemoradiotherapy PET scan of the patient in **A**.



A



B

Figure 115-3 **A.** Pre- and postchemoradiotherapy CT scan of a patient with medically inoperable T3N1 non–small-cell lung carcinoma in left lower lobe lung. **B.** Pre- and postchemoradiotherapy PET scan of the same patient shown in **A**. *(Data from multiple prospective trials of the Radiation Therapy Oncology Group (RTOG) and other clinical trials.)*

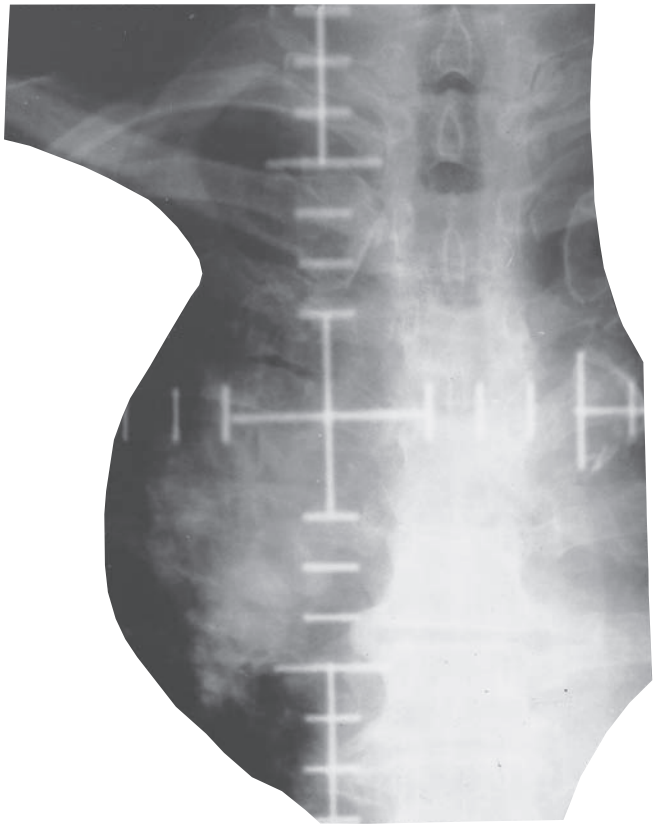
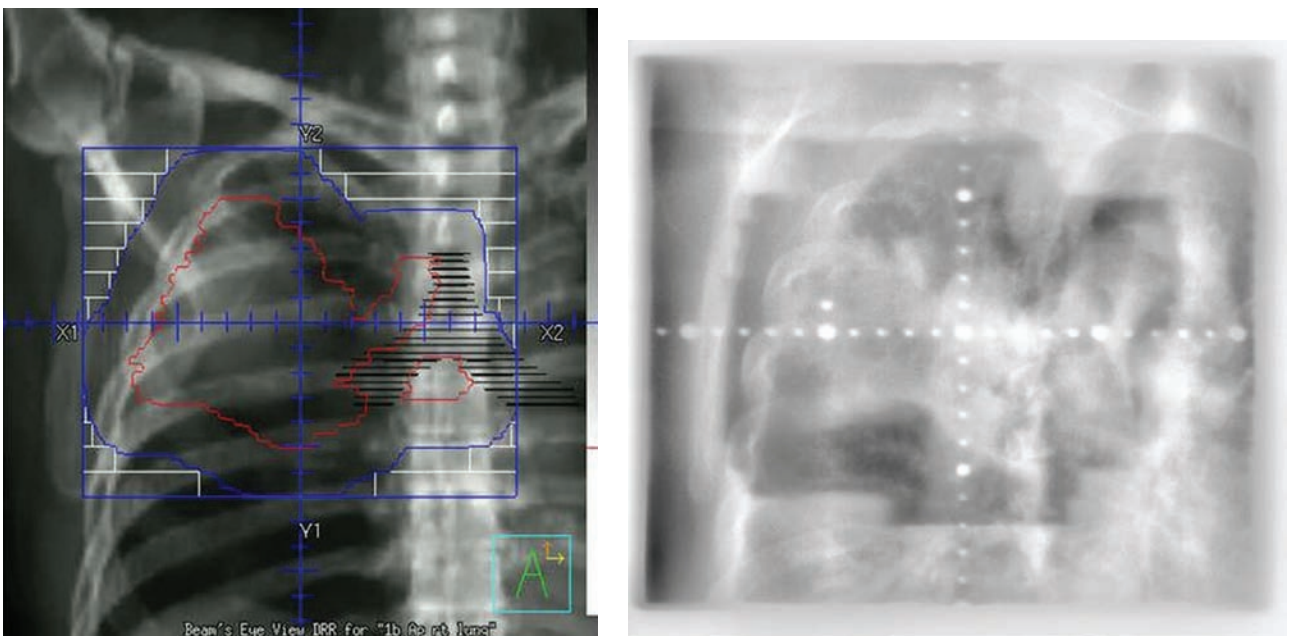


Figure 115-4 Radiotherapy simulation film (highly magnified) of a patient with medically inoperable NSCLC. The area being irradiated is showing here with the actual radiation field. CT-assisted radiation dosimetry revealed the amount of normal lung tissue in the treated field to be under 15%.

combination with chemotherapy. A concern about local failure just outside of the irradiated volume (also known as "marginal miss") with these newer techniques exists; however, the risk of this kind of failure appears to be relatively low compared with central local or distant failure. Most studies show that the risk for a marginal miss recurrence is between 5% and 10%, compared with 30% to 60% risk for central local recurrence and/or distant metastases. A randomized trial that enrolled 200 patients with inoperable stage III NSCLC showed similar 5-year survival rates with "involved field" irradiation versus elective nodal/comprehensive irradiation. Notably, overall response rates and local control rates were better, and toxicity lower, in association with use of the smaller fields.[21]

Through advances in chemoradiotherapy over the past 20 years, there have been improvements in the prognosis for locally advanced, unresectable NSCLC, as reviewed in Table 115-3. With supportive care alone (e.g., antibiotics, expectorants, oxygen, etc.) expected survival is less than 6 months and only about 5% of patients are alive at 2 years. Single-agent radiotherapy improves the median survival to about 9 months, with approximately 20% of patients alive at 2 years. Sequential induction chemotherapy followed by radiotherapy further improves these values to approximately 14 months and 33%, whereas concurrent chemoradiotherapy increases these values to 17 months and 40%, respectively. Several phase II studies incorporating newer chemotherapy agents/schedules with modern radiotherapy have reported median survival of about 2 years, with approximately 20% 5-year survival. Interpretation of these improved outcomes is confounded by patient selection bias and stage migration, particularly with the widespread use of PET scan–based staging. Improvement in supportive care is also likely a contributing factor. However, the improvements in the prognosis for stage III nonoperative NSCLC are well documented by large, prospective randomized trials and should be considered valid. It must be stressed that the trials in which the outcomes were positive involved patients with good performance status, absence of malignant pleural effusions, and minimal weight loss.[22] Not all patients with presumed unresectable disease would benefit from highly aggressive concurrent chemoradiotherapy.



A B

Figure 115-5 **A.** Digitally reconstructed radiograph (DRR) (radiation planning) film for "radical en bloc" radiotherapy for a patient with T4N2M0 non–small-cell lung carcinoma of the right upper lung. The actual area being irradiated is inside the *blue boundaries*. All other areas are shielded via primary collimation or secondary multileaf collimation. **B.** Portal imaging of the same field in (**A**) taken on the actual treatment machine verifying the treatment field.

TABLE 115-3 Review of Relative Efficacy of Various Treatments for Locally Advanced Nonoperative but Nonmetastatic Non–Small-Cell Lung Carcinoma

Treatment	Approximate Local Response Rate (%)	Approximate Median Survival (mo)	Approximate 3-Year Survival Rate (%)
RT alone—40 Gy	45	8	8
RT alone—50–60 Gy	60	9	10
RT alone—70 Gy	70	11	15
Sequential chemo followed by RT (60 Gy)	70	14	25
Concurrent Chemo–RT (60 Gy)	80	17	35

Source: Data from multiple prospective trials of the Radiation Therapy Oncology Group (RTOG) and other clinical trials.

Current research efforts are focused on optimizing radiation techniques and integrating new molecularly targeted therapies into the treatment of locally advanced NSCLC. As noted, there has been a paradigm shift away from large-field/medium-dose radiotherapy toward small-field/high-dose radiotherapy. This will hopefully continue to improve the therapeutic ratio of radiotherapy while making it more feasible to introduce new agents with less concern about excessive overlapping toxicities. Preclinical data suggest a benefit from combining radiotherapy with agents that target signal transduction and/or angiogenesis pathways. While this approach has been validated in some extrathoracic tumor sites (e.g., head and neck cancer), it is still investigational in lung cancer.

■ DEFINITIVE THERAPY (NONOPERATIVE NON–SMALL-CELL LUNG CANCER STAGE I)

Patients with "medically inoperable" (i.e., with medical contraindications to definitive surgery) stage I NSCLC who are treated with radiotherapy have a significantly improved prognosis compared with locally advanced "technically unresectable" stage II/III NSCLC. This is a major argument in favor of intervention with radiotherapy prior to disease progression to stage III. Relatively small radiotherapy fields can be safely used for most patients with stage I disease, and high doses can be administered. A traditional radiotherapy course consists of 60 to 66 Gy in conventional fractionation (1.8–2 Gy once daily). With this approach, reported 5-year local control rates are in the range of 30% to 50%, with 5-year survival ranging from 10% to 30%.[23,24] Even though the local control rate is inferior to surgical series, many of these patients die from intercurrent disease rather than their lung cancer. Since early-stage NSCLC is not inherently a systemic disease, there is interest in escalating the radiation dose to improve the local control rate.

Stereotactic Body Radiotherapy

The combination of multiple beam angles to achieve sharp dose gradients, high-precision localization, and a high dose per fraction in extracranial location is referred to as stereotactic body radiotherapy (SBRT) (Fig. 115-6). This technique allows precise targeting and delivery of high-dose radiation. SBRT for lung cancer

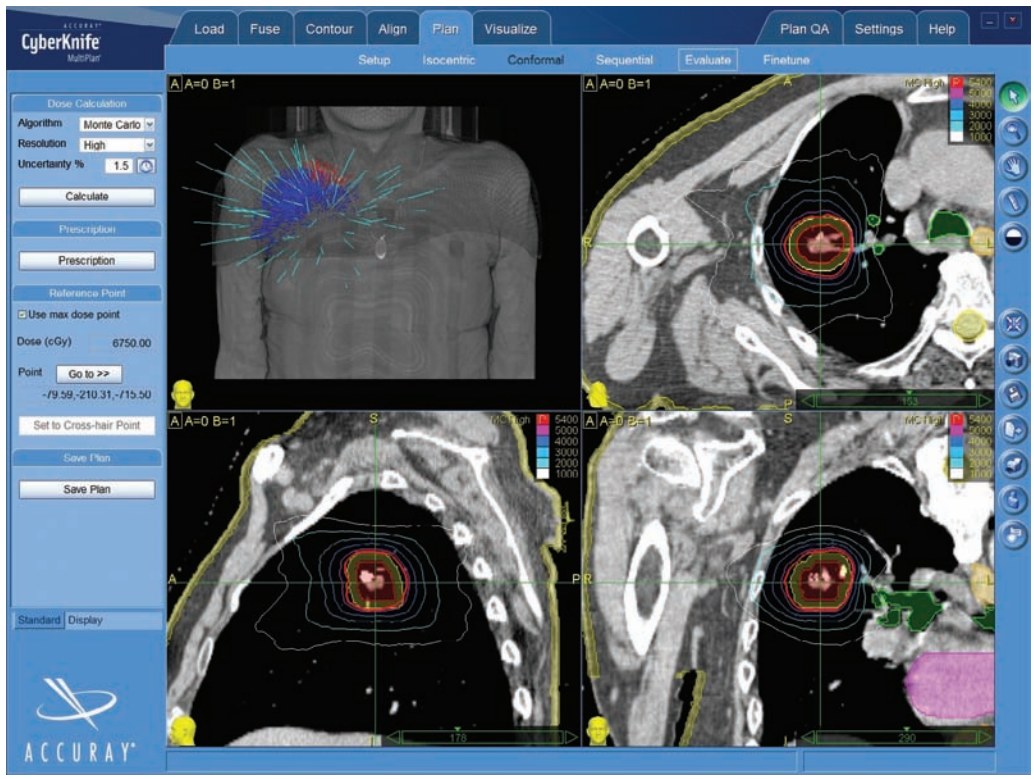


Figure 115-6 This figure illustrates the multiple beam arrangement and the radiation isodose distribution in treatment for medically inoperable peripheral stage I non–small-cell lung cancer using SBRT technique.

incorporates various systems to take tumor motion into consideration along with image guidance to decrease the set-up uncertainty. Both these components allow reduction in treatment volume, which enables delivery of markedly higher doses with fewer treatment fractionations. There have been several reports showing effectiveness of this treatment approach with very high local control rate. The only prospective multi-institutional study showed feasibility of delivering 20 Gy in 3 fractions (60 Gy total), a dose of radiation that is generally considered uniformly ablative of malignant cells.[25] Preliminary results suggest that SBRT offers extremely high local control rates approaching those achievable with lobectomy. However, long-term data are still pending, and at this time relatively few centers have extensive experience in this highly complex treatment. Furthermore, the optimal dose and fractionation are not clear because of the variation in dose and fractionation schedule used by different groups. Based on the RTOG phase II prospective study, for peripherally located stage I medically inoperable tumor, 54 Gy in 3 fractions is currently considered to be the standard.[25,26]

PALLIATIVE THERAPY

Palliative radiation therapy is most often used in situations in which the patient's quality of life is, or could be, substantially compromised. Situations in which thoracic radiotherapy is commonly applied for palliation include locally advanced disease with superior vena cava syndrome, hemoptysis, dyspnea, pain, or obstructive pneumonia, and metastatic disease.[27,28] Cough, often due to partial bronchial obstruction, is frequently palliated by radiotherapy. Atelectasis is rarely reversed by radiotherapy, although consideration should be given to irradiation to prevent refractory postobstructive atelectasis and pneumonia when impending obstruction of a mainstem or lobar bronchus is identified by bronchoscopy. A summary of the response rate (partial relief) of symptoms is shown in Table 115-4.

Palliative radiotherapy generally involves lower total doses and smaller fields than does definitive radiotherapy. Larger daily fraction size is used (2.5–4 Gy once daily) in the attempt to achieve relatively rapid palliation and minimize the number of trips to the radiotherapy department. In addition, late radiotherapy complications (which are related to larger fraction size) are less relevant in this patient population. There is no standard palliation regimen, and treatments have ranged from a single fraction of 8 to10 Gy (a very popular European regimen) to a full course of 60 Gy in standard 2 Gy once daily fractions. A typical palliative radiotherapy schema in the United States is to deliver 3 Gy × 10 fractions (30 Gy total), which may be followed by a second similar course of treatment, either after a several week break, or later, at the time of further local progression.

TABLE 115-4 Response Rate to Palliative Radiotherapy

Symptom	Response Rate (%)
Atelectasis	20
Cough	35–65
Dyspnea	35–50
Hemoptysis	75–85
Pain	50–75
SVC syndrome	60–80
Weight loss/anorexia	30–50
Vocal cord paralysis	5
Overall symptomatic response	60–75

SVC, superior vena cava.

After full-course external-beam irradiation, patients commonly develop symptoms associated with recurrent disease. Occasionally, it may be appropriate to offer reirradiation. If this is purely due to endobronchial obstruction, the patient may be a candidate for endobronchial irradiation.[29] This bronchoscopically guided treatment uses an Iridium-192 source, with a depth penetration that is superior to current laser or photodynamic treatments. However, it does carry a 5% to 10% risk of massive hemoptysis (presumably the result of tumor lysis with bronchovascular fistula).

Finally, radiotherapy plays an important role in the palliation of metastatic sites, including brain and bone metastases. Whole-brain irradiation is appropriate therapy for multiple brain metastases. In addition to palliating neurologic symptoms in many patients, it marginally improves survival compared with steroids alone. In addition, patients with limited brain metastases and a good performance status appear to benefit from a combination of whole-brain irradiation plus either surgical resection or stereotactic radiosurgery boost.[30] For bony metastases, most patients achieve at least partial pain relief from palliative radiotherapy. In some cases this can be given in a single 8 Gy × 1 fractionation. Other cases may require a 1- to 2-week course of radiotherapy. Disfiguring metastases to the skin, subcutaneous tissues, and/or lymph nodes can be improved by similar modest dosages of irradiation. Pain from adrenal metastases can be palliated with radiotherapy in patients in whom the radiotherapy field would not include an excessive amount of liver, kidney, or bowel. Radiotherapy is not generally useful for diffuse metastatic disease to the liver or bilateral lungs.

TOXICITY OF THORACIC RADIOTHERAPY

Toxicity from radiotherapy occurs both as *acute* side effects, generally defined as those occurring during or within 90 days after the completion of a course of irradiation, and *late* effects, which do not develop until at least 90 days after the completion of irradiation.[31–35] Although some of the same factors that predict acute effects also increase the likelihood of late effects, the acute effects themselves do not necessarily lead to the late, long-term complications. Conversely, some patients who experience minimal to no acute side effects may nonetheless be at risk for significant late complications. Most radiation toxicities reflect localized damage to tissue within the irradiated portal. However, some effects are more generalized (e.g., fatigue, immunosuppression, and the rare complication of acute respiratory distress syndrome). The grade of radiation toxicity is generally reported on a 1 to 5 scale, with grade 1 toxicity representing mild effects (e.g., dyspnea on exertion) and grade 5 representing fatal toxicity.

In the treatment of thoracic malignancies, where high irradiation doses and large fields are often used, the organs of greatest concern for both acute and late complications are the lung, esophagus, and heart. Significant dermatologic toxicity has been virtually eliminated by the use of megavoltage equipment. Likewise, with modern treatment planning techniques, spinal cord complications should be extremely rare. Other structures at risk for injury by thoracic irradiation include the brachial plexus, the tracheobronchial tree, the great vessels, the ribs, and the sternum. Although many complications of thoracic irradiation are manageable, the most important strategy is prevention through sophisticated treatment planning and appropriate selection of patients for treatment.

LUNG COMPLICATIONS

Radiation pneumonitis and pulmonary fibrosis are the most common serious complications of thoracic irradiation. Radiation pneumonitis represents acute/subacute lung injury. It usually occurs from 1 to 4 months after irradiation, although it may occur during a course of particularly intensive radiotherapy, often when combined with chemotherapy. Dyspnea is the most characteristic symptom;

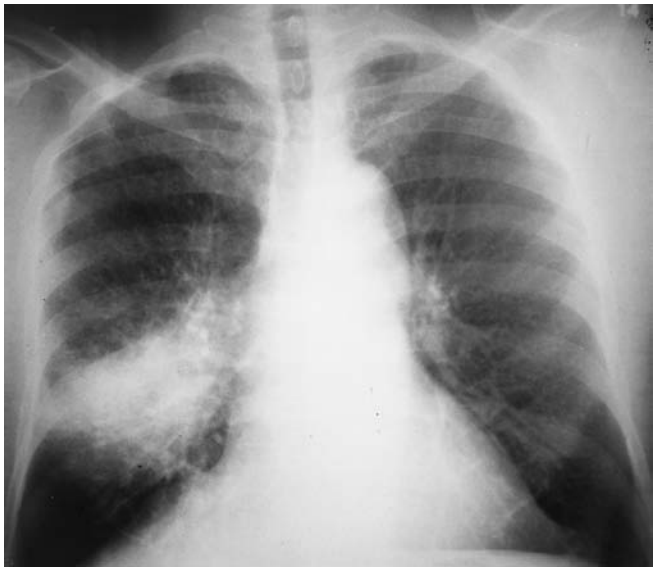


Figure 115-7 Prechemo radiotherapy chest radiograph of a patient with limited-stage small-cell carcinoma of the right lower lobe.

cough, low-grade fever, and pleuritic chest pain often are also present (Figs. 115-7–115-9). Although infiltrates outside of the radiation portal do not completely rule out radiation pneumonitis, they make the diagnosis less likely. Community-acquired pneumonia and opportunistic infections as well as progressive malignancy can mimic radiation pneumonitis. Therefore, appropriate testing and consultation with the patient's radiation oncologist and/or a pulmonologist are indicated before empiric corticosteroids are begun. Mild cases should be treated supportively, reserving steroids for more severe symptoms. For severe radiation pneumonitis, prednisone 20 mg, three times per day, for approximately 2 weeks is a suggested regimen; tapering is done slowly during the subsequent 2 to 4 weeks.

The incidence of serious (≥grade 3) radiation pneumonitis ranges from 5% to 15%, and the risk depends on several variables. The most important factor appears to be the amount of normal lung tissue irradiated. Other factors that appear to increase the risk of radiation pneumonitis include radiation dose and dose per fraction (i.e., larger fraction size increases the risk) and tumor location

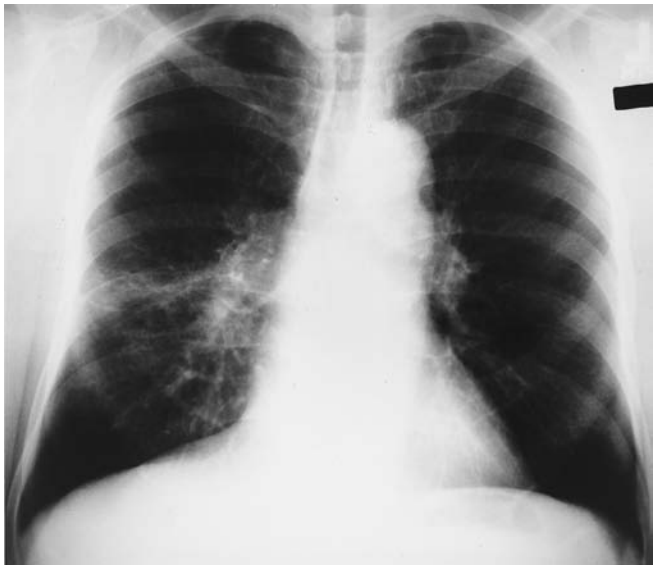


Figure 115-8 Chest radiograph 1 month after definitive radiotherapy and chemotherapy for the patient shown in Figure 115-5.

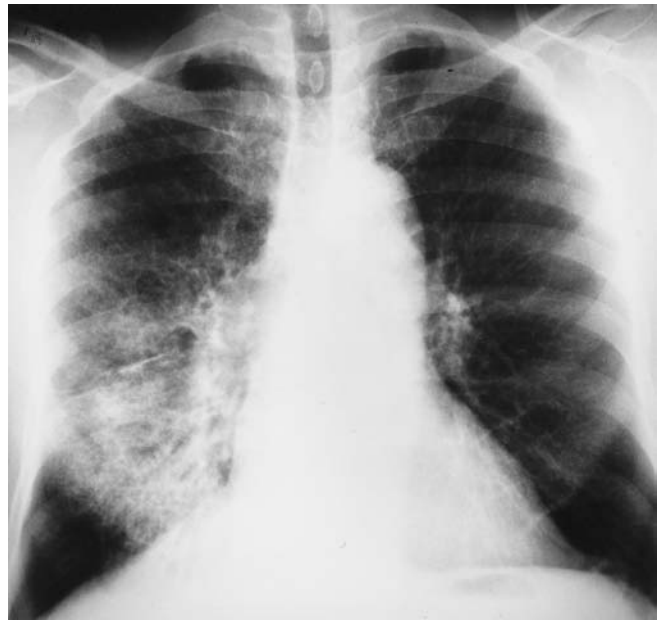


Figure 115-9 Chest radiograph 4 months after completion of radiotherapy for the patient shown in Figures 115-7 and 115-8. He presented with severe dyspnea on exertion. Radiographic infiltrates conform to the shape of his radiation portal. He responded promptly to steroids but soon developed fatal brain metastases.

(i.e., lower lobe lesions have a higher risk). The use of chemotherapy (particularly the anthracyclines, methotrexate, bleomycin, and mitomycin) and poor pulmonary function before treatment also increase the risks of serious damage to the lungs by radiation.

On rare occasion, patients may develop acute respiratory distress syndrome shortly after irradiation. The chest radiograph reveals

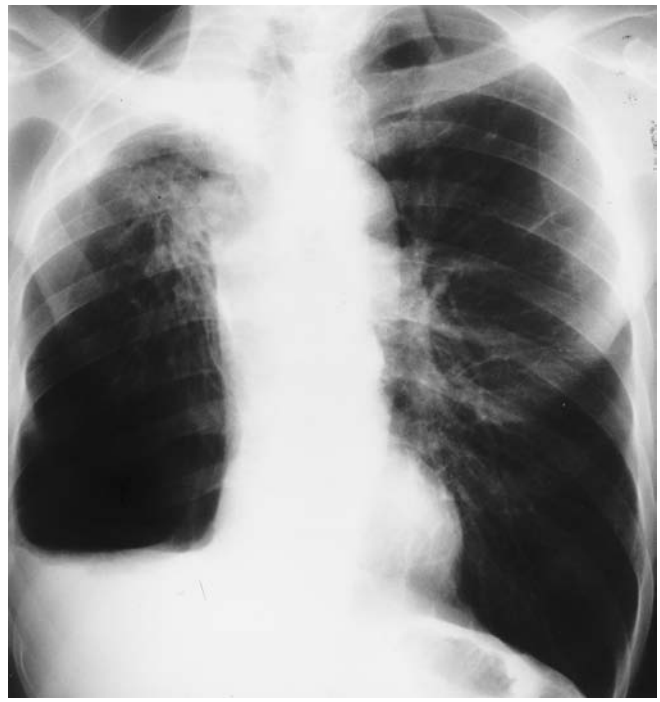


Figure 115-10 Chest radiograph of a patient 6 years after definitive radiotherapy for stage III unresectable non–small-cell lung carcinoma. Radiation fibrosis in the right upper lobe with mediastinal shift to the treated side and an ipsilateral pleural effusion and thickening is evident. Patient remained asymptomatic.

diffuse infiltrates both within and outside of the radiotherapy portal. It has been hypothesized that a severe autoimmune response may be involved; whereas mild and moderate radiation injury becomes manifest only in the irradiated portion of lung, a severe autoimmune response results in generalized bilateral lung injury.

The late complication of radiation fibrosis develops from 3 to 18 months after radiotherapy. All patients irradiated definitively for lung carcinoma develop some degree of radiologic radiation fibrosis in the portion of the lung that was heavily irradiated (Fig. 115-10). If this is a small volume, it should be asymptomatic, and the major difficulty is in distinguishing between fibrosis and residual, or recurrent, tumor. In clinically significant radiation fibrosis, however, there is usually a progressive decrease in the diffusing capacity, which may be combined with a more modest decrease in the FVC, reflecting the restrictive nature of radiation fibrosis. Unfortunately, established fibrosis does not respond to corticosteroids or any other therapy. Longitudinal studies in Hodgkin disease patients suggest that some recovery of lung function is possible by approximately 3 years after treatment. It is less clear if lung cancer patients, who are far older and more chronically ill than most lymphoma patients, can expect appreciable recovery.

■ ESOPHAGEAL COMPLICATIONS

Most patients receiving moderate- to high-dose radiotherapy for centrally located lung cancer experience an acute mucositis of the esophagus (and/or tracheobronchial tree) that is similar to that seen with other epithelial surfaces after radiation therapy. With standard radiotherapy (60 Gy in standard fractionation) this mucositis is almost always self-limited and usually responds to topical agents, such as sucralfate slurry or "magic mouthwash" combinations (e.g., antacid, viscous lidocaine, and diphenhydramine) with or without nonopioid and/or mild opioid pain medications. However, with more intensive radiotherapy or with concurrent chemotherapy, the incidence of grade 3 inflammation is higher, the recovery period is longer, and the need for aggressive pain management is greater.

Esophageal stricture is a late complication following thoracic radiotherapy. The risk of esophageal stricture is strongly related to the dose to the esophagus, approximately 1% with 50 Gy, 10% with 60 Gy, and as high as 50% with 70 Gy. It is likely that the concurrent use of chemotherapy potentiates this effect. Most cases of radiation esophageal stricture respond well to endoscopic dilatation although the procedure may have to be repeated. More severe complications, such as tracheoesophageal fistula or perforation, fortunately are rare.

■ HEART AND GREAT VESSELS

Acute effects of radiotherapy on the heart during treatment are uncommon, with cardiac events more commonly related to the tumor itself (e.g., atrial fibrillation due to invasion of the pericardium). Radiation pericarditis occurs during or after treatment in about 5% of patients, depending upon the radiation dose and volume of pericardium irradiated. As in the case of radiation pneumonitis, distinguishing between radiation pericarditis and tumor progression can be difficult. Most cases are self-limited and are treated supportively with antipyretics, analgesics, and occasionally with antiarrhythmic agents. Pericardiocentesis for tamponade is rarely required. Occasionally, severe constrictive changes may develop, leading to signs and symptoms of heart failure and necessitating pericardiectomy. In addition to the risk of radiation pericarditis, irradiation has increased long-term morbidity and mortality from heart disease in patients cured of Hodgkin disease, seminoma, and breast cancer, presumably due to accelerated coronary artery disease. Long-term cardiac complications of radiotherapy are less commonly encountered in patients with lung cancer, since few patients survive long enough to manifest these effects. Nonetheless, it is important to keep in mind that mediastinal irradiation is a risk factor for coronary disease, and should be taken into account in lung cancer survivors when deciding on screening and management of cardiac issues.

With the use of higher-dose radiotherapy, such as with SBRT, a small but finite number of patients can suffer injury to the mediastinal/hilar great vessels, including a risk of life-threatening hemorrhage. Although this is a rare complication, it has led to caution with the use of SBRT for centrally located and/or larger lung tumors.

■ BRACHIAL PLEXUS AND CHEST WALL

Radiation-induced inflammation and fibrosis of nerves, muscle, or bone can lead to long-term complications. Brachial plexopathy is uncommon with radiation doses of less than 60 Gy, but can be a concern in long-term survivors of superior sulcus tumors. More recently, it has become apparent that some patients successfully treated with SBRT for peripheral lung cancer experience chronic chest wall pain and/or rib fracture. As with other radiation toxicities, the dose to the chest wall and volume of the chest wall irradiated are important predictors. Treatment is symptomatic and supportive, including opioid and nonopioid pain medications.

ADVANCES IN RADIOTHERAPY

"Several recent advances in the field include radiation dose-fractionation modulation, enhancements in technical planning and delivery of radiation, combined modality therapy, and use of radiosensitizers. Each is discussed below."

■ RADIATION DOSE–FRACTIONATION MODULATION

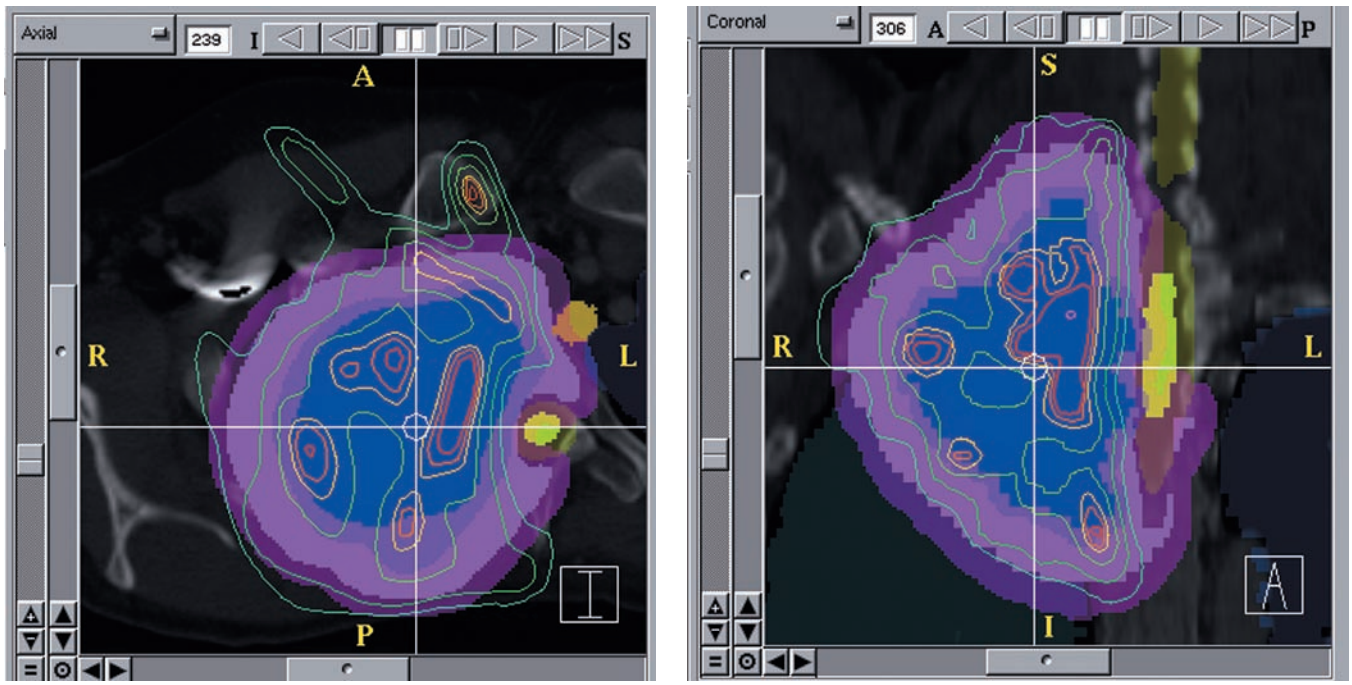
As the understanding of the relationship between radiation and cellular kinetics has grown, mathematical models have been developed to predict the responses of both normal tissue and tumor to radiation. This capability has led to many creative new fractionation schemes designed to maximize the destruction of tumor while minimizing damage to normal tissue. The difference in cellular kinetics between tumor cells and normal cells makes these new schemes possible and attractive. Both tumor cells and normal cells are injured by radiation; however, normal cells usually have a greater ability to repair this damage than do the tumor cells and can repopulate more between fractions.

Hyperfractionation utilizes multiple daily fractions in an effort to reduce the late effects in normal tissue without decreasing tumor control. The overall treatment time is the same as conventional schedules, but multiple smaller fractions are given each day, and total doses are increased. By giving multiple smaller fractions, the normal tissues are able to repair a greater percentage of the damage during the course of treatment. This may allow higher total cumulative doses of radiotherapy to be safely administered.

Accelerated treatment administers a larger total dose of radiation per day and also decreases the overall treatment time.[36] The final dose of radiotherapy may be similar to or even somewhat less than that of conventional treatment. Accelerated treatment may be given via hyperfractionation (e.g., 1.5 Gy BID-TID) or as hypofractionation (e.g., 4 Gy once daily). It is designed to reduce the amount of tumor repair and repopulation that occurs during treatment of rapidly dividing tumors and, therefore, improve local control.

Extreme hypofractionated treatment, as given with SBRT administers a very large dose of radiotherapy each day, typically for only three to five total treatments. This type of treatment does not discriminate well between tumor and normal cells, and is sometimes also known as "ablative" radiotherapy. For this treatment, to be safe, extremely small radiation fields must be used, and critical uninvolved organs must be carefully avoided, using stereotactic techniques.

In some settings, altered fractionation appears to increase local–regional control compared with standard fractionation. Because of toxicity concerns, it is usually not combined with concurrent chemotherapy in the treatment of NSCLC.



A B

Figure 115-11 High-technology radiation therapy involves the design of multiple conformal radiation beams directed in three-dimensional space from various angles and using variable field shapes and intensities. These slides illustrate the radiation dosimetry for a patient with a Pancoast tumor (T4N2M0) of the right upper lobe (**A**, axial view of radiation treatment planning CT scan; **B**, coronal view). The spinal cord is (relatively) spared from maximal radiation doses.

■ TECHNICAL PLANNING AND DELIVERY OF RADIATION

Complementing the advances in dose–fractionation schedules in radiotherapy are advances in technical planning and delivery of radiotherapy. Specifically, three-dimensional conformal radiation therapy, which includes newer techniques such as intensity-modulated radiation therapy (IMRT), proton-beam radiotherapy, and SBRT, is used in efforts to improve local control while minimizing toxicity. Utilizing three-dimensional planning of the tumor and surrounding normal tissue, the radiation beam(s) can be precisely conformed and modulated to the shape and size of the tumor volume (Fig. 115-11). Powerful computer software allows for detailed analysis of anticipated radiation dose/volume distributions, so that adjustments in the treatment plan can be made if necessary (Fig. 115-12). This information includes comprehensive dose–volume histograms, which quantitatively plot the volume of a given organ (or tumor/target) receiving a given dose of radiation. Dose–volume histogram analysis has demonstrated a powerful relationship between the risk of radiation pneumonitis and the amount of lung tissue irradiated to a certain threshold dose, usually considered to be 20 Gy in most studies.

In the future, these techniques may simultaneously allow a higher dose to the tumor and lower dose to normal tissues such as the spinal cord, esophagus, heart and great vessels, tracheobronchial tree, and normal lung tissue, offering an improved therapeutic ratio. Technologies investigating this include SBRT, respiratory-gated radiotherapy, and proton-beam radiotherapy.

■ COMBINED MODALITY THERAPY/RADIOSENSITIZERS

The rationale for combining radiotherapy with other anticancer treatments is twofold. First, it is expected that the nonradiotherapy treatment can sterilize tumor cells located outside of the radiation field (this is also known as spatial cooperation). Second, it is hypothesized that these other treatments act as radiosensitizers, turning a sublethal dose of radiation into a lethal dose of radiation. Both concepts apply to standard cisplatin-based polychemotherapy.

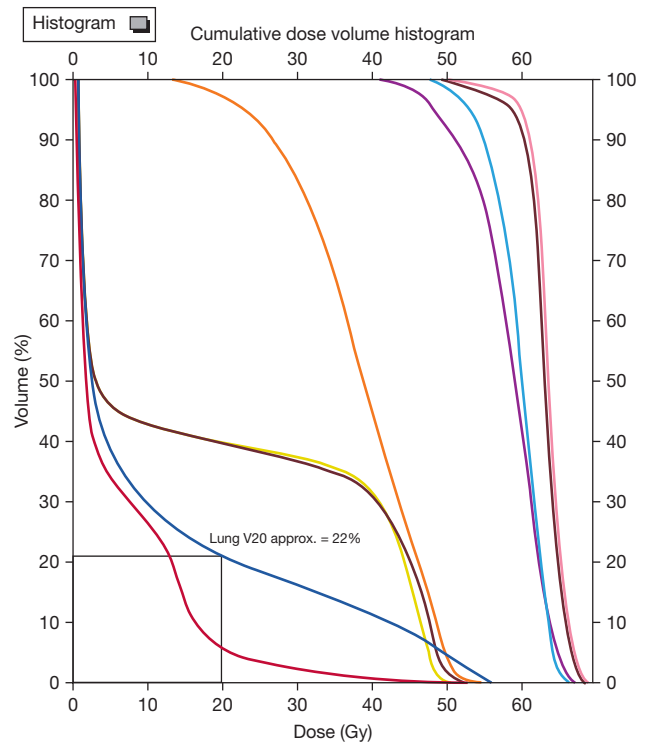


Figure 115-12 This figure illustrates the cumulative radiation dose–volume histogram plots for the patient from Figure 115-7. This graph includes the DVH curves for multiple normal organs (lung, heart, esophagus, spinal cord) as well as DVH curves for the tumor itself and electively irradiated targets adjacent to the gross tumor. The degree of radiation exposure to the normal lung tissue is expressed as the lung V20, the percent of the patient's total lung volume that receives a dose of at least 20 Gy, which is expected to devitalize that portion of lung. In this case the V20 is approximately 20%, which is generally considered a "safe" amount of radiation lung exposure and low risk for clinical radiation pneumonitis.

However, the toxicity of combined chemoradiotherapy appears to be at the limits of acceptability. In addition, conventional chemoradiotherapy has suboptimal effects against lung cancer. Thus, less toxic and better targeted drugs are needed. It is increasingly recognized that some cases of NSCLC are "driven" by a specific gene, such as an EGFR mutation or EML–ALK rearrangement. The corresponding proteins can be inhibited by a small molecule drug (e.g., erlotinib for EGFR-mutated NSCLC or crizotinib for EML–ALK rearranged NSCLC). These two drugs have demonstrated efficacy as single agents in stage IV NSCLC, but have not been adequately tested in cases of stage I to III NSCLC in which the appropriate gene aberration has been detected. Early phase research is ongoing.

SUMMARY

External-beam radiotherapy plays a major role in the treatment of NSCLC. It improves local control and enhances curability in patients with marginally resectable NSCLC. Patients with medically inoperable NSCLC have a good chance for durable local control with high-dose radiotherapy, particularly with modern technology including SBRT. In patients with unresectable NSCLC, radiotherapy (combined with chemotherapy) maximizes the median survival and offers occasional cure. Finally, radiotherapy often provides good palliation for patients with incurable and/or metastatic lung cancer.

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CHAPTER 116

Small Cell Lung Cancer: Diagnosis, Treatment, and Natural History

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Small cell lung cancer (SCLC) is, in many ways, a unique tumor. Untreated, it is a highly virulent malignancy, with a life expectancy best measured in weeks. Conversely, it displays exquisite chemosensitivity, resulting in partial or complete responses in the majority of cases. Unfortunately, these responses are typically short-lived, and as a result, more than 95% of SCLC patients die from their disease. Over the past 25 years, little progress has been made in prolonging the survival of patients with SCLC, despite numerous attempts to refine and improve the present therapy. This chapter reviews the biology, epidemiology, diagnosis, clinical presentation, staging, and current management of this difficult disease.

EPIDEMIOLOGY

Lung cancer remains the leading cause of cancer death in men and women in the United States. In 2012, estimates called for 226,160 cases of newly diagnosed lung cancer (116,470 men and 109,690 women) and 160,340 deaths (87,750 in men and 72,590 in women) from this disease.[1] A review of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Incidence Public Use database found that the proportion of lung cancer cases ascribed to SCLC has declined from a peak of 17.62% in 1986 to 12.95% in 2002.[2] A similar review of the National Cancer Database (NCDB) identified that SCLC constituted 19.5% of all new lung cancer diagnoses in 1992 and that this had decreased to 15.7% by 2007.[3] Of note, women now make up approximately 50% of SCLC cases, which is up from 28% in 1973.

The primary etiologic agent responsible for SCLC is tobacco smoke. A recent meta-analysis of nine case-control studies that included 11 European countries and Canada reported that the odds ratios in current smokers for the development of SCLC are 45.7 and 21.7 in men and women, respectively.[4] In the analysis, the risk increased markedly with both the intensity and duration of smoking, with males currently smoking >30 cigarettes daily having an odds ratio of 111.3 of developing SCLC. While >95% of cases of SCLC occur in current or former smokers, other etiologic agents including bischloromethyl esters, nickel, vinyl chloride, asbestos, cadmium, radon, arsenic, and radiation have been implicated as possible contributors to the development of this disease.[5] However, the true impact of exposure to each of these agents is not well quantified in the literature.

PATHOLOGY

Barnard[6] published the first report of SCLC in 1926, in which he described mediastinal tumors of epithelial origin that he called "Oat Cell Sarcoma" due to the histologic resemblance of the cells to oat grains. Since that description, the pathologic classification of SCLC has undergone frequent and extensive revision. Specifically, over the past five decades, the World Health Organization (WHO) proposed several different classification schemas that divided SCLC into a variety of subtypes that were, in retrospect, of limited utility in defining entities with truly different biologic behavior.

In 1999, the WHO joined with the International Association for the Study of Lung Cancer (IASLC) pathology panel to develop a revised classification of lung and pleural tumors. In the updated classification schema, neuroendocrine tumors are viewed as a spectrum extending from low-grade typical carcinoid to intermediate-grade atypical carcinoid to high-grade neuroendocrine tumors, a new entity called large

TABLE 116-1 Features of Neuroendocrine Lung Tumors

	Typical Carcinoid	Atypical Carcinoid	LCNEC	SCLC
NE features	Well differentiated	Well differentiated	Poorly differentiated	Poorly differentiated
Cell size	Intermediate	Intermediate	Large to intermediate	Small to intermediate
Mitotic rate	Low <2 mitoses/2 mm^2	Intermediate 2–10 mitoses/2 mm^2	High Median 70 mitoses/2 mm^2	High Median 80 mitoses/2 mm^2
NE markers by IHC	+++	++–+++	+–+++	±
Necrosis	—	+ (focal)	+++	+++
KI-67 index	≤5%	5–20%	50–100%	80–100%
5-y survival	90–95%	60–70%	10–40%	≤5–10%

IHC, immunohistochemistry; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; SCLC, small cell lung cancer.
Source: Adapted with permission from West WW. "Pathology of Lung Cancer." In Ganti AK, Gerber DE, eds. Lung Cancer, 11th edition. Oxford American Oncology Library. Oxford University Press; 2013.

cell neuroendocrine carcinoma (LCNEC) and SCLC (Table 116-1).[7] This schema also identifies only one variant of SCLC ("SCLC combined"), which should be utilized when at least 10% of the tumor is composed of non–small-cell carcinoma elements.

Light microscopy is typically sufficient for making a diagnosis of SCLC. The cells are generally small (<4 lymphocytes or 20 μm in diameter) with scant cytoplasm, poorly defined borders, absent or inconspicuous nucleoli, and fine granular nuclei (so called "salt and pepper" chromatin).[7] The cells also often display nuclear molding, which is the propensity of the nuclei to be deformed by contact with adjacent cells or structures (Fig. 116-1). SCLC is quite proliferative and there are, therefore, rarely fewer than 10 mitoses per 10 high power fields. The cells are also quite fragile, and as a result, crush artifact is frequently observed on SCLC biopsies.[8] Inflammatory response and desmoplastic reactions are usually absent. Although biopsy specimens are ideal, cytologic specimens alone are often sufficient for diagnosis, with a sensitivity of 60% to 90% and a specificity of greater than 95%.[8,9]

While a diagnosis of SCLC can typically be made with morphology alone, immunohistochemical stains can assist in confirmation and can differentiate SCLC from lymphomas and other thoracic malignancies that can have a similar histologic appearance (Table 116-2). SCLC usually stains positive with epithelial markers (keratin, epithelial membrane antigen, and BER-EP4). In contrast, lymphoma is suggested by antibodies against the common leukocyte antigen, with negative epithelial markers. In addition, evidence of neuroendocrine differentiation is almost universal with >75% of SCLC staining positive with at least one neuroendocrine marker (neuron-specific enolase, chromogranin A, CD56 [neural cell adhesion molecule {NCAM}], synaptophysin). CD56, cytokeratins, TTF-1, and CD45 are useful in the diagnosis of SCLC in biopsies with extensive crush artifact and can help confirm the diagnosis in cases with equivocal features.[10] Other neuroendocrine markers that can be found include dopa decarboxylase, calcitonin, Leu-7, gastrin-releasing peptide (GRP), and insulin-like growth factor-1 (IGF-1).[8,11,12]

TUMOR BIOLOGY

Most cancers arise as a consequence of genetic abnormalities caused by exposure to environmental carcinogens. Both activation of a dominant oncogene and inactivation of a tumor suppressor

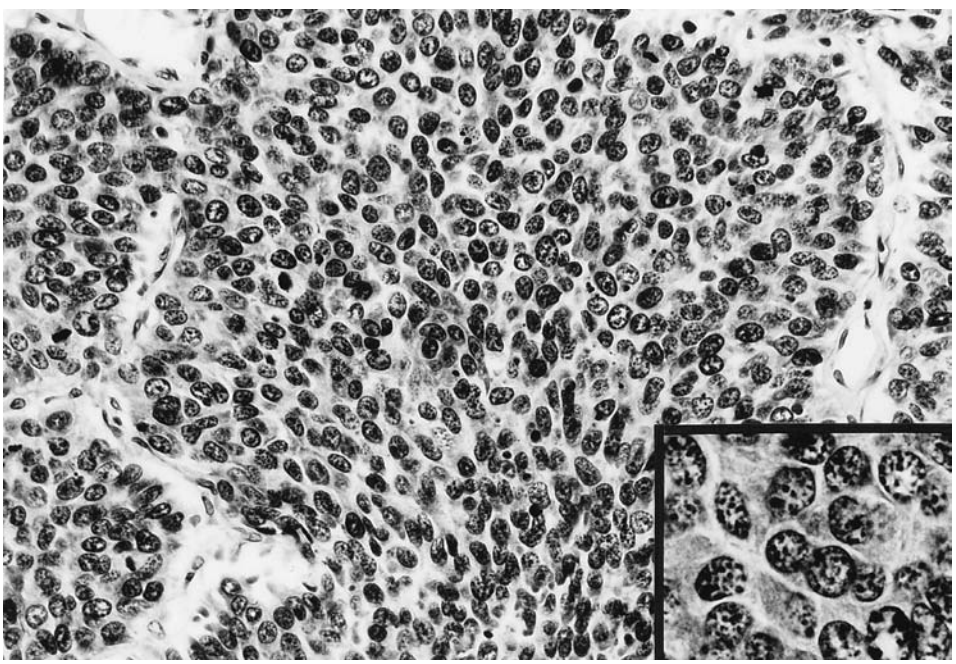


Figure 116-1 Photomicrograph of pure small cell carcinoma, demonstrating a homogeneous cell population with salt and pepper chromatin and moderately prominent nucleoli (H&E, 250×; *inset* 400×). *(Used with permission of Dr. Michael T. Lomis, Vanderbilt University.)*

TABLE 116-2 Immunohistochemical Profile of Small Cell and Other Primary Lung Cancers

	Positive Cases (%)			
		Non–Small Cell		
	Small Cell	Adenocarcinoma (Nonmucinous)	Adenocarcinoma (Mucinous)	Squamous Cell
CK-7	35	>95	90	40
CK-20	<5	10	50	<5
TTF-1	85	80	30	5
Napsin A	<5	85	<5	20
Synaptophysin	55	15	N/A	5
Chromogranin A	40	<5	N/A	5
CD56	95	<5	N/A	10
P63	<5	25	N/A	>95
CK 5/6	<5	15	N/A	90
34βE12	<5	55	N/A	>95
CDX-2	<5	<5	45	<5

CD, cluster of differentiation; CK, cytokeratin; TTF, thyroid transcription factor.
Source: Adapted with permission from West WW. "Pathology of Lung Cancer." In Ganti AK, Gerber DE, eds. Lung Cancer, 11th edition. Oxford American Oncology Library. Oxford University Press; 2013.

gene can lead to the development of a malignant phenotype. Recent genomic analyses of SCLC have revealed this malignancy to have one of the highest mutational rates of any cancer (7.4 mutations per million base pairs, compared to 6.3 for melanoma and 0.4 to 1.5 for various other solid and liquid tumors).[13] In SCLC the most common genetic abnormalities include loss of chromosomal material associated with inactivation of specific tumor suppressor genes.[14] Specific molecular aberrations identified in SCLC are listed in Table 116-3.

TUMOR SUPPRESSOR GENES

Mutations of the TP53 gene at 17p13.1, the most common gene abnormality in all human cancers, are found in 75% to 80% of SCLC.[13,15] Loss of heterozygosity of chromosomes 9p and 10q (the site of the PTEN gene) is present in the majority of cases.[13,16] The retinoblastoma gene *(RB1)* at 13q14.11 encodes a nuclear protein involved in cell-cycle control, and inactivating mutations of this gene are found in more than 90% of SCLC.[13,15,17]

Deletions in 3p are found in nearly all (90%) SCLC tumors and cell lines. Three tumor suppressor genes of particular interest are located in this region: Fragile histidine triad gene (*FHIT*) at 3p14.3 encoding the enzyme diadenosine triphosphate hydrolase, RAS effector homolog *(RASSF1A)* at 3p21.3 encoding a microtubule-binding protein, and *RARB* at 3p24 encoding the retinoic acid receptor β.[18–20] All three gene products are important in cell cycle control or induction of apoptosis.

ONCOGENES

Dominant oncogene abnormalities are less common in SCLC. Overexpression of myc oncogene through gene amplification is seen in approximately 25% of SCLC patients.[21,22] The myc oncogenes *c-myc, n-myc,* and *l-myc* are closely related nuclear DNA-binding phosphoproteins involved in gene regulation. In two retrospective studies, the presence of *myc* DNA amplification in tumor cell lines and *myc* family DNA amplification was associated with shortened survival in SCLC patients. In laboratory studies, transfection of *myc* into a SCLC cell line was found to be associated with faster growth, a greater cloning efficiency in soft agarose, altered cell structure, and altered histology in athymic nude mice. These findings connote a more aggressive form of SCLC in association with *myc* amplification.

In contrast to non–small-cell lung cancer (NSCLC), mutations in the EGFR and K-ras oncogenes are rare in SCLC. However, it has recently been demonstrated that histologic evolution from NSCLC to SCLC may account for some cases of acquired resistance to EGFR inhibitors. In a series of 37 cases of *EGFR*-mutant NSCLC that developed acquired resistance to EGFR tyrosine kinase inhibitors, drug resistance mechanisms included expected genetic changes such as *EGFR* T790M mutations (49% of cases) and *MET* amplification (5%). Somewhat unexpectedly, transformation to SCLC was noted in 14% of cases.[23] These cases were sensitive to standard SCLC treatments, stressing the importance of repeatedly assessing tumor histology and biology throughout the course of treatment as these may dictate needed modifications in therapy.

TABLE 116-3 Molecular Abnormalities in Small Cell Lung Cancer

Gene	Chromosome	Protein	Frequency
Fragile histidine triad (FHIT)	3p14.3	Diadenosine triphosphate hydrolase	~90%
RAS effector homolog (RASSF1A)	3p21.3	Microtubule-binding protein	~90%
Retinoic acid receptor β (RARB)	3p24	Retinoic acid receptor β	~90%
Retinoblastoma (RB1)	13q14.11	Nuclear protein involved in cell-cycle progression	~90%
TP53	17p13.1	P53: multifunctional transcription factor	75–80%
c-kit receptor	4q12	Transmembrane receptor tyrosine kinase	70%
c-myc/N-myc/L-myc (amplification)	8q24/2p24–25/1p34–35	Nuclear DNA–binding phosphoproteins	~25%
K-ras (point mutation)	12p11–12	G-protein regulator of cellular signal transduction	Rare

AUTOCRINE GROWTH PATHWAYS

SCLC has long been associated with the production of numerous peptides, including antidiuretic hormone (ADH), adrenocorticotropic hormone (ACTH), and calcitonin. The autocrine growth promotion potential of these peptides was first proposed almost 25 years ago. The classic autocrine agent in SCLC is GRP, a mammalian analog of the amphibian hormone bombesin.[24] SCLC cells produce GRP, as well as neuromedin B, which bind to one of three receptors (GRP receptor, neuromedin B receptor, and bombesin receptor subtype 3) to activate the autocrine-stimulated growth loop.

A second autocrine growth loop involves the c-kit receptor, which is found in the majority of gastrointestinal stromal tumors (GIST), as well as up to 70% of SCLC tumors.[25] The ligand stem-cell factor is produced by small cell cancers, which in turn binds to the c-kit receptor to stimulate cell growth. The tyrosine kinase inhibitor imatinib, although effective in GIST, was not shown to have any antitumor activity in two phase II trials in SCLC. Elevated levels of IGF-1 have been detected in more than 90% of SCLC tumors and cell lines, and receptors for IGF-1 are found on SCLC cell lines, suggesting autocrine growth activity.[26]

NATURAL HISTORY

The natural history of untreated SCLC is characterized by early dissemination and death. Unlike NSCLC, it is always considered a systemic disease at diagnosis, even if it appears clinically confined to the chest. Postmortem examinations performed on patients who died from other causes shortly after the "complete" surgical resection of their SCLC have demonstrated identifiable metastases in up to 70% of cases.[27] Evidence of distant spread can be found in virtually any organ system. The most common sites of involvement, however, are the liver, bone and bone marrow, and central nervous system (CNS) (Table 116-4).[28] This pattern of spread dictates how the search for metastatic disease is undertaken (see "Section Staging and Pretreatment Evaluation").

Patients with SCLC have a short life expectancy if therapy is not initiated in a timely fashion. The median survival for untreated patients is 4 to 6 months if they have disease that is apparently confined to the chest, and 5 to 9 weeks if they present with metastatic disease. With therapy, survival improves significantly (see Section "Treatment"). Chemotherapy with or without irradiation can extend median survival to an average of 14 to 20 months for those with thorax-confined disease and 7 to 10 months for those with more extensive spread. At 2 to 3 years, a consistent 10% to 25% of limited-stage (LS) patients will still be alive, although cure is not guaranteed even in these relatively long-term survivors (see Section "Late Complications"). Recent trials indicate that 2-year survival may be as high as 40% for aggressively treated LS patients. Two- to three-year survival remains under 5% for those with metastatic disease.

TABLE 116-4 Involvement of Extrathoracic Sites at Diagnosis after Pretreatment Staging Studies in Small Cell Lung Cancer

Extrathoracic Site	Patients with Finding (%)
Final stage	
Limited stage	30–40
Extensive stage	60–70
Bone	19–38
Liver	17–34
Bone marrow	17–23
Brain	0–14
Lymph nodes	7–25
Soft tissue	3–11

Source: Data from Abrams J, Doyle LA, Aisner J. Staging, prognostic featurs and special considerations in small cell lung cancer. Semin Oncol. 1988;15:261–277 and Ihde DC. Staging evaluation and prognostic factors in small cell lung cancer In Aisner J, ed. Lung cancer. New York, NY; Churchill Livingstone; 1985:241–268.

STAGING AND PRETREATMENT EVALUATION

Staging a cancer defines the anatomic extent of the tumor, helps determine prognosis, and guides treatment options. The official staging for SCLC is the same as for NSCLC and utilizes the American Joint Cancer Commission staging system, which defines stage based on the extent of the primary tumor, the degree of nodal involvement, and the presence or absence of distant metastasis (TNM staging). Virtually all clinicians, however, prefer the original staging system for SCLC proposed several decades ago by the Veterans Affairs Lung Cancer Study Group as it better segregates patients into two groups with clearly different prognoses and treatment options. In this system, disease confined to one hemithorax that is able to be encompassed by a single, tolerable radiation port is considered LS.[29] This typically includes patients with hilar, mediastinal, and ipsilateral supraclavicular lymphadenopathy. There is debate regarding whether patients with contralateral hilar and supraclavicular lymphadenopathy or those with ipsilateral pleural effusion should be placed in the LS category. However, most clinical trials for LS disease exclude these patients. Any spread of disease beyond the extent described earlier is defined as extensive stage (ES) disease. A third stage ("very limited stage [VLS] disease") has been proposed by some to define those patients with small primary tumors and no identifiable regional lymphadenopathy or distant metastases, as this group of patients may be considered for surgery (see Section "Treatment"). In most modern series, the majority of patients (60%–65%) present with ES disease, with LS (30%–35%) and (<5%) making up the remainder.[2,3]

Once a diagnosis of SCLC is established the initial pretreatment evaluation should include a complete history and physical examination, and basic laboratory studies including a complete blood count (CBC), serum electrolytes, and liver and renal function tests. A serum lactate dehydrogenase (LDH) level may provide additional prognostic information (see Section "Prognostic Factors"). Current guidelines call for computed tomography scans of the chest (including the liver and adrenal glands) as initial imaging.[30,31] Ten to 18% of SCLC patients have brain involvement at presentation,[32,33] and it is therefore recommended by many that all patients with SCLC undergo imaging of the brain at diagnosis, preferably magnetic resonance imaging (MRI). Certainly, those patients with symptoms suggesting brain involvement require prompt evaluation.

Bone metastases from SCLC are also frequent at presentation. Historically, bone scan was the study of choice to evaluate those patients with bony symptoms or an elevated alkaline phosphatase suggesting possible spread of disease to the bone. More recently, fluorodeoxy glucose positron emission tomography (FDG-PET) has supplanted bone scan at many centers. SCLC is a highly metabolically active tumor, and is therefore typically quite FDG avid at both the primary and metastatic sites. Case series suggest that PET scan can improve staging accuracy in SCLC and that PET will correctly upstage as many as 19% of patients previously thought to have LS disease.[34–39] While the U.S. Centers for Medicare & Medicaid Services (CMS) does not consider SCLC an appropriate indication for PET scanning, most payors will cover this procedure in SCLC, and the National Comprehensive Cancer Network recommends PET, if available, as an initial staging study for all SCLC patients.

Another staging study of historical interest is bone marrow biopsy and aspiration. SCLC is one of a few cancers known to commonly cause bone marrow metastases and, as a result, bone marrow evaluation was standard in SCLC patients for many years. However, most patients with bone marrow involvement have significant

abnormalities on their CBC (notably leukoerythroblastosis), and exceedingly few patients have bone marrow as the only site of metastasis. Therefore, the utility of this test appears limited to those few patients with LS disease after complete radiographic staging and an abnormal CBC.

In general, with the possible exception of brain imaging to rule out occult disease, once the presence of metastatic SCLC has been established, further radiographic evaluation to identify additional sites of metastatic disease is not warranted. In that setting, subsequent evaluation should be symptom guided.

CLINICAL PRESENTATION

No aspect of the clinical presentation of SCLC distinguishes it from NSCLC or even from neoplasms metastatic to the lungs. However, the duration of symptoms of SCLC tends to be very short, due to the rapid dissemination of the disease. The typical patient is a middle-aged or elderly smoker who presents with symptoms attributable to his or her pulmonary and mediastinal disease: Cough, dyspnea, chest pain, hoarseness, and/or hemoptysis. Because of the usual endobronchial location of the tumor, patients often have accompanying postobstructive pneumonia.

Constitutional symptoms may include weakness, anorexia, weight loss, and, rarely, fever. Symptoms may also arise from distant metastases, including headache or seizures in patients with CNS disease, and abdominal or bone pain with hepatic and osseous metastases; or from regional disease with attendant superior vena cava obstruction, manifesting as facial fullness, upper extremity swelling, headache, and dysphagia. In rare instances, patients present with symptoms from a paraneoplastic syndrome. The more common of these rare presentations are inappropriate secretion of ADH (syndrome of inappropriate antidiuretic hormone secretion [SIADH]) and other causes of hyponatremia, Cushing syndrome, Lambert–Eaton syndrome, and other paraneoplastic neuropathies or neurologic disorders (see Section "Paraneoplastic Phenomena").

Physical examination may yield only the stigmata of chronic obstructive pulmonary disease, or it may demonstrate lymphadenopathy, hepatomegaly, bone tenderness, or neurologic findings. Signs of the superior vena cava syndrome include venous distention of the neck and chest wall, cyanosis, facial plethora, and upper extremity edema.

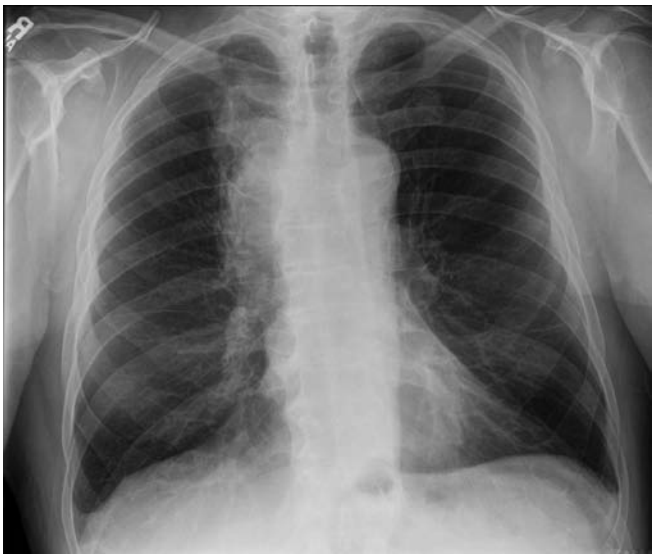
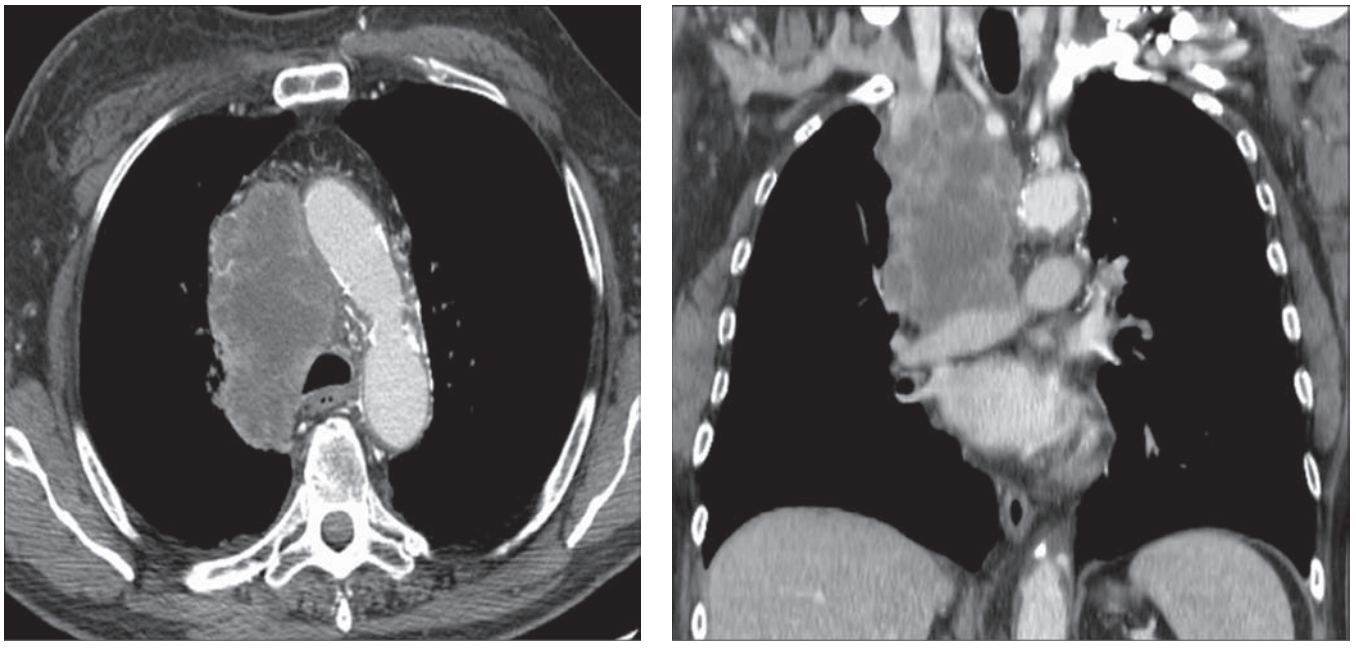


Figure 116-2 Chest radiograph of a patient with SCLC demonstrating increased right paratracheal soft tissue prominence. Note that the right paratracheal line is greater than 3 mm. *(Used with permission of Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*

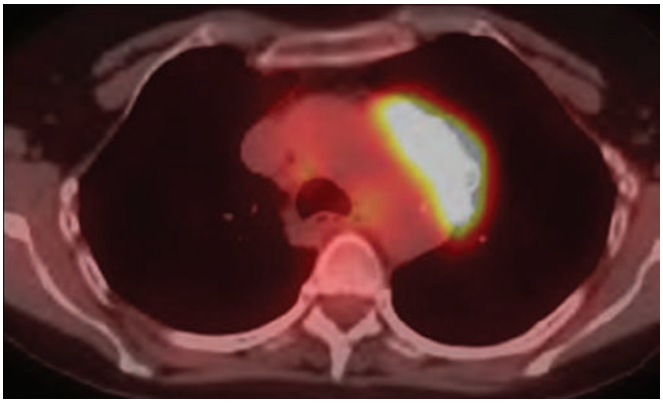
Radiographic studies typically demonstrate a central mass (75% of patients) with or without hilar nodal involvement (Figs. 116-2–116-4). Postobstructive atelectasis and pneumonia are very common with SCLC, but cavitation on chest radiograph suggests the alternative diagnosis of squamous cell lung cancer.

Laboratory evaluation reveals mild abnormalities of liver function (usually elevated alkaline phosphatase, and less commonly SGOT, SGPT, or bilirubin) and/or elevated LDH in about 50% of patients. Leukopenia and thrombocytopenia are unusual.

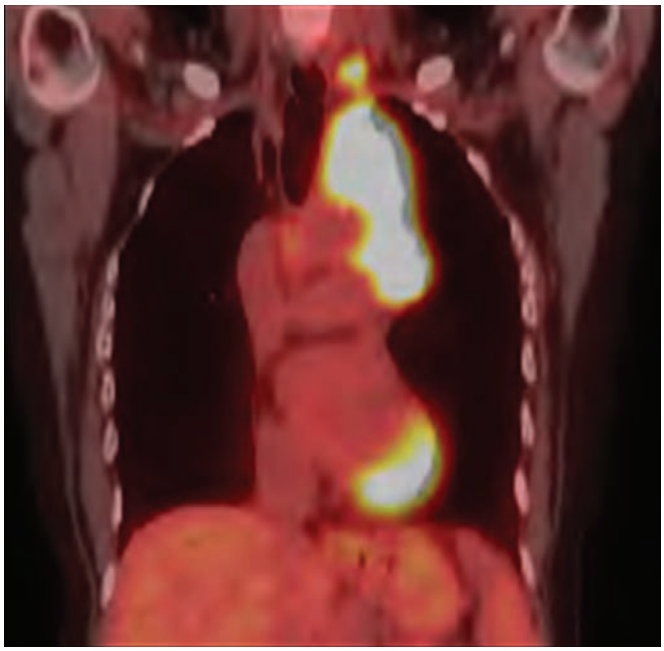


A B

Figure 116-3 Axial (**A**) and coronal (**B**) CT images of the chest of a patient with SCLC demonstrating a large, heterogeneous mass extending through the right mediastinum. *(Used with permission of Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*



A



B

Figure 116-4 Axial (**A**) and coronal (**B**) fused PET/CT images of a patient with SCLC show increased glucose avidity along the left mediastinal boarder. *(Used with permission of Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*

Two special situations warrant brief discussion. Organ involvement from SCLC can lead directly to failure of that organ, but SCLC may also impact organ function indirectly. For example, hepatic insufficiency from frank neoplastic involvement, based on the clinical picture of jaundice and abnormal liver function, is a well-described phenomenon and usually signals a poor outcome. If the same clinical picture is a result of extrahepatic biliary obstruction from nodal metastases, also well described in the literature, the patient has a better prognosis than one with diffuse liver replacement.[40] Horner syndrome, with ptosis, anhydrosis, facial edema, and sensory neuropathic pain and functional loss, is more commonly associated with NSCLC, but it has also been reported in patients with small cell disease. Obtaining a tissue diagnosis from an apical pulmonary mass is thus mandatory before radiotherapy or other treatment is started.

PARANEOPLASTIC PHENOMENA

Certain cancers cause various symptoms not attributable to direct tumor invasion or compression. Labeled *paraneoplastic syndromes* in the 1940s, these conditions are primarily due to tumor secretion of functional peptides and hormones (as occurs in endocrine paraneoplastic syndromes (Table 116-5)) or immune cross-reactivity between tumor and normal host tissues (as occurs in neurologic paraneoplastic syndromes (Table 116-6)). Paraneoplastic syndromes may be seen in any type of cancer but historically are most frequently associated with SCLC.

PARANEOPLASTIC ENDOCRINE SYNDROMES

Because paraneoplastic endocrine syndromes are generally due to tumor production of hormones or peptides that lead to metabolic derangements, successful treatment of the underlying tumor often

TABLE 116-5 Selected Paraneoplastic Endocrine Syndromes Occurring in Small Cell Lung Cancer

Syndrome	Presentation/Symptoms	Laboratory Values	Management/ Treatment[a]
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia Mild = serum sodium 130–134 mmol/L Moderate = serum sodium 125–129 mmol/L Severe = serum sodium less than 125 mmol/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Fluid restriction (and encourage adequate salt and protein intake) Discontinuation of offending drugs Demeclocycline Vasopressin-receptor antagonists Conivaptan Tolvaptan Hypertonic (3%) saline **(if acute onset)**
Cushing syndrome	Muscular weakness, peripheral edema, hypertension, weight gain	Hypokalemia typically less than 3.0 mmol/L Elevated baseline serum cortisol greater than 800 nmol/L Normal to elevated midnight serum ACTH (not suppressed with dexamethasone) greater than 100 ng/L	Ketoconazole Octreotide Aminoglutethimide Metyrapone Mitotane Etomidate Mifepristone

[a] *In addition to treating the underlying malignancy.*

ACTH, adrenocorticotropic hormone; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Source: Adapted with permission from Pelosof LC, Gerber DE. Paraneoplastic Syndromes: an Approach to Diagnosis and Treatment. Mayo Clin Proc. 2010;85(9):838–854.

TABLE 116-6 Selected Paraneoplastic Neurologic Syndromes Occurring in Small Cell Lung Cancer

Syndrome	Clinical Presentation	Associated Antibodies	Additional Diagnostic Studies	Management/ Treatment
Limbic Encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (ANNA-1) anti-CRMP5 (anti-CV2) anti-Ma anti-amphiphysin	**EEG** epileptic foci in temporal lobe(s); focal or generalized slow activity **FDG-PET** increased metabolism in temporal lobe(s) **MRI** hyperintensity in medial temporal lobe(s) **CSF** pleocytosis, elevated protein, elevated IgG, oligoclonal bands	IVIG Corticosteroids Plasma exchange Cyclophosphamide Rituximab
Paraneoplastic Cerebellar Degeneration (PCD)	Ataxia, diplopia, dysphagia/ dysarthria; prodrome of dizziness, nausea, vomiting	anti-Hu (ANNA-1) anti-Yo anti-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anti-VGCC anti-mGluR1	**FDG-PET** increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum **MRI** cerebellar atrophy (late stage)	IVIG Corticosteroids Plasma exchange Cyclophosphamide Rituximab
Lambert–Eaton Myasthenic Syndrome (LEMS)	Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in myasthenia gravis); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	anti-VGCC (P/Q type)	**EMG** low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	3,4-Diaminopyridine (DAP) Guanidine Pyridostigmine Corticosteroids Azathioprine IVIG Plasma exchange
Subacute (Peripheral) Sensory Neuropathy	Paresthesias/pain (typically upper extremities before lower) followed by ataxia; multifocal/asymmetric distribution; all sensory modalities decreased but especially deep sensation/pseudoathetosis of hands; deep tendon reflexes decreased/absent; onset over weeks to months	anti-Hu (ANNA-1) anti-CRMP5 (anti-CV2) anti-amphiphysin	**NCS** reduced/absent sensory nerve action potentials **CSF** pleocytosis, high IgG, oligoclonal bands	Corticosteroids Cyclophosphamide IVIG Plasma exchange
Autonomic Neuropathy	Panautonomic neuropathy, often subacute (weeks) onset, involving sympathetic, parasympathetic, and enteric systems: Orthostatic hypotension, GI dysfunction, dry eyes/mouth, bowel/ bladder dysfunction, altered pupillary light reflexes, loss of sinus arrhythmia *Chronic Gastrointestinal Pseudoobstruction* *(CGP):* Constipation, nausea/vomiting, dysphagia, weight loss, abdominal distension	anti-Hu (ANNA-1) anti-CV2 (CRMP5) anti-nAchR anti-amphiphysin	**Abdominal x-ray/barium studies/CT** GI dilatation but no mechanical obstruction (for CGP) **Esophageal manometry** achalasia or spasms (for CGP)	*For orthostatic hypotension:* Water, salt intake Fludrocortisone Midodrine Caffeine *For pseudoobstruction:* Neostigmine

ANNA, antineuronal nuclear antibody; CRMP, Collapsin Response Mediator Proteins; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; EMG, electromyography; FDG-PET, fluorodeoxyglucose positron emission tomography; IVIG, intravenous immunoglobulin; mGluR1, metabotropic glutamate receptor subtype 1; MRI, magnetic resonance imaging; nAchR, nicotinic acetylcholine receptor; NCS, nerve conduction study; VGCC , voltage-gated calcium channel.
Source: Adapted with permission from Pelosof LC, Gerber DE. Paraneoplastic Syndromes: an Approach to Diagnosis and Treatment. Mayo Clin Proc. 2010;85(9):838–854.

improves these conditions. These disorders are typically detected after a cancer diagnosis. Development of a paraneoplastic endocrine syndrome does not necessarily correlate with cancer stage or prognosis.[41]

Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH is characterized by hypo-osmotic, euvolemic hyponatremia. Although it affects only 1% to 2% of all patients with cancer, SCLC accounts for most of these cases, with approximately 10% to 45% of all patients with SCLC developing SIADH.[42] In SIADH, tumor cells produce ADH (also known as arginine vasopressin or vasopressin) and atrial natriuretic peptide.[43,44]

The symptoms of SIADH depend on the degree and rapidity of onset of hyponatremia. Mild symptoms include headache, memory difficulties, and weakness. More severe symptoms (altered mental status, seizures, coma, respiratory collapse, death) may be seen with

serum sodium levels less than 125 mEq/L, especially if developing within 48 hours.[45] If hyponatremia develops over a longer time period, neurologic complications may not develop.

The time course of hyponatremia also impacts treatment. With symptomatic hyponatremia developing within 48 hours, the serum sodium level may be raised 1 to 2 mEq/L/h and usually no more than 8 to 10 mEq/L in the first 24 hours. With chronic hyponatremia, due to the brain generating endogenous osmoles to minimize intracellular swelling, rapid correction may lead to water egress, brain dehydration, and *central pontine and extrapontine myelinolysis*. This condition, which may be irreversible, features lethargy, dysarthria, spastic quadriparesis, and pseudobulbar palsy. Accordingly, a correction goal of 0.5 to 1.0 mEq/L is recommended for these patients.[42,45]

Successful treatment of the underlying tumor (which is frequently attainable given the chemosensitivity of SCLC) may normalize sodium levels in days to weeks.[42] In the short-term, fluid restriction (usually <1000 mL/d) along with adequate dietary protein and sodium (with the use of salt tablets if needed) may be implemented. In many instances, administration of standard intravenous fluids may exacerbate SIADH. Normal (0.9%) saline has an osmolality of 308 mOsm/kg, which is often less than urine osmolality in SIADH. Thus, normal saline infusion will result in free water retention and worsening of the hyponatremia. By contrast, hypertonic (3%) saline has an osmolality of 1026 mOsm/kg, which almost always exceeds that of the urine. The primary pharmacologic treatment of SIADH is demeclocycline (usually given at a dose of 300–600 mg per day, but can be increased to 1200 mg per day), an antibacterial agent that interferes with the renal response to ADH. In patients on demeclocycline responding to chemotherapy, careful monitoring is required to ensure against overcorrection and resulting hypernatremia.

Cushing Syndrome

Approximately 5% to 10% of cases of Cushing syndrome (hypercortisolism) are paraneoplastic, and 50% to 60% of these paraneoplastic cases occur with neuroendocrine lung tumors (SCLC and bronchial carcinoids).[46] Paraneoplastic Cushing syndrome is due to tumor secretion of ACTH or corticotropin-releasing factor (CRF). In turn, this results in adrenocortical hyperplasia and release of cortisol. Clinical features include hypertension, hypokalemic metabolic alkalosis, hyperglycemia, edema, and muscle weakness. Compared to Cushing disease (i.e., hypercortisolism due to a pituitary adenoma) onset is often more abrupt and weight gain with centripetal fat distribution is less common.

Ectopic (i.e., paraneoplastic) Cushing syndrome is distinguished from a pituitary source by failure to respond to high-dose dexamethasone suppression. For this test, 2 mg of dexamethasone is administered orally every 6 hours for 72 hours. Levels of urine 17-hydroxycorticosteroid (an inactive product of cortisol metabolism) are measured at 9 am and midnight of days 2 and 3 of the test. The test is considered positive if 17-hydroxycorticosteroid levels are reduced by 50% or more. The primary tumor is then located using CT, MRI, or somatostatin receptor scintigraphy (i.e., octreotide scan). Due to the distinct biochemical profile of paraneoplastic Cushing syndrome, inferior petrosal sinus sampling (to rule out a pituitary etiology) is generally not required.[46]

Therapy includes treatment of the underlying tumor and agents that inhibit steroid production. These include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Ketoconazole is usually the best tolerated of these options, despite nausea, hepatotoxicity, and potential for drug–drug interactions. Supportive care includes antihypertensive agents and diuretics, with careful monitoring of serum potassium. Adrenalectomy may be considered when medical therapy is not successful.

Other Paraneoplastic Endocrine Syndromes

Although paraneoplastic hypercalcemia can be seen with several malignancies (including squamous NSCLC, breast, renal, and lymphoma), it is extremely unusual in patients with SCLC, even among cases with skeletal involvement. Similarly, tumor-associated hypoglycemia, a rare paraneoplastic phenomenon occurring most commonly in sarcomas, mesothelioma, and gastrointestinal cancers, is also unusual in SCLC.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

Immune cross-reactivity between tumor cells and components of the nervous system gives rise to paraneoplastic neurologic syndromes. *Onconeural antibodies* are produced by a patient in response to a developing cancer. Due to antigenic similarity, these onconeural antibodies and associated T lymphocytes inadvertently attack the nervous system as well.[47] Although paraneoplastic neurologic syndromes occur in less than 1% of cancer patients overall, they are seen in up to 5% of patients with SCLC and up to 10% of patients with lymphoma or myeloma.[48] Overrepresented malignancies either produce neuroendocrine proteins (e.g., SCLC), contain neuronal components (e.g., teratomas), involve immunoregulatory organs (e.g., thymomas), or affect immunoglobulin production (e.g., lymphoma, myeloma). The potential for immune cross-reactivity with SCLC is apparent through its immunophenotypic profile. CD56, which is positive in the majority of SCLC cases, is also known as NCAM.

In direct contrast to paraneoplastic endocrine syndromes, over 80% of cases of paraneoplastic neurologic syndromes are detected prior to a cancer diagnosis.[41] Because most patients diagnosed with an apparent paraneoplastic neurologic syndrome will not have known cancer at the time, screening for an underlying tumor is indicated. This process includes complete history and physical examination, as well as imaging studies. If chest, abdomen, and pelvic CT scans are negative, FDG-PET or combined PET-CT may identify the underlying tumor, particularly in the case of an early central SCLC, which may be difficult to identify anatomically amid surrounding mediastinal structures.[49] Occasionally, the clinical syndrome and associated antibodies may sufficiently suggest a particular cancer to prompt disease-specific imaging modalities such as mammography. If no malignancy is identified, it is reasonable to consider clinical and radiographic surveillance every 3 to 6 months for 2 to 3 years. Beyond that time, the likelihood of a subsequent cancer diagnosis decreases substantially.[50]

Because tumor cells do not directly produce the causative agents (i.e., onconeural antibodies) and because these antibodies may cause permanent neuronal damage, successful cancer treatment does not necessarily result in neurologic improvement. Immunosuppressive therapy – including corticosteroids, other agents, intravenous gamma globulin, and plasma exchange – is a principal component of therapy.

Establishing a diagnosis of a paraneoplastic neurologic syndrome may require imaging, serologies, electroencephalography, electromyography, nerve conduction studies, and cerebrospinal fluid (CSF) analysis for signs of inflammation. Onconeural antibodies lack both sensitivity and specificity, as up to 30% of patients with apparent paraneoplastic neurologic syndromes do not have detectable antibodies and well-defined onconeural antibodies may be detected in individuals with no neurologic illness.[51]

The impact of these conditions on prognosis is complex and multifactorial. Development of a paraneoplastic neurologic syndrome may result in diagnosis of a cancer at an otherwise clinically occult and highly treatable stage. Conversely, the syndrome itself may cause substantial morbidity, independent of the underlying malignancy. Finally, onconeural antibodies may indicate an antitumor immunologic effect; patients with SCLC who have anti-Hu antibodies are more likely to have complete response to therapy and have longer survival than patients without anti-Hu antibodies.[52] While such observations raise the question whether treatment of paraneoplastic neurologic syndromes with immune modulation could lead to cancer progression, this hypothetical scenario has not been reported clinically.[41]

In SCLC, well-described paraneoplastic neurologic syndromes include limbic encephalitis (LE), cerebellar degeneration,

Lambert–Eaton myasthenic syndrome (LEMS), subacute (peripheral) sensory neuropathy, and autonomic neuropathy.

Limbic Encephalitis

LE features mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction), with onset over days to months. In SCLC, which accounts for 40% to 50% of LE cases, the associated antibody is usually anti-Hu (also known as antineuronal nuclear antibody-1 [ANNA-1]). Characteristic findings may also be seen on electroencephalogram, MRI, and CSF analysis.[53]

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD), manifesting with ataxia, dysarthria, and diplopia, is seen with SCLC (incidence approximately 2%), as well as with gynecologic malignancies and lymphomas. Antibodies that react against cytoplasmic proteins of cerebellar Purkinje cells are often found in these patients. One such antibody, anti-Yo, attacks the cdr2 proteins in the Purkinje cells. Treatment may include steroids, plasmapheresis, and chemotherapy.

Lambert–Eaton Myasthenic Syndrome

LEMS is a result of IgG autoantibodies directed against presynaptic P/Q-type voltage-gated calcium channels. These antibodies are estimated to occur in 5% of patients with SCLC. Clinically, the syndrome presents with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely with cranial nerve symptoms. As contrasted with patients with myasthenia gravis, strength *improves* with serial effort, and the weakness associated with LEMS improves over the course of the day. Plasma exchange and intravenous immunoglobulin can provide short-term benefit, whereas 3,4-diaminopyridine (which enhances the release of acetylcholine from presynaptic terminals), prednisone, and azathioprine can provide limited long-term benefit. Some patients who respond to chemotherapy have resolution of the neurologic abnormalities.

Subacute (Peripheral) Sensory Neuropathy

With onset over weeks to months, this syndrome initially features paresthesias and pain (typically multifocal, asymmetric, with upper extremities involved before lower), followed by ataxia. Nerve conduction studies demonstrate reduced or absent sensory nerve action potentials. A number of onconeural antibodies, including Anti-Hu, may be seen. Lung tumors (principally SCLC) account for 70% to 80% of cases.

Autonomic Neuropathy

Paraneoplastic autonomic neuropathy typically has a subacute onset over weeks and may involve sympathetic, parasympathetic, and enteric systems.[54,55] Symptoms include orthostatic hypotension, gastrointestinal dysfunction (pseudoobstruction), and dry eyes and mouth. A number of onconeural antibodies, including anti-Hu and anti-CRMP5 (anti-CV2), may be detected.[56] Other findings suggestive of this condition are loss of sinus arrhythmia (naturally occurring variation in heart rate that occurs during a breathing cycle) on EKG, GI dilatation without obstruction on abdominal imaging, and achalasia or spasms on esophageal manometry. Supportive care may include fludrocortisones, midodrine, caffeine, and neostigmine (for pseudoobstruction).[57]

EXTRAPULMONARY SMALL CELL CARCINOMA

The knowledge that small cell cancers can arise from tissues other than the lungs has existed since 1930.[58] Extrapulmonary small cell cancer (EPSCC) remains relatively rare, accounting for <5% of diagnosed small cell cancers.[59] EPSCC can arise from a variety of primary sites, including the female genital tract (commonly the uterine cervix), the genitourinary organs (primarily bladder and prostate), the head and neck, the gastrointestinal tract, and breast.[60,61]

Staging of EPSCC is similar to that of SCLC. LS is defined as disease confined to the primary site and regional lymph nodes. Any spread beyond the regional lymph nodes is ES disease. Most authorities would perform the same staging evaluation on these patients as in those with SCLC.

Due to the rarity of this entity, the optimal treatment of EPSCC is not clearly defined. Most case series are from single institutions and include EPSCC from a variety of primary sites. In general, the treatment approaches have been adapted from those utilized in SCLC. Surgery has been shown to be curative in selected patients with organ-confined disease. Unfortunately, as with SCLC, EPSCC is often characterized by early metastasis and a fairly aggressive course. Combined chemotherapy and radiation can be utilized for LS disease. ES EPSCC responds to platinum-based chemotherapies in approximately 75% of the cases, but these responses are typically short-lived. In a recent large retrospective single institution review from Australia, those EPSCC patients with LS disease had a median survival of 1.4 years and a 1-year survival rate of 63%, while those with ES stage disease had median and 1-year survivals of 0.7 years and 24%, respectively.[60] In their cohort, patients with a primary lesion in the female genital tract or the head and neck had superior outcomes when compared to other primary sites.

PROGNOSTIC FACTORS

A variety of pretreatment factors have been reported as having value in predicting therapeutic outcomes for patients with SCLC. Since the aggressiveness of therapy may depend on this perceived outcome, it is important to determine before treatment how a patient is *likely* to do. The strongest and most consistent prognosticators from nearly all studies have been stage of disease (limited vs. extensive) and performance status at presentation. The importance of stage has already been mentioned. ES patients have a lower chance of achieving a complete response to chemotherapy and a much shorter survival than those with LS disease. The performance status or ability of the patient to carry out normal daily activities has a profound effect both on the ability to tolerate chemotherapy and the efficacy of the drugs that are administered (Table 116-7). In general, SCLC patients with a poor performance status have a lower chance of response to chemotherapy, a higher probability of experiencing clinical toxicity, and a worse overall survival.[62–64] However, as opposed to NSCLC patients, poor performance status does not automatically exclude SCLC patients from receiving aggressive treatment. The occasional SCLC patient with significant functional impairment can experience improvement with chemotherapy.

The impact of gender on prognosis is debated. Some, but not all, studies have found that female gender is an independent predictor of better survival in SCLC.[62–65] In several of these series, the improved prognosis seen in women was limited to those with LS disease and those of younger age (<60 years old).[64,65]

The only serum marker consistently shown to be of prognostic value in SCLC is the serum concentration of LDH. This enzyme is known to be a nonspecific marker of cell turnover and pulmonary inflammation. A baseline (pretreatment) serum LDH is elevated in 33% to 57% of all SCLC patients and in as many as 85% of patients with ES disease. In most SCLC series, a normal baseline LDH is an independent predictor of better outcome, with hazard ratios of 1.6 to 1.9 for overall survival.[62,64]

The continued use of tobacco is also a potential adverse prognostic factor. Videtic et al.[66] evaluated the impact of continued smoking in patients with LS SCLC. In a retrospective review of 215 patients who received curative intent chemotherapy and radiation for LS disease from 1989 to 1999 patients who continued to smoke during treatment had a significantly inferior survival to those who quit smoking (median survivals 13.6 months and 15.8 months; 5-year survival rates of 4% and 8.9%, respectively). Though one might assume that those patients who continued to smoke tolerated treatment more poorly, the authors found no statistical differences between the groups in the numbers of patients that required breaks in treatment due to toxicity.

TABLE 116-7 Performance Status Scales

KARNOFSKY			ECOG	
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease	0	Fully active, able to carry on all predisease performance without restriction
	90	Able to carry on normal activity; minor signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
	80	Normal activity with effort; some signs or symptoms of disease		
Unable to work; able to live at home and care for most personal needs, varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
	60	Requires occasional assistance, but is able to care for most of his personal needs		
	50	Requires considerable assistance and frequent medical care	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance		
	30	Severely disabled; hospital admission is indicated although death not imminent	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
	20	Very sick; hospital admission necessary; active supportive treatment necessary		
	10	Moribund; fatal processes progressing rapidly		
	0	Dead	5	Dead

Source: Data from Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisted: reliability, validity, and guidelines. J Clin Oncology. 1984;2(3):187–193; Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–655.

There are several possible explanations for these results. Nicotine has been shown to serve as a growth factor for some SCLC cell lines.[67] Smokers often have increased carboxyhemoglobin levels with resultant lower oxygen saturations than nonsmokers, and this may reduce the antitumor effects of radiation, which are at least partially oxygen dependent.[68–70] Lastly, it is well established that SCLC patients who survive are at increased risk of developing additional smoking-related malignancies, as well as other smoking-related illnesses. It is likely that continued smoking further increases these risks. Though this retrospective study has limitations, it suggests a compelling rationale for aggressive attempts at smoking cessation in this population.

TREATMENT

The roles of surgery, chemotherapy, and radiation in the treatment of SCLC are considered below. In addition, special circumstances, including treatment in the elderly and in those with poor performance status, are discussed.

■ SURGERY

Surgery was abandoned as a standard treatment modality for the majority of patients with SCLC in the 1970s following the publication of the results of a trial by the British Research Medical Council randomizing patients with LS disease to single modality treatment with radiation or surgery. Though outcomes were poor in both treatment arms, the 5- and 10-year survivals were significantly inferior with surgery.[71] A subsequent Lung Cancer Study Group trial also failed to demonstrate a benefit to surgery when compared with radiation in 340 LS patients following induction chemotherapy.[72] A legitimate criticism of these trials is that patients were inadequately staged when compared with modern standards. In addition, in both trials, only a small fraction of eligible patients had clinical stage I and II disease, which are the groups theoretically most likely to benefit from resection.

Over the past decade, there has been a renewed interest in surgery as a potential treatment modality for highly selected patients with very limited stage (VLS) SCLC. A number of primarily retrospective single institution series have reported outcomes with surgery followed by adjuvant chemotherapy (and sometimes radiation) in patients with LS SCLC. In patients with pathologic stage I disease, the ~5-year survival ranges from 40% to 86%.[73–75] In addition, analyses of the SEER database and the NCDB have shown improved outcomes for those patients with VLS SCLC that are treated with surgery.[3,76,77] Unfortunately, interpretation of these retrospective series and database reviews is hampered by inherent selection bias as well as by the heterogeneity of adjuvant treatment (chemotherapy and radiation) utilized. Ultimately, only randomized trials comparing surgery followed by adjuvant chemotherapy to definitive chemotherapy and radiation in SCLC patients with VLS disease will clearly define the role of surgery in this population.

Current guidelines suggest that surgical resection should be considered only in patients with clinical stage I (T1 or T2, N0, M0) SCLC and with adequate cardiac and pulmonary function to tolerate a thoracotomy. Patients should undergo rigorous staging, including invasive evaluation for mediastinal nodal disease as well as extensive radiographic assessment for distant metastases. Following complete resection, it is recommended that patients without nodal metastases receive adjuvant chemotherapy and that those with nodal metastases receive concurrent chemotherapy and radiation. Prophylactic cranial irradiation (PCI) can also be considered in selected patients (see below). At most centers, fewer than 5% of SCLC patients will be considered candidates for a surgical approach.[73]

■ CHEMOTHERAPY

Chemotherapy for SCLC can be considered with regard to first-line and second-line regimens.

First-Line Chemotherapy

In contrast to NSCLC, SCLC is classically associated with exquisite chemosensitivity, which may reflect its rapid doubling time and high growth fraction. In reality, the difference in treatment outcomes is modest with comparable median survivals in SCLC and NSCLC following chemotherapy for metastatic disease. Numerous chemotherapeutic agents have demonstrated activity in SCLC (Table 116-8). Untreated, patients with SCLC rarely survive more than a few months. Chemotherapy markedly prolongs survival compared to best supportive care.[78] In LS disease, chemotherapy combined with thoracic

TABLE 116-8 Chemotherapeutic Agents with Activity in Small Cell Lung Cancer

Platinum compounds (cisplatin, carboplatin)
Podophyllotoxins (etoposide, teniposide)
Camptothecins (irinotecan, topotecan)
Alkylating agents (ifosfamide, cyclophosphamide)
Anthracyclines (doxorubicin, epirubicin, amrubicin)
Taxanes (paclitaxel, docetaxel)
Vinca alkaloids (vincristine, vinorelbine)
Nitrosoureas (lomustine [CCNU])
Antimetabolites (methotrexate, gemcitabine)

radiation achieves a response in 80% to 90% of patients, and a complete response in the range of 40% to 60%. In LS disease, median survival in treated patients is 15 to 20 months, with 5-year survival rates of 10% to 13%. In ES disease, the response rate is 60% to 80%, with a complete response rate around 15% to 35%. The median survival for ES patients treated with chemotherapy remains 7 to 9 months, with few long-term survivors. Patients with bulky or ES disease may be considered at risk for tumor lysis syndrome, although this event is quite rare in clinical practice. Prophylaxis against this complication, which generally includes hydration and allopurinol, may be considered.[79] It should also be noted that systemic chemotherapy frequently yields intracranial responses in patients with brain metastases, with response rates ranging from 27% to 85%.[80,81]

The earliest treatments for SCLC included alkylating agents, such as nitrogen mustard and subsequently cyclophosphamide, given as monotherapy. As responses to single agents were rare, the focus changed to combinations of drugs, each with independent activity against SCLC. When given in combination, these drugs had synergistic activity, and lowered the likelihood of complete tumor resistance. Until the mid-1980s the combination of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) was commonly used as first-line therapy. For the past three decades, platinum-based regimens have become the most frequently used combinations. A meta-analysis of 19 randomized trials encompassing over 4000 cases demonstrated an increase in response rates and decrease in risk of death for patients receiving cisplatin-containing chemotherapy.[82]

Currently, the two-drug regimen of cisplatin and etoposide (PE) is considered the standard of care for SCLC chemotherapy. In randomized trials, this combination appears to be at least as effective as CAV and has less toxicity.[83,84] The PE regimen is typically given over 3 days (cisplatin on day 1, etoposide on days 1–3) every 3 weeks for four to six cycles. Modifications to the PE regimen have included the substitution of carboplatin for cisplatin, replacing etoposide (a topoisomerase II inhibitor) with irinotecan or topotecan (topoisomerase I inhibitors), adding other agents, increasing dose intensity, and prolonging the duration of chemotherapy.

Carboplatin has a more favorable toxicity profile than cisplatin, with less nephrotoxicity, ototoxicity, neurotoxicity, and emetogenicity. Because pre- and posthydration are not required, its administration is also more convenient (typically 45 minutes for carboplatin vs. 4–6 hours for cisplatin, including hydration). In a randomized trial comparing the two agents, cisplatin demonstrated slightly higher overall and complete response rates than did carboplatin: Overall response 64% versus 50%; complete response 16% versus 10%. However, there was no significant difference in overall survival.[85] Based on a more favorable toxicity profile, most clinicians in the United States employ carboplatin–etoposide for the treatment of ES SCLC, with cisplatin–etoposide preferred for the treatment of LS SCLC due to the possibility of a higher response rate.

Cisplatin plus irinotecan has been compared to cisplatin plus etoposide in a number of clinical trials. In a Japanese study, the irinotecan-containing arm demonstrated a significantly higher response rate (84% vs. 68%), longer median survival (12.8 months vs. 9.4 months), and higher 2-year survival rate (19.5% vs. 5.2%).[86] However, three larger studies performed in Western populations did not confirm these findings, raising the possibility of pharmacogenomic differences between the populations.[87–89]

Three- and four-drug regimens, in which agents such as paclitaxel, ifosfamide, cyclophosphamide, and epirubicin are added to PE have yielded mixed results. Some studies have demonstrated higher response rates and modest prolongation of survival, but often at the cost of increased toxicity, including higher rates of treatment-related mortality in some instances.[90–92] Administration of non–cross-resistant regimens such as PE and CAV in alternating or sequential fashion has not consistently demonstrated a survival benefit.[93] Several studies have explored increasing chemotherapy dose intensity via dose escalation, shortening the interval between cycles, and providing hematopoietic support through growth factor administration or stem cell transplantation.[94–96] None of these approaches has demonstrated consistent benefit.

Maintenance chemotherapy, which has recently emerged as a new standard of care for advanced NSCLC, has also been studied in SCLC. In these trials, patients with nonprogressing disease after four cycles of combination induction therapy immediately proceed to maintenance monotherapy with agents such as topotecan or etoposide.[97,98] Individual trials have not demonstrated a significant increase in overall survival. Although a meta-analysis has suggested a modest survival advantage,[99] few if any oncologists employ this approach in the management of SCLC.

Based on the extant literature, it appears the optimal therapy for a majority of SCLC patients is PE with the addition of thoracic radiotherapy for those with LS disease (vide infra). Treatment beyond four to six cycles is unwarranted in the first-line setting. There is little support for the use of dose intensification or so-called "dose dense" therapy as a course of routine treatment. Furthermore, the need for expensive supportive care drugs such as colony-stimulating factors or erythropoietin is greatly diminished if one uses EP at standard dosing.

Second-Line Chemotherapy

Although the majority of SCLC patients treated with first-line chemotherapy demonstrate tumor shrinkage, most eventually relapse. Response to first-line therapy tends to be brief, with median duration 6 to 8 months. Along with performance status and tumor extent (i.e., limited vs. extensive), the time to relapse after first-line therapy is among the most important prognostic factors in SCLC.[100] The timing of relapse also has implications when considering further treatment options. Patients with disease progression can be categorized as *sensitive relapse* (tumor progression >90 days after last day of initial treatment), *resistant relapse* (tumor progression ≤90 days after last day of initial treatment), or *refractory* (tumor progression during initial therapy or unresponsiveness to initial therapy). For patients with sensitive relapse, response rates to second-line chemotherapy are 30% to 40%, and median survival is approximately 6 months. For those with resistant relapse or refractory disease, responses occur in less than 10% of cases.

In the United States, the topoisomerase I inhibitor topotecan is currently the only drug FDA approved for second-line treatment. Oral and intravenous topotecan formulations used as a single agent exhibit response rates of 11% to 37%.[101–103] Modest response rates have also been demonstrated with the use of single agents such as irinotecan, paclitaxel, docetaxel, oral etoposide, vinorelbine, gemcitabine, and amrubicin. These responses are rarely durable.

While molecularly targeted therapies (namely monoclonal antibodies and small molecule inhibitors) now have an established role in the treatment of NSCLC, these agents have demonstrated little activity against SCLC. Because c-Kit is frequently overexpressed in

SCLC, the c-Kit inhibitor imatinib has been studied in SCLC but has not demonstrated a response rate or survival benefit, even in populations selected according to tumor c-Kit status.[104,105]

Antiangiogenic agents such as the antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab – which is approved for nonsquamous NSCLC – have also been evaluated in SCLC. While efficacy data were promising in LS SCLC, concerns emerged over the possibility of increased rates of tracheoesophageal fistula formation.[106] For ES SCLC, the combination of PE plus bevacizumab yielded a response rate of 64%, median progression-free survival of 4.7 months, and median overall survival of 10.9 months.[107] Bcl-2, an antiapoptotic protein found in high concentrations in SCLC cell lines and tumors, has been targeted with the antisense nucleotide oblimersen. Despite extensive preclinical data supporting this approach, in a phase II trial of carboplatin–etoposide plus oblimersen or placebo, outcomes were worse with the addition of oblimersen (1-year survival 24% vs. 47%).[108]

■ RADIATION THERAPY

The role of radiation in treatment of SCLC may be considered with respect to thoracic radiation and prophylactic cranial irradiation.

Thoracic Radiation Therapy

SCLC is a malignancy that is sensitive to radiation. Thoracic radiation therapy (TRT) as a single modality results in an objective tumor response rate of 75% in LS disease, and may cure as many as 5% of these patients.[71] Initial clinical trials combining TRT with chemotherapy yielded mixed results. For the most part, these early trials demonstrated a decrease in local recurrence but no clear survival benefit. However, two meta-analyses published in 1992 reported a statistically significant 5% improvement in overall survival with the addition of radiation to chemotherapy in SCLC patients with LS disease.[109,110] These reports established concurrent chemotherapy and radiation as the standard of care for fit patients with LS SCLC. Significant questions remained regarding the optimal timing, dose, and fractionation of radiation. A number of trials have evaluated early (typically <30 days after initiation of chemotherapy) versus late radiation and have yielded conflicting results. Both a subsequent meta-analysis and systematic review of the available data concluded that early radiation resulted in a small, but significant, improvement in overall survival and have established early TRT as the preferred approach for patients with LS disease.[111,112]

The optimal fractionation and dose of TRT are also unknown. The Eastern Cooperative Oncology Group conducted a randomized trial in LS SCLC patients comparing twice-daily TRT to 45 Gray (Gy) with the prior standard of once-daily TRT to 45 Gy. Both treatment arms received standard EP chemotherapy. They reported a significantly improved median (23 vs. 19 months) and 5-year (27% vs. 11%) survival favoring twice-daily TRT.[113] Despite these results, this strategy has not been widely adopted, presumably due to the inconvenience of administering twice-daily TRT. Many experts advocate once-daily TRT to 60 to 70 Gy, a radiobiologic dose that is similar to 45 Gy administered twice daily, although there are not yet data to definitively validate this approach.

Radiation plays primarily a palliative role in ES disease, and can be used for symptomatic control in bony, pulmonary, and brain metastases. One randomized trial from Europe evaluated the addition of TRT to patients with ES disease and reported an improvement in median overall survival from 11 to 17 months favoring those who received TRT.[114] In this study, patients with ES disease who experienced a complete response at all distant metastatic sites after three cycles of chemotherapy were randomized to TRT and continued chemotherapy or chemotherapy alone. However, the results of this trial are inconsistent with multiple other studies that failed to demonstrate a survival benefit with TRT. Nonetheless, ongoing trials are attempting to confirm a benefit to TRT in highly selected ES patients with an excellent response to chemotherapy.

Prophylactic Cranial Irradiation

As detailed earlier, the brain is a frequent site of metastatic spread in SCLC. Ten percent to 18% of patients have brain involvement at presentation, and 60% to 80% of SCLC patients who survive at least 2 years will develop brain metastases.[32,33,115] The prevailing assumption is that micrometastases in the brain are relatively protected from systemic chemotherapy by the blood–brain barrier. Given these facts, a number of randomized trials evaluated PCI in LS SCLC patients who had a complete or near-complete response with chemotherapy and TRT. These studies reproducibly showed significant reductions in the incidence of brain metastases with PCI but had conflicting results regarding the impact of PCI on overall survival. In 1999, an individual patient data meta-analysis of all available randomized trials reported a 5.4% increase in overall survival at 3 years (15.3% vs. 20.7%) favoring PCI. PCI also reduced the cumulative risk of brain metastases at 3 years from 58.6% to 33.3%.[116]

Until recently, the consensus opinion was that patients with ES disease were not likely to benefit from PCI. Given the poor prognosis in ES patients and the relatively limited ability to control their generally widespread metastatic disease, it was presumed that they would succumb to their systemic disease prior to occult micrometastatic disease in the brain producing a significant clinical impact. However, a trial from Europe has challenged that assumption. Patients with ES disease who experienced at least a partial response to chemotherapy were randomized to PCI or observation. The primary end point, symptomatic brain metastases, was reduced from 41.3% in the observation arm to 16.8% with PCI. Surprisingly, both median survival (6.7 months vs. 5.4 months) and 1-year survival (27.1% and 13.3%) were significantly improved with PCI.[117] In short-term quality-of-life analyses, overall functioning was similar between the two groups, but fatigue and hair loss were more frequent with PCI.

Current guidelines recommend consideration of PCI for all LS patients with a good performance status who have attained a complete or near-complete response after chemotherapy and radiation. In addition, fit ES patients whose disease responds to initial chemotherapy are also candidates for PCI. Concern has been raised about long-term neurocognitive impairment from PCI, which includes potential effects on communication and memory that may be dose dependent.[118,119] Therefore, before undergoing PCI, patients should be counseled regarding the expected risks and benefits of this intervention.

■ TREATMENT IN THE ELDERLY AND PATIENTS WITH A POOR PERFORMANCE STATUS

In most patients with metastatic solid tumors and a poor performance status, chemotherapy is felt to be of limited benefit given the high likelihood of severe toxicity and the low chance of a significant durable tumor response. As noted earlier, given the relative chemosensitivity of SCLC, an impaired performance status does not necessarily preclude treatment. Some SCLC patients with functional impairment can experience significant tumor response and resultant modest improvements in their performance status after treatment with chemotherapy.

Similarly, age should not be the sole criterion by which treatment decisions in SCLC are based. In recent series, the median age at diagnosis in SCLC is >65 years and approximately 40% of patients are ≥70 years.[3] Clearly, elderly (typically defined as >70 years old) patients with SCLC will be encountered frequently in clinical practice. Treatment of these patients is complicated by underlying comorbidities as well as decreased organ function that may lead to poor tolerance of treatment. Unfortunately, the elderly are typically underrepresented in clinical trials in SCLC and therefore there is little definitive prospective data on the appropriate management of this group. The available information suggests that elderly patients who are able to tolerate standard treatment for SCLC fair as well as their younger counterparts.[120] In addition, prospective randomized trials of "less intensive treatment" in those felt to be at risk for excess

toxicity from standard therapy found inferior survival and palliation on the "less intensive" treatment arms.[121] Current recommendations are to consider comorbidities and functional capacity, rather than age alone, when making treatment recommendations for these patients.

LATE COMPLICATIONS

The treatment of SCLC can cause more morbidity than the neoplasm itself. Both radiotherapy and chemotherapy cause side effects specific to the agent used. Irradiation can have early (esophagitis, pneumonitis, superficial skin burns) and late (pulmonary fibrosis, late cardiac disease, myelitis) toxicities. Chemotherapy toxicities depend on the specific regimen used, but they generally include alopecia, nausea and vomiting, and myelosuppression. Bone marrow suppression can lead to life-threatening bleeding episodes (from thrombocytopenia), but more commonly is associated with neutropenic fevers, and occasionally fatal infections. Published series have demonstrated that episodes of febrile neutropenia occur in roughly 30% of treated patients, documented infection in 5% to 15%, and fatal infection in 7%. Prevention of infection in patients treated with chemotherapy with or without irradiation has received significant attention. Measures have included prophylactic use of antibiotics and granulocyte colony-stimulating factor (GCSF). Recently, a large randomized trial showed that GCSF in addition to chemotherapy led to a reduction of the number of episodes of neutropenic fever and documented infections. Many oncologists do not agree that this is a cost-effective measure, however.

Given that the majority of patients with SCLC are older and have extensive smoking histories, it is not surprising that cardiovascular, cerebrovascular, and pulmonary diseases are extremely common in this population. Thus, a large portion of long-term survivors of SCLC succumb to these other diseases. Up to one-third of all long-term surviving patients, especially those who continue to smoke, have recurrence of their SCLC, or more rarely, develop a new SCLC. Other aerodigestive cancers, particularly NSCLC, are extremely common, leading some investigators to propose trials of chemoprevention agents in long-term survivors of SCLC. Finally, patients with SCLC have an increased risk of developing a hematologic malignancy. Secondary leukemias are believed to be related to treatment, especially if chemotherapy with alkylating agents was employed. Some of these posttreatment leukemias have also shown a deletion of chromosome 3, suggesting an underlying predisposition or common ancestor cell to both cancers, instead of a secondary leukemia arising from alkylating chemotherapy-induced genetic damage. Overall, 2-year survivors of SCLC face a 3.5-fold increased risk of a second cancer (mostly NSCLC) compared to the general population. The risk of a second lung cancer is increased 13-fold among those patients who received TRT and sevenfold among those who did not undergo radiation, with ongoing smoking further escalating risk.[122] Accordingly, long-term surveillance is mandatory in these otherwise cured patients.

CONCLUSION

SCLC is distinct from the other three major histologic varieties of pulmonary malignancies, which tend to behave similarly and are lumped together under the generic rubric "NSCLC." It is biologically more active, secreting multiple hormones and neural markers, resulting in a number of paraneoplastic syndromes. It is thought of as a systemic disease, and treatment nearly always includes chemotherapy. Although the tumor is highly responsive to chemotherapy, and survival is markedly prolonged with drug treatment, the complete eradication of SCLC remains a relatively rare event. Long-term survivors are still subject to a host of cardiopulmonary conditions, as well as second malignancies and recurrence of their SCLC. Over the last 30 years, clinical trials have made little progress in prolonging the survival of SCLC patients, and developments clearly lag behind those made in the more common NSCLC. In the era of tumor genomic profiling and molecularly targeted therapies, there is hope that new insights into tumor biology and novel therapies may show promise in the treatment of this aggressive and often fatal cancer.

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CHAPTER 117

Primary Lung Tumors Other than Bronchogenic Carcinoma: Benign and Malignant

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Steven M. Keller

Bronchogenic carcinoma represents the overwhelming majority of pulmonary neoplasms. However, a great variety of tumors originate in the lung.[1] Benign neoplasms (Table 117-1) comprise less than 1% of all resected lung tumors and nonbronchogenic primary pulmonary malignancies (Table 117-2) account for 3% to 5% of all lung tumors. Numerous classifications of these rare tumors have been devised, though none are widely accepted. Due to the disparate histogenesis of these varied tumors, it is best to discuss them individually.

BENIGN TUMORS

A broad array of benign primary lung tumors has been recognized, as discussed below.

MUCUS GLAND ADENOMA

Mucus gland adenoma, also known as bronchial cystadenoma, is a benign epithelial tumor that originates in the bronchial submucus glands and presents as an exophytic endobronchial mass.[2] Mucus gland adenoma occurs in adults and children and has no gender predilection.[3] The tumor occurs in the segmental or lobar bronchi and symptoms are due to obstruction or hemorrhage. Histologically, mucus-filled acini are lined with well-differentiated mucus-secreting cells, without any evidence of invasion. Radiographically, mucus gland adenomas appear as coin lesions on chest radiograph, or with an "air-meniscus" sign on CT scan. Treatment is endoscopic local excision. However, lobectomy may be required if the distal lung is destroyed.

SQUAMOUS PAPILLOMA

Tracheal papillomatosis, a form of recurrent respiratory papillomatosis (RRP), occurs in both children and adults.[4] When symptomatic, patients can present with dyspnea, cough, hemoptysis, and symptoms simulating reactive airway disease.[5] Histologically, papillomas consist of stratified squamous epithelium with a fibrovascular core. Imaging studies demonstrate lesions within the trachea and bronchi. Bronchoscopy is the diagnostic modality of choice. Squamous metaplasia and malignant transformation occur in 0.3% to0.5% of patients with RRP and have been linked to radiation exposure, tobacco use, and bleomycin.[4] Infection with HPV 11, HPV 16, or HPV 18 rather than HPV 6 is associated with a worse prognosis. Endoscopic excision is the treatment of choice for tumors with malignant transformation or causing airway obstruction.

Solitary bronchial papillomas affect adults in their fifth to seventh decades. When present, obstructive bronchiectasis may necessitate resection of distally destroyed lung. Parenchymal lesions are rare and can be associated with diffuse viral contamination or dissemination of fragments related to prior tracheostomy or surgical excision.[6,7] Lung involvement manifests as multiple slow-growing solid or cavitary nodules and carries a poor prognosis (Fig. 117-1).[7]

CAVERNOUS HEMANGIOMA

Cavernous hemangiomas of the lung are found in all age groups and may be single or multiple.[8,9] They may cause symptoms of hemoptysis, respiratory distress, or congestive heart failure. Histologically, cavernous hemangioma consists of flattened endothelial cells lining dilated vascular spaces. These cells stain positive for anti-von

TABLE 117-1 Benign Tumors of the Lung

Solitary Tumors	Other Solitary Tumors	Multiple Tumors
Epithelial tumors	Alveolar adenoma	Benign metastasizing leiomyoma
Clara cell adenoma	Pulmonary paraganglioma—chemodectoma	Lymphangioleiomyomatosis
Mucus gland adenoma	Glomus tumor	Cystic fibrohistiocytic tumors
Oncocytoma	Nodular amyloid	
Squamous papilloma	Pleomorphic adenoma—mixed tumor	
Soft tissue tumors	Pulmonary meningioma	
Cavernous hemangioma	Sclerosing hemangioma—pneumocytoma	
Chondroma	Sugar tumor—benign clear cell tumor	
Fibroma fibrous polyp	Teratoma	
Fibromyxoma		
Inflammatory myofibroblastic tumor/ plasma cell granuloma		
Granular cell myoblastoma		
Hamartoma		
Leiomyoma		
Lipoma		
Neurilemmoma—schwannoma		
Neurofibroma		
Pulmonary hyalinizing granuloma		

TABLE 117-2 Rare Primary Malignant Neoplasms of the Lung

Blastoma
Carcinoid tumors
Carcinosarcoma
Epithelioid hemangioendothelioma (IVBAT)
Malignant lymphoreticular disorders
Hodgkin disease
Non-Hodgkin lymphoma
Plasmacytoma
Malignant melanoma
Malignant germ cell tumors
Malignant teratoma
Choriocarcinoma
Salivary gland-type tumors
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Acinic cell tumor
Sarcoma
Chondrosarcoma
Osteosarcoma
Soft tissue sarcoma
Miscellaneous
Ependymoma, malignant
Ewing sarcoma
Lymphoepithelioma
Pseudomesotheliomatous carcinoma

Willebrand factor antibody and CD34, identifying them as endothelial in origin. Treatment for solitary lesions is excision.

SCLEROSING HEMANGIOMA

Sclerosing hemangioma (SH) is an epithelial tumor arising from respiratory epithelium. Histologically, the tumor has four components: solid, papillary, sclerotic, and hemorrhagic.[10] The majority of patients are women, predominantly middle-aged.[10–14] There is a higher incidence in Asia. Most patients are asymptomatic, but can present with chest pain, cough, pleurisy, and hemoptysis. SH appears as a solitary, juxta-pleural, well-defined nodule (Fig. 117-2) with smooth margins and strong enhancement. Calcifications are reported in 30% to 40%.[11,12] Tumors can be multiple and bilateral. There are very rare reports of lymph node metastases. Imaging and bronchoscopy are often not sufficient to make the diagnosis and resection is indicated. PET can show false-positive results. Limited, but complete resection is usually curative.

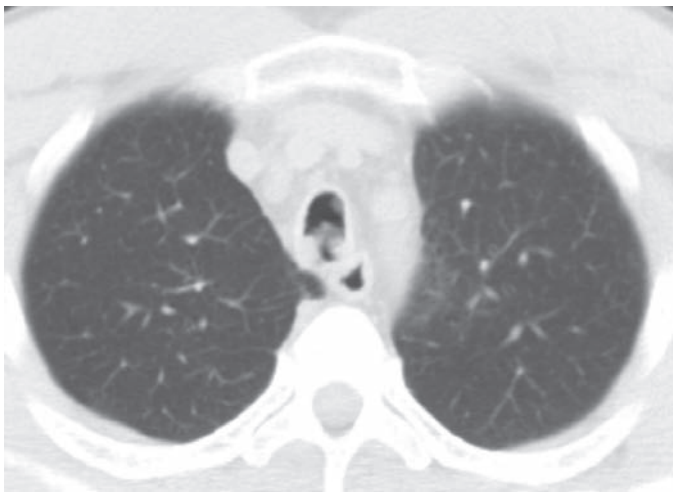
CHONDROMA

Chondromas of the lung may be solitary or multiple, unilateral or bilateral, and are usually asymptomatic slow-growing tumors. The association of multiple peripheral pulmonary chondromas with gastric stromal sarcoma and extra-adrenal paraganglioma has been described as the "Carney triad".[15] The majority of patients with Carney triad are young women. Chondromas consist almost exclusively of cartilage that may be calcified or ossified. The presence of a fibrous pseudocapsule and the absence of fat and entrapped epithelium distinguish chondroma from pulmonary hamartoma.[16] Chondromas present as calcified nodules and can sometimes be mistaken for gastric sarcoma metastases. Lung-sparing resections are curative in 44% of patients, the rest develop new chondromas. MRI-guided laser thermotherapy has been described for ablation of multiple chondromas.[17]

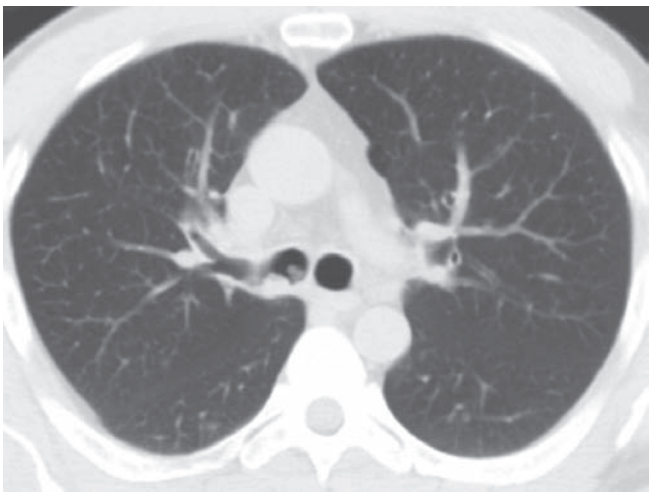
INTRAPULMONARY SOLITARY FIBROUS TUMOR

Solitary fibrous tumors (SFTs) are distinct spindle cell neoplasms that usually grow on a stalk arising from the visceral pleura[18,19] and are almost always diagnosed following resection of an asymptomatic lung mass found on routine radiography. These tumors are classified as benign or malignant based on histologic findings such as mitotic activity, pleomorphism, presence of necrosis, and invasiveness.[19] Tumor cells are immunoreactive for vimentin but not keratin, desmin, or actin, suggesting fibroblastic differentiation from a submesothelial origin.[18] They are also positive for CD34.

SFTs that arise within the lung parenchyma without histologic continuity with the pleura are extremely rare. Intrapulmonary SFTs may contain entrapped alveolar epithelium within the spindle cell proliferation.[19] Clinically, intrapulmonary SFTs are assumed to behave similarly to the pleural tumors. Radiographically, the

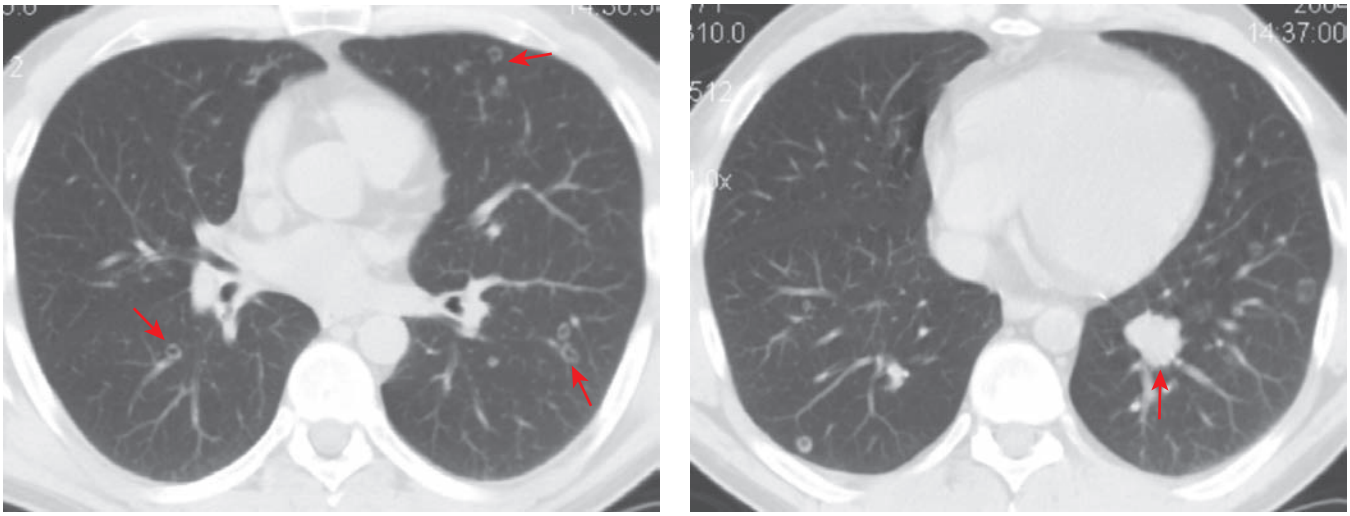


A



B

Figure 117-1 Axial images with lung algorithm from a noncontrast CT of the thorax of a 40-year-old man with laryngeal and tracheal papillomatosis with extension into the pulmonary parenchyma demonstrating polypoid lesions in the trachea (**A**) and right mainstem bronchus (**B**), multiple bilateral cavitary pulmonary nodules *(arrows)* (**C**), and lobulated solid nodule in the left lower lobe that was pathologically proven to be a squamous cell carcinoma arising in a papilloma *(arrow)* **(D)**. *(continued)*



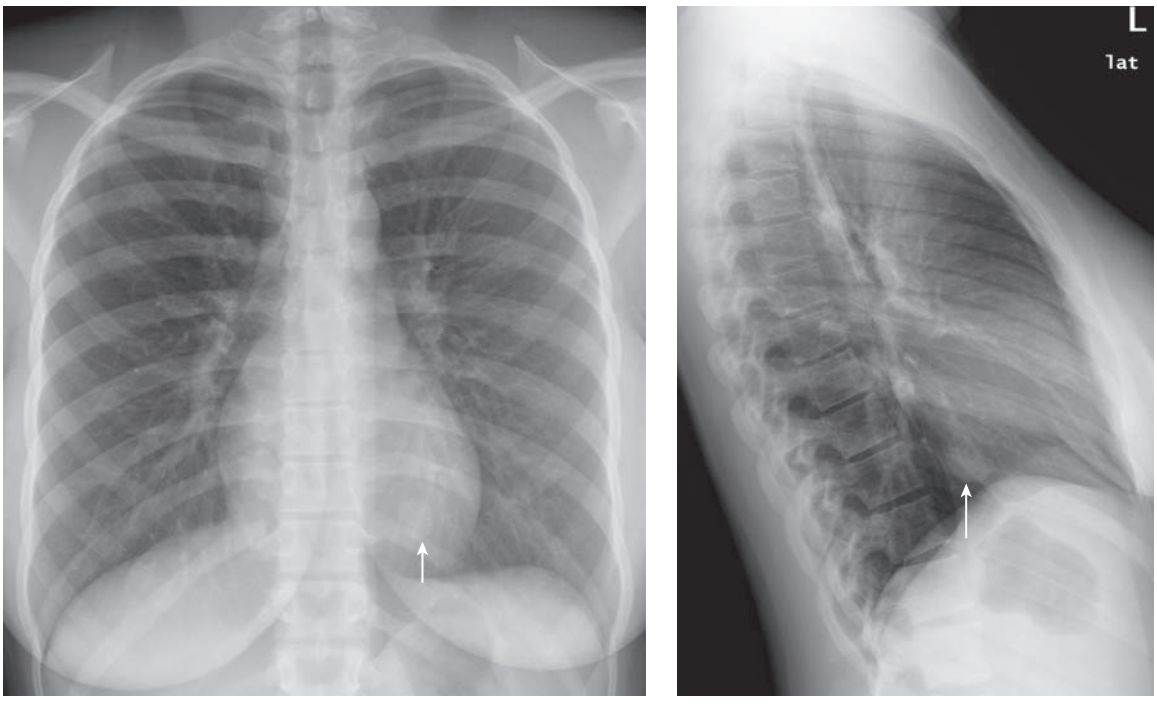
C D

Figure 117-1 *(Continued)*

tumor appears as an oval or round nodule or mass of variable size. Treatment is resection and prognosis is generally good. It has been reported, however, that neither the size of the tumor nor its morphology is reliable predictor of clinical behavior and biologic potential of these tumors.[20] Adequate excision and follow-up are necessary.

■ INFLAMMATORY MYOFIBROBLASTIC TUMOR (PLASMA CELL GRANULOMA)

Inflammatory myofibroblastic tumor (IMT) is more commonly seen in children and adolescents, though it is also found in adults and has no gender predilection.[7,21–23] Patients are usually symptomatic, presenting with cough, fatigue, or weight loss. Previously thought to be an unchecked inflammatory response to viral/foreign antigens, IMT has been confirmed to be of neoplastic origin. Rearrangement of the anaplastic lymphoma kinase gene on chromosome 2p23 results in the expression of the ALK-1 protein. IMT is locally aggressive, can be multifocal, relapse and even metastasize. Radiographically, IMT presents as a mass or nodule with lobulated or spiculated borders closely related to the airways (Fig. 117-3). Calcification and cavitation are rare.[7] Histologically, plasma cells and spindle cells are seen with varying degrees of mitosis, necrosis, and vascular invasion. Tumors stain for vimentin, actin, and epithelial membrane antigen. Transbronchial/transthoracic biopsy often reveals mixed inflammatory cells with predominantly plasma cells in a background of fibroblastic proliferation, granulation tissue, and histiocytes with nuclear atypia. Thus, both fine-needle aspiration and frozen section are nonspecific and complete



A B

Figure 117-2 Frontal (**A**) and lateral chest (**B**) radiographs demonstrating a well-defined nodule at the left lung base *(arrows)* of a 21-year-old woman with a sclerosing hemangioma.

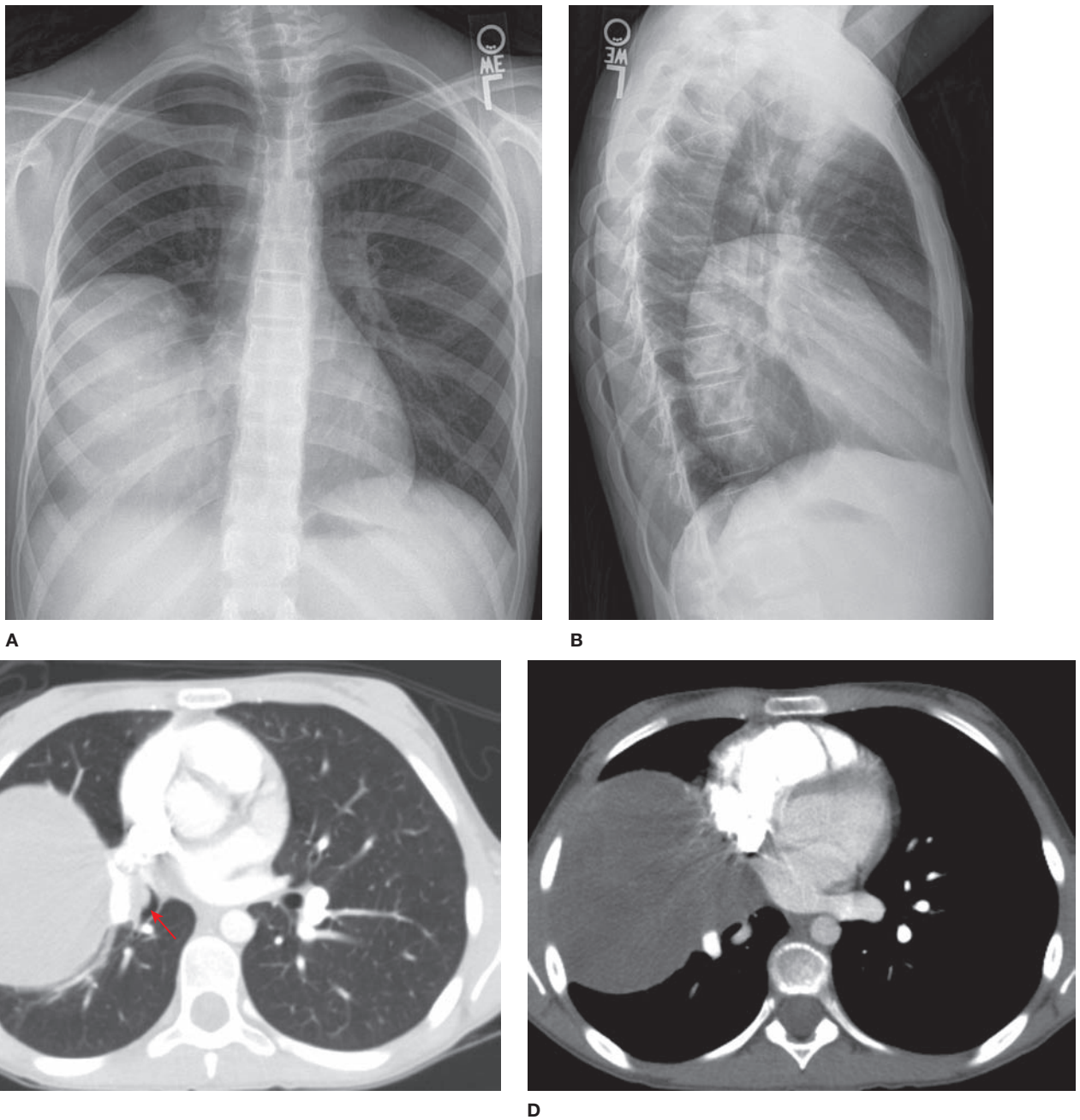


Figure 117-3 Frontal (**A**) and lateral chest (**B**) radiographs demonstrating a large mass in the right hemithorax and axial images (**C**, **D**) from a contrast-enhanced CT of the thorax demonstrating a well-defined mildly heterogeneous mass with an endobronchial component *(arrow)* of an 11-year-old girl with an inflammatory myofibroblastic tumor.

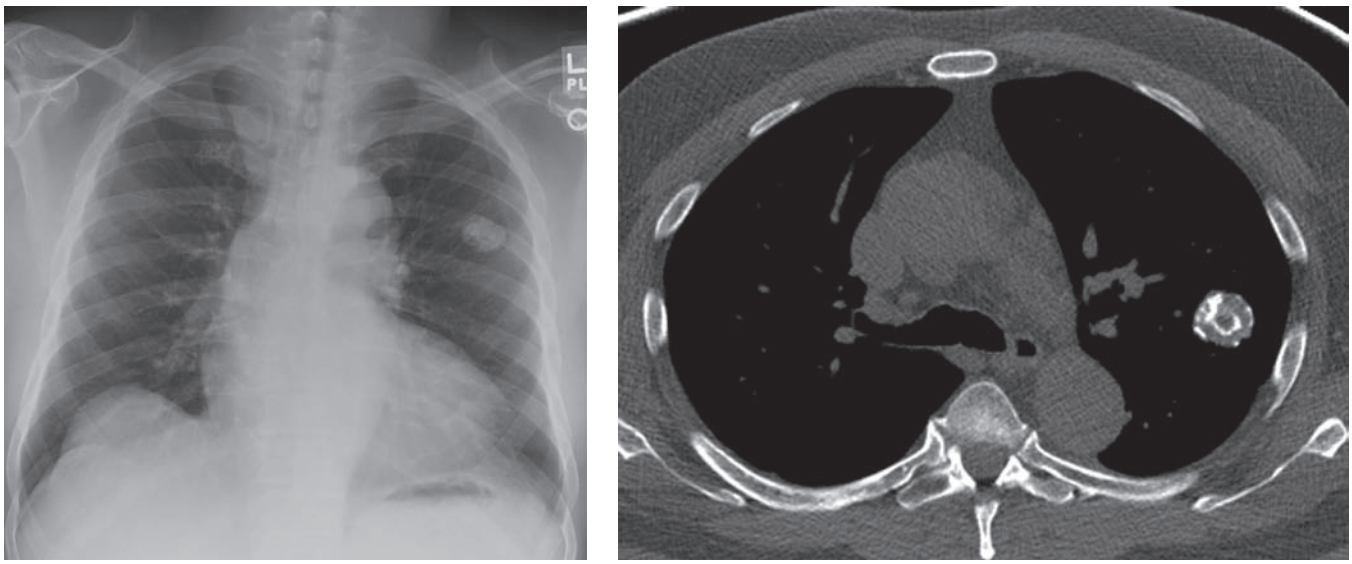
resection is necessary for establishing a diagnosis. Incomplete resection can result in recurrence, which can be treated with repeat resection. Symptoms, incomplete resection, as well as large size are predictors of mortality. Steroids, nonsteroidal antiinflammatory drugs, and laser therapy have been used with variable results in cases where complete resection cannot be achieved. Treatment with chemotherapy and radiation therapy remains controversial.[23]

GRANULAR CELL MYOBLASTOMA

Granular cell tumors are uncommon benign neoplasms that are thought to arise from Schwann cells.[24] Usually discovered incidentally on a chest radiograph, they are endobronchial in location and multicentric. Peribronchial extension is seen in half of the tumors. However, distant metastases have not been reported. They occur equally in men and women, with a median age of 42 years. Microscopically, sheets of granular cells with abundant lysosomes, which stain positive with periodic acid–Schiff stain, are present. Tumor cells also stain positive for S-100 and myelin basic proteins. Large tumor size, necrosis, increased mitosis, and p53 as well as Ki-67 immunoreactivity are consistent with malignant change. Treatment consists of local excision, either endoscopically (laser) or by sleeve resection. Larger resections are reserved for postobstructive bronchiectasis or abscess. Up to 13% of granular cell tumors coexist with other neoplasms such as esophageal, renal, and lung carcinomas.

HAMARTOMA

Hamartomas (mesenchymomas) are the most common benign tumors of the lung and are commonly seen in males in the sixth



A B

Figure 117-4 Radiographic appearance of a hamartoma. **A.** Frontal radiograph of the chest demonstrating a well-defined nodule with "popcorn" calcification in the left upper lobe. **B.** Axial image from a noncontrast CT demonstrating a well-defined nodule with course calcification and foci of fat.

decade.[25–28] They are slow growing and can be multiple. The majority are detected incidentally as peripheral round nodules on a chest radiograph. Only 20% are endobronchial (Fig. 117-4). The classic popcorn calcification is seen in 30% of hamartomas. Histologically, hamartomas consist of cartilage, fat, bone, connective tissue, and smooth muscle cells surrounding clefts lined with bronchial epithelium. Presence of fat and calcifications helps make the diagnosis on CT. Use of chemical shift MRI has been investigated as a tool to detect fat deposits in hamartomas with inconclusive CT findings.[29] Fine-needle aspiration has a high false-positive rate and low accuracy in diagnosing hamartomas. Malignant transformation is rare. Therefore, small peripheral hamartomas may be safely observed. Excision is indicated for obstructive symptoms or if the diagnosis is in doubt. Parenchyma-sparing resection should be performed. Recurrences are rare, although hamartomas may be associated with increased risk of developing primary lung cancers.[30]

■ LEIOMYOMA

Primary solitary leiomyoma accounts for 2% of all benign lung tumors and may present as endobronchial obstruction or as an asymptomatic peripheral radiographic nodule. Typically, primary solitary leiomyoma affects patients in their fourth decade. The tumor is slightly more common in women. Surgical resection is the treatment of choice, although laser resection of endobronchial tumors offers prolonged palliation.

Benign metastasizing leiomyoma consists of multiple pulmonary nodules of well-differentiated smooth muscle, resulting from hematogenous spread from a benign uterine leiomyoma (Fig. 117-5).[31–33] Tumors are strongly positive for Smooth Muscle Actin (SMA) and negative for CD117. Benign metastasizing leiomyoma is ER and PR positive and may respond to hormonal therapy.

MALIGNANT TUMORS

The diverse spectrum of malignant primary lung tumors, other than bronchogenic carcinoma, is discussed below.

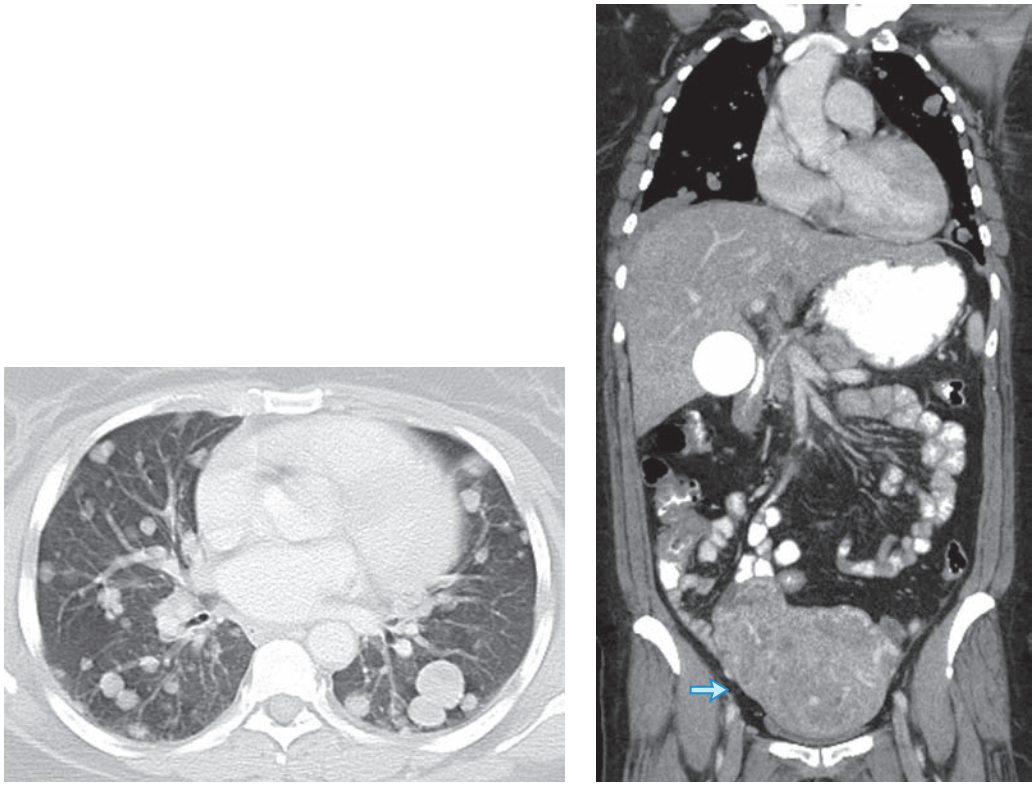
■ PULMONARY BLASTOMA

Pulmonary blastomas are divided into three subgroups: biphasic pulmonary blastoma (BPB), well-differentiated fetal adenocarcinoma (WDFA), and pleuropulmonary blastoma (PPB).[34–38] WDFA contains neoplastic epithelial glandular elements in an endometrioid pattern without mesenchymal malignancy. PPB is a dysontogenetic neoplasm having mesenchymal malignant elements (liposarcoma, rhabdomyosarcoma, or chondrosarcoma) without epithelial malignancy. BPB contains both epithelial and mesenchymal malignant elements, which mimic fetal lung. PPB is further subclassified as type I (purely cystic), type II (cystic and solid), and type III (purely solid). PPB occurs in infants and young children; WDFA and BPB occur in young adults, with a mean age of 35 years. Many patients with BPB and WDFA have a history of tobacco use. All three are fast-growing tumors that present in the periphery of the lung with a predilection for the lower lobes. Patients may be asymptomatic or may present with cough, hemoptysis, dyspnea, chest, or back pain. Radiographically, pulmonary blastomas appear as large solitary smooth masses. Fine-needle aspiration is usually nondiagnostic due to extensive necrosis and lack of cellular material. Neoadjuvant chemotherapy has been used to downstage the tumors before surgical resection. Adjuvant chemotherapy is combined with local radiation for control after resection. Poor prognostic factors are large tumor size, mediastinal or pleural involvement, and nodal metastasis. The central nervous system is the most common site of distant metastasis. Mutations of p53 gene are seen more frequently with BPB and PPB than with WDFA, suggesting a worse prognosis. Type II and III PPBs have an overall survival of 42% at 5 years, despite multimodality treatment.

■ CARCINOID

Carcinoid tumors are malignant neuroendocrine tumors arising from Kulchitsky (APUD system) cells and are classified by the World Health Organization into typical carcinoid (TC) and atypical carcinoid (AC) on the basis of presence of necrosis and mitotic activity.[39,40] Mean age at presentation is 55 years, but AC is seen in significantly older patients with a history of smoking. Seventy-five percent of carcinoids are central, endobronchial tumors and present commonly with postobstructive pneumonia, hemoptysis, or wheezing. Uncommonly, carcinoids may present with paraneoplastic syndromes such as Cushing syndrome due to ectopic adrenocorticotropic hormone production, or even acromegaly from ectopic growth hormone and insulin-like growth factor-1 production.

Radiologically, carcinoids present as solitary nodules (30%), infiltrates (60%), and calcified nodules (30%) (Fig. 117-6). CT scan



A B

Figure 117-5 Axial image (**A**) with lung algorithm from a contrast-enhanced CT of the thorax, abdomen, and pelvis demonstrating multiple bilateral well-defined pulmonary nodules and coronal reformatted image (**B**) with soft tissue window from the same study demonstrating enlarged heterogeneous uterus *(arrow)*, consistent with multiple leiomyomas, of a 55-year-old woman with a history of uterine leiomyomas and benign metastasizing pulmonary leiomyomas.

reveals a well-defined central tumor deforming an airway with punctate calcification and homogeneous contrast enhancement with or without hilar lymphadenopathy. Carcinoids demonstrate high signal intensity on T2-weighted MRI[41] and are hypometabolic on FDG-PET scans. Somatostatin receptor scintigraphy can be used in detecting occult primary tumors, staging, and localization of metastatic disease.

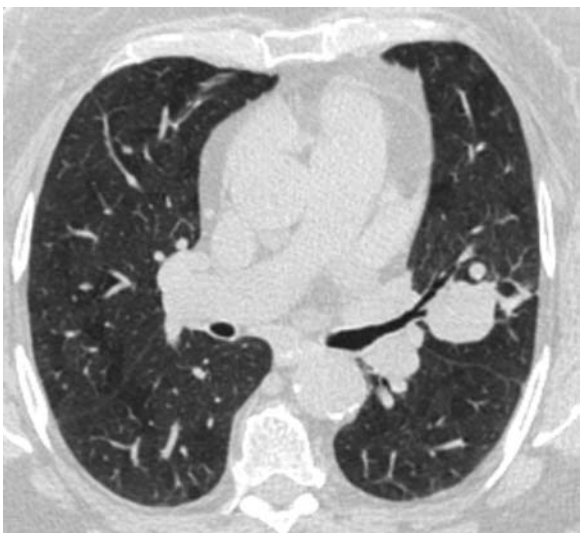


Figure 117-6 Atypical carcinoid in a 74-year-old woman. Axial image with lung algorithm from a noncontrast CT of the thorax demonstrating a well-defined mildly lobulated nodule in the lingula with extension into the lingular bronchus. Incidentally noted is diffuse mosaic attenuation of the pulmonary parenchyma, consistent with air trapping, a nonspecific sign of small airway disease.

Bronchoscopy frequently demonstrates a polypoid pinkish/yellow mass with intact overlying epithelium. Brushings and washings are usually nondiagnostic. Endobronchial biopsy is diagnostic in approximately 50% of patients, but rarely may precipitate a carcinoid crisis.

Carcinoids are characterized by an organoid growth pattern with uniform cells containing finely granular eosinophilic cytoplasm and nuclei with a fine chromatin pattern. Chromosome analysis shows evidence of 11q and 3p deletion in AC, with loss of 18q in metastatic carcinoid. Overexpression of p53 and loss of heterozygosity of 11q13 are seen in AC, which correlates with tumor aggressiveness. Five percent of patients with MEN I syndrome have associated sporadic carcinoids. Inactivation of the MEN I gene is seen in 67% of TC, and 25% of AC.

Treatment of choice for TC is surgical resection. Lobectomy and lymph node dissection are preferred because 20% of TC and 60% of AC are associated with nodal metastases. Bronchoplastic sleeve resection for central lesions of early-stage TC is preferable to pneumonectomy. *cis*-Platinum and etoposide-based chemotherapy is indicated for unresectable disease, as well as metastases. However, the response rate is only 22%, with a median survival of 20 months. Biotherapy with interferon alpha and octreotide is used for the treatment of carcinoid syndrome with symptomatic relief in 70% of patients. Liver embolization can be used to debulk liver metastases in symptomatic patients. Targeted radiotherapy with radiolabelled octreotide or metaiodobenzylguanidine remains investigational.

Recurrence-free survival is common in patients with TC. Tumor histology and nodal status are the main predictors of mortality. Completeness of resection, symptoms, and age are also significant

prognostic factors. Five-year survival rates following complete resection of TC and AC are 87% to 100% and 44% to 77%, respectively. Survival decreases to 25% to 69% in the presence of nodal metastases. There is no correlation between tumor size and presence of nodal involvement. Sixty-three percent of patients with nodal mediastinal metastases develop distant metastases, most commonly in the liver. Carcinoid syndrome occurs rarely (2%) and results from release of 5-HT. Urinary 5-HIAA is used to monitor disease activity in patients with carcinoid syndrome.

CARCINOSARCOMA

Carcinosarcoma is a biphasic tumor consisting of carcinomatous and sarcomatous elements containing differentiated cartilage, bone, or skeletal muscle.[42–44] This tumor is seven times more common in males than in females. The median age at presentation is 65 years. The upper lobes are affected in 60% of cases. Carcinosarcomas are divided into two groups: central endobronchial and peripheral solid parenchymal (Fig 117-4). Symptoms of airway obstruction or postobstructive pneumonia are common. However, one-third of all patients are asymptomatic. These tumors eventually invade the mediastinum and chest wall, causing pain.

Carcinosarcomas are firm, rubbery, or fleshy masses with areas of necrosis and cavitation. The carcinomatous elements are squamous cell carcinoma (46%), adenocarcinoma (31%), and adenosquamous carcinoma (19%). The sarcomatous elements are rhabdomyosarcoma (51%), chondrosarcoma, and osteosarcoma. The carcinomatous elements are often displaced to the periphery, suggesting rapid growth of the central sarcomatous elements, which form the bulk of the tumor. Immunohistochemical staining for keratin is positive for both the epithelial and mesenchymal components, suggesting that carcinosarcomas are of a monoclonal epithelial origin that has undergone sarcomatoid metaplasia. Metastases are found in lymph nodes, bone, kidney, liver, and lung and commonly contain only one of the components of the primary tumor. Complete surgical resection is usually possible and the 5-year survival rate ranges between 21% and 49%. Endobronchial location and tumor stage do not correlate with survival. However, tumor size greater than 6 cm is associated with poor survival.

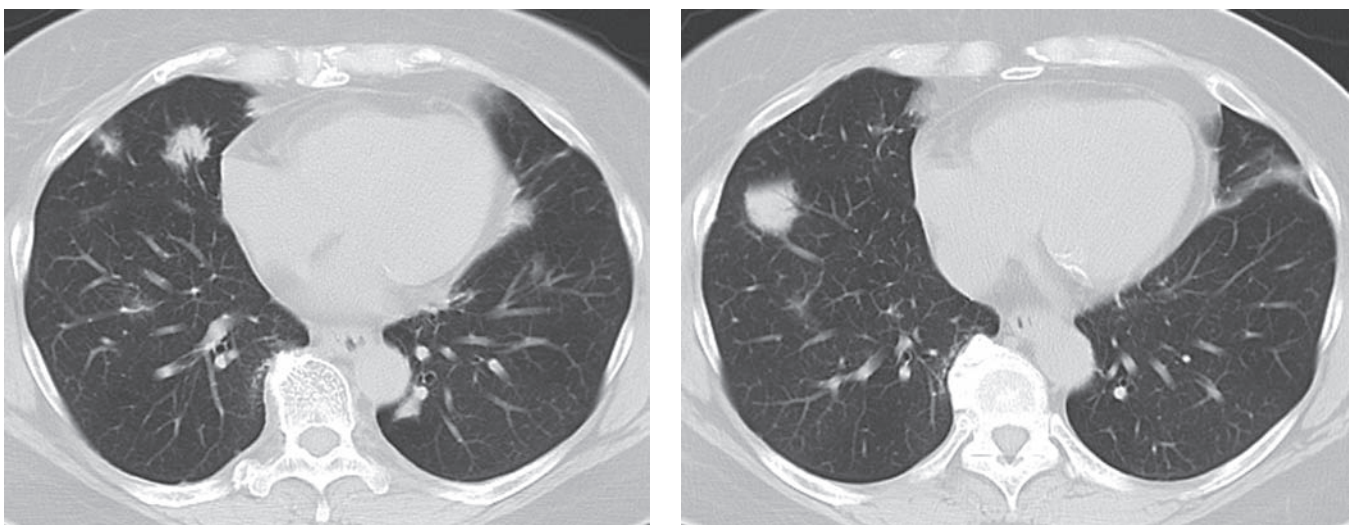
EPITHELIOID HEMANGIOENDOTHELIOMA

Originally named intravascular bronchoalveolar tumor (IVBAT), this neoplasm has since been demonstrated to be of endothelial origin on the basis of immunohistochemical staining for factor VIII-related antigen, CD31, CD34, and/or FLI-1.[45,46] Epithelioid hemangioendothelioma is best considered a low-grade sarcoma and is usually multicentric in origin. It is a disease of young women, with over 70% of cases seen in women with mean age of 40 years. Patients are usually asymptomatic, though they may present with respiratory symptoms. Multiple perivascular nodules less than 1 cm in diameter or diffuse thickening of interlobular septae are present on CT scan. Microscopically, epithelioid hemangioendothelioma consists of eosinophilic cells forming trabeculae or nests with characteristic central acellular sclerotic areas and lymphovascular and bronchiolar invasion. Pleural, intravascular, and endobronchial spread is associated with a poor prognosis, as are liver and lymph node metastases. Complete resection is the treatment for localized tumors.[47] Diffuse tumors have been treated with chemotherapy, interleukin-2, and interferonalpha-2b with mixed results. Radiation is ineffective and is used only for palliation of bone pain. Partial spontaneous regression has also occasionally been reported.

LYMPHOMAS

Primary pulmonary lymphomas account for less than 1% of all lung cancers. Criteria used for the diagnosis of primary pulmonary lymphoma include involvement of the lung with or without mediastinal involvement and absence of extra thoracic lymphoma at the time of diagnosis or for 3 months thereafter.[48]

Primary pulmonary B-cell non-Hodgkin lymphoma (NHL), also known as MALT (mucosa-associated lymphoid tissue) or BALT (bronchus-associated lymphoid tissue), accounts for up to 80% of primary pulmonary lymphomas. This small low-grade B-lymphocyte lymphoma is associated with a 5-year survival greater than 80%. The tumor is thought to arise due to chronic inflammation secondary to smoking, infection, or autoimmune disease (Sjogren syndrome, rheumatoid).[49] Age of onset is typically 50 to 60 years, with equal gender distribution. Respiratory symptoms include cough, dyspnea, and hemoptysis; half of the patients are asymptomatic. Extrapulmonary symptoms such as fever and weight loss occur in less than one quarter of patients. Radiographically, a localized alveolar opacity with blurred margins is seen, often associated with air bronchograms (Fig. 117-7). CT demonstrates bilateral multifocal disease in 70% of cases. CT-guided biopsy is diagnostic in 25%. Bronchoalveolar lavage is diagnostic if a lymphocytic alveolitis is present with B lymphocytes constituting greater than 10% of the total cells. Microscopically,



A B

Figure 117-7 Axial images with lung algorithm from a non-contrast CT of the thorax demonstrating irregularly marginated pulmonary opacities with air bronchograms in the right middle (**A**) and right lower lobes (**B**) of a 60-year-old woman with mucosa-associated lymphoid tissue.

MALT is defined as a lesion containing small lymphoid cells, lymphoepithelial lesions showing migration of lymphoid cells from the marginal zone to bronchiolar epithelium, reactive follicular hyperplasia, and rare blastic cells. Immunohistochemistry demonstrates B cell phenotype (CD19, CD20) and monoclonality. Bone marrow biopsy may show involvement in 25% of cases. Evaluation of other mucosal sites with upper endoscopy, ENT examination, and CT scan of salivary and lacrimal glands should be performed. Serum immunoelectrophoresis will reveal a monoclonal gammopathy (IgM) in 20% to 60% of patients. Elevated beta-2 microglobulin is associated with a poor prognosis. Solitary tumors should be removed. Long-term surveillance is necessary due to late local or systemic relapse after resection. Chemotherapy is recommended for residual, bilateral, progressive, or recurrent disease. Various regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab have been used with success.

High-grade NHL-B, also known as large B-cell lymphoma, accounts for up to 15% of primary pulmonary lymphomas. Immunosuppression, HIV infection, and Sjogren syndrome are underlying disorders often associated with large B-cell lymphomas. These lymphomas are usually found in older patients and commonly present with either pulmonary or systemic symptoms. Radiologic presentation includes solitary or multiple nodules, masses, consolidations, adenopathy, pleural effusion, and, rarely, direct chest wall invasion (Fig. 117-8).[50] Bronchoscopy may reveal infiltrative bronchial stenosis. Transbronchial biopsy is often diagnostic. Microscopically, large blast-like lymphoid cells with frequent mitosis, necrosis, and bronchovascular invasion are seen. Survival is poorer than in small B-cell lymphomas, especially in those patients with underlying disorders. Resection is followed by combination chemotherapy. Progression of disease and recurrence occur earlier and more commonly than in small B-cell lymphoma.

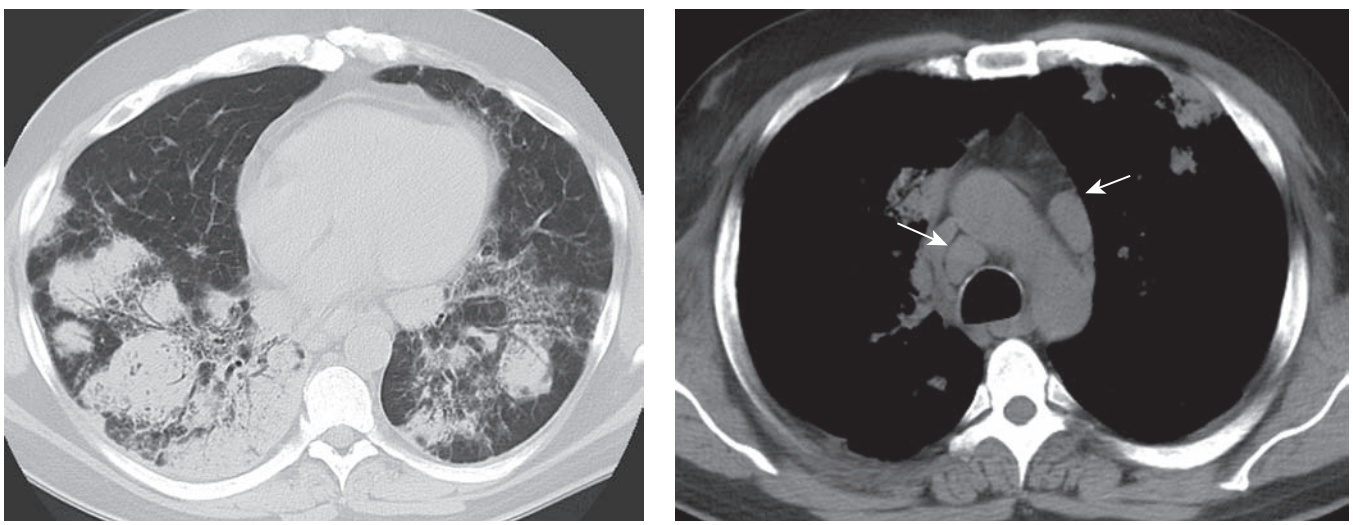
Lymphomatoid granulomatosis (LG), also known as an angiocentric immunoproliferative lesion (AIL), presents with either pulmonary or systemic symptoms and commonly affects patients in their sixth decade. Radiographically, multiple bilateral ill-defined nodular opacities, mainly affecting the lower lobes, are seen. These opacities can cavitate and disappear secondary to infarction of the granulomatosis lesions. Extrapulmonary involvement occurs in the CNS, skin, upper respiratory tract, or renal systems. Neurologic deficits can be central or peripheral. Skin lesions include erythema or nodules, with or without ulceration. Joint, ocular, and gastrointestinal manifestations have also been reported. Microscopically, an angiocentric lymphocytic infiltrate mixed with occasional large blastic cells compressing the lumen of arterioles and eroding into bronchioles is seen. Immunohistochemistry demonstrates the B cell origin of the lymphocytes, which also express Epstein–Barr virus latent membrane protein. Initial assessment should include brain MRI, CT scan of the abdomen for renal or lymphoid involvement, and a bone marrow biopsy. Localized LG should be removed. Combination chemotherapy is reserved for diffuse disease. Radiotherapy is useful for CNS involvement. Despite aggressive therapy, median survival approximates 4 years. Poor prognostic factors include early age of onset, CNS involvement, hepatosplenomegaly, leukopenia, fever, anergy, and predominant blast cells with necrosis.

There are only 13 cases reported of NK/T cell primary pulmonary lymphoma. Patients are elderly and females are affected twice as commonly as males. Radiographically, bilateral diffuse nodularities are seen. Diagnosis requires a surgical lung biopsy and immunohistochemistry, which reveals T cell markers. Microscopically, homogeneous cells with architectural effacement and dysplasia are seen. Monoclonality of the T cells is demonstrated by TCR gene rearrangement. Prognosis is very poor despite surgical resection and CHOP-based chemotherapy.

Primary pulmonary Hodgkin lymphoma peaks in the third and sixth decades. Most patients are females. Symptoms may be respiratory or systemic. Radiographically, multinodular and massive parenchymal involvement is seen with occasional cavitation. Bronchoscopy and Broncho-alveolar Lavage (BAL) are inconclusive and surgical lung biopsy is required to confirm the diagnosis. The most frequent histologic subtype is the nodular sclerosing variety. Combination chemotherapy, radiation, and surgery are the common modalities of treatment. Multilobar or bilateral disease is associated with a poor prognosis.

■ PLASMACYTOMA

Plasmacytomas arise from monoclonal plasma cells. The diagnostic criteria for extramedullary plasmacytoma are a biopsy-proven plasma cell proliferation and the absence of bone marrow infiltration, osteolytic lesions, renal failure, and hypercalcemia.[51–53] The average age at presentation is 54 years with equal distribution



A B

Figure 117-8 Representative axial CT images from a 49 year-old man with AIDS and diffuse large B-cell lymphoma. **A.** Lung window demonstrating ground glass and consolidative opacities with rounded configuration and air bronchograms in the lower lobes bilaterally. **B.** Soft tissue window demonstrating mediastinal lymphadenopathy *(arrows)*.

between males and females. Plasmacytomas commonly present as a hilar mass, but lobar consolidation or bilateral diffuse infiltrates with air bronchograms may also be seen. Serum electrophoresis reveals an M-protein spike, which usually consists of IgG kappa chains, and correlates with the tumor burden. Treatment is surgical resection, but chemotherapy with melphalan and prednisolone has been used with good results. The 5-year survival rate is 40%. These tumors need to be distinguished from marginal zone B-cell lymphomas of MALT origin. Forty percent of patients develop multiple myeloma and so surveillance with serum and urine electrophoresis, bone marrow biopsy, skeletal bone survey, and clinical monitoring is necessary.

MELANOMA

Primary pulmonary melanoma is an extremely rare lung tumor for which several theories have been suggested: aberrant migration of melanocytes from the primitive foregut, melanogenic metaplasia of bronchial epithelium, or melanocytic differentiation of neuroendocrine precursor Kulchitsky cells.[54–58] Jensen and Egedorf first suggested the clinical criteria for the diagnosis of primary pulmonary melanoma: (1) no previously removed skin or ocular melanomas, (2) solitary tumor, (3) morphology compatible with a primary tumor, (4) no melanoma in other organs at surgery, and (5) no evidence of primary elsewhere on autopsy.[54] Histopathologic criteria include junctional change with nesting of malignant cells beneath bronchial epithelium, and invasion of bronchial epithelium in an area without ulceration. Aggressive resection is the treatment of choice and offers the best chance for cure. Chemotherapy and immunotherapy are used for widespread disease.

MALIGNANT GERM CELL TUMORS

Malignant teratoma and choriocarcinoma are the two malignant germ cell tumors that arise in the lung.[59] Teratomas show elements from all three germ layers. Half of the primary pulmonary teratomas are malignant. Patients present with cough, hemoptysis, or chest pain. The most specific symptom—trichoptysis—is rarely present. Radiographically, the mass may show calcification with peripheral radiolucency. Resection is the treatment of choice. Adjuvant chemotherapy is usually a combination of *cis*-platinum, bleomycin, and etoposide.

Choriocarcinomas are usually seen in women or elderly men who present with symptoms of feminization. The most common symptom is hemoptysis. Various theories have been postulated to explain the origin of pulmonary choriocarcinomas: neoplastic transformation of misplaced primordial germ cells, spontaneous regression of an occult genital primary leaving behind pulmonary metastatic lesions, neoplastic transformation of placental emboli at the time of delivery or abortion, and neoplastic transformation of somatic neoplastic cells. The choriocarcinoma syndrome consists of bleeding from the primary lung lesion and elevation of beta-human chorionic gonadotropin (β-HCG). Choriocarcinoma can be distinguished from a large cell carcinoma producing ectopic β-HCG by immunohistochemistry, which will stain for thyroid transcription factor-1 (a marker of pulmonary origin) and not for β-HCG. Histologically, cytotrophoblastic cell nests are seen covered by syncytiotrophoblasts, with evidence of widespread necrosis and hemorrhage, as well as a lack of fibrovascular stroma. Surgical resection followed by adjuvant chemotherapy is recommended. Unlike their gestational counterparts, pulmonary choriocarcinomas are unresponsive to radiotherapy. Distant metastases can occur in the brain, kidneys, and contralateral lung.

SALIVARY GLAND-TYPE TUMORS

Adenoid cystic carcinoma (ACC) is the most common salivary-gland tumor found in the lung[60] and is thought to arise from ductal/myoepithelial cells of bronchial submucosal glands. Centrally located ACC arises in the trachea or mainstem bronchi and presents as an exophytic endobronchial mass causing obstructive symptoms. Overlying mucosa is often grossly normal. Peripheral ACC is uncommon. Males and females are equally affected. Histologically, there are three subtypes: cribriform, tubular, and solid. ACCs are slow-growing neoplasms that exhibit centripetal spread in the airways as well as perineural growth. Therefore, extensive resections are required. These tumors are extremely radiosensitive and local recurrences or residual disease may be treated with radiation. Following complete resection, 5- and 10-year survival of 91% and 76%, respectively, have been reported.

Mucoepidermoid carcinomas usually arise in mainstem bronchi or the proximal lobar bronchi. The right bronchial tree is more commonly affected in children. Patients present with symptoms of obstruction due to a polypoid endobronchial mass. Bronchoscopic biopsy is diagnostic. Three histologic grades have been defined (low, intermediate, and high) based upon the presence of cystic spaces, cell type (mucus cells, intermediate cells, and epidermoid cells), cellular pleomorphism, and mitosis. Complete resection with mediastinal lymph node dissection is the treatment of choice. High-grade tumors are more common in adults and may invade adjacent structures, lymph nodes, vascular, and perineural spaces. Incomplete resection is more likely in high-grade tumors and postoperative chemoradiation may be necessary. High-grade tumors are uniformly fatal in 11 to 28 months.

Acinic cell tumors (Fechner tumors) are usually found in the salivary glands and hence a diligent search for an extrathoracic primary is essential. Symptoms vary and are determined by whether the tumor is centrally located in the airway or peripheral in location. Histologically, these tumors demonstrate a pattern resembling a neuroendocrine tumor and may need to be differentiated from the more common carcinoid tumor. Acinic cell tumors are slow-growing and recurrence or metastases after complete excision has not been reported.

SARCOMAS

Primary pulmonary sarcomas account for less than 0.5% of all lung tumors.[61] Mean age at presentation is 53 years with a slight predominance in males. A history of smoking or previous radiation exposure may be present. Usual symptoms are chest pain and cough. Sarcomas appear as large (mean diameter 5 cm), solitary peripheral, or hilar nodular opacities usually located in the upper lobes. Bronchoscopy may show either extrinsic compression or a polypoid endobronchial mass. The variety of soft tissue pulmonary sarcomas reflects the range of mesenchymal tissue found in the lung (Table 117-3). The most common primary pulmonary

TABLE 117-3 Primary Soft Tissue Sarcomas of the Lung

Leiomyosarcoma
Spindle cell sarcoma
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Angiosarcoma
Fibrosarcoma
Malignant hemangiopericytoma
Neurogenic sarcoma
Synovial sarcoma
Kaposi sarcoma
Liposarcoma

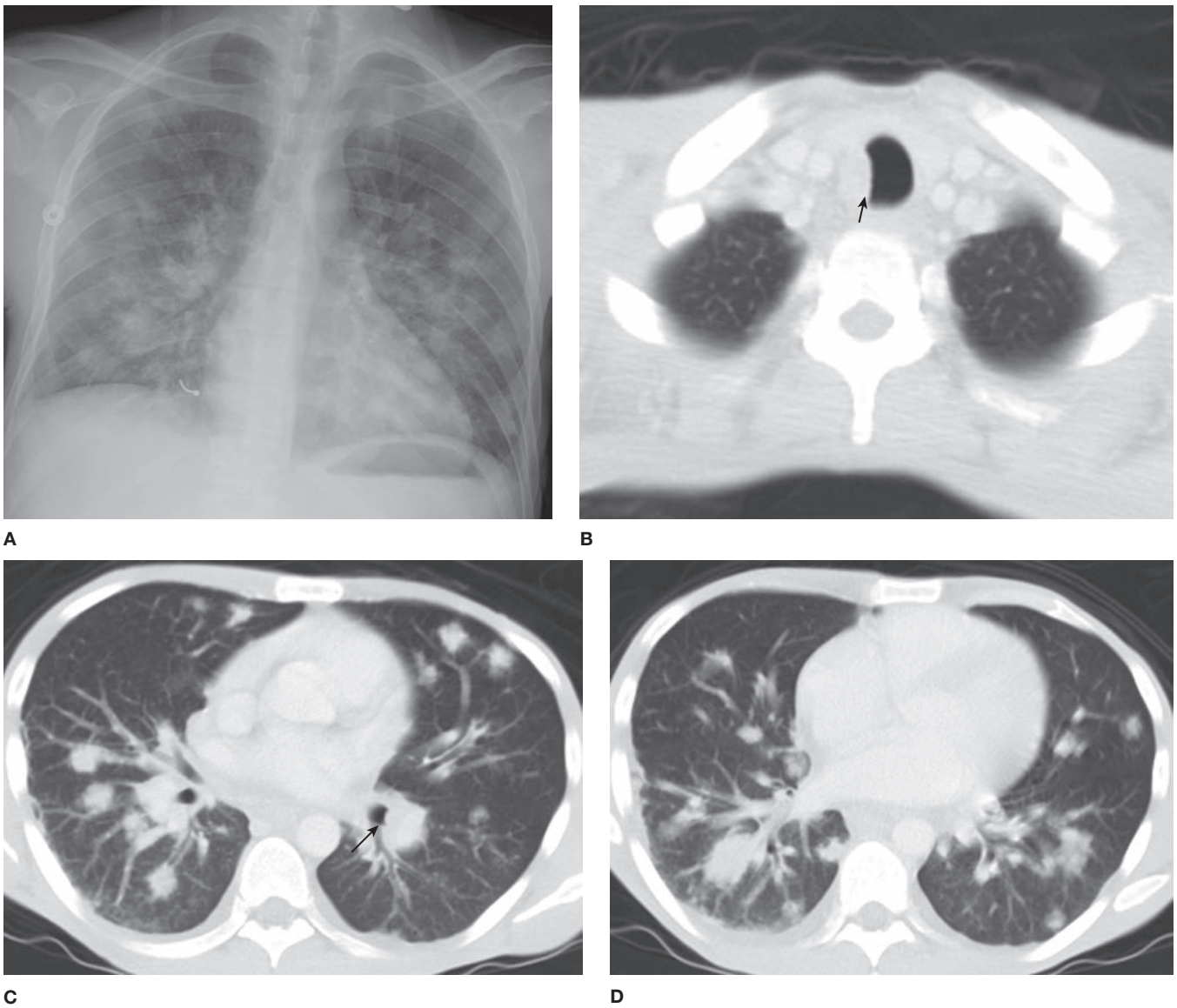


Figure 117-9 **A.** Frontal radiograph of the chest of a 35-year-old man with AIDS and Kaposi sarcoma demonstrating multiple bilateral "flame-shaped" pulmonary opacities with mid and lower lung zone predominance. Incidentally noted, is a linear metallic density at the right lung base, consistent with an aspirated earring. **B–D.** Axial images with lung algorithm from a noncontrast CT of the thorax of the same patient demonstrating endobronchial lesions *(arrows)* as well as multiple bilateral ill-defined pulmonary nodules in peribronchovascular distribution. Thoracic lymphadenopathy was also present in this patient (not shown).

sarcoma is leiomyosarcoma (30%), followed by malignant fibrous histiocytoma and synovial sarcoma. Histologic subtypes can be differentiated on the basis of immunohistochemical markers such as vimentin, desmin, actin, and epithelial membrane antigen. Treatment is wide resection with mediastinal lymph node dissection. Residual disease is treated with radiotherapy or re-resection. Recurrences can be resected with good results. Ifosfamide-based chemotherapy has also been used in the neoadjuvant and adjuvant setting for positive margins or positive lymph nodes. Median survival is 48 months and 5-year survival is 38% to 69%. Size and grade do not correlate with increased mortality. Incomplete resection is associated with poor survival.

Chondrosarcomas of the lung can occur either within central bronchi or peripherally in the lung parenchyma. Tumors consist of islands of chondroid and osteoid cells with foci of mineralization within sheets of small hyperchromatic mesenchymal cells. Chondrosarcomas are slow-growing and rarely metastasize. Complete resection is usually curative.

Osteosarcomas of the lung present with cough or hemoptysis and appear as large cavitating masses. Prognosis for patients with these rapidly growing tumors is poor and recurrence is seen in 50% of patients following resection. The majority of patients succumb within months from metastases to the lung, liver, lymph nodes, and bone. The role of adjuvant therapy remains unproven.

Pulmonary involvement with Kaposi sarcoma usually occurs in patients with AIDS and CD4 counts less than 100 cells/mm^3. A characteristic CT finding is the presence of bilateral symmetric ill-defined nodules in a peribronchovascular distribution.[62,63] The nodules have a mid and lower lung predominance. Peribronchovascular and interlobular septal thickening is another common finding. Endobronchial lesions, pleural effusions and nodularity, and lymphadenopathy within the thorax can also be present (Fig. 117-9). Prognosis is poor.

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CHAPTER 118

Extrapulmonary Syndromes Associated with Lung Tumors

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A wide variety of extrapulmonary syndromes have been reported with lung cancer. This chapter will focus primarily on paraneoplastic syndromes, a heterogeneous group of disorders associated with cancer but not due to direct invasion, obstruction, or metastasis.[1,2] As many paraneoplastic syndromes share similar underlying mechanisms, they may be classified as endocrine, hematologic, and neurologic syndromes. More broadly speaking, they are either hormonally or immunologically based.

Paraneoplastic syndromes affect up to 8% of patients with cancer,[3] and of all malignancies, lung cancer is most commonly associated with these syndromes. The subtype of lung cancer most commonly associated with paraneoplastic syndromes is small-cell lung cancer (SCLC), but some such as hypertrophic pulmonary osteoarthropathy (HPO) and hypercalcemia are more common in non–small-cell lung cancer (NSCLC).[4]

Endocrine and hematologic syndromes associated with lung tumors are listed in Table 118-1. The endocrine syndromes are characterized by the ectopic production by tumor cells of biologically active peptide hormones that bind to receptors in adjacent or distant organs, giving rise to a clinical syndrome. Hematologic syndromes develop in patients with lung cancer through the production by tumor cells of cytokines that activate progenitor cells in the bone marrow. Neurologic syndromes, such as encephalomyelitis and subacute sensory neuropathy, are caused by the induction of

TABLE 118-1 Endocrine and Hematologic Syndromes Associated with Lung Tumors

Syndrome	Tumor	Proteins/Cytokines
Hypercalcemia of malignancy	Non–small-cell	Parathyroid hormone-related peptide
		Parathormone
Hyponatremia of malignancy	Small-cell	Arginine vasopressin
	Non–small-cell	Atrial natriuretic peptide
Ectopic ACTH syndrome	Small-cell	Adrenocorticotropic hormone
	Carcinoid tumors	Corticotropin-releasing hormone
Acromegaly	Carcinoid tumors	Growth hormone–releasing hormone
	Small-cell	Growth hormone
Carcinoid syndrome	Carcinoid tumors	Serotonin
	Large-cell	
	Small-cell	
Granulocytosis	Non–small-cell	G-CSF
		GM-CSF
		IL-6
Thrombocytosis	Non–small-cell	IL-6
	Small-cell	
Thromboembolism	Non–small-cell	Unknown
	Small-cell	

antibodies directed against proteins expressed by the lung cancer cells and directed against antigens present on cells in the nervous system. In clinical practice, an understanding of the extrapulmonary syndromes is important for several reasons: (1) recognition of a syndrome may serve as a harbinger of an occult malignancy or may signify disease recurrence; (2) the course of the endocrine and hematologic syndromes usually parallels the course of the lung cancer, although the neurologic syndromes frequently do not; and (3) appropriate treatment of the extrapulmonary syndrome often reduces the patient's morbidity and may allow definitive treatment of the cancer. In general, definitive treatment of the underlying tumor is the most effective form of therapy for the paraneoplastic syndromes, so their presence should not preclude treatment of lung cancer with curative intent as most syndromes are reversible once the patient receives treatment.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia is commonly seen in cancer patients[5,6] and lung cancer is the most common solid tumor associated with it, occurring in up to 20% of patients.[7,8] It is overall the most common of the paraneoplastic syndromes. It occurs most frequently in patients with squamous cell lung cancer, but is occasionally seen in patients with adenocarcinoma and very rarely in patients with SCLC.[9]

BIOLOGY

Etiologic mechanisms for hypercalcemia in patients with lung cancer include parathyroid hormone–related peptide (PTHrP) production, increased levels of the active metabolite of vitamin D (calcitriol, also called 1,25-dihydroxyvitamin D_3), and localized osteolytic hypercalcemia.[5,10] Most cases of hypercalcemia in patients with lung cancer are caused by the ectopic production of PTHrP by tumor cells (referred to as humoral hypercalcemia of malignancy).[11–13] The PTHrP gene expresses three messenger RNAs (mRNAs) that encode three distinct peptides, each differing at the COOH-terminal region (Fig. 118-1). Eight of the first 13 amino acids in PTHrP are homologous with PTH, so similar functional activity is shared between the two peptides. PTHrP mRNA and peptides have been demonstrated in cancer cells from patients with lung cancer and hypercalcemia. PTHrP has been shown to bind to PTH receptors in the bone and kidney, which causes increased osteoclastic bone resorption, decreased bone formation, and decreased calciuria, leading to hypercalcemia.[14,15] Levels of 1,25-dihydroxyvitamin D_3 are suppressed in patients with PTHrP-induced hypercalcemia, but are raised in patients with primary hyperparathyroidism. This difference occurs because renal α-hydroxylase activity is low in PTHrP-induced hypercalcemia, unlike primary hyperparathyroidism.[16] PTH production by lung cancer cells has also been described, but it is a very rare cause of hypercalcemia of malignancy.[17–19] Other factors that cause bone resorption have been identified in the plasma of patients with lung cancer, including transforming growth factor-α and a vitamin D metabolite. These are very rare, however, and their causative role in hypercalcemia has not been shown conclusively.

DIAGNOSIS

The early symptoms of hypercalcemia include thirst, malaise, fatigue, anorexia, polyuria, constipation, nausea, and vomiting. As hypercalcemia becomes increasingly severe (>14.0 mg/dL), confusion, lethargy, coma, and death can occur. The demonstration of a suppressed intact parathyroid hormone (iPTH) level and a low or normal calcitriol level along with an increased concentration (>10.5 mg/dL) of calcium in the serum of a patient with NSCLC should suggest this paraneoplastic syndrome. This is in contrast to the findings of elevated iPTH and calcitriol levels in primary hyperparathyroidism, which may occur in up to 10% of patients with cancer. A complete diagnostic evaluation includes measuring serum concentrations of iPTH, PTHrP,[20] 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, calcium, albumin, magnesium, and phosphorus. Other potential causes of elevated serum calcium should also be excluded. Thiazide diuretics, vitamin D or lithium administration, hyperthyroidism, and sarcoidosis are potential causes.[21] Bone scintiscan should be obtained to exclude bone metastases. An elevated PTHrP level in the absence of bone metastases establishes the diagnosis of humoral hypercalcemia of malignancy caused by ectopic PTHrP.[15,20]

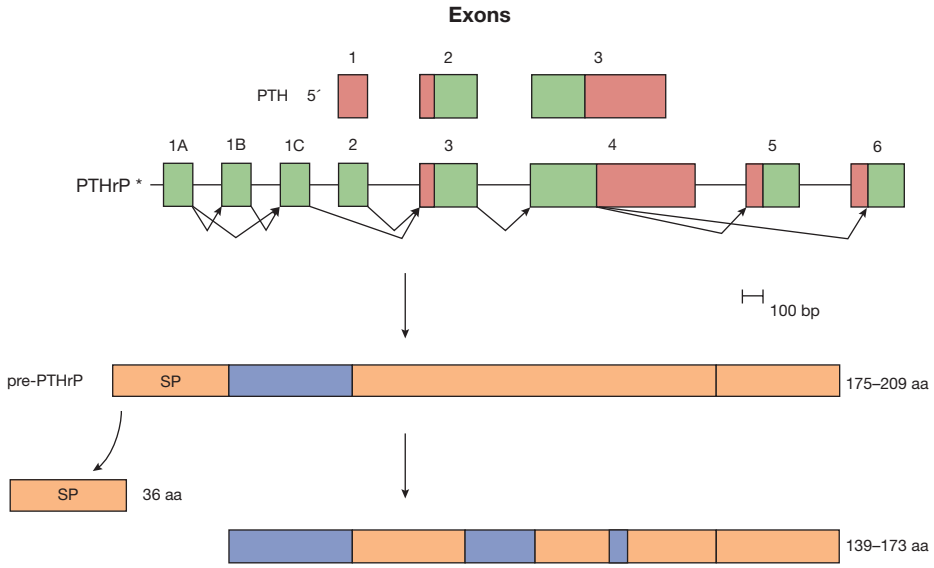

Figure 118-1 Parathyroid hormone and parathyroid hormone-related peptide. The human PTH gene has three exons, which constitute the protein-coding segments. The protein-coding segments are represented by the *black boxes*. The PTHrP gene is more complex, with eight exons. Through alternative splicing, three different isoforms of mRNA can be produced. These isoform mRNAs encode the pre-PTHrP proteins, which vary in size from 175 to 209 amino acids (aa). Thirty-six amino acids are removed from the amino terminal end as the signal peptide. Three different PTHrP molecules are produced, with 139 to 173 aa. The rectangular region at the carboxy terminal represents the different lengths of PTHrP. The N-terminal region (1–34 aa) mimics the classic PTH-like function (*hatched box*). The midregion (67–86 aa) of the peptide stimulates placental calcium transport (*shaded box*). The C-terminal region (107–111 aa) inhibits osteoclastic bone resorption (*double hatched box*).

■ TREATMENT

As with other paraneoplastic syndromes, treatment of the underlying cancer is the most effective method of treating the humoral hypercalcemia associated with lung cancer. Until this can occur, medical management of hypercalcemia must be considered. If asymptomatic or mildly symptomatic, hypercalcemic patients with calcium levels <12 mg/dL (3 mmol/L) do not require immediate treatment. Similarly, a serum calcium level of 12 to 14 mg/dL (3–3.5 mmol/L) may be well-tolerated chronically, and may not require immediate treatment. However, an acute rise to these concentrations may cause a marked change in sensorium, requiring intervention. In addition, patients with a serum calcium concentration >14 mg/dL (3.5 mmol/L) require treatment, regardless of symptoms.[22,23] Treatment includes intravenous saline, with the addition of furosemide diuresis only after correction of intravascular volume depletion. Subcutaneous calcitonin has a rapid onset of action and is most useful in severe cases. Mithramycin and long-acting bisphosphonates, such as pamidronate, are effective for long-term control of hypercalcemia.[24] Corticosteroids exert their effect through inhibition of dihydroxyvitamin D_3 synthesis and therefore have less effect in patients with elevated PTHrP.

Humoral hypercalcemia usually develops in patients with advanced progressive cancer and is associated with a median survival of about 1 month.[25,26] Nonetheless, in some cases, treatment of hypercalcemia serves an important palliative role by improving symptoms and allowing patients to be discharged from the hospital.

HYPONATREMIA OF MALIGNANCY

Hyponatremia is a frequent complication in patients with cancer. It occurs at presentation in approximately 15% of patients with SCLC and 1%of patients with NSCLC.[27] The ectopic production of arginine vasopressin (AVP) by cancer cells plays a causal role in the majority of cases.[27] This form of hyponatremia is recognized as the *syndrome of inappropriate antidiuretic hormone* (SIADH). Up to one-third of patients with lung cancer and hyponatremia do not demonstrate elevation of AVP in their tumors or plasma.[28–30] In these patients, the ectopic production of atrial natriuretic peptide (ANP) has been implicated, but the exact contribution of this hormone remains to be defined.[28]

■ BIOLOGY

AVP is a 9-amino acid peptide normally produced by the neurohypophysis. The peptide binds to receptors in the kidney to reduce the excretion of free water. When plasma osmolality exceeds 280 mOsm/kg, the release of AVP from the pituitary increases, causing the kidney to retain more free water and maintain fluid and osmolar balance. In patients with SCLC, ectopic production of AVP causes hyponatremia by inhibiting free-water excretion in the distal tubule of the kidney. AVP mRNA is expressed in SCLC cells and the peptide is translated and secreted (Fig. 118-2). Measured levels of AVP in plasma are often increased.[31]

There is a subgroup of patients with SCLC and hyponatremia, however, who have no detectable levels of plasma AVP.[32] Similar findings have been shown in SCLC cell lines.[33] The tumors from these patients express ANP mRNA, secrete the peptide, and have high levels of ANP in their plasma.[34] ANP is the leading candidate to be the natriuretic factor that Bartter and Schwartz proposed in their original description of SIADH. Further investigation into the precise role of ANP in patients with SCLC and hyponatremia of malignancy is ongoing.

■ DIAGNOSIS

In patients with lung cancer, hyponatremia is most frequently diagnosed as a laboratory abnormality in the absence of significant symptoms. The symptoms of acute hyponatremia do not typically occur because the syndrome develops over a prolonged period in concert with the growth of the lung cancer. When symptomatic, mild hyponatremia (serum sodium <135 mmol/L) can cause headache, difficulty concentrating, nausea, weakness, and fatigue. Severe hyponatremia (serum sodium <125 mmol/L), especially when it develops rapidly, can lead to serious symptoms including confusion, hallucinations, seizures, coma, respiratory arrest, decerebrate posturing, and death.[35]

The diagnosis of SIADH is based on the following criteria: (1) plasma hypo-osmolality (<280 mOsm/kg); (2) osmolality of urine greater than serum (usually >500 mOsm/kg); (3) persistent urinary excretion of sodium in the absence of diuretics (>20 mEq/L); (4) absent signs of volume depletion; and (5) normal renal, adrenal, and thyroid function.[36]

In patients with lung cancer, nonmalignant causes of hyponatremia should be considered in the initial evaluation. These include diuretic use, renal disease, cardiac dysfunction, hypoadrenalism, thyroid disease, and dilutional hyponatremia. Medications as a cause for hyponatremia should also be addressed. Patients with lung

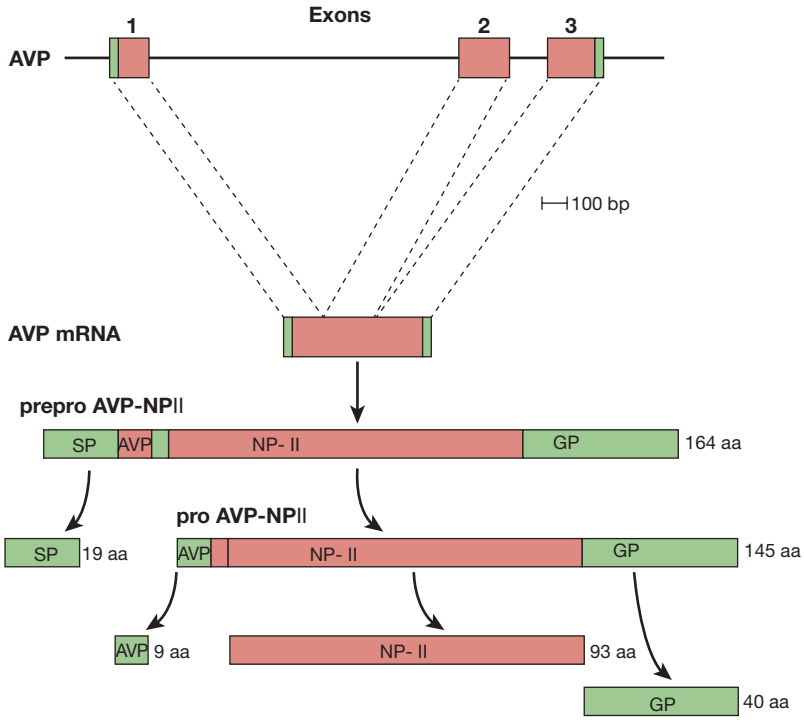

Figure 118-2 Arginine vasopressin. The three exons of the human AVP gene rise to a 700-base arginine vasopressin mRNA. The mRNA is translated into a 164-amino acid (aa) preprohormone with a 19-amino acid amino terminal signal peptide (SP). The SP is cleaved, giving rise to a 145-amino acid prohormone. This prohormone is processed into the nonapeptide AVP, a 93-amino acid neurophysin (NP), and a 40-amino acid glycoprotein (GP). The black portions of the boxes represent the protein-coding portion of the gene and mRNA.

cancer are commonly treated with cisplatin and narcotics, both of which can cause SIADH.

TREATMENT

The initial therapy for hyponatremia caused by lung cancer is treatment of the underlying malignancy. This often involves multimodality therapy with surgical excision, radiation, and/or chemotherapy. Even with tumor response to therapy, hyponatremia often persists or may recur following tumor progression. In SCLC, there are data to suggest that those patients who do not fully regain normal values of plasma sodium have a poorer survival than those patients who do.[37,38]

Asymptomatic patients with chronic hyponatremia are at low risk for serious neurologic sequelae, but are at risk of developing osmotic demyelination with rapid correction of the serum sodium concentration.[39] Treatment is therefore aimed at gradual correction. Fluid restriction, which can be estimated by urinary and plasma electrolytes, but is usually started at 500 mL per day, is a cornerstone of therapy.[40] Pharmacologic therapy may be indicated when fluid restriction is ineffective or poorly tolerated. Demeclocycline blocks the action of AVP on the renal tubule, thereby reducing urine osmolality and increasing serum sodium levels; however, its effects can be variable and it can cause nephrotoxicity.[35] Lithium and phenytoin also inhibit the effects of AVP on the renal tubule, but are no longer recommended for treatment. A more recent option for the treatment of hyponatremia is vasopressin receptor antagonists. Conivaptan is a nonselective vasopressin receptor antagonist indicated for patients with moderate-to-severe hyponatremia with nonsevere symptoms and is administered intravenously.[41] Tolvaptan is an orally active, selective AVP receptor 2 (V2) antagonist that has a similar indication. By blocking AVP effects in the renal collecting duct, aquaresis is promoted, leading to a controlled increase in serum sodium levels.[42]

For patients who present with severe, symptomatic hyponatremia characterized by seizure, delirium, or coma, rapid treatment is warranted.[43] The widely accepted goal of therapy is to correct the serum sodium by 1 to 2 mmol/L per hour through the infusion of 3% saline. The administration of concomitant furosemide is also recommended. The magnitude of correction within the first 24 hours is suggested to be no more than 8 to 10 mmol/L and no more than 18 to 25 mmol/L in the first 48 hours to avoid osmotic demyelination. An alternative approach is to treat until acute symptoms resolve and then adjust the correction rate.[44]

ECTOPIC ADRENOCORTICOTROPIC HORMONE (ACTH) SYNDROME

Lung cancers are the most common neoplasms that cause ectopic ACTH production and Cushing syndrome, accounting for 50% of all cases. SCLC accounts for 80% to 90% of cases associated with lung cancer. Carcinoid tumors (10%) and bronchial adenocarcinomas (5%) have also been reported to produce biologically active ACTH. While biochemical abnormalities suggestive of ectopic ACTH production are reported in 30% to 50% of SCLC, Cushing syndrome is clinically present in only 1% to 5% of SCLC.[45–50] Hypercortisolism is important to recognize as it increases the risk of therapy-induced complications[51,52] such as opportunistic infections and venous thromboembolism (VTE).[53–55]

BIOLOGY

Most cases of Cushing syndrome associated with lung cancers are caused by ectopic production of ACTH by the tumor.[56] The precursor gene, proopiomelanocortin (POMC), is expressed in the cancer cells, and a 241-amino acid prohormone is translated and then cleaved into ACTH (39 amino acids), melanocyte-stimulating hormone, and opiate-like hormones (Fig. 118-3). The ACTH binds to receptors in the adrenal gland, causing them to produce excessive glucocorticoid and mineralocorticoid hormones.[57]

Ectopic production of corticotropin-releasing hormone (CRH) has been reported as a cause of Cushing syndrome in a small number of patients with SCLC or bronchial carcinoids.[49] CRH is a 41-amino acid peptide normally produced in the paraventricular nuclei of the hypothalamus that stimulates the release of ACTH from the pituitary.

CLINICAL PRESENTATION AND DIAGNOSIS

Ectopic ACTH production occurs with equal frequency in males and females, but Cushing syndrome has an 8:1 female preponderance. Patients who have slow-growing carcinoid tumors often present with the clinical features of Cushing syndrome: truncal obesity, moon facies, striae, polyuria, and polydipsia. In contrast, patients with SCLC often present with other signs of mineralocorticoid and glucocorticoid excess due to the rapidity of tumor growth: edema, weakness, hypertension, and hypokalemic alkalosis.

The diagnostic evaluation of ectopic ACTH syndrome starts by excluding iatrogenic Cushing syndrome in order to avoid unnecessary chemical testing. Once iatrogenic disease has been excluded, initial testing should include the following: 24-hour urinary-free cortisol, late-night salivary cortisol, and the low-dose dexamethasone suppression test.[58–61] The diagnosis of Cushing syndrome is

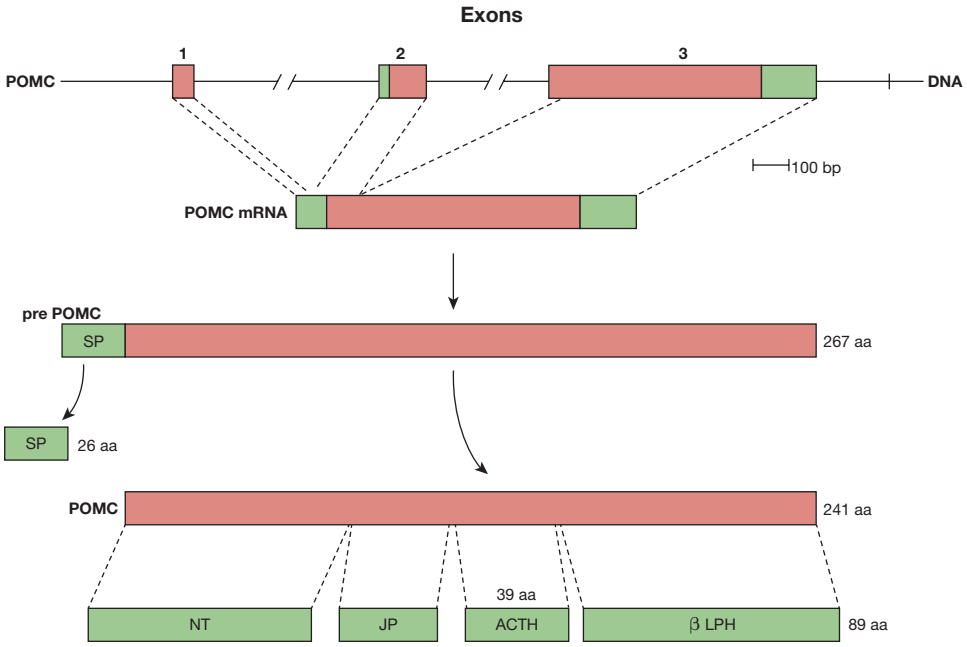

Figure 118-3 Proopiomelanocortin. The three exons of the POMC gene give rise to a 1072-base POMC mRNA. The mRNA is translated into a 267-amino acid pre-POMC with a 26-amino acid amino terminal signal peptide (SP). The SP is cleaved, creating the 241-amino acid POMC. The POMC peptide is cleaved into many products, including the N-terminal peptide (NT), the joining peptide (JP), a 39-amino acid mature ACTH, and β-lipotropin (β-LPH). The molecules can also undergo further processing. The black portions of the exons represent the protein-coding portion of the gene and mRNA.

established when at least two of these tests are unequivocally abnormal. Demonstration of an increased plasma ACTH level (>22 pg/mL) confirms that the hypercortisolism is ACTH-dependent. Finally, persistently elevated serum cortisol in response to a high-dose dexamethasone suppression test differentiates ectopic ACTH syndrome from a pituitary source.[58,62,63] Bronchial carcinoids are an exception, because in some tumors, ACTH and cortisol levels have been suppressed by dexamethasone.[64,65]

In patients with clinical features of Cushing syndrome in whom the dexamethasone suppression test is equivocal, a CRH stimulation test or bilateral inferior petrosal vein sampling will provide the definitive diagnosis. After CRH infusion, pituitary tumors release increased amounts of ACTH, whereas pituitary-independent lung tumors should not. Similarly, in pituitary-dependent Cushing syndrome, petrosal vein sampling will reveal a gradient between the level of ACTH in the petrosal vein and the peripheral concentration. In contrast, patients in whom ACTH is ectopically produced demonstrate no gradient between the petrosal vein and the peripheral blood.[66,67]

TREATMENT

Management of a patient with lung cancer and ectopic ACTH syndrome requires therapy directed at both the underlying tumor and the hypercortisolism. The treatment for a patient with ectopic ACTH production is to remove the source of the ACTH. This requires combination chemotherapy, with or without irradiation, for patients with SCLC and surgical resection and/or radiation for patients with carcinoid tumors. Chemotherapy for patients with SCLC and ectopic ACTH syndrome has been problematic. Patients often have a poor response to chemotherapy and are susceptible to early infection and death. Early control of a patient's glucocorticoid excess is beneficial and may reduce the morbidity of treatment.

When removal of the ectopic source of ACTH is not possible, pharmacologic agents directed at blocking adrenal cortisol production may be successful. These drugs include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Ketoconazole is an imidazole derivative that inhibits steroidogenesis at both adrenal and gonadal sites; it may be the most effective and least toxic agent available.[68,69] Metapyrone and aminoglutethimide also have shown limited success by inhibiting adrenal steroid synthesis. Octreotide, a somatostatin analog, can suppress ectopic ACTH production and has been reported to be useful in some of these patients.[68] Bilateral adrenalectomy should be considered in patients who fail medical therapy.[62,70]

In some patients, the clinical signs and symptoms of ectopic ACTH production develop before the development of a clinically obvious lung cancer. In these cases, symptomatic management of hypercortisolism is undertaken and periodic imaging studies are performed because these patients may have a slow-growing carcinoid tumor that will be amenable to surgical resection.[64,71]

ACROMEGALY

Only 1% of acromegaly is caused by ectopic production of growth hormone–releasing hormone (GHRH) or growth hormone (GH) by tumors.[72] Of these, the majority are caused by carcinoid tumors of the lung and intestine.[73]

BIOLOGY

The ectopic production of GHRH or GH by lung cancers has been demonstrated to cause acromegaly. In most cases, the GHRH gene is expressed by the cancer cells, and a 40- or 44-amino acid peptide is produced.[74] Circulating GHRH peptide binds to receptors in the pituitary gland resulting in the production of excessive amounts of GH.[75] GH then mediates its effects through GH receptors in soft tissue and by stimulating the production of insulin-like growth factor-1 (IGF-1).

Although many carcinoid tumors express immunoreactive GHRH and result in abnormal GH secretion,[76–78] most patients with these tumors are not clinically acromegalic. It has been suggested that the observed high incidence of GHRH expression and low incidence of clinical acromegaly may be due to inadequate tumor production of GHRH or due to the impaired bioactivity of the circulating GHRH.[75]

DIAGNOSIS

The earliest features of GH excess are hypertrophy of the extremities and face (often manifest as increased glove, shoe, and ring size), thickened leathery skin, prominent skin folds, hyperpigmented skin, and hair growth. Bony changes, hypertension, and diabetes mellitus are later, less common findings.

The presentation of a patient with a lung mass and signs of acromegaly should raise suspicion of ectopic acromegaly especially if the mass is found to be carcinoid. The diagnosis of ectopic acromegaly is established by elevated serum levels of GHRH or GH, the absence of a pituitary tumor, complete recovery following lung tumor

resection, positive GHRH immunostaining, detection of GHRH mRNA, positive bioassay (cultured rat pituitary cells produce GH in response to tumor extract), or GHRH extraction from the tumor tissue.[79] Because coincidental pituitary tumors and solid tumors have been described, patients who have lung cancer in association with low GHRH levels and high GH and IGF-1 levels should undergo magnetic resonance imaging (MRI) to exclude a pituitary tumor.

TREATMENT

Management of ectopic acromegaly involves surgical resection of the tumor and is often curative in those with lung carcinoid. In those with unresectable or metastatic cancers, medical therapy with somatostatin analogs, such as octreotide and bromocriptine, have been shown to be effective.[80,81] Bromocriptine acts by inhibiting GH release by the pituitary; octreotide lowers both GH and IGF-1 levels in plasma and also appears to inhibit GHRH release by tumors. Clinical abatement of acromegalic features has been reported in patients treated with octreotide.

CARCINOID SYNDROME

Ectopic serotonin production is rare in lung neoplasms, occurring in 1% to 5% of patients with pulmonary neuroendocrine tumors (NETs).[82] Hallmarks of the syndrome include skin flushing of the upper thorax, secretory diarrhea, and bronchoconstriction. It is important to recognize an acute carcinoid crisis in patients with lung cancer as it can be precipitated by chemotherapy, biopsy, anesthesia, surgery, or the use of adrenergic drugs. It is a result of a massive serotonin release, and can lead to cardiopulmonary failure.[83]

The evaluation for carcinoid syndrome begins with a 24-hour urine collection for the main metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). This test has a specificity of approximately 90%.[84] Detection of occult NETs in patients presenting with a carcinoid syndrome may be aided by testing for serum biomarkers of NETs such as neuron-specific enolase (NSE) and chromogranin A.[85] When these serum biomarkers are negative in a patient with high clinical suspicion of a NET, radionuclide-labeled octreotide scintigraphy is useful as up to 80% of pulmonary NETs express somatostatin receptors.

In patients who are surgical candidates, surgery is the optimal treatment of carcinoid syndrome. Otherwise, control of symptoms should be the goal via somatostatin analogs, serotonin receptor blockers, interferon, and antidiarrheal medications. In addition, carcinoid crisis can be prevented or treated with intravenous octreotide acetate.[83]

HEMATOLOGIC SYNDROMES

Most hematologic syndromes associated with lung tumors are not as well characterized as the endocrine syndromes, and an ectopic hormone responsible for the syndrome has not been identified in most tumor tissues. In many of the hematologic syndromes, such as granulocytosis and thrombocytosis, clinical sequelae are often absent. As with the endocrine paraneoplastic syndromes, the most appropriate therapy for the hematologic syndromes is the treatment of the underlying neoplasm.

GRANULOCYTOSIS

NSCLC is the most common cancer associated with granulocytosis. Fifteen to twenty percent of patients with NSCLC have granulocytosis, with absolute white blood counts ranging from 10,100 to 25,000 (normal range is 4000–10,000). Its presence is associated with a poorer prognosis compared to patients without granulocytosis.[86–88] Although granulocyte colony-stimulating activity can be demonstrated in serum and/or urine in 80% of affected patients, tumor production of granulocyte colony-stimulating factor, granulocyte monocyte colony-stimulating factor, or interleukin-6 (IL-6) has been shown in only a minority of patients.[89,90]

Virtually all patients with lung cancer who present with tumor-associated granulocytosis are asymptomatic. The diagnosis is suggested by the presence of an increased white blood count in which neutrophils predominate without immature forms, in the absence of non-neoplastic causes. An increased leukocyte alkaline phosphatase score and a normal bone marrow are consistent with this diagnosis.

THROMBOCYTOSIS

Thrombocytosis is common in patients with lung cancer, afflicting 16% to 32% of patients with both NSCLC and SCLC.[91,92] The pathogenesis of thrombocytosis in patients with lung cancer has not been definitively elucidated. IL-6, which is a cytokine for megakaryocytes, has been demonstrated in cell lines from patients with lung cancer and thrombocytosis, and increased levels of IL-6 have been demonstrated in the plasma of such patients. Thrombopoietin is increased in patients with lung cancer and thrombocytosis but is decreased in patients with essential thrombocytosis. The identification of the thrombopoietin gene may lead to a better understanding of the role of this protein in paraneoplastic thrombocytosis.

Patients with thrombocytosis are nearly always asymptomatic and do not have an increased incidence of thromboembolism. The diagnosis of cancer-associated thrombocytosis is suggested by an increased platelet count ($>500{,}000/mm^2$) in a patient with newly diagnosed lung cancer, and it is associated with advanced disease and worse clinical outcomes.[93,94] A primary myeloproliferative disorder can be excluded by a bone marrow biopsy.[95] In addition, the presence of the JAK2 V617F mutation may indicate essential thrombocytosis (present in 50% of cases) since it is not present in cases of reactive thrombocytosis.[96]

THROMBOEMBOLISM

Of all disease states, lung cancer is known to have one of the strongest associations with VTE.[97] The incidence of VTE in patients with lung cancer is approximately 40 to 100 cases per 1000 person-years compared to 1 to 2 cases per 1000 person-years in the general population. It is also notable that 20% of patients who present with recurrent idiopathic venous thrombosis are found to have an underlying diagnosis of cancer.[98] The spectrum of causes of thrombosis in patients with lung cancer is broad, including disseminated intravascular coagulation (DIC), Trousseau syndrome (recurrent migratory venous thrombophlebitis), nonbacterial thrombotic endocarditis, and obstruction of great vessels.[99,100] Surgical procedures and chemotherapy have also been demonstrated to increase cancer patients' risk of thrombotic complications.[101]

Cancer cells are able to directly activate the clotting cascade via two procoagulants: tissue factor (TF) and cancer procoagulant (CP). Increased expression of human TF has been shown in NSCLC tissue, and active TF-bearing microparticles, which may originate from tumor cells, have been demonstrated in the circulation of cancer patients.[102,103] Microparticle-associated TF activity has been proposed as a mechanism for the prothrombotic state in cancer patients.[104]

The treatment of VTE associated with active lung cancer differs from standard treatment of VTE. It was previously shown that for recurrent thromboses, long-term subcutaneous heparin is more efficacious than warfarin.[105] More recently, a meta-analysis of six randomized controlled trials in cancer patients being treated with long-term anticoagulation for VTE found no statistically significant survival benefit for low molecular weight heparin (LMWH) compared to warfarin, but a statistically significant reduction in VTE with LMWH, with no significant difference in bleeding. [106,107]

NEUROLOGIC SYNDROMES

There are a number of paraneoplastic neurologic syndromes associated with lung cancer. Encephalomyelitis, cerebellar degeneration, retinopathy, opsoclonus/myoclonus, and the Lambert–Eaton

TABLE 118-2 Neurologic Syndromes Associated with Lung Cancer

Syndrome	Tumor	Antibody	Antigen
Encephalomyelitis/subacute sensory neuropathy	Small-cell	Anti-Hu	Hu-D antigen: 35–40-kDa neuronal nuclear protein
Cancer-associated retinopathy	Small-cell	Antirecoverin	23-kDa protein specific to photoreceptor cells (recoverin)
Lambert–Eaton syndrome	Small-cell	Anti-P/Q channel	P/Q-type calcium channel

syndrome have all been described and are most commonly associated with SCLC. The majority of these syndromes are a result of an autoimmune response directed at shared antigens present in both cancer cells and normal neural tissue. The autoantibodies associated with each neurologic syndrome are listed in Table 118-2.

■ ENCEPHALOMYELITIS/SUBACUTE SENSORY NEUROPATHY

The paraneoplastic syndrome of encephalomyelitis/subacute sensory neuropathy was first described in a patient with SCLC. More than 70% of cases of paraneoplastic encephalomyelitis are diagnosed in patients with SCLC, with a wide range of clinical presentations. A specific antibody, anti-Hu, which reacts with the HuD antigen expressed by lung cancer cells and neuronal tissues, has been identified in many patients who develop this syndrome. Approximately 20% of patients with SCLC are seropositive for anti-Hu but only a few will develop a paraneoplastic neurologic disorder.[108]

Biology

Anti-Hu is an IgG antibody found in the sera and cerebrospinal fluid of patients with sensory neuropathy and encephalomyelitis. Patients with anti-Hu have an immune response targeting a family of proteins known as Hu, which are expressed in both neurons and SCLC cells. They are RNA-binding proteins involved in the post-transcriptional regulation of RNA in neurons.[109] The HuD gene has been mapped to the chromosome 1p region and appears to be a marker of neuroendocrine differentiation in these cells.

Diagnosis

The location and severity of neuronal loss predict the patient's clinical symptoms. Neuronal loss may be limited to one area of the nervous system, but more frequently involve multiple areas over time.[31] Onset of symptoms is subacute and precedes the diagnosis of SCLC in greater than 70% of cases, thus warranting a complete diagnostic evaluation for occult malignancy in those presenting with encephalomyelitis or subacute sensory neuropathy. One-half of patients undergo progressive sensory loss in the hands and feet. Others present with a limbic encephalopathy characterized by memory loss, behavioral changes, and seizures. Focal myelopathy with weakness, brain stem signs (nystagmus, dysarthria), and autonomic nervous system dysfunction also occur in patients with this syndrome. CT scans are typically normal in these patients, but MRI studies may show increased T2 signal in affected areas of the brain.

Pathologic examination demonstrates neuronal loss and inflammatory infiltrates in areas of the nervous system including the brain stem, hippocampus, spinal cord, and dorsal root ganglia.[110] Serum and cerebrospinal fluid from patients with paraneoplastic encephalitis will often reveal the anti-Hu antineuronal antibody.

Treatment

Early diagnosis and treatment of the underlying tumor offers the best chance for stabilizing the neurologic syndrome.[111] Alternative therapies with immunosuppressive agents and plasmapheresis, with the goal of clearing the responsible immunoglobulin, have been shown to be effective in only 10% to 20% of patients. Patients with anti-Hu positive neurologic paraneoplastic syndromes are more likely to die of neurologic causes including respiratory muscle failure, autonomic failure, and progressive diffuse encephalopathy rather than from metastatic cancer.[112,113]

■ PARANEOPLASTIC CEREBELLAR DEGENERATION

Paraneoplastic cerebellar degeneration is manifested by symptoms including ataxia, nystagmus, dysarthria, mental changes, muscular and sensory deficits, and diplopia. It has been recognized in 12% of patients with paraneoplastic neurologic syndromes secondary to lung cancer.[114] Pathologically, there is the diffuse loss of Purkinje cells accompanied by thinning of the molecular and granular layers, and degeneration of the long tracts of the spinal cord.[115] In patients with SCLC, paraneoplastic cerebellar degeneration can occur with or without the presence of Hu antineuronal antibodies, indicating that the syndrome can develop via different immunologic mechanisms.[112]

■ OPSOCLONUS AND MYOCLONUS

Opsoclonus is a disorder consisting of involuntary rapid conjugate eye movements in vertical and horizontal directions. It is often associated with myoclonus in patients with solid tumors. This syndrome of opsoclonus/myoclonus has been identified in both SCLC and NSCLC. Opsoclonus/myoclonus is the main presentation of paraneoplastic cerebellar degeneration associated with anti-Ri antibodies.[116] Anti-Ri binds to two proteins (55 and 80 kDa) expressed in the dentate nucleus.[117] Anti-Ri antibodies have also been identified in those presenting with a broad variety of neurologic symptoms.[118] The anti-Hu antibody has been identified in some patients with SCLC and opsoclonus/myoclonus. Patients with a known lung cancer presenting with any spectrum of neurologic symptoms should have serologic evaluation for these antibodies.

■ CANCER-ASSOCIATED RETINOPATHY

Cancer-associated retinopathy is a rare paraneoplastic syndrome that occurs predominantly in patients with SCLC. Autoantibodies have been identified in patients with this disorder that bind to a photoreceptor-specific protein called recoverin.[119,120]

Biology

Retinal ganglion cells and their processes are characteristically lost in this disorder because of the autoantibodies that bind to recoverin, a 23-kDa photoreceptor-specific protein found in rods and cones as well as in SCLC cells. The autoantibodies that cause the cancer-associated retinopathy specifically bind to the recoverin protein and do not recognize other retinal proteins.[86,87,121,122]

Diagnosis

The clinical triad of photosensitivity, ring-scotoma visual field loss, and attenuation of retinal arteriole caliber is considered highly suggestive of cancer-associated retinopathy. The typical patient presents with symptoms of rapid visual loss, night blindness, and color loss. On physical examination, most patients show visual field deficits, disk pallor, and cells in the vitreous body, along with arteriolar narrowing.

Demonstration of the antirecoverin antibody in a patient with signs of retinopathy establishes the diagnosis. As with paraneoplastic

cerebellar degeneration, cancer-associated retinopathy is often the first sign of an occult carcinoma. Therefore, an evaluation for lung cancer should be performed in all patients who present with this syndrome.[88,123,124]

Treatment

In contrast to those with the other paraneoplastic neurologic syndromes, more than half of patients with cancer-associated retinopathy have been reported to respond with visual improvement after systemic steroid therapy. Treatment of the primary tumor without immunosuppressive therapy has not been shown to result in visual improvement in patients with cancer-associated retinopathy, and most of these patients develop progressive visual loss and blindness within 18 months.[125]

LAMBERT–EATON SYNDROME

The Lambert–Eaton syndrome afflicts fewer than 2% of lung cancer patients but has been reported in up to 5% of patients with SCLC. Conversely, 50% to 60% of all patients with Lambert–Eaton syndrome will be diagnosed with SCLC.[126]

Biology

Lambert–Eaton syndrome is a consequence of the development of antibodies to P/Q-type voltage-gated calcium channels in motor and autonomic nerve terminals, leading to inhibition of acetylcholine release.[127] The resulting weakening of the neuromuscular signal results in neurologic dysfunction. This antibody also binds to the 58-kDa synaptic vesicle protein synaptotagmin, which is present in SCLC cells.[128] These antibodies have been detected in 85% to 90% of patients with Lambert–Eaton syndrome and some reports cite close to 100% detection in those with SCLC.[129]

Diagnosis

Lambert–Eaton syndrome is diagnosed based on clinical signs and symptoms, electrophysiologic studies, and antibody testing. The classic clinical triad is proximal muscle weakness (usually the first symptom noted), autonomic dysfunction, and areflexia.[130] Physical examination reveals decreased or absent tendon reflexes. Because there is a short-term return of reflexes following muscle contraction in 40% of patients, these should be tested after a period of rest.[131] Electrophysiologic studies with repetitive nerve stimulation are often diagnostic of Lambert–Eaton syndrome. A decrement in the amplitude of the muscle action potential of at least 10% is considered abnormal, a finding seen in the overwhelming majority of patients with Lambert–Eaton syndrome. Nerve stimulation post exercise demonstrates an amplitude increase, which has a high sensitivity and 100% specificity for Lambert–Eaton syndrome and distinguishes this entity from myasthenia gravis.[132,133]

Treatment

Treatment of the underlying SCLC with chemotherapy often can effectively treat Lambert–Eaton syndrome. Should symptoms persist, the first choice of treatment is 3,5-diaminopyridine which results in functional improvement the majority of the time. There are two proposed mechanisms of action. First, by blocking voltage-gated potassium channels, the action potential at the motor nerve terminals is prolonged and the opening time of the voltage-gated calcium channels is lengthened.[134] Second, neuromuscular transmission is potentiated by targeting a subunit on the voltage-gated calcium channel directly.[135] In those with severe weakness and impairment that develops gradually over time and fails to improve despite treatment of the underlying cancer and a trial of 3,5-diaminopyridine, combined therapy with prednisone and azathioprine has been shown to be effective.[136] For those with severe weakness and severe impairment that develops rapidly, treatment with intravenous immunoglobulin or plasmapheresis is indicated as it can provide marked improvement in strength although transient while treatment for SCLC is started.[137]

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

HPO is characterized by the abnormal proliferation of the cutaneous and osseous tissues at the distal parts of the extremities. While any intrathoracic malignancy may be associated with HPO, the disease is secondary to primary lung cancer in 80% of cases.[138] HPO is estimated to occur in 0.7% to 4.5% of patients with lung cancer.[138–141]

BIOLOGY

While the exact mechanisms of HPO have not been elucidated, there are a number of theories. One suggests that arteriovenous shunting within the tumor allows platelet clumps and megakaryocytes that are usually cleared by the pulmonary endothelium to enter the systemic circulation and deposit in the distal vasculature, causing the local release of growth factors including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).[142] PDGF causes proliferation of fibroblasts and an increase in vascularity and permeability resulting in connective tissue changes that are the hallmark of clubbing.[143] VEGF leads to vascular hyperplasia, osteoblastic differentiation with new bone formation, and edema; all are features of HPO.[144] Ectopic production of these growth factors by the lung cancer is an alternative hypothesis.[145] Finally, there is a neurogenic hypothesis that proposes a vagally-mediated alteration in limb perfusion. This is supported by experimental and clinical observation of resolution of HPO symptoms following unilateral vagotomy.[146]

DIAGNOSIS

HPO is diagnosed by clinical symptoms and radiographic findings. The classic triad consists of digital clubbing, arthritis, and bilateral, symmetrical periosteal formation of new bone. The latter finding is often present on plain films of the long bones but bone scintigraphy is the most sensitive method for the detection and evaluation of the extent of HPO-associated periostitis (Fig. 118-4). With its ability to delineate the subtleties of the disease, scintigraphy often reveals abnormalities that precede plain radiograph changes.[147] Scintigraphy findings range from symmetrical increased "bracelet-like" uptake to diffuse uptake in the juxta-articular regions and distal portions of the long bones.[148] Fluoro-18-deoxyglucose positron emission tomography (PET) is the preferred imaging modality for the clinical staging of lung cancer. There are case reports documenting the ability of PET to detect periosteal new bone formation of HPO and is more sensitive and specific than bone scintigraphy for detecting bone metastasis as an alternative cause of long bone pain.[149,150,151]

TREATMENT

With resection and/or treatment of the primary tumor, the symptoms of HPO will improve and often times resolve completely.[141,152,153] When the primary cause cannot be eliminated, there are a variety of symptomatic treatments for HPO, based largely on the theorized mechanisms of pathogenesis, that anecdotally have been demonstrated to have efficacy.[154] Performance of unilateral vagotomy on the ipsilateral tumor side has led to complete resolution of pain and radiographic regression of HPO.[155,156] There are a number of case reports to support the use of nonsteroidal anti-inflammatory drugs including ketorolac, indomethacin, and the COX-2 inhibitor rofecoxib.[142,157,158] Prostaglandin E is effectively reduced with these medications, thereby decreasing periostitis and HPO symptoms. The somatostatin analog octreotide has also been used with success in the treatment of HPO and is thought

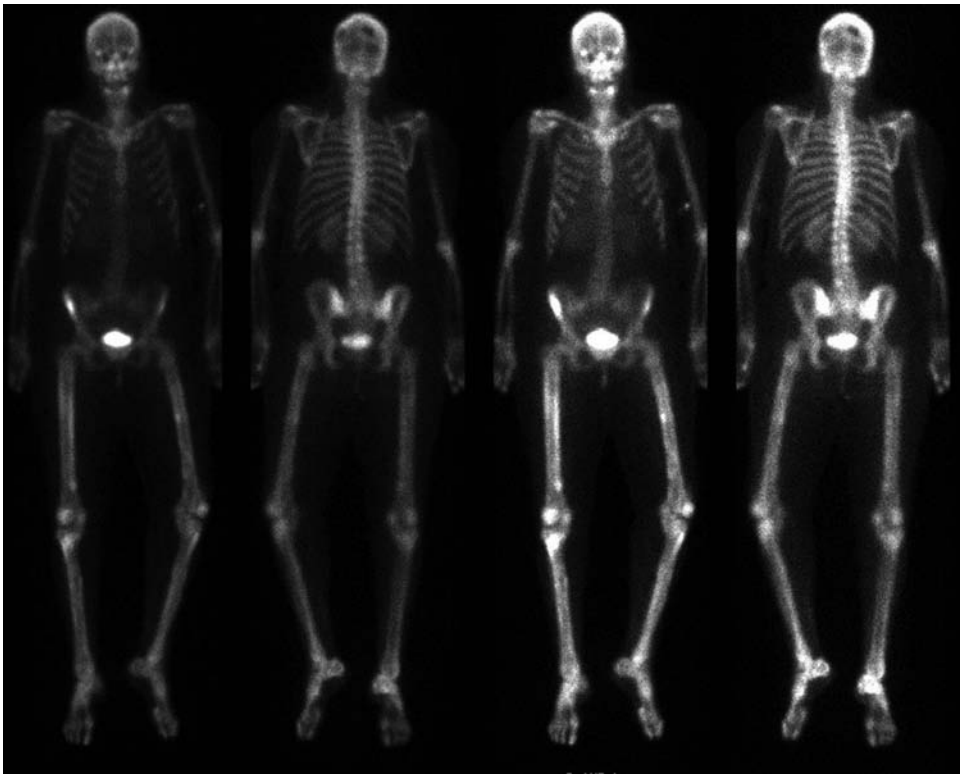

Figure 118-4 Tc99 bone scintigraphy reveals symmetric diffusely increased uptake mainly along the cortical margins of both femurs (seen best in the two delayed phase images on the right).

to be efficacious due to inhibition of VEGF and endothelial proliferation.[159,160] Bisphosphonates are potent inhibitors of bone metabolism and also decrease the levels of VEGF and symptomatic improvement has been demonstrated with both pamidronate and zoledronic acid.[161,162]

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CHAPTER 119

Pulmonary Metastases: The Role of Surgical Resection

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Pulmonary metastasectomy refers to the resection of secondary pulmonary malignancy. Most patients who develop pulmonary metastases are not curable, owing to presentation with extrathoracic metastases and lack of effective systemic therapy. Although there are no prospective, randomized trials comparing pulmonary metastasectomy to medical therapy or observation, metastasectomy has gained wide acceptance for patients who present only with metastases to the lungs. Several retrospective studies demonstrate an apparent survival advantage in patients with secondary pulmonary malignancy who undergo complete resection, comparing survival after resection to historical data for unresected patients, for whom survival is poor.

An important study that assessed the long-term results of pulmonary metastasectomy was based on an analysis of the International Registry of Lung Metastases.[1] This collaborative project retrospectively reviewed 5206 cases of lung metastasectomy performed in several institutions. Patients with a single metastasis had a survival of 43% at 5 years, compared with 34% in those with two or three metastases, and 27% in those with four or more metastases. The most important determinant of survival, however, was resectability: the ability to achieve complete resection of all recognizable pulmonary metastases. The overall 5-year survival for patients who underwent complete resection was 36%, with a median survival of 35 months. In those patients who had undergone incomplete resection, the 5-year survival was only 13%, and the median survival was 15 months.[1] These findings suggest that surgical resection offers a survival advantage for some patients.

A prognostic model was also created to select those who would benefit most, including the parameters of resectability, disease-free interval (DFI), and the number of metastases. Four distinct prognostic groups were identified: group 1 is the resectable group with no risk factors (DFI > 36 months and single metastasis); group 2 is the resectable group, with one risk factor (DFI < 36 months or multiple metastases); group 3 is the resectable group, with two risk factors (DFI < 36 months and multiple metastases); and group 4 is the unresectable group. Median survival was 61 months for group 1, 34 months for group 2, 24 months for group 3, and 14 months for group 4.[1] This prognostic model was presented as a reasonable guide to select patients for surgery.

In general, to be considered for pulmonary metastasectomy patients must fit the following criteria: the primary disease is controlled (or controllable); there is no other distant disease; complete resection of pulmonary involvement is achievable with adequate pulmonary reserve; and there are no effective medical therapies. For pulmonary metastasectomy to have survival value, the primary tumor itself must be controlled or controllable. If the pulmonary metastases are recognized metachronously, the site of the primary tumor is examined to exclude local recurrence. If the pulmonary disease has presented synchronously, the primary tumor is assessed and a decision is made regarding management. If no other metastatic disease is present, staged resection of the primary tumor and the pulmonary nodules is a reasonable approach if complete resection can be achieved. In some cases, management of a potentially resectable primary tumor is deferred until after attempted metastasectomy, with the understanding that inability to achieve complete resection would preclude surgical management of the primary tumor.

Assessment of the ability to achieve complete resection with adequate pulmonary reserve includes appraisal of the number of nodules, consideration of the location of nodules, and estimation of the postoperative pulmonary function. For patients with unilateral involvement of three or fewer nodules and preserved pulmonary function (forced expiratory volume in 1 second [FEV1] > 80%), the assessment is straightforward. For patients with bilateral involvement of five or more nodules, the calculation is more difficult, especially if any of the lesions are central and require anatomic resection (either segmentectomy or lobectomy). There is no consensus regarding the number of nodules and the ability to achieve complete resection, but increasing numbers of pulmonary nodules are associated with a higher risk of unresectability.

The ability to achieve complete resection is considered integral to achieving the potential survival benefit of metastasectomy. CT scan of the chest is regarded as the most important preoperative radiologic examination, but its ability to detect all metastatic nodules is uncertain. Thus, some surgeons also rely on manual palpation to locate nodules that may escape CT detection. McCormack et al.[2] prospectively studied the usefulness of video-assisted thoracoscopic surgery (VATS) versus thoracotomy for metastasectomy in 50 patients with nodules suspected to be pulmonary metastases on CT scan. They performed VATS resection of nodules identified on the CT scan and then proceeded with an open thoracotomy with bimanual palpation to find and resect undetected lesions. Of the first 18 patients, 10 were found to have malignant lesions that were missed by CT and VATS. The authors concluded that the CT scan would fail to detect all nodules and, therefore, that VATS for a metastasectomy would not result in complete resection.[2] Kidner et al.[3] came to the same conclusion after evaluating patients with melanoma metastases. Although single-detector row helical CT scans produce 3- to 5-mm-thick image reconstruction, thin-slice multidetector row CT scanners allowed the entire lung to be scanned with 1-mm sections in as little as 5 seconds. Kang et al.[4] used the thin-slice 16-detector row CT scan preoperatively in 27 patients and compared the findings to the pathology report after resection. In nonosteosarcoma patients, the CT found 67 of 69 metastatic nodules detected by bimanual palpation intraoperatively. Based on observations like this, thin-slice CT scanners are preferred for the evaluation of pulmonary metastases.

Staging for distant metastatic disease is performed prior to pulmonary resection, based on the primary tumor. In most patients, CT of the chest and abdomen is performed to exclude liver metastases. PET scan is also commonly used to assess metastatic disease in patients with epithelial tumors and melanoma, but the effectiveness of PET is questionable.[5] Mayerhogger et al. analyzed the utility of PET in a study of 181 patients with pulmonary metastases. The sensitivity of PET was 7.9% for lesions of 4 to 5 mm; 33.3% for lesions 6 to 7 mm; 56.8% for lesions 8 to 9 mm; 63.6% for 10 to 11 mm; 100% for 12 mm or higher ($p < 0.0010$);[6] thus, the larger the lesion, the more sensitive the PET results. Any patient with pulmonary metastases who presents with neurologic symptoms should undergo magnetic resonance imaging of the brain to exclude involvement of the central nervous system.

TABLE 119-1 Survival After Pulmonary Resection for Metastatic Colorectal Carcinoma

	No. of Patients	Median Survival (mo)	5-Year Overall Survival (%)	10-Year Overall Survival (%)
Hamaji et al.[12]	518	52.5	47.1	27.7
Iida et al.[10]	1030	69.5	53.5	30.4
Rotolo et al.[8]	23	74	56	Not reported
Welter et al.[7]	175	47.2	39.1	20
Lo et al.[9]	80	46.6	42.5	35.5
Casali et al.[11]	64	47	36	Not reported

OUTCOMES ACCORDING TO HISTOLOGY

Pulmonary metastasectomy can be considered for a variety of primary tumors, as discussed in the following sections.

■ COLORECTAL CANCER

Colorectal cancer is the most common primary histology for patients with potentially resectable pulmonary metastases. Table 119-1 lists recent studies of patients with colorectal cancer who underwent resection for pulmonary metastases; 5-year survival ranged from 36% to 56%.[7–12] In spite of the improved outcomes from pulmonary metastasectomy in some patients with colorectal cancer, the survival of most patients with pulmonary colorectal metastases will not be improved by pulmonary resection. Thus, much focus has gone into determining which patients with colorectal metastases to the lungs should in fact undergo surgery and which patients should not be offered futile resection. In an analysis by Phannschmidt et al.,[13] none of the following factors were of prognostic value: unilateral versus bilateral disease, number of nodules, size of the dominant nodule, DFI, elevated preoperative serum level of carcinoembryonic antigen (CEA), use of chemotherapy, the type of surgical approach used, or repeat pulmonary resection for local recurrent disease. Recently, Iida retrospectively analyzed 1030 patients who underwent pulmonary metastasectomy for colorectal carcinoma, documenting a 5-year survival rate of 53.5% and median survival of 69.5 months. In this series, the number of nodules, tumor size, pre-op CEA, and lymph node involvement were all independent predictors of survival.[10] Onaitis et al.[14] found that the recurrence-free survival was 28% and overall survival was 78% at 3 years in 377 patients who underwent resection of pulmonary colorectal carcinoma metastases. DFI less than a year, female gender, and numerous metastases (>3) were independent significant predictors of recurrence.[14] Gonzalez et al. recently performed a meta-analysis of 25 studies encompassing 2925 patients, and analyzed factors that impacted survival after lung metastectomy for colorectal cancer. They found that a short DFI, multiple lung metastases, positive hilar or mediastinal lymphadenopathy, and elevated prethoracotomy CEA levels were associated with poor survival.[15] Review of these and other studies (see Table 119-2) demonstrates that there is not yet a consensus as to which factors have impact on survival.

In recent years, the selection criteria for pulmonary metastasectomy have expanded to include patients with limited hepatic metastases. There has been no reported difference in outcome in patients with and without history of previously resected hepatic metastases at the time of pulmonary resection, and thus many surgeons perform pulmonary metastasectomy even in patients who have undergone hepatic resection for colorectal metastases at an earlier stage.[13,14,17] Patients who undergo combination hepatic and pulmonary metastasectomy have a 30% 5-year survival rate.[17] Pfannschmidt et al.[13] found similar results with no significant difference in outcome observed between patients with and without history of previously resected hepatic metastases at the time of pulmonary resection with 5-year survival rates between 30% and 42%.[13]

■ SARCOMA

Dear et al. analyzed 114 patients who underwent resection of pulmonary metastases for bone and soft tissue sarcomas. They found that the 5-year survival was 43% and the relapse-free survival was 19%. An incomplete surgical resection was associated with an increased risk of death, but neither the diameter of the largest resected metastasis nor a DFI of <18 months was independent prognostic factors.[18] Treasure et al.[19] performed a systematic review of studies involving a total of 1357 patients with pulmonary sarcoma metastases. Among patients who underwent pulmonary metastasectomy, they found a 5-year survival of 34% for patients with metastatic osteogenic sarcoma and 25% for patients with soft tissue sarcomas, as compared to a 5-year survival of 20% to 25% for all osteogenic sarcoma patients and 13% to 15% for soft tissue sarcoma patients. In this review, patients with fewer metastases and longer DFI had longer survival. These authors suggest that pulmonary resection of osteogenic sarcoma, including repeat pulmonary metastasectomy, is a safe and viable option.

TABLE 119-2 Prognostic Factors Associated with Survival after Pulmonary Metastasectomy for Colorectal Cancer (by Multivariate Analysis)

	No. of Patients	No. of Mets	DFI	CEA Level	Nodal Disease	Incomplete Resection
Gonzalez et al.[15]	2925	SS	SS	SS	SS	~
Iida et al.[10]	1030	SS	~	SS	SS	SS
Onaitis et al.[14]	378	SS (>3)	SS (<1 y)	~	~	~
Welter et al.[7]	175	SS (>1)	ns	ns	ns	~
Lo et al.[9]	80	ns	SS (<1 y)	SS (>20 μg/dL)	~	SS
Casali et al.[11]	142	ns	ns	~	SS	~
Saito et al.[16]	165	ns	ns	SS (>10 μg/dL)	SS	~
Pastorino et al.[1]	5206	SS (>1)	SS (<3 y)	~	~	~

ns, not significant; SS, statistically significant; ~, not reported; DFI, disease-free interval.

RENAL CELL CARCINOMA

Evidence suggests that patients with pulmonary metastases from renal cell carcinoma also derive a survival benefit from metastasectomy. Murthy et al.[20] studied 92 patients who underwent pulmonary metastasectomy secondary to renal cell cancer metastases. Complete resection was achieved in 68% of the patients, with an associated 5-year survival of 45%, compared with only 8% in those who were incompletely resected. Assouad et al.[21] found similar results in their evaluation of 65 patients with renal cell pulmonary metastases. The 5-year overall survival in those who underwent complete resection was 37.2%. They also found that mass size and lymph node involvement were important prognostic factors.[21]

MELANOMA

Chua et al. evaluated 292 patients who underwent pulmonary melanoma metastasectomy. The median overall survival was 23 months and the 5-year survival was 34%. Metastasis size greater than 2 cm and positive surgical margins were independently associated with poorer progression-free survival and overall survival. The presence of more than 1 metastasis was independently associated with poorer overall survival as well.[22] Petersen et al.[23] have also reported the survival benefits after the resection of lung metastases from melanoma. They analyzed 1720 patients with melanoma with pulmonary metastases and found that patients with complete resection had a median survival of 19 months and a 5-year survival of 21%; these outcomes were superior to those of patients who had incomplete resections, with a median survival of 11 months and a 5-year survival of only 13%.[23]

OTHER MALIGNANCIES

Pulmonary metastasectomy may be considered for patients with primary tumors of other histologic types, such as breast cancer,[24] uterine cancer,[25] and prostate cancer,[26] although patients with these malignancies are less likely to meet the criteria for operability.

PROGNOSTIC FACTORS

Important prognostic factors in considering resection of lung metastases include lymph node involvement and the extent of surgical resection, as discussed below.

LYMPH NODE INVOLVEMENT

The systematic review by Pfannschmidt et al.[13] revealed that mediastinal and pulmonary lymph node involvement were ominous prognostic factors only in studies in which nearly all the patients had undergone a systematic mediastinal and hilar lymph node dissection concurrent with pulmonary metastasectomy. The 5-year survival of the group with lymph node involvement was 0% to 33.5%, compared with 38.7% to 71% for patients with no thoracic lymph node metastases. In contrast, lymph node involvement did not predict survival in studies in which lymph node dissection was not routinely performed, or in studies in which lymph node dissection was carried out only in cases when node enlargement was detected by computed tomographic scan.[13] Many studies have evaluated the impact of positive nodes during mediastinal lymph node dissection in patients with metastatic disease.[11,16,27] All show worse survival in the presence of positive mediastinal lymph nodes. Recently, Hamaji et al.[12] concluded that mediastinal lymph node metastases are a significant negative prognostic factor for survival after pulmonary metastasectomy for metastatic colorectal cancer. Dominguez-Ventura and Nichols[28] went on to suggest that a complete mediastinal lymphadenectomy be performed for all patients undergoing pulmonary metastasectomy to better define a patient's prognosis and to guide adjuvant therapy. As these previously mentioned studies suggest, lymph node involvement is likely a negative prognostic factor, but debate still arises concerning which patients should be offered surgical exploration for resection in the setting of clinical nodal involvement. Based on the evidence of negative prognostic value, biopsy or resection of mediastinal or hilar lymph nodes would provide valuable information to guide further decision-making.

EXTENT OF SURGICAL RESECTION

Most pulmonary metastases are located peripherally and are frequently immediately subpleural, amenable to a wedge resection. When metastatic disease is more central, the anatomic resection should be performed with the goal of preserving as much pulmonary parenchyma as possible. Of the 5206 patients who were analyzed in the International Registry of Lung Metastases, 67% underwent a wedge resection, 9% a segmentectomy, 21% a lobectomy or bilobectomy, and 3% underwent a pneumonectomy.[1] It appears that wedge resection, if feasible, is as effective as anatomic resection. In their systematic review focused on the outcomes of pulmonary metastasectomy for colorectal cancer, Pfannschmidt et al.[13] suggested that the extent of resection was not an important prognostic factor for survival. These results support the practice of performing limited resection when possible to preserve lung parenchyma and function while achieving clear margins.

SURGICAL APPROACHES IN PULMONARY METASTASECTOMY

Potential surgical approaches to pulmonary metastasectomy include thoracotomy, thoracoscopy, thoracoscopy with subxiphoid manual palpation, median sternotomy, bilateral synchronous thoracotomies, and bilateral transsternal thoracotomy. In the International Registry, the surgical approach was unilateral thoracotomy in 58%, bilateral synchronous or staged thoracotomy in 11%, median sternotomy in 27%, and thoracoscopy in 2%.[1] Conventional open surgical approaches include thoracotomy, sternotomy, and bilateral transsternal thoracotomy (clamshell). The most frequently used approach is the posterolateral thoracotomy, which provides excellent exposure and the ability to palpate the lung for lesions not detected radiographically. The drawbacks of thoracotomy include postoperative pain and the inability to perform bilateral resection during a single operative session in most patients. Median sternotomy offers the advantage of assessing both lungs prior to resection and achieving bilateral resection, with less postoperative pain compared with bilateral thoracotomy (staged or simultaneous). However, a sternotomy provides suboptimal exposure of the posterior lung fields, and it is inadequate for sublobar anatomic resection of the lower lobes in most patients. Finally, a bilateral transsternal thoracotomy, also termed clamshell approach, can be used. This approach provides excellent bilateral exposure of all lung fields and adequate exposure for any anatomic resection. The disadvantages of this approach include acute and chronic postoperative pain, and the sacrifice of both internal mammary arteries. Most patients considered for resection for metastatic disease have bilateral involvement.[29] Roth et al.[29] studied outcomes in matched patients with unilateral metastases from extremity soft tissue sarcomas diagnosed on CT scan. They compared patients who underwent metastasectomy by a thoracotomy to those who underwent median sternotomy for their unilateral disease, and they found that there was no difference in survival. They concluded that neither the type of incision nor the use of bilateral bimanual palpation influenced outcomes.[29] Although the achievement of complete resection is the most important prognostic variable associated with survival, there is no evidence that the use of staged bilateral resection is inferior to a single bilateral approach.

Thoracoscopic resection is gaining favor. Potential advantages of the minimally invasive approach include smaller incisions, less postoperative pain, shorter length of stay, fewer adhesions at reoperation, and better compliance with adjuvant therapies if indicated.[30–35] The argument against the minimally invasive approach is that small (<5 mm) malignant nodules may be missed without the benefit of

bimanual palpation.[2,36,37] Recently, Eckardt performed thoracoscopic pulmonary metastasectomy on 37 patients followed by open thoracotomy. In this series, 92% of the lesions were found during VATS, but 29 lesions were resected by the thoracotomy approach that followed.[38] Of the 29 lesions missed by VATS, only 6 were metastases (21%), while 19 were benign (66%) and 3 were subpleural lymph nodes (10%). They concluded that a significant proportion of missed nodules proved to be malignant (~20%), although this is a small fraction of all nodules. The authors did not address the clinical significance, however, of missing 6 malignant nodules, nor the clinical significance of resecting a much larger number of benign nodules.

In spite of data that suggest that lesions might be missed via thoracoscopic means, the biology of pulmonary metastases may, in fact, support the use of thoracoscopic resection.[39] First, any resected metastatic disease was presumably present (at least microscopically) prior to the treatment of the primary lesion, and has been "missed" for a significant period of time. There is no evidence to suggest that the timing of resection of nodules that would be missed at thoracoscopic resection, which are usually <5 mm in diameter, is critical to the final outcome. Second, multiple resections do not adversely affect the overall outcome of patients with metachronously detected metastases. Third, patients who subsequently develop unresectable disease will not have benefited from thoracotomy. Fourth, resection may be less stressful for patients, and therefore result in less immunosuppression, resulting in a more favorable disease course.

Currently, there is no evidence that resection of pulmonary metastases at the time that they become radiographically apparent is any less efficacious than open procedures that remove all nodules, benign and malignant, before their radiologic identification. Gossot et al.[40] recently documented that patients with sarcomatous pulmonary metastases had favorable long-term survival after thoracoscopic resection. In this study, 31 patients who underwent thoracoscopic resection had similar 1-year, 3-year, and 5-year overall and disease-free survivals when compared with the 29 matched controls who underwent thoracotomy resection. Repeat procedures for further surgical resection were required in 36% and 41% of patients in the VATS and thoracotomy groups, respectively.

Several other recent studies also suggest that VATS resection of pulmonary metastases yields comparable survival to thoracotomy. Chao et al. performed a case-matched study of 53 patients with pulmonary metastases from colorectal carcinoma who underwent open resection compared to 90 who underwent a VATS approach. They studied 35 pairs of patients matched for tumor number, diameter, and surgical procedure. Both groups had similar recurrence and 5-year overall survival rates, suggesting that VATS is not inferior to that of open thoracotomy for pulmonary metastasectomy.[41] Nakajima et al.[42] studied 143 patients with pulmonary metastases secondary to colorectal cancer who were diagnosed by helical CT scan. In this study, 71 patients underwent open thoracotomy, whereas 72 patients underwent VATS; 22 patients in the open group and 21 patients in the VATS group had multiple lesions. The authors reported superior 5-year survival (49.3%) in the VATS group compared with 39.5% in the open group ($p = 0.047$). The 5-year disease-free survival was 34.4% for the VATS group and 21.1% for the open group ($p = 0.064$). The authors suggest that VATS metastasectomy is a safe and valuable alternative to the open thoracotomy in selected patients.[42]

Finally, in a study comparing VATS (79 patients) to open (43 patients) approach for pulmonary metastases from colorectal cancer, there was no difference between the groups in the number of additional nodules found at surgery and no difference in the development of ipsilateral recurrence at 2 years.[43]

Based on these findings, there is no evidence to suggest that the thoracoscopic approach is inferior to open approaches in selected patients. The role of thoracoscopic resection in patients with many nodules (>5–10) has not been tested.

The use of multiple sequential pulmonary resections for recurrent disease has also been studied in patients who develop pulmonary metastases in the absence of extrathoracic disease. Welter et al.[7] found that repeat resections of pulmonary metastases secondary to colorectal cancer was safe and provided long-term survival. The authors reported 5-year survival of 53.8% in those who had repeat resection of pulmonary metastases. This study suggests that a second metastasectomy can be performed when new lesions grow are detectable, with good outcomes. The outcome of patients who underwent a second metastasectomy in the International Registry was also excellent. The 5- and 10-year survival rates were 44% and 29%, respectively, compared with 34% and 25%for patients having had one operation.[1] The favorable long-term results suggest a curative benefit of repeated salvage operations, rather than a simple selection effect, with no apparent disadvantages. These results suggest that the biology of the tumor is more important than the strategy of resection. Some lesions that are not detected by CT scan may be removed once they are detected at a later date without negatively influencing survival, because their biology is less aggressive; whereas resection of every possible lesion in a patient with very aggressive tumor biology may still lead to poor survival.

OTHER TREATMENT OPTIONS

Alternatives to surgical resection of pulmonary metastases include isolated lung perfusion using chemotherapeutic agents and various ablation techniques.

■ ISOLATED LUNG PERFUSION

Although surgical resection is effective for some patients with metastatic disease involving the lung, the majority of patients with pulmonary metastases develop unresectable disease, either due to extensive pulmonary involvement or due to extrathoracic involvement. In addition, some patients present with disease not amenable to resection. The concept of isolated lung perfusion has been developed to treat unresectable disease. Isolated lung perfusion involves direct infusion of chemotherapeutic drugs into the affected lung, allowing higher doses of agents to be infused locally, without the systemic side effects that would accompany such doses.

Den Hengst et al. studied 23 patients in a phase I clinical trial who underwent isolated lung perfusion using melphalan for unresectable colorectal, renal, sarcoma, and salivary gland tumor metastases to the lung. They showed that the overall and disease-free 5-year survival rates were 54.8% and 27.5%, respectively, with an overall median survival time of 84 months and disease-free median survival time of 19 months. They noted no major long-term pulmonary toxicity.[44] A novel option for isolated lung perfusion is currently under investigation, thoracoscopic lung suffusion, which is less invasive than lung perfusion and limits the systemic absorption of chemotherapy.[45]

■ ABLATION TECHNIQUES

Several ablation techniques are being studied to treat patients who have a limited number of pulmonary metastases that are not operable based on medical issues, such as cardiac status. Stereotactic radiosurgery is one option for ablation, and this technique may be coupled with image-guided robotics (CyberKnife, Accuray, Sunnyvale, CA). Snider et al. used CyberKnife on 24 high-risk patients with biopsy-proven single-peripheral lung metastases. A mean dose of 52 Gy was delivered in three fractions. The 2-year Kaplan–Meier local control and overall survival rates were 87% and 50%, respectively. They concluded that CyberKnife is an effective treatment for high-risk surgical patients with single, small, peripheral lung metastases.[46]

SUMMARY

Metastases to the lungs are common in patients with malignancy, and isolated pulmonary metastases may be seen in patients with many types of cancer. Despite the absence of prospective, randomized

controlled trials, it seems highly likely that pulmonary metastasectomy does improve outcomes in appropriately selected patients. Selection criteria include established control of the primary tumor, an absence of extrathoracic involvement, and disease amenable to complete resection with adequate residual pulmonary reserve. Many studies have investigated prognostic factors related to pulmonary metastasectomy, including the number of nodules, size of the dominant nodule, ability to achieve complete resection, histology, and DFI. Although each of these factors may influence outcome, the most important determinant of long-term survival is achieving a complete resection.

To optimize postoperative pulmonary function, parenchymal-sparing techniques are used whenever possible. Wedge resection is the most common surgical procedure, but more central lesions may require segmentectomy, lobectomy, and (rarely) pneumonectomy. Although posterolateral thoracotomy with manual palpation is considered important to identify all nodules and achieve complete resection, many surgeons prefer thoracoscopic resection and there is no evidence that this approach is inferior, as measured either by survival or by ipsilateral intervention. In addition to advantages in quality-of-life outcomes, the thoracoscopic strategy also simplifies reoperation when necessary and may prevent futile thoracotomy. Although complete resection is essential to improve survival, it is possible that staged complete resection is equally effective.

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SECTION 15 Lymphoproliferative Disorders

CHAPTER 120

Lymphoproliferative and Hematologic Diseases Involving the Lung and Pleura

Douglas B. Flieder

Lymphoproliferative disorders of the lung and pleura comprise a varied but rare group of localized and diffuse processes that span the morphologic gamut from reactive to neoplastic and include several peculiar lesions that do not fit conventional definitions of either hyperplasia or neoplasia. Although most diagnoses are based on light microscopy, immunohistochemical and molecular investigations have assumed a vital role. Nomenclature and classification schemes have undergone drastic changes over the past quarter century and current definitions appear reasonable. Malignant lesions are best classified according to the current World Health Organization (WHO) scheme.[1] This chapter presents the clinicopathologic features of primary and secondary pulmonary and pleural hematolymphoid lesions.

ANATOMY AND HISTOLOGY OF THE PULMONARY LYMPHOID SYSTEM

Pulmonary lymphatics are divided into two interconnecting channels that drain to peribronchial, hilar, and/or mediastinal lymph nodes and eventually into the thoracic duct, right lymphatic duct, and subclavian veins.[2] One system drains through the visceral pleura around the lung into mediastinal lymph nodes and the other drains from central lung parenchyma to peribronchial and hilar lymph nodes. The lymphatics communicate at lobar, lobular, and pleural boundaries and thus serve each other as potential collaterals.[3,4] Although not usually obvious in histologic sections of normal lung, lymphatics are prominent in disease states ranging from pulmonary edema to lymphangitic carcinoma. In the latter, lymphatic channels distended with malignant cells are apparent within the visceral pleura, interlobular septa, and adventitia of arteries, veins, and bronchioles. Of note, alveolar septa do not contain lymphatic channels. All lymphatics contain valves and flat endothelial cells line the discontinuous basal lamina. Larger lymphatics contain smooth muscle and collagen.

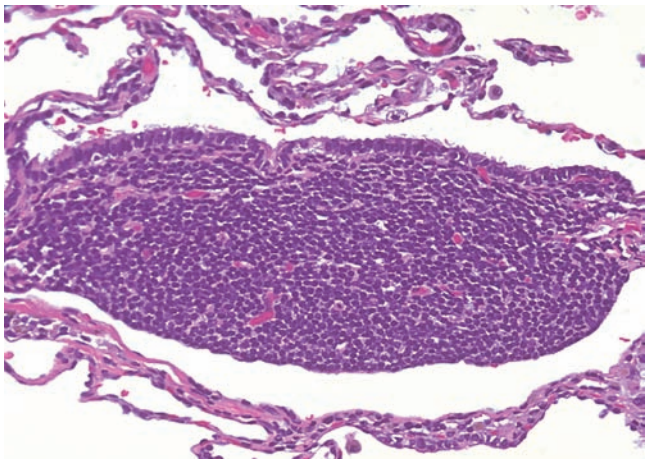


Figure 120-1 Bronchus-associated lymphoid tissue. The submucosal collection of lymphoid cells is intimately associated with overlying bronchiolar epithelium. Hematoxylin and eosin, 40× original magnification.

Small submucosal aggregates of lymphoid cells are often prominent at bronchial bifurcations and near distal respiratory bronchioles (pulmonary microtonsils) and represent bronchus-associated lymphoid tissue (BALT) (Fig. 120-1).[5–7] Whether humans are born with this specialized secondary lymphoid system, or whether the aggregates of B lymphocytes, T lymphocytes, HLA-DR+ interdigitating cells, follicular dendritic cells, and lymphoid follicles with overlying flattened and attenuated specialized epithelium develop in response to antigenic stimulation is controversial.[8,9] Viruses, connective tissue disorders, tobacco use, and obstructive pneumonia are just a few pathologic processes known to induce BALT (Table 120-1). Unlike typical lymph nodes that rely on

TABLE 120-1 Diseases Associated with Hyperplasia of Bronchus-Associated Lymphoid Tissue

Autoimmune diseases
Allergy such as asthma
Autoimmune hemolytic anemia
Celiac sprue
Hashimoto thyroiditis
Myasthenia gravis
Pernicious anemia/agammaglobulinemia
Primary biliary cirrhosis
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren syndrome
Transverse myelitis
Immunodeficiency syndromes
Common variable immunodeficiency
Unexplained childhood immunodeficiency
Virus-associated
Epstein–Barr virus
Hepatitis viruses
Human immunodeficiency virus
Drug-induced forms
Allogeneic bone marrow transplantation
Dilantin
Infections
Chlamydia
Mycoplasma
Tuberculosis
Familial

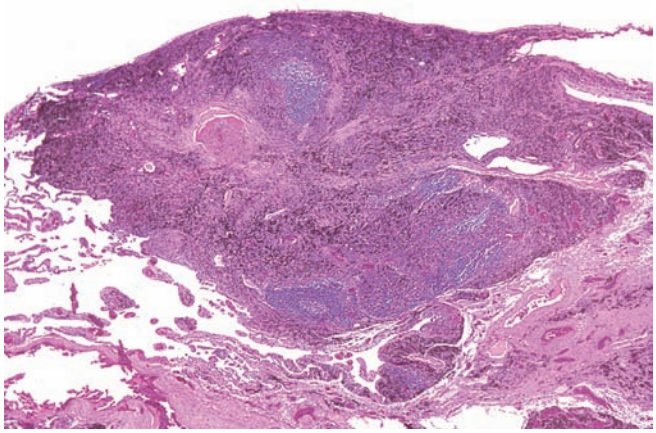


Figure 120-2 Intrapulmonary lymph node. Subpleural lymph nodes often accumulate carbon pigment and become fibrotic. The radiologic differential diagnosis includes carcinoma, while a fine-needle aspirate sample may mimic malignant lymphoma. Hematoxylin and eosin, 4× original magnification.

afferent lymphatics for antigen retrieval, BALT is integrated into lung tissue and antigen is sampled directly from the bronchial and bronchiolar lumens through specialized "lymphoepithelium." Immunoglobulins, most notably IgA, are synthesized and secreted by lymphocytes directly into airway lumens. Amazingly, this system appears capable of mounting a competent adaptive immune response. In addition, BALT B-lymphocytes circulate and "home" to other mucosal sites such as the conjunctiva, salivary glands, stomach, and intestines to create a common mucosal immune system, the mucosa-associated lymphoid system (MALT).[6] Thus, responses induced in one location can be replicated at other sites.[10] Malignant lymphoma arising in one MALT location can secondarily involve other MALT sites. BALT appears to be the origin of many primary pulmonary lymphoid lesions.[11]

Intrapulmonary lymph nodes (IPLs) may be part of the pulmonary immune system and may also be induced by antigenic stimuli rather than normal embryologic development.[12] Autopsy studies suggest a prevalence of 18%, and although many are related to bronchi of the first few orders, peripheral subpleural locations are not uncommon. In this age of high-resolution computed tomography (HRCT) and lung cancer screening programs, up to 80% of reported cases of IPLs occur in men with histories of tobacco use and almost 35% of cases are multiple.[13] They appear as round to angulated sharply circumscribed subpleural opacities up to 2 cm in diameter and are found along interlobular septa or within major and minor fissures. IPLs histologically resemble classic lymph nodes with well-developed cortical and medullary areas.[12,14] Sinus histiocytes frequently contain abundant anthracosilicotic pigment and silicotic nodules with calcifications may form (Fig. 120-2). In patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), IPLs may be involved and, rarely, primary lung carcinoma or carcinoma from a nonpulmonary site can metastasize to IPLs. Most importantly, IPLs can be clinically, radiographically, and cytologically mistaken for malignancy.[15,16] Although fine-needle aspirates can exclude the possibility of carcinoma, an erroneous diagnosis of lymphoma might be considered.

GENERAL CONSIDERATIONS

Although internists, pulmonologists, and radiologists often diagnose pulmonary diseases on the basis of clinical and radiographic findings and rely on tissue samples merely for confirmation, lymphoid lesions of the lung are often unsuspected diagnoses rendered by pathologists. Yet clinical and radiologic studies are essential in the interpretation of all lesions. Often, light microscopic considerations can be excluded purely on the basis of radiographic findings. For example, whereas pulmonary lymphomas can be localized or diffuse, lymphoid interstitial pneumonia (LIP) is always bilateral and diffuse.

Although fine-needle aspirate biopsies and transbronchial biopsies supplemented with ancillary studies may suffice for a diagnosis of malignant lymphoma, architectural and cytologic variability necessitates generous sampling. Since cellular monotony is not the sole criterion for malignancy, pulmonary lymphoid lesions often require wedge biopsies for diagnosis. Whereas sheets of uniform cells may be diagnostic of lymphoma, many malignant processes such as Hodgkin lymphoma (HL) and T-cell lymphoma are polymorphous and admixed with inflammatory cells. Secondary changes and biopsy-related artifacts may also confound the interpretation of a small sample.

Larger samples also allow for low-magnification pattern recognition. A "lymphatic distribution" may be seen in nonlymphoid processes such as sarcoidosis, yet is most striking in lymphoproliferative lesions reflecting the homing of lymphoid cells to endogenous pulmonary lymphatic routes. Although malignant lymphoid processes usually obliterate underlying lung architecture, diffuse alveolar septal expansion with lymphoid cells without a beaded lymphangitic pattern tends to represent an inflammatory rather than neoplastic process.

In addition to histologic examination, immunophenotyping is routinely performed and has become indispensable in diagnosing and classifying lymphoid lesions of the lung. Immunohistochemical studies can be reliably performed on formalin-fixed, paraffin-embedded tissue, whereas flow cytometry is useful for demonstrating immunoglobulin light-chain restriction. Aberrant antigen expression by either method also allows for subclassification. Polymerase chain reaction (PCR) may be required in up to 20% of cases to prove clonality.[17] Either rearrangement of the immunoglobulin heavy-chain gene joining region (*JH*) or the T-cell receptor γ-chain gene (TCR-γ) can be investigated. Lastly, chromosomal abnormalities indicative of specific lymphomas such as t(14;18) translocation and bcl-2 gene rearrangement in follicular lymphoma or t(11;14) translocation and cyclin D1 (bcl-1) gene rearrangement in mantle cell lymphoma may be helpful.

Given the complex evaluation required of these lesions, it is incumbent upon the clinician to deliver the fresh tissue sample to the pathologist along with his or her concern for lymphoma. Although formalin-fixed or B5 fixed, paraffin-embedded samples may suffice for diagnosis and immunohistochemical evaluation, cell suspensions and fresh frozen tissue are required for flow cytometry, cytogenetics, and many molecular studies.

Lastly, although clonality indicates malignancy, clonality in pulmonary lymphoid lesions may not predict clinical outcome. Many pulmonary lymphomas have long indolent courses with 10-year survival rates of more than 80% yet LIP, a polyclonal process, is progressive with one-third of affected patients dying of end-stage pulmonary fibrosis.[18,19]

REACTIVE LYMPHOID PROCESSES

Although the terminology used to describe inflammatory processes of the lung has remained relatively static over the past 25 years, immunohistochemistry and molecular genetic analysis have redefined diagnostic criteria. Processes arising from BALT include nodular lymphoid hyperplasia (NLH), follicular bronchitis/bronchiolitis (FBB), diffuse lymphoid hyperplasia (DLH), and LIP. Pulmonary hyalinizing granuloma (PHG) is included in this section for historical reasons only. Although the lesions are best considered either localized or diffuse, clinicopathologic entities including Castleman disease (CD) can manifest with either distribution.

■ LOCALIZED REACTIVE LYMPHOID PROCESSES

Localized reactive lymphoid processes, including nodular lymphoid hyperplasia, pulmonary hyalinizing granuloma, amyloidosis, and light chain deposition disease are discussed below.

Nodular Lymphoid Hyperplasia

Known to previous generations of pulmonologists and hematopathologists as "pseudolymphoma," this reactive process was recognized as a form of BALT hyperplasia in the mid-1980s.[20] Although NLH was once considered to be quite common, ancillary studies have convincingly demonstrated that most cases were actually low-grade lymphomas.[21] Thus true NLH is now considered a legitimate but exceedingly rare polymorphous nodular lymphoid lesion of the lung.[22] Neutrophilic microabscesses and foreign body giant cells found in several reported cases indicate that the lesion may be the result of an inflammatory stimulus. Interestingly, immunohistochemical studies have documented B-cell lymphomas of BALT within pre-existing reactive masses of BALT, such that one could, in the most general sense, consider NLH a precursor lesion.[11,20]

Most affected individuals are middle aged with a nearly equal gender incidence.[22,23] Patients are usually asymptomatic, although a small percentage may have autoimmune diseases such as systemic lupus erythematosus or Sjögren syndrome, or polyclonal hypergammaglobulinemia. Lesions usually appear as solitary subpleural radiographic nodules with air bronchograms, but several nodules or localized infiltrates can be seen, the latter finding serving as a reminder that the distinction between nodular and diffuse processes is arbitrary.[24] Up to one-third of cases feature regional lymphadenopathy.

Excised tan-white rubbery to firm nodules measure from 0.6 to 6.0 cm. Histologically, the well-demarcated lesions may feature slight extension along alveolar septa and central scarring. Normal lung parenchyma is overrun by large reactive germinal centers with well-preserved mantle zones, and lymphoepithelial lesions are not seen (Fig. 120-3). Interfollicular areas are filled with plasma cells and mature lymphocytes. The follicles are clearly reactive with a variety of cell types, mitoses, and macrophages. Regional lymph nodes often feature reactive follicular hyperplasia.

Immunohistochemical studies demonstrate a mixture of B- and T-cells. The B-cells express both κ and λ light chains, that is, lack light chain restriction. Aberrant B-cell staining for CD5, CD23, or CD43 is not seen, and the germinal centers do not stain with bcl-2.[22,25] Immunoglobulin heavy chain gene rearrangement or evidence of t(14;18) breakpoints is not observed. These ancillary findings are of the utmost importance since light microscopy alone may not differentiate NLH from an extranodal marginal zone B-cell lymphoma of MALT. The latter usually features infiltrative growth, but may have reactive follicles and polytypic plasma cells with only a focal monotypic cell population.

Surgical excision is usually curative, although a small percentage of patients develop local recurrences at the original surgical site. Neither systemic spread nor death has been reported.[22,25]

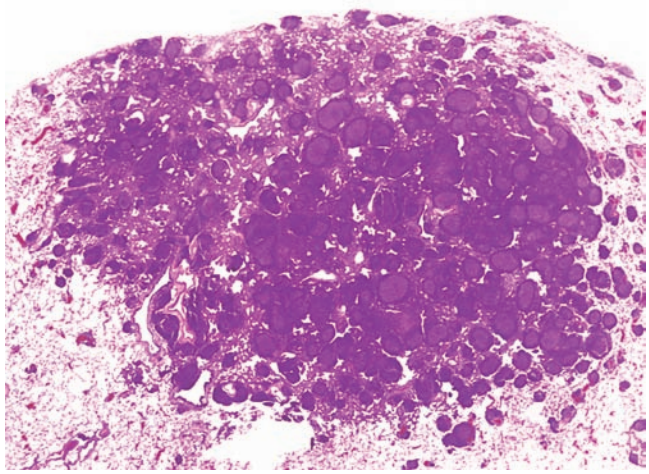


Figure 120-3 Nodular lymphoid hyperplasia. The lesion is composed of benign reactive germinal centers. Although radiographically nodular, germinal centers spill out into surrounding lung. Immunohistochemistry is required to exclude a diagnosis of malignant lymphoma. Hematoxylin and eosin, 1× original magnification.

Pulmonary Hyalinizing Granuloma

PHG is neither a lymphoid nor granulomatous lesion per se, but an ever-present lymphoid component allows for its discussion in a hematolymphoid chapter. This peculiar fibrosing process shares clinicopathologic and morphologic features with sclerosing mediastinitis, inflammatory pseudotumor of the orbit, Riedel thyroiditis, and idiopathic retroperitoneal fibrosis.[26] In fact, approximately one-fourth of cases feature concomitant mediastinal or retroperitoneal disease.[27,28] The etiology is unknown but it has been speculated to represent either an autoimmune phenomenon or exaggerated host response to mycobacteria or fungi.

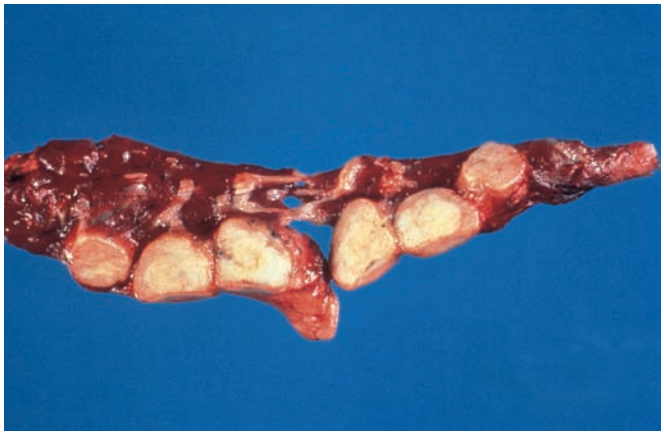
Age at presentation ranges from 24 to 77 years and women are affected twice as often as men. Most patients present with mild symptoms including cough, shortness of breath, fever, and fatigue but up to 25% of reported individuals are asymptomatic. Laboratory studies include positive antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, and Coombs-positive hemolytic anemia.[28] Elevated serum or tumor immunoglobulin G4 (IgG4) levels are rarely reported.[29,30] Skin testing often demonstrates exposure to *Mycobacterium tuberculosis* or *Histoplasma capsulatum,* but cultures and stains for microbes are negative. Radiographs reveal less than 4.0 cm bilateral and multilobar ill-defined homogeneous nodules that resemble metastases.[31] Unilateral and solitary cases measuring up to 15 cm have been reported. Although not common, focal central irregular calcification may suggest metastatic bone-forming neoplasms. Central cavitation is rare.

Lesions are sharply circumscribed white-tan rubbery masses composed of irregular concentric whorls of hyalinized collagen encasing vessels and airways (Fig. 120-4A).[27,28] The center of the lesion is paucicellular, whereas peripheral thick collagen bands are separated by mature T-lymphocytes, plasma cells, fibroblasts, and occasional giant cells (Fig. 120-4B). Blood vessels may feature transmural inflammation without necrosis. Microscopic calcifications can be seen, but granulomas are not present despite the designation PHG. The tumoral interface with lung parenchyma features reactive germinal centers, whereas adjacent lung may feature organizing pneumonia and hyperplasia of BALT. The morphologic differential diagnosis includes rheumatoid nodule, amyloidosis, granulomatosis with polyangiitis (Wegener granulomatosis), malignant lymphoma, inflammatory myofibroblastic tumor, and infections.[29] Clinicians should not be comfortable with a diagnosis of PHG rendered on anything less than a completely removed lesion.

PHG tends to enlarge slowly and does not recur after surgical resection. However, growth of unresected or unresectable nodules can lead to respiratory compromise.[28]

Amyloidosis and Light Chain Deposition Disease

Immunoglobulin light chains can accumulate in many tissues in different forms, depending on the underlying condition and particular organ cytoskeleton. Clinically recognizable disease in the lung can manifest as tracheobronchial disease, solitary or multiple nodules, cystic lung disease, or in a diffuse interstitial parenchymal pattern.[32,33]



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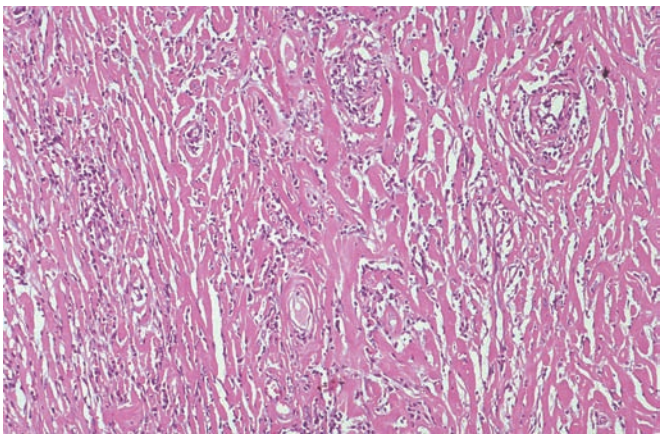


B

Figure 120-4 Pulmonary hyalinizing granulomas. **A.** Multiple well-circumscribed tan firm nodules can compromise respiratory function. **B.** Pink hyalinized collagen bands encircle vessels. Scant benign lymphoid infiltrates percolate between the collagen. Hematoxylin and eosin, 10× original magnification.

Most cases of diffuse light chain deposition in the lung are part of multiorgan involvement, are associated with plasma cell dyscrasia, have dismal clinical outcomes, and are not discussed further in this section.

Solitary and multiple amyloidoma are seen most often in older individuals, with a mean age of 67 years.[32] Central and solitary lesions are often incidental findings but airway or visceral pleural distortion may produce cough, hemoptysis, or pleuritic chest pain. A radiographic diagnosis can be suggested when calcification or ossification is noted (20%–50% of the time); otherwise, the clinical impression is that of a neoplasm.[34]

Serum or urine monoclonal proteins are found in 10% of patients, and this lung pathology may be associated with lymphoproliferative diseases such as benign monoclonal gammopathy of undetermined significance, Sjögren syndrome, Crohn disease, NLH, LIP, extranodal marginal zone B-cell lymphoma of MALT, or multiple myeloma.[32,35–37] Solitary amyloidoma without underlying blood dyscrasias probably represent a hyperimmune response to unknown antigens.

Waxy hard gritty and yellow-tan nodules measure up to 15 cm and are composed of amorphous eosinophilic hyaline material that obliterates lung parenchyma but spares many arterioles (Fig. 120-5). Lymphocytes, plasma cells, and multinucleated giant cells percolate through the amyloid, but the infiltrate is most dense at the periphery of the nodules. Calcification and ossification with secondary marrow space formation is common. Congo red staining examined by polarizing microscopy reveals lesional apple-green birefringence. Immunohistochemical studies usually demonstrate λ light-chain composition and negative immunoreactivity for amyloid A and transthyretin.[37,38] Plasma cells are most often polytypic; however, small foci of monoclonal plasma cells within foci of polytypic plasma cells have been identified.[39] Ultrastructurally, amyloid is composed of disorderly nonbranching hollow-core 8- to 10-nm fibrils. These extracellular deposits of chemically diverse proteins form a three-dimensional twisted β-pleated sheet. Resected lesions may not demonstrate malignancy, but patients should be screened for underlying monoclonal B-cell proliferations including multiple myeloma and overt B-cell malignancies.

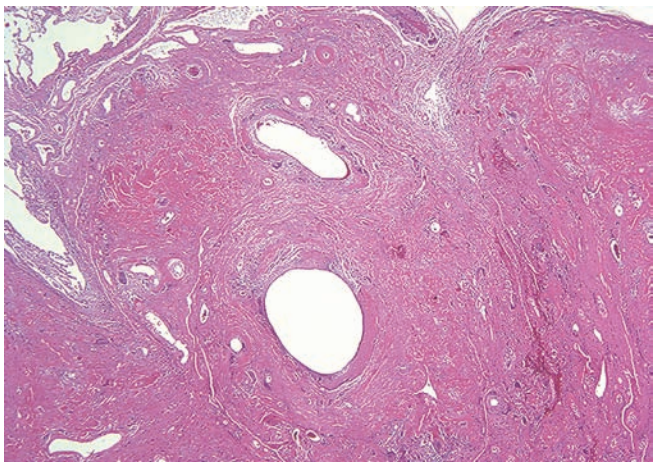


Figure 120-5 Nodular amyloidosis. Amorphous pink material replaces air spaces and overruns airways. In the absence of Congo red apple-green birefringence one should consider the possibility of nodular light chain deposition. Hematoxylin and eosin, 4× original magnification.

In stark contrast to nodular amyloidosis, pulmonary light chain deposition disease (LCDD) is associated with an underlying blood dyscrasia or renal failure in more than 50% of affected individuals.[40–42] Most patients have free κ monoclonal light chains (IgG, IgA, and IgM in decreasing order) in their urine or serum.[43] The clinical and light microscopic appearance of LCDD is similar to amyloid, and one might mistake a case lacking the characteristic Congo red staining as simply a poorly stained example of amyloid. These light chain deposits are composed of amorphous granular or globular electron dense material.[43] One should consider this entity when dealing with a nonamyloidotic deposit given its strong association with lymphoid malignancies including but not limited to multiple myeloma and renal failure.[43,44]

■ DIFFUSE REACTIVE LYMPHOID PROCESSES

Although NLH most likely represents a local response to an extrinsic stimulus and is clinically relevant owing to its radiographic appearance as a coin lesion and morphologic similarity with extranodal marginal zone B-cell lymphoma of MALT, the DLHs, FBB, and LIP represent a continuum of BALT hyperplasia often seen in patients with systemic diseases (Table 120-1).[20,25,45] The extent of lung involvement is due in large part to host immune factors.[46] Although thoracoscopic or open lung biopsies are required to establish these diagnoses and exclude other processes, including interstitial lung diseases and malignant lymphoma, morphology does not suggest etiology.

Follicular Bronchitis/Bronchiolitis

DLH *restricted* to the walls of airways and peribronchial tissue is referred to as FBB. FBB is often seen in individuals with

bronchiectasis, chronic infections, and chronic obstructive pulmonary diseases, including asthma.[45,47] The entity may also be seen in association with connective tissue diseases, congenital or acquired immunodeficiencies, or bone marrow transplantation; or as a manifestation of a hypersensitivity reaction.[48,49] When the process spreads along lymphatic routes of the pulmonary lobule some prefer the designation DLH instead of FBB.

Patients with FBB in association with connective tissue disease are usually in their forties and most often suffer from rheumatoid arthritis (RA) or Sjögren syndrome.[50,51] Patients with immunodeficiency syndromes such as acquired immunodeficiency syndrome (AIDS), common variable immunodeficiency, IgA deficiency, and Evans syndrome present in childhood, whereas those with hypersensitivity syndromes are usually in their sixth decade of life. Patients may also suffer with chronic low-grade infections such as mycoplasma, chlamydia, or Epstein–Barr virus (EBV).[45]

Individuals with FBB present with dyspnea, cough, and fever; some may have recurrent pneumonia or weight loss. Pulmonary function tests reveal restrictive, obstructive, or normal patterns.[47] Those with RA often have a very high rheumatoid factor on the order of 1:640 to 1:2560. Peripheral eosinophilia may be noted in those with hypersensitivity syndromes. Arterial blood gases show arterial hypoxia with a widened $AaPO_2$ gradient and hypocapnia. Chest radiographs feature bilateral diffuse reticular and nodular opacities, whereas HRCT show up to 12-mm centrilobular and peribronchial nodules with or without areas of ground-glass opacity.[24,52]

Gross pathology demonstrates numerous minute (1- to 2-mm) nodules adjacent to airways. Microscopically, nodular aggregates of B-cell rich lymphocytes and plasma cells with reactive germinal centers expand bronchial and/or bronchiolar submucosa and budge into and permeate overlying epithelium (Fig. 120-6). Rare T-cells wander beyond the follicles into adjacent alveolar septa.[25] Smaller airway lumens are distorted and narrowed predisposing to mucostasis and subsequent infections. Lymphoid follicles along interlobular septa and beneath the pleura represent a more diffuse form of lymphoid hyperplasia and warrant the descriptive diagnosis DLH.

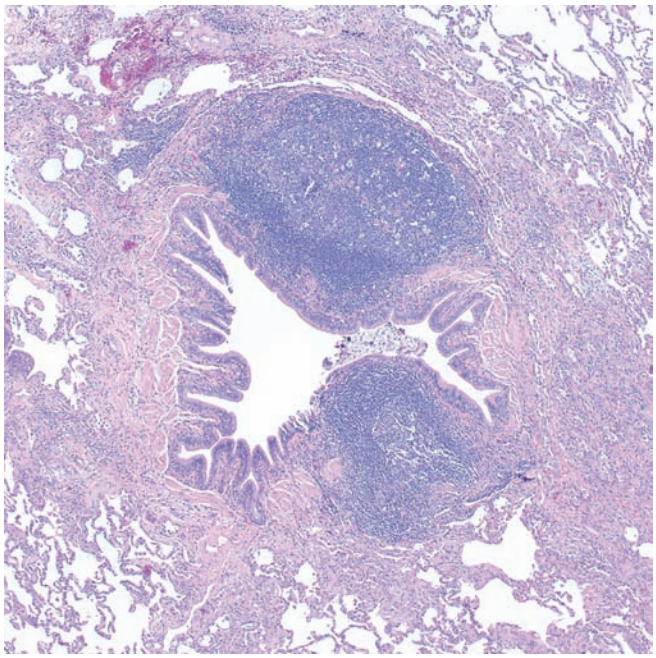


Figure 120-6 Follicular bronchitis/bronchiolitis. Reactive germinal centers expand airway submucosa and compress the lumen. Mucus accumulation often leads to infection and bronchiolectasis. Alveolar parenchyma is spared. Hematoxylin and eosin, 4× original magnification.

Treatment of FBB with corticosteroids has variable results.[47,48] Those with peripheral eosinophilia are reportedly steroid responsive.

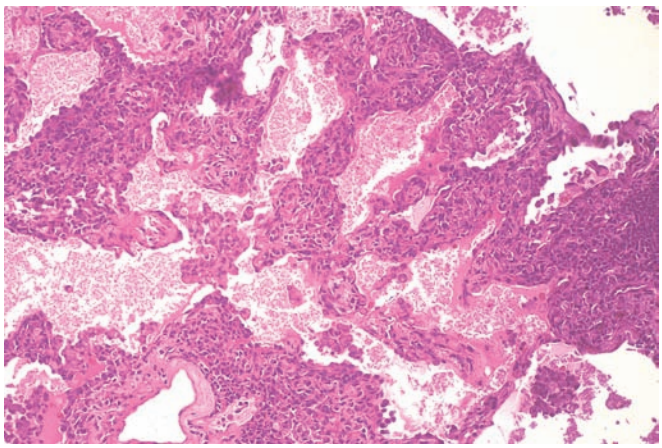
Lymphocytic Interstitial Pneumonia

Although LIP is included in the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias, this multifactorial but rarely idiopathic process represents the most florid form of BALT hyperplasia and may be difficult to differentiate from florid FBB and low-grade malignant lymphoma.[53] Almost all patients with LIP have immunologic disorders, dysproteinemias, or viral infections, including EBV and, especially in children, human immunodeficiency virus (HIV).[54–57] The age and sex distribution reflect these different populations. This clinicopathologic process is rare in the HIV-negative population, but represents a pulmonary manifestation of chronic graft-versus-host (GVH) disease in bone marrow transplant patients.[54] A strong association with Sjögren syndrome is also noted.[58] Most HIV-negative patients are middle-aged Caucasian women.

The clinical presentation includes cough and/or dyspnea in addition to symptoms and signs related to underlying diseases. More than 60% of patients have dysproteinemias, which can precede the onset of LIP or occur any time during the clinical course.[54,59,60] Most of these cases are associated with hypergammaglobulinemia; only 10% of cases are associated with hypogammaglobulinemia. A monoclonal spike on serum immunoelectrophoresis suggests a diagnosis of lymphoma rather than LIP. Pulmonary function tests reveal reduced lung volumes and diffusing capacity for carbon dioxide (D_{LCO}), and hypoxia is common.[54] Bronchoalveolar lavage (BAL) analysis shows an increased percentage of lymphocytes. Chest radiographs demonstrate bilateral reticular and nodular opacities, ground-glass opacities, and parenchymal consolidation with lower lung zone predilection. Computed tomography demonstrates diffuse ground-glass opacities, ill-defined centrilobular nodules, bronchovascular and interlobular thickening, and scattered less than 3.0-cm thin-walled cysts.[61–63]

The lungs are typically firm and tan-gray and end-stage cases feature honeycomb change with subpleural cysts. Although the radiographs and gross appearance suggest parenchymal consolidation, histologically LIP shows a diffuse prominently *interstitial* infiltrate of small lymphocytes, plasma cells, larger mononuclear cells, and histiocytes (Fig. 120-7A). Although these infiltrates are centered on airways, vessels, and interlobular septa, and include peribronchiolar lymphoid follicles, infiltration into alveolar septa is always present and distinguishes LIP from FBB (Fig. 120-7B). Small nonnecrotizing granulomas, reactive germinal centers, and infiltration into overlying respiratory epithelium are often seen, whereas lymphocytes frequently spill into alveolar spaces. In long-standing lesions, hyaline, collagen, or even amyloid widens the interstitium leading to honeycomb fibrosis. The lymphoid follicles largely consist of cytologically bland B-cells, whereas the interstitial lymphocytes are mostly T-cells. This pattern suggests that the lung can function like a giant lymph node.[25] Immunoglobulin heavy chain restriction or gene rearrangement is lacking. In addition to malignant lymphoma, nonspecific interstitial pneumonia (NSIP) and infections including *Pneumocystis* should be excluded.

Given the rarity of LIP, controlled treatment trials have not been undertaken. Corticosteroids are the primary therapy in addition to other immunosuppressive agents, such as cyclophosphamide and chlorambucil, with variable results. One-third of patients have resolution, one-third stabilize, and the remaining third progress.[18,54,60] Nonresponders often die of therapy-related infections, but occasional individuals die of end-stage pulmonary fibrosis. Lymphomatous transformation is very unusual; older reports



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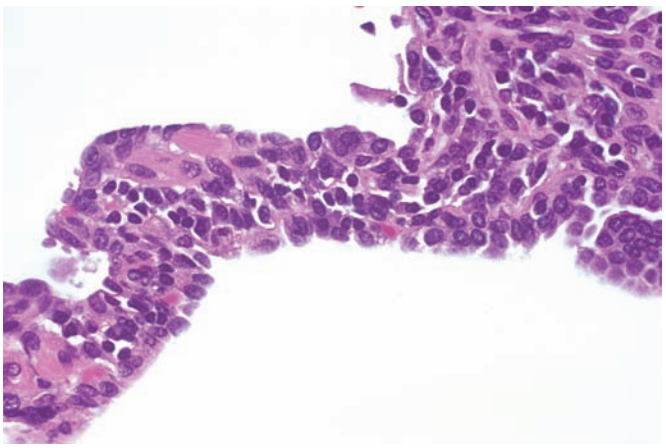

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Figure 120-7 Lymphocytic interstitial pneumonia. **A.** Diffuse alveolar septal expansion with lymphocytes is usually a manifestation of underlying disease. Hematoxylin and eosin, 50× original magnification. **B.** Benign lymphocytes and plasma cells interfere with gas exchange. The morphologic differential diagnosis includes pneumocystis infection. Hematoxylin and eosin, 60× original magnification.

of such most likely represented malignant lymphomas from the start.[64]

In patients with HIV infections or AIDS, LIP is part of a spectrum of lymphoid proliferations with virtually identical morphologies, but differing clinical presentations. Individuals with so-called *diffuse infiltrative lymphocytosis syndrome* (DILS) featuring sicca syndrome with increased numbers of circulating CD8+ T-cells in the blood, generalized lymphadenopathy, and enlarged parotid glands, are at high risk of developing LIP.[65]

LIP is most common is HIV-positive children and is a CDC category B indicator condition in children younger than age 13.[66,67] In fact, up to 17% of HIV-positive children have LIP.[68] Most present in their second or third year with lung infiltrates, failure to thrive, and increasing respiratory distress. The chest radiograph shows a diffuse micronodular or linear interstitial pattern with hilar and mediastinal widening.[69] Therapy is uncertain, response to steroids is unpredictable, and mean survival is 33 months.[70]

In HIV-positive adults, LIP is quite rare, and tissue sampling is required for diagnosis.[57] Most patients present with generalized lymphadenopathy and polyclonal hypergammaglobulinemia. BAL samples feature lymphocytes with CD8+ cells comprising up to 90% of the lymphoid cells.[71] Histologically, the lymphoid infiltrates are predominantly T-cells with few plasma cells. Germinal center formation is not a frequent finding. HIV-positive adults with LIP rarely die of the process, but rather of other AIDS-related diseases.

Castleman Disease

CD, the eponymous term for angiofollicular lymph node hyperplasia, encompasses two clinically and pathologically distinct entities. Solitary lesions usually feature hyaline-vascular (HV-CD) morphology, whereas multicentric disease almost always has a plasma cell pattern (PC-CD).[72]

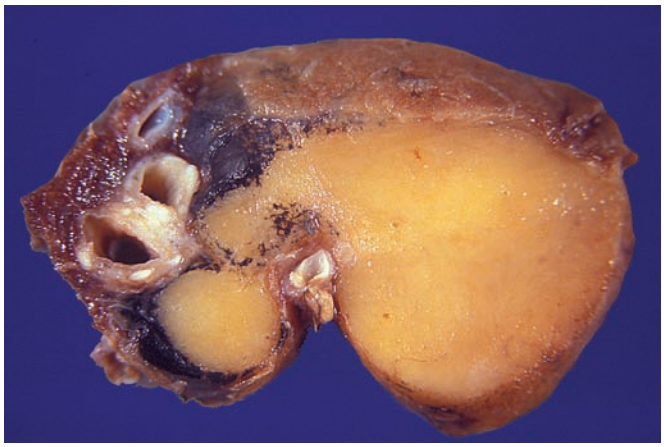
Solitary CD is an uncommon form of lymphoid hyperplasia that usually presents as an incidental mediastinal mass in asymptomatic young to middle-aged individuals of either gender.[73] Pleural, chest wall, and extrathoracic involvement have been reported, but pulmonary parenchymal disease is a true rarity and most reported cases likely represent nodal rather than true pulmonary disease (Fig. 120-8A).[73–78] Solitary HV-CD lesions are usually asymptomatic or rarely cause compression-related symptoms.

Ninety percent of solitary CDs feature hyaline-vascular morphology, whereas the remainder are the plasma cell variant. HV-CD lymph nodes are enlarged and feature prominent lymphoid follicles with small atrophic germinal centers penetrated by hyalinized venules with plump endothelial cells originating in the interfollicular zone (Fig. 120-8B). Expanded mantle zones have concentric rings of lymphocytes imparting an onionskin appearance. TdT+ T-lymphoblastic populations are increased in this entity.[79] The solitary plasma cell variant only involves lymph nodes and has not been reported in the lung. Lymph nodes are hyperplastic with enlarged germinal centers and sheets of interfollicular plasma cells. Clinical suspicion of malignancy typically prompts surgical resection of solitary lesions. Excision results in the disappearance of any symptoms.[80] Neoadjuvant anti-CD20 monoclonal antibodies can shrink lesions prior to surgery.[81]

Multicentric Castleman disease (MCCD) is best considered a virus-driven polyclonal lymphoproliferative process that shares virtually no features with solitary CD.[72,82,83] In general, MCCD presents in the fourth and fifth decades of life but earlier in HIV-positive individuals.[82,84,85] An increased incidence is noted in the highly active antiretroviral therapy (HAART) era.[86] Signs and symptoms include fever, sweating, malaise, anemia, lymphadenopathy, hepatosplenomegaly, ascites, and pleural and pericardial effusions. MCCD appears to be a consequence of infection with human herpesvirus 8 (HHV-8), which in turn promotes production of interleukin-6 (IL-6).[72] Laboratory abnormalities include an elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and bone marrow plasmacytosis that may lead to pancytopenia.[87] A chronic demyelinating polyneuropathy may present as part of POEMS syndrome (Crow–Fukase disease).[88] Patients may also develop non-HL. HIV-positive patients with MCCD have a greater likelihood of pulmonary involvement.[89]

Pulmonary histomorphology correlates with HRCT scan findings of peribronchovascular interstitial thickening and centrilobular nodules (Fig. 120-9A).[90,91] Polyclonal peribronchiolar lymphoplasmacytic infiltrates with focal extension into interlobular and alveolar septa may rarely be associated with honeycomb change (Fig. 120-9B). HHV-8 can almost always be demonstrated in lung samples, including BAL, by PCR and in situ hybridization with an HHV-8 probe.[92] Although MCCD shares many features with LIP, the plasma cell–rich nature of the infiltrate and presence of HHV-8 discriminate between the two.

Treatment is primarily nonsurgical but survival beyond 5 years is rare.[87] Although splenectomy may provide brief relief,



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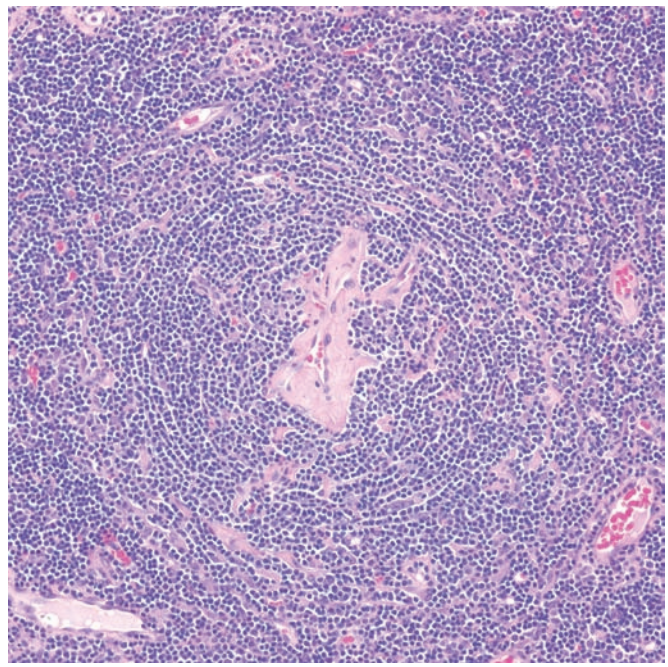

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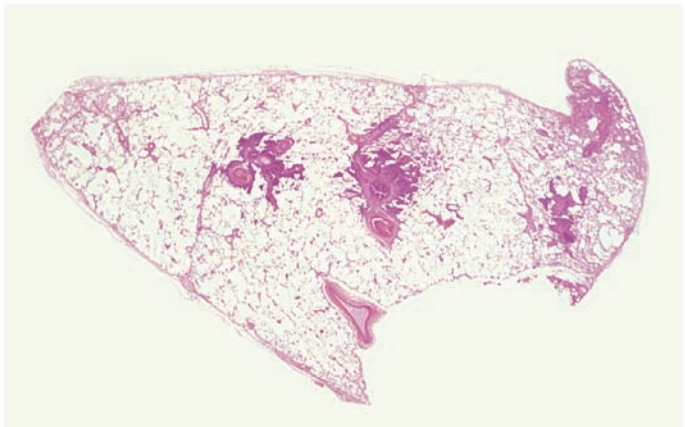
Figure 120-8 Solitary Castleman disease. **A.** Involved peribronchial lymph nodes are often mistaken for pulmonary parenchymal disease. Airway and vessel distortion may cause symptoms. **B.** Solitary lymph nodes and rare lung lesions feature hyaline-vascular morphology. Small germinal centers are penetrated by hyalinized venules. The follicle mantle zone rings the burnt-out center in an onionskin pattern. Hematoxylin and eosin, 20× original magnification.

chemotherapeutic regimens with or without immunotherapy, including anti–IL-6 and anti-CD20 monoclonal antibodies, appear to induce the longest remissions.[74,84,93] An 85% 1-year survival rate is now reported.[93]

Immunoglobulin G4–related Lung Disease

IgG4-related disease is a recently recognized fibroinflammatory condition with diverse organ manifestations linked by a unique histologic appearance.[94] As such, IgG4-related disease mirrors sarcoidosis. Despite a highly variable clinical presentation, the common histologic appearance, elevated serum, and tissue IgG4 levels along with a clinical response to immunosuppression warrant the creation of the broad yet poorly understood entity.[95] While most of the initial observations were made in individuals with autoimmune pancreatitis and/or lacrimal and salivary gland disease, the process is now recognized in almost every organ system.[96–98] General and organ-specific diagnostic criteria have been developed.[95,99] IgG4-related pulmonary disease likely accounts for many fibroinflammatory conditions of unknown etiology including but not limited to inflammatory pseudotumor, interstitial pneumonia, and fibrosing (sclerosing) mediastinitis.[26,100] Some patients with autoimmune idiopathic pancreatitis also have lung manifestations.[101]

Most patients with lung disease are males in their seventh decade of life.[102] One half of patients have respiratory symptoms



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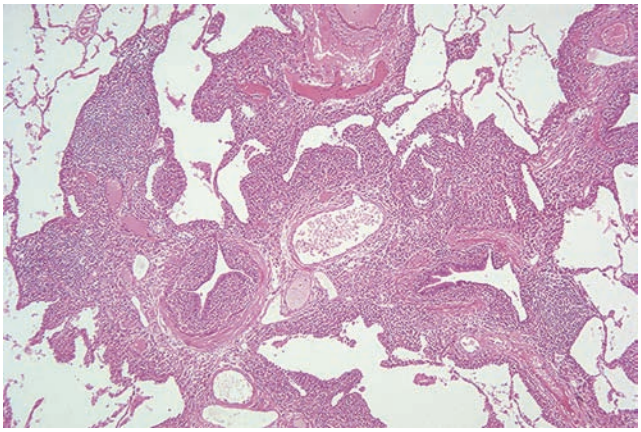

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Figure 120-9 Multicentric Castleman disease. **A.** The broncho-centric nature of this KSHV/HHV8-driven systemic process is apparent at scanning microscopy. Hematoxylin and eosin, 1× original magnification. **B.** The lymphoplasmacytic infiltrate is confined to the pulmonary interstitium. Honeycomb change may develop. Hematoxylin and eosin, 10× original magnification. *(Glass slides used with permission of Dr. J. English, University of British Columbia and Vancouver Hospital, Vancouver, BC.)*

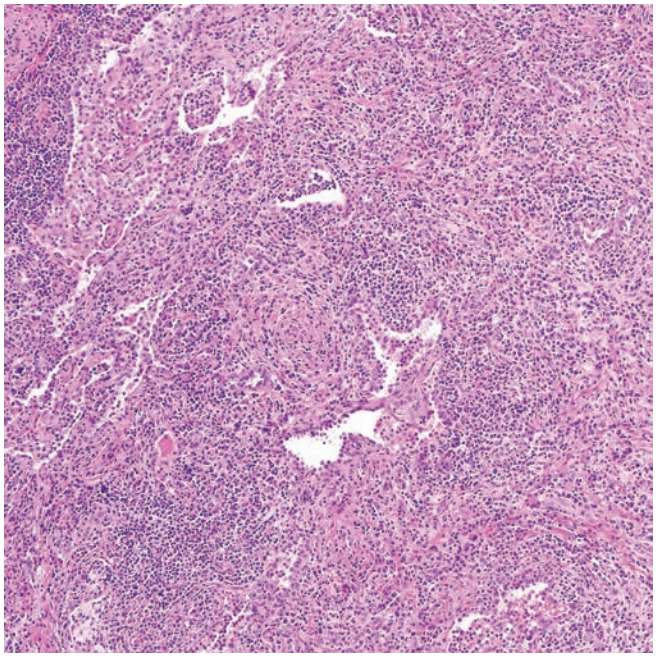


Figure 120-10 Immunoglobulin G4–related lung disease. Pulmonary parenchyma is practically overrun with lymphoplasmacytic infiltrates and developing fibrosis. Residual airspaces contain histiocytes. Hematoxylin and eosin, 10× original magnification. *(Used with permission of Dr. W. Travis, Memorial Sloan Kettering Cancer Center, New York, NY.)*

such as cough, exertional dyspnea, hemoptysis, and/or chest pain. Constitutional symptoms are uncommon.[103] No risk factors are recognized. Radiographic appearances vary and correlate with histomorphologic findings.[104] Solid nodules, bronchovascular, alveolar interstitial, pleural, and airway patterns may be seen, alone or in various combinations.[102] The three major histopathologic features are (1) dense lymphoplasmacytic infiltrate, (2) fibrosis, arranged at least focally in a storiform pattern, and (3) obliterative phlebitis (Fig. 120-10).[95] IgG4-related pulmonary disease may lack distinct storiform fibrosis while pulmonary arteries, in addition to veins, may be involved.[105] Furthermore, vascular changes without vessel lumen obliteration, concentric bronchiolar inflammatory infiltration with germinal centers, and/or prominent eosinophils may be seen.[106] Not surprisingly, histomorphologic findings can be considered highly suggestive, probable, or insufficient.[95] Unfortunately, the major findings are also seen in a myriad of entities, including but not limited to infections and organizing injuries related to, for example, granulomatosis with polyangiitis (Wegener granulomatosis).[107]

Tissue and serum IgG4 and IgG levels serve as supplemental data since a diagnosis is based on light microscopic findings. Immunohistochemical stain evaluation requires that one count the three 40x microscopic fields with the highest number of IgG4+ plasma cells and also count the number of IgG+ plasma cells in those same areas. According to the consensus statement, >50 IgG4+ cells per high-power field and >20 IgG4+ cells per high-power field are adequate cutoffs in surgical and nonsurgical lung biopsies, respectively.[95] The IgG4+/IgG+ plasma cell ratio should be >40%. However, other lung processes including idiopathic NSIP, usual interstitial pneumonia, connective tissue disease-associated interstitial pneumonias as well as inflammatory myofibroblastic tumor may have increased IgG4+ cell counts.[108] Elevated serum IgG4 levels are noted in most patients, although other respiratory, hepatobiliary tract, and connective tissue diseases may be associated with high serum levels.[103,109]

Standard therapy is not well delineated but most patients respond to glucocorticoids within weeks to months.[110,111] Resistant cases may improve with anti-CD20 monoclonal antibody therapy.[112] Relapses are common after therapy cessation. An increased risk for non-HL is postulated.[113]

MALIGNANT LYMPHOID LESIONS

Within the hematopathology field, past decades will probably be best remembered for the myriad of classification schemes and ever-changing nomenclature. Thankfully, the current WHO classification represents a consensus list of lymphoid neoplasms that appear to be distinct clinical entities.[1] Although complex, this scheme is reproducible among trained pathologists. Diagnoses are based on clinical, morphologic, immunophenotypic, and genetic features and not simply on morphologic, immunophenotypic, or even clinical subtleties. B-cell neoplasms, T- and NK-cell neoplasms, and HL are subgrouped according to lineage and stage of differentiation. Within this general context one can understand the practicality of a seemingly cumbersome diagnosis, such as pulmonary extranodal marginal zone B-cell lymphoma of MALT type, given the belief that these lymphomas arise from acquired BALT.

PRIMARY PULMONARY NON-HODGKIN LYMPHOMA

Although more than half of patients with nodal lymphoma have lung involvement, primary pulmonary lymphomas comprise less than 0.5% of primary lung neoplasms.[114,115] Furthermore, the most common primary lung lymphoma, marginal zone non-HL of MALT origin, represents less than 10% of extranodal lymphomas.[116] Non-HLs are considered lung primaries when the lung is the major site of disease at the time of diagnosis.[117,118] Thus, up to 20% of these lung lymphomas involve hilar and/or mediastinal lymph nodes. Pulmonary lymphomas have a range of morphologies and clinical aggressiveness such that separating the tumors into low- and high-grade categories is a dangerous oversimplification. Although most lung non-HLs differ from nodal lymphomas and are thought to have their origin in BALT, traditional nodal non-HLs, such as follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and CD30+ anaplastic large cell lymphoma, also present as pulmonary primaries (Table 120-2).[19,119–122]

EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE

Recent recognition that most primary pulmonary lymphomas arise from BALT revolutionized our thinking about extranodal lymphoid lesions. This hypothesis suggests that some degree of lymphoid hyperplasia is a necessary precondition for the development of these lymphomas and explains the association with inflammatory and autoimmune processes as well as the common finding of reactive germinal centers in lymphomas of BALT. These relatively indolent lymphomas must be discerned from both reactive processes, including NLH and LIP as well as more aggressive lymphomas.

Patients tend to be in their fifth through seventh decades of life with a slight male preponderance.[23,123] Those younger, including children, almost always have pre-existing immunosuppression such as HIV infection.[19] Most individuals are asymptomatic and are noted to have an abnormality on a routine chest radiograph. The presence of dyspnea, cough, hemoptysis, and shortness of breath reflect extensive disease causing airway constriction, poor compliance, and atelectasis. "B" symptoms are rare.[119] Mean lymphocyte counts are typically normal and peripheral blood does not show a leukemic phase, whereas a monoclonal gammopathy, usually IgM, is noted in up to 30% of patients.[124]

Chest radiographs and HRCT scans show either peripheral or perihilar solitary or multiple masses or alveolar opacities with air bronchograms.[125,126] Cavitation, calcification, and pleural effusions are very rare, and hilar adenopathy is present in less than 25% of

TABLE 120-2 Lymphoid Neoplasms Commonly Involving the Lungs

B-cell neoplasms
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Plasma cell myeloma
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Intravascular large B-cell lymphoma
Burkitt lymphoma/leukemia
B-cell proliferations of uncertain malignant potential
Lymphomatoid granulomatosis
Posttransplant lymphoproliferative disorder
T-cell and NK-cell neoplasms
Mature T-cell and NK-cell neoplasms
Mycosis fungoides
Sézary syndrome
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma
Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma

cases.[24] The interval between the finding of a radiologic abnormality and definitive pathologic diagnosis averages over 5 years, reflecting the tendency of this tumor to remain localized for a long period.[23,123] Thus, it is not surprising that up to 80% of individuals present with stage I disease.[19,117,118,120]

Grossly, nodular areas vary from 2.0 to 20 cm and are tan and fleshy. Underlying lung architecture may be preserved (Fig. 120-11A). At low magnification these lymphomas appear as diffuse infiltrates surrounding reactive follicles with peripheral tracking along bronchovascular bundles and interlobular septa (Fig. 120-11B,C). Invasion of bronchial cartilage and visceral pleura are common. At high magnification, the small lymphoid cells may have round nuclei with little cytoplasm (centrocyte-like) or irregular nuclear contours and abundant clear cytoplasm (monocytoid differentiation) (Fig. 120-11D). Plasmacytic differentiation is also common. Scattered larger cells (immunoblasts) can also be seen. Malignant cells often infiltrate reactive germinal centers (follicular colonization) as well as bronchial, bronchiolar, and alveolar epithelium (lymphoepithelial lesions). This latter finding is seen in up to 90% of cases, but is not a useful diagnostic criterion.[122,124] Secondary features include fibrosis, sclerosis, and amyloid and sarcoidal granulomas.[37,38] Involved mediastinal lymph nodes feature typical morphology of nodal marginal zone B-cell non-HL.

When light microscopic features favor a diagnosis of this lymphoma, all available ancillary studies should be utilized to make a definitive diagnosis. The neoplastic cells are monoclonal B-cells, which may be identified with CD20 or CD79a stains.[122,123] Light chain restriction is present in all cases with equal κ and λ percentages; however, PCR amplification of the immunoglobulin heavy chain gene from paraffin sections detects monoclonality in only 60% of tumors.[127] Fifty percent to 60% of marginal zone B-cell lymphoma of MALT type demonstrate t(11;18), whereas t(1;14) or trisomy 3 may also occur.[128–130]

The differential diagnosis includes NLH, LIP as well as pulmonary involvement with a variety of different malignant lymphomas, such as lymphoplasmacytoid lymphoma/immunocytoma. These distinctions are of paramount importance and the surgical pathologist or hematopathologist has the necessary tools to make a correct diagnosis.

Pulmonary marginal zone B-cell lymphomas of MALT are indolent tumors with 85% to 95% 5- and 10-year survival rates.[23,117,118,123,131] In several studies, median survival was not reached at 10 years. Thus, patients with resectable disease are treated with resection, but those with diffuse lung involvement may be followed and treated with chemotherapy with or without anti-CD20 antibodies.[119,131] Patients with systemic symptoms at presentation may have a worse prognosis. Lymphoma recurs in the lungs or in other MALT sites such as salivary gland, orbital, or gastrointestinal tract in almost half of patients, and up to 15% of patients experience transformation of their lymphomas into more aggressive and usually deadly forms including diffuse large B-cell non-Hodgkin lymphoma (DLBCL).[23,124]

■ OTHER NON-HODGKIN LYMPHOMAS

Non-HLs other than extranodal marginal zone B-cell lymphomas originating in the lung are very rare and comprise less than one-fourth of primary lung lymphomas.[23,120,122,124,132] These tumors represent a heterogeneous group consisting primarily of DLBCL with fewer cases of follicular lymphoma, and rare examples of mantle cell lymphoma, lymphoplasmacytic lymphoma/immunocytoma, Burkitt lymphoma, anaplastic large cell lymphoma, and peripheral T-cell lymphomas.[132–136] Rare AIDS-related primary pulmonary B- and T-cell lymphomas containing EBV RNA are also described.[137,138] Of note, only primary pulmonary DLBCL appears to arise from BALT and is also weakly associated with both fibrosing interstitial lung diseases and connective tissue diseases.[120,123]

Although each lymphoma subtype has particular morphologic features, primary pulmonary DLBCL is best characterized clinically.[120,122–124] Patients are usually adults but younger individuals with immunodeficiency states may be affected.[114,119,124] Unlike those with extranodal marginal zone B-cell lymphomas of MALT, most patients present with shortness of breath, fever, chest pain, and hemoptysis and frequently develop extrapulmonary lesions and paraneoplastic syndromes shortly after diagnosis. Restrictive physiology is often observed. Imaging studies reveal solitary or multifocal nodules or infiltrates measuring at least 3.0 cm.[123] Cavitation and pleural effusions are frequently seen and regional lymph nodes are involved in up to 50% of cases.

Resected lesions are white-tan and fleshy with areas of necrosis. Histologically, largely necrotic nodules or striking lymphangitic growth with parenchymal destruction are accompanied by inflammatory infiltrates. Infarction is not uncommon. Sheets of malignant mitotically active B-cells are two to four times the size of normal lymphocytes (Fig. 120-12). Vascular infiltration and pleural involvement are common features and airway destruction leads to postobstructive pneumonia. Residual BALT hyperplasia and low-grade marginal zone lymphoma may be seen at the periphery of the mass. Neoplastic cells express pan-B antigens CD20 and CD79a. Monotypic immunoglobulin light chain expression can be demonstrated.[139] Although the cytologic atypia and necrosis in these lymphomas make it easy to distinguish them from benign lymphoid

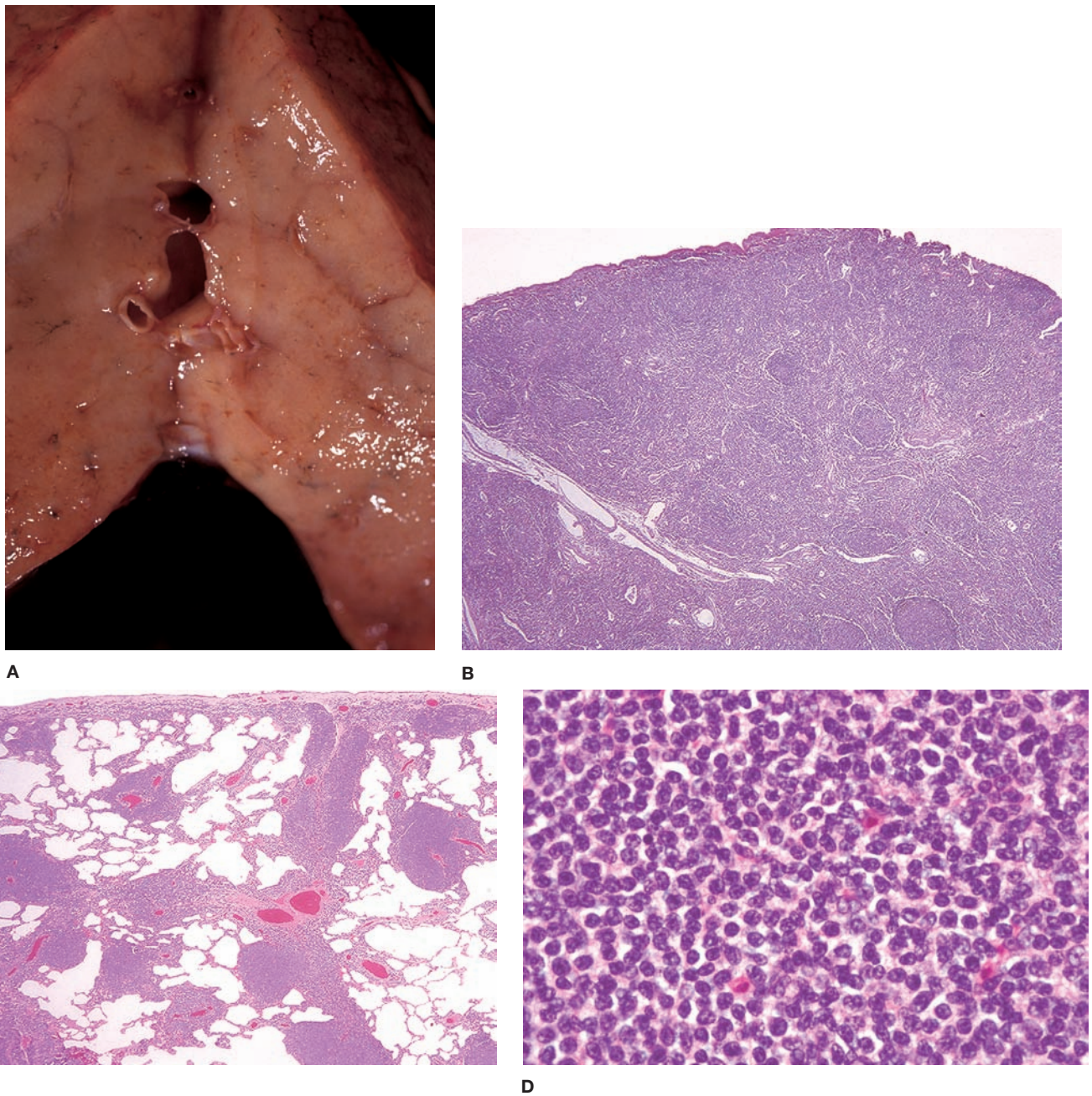


Figure 120-11 Extranodal marginal zone B-cell lymphoma of MALT type. **A**. Tan fleshy tumor fills alveolar spaces but preserves lobular architecture. **B.** Malignant lymphoid cells overrun lung tissue. Germinal centers are usually prominent. Hematoxylin and eosin, 4× original magnification. **C.** Malignant lymphoma often tracks along lymphatic pathways beyond the dominant mass lesion. If such a region was sampled the differential diagnosis would include diffuse lymphoid hyperplasia. Involvement of visceral pleura suggests the malignant nature of the process. Hematoxylin and eosin, 4× original magnification. **D.** Most pulmonary marginal zone B-cell lymphomas of MALT type are composed of small monotonous round (centrocyte-like) B-lymphocytes. Hematoxylin and eosin, 40× original magnification.

processes and extranodal marginal zone lymphomas, confusion with poorly differentiated carcinomas or HL can occur.

Localized DLBCL is potentially curable with surgery and adriamycin-based chemotherapy, but 5-year survival rates do not surpass 60% and the median survival is only 3 years.[19,114,119] Only half of HIV-positive patients achieve clinical remission and those remissions usually last only 6 months.

■ LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis (LYG) is one of the most confusing lesions in all of human disease. The original investigators were not certain whether this lung-based process, which also involves the central nervous system, skin, and other organs, was a malignant lymphoma or a variant of granulomatosis with polyangiitis (Wegener granulomatosis).[140] Since that time erroneous ideas concerning its etiology and histogenesis have muddled the entity even further. We now recognize LYG as an EBV-driven B-cell lymphoproliferative disorder arising in individuals with either obvious or clinically undetected defects in cell-mediated and perhaps also humoral immunity.[1,141–144] In many ways, LYG is similar to post-transplant lymphoproliferative disorder (PTLD) with a spectrum of clinical behaviors.

Although quite rare, LYG has characteristic clinical features.[145,146] Patients usually present in the fifth or sixth decades of life but

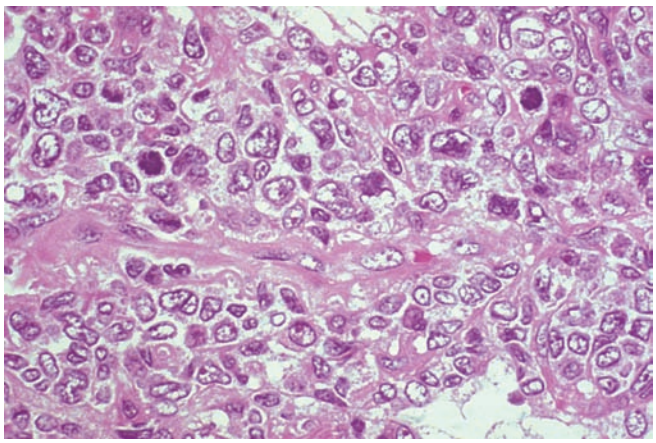


Figure 120-12 Diffuse large B-cell lymphoma. This lymphoma is composed of large cells with irregular nuclear features and significant mitotic activity. The B-cell phenotype is demonstrated by flow cytometry or immunohistochemistry. This lymphoma not only looks more aggressive than marginal zone B-cell lymphoma of MALT type, but also follows an aggressive clinical course. Hematoxylin and eosin, 40× original magnification.

children and the elderly can be stricken. Men are affected two to three times as often as women. Dyspnea, cough, chest pain along with fever, and malaise and weight loss are the most common presenting complaints and up to 40% of patients also have skin nodules, ulcers, rashes, peripheral neuropathies, or symptoms referable to central nervous system involvement. Gastrointestinal, musculoskeletal, or nodal involvement is uncommon. Presentation as an asymptomatic solitary lung nodule is very rare.

Laboratory findings can include either leukocytosis or leukopenia and elevated serum IgG or IgM.[145] Cerebrospinal fluid may have abnormal protein and glucose levels. Serologies for autoimmune diseases are negative but evidence of EBV infection has been reported.

Chest imaging in up to 70% of patients reveals bilateral middle and lower zone lung nodules as large as 10 cm.[140,145,147] Coalescence and cavitation are often seen. Nonspecific reticulonodular infiltrates as well as solitary infiltrates or masses are less common findings. Pleural effusion is present in up to one-third of patients.

Macroscopically the lungs and other affected organs contain yellow-white well-demarcated masses with either solid or granular textures (Fig. 120-13A). Microscopically LYG is composed of nodular lymphoid infiltrates centered on lymphatic routes including bronchovascular bundles. As the lesions increase in size, blood vessels are encircled, infiltrated, and perhaps occluded but not obliterated by the process (Fig. 120-13B). The infiltrate and nodules are composed of a heterogeneous population of small, intermediate, and large lymphocytes (Fig. 120-13C). The large cells are in the minority but can be very atypical or pleomorphic, stain as B-cells (CD20+ and CD79a+) and are EBV-infected according to PCR and in situ hybridization studies. CD30 positivity is also noted in infected monoclonal cells. The smaller and more numerous cells stain as T-cells (CD3+, CD4+, and/or CD8+). Secondary features include interstitial and consolidative pneumonia. Despite its designation, granulomas are not seen.

The grading system for LYG is based on the number of atypical large EBV-infected cells (Table 120-3). Grade 1 lesions probably include cases of so-called *benign lymphocytic angiitis* and *granulomatosis,* whereas grade 3 proliferations are alternatively considered a subtype of diffuse large cell lymphoma (DLCL). With greater relative numbers of EBV-infected cells, one observes more necrosis and a more aggressive clinical course.[1] Given the complex histologic features of LYG and need to identify scattered large cells in an inflammatory mass, diagnosis and accurate grading almost always requires a surgical lung biopsy.

Although similar to T-cell–rich B-cell lymphomas such as angiocentric nasal NK/T-cell lymphoma and PTLD, the former entity lacks EBV-infected monoclonal B-cells and the latter lacks the angiocentricity of LYG. Other diagnostic considerations include HL and necrotizing inflammatory conditions.

The natural history is variable and clinical behavior ranges from indolent to aggressive.[148] Spontaneous remissions and therapy-induced remissions occur but more than 60% of patients die, with a median survival of 14 months.[145] Although most organ systems can be involved, lymphoid tissue including the spleen is only involved in 25% of patients who develop grade 3 lesions. Hemophagocytic syndrome is related to systemic EBV infection rather than bone marrow involvement. Histologic grade correlates with outcome. Most patients have either grade 1 or 2 disease; one-third of those with grade 1 lesions progress to grade 3/malignant lymphoma, whereas two-third of those with grade 2 lesions develop grade 3/malignant lymphoma. Asymptomatic patients or those with minimal disease and grade 1 or 2 histology may be observed; those with symptomatic grade 1 or 2 histology require treatment with corticosteroids or single or multiagent chemotherapy. Clinically aggressive grade 1 and 2 and all grade 3 lesions are treated as DLCL with combination chemotherapy.[148] Therapies targeting EBV-bearing B-cells (interferon-α2β) or reactive T-cells (i.e., cyclosporine) as well as stem cell transplantation, have been reported.[148,149]

■ INTRAVASCULAR LARGE B-CELL LYMPHOMA

Intravascular large B-cell lymphoma (IVLBCL) is a rare non-HL characterized by lymphoma cells only in the lumina of small vessels, particularly capillaries.[1,150] A Western variant manifests with symptoms related to the involved organ, while an Asian variant presents with multiorgan failure, hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome.[151,152] Although patients with the Western variant most often present with neurologic or dermatologic manifestations, older patients may complain of fever, dyspnea, cough, chest pain, or present with respiratory failure.[153–156] Hypoxia and decreased diffusion capacity are seen. Chest radiographs demonstrate reticulonodular infiltrates, whereas CT scans can show patchy ground-glass opacities.[153,154,157]

TABLE 120-3 Histologic and In Situ Hybridization Grading of Lymphomatoid Granulomatosis

Grade 1
Angiocentric polymorphous infiltrate without atypia or necrosis
Rare EBV-infected cells (<5 per high-power [40×] field)
Grade 2
Angiocentric, predominantly polymorphous, infiltrate with occasional large or atypical lymphoid cells and parenchymal necrosis
Scattered EBV-infected cells (5–20 per high-power [40×] field)
Grade 3
Angiocentric and destructive monomorphous infiltrate with widespread necrosis
Sheets of EBV-infected cells (>20 per high-power [40×] field)

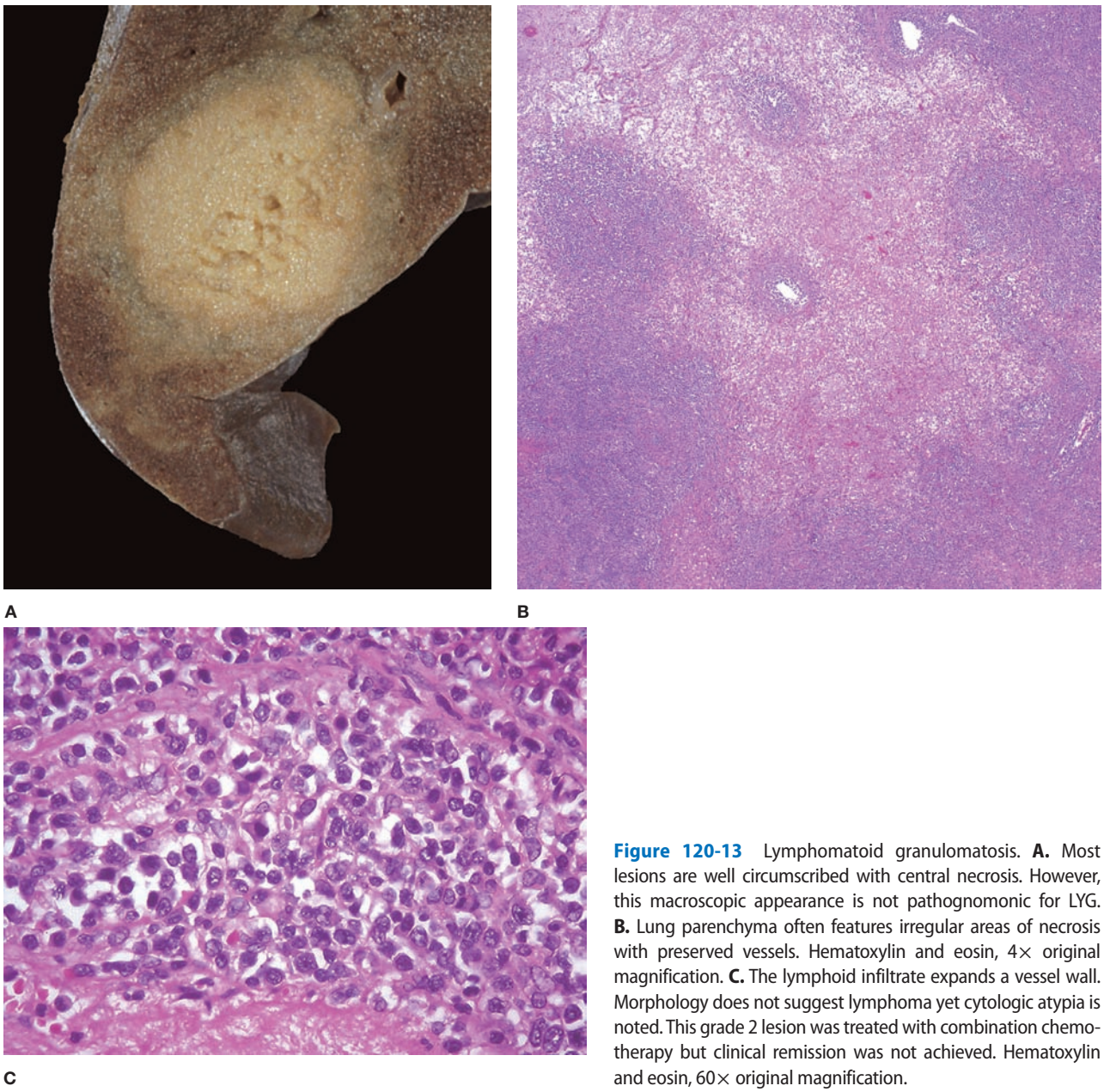


Figure 120-13 Lymphomatoid granulomatosis. **A.** Most lesions are well circumscribed with central necrosis. However, this macroscopic appearance is not pathognomonic for LYG. **B.** Lung parenchyma often features irregular areas of necrosis with preserved vessels. Hematoxylin and eosin, 4× original magnification. **C.** The lymphoid infiltrate expands a vessel wall. Morphology does not suggest lymphoma yet cytologic atypia is noted. This grade 2 lesion was treated with combination chemotherapy but clinical remission was not achieved. Hematoxylin and eosin, 60× original magnification.

Low magnification histology demonstrates a diffuse interstitial process resembling cellular interstitial pneumonia yet higher magnification reveals large cells with prominent nucleoli confined to arteries, veins, lymphatics, and especially capillaries (Fig. 120-14). Fibrin thrombi may be noted.

Although all cases of IVLBCL are B-cell lymphoma (CD19+, CD20+, CD79a+), a T-cell phenotype associated with EBV has been described and should be considered a different entity.[158–160] Although the intravascular nature of the lymphoma is not understood, absence of adhesion molecules CD54 (I-CAM-1) and CD29 (β_1 integrin) may prevent neoplastic cell–endothelial cell interactions and extravascular spread.[161]

Half of cases are diagnosed at autopsy yet a diagnosis is possible on thoracoscopic and even transbronchial biopsies.[155,162,163] Immunohistochemical stains are necessary to discern IVLBCL from metastatic carcinoma, malignant melanoma, and leukemia. Although prognosis is poor, complete remission and long-term survival can be

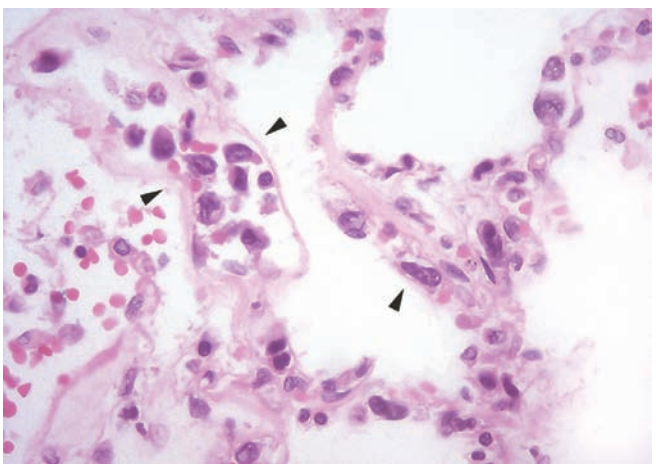


Figure 120-14 Intravascular large B-cell lymphoma. Malignant lymphoid cells remain confined to vascular channels *(arrowheads)*. Hematoxylin and eosin, 60× original magnification.

achieved with prompt diagnosis and aggressive combination chemotherapy and perhaps anti-CD20 monoclonal antibodies.[160,164]

HODGKIN LYMPHOMA

Primary pulmonary HL is very rare.[165] This is in part due to the requirement that, unlike non-HL, regional lymph nodes be free of disease to qualify as a lung primary.

Primary pulmonary HL shows the usual bimodal age distribution of systemic HL but patients are slightly older.[166–168] Women outnumber men by 1.5 to 1. Symptoms include cough, dyspnea, hemoptysis, and chest pain and one-third of patients experience B symptoms.[166] Radiographs demonstrate reticulonodular and linear infiltrates or multiple nodular lesions. Solitary lesions and consolidation are also seen. Upper lobe disease is most common, and atelectasis and cavitation are frequently observed.[169]

Tumors have a multinodular white firm macroscopic appearance and histologically grow along lymphatic routes in the lung. When small nodules coalesce, central necrosis is apparent. Visceral pleura is often infiltrated while bronchial involvement can result in plaque-like nodules, polypoid endobronchial masses, or airway collapse.[170,171] Within the WHO histologic classification of HL, one cannot be certain if nodular lymphocyte–predominant HL and the four subtypes of classical HL all involve the lung. Nodular sclerosis and mixed cellularity subtypes of HL are more commonly seen than lymphocyte rich, whereas lymphocyte depleted has not been reported in primary pulmonary HL.[166,167] Diagnosis requires the identification of Reed–Sternberg cells or variants (usually CD15+ or CD30+) within the appropriate inflammatory background. Central necrosis, granulomatous inflammation, and vascular permeation by the polymorphous infiltrate are commonly seen.

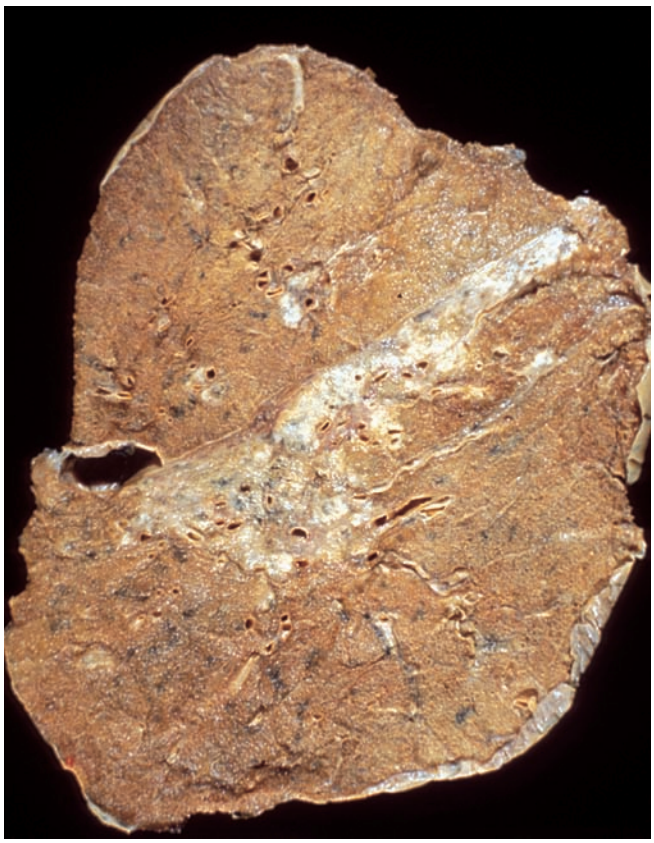
The morphologic differential diagnosis includes inflammatory and malignant processes. Infections, granulomatosis with polyangiitis (Wegener granulomatosis), and sarcoidosis as well as poorly differentiated carcinomas, LYG, and a variety of non-HLs must be considered. The nonneoplastic entities can be discerned histologically, whereas the neoplasms require at least immunohistochemical studies.

The prognosis for patients with primary pulmonary HL is variable.[168] Individuals with all types and stages of primary pulmonary HL have a 5-year survival of almost 75%.[166,167] Relapses occur in the lung and elsewhere and appear associated with multiple lobe involvement, pleural invasion, cavitation, and presence of B symptoms.

SECONDARY LYMPHOMA INVOLVING THE LUNG

Secondary lung involvement with nodal and extranodal lymphomas is significantly more common than primary pulmonary lymphoma. Lung involvement with common nodal and disseminated lymphomas surpasses 50% during life and at autopsy.[165,172–174] Clinical and radiologic features may suggest an infectious process, but tissue samples demonstrate a lymphangitic pattern of disease (Fig. 120-15A). Patchy infiltrates and endobronchial masses are, however, not uncommon.[175]

Morphology does not usually allow for distinction between primary and secondary lung disease. For example, pulmonary involvement with nodal marginal zone lymphoma is indistinguishable from primary pulmonary extranodal B-cell lymphoma of MALT. Thus, clinical history and review of previous diagnostic material are necessary for proper diagnosis. Secondary lymphomas involving the lung can also transform to more aggressive histology with increased numbers of large cells. This phenomenon is not infrequently seen in samples from patients with CLL/SLL.



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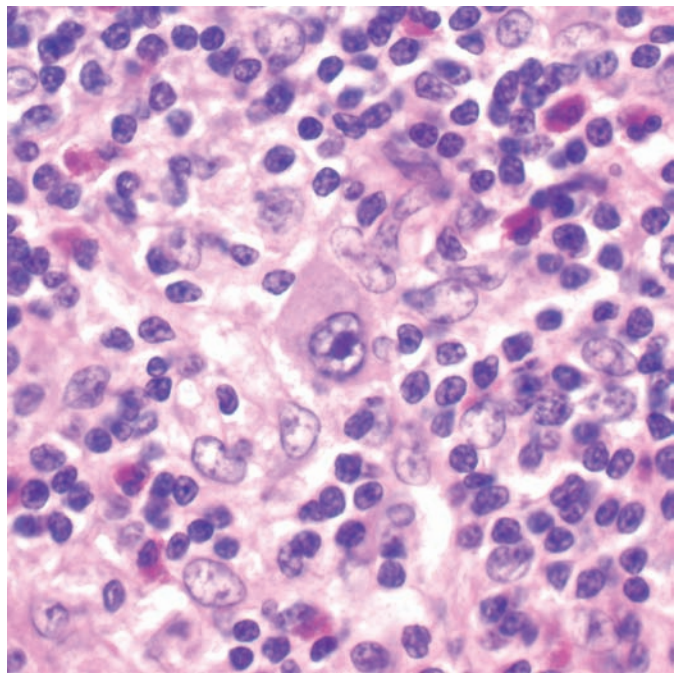


B

Figure 120-15 Lung involvement with Hodgkin lymphoma. **A.** The striking lymphangitic distribution of this dense white tumor indicates secondary pulmonary involvement. **B.** A uninucleate Reed–Sternberg cell with typical prominent nucleolus *(center)* is surrounded by lymphocytes and eosinophils. Hematoxylin and eosin, 60× original magnification.

Several particular systemic lymphoproliferative disorders that may present with significant lung pathology warrant additional discussion. Mycosis fungoides may involve the lung after dissemination of cutaneous disease or as part of the Sézary syndrome. Indeed, the lung is the second most common extracutaneous site after lymph nodes.[176,177] Clinical and radiographic features often mimic pneumonia or even acute respiratory distress syndrome with nodular and diffuse disease.[178] Tissue samples demonstrate air space and interstitial infiltrates along lymphatic routes in addition to occasional granulomas, extensive vascular infiltration, and necrosis. Cells range from small with irregular twisted nuclei to large with prominent nucleoli.

The lungs are also frequently involved with angioimmunoblastic T-cell lymphoma.[179] Although originally described as a reactive process (angioimmunoblastic lymphadenopathy with dysproteinemia), this malignant disease in the lung can be mistaken for interstitial pneumonia.[180–182] However, the lymphatic distribution of atypical "clear" cells with indented nuclei admixed with immunoblasts, plasma cells, and histiocytes is neoplastic and must be distinguished from HL. Pulmonary involvement with HL is recognized at presentation in more than 10% of patients with mediastinal or extrathoracic disease. Fifty percent of patients with HL have relapses in the lung and almost 60% are noted to have pulmonary involvement at autopsy.[165,183] Unlike primary pulmonary HL, secondary involvement rarely manifests with large nodules, whereas infiltrates often surround blood vessels and may feature greater numbers of atypical cells and fewer inflammatory cells than in primary HL (Fig. 120-15B).[184]

■ PLASMACYTOMA/MULTIPLE MYELOMA

Extraosseous plasmacytomas most often affect the upper respiratory tract. Primary plasmacytomas of the lung are exceedingly rare; patients are usually in their fifth and sixth decades of life and asymptomatic.[44,185,186] Cough, dyspnea, and hemoptysis have been reported. Unlike multiple myeloma, individuals may lack a serum M-protein or Bence Jones light chains in the urine. Radiographs most commonly demonstrate a midlung or hilar solitary mass, but peripheral lesions amenable to transthoracic-needle aspiration biopsy occur.[187–189]

Tumors range from 2.5 to 8.0 cm and most often involve a major bronchus with occasional involvement of regional lymph nodes. Histologically, sheets of plasma cells including binucleate forms overrun lung parenchyma and bronchial cartilage (Fig. 120-16). Fibrous bands course through the tumor and amyloid or light chain may be associated with the neoplasm. κ and λ light chains as well as IgG, IgA, and IgD can be expressed immunohistochemically or produced as M-proteins by the tumor.[185,190,191] The pathologist must discriminate between plasmacytoma and marginal zone lymphoma with plasmacytoid features as well as inflammatory myofibroblastic tumor.

Although the natural history of this rare tumor is not well delineated, it appears that cases are either cured with either surgical excision or radiation therapy, or evolve into multiple myeloma.[185,192,193] The presence or absence and amount of M-protein may mirror tumor burden and clinical course while an increase or decrease in levels may be associated with recurrence or successful treatment, respectively. An overall 5-year survival of 40% has been reported.[185,194]

Pulmonary involvement with multiple myeloma is more common than pulmonary plasmacytoma.[40,195,196] Lung involvement may be nodular or have a diffuse lymphangitic pattern.[197] Nodular or diffuse amyloid deposition may accompany the neoplastic cells. Intracytoplasmic crystalline casts similar to those seen in the kidney are occasionally observed.[198]

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Posttransplant lymphoproliferative disorder (PTLD) is a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in solid organ or bone marrow allograft recipients. Eighty percent of cases are associated with EBV infection in the setting of decreased T-cell immune surveillance; the etiology of EBV-negative PTLD is unknown.[1,184] Most cases are of host origin while approximately 10% of cases are of donor origin.[1] Those of donor origin are more common in lung and heart–lung transplantation patients due to the presence of donor BALT in the lungs.[199–203]

Allograft and extranodal MALT sites including Waldeyer ring, lung, and gastrointestinal tract, are usually involved and incidence varies based on type of allograft and immunosuppression regimen. One percent of renal transplant patients but up to 10% of lung transplant recipients are stricken.[202]

The majority of cases of PTLD in lung transplant recipients and approximately 10% of cases in other solid organ transplant recipients manifest with pulmonary lesions. Individuals may be asymptomatic or present with constitutional symptoms. In lung transplant patients, respiratory failure may occasionally occur. Radiographs demonstrate nodular or diffuse reticulonodular infiltrates, solitary nodules, or multiple mass lesions with or without regional lymphadenopathy.[204]

Morphologic categories of PTLD include early lesions, polymorphic PTLD, monomorphic PTLD, HL, and HL-like PTLD (Table 120-4).

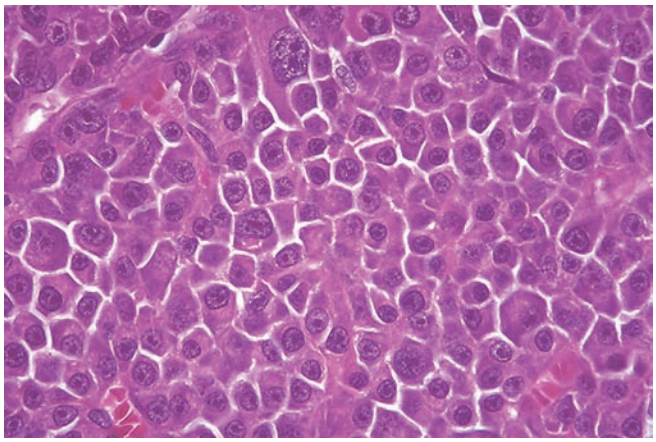
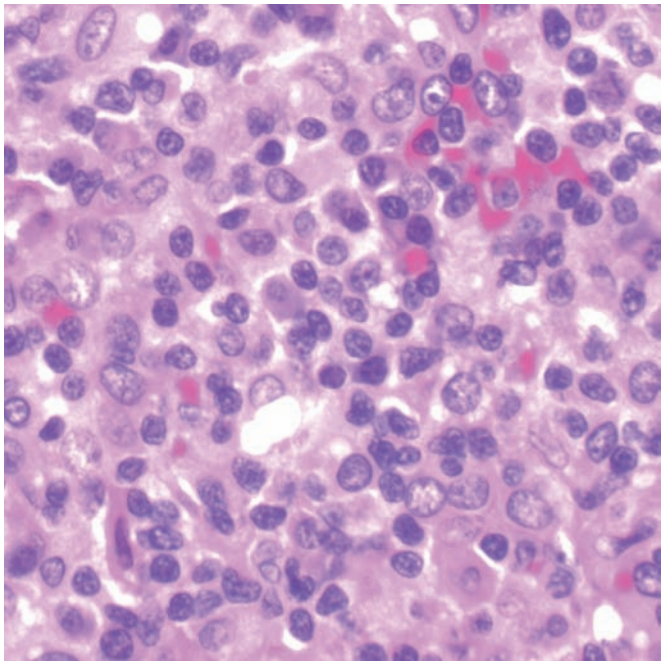


Figure 120-16 Plasmacytoma of lung. Sheets of plasma cells usually form a solitary nodule. Cytologic atypia is often seen. Since this lesion is less common than pulmonary involvement with multiple myeloma, clinical correlation is always required. Hematoxylin and eosin, 40× original magnification.

TABLE 120-4 Posttransplant Lymphoproliferative Disorders

Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
Polymorphic PTLD
Monomorphic PTLD
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt/Burkitt-like lymphoma
Plasma cell myeloma
Plasmacytoma-like lesions
T-cell neoplasms
Peripheral T-cell lymphoma, unspecified
Hodgkin lymphoma and Hodgkin lymphoma-like PTLD



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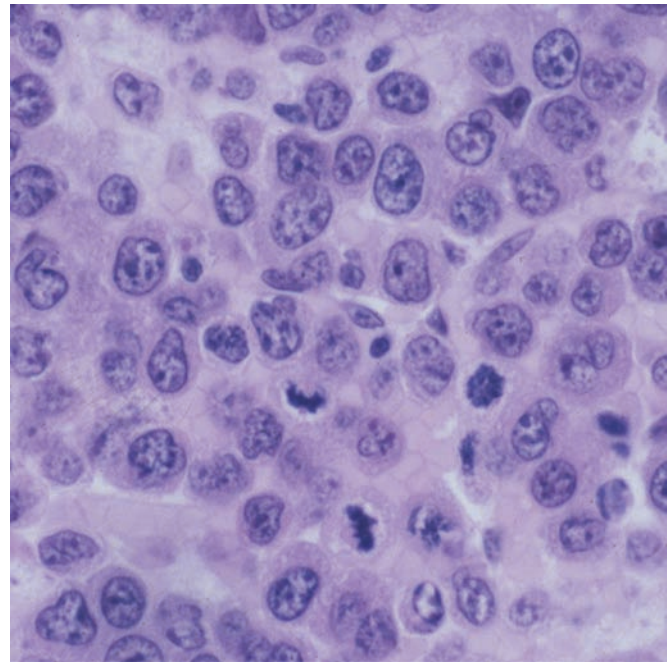

B

Figure 120-17 Posttransplant lymphoproliferative disorder. **A.** This polymorphic lesion features small and large lymphocytes admixed with plasma cells. Hematoxylin and eosin, 60× original magnification. **B.** Monomorphic lesions often comprise large atypical cells with numerous mitoses. According to the WHO scheme this lesion is classified as a diffuse large B-cell lymphoma. Hematoxylin and eosin, 60× original magnification.

Most proliferations are B-cell processes, although T-cell lesions are seen.[205] Early lesions usually involve lymph nodes and Waldeyer ring rather than lung; lymphoid tissue is hyperplastic with either sheets of plasma cells or paracortical expansion with immunoblasts that resemble infectious mononucleosis morphology. Polymorphic and polyclonal proliferations feature mixtures of small lymphocytes, plasma cells, and immunoblasts and may progress to monomorphic monoclonal proliferations with sheets of large transformed cells resembling aggressive lymphoma (Fig. 120-17A,B). In fact, the monomorphic monoclonal proliferations are subclassified according to lymphoma classification.[1] HL and HL-like PTLD are very rare and purportedly similar to methotrexate-related HL.[206] The morphologic findings may be difficult to differentiate from allograft rejection; immunophenotyping is essential, whereas molecular genetic testing for clonality and in situ hybridization studies for EBV may be necessary. For these reasons, tissue procurement rather than fine-needle aspiration biopsy is preferred for diagnosis.

Treatment often starts with reductions in immunosuppression, though this runs the risk of losing the allograft.[207] Early lesions usually regress while only a proportion of polymorphic and monomorphic PTLD respond.[208] Neither morphology nor molecular characterization of the PTLD can predict response to reduction in immunosuppression. Nonresponders, or those with bulky or multisystem disease are treated with anti-CD20 antibody therapy (rituximab).[209] Cytotoxic chemotherapy and perhaps radiation therapy are reserved for refractory cases and those who are CD20 negative. Early diagnosis with prompt reduction of immunosuppression and/or anti-CD20 antibody therapy has improved the prognosis of patients with PTLD.[210,211]

LEUKEMIC INFILTRATES INVOLVING THE LUNG

Secondary effects of leukemia or therapy including infections, alveolar proteinosis, leukemic cell lysis pneumopathy, hemorrhage, and chemotherapy toxicity afflict many leukemia patients but significant direct lung involvement with leukemia affects less than 10% of individuals.[212,213] Leukemic lung infiltration is often found at autopsy or as an "incidental" finding in a tissue sample demonstrating an infectious process, and only causes symptoms in those patients with high (40% or greater) blast counts.[214] Cough, dyspnea, and hemoptysis may precede the leukemia diagnosis for months or develop suddenly.[215] Bronchiolar involvement producing asthma-like symptoms has been reported. Radiographic findings run the gamut from localized to diffuse infiltrates.[216–218]

All leukemia subtypes can involve the lung but acute myeloid leukemia, acute lymphoblastic leukemia, and CLL/SLL are most often seen.[219] Infiltrates are predominantly restricted to the pulmonary lymphatic distribution and rarely form micronodules (Fig. 120-18). Bronchiolocentricity may be mistaken for bronchiolitis. Infiltrates can be subtle and chloroacetate esterase and myeloperoxidase stains may be useful in diagnosis and subtyping. Leukemic counts greater than 200,000/μm cause capillary leukostasis with resultant thrombosis. Pulmonary edema, infarct, and diffuse alveolar damage may result.

Patients with agnogenic myeloid metaplasia (myelofibrosis) occasionally have pulmonary manifestations.[220–223] Diffuse and nodular foci of extramedullary hematopoiesis usually follow lymphatic routes and associated fibrous tissue can form large nodules. Interstitial fibrosis often results and may be mistaken for a primary chronic fibrosing interstitial pneumonia.[224]

In addition to acute complications of leukemia, patients undergoing bone marrow transplantation for leukemia may experience a variety of pulmonary complications including pulmonary edema, diffuse alveolar damage/acute respiratory distress syndrome, bacterial, fungal, and viral infections and GVH disease.[214] Acute GVH rarely involves the lung but lymphocytic bronchiolitis, LIP, constrictive bronchiolitis, and pulmonary fibrosis are all considered within the spectrum of chronic pulmonary GVH. However, these manifestations may also represent cytotoxic chemotherapeutic effect.

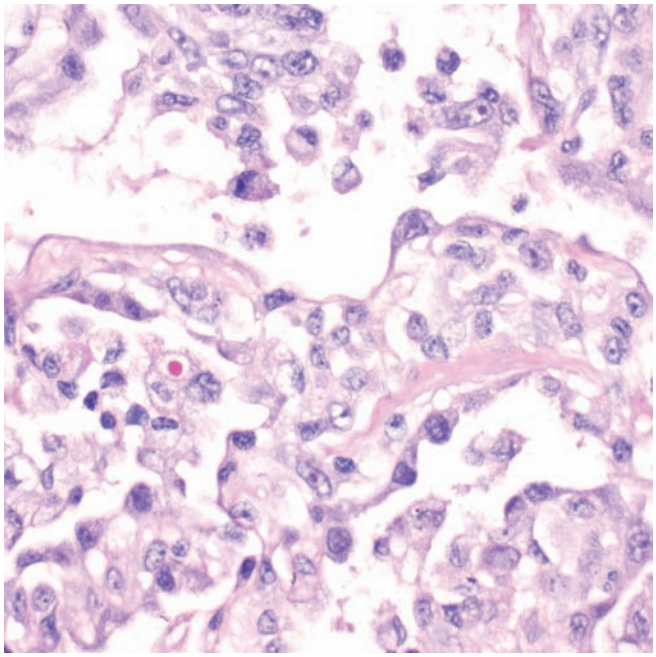

Figure 120-18 Leukemic infiltrate in the lung. Primitive mononuclear cells with clumped chromatin (blasts) expand alveolar septa and spill into air spaces. Although an infectious process was suspected clinically, acute myeloid leukemia represented the only lung pathology. Hematoxylin and eosin, 60× original magnification.

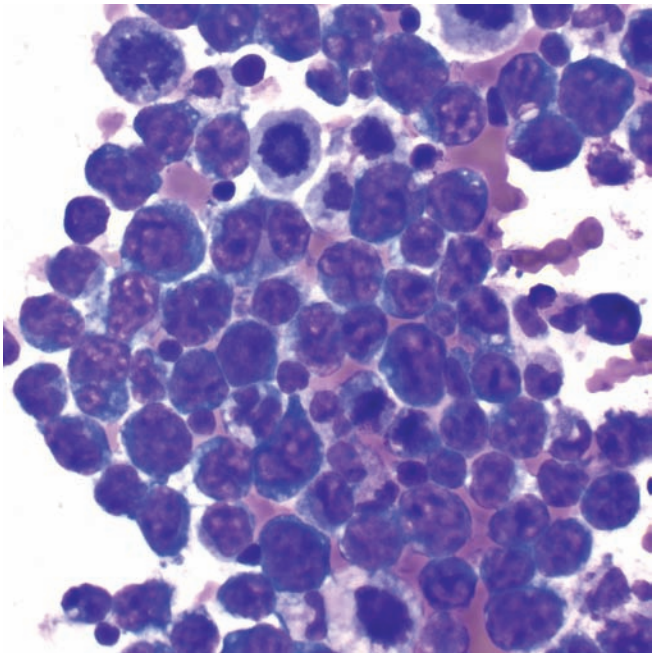

Figure 120-19 Primary effusion lymphoma. This pleural cytology demonstrates a large cluster of pleomorphic cells. This KSHV/HHV8-associated lymphoma is of B-cell origin despite the absence of immunohistochemical staining for B-cell markers. Modified Wright–Giemsa, 60× original magnification.

PLEURAL LYMPHOMAS

Disseminated lymphomas frequently affect the visceral pleura and pleural cavity. Non-HLs often invade the visceral pleura while HL often causes pleural effusions due to mediastinal lymph node involvement and secondary lymphatic obstruction. Leukemia and multiple myeloma infrequently manifest with pleural involvement.[225] Diagnosis often can be established with effusion cytology and flow cytometry; parietal pleural biopsies are rarely required.

Primary pleural lymphomas are much less common and only two types have been described: Primary effusion lymphoma (PEL) and pyothorax-associated lymphoma (PAL). Both are associated with EBV but similarities end there.

■ PRIMARY EFFUSION LYMPHOMA

Primary effusion lymphoma (PEL) is a rare large B-cell lymphoma that presents as either a pleural, pericardial, or peritoneal cavity effusion without a detectable tumor mass.[226] All cases are associated with Kaposi sarcoma–associated herpesvirus/Human herpes virus-8 (KSHV/HHV8) and most occur in young to middle-aged HIV-positive homosexual males.[227] Rare cases have been reported in supposedly immunocompetent elderly individuals and HIV-negative cardiac transplant patients.[228] A solid tissue-based variant is also recognized.[229] Some patients have pre-existing Kaposi sarcoma and rare cases are associated with MCCD.[230] In addition, most cases are coinfected with EBV but a pathogenetic role for this virus has not been elucidated.[231,232]

Effusion cytology specimens demonstrate large lymphoid cells with large round to irregular nuclei and frequent multinucleation as well as numerous mitotic figures (Fig. 120-19). Plasma cell features may be prominent and anaplastic cells can be seen. Pleural biopsies feature tumor cells admixed with fibrin. Chest wall or lung invasion are very rare findings. B-cell lineage is confirmed by immunoglobulin gene rearrangement studies but neoplastic cells rarely express B-cell markers. CD45, CD30, and plasma cell markers CD38 and CD138 are expressed. These findings suggest a postgerminal center B-cell origin. Rare cases with T-cell lineage have been reported.[233]

This lymphoma is extremely aggressive with survival measured in months. Combined antiviral therapy and chemotherapy are offered.[234,235]

■ PYOTHORAX-ASSOCIATED LYMPHOMA

Pyothorax-associated lymphoma (PAL) develops in the pleural cavities of immunocompetent patients with chronic suppurative pleuritis. Most cases arise decades after artificial pneumothorax for treatment of tuberculosis or pleuritis secondary to pulmonary asbestosis.[236] Approximately 2% of individuals with chronic pyothorax develop PAL. EBV is strongly associated but the pathogenesis is not clearly understood.[237] It is postulated that immunocompetent cells cannot enter the diseased pleural cavity resulting in local immunodepression facilitating proliferation of EBV-infected lymphocytes.

Patients, more often males, are usually in their sixth to eighth decades of life and usually present with chest pain, back pain, or shoulder pain and dyspnea.[236] Radiographic studies demonstrate an intense ^{18}F fluorodeoxyglucose positron emission tomography–positive visceral or parietal pleural mass invading chest wall, lung, pericardium, or diaphragm in the setting of pleural fibrosis and calcification.[238,239] In contrast to PEL, pleural effusion is not seen. Solid organ involvement is rare.[237]

Biopsy and resection specimens show masses composed of sheets of large atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm (Fig. 120-20). Mitotic figures and apoptotic bodies as well as necrosis abound. Immunohistochemical studies discern this high-grade lymphoma from PEL. Typically lymphoma cells associated with PAL stain for B-cell antigens CD20 and CD79a, plasma cell markers CD38 and CD138, and on occasion a T-cell marker such as CD2, CD3, CD4, or CD7.[1,240] Immunohistochemistry is positive for EBV, whereas KSHV/HHV8 is absent.[241,242]

The prognosis for patients with PAL is dismal with most deaths occurring within 1 year. However, combination chemotherapy

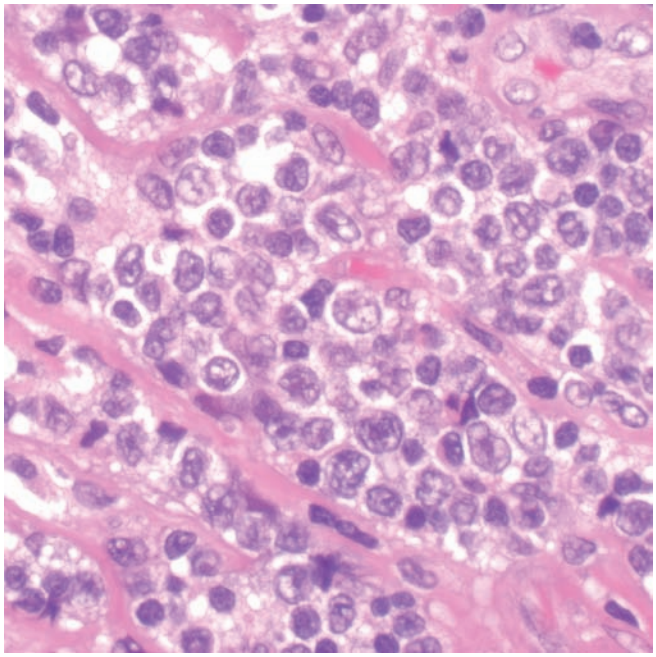

Figure 120-20 Pyothorax-associated lymphoma. Unlike primary effusion lymphoma, this aggressive large-cell B-cell lymphoma is pathogenetically linked to EBV and forms a mass lesion. Hematoxylin and eosin, 60× original magnification.

and radiotherapy may prolong survival with 5-year survival rates of 20%.[236]

CONCLUSIONS

Pulmonary and pleural lymphomas and reactive processes are uncommon entities with rich historical contexts. Current immunohistochemical and molecular methods allow for accurate reproducible classification. Since most lesions arise from BALT, using this construct to order most lung lymphoid proliferations is very appealing. The wide variety of diseases associated with underlying immunologic disorders is only surpassed by the complexities of the primary lymphoproliferative disorders themselves. Clinicopathologic correlation is required for interpretation of virtually all these lesions. Sound diagnoses combined with improved therapies will hopefully improve patient quality of life and survival.

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PART 17

Infectious Diseases of the Lungs

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CHAPTER 121

Pulmonary Clearance of Infectious Agents

Theodore J. Standiford
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INTRODUCTION

The primary function of the lungs is the exchange of gases at a rate required to support tissue metabolism. During gas exchange, the lung is continuously exposed to a varied burden of foreign substances, including infectious agents. In addition, the lung is repeatedly challenged with microbes via aspiration of secretions from the upper respiratory tract, particularly during sleep. The lung must defend itself against this potentially hostile environment while maintaining the alveolar architecture required for adequate gas exchange. This group of nonrespiratory functions has been collectively termed *pulmonary host defenses.*[1]

MECHANICAL DEFENSES

Mechanical defenses include those present in the nasopharynx and conducting airways of the lung.

■ NASOPHARYNGEAL AIRWAYS

Nasal hairs remove most particulates larger than 10 μm. Brisk airflow and rapid changes in direction of the airstream within the nose promote inertial deposition of large particulates, which are cleared primarily by swallowing, sneezing, or coughing. Mucociliary clearance participates in the removal of particulates from the nasopharynx. Ciliated mucosa is present on the nasal septum and turbinates; mucociliary action sweeps mucus toward the posterior pharynx, where secretions are either swallowed or cleared from the throat.[2–4]

■ CONDUCTING AIRWAYS

Defense mechanisms within the conducting airways include the so-called "mucociliary escalator" and a number of constituents of airway secretions.

Mucociliary Escalator

Most particulates larger than 2 μm in diameter affect the conducting airways. Mucociliary clearance and coughing are the principal means of mechanical defense.[3] The mucosa of the conducting airways is lined with mucus secreted by goblet cells, bronchial glands, and Clara cells. The mucus blanket is composed of two distinct layers: a watery sublayer, in which most ciliary movement takes place, and an upper viscous layer that is just penetrated by the ciliary tip.[2,4,5] Mucus is propelled cephalad within the respiratory tract by the pseudostratified ciliated epithelium that lines the conducting airways. Each ciliated cell has approximately 200 cilia, which are approximately 5 to 6 μm in length and have a beat frequency of 12 to 14 beats per second. Particulates can be cleared from the trachea and distal airways within minutes to hours.

Airway Secretions

Airway epithelial cells secrete a broad array of antimicrobial molecules.[6,7] Iron is essential for survival of many microbes.[8] Iron is sequestered in cells or firmly complexed to transport proteins. Microbes compete for this iron with their own transport proteins, known as siderophores. Lactoferrin, transferrin, and lipocalin-2 are host-derived molecules that effectively complex free iron in mucosal secretions, suppressing bacterial growth by limiting iron required for bacterial replication.[9]

Lysozyme is secreted in abundant quantities in human airways (10–20 mg per day). This enzyme catalyzes the hydrolysis of peptidoglycan constituents of the cell walls of most bacteria and some fungi. Airway secretions contain both serum-derived antiproteases (α_1-antitrypsin, α_2-chymotrypsin, and α_2-macroglobulin) and airway epithelial cell-derived antiproteases (secretory leukocyte protease inhibitor [SLPI] and elafin). Airway secretions and alveolar lining fluid also contain the small cationic antimicrobial peptides β-defensin and cathelicidin.[10–12] These proteins exert broad antimicrobial activity against bacteria, fungi, and viruses through hydrostatic interactions with cell membranes resulting in cell rupture.[10,13] Different classes of antimicrobial molecules can function in a synergistic fashion to markedly enhance microbial killing.[14] For instance, sub-MIC concentrations of lysozyme and lactoferrin can substantially enhance the bacterial killing activity of β-defensins and cathelicidins. The respiratory epithelium has the ability to generate reactive oxygen species at bactericidal concentrations. Hydrogen peroxide is produced in the airway via the dual NADH oxidase/peroxidase (Duox) system, which is induced during infection.[5,15] The bactericidal activity of H_2O_2 is greatly enhanced in the presence of lactoperoxidases produced in abundance by the airway epithelium.

INNATE IMMUNITY

Host defenses against invading microbial pathogens consist of two components: innate immunity and adaptive immunity. Innate immune recognition occurs via germ-line encoded receptors that recognize conserved molecular features common to multiple microorganisms (Fig. 121-1).

■ INNATE IMMUNE RECOGNITION

Microbial recognition is complex because microbes display molecular heterogeneity and have high mutation rates. The innate immune system recognizes a broad spectrum of pathogens using a repertoire of invariant extracellular and intracellular receptors that recognize highly conserved microbial molecules including combinations of sugars, proteins, lipids, and distinct nucleic acid motifs. The receptors that recognize these molecular patterns are termed pattern recognition receptors (PRRs). The ligands recognized by PRRs are pattern-associated molecular patterns (PAMPs). PAMPs share certain features. Specifically, PAMPs are invariant structures shared by classes of pathogens, are produced only by microbes, and are essential for microbial pathogenicity or microbial survival. PRRs can also recognize certain host-derived signals, referred to as danger-associated molecular patterns or DAMPs.[16,17]

PRRs can be divided into three general classes: secreted, endocytic, and signaling receptors. C-reactive protein (CRP), mannan-binding lectin (MBL), and serum amyloid protein (SAP) are secreted

*Deceased.

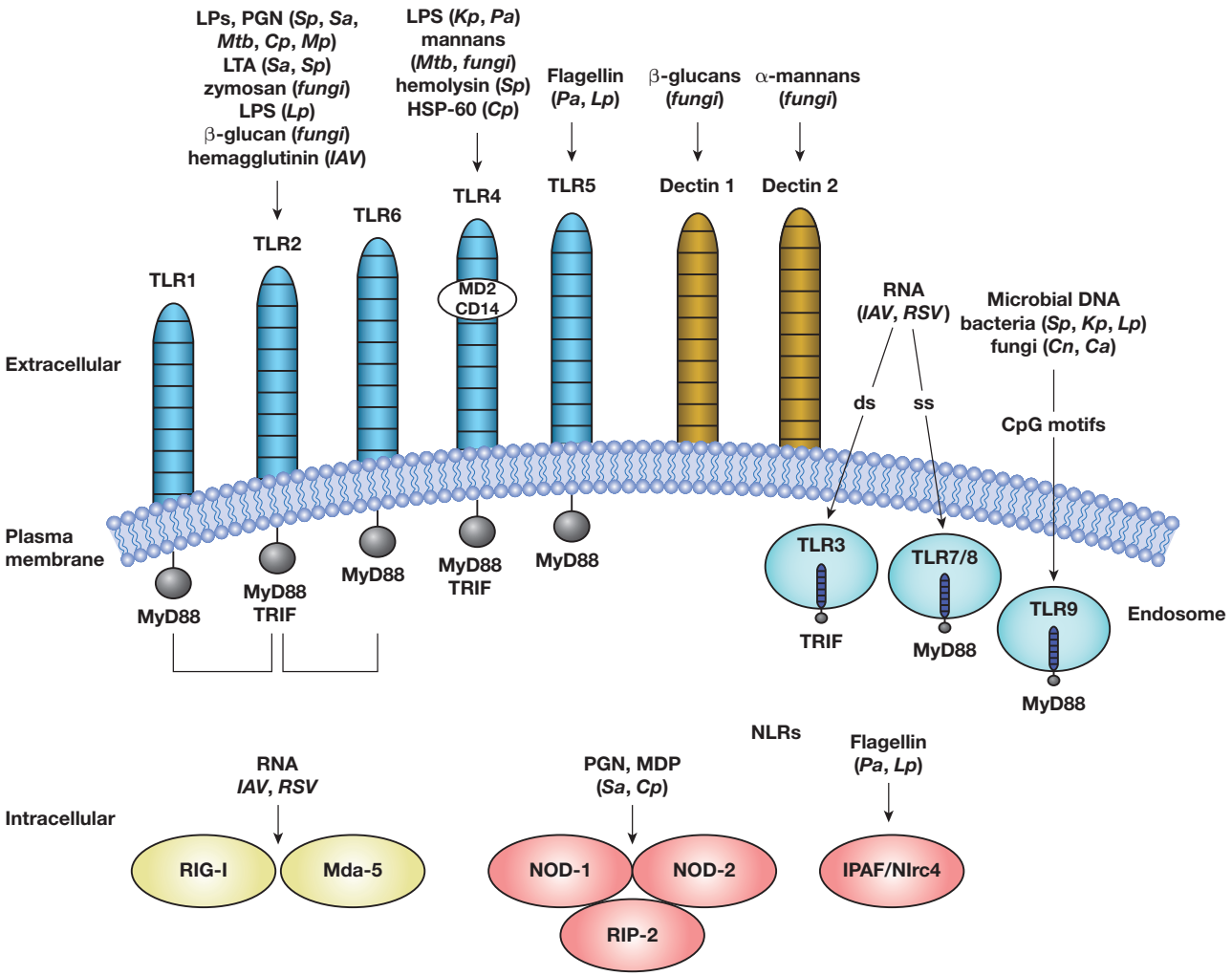

Figure 121-1 Pattern recognition receptors. TLRs, NLRs, dectin receptors, and RIG-I system for detection of extracellular and intracellular PAMPs. TLRs 1, 2, 4 to 6 and dectin receptors are extracellular; TLRs 3, 7/8, and 9 detect PAMPs within endosomes; NLRs and RIG-I detect PAMPs within the cytoplasm. All are signaling receptors. Pattern-associated molecular patterns, PAMPs; LPs, lipoproteins; LPS, lipopolysaccharide; LTA, lipoteichoic acid; PGN, peptidoglycan; MDP, muramyl dipeptide. Pathogens: *Sp*, *S. pneumoniae*; *Sa*, *Staphylococcus aureus*; *Kp*, *K. pneumoniae*; *Cp*, *Chlamydia pneumoniae*; *Mp*, *M. pneumoniae*; *Lp*, *L. pneumophila*; *Mtb*, *M. tuberculosis*; *Cn*, *Cryptococcus neoformans; Ca, C. albicans*; *IAV*, *Influenza virus; RSV, respiratory syncytial virus.*

pattern recognition molecules. CRP and SAP function as opsonins and bind to Clq to activate the classic complement pathway. MBL binds to mannose residues that are abundant on the surface of many microbes. Macrophage mannose receptor (MMR) interacts with Gram-positive and Gram-negative bacteria and fungal pathogens and mediates phagocytosis. Macrophage scavenger receptors (MSRs), including SR-AI/II and MARCO, have broad specificity for varied polyanionic molecules, including environmental particles, apoptotic cells, and microbial components.[18,19] Microbial ligands include double-stranded RNA (dsRNA), LPS, and lipoteichoic acid, and these scavenger receptors mediate binding and internalization of nonopsonized bacteria such as *Escherichia coli* and *Staphylococcus aureus*. While not considered classical signaling receptors, scavenger receptors can stimulate respiratory burst but not inflammatory cytokine production.[20] Signaling PRRs induce expression of inflammatory cytokines, chemokines, and other innate effector molecules following binding of PAMPs. Signaling PRRs include toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors, the RNA helicase retinoic acid-inducible gene I (RIG-I) system, and dectin receptors.

TLRs are critical elements of innate immune recognition.[17,21–23] Thirteen TLRs have been described in mammals and are expressed by both traditional immune cells (macrophages, dendritic cells [DCs], mast cells, neutrophils, eosinophils, natural killer [NK] cells) and lung structural cells (epithelial cells, fibroblasts, and endothelial cells).[24–26] TLRs differ from one another in ligand specificity, expression patterns, and the genes they induce. TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the surface of cells, whereas TLR3, TLR7, TLR8, and TLR9 are intracellular, primarily in the endosomal compartment. TLR2 recognizes a wide range of microbial constituents expressed primarily by Gram-positive bacteria, mycobacterium, fungi, and certain viruses.[27–34] These PAMPs include lipoproteins, peptidoglycan, lipoteichoic acid, lipoarabinomannan, hemagglutinin, and zymosan.[35] TLR2 also forms heterophilic dimers with other TLRs such as TLR1 and TLR6, substantially increasing the repertoire of ligands recognized by TLR2. TLR3 recognizes dsRNA produced by most viruses during replication.[36,37] TLR4 is the primary receptor for LPS recognition and is required for clearance of many Gram-negative bacteria, including *E. coli*, *Haemophilus influenzae*, and *Klebsiella pneumoniae*.[38,39] TLR4 also recognizes endogenous ligands such as heat shock proteins, matrix components, surfactant proteins, and β-defensins.[16] TLR5 is activated by flagellin, the principal component of bacterial flagella.[40] TLR7 and TLR8 recognize single-stranded RNA (ssRNA) from viruses such as human immunodeficiency

virus and influenza virus.[41] TLR9 recognizes unmethylated CpG motifs present in bacterial, mycobacterial, and fungal DNA but not in mammalian DNA.[42,43] This TLR mediates DC activation that is required for innate responses to bacteria (*Streptococcus pneumoniae*, *K. pneumoniae*, *Legionella pneumophila*) and fungi (*Candida albicans*, *Cryptococcus neoformans*).[43–45] Nearly all TLRs require the adaptor molecular MyD88 for downstream signaling, whereas TLR3 requires the adaptor TRIF. Several TLRs, including TLR2 and TLR4, can signal through both MyD88 and TRIF-dependent pathways, with the MyD88 pathway serving as the dominant pathway in innate antimicrobial responses to bacterial challenge.[46–48]

Another class of signaling PRRs is the NOD-like receptors (NLRs).[49] NLRs exist intracellularly and function to activate the inflammasome, an intracellular multimeric protein complex that regulates the maturation and release of proinflammatory cytokines of the IL-1 family (IL-1, IL-18). NLRs are activated by a diverse group of PAMPs, including the bacterial cell wall components peptidoglycan and muramyl dipeptide (MDP), bacterial flagellin, and several bacterial toxins.[50,51] NLRs and their adaptor molecules contribute to protective immunity against several respiratory pathogens, including *Staphylococcus aureus*, *L. pneumophila*, and *Chlamydia pneumoniae*.[52,53] NLRs can act cooperatively with TLRs to amplify innate responses. For instance, TLR5 and the NLR IPAF/Nlrc4 function cooperatively to optimally eradicate flagellated bacteria such as *Pseudomonas aeruginosa* and *L. pneumophila* from the alveolus.[54]

RIG-I is a complimentary system to sense and respond to intracellular dsRNA.[41,55,56] RIG-I is expressed most prominently by myeloid (conventional) DC and respiratory epithelial cells and is important for virus-induced type I interferon production. During influenza infection, both TLR7 and RIG-I are required for maximal antiviral IFN-α/β responses, with TLR7 mediating IFN production from plasmacytoid DC (pDC), and RIG-I necessary for myeloid DC (mDC) IFN responses.

Dectins are signal-transducing type II transmembrane proteins of the C-type lectin family that are expressed mainly in DC, macrophages, and neutrophils.[57–59] Dectin-1 recognizes β-glucans, whereas dectin-2 recognizes α-mannans. Both β-glucans and α-mannans are major cell wall components of fungi, including *Pneumocystis jiroveci* (formally *Pneumocystis carinii*), *Aspergillus fumigatus*, and *C. albicans*.[58–60] Activation of dectins can induce reactive oxygen species, production of cytokines and chemokines (CXCL1, CXCL8, IL-23, IL-17A, and IL-22), and influx on PMN. Collectively, dectins are crucial for recognition and host defense against fungal infection.

ALVEOLAR MACROPHAGES

Alveolar macrophages are a heterogeneous population of phagocytes that constitute the first line of defense against microbes that reach the alveolus.[34,61] These cells are derived from circulating monocytes and proliferating macrophage precursors in the interstitium of the lung. Alveolar macrophages have a life span of months to years. The signals and ligands that modulate monocyte traffic into the normal lung have not been defined. Other macrophage populations exist in the lung, including within the airway, interstitium, pleura, and intravascular space. These various macrophage populations are phenotypically distinct for one another and from macrophages that reside in the alveolar space.

The antimicrobial function of the alveolar macrophage is dependent on four essential attributes. Macrophages recognize signals, migrate in response to stimuli, secrete mediators, and ingest and kill microbes.[34] Macrophages recognize signals in their microenvironment via PRRs and surface receptors capable of binding specific ligands, including complement proteins, immunoglobulins, cytokines, PAMPs, and toxins (Fig. 121-2). Ligation of TLRs induces transcriptional activation of inflammatory cytokines (TNF-α, IL-1, IL-6, and the IL-1 family members IL-36 α/γ), chemokines, and signals that regulate the differentiation and activation of lymphocytes, such as IL-10, IL-12, transforming growth factor (TGF-β), and IFN-γ. Early response cytokines produced by alveolar macrophages network with structural cells within the alveolus (e.g., alveolar epithelial cell [AEC]).[62,63] As compared to monocytes and macrophages in other tissue compartments, alveolar macrophages preferentially produce 5-lipoxygenase rather than cyclooxygenase products, including LTB_4 and LTC_4, resulting in robust PMN recruitment and activation.[64] In the quiescent state, alveolar macrophages present antigen poorly. However, PRR ligation results in upregulation of costimulatory molecules (CD80, CD86) and transforms these cells into capable antigen-presenting cells (APCs).[34]

Alveolar macrophages migrate within the alveolar space in response to both endogenous signals and mechanical stimuli. The movement of these cells in response to bacteria is dependent upon chemotactic signals, including surfactant proteins (SP-A), and chemokines (CCL2/MCP-1), and adhesion molecule (ICAM-1)

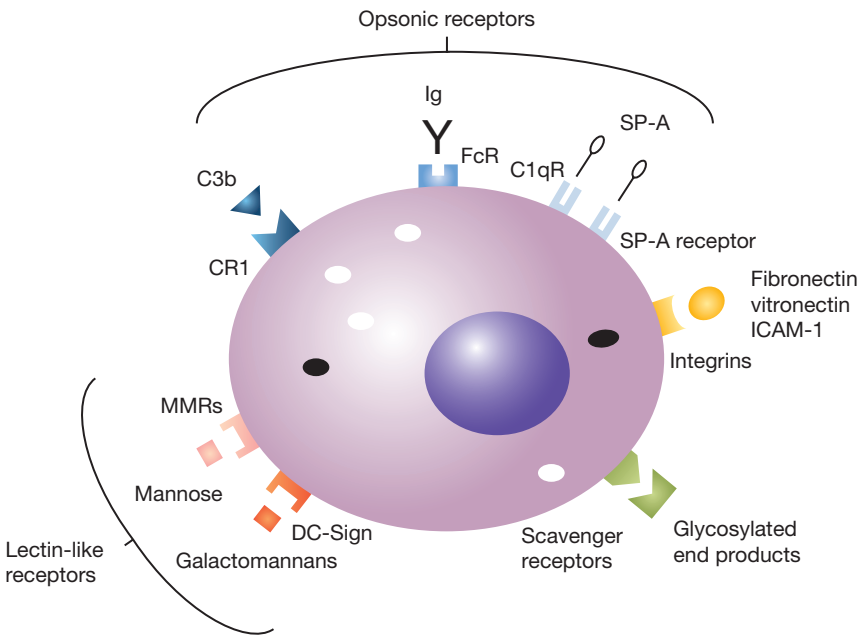

Figure 121-2 Cell-surface receptors expressed by alveolar macrophages that mediate adherence, movement, and pathogen internalization. Opsonic receptors mediate attachment and phagocytosis of pathogens opsonized with C3b, immunoglobulin, or SP-A. Lectin-like receptors and scavenger receptors mediate attachment and internalization of nonopsonized microbes expressing specific carbohydrate moieties. Integrins mediate alveolar macrophage binding to and migration along matrix components or alveolar epithelium.

expression by AECs.[65–67] Mechanical stretch can stimulate directed movement of alveolar macrophages, although the soluble signals involved in this response have not been defined.

Alveolar macrophages are highly phagocytic cells. The opsonization of microbes by the complement component C3b or immunoglobulin binding greatly facilitates phagocytosis. Macrophages express two distinct receptors for C3b. Complement receptor 1 (CR1) preferentially binds C3b, whereas the complement receptor 3 (CR3, Mo-1, MAC-1, CD11b/18) is a member of the β_2 integrin family required for cell–cell and cell–substrate adhesion. Three Fcγ receptors recognize the Fc domain of immunoglobulin G (IgG). All FcRs function as signal-transducing molecules. FcγRI, FcγRII, and FcγRIII trigger both phagocytosis and cytolytic responses, with FcγRII and FcγRIII the most indispensible.

The alveolar macrophage also expresses multiple cell-surface receptors that promote binding and internalization of nonopsonized particulates, including microbes. MMR binds mannose and mediates phagocytosis of yeasts, zymosan particles, and *P. jiroveci* (see Fig. 121-2). Scavenger receptors bind apoptotic cells and acellular debris and serve as a major mechanism to internalize nonopsonized Gram-positive and Gram-negative bacteria (*Staphylococcus aureus*, *S. pneumoniae*, *E. coli*).[18,19] SP-A-opsonized microorganisms bind to specific high affinity receptors and C1q receptors, triggering internalization and increased cell-surface expression of macrophage Fc receptors, mannose receptors, and scavenger receptors. DC-specific intracellular adhesion molecule 3-grabbing nonintegrin (DC-Sign) is a type II membrane C-type lectin expressed by DC and alveolar macrophages.[68] This PRR recognizes galactomannans of diverse pathogens, including bacteria, mycobacteria, fungi, and viruses.[69] Binding of microbes to DC-Sign can signal an IL-10 predominant anti-inflammatory response, thus subverting from a killer to a permissive phenotype in responding cells.

Phagocytosis requires sequential, circumferential interaction of phagocyte surface receptors with complementary ligands on the surface of the particle. The ingested microbe is initially contained within a phagosome that subsequently fuses with lysosomes to form phagolysosomes. TLR stimulation is linked to phagosomal maturation. The killing capacity of resting alveolar macrophages is low, and these cells require activation signals from the microenvironment for intracellular killing to occur. Activation stimuli include microbial products, inflammatory cytokines, and plasma proteins. Most notable is IFN-γ, the primary activator of macrophage antimicrobial effector responses. Other activating cytokines include TNF-α, IL-1, and GM-CSF, which provide a priming signal to augment macrophage differentiation and microbicidal activity.[70]

Both oxidative and nonoxidative processes are used to kill ingested microbes. Alveolar macrophages display less potent antimicrobial activity as compared to blood monocytes. Loss of granular peroxidase and a more modest respiratory burst account for reduced microbicidal activity. Resident alveolar macrophages contain minimal myeloperoxidase (MPO), and as a consequence the MPO-H_2O_2-halide system is less robust in resident macrophages than in recruited macrophages. Microbes are also killed by macrophage-dependent nonoxidative mechanisms, including proteases, lysozyme, nitric oxide products, defensins, and cathelicidins.

INNATE LYMPHOID CELLS

A population of lymphoid cells, referred to as innate lymphoid cells (ILCs), are present in the respiratory tract.[71] These cells produce large amounts of cytokines early in response to microbial invasion. Cytokines produced by ILC, including NK, natural killer T (NKT), and γδ T cells, drive protective innate and adaptive immune responses in the lung (Figs. 121-3 and 121-4).

NK cells are present in large quantities within the lung, making up approximately 10% of the entire lymphocyte population. NK cells are also rapidly recruited to the lung in response to infection, where they are activated by cytokines (IL-12, IL-15, IL-18, and TNF-α) produced by lung macrophages and DC.[72,73] Upon activation, NK cells produce robust quantities of TNF-α and IFN-γ, which are required for optimal pulmonary macrophage microbicidal activity during bacterial, mycobacterial, and fungal infection.[74] NK cells also mediate protective immunity during influenza infection via perforin-mediated lysis of virally infected cells and stimulate epithelial regeneration via release of IL-22.[75] Overzealous innate responses by NK cells can sometimes be detrimental to the host, as is the case in experimental respiratory syncytial virus (RSV) or influenza infection.[73,76,77] In addition to contributing to early innate responses, NK cells also substantially shape the development of adaptive immunity against the invading pathogen. Genetic deficiencies in NK cell function are associated with recurrent viral and bacterial infections, including those involving the respiratory tract.

NKT cells are a subset of lymphocytes that recognize glycolipid rather than protein antigens presented by CD1d, a nonpolymorphic major histocompatibility complex (MHC) class I-like antigen.[78,79] The majority of NKT cells express an invariant T-cell antigen receptor that is highly conserved among species. Activation of NKT cells by bacterial (*Streptococcus* spp.) or viral (influenza) glycolipids results in expression of TNF-α, chemokines, IFN-γ, and IL-17 required for microbial clearance.[80] Different subsets of NKT cells can either augment or suppress the development of innate and acquired immunity, suggesting an important regulatory role of these cells during lung infection.

Gamma–delta T cells are a unique innate T-cell subset that are small in number (approximately 1%–2% of the lung lymphocyte population) and localized to mucosal and epithelial surfaces. However, during respiratory infection the numbers of γδ T cells in the lung increase considerably (>30-fold), a process that is due primarily to local expansion rather than recruitment.[81,82] Upon activation by bacteria (*S. pneumoniae*, *K. pneumoniae*), γδ T cells function as a rich and early cellular source of TNF-α, chemokines, IFN-γ, IL-17, and IL-22. Like NKT cells, a heterogeneous population of γδ T cells exist, with specific subsets functioning to control the magnitude of DC and macrophage recruitment and activation during the resolution phase of pulmonary inflammation.[83] This nuanced response by γδ T cells is necessary to maintaining the immune and structural integrity of the lung during infection.

A novel population of lineage–negative ILCs have recently been described, including in the lung. Type I innate lymphoid cells (ILC1) produce primarily IFN-γ upon activation, where as type III ILC (ILC3) express large quantities of IL-17 and IL-22. The role of these cells in lung mucosal immunity is not yet known.

ALVEOLAR EPITHELIAL CELLS

The alveolar–capillary membrane is a dynamic assembly of innate immune cells that generate chemokines required to recruit and activate specific inflammatory cells during microbial insults. AECs are key participants in the innate response to microbial challenge.[8,84] These cells express an array of both extracellular and intracellular signaling PRRs that trigger the release of a variety of inflammatory cytokines (IL-1, IL-6, IL-36 α/γ, type I and III interferons, GM-CSF) and chemokines (CXCL1/KC, CXCL2/MIP-2, CXCL5/LIX, CXCL8/IL-8, CCL2/MCP-1, CCL20/MIP-3α) that regulate the engagement and activation of phagocytic cells.[7,24,70,84–87] AEC also secrete molecules that directly mediate antimicrobial killing, including large antimicrobial proteins (lysozyme, lactoferrin, calgranulins A and B, SLPI) and small antimicrobial peptides (β-defensins, cathelicidins).[12] Type II AEC produce surfactant proteins SP-A and SP-D, members of the collectin family of lectins. SP-A contains a carbohydrate recognition domain that binds to exposed carbohydrate residues on the surface of microbes, serving as an opsonin to promote internalization of diverse pathogens (Gram-positive and

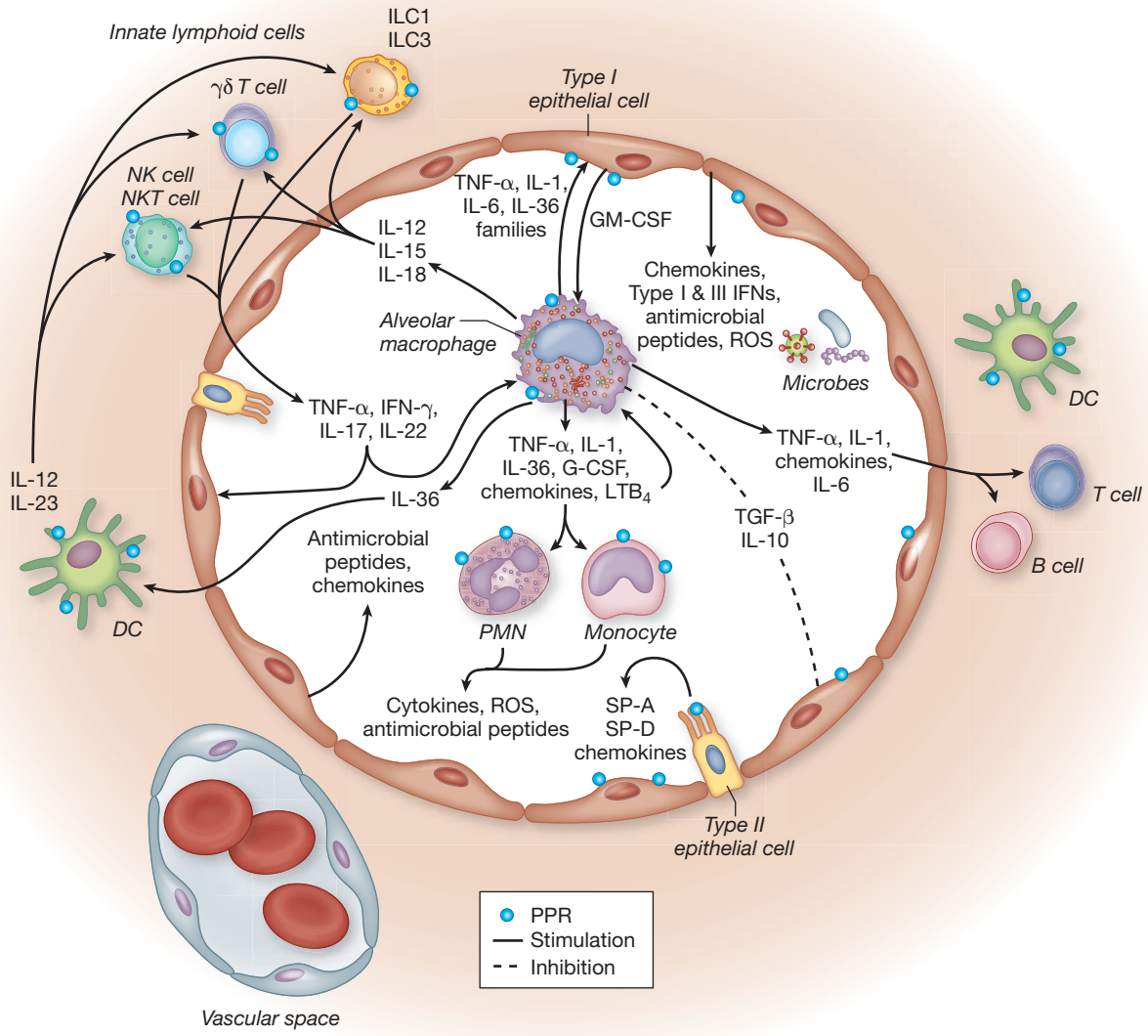

Figure 121-3 Initiation and regulation of inflammatory responses in the lower respiratory tract. Chemotaxins are generated sequentially following the entry of bacteria or bacterial products into the alveolus. PAMPs stimulate alveolar macrophages to produce proximal cytokines (TNF-α, IL-1β, IL-1, and IL-6 family members) and LTB_4. Proximal cytokines induce gene expression and production of chemokines and growth factors by epithelial cells and fibroblasts present in the alveolar–capillary wall and induce the expression of adherence molecules on inflammatory cells and endothelial cells. Microbes induce macrophages to produce IL-12, IL-15, and IL-18 to stimulate the expression of activating cytokines (e.g., IFN-γ, TNF-α) from ILC. ILC also produce IL-17 and IL-22 in response to IL-23 production from DC. IL-17 stimulates the paracrine induction of IL-1, IL-6, and CXC chemokines by parenchymal cells, whereas IL-17 and IL-22 drive antimicrobial peptide release from the alveolar epithelium.

Gram-negative bacteria, fungi, and viruses) by alveolar macrophage and type II AECs.[65] SP-A also increases secretion of GM-CSF, promotes directed migration of alveolar macrophages, and regulates macrophage oxidant production.[65,88] SP-D mediates agglutination of bacteria, fungi, and influenza, facilitating uptake by PMN and other phagocytic cells.[89]

INITIATION AND REGULATION OF THE INFLAMMATORY RESPONSE

A dual phagocytic system involving resident and recruited macrophages and recruited PMN is required for the clearance of bacteria from the lower respiratory tract (Fig. 121-3). Neutrophils ingest microbes by phagocytosis.[90] Effective killing requires products of granule constituents and molecular oxygen. Hydrogen peroxide and reactive oxygen intermediates are involved in neutrophil-mediated killing. The MPO-H_2O_2-halide system is a crucial participant in oxygen-dependent killing by neutrophils. Granule components are also crucial in PMN-mediated microbial killing. Microbicidal molecules found in azurophil granules include lactoferrin, lysozyme, cathepsin G, elastase, and cationic proteins such as α-defensins and cathelicidins. Neutrophil extracellular traps (NETs) are complex structures composed of nuclear chromatin, histones, and a variety of granular antimicrobial proteins.[91,92] NETs are released from azurophilic granules during infectious challenge and are capable of physically ensnaring bacteria. These structures facilitate the interactions between bacteria and antimicrobial effectors, ultimately leading to enhanced bacterial killing.[93]

Recruitment of PMNs from the blood into the alveolus is initiated by upregulation of selectins and β-integrins on the surface of leukocytes and endothelium, concurrent with the establishment

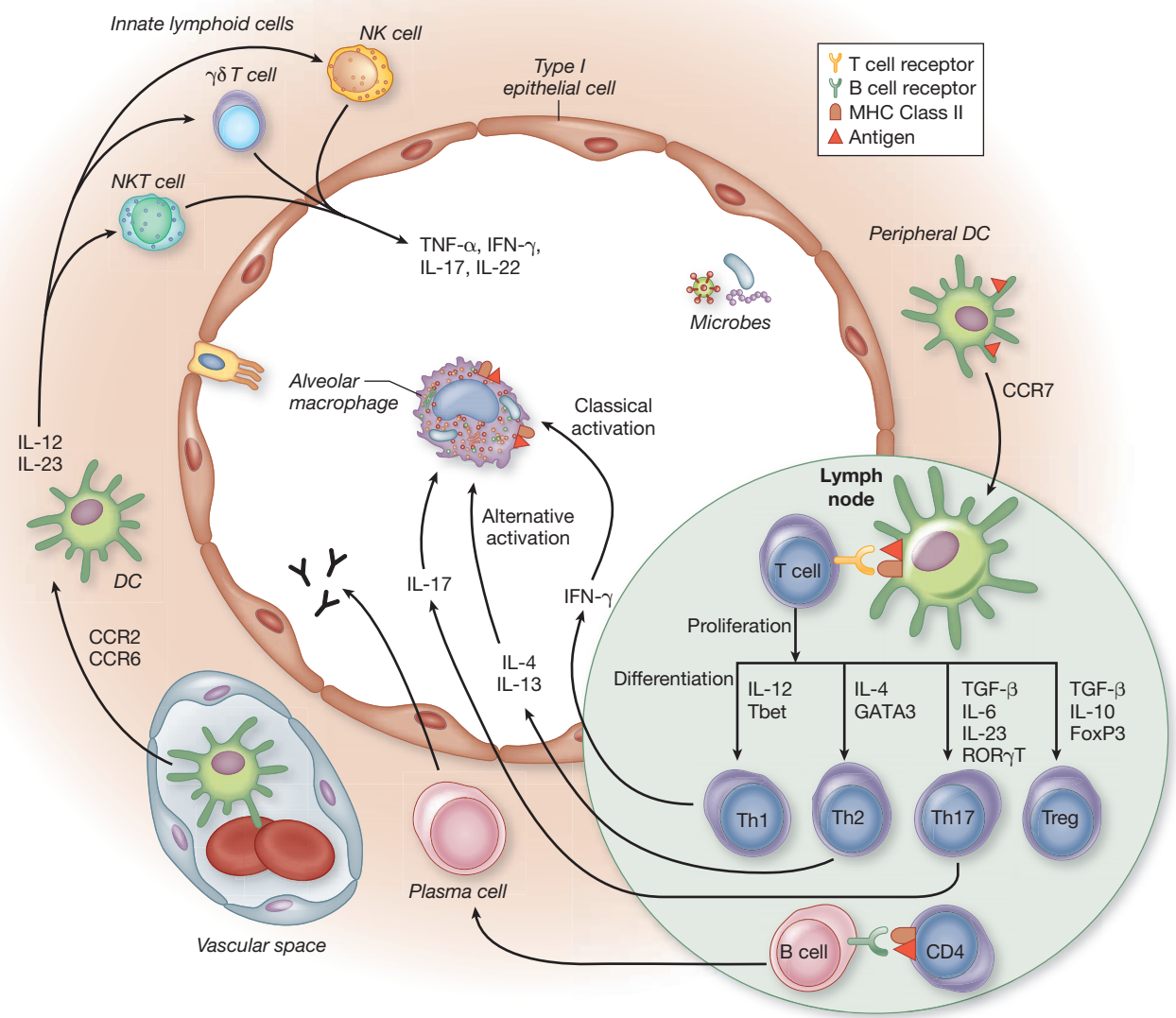

Figure 121-4 Initiation and regulation of specific immune responses in the lung. Dendritic cells located in the interstitium of the lung and in the airway epithelium function as sentinel antigen-presenting cells. Dendritic cells reside in close contact to airway epithelial cells, alveolar epithelial cells, and interstitial macrophages. Following exposure to microbial antigens, inflammatory DCs are recruited into the lung interstitium and alveolus in a CCR2- and CCR6-dependent fashion. DC differentiation occurs as a result of exposure to cytokines produced by cells of the innate immune system (macrophages) and cytokine produced as a result of injury to epithelial cells. Differentiated DC migrates to local nodes in a CCR7-dependent fashion where they present antigen to naive T lymphocytes. The control of CD4 T-lymphocyte subset differentiation occurs via complex, cross-regulatory interactions mediated by cytokines (e.g., IL-12, IL-4, IL-6, TGF-β, and IL-23) and transcription factors. Cytokines produced by Th1, Th2, and Th17 cells regulate macrophage activational state. Initial events in B-lymphocyte proliferation and differentiation occur in T lymphocyte-dependent areas of regional LNs. Proliferation, somatic hypermutation, and selection occur within the lymphoid follicle. B lymphocytes then migrate to bone marrow and to the lung, where they undergo differentiation to mature antibody-producing plasma cells.

of chemotactic gradients within the lung interstitium and alveolar space.[63] Chemotactic gradients are established in part by matrilysin-mediated shedding of syndecan–chemokine complexes into the alveolar space.[94] Early recruitment of PMN to the lung (<4 h) is directed by cytokines, chemokines, and leukotrienes secreted by pulmonary macrophages, whereas sustained neutrophil influx (24 h) appears to be driven by chemokines produced by lung structural cells, including AEC.[95] CXC chemokines that mediate PMN influx during lung infection include CXCL1/KC, CXCL2/MIP-2, and CXCL5/LIX in the mouse and CXCL8/IL-8 in humans.[63,95,96]

Recruited, or exudate, macrophages represent an essential arm of the innate response in lung bacterial and fungal infection. The recruitment of these cells to the lung requires specific chemokines and chemokine receptors. In particular, CCL2/MCP-1 with the receptor CCR2 mediates the influx of exudate macrophages in Gram-negative pneumonia.[97] MCP-1 also serves as an autocrine inducer of cytokine (G-CSF) and CXC chemokine (CXCL1, CXCL2) production from alveolar macrophages, further amplifying the neutrophilic response during pneumonia.[98] CCL3/MIP-1α is an additional CC chemokine that participates in both exudate macrophage and PMN recruitment during bacterial infection.[99]

Sentinel DC and macrophages produce IL-12, IL-15, IL-18, and IL-23 within minutes to hours after exposure to LPS and microbial products. Interleukin-12, IL-15, and IL-18 induce the release

of the activating cytokine IFN-γ from ILCs early in the innate response and antigen-specific T cells later in the adaptive response. Interleukin-23 triggers rapid (hours) production of IL-17 and IL-22 from tissue resident α/β, γδ, NKT cells, and ILC3.[100] IL-17 promotes production of IL-1, IL-6, TNF-α, CXC chemokines, IL-22, and antimicrobial peptides from both alveolar macrophages and cellular constituents of the alveolar–capillary membrane.[100–102] IL-22, like IL-17, stimulates effector responses, including mucus production and antimicrobial peptide expression from the respiratory epithelium.[103] Interleukin 1 family members, including IL-36 α and β, also serve as relevant proximal signals in the induction of cytokines and chemokines from DC and structural cells of the lung.

Robust innate responses are required for effective control of pathogens at mucosal sites of invasion. However, these responses need to be tempered to allow for protection and restoration of lung architecture. Certain cells and soluble factors present within the lung microenvironment contribute to the fine-tuning of innate responses. For instance, surfactant proteins A and D can antagonize binding of DAMPs and PAMPs to TLR4, hence reducing downstream inflammatory mediator release.[104–106] Inhibitors of TLR signaling, such as IRAK-M, suppress deleterious inflammation in influenza infection.[107] Anti-inflammatory molecules, including IL-10 and IL-1 receptor antagonist, produced by NKT, γδ T cells, and exudate macrophages, contribute to the resolution of inflammation.[108] Finally, the update of apoptotic neutrophils and other cells by lung macrophages signal an anti-inflammatory program that facilitates tissue repair.

ADAPTIVE IMMUNE RESPONSES

Microbial infections that elude the innate defense mechanisms and inflammatory responses generate a threshold dose of antigen, which is needed to trigger adaptive immune responses. Adaptive immune responses consist of two major effector systems, antibody- and cell-mediated immunity, which are generated by antigen-specific B and T lymphocytes, respectively. B and T lymphocytes rearrange their Ig and T-cell receptor (TCR) genes to maintain approximately 10^{11} different clones of B and T lymphocytes that express distinct antigen receptors. B lymphocytes recognize native antigens including carbohydrates, proteins, and simple chemical groups. T-lymphocyte receptors recognize only peptides derived from protein antigens bound to cell-surface proteins from the MHC.

Antigen-specific immune responses require at least 7 to 10 days for their development; this time is required for the proliferation and differentiation of antigen-specific T and B lymphocytes. During the development of specific immune responses, pathogens may continue to grow in the host or be held in check by innate and inflammatory mechanisms. The generation of specific immune responses to infectious antigens can be divided into three phases: the afferent phase, central control/processing phase, and efferent phase.

AFFERENT IMMUNE RESPONSE

APCs and ILCs provide an essential link between innate and adaptive immunity (Fig. 121-4).[109–117] DCs are the most potent APC for T cells. DCs are bone marrow-derived cells which take up residence in peripheral tissues at epithelial borders throughout the mammalian host where they become specialized for recognition of pathogens and microenvironmental tissue damage during antigen uptake and presentation. Following antigen uptake, they migrate to lymph nodes (LNs) or mucosa-associated lymphoid tissue.

Mucosa-associated lymphoid tissues are organized into unique inductive and effector sites. Inductive sites include specialized lymphoid follicles underlying the epithelium, such as nasopharynx-associated lymphoid tissue (NALT) and bronchial-associated lymphoid tissue (BALT) in the upper and lower airway, respectively, and Peyer's patches (PPs) and isolated lymph follicles (ILFs) in the gut, and downstream LNs, including cervical and mediastinal LNs draining the respiratory mucosa and mesenteric LNs draining the intestinal mucosa.[118,119] Clones of lymphocytes are triggered by APCs to proliferate and differentiate into effector cells. Antigen-specific lymphocytes remain expanded after elimination of an infection (memory lymphocytes). Memory lymphocytes provide a much more rapid response to a second exposure to antigen.

Two broad subsets of DC have been identified[109,120,121]: myeloid DC (mDC) and plasmacytoid DC (pDC). mDC express CD11c, CD11b, and varying levels of MHC class II and costimulatory molecules (CD40, CD80, and CD86). Human pDC express blood DC antigen (BDCA)2, whereas murine pDC express CD11c, GR-1, and B220. mDC contribute to a variety of T-cell responses or tolerance and pDC have been implicated in antiviral immunity and in murine models of asthma.

DCs exist in both immature and mature forms. Immature DCs are concerned mainly with antigen capture. DCs are mobilized from bone marrow precursors to peripheral blood in response to pulmonary inflammation. Monocytes contribute to the pool of newly recruited DC through transendothelial migration in which peripheral blood monocytes differentiate into tissue DC after crossing the vascular endothelium. CCR2 is a critical receptor in the recruitment of DC during inflammatory responses.[122,123] CCR6 mediates recruitment of DC specifically to the airways and alveolar space in response to CCL20 (macrophage inflammatory protein [MIP]-3α) secreted by respiratory epithelial cells.[124]

DC maturation is dependent on sensing of infection,[109,120,121] which may occur either directly by detection of pathogen products using PRRs, activation by inflammatory signals such as TNF-α, or indirectly through exposure to endogenous danger signals such as material released from damaged cells (e.g., DAMPs). Ingested antigens are rapidly processed for antigen presentation by one of two pathways.[125] The endocytic pathways process protein antigens obtained from the extracellular space in phagolysosomes converting them to small polypeptides. The polypeptides are loaded on to MHC class II molecules to prime DC for further presentation to MHC class II restricted CD4+ T helper lymphocytes. The endogenous pathway processes peptides from the intracellular environment and loads them onto MHC class I molecules for presentation to MHC class I restricted CD8+ T cells. Mature DCs upregulate MHC class II and costimulatory molecules allowing a phenotype focused on antigen presentation and the stimulation of naïve T cells.

DC maturation is accompanied by changes in the expression of chemokine receptors.[109,120,121] CCR1, CCR2, CCR5, and CCR6 are downregulated. CCR7 expression is enhanced allowing DC to respond to chemokine gradients of secondary lymphoid tissue chemokines (SLC/CCL21) and Epstein–Barr virus-induced molecule1 ligand chemokine (ELC/CCL19) emanating from local lymphatics and draining LNs. Mature DCs leave the local inflammatory environment carrying their antigenic load to draining LNs. DC–T-cell interactions within the draining LN are complex. T-cell stimulation, proliferation, and activation result if antigen recognition occurs. Induction of Th1, Th2, Th17, or T-regulatory responses may be the end result.[113,115,126]

The engagement of PRRs on DCs leads to increased expression of MHC-peptide complexes and costimulatory molecules as well as the production of immunomodulatory cytokines, all of which have a profound effect on T-cell priming and differentiation.[109,120,121] Triggering of the TCR occurs following an interaction with an antigen/MHC complex and provides "signal one" to the T cell. T-cell maturation results in upregulation of important costimulatory molecules. Specifically, DCs increase the expression of B7.1 (CD80) and B7.2 (CD86), which bind CD28 on T cells providing "signal two" to activate antigen-specific T cells.

Until recently, CD4 T helper cells were believed to be the most significant sources of regulatory cytokines during the development

of immune responses in the lung; however, it is now clear that ILC produce large amounts of cytokines early in a response that drive the development of Th1, Th2, and Th17 responses.[111,112] These cells produce many of the same cytokines as CD4 Th cells, but they do not express a TCR or cell-surface markers associated with other lineages. Thus, they are not antigen-specific. These ILCs include ILC1 (IFN-γ-expressing NK cells), ILC2 (IL-5 and IL-13-expressing nuocytes), and ILC3 (IL-17- and IL-22-expressing RORγ ILC and lymphoid tissue-inducer (LTi) cells). Activation of ILCs is an important step in the development of adaptive immunity and polarization of T-cell responses.

CD4+ T cells coordinate antigen-specific immune responses against inhaled antigens.[113–117,120] Separate, distinct subsets of CD4+ T helper (Th) cells mediate a variety of distinct adaptive immune response "programs." Antigen exposure can initiate the afferent phase of the adaptive immune response that includes all subsequent events that lead to the formation of a poised antigen-specific response. The priming of CD4+ Th cells from naïve precursor CD4+ T cells is a critical component of the afferent phase. CD4+ Th cells aid B cells in the production of antibodies that mediate components of the hypersensitivity reaction. Endowed with antigen-specific receptors, T cells and antibodies mediate the efferent phase of the adaptive immune response that encompasses all the immune activities directed at the antigen source. APC acquire antigen at the site of introduction and migrate to draining LNs to prime naïve CD4+ T cells. Naïve CD4+ T cells undergo multiple rounds of division and progress through multiple stages of differentiation along the pathway to becoming effector CD4+ Th cells.[127–129]

CD4+ Th cells differentiate into one of several distinct subsets that in turn mediate a distinct adaptive immune response "program."[113,115,126,130,131] Each program has a genetic foundation in CD4+ Th cells. Master regulation by a specific transcription factor promotes the acquisition of a particular Th phenotype at the expense of the other phenotypes. Tbet (Tbx21) promotes Th1 development, GATA3 promotes Th2 development, and RORγT promotes Th17 development. Likewise, CD4+ T-regulatory (Treg) cells that inhibit CD4+ Th activity to limit harmful inflammation are specified by the transcription factor Foxp3. During CD4+ Th cell activation, the cytokine milieu present (from DC and ILC early in the response and other inflammatory cells during chronic inflammation) guides cellular differentiation along one of the particular pathways. IL-12 along with IFN-γ promotes Th1 cell development, IL-4 promotes Th2 cell development, and the combination of TGF-β and IL-6 promotes Th17 development. IL-23 drives the expansion of the Th17 cell population. The presence of TGF-β alone supports the differentiation of Treg cells.

Cytokine production represents a key effector function by which CD4+ Th cells coordinate adaptive immune responses.[113,115,126,130,131] By producing a distinct set of cytokines, each CD4+ Th cell subset coordinates a distinctive adaptive immune response program that likely developed evolutionarily to counter a particular pathogenic threat. Th1 cells produce IFN-γ, along with IL-2 and TNF-α, and help protect against intracellular pathogens, but also mediate delayed-type hypersensitivity. Th2 cells produce IL-4, IL-5, and IL-13 and promote a response to parasite infection and responses where mucus shedding and expulsion are beneficial, as well as humoral immunity. Th17 cells produce IL-17 required for protection against several extracellular pathogens.

EFFERENT IMMUNE RESPONSES

Antigen-specific T cells must migrate via the blood stream to peripheral sites of ongoing infection (Fig. 121-4).[117,132] Chemokine–chemokine receptor and adhesion molecule–ligand interactions are involved. While DCs often migrate to local lymphoid tissue after activation, a subset of recruited DCs remains in the lung rather than migrating to draining LNs.[114,120,122] These recruited nonmigratory pulmonary DCs present antigen to newly recruited T cells to drive T-cell polarization and stimulate cytokine release. Cytokines produced by specific CD4 and CD8 lymphocytes play a central role in the ongoing recruitment of inflammatory mononuclear phagocytes and other effector lymphocytes. Monocytes and NK cells are recruited into the complex peripheral infectious environment.

Viruses including influenza, parainfluenza, RSV, Hantavirus, coronavirus (severe acute respiratory syndrome), herpesvirus, and CMV cause significant pulmonary disease. Viruses are intracellular pathogens; the killing of virally infected cells by MHC class I restricted CD8 cytotoxic T lymphocytes (CTLs) is required. CTLs kill target cells by two mechanisms (Fig. 121-5). Cytolytic mediators, including perforins and granzymes, are released from cytoplasmic granules. Perforins induce pore formation and osmotic cell lysis and granzymes are proteases that activate cell caspases, resulting in apoptosis. Killing of virally infected cells can also result from the direct induction of apoptosis by Fas/Fas ligand interactions and release of TNF-related apoptosis-inducing ligand (TRAIL) by CTL.[133] Viral infection of target cells results in reduced MHC class I expression, triggering perforin/granzyme-mediated killing by local and recruited NK cells.

The development of cell-mediated immunity to viral infections proceeds by mechanisms presented earlier, but may also proceed locally within the lung. Priming can occur in BALT, a submucosal lymphoid tissue found in the major bronchi.[118,119] Localized priming of the cell-mediated immune response may play a crucial role in viral host defense.

Memory T-cell responses are important in certain viral illnesses and following administration of antiviral vaccines.[116,117,129] Two subsets of memory T cells have been defined. Effector memory T cells are found within the lung, are short lived, retain markers of activation, and have effector functions; these cells lack expression of lymphoid trafficking molecules CCR7 or CD62L. Central memory T cells reside predominantly within lymphoid organs, persist for long periods of time, and express CCR7 and CD62L.

Numerous strains of bacteria and certain fungi have evolved the capacity to invade and survive within host leukocytes, primarily macrophages, to evade recognition and elimination by innate immune responses. Cell-mediated immunity is required to successfully eradicate these microbes. Cytokines produced by CD4 and CD8 T lymphocytes play a central role in the activation of microbicidal function in phagocytic cells (see Fig. 121-5). IFN-γ produced by both CD4 and CD8 T lymphocytes is the most important macrophage-activating factor. Macrophage activation is further enhanced by TLR stimulation and by inflammatory cytokines such as TNF-α and GM-CSF. Activated macrophages kill microbes. Intracellular microbes are exposed to toxic acid hydrolysis and cationic peptides in phagolysosomes. Expression of inducible nitric oxide synthase results in enhanced nitric oxide synthesis and the synthesis of reactive nitrogen intermediates that have antimicrobial properties. Induction of the respiratory burst results in generation of superoxide, hydrogen peroxide, and toxic reactive oxygen intermediates. The induction of macrophage apoptosis in response to intracellular infection has been shown to be of importance in blocking cell-to-cell spread of certain intracellular infections.

Granuloma formation is an important mechanism of host defense to intracellular microbes.[134,135] The recruitment of monocytes and lymphocyte populations to the site of infection is required for granuloma formation. Macrophages coalesce into large, epithelioid, and multinucleated giant cells. DC, CD4+ T lymphocytes, and CD8+ T lymphocytes form a loose meshwork that serves to contain

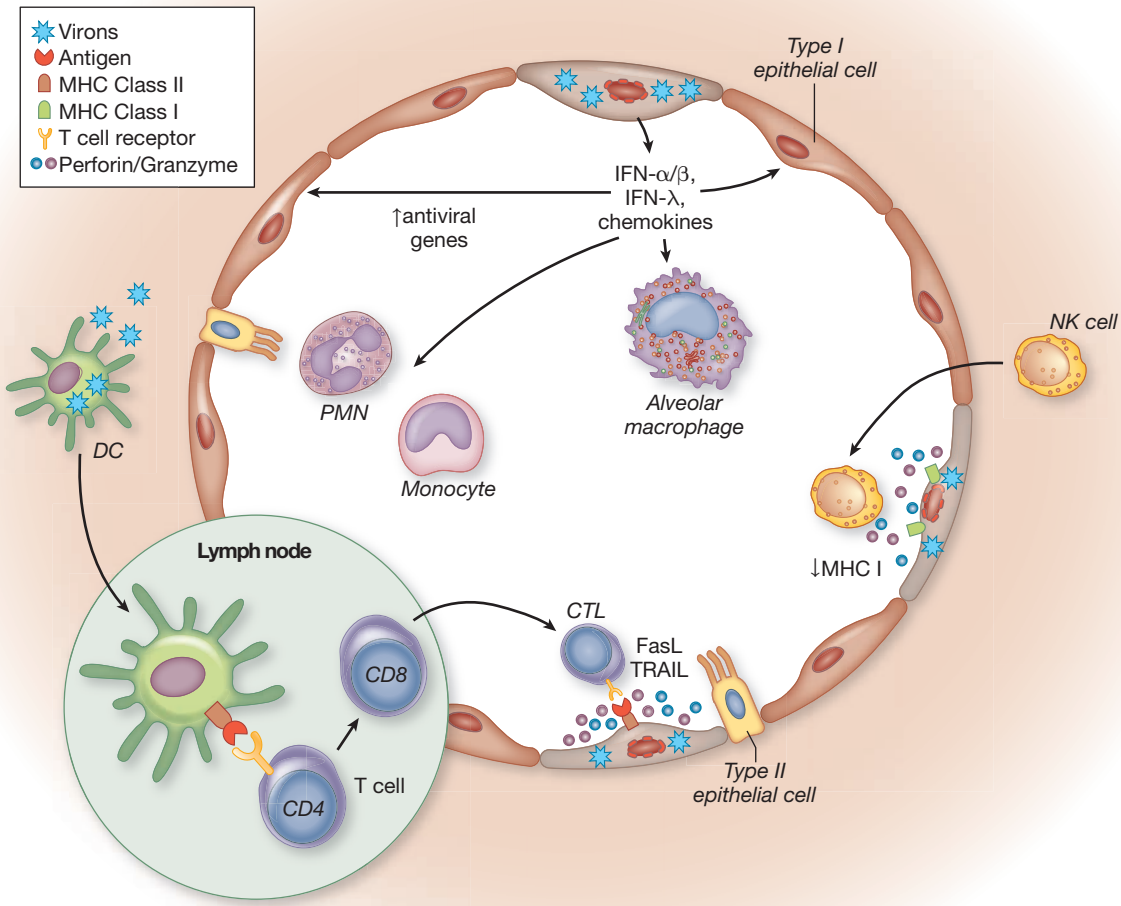

Figure 121-5 Initiation of antiviral immunity in the lung. Viral infection of respiratory epithelium results in induction of type I (α/β) and type III (λ) interferons, which stimulate the paracrine expression of antiviral genes by neighboring epithelial cells. Chemokines produced by epithelial cells promote inflammatory cell recruitment/activation. The development of CD8 effector T cells generally requires cognate interactions with CD4 T cells. Cytotoxic T cells (CTLs) recognize viral antigen presented in the context of MHC class I, resulting in apoptosis of virally infected target cells by perforin/granzyme, FasL, or TRAIL-dependent mechanisms. NK cells also kill virally infected cells by releasing pore-forming granules.

microorganisms. Granulomas are sites of ongoing production of inflammatory cytokines, including TNF-α, IFN-γ, and chemokines capable of recruiting additional effector cells.

CONTROLLING THE ADAPTIVE RESPONSE VIA REGULATORY T CELLS

The immune system possesses various mechanisms to control and regulate inflammation and adaptive responses to prevent and minimize reactivity to self-antigens or an over exuberant response to a pathogen. One of these mechanisms is through the generation of Treg cells.[130,136] CD4+CD25+ Treg cells are the best characterized subset. These cells represent 5% to 10% of the CD4+ T lymphocytes in healthy adult mice and humans. CD4+ Treg cells are recognized for the production of cytokines with anti-inflammatory activity, including IL-10 and TGF-β, and are able to limit CD4+ Th responses.

There are a number of subsets of Treg cells, with the major distinction being (1) Tregs that are induced in the periphery following antigen encounter (inducible Tregs, iTreg) and (2) Tregs that arise from normal T-cell thymic development (naturally occurring Tregs, nTreg). Both types of Treg cells have been shown to play a role in mucosal inflammation and infection. Activated Treg cells can suppress not only antigen-specific responses but also unrelated immune responses in a non–antigen-specific manner either through cell contact or through the regulatory cytokines they produce—a mechanism known as bystander suppression.

nTreg cells can prevent immunopathology in a variety of infections and the mechanisms by which nTreg regulate inflammation appear to vary between stimuli and include cell-contact and soluble mediators. Activated nTreg cells efficiently control self-reactive T cells and innate responses (thereby limiting tissue damage) in mouse models of chronic infection and inflammation. nTreg cells,

TABLE 121-1 Pulmonary Host Defense–Microbe Interactions

Host Mood	Defense Mechanism	Timing	Microbial Behavior
Content	Mechanical: epithelial barrier; mucociliary escalator	Continuous	Commensal
Irritated	Innate Immunity: macrophages, innate lymphoid cells	Hours to days	Replication in the airway and alveolar space
Interested	Inflammation: macrophages/PMN	Minutes to hours	Invasion
Angry	Antigen-specific immunity: DC; CD4, CD8 T lymphocytes; B lymphocytes	3–7 d	Tissue invasion/replication in phagocytes
Frustrated	Immunopathology: macrophages; CD4, CD8 T cells; NK cells, B cells	Weeks	Persistence of microbe

however, can also inhibit allergen-induced airway hyperreactivity through IL-10-dependent mechanisms or by inhibiting antigen presentation by DCs. The antigen specificity of iTreg cells is largely microbial or environmental antigens, whereas the nature of the antigens recognized by nTreg cells is not clear. nTreg cells are believed to recognize a wide array of self-antigens as a consequence of their development and selection in the thymus. During the onset of acute disease, nTreg cells have the potential to recognize self-antigens that are released by tissue damage; however, evidence from chronic infection suggests that nTreg cells can also recognize microbial antigens.

iTreg cells are generated in the periphery during an immune response and act in an antigen-specific manner. Several subsets of iTreg cells have been defined and iTreg cells do not constitutively express Foxp3 or CD25 but can express high levels upon activation. Foxp3 appears to act as a cell lineage differentiation factor because it correlates closely with suppressor activity, irrespective of CD25 expression. iTreg cells are often the most potent source of IL-10 in downregulating inflammatory responses to infections or allergens.

EFFERENT B LYMPHOCYTE-MEDIATED IMMUNE RESPONSES IN THE LUNG

Immunoglobulins are a major protein constituent of the fluid that lines the luminal surface of conducting airways and alveolar lining fluid. Effector functions for antibodies include opsonization, complement fixation, antibody-dependent cellular cytotoxicity (ADCC), agglutination, and neutralization (Fig. 121-4). Approximately 20% of the total protein present in bronchoalveolar lavage fluid consists of IgG, IgM, and IgA. IgA is the predominant immunoglobulin in secretions of the trachea and major bronchi while both IgG and IgE are present as well. IgG is the predominant immunoglobulin in alveolar lining fluid.

Humans produce more IgA than any other Ig class. The secretory IgA found in external secretions consists of two molecules of IgA that are held together by a joining chain and by a secretory component, a glycoprotein produced by epithelial cells. The role of IgA in pulmonary defenses remains enigmatic. The usual specificity of IgA antibodies is antiviral. Specific IgA antibodies against hemagglutinating antigen have been isolated from patients infected with influenza A. IgA may also be important in inhibiting bacterial adherence to the respiratory epithelium and may also serve as an antitoxin. Finally, IgA may also have a role as an opsonin, since human alveolar macrophages bear Fc receptors that bind either IgA1 or IgA2. Certain bacteria elaborate proteases that digest IgA; these proteases may provide a selective colonization advantage to the microbes.

Specific antibody is an important component in lower respiratory tract defenses against extracellular microbes. Many extracellular bacteria possess polysaccharide capsules that allow them to evade phagocytic cells. Antibodies function as: (a) opsonins that allow phagocytes to recognize and ingest microbes via the involvement of Fc receptors; (b) activators of complement, which enhances opsonization and leads to direct lysis of some bacteria; and (c) as neutralizing antibodies that neutralize pathogens or their toxins by binding to microbes or their products, thereby preventing injury to cells. Immunoglobulins are clearly present in the epithelial lining fluid of the lower respiratory tract. Serum IgG can gain access to the alveolar space in normal subjects and during inflammation when large changes in alveolar permeability occur. Systemic immunization enhances pulmonary clearance of many bacteria in animal models and enhanced clearance correlates with the appearance of antibodies in serum and bronchoalveolar lavage fluid that are directed against the organisms. Thus, it seems likely that alveolar antibodies are derived in large part from serum and, accordingly, it seems likely that direct airway immunization would not be required to obtain protective antibodies in the lung.

CONCLUSION

Infections are the evolutionary force for the development of a complex system of pulmonary host defenses. A coordinated response of many different cells is required for the lung to clear pulmonary pathogens. An increasingly complex and potentially injurious cascade of host responses is mobilized following pulmonary microbial challenges (Table 121-1). Although the interactions of microbes in the host are invariably complex, models of pulmonary infection have provided crucial information regarding the regulation of inflammatory and immune responses. These insights should eventually allow the development of rational strategies regarding vaccination and immunotherapy. The use of animal models offers the possibility of understanding the mechanisms that regulate immune responses sufficiently well so that the response to a specific antigen could be controlled. A more complete understanding of host defense would allow the stimulation of deficient responses and the suppression of harmful responses to microbial pathogens and other antigens that enter the lung.

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CHAPTER 122

Approach to the Patient with Pulmonary Infection

Jay A. Fishman

OVERVIEW

Pneumonia is a common cause of infection-related mortality and is one of the most important challenges in clinical medicine. Inappropriate or delayed treatment of pulmonary infection contributes to poor clinical outcomes, avoidable drug exposures, and emergence of antimicrobial resistance. Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent. The clinical syndrome of pneumonia may include fever or hypothermia, sweats, rigors, or chills, pulmonary symptoms, such as cough, sputum production, dyspnea, pleurisy, or pulmonary lesions observed on radiographic examination. Nonspecific symptoms are common, including loss of appetite, fatigue, and confusion. The diagnosis and management of pneumonia has been complicated by the recognition of newer pathogens, expanded antimicrobial resistance, increased populations of immunocompromised patients, and by newer diagnostic tools and antimicrobial agents.

Pneumonitis reflects inflammation due to both infection and noninfectious causes. A variety of eponyms have been applied to various forms of pneumonia that *may* reflect the epidemiology of the process and the likely causative organisms: aspiration pneumonia, community-acquired pneumonia (CAP), nosocomial pneumonia, immunocompromised host, and atypical pneumonia (Table 122-1). These descriptions, coupled with the radiologic appearance and patient-specific epidemiologic factors, are useful in considering empiric therapy while awaiting microbiologic data. These categories may be misleading, emphasizing the importance of obtaining a definitive microbiologic diagnosis in optimizing clinical care (Table 122-2).

TABLE 122-1 Categorization of Pneumonia by Clinical Setting

Community-acquired pneumonia
Typical (i.e., classic) pneumonia
Atypical pneumonia
Aspiration pneumonia
Pneumonia in the elderly
Community acquired
Nursing home residents
Nosocomial pneumonia
Hospital-acquired pneumonia (HAP)
Ventilator-associated pneumonia (VAP)
Healthcare-associated pneumonia (HCAP)
Pneumonia in immunocompromised hosts
Immunoglobulin and complement deficiencies
Granulocyte dysfunction or deficiency (cyclic neutropenia, chronic granulomatous disease, leukocyte adhesion defects, myeloperoxidase, or G6PD deficiency)
Innate immune defects (NK deficiency, defects of interleukin/interferon-gamma pathways, pattern recognition receptor pathway defects)
Cellular and combined immune deficiencies
Neoplastic disease (notably hematopoietic malignancy and therapies)
Solid-organ and hematopoietic transplant recipients
Untreated HIV infection
Immune reconstitution syndromes (IRIS)
SCID and congenital deficiencies
Autoimmune and connective tissue disorders
Other immunocompromised patients
Cystic fibrosis and anatomic disorders (bronchopulmonary sequestration, tracheomalacia, or bronchomalacia)

TABLE 122-2 Routine Evaluation of Patients with Suspected Pneumonia

History
Age
Community (respiratory viruses, antimicrobial resistance) vs. hospital (ventilator)
Pace of onset, dyspnea
Recent infections (postviral pneumonia, endocarditis, aspiration)
Recent hospitalization or exposure to medical facilities (extended care)
Underlying conditions (mental status, immunity, cardiopulmonary, medications)
Exposures (illness, children, institutions, animals, gardens, travel)
Antimicrobial therapies, home infusion therapy, vaccinations
Duration of hospitalization or endotracheal intubation
Physical Examination
Laboratory
Complete blood count with differential counts
Electrolytes, liver function tests, BUN, creatinine
Radiology
PA and lateral chest radiograph (depending on host and severity of illness)
Consider: Chest CT with contrast, echocardiogram, thoracentesis
Microbiology *(adapted to clinical setting and severity of illness)*
Sputum Gram stain, culture, and sensitivity (susceptibility testing)
Nasal swab (direct immunofluorescence) for respiratory virus panel (influenza, RSV, parainfluenza, adenovirus, metapneumovirus)
Blood cultures two
Consider in appropriate setting:
• Pneumococcal urinary antigen
• Legionella urinary antigen
• Histoplasma urinary antigen
• Acid-fast smear (modified acid-fast smear) and culture
• Acute and convalescent sera (Mycoplasma, Chlamydophila, Q-fever [Coxiella burnetti], Histoplasma, Coccidioides, Tularemia, Anthrax)
• HIV status
• Molecular assays (Cytomegalovirus, Epstein–Barr virus, Adenovirus)

Consideration of any unique exposures and potential immune deficits in each host will define the urgency of empiric antimicrobial therapies. Physical findings may also be unreliable—particularly as reliance on radiologic techniques has displaced physical examination as an art form. Dual processes are common (e.g., superinfection of viral illness). Physical findings are often muted in the immunocompromised host. "Crackles" or "rales" are "appreciated" more often than the actual incidence of pulmonary consolidation. Commonly, radiographic appearances are "confused" with etiologic diagnoses: consolidation, bronchopneumonia, miliary patterns, nodules, abscesses, fluid collections, pleural effusions, interstitial pneumonitis, and lymphadenopathy. The goal of the clinician is to distinguish infectious from noninfectious processes, such as heart failure, malignancy, or pulmonary embolism; to initiate appropriate antimicrobial therapy quickly; and to define the microbiology of infectious pulmonary processes to facilitate management and reduce unnecessary exposures to antimicrobial agents.

THE ROLE OF HOST DEFENSES

The presence of pneumonia should be taken as evidence of an immune defect relative to the epidemiologic pressure of the microorganisms (see Chapter 121). Organisms of high native virulence (adhesion, invasive enzymes, motility, intracellular pathogens) may cause infection with a small inoculum size in an immunologically normal host (see Chapter 123). Organisms of low virulence should cause infection only if there is an immune or anatomic predisposition to infection or a high organism burden.[1] Microorganisms may reach the lungs via the airways, bloodstream, or lymphatics. Defects in specific components of the immune system (innate and acquired) predispose to specific types of infection (Table 122-3).

An important first step in many infections is colonization of the upper airway via adhesion of organisms to epithelial surfaces. These surfaces are normally protected by mechanical clearance of organisms via the nose or oropharynx, local production of complement and IgA, saliva, sloughing of epithelial cells, and bacterial interference by "normal flora." Changes in these surfaces (diminished IgA secretion, changes in production of adhesins, fibronectin, altered lectin binding) predispose to adhesion of microorganisms. Organisms carrying enzymes that can degrade IgA exotoxins, adhesion proteins or pili—are favored in colonizing the respiratory epithelium. Mucociliary clearance may be disrupted by cigarette

TABLE 122-3 Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia	Leukemia, cytotoxic chemotherapy, AIDS, drug toxicity, Felty syndrome	Enteric gram-negative, Pseudomonas, S. aureus, S. epidermidis, streptococci, Aspergillus, Candida, and other fungi
Neutrophil chemotaxis	Diabetes, alcoholism, uremia, Hodgkin disease, trauma (burns), lazy leukocyte syndrome, CT disease	S. aureus, Candida, streptococci
Neutrophil killing	CGD, myeloperoxidase deficiency	S. aureus, E. coli, Candida, Aspergillus, Torulopsis
T-cell defects	AIDS, congenital, lymphoma, sarcoidosis, viral infection, CT disease, organ transplants, steroids	Intracellular bacteria (Legionella Listeria, mycobacteria sp.), HSV, VZV, CMV, EBV, parasites (Strongyloides, Toxoplasma), fungi (P. jiroveci, Candida, Cryptococcus)
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, ALL	S. pneumoniae, H. influenzae, Salmonella and Campylobacter spp., Giardia lamblia
Splenectomy	Surgery, sickle-cell, cirrhosis	S. pneumoniae, H. influenzae, Salmonella spp, Capnocytophaga
Complement	Congenital/acquired defects	S. aureus, Neisseria spp. H. influenzae, S. pneumoniae
Anatomic	IV/Foley catheters, incisions, anastomotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

ALL, acute lymphocytic leukemia; CGD, chronic granulomatous disease; CT, connective tissue disease; IV, intravenous.

smoking, or prior infections with viruses, *Haemophilus influenzae*, or *Mycoplasma pneumoniae*.

Aspiration may result from altered glottic closure (neurologic injury, sleep apnea, airway intubation, alcohol, anesthesia). Once past the glottis, most bacteria and viruses are small enough (up to 2 μ) to reach the alveoli unless impeded by alveolar lining fluid containing surfactant, IgG, complement, and other proteins. Surfactant includes a variety of components that serve to activate alveolar macrophage and neutrophil functions and may serve as an opsonin (SP-A and SP-D) for many organism types. Organisms surviving the upper airway defenses are left to the cellular components of the lower airways including T- and B-lymphocytes, macrophages, and dendritic cells.

Pulmonary defense mechanisms are also disrupted by systemic infections (sepsis), hyperglycemia and diabetes, acidosis, hypoxemia, pulmonary edema, malnutrition, uremia, age, and lung injury (ARDS). Endotoxin and lipopolysaccharide diminish clearance of bacteria from the lungs. Viral infections may diminish neutrophil and macrophage functions including phagocytosis, chemotaxis, and oxidative metabolism.

GENERAL GUIDELINES IN EVALUATING PATIENTS WITH PNEUMONIA OR OTHER RESPIRATORY INFECTIONS

The individual with pulmonary infection often presents in an ambulatory setting. Evaluation of the patient with possible pneumonia depends on a series of questions that provide clues to management, including the need for hospitalization and selection of antimicrobial agents. Subsequently, microbiologic data provide the basis for adjusting antimicrobial therapy. These initial questions include:

1. **Is the process life-threatening?** What is the rate of progression of the process? Is it rapidly progressive or gradual? Is there time to delay therapy or diagnostic procedures?
2. **Does the patient have immune deficits?** Could the process be underestimated based on the absence of normal inflammatory responses (see Chapters 20 and 121)?
3. **What are the most common infections in the community or hospital or institution where this "infection" was acquired?** In this appraisal, it is helpful to resort to the clinical groupings: community-acquired, nosocomial (hospital, ventilator, healthcare facility), and pneumonia in the immunocompromised patient. Such groupings provide a guide to empiric therapy while evaluation is underway. It is important to understand the incidence of tuberculosis, AIDS, respiratory viral infections, and antimicrobial-resistant organisms (e.g., Pneumococcus or Staphylococcus) in the community and of antimicrobial resistance in the institution. Dual infections are common (e.g., viral plus bacterial) and initial therapy must include both common bacterial and "atypical" pathogens (i.e., Mycoplasma, Chlamydophila, and Legionella species).
4. **What are the gross radiologic features of the pulmonary process?** Frank pneumonia with or without sputum production, focal infiltrates, lung abscess, chronic cavitary lesion, bronchiectasis, miliary lesions? As a corollary, since pulmonary infections are occasionally generated by the hematogenous rather than the bronchogenic route, consider possible extrapulmonary processes in the pathogenesis of pulmonary infection.
5. **For ambulatory patients, does the patient need to be admitted to the hospital for management?**[2–5] Does the patient have social supports in the community? Can he/she manage oral medications, other therapies, and follow-up visits from home? Does the patient need supplemental oxygen, assisted ventilation, surgery, blood products, monitoring, or isolation?

Initial antimicrobial therapies should be considered to be therapeutic trials—given adequate time to demonstrate effectiveness and subject to revision if ineffective.

■ CLINICAL EVALUATION

The clinical history often suggests the etiology of pulmonary infection. A history of prior infections or underlying clinical conditions (COPD, immune deficits, altered mental status, prior infections) often provides the basis for empiric therapy.

Consider the *epidemiologic history* (i.e., travel, contacts, exposures, vaccines, medications, prior infections, or hospitalizations): Has the patient traveled or have any hobbies (gardening, hiking, cooking) that might provide an epidemiologic clue (see Table 122-4)?

What are the patient's *symptoms:* What is the pace of the evolution of respiratory symptoms and of other systemic signs? Prior mild respiratory illness ("the flu") with improvement and then rapid deterioration is suggestive of bacterial superinfection of viral pneumonitis consistent with *Staphylococcus aureus* or other bacterial infection, especially in the patient known to have respiratory colonization. Pneumococcal pneumonia may be associated with a single severe rigor with fever and often with symptomatic herpes labialis. The abrupt onset of illness with recurrent (over several days) shaking chills, particularly if associated with mild diarrhea for 1 or 2 days, might suggest Legionnaires' disease. Gastrointestinal symptoms and confusion may be seen with any infection, but are notable

TABLE 122-4 Epidemiologic Exposures Associated with Pneumonia

Pathogen	Epidemiology
Anthrax	Bioterrorism; animals, hides, raw wool, goat hair
Brucella sp.	Domestic animals, dairy products, abattoir, veterinarian
Chlamydophila psittaci	Birds: parrots, budgerigars, cockatoos, pigeons, turkeys
Coccidioidomycosis	Southwest USA, Southern California, San Joaquin Valley
Coxiella burnetii (Q-fever)	Goats, sheep, cattle, domestic animals (feces, amnionic fluid, placenta, milk)
Cryptococcus neoformans and grubii	Birds (pigeons), caves, bats
Cryptococcus gattii	Eucalyptus trees
Hantavirus	Rodent droppings/urine (virtually all states)
Histoplasmosis	Bird/bat droppings, endemic regions
Legionella	Contaminated aerosols, pooled water
Leptospirosis	Rodents, animals, water contaminated by animal urine
Melioidosis	West Indies, Australia, Southeast Asia, South Central America
Pasturella multocida	Dogs, cats
Plague *(Yersinia pestis)*	Bioterrorism, Squirrels, chipmunks, rabbits, prairie dogs, rats
Paracoccidioides	South America (Brazil)
Rhodococcus	Horses, soil, farms
Middle eastern respiratory syndrome (MERS): Coronavirus	Endemic regions (Saudi Arabia)

in pneumococcal and Legionnaires' infections. The differential is broader in immunocompromised hosts with pulmonary-brain (*Nocardia* species, moulds) or GI-brain *(Strongyloides)* syndromes.

Skin lesions (e.g., furuncles, endocarditis, or gram-negative sepsis), lymph nodes (symmetrical or regional), retinal examination, ear examination (bullous myringitis with *Mycoplasma* infection), periodontal disease or absent gag reflexes (with aspiration pneumonia), chest splinting, neurologic disease (pulmonary-brain syndromes) are often ignored but provide valuable clues. The elderly patient with pneumonia will often present with globally depressed mental status while the immunocompromised host may have focal neurologic deficits consistent with embolic or invasive disease. Dullness to percussion, bronchial breath sounds, egophony ("E to A changes") are suggestive of pulmonary consolidation but may be absent. Patients infected with *Pneumocystis jiroveci*, *Mycoplasma*, or viruses (or severe immune compromise) may have a normal chest examination despite abnormal chest radiographs and marked hypoxemia.

Many systemic processes are reflected in abnormalities of blood counts, urinalysis, and routine blood chemistries. Most patients with bacterial pneumonia will have elevated white blood cell counts and increased neutrophils on differential. Viral pneumonia may depress the white cell count. Mixed pictures are common. Mild liver function abnormalities might suggest Q-fever, tularemia, miliary tuberculosis, or Legionnaires' disease, but are commonly seen with systemic infection. The presence of pigmented casts in the urine and markedly elevated serum levels of creatine phosphokinase might focus attention on the possibilities of influenza virus pneumonia, Legionnaires' disease, or a pulmonary infiltrate associated with intravenous drug abuse. Rapid screening tests (e.g., for respiratory viruses) are useful, but have limitations in terms of sensitivity.

Clinical measures detect pneumonia in about 79% of cases. Newer assays have been introduced, including measurements of serum procalcitonin (PCT) and C-reactive protein (hsCRP) levels.[6] In prospective trials, PCT appears to be sensitive both to the presence and severity of pneumonia and to concomitant bacteremia associated with pneumonia.[7] These assays may augment clinical judgment, but are not universally available.

Radiographs allow the practitioner to assess the severity of pneumonia and to distinguish this process form acute bronchitis, which, when infectious, is often viral in etiology (see Chapter 30). No radiographic findings are specific enough to define the microbial origin of a given pneumonia or pulmonary infiltrate. The only definitive way to obtain a specific etiologic diagnosis is through demonstration of the infecting organism—that is, by examination of stained smears of sputum and pleural fluid or other biologic materials, by culture of respiratory secretions and blood, or by demonstration of nucleic acids or proteins from an infecting microorganism, or by demonstrating an increase in antibody titer against the infecting microorganism. Nonetheless, the radiographic picture, taken along with other clinical information, may suggest one or several etiologic agents (see below). Multilobar involvement and the presence of pulmonary effusions are poor prognostic features.

In practice, initial therapy is empiric and based primarily on available clinical clues. The selection of drug(s) for empiric therapy depends on the clinical setting and on the gravity of the pulmonary process. The selection of specific antimicrobial agents is considered in detail in subsequent chapters.

In addition to the decision regarding empiric antibiotics, a key decision in management is whether the patient with suspected pneumonia merits hospitalization (see Chapter 128). In practice, this is often a function of a judgment as to whether appropriate therapy is available in the community with social supports adequate to caring for the patient's needs (medications, food, comfort) and to bring the patient back for further care if indicated. Multiple semiquantitative methods have been developed to assist in this process.[8]

The Pneumonia Severity Index (PSI) developed by Fine et al. stratifies patients according to 20 variables and has greater discriminatory power for mortality than the less complex CURB indices.[9,10] The "confusion of new onset, urea greater than 7 mmol/L (19 mg/dL), respiratory rate of 30 breaths per minute or greater, and blood pressure less than 90 mm Hg systolic or diastolic blood pressure 60 mm Hg or less with age 65 or older (CURB 65) rely on fewer variables to identify patients at high risk of mortality.[10] With one point per variable, risk of death at 30 days increases as the score increases (four points predicts 41.5% hospital mortality).[8] Hospital admission is generally advised for those with CURB 65 of two to three points, and ICU admission considered for four to five points.

The Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) Guidelines for Severe Pneumonia and Intensive Care Unit Admission identify the sickest patients, who may ultimately require ventilatory support. The Guidelines can be found online at http://pda.ahrq.gov/clinic/psi/psi.htm and www.mdcalc.com/psi-port-score-pneumonia-severity-index-adult-cap.

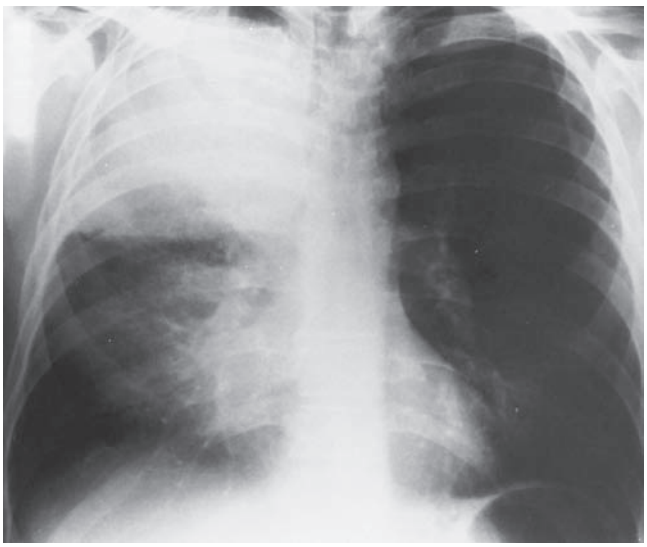
RADIOGRAPHIC FEATURES OF PNEUMONIA

No radiologic pattern provides a specific etiologic diagnosis (see also Chapter 30). However, the radiographic pattern, combined with clinical and epidemiologic information, may allow narrowing of the diagnostic considerations while microbiologic data are assembled. Several radiographic patterns may be helpful in categorizing infectious and noninfectious causes: (1) airspace or alveolar pneumonia, (2) broncho- or lobular pneumonia (Fig. 122-1), (3) interstitial pneumonia, and (4) nodular infiltrates. The chest radiographs of a particular patient may not fit neatly into one or another of these categories. Multiple patterns may suggest different etiologies or progression of a disease process. These patterns are generally best defined by CT scanning, which may also detect patterns within a pulmonary process, including lung necrosis; bronchial obstruction (e.g., due to hilar lymphadenopathy or endobronchial tumor); underlying parenchymal disease accounting for pleural effusion, empyema, or loculated fluid collections; bronchiectasis; or fungus balls within cavitary lesions. Subtle changes, including interstitial patterns or infections in immunocompromised hosts (e.g., *P. jiroveci*), are often better assessed using CT scanning. CT scanning can also assist in determining the best invasive diagnostic approach (needle, BAL, open biopsy) for diagnostic procedures.

PERIPHERAL AIRSPACE CONSOLIDATION: ALVEOLAR AND LOBAR PNEUMONIA

This form of infiltrate occurs when certain organisms, notably *Streptococcus pneumoniae*, induce inflammatory edema in peripheral alveoli. When the extent of the consolidation involves an entire lobe, this is the classic *lobar pneumonia*. Often the process is not that extensive, although the pathogenesis is the same. An air bronchogram is characteristic. Loss of volume is absent or minimal during the acute stage of consolidation, but some atelectasis may develop due to obstruction of bronchi by exudate.

Klebsiella pneumoniae is another common cause of CAP, which, like pneumococcal pneumonia, shows homogeneous parenchymal consolidation containing air bronchograms. Although *K. pneumoniae* pneumonia classically affects the right upper lobe and



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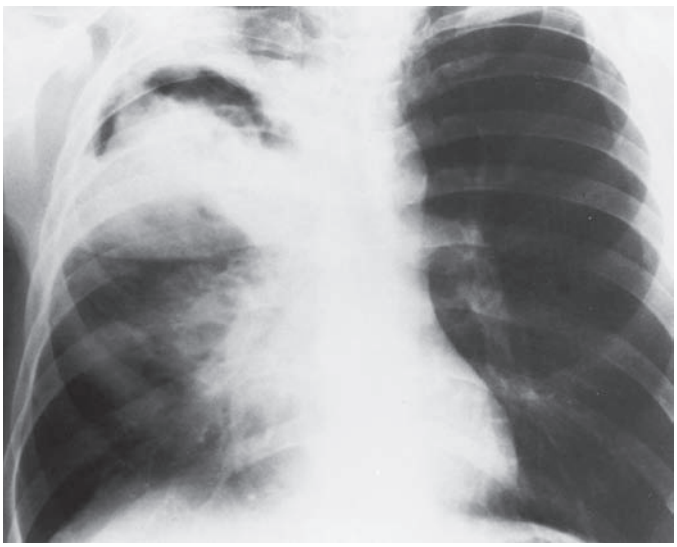

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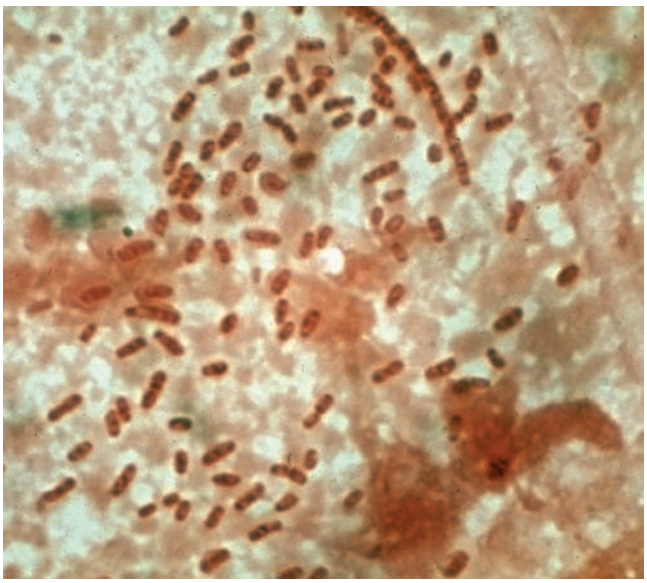

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Figure 122-1 **A.** Dense lobar consolidation involving right upper lobe and right middle lobe in an alcoholic patient with *Klebsiella pneumoniae* pneumonia. The minor fissure is bulging downward. **B.** Same patient 7 days later. Despite antibiotic therapy, *K. pneumoniae* pneumonia progressed to become a necrotic process with formation of multiple abscesses. **C.** Sputum Gram stain from patient with K. pneumoniae infection reveals gram-negative rod forms with trace of a surrounding capsule. *(Used with permission of Dr. R. Greene.)*

produces a dense, homogeneous lobar consolidation with bulging of the fissure, these features are not pathognomonic and cannot be relied on for diagnosis without supportive bacteriologic data (Fig. 122-1). The propensity for *K. pneumoniae* to produce tissue destruction and abscess formation may result in a shrunken, rather than an expanded, lobe. Pneumococcal pneumonia may also cause bulging of the fissure, albeit less commonly and less prominently. Extensive alveolar consolidation may occur with a variety of other bacterial causes of pneumonia, including mixed anaerobes of aspiration pneumonia and a variety of gram-negative bacilli implicated in nosocomial pneumonias. Occasionally, an unusual configuration of airspace consolidation, *spherical pneumonia*, occurs, particularly in children, with pneumococcal or *H. influenzae* pneumonia. It has also been reported with Q-fever (*Coxiella burnetti*).

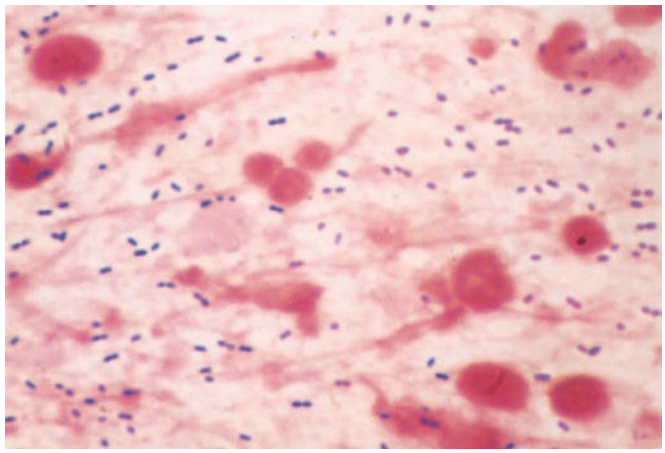
In the immunocompromised host, alveolar consolidation on the plain chest radiograph may be delayed and appreciated only by chest CT scan. Among infectious etiologies, common pathogens, such as *S. pneumoniae,* cause infection in this group of patients and are often of greater severity than in the normal host, often despite less radiologic evidence for infection. Bacterial superinfection of viral processes (e.g., influenza, cytomegalovirus [CMV]) is also common. However, if the consolidation is lobar or multilobar, *Legionella pneumophila* and *M. pneumoniae* are common. Other, less likely, infectious agents are fungi (e.g., *Aspergillus*), *Nocardia*, and *Mycobacterium tuberculosis*. Less often, viruses alone (e.g., CMV) elicit a predominantly alveolar pattern. Bilateral diffuse involvement with an airspace pattern resembling pulmonary edema is uncommonly seen in *P. jiroveci* pneumonia, but may also reflect noninfectious etiologies.

CENTRILOBULAR AND PERIBRONCHIOLAR OPACITIES: BRONCHOPNEUMONIA

In bronchopneumonia, the focus of infection and the inflammatory response is in the walls of the bronchi and surrounding peribronchiolar alveoli, producing a segmental, patchy multifocal distribution. Segmental involvement may become confluent to produce a more homogeneous pattern. Bronchopneumonic patterns are commonly observed in pulmonary infections due to *S. aureus* or nonencapsulated *H. influenzae*. With *S. aureus* infections, macro- and microabscess formation may occur rapidly. Also, pneumatoceles occur during the first week of lung impairment in about half the children with *S. aureus* pneumonia. These cystic spaces are believed to be the consequence of a check valve opening between a peribronchial abscess and an adjacent bronchus.

A bronchopneumonic pattern of consolidation is commonly observed when CAP follows viral infection or pneumonia is engrafted on underlying bronchiectasis or chronic bronchitis. In such predisposing circumstances, *S. pneumoniae* infection may produce a bronchopneumonic pattern rather than a lobar consolidation (Fig. 122-2). In the presence of underlying emphysema, the radiographic pattern of pneumococcal pneumonia may also be altered from its usual homogeneous pattern to one that contains multiple radiolucencies (representing unconsolidated emphysematous areas) that may be misinterpreted for abscesses.

Segmental bronchopneumonia is the radiographic picture in pneumonia due to *Chlamydophila pneumoniae* (Taiwan acute respiratory agent or TWAR), *M. pneumoniae,* and in many viral pneumonias. Any of the bacterial species that cause nosocomial pneumonia may produce a radiographic pattern of bronchopneumonic consolidation.



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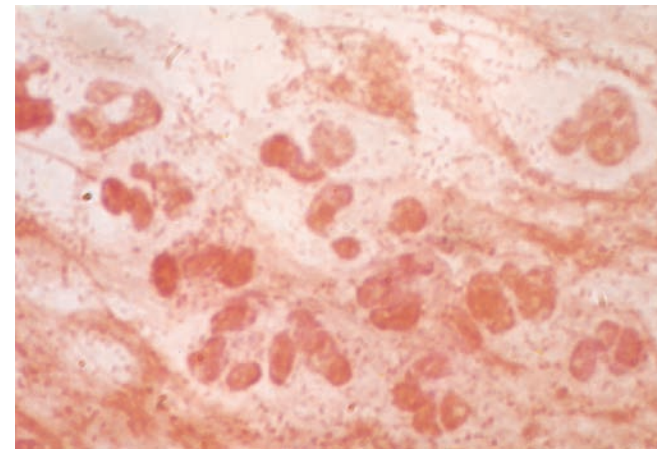

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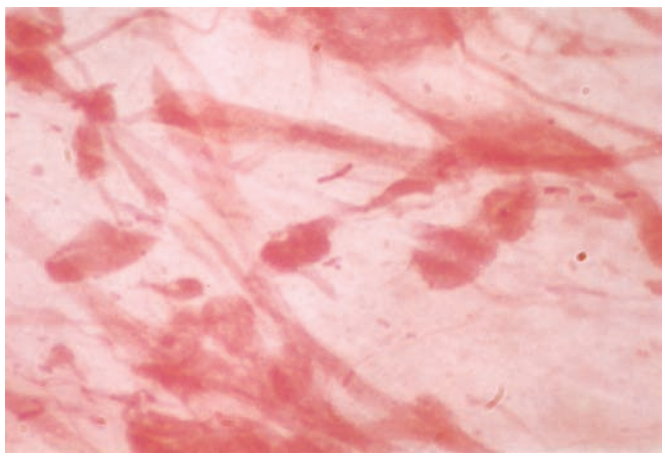

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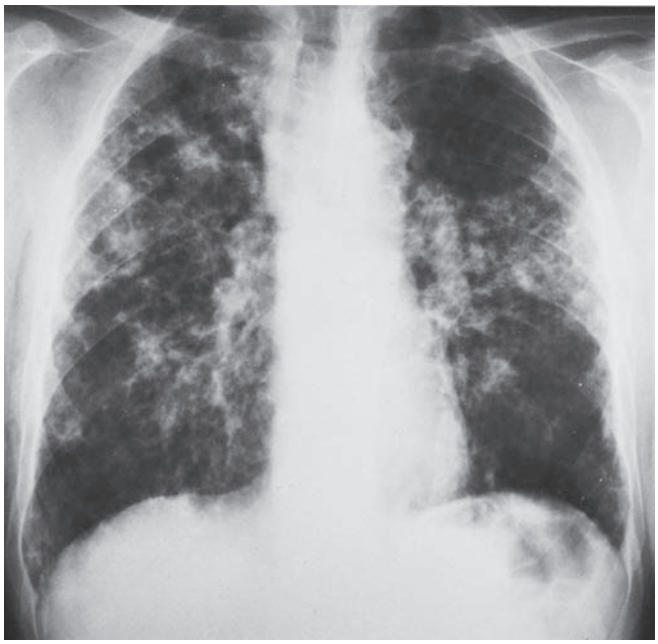
Figure 122-2 **A.** Gram-stained smear of sputum from patient with pneumococcal lobar pneumonia ×1000. In this field there are numerous gram-positive lancet-shaped diplococci and polymorphonuclear leukocytes. **B.** Gram-stained smear of sputum from patient with bronchopneumonia superimposed on chronic bronchitis. This field (×1000) is teeming with gram-negative coccobacilli. Many polymorphonuclear leukocytes are present. *H. influenzae* was isolated from sputum as predominant organism. **C.** Gram-stained smear of sputum from patient with lobar pneumonia due to *K. pneumoniae*. In this field (×1000) there are moderate numbers of polymorphonuclear leukocytes and large, thick gram-negative bacilli. *(Used with permission of H. Provine.)*

Noninfectious etiologies of bronchopneumonia include aspiration of gastric contents, bronchioloalveolar cell carcinoma, granulomatous disease in pneumoconiosis, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), autoimmune diseases, and bronchiolitis obliterans.

■ INTERSTITIAL PNEUMONIA (PERIBRONCHOVASCULAR INFILTRATE)

A reticular or reticulonodular pattern of infiltration is the radiographic representation of interstitial inflammation—that is, a peribronchovascular infiltrate. In otherwise healthy persons, *M. pneumoniae* is high on the list of community-acquired causes of a radiographic pattern of interstitial pneumonia. In some instances, interstitial infiltration progresses to produce patchy consolidation of airspaces, most often in the lower lobes. Pneumonias due to respiratory viruses sometimes have an interstitial pattern that progresses to patchy segmental consolidation or to diffuse airspace disease that resembles pulmonary edema. A variety of noninfectious causes of interstitial lung disease (e.g., hypersensitivity lung disease, collagen vascular disease, and sarcoidosis) may also produce a reticular pattern on the chest radiograph (Fig. 122-3).



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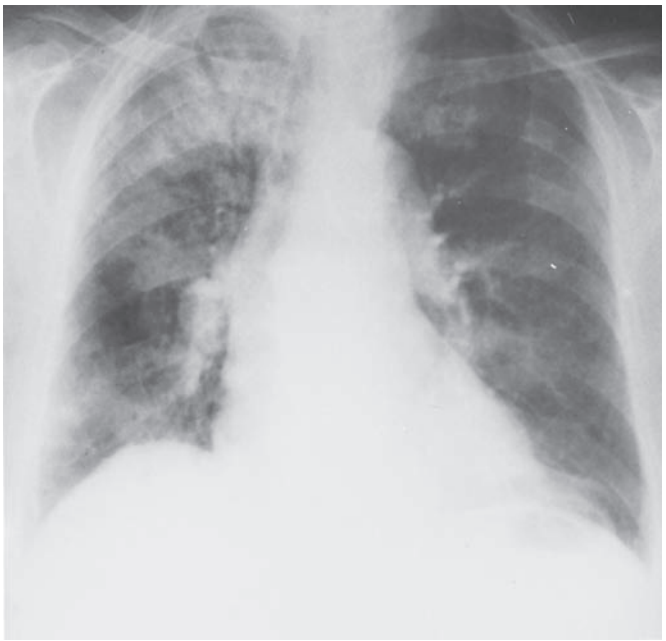

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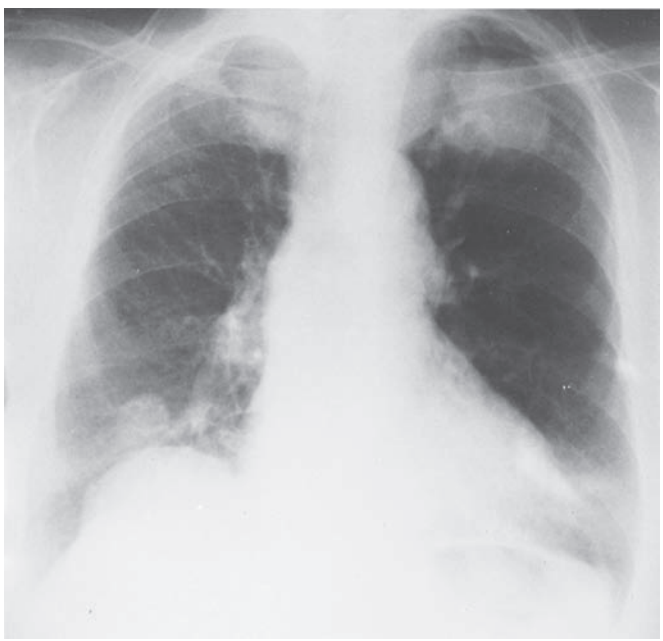

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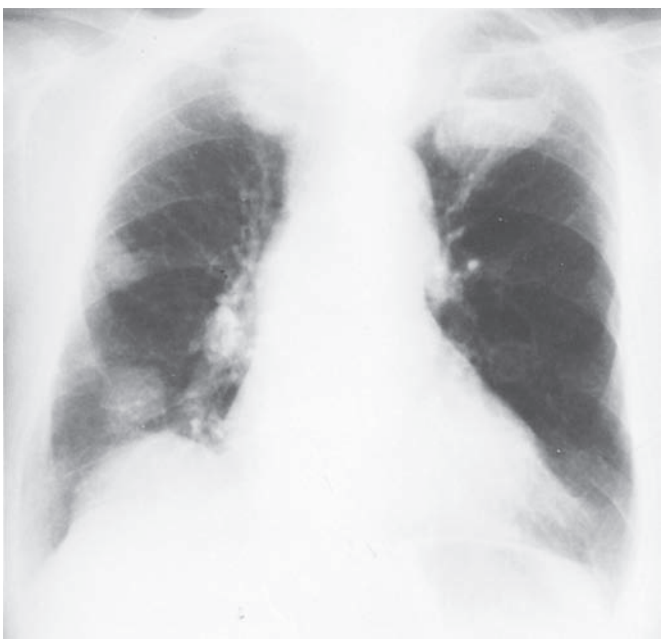

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Figure 122-3 Wegener granulomatosis. **A.** Onset with chills and fever in a previously healthy 64-year-old man. Lung biopsy was interpreted as Wegener granulomatosis. Partial clearing in response to combined chemotherapy (cyclophosphamide and prednisone). **B.** Onset with malaise, headaches, and fever in a previously healthy 62-year-old woman. Bilateral maxillary sinusitis. Widespread nodular pulmonary infiltrates are most marked on the right. **C.** Same patient as **B** after 3 years of intermittent combined chemotherapy. Bilateral large masses. **D.** Same patient as **C**, 2 months later. Necrosis within mass in left upper lobe has produced a fluid level.

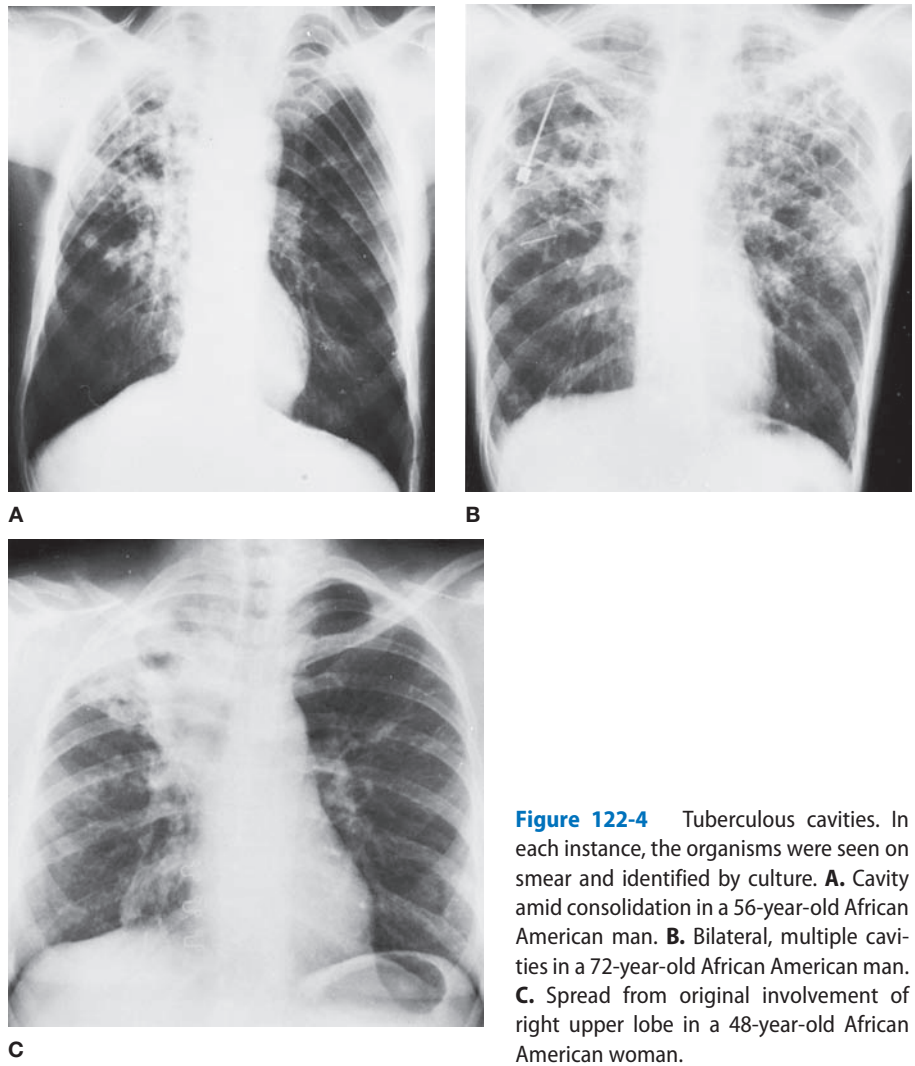

Figure 122-4 Tuberculous cavities. In each instance, the organisms were seen on smear and identified by culture. **A.** Cavity amid consolidation in a 56-year-old African American man. **B.** Bilateral, multiple cavities in a 72-year-old African American man. **C.** Spread from original involvement of right upper lobe in a 48-year-old African American woman.

In immunocompromised patients, particularly in those with AIDS in the absence of effective antiviral therapy, the infectious causes of interstitial pneumonia are broadened to include *P. jiroveci* pneumonia and opportunistic viral agents (e.g., CMV, varicella-zoster, herpes simplex). Noninfectious causes of a reticular pattern on chest radiography in an immunocompromised host include drug-induced (e.g., bleomycin, methotrexate, or sirolimus) pneumonitis, early radiation pneumonitis, and pulmonary edema.

NODULAR INFILTRATES: ROUND PNEUMONIA

Nodular infiltrates are considered here as well-defined large (greater than 1 cm on the chest radiograph) round focal lesions. Such a lesion may represent small aspirational abscesses (without air–fluid levels), a fungal or tuberculous granuloma, or a lesion of pulmonary nocardiosis. Multiple nodular infiltrates may also represent the necrotic lesions that develop in the lung secondary to the septic vasculitis produced by staphylococcal or pseudomonal bacteremia or the consequences of fungemic spread of candidal infection from an infected intravascular catheter. Infected nodular pulmonary lesions are sometimes caused by septic pulmonary infarcts produced by infected emboli that originate from right-sided bacterial endocarditis, septic thrombophlebitis of pelvic veins, or septic jugular vein phlebitis. On rare occasions, similar nodular lesions are produced by necrotic (but not infected) pulmonary infarctions; primary or metastatic neoplastic lesions may have a similar appearance. Nodular lesions that undergo rapid necrosis with cavity formation can be a feature of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) (Fig. 122-4).

In the immunocompromised patient, nodular infiltrates may be due to bacteremic or fungemic spread of infection, most often as a result of nosocomial infection caused by an infected intravenous catheter. In this type of patient, nodular lesions should bring to mind the possibilities of pulmonary nocardial infection, aspergillosis, or other fungal infections. Tuberculous granulomas in the lungs may develop or enlarge in the immunosuppressed patient. Metastatic neoplasm or lymphoma sometimes presents a similar radiologic picture. Multiple small nodules, larger than miliary lesions but smaller than the gross nodular lesions described above, raise the possibility of varicella-zoster or CMV infection of the lung.

MILIARY AND MICRONODULAR PULMONARY DISEASE

Disseminated miliary lesions of infectious nature suggest tuberculosis, nontuberculous mycobacteria, and endemic fungi (histoplasmosis, or blastomycosis) in either the normal or immunosuppressed host. In the immunosuppressed patient, a miliary pattern may also be seen in disseminated cryptococcal infection or bacteremic spread of bacterial or candidal infection (Figs. 122-5 and 122-6).

APPLICATION OF RADIOGRAPHIC TECHNIQUES TO THE CLINICAL DIAGNOSIS OF PNEUMONIA

A consistent approach to the incorporation of radiographic imaging in evaluating a patient with suspected pneumonia is helpful.

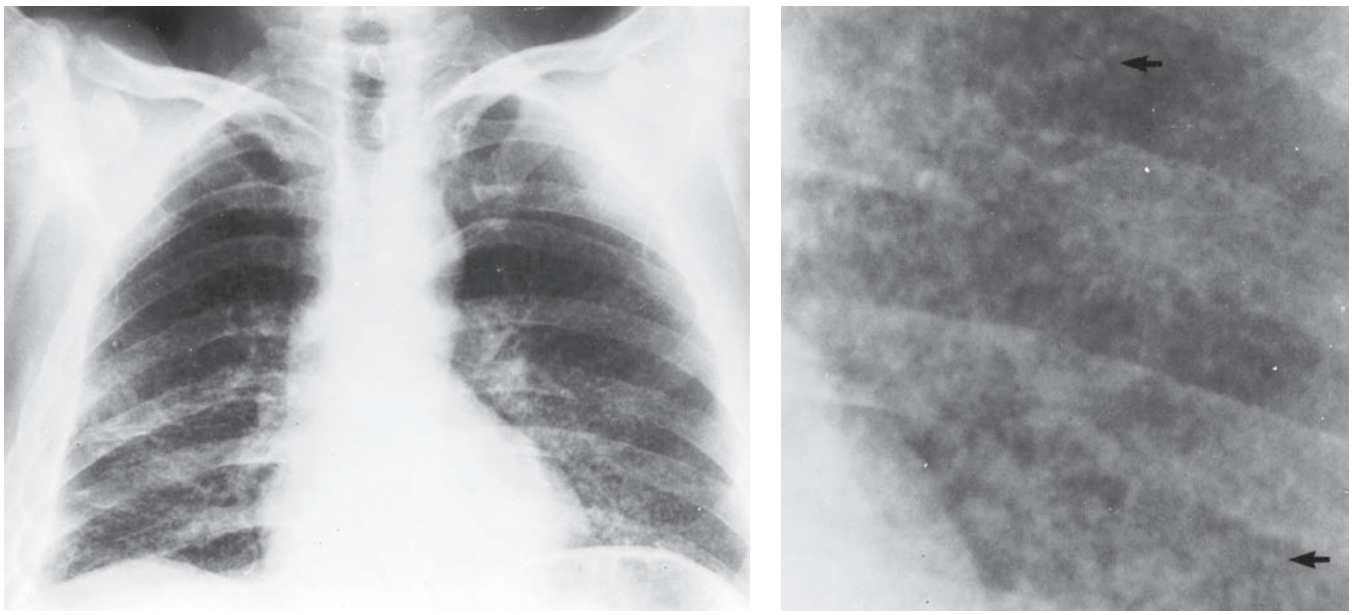

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Figure 122-5 Miliary tuberculosis in a 45-year-old immigrant from Portugal with old calcified tuberculous empyema on the right. **A.** Fine nodularity present in both lungs. **B.** *Arrows* point to individual miliary lesions, which are more readily visible with added magnification. *(Used with permission of Dr. R. Greene.)*

One such approach incorporates the following four steps: (1) *Define the radiographic pattern* as lobar (Fig. 122-1) or segmental consolidation, patchy bronchopneumonia, nodules (large, small, or military) (Fig. 122-5), or an interstitial process (Table 122-5). Many large round pulmonary densities in a renal transplant recipient suggest *Nocardia* infection, rather than *Pneumocystis* pneumonia, whereas in a heroin addict with cough, fever, and pleuritic chest pain, such densities suggest acute right-sided endocarditis rather than pneumococcal pneumonia. (2) *Compare the radiograph with prior studies:* Is the process old or new? Are there multiple processes? Has the patient had surgery in the intervening period? Is the spleen enlarged or absent? (3) Consider *confounding*

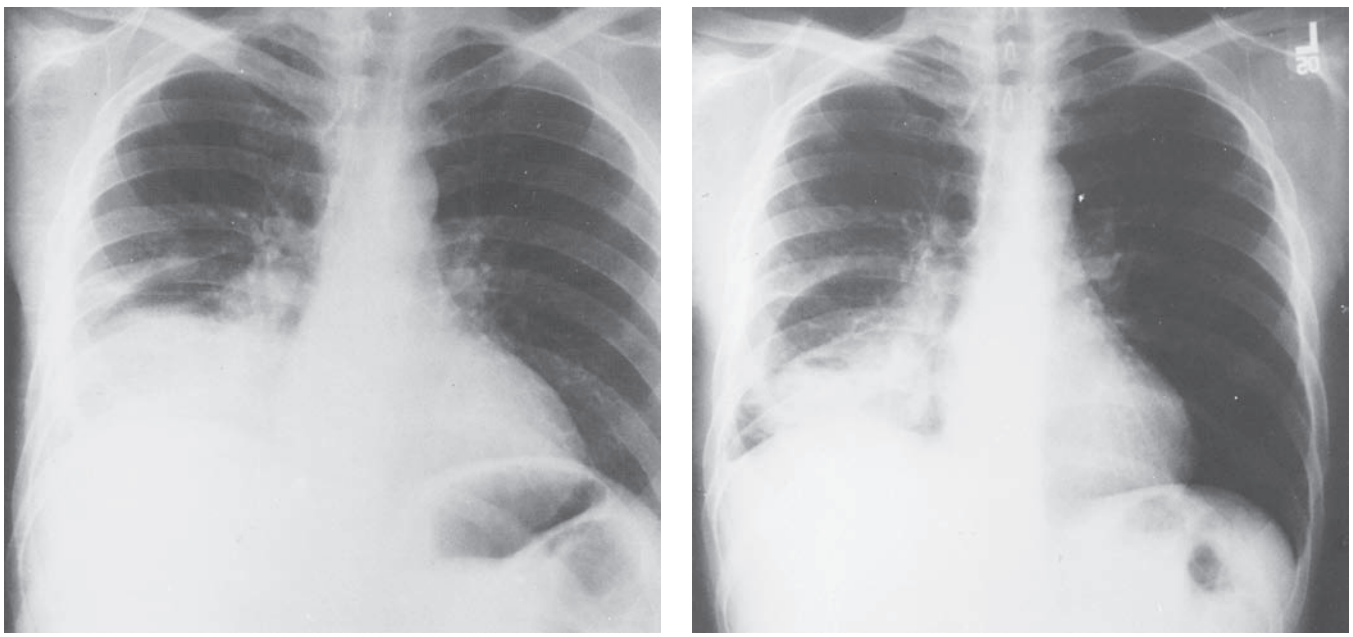

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Figure 122-6 Necrotizing pneumonia, probably secondary to aspiration in a 39-year-old man, smoker and drinker, previously healthy. Onset with cough, shortness of breath, fever, and right-sided pleuritic pain. Despite antibiotics, signs and symptoms progressed to include high fevers, night sweats, greenish sputum, leukocytosis, and manifestations of hypertrophic osteoarthropathy. **A.** On admission, there was consolidation of right lower lobe, a right hilar mass (or adenopathy), and right pleural effusion. Mediastinoscopy and bronchoscopy revealed no tumor. **B.** Three months later, the process in the right lower lobe is more circumscribed. Right lower lobectomy revealed extensive necrotizing pneumonia, multiple abscesses, and "reactive" lymph nodes. Postoperatively, the patient was free of signs and symptoms, including hypertrophic osteoarthropathy.

TABLE 122-5 Radiographic Features and Differential Diagnosis of Pneumonia in the Immunocompetent Host

Consolidation/focal opacity	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, Legionella species, *Staphylococcus aureus*, *Mycobacterium tuberculosis* and "atypical" Mycobacteria (*M. avium* complex)
Cavitation	*S. aureus, anaerobic bacteria, M. tuberculosis, gram-negative aerobic bacteria, Aspergillus species, geographic/endemic fungi (Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis)*
Interstitial infiltrates	*Viruses, M. pneumoniae, M. tuberculosis, geographic/endemic fungi, Chlamydophila psittaci, drug*
Miliary	*Mycobacterium tuberculosis, geographic/endemic fungi, viruses, M. pneumoniae*
Lymphadenopathy	*M. tuberculosis, Viral (EBV, CMV, rubella), geographic/endemic fungi, Chlamydophila psittaci, cat-scratch*

variables: Is it too early in the process to detect radiologic changes (first 18–24 hours)? Is the patient neutropenic (early viral or fungal pneumonitis) or otherwise immunocompromised (*P. jiroveci* pneumonia with minimal or no findings on plain chest radiographs)? Dehydration is commonly cited as a cause of false-negative chest radiographs—but, in general, this concept is probably over-rated. (4) Consider *CT scanning:* CT scanning is sensitive to changes unrecognized in plain radiographs and may be useful in guiding invasive procedures.

EXAMINATION OF CLINICAL SPECIMENS AND ESTABLISHMENT OF A MICROBIOLOGIC DIAGNOSIS

The traditional approach to pneumonia places great emphasis on establishing a specific microbiologic diagnosis for pneumonia. An appropriately stained smear of sputum or pleural fluid, bronchoalveolar lavage (BAL) fluids, blood buffy coat, skin lesions, or throat swabs *may* provide a provisional diagnosis and allow deployment of more targeted antimicrobial therapy. This is discussed in detail below. Examination of sputum samples should not delay treatment.

Guidelines of the IDSA/ATS require administration of antimicrobials within 6 hours of presentation, notably for elderly, critically ill, and immunocompromised individuals.[11] However, in practice, the yield of most microbiologic evaluations is poor and the outcomes of therapy for pneumonia not requiring hospitalization quite good.[12]

Bartlett has observed that sequential clinical series appear to demonstrate a gradual reduction in the frequency with which the Pneumococcus is identified as the etiologic agent of CAP. The prevalence of *S. pneumoniae* in clinical studies from North America (20%–60%) and Great Britain (60%–75%) and in 4416 patients by Bullowa et al. in 1937 (81%) have gradually dropped to 5% to 12% in more recent studies. In more recent studies, the Pneumococcus has been replaced by viruses, aspiration, and a broad array of bacteria. This observation likely reflects the identification of organisms not identified in early studies by advanced techniques, a reduction in the detection of the Pneumococcus due to successful empiric therapy, shifts in "community flora" by antimicrobial therapies, as well as reduced efforts to obtain a microbiologic diagnosis.

In practice, most patients with pneumonia are treated empirically. In the United States, the performance and interpretation of Gram stain analyses is restricted to licensed laboratory technicians (CLIA88), which makes more difficult the rapid analysis of clinical specimens. The availability of rapid culture–independent microbiologic assays for viral respiratory infections and for some common pathogens (e.g., antigen detection for pneumococcal or *Legionella* infections, rapid viral screens) has, to some extent, reduced the need for other modalities of diagnosis.[13] Further, the availability of an etiologic diagnosis in CAP may not reduce mortality or the length of hospitalization in normal hosts, likely a reflection of improved antimicrobial therapies.[14,15] Thus, for community-acquired infection, etiologic diagnosis is often reserved for the sickest patients requiring hospitalization.

Multiple factors may mitigate an effort to obtain an etiologic diagnosis for pneumonia: increasing antimicrobial resistance in the community and in hospitals with the availability of in vitro susceptibility testing; a growing population of immunocompromised hosts in whom appropriate therapy is essential; for the adjustment of therapy when initial therapy fails; to establish the epidemiology of infection (public health); and to support antimicrobial stewardship programs.

SPECIMEN QUALITY

A microorganism isolated from deep coughed sputum cultures obtained before the initiation of antimicrobial therapy is considered relevant if detected in respiratory specimens, blood, or both, excluding normal skin or mucosal flora and the specimen is of good quality, that is, >25 leukocytes and <10 epithelial cells per high-power field. Specimens should be plated for cultures within 2 hours or stored at 4°C until plated. In practice, many patients with pneumonia (~30%) cannot produce good sputum samples, many have had prior therapies that alter the success of microbial cultures (15%–30%), and 40% to 60% of cultures are negative.[16–19] A specific etiology can be established in less than 50% of cases using routine studies (sputum and serologies). Sputum induction using inhaled nonbacteriostatic saline mist and chest percussion may increase the yield for Pneumocystis, mycobacteria, and malignancy on cytologic examination.

MICROBIOLOGIC TESTING

Noninvasive studies may provide information indicating the specific microbial cause of a pulmonary infection or may narrow the field of likely etiologic agents.

The Gram Stain and Point-of-Care Testing

Gram-stained smears provide information not only regarding the morphology and the tinctorial properties of bacteria (and some fungi) but also about the presence of polymorphonuclear leukocytes and squamous epithelial cells, the latter indicating that the specimen originated in the upper, rather than the lower, respiratory tract (Fig. 122-7). Other special staining methods provide additional data including Kinyoun and modified acid-fast stains for mycobacteria, *Actinomyces*, or *Nocardia* species, Wright–Giemsa or a variant such as Diff-Quik or direct fluorescent antibody staining of induced sputum samples for *P. jiroveci* or *Legionella species* may provide a diagnosis. Calcoflour white and silver stains are available to stain filamentous moulds.

Culture of sputum or blood or other bodily fluids may provide a specific etiologic diagnosis when evaluation of a sputum smear

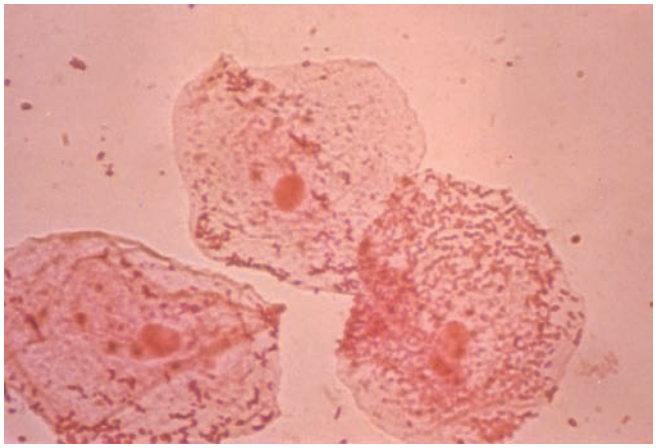


Figure 122-7 Three large oropharyngeal epithelial cells from a specimen of "sputum" that is inadequate for Gram stain analysis and culture because of its origin in the upper respiratory tract. Note the large number of organisms agglutinated on the surface of the squamous epithelial cells (×400).

have not supplied a provisional diagnosis, either because the infecting agent cannot be distinguished from components of the normal upper respiratory tract flora incorporated in the specimen or because the particular microorganism is not visible on Gram-stained smear (e.g., *Aspergillus, Mycobacterium, Mycoplasma,* or *Legionella* species).

Cytologic Examination

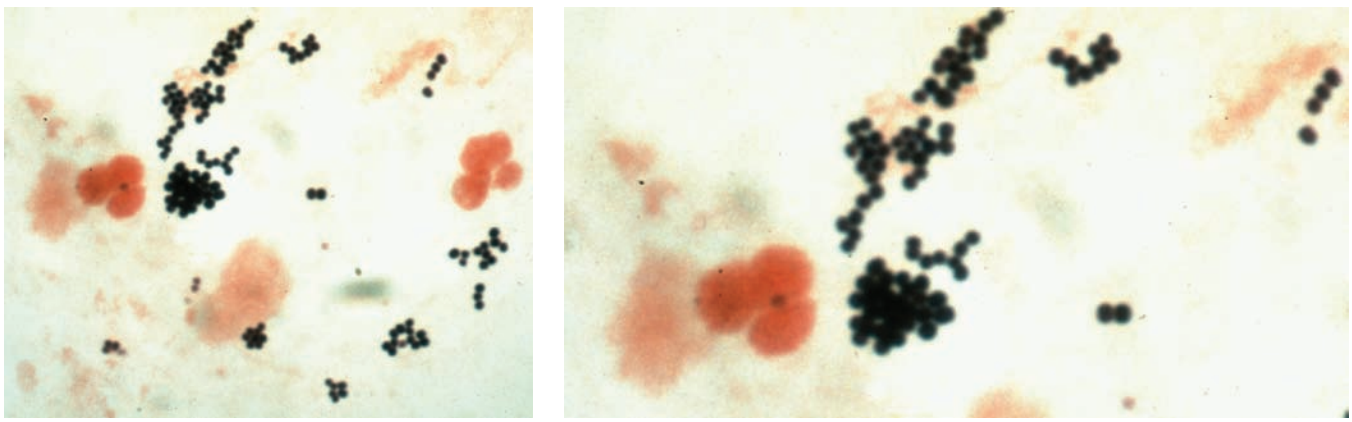
Examination of Gram-stained sputum smears can be of major value in pinpointing a bacterial cause of pneumonia and guiding initial and subsequent therapy. In practice, therapy is generally initiated prior to the availability of sputum examination. The quality of samples of expectorated or induced sputum for culture and interpretation stained smears can be determined by cytologic examination. Ten or more squamous epithelial cells (normally exfoliated from the oropharynx) per low-power (×100) magnification field indicate that the specimen is unsatisfactory; culture of such a specimen correlates poorly with results from culture of a transtracheal aspirate (Fig. 122-7). The presence of numerous polymorphonuclear neutrophils on Gram-stained smear (10–25 or more per low-power microscopic field) in the absence of an excessive number of squamous cells (see above) is indicative of a good specimen for bacteriologic evaluation.

Examination of Gram-Stained Smears for Bacteria

The oil immersion fields examined, and the immediately adjacent fields should not contain any squamous cells; each should also contain at least three or four neutrophils (in nonneutropenic hosts). The presence of squamous cells not only indicates that the specimen is derived from the upper respiratory tract but also may be confusing to the uninitiated because of the large number of bacteria, often gram-positive diplococci, which might be mistaken for *S. pneumoniae*, adherent to the surface of these cells.

Multiple bacterial respiratory tract pathogens have characteristic morphologies and strongly suggest an etiologic role when present in a suitable respiratory specimen containing inflammatory cells (in the absence of neutropenia). However, many common organisms are not visualized on stained smears. Such organisms include *S. pneumoniae* (gram-positive oval or lancet-shaped diplococci), *H. influenzae* (small, pleomorphic gram-negative bacilli), *M. catarrhalis* (gram-negative, biscuit-shaped diplococci), or the similar-appearing *Neisseria meningitis*, enteric gram-negative bacilli (not distinguishable from one another with respect to species except for large encapsulated rods that are suggestive of *Klebsiella*), and *S. aureus* (large gram-positive cocci in small groups or clusters) (Fig. 122-8). Since normal oral flora includes a variety of streptococcal species that are morphologically somewhat similar to *S. pneumoniae*, sputum smears may be misinterpreted. Thus, a predominance of gram-positive diplococci in multiple appropriate oil immersion fields needs to be observed to implicate *S. pneumoniae* (Fig. 122-9).[19] A quantitative aspect to the evaluation has been suggested: at least 10 gram-positive lancet-shaped diplococci per oil immersion field predicts the isolation of *S. pneumoniae* from sputum cultures with specificity of 85% and sensitivity of 62%.

Gram-stained smears may be helpful not only in the etiologic diagnosis of community-acquired bacterial pneumonia due to the usual respiratory pathogens, but also in supporting a diagnosis of atypical pneumonia when sputum examinations repeatedly show neither neutrophils nor bacteria. Uncommon bacterial species may be implicated in a pulmonary infection on the basis of unusual morphology on Gram-stained smear: irregularly staining, beaded, delicate gram-positive branching filaments suggest either *Nocardia*



A B

Figure 122-8 **A.** Left upper lobe pneumonia in a 17-year-old girl due to *S. aureus* that has progressed to formation of a huge lung abscess. Note air–fluid level. *(Used with permission of Dr. R. Greene.)* **B.** *S. aureus* on Gram-stained smear from a drug addict with right-sided bacterial endocarditis. In this field (×1000) there are polymorphonuclear leukocytes and clusters of gram-positive cocci. *(Used with permission of H. Provine.)*

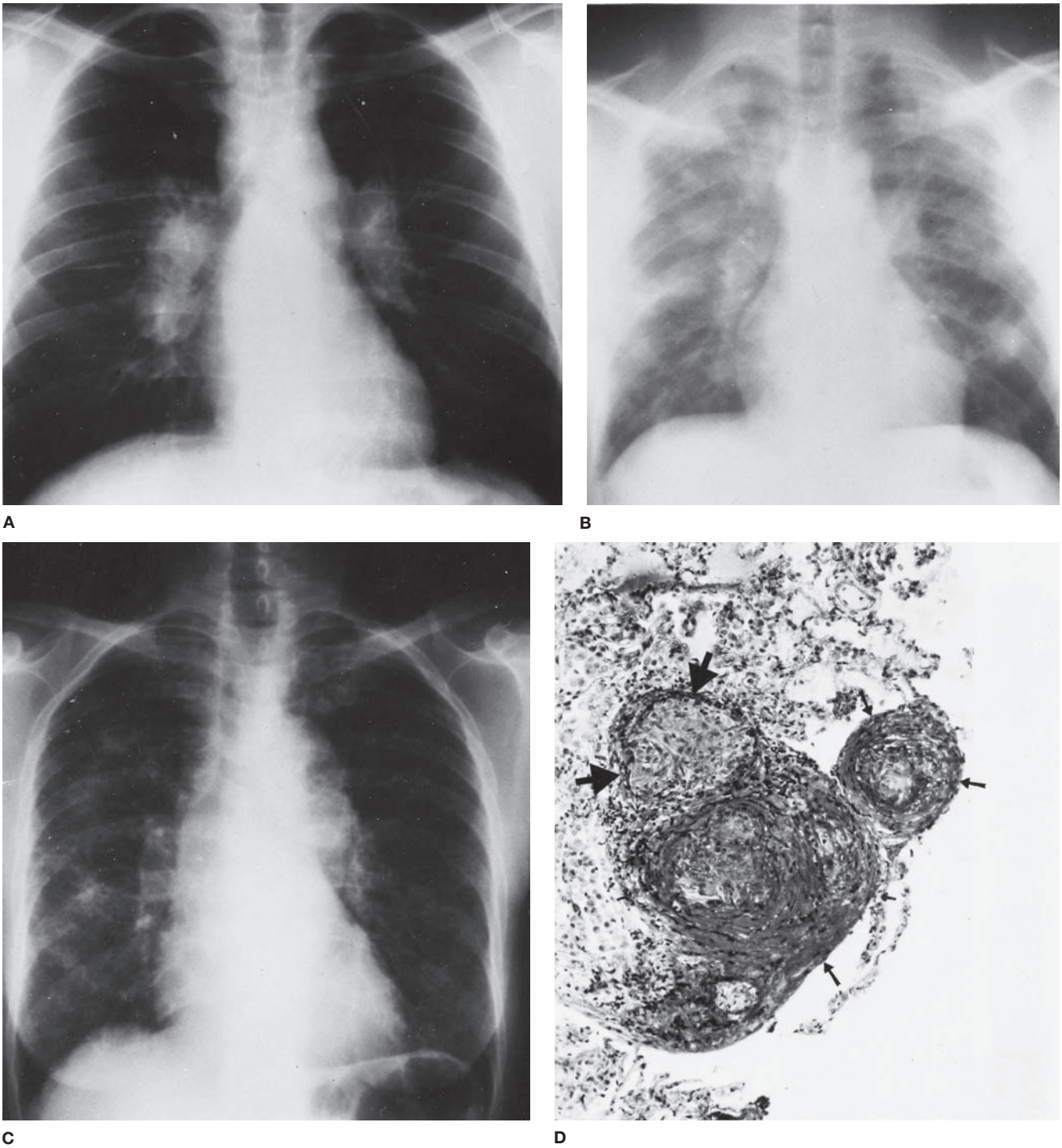


Figure 122-9 **A–C.** Chest radiographs illustrating the various stages of sarcoidosis. **A.** Stage I, bilateral hilar adenopathy. **B.** Stage II, bilateral hilar adenopathy with parenchymal infiltrates. **C.** Stage III, parenchymal infiltrates without hilar adenopathy. **D.** Transbronchial lung biopsy from a patient with sarcoidosis. *Small arrows* indicate granuloma with a surrounding rim of collagen (confirmed by positive trichrome staining). The *large arrows* indicate a granuloma without a surrounding rim of collagen. Original magnification ×10.

or *Actinomyces* (Fig. 122-10). Several organisms, uncommon causes of pulmonary infection, have morphologic characteristics that may mimic other, more common respiratory pathogens. *Pasteurella multocida* and *Acinetobacter* species, both small gram-negative coccobacilli, have each been mistaken in sputum of patients with pulmonary infections for either *H. influenzae* or *M. catarrhalis*.

Sputum or pleural fluid with foul odor provides evidence of activity of anaerobic organisms in infective processes such as lung abscess, aspiration pneumonia, empyema, and, occasionally, bronchiectasis. In these settings, the findings on Gram-stained smear may corroborate the preliminary diagnosis. Organisms of the *P. melaninogenicus–P. asaccharolyticus* group are small gram-negative coccobacilli. *Fusobacterium nucleatum* is a long, tapering, pale-staining gram-negative bacillus with irregularly staining gram-positive internal granules. Purulent secretions or pus from such anaerobic infections contains numerous neutrophils and usually a

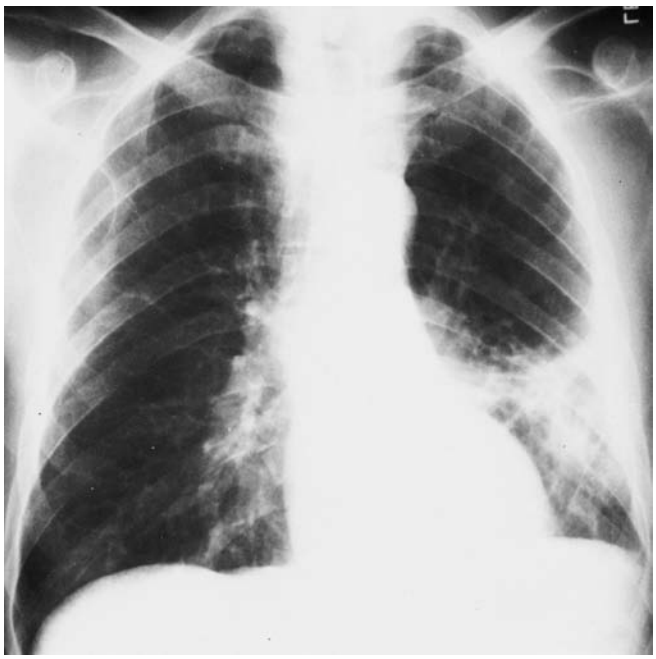


Figure 122-10 Actinomycosis in a 54-year-old chronic alcoholic man with pyorrheic gums who was admitted with signs of brain tumor. Chest radiograph shows mass in left lower lobe. Computed tomography is consistent with brain metastasis. Transthoracic needle aspirate revealed *Actinomyces israelii*.

mixture of bacterial species, including anaerobic and microaerophilic streptococci on stained smear.

Examination of Ziehl–Neelsen or Fluorochrome-Stained Smears for Mycobacteria

The number of new cases of tuberculosis in the United States steadily declined over past decades, reaching a nadir in 1995. During the period 1985 to 1991, the rate of development of new cases (increasingly due to multidrug-resistant [MDR] strains of *M. tuberculosis*) increased, primarily associated with microepidemics among the urban poor, racial and ethnic minorities, drug abusers, hospital and correctional facility populations, and patients with HIV infection. TB has decreased in AIDS due to the efficacy of highly active antiretroviral (HAART) therapies.

Pulmonary tuberculosis in the aforementioned settings may take the form of chronic cavitary tuberculosis or forms more likely to suggest pyogenic or atypical pneumonia—that is, progressive primary tuberculosis and tuberculous pneumonia (see Chapter 131). Acid-fast smears of sputum may provide the very first evidence of this disease. Mycobacteria are seen on smears of about 50% of specimens that subsequently prove to contain *M. tuberculosis*. Most laboratories currently employ a fluorochrome stain with auramine–rhodamine (mycobacteria fluoresce orange-yellow) for initial examination of sputum or other body fluids. Molecular diagnostics (PCR) for *M. tuberculosis* are also available for direct application to clinical specimens.

Atypical mycobacteria may be demonstrated on sputum smears of patients, usually older people with slowly progressive pulmonary disease or in immunocompromised hosts (see Chapter 132). Disseminated *M. avium complex* infection in patients with AIDS is usually diagnosed by isolation of the organism from blood culture or by histopathologic diagnosis on biopsy. However, the organism may be demonstrated on acid-fast smears and culture of respiratory secretions even though there may be little radiographic evidence of pulmonary infection directly attributable to its presence. Improved culture techniques are available to more rapidly isolate mycobacteria from clinical specimens. Modified Ziehl–Neelsen–stained smears are helpful in detecting Nocardia.

Fungal Wet Mounts (Potassium Hydroxide, KOH) Preparations

Fungal wet mounts, smears stained with Calcofluor white chemifluorescent agent or phase-contrast microscopy, are employed when epidemiologic considerations suggest community-acquired pulmonary mycoses (particularly coccidioidomycosis and blastomycosis). They should be a routine part of evaluation of respiratory secretions and lung biopsy materials from immunocompromised patients in whom additional fungal pathogens (e.g., *Aspergillus* and mucormycosis) may be active. In patients with allergic bronchopulmonary aspergillosis, or with the unexpected detection of *Aspergillus* in sputum, fungal hyphae must be considered in the clinical context of each patient.

Rapid Detection by Direct Immunofluorescent Microscopy

Direct immunofluorescent antibody (DFA) staining may be useful in rapid diagnosis of respiratory tract pathogens. DFA staining reagents for *L. pneumophila* are commercially available. Their use is not recommended in examination of sputum specimens because of the presence of cross-reacting species (*Bacteroides* species, *Pseudomonas* species, *Bordetella pertussis*) in the upper respiratory tract. However, biopsy specimens of lung (needle, bronchoscopic, or surgical), bronchoscopic aspirates, BAL washings, and pleural fluid samples are suitable for DFA staining for *L. pneumophila*.

Although a variety of stains (toluidine blue O, methenamine silver, Wright–Giemsa, Diff-Quik, Calcofluor) are useful in identifying *P. jiroveci* in induced sputa or BAL specimens, or on imprint smears of tissue specimens, the most widely used diagnostic technique utilizes immunofluorescence with monoclonal antibodies against *P. jiroveci*. Rapid viral diagnosis (RSV, influenza, parainfluenza, adenovirus) by DFA may be applied to specimens from bronchial lavage or brushings or from nasopharyngeal swabs or washings. Anti-*B. pertussis* DFA may be used on nasopharyngeal aspirate smears in the presumptive diagnosis of pertussis.

DFA may be used to detect viral antigens (adenovirus, influenza A and B, parainfluenza, and RSV, as well as CMV and HSV) in specimens of bronchial brushings, BAL, or nasopharyngeal washings. Enzyme immunoassay may also be used to detect viral antigens in respiratory secretions.

Giemsa and Other Special Stained Smears for the Diagnosis of Pneumocystis Infection

Since *P. jiroveci* pneumonia is an alveolar process, examination of routinely collected expectorated sputum samples for *P. jiroveci* is generally not regarded as rewarding in immunosuppressed patients with neoplastic disease or transplant recipients. In patients with AIDS and in others with advanced pneumonia, induced sputum examination for *P. jiroveci* may be helpful. Otherwise, fiberoptic bronchoscopy and transbronchial biopsy, combined with BAL, provide the highest diagnostic yield.

Sputum induction employing aerosolized, hypertonic saline provides a diagnosis in up to 80% of cases, particularly if coupled with microscopy of antibody-stained cytocentrifuged specimens. Immunofluorescent assays use monoclonal antibodies to *P. jiroveci* with induced sputum specimens and have a sensitivity of 69% to 92%, compared with that of 28% to 80% for tinctorial stains. Toluidine blue O and methenamine silver stains stain only the cyst (<10% of the organism burden) and not the trophozoite forms of *P. jiroveci*. Giemsa and Diff-Quik stain trophozoites and intracystic sporozoites. If results of examination of induced sputum are negative and clinical circumstances warrant further attempts at diagnosis, follow-up bronchoscopy with transbronchial biopsy or BAL is performed. The sensitivity of each of these procedures for the diagnosis of *P jiroveci* pneumonia is over 90%.

Special Microscopic Examinations

Occasionally, in the setting of apparent pulmonary inflammation with features atypical for infection, microscopic examinations using stains other than Gram stain may be indicated. For example, Wright-stained smears may show the presence of eosinophils in allergic pulmonary aspergillosis or other causes of pulmonary infiltrates that are accompanied by eosinophilia. Cytologic examination of exfoliated sputum using Papanicolaou stain may reveal a pulmonary neoplasm. Birefringent calcium oxalate crystals (needlelike in rosettes or arranged like sheaves of wheat) in sputum cytologic specimens have been reported as suggesting pulmonary infection with *Aspergillus* (aspergilloma and, occasionally, invasive aspergillosis).

In the intubated or tracheotomized patient, whose tracheobronchial secretions commonly contain neutrophils and often some bacteria on Gram-stained smears, it may be difficult to distinguish between colonization and nosocomial pneumonia.[20,21] The presence on light microscopy (×400) of characteristic elastin fibers with split ends (in a drop of tracheal aspirate to which a drop of 40% KOH has been added), in the appropriate clinical setting, is a strong indicator of a necrotizing pulmonary infection.

Intense bacteremia sometimes accompanies pulmonary infections, and the etiologic agent may be demonstrable on stained smears of the buffy coat of centrifuged blood: pneumococci have been identified in Gram-stained or Wright–Giemsa–stained smears of buffy coats from splenectomized patients; occasionally, *M. avium-intracellulare* has been found intracellularly in acid-fast stains of buffy coats from patients with AIDS.

Additional special microscopic examinations may be indicated for immunocompromised patients who have patchy pulmonary infiltrates on the chest radiograph. For example, the presence of the hyperinfection syndrome of strongyloidiasis (often accompanied by *Escherichia coli* bacteremia) can be established by the finding of filariform larvae in the sputum and in the stool after the latter is suitably prepared by concentration techniques. Although eosinophilia is often present in patients with strongyloidiasis, it may be absent in the hyperinfection syndrome.

■ SPUTUM CULTURES

In most patients with the common types of community-acquired and nosocomial bacterial pneumonia, the etiologic diagnosis can be made on the basis of the combined results of a Gram-stained smear of sputum and of proper culture of a suitable exudative portion of a freshly obtained sputum specimen. The criteria for a proper sample of sputum have been noted earlier. Culture generally entails streak dilution on blood agar and McConkey media. Expectorated sputum should not be cultured anaerobically, since contamination with oral anaerobes is inevitable. Blood agar best supports the growth of gram-positive cocci and most gram-negative rods and is especially useful for evaluation of the colony morphology and hemolysis of streptococci. McConkey agar is selective for gram-negative bacteria and is used to determine bacterial ability to ferment lactose (lactose-positive or -negative organisms). Chocolate agar is not used routinely, but allows recovery of *H. influenzae* and other fastidious organisms. Because patients with Legionnaires' disease often have little sputum production and growth requires special media, most attempts to isolate *Legionella* resort to specimens obtained either by induced sputum samples, fiberoptic bronchoscopy, or lung biopsy or at thoracentesis. Cultures of such materials are plated on buffered charcoal-yeast extract (BCYE) agar. Occasionally, *Legionella* species can be isolated from sputum with the use of a semiselective medium, either BCYE or BCYE-containing cefamandole, polymyxin B, and anisomycin. Culture is the most definitive method for diagnosis of *Legionella* infection. Unfortunately, it may take 5 or more days for colonies to appear.

Cultures for mycobacteria are undertaken when clinical circumstances raise the possibility of pulmonary infections due to *M. tuberculosis* or atypical mycobacteria. Similarly, cultures of sputum for primary invasive mycotic agents (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*) are dictated by clinical and epidemiologic circumstances. In immunosuppressed patients, cultures of sputum are also directed toward a variety of opportunistic fungi, including *Cryptococcus neoformans*, *Aspergillus* species, and Mucoraceae.

Most hospitals do not have facilities for isolating viruses by tissue culture. This lack poses little problem in dealing with most community-acquired viral pneumonias, for which viral isolation is not necessary and the cost is prohibitive. However, viral isolation from throat washings is warranted in certain circumstances (e.g., to prove the presence of an outbreak of influenza) and to identify a specific viral agent, such as an adenovirus or SARS, as the cause of a serious pneumonia that is not responding to antibacterial therapy. Cultures may be grown in cell lines susceptible to the viral infections under consideration in either standard "tube cultures" or "shell vial" cultures (rapid culture achieved by centrifugation of specimens against the cultured cells). Viral replication in the tissue culture can be confirmed within 48 hours after inoculation with the use of fluorescent monoclonal antibodies. Because CMV and herpes simplex are frequently present in the oral secretions of immunosuppressed patients, isolation of these viruses is apt to be meaningful only if the materials used for the isolation procedure were obtained either by bronchoscopy with protected specimen brush (PSB) or with BAL, lung biopsy, or transtracheal aspiration. In practice, diagnostic cultures (e.g., for CMV, other herpesviruses, and adenovirus) have been replaced by quantitative molecular amplification assays (nucleic acid tests, NAT, polymerase chain reaction, PCR) or antigen detection systems (Table 122-6) that are more rapid and cost efficient than culture systems (see below).

■ BACTERIAL AND VIRAL ANTIGEN DETECTION

The quellung reaction was extensively used in the preantimicrobial agent era to identify *S. pneumoniae* in sputum.[22,23] It entails the use of light microscopy to detect capsular swelling after pneumococcal antiserum has been added to a loopful of sputum. The occurrence of the quellung reaction was shown to correlate closely with the presence of *S. pneumoniae* in sputum culture—in about 90% of the patients. Pneumococcal antigens may also be detected in the sputum of patients with pneumococcal pneumonia by ELISA, latex particle agglutination, or counterimmunoelectrophoresis; none of these techniques is commonly used at present. Antigen detection in sputum may have as high a sensitivity as 70% to 90%; but specificity is a problem, with about 20% false positives, probably due in part to the difficulty in distinguishing oropharyngeal contamination and colonization (e.g., in patients with chronic bronchitis without pneumonia).

In many patients, an etiologic diagnosis cannot be made on the basis of initial smears or cultures, antimicrobial therapy has been initiated before cultures were obtained or adequate sputum samples are not available. In the setting of likely CAP, urinary antigen tests for *Pneumococcus or Legionella (SG1)* or nasal swabs for direct immunofluorescence or culture for viral antigens (influenza, parainfluenza, metapneumovirus, adenovirus, respiratory syncytial virus [RSV]) are often helpful.[13,23–28] In adults hospitalized with CAP due to *S. pneumoniae*, generally without bacteremia (which increases sensitivity), the sensitivity of the pneumococcal urinary antigen assay was 71% and specificity was 96%.[29,30] The *L. pneumophila* antigenuria test is positive despite antimicrobial agent administration; antigenuria may persist for weeks or months after recovery from pneumonia.[31,32] The assay is available only for *L. pneumophila* serogroup 1, and this serogroup is responsible for only 80% of *L. pneumophila* infections.

Rapid, point-of-care tests for influenza viruses have good specificity but only 50% to 70% sensitivity; retesting using more sensitive

TABLE 122-6 Assays for Viral Agents of Adults

Virus (Type)	Season	Culture/Specimen	Culture Days to Positive	DFA/Serology	Molecular Amplification+
Influenza A/B (RNA)	Winter	Nasopharyngeal wash/BAL	3–5 (low yield)	+/+ (rapid antigen tests poor)	Qual (rapid, sensitive, specific)
RSV (RNA)	Fall, Winter	Nasopharyngeal wash/BAL	5–7	+/+	Qual
Parainfluenza (RNA)	Fall, Spring	Nasopharyngeal wash/BAL	5–7	+/+	Qual
Adenovirus (DNA)	All	Nasopharyngeal swab, stool	3–5	+/+	Qual/Quant
Measles (RNA)	All	Conjunctiva, nasopharynx; BAL, blood, urine	2–15	Fair −/+	−
EBV (DNA)	All	PBL-PCR, mono spot, serum	1–7	−/+	Qual/Quant (New WHO standards)
CMV (DNA)	All	Blood, urine, BAL saliva	2 (shell vial)-14	+/+	Qual/Quant PCR (WHO standards) antigenemia pp65
VZV (DNA)	All, especially Spring	Vesicle, throat, BAL, blood	slow	+/+	Qual/Quant
HSV1, HSV2 (DNA)	All	Vesicle, BAL, blood	1–2	+/+	Qual/Quant (HSV1/2)
MERS-CoV (RNA)[a]	Middle East	BAL, sputum	na	+/+	Qual (RTPCR)
Human metapneumovirus (RNA)	All, especially Spring				Qual

+Quant, quantitative assay; Qual, qualitative assay; RTPCR, real-time reverse-transcription polymerase chain reaction assays.
[a]Testing of multiple specimens including lower and upper respiratory samples, serum, and stool samples.

assays may be required if clinical suspicion is high. Recently introduced multiplex molecular assays (PCR) for up to 16 respiratory viruses has been adopted by some clinical laboratories.[33] Molecular testing allows detection of *Legionella and Mycoplasma, and some Chlamydophila* species; quantitative PCR may assist in separating infection from colonization. Using this array of diagnostics, likely pathogens may be detected in up to 78% to 89% of cases of CAP. While the pneumococcus remains the most common pathogen at 38%, this pathogen was more often detected by molecular and urinary tests than sputum culture and examination.[28] Respiratory viruses are also common (29%).

For the immunocompromised host, the epidemiologic history may suggest other risk factors such as *Histoplasma* (urinary antigen), viral infections (serum antigenemia or nucleic acid testing) (see Tables 122-2 and 122-6), or the serum cryptococcal antigen assay. Retrospectively, serologic testing may reveal diagnoses such as psittacosis or Q-fever. The CMV antigenemia assay detects matrix protein pp65 and can be detected with the use of fluorescent or peroxidase-labeled antibody staining of peripheral blood neutrophils. This assay is semiquantitative. Quantitative and sensitive NAT assays are available for most clinically important viruses (Table 122-6 and see below). These are positive days in advance of antigenemia assays and are useful in management as well as diagnosis of acute infection. Strict criteria for CMV pneumonia include demonstration of the virus, typical cytologic changes, and absence of other evident pathogens. This is applicable in immunocompromised patients, in whom CMV is frequently isolated but in whom CMV rarely causes pneumonia. In contrast, isolation of CMV from BAL fluid in blood or bone marrow transplant recipients with pneumonia is sufficient evidence to make the diagnosis and institute treatment, in view of the high frequency and mortality of CMV pneumonia in these patients.

■ MOLECULAR DIAGNOSTIC TESTING

A variety of nucleic acid target amplification tests (NAT, often polymerase chain reactions or PCR) are available for the direct detection of pulmonary pathogens. PCR tests can detect *M. tuberculosis* (as distinct from nontuberculosis mycobacteria) directly from sputum and BAL specimens. These tests have shown a sensitivity of 90% to 100% in specimens that are acid-fast bacillus (AFB) smear–positive but a sensitivity of only 65% to 85% for specimens that are smear negative. Consequently, these PCR assays have been approved for use only on AFB smear–positive specimens. In some major medical centers, PCR assays for the detection of *C. pneumoniae* and *M. pneumoniae* on nasopharyngeal or throat swab specimens are available to markedly shorten (by 1–2 days) the time required to isolate these organisms by culture (up to 3 weeks).

Molecular detection of HSV, adenovirus, CMV, EBV, and other pathogens are used primarily with blood specimens but may also be used in BAL or CSF samples. In immunosuppressed patients with pneumonia, a broad array of opportunistic viral infections (CMV, RSV, varicella-zoster virus, herpes simplex) are diagnostic considerations. In vitro testing of CMV, including molecular antiviral resistance testing, may provide data regarding appropriate antiviral therapy. The interpretation of NAT assays with respiratory secretions is nonstandardized—and blood studies are preferred. Molecular amplification is under development for many common pulmonary pathogens including *P. jiroveci, L. pneumophila, and Candida and Aspergillus species.* PCR tests have been developed for agents of bioterrorism.

Blood Cultures

Blood cultures should always be performed in patients with suspected bacterial pneumonia.[34] Bacteremia occurs in approximately 30% of patients with pneumococcal pneumonia who represent up to two-thirds of those with positive blood cultures.[35–37] Blood cultures are more often positive in sicker patients: those with hypotension, renal and liver dysfunction, pleurisy and tachypnea, and embolic disease. Bacteremia in patients with pneumonia may indicate that the pulmonary infection is secondary to a focus of infection elsewhere (e.g., acute right–sided *S. aureus* endocarditis or *Pseudomonas aeruginosa* infection of thermal burns). In patients with AIDS and disseminated *M. avium-intracellulare* infection, mycobacterial blood cultures are almost always positive. The lysis centrifugation technique permits ready and rapid isolation of the mycobacterium and quantifies the intensity of the bacteremia. *L. pneumophila* has been isolated with some frequency from automated radiometric blood culture bottles, but blind subculture onto

BCYE agar is necessary because growth in the liquid medium does not achieve detectable levels.

Serologic Tests and Fungal Antigens

Serologic tests are sometimes of considerable help in establishing the causes of a number of pulmonary infections when the causative agents are difficult to isolate. However, this approach, requiring the demonstration of a fourfold or greater rise in titer between acute and convalescent samples, neither enables rapid diagnosis nor provides assistance in initial selection of antimicrobial therapy.

Microimmunofluorescence serologic tests are of value in the diagnosis of psittacosis (*Chlamydophila psittaci*). A fourfold rise in IgG or the presence of IgM antibody indicates recent infection.

The indirect immunofluorescent antibody test (fourfold titer rise to 1:128 or higher indicates recent infection) may provide a retrospective diagnosis of Legionnaires' disease, but the antibody rise occasionally may not be demonstrable for 4 to 6 weeks after the clinical onset. Antibodies may persist for months or up to a year or more. Thus, a single titer of 1:256 or higher may reflect a prior *Legionella* infection.

Cold agglutinins develop in about half the patients with *M. pneumoniae* pneumonia, but such antibodies occur in other conditions; complement fixation testing is the preferred diagnostic procedure.

The most sensitive and specific serologic test for infection with *C. pneumoniae* is the microimmunofluorescence test. A fourfold rise in IgG titer or an IgM titer of 1:16 or more reflects an acute infection.

The complement fixation test is usually used to confirm a diagnosis of Q fever pneumonia, but microimmunofluorescence, microagglutination, and enzyme-linked immunosorbent assays have been used to diagnose acute *Coxiella burnetii* pulmonary infection.

Tularemic pneumonia can be diagnosed serologically with an agglutination test for *Francisella tularensis*.

Serologic tests are also helpful in the diagnosis of invasive infection due to the primary pulmonary mycotic pathogens.

Serum IgM precipitins (latex agglutination, immunodiffusion) appear with primary coccidioidomycosis. Abnormally high complement fixation titers (at least 1:32) are present in most patients who have disseminated infection due to *C. immitis*.

A fourfold increase in complement fixation titer to yeast and to mycelial phases of *H. capsulatum* (or possibly a single titer of 1:64 or higher) and the presence of H and M precipitin bands strongly suggest histoplasmosis.

Complement fixation tests for blastomycosis lack sensitivity and specificity: titers of at least 1:8 suggest recent or active disease, particularly if precipitins to the A antigen are also present.

Cryptococcal antigenemia is detectable from latex particle agglutination in patients with cryptococcal pneumonia or disseminated cryptococcal infection.

Sporotrichosis can be diagnosed with a serologic agglutination test when the titer is 1:80 or greater.

Pulmonary toxoplasmosis is uncommon in seronegative individuals although acute toxoplasmosis is seen in endemic regions (Caribbean, France) and after organ transplantation.

Serologic tests (paired acute and convalescent sera) may be helpful for the retrospective diagnosis of infections due to influenza A and B, RSV, adenoviruses, and parainfluenza viruses.

Fungal pneumonia is generally a function of anatomic (fungus ball) or immune dysfunction (e.g., neutropenia). Screening assays have been developed to assist in the detection of fungal infection in high-risk patients. 1,3-β-D-glucan, a cell wall component of many fungal cell walls. Candida species, while frequently isolated in respiratory specimens, rarely cause pneumonia other than in infracted lung or as a function of embolic disease (e.g., endocarditis in injection drug users). Thus, a positive β-D-glucan assay in the immunocompromised host is likely a reflection of infection due to Pneumocystis, Cryptococcus, Aspergillus (or other moulds) species.[38,39] The sensitivity for proven or probable invasive fungal infection in various hosts is generally in the 50% to 77% range (often lower in practice) and specificity of 80% to 95%. The specificity is altered due to false-positive results from intravenous immunoglobulin and albumin, intravenous piperacillin–tazobactam and amoxicillin–clavulanic acid, cellulose hemodialysis membranes, gauze packing after surgery, and *Pseudomonas* bacteremias.

For *Aspergillus* species, galactomannan, a component of the cell wall, can be measured in serum by enzyme-linked immunoassay and has been shown to correlate with the burden of fungal disease (see also Chapter 133).[40–43] A meta-analysis of the performance characteristics of the assay in serum demonstrated a sensitivity of 0.71 (95% CI 0.68–0.74) and specificity of 0.89 (95% CI 0.88–0.90) using an index cutoff of 0.5 in immunocompromised patients with proven invasive aspergillosis.[42] Individual studies reveal variability in assay performance. In BAL fluids from stem cell transplant patients, the GM has a reported sensitivity of 0.61 (95% CI 0.46–0.75) and specificity of 0.98 (95% CI 0.89–1.0) using an index cutoff of 1.0.[44] Despite widespread use of the serum galactomannan assay for the early diagnosis of invasive disease, it is unclear that this assay results in the earlier initiation of appropriate antifungal therapy or is cost effective.

■ SKIN TESTS OF DELAYED HYPERSENSITIVITY

The tuberculin skin test (TST) is of great importance in the evaluation of a pulmonary infection of unknown origin. The intermediate (5 tuberculin units) purified protein derivative (IPPD) test should be used if no information is available about previous testing. A positive test does not distinguish between prior and current infection. A negative second-strength PPD skin test in a patient who is not anergic is evidence against a tuberculous origin of a pulmonary process in a normal host. Several caveats are noteworthy: since it may take 4 to 6 weeks for the skin test to become positive, the TST may be initially negative in progressive primary pulmonary tuberculosis, and in the patient who was infected long ago, cutaneous hypersensitivity may wane; in the elderly person, in whom waning has occurred, repeat testing several weeks later may show a positive result (booster effect) even if the original IPPD skin test was negative.

A PPD reaction of ≥5 mm is considered positive in HIV-infected and other immunosuppressed hosts, recent exposures and in some cases of x-ray positive, remote tuberculosis. PPD ≥10 mm is positive for individuals form an endemic region, intravenous drug users, TB laboratory personnel, and group housing residents. Positive PPD tests should be ≥15 mm induration in other hosts.

Interferon gamma release assays (IGRAs) carry a 70% to 90% concordance with PPD testing and are used in all circumstances in which TST is currently used.[45–47] The IGRA is more specific than TST but more expensive and requires whole blood testing.

Fungal skin tests do not distinguish between current and past infection; indeed, active disease is often accompanied by a negative skin test. The coccidioidin skin test is the best of the available tests, but the diagnosis of coccidioidomycosis is not excluded by a negative test. Blastomycin and histoplasmin skin tests are of little value because of frequent false-negative results and cross reactions. Also, the performance of the histoplasmin skin test may falsely elevate antibody levels to the *H. capsulatum* mycelial antigen.

A negative skin test response to a specific antigen must be interpreted in the light of possible anergy. A battery of control antigens (mumps, *Candida*, *Trichophyton*, streptokinase–streptodornase) serves to detect such anergy, but these reagents are increasingly unavailable and costly.

INVASIVE DIAGNOSTIC PROCEDURES

Some techniques developed to avoid potential contamination of sputum samples with upper airway flora have generally become less popular, including transtracheal aspiration, transthoracic aspiration, and even routine bronchoscopy.

Transtracheal aspiration involves placement of a 12-to 14-gauge intracath via the cricothyroid membrane with avoidance of air leakage and aspiration using a syringe.[48,49] This technique was very useful but occasionally complicated by bleeding, air leak, and lack of experience. Transthoracic needle aspiration similarly had a good yield but has also fallen into disfavor.[22,34]

Bronchoscopy also suffers from upper airway contamination and may be replaced by a variety of techniques: quantitative cultures of wedged terminal BAL specimens; double-lumen or PSB bronchoscopy; plugged telescoping catheter (PTC) sampling; fiberoptic bronchoscopy with transbronchial biopsy; CT-guided needle biopsy of the lung; and open lung biopsy via limited or video-assisted thoracoscopic surgery (VATS).[21,50–52] Important considerations include the type and location of the pulmonary lesion, the ability of the patient to cooperate with the required manipulations, the presence of coagulopathies, and experience at the particular hospital in performing each of the procedures. For patients who are critically ill or unlikely to tolerate invasive infections (immunocompromised hosts, recent major surgery, heart or liver or renal failure, COPD), it is reasonable to consider more invasive diagnostic procedures early in the clinical course, bearing in mind the risks inherent to invasive tests. In such patients, empiric antimicrobial therapies carry the risk of obscuring a specific microbiologic diagnosis as well as drug-associated toxicities. Such an approach may also be required if the patient's condition continues to deteriorate despite empiric antimicrobial therapy. The selection of such procedures should be based on the nature of the illness and the likelihood of success for each procedure at the institution.

Each procedure is best suited to lesions with selected location and radiographic appearance. Fiberoptic bronchoscopy using specialized devices to shield against oropharyngeal contamination (protected specimen brushing) can obtain tracheobronchial secretions for culture in acute bacterial pneumonias. A peripheral nodule or cavity (more than 1 cm in diameter) that is readily visualized on conventional (posteroanterior and lateral) radiographs and fluoroscopy and is in an accessible location may be aspirated and biopsied by needle percutaneously. A nodule that is inaccessible to needle aspiration, or a process placed peripherally, where the need for histopathology is not apt to be met by needle aspiration and biopsy, is best approached by open lung biopsy.

FLEXIBLE FIBEROPTIC BRONCHOSCOPY WITH LUNG BIOPSY

Fiberoptic bronchoscopy, in conjunction with transbronchial lung biopsy, provides an etiologic diagnosis in about 50% to 80% of immunosuppressed patients who do not have AIDS and in 60% to 90% of patients who do have AIDS, in whom *P. jiroveci*, CMV, and *M. avium-intracellulare* infections are common. Contraindications to transbronchial biopsy include inability of the patient to cooperate, marked hypoxemia, bleeding disorders (particularly those associated with hypoprothrombinemia, thrombocytopenia refractory to platelet transfusion, and uremia), and pulmonary hypertension. In such patients, correction of bleeding tendency and/or open procedures may be preferred. Fiberoptic bronchoscopy combined with transbronchial biopsy and segmental BAL is the usual initial invasive diagnostic procedure in the immunocompromised patient with an undefined diffuse pulmonary process. If this fails to provide a diagnosis, open lung biopsy is indicated.

Tissue specimens are processed for histopathologic examination (hematoxylin and eosin stain, tissue acid–fast stains, Gomori methenamine–silver stain, periodic acid–Schiff stain, tissue Gram stain, and Dieterle silver stain). Impression smears from tissues are made with sterile slides, which, after appropriate fixation, are stained with Giemsa, Gram, Ziehl–Neelsen, and methenamine silver (for *P. jiroveci*) stains, as previously described. As indicated, DFA staining for *Legionella* and monoclonal antibody staining for *P. jiroveci* are performed on separate impression smears. Appropriate cultures are made with tissue obtained either transbronchially or at open lung biopsy.

Bronchoalveolar Lavage

In patients with AIDS, fiberoptic bronchoscopy coupled with wedged, terminal, subsegmental BAL has proved particularly useful, providing a diagnosis in more than 95% of cases of *Pneumocystis* pneumonia. BAL alone, without transbronchial biopsy, is often substituted in patients who are thrombocytopenic, on mechanical ventilation, or severely hypoxemic. It should be noted that the yield in non-AIDS immunocompromised hosts is significantly less than in AIDS. Biopsies are often useful in these populations. The material obtained by BAL is processed for smear and culture. As indicated earlier, a variety of stains are available for demonstrating the presence of *Pneumocystis* in the cytocentrifuged material. Stained, cytocentrifuged BAL specimens can also be helpful in establishing other diagnoses: Papanicolaou stain is useful in detecting neoplastic cells and in identifying viral cytopathic effects in epithelial cells.

In at least two-thirds of immunosuppressed patients with CMV pneumonia, the diagnosis can be made from the finding of inclusion bodies in cytocentrifuged BAL specimens and with immunofluorescent monoclonal antibody staining. CMV is isolated more often on culture in these patients, but culture alone is not sufficient to establish the diagnosis, since viral isolation may represent only viral shedding in the presence of pulmonary disease due to other causes.

INVASIVE DIAGNOSTIC TESTING IN VENTILATOR-ASSOCIATED PNEUMONIA

PSB techniques with quantitative culture and protected-catheter BAL, also with quantitative culture, have been employed to obtain bacteriologic information while minimizing opportunity for contamination from colonization of the upper airway in patients with ventilator-associated pneumonia (VAP). The role of quantitative diagnostic techniques in the evaluation of patients with healthcare-associated pneumonia (HCAP) or VAP remains controversial (discussed below) because of questions of reproducibility and the optimal threshold concentration of bacteria. In at least one study, tracheal aspirate cultures correlated with PSB cultures in patients with VAP, suggesting no added value to use of such an invasive procedure to direct initial therapy. The routine use of such tests requires standardization of techniques at the institutional level.

PERCUTANEOUS TRANSTHORACIC NEEDLE LUNG BIOPSY

Percutaneous needle biopsy is often the invasive diagnostic procedure of choice for a sizable (greater than 1.0 cm) pulmonary nodule or cavity that is located peripherally. The use of smaller-gauge needles has reduced the frequency of pneumothorax as a complication. Diagnostic yields of 60% to 80% have been obtained in immunocompromised patients with pneumonia. This procedure has also provided the diagnosis in 70% of patients in whom the underlying lesion was granulomatous. The small core of tissue and aspirated fluid is examined by stained smear and culture for various infectious agents (see "Flexible Fiberoptic Bronchoscopy with Lung Biopsy"). Cytologic examination should be done for neoplastic cells. Because of the nature of the specimen, however, histopathologic examination is generally fruitless. In patients in whom respiratory status is tenuous, or in whom lymph node biopsy or sampling of pleural fluid may be desired, VATS or open biopsy may be preferred.

OPEN LUNG BIOPSY

Open lung biopsy and, more recently, VATS, constitute the most definitive procedures for histopathologic diagnosis in the immunocompromised host. They provide sufficient lung tissue for the diagnosis and also make it possible to sample several different

sites. Surgical lung biopsy is particularly suitable for evaluating processes that may not be infectious (e.g., neoplasm such as Kaposi sarcoma, antineoplastic drug toxicity, drug hypersensitivity, and lymphocytic interstitial pneumonia). Open lung biopsy has provided a specific diagnosis in 60% to 90% of non-AIDS immunocompromised patients. Major advantages include large specimen size and the ability to control bleeding, air leaks, and the airway. Its disadvantages relate to the thoracotomy: the need for general anesthesia, the inherent delay in preparing the patient for the surgical procedure, the need for intubation, the usual placement of a chest tube, and postoperative splinting due to incisional pain. Some of these complications are decreased in VATS. The mortality from the procedure is about 1%. Bleeding is a complication in about 1% of patients and delayed pneumothorax in about 9% of patients.

For the patient in whom the pace of the illness does not allow a sequential diagnostic approach, open lung biopsy may have to be procedure of first choice. It is also preferred in the patient who is unable to cooperate with fiberoptic bronchoscopy or in whom thrombocytopenia or hypoxemia present additional problems for transbronchial biopsy.

Processing of lung biopsy specimens should include special stained imprint smears for *P. jiroveci*, bacteria (including *Nocardia* and mycobacteria), fungi, and viral inclusion bodies; cultures for bacteria, viruses, fungi, and mycobacteria; and tissue sections stained for histology and for infectious agents.

CATEGORIZATION OF PULMONARY INFECTIONS ACCORDING TO PATHOLOGIC AND PATHOGENETIC FEATURES

Pulmonary infections can be categorized according to distinctive pathologic, anatomic, and radiologic features. Some general patterns are presented for their value in differential diagnosis and are discussed in detail in subsequent chapters.

BACTERIAL PNEUMONIA

Bacterial pneumonia commonly results from bronchogenic spread of infection following microaspiration of pharyngeal secretions. Such particles reach terminal airways and alveoli to initiate infection, which has the anatomic distribution and radiologic appearance of subsegmental, segmental, or lobar consolidation. Pneumonia may be patchy in distribution, with a peribronchial and multifocal distribution, in association with aspiration and bronchial plugging, superinfection of pre-existing chronic bronchitis, diffuse acute tracheobronchial inflammation (e.g., influenza, parainfluenza), and with specific infecting microorganisms (e.g., oral anaerobic bacteria). The progression of a pulmonary infiltrate or lobar consolidation to parenchymal destruction (necrotizing pneumonia or lung abscess) is usually the consequence of one or more of three factors: the intrinsic virulence of the infecting organism(s), the presence of bronchial obstruction or other anatomic abnormality, or immune compromise in the host (Fig. 122-1).

Pneumonia may develop via the bacteremic, rather than bronchogenic, route. The clinical setting and the radiographic pattern usually suggest this form of pathogenesis. The intravenous-drug abuser with *S. aureus* bacteremia and acute right–sided endocarditis presents with fever, cough, purulent sputum, a murmur of tricuspid insufficiency, numerous irregular infiltrates, and rounded densities on chest radiograph. Similarly, burn patients with *P. aeruginosa* bacteremia and multiple nodular pulmonary densities, are likely to have bacteremic *Pseudomonas* pneumonia with pulmonary bacterial arteritis. Septic pulmonary emboli, arising from septic thrombosis of the jugular vein may cause a clinical and radiographic picture suggestive of multifocal bronchopneumonia. On the chest radiograph, however, the lesions are nodular; histologically, they represent septic pulmonary infarcts (following emboli) upon which are engrafted pyogenic infection and abscess formation.

LUNG ABSCESS

A lung abscess is an area of pulmonary infection with parenchymal necrosis. Lung abscesses may be solitary or may occur as multiple discrete lesions. Most often it is secondary to aspiration of anaerobic or anaerobic and aerobic organisms that are colonizers of the upper respiratory tract and may be associated with periodontal disease (Fig. 122-6). Superinfection of damaged or infarcted lung tissue (e.g., as in aspirational pneumonia with chemical injury and anaerobic superinfection or primary anaerobic infection) may progress to necrosis with microscopic foci of abscess formation. Confluence of small necrotic foci can either create one or more lung abscesses or lead to a progressively fibrotic, shrunken, and destroyed lobe.

Pulmonary gangrene is an unusual consequence of severe pulmonary infection characterized by sloughing of a pulmonary segment or lobe. This process affects an entire segment or lobe secondary to thrombosis of both bronchial and pulmonary arteries with pulmonary infarction. The organism most commonly implicated has been *K. pneumoniae*, but others have been *S. pneumoniae*, *E. coli*, mixed anaerobes, *H. influenzae*, and *S. aureus*. If there is some degree of ball-valve bronchial obstruction, air may enter while contained pus may fail to drain, producing the radiographic picture of an air–fluid level.

Other causes of lung abscess are (1) progression of a bronchogenic pneumonia due to a pathogen with necrotizing potential (e.g., *K. pneumoniae*, Fig. 122-1), or *Nocardia asteroides* in an immunocompromised patient, (2) bacteremic spread of infection, and (3) septic pulmonary emboli. Lung abscesses complicating necrotizing pneumonia should be distinguished from pneumatoceles; the latter are thin-walled, air-filled structures that often develop early in the course of staphylococcal pneumonia, particularly in infants and young children, and usually disappear over the course of a few months. Lung abscesses should also be distinguished from acute or chronic cavitary pneumonia, which are often multiple and associated with specific pathogens (e.g., mycobacteria) or hosts (e.g., moulds in neutropenia).

BRONCHITIS AND BRONCHIECTASIS

Acute bronchitis is an inflammatory process, usually of viral origin, confined to the bronchi and bronchioles; it does not extend appreciably to surrounding pulmonary parenchyma and is not evident on radiographic examination. Purulent inflammatory secretions are common even though there may be no discernible bacterial infection. Such purulent secretions represent bacterial superinfection. The diagnosis of an acute exacerbation of chronic bronchitis is based solely on clinical grounds; the manifestations are increased cough, dyspnea, and enhanced production of purulent sputum, with or without fever, in a patient with chronic obstructive pulmonary disease. Bacteriologic examination in the absence of antimicrobial pressure generally reveals large numbers of pneumococci or nontypable *H. influenzae*, either as infecting organisms or as chronic colonizers of the bronchial tree. Patients with acute exacerbations of chronic bronchitis tend to improve with antimicrobial treatment while those with chronic bronchitis are less likely to improve with therapy.

Bronchiectasis is characterized by destruction of epithelial, elastic, and muscular elements of bronchi, resulting in their irreversible dilatation. The major proximate cause is repeated or chronic bacterial infection. Nontuberculous mycobacterial infections may contribute. However, predisposition to such infections may reflect a variety of factors, including certain types of prior infection (pertussis, adenovirus, or rubeola infections, necrotizing pneumonia), bronchial obstruction, immunodeficiencies, congenital anatomic lung disease (e.g., congenital tracheobronchomegaly), and other hereditable disorders, such as ciliary dysfunctional states and

α_1-antitrypsin deficiency. Cystic fibrosis is a common predisposing factor for bronchiectasis. As a result of repeated infections, stasis of secretions, and peribronchial fibrosis, bronchi are grossly distorted or completely destroyed. Although pneumonia or lung abscess may accompany recurrent acute infections, exacerbations are usually confined to bronchial and peribronchial tissues.

CHRONIC CAVITARY PULMONARY DISEASE

Chronic cavitary pulmonary disease is most often related to tuberculosis, but may be seen in a_1-antitrypsin deficiency, echinococcal disease, granulomatous polyangiitis, and other structural disorders. Tuberculosis commonly begins with a focus of pneumonitis, usually in the subapical posterior portion of an upper lobe. This patch of pneumonitis occurs at a latent site of earlier metastatic infection (Simon focus) produced by lymphohematogenous spread from primary pulmonary tuberculous lesions. Progressive caseation necrosis at this site, followed by drainage of caseous material through the bronchial tree, produces a cavity (Fig. 122-4). The cavity is encased in a rigid wall of fibrous tissue.

In addition to pyogenic lung abscess and pulmonary tuberculosis, other pulmonary infections may produce chronic cavities. These include *Nocardia* infections, *Rhodococcus equi* infections, actinomycosis, and chronic primary pulmonary mycoses (particularly histoplasmosis, occasionally coccidioidomycosis, uncommonly blastomycosis). Sporotrichosis may affect the lung and produce thin-walled cavities. Parasitic infestation of the lung (paragonimiasis, echinococcosis) may also form cavities.

Pulmonary cavities may also occur in noninfectious disorders (e.g., granulomatosis with polyangiitis, lymphoma or bronchogenic carcinoma, bland pulmonary infarcts, and intrapulmonary nodules of rheumatoid lung disease) (Fig. 122-3). Such cavitary lesions, as well as the cystic lesions that occur in chronic pulmonary sarcoidosis (Fig. 122-9) and in the markedly dilated bronchi of saccular bronchiectasis, may become superinfected with *fungus balls*. These represent tangled masses of fungal hyphae and debris lying freely within pulmonary cavities generally as noninvasive saprophytic growths in the immunologically normal host. The mycotic agents responsible are most commonly *Aspergillus* species (usually *A. fumigatus*), and the fungus ball are called aspergillomas. Invasion of the cavity wall may occur as with immune compromise; hemoptysis originating from the cavity wall is common and may be severe.

MILIARY LESIONS

Hematogenous dissemination of tuberculosis may follow initial infection in children or adults. It also can result from breakdown of formerly quiescent sites of pulmonary or extrapulmonary infection. Clinically unexplained fever may be accompanied by miliary lesions (like millet seeds, very small and uniform in shape) on the chest radiograph; histologically, these lesions are foci of granulomatous reaction (Fig. 122-5). Similar radiographic lesions also occur in the course of hematogenously disseminated bacterial and mycotic infections, including cryptococcosis and histoplasmosis.

THE CLINICAL SPECTRUM OF RESPIRATORY VIRAL INFECTIONS

Respiratory viral infections are a major cause of morbidity worldwide. Findings may predominate in either the upper or lower respiratory tract.

Viral Infections of the Upper Respiratory Tract

Patients present with cough, sore throat, bronchoconstriction, fever, rhinitis, and suffusion of mucus membranes. The majority of these infections are upper respiratory infections and of significance only as causes of discomfort and as predisposing conditions for lower respiratory infections. Spread is via aerosolized droplets and hand contamination. The most prominent viral pathogens include rhinovirus and coronavirus for which no specific antimicrobial therapies are available. Commonly, adenovirus, parainfluenza virus, RSV, and influenza virus may also cause this syndrome. Infections with respiratory viruses occur predominantly in the winter and early spring. Less commonly, reovirus, enteroviruses, metapneumoviruses, and picornaviruses may cause the same symptoms.[53,54]

Of nonviral etiologies, treatable infections with *M. pneumoniae* and *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* also cause significant upper, as well as lower, respiratory tract infections. The main differential for these infections includes allergic, vasomotor, or atrophic rhinitis or nasal polyposis. These syndromes should be considered in patients with atopic history and recurrent upper respiratory infections. While these infections are generally self-limited, common complications include sinusitis, otitis, and bronchitis, exacerbations of chronic pulmonary disease (chronic bronchitis), asthma, and bacterial superinfection with pneumonia.

VIRAL INFECTIONS OF THE LOWER RESPIRATORY TRACT

Influenza virus is an agent of the family orthomyxoviridae that may be associated with sizable outbreaks or major epidemics of upper respiratory infections. Influenza is classified into three subtypes based on antigenic differences: influenza A, B, and C.

Primary influenza viral pneumonia usually occurs in the setting of an outbreak of influenza A infections. It impacts disproportionately patients with underlying heart disease (mitral stenosis), chronic pulmonary disease, pregnancy, and immunocompromised individuals. Unlike secondary bacterial pneumonia after influenza – a complication that occurs after a period (1–4 days) of improvement following typical upper respiratory illness – primary influenza pneumonia immediately follows typical influenza. Two classes of drugs are available to treat influenza A including M2 matrix protein inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamavir, oseltamavir, and peramavir). Resistance is emerging to both groups. Influenza A infects a wide range of hosts species including human, pigs, birds, horses, and marine animals, while influenza B and C are generally restricted to humans. As a result, influenza A may move between host species, risking recombination, mutation (drift) and geographic spread.

Recent outbreaks of pandemic influenza (e.g., avian influenza, 2004–2007, A/H5N1) were most likely to arise in birds as all of the hemagglutinin and neuraminidase variants are carried in that population with viral replication in the gastrointestinal tract and secretion in high titers in feces. The spread of mild variants of H5N1 influenza is common in Asian populations. Pandemic outbreaks of "swine flu" (1918 and 2009 pandemic A/H5N1) was the result of avian, human, and swine influenza viruses in Mexico, and was associated with significant mortality, notably in those with underlying diabetes, COPD, and obesity.

Rarely, viral pneumonia develops in an otherwise healthy person in the course of systemic infection with viruses whose principal impact is extrapulmonary. Pulmonary infiltrates occur in 16% of young adults with varicella, but only 2% to 4% have clinical manifestations suggestive of pneumonia. Some cases of mild pneumonitis have been observed in patients receiving live varicella vaccine. Pneumonia in children with varicella is more likely to represent bacterial superinfection than primary viral pneumonia. On rare occasions, pulmonary infiltrates develop in patients with clinical infectious mononucleosis; the infiltrates represent atypical pneumonia due to Epstein–Barr virus.

A novel Hantavirus, Sin Nombre virus, emerged acutely in 1993, in the Four Corners area of New Mexico, Arizona, Colorado, and Utah, USA. Cases had been reported worldwide but primarily in the west and southwestern United States.[55] The principal host for Sin Nombre virus is the deer mouse, and infection is acquired

through exposure to this rodent, rodent excreta, or contaminated dust. The Hantavirus pulmonary syndrome begins with a 3- to 6-day prodromal period consisting of myalgias and fever, sometimes accompanied by gastrointestinal symptoms. The prodrome is followed by progressive cough, dyspnea, tachycardia, and hypotension. Bleeding may occur. Laboratory findings include hemoconcentration, leukocytosis, thrombocytopenia. The chest radiograph demonstrates interstitial edema, peribronchial cuffing, and bilateral airspace (bibasilar and perihilar) disease. The patient develops pulmonary edema (interstitial and alveolar) consistent with a diffuse pulmonary capillary leak syndrome. The case fatality rate for the Hantavirus pulmonary syndrome is 50%.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness that first appeared in Southern China in November 2002 before spreading globally. SARS is caused by a previously unrecognized coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS-CoV is transmitted most readily by respiratory droplets. Illness begins with a high fever (measured temperature greater than 38.0°C) with chills and malaise. Diarrhea is seen in approximately 10% to 20% of patients. After 2 to 7 days, SARS patients may develop a dry, nonproductive cough that might be accompanied by or progress to a condition in which the oxygen levels in the blood are low (hypoxia). In 10% to 20% of cases, patients require mechanical ventilation. Most patients develop pneumonia. The incidence of pneumonia is greatest in immunocompromised individuals.

Between November 2002 and July 2003, a total of 8098 people worldwide developed SARS and 774 died. No new cases were reported after July 2004. However, a related infection emerged in 2012 in Saudi Arabia called the Middle Eastern Respiratory Syndrome (MERS) caused by a coronavirus called MERS-CoV. This is a severe acute respiratory illness presenting with fever, cough, and shortness of breath, after exposure in or near the Arabian Peninsula. Spread is achieved by close contact but sustained spread has not been identified. About half of known cases have died.

Human metapneumovirus (HMPV) is a ubiquitous virus (*Pneumovirinae* subfamily, *Paramyxoviridae* family) that is a major cause of acute respiratory infection, particularly in children and in immunocompromised individuals.[54] The virus has phenotypic and clinical characteristics similar to those of RSV, often presenting with bronchiolitis. This virus may coinfect individuals with other viral pathogens.

In the immunocompromised host, viral infection is most often due to CMV or community-acquired respiratory viruses, although varicella-zoster and herpes simplex viral pneumonias occur. In this population, the frequency, duration, and severity of viral illness exceed that of the general population. CMV pneumonia in the solid-organ transplant recipient occurs most often in seronegative (naive) recipients of donor organs from seropositive (latently infected) individuals. Conversely, in hematopoietic stem cell recipients, the seropositive recipient of cells from a seronegative donor is at greatest risk. The syndrome of hypoxia with diffuse interstitial infiltrates may predispose to or coexist with a similar syndrome due to *P. jiroveci*. This is most severe in the lung transplant recipient. By contrast, CMV pneumonitis in the hematopoietic stem cell transplant recipient (HSCT) occurs with the activation of CMV in the seropositive recipient of cells from a seronegative donor. With engraftment, the naive immune system reacts against CMV antigens expressed in the lungs. Superinfection is common; graft-versus-host disease may complicate the differential diagnosis.

FUNGAL PNEUMONIA

Fungal pneumonia occurs most often in immunocompromised hosts. However, in the normal host, infection due to the endemic or geographic fungi (*H. capsulatum, C. immitis*) or to *C. neoformans* may be asymptomatic or may present with systemic signs often confused with acute bronchitis, viral infection, mycobacterial infection, or aseptic meningitis. Otherwise, fungal infection of the lungs is most common with anatomic defects (aspergilloma) or aspiration (*Candida* species), but it is otherwise rare in individuals without immune defects. A few syndromes merit consideration.

P. jiroveci causes pneumonia with prominent hypoxia and often few physical or radiologic findings in immunocompromised individuals, particularly those on corticosteroids. As this infection is easily prevented, consideration should be given to prophylaxis in any individual receiving chronic immunosuppressive therapy or with HIV infection or AIDS unresponsive to antiretroviral therapy.

Aspergilloma was traditionally considered to be a noninvasive colonization of pulmonary cavities. However, gross hemoptysis may complicate management and dissemination may occur at the time of surgical resection. Immune suppression may convert benign disease into invasive infection.

Mucormycosis (due to the *Mucoraceae*) causes rapidly progressive sinus and lung infection that requires surgical resection for cure. This infection is most common in diabetics. Fusarium species typically disseminate via the bloodstream, producing diffuse infiltrates.

PARASITIC PNEUMONIA

Parasitic pneumonia is uncommon without endemic exposures. Pneumonia generally occurs when the normal lifecycle of the organism includes the lungs. Infection by *Entameba histolytica* causes pleuropulmonary disease as a result of (1) *sympathetic* reaction to an unruptured abscess within the liver; (2) empyema, after rupture of the liver abscess into the pleural space; or (3) parenchymal involvement with abscess, consolidation, or hepatobronchial fistula after the rupture of a liver abscess. Amebae that have broached the mucosal barrier are thought to gain entry to the liver via the portal vein. Subsequent liver abscesses can be either purely amebic or mixed bacterial and amebic. Other less common routes exist, including hematogenous spread that can lead to metastatic abscesses of brain, lung, and other organs. *Acanthamoeba* species cause subacute meningoencephalitis or keratitis secondary often after hematogenous spread of dermal or pulmonary disease.

Some form of pulmonary complication occurs in 3% to 10% of patients with falciparum malaria. Noncardiogenic pulmonary edema may develop suddenly, even after appropriate antimalarial therapy has been instituted and even after parasites are no longer detected on blood smears. Acute acquired infection due to *Toxoplasma gondii* in the immunocompetent host is generally asymptomatic, with cervical lymphadenopathy as the hallmark of disease. It may be confused with mononucleosis caused by Epstein–Barr virus or CMV. Fever, malaise, sore throat, and hepatosplenomegaly are also seen, and the peripheral blood may manifest atypical lymphocytosis. Rarely, acute acquired disease may present with severe dissemination, marked by pneumonitis, hepatitis, encephalitis, polymyositis, or myocarditis.

In the immunocompromised host, acute toxoplasmosis is most often associated with necrotizing encephalitis as a result of brain cyst reactivation, although myocarditis, hepatosplenomegaly, fever, and interstitial pneumonitis are also common. Pulmonary infections due to migrating worms include Loeffler-like syndrome with *Ascaris lumbricoides*, postobstructive pneumonitis and polymicrobial systemic sepsis and meningitis due to *Strongyloides stercoralis*, cysts and nodules due to *Echinococcus granulosus*, *Paragonimus westermani and Schistosoma species,* and pulmonary eosinophilia in filariasis.

OVERVIEW OF THE MAJOR PNEUMONIA SYNDROMES

The major clinical syndromes are considered elsewhere in this text. This section serves as an overview for the clinician.

TABLE 122-7 Underlying Conditions Contributing to Adverse Outcomes from Pneumonia

Alcohol consumption
Increasing age
Leukopenia
Congestive heart failure
Coronary artery disease
Diabetes mellitus
Immune compromise
Neurologic disease
Active malignancy
Clinical signs including: dyspnea/tachypnea, hypothermia, chills, hypotension, confusion or altered mental status
Laboratory tests: hyponatremia, hyperglycemia, azotemia, hypoalbuminemia, liver function test abnormalities
Radiographic infiltrates and pleural effusions, postobstructive pneumonia
Microbiology: gram-negative bacilli, *S. aureus*, mixed flora (aspiration), bacteremia

COMMUNITY-ACQUIRED PNEUMONIA

Over one million people are admitted to the hospital each year for pneumonia. Initial evaluations of pulmonary processes in the outpatient setting require a clinical assessment of whether the individual merits admission to the hospital for management (see Chapter 128).[14] This judgment is based on whether the patient can manage at home (needs oxygen or intravenous antimicrobials, weakness, cannot eat independently or take oral medications, other pre-existing medical or psychiatric conditions, substance abuse, home supports) and whether the patient is at risk for disease progression. Many factors have been implicated in risk for death due to pneumonia. These include both common (alcoholism) and less common (immune deficiency) underlying conditions (see Table 122-7). The Pneumonia Outcomes Research Team (PORT) Severity Index is a quantitative tool that assesses the severity of a patient's illness, prognosis, and the need for hospitalization.[3,5,56] This index provides the basis of North American practice guidelines for CAP and is discussed subsequently (see Chapter 128).

CAP is a major cause of infectious morbidity and mortality. Depending on the causative organisms, the mortality of CAP ranges from 10% to 15% for pneumococcal infection to 60% for *P. aeruginosa*.[57] Adverse clinical prognostic factors included comorbid conditions (neurologic or neoplastic disease, cirrhosis, congestive heart failure, respiratory compromise, diabetes, hepatic and renal dysfunction, immune deficiency), bacteremia, and multilobar involvement.

As was noted previously, microbiologic diagnosis is now uncommon. *S. pneumoniae* remains a common cause of bacterial CAP. *H. influenzae*, usually unencapsulated strains, may produce pneumonia in patients with chronic bronchitis or in the chronic alcoholic. During an outbreak of respiratory viral infections, bacterial superinfection often occurs, most often in the elderly or in patients with chronic cardiopulmonary disease or immune deficits. Patients with secondary bacterial pneumonia often have up to 4 days of clinical improvement after the initial illness before the onset of overt pulmonary infection. The superinfecting microorganisms are the pathogens that ordinarily colonize the upper airways and include *S. pneumoniae*, *H. influenzae*, *S. aureus*, *Streptococcus pyogenes*, *M. catarrhalis*, and *K. pneumoniae*.

The use of antimicrobial agents at the time of the initial respiratory infection may selectively promote the emergence of more resistant bacterial flora in the respiratory tract. *S. aureus* is increasingly common, notably with methicillin resistance, in the setting of an ambient influenza outbreak.[58]

ATYPICAL PNEUMONIA SYNDROMES AND ENDEMIC MYCOSES

In the evaluation of patients with CAP, it is often helpful to consider separately a group of patients whose illness is characterized by minimal sputum that does not reveal a predominant microbial etiology on routine smears (Gram stain, Ziehl–Neelsen) or cultures (including for mycobacteria or *Legionella* species). The clinical onset of illness is generally subacute with a radiologic picture consisting of patchy infiltrates or an interstitial pattern than a lobar consolidation. Fever and peripheral leukocytosis are less common or intense than in common bacterial pneumonias. For convenience, this grouping has been designated *atypical pneumonia*.

The entities in the category of atypical pneumonia are heterogeneous (Table 122-8). The syndrome may account for up to 60% of cases of CAP. *M. pneumoniae* is the causative agent in about 25% of the cases of atypical pneumonia. Respiratory viruses are responsible for about another 30% and should be considered in the initial evaluation.

C. pneumoniae (formerly known as *Chlamydia* strain TWAR) is an infectious agent, can be spread from person to person and appears to be responsible for 12% to 21% of cases of atypical pneumonia. This form of pneumonia typically occurs in young adults as a sporadic mild pneumonia, but may have enhanced severity when coinfecting individuals with pneumococcal infection. In adults, *M. pneumoniae* pneumonia, in contrast to bacterial pneumonia, often begins insidiously with malaise, fever, and prominent headache. Sore throat is common, but coryza is minimal or absent. Nonproductive cough develops over the next few days and is the hallmark of this disease. Skin rash (erythema multiforme) and bullous myringitis, usually appearing late in the course of illness, are uncommon findings but, when present, do suggest the diagnosis. Mini-outbreaks of *M. pneumoniae* infection in households, schools, and military camps may not be appreciated because of the long incubation period (3 weeks) and variation in clinical presentation.

TABLE 122-8 Causes of "Atypical Pneumonia"

Mycoplasma
M. pneumoniae
Chlamydophila
C. psittaci (psittacosis), *C. pneumoniae*
Bacteria
Legionella spp., *F. tularensis*, *Y. pestis*, *B. anthracis* (*Agents of bioterrorism*)
Fungi
Histoplasma, *Blastomyces*, *Coccidioides*, *Pneumocystis*
Aspiration pneumonitis
Sterile or mixed upper respiratory and oral flora
Viral agents
Respiratory tract viruses: Influenza, adenovirus, respiratory syncytial virus (RSV), parainfluenza virus, metapneumovirus
Varicella-zoster, measles, Epstein–Barr virus (EBV), cytomegalovirus (CMV), Hantavirus
Rickettsia
C. burnetii (Q-fever)

Q-fever, due to *C. burnetii*, is suspected on the basis of epidemiologic clues. Transmission of this disease to humans occurs as a result of inhalation of aerosols from surroundings contaminated by placental and birth fluids of infected livestock (cattle, sheep, goats), wild rabbits, and domestic animals (cats). Veterinarians, ranchers, taxidermists, and others that handle livestock are at particular risk. Since the incubation period of Q-fever is approximately 20 days, a source of exposure may be overlooked. Although the clinical picture resembles that of *M. pneumoniae* pneumonia, the onset may be more abrupt, with chills and high fever. Liver function abnormalities or clinical hepatitis in a patient with atypical pneumonia is suggestive of Q-fever. In some geographic areas (Australia, France), hepatitis has been the most frequent clinical presentation of *C. burnetii* infection; in others (Spain, Nova Scotia), pneumonia has been the major presenting sign.

Chlamydia trachomatis causes pneumonia in the newborn but has not been proved to be a cause of pneumonia in adults. *C. psittaci*, the causative agent of psittacosis, is spread to humans by avian species. Although psittacine birds (parakeets, parrots) are the major reservoir, human infection can be acquired from pigeons, sparrows, and turkeys. In a patient with atypical pneumonia, the clinical features that raise the possibility of this etiology are relative bradycardia, splenomegaly and hepatomegaly, and hepatic dysfunction. *C. pneumoniae* produces atypical pneumonia without the usual bird-to-human transmission of *C. psittaci* infection.

Legionella infections (due to *L. pneumophila* and other *Legionella* species) account for 2% to 4% of cases of atypical pneumonia. Although *Legionella* is an important nosocomial pathogen, it is also responsible for community-based sporadic cases and major outbreaks. The occurrence of summer outbreaks associated with the use of air conditioners, pooled water, and evaporative condensers should call attention to this possible cause of pneumonia. Various extrapulmonary manifestations are common with Legionnaires' disease including relative bradycardia, diarrhea for 24 hours at the onset of illness, confusion and obtundation, mild renal dysfunction (azotemia, microscopic hematuria, proteinuria), acute rhabdomyolysis, and mild hepatic dysfunction. Although many of these manifestations also occur with other pneumonias, the coincidence of several of these features should raise the possibility of *Legionella* infection. This is particularly important in view of the fact that the antimicrobial therapy (macrolides, fluoroquinolones) for Legionnaires' disease differs from that for the more common bacterial pneumonias. The mortality from Legionnaires' disease, if inadequately treated, can be as high as 15%. Recurrent chills, which occur over several days in Legionnaires' disease, are rare in pneumococcal pneumonia unless septic complications (e.g., endocarditis and pericarditis) develop. Although the initial radiographic picture of *Legionella* pneumonia is often that of an interstitial, segmental, or bronchopneumonic pneumonia, if the disease is untreated, it progresses to lobar or multilobar consolidation, a picture that mimics pneumococcal or *Klebsiella* pneumonia.

The other noteworthy bacterial types of atypical pneumonia are those due to *F. tularensis* (tularemic pneumonia), *Yersinia pestis* (plague pneumonia), and *Bacillus anthracis* (anthrax pneumonia). These are all singularly uncommon causes of pneumonia, and the principal clues to diagnosis again derive from epidemiologic considerations, including the risk of bioterrorism.

Exposure to *F. tularensis* comes through contact with tissues of an infected animal (rabbit), animal bites (coyote, cat), inhalation of infectious aerosols, tick or deerfly bites, or ingestion of contaminated water or poorly cooked meat from an infected animal. Ulceroglandular tularemia, or the typhoidal form of tularemia, may be complicated by patchy pulmonary infiltrates. Indeed, it is likely that typhoidal tularemia often represents infection initially acquired via the bronchogenic route. Plague is less common than tularemia in the United States and is strictly localized to southwestern states, including California. The diagnosis should be considered in a person from an endemic area who has a septic illness (septicemic plague) or painful localized lymphadenopathy with fever (bubonic plague) and a history of bites by rodent fleas or of handling tissues of infected animals, such as prairie dogs or coyotes. Pneumonia occurs as a complication in 10% to 15% of patients with bubonic or septicemic plague. Primary (inhalation) pneumonic plague is extremely rare and occurs only as a result of exposure to aerosolized particles from an infected animal or following close contact with cases of plague pneumonia.

Anthrax pneumonia (inhalation anthrax) is also extremely rare in Western regions; it is a consequence of the inhalation of anthrax spores during the processing, or use, of goat skin, hair or wool (usually imported from the Middle East, Asia, or Africa). The presence of influenza-like illness with chest radiographs demonstrating mediastinal widening and pleural effusions, less commonly with infiltrates, was observed with anthrax spread in 2001 via contaminated U.S. mail. After an initial phase with improvement over 3 to 5 days, the abrupt onset of high fever and severe respiratory distress (dyspnea, stridor, cyanosis) progresses to shock and respiratory failure over 24 to 36 hours.

The principal clues to the presence of pulmonary mycoses are epidemiologic (see Chapter 134). Thus, the principal endemic areas for histoplasmosis in this hemisphere are in the Midwestern United States and Central America. However, disease can be found in other locales (e.g., Northeastern US) and after travel. The organism is present in high concentrations in soil sites where avian, chicken, or bat excrement has accumulated. Movement of soil in such endemic areas by cleaning chicken coops or bird roosts, in old attics, or caves can expose people to high concentrations of airborne spores that, when inhaled, produce an acute pneumonia.

Blastomycosis occurs in most states in this country, but the endemic area is principally in the southeastern and south central areas. Rural exposure to soil contaminated with animal excrement appears to be a risk factor. Skin lesions, either verrucous or ulcerative, are the most common extrapulmonary manifestations of blastomycosis and afford a clinical clue to diagnosis.

Coccidioidomycosis is endemic in the southwestern United States (California, particularly the San Joaquin Valley, and Arizona) and in neighboring portions of Mexico. Infection is usually acquired in these areas by inhalation of highly infectious arthrospores. Occasionally, major dust storms carry the arthrospores considerable distances from their soil source and produce unexpected outbreaks of infection. Archeologic digs sometimes cause infection in those living elsewhere who receive an artifact uncovered in the explorations. Erythema nodosum may be associated with any of the primary pulmonary mycoses, but most often with coccidioidomycosis. The coincidence of this hypersensitivity skin lesion and an atypical pneumonia syndrome in a person from an endemic area suggests the possibility of one of these pulmonary mycoses.

Paracoccidioidomycosis (South American blastomycosis) is endemic to Brazil and in Colombia, Venezuela, and Argentina. This disease is caused by *Paracoccidioides brasiliensis*. In adults, the manifestations of this disease are mainly pulmonary; radiographs show patchy or confluent areas of consolidation, often bilateral. Cases have occurred in North America and Europe, but in those instances, the patients had previously resided in endemic areas where initial infection presumably had been acquired.

■ ASPIRATION PNEUMONIA

Aspiration pneumonia may occur after an overt episode of aspiration (e.g., of gastric contents) or of bronchial obstruction by a foreign body. More often the predisposing circumstances are clear-cut (e.g., alcoholism, nocturnal esophageal reflux, pyorrhea, a

prolonged session in the dental chair, epilepsy, or chronic sinusitis in a patient with absent gag reflex) (see Chapter 127). If untreated, aspiration pneumonia may progress rapidly to a necrotizing process that is usually due to anaerobic organisms. The process may involve a pulmonary segment, a lobe, or an entire lung, with ultimate extension to the pleura ("putrid empyema"); in some patients, the necrotizing pneumonia culminates in lung abscesses.[59] In others, aspiration produces an illness of several weeks' duration that is characterized by malaise, productive cough, and low-grade fever. If a chest radiograph is first taken after several weeks of untreated illness, it may show little, if any, evidence of pneumonia but will clearly identify a well-formed lung abscess.

In community-acquired aspiration pneumonia, bacteriologic studies provide a statistical basis for selecting initial antimicrobial therapy. Anaerobic bacteria are etiologically implicated in about 90% of community-acquired aspiration pneumonias and lung abscesses.[60] In 40% to 65% of these patients, anaerobic organisms are the sole infecting agents; in 40% to 45%, the cause is a mixture of anaerobes and aerobes. The most common anaerobes are *Prevotella melaninogenica*, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, peptostreptococci, peptococci, and microaerophilic streptococci. β-Lactamase–producing *Bacteroides* species, *P. melaninogenica*, and members of the *B. fragilis* group are present in about 15% of cases. *P. melaninogenica* may be the most important contributor in such mixed infections. The aerobic indigenous flora in mixed aerobic–anaerobic infections includes *Streptococci viridans*, *M. catarrhalis*, and *Eikenella corrodens*.

A rare form of anaerobic aspiration pneumonia (actinomycosis) that is community acquired is that due to *Actinomyces israelii*, part of the normal flora in the gingival crevice or may contribute to chronic sinus infection. The direct extension of such a necrotizing pneumonia to the pleura and chest wall is a characteristic finding that strongly suggests the diagnosis of actinomycosis.

Although anaerobic members of the oropharyngeal flora have a pre-eminent role in community-acquired aspiration pneumonia and lung abscess, occasionally colonizing gram-negative enteric bacilli such as *K. pneumoniae*, *E. coli*, and *Proteus* species may be the cause (notably in alcoholics).[59,60] Persistence of a necrotizing pneumonia or lung abscess despite antimicrobial therapy that would be expected a priori to be effective raises the possibility of an underlying obstruction, often in the form of bronchogenic carcinoma, particularly if the patient is edentulous.

Pneumonia in the Elderly

CAP in the elderly (over 60 years) primarily affects two populations: one that lives at home and another residing in nursing homes. The latter, from the point of view of oropharyngeal flora and the extent of exposure to antimicrobial agents, is generally considered as a part of HCAP, with a predisposition to nosocomial infection (see below) with an increased rate of antimicrobial resistance.[61] Pneumonia in the elderly has a more gradual onset, with less fever and cough, often with a decline in mental status or confusion and generalized weakness, often with less readily elicited signs of consolidation on examination. Among the bacterial causes of CAP in the elderly, *S. pneumoniae* is the most frequent, accounting for 30% to 60% of cases. *H. influenzae*, primarily nontypable strains, is the second most common cause (about 20%). *M. catarrhalis* is another cause of pneumonia in this age group, primarily in patients with chronic bronchitis. Aspiration pneumonia due to mixed aerobic–anaerobic flora occurs in this age group, particularly because of the presence of a diminished gag reflex or impaired pharyngeal motor function.

In nursing home residents or persons with recent hospitalizations, increased oropharyngeal colonization with gram-negative bacilli occurs, due to antimicrobial exposure, or exposure to the hospital environment or to other recent patients.[62] Microaspirational events predispose to pneumonia due to species such as *K. pneumoniae, E. coli* and other Enterobacteriaceae, and *P. aeruginosa*. Such gram-negative bacilli have been implicated as the cause in 25% to 40% of elderly nursing home residents with pneumonia. *S. aureus* is responsible for 2% to 10% of cases of CAP in the elderly overall, more commonly in nursing home residents and during community outbreaks of influenza. Common forms of CAP are also seen in the elderly.

HEALTHCARE-ASSOCIATED, HOSPITAL-ACQUIRED, VENTILATOR-ASSOCIATED, AND NONRESOLVING PNEUMONIAS

The hospitalized patient with pneumonia poses the dual challenge of infection with nosocomial pathogens and the presence of concomitant processes—the "sick" patient (Fig. 122-11) (see Chapter 129).[63]

Nosocomial pneumonia occurs at a rate of 5 to 10 cases per 1000 hospital admissions. The incidence increases 6- to 20-fold in patients receiving assisted ventilation. Hospital-acquired pneumonia (HAP) develops over 48 hours into hospitalization, while VAP occurs more than 48 to 72 hours after endotracheal intubation. HCAP includes patients with infection developing within 90 days of hospitalization, residents in a nursing home or long-term care facility, or had recent exposure to hemodialysis, intravenous antimicrobial therapy, chemotherapy, wound care, hospital-associated clinics. HAP accounts for up to a quarter of ICU infections. VAP occurs in up to a quarter of intubated patients in some series, generally in the first 4 days of intubation.[20,64,65]

Early-onset (first 3 days) nosocomial pneumonia is more often due to organisms without antimicrobial resistance including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Community-acquired atypical pathogens (*Mycoplasma, Chlamydophila*) may also be seen early in hospitalization. Beyond 5 days of hospitalization, or in those with recent hospitalization or with prior antimicrobial therapy, infection is more often due to MDR organisms (*K. pneumoniae*, other *Enterobacteriaceae, Acinetobacter* species, and *P. aeruginosa*) and mortality is increased.[64,65] Attributable mortality for nosocomial pneumonia exceeds 50%.

In practice, pneumonia is defined as the presence of new or progressive radiologic infiltrate coupled with evidence that the infiltrate is of infectious origin—fever >38°C, leukocytosis or leucopenia, and/or purulent secretions. Two out of three criteria are generally considered adequate. Tracheal aspirates generally contain the offending organism(s) but may be contaminated by upper tract flora, notably with tracheobronchitis. Semiquantitative cultures are used to discriminate between pathogens and commensals. Gram staining of such specimens will provide added information about host response (neutrophils and macrophages) and predominant bacterial forms. In immunocompromised hosts, fungal smears and cultures, cultures and microscopy for Legionella, Nocardia, and mycobacteria should also be obtained. A good sputum specimen or aspirate lacking bacteria or inflammatory cells (in a nonneutropenic host) should suggest other diagnoses (nonbacterial or noninfectious). While the majority of HAPs are bacterial, nosocomial infection due to respiratory viruses and Legionella species are common. A negative Gram stain of a good tracheal aspirate has a strong negative predictive value (~94%) for VAP.

Use of appropriate antimicrobial agents initially has a major beneficial impact on patient survival.[66] Prior antimicrobial therapy and colonization patterns must be considered as risk factors for antimicrobial-resistant pathogens.[62] The major pathogens in "hospital-acquired" pneumonia vary between institutions and within hospitals. Thus, empiric therapies must be individualized by institution as well by patient. Initially broad-spectrum antimicrobial therapy directed at the likely pathogens (by clinical assessment) and to the major resistant flora of the given institution is likely to avoid inappropriate

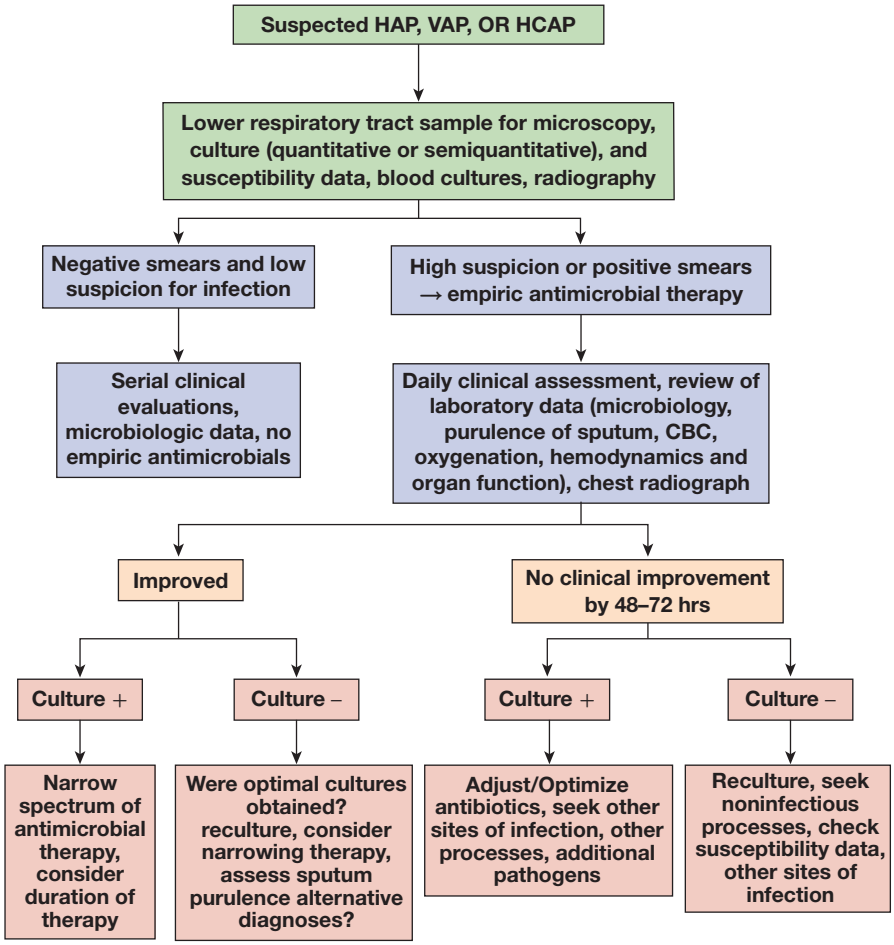


Figure 122-11 Algorithm for the evaluation of patients with nosocomially acquired pneumonia. Careful reassessment of patients on a daily basis is needed to assure an adequate response to therapy. Clinical judgment is the best guide to the use of empiric therapy.

selection of agents. This must be coupled with "de-escalation" of therapy based on culture data. Initial therapy should utilize appropriate doses of bactericidal therapies (including loading doses). If the patient has recently received antimicrobial therapy, drugs from a different class should be used in initial therapy. In normal hosts, sputum Gram stains are useful in gauging response to therapy (disappearance of neutrophils) while chest radiographs and oxygenation are helpful in evaluating response to therapy. Re-evaluation of antimicrobial selections must be made as microbiologic data become available and the clinical progress of the patient is observed.

MDR pathogens provide special challenges. Risk factors for MDR infection include recent hospitalization or antimicrobial therapy, exposure to clinical environment (dialysis, clinic, home intravenous therapy), and immune compromise (see Table 122-9). In intensive care units, *Burkholdaria* (formerly *Pseudomonas*) *cepacia*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*, and *Acinetobacter baumannii* (formerly *Acinetobacter calcoaceticus* variant *anitratus*) have been implicated in localized outbreaks of nosocomial pneumonia. Combination therapy for gram-negative bacterial pneumonia is generally reserved for two situations: suspected *Pseudomonas* pneumonia or in the initial therapy of nosocomial pneumonia while susceptibility data are pending. Community- and hospital-acquired *S. aureus* is increasingly resistant to beta-lactam antimicrobial agents[58] (MRSA). Both Vancomycin and linezolid are reasonable alternatives for MRSA in this setting.

FAILURE OF THERAPY

Nonresolving pneumonia is observed as a result of inappropriate antimicrobial therapy, superinfection, inadequate host response, obstruction, empyema, noninfectious processes, or recurrent infection.[67] Inappropriate antimicrobial therapy includes inadequate dosing, agents that fail to penetrate infected lung tissue (e.g., aminoglycosides), or use of agents to which the organisms are resistant.[66] Empyema or loculated infection may occur during the course of appropriate therapy for pneumonia. Relapsed infection is common in intubated patients colonized with resistant microorganisms. Superinfection with resistant organisms (including

TABLE 122-9 Factors in the Emergence of Antimicrobial Resistance

Increase in "high-risk" (immunodeficient) population
Prolonged survival of persons with chronic diseases
Greater severity of illness of hospitalized patients
Newer devices and procedures in use
Increased introduction of resistant organisms from the community
Congregate facilities (e.g., jails, day care centers)
Increased use of antibiotics in animals and agriculture
Physician practices that contribute to inappropriate antibiotic use
Providing antibacterial drugs to treat viral illnesses
Using inadequate diagnostic criteria for infections that may have a bacterial etiology
Providing expensive, broad-spectrum agents that are unnecessary
Prescribing antibiotics at an improper dose or duration
Lack of rapid, accurate diagnostic tests to distinguish between viral and bacterial infections
Selection of antibiotic-resistance genes via abuse of antimicrobial agents
Ineffective infection control and isolation practices and compliance

TABLE 122-10 Noninfectious Causes of Febrile Pneumonitis Syndrome (Mimics of Pulmonary Infection)

Drug-induced pulmonary disease
Extrinsic allergic alveolitis
Injury due to inhaled toxic gases, dusts, chemicals
Acute eosinophilic pneumonia
Pulmonary infiltrate with eosinophilia (PIE syndrome)
Chronic eosinophilic pneumonia
Interstitial lung disease associated with autoimmune/connective tissue disorders
Systemic lupus erythematosus
Polymyositis–dermatomyositis
Mixed connective tissue disease
Interstitial lung disease associated with pulmonary vasculitis
Granulomatous polyangiitis (Wegener granulomatosis)
Lymphomatoid granulomatosis
Churg–Strauss syndrome (allergic angiitis and granulomatosis)
Polyangiitis overlap syndrome
Interstitial lung disease associated with airway disease
Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Bronchiolitis obliterans (OB) and bronchiolitis obliterans with organizing pneumonia (BOOP)
Acute or subacute interstitial pulmonary fibrosis (AIP)
Chronic interstitial pneumonias of unknown origin
Usual interstitial pneumonia (UIP)
Lymphocytic interstitial pneumonia (LIP)
Desquamative interstitial pneumonia (DIP)
Giant cell interstitial pneumonia (GIP)
Pulmonary neoplasms
Sarcoidosis
Pulmonary infarction
Acute chest syndrome in sickle-cell crisis
Radiation pneumonitis
Lipoid pneumonia (exogenous or endogenous)
Acute respiratory distress syndrome (ARDS)
Extrapulmonary sepsis
Oxygen toxicity, chemical inhalation or aspiration, or aspiration of gastric contents
Pancreatitis
Fat embolization (surgery, trauma)
Shock of various etiologies
Drug overdose (aspiration)
Chest trauma
Pulmonary leukoagglutinin transfusion reactions
Pulmonary alveolar proteinosis
Plasma cell granuloma
Eosinophilic granuloma
Idiopathic pulmonary hemosiderosis
Goodpasture syndrome
Miscellaneous

fungi, *M. tuberculosis*) may occur in the hospital setting as well as viral coinfection with community-acquired respiratory viruses. Untreated bacteremia (endocarditis, abdominal abscess, catheter-associated infections) or septic pulmonary emboli may cause persistent lung infections.

In the compromised host, repletion of antibodies, neutrophils (colony-stimulating factor), treatment of concomitant viral infections (HIV, CMV), and repeat culturing may assist in management. Obstruction or empyema must resolve to allow resolution of infection. Recurrent infection may be observed if the patient is aspirating, has sinusitis, has a misplaced feeding tube, has airway compromise, or has pulmonary infarction. Additional cultures and radiologic studies (CT scans) may assist in defining lung processes failing to respond to therapy. Bronchoscopic evaluation and, in selected patients, lung biopsy may assist in management.

NONINFECTIOUS PROCESSES MIMICKING PULMONARY INFECTIONS

The list of noninfectious disorders that mimic pulmonary infections is extensive (Table 122-10). These should be considered in the course of taking the initial history.

The likelihood of noninfectious etiologies of pulmonary disease increases if the Gram-stained smear and culture of sputum are unrevealing, if the initial response to empiric antimicrobial therapy proves unsatisfactory, or if radiographic findings are atypical. Similar histologic appearances result from both infectious and noninfectious etiologies. The presence of a maculopapular skin rash, generalized lymphadenopathy, joint or rheumatologic symptoms, and/or peripheral eosinophilia should suggest hypersensitivity. However, as noninfectious and infectious processes often coexist, it is essential to exclude infectious causes of pulmonary dysfunction before treating (e.g. hypersensitivity reactions). Immunosuppressive agents, notably corticosteroids, will reduce inflammation due to both infectious and noninfectious causes.

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CHAPTER 123

Pulmonary Infection in Immunocompromised Hosts

Jay A. Fishman

OVERVIEW

A growing group of individuals who have acquired immunodeficiency syndrome (AIDS), who are receiving immunosuppression for solid-organ transplantation, bone marrow transplantation (BMT), or for autoimmune ("connective tissue" diseases), who have primary immune deficiencies, or who have been treated with chemotherapeutic regimens for cancer, have increased susceptibility to infection as a result of acquired or intrinsic immune deficiencies. Prolonged survival of such immunocompromised individuals reflects the deployment of newer laboratory assays and newer antimicrobial agents, including antifungal, antibacterial, and antiviral agents (e.g., ganciclovir, foscarnet, oral agents) and highly active antiretroviral therapies (HAART) for HIV infection, hematopoietic growth factors, and clinical experience in caring for such patients. Wide use of immunosuppressive drugs, including "biologic agents," which are generally antibodies targeting specific cell types or pathways of inflammation, has further expanded susceptible populations.

Major challenges in providing care to these patients include systemic infections for which therapies or vaccines are limited or absent (e.g., management of respiratory viruses) and progressive antimicrobial resistance of common pulmonary pathogens, including *Staphylococcus aureus*, *Enterococcus*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas* (formerly *Xanthomonas*), and *Burkholderia* species. In addition, selection of novel strains of bacteria, including nontuberculous mycobacteria and *Nocardia* species, has proved challenging. Resistance has increased to antimicrobial agents commonly used for prophylaxis (i.e., TMP-SMX and fluoroquinolones).

An essential difference exists in the management of pneumonia in immunocompromised individuals when compared with normal hosts. *Given the broad spectrum of potential pathogens and of noninfectious processes that may mimic infection, coupled with the inherent toxicities of many therapies, a specific microbiologic diagnosis should be considered essential to the management of pulmonary processes in the immunocompromised host.*

GENERAL PRINCIPLES OF MANAGEMENT OF OPPORTUNISTIC INFECTION

Important principles underlying the management of opportunistic infections in immunocompromised patients are discussed below.

Opportunistic infection is defined as infection occurring as a result of compromised immune function and that would not be expected to occur, or would otherwise cause disease of lesser intensity in the presence of normal immune function. Thus, immunocompromised individuals are subject to infections commonly present in the community; however, these infections are likely to be of greater frequency or severity than in the immunologically normal host. In addition, infection in these patients may be caused by organisms of low native virulence or that cause insignificant disease in the normal host, including such organisms as *Pneumocystis jiroveci (PCP)* or cytomegalovirus (CMV).

The risk of infection in any patient is determined by the interaction of two factors: the potential pathogens to which the individual is exposed (epidemiologic exposures), and a measure of the individual's susceptibility to infection, termed the "net state of immunosuppression" (Table 123-1).[1–3] The occurrence of infection in an individual at a time when the immune status of the patient is thought to be nearly normal is evidence that either an excessive environmental exposure has occurred or that the immune status of the individual is depressed. Conversely, even minimal environmental exposures may cause invasive infection in an individual who is maximally immunosuppressed.

EPIDEMIOLOGIC EXPOSURES

Epidemiologic exposures of importance to the immunocompromised patient may be divided into three general categories: those occurring within the community, those occurring within the hospital, and those associated with infection transmitted with donor cells or organs (transplantation). Exposures within the community vary, based on such factors as geography and socioeconomic status, and may be recent or remote in time. Thus, opportunistic pathogens acquired in the community include the geographically restricted systemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis), *Mycobacterium tuberculosis, Strongyloides stercoralis, Leishmania donovani, P. jiroveci, Legionella* species, and community-acquired respiratory viral infections (e.g., influenza, adenovirus [AV], respiratory syncytial virus [RSV], parainfluenza virus [PIV], and metapneumovirus). Common viral agents may include herpes simplex virus (HSV), CMV, varicella-zoster virus [VZV], and hepatitis B and C viruses. Due to the limited effectiveness of many vaccines in immunocompromised individuals, infections due to influenza, *Streptococcus pneumoniae,* and *Haemophilus influenzae* are common.

TABLE 123-1 Factors in the "Net State of Immune Suppression"

Immunosuppressive therapy
Dose
Duration
Temporal sequence
Underlying immune deficiency
Autoimmune disease
Functional immune deficits
Mucocutaneous barrier integrity
Catheters
Epithelial surfaces
Devitalized tissue
Fluid collections
Neutropenia, lymphopenia
Metabolic conditions
Uremia
Malnutrition
Diabetes
Alcoholism with cirrhosis
Viral infection
Cytomegalovirus
Epstein–Barr virus
Hepatitis B and C
Human immunodeficiency virus
Respiratory viruses

Within the hospital, excessive environmental exposures may be divided into two general categories: domiciliary and nondomiciliary. Domiciliary exposures occur on the hospital unit where the patient is housed. When the air, food, equipment, or potable water supply is contaminated with pathogens such as *Aspergillus* species, *Legionella* species, or vancomycin-resistant enterococci (VRE), clustering of cases of infection in time and space will be observed. As a result, an increased incidence of nosocomial pneumonia or catheter and wound infections may be seen. Nondomiciliary exposures occur when the patient is transported to contaminated operating rooms, radiology suites, or catheterization laboratories for procedures. Nondomiciliary outbreaks, although possibly more common, are more difficult to detect because of the lack of clustering on a particular hospital unit. The leading clue to the presence of a nosocomial hazard is the occurrence of opportunistic infection in a patient whose net state of immunosuppression would not normally lead to such an event or nosocomial infection with organisms not known to be present on the clinical unit on which the patient is housed.

NET STATE OF IMMUNOSUPPRESSION

The "net state of immunosuppression" (Table 123-1) is a conceptual framework for the host factors that contribute to infectious risk.[1] These include: the dose, duration, and temporal sequence in which immunosuppressive drugs are deployed; injuries to the primary mucocutaneous barrier to infection (e.g., indwelling catheters and drains); leaks and fluid collections (hematoma, effusions, ascites); ischemic or underventilated tissues; surgical anastomoses; neutropenia or lymphopenia; underlying immune deficiency; pulmonary aspiration injury; metabolic problems including protein–calorie malnutrition, uremia, and hyperglycemia; and infection with immunomodulating viruses (CMV, Epstein–Barr virus or EBV, hepatitis B or HBV, and hepatitis C or HCV, influenza, and the human immunodeficiency viruses, HIV). These viruses predispose to other opportunistic infections and also to graft rejection and to graft-versus-host disease (GVHD). Foreign materials (e.g., vascular grafts, heart valves, sutures) provide a nidus for infection for an organism that would not be capable of causing infection under normal conditions. Thus, *Salmonella* infection in the organ transplant recipient "homes" to vascular anastomoses or grafts and may persist despite appropriate therapy, causing mycotic aneurysms.

The sum of the congenital, metabolic, operative, and surgery-related factors is the patient's "net state of immune suppression." Generally, more than one factor is present in each host; the identification of the relevant factors, and correction when possible, is central to the prevention and treatment of infection in these hosts. For example, in the lung transplant recipient with CMV infection and thoracic fluid collections, the net state of immune suppression includes the immunosuppression used to maintain graft function; diminished immunologic responsiveness due to CMV; the risk of empyema and bacteremia from fluid collections at surgical sites; exposure to, and colonization with, community-acquired and nosocomial organisms; and new infections (e.g., aspiration, *Clostridium difficile* colitis) that may occur during the prolonged waiting period for a compatible organ. When the organ for transplantation becomes available, it may carry latent infection (e.g., CMV, EBV) or organisms acquired by the donor during hospitalization (e.g., bacteremia) or procurement. The recipient is often critically ill and is subjected to a major surgical procedure. After surgery, the lungs are apt to be compromised, recovery of function in the allograft is often slow, immunosuppressive drugs are initiated, intravenous and urinary catheters and drains are placed, and major incisions need to heal. Drug toxicities are common and may result in renal dysfunction, confusion, or neutropenia. The sum of the underlying, operative, and transplant-related factors is the *net state of immune suppression*.

Pulmonary defense mechanisms are compromised to varying degrees in immunocompromised hosts (see Chapter 121). Structural defects (fibrosis, airway or lymphatic obstruction by tumor, emphysema) interfere with normal clearance mechanisms. Clearance mechanisms are further impaired by excess mucus and ciliary defects, as in cystic fibrosis, congenital defects, and postlung transplantation, including those due to recent viral or bacterial infections. For example, *Mycoplasma* shears off epithelial cilia, incapacitating the mucociliary elevator. Viral infections may immobilize pulmonary macrophages (CMV), produce local or systemic immunosuppression, and disrupt the local cytokine network. Alveolar macrophages are diminished in number and function in neutropenic hosts and in stem cell transplant (SCT) recipients. These effects are amplified in the lung transplant recipient in whom the impact of systemic immunosuppression is added to the possible effects of tracheal anastomotic narrowing and tissue ischemia, an impaired cough reflex, progressive bronchiolitis obliterans syndrome, decreased pulmonary T-cell and macrophage functions, hypogammaglobulinemia, and disrupted lymphatic drainage. Thus, in the solid-organ transplantation recipient, the immunosuppression used to prevent graft rejection, as well as technical factors, the diminished host immune responses in the major histocompatibility-mismatched organ, and the impact of immunosuppressive viral infections are the main mediators of susceptibility to infection.

In the stem cell recipient, the intensity of immunosuppression varies with the degree of histocompatibility mismatch between donor and recipient. Nonmyeloablative regimens have reduced the duration of the initial period of neutropenia. However, susceptibility to infection in both autologous and allogeneic HCT recipients persists despite immune reconstitution. Innate immune function is reduced early (first 6 months) as NK cells and alveolar macrophages suffer dysregulation of cytokine, eicosanoid (leukotrienes, prostanoids), and intracellular signaling, and alterations in scavenger receptors, resulting in reduced phagocytosis and bacterial and fungal killing. Over time, persistent reductions are observed in multiple T- and B-cell lineages and maintained in the setting of chronic GVHD. T-cell functions are suppressed by the immunosuppressive agents used to prevent or treat GVHD.

TIME LINES OF INFECTION

With standardized immunosuppressive and chemotherapeutic regimens, specific types of infections often occur in a predictable pattern ("time line") as a reflection of the specific risk factors (Figs. 123-1 and 123-2) present at each phase of the posttransplantation course. These time lines are altered by specific immunosuppressive regimens, use of antimicrobial prophylaxis, and individual factors (e.g., underlying immune deficits, microbial colonization, organ dysfunction, epidemiologic exposures), but they are useful in considering the "likely" etiology of infectious syndromes in immunocompromised hosts.

The time lines (Figs. 123-1 and 123-2) are used in a number of ways: (1) To develop a *differential diagnosis* for infectious syndromes by time posttransplant—what type of infections are most likely at various times after transplantation. (2) To develop prophylactic strategies for each patient population based on general considerations (e.g., duration of neutropenia or of T-cell defects) and patient- or institution-specific patterns (e.g., microbial resistance, drug allergies). (3) To identify *excess epidemiologic hazards*, including *nosocomial hazards*, for example, *Aspergillus*, MRSA, VRE, which may be clustered in time and space, by inpatient unit, by procedures, or surgical suite; *community exposures*, for example, respiratory viruses, *Legionella*, other outbreaks (SARS); and *individual risks*, including unique exposures (e.g., hobbies), travel, and occupational hazards. (4) *To assess excessive immunosuppression*—too many infections or unusual severity and/or at the wrong time on

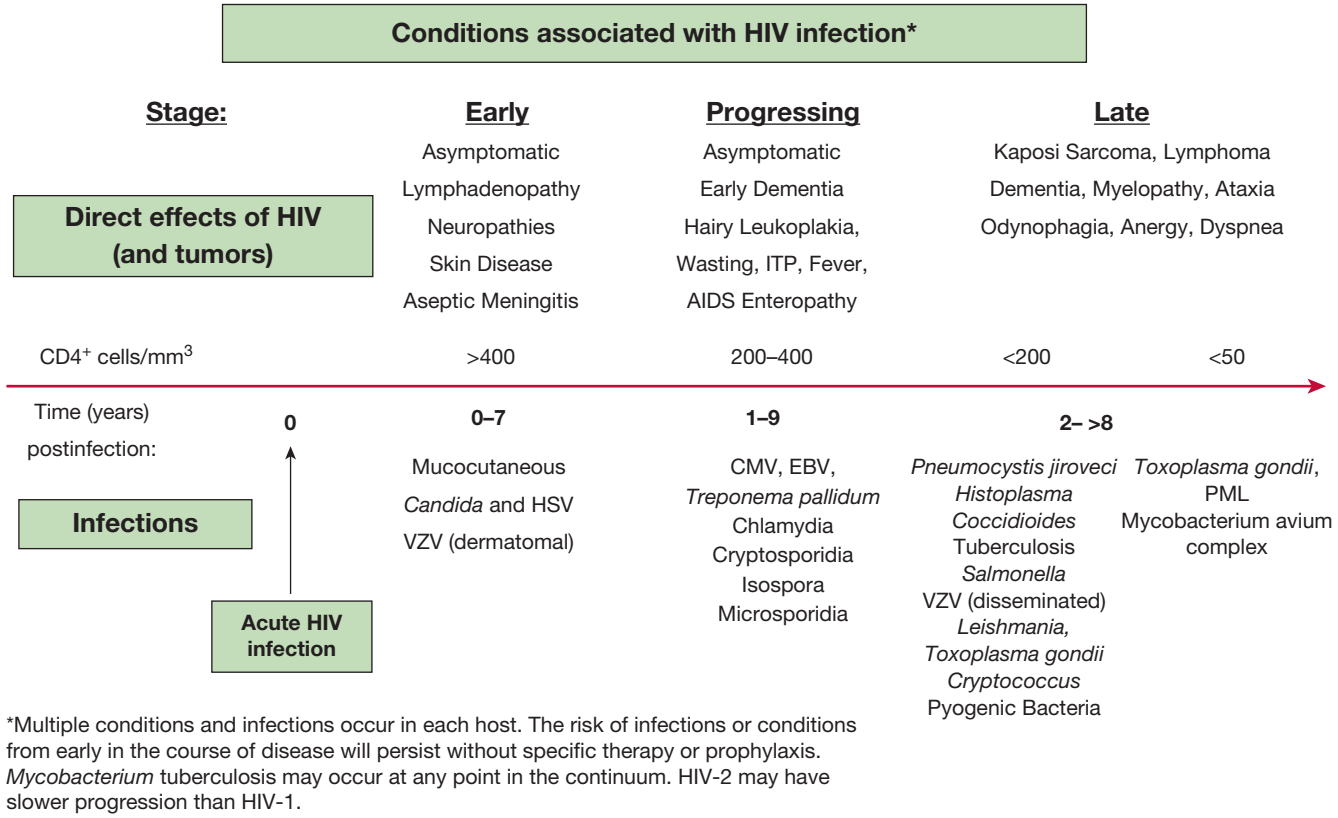


Figure 123-1 The progression of AIDS-associated conditions without effective antiretroviral therapy.

time line suggesting that a problem exists with routine immunosuppressive regimens.

The patterns are altered by antimicrobial prophylaxis, by antiviral therapies for HIV, CMV, and hepatitis B and C viruses, the broader range of immunosuppressive and chemotherapeutic agents, and the use of nonmyeloablative conditioning regimens for HCT. However, the general concepts and major determinants of infection remain the same—the epidemiology of the patient and the intensity of immunosuppression coupled with mucosal injuries and other individual risk factors. Superimposed viral infections will increase the risk of opportunistic infection at any point along the time line.

In immunocompromised hosts, the risks of infection may be *relatively stable* over time, as in the diabetic with vasculopathy and neuropathy who is prone to skin and soft tissue infections. The risks

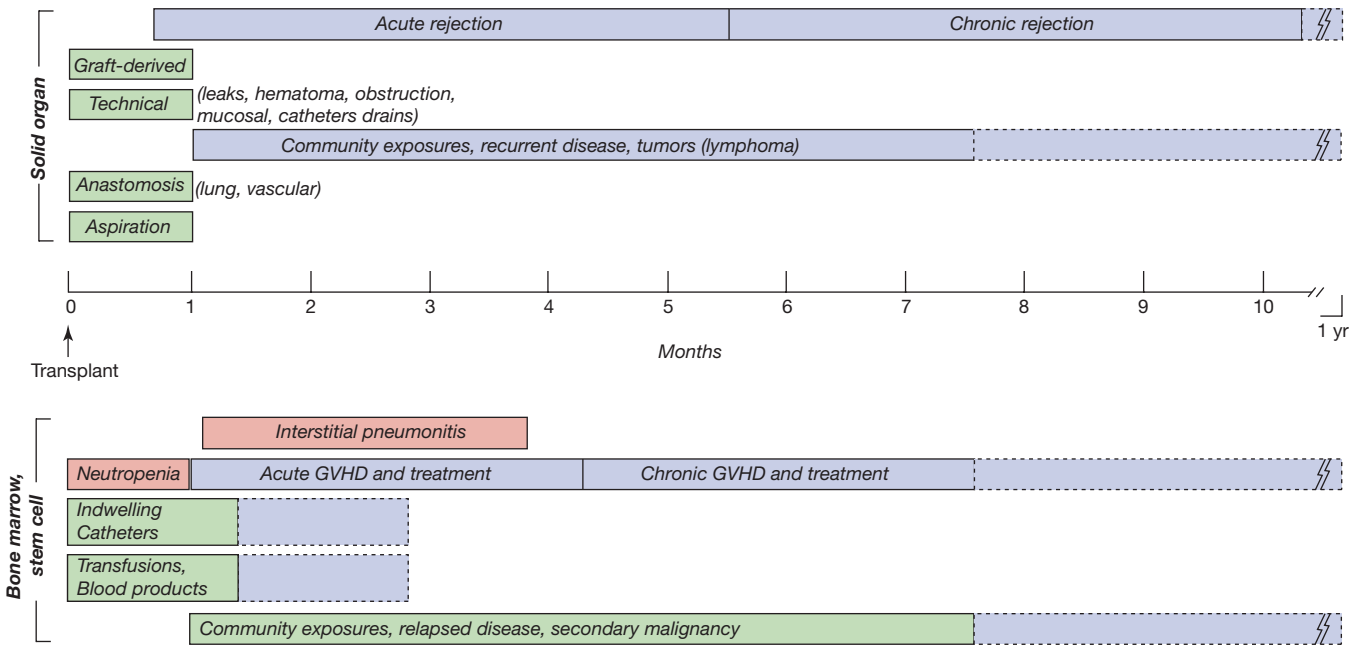


Figure 123-2 The time lines of conditions predisposing to infection in solid-organ transplantation (above the time line) and in bone marrow and stem cell transplantation (below the time line). Patients vary in individual susceptibility patterns and with regard to prophylactic therapies.

TABLE 123-2 Pretreatment Evaluations for Infectious Disease Risk in Immunocompromised Hosts

Anticipated Immune Deficit	Common Serologic and Other Assays	Routine Evaluations
Biologic agents (antibody therapies)	PPD/IGRA-TB, hepatitis A, hepatitis B, MMR, Histoplasma[a], Coccidioides[a]	Chest radiograph (and/or CT)
Solid-organ transplantation	CMV, EBV, HSV, VZV, HBV, HCV, HIV, MMR, PPD/IGRA-TB, Toxoplasma, VDRL, Strongyloides[a], T. cruzi[a], Coccidioides[a], Histoplasma[a]	Chest radiograph (and/or CT), urine cultures, sputum culture[a]
Hematopoietic cell transplant	CMV, EBV, HSV, VZV, HIV, HBV, HCV, T. cruzi[a], PPD/IGRA-TB, VDRL, HTLV, Strongyloides[a], T. cruzi[a], Coccidioides[a], Histoplasma[a], malaria[a]	Chest radiograph (and/or CT), *S. aureus* nasal culture, VRE rectal swab, *Aspergillus* nasal swab, serum galactomannan assay[a]; improved donor HLA matching
HIV/AIDS	HIV, PPD/IGRA-TB, toxoplasma	Chest radiograph (and/or CT), parasitic evaluation[a]

[a]*Where indicated by history.*

IGRA-TB, Interferon-gamma release assay for tuberculosis; CMV, cytomegalovirus; VZV, varicella-zoster virus; HSV, herpes simplex virus; EBV, Epstein–Barr virus; HTLV, human T lymphotrophic virus; VDRL, venereal disease research laboratory; TB, tuberculosis; HBV, Hepatitis B (hepatitis B surface antigen. antibodies to hepatitis B surface antigen antibodies to hepatitis B core antigen) ± viral load; HIV: HIV-1, -2 antibodies ± viral load; VRE, vancomycin-resistant Enterococcus.

of infection may be *time-limited,* as in the postsurgical patient without complications. The risk of infection may be *cumulative and progressive,* as in the untreated patient with AIDS, in whom infection is a function of declining immune function and immune memory, falling CD4– lymphocyte counts, rising viral loads, and the effects of persistent infections (CMV, *Cryptosporidium*) (Fig. 123-1). In these individuals, the occurrence of new types of infection suggests the progression of immune compromise.

The risks of infection may also *change predictably with time* as a function of relatively standardized immunosuppressive regimens and the evolving condition of the patient, as in allogeneic HCT or solid-organ transplantation. For example (Fig. 123-2), in the early phase after bone marrow or hematopoietic cell transplantation or the "pre-engraftment phase," the risk for infection is driven by neutropenia and mucositis and is generally related to nosocomial or endogenous exposures (gram-negative and gram-positive bacteria, *Candida* and *Aspergillus* species) during neutropenia. With nonmyeloablative preparative regimens, this period is generally 14 to 21 days, but it may be significantly longer. This reflects microbial colonization, pre-existing infections, and the impact of vascular access catheters, as well as defects in innate immune function and in mucosal barriers. Subsequently, following marrow engraftment ("early postengraftment phase" of 3 weeks to 3–6 months), but with continued immunosuppression and the absence of full cellular immune function, viral infections predominate, including pneumonitis or colitis (HSV, shingles, CMV, respiratory and enteric viruses), as well as encapsulated bacteria, *Pneumocystis,* and *Aspergillus*. In this period, unusual infections (toxoplasmosis) and endemic pathogens must also be considered. Thus, "common" pathogens might be dengue virus and tuberculosis in Southern Asia, or paracoccidioides and tuberculosis in Brazil. Full immune recovery is not achieved before 12 to 24 months, and gaps in immune function may persist for longer periods. During the development of, and treatment for, acute and chronic GVHD, susceptibility to infection is a function of the intensity of immunosuppression and mucosal injuries (from GVHD, chemotherapy, radiation, or infections such as *C. difficile* colitis). In patients with GVHD in particular, bronchiolitis obliterans, posttransplant lymphoproliferative disorders, and idiopathic pneumonitis syndrome may be observed. Nonmyeloablative conditioning has reduced the rate of diffuse alveolar hemorrhage (early), hepatic veno-occlusive disease (HVOD), and idiopathic pneumonitis syndrome.

In the solid-organ transplant recipient, immunosuppression is used for the life of the transplanted organ. Early (first month) nosocomial infections (surgical and nosocomial) and donor-derived infections are observed but opportunistic infections are not generally observed as the full impact of immunosuppression is not yet appreciated. After a month, as the effects of immunosuppression are maximized, viral infections (CMV, EBV, other herpesviruses, BK polyomavirus, respiratory viruses) predominate, and opportunistic pathogens (*Nocardia*, *Toxoplasma*, *Cryptococcus*, *Pneumocystis*, mycobacteria, and endemic species) are observed. The endemic species include community-acquired infections, such as geographically restricted fungi (*Histoplasma, Coccidioides, Blastomycosis, Paracoccidioides*) and parasites (Chagas', *Leishmania*).

Because each risk factor renders the patient susceptible to infection by new groups of pathogens, infections occurring with the "wrong" pathogen or at the wrong time suggest an undiscovered "immune deficit" (fluid collection, neutropenia) or an unusual epidemiologic exposure (Table 123-2). The occurrence of specific infections can be prevented by the use of antimicrobial prophylaxis, vaccines, and behavioral modifications (e.g., no raw vegetables or digging in gardens without masks). This will result in a "shift to the right" of the time line in that infections are delayed but incompletely prevented unless the intensity of immunosuppression is reduced.

MICROBIAL VIRULENCE

The risk of infection in any individual patient depends not only on the sum of the immune deficits and epidemiologic exposures, but also on the *virulence* of the organism relative to pulmonary defense mechanisms. Innate and adaptive immune responses will be blunted by immunosuppression, but also, when activated by infection, contribute to rejection of lung allografts or to GVHD. Such factors as the distribution of toll-like receptors (TLRs) and other pattern recognition receptors (PRRs), microbial production of biofilm, and antimicrobial resistance patterns will influence the pathogenesis of infection. Host cells may *enhance* the virulence of the invading organism by the *induction of genes in that organism* that contribute to bacterial persistence or invasion. Thus, resistance to phagocytosis is induced by target cells in *Yersinia* infections.

Another example of the host–pathogen interaction is the role of CMV in transplantation. CMV is the cause of common clinical syndromes in immunocompromised patients. Among these are fever and neutropenia, pneumonitis, hepatitis, glomerulonephritis, gastritis, colitis, retinitis, and mononucleosis-like syndromes. CMV also induces an array of host responses (i.e., immune suppression,

TABLE 123-3 Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia	Leukemia, cytotoxic chemotherapy, AIDS, drug toxicity, Felty syndrome	Enteric gram-negative bacteria, Pseudomonas, S. aureus, Staphylococcus epidermidis, streptococci, Aspergillus, Candida, other fungi
Neutrophil chemotaxis	Diabetes, alcoholism, uremia, Hodgkin disease, trauma (burns), lazy leukocyte syndrome, CT disease	S. aureus, Candida, streptococci
Neutrophil killing	CGD, myeloperoxidase deficiency	S. aureus, E. coli, Candida, Aspergillus, Torulopsis
T-cell defects	AIDS, congenital, lymphoma, sarcoidosis, viral infection, HCT, solid-organ transplants, steroids, purine analogs (fludarabine)	Intracellular bacteria (Legionella, Listeria, mycobacteria), HSV, VZV, CMV, EBV, parasites (Strongyloides, Toxoplasma), fungi (P. jiroveci, Candida, Cryptococcus)
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, ALL	S. pneumoniae, H. influenzae, Salmonella, and Campylobacter spp., Giardia lamblia, gram negative (E. coli, skin)
Splenectomy	Surgery, sickle-cell anemia, cirrhosis	S. pneumoniae, H. influenzae, Salmonella spp., Capnocytophaga canimorsus
Complement	Congenital/acquired defects	S. aureus, Neisseria spp., H. influenzae, S. pneumoniae, Capnocytophaga
Anatomic	IV/Foley catheters, incisions, anastomotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

upregulation of histocompatibility antigens and other cell surface antigens, tumor necrosis factor alpha (TNFα) secretion, diminished antigen presentation, graft rejection) that contribute to the host's susceptibility to infection.[4] This is the result of "viral parasitism"—alterations in the target cell including decreased mobility, phagocytosis, and apoptosis, to assure the survival of the virus. Thus, the concept of "immune status" and "epidemiologic exposure" may require modification based on the virulence and immunoregulatory effects of some pathogens.

The incidence of antimicrobial resistance among bacteria, fungi, and viruses is amplified in the immunocompromised host due to repeated exposures to antimicrobial therapies (often for excessive periods at inadequate doses) and repeated hospitalizations. Increasingly, *Streptococcus* and other gram-positive species are detected with resistance to penicillins, fluoroquinolones, and macrolides. Enterococci are resistant to β-lactam antimicrobials, macrolides, vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, and aminoglycosides. *Pseudomonas, Stenotrophomonas,* and the enteric gram-negative bacteria are often resistant to fluoroquinolones and the broad-spectrum carbapenems. *Candida* and *Aspergillus* species may be resistant to the azole antifungals.

PRETREATMENT EVALUATION AND PROPHYLAXIS

Guidelines for the prevention of infection in common immunodeficiency states are available for HCT, solid-organ transplantation, and AIDS.[5–10] The clinical *evaluation of the patient prior to immunosuppression* may be very helpful in preventing disease (Table 123-3). This evaluation should include a careful epidemiologic history (travel, immigration, exposures including tuberculosis, HIV, endemic fungi and *S. stercoralis*), a vaccination history including *Pneumococcus* and *H.* influenza, varicella zoster, measles, mumps and rubella, diphtheria, pertussis and tetanus, and hepatitis B, exposure to Bacillus Calmette-Guerin (BCG), and chest radiography. Testing for tuberculosis (skin test or interferon-gamma release assay, IGRA) should be routine. Careful evaluation (baseline chest computed tomography [CT] scans) and pretreatment of PPD-positive patients and patients from areas endemic for tuberculosis are advised before HCT and common in solid-organ recipients. *Live virus vaccinations should be avoided in immunocompromised hosts and are best provided well in advance of immunosuppression.* Pretransplant cultures may guide prophylaxis and establish the presence of antimicrobial susceptibility patterns in advance of invasive infection. Serologic studies are often helpful in the stratification of risk for infection in the immunocompromised host (see Table 123-3). The use of CMV seronegative blood products in seronegative individuals may avoid acute infection during periods of intensive immunosuppression.[11]

Given the routine use of antimicrobial prophylaxis in the face of persistent immune defects, infection remains common due to organisms that are resistant to the agents employed. Prophylaxis falls into three categories: (1) Primary or universal prophylaxis in which all at-risk patients receive an agent to prevent common infections (TMP–SMX for *Pneumocystis*). (2) Secondary prophylaxis initiated after treatment to maintain remission or prevent recurrence. (3) Preemptive therapy in which a sensitive diagnostic assay is used for screening with treatment initiated based on the presence of a positive assay to avoid progression of disease. Oral agents including TMP-SMX, fluoroquinolones, acyclovir (and related agents), and azole antifungal drugs have widespread use in the management of immunosuppressed hosts. Oral decontamination regimens (i.e., nonabsorbable antimicrobials) have not been proven to prevent disease beyond limited periods of time, and are poorly tolerated because of taste, consistency, malabsorption of glucose and xylose bases, and cost.

INITIAL MANAGEMENT OF THE IMMUNOCOMPROMISED HOST WITH INFECTIOUS SYNDROMES

Infections in immunocompromised hosts often present without the expected signs and symptoms of infection. The presence of nonspecific clinical manifestations may delay identification of the critically ill patient. In the outpatient setting, the practitioner must have a low threshold for performing diagnostic tests (e.g., blood counts, cultures, radiographs) on patients with minimal symptoms. Appropriate cultures and invasive studies such as bronchoscopy or biopsy are best performed early in the course of possible infection and prior to the initiation of antimicrobial therapy.[12] The handling of clinical samples is outlined in Table 123-4 and in Figure 123-3. In practice, most febrile or possibly infected immunocompromised patients are treated empirically while awaiting data that identify specific pathogens. The selection of empiric therapy depends on the nature and intensity of the patient's immune deficit(s), risk for poor outcome (severe neutropenia, sepsis), the likely sites of infection, antimicrobial susceptibility patterns at the institution, and the toxicities and cost of the appropriate regimen. Synergistic

TABLE 123-4 Routine Laboratory Evaluation of Bronchoalveolar Lavage Specimens in Immunocompromised Hosts

Pathology
Wright–Giemsa stain
Papanicolaou stain
Silver stain
Modified Jimenez stain (or other suitable for detecting *Legionella*)
Fluorescent antibody stain for *Pneumocystis*
Microbiology
Stains:
Gram's:
Wet mount KOH or calcofluor white
Modified acid-fast
Fluorescent antibody stain for *Legionella*
Antigen/Molecular:
Cytomegalovirus
Mycoplasma PCR
Legionella urinary antigen
Cryptococcal serum antigen
Culture:
Bacterial (aerobic), semi- or quantitative method
Fungal (consider epidemiology: *Aspergillus*, *Cryptococcus*, *Histoplasma*, mucormycosis—do not grind)
Legionella sp. (chocolate yeast extract)
Mycobacterial culture (tuberculosis and nontuberculous)
Nocardia/Actinomyces
Virology
Assays (molecular, ELISA, fluorescence, culture) for:
Cytomegalovirus (consider resistance testing)
Herpes simplex virus
Adenovirus
Respiratory syncytial virus
Influenza
Parainfluenza
Metapneumovirus
Endemic viruses (e.g., SARS, West Nile)

antimicrobial therapy for known or suspected pathogens must be used when available. *Agents or classes of agents used for prophylaxis should not be used for therapy of possible break-through infection*. Compromises are often made; loss of renal function will significantly hinder patient management. Thus, a balance is often made between optimal empiric therapy (e.g., empiric broad-spectrum antifungal therapy with lipid amphotericin vs. other agents) and other aspects of patient management. However, progression of infection while on static or inadequately dosed antimicrobial agents must be avoided.

Clinical signs predicting poor outcomes mitigate to broader initial therapy (e.g., including antifungal or antiviral agents) with adjustment based on microbiologic data at 24 to 72 hours and after the patient is stabilized. These worrisome signs include hypotension, newly altered mental status, meningitis, or encephalitis, diffuse or necrotic skin lesions, bleeding diathesis or new thrombocytopenia, vascular thrombosis, hypoxemia, typhlitis or acute abdomen, severe hyperglycemia, pancreatitis, or lactic acidosis, hypercalcemia, perirectal abscess, gas gangrene, or Fournier gangrene. The radiologic appearance of pneumonia is altered by immune suppression (Fig. 123-4). Radiographic patterns may also change during the care of the patient (e.g., cavitation of pulmonary nodules after the resolution of neutropenia).

Antimicrobials alone may not suffice in the treatment of infection in the immunocompromised host.[9] Infections may respond to a decrease in exogenous immune suppression, to correction of neutropenia by growth factors, or to treatment of simultaneous infections that predispose to superinfection (e.g., RSV, CMV). It should be noted that cessation of corticosteroids may provoke adrenal corticosteroid insufficiency with associated hypotension and metabolic complications. Similarly, cessation of immunosuppression may provoke GVHD or graft rejection or flares in other underlying diseases, and immune reconstitution syndromes will unnecessarily complicate the management of pneumonia and other processes.

Drainage of collections of infected fluid such as empyemas, hematomas, or lymphoceles, or removal of drains or catheters will enhance the clinical response. Identification of metastatic sites of infection (e.g., infections spreading from the lungs to the central nervous system due to *Nocardia, Aspergillus,* or *Cryptococcus* species) may facilitate diagnosis and management. The identification of *new* infectious disease syndromes has occurred in individuals with immune deficits. Thus, the cluster of cases of *P. jiroveci* pneumonia in homosexual males was the first indicator of a new viral pathogen (HIV-1), and the role of *Cryptosporidium* as a common cause of diarrhea in both normal and compromised individuals was elucidated as a result of diarrheal disease in AIDS patients in the 1980s. Similarly, many uncommon bacteria *(Bartonella species, Rhodococcus equi)*, viruses (Kaposi sarcoma-associated herpesvirus/human herpesvirus 8, polyomaviruses, SARS coronavirus), fungi *(Penicillium, Scedosporium)*, and parasites *(Microsporidia)* have been identified in immunocompromised patients. Thus, continuing consideration of new pathogens or novel presentations of known pathogens is essential for the care of the immunocompromised patient.[13]

RECOGNITION OF CONCOMITANT NONINFECTIOUS PROCESSES

The occurrence of multiple simultaneous infections or conditions often complicate and delay appropriate therapy (Fig. 123-4). For example, CMV infection may complicate the treatment of graft rejection or GVHD and contribute to the pathogenesis of *Pneumocystis* or *Toxoplasma* pneumonia. In the compromised host with fever and pneumonitis, chest radiographs may be difficult to interpret. Noninfectious causes of pulmonary infiltrates may coexist with infection, and atypical patterns predominate. Drug toxicities (bleomycin, cyclophosphamide, sulfa drugs), leukoagglutinin reactions, engraftment or immune reconstitution syndromes, radiation injury, pulmonary emboli, and lesions of metastatic cancer may coexist with opportunistic infection (Fig. 123-5). The "typical" evolution of pulmonary infection may be altered by the presence of underlying (e.g., interstitial) pulmonary disease, as well as by diminished inflammatory responses. It is commonly necessary to repeat tests, to utilize CT, or to use invasive diagnostic modalities (biopsy) in the evaluation of the patient who is unresponsive to therapy. Complications of therapy may contribute to the development of new infections: TMP-SMX can cause pneumonitis, hepatitis, or Stevens–Johnson syndrome; ganciclovir can cause neutropenia; transfusion reactions can cause pulmonary infiltrates and hemolysis; cyclosporine can cause hemolytic-uremic syndrome; and antimicrobials can contribute to thrush and *C. difficile* colitis.

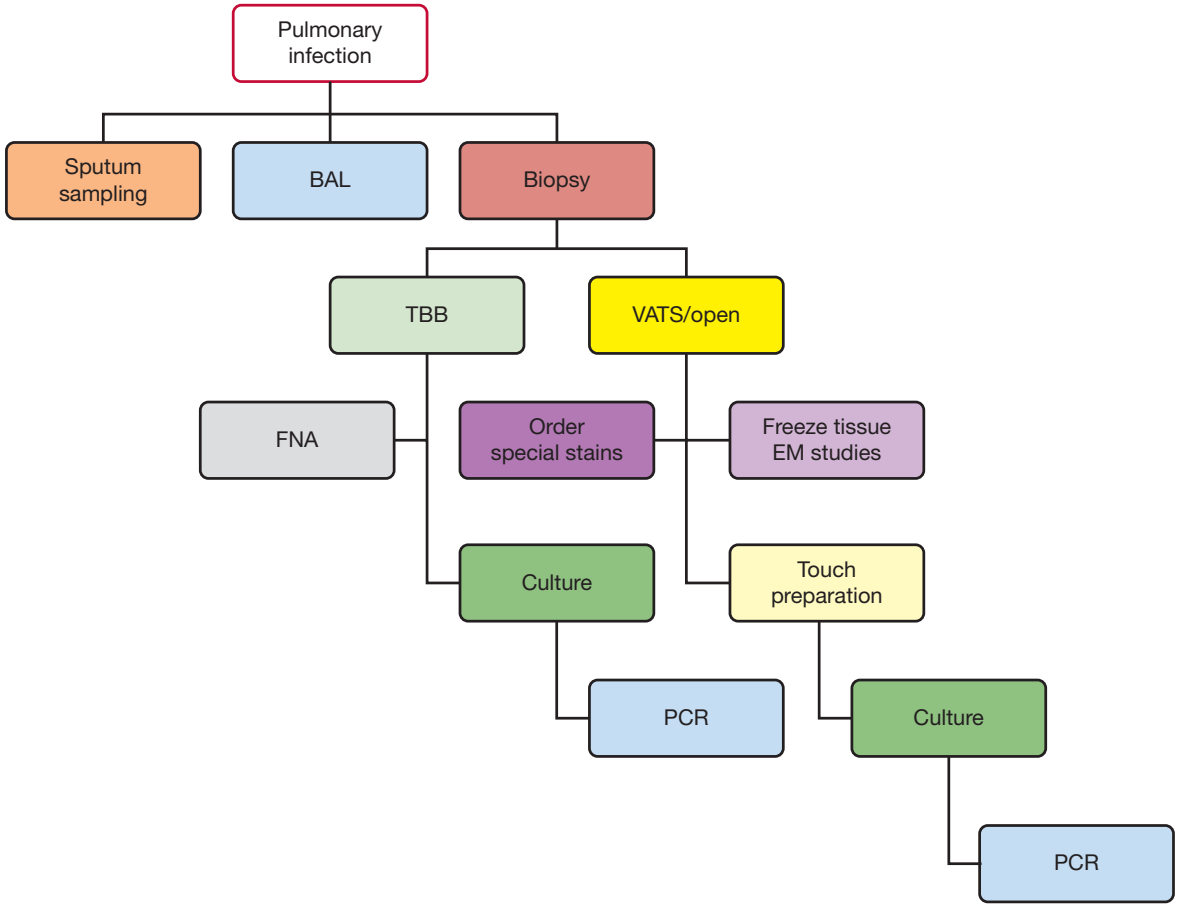


Figure 123-3 The diagnostic workup of pulmonary infection.

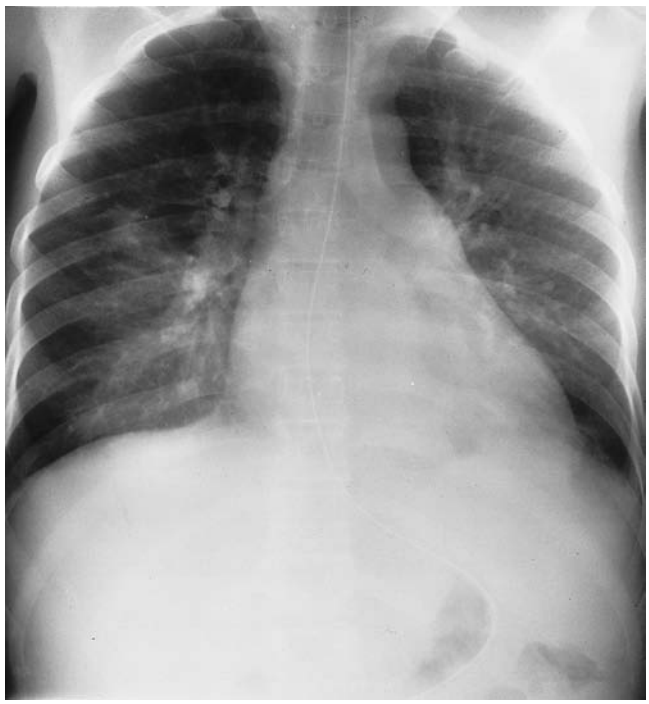


Figure 123-4 Chest radiograph of a 48-year-old heterosexual man with community-acquired pneumonia unresponsive to therapy. The patient was diagnosed as having AIDS on the basis of HIV seropositivity, CD4+ lymphocyte count of 113 per milliliter, and *P. jiroveci* and *Mycobacterium avium-intracellulare* complex pneumonia.

HIV INFECTION AND AIDS

The spectrum of common infections varies with specific immune defects in each type of host (Table 123-2), including HIV infection.

The management of HIV infection has been dramatically altered for those individuals with access to combinations of drugs in "highly active antiretroviral therapies" or HAART.[14,15] Prior to therapy, there is marked variability in the pattern of disease progression with viral load reaching a near steady state by approximately 6 months after infection. Rapid loss of CD4+ lymphocytes correlates with HIV viral load and precedes waning humoral immunity.[16–23] Of note, B cells demonstrate activation and proliferation with nonspecific polyclonal hypergammaglobulinemia. Thus, susceptibility to bacterial infections and recurrent pneumonia rises with deficiency in the production of specific antibodies. The degree of immunodeficiency correlates with loss of CD4+ cells with untreated progression to AIDS occurring within 8 to 10 years; levels of less than 50/mm^3 have a median survival of less than 2 years.

Underlying lung disease is common in HIV-infected patients even before the development of opportunistic infection. While FEV_1 and FVC are nearly normal, 11% to 13% of patients with CD4+ lymphocyte counts below 200/mm^3 or with a history of AIDS-associated extrapulmonary diseases (including thrush and varicella-zoster infections) and weight loss have decreased D_{LCO} measurements. Intravenous drug users have a higher incidence of abnormal FVC, FEV_1, and D_{LCO} measurements (33.3%), consistent with patterns of cigarette smoking and racial distribution. Thus, susceptibility to pulmonary infection is further exacerbated in this population.

One of the features of HAART is a syndrome of inflammatory responses referred to as the "immune reconstitution syndrome,"

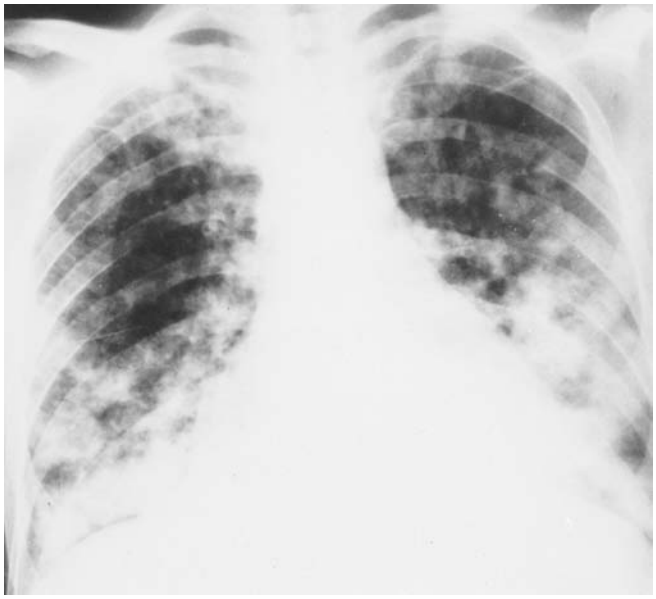


Figure 123-5 Chest radiograph of a 36-year-old homosexual man not known to be HIV-1 infected, with bilateral nodular infiltrates due to pulmonary Kaposi sarcoma.

which generally occurs within the first 3 months of starting effective antiretroviral therapy. This is thought to represent a hyperacute response to pathogens to which the HIV-infected individual has been exposed. It has been observed in *P. jiroveci* pneumonia, CMV retinitis and vitritis, disseminated *Mycobacterium avium* complex (MAC), tuberculosis, and histoplasmosis as pneumonitis and lymphadenitis, cryptococcosis with meningitis, hydrocephalus, and necrotizing lymphadenitis, and with acceleration of hepatitis C virus infection including cryoglobulinemia and renal failure. Thus, effective antiviral therapy may result in more intense symptoms and unusual manifestations of some opportunistic infections while the overall incidence of new infections has declined.

For adults and adolescents (i.e., persons aged ≥13 years), the surveillance case definitions for HIV infection and AIDS were revised into a single case definition for HIV infection in 2008 that includes AIDS and incorporates HIV infection staging classification system.[24] A confirmed case meets the laboratory criteria for diagnosis of HIV infection and one of the four HIV infection stages (stage 1, stage 2, stage 3, or stage unknown).

- **HIV infection, stage 1:** No AIDS-defining condition and either CD4+ T-lymphocyte count of ≥500 cells/μL or CD4+ T-lymphocyte percentage of total lymphocytes of ≥29.
- **HIV infection, stage 2:** No AIDS-defining condition and either CD4+ T-lymphocyte count of 200 to 499 cells/μL or CD4+ T-lymphocyte percentage of total lymphocytes of 14 to 28.
- **HIV infection, stage 3 (AIDS):** CD4+ T-lymphocyte count of <200 cells/μL or CD4+ T-lymphocyte percentage of total lymphocytes of <14, or documentation of an AIDS-defining condition. Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of ≥200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of ≥14.
- **HIV infection, stage unknown:** No information available on CD4+ T-lymphocyte count or percentage and no information available on AIDS-defining conditions.

Anti-HIV therapy should be started before the immune system is irrevocably compromised. Most practitioners are treating all individuals with progressive HIV infection, and all HIV-infected individuals with CD4 counts below 200/mm^3. HAART has resulted in the recrudescence of immunity as manifested by rising CD4+ lymphocyte counts and diminished signs of opportunistic infection and cancer associated with severe T-cell deficits. In treated individuals, this has reduced the incidence of AIDS, AIDS-defining diagnoses, hospitalizations, and mortality by 60% to 80%. Treatment of HIV infection appears to virtually eliminate the risk of *Pneumocystis* pneumonia in AIDS patients with and without prior *Pneumocystis* pneumonia. The risk of MAC, tuberculosis, and CMV has also decreased. Thus, prophylactic (both primary and secondary) and therapeutic regimens must be considered in light of the individual's immune status. Not all patients respond to HAART or maintain viral suppression during therapy. The specifics of antiviral therapy will not be considered here.

HIV TESTING

HIV testing should be considered for all persons either in high-risk groups or with unusual infections (Table 123-5). High-risk groups include intravenous drug users, sexually active homosexual or bisexual men, hemophiliacs or individuals who have required blood or clotting factors, persons with sexually transmitted diseases (especially syphilis), people with heterosexual contacts with one of these increased risk groups, pregnant women or newborns with such contacts, healthcare workers with exposure to body fluids or needle stick injury, and all patients with conditions commonly associated with AIDS.

Testing for HIV infection is generally divided into viral culture assays (uncommon now that molecular resistance tests are available), antibody tests (Western blots), and specific, quantitative (molecular) viral tests including molecular antiviral susceptibility testing. Most patients produce antibodies to HIV within 6 to 8 weeks, and almost 100% will have detectable antibodies by 6 months after exposure. These tests are well standardized and easy to perform, but are troubled by false positives (cross-reacting antibodies) and false negatives (e.g., in the early or "window" period). Between 4% and 20% of Western blot tests are *indeterminate* because of seroconversion in progress, loss of antibody in advanced HIV disease, cross-reacting antibodies in pregnancy, blood transfusions, autoantibodies from collagen vascular disease, infection with HIV-2, recent influenza vaccination, or in recipients

TABLE 123-5 AIDS-Defining Diagnoses[a]

Diagnosis	Incidence (%)
Pneumocystis pneumonia	42.6
Thrush— esophageal candidiasis	15.0
Kaposi sarcoma	10.7
Wasting syndrome	10.7
Mycobacterium avium complex infection	4.8
Tuberculosis	4.5
Cytomegalovirus	3.7
Dementia	3.6
Recurrent bacterial pneumonia	3.0
Toxoplasmosis	2.6
Lymphoma—immunoblastic	1.9
Cryptosporidiosis	1.5
Burkitt lymphoma	1.5
Histoplasmosis	1.0
Cervical cancer—invasive	0.9
Herpes simplex infection	0.5

[a]*Local epidemiology is a major determinant of infectious risk.*

of trial HIV vaccines. These subjects should be retested and inconclusive assays resolved with specific viral (molecular, p24 antigen, or culture) testing. *Specific viral tests* include the p24 antigen detection, molecular amplification by PCR, and culture-based assays. These are positive earlier than the antibody tests and therefore may be useful in primary infection before the development of antibody; they have high sensitivity (95%–99%). Quantitative techniques are very useful in assessing the response to antiviral therapy and disease progression.

Measures of HIV viral RNA in plasma may not correlate with the CD4+ lymphocyte count. The CD4 count provides a surrogate marker for the response to antiviral therapy and the risk of opportunistic infection and death. At present, the best predictive value of testing is the combination of viral load with CD4+ lymphocyte enumeration. Viral RNA levels in long-term nonprogressors are consistently under 10,000 copies/mL, while progression and immunologic deterioration are often associated with loads over 50,000 to 100,000 copies. Patients with viral loads of 10,000 to 50,000 are considered at intermediate risk. Viral load changes generally precede CD4 count changes. Immune alterations due to infection (e.g., CMV) or immune modulation therapy (interferons) are not yet interpretable.

IMMUNIZATION

Immunization is a part of the routine management of AIDS. In general, HIV-infected persons are susceptible to the same community-acquired respiratory pathogens as the normal host but with a greater severity of disease. Thus, patients should be vaccinated early in the course of disease when they are clinically stable. Live vaccines are generally contraindicated, but measles vaccine is generally well tolerated in children, and MMR is recommended for unvaccinated adults born after 1957 or vaccinated between 1963 and 1967. The efficacy of vaccination in this population is not clear; HIV viral loads may temporarily increase after vaccination. However, general practice suggests that pneumococcal, influenza (inactivated whole virus and split virus vaccines), *H. influenzae,* hepatitis B recombinant vaccine, and MMR be given as indicated.

OPPORTUNISTIC INFECTIONS IN AIDS

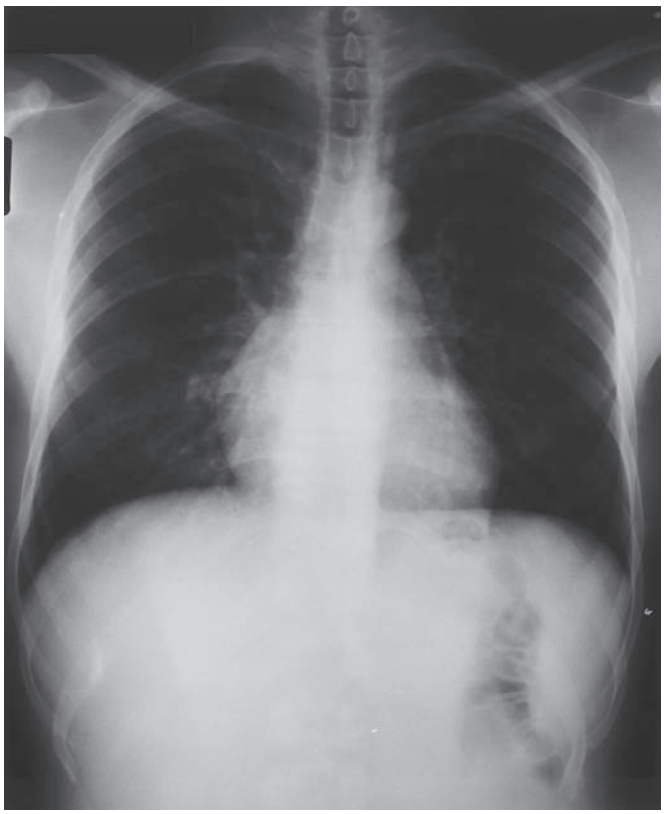
The problem of opportunistic infection in the untreated or newly diagnosed AIDS patient is unique because of the *progressive decline* in immune function when compared with the intermittent compromise seen after chemotherapy or the relatively stable immunosuppression utilized after solid-organ transplantation (Table 123-6). As a result of the progressive and cumulative risks, the incidence of opportunistic infections *increases* over time. A "time line" exists for the common infections and noninfectious manifestations seen in progressive AIDS, relating to the total CD4+ lymphocyte count as a measure of susceptibility (Fig. 123-1). In an individual, the time line is also related to the patient's viral load, but an exact correlation does not exist. The specific pattern of opportunistic syndromes will change for individual patients, but it reflects the overall progressive immunological deterioration of untreated AIDS.

Many opportunistic pulmonary infections in AIDS patients were initially assumed to be reactivation of latent infection. However, some of these processes – including *P. jiroveci, Toxoplasma gondii,* tuberculosis, and histoplasmosis – represent a mix of both new exposures and old disease. Similar observations have been made in terms of the drug susceptibility of mycobacterial isolates in recurrent disease (see Chapter 131) (Fig. 123-6). The clinical manifestations of opportunistic infections in AIDS are altered by prophylactic and therapeutic regimens, adverse drug reactions, and drug interactions. Toxicities of both prophylactic and therapeutic drug regimens (particularly rash, marrow suppression, and hepatic toxicities) are much more frequent in HIV-infected patients and are exacerbated by the simultaneous use of antiviral therapies.

TABLE 123-6 Infectious Agents and Syndromes Commonly Associated with AIDS

Viral (with HIV-1, HIV-2)
Cytomegalovirus (retinitis, colitis)
Herpes simplex (persistent mucocutaneous ulcer, bronchitis, pneumonia, esophagitis)
Varicella zoster
Epstein–Barr virus (lymphoma, CNS lymphoma)
Parvovirus B19
HHV-6
HHV-8 (Kaposi sarcoma)
HTLV-1, HTLV-2
HIV-associated wasting syndromes or dementia
JC virus (progressive multifocal leukoencephalopathy)
Parasitic
T. gondii
Cryptosporidium (persistent diarrhea >1 mo)
Isospora belli (persistent diarrhea >1 mo)
Microsporidium
Cyclospora
Strongyloides (extraintestinal)
Fungal
Candida species (thrush, vaginitis, tracheitis)
C. neoformans (extrapulmonary)
Histoplasma capsulatum (extrapulmonary, marrow, gastrointestinal)
Blastomyces dermatitidis
Aspergillus species
Petriellidium boydii
Coccidioides immitis (extrapulmonary)
Paracoccidioides species
Penicillium species
P. jiroveci
Sporothrix schenckii
Bacterial
Campylobacter species
Mycobacterium avium-intracellulare complex, *Mycobacterium kansasii* (disseminated, bacteremia, marrow)
M. tuberculosis (pulmonary or disseminated)
Legionella species
Nocardia species
Encapsulated gram-positive bacteria
Salmonella species (nontyphoid, recurrent bacteremia)
R. equi
Bartonella species
Other
Lymphoma (non-Hodgkin's or B cell or unknown phenotype, small, noncleaved lymphoma, immunoblastic sarcoma)
Pneumonia—recurrent bacterial
Cervical cancer, invasive

Primary prophylaxis in AIDS patients who maintain CD4+ lymphocyte counts above 200/mm^3 for over 3 to 6 months and with low or undetectable viral loads appears to be unnecessary, at least for *P. jiroveci* and mycobacterial infections.[25] For individuals with CD4+ lymphocytes below 100/mm^3 the incidence of PCP is



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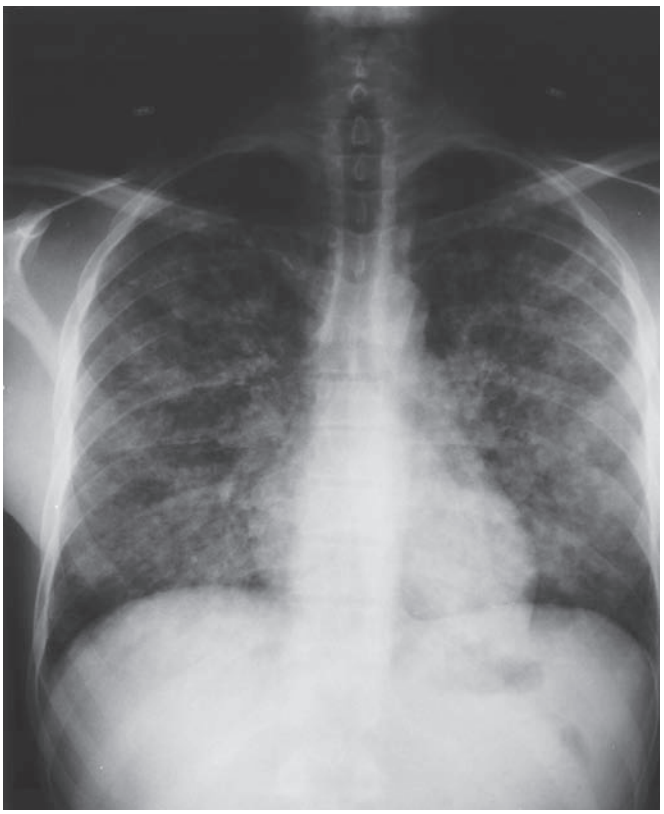


B

Figure 123-6 Chest radiographs of a 39-year-old man with AIDS on zidovudine, ritonavir, and TMP-SMX prophylaxis, and with a CD4+ lymphocyte count of 89 per milliliter. The patient presented to the outpatient clinic with low-grade fever, fatigue, and mild cough. **A.** Physical examination and chest radiograph were unremarkable. The patient was anergic on both PPD and control skin testing. Induced sputum examination was negative for bacteria, for *P. jiroveci,* and by mycobacterial stains. Blood cultures for mycobacteria were obtained. **B.** Ten days after initial presentation, the patient was admitted to the hospital with minimal dyspnea and cough; chest radiograph was remarkable for bilateral pulmonary reticulonodular infiltrates. Bronchoalveolar lavage samples were positive for mycobacteria. The organisms were subsequently identified from cultures of both blood and sputum as *M. tuberculosis,* resistant to both isoniazid and ethambutol. Induced sputum sample cultures remained negative for mycobacteria.

40% to 50% and toxoplasmosis 33% per year without prophylaxis. TMP–SMX prophylaxis (a single strength tablet daily) prevents most toxoplasmosis and nocardiosis, listeriosis, salmonellosis, and other common infections.[26–29] For MAC, prophylaxis should be considered for HIV-infected individuals with less than 50 to 100/mm^3 CD4+ lymphocytes with azithromycin (or clarithromycin).[30,31] For other infections and secondary prophylaxis, the data are less clear. Up to 15% to 20% of AIDS patients have more than one opportunistic infection at one time. The spectrum of clinical diagnoses in pulmonary disease in AIDS includes bacterial infection (45.5%), *P. jiroveci* pneumonia (27%), Kaposi sarcoma (7%), bronchitis (5%), *M. tuberculosis* (4.3%), other mycobacteria (4%), lymphoma (2.1%), and a variety of other processes. Common community-acquired upper respiratory infections, manageable on an ambulatory basis, constitute more than 50% of respiratory illnesses in HIV-infected persons. The incidence of fungal infections varies by geographic region, while the rate of demonstration of viral pulmonary infection is closely related to the diagnostic testing techniques used at each center and to seasonal variation.

APPROACH TO THE DIAGNOSIS OF OPPORTUNISTIC PULMONARY INFECTIONS IN AIDS

With the wide array of potential pathogens causing disease in HIV-infected patients, the frequency of atypical and multiple infections, and the urgency to diagnosis of infection in the immunocompromised host, a systematic approach to lung disease in these hosts is imperative. A few general rules are useful.

1. *Prophylaxis is generally effective.* When failure of prophylaxis occurs, it is usually due to noncompliance, malabsorption of drugs, emerging antimicrobial resistance, or coinfection or tumor that alters the local environment. For example, it is often impossible to eradicate *Candida* esophagitis unless erosive esophageal HSV infection is also treated. *Pneumocystis* is difficult to treat in the presence of CMV infection or bronchial obstruction.
2. Specific therapies for individual infections have a *high incidence of adverse reactions in the HIV-infected patient.* Thus, presumptive or empiric therapy without microbiologic confirmation, though often appropriate, has a greater risk in this population than in the normal host.
3. The *utilization of newer diagnostic tests* has improved the care of AIDS patients. The interpretation of some tests is unclear, and the availability of some tests (urinary *Histoplasma* antigen or immunoperoxidase stains for *T. gondii*) is not universal. The *induced sputum examination* has been useful in the early, noninvasive diagnosis of *Pneumocystis* infection, and for mycobacterial disease in the absence of spontaneous sputum production. The sensitivity of sputum induction for *Pneumocystis* infection approaches 90%, but the negative predictive value of the test is only 50%. The cost and sensitivity of this procedure cannot be justified for the routine diagnosis of bacterial infections,

TABLE 123-7 Roentgenographic Findings in Opportunistic Pulmonary Diseases in AIDS

Diffuse Infiltrates	Cavitary Lesions	Hilar Adenopathy	Focal Infiltrates	Nodular Lesions	Pleural Effusions
P. jiroveci	Tuberculosis	Tuberculosis	Legionella sp.	C. neoformans	Tuberculosis
Tuberculosis	Pyogenic bacteria	Lymphoma	Tuberculosis	H. capsulatum	Fungal
T. gondii	Aspergillosis	Kaposi sarcoma	P. jiroveci	Tuberculosis	Pyogenic
H. capsulatum	C. neoformans	C. neoformans	S. pneumoniae	P. jiroveci	Lymphoma
				Kaposi sarcoma	Kaposi sarcoma
P. jiroveci and other agents	P. jiroveci	HIV acute	Kaposi sarcoma	Lymphoma	
	R. equi				
Lymphocytic interstitial pneumonitis	Septic emboli (addicts) C. neoformans	EBV acute	Nocardia asteroides	Septic emboli	

particularly in persons capable of producing sputum samples. The use of *more invasive tests,* such as bronchoscopy, with the obvious limitations of cost and risk to the patient, has the advantage of providing subglottic specimens and the potential for diagnosis of a broader range of pathogens. The interpretation of positive cultures for CMV or for MAC may be uncertain without tissue histopathology for confirmation. In patients with a rapidly deteriorating clinical condition or a failure to respond to initial therapy, bronchoscopy with biopsy or needle aspiration may be preferable to bronchoalveolar lavage (BAL) or sputum induction as an initial procedure. In general, noninvasive, nuclear isotope-based radiologic tests are rarely useful in the diagnostic evaluation of pulmonary disease in AIDS patients.

4. The *rate of progression of infection* is often a clue to the type of disease. Thus, community-acquired pneumonia develops rapidly (in 2–5 days), while the initial episode of *Pneumocystis* pneumonia generally evolves more slowly (over 7–12 days) in AIDS (as compared with other compromised hosts). Fungal infection and mycobacterial infection are generally preceded by systemic complaints. Pyogenic pulmonary infection is generally associated with sputum production, while the "atypical" infections may have little or no sputum despite cough and dyspnea.
5. The *radiographic pattern* is often suggestive of the diagnosis (Table 123-7). All "typical" patterns are altered by progressive immune deficits and coexisting or prior lung disease. *Diffuse infiltrates* (alveolar or interstitial) may be seen with a homogeneous distribution, as in *P. jiroveci, T. gondii,* CMV, mycobacterial species, *Histoplasma,* or *Coccidioides* (Fig. 123-7). Drug toxicity may also cause pulmonary infiltrates. Inhomogeneity with these pathogens reflects altered pulmonary parenchyma from previous disease, obstruction (e.g., with tumor, *S. stercoralis*), or upper zone disease or pneumothorax in *Pneumocystis* pneumonia (Fig. 123-8). Tumors may appear with interstitial radiographic patterns in HIV disease. Lymphoid interstitial pneumonitis is an interstitial process of unknown origin that is seen in AIDS patients. Diffuse interstitial infiltrates are often due to *P. jiroveci,* but not in patients receiving TMP–SMX prophylaxis and rarely without hypoxemia. Thus, the presence of a sepsis-like picture with a diffuse interstitial infiltrate in a patient receiving anti-*Pneumocystis* prophylaxis might suggest mycobacterial disease, *Legionella* infection, or *Cryptococcus neoformans. Focal airspace disease* is most often seen with bacterial infections (pyogenic, mycobacteria, *Legionella* species), *Mycoplasma pneumoniae* (viral influenza, AV, CMV), and mixed infections (e.g., CMV and *P. jiroveci*). Occasionally, primary cryptococcal pneumonia, *Aspergillus* infection, or obstructive disease will present with focal infiltrates. Each of these processes may evolve to frank *cavitation*, particularly infections due to pyogenic bacteria (*Staphylococcus, Klebsiella, S. pneumoniae*) or *M. tuberculosis*. Small cavities are seen with *P. jiroveci,* mycobacteria, and metastatic tumors. Large cavities are uncommon; *M. tuberculosis* or aspergilloma is most often present. *Nodular lesions* can be seen with any of the metastatic tumors or hematogenous infections. Endocarditis, KS, toxoplasmosis, tuberculosis, MAC, and *Cryptococcus* may all progress from nodules to small cavities (Fig. 123-9). In particular, unusual bacterial pathogens *(Bartonella, Rhodococcus, Candida, Salmonella)* have been observed as pulmonary nodules associated with right-sided endocarditis in AIDS patients (Fig. 123-10). *Intrathoracic adenopathy* is common in untreated AIDS patients, most often with infections earlier in the course of disease (CD4+ count greater than 400 per mL) and with tumors later in disease. Fungal infections *(Cryptococcus, Histoplasma, Coccidioides)*, CMV, and mycobacterial infections may also cause adenopathy. Adenopathy should prompt invasive diagnosis in the absence of a clear etiology in AIDS. *Pleural effusions* are common with tuberculosis, other pyogenic bacterial infections, and tumors.
6. The *CD4+ lymphocyte count* is a good indicator of susceptibility to specific infections, while the viral load is most closely associated with overall disease prognosis. Unresolving community-acquired pneumonia due to *S. pneumoniae,*

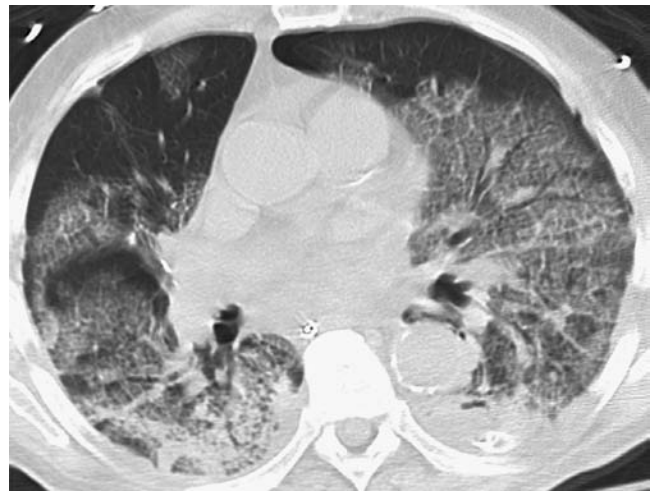
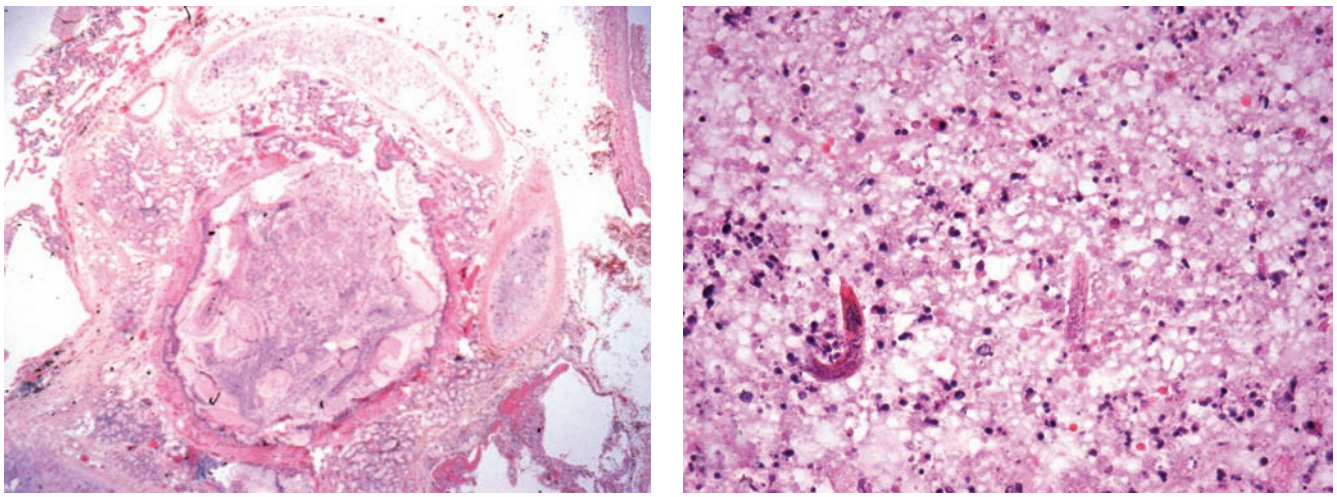


Figure 123-7 Diffuse ground-glass opacity of *P. jiroveci* pneumonia in AIDS at the time of initial presentation predominantly involved the subpleural lung and spared the central lung.



A B

Figure 123-8 **A.** A mucus plug in a small airway. **B.** Higher power view reveals the larval form of *Strongyloides stercoralis*.

H. influenzae, Mycoplasma, or *Legionella* species may be the sentinel infection of HIV disease. As host immunity declines, other opportunistic infections will occur. *M. tuberculosis,* an organism of high virulence, will cause infections at any CD4+ lymphocyte count but will occur increasingly as the CD4+ lymphocyte count falls below 500 per mL. In contrast, less virulent organisms will cause disease only with greater degrees of immune compromise.

7. *Chronic or recurrent sinus infection* may provide a source of *Pseudomonas* or *Aspergillus* for pulmonary infection.
8. The *spectrum of pulmonary disease varies by geographic region* and by HIV transmission category.
9. *Physical findings* are often useful in establishing a differential for pulmonary disease in contrast, often, with other types of immunocompromised hosts.

INFECTION IN PATIENTS WITH CANCER OR HCT

Patients with underlying malignancy who are treated with chemotherapy or HCT represent special challenges with respect to evaluation and management of known or suspected infectious diseases.

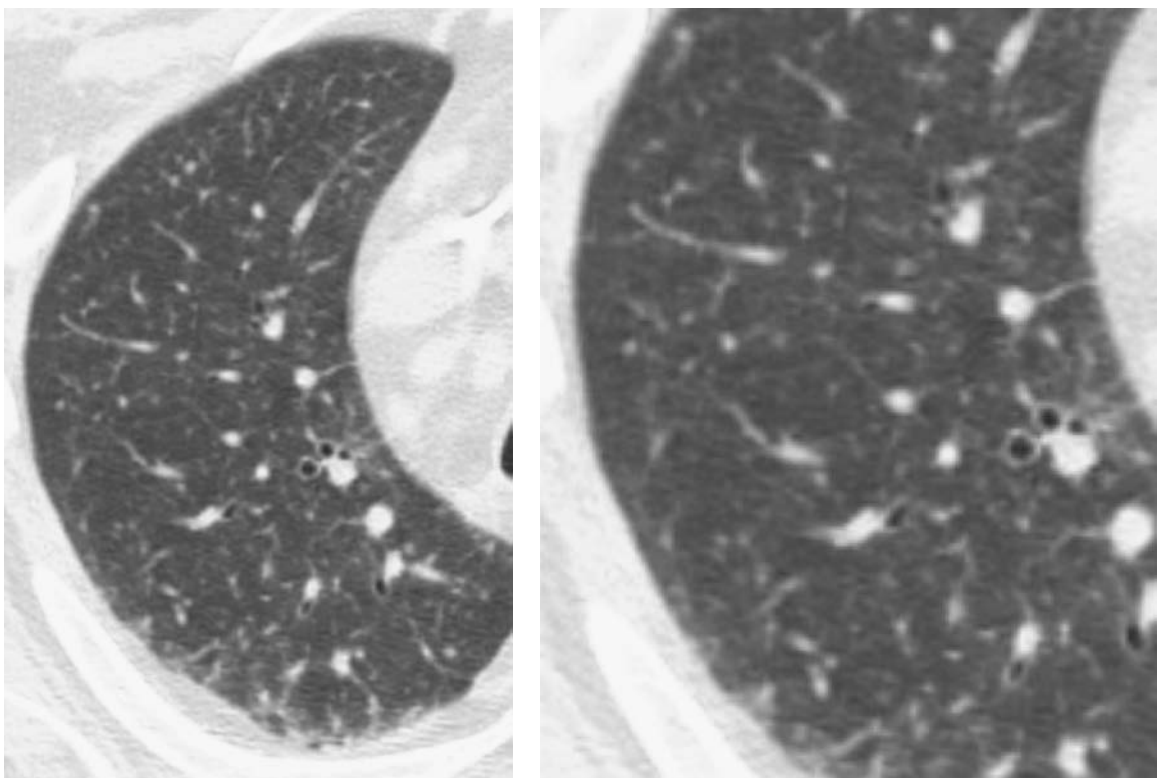
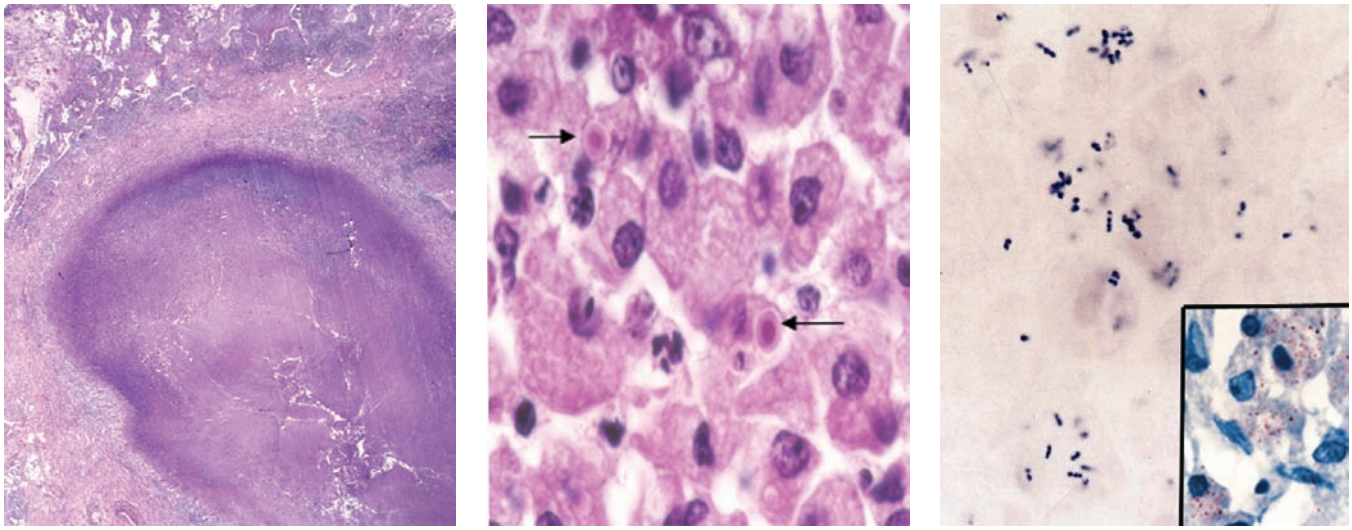


Figure 123-9 Miliary cryptococcal pneumonia in a 62-year-old man undergoing intensive chemotherapy for pancreatic cancer. *C. neoformans* was isolated from bronchoalveolar lavage specimens and cerebrospinal fluid (CSF). Cryptococcal antigen was positive in serum and CSF at titers greater than 1:1024. CT scan demonstrates diffuse 1- to 3-mm micronodules in both lung fields, often difficult to distinguish from small blood vessels on end. This requires review of serial CT cuts to distinguish nodules from tubular vessel structures.



A B C

Figure 123-10 **A.** *Rhodococcus equi* pneumonia in AIDS produced a cavitary lung nodule in a lung biopsy specimen. **B.** The host response includes histiocytic inflammation and small calcified concretions termed Michaelis–Gutmann bodies *(arrows)*. **C.** The organism is a gram-positive coccobacillus that also stains with the modified Ziehl–Neelsen stain *(inset)*.

Important aspects of the underlying basis for their immunocompromised status are discussed below.

■ IMMUNE DEFECTS DUE TO TUMORS AND CHEMOTHERAPY

The incidence of infection in cancer patients is determined, in part, by the nature of the underlying neoplasm. Studies of pneumonia in cancer patients suggest the following approximate incidences of infection:

- Conventional bacteria—37%
- Fungi—14%
- Viruses—15%
- *P. jiroveci* (formerly *Pneumocystis carinii*)—8%
- *Nocardia asteroides*—7%
- *M. tuberculosis*—1%
- Mixed infections—20%

In the series by Bodey et al.,[32,33] fatal infections in acute leukemics were caused by bacteria in 66%, fungi in 33%, viruses in 0.2%, and protozoa (including *P. jiroveci*, now considered a fungus) in 0.1% (Fig. 123-11). In contrast, fatal infection in lymphoma patients (86%) and solid-tumor patients (94%) were more often bacterial in the preprophylaxis era. The rate of cryptococcal infection in chronic lymphocytic leukemia was more than double that in Hodgkin disease (24.3 vs. 10.9 per 1000), and the rate in breast cancer was only 0.159 per 1000.

Other tumors are associated with specific infections. For example, lung cancer is associated with tuberculosis at a rate of 92 per 1000, second only to the rate in patients with Hodgkin disease (96 per 1000) due to cellular immune deficits. Without therapy, the degree of depression in cellular immunity (delayed-type hypersensitivity) is more prominent in lymphoma, whereas humoral immunity is impaired to a greater degree in diseases affecting B-lymphocyte function, such as multiple myeloma and chronic lymphocytic lymphoma. Thus, the patient with lymphoma is particularly susceptible to intracellular organisms, including *Listeria monocytogenes*, *M. tuberculosis*, viruses, and fungi. The patient with myeloma is more apt to develop pneumonia or bacteremia due to *H. influenzae*, *S. pneumoniae*, and a variety of other acute bacterial infections. Acute leukemia is associated with a depression in the number and function of circulating granulocytes and is associated with severe pyogenic, bacterial infections. Patients with acute and relapsed leukemia have demonstrated impaired phagocytosis and killing of fungi and bacteria by these cells, which may appear morphologically normal. *These defects may persist well into periods of remission and may progress along with progression of the underlying disease.*

The impact of the various forms of chemotherapy on host defenses must be added to those caused by the underlying malignancy. Multiple immune functions are impaired by chemotherapy, including the phagocytosis and killing of bacteria by neutrophils (corticosteroids, carmustine, radiation); antibody production (methotrexate, cyclophosphamide, L-asparaginase, 6-mercaptopurine); uptake and processing of antigen by macrophages (corticosteroids,

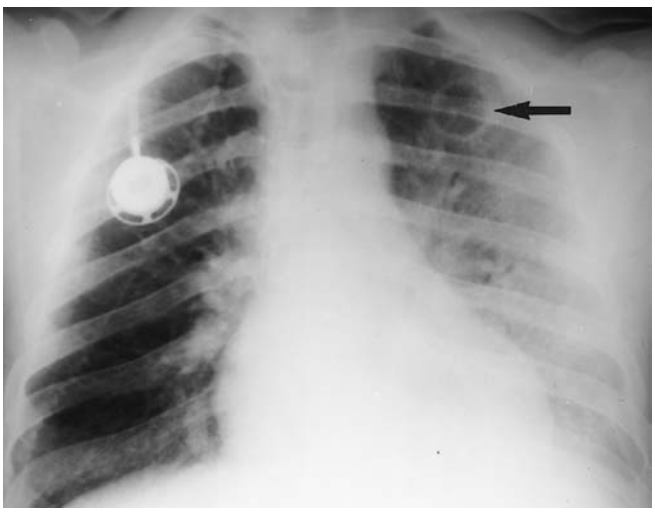


Figure 123-11 Lung abscess (*arrow*) in a febrile patient following intensive chemotherapy for relapsed acute myelogenous leukemia. Patient developed fever while granulocytopenic (<50 neutrophils/mm^3 for 8 days) without localizing symptoms and a clear chest radiograph. When the neutrophil count exceeded 200/mm^3, a lung abscess was detected in the left upper lobe. *Aspergillus fumigatus* was detected in fluid obtained from the abscess via CT-guided percutaneous needle aspiration. The infection responded well to amphotericin B.

cyclophosphamide, dactinomycin); recognition of antigens by T and B lymphocytes (corticosteroids, cyclophosphamide); and antigen-driven lymphocyte proliferation (methotrexate, 5-fluorouracil, fludarabine, cytarabine, L-asparaginase, dactinomycin, 6-mercaptopurine, hydroxyurea). Predisposition to infection induced by chemotherapy may mask more subtle defects due to underlying disease; for example, the effects of granulocytopenia due to intensive chemotherapy will generally predominate over the effects of underlying lymphoma or myeloma.

NEUTROPENIA

The most common predisposing condition for infection in the patient with cancer is granulocytopenia, often due to chemotherapy and occurring while awaiting engraftment of hematopoietic transplants. The *function* of inflammatory cells and of other immune (e.g., mucosal) barriers are also of great importance and are much more difficult to assess. The risk of infection increases as granulocyte counts decrease (Table 123-8). Thus, the risk of infection in the patient with neutropenia (under 1000 total granulocytes per mm^3) increases when granulocyte numbers fall further, to below 500/mm^3; the risk is greatest when counts are lower than 100/mm^3.[32,33]

The many causes of neutropenia differ qualitatively (Table 123-8). They include iatrogenic neutropenia (chemotherapy, drug toxicities), aplastic anemia and other immune neutropenia, hereditary and acquired cyclic neutropenia, and malignancy-associated (especially acute leukemias) and infection-induced neutropenia. The rate of decline in white blood cell numbers and the duration of neutropenia influence the risk of infection. Thus, the patient with acute leukemia and rapidly falling neutrophil counts is at greater risk than the person in whom counts are falling slowly or are stable.

TABLE 123-8 Causes of Neutropenia

Iatrogenic
Cancer chemotherapy
Drug toxicities (TMP–SMX, chloramphenicol, ganciclovir, AZT, allopurinol)
Infection
Viral (cytomegalovirus, HIV, Epstein–Barr virus, hepatitis B)
Parasitic *(Leishmania)*
Bacteria *(Clostridium)*
Acute neutropenia of sepsis/endotoxemia (gram-negative sepsis)
Bone marrow failure of neonatal sepsis
Immune
Drug-induced autoimmunity (haptenic: penicillins, sulfa drugs)
Aplastic anemia (includes idiosyncratic reactions: phenothiazines, chloramphenicol)
Alloimmune neonatal neutropenia (maternal–fetal incompatibility)
Congenital autoimmune neutropenia
Primary autoimmune (systemic lupus erythematosus, Felty syndrome, rheumatoid arthritis)
Transfusion-induced
Antineutrophil antibody-mediated
Cyclic neutropenia (CD57 lymphocyte expansion)
Hereditary
Infantile genetic agranulocytosis
Familial neutropenia
Cyclic neutropenia (autosomal dominant)
Old age

THE MICROBIOLOGY OF INFECTION IN NEUTROPENIA AND CANCER

Pulmonary infections in patients with functional or quantitative defects in neutrophils can reach the lungs via inhalation, microaspiration of colonizing organisms, and bacteremia after nonrespiratory penetration and bacteremia (e.g., from vascular catheters or disrupted mucosal surfaces). The classic presentations of pneumonia, transmural inflammation, and perforation of the cecum or "typhlitis" (often with *Pseudomonas*, anaerobic bacteria including *Clostridium septicum*) may be the first signs of life-threatening infection in a neutropenic patient. Decisions regarding management of these patients are made empirically because of the urgency of therapy in the immunocompromised host. Distinctions between pulmonary and extrapulmonary infections often become blurred in the attempt to treat most of the likely pathogens in a febrile neutropenic cancer patient. Often an unsuspected pulmonary pathogen is detected on routine blood or urine culture or from a biopsy of an extrapulmonary infected site.

Common infections in the neutropenic host and the patient with cancer are most often the result of colonization with, and infection by, pyogenic bacteria, including *S. pneumoniae*, *S. aureus*, the Enterobacteriaceae, *Pseudomonas aeruginosa*, *H. influenzae*, and *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*. Common fungal pathogens include *Aspergillus* species, *Mucor*, *Absidia*, and *Rhizopus* species (Table 123-9). *Candida* species are often isolated from sputum samples but rarely cause pneumonia in the absence of pulmonary injury, hemorrhage, or fungal embolus. The emergence of bacteria and fungi with antimicrobial resistance takes on special importance in the neutropenic host because therapy is generally empiric and is started before microbiologic data become available. The common "resistant" organisms include vancomycin-resistant *Enterococcus faecium* and *faecalis* (now also resistant to linezolid,

TABLE 123-9 Factors in the Development of Fungal Infections in Patients with Cancer

Age/performance status
Prior chemotherapy or radiotherapy: dose and duration
Steroids
Purine analogs
Prior infections (specific isolates)
Recent antimicrobial use (resistance)
Broad-spectrum antimicrobials
Prophylactic agents
Functional immune status (cell number, activity)
Hematopoietic transplantation-related
Delayed engraftment or function of marrow
Graft-versus-host disease and treatment
Degree of donor–recipient histocompatibility mismatch
Insufficient dose of stem cells (CD34+)
Total T-cell number
Integrity of mucosal barriers (catheters, gastrointestinal)
Neutropenia (severity, duration >2 wk)
Hospital environment
Home environment—hobbies, travel
Nonhematopoietic organ failure (e.g., dialysis)
Other simultaneous infections (e.g., cytomegalovirus)

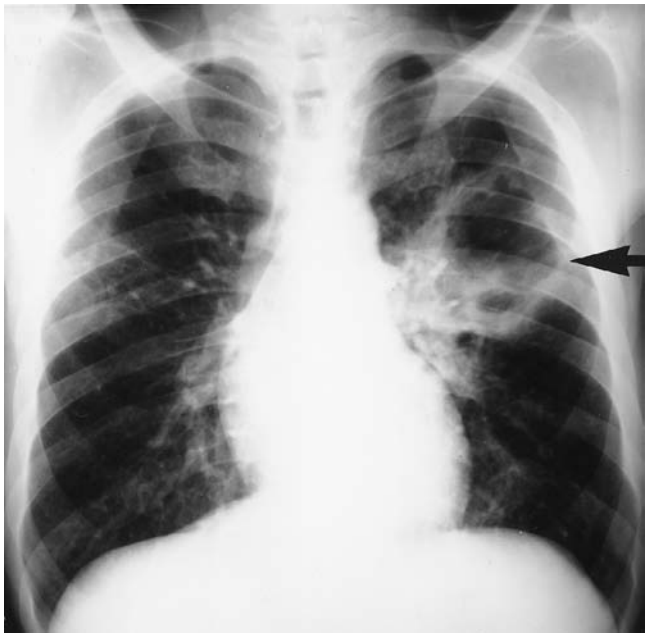


Figure 123-12 Postobstructive pneumonia and lung abscess (*arrow*) in a 45-year-old man with adenocarcinoma of the lung in the right hilum. The abscess was drained via a bronchoscopic approach. Cultures of the abscess fluid grew common oral bacterial flora, including *Prevotella melaninogenica* and *Bacteroides* species.

quinupristin-dalfopristin), methicillin-resistant *S. aureus*, inducible chromosomal and acquired plasmids encoding b-lactamases in gram-negative bacteria, and azole (i.e., fluconazole) resistance of *Candida* species.[34] In individual patients, the spectrum of colonizing organisms changes over time with antimicrobial use and chemotherapy. Seeding from blood-borne infection (e.g., due to vascular access catheters or localized infection) may occur. Patients with solid lung tumors may develop obstructive pneumonia or pulmonary hemorrhage, followed by superinfection with the flora of the upper respiratory tract and oropharynx (Fig. 123-12).

■ FUNGI AND LESS COMMON PATHOGENS

Combined cellular and granulocytic deficiencies occur with chemotherapy. As a result, pathogens normally controlled by cellular immune mechanisms (especially intracellular pathogens) can be detected; among these are *M. tuberculosis*, *Brucella* species, the geographic fungi, *C. neoformans*, *S. stercoralis*, *Salmonella*, and *P. jiroveci*. Fungal infections occur with increasing frequency, most often in acute leukemia and following stem cell transplantation with GVHD (see Table 123-9). Atypical presentations of infection may be from a portal of entry other than the gastrointestinal tract or the lungs. Thus, the first clinical signs of infection may be "spontaneous" or line-associated bacteremia or fungemia presenting as idiopathic hypotension, confusion, altered renal function, or skin lesions including black or necrotic skin lesions (e.g., ecthyma gangrenosum) seen most often with gram-negative bacteria, *Bacillus* species, *Fusarium* species, or dematiaceous molds. Pneumonia may accompany skin, sinus, or central nervous system infection with infection due to *Aspergillus* species, mucormycosis, *Nocardia asteroides*, *C. neoformans*, and the herpes viruses (herpes simplex or varicella zoster). The Mucoraceae *(Rhizopus, Mucor, Absidia)*, like the *Aspergillus* species, may present with invasive disease of the sinuses and periorbital and frontal cortex and rapidly progressive hemorrhagic pneumonia with infarction and fungemia (See also Chapter 133).[35] Invasive disease of the sinuses and periorbital and frontal cortex is especially prevalent in neutropenic

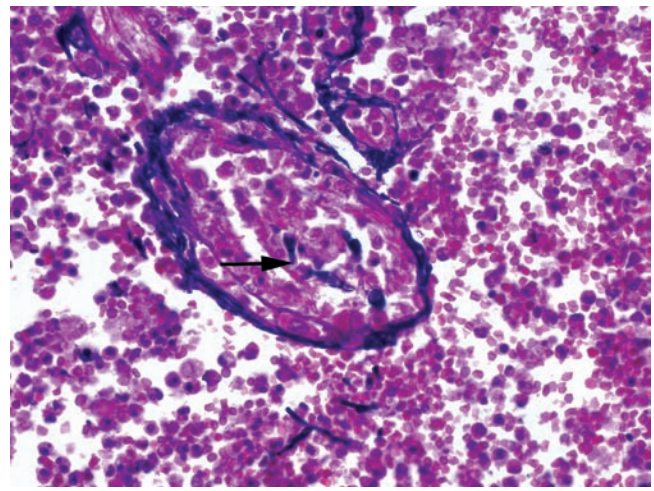


Figure 123-13 Disseminated *T. beigelii* infection in a patient undergoing chemotherapy for acute leukemia. GMS-H&E reveals hyphae (*arrow*) in a blood vessel with surrounding hemorrhage.

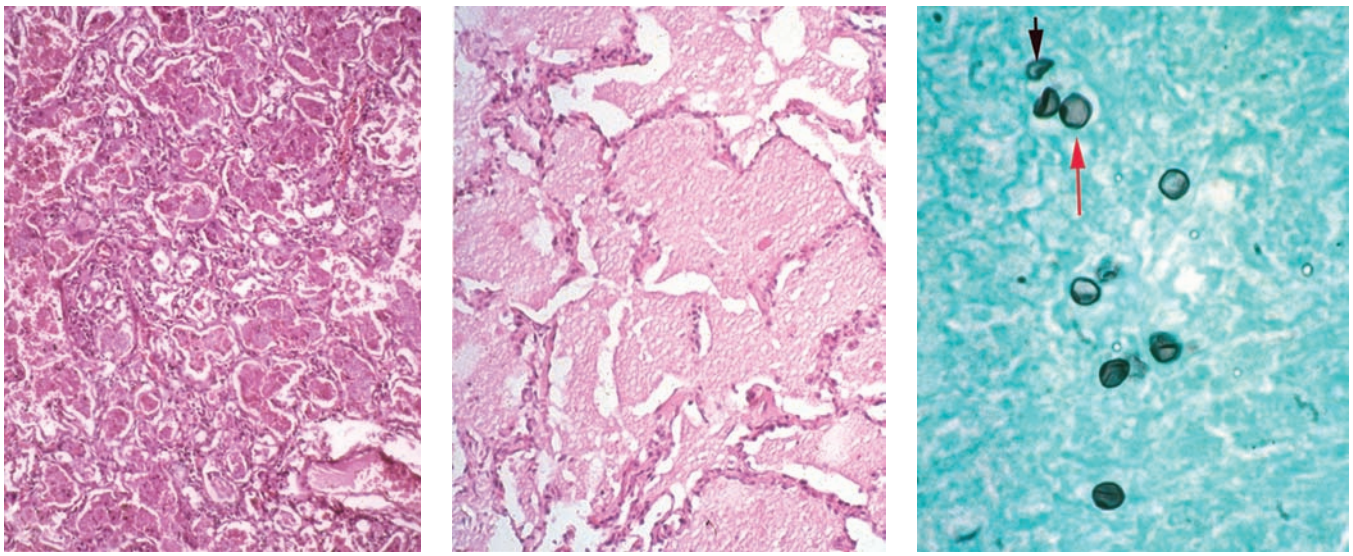
diabetics and in patients treated with deferoxamine, with prolonged corticosteroid therapy, or with broad-spectrum antimicrobials. The primary treatment of this invasive disease is surgical debridement in addition to antifungal therapy.

In patients with neutropenia or acute leukemia, a group of "benign" dermatophytes – including *Trichosporon beigelii*, *Aureobasidium*, *Alternaria*, *Curvularia*, *Phialophora*, *Wangiella*, and *Cladosporium*—have been associated both with disease of the skin and with invasive infection of the lungs, the sinuses, and the central nervous system (Fig. 123-13). Occasionally infections are caused by "atypical fungi" (e.g., *Saccharomyces cerevisiae*, *Scedosporium/Pseudallescheria species*, *Cunninghamella bertholletiae*, *Drechslera*, *Fusarium* species, *Geotrichum candidum*, and *Penicillium* species). *Fusarium* causes infection of the bloodstream and lungs that is indistinguishable from that due to *Aspergillus*, but with greater tendency to cutaneous involvement. The cardinal sign of *Pneumocystis* pneumonia is the presence of arterial hypoxemia out of proportion to physical or radiologic signs (Fig. 123-14).

■ VIRAL INFECTIONS

Viral infections are increasingly prevalent in patients with cancer. This is a reflection of prolonged T-cell defects, use of depleting antilymphocyte antibodies, and improved molecular diagnostic assays. HSV and VZV are frequently reactivated during periods of neutropenia or as a sign of the presence of new malignancies. Patients who are undergoing chemotherapy for Hodgkin disease or following HCT are at greater risk than other immunocompromised hosts (35%–50% in the first year). Specific antiviral prophylaxis is effective in reducing the incidence and severity of these relapses. Most often, these viruses cause painful, but relatively benign, skin or mucosal (especially esophageal, gastrointestinal, and perianal) lesions. These lesions may progress in neutropenic patients and the skin rash may become more diffuse, with hemorrhagic or nonhemorrhagic lesions extending beyond dermatomal limits.

Systemic dissemination to visceral organs occurs in 10% of patients with disseminated skin disease commonly involving the liver, lungs, brain, or gastrointestinal tract. Nasal, oropharyngeal, or esophageal HSV or VZV infections may spread directly to the lungs with the development of vesicular lesions in the trachea, or may cause viral pneumonitis in the parenchyma as a result of viremia secondary to cutaneous reactivation. Primary varicella pneumonia may accompany chickenpox in adults and in the compromised



A B C

Figure 123-14 **A.** The lung in a patient with *P. jiroveci* pneumonia demonstrates the filling of the alveolar space with eosinophilc frothy materials including trophozoites and macrophage debris. This appearance can be confused with alveolar proteinosis (seen in **B**) or fibrinous pulmonary edema (not shown). **C.** The cyst form of Pneumocystis is demonstrated using silver stain (GMS). Characteristic features include 4 to 6 micron size, the absence of "fungal" budding, and boat-shaped cysts, with pericapsular accentuation (*red arrow*)

host. Pulmonary invasion occurs within the first 7 days of illness, with mortality approaching 18%. Chest radiographs reveal nodular or interstitial infiltrates in up to 16% of adults with chickenpox, whereas only 10 to 25 of these have clinical symptoms. Pulmonary invasion by HSV and VZV in the neutropenic host should be considered a life-threatening emergency. In the granulocytopenic host, pulmonary CMV infection may be fatal. Therapy for CMV infection may include antiviral agents (ganciclovir, foscarnet, cidofovir) with some important toxicities as well as antibody repletion.

The community-acquired respiratory viruses are an important cause of pneumonia as well as predisposing to bacterial and fungal superinfection.[36–39] Nosocomial acquisition is common. AV, influenza, PIV, metapneumovirus, and RSV may be diagnosed with rapid molecular assays or using multiplexed screening panels (direct immunofluorescence).

■ PARASITIC INFECTION

The predominant parasitic infection enhanced by immune compromise is that due to *S. stercoralis*, a nematode that infects more than 100 million people worldwide, producing lifelong infection. *Strongyloides* is distinguished by its *ability to complete the replicative cycle within the human host* (Fig. 123-8). Malnutrition is a major cofactor; neutropenia and corticosteroids are common coinducers of parasitic replication. In the normal pattern of infection, the filariform larvae penetrate the skin, follow the veins to the lungs, and are then swallowed, entering the small intestine. The "hyperinfection syndrome" is the result of activation in the gastrointestinal tract by immune suppression, which causes penetration or transudation of worms across the wall, carrying gastrointestinal organisms with them. Peritonitis, bacteremia, and gram-negative, eosinophilic meningitis may result. Pneumonia may result from bacteremia or from obstruction of small airways and pneumonitis; the pulmonary infection fails to resolve without therapy directed at eliminating the nematode.

In endemic regions, activation of *T. gondii*, Chagas' disease (*Trypanosoma cruzi*), pulmonary or disseminated microsporidiosis or cryptosporidiosis (rare), leishmaniasis, and acute infection with *Acanthamoeba* and *Naegleria* species (primary amebic meningoencephalitis) must be considered in the differential of systemic and pulmonary infections.[40] Splenectomized hosts are at special risk for intense infection due to babesiosis, malaria, and ehrlichiosis/anaplasmosis.

■ CLINICAL APPROACH TO INFECTION IN THE PATIENT WITH CANCER

Clinical recognition of infection is often delayed in the neutropenic patient or patient with cancer because the inflammatory response is diminished (decreased numbers or mobilization of granulocytes) and the usual signs of infection are absent. Thus, in neutropenic patients, pneumonia may not be associated with sputum production and radiologic changes. In the febrile neutropenic patient with leukemia, the source of obscure infection is often the perineal and perirectal areas; less common are infections of the urinary tract, skin (including venous lines and wounds), and the lungs. In nonhematopoietic cancer patients, however, pulmonary infections predominate. A site of origin for a febrile episode is undetermined in 20% to 50% of patients. Many infections are detected only at autopsy, notably in patients with disseminated fungal or combined fungal and bacterial infections. Mortality in the febrile neutropenic population is 30% to 50%. Noninfectious causes of fever are common; among them are pulmonary thromboembolism, tumor, radiation pneumonitis, atelectasis with pulmonary edema, drug allergy or toxicity, and pulmonary hemorrhage. Often, the resolution of fever in response to a trial of antimicrobials is the only evidence of infection.

■ FEVER AND PULMONARY INFILTRATES

Pulmonary disease in the patient with cancer is clinically challenging, owing to the large array of processes that may cause radiologic infiltrates (Table 123-10). Noninfectious causes of pulmonary infiltrates and fever (edema, cancer, radiation injury, drug toxicity, leukoagglutinin transfusion reaction, pulmonary embolus, hemorrhage, alveolar proteinosis) are common (up to 25%) and may closely mimic infection (discussed also in Chapter 122). Conversely, the absence of inflammatory cells or mobilization may mask signs of significant infection. In the patient undergoing chemotherapy or in

TABLE 123-10 Common Causes of Pneumonia in Patients with Cancer Based on Radiographic Abnormalities and Disease Progression

Abnormality on Chest Radiograph	Common Cause by Rate of Disease Progression[a]	
	Acute (<24 h)	Subacute-Chronic
Consolidation	Bacteria (including *Legionella*) pulmonary embolus, hemorrhage, pulmonary edema	Fungi, Nocardia, tuberculosis (drug, virus [RSV], *P. jiroveci*, radiation)
Interstitial infiltrate	Pulmonary edema (including drug) Leukoagglutinin reaction (bacterial)	Viral, *Pneumocystis*, radiation, drug (fungi, Nocardia, tuberculosis, tumor)
Nodular infiltrate	Bacteria, edema (CMV, VZV)	Tumor, fungal, Nocardia, TB *Pneumocystis* (CMV)

[a]*Common causes (and less common in parentheses) in the absence of specific epidemiologic exposures or past history.*

the neutropenic host, cough, sputum, radiologic infiltrates or cavitation, and fever may all be absent. Infection may spread to the chest from contiguous structures (e.g., perforation of the esophagus due to *Aspergillus*) or may complicate anatomic changes (e.g., bronchial obstruction in lung cancer).

RADIOLOGIC CLUES TO DIAGNOSIS

A number of clues are available to assist in the differential diagnosis of pulmonary infiltrates in patients with cancer. For example, the clinical and radiographic appearance and progression of disease may suggest a diagnosis based on the time course and nature of the infiltrate (Table 123-10). In general, acute processes include both bacterial infections and noninfectious injuries, such as pulmonary embolus or edema. Subacute processes include *P. jiroveci*, viral, *Mycoplasma*, or *Nocardia* or *Aspergillus* infections. More chronic processes include drug-induced, radiation-induced, mycobacterial, nocardial, or malignant invasion of the lungs.

In particular, bronchial obstruction by tumor or enlarged lymph nodes may cause atelectasis or postobstructive pneumonia (Fig. 123-12). The underlying process may be suggested by pneumonia that fails to respond to antimicrobial therapy or recurs in the same location after successful treatment. Tumor masses, especially those due to lymphoma, may cavitate, giving the appearance of a lung abscess. Finally, it is important to bear in mind that a chronic process may be superinfected by an acute bacterial, viral, or drug-induced lung injury.

Clinical assessment, coupled with the radiologic pattern of lung disease, is usually the basis for forming a differential diagnosis for the patient with fever and pneumonitis. CT scanning has greatly improved differentiation of some processes. For example, in patients with simultaneous processes affecting the lung (e.g., aspiration and tumor), CT scans disclose distinctive patterns of parenchymal involvement (consolidation and infiltrative lesions with associated adenopathy) better than do conventional chest radiographs. Subtle interstitial infiltrates *(P. jiroveci)* or nodules *(Cryptococcus)* are better detected by CT scans than by conventional radiographs.

NONINFECTIOUS PNEUMONITIS

Following a dose of radiation to the lungs >2000 rads, radiation injury may be seen. The injury may become evident either acutely or more than 6 months after the initial exposure. The acute form of radiation pneumonitis may present as bronchitis or esophagitis, with dry cough, fever, fatigue, hypoxemia, and dyspnea that develop over 6 to 12 weeks. The histologic picture reveals vascular damage, mononuclear infiltrates, and edema. The severity of lung injury due to radiation appears to correlate with the rapidity of the withdrawal of steroid therapy, but it may also reflect the emergence of the underlying inflammatory response. Radiation fibrosis usually occurs in 6 to 9 months, and pulmonary function may take up to 2 years to plateau (see Chapter 59).

Acute, drug-induced lung disease may reflect hypersensitivity to chemotherapeutic agents (see Chapter 65) or to sulfonamide agents. Methotrexate, bleomycin, and procarbazine can cause a syndrome of nonproductive cough, fever, dyspnea, and pleurisy with skin rash and blood eosinophilia. Chest radiographs demonstrate diffuse reticular infiltrates. Cyclophosphamide may cause a syndrome of subacute pulmonary disease with interstitial inflammation and pulmonary fibrosis, with fever, dyspnea, fatigue, and cough. Drug toxicity for agents such as bleomycin, BCNU, and CCNU may be related to the cumulative dose (for bleomycin, over 450 mg) and patient age. Synergistic toxicity for the lung occurs between radiation and a variety of chemotherapeutic agents (e.g., bleomycin, mitomycin, busulfan) and supplemental oxygen use. A variety of noninfectious processes may mimic infection. Alveolar proteinosis may be associated with hematologic malignancies or accompany infection due to *Nocardia* or, less often, *Cryptococcus*, *Aspergillus*, *M. tuberculosis*, and *Histoplasma*.[41] Pulmonary infarction may mimic infections in association with hemoptysis, leukocytosis, pleuritic chest pain, and segmental pleural-based infiltrates on the chest radiograph.

INITIAL MANAGEMENT OF THE PATIENT WITH CANCER AND FEVER: STRATIFICATION OF RISK

Each patient presenting with signs of infection must be evaluated in terms of the perceived risks of infection and noninfectious causes of fever and for the presence of neutropenia or other immune dysfunctions. Attempts to manage patients with greater efficiency and to shorten hospital stays have led to the development of *critical pathways*, which include standard patterns of evaluation and treatment for many patients, including those with cancer. Such uniform approaches are useful in establishing a *minimal standard* of care, but they do not address concerns about the pitfalls of failing to individualize therapy.

The safe application of critical pathways for the outpatient management of neutropenic patients necessitates careful stratification of these compromised patients by experienced clinicians in terms of their risk for infectious complications. *Any sign of infection* requires at least a brief hospitalization (1–3 days), with careful evaluation. Experienced oncologists manage some febrile neutropenic patients as outpatients. Any febrile neutropenic patient – or patient in whom absolute neutrophil count (ANC) is expected to fall below 1000/mm^3 – with localizing signs (headache, altered mental status, rash, dyspnea, chest pain, pain over an indwelling catheter site, pulmonary infiltrates) should be considered for emergency admission. In particular, patients with leukemia or lymphoma, uncontrolled metastatic cancer, recent need for antimicrobials, or ANC under 100 (or expected to fall below 100) are generally considered "higher-risk"

patients and are best managed as inpatients until clinically stable. Patients with a history of frank rigors, hypoxia, or hypotension merit admission. Any febrile patient with cancer needs an assessment of vital signs; oxygen saturation; complete blood count with differential; electrolytes, blood urea nitrogen, and creatinine (to assess for urinary obstruction by tumor or acute drug toxicity); blood cultures (at least one from a peripheral site and one from any indwelling catheter); urine sediment examination and culture; sputum Gram stain examination and culture; and chest radiograph. After a careful physical examination, the threshold should be low for lumbar puncture and determination of serum or spinal cryptococcal antigen. The patient's history and medical record should be reviewed, with attention to current drugs, recent chemotherapy (especially corticosteroids), recent microbiologic data and antimicrobial use, allergies, and exposures.

EMPIRIC USE OF ANTIMICROBIALS IN FEVER AND NEUTROPENIA

After appropriate smears and cultures have been obtained, empiric antimicrobial therapy in the febrile neutropenic patient is required. The specific antimicrobials selected for "routine use" in the febrile neutropenic patient remain controversial. Ultimately, this is because many combinations appear to work equally well, and because there are few studies of various combinations in identical patient populations using the same entry and end-point criteria. The antimicrobials selected must "cover" previously documented infections or surveillance culture data, physical findings, known hospital flora, and potential community exposures.

Initial therapy should assume that the organisms causing infection are likely to be resistant to current prophylactic or therapeutic antimicrobials. Many infections are loculated and require drainage (e.g., sinusitis, postobstructive pneumonitis) (Fig. 123-12). Patients thought to be at *low risk* for infection or other complications (nonleukemic, underlying cancer not progressing, no serious coexisting illness, no recent infections or courses of antimicrobials, expected ANC to remain above 100) may be *considered* for home management after 24 hours (to await blood culture data), based on the clinical assessment. In these patients, empiric antimicrobials should target gram-negative organisms and be based on the known resistance patterns in the institution and in the patient. Monotherapies include antipseudomonal beta-lactams (ticarcillin-clavulanate, piperacillin-tazobactam, third or fourth generation cephalosporins) or carbapenems. Optimal antimicrobial therapy should include synergistic therapy for *Pseudomonas* infection in medical centers where this organism is prevalent or if the patient is colonized and/or profoundly neutropenic. Aminoglycosides remain useful for synergy but have limited activity in pneumonia and have been supplanted by fluoroquinolones if these agents have not been used recently for prophylaxis or therapy.

A decision regarding coverage for gram-positive organisms including MRSA (e.g., vancomycin) or VRE is based on the possibility of catheter-associated infection and clinical judgment. Such patients might include those with skin wounds, decubitus ulcers, hypotension, or indwelling vascular access catheters. Gram-positive bacterial infections generally progress more slowly than do the gram-negative infections; the *routine use* of vancomycin in these patients does not appear to be justified, because of the increased risk of VRE. Routine surveillance for VRE may be of assistance in adjusting the regimen if fever persists. Routine use of antifungal agents is complicated by the common use of fluconazole in prophylaxis. High-risk patients, especially if colonized with yeasts (thrush, skin, and/or urinary), may merit empiric coverage with echinocandin agents until blood culture data are available.

If an abdominal or anaerobic bacterial source is suspected, clindamycin or metronidazole can be added. Anaerobic infections other than those due to *Bacteroides fragilis* are uncommon as a source of major morbidity in these patients. Restrictions on the use of clindamycin have been instituted at many centers because of outbreaks of *C. difficile* colitis. Topical oral antifungal therapy (clotrimazole, nystatin) is commonly administered with broad-spectrum parenteral antimicrobials. Antimicrobials may be adjusted on the basis of microbiologic data or if the patient is afebrile for 7 to 10 days with the ANC over 500 and increasing.

Empiric therapy must be individualized. In a patient receiving empiric therapy who becomes afebrile on antimicrobials by 72 hours and with a neutrophil count above 500/mm^3, the antimicrobials may be stopped after 7 days and the patient reevaluated if no localizing source is found or untreated pathogens detected. Patients who are clinically well and who become afebrile with neutrophil counts of 100 to 500 per mm^3 should be afebrile for 5 to 7 days before antimicrobials are stopped to reevaluate sources of infection. If the patient is not clinically well (e.g., has mucositis, fewer than 100 neutrophils per mm^3, or unstable vital signs), the antimicrobials should be continued until the patient is stable and afebrile for 48 to 72 hours.

Unless a specific source of infection is located and the pathogen(s) identified, patients with persistent fever and neutropenia should have antimicrobials broadened 48 to 72 hours after the start of therapy. The options include (1) addition of vancomycin (or other gram-positive agent if colonized with resistant organisms such as VRE); (2) addition of antianaerobic therapy for oral mucositis or gingivitis, abdominal pain, or perirectal tenderness; (3) expansion of gram-negative bacterial coverage (generally adding a second agent from a different class of antimicrobials); (4) consideration of antiviral therapy in patients with esophagitis or a history of HSV or VZV or at risk for CMV infection; and (5) addition of antifungal therapy. The toxicities of antifungal agents must be considered carefully in these patients, notably those with decreased renal function or systemic fungal infection. The use of amphotericin B products (generally lipid associated) must be in full dose and patient must be well hydrated and volume expanded (using blood or saline) with attention paid to magnesium and potassium maintenance. Slowly advancing doses of this drug have been advocated without supporting data and entail the disadvantage of delay in achieving adequate therapy. Voriconazole (and other azoles) have significant interactions via the hepatic P450 metabolic system and the intravenous incipient has been associated with cardiac arrhythmias in renal dysfunction. The echinocandins have fewer drug interactions but are rarely the drug of choice for initial therapy of filamentous fungal infection. The *Mucoraceae* lack susceptibility to both voriconazole and echinocandins. *Cryptococcus* lacks susceptibility to echinocandins.

Special attention must be paid to any symptoms of pulmonary disease, the presence of new pulmonary infiltrates on chest radiographs, or the presence of sinus or CNS symptoms in patients with persistent fevers. New infiltrates should prompt examinations of sputum and procurement of specimens (open biopsy, thoracoscopic biopsy, or bronchoscopy, preferably with biopsies, or needle aspirates under tomographic guidance) for histologic and microbiologic evaluation.

BONE MARROW AND STEM CELL TRANSPLANTATION

Pulmonary manifestations of bone marrow and stem cell transplantation include a broad spectrum of infectious and noninfectious etiologies. Important pulmonary disorders complicating these procedures are discussed in detail below.

TEMPORAL SEQUENCE OF PULMONARY DISEASE SYNDROMES

The patterns of infection in hematopoietic transplantation have shifted due to early engraftment with hematopoietic stem cell

TABLE 123-11 Pulmonary Complications in BMT/HCT

Pulmonary edema syndromes (engraftment syndrome)
Infectious pneumonia
Bacterial
Fungal
Viral
Protozoal
Idiopathic pneumonia
Oral mucositis
Pulmonary veno-occlusive disease
Bronchopneumonia
Idiopathic pneumonia
Viral pneumonia
Airflow obstruction (obliterative bronchiolitis)

[a]*Obstructive airflow among marrow recipients with chronic GVHD.*

transplantation (HCT) compared with BMT and the use of nonmyeloablative transplantation (Fig. 123-2).[42] The impact is apparent in the shorter duration of neutropenia in the initial phase, early engraftment—but has not decreased the incidence of GVHD or the infections associated with immunosuppressive treatment of GVHD (Table 123-11).[43] Specific pulmonary complications can be grouped according to the status of the individual patient: preengraftment neutropenia (1–4 weeks), engraftment (fever and cytokine release, renal dysfunction), early and late postengraftment (up to approximately 26 weeks and 1 year), and late infections (based on the status of host immunity and epidemiology). Although this division is clinically useful, overlap occurs in the timing of specific complications, and the categorization of pulmonary complications is often arbitrary, since the cause of many respiratory abnormalities is uncertain. As a result, the microbiologic evaluation often accompanies empiric therapy including antimicrobial agents and diuresis (Fig. 123-15).

Inadequate tools are available to accurately assess the individual's immune function. Mucociliary clearance and macrophage function are decreased, often for years after transplantation.[44,45] T-cell depleted grafts and patients treated with T-cell depleting antibodies have less GVHD but more viral and fungal infections. Treatments including B-cell depletion have more bacterial infections due to encapsulated organisms. Prophylaxis served only to delay infection and to select resistant organisms unless immune function is restored. Killed organism vaccination is appropriate by 1 year post transplant with use of live vaccines reserved until immune function has normalized, generally by 2 years post transplantation.

In the early phase, neutropenia predominates with mucositis (and aspiration) being common, herpes simplex (in seropositive recipients), idiopathic pneumonia (respiratory viruses, CMV, pulmonary edema), *Aspergillus* infection, and line-associated infections (*Candida* species, gram-positive and gram-negative bacteria).[42,46] Viral pathogens predominate after engraftment but before T-cell function normalizes—CMV, VZV, AV (and other respiratory viruses), but also *P. jiroveci* (PCP), *T. gondii,* and molds (see Figs. 123-16 and 123-17).[47–50] Routine prophylaxis (TMP-SMX, antivirals) is generally effective in preventing such infections but may be limited by toxicity. Late and uncommon infections may occur at any time in the post-HCT course notably in those with persistent immune deficits.[51,52] Such individuals are at persistent risk for infections due to *Legionella, Nocardia, Mycoplasma*, mycobacteria, *S. stercoralis*, *Cryptosporidium* species, Epstein–Barr virus (EBV), posttransplant lymphoproliferative disorder or PTLD, and in those with hypogammaglobulinemia-encapsulated organisms including *S. pneumoniae, Neisseria meningitidis, and H. influenzae*.[53–55]

The most important characteristic that separates patients receiving ablative or nonmyeloablative conditioning for allografts from those receiving syngeneic or autologous marrow or stem cells is the occurrence of GVHD in the former group. Syngeneic and autologous graft recipients share early risk factors, such as neutropenia, with patients receiving allogeneic transplants and are at risk for early pulmonary complications, such as bacterial or fungal pneumonia and noninfectious treatment-related pulmonary injury.[56,57] Transplant recipients who have delayed engraftment or subsequent marrow failure are at continued risk for bacterial or fungal infection.[58,59] Allogeneic marrow recipients with GVHD, including those undergoing nonmyeloablative transplants, have continued abnormalities in immune function that increase the risk of opportunistic infections.[60] Among patients with chronic GVHD, infection and pneumonia due to encapsulated organisms (e.g., *S. pneumoniae, H. influenzae,* and *S. aureus*) appear related to deficiencies in specific antibody production, use of anti-CD20 antibodies, recurrent viral infections, resistance to common antimicrobials used for prophylaxis, and possibly continued defects in macrophage and NK cell functions.[61,62]

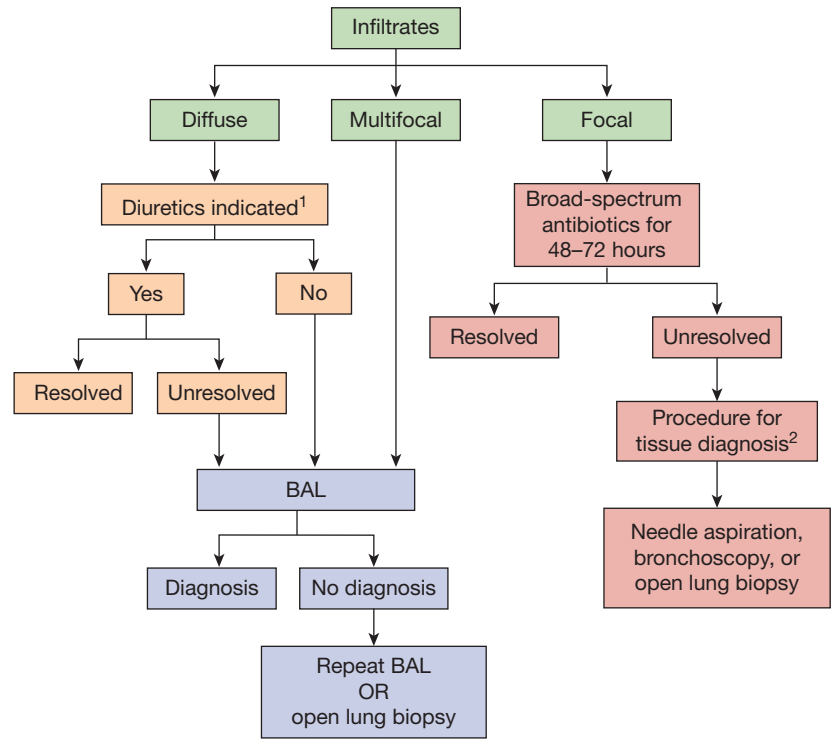
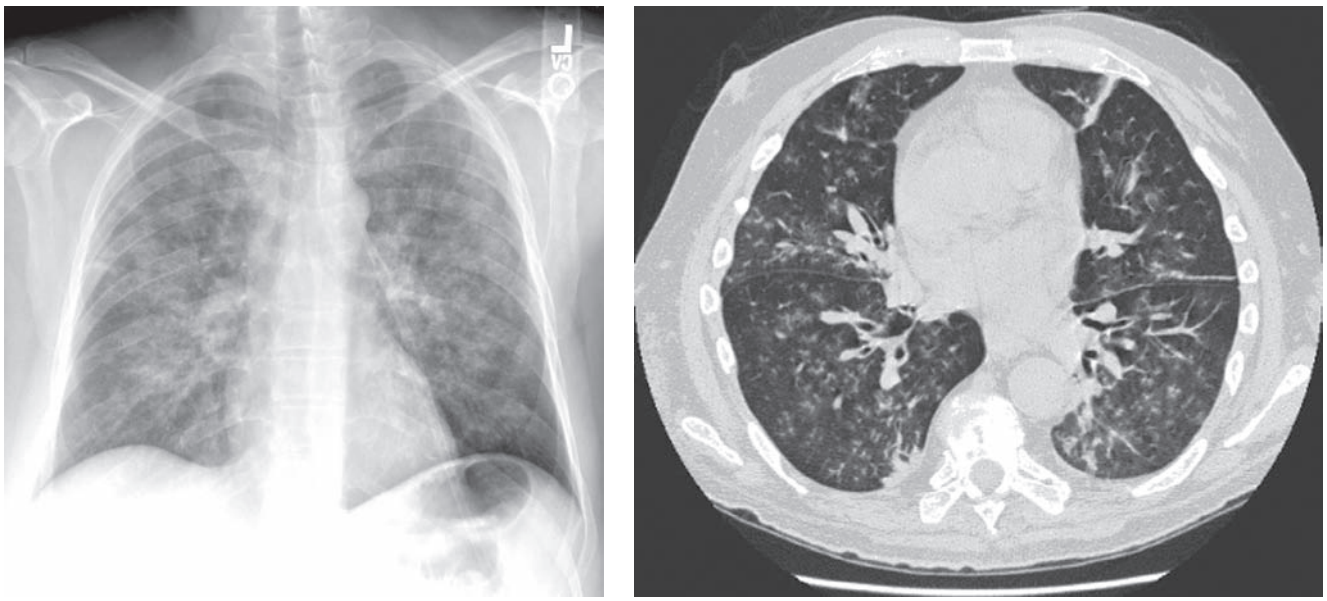


Figure 123-15 Diagnostic approach to pulmonary infiltrates after hematopoietic stem cell transplantation. [1]Diuretics often indicated in the first 30 days after transplantation. [2]Choice of procedure often influenced by results of CT scan of thorax.



A B

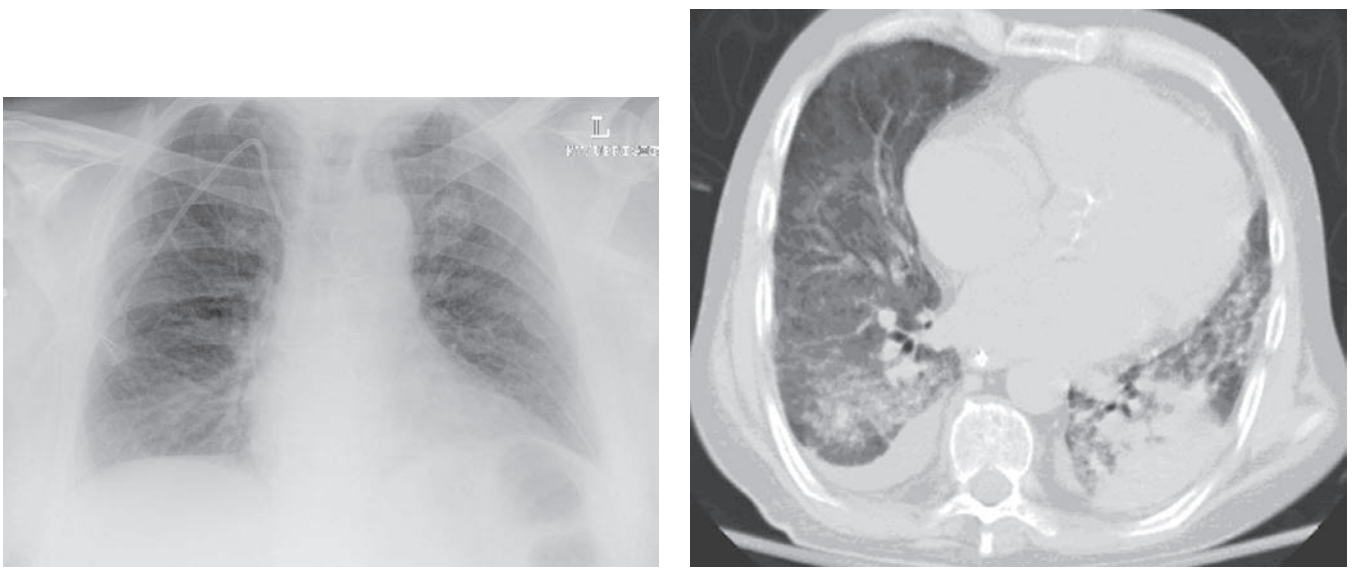
Figure 123-16 Adenovirus pneumonia during week after marrow engraftment following allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia. Routine chest radiograph (**A**) reveals diffuse pneumonia while CT scan (**B**) demonstrates bronchiolitis. The patient failed to respond to cidofovir therapy but cleared infection after infusion of autologous stem cells.

■ COMMON CLINICAL PRESENTATIONS

Signs and symptoms of pulmonary disorders related to marrow and hematopoietic stem cell transplantation are often nonspecific (Fig. 123-15). Tachypnea is common, as are fever, cough, and crackles. However, any or all of these may be absent at the time of presentation of pulmonary complications. Routine chest radiographs are obtained frequently during the first weeks of neutropenia and often provide the first indication of pulmonary impairment.

■ DIFFUSE INFILTRATES

Diffuse infiltrates are common radiographic abnormalities noted in marrow recipients.[63] However, these infiltrates are most often nonspecific. Infectious causes for diffuse infiltrates have been documented in fewer than 20% of marrow recipients undergoing open lung biopsy within 30 days after marrow transplantation. Within this early period, pulmonary edema syndromes predominate. The edema may be associated with cardiac decompensation or intravascular volume excess, or with acute respiratory distress syndrome (ARDS) and pulmonary capillary leak due to treatment-related toxicities or sepsis syndrome. Infections presenting with diffuse infiltrates within the first weeks after transplantation include respiratory viral causes, such as RSV or AV, while CMV is uncommon (Fig. 123-16). Alveolar hemorrhage may contribute to the radiographic infiltrates in



A B

Figure 123-17 Diffuse process on plain radiograph (**A**) of *Pneumocystis* pneumonia 8 weeks following hematopoietic stem cell transplantation for T-cell lymphoma. CT scan (**B**) revealed pattern most consistent with aspiration pneumonia. Bronchoalveolar lavage revealed *Pneumocystis* and antimicrobial-resistant *K. pneumoniae*. Treatment of both processes resulted in resolution of infection.

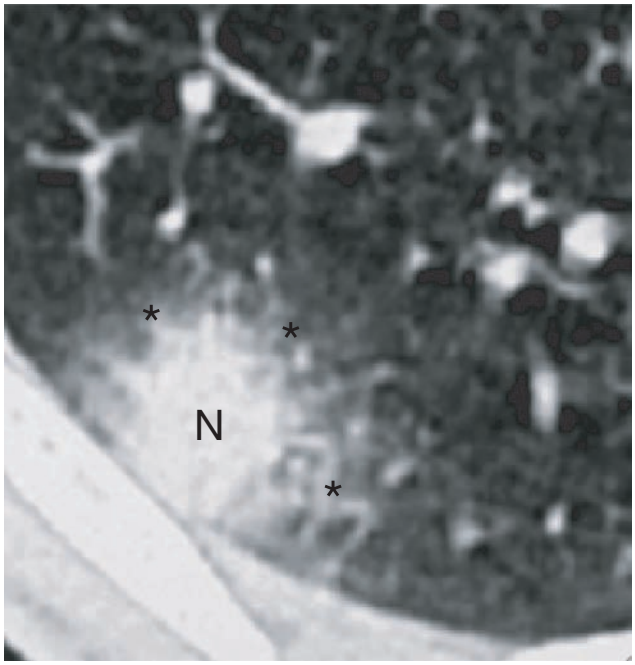


Figure 123-18 "Halo" sign in angioinvasive aspergillosis. CT scan of patient with fever and prolonged neutropenia during therapy for hematopoietic malignancy demonstrates a macronodule (N) surrounded by a halo of ground-glass opacity (*).

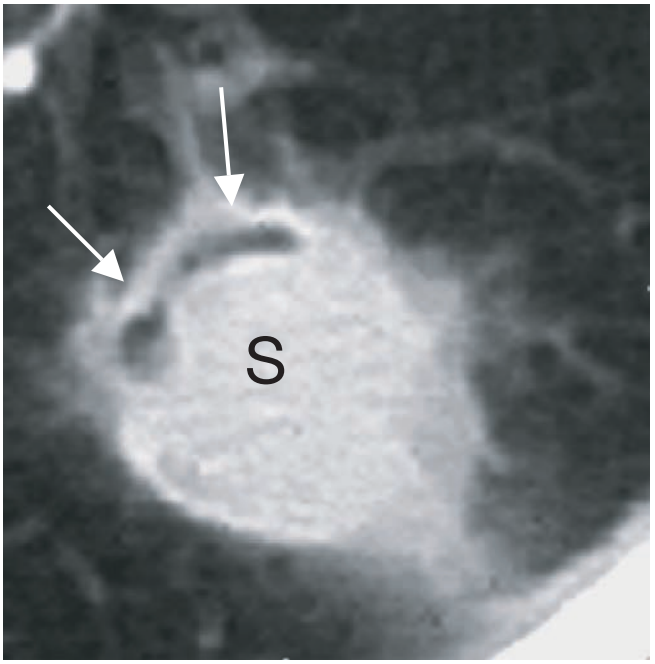


Figure 123-19 Air-crescent sign in late angioinvasive aspergillosis. CT scan of a patient with hematologic malignancy after recovery from profound neutropenia demonstrates a cavitary macronodule with an air crescent *(arrows)* at 10 to 1 o'clock outlining a central necrotic sequestrum (S).

the presence of thrombocytopenia, regardless of the cause of the lung injury.

After marrow engraftment, infections are a major reason for diffuse radiographic abnormalities. CMV was most common in the past, but is now less common in patients receiving appropriate prophylaxis or monitoring. Diffuse pneumonia due to bacterial infections (occasionally disseminated nontuberculous mycobacterial disease, *Mycoplasma* or *Chlamydophila*) also is unusual; however, diffuse involvement with fungus may occur in as many as 20% of diffuse infiltrates and may be extremely difficult to detect.

■ FOCAL LESIONS

Focal parenchymal infiltrates are frequent due to infection regardless of the time of presentation after transplant. Focal consolidations or masses are related to local fungal infection in 80% of marrow transplant recipients receiving broad-spectrum antimicrobials.[64] Classic signs of *Aspergillus* infection include pleural-based nodules with surrounding "halo" of ground-glass opacity (Fig. 123-18), occasionally with cavitation or development of the "air-crescent sign" (Fig. 123-19). Other causes are *Legionella* species, *Nocardia,* relapse of lymphoma in patients transplanted for that disorder, bronchiolitis obliterans with organizing pneumonia (BOOP), and, rarely, infarct due to thromboembolic disease.[65]

■ ASPIRATION

Desquamation of the oropharyngeal mucosa is a frequent complication after intensive chemotherapy, and the stomatitis is often referred to as "mucositis." It develops within the first week after radiotherapy and reaches its greatest severity after 10 to 14 days, and impaired mucociliary clearance is common. Recurrent aspiration of oropharyngeal contents is common among transplant recipients with oral mucositis due to sedation, poor cough reflex, and dysphagia.[66] These patients may present with basilar infiltrates or consolidation. Infection by HSV-1 of the oropharynx or esophagus may be confused with mucositis and may progress to pneumonia.

■ PLEURAL EFFUSIONS

Pleural effusions are common in the first weeks after marrow transplantation and are rarely related to an identifiable infectious source. Pleural effusions may be associated with fluid retention of any cause, especially with ascites secondary to HVOD. HVOD may occur in as many as 60% of patients after total-body irradiation or in association with GVHD. Characteristics include weight gain within the first weeks after transplantation and elevation of the serum bilirubin, which usually precede the development of pleural effusions. The effusions are frequently bilateral. Bilateral pleural effusions in the presence of weight gain can be approached conservatively without diagnostic thoracentesis. Cautious diuresis coupled with treatment of GVHD often produces satisfactory results. Small effusions are common and may be associated with treatment-related pleuropericarditis or thromboembolic events, but a specific cause is seldom determined. A large unilateral or rapidly accumulating effusion in the presence of fever or ipsilateral chest pain may represent hemorrhage or infection and should be evaluated promptly by thoracentesis.

■ NONINFECTIOUS ETIOLOGIES

Noninfectious causes of lung injury after marrow and hematopoietic stem cell transplantation include a spectrum of syndromes: idiopathic pneumonia, alveolar hemorrhage, pulmonary edema, obliterative bronchiolitis or BOOP.[56,57,67–70] Idiopathic pneumonia is characterized as a syndrome of hypoxemia and radiographic nonlobar infiltrates in the absence of congestive heart failure and without evidence of an infectious origin.[71,72] It is included as a form of "interstitial" pneumonia.[57,73,74] The term *interstitial pneumonia* in marrow transplant recipients refers to the syndrome of diffuse inflammatory pulmonary disease presenting with fever and tachypnea. This term includes noninfectious causes, as well as infectious pneumonia due to viruses (CMV). To avoid the ambiguity of the term *interstitial* in relation to inflammatory and other disorders of the lung, it is preferable to classify the clinical conditions as *diffuse*

pneumonia on the basis of the radiographic presentation. Most noninfectious causes of lung injury are attributed to treatment-related toxicities. Alkylating chemotherapy agents and ionizing irradiation are likely contributors; however, ARDS secondary to sepsis syndrome also may occur. While pneumonia is associated with the presence of GVHD, whether GVHD causes a direct lung injury is unproved. The role of unrecognized infections remains a concern.

IDIOPATHIC PNEUMONIA SYNDROME

The largest studies of idiopathic pneumonia after allogeneic marrow transplantation estimate the incidence at 12% to 17%. The spectrum of idiopathic lung injury is referred to as a "syndrome" (idiopathic pneumonia syndrome, or IPS) in recognition of the multiple causes and varied clinical presentation of this process.[57,71–74] The diagnosis of IPS is defined by a BAL that does not reveal an infection in the presence of nonlobar radiographic infiltrates and physiologic changes consistent with pneumonia. A common series of laboratory evaluations is presented in Table 123-4. Many clinicians use IPS to describe noninfectious lung injury occurring within the first 3 to 4 months after transplantation.

The causes of diffuse idiopathic pneumonia are often multiple and include treatment-related toxicities due to radiation or chemotherapeutic agents.[71,72,75] However, sepsis-related pulmonary toxicity may account for a proportion of cases of diffuse idiopathic pneumonia with histology consistent with ARDS. While GVHD is associated with an increased incidence of idiopathic lung injury, it is unclear whether this is a cell-mediated immune response to the lung or related to an increased incidence of sepsis in these immunosuppressed patients. Also, administration of large volumes of blood products during the transplantation procedure may lead to pulmonary vascular injury through leukoagglutination reactions. Other unusual causes of noninfectious diffuse pneumonia after marrow transplantation are leukemic infiltration due to relapse of primary malignancy, injection of malignant cells with reinfused autologous marrow, and fat embolization due to marrow infusion. Several cases of fat embolization have been associated with pulmonary hemorrhage and steroid administration.

The clinical presentation of IPS is nonspecific. Most patients develop a syndrome of fever, nonproductive cough, and tachypnea. Hypoxemia with hyperventilation is common. The onset is most often rapid, occurring over a few days. Occasionally, insidious onset similar to that of idiopathic pulmonary fibrosis is seen. The median onset is within the first 3 weeks of transplantation, but it may occur months later. The chest radiograph shows diffuse intra-alveolar and/or interstitial infiltrates. The presentation is not sufficiently distinct to be readily differentiated from that of pulmonary edema syndromes or diffuse infectious pneumonia. Marked tachypnea in the absence of radiographic infiltrates should raise the suspicion of obstructive airway disease or pulmonary veno-occlusive disease (PVOD), rather than idiopathic pneumonia.[76]

IPS after marrow transplantation represents a histologic spectrum ranging from a primarily interstitial reaction with diffuse or focal widening of the alveolar septa and interstitial spaces with mononuclear inflammatory cells and edema to diffuse alveolar damage (DAD) with alveolar epithelial necrosis, intra-alveolar hyaline membranes, edema and hemorrhage, and type 2-cell hyperplasia. The predominantly interstitial presentation has been referred to as *idiopathic interstitial pneumonia,* whereas the pathology of DAD is identical to that of ARDS. Variable degrees of alveolar hemorrhage may be seen with either of these presentations. By definition, all microbiologic and histologic evaluations for infectious agents (viral, protozoal, fungal, and bacterial) are negative in idiopathic pneumonia. The importance of a thorough microbiologic examination lies in the fact that these histologic presentations are similar to those of infectious pneumonia, especially CMV pneumonia.

Mortality from idiopathic lung injury after marrow transplantation remains over 70%. The diagnosis of idiopathic lung injury rests largely on the results of BAL. Lung biopsy (transbronchial or open) appears to add little to the diagnostic sensitivity of BAL for infection in the presence of diffuse parenchymal infiltrates. At present, histopathology does not help to direct therapy in idiopathic lung injury after hematopoietic stem cell transplantation. Lung biopsy should be considered in cases with patchy or multifocal infiltrates because of the higher incidence of infection and concern for false-negative results from BAL. There are no randomized studies of treatment of idiopathic lung injury after marrow transplantation. High-dose corticosteroids (ranging from 1 to 16 mg/kg per day of methylprednisolone) and other forms of intensive immune suppression are commonly used.

PULMONARY HEMORRHAGE

Robbins et al. described a potentially specific form of idiopathic pneumonia: diffuse alveolar hemorrhage (DAH).[77,78] The syndrome consisted of progressive dyspnea, hypoxemia, cough, and a progressively bloodier return from BAL in autologous marrow recipients, usually within 2 weeks of transplant. The incidence of DAH was 20.5% and was associated with age over 40 years, high fever, transplantation for a solid tumor, severe mucositis, white blood cell recovery, and renal insufficiency. Thrombocytopenia was a common finding, and patients with DAH received more platelet transfusions than patients without DAH. It is unclear whether this hemorrhagic pneumonia represents a unique syndrome or represents severe lung injury in the presence of a bleeding diathesis (see Chapter 68).

PULMONARY EDEMA SYNDROMES

Biventricular failure after transplantation is often iatrogenic and associated with excessive fluid administration and an increase in total body weight. Radiographic evidence of pulmonary edema after marrow transplantation has been reported in up to 50% of patients, most occurring in the second week. Close attention to the total amount of sodium and fluids administered can lead to dramatic reduction in the incidence of pulmonary edema. Also, pulmonary edema may be associated with left ventricular decompensation related to cardiotoxic cytoreductive regimens, including anthracyclines in excess of 500 mg/m^2 and high-dose cyclophosphamide. Posttransplantation cardiac and pericardial toxicity occur in 4% to 10% of cases, usually associated with total-body irradiation and cyclophosphamide, often in the setting of prior anthracycline administration. The utility of cardiac imaging studies before transplantation to predict heart failure is limited.

The most frequent noncardiac association with pulmonary edema is HVOD. The syndrome is often associated with interstitial pulmonary edema, the formation of pleural effusions, and renal failure. Noncardiac pulmonary edema also develops in association with acute GVHD and may be due, in part, to DAD and capillary leak. The presentation of pulmonary edema is nonspecific and usually occurs within 30 days after marrow infusion. Marrow recipients are often febrile and tachypneic at this time in the transplant course, and recipients of allogeneic marrow may display evidence suggestive of acute GVHD. Thus, the distinction between pulmonary edema and idiopathic pneumonia often cannot be made with certainty without pulmonary artery catheterization. However, recent increase in total body weight appears to correlate well with total-body fluid accumulation and should prompt a trial of diuretic therapy and a search for other signs of GVHD (GI, liver, skin) before consideration of invasive diagnostic procedures. Noninvasive assessment of cardiac function with

ultrasonographic or radionuclide techniques is often warranted to guide treatment.

NEW-ONSET AIRFLOW OBSTRUCTION AND OBLITERATIVE BRONCHIOLITIS

About 10% of allogeneic marrow recipients with chronic GVHD are likely to develop airflow obstruction consistent with obliterative bronchiolitis.[79,80] However, the reported incidence of obliterative bronchiolitis varies, in part, with the method used to identify the presence of the disease. Factors associated with the increased risk of GVHD, such as increasing age and HLA-nonidentical marrow grafts, are not independent risk factors for the development of obliterative bronchiolitis.[67–69,81,82] The cause of obliterative bronchiolitis after marrow transplantation is unknown (see Chapter 106).

The main manifestation of new-onset airflow obstruction is the insidious onset of tachypnea, dyspnea on exertion, and dry, nonproductive cough. Fever is uncommon. Although the chest radiograph is commonly interpreted as normal, high-resolution chest CT often reveals parenchymal hypoattenuation and segmental bronchial dilatation.[76] Auscultation of the chest may reveal scattered expiratory wheezing and occasionally diffuse inspiratory crackles, but results are sometimes normal. Arterial blood-gas analysis reveals moderate hypoxemia and, in the later stages, hypercarbia. Systemic evidence of GVHD is usually present. The major differential diagnoses of the gradual onset of nonspecific respiratory symptoms in the presence of a normal chest radiograph include PVOD and pulmonary embolism. Obliterative bronchiolitis is characterized by reduction in expiratory airflow on spirometry and increases in residual lung volumes not found in the other two diseases. Obstruction may be recognized incidentally as a result of coinfection due to respiratory viruses or *Pneumocystis*.

Patients with early onset of airflow obstruction after marrow transplantation tend to have a rapid decline in pulmonary function and a fatal outcome. These patients may not survive long enough to develop manifestations of chronic GVHD but usually display acute GVHD after BMT or HCT. It is possible that infection plays a role in the development of the airflow obstruction in some of these patients. Marrow and stem cell recipients with later onset of airflow obstruction tend to have a more gradual decline in lung function. Airflow may stabilize in 50% of these patients.

There are no prospective trials of treatment for new-onset airflow obstruction. At present, the accepted approach to these patients is to aggressively control with immunomodulating agents the chronic GVHD that most often accompanies the airflow obstruction. Treatment usually consists of increased immunosuppression. Reversal of the airflow obstruction is uncommon. The usual goal of management is stabilization of the obstruction. For this reason, prompt recognition and treatment for this progressive process are critical. Supportive measures include prophylaxis against *P. jiroveci* pneumonia and *S. pneumoniae* infection, inhaled bronchodilators, supplemental immunoglobulin administration to maintain normal serum levels, and prompt treatment of intercurrent infections.

PULMONARY VENO-OCCLUSIVE DISEASE

PVOD is a rare complication of treatment with chemotherapeutic regimens, and as a solitary pulmonary complication, PVOD is an uncommon but potentially catastrophic complication after transplantation. The primary histologic lesion of PVOD – obstruction of the pulmonary veins and venules by loose intimal fibrosis proliferation – may be difficult to detect with hematoxylin and eosin stains alone, and specific stains for elastic tissues, such as Verhoeff–van Gieson stain, are required to demonstrate the fibrotic reaction in the veins. The typical presentation of PVOD is that of insidious dyspnea on exertion and resting tachypnea within 3 to 4 months after transplantation. Significant hypoxemia may occur along with hyperventilation. The chest radiograph is often unrevealing. On cardiac examination, there is evidence of pulmonary hypertension. Auscultation of the lungs is often normal, although scattered inspiratory crackles may be heard. Noninvasive examinations, echocardiography, perfusion ventilation nucleotide scans, and electrocardiograms are nondiagnostic. Pulmonary function testing (PFT) may be consistent with mild restrictive defect, but airflow obstruction, suggesting obliterative bronchiolitis, is absent. BAL has failed to demonstrate pathogens or inflammatory cells. The diagnostic procedure of choice is a pulmonary angiogram. Right heart catheterization reveals elevated pulmonary artery pressure, with normal pulmonary artery wedge pressures. Angiography excludes the presence of thrombi as a cause of the pulmonary hypertension. In most cases presenting after treatment for malignancy, the disease follows an insidious course, with progressive hypoxemia and dyspnea on exertion due to pulmonary hypertension. Some patients recover with high-dose corticosteroid therapy or other immunosuppressive therapy.

INFECTIOUS ETIOLOGIES

The spectrum of infectious agents complicating stem cell and BMT is broad. Major categories of pathogens are discussed below.

Cytomegalovirus and Viral Pneumonias

In hematopoietic stem cell and BMT recipients, CMV pneumonitis occurs in the CMV-seropositive recipient of CMV-seronegative grafts. Because much of the lung injury is due to immune responses to CMV antigens, the full pneumonitis develops not during lymphopenia but rather with the engraftment of the marrow and with the reemergence of immune function. Viral replication is not needed for CMV pneumonitis to occur. The incidence of CMV pneumonia has declined significantly in recent years with routine prophylaxis and monitoring. Most CMV infection occurring in seropositive patients is due to reactivation of latent infection. The risk of infection in seronegative patients with seronegative marrow or stem cell donors is attributable to blood product exposure, and this risk can be virtually eliminated by use of screened seronegative or filtered blood products.

The clinical presentation of CMV pneumonia is not distinct from that of other entities associated with diffuse pneumonia. Patients with CMV pneumonia may have nonproductive cough, dyspnea, hypoxemia, or fever, with a median onset of 60 days after marrow transplant. Onset within the first 2 weeks is unusual. The period of risk of CMV pneumonia generally ends by approximately the fourth or fifth month after transplant, although later cases occur among patients with chronic GVHD or after autologous transplant. The chest radiograph generally shows bilateral infiltrates; in later stages, diffuse consolidation occurs. Unilateral, focal, and even nodular infiltrates have been seen in the early stages.

Treatment of proven CMV pneumonia remains disappointing, despite the availability of effective antiviral agents, including ganciclovir, cidofovir, and foscarnet and CMV-specific immunoglobulins.[83] Early therapy (any effect takes at least 5 days) should allow survival of up to 80%, but poor outcomes are common, notably in patients with respiratory failure at time of initial treatment. CMV pneumonia can be prevented in most cases with the prophylactic administration of ganciclovir or oral valganciclovir to seropositive recipients. Most seropositive patients who are at the highest risk of developing CMV pneumonia can be prospectively identified by CMV antigenemia or molecular assays on blood or sputum. Prospective use of these techniques after allogeneic transplantation permits preemptive treatment with ganciclovir, which appears to eliminate the incidence of CMV pneumonia. The side effects of the antiviral agents (neutropenia, thrombocytopenia, renal toxicity, neurotoxicity, magnesium wasting) may be limiting.

Other Viral Infections: RSV, Parainfluenza Virus, Adenovirus, Metapneumovirus, HSV, HHV-6

The respiratory viruses, particularly RSV, influenza, picornaviruses, and human metapnuemovirus (hMPV), are increasingly recognized as significant pathogens in these populations (see also Chapters 128 and 130).[84] Nosocomial transmission from infected healthcare workers has been documented. RSV is the most common respiratory viral pathogen in transplant recipients, but little progress has been made in managing RSV infections. Influenza annually causes increased morbidity and mortality in transplant recipients. M2 and neuraminidase inhibitors, alone or in combination, result in shorter duration of viral replication, decreased progression to lower tract disease, and reduced mortality. PIV continues to be recognized as a significant pathogen that is a risk factor for the development of acute and chronic rejection. Therapeutic options remain limited for PIV infections. AV has recently been shown to cause asymptomatic viremia in association with respiratory infection that resolves without therapy. Approximately 20% of marrow transplant patients with AV infection develop pneumonia (Fig. 123-16). Cidofovir appears to be the drug of choice in managing disseminated or life-threatening adenoviral infections, but not all strains are susceptible. Rhinoviruses have recently been recognized to cause significant lower tract disease and increased mortality. hMPV and coronaviruses, including severe acute respiratory syndrome (SARS)-associated coronavirus, have been recently discovered and are increasingly recognized as significant pathogens in immunocompromised hosts. Therapeutic options for both viruses are not yet clearly defined.

Pneumonia due to HSV or VZV occurs uncommonly. HSV pneumonia is generally due to contiguous spread of virus to the trachea or aspiration from the oropharynx, although it may be due to generalized infection with viremia. Pneumonia due to VZV occurs among patients with disseminated infection and viremia. Both situations have become exceedingly uncommon with the advent of acyclovir treatment and, in the case of HSV, acyclovir prophylaxis. Human herpesvirus 6, the cause of childhood roseola (exanthema subitum), has been detected in the lungs of some patients with idiopathic pneumonia. It is unclear whether this virus is a cause of pneumonia or merely latently reactivated, since virtually all adults are seropositive for the virus.

Fungal Infections

Fungal infections are reviewed in detail elsewhere (Chapter 133). Major risk factors for invasive fungal infections are the level and duration of neutropenia, age of the patient, the presence of GVHD, total number of other infections, and immunosuppressive administration after BMT or HCT. The frequency of *Aspergillus* infections is similar in recipients of allogeneic and autologous transplants, but they occur during periods of neutropenia before engraftment among autologous marrow recipients and after engraftment and during GVHD among allogeneic recipients.

Pneumocystis pneumonia occurs in as many as 10% to 15% of HCT recipients without the use of TMP-SMX prophylaxis, although regional and center-to-center variations exist. Except for patients being treated for chronic GVHD (who remain at risk and who should continue to receive prophylaxis), the risk period for *Pneumocystis* pneumonia ends approximately 120 days after transplantation. Because it is highly effective, TMP-SMX is the prophylactic regimen of choice. Other regimens have been discussed elsewhere. Patients with allergies to sulfa may undergo desensitization so that prophylaxis with TMP-SMX can be administered.

Other Nonbacterial Infections

Most infections with *T. gondii* infection have had only central nervous system disease diagnosed and treated during life, while involvement of heart and lungs may be documented at postmortem. Chest radiographs show diffuse, patchy involvement. These patients have also had concomitant bacterial or viral infections. Most infections have been fatal.

PULMONARY FUNCTION TESTING IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Pulmonary function testing (PFT) (see Chapter 33) is a standard part of the pretransplant evaluation at many centers. The results form baseline data for comparison with later testing, and have been used as an indication to exclude a candidate for transplantation. Abnormalities in the measures of airflow, lung volume, and diffusing capacity have been associated with increased risk of pulmonary complications after transplantation. After accounting for other clinical characteristics associated with death after transplantation (age, relapsed malignancy, HLA-mismatched graft), restrictive lung defect (decreased total lung capacity), hypoxemia, and reduced diffusing capacity are associated with statistically increased risk of death, especially within the first few months after transplant. The risks associated with these PFT results are applicable to autologous as well as allogeneic marrow recipients, suggesting that they predict mortality due to treatment-related toxicities. Hypoxemia and reduced diffusing capacity were independently associated with death, each carrying risk.

PFT performed after marrow transplantation has consistently revealed reductions in lung volumes and diffusing capacities associated with total-body irradiation and intensive chemotherapy. PFT abnormalities have been reported to include declines in lung volume, gas diffusion, and airflow. Losses of lung volume are more pronounced among patients who survive pneumonia after transplant. The declines in lung volume may be at least partly reversible within 2 years after transplantation, while the low diffusing capacity reportedly persists for several years. Development of airflow obstruction has been seen in approximately 10% of allogeneic marrow recipients in the presence of chronic GVHD and most often is related to obliterative bronchiolitis. Such PFT results strongly suggest that lung parenchymal and vascular injury is common features of marrow transplant, even in the absence of recognized infection or idiopathic pneumonia.

SOLID-ORGAN TRANSPLANTATION

In solid-organ transplant recipients, the time of onset of pulmonary manifestations of disease, coupled with the radiographic appearance, provide helpful clues regarding etiology.

■ TIMETABLE OF INFECTION

As immunosuppressive regimens have become standardized in recent years, it has become apparent that different infectious processes occur at different points in the posttransplant course.[1,60] That is, although pneumonia may occur at any point in the posttransplant course, its etiology varies according to time elapsed since transplantation (Fig. 123-2).

■ INFECTIONS IN THE FIRST MONTH FOLLOWING TRANSPLANTATION

In the first month after transplant, two major causes of pulmonary infection apply to all forms of organ transplantation. The first is the recurrence of pneumonia that was present prior to transplantation (in the lung allograft donor or in the recipient) but was incompletely treated, and which may be exacerbated after transplant due to superinfection with nosocomially acquired gram-negative bacilli and fungal species. This is most commonly seen in patients with end-stage liver or cardiac disease who require critical care support prior to transplant. Second, infection due to aspiration of nosocomial flora is often the result of postoperative vomiting (because of gastric distention or metabolic dysfunction) or due to a technical problem with the endotracheal tube in the perioperative period. The risk of antimicrobial-resistant

pneumonia increases with the duration of the pretransplant hospitalization, as well as with the duration of posttransplant intubation or ventilatory restriction (following the transplant surgery).

Donor-derived infection has been recognized in many recipients of lung transplants (mycobacteria, *Aspergillus*, colonizing gram-negative bacteria), occasionally with rapid progression after transplantation. It is essential to distinguish early lung allograft dysfunction from diffuse infection due to donor-derived viruses (HSV, VZV, CMV, respiratory viruses) or other pathogens (e.g., *Mycoplasma*). Extensive pulmonary injury before transplant places the patient at high risk for postoperative pneumonia that is poorly responsive to therapy. In the special case of the lung transplant patient who may require prolonged intubation, bacterial pneumonia and infection that threatens the bronchial anastomosis, particularly with *Aspergillus*, are special concerns (Figs. 123-20 and 123-21). These patients require exquisite attention to the technical aspects of the transplant procedure, to the management of the endotracheal tube, and the maintenance of pulmonary toilet (including, on occasion, repeated therapeutic bronchoscopy).

Notable by their absence in the first posttransplant month are the opportunistic infections, despite the fact that the highest daily doses of immunosuppression are administered during this first month. This emphasizes that it is the *sustained exposure to immunosuppressive therapy,* "the area under the curve," that is the major determinant of the net state of immunosuppression.

■ INFECTIONS ONE TO SIX MONTHS FOLLOWING TRANSPLANTATION

In the period 1 to 6 months after transplant, the nature of pulmonary infections changes markedly. During this time period the immunomodulating viruses, particularly CMV, are of importance in terms of direct effects (invasive disease) and immunologic or indirect effects (rejection, opportunistic infections). CMV may directly cause pneumonia; CMV may contribute to the incidence of graft rejection necessitating increased exogenous immune suppression and increasing the risk of opportunistic infection; or CMV (and the other immunomodulating viruses) are globally immunosuppressive and can enhance the likelihood of pulmonary infections due to *P. jiroveci, Aspergillus* species, and *Nocardia asteroides* in the *absence* of an unusual epidemiologic exposure (Fig. 123-20).

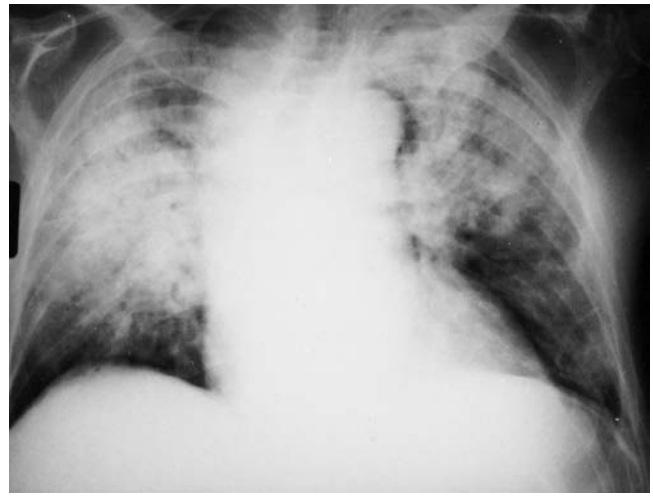
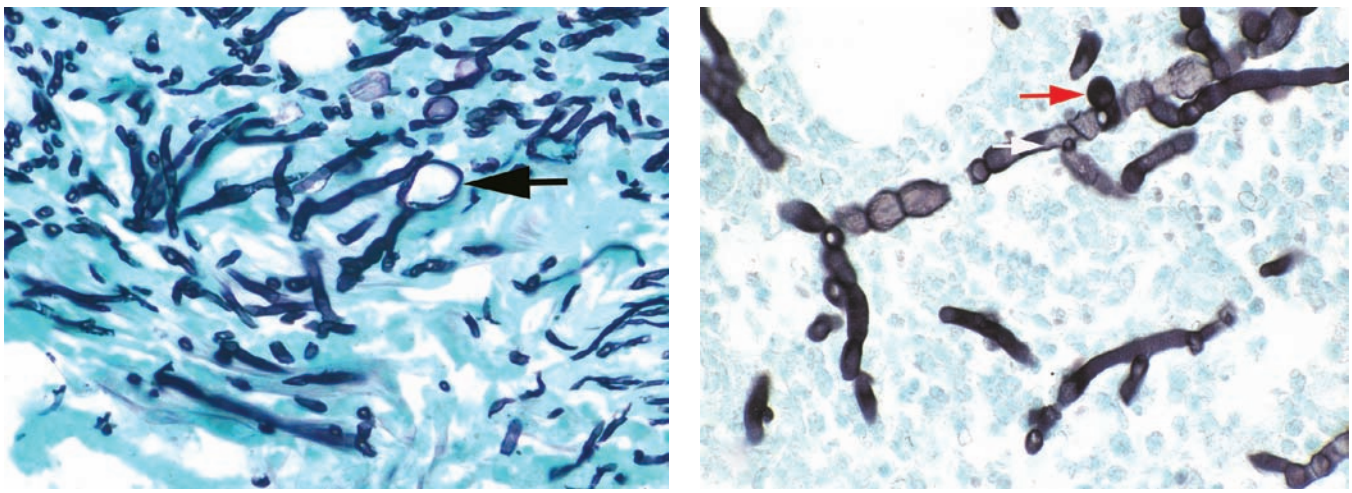


Figure 123-20 Invasive pulmonary aspergillosis after liver transplantation. A diffuse *Klebsiella* pneumonia was treated with a good clinical response to therapy. After 2 days without fever, the patient became febrile with increasing shortness of breath although the chest radiograph remained unchanged. One day after this radiograph was taken, the patient died. Autopsy revealed two processes in the lungs: a diffuse gram-negative pneumonia and focal areas of invasive aspergillosis restricted to the right lower and middle lobes. This figure illustrates the difficulty in differentiating the focal areas of *Aspergillus* superinfection from the primary bacterial process.

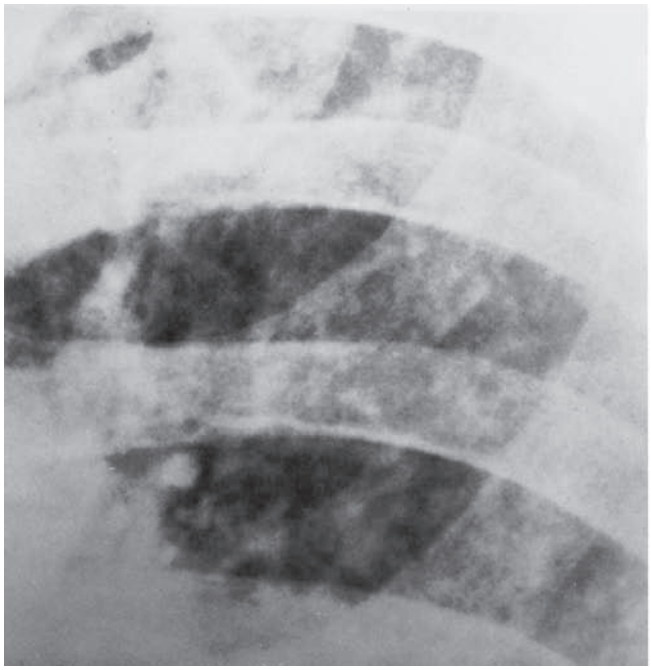
Unlike the bone marrow transplant recipient, the risk of active CMV *disease* (as compared with viral secretion) in the solid-organ transplant recipient is greatest in the CMV-seronegative recipient of an organ from a seropositive donor. Thus, CMV prevention and the utilization of diagnostic techniques for CMV viremia (e.g., quantitative nucleic acid testing, antigenemia assays, less often shell vial cultures with early antigen detection) are important parts of the therapeutic program.[85,86]

During this period, *in the absence of specific prophylaxis,* significant nonviral pulmonary infections are also common, including those



A **B**

Figure 123-21 **A.** *Scedosporium (Pseudoallescheria boydii)* at the dehisced anastomotic site of a recent lung transplant. The organism is septate and branching and can be confused with *Aspergillus* species but may not respond to routine anti-*Aspergillus* therapy. Prominent terminal chlamydospores *(arrow)*, evoking the image of a tadpole, are a distinguishing feature. **B.** *Fusarium* sp. is septate with nonparallel walls, and branches predominantly at right angles, and n*arrows* at the branch points *(white arrow)*. Blastoconidia can be seen in many cases *(red arrow)*.



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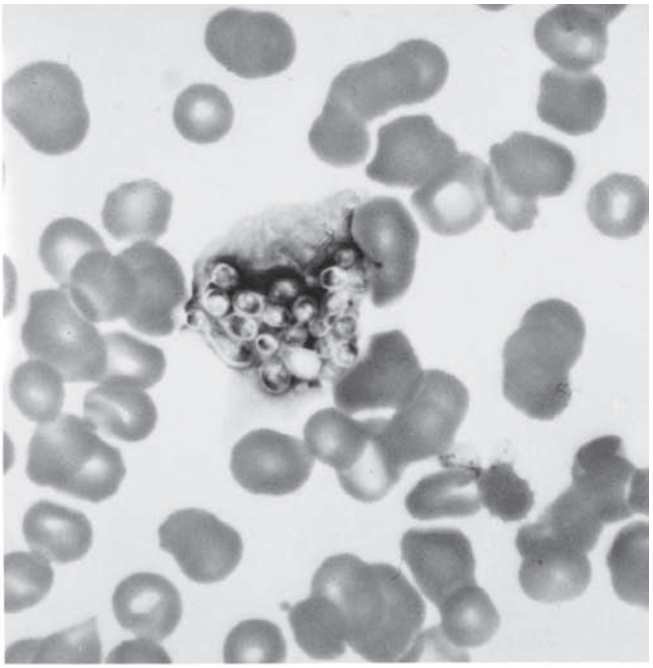


B

Figure 123-22 *H. capsulatum.* A 56-year-old man, lifelong resident of Kansas, presented 2½ years after a renal transplant with fever, nonproductive cough, and 3-month weight loss. The chest radiograph was diffusely abnormal. **A.** Close-up reveals extensive micronodular disease. **B.** Peripheral blood smear shows a macrophage laden with *H. capsulatum.* Treatment with liposomal amphotericin B resulted in clearing of the radiograph and cure of the infection.

due to *P. jiroveci, Aspergillus* species, endemic fungi (*Histoplasma, Coccidioides*) and *Nocardia asteroides* (Fig. 123-22).[87–89] There is important regional variation in the occurrence of each of these pathogens. At centers with high endemicity of these infections, low dose TMP-SMX prophylaxis (which effectively eliminates *Pneumocystis* and nocardial infection) and epidemiologic protection against *Aspergillus* (as with a HEPA-filtered air supply within the hospital) are effective, particularly in the context of effective CMV prevention.

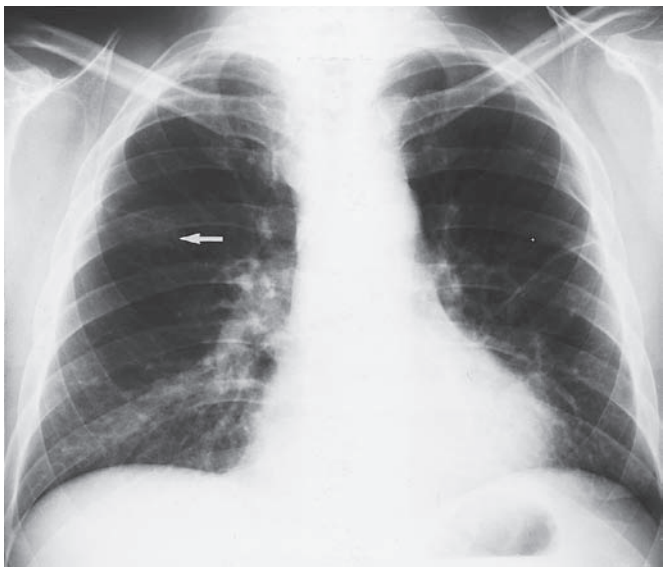
■ INFECTIONS BEYOND SIX MONTHS FOLLOWING TRANSPLANTATION

In the period more than 6 months after transplant, patients can be divided into two groups in terms of the forms of pulmonary infection that can develop. Most patients will have had a good result from their transplant and will have good allograft function and receive relatively modest levels of maintenance immunosuppression. These patients are subject to community-acquired respiratory virus infection, particularly influenza and RSV, and pneumococcal pneumonia. The remaining patients have had a less positive outcome from their transplant; these individuals have less satisfactory graft function and require far more intensive acute and chronic immunosuppressive therapies to manage rejection. These patients, often termed "chronic ne'er do wells," are the subgroup of transplant patients at highest risk for pulmonary infection with such organisms as *P. jiroveci, C. neoformans, Nocardia asteroides,* and *Aspergillus* species (Fig. 123-23). Fungal infections are increasingly recognized in this population.[90–97] For this subgroup of patients, prolonged TMP-SMX prophylaxis and a consideration of antifungal prophylaxis in individuals from regions with high rates of endemic fungal infections are indicated (Fig. 123-22). Notable among the ne'er do well group is the liver transplant recipient with recurrent hepatitis C infection, the lung transplant with cystic fibrosis and resistant *Pseudomonas, Burkholderia*, or *Stenotrophomonas* infections, and the kidney transplant with chronic allograft dysfunction.[98,99] Mucociliary clearance is diminished in the lung recipient, often for the duration of graft survival.[100]

■ RADIOLOGIC CLUES TO THE DIAGNOSIS OF PNEUMONIA IN THE ORGAN TRANSPLANT PATIENT

The presentation and evolution of the chest radiograph provide important clues to both the differential diagnosis of pulmonary infection in the transplant patient and the appropriate diagnostic workup that should be undertaken (Table 123-12). The following radiologic parameters are useful in developing clinical-radiologic-pathologic correlations: (1) Time of appearance, rate of progression, and time to resolution of pulmonary roentgenographic abnormalities in relation to clinical events. (2) Distribution of radiologic abnormalities. An abnormality confined to one anatomic area is considered *focal,* whereas widespread lesions are considered *diffuse.* Abnormalities that are present in more than one area, but are countable, are termed *multifocal.* As visualized particularly on CT scanning, abnormalities may be located *centrally* or *peripherally* or both. (3) Which of three types of pulmonary infiltrate is present? The first type is a *consolidation,* in which there is substantial replacement of alveolar air by material of tissue density, typically with air bronchograms and a peripheral location of the abnormality. The second type is *peribronchovascular* (or *interstitial*), in which the infiltrate is predominantly oriented along the peribronchial or perivascular bundles. Finally, *nodular* lesions are space-occupying, nonanatomic lesions with well-defined, more or less rounded edges surrounded by aerated lung.

By combining this classification with information concerning the rate of progression of the illness (Table 123-12), a useful differential diagnosis is then generated.[101,102] Thus, focal or multifocal consolidation of acute onset will quite likely be caused by bacterial infection. Similar multifocal lesions with subacute to chronic progression are more likely secondary to fungal, tuberculous, or nocardial infections. Large nodules are usually a sign of fungal or nocardial infection in this patient population, particularly if they are subacute to chronic in onset.



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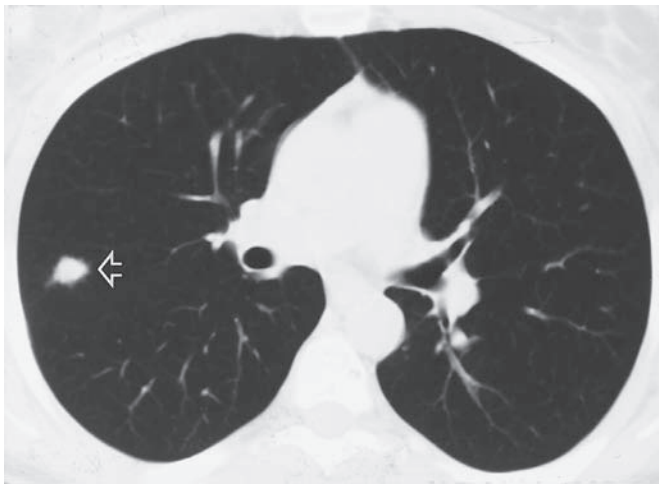

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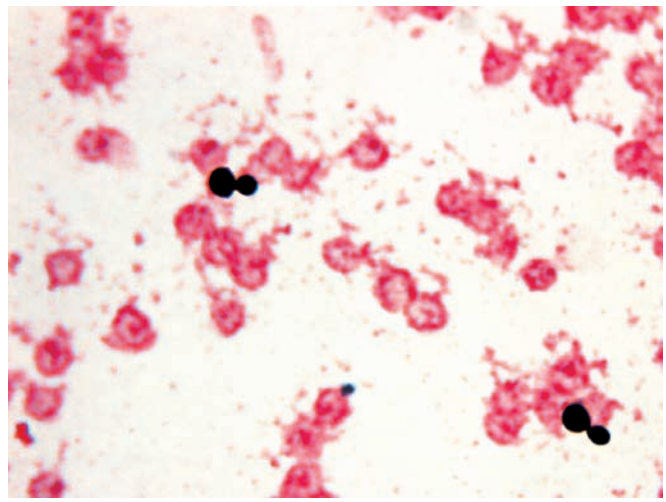


C

Figure 123-23 *C. neoformans* in an asymptomatic renal transplant patient. The patient presented with minimal complaint of nonproductive cough of a few weeks duration. **A.** The chest radiograph was essentially clear other than a shadow in the right midlung field *(arrow)*. **B.** Chest tomography revealed a nodular lesion in the right midlung field *(arrow)*. Percutaneous needle aspiration of this lesion yielded *C. neoformans* on fungal culture. **C.** Nonhealing ulcer at site of previous intravenous catheter in the same patient subsequently grew *C. neoformans*.

TABLE 123-12 Differential Diagnosis of Fever and Pulmonary Infiltrates in the Organ Transplant Recipient According to Roentgenographic Abnormality and the Rate of Progression of the Symptoms

	Etiology According to the Rate of Progression of the Illness	
Chest Radiographic Abnormality	Acute[a]	Subacute–Chronic[a]
Consolidation	Bacterial (including Legionnaires' disease) Thromboembolic Hemorrhage (pulmonary edema)	Fungal Nocardia Tuberculosis Viral (Drug-induced, radiation, *Pneumocystis* tumor)
Peribronchovascular	Pulmonary edema (Leukoagglutinin reaction bacterial)	Viral *Pneumocystis* (Fungal, nocardial, tuberculous, tumor)
Nodular infiltrate[b]	(Bacterial, pulmonary edema)	Fungal Nocardial Tuberculous *(Pneumocystis)*

[a]*An acute illness develops and requires medical attention in a matter of relatively few hours. A subacute–chronic process develops over several days to weeks. Note that unusual causes of a process are in parentheses.*

[b]*A nodular infiltrate is defined as one or more large (>1 cm^2 on chest radiography) focal defects with well-defined, more or less rounded edges, surrounded by aerated lung. Multiple tiny nodules of smaller size, as sometimes caused by such an agent as CMV or varicella-zoster virus, are not included here.*

Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, are usually caused by viruses (especially CMV) or *P. jiroveci* (or, in the lung transplant patient, rejection).[103] Additional clues can be found by examining the pulmonary lesion for the development of cavitation, with cavitation suggesting such necrotizing infections as those caused by fungi, *Nocardia,* and certain gram-negative bacilli (most commonly with *Klebsiella pneumoniae* and *P. aeruginosa*). The depressed inflammatory response of the immunocompromised transplant patient may greatly modify or delay the appearance of a pulmonary lesion on radiograph, particularly if neutropenia is complicating the effects of the antirejection therapy. CT of the chest has revolutionized the evaluation of these immunocompromised patients, and CT is particularly useful when the chest radiograph is negative or when the radiologic findings are subtle or nonspecific. An additional important application of CT in this patient population is defining the extent of the disease process. Particularly with opportunistic fungal and noncardial infection, precise knowledge of the extent of the infection at diagnosis, and the response of all sites to therapy, will lead to the best therapeutic outcome, as therapy should be continued until all evidence of infection is eliminated, not just the primary site. CT findings are also quite useful in defining which invasive diagnostic procedure should be utilized to obtain diagnostic samples and in identifying the anatomic site at which sampling should be directed to optimize the diagnostic yield.

PRIMARY IMMUNE DEFECTS

Primary immune deficiencies are defined as alterations in the immune system that are congenital, as opposed to those related to chemotherapy, autoimmune disease, organ transplant, or chronic systemic disease. Clinical problems that require evaluation of the immune system include chronic or recurrent bacterial or fungal infections of the skin, sinuses, and respiratory and digestive tracts and repeated infections with unusual viruses. Other suggestive signs and symptoms are persistent atypical rashes, chronic diarrhea, failure to thrive, paucity of lymphoid tissue, lymphadenopathy, chronic conjunctivitis, and unusual reactions to live virus vaccines. Patients are often unresponsive to common vaccines.[104] About two-thirds of such disorders affect the production of immunoglobulins, while the remainder include cellular immune deficits, defects in phagocytosis, complement, innate immune function, or combined deficits.[105]

The initial evaluation begins with a physical examination, identification of any ongoing infectious process, and routine laboratory studies including a complete blood count and differential, chemistries and urinalysis. Lymphopenia is defined as an absolute lymphocyte count <1500 cells/μL in adults. Leukopenia is found in many primary disorders of the monocyte, macrophage and neutrophil lines. By contrast, leukocytosis may suggest chronic infections. Common metabolic disorders (diabetes, renal dysfunction, malnutrition) should be identified as well as protein losing enteropathy or renal wasting. The evaluation of recurrent infections will ultimately analyze all compartments of the host defense system, including anatomic structures, mucociliary function, B- and T-cell activity, phagocytic cell function, and complement activity.[106,107] Definitive diagnosis often requires specialized laboratory techniques including genetic analyses available only at referral centers. Table 123-13 outlines some of the initial and confirmatory screening tests available to most clinicians. As genetic studies have progressed, defective pathways have been identified to account for some of the more

TABLE 123-13 Immunologic Evaluation of Primary Immune Deficiencies

Suspected Abnormality	Screening Tests	Confirmatory Tests
Antibody	Serum IgM, IgG, IgA levels IgG antibody response to protein (diphtheria, tetanus, influenza) and polysaccharide (pneumococcus, *Haemophilus influenzae*) antigens Isohemagglutinin titers for IgM antibody response Serum IgG subclass levels	B-cell enumeration (total B [CD20] and surface IgM-, IgG-, IgA-, IgD-bearing B cells) In vitro immunoglobulin synthesis
Cell-mediated immunity	Total lymphocyte count Delayed hypersensitivity skin tests (diphtheria, tetanus, *Candida,* PPD, SK/SD for T-cell function) Tests for HIV antibodies	Enumerate total T cells and T-cell subsets (CD3, CD4, CD8) Measure T-cell function with mitogenic, antigenic, and allogeneic (mixed lymphocyte reaction) responses, lymphokine production, cytotoxic assay Assays for Th and Ts activity Enzyme assay (ADA, PNP) for ADA or PNP deficiency
Complement	CH_{50} or CH_{100} for classical pathway activity APH_{50} for alternative pathway activity Serum C2, C3, C4, C5, and factor B levels	Other specific component levels C1 esterase inhibition levels C1 esterase functional component
Phagocytic	NBT test for respiratory burst activity (defect in CGD) Serum IgE levels for HIE	Leukocyte adhesive protein analysis: (CD11 a/CD18, CD11 b/CD18, and CD11 c/CD18) Adherence and aggregation Chemotaxis and random motility Phagocytosis Assays for respiratory burst activity (chemiluminescence, oxygen radical production) Bacterial killing test Enzyme assay (MPO, glucose-6-phosphate dehydrogenase) for phagocyte enzyme defects Cytochrome *b* or cytosolic protein measurement for CGD

common immune deficiencies and some have been corrected by stem cell transplantation.

■ ANTIBODY (B-CELL) DEFICIENCY

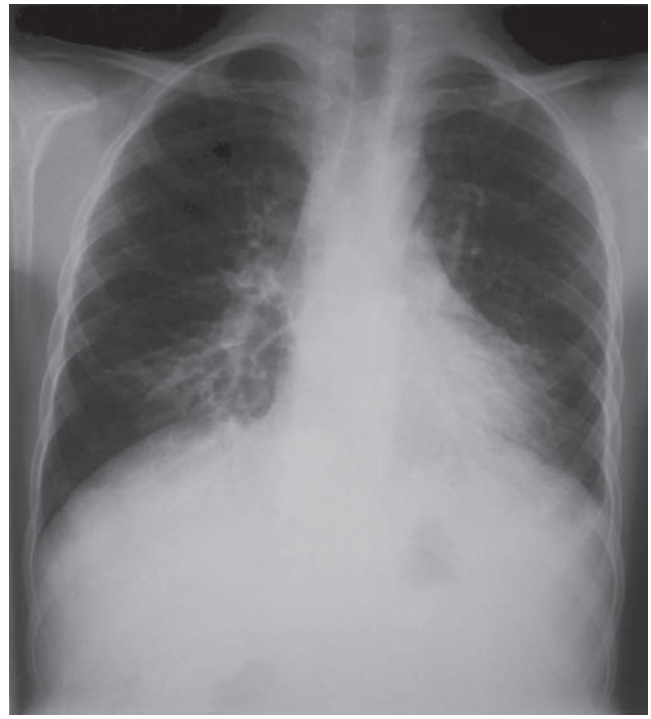
Antibody deficiency states are among the most common of the primary immunodeficiency diseases.[105] Although the defect in immunoglobulin production can occur at any point in B-cell maturation/activation or secretion of antibody, or even in T- and B-cell interaction, the end result is a decrease in serum antibody levels or the inability to respond to antigens with specific antibody. Patients typically present with recurrent sinopulmonary infections caused by encapsulated bacteria such as *S. pneumoniae, H. influenzae* (both type b and nontypable), and *S. aureus*. Diseases caused by *Mycoplasma*, enteroviruses, and intestinal parasites are also occasionally seen. The incidence of autoimmune abnormalities and hematologic malignancies is also significant in patients with these defects. Treatment for most of these defects relies on the administration of gammaglobulin. Annual chest radiographs and pulmonary function tests are especially helpful, given that the lung disease in patients with hypogammaglobulinemia may be insidious in onset and progression.

■ X-LINKED AGAMMAGLOBULINEMIA

X-linked agammaglobulinemia (XLA or Bruton agammaglobulinemia) is a relatively common inborn error of immunity, occurring in 1 per 50,000 live births. A block in the normal maturation of immunoglobulin-producing B cells (block in V_HDJ_H recombination) results in the absence or severe reduction of serum immunoglobulin, absence of circulating mature B cells, and absence of plasma cells in all lymphoid tissue. T-cell number and function are intact. Inheritance is sex-linked recessive, although a clinically indistinguishable syndrome with autosomal recessive inheritance has been observed in some patients. Recent studies have localized the defect to a protein tyrosine kinase gene (Bruton tyrosine kinase, *btk*) on the proximal region (q21.3–q22) of the X chromosome. After maternal antibody is consumed (usually after the first 4–6 months of life), patients develop sinopulmonary infections, bacteremia, and meningitis with encapsulated gram-positive and gram-negative bacteria, such as *H. influenzae, S. pneumoniae, S. aureus, P. aeruginosa,* and *Mycoplasma pneumoniae.* Respiratory disease due to *P. jiroveci* or gastrointestinal infection with *Giardia lamblia* is also commonly observed. Although viral infections are not typical, enterovirus (polio and echo) and hepatitis viruses may cause severe or fatal disease. Autoimmune diseases, such as rheumatoid arthritis, occur in up to 20% of patients, while lymphomas and other lymphoreticular malignancies occur in approximately 5% of cases. IgG levels are very low (less than 100 mg/dL), and IgA and IgM are often undetectable.

■ COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVI) is a not uncommon defect due, in general, to B-cell activation or differentiation defects, resulting in low serum levels of IgG and depressed levels of IgA or IgM. B cells may be normal, high, or low, and T-cell number and function, although usually normal at diagnosis, deteriorate with time. Although the disease is familial, it is not strictly X-linked or autosomally inherited. In some patients, the genomic defects of both CVI and isolated IgA deficiency appear to be localized to the major histocompatibility complex region of chromosome 6. The disease is characterized by the development of recurrent sinopulmonary infections or chronic bronchiectasis in childhood or adulthood. Chest radiograph findings consistent with atelectasis, bronchiectasis, and/or interstitial markings, along with pulmonary function tests revealing mild to severe obstruction and restrictive disease, are seen in 60% to 80% of CVI patients (Fig. 123-24). A few patients with CVI present with infections with unusual organisms, such as



A

		Actual	Pred.	%Pred.
LUNG MECHANICS				
FVC	(L)	1.03	2.92	35
FEV1	(L)	0.97	2.56	38
FEV1/FVC	(%)	94	88	
FEF 25%	(L/sec)	7.10	4.82	147
FEF 50%	(L/sec)	2.98	3.51	85
FEF 75%	(L/sec)	0.80	1.89	43
FEF MAX	(L/sec)	7.34	6.46	114
FEF 25–75%	(L/sec)	2.29	2.95	78

B

Figure 123-24 **A.** PA chest radiograph of an adolescent boy with common variable immunodeficiency demonstrating marked bibasilar opacification, atelectasis, and infiltrative changes. Sputum culture grew only *H. influenzae* (nontypable). **B.** Pulmonary function tests from the same patient demonstrate significant restrictive disease; concurrent obstructive disease was supported by RV/TLC measurements. Marked improvement in radiographs and pulmonary function tests occurred with the use of continuous, rotating ciprofloxacin, cefaclor, and clarithromycin, in conjunction with aggressive chest percussion via a percussor vest and inhaled DNase.

P. jiroveci, mycobacteria, or fungi. Recurrent attacks of both herpes simplex and zoster are not uncommon.

■ SELECTIVE IGG SUBCLASS DEFICIENCIES

Patients with selective IgG subclass deficiencies have recurrent sinopulmonary infections associated with normal or decreased total concentrations of serum IgG, but with selective deficiencies of IgG subclass 1, 2, 3, or 4. Patients with IgG2 subclass deficiency can make antibody, but the spectrum of the response is decreased, resulting in recurrent infection. Recent studies suggest a critical role for IL-6 and IFN-γ in enhancing IgG subclass production. Titers to bacterial polysaccharide antigens are low even after immunization, since antibody responses to polysaccharides reside predominantly in the IgG2 subclass. Titers to protein antigens such as tetanus or diphtheria toxoids may be normal. IgG2 subclass deficiency

may be associated with IgG4 subclass deficiency, IgA deficiency, Wiskott–Aldrich syndrome (WAS), and ataxia-telangiectasia (AT). Persons with low or absent IgG2 or IgG4 appear to be particularly predisposed to recurrent or severe pneumonias and middle ear infections. Selective IgG3 deficiency is also associated with recurrent sinopulmonary infections, but the mechanism is not clear. These IgG3-deficient patients have normal responses to both common protein (Dt) and polysaccharide antigens; however, responses to influenza or rubella vaccine may be abnormal. Treatment is based on clinical findings of recurrent infections, rather than isolated laboratory abnormalities. It is important to document not only a low concentration of a subclass but also failure to make specific antibody when immunized, before immunoglobulin therapy is contemplated.

■ SELECTIVE IGA DEFICIENCY

This most common of all the inborn defects of humoral immunity, occurring in 1 per 700 persons, accounts for more than 1% of recurrent infections in children. The defect is assumed to be a differentiation block affecting IgA-committed B cells. Typically, peripheral counts of patients with IgA deficiency show normal numbers of mature B lymphocytes, as well as normal numbers and proportions of CD4 and CD8 cells. Selective IgA deficiency has been defined as serum IgA less than 5 mg/dL in severe deficiency and greater than 5 mg/dL but less than 2 SD below the age normal mean in partial IgA deficiency. The diagnosis and treatment of IgA deficiency depend not only on the serum level of IgA but also on the history and results of related diagnostic studies, particularly the immune workup. In general, treatment relies on the administration of appropriate antimicrobials for acute infection or chronic suppressive therapy for chronic infection. When IgA deficiency is associated with IgG2 deficiency, IVIG depleted of IgA may be indicated.

■ HYPER-IGM IMMUNODEFICIENCY

These patients have absent or markedly reduced IgA, IgE, and IgG levels, elevated levels of IgM, circulating mature B lymphocytes bearing IgM or IgD and plasma cells, as well as hyperplastic lymphoid tissue. Recurrent neutropenia, probably secondary to autoimmune phenomena, may coexist with the humoral defect. Because antibody protection for the gastrointestinal and respiratory tracts is normally provided by IgA and IgG isotypes, patients with this syndrome are especially prone to respiratory and GI infections with pyogenic organisms. They are also predisposed to *P. jiroveci* pneumonia. As with other immunoglobulin deficiencies, patients with the hyper-IgM syndrome have very high rates of autoimmune (involving the formed elements of the blood) and lymphoproliferative disorders.

■ COMPLEMENT DISORDERS

Disorders due to primary deficiencies of complement components are rare causes of pulmonary infections. Disorders fall into two general categories, including deficiencies in components of the complement activating cascades and deficiencies in complement regulatory proteins.[108,109] The former includes inherited disorders of complement components and presents with recurrent infections and/or autoimmune disorders such as systemic lupus. Deficiency of C1 inhibitor causes hereditary angioedema, a disorder of unregulated systemic swelling, while incomplete deficiencies of other complement inhibitors predispose to atypical hemolytic-uremic syndrome (aHUS). Eculizumab is a humanized monoclonal antibody and terminal complement inhibitor used in aHUS to inhibit thrombotic microangiopathy and to protect renal function. Complement function can be assessed by determining the total hemolytic activity in serum (CH50), which measures the ability of serum to lyse antibody-coated sheep cells. A low-to-absent CH50 suggests a deficiency in a classic pathway complement component. Levels of specific complement components can then be determined.[110]

Congenital absence of C3 or consumption of C3 due to deficiency of factor I (C3b inactivator) results in a clinical picture like that seen in deficiency of the critical antibody opsonins, including infections due to pyogenic bacteria including severe and recurrent pneumonias due to *S. pneumoniae, H. influenzae,* and Enterobacteriaceae.

The terminal complement components, C5–9, form the cytolytic membrane attack complex (MAC), and deficiency of any one of these will block MAC formation. C5–9 deficiencies predispose to disseminated infection with *N. meningococci* and *N. gonococci.*

C1 esterase inhibitor deficiency results in persistent consumption of C2 and C4 by the C1 esterases, resulting in release of vasoactive kinins and the development of nonpruritic angioedema. Although angioedema can occur in any tissue, including the GI tract, edema of the upper airway can be life-threatening. Diagnosis is suggested by family history (autosomal dominant state), edema without pruritus, and chronically decreased C4 and C2 levels, especially during the 24 to 72 hours of the episode. Patients with the familial form of the disease will have low-to-absent C1 esterase inhibitor concentrations. Angioedema with later onset, without a familial pattern, may be due to the absence of the functional component of the inhibitor, which may be associated with malignancy. Treatment is with danazol or purified C1 inhibitor for acute attacks.

■ DISORDERS OF CELL-MEDIATED IMMUNITY

Although the most characteristic infections in patients with cellular immune deficiency are those caused by opportunistic intracellular pathogens, including protozoa (*P. carini* and *T. gondii*), fungi (*Candida* and *Aspergillus* species), viruses (particularly those of the herpesvirus family), and some intracellular bacteria (including *Listeria* and *Mycobacteria species*), defects in humoral or phagocyte defense mechanisms may also be seen.

DiGeorge Syndrome

DiGeorge syndrome (DGS) is a constellation of abnormalities resulting from dysmorphogenesis of the third and fourth pharyngeal pouches.[111,112] Patients have hypoplasia or aplasia of the thymus and the parathyroid glands, complex cardiac malformations, esophageal atresia, bifid uvulas, cleft palate, short philtrums, mandibular hypoplasia, hypertelorism, and low-set notched ears. The severity of immunologic manifestations varies from severe forms with complete thymic aplasia, resembling severe combined immunodeficiency disease (SCID) (see below), to only latent hypoparathyroidism, which may also be seen in relatives of patients with DGS. Most patients have partial T-cell function, which may improve with age, presumably due to the adaptation of functional extrathymic sites for T-lymphocyte maturation. T-cell numbers are typically reduced, with reduced percentages of CD3 and CD4 cells, but CD8 cells may be normal or even elevated. Patients with more significant CD4 T-cell deficiency seem to have more frequent and severe infections requiring hospitalization. B-lymphocyte counts are usually normal; antibody production is also usually normal, but of poor biologic quality. Some patients may have low IgA or elevated serum IgE levels. Surviving infants often have the tendency to acquire parathyroid function, cell-mediated immunity, and functional T cells. Patients are prone to severe viral pneumonias, particularly those of the herpes and measles family. Pneumonias due to fungal and gram-negative bacilli and *P. jiroveci* also occur.

Severe Combined Immunodeficiency Disease

SCID is a syndrome of heterogeneous lymphocyte stem cell defects that affect both T- and B-cell function, resulting in profound hypogammaglobulinemia and absence of T-cell function. An array of genetically encoded SCID disorders appear to be linked by failure of immune cell signaling mechanisms.[113] Laboratory analysis may reveal lymphopenia (10%–20%) and normal or increased numbers

of circulating B cells, but severely reduced IgG levels. In general, patients with SCID syndrome present with a triad of mucocutaneous candidiasis, intractable diarrhea, and *P. jiroveci* pneumonia, evident shortly after birth or within 6 to 9 months of life and progressing to severe failure to thrive.[114,115] Within a few days after birth, patients may also develop a morbilliform rash that is probably a manifestation of GVHD from passively transferred maternal lymphocytes. Infections with a wide range of microbes occur in all forms of SCID, including viral pathogens, particularly herpesviruses (herpes, CMV, varicella), adenovirus, measles, influenza, and *Legionella.* Fatal giant-cell pneumonia has resulted from measles infection and live measles vaccination, and progressive vaccinia has occurred after smallpox vaccination.

Purine Nucleoside Phosphorylase

Absence of the enzyme purine nucleoside phosphorylase (PNP) is associated with marked cell-mediated immunodeficiency but intact humoral immunity. The gene encoding the enzyme is localized to chromosome 14q13.1. Patients are prone to disseminated viral infections, *P. jiroveci* infection, mucocutaneous candidiasis, and chronic diarrhea. Neurologic disorders afflict more than 50% of patients, and more than a third of patients with PNP develop autoimmune diseases.

Wiskott–Aldrich Syndrome

WAS is caused by a defect localized to the short arm of the X chromosome (Xp11.22–11.3), resulting in severely impaired production of antibodies to polysaccharide antigens, as well as variable reductions of T-cell numbers and impaired mitogen responses that tend to worsen with age. Both T-cell numbers and function progressively decrease, and profound lymphopenia becomes apparent at approximately 6 years of age. Most patients have abnormalities of serum immunoglobulin levels, with low IgM and isohemagglutinin concentrations, a tendency toward elevated IgA and IgE levels, and normal or slightly depressed IgG levels. Males afflicted with this syndrome suffer from a triad of recurrent infections, thrombocytopenia, and a skin disease indistinguishable from atopic dermatitis. Typical infections include pyoderma or cellulitis associated with eczematous eruptions, chronic otitis media with persistent otorrhea and/or mastoiditis, and chronic pneumonitis. Encapsulated pyogenic bacteria, such as *S. pneumoniae, H. influenzae,* herpesvirus, and *P. jiroveci,* are the most frequently identified pathogens.

Ataxia-Telangiectasia

AT syndrome is characterized by profound deficiencies of cellular immunity, (including lymphopenia, defects in cutaneous anergy, decreases in Th:Ts ratios, decreases in cytotoxic T cells, and an increase in immature T cells with increased gamma/delta TCR expression), impaired humoral responses (thymic hypoplasia associated with IgA deficiency, IgE deficiency, and IgG2 and IgG4 subclass deficiency), and a constellation of progressive cerebellar ataxia with degeneration of Purkinje cells. The defective genes of the two most common AT variants map to chromosome 11q22.3, which may result in a recombination defect that interferes with the rearrangement of T-cell and B-cell genes, an inability to repair damaged DNA, and a failure of normal organ maturation. Telangiectasias, particularly ocular and cutaneous, and a high incidence of malignancies, particularly non-Hodgkin lymphoma, and breast cancer (in heterozygous female carries of the AT allele) are seen. AT is also associated with insulin-resistant diabetes mellitus, gonadal agenesis, premature aging, elevated levels of serum a_1-fetoprotein and carcinoembryonic antigen, and hypersensitivity of fibroblasts and lymphocytes to ionizing radiation, reflecting an inability to repair damaged DNA. Patients suffer from an increased incidence of bacterial and viral sinopulmonary infections, and many eventually develop chronic bronchiectasis. The most frequent pulmonary pathogens are *S. aureus* and other encapsulated bacteria. Concurrent IgG2 (50%), IgG4, and IgA deficiencies (70%) may be associated with the tendency toward recurrent infections of the respiratory tract. Approximately 80% of patients have depressed IgE levels.

■ PHAGOCYTIC DEFECTS

Compromised immunity may be related to inadequate phagocyte numbers or to deficient phagocyte function. Disorders representing each of these categories are discussed below.

Disorders of Phagocyte Numbers

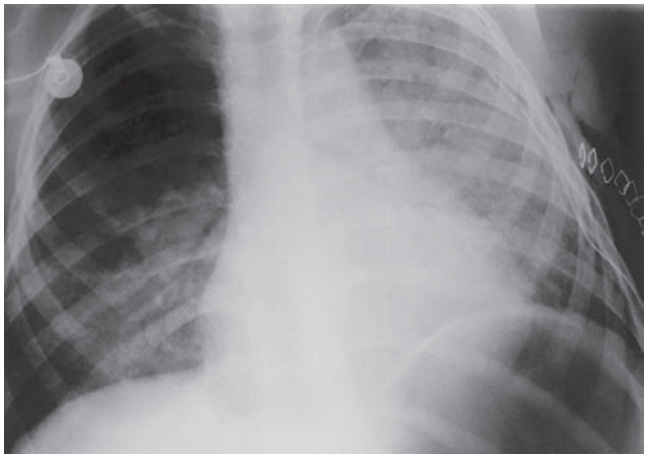
These disorders include cyclic neutropenia, Felty syndrome, Kostmann syndrome, Shwachman–Diamond syndrome, and autoimmune neutropenia. They are characterized by absolute PMN counts as low as 50 to 200/mm but typically lower than 1000/mm.[116] Owing to the presence of a compensatory monocytosis, these disorders are associated with a low incidence of severe respiratory infections, although pneumonia is seen – as are furunculosis, subcutaneous abscess, and otitis media. Typical pathogens include *S. aureus, P. aeruginosa,* and enteric bacteria.

Defects of Phagocyte Function

A variety of syndromes characterized by alterations in phagocytic function have been described. The most commonly observed are noted briefly in subsequent sections.

Chronic Granulomatous Disease Chronic granulomatous disease (CGD) is caused by a defect in a membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytic cells, resulting in the failure of phagocytic cells to produce superoxide, hydrogen peroxide, and other reduction products of oxygen that are necessary for killing certain microbial species.[117] Diagnosis is made by the inability of neutrophils to reduce nitroblue tetrazolium (NBT) from yellow to blue-black formazan and by the inability of neutrophils to kill staphylococci or other catalase-positive microorganisms. Additional laboratory findings suggestive of CGD include leukocytosis, elevation of erythrocyte sedimentation rate, abnormal chest radiographs, and hypergammaglobulinemia.

Onset is typically in infancy, childhood or, less commonly, early adolescence, with a male-to-female ratio of 6:1. All forms of CGD are characterized by abscess formation at sites of bacterial tissue invasion and in lymph nodes, liver, and lung. Patients present with severe recurrent lymphadenitis and infections of the skin, sinopulmonary and GI tracts. Severe and recurrent pulmonary infections occur in almost all patients with CGD, including bronchopneumonia, empyema, lung abscess, and hilar adenopathy syndromes. Most young adult patients demonstrate chronic bilateral infiltrates, pulmonary fibrosis, or pulmonary calcifications associated with restrictive/obstructive disease. Aggregates of granulomas, leading to mechanical obstruction, may form as a response of activated macrophages to microbial persistence and chronic antigenic stimulation. *S. aureus* represents by far the most common cause of infections in CGD. Other catalase-positive and non–H_2O_2-producing organisms include *Escherichia coli, Klebsiella,* and *Enterobacter* species, *Serratia marcescens, Salmonella* and *Pseudomonas* species. Pneumonias in CGD patients may be caused by *M. tuberculosis,* atypical mycobacteria, and *P. jiroveci.* In specific geographic locations, such as the southeastern United States, *Chromobacterium violaceum* has been recognized as the cause of infection in several CGD patients. *Nocardia* infection, particularly of the respiratory system, is also relatively common, as are fungal infections (Figs. 123-25 and 123-26). Antimicrobials and interferon-gamma have been useful in therapy.[118]



A

LUNG MECHANICS		Actual	Pred.	%Pred.
FVC	(L)	0.75	1.05	72
FEV1	(L)	0.68	0.92	74
FEV1/FVC	(%)	91	87	
FEF 25%	(L/sec)	1.71	1.25	136
FEF 50%	(L/sec)	1.27	1.03	123
FEF 75%	(L/sec)	0.50	0.61	83
FEF MAX	(L/sec)	1.75	1.94	90
FEF 25–75%	(L/sec)	0.99		

B

Figure 123-25 **A.** PA chest radiograph of a child with CGD who originally presented as an infant with recurrent pneumonia in the right upper lobe diagnosed radiographically as cystic adenomatoid malformation. Subsequent histologic examination and culture revealed this to be nocardial pneumonia. This radiograph reveals recurrent diffuse nocardial pneumonia. **B.** Pulmonary function tests from the same patient showing mild restrictive disease, probably secondary to right upper lobectomy and recurrent airspace disease.

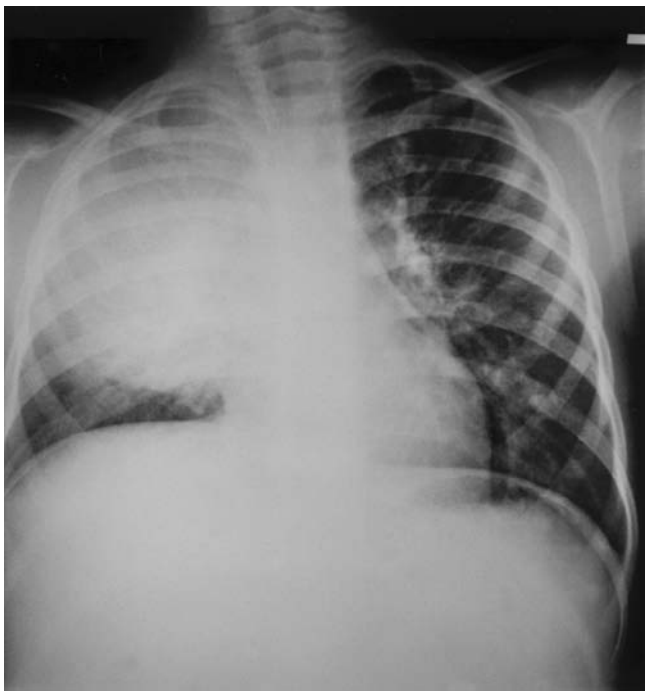


Figure 123-26 PA chest radiograph in a patient with CGD demonstrating nocardial abscess of right upper lobe, extending into the anterior chest wall.

Glucose-6-Phosphate Dehydrogenase Deficiency This is a variant of CGD, in which glucose-6-phosphate dehydrogenase (G6PD) levels are less than 1%, resulting in an inability to generate oxygen by-products and a slightly milder form of disease than that in patients with CGD.

Chediak–Higashi Syndrome Chediak–Higashi syndrome (CHS) is a rare autosomal recessive defect characterized by abnormal fusion of azurophilic lysosomes of neutrophils and cytoplasmic granules of monocytes and lymphocytes. This defect results in impaired microbicidal activity of phagocytes due to the presence of giant lysosomal granules, which have abnormal postphagocytic phagolysosomal fusion and degranulation. In addition, neutrophil counts tend to be low, secondary to their rapid turnover. Chemotactic defects and impaired natural killer cell activity have also been noted. Patients present with recurrent skin and upper and lower respiratory tract infections, including recurrent or chronic otitis media, sinusitis, and pharyngitis, in addition to lower respiratory tract infections, including bronchopneumonia. Segmental or lobar lung involvement may account for up to 30% of documented infections. Most infections are due to *S. aureus, H. influenzae,* group A streptococcus, and gram-negative enteric organisms (*Klebsiella, Proteus, Shigella, Pseudomonas*). *Aspergillus* and *Candida* represent less common etiologic agents. Respiratory failure can occur with extensive histiocytic infiltration of the lungs during an accelerated lymphoma-like proliferative phase marked by widespread tissue infiltrates of lymphoid and histiocytic cells, usually without malignant histologic characteristics. Anemia, hypersplenism, and platelet dysfunction, associated with the accelerated phase, and albinism or hypopigmentation, due to abnormal fusion of melanocyte pigment organelles, are also seen.

Leukocyte Adhesion Deficiency Patients with this autosomal recessive disease lack or have markedly reduced α_2 integrins, essential glycoprotein constituents of the CD11/CD18 receptor complex that mediates leukocyte adhesion. Recurrent necrotic and indolent infections of soft tissues, primarily in skin, mucus membranes, and the intestinal tract, are the clinical hallmarks of this disease. The recurrent infections reflect a profound impairment of leukocyte mobilization into extravascular inflammatory sites, despite peripheral blood granulocyte counts of 15,000 to 161,000/mm. A wide spectrum of gram-positive or gram-negative bacteria (*S. aureus* and gram-negative enteric bacteria) and fungal microorganisms (*Candida* and *Aspergillus*) infect LAD patients, similar to those with neutropenia syndromes (Fig. 123-27).

■ HYPERIMMUNOGLOBULIN E SYNDROME

Also known as the hyper-IgE (HIE) recurrent infection or Job syndrome, this unusual disorder appears to be autosomal dominant with incomplete penetrance or sporadic and is related in many cases to defects in the signal transducer and activator of transcription 3 gene (STAT3).[119–121] This syndrome presents in adults with elevated serum levels of polyclonal IgE and are susceptible to disseminated nontuberculous mycobacterial infections, viral infections, and fungal infections including histoplasmosis and molds. Some patients develop alveolar proteinosis. Patients demonstrate circulating monocytopenia, B lymphocytopenia, and NK cytopenia. Many patients develop malignancy involving the hematopoietic system or of the female genital tract.

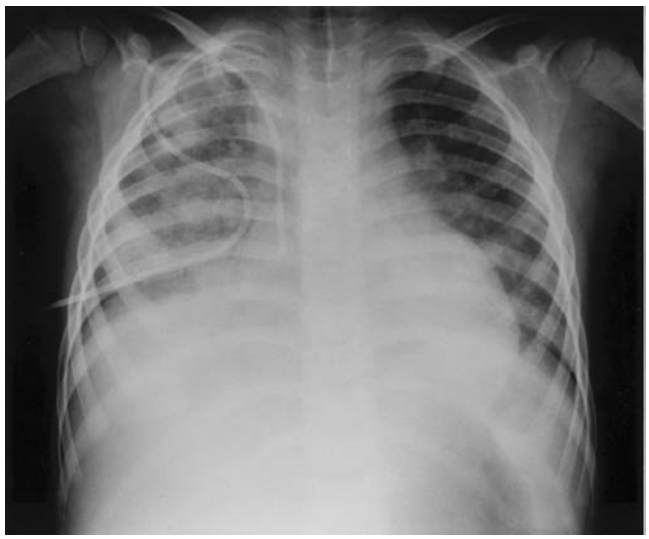
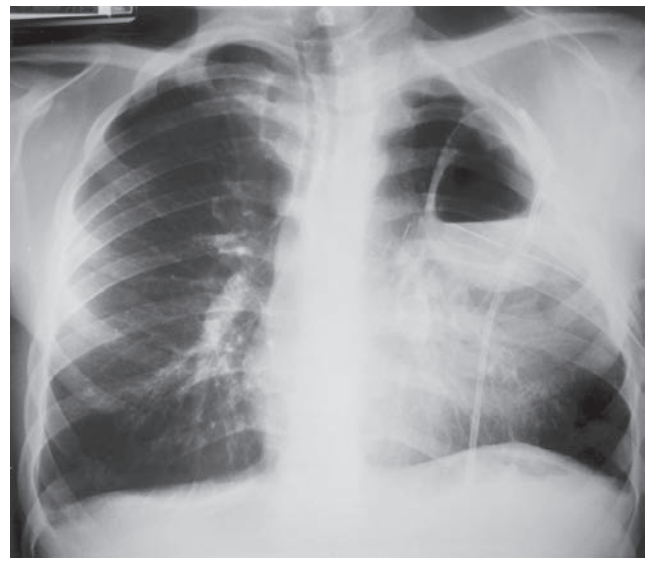


Figure 123-27 PA chest radiograph in a child with CD18 neutrophil receptor deficiency demonstrating extensive airspace disease due to probable candidal and pyogenic bacterial pneumonia.



A

		Actual	Pred.	%Pred.
LUNG MECHANICS				
FVC	(L)	3.14	3.90	81
FEV1	(L)	2.66	3.66	73
FEV1/FVC	(%)	85	94	
FEF 25%	(L/sec)	6.08	5.08	120
FEF 50%	(L/sec)	3.05	3.69	83
FEF 75%	(L/sec)	1.29	1.99	65
FEF MAX	(L/sec)	6.95	6.22	112
FEF 25–75%	(L/sec)	2.86	3.24	88

B

Figure 123-28 **A.** PA chest radiograph in a patient with Job syndrome, after left upper lobectomy for bronchiectasis due to *Aspergillus fumigatus,* resulting in recurrent, severe hemoptysis. Chest radiograph shows residual bronchopleural fistula with loculated air collection in the left upper lobe, extensive airspace disease in the left lower lobe, and pleural thickening. **B.** Pulmonary function tests from the same patient showing mild restrictive disease despite his extensive left-sided pulmonary disease.

Most patients have mild to moderate eosinophilia, despite lacking a significant history of classic allergic diseases. All patients have chronically elevated erythrocyte sedimentation rates. Diagnosis of HIE can be established in patients (usually during infancy) with a history of staphylococcal infections of the skin and sinopulmonary tract, and IgE levels at least 10 times normal. Coarse facies, chronic eczematous eruptions, cold cutaneous or subcutaneous abscesses, eosinophilia, and mucocutaneous candidiasis are also seen, as are recurrent bone fractures and osteopenia. "Cold abscesses" are not seen in all HIE patients, but are rare in other immunodeficiency states. They can present in any part of the body as fluctuant masses, with little evidence of inflammation and often without fever. Drainage of these abscesses usually reveals large volumes of purulent material, which almost always grow *S. aureus*. Otitis externa and chronic otitis media, occasionally complicated by mastoiditis, are common in HIE patients. Recurrent bronchitis represents the most common pulmonary manifestation of HIE. Patients often suffer several days a month of productive cough, rarely associated with fever. Less commonly, pneumonia, with or without associated complications – including bronchiectasis, lung abscess, empyema, pneumatocele formation, and bronchopleural fistula formation – may represent serious and potentially devastating features in HIE patients. *S. aureus* and *H. influenzae* are the most frequent causes of pneumonias in HIE, but fungal infections may complicate management (Fig. 123-28). Management relies on the use of narrow-spectrum antistaphylococcal prophylaxis, such as cloxacillin or dicloxacillin. TMP-SMX may also be employed as a prophylactic agent.

■ DEFECTS IN INNATE IMMUNITY AND PATTERN RECOGNITION RECEPTORS

The innate immune system responds to microbial products via a system of germ-line encoded PRRs. In addition to physical barriers (skin, mucosa), phagocytes and antimicrobial peptides (AMPs) (e.g., defensins), epithelial enzymes (lysozyme), cytokines and inflammatory mediators (including the complement system), the PRRs play a central role in the recognition and response to microbial invasion. The microbial components recognized by PRRs are called pathogen-associated molecular patterns (PAMPs). PRRs sit at the interface of the innate and adaptive immune systems to accelerate development of focused, specific immune responses. Defects in innate immune mechanisms are being recognized in individuals with recurrent infections.

Secreted and circulating PRRs participate in direct microbial killing and opsonization and include AMPs, defensins, lectins, cathelicidin, collectins, and pentraxins. The AMPs disrupt the cell membranes of many organism types including bacteria, fungi, parasites, and enveloped viruses. The collectins bind to microbial cell wall carbohydrate or lipid moieties to enhance microbial killing or phagocytosis. The pulmonary surfactant proteins SP-A and SP-D are collectins that bind oligosaccharides on many bacteria, fungi and viruses. The lectins are proteins that bind microbial carbohydrates and include mannose binding lectin (MBL), the ficolins and galectins. MBL is an acute-phase reactant produced by the liver that binds terminal mannose residues of carbohydrates to opsonize many organisms for phagocytosis via the C1q receptor with activation of the complement pathway. MBL deficiency is associated with frequent infections of various types. The pentraxins are acute phase reactants secreted in response to inflammatory cytokines and/or binding of TLRs. C-reactive protein (CRP) is a pentraxin that opsonizes pneumococci via the C-polysaccharide with fixation of C1q and activation of the complement system.

Defects are likely to be detected in many of the transmembrane PRRs expressed on neutrophils, monocytes, macrophages, epithelial cells, and on antigen-presenting cells including monocytes, macrophages, dendritic cells, and B lymphocytes. In this group, the TLRs are a series of transmembrane and intracellular PRRs that recognize a variety of PAMPS, including microbial cell wall components, proteins, and nucleic acids. Binding of the TLR results in changes in the transcriptional regulation controlling inflammatory processes. The first identified was TLR4 which binds bacterial endotoxin (LPS) and via the MyD88-dependent signaling pathway, activates proinflammatory cytokines, including TNF, interleukin (IL)-6, and proIL-1. TLRs 3, 4, 7, 8, and 9 can activate antiviral type-1 interferons. Families with deficiencies in TLR-3, -4, -7, -8, or -9 signaling suffer severe HSV infections including encephalitis. TLR4 mutations may also predispose to pulmonary complications after stem cell transplantation.[122] The transmembrane C-type lectin receptors (Dectins 1 and 2 and MINCLE) bind sugars (glucans and glycans) notably on fungi. Defects in Dectin 1 or its signaling pathways are associated with recurrent mucocutaneous fungal infections while phagocytosis and killing of fungi by leukocytes is normal. Thus, in individuals with a history of unusual infections, genetic defects in the innate immune system might be considered.

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CHAPTER 124

Microbial Virulence Factors in Pulmonary Infections

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OVERVIEW: MICROBIAL PATHOGENESIS

Beginning at birth, microbial organisms enter and leave the body, primarily on external or mucosal surfaces. Some of these predominantly commensal organisms become resident; others are transient; and still others establish latent foci in otherwise sterile spaces. Over a lifetime, a person is the reservoir for hundreds of strains of viruses, thousands of bacterial species, and a scattering of fungi and parasites. When these organisms violate their niche, invade, or produce toxic products, and at the same time overcome innate and adaptive host defenses, virulent interactions take place and occasionally lead to disease. Organisms can cause disease without entering or adhering to tissues by releasing toxic products. However, all infections caused by obligate intracellular parasites such as viruses require attachment of microbes onto cells and subsequent intracellular invasion as typified by the viral hemagglutinin molecule on the surface of the influenza virus, which determines species and tissue tropism, transmissibility, and replication.[1,2]

Binding to cells does not always occur with bacterial pathogens, particularly in the lung. In contrast to the GI tract where most bacterial pathogens must attach to surfaces and some, such as *Shigella dysenteriae*, do enter into cells, many studies with common respiratory bacterial pathogens such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, and others have found that avoidance of binding to respiratory epithelial cells promotes progression of infection and development of disease. Thus, the statement that one often encounters that bacterial binding to epithelial cells initiates infection in

the respiratory tract is not correct for some prominent lung pathogens. This is likely due, in large part, to the role of bacterial cell binding to the respiratory epithelium in promoting clearance of most organisms entering the lung (see Chapter 121). This occurs by a variety of nonspecific innate immune mechanisms that are potently activated by microbial binding to epithelial surface or, following binding and internalization, binding to intracellular toll-like receptors (TLRs) and other conserved pattern-recognition molecules. Along with induction of cytokine synthesis and release there is a rapid activation of beneficial inflammation and clearance. In some situations, however, organisms are able to avoid such clearance and propagate and produce clinical symptoms. For example, in neutropenic mice, the infectious dose of *P. aeruginosa* applied to the nose of an anesthetized animal that produces a lethal pneumonia and sepsis can be in the range of 10 to 50 bacterial cells, whereas in a neutrophil-sufficient setting usually 10^7 to 10^8 bacterial cells are needed to initiate infection. Clearly, avoiding polymorphonuclear leukocyte (PMN)-mediated clearance initiated by innate immunity is essential for serious disease due to *P. aeruginosa*. This finding highlights how pathologic conditions in the host can predispose to entry and survival of microbes, ranging from breaks in mucosal surfaces to defects in the immune system (see Chapter 121). Organisms become parasites when they express the requisite *virulence determinants* to gain entry and overcome or evade host defenses.

An important step in establishing infection occurs when the potential pathogen encounters the immune system. There are numerous mechanisms whereby the immune system detects and tries to limit the extent of microbial challenge, including inflammation (acute and chronic), phagocytosis (neutrophils and macrophages), complement activation, and humoral and cellular immune responses. The immune system also maintains surveillance for organisms that invade phagocytes, propagate, and resist killing, and also for organisms that invade nonphagocytic cells. Means by which microbes can be controlled range from physical clearance mechanisms to phagocytosis (followed by oxidative or nonoxidative killing) to nutritional depletion (e.g., sequestration of iron, which is an essential nutrient for bacterial growth).

Microbes have evolved a variety of strategies to overcome host defenses, evade the immune system, scavenge for nutrients, eradicate competing bacteria, and survive to spread to other hosts. These processes can lead to tissue damage and even death of the host. However, ultimate survival of the microbe requires eventual spread to a new host. A new "generation" of microbes is established (by clonal division) approximately once an hour, whereas a new generation of humans occurs about once every 20 years. Thus, the microbes have a clear genetic advantage in selecting properties that enhance virulence and survival. In response, the human immune system has developed a variety of defenses against a broad range of pathogenic mechanisms. Infections can occur at specific sites on surfaces or within the body or involve local, distal (metastatic), or systemic spread. Infection can occur without damaging cells, through direct cellular damage by microorganisms or their toxins, or as a consequence of the immune response. When physiologic disruption or cellular damage occurs, the host needs to recover and repair the damage. In addition, the immune system attempts to recognize the pathogen and develop an effective adaptive immune response involving T cells and antibody to prevent reinfection. Pathogens have also evolved a series of mechanisms to avoid immune detection, including local interference with immune processes, antigenic variation, avoidance of inducing immune responses, or inducing ineffective immune responses.

Organisms are constantly evolving to meet the demands and opportunities of modern society. Just as the cities of the Middle Ages brought together humans and rats and caused outbreaks of bubonic plague, the use of antibiotics, chemotherapy, and various medical devices has led to a number of new pathogenic interactions between microbes and humans. A key to understanding the pathophysiology of infectious diseases and appreciating the complexity of both the immune system and the microbial world is knowledge of the facts and processes of each; this knowledge base is necessary for an appreciation of the ideas presented above and the conceptual basis of immunity and infection as related to respiratory tract infections.

GENERAL MECHANISMS OF INFECTIOUS PROCESSES IN THE RESPIRATORY TRACT

The pathogenesis of acute and chronic microbial infections of the lung entails complex interactions between the microorganisms and a variety of host defense mechanisms. The general steps and molecular factors involved in the pathogenesis of microbes causing lung infections are summarized in Table 124-1. Although the alveolar spaces are generally sterile, low levels of microorganisms are continually inhaled into the lungs. Inoculation of the lungs can occur from a variety of sources, including aspirated oropharyngeal secretions or bacteria in small aqueous droplets inhaled directly via the nose or mouth. Most commonly, inhaled organisms, either alone or in association with particles of mucus, gain access to the lower airways. They are generally either cleared by mucociliary flow or scavenged by phagocytes (see Chapter 121). Particulates greater than 10 μm in diameter are deposited in the larger airways. Particles of less than 5 μm that are not cleared in the larger airways can be deposited in the alveoli. Most particulate matter is not infectious, and only spores or organisms that remain viable can cause infection. Thus, the pathogenesis of microbial infection will initially depend on a microbe's ability to enter the respiratory system and avoid clearance by mechanical and innate immune mechanisms.

As noted earlier, microorganisms can reach the lower airways from various sources. Organisms in ambient air can be inhaled as droplet nuclei—particularly in closed environments, where density is great and infected individuals can deposit organisms into the air. Perhaps the most important source of organisms causing pneumonia

TABLE 124-1 Steps and Molecular Factors for Infectious Microorganisms to Cause Lung Disease

Step	Molecular Factors	Result
Attachment to or entry into the body	Pili, flagella, surface proteins, LPS, specific ligands for receptors on host cells, or mucins	Establish organisms in a host
Multiplication	Iron-binding factors; quorum-sensing signals, biofilm matrix	Increase microbial numbers; activate other virulence systems; initiate clinical symptoms
Local spread in the lungs	Capsular polysaccharides, antiphagocytic factors, motility (pili and flagella), toxins	Evade defenses and the natural barriers to spread
Damage to lung tissue, dissemination to bloodstream	Exotoxins (including type III secretion system), LPS, cytotoxins, immunosuppressive factors	Inflict pathology due to the infectious agent, cause systemic evidence of infection (sepsis, septic shock)
Shedding (exit) from the body	None identified	Leave body at site and on a scale that ensures spread to a new host

is the flora of the upper respiratory tract. A large ecosystem of microorganisms that includes both pathogenic and nonpathogenic bacteria and fungi normally resides in the upper airways (see Chapters 127 and 133). The quantity and species diversity of many of these organisms can be stable over long periods, but transient colonization with a variety of microbes also occurs with some frequency, and these changes are often correlated seasonally and/or with concomitant infections with respiratory viruses. For example, *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* are more frequently isolated from the nasopharynx or throat during the winter months. Bacteria colonizing the nasopharynx of healthy children are often associated with the concurrent presence of certain viruses and bacteria, for example, *Staphylococcus aureus* with influenza but not rhinoviruses or pneumococcus; pneumococcus with rhinoviruses, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[3] In addition, organisms that make up the normal microbial flora in other parts of the body can be transferred to the lung, where they can cause infection. In early-onset group B streptococcal pneumonia and sepsis in neonates, the organisms are transferred during birth from the vaginal canal of the mother to the respiratory tract of the infant.

Organisms causing infections at other body sites can spread to the lungs. Although not common, hematogenous spread from the bloodstream to the lungs can occur, perhaps most notably in Lemierre disease related to septic thrombophlebitis due to the anaerobe *Fusobacterium necrophorum*. The existence of heavy colonization or infection in the upper airways also increases the potential for infection in the lungs by a variety of mechanisms, mostly by a simple dose effect, whereby a large burden of potentially pathogenic organisms overwhelms the clearance mechanism of the lungs. Another mechanism for pneumonic infection can result from conditions that perturb the specific and nonspecific defenses, leading to respiratory infection as a sequela of another pathogenic process. A common example of this process is bacterial infections secondary to influenza virus. The neuraminidase of influenza virus has been shown to play a synergistic role in pneumococcal pneumonia models by cleaving the sialic acid residues on host glycoconjugates, thereby leading to increased adherence of the bacterium.[4] Activation of the innate immune response to viral RNA, modeled by polyI:C-mediated stimulation of the TLR3 and RIG-I pathways, which induce Type I interferons, can also increase susceptibility of mice to pneumococcal and *S. aureus* pneumonia.[5] During the adaptive immune response to influenza in mice, interferon-gamma can interfere with alveolar macrophage phagocytic function and heighten susceptibility to *S. pneumoniae* pneumonia.[6] Finally, any process that disrupts the physiologic and physical barriers between the upper and lower airways can lead to infection—for example, the placement of an endotracheal tube or changes in normal clearance mechanisms associated with cystic fibrosis.

Once a microorganism gains access to the lower respiratory tract, it must be able to resist clearance from this space, remain viable, and multiply. Usually organisms will either multiply locally, resisting local defenses, or spread to other body sites by traversing epithelial barriers that normally inhibit microbial spread. In order for extracellular organisms to multiply, they must scavenge for nutrients. Of particular note is the universal requirement for iron, which must be extracted from iron-binding molecules such as transferrin. Many bacteria produce iron-binding substances known as siderophores that have an affinity for iron of greater than 10^{18} M and bind to high-affinity receptors on the bacterial surface. Organisms must also resist opsonophagocytosis or be able to survive and multiply within phagocytes. Subsequent to microbial growth and resistance of host defenses, damage to the host tissues occurs. This process is aided by a variety of pathogenic factors and results in invasion of tissues often with destruction of cells. Secreted toxins can act locally and/or systemically spread to cause clinical symptoms. Many Gram-negative bacilli possess a type III secretion system that can function like a hypodermic needle to inject toxins directly into host cells. The potential for inflammation to cause tissue destruction can be a devastating consequence of microbial growth in normally sterile lung sites. Finally, although not necessary for the pathologic process to take place, most organisms that successfully multiply will have mechanisms with which to leave the body and transmit disease, thereby propagating their species.

MOLECULAR FACTORS AND PROCESSES IN RESPIRATORY INFECTIONS

The study of pathogenic microorganisms has benefited greatly from the ability to identify microbial factors that are at work to elicit a particular pathologic process. Often these factors by themselves are responsible for a particular aspect of the infectious process, whereas at other times these factors act in consort to promote microbial colonization, growth, infection, and ultimately host responses and disease.

The success of the microorganism in establishing infection (the presence of a microorganism in a tissue where it is not normally found) and causing disease (the signs and symptoms of clinical illness) is predicated on the organism's ability to elaborate specific molecular factors that allow it to progress from the colonization to the disease state. Factors that inhibit or neutralize the host's response to eliminate the organism are also critical for pathogenesis. The ability of specific microorganisms to produce virulence or pathogenic factors, even among bacterial strains of the same species, is highly variable and is doubtless a major reason for the differences in pathogenicity among closely related strains of bacteria. Initially, most microbes that establish themselves in the respiratory tract will bind to host tissues including mucins and other factors in mucus, often in a specific manner. For example, *P. aeruginosa* places at the tip of the flagella that provide mobility to the organism, a protein called FliD that mediates adherence to respiratory mucin[7] and *H. influenzae* similarly uses its pilus to bind to mucins[8] and anchor the cells within the respiratory tract. Pathogens will produce specific molecules to promote this process. Some potentially pathogenic microorganisms, such as *S. pneumoniae*, *S. aureus*, and *N. meningitidis*, can establish colonization in the nasopharynx or throat without causing harmful effects. Almost everyone is colonized by these potential pathogens many times during life. Viruses and obligate intracellular parasites, such as *Chlamydia*, usually must find their way to the lower respiratory tract and invade a specific cell in order to start growing. Some bacterial pathogens, such as *Legionella pneumophila* and *Mycobacterium tuberculosis*, need to encounter alveolar macrophages where they are ingested but resist destruction within these cells.

In some cases, as long as a potential pathogen confines itself to a local site, no disease will ensue. At other times, growth at the local site and/or elaboration of toxins can cause frank disease; this is the mechanism of group A streptococcal pharyngitis and whooping cough caused by *Bordetella pertussis*. In general, the nasopharynx and throat readily tolerate the presence of a dynamic bacterial population, comprising mostly nonpathogenic strains along with potential pathogens that often come and go quietly, not spreading to other tissues or causing disease except when other factors intersect, such as a respiratory viral infection or other types of host stressors.

Most of the initial host response to pathogens in normally sterile sites, indicative of infection, involves the basic inflammatory responses of innate immunity. The microbes generally initiate this response by activating complement, binding quasi-specific host molecules such as mannose-binding lectin, and generating other tissue signals via cell-associated pattern-recognition molecules such as the TLRs[9,10] that lead to an influx of inflammatory cells and serum factors into the site of infection (see Chapter 121). Inflammation leads to clinical symptoms in the form of a sore throat, sneezing, coughing, feeling of malaise, and so on. Some particularly virulent microbes can rapidly produce much more serious disease as the organisms

spread and cause inflammation diffusely throughout the respiratory tract. Failure to control microbial growth and sustained inflammation leads to pathologic tissue destruction. The balance between the host inflammatory response and microbial growth is the key factor in the disease process. As is often the case with microbial infection, inflammation is a double-edged sword, critically important for resolution of infection but also responsible for tissue damage.

SPECIFIC VIRULENCE MECHANISMS OF MICROBIAL PATHOGENS

Much of our knowledge in the area of molecular mechanisms that microbial pathogens use to establish and cause respiratory infections is derived from studies of bacteria. In the case of viruses, clear factors, such as the neuraminidase and hemagglutinin proteins on the coat of the influenza virus, are needed to promote viral shedding from infected cells followed by binding to uninfected cells, which leads to subsequent cellular invasion, viral replication, inflammation, and disease. All viruses causing respiratory infections must enter cells in some manner that includes binding of a specific viral factor to a specific host cellular receptor. Intracellular nonviral microbes such as *Chlamydia* are probably taken into cells nonspecifically by phagocytosis or endocytosis.

A fairly good understanding of the molecular basis for the pathogenesis of *B. pertussis* infection has been established. *Bordetella pertussis* binds exclusively to the cilia on ciliated respiratory epithelium, using at least two bacterial cell-surface factors, designated pertactin and filamentous hemagglutinin (FHA). A fraction of the organism's cell wall, the muramyl dipeptide, is then extensively produced and secreted, and this factor is toxic to the ciliated tracheal cells. These cells are extruded from the epithelial surface, perhaps in an attempt to clear the bacteria from the respiratory tract. Secretion of pertussis toxin also contributes to the pathology. Pertussis toxin is composed of two subunits, designated A and B; the B subunit binds to receptors on host cells, allowing the A subunit to enter the cell. The A subunit transfers the ADP-ribosyl part of NAD to a membrane-bound, GTP-binding protein that normally inhibits the enzyme adenyl cyclase. This leads to increased synthesis of cAMP. Pertussis toxin can also inhibit neutrophil recruitment, thereby delaying antibody-dependent clearance of the bacterium even in immune hosts.[11]

Other extracellular pathogens that cause lung infections establish themselves in tissues by binding to either cellular receptors or factors in the mucus, notably mucin. Several bacterial pathogens that frequently cause pneumonia—including *P. aeruginosa*, *H. influenzae*, *S. aureus*, *S. pneumoniae*, *K. pneumoniae*, and some *Escherichia coli*—bind specifically to terminal or internal GalNAc-β(1–4)-Gal sequences lacking sialic acid residues commonly found on cellular glycolipids in the respiratory tract. *Pseudomonas aeruginosa* itself has been prominently studied in regard to binding to respiratory mucins as a mechanism to establish and maintain infection in the lung. Nontypeable *H. influenzae* also appears to utilize pilus-mediated adherence to human respiratory mucins to establish chronic infections in the lung.

Intracellular respiratory bacterial pathogens usually are ingested by alveolar macrophages and must resist phagocytic killing in order to establish infection and cause disease. *Mycobacterium tuberculosis* enters these cells in the lower and middle airways with high airflow, as it is an obligate aerobic organism (see Chapter 131). Bacterial ligands and cellular receptors involved in this process are not fully characterized, although dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) on dendritic cells and macrophages appears to play a role.[12] Following inhalation, most individuals will effectively clear or contain the tubercle bacilli, while in a minority the bacteria escape from the macrophage phagolysosome, or prevent its formation in the first place, leading to bacterial growth and host inflammation and resulting in lesions typical of tuberculosis. On the opposite side of the time spectrum from *M. tuberculosis*, inhaled spores of *Bacillus anthracis* are phagocytosed by alveolar macrophages but within 6 hours can germinate, escape from phagosomes, replicate within the cytoplasm, and escape from the macrophage to enter the lymphatics or bloodstream.[13]

Respiratory pathogens elaborate additional virulence factors beyond those needed to establish infection in normally sterile tissues. Many respiratory bacterial pathogens are encapsulated—a critical factor in promoting bacterial resistance to phagocytic killing. Neutralization of this antiphagocytic property by specific antibody results in high-level host immunity. Successful vaccines against *S. pneumoniae*, *H. influenzae* type b, and certain serogroups of *N. meningitidis* have been developed by engendering capsule-specific immunity via immunization, and comparable vaccines against *P. aeruginosa*, *K. pneumoniae*, group B streptococcus, and *S. aureus* are in various stages of development and testing in humans. Many studies support a role for the M protein capsule-like antigen of group A streptococcus in preventing phagocytosis of this organism along with the nonimmunogenic hyaluronic acid capsule, both playing prominent roles as antiphagocytic factors for group A streptococci.[14]

Regulation of the expression of virulence factors is tightly controlled by the pathogen via complex networks of two-component regulatory systems and other systems. In *P. aeruginosa*, quorum sensing (cell-density-dependent gene expression) via small organic molecules called acyl homoserine lactones has been shown to be important for virulence in pneumonia models both by regulating expression of secreted toxins and by inducing inflammation.[15] *Staphylococcus aureus* strains control virulence through regulatory peptides involved in activating and suppressing the accessory gene regulator *(agr)* network, with similar systems found in other Gram-positive pathogens as well.[16] Interfering with these systems with appropriate inhibitors holds promise for future therapeutic interventions in bacterial pneumonia.

Many respiratory pathogens, particularly *P. aeruginosa* and *S. aureus*, elaborate some very potent toxins. *Pseudomonas aeruginosa* secretes elastase, an enzyme that can interfere with innate immunity in the lung by cleaving surfactant protein D, thereby abrogating its role in bacterial clearance.[17] In addition to toxins secreted extracellularly, protein effectors of the type III secretion system of *P. aeruginosa* can be directly injected into host cells, injuring the alveolar epithelium and subsequently allowing the release of proinflammatory cytokines such as TNF-α into the circulation, resulting in septic shock. *Pseudomonas aeruginosa* also possesses a type VI secretion system that lyses nearby bacteria, allowing it to dominate its local environment.[18] The emergence of strains of community-acquired methicillin-resistant *S. aureus* (MRSA) associated with severe cases of necrotizing pneumonia appears to be related to elaboration of the alpha-hemolysin toxin (also called α-toxin), which injures epithelial cells after binding to a specific receptor, the zinc-dependent metalloprotease ADAM10.[19] The increased virulence of these MRSA strains was initially attributed to the Panton–Valentine leukocidin (PVL),[20] a pore-forming toxin specific for white blood cells, but subsequent work has shown that the PVL-producing strains are relatively rare causes of systemic infection[21] and these genes are mostly a marker for strains causing skin and soft-tissue infections with no real role in pneumonia.[22,23] The Gram-negative endotoxin, also called lipopolysaccharide (LPS), can cause serious damage to lung tissues, although the lung seems relatively resistant to the effects of inhaled endotoxin when compared with the systemic response to circulating LPS.

EXAMPLES OF THE MOLECULAR PATHOGENESIS OF ACUTE AND CHRONIC BACTERIAL RESPIRATORY INFECTIONS

Pneumococcal pneumonia is the prototypic acute bacterial respiratory infection. As important a pathogen as *S. pneumoniae* is in the respiratory tract, the understanding of how it causes pneumonia and sepsis is not extensive. The capsular polysaccharide is a critical

virulence factor, but beyond this, the role of other bacterial products in pathogenesis is mostly unknown. The cell-wall bacterial phosphorylcholine of virulent *S. pneumoniae* has been shown to bind to the G protein–coupled platelet-activating factor (PAF) receptor following inflammatory activation of human cells.[24] This leads to invasion of epithelial and endothelial cells, indicating a mechanism whereby *S. pneumoniae* could escape through the lung epithelium via the vascular endothelium into the circulation to cause sepsis. The fact that lung inflammation increases PAF receptor levels is likely another reason for the hypersusceptibility of people with viral upper respiratory infections to secondary infection with *S. pneumoniae.*

Chronic lung infections can be caused by a variety of bacterial pathogens, many of which occur in persons with underlying lung disease. Patients with chronic obstructive pulmonary disease are particularly susceptible to chronic infection with nontypeable *H. influenzae*, although beyond the propensity of the organism to bind to respiratory mucins,[8] the molecular bases for infection and disease are mostly unclear. Interestingly, co-colonization experiments with *H. influenzae* and *S. pneumoniae* in mice have found that *H. influenzae* predominates due to *H. influenzae*-induced complement-dependent phagocytic killing of *S. pneumoniae*.[25]

Among patients with cystic fibrosis (CF), 80% to 90% will become chronically infected with *P. aeruginosa* (see Chapter 50). This infection is currently the major factor limiting their life expectancy. Of note, while use of newer technologies that identify the complex mixtures of microbial DNA in samples of human tissues and secretions has greatly expanded our insights and understandings into the microbial communities or microbiomes present in the GI and vaginal tracts, skin, and oropharynx, the role they play in chronic respiratory infections is still under assessment. In CF, increasing concurrence with the concept of a community of microbes being associated with disease has to be placed in the context of findings that, when examining tissues from autopsies or lung transplants, only traditional CF pathogens such as *P. aeruginosa* are found by either culture or DNA analysis. In contrast, the microbiome community DNA is found in oropharyngeal swabs and expectorated sputum that must come through the oropharynx in order to be collected,[26] likely confounding the conclusion that these organisms are truly present in the lung and contributing to disease pathogenesis.

Thus, *P. aeruginosa* remains the major infectious entity associated with pulmonary decline in CF and a large research effort has focused on understanding how this pathogen infects the vast majority of patients with a genetic defect that does not appear related to chronic bacterial lung infection. In patients with CF, mutations are found in the CF transmembrane conductance regulator (CFTR) gene, which codes for a large protein that regulates chloride ion secretions directly and also appears to affect the flow of glutathione and bicarbonate. Seventy percent of people carry at least one mutant CFTR allele that lacks the codon for the phenylalanine at position 508 (ΔF508 mutation), making one-half of affected persons (~49%) homozygous for this mutation. The lack of phenylalanine at position 508 leads to an inability of the mature protein to get into the cell membrane.

The relationship of mutant CFTR and hypersusceptibility to chronic *P. aeruginosa* infection is undergoing intensive study. Pier et al. have proposed that clearance of *P. aeruginosa* from the lung following inhalation of bacteria is critically dependent on CFTR-controlled internalization of the bacterium by lung epithelial cells followed by rapid activation of innate immunity involving NF-κB nuclear translocation and production of inflammatory cytokines such as IL-6, IL-8, and CXCL1.[27,28] The combined effects of epithelial cell internalization and shedding along with rapid activation of innate immunity that most likely brings in neutrophils to phagocytose and eliminate any other extracellular bacteria can lead to efficient microbial clearance. Resolution of this response via apoptosis has also been shown to be important in the CFTR-dependent response of the lung to *P. aeruginosa*. The CFTR protein has been identified as the actual cellular receptor for clearance of *P. aeruginosa* from the lung. In a neonatal mouse model of clearance of *P. aeruginosa* from the lungs after nasal inoculation of bacteria, it was found that blocking of CFTR-mediated epithelial cell ingestion of *P. aeruginosa* led to higher bacterial burdens in the lung. Similarly in transgenic CF mice there is reduced epithelial cell uptake of *P. aeruginosa* and increased overall bacterial burdens in the lung. Of note, there appeared to be little to no binding of bacteria to tracheal epithelial cells in the infected CF mice, whereas extensive binding, ingestion, and shedding of *P. aeruginosa* by epithelial cells could be seen in tracheas of infected wild-type mice. Thus, *in vivo*, *P. aeruginosa* binding to CF epithelial cells is not observed, a situation completely consistent with results from histopathologic examination of lungs taken at transplant or autopsy from CF patients, where *P. aeruginosa* also is not seen binding to the epithelium but rather encased in mucus plugs within the airways. Overall, the initial establishment of *P. aeruginosa* infections in the lungs of CF patients can be directly attributable to the lack of functional CFTR in cell membranes to bind to this microbe and initiate appropriate innate immune responses, which overall prevents efficient bacterial clearance from the lung. Reduced airway surface pH, as noted in the recently developed CF pig model,[29] may also play a role in impaired innate defenses against *P. aeruginosa* and other bacteria in the CF lung.

The pathogenesis of chronic *P. aeruginosa* lung infections in CF patients is more extensive. After avoiding initial clearance, the bacteria adhere to mucins and become embedded in mucus plugs within the airways[30] and eventually undergo a phenotypic conversion wherein they lose both their ability to produce the long *O*-polysaccharide side chains that are usually on the LPS and acquire the ability to elaborate copious quantities of a bacterial exopolysaccharide called alginate. The hypermutable phenotype seen in *P. aeruginosa* strains from CF patients likely speeds this adaptation.[31] Alginate is unable to provoke a protective antibody response in the host[32] and encases the bacteria in microcolonies within a hypoxic microenvironment in the lung.[33] Within this protective coating, phagocytes such as neutrophils are unable to ingest and kill the microorganisms. This leads to a vicious cycle of additional but ineffective inflammation and bacterial growth, the result of which is tissue destruction subsequent to the chronic inflammatory process. Alterations in the lipid A structure of the *P. aeruginosa* LPS in strains isolated from CF patients appear to confer resistance to antimicrobial peptides and a hyperinflammatory response.[34] For most of the patient's life, *P. aeruginosa* infection appears to remain confined to endobronchial surfaces, which become plugged with mucus while the airway tissues are being destroyed, although recently reported histopathologic results from lungs of CF patients who died in the 1970s prior to more modern medical management with aggressive antibiotic therapy used in some countries also showed extensive alveolar involvement.[35] The finding of quorum-sensing signals in the CF lung suggests that the *P. aeruginosa* may exist as a biofilm (defined as a structured community of bacteria encased in a self-produced matrix), which likely contributes to the recalcitrance of this infection to antibiotics,[36] as does the recently described ability of *P. aeruginosa* to produce the gases hydrogen sulfide and nitric oxide in order to resist the oxidative stress induced by antibiotics.[37,38] Thus, the pathogenesis of chronic *P. aeruginosa* infection in CF involves at least two components: an initial phase of hypersusceptibility to infection that is predicated on an inability of CF patients to kill or clear inhaled *P. aeruginosa* cells and a subsequent phase directly related to the bacterium's ability to elaborate alginate, which allows the organism to resist host defenses while continuing to provoke inflammation that damages lung tissues.

From these two examples we garner some important insights into mechanisms whereby bacterial pathogens cause lung infections.

Many of the principles apply to other types of pathogenic microbes that follow the basic scenario of entry, attachment, multiplication and survival, elicitation of inflammation, and ultimately tissue damage and compromise of respiratory function. Although each of these steps can often be characterized at a highly specific molecular level, usually using isolated factors such as toxins to elicit clinical symptoms of disease, the overall pathogenesis of disease requires that elaboration of molecular factors of pathogenesis be coordinated and that each step in the process occur under the proper circumstances and at the right time. Research in identifying and understanding the microbe's genetic and molecular factors that control and coordinate pathogenesis is in its infancy. Presumably, greater understanding of particular factors and the interactions among both the factors and host tissues will lead to development of better vaccines and other therapies that will minimize the occurrence of microbial infections in the lung.

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CHAPTER 125

Principles of Antibiotic Use and the Selection of Empiric Therapy for Pneumonia

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Antibiotics are the foundation of therapy for respiratory tract infections. This approach varies with the type of pneumonia, age of the affected patient, presence of various comorbid illnesses and risk factors for infection by specific pathogens, and the severity of the acute illness. For most of the patients, initial therapy is empiric, aimed at a broad spectrum of potential pathogens (see Chapter 122). Once culture data become available, therapy can be pathogen-specific making it possible to de-escalate to fewer drugs with a narrower antimicrobial spectrum.[1,2] In some cases, initial empiric therapy must be continued because no etiologic pathogen is identified (see Chapter 123).

When a pathogen is defined, the term "appropriate" refers to the use of at least one antimicrobial agent that is active in vitro against the etiologic pathogen.[1] The term "adequate" includes not only appropriate therapy, but also the use of that agent in the correct dose, via the right route, given in a timely fashion, and with penetration to the site of infection. Timely and appropriate antibiotic therapy can improve survival in patients with community-acquired pneumonia (CAP) and nosocomial pneumonia or hospital-acquired pneumonia (HAP) and the benefits are most evident in patients who are not otherwise terminally ill.[1,3–5] In general, with severe illness, those receiving antibiotics earlier in their course have a lower mortality than those receiving delayed therapy, with the risk of death rising 7% to 8% for each hour of delay of therapy during the first 6 hours of septic shock and hypotension.[6]

The term HAP encompasses pneumonia in nonventilated patients, ventilated patients, and those with healthcare-associated pneumonia (HCAP) (see Chapter 129). Ventilator-associated pneumonia (VAP) is nosocomial pneumonia that develops after at least 48 hours of preceding mechanical ventilation, and thus some ventilated HAP patients may not have VAP, since they do not satisfy this definition of prolonged preceding mechanical ventilation. HCAP includes those coming from nursing homes, those in the hospital for more than 2 days in the past 90 days, those with a history of regular visits to places like dialysis or infusion centers, or those getting home wound care. Because of their exposure to the healthcare environment, some patients with HCAP are at risk for infection with multidrug-resistant (MDR) pathogens, although not all of these patients are at the same risk. Presence of this entity has blurred the distinction between CAP and HAP, since HCAP patients may reside in the "community," but be infected with organisms very similar to those present in patients with HAP.

In the setting of CAP, effective initial antibiotic therapy is associated with a marked improvement in survival, compared to ineffective therapy, particularly in patients with severe illness.[3,7] In several studies, identification of the pathogens causing severe CAP did not lead to an improved survival rate, while the use of a broad-spectrum, empiric regimen directed at likely pathogens reduced mortality (see Chapter 128). Further, patients with CAP have reduced mortality if initial antibiotic therapy is provided within 4 hours of arrival to the hospital. In the treatment of VAP, data show that appropriate therapy should be given as soon as the infection is clinically identified and lower respiratory tract samples have been collected for culture. Delay of even 24 hours in starting therapy is an important mortality risk factor in VAP.[1,5]

Even with the use of correct agents, not all patients recover. The fact that some HAP patients die in spite of microbiologically appropriate therapy is a reflection of the degree of antibiotic efficacy, as well as a reflection of host response capability (which may in part have a genetic determination). In some HAP patients, death is the result of the serious underlying illness; the percentage of deaths that occur because of infection, termed "attributable mortality" of HAP, has been estimated to be as high as 50% to 60%.[8] However, the timely use of appropriate antimicrobial therapy can reduce this attributable mortality to as low as 20%, and recent studies suggest that excess mortality in VAP may be even lower.[8,9]

In recent years, a number of guidelines for empiric therapy for both CAP and HAP have been developed, but several caveats should be remembered. First, although current guidelines are evidence-based, outcome studies are required to demonstrate their utility in clinical practice. Second, guidelines must be re-evaluated relative to local patterns of antibiotic susceptibility. In the case of CAP, the emergence of penicillin-resistant pneumococcus, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and epidemic viral illness (influenza, SARS) may affect the selection of initial therapy. In the setting of HAP, each hospital has a unique flora and antimicrobial susceptibility patterns; knowledge of such patterns is essential for selection of the optimal agents.

The majority of data establishing "standard" antibiotic doses are derived from studies in healthy volunteers or ward patients, which

have been extrapolated into a wide range of patients, including the elderly, the obese, and the critically ill, with differing clearances of these agents. Critically ill patients may manifest significantly altered end-organ function whereas those with sepsis may have a hyperdynamic circulation and augmented renal clearance (ARC), necessitating higher than normal doses of antibiotics to achieve effective serum and intrapulmonary concentrations. In these patients, as well as in obese individuals who have an altered volume of distribution (Vd) of some drugs, subtherapeutic concentrations may result in treatment failure or in selection of antimicrobial-resistant organisms.[10]

In this chapter, the principles underlying antibiotic use are examined, followed by a discussion of the commonly used antibiotics for respiratory tract infections, and the principles of empiric therapy of both CAP and HAP. Further, pharmacokinetics and pharmacodynamics (PK/PD) considerations are a theoretical way to optimize the delivery of antibiotics; recent data indicate that the use of such "optimized therapy" may have clinical benefits.[11] To preserve antibiotics for future use, it is necessary to understand mechanisms of antibiotic resistance and to practice antimicrobial stewardship by focusing on proper antibiotic dosing, de-escalation therapy, the development of local protocols for antibiotic choice, but not necessarily by restricting access to potentially effective broad-spectrum agents for seriously ill patients.

PRINCIPLES OF ANTIBIOTIC USE

Antibiotics interfere with the growth of bacteria using various mechanisms including undermining the integrity of their cell wall, interfering with bacterial protein synthesis, or common metabolic pathways.[12] The mechanism of activity can be used to define whether an agent is bacteriostatic or bactericidal, terms discussed in the section "Mechanism of Action."

MECHANISM OF ACTION

Bactericidal antibiotics kill bacteria, generally by inhibiting cell-wall synthesis or by interrupting a key metabolic function of the organism. Agents of this type include the penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, daptomycin, colistin/polymyxin, rifampin, and metronidazole. **Bacteriostatic agents** are antibiotics that inhibit bacterial growth but generally do not interfere with cell-wall synthesis, and rely on host defenses to eliminate microbes. Agents of this type include the macrolides, tetracyclines, sulfa drugs, chloramphenicol, linezolid, and clindamycin.

The terms bactericidal and bacteriostatic are broad categorizations, and may not apply for a given agent relative to all organisms, with certain antimicrobials being bactericidal for one bacterial pathogen but bacteriostatic to another.[15] The use of a specific agent is dictated by the susceptibility of the causative organism(s) in a given anatomic location to individual antibiotics. When neutropenia or immune compromise are present or if there is accompanying endocarditis or meningitis the use of bactericidal agents is preferred (see Chapter 123). Thus, for most patients with pneumonia, it is not essential to choose a bactericidal agent. One additional consideration is that certain organisms such as *S. aureus* can produce toxins, and the optimal agent must be able to kill the bacteria and also to inhibit the production of disease-mediating toxins. Agents that inhibit bacterial toxin production include clindamycin, rifampin, and linezolid.

The **Minimum Inhibitory Concentration (MIC)** is the minimum antibiotic concentration necessary to inhibit the growth of 90% of a standard sized inoculum, leading to no visible growth in a broth culture. The MIC is used to define the sensitivity of a pathogen to a specific antibiotic, under the assumption that the concentration required for killing (the MIC) can be reached in the serum in vivo. This term must be interpreted cautiously in the treatment of pneumonia, because the clinician must consider the MIC data in light of the penetration of an agent into lung tissues, with some agents achieving higher than serum levels at respiratory sites of infection and others reaching lower levels.[13,14]

The **Minimum Bactericidal Concentration (MBC)** is the minimum concentration needed to cause a 3-logarithmic decrease (99.9% killing) in the size of the standard inoculum, and generally all pathogenic bacteria are killed at this concentration.

The **Mutation Prevention Concentration (MPC)** is the lowest concentration of an antimicrobial agent that prevents bacterial colony formation from a culture containing greater than 10^{10} bacteria.[13] At lower than MPC concentrations, spontaneous mutants can persist and be enriched among the organisms that remain during therapy. The concept has been most carefully studied with the pneumococcus and fluoroquinolones. In general the MPC is higher than the MIC, implying that it is possible to use an antimicrobial to successfully treat a clinical infection but with inadequate levels to eradicate the bacteria. These remaining organisms may provide a basis for the emergence of antimicrobial-resistant bacteria.

IMPORTANT PHARMACOKINETIC–PHARMACODYNAMIC VARIABLES

Pharmacokinetics refers to the absorption, distribution, and elimination of a drug in the body, which can be used to describe the concentration of a drug in the serum. **Pharmacodynamics** refers to the physiological and biochemical effects of a drug on the body or any organisms within the body, the mechanisms of action and the relationship between a drug's concentration and effect. Bacterial killing is affected by the way in which an antibiotic reaches the site of infection considering the frequency of administration and dose administered, thus defining a close relationship between PK/PD. There are three types of bactericidal antibiotics.[13]

First, are those that kill in relation to the duration in which the nonprotein-bound free concentration of the agent stays above the MIC of the target organism, $fT > MIC$ **(Time-dependent killing)**.[16] Examples include the β-lactams, carbapenems, aztreonam, macrolides, and linezolid. For maximal efficacy, β-lactam concentrations should be maintained at four times the MIC, for approximately 40% to 70% of the dosing interval, depending on the agent being employed.[14] Second, are agents that kill in relation to how high the peak concentration is, relative to the MIC, defined by the C_{max}:MIC ratio **(Concentration-dependent killing)**.[17] Examples include the aminoglycosides and fluoroquinolones, as well as the ketolides and daptomycin. Finally, agents like the glycopeptides and fluoroquinolones also have efficacy defined by the area under the concentration–time curve divided by the MIC (AUC: MIC ratio, or AUIC) to define the optimal PK/PD index.[18,19]

To optimize time-dependent killing, dosing should be chosen to achieve the maximal time above the MIC of the target organism; this can be done with continuous or prolonged (over 3–4 hours) infusions. The rate of killing is saturated once the antibiotic concentration exceeds four times the MIC of the target organism. In spite of these considerations, for many organisms, the concentration of the antibiotic only needs to be above the MIC for 40% to 50% of the dosing interval, and possibly for as little as 20% to 30% of the interval as for the carbapenems.[13] For the time-dependent killing drugs listed above, the pharmacodynamic parameter that best predicts clinical efficacy is the time above the MIC.

The target AUIC for gram-negative bacteria is 125 or greater, whereas for most antibiotics that treat the pneumococcus, the target value is at least 30. Some studies have shown that aiming for C_{max}/MIC target of 12 for fluoroquinolones against pneumococcus is optimal. Appropriate use of these agents would entail infrequent administration but with high doses, which is the underlying principle behind the once-daily administration of aminoglycosides.

The **Post-Antibiotic Effect (PAE)** maintains the efficacy of the antibiotic after the serum (or lung) concentrations have fallen below

the MIC of the target organism. Thus, with once-daily aminoglycoside dosing regimens, the patient achieves a high peak concentration (maximal killing), and a low trough concentration (minimal nephrotoxicity) with the PAE achieving continued antimicrobial effects. While most agents exhibit a PAE against gram-positive organisms, prolonged PAEs against gram-negative bacilli are achieved by the aminoglycosides and fluoroquinolones.[13] For pneumococcus, a PAE exists for the macrolides/azalides, clindamycin, vancomycin, quinupristin/dalfopristin, tetracyclines, and the oxazolidinones (such as linezolid). Most of the agents that kill in a concentration-dependent fashion have a prolonged PAE. Agents with little or no PAE against gram-negatives are generally also agents that kill in a time-dependent fashion and are administered several times daily. The β-lactams (including the penicillins, cephalosporins, and monobactams) generally have little or no PAE against gram-negatives; one notable exception is imipenem, which has a modest PAE against *Pseudomonas aeruginosa*. In clinical practice, the use of once-daily aminoglycoside dosing has had variable benefits in both efficacy and toxicity, but the advent of this type of dosing regimen follows from an understanding of pharmacodynamic principles. **Postantibiotic Leukocyte Enhancement (PALE)** refers to the ability of functioning leukocytes to kill organisms in the postantibiotic phase of growth. Thus, when the patient has functioning neutrophils, the PAE of some agents is extended by their PALE.

Inflammatory effects. Recently, some investigators have suggested that antibiotics should be selected based on whether they stimulate inflammation and cytokine production in response to the presence of the bacterial cell-wall lysis products.[15] Certain antibiotics liberate bacterial cell-wall products that interact with cytokine-producing cells, stimulating the production of high levels of cytokines such as tumor necrosis factor. In theory, this could lead to the development or the worsening of sepsis syndrome. This may be a consideration in patients with *Pneumocystis jiroveci* pneumonia or pneumococcal meningitis who may benefit from the use of corticosteroids with antimicrobial therapy in these infections. In general, the clinical role of cytokine release is uncertain, but bactericidal antibiotics tend to produce a greater host inflammatory response than bacteriostatic agents. Antibiotics that are cell-wall active, and that kill slowly, have been associated with the greatest cytokine release.

As was noted previously, the use of antibiotics that inhibit protein synthesis (linezolid, clindamycin) may have an advantage in toxin-mediated illnesses, such as those caused by certain strains of *S. aureus*, when compared with cell-wall active bactericidal antibiotics.[20]

FACTORS AFFECTING ANTIBIOTIC CONCENTRATIONS

Alterations in lung penetration, protein binding, and changes in drug Vd and clearance (Cl), can significantly influence antibiotic concentrations achieved at a site of infection and, therefore, the probability of microbiological success.[10] The pharmacokinetic profile of piperacillin was explored in a small cohort of septic and critically ill patients, demonstrating a wide distribution of values (up to 14-fold variation) for drug clearance, Vd, and half-life[21] despite "normal" biochemical renal indices in all patients. Similar data are available for other antibiotics in this setting,[22] confirming that in a significant fraction of critically ill patients, drug elimination is likely to be markedly different from healthy volunteers, and thus it is challenging to define optimal dosing in these patients.

Beyond the immediate threat of treatment failure, subtherapeutic antibiotic concentrations are a risk factor for the selection of drug-resistant organisms.[23] Tigecycline resistance was identified within months of the commercial release of this antibiotic, and this may have been related to suboptimal concentrations at the site of infection.[24] In this respect, accurately identifying patients at risk of suboptimal drug exposure for a given causative pathogen remains a difficult clinical problem. While therapeutic drug monitoring (TDM) provides the most robust means of identifying subtherapeutic concentrations, its availability for all classes of antibiotic is largely limited to specialized centers.[25–27] In addition, changing organ function during the course of critical illness will affect antibiotic PK parameters, necessitating a regular review of dosing requirements.

PENETRATION INTO THE LUNG

A key requirement for the successful treatment of pneumonia is the achievement of therapeutic drug concentrations at the site of infection; in pneumonia, the targets are the lung parenchyma and alveoli (Table 125-1).[28] The drug concentration within the epithelial lining fluid (ELF) has been the most commonly used surrogate in pneumonia therapy. Research over a number of years has established that there is wide variability both within and between antibiotic classes in terms of ELF penetration.[29] The physiochemical properties that govern drug movement across biological membranes include the degree of ionization, fat solubility, molecular weight, and protein binding. Despite accounting for such characteristics, many of the differences between antibiotics in ELF to plasma concentration ratios (C_{ELF}:C_{Plasma}) remain poorly understood.[29] Sputum and bronchial concentrations may be the most relevant measurements for bronchial infections, whereas the concentrations in lung parenchyma, ELF, and cells such as macrophages and neutrophils may be more important for pneumonia. The localization of the pathogen may also be important; intracellular organisms such as *Legionella pneumophila* and *Chlamydophila pneumoniae* may be best eradicated by agents that achieve high intracellular concentrations in macrophages.

Macrolides have good penetration into ELF (e.g., C_{ELF}:C_{Plasma} >10 for azithromycin),[29] whereas β-lactams have varying penetration ratios,[30] without a predictable pattern. Vancomycin demonstrates limited lung penetration (C_{ELF}:C_{Plasma} <1),[31] while both linezolid and fluoroquinolones are reported to have ELF concentrations equivalent to or greater than those in plasma (C_{ELF}:C_{Plasma} ≥1).[32–34] Specific data from critically ill subgroups are generally limited, and in those where results have been reported, significant interpatient variability has been noted.[35]

TABLE 125-1 Penetration of Antibiotics into Respiratory Secretions

Good Penetration: Lipid Soluble, Concentration of the Antibiotic is Not Inflammation-Dependent
Fluoroquinolones
Macrolides (newer azalides: azithromycin, clarithromycin)
Tetracyclines
Tigecycline
Clindamycin
Trimethoprim/sulfamethoxazole
Linezolid
Poor Penetration: Relatively Lipid Insoluble, Concentration of the Antibiotic is Inflammation-Dependent
Aminoglycosides
Vancomycin
Polymyxins (colistin)
β-lactams
Penicillins
Cephalosporins
Monobactams
Carbapenems

The local concentration of an antibiotic must be considered in light of the activity of the agent at the site of infection. For example, antibiotics can be inactivated by certain local conditions. Aminoglycosides have reduced activity in acidic pH, which may be present in infected lung tissues. In addition, some bacteria develop resistance by producing destructive enzymes (such as β-lactamases), by altering the permeability of the outer cell wall, by changing the target site of antimicrobial action, or by pumping (efflux) of the antimicrobial from the interior of the cell. In these conditions a high local concentration of antimicrobial may help to offset bacterial resistance mechanisms.

The concentration of an antibiotic in lung parenchyma depends on the penetration through the walls of the bronchial capillaries, which have a fenestrated endothelium. Antibiotics penetrate in proportion to their molecular size and protein binding with small molecules that are not highly protein bound passing readily into the lung parenchyma. When inflammation is present, penetration is increased. Antibiotics reaching the ELF must pass through the pulmonary vascular bed with a nonfenestrated endothelium. This presents an advantage for lipophilic agents generally not inflammation-dependent.

Lipophilic agents include chloramphenicol, the macrolides (including the azalides and ketolides), linezolid, clindamycin, the tetracyclines, the quinolones, and trimethoprim–sulfamethoxazole (TMP-SMX). Agents that are poorly lipid soluble are inflammation-dependent for entry into the ELF; these include the penicillins, cephalosporins, aminoglycosides, vancomycin, carbapenems, and monobactams.

Active transport can facilitate antibiotic entry into lung tissue and phagocytes. Agents that are concentrated in phagocytes in this manner include the macrolides, clindamycin, and the fluoroquinolones. Antibiotics, such as the β-lactams, that are not concentrated in phagocytes by active transport remain in the extracellular space, which constitutes 40% of the weight of bronchial tissue; thus, penicillins achieve only about 40% of the serum level in lung tissue.

Drugs that penetrate well into the sputum or bronchial tissue include the quinolones, the newer macrolides and azalides (azithromycin and clarithromycin), the ketolides (telithromycin), the tetracyclines, clindamycin, and TMP-SMX. On the other hand, the aminoglycosides, vancomycin, and to some extent the β-lactams, penetrate less well into these sites. With the use of once-daily aminoglycoside dosing, high peak serum concentrations can be achieved, but the alveolar lining fluid concentration in patients with pneumonia is only 32% of the serum level over the first 2 hours; the two sites have more similar concentrations later in the dosing interval.[36] Since aminoglycosides require high peak concentrations for optimal killing, their poor penetration with systemic administration often impacts efficacy suggesting a potential role for delivery by the aerosol route.

VOLUME OF DISTRIBUTION

The Vd defines the relationship between the drug concentration observed in plasma and the dose administered. Values exceeding 3 L imply a distribution outside the plasma. Hydrophilic drugs that are poorly lipid soluble diffuse freely into interstitial fluid but do not penetrate cells. Thus only the free, nonprotein-bound drug can be distributed outside the plasma. Aminoglycosides and β-lactams are hydrophilic and will distribute into the extracellular space (~0.6 L/Kg).[37] Lipophilic agents such as the macrolides and quinolones are extensively distributed in body tissues, and serum levels underestimate the effect at the site of infection. This observation explains the efficacy of azithromycin, which achieves relatively low serum levels with high intracellular concentrations in phagocytes and can treat pneumonia.

Vd is also affected by obesity. Dosing based on ideal body weight may lead to underdosing in general, while for hydrophilic antibiotics, dosing based on total body weight may result in excessive drug levels. In critical illness, the Vd of many agents can differ from that in healthy subjects, primarily as a reflection of changes in microvascular function. Also volume resuscitation, an ubiquitous intervention in critical illness, may increase Vd for hydrophilic agents in the face of increased capillary permeability and interstitial edema.[38] Sánchez et al.[39] described the hemodynamic changes observed after fluid resuscitation for septic shock, showing that antibiotics such as the β-lactams, aminoglycosides, and glycopeptides "go where the water goes," meaning that in critical illness, these drugs will be preferentially "dragged" into the interstitial space by extravascular movement of free fluid. The Vd of such drugs is much higher than in the absence of "leaky" capillaries. This effect is associated with decreased serum concentrations for any given dose with thus a larger dose required to compensate for the increased Vd. As patients improve, fluid redistribution from tissues into the vascular space occurs, resulting in a significant decrease in the Vd.[40] Thus for drugs that distribute into extravascular interstitial fluid, an initial loading dose[41] is required to adequately "fill" these compartments and the Vd will change in parallel with the patients' physiology. This may explain why higher doses of vancomycin were needed to reach target serum concentrations in ICU patients in whom standard "ward" doses are likely to be inadequate. A larger Vd is also well described for β-lactams.[42]

PROTEIN BINDING

Many antibiotics demonstrate plasma protein binding, to either albumin or alpha-1-acid glycoprotein (AAG)[37] which can be disturbed in critical illness with many patients manifesting hypoalbuminemia.[43] The free fraction of the drug is eliminated with low plasma protein concentrations resulting in an increase in Vd and CL for highly protein-bound agents such as flucloxacillin, ertapenem, ceftriaxone, and teicoplanin.[43,44] Measuring the free drug concentration can be technically difficult, thus most published research has focused on total serum levels without correction for protein binding based on data from healthy volunteers.

DRUG CLEARANCE

Drug Cl represents the volume of plasma cleared of a specific pharmaceutical per unit time, and can involve organ independent enzymatic degradation, hepatic metabolism, or renal elimination of the parent compound or metabolites. During critical illness many aspects of these elimination pathways are disturbed. There are changes in major organ blood flow, saturation of enzyme systems, or complex drug–drug interactions.[37] Few data are available that describe the impact of changes in hepatic function on antibiotic PK–PD.

For many antibiotics (such as the aminoglycosides, β-lactams, and glycopeptides), renal drug clearance is directly proportional to Creatinine clearance (CrCl).[37] With the administration of large volumes of fluid and the use of vasoactive agents in critically ill patients with sepsis, trauma, burns, and in neurosurgery patients, there is often an increased cardiac output and organ perfusion with enhanced delivery of solute to drug eliminating organs leading to the phenomenon of ARC. With ARC, serum creatinine concentrations are almost always within the "normal range," while measured creatinine clearance is elevated, even as high as 200% of normal.[44] In such patients the use of an isolated serum creatinine concentration to extrapolate GFR is not possible; dosing derived from noncritically ill patient populations may fail to account for ARC.[45] In this setting, a timed urinary CrCl provides a simple, cheap, and repeatable estimate of renal drug elimination,[46] and affords an alternate means of identifying such patients. Recent research has confirmed an association between ARC and suboptimal trough β-lactam concentrations in critical illness,[47] thereby impacting the likelihood of achieving the necessary $fT > MIC$ targets. From an antibacterial prescribing perspective, ARC will lead to an increased rate of drug elimination, and

may necessitate more frequent intermittent doses or administration by continuous or extended infusion.[22]

A paucity of data to guide dose selection is also present when patients receive extracorporeal renal replacement therapy (RRT). In such instances, native renal drug elimination is limited (although not completely absent), whereas nonrenal mechanisms may assume a greater role in total body clearance. As a consequence, highly variable antibiotic concentrations have been observed in patients receiving RRT.[48] The variety of RRT modalities available further complicates such determinations due to variations in the parameters employed (including blood flow rates, effluent flow rates, and membrane pore size) and the unique physiochemical characteristics of each drug.[49] Not surprisingly, optimal dosing strategies in RRT remain largely uncertain.[50]

ANTIMICROBIALS USED IN THE THERAPY OF RESPIRATORY TRACT INFECTIONS

A variety of classes of antibiotics are used in treatment of respiratory tract infections. Each is discussed below.

MACROLIDES (INCLUDING AZALIDES)

Macrolides are bacteriostatic agents that bind to the 50 S ribosomal subunit of the target bacteria and inhibit RNA-dependent protein synthesis. They have good activity against pneumococci as well as "atypical" pathogens (*C. pneumoniae, Mycoplasma pneumoniae, Legionella*). Older macrolides including erythromycin are not active against *Haemophilus influenzae* and have poor intestinal tolerance so that prolonged therapy is difficult. The newer agents in this class include azithromycin (also referred to as an azalide) and clarithromycin. These agents have enhanced activity against *H. influenzae* (including β-lactamase producing strains), although on an MIC basis, azithromycin is more active. Erythromycin is active against *Moraxella catarrhalis* although the new agents have enhanced activity against this pathogen. Among the new macrolides, azithromycin is more active than clarithromycin against not only *H. influenzae* and *M. catarrhalis*, but also *M. pneumoniae*. On the other hand, clarithromycin is more active than azithromycin against *Streptococcus pneumoniae, Legionella,* and *C. pneumoniae.*

Both of the newer agents have better intestinal tolerance than erythromycin and penetrate well into sputum, lung tissue, and phagocytes. Clarithromycin, which has an active 14-hydroxy metabolite that is antibacterial, is administered twice a day orally at a 500-mg dose for 7 to 10 days in the treatment of CAP and acute exacerbations of chronic bronchitis (AECB). A new preparation of extended-release clarithromycin is administered as a 1000-mg dose once daily and has been effective as a 7-day course of therapy for AECB. Azithromycin has a longer half -life than clarithromycin, and concentrates in tissues, achieving very low serum levels when administered orally. The dosing regimen for CAP is usually 500 mg daily for 3 days in outpatients, but an extended release preparation allows the administration of 2000 mg as a one-time dose for CAP. For the hospitalized patient, an intravenous preparation of azithromycin is available and is dosed as 500 mg daily, with the duration defined by the clinical course of the patient, but usually for 7 to 10 days.[3] Because of its intravenous administration, the serum levels achieved have been adequate for the therapy of bacteremic pneumococcal pneumonia.[51]

Clinical studies of CAP have consistently shown a benefit of using macrolide therapy, usually in conjunction with a β-lactam, but the mechanism for this favorable effect is not known.[52,53] Speculation has included the possibility of atypical pathogen coinfection, a possibility supported by studies that have found the benefit of the addition of a macrolides to vary over the course of time. Another explanation is the anti-inflammatory effects possessed by macrolides, which may explain their benefit in improving quality of life in patients with cystic fibrosis. Macrolides have a myriad of other effects, including interference with "quorum sensing" between bacteria, which could inhibit the in vivo proliferation of *P. aeruginosa* after colonization has occurred. A recent study has shown that azithromycin may prevent progression of pseudomonal colonization to VAP.[54]

Although macrolides remain an important therapeutic option for community respiratory tract infections, pneumococcal resistance is becoming increasingly common, resistance may have plateaued at ≈30% in the United States[55,56] especially in patients who have received an agent of this class in the past 3 months.[57] In addition, macrolide resistance can also coexist with penicillin resistance with up to 30% to 40% of penicillin-resistant pneumococci also erythromycin-resistant. The clinical relevance of these in vitro findings remains to be defined. However, there are two forms of pneumococcal macrolide resistance, one involving efflux of the antibiotic from the bacterial cell and the other involving altered ribosomal binding of the antibiotic. The former mechanism is associated with much lower levels of resistance than the latter and is present in two-thirds of the macrolide-resistant pneumococci in the United States. The latter form of resistance is less common and, when present, makes macrolide therapy for pneumococcal infection ineffective.

TETRACYCLINES

The tetracyclines are bacteriostatic agents that act by binding the 30S ribosomal subunit and interfering with protein synthesis. These agents can be used in CAP because they are active against *H. influenzae* and atypical pathogens, but in the United States, pneumococcal resistance to tetracyclines may be approaching 20%, and may exceed 50% among organisms with high-level penicillin resistance. Photosensitivity is the major side effect, limiting the use of these agents in sun-exposed patients. This drug still remains as a good alternative to treat patients with suspected atypical pneumonia infection in those with electrocardiographic QT prolongation.

TIGECYCLINE

Tigecycline is the first clinically available drug from a new class of antibiotics, the glycylcyclines. It is structurally similar to the tetracyclines, and contains a central four-ring carbocyclic skeleton, but is a derivative of minocycline. Tigecycline is bacteriostatic and is a protein synthesis inhibitor that acts by binding to the 30 S ribosomal subunit of bacteria, thereby blocking entry of aminoacyl-tRNA into the ribosome during prokaryotic translation.

This drug is approved to treat complicated skin and skin-structure infections and complicated intra-abdominal infections, but can also be used in CAP caused by *S. pneumoniae, H. influenzae,* and *L. pneumophila.* With the exception of gastrointestinal adverse events, tigecycline was generally well tolerated. It is not approved for the therapy of MRSA pneumonia or HAP. In a study by Freire et al.[58] tigecycline was compared with imipenem/cilastatin in a multicenter, randomized, double-blind study of HAP in 945 patients. Tigecycline at a dose of 100 mg per day was found to be noninferior to imipenem/cilastatin in a modified intent-to-treat analysis but not in the clinically evaluable population and not in VAP. Some data suggest that efficacy may have been limited by the relatively low dose studied. Guner et al.[59] compared tigecycline alone or in combination therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii*, a major MDR VAP pathogen. This retrospective study of 33 patients showed a 30-day overall mortality rate and attributable mortality rates of 57.6% and 24.2%, respectively. Tigecycline should not be used as monotherapy of VAP, but could be part of a combination when treating resistant *Acinetobacter* strains.

TRIMETHOPRIM–SULFAMETHOXAZOLE

This combination antibiotic is the mainstay of therapy against *Pneumocystis* pneumonia. In the past, given its antimicrobial spectrum, ease of use and low cost, it was an effective agent for CAP

and AECB. It has bactericidal activity against the pneumococcus, *H. influenzae* and *M. catarrhalis*, but not against atypical pathogens. Recently, it has become less popular because of the emergence of pneumococcal resistance at rates of at least 30%, since 80% to 90% of organisms that are penicillin resistant are also resistant to TMP-SMX. The sulfa component of the drug inhibits the bacterial enzyme responsible for forming the immediate precursor of folic acid, dihydropteroic acid. Trimethoprim is synergistic with the sulfa component and inhibits the activity of bacterial dihydrofolate reductase. TMP-SMX is available in a fixed combination of 1:5 (TMP:SMX), and is dosed as either 80/400 mg or 160/800 mg orally twice a day for 10 days, but the dosage should be adjusted in renal failure. An intravenous preparation is also available. Side effects generally result from the sulfa component and include rash, GI upset, and occasional renal failure (especially in elderly patients).

BETA-LACTAM ANTIBIOTICS

β-Lactam antibiotics are bactericidal agents that interfere with the synthesis of bacterial cell–wall peptidoglycans by binding to bacterial penicillin–binding proteins. They share a β-lactam ring with structural modifications determining classification: (a) penicillins with the β-lactam ring is bound to a five-membered thiazolidine ring; (b) cephalosporins with the β-lactam ring bound to a six-membered dihydrothiazine ring; (c) carbapenems with modifications in the thiazolidine ring (imipenem, ertapenem, and meropenem); (d) monobactams with absence of a second ring structure found in the carbapenems (aztreonam).These agents can also be combined with β-lactamase inhibitors such as sulbactam, tazobactam, or clavulanic acid, to create the β-lactam/β-lactamase inhibitor drugs, which may overcome the bacterial resistance mechanism of β-lactamase production.

The penicillins used for respiratory tract infections include the natural penicillins (penicillin G and V), the aminopenicillins (ampicillin, amoxicillin), the anti-staphylococcal agents (nafcillin, oxacillin), the anti-pseudomonal agents (piperacillin, ticarcillin), and the β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, and ticarcillin/clavulanate). Among the anti-pseudomonal penicillins, piperacillin is the most active agent.

The cephalosporins span four generations. The earlier agents were generally active against gram-positive bacteria without activity against the more complex gram-negatives or anaerobes, and were susceptible to destruction by bacterial β-lactamases. The newer generation agents are generally more specialized, with broader-spectrum activity and with resistance to breakdown by bacterial enzymes. The second generation and newer agents are resistant to bacterial β-lactamases, but recent data suggest that cefuroxime may not be an optimal pneumococcal agent if resistance is present.[60] The third-generation agents such as ceftriaxone and cefotaxime are active against penicillin-resistant pneumococci, while ceftazidime is not reliable against the pneumococcus but is active against *P. aeruginosa*. The third-generation agents may induce β-lactamases among certain gram-negatives (especially the *Enterobacteriaceae* spp.) and thus may promote the emergence of resistance during monotherapy. The fourth-generation agent, cefepime, is active against pneumococci and *P. aeruginosa* but is also less likely to induce resistance among the *Enterobacteraceae* than the third-generation agents. Ceftaroline is a new, advanced-generation cephalsosporin that has been approved for the therapy of CAP; although it has in vitro activity against MRSA, it has not been studied in a randomized controlled trial for pneumonia due to this pathogen and its efficacy in this setting is unknown.

Imipenem, doripenem, and meropenem are the carbapneems, the broadest-spectrum agents in this class, being active against gram-positives, anaerobes, and gram-negatives including *P. aeruginosa*. They have shown efficacy for patients with severe pneumonia, both community-acquired and nosocomial. A nonpseudomonal carbapenem, ertapenem is also available and has been used effectively in the therapy of CAP and HCAP. Aztreonam is a monobactam that is antigenically distinct from the β-lactams and can be used in penicillin allergic patients. It is only active against gram-negative organisms, having a spectrum very similar to the aminoglycosides.

The role of continuous or extended infusions for time-dependent antibiotics has been extensively studied as a means to optimize *f*T > MIC, with numerous studies suggesting an improved ability to achieve the required PK-PD targets,[61,62] particularly with more virulent bacteria. The clinical benefit is uncertain, with only a limited number of studies demonstrating improved outcomes. Chytra et al.[63] performed a randomized, open-label controlled trial, comparing continuous versus intermittent application of meropenem in critically ill patients with severe infection with approximately 50% requiring treatment for a respiratory tract infection. Continuous infusion resulted in higher microbiological success with a shorter duration and lower dose of meropenem although no differences in clinical cure rates or outcomes were observed.[63] Similar data have been reported by Dulhunty et al.[64] using three commonly prescribed β-lactams and showing that continuous infusion was associated with a significantly improved ability to achieve optimal PK-PD targets along with higher clinical cure rates; however, no difference was identified in ICU-free days or hospital survival. Recently, Arnold et al.[65] found that 3-hour infusions of β-lactams for gram-negative infection were not more effective than 30-minute infusions based on endpoints of mortality, duration of therapy, and use of de-escalation.

The unique challenges to effective antibiotic dosing for pneumonia in critical illness have been highlighted in studies of new or emerging antibiotics. A recent clinical study of prolonged infusion and short duration (7 days) therapy of doripenem was compared to 10 days of imipenem/cilastatin for the treatment of VAP, and showed greater mortality and lower clinical cure rates in those receiving shorter durations of therapy even though the PK/PD targets might have been achieved by the extended infusion in patients with ARC.[66,67] These data are consistent with an earlier trial (ClinicalTrials.gov Identifier: NCT00229008) examining the use of ceftobiprole versus ceftazidime/linezolid for the treatment of nosocomial pneumonia in which subgroup analyses, showed a trend favoring ceftazidime/linezolid in VAP patients, particularly those <45 years of age, and with a CrCl ≥150 mL/min.[68] These findings illustrate the impact of ARC on drug dosing and reinforce the need to further investigate optimal dosing strategies in those with critical illness.

FLUOROQUINOLONES

Fluoroquinolones are bactericidal agents that act by interfering with bacterial DNA gyrase and/or topoisomerase IV, leading to impaired DNA synthesis repair, transcription, and other cellular processes and resulting in bacterial cell lysis. Quinolones inhibit many forms of bacterial topoisomerase enzymes including DNA gyrase. The earlier quinolones (such as ciprofloxacin and ofloxacin) are active primarily against DNA gyrase, which accounts for efficacy against gram-negative bacteria. The newer agents (levofloxacin and moxifloxacin) bind both DNA gyrase and topoisomerase IV, accounting for efficacy against even drug-resistant gram-positive organisms, including drug-resistant *S. pneumoniae* (DRSP). Resistance to fluoroquinolones can occur via a variety of mechanisms including mutations in the topoisomerase enzymes, by altered permeability of the bacterial cell wall or efflux of the antibiotic from inside of the bacteria.[69]

The quinolones kill in a concentration-dependent fashion allowing optimal antibacterial activity with infrequent dosing and high peak concentrations and high ratios of AUC/MIC or C_{max}/MIC. In addition, because quinolones have a PAE against both gram-positive and gram-negative organisms, killing is maintained after local concentrations fall below the MIC of the target organism. These properties allow the fluoroquinolones to be infrequently dosed

often at once daily, particularly given the relatively long half-life of the newer compounds. The factor limiting once-daily dosing for all quinolones is the toxicity associated with higher doses of some agents such as ciprofloxacin, given concerns related to neurotoxicity and possible seizures.

Two features of quinolones that make them well suited to respiratory infections are good oral bioavailability and excellent penetration into respiratory secretions and inflammatory cells within the lung, achieving local concentrations that often exceed serum levels; similar serum and tissue levels can be reached with oral or intravenous administration. Given good lung penetration, the quinolones may be clinically more effective than predicted by MIC values and may be better than other agents in prolonging the "disease-free" interval between exacerbations of COPD, a finding that has been demonstrated for moxifloxacin.[70] High bioavailability allows some "borderline" patients (such as nursing home patients) with pneumonia to be managed with outpatient oral therapy and maintain high therapeutic levels in the serum. In addition, these agents permit an easy transition from intravenous to oral therapy of inpatients with pneumonia, facilitating early discharge when the patient is clinically improving.

The fluoroquinolones are active against β-lactamase producing organisms like *H. influenzae* and *M. catarrhalis* making them very useful for patients with AECB. However, the newer agents (levofloxacin and moxifloxacin) extend the activity of the quinolones with enhanced gram-positive activity as well as by being more active against *C. pneumoniae* and *M. pneumoniae* when compared to the older agents. The new agents are also highly effective against *L. pneumophila* and may be the drug of choice for this organism. For *P. aeruginosa*, as in certain patients with CAP, AECB, and HAP, only ciprofloxacin (750 mg twice daily orally or 400 mg every 8 hours intravenously) or levofloxacin (750 mg orally or intravenously daily) are active enough for clinical use.[1] Since the older agents (ciprofloxacin and ofloxacin) have borderline activity against the pneumococcus, if they are used for AECB or CAP, the dose should probably be optimized to either 750 mg twice daily of ciprofloxacin for AECB or 750 mg once daily of levofloxacin for CAP or AECB.

In clinical trials, all of the newer agents have been effective in treating AECB with 5 days of therapy. In CAP, therapy is usually for 7 to 14 days, but levofloxacin at 750 mg daily can be used for 5 days. Levofloxacin, but not moxifloxacin, is renally excreted, and thus requires dosage adjustment in patients with renal insufficiency. There are no good studies of severe CAP demonstrating efficacy of any of the quinolones as monotherapy, although monotherapy has been shown to be effective in both nosocomial pneumonia and AECB. These agents also differ in the degree of protein binding. The relevance of this feature to clinical outcome is uncertain, but agents like levofloxacin and moxifloxacin are not highly protein bound and have higher free serum concentrations. Although the newer agents are highly active against both penicillin sensitive and resistant pneumococci, there is concern that widespread use may increase pneumococcal resistance to these agents. Recent data show that many pneumococci (up to 20%) have quinolone-resistance determinant genes present but have not developed full resistance.[69] Risk factors for quinolone resistance among pneumococci are recent hospitalization, recent quinolone therapy, and residence in a nursing home.

One major distinction among the new quinolones is their profile of toxic side effects. A number of agents have been removed from clinical use because of toxicities including QT prolongation (grepafloxacin), hypoglycemia (gatifloxacin), phototoxicity (sparfloxacin), and liver necrosis (trovafloxacin). The side effect profiles of other new agents have generally been acceptable, but the risks of use should be weighed against the benefits. A study comparing moxifloxacin to levofloxacin in elderly hospitalized patients with CAP and a high incidence of heart disease, showed comparable safety, with low-frequency cardiac arrhythmias and *Clostridium difficile* diarrhea among both groups.[71]

AMINOGLYCOSIDES

The aminoglycosides are bactericidal agents that act by binding to the 30 S ribosomal subunit of bacteria, thus interfering with protein synthesis. Aminoglycosides have primarily a gram-negative spectrum of activity and are usually used in combination with other agents targeting difficult organisms such as *P. aeruginosa* or other resistant gram-negative bacteria. When combined with certain β-lactam agents they can achieve antibacterial synergy against *P. aeruginosa*. Amikacin is least susceptible to enzymatic inactivation by bacteria whereas tobramycin is more active than gentamicin against *P. aeruginosa*. Aminoglycosides penetrate poorly into lung tissue, and can be inactivated by the acidic environment of pneumonic lung tissue. Because of poor penetration, some investigators have used nebulized aminoglycosides for the therapy and/or prevention of gram-negative pneumonia, but clinical data are limited for this application. Clinical trials conducted for nosocomial pneumonia therapy revealed that the use of an aminoglycoside with a β-lactam antibiotic compared to a β-lactam monotherapy alone was not more effective and the combination did not prevent the emergence of *Pseudomonal* resistance. In the treatment of bacteremic *Pseudomonal* pneumonia, aminoglycoside combination therapy may be more effective than monotherapy.[1,72]

As discussed above, aminoglycosides kill in a concentration-dependent fashion, and can be dosed once daily to optimize killing while minimizing toxicity (primarily in renal insufficiency). In clinical practice, this has not been proven to occur, and once-daily dosing is comparable in efficacy and nephrotoxicity to multiple dose regimens.[73] When aminoglycosides are used, it is necessary to monitor serum levels to minimize the occurrence of acute renal failure. Peak concentrations correlate with efficacy, but only have meaning with multiple daily doses, and their utility in once-daily regimens has not been established. Trough concentrations are monitored to minimize toxicity and probably should be followed regardless of dosing regimen.

METHICILLIN-RESISTANT *S. AUREUS* INFECTIONS

MRSA has emerged as an important pathogen in patients with nosocomial pneumonia, particularly VAP and in association with necrotizing post-influenza pneumonia. In the past, vancomycin was the agent used most commonly against this pathogen. However, there have been concerns about the limited efficacy of vancomycin, primarily because of poor penetration into respiratory secretions. In addition, vancomycin is dosed intermittently with the goal of maintaining trough concentrations between 15 and 20 μg/mL; in critically ill patients this level may be associated with nephrotoxicity and may not be effective for organisms with MIC values >1 μg/mL. Vancomycin is often underdosed in critically ill patients with pneumonia and ARC.[74] Higher doses may be required in those receiving RRT. Use of a weight-based loading dose (approximately 35 mg/kg, using actual body weight) followed by continuous infusions (adjusted according to the CrCl) has been advocated by some investigators to rapidly achieve therapeutic vancomycin concentrations in critical illness, but without proven benefit.

Quinupristin/dalfopristin has been tested in patients with VAP and was not as effective against MRSA as vancomycin in spite of good in vitro activity. There are several other agents in various stages of development that have activity against MRSA that have not been proven to be useful for the therapy of respiratory tract infections. This includes daptomycin, which is inactivated by pulmonary surfactant, thus explaining a lack of efficacy in pneumonia therapy trials. Tigecycline and ceftaroline are available for nonrespiratory tract infections caused by MRSA, but efficacy of these agents in the therapy of MRSA pneumonia is not known.

LINEZOLID

Linezolid is the first agent in a new antibiotic class, the oxazolidinones, which act by inhibiting bacterial protein synthesis, and has activity against MRSA. Oxazolidinones bind to the 50 S ribosomal subunit preventing binding to transfer RNA and blocking formation of the 70 S initiation complex. Oxazolidinones inhibit production of antibacterial toxins such as the Panton-Valentine leukocidin, which can be produced by community-acquired MRSA strains. Linezolid is active against MRSA as well as against DRSP, and vancomycin-resistant enterococci (VRE) (both *Enterococcus faecium* and *Enterococcus faecalis*). This agent has a high bioavailability with serum levels the same with oral or iv therapy. Renal and nonrenal clearance occurs, and dosing adjustments are not needed for patients with renal failure.

Given the increased recognition of the unique PK-PD changes in critical illness, empiric use of linezolid instead of high-dose vancomycin has a theoretical advantage for the treatment of MRSA pneumonia. One prospective double-blind controlled trial involving patients with confirmed MRSA pneumonia, randomized to receive either linezolid (600 mg 12 hourly) or vancomycin (15 mg/kg every 12 hours with dose adjustment on the basis of trough levels) for 7 to 14 days, showed higher clinical success with linezolid with similar 60-day mortality rates between groups.[75]

Linezolid is a reasonable alternative for patients with treatment failure while receiving vancomycin, for isolates with vancomycin MIC values >2 μg/mL, with allergic reactions, or vancomycin-induced nephrotoxicity.[76] Side effects are not common and include nausea, diarrhea, anemia, and thrombocytopenia (especially with prolonged use). It is a weak monoamine oxidase inhibitor.

TELAVANCIN

Telavancin is a semi-synthetic derivative of vancomycin and a bactericidal agent that inhibits bacterial cell-wall synthesis and has been used to treat MRSA pneumonia, and is now approved for this use in the United States. In a prospective randomized double-blinded trial, telavancin was compared against vancomycin in the treatment of MRSA HAP in 1503 patients.[77] Higher cure with monomicrobial *S. aureus* were seen with telavancin and it was more effective than vancomycin for MRSA with vancomycin MIC values >1 μg/mL.[78]

POLYMYXINS

Polymyxins are bactericidal antibiotics that work in a concentration-dependent fashion, and include polymyxin B and E, the latter known as colistin. After binding to lipopolysaccharide (LPS) in the outer membrane of gram-negative bacteria, polymyxins disrupt both the outer and inner membranes, causing increased permeability of the bacterial cell wall to other antibiotics. Gram-negative bacteria can develop resistance to polymyxins through various modifications of the LPS structure that inhibit the binding of polymyxins to LPS. Colistin is used in the treatment of gram-negative bacterial infections.

Polymyxins can be used for pneumonia caused by strains of MDR *P. aeruginosa, Acinetobacter* resistant to carbapenems, or carbapenemase-producing *Enterobacteriaceae*. Polymyxins are not absorbed from the gastrointestinal tract and therefore they are administered intravenously or by inhalation. Elimination is primarily renal, and they are 50% protein bound. Major side effects include nephrotoxicity and neurotoxicity (neuromuscular block, confusion, ataxia, visual disturbances, and dizziness).[79]

A retrospective matched case-control study comparing intravenous (IV) colistin or aerosolized (AS) plus IV colistin in the treatment of VAP by MDR pathogens, in which *A. baumannii* was the most common pathogen, followed by *Klebsiella pneumonia* and *P. aeruginosa* showed no significant differences between the groups for eradication of pathogens, clinical cure, and mortality.[80] Optimal pneumonia dosing is not fully established. Dosing is from 3 million (240 mg) units to 5 million (400 mg) units every 8 hours.

AEROSOLIZED ANTIBIOTICS FOR RESPIRATORY TRACT INFECTIONS

Lung penetration of many intravenous antibiotics, including aminoglycosides and colistin, is limited despite appropriate antibiotic administration. Increased dosages and prolonged duration of therapy used to treat resistant organisms can be associated with greater systemic toxicity with an increased risk of development of antimicrobial resistance.[81,82] Aerosolized antibiotics might address these concerns by direct delivery to the site of respiratory infection, particularly for agents that penetrate poorly into the lung with systemic administration. Direct delivery of antibiotics is usually achieved by nebulization, which achieves high intrapulmonary concentrations with generally low systemic absorption, reducing the risk of systemic toxicity. The majority of studies of inhaled antibiotics have been done in nonventilated patients with cystic fibrosis, and chronic bronchial infection with *P. aeruginosa*, including patients with bronchiectasis. Nebulized tobramycin has been shown to improve pulmonary function, as well as decrease the density of *P. aeruginosa* in sputum and thus reduce the risk of hospital admission[83] in cystic fibrosis.

The use of this approach in mechanically ventilated patients has been reported for patients with either infectious tracheobronchitis or VAP, particularly when the infections involve highly resistant gram-negative bacteria (*P. aerogenosa, Klebsiella,* and *Acinetobacter*) and in whom topical delivery of antibiotics might allow effective therapy of pathogens that cannot be eradicated by systemic therapy. The appropriate dose of aerosolized antibiotics is uncertain, but can be calculated using the intravenous dose for that particular medication and adding to it the amount of drug with extrapulmonary deposition. When concentration-dependent killing antibiotics are administrated, higher peak tissue concentration is associated with greater bactericidal activity, while time-dependent antibiotics are required to maintain lung tissue concentrations above the MIC of the target organism for a prolonged period.[84–89]

Factors that influence lung deposition of nebulized antibiotics during mechanical ventilation include aerosol particle size, type of the nebulizer, physical characteristics of the carrying gas, respirator settings, pneumonia severity, and degree of lung aeration (bronchopneumonia differs from consolidation).[90–92] Ultrasonic or vibrating plate nebulizers are preferred to jet nebulizers.[93–95] Aerosolized particles with median mass aerodynamic diameter of 1 to 5 μm can reach the distal bronchioles and alveolar space.[96] A volume control mode of mechanical ventilation has been used with a constant inspiratory flow, but may require sedation during aerosol administration.[95,97] Nebulization should be synchronized to the inspiratory cycle, while the inspiratory to expiratory ratio is maintained at 1:1, and the nebulizer can be placed in the inspiratory tubing or in line between the endotracheal tube and the Y connector.[95,98,84] Conventional humidifiers need to be used in the ventilator, but humidification is discontinued during nebulization.[91] While the optimal method of administration of aerosol therapy is unknown, most studies have shown that nebulization can be effective and achieve more uniform distribution than direct instillation and, with modern delivery methods, more than 50% of the nebulized dose is retained in the lung.

In experimental studies, it has been shown that the alveolar capillary membrane permeability is markedly increased during lung parenchymal infection.[85,88] Thus, inhaled antibiotics like aminoglycosides and cephalosporins, but not colistin, could be absorbed into the systemic circulation, with some potential for toxicity. The BAY41–6551 (NCT01004445) drug-device investigational combination using amikacin has demonstrated high-level local drug delivery with low corresponding systemic levels.[99]

Several recent studies have shown that inhaled antibiotics can be used as either sole therapy or adjunctive (to intravenous) therapy for MDR gram-negative VAP. Cure rates above 60% have been reported, especially with the use of the vibrating mesh plate, small particle

nebulizer. Aerosolized antibiotics have shown efficiency in studies to treat the lung infection as well as the bacterial reservoir within the biofilm of the endotracheal tube. One randomized trial compared nebulized amikacin and ceftazidime (without systemic therapy) in the treatment of *Pseudomonal* VAP to intravenous treatment with the same medications. The study showed that nebulized medications were able to treat VAP but prevented treatment-related acquisition of antibiotic resistance that was seen in patients receiving intravenous antibiotics.[100]

Another prospective randomized trial examined the impact of adjunctive inhaled amikacin, using a vibrating mesh plate nebulizer in patients with VAP, many of whom had MDR gram-negative infection, and showed that inhaled therapy led to less systemic antibiotic use and more de-escalation than adjunctive inhaled saline.[99] In an older study, the addition of endotracheal tobramycin did not improve clinical outcome compared to placebo in VAP, although microbiologic eradication was significantly greater in the patients receiving aerosolized antibiotics.[101] In this trial, the lack of benefit may have been related to the use of suboptimal nebulization devices; recent studies using older nebulization devices have not been successful. In general, sporadic small and uncontrolled series have shown that when patients have VAP due to MDR *P. aeruginosa* or *Acinetobacter* spp., aerosolized aminoglycosides or colistin may be helpful as adjunctive therapy to systemic antibiotics.[95,102]

In mechanically ventilated patients, even though local antibiotic administration has been successful, there has been concern about the emergence of MDR gram-negatives with nebulized antibiotic therapy. Most current studies of VAP using either aminoglycosides or polymyxin B have not shown resistance to emerge. One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations. A specially formulated preparation of tobramycin for aerosol administration has been designed to avoid this complication.

PRINCIPLES OF THERAPY FOR RESPIRATORY TRACT INFECTIONS

Principles of therapy underlying treatment of community-acquired, healthcare-associated, and hospital-acquired pneumonia are considered below.

■ COMMUNITY-ACQUIRED PNEUMONIA

Empiric therapy for CAP is selected by categorizing patients on the basis of the presence or absence of cardiopulmonary disease or other specific "modifying" factors that make certain pathogens more likely, severity of illness, and place of therapy (outpatient, inpatient, ICU). Table 125-2 describes the common pathogens causing CAP in specific patient populations. Figure 125-1 describes

TABLE 125-2 Common Pathogens Causing CAP in Specific Patient Populations (In Order of Decreasing Frequency)

Outpatient, no cardiopulmonary disease or modifying factors	*S. pneumoniae, M. pneumoniae, C. pneumoniae* (alone or as mixed infection), *H. influenzae*, respiratory viruses, others (*Legionella* sp, *M. tuberculosis*, endemic fungi)
Outpatient, with cardiopulmonary disease and/or modifying factors[a]	All the above plus: DRSP, enteric gram-negatives, and possibly anaerobes (with aspiration)
Inpatient, with cardiopulmonary disease and/or modifying factors[a]	*S. pneumoniae* (including DRSP), *H. influenzae, M. pneumoniae, C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric gram-negatives (which can include *P. aeruginosa*), anaerobes (aspiration), viruses, *Legionella* sp., others (*M. tuberculosis*, endemic fungi, *Pneumocystis jiroveci*)
Inpatient, with no cardiopulmonary disease or modifying factors	All of the above, but DRSP and enteric gram-negatives are not likely. These patients are rarely admitted to the hospital
Severe CAP, with no risks for *P. aeruginosa*	*S. pneumoniae* (including DRSP), *Legionella* sp., *H. influenzae*, Enteric gram-negative bacilli, *S. aureus*, *M. pneumoniae*, respiratory viruses, others (*C. pneumoniae, M. tuberculosis* endemic fungi)
Severe CAP, with risks for *P. aeruginosa*[a]	All of the pathogens above plus *P. aeruginosa*

[a]*Some patients in this category are now classified as having HCAP if they have risk factors such as hospitalization in an acute care hospital for 2 or more days within 90 d of the infection; those residing a nursing home or long-term care facility; those who have received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 ds of the current infection; or individuals who have attended a hospital or hemodialysis clinic.*

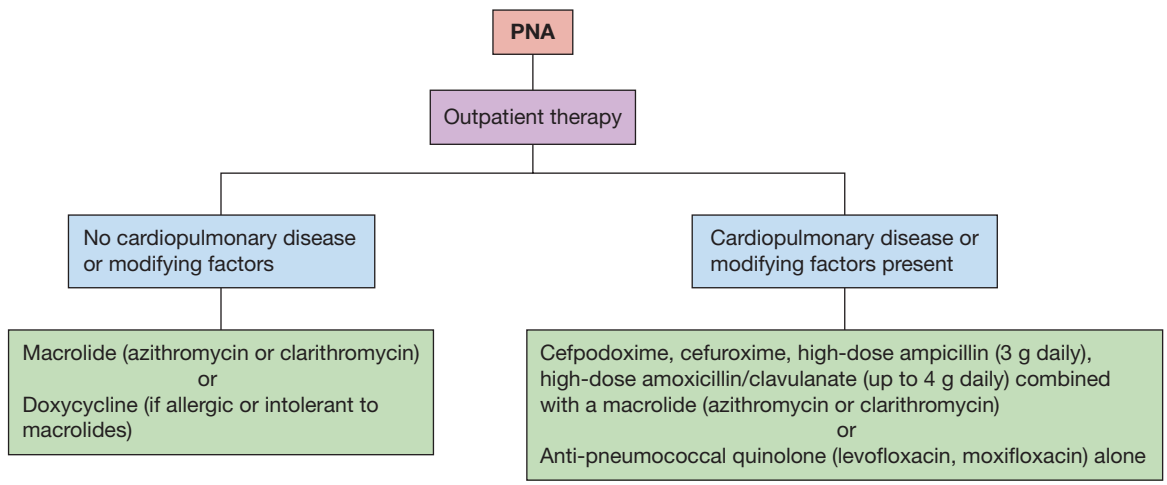


Figure 125-1 Antibiotic preferences for outpatient CAP management based on patient risk factors.

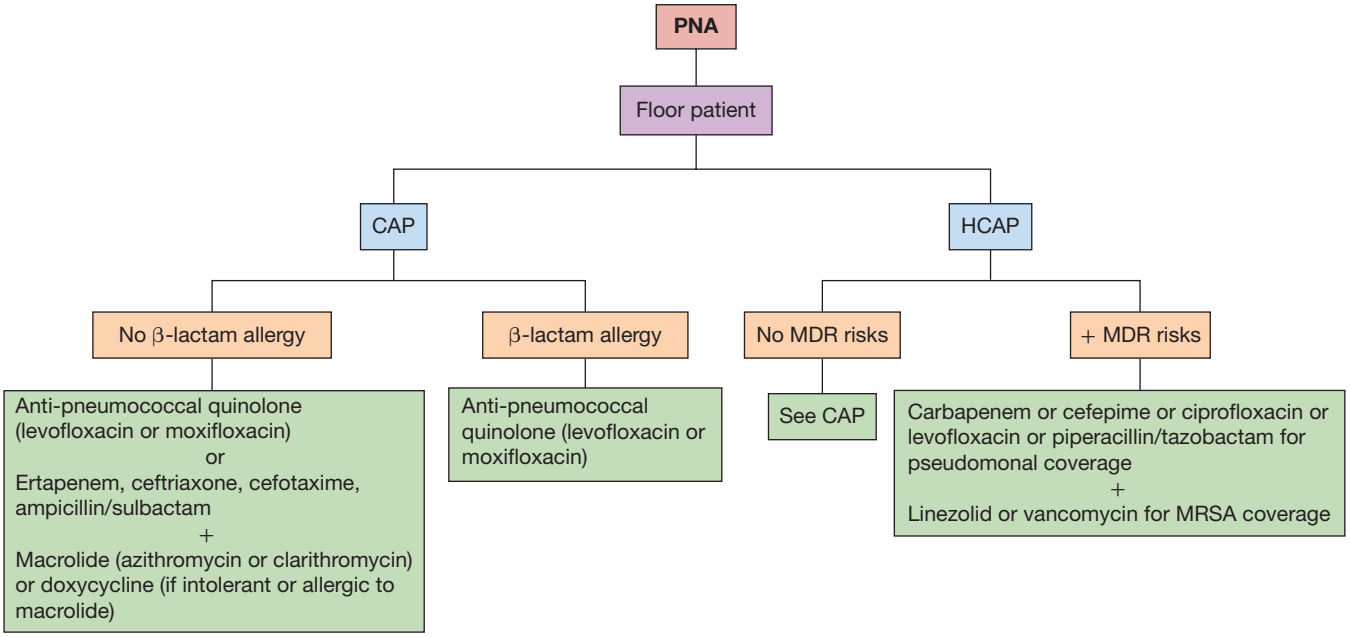


Figure 125-2 Antibiotic preferences for hospitalized CAP management (non-ICU) based on patient risk factors and allergies.

antibiotic preferences for the treatment of CAP in an outpatient setting, based on patient characteristics and risk factors. Figure 125-2 describes the antibiotic preferences for the treatment of pneumonia for non-ICU hospitalized patients (hemodynamically stable) based on risk factors and allergy status.

Modifying factors that increase the risk for infections with specific pathogens include[3]:

MDR: Hospitalization for 2 or more days in the past 90 days, broad-spectrum antibiotics within the past 3 months, immune suppression, poor functional status, admission to an ICU with a high rate of MDR organisms, residence in a nursing home or long-term care facility, or regular visits to a hospital clinic or hemodialysis center. These last two risk factors would actually classify the patient as having HCAP and not CAP.

DRSP: Age >65 years, β-lactam therapy within the past 3 months, alcoholism, immune suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in a day care.

Enteric gram-negative bacteria: Residence in a nursing home (which is actually an HCAP risk), underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy. Specific risks for *P. aeruginosa include* structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone/d), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition.

Post-influenza pneumonia can be caused by *S. aureus* (including community-acquired MRSA), *H. influenzae, or* pneumococcus. Oral anaerobes occur in the presence of poor dental hygiene.

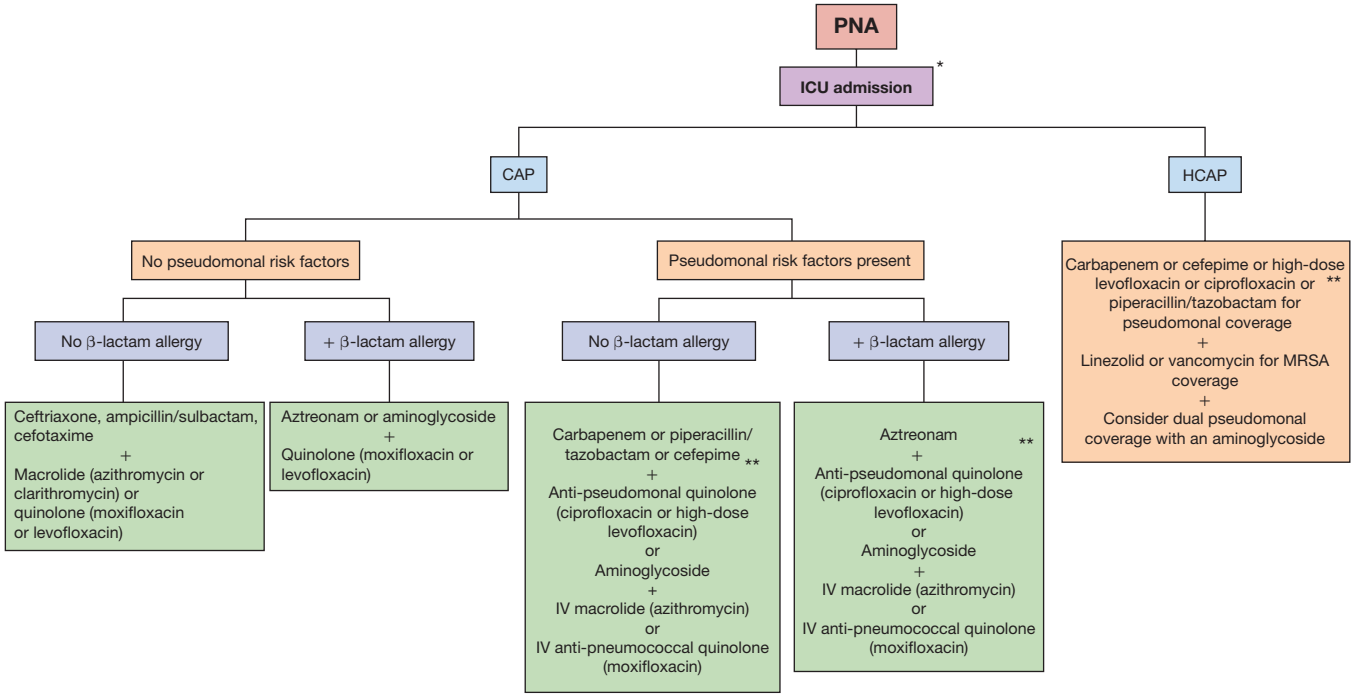
From the available data, either a fluoroquinolone or a β-lactam/macrolide combination regimen is therapeutically equivalent in nonsevere CAP. Although not proven, it may be useful to use these two types of regimens interchangeably, striving for "antibiotic heterogeneity" being sure to select an agent in a different class from those the patient received in the past 3 to 6 months. Recent data have shown that if patients have received a macrolide, fluoroquinolone or penicillin in the past 3 months, then a subsequent infection with pneumococcus is more likely to be resistant to the agent received in the past than to other agents.[58] Although oral quinolones may be as effective as intravenous quinolones for admitted patients with moderately severe illness, most admitted patients should receive initial therapy intravenously to be sure that the medication has been absorbed. Once the patient shows a clinical response, oral therapy can be initiated. Selected inpatients with mild to moderate disease can initially be treated with the combination of an intravenous β-lactam and an oral macrolide, switching to exclusively oral therapy once the patient shows a good clinical response.

Figure 125-3 shows antibiotic preferences to treat CAP in ICU patients based on risk factors and allergy status. In the ICU population, all individuals should receive combination therapy directed at DRSP and atypical pathogens; only those with appropriate risk factors should have coverage for *P. aeruginosa*. Monotherapy should not be used in any ICU admitted CAP patient. In the therapy of *P. aeruginosa*, combination therapy is often needed, but a quinolone may not always be a good choice for use given antimicrobial resistance patterns at many hospitals.

In the empiric therapy of CAP, there is a limited need for routine therapy against MRSA; however, a strain of this organism (community-acquired [CA] MRSA) has been described to cause a severe, necrotizing form of CAP after influenza.[20] Although the frequency of this organism is currently low, vigilance is needed for determining the role of this organism in the future. Optimal therapy for CA-MRSA is uncertain, but the organism produces exotoxins and may be best treated by using both an antibiotic and a toxin production inhibitor. This can done using linezolid alone or vancomycin with clindamycin. These algorithms suggest that all patients should receive empiric therapy that provides coverage for atypical pathogens, based on outcome studies showing improved survival with this approach, and may reflect a high frequency of coinfection by atypical pathogens. In fact, even with bacteremic pneumococcal pneumonia, particularly in the ICU, mortality is reduced when a β-lactam is used with a macrolide, compared to β-lactam monotherapy.[53,54,103]

HEALTHCARE-ASSOCIATED PNEUMONIA

When the patient has HCAP, therapy is dictated by risk factors for MDR pathogens, which include severe pneumonia, recent hospitalization, recent antibiotic therapy, poor functional status, and immune suppression. Not all HCAP patients require empiric therapy directed at MDR pathogens; those without severe CAP and 0 to 1 risk factors can be treated with the same regimen as those with CAP admitted to the hospital (a β-lactam/macrolide combination or fluoroquinolone



*Consider linezolid or vancomycin against MRSA in selected patients.
**Anti-pseudomonal quinolones may not be effective in hospitals with high rates of pseudomonal resistance to these agents.

Figure 125-3 Antibiotic preferences for inpatient-ICU-admitted CAP management based on patient risk factors and allergies.

monotherapy). Those with severe HCAP and no other risk factors should be treated as if for severe CAP, with a β-lactam and either a quinolone or a macrolide. If the HCAP patient has nonsevere pneumonia and at least two MDR risk factors, or severe pneumonia and at least one risk factor, they are treated like HAP, generally with dual pseudomonal therapy plus therapy for MRSA.[104]

■ HOSPITAL-ACQUIRED PNEUMONIA

Prompt empiric therapy should be initiated as soon as there is clinical suspicion of hospital-acquired infection, since mortality is increased if incorrect antibiotics are used or if a delay in antibiotic initiation occurs.[1,5,105] A lower respiratory tract culture (sputum, tracheal aspirate, protected brush, BAL) should be collected prior to initiation of antibiotic therapy, and samples can be cultured quantitatively or semiquantitatively, depending on local expertise.

A narrow-spectrum regimen can be used for patients at risk for infection with the "core pathogens" (nonresistant enteric gram-negatives, pneumococcus, *H. influenzae*, and methicillin-sensitive *S. aureus*) and with no risk factors for MDR pathogens, although very few patients fall into this category. Antimicrobial options include ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. For penicillin allergy, a quinolone or the combination of clindamycin and aztreonam can be selected.

Combination therapy with a broad-spectrum regimen containing at least two anti-pseudomonal agents should be used for patients with risk factors for MDR pathogens. Specific choices should be guided by knowledge of local microbiology patterns and should include an aminoglycoside or an anti-pneumococcal quinolone (ciprofloxacin or high-dose levofloxacin) and an anti-pseudomonal β-lactam such as cefepime, ceftazidime, imipenem, meropenem, or piperacillin/tazobactam. If there is concern about MRSA, a third agent can be added using either linezolid or vancomycin. Linezolid may be the preferred in patients with proven MRSA VAP and renal insufficiency or in those receiving other nephrotoxic medications (such as an aminoglycoside).

Initial therapy should be given in full recommended doses adjusted as needed for renal function: cefepime 1 to 2 g every 8 to 12 hours; imipenem 500 mg every 6 hours or 1 g every 8 hours; meropenem 1 g every 8 hours, piperacillin/tazobactam 4.5 g every 6 hours; levofloxacin 750 mg daily or ciprofloxacin 400 mg every 8 hours; vancomycin 15 mg/kg every 12 hours leading to a trough level of 15 to 20 mg/L; linezolid 600 mg every 12 hours; and aminoglycosides of 7 mg/kg per day of gentamicin or tobramycin and 20 mg/kg of amikacin.[1]

When choosing empiric therapy, it is important to select agents from a different class of antibiotics than the patient has received in the past 2 weeks, with a plan to de-escalate to monotherapy once culture and clinical response data are available. If *P. aeruginosa* is present, consider stopping the aminoglycoside after 3 to 5 days and finish with a single agent to which the organism is sensitive. If it is a non-pseudomonal infection, it is best to switch to a single agent that the organism is sensitive to, using either imipenem, meropenem, cefepime, piperacillin/tazobactam, ciprofloxacin, or high-dose levofloxacin.

The drug of choice for *Acinetobacter* spp. is a carbapenem, but colistin should be considered with carbapenem resistance. Tigecycline monotherapy is not recommended, but this agent can be combined with a carbapenem, colistin, or sulbactam. Aerosolized aminoglycosides or colistin can be added as adjunctive therapy in patients with highly resistant gram-negative pathogens.

The use of empiric combination therapy in VAP is controversial, and there few data to suggest that use of an aminoglycoside with a β-lactam is more effective than β-lactam monotherapy. Dual therapy may have value if the patient is neutropenic or if pseudomonal bacteremia is present, but both situations are uncommon. Thus, the most compelling reason for using empiric combination therapy in patients with suspected MDR pathogens, is to provide a broad enough spectrum of agents to increase the likelihood that the initial therapy is appropriate. Once the organism is identified, it is possible to de-escalate therapy. New data suggest that with pneumonia and sepsis, dual adequate therapy is more effective than single effective therapy, possibly because of more rapid bacterial eradication.[106]

DE-ESCALATION OF ANTIBIOTIC THERAPY

Antibiotic overuse causes resistance, which can in turn lead to inappropriate empiric therapy. To minimize this risk, it is necessary to de-escalate after an initial broad-spectrum therapy, which can involve using fewer drugs, drugs of a narrower spectrum, and short durations of therapy.[2] It is possible to effectively treat VAP with 6 to 8 days of therapy, provided that the initial therapy is appropriate.[1] The optimal duration of therapy for infections caused by *P. aeruginosa* and MRSA is still uncertain, but prolonged therapy may be no better than short duration therapy, in the absence of bacteremia.

In clinical studies of VAP, the rate of de-escalation has varied from 22% to 74%, with the highest rates being in those who are treated with a protocol for de-escalation, when initial therapy is appropriate, when initial cultures are positive (although it can be done with negative cultures), when the therapy involves broad-spectrum agents and multiple agents, and if the frequency of MDR pathogens is not high.[2] De-escalation does not appear to be dangerous and may be associated with reduced mortality, compared to no change in antibiotics. The decision to change antibiotics is made by assessing clinical features such as fever, leukocytosis, and purulence of secretions, radiographic patterns, and oxygenation. In general, the best clinical predictor of response is improvement in oxygenation, which usually occurs by day 3 in survivors of VAP, but not in nonsurvivors. If the patient is improving, then cultures should be checked, and efforts made to de-escalate and shorten duration of therapy. In some instances, all signs of pneumonia are gone by day 2 to 3, respiratory cultures are negative and in retrospect, the diagnosis was heart failure or atelectasis, and antibiotics can be completely stopped.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial control or stewardship programs involve a number of interventions, but require a committed champion and a good knowledge of local antibiotic usage patterns. The principles of antimicrobial stewardship have been compiled into a guideline, where the focus is on prospective audit and feedback of antibiotic use, de-escalation of broad-spectrum therapy, proper dosing, and the development of local guidelines for antibiotic use, based on knowledge of local microbiology.[107] Antibiotic restriction was not a highly recommended strategy, nor was restricting access to specific antibiotics.

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CHAPTER 126

Infections of the Upper Respiratory Tract

Thomas M. File Jr.

Upper respiratory tract infections are the most common infections and the most frequent reasons for office visits in the United States. Most upper respiratory infections are minor and self-limiting and do require specific antimicrobial therapy, but some (e.g., peritonsillar abscess [PTA], epiglottitis, invasive fungal sinusitis) may be life-threatening.[1]

THE COMMON COLD

The common cold is a mild, self-limiting infection and is the most frequent acute illness in the United States.[2] Approximately 500 million noninfluenza viral respiratory infections occur yearly, resulting in estimated direct costs of $17 billion and indirect costs of $22.5 billion annually.[3] Six major viral families are responsible: rhinovirus (30%–40% of cases); influenza virus (25%–30%); coronavirus (10%–15%); adenovirus (5%–10%); parainfluenza virus (5%); and respiratory syncytial virus (RSV) (5%). Each virus has several serotypes; rhinovirus has 100. More recently recognized viruses, such as human metapneumovirus and bocavirus can also cause the common cold.[4] Adults have an average of two to four colds and children six to eight colds per year.

In the United States, the incidence of colds is seasonal, with most occurring fall through spring. Young children are the main reservoir of respiratory viruses, and adults with children have more colds than those without. Transmission probably occurs either by inhalation of infectious droplets or by hand-to-nose "self-inoculation" after touching infectious secretions. The pathogenesis of rhinovirus infections is thought to include viral entry into the nose followed by infection of the epithelial cells of the upper airway. Frequent use of alcohol-based hand sanitizers or virucidal impregnated nasal tissues may reduce transmission.[5] Symptoms (sneezing, nasal discharge and congestion, and a "scratchy" throat) develop 16 to 72 hours after inoculation, and last for 1 to 2 weeks. Fever is uncommon in adults but may occur in children. Acute viral bronchitis is commonly associated with the common cold in adults. The peak of rhinoviral excretion in nasal secretions coincides with the peak of clinical illness. Complications of the common cold include bacterial superinfections of the upper respiratory tract, such as acute otitis media (AOM) and acute sinusitis, and exacerbations of asthma.[6]

Treatment of the common cold is symptomatic. Symptoms of rhinorrhea and sneezing may be improved by the use of intranasal ipratropium.[7] Antihistamine use alone in patients with the common cold is of minimal benefit and frequently results in troublesome side effects.[8] Guidelines from the American College of Chest Physicians do not recommend use of cough suppressants (codeine or dextromethorphan) for cough associated with upper respiratory infections.[9] Treatment with antibiotics for uncomplicated upper respiratory tract infections causes more harm than benefit and should not be used.[10,11] The value of zinc, vitamin C, Echinacea, and other herbal products has not been definitely proven.[12–14] Careful hand washing and use of hand disinfectants may be the most effective preventive measures.[15]

PHARYNGITIS

Acute pharyngitis is one of the most frequent illnesses for which physicians are consulted, with an estimated 12 million visits per year in the United States.[16] The great majority of cases are caused by viruses and often occur as part of the common cold for which antimicrobial therapy is not warranted. These cases are mild, nonexudative, and self-limiting.

The major causes of pharyngitis are listed in Table 126-1. Bacterial agents other than Group A streptococcus (GAS) that may cause pharyngitis include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae, Neisseria gonorrhoeae*, groups C and G streptococci, *Arcanobacterium haemolyticum, Fusobacterium necrophorum, and Corynebacterium diphtheriae*.

Patients with pharyngitis typically complain of sore throat, particularly when swallowing. Fever is lacking for most viral infections but often present with GAS. Patients may note "swollen glands"

TABLE 126-1 Microbial Etiology of Acute Pharyngitis

Organisms	Clinical Syndrome(s)
Bacterial	
Group A streptococcus	Pharyngotonsillitis, scarlet fever
Group C and group G streptococcus	Pharyngotonsillitis
Arcanobacterium haemolyticum	Scarlatiniform rash, pharyngitis
Neisseria gonorrhoeae	Tonsillopharyngitis
Corynebacterium diphtheriae	Diphtheria
Mixed anaerobes	Vincent angina
Fusobacterium necrophorum	Lemmiere syndrome, peritonsillar abscess
Francisella tularensis	Tularemia (oropharyngeal)
Yersinia pestis	Plague
Yersinia enterocolitica	Enterocolitis, pharyngitis
Viral	
Adenovirus	Pharyngoconjunctival fever
Herpes simplex virus 1 and 2	Gingivostomatitis
Coxsackievirus	Herpangina
Rhinovirus	Common cold
Coronavirus	Common cold
Influenza A and B	Influenza
Parainfluenza	Cold, croup
EBV	Infectious mononucleosis
Cytomegalovirus	CMV mononucleosis
HIV	Primary acute HIV Infection
Mycoplasma	
Mycoplasma pneumoniae	Pneumonitis, bronchitis
Chlamydia	
Chlamydophla pneumoniae	Bronchitis, pneumonia
Chlamydophla psittaci	Psittacosis

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus.
Source: Reproduced with permission from Shulman ST, Bisno AL, Clegg HW, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55(10):e86–e102.

TABLE 126-2 Antibiotic Regimens Recommended for Group A Streptococcal Pharyngitis

Drug, Route	Dose or Dosage	Duration or Quantity
For individuals without penicillin allergy		
Penicillin V, oral	Children: 250 mg twice daily or 3 times daily; adolescents and adults: 250 mg 4 times daily or 500 mg twice daily	10 d
Amoxicillin, oral	50 mg/kg once daily (max = 1000 mg); alternate: 25 mg/kg (max = 500 mg) twice daily	10 d
Benzathine penicillin G, intramuscular	<27 kg: 600,000 U; ≥27 kg: 1,200,000 U	1 dose
For individuals with penicillin allergy		
Cephalexin,[a] oral	20 mg/kg/dose twice daily (max = 500 mg/dose)	10 d
Cefadroxil,[a] oral	30 mg/kg once daily (max = 1 g)	10 d
Clindamycin, oral	7 mg/kg/dose 3 times daily (max = 300 mg/dose)	10 d
Azithromycin,[b] oral	12 mg/kg once daily (max = 500 mg)	5 d
Clarithromycin,[b] oral	7.5 mg/kg/dose twice daily (max = 250 mg/dose)	10 d

Max, maximum.
[a]Avoid in individuals with immediate type hypersensitivity to penicillin.
[b]Resistance of GAS to these agents is well-known and varies geographically and temporally.
Source: Reproduced with permission from Shulman ST, Bisno AL, Clegg HW, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55(10):e86–e102.

or anterior neck pain related to lymphadenopathy. When throat symptoms are due to a viral upper respiratory, symptoms such as nasal congestion, coryza, hoarseness, sinus discomfort, ear pain, or cough are common. A severe, usually exudative pharyngitis occurs in about half of the patients with either adenovirus infection or Epstein–Barr virus mononucleosis. The pharyngitis seen in herpangina, due to group A coxsackievirus, is characterized by a vesicular enanthem. Lesions (usually only two to six) begin as papules on the soft palate between the uvula and tonsils. These vesiculate and then ulcerate. Primary herpes simplex virus may cause a severe vesicular or ulcerative pharyngitis; when there is an overlying exudate, it may mimic streptococcal pharyngitis.

GAS is the most important bacterial cause of pharyngitis because of its suppurative (e.g., PTA) and nonsuppurative complications (e.g., rheumatic fever, acute post streptococcal glomerulonephritis).[17] Patients with GAS may have a severe exudative pharyngitis accompanied by fever, leukocytosis, and cervical lymphadenopathy, or they may have a mild pharyngitis that mimics that of the common cold. Manifestations independently associated with group A streptococcal pharyngitis include tonsillar exudates, cervical lymphadenitis, lack of cough, and history of fever. However the signs and symptoms of GAS and nonstreptococcal pharyngitis overlap so broadly that diagnosis on this basis of clinical grounds alone lacks acceptable accuracy.

Diagnosis of streptococcal pharyngitis is made by culture or by rapid antigen detection test.[17] The latter is 95% specific but not as sensitive as culture. Therefore, a negative test requires culture confirmation in children and adolescents, whereas a positive test is sufficient for the diagnosis. In adults, practice guidelines suggest that it is not necessary in usual circumstances to require culture backup because of the low incidence of GAS pharyngitis in adults and because the risk of subsequent acute rheumatic fever is generally exceptionally low in adults with acute pharyngitis. The use of a clinical algorithm without microbiological confirmation has been suggested as an acceptable alternative basis for the diagnosis of infection in adults (based on the presence of fever, adenopathy, and exudates, and lack of cough).[18] However, use of this diagnostic strategy would result in treatment of an unacceptably large number of adults with nonstreptococcal pharyngitis; that is an undesirable result in this age group, which has a low prevalence of GAS pharyngitis and a very low risk of rheumatic fever or rheumatic carditis.

Penicillin or amoxicillin is the recommended drug of choice for GAS. Treatment in penicillin-allergic individuals may include a first-generation cephalosporin (for those not anaphylactically sensitive) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days (Table 126-2). A PTA (quinsy) may follow untreated streptococcal pharyngitis—see Deep Neck Infections.

Other bacteria may also cause pharyngitis. Group C and G streptococci may cause an exudative pharyngitis and may be endemic or related to foodborne outbreaks. *A. haemolyticum* may cause an exudative pharyngitis along with a maculopapular rash, and typically occurs in children and young adults. Diphtheria, caused by *C. diphtheriae,* is rare in the United States. Sore throat is a common symptom (in 90%), and findings include mild pharyngeal injection and an overlying adherent gray membrane (especially over the tonsillar pillars) that bleeds if removal is attempted. *N. gonorrhoeae* may cause a mild pharyngitis, although most cases are asymptomatic. *Neisseria meningitidis* has rarely been noted as a cause of pharyngitis, but it is often isolated from throat cultures because the meningococcal carrier state is common. Carriers are not treated except in epidemic situations or if they have had close contact with a case of invasive meningococcal disease. *C. pneumoniae* and *M. pneumoniae* may cause a mild pharyngitis.

The anaerobe *F. necrophorum* is the causative agent of most cases of Lemmiere syndrome, septic thrombophlebitis of the internal jugular vein, which often results in metastatic pulmonary infections.[19] Lemmiere syndrome should be suspected in patients with pharyngitis (usually severe), unilateral neck pain with swelling, septic pulmonary emboli, and persistent fever despite antimicrobial therapy. Patients typically present acutely with high fever (>39°C) and rigors, often accompanied by respiratory distress. Since *F. necrophorum* is often β-lactamase producing, empiric therapy should include a β-lactamase resistant β-lactam antibiotic, such as ampicillin–sulbactam (3 g every 6 hours), piperacillin–tazobactam (4.5 g every 6 hours), ticarcillin–clavulanate (3.1 g every 6 hours), or monotherapy with a carbapenem. Surgical ligation or excision of the internal jugular vein may be necessary. The role of anticoagulation for jugular vein suppurative thrombophlebitis is controversial and generally not recommended.

ORAL CAVITY INFECTIONS

The oral cavity extends from the lips to the circumvallate papillae of the tongue. Various streptococci (e.g., *Streptococcus mutans,*

Streptococcus mitis, Streptococcus salivarius) and anaerobes (e.g., *Peptostreptococcus, Veillonella, Lactobacillus, Bacteroides, Prevotella*) heavily colonize this area, and are the main pathogens in dental and oral cavity infections. *S. mutans* is a major pathogen in dental cavities. Gingivitis and periodontitis are associated with anaerobic gram-negative rods such as *Prevotella intermedia* and *Porphyromonas gingivalis*. Mouth anaerobes are the major cause of Vincent angina (acute necrotizing ulcerative gingivitis, or trench mouth). Patients have gingival pain, halitosis, cervical adenopathy, and ulcerations of the interdental papillae. Treatment is with oral clindamycin or penicillin plus metronidazole.[20]

DEEP NECK INFECTIONS

Deep neck infections include PTA (quinsy), retropharyngeal abscess, parapharyngeal space abscess, and infections of the sublingual or submandibular spaces.[21,22] Pharyngeal space infection most often arises via contiguous spread of infection from a peritonsillar or retropharyngeal abscess. PTA is located between the tonsil and pharyngeal muscles. Most PTAs present as a severe sore throat (usually unilateral), fever, subdued voice; drooling and trismus are often present. Examination of the oral pharynx includes an extremely swollen and fluctuant tonsil with deviation of the uvula to the opposite side. If drooling is present care must be taken not to be aggressive during the examination of the oral cavity in case if epiglottis is present. Computed tomography (CT) with IV contrast distinguishes PTA from cellulitis and also demonstrates the spread of infection to contiguous deep neck spaces. PTAs are often polymicrobial. The predominant bacterial species are *Streptococcus pyogenes, Staphylococcus aureus*, and respiratory anaerobes. Management consists of drainage (needle aspiration or incision and drainage) and antimicrobial therapy (e.g., ampicillin–sulbactam or clindamycin).[23]

Ludwig angina is a rapidly spreading cellulitis of the sublingual and submandibular spaces. It usually begins from the floor of the mouth from an infected mandibular molar tooth. The sublingual area becomes edematous, pushing the tongue to the roof of the mouth. The infection is bilateral and can cause acute airway obstruction. Patients present with fever, difficulty swallowing, drooling, and prominent submandibular and sublingual swelling. They may lean forward to maximize the airway diameter and may have a muffled voice. CT is the imaging modality of choice for the diagnosis of Ludwig angina and other deep neck space infections. They should be admitted for airway monitoring, as intubation or tracheostomy may be necessary. Intravenous antibiotics active against streptococci and anaerobes should be given (e.g., ampicillin/sulbactam, clindamycin, penicillin G plus metronidazole). Surgical incision of the infected soft tissue compartment may be necessary. Mediastinitis is a rare complication resulting from spread into the parapharyngeal space and from there to the retropharyngeal space and the superior mediastinum.

LARYNGITIS

Laryngitis, or inflammation of the larynx, is characterized by hoarseness. Acute laryngitis is usually caused by the same viruses that cause the common cold, usually resolves within 3 weeks, and treatment is symptomatic.[24] Hoarseness may accompany infections with human metapneumovirus and primarily associated with bronchiolitis in young children. Herpes simplex virus may cause acute laryngitis; ulcerations or vesicles are typically seen. Streptococcal pharyngitis may be associated with laryngitis and should be treated with penicillin. Patients with chronic hoarseness often have gastroesophageal reflux disease, but must be examined for laryngeal malignancies. In rare instances, fungi or mycobacteria may cause chronic laryngitis. In chronic progressive disseminated histoplasmosis, ulcers may occur on the larynx, as well as on the tongue, buccal mucosa, and gingiva (see Chapter 134). Blastomycosis may also produce laryngeal ulcers. Tuberculosis (TB) may cause laryngeal lesions that mimic a laryngeal neoplasm. Patients typically present with hoarseness but often lack systemic symptoms to suggest TB (see Chapter 131).[25] They may have negative sputum smears for acid-fast bacilli and a clear chest radiograph. In a retrospective study of 22 patients with laryngeal TB, had clear lungs and only 7 had active pulmonary TB.[26] The patients with concurrent pulmonary TB characteristically had multiple ulcerative lesions on their vocal cords, whereas those with clear lungs had nonspecific, polypoid, single laryngeal lesions.

CROUP

Croup, or acute laryngotracheitis, is characterized by inflammation of the larynx and trachea, associated with subglottic edema and occurs most often in children ages 3 months to 3 years old, with peak incidence in the second year of life.[27] It is more common in boys. Most cases occur in fall, winter, and spring; the most common cause, parainfluenza virus (usually type 1), has caused biennial epidemics in the fall in the United States. Croup is characterized by fever, inspiratory stridor, and a "seal's bark" cough. In severe cases, there is both inspiratory and expiratory stridor. There is typically a fluctuating course, and there can be alternating clinical improvement and worsening within an hour. Croup usually follows the onset of upper respiratory tract infection symptoms by 1 to 2 days. Other viruses that can also cause croup include RSV, adenovirus, human coronaviruses; influenza and *M. pneumoniae* are uncommon causes.

The diagnosis of croup is based primarily on clinical grounds. A diagnosis of the viral etiology may be made by one of the rapid viral antigen detection techniques (e.g., PCR) on nasopharyngeal swabs. The most important differential diagnosis in the acute clinical setting is epiglottitis (see below). Children with epiglottitis usually lack the characteristic seal's bark cough of croup, appear more toxic, and their illness worsens more rapidly.

Appropriate management of croup depends upon an assessment of severity of illness. A commonly used scoring system for evaluating the severity of croup is the Westley croup score, the elements (and score) are as follows[28]:

- Level of consciousness: Normal, including sleep = 0; disoriented = 5
- Cyanosis: None = 0; with agitation = 4; at rest = 5
- Stridor: None = 0; with agitation = 1; at rest = 2
- Air entry: Normal = 0; decreased = 1; markedly decreased = 2
- Retractions: None = 0; mild = 1; moderate = 2; severe = 3

Children with mild symptoms, defined by a Westley croup score of ≤ 2, can be treated as outpatients and be treated symptomatically with humidity, fever reduction, and oral fluids. Close follow-up of response is recommended. Patients with moderate to severe croup (score ≥ 3) should be evaluated in a facility equipped to handle airway obstruction.

Treatment of croup consists of nebulized epinephrine, corticosteroids, and humidified air, although the value of humidified air has been questioned.[29,30] Nebulized epinephrine is associated with clinically and statistically significant transient reduction of symptoms of croup 30 minutes posttreatment. Children should be monitored for rebound edema for several hours after initiation of therapy. Corticosteroids are also beneficial.[31–33] Dexamethasone and budesonide are effective in relieving the symptoms of croup as early as 6 hours after the treatment. Fewer return visits and/or (re)admissions are required and the length of time spent in hospital is decreased. Oral or intramuscular dexamethasone has shown benefit for moderate to severe croup, and a single dose of oral dexamethasone is beneficial for mild croup.

EPIGLOTTITIS

Acute epiglottitis (supraglottitis) is a medical emergency, as it can rapidly lead to airway obstruction. It begins as a cellulitis between the base of the tongue and the epiglottis, pushing the epiglottis posteriorly. It then involves the epiglottis itself, with rapid swelling

and airway compromise. Epiglottitis has become a rare disease in children since the advent of vaccination against *Haemophilus influenzae* type b (Hib) in 1985, which decreased the incidence of all types of invasive Hib disease by over 99%.[34] In the prevaccine era, the incidence of epiglottitis was highest in children ages 2 to 4. Disease in children is due to rare cases of Hib vaccine failure or to other organisms, including nontypable *H. influenzae*. In one study, the incidence of acute epiglottitis in children was 0.02 cases/100,000 population/y.[35] The incidence in adults was a mean of 1.9 cases/100,000 population/y. Two uniquely recognized vulnerable populations for epiglottitis are infants and the elderly. Blood cultures are usually negative in adults and cultures of the epiglottis difficult or dangerous to obtain, so the etiology is often unknown. Pathogens isolated from throat cultures in adults with supraglottitis include *H. influenzae*, *H. parainfluenzae, Streptococcus pneumoniae,* GAS, and *S. aureus*. Viral epiglottitis is very rare and poorly substantiated. In children, the onset of symptoms occurs rapidly, usually within 6 to 12 hours, and patients appear toxic. Patients are febrile, irritable, complain of sore throat and dysphagia, prefer to sit leaning forward, and may be drooling. Inspiratory stridor may occur, but the barking cough seen in croup is absent. Adolescents and adults usually have a less fulminant presentation, often with 2 to 3 days of symptoms.[36] Severe sore throat, odynophagia, and fever are the main presenting symptoms, each occurring in 90% of adults in a recent study; muffled voice was present in 70%. In adults, diagnosis is made by direct flexible fiberoptic nasolaryngoscopy, a procedure that takes just minutes to perform in the emergency room by an otolaryngologist. A swollen, erythematous epiglottis is seen. Examination of a child in whom epiglottitis is a consideration should occur in a setting where the airway can be secured immediately if necessary.[37,38] Children suspected of having epiglottitis should be transported, sitting up, to the operating room for direct endoscopic visualization of the epiglottis. An uncuffed endotracheal (or nasotracheal) tube should be immediately inserted (or, if necessary, a tracheostomy performed) if a "cherry red" edematous epiglottis is seen. Lateral neck radiographs, used in the past to demonstrate the "thumb sign" of an edematous epiglottis, are rarely used now as they may be falsely negative and may cause a critical delay in securing the airway.

All patients with epiglottitis should be monitored in an intensive care unit. Children with epiglottitis should be intubated for airway protection, whereas adults whose endoscopic examination reveals no impending airway compromise may be managed with close observation. The empiric regimen generally should provide coverage against the following pathogens: *H. influenzae*; Penicillin-resistant *S. pneumoniae*; β-hemolytic streptococci; *S. aureus*, including community-acquired methicillin-resistant *S. aureus* (MRSA) strain (e.g., combination therapy with a third-generation cephalosporin—ceftriaxone or cefotaxime – and an antistaphylococcal agent active against MRSA—clindamycin or vancomycin). If the patient with epiglottitis due to *H. influenzae* has household contacts that include an unvaccinated child younger than 4 years, the patient and all members of the household should receive rifampin prophylaxis to eradicate carriage of the organism.

BACTERIAL TRACHEITIS

This rare disorder, sometimes called membranous croup, presents acutely like epiglottitis but primarily involves the subglottic region like croup.[39,40] Bacterial tracheitis almost always occurs in the setting of prior airway mucosal damage, as occurs with antecedent viral infection. It may represent bacterial superinfection of a viral tracheitis. The majority of cases occur in the fall and winter, coinciding with the typical seasonal epidemics of parainfluenza, RSV, and seasonal influenza. It usually affects children between 3 weeks and 13 years of age, and is uncommon in adults. Patients present with the acute onset of high fever, stridor, and dyspnea after a viral prodrome. Drooling is uncommon. They usually have leukocytosis. They do not respond to racemic epinephrine or corticosteroids. Lateral neck or anteroposterior radiographs typically show narrowing of the subglottic trachea that may be indistinguishable from that in viral croup. On endoscopy, patients have a normal epiglottis but the subglottic trachea is covered with a thick exudate. Inspissated secretions may produce a pseudomembrane. Cultures of tracheal secretions yield *S. aureus* in approximately half of the cases; other organisms include GAS, *S. pneumoniae*, and *H. influenzae*. Gram-negative bacilli have been rarely described. Treatment consists of maintenance of the airway, fluid resuscitation (if needed), and administration of appropriate antimicrobial agents. Many patients require immediate intubation; some require tracheostomy. Up to 60% will have concurrent pneumonia. Management consists of broad-spectrum intravenous antibiotics active against *S. aureus* and *H. influenzae* (e.g., ceftriaxone plus vancomycin), along with airway humidification and aggressive pulmonary toilet.

SINUSITIS (RHINOSINUSITIS)

Sinusitis is defined as an inflammation of the mucosal lining of the paranasal sinuses and can be caused by various factors including allergy, environmental irritants, and infection by viruses, bacteria, or fungi.[41–44] It is more appropriately referred to as rhinosinusitis because there is almost always coexisting inflammation in the nasal mucosa. Rhinosinusitis can be classified on the basis of duration of symptoms into acute, subacute, and chronic. Acute rhinosinusitis lasts up to 4 weeks and is usually caused by a viral or bacterial infection. Chronic sinusitis lasts more than 12 weeks and may result from a wide range of allergic and nonallergic causes. Rhinosinusitis is an extremely common condition. In a national health survey conducted during 2008, nearly one in seven (13.4%) of all noninstitutionalized adults were diagnosed with rhinosinusitis within the previous 12 months.[41] Incidence rates among adults are higher for women than men (by 1.9-fold), and adults between 45 and 74 years are most commonly affected. Recent estimates suggest that the direct annual costs of sinusitis are approximately $5.8 billion in the United States.[41] Rhinosinusitis ranks among the top five reasons for antibiotic prescriptions for adults. Ninety percent to 98% of patients presenting with symptoms of sinusitis have viral causes and will not benefit from antibiotics. The overuse of antibiotics among this population has contributed largely to the emergence of antimicrobial resistance.

The paranasal sinuses develop as outpouches of the nasal cavity. The maxillary and ethmoid sinuses are present at birth, the frontal sinus develops after age 2, and the sphenoid sinus develops after age 7. The sinuses are lined with respiratory epithelium that includes ciliated cells and mucus-producing goblet cells. The cilia normally move the mucus blanket toward the sinus ostia (and then to the nasopharynx) at a speed of up to 1 cm/min. Inflammation causes a marked decrease in the beat frequency of the cilia, as well as narrowing or obstruction of the sinus ostia due to mucosal edema. The resulting disruption of mucociliary transport results in sinusitis. The frontal, anterior ethmoid, and maxillary sinuses open into the middle meatus, whereas the posterior ethmoid and sphenoid sinuses open into the superior meatus. The osteomeatal complex, an area between the middle and inferior nasal turbinates representing the confluence of drainage from the paranasal sinuses, is a particularly important anatomic site because of its potential for mucosal thickening and impaired drainage from viral infection leading to sinus infection. A viral etiology associated with a URI or the common cold is the most frequent cause of acute rhinosinusitis. Secondary bacterial infection of the paranasal sinuses following an antecedent viral URI is relatively uncommon, estimated to be 0.5% to 2% of adult.[41] Viral infections increase the amount of mucus produced and

may damage ciliated cells. Another predisposing factor for sinusitis is allergic rhinitis, which may cause ostial obstruction by mucosal edema or polyps. Dental infections, especially of the upper teeth that abut the maxillary sinus (second bicuspid, first and second molars), may cause some cases of maxillary sinusitis. Anatomic obstruction of the sinus ostia due to a deviated septum, tumor, granulomatous disease (e.g., granulomatous polyangiitis, formerly known as Wegener granulomatosis), or nasotracheal or nasogastric tubes may also lead to sinusitis. Barotrauma from deep-sea diving or airplane travel, chemical irritants, and mucus abnormalities (e.g., cystic fibrosis) are other risk factors for sinusitis.

■ ACUTE BACTERIAL RHINOSINUSITIS

Symptoms of acute bacterial rhinosinusitis (ABRS) include purulent nasal or postnasal drainage, nasal congestion, and sinus pain or pressure. Nasal discharge and cough (which may be worse at night) are both common, whereas the presence of fever headache, or facial pain is more variable. The location of this pain depends on the sinus affected. Patients usually complain of pain in their cheek or upper teeth in maxillary sinusitis, the sides of the bridge of the nose in ethmoid sinusitis, supraorbital or frontal pain in frontal sinusitis, and retroorbital, frontal, occipital, or vertex pain in sphenoid sinusitis. Fever occurs in about half of the adults with ABRS. The gold standard for the diagnosis of ABRS is the recovery of bacteria from the cavity of a paranasal sinus.[45] However, sinus aspiration is an invasive, time-consuming, and potentially painful procedure that does not have utility in the daily practice of primary care physicians. Endoscopically guided cultures of the middle meatus may be used as a surrogate for sinus aspirates in patients with ABRS. Performance of such cultures is beyond the scope of most primary care physicians, and its validity in children has not been established. Thus, the diagnosis of ABRS in most randomized controlled trials (RCTs) of antimicrobial is based on suggestive clinical manifestations.

Appropriate therapy is based on the presence of compatible symptoms and signs of acute rhinosinusitis with radiographic confirmation of sinus involvement. Unfortunately, these diagnostic criteria do not adequately distinguish bacterial from viral infection. Imaging studies such as plain radiographs or CT are frequently used by clinicians for the diagnosis of ABRS. Unfortunately, these studies are nonspecific and also do not distinguish bacterial from viral rhinosinusitis[46] With no simple test to quickly determine whether an infection is viral or bacterial, many physicians prescribe antibiotics to play it safe. Such practices can lead to increased antibiotic resistance, exposure to drug side effects, and higher costs without resolution of their symptoms. Recent guidelines suggest antimicrobial therapy is appropriate in the following scenarios[41]:

- Symptoms of sinusitis lasting for more than 10 days without improving.
- Severe symptoms of sinusitis associated with fever of 102° F (38.9°C) or higher, nasal discharge, and facial pain for 3 to 4 days.
- Symptoms of viral sinusitis that continue to gradually worsen more than 5 or 6 days and are accompanied by new fever, headache, or increased nasal discharge, typically following a viral upper respiratory infection of 5 or 6 days.

The bacteriology of sinusitis has been well defined only for acute, community-acquired maxillary sinusitis.[45,47] Sinus puncture studies of adults with this infection have revealed that over 50% of cases are due to *S. pneumoniae* or nontypable *H. influenzae* (Table 126-3. Other pathogens include other streptococci, anaerobes, *Moraxella catarrhalis*, and rarely *S. aureus*. Studies of sinuses other than the maxillary sinus are hindered by the difficulty of obtaining culture material that is not contaminated by nasal flora.

The approach to therapy of ABRS is represented in Figure 126-1. Treatment should be empiric and target the bacterial pathogens noted above.[41,48] Oral therapy (e.g., amoxicillin–clavulanate, cefuroxime, levofloxacin) is sufficient except in severe disease or in patients who also have a complication of sinusitis (e.g., orbital sinusitis) (see Table 126-4). The recommendation of amoxicillin/clavulanate rather than amoxicillin for first-line therapy is a major change from prior consensus recommendations.[41] This recommendation for adults is primarily based on in vitro data and awareness of trends indicating an increasing rate of *H. influenzae* etiology as a result of use of the conjugate pneumococcal vaccine in pediatrics that has significantly reduced transmission of *S. pneumoniae* to adults. The recommended duration of therapy for uncomplicated ABRS in adults is 5 to 7 days.[41,49] In children with ABRS, a longer treatment duration of 10 to 14 days is recommended. Intranasal saline irrigation with either physiological or hypertonic saline is recommended as an adjunctive treatment in adults with ABRS.[41,50] Neither topical nor oral decongestants and/or antihistamines are recommended as adjunctive treatment in patients with ABRS.[41,51] Despite the common use of decongestants and antihistamines in patients with ABRS, there is scant evidence to support that they hasten recovery. Although patients may subjectively feel improvement in nasal airway patency, objective rhinometric findings do not support this impression.

TABLE 126-3 Pathogens Isolated from Sinus Aspirates in Patients with Acute Bacterial Rhinosinusitis

Microbial Agent	Publications before 2000		Publications in 2010	
	Adults (%)	Children (%)	Adults (%)	Children (%)
S. pneumonia	30–43	44	38	21–33
H. influenza	31–45	30	36	31–32
M. catarrhalis	2–10	30	16	8–11
S. pyogenes	2–1	—	13	—
S. aureus	2–3	—	13	1
Gram-negative bacilli[a]	0–24	2	—	—
Anaerobes[b]	0–12	2	—	—

[a]*Includes Enterobacteriaceae spp.*
[b]*Bacteroides, Fusobacterium, Peptostreptococcus.*
Source: Reproduced with permission from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e1-e41.

■ NOSOCOMIAL BACTERIAL SINUSITIS

Nosocomial bacterial sinusitis is usually seen in patients in the intensive care unit, and often considered in those with fever of unknown origin.[52] The incidence is higher in patients with nasotracheal tubes. It is also higher in patients with nasogastric tubes versus those without, 20 versus 12 cases per 1000 patient-days in one study. A sinus CT scan showing sinus opacification or an air–fluid level suggests the diagnosis. Bedside nasal endoscopy performed by an otolaryngologist may be helpful in obtaining cultures, either by endoscopically directed cultures of purulent meatal secretions or by maxillary sinus (antral) puncture. Antral puncture may not be indicated in all intensive care unit patients suspected of having sinusitis, however. One study found that only 8% of antral punctures yielded positive cultures in patients with normal endoscopic examinations.[53] The pathogens in nosocomial sinusitis are usually *S. aureus* and gram-negative bacilli, and often include antibiotic-resistant organisms. Empiric treatment should be directed against these organisms

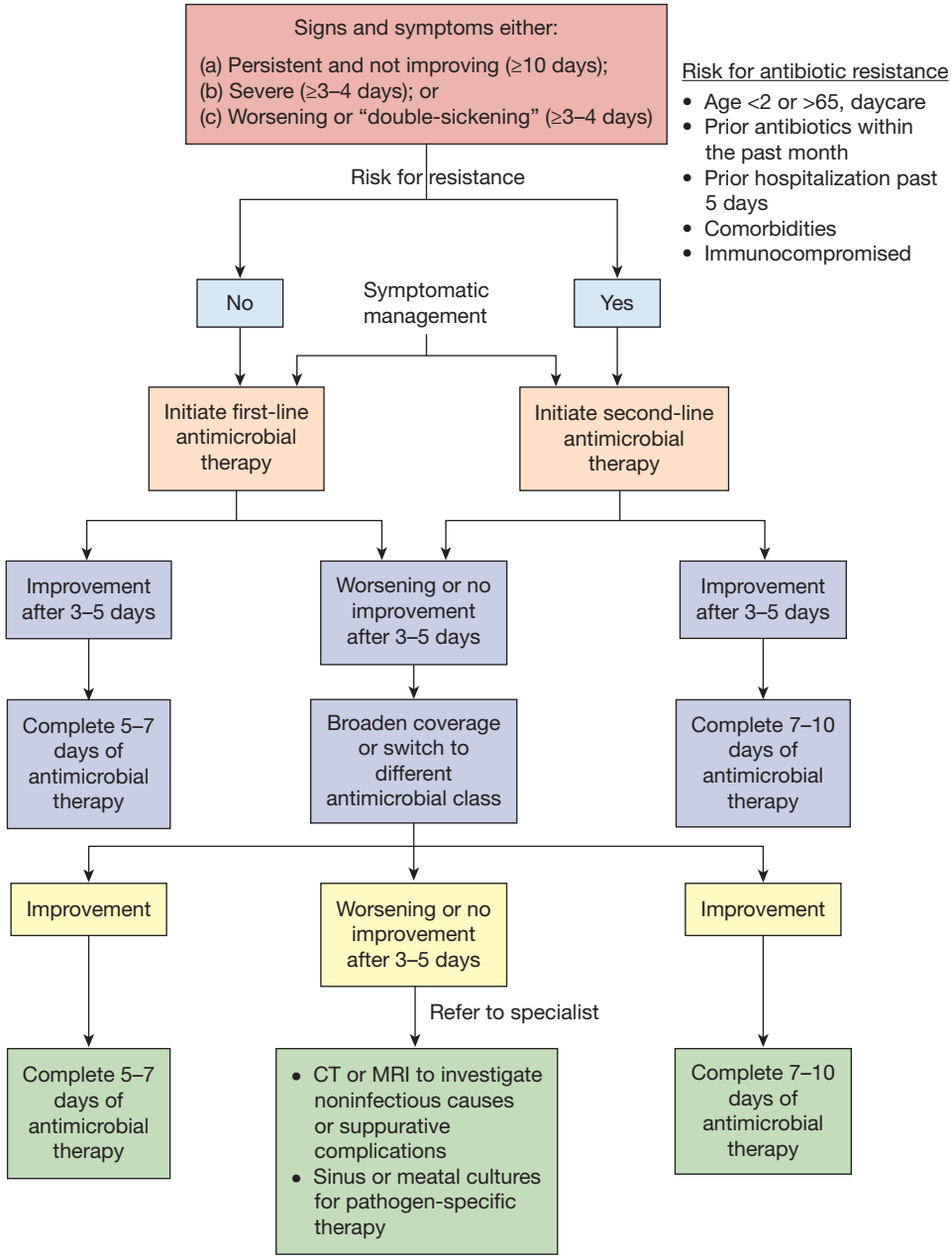

Figure 126-1 The approach to therapy of acute bacterial rhinosinusitis (ABRS). *(Reproduced with permission from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e1–e41.)*

(e.g., intravenous vancomycin plus cefepime) until culture results are known. In immunocompromised patients or poorly controlled diabetics, invasive fungal etiology (e.g., *Aspergillus*, Mucor) should be considered; diagnosis is most often established by biopsy and if suspected an otolaryngologist should be consulted.

■ CHRONIC BACTERIAL SINUSITIS

Chronic sinusitis is an ill-defined term but usually is characterized by symptoms that last for 12 weeks or longer.[54] The cardinal symptoms are persistent dull pain, postnasal mucopurulent drainage, nasal obstruction, foul odor and taste, and fatigue. True fever is rare, although many patients complain of having temperatures around 99°F (37.2°C). Most patients have stable, low-grade symptoms punctuated by episodes of acute sinusitis. These episodes may be signaled by a change to purulent secretions and increased sinus pressure. Factors that may contribute to the development of chronic bacterial sinusitis (CRS) include exposure to allergens and irritants, defects in mucociliary function, immunodeficiency, and infections with bacteria, viruses, and fungi. The common endpoint is local inflammation and swelling of the sinonasal mucosa and impairment of normal sinus drainage.

CRS can be classified into three distinct syndromes: Chronic rhinosinusitis with polyposis (20%–33% of cases); allergic fungal rhinosinusitis (8%–12%); and chronic rhinosinusitis without nasal polyposis (the majority of cases). CRS with polyposis affects immunocompetent patients and is associated with asthma and adverse reactions to aspirin and other nonsteroidal anti-inflammatory drugs. In such cases large polyps are often visible with anterior rhinos copy, whereas smaller polyps require nasal endoscopy or imaging such as CT. A sinus CT scan is indicated in patients with chronic sinusitis, both to define the extent of disease and to exclude other causes of their symptoms. Patients should be evaluated by an otolaryngologist to exclude conditions that may be causing obstruction, such as a deviated septum, nasal polyps, granulomatous polyangiitis (Wegener disease), or cancers such as adenocystic carcinoma.

TABLE 126-4 Antimicrobial Regimens for Adults with Acute Bacterial Rhinosinusitis

Indication	First-Line (Daily Dose)	Second-Line (Daily Dose)
Initial empirical therapy	Amoxicillin–clavulanate (500 mg/125 mg PO tid or 875 mg/125 mg PO bid)	Amoxicillin–clavulanate (2000 mg/125 mg PO bid) Doxycycline (100 mg PO bid or 200 mg PO qd)
β-lactam allergy		Doxycycline (100 mg PO bid or 200 mg PO qd) Levofloxacin (500 mg PO qd) Moxifloxacin (400 mg PO qd)
Risk for antibiotic resistance or failed initial therapy		Amoxicillin–clavulanate (2000 mg/125 mg PO bid) Levofloxacin (500 mg PO qd) Moxifloxacin (400 mg PO qd)
Severe infection requiring hospitalization		Ampicillin-sulbactam (1.5–3 g IV every 6 h) Levofloxacin (500 mg PO or IV qd) Moxifloxacin (400 mg PO or IV qd) Ceftriaxone (1–2 g IV every 12–24 h) Cefotaxime (2 g IV every 4–6 h)

bid, twice daily; IV, intravenously; PO, orally, qd, daily; tid, 3 times a day.
Source: Reproduced with permission from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e1–e41.

Medical therapy often requires a combination of topical or oral glucocorticoids, antibiotics, and nasal irrigation. When these measures fail, the patient should be referred to an otolaryngologist for consideration of sinus surgery. Numerous studies of the bacteriology of chronic sinusitis have reported the recovery of mixed polymicrobial flora of gram-positive and gram-negative aerobic and anaerobic bacteria.[55] An appropriate empirical antimicrobial agent for these pathogens is amoxicillin–clavulanate. Clindamycin can be used in penicillin-allergic patients. A culture (preferably through sinus puncture) should be obtained in patients who fail to have significant improvement such that pathogen-directed antimicrobial therapy can be selected.

■ COMPLICATIONS OF BACTERIAL SINUSITIS

Orbital infections are caused by penetration of the orbit as a result of spread from an infected sinus. The spectrum of orbital infections can be classified into five groups[56]:

- Periorbital cellulitis
- Orbital cellulitis
- Subperiosteal abscess
- Orbital abscess
- Cavernous sinus thrombosis

The most common complication of bacterial sinusitis is preseptal cellulitis or deeper orbital infection, conditions usually grouped under the heading "orbital cellulitis" (Fig. 126-2). Most cases are secondary to ethmoid sinusitis, since the ethmoid is separated from the orbit by only a very thin plate of bone, the lamina papyracea. Preseptal cellulitis only involves the eyelids and surrounding skin anterior to the orbital septum, but not the structures of the orbit. The lids appear red and edematous, but vision is normal and there are no orbital findings. In patients with orbital cellulitis, subperiosteal abscess, or orbital abscess, the eyelids are also red and swollen, but examination of the eye reveals one or more orbital findings as well. These include proptosis, limitation of extraocular movements, and decrease in vision. In subperiosteal and orbital abscess, the abscess is almost always located medially or superomedially in the orbit (reflecting the involvement of the adjacent ethmoid sinus), and the eye looks "down and out." A CT scan should be performed on any patient with orbital findings. An orbital or subperiosteal abscess usually requires emergency surgical drainage. Some authors also advocate a CT scan for children with apparent preseptal cellulitis, as some have a subclinical abscess.

Most patients with uncomplicated orbital cellulitis can be treated with antibiotics alone; but specialists of both ophthalmology and otolaryngology should be consulted since surgery is required for

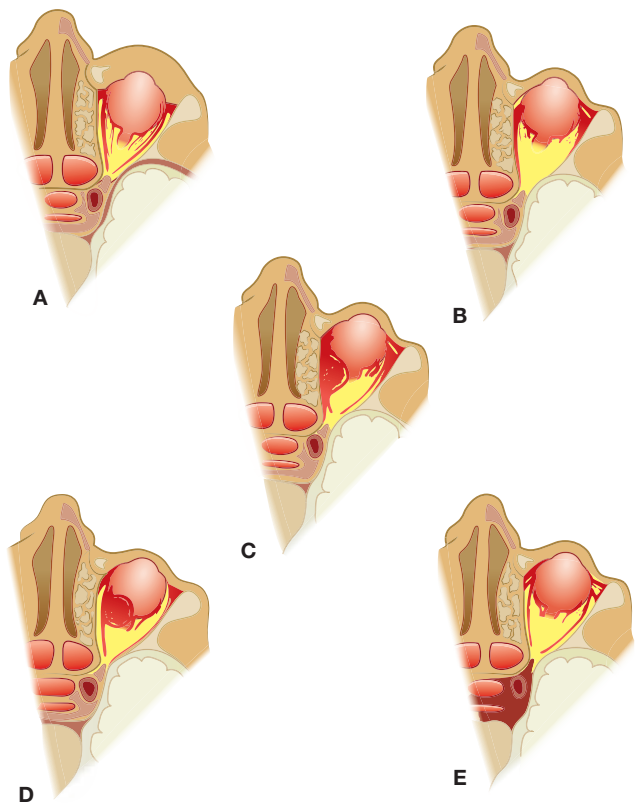

Figure 126-2 Orbital complications of sinusitis. **A.** Preseptal cellulitis. **B.** Orbital cellulitis. **C.** Subperiosteal abscess. **D.** Orbital abscess. **E.** Cavernous sinus thrombosis. *(Reproduced with permission from Chandler JR, Langenbrunner DJ, Stevens FR. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80(9):1414–1428.)*

many patients with abscess.[57] Antimicrobials should be directed at *S. aureus, S. pneumoniae*, other streptococcal species, and gram-negative bacilli (e.g., vancomycin plus ceftriaxone or ampicillin/sulbactam). The main indications for surgery are a poor response to antibiotic treatment, worsening visual acuity or pupillary changes, or evidence of an abscess, especially a large abscess (>10 mm in diameter) or one that fails to respond promptly to antibiotic treatment. "Pott's puffy tumor," or subperiosteal abscess of the frontal bone, is a complication of frontal sinusitis. Patients present with frontal pain and a tender, doughy swelling over the forehead. Treatment consists of 6 weeks of intravenous antibiotic therapy, and surgical drainage of the frontal sinus and subperiosteal abscess may be necessary.

Intracranial complications of sinusitis usually result from frontal or sphenoid sinusitis. These include epidural abscess, subdural empyema, meningitis, cerebral abscess, and dural vein thrombophlebitis. Because of the proximity of the sphenoid sinus to the cavernous sinus, sphenoid sinusitis also may cause cavernous sinus thrombophlebitis. Cavernous sinus thrombosis may occur as a complication of orbital infection (in which case ocular signs dominate the clinical picture with orbital pain, chemosis, proptosis, and oculomotor palsies) or sphenoid sinusitis. Symptoms and signs can be grouped in three major syndromes[58]

- Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
- Focal syndrome (focal deficits, seizures, or both)
- Encephalopathy (multifocal signs, mental status changes, stupor, or coma)

Magnetic resonance imaging (MRI) using gradient echo T2 susceptibility–weighted sequences in combination with MR venography is the most sensitive imaging method for demonstrating the thrombus. Although not definitive evidence, there is a general consensus that anticoagulation is the appropriate treatment. Broad-spectrum antimicrobials should be administered when there is evidence of active infection from the sinuses or the orbits.

FUNGAL SINUSITIS

Fungal sinusitis (see also Chapter 133) can be associated with four major forms[59]:

- Acute invasive sinusitis—risk factors include immunocompromised state, corticosteroids, diabetes with ketoacidosis and the most common pathogens are Aspergillus and the Zygomyces (e.g., Mucor spp.).
- Chronic invasive sinusitis—characterized by chronic symptoms and often invasion into bony structures and the orbit and possibly the brain; Aspergillus is seen most commonly.
- Mycetoma—fungus balls that do not invade the mucosa usually due to Aspergillus or dematiaceous fungus (e.g., Curvilaria, Alternaria, Cladosporium).
- Allergic fungal sinusitis (AFS)—allergic response to colonization of certain molds, mostly aspergillus; often associated with nasal polyps.

Patients with acute invasive disease are usually seriously ill. The diagnosis of acute invasive fungal sinusitis in an immunocompromised patient or diabetes is extremely urgent since it carries a significant risk of mortality (see also Chapter 123). Rhinocerebral mucormycosis is a life-threatening infection due to molds of the order Mucorales *(Rhizopus, Mucor, Absidia).* Approximately 70% of patients with mucormycosis have diabetes, whereas other risk factors include corticosteroid therapy or other immunosuppressant therapy, or hematological malignancies. Patients usually present with signs mimicking bacterial orbital cellulitis involving one eye, with swollen eyelids, proptosis, decreased extraocular movements, and decreased vision in that eye. If there are bilateral eye findings, involvement of the cavernous sinus should be suspected. Significant facial pain, headache, purulent or bloody rhinorrhea, and fever are commonly present. Progressive symptoms related to ophthalmic or CNS invasion may occur. CT and MRI scans are very useful in differentiating invasive from noninvasive infection and defining the extent of disease. Patients in whom the diagnosis is suspected should undergo immediate endoscopy by an otolaryngologist to look for a characteristic black eschar signifying infarcted intranasal or sinus mucosa. The eschar and adjacent tissue should be biopsied and examined for fungus on frozen section by a pathologist. Treatment of mucormycosis requires a combination of aggressive surgical debridement and intravenous amphotericin or liposomal amphotericin therapy. Voriconazole is not active against mucormycosis. Posaconazole is a new agent that may be effective in patients who fail debridement and amphotericin therapy.

Aspergillus and other fungi (e.g., *Bipolaris, Curvularia, Exserohilum*) may also cause invasive fungal sinusitis. Immunocompromised patients, such as those who have received organ transplants, usually present acutely. Treatment is aggressive surgical debridement and systemic antifungal therapy. Normal hosts, in contrast, usually present subacutely, with weeks to months of symptoms. Fungi in the ethmoid and sphenoid sinuses may invade the orbital apex and cavernous sinus, affecting cranial nerves III to VI. Symptoms include headache, unilateral retroorbital pain, proptosis, ptosis, limitation of eye movement, decreased vision, and hypesthesia in the distribution of cranial nerve VI on the affected side. Symptoms of sinusitis are often absent. Diagnosis is suggested by the clinical findings and CT and MRI scans showing inflammation in the orbital apex or cavernous sinus. The diagnosis is made by demonstrating tissue-invasive fungi on pathology. Treatment is with appropriate systemic antifungal therapy (e.g., voriconazole for *Aspergillus*). Unlike immunocompromised patients with invasive fungal disease or patients with rapidly progressive mucormycosis, nonimmunocompromised patients may not require extensive surgical debridement as the disease is slowly progressive, allowing time for assessment of antifungal therapy. A patient with chronic fungal infection usually present with facial pain and swelling, but the acuity of infection is much less than for acute invasive disease. Patients are usually afebrile. There is a high recurrence rate and it is not unusual that all infected tissue cannot be removed by surgical debridement. Thus, long-term antifungal therapy (e.g., an azole) is often required.

Sinus aspergilloma is a noninvasive fungal disease that may cause symptoms of obstruction and chronic sinusitis. Usually only one sinus (most often maxillary) is affected, and symptoms are therefore unilateral. Surgical removal of the fungus ball is usually curative. Careful review of the pathological slides is required to verify that there is no tissue invasion.

AFS is characterized by the presence of "allergic mucin" in the involved sinuses and is thought to be due to a local hypersensitivity reaction to fungi.[60,61] Mold spores are ubiquitous in the environment and in the nasal mucus, where they are trapped after being inhaled. Diagnostic criteria include: no underlying immunosuppression; presence of atopy, nasal polyps; allergic mucin found at surgery or endoscopy; and no invasion of mucosa or bone. Patients with AFS present with chronic sinusitis symptoms, and most have a history of nasal polyposis, aspirin allergy, and asthma. The CT typically shows inhomogeneous opacification of one or more sinuses, and there may be evidence of bony erosion of the sinus. Erosion is due to pressure necrosis, not fungal invasion. On MRI, the affected sinus often appears black on T2 ("T2-weighted signal void"), a finding also seen in other types of fungal sinusitis. The diagnosis of AFS may be suspected at surgery because allergic mucin is tenacious, with the consistency of anchovy paste. It has histological features similar to that of mucin found in allergic bronchopulmonary aspergillosis, with many eosinophils and Charcot–Leyden crystals. Fungal hyphae are found in the mucus of half of the cases, but there is no evidence of tissue invasion. Surgical removal of the inspissated mucus, along

with intranasal steroids or short courses of oral steroids, seems to be effective. There is no proven role for antifungal agents.

EAR AND MASTOID INFECTIONS

The spectrum of acute and chronic infections of the ear and mastoid is considered below.

OTITIS EXTERNA

The external auditory canal is about 2.5 cm long. It is lined by a thin layer of skin, which covers cartilage in the lateral half of the canal and bone in the medial half. In the bony portion, the skin lacks a subcutaneous layer and is attached directly to the periosteum; therefore, minimal inflammation of the bony canal causes significant pain and/or injury. Glands secrete cerumen, which acidifies the canal and suppresses bacterial growth. Desquamated skin and retained moisture make the canal especially susceptible to *Pseudomonas aeruginosa,* a hydrophilic organism.

Acute otitis externa, or swimmer's ear, occurs mostly in summer months and is often a result of exposure to water.[62,63] It may be due to a decrease in canal acidity and the resulting bacterial overgrowth. Any trauma such as from excessive probing of the ear canal with a cotton swab can also create abrasions along the thin layer of skin in the ear canal predisposing to infection. The ear is pruritic and often extremely painful; the canal appears swollen and red. Tenderness when the auricle is manipulated or pulled is an indicative finding of external otitis. The usual pathogens are *P. aeruginosa, S. aureus,* and streptococci; anaerobes have been implicated in some cases.[64] Treatment consists of cleaning the ear (aural toilet) and topical antibiotic drops. Topical antibiotics are highly effective for treating external otitis (e.g., a quinolone otic solution). One systematic review found that topical antibiotics increased absolute clinical cure rate compared to placebo by 46% (95% CI 29%–63%).[65] A meta-analysis of randomized trials, which included three studies comparing antimicrobial/glucocorticoid versus antimicrobial alone, found comparable clinical and bacteriological cure rates at 7 days for regimens with and without glucocorticoids.[66] The addition of a hydrocortisone to either acetic acid or ciprofloxacin, however, did decrease time to symptom resolution by 1 day. Acidifying the ear canal inhibits bacterial growth. Commonly used acidifying solutions are acetic acid, boric acid, hydrochloric acid, and sulfuric acid. Acidifying solutions are generally safe, but may be associated with local irritation manifested by burning or stinging. In the presence of tympanic membrane perforation, acidifying solutions can be particularly irritating to the mucosa of the middle ear. The ear should be protected from water during recovery from external otitis. This can be accomplished by placing a cotton ball coated with petroleum jelly in the ear canal while bathing.

Invasive ("malignant") otitis externa (MOE) is a potentially life-threatening osteomyelitis of the temporal bone and skull base. It occurs primarily in elderly diabetics but also found in immunocompromised patients (e.g., in HIV) and is nearly always caused by *P. aeruginosa.*[67] The infection begins in the external canal, then invades the adjacent soft tissues, petrous apex of the temporal bone, and eventually the skull base. The typical patient is an older diabetic whose diabetes is in good control, who presents with unilateral hearing loss, usually severe ear pain, and drainage progressive over the previous weeks to months. In one case-control study patients with MOE were more likely to have antecedent history of ear irrigation (generally for the purposes of removing cerumen) compared with matched controls.[68] The symptoms may have been misdiagnosed as chronic otitis media, a condition not characterized by otalgia. There is often a history of irrigation of the ear canal for wax removal a few days before the onset of ear pain. On examination, the ear canal is edematous, and there is granulation tissue in the inferior wall about halfway down the canal (the area overlying the bony-cartilaginous junction). As the infection advances, osteomyelitis of the base of the skull and temporomandibular joint osteomyelitis can develop. Progression of the osteomyelitis can be associated with cranial nerve palsies. Some patients also present with unilateral facial paralysis from involvement of cranial nerve VII; other cranial nerves (VI, IX, and X) may also be involved. Fever occurs in less than half of the patients and the white blood cell count is usually normal. The sedimentation rate is almost always very elevated, however, typically in the 80 to 100 range. A CT and an MRI scan are essential for defining the extent of involvement. Bony involvement is best seen on CT, while soft tissue changes are best seen on MRI. Cultures should be obtained of ear canal drainage or of superficial biopsies of canal granulation tissue; more extensive surgery is not usually indicated. Nearly all cases are due to *P. aeruginosa*, but cultures are important in determining antibiotic sensitivity and in excluding rare causes of invasive otitis (e.g., *S. aureus, Proteus, Aspergillus*). As soon as cultures are obtained, empiric treatment directed at *Pseudomonas* should be started (e.g., anti-pseudomonal β-lactam; or anti-pseudomonal quinolone) and therapy is continued for at least 6 weeks. Aminoglycosides should be avoided due to the toxicities associated with therapy, especially in the elderly diabetics with hearing loss who typify the patient with MOE.

■ ACUTE OTITIS MEDIA

AOM is the most common bacterial infection seen in pediatric patients, and treatment of AOM is the most common reason children receive antibiotics.[69] AOM follows eustachian tube dysfunction, which is most often seen with a viral upper respiratory infection. The middle ear is connected to the nasopharynx by the eustachian tube. AOM (Fig. 126-3), or infection of the middle ear, is thought to result from bacterial entry into the middle ear via the eustachian tube. It is often initiated by a viral upper respiratory infection, and is most common in fall through spring. The incidence of AOM decreases with age. More than two-thirds of children under age 3 have had at least one episode of otitis media, while the incidence in adults is only 0.25%. There are several risk factors for AOM (Table 126-5). The most common symptoms are ear pain and decreased hearing. Children often have fever, but this is less common in adults. There are two parts to establishing the diagnosis of AOM: evidence of middle-ear effusion and abnormalities of the tympanic membrane that indicate inflammation. Both must be present for diagnosis to be confirmed. The tympanic membrane is usually red, opaque, and bulging. Spontaneous perforation of the tympanic membrane may occur, resulting in otorrhea and, frequently, decreased pain. *S. pneumoniae*, nontypable *H. influenzae*, and *M. catarrhalis* are the leading pathogens. Whereas viruses play a pivotal role in predisposing the host, middle-ear taps of children with AOM rarely yield a viral pathogen alone.

Of all the features associated with AOM, establishing appropriate therapy has recently undergone the greatest change and yet is associated with the most significant controversy. Most notably, many experts have advocated that selected patients might appropriately be observed and not treated with antibiotics. However, randomized trials suggest that signs and symptoms of AOM resolved more quickly in children and the risk of perforation with otorrhea is reduced in those initially treated with antibiotics compared with placebo.[70,71] The decision to withhold antibiotic therapy should be reserved for patients otherwise healthy, >2 years of age, with mild illness. Treatment of AOM is usually empiric and should be directed against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Approximately 50% of *H. influenzae* strains and 100% of *M. catarrhalis* strains produce β-lactamase, and approximately 30% of *S. pneumoniae* are not susceptible to penicillin (15% are highly resistant) due to altered penicillin-binding protein. Amoxicillin should not be effective for any of these resistant organisms, yet approximately 20% of children with *S. pneumoniae*, 50% with *H. influenzae*, and 75% with *M. catarrhalis* will clear their AOM despite no or ineffective antibiotic therapy.

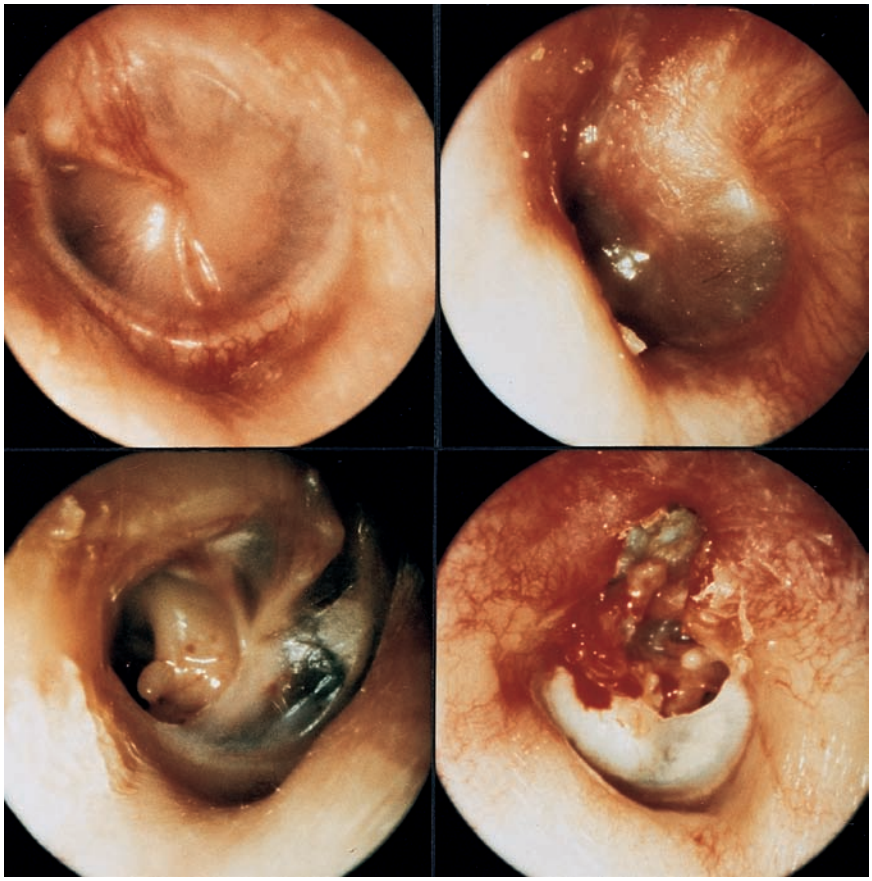

Figure 126-3 Clockwise, from top left, tympanic membranes: normal ear, resolving acute otitis media, chronic suppurative otitis media (CSOM) with cholesteatoma, CSOM without cholesteatoma. *(Used with permission of Steven D. Rauch, MD.)*

Therefore, recent practice guidelines by the American Academy of Pediatrics recommend amoxicillin as first-line therapy for most children with AOM at doses of 80 to 90 mg/kg per day. Amoxicillin–clavulanate is recommended for children who present with severe disease, defined as fever of 39°C (102.2°F) or higher and/or severe otalgia, or for amoxicillin-treatment failures as determined at 48 to 72 hours. For most children with non-type I allergy to penicillin, cephalosporins (cefdinir, cefpodoxime, cefuroxime) are recommended, and azithromycin or clarithromycin is recommended for those with type I allergy. Ceftriaxone is recommended for children with severe disease and who are either penicillin-allergic with a non-type I penicillin allergy or who have failed initial antibiotic therapy with amoxicillin–clavulanate. Clindamycin is recommended in patients who have failed therapy and have a type I allergy to penicillin.

TABLE 126-5 Major Risk Factors for Acute and Recurrent Otitis Media

Onset of otitis media in infancy
Male gender
Sibling with recurrent acute otitis media
Bottle feeding only
Parents who smoke at home
Daycare attendance
Craniofacial anomalies

OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME), also called serous otitis, refers to the persistence of middle-ear fluid without symptoms or other signs of infection.[72] This condition may occur spontaneously as a result of eustachian tube dysfunction, or may occur as a result of AOM. Approximately 50% of children will have OME in the first year of life, and 90% before school age. Diagnosis is made by otoscopy. The majority of episodes resolve spontaneously, but 30% to 40% have recurrent OME and 5% to 10% have OME episodes that last at least 1 year. The American Academy of Pediatrics published practice guidelines in 2004 that state that antihistamines and decongestants are ineffective, and that antibiotics and corticosteroids have no long-term efficacy and thus are not recommended routinely for treating OME. These guidelines recommend hearing tests for children with persistent OME at 3 months; decisions regarding the need for tympanostomy tube placement may be determined by these test results. Children with OME at special risk for developmental delays (e.g., who also have blindness, autism, Down syndrome) should have earlier hearing, speech, and language assessments.

CHRONIC SUPPURATIVE OTITIS MEDIA

Chronic suppurative otitis media (CSOM) is an inflammatory disease of the middle ear and mastoid characterized by tympanic membrane perforation, hearing loss, and persistent or recurrent otorrhea.[73] It is associated with irreversible pathological changes of the mucosa of the middle ear and mastoid. There are two major subtypes of CSOM: CSOM with cholesteatoma and CSOM without cholesteatoma.

In CSOM with cholesteatoma, there is a perforation of the tympanic membrane, usually at the margin, which leads into a sac within the middle ear lined by skin. This sac constitutes a cholesteatoma, which contains desquamated keratin and may be superinfected with bacteria. Bacterial overgrowth results in purulent drainage via the perforation. An important feature of a cholesteatoma is its ability to enlarge by erosion of surrounding bone, which can result in serious intratemporal and intracranial complications. In CSOM without cholesteatoma, there is a chronic central perforation of the tympanic membrane. Bacterial infection of the middle ear or mastoid can occur and leads to purulent drainage through the perforation ("active" chronic otitis media). Such drainage may be constant or episodic. The latter may be incited by an upper respiratory infection or by exposure of the ear canal to water.

The classic symptoms of both types of CSOM are painless otorrhea and hearing loss. Diagnosis is made with otoscopy, which reveals otorrhea in the presence of a perforated tympanic membrane. The appearance of the tympanic membrane varies with the type of CSOM (Fig. 126-3). Audiological assessment usually reveals a conductive type of hearing loss. Cultures of ears with CSOM in both adults and children often yield *S. aureus, Pseudomonas* and other gram-negative bacilli, and anaerobes. Most cases of CSOM with cholesteatoma require a mastoidectomy and tympanoplasty to remove the cholesteatoma and reconstruct the middle-ear sound transmission mechanism. Cases of "active" CSOM without cholesteatoma are treated with

ear cleaning and topical antibiotic otic drops (e.g., a quinolone otic agent). Oral antibiotics are also sometimes used. The choice of antibiotics should be guided by culture results from the purulent middle-ear drainage, but most cases are treated empirically with a topical quinolone (e.g., ofloxacin 0.3% otic solution). Topical quinolones have proven to be nonototoxic and effective. Topical aminoglycoside therapy, commonly used in the past, is used infrequently now due to concern for ototoxicity.[74] Surgery is indicated for patients who develop complications of chronic otitis, to remove infected tissue in the middle ear or mastoid, and to repair ear damage that results in hearing loss. Cholesteatoma removal is typically performed in conjunction with tympanoplasty and, if the lesion extends superiorly or posteriorly, mastoidectomy.[63] Surgery may be indicated in some cases of CSOM without cholesteatoma if medical therapy fails to control otorrhea or if surgery will improve hearing.

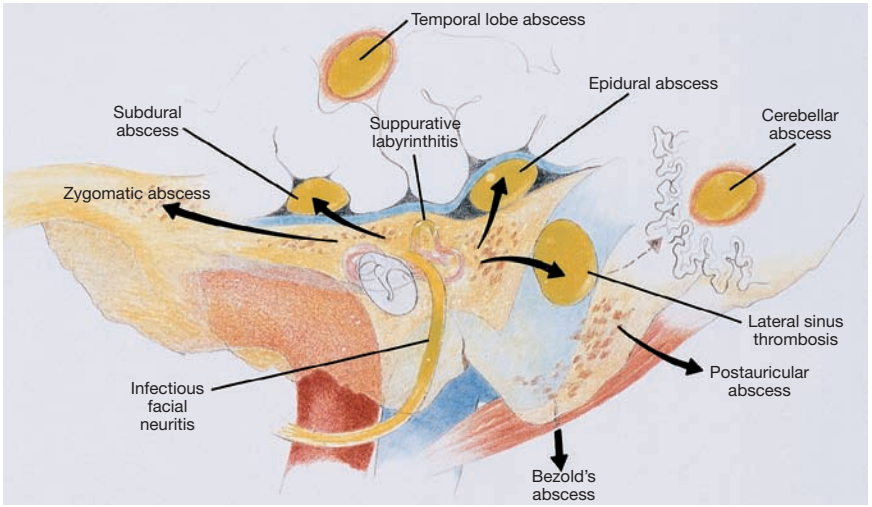

Figure 126-4 Complications of chronic otitis media. *(Reproduced with permission from Nadol JB, Schnuknecht HF. Surgery of the Ear and Temporal Bone. New York, Raven Press, 1993.)*

■ ACUTE MASTOIDITIS

The mastoid is the portion of the temporal bone posterior to the middle ear that contains a honeycomb of air cells lined by low, cuboidal epithelium. These air cells connect with the middle ear. Some degree of mastoid mucosal inflammation invariably accompanies episodes of AOM and is also present in many cases of CSOM. A CT scan of a patient with a middle-ear effusion or infection will often also show opacification of the mastoid air cells without destruction of the cells, and this usually represents a sterile effusion in the mastoid rather than acute mastoiditis. In contrast, acute mastoiditis is an acute bacterial infection of the mastoid. Untreated, this infection often results in breakdown of the bony partitions between the mastoid air cells and can extend beyond the mastoid compartment. Acute mastoiditis has become rare in the antibiotic era, and occurs primarily in children.[75] Studies evaluating the incidence subsequent to utilization of the strategy of a nonantimicrobial, observational approach in selected patients with AOM has been conflicting.[76–78] It occurs with the first episode of AOM in 10% to 50% of children, but may also occur with an episode of recurrent AOM. Patients present with pain, tenderness, and swelling over the mastoid. Fever is common. The pinna is pushed out and forward when there is a subperiosteal abscess or cellulitis. A CT scan may demonstrate bony destruction or a mastoid abscess. Major pathogens include *S. pneumoniae*, GAS, *H. influenzae, and S. aureus. Pseudomonas aeruginosa* and enteric gram-negative bacilli are also and should be considered especially if a history of recurrent AOM and recent antibiotic use. Antimicrobial therapy directed at the likely organisms (e.g., vancomycin plus cefepime or piperacillin/tazobactam if risks for gram-negative bacilli) and drainage of the middle ear and mastoid are the cornerstones of therapy for acute mastoiditis.

■ COMPLICATIONS OF ACUTE AND CHRONIC OTITIS MEDIA

Otogenic complications are more likely to occur from chronic otitis media than from AOM (Fig. 126-4). Extracranial complications include sensorineural hearing loss, labyrinthitis and the resulting vertigo, facial nerve palsy, and osteomyelitis of the petrous portion of the temporal bone. In mastoiditis, infection may track under the periosteum of the temporal bone and cause a subperiosteal abscess, or may break through the mastoid tip and cause an abscess in the neck deep to the sternocleidomastoid muscle (Bezold abscess). Intracranial complications include epidural abscess, thrombophlebitis of the dural veins, meningitis, and temporal lobe abscess.

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CHAPTER 127

Aspiration, Empyema, Lung Abscesses, and Anaerobic Infections

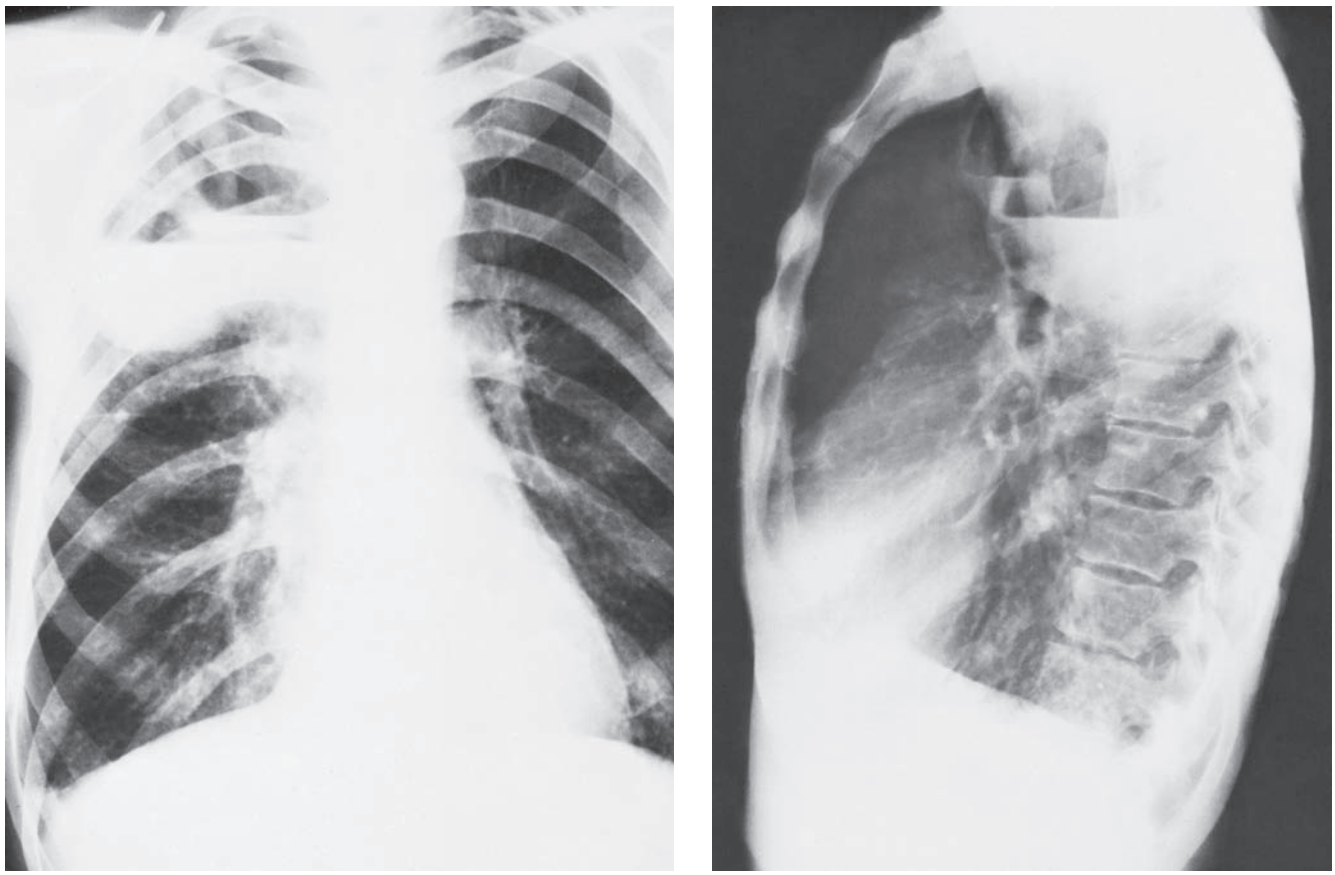
Kyle B. Enfield
Costi D. Sifri

OVERVIEW

Aspiration pneumonia, lung abscess, and necrotic lung are parenchymal lung diseases. Aspiration pneumonia refers to the pulmonary consequences that follow abnormal entry of fluid, particulate substances, or endogenous secretions from the upper airways or gastric contents into the lower airways (see also Chapter 69). To develop aspiration pneumonia, a series of formidable host defense mechanisms that normally protect the lower airways must be overcome, including glottic closure via the cricopharyngeus muscle, the cough reflex, ciliary clearance, and other defense mechanisms. The material aspirated must generate an inflammatory response or cause obstruction. The nature of the pneumonia that develops depends on the inoculum and the host response. Anaerobic bacteria are the most common pathogens in this setting, reflecting both pathogenic potential and importance in the normal flora of the upper airways. Risk factors for aspiration may be transient (anesthesia, intoxication) or persistent (e.g., neuromuscular disorders, achalasia) with the risk for recurrence depending on recognition and resolution of the inciting defect.[1,2]

Lung abscesses reflect infection with an unusual microbial burden (e.g., acute aspiration), a failure in microbial clearance mechanisms (e.g., bronchial obstruction), or both, leading to necrosis of pulmonary tissue and formation of cavities containing necrotic debris or fluid (Fig. 127-1). The formation of multiple smaller (less than 2 cm) abscesses in pulmonary tissue is occasionally referred to as necrotizing pneumonia or lung gangrene. Both lung abscess and necrotizing pneumonia are manifestations of the same pathologic processes, and the distinction is, therefore, arbitrary.[3]

Empyema refers to a purulent collection in any body site but is commonly used to indicate infection of the pleural space.[4] Empyema is typically associated with underlying pulmonary parenchymal



A B

Figure 127-1 **A.** Anaerobic pneumonia with abscess formation in a 48-year-old alcoholic man. The abscesses are located in the posterior segment of right upper lobe, a dependent segment that is seen best on lateral view (**B**).

infection but may also be associated with blood-borne infection, thoracic surgery, trauma, abdominal infection, or neoplasm.[3] Failure to recognize and treat either empyema or lung abscess is associated with a poor clinical outcome.[5,6] In the preantibiotic era, lung abscess was associated with a mortality approaching 40%.[7] However, controversy exists over the best approaches to both processes in terms of antimicrobial selection and physical drainage.[5,6]

HISTORY

In 1893, Veillon[8] published a review of "fetid infections," first marking the published record of infections due to anaerobic pathogens. However, anaerobes are now largely forgotten potential pathogens in pulmonary infection, including in both community- and healthcare-associated pneumonia.[1] The clinical and bacteriologic features of anaerobic infections of the lung have been documented by extensive studies during two periods of investigation.[1] The first was at the turn of the century, when anaerobic bacteria were initially reported as important causes of empyema. This early work continued through the late 1920s, when David Smith conducted classic studies on the pathogenesis of lung abscess. At that time, approximately one-third of patients with lung abscess died. Smith noted that the bacteria in the walls of the abscess at autopsy resembled the bacteria found in the gingival crevice, leading him to conclude that aspiration was the major mechanism in pathogenesis. He subsequently supported this hypothesis by inoculating the trachea of experimental animals with gingival crevice material to reproduce the sequence of events of pneumonitis, followed by lung abscess formation in 7 to 10 days.[9] Bacteriologic studies of the inoculum showed that four bacterial species were critical, and all were anaerobic bacteria: a fusiform bacterium now recognized as *Fusobacterium nucleatum*, *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*), *Peptostreptococcus*, and an anaerobic spirochete. This study is one of the first demonstrations of bacterial synergy, defined as the demonstration that two or more bacterial species are required to produce a pathologic process that could not be reproduced by any single component of the inoculum.[9]

In the first two or three decades of the antibiotic era, the role of anaerobic bacteria in this and other pathologic processes was largely ignored. Patients with lung abscesses often had putrid sputum and no identifiable pathogen; these infections were frequently referred to as nonspecific lung abscess. Although the microbial cause was unknown, it was well established that these patients almost invariably responded to penicillin treatment. The role of anaerobes in empyema was also largely ignored. Much of this neglect is ascribed to the paucity of laboratories capable of cultivating oxygen-sensitive bacteria. Studies of anaerobic bacteria were spawned by the ability to culture anaerobes in clinical laboratories with the introduction of anaerobic gas–generating culture jars, the description of the taxonomy of these organisms, and the availability of new antimicrobial agents (clindamycin, metronidazole, cefoxitin) for the therapy. The introduction and widespread use of transtracheal aspiration (TTA) in the late 1960s made it realistic to collect uncontaminated specimens from the lower airways that could be used for anaerobic cultures. TTAs are seldom performed today, so anaerobic bacteria are rarely established as pulmonary pathogens. These organisms are often suspected on the basis of the etiologic route of infection (e.g., oropharyngeal flora) and their importance in patients with aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema.[1]

PATHOPHYSIOLOGY OF ASPIRATION, EMPYEMA, AND LUNG ABSCESS

The bacteria implicated in anaerobic lung infections represent the normal flora of the oral cavity—primarily the gingival crevice, where anaerobic bacteria are found in concentrations that approach the geometric limits with which bacteria occupy space: 10^{12}/g.[10] Compromised consciousness or dysphagia is the most frequently predisposing risk factor for clinically significant aspiration. Common conditions associated with clinically significant aspiration include alcoholism, general anesthesia, seizure disorder, drug abuse, esophageal lesions, hepatic failure with decreased level of consciousness, and neurologic deficits associated with dysphagia.[11]

Additional conditions that appear to predispose to anaerobic infections include pulmonary infarction, obstruction due to carcinoma or a foreign body, and bronchiectasis. These conditions are associated with stasis or necrosis of tissue, which presumably accounts for the association with anaerobic infections. The use of acid suppressing medication has also been associated with community-acquired, hospital-acquired, and ventilator-associated pneumonia, presumably due to loss of the gastric acid barrier to bacterial growth.[12–14]

A somewhat unique feature of anaerobic lung infections is the proclivity for necrosis of tissue, resulting in abscess formation or a bronchopleural fistula associated with empyema.[15] Virulence factors of anaerobic bacteria presumed to account for this association include the capsular polysaccharide of anaerobic gram-negative bacilli. The most extensively studied is the polysaccharide of *Bacteroides fragilis*, but the same observations may apply to *P. melaninogenica* and other anaerobic gram-negative bacilli.[16,17] The capsule of *B. fragilis* consists of a family of polysaccharides composed of oligosaccharide repeating units with sugars containing positively charged free amino groups and negatively charged carboxyl, phosphate, and amino groups.[18–20] These positive and negative charges mediate the capacity to induce abscess formation in experimental animals.[21,22] Another virulence factor possessed by most anaerobic bacteria is the production of short-chain fatty acids that inhibit phagocytic killing at low pH levels.[23,24] Short-chain volatile fatty acids are metabolic products of anaerobic bacteria that are used to classify these organisms taxonomically, and they appear to be responsible for the putrid odor that is often a characteristic feature of infections by these organisms.[25,26]

MICROBIOLOGY

Bacteriologic findings of anaerobic lung infections from two large series are summarized in Table 127-1. Most of these infections involve multiple bacterial species, and approximately half of the patients have anaerobic bacteria combined with potentially pathogenic aerobic or facultative anaerobes. Analysis of community-acquired infections involving only anaerobes versus those that are mixtures of aerobic and anaerobic bacteria shows common clinical features with no difference in terms of the frequency of suspected aspiration, indolent presentation, or the frequency of putrid discharge. The implication is that a putrid lung abscess with *Escherichia coli* in expectorated sputum or anaerobic bacteria plus *E. coli* in a TTA should usually be considered an anaerobic infection. Caution is advised in applying these conclusions to nosocomial pulmonary infections, since this is a setting in which the aerobic component of the infection is probably more important.

The establishment of anaerobic bacteria in pulmonary infections requires specimens of respiratory secretions that are devoid of contamination from the upper airways. The usual procedures satisfying this criterion are TTA, transthoracic aspiration, open lung biopsy, thoracentesis, and more recently, bronchoscopy with quantitative cultures. In addition, there must be appropriate laboratory expertise for the cultivation of anaerobic bacteria. The incidence of anaerobic lung infections reported in published studies from the antibiotic era that satisfy both requirements is summarized in Table 127-2.

TABLE 127-1 Bacteriology of Anaerobic Lung Infections

	Bartlett	Marina et al.
Period reviewed	1968–1975	1976–1991
Patients	193	110
Total anaerobic isolates	461	404
Major isolates		
Gram-negative bacilli		
Bacteroides fragilis group	38[a]	18
Pigmented Prevotella[b]	76	63
Nonpigmented Prevotella	—	40
Bacteroides ureolyticus	—	23
Fusobacterium nucleatum	56	34
Bacteroides spp. (other)	37	138
Peptostreptococcus/peptococcus[c]	126	39
Gram-positive bacilli		
Clostridium spp.	18	12
Eubacterium spp.	18	22
Actinomyces	5	1
Lactobacillus	8	22
Propionibacteria	10	9

[a] *Numbers indicate the total number of isolates. Some of the differences are due to taxonomic changes.*
[b] *Pigmented Prevotella refers to organisms previously classified as B. melaninogenicus.*
[c] *Most peptococci have been reclassified as Peptostreptococcus.*

Most published reports deal with the role of anaerobic bacteria in aspiration pneumonia or lung abscess, and these show recovery rates ranging from 62% to 100%. The usual specimens in these studies are TTA and transthoracic aspiration. One of the best studies is by Beerens and Tahon-Castel,[27] who used transthoracic needle aspiration to characterize the flora in lung abscesses; this series showed recovery of anaerobic bacteria, usually in pure culture, in 22 (85%) of 26 cases.

The major bacterial isolates in patients with anaerobic lung infections are *Peptostreptococcus*, *F. nucleatum*, and *P. melaninogenica*. Aerobic and microaerophilic streptococci are commonly present and may contribute to the pathogenic events. At least 15% to 25% of anaerobic bacteria responsible for lung infections are resistant to penicillin, generally due to penicillinase production. These susceptibility data are rarely available in individual cases unless specifically requested.

There have been few studies to identify the frequency of anaerobic bacteria in unselected cases of community-acquired pneumonia. One was by Ries et al.,[28] who performed TTAs in patients hospitalized with a diagnosis of pneumonia and recovered anaerobic bacteria in 29 (33%) of 89 cases. A more recent study by Pollock et al.,[29] using fiberoptic bronchoscopy with a protected catheter and quantitative cultures, showed recovery of anaerobes in 16 (22%) of 74 patients. These two reports suggest that anaerobic bacteria are relatively common pathogens among patients with community-acquired pneumonia and presumably account for a substantial proportion of cases that are now considered enigmatic. In nosocomial pneumonia, a study by Bartlett et al.[30] utilized TTA in 159 consecutive patients and showed anaerobes in 56 (35%). Nevertheless, most of these patients also showed the concurrent presence of aerobic gram-negative bacilli or *Staphylococcus aureus*, and their clinical course was determined largely by the aerobic pathogens.

TABLE 127-2 Incidence of Anaerobic Infection of the Lung

Number of Patients			
With Anaerobes	Total	Percent	Reference
Lung abscess			
53	57	93	Bartlett et al.[30]
22	26	85	Beerens and Tahon-Castel[27]
9	10	90	Brook and Finegold[101]
37	41	90	Gudiol et al.[102]
Aspiration pneumonia			
61	70	87	Bartlett et al.[30]
17	17	100	Gonzales-C and Calia[103]
29	47	62	Lorber and Swenson[82]
69	74	93	Brook and Finegold[101]
Empyema			
63	83	76	Bartlett et al.[30]
23	45	51	Beerens and Tahon-Castel[27]
28	72	39	Sullivan et al.[104]
Community-acquired pneumonia			
28	89	33	Ries et al.[28]
16	74	22	Pollock et al.[29]
Nosocomial pneumonia			
56	159	35	Bartlett et al.[30]

CLINICAL FEATURES

Nearly all patients with anaerobic lung infections have the usual constitutional findings for patients with infection (Table 127-3). A review of 193 bacteriologically confirmed cases showed that the mean peak temperature for hospitalized patients was 39.1°C and all but five patients were febrile. The average peripheral leukocyte count was 15,000/mL^3. Patients who presented with the suppurative complications had a longer duration of symptoms before presentation; this was commonly associated with other evidence of chronic disease, including weight loss and anemia. Another common feature of patients with suppurative complications was putrid sputum or empyema fluid, which was noted in 40% to 60%. It should be emphasized that the putrid discharge in these cases is considered diagnostic of anaerobic infection, since aerobic bacteria are not capable of producing this characteristic odor either *in vitro* or *in vivo*. Thus, anaerobic bacteria may cause a diverse range of pulmonary infections, which may be acute, subacute, or chronic. The anaerobic etiology is rarely established or even suspected in patients with acute pneumonitis. This compares with aspiration pneumonia, where anaerobes are presumed pathogens in most community-acquired infections and may contribute to many nosocomial cases. By contrast, anaerobic bacteria are readily recognized as probable pathogens in patients who have the late suppurative complications, such as lung abscess or empyema.

One review of 46 patients with anaerobic bacterial pneumonitis showed clinical features that were similar to those of pneumococcal pneumonia.[31] The diagnosis was established by TTA, and the results in this group were compared with those in a second group of patients in whom TTAs yielded *Streptococcus pneumoniae*. The two groups were similar in terms of age, changes on the chest radiograph, peak temperature, and peripheral leukocyte count. Significant differences in the group with anaerobic infections were the lack of rigors, a somewhat longer duration of symptoms before presentation, and a more frequent association with predisposing conditions for aspiration.[31] An important point to emphasize is that patients seen in this early stage of infection rarely have the features that are commonly associated with anaerobic lung infections, such as putrid sputum, tissue necrosis with abscess formation, or a chronic course. These infections presumably account for some and possibly many of the cases of community-acquired pneumonia in which no etiologic diagnosis is established despite extensive study; such cases account for 40% to 50% of cases in most series. Features of anaerobic infections that are nearly unique are the association with conditions that predispose to aspiration and infection in the gingival crevice, putrid discharge, and a high frequency of suppurative complications in late-stage disease.

ASPIRATION SYNDROMES

Aspiration is a relatively common event that is typically well tolerated. Numerous studies indicate that virtually all healthy persons aspirate, but that this is usually inconsequential. In one study, airway protective mechanisms were challenged by placing contrast material in the mouths of sleeping patients. The following morning, most patients had radiographic evidence of aspiration, defined as contrast material seen on imaging of the lungs, but no evidence of a disease process.[32] Similarly, dye markers placed in the stomach of postoperative patients has later been aspirated from the tracheobronchial tree, indicating aspiration of gastric contents during general anesthesia in 7% to 16%.[33,34] Scintigraphic methods have also been used to demonstrate frequent aspiration in patients with intubation of the airways or gastrointestinal tract.[35,36] None of these studies, however, have demonstrated any clinical consequences from occult aspiration. The conclusion is that aspiration is relatively common but

TABLE 127-3 Clinical Features of Anaerobic Pulmonary Infections[a]

	Lung Abscess (83 pts)	Empyema (51 pts)	Pneumonitis (only) (79 pts)	Total (193 (pts)
Age (median)	52 y	49 y	60 y	51 y
Peak temperature (mean, °F)	102.1	102.4	102.6	102.4
Peripheral leukocyte count (median/mm)	15,000	21,600	13,700	15,000
History of weight loss	36 (43%)	28 (55%)	3 (4%)	57 (30%)
Putrid discharge	41 (49%)	32 (63%)	4 (5%)	62 (32%)
Lethal outcome	3 (4%)	3 (6%)	3 (4%)	8 (4%)

[a]*Based on retrospective chart review of 193 cases established by recovery of anaerobes as dominant flora in TTA, pleural fluid, or blood culture.*

Source: Data from Bartlett JG. Anaerobic bacterial infections of the lung. Chest. 1987;91:901–909; Bartlett JG. Anaerobic bacterial infections of the lung and pleural space. Clin Infect Dis. 1993;16:S248–S255; Marina M, Strong CA, Civen R, et al. Bacteriology of anaerobic pleuropulmonary infections: Preliminary report. Clin Infect Dis. 1993;16:S256–S262.

TABLE 127-4 Classification of Aspiration Pneumonia

Inoculum	Pulmonary Sequelae	Clinical Features	Therapy
Acid breathing	Chemical pneumonitis	Acute dyspnea, tachypnea; tachycardia; cyanosis, bronchospasm, fever Sputum: pink, frothy Radiographic infiltrates in one or both lower lobes Hypoxemia	Supplemental oxygen, bronchodilators, mechanical ventilation as needed
Oropharyngeal bacteria	Bacterial infection	Usually insidious onset Cough, fever, purulent sputum Radiographic infiltrate in dependent pulmonary segment or lobe ± cavitation	Antibiotics
Inert fluids	Mechanical obstruction Reflex airway closure	Acute dyspnea, cyanosis ± apnea Pulmonary edema	Tracheal suctioning, supplemental oxygen, mechanical ventilation as needed
Particulates	Mechanical obstruction	Dependent on level of obstruction, ranging from acute apnea and rapid death to irritating chronic cough ± recurrent superimposed infections	Extraction of matter Antibiotics for infection

usually resolves spontaneously. The decisive factor for the development of lung complications depends on the frequency, volume, and character of the material in the inoculum. The aspiration of large volume or frequent aspirations lead to three distinct syndromes according to the nature of inoculum: chemical pneumonitis, bacterial infection, and airway obstruction. The nature of inoculum also dictates the pathogenesis of pulmonary complications, clinical presentation, and management strategies (Table 127-4).

CHEMICAL PNEUMONITIS

Chemical pneumonitis refers to aspiration of an inoculum that is inherently toxic to the lungs. Examples include acid, animal fats such as milk and mineral oil, and volatile hydrocarbons. These substances are toxic to the lower airways and initiate an inflammatory reaction. The effect of acid on the lungs was initially described in animal studies in World War I and subsequently confirmed in humans by Mendelson. His work was the first to describe gastric acid pneumonitis leading to chemical pneumonitis in humans, which came to be referred to as Mendelson's syndrome.[37] This is a severe pneumonitis with fever, hypoxia and respiratory alkalosis, which typically clears rapidly in healthy hosts within 4 to 7 days but may progress following lung injury and superinfection to pneumonia, lung abscess, or acute respiratory distress syndrome (ARDS) (see Chapters 140 and 141). Factors that contribute to hypoxemia are pulmonary edema, reduced surfactant activity, reflex airway closure, hyaline membrane formation, and alveolar hemorrhage. Pulmonary function tests show decreased compliance, abnormal ventilation–perfusion, and reduced diffusing capacity.[2] The pathophysiology of gastric acid pneumonitis has been studied in experimental animals with intratracheal instillation of graded acid inocula. This work shows that the pH must be 2.5 or less, and a relatively large inoculum, usually a minimum of 0.3 to 0.6 mL/kg, is required for the inflammatory process to be initiated.[38–41] It is possible that smaller volumes initiate a less dramatic presentation or may go undetected.[39,41] Support for this hypothesis is the observation of frequent bouts of pneumonitis and otherwise unexplained pulmonary fibrosis in patients with gastric reflux or esophageal disease.[42–44]

Pathologic changes in acid pneumonia occur rapidly. Atelectasis occurs within seconds and is extensive within minutes. There is also peribronchial hemorrhage, pulmonary edema, and bronchial epithelial cell degeneration. The alveolar spaces fill with neutrophils within hours and hyaline membranes are seen within 48 hours. Resolution begins by the third day and may be complete or may result in residual scarring of the pulmonary parenchyma.[45,46] Long-term follow-up studies in patients who have gastric acid pneumonia show either complete recovery or radiographic evidence of pulmonary fibrosis with abnormal gas exchange.[47,48] Pulmonary fibrosis may also be associated with repeated, small, "silent" aspirations of gastric secretions without clinically overt pneumonitis (see Chapters 56 and 57). [42,49]

The diagnosis of acid pneumonia is usually presumed on the basis of clinical observations such as the abrupt onset of dyspnea in a patient who is aspiration prone and has radiographic evidence of infiltrates, usually in the lower lobes. Other characteristic clinical features are the rapid clearing of the infiltrates and progression to ARDS.[46,50] Bronchoscopy demonstrates erythema of the bronchi, suggesting a "chemical burn."[51] Confirmation of the acid inoculum is not possible because of rapid neutralization by pulmonary edema fluid and bronchial secretions within minutes after aspiration.

The treatment of gastric acid aspiration includes tracheal suction to clear fluids and particulate matter that may have been concurrently aspirated. Supportive care consists primarily of ventilatory support with positive pressure ventilation and resuscitation with intravenous fluids.[46,52] While use of corticosteroids dates back to the 1950s, clinical trials have not shown them to be beneficial.[53–55] Antimicrobial agents are reserved for superinfection.

ASPIRATION PNEUMONIA

While not as fulminant as chemical pneumonitis,[56] bacterial infection following aspiration is associated with an increased risk of prolonged hospitalization and death.[57,58] In the preantibiotic era, the natural history of these infections could be followed. The initial presentation was similar to chemical pneumonitis, usually combined with purulent sputum. After 8 to 14 days, progression to tissue necrosis with abscess formation or extension into the pleural space may occur. This stage is marked by putrid discharge and cavitation.[59–61] The distinction between aspiration pneumonia and other forms of pneumonia is largely based on the clinical characteristics, but clear overlaps exist. For example, healthy elderly patients with community-acquired pneumonia have a markedly higher incidence of silent aspiration than matched control patients.[62] While no gold standard for the diagnosis of aspiration exists, studies suggest that 5% to 15% of community-acquired pneumonia may be due to aspiration.[11,63,64] The incidence of aspiration pneumonia in elderly patients with community-acquired pneumonia may be much

higher.[65,66] The diagnosis of aspiration pneumonia is often inferred from patient characteristics. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum, and patients with necrotizing pneumonia or lung abscess on chest radiograph.[46,67–69]

MECHANICAL OBSTRUCTION

Aspiration may involve fluid or particulate material. In this form of aspiration pneumonia, the inoculum is not toxic to the lung but may cause obstruction or reflux airway closure. In most cases there is only transient, self-limited hypoxemia due to rapid clearance.[45] Some patients develop pulmonary edema, with hypoxemia and reduced compliance apparently due to an intrinsic pulmonary reflex closure.[45] Other patients suffer sequelae due to failure to clear relatively large volumes of the aspirate, such as near-drowning victims and patients with profound neurologic deficits or in coma. The obvious critical intervention is tracheal suction.

Aspiration with mechanical obstruction may also be associated with solid particles. Foreign-body aspiration is most frequent in children 1 to 3 years of age.[70–72] The most common objects in the lower airways are vegetable particles, inorganic materials, and teeth.[70–72] The severity of the obstruction depends on the relative size of the material aspirated and the caliber of the lower airways. Large objects may cause obstruction at the level of the larynx or trachea, leading to sudden respiratory distress, cyanosis, stridor, and in some cases, aphonia.[73,74] This is referred to as café coronary syndrome because it often involves meat aspiration during restaurant dining and may simulate an acute myocardial infarction.[75] Aspiration of smaller particles may result in complete obstruction of more distant components of the tracheobronchial tree or partial obstruction. Chest radiographs often show atelectasis or obstructive emphysema.[76] Common symptoms include chronic cough, fever, hemoptysis, and dyspnea.[77,78] An important clue in some cases is unilateral wheezing.[79] Bacterial infection is not important in the early stages of obstruction but is a common feature when obstruction has been present for more than 1 week.[80] The most common pathogens are anaerobic bacteria from the upper airways. These patients may respond well to antibiotics, but often have recurrent infections in the same pulmonary segment.[70] The most important therapeutic intervention is removal of the foreign body, usually with bronchoscopy.[71]

RADIOLOGIC DIAGNOSIS

Chest radiographs in patients with anaerobic lung infections typically demonstrate infiltrates (with or without cavitation) involving dependent pulmonary segments.[1,46] The favored locations are the superior segment of the lower lobes or posterior segments of the upper lobes; these are dependent in the recumbent position. The basilar segments of the lower lobes are favored in patients who aspirate in the upright position. The right lung is more frequently affected, owing to the more direct takeoff of the right mainstem bronchus.

LABORATORY DIAGNOSIS

Aspiration pneumonitis is a clinical diagnosis. It is generally assumed that there is an anaerobic component to pneumonia in patients with altered consciousness or after surgical procedures. It is important to emphasize the utility of the Gram stain in making the diagnosis of anaerobic lung infection. Often culture data are not available to confirm the presence of these organisms. However, most anaerobic gram-negative bacteria have unique morphologic features that make them relatively easy to identify or suspect on direct Gram stain. For example, peptostreptococci appear like their aerobic counterparts. Aspiration pneumonia is usually a mixed infection involving multiple bacteria; about half of the cases demonstrate mixtures of aerobic and anaerobic bacteria.[1,81,82] Thus, the detection of polymicrobial flora or bacteria with the unique morphology of anaerobes on any specimen that is devoid of contamination by normal flora represents an important clue to the probable presence of anaerobic infection.

Determination of the microbiology of anaerobic infections of the lower airways requires a specimen devoid of contamination by the flora of the upper airways or quantitative cultures that distinguish pathogens from normal flora. Uncontaminated specimens that are considered valid for anaerobic culture include pleural fluid, TTAs, transthoracic aspirates, and specimens obtained at thoracotomy or thoracoscopy. Quantitative cultures of specimens obtained at fiberoptic bronchoscopy, either by BAL or with the protected brush, may also be used for this purpose.[1] Anaerobic bacteriology should not be obtained from standard bronchoscopic aspirates. Quantitative culture of lower airway secretions improves diagnostic accuracy with virtually any specimen that is subject to contamination, including expectorated sputum and tracheostomy aspirates. Most studies employing these techniques have used them to detect aerobic bacteria; relatively few studies evaluated anaerobic cultures. Whether treatment decisions based on quantitative cultures of anaerobic pathogens improve treatment outcomes has not determined.

When possible, respiratory samples should be obtained before the inception of antibiotic treatment. In clinical practice, specimens are often not obtained for anaerobic culture until the patient has developed complications of persistent infection, which greatly reduces their yield. Thus, the anaerobic pathogens should be considered in the appropriate clinical context, even when only aerobic organisms are isolated.

It is essential that material obtained for culture be placed under anaerobic conditions promptly before transport to the laboratory. A sealed syringe provides the best container, with delivery of the specimen to the laboratory within 20 to 30 minutes for immediate plating. It is imperative that air bubbles be eliminated from the syringe and needle. Special anaerobic transport tubes are also available for brush or liquid specimens. It is important to obtain additional pulmonary specimens for culture and antibiotic susceptibility measurements from patients failing to respond to initial therapy (Fig. 127-2). Such data may demonstrate the presence of unrecognized or antibiotic-resistant organisms. Most of these infections are polymicrobial and many of the organisms grow slowly *in vitro*. Thus, it often takes several days to separate, identify, and report results of anaerobic cultures. There is great variation in the availability and quality of *in vitro* susceptibility tests. These factors illustrate the need for empiric decisions regarding antibiotic selection.

PREVENTION

The reversibility of underlying conditions predisposing to aspiration must be considered. It has recently been recognized, for example, that aspiration in lung transplant recipients is a major predisposing factor to graft injury and obliterative bronchiolitis.[83] In the general patient population, nasogastric-feeding tubes, sedation, lying flat in bed while sleeping, reflux, and frequent choking are associated with aspiration and should suggest strategies for remediation.[46] Gastric surgery for obesity has also been associated with a high incidence of aspiration disease.[84]

Positioning, dietary changes, medications, oral hygiene, and tube feeding, among other interventions, have been proposed to prevent aspiration both in hospitalized and nonhospitalized patients, particularly in the elderly. However, studies have failed to support a specific intervention in the outpatient setting.[85] While using nectar or honey-thickened liquids decreases aspiration among patients with dementia or Parkinson disease,[86] the incidence of pneumonia is not changed.[87]

Methods to prevent aspiration have been studied most extensively in hospitalized patients, especially in those who are aspiration prone. Most important is use of semirecumbent or upright positioning.[88] Additional measures to prevent aspiration with variable efficacy include tracheostomy, reducing gastric contents by suction or metoclopramide, feeding via gastrostomy tube, and neutralization of gastric acid. Many of these procedures may alter colonization

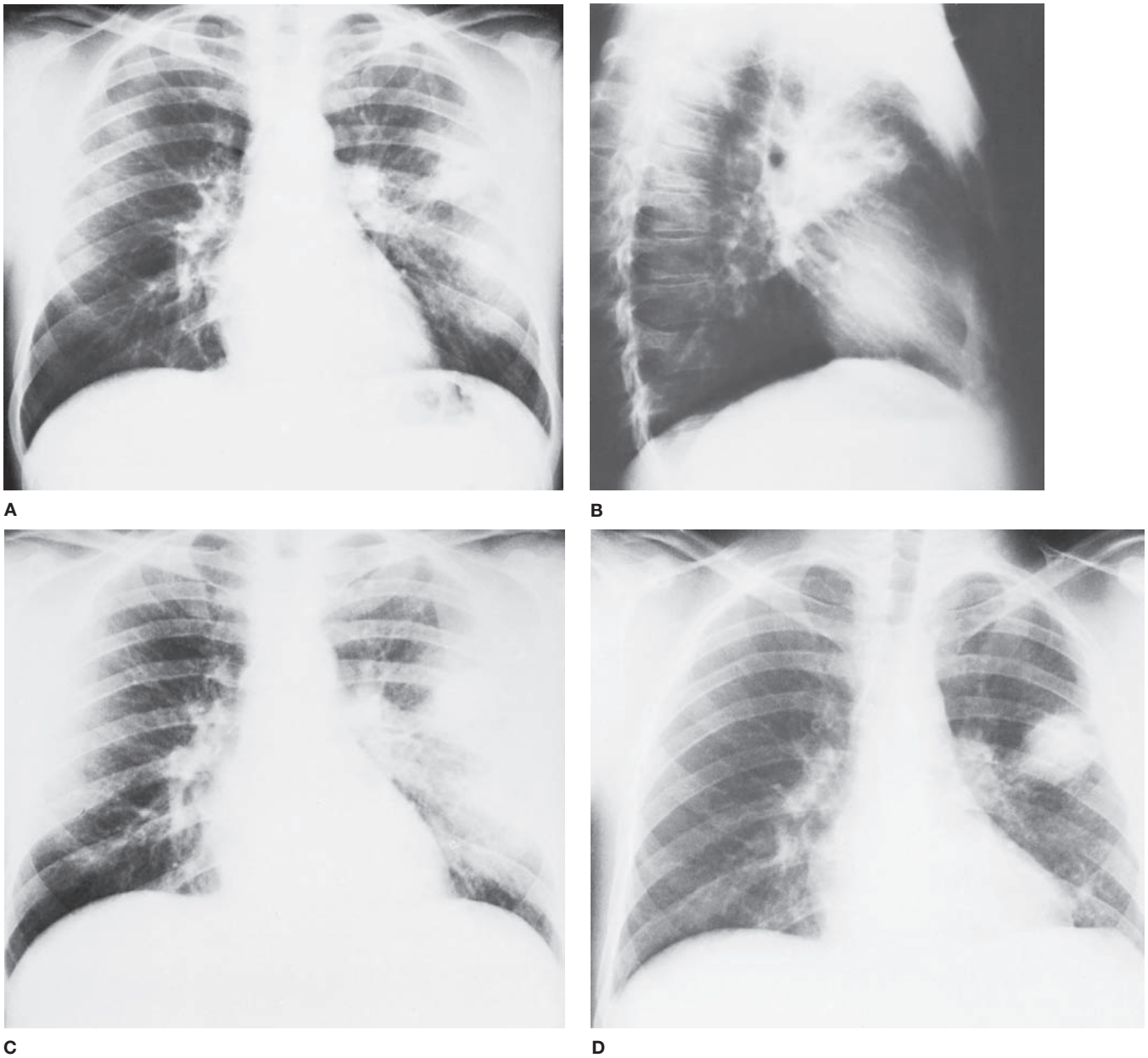


Figure 127-2 Failure of penicillin therapy for anaerobic lung abscess in a 29-year-old alcoholic man. **A.** Admission chest radiograph reveals a radiolucent area within a zone of consolidation in the left upper lung field. **B.** Lateral view demonstrates multiple cavities. The patient was treated for 5 days with penicillin (6 million units per day intravenously), followed by the same dosage orally for 10 days. **C.** Radiographic infiltrate persists but no cavity is visible. **D.** Six weeks after the cessation of penicillin therapy, the abscess has recurred in the same area. Marked pleural reaction is noted in the vicinity of the recurrent disease.

patterns and potentially may predispose to more significant infections. Neutralization of gastric acid may increase colonization of the oropharynx and thereby increase the risk of bacterial infection following aspiration of gastric contents. Tracheostomy is useful in some patients with repeated aspiration, but inflation of the balloon may occlude the esophagus and promote aspiration of upper airway contents. Patients who require nasogastric feedings are aspiration prone; percutaneous endoscopic gastroscopy (PEG) may be alternative method to address this issue, but study results are quite variable. A recent meta-analysis of nine studies found that while PEG feeding was superior to nasogastric tube feeding in providing consistent nutritional support, the incidence of pneumonia was no different between the two groups.[89] Alternative procedures sometimes considered to prevent or limit aspiration include is postpyloric feeding jejunostomy and Nissen fundoplication.

■ ANTIMICROBIAL THERAPY

It is essential, whenever possible, to obtain microbiologic samples from the lungs and blood in advance of antimicrobial therapy. As for all pneumonias, inappropriate initial therapy has an adverse impact on outcome. The initial choice of antimicrobial agents should be guided by the Gram stain and the likely bacteriology of the infection and then adjusted as culture data become available. The history and a review of previous culture results may be useful in the selection of specific antibiotics. The standard drug historically for aspiration pneumonia and lung abscess involving anaerobic bacteria has been penicillin, usually given intravenously or with high-dose oral treatment. However, in the face of increasing penicillin resistance among *S. pneumoniae* and in 40% to 60% of strains of fusobacteria and *P. melaninogenica* as well as anaerobic gram-negative bacilli, alternatives should be considered for empiric

TABLE 127-5 Antibiotic Treatment of Anaerobic Lung Infections: Results of Two Randomized Trials

Source	Treatment	# Pts	Number of Patients with		Mean Days to Symptom Resolution	
			Failure	Relapse	Fever	Putrid Sputum
Levinson (1983)	Penicillin (6 million units/d)	21	5 (29%)	3 (19%)	7.7	7.8
	Clindamycin (1.8 g/d)	17	0[a]	0	4.7[a]	4.1[a]
Gudiol (1990)	Penicillin (12 million units/d)	18	7 (39%)	2 (11%)	7.2	7.3
	Clindamycin (2.4 g/d)	19	1 (5%)	0	6.4	3.9[a]

[a]*Difference for treatment favoring clindamycin is statistically significant.*

therapy. In early therapeutic trials in patients with lung abscess involving anaerobic bacteria (Table 127-5), clindamycin proved superior to penicillin in terms of response rates and time to defervescence. Alternative regimens that have been used successfully based on anecdotal experience include amoxicillin–clavulanate and penicillin combined with metronidazole. Metronidazole should not be used as a single agent in patients with anaerobic lung infections, since there is a poor response in about 50%.[90,91] The presumed explanation is the contributing role of aerobic and microaerophilic streptococci, which are resistant to this drug.

Many other antimicrobial agents are likely to be useful in anaerobic or mixed aerobic–anaerobic infections: combinations of a β-lactam and β-lactamase inhibitor (ticarcillin–clavulanate, ampicillin–sulbactam, amoxicillin–clavulanate, piperacillin–tazobactam), imipenem or meropenem, and second-generation cephalosporins such as cefoxitin or cefotetan. Macrolides (erythromycin, clarithromycin, and azithromycin) offer good *in vitro* activity against most species except fusobacteria. Tetracyclines show limited activity against many anaerobic bacteria *in vitro*; vancomycin is active only against gram-positive anaerobes. Oxacillin and nafcillin are much less active. Drugs that have virtually no activity against anaerobes include aminoglycosides, first-generation fluoroquinolones, aztreonam, and trimethoprim-sulfamethoxazole (TMP-SMX). Moxifloxacin has broad coverage that includes anaerobes[92] however, increasing resistance in *Bacteroides* spp. raises concerns for the suitability of moxifloxacin monotherapy.[93]

The appropriate duration of therapy is unclear. No clinical trials have been performed to determine optimal treatment term. Typically the duration is dependent on the clinical and radiographic response of the patient. Patients should be treated at least until fever, putrid sputum, abscess fluid has resolved, and any fluid collections have resolved or stabilize, typically over 2 to 3 weeks. In the absence of abscess formation, a course of 7 to 10 days of antibiotics is recommended, but longer courses are often necessary. Relapse is common and may involve organisms resistant to initial antibiotic agents (Fig. 127-2).

LUNG ABSCESS

Because the most important predisposing condition for lung abscess is aspiration, lung abscesses are most often located in the posterior segment of the right upper lobe, less often in the left upper lobe, and the apical segments of the lower lobes (Fig. 127-1). Periodontal disease is highly associated with lung abscess formation; in edentulous people, lung abscesses are uncommon and may suggest the presence of an obstructing lesion of the bronchus, pulmonary embolus, septic embolus, or unsuspected pathogen. Nosocomial aspiration often involves gram-negative bacteria, particularly organisms with hospital-acquired antibiotic resistance patterns. Many of these infections progress to suppurative complications, with presentation as lung abscess or empyema. Usually 1 to 2 weeks are required for cavity formation.

Lung abscesses generally develop after inflammation produces tissue necrosis with cavitation. In the presence of pre-existing cavitary disease, for example, due to emphysema or old tuberculous lesions, infection may proceed without frank necrosis. The abscess cavity may become lined with regenerated epithelium. Local obstruction may produce bronchiectasis or emphysema in the surrounding lung.

The classification of lung abscesses is based on the duration and likely cause of the process. Acute abscesses are less than 4 to 6 weeks old, whereas chronic abscesses are of greater duration. Primary abscesses are infections due to aspiration or to pneumonia in the normal host; secondary abscesses are due to pre-existing conditions (obstruction, spread from an extrapulmonary site, bronchiectasis, immune compromise). Abscesses with foul odors associated with anaerobic organisms are often called putrid abscesses.

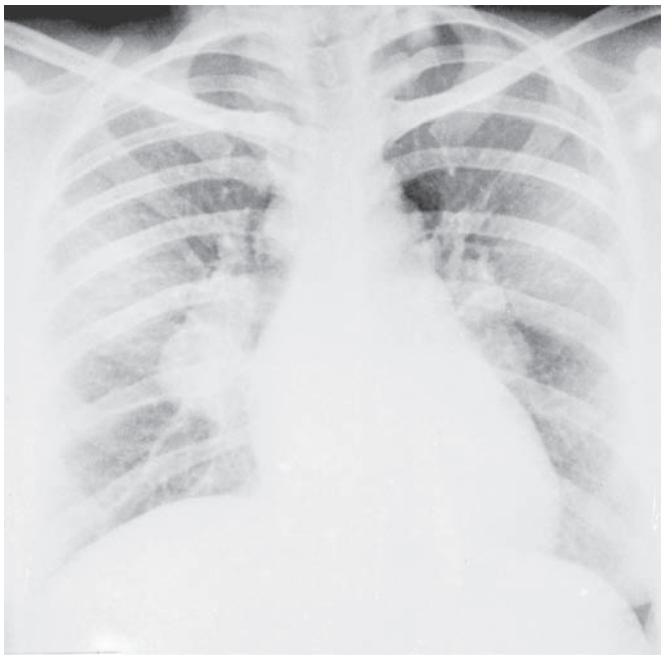
MICROBIOLOGY

In lung abscesses, anaerobes are recoverable from up to 93% of patients.[15] In some patients, anaerobic organisms of presumably greater virulence (e.g., *Fusobacterium* or *Peptostreptococcus*) may be found as the sole infecting organism. In studies by Bartlett and Finegold,[3] 46% of patients with lung abscesses had only anaerobes isolated in cultures, while an additional 43% had a mixture of anaerobes and aerobic bacteria. In addition to anaerobes, among the organisms often implicated in lung abscess formation or in necrotizing pneumonia included are *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. Infrequently, other gram-negative bacilli, such as *E. coli* and *Haemophilus influenzae* type B, may cause pulmonary necrosis. Uncommon but important causes of cavitating pneumonia are *Nocardia* spp., *Paragonimus westermani*, *Legionella* species, *Burkholderia pseudomallei*, *Burkholderia mallei* (glanders), and tuberculosis. Certain fungal infections may cause cavitation in diabetic and immunocompromised hosts (e.g., the *Mucoraceae*, *Aspergillus* species). *Entamoeba histolytica* is an important but uncommon cause of lung abscess, almost always in the basilar portion of the right lower lobe.

CLINICAL FEATURES

The clinical presentation of lung abscess may be coincident with the initial presentation of pneumonia or other underlying condition or may occur later in the clinical course. Suspicion may be heightened by the presence of conditions predisposing to aspiration or anaerobic pneumonia: alcoholism or other causes of altered consciousness, anesthesia, dysphagia or pharyngeal dysfunction, gingivitis or pyorrhea (purulent inflammation of the gums), blunt or penetrating chest trauma or lung surgery, obstruction due to neoplasm, bronchiectasis, or pulmonary embolism. Bad breath or putrid sputum may be noted. However, the absence of a foul odor does not exclude the possibility of anaerobic infection, since certain anaerobes do not generate the end products of metabolism responsible for this type of odor, and communication may be lacking between the lesion and tracheobronchial tree. A change in sputum production, either increased or decreased, may be noted in patients with chronic bronchitis or bronchiectasis.

The patient with primary lung abscess gradually develops fever, cough, pleurisy, chest heaviness, shoulder pain, and malaise.



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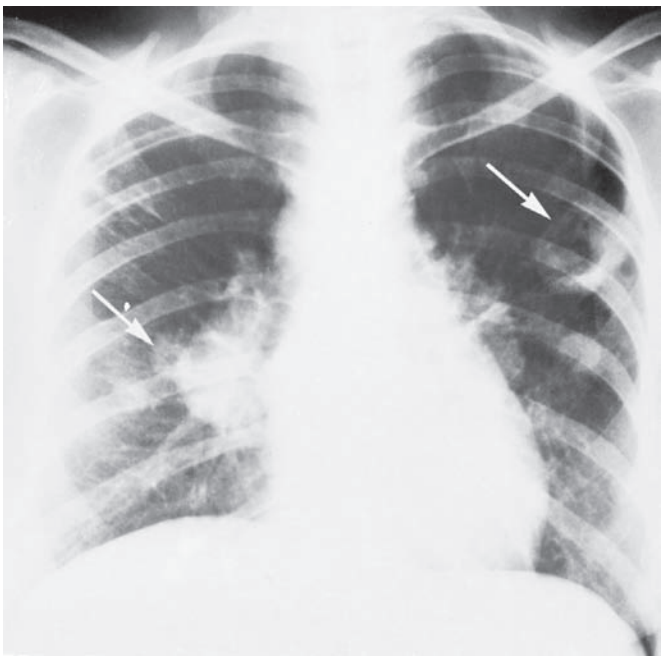

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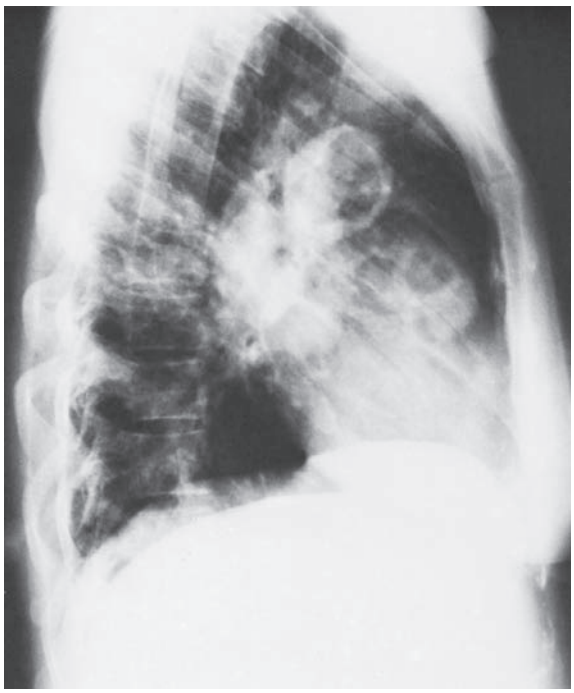


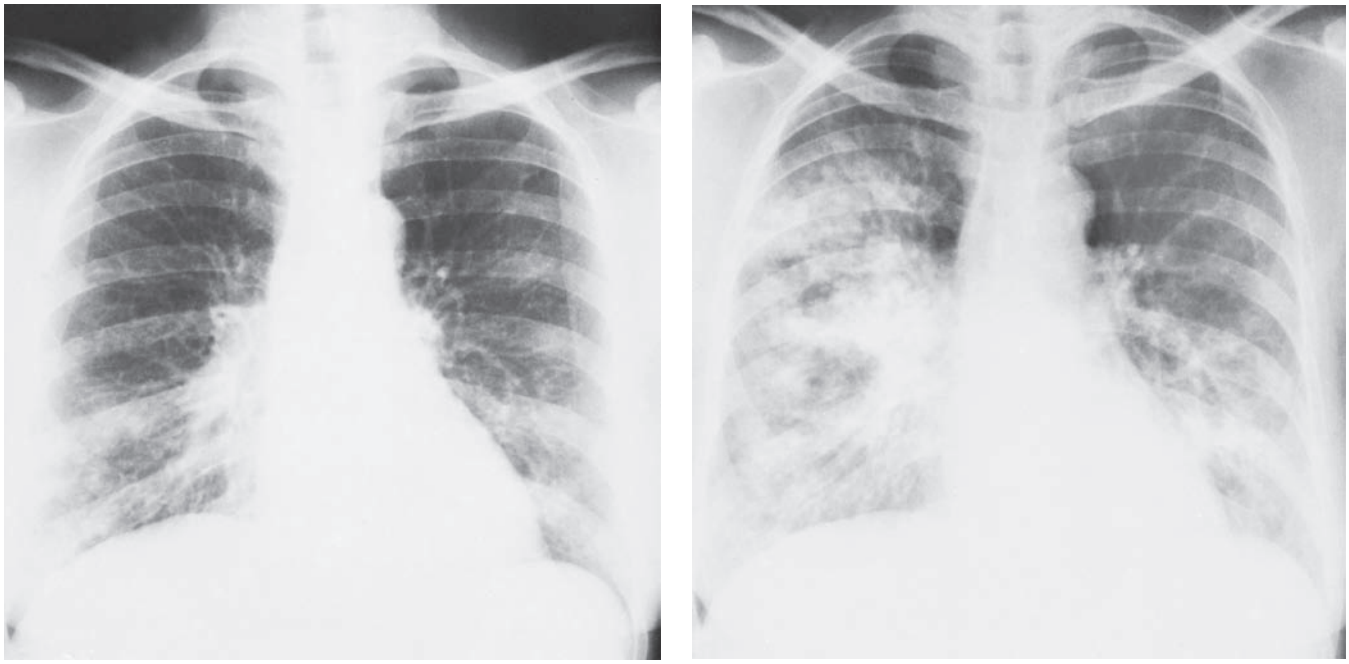
C

Figure 127-3 Septic emboli due to *Pseudomonas aeruginosa* in a 33-year-old woman with sarcoidosis and pyelonephritis following spontaneous abortion. The patient presented with headache, fever, backache, and purulent sputum. Pseudomonas grew from the sputum culture. **A.** Chest radiograph before present illness. Bilateral hilar adenopathy of sarcoidosis. **B.** Posteroanterior view of chest shows bilateral cavitary lesions *(arrows)*. **C.** Lateral view. The lesions are more dramatically seen.

Pneumonia may be present or suspected from history for a period of 1 to 3 weeks before the recognition of the lung abscess. By contrast, secondary lung abscesses – due, for example, to septic pulmonary emboli with infarction – can evolve over 48 to 72 hours (Fig. 127-3). Clinically, the distinction between primary and secondary abscesses may be unapparent at the time of presentation but is important in the proper management of the patient. Thus, the patient with staphylococcal or streptococcal endocarditis may present with pneumonia, lung abscess, and empyema. The main clue to the presence of underlying endocarditis may be the development of new lung abscesses during the course of therapy. The patient with lung abscesses complicating subdiaphragmatic infection, for example, due to amebic abscess of the liver or pancreatic phlegmon, may have abdominal signs in addition to acute pulmonary disease. Seizures due to brain abscesses are occasionally the presenting clinical manifestation of bacteremia due to lung abscesses.

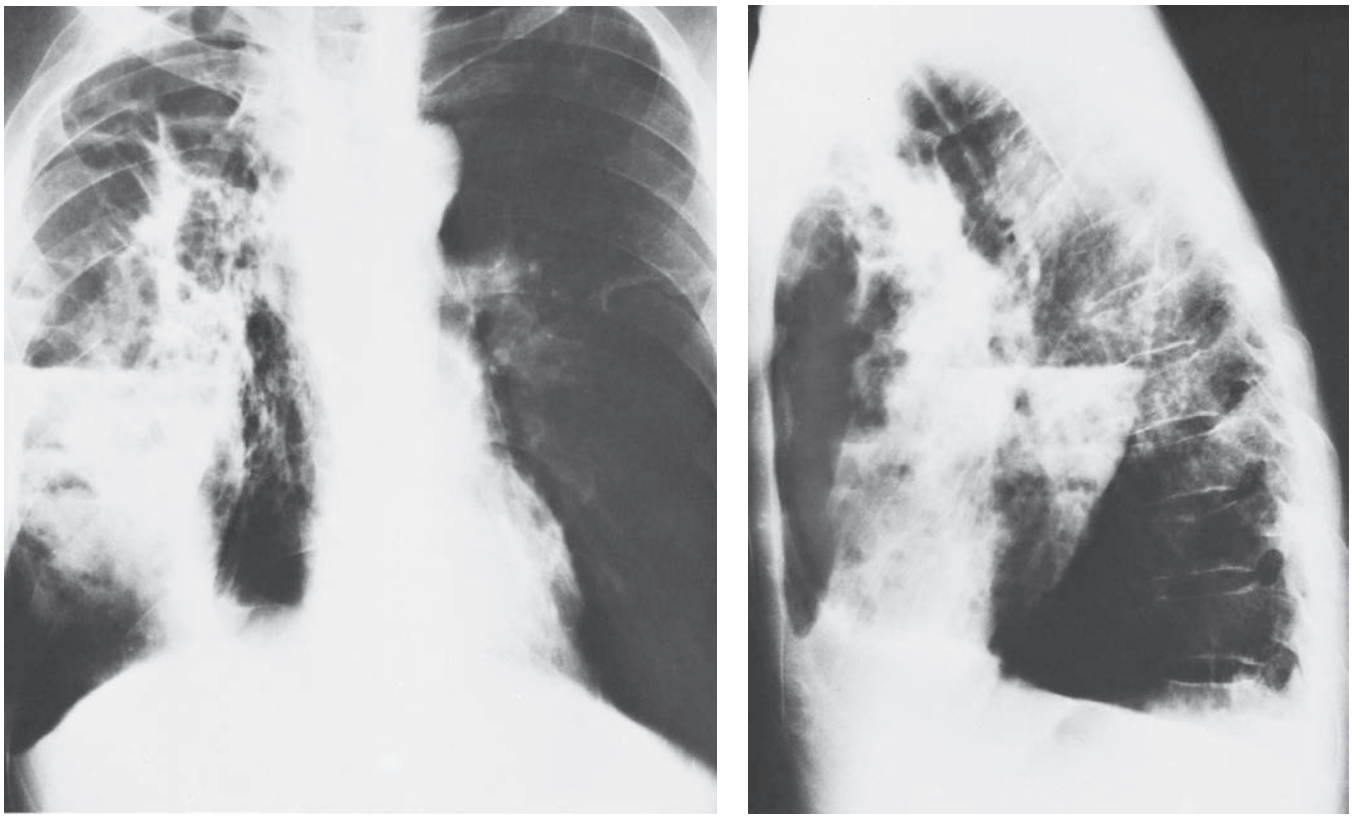
■ RADIOLOGIC DIAGNOSIS

The classic radiographic appearance of a lung abscess is an irregularly shaped cavity with an air–fluid level. Because the presentation is often indolent, numerous chest radiographs may be needed to follow the evolution of pneumonia into necrotizing pneumonia and then a pulmonary cavity (Figs. 127-4 and 127-5). Anaerobic infection is suggested by rapid pulmonary cavitation within a dense segmental consolidation; there may be rapidly enlarging nodular lesions, with or without cavitation. Although anaerobic pulmonary infections may be acute and fulminating, almost two-thirds have a subacute or chronic presentation. Natural progression of virulent



A B

Figure 127-4 Fulminating anaerobic pneumonia in a 44-year-old woman with onset of pneumonia 6 days before admission. **A.** Day of admission. Patchy consolidation in right lower lung field and behind the cardiac silhouette. **B.** One day after admission: Extensive patchy alveolar infiltrates bilaterally with areas of rarefaction on right suggestive of cavitation. The patient died 2 days later.



A B

Figure 127-5 "Gangrene" of the lung after aspiration, anteroposterior (**A**) and lateral (**B**) views. Extensive cavitation following necrotizing pneumonia in a 65-year-old man.

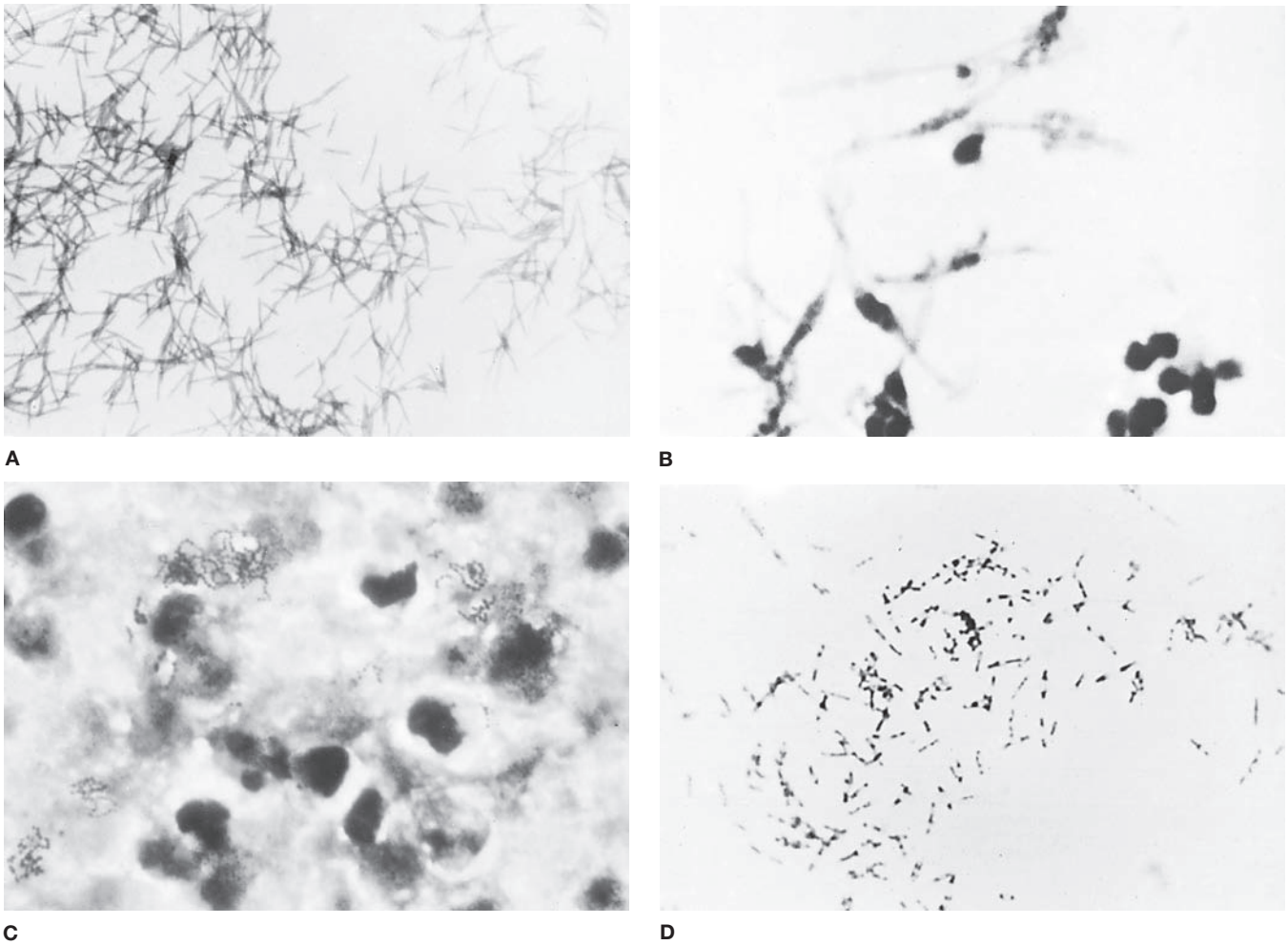


Figure 127-6 Bacteriology of empyema and lung abscess. **A.** *Fusobacterium nucleatum*, microscopic morphology. Organism is thin and delicate gram-negative bacillus with tapered ends (sometimes filamentous). **B.** Pleomorphic gram-negative bacillus with filaments containing swollen portions and with large round bodies. This appearance is seen with *F. necrophorum*, *F. mortiferum*, and *F. varium*. **C.** Pus showing microaerophilic streptococcus. **D.** Microscopic morphology of *Bacteroides fragilis*. Organism is an irregularly stained, gram-negative rod. Bipolar staining may be seen.

infection, delays in appropriate therapy, or tissue infarction may allow the underlying infection to progress into pulmonary gangrene (Fig. 127-5). Seeding of infection or rupture of a lung abscess into the pleural space may cause empyema (Fig. 127-3). Up to one-third of lung abscesses may be accompanied by empyema. Solitary cavities are generally observed with primary lung infections, whereas many smaller collections may be found in metastatic infection. Chest tomography will define the size and location of abscesses, and may distinguish between related processes (empyema, infarction) better than conventional radiographs. The common organisms and conditions associated with lung abscesses are listed in Table 127-6.

■ LABORATORY DIAGNOSIS

Microbiologic specimens from patients with lung abscesses should be obtained, if possible, without contamination by oral flora, especially after nosocomial colonization. Thus, invasive procedures are preferred to routine sputum samples. In particular, the diagnosis of anaerobic infection is complicated by the prevalence of large numbers of anaerobes as normal flora in the mouth and upper respiratory tract (Figs. 127-6 and 127-7). However, there may also be significant colonization with nosocomially acquired pathogens in hospitalized patients.

Blood and sputum cultures should be obtained as adjunctive guides to therapy. When empyema or bacteremia complicates lung abscess, adequate specimens for microbiologic evaluation may be obtained from the pleura or blood. However, to obtain adequate specimens from the abscess, bronchoalveolar lavage, use of a protected double-lumen catheter or percutaneous transthoracic aspiration under radiographic guidance is recommended. The specific procedure selected depends on the location of the infection and the expertise of the institution. Specimens collected through a fiberoptic bronchoscope, using bronchoalveolar lavage or a plugged double-lumen sampling catheter with a protected sampling brush, are generally preferred; these require the use of quantitative cultures. Growth at a dilution of 10 from a protected brush represents approximately 1×10^{10} organisms per milliliter in the lower respiratory tract. Recovery of nonbacterial and anaerobic bacteria from these specimens has not been well standardized. Specimens obtained from blind, deep suctioning via an endotracheal tube may also be useful if cultured quantitatively and examined microscopically.

■ TREATMENT

The treatment of lung abscess must be guided by the microbiology and knowledge of any underlying or associated conditions that may predispose to the development of severe pulmonary infection. A small abscess in an otherwise healthy person may respond to conservative management with antimicrobial therapy and chest

TABLE 127-6 Organisms and Conditions Associated with the Radiographic Appearance of Lung Abscess

Infectious
Bacteria Anaerobes, *Staphylococcus aureus,* Enterobacteriaceae (e.g. *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, *Burkholdaria pseudomallei*, streptococci, *Legionella* spp., *Nocardia asteroids*, *Rhodococcus equi*, *Actinomyces* spp.
Mycobacteria (often multifocal) *M. tuberculosis, M. avium* complex, *M. kansasii*, *M. malmoense*, other nontuberculous mycobacteria
Fungi *Aspergillus* spp., zygomycetes, *Histoplasma capsulatum*, *Blastocystis hominis, Coccidioides immitis, Cryptococcus neoformans*, *Pneumocystis jiroveci*, *Penicillium marneffei*
Parasites *Entamoeba histolytica, Paragonimus westermani, Strongyloides stercoralis* (post-obstructive)
Miscellaneous Empyema (with air-fluid level), septic embolism (endocarditis)
Noninfectious and Predisposing Conditions
Anatomic, fluid-filled cysts, bland infarction, bronchiectasis, vasculitis, Goodpasture's syndrome, granulomatosis with polyangiitis (formerly, Wegener granulomatosis), periarteritis, obstruction (neoplasm, foreign body), pulmonary sequestration, pulmonary contusion, carcinoma

physical therapy. A rapidly expanding pulmonary abscess in an immunocompromised host (e.g., due to one of the *Mucoraceae*) requires urgent lung resection in addition to antimicrobials. Intermediate to these approaches is the use of bronchoscopic-guided or radiographically guided catheter drainage of any fluid and necrotic debris. In the absence of antibiotics, the mortality of lung abscess is approximately 33%.[94] However, up to half of patients surviving a lung abscess acutely in the preantibiotic era had significant pulmonary complications, including recurrent infections and abscesses, pleural empyema and adhesions, chronic bronchitis, and bronchiectasis. The introduction of penicillin, orally or parenterally administered, resulted in resolution or collapse of the abscess in up

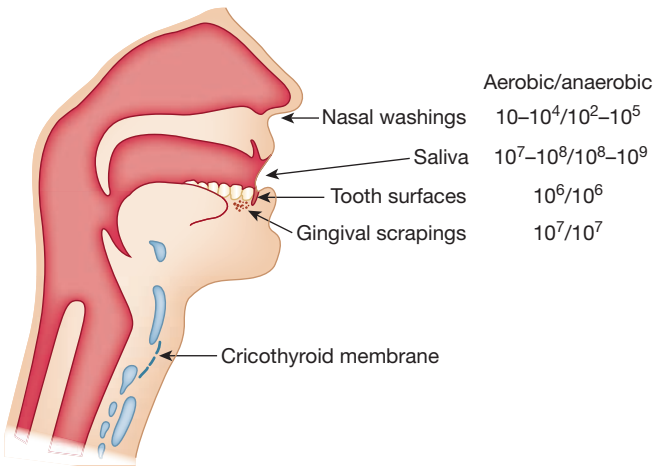


Figure 127-7 Sagittal section illustrating presence of large numbers of organisms, including anaerobes, as indigenous flora in upper respiratory tract. (Values given as number of aerobic/anaerobic organisms per milliliter.) *(Used with permission of PD Hoeprich.)*

to 90% of patients (although long courses of treatment were often needed). Therefore, these patients could avoid surgical resection.

The role of drainage or surgery is based on serial clinical assessments of the patient. Bronchoscopic drainage may be most useful in the relief of abscesses without air–fluid levels, which indicate the possibility of persistent connection with the bronchi.[95] However, experience dictates caution with the bronchoscopic drainage of closed cavities; spillage of cavity contents into other lung segments may produce catastrophic pulmonary dysfunction. Further, there are few data to suggest that bronchoscopic drainage offers a significant advantage in terms of rapidity of recovery in the immunologically normal host. In patients with coexistent empyema and lung abscess, it is often useful to address drainage of the empyema first, stabilizing the patient, and then considering further procedures for the lung abscess. In critically ill patients or those with bronchial obstruction related to the abscess cavity, bronchoscopic drainage should be considered.

Bronchoscopy and chest CT have major roles in the evaluation of the patient failing therapy. Persistence of bacteremia or high-grade fevers after 72 hours, or the absence of change in sputum production or character or in the radiographic images over 7 to 10 days suggests unappreciated anatomic or microbiologic problems. Obstruction or resistant organisms (including fungi, parasites, or mycobacteria) may be present. Multiple loculations may be present, or empyema, including drainage of the abscess into the pleural space, may develop. New sites of infection, including extrathoracic sites, may have developed in the bacteremic patient. Progression of pulmonary infiltrates may occur after the initiation of appropriate antibiotic therapy, reflecting the relatively poor activity of many antibiotics at the low pH levels of poorly ventilated and underperfused, infected lung tissues, as well as the delayed radiographic response to treatment.

Surgical resection of necrotic segments of lung is helpful if the response to antibiotics is poor, for large abscesses, or when ventilation–perfusion scans suggest little residual lung function in a limited necrotic region. Infarcted lung or rapidly progressive infection may force surgical resection of the affected tissue. Surgery is also indicated if airway obstruction limits drainage. Such presentations are seen in the presence of tumor or a foreign body. In patients thought to be poor surgical risks, percutaneous drainage via catheters may be a useful temporizing measure. However, leakage of the abscess contents into the pleural space in such patients may be disastrous and must be avoided.

Mortality in patients with lung abscesses reflects the quality of the host's inflammatory response and overall condition. Patients with large abscesses (over 5–6 cm), progressive pulmonary necrosis, obstructing lesions, aerobic bacteria (especially *K. pneumoniae*, *S. aureus*, or *P. aeruginosa*), immune compromise, old age, malnutrition, or systemic debility, and those with major delays in seeking medical attention have a significantly increased mortality.[96]

EMPYEMA

The microbiology, diagnosis, clinical features, and management of empyema are considered below.

MICROBIOLOGY

Pleural infections are associated with a significant degree of morbidity and mortality, with death or surgical intervention in more than 30% of patients.[97,98] In the preantibiotic era, up to 11% of cases of pneumococcal pneumonia were associated with empyema, and 64% of all cases of empyema were associated with *S. pneumoniae*. β-Hemolytic streptococci (15%) and staphylococci (8%) were the other organisms most commonly isolated from empyema fluid. In the 1960s and 1970s, with new culture techniques, one study found only anaerobic bacteria in pleural empyema fluid in 35% of cases, and a mixture of aerobic and anaerobic bacteria in 41% in a series of 83 medical patients who had not received antibiotics or surgical intervention (Tables 127-7 and 127-8; Figs. 127-6, 127-8 and 127-9). With the introduction of

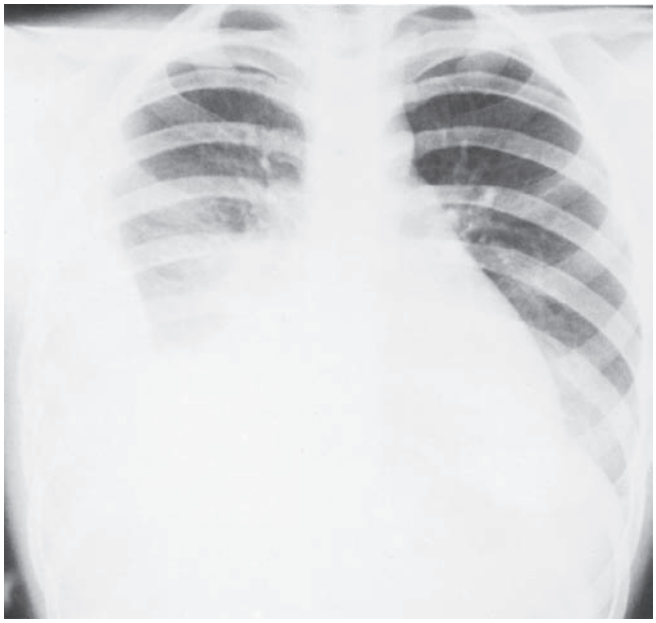


Figure 127-8 Large anaerobic empyema accompanying right middle-lobe pneumonia.

the sulfa drugs and penicillins, the expansion of thoracic surgery, and the emergence of antibiotic resistance in the staphylococci, the isolation of *S. pneumoniae* from empyema fluids decreased and that of *S. aureus* and other nosocomial pathogens increased. In more recent studies of empyema, the pneumococcus accounts for only 5% to 10% of cases, whereas anaerobes are found in 25% to 40%. The highest yield reported in recent years is a collaborative study at Cook County Hospital in Chicago and two VA hospitals in Los Angeles. Anaerobes were recovered in 63 (76%) of 83 cases.[4]

Anaerobic Bacteria in Empyema

The frequency of anaerobic infection of the lung and pleural space is a function of the colonization pattern of the individual patient, including the presence of hospital-acquired pathogens, and the role of aspiration in many of these infections (Tables 127-7 and 127-8). The most frequent isolates are the anaerobes *Prevotella*, *F. nucleatum*, and *Peptostreptococcus* and the streptococci (Figs. 127-4 and 127-5).

TABLE 127-7 Bacteriology of Anaerobic Empyema: Predominant Flora

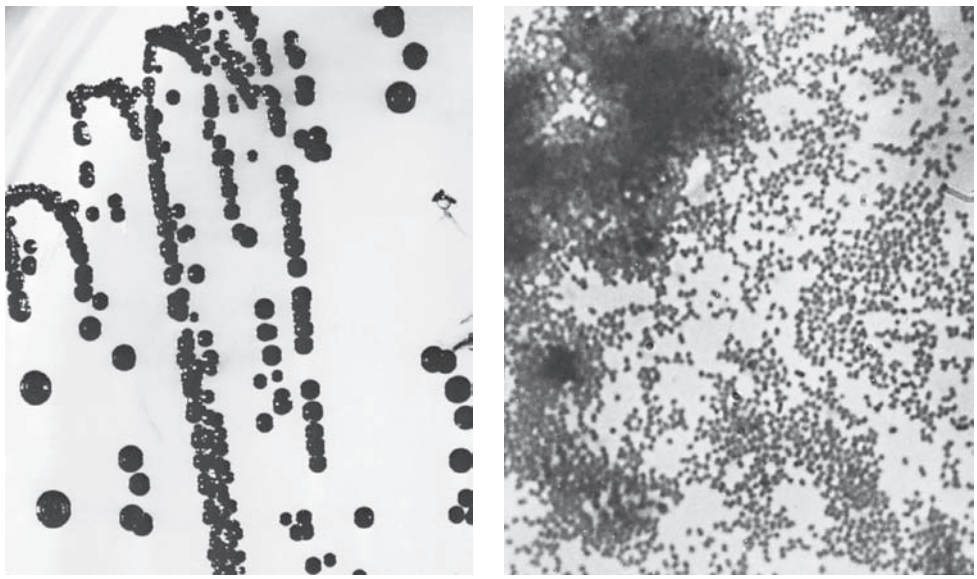
Organism	Number of Isolates
Anaerobic isolates	
Fusobacterium nucleatum	19
Prevotella denticola-melaninogenica group	10
Prevotella oris	9
Prevotella intermedia–nigrescens group	8
Prevotella oralis	4
Prevotella buccae	3
Bacteroides fragilis	5
Other *B. fragilis* group	6
Unidentifiable *Bacteroides* spp.	4
Bacteroides gracilis	3
Campylobacter spp.	3
Peptostreptococcus micros	9
Peptostreptococcus anaerobius	5
Peptostreptococcus spp.	4
Peptostreptococcus magnus	3
Streptococcus intermedius	5
Eubacterium spp.	7
Lactobacillus spp.	7
Actinomyces spp.	4
Actinomyces odontolyticus	3
Propionibacterium acnes	4
Clostridium perfringens	3
Clostridium spp.	3
Aerobic Isolates	
α-Hemolytic streptococcus	21
Nonenterococcal group D streptococcus	4
Coagulase-negative staphylococci	4
Proteus spp.	3

Source: Data from Cien R, Jousimies-Somer H, Marina M, et al. A retrospective review of cases of anaerobic empyema and update of bacteriology. Clin Infect Dis. 1995;20:S224–S229.

TABLE 127-8 Correlation of Infecting Organism and Conditions Underlying Anaerobic Pleuropulmonary Infection

Bacteria	Aspiration	Tonsillitis, Tonsillectomy	Gingivitis, Dental Extraction, Pyorrhea	Bronchiectasis	Bronchogenic Carcinoma	Chest Trauma, Thoracotomy	Peritoneal Infection or Source in Bowel	Pelvic Infection
Bacteroides fragilis group	11	1	0	3	1	3	16	1
Pigmented gram-negative anaerobic rods	13	0	7	2	0	0	2	0
Fusobacterium nucleatum	24	2	7	4	4	4	6	1
Fusobacterium necrophorum	2	45	2	1	2	0	5	4
Peptostreptococcus	27	5	9	4	2	10	6	8
Microaerophilic streptococcus	17	0	5	0	4	0	5	1
Anaerobic, non–spore-forming, catalase-negative, gram-positive rods	6	1	0	1	2	1	3	0
Clostridium	6	3	1	0	0	15	7	

Source: Data from Finegold SM: Anaerobic Bacteria in Human Disease. New York, Academic, 1977.



A B

Figure 127-9 *Prevotella melaninogenica*. **A.** Distinctive black colonies (on blood-containing medium); pigment is hematin. **B.** Microscopically, the organism is a coccobacillus.

In early studies, the *B. fragilis* group was isolated from 15% to 20% of patients with anaerobic pleuropulmonary infections. However, later studies employing newer techniques and utilizing newer taxonomic criteria found *B. fragilis* group in only 6.8% of 46 patients with pleural empyema specimens. The *B. fragilis* group is important because of resistance to penicillin (a property shared by a number of common anaerobes) and other antimicrobial agents. Subdiaphragmatic infection may extend to the lung or pleural space by way of lymphatics, directly through the diaphragm or defects in it, or by way of the bloodstream. Anaerobic pulmonary and pleural processes rarely extend to the chest wall unless associated with actinomycosis, tuberculosis, or tumor.

Nonanaerobic infections

In immunologically normal adults, the aerobic organisms currently most often associated with empyema and lung abscesses are *S. aureus*, β-hemolytic streptococci, and various gram-negative aerobic or facultatively anaerobic bacilli, particularly *P. aeruginosa*, *E. coli*, *Klebsiella* species, and other nosocomial enteric gram-negative organisms—reflecting infections associated with pneumonia treated with antimicrobial agents to which the causative organism is resistant, with thoracic surgery or high-grade bacteremias. Mixed aerobic–anaerobic infections are often related to subdiaphragmatic processes. Increasingly, *Mycobacterium tuberculosis*, *Nocardia asteroides*, and fungi have been identified. In the immunocompromised host, the infecting organisms will more often be gram-negative bacteria (especially *Pseudomonas* and *Enterobacter)*, less virulent streptococci, *Aspergillus*, *Candida* species, or will be due to reactivation of latent or subclinical infections due to *M. tuberculosis*. In all hosts, the colonization pattern of the individual will often predict the causative organisms, even if these are not easily isolated.

■ CLINICAL FEATURES

The pathogenesis and presentation of both pleural empyema and lung abscesses are often indistinguishable. Shared presentations of empyema and lung abscess include the indolent development of symptoms, most often fever, sweats, cough, dyspnea, weight loss, and pleurisy; an association with conditions predisposing to aspiration events (altered consciousness, dysphagia, and gingivitis); and foul odors of sputum or breath associated with anaerobic bacteriology. Lung abscesses and empyemas often coexist. Both are generally associated with primary pneumonias.

The clinical presentation of empyema is determined by the underlying cause of infection. Empyema associated with aspiration pneumonia may develop over 1 to 3 weeks, usually with associated symptoms of pneumonia. The patient may have high fever and leukocytosis. Physical examination reveals dullness to percussion and decreased breath sounds on auscultation. These changes may be quite localized in the setting of loculated fluid. The empyema fluid is generally purulent by the time of detection, but pleural infection may be noted only after treatment for pneumonitis has failed to resolve fever or pleurisy. Empyema associated with thoracic surgery may be radiologically "hidden" in areas of the chest not drained by chest tubes or behind relatively benign pleural effusions. The patient may appear minimally toxic or severely ill, depending on the extent of the infection and organisms present. The presentation is modified by routine prophylactic antibiotic use, sedation, intubation, and antipyretics. Acute empyema may be seen in staphylococcal and streptococcal infections and following rupture of hepatic abscesses, especially those due to *E. histolytica*.

■ RADIOLOGIC DIAGNOSIS

With empyema, chest radiographs generally reveal fluid, most often in the costophrenic angles; free-flowing effusions layer on lateral decubitus radiographs. Loculations and pleural disease are often best defined by computed tomography of the chest, which should include the neck and diaphragms to rule out extrathoracic sites of infection. Spinal disease is better detected with magnetic resonance imaging (MRI). Before invasive diagnostic procedures, a careful history and physical examination may suggest a reason for the accumulation of pleural fluid. Noninfectious causes include bland pulmonary embolus, malignant effusion, benign postsurgical changes, pericardiotomy syndrome, collagen vascular diseases (systemic lupus, rheumatoid arthritis), congestive heart disease, sympathetic effusion related to subdiaphragmatic disease (pancreatitis), leakage of ascites or peritoneal dialysis fluids, and hemorrhage (from venous access catheters or aortic tears). Infectious causes include extension of all classes of pulmonary infections from the lungs (parapneumonic), esophageal rupture, parapharyngeal space drainage, drainage or sympathetic effusion due to hepatic or subdiaphragmatic abscesses, septic metastasis, and direct infection via thoracic defects or chest tubes used for pleural drainage. Pyopneumothorax, in the absence of bronchopleural fistula, prior surgery, or prior

thoracentesis, suggests the possibility of gas formation by bacteria implicated in the infection. Although nonspecific, pyopneumothorax suggests a component of anaerobic infection.

LABORATORY DIAGNOSIS

The diagnosis of empyema is based on the characteristics of thoracic fluid. The urgency to diagnosis is due to the development of pleural scar and of loculated effusions in the presence of undrained pus. Thus, diagnostic thoracentesis should be attempted unless the nature of the pleural fluid is clear or the clinical risk to the patient is too great. Pleural fluid analysis should include Gram stain and cultures (routine, anaerobic, mycobacterial, and fungal), parasitologic examination when appropriate, fluid cell count and differential, cytology, pH, lactic dehydrogenase, total protein, and glucose measurements at a minimum. (see Chapter 76) Purulent fluid requires drainage. Empyema is diagnosed on the basis of the neutrophilic predominance in fluids with more than 25,000 white blood cells per milliliter. Parapneumonic effusions will generally have lower white blood counts, negative Gram stains and cultures, a pH over 7.3, and glucose over 50% of serum glucose levels. Parapneumonic fluids may become infected over time. Blood cultures and sputum cultures should be obtained as adjunctive guides to therapy.

TREATMENT

The management of empyema includes antimicrobial treatment, identification and treatment of any anatomic processes, and drainage of the infected fluid. The approach to a specific patient is based on the clinical status of the patient as well as the microbiology of the infection. For example, patients with empyema following thoracic surgery and other hospitalized patients may have useful culture data available from chest tube drainage samples or sputum cultures to assist in the selection of antibiotics. The Gram stain may indicate the predominant organism type. Mixed aerobic and anaerobic organisms may be the first suggestion of esophageal tear or parapharyngeal infection. Fastidious organisms (*S. pneumoniae*, anaerobes) may be seen on Gram stain but not isolated in culture. Antibiotic susceptibility data should be used to guide therapy, especially in nosocomially acquired infection. Local administration of antibiotics (e.g., inhaled, instilled) is unnecessary and may be irritating; intrapleural injection of antibiotics should be reserved for pleural ablation (pleurodesis), as may be achieved with erythromycin.

The decision to drain a pleural fluid collection is based on the characteristics of the fluid. In the presence of pleural fluid and unexplained fever, leukocytosis, or bacteremia, or in the postoperative patient, thoracentesis should be performed routinely. Noninfected parapneumonic pleural effusions resolve with appropriate treatment of the underlying infections. Drainage is required if infection or frank pus is present. Highly viscous or purulent fluids and fluids with acid pH also require the insertion of a chest tube via thoracostomy or the thoracoscopic drainage of the fluid. In approximately one-third of patients, however, drainage through a chest tube along with antibiotic treatment fails to cure an empyema, necessitating surgical intervention.[99] This may be improved through use of DNase plus tissue-plasminogen activator (t-PA) instilled through the chest tube. The use of these two agents in combination has been shown to decrease the number of patients who require surgical intervention.[100]

In the early or exudative phase of parapneumonic effusion, the fluid is thin and serous or serosanguineous. This may resolve during appropriate antibiotic therapy either without drainage or with multiple needle aspirations. If the pH is over 7.3, this method may be preferred. If the pH is less than 7.0, however, complete drainage should be performed, often requiring closed chest tube insertion. If the pH is between 7.0 and 7.3, failure to demonstrate improvement of infection or inflammation on multiple thoracenteses over 3 to 4 days should lead to consideration of formal drainage, especially if the primary process is adequately treated. Loculation of pleural fluid or failure to respond to antimicrobial therapy may require either multiple thoracenteses guided by ultrasound or chest tomographic evaluation (CT scans) or surgical intervention. Bloody fluid or persistent parapneumonic fluid should prompt cytologic evaluation and CT scans for lung masses or undrained mediastinal or retrocardiac collections.

Empyema diagnosed later in the course, persistently infected pleural fluid, viscous fluid, or fluids with acid pH may require large-bore tube drainage. This heavily proteinaceous fluid is characteristic of the fibropurulent phase of the evolving empyema. Indications for closed chest tube placement include bronchopleural fistula with empyema, loculated fluid unresponsive to thoracentesis and antibiotics, the presence of blood clots, and rapidly accumulating empyema not otherwise manageable. Under suction, and with removal of the gel-like material, pus, and clots, the lung expands and obliterates the empyema space. Failure to expand the underlying lung, persistence of drainage beyond 7 days, inability to achieve drainage assessed radiologically, fever without change in 2 to 3 days, or pus formation with persistent infection (as opposed to colonization of the chest tubes) necessitates a search for undrained foci of infection, failure to close a bronchopleural fistula or esophageal tear, undetected rupture of a lung abscess, or antibiotic failure. As the infection enters the chronic phase, open drainage with rib resection or pleurocutaneous fistula formation may be needed, with or without decortication, to achieve lung expansion and healing. Open drainage is obtained by making the pleura adherent to the chest wall during the insertion of chest tubes directly into the empyema cavities. Drainage achieved too late in the course of infection may result in the development of pleural scar and fibrous peel with restrictive pulmonary physiology. Decortication may be needed to achieve sterilization of the pleural space and restore lung expansion. Thoracoscopic drainage of empyema has been used with excellent results at a number of institutions, particularly in children. Often, thoracoscopic drainage of empyema is used as a temporizing maneuver (e.g., following acute rupture of a lung abscess into the pleural space). Patients achieving rapid re-expansion of the lungs may avoid open drainage procedures while achieving limited decortication and disruption of loculations. Alternatively, once a patient is stabilized and can better tolerate open drainage, or has demonstrated an inability to resolve the empyema without further drainage, surgical intervention may be needed. Early, aggressive treatment of empyema may reduce the duration of hospitalization and the risk of nosocomial superinfection.

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CHAPTER 128

Acute Bronchitis and Community-Acquired Pneumonia

Thomas J. Marrie

ACUTE BRONCHITIS

Acute bronchitis is an inflammation of the tracheobronchial tree, usually in association with a generalized respiratory infection affecting 40/1000 adults each year in the United Kingdom.[1] It is the fifth most common diagnosis in patients presenting with cough.[2] It occurs most commonly during the winter months and is associated with respiratory viruses, including rhinovirus, coronavirus, influenza viruses, and adenovirus. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* may also cause bronchitis. Secondary invasion with bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* may also play a role in acute bronchitis. However in only 50% of persons with acute bronchitis have a pathogen identified.[1]

Cough is the most prominent manifestation of acute bronchitis. Initially, the cough is nonproductive, but later mucoid sputum is produced. Still later in the course of the illness, purulent sputum is present. Many patients with acute bronchitis also have tracheitis. Symptoms of tracheal involvement include burning substernal pain associated with respiration and a very painful substernal sensation with coughing. Rhonchi and coarse crackles may be heard on examination of the chest; however, there are no signs of consolidation and the chest radiograph shows no opacity. Cough persists on average 11.4 days.[1,2]

Most cases of acute bronchitis require measures directed only at relieving cough. There are very few good clinical trials comparing various symptomatic relief measures to placebo so we do not know whether or not they are better than placebo.[1] Such measures include analgesics, antihistamines, antitussives, inhaled or oral beta$_2$-agonists, expectorants and mucolytics. For patients with fever or a predominant tracheitis component and purulent sputum, the sputum should be gram stained and cultured. If there is a predominant microorganism seen in the presence of more than 25 polymorphonuclear neutrophils and fewer than 10 squamous epithelial cells per low-power field, antibiotic therapy directed against *S. pneumoniae* and *H. influenzae* should be instituted. Most patients, however, do not require antibiotic therapy for acute bronchitis; it is a self-limited disease. Indeed, overuse of antibiotics in this setting is a driver of antimicrobial resistance.

COMMUNITY-ACQUIRED PNEUMONIA: EPIDEMIOLOGY, CLINICAL ASSESSMENT, AND DIAGNOSTIC WORK-UP

Pneumonia is defined as inflammation and consolidation of lung tissue due to an infectious agent (see also Chapter 122). Pneumonia that develops outside the hospital is considered community-acquired pneumonia (CAP). A clinical definition of pneumonia is two or more of the following symptoms/physical findings: productive cough, purulent sputum, dyspnea or tachypnea (respiratory rate >20 breaths per minute), rigors or chills, pleuritic chest pain in conjunction with a new opacity on chest radiograph.[3] Pneumonia developing 72 hours or more after admission to hospital is nosocomial, or hospital acquired. There is still some debate as to whether nursing home–acquired pneumonia (NHAP) should be considered community-acquired or nosocomial pneumonia. In recent years, the concept of healthcare-associated pneumonia (HCAP) has arisen. This term was introduced in 2005 to

recognize that as a result of the shift of many inpatient hospital services to home, ambulatory care facilities and extended care facilities patients were at risk for infections that resembled hospital-acquired infections.[4] HCAP was defined as pneumonia in patients who have been hospitalized in an acute-care hospital for 2 or more days in the past 90 days, have been residents in a nursing home or long-term care facility (nursing home–acquired pneumonia, or NHAP), received intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days, or attended a hospital or hemodialysis clinic.[5]

This chapter focuses on CAP.

EPIDEMIOLOGY

CAP is both a common and serious illness. In combination with influenza, it is the most frequent cause of infection-related death and the eighth leading cause of death overall in the United States.[6,7] CAP occurs in approximately 4 million adults in the United States—accounting for 10 million physician visits, 1.1 million hospitalizations, and 50,000 deaths per year.[8–10] It accounts for ~3.5 million deaths each year globally and is the highest cause of mortality among infectious diseases.[11] Changes in the epidemiology (both emergence of new pathogens and changing antimicrobial susceptibility of old ones) of the various pathogens, difficulty in making an etiologic diagnosis and complex guidelines for management make this illness a challenge for both patients and their physicians.

The overall attack rate is about 12 cases per 1000 persons per year. In adults, the rate of admission to hospital for the treatment of pneumonia is low from age 17 to 55 years, at which point it begins to increase. The attack rates are highest at the extremes of age.

The epidemiology of pneumonia has changed in recent years. This is due in part to changes in the population at risk and in part to the discovery of new microbial agents that cause pneumonia and changes in antimicrobial susceptibility of old microbial agents, such as *S. pneumoniae, H. influenzae,* and *Staphylococcus aureus.* Population changes include continued increase in the number and proportion of patients who are 65 years of age or older.

There has been a steady increase in the number of organ transplant recipients in the general population and in the number of patients with HIV infection. This has created a subset of patients with CAP who may be infected not only with the traditional pathogens that cause pneumonia but also with opportunistic pathogens; furthermore, these patients may have severe or atypical presentations of this infection. Newer pathogens recognized as causing pneumonia include Hantavirus, SARS CoV, human metapneumovirus, *S. aureus* isolates carrying the Panton-Valentine leukocidin (PVL) genes, and methicillin-resistant *S. aureus* (MRSA). *Pneumocystis jiroveci,* previously a rare cause of pneumonia in intentionally immunocompromised patients, is a common cause of pneumonia in HIV-infected patients with CD4 counts of less than 200/μL.

In a study carried out in a Swedish town in which all persons 60 years of age and older were studied, independent risk factors for CAP were alcoholism, relative risk (RR) 9; asthma, RR 4.2; immunosuppression, RR 1.9; age greater than 70 years versus age 60 to 69 years, RR 1.5.

Risk factors for specific etiologies of pneumonia may differ from those for pneumonia as a whole. Thus, dementia, seizures, congestive heart failure, cerebrovascular disease, and chronic obstructive lung disease were risk factors for pneumococcal pneumonia in one study. In other studies, cigarette smoking and asthma have been found to be independent risk factors for invasive pneumococcal disease. Among HIV-infected patients, the rate of pneumococcal pneumonia is 41.8 times higher than those in the same age group who are not HIV infected. However, with the advent of highly active antiretroviral therapy, the incidence of pneumococcal bacteremia among HIV-infected persons has dropped from 24.1 episodes per 1000 patient-years to 8.2 per 1000 patient-years. Up until a recent study from the Centers for Disease Control and Prevention, the effect of chronic illness on the incidence of invasive pneumococcal disease in adults was underappreciated. In this study, the overall incidence rates of invasive pneumococcal disease was 8.8/100,000 adults. For those with diabetes it was 51.4; 62.9 for adults with chronic lung disease; 93.7 for those with chronic heart disease; and 100.4 among those who abused alcohol. The rate was highest in adults with solid cancer, 300.4, and HIV/AIDS, 422.9.

Risk factors for Legionnaires' disease include male gender, tobacco smoking, diabetes, hematologic malignancy, cancer, end-stage renal disease, and HIV infection. Risk factors for severe respiratory syncytial virus infection in elderly persons include the presence of underlying chronic pulmonary disease (odds ratio [OR] 3.97), functional disability (OR 1.67), and low serum neutralizing antibody titer (OR 5.89). The usual risk factors for aspiration pneumonia are altered level of consciousness and various neurologic diseases that interfere with the swallowing mechanism. Recently, there has been an association between the use of gastric acid suppressive drugs and aspiration pneumonia. The incidence rates of pneumonia in non–acid-suppressive drug users and those who used these agents was 0.6 and 2.45 per 100 person-years, respectively. The risk seemed to be highest among those using proton pump inhibitors.

There is seasonal variation in the rate of pneumonia. Both attack rates and mortality rates are highest in the winter months. This is likely due to many factors, including more time spent indoors (crowding) and hence more opportunity for person-to-person spread of infectious agents. In a study carried out in Tennessee, the weekly frequency of invasive pneumococcal disease correlated with the weekly frequency of isolation of respiratory syncytial virus and influenza virus.

Antimicrobial resistance of the common bacterial pathogens is also a key component of the epidemiology of CAP. Penicillin-resistant *Staphylococcal pneumoniae* (PRSP) is now a fact of life in most North American communities. Many of the PRSP isolates are resistant to three or more antibiotic classes (multidrug resistance). In one study, 14% of bacteremic *S. pneumoniae* isolates were resistant to penicillin, 12% to ceftazidime, and 24% to trimethoprim–sulfamethoxazole. In a recent study, the investigators examined 1817 *S. pneumoniae* isolates collected from patients with community-acquired respiratory tract infections at 44 US medical centers during the winter of 2002 to 2003. The overall rates of resistance were as follows: penicillin 34.2%; ceftriaxone 6.9%; erythromycin 29.5%; clindamycin 9.4%; tetracycline 16.2%; and trimethoprim–sulfamethoxazole 31.9%. There was no resistance to the following agents: vancomycin, linezolid, and telithromycin. Multidrug resistance was present in 22.2% of the isolates and 2.3% of the isolates had ciprofloxacin MICs of greater than or equal to 4 μg/mL. Currently in the United States about 26% of *S. pneumoniae* are resistant to penicillin and 25% are resistant to erythromycin.[12] However within serotype nonsusceptibility varies widely across the various states.[12] Serotypes 6C, 15A, 19A, 23A account for most of the penicillin nonsusecptibility and 6C, 15A, 19A, and 22F account for most of the isolates that are both penicillin and erythromycin nonsusceptible.[12] Fortunately, it is possible to predict who is likely to have pneumonia due to PRSP. Previous use of beta-lactam antibiotics, alcoholism, noninvasive pneumococcal disease, age less than 5 or greater than 65 years, and immunosuppression are risk factors for PRSP pneumonia. In Canada, *S. pneumoniae* resistance to levofloxacin remains very low, peaking at 1.5% in 2008, while no isolates tested in 2011 were resistant.[13] However in Spain 3.3% of *S. pneumoniae* isolates are resistant to levofloxacin and there is evidence of clonal spread.[14]

CLINICAL MANIFESTATIONS

Symptoms that are suggestive of pneumonia include fever, chills, pleuritic chest pain, and cough. The cough may be nonproductive (dry) or productive of mucoid or purulent sputum. It may be rusty in color and frankly bloody; in patients with a lung abscess (anaerobic infection), it may have a foul odor. The latter is suggestive of anaerobic infection.

TABLE 128-1 Clues to the Etiology of Pneumonia from the History and Physical Examination

Feature	Organism
Environmental	
Exposure to contaminated air-conditioning cooling towers, recent travel associated with a stay in a hotel, exposure to a grocery store mist machine, visit or recent stay in a hospital with contaminated (by *L. pneumophila*) potable water	*Legionella pneumophila*
Pneumonia after windstorm in an endemic area	*Coccidioides immitis*
Outbreak of pneumonia in shelters for homeless men, jails, military training camps	*Streptococcus pneumoniae; Mycobacterium tuberculosis*
Exposure to contaminated bat caves, excavation in endemic areas	*Histoplasma capsulatum*
Animal contact	
Exposure to infected parturient cats, dog, cattle, sheep, or goats	*Coxiella burnetii*
Exposure to turkeys, chickens, ducks, or psittacine birds	*C. psittaci*
Exposure to mouse droppings	Hantavirus
Travel history	
Travel to Thailand or other countries in Southeast Asia	*Burkholderia (Pseudomonas) pseudomallei (melioidosis)*
Pneumonia in immigrants from Asia, India, Africa	*M. tuberculosis*
Travel almost anywhere	*Legionella species*
Occupational history	
Pneumonia in a healthcare worker who works in a large city hospital with patients infected with HIV	*M. tuberculosis*
Welding	*S. pneumoniae*
Host factors	
Diabetic ketoacidosis	*S. pneumoniae* *Staphylococcus aureus*
Alcoholism	*S. pneumoniae* *Klebsiella pneumoniae* *S. aureus*
Chronic obstructive lung disease	*S. pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Pseudomonas aeruginosa* (in the subset of patients with advanced COPD)
Solid-organ transplant recipient (pneumonia occurring >3 mo after transplant)	*S. pneumoniae* *H. influenza* *Legionella* spp. *Pneumocystis jiroveci* *Cytomegalovirus* *Strongyloides stercoralis*
Sickle cell disease	*S. pneumonia*
HIV infection with	*P. jiroveci*
CD4 cell count <200/μL	*S. pneumonia* *H. influenza* *Cryptococcus neoformans* *M. tuberculosis* *Rhodococcus equi*
Physical findings	
Periodontal disease and foul-smelling sputum	Anaerobes, may be mixed aerobic-anaerobic infection
Bullous myringitis	*Mycoplasma pneumoniae*
Absent gag reflex, altered level of consciousness, or a recent seizure	Polymicrobial (oral aerobic and anaerobic bacteria) can be macro- or microaspiration
Encephalitis	*M. pneumonia* *C. burnetii* *L. pneumophila*
Cerebellar ataxia	*M. pneumonia* *L. pneumophila*
Erythema multiforme	*M. pneumonia*
Erythema nodosum	*C. pneumonia* *M. tuberculosis*
Ecthyma gangrenosum	*P. aeruginosa* *Serratia marcescens*
Cutaneous nodules (abscesses) and CNS findings	*Nocardia* spp.

Source: Reproduced with permission from Marrie TJ. Community acquired Pneumonia. Clin Infect Dis. 1994;18(4):501–513.

Elderly patients complain of fewer symptoms than do younger patients. Indeed, those greater than 75 years of age with pneumonia had 3.3 fewer total symptoms than did patients aged 18 to 44 years with pneumonia.

For some time it was held that typical pneumonia (due to pyogenic organisms such as pneumococcus, staphylococcus, or *H. influenzae)* could be distinguished from that due to *M. pneumoniae*, *Legionella* spp., and *C. pneumonia* – so-called atypical pneumonia agents – on the basis of a distinct clinical presentation. Atypical pneumonia is said to be characterized by a more indolent illness than that of typical pneumonia, with a cough that is nonproductive or productive of mucoid sputum only. Careful studies have shown that one cannot reliably distinguish between typical versus atypical pneumonia on clinical grounds. However, this is not to say that a careful history and physical examination are not helpful in suggesting a cause of the pneumonia. Table 128-1 gives a partial list of clues to the cause of pneumonia that may be obtained from the history and physical examination.

Nonrespiratory symptoms such as headache, nausea, vomiting, abdominal pain, diarrhea, myalgia, and arthralgia are also common symptoms in patients with pneumonia. It is wise to remember that the elderly complain of fewer symptoms with pneumonia than do younger patients.

In some instances extrapulmonary signs and symptoms may dominate the clinical picture. Thus, *M. pneumoniae* may be complicated by a variety of neurologic manifestations including encephalitis, meningitis, and cranial nerve palsies. In addition a maculopapular skin rash is not uncommon. Occasionally, Stevens–Johnson syndrome develops. Patients with *Legionella* pneumonia may have glomerulonephritis or cerebellar ataxia. One should also remember that pyogenic bacteria that cause pneumonia *(S. aureus, S. pneumoniae)* can cause metastatic infections such as endocarditis, brain abscess, and meningitis. Indeed, all patients with pneumonia and *S. aureus* bacteremia should have a careful evaluation for endocarditis.

■ PHYSICAL EXAMINATION

Fever is usually present, but some patients may be hypothermic (a poor prognostic sign), and some (20%) are afebrile at the time of presentation with pneumonia. Crackles are heard on auscultation over the affected area of lung, and physical findings of consolidation (dullness to percussion, increased tactile, vocal fremitus, whispering pectoriloquy, and bronchial breath sounds) are present in about 20% of patients with pneumonia. A pleural friction rub is heard in about 10% of cases. Early in the course of the illness physical examination of the chest may be normal. It is most important to count the respiratory rate for at least 1 minute in patients suspected of having pneumonia. A respiratory rate of ≥28 breaths per minute in an adult is indicative of severe pneumonia and an alert that such patients are at high risk for respiratory failure.

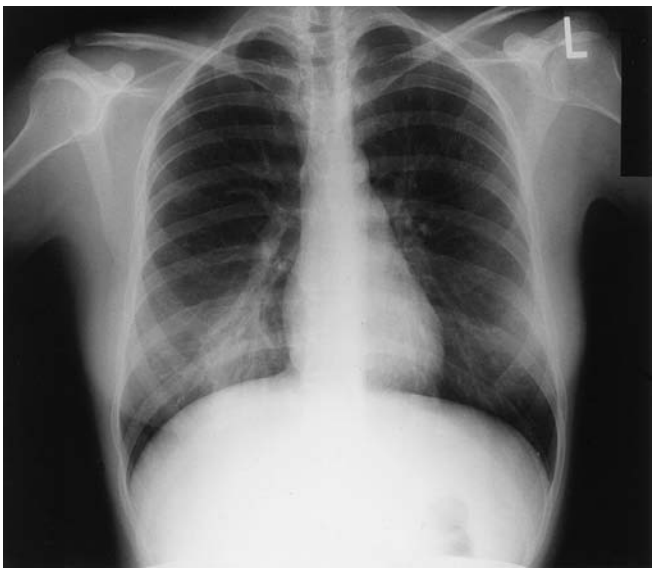

Figure 128-1 Right lower lobe pneumonia due to *Coxiella burnetii* (Q fever). This young woman developed pneumonia after exposure to the products of conception of her infected pet cat.

■ RADIOGRAPHIC DIAGNOSIS

A clinical suspicion of pneumonia usually prompts a chest radiograph. An opacity on the chest radiograph is considered the gold standard for the diagnosis of pneumonia. However, this opacity may be due to infection, infarction, hemorrhage, edema fluid, malignancy, or inflammation caused by a variety of processes, such as vasculitis or adverse drug reactions. Several studies have shown that radiologists cannot differentiate bacterial from nonbacterial pneumonia on the basis of the radiograph. Representative chest radiographs of patients with pneumonia are shown in Figures 128-1 to 128-4. For patients with pneumonia treated on an ambulatory basis, there is considerable disagreement (in up to 50% of cases)

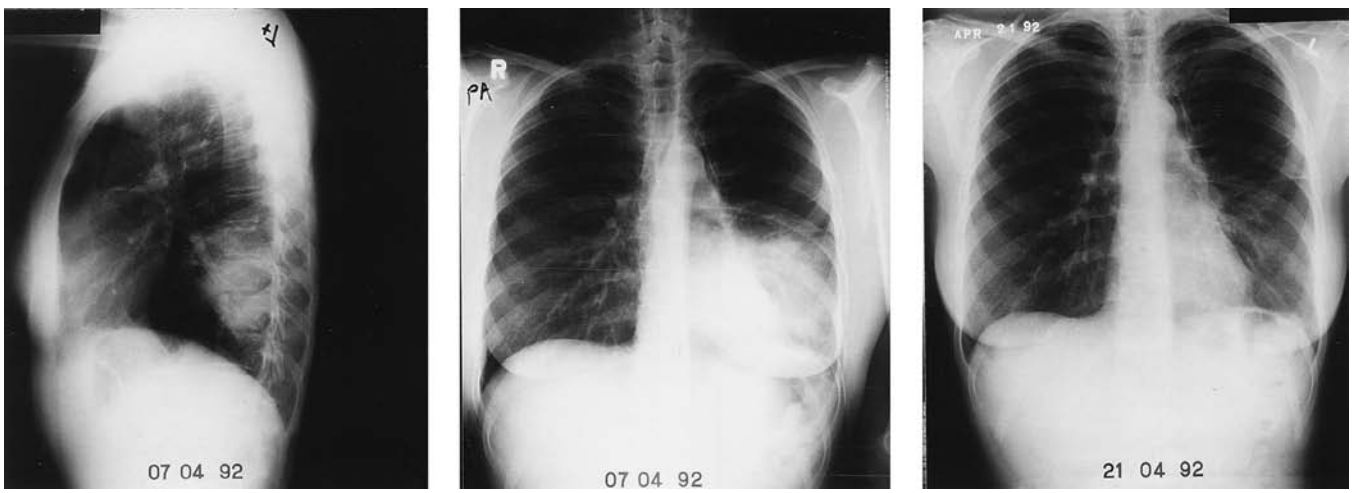

Figure 128-2 Serial chest radiographs of a 32-year-old nurse with *Chlamydia psittaci* pneumonia. She was severely ill with fever, chills, and headaches. She had severe fatigue for 8 months after this episode of pneumonia.

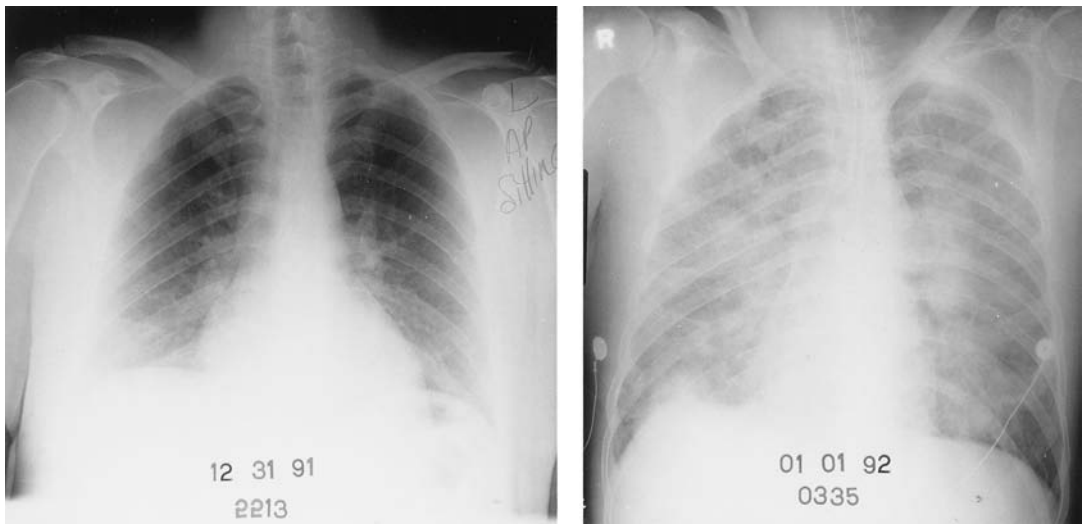

Figure 128-3 Chest radiographs showing rapidly progressive diffuse pulmonary opacities in a 22-year-old man with bacteremic *Streptococcus pneumoniae* pneumonia. This patient had had his spleen removed 6 years earlier. He rapidly developed septic shock and died about 8 hours after admission.

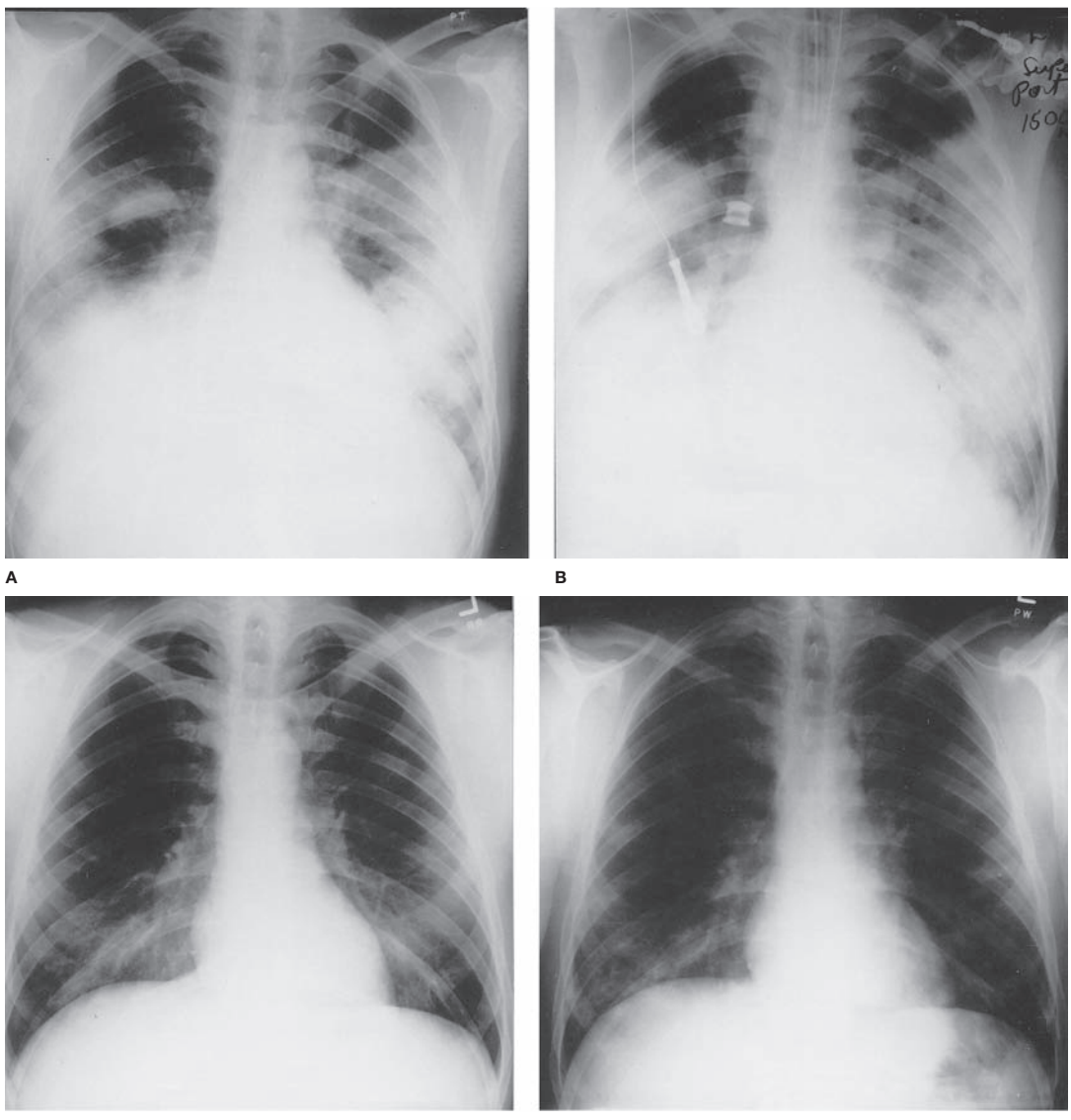

Figure 128-4 Serial chest radiographs (temporal sequence: A., B., C., D.) of a 40-year-old man with pneumonia due to *Legionella pneumophila* serogroup 6.

between the radiologist's reading of the chest radiograph regarding the presence of pneumonia compared with that of the attending physician. In about 20% of patients with symptoms compatible with pneumonia and a plain chest radiograph read as normal or no pneumonia by the radiologist, computed tomography of the chest will be compatible with pneumonia. It is noteworthy that when patients who are admitted to hospital with a clinical diagnosis of pneumonia (radiologist says no pneumonia) are compared with those with radiologist-confirmed pneumonia, there is no difference in mortality between the two groups. While the percentage of patients with positive blood cultures does not differ between the groups, the microorganisms isolated do; about 60% of the isolates for those with definite pneumonia are *S. pneumoniae* compared with 31% for those with clinical pneumonia.

■ ETIOLOGIC DIAGNOSIS

Pneumonia represents a difficult challenge for the clinician, since the etiology cannot be determined from the clinical presentation and data from microbiologic studies are not available for at least 48 hours. Even then, in the case of microorganisms isolated from the sputum, one cannot be sure that this is the organism causing the pneumonia, and not just a microorganism that had colonized the upper airway through which the sputum passed on its way to the specimen jar. For this reason, it is useful to categorize the etiology of pneumonia as definite or probable (Table 128-2).

Newer tests that can be used to help make an etiologic diagnosis of pneumonia include testing urine for antigens of *S. pneumoniae* or *Legionella*. However, only tests for *Legionella pneumophila* serogroup 1 are readily available. Nasopharyngeal swabs can be test for a variety of pathogens using multiplex polymerase chain reaction.

The etiology of CAP as determined in prospective studies is given in Tables 128-3 to 128-5. Table 128-4 shows data for patients with severe pneumonia requiring admission to intensive care units. Table 128-5 gives the etiologic data for bacterial pneumonia in patients with HIV infection. Early in the course of the HIV epidemic, *P. jiroveci* accounted for most cases of pneumonia. Now, with widespread use of prophylaxis to prevent *Pneumocystis* pneumonia, bacterial pneumonia is more common in HIV disease than previously seen (see Chapter 123). Indeed, the rates of pneumococcal pneumonia and *H. influenzae* pneumonia are 20 times higher among HIV-infected persons than in those of an age- and sex-matched population without HIV infection. In any young person with pneumococcal bacteremia, consider underlying HIV infection. However, one should not forget about *P. jiroveci* pneumonia, since many persons do not know they have HIV and this form of pneumonia is the presenting manifestation of HIV disease in these individuals. Likewise, one should never forget *Mycobacterium tuberculosis* as a cause of pneumonia, especially in the elderly.

While the data given in the tables are old, these studies remain some of the best that have been done to determine the etiology of pneumonia. In a study carried out at a Veterans Administration Hospital in Houston, Texas during 2011 and 2012, using the most up to date methods, no etiology was found in 45.9%; 23% bacterial cause; 16% viral (about 20% of these had a coinfection with a bacterial pathogen); 26% had a syndrome indistinguishable from bacterial pneumonia and 17% were clearly uninfected.[15]

Given the difficulty in making an etiologic diagnosis investigators have sought a biomarker that would distinguish bacterial infection from viral infection or noninfectious causes. Procalcitonin is the biomarker that has been most intensively studied. Procalcitonin is the hormone precursor of calcitonin expressed by C cells of the thyroid gland. The rationale for measuring procalcitonin is that its conversion to calcitonin is inhibited by a number of cytokine and bacterial endotoxins, hence in bacterial infections procalcitonin levels will be high. Indeed a number of studies have shown that serum procalcitonin levels rise and fall rapidly in bacterial infections. A level of 0.25 ng/mL or higher in the setting of pneumonia is felt to be predictive of a bacterial infection as the cause.[16] While a number of studies to date have validated the usefulness of procalcitonin as an aid to starting or stopping antimicrobial therapy, it is only that an aid.

■ ADMISSION DECISION

Once a diagnosis of pneumonia has been made, the next decision is whether or not to admit the patient to the hospital. Now, more than ever, there is considerable pressure to treat as many patients as possible at home. In order to do this, it is important to know the factors that are predictive of complicated course in pneumonia, some of which are given in Table 128-6. Several clinical rules that predict mortality have been developed that are often used to guide the admission decision. Two of these are the pneumonia severity index, often known as the patient outcomes research team (PORT) score (Tables 116-7 and 116-8) and the CURB-65 (confusion; urea; respiratory rate; blood pressure; age >65 years) rule (Table 116-9).[17,18] The former, developed by Fine et al.,[17] assigns points to each of 20 different items that had been shown to be associated with mortality (see Table 128-7). This system allows categorization of patients with pneumonia into five strata, with increasing risk for mortality from risk classes I to V. Mortality is less than 1% for patients in risk classes I to III, but increases to 9% in class IV, and

TABLE 128-2 Guidelines for Determining the Degree of Certainty of the Etiology of CAP

Definite
Blood cultures positive for a pathogen
Pleural fluid positive for a pathogen
Presence of *Pneumocystis jiroveci* in induced sputum or in bronchoalveolar lavage fluid
A fourfold or greater rise in antibody titer to *Mycoplasma pneumoniae, Chlamydia pneumoniae, Coxiella burnetii*, or other pathogens for which serologic testing is available
Isolation of *Legionella pneumophila* or a fourfold rise in antibody titer or positive urinary antigen test for *Legionella*
Positive direct fluorescence antibody test for *Legionella* plus an antibody titer of ≥1:256 for *Legionella*
Serum or urine positive for *Streptococcus pneumoniae* antigen
Isolation of Mycobacterium *tuberculosis* from sputum
Amplification of nucleic acid of *Legionella* species from a nasopharyngeal swab specimen
Probable
Heavy or moderate growth of a predominant bacterial pathogen on sputum culture and a compatible Gram stain
Light growth of a pathogen in which sputum Gram stain reveals a bacterium compatible with the culture results
Amplification of nucleic acid of *M. pneumoniae*; *C. pneumoniae*; influenza viruses A and B; parainfluenzae viruses 1, 2, 3; adenovirus, respiratory syncytial virus; human metapneumovirus from a nasopharyngeal swab specimen
Aspiration pneumonia as diagnosed on clinical grounds

Source: Data from Fang GD, Fine M, Odoff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: A prospective multicenter study of 359 cases. Medicine. 1990;69(5):307–316.

TABLE 128-3 Etiology of Community-Acquired Pneumonia Requiring Hospitalization: North America

Reference	Fang et al.	Marrie et al.	Bates et al.
Number of patients studied	359	719	151 (154 episodes)
Number (%) of patients with sputum cultured	336 (94)	257 (36)	None[a]
Location	Pittsburgh, PA	Halifax, NS	Little Rock, Ark
Time period of study	Jul 1/86–Jun 30/87	Nov 1/81–Mar 18/87	1985
Number (%) with pneumonia of:			
Unknown cause	118 (32.9)	340 (47)	75 (48.7)
More than one cause (polymicrobial)	10 (2.8)	74 (10.3)	10 (6.4)
Streptococcus pneumoniae	39 (10.9)	61 (8.5)	9 (5.8)
Aspiration	12 (3.3)	52 (7.2)	Not stated
Mycoplasma pneumoniae	7 (2)	40 (5.6)	5 (3.2)
Influenza A virus	Not tested	40 (5.6)	7 (4.5)
Staphylococcus aureus	12 (3.3)	29 (4.0)	9 (5.8)
Haemophilus influenzae	39 (10.9)	27 (3.7)	2 (1.3)
Coxiella burnetii	Not tested	22 (3.1)	0
Influenza B virus	Not tested	17 (2.4)	0
Pneumocystis jiroveci	9 (2.5)	14 (1.9)	0
Legionella spp.	24 (6.7)	16 (2.2)	14 (9)
Mycobacterium tuberculosis	4 (1.1)	10 (1.4)	3 (1.9)
Chlamydophila pneumoniae	22 (6.1)	18/301 (6)[b]	12 (7.8)
Postobstructive	19 (5.3)	13 (1.8)	Excluded
S. epidermidis	0	0	4 (2.6)
Aspergillus spp.	0	0	1 (0.6)
Nocardia spp.	0	0	1 (0.6)
Francisella tularensis	Not tested	Not tested	5 (3.2)
Streptococcus spp.	10 (2.8)	19 (2.6)	4 (2.6)
Anaerobic bacteria	0	4 (0.6)	2 (1.3)
Other aerobic gram-negative bacteria	21 (5.9)	22 (3.1)	8 (5.2)

[a]*This study did not use information from sputum cultures in determining cause. Some patients had a variety of invasive diagnostic procedures.*
[b]*Only 301 patients had serum samples tested for antibodies to Chlamydophila pneumoniae.*
Source: Data from Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: A prospective multicenter study of 359 cases, Medicine. 1990;69:307–316; Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis. 1989;11:586–599; Bates JH, Campbell GD, Barren AL, et al. Microbial etiology of acute pneumonia in hospitalized patients. Chest. 1992;101:1005–1112.

TABLE 128-4 Etiology of CAP in Patients Requiring Admission to an ICU

Reference	(BTS; PHLS)	Torres et al.	Pachon et al.	Ortqvist et al.
No. studied	60	92	67	53
Mean age (y)	54	53	56.8	52
Number of patients (%) died	29 (48)	18 (20)	14 (21)	13 (25)
No. (%) with pneumonia due to:				
Unknown	25 (42)	44 (48)	45 (67)	25 (47)
Streptococcus pneumonia	11 (18)	13 (14)	12 (17)	15 (28)
Haemophilus influenza	7 (12)			
Legionella pneumophila	7 (12)	13 (14)	7 (10)	
Mycoplasma pneumonia	4 (7)	6 (7)		3 (5)
Influenza virus	3 (5)			2 (4)
Staphylococcus aureus	2 (3)	1		2 (4)
Streptococcus spp.		3 (3)		
Chlamydophila psittaci				2 (4)
Other aerobic gram-negative bacilli	2 (3)	5 (5)	8 (12)	

Source: Data from British Thoracic Society Research Committee and the Public Health Laboratory Service: The aetiology, management, and outcome of severe community-acquired pneumonia on the intensive care unit. Respir Med. 1992;86:7–13; Torres A, Serra-Battles J, Ferrer A, et al. Severe community-acquired pneumonia: Epidemiology and prognostic factors. Am Rev Respir Dis. 1991;144:312–318; Pachon J, Prados MD, Capote F, et al. Severe community-acquired pneumonia: Etiology, prognosis and treatment. Am Rev Respir Dis. 1990;142:369–373; Ortqvist A, Sterner G, Nilsson JA. Severe community-acquired pneumonia: Factors influencing need of intensive care treatment and prognosis. Scand J Infect Dis. 1985;17:377–386.

TABLE 128-5 Etiology of Bacterial CAP in 216 Patients with HIV Infection[a]

Cause of Pneumonia	Number (%)
Cause of pneumonia (no., %)	
Haemophilus influenzae	4 (1.9)
Streptococcus pneumoniae	66 (30.6)
Moraxella catarrhalis	1 (0.5)
Other streptococcus	15 (6.9)
Cause unknown	54 (25)
Mixed infections	13 (6)
Haemophilus spp.	42 (19.4)
Klebsiella pneumoniae	4 (1.9)
Staphylococcus aureus	10 (4.6)
Pseudomonas aeruginosa	5 (2.3)
Serratia marcescens	1 (0.5)
Neisseria meningitidis	1 (0.5)

[a]*Study of 216 episodes of pneumonia in San Francisco from May 1990 to April 1991.*

Source: Adapted with permission from Burack JH, Hahn JA, Saint-Maurice D, et al. Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection: Implications for rationale empiric antibiotic therapy. Arch Intern Med. 1994;154(22):2589–2596.

TABLE 128-6 Risk Factors for a Complicated Course or Mortality in Patients with CAP

Age >65 years
Comorbid illnesses that are likely to be made worse by the pneumonia, especially chronic renal failure, ischemic heart disease, congestive heart failure, severe COPD, concurrent malignancy
Postsplenectomy state
Altered mental status
Alcoholism
Immunosuppressive therapy
Respiratory rate >30 breaths per minute
Diastolic blood pressure <60 mm Hg; systolic blood pressure <90 mm Hg
Hypothermia
Creatinine >150 mM/L or BUN >7 mM/L
Leukopenia <3000/μL or leukocytosis >30,000/μL
Po_2 <60 mm Hg or Pa_{O_2} >48 mm Hg while breathing room air
Albumin <30 g/L
Hemoglobin <9 g/L
Pseudomonas aeruginosa or *Staphylococcus aureus* as the cause of the pneumonia
Bacteremic pneumonia
Multilobe involvement on chest radiograph
Rapid radiographic progression of the pneumonia, defined as increase in the size of the pulmonary opacity of ≥50% within 36 h

TABLE 128-7 Community-Acquired Pneumonia Severity-of-Illness Scoring System: Assignment of Points[a]

Patient Characteristics	Number of Points
Demographic factors	
Age	
Men	Age in years
Women	Age in years minus 10
Nursing home resident	Age plus 10
Coexisting illnesses (definitions listed below)	
Neoplastic disease[b]	30
Liver disease[c]	20
Congestive heart failure[d]	10
Cerebrovascular disease[e]	10
Renal disease[f]	10
Physical examination findings	
Altered mental status[g]	20
Respiratory rate >30/min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35°C (95°F) or >40°C (104°F)	15
Pulse rate >125/min	10
Laboratory and roentgenographic findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL (11 mmol/L)	20
Sodium <130 mmol/L	20
Glucose >250 mg/dL (14 mmol/L)	10
Hematocrit <30%	10
Partial pressure of arterial oxygen <60 mm Hg	10
Pleural effusion	10

[a]*Based on Pneumonia Patient Outcomes Research Team (PORT) cohort study data.*
[b]*Any cancer (except basal or squamous cell carcinoma of the skin) active at presentation or within 1 y of presentation for CAP.*
[c]*Clinical or histologic cirrhosis or chronic active hepatitis.*
[d]*Diagnosis documented by history or by findings on physical examination, chest film, echocardiogram, multiple gated acquisition scan, or left ventriculogram.*
[e]*Clinical diagnosis of stroke or transient ischemic attack, or stroke documented by MRI or CT.*
[f]*History of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in this medical record.*
[g]*Disorientation as to person, place, or time that is not known to be chronic; stupor or coma.*

to 27% in class V (see Table 128-8). Patients in risk classes I and II can usually be treated at home; those in risk class III may require a period of observation in the emergency room before a decision is made about the optimal site of treatment. Patients with pneumonia generally prefer to be treated at home if it can be done safely. As more experience has been gained with this prediction rule, not unexpectedly we have learned that the rule is only a guide. It does not factor social circumstances into the score and since the score is heavily age dependent, many young patients fall into the first three classes when it is readily apparent that they should be admitted.

In the CURB-65 rule the score can range from 0 (none of the elements present) to 5 (all of them present). For a score of 0 the mortality rate is 0.7%; 1% to 3.2%; 2% to 3%; 3% to 17%; 4% to 41.5%, and 5% to 57% (see Table 128-9).[18]

TABLE 128-8 30-Day Mortality Rate for Patients with Community-Acquired Pneumonia According to Risk Class in the Pneumonia Severity of Illness Scoring System

Risk Class	Criteria	Outpatients Mortality	Inpatients Mortality
I	Age <50 y. No existing illnesses or vital sign abnormalities	0	0.5%
II	<70 points	0.4%	0.9%
III	71–90 points	0	1.25%
IV	91–130 points	12.5%	9.0%
V	>131 points	NA	27.1%
	Mean mortality rate	0.6%	8.0%

However, the most important element in the admission decision is the physician's judgment. Prediction rules are no substitute for this. Functional status of your patient in the week prior to admission is also a powerful predictor of mortality. In one study, for those who were fully functional, the in-hospital mortality rate was 3.9%; for those walking with assistance, it was 5.6%; for those who used a wheelchair, it was 20%; and for those who were bedridden, it was 25%.[19]

DIAGNOSTIC WORK-UP

Patients who are well enough to be treated as outpatients need minimal diagnostic work-up. This should include a chest radiograph, complete white blood count, electrolytes, creatinine, and oxygen saturation by pulse oximetry. It is worth noting that there is controversy as to whether or not all patients who present in an office setting and are suspected of having pneumonia should have the described work-up. However, there is no doubt that those who present to a hospital emergency department and are suspected of having pneumonia should at the very least have the work-up outlined earlier. All individuals who have pleuritic chest pain and symptoms and signs suggestive of pneumonia should have a chest radiograph, and pulmonary thromboembolic disease should be part of the differential diagnosis. Pulmonary infarction can mimic pneumonia on occasion. Despite the opinion of some experts, a sputum specimen should be submitted for culture whenever possible. Blood cultures should be done on all ambulatory patients with fever (oral temperature ≥38°C) and suspicion of pneumonia.

In patients who are ill enough to be admitted to the hospital, two sets of blood cultures should be performed. About 10% of patients with pneumonia have positive blood cultures. *S. pneumoniae* is the most common cause of bacteremic pneumonia, accounting for 60% of all cases. Despite the controversy about the utility of sputum Gram stain and culture, this is still a useful test. Take the time to obtain the specimen yourself. One of the chief reasons why this test has fallen into disrepute is that collecting the specimen is a task assigned to other members of a busy healthcare team. A sample collected hours after antimicrobial therapy has been initiated is useless.

All patients who present to the hospital with pneumonia should have their oxygenation status assessed. This can be done by pulse oximetry, and a blood gas analysis should be obtained if the oxygen saturation is less than or equal to 90%. Patients with chronic obstructive lung disease should have blood gases done because hypercarbia cannot be detected by pulse oximetry.

TABLE 128-9 CURB-65 Rule Severity of Illness Scoring System for Community-Acquired Pneumonia

Confusion : new mental confusion
Urea >7 mM/L
Respiratory rate >30 breaths per minute
Blood pressure: diastolic BP <60 mm Hg or systolic blood pressure <90 mm Hg
Age ≥65 y of age
Group 1: 0 or 1 of the above; mortality low – 1.5%. Likely suitable for treatment at home
Group 2: 2 of the above; mortality – 9.2%. Hospitalization for treatment
Group 3: 3 or more of the above; mortality – 22%. Likely requires admission to ICU

Source: Data from Lim WS, van der Eerden MM, Laing R, et al. Defining community-acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax. 2003;58(5):377–382.

SPUTUM GRAM STAIN AND CULTURE

A sputum specimen should be cultured only if a smear of a representative portion shows more than 25 polymorphonuclear neutrophils and fewer than 10 squamous epithelial cells per low-power field. The Gram stain on such a specimen is useful. If only one morphologic type of bacteria is seen in such a specimen, it is likely that this microorganism is causing the pneumonia. Indeed, in one study, when more than 10 gram-positive lancet-shaped diplococci were seen, the sputum was considered positive for pneumococci. This criterion was met in 62% of specimens that were culture positive for *S. pneumoniae*. The value of sputum culture in the diagnosis, management, and outcome of CAP remains a matter of controversy. The Infectious Diseases Society of America pneumonia guidelines in 2000 recommended gram staining and culture of expectorated sputum for inpatients with CAP.[20] The reasons for this recommendation are to permit optimal antibiotic selection directed to causative agent; limit injudicious antibiotic use in terms of cost, inducible resistance, and adverse drug reactions; allow for a rational basis for change from parenteral to oral therapy and any change in therapy necessitated by an adverse drug reaction; identify drug-resistant pathogens and monitor trends such as penicillin-resistant *S. pneumoniae*, beta lactamase–producing *H. influenzae*, or MRSA; and prompt tracing of the contacts of those with *Neisseria meningitidis* pneumonia. On the other hand, the American Thoracic Society pneumonia guidelines recommend sputum culture only if a drug-resistant pathogen, or an organism not covered by usual empiric therapy, is suspected.[21] The most recent version of the Infectious Diseases Society of America Guidelines now state that a pretreatment Gram stain and culture of sputum should be obtained only if a good quality specimen can be obtained.[22]

In patients with HIV infection, sputum production may be induced by inhalation of hypertonic saline, which irritates the tracheobronchial tree and produces bronchorrhea. This results in a specimen that is useful for examination for *P. jiroveci*, thereby obviating the need for bronchoscopy.

Patients who are ill enough to require admission to an intensive care unit for the treatment of their pneumonia should have an aggressive diagnostic work-up. This will usually include at least a bronchoscopy, with use of a protected brush to sample respiratory secretions and bronchoalveolar lavage. If this is carried out before the initiation of antibiotic therapy, the diagnostic yield is up to 80%. When this procedure is performed after 72 hours or more of antibiotic therapy, however, the microbiologic yield is much lower, 18%.

Transthoracic needle aspiration can be used when the basal segment(s) of the lungs is (are) consolidated. A 20-gauge 3.5-inch needle is used to inject 2 to 3 mL of non-bacteriostatic saline into the lung. This is then aspirated and placed into a blood culture bottle. The diagnostic yield from this procedure ranges from 33% to 85%. This procedure is contraindicated in those who are receiving mechanical ventilation. Occasionally, patients with CAP require an open lung biopsy. However, this is usually a last resort in a patient whose condition continues to deteriorate and there is no etiologic diagnosis despite the usual work-up, including bronchoscopy.

An acute-phase serum sample should be obtained from all patients who are admitted to hospital with CAP. If the patient responds promptly to antibiotic therapy, there is no need to obtain a convalescent sample. If the patient responds poorly to therapy, however, a convalescent sample should be obtained 3 to 6 weeks after the acute-phase sample. The diagnostic battery ordered depends on local epidemiologic conditions. In general, *M. pneumoniae*, *C. pneumoniae*, *Coxiella burnetii*, *Legionella pneumophila*, adenovirus, influenza A and B viruses, parainfluenza viruses 1, 2, and 3, and respiratory syncytial virus antibodies can be measured in most laboratories. Antibody titers to *S. pneumoniae* pneumolysin and detection of immune complexes to this antigen maybe a tool for diagnosis of pneumococcal pneumonia in those who do not have sputum available for culture. However, this test is not widely available.

L. pneumophila serogroup 1 infection can be reliably diagnosed from detection of antigen in urine with a radioimmunoassay or an enzyme-linked immunosorbent assay. In the absence of an outbreak, *Legionella* spp. accounts for about 2% of cases of CAP. Thus, the dilemma is when to order this test. To some extent this depends on local epidemiology (in some hospitals the test is ordered for all patients sick enough to be admitted for treatment of CAP), but in general for patients with severe pneumonia this test probably should be done.

There is also a urinary antigen test for pneumococcal pneumonia. This test detects C polysaccharide, which is present in all serotypes of *S. pneumoniae*. It is reasonably sensitive and specific when bacteremic pneumococcal pneumonia is used as the gold standard. The question is, what is its usefulness in patients with negative blood cultures? There are false positives in children with nasopharyngeal colonization with *S. pneumoniae*.

Multiplex polymerase chain reaction (PCR) is a tool that may be useful in the etiologic diagnosis of CAP. Currently, from one specimen such as a nasopharyngeal swab or sputum, the following agents can be detected by multiplex PCR: *M. pneumoniae*; *C. pneumoniae*; *Legionella* spp.; influenza viruses A and B; parainfluenza 1,2,3 viruses; adenovirus; respiratory syncytial virus; human metapneumovirus; coronaviruses; and rhinoviruses. Using this technology, we have learned that viral pneumonia is more common in adults than was previously recognized. However, more study is necessary before we know the role of multiplex PCR in our diagnostic armamentarium.

Other Tests

C-reactive protein, serum procalcitonin, and neopterin have been used in an attempt to distinguish viral from bacterial infection. An ultrasensitive assay for procalcitonin looks promising in that at a level of less than or equal to 0.25 µg/L, antibiotic therapy has been successfully discontinued in patients with pneumonia. The inference is that patients with this level of procalcitonin have viral pneumonia or a non-infectious, non-inflammatory cause for the pulmonary opacity.

TREATMENT

The initial therapeutic approach to pneumonia is empirical (see also Chapters 122 and 125).[23] Categorize the severity of the pneumonia as mild, moderate, or severe. It is then usually self-evident where the patient should be treated; at home, in the hospital, or in an intensive care unit. Table 128-10 outlines the guidelines for initial antimicrobial therapy for CAP as proposed by the American Thoracic Society and the Infectious Diseases Society of America. A key concept in selecting empiric antibiotic therapy is to inquire about antibiotic therapy in the past 3 months and then select an agent that has not been used in that time period. If a macrolide has been used in this time period, then up to 35% of *S. pneumoniae* isolates are resistant to a macrolide compared with 7% if the patient did not have macrolide therapy in this time period. For penicillin or a cephalosporin, resistance increases from 5% to 9% in this setting. Thus, use a different class of antibiotic than the one the patient received in the past 3 months.

Since in everyday practice an etiologic diagnosis is frequently not made, antibiotic therapy has to be empirical. Osterheet et al. attempted to answer the question of whether combination therapy or monotherapy with a fluoroquinolone (as recommended by the North American guidelines) is better than other therapy for the empiric treatment of CAP. They carried out a Medline search of studies published from January 1997 to April 2003. Only eight of the 135 articles fit their criteria for further analysis. In six of the eight studies, a significant reduction in all-cause mortality was found for patients treated with a combination of a beta-lactam plus a macrolide or with monotherapy with a fluoroquinolone. Three of these

TABLE 128-10 Initial Empiric Antimicrobial Therapy for CAP

Outpatient
• If previously healthy and no recent antibiotic therapy: a macrolide (strong recommendation), doxycycline (weak recommendation)
• Presence of comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, diabetes, or malignancy or use of antibiotics within the past 3 mo: a respiratory fluoroquinolone–levofloxacin 750 mg or moxifloxacin or gatifloxacin. A beta-lactam plus a macrolide.
• In regions with a high rate (>25%) of infection with high level (MIC ≥ 16 µg/mL) macrolide-resistant Streptococcus pneumoniae, consider use of alternate agents listed above for patients with comorbidities.
Inpatient
Non-ICU
A respiratory fluoroquinolone
A macrolide plus beta-lactam
ICU
Pseudomonas infection is not a consideration: a beta-lactam plus either azithromycin or a respiratory fluoroquinolone
Pseudomonas infection is not a consideration but patient has a beta-lactam allergy: a respiratory fluoroquinolone and aztreonam
Pseudomonas infection is an issue: an antipneumococcal, antipseudomonal beta-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem plus ciprofloxacin or levofloxacin 750 mg; or the above beta-lactam plus aminoglycoside and azithromycin. Or the above beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients use aztreonam instead of the beta-lactam)
If community-acquired MRSA is a consideration add vancomycin, or linezolid

Source: Modified with permission from Mandell LA, Wunderink RG, Bartlett JG et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 (Suppl 2):S27–S72.

studies involved only patients with bacteremic pneumococcal pneumonia and in one study an effect was noted in one study year, 1993, but not in 1995 or 1997. Seven of the studies were retrospective and two involved administrative data bases. Clearly, a properly designed and conducted randomized clinical trial is necessary to answer this, the most fundamental question in the treatment of CAP.

Data from several retrospective studies suggest that combination therapy of bacteremic pneumococcal pneumonia with a macrolide and a beta-lactam is better than single-agent therapy. Unfortunately, we do not have randomized control data to advise us. Recent data indicate that intravenous cefuroxime should not be used to treat bacteremic pneumococcal pneumonia, because the failure rate is higher than with other regimens.

Once an etiologic diagnosis has been made, treatment should be changed to the cheapest, narrowest-spectrum agent effective against that microorganism. For example, if penicillin susceptible *S. pneumoniae* is determined to be the cause of the pneumonia, penicillin therapy is still the most appropriate treatment.

The response of patients to treatment depends on the severity of the pneumonia and the presence of comorbidities that may be made worse by the pneumonia. Outpatients with mild to moderate pneumonia do very well. Mortality is rare (less than 1%), and only about 4% of patients fail therapy and require hospitalization. The issue of the most appropriate treatment for patients with pneumonia due to PRSP is unclear. We do know that pneumonia due to this microorganism can be treated successfully with high-dose intravenous penicillin. We also know that treatment with penicillin is not successful if there is concomitant pneumococcal meningitis. In this setting, vancomycin and ceftriaxone are recommended. If beta-lactam antibiotics are used, the concentration of the antibiotic must exceed the MIC of *S. pneumoniae* 40% of the time for cure of pneumococcal pneumonia. In one study, high-dose amoxicillin was the most effective oral beta-lactam antibiotic for the treatment of PRSP. Macrolide-resistant *S. pneumoniae* is also an issue in many communities. Because most cases of ambulatory pneumoniae are of unknown etiology and since there is less than 1% mortality among patients with pneumonia treated on an ambulatory basis, a worse outcome for macrolide treated patients versus other antibiotics may not be detected unless large RCTs are performed. Macrolide susceptibility of *S. pneumoniae* is defined as an MIC of up to 0.5 mg/L. The mean MICs for strains resistant because of an efflux mechanism is 10 mg/L; this accounts for 55% of the macrolide resistance in *S. pneumoniae*. Modification of the target (ribosomal) site accounts for 45% of the resistance and results in MICs of 64 mg/L. Thus, strains with resistance due to efflux mechanism may very well respond to treatment with a macrolide, whereas those due to target alteration will not. Resistance due to the efflux mechanism is more common in North America, while the reverse is true in Europe, that is, most resistance is due to target alteration.

The overall mortality for those admitted to hospital for treatment of pneumonia is 8% to 10%. In patients with NHAP, it may approach 40%. For many of these patients, pneumonia is the final common pathway for a variety of chronic debilitating illnesses.

A recent concept in therapy of pneumonia requiring hospitalization is early switch to oral antibiotics. Patients who are stable by hospital day 3 (as evidenced by temperature of 37.5°C or less for 16 hours, white blood cell count returning toward normal, normal hemodynamics, no requirement for auxiliary oxygen, no complications of pneumonia such as empyema, and ability to take antibiotics by mouth) can be switched to antibiotics and discharged shortly thereafter. About one-third of patients qualify for this therapy. Prompt administration of antimicrobial therapy following a diagnosis of pneumonia intuitively makes sense. One study showed a lower mortality rate for elderly patients who received the first dose of antibiotics within 8 hours of presentation to an emergency department. In another large administrative data base study of over 18,000 patients among the 24.4% who were receiving antibiotics prior to presentation, antibiotic therapy within 4 hours of presentation was associated with a reduction in length of stay but not in mortality. Among the 75.6% of patients who were not receiving antibiotics prior to admission, there was both a reduction in length of stay and mortality for those who received their first dose of antibiotic within 4 hours of presentation.

In a study of 399 patients with CAP treated on an ambulatory basis, symptoms had resolved within 14 days in 67%. The mean time to return to work in this population was 6 days compared with a median of 22 days for those who required hospitalization.

Some patients see their condition fail to improve or indeed worsen during therapy. Table 128-11 gives the factors that should be considered in this setting. One should not forget MRSA as a cause

TABLE 128-11 Considerations When Pneumonia Fails to Resolve or Worsens During Therapy

Reconsider the diagnosis of pneumonia: Could this be pulmonary infarction, malignancy, vasculitis, drug reaction, or eosinophilic pneumonia?
Reconsider the etiologic diagnosis: Are you treating the appropriate microorganism(s)?
Remember that 10% of cases of community-acquired pneumonia are polymicrobial.
Tuberculosis can mimic pyogenic pneumonia. Also consider unusual organisms such as *Actinomyces* or *Nocardia* species.
Are you dealing with a resistant microorganism? *Streptococcus pneumoniae* resistant to penicillin, erythromycin, and tetracycline is common in several European countries and the United States.
Has your patient developed nosocomial pneumonia? Such an event is common, particularly in patients who require endotracheal intubation and assisted ventilation. Is your hospital's potable water supply contaminated by *Legionella* spp.? If so, consider nosocomial Legionnaires' disease. Nosocomial Legionnaires' disease should be a consideration anytime a patient with CAP is improving and develops nosocomial pneumonia.
Could this be postobstructive pneumonia (i.e., is endobronchial obstruction present)?
Have you considered empyema? Pus in the pleural space will continue to cause fever until it is drained.
Has metastatic infection occurred? Occasionally, patients who are bacteremic as a result of their pneumonia develop endocarditis, meningitis, septic arthritis, or a deep abscess such as splenic or renal abscess.
Always consider drug fever.

Source: Data from Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003;37:1405–1433; Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community acquired pneumonia: An evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis. 2000;31:383–421; Niederman MS, Mandell LA, Anzueto A, et al. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. 2001;163:1730–1754.

of failure of initial treatment in patients with CAP. Also, in those who are admitted from nursing homes, consider extended spectrum beta-lactamase (ESBL) producing enterobacteriaceae. Radiographic evidence of resolution of pneumonia lags behind clinical resolution and correlates with age and the presence of chronic obstructive pulmonary disease (COPD). In general, those who are under 50 years of age and have no COPD show radiographic resolution of pneumonia within 4 weeks. In contrast, resolution requires 12 or more weeks for those with pneumonia who are older than 50 years and have coexistent COPD or alcoholism. In about 2% of patients, pneumonia is the presenting manifestation of carcinoma of the lung (postobstructive pneumonia). It is important to demonstrate that the pneumonia has resolved radiographically for those who are at risk for carcinoma of the lung. In general, all tobacco smokers and those who are 50 years of age or older and have pneumonia should have a chest radiograph to determine whether or not the pneumonia has completely resolved. Table 128-11 gives an approach to the patient whose pneumonia is not responding to therapy.

■ ADJUNCTIVE THERAPY

Low-dose corticosteroid therapy is beneficial to those who are relatively adrenal insufficient (less than 9 μg/mL response in cortisol level to a dose of adrenocorticotrophic hormone). Hyperglycemia has been shown to be associated with higher mortality rates in patients who require hospitalization for CAP, so it is likely that control of hyperglycemia will be beneficial to patients with pneumonia and elevated blood sugar.

■ TREATMENT OF PNEUMONIA IN THE NURSING HOME

In one study, if more than two of the following factors were present – respiratory rate greater than 30 per minute, temperature greater than 100.5°F, pulse rate greater than 90 beats per minute, and feeding dependence and mechanically altered diet – the failure rate of therapy of pneumonia in the nursing home was high. It is important to take patients' wishes into consideration in the decision to treat in the nursing home or transfer to the hospital. Treatment with ampicillin for NHAP was associated with a significantly higher failure rate than was treatment with ceftriaxone. It seems that, given their antimicrobial spectrum and almost complete absorption following an oral dose, treatment of NHAP with one of the "respiratory fluoroquinolones" is appropriate, although data from RCTs are still lacking for this group of patients.

PREVENTION

Influenza vaccination of the elderly results in reduction in the rate of hospitalization for pneumonia and influenza by 48% to 57%. The role of pneumococcal vaccine has not been as clearly defined as that of influenza vaccine; however, the Advisory Committee on Immunization Practice recommends pneumococcal vaccine for persons older than 65 years of age. A somewhat unexpected benefit of the use of a protein-polysaccharide conjugated pneumococcal vaccine during childhood has been the reduction of invasive pneumococcal disease in 20- to 39-year olds and among those equal to or greater than 65 years of age. Indeed, in the United States, the incidence of invasive pneumococcal disease among adults 50 years and older declined from 40.8 cases/100,000 prior to the introduction of the vaccine to 29.4 only 4 years later. The rate of death following an episode of invasive pneumococcal disease among adults aged 50 years or older decreased from 6.9 to 5.7/100,000. The authors estimated 6250 fewer cases and 550 fewer deaths per year among those 50 years of age and older in the United States compared with the years prior to introduction of the conjugate vaccine. A recent study by CDC found that one decade after the introduction of the conjugate vaccine there are 168,000 fewer hospitalizations for pneumonia annually among children and adults in the United States.[24] The rate of hospitalization for pneumonia among adults 85 years of age and older decline by 1300.8 per 100,000 per year.[24]

The United States Advisory Committee on Immunization Practices recommends dual vaccination with PPSV23 and 13-valent conjugate vaccine (PCV13) in adults with immunocompromising conditions (e.g., HIV infection, cancer, functional or anatomic asplenia, solid-organ transplantation), cerebrospinal fluid leaks, cochlear implants, chronic renal insufficiency, or nephrotic syndrome.[25]

Prevention of aspiration in those at risk (post-stroke, advanced Parkinson disease, and advanced Alzheimer disease) is difficult. Head positioning, stimulation techniques, exercises to enhance the swallowing reflex, and eating pureed foods can all help to reduce the risk of aspiration. In addition, intensive oral care (cleaning teeth after every meal with an applicator of povidone iodine, and frequent dental care to control plaque) reduced the rate of pneumonia from 19% in the control group to 11% in the treatment group.

Of course, all those who are asplenic should be vaccinated with pneumococcal vaccine, *H. influenzae* B vaccine, and meningococcal vaccine. If possible, this should be done prior to splenectomy.

Patients with hypogammaglobulinemia should have periodic infusions of gammaglobulin in a regimen designed to keep the levels high enough to prevent infection.

QUALITY OF CARE MEASURES: PNEUMONIA

The following have been adopted as quality of care measures for patients with CAP requiring admission to the hospital: blood cultures prior to administration of antibiotics; measurement of oxygenation status; administration of antibiotics within 6 hours of presentation to the emergency department; ascertainment of influenza; and pneumococcal vaccination status and administration of these vaccines as necessary. In addition, for those who smoke tobacco products, at the very least information about cessation, and preferentially counseling regarding cessation of smoking.[26]

A number of studies have examined the effect of using guidelines on patient care, and while the designs have differed, there is a strong suggestion that following guidelines has a "halo effect" in improving patient care and results in decreased mortality and, in some instances, reduced length of stay.[27]

END-OF-LIFE DECISION MAKING

Many patients with CAP are elderly and many of these enter the hospital with advance directives. For all of these patients it is important to discuss life-sustaining measures such as assisted ventilation and admission to an intensive care unit should the need arise.

SPECIFIC PATHOGENS

■ *STREPTOCOCCUS PNEUMONIAE*

S. pneumoniae is still a common cause of pneumonia. Patients with bacteremic pneumococcal pneumonia are more likely to have diabetes mellitus, COPD, or alcoholism than those who have other causes of CAP. Capsular polysaccharide types 14, 4, 1, 6A/6B, 3, 8, 7F, 23F, and 18C are the most frequent causes of pneumococcal disease. The minimal inhibitory concentration (MIC) of penicillin for susceptible strains is under 0.06 μg/mL; isolates with MICs of 0.1 to 1 μg/mL are of intermediate resistance, and those with MICs of at least 2 μg/mL are highly resistant. These levels were established for central nervous system infections, for which trough concentrations of penicillin at 10 times MIC are necessary for cure. Generally, with intravenous antibiotics, high concentrations can be achieved in pulmonary tissue; therefore, even resistant strains of *S. pneumoniae* usually respond to treatment with high doses of penicillin or third-generation cephalosporin. If there is concomitant meningitis, however, both a third-generation cephalosporin and vancomycin should be given.

S. pneumoniae antibiotic resistance may be associated with increased mortality and morbidity in patients with pneumonia due to this pathogen. While the most important factors influencing death in pneumococcal pneumonia, were older age and underlying disease, rather than resistance to beta-lactam agents, however, when deaths during the first 4 hospital days were excluded, mortality was significantly associated with infection by an isolate with a penicillin MIC ≥4.0 μg/mL or a cefotaxime MIC ≥2.0 μg/mL.[27] In a study of 192 patients with bacteremic pneumococcal pneumonia, those with isolates that were not susceptible to penicillin were four times more likely to have a suppurative complication.[28]

STAPHYLOCOCCUS AUREUS

Pneumonia due to this agent is usually of sudden onset, affects persons with comorbid illnesses (except during influenza outbreaks, when healthy young adults may be infected), and is frequently complicated by cavitation (20%), pneumothorax (10%), jaundice (8%), empyema (5%), acute renal failure (5%), and pericarditis (2%).

MRSA is a rare cause of CAP. It does occur, however, and once established in a region, it can be a major problem. Vancomycin or linezolid is used to treat MRSA, whereas cloxacillin or nafcillin is used to treat methicillin-susceptible strains. Surgical drainage is necessary for the treatment of empyema. If multiple-rounded opacities are seen in a patient with *S. aureus* pneumonia, suspect right-sided endocarditis. Toxic shock syndrome may complicate *S. aureus* pneumonia. Strains of *S. aureus* with the gene for PVL have been described recently. PVL is an extracellular product of *S. aureus.* It is associated with primary skin infections such as furunculosis, and severe necrotizing pneumonia. In a recent report of eight cases of severe CAP caused by *S. aureus* strains carrying the PVL gene, six were fatal. The patients were all immunocompetent children or young adults. All had a preceding influenza-like syndrome before developing pneumonia, and the six deaths occurred shortly after diagnosis. Necropsy showed diffuse necrotizing hemorrhagic pneumonia. In another study, PVL-positive infections were more often marked by temperature greater than 39°C ($p = 0.01$), heart rate above 140 beats per minute ($p = 0.02$), hemoptysis ($p = 0.005$), onset of pleural effusion during hospital stay ($p = 0.004$), and leucopenia ($p = 0.001$). The survival rate 48 hours after admission was 63% for the PVL-positive patients and 94% for PVL-negative individuals ($p = 0.007$). Histopathologic examination of lungs at necropsy from three cases of necrotizing pneumonia associated with PVL-positive *S. aureus* showed extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive hemorrhagic necrosis of interalveolar septa. Both methicillin-sensitive and methicillin-resistant strains have been described. Current evidence would favor linezolid as the drug of choice for the treatment of MRSA pneumonia.[29] Newer antibiotics with activity against MRSA include ceftaroline and ceftobiprole.[30]

HAEMOPHILUS INFLUENZAE

This cause of pneumonia is more common in older patients with COPD. Both type B and non-B strains can cause pneumonia. About 30% of all *H. influenzae* isolates now produce beta-lactamase and hence are resistant to ampicillin and amoxicillin. Between 7% and 14% of *H. influenzae* isolates are resistant to trimethoprim–sulfamethoxazole. More than 90% of *H. influenzae* isolates are resistant to erythromycin; and 1% to 2% are resistant to tetracycline. Amoxicillin–clavulanic acid and a second- or third-generation cephalosporin reliably treat *H. influenzae* pneumonia.

STREPTOCOCCUS PYOGENES (GROUP A STREPTOCOCCUS)

This agent is uncommon as a cause of pneumonia. One of its presentations is pneumonia accompanied by explosive pleuritis. Cases of group A streptococcal (GAS) pneumonia maybe accompanied by "toxic strep syndrome." Clindamycin, 600 mg given intravenously every 8 hours is superior to penicillin for the treatment of serious GAS infections. Of 2079 cases of invasive GAS infection, 222 (11%) had pneumonia. The median age was 56 years. Underlying illness was present in 61% of cases. Most cases were community acquired (81%). The case fatality rate was 38% for GAS pneumonia, compared with 12% for the entire cohort with invasive GAS infection. In 2002, the largest outbreak of 127 cases of GAS pneumonia in the United States occurred among military recruits in San Diego. The epidemic continued despite prophylaxis with penicillin and required additional prophylaxis to end it.

MYCOPLASMA PNEUMONIAE

Mycoplasmas including *M. pneumoniae* are the smallest free living organisms with a size (125–150 μm) similar to that of myxoviruses. They are highly pleomorphic due to lack of a cell wall but do have a triple-layered cell membrane that is 75 to 100 Angstroms thick.[31] *M. pneumoniae* accounts for up to 30% of pneumonias treated on an outpatient basis. *M. pneumoniae* infections are endemic in densely populated areas with cyclic increases that result in prolonged epidemics and not infrequently when one member of the family has this infection it spreads to other members of the family.[32,33] Outbreaks have occurred in schools, military bases, and summer camps. The extrapulmonary manifestations of *M. pneumoniae* are many and include cold agglutinin–induced hemolytic anemia, thrombocytopenia, encephalitis, cerebellar ataxia, Guillain–Barré syndrome, Stevens–Johnson syndrome, and myocarditis. This is primarily a disease of younger patients, but it accounts for 5% of all cases of pneumonia in persons 65 years of age or older.

Antimicrobial susceptibility of *M. pneumoniae* can be determined by agar dilution or by the broth-dilution method usually in the form of the metabolism inhibition test. Using these methods, *M. pneumoniae* is susceptible to macrolides, tetracyclines, quinolones, streptomycin, pristinamycin, and ketolides.[34] Erythromycin-resistant strains of *M. pneumoniae* have been isolated from treated patients.[34] Such resistance is due to point mutations in 23rRNA gene and while worrisome so far it is uncommon. Macrolides (erythromycin, clarithromycin, and azithromycin) or tetracyclines are the treatment of choice. Such therapy results in resolution of fever in about 3 days compared with 10 days for placebo.[35] Diagnosis is confirmed serologically or by polymerase chain reaction. Culturing the organism is difficult and is only available in a few specialized laboratories.

LEGIONELLACEAE

From July 21 to 24, 1976, the 58th Annual Convention of the American Legion was held at a hotel in Philadelphia and 182 of the attendees at the convention developed pneumonia.[36] One hundred forty-seven (81%) were hospitalized, and 29 (16%) died. This outbreak of pneumonia of apparent unknown cause triggered an exhaustive epidemiologic and microbiologic investigation by the Centers for Disease Control and Prevention (CDC), culminating in the isolation of a new microorganism, *Legionella pneumophila,* about 6 months later.[37]

From 1976 to present, this family of microorganisms has been found to include 50 species and more than 70 serogroups (there are 15 serogroups of *L. pneumophila*). Two clinical syndrome result from infection with these microorganisms: Legionnaires' disease and a self-limited flu-like illness (Pontiac fever). *L. pneumophila* serogroup 1, the microorganism responsible for the 1976 outbreak in Philadelphia accounts for 70% to 90% of the cases of Legionnaires' disease. Legionnaires' disease can be community or hospital acquired, and it can occur in sporadic, endemic, and epidemic forms. Exposure to contaminated water (showers, cooling towers, or even ingestion of such water and subsequent microaspiration) is the prime mode of acquisition of this illness. Older age, male gender, immunosuppression (especially with

corticosteroids), nosocomial acquisition, end-stage renal disease, and infection with *L. pneumophila* serogroup 5 are risk factors for death from this infection. On a molecular level, a mutation leading to a stop codon at position 392 resulted in a dysfunctional toll-like receptor 5 protein unable to recognize flagellin. This was a risk factor for *Legionella pneumophila* infection. There is now considerable evidence that quinolone antibiotics are superior to macrolides for the treatment of Legionnaires' disease. Azithromycin appears to be the macrolide of choice if this class of antibiotics is used. The disease may continue to progress for up to 4 days despite optimal therapy. Other options are doxycycline, 100 mg given twice intravenously in 24 hours and then 100 mg OD intravenously. Mild to moderately severe LD can be treated for 7 to 10 days while severe cases or LD in immunocompromised hosts should be treated for at least 21 days.

Prompt therapy with agents listed earlier has lowered the mortality rate from LD from around 26% to 5%.[38,39]

HANTAVIRUS

In May 1993, reports of deaths due to severe pulmonary disease were received by the New Mexico Department of Health. Many of the affected persons were residents of the Navajo reservation located near the Four Corners area of New Mexico, Arizona, Colorado, and Utah. Within a few months a new Hantavirus (sin nombre, "no name" virus) had been isolated and shown to be responsible for this outbreak, which affected 17 persons.[40] Hantavirus pulmonary syndrome (HPS) is characterized by a flu-like prodromal illness, followed by rapidly progressive noncardiogenic pulmonary edema. Fever, myalgia, cough or dyspnea, nausea or vomiting, and diarrhea are the most common symptoms. Hypotension, tachypnea, and tachycardia are the usual findings on physical examination. Leukocytosis (often with a severe left shift), thrombocytopenia (median lowest platelet count 64,500/mm^3), prolonged prothrombin and partial thromboplastin times, and elevated serum lactate dehydrogenase concentration are the most common laboratory findings. The mortality rate was high (88%) in the Four Corners outbreak. The initial chest radiograph showed infiltrates in 65% and no abnormality in 24% of patients. Subsequently, 16 patients (94%) had rapidly evolving bilateral diffuse infiltrates. In the few months after identification of this new Hantavirus, two more new Hantaviruses were identified in the United States and cases of HPS continue to be reported. The deer mouse, *Peromyscus maniculatus*, is the primary rodent reservoir for this virus.

The pathogenesis of the infection is that Hantavirus non-lytically infects endothelial cells disrupting their integrity resulting in low-pressure pulmonary edema, which is manifest as severe pneumonia.[41]

CHLAMYDOPHILA PNEUMONIAE

In 1986, Grayston et al.[42] described a new species of Chlamydia as a cause of respiratory tract infections. This organism was later named *C. pneumoniae*.[43] This intracellular pathogen of humans is spread by aerosols. It causes sinusitis, pharyngitis, bronchitis, otitis media, and pneumonia. The last can be as a result of primary infection or as reactivation of latent infection. Primary infection affects mainly young adults and maybe followed by reactive airway disease. Two weeks of treatment with doxycycline is adequate. Clarithromycin is very active in vitro against *C. pneumoniae*, but whether it is superior to doxycycline is not known.

The reactivation type of infection occurs in older adults, often as part of a polymicrobial infection. The rate of *C. pneumoniae* in this setting is unknown.

Diagnosis is by isolation of the organism from respiratory secretions or by serology. A greater than fourfold rise in IgM or IgG by microimmunofluorescence test or a single IgM titer of at least 1:16 or an IgG titer of at least 1:512 is considered diagnostic.

In everyday practice it is probably not worthwhile trying to diagnosis *C. pneumoniae* infection because of its low impact and therapies that are empirically selected to treat pneumonia are effective against this agent.

SEVERE ACUTE RESPIRATORY SYNDROME (CORONAVIRUS)

In November 2002, an outbreak of severe acute respiratory syndrome (SARS) started in Guangdong Province in southern China and spread worldwide, affecting more than 8000 persons. SARS was due to a novel coronavirus that jumped the species barrier from civet cats to humans.[44] In 2013, it was shown that the reservoir of this virus is the Chinese horseshoe bat and that the virus uses the ACE-2 receptor to gain entry into human cells.[45] This bat virus uses angiotensin converting enzyme 2 as a receptor to enter the host cell and trigger a massive cleavage of this enzyme resulting in severe physiological derangements that manifest as severe pneumonia.[46]Patients with typical SARS usually present 2 to 10 days following exposure with nonspecific symptoms including fever, myalgia, headache, malaise, and chills. Three to five days later, a nonproductive cough and dyspnea develop. Twenty percent of patients subsequently develop worsening respiratory distress requiring admission to an intensive care unit. Approximately 10% of all patients die from progressive respiratory distress or complications of their hospital admission, typically around the third week of symptomatic illness.

Approximately 75% of patients have unilateral or bilateral infiltrates on chest radiograph at the time of presentation. The majority of those without visible infiltrates have ground-glass opacities detectable on high-resolution computer tomography at the time of presentation or progress to develop radiographic infiltrates. Generally, radiographic opacities peak between 8 and 10 days after onset of illness and then improve, correlating with the worsening and improvement of respiratory symptoms, but progressive radiographic deterioration may occur associated with a more protracted clinical course. There is no effective antiviral therapy. The management of severe cases is that of the management of severe respiratory failure. Attention to infection control measures designed to prevent spread of SARS is most important.

MIDDLE EAST RESPIRATORY SYNDROME (CORONAVIRUS)

In 2012 a novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), causing severe respiratory illness emerged in Saudi Arabia. Additional cases and clusters of MERS-CoV infections have been detected subsequently in Saudi Arabia, other Arabian Peninsula countries, and other countries.[47] Just like SARS-CoV bats are the likely host and in the case of MERS-CoV it appears that camels are an intermediary host.[48]

HUMAN METAPNEUMOVIRUS

Human metapneumovirus is a newly described member of the *Paramyxoviridae* family. Since its initial description in 2001, when it was isolated from nasopharyngeal aspirates of young children in the Netherlands, it has been described worldwide. Despite almost universal infection in early childhood, repeat infections do occur in adulthood, and it appears to account for about 2% to 3% of cases of pneumonia in adults. Unfortunately, there are no clinical or routine laboratory features that allow one to distinguish this type of pneumonia from bacterial pneumonia.

MIMIVIRUS

Acanthamoeba polyphaga mimivirus (mimivirus) is a giant DNA virus which was isolated in 1992 during the investigation of an outbreak of CAP in Bradford (England). This giant virus was isolated in the water system of a cooling tower and was first suspected to be a Legionella-like amoebal pathogen by Rowbotham.[49,50] This virus stains gram-positive and it is an uncommon but definite cause of some cases of CAP.

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CHAPTER 129

Healthcare-Acquired Pneumonia, Including Ventilator-Associated Pneumonia

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INTRODUCTION

Healthcare-associated infections (HAIs) impose a significant economic and clinical burden on healthcare systems. The burden is magnified by increasing infection rates due to multi-drug resistant (MDR) pathogens. Nosocomial pneumonia remains an important etiology of HAIs and consists of three distinct entities: healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[1] Definitions for each of these conditions can be seen in Table 129-1. Three device-associated HAIs are reported to the National Safety Healthcare Network (NHSN), the surveillance branch of the Centers for Disease Control and Prevention (CDC). These include central line–associated blood stream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and VAP. According to an annual summary by the NHSN published in 2008, VAP accounted for 15.9% of all the reported HAIs, placing third among device-associated HAIs.[2] Nosocomial pneumonia results in excess healthcare utilization and leads to greater mortality. This chapter focuses on the microorganisms responsible for infection, the complexities surrounding the diagnosis, and the preventive and therapeutic management strategies used to combat nosocomial pneumonia.

EPIDEMIOLOGY

HAP, although not a reportable infection, is thought to occur at a rate of 5 to 10 cases per 1000 hospital admissions, and numerous studies indicate that VAP occurs in 9% to 27% of all intubated patients.[1] In a 1-day prevalence study involving critically ill patients across Western Europe, pneumonia was the most common ICU-acquired

TABLE 129-1 Definitions of Nosocomial Pneumonia[a]

Pneumonia Category	Definition
HCAP, healthcare-associated pneumonia	Pneumonia diagnosed in any patient who was hospitalized in an acute care hospital for 2 or more days within 90 d of the diagnosis; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 d of the current infection; or attended a hospital or hemodialysis clinic
HAP, hospital-acquired pneumonia	Pneumonia diagnosed 48 h or more after hospital admission
VAP, ventilator-associated pneumonia	Pneumonia diagnosed 48 h or more after endotracheal intubation

[a]*Clinical criteria for pneumonia include new or progressive lung infiltrate and at least two of the following: hyperthermia or hypothermia, elevated white blood cell count, purulent tracheal secretions or sputum, and worsening oxygenation.*

TABLE 129-2 2010 NHSN VAP Rates Based on ICU Location in Major Teaching Hospitals

ICU Location	VAP Cases	Ventilator Days	Rate[a]
Burn	89	15,379	5.8
Medical	208	153,408	1.4
Medical/Surgical	307	167,857	1.8
Neurologic	71	14,837	4.8
Neurosurgical	165	53,966	3.1
Surgical	374	106,736	3.5
Cardiothoracic	218	132,307	1.6
Trauma	555	92,460	6.0

[a]*Expressed as number of VAP cases per 1000 ventilator days.*
Source: Data from Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. Am J Infect Control. 2011;39(10):798–816.

infection occurring in 10% of patients and accounting for 47% of all ICU-acquired infections.[3] An additional large study conducted in Europe revealed a similar pneumonia rate of 9%.[4] These two studies, in addition to others,[5] demonstrated that mechanical ventilation served as the most important risk factor for nosocomial pneumonia. Therefore, the CDC now reports the incidence of nosocomial pneumonia as cases per 1000 ventilator days.

The NHSN functions as the CDC's surveillance system for HAIs and collects data from more than 5000 participating healthcare facilities. The NHSN data summary report from 2010 categorized rates of VAP based on ICU location.[6] Rates of VAP were highest in burn, surgical, trauma, and neurological/neurosurgical ICUs ranging from 2.5 to 6 cases per 1000 ventilator days. VAP was diagnosed less frequently in medical and medical/surgical ICUs occurring at a rate of 1 to 1.8 cases per 1000 ventilator days (Table 129-2). Recently, the validity of the surveillance system utilized by the NHSN to identify VAP has been questioned. The CDC/NHSN pneumonia (PNEU) definitions (Table 129-3) were thought to lack accuracy, objectivity, and consistency. As a result, the NHSN implemented a new surveillance algorithm for identifying ventilator-associated events (VAEs) in January 2013. The goal of the new algorithm is to identify complications of mechanical ventilation including, but not limited to, to VAP by using objective changes in ventilator parameters indicative of worsening oxygenation (Fig. 129-1).

VAP risk is highest early in the course of hospitalization and increases over time. A multicenter prospective cohort analysis conducted in Canada demonstrated a VAP rate of 14.8 cases per 1000 ventilator days, half occurring on or before day 7.[7] While the cumulative risk for developing VAP increased with duration of ICU stay, the daily risk increased until day 5 and then subsequently decreased. Early-onset VAP usually confers a better prognosis as culprit organisms are more sensitive to antibiotics as opposed to the MDR pathogens often responsible for late-onset VAP (see also Chapter 125).[1]

Determining the economic impact of VAP and the associated morbidity and mortality has been difficult. Critically ill patients have multiple, evolving, complex disease processes making it difficult to isolate VAP as the sole cause of excess cost, morbidity, or death. Multiple studies have been performed with variable results. A case-control analysis revealed a crude mortality of 54%, an attributable mortality of 27%, and a 13-day increase in ICU length of stay compared to matched controls.[8] The effect of VAP on clinical outcomes was slightly reduced in a larger, case-matched, prospective cohort study that demonstrated an attributable ICU length of stay of 4 days and an attributable mortality of 6%.[9] Other case-matched trials failed to show any difference in mortality. A retrospective, matched cohort study using a large US database estimated an increase of >$40000 in mean hospital charges per patient.[10] In addition, a more recent retrospective, matched cohort study using the ICD-9 code to identify VAP revealed a mean

TABLE 129-3 NHSN PNEU Definitions

PNEU Type	Definition
PNU1	Two or more serial chest radiographs with at least **one** of the following: new or progressive and persistent infiltrate, consolidation, or cavitation and At least **one** of the following: • fever (>38°C) • leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm^3) • altered mental status in an adult ≥70 y of age without an alternative etiology and At least **two** of the following: • new onset of purulent sputum or change in character of sputum or increased secretions/suction requirements • new onset or worsening cough, dyspnea, or tachypnea • rales or bronchial breath sounds • worsening gas exchange
PNU2	Two or more serial chest radiographs with at least **one** of the following: new or progressive and persistent infiltrate, consolidation, or cavitation At least **one** of the following: • fever (>38 °C) • leukopenia (<4000 WBC/mm^3) or leukocytosis (≥12000 WBC/mm^3) • altered mental status in an adult ≥70 y of age without an alternative etiology and At least **one** of the following: • new onset of purulent sputum or change in character of sputum or increased secretions/suction requirements • new onset or worsening cough, dyspnea, or tachypnea • rales or bronchial breath sounds • worsening gas exchange and At least **one** of the following: • positive blood culture not related to another source of infection • positive pleural fluid culture • positive quantitative culture from minimally contaminated LRT specimen • ≥5% of BAL cells containing intracellular bacteria • histopathologic examination revealing **one** of the following: abscess formation, positive quantitative culture, or invasion of lung parenchyma by fungal hyphae or pseudohyphae

PNU3 is a separate definition applied to immunosuppressed patients. Definitions can be found at www.cdc.gov/nhsn.

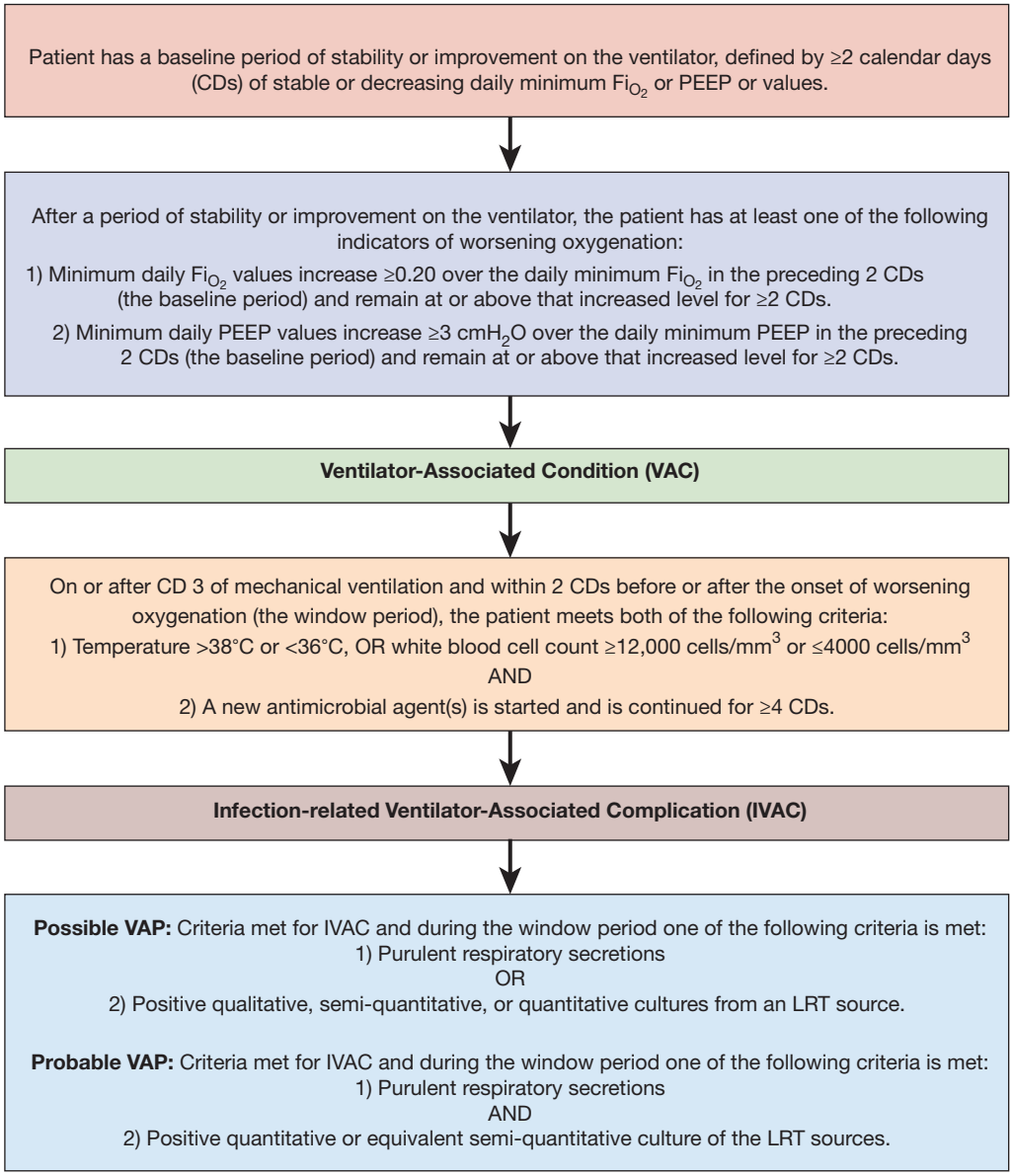

Figure 129-1 Abbreviated NHSN surveillance algorithm for ventilator-associated events.

hospitalization costs of $99598, $39828 greater than those patients without VAP.[11] Recent advances in statistical methodology allow for the control of the effect that severity of illness can have on the attributable mortality associated with VAP, not only at the time of infection but over the course of a hospitalization during disease evolution. Employing a statistical technique from the field of causal inference, an analysis of a large French national database resulted in a milder estimation of attributable mortality associated with VAP, 1% on day 30 and 1.5% on day 60.[12] Additional factors, particularly the timely initiation of appropriate antibiotics, certainly affect the aforementioned estimates. While debate continues over the attributable mortality of VAP, the condition imposes a significant clinical and economic burden.

MICROBIOLOGY

Etiologic agents for nosocomial pneumonia depend on multiple factors including underlying disease, geography, ICU population, duration of mechanical ventilation, previous antibiotic therapy, and the method used to obtain respiratory cultures. Historically, aerobic gram-negative bacilli (GNB) represent the most prevalent pathogens causing nosocomial pneumonia. Enterobacteriaceae embody an important group of bacteria given the importance of aerodigestive colonization in the pathogenesis of VAP. Microorganisms within this group include *Klebsiella*, *Escherichia coli*, *Enterobacter*, *Citrobacter*, *Proteus*, and *Serratia* species. Additional GNB include *Pseudomonas*, *Acinetobacter*, and *Stenotrophmonas* species. These bacteria are ubiquitous in the environment and have minimal nutritional requirements making them suitable for the colonization of hospitalized patients. Summarizing VAP data from 24 trials, GNB represented 58% of recovered organisms.[5] *Pseudomonas aeruginosa* was the most prevalent pathogen accounting for 24% of cases. According to a more recent report by the NHSN in 2008, at least 47% of cases of VAP reported in 2006 and 2007 were due to GNB (Table 129-4).[2]

With the emergence of MDR pathogens, gram-positive organisms, mainly methicillin-resistant *Staphylococcus aureus* (MRSA), have become an increasingly important cause of VAP. A review of the European Prevalence of Infection in Intensive Care study revealed that 31% of nosocomial pneumonias were due to *S. aureus*,[3] and the previously mentioned summary of 24 trials determined that *S. aureus* was responsible for 20.4% of cases of VAP.[5] In the NHSN report from 2008, *S. aureus* accounted for 24% of reported cases and

TABLE 129-4 Distribution and Rank of 5960 Isolated Pathogens Associated with VAP Reported to the NHSN between January 2006 and October 2007

Pathogen	Number of Isolates (%)	Rank
CoNS[a]	79 (1.3)	9
Staphylococcus aureus	1456 (24.4)	1
Enterococcus species	77 (1.3)	10
Candida species	160 (2.7)	7
Escherichia coli	271 (4.6)	6
Pseudomonas aeruginosa	972 (16.3)	2
Klebsiella pneumoniae	446 (7.5)	5
Enterobacter species	498 (8.4)	3
Acinetobacter baumannii	498 (8.4)	3
Klebsiella oxytoca	128 (2.2)	8
Other	1375 (23.1)	

[a]*Coagulase-negative staphylococci.*

Source: Data from Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol. 2008;29(11):996–1011.

was the most common etiologic agent, greater than *P. aeruginosa* (16%).[2]

Bacteria responsible for community-acquired pneumonia such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* can cause VAP but occur less frequently and often earlier in an episode of mechanical ventilation. Anaerobes, fungi, and *Legionella* species are uncommon causes of VAP but cases have been reported. Also, multiple microorganisms can infect a host leading to polymicrobial infection.

As mentioned earlier, multiple factors can influence the specific microorganism responsible for VAP, but the most important and well studied are the duration of mechanical ventilation at the time of diagnosis, prior antimicrobial use, and local hospital infection patterns. An investigation into the role of stress ulcer prophylaxis on the development of nosocomial pneumonia demonstrated that common organisms such as *S. pneumoniae* and *H. influenzae* along with *S. aureus* were responsible for the majority of cases of early-onset pneumonia.[13] In contrast, GNB other than *H. influenzae* accounted for most cases of late-onset pneumonia. A multivariate analysis conducted in France determined that duration of mechanical ventilation and prior broad-spectrum antibiotic use were significant risk factors for VAP due to potentially drug-resistant bacteria such as MRSA, *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.[14] Furthermore, a Spanish retrospective review proved that previous antibiotic use resulted in higher rates of *P. aeruginosa* and increased mortality likely due to drug resistance.[15] The variability of microorganisms isolated in cases of VAP among four different centers in Spain and France despite similar patient characteristics highlighted the importance of recognizing a center's local infection profile.[16]

PATHOPHYSIOLOGY

Nosocomial pneumonia most often occurs through the aspiration of microorganisms colonizing the aerodigestive tract in a host with altered immunity. Direct inhalation or hematogenous dissemination of bacteria is less frequent route of infection. Aspiration during sleep is present in a large number of normal subjects, but the volume aspirated is small and more importantly the pathogenicity of the microorganisms is diminished. Hospitalized patients are considered more likely to aspirate larger volumes of virulent bacteria with greater frequency due to decreased sensorium, difficulty swallowing, and impaired gut motility.

The role of colonization of the upper respiratory and digestive tracts has been extensively evaluated. Previous studies demonstrated that 23% of patients admitted to a medical ICU colonized with GNB developed a nosocomial respiratory infection compared to only 3% of noncolonized patients.[17] Later, genomic DNA analysis proved that strains of bacteria isolated from the lower respiratory tract (LRT) in cases of nosocomial pneumonia were identical to those strains colonizing the oropharynx and/or stomach.[18] Hospitalized patients are at risk for colonization due to the potential for contaminated respiratory equipment and hospital water systems, the transmission of bacteria via healthcare workers, the spread of microorganisms through respiratory droplets, and pharmacologically induced alterations in gastric pH.

The endotracheal tube serves as a reservoir for bacteria from the upper airway to leak around the cuff and gain entry into the LRT. Manufacturers have developed novel endotracheal tubes with antimicrobial properties that prevent biofilm formation.[19] Humidifiers and nebulizers can be infected allowing for the transfer of microorganisms between patients by respiratory personnel. Contaminated water supply systems have led to previous outbreaks of nosocomial *Legionella* species. Fungal infections have resulted from hospital renovations and construction, contaminated air supply, and poor filtration.

Critically ill patients requiring mechanical ventilation are prone to develop stress ulcers and thus are often treated with histamine Type 2 (H_2) antagonists and proton pump inhibitors for prevention.[20] In addition, patients frequently require enteral nutrition. Although these strategies provide effective prophylaxis and nutrition, alterations in gastric pH promotes growth of bacteria in a normally sterile environment potentially increasing the risk for nosocomial pneumonia.[13,21]

The early, hyperinflammatory response that occurs in trauma and sepsis can cause multisystem organ failure and death. Improvements in the management of sepsis have decreased rates of early death and patients now often succumb to protracted or nosocomial infections. Recent evidence suggests that a subset of patients who survive the cytokine storm associated with the proinflammatory response of sepsis develop an immunodeficient state promoting viral reactivation and nosocomial infection including pneumonia. Immunomodulator therapies are currently being investigated.[21]

RISK FACTORS

Given the important pathophysiologic roles of aspiration and colonization of the aerodigestive tract, it is logical that the significant risk factors for nosocomial pneumonia involve these processes. A complete list of risk factors can be visualized in Table 129-5.

Mechanical ventilation is the single most important risk factor for nosocomial pneumonia increasing the risk up to 20-fold.[1,4,22] Reintubation also has been associated with the development of VAP.[23] Condensate within the ventilator tubing can become colonized with bacteria and lead to infection if introduced into the LRT. A 2012 Cochrane review found that heat-moisture exchangers that collect less moisture may reduce the incidence of VAP when compared to heated humidification.[24] There is no evidence that frequent changes of the ventilator circuit reduce VAP rates,[25,26] nor does early tracheotomy.[27]

Severity and type of disease are known risk factors for nosocomial PNA. An Apache II score ≥16 and an organ system failure index of 3 or greater have both been linked to VAP.[4,28] Nosocomial PNA occurs more frequently in postsurgical patients, particularly burn and trauma victims.[6,29] Incidence is also higher in COPD likely due

TABLE 129-5 Risk Factors for Nosocomial Pneumonia Determined by Regression Analysis

Aspiration	Colonization	Dual	Other
Supine position	Frequent ventilator circuit changes	Mechanical ventilation	Severity of illness (Apache, SOFA)
Nasogastric tube	Prior antibiotic use	Reintubation	ARDS
Enteral nutrition	COPD	Surgery (trauma, burn, neurosurgery)	Age >60
Decreased endotracheal tube cuff pressure			Transport out of ICU
Neuromuscular disease			PRBC transfusion
Coma/head trauma			
ICP monitor			

Source: Data from Cook DJ, Kollef MH. Risk Factors for ICU-Acquired Pneumonia. JAMA. 1998;279(20):1605–1606.

to greater colonization rates and ARDS as a result of prolonged mechanical ventilation.[30–32]

Aspiration occurs more frequently in the supine position and can be exacerbated by the presence of a nasogastric tube combined with early enteral nutrition.[33–36] Postpyloric feeding may reduce gastroesophageal reflux but the impact on VAP incidence is uncertain. Antacids and histamine Type 2 (H_2) antagonists used for stress ulcer prophylaxis have proved to be independent risk factors for nosocomial PNA as alterations in gastric pH promote colonization.[37,38] In addition, prior antibiotic administration can select for infection by MDR microorganisms.[14,28]

DIAGNOSIS

The diagnosis of nosocomial pneumonia has traditionally been difficult. It should be suspected in any patient with a new or progressive radiographic infiltrate and signs or symptoms indicative of infection such as fever, leukocytosis or leukopenia, purulent sputum, and worsening oxygenation. The accuracy of using the aforementioned clinical findings in diagnosing nosocomial pneumonia ranges depending on the number and type of clinical criteria and is complicated by the lack of a gold standard reference. Even postmortem histologic examination is not 100% specific. The addition of microbiological data to clinical criteria has not definitively improved diagnostic accuracy. The problems associated with diagnosing VAP produced challenges for surveillance systems such as the NHSN. Therefore, as mentioned previously, the CDC created a new surveillance algorithm for the identification of VAEs that include both infectious and noninfectious complications of mechanical ventilation (Fig. 129-1). Due to the lack of a proven diagnostic method, two different strategies have been used and compared using clinical or bacteriologic criteria, each associated with advantages and disadvantages.[1]

The clinical strategy employs the abovementioned clinical and radiographic criteria in diagnosing nosocomial pneumonia. A combination of two out of three clinical criteria and a radiographic infiltrate yielded a sensitivity of 69% and a specificity of 75% for the diagnosis of VAP in 25 mechanically ventilated patients using histology and quantitative lung tissue culture on autopsy as the reference. Increasing the number of clinical criteria resulted in greater specificity but at the cost of lesser sensitivity.[39] However, in a postmortem analysis of 39 mechanically ventilated patients, clinical criteria did not provide a reliable positive predicted value for histologic pneumonia.[40] A semiquantitative endotracheal aspirate culture can be used to identify a pathogen and, if positive, has been shown to correlate with quantitative cultures of the LRT obtained via protected specimen brush (PSB).[41] Also, a negative endotracheal aspirate culture has high sensitivity and good negative predictive value if antibiotics have not recently been changed.[42] However, semiquantitative cultures are not as reliable as quantitative cultures of the LRT due to an inability to differentiate between colonization and infection. The use of clinical criteria and a reliance on semiquantitative cultures can be overly sensitive resulting in unnecessary antibiotic use and potentially delay the identification of extrapulmonary infection.

The bacteriologic strategy uses quantitative cultures of the LRT via endotracheal aspirate, PSB, or bronchoalveolar lavage (BAL) to confirm or eliminate the diagnosis of nosocomial pneumonia based on thresholds of bacterial growth. These thresholds differ depending on the method of respiratory sampling and are as follows: $\geq 10^5$ colony-forming units (CFU)/mL for an endotracheal aspirate, $\geq 10^4$ CFU/mL for a BAL, and $\geq 10^3$ CFU/mL for a PSB. Results of these procedures guide decisions such as when to initiate or stop antibiotics and which drug should be used against the offending agent. There are no definitive data to support the use of one sampling technique over another; however, the cellular analysis of BAL fluid may provide an advantage as a sample containing <50% neutrophils produced excellent negative predictive value in one study.[40] Also, given the multifocal nature of VAP, even mini-BAL samples obtained blindly without the use of bronchoscopy can be effective.[43–45] The bacteriologic strategy has resulted in less and more narrowed antibiotic use, an important point given the surge of antibiotic-resistant microorganisms in the ICU setting.[46–48] A major disadvantage with this approach is the concern for false negatives, which could result in cases of nosocomial pneumonia going untreated, especially in the setting of recently introduced antibiotics.[49]

Multiple studies have compared the clinical and bacteriologic strategies. Only one prospective, randomized trial demonstrated a mortality benefit at 14 days when using the bacteriologic strategy.[46] Others have failed to reproduce these findings, including a large study conducted by the Canadian Critical Care Trials Group and a comprehensive meta-analysis.[50,51] In addition, the bacteriologic strategy does not seem to reduce the duration of mechanical ventilation or ICU length of stay. Ultimately, the decision to employ either strategy rests with the clinician on a case-by-case basis. If bronchoscopic sampling can be performed safely and the appropriate personnel is available, it is reasonable to utilize this approach as antibiotic decisions may change based on culture results. If the clinical strategy is used, the clinician should reevaluate the patient often for guidance on antibiotic usage. Regardless of the diagnostic strategy, an unstable patient with a high pretest probability of nosocomial pneumonia should be initiated on empiric antibiotics as a delay in antibiotic administration leads to higher mortality.[52–57] A diagnostic algorithm adapted from the Washington Manual of Critical Care Medicine can be seen in Figure 129-2.

PREVENTION

Prevention of nosocomial pneumonia centers on minimizing mechanical ventilation and reducing aspiration and bacterial

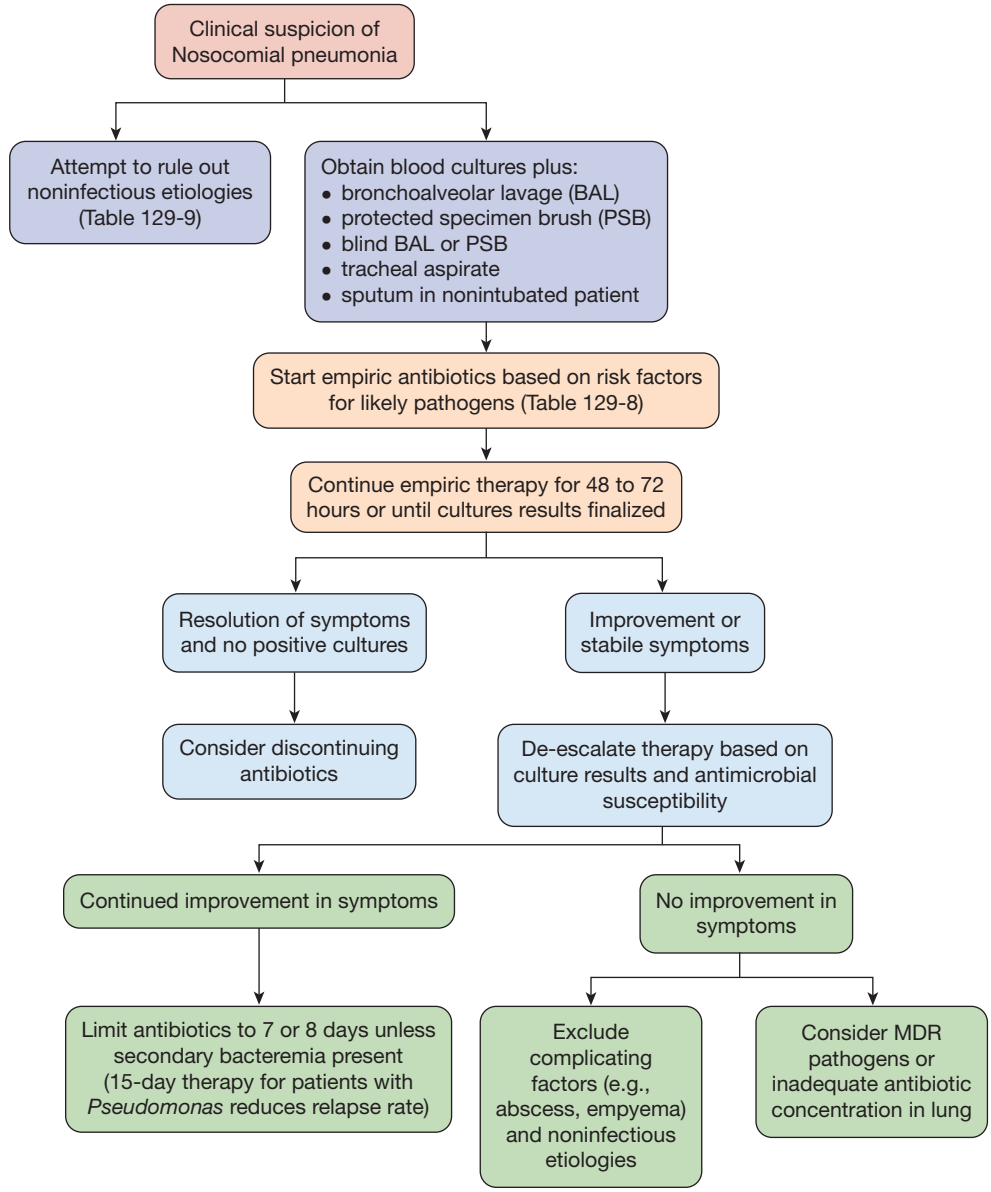

Figure 129-2 A step-by-step approach to the management of nosocomial pneumonia. *(Reproduced with permission from Kollef M, Isakow WA. The Washington Manual of Critical Care, 2nd edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.)*

colonization. As mentioned previously, mechanical ventilation is the most important risk factor for nosocomial pneumonia.[1,4,22] Therefore, avoiding intubation and reintubation, shortening the duration of mechanical ventilation, and employing noninvasive methods to improve oxygenation and ventilation when indicated can prevent pneumonia.[22,23,58]

Multiple methods designed to reduce bacterial colonization of the aerodigestive tract have been evaluated for their impact on VAP incidence. Selective decontamination of the digestive tract (SDD) administers nonabsorbable antimicrobial agents directly to the oropharynx and stomach to prevent colonization with GNB and *S. aureus*. While SDD has been shown to have a beneficial effect on nosocomial infection rates and even survival, potential negative effects include cost and the selection for antibiotic-resistant microorganisms when utilized in ICUs with high rates of endemic antibiotic resistance.[59–62] Alternatively, selective oropharyngeal decontamination (SOD) with nonabsorbable antibiotics or chlorhexidine provides a cheaper approach with similar efficacy.[62,63] While systemic antibiotics given once at the time of intubation may reduce early-onset VAP, the routine use of prolonged prophylactic, systemic antibiotics cannot be recommended.[64,65] In addition, probiotics may reduce VAP rates but no studies to date demonstrate a survival benefit.[66]

Strategies to reduce aspiration have also been studied. Patients should not be managed in a supine position, but rather placed in a semi-recumbent position.[67] Continuous aspiration of subglottic secretions has decreased the incidence of VAP in cardiac surgery patients.[68,69] Also, postpyloric feeding may reduce aspiration but the effect on infection rates and mortality is unknown. In addition, there is no evidence favoring a specific time point for the initiation of enteral feeding.[70]

The Institute for Healthcare Improvement developed a programmatic bundle, used by many healthcare institutions in the United States, designed to improve the care of mechanically ventilated patients. Components addressing the prevention of VAP include positioning the patient with the head of the bed elevated at 45 degrees, daily sedation holidays coupled with an assessment of readiness to extubate, and daily oral care with chlorhexidine. Each component, when evaluated independently, has been associated with the prevention of VAP.[71] A similar bundling strategy

TABLE 129-6 Strategies for the Prevention of Nosocomial Pneumonia

Strategy	Recommendation	Evidence Level
Topical iseganan	No	1
Oro-digestive decontamination[b] (Topical/topical plus intravenous antibiotics)	No	1
Oral chlorhexidine	Yes	1
Aerosolized antibiotics[b]	No	1
Intravenous antibiotics[b]	No	1
Specific stress ulcer prophylaxis regimen	No	1
Short-course antibiotic therapy(when clinically applicable)	Yes	1
Routine antibiotic cycling/rotation/heterogeneity[a]	No	2
Restricted (conservative) blood transfusion	Yes	2
Use of noninvasive mask ventilation	Yes	1
Avoid reintubation	Yes	2
Avoid patient transports	Yes	2
Orotracheal intubation preferred for airways	Yes	1
Orogastric intubation preferred for feeding tubes	Yes	2
Routine ventilator circuit changes	No	1
Use of heat-moisture exchanger	Yes	1
Closed endotracheal suctioning	Yes	1
Subglottic secretion drainage	Yes	1
Shortening the duration of mechanical-ventilation	Yes	1
Adequate intensive care unit staffing	Yes	2
Silver-coated endotracheal tube	Yes	1
Polyurethane endotracheal tube cuff	Yes	1
Semi-erect positioning	Yes	1
Rotational beds	Yes	1
Chest physiotherapy	No	1
Early tracheostomy	No	1
Use of protocols/bundles incorporating multiple prevention elements	Yes	2

Evidence levels: 1, supported by randomized trials; 2, supported by prospective or retrospective cohort studies.
VAP, ventilator-associated pneumonia.
[a]May be useful in specific clinical circumstances (outbreaks of a multi-drug resistant bacterial infection).
[b]Routine antibiotic prophylaxis not recommended due to potential emergence of antibiotic-resistant bacteria.
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developed by French investigators was evaluated prospectively in a single medical ICU. Components of the bundle included hand hygiene, head of bed elevation, maintenance of tracheal cuff pressure, avoidance of gastric overdistention, good oral hygiene, and minimization of tracheal suction. After an initial educational program for healthcare personnel, compliance with each component increased throughout the 24-month long study.[72] In a companion evaluation, total VAP rates decreased from 22.6 to 13.1 per 1000 ventilator days after implementation of the bundle.[73] A multicenter trial conducted in Spain employing a bundle with comparable measures reduced VAP rates from 12.9 to 9.8 per 1000 ventilator days despite a compliance rate of less than 30% for all five measures.[74] Thus, the bundling strategy appears to reduce VAP rates and could potentially produce a more substantial impact with improved compliance. Table 129-6 contains a list of recommended prevention strategies.

TREATMENT

When initiating empiric antibiotics for the treatment of nosocomial pneumonia, one first needs to assess the patient's risk for infection with MDR microorganisms. Table 129-7 lists these risk factors.[1] Patients with HCAP have been shown to have a comparable microbiological profile to those with HAP and VAP and should therefore be treated in a similar fashion.[75,76] Table 129-8 contains recommended antibiotic strategies for the treatment of nosocomial pneumonia after risk stratification for MDR microorganisms.[1]

Failure to initiate the appropriate antibiotics in a timely fashion results in excess morbidity and mortality.[52–57] Inappropriate

TABLE 129-7 Risk Factors for MDR Pathogens

Antimicrobials in previous 90 d
Current hospitalization for 5 d or greater
High rates of local antibiotic resistance
Hospitalization for 2 d or greater in the previous 90 d
Nursing home or extended care facility resident
Home infusion therapy
Chronic dialysis in previous 30 d
Wound care at home
Immunosuppression

TABLE 129-8 Antibiotic Recommendations for Nosocomial Pneumonia

Pneumonia Category	Microorganisms	Empiric Therapy	Additional Information
HCAP/HAP/VAP No risk for MDR pathogens and hospitalized <5 d	*Streptococcus pneumonia* *Haemophilus influenzae* *Methicillin-sensitive Staphylococcus aureus* *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* species *Proteus species* *Serratia marcescens*	Third-generation cephalosporin (Ceftriaxone) Or Ampicillin–sulbactam Or Respiratory fluoroquinolone (Levofloxacin or Moxifloxacin) Or Non-antipseudomonal carbapenem (Ertapenem)	Azithromycin should be considered for atypical coverage in very ill patients or ones with a high suspicion for atypical organisms or *Legionella* who are not on a respiratory fluoroquinolone
HCAP/HAP/VAP At risk for MDR pathogens or hospitalized for ≥5 d	*Pseudomonas aeruginosa* *Klebsiella pneumonia* (extended-spectrum β-*lactamase+)* *Acinetobacter* species *Legionella pneumophila* Methicillin-resistant *S. aureus*	Antipseudomonal cephalosporin (Cefepime, Ceftazidime) Or Antipseudomonal carbapenem (Imipenem or Meropenem) Or Antipseudomonal penicillin with β-lactamase inhibitor (Piperacillin–tazobactam) **Plus** Antipseudomonal fluoroquinolone (Ciprofloxacin or Levofloxacin) Or Aminoglycoside (Gentamycin, Tobramycin, or Amikacin) **Plus** Anti-MRSA agent (Linezolid or Vancomycin)	Carbapenems are often effective against ESBL organisms (*E. coli, Klebsiella*) or *Acinetobacter* species For patients with penicillin allergy consider substituting β-lactam with: • Aztreonam • Meropenem (<1% cross reactivity to penicillin allergy) Inhaled antibiotics have been used in selected populations and should be used only after consultation with a subspecialist

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antibiotics are those that do not have in vitro activity against the offending pathogen. A large, multicenter study conducted in Spain demonstrated that in 565 cases of nosocomial pneumonia, a change in the initial empiric antibiotic regimen was required in 43.7% of cases. The most frequent reason for a change in therapy was inadequate antimicrobial coverage, which resulted in greater attributable mortality.[53] A multivariate analysis of 107 patients with VAP determined that a delay in appropriate antibiotics for ≥24 hours was an independent risk factor for in-hospital mortality.[54] A separate multivariate analysis proved that prior antibiotic use was an independent risk factor for inappropriate antibiotic therapy; therefore, one should consider the possibility of drug resistance associated with previous antimicrobial agents.[14,57,77] A protocol-based approach to empiric antibiotics resulted in a greater rate of appropriate antibiotics and a reduction in antibiotic duration.[78] In addition, knowledge of each healthcare facility's antimicrobial drug resistance profile is of paramount importance.[16]

Choosing the correct dose of an antibiotic and the route of administration are essential in the treatment of nosocomial pneumonia (see Chapter 125). It is important to know the mechanism of action of each antibiotic. For example, β-lactam antimicrobial agents kill in a time-dependent fashion requiring a serum concentration above the microorganism's minimal inhibitory concentration (MIC). This knowledge has led to the proposition of prolonged infusions, a practice that remains controversial.[79,80] On the other hand, aminoglycoside agents kill bacteria in a concentration-dependent manner leading to newer extended interval dosing parameters. Antibiotics should initially be given intravenously in all cases of nosocomial pneumonia; however, transitioning to oral therapy in certain cases has been proven to be safe and effective.[81] Aerosolized antibiotics offer an appealing treatment route as direct antibiotic delivery to the LRT can create high drug concentrations within the lung parenchyma avoiding systemic delivery and the associated toxicities. However, the challenges accompanying aerosolizing small particles through a mechanical ventilator have limited the use of inhaled antibiotics. While there is no proven clinical benefit, future advancements in nebulizers and drug delivery may create a role for the adjunctive use of aerosolized antibiotics, especially as a way to prevent the emergence of MDR pathogens.[82] Finally, while traditionally thought to have a synergistic effect on the eradication of gram-negative organisms, combination therapy rather provides a greater likelihood of appropriate empiric therapy in the case of MDR microorganisms.[83]

When determining treatment duration for nosocomial pneumonia, the goal is to eradicate the microorganism without allowing for colonization of the host with MDR pathogens. Clinical improvement with appropriate antibiotic therapy usually occurs in 3 to 5 days as shown in a cohort of 63 patients with VAP in which CPIS scores were obtained before and after antibiotic initiation.[84] Survivors had improving CPIS scores by day 3 compared with nonsurvivors. Currently, 7 days is a reasonable duration of treatment, but prolonged therapy should be considered in the case of *P. aeruginosa*. A large French analysis demonstrated that patients with VAP had similar mortality and infection recurrence rates when treated with 8 days of antibiotics versus 15 days. Patients infected with nonfermenting GNB who received only 8 days of treatment had a higher infection recurrence rate compared to the prolonged therapy group, but no difference in mortality was noted.[85] A recent systematic review found no mortality difference between a short course of antibiotics (7–8 days) versus a longer course (10–15 days) in the management of VAP. However, there was a strong trend toward lower relapse rates when using a longer course of antibiotics mainly limited to VAP cases caused by nonfermenting GNB.[86]

TABLE 129-9 Noninfectious Causes of Fever and Pulmonary Infiltrates Mimicking Nosocomial Pneumonia

Chemical aspiration without infection
Atelectasis
Pulmonary embolism
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung contusion
Infiltrative tumor
Radiation pneumonitis
Drug reaction
Bronchiolitis obliterans organizing pneumonia

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In addition, a 7-day course of doripenem compared to a 10-day course imipenem–cilastatin in the management of VAP due to GNB resulted in higher rates of clinical failure and mortality, particularly in those patients infected with *P. aeruginosa*.[87] Empiric antibiotics should be deescalated in responders. Nonresponders should be evaluated for emergence of antimicrobial resistance, extrapulmonary infection, complications of pneumonia such as empyema, and noninfectious causes of fever and pulmonary infiltrates (Table 129-9).

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CHAPTER 130

Viral Infections of the Lung and Respiratory Tract

John Treanor

GENERAL PRINCIPLES

Viral infections of the upper and lower airways have a major impact on health. Acute respiratory illnesses, largely caused by viruses, are the most common illness experience for otherwise healthy adults and children (see Chapter 126). The National Health Interview Survey suggests that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year, and account for 54% of all acute conditions exclusive of injuries.[1] A total of 44% of these illnesses require medical attention, and result in 287 days of restricted activity, 94.4 days lost from work, and 182 days lost from school per 100 persons per year. Estimates from family-based surveillance suggest that approximately one-fourth of these illnesses result in consultation with a physician. Illness rates for all acute respiratory conditions are highest in young children; children below the age of 9 are estimated to experience between five and nine respiratory illnesses per year, whereas adults experience between three and five such illnesses.[2,3]

Mortality due to acute viral respiratory infection in otherwise healthy individuals in economically developed countries is relatively rare, with the exception of epidemic influenza. However, acute respiratory infection is a major cause of childhood mortality in developing countries, and it is estimated that 4.5 million children under 5 years of age die annually from acute respiratory infection.[4] Viruses are identified in about 3% to 40% of cases of respiratory disease in this setting, and are estimated to play a contributing role in approximately 20% to 30% of deaths. In addition, new and emerging respiratory viruses such as Hantavirus, emerging coronaviruses associated with severe acute respiratory syndrome (SARS) or middle eastern respiratory syndrome (MERS), and transmission of influenza viruses from avian or swine sources to man, pose a continuing threat.

EPIDEMIOLOGY

Many of the viruses associated with acute respiratory disease display a significant seasonal variation in incidence. Although the exact seasonal arrival of each virus in the community cannot be predicted with precision, certain generalizations are useful diagnostically and in planning control strategies. For example, influenza and respiratory syncytial virus (RSV) epidemics both occur predominantly in the winter months, with a peak prevalence in January to March in the northern hemisphere. Parainfluenza virus type 3 (PIV-3) infections show a predominance in the spring, whereas types 1 and 2 (PIV-1 and PIV-2) cause outbreaks in the fall to early winter. Rhinoviruses may be isolated throughout the year, with increases in frequency in the spring and fall. The peak prevalence of enteroviral isolations is in late summer and early fall, whereas adenoviruses are isolated at roughly equal rates throughout the year. The herpes viruses also do not show significant seasonal variation in incidence, except for varicella, which occurs throughout the year, but more commonly in late winter and early spring.

The reasons for these seasonal changes are not entirely clear. One mechanism may involve seasonal effects on virus transmissibility either because of more favorable environmental conditions for virus survival[5] or behavioral changes that increase transmission, such as indoor crowding. Heretofore unknown effects of season on host susceptibility or response to infection could also play a role.

CHARACTERISTICS OF THE VIRUSES

Viruses of importance in the respiratory tract include both those considered to be principal respiratory viruses, whose replication is generally restricted to the respiratory tract, and others in which respiratory involvement is part of a generalized infection. The classification of these viruses depends in part on the type and configuration of the nucleic acid in the viral genome, the characteristics of the viral structural proteins, and the presence or absence of a lipid-containing envelope surrounding the virus particle (Table 130-1). The number of distinct antigenic types in each of the virus families varies. For example, the adenovirus and rhinovirus groups are composed of large numbers of antigenically (serotypically) distinct immunotypes, but other groups, such as paramyxovirus and coronavirus, are composed of only a limited number of immunotypes. The degree of antigenic stability of the virus is an important factor in determining the frequency of reinfection. This characteristic is particularly important for influenza type A virus, which periodically undergoes both minor and major changes in its surface antigens.

TRANSMISSION

The routes by which the different respiratory viruses spread from person to person are still not established with certainty. Rhinovirus and RSV spread, at least in part, by direct hand contact with contaminated skin and environmental surfaces. This is followed by self-inoculation of infectious virus onto the nasal mucosa or conjunctiva. Others, including influenza, measles, and varicella zoster viruses (VZV), spread at times in small-particle aerosols. Many viruses may spread by means of large-particle aerosols over short distances (1 m). The relative importance of the various transmission routes under natural conditions for each virus is unknown.

A number of respiratory viruses have been documented to cause outbreaks of infection in closed populations. In hospitals, nurseries, day care centers, and homes for the elderly, secondary spread to staff members and other patients may occur. Such outbreaks have been observed for viruses that appear to be spread by small-particle aerosols, including measles and VZV, and for those spread by direct contact with infectious secretions, such as RSV, rhinoviruses, and coronaviruses, where there is frequent close contact between patients and staff.

PATHOGENESIS OF INFECTION

The initial sites of infection and pathogenesis differ for the various virus groups. Some, such as rhinovirus, are associated mainly with upper respiratory tract involvement. Others, such as influenza, commonly invade the lower airways and sometimes pulmonary parenchyma in addition to causing upper airway disease. The viruses also differ in the amount of damage produced in the cells lining the respiratory tract. Extensive damage to the respiratory epithelium is a characteristic feature of the influenza virus infection, but biopsy

TABLE 130-1 Common Respiratory Viruses

Virus	Family	Genome	Seasonality	Diseases	Vaccine	Antivirals
Influenza virus	Orthomyxoviridae	ss RNA (–)	Yes (winter)	Influenza, croup, bronchitis, pneumonia	Yes	Yes (oseltamivir, zanamivir)
Respiratory syncytial virus (RSV)	Respiroviridae	ss RNA (–)	Yes (winter)	Bronchiolitis, pneumonia	No	Yes (ribavirin)
Metapneumovirus (hMPV)	Respiroviridae	ss RNA (–)	Yes (winter)	Bronchiolitis, pneumonia	No	No
Parainfluenza virus (PIV)	Paramyxoviridae	ss RNA (–)	Yes (winter)	Croup (PIV1), pneumonia (PIV3)	No	No
Measles	Paramyxoviridae	ss RNA (–)	No	Croup, pneumonia	Yes	No
Rhinovirus	Picornaviridae	ss RNA (+)	Yes (spring, rail)	Common cold	No	No
Coronavirus (CoV)	Coronaviridae	ss RNA (+)	No	Common cold (OC43), pneumonia (HuCoV-SARS)	No	Yes (interferon alpha?)
Sin nombre virus	Bunyaviridae	ss RNA (+/–)	No	Pneumonia	No	No
Adenovirus	Adenoviridae	ds DNA	No	Croup, pneumonia	Yes	No
Herpes simplex virus	Herpesviridae	ds DNA	No	Pneumonia	No	Yes (acyclovir, famciclovir)
Varicella zoster virus	Herpesviridae	ds DNA	No	Pneumonia	Yes	Yes (acyclovir, famciclovir)
Cytomegalovirus	Herpesviridae	ds DNA	No	Pharyngitis, pneumonia	No	Yes (ganciclovir, cidofovir)
Epstein–Barr virus	Herpesviridae	ds DNA	No	Pharyngitis	No	No
Bocavirus	Parvoviridae	ss DNA (+/–)	No	Bronchiolitis, colds	No	No

studies show little evidence of nasal epithelial damage in persons with rhinovirus colds. Instead, colds are related both to virus damage to the respiratory tract and to the host responses to infection, including immunologic events, release of mediators of inflammation, and neurogenic reflexes.

An additional important feature of respiratory virus infections is their effect on the resident bacterial flora of the upper airways. Respiratory virus infections have been found to alter bacterial colonization patterns, increase bacterial adhesion to respiratory epithelium, and reduce mucociliary clearance and phagocytosis. These impairments of host defenses by virus allow colonization by pathogenic bacteria and invasion of normally sterile areas, such as the paranasal sinuses, middle ear, and lower respiratory tract, resulting in secondary infection.

A summary of the specific viral etiologies most commonly associated with syndromes of upper respiratory tract infection is given in Table 130-2. These infections are discussed in detail in Chapter 126. The following sections briefly summarize the important points of viral respiratory tract infections.

TABLE 130-2 Virus-Associated Respiratory Tract Infections

Clinical Syndrome	Associated Viruses
Common cold	Rhinovirus, other picornaviruses, RSV, PIV, coronavirus, adenovirus
Pharyngitis	Rhinovirus, influenza, EBV, CMV, HSV, HIV
Tracheobronchitis	Influenza, adenovirus, rhinovirus
Croup	PIV1, PIV2, influenza, adenovirus, measles
Bronchiolitis	RSV, hMPV, HuCoV-NL63, bocavirus
Pneumonia: Adults	Influenza, adenovirus, RSV, PIV, measles, VZV, sin nombre virus, HuCoV-SARS
Children	RSV, PIV, influenza, measles, adenovirus, rhinovirus, CMV
Immunocompromised	CMV, HSV, VZV, adenovirus, RNA viruses

■ DIAGNOSTIC TESTS

While specific diagnostic tests will be discussed in the appropriate sections, the development of molecular diagnostic techniques, particularly multiplexed nucleic acid–based tests, has generally supplanted most other diagnostic modalities. In most cases, however, diagnostic testing should be considered in the context of whether the results will have an impact on patient management.

THE COMMON COLD

Below are considered the clinical features, etiology, pathogenesis, diagnostic evaluation, and management of the common cold.

■ CLINICAL FEATURES

The term "cold" really does not constitute a single entity, but rather a group of similar illnesses of differing cause (see also Chapter 126). However, all colds include symptoms of rhinitis with variable degrees of pharyngitis. Predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but fever is not a typical feature of uncomplicated colds. Cough and hoarseness are variably present and may be more frequent in the elderly,[6] but other lower respiratory tract signs and symptoms are not typical of colds and should raise suspicion of other entities.

Physical findings are nonspecific and most commonly include nasal discharge and pharyngeal inflammation. More severe disease, with higher fever, may be seen in children. Although colds are generally self-limited, symptoms may last for a surprisingly long period of time, with a median duration of illness of approximately 9 to 10 days in adults.[7] Recognized complications of colds include secondary bacterial infections of the paranasal sinuses and middle ear, and exacerbations of asthma, chronic bronchitis, and emphysema. Colds are frequently associated with involvement of the middle ear, likely due to eustachian tube dysfunction. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults, and in a higher proportion in young children.

Colds are also associated with detectable abnormalities of the paranasal sinuses, which may or may not be evident clinically. Mucosal thickening and/or sinus exudates have been observed in as many as 77% of subjects with acute colds.[8] These abnormalities are transient

and usually not associated with symptoms, although they may persist 21 days or longer. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults,[9] and in a higher proportion in young children.[10] Rhinoviruses and other common cold viruses have been detected in middle ear fluids in approximately 20% to 40% of cases of otitis media with effusion in children.[11] Infections with RSV, influenza, and adenoviruses are often also associated with otitis media.[10] However, clinically manifest acute sinusitis is seen in a small (0.5%–5%) proportion of individuals with naturally occurring colds.

Clinical colds in atopic individuals may be more severe or more likely to result in wheezing than in normal individuals, and rhinoviruses have been identified as major causes of asthma exacerbations in children and adults.[12] Rhinovirus colds may increase asthma by augmenting airway allergic responses such as histamine release and eosinophil influx after antigen challenge. Rhinoviruses have also been identified as important causes of exacerbations of chronic obstructive pulmonary disease (COPD).[13,14]

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

Epidemiologic studies have established that the great majority of common colds are associated with infection with the human rhinoviruses or other picornaviruses. Other agents frequently associated with common colds include coronaviruses, PIV, and RSV, with a variety of other agents implicated occasionally. The clinical characteristics of illness due to each of these viruses are similar, and a specific viral etiology generally cannot be deduced on clinical grounds alone. Epidemiologic studies have indicated that on an annual basis, any one antigenic type of virus is responsible for less than 1% of all colds.

The differential diagnosis of individuals presenting with typical signs and symptoms is not extensive. However, in the presence of additional signs or symptoms that are not part of this clinical description, such as high persistent fever, signs of respiratory distress, or lower respiratory tract disease, alternative diagnoses should be sought. Allergic causes should be considered in individuals who present with recurrent symptoms restricted to the upper respiratory tract.

PATHOGENESIS

Studies of the pathogenesis of the common cold have largely focused on rhinoviruses, the most commonly implicated viral etiology. In situ hybridization studies of nasal biopsy specimens from rhinovirus-infected subjects demonstrate that infection is largely confined to relatively small numbers of ciliated nasal mucosal epithelial cells, although occasional nonciliated cells are also infected.[15] Sloughing of these epithelial cells is seen in naturally occurring colds, but the epithelial lining remains intact, with structurally normal cell borders. Infection is associated with significant increases in the numbers of polymorphonuclear leukocytes in nasal mucosa and secretions, probably due to elaboration of IL-8 by infected cells.[16] Although rhinoviruses are not able to grow efficiently at body temperature, virus can be detected within cells of the lower airway even in uncomplicated colds in healthy subjects.[17]

In general, the number of infected cells appears to be quite limited, even in fairly symptomatic individuals, and there is no clear correlation between the level of virus replication or the number of cells infected, and the level of symptomatology. These results have suggested that virus-induced cellular injury is not the direct cause of symptoms in rhinovirus colds, but rather that inflammatory mediators play an important role. Analysis of the nature of the mucosal exudate during rhinovirus colds suggests that the nasal secretions during the initial response to rhinovirus infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions,[18] whereas later glandular secretions (lactoferrin, lysozyme, and secretory IgA) predominate. Similar observations have been made in allergic rhinitis. However, in contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds, as nasal histamine levels do not increase, and therapy with selective H1 antihistamine is not effective.[19,20] Nasal secretion kinin levels do correlate with symptoms in natural and experimental colds, and intranasal administration of bradykinin mimics the induction of signs and symptoms in the common cold,[20,21] including increased nasal vascular permeability, rhinitis, and sore throat.

DIAGNOSTIC TESTS

Molecular diagnostic tests have been developed for many of the viruses associated with the common cold. Since there is no specific therapy and the clinical characteristics of colds due to different viruses are similar, use of techniques for specific viral diagnosis in the common cold is generally limited to the research setting.

TREATMENT AND PREVENTION

The recommended treatment for colds is to use individual remedies to treat specific symptoms. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective sedating antihistamines such as brompheniramine, chlorpheniramine, or clemastine fumarate.[22,23] The effect is probably due to the anticholinergic properties of these drugs but treatment with selective H1 inhibitors is not effective. Studies of pseudoephedrine have demonstrated measurable improvements in nasal air flow consistent with a decongestant effect. In previously healthy children and adults, there is no danger from the routine use of cough suppressants, although they should be used cautiously in patients with underlying COPD. Cough syrups–containing expectorants are of unproved value in common colds, although guaifenesin may reduce the cough reflex.

Symptomatic therapy with systemic anticholinergic drugs or anticholinergic-sympathomimetic combinations has not been shown to confer any benefit, and to be associated with significant side effects, especially in children.[24,25] In addition, the use of the decongestant phenylpropanolamine is associated with an increased risk of hemorrhagic stroke,[17,26] and this drug has been removed from over-the-counter cold remedies.

Topical application of vasoconstrictors such as phenylephrine or ephedrine provides relief of nasal obstruction, but may be associated with a rebound of symptoms upon discontinuation if used for more than a few days. Thus, nasal sprays–containing decongestants should be used for no more than 3 days. Topical application of ipratropium, a quaternary anti-cholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds.[27] This agent probably exerts its major effect on the parasympathetic regulation of mucus and seromucous glands.

There has been considerable interest in the development of antiviral agents for the common cold. Several problems confront the successful development of such an antiviral agent. Because of the numerous etiologic agents, the ideal drug would require a wide spectrum of activity. In addition, many drugs that appear to have excellent in vitro activity have failed in clinical trials, apparently because they did not reach sufficient levels within the nasal mucosa where virus replication occurs. Finally, because symptoms in colds are not clearly related to the level of virus replication, a successful treatment strategy may also require use of drugs to antagonize the effects of inflammatory mediators.[28]

LARYNGITIS AND PHARYNGITIS

In this section, the clinical features, etiology, differential diagnosis, pathogenesis, diagnostic evaluation, and management of laryngitis and pharyngitis are discussed.

CLINICAL FEATURES

Pharyngitis is a common complaint of both adults and children, and is one of the more common reasons for seeking outpatient medical care. In general, this syndrome refers to individuals who present with the primary complaint of sore throat, and should probably be

reserved for those individuals who manifest some objective evidence of pharyngeal inflammation as well. The clinical manifestations of pharyngitis are dominated by the specific causative agent. However, generally the syndrome can be divided into those cases in which nasal symptoms accompany pharyngitis, which are predominantly viral in nature, and those cases without nasal symptoms, which have a somewhat more diverse spectrum of etiologic considerations, including both group A and nongroup A streptococci, chlamydia (strain TWAR), mycoplasma, and other agents.[29]

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

Rhinovirus colds are frequently accompanied by pharyngitis, although objective signs of pharyngeal inflammation are uncommon. Adenovirus infections are frequently associated with pharyngitis, and a specific syndrome of pharyngoconjunctival fever, consisting of fever, pharyngitis, and bilateral conjunctivitis is associated with adenovirus types 3 and 7. A variety of enteroviral serotypes are associated with febrile pharyngitis. Herpangina is a specific Coxsackie virus-induced pharyngitis in which small (1–2 mm) vesicular lesions of the soft palate rupture to become small white ulcers. Pharyngitis is a typical component of acute influenza in which individuals experience the sudden onset of systemic symptoms of fever, myalgias, and malaise accompanied by upper respiratory signs and symptoms, including pharyngitis. Primary oral infection with herpes simplex virus may present with pharyngitis, typically with vesicles and shallow ulcers of the palate, and cervical lymphadenopathy.

Pharyngitis may be the presenting or predominating symptom in more generalized viral infections. Pharyngitis is a significant complaint in approximately one-half of cases of the acute mononucleosis syndrome due to Epstein–Barr virus. Pharyngitis in this syndrome is generally exudative and is accompanied by cervical and generalized lymphadenopathy, as well as fever, hepatosplenomegaly, and other systemic symptoms. The heterophile antibody test is typically positive in the second week of illness. Cytomegalovirus (CMV) can cause an identical syndrome that is monospot negative. CMV may be associated with pharyngitis more commonly in children than in adults. An acute mononucleosis-like syndrome with pharyngitis may also be the presenting manifestation of primary HIV infection. Viruses in the hemorrhagic fever group produce an acute pharyngitis that occurs early in the disease, before skin lesions appear. Also, exudative pharyngitis is a common clinical manifestation in Lassa fever.

The differential diagnosis of acute pharyngitis generally centers upon the differentiation of streptococcal from viral etiologies. Features suggestive of streptococcal pharyngitis include tonsillar swelling, moderate to severe tenderness on palpation, enlargement of lymph nodes, presence of scarlatiniform rash, and absence of coryza. The presence of nasal symptoms or of conjunctivitis favors a viral etiology, and as described, some viral syndromes may present with distinguishing characteristics that help in their identification. Generally, acute pharyngitis in children less than 3 years of age is predominantly viral in origin. The presence of exudate is suggestive of bacterial etiology, but exudates may also be seen with adenovirus or EBV.

PATHOGENESIS

As described, pharyngitis in the common cold is probably the result of chemical mediators of inflammation, which are potent stimulators of pain nerve endings. Potentially similar mechanisms may account for pharyngitis in other viral syndromes as well. Direct viral damage and other host inflammatory responses may also contribute. Pharyngitis occurs most often as part of the common cold syndrome and thus is usually associated with the same viruses that cause colds. In some cases, pharyngeal symptoms predominate to a degree that overshadows other complaints. The kinins are potent stimulators of pain nerve endings, and high levels of bradykinin and lysyl bradykinin are present in nasal secretions of patients with rhinovirus colds. Intranasal application of bradykinin promotes sore throat and nasal symptoms in volunteers, supporting a role for these agents in the pathogenesis of cold symptoms.

DIAGNOSTIC TESTS

Identification of viral causes of pharyngitis is generally possible through isolation in cell culture, but is seldom attempted in clinical practice. Rapid antigen detection tests are available for RSV and influenza A virus.

Rapid diagnostic tests are widely available for the office identification of group A streptococci, and are indicated in most cases in which the etiology is uncertain. When highly sensitive tests are used, backup cultures are generally not necessary. Routine studies for other bacterial and nonbacterial pathogens are usually not obtained. When guideline recommendations for the selective use of throat cultures are used with antibiotic treatment based only on positive rapid test or throat culture, results can reduce unnecessary use of antibiotics for treatment of pharyngitis.[30]

TREATMENT AND PREVENTION

The treatment of most cases of viral pharyngitis is symptomatic, as noted in the section on common colds. Patients suspected of having influenzal pharyngitis who are seen within the first 2 days of illness can be treated with antiviral therapy (see the discussion on influenza virus). In immunosuppressed patients with chronic herpetic pharyngitis or normal hosts with primary gingivostomatitis, acyclovir therapy is recommended (see the discussion on herpes simplex virus).

Treatment of group A streptococcal infections with antimicrobial agents is generally initiated to prevent rheumatologic complications of this infection, and because treatment of acute streptococcal pharyngitis is associated with more rapid resolution of symptoms,[31] although the absolute benefits are rather modest.

CROUP

Important clinical features, aspects of pathogenesis, diagnosis, and management of croup are presented below.

CLINICAL FEATURES

Croup, or viral laryngotracheobronchitis, is a clinically distinct illness that predominantly affects children under the age of 3. The illness typically begins with upper respiratory tract symptoms of rhinorrhea and sore throat, often with a mild cough. After 2 or 3 days, the cough deepens and develops a characteristic brassy, barking quality, which is similar to a seal's bark. Fever between 38 and 40°C is common, although those with croup due to RSV may have normal temperatures. The child may appear apprehensive and most comfortable sitting forward in bed. The respiratory rate is elevated, but usually not over 50; this contrasts with bronchiolitis, in which more severe tachypnea is often seen. Chest wall retractions, particularly in the supraclavicular and suprasternal areas, may be observed. Children with this finding on presentation have a higher risk of hospitalization or of requiring ventilatory support.

The characteristic physical finding of croup is inspiratory stridor. Inspiration is prolonged, and in very severe cases, some degree of expiratory obstruction may also be seen. Rales, rhonchi, and wheezing, which reflect the characteristic involvement of the lower respiratory tract, may be heard on physical examination. A fluctuating course is typical for viral croup, and the child may appear to worsen or improve within an hour. The typical duration of croup is 3 to 4 days.

Hypoxemia occurs in 80% of children with croup severe enough to require hospitalization. The degree of hypoxia is generally difficult to ascertain clinically, but pulse oximetry provides a reliable and noninvasive means to monitor the state of oxygenation. Children who develop respiratory insufficiency as a result of increasing fatigue also may have elevations in Pa_{CO_2}.

Children with croup characteristically exhibit subglottic narrowing of the tracheal air shadow on PA films of the neck, the so-called "steeple" sign). This finding may be useful in differentiating croup from epiglottitis. However, radiographs are limited in accuracy, and when the diagnosis is uncertain, radiologic and pharyngeal examination should be avoided because of the risk of cardiorespiratory arrest in acute epiglottitis. Emergency assessment by an otolaryngologist or an anesthesiologist is indicated in this situation. Chest X-rays may reveal parenchymal infiltrates which are part of the characteristic involvement of the lower respiratory tract in this syndrome.

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

PIV-1 and PIV-2 are the most common viruses responsible for croup, accounting for about 75% of cases,[32] and the seasonal incidence of croup reflects the seasonal variations in PIV incidence. Less common causes of croup include RSV, influenza A or B viruses, measles, rhinoviruses, and adenoviruses as well as *Mycoplasma pneumoniae.* PIV-2, influenza A viruses and measles are associated with more severe disease, but generally, the clinical presentation of the croup syndrome due to individual agents is similar.

The majority of cases of inspiratory stridor in children are caused by viral croup. However, it is critical to distinguish these syndromes from other, potentially more serious causes of airway obstruction such as bacterial epiglottitis and tracheitis early in clinical management. Epiglottitis is an acute cellulitis of the epiglottis and surrounding structures. Patients present with acute respiratory distress and drooling, but the barking cough of croup is absent. Since the introduction of effective vaccines for the major bacterial cause or epiglottitis, *Haemophilus influenzae* type b (Hib), the incidence of epiglottitis in children has also declined considerably. In adults, and rarely in children, epiglottitis may be caused by a variety of other bacterial agents such as *Haemophilus parainfluenzae* or alpha hemolytic streptococci, which may spread from a contiguous focus of infection. Bacterial tracheitis is a relatively rare syndrome that mimics croup. Abundant purulent sputum is often present. Bacterial tracheitis is usually caused by *Staphylococcus aureus* or Hib; other bacteria such as *Streptococcus pneumoniae* have also been associated with this syndrome. Other infectious causes of stridor, including peritonsillar or retropharyngeal abscess, or diphtheria, should be considered. Evidence of noninfectious causes of stridor such as trauma or aspiration of a foreign body, should also be sought in the history and physical examination.

PATHOGENESIS

The severity of clinical symptoms in PIV croup appears to be directly related to the level of virus replication.[33] The viral infection in croup produces inflammation both in the upper respiratory tract, and in the lung parenchyma. The classic signs of croup, including the barking cough and inspiratory stridor, arise mostly from inflammation occurring in the larynx and trachea. Inflammatory changes are seen by histology in the epithelial mucosa and submucosa of the larynx and trachea. The cellular infiltrate includes histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes. The inflammation and obstruction are greatest at the subglottic level, which is the least distensible part of the airway because it is encircled by the cricoid cartilage. Consequently, localized inflammation and edema lead to obstruction to airflow. The impeded flow of air through this narrowed area produces the classic high-pitched vibration. Obstruction is greater during inspiration because it occurs in the extrathoracic portion of the airway, and is enhanced in small children because the walls of the airways in these individuals are relatively compliant. Obstruction of airflow results in an initial decline in tidal volume, which is compensated by an increase in respiratory rate to maintain adequate alveolar ventilation. However, if the obstruction increases, the work of breathing may increase until the child tires, and as the respiratory rate declines, the child develops hypercarbia and respiratory failure.

Involvement of the lower respiratory tract with resulting hypoxia is integral to the pathophysiology of croup.[34] Inflammatory changes are noted throughout the respiratory tract, including the linings of the bronchi, bronchioles, and even the alveoli. Although some degree of hypoxia can be explained on the basis of hypercarbia, the major pathophysiologic mechanism is ventilation–perfusion mismatching.

Pulmonary edema may complicate severe croup and upper airway obstruction. The onset of pulmonary edema often is immediately following intubation. Pulmonary edema in these cases does not appear to be due to pulmonary artery hypertension, but to local hypoxia, and increased alveolar–capillary transmural pressure.

In addition to these anatomic pathophysiologic events, immunologic mechanisms may also play a role in some manifestations or in determining the severity of disease. Virus-specific IgE responses appear earlier and are of greater magnitude in patients with PIV-associated croup than in age-matched controls with simple upper respiratory illness. Histamine is also detectable in upper respiratory tract secretions in this condition. There also appears to be a relationship between croup and subsequent reactive airways disease and/or heightened responsiveness to bronchodilators, particularly in children with recurrent croup.

DIAGNOSTIC TESTS

PIVs and other viruses associated with croup can be isolated in cell culture, and specific viral diagnosis can be made by PCR, but the clinical syndrome is sufficient for the diagnosis, and management generally does not depend on identification of the specific agent.

TREATMENT AND PREVENTION

Because the majority of hospitalized children are hypoxic, oxygen is the mainstay of treatment for severe disease, and should be given to all hypoxemic patients. Use of helium as the carrying gas, rather than air, has been suggested as a method to decrease the work of breathing. However, this approach requires use of 70% helium to be effective and limits the amount of oxygen which can be delivered.[35] Humidified air, or mist therapy is commonly used, and has several potential roles. Desiccation of the inflamed epithelial surfaces is decreased, and the viscosity of the exudate is reduced. However, the value of mist therapy has not been proven, and it should be recognized that water from the standard home-use vaporizer cannot reach the lower respiratory tract because of the large particle size. In addition, removal of the child from the parents and placement in a mist tent can be more distressing to the child than beneficial.

Administration of nebulized racemic epinephrine generally gives rapid, symptomatic relief in croup.[36] It is believed that alpha-adrenergic stimulation by this drug causes mucosal vasoconstriction, leading to decreased subglottic edema. Several randomized trials have demonstrated a rapid beneficial effect on airway obstruction.[37,38] The onset of action is rapid, often within minutes, but the duration of relief is also limited, lasting 2 hours or less. Therefore, treated subjects should be observed closely for clinical deterioration. Although symptomatic relief is considerable, use of epinephrine is not associated with improvements in oxygenation, probably because the defect in oxygen is associated with ventilation–perfusion mismatching due to lower respiratory tract involvement. In addition, tachycardia may occur. Thus, inhaled epinephrine is generally reserved for children who fail to respond to more conservative management,[39] although some centers use it routinely.

Steroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup, including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of intramuscular, oral, or nebulized steroids appears to be equally effective.[40,41] Administration of single-dose steroid therapy in this setting has not been associated with significant side effects,[42] and should probably

be used in any patient with illness significant enough to require an emergency room or clinic visit.

Antiviral agents effective against some of the viruses responsible for croup are available, but have not been tested for efficacy in this situation. However, the potential benefit of the use of antiviral agents in the typical self-limited course of croup would likely be limited. Since croup is a viral illness, antibiotic therapy is of no benefit.

Effective prevention of croup will largely depend on the development of vaccines for the individual viral agents responsible for this syndrome. Vaccines are currently available for both measles and influenza. There are currently no vaccines available for PIV.

TRACHEOBRONCHITIS

Clinical features, pathogenesis, diagnosis, and management of tracheobronchitis are discussed below.

CLINICAL FEATURES

In addition to causing croup and bronchiolitis, viral infection of the trachea and bronchi may cause tracheitis or tracheobronchitis. The diagnosis of acute bronchitis is usually applied to cases of acute respiratory disease with severe and prolonged cough that continues after other signs and symptoms of the acute infection have subsided. Cough occurs during the first week of illness in 30% of rhinovirus colds in young adults and in 80% or more of cases of influenza A virus infection, in which it is often prolonged. Adenovirus infections characteristically involve the tracheobronchial tree, with resultant bronchitis that in military populations is part of the syndrome of acute respiratory disease. Tracheitis is characterized by tracheal tenderness, which can be elicited by gentle pressure on the anterior trachea just below the cricoid cartilage. Substernal discomfort on inhalation and nonproductive paroxysmal cough are noted. Paroxysmal nonproductive cough is also characteristic of tracheobronchitis, and is usually much more severe at night. Later in the course of illness, small amounts of clear or whitish sputum may be produced. Accompanying symptoms may include fever, headache, myalgias, malaise, and anorexia. After several days of coughing, chest wall or abdominal discomfort that is muscular in nature may be noted. Physical findings are generally nonspecific; examination of the chest may reveal no adventitious sounds, but more commonly diffuse rhonchi and occasional wheezing. Physical signs such as egophony, pleural friction rubs, or areas of dullness to percussion, are not present.

PATHOGENESIS

The mechanisms of cough production in viral infection are not well understood but may include direct damage to the respiratory mucosa, release of inflammatory substances in response to the infection, increased production and/or decreased clearance of respiratory secretions, and stimulation of airway irritant receptors. Intranasal application of several prostaglandins also produces cough in uninfected volunteers.[43] Infection may also enhance airway reactivity, leading to increased sensitivity to cold air and pollutants such as smoke.

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

Tracheobronchitis is most typically caused by influenza A or B virus. In adults other common respiratory viruses such as PIV or RSV may present with prolonged cough. Herpes simplex has been associated with necrotizing tracheobronchitis in nonimmunocompromised hosts. This syndrome is often accompanied by refractory bronchospasm.

The differential diagnosis of acute bronchitis includes nonviral infections and noninfectious etiologies such as cough-variant asthma. *M. pneumoniae* and *Chlamydia pneumoniae* infections cause prolonged cough. *Bordetella pertussis* infection should also be considered in the differential diagnosis. In otherwise healthy persons, workup of acute cough should be directed toward determining the presence of pneumonia.

DIAGNOSTIC TESTS

Influenza viruses can be isolated in cell culture, as can many of the other viruses associated with bronchitis. In addition, rapid antigen tests or nucleic acid tests are available for some of these viruses. Specific viral diagnosis is generally not necessary for appropriate management of bronchitis.

TREATMENT AND PREVENTION

Treatment in adults is best effected by prescribing rest, aspirin for headache and fever, cold water vapor inhalation; and a cough syrup such as guaifenesin with dextromethorphan. For children, a cough suppressant may be helpful. In the absence of signs of pneumonia, treatment of prolonged cough with antibacterial agents is of no benefit.[44,45]

BRONCHIOLITIS

Clinical features, pathogenesis, diagnosis, and management of bronchiolitis are discussed in this section. The reader is also referred to Chapter 51.

CLINICAL FEATURES

Bronchiolitis is a fairly characteristic syndrome whose presenting symptoms are dominated by the major pathophysiologic defect, obstruction to expiratory air flow.[46] The onset of lower respiratory symptoms is usually preceded by rhinitis, often with nasal congestion and discharge. More severe symptoms characteristically occur 2 to 3 days later, but in some cases are concurrent with the onset of upper respiratory symptoms. In many instances, there may be a history of exposure to an adult or sibling with a cold or other minor respiratory illness, or history of exposure to other cases of bronchiolitis in the day care setting.

The hallmark of disease is wheezing, which can be quite marked, with flaring of the nostrils and use of accessory muscles of respiration. Cough may or may not be prominent initially, and when cough is present, it may be paroxysmal in nature. Slight cyanosis is often observed, but the presence or absence of cyanosis is not a reliable indicator of the degree of oxygenation or of the severity of disease. Physical findings are generally confined to the chest, with the development of rales, which are usually musical in the beginning, and then become moister. Hyperresonance of the chest may be observed, and the liver may be displaced downward. The respiratory rate is elevated, with rates of from 50 to 80 breaths per minute. Fever is frequently present at the beginning of the illness, but may no longer be present at the time lower respiratory tract involvement develops. Among hospitalized infants, one-third or more are afebrile, but have marked lower respiratory tract disease. Thus, the presence or absence of fever does not indicate the severity of the child's illness. Mild conjunctivitis is noted in about one-third of cases, with pharyngitis of varied severity in about one-half, and otitis media in 5% to 10%. The hospital course is variable, but most infants show improvement in 3 to 4 days.[47]

Radiologic findings are generally nonspecific, with reported findings including air trapping, consolidation, and collapse.[48] However, there is no correlation between the chest X-ray findings and the clinical course.[49] Chest X-rays should be obtained to rule out alveolar-filling defects suggestive of bacterial pneumonia and in those infants with severe disease, sudden deterioration, or underlying disorders. Results of routine laboratory tests are generally unremarkable. The peripheral white blood cell count is usually not elevated. Electrolyte disturbances, most notably, hyponatremia, may be seen with severe disease, particularly if excessive amounts of hypotonic fluid are administered. Acute disease may be associated with elevations in pulmonary artery pressure, but echocardiographic studies are usually unremarkable in infants with structurally normal hearts.

Bronchiolitis is a disease predominantly of infancy, and the peak age incidence is between 2 and 6 months of age, with over 80% of cases occurring in the first year of life. The risk of hospitalization

and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition, infants born prematurely, and those who are less than 6 weeks of age at the time of presentation are also at increased risk of hospitalization. More severe disease has also been documented in children with a family history of asthma, and those exposed to cigarette smoke in the family setting.

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

RSV causes the majority of cases of bronchiolitis and during the RSV epidemic season, essentially all cases are due to this virus. Overall, RSV is recovered from about three-fourths of all infants admitted to the hospital with bronchiolitis.[46] Several other respiratory viruses are associated with bronchiolitis, including PIVs, influenza virus, mumps, and rhinoviruses. The epidemiology and pathophysiology of parainfluenza bronchiolitis are similar to that of RSV, and particularly severe disease may be associated with PIV-3. Adenoviruses types 3, 7, and 21 are relatively uncommon causes, but may be associated with more severe disease, including the development of bronchiolitis obliterans. Rhinoviruses represent a small but significant proportion of cases of bronchiolitis,[50] and may mimic RSV infection in infants with bronchopulmonary dysplasia. Rhinoviruses and *Mycoplasma pneumoniae* become more important causes of infection-induced wheezing as children become older. Surveys of bronchiolitis in various parts of the world have suggested a similar pattern of viral etiologies.

A significant number of cases are associated with the human metapneumovirus (hMPV).[51] The clinical picture most closely resembles that of RSV, and bronchiolitis is the major manifestation in children. Clinical features include wheezing and hypoxia. There are no clinical features that can distinguish between disease caused by hMPV and RSV, although generally those due to RSV may be more severe. Human coronaviruses have also been associated with lower respiratory tract disease in infants.[52] An additional recently described human parvovirus, the human Boca virus, has been found in as many as 20% of cases of acute wheezing in young children. This virus is often detected in the presence of other viruses, and the exact role it plays in this syndrome has not been determined completely.[53]

The differential diagnosis of diseases characterized by expiratory airflow obstruction in infants is relatively small. Pertussis can occasionally be confused with bronchiolitis; however, more frequent vomiting and more paroxysmal cough would be clues to the diagnosis. Anatomic defects such as vascular rings can cause obstruction of the airway. Foreign bodies should be considered strongly, especially in young infants. Gastroesophageal reflux is an additional consideration. The major differential diagnostic consideration is asthma, which is uncommon under the age of 1 year.

PATHOGENESIS

The pathophysiology of infectious bronchiolitis has been described most completely in the case of infection with RSV.[46] The average incubation period is 4 to 5 days, with a range of 2 to 8 days. Virus replication is limited to the respiratory tract mucosa, which may be involved through its entire length. Involvement of the lower respiratory tract probably occurs by cell-to-cell spread through the respiratory epithelium or aspiration of upper respiratory secretions. Pathologic findings in RSV bronchiolitis include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar mononuclear inflammation. Virus-induced cytopathology and associated submucosal edema leads to obstruction of smaller bronchioles, particularly in infants, with distal collapse or air-trapping.

Viral infection of epithelial cells of the bronchioles leads to destruction and necrosis of the ciliated epithelium. Lymphocytes can be seen in increased numbers in the peribronchial tissues. The submucosa becomes edematous, and there is increased production of mucus. Ultimately, dense plugs of alveolar debris and strands of fibrin form within small bronchi and bronchioles, which may partially or completely obstruct airflow. The pathogenic basis for respiratory difficulty in bronchiolitis is related to obstruction of these small airways. Hypoxemia is the major abnormality of gas exchange, with ventilation–perfusion imbalance the major cause of the hypoxemia. In addition to hypoxia, hypercarbia and respiratory acidosis have been observed in some severely ill infants.

Infants are particularly susceptible to the consequences of viral infection for several reasons. The peripheral airways are disproportionately narrow in the early years of life. In addition, collateral channels of ventilation, such as the pores of Kohn, are deficient both in number and size in the infant lung. Finally, the airways of infants are intrinsically more reactive to bronchospastic stimuli than are the airways of older children.[54]

The possibility that immune responses are involved in the pathogenesis of RSV bronchiolitis has received considerable attention. The presence of pre-existing infection-induced antibody does not appear to play a role in enhancing the severity of disease because maternal antibody, or passively transferred antibody is protective. It has also been postulated that cellular immune responses may be involved in the pathogenesis, since infants infected with RSV who have clinical bronchiolitis have higher levels of cell-mediated immunity to RSV than those with uncomplicated upper respiratory tract disease. Immediate hypersensitivity type reactions have also been postulated to play a role in the pathogenesis of wheezing in bronchiolitis. Production of virus-specific IgE and subsequent release of mediators of bronchoconstriction have been documented with RSV and PIV bronchiolitis. Leukotriene C4, a potent stimulant of airway smooth muscle constriction and mucus secretion, is also released into the airway in acute bronchiolitis.[55] Elevated levels of histamine and prostaglandin $F_2\alpha$ metabolite have been found during acute bronchiolitis and increased levels of eosinophilic cationic protein in nasopharyngeal secretions, suggesting that release of chemical mediators of inflammation in response to viral antigens is one factor contributing to the development of severe bronchiolitis.

The innate immune response also plays an important role in the pathogenesis of RSV disease in infants, and it has been recognized that single nucleotide polymorphisms in several genes that control the inflammatory response have an important impact on the severity of RSV disease. Examples include polymorphisms in the genes for IL-4, IL-8, and IL-13, and in TLR-4 and the CCR5 receptor, among others (see Chapter 121).

Following recovery from acute bronchiolitis, some children experience continued episodes of wheezing, especially during viral upper respiratory infections. Estimates are that from 5% to 50% of children diagnosed as having bronchiolitis in infancy go on to develop recurrent episodes of wheezing. Generally wheezing episodes wane in frequency over the next several years. After clinical bronchiolitis, some individuals also may demonstrate increased bronchial responsiveness to histamine or cold challenge, which generally decreases over time. The mechanism by which RSV or other viral infection might lead to increased episodes of wheezing is unclear. Some individuals develop elevated levels of viral-specific IgE, which may play a role in triggering bronchospasm upon re-exposure. In some studies, persistent wheezing correlates with a family history of asthma, and with higher levels of IgE.

DIAGNOSTIC TESTS

Rapid viral diagnosis can be made by identification of viral antigens in nasopharyngeal secretions. Both immune-based assays, such as immunofluorescence or enzyme-linked immunosorbent assay (ELISA), and nucleic acid–based techniques, such as hybridization or polymerase chain reaction (PCR), have been developed. Immune-based techniques are generally preferable for routine

diagnostic purposes, and several kits are commercially available. The sensitivity of such techniques is dependent on the quality of the nasopharyngeal specimen, with nasopharyngeal aspirates superior to brushings or swabs. Commercially available immunofluorescence or ELISA antigen detection has a sensitivity of about 75% to 90% relative to culture for specimens collected from children, who shed large quantities of virus. The sensitivity of such tests in adults, who shed lower quantities of virus, is much lower (generally less than 20%). In transplant patients with suspected RSV pneumonia, samples of the lower respiratory tract by bronchoalveolar lavage are more sensitive than throat swabs for the detection of RSV.

TREATMENT AND PREVENTION

Recommendations regarding the treatment and prophylaxis of bronchiolitis have been summarized recently.[56] Correction of hypoxemia is the most important aspect of managing RSV lower respiratory tract disease. Oxygenation should be monitored by pulse oximetry, and oxygen administered to infants whose oxygen saturation consistently falls below 90%. Since bronchiolitis is a viral disease which is infrequently complicated by bacterial superinfection, routine treatment with antibiotics is not warranted. Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often needed, but care must be taken to avoid inducing hyponatremia. Fluid intake and electrolyte concentrations should be carefully monitored in all infants with severe bronchiolitis, as hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur.

Data concerning the potential benefits of bronchodilator therapy are somewhat conflicting. Generally, bronchodilators produce modest short-term improvements in clinical scores, but do not improve oxygenation, rates of hospitalization, or duration of hospital stay.[57–59] In addition, bronchodilating drugs may contribute to increased restlessness and cardiovascular stress. Because some children do respond to these drugs,[60] a reasonable strategy is a short trial of nebulized bronchodilator with continued therapy only in selected children who respond.

The majority of studies of systemic corticosteroids have also failed to demonstrate a beneficial effect in acute bronchiolitis,[61,62] and oral corticosteroids do not appear to have a beneficial effect in terms of long-term outcomes, either. Steroids may also be associated with evidence for delayed viral clearance. Although a recent meta-analysis suggested that systemic steroids have a small but statistically significant effect in decreasing length of stay,[63] the clinical significance is minimal; therefore, corticosteroids should not be used routinely.

Antiviral therapy with ribavirin (1-β-D-ribofuranosyl-1,2,3-triazole-3-carboxamide) remains controversial. Ribavirin is a broad-spectrum antiviral agent with antiviral activity against multiple respiratory viruses including RSV in a variety of cell culture systems and animal models. It does not achieve suitable levels in respiratory secretions when administered systemically, so that therapy of bronchiolitis has used aerosolized drug. Although initial randomized placebo-controlled trials of ribavirin small–particle aerosol showed benefit in treatment of bronchiolitis, subsequent experience with use of the drug in clinical practice did not confirm this clinical benefit. These findings, and the expense of this drug, suggest that ribavirin should be considered only in selected infants and young children with severe illness or at high risk for serious RSV disease.

Bronchiolitis due to RSV can be prevented by passive transfer of antibody against this agent. A humanized neutralizing monoclonal antibody to the RSV F protein, palivizumab (Synagis) has significant protective efficacy in a population of infants with prematurity or bronchopulmonary dysplasia, as well as in children with hemodynamically significant congenital heart disease. Current recommendations for the use of passive antibody prophylaxis are to consider use in infants and children less than 2 years of age with chronic lung disease or congenital heart disease, and in infants born at 32 weeks of gestation or earlier (who would be expected to receive little placental transfer of maternal antibody). Palivizumab may be considered for infants born between 32 and 35 weeks who have at least two additional risk factors, such as exposure to second-hand smoke or attendance at day care.[56] Palivizumab is not effective for therapy of RSV disease.

Interruption of nosocomial transmission may be facilitated by thorough handwashing, decontamination of surfaces and inanimate objects, and isolation or cohorting of infected infants. Use of disposable eye–nose goggles by pediatric staff reduces the risk of nosocomial RSV infection in both staff and patients. Regular use of gowns, gloves, and possibly masks by hospital staff caring for infected children may also reduce the risk of nosocomial RSV spread. Protective isolation of high-risk infants or deferring their elective admission has been recommended during institutional outbreaks of RSV.

Vaccines are available to prevent bronchiolitis due to influenza virus and mumps, but there is no vaccine currently available for prevention of bronchiolitis due to RSV. There are multiple significant hurdles to the development of such a vaccine, including the very young age at which the disease presents, the suppressive effect of maternal antibody on vaccine responses, and the potential for enhanced disease in vaccine recipients.[64]

INFLUENZA

Clinical features, epidemiology, pathogenesis, and diagnosis of influenza are discussed below. Treatment and prevention are discussed separately in the section that follows.

CLINICAL FEATURES

The onset of influenza is typically abrupt, and the illness is characterized by the predominance of systemic symptoms, including fever, prostration, myalgias, and malaise. Respiratory symptoms may be relatively minimal, particularly early in the course, and include nasal complaints, sore throat, hoarseness, and nonproductive cough. Because of the involvement of tracheal epithelium in infection, complaints of burning throat and substernal pain may be seen. Among healthy adults, the best clinical predictors of influenza virus positivity are the presence of cough and fever in patients presenting during epidemics.[65]

Other than fever, there are usually few findings on physical examination. Affected individuals may exhibit rhinitis, pharyngitis, conjunctival injection, and tracheal tenderness. The chest is usually clear in uncomplicated cases. Most acute symptoms resolve in 3 to 5 days, but complete recovery may take weeks. The clinical features of influenza A and B virus infection are similar.

Influenza is an important cause of acute febrile illness in children during epidemics. Generally symptoms of influenza are similar to those in adults, although children may have higher fever with febrile seizures. As described, influenza may be associated with otitis media or croup in children.

Pneumonia represents the most severe complication of influenza virus infection in both normal and compromised hosts. Primary influenza viral pneumonia is characterized by rapid progression of dyspnea, cough and cyanosis, and the development of acute respiratory distress syndrome (ARDS). Chest roentgenographs reveal bilateral interstitial infiltrates, sputum production is scanty, and Gram stain reveals few organisms. Secondary bacterial pneumonia may present 1 to 2 weeks after apparent recovery from an acute influenza episode with recurrence of fever, and signs and symptoms of typical lobar pneumonia. Pneumonia is described in more detail below.

EPIDEMIOLOGY

Influenza is typically associated with seasonal epidemics of greater or lesser severity, which occur during the winter months in temperate climates in both the northern and southern hemispheres. Outbreaks in the northern hemisphere are usually noted between the months of November and March or April, and typically last for from 4 to

6 weeks in any given community. The reasons for the seasonal behavior of influenza are not known but have been the subject of much interest. Some suggested mechanisms have included the seasonal effects of heat and humidity on the viability of virus in the environment, behavioral patterns that facilitate transmission, such as attendance at schools, or sunlight effects on baseline immune function.

Seasonal influenza epidemics are regularly associated with excess morbidity and mortality,[66] and both influenza A and B can be associated with severe illness. During interpandemic years, influenza is characterized by a "U-shaped" epidemic curve, in which attack rates and medically attended illness rates are generally highest in infants and young children, whereas mortality is generally highest in the elderly. Young children are generally more susceptible to influenza infection than are adults, and shed higher levels of virus for longer periods. Healthy children younger than 1 year of age are hospitalized for influenza at rates comparable to those of older children and adults with chronic high-risk conditions[67,68] and are special targets of prevention measures.

Excess morbidity and mortality are particularly high in those with underlying medical conditions, including chronic cardiovascular or pulmonary disease, chronic metabolic disease including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunodeficiency, including HIV. Recently, it has been recognized that individuals with neuromuscular conditions affecting the ability to clear respiratory secretions,[69] and persons with morbid obesity,[70] are also at high risk for influenza hospitalization. Women in all stages of pregnancy, and in the immediate postpartum period, also have increased rates of hospitalization, ICU admission, and deaths during influenza epidemics.[71,72]

Antigenic variation is the hallmark of the epidemiology of influenza, and occurs in two forms referred to as antigenic "drift" and antigenic "shift." Drift refers to the gradual accumulation of mutations, primarily in the hemagglutinin (HA) and neuraminidase (NA) proteins of the virus, that allow the virus to escape from antibody generated against previous strains. New, drifted strains generally appear every several years, and tend to replace previous strains. Antigenic drift occurs in both influenza A and influenza B viruses. In addition, recent influenza B viruses have evolved into two antigenically distinct lineages termed the "Yamagata" and "Victoria" lineages,[73,74] which currently cocirculate.

Influenza A viruses exist as multiple antigenically distinct HA or NA subtypes. There are currently recognized 17 HA subtypes (H1–H17) and 9 NA subtypes (N1–N9), although current seasonal viruses are restricted to the H1N1 and H3N2 subtypes. When one influenza A subtype is replaced by another, a phenomenon recognized as antigenic shift, the new virus encounters a population with little or no prior immunity. World-wide epidemics of severe disease, referred to as pandemics, are usually the result.

Pandemics associated with antigenic shift have been noted multiple times in the 20th and 21st centuries. In 1918, H1N1 viruses emerged and replaced previous H3N2 viruses, in 1957 H2N2 viruses replaced H1N1 viruses, and in 1968 H3N2 viruses replaced the H2N2 viruses. In 1977, an H1N1 virus antigenically similar to H1N1 viruses from 1950 emerged to cause disease primarily in born after 1950, but did not replace previous H3N2 viruses. Finally, in 2009 a new H1N1 virus (the so-called pH1N1 virus or "swine flu") emerged that was antigenically similar to H1N1 viruses prior to 1947 and cause disease predominantly in young adults and children. Since then, both H3N2 and pH1N1 viruses have circulated in humans. Influenza A viruses are zoonotic in multiple animal species including migratory waterfowl and swine, and epidemiologic data strongly support the notion that new pandemic influenza A viruses arise from this reservoir (see below).

PATHOGENESIS

The mechanisms responsible for the transmission of influenza viruses from person to person have never been completely defined, and it is likely that both large particles (i.e., droplet) and small particles (aerosol) released from the airway during coughing and sneezing play a role. Once virus is deposited on the respiratory tract epithelium, it can attach to and penetrate columnar epithelial cells if not prevented from doing so by specific secretory antibody (IgA), by nonspecific mucoproteins to which virus may attach, or by the mechanical action of the mucociliary apparatus. The duration of the incubation period to the onset of illness and virus shedding varies from 18 to 72 hours depending in part on the inoculum dose. Viral shedding in the respiratory tract is first detected just before the onset of illness (within 24 hours), rapidly rises to a peak and remains elevated for 24 to 48 hours, and then rapidly decreases to low titers. Usually influenza virus is no longer detectable after 5 to 10 days of virus shedding. Both the duration as well as the level of virus shedding is typically longer in young children than in adults and in immunocompromised individuals. In general, the course of the clinical illness correlates temporally with the pattern of virus shedding, and severity is correlated with the quantities of virus shed.

Bronchoscopy of individuals with typical, uncomplicated acute influenza has revealed diffuse inflammation of the larynx, trachea, and bronchi, with mucosal injection and edema. Histologic findings on autopsy of more severe cases show extensive necrotizing tracheobronchitis, with ulceration and sloughing of the bronchial mucosa, extensive hemorrhage, hyaline membrane formation, and a paucity of polymorphonuclear cell infiltration. Abnormalities of pulmonary function are frequently demonstrated in otherwise healthy, nonasthmatic young adults with uncomplicated (nonpneumonic) acute influenza. Demonstrated defects include diminished forced flow rates, increased total pulmonary resistance, and decreased density-dependent forced flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter,[75] as well as increased responses to bronchoprovocation. In addition, abnormalities of carbon monoxide diffusing capacity and increases in the alveolar–arterial oxygen gradient have been seen. Of note, pulmonary function defects can persist for weeks after clinical recovery.

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

Generally, clinical features alone cannot distinguish between the syndrome of influenza caused by either influenza A or B viruses, although attention to ongoing community surveillance can be very helpful in assessing the likely agents. Influenza-like illness can also be caused by a variety of other viruses, including RSV, adenovirus, and PIV. Knowledge of the currently circulating viruses can be very helpful.

DIAGNOSTIC TESTS

Rapid viral diagnosis based on immunologic detection of viral antigen in respiratory secretions is widely used for influenza diagnosis. All of these tests are designed to detect both influenza A and B, but only some of the tests differentiate between the two. Some of the tests that are minimally complex may be eligible for waivers that allow them to be used in the office setting. In general, sensitivities in adults and elderly patients tend to be lower than reported in young children, who tend to shed much larger quantities of virus in nasal secretions and therefore have much higher concentrations of antigen in their samples. Although all types of respiratory samples can be used in such tests, the sensitivity appears to be better with nasopharyngeal swabs and aspirates than with throat swabs or gargles.

Molecular diagnostic tests are becoming increasingly popular for influenza diagnosis, and are frequently coupled with the detection of other respiratory viruses, especially RSV. Nasopharyngeal samples remain the most sensitive of samples, but it has been noted that in some patients with pneumonia, sputum samples have been positive when nasal samples were negative. As is the case for all diagnostic testing, specific influenza testing should be focused on those cases where a specific diagnosis will have implications for therapy or infection prevention.[76]

TABLE 130-3 Features of Influenza Vaccines

	Trivalent Vaccine	Live Attenuated Vaccine
Produced in	Eggs	Eggs
Administration	Intramuscular infection	Intranasal spray
Immune response	Serum antibody	Mucosal immunity
Formulation	Inactivated	Live, attenuated
Storage	4C	4C
Side effects	Sore arm at injection site	Runny nose
	In some years, increased risk of Guillain–Barré syndrome	Increase in wheezing in children <1 y
Indications	Any person >6 mo	Healthy persons >1–49 y
Efficacy		
Children	++	++++
Healthy adults	++++	++++
Elderly	+++	+

TREATMENT AND PREVENTION

Treatment and prevention of influenza are considered with respect to vaccines, antiviral therapy, and antiviral prophylaxis.

VACCINES FOR INFLUENZA

Two types of vaccines, inactivated and live, are currently available for the prevention of influenza (Table 130-3). Inactivated influenza vaccines are designed to induce primarily serum antibody to the HA and NA. Multiple formats of inactivated vaccines are available, including inactivated, chemically disrupted and purified HA and NA antigens generated from viruses grown in embryonated hen's eggs or from viruses grown in cell culture, and purified HA recombinant protein expressed in insect cells using baculovirus technology. Virion-based vaccines are typically formulated to contain 15 μg of each HA in the final product, while the recombinant vaccine contains 45 μg, and a recent, high-dose vaccine containing 60 μg of each HA is licensed for use in individuals 65 and older. Current vaccines contain one example of influenza A (H1N1), and A (H3N2), based on the most current epidemiologic predictions of the likely circulating strains in the coming season, and may contain one example of influenza B (trivalent vaccine, or IIV3) or examples of both influenza B lineages (quadrivalent vaccine, or IIV4). Current recommendations do not include a preference for any specific format of inactivated vaccine, although this may change as more data become available.

The live attenuated influenza vaccine is primarily designed to induce mucosal antibody in the respiratory tract, although specific correlates of protection have not been developed. The vaccine is generated by genetic reassortment between circulating wild-type strains and attenuated master donor viruses for both influenza A and B, and is currently formulated as a quadrivalent preparation. The live vaccine is currently licensed for use in adults and children from 2 to 49 years of age.

Current recommendations for the use of influenza in the United States[77] and several other countries call for a strategy of universal vaccine, in which vaccine is offered annually to the entire population. Efforts at vaccination should be especially targeted at persons who, for reasons of age or medical conditions, are at increased risk for developing complications, hospitalization, or death due to influenza, and contacts who may transmit infection to these high-risk individuals. Persons who may transmit to high-risk persons include family members, out of family caregivers, and importantly, healthcare providers.

ANTIVIRAL THERAPY

Two classes of antiviral agents have been developed with efficacy against influenza A in humans (Table 130-4). The adamantanes (amantadine and rimantadine) are referred to as the M2 inhibitors, because their mechanism of action is the result of inhibition of the viral M2 protein, an ion channel involved in viral uncoating. M2 inhibitors are only active against influenza A viruses, because influenza B viruses do not contain an M2 protein. Although the M2 inhibitors are highly effective drugs for the prophylaxis and therapy of influenza A, resistant viruses are generated quite readily in treated individuals,[78] and can be transmitted to, and cause disease in contacts. Currently, the great majority of influenza A (H3N2) viruses worldwide, as well as most Clade 1 H5N1 viruses, are completely resistant to M2 inhibitors.[79] Therefore, M2 inhibitors are no longer recommended for use as antiviral agents against influenza.

A second class of agent is referred to as the NA inhibitors, because they are potent and selective inhibitors of the NA enzymes of both influenza A and B viruses. In cell culture, inhibition of NA function is predominantly manifested as inhibition of cell-to-cell spread of virus. The results of clinical trials of the two licensed drugs, oseltamivir and zanamivir, have been very similar, and both drugs also have an excellent safety profile.

TABLE 130-4 Antivirals Active Against Influenza

Drug	Dosage in Adults	Dosage in Children	Comments
Oseltamivir	75 mg PO BID for 5 d	≤15 kg: 30 mg twice daily	Controlled trials available in adults, elderly, and children
		>15–23 kg: 45 mg twice daily	Approximately 1–2 d earlier resolution of symptoms, reduced otitis in children
		>23 kg: 60 mg twice daily	Other effects demonstrated include earlier return to work, decreased diagnosis of bronchitis
		>40 kg: 75 mg twice daily	Meta-analysis shows reduced hospitalization rates
			Well tolerated, main adverse event is nausea
Zanamivir	10 mg via inhalation BID for 5 d	≥7 y: 10 mg via inhalation twice daily	Similar safety and efficacy profile as oseltamivir, without nausea
		<7 y: not recommended	Reports of exacerbations of reactive airways disease
Amantadine	<65 y: 100 mg twice daily for 5 d	1–9 y: 5 mg/kg/d, not to exceed 150 mg/d in two divided doses	High levels of resistance in current influenza A viruses
	>65 y: 100 mg once daily	10–12 y: 100 mg twice daily	
Rimantadine	100 mg twice daily for 5 d	≤12 y: not recommended	High levels of resistance in current influenza A viruses
	>65 y: 100 mg once daily		Not approved for use in children

As a general principle, it is clear that early initiation of therapy is critical to the effectiveness of antiviral therapy of acute influenza. This general observation is consistent with the typical pattern of viral shedding in an immunologically primed individual in which the peak of virus shedding is in the first few days of illness, and is rapidly controlled by the immune system. Therapy initiated beyond 48 hours of symptoms does not appear to be useful in immunocompetent adults and children, and the greatest benefit is seen when therapy is begun within 12 or 24 hours after the onset of symptoms. Relatively little controlled data are available related to the use of antivirals in immunocompromised individuals with influenza or in primary influenza infections, and it is unclear whether these same constraints would apply in these situations.

Meta-analysis of results of these trials has also suggested that early treatment may reduce the frequency of influenza-related complications, with reductions in the use of antibacterials and in hospitalization.[80] However, pooled analyses of these studies of early therapy with zanamivir[81] and oseltamivir[80,82] demonstrated a significant reduction in the rate of influenza complications in treated individuals. The subsequent experience in the emerging epidemic of pH1N1 virus has also suggested a beneficial effect of early therapy on complications. These include observations in hospitalized patients[83,84] and surveillance data suggesting that therapy as late as 5 days improved survival of hospitalized patients.[85] Surveillance data have also suggested that treated children had lower rates of complications.[86]

Although the benefits of antiviral therapy were initially demonstrated as a shortening of illness duration in healthy adults with uncomplicated influenza, this is generally not considered the priority target group for antiviral therapy. Current recommendations include the use of antivirals in individuals at risk for more severe influenza, or in individuals with severe disease or requiring hospitalization.[76] Treatment should be started as early as possible, but even delayed therapy can be of benefit in hospitalized patients.

ANTIVIRAL PROPHYLAXIS

Although not a substitute for vaccination, antiviral drugs can be used for prevention as well as treatment. Generally, two strategies for antiviral prophylaxis have been evaluated. Seasonal prophylaxis refers to the strategy of administration of drug throughout the entire period of potential influenza exposure, that is, the influenza season, typically 6 to 8 weeks in any given community. The second strategy administers prophylaxis for a relatively shorter period of time to a person who has close contact with an index case known or suspected to have influenza. Examples of this strategy include administering prophylaxis to family members of a person with influenza, and administering prophylaxis to patients who may be exposed during a nosocomial outbreak at a healthcare institution such as a nursing home or hospital.

VIRAL PNEUMONIA

Clinical features and specific etiologies of viral pneumonia in healthy adults, children, and immunologically compromised individuals are presented below.

CLINICAL FEATURES

As described, viral infections of the lower respiratory tract represent a wide spectrum of clinical entities including croup and bronchiolitis, tracheobronchitis, and reactive airway changes. The development of pneumonia is defined by inflammation of the lung parenchyma, often associated with visible changes on chest X-ray or abnormalities of other radiologic studies such as gallium scanning and accompanied by the development of abnormalities of alveolar gas exchange. Although there can be considerable variety to the presentation of this syndrome depending on the age and immunologic competence of the host and the specific viral pathogen, there are certain general features that are described in the following.

Viral pneumonia in adults is usually associated with nonproductive cough, although production of frothy, pink-tinged sputum is seen in some severely ill individuals. Cyanosis and hypoxemia are prominent features of severe primary viral pneumonia. Physical findings are often nonspecific. The patient may appear acutely ill, conjunctivitis and rhinitis may be noted, and the trachea may be somewhat tender if accompanied by viral tracheitis. There is an increased respiratory rate, and diffuse rales and wheezes. A variety of chest X-ray patterns have been described, including lobar infiltrates, but most typically primary viral pneumonia presents with diffuse, bilateral interstitial infiltrates. However, there are really no X-ray patterns that reliably differentiate between bacterial and viral pneumonia. The sputum is relatively scant, generally shows few polymorphonuclear leukocytes, and Gram stain reveals minimal numbers of bacteria.

The basic presentation of viral pneumonia in children is similar. The clinical presentation varies considerably with the specific causative agent, but typically includes fever and lower respiratory tract signs and symptoms, such as difficulty breathing, nonproductive cough, and physical findings of wheezing or increased breath sounds. Young infants may present with apneic episodes with minimal fever. The clinical presentation may be dominated by the associated croup or bronchiolitis, which are frequently present.

Underlying cardiopulmonary diseases, such as valvular heart disease or COPD, are well-recognized risk factors for viral pneumonia in adults and children. Pregnancy, particularly in the second and the third trimester, has been recognized as a risk factor for cardiopulmonary hospitalizations associated with influenza epidemics.

Bacterial superinfection is a common complication of viral lower respiratory tract infection, particularly in adults. The classic presentation is that of a typical episode of viral illness with more or less complete recovery, followed 2 to 14 days later by a recurrence of fever and development of cough and dyspnea.[87] CXR reveals lobar infiltrates, and the clinical course is typical of bacterial pneumonia. In addition, combined bacterial and viral pneumonia, with clinical features of each, are common in adults and with certain viruses in children. Bacterial superinfection of viral pneumonia can occur with many bacteria, but the most common bacteria responsible for bacterial pneumonia complicating influenza is *S. pneumoniae*. There are also increases in the relative frequency of staphylococci and *Haemophilus influenzae*.

VIRAL ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

Evaluation of the specific cause of acute pneumonia, and in particular, attribution of pneumonia to a particular viral etiology, is complicated by difficulty in obtaining appropriate samples for culture, in isolating or detecting certain pathogens, and the frequent asymptomatic shedding of some viruses, such as herpes viruses or adenoviruses. Serologic diagnosis essentially establishes a temporal, but not causal, relationship between viral infection and a clinical syndrome, which may be misleading during times of high prevalence of a particular viral agent. With these qualifications in mind, it is reasonable to make several broad generalizations regarding the role of viruses in acute pneumonia. The impact of viral pneumonia and the spectrum of associated viral agents are highly dependent on the age group and immune status of the host. Viruses are clearly important and are the frequent causes of pneumonia in young children. The role of viruses becomes less apparent in older children, and in healthy adults, pure viral pneumonia is rare, and is predominantly due to influenza. Elderly adults may experience more significant lower respiratory tract signs and symptoms following infection with agents which normally cause upper respiratory tract illness in younger adults, but generally have similar rates of viral pneumonia as do healthy young adults. Finally, viral pneumonia is an important cause of morbidity and mortality in individuals with compromised immune systems, with a broader spectrum of viral agents than seen in immunologically intact individuals.

■ IMMUNOLOGICALLY INTACT ADULTS

A variety of viruses may cause pneumonia in immunologically intact adults.

Influenza

The majority of cases of viral pneumonia in immunocompetent adults are probably due to, or associated with influenza viruses. The syndrome of primary influenza viral pneumonia was first well documented in the 1957 to 1958 outbreak. The illness begins with a typical onset of influenza, followed quickly by a rapid progression of fever, cough, dyspnea, and cyanosis. Physical examination and chest radiographs reveal bilateral findings consistent with the adult respiratory disease syndrome. Sputum Gram stain fails to reveal significant bacteria, and bacterial culture yields sparse growth of normal flora, whereas viral cultures yield high titers of influenza A virus. Such patients do not respond to antibiotics and the mortality is high.

Secondary bacterial pneumonia is an important complication of influenza. The classic description is of an influenza illness followed by a period of improvement lasting usually 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest X-ray. The most common bacteria implicated are *S. pneumoniae*, and a significantly increased frequency of *S. aureus*,[88,89] including methicillin-resistant *S. aureus* (MRSA).[90] Many patients present with mixed viral and bacterial pneumonia. Bacterial superinfections of influenza have been postulated as a major cause of death during the pandemic of 1918.[91]

Respiratory Syncytial Virus

RSV frequently causes detectably altered airway reactivity in adults, and on occasion, lower respiratory tract involvement becomes clinically manifest as pneumonia in otherwise healthy adults. RSV is being increasingly recognized as a cause of significant lower respiratory tract disease in the elderly.[92] It has been estimated that 2% to 4% of pneumonia deaths among the elderly in the United States may be due to RSV.[93]

Parainfluenza Virus

PIVs are most typically associated with viral pneumonia in children, particularly serotype 3 (PIV-3). However, occasionally these viruses may be associated with pneumonia in adults. Frequent contact with small children is probably a risk factor. PIVs have occasionally been reported as causes of pneumonia in adults and in the elderly.[94]

Adenovirus

Adenovirus was first recognized as a cause of viral pneumonia in military recruits and has since been recognized as a rare cause of pneumonia in civilian adults and children. Outbreaks in institutionalized populations occur. The clinical characteristics of adenovirus pneumonia are similar to those of other pneumonias, so that it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. In fatal cases there has been extensive pulmonary damage, with death occurring 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and a septic shock picture has been described. Bacterial superinfection, particularly with *Neisseria meningitidis*, may occur. Since 1996, a specific variant of adenovirus type 7 (Ad7d2) has been responsible for several civilian outbreaks and a large military outbreak. The appearance of new Ad 7 genotypes may herald a shift in the predominant strains with greater disease impact.[95] Recent reports have emphasized the emergence of a relatively rare adenovirus serotype 14 responsible for severe community-acquired pneumonia in adults and children.[96]

Measles

Measles can be complicated clinically by severe pneumonitis in a small percentage of healthy adults, and bacterial superinfection is common.[97] In patients with altered cell-mediated immune function, and rarely in apparently normal persons, infection by wild measles virus can cause a lethal giant cell pneumonia with or, in about 30% of patients, without rash.[98] Measles has largely been controlled by vaccination, but outbreaks continue to occur.

Varicella Zoster Virus

Viral pneumonia is the major complication of VZV in normal adults, in whom it occurs with an estimated 25-fold higher frequency than in children.[99] Smoking is a significant risk factor. Pneumonia associated with varicella is usually apparent 1 to 6 days after the onset of rash. Symptoms include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. The intensity of the rash does not necessarily correlate with the severity of pneumonia. The characteristic radiographic pattern is that of diffuse nodular (1–10 mm) infiltrates, which may resolve with miliary calcific densities. Hilar adenopathy, pleural effusions, and peribronchial infiltrates are frequently present. Pulmonary infarction may complicate the clinical picture. Pulmonary function studies have found normal spirometric values but decreased carbon monoxide diffusing capacity, which may persist for months. One prospective radiologic study of military recruits with varicella found abnormalities in approximately one in six patients, but only one-fourth of those with radiographic changes had cough, and none experienced severe disease.[100]

■ CHILDREN

A wide variety of viruses may produce pneumonia in children. Each is discussed below.

Respiratory Syncytial Virus

In most series, RSV has been associated with the largest proportion of viral pneumonia in young children, particularly if accompanied by bronchiolitis. It should be noted in this regard that bronchiolitis and pneumonia represent a spectrum of lower respiratory tract involvement with RSV, frequently coexist, and are not clearly distinguishable. The most typical finding is diffuse interstitial pneumonitis (Fig. 130-1). Lobar or segmental consolidation is evident by CXR in about one-fourth of children with RSV lower respiratory tract disease.

Parainfluenza Virus

PIVs are second only to RSV as causes of pneumonia in children. As described, lower respiratory tract involvement is integral to the pathophysiology of croup, but pneumonia with pulmonary infiltrates is most commonly associated with PIV-3.

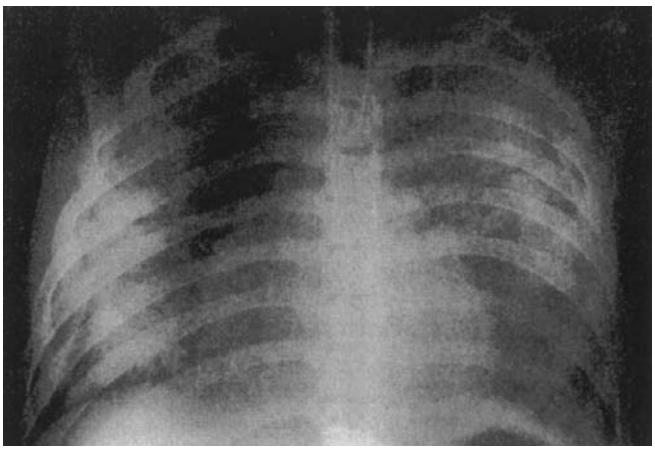

Figure 130-1 Premature infant at 3 months of age with respiratory syncytial virus pneumonia. *(Reproduced with permission from Duchin et al. Hantavirus pulmonary syndrome. N Engl J Med. 1994;330(14):949–955.)*

Influenza Virus

Influenza A and B viruses are both significant causes of pneumonia in children, especially during periods of epidemic prevalence. In infants and children, the most frequent manifestation of influenza pneumonia is an interstitial pneumonitis similar in appearance and course to those of the other predominant viral agents of pneumonia in this age group, except that a secondary bacterial pneumonia may occur more frequently than with RSV or PIVs.

Adenovirus

Adenoviruses are frequently isolated from children with respiratory disease and are implicated in about 10% of childhood pneumonias. However, the true impact of adenoviruses as causes of pneumonia in this age group is difficult to assess because of the long and intermittent asymptomatic respiratory shedding of these viruses in children. Hilar adenopathy on CXR is somewhat more common with this form of pneumonia than other types.

Measles

Pneumonia is the most frequent serious complication of measles. The prodrome of typical measles lasts 2 to 8 days and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucus membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically disappears after 5 to 6 days in the order in which it appeared. Defervescence and symptom improvement occur several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (less than 2000 cells/mm^3) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Cytomegalovirus

Respiratory distress is part of the clinical picture in infants with congenital CMV disease. Older infants and children may exhibit prolonged respiratory disease with bronchitis or pneumonia associated with CMV carriage.

Rhinovirus

Rhinoviruses have also been associated with a significant proportion of community-acquired pneumonias in children, despite the relative inability to grow efficiently at body temperature. Other viruses that may occasionally cause viral pneumonia in children include enteroviruses, rubella virus, and herpes simplex virus.

■ IMMUNOCOMPROMISED INDIVIDUALS

Individuals with diminished host immunity may develop severe, life-threatening pulmonary infections with the entire spectrum of RNA and DNA viruses, including both viruses that are typical causes of lower respiratory tract disease in normal hosts, and other, more opportunistic viral pathogens (see also Chapter 123).[101] DNA viruses have received the most recognition in this regard.

Cytomegalovirus

CMV is frequently detected in respiratory samples from immunosuppressed individuals, particularly transplant recipients, or individuals infected with the human immunodeficiency virus (HIV) with severe pneumonia. The highest risk in the transplant population without antiviral prophylaxis is 1 to 3 months posttransplantation, with the peak incidence at 8-week posttransplant. Diffuse interstitial pneumonitis is the most frequent presentation, but multiple other radiographic presentations have been reported, including nodular infiltrates resembling *Nocardia* infection. Multiple associated findings are present in severe infection, and reflect the disseminated nature of the infection; the presence of neutropenia, abnormalities of liver function tests, and mucosal ulcerations may be clinical clues to the diagnosis.

Characteristically, patients with CMV pneumonia have sustained fever, nonproductive cough, and dyspnea. Rales and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis. Chest radiographic changes are usually bilateral, with diffuse or focal haziness involving the mid and lower lung fields. Both miliary and interstitial radiographic patterns have been described. Often the perihilar distribution of the infiltrate is suggestive of pulmonary edema. Common CT scan findings include small nodules, consolidation, and ground-glass attenuation.

Assessing the role of CMV in an immunosuppressed patient can be challenging, since in HIV patients CMV is frequently detected along with other pathogens, such as *Pneumocystis*, and the role of CMV in the pneumonia can be unclear.[102] In transplant patients, the detection of CMV by itself does not necessarily indicate end-organ involvement. For transplant patients, it has been suggested that higher levels of CMV in pulmonary specimens or viremia may be more indicative of CMV pneumonia.[103]

Herpes Simplex Virus

HSV infection of the lower airway may occur either as the result of direct extension of infection from the tracheobronchial tree to the lung or as the result of hematogenous dissemination of virus from mucocutaneous lesions of the upper airway or genitourinary tract. Dyspnea, cough, and hypoxemia are usually seen, but the clinical features of the pneumonia generally do not permit an etiologic diagnosis to be made antemortem. Focal or multifocal infiltrates are thought to indicate direct extension, whereas diffuse bilateral infiltrates may occur due to presumed hematogenous dissemination of virus.[104] CT scan findings include multifocal segmental and subsegmental ground-glass opacities,[105] but are not distinctive. In one study, more than one-half of the patients had concomitant pulmonary infection with other microorganisms, including bacterial, *Candida* and *Aspergillus* species, and CMV.

Isolation of HSV from lower respiratory tract secretions is been common in mechanically ventilated patients and may be associated with a poor outcome.[106] However, clinical outcomes of HSV-positive patients are not significantly different from those of HSV-negative patients,[107] and it can be difficult to determine whether HSV is playing a specific role in the lower respiratory tract disease.

Varicella Zoster Virus

VZV is an important problem in individuals with hematologic malignancies and others with iatrogenic immunosuppression, with the greatest risk seen in organ transplantation. Prolonged fever and/or recurrent crops of lesions are predictors of visceral dissemination, and pneumonia is generally seen in this setting. Pulmonary manifestations may include pleuritic chest pain due to vesicular lesions of the pleura, and, as is also true in normal hosts, the CXR may demonstrate nodular lesions.

Adenoviruses

Adenoviruses are significant causes of morbidity and mortality in immunocompromised patients, particularly after transplantation. In contrast to infection in normal hosts, infection in immunocompromised subjects tends to be disseminated, with isolation of virus from multiple body sites including lung, liver, gastrointestinal tract, and urine.[108] In addition, the spectrum of serotypes includes both those found in immunocompetent individuals as well as a markedly increased frequency of isolation of higher-numbered serotypes found rarely in immunologically normal subjects.

RNA Viruses

RNA viruses have also received increasing recognition as potential causes of significant morbidity and mortality in this population.[109] RSV has been well recognized as a cause of pneumonia in recipients of bone marrow[110] and solid-organ transplantation.[111] Nosocomial transmission of RSV in this setting has been well documented, and may be the source of many infections in this susceptible population. The illness typically begins with nondescript upper respiratory symptoms that progress over several days to severe, life-threatening lower respiratory tract involvement. Mortality rates of 50% or higher are typical, particularly if disease occurs in the pre-engraftment period. PIVs have also been reported as an infrequent lower respiratory tract pathogen in both solid-organ and hematopoietic transplantation. PIV-3 has been most commonly serotype isolated, but all four serotypes have been implicated. Influenza may also cause severe disease in transplant recipients, but most subjects have survived. Rhinovirus infections in this population are also common, but tend to be associated less frequently with lower respiratory tract disease. However, chronic rhinovirus infection, with graft rejection, has been described in lung transplant recipients.

Measles giant cell pneumonia is a severe, usually fatal form of pneumonia associated with measles infection in immunosuppressed individuals. Most cases have occurred in those with hematological or other malignancies, or individuals with AIDS. Recent outbreaks of measles worldwide, coupled with the increasing incidence of HIV infection, has increased the frequency and impact of measles giant cell pneumonia. Giant cell pneumonia also occurs in significantly malnourished individuals. Multinuclear giant cells with intranuclear inclusions are seen, and may be demonstrable in fluid obtained by bronchoalveolar lavage. An important feature of measles pneumonia in immunocompromised hosts is that many patients present without rash or other typical manifestations of measles, and a high index of suspicion must be maintained. It has been speculated that such hosts may not mount the cellular immune responses involved in the pathogenesis of rash in immunologically intact individuals. In hospitalized patients, mortality rates are approximately 70% in oncology patients and 40% in HIV-infected patients.[112]

■ EMERGING VIRUSES

In addition to these viruses, which have a widespread distribution and cause sporadic cases of viral influenza, two novel emerging pathogens have caused severe outbreaks of respiratory disease in previously healthy adults.

Hantavirus Pulmonary Syndrome

Clinical features of the Hantavirus pulmonary syndrome (HPS) include onset of severe pulmonary dysfunction after a 2- to 3-day prodrome of nonspecific influenza-like symptoms of fever, myalgias, cough, gastrointestinal symptoms, and headache.[113] Laboratory abnormalities included leukocytosis, increased hematocrit due to hemoconcentration, and thrombocytopenia with coagulopathy.[114] However, clinical bleeding is unusual, in contrast to other systemic Hantavirus syndromes. Moderately elevated levels of serum lactate dehydrogenase and aspartate aminotransferase are typically seen. A variety of radiographic abnormalities have been described. Radiographic findings that may help to distinguish HPS from ARDS include early, prominent interstitial edema, and nonperipheral distribution of initial airspace disease.[115]

Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and gastrointestinal symptoms, and generalized malaise. Upper respiratory symptoms are usually absent. After a variable period of several days, the patient presents with mild, nonproductive cough and progressive dyspnea resulting from leakage of high-protein edema fluid into the alveoli. On physical examination patients are febrile, with tachypnea and tachycardia with mild hypotension. Examination of the chest may reveal rales but is otherwise unremarkable.

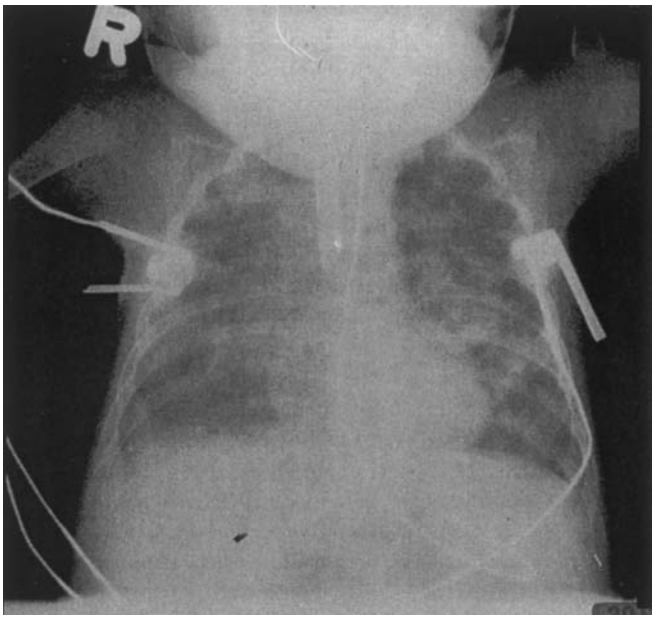

Figure 130-2 Chest radiograph showing diffuse interstitial and alveolar infiltrates in a patient with Hantavirus infection. *(Used with permission of Dr. Janet Englund, Baylor College of Medicine.)*

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated lung function tests (LFTs). The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts, is highly suggestive of HPS.[114] Multivariate analysis has identified dizziness, nausea, and the absence of cough as clinical symptoms predictive of HPS, as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features which help distinguish HPS from other causes of acute respiratory distress such as pneumococcal pneumonia and influenza.[116] Mild renal abnormalities may be detected, but unlike hemorrhagic fever with renal syndrome (HFRS), do not progress to a renal failure.

Chest radiographs typically shows both interstitial and alveolar infiltrates and resembles noncardiogenic pulmonary edema (Fig. 130-2). Pleural effusions are present in most cases. Early in the course of HPS these effusions are transudative, whereas later they develop higher fluid protein content and in severe cases have the protein characteristics of plasma. Cardiopulmonary manifestations in severe cases include a shock state with low cardiac index, low stroke volume index, and high systemic vascular resistance. Typically, the pulmonary artery wedge pressure is normal or low. Progression is associated with worsening cardiac dysfunction and development of lactic acidosis. The case-fatality rate averages approximately 30% to 40%. In those patients who survive, recovery is usually complete, but some patients have manifested long-term pulmonary dysfunction. The syndrome in children and adolescents is similar to that in adults.

Novel Coronaviruses (SARS and MERS)

In recent years, two previously undescribed coronaviruses have emerged to cause severe lower respiratory tract illness in humans. Both of these viruses share the property that they are indigenous to some other animal species, and were transmitted to humans with resulting severe disease (see Chapters 122 and 138). The first epidemic to be recognized was referred to as severe acute respiratory distress syndrome, or SARS. Epidemics of SARS were initially recognized in southern China in 2003 and subsequently spread throughout the world. The etiologic agent was identified as a novel coronavirus, designated the Human SARS Coronavirus (HuCoV-SARS).[117] After an intense

epidemic associated with 8096 cases and 774 deaths, the disease disappeared, largely due to aggressive infection control practices. Extensive sequence data strongly suggests that HuCoV-SARS was introduced into human populations from an animal species, likely the palm civet or a related animal. In 2012, cases of a similar severe respiratory illness were recognized in a variety of middle eastern countries, now referred to as the MERS has been named MERS-CoV. This virus is closely related to coronaviruses found in bats, but the epidemiologic data suggest that a currently unidentified intermediate animal host, possibly the camel, is involved in transmission to humans.

The two viruses differ in their epidemiologic behavior to date. In the case of HuCoV-SARS, transmission appeared to be by droplet spread and required close contact. The virus was quite contagious, with an estimated reproductive number of approximately 3. In addition, a poorly understood phenomenon was observed, in which certain individuals appear to be responsible for an extraordinarily large number of transmissions, or so-called "super spreaders." Virus shedding was at its peak at the time that illness was most severe,[118] and the preponderance of transmission occurred in the hospital setting. Ultimately, this allowed the pandemic to be controlled largely by isolation and other infection prevention procedures. In contrast, little if any sustained person-to-person transmission has been observed to date with CoV-MERS, although obviously there is concern that the virus could gain this ability at some later time.

Because of the far greater number of cases of SARS, much more is known about the presentation and clinical features of pneumonia due to this virus. The most common symptoms on presentation were fever, chills and/or rigors, and myalgias. Cough and dyspnea were the predominant respiratory symptoms but were not always present initially. Upper respiratory symptoms, such as rhinorrhea or sore throat, were infrequent. In addition, about one-third of patients had diarrhea at some point in the clinical course. Respiratory disease was progressive and became more severe over 4 to 7 days, leading to significant hypoxemia. About 20% of patients required respiratory support. The overall case-fatality rate was about 10%, but was much higher in older adults. In contrast, children appeared to have milder disease.[119] Although SARS in children had a similar presentation, younger children generally did not require oxygen therapy, and had a relatively benign clinical course. To date, MERS has had a similar presentation to SARS, although gastrointestinal symptoms may be more prominent.[120]

Radiologic abnormalities included unilateral or bilateral ground-glass opacities or focal unilateral or bilateral areas of consolidation. In hospitalized patients the abnormalities tended to progress to bilateral airspace consolidation. In most patients, peripheral involvement is seen, often involving the lower lung zones. Common findings on CT included ground-glass opacification, and interlobular septal and intralobular interstitial thickening. Pulmonary fibrosis may develop after recovery from the acute illness.[121]

HUMAN INFECTIONS WITH ANIMAL INFLUENZA A VIRUSES

Humans are susceptible to infections with influenza A viruses resident in a variety of animal species, such as swine, horses, and migratory waterfowl. The 2009 pandemic of H1N1, which originated in swine and was due to a virus with a complex genetic makeup of gene segments from human, avian, and swine influenza viruses, is the most recent example of how pandemic influenza arises from animal sources. For this reason, there has been substantial effort put into surveillance for influenza at the animal–human interface, and several small outbreaks of severe disease in humans resulting from transmission of viruses from avian sources have been recognized. The most severe cases have been due to viruses of the H5 or H7 HA subtype, but neither of these viruses have exhibited sustained human-to-human transmission to date.

The available data regarding the signs and symptoms of H5N1 infection is mostly from hospitalized patients.[122,123] Most patients present with the nonspecific complaints of cough and shortness of breath. In many patients, there is a progression of symptoms leading to respiratory failure requiring ventilation and other supportive measures. Atypical symptoms such as nausea, vomiting, encephalopathy, bleeding gums and nose have been reported. Watery diarrhea may be present prior to the onset of respiratory symptoms. The majority of patients have an abnormal chest X-ray with diffuse and multifocal or patchy infiltration, but pleural effusions are rare.

Aberrant cytokine responses (sometimes referred to as "cytokine storm") have been implicated in the pathogenesis of H5N1 disease. Autopsy findings in humans have revealed changes of a reactive hemophagocytic syndrome, ARDS and multi-organ failure, findings typically associated with production of high levels of cytokines like TNF-α and interferons.

H7 viruses have also caused large outbreaks in humans. In the Netherlands, an outbreak of H7N7 infection associated with a major epidemic in domestic poultry caused numerous human cases.[124,125] Most of these consisted of mild respiratory disease with conjunctivitis, but there was one death from pneumonia. More recently, an outbreak of human H7N9[126] infection was reported in several provinces in China. In contrast to previous reports of H7 disease in humans, this outbreak was associated with significant lower respiratory tract disease and a mortality rate of approximately 30%. In this outbreak, the majority of severe cases were seen in older adults, many of whom had comorbid conditions.[126,127] While these outbreaks have not spread widely and sustained person to person transmission has not been observed, human infections with novel avian viruses continue to pose a potential pandemic threat.

PATHOGENESIS OF VIRAL PNEUMONIA

The pathogenesis of viral infections of the lower respiratory tract can conveniently be considered in terms of infections initiated in and primarily confined to the respiratory tract, or so-called primary viral pneumonia, such as with influenza or RSV; processes in which infection is initiated in the respiratory tract with subsequent systemic manifestations, such as in measles or varicella, and processes in which respiratory tract involvement is secondary to a systemic infection, such as with CMV. Each of these situations may lead to what is recognized clinically as a viral pneumonia. In this discussion, the general features of primary viral pneumonia are discussed using influenza as a model, and pathogenesis of other forms of viral pneumonia are discussed briefly in comparison.

In primary influenza viral pneumonia, virus infection reaches the lung either by contiguous spread from the upper respiratory tract, or inhalation of small-particle aerosols. Infection initially occurs in ciliated respiratory mucosal epithelial cells of the trachea, bronchi, and lower respiratory tract, and leads to widespread destruction of these cells. The trachea and bronchi contain bloody fluid, and the mucosa is hyperemic. Tracheitis, bronchitis, and bronchiolitis are seen, with loss of normal ciliated epithelial cells. Submucosal hyperemia, focal hemorrhage, edema, and cellular infiltrate are present. The alveolar spaces contain varying numbers of neutrophils and mononuclear cells admixed with fibrin and edema fluid. The alveolar capillaries may be markedly hyperemic with intra-alveolar hemorrhage. Acellular, hyaline membranes line many of the alveolar ducts and alveoli.

The pathologic changes in the lower respiratory tract in children with viral pneumonia due to RSV and PIV are nonspecific and include epithelial necrosis with bronchiolar mucus plugging and widespread inflammation and necrosis of lung parenchyma, and severe lesions of the bronchial and bronchiolar mucosa as well. In fatal cases of RSV pneumonia in children, hemorrhagic pneumonia with peribronchial mononuclear infiltration and cytoplasmic inclusion bodies in epithelial cells are seen.

Bacterial superinfection is a well-recognized complication of viral pneumonia and accounts for a large proportion of the morbidity and mortality of viral lower respiratory tract disease, especially in adults. Consequently, the spectrum of disease and pathophysiology of bacterial superinfection have been studied intensively, and a number of factors identified in viral respiratory disease which could play a role in increasing the risk of bacterial infection.[128] The disruption of the normal epithelial cell barrier to infection, and loss of mucociliary clearance undoubtedly contribute to the enhancement of bacterial pathogenesis. The physiologic consequences of these alterations have been demonstrated as markedly decreased mucociliary clearance of labeled particles in human subjects with acute, naturally acquired influenza.[129] Animal models have also suggested that virally induced inflammatory responses, particularly the type I interferon response, also contributes to the downregulation of host antibacterial defense mechanisms.[130,131]

The HPS represents an additional example of a viral infection that involves the lung as part of a systemic infection. The pathogenesis of HPS involves extensive infection of endothelial cells throughout the body, which is particularly intensive within the endothelial cells of the lung. Abundant viral antigen and nucleic acid can be detected within these cells. Microscopic examination of the lung reveals mild to moderate interstitial pneumonitis with variable degrees of congestion, edema, and mononuclear cell infiltration. The cellular infiltrate is composed of a mixture of small and large mononuclear cells, which consist predominantly of T lymphocytes, and macrophage/monocyte cells. The picture is one of immune-mediated capillary leak and not of cell necrosis or inflammatory pneumonitis. High levels of cytokines have been detected in the blood and likely mediate the endothelial damage.

CMV pneumonia is a problem predominantly in individuals with compromised immune systems, particularly after transplantation, and also represents a systemic infection that involves the lung secondarily. There are several features of this disease in the transplant setting that suggest that both host and viral factors interact in pathogenesis.[132] CMV pathogenicity is enhanced in transplant recipients and frequently occurs at the site of the transplanted organ. The risk of CMV pneumonitis is highest in individuals at the highest risk for graft-versus-host disease. Finally, treatment with antivirals alone is ineffective, while treatment with antivirals and immune globulin, which serve to mitigate the graft-versus-host component, is effective.

The pathogenesis of CMV pneumonia is partly related to viral replication but also is thought to have an immunopathologic basis. The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients. Two patterns of histopathology have been described in the lung tissue of bone marrow transplant patients with serious pneumonia. One is a miliary pattern, with multiple focal lesions showing extensive cytomegaly with localized necrobiosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response. The other is of interstitial character, with alveolar-cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

DIAGNOSTIC TESTS

Epidemiologic or clinical features of the presentation of viral pneumonia, such as the time of year, history of exposures, or, in some situations, presence of systemic signs or symptoms, such as rash, may be very useful in establishing the potential viral etiologies in specific cases of viral pneumonia. However, the clinical presentation is rarely distinctive enough to allow a specific viral diagnosis to be made on clinical grounds alone. Specific diagnosis generally depends on isolation of viral agents from appropriate respiratory specimens. Many of these viruses can be isolated from nasopharyngeal swab or wash specimens, or from lower respiratory tract secretions. Rapid antigen detection tests are available for the detection of RSV and influenza A virus in respiratory secretions. Definitive attribution of pneumonia to viruses that are typically shed asymptomatically in the upper respiratory tract, such as herpes simplex virus, is more difficult and requires detection of virus in the lower respiratory tract, usually in association with pathologic evidence of invasive disease.

Differentiation between viral and bacterial forms of pneumonia on clinical grounds can be difficult in children, and radiologic criteria do not always distinguish these entities well and mixed viral and bacterial pneumonia may be present. However, in normal infants and children with RSV or PIV pneumonia, bacteria do not appear to play an important role, and routine addition of antibacterial agents is not useful. The exception to this observation is in developing countries, where mixed viral and bacterial pneumonias in children are frequent and severe.

TREATMENT AND PREVENTION

Therapy of viral pneumonia is dependent on the severity of disease, the age and immune status of the host, and the specific causative viral agent. General supportive measures, particularly the management of hypoxia, are critically important, and some patients have required high-frequency ventilation or extracorporeal membrane oxygenation. Since mixed viral–bacterial infections or bacterial superinfections are common, antibacterial agents may be required, for example, in patients with lobar pneumonia or productive sputum.

Antiviral therapy is generally indicated for severe disease and in immunocompromised hosts, and should be guided by the results of diagnostic tests. As described above, the NA inhibitors zanamivir and oseltamivir have mostly been studied in uncomplicated influenza in healthy adults, but it seems reasonable to use antiviral agents if the patient is still virus positive at the time of presentation. Because of widespread resistance, use of the drugs amantadine or rimantadine is no longer recommended.

The only option available for the other RNA viruses is ribavirin, but there is little evidence of efficacy of this agent for any viral pneumonia. In immunocompromised hosts, treatment of established RSV pneumonia has not been successful. One approach that appears promising is treatment with ribavirin, possibly in combination with immunoglobulin, early in the illness when predominantly URI symptoms are present. Controlled trials in PIV infection are not available, although anecdotal reports suggest potential efficacy. Limited controlled trials have suggested that aerosolized ribavirin may reduce the severity of symptoms in children with measles, and some immunocompromised patients with measles pneumonia have done well following treatment with aerosolized or intravenous forms of the drug. Intravenous ribavirin is effective in the treatment of several human Hantavirus diseases, including Lassa fever and HFRS, but was not effective in a controlled trial of therapy of HPS.

Antiviral agents with proven clinical usefulness for human coronavirus infection are currently unavailable. However, the severity of the SARS coronavirus epidemic has led to an extraordinary effort to discover and develop effective antivirals, and it is likely that multiple agents will be reported in the near future. The most promising to date appears to be the type I interferons (alpha and beta), which are highly active in cell culture. Multiple agents have potential activity against SARS-CoV, including chloroquine, protease inhibitors, ribavirin, type I interferons, niclosamide, and anti-inflammatory agents such as indomethacin.[133–135] Treatment with parenteral interferon at doses used typically to treat hepatitis C virus infection appeared to lead to clinical improvement in a small series of patients in the Toronto epidemic.

Acyclovir is active in vitro against herpes simplex virus types 1 and 2; it is approximately 10-fold less active against VZV and does not have clinically useful activity against CMV or Epstein–Barr virus. Although controlled clinical trials of this drug in herpes simplex pneumonia have not been conducted, the drug has proven clinical efficacy in other herpesvirus infections and would be indicated in any serious HSV lower respiratory tract infection. Acyclovir is also effective in the therapy of varicella, and intravenous acyclovir has been effective when initiated early in the course of varicella pneumonia. The related drugs

famciclovir and penciclovir are similar to acyclovir in their spectrum of activity against herpes viruses. Viruses resistant to the activity of these drugs have been isolated from treated patients, and may be susceptible to the antiherpes drug phosphonoformic acid (foscarnet).

Once CMV pneumonitis is established, particularly in allogeneic bone marrow transplant patients, it is very difficult to treat. Ganciclovir is highly active against CMV in vitro but monotherapy is not always effective in pneumonitis in BMT recipients. The combination of ganciclovir therapy and intravenous CMV immune globulin can reduce mortality from approximately 90% to 50% or lower in these patients.[136] The effect of the immune globulin in this situation may be mostly to ameliorate graft-versus-host disease. Combination therapy is not generally required in solid-organ transplant recipients with CMV pneumonia. Cidofovir and foscarnet are other antiviral drugs with activity against CMV. Both have been used to successfully treat CMV retinitis, but their effectiveness for treating CMV pneumonia has not been established. All of the available CMV antivirals have serious side effects that limit their usefulness.

Guidelines for reducing the risk of CMV disease in stem cell transplant recipients have recently been published.[137] Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors should receive only leukocyte-reduced or CMV-seronegative RBCs and/or leukocyte-reduced platelets. In mismatched solid-organ transplant recipients (donor+/recipient−), posttransplant prophylaxis with oral ganciclovir or its prodrug valganciclovir significantly reduces the risk of CMV disease, although late-onset disease still occurs. Another strategy is preemptive therapy with ganciclovir or another anti-CMV agent when screening detects infection, but before disease develops. This strategy requires the use of routine monitoring using sensitive and specific laboratory tests for the diagnosis.

Antiviral treatment of proven value for adenovirus infection is not available. Both the broad-spectrum antiviral agents ganciclovir and cidofovir are active in vitro, and an increasing number of reports indicate that intravenous ganciclovir may be useful in seriously ill patients, although at the expense of significant renal toxicity. Cidofovir has also been used for preemptive therapy in high-risk immunocompromised patients.

Various forms of intravenous immunoglobulin have also been evaluated in viral pneumonia. As mentioned, IVIG is important in the treatment of CMV pneumonia in bone marrow transplant recipients; the effect is unrelated to the titer of CMV-neutralizing antibody contained in the preparation, and may act through modulation of the immune response. Intravenous immunoglobulin is effective for the prevention of measles after the exposure of susceptible individuals, and may be useful in the treatment of measles pneumonia, especially when combined with ribavirin. As described earlier, a humanized, neutralizing monoclonal antibody directed against the F protein of RSV (palivizumab) is highly effective for the prevention of severe RSV disease in at-risk infants, but is not effective for therapy of established disease.

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CHAPTER 131 Tuberculosis

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Ryan Cooper

INTRODUCTION

Tuberculosis (TB) is a severe and contagious disease caused by infection with members of the *Mycobacteria tuberculosis* complex (MTBC). Most often involving the lungs, TB is transmitted by cough, with an infectious dose of less than 10 bacteria.[1] Case fatality rates in untreated active pulmonary TB approach nearly 60%.[2] Major medical advances of the past half-century have brought effective treatment capable of cure in nearly all identified cases.[3,4] Despite this TB causes hundreds of thousands of deaths worldwide every year. The morbidity and mortality burden of TB is not uniformly distributed throughout the globe but rather disproportionately affects those living in poverty and those from resource-limited settings.[5]

EPIDEMIOLOGY AND MICROBIOLOGY

In this section, aspects of the epidemiology and microbiology of tuberculosis are presented.

GLOBAL BURDEN OF TB AND RECENT PROGRESS

In 1990, the World Health Organization (WHO) declared TB a global emergency and in response, developed the directly observed therapy strategy (DOTS), promising to "Stop TB" by finding and treating infectious cases in resource-limited settings.[6,7] Within a few years of its design, the World Bank labeled the DOTS strategy the most cost-effective health-intervention ever deployed and by 2012, an estimated 51 million people had been treated and an estimated 20 million lives saved.[8–10] Since 2004, TB incidence is falling in all WHO regions and in each of the 22 highest burden countries.

Although global TB incidence is falling, TB remains a leading cause of global infectious mortality, second only to HIV infection.[11,12] There were 8.7 million new cases of TB and 1.4 million deaths globally in 2011. Moreover, many TB deaths occur in young, previously healthy adults, and as such, TB is a top 10 cause of lost disease adjusted life years (DALYs).[7]

Broadly speaking, there are three major threats to global TB control: (1) Poor social conditions including inadequate housing and nutrition,[5] (2) Immune compromise related to the HIV pandemic,[2,13] and (3) Emergence of drug-resistant TB.[14,15]

POVERTY AND TB

Globally, TB distribution correlates closely with poverty and human development indices.[16–19] Population health factors such as water sanitation, childhood immunization rates, and life expectancy also independently predict TB incidence.[20,21] A corollary of these relationships is that only 1% of the global TB burden occurs in the industrially developed countries of North America and Europe while more than 90% arises in Asia and Africa (Fig. 131-1) (Table 131-1).[10]

HIV AND TB: CO-PANDEMICS

HIV-induced immune suppression increases the risk of progression to active TB nearly 100-fold.[22–26] Worldwide, TB is the most common opportunistic illness and a leading cause of death in patients with AIDS.[27] HIV coinfection complicates 13% of all TB cases worldwide.[10] As both a potent and common risk factor, HIV contributes substantially to TB incidence, especially in Sub-Saharan Africa.[2,13]

DRUG-RESISTANT TB

In 2011, there were over 600,000 prevalent cases of multidrug-resistant (MDR) TB, defined by resistance to the two most

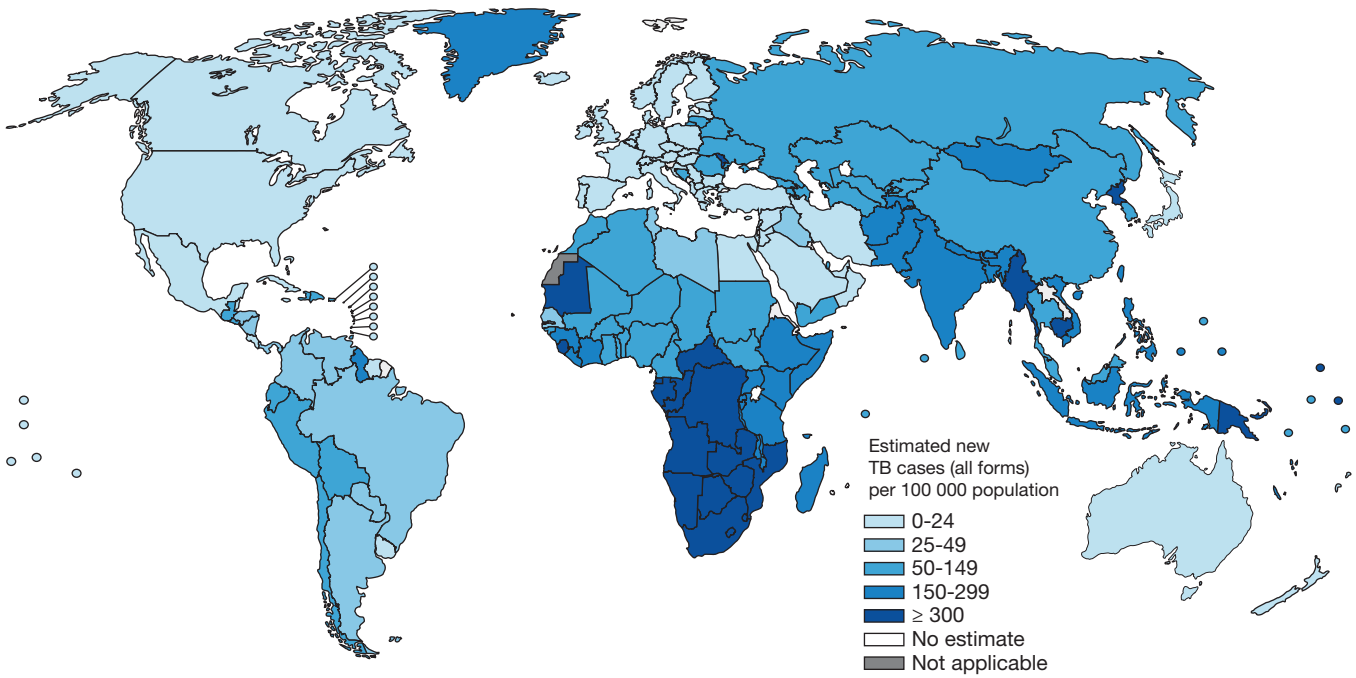

Figure 131-1 Estimated TB incidence by Country 2011. *(Reproduced with permission from 2012. Global Tuberculosis Report, World Health Organization.)*

TABLE 131-1 TB Incidence and Incidence Rate in 2011 for the 22-High TB Burden Countries and the United States

Country	TB Incidence (per 100,000 population) in 2011	Number of New TB Cases in 2011
Afghanistan	189	61,000
Bangladesh	225	340,000
Brazil	42	83,000
Cambodia	424	61,000
China	75	1,000,000
DR Congo	327	220,000
Ethiopia	258	220,000
India	181	2,200,000
Indonesia	187	450,000
Kenya	288	120,000
Mozambique	548	130,000
Myanmar	381	180,000
Nigeria	118	190,000
Pakistan	231	410,000
Philippines	270	260,000
Russian Federation	97	140,000
South Africa	993	500,000
Thailand	124	86,000
Uganda	193	67,000
UR Tanzania	169	78,000
Viet Nam	199	180,000
Zimbabwe	603	77,000
United States	3.2	9951

Source: Data from Global Tuberculosis Report, World Health Organization; 2012.

important first-line antimicrobials, isoniazid and rifampin.[10,28,29] MDR-TB accounted for approximately 3.7% of newly diagnosed TB cases and 20% of relapsed cases globally. Reliable global estimates of MDR-TB are difficult to obtain since rigorous drug-susceptibility testing (DST) is not available in most resource-limited settings endemic for TB.[28,30] Eastern European countries have particularly high rates of MDR-TB; a phenomenon considered linked to the underinvestment in national TB programs and the social disruption that occurred following the collapse of the Soviet Union in the 1990s.[31] MDR-TB is 100 times more costly to manage than is drug-susceptible TB, requiring prolonged courses of expensive and difficult to procure second-line drugs.[32] In South Africa, MDR-TB prevalence is 3.2% but associated treatment costs account for one-third of the entire national TB program budget.[32] Treatment outcomes are substantially worse in MDR-TB.[29] Extensively drug resistant TB, or TB resistant to all currently available bactericidal agents, has been reported in nearly 60 countries.[29,30] The increasing prevalence of MDR-TB is particularly chastening because it is entirely a "man-made" phenomena.[31,33] With better management of TB programs, the emergence of resistance can be prevented and prevalence of MDR-TB can be reduced.[14,15]

NEWER THREATS TO GLOBAL TB CONTROL

Diabetes, smoking, and malnutrition can also impair immunologic containment of TB infection. Their prevalence continues to increase globally and the cumulative impact may well threaten global TB control in the future.[8,17,34]

TB EPIDEMIOLOGY IN THE UNITED STATES: HISTORICAL PERSPECTIVE

In the first half of the 20th century TB was a leading cause of morbidity and mortality in the United States. In 1920 pulmonary TB accounted for nearly 1 in 13 of all deaths, outranking cancer.[6,35,36] Improvements in social conditions and population health during the early 20th century led to significant reductions in TB incidence and, with the introduction of effective chemotherapy in the 1950s, incidence declined even further.[4] By the 1970s, TB incidence in the United States had reached historical lows, less than 10 cases per 100,000 people and TB seemed on the brink of elimination. Unfortunately, public health funding for TB control was then greatly reduced and by the mid-1980s a nationwide resurgence ensued, particularly in the major urban centers.[6,37–39] It is estimated that during the 1980s and early 1990s, when TB funding in the United States was nearly eliminated, 64,000 excess cases occurred.[37,40]

CURRENT US TRENDS IN TB EPIDEMIOLOGY

With renewal of Government investment in the mid-1990s TB control was reestablished and TB rates have since declined every consecutive year in the United States (Fig. 131-2).[41] By 2012, there were less than 10,000 total reported cases of TB in the United States, or just 3.2 cases per 100,000 people, the lowest rate ever reported.[41]

TB remains a concern within specific demographic groups. The foreign born, especially newly arrived immigrants, account for an increasing proportion of TB cases in the United States, representing nearly two-thirds of all US cases in 2012 (Fig. 131-3).[41] Mexico (22%) and the Philippines (12%) are the most common countries of origin of imported TB.[42,43] In foreign-born US residents, TB usually represents reactivation of infection remotely acquired in TB-endemic countries prior to arrival rather than new infection resulting from local transmission.[43]

Among the US born, TB burden is concentrated in indigenous peoples, incarcerated populations, and the unstably housed.[40,43–46] In these groups, "mini" outbreaks of TB resulting from recent transmission occur with some regularity, especially in major urban centers. Several authors have shown that race, substance abuse, malnutrition, and socioeconomic status are each independently correlated with TB incidence in the United States.[18,47–51]

Childhood TB incidence reflects ongoing TB transmission and as such, is important indicator of TB control within a community. In

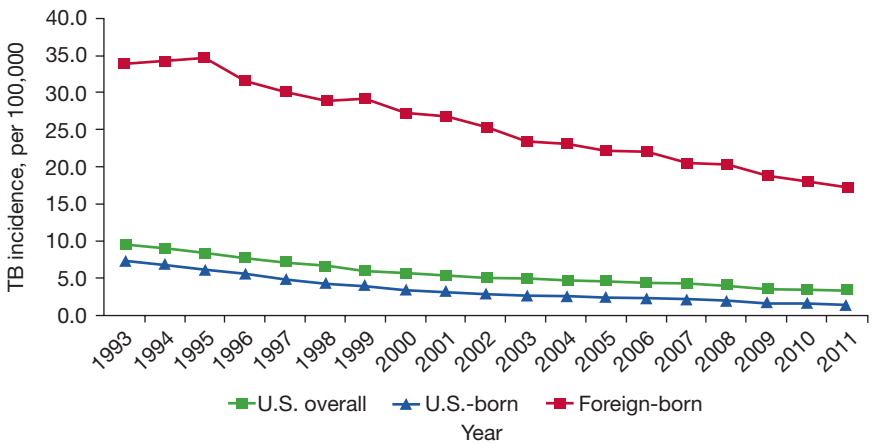

Figure 131-2 TB Case Rates in US-born versus Foreign-born persons, United States, 1993 to 2011. *(Reproduced with permission from Frieden T. Reported Tuberculosis in the United States, 2011. CDC; 2012).*

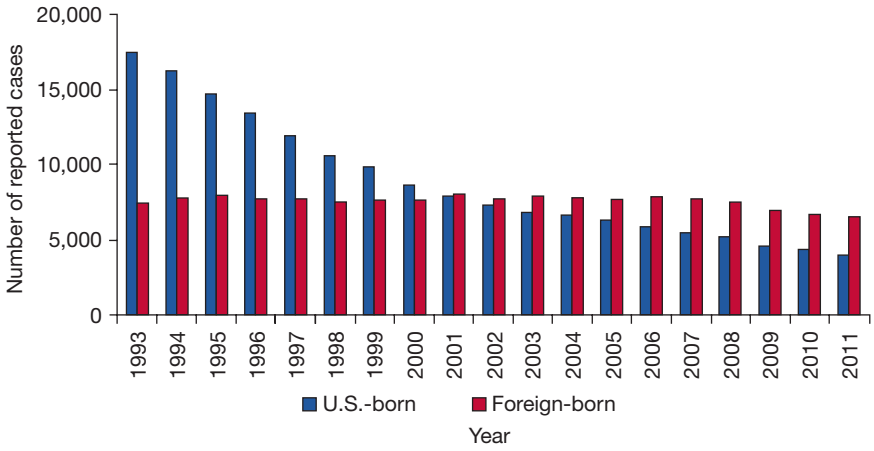

Figure 131-3 Number of TB cases in US-born versus Foreign-born persons United States, 1993 to 2011. *(Reproduced with permission from Frieden T. Reported Tuberculosis in the United States, 2011. CDC; 2012).*

the United States, 80% of childhood TB occurs in US-born children, and mostly those from racial and ethnic minority groups.[43]

MICROBIOLOGY OF TUBERCULOSIS

Mycobacterium tuberculosis as the causal agent of TB was first conclusively demonstrated in 1882 by Robert Koch and acknowledged with a Nobel Prize in 1905.[52]

M. tuberculosis is a slender, slightly curved, rod-shaped bacterium (or bacillus) averaging 3 by 0.3 μ in size and visible by light microscopy. It is nonmotile, nonencapsulated, and nonspore forming. *M. tuberculosis* is strictly aerobic.[53,54] Traditionally, mycobacteria are grown on solid, enriched media where rough, pigmented colonies generally appear 4 to 6 weeks after inoculation. MTBC can also be cultivated in specialized liquid media where characteristic "cords" visible by light microscopy are formed. Rapid liquid culture systems (e.g., BACTEC) have been adapted for use with mycobacteria and shorten time to detection of growth to a little as 9 to 16 days, depending on the initial concentration of the bacteria in the specimen tested.[55,56]

MTBC: Eight closely related mycobacterial species capable of causing human TB have been identified and together they comprise the MTBC: *M. tuberculosis* (Koch bacillus), *M. bovis* (the agent of bovine TB), *M. caprae* (bovine TB), *M. africanum* (a not infrequent cause of human TB in West Africa), *M. microti* (agent of rodent TB), *M. pinnipedii* (agent of TB in seals and a rare zoonotic disease in marine biologists attending to them), and *M. canettii* (an ancient bacillus and rare cause of human TB in East Africa) (Table 131-2).[55,57,58]

TABLE 131-2 Members of the Mycobacterium Tuberculosis Complex (MTBC)[a]

Species	Primary Reservoir Host	Geography
M. tuberculosis	Humans	Worldwide
M. bovis	Cattle, deer, elk, bison, badger, opossum	Worldwide
M. bovis BCG	Human	Worldwide
M. caprae	Goats	Worldwide
M. africanum	Human	West, Central Africa
M. microti	Vole, rodents	
M. pinnipedii	Seal, sea lion	
M. canettii	Human	East Africa

[a]*While all members of the MTBC can infect humans, some are zoonotic diseases.*

M. tuberculosis causes the vast majority of TB today. In the early 20th century, *M. bovis* accounted for up to 20% of all cases of human TB but with modern surveillance of animal herds and widespread use of milk pasteurization, *M. bovis* now causes less than 1% of reported TB cases in the United States.[59,60] Sporadic outbreaks of *M. bovis* infection still occur in the United States, and ongoing surveillance is important for food-chain safety. Human-to-human transmission of *M. bovis* has been demonstrated.[61]

MYCOLIC ACID AND THE *MYCOBACTERIUM* GENUS

The MTBC are members of the diverse *Mycobacterium* genus. The outstanding feature of the mycobacteria is their lipid-rich cell wall containing very high concentrations of mycolic acids.[53,54,56,62] This cell wall prevents reliable uptake of Gram stain. With phenol additive mycobacteria can eventually be stained to facilitate light microscopy. Once stained, removal of dye is extremely difficult, resisting even acid alcohol wash (hence "acid-fast bacilli" [AFB]). Lipids in the mycobacterial cell wall also help resistance to drying, a property that allows MTBC to retain infectiousness even within dried droplet nuclei. The metabolic investment required to produce mycolic acids significantly slows growth rate[56]and prolongs the time to detection in incubated clinical specimens submitted to laboratory.[53] The mycolic acid containing cell wall of mycobacteria is also a major virulence factor, helping mycobacteria avoid innate immune defenses and intracellular killing by nonactivated host phagocytes.[63]

COMPARISON TO OTHER MYCOBACTERIA

The nontuberculous mycobacteria (NTM) are free-living saprophytic bacteria, commensal inhabitants of the soil and/or aquatic environments (see Chapter 132). The NTM are nontransmissible under ordinary conditions, and only rarely infect humans as opportunists. In contrast, MTBC are transmissible, obligate primary pathogens without an environmental reservoir.[55]

TRANSMISSION

Important considerations in the transmission of tuberculosis are discussed below.

Droplet Nuclei

In the late 1930s, William Wells, sanitation engineer at Harvard University first conceived of "droplet nuclei" for airborne transmission of infectious diseases.[64] He found that forceful expiratory efforts such as coughing and sneezing, discharge minute respiratory droplets of sputum containing viable bacilli that, when increasingly reduced in size by evaporation, become infectious droplet nuclei, each measuring less than 5 μ.[65] Certain healthcare procedures, for example, bronchoscopy, sputum induction, autopsy, and even irrigation of abscesses, also produce infectious droplet nuclei.[66]

Due to small size, droplet nuclei have an extremely slow settling rate in air (0.5 mm/s or less). This permits their transport by air currents for significant distances. Larger respiratory droplets, on the other hand, settle out of the air quickly, and travel only a few feet from the source case. The microbes suspended within droplet nuclei are highly susceptible to germicidal levels of ultraviolet light.[2,67] The small size of droplet nuclei also facilitates penetration of the bronchial defenses allowing access to terminal alveolar macrophages. The fairly tortuous and branched path of the pharynx and bronchial tree ensures that larger respiratory droplets are instead deposited

TABLE 131-3 Key Distinguishing Features of Droplet Nuclei And Respiratory Droplets

	Droplet Nuclei Transmission	Respiratory Droplet Transmission
Particle size	1–5-μm-diameter particles (dried residua of larger particles)	>100 uM-diameter particles
Time for article to settle out of air	Suspended indefinitely	Settle within seconds, 1 m from source
Site reached by particle in recipient airway	Alveolar deposition	Upper airway deposition
Number of microbes per particle	Contain few microbes	Contain many microbes
UV-light susceptibility	Susceptible	Resistant
Example pathogens	Measles, TB, Varicella	RSV, influenza, staphylococcus

Source: Reproduced with permission from Garay S, Rom W. Tuberculosis, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

on the mucosal lining of the airway or trapped in the mucociliary elevator and expelled (Table 131-3).[65]

Airborne Transmission of TB

In the 1950s, Richard Riley, a medical student working with Wells, elegantly demonstrated that TB is near exclusively transmitted by droplet nuclei. Riley commandeered a TB ward of six rooms for his study. The air from each individual room was ventilated to an upper chamber, where caged guinea pigs were kept, sometimes passing through an adjustable UV light source.[68] Guinea pigs are considered uniquely susceptible to infection with *M. tuberculosis,* even by dilute aerosols, and their use allowed quantification of degree of patient infectiousness.

Relatively few respiratory diseases are preferentially transmitted via the airborne route; these include TB, measles, varicella, and smallpox. Most infectious respiratory diseases (including, e.g., pertussis, influenza, the common cold, and pneumococcal pneumonia) are instead transmitted by direct contact with larger respiratory droplets leading to colonization of the host nasopharynx before subsequent lung invasion.

Risk Factors for TB Transmission

The risk of TB infection is a function of exposure to the tubercle bacilli. In turn, this depends on the interaction of three factors: infectiousness of the source case, environmental conditions that impact droplet nuclei concentration per volume of air, and duration of contact with the source (Table 131-4).

Source Case Infectiousness

An important finding from Riley's studies was the extreme variability in infectiousness of TB patients.[69,70] The dominant predictors of infectiousness in source cases are the presence of cough, lung cavitation on chest radiograph, and acid-fast bacilli visible in sputum by smear microscopy. Sputum-smear microscopy positive cases excrete about 10^8 bacilli per mL of sputum compared to less than 10^3 bacilli per mL of sputum in smear-negative cases.[66] About 35% of close contacts of sputum smear–positive patients will become infected, compared to less than 10% from sputum smear–negative cases (Fig. 131-4).[66,71–73]

Riley also demonstrated that effective anti-TB treatment could rapidly render patients noninfectious, usually within a few days of initiation.[74] The implications for discontinuing hospital isolation are somewhat controversial.[75] As a matter of convention, pulmonary TB patients are usually considered noninfectious after 2 weeks of effective chemotherapy, provided drug resistance and nonadherence are excluded.[76]

TABLE 131-4 Factors Associated with Number of Infectious Droplet Nuclei per Volume of Air and TB Transmission

Characteristics of Source Case	Environmental Factors
Sputum-smear positivity for AFB	Air circulation, ventilation
Cough strength and frequency	Room volume
Presence of lung cavitation	Humidity
Effective treatment	UV light
Delayed diagnosis	Proximity to the source case
Laryngeal tuberculosis	Duration of contact with infected air

Source: Data from Sepkowitz KA. How contagious is tuberculosis? Clin infect Dis. 1996;23(5):954–962.

Conducive Environment

Important environmental factors influencing TB transmission include ventilation (or room air changes per hour) and ultraviolet light.[66,77,78] Proximity and duration of contact with source case are also determinants of TB transmission. Household contacts are several times more likely to be infected than are casual contacts from the community.[66,72] Thus crowded housing with poor ventilation and inadequate natural lighting – such as occurs in prisons, homeless shelters, American inner-city housing projects, and the large urban slums of the developing world – are particularly conducive for TB spread.[16,79]

Host Susceptibility

Genetic determinants of innate immunity are likely important host susceptibility factors but are poorly understood.[63,80] Some studies suggest that previous TB infection (as manifested by tuberculin skin test positivity) may partially protect against reinfection, although the degree of protection has not been quantified.[81–83] Vaccination with attenuated *M. bovis* Bacille Calmette-Guérin (BCG) strain probably does not reduce the risk of infection with MTBC, even if it does reduce the subsequent chance of developing disseminated active disease once infected.[66,80,84]

NATURAL HISTORY AND PATHOPHYSIOLOGY OF TB INFECTION

It is estimated that one-third of all humans are infected with TB.[85] However, only a small fraction of the individuals within this massive reservoir ever develops active TB; most infections remain latent without apparent ill effect on the host. Risk factors associated with progression to active disease once infected are shown in Table 131-5.

■ FROM EXPOSURE TO INFECTION AND THE INNATE IMMUNE RESPONSE

The natural history of TB infection is outlined in Figure 131-5. Following exposure to an infectious source case, many contacts do not become infected, and will not convert their TST—either because infectious droplet nuclei did not reach their terminal alveoli or because any successful invaders were immediately cleared by intrinsic microbicidal activity of macrophages.[3]

However, in some individuals, invading mycobacteria engulfed by alveolar macrophages manage to evade intracellular killing.

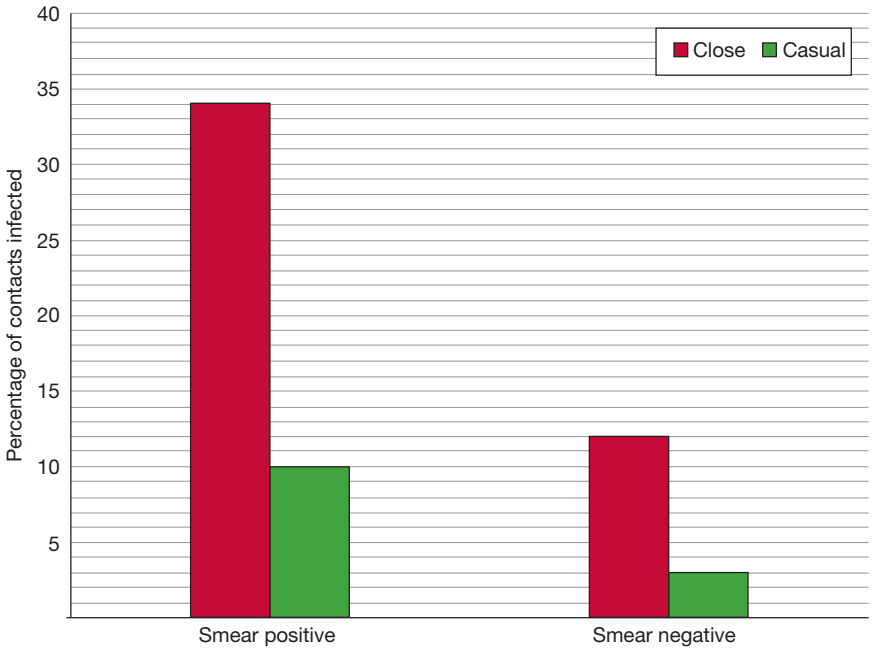

Figure 131-4 Infectiousness of tuberculosis by bacteriologic status of and proximity to source case. *(Reproduced with permission from Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975;50(1):90–106).*

Mycobacteria bypass innate immune mechanisms and replicate without limitation, spreading to regional lymph nodes, and silently disseminate hematogenously.[1,57,80] After a few weeks, dendritic cells are activated and produce cytokines such as tumor necrosis factor alpha (TNF-α) that recruit blood-borne monocytes and lymphocytes to sites of infection, setting the stage for the adaptive cellular immune response.[80]

THE ADAPTIVE IMMUNE RESPONSE AND CONTAINMENT OF MYCOBACTERIAL INFECTION

The main effectors of the adaptive, cell-mediated immune (CMI) response to mycobacteria are the CD4-positive subset of T lymphocytes.[80] Once stimulated, T lymphocytes release their own battery of cytokines (including interferon-gamma [IFN-γ]) that serve to reciprocally activate infected macrophages and trigger-enhanced intracellular mycobacteria killing. This is the basis for the tuberculin skin test and IFN-γ release assays, which become positive with the development of a host CMI response. Over the next few weeks, the CMI directs necrotizing granuloma formation, which usually contains bacillary replication.

PRIMARY DISEASE

About 5% of immune competent individuals do not control initial mycobacterial replication and instead progress to primary TB disease, usually within 18 months. The risk of progression to primary disease is even higher in those with compromised CMI or other risk factors. Primary disease may occur at the initial site of lung entry (typically the mid and lower lung zones where greater airflow directs droplet nuclei deposition), regional lymph nodes, or rarely at metastatic sites initially seeded during early occult hematogenous dissemination.

TABLE 131-5 Risk Factors for Progression to Active TB in Those Latently Infected. Low-Risk Reactor—TST Positive with no Known Risk Factor, Normal Chest Radiograph

Risk Factor	Annual Risk of Infection	Relative Risk	Reference
Human immunodeficiency infection	5.0–10	50–100	Wood (2000), Selwyn (1989)
Transplantation, immunosuppressant therapy	7.4	20–74	Torre (2009), Aguado (1997), Singh (2002)
Silicosis	3.0	30	Cowie (1994)
End-stage renal disease on hemodialysis	2.5	10–25	Christanopoulis (2007)
Solid-organ cancer	1.4	3–12	Kamboj (2006)
Hematological malignancy	—	40	Kamboj (2006)
Recent TB infection, within 2 y	1.5	15	Sutherland (1976)
Fibronodular changes on chest radiography	0.6	6–19	Grzybowski (1975), Cain (2008), Menzies (2008)
Tumor necrosis factor antagonists	0.4	2–4	Keane (2001), Brassard (2006), Gomez (2007)
Diabetes mellitus	0.4	2–8	Dooley (2009)
Corticosteroid therapy	—	5	Jick (2005), Brassard (2009)
Heavy alcohol use (>40 g/d)	—	3–4	Lonnroth (2008), Olin (1966)
Malnutrition, underweight (BMI <20 kg/m^2)	0.3	2–3	Cigielski (2004)
Cigarette smoker (1 pack/d)	0.3	2	Bates (2007), Lin (2007)
Calcified granulomata on chest radiograph	0.2	2	Menzies (2008)
Indoor air pollution	—	2	Lonnroth (2009)
Refugee from TB endemic country, recent arrival	3.0	30	Greenway (2008)
Vitamin D deficiency	—	1.5	Wilkinson (2000), Nnoham (2008)
Age <5	0.2–0.4	2–4	Horsburgh (2004), Comstock (1974)
Low-risk reactor	0.1	1	Menzies (2008)

Source: Data from Long R, Hoeppner V, Orr P, et al. Marked disparity in the epidemiology of tuberculosis among Aboriginal peoples on the Canadian prairies: the challenges and opportunities. Can Respir J. 2013;20(4):223–230.

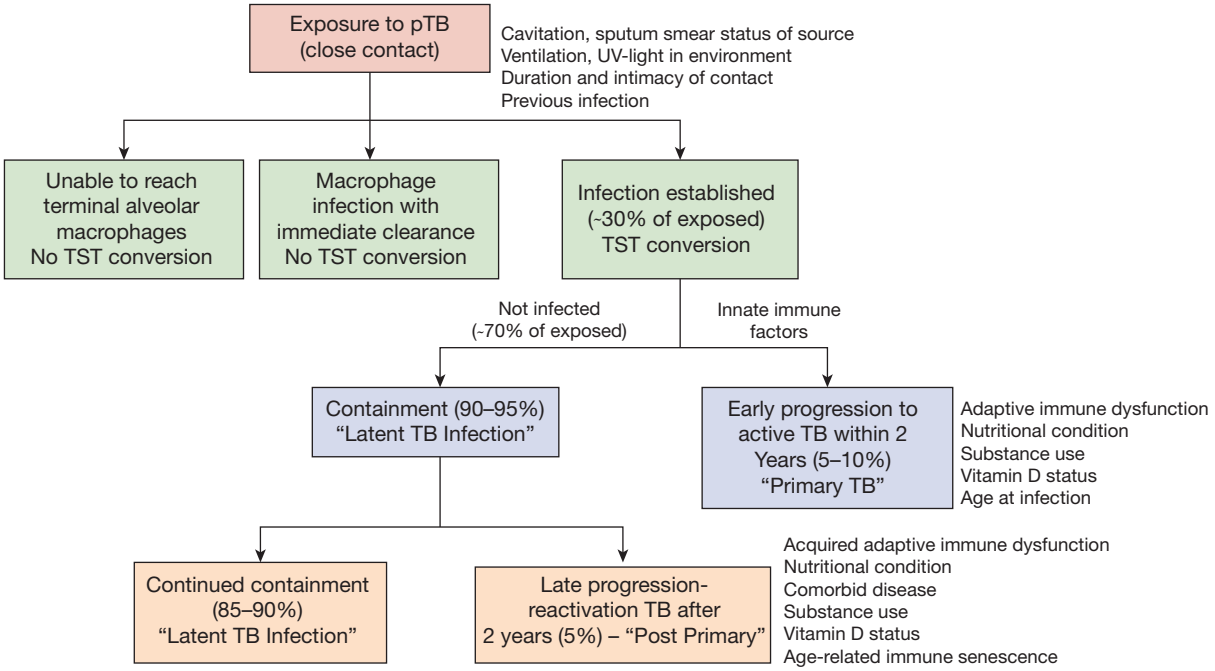

Figure 131-5 Natural history of TB infection. pTB, pulmonary tuberculosis; TST, tuberculin skin test. *(Reproduced with permission from Comstock GW. Epidemiology of tuberculosis. Am Rev Respir Dis. 1982;125(3 Pt 2):8–15).*

■ REACTIVATION DISEASE FROM LATENT INFECTION

For the individuals who successfully contain the initial infection and avoid primary disease, mycobacteria lie latent within healed, fibrotic and/or calcific granulomata. At this stage, mycobacteria cannot be cultured from host sputum or tissue specimens and symptoms are not present. It is believed that latent tuberculous infection (LTBI), with the potential for future reactivation, persists for life of the host.[86]

In a small minority, granulomas break down, mycobacteria replication increases, and symptomatic disease develops. Such reactivation can occur with age-related immune senescence or in those with acquired risk factors for active TB. Reactivation most commonly occurs in the apical-posterior segments of the lungs, where higher oxygen tension favors bacillary replication, but disease can occur at any previously seeded site.[1] Once reactivated, bacilli can usually be cultured from sputum and/or tissue samples.

■ CASEATION AND CAVITATION

Differences in quality of host adaptive immune response determine clinical presentation.[57,80] Some individuals develop a particularly robust, caseating granulomatous inflammatory response with resultant tissue destruction and lung cavitation—they discharge large amounts of bacilli into airways and are highly contagious. At the other end of the spectrum, a severely weak or immature granulomatous response allows hematogenous dissemination of bacilli, accompanied by widespread inflammatory foci of poorly formed granulomas. Each focus typically enlarges to about 3 mm in size, or about the size of millet seed. This severe form of TB (miliary TB) has a high case-fatality rate.

CLINICAL MANIFESTATIONS

TB had had a number of illuminating vernacular names through history. In ancient Greece, TB was called "phthisis" meaning to waste away. And in Rome, "tabes" was used, indicating wasting and overall decay. "Consumption," a term applied to TB in 19th century England is particular evocative, referring to the observation that TB sufferers appear to be gradually "consumed" by the disease, becoming lighter and less robust over months.[87]

■ SITE OF DISEASE AND CLINICAL PRESENTATION

TB is predominantly a respiratory disease, affecting the lungs in about 80% of cases (Table 131-6).[43,88] About 30% of TB cases involve an extrapulmonary site, occurring either with or without concomitant lung involvement. TB can affect virtually any organ, although peripheral lymph nodes and pleural space are the most common extrapulmonary sites.[89]

Classically TB presents insidiously over weeks, with persistent local symptoms correlating to granulomatous inflammation (e.g.,

TABLE 131-6 Proportion of Reported TB Cases in the United States, by Predominant Site of Disease

	Site or Type of Disease	Percentage (%)
Pulmonary		66.7
	Sputum smear–positive pulmonary	40.1
	Sputum smear–negative pulmonary	26.6
Extrapulmonary		21.2
	Pleural	3.8
	Peripheral lymph node	8.2
	Central nervous system	1.3
	Abdominal	1.2
	Bone and joint	2.3
	Genitourinary	1.1
	Other	4.0
Both		12.1
Total		100

Source: Data from Shah NS, Cavanaugh JS, Pratt R, et al. Epidemiology of smear-negative pulmonary tuberculosis in the United States, 1993–2008. Int J Tuberc Lung Dis. 2012;16(9):1234–1240 and Frieden T. Reported Tuberculosis in the United States, 2011, CDC. 2012.

cough in the case of pulmonary TB, neck mass for cervical lymph node TB) plus constitutional symptoms that correlate to the production of pyrogenic cytokines such as TNF-α (e.g., fevers, night sweats, anorexia, weight loss). Initially the cough may be dry but after several months becomes productive. Fever may be absent, especially in the elderly.[90] With advancing disease, hemoptysis, anorexia, and weight loss can occur.[91–93] Importantly, some patients are asymptomatic even with clear TB disease activity demonstrable on culture or radiography—a prospect that frustrates TB control program efforts at active case finding.[3,94]

■ PHYSICAL EXAMINATION

Even when relatively extensive disease is present, pulmonary TB most often produces no detectable abnormality on physical examination.[91,94] It is important to examine for signs of extrapulmonary disease such as lymphadenopathy, abdominal, or bone and joint involvement, particularly in HIV-infected individuals. Tachypnea and hypoxia are relatively rare except with extensive lung destruction or miliary disease.

■ CHEST RADIOGRAPHY IN PULMONARY TB

Radiographic findings of TB are well described.[94–96] Sensitivity for active TB is 70% to 80%, and even less in patients with HIV or other severe immune compromise. Further, chest radiography is only moderately specific and there is generally poor agreement between chest film readers.[97–99] Chest radiography alone also cannot reliable distinguish between active and healed, latent TB.[97,98,100]

Typical Chest Radiograph Patterns

Four radiographic features suggest active TB: (1) Nodular opacities located in the apical-posterior segments of the upper lobes or superior segment of the lower lobes, (2) associated volume loss and fibrosis, (3) lung cavitation, and (4) endobronchial spread. Endobronchial spread to dependent lung segments fills lung acinar units, resulting in 4- to 5-mm size nodular opacities on plain film (acinar shadows) and a "tree-and-bud" pattern on computed tomography (CT) (Figs. 131-6 and 131-7).[95,98,101]

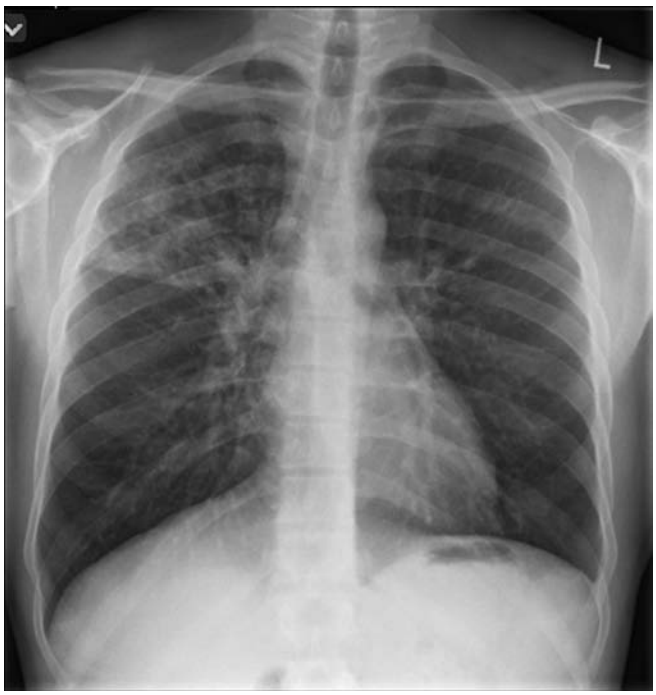

Figure 131-6 This 32-year-old male refugee recently arrived from Eritrea. He presented with persistent cough and fevers despite completing two courses of antimicrobial therapy directed against bacterial community–acquired pneumonia. Sputum sample was both smear positive and culture positive for MTBC.

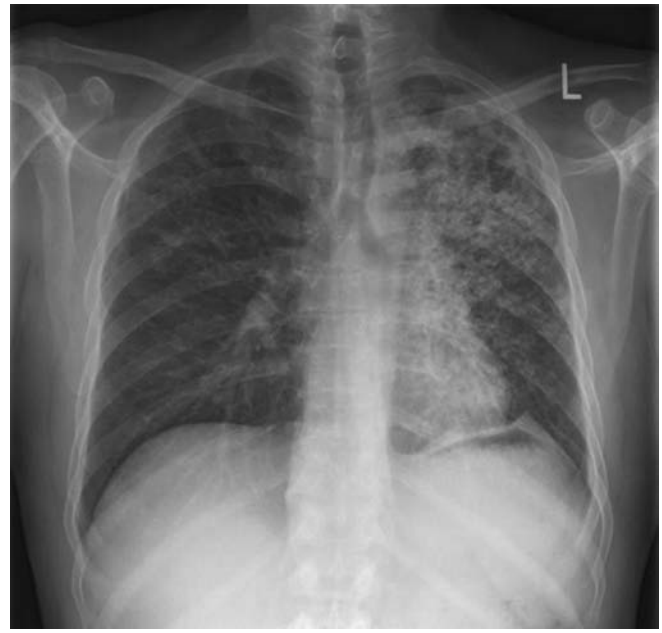

Figure 131-7 This 36-year-old man Aboriginal man with history of homelessness. This radiograph demonstrates typical manifestations of reactivation TB: upper lobe nodular opacities, cavitation, acinar shadowing from endobronchial spread, and fibrosis.

Atypical Chest Radiograph Patterns

Atypical radiographic patterns are seen in children, the elderly, the immunocompromised, and those with primary disease.[96,100,102] Atypical features include lower lung zone infiltrates without cavitation, unilateral pleural effusion (Fig. 131-8), and ipsilateral hilar or

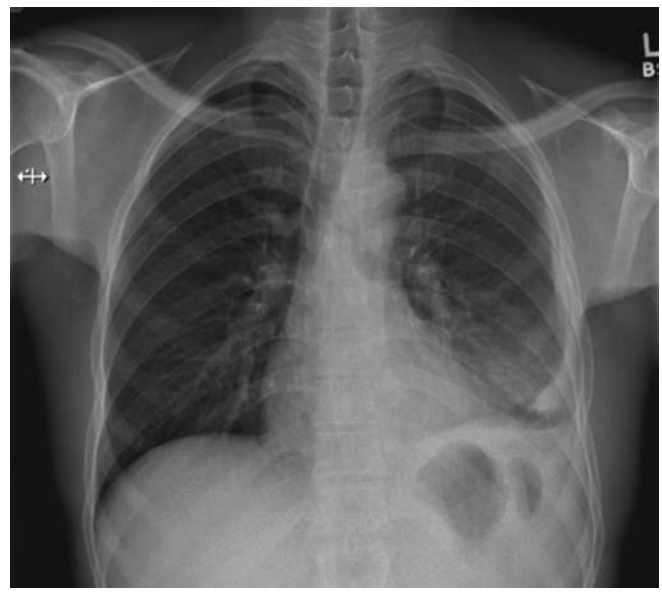

Figure 131-8 This 22-year-old man identified as a close household contact of a smear-positive case of pulmonary tuberculosis. Seven weeks later he developed fevers and cough. This radiograph demonstrates unilateral pleural effusion with compressive atelectasis. Diagnostic thoracocentesis revealed a transudate with cellular infiltrate, predominantly lymphocytic. Sputum was culture negative for mycobacteria but pleural specimen eventually grew MTBC.

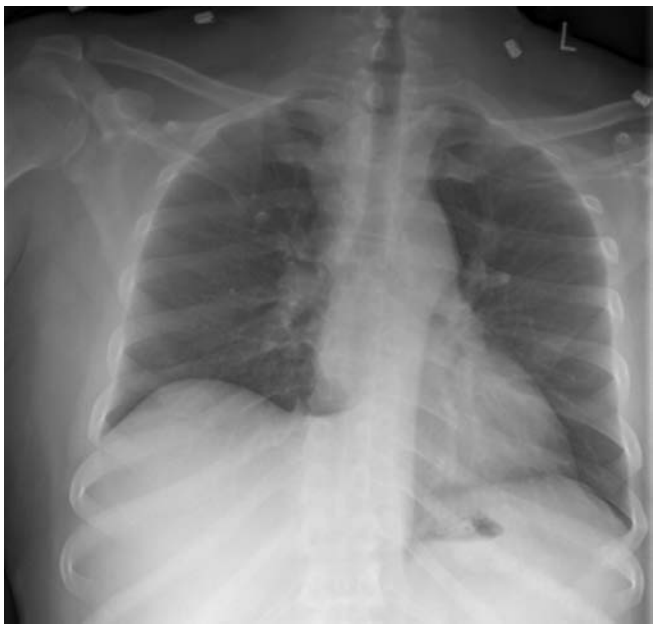

Figure 131-9 This 42-year-old HIV+ man with a CD4 count of 150 cell/mm^3 presented with cough. Significant mediastinal and right hilar adenopathy are present without apparent lung parenchymal disease. Sputum cultures were smear negative but culture positive for MTBC.

mediastinal adenopathy (Fig. 131-9). Intrathoracic TB lymphadenitis is often better appreciated on CT where lymph node enlargement, rim enhancement, and low central attenuation are characteristic.[95]

Miliary TB is rare but when present, produces a distinctive, readily recognizable radiographic pattern: Innumerable, interstitial nodules uniformly distributed throughout all lung fields, without reduction in lung volumes (Fig. 131-10).

DIAGNOSIS OF TB

Most US clinicians will practice for years without ever encountering a case of TB. For every 450 ambulatory visits for community-acquired pneumonia (CAP), and for every few dozen cases of lung cancer, there is on average one case of TB in the United States.[103,104] In low-incidence settings, many patients diagnosed with TB will have experienced multiple contacts with the healthcare system before the diagnosis of TB is considered.[105,106]

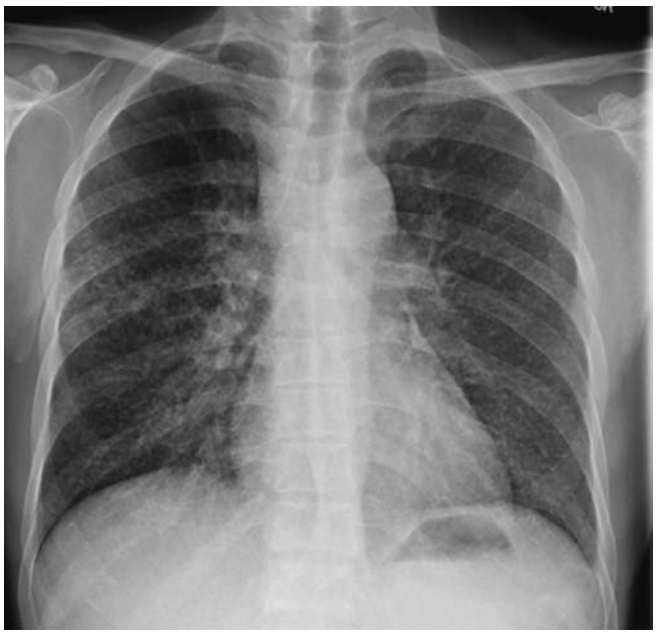

Figure 131-10 This 36-year-old HIV+ man presented with fevers. Chest radiograph identified right upper lobe infiltrate and a background miliary pattern consisting of innumerable noncalcified nodules measuring 2 to 3 mm, randomly distributed.

Thus the diagnosis of TB requires a very high-index of suspicion considering epidemiologic risk factors and suggestive clinical–radiographic features (Fig. 131-11). Ultimately, the definitive diagnosis requires culture confirmation.

■ LABORATORY INVESTIGATIONS

Anemia is commonly observed in TB, usually due to chronic inflammatory state or malnutrition.[94] Syndrome of inappropriate ADH can complicate pulmonary or central nervous system TB.[107] Historically, disseminated TB was an important cause of adrenal insufficiency. Hypercalcemia is a relatively frequent complication of TB.[108] Activated macrophages within granulomas upregulate 1-alpha-hydroxylase, which can in turn activate vitamin D and lead to increase in calcium absorption.[109–111] Hypercalcemia of TB can be symptomatic and occasionally leads to nephrocalcinosis, nephrolithiasis, or acute volume depletion. Vitamin D supplementation during TB therapy may increase the risk of hypercalcemia.[112]

Specimen Collection

Protocols to ensure proper specimen handling, storage, transport, and labeling are available.[94] Ideally, specimen collection should occur before initiation of therapy to increase yield.

For the diagnosis of pulmonary TB at least three sputum samples, each 5 to 10 mL, should be collected at least 1-hour apart. For those patients unable to expectorate spontaneously, sputum induction (with nebulized hypertonic saline) or bronchoalveolar lavage (BAL) is an alternate established method.[113] Induced sputum samples produce slightly higher yield than do BAL samples (87% vs. 73%), and sputum induction is much better tolerated, less invasive, and lower cost.[114,115] If bronchoscopy is performed to evaluate other diagnostic considerations, then an additional sputum sample collected immediately after bronchoscopy may have particularly high-yield for mycobacterial identification.[113]

For diagnostic confirmation of extrapulmonary TB, tissue or fluid samples should be submitted fresh (or in sterile normal saline) without addition of preservative (e.g., formalin) because this will prevent subsequent identification, culture, and DST in the microbiology laboratory. It is important to notify both the laboratory and clinician before collecting a specimen if extrapulmonary TB is suspected to allow the laboratory to take appropriate biosafety precautions during specimen handling to prevent laboratory transmission of TB.

Direct Microscopy for AFB

Sputum-smear microscopy is more than 110 years old but remains the most widely used investigation for active TB today.[52] Two methods are commonly used for acid-fast staining of mycobacteria: carbolfuchsin (e.g., Ziehl–Neelsen [ZN]) and fluorochrome-based procedures (e.g., auramine–rhodamine dye). Fluorescent methods slightly improve sensitivity over ZN and also allow the use of lower microscopic magnification during inspection of the slide, significantly shortening the time required to examine an entire specimen.[116]

Sputum microscopy is widely available and low cost. It is performed directly on clinical specimens allowing rapid turn-around-time, thus facilitating prompt recognition, isolation, and treatment of infectious TB cases. Microscopy also provides prognostic information: Smear-positive TB cases are more infectious and have much higher case-fatality rates if untreated than do sputum smear–negative cases.[72,117,118]

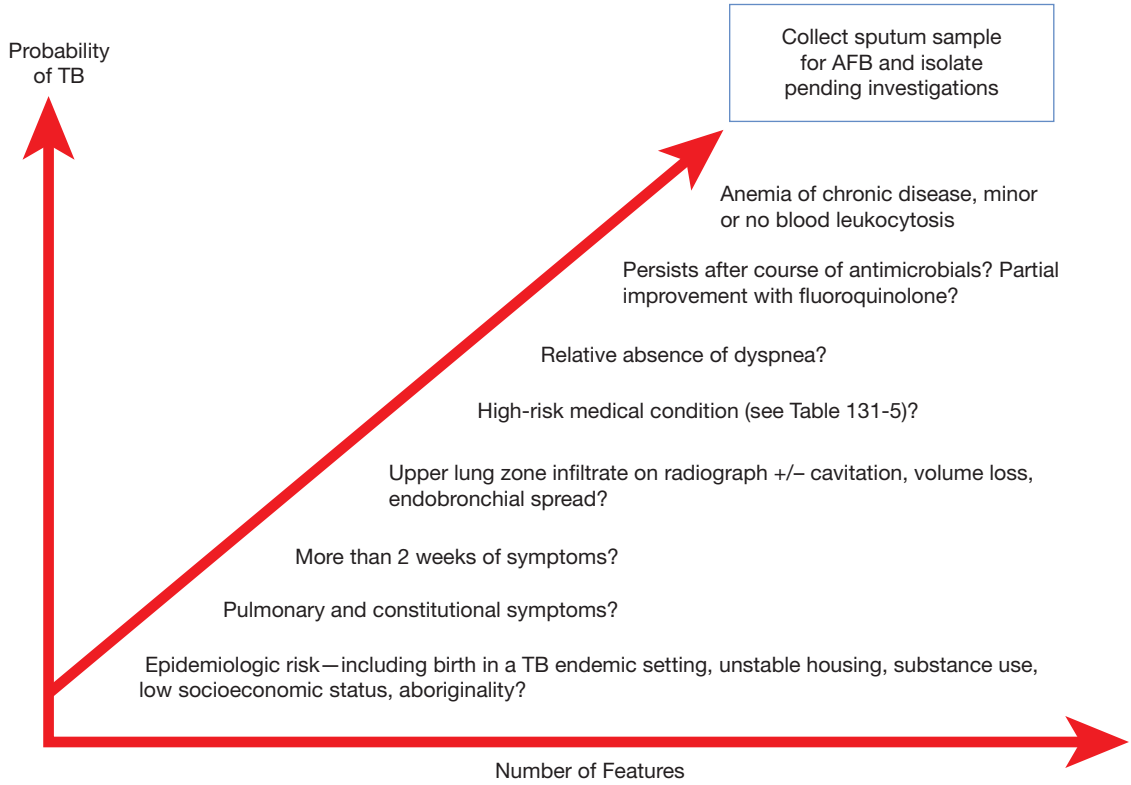

Figure 131-11 Clinical factors increasing index of suspicion for tuberculosis. Increasing probability of TB warrants further investigation, especially collection of respiratory samples for mycobacterial stain and culture. For hospitalized patients, or those in congregate living settings, increasing suspicion warrants prompt isolation pending results of investigations. *(Used with permission of Richard Long, unpublished observations).*

However, sputum-smear microscopy has well-known limitations. Sensitivity for pulmonary TB is only about 60% to 70%, and even lower in extrapulmonary specimens and in those with HIV coinfection. That NTM also stain acid-fast lowers the specificity of smear microscopy.[119–121] In low TB prevalence settings, NTM are recovered from about 30% to 50% of AFB smear–positive sputum samples.

Mycobacterial Culture

Mycobacterial culture remains the gold standard for the diagnosis of active TB. About 5000 to 10,000 bacilli per milliliter of specimen are required for detection by smear microscopy and about 100 bacilli per millimeter for nucleic acid amplification (NAAT); culture methods can detect as few 10 viable bacilli per millimeter of sample.[94] In addition, biochemical and phenotypic testing of isolated organisms provides near perfect specificity, distinguishing even between individual members of the MTBC. Of particular importance, isolation of the infecting organism permits DST and is required to conduct molecular subtyping (i.e., DNA fingerprinting).

Culture of MTBC from clinical specimens takes, on average, between 2 to 4 weeks, but as long as 8 weeks in some specimens with low initial concentration of organism.[122] Culture requires a Level III biosafety laboratory to prevent transmission to laboratory technicians and availability of such facilities is poor in most high-burden, resource-limited settings.

Nucleic Acid Amplification

NAAT is a useful tool in the diagnosis of TB offering higher sensitivity than microscopy and shorter turn-around-times than culture.[100,123,124] Sensitivity of NAAT in AFB smear–positive respiratory samples is excellent, usually greater than 95%.[123] However, in paucibacillary specimen types, such as AFB smear–negative sputum and extrapulmonary samples, the sensitivity is reduced to 40% to 60%, with a negative predictive value inadequate to exclude a diagnosis of TB.[125–129] Specificity of NAAT methods is very high, ranging between 90% and 100% for all specimen types.

Performance of traditional NAAT requires sophisticated laboratory facilities. Recently, an automated in-cartridge assay (Xpert/MTB-RIF [Cepheid, Sunnyvale, California]) was developed to allow NAAT directly from unprocessed clinical specimens, without the need for centralized reference laboratory, even in resource-limited settings.[130–132] The Xpert/MTB-RIF simultaneously detects mutations within the mycobacterial RNA-polymerase gene that correlate with rifampin-drug resistance, thus identifying MDR cases several weeks before culture-based testing. The WHO has signaled its intent to deploy this tool in high-burden, resource-limited settings throughout the world.[132]

Testing for Latent TB infection

There are two main tests for the identification of LTBI: (1) Tuberculin skin test (TST) and (2) IFN-γ release assays (IGRAs). Both are indirect, in that they evaluate the presence of host cell–mediated immunity rather than detect actual mycobacterial organisms or antigens.[133] As such, neither can distinguish active disease from latent infection. Both tests have very poor sensitivity and predictive value for active TB and use in this context is discouraged.[134,135] These tests are better used to assess candidates for LTBI treatment (discussed below).

MANAGEMENT OF ACTIVE TB

Prior to the availability of chemotherapy, prevailing wisdom prescribed fresh air, nutrition, sunlight, and rest for treatment of TB. In 1947, clinical outcomes of smear-positive pulmonary TB patients treated at a sanatorium in the United Kingdom were recorded: within 4 years of entry, 55% died, 20% remained chronically affected, and 25% experienced remission.[136] With the discovery of chemotherapy for TB, mortality dropped orders of magnitude and within a decade TB sanatoria were shuttered.[6,137]

TABLE 131-7 Drug Regimens for Treatment of Active Tuberculosis in Adults, Caused by Susceptible Organism

	Initial Phase (First 2 Mo)	Continuation Phase	Comments
Regimen 1	INH + RIF + PZA + EMB[a] Given daily or 5×/wk	4 mo INH + RIF Given daily or 3×/wk[b]	Extend continuation phase to 7 mo if risk of relapse present[c]
Regimen 2	INH + RIF + EMB[a] Given daily or 5×/wk	7 mo INH + RIF daily or 3×/wk	This "PZA-free" regimen can be used if risk factors for hepatotoxicity[d] or in pregnancy
Regimen 3	INH + RIF + PZA+EMB[a] Given 5×/wk for first 2 wk then ×wk for next 6 wk[e]	4–7 mo INH + RIF Given 3×/wk	Intermittent therapy should always be provide as DOT[e]
Regimen 4	INH + RIF + PZA + EMB[a] Given daily or 5×/wk	4 mo RPT weekly and INH 900 mg weekly	Not eligible for this regimen if cavitary disease, positive sputum cultures at 2 mo, or if HIV+

[a]*EMB is given pending results of INH susceptibility testing—if isolate confirmed fully susceptible than EMB is discontinued.*
[b]*Rifapentine and INH 900 mg given once-weekly in the continuation phase have been tested in small clinical trials but treatment outcomes were inferior and rifamycin resistance emerged on treatment in some patients; thus this schedule is probably best avoided.*
[c]*Risk factors for relapse include cavitation on chest radiograph, culture positive after 2 mo of therapy, poorly controlled HIV infection.*
[d]*Risk factors for PZA hepatotoxicity include advanced age or underlying liver disease.*
[e]*Intermittent therapy during the intensive phase is associated with slightly poorer treatment outcomes in patients with extensive disease or HIV coinfection. See text for adjunctive corticosteroid use recommendations.*
Source: Data from Blumberg H, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603–662 and Zumla A, Raviglione M, Hafner R, von Reyn CF. Tuberculosis. N Engl J Med. 2013;368(8):745–755.

■ PRINCIPLES OF TB THERAPY

The aims of TB therapy are to (1) Interrupt transmission by rapidly rendering patients noninfectious, (2) relieve symptoms and prevent mortality, (3) prevent the emergence of drug resistance, and (4) prevent future relapse by providing a definitive cure.

To achieve these aims, treatment regimens must include combination of potent bactericidal drugs which are provided for a minimum of 6 months. The choice of regimen should be guided by the results of DST. TB regimens are divided into an initial intensive phase, designed to quickly reduce large bacillary burden, followed by a prolonged continuation phase that consolidates antimycobacterial killing while allowing intermittent dosing and lower pill-burden. A high level of adherence is required to prevent relapse and emergence of resistance. Rifamycins have a critical role in preventing relapse and whenever possible should be provided throughout the treatment. Several randomized clinical trials have established standardized treatment regimens as outlined in Table 131-7. Reported success rates with these regimens approach 95%.[138–140]

■ FIRST-LINE TB DRUGS

Current first-line TB drugs include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (see Table 131-8).

TABLE 131-8 TB Drug Dosing and Important Adverse Reactions

Drug[a]	Daily Dose (Maximum Dose)	Thrice-Weekly Dose	Renal Dose: for IHD or eGFR <30 mL/min	Selected Adverse Events
Isoniazid (INH)	5 mg/kg (300 mg)	10 mg/kg (600)	No change	Hepatotoxicity Peripheral neuropathy
Rifampin (RIF)	10 mg/kg (600 mg)[b]	10 mg/kg (600 mg)[b]	No change	Thrombocytopenia Drug–drug interactions[c]
Rifapentine (RPT)	—	10 mg/kg (600 mg), given once-weekly	No change	Drug–drug interactions
Pyrazinamide (PZA)	20–25 mg/kg (2000 mg)	30–40 mg/kg (4000 mg)	25–35 mg/kg 3×/wk	Hepatotoxicity Hyperuricemia Arthralgia
Ethambutol (EMB)	15–20 mg (1600 mg)	25–35 mg/kg (2400 mg)	15–25 mg/kg 3×/wk	Optic neuritis
Moxifloxacin or Levofloxacin	400 mg 750–1000 mg	NS	No change; 750 mg 3×/wk	GI upset QT prolongation Insomnia Tendinopathy

NS, not yet studied; IHD, intermittent hemodialysis.
[a]*All drugs are provided orally; however, INH, RIF, and the flouroquinolones are available as intravenous formulations.*
[b]*Higher doses of rifampin are well tolerated and perhaps more efficacious; ongoing trials are examining higher dosing schedules.*
[c]*Drug–drug interactions mediated mostly through cytochrome p450–3a4 enzyme induction.*
Source: Data from Blumberg H, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603–662 and World Health Organization & Initiative, S.T., 2010. The treatment of tuberculosis guidelines. 4 ed. Geneva.

INH, first introduced in 1952, remains a cornerstone of TB treatment. It has potent bactericidal activity and effects rapid decline of sputum bacillary load within days of administration and thus rapidly reduces infectiousness.[141] INH is generally well tolerated but can cause hepatotoxicity, requiring cessation of therapy in a small subset of patients. Risk factors for severe INH-related hepatotoxicity include older age and pre-existing liver diseases.[142] Peripheral neuropathy can develop in elderly, malnourished, or diabetic patients taking INH, but this risk is lowered with concomitant administration of pyridoxine (vitamin B6).

RIF revolutionized TB therapy following its introduction in 1968 and has since become a critical component of modern, short-course TB regimens.[141,143,144] Rifampin and other rifamycins appear to have unique relapse-preventing properties that allow the duration of chemotherapy to be shortened to 9 months or less. In the absence of rifampin, relapse rates are unacceptably high, and treatment must be given more than 18 months.

RIF is very well tolerated in the vast majority of patients. Rarely, hypersensitivity reactions occur, including thrombocytopenia, flu-like syndrome, and neutropenia. Rifampin is a strong inducer of the cytochrome p450 oxidation system (CYP450) and interacts with a multitude of other medications.[145] Rifampin produces a benign orange-red discoloration of body fluids (urine, tears, sputum, feces, sweat) and can permanently stain contact lenses and dentures.

Rifapentine (RPT) is also a rifamycin but with a half-life 5 times longer than RIF, which allows the drug to be given once-weekly. The prolonged half-life makes RPT an attractive agent for use in intermittent treatment regimens in order to facilitate adherence.[146] However, use of weekly dosed RPT is associated with relapse and acquired resistance in those with extensive disease, slow sputum culture conversion, or HIV coinfection.[146–148] RPT strongly induces CYP450 leading to multiple potential drug–drug interactions. Other rifamycins (e.g., rifabutin) produce lower levels of CYP450 induction. RPT is generally well tolerated but hypersensitivity syndromes including fever, myalgia, and cytopenias occurred in about 3% of patients in a clinical trial of LTBI treatment.[149]

PZA is bactericidal and when added to treatment regimens containing RIF permits shortening duration to 6 months.[150] Arthralgias are the most frequently reported adverse event and can be alleviated by the administration of nonsteroidal anti-inflammatories. PZA can also cause severe hepatotoxicity, especially in the elderly and those with pre-existing liver disease.

EMB is the weakest first-line agent, contributing little to early bactericidal activity or to relapse prevention. However, it is effective in preventing the emergence of resistance to isoniazid. It is generally well tolerated. Optic neuritis, the main adverse drug event, occurs infrequently with the currently recommended dosages except in the presence of renal impairment. EMB is added to the initial phase of treatment regimens pending results of susceptibility testing; but absent confirmed drug-resistance, EMB is discontinued.

Later-generation fluoroquinolones (FQs) are well-tolerated oral drugs with potent bactericidal activity against MTBC.[151–155] Based on accumulating clinical evidence, FQs may enter first-line treatment regimens in the near future.[156] However, FQs are currently indicated for intolerance or resistance to other first-line drugs.[157]

FQs are not uncommonly prescribed for CAP that later proves to be pulmonary TB.[158] FQ monotherapy can temporarily alleviate TB symptoms and can reduce the yield of TB sputum cultures, thus significantly contributing to diagnostic delay.[159] Inadvertent monotherapy of TB initially mistaken for CAP also risks the development of FQ resistance, potentially compromising future TB treatment options.[158] FQs should be used cautiously for suspect CAP in patients at significant epidemiologic risk for TB.

ADJUNCTIVE CORTICOSTEROID USE

Treatment of TB is occasionally complicated by paradoxical treatment responses whereby clinical deterioration develops a few weeks into an otherwise effective treatment.[160,161] The response is characterized by a robust inflammatory reaction, typically at the site of initial disease, without apparent microbiologic failure or bacillary replication. The paradoxical response is most commonly observed in extrapulmonary disease.[162] Paradoxical responses are typically self-limited, even when TB treatment is continued. Symptomatic benefit is sometimes observed following a brief course of corticosteroid treatment.[161] Important differential diagnostic considerations of paradoxical responses that should be excluded prior to treatment with corticosteroids include treatment nonadherence, inadequate dosing, drug malabsorption, or drug-resistant TB.

For disease of the pericardium and the CNS, the consequences of a paradoxical response are potentially life threatening including increased intracranial pressure and constrictive pericarditis, respectively. Meta-analyses have suggested an appreciable benefit to simultaneous initiation of corticosteroids along with TB treatment for these forms of TB.[163–165] The regimens tested in the clinical trials varied but 40 to 80 mg of prednisone per day for 6 to 12 weeks is a common prescription.

DIRECT OBSERVATION OF THERAPY

Direct observation of therapy (DOT) ensures adherence, thus improving treatment outcomes and preventing emergence of resistance.[166] Because physicians are poor at predicting which patients will adhere to therapy, DOT is recommended for all patients.[138]

INTERMITTENT DOSING

Direct supervision of therapy by healthcare workers is facilitated by intermittent treatment regimens (e.g., 5 days per week, or Monday—Wednesday–Friday or even twice-weekly). Intermittent dosing schedules take advantage of the slow growth of MTBC and the postantibiotic effect of TB drugs.[167,168] However, acquired drug resistance has been documented with intermittent dosing schedules, especially in patients with extensive disease or poorly controlled HIV coinfection.

TREATMENT MONITORING

Bacteriologic monitoring (e.g., monthly sputum cultures until negative) is the preferred method of follow-up for pulmonary TB cases. A persistently positive sputum culture 2 months after starting effective treatment is a marker for relapse and treatment extension is suggested. Culture positivity at 3 months is highly suggestive of treatment failure and patients must be carefully evaluated to identify potential causes (e.g., nonadherence, malabsorption, acquired resistance, drug–drug interactions). Treatment failure is defined as persistently positive cultures 4 months into treatment.

ADVERSE EFFECTS

Severe side effects necessitating drug discontinuation are rare with standard TB treatment regimens. A commonly encountered adverse event is drug-related hepatotoxicity.[138,142] Transient, mild elevation in liver enzymes early in the course of therapy occurs in about 20% of patients and is usually inconsequential, usually resolving without intervention and without treatment interruption. However, for patients with symptomatic and/or marked elevation of transaminases (above 3–5× the upper limit of normal) treatment should be immediately discontinued and drugs cautiously reintroduced one at a time under close monitoring once the liver enzymes and function has returned to normal.

DRUG-RESISTANT TB

Drug resistance to any of the first-line TB drugs occurs in about 8% of TB cases in the United States.[41] Mono-resistance to INH, the most

TABLE 131-9 Hierarchy of Second-Line TB Drugs

Group		Drugs
Group 1	First-line oral—bacteriocidal	PZA, Ethambutol, Rifabutin
Group 2	Injectable agent	Amikacin, Kanamycin, Capreomycin
Group 3	Fluoroquinolones	Moxifloxacin, Levofloxacin, Gatifloxacin, Ofloxacin
Group 4	Second-line oral (BD-TID)—bacteriostatic	Ethionamide, PAS, Cycloserine
Group 5	Agents with unclear efficacy	Linezolid, Clofazimine, Clarithromycin, INH 900 TIW, Amoxicillin-clavulanate, Imipenem–Cilistatin

TIW, three times weekly.
Treatment regimens for MDR-TB should be guided by drug-susceptibility testing. Typically use between 4 and 6 agents with predicted activity. Wherever possible a fluoroquinolone and injectable agent should be used initially. The lower the group number, the more preferred are the drugs on the basis of efficacy and anticipated tolerability.
Source: Data from Drug-resistant Tuberculosis: a Survival Guide for Clinicians, 2nd ed. Curry National Tuberculosis Center; 2008.

common resistance pattern observed, does not appear to compromise TB treatment outcomes substantially as long as RIF, EMB, and PZA can be continued throughout.[138,169–171] Although definitive data are lacking, an FQ can probably replace INH in standard treatment regimens.

Multidrug resistance was demonstrated in less than 1.6% of all TB cases in the United States in 2012.[41] Among patients with a history of previous TB treatment, MDR-TB prevalence was 8.2%. The majority (86%) of MDR-TB cases in the United States occur in foreign-born individuals. Multidrug resistance has a great impact on treatment outcomes in TB, with success rates ranging from 52% to 77%.[172–176] Multidrug resistance also adds substantially to the costs of treatment.[32,177] Further, second-line agents used in treatment of MDR-TB have significant toxicities, high rates of intolerance, high-pill burdens, and inconvenient dosing regimens, making adherence difficult.[178] Finally, MDR-TB requires at least 18 to 24 months duration.[15,179,180] The management of MDR-TB is complex and referral to specialized centers that offer experience and expertise is strongly recommended. Second-line TB agents and important side effects are listed in Tables 131-9 and 131-10.

Several promising new drugs with novel mechanisms of action are in clinical development.[181] Bedaquiline and delamanid have each proven efficacious in phase 2b trials but demonstration of safety is pending larger trials.[182–184] PA-824, SQ-109, and sutezolid have also shown efficacy in small clinical studies and appear ready for further clinical development.[179,185] Linezolid, an oxazolidinone commonly used in treatment of resistant gram-positive infections, has been shown to be effective for the treatment of MDR-TB in controlled trials but treatment-limiting toxicities are common with prolonged durations.[186]

■ TREATMENT ISSUES IN SPECIAL POPULATIONS

Treatment considerations in two special patient populations—those coinfected with HIV and solid organ transplant recipients—are discussed below.

HIV Coinfection

Standard regimens used for the treatment of TB in HIV-uninfected individuals have similar efficacy in HIV-infected individuals, provided these patients are also effectively treated with antiretroviral therapy (ART).[187] However, the addition of ART to TB treatment can result in overlapping drug toxicity and intolerances including peripheral neuropathy, hepatotoxicity, and GI upset. Potent bidirectional drug–drug interactions between rifampin and several classes of antiretroviral drugs can amplify toxicity and undermine HIV virologic control. A number of studies have also found reduced serum concentrations of TB drugs in patients coinfected with HIV, thought to be due to decreased gastrointestinal absorption.[188] In turn, low serum drug concentrations may increase the risk of treatment relapse or acquired rifamycin resistance. Intermittent RPT in the continuation phase is associated with higher relapse rates in HIV-infected individuals and should be avoided.[146]

Successful HIV treatment with ART leads to immune reconstitution and, in patients with concurrent active TB, restores the host inflammatory response to TB infection. This can clinically present as transient worsening of TB disease a few weeks following initiation of ART (a phenomenon known as immune reconstitution inflammatory syndrome or TB-IRIS). TB-IRIS can occur following ART initiation in patients already on treatment for TB (paradoxical type) or in patients with previously undiagnosed TB (unmasking type). TB-IRIS produces significant morbidity, occasionally requiring glucocorticoid therapy for symptom control.[189] However, in patients diagnosed simultaneously with HIV and TB, treatment outcomes, relapse rates, and overall mortality are greatly improved when ART is added early, within a few weeks of initiating TB treatment, even if this strategy noticeably increases risk of TB-IRIS.[190,191]

TABLE 131-10 Second-Line TB Drugs and Selected Toxicities

Agent	Common and/or Important AEs	
Ethionamide (take with B6)	GI upset	Hypothyroidism
		Hepatotoxicity
		Neuropathy
PAS (p-aminosalicylic acid)	GI upset (less with PASER formulation)	Hypothyroidism
		Hepatotoxicity
Cycloserine (take with B6)	Headache	Neurologic and psychiatric impairment
Amikacin	Nephrotoxicity	Ototoxicity
Linezolid	Cytopenia	Irreversible and reversible
	MAO inhibition	Neuropathy and optic neuritis
Moxifloxacin	Nausea, GI upset	Tendinopathy
Capreomycin	Nephrotoxicity	Ototoxicity, Neuropathy

Source: Data from Drug-resistant Tuberculosis: a Survival Guide for Clinicians. 2nd ed. Curry National Tuberculosis Center; 2008.

Solid-Organ Transplantation

The majority of TB cases in solid-organ transplant recipients arise from reactivation of latent infection acquired prior to transplantation.[192] Donor-derived TB transmitted with organ transplantation is very rare. Overlapping drug toxicity and significant drug–drug interactions complicates treatment of TB in transplant recipients.[193] Rifampin significantly lowers serum drug concentrations of immunosuppressant medications, which can precipitate organ rejection. Rifabutin, a rifamycin with less CYP450 activity than either RIF or RPT, has good activity against MTBC and can be used instead of RIF in standard TB regimens, albeit with a less robust evidence base.[194,195] Liver transplant recipients are particularly prone to INH and PZA hepatotoxicity and alternative treatment regimens may be required.[196]

TARGETED TESTING AND TREATMENT OF LATENT TB INFECTION

The use of anti-TB drugs in latently infected patients to prevent subsequent progression to active disease was first reported in the early 1950s.[197] Dozens of controlled clinical trials subsequently confirmed that isoniazid reduced the risk of TB in those with positive TST by 60% to 90%, depending on the level of adherence.[198–200] An estimated 4% of the US population is latently infected[201] but currently available tests do not reliably predict which infected individuals will eventually develop active disease.[202] Furthermore, up to 5% of those treated for latent infection will experience an adverse event, rarely this can be severe hepatotoxicity and fulminant hepatic failure.[142,203,204] Thus, the decision to treat LTBI must be individualized, balancing the risk of developing active TB against the potential for adverse events.

■ DIAGNOSIS OF LTBI

The diagnosis of latent TB infection hinges on a positive TST and/or IGRA (discussed above). Once infected with MTBC, it is believed that the potential for reactivation persists for the lifespan of the host.

■ TUBERCULIN SKIN TEST

The TST is more than 100 years old.[205] The most commonly used method for administering the TST is the Mantoux technique: Here, 5 tuberculin units of purified protein derivative (PPD) from *M. tuberculosis* are injected intradermally on the inner surface of the left forearm. In those individuals with cell-mediated immunity to PPD, a delayed type hypersensitivity (DTH) response will occur, manifest as a circular indurated skin reaction arising at the site of injection 48 to 72 hours later.

Several factors can undermine the predictive value of the TST for latent TB infection.[133] Potential causes of false-negative reactions include immune compromise, malnutrition, chronic renal failure, improper administration, and expiration of tuberculin.[204,206] TB disease itself reduces test sensitivity, with up to 25% of TB cases TST negative. The TST is also prone to false-positive reactions. PPD is a relatively crude extract of mycobacterial antigens, many of which are conserved between mycobacterial species. Sensitization to PPD can develop after routine exposure to environmental NTM or following previous vaccination with BCG.[133]

Although technically simple, significant training and expertise is required for reliable test performance and interpretation. Roughly speaking, the larger the reaction size, the more likely latent TB infection. The predictive value of the test varies by prevalence of LTBI and immunocompetence and different reaction size criteria are used to define positivity in different populations[204] (see Table 131-11).

■ INTERFERON-γ RELEASE ASSAYS

IGRAs are in vitro blood tests of CMI response; they measure T-cell release of IFN-γ following stimulation by synthetic peptide antigens specific to *M. tuberculosis*.

TABLE 131-11 Interpretation of Tuberculin Skin Test

TST—Reaction Size (mm)	Situation Where This Reaction is Considered Positive (i.e., Indication for Treatment of LTBI)
0–4	LTBI treatment not generally indicated
	Children <5 y who are recent close contacts should start INH pending repeat TST performed 8 wk from last contact
≥5	HIV infection
	Recent close contact of infectious case
	Fibrotic changes on chest X-ray consistent with old TB (but not previously treated)
	Organ transplantation
	Other immunosuppressed patients (TNF-α, chemotherapy, glucocorticoids[a])
≥10	Other high-risk conditions—silicosis, diabetes, malignancy,[b] underweight, CKD requiring dialysis
	Children less than 4 y of age
	Recent immigrants from TB endemic countries (>125 per 100,000 incident TB cases per year) within past 5 y
≥15	Healthy, low-risk reactor[c]

CKD, chronic kidney disease.
[a]Glucocorticoids at doses >15 mg/d prednisone equivalent for at least 1 month.
[b]Lymphoproliferative disease, head and neck and lung neoplasm.
[c]Healthy low-risk reactors may not require LTBI treatment as risk of treatment related toxicities may outweigh clinical benefit.
Source: Data from Horsburgh CR, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364(15):1441–1448.

Replacing the mixture of antigens contained in PPD with specific synthetic peptides greatly improves the specificity of IGRAs compared to TST, especially in populations previously vaccinated with BCG.[207,208] The sensitivity of the IGRA is comparable to the TST, even in immunocompromised hosts, although the absence of a gold standard makes precise estimation difficult.[209–211]

IGRA appear less reproducible on repeated testing than is TST, especially when values of IFN-γ release are near the quantitative threshold for reporting positive (i.e., borderline positive).[212] This can result in spontaneous conversions and reversion on serial testing of the same individual, with uncertain clinical implications.[213]

There are two currently approved IGRA tests available in the United States: the QuantiFERON-TB Gold In-Tube assay (Cellestis Limited, Australia) and the T-SPOT.TB assay (Oxford Immunotec, United Kingdom).

■ WHICH TEST TO USE IN LTBI

Either the TST or the IGRA are acceptable for the diagnosis of LTBI.[135] The improved specificity of IGRAs, and the need for a single patient visit, make this test attractive. IGRAs are associated with high testing costs and require laboratory infrastructure and significant technical expertise. The improved specificity of the IGRA might reduce the number of candidates for LTBI treatment but whether this translates to cost-effectiveness is controversial.[214] TST is preferred for serial testing, for example of healthcare workers repeatedly exposed to infectious TB, a setting where the IGRA performance has not been defined. Use of both tests simultaneously, where a positive result on either the TST or the IGRA signals latent

infection, may help improve sensitivity of LTBI screening in those with compromised immunity.[214,215]

■ DECISION TO TREAT LTBI

The first step in deciding whether to treat for LTBI is to assess the likelihood that a positive TST or IGRA represents true TB infection. Both tests perform poorly in low-prevalence populations and a true positive result is much more likely in those exposed to active TB or from high-risk epidemiologic groups such as foreign-born, travelers to TB endemic countries, homeless, and incarcerated populations.

The second step is to estimate likelihood of progression to active TB if actually infected[211] (see Table 131-2). The third step is to evaluate potential risks for adverse reactions to treatment. The main adverse effect of LTBI treatment is INH-related hepatotoxicity. The strongest predictor of hepatotoxicity is age. Those younger than 20 years old have less than a 0.1% chance of hepatotoxicity during LTBI treatment, whereas those over 65 years are exposed to a risk around 2% to 5%. An internet-based calculator is available to assist in balancing these probabilities and informing treatment decisions.[216]

Treatment of LTBI has only been demonstrated to be effective in those with a positive TST or IGRA. Several clinical trials have failed to demonstrate a benefit of treatment in immunocompromised individuals at risk but with a negative TST or IGRA.[217,218]

Before the treatment of LTBI is started, active disease must be excluded carefully by means of history, physical examination, chest radiography, and sputum culture, in order to avoid inadvertent monotherapy of active TB that could lead to resistance.

■ TREATMENT FOR LTBI

The best studied treatment of LTBI is self-administered INH taken daily for 9 months.[200,219] Other acceptable regimens are shown in Table 131-12. Shorter treatment regimens for LTBI typically result in improved completion rates. Intermittently dosed regimens have less supporting efficacy data but might be used in settings where adherence to unsupervised treatment is expected to be poor. Contacts of INH-monoresistant cases can be offered 4 months of RIF daily. Contacts of MDR-TB can be offered therapy with an FQ daily for 9 months although data are limited.

Patients receiving LTBI treatment should be monitored at least monthly for clinical symptoms of hepatitis. They should also be educated about the symptoms of hepatitis and instructed to stop the medication immediately and seek prompt evaluation to reduce risk for progression to severe disease.

TB VACCINATION

Laboratory attenuation of *M. bovis* by repeated sub-cultivations in bile acids by French researchers Albert Calmette and Camille Guerin eventually led to the creation of a TB live-attenuated vaccine BCG in 1928.[220,221] This vaccine is rarely used in the United States today, but worldwide remains one of the most commonly delivered childhood vaccines with coverage rates approaching 100% in most resource-limited settings. Despite its wide use, there remains some controversy as to its actual efficacy, and some concern that ongoing sub-culture to produce the vaccine is resulting in loss of activity.[222] Disseminated infection with BCG has been documented in severely immune-compromised children and universal vaccination is therefore no longer recommended in low-prevalence settings.[223] In the Unites States, BCG is perhaps more commonly encountered as a therapeutic agent for management of bladder transitional cell carcinoma. Disseminated TB has been documented in this patient group but human-to-human transmission is not reported.[224,225]

Ongoing research is directed toward a vaccine to replace BCG, ideally with improved efficacy against both infection and progression to TB.[226] However, after millennia of coevolution, the host–pathogen relationship is extremely complex and inadequate understanding of TB immunity and correlates of protection hamper progress in vaccine development.

CONCLUSION

TB has become an uncommon cause of cough in the United States and a high index of suspicion is required. Diagnostic delay occurs frequently despite availability of accurate diagnostic technologies. In settings of chronic medical illness, immunocompromise, and social depravation, TB can flourish. Treatment is effective and can significantly reduce a high case-fatality rate. Current research is directed to shortening the duration of therapy to facilitate adherence and treatment completion rates. New drugs are being developed and promise

TABLE 131-12 Acceptable Dosing Regimens for Treatment of Latent Tuberculosis Infection

Regimen	Adult Dosing (Oral)	Mode of Administration	Evidence Base
Isoniazid[a]	300 mg daily 9 mo	SAT	Strong evidence, based on several RCTS (Siamera, 2000); Higher efficacy with 9 mo
	300 mg daily 6 mo	SAT	
Isoniazid plus rifampin	Isoniazid 300 mg and rifampin 600 mg daily for 3 mo	SAT	Strong evidence (HKCS, 1992 Ena 2005; Whalen, 1997)
Rifampin	600 mg daily for 4 mo	SAT	Moderate evidence (HKCS, 1992; Menzies, 2008), 1 Cohort (Villarino, 1997)
Isoniazid Intermittent	900 mg 2×/wk 6–9 mo[b]	DOT	Weak evidence (Mwinga, 1998)
Isoniazid and Rifampin Intermittent	Isoniazid 600 mg and rifampin 600 mg twice-weekly for 3 mo	DOT	Weak evidence (McNab, 2000)
Isoniazid and Rifapentine Intermittent[c]	Isoniazid 900 mg and rifapentine 900 mg each weekly for 12 wk, each dose directly observed	DOT	Moderate evidence (Sterling, 2011; CDC/ATS, 2011)

SAT, self-administered treatment; DOT, directly observed treatment.

[a]Pyridoxine supplementation (25–50 mg daily) often provided to prevent INH-associated peripheral neuropathy, especially if risk factors including alcohol use disorder, diabetes, malnutrition, uremia, and HIV infection.

[b]Twice-weekly regimens should be provided under direct observation.

[c]This regimen not tested in children or pregnant women or those infected with HIV; the only trial of this regimen provided as DOP.

Source: Data from Blumberg H, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603–662; and Horsburgh CR, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364(15):1441–1448.

to improve outcomes in MDR disease. Ongoing national surveillance and funding of TB control programs is required to maintain low TB incidence in the United States. However, given that an increasing proportion of TB is imported, further reduction in TB incidence will ultimately require investment in TB control globally. Even in the wealthy countries of the West, TB is not conquered but continues to smolder, threatening reemergence where social injustice prevails and where the vigilance of TB control programs is relaxed.

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CHAPTER 132

Diseases due to Nontuberculous Mycobacteria

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Nontuberculous mycobacteria (NTM) are ubiquitous in our environment so that exposure to these organisms is universal and unavoidable.[1] Unlike traditional tuberculosis, most of the approximately 150 currently identified NTM species are either nonvirulent or have low virulence for humans. The prevalence of NTM is rising in the United States, with many epidemiologic reports suggesting that NTM lung disease has surpassed tuberculosis.[2,3] Clinicians are encountering NTM infections with increasing frequency and a general knowledge of common pathogens and diagnostic criteria are essential for the care and successful treatment of these individuals.

Prior to the AIDS epidemic, most NTM cases presented as indolent, cavitating pulmonary infections in persons with underlying lung diseases such as chronic obstructive pulmonary disease (COPD) or previous tuberculosis. During the 1980s, infections due to the more common NTM (*Mycobacterium avium*, some *M. kansasii,* some unclassified) emerged as complications of acquired immunodeficiency syndrome (AIDS). *M. avium* and *M. intracellulare* were termed *M. avium* complex or MAC infections.[4,5] Subsequently, a syndrome of predominantly mid–lung zone bronchiectasis with MAC pulmonary infection was described in otherwise healthy middle-aged women, many with distinct body morphotypes including scoliosis, pectus excavatum, and mitral valve prolapse.[6,7] This syndrome is often referred to as Lady Windermere syndrome.[8] Mycobacterial infections after solid-organ and hematopoietic transplantation have also increased in frequency, reflecting both increased exposure and/or improved diagnostic methods, and almost universal use of central venous access devices.[9] In the absence of mandatory infection reporting, the true incidence of positive cultures or NTM disease in the general population and transplant recipients in the United States can only be estimated.

ORGANISMS AND DEVELOPMENT OF DISEASE

The microbiology, epidemiology, and pathogenesis of nontuberculous mycobacterial infections are considered below.

MICROBIOLOGY

Almost 150 NTM species have now been identified and speciated. The increased number of species reflects improved microbiologic techniques for isolating NTM from clinical specimens and the use of 16 S rRNA gene sequencing as a standard for defining new species.[10,11] To simplify understanding of these organisms, particularly as applied to clinical circumstances, they often are grouped into complexes of closely related species. The *M. avium* complex, for example, consists of multiple species, with the most frequent being *M. avium and M. intracellulare.* Certain species, such as *M. kansasii* are associated with human disease more often than others and are presumed to be more virulent while species such as *M. gordonae*, *M. terrae complex,* and *M. mucogenicum* most often represent contamination of the respiratory tract from exposure to tap water.[12]

A number of important considerations in the laboratory evaluation should be recognized:

1. Clinicians must be aware that these organisms may be present and request mycobacterial cultures in appropriate specimens. The Gram stain will not adequately detect mycobacteria. The preferred staining procedure is the fluorochrome method, although the Ziehl–Neelsen method and Kinyoun stain are less sensitive alternatives. NTM are often more sensitive to the acid-fast decolorization procedure.
2. Some specific guidelines have been adopted to avoid potential sources of contamination, especially tap water, in specimen collection. Mouth rinsing or brushing of teeth before collection should not be done. Specimens should be submitted without fixatives. Refrigeration of samples at 4°C should be used if transportation to the laboratory is delayed for over 1 hour.
3. Specimens should be cultured using both liquid and solid media. Species that are often associated with cutaneous and lymph node disease may require special growth conditions and/or lower incubation temperatures (28–32°C), including *M. haemophilum, M. genavense, M. marinum* and the rapidly growing mycobacteria (RGM). Methods for the isolation of NTM in clinical laboratories have been approved by the Clinical and Laboratory Standards Institute (CLSI).[13]
4. Molecular testing is used primarily (initially) to distinguish *M. tuberculosis* from NTM species. DNA probes exist for the most commonly encountered slowly-growing NTM species (*M. avium* complex or MAC, *M. avium, M. intracellulare, M. kansasii*, and *M. gordonae*). There are no probes for rapidly growing species such as *M. fortuitum* or *M. abscessus*.
5. NTM should be identified to the species level.
6. American Thoracic Society (ATS) guidelines and CLSI recommend that routine susceptibility testing be limited for MAC isolates to the macrolides (clarithromycin) and for *M. kansasii* isolates rifampin and clarithromycin.[12,13] For less frequently isolated, slowly growing mycobacteria such as *M. simiae, M. xenopoi,* etc. more extensive testing is recommended.[13]
7. For rapidly growing mycobacteria, in particular *M. fortuitum, M. abscessus, M. chelonae*, isolates should be tested against a more extended array of antibiotics including amikacin, imipenem, and clarithromycin.

Respiratory Specimens

To establish the diagnosis of NTM lung disease, sputum is often induced with 7% hypertonic saline or collected via bronchoscopy (Table 132-1). Alternatively, three expectorated specimens may be collected on different days. Respiratory specimens can be shipped to the laboratory by mail using standard shipping guidelines for laboratory samples. Lung biopsy or other tissue (e.g., lymph node) biopsy specimens can also be used for cultures.

EPIDEMIOLOGY AND PATHOGENESIS

NTM are ubiquitous in the environment, often isolated from soil and water, including household water sources. There is increasing concern that biofilms that form in municipal and household water supplies may be a significant harbor of NTM.[14–16] *M. avium*, *M. kansasii*, *M. simiae*, and *M. xenopi* are readily recovered from tap water in areas where these species are common. There has been no documentation of animal-to-human and rarely human-to-human transmission of NTM, including highly susceptible hosts (e.g., those with cystic fibrosis).[17–23]

NTM may cause both asymptomatic infection and symptomatic disease in humans. NTM are often detected in asymptomatic patients awaiting organ transplantation with diffuse nodular or interstitial lung disease. Skin test studies in adults indicate that a substantial proportion have had prior infection with NTM, notably in the southeastern

TABLE 132-1 Clinical and Microbiologic Criteria for Diagnosing Nontuberculous Mycobacterial (NTM) Lung Disease

Clinical (both required)

1. Pulmonary symptoms

   And

2. Radiographic abnormalities—nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography scan that shows multifocal bronchiectasis multiple nodules

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples

   Or

2. Positive culture result from at least one bronchial wash or lavage

   Or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

Source: Adapted with permission from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An Official ATS/IDSA Statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367–416.

TABLE 132-2 Common Treatment Regimens for MAC

Nodular/bronchiectasis

1. Azithromycin 250–500 mg once daily or clarithromycin 500 mg twice daily orally three times weekly

   And

2. Ethambutol 25 mg/kg orally three times weekly

   And

3. Rifampin 600 mg orally or rifabutin 150–300 mg orally three times weekly

Cavitary disease

1. Azithromycin 250–500 mg daily or clarithromycin 500–1000 mg twice daily

   And

2. Ethambutol 15 mg/kg orally daily

   And

3. Rifampin 600 mg or rifabutin 150–300 mg orally daily

   Plus

4. Streptomycin 5–15 mg IM three times weekly or amikacin 5–15 mg IV three times weekly for at least 3 mo[a]

[a]*Peak levels should be monitored at least weekly with a goal of 20–25 μg/mL.*

United States.[24] While disease is often asymptomatic (and often in individuals with other underlying lung disease), in the immunologically normal host, NTM has not been shown to lead to latent infection. However, disease may be exacerbated by immune suppression.

The most common clinical manifestation of NTM infection is lung disease, but lymphatic, skin/soft tissue, and disseminated disease are also encountered.[25,26] CDC reports that of NTM isolates reported to the Public Health Laboratory System (PHLIS) database between 1993 and 1996, 75% were pulmonary, 5% were from blood, 2% from skin/soft tissue, and 0.4% from lymph nodes.[3] Disseminated NTM, primarily *M. avium*, infections occurs in HIV-infected patients with CD4+ T-lymphocyte counts below 50/cc.[27,28]

In individuals with congenital immune deficiencies such as chronic granulomatous disease, there may be defects in production of interferon (IFN)-γ or interleukin (IL)-12, or defects in receptors or pathways controlling responses to IFN-γ.[29,30] These IFN-γ pathway defects include receptor and signaling mutations in the nuclear factor-κB essential modulator, IFN-γ receptor 1 and receptor 2, IL-12 receptor 1 subunit, IL-12 subunit p40, and the signal transducer and activator of transcription 1 (STAT1). These defects are important given the role of macrophages in the innate immune response to NTM with IL-12 and IFN-γ essential for intracellular killing of mycobacteria. These patients, however, represent a small minority of patients with NTM disease.

Inhibitors of tumor necrosis factor (TNF-α) suggests that TNF also is essential in the prevention of disease activation.[31–34] These agents have been used in a variety of chronic inflammatory conditions, including inflammatory bowel disease and rheumatoid arthritis. The effect of these agents may persist for months to years after administration. In addition to NTM infection, such agents have been associated with activation of *Aspergillus species*, histoplasmosis, coccidioidomycosis listeriosis, and especially *M. tuberculosis*.[33,34]

Pulmonary Disease

There are two distinct prototypes of individuals with pulmonary NTM disease including nonsmoking postmenopausal women with nodular bronchiectasis, primarily involving the right middle lobe and the lingula (the Lady Windermere disease) and individuals with a long history of tobacco use and severe chronic obstructive lung disease (COPD) who present with fibrocavitary upper lobe changes. Women without obvious immune defects who have developed pulmonary NTM disease often have distinct body characteristics that may include scoliosis, low body mass index, pectus excavatum, mitral valve prolapse, and joint hypermobility.[6,7] The relationship between these physical traits and NTM infection remains elusive. Cavitary lung disease associated with COPD patients present formidable challenges to the clinician as treatment generally requires prolonged IV therapy as well as consideration of adjunctive surgery (Table 132-2). Disease (especially upper lobe fibrocavitary disease) should be treated as caused by *M. tuberculosis* until identification of the organism proves otherwise.

CLINICAL PRESENTATION

Most patients have pre-existing structural lung disease (Figs. 132-1 and 132-2) and present with chronic cough or sputum production, often with nonspecific signs, including dyspnea, fatigue, malaise, low-grade fevers, and weight loss. Both types of lung disease may present with hemoptysis. Physical examination is generally unrewarding, with auscultation of lungs ranging from diffuse rhonchi and wheezes to inspiratory squeaks. As noted, some women have a characteristic morphotype and are frequently otherwise in very good health.

Three forms of disease merit comment: hypersensitivity pneumonitis (HP) with NTM infection, infection in cystic fibrosis, and infection in transplant recipients. The hypersensitivity lung disease has been termed "hot tub lung." This unique form of HP is primarily seen after exposure to NTM from indoor hot tubs and spas, and occasionally contaminated showers, with aerosolization devices.[35–38] The hot tubs are often poorly maintained and the water contain large numbers of NTM (almost all *M. avium*). Treatment predominately includes exposure avoidance with the use of prednisone and/or antimicrobial agents.[12]

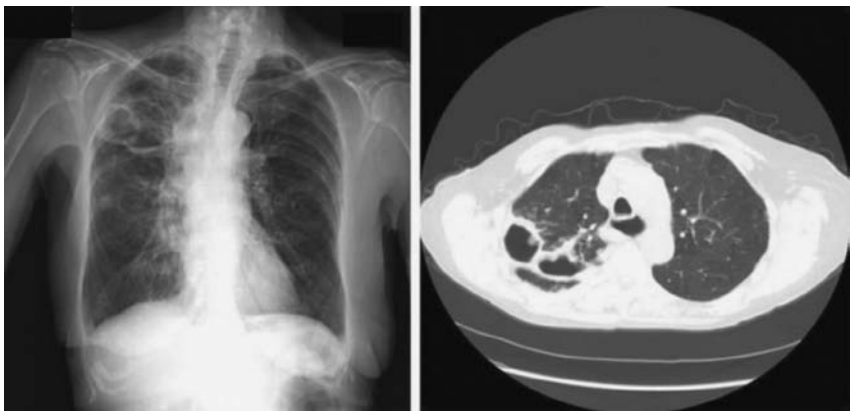

Figure 132-1 Right upper lobe cavitary MAC disease in a patient with COPD. **(A)** Chest radiograph. **(B)** CT scan.

A similar HP syndrome is seen in metal grinders (auto/machine workers, etc.) associated with exposures to metalworking fluids (paraffins, pine oils, and polycyclic aromatic hydrocarbons) containing mycobacteria.[39,40] This syndrome is associated almost exclusively with *M. immunogenum*, a rapidly growing mycobacterium. Onset of symptoms is subacute and is generally in nonsmokers without a clear disposition to infection. Chest radiographs and chest CT scans have diffuse small nodules with ground-glass infiltrates. Lung biopsy generally reveals centrilobular and bronchocentric nonnecrotizing granulomata, although some cases may have necrotizing granulomas, bronchiolitis and organizing pneumonia, or interstitial inflammation.

In cystic fibrosis, NTM are being increasingly isolated, often with uncertain clinical significance. As many as 20% of adolescent cystic fibrosis individuals, especially in the south in areas of Florida, Texas, and Louisiana, have at least one culture positive for NTM.[12,19] As a result, all routine sputum samples obtained in these patients should be cultured for both routine pathogens such as *Pseudomonas aeruginosa* and for NTM. This is especially important in patients who are given long-term azithromycin (a macrolide) for its anti-inflammatory properties. *M. abscessus* is the most common NTM in this setting and is increasingly being treated as a pathogen.

In solid-organ transplant recipients, NTM disease has been historically difficult to define with the most common manifestations of infection including cutaneous and pleuropulmonary disease (see Chapter 123).[9,41–43] Catheter-related infection is the most commonly reported manifestation of NTM disease in hematopoietic stem-cell transplant recipients.[9] In such hosts, skin and pulmonary lesions should be biopsied for histology, special staining, and microbiologic cultures, including bacteria, *Nocardia* species, fungi, and mycobacteria. NTM infections associated with catheters may be documented by tunnel or blood cultures. The RGM, especially *M. fortuitum,* are the most common pathogens. The pattern of NTM infection in transplantation differs from that of disseminated HIV-infection (more commonly *M. avium* complex), which limits extrapolation of therapeutic data from HIV-infected individuals to this population. Drug interactions are common and outlined in Table 132-3. Catheter-related infections have also been associated with a newly described pigmented RGM, *M. bacteremicum*.[44]

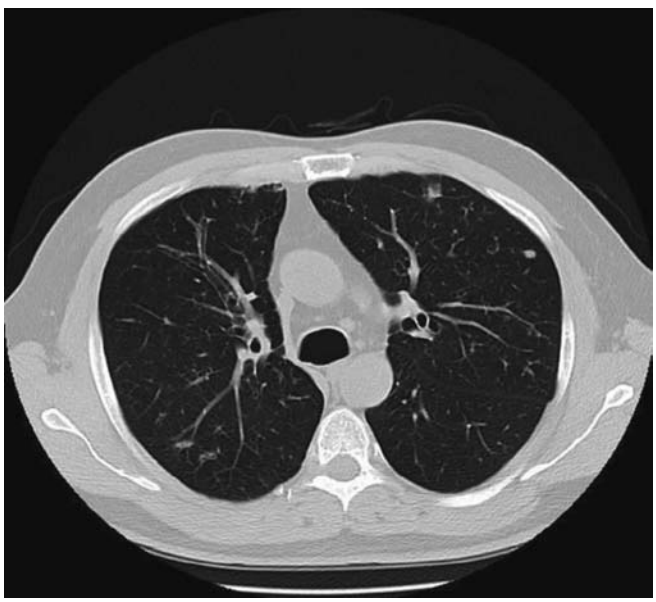

Figure 132-2 Chest CT scan showing bronchiectasis and nodular opacities in an 86-year-old female with MAC.

RADIOGRAPHY

Radiographic patterns associated with the aforementioned two phenotypes are uniquely distinct. The classic "Lady Windermere" pattern is associated with mid-lung field nodules and bronchiectasis, which may be accompanied by cavitations. On the opposite end of the spectrum, patients with COPD who have a long smoking history often present with large cavitary changes predominately located in the upper lobe lung zones, usually associated with a fibrotic pattern. There can be overlap of these disease spectrums making radiographic findings often diffuse and nonspecific.

TREATMENT

The approach to treatment varies with the species. Most species respond to regimens of several drugs. Toxicity and drug interactions are common (Tables 132-3 and 132-4). Therapy should be based on selected antimicrobial susceptibility testing that differs with each species or species complex. During therapy, monitoring for toxicity of drugs is essential. Such testing should include visual acuity, red–green color discrimination (ethambutol and rifabutin), liver enzymes (clarithromycin, azithromycin, rifabutin, rifampin, and isoniazid), auditory and vestibular function (streptomycin, amikacin, and azithromycin), renal function (streptomycin and amikacin), and leukocyte and platelet counts (rifampin, rifabutin, linezolid, trimethoprim–sulfamethoxazole and streptomycin). Clarithromycin enhances rifabutin toxicity (especially uveitis), whereas the rifamycin (rifampin more than rifabutin) is a potent inducer of the cytochrome p-450 system and can lower clarithromycin serum drug levels as well as steroids, anticoagulants, statins and β- blockers as a result of increased metabolism.

SURGERY

Lung resection for NTM was historically seen as a desperation or last resort measure in patients with severe, unresponsive disease. Surgery in the premacrolide era was often accompanied by significant perioperative complications.[45] Multiple studies have described surgical intervention in the era of macrolide use with relatively low operative mortality.[46–49] Surgery has also been shown to be an important adjunctive therapy for patients with *M. abscessus* lung disease, a pathogen that is especially difficult to treat effectively with medication alone.[50–52] The reports of surgical therapy for NTM disease thus far do not establish consensus guidelines for selecting the best patient candidates for surgery, choosing the most advantageous timing for operative intervention and choosing the specific surgical procedures with the best risk/benefit ratio in various clinical circumstances. Most specialists agree

TABLE 132-3 Interactions Between Drugs Used to Treat NTM and Immunosuppressive Medications

NTM Medication	Immunosuppressive Agent	Anticipated Reaction
Rifamycins (rifampin > rifabutin)	Calcineurin inhibitors (CNI) (cyclosporin, tacrolimus)	Decreased level of CNI
	Sirolimus	Loss of sirolimus efficacy
	Steroids	Decreased steroid effectiveness
Macrolides (clarithromycin, azithromycin)	Calcineurin inhibitors (CNI) (cyclosporin, tacrolimus)	Increased CNI level and risk of toxicity
Ethambutol	NS	N/A
Aminoglycosides (streptomycin, amikacin)	Calcineurin inhibitors (CNI) (cyclosporin, tacrolimus)	Possible additive or synergistic risk of renal impairment
Clofazimine	NS	N/A
Fluoroquinolones	NS	N/A
Isoniazid	NS	N/A
Doxycycline	NS	N/A
Cefoxitin	NS	N/A
Imipenem	Cyclosporin	May result in neurotoxicity (mental confusion, agitation, tremor)

NS, no significant interaction; N/A, not applicable.

that adjunctive surgical intervention in the hands of an experienced multidisciplinary team and center offers benefit to a selective population of NTM patients who have either NTM disease that is difficult to treat with antibiotic therapy or who have not responded favorably in spite of aggressive medical therapy. Surgical therapy is clearly beneficial to many NTM lung disease patients but many aspects of adjunctive surgical therapy have yet to be clearly defined.

■ TREATMENT OF SPECIFIC NTM INFECTIONS

Important pathogenic NTM species are considered below, including *M. avium* complex, *M. kansasii, M. abscessus, M. chelonae,* and *M. fortuitum*.

Pulmonary *M. Avium* Complex

Mycobacterium avium complex (MAC) is the most frequently encountered pathogenic NTM species in North America.[3,25] Treatment for MAC lung disease vastly improved in the era following the introduction of macrolides.[53–55] For patients with nodular lung disease and bronchiectasis, three times weekly dosing of clarithromycin 1000 mg or azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg are recommended by the American Thoracic Society.[12] Dosing adjustments are usually needed for patients who weigh less than 50 kg or are 80 years or older. These patients are generally intolerant of daily therapy.

For fibrocavitary or severe nodular/bronchiectatic disease, a daily regimen may be used that includes clarithromycin 500 to 1000 mg/d or azithromycin 250 mg/d, ethambutol 15 mg/kg per day and rifampin 10 mg/kg per day (maximum 600 mg) or rifabutin 150 to 300 mg/d. For patients with cavitary changes on either daily or three times weekly oral drugs, amikacin or streptomycin given IV or IM at a dose of approximately 7 mg/kg three times weekly for the first 3 months is recommended. For therapy with ethambutol, a baseline visit to an ophthalmologist as well as clinic visual acuity and color vision testing are recommended. In addition, a baseline

TABLE 132-4 Adverse Events of Drugs Used to Treat NTM

NTM Medication	Most Common Adverse Events
Rifamycins (rifampin, rifabutin)	Flu-like fever, rash, bone marrow suppression, uveitis (rifabutin), discoloration of body fluids, hepatotoxicity, nausea, drug interactions
Macrolides (clarithromycin, azithromycin)	Nausea, vomiting (azithromycin), QT prolongation, myopathy, granulomatous hepatitis (clarithromycin), hearing diminished
Ethambutol	Visual changes/optic neuritis, peripheral neuropathy, rash, renal insufficiency
Aminoglycosides (streptomycin, amikacin)	Perioral numbness, eosinophilia, nephrotoxicity, ototoxicity, neurotoxicity
Clofazimine	Skin discoloration, visual changes, joint pain, eosinophilic enteritis, nausea
Fluoroquinolones	Joint or muscle pains, tendon toxicity, QT prolongation, hepatotoxicity, nephrotoxicity, rash, dizziness, headache
Isoniazid	Hepatotoxicity, neuropathy, jaundice, rash, neurotoxicity, optic neuritis, drug interactions, lupus-like syndrome
Tigecycline	Nausea, vomiting, diarrhea, anorexia
Cefoxitin	Rash, nausea, diarrhea
Imipenem	Nausea, rash, visual disturbances, dizziness, seizures
Linezolid	Nausea, peripheral neuropathy, myelosuppression, rash, GI side effects, optic neuritis
Doxycycline/Minocycline	Photosensitivity, skin rash, nausea, vomiting, bluish skin discoloration
Trimethoprim–suflamethoxazole (TMP-SMX)	Rash (rarely Stevens–Johnson syndrome), fever, myelosuppression, renal insufficiency, agranulocytosis, hepatotoxicity, myalgias

hearing test is needed for patients on an aminoglycoside and should be repeated at intervals during the course of treatment. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy. A macrolide with a single companion drug, ethambutol, may be adequate for minimal nodular/bronchiectatic MAC disease if the patient is intolerant to a rifamycin but this has not been studied. Patients are considered treatment failures if they have not had response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy or achieved culture negativity of sputum after 12 months of therapy. Common factors in such patients include medication nonadherence, the use of inadequate regimens (e.g., clarithromycin with a fluoroquinolone only) and emergence of a macrolide-resistant MAC isolates. Use of a quinolone and a macrolide and macrolide monotherapy are not recommended due to poor response and the frequent emergence of resistance.[56,57] It should also be noted that patients respond best to the first course of MAC treatment; therefore, adherence and use of a multidrug regimen are essential. Early specialist referral in patients with complex disease (i.e., cavitary changes, need for an aminoglycoside) is generally warranted.

M. Kansasii

M. kansasii can also present as upper lobe cavitary disease in smokers with COPD. This organism is susceptible to antituberculous agents, especially rifampin and ethambutol.[58–60] The standard recommended therapy in the United States by the ATS is a daily three-drug regimen of isoniazid, rifampin, and ethambutol plus pyridoxine (50 mg/d).[12] The rifampin dose is 10 mg/kg per day to a maximum of 600 mg daily, and ethambutol is given at 15 mg/kg per day. An initial 2 months of ethambutol at 25 mg/kg per day is no longer recommended. The duration of treatment is usually 18 to 24 months, although good results with 12 months of therapy have been reported.[59]

The role of isoniazid in this regimen is not clear (the MICs are 100× higher than with MTB). Clarithromycin, however, is highly active with *M. kansasii* as it is with other slowly growing NTM species. A three times weekly three-drug oral regimen (azithromycin or clarithromycin, rifampin, and ethambutol) with 12 months of culture negativity has been reported with 100% cure rate.[61,62] Other drugs usually given in three-drug combinations are effective for retreatment of disease that has become resistant to rifampin; they include clarithromycin, trimethoprim/sulfamethoxazole, streptomycin, and amikacin. Relapse after treatment with rifampin-containing regimens is uncommon.

M. Abscessus ssp *Abscessus* and *M. Abscessus* ssp *Massiliense*

M. abscessus is the third most frequently recovered NTM pulmonary pathogen in the United States. Pulmonary infections are the most common form of disease. Two major subspecies are recognized, subspecies (ssp) *abscessus* and ssp *massiliense*. These patients are generally women, nonsmokers, without previously recognized lung disease, presenting with symptoms of fatigue and bronchiectasis. CT scanning reveals mid-lung field small nodules with bronchiectasis ("nodular bronchiectasis"). These are the same patients who get similar disease due to MAC. Cavity formation is rare with this type of disease. Dual infection with MAC can occur. Disease is slowly progressive if left untreated. *M. abscessus* has complicated lung transplant surgery causing sternal osteomyelitis.

M. abscessus isolates are uniformly resistant to standard antituberculous agents. Approximately 80% of isolates of *M. abscessus ssp abscessus* carry a functional *erm* gene with subsequent in vivo macrolide resistance, which may not be reflected by the initial 3-day in vitro MIC of the organism for the macrolide.[63] Untreated isolates of *M. abscessus ssp massiliense* are all macrolide susceptible as their *erm* gene is nonfunctional (and hence the disease is much easier to treat).[64,65] Drugs that may be useful include the macrolides, linezolid, tigecycline, imipenem, amikacin, and cefoxitin. Combination therapy, usually for a minimum of 4 to 6 months, is mandatory for significant disease.

No antibiotic regimens based on in vitro susceptibilities have been shown to produce long-term sputum conversion for the 80% of patients with *M. abscessus ssp abscessus* lung disease with a functional *erm* gene.[50,52,66] For macrolide susceptible and resistant *M. abscessus* isolates, a combination of parenteral drugs should be used based on in vitro susceptibilities. Side effect monitoring and lower doses of antibiotics are often warranted to achieve therapeutic goals.

M. Chelonae and *M. Fortuitum*

M. chelonae is an RGM that causes skin and soft tissue disease similar to that of *M. abscessus.* Unlike *M. abscessus* and *M. fortuitum*, *M chelonae* does not carry an *erm* gene and therefore effective therapy with a macrolide may be more obtainable in these individuals.[63] This is one example that supports the need for mycobacteriology laboratories to offer molecular analyses with accurate species identification of RGM to guide and implement effective treatment regimens. Isolates of *M. chelonae* are susceptible to doxycycline (25% of isolates), ciprofloxacin (25% of isolates), tobramycin (100% of isolates), clarithromycin (100% of isolates), imipenem (70% of isolates), clofazimine, and linezolid (65% of isolates). *M. chelonae* are resistant to cefoxitin.[67–69]

M. fortuitum is also a rapid grower similar to that of *M. abscessus*. It is a recognized as a rare cause of lung disease, almost always associated in patients with achalasia and rarely other gastroesophageal reflux disorders with recurrent aspirational lung disease.[12,70] It is not a recognized cause of pulmonary disease in other settings. Multidrug therapy with agents shown to be susceptible in vitro including, amikacin, newer quinolones, tetracyclines and trimethoprim/sulfamethoxazole, should be given for 12 months or until clinical resolution of disease recognizing that without therapy for the underlying gastrointestinal disorder, symptoms rarely improve. *M. fortuitum* isolates are usually susceptible to fluoroquinolones, doxycycline and minocycline (50%), sulfonamides and trimethoprim/sulfamethoxazole, amikacin, imipenem, tigecycline, and approximately one-half of the isolates are susceptible to cefoxitin.[67,68,71] Most *M. fortuitum* isolates have a functional *erm* gene so most are macrolide resistant.[72,73]

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CHAPTER 133

Aspergillus, Candida, and Other Opportunistic Mold Infections of the Lung

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PULMONARY ASPERGILLOSIS

Aspergillus is a ubiquitous saprophytic mold that plays an essential role in recycling carbon and nitrogen.[1] This fungus has a simple biological cycle characterized by a high sporulating capacity, which results in the release of conidia at high concentrations (1–100 conidia/m^3) into the atmosphere. *Aspergillus* conidia have a diameter small enough (2–3 μm) to reach the pulmonary alveoli.[1,2] However, while humans constantly inhale *Aspergillus* conidia, such conidia are effectively eliminated in immunocompetent individuals.[3]

EPIDEMIOLOGY

Infections by *Aspergillus* species cause a wide spectrum of illnesses in humans depending on the immune status of the host (Table 133-1). Hence, in immunocompetent hosts, isolation of *Aspergillus* spp. in respiratory secretions typically reflects colonization, not infection. Under physiologic conditions, inhalation of *Aspergillus* spp. does not trigger immune responses because fungal spores are covered by a hydrophobin layer that masks recognition of immunostimulatory fungal cell wall molecules by host immune cells.[1–3] In atopic individuals, the fungus triggers robust immune reactions, including allergic rhinitis, asthma, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis (ABPA).[4] In patients with pre-existing cavitary pulmonary lesions, saprophytic growth of *Aspergillus* spp. can lead to aspergilloma formation. Finally, in immunocompromised individuals, some *Aspergillus* conidia germinate into the lung to form hyphae, the invasive form of the fungus, which causes a severe, frequently fatal angioinvasive infection called invasive pulmonary aspergillosis (IPA).[5–7] The degree of fungal invasion, response to antifungal therapy, and outcome of invasive aspergillosis (IA) depend on the type and severity of immunosuppression. Thus, in patients with subtle or no immune defects, chronic forms of *Aspergillus* infections in the lung have been described, which are characterized by an indolent clinical course with the development of progressive cavitary lesions, and minimal or no evidence of parenchymal invasion.[8] A less acute form of IA, frequently called subacute IPA, has been described in patients with acquired immunodeficiency syndrome (AIDS) and those with genetic defects in NADPH oxidase (chronic granulomatous disease or CGD), whereas progressive IPA is encountered in severely immunocompromised hosts.[1,2,6,7] There is no doubt that since the first description in the 1940s, IA has emerged as the major problem of modern mycology. Currently, IA is a leading cause of death in severely immunocompromised individuals, with crude mortality rates approaching 50% to 70% in patients with leukemia and recipients of hematopoietic stem cell transplants (HSCTs).[5,6] In addition, invasive *Aspergillus* has

TABLE 133-1 Spectrum of Pulmonary Aspergillosis

Clinical Manifestation	Immune Status	Underlying Lung Architecture	Degree of Tissue Invasion
Simple colonization	Normal	Chronic obstructive airway disease	None
Hypersensitivity reactions			
Allergic bronchial asthma	↑[a]	Normal	None
ABPA	↑	Excess airway mucus	None
Bronchocentric granulomatosis	↑	Excess airway mucus	None
Extrinsic allergic alveolitis	↑	Normal	None
Saprophytic growth			
Aspergilloma	Normal	Pre-existing cavity	None
Invasive infection			
IBA[b]	↑	Lung transplantation	+ +
Bronchial stump aspergillosis	Normal	Pneumonectomy	+
CPA[c]	↓[d]	Chronic obstructive airway disease	+
IPA[e]	↓↓↓[f]	Normal	+ + +

[a] *↑Hyperactive humoral response.*
[b] *Includes tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. The latter two forms typically manifest as anastomotic infections in lung transplant recipients.*
[c] *Includes the following forms: CNPA, CCPA, and CFPA. Aspergillus hyphae occasionally invade the lung parenchyma in CNPA. Significant overlap exists among these entities.*
[d] *↑Suppressed immune response.*
[e] *May have features of invasive disease surrounding the cavity. It occurs in two settings with distinct histopathologies and immunopathogenesis: angioinvasive IPA in profoundly neutropenic patients and nonangioinvasive IPA in immunocompromised nonneutropenic individuals, including those receiving corticosteroid-based treatment, recipients of HSCTs with severe GvHD, patients with AIDS, recipients of solid-organ transplants, and patients with CGD. Mixed forms and significant overlap exist.*
[f] *↓↓↓Severely depressed immune response, neutropenia.*

emerged as an important pathogen in an expanding spectrum of nonneutropenic patients with chronic debilitating diseases who receive corticosteroids and/or other immunosuppressive therapies. Thus, IPA is increasingly encountered in patients with inflammatory and autoimmune diseases, chronic obstructive lung disease, and prolonged ICU stays.[2] At the same time, over the past two decades, we have witnessed a significant expansion in the antifungal armamentarium with the introduction of several agents with anti-*Aspergillus* activity. In addition, promising new non–culture-based diagnostic methods are being developed, and considerable progress has been made in understanding the epidemiology and immunopathogenesis of IA. As a result, a significant improvement in IA-attributable mortality has been noted. As IPA currently accounts for more than 90% of invasive *Aspergillus* infections we devote a significant portion of this chapter to this type of pulmonary aspergillosis.

MYCOLOGY AND HOST DEFENSES

Of the nearly 200 *Aspergillus* spp., only 20 have been encountered as pathogenic in humans.[1] *Aspergillus fumigatus* is the most frequently identified of these species; however, other species, such as *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus nidulans* have emerged as important pathogens in immunocompromised individuals. Appropriate identification of *Aspergillus* species is important because of differences in epidemiology, host tropism, virulence, and susceptibility to antifungal agents. For example, *Aspergillus nidulans* is the second most encountered mold in CGD patients, causing almost exclusively invasive infections in this specific host. In addition, certain species including *A. terreus, A. flavus, and A. nidulans* are clinically resistant to AMB.[2,6] Recent studies using molecular identification methods discovered "cryptic" clinical isolates of *Aspergillus*, including *Aspergillus lentulus, Aspergillus calidoustus, and Aspergillus glaucus,* that had been misclassified as *A. fumigatus* and display inherent resistance to certain antifungal agents. Notably, *A. fumigatus* is nearly always the cause of allergic pulmonary disease.[4] *Aspergillus* spp. are rapidly growing, hardy molds identified by the macroscopic appearance of the colony and by microscopic examination of the spore-bearing structures.[1] Microscopically, *Aspergillus* spp. are characterized by the production of uniform 4- to 6-mm wide hyphae with parallel walls and distinct septa. Dichotomous branching of hyphae occurs at 45-degree angles.[1] However, other filamentous fungi, such as *Fusarium, Acremonium,* and *Scedosporium* species share the same histopathological features with *Aspergillus* spp.[1] A wide range of microscopic appearances may be observed in clinical specimens.

Sputum specimens obtained from patients and examined by direct mounting or with KOH and ink may reveal the typical 45-degree branching hyphal fragments of aspergilli, which are often associated with eosinophils and Charcot–Leyden crystals in patients with ABPA.[1] Stained tissue sections reveal regular hyaline septate hyphae that are best observed with the use of periodic acid–Schiff (PAS) and Gomori methenamine silver (GMS) stain.[1] Fungus ball specimens obtained from cavities connected to bronchi have hyphae that often appear to be lifeless and stain poorly. Also, although seldom seen, the fruiting heads and conidia may appear to be well formed.

HOST IMMUNE RESPONSES

Recent years have witnessed improvements in understanding of the immunological mechanisms of host resistance to *Aspergillus* spp. Protection of the normal host against *Aspergillus* infection is mediated by a highly coordinated response that involves both innate and adaptive immunity (see also Chapters 121 and 123).[3] Acquired quantitative and qualitative defects in phagocytic cell function associated with prolonged and profound neutropenia and corticosteroid-induced dysfunction of macrophages and monocytes have long been recognized as the major risk factors for IA. In addition, functional phagocytic defects due to mutations in NADPH oxidase seen in patients with CGD are associated with impaired phagocytic cell function and unique susceptibility to IA.[3]

Innate Immunity Consists of Three Main Effector Cell Types: (a) myeloid-derived dendritic cells that orchestrate innate and adaptive immune responses by transferring and presenting fungal antigens to T cells in resident lymph nodes; (b) pulmonary alveolar macrophages that ingest and kill inhaled conidia, primarily via oxidative reactive oxygen species (ROS)-dependent mechanisms; and (c) circulating polymorphonuclear and mononuclear cells, which are recruited to the lungs and actively participate in elimination of conidia and hyphae that escape killing by resident myeloid cells.[3] Intracellular killing of *Aspergillus* spores within professional phagocytes occurs in acidified phagolysosomes and depends on the production of ROS. Neutrophils are unique in the ability to cause damage to *Aspergillus* hyphae via the release of potent antimicrobial effector molecules that are stored in specialized granules. The release of DNA filaments decorated with antimicrobial effector molecules (neutrophil extracellular traps or NETs) upon neutrophil death is a recently identified antifungal effector pathway that is efective in patients with CGD.[3]

In addition to professional phagocytic cells, other innate immune cell subsets appear to play important roles in *Aspergillus* host defense, including platelets, plasmacytoid dendritic cells, natural killer (NK) cells, and invariant NK T (iNKT) cells. These innate immune cells mediate antifungal activities either directly via the release of cytotoxic molecules or indirectly via the production of cytokines that activate professional phagocytes.[3]

Humoral factors also participate in the initial events of host response to *Aspergillus* infection. Resting conidia, germinating conidia, and hyphae are all potent activators of both the alternative and classical components of the complement cascade, promoting opsonization and chemotaxis.[3] In addition, soluble C-type lectins, including mannose-binding lectins, and surfactant protein A (SP-A) and D (SP-D), which are present in alveolar fluid, enhance chemotaxis, binding, phagocytosis, and oxidative killing of conidia. C-type lectins also appear to be able to agglutinate, immobilize, and inactivate conidia.[3] Importantly, alteration in SP-D and polymorphisms in mannose-binding lectin encoding genes are associated with an increased risk of chronic pulmonary aspergillosis (CPA).[8] Another soluble pattern recognition receptor, the pentraxin PTX3, has been shown to bind to a range of microbial products, including *Aspergillus* conidia, and to confer resistance to the fungus.[3] PTX3-deficient mice were susceptible to IPA because of impaired recognition of aspergilli by alveolar macrophages and dendritic cells and inappropriate induction of a Th2 response.[3]

In recent years, the role of adaptive immunity in *Aspergillus* host defense has been increasingly appreciated. Activation and maturation of dendritic cells following uptake of *Aspergillus* spores are critical for antigen presentation, T-cell expansion, and initiation of adaptive immunity. Activation of different pattern recognition receptors in dendritic cells by microbial ligands, including *Aspergillus* immunostimulatory cell wall molecules, leads to the production of distinct sets of cytokines that drive development of different Th cell subsets. Activation of toll-like receptor (TLR)-2 and TLR4 in dendritic cells has been linked to the induction of IL-12 leading to interferon-γ (IFN-γ)–producing Th1 cells, which are considered to confer broad protective immunity against fungi. In contrast, Th2 responses mediated by IL-4 lead to increased susceptibility to fungal infections. More recently, a subset of Th

cells, called IL-17–producing Th (Th17) cells, has been identified and implicated in mucosal immunity against fungi. Sensing of the fungal polysaccharide β-glucan by *Dectin-1* receptor on dendritic cells drives activation of antifungal Th17 responses.[3] Impaired IL-17 production has been associated with increased susceptibility to IPA in mice. In humans, patients with mutations in STAT3 have selective impairment of IL-17–producing T cells and are prone to infections with *Aspergillus*. However, unabated Th17 responses can become detrimental for infectious outcome because of unbalanced inflammatory responses. Under physiologic conditions, Th17 cells are kept in check by IL-10–producing T-regulatory cells (T regs). However, defective ROS production in CGD is associated with compromised T reg activity, unrestrained Th17 proinflammatory responses and associated tissue pathology.[3]

Overall, a balanced inflammatory response is required for abrogation or effective resolution of invasive *Aspergillus* infection. Thus, while an early and effective proinflammatory response is required to restrict infection, an uncontrolled inflammatory response is detrimental and may eventually facilitate fungal persistence. To that end, high-level production of IL-10 by T regs may be beneficial by contributing to resolution of the inflammatory response.[3] On the other side, immune tolerance may lead to adverse outcomes of infection. For example, expansion of myeloid suppressor cells that result in defective Ag presentation and Th cell priming has been described in *Pneumocystis* pneumonia in mice and adoptive transfer of these cells had an adverse effect on the resolution of infection. Whether a similar expansion of myeloid suppressor cells occurs in IA is currently unknown.

Immune augmentation therapies have become a top priory in fungal immunology research. Administration of Th1 cytokines has been successfully employed in the mouse model of IA. Thus, tumor necrosis factor-alpha (TNF-α), IFN-γ, interleukin (IL)-12, and IL-15 enhance effector function of professional phagocytes and have been shown to confer protection against *Aspergillus* infection in animal studies.[3] The protective Th1 response was characterized by the presence of antigen-specific CD4+ T cells that produce IFN-γ and IL-2. Furthermore, dendritic cell–based vaccination strategies, generation of Th1/Th17 *Aspergillus*-specific T cells in naive mice or adoptive transfer of *Aspergillus*-specific CD4+ T cells in immunocompromised mice, all resulted in improved outcomes of IA in mice.[2,3] Finally, restoration of immune dysfunction via cooperative activation of TLR and C-type receptor signaling resulted in cure of a chronic fungal disease of the skin in mice and could be explored as a therapeutic strategy for IA.

However, in contrast to the animal studies, in severely immunocompromised patients with IPA, immune augmentation therapies have been of unclear benefit using myeloid growth factors, Th1 recombinant cytokines or T-cell–based adoptive transfer. Thus, translating recent advances in fungal immunology to novel therapeutics against IA in humans remains a challenge. In particular, translation of results of ex vivo experiments and studies in mice with genetic defects in receptors, signaling molecules, cytokines, or chemokines into clinical practice has been difficult in view of the complex and multifactorial pathophysiology of IPA in humans. Furthermore, immune augmentation strategies and vaccination-induced protective immune therapies could be suboptimal in profoundly immunocompromised individuals. Better understanding of the immunopathogenesis of IPA at the cellular and molecular level coupled with efforts to validate research findings from mice in humans could facilitate the development of immune-based augmentation therapies.

Aspergillus virulence factors

There is debate over which factors determine *Aspergillus* virulence and pathogenicity.[1,2] Several putative virulence factors in *A. fumigatus* have been identified, including various proteolytic enzymes (elastases, collagenases, trypsine), phospholipases, ribotoxin, hemolysin, gliotoxin, and many other enzymes and toxins.[1,2] The mycotoxin gliotoxin in particular has received attention and been studied extensively.[2] Gliotoxin exhibits immunomodulatory properties, as it has been shown to inhibit the phagocytosis of macrophages, promote apoptosis of macrophages, inhibit ROS production in human neutrophils and block B- and T-cell activation. Of interest, gliotoxin deletion mutants displayed attenuated virulence in corticosteroid-immunosuppressed mice but not in mice rendered neutropenic by treatment with cyclophosphamide, implying a direct in vivo cytotoxic effect of gliotoxin in cellular immunity.

Importantly, tissue necrosis and angioinvasion are prominent features of IA in immunocompromised patients. Of interest, gliotoxin has been shown to block angiogenesis during invasive *Aspergillus* growth.[2,3] In fact, restoration of anti-angiogenic activity of *Aspergillus* via administration of pro-angiogenic factors was recently shown to potentiate activity of antifungal therapy in murine IPA. In addition, adaptation in the hypoxic environment during tissue necrosis is a prominent feature of invasive *Aspergillus* growth. In fact, an *Aspergillus* mutant deficient in a sterol regulatory element-binding protein required for hypoxia adaptation (Δ*SrbA*) was completely avirulent in mice.[2,3] Iron metabolism is important for *Aspergillus* in vivo growth and mutants defective in siderophore secretion pathway fail to grow in vivo and are avirulent following infection of neutropenic mice. In addition, some have postulated that the production of catalases, superoxide dismutases, and mannitol by *Aspergillus* may protect the fungus from oxidative damage induced by phagocytic cells.[2,3] Moreover, the melanin pigment and rigid protein coat layer composed of hydrophobic rodlet fascicles on the *Aspergillus* conidial surface may confer resistance to phagocytosis.[2] In fact, melanin may act as a virulence factor by masking surface immunostimulatory molecules, blocking ROS production and acidification of fungal phagosomes. On the other hand, recent evidence from comparative genomic analysis across filamentous fungi suggests that *A. fumigatus* virulence results from the immunosuppression or possibly genetic susceptibility of the host rather than from specific, unique fungal determinants.[2,3] Hence, *A. fumigatus* appears to be a saprotrophic fungus that only becomes pathogenic for very simple biological reasons: it is present in high concentrations in the atmosphere, it grows faster than any other airborne fungi at physiologic mammalian temperatures (above 37°C), and it can overcome the defense of the host not because of specific virulence mechanisms but because of inefficient host immune responses. Taken together, these data suggest that approaches targeted at augmenting cellular immunity, such as neutralization of Th2 cytokines, enhancement of Th1 responses, and dendritic-cell vaccine-based vaccination warrant investigation as therapeutic modalities for invasive *Aspergillus* infections.[2,3]

■ CLINICAL MANIFESTATIONS

The varied clinical manifestations of disease related to Aspergillus species are considered in detail below.

Hypersensitive Reactions

Hypersensitivity lung diseases that result from exposure to *A. fumigatus* allergens include allergic asthma, ABPA, and hypersensitivity pneumonitis.[4,6] In atopic individuals, inhalation of *Aspergillus* spores triggers an IgE-mediated allergic inflammatory response in the bronchial mucosa, leading to excessive mucus production, bronchial obstruction, and asthma.[4,6] Similarly, ABPA develops following sensitization to *A. fumigatus* allergens in a unique subset of atopic individuals and patients with cystic fibrosis (CF), who are genetically susceptible for ABPA.[4] The immune response to *Aspergillus* antigens in both patients with allergic asthma and those with ABPA is characterized by a robust Th2 polarized CD4+ response.

TABLE 133-2 Hypersensitive Reactions to *Aspergillus*

	Asthma	ABPA	Extrinsic Allergic Alveolitis
Pathology	Hypertrophied mucus glands	Colonization of airways, viscid mucoid impaction, tissue eosinophilia	Lymphocytic infiltration of interstitium, noncaseating granuloma
Radiographic features			
Early	Normal, hyperinflation	Migratory peripheral infiltrates, atelectasis, bronchiectasis	Diffuse alveolar-interstitial infiltrates
Late	Normal, hyperinflation	Fibrosis	Reticulonodular interstitial opacities
Skin test reactions to *Aspergillus* antigens			
Immediate	Positive	Positive	Positive
Delayed	Negative	Positive	Positive
Peripheral eosinophilia	Negative[a]	Positive	Negative
IgG *Aspergillus* precipitins	Positive (up to 25%)	Positive	Positive
Serum IgE levels	Normal or mildly elevated	Marked elevation	Normal

[a]*Occasionally positive.*

In nonatopic individuals, persistent airway colonization and, more rarely, a type of hypersensitivity pneumonitis called *extrinsic allergic alveolitis* can occur as a result of massive or repeated inhalation of *Aspergillus* conidia.[4,8] Hypersensitivity pneumonitis in these patients manifests with dyspnea because of pulmonary constriction and an influenza-like syndrome with fever, malaise, and fatigue. In contrast to other allergic diseases caused by *A. fumigatus*, hypersensitive pneumonitis is characterized by extensive infiltration of neutrophils in the acute phase as a result of a Th1 CD4+ response.[4,8] Early recognition of these syndromes is important for early initiation of appropriate treatment to prevent progression to permanent lung damage. Table 133-2 summarizes the hypersensitivity syndromes that result from exposure to *Aspergillus*.

Simple Colonization

Although there is not a uniform definition of colonization, it should be considered in cases of isolation of *Aspergillus* spp. from cultures of the respiratory tract in patients without evidence of invasive or allergic disease.[8] Patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD) are at increased risk for persistent *Aspergillus* colonization. Tissue invasion by aspergilli is not a feature of saprophytic colonization, although IPA following subsequent dysfunction of host defenses may develop. In fact, *Aspergillus* colonization has been shown to be a marker for the development of IA in immunocompromised individuals, particularly lung and bone marrow transplant recipients, and may precede invasion for up to 3 months.[8] Quantitative real-time polymerase chain reaction (PCR) and measurement of BAL *Aspergillus* galactomannan antigen are both highly sensitive and specific assays in distinguishing *Aspergillus* colonization from invasive infection.[2,6]

Allergic Bronchial Asthma

Asthmatic patients may become sensitized to *Aspergillus* conidia as a consequence of thick bronchial secretions that trap fungal spores.[4,8] These spores seldom germinate in the bronchial airways. Allergic bronchial asthma develops in patients who are atopic and is perpetuated by inhalation of *Aspergillus* antigens, which typically causes acute bronchospasm. The presence of transient infiltrates has been described during the immediate reaction but is not frequent. As is typical in asthma of other etiologies, eosinophils and serum IgE antibody are increased. Immediate skin reactions to *Aspergillus* antigens are positive, but specific precipitating antibodies (IgG) are usually negative.[4,8] Avoidance of exposure to *Aspergillus* spores can diminish the frequency and severity of bronchospasm in this group of patients. *Aspergillus* bronchitis is a rare, distinct clinical entity that has been recently described in immunocompetent individuals with structural lung disease, chronic pulmonary symptoms, and lack of response to antibiotic therapy. All of these patients had evidence of *Aspergillus* growth in their lungs, marked improvement following antifungal therapy and did not fulfill criteria for asthma or other forms of invasive or chronic aspergillosis.

Allergic Bronchopulmonary Aspergillosis

The important clinical entity of allergic bronchopulmonary aspergillosis (ABPA) is discussed below. The reader is also referred to Chapters 48 and 71.

Immunopathogenesis and Risk Factors It has been recently proposed that ABPA develops in genetically susceptible patients with asthma or CF because of increased activity of *A. fumigatus*-specific Th2 CD4+ cells (see also Chapter 48).[4] Hence, in addition to a history of atopy, predisposing factors for ABPA include immunogenetic human leukocyte antigen (HLA)-distinct phenotypes (e.g., HLA-DR 2- and HLA-DR 5-specific alleles), mutations in the CF transmembrane conductance regulator (CFTR) gene, polymorphisms of the collagen region of the SP-A2, and/or other collections (e.g., mannose-binding lectins).[4,8] In addition, particular physicochemical characteristics of respiratory secretions and a history of environmental exposure may play a role in ABPA pathogenesis.[4,8] The role of newly identified Th17 pathway, which has a critical role in inflammation via neutrophil recruitment has not been extensively evaluated in ABPA. However, in a mouse model of asthma, Dectin-1 dependent IL-22 production was important for disease development. In addition, TNF-α–producing inflammatory DCs have been recently shown to be important regulators of IL-17–producing T cells and neutrophilia in a mouse model of ABPA.

In patients with ABPA, inhaled *A. fumigatus* conidia are able to colonize, persist, and germinate, leading to growth of hyphae in mucus plugs, which are often observed in expectorated sputum.[4] During this process, *A. fumigatus* releases a panel of proteases and other toxins that are capable of further compromising mucociliary clearance, breaching the airway epithelial barrier, and activating the immune system in the lung.[4]

IgE molecules on the surface of mast cells initially recognize *A. fumigatus* antigens. Binding of these antigens with IgE causes mast-cell degranulation, releasing mediators that cause vasodilatation and vascular leakage so that serum components, including anti-*Aspergillus* IgG, enter the bronchi and combine with *Aspergillus* antigens to form IgG-containing immune complexes.[4] These complexes activate the

complement cascade leading to inflammation and pulmonary damage. Importantly, investigators have identified specific *Aspergillus* antigens capable of inducing IgE and IgG responses in patients with ABPA but not in patients who did not have ABPA, implying that an aberrant host response occurs in patients with ABPA.[4]

The key element in the immunopathogenesis of ABPA appears to be an abnormal T-lymphocyte cellular immune response to *A. fumigatus* conidia. Hence, A. *fumigatus* allergens released by mycelia are processed by antigen-presenting cells bearing HLA-DR 2 or HLA-DR 5 and presented to T cells within the lymphoid tissue of the lung.[4,8] The T-cell response to *Aspergillus* allergens is then shifted toward a Th2 CD4+ cell response with synthesis and secretion of the cytokines IL-4, IL-5, and IL-13.[4,8] In addition, production of chemotactic cytokines (chemokines) by inflammatory cells, including monocyte chemoattractant protein-1 (MCP-1/CCL2), eotaxin (CCL11), IL-8, and macrophage inflammatory protein-1α (MIP-1α/CCL3) appears to promote the Th2 cell response.[4,8] In addition, T cells, B cells, NK cells, and eosinophils may be hyperresponsive to IL-4.[4,8] This leads to a positive-feedback amplification loop of Th2 CD4+ cells, synthesis of IL-4, and polyclonal activation of CD23+ CD86+ B cells.[4,8]

Clinical Features ABPA is a hypersensitivity disease of the lung that is virtually almost always related to *A. fumigatus* (discussed in detail in Chapter 48). Some key points are highlighted here. Seven percent to 14% of patients with poorly controlled asthma and 7% to 9% of those with CF meet the diagnostic criteria for ABPA.[4] In fact, nearly all patients with ABPA have a history of chronic asthma. Rarely, patients present without symptoms or physical findings despite having radiographically detected abnormalities. Clinically, ABPA manifests with episodic wheezing, malaise, low-grade chronic fevers and cough, sputum containing brown flecks and plugs, chest pain, pulmonary infiltrates, and sputum and blood eosinophilia.[4,8] Patients may have a history of recurrent pneumonias and frequent use of antibiotic therapy. Mucus plugs form in the proximal bronchi and can progress to mucoid impaction, resulting in atelectasis with transient pulmonary infiltrates. Mucus plugs often yield aspergilli in culture (Figs. 133-1 and 133-2). As ABPA progresses, central bronchiectasis becomes a dominant feature of the disease and may result in chronic bronchorrhea and occasionally hemoptysis, development of clubbing, and fixed, characteristic radiographic abnormalities.[4,8] In patients with CF in particular, ABPA often manifests with hemoptysis and may be complicated by pneumothorax.[4]

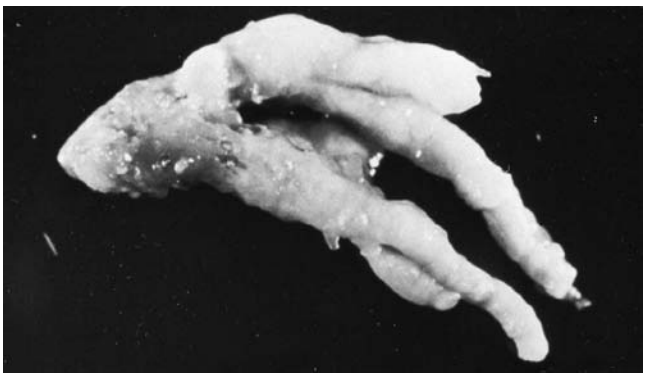
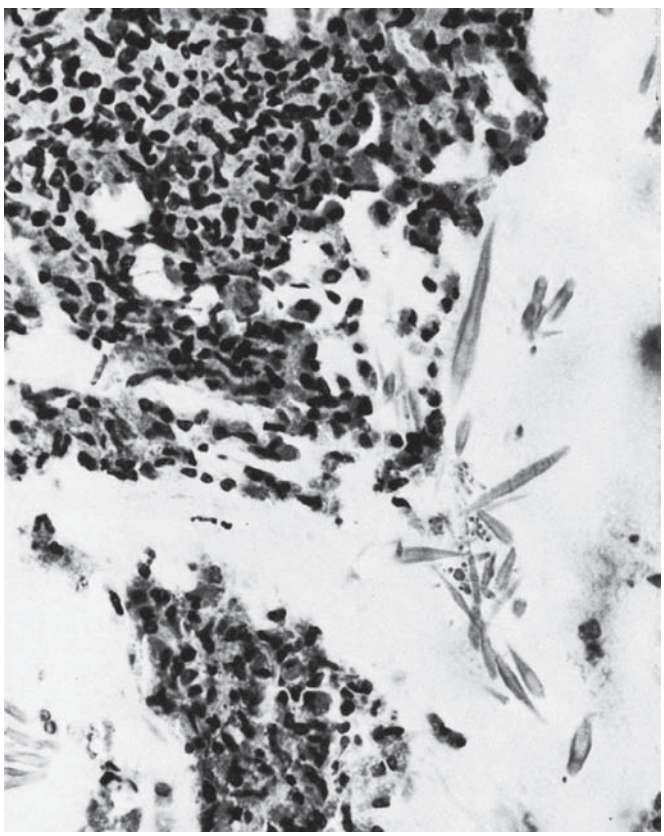
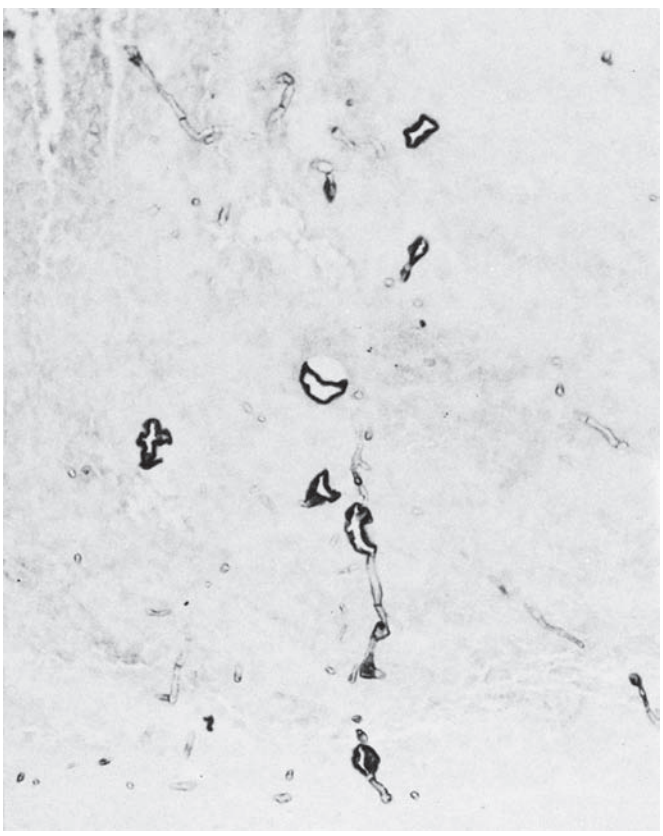


Figure 133-1 Mucus plug expectorated by a patient with ABPA. Of note is the tapering, cylindrical shape with branching characteristic of the parent bronchi. *(Used with permission of Dr. Frederic Askin, Chapel Hill, NC.)*

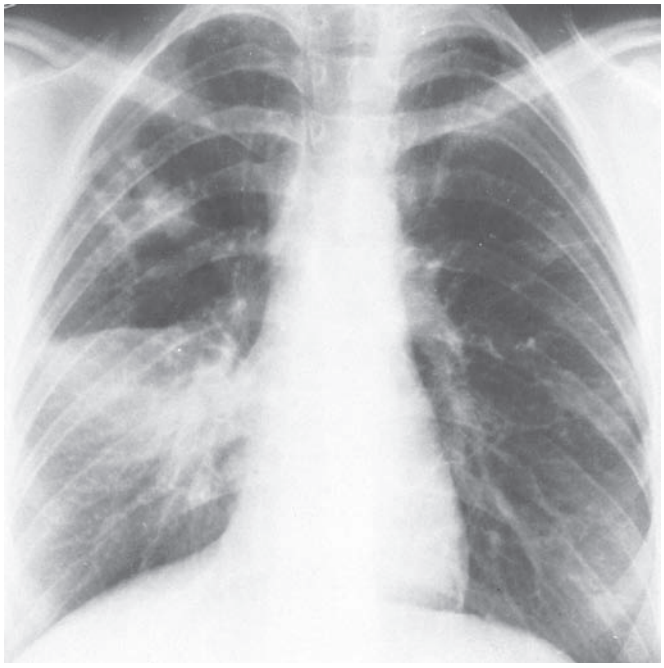


A

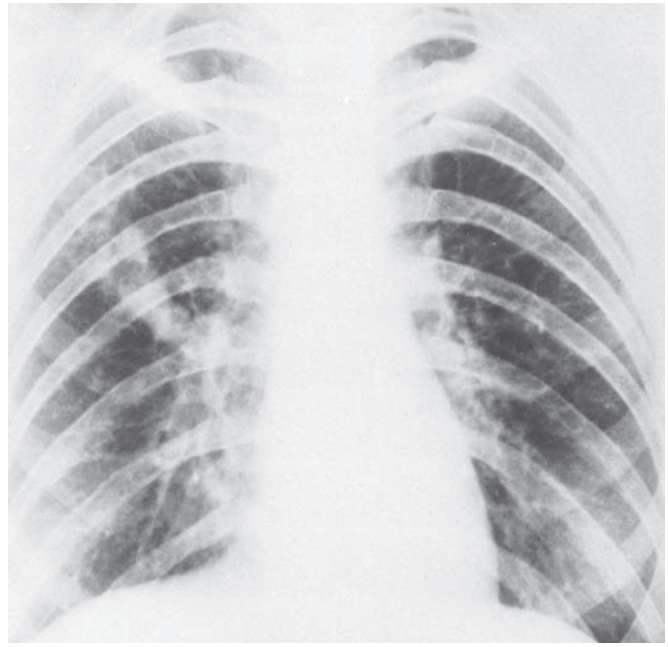


B

Figure 133-2 High-magnification photomicrograph of inspissated mucus in mucoid impaction of the bronchus. **A.** Groups of Charcot–Leyden crystals adjacent to clusters of necrotic eosinophils. H&E stain, ×520. **B.** *Aspergillus* hyphae. Of note is the transition from regular, thin septate hyphae to dilated, often folded degenerating forms. H&E stain, ×354. *(Used with permission of Drs. S. Albelda and G.H. Talbot.)*



A



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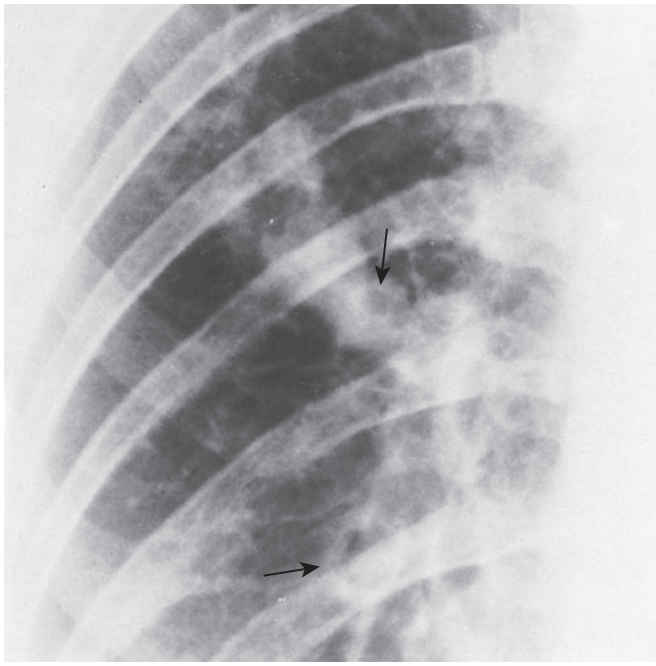


C

Figure 133-3 A 23-year-old woman with documented ABPA. **A.** Chest radiograph showing mucoid impaction in the right upper lobe and alveolar consolidation in the right middle lobe. **B.** Eight months later, the alveolar consolidation has resolved, and the appearance of the mucoid impaction in the right upper lobe has changed. **C.** Close-up of the right lung in **B** showing the "gloved finger" appearance of mucoid impaction as well as ring shadows *(arrows)* characteristic of bronchiectasis. *(Used with permission of Drs. S. Albelda and G.H. Talbot.)*

Radiographic Findings The radiographic features of ABPA have an essential role in diagnosis, as they may distinguish ABPA from simple, chronic asthma. Pulmonary infiltrates in cases of ABPA are initially transient, but they ultimately progress to permanent radiographic changes.[4,8] In many instances, the "ring sign" indicative of bronchial wall thickening, "parallel" shadows or "tram lines" suggestive of bronchiectasis, and branching "finger-in-glove" opacification of the dilated bronchi because of mucoid impaction are seen on regular chest radiographs of patients with ABPA (Fig. 133-3).[4,8] The presence of proximal bronchiectasis (Figs. 133-3 and 133-4), which is characterized by normal filling of bronchi distal to the sacular bronchial lesion, is considered a hallmark for the diagnosis of ABPA.[4] ABPA lesions are either focal or bilateral and tend to occur more frequently in the upper lobes. Late radiographic findings in patients with ABPA include cavitation, local emphysema, contracted upper lobes, and honeycomb fibrosis.

Chest computed tomography (CT) has been a significant aid in diagnosing ABPA because it is more sensitive than regular chest radiography; however, there are no pathognomonic CT findings for this entity.[4,8] Besides central bronchiectasis, CT findings highly suggestive of ABPA include the presence of varicose or cystic bronchiectasis of segmental and subsegmental bronchi (90% in ABPA vs. 30% in simple asthma), mucoid impaction of the segmental and subsegmental airway (67% in ABPA vs. 4% in simple asthma), and small airway abnormalities such as centrilobular nodules and tree-in-bud opacities (93% in ABPA vs. 28% in simple asthma).[4,8] In patients with CF especially, CT diagnosis of ABPA is particularly challenging, as there is a significant overlap in the radiographic features of both entities.[4] In fact, the presence of high-attenuation mucus plugs because of dystrophic calcification is the only CT finding that favors the diagnosis of ABPA in patients with CF.

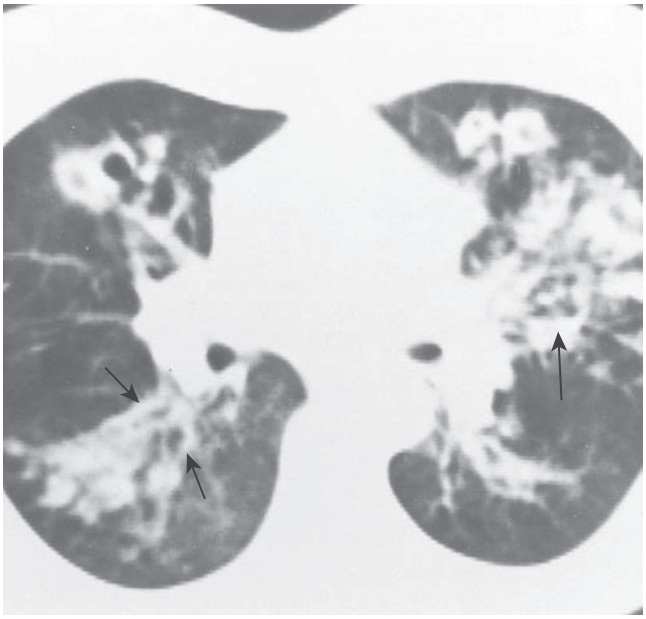


Figure 133-4 Proximal saccular bronchiectasis characteristic of ABPA. The CT scan reveals multiple rounded, dilated bronchi *(small arrows)*. Of note is the air–fluid level *(large arrow)*. *(Used with permission of Drs. S. Albelda and G.H. Talbot.)*

Diagnosis The "classic" patient with ABPA fulfills the criteria listed in Table 133-3. It has been suggested that the minimal essential criteria for the diagnosis of ABPA include the presence of (a) asthma, (b) immediate cutaneous reactivity to *Aspergillus* antigens, (c) elevated total serum IgE levels (>1000 U/mL), (d) elevated serum IgE and IgG levels to *A. fumigatus,* and (e) central bronchiectasis.[4,8] However, asymptomatic pulmonary involvement occurs in patients with ABPA and may lead to diagnostic uncertainty, delayed diagnosis, and irrevocable structural lung damage. Furthermore, corticosteroid-based therapy for asthma may mask the signs of ABPA, leading to a progressive decline in pulmonary function. Because the above criteria may not apply in such cases, some have proposed that serological evidence (all three serological tests listed in Table 133-3 and immediate skin reactivity test to *Aspergillus* antigens need to be positive) even without the presence of bronchiectasis may be sufficient to support an early diagnosis of ABPA.[4,8] In addition, the diagnostic criteria for ABPA in patients with CF were recently modified, because of the overlapping features between these entities. The new criteria consist of (a) clinical and/or pulmonary function deterioration from baseline status, (b) positive immediate cutaneous reaction to *A. fumigatus* antigens or elevated IgE *A. fumigatus* antibody serum level, (c) elevated serum total IgE level >1000 U/mL, (d) elevated serum IgG *A. fumigatus* antibody level or positive *A. fumigatus* precipitins, and (e) abnormal chest imaging findings or a change in baseline abnormalities.[4]

Important clinical clues that should alert clinicians to the possibility of ABPA include refractory asthma or asthma with any of the following features: bronchiectasis, radiographic infiltrates, prominent eosinophilia, and expectorated brown plugs that may contain eosinophils or hyphae (Fig. 133-2).[4] In addition, in patients with CF, prominent wheezing is considered to be suggestive of ABPA. Rarely, ABPA may be caused by non-*fumigatus* aspergilli or other fungi; in such cases, the serological tests will be negative.

Because no single clinical or immunological feature is diagnostic for ABPA, this disease is underdiagnosed. Until recently, serological diagnosis of ABPA was based on *Aspergillus* crude extracts, which are cumbersome, lack reproducibility, and frequently cross-react with other antigens. However, recent studies indicate that standardized recombinant *A. fumigatus* allergens have the potential to substantially increase the specificity and sensitivity of diagnosis of *A. fumigatus*-related diseases, including ABPA.[4,8] Several recombinant *A. fumigatus* allergens, including Aspf1, Aspf2, Aspf3, Aspf4, Aspf6, and Aspf16, show high specificity for the detection of sensitization to *A. fumigatus* and for the diagnosis of ABPA and appear to be superior to crude *Aspergillus* allergen extracts.[4] However, because the sensitivity of each recombinant *A. fumigatus* allergen is suboptimal, use of a panel of recombinant allergens is favored to increase the sensitivity of the diagnosis of ABPA. This diagnostic approach remains investigational. Further standardization and development of commercially available immunoassays containing a combination of these allergens holds promise for improving the diagnosis of ABPA.

Because patients with CF are at high risk for ABPA, initiation of annual screening in patients with >6 years of age for ABPA with monitoring of serum total IgE levels has been recommended with further diagnostic workup for ABPA in cases with IgE levels >500 U/mL.[4] Likewise, because treatment with corticosteroids has a significant impact on disease progression, screening CT has been advocated for asthmatics with a skin-prick hypersensitivity test positive for *A. fumigatus* extracts to identify ABPA at an early stage.[4,8]

Histopathology Because the diagnosis of ABPA is based on clinical and laboratory criteria, use of lung biopsy to confirm the diagnosis is usually not required. The presentations of the hypersensitivity syndrome associated with fungi are discussed in detail in Chapter 48. Some of the histopathological presentations associated with ABPA overlap those of invasive *Aspergillus* infection. Thus, eosinophilic infiltrates may be present in patients with a chronic invasive *Aspergillus* infection as well as in those with other allergic lung entities, such as Löffler syndrome, tropical eosinophilic pneumonia, and chronic eosinophilic pneumonia (see Chapters 71 and 137).[4,8] Mucoid impaction associated with ABPA or other fungi may predispose patients to bacterial superinfection (Figs. 133-1 and 133-2). Necrotizing granulomas in association with the presence of *Aspergillus* spp. in asthmatic patients may be observed and is

TABLE 133-3 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA)

Primary
Episodic bronchial obstruction (asthma)
Peripheral blood eosinophilia (>1000/mm^3)
Immediate type skin reactivity to *Aspergillus* antigens[a]
Precipitating serum antibodies (precipitins) against *Aspergillus* antigens[a]
Elevated serum IgE concentrations (>1000 ng/mL)[a]
Elevated serum IgE and/or IgG antibodies specific to *A. fumigatus*[a]
History of pulmonary infiltrates (transient or fixed) on chest radiographs or CT scans
Central bronchiectasis on chest CT scans
Secondary
A. fumigatus in sputum (by repeated culture or microscopic examination)
History of expectoration of brown plugs or flecks
Arthus reactivity (late skin reactivity) to *Aspergillus* antigen

[a]*Test must be positive for serological diagnosis in asymptomatic patients.*
Source: Adapted with permission from Rosenberg M, Patterson R, Mintzer R, et al., Clinical and Immunological criteria for the diagnosis of allegic bronchopulmonary aspergillosis. Ann Intern Med. 1977;86:405–414.

TABLE 133-4 Staging System for Allergic Bronchopulmonary Aspergillosis (ABPA)

Stage	Symptoms	Radiographic Features	Laboratory Features	Management
I. Acute	Fever, productive cough, wheezing	Pulmonary infiltrates, mucoid impaction	Blood eosinophilia, elevated serum IgE level, positive skin test	Corticosteroids to achieve remission
II. Remission	Asymptomatic	Normal	Decrease in IgE and blood eosinophilia	Careful follow-up
III. Exacerbation	All or some of acute-stage symptoms	All or some of acute-stage findings	At least a doubling of IgE in asymptomatic patients and an increase in IgE in symptomatic patients	Retreat with steroids to induce remission
IV. Corticosteroid dependent	Symptomatic steroid-requiring asthma	Variable	Usually continued elevation of IgE	Long-term steroids to control asthmatic symptoms and keep IgE levels at baseline
V. Fibrotic	Severe dyspnea, fibrotic lung disease, as well as bronchospasm	Pulmonary fibrosis	Restrictive plus reversible and irreversible obstructive function tests; may have continued increased IgE	Long-term corticosteroid use

Source: Adapted with permission from Mendelson EB, Fisher MR, Mintzer RA, et al., Roenterographic and clinical staging of allergic bronchopulmonary aspergillosis. Chest 1985;87:334–339, and Patterson R, Greenberger PA, Radin RD et al. Allergic bronchopulmonary aspergillosis: Staging as an aid to management. Ann Intern Med 1982;96:286–291.

considered part of the ABPA syndrome.[4,8] The histopathological distinction between ABPA, with fungal elements restricted to the airways, and semi-invasive or fully IA may be obscured by tissue necrosis or poor granuloma formation. These presentations are discussed further below and in Chapter 51.

Treatment ABPA may progress through five stages based on clinical, serological, and radiographic findings, which are summarized in Table 133-4.[4,8] Importantly, the first four stages are potentially reversible without long-term sequelae; only the last stage, which is characterized by fibrosis and bronchiectasis, is irreversible. The goals of therapy for ABPA are to treat acute exacerbations of disease and prevent the development of fibrosis and bronchiectasis. Therefore, early diagnosis of ABPA before permanent lung damage occurs is critical. Therapeutic modalities for ABPA include oral corticosteroids, metered-dose inhaler medications, and systemic antifungal agents.[4,8]

Use of oral corticosteroids remains the cornerstone of the treatment of ABPA.[4,8] These agents suppress the inflammatory response provoked by *Aspergillus* infection rather than eradicate the fungus. Recommended corticosteroid doses for acute exacerbations of ABPA are 0.5 to 1.0 mg/kg of prednisone equivalent daily for 1 to 2 weeks, followed by 0.5 mg/kg per every other day for 6 to 12 weeks. The physician should then attempt to taper the patient's corticosteroid dosage. However, some patients cannot be successfully weaned off corticosteroids and may require a daily maintenance dose of at least 7.5 mg.

Increasingly, use of itraconazole, an azole antifungal with activity against *Aspergillus* spp., has been employed as adjunctive fungal antigen-reducing therapy for ABPA, especially in patients with frequent relapses or corticosteroid dependence.[4,8] A randomized controlled study reported that oral administration of itraconazole (200 mg twice daily) was beneficial in terms of significant improvement of symptoms, pulmonary function, chest radiographic findings, and serum IgE levels in asthmatic patients with ABPA; uncontrolled studies suggested a similar benefit in patients with CF and ABPA.[4,8] However, use of itraconazole requires determination of drug levels to ensure adequate absorption and poses significant issues with long-term tolerability and drug–drug interactions.[5,6] Another important issue of prolonged itraconazole use is the emergence of azole-resistant *Aspergillus* isolates. In addition, itraconazole has a 40% failure rate in ABPA treatment.[6] The newer triazole voriconazole has improved fungicidal activity against *Aspergillus* spp. and better bioavailability when compared with itraconazole.[5,6] A recent retrospective study in 20 ABPA patients who failed or were intolerant to itraconazole and received either voriconazole or posaconazole found sustained clinical and immunologic responses and reduced corticosteroid requirements at 12 months in over 75% of treated patients.[5–7] However, high relapse rates (up to 57%) have been reported following discontinuation of azole treatment in patients with ABPA, and there are concerns for the development of secondary resistance in *Aspergillus* following prolonged courses of antifungal therapy.

Use of inhaled corticosteroids may help control the symptoms of asthma but does not prevent episodes of eosinophilic infiltration and mucus impaction and is generally thought to have no influence on progressive lung damage.[4,8] Inhaled bronchodilators such as β agonists, anticholinergics, and leukotriene antagonists may be used to treat asthma-related symptoms.[4,8] Inhaled antifungal agents such as nystatin and amphotericin B deoxycholate (AMB-D) may offer temporary suppression of colonization, but penetration of these agents into plugged bronchi is limited and recolonization rapidly occurs once therapy ends. Meticulous bronchial toilet is important for clearance of *A. fumigatus* from the airway. Thus, physical therapy with postural drainage is an important adjunctive treatment. Increased hydration, use of expectorants, and in selected patients, bronchial lavage may aid in viscid mucus clearance. Avoidance of environmental reservoirs of *Aspergillus* spp. such as compost heaps, grain silos, and decayed organic matter may help prevent exacerbation of ABPA. In patients with CF ABPA, differentiating between a bacterial exacerbation of CF and an ABPA flare is important, because initiation of corticosteroids may have detrimental effects in patients with bacterial infection; a serological assessment is essential as part of this evaluation.[4]

Immunotherapy with the injection of conventional allergens has not been shown to be of value for ABPA.[4,8] However, newer immunomodulatory approaches, including immune modulation toward a Th1 response by using *A. fumigatus* synthetic peptides, DNA-based vaccines, and immunostimulatory molecules such as cytosine polyguanine oligonucleotides, are being explored in animal models with promising results.

Monitoring of treatment efficacy and toxicity is imperative. Long-term follow-up of patients with ABPA has shown that increasing serum levels of IgE is often a harbinger of a clinical flare of the disease and that the levels of IgE decline correlate with a clinical response to corticosteroids.[4,8] Thus, a prudent course of action is

to determine baseline serum IgE levels when ABPA has been controlled by corticosteroid-based therapy and then monitor serum IgE levels regularly (every 1—2 months). Total serum IgE levels usually should decrease by at least one-third within 6 weeks from the initiation of corticosteroid-based treatment; infiltrates should be resolved after 1 to 2 months, and the results of pulmonary function tests should improve. Although serum IgE levels seldom return to normal, reinstitution of corticosteroids should be considered even in asymptomatic patients if the serum IgE level is double that of the baseline value.[4,8] In patients with symptomatic ABPA, chest radiographs should be obtained every 3 months during the first year of follow-up and yearly thereafter; pulmonary function tests should also be performed yearly.[4,8] However, no one has identified certain prognostic indicators for progression or regression of ABPA, and whether "pre-emptive" treatment of asymptomatic flares alters the natural history of the disease remains controversial.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is a rare hypersensitivity syndrome that is characterized histologically by replacement of bronchial mucosa with necrotizing granulomatous tissue.[8] Also, eosinophilic infiltration of bronchioles and fibrosis is prominent, whereas there is no evidence of *Aspergillus* invasion. *Aspergillus* hyphae have been demonstrated within the lesions in approximately half of the cases of bronchocentric granulomatosis. This syndrome is associated with asthma in half of the patients described and likely represents a severe exuberant focal manifestation of ABPA rather than the more generalized pulmonary pathology evident in patients with ABPA.[8] Patients typically present with chronic symptoms, such as malaise, cough, low-grade fever, dyspnea, dull chest pain, and hemoptysis associated with a focal lesion on chest radiographs, often in an upper lobe. Occasionally, radiographic findings of multiple nodular or mass-like lesions simulate metastatic carcinoma.[8] Diagnosis of bronchocentric granulomatosis is made based on biopsy or often retrospectively after removal of the lesion, which is curative. Some patients, especially those with multifocal lesions, may need corticosteroid-based therapy for ABPA.[8]

Extrinsic Allergic Alveolitis

Heavy or repeated exposure to *Aspergillus* conidia and mycelia may result in a hypersensitivity reaction affecting the alveoli in nonatopic individuals known as *extrinsic allergic alveolitis (*see Chapter 58).[8] Malt workers, distillers, brewers, and others exposed to moldy straw or grain have suffered attacks consisting of cough, dyspnea, fever, chills, myalgia, and malaise 4 to 8 hours after exposure to *Aspergillus* antigens.[8] Repeated exposures may lead to malt worker's lung or farmer's lung or to the development of granulomatous disease or interstitial fibrosis. The immunopathogenesis of extrinsic allergic alveolitis involves cell-mediated immunity (type IV response) and immune complex deposition (type III response) and likely involves an intricate interaction between these immune mechanisms.[8]

Radiographic changes in the acute syndrome include diffuse alveolar-interstitial infiltrates that may resolve with the removal of the inciting antigen. Patients with chronic extrinsic allergic alveolitis may have fine reticulonodular interstitial infiltrates that may progress to pulmonary fibrosis with honeycombing.[8] Serum IgG antibodies (precipitins) against *Aspergillus* antigens are present in patients with extrinsic allergic alveolitis; however, the serum IgE level is typically normal. Skin tests usually demonstrate an Arthus reaction at 4 to 8 hours and occasionally may be preceded by an immediate wheal and flare reaction and followed by a delayed reaction (36–48 hours afterward). Removal or avoidance of the source of antigen exposure is crucial in the management of extrinsic allergic alveolitis, as spontaneous recovery often ensues once exposure has ended.[8] Administration of corticosteroids is helpful in aiding the resolution of acute symptoms and reduces the likelihood of structural damage. However, corticosteroids are not helpful once fibrosis has developed.

Aspergilloma

Saprophytic colonization of a parenchymal lung cavity by *Aspergillus* is referred to as *aspergilloma*, *mycetoma*, or a *fungus ball.*[8] A fungus ball consists of both dead and living mycelial elements, fibrin, mucus, amorphous debris, inflammatory cells, and degenerating blood and epithelial elements. The mycelial mass may lie free within the cavity or be attached to the cavity wall by granulation tissue. Spontaneous shrinkage or disappearance of aspergilloma has been reported in 7% to 10% of cases and is often associated with bacterial superinfection of the cavity.[8] Aspergillomas only rarely increase in size. Most aspergillomas are caused by *A. fumigates*, but some, especially in patients with diabetes mellitus, are caused by *A. niger*, in which case oxalic acid crystals may be seen in the sputum.[8] Rare cases of extrapulmonary sites of aspergillomas involving the skin, brain, retroperitoneal area, and sinuses have been described.

Pathophysiology The pathogenesis of aspergilloma usually involves colonization and proliferation of the fungus in a pre-existing pulmonary cavity (secondary aspergilloma). The cause of a pre-existing cavity is most commonly prior cavitary tuberculosis; aspergilloma has been reported in 11% to 17% of patients with post-tuberculosis cavities.[8] In fact, 20% of patients who recover from cavitary tuberculosis develop aspergillomas within the next 3 years. Of interest, in developing countries tuberculosis is the predisposing factor for over 90% of cases of aspergilloma. However, an aspergilloma may complicate a wide spectrum of cavitating pulmonary diseases, such as sarcoidosis, histoplasmosis, blastomycosis, AIDS (especially in cases of atypical *Pneumocystis jiroveci* pneumonia), pneumonia and/or lung abscess, pulmonary or bronchial cysts, bronchiectasis, pulmonary fibrosis, asbestosis, adenocarcinoma, ankylosing spondylitis, rheumatoid nodules, cyanotic heart disease, and pulmonary infarction.[8]

Primary aspergilloma, which arises within the bronchial tree with the proliferation of *Aspergillus* leading to a pulmonary cavity, is far less common. The clinical conditions leading to the initiation of a cavitary process and formation of a fungus ball include IPA, chronic necrotizing pulmonary aspergillosis (CNPA), and ABPA. IPA may lead to primary aspergilloma during bone marrow recovery, as the host is able to mount an inflammatory response and ward off the fungus. Pneumothorax may be a severe complication of pulmonary mycetoma that is reported as a rare occurrence in patients with hematological malignancies.[8] ABPA may cause bronchiectasis in the chronic phase of the disease and result in aspergilloma secondary to growth of a fungus distal to a plugged bronchus.[4,8] In fact, aspergillomas have been found in 7% of patients with ABPA in one study. Thus, aspergilloma may provide a stimulus for the perpetuation of ABPA.

Typical biofilm structures have been observed in aspergillomas from patients and in a murine model of IPA. Aspergilloma formation is linked with the ability of the fungus to form an extracellular hydrophobic matrix with typical biofilm characteristics under different static conditions including interaction with bronchial epithelial cells. This extracellular matrix is composed of galactomannan, α-1,3-glucans, monosaccharides and polyols, melanin and proteins including major antigens and hydrophobins. In particular, the presence of α-1,3-glucans in the extracellular matrix has a predominant role in the agglutination of *Aspergillus* germinating spores and hyphae and the subsequent aspergilloma formation. Melanin production during infection could also play a role in facilitating lung tissue invasion possibly by attenuating or evading immune response. Defective extracellular matrix penetration by most antifungal agents makes them significantly less effective when *A. fumigatus* is grown under biofilm versus planktonic conditions. Thus, chronic

exposure and suboptimal azole concentrations in fungal biofilms could explain the emergence of azole resistant *A. fumigatus* isolates reported in these patients.[2,3,8]

Clinical Features/Diagnosis Hemoptysis is the typical manifestation of aspergilloma, as it is seen in 50% to 90% of patients.[8] Hemoptysis is typically infrequent and mild but can be occasionally massive or even fatal. The presence of any other symptoms, including dyspnea, fever, malaise, and weight loss, in patients with aspergilloma should be attributed to the underlying cavitary pulmonary disease or bacterial superinfection or suggest the presence of an overlapping IPA syndrome such as CNPA. The diagnosis is usually made based on clinical and chest radiographic features coupled with serological evidence of precipitating antibodies to *Aspergillus* spp.

Chest radiographs reveal a solid round mass within a cavity (3–5 cm diameter) partially surrounded by a radiolucent crescent (Monod's sign) (Fig. 133-5).[8] Movement of the fungus ball within the cavity may be appreciated when comparing upright and decubitus images. A solitary lesion in the upper lung fields is the most common radiographic feature of aspergilloma, as pre-existing tuberculosis cavities is the most common predisposing condition. However, aspergillomas can be bilateral and multiple. In many cases,

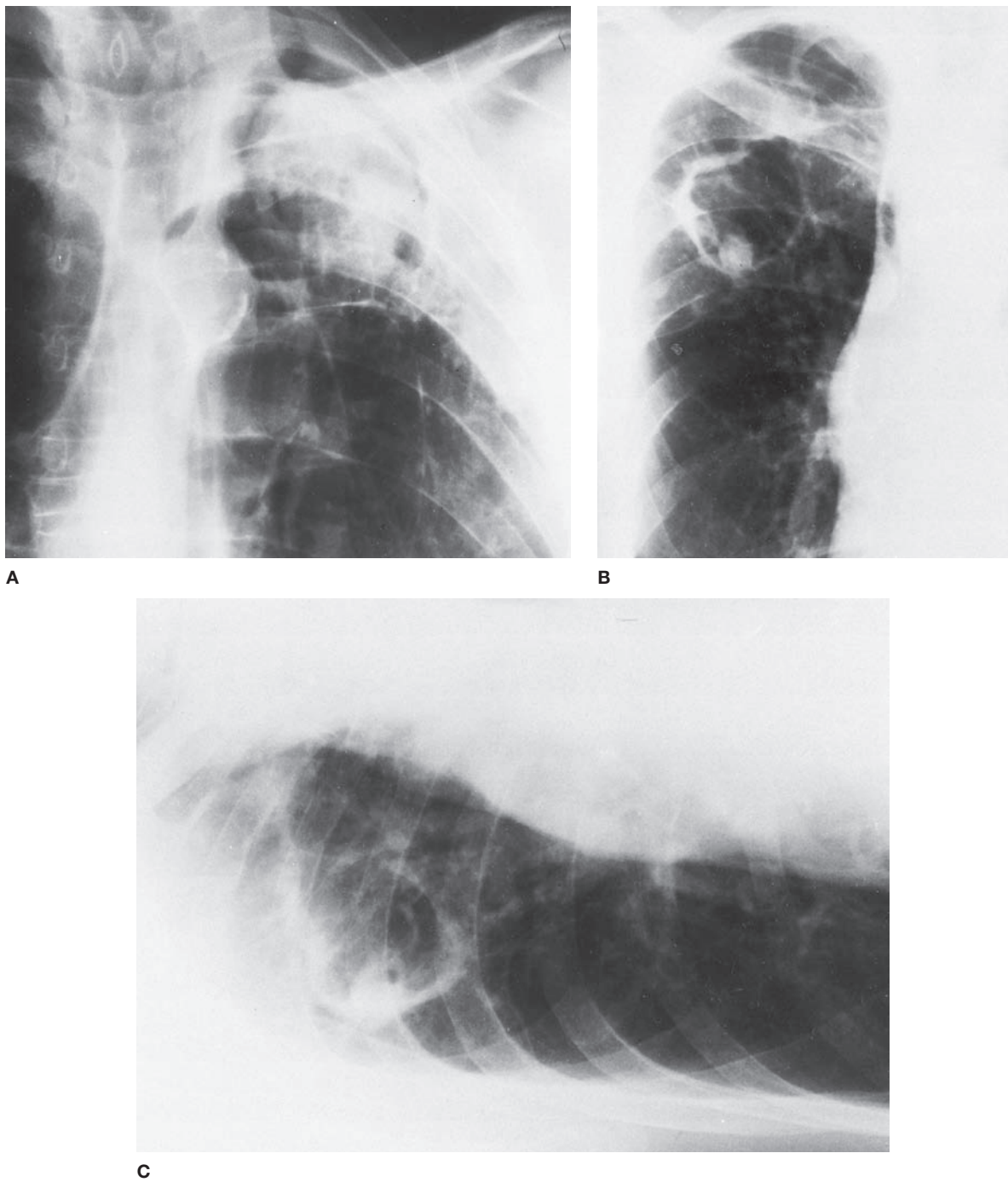


Figure 133-5 Radiographic appearances of pulmonary aspergillomas. **A.** A 51-year-old man with a history of tuberculosis showing the classic crescent-shaped patch of air (Monod's sign) as well as marked pleural thickening. **B.** A 49-year-old man with ankylosing spondylitis in whom an aspergilloma developed inside a thin-walled cavity. **C.** Decubitus film of the patient in *B* showing a fungus ball that moved when the patient changed position. *(Used with permission of Drs. S. Albelda and G.H. Talbot.)*

chest CT may be helpful in further delineating the radiographic features of an aspergilloma that are not apparent on chest radiographs. On CT scans, globules of gas are often seen within the hyphal mass. CT angiography may also provide useful information for patients with hemoptysis by identifying hypertrophic bronchial arteries that often supply the cystic wall of aspergillomas.[4,8]

Although sputum cultures are positive for *Aspergillus* in more than half of all patients with aspergilloma, culture is not a sensitive and specific diagnostic marker.[8] Precipitating antibodies to *Aspergillus* antigens are present in the sera of more than 95% of patients with aspergilloma; however, some patients receiving corticosteroids may be seronegative.[8] Eosinophilia, IgE, and skin-test reactivity may be seen in individuals who are allergic to the fungus, but these are not consistent findings. The main challenge for the clinician is to differentiate aspergilloma from other lung conditions, including lung cancer, cavitating Wegener granulomatosis, a blood clot in a pre-existing cavity, a disintegrating hydatid cyst, and a pulmonary abscess, all of which often share radiographic features with aspergilloma. Therefore, a positive precipitin reaction for *Aspergillus* is particularly helpful in establishing the diagnosis of aspergilloma. Clinical judgment and a low threshold for performing a lung biopsy in atypical cases are required.

Predictors of poor prognosis for aspergilloma include a progressive increase in the size and/or number of aspergillomas, severe underlying lung disease with a poor lung reserve, immunosuppressive therapy, AIDS, sarcoidosis, a rising *Aspergillus*-specific IgG titer, and repetitive episodes of severe hemoptysis.[4,8]

Treatment There is no consensus on the treatment of aspergilloma because of a lack of controlled studies. Because life-threatening hemoptysis occurs only in a minority of patients, subjecting all patients with aspergilloma to surgical therapy, which is often associated with significant morbidity and mortality, seems to be inappropriate.[8] Management options for aspergilloma currently include systemic or local administration of antifungal agents, surgical resection, and conservative management with careful follow-up without specific medical or surgical intervention.[8] Often, the best course of action for asymptomatic patients with aspergilloma is carefully repeated clinical evaluation with periodic chest radiographs without surgical intervention. Therapeutic considerations must include the individual patient's health status with attention to the potential risks of each treatment.

The definitive treatment of aspergilloma is surgical resection. However, in many patients, surgery is contraindicated because of severe underlying pulmonary dysfunction; the operation per se is associated with significant mortality and serious postoperative complications such as hemorrhage, bronchopleural fistula, bacterial superinfection, and empyema.[6,8] Therefore, it has been suggested that surgical resection of aspergilloma should be restricted to patients with severe, life-threatening hemoptysis and preserved pulmonary function. Surgical resection should also be considered for patients with poor prognostic features (e.g., chronic immunosuppression, sarcoidosis, and increasing *Aspergillus*-specific IgG titers).[6,8] Extrapleural resection has been reported to improve outcome. For patients who are unfit for surgical resection, an alternative approach is cavernostomy, which is performed under local anesthesia; however, cavernostomy is also associated with mortality and mediocre results.[6,8] This procedure should be considered as a last resort.

Intracavitary instillation of an antifungal agent is a promising alternative treatment in patients with severe pulmonary dysfunction who are poor candidates for surgery. CT-guided percutaneous instillation of AMB-D has been shown to be effective for aspergilloma in several cases of massive hemoptysis, with resolution of hemoptysis within 5 days.[8] The response to percutaneous injection of AMB-D was sustained with no recurrences for several months, improvement or even resolution of radiographic abnormalities, and reduction of serum *Aspergillus* antibody titers.[4,6,8] Endobronchial instillation of ketoconazole via fiberoptic bronchoscopy has also been successful.[8] Overall, topical therapy with antifungal agents is ideal for patients with a solitary aspergilloma who have severe hemoptysis and contraindications to surgical resection.

Bronchial arterial embolization (BAE) has been extensively used in the management of hemoptysis in patients with aspergilloma.[4,8] However, this approach has proven to be only temporarily effective, and recurrence of hemoptysis usually occurs because of the presence of collateral vessels in the involved area. Hence, BAE seems to be appropriate only as a "bridge" procedure in patients with massive hemoptysis until surgical resection of the aspergilloma can be performed. Also, radiation therapy has been shown to be effective for aspergilloma, even in patients with massive hemoptysis.[4,8] This modality has been recommended for cases of recurrence of life-threatening hemoptysis after BAE.

Itraconazole is an orally administered antifungal agent with activity against *A. fumigatus* and high tissue penetration into the lung. The use of itraconazole for aspergilloma has been reported in several noncontrolled studies.[4,8] Data from these studies showed that the use of itraconazole capsules at doses ranging from 200 to 400 mg/d for 6 to 18 months resulted in radiographic and symptomatic improvement in almost two-thirds of the patients and may have a place for the treatment of aspergilloma.[8] Serum itraconazole levels were not measured in most of these studies, but a recent study of treatment of pulmonary aspergilloma with itraconazole (100–200 mg/d) demonstrated sufficient itraconazole levels within the aspergilloma cavities.[4,8] The major limitation of itraconazole is that it works slowly; thus, use of it would not be prudent in cases of life-threatening hemoptysis. In addition, recurrence of aspergilloma often follows discontinuation of itraconazole treatment, whereas acquisition of secondary resistance of *A. fumigatus* isolates to itraconazole has been described in patients with aspergilloma following prolonged treatment. Voriconazole has been successfully used to treat pulmonary aspergilloma caused by itraconazole-resistant *A. fumigatus* isolates, although cases of voriconazole failure in patients with aspergillomas have also been reported. There is evidence of development of secondary resistance to voriconazole during long-term treatment of patients with aspergillomas.

Invasive Bronchial Aspergillosis

The term invasive bronchial aspergillosis (IBA) refers to infection involving the large airways. Further subclassification of IBA based on the bronchoscopic appearance has been proposed, including tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. In fact, these entities represent a continuous spectrum of this infection.[7,8] An alternative, more functional classification based on the depth of tissue invasion by *Aspergillus* includes (a) superficial infiltration type; (b) full-layer involvement type; (c) occlusion type (airway occlusion ≥50% of the original diameter of involved bronchi; and (d) mixed type. The potential impact of this classification system on the management of IBA has not been validated.

Aspergillus tracheobronchitis is the least invasive form of IBA and is characterized by the presence of a superficial tracheobronchial inflammation, intact mucosa with no evidence of ulcers, and pseudomembranes or other abnormalities; *Aspergillus* spp. are identified in mucus exudates.[7,8] In contrast, pseudomembranous tracheobronchitis is characterized by significant necrosis of bronchial epithelium and formation of pseudomembranous plaques, which are white, gray, or black in color. These lesions may progress and result in extensive invasion of the large airways; however, in the majority of patients, the depth of invasion does not extend beyond

the bronchial cartilage.[7,8] Finally, ulcerative tracheobronchitis is the most aggressive form of IBA and manifests with endobronchial plaques, nodules, or areas of ulceration and necrosis; in addition, the infection may extend to the adjacent pulmonary parenchyma and pulmonary vasculature.[7,8] Late sequelae of ulcerative tracheobronchitis include the formation of excessive granulomatous tissue with resulting bronchial stenosis.

The pseudomembranous form of IBA is typically seen in lung transplant recipients, who accounted for almost 40% of published cases.[6,8] In fact, IBA is the most common infection within 3 months following lung transplantation, whereas IPA tends to occur much later in this patient population. Occasionally, pseudomembranous tracheobronchitis is found in various clinical settings including HSCT, hematological malignancies, metastatic renal cell carcinoma, post-influenza, COPD, AIDS, systemic lupus erythematosus, metabolic abnormalities including DM, and even in immunocompetent individuals.[7,8] Patients may be initially asymptomatic or have symptoms attributed to the underlying illness with negative chest radiographs. However, as the infection progresses, symptoms become more pronounced, including characteristic stridor, resulting in respiratory failure and ultimately death. Persistent stridor in neutropenic or severely immunocompromised patients should raise suspicion for IBA; however this symptom occurs in less than one-quarter of all cases. Importantly, *Aspergillus* galactomannan antigen has limited value in IBA diagnosis as it is positive in only 60% of the cases.[5,6]

The ulcerative form of IBA occurs almost exclusively at the site of bronchial anastomosis in lung transplant recipients.[6] Bronchoscopically, the appearance is that of severe tracheobronchitis with multiple ulcers at the site of anastomosis. The symptoms are similar to those of pseudomembranous IBA. Complications include acute IPA, severe bronchial stenosis, anastomotic dehiscence, and bronchial necrosis with bronchoarterial anastomotic fistula.[6] Rarely, ulcerative IBA develops in patients with AIDS or solid tumors.[6] Diagnosis of all forms of IBA requires a high index of suspicion and is established only by bronchoscopic examination.

Bronchial stump aspergillosis is an unusual complication of lung resection.[5–7] The period from pneumonectomy to the onset of infection usually ranges from 6 to 12 months, although noted to occur after 3 years in one case. Patients may present with a productive cough and hemoptysis, sputum that may be putrid, and occasionally, expectoration of fungal material or suture thread.[5–7] Chest radiographs are usually unchanged when compared with those taken at baseline. The cause is secondary *Aspergillus* infection of silk suture material used to close the bronchus after pulmonary resection. Local inflammation, compromised tissue viability, and the use of silk sutures favor the establishment of *Aspergillus* infection. Substitution of nylon monofilament for silk sutures at surgery has significantly reduced this infectious complication.[5–7]

All of the forms of IBA, including bronchial stump anastomosis, require prompt treatment with systemic antifungals for IA (discussed in detail below). Data from controlled studies of the treatment of IBA are lacking, however. A common, although unproven practice is to combine systemic antifungal therapy, such as intravenous AMB-D or voriconazole, with aerosolized AMB-D.[5–7] Notably, most reported failures occurred following cessation of the treatment. Finally, surgical resection and stent placement may be necessary in conjunction with antifungal therapy if dehiscence of the anastomosis occurs because of tracheobronchial aspergillosis.[5–7]

Chronic Pulmonary Aspergillosis

Chronic forms of *Aspergillus* infection of the lung have long been recognized.[8] CPA occurs in patients with chronic cavitary lung disease and is characterized by an indolent clinical course evolving over months to years, constitutional symptoms, serum precipitins to *A. fumigatus*, elevated acute phase markers of inflammation, and an immune status that ranges from normal to mild immunosuppression. Locally invasive (semi-invasive) *Aspergillus* infection may be evident histopathologically. However, both angioinvasion and dissemination are absent. A variety of terms have been used for CPA, including pulmonary aspergillosis with cavitation, complex aspergilloma, chronic granulomatous aspergillosis, semi-invasive pulmonary aspergillosis, and CNPA.[8]

In an attempt to better define CPA, a subclassification of this entity based on clinical and radiographic findings was recently proposed, introducing the terms CNPA, chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrotic pulmonary aspergillosis (CFPA).[8] CNPA comprises a syndrome of slowly progressive cavitary lung disease, chronic respiratory symptoms, and the presence of precipitating antibodies against *Aspergillus*. Some cases of CNPA have invasion of the lung parenchyma by *Aspergillus* spp. However, in most of the described cases, there is no tissue invasion despite the presence of extensive and progressive tissue damage. CCPA refers to cases in which there is formation and expansion of multiple cavities over time, whereas CFPA refers to cases in which cavity formation is followed by a pronounced fibrotic reaction.[8] In addition, it has been recommended that any case with proven hyphal invasion of tissue should be classified as CNPA.

Defects in mucociliary clearance associated with structural lung disease appear to be a critical factor in the pathogenesis of CPA.[8] Prior mycobacterial lung infection, emphysema and/or COPD, bullae, asthma, sarcoidosis, pneumoconiosis, lung cancer, thoracic surgery, upper lobe fibrosis complicating ankylosing spondylitis, marijuana use, and a history of *Legionella* infection have been described as predisposing conditions for CPA. In addition, subtle but essential defects in innate immunity may play a role in the pathogenesis of CPA (see Chapter 121). Hence, defects in mannose-binding lectins, alterations in SP-D, certain polymorphisms in cytokine encoding genes such as transforming growth factor-β, TNF-α, IFNγ, and IL-15, and systemic illnesses associated with a degree of immunosuppression, such as corticosteroid-based therapy, diabetes mellitus, AIDS, and alcohol abuse, have all been associated with CPA in humans.[8] However, the precise pathophysiological mechanism of new cavity formation remains uncertain.

CPA tends to affect middle-aged individuals who are relatively immunocompetent and more male than female individuals.[8] CPA has an indolent and progressive course that lasts for years. Chronic productive cough and weight loss with mild hemoptysis, dyspnea, and fatigue are the usual presenting symptoms. Pleural fibrosis and *Aspergillus* empyema appear to complicate some cases of CPA.[8]

Although the diagnosis of CPA may be suspected with a single chest radiograph, sequential chest radiographs are typically required to confirm the progressive nature of CPA lesions. CT is particularly useful in defining the precise pattern and extent of the disease. Typical radiographic findings include the presence of one or more cavities, which may or may not contain fungus balls, often located in the upper lobes.[8] New cavity formation and expansion of preexisting cavities are also characteristic of CPA. Pericavitary infiltrates and adjacent pleural thickening are frequently observed and appear to correlate with the overall disease activity.[8] With appropriate treatment, these radiographic abnormalities may regress, leaving residual thin-walled empty cavities.

The combination of characteristic clinical and radiological findings and either the presence of *Aspergillus* precipitins or the isolation of *Aspergillus* spp. from respiratory samples is highly indicative of CPA.[8] Although the demonstration of precipitating antibodies to *Aspergillus* is the cornerstone and a prerequisite for the diagnosis of CPA, these antibodies may be negative, especially in case of infection with non-*fumigatus Aspergillus* spp.[8] Histopathology demonstrates chronic inflammation and fibrosis, sometimes with granulomatous features with or without visible hyphae. The absence

of hyphae does not exclude the diagnosis of CPA because of the paucity of high fungal burden in patients with CPA.

Differentiating CPA from other serious lung conditions that require specific therapy, such as cancer and chronic cavitary mycobacterial and endemic fungal infections, as well as other inflammatory lung conditions is a major challenge as overlap is not uncommon. In fact, there is a strong association between CPA and atypical mycobacterial infections. In these cases, imaging is not helpful, so biopsy and comprehensive microbiological studies must be used to exclude the co-existence of CPA with such entities. In addition, CPA differs from simple aspergilloma because of the presence of constitutional symptoms, the development of persistent pericystic lung nodules or pleural thickening, consolidations or ground-glass opacities, and the development and/or progression of cavities.[8] Finally, one should always consider the possibility of a pyogenic infection in a cavity that may require drainage and appropriate antibacterial treatment.

CPA requires prolonged treatment with systemic antifungal agents. In the literature, most patients with CPA have received treatment with oral itraconazole, whereas IV AMB-D has been successfully used in refractory cases.[8] In a series of 18 patients, use of itraconazole capsules resulted in improvement or stabilization of disease in 71% of the cases.[8] Use of voriconazole has been associated with favorable responses in small case series with response rates ranging from 30% to 80% and should be considered as another treatment option. Posaconazole has also successfully used with 61% response rate in 79 patients with CPA. However, emerging rates of azole resistance in *Aspergillus* isolates recovered from patients with CPA have been reported, although there is controversy on whether in vitro resistance of *A. fumigatus* to azoles correlates with worse clinical outcome. In addition, serious side effects necessitating discontinuation of treatment with azoles occur in up to 27% of the patients. Alternative treatment strategies include intravenous use of polyenes or echinocandins. Although the reported response to IV AMB-D (81%) appears to be slightly better than that to itraconazole, administration of AMB-D may require prolonged hospitalization and is associated with considerable toxicity, especially nephrotoxicity.[8] In a recent randomized study, treatment with IV micafungin had comparable (60%) rates of response with IV voriconazole (51%) and significantly less adverse effects in patients with CPA and could represent an alternative especially in cases where azole resistance in a concern.[6] Anecdotal reports of improved outcome as a result of adjunctive immunomodulating treatment with IFN-γ have also been reported.[8]

Surgery plays a limited role in the treatment of CPA because of the poor overall lung function in many patients. Major postoperative complications, such as respiratory failure, bronchopleural fistulae, pleural extension of aspergillosis, and even dissemination of *Aspergillus* can occur.[8] Thus, surgery should be reserved for selected patients with a reasonable respiratory reserve for whom there are no other treatment options. For example, surgery may be appropriate for patients with severe hemoptysis if embolization fails.

Although systemic antifungal therapy for CPA seems to be beneficial, assessment of response to it is difficult to gauge because the activity of the disease may fluctuate over time. Weight gain and improved energy levels are the earliest and most reliable indicators of response. Inflammatory markers also improve albeit more slowly, and they usually remain elevated even during long-term therapy. Relapse months or years after discontinuation of treatment is frequently reported.

Invasive Pulmonary Aspergillosis

An important clinical manifestation of Aspergillus-related disease is invasive pulmonary aspergillosis, discussed in detail below.

Epidemiology *Aspergillus* has emerged as one of the most common causes of infectious death in severely immunocompromised patients, with mortality rates approaching 70% in patients with leukemia and recipients of HSCTs.[2,5–7] Surveillance studies demonstrated a three- to fourfold increase in the frequency of *Aspergillus* infections at major cancer centers over the past two decades. In fact, IPA has surpassed invasive candidiasis as the most common fungal infection found at autopsy at several institutions; approximately 15% to 20% of patients with leukemia die of fungal pneumonia caused by *Aspergillus* spp. Similarly, in allogeneic HSCT recipients, 15% to 30% of deaths are caused by refractory fungal infections, mainly caused by *Aspergillus* spp., and most of these infections occur late in the postengraftment period in the setting of graft-versus-host disease (GvHD).[2,5–7] Large prospective multicenter surveillance studies contacted by the Transplant-Associated Infection Surveillance Network (TRANSNET) and Prospective Antifungal Therapy (PATH) Alliance has furthered insights into the epidemiology of IA in the United States. From both studies, IA has emerged as the most common invasive fungal infection in HSCT and solid-organ transplant recipients (43% and 59% of all IFIs, respectively) over invasive candidiasis and mucormycosis, with a 12-month cumulative incidence of 1.6%. Overall mortality in these patients was estimated to be approximately 36% and 75% at 12 weeks and at 1 year, respectively.[5–7]

Changes in HSCT practices over the past decade have greatly impacted the epidemiology of IPA. Autologous HSCT is associated with a low risk of IPA because of shortened periods of preengraftment neutropenia and a lack of GvHD. On the other hand, IPA has a bimodal distribution in allogeneic HSCTs, with patients at risk before and after bone marrow engraftment. The increasing use of peripheral blood stem cells, growth factors, and nonmyeloablative conditioning regimens (mini-transplants) in allogeneic HSCT has shortened the duration of preengraftment neutropenia and the incidence of IPA shortly post HSCT. In contrast, late (40–80 days after engraftment) and very late (80+ days after engraftment) IPA has increased.[5–7] This trend is associated with increased use of matched unrelated-donor (MUD) allogeneic transplants and with interrelated risk factors, such as lymphopenia, chronic GvHD, corticosteroid-based therapy, and/or CMV infection.[5–7] Among HSCT recipients, IPA now predominantly occurs as a community-acquired rather as a nosocomial infection in nonneutropenic patients late after engraftment, in whom GvHD and management with increasingly intense immunosuppression have emerged as the major risk factors. Of interest, recent studies in HSCT recipients implicate geoclimatic changes, associated with high environmental spore counts following periods of high temperature and low precipitation, as a factor for the development of IPA.

In addition to the "classic" groups of patients at risk for IPA, such as those with prolonged, profound neutropenia because of a hematological malignancy (5%–25% risk) or aplastic anemia; recipients of allogeneic HSCTs (5%–30% risk), or lung transplants (17%–26% risk); those with AIDS, severe combined immunodeficiency, or CGD (25%–40% lifetime risk); burn patients; and patients receiving chronic corticosteroids, IPA has been increasingly described in new groups of patients.[5–7] Hence, patients with systemic lupus erythematosus, patients with multiple myeloma who receive high-dose steroids, and premature neonates are prone to the development of severe IPA. Furthermore, several cases of IPA have been lately reported in patients with Crohn disease or rheumatoid arthritis who received treatment with TNF inhibitors (e.g., infliximab).[5–7] Even the use of high-potency inhaled steroids may predispose some apparently normal hosts to IPA in rare instances. IA is considered an emerging infection in patients with prolonged stay in intensive care units (ICUs). ICU aspergillosis is a distinct clinical entity that is probably underreported.[2,5–7]

IPA caused by *Aspergillus* spp. less susceptible to antifungals than *Aspergillus fumigatus* such as *A. terreus and A. flavus* has also been

reported in individual institutions.[2,5–7] This phenomenon may be at least partially a reflection of antifungal selection pressure determined by extensive empirical and prophylactic use of antifungal agents in high-risk patients. Alternatively, because non-*fumigatus* aspergilli cause nosocomial infections more frequently than does *A. fumigatus*, an epidemiological niche for these species may also account for their predominance in some institutions. *A. terreus* is clinically resistant to AMB, but species, including *A. flavus, Aspergillus lentulus, Aspergillus nidulans, Aspergillus ustus, Aspergillus glaucus,* and others, can also demonstrate resistance to antifungal agents.

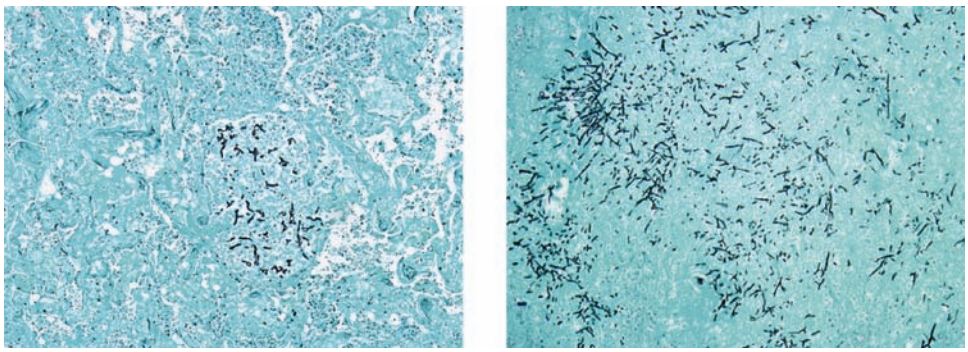
A number of nosocomial clusters of IPA have been reported over the past three decades mostly associated with hospital construction and defects in air-handling equipment. Air and environmental surfaces have been the focus of most investigations. Water has been implicated as an additional source of nosocomial transmission of *Aspergillus* spp., although this has not been confirmed in other studies.[2,5–7] An outbreak of IPA after major cardiac surgery caused by abnormally high levels of fungal spores in the air of the ICU has been recently reported.

Pathogenetic Mechanisms Because *Aspergillus* is a saprophytic mold that colonizes in the respiratory tract of immunocompromised patients, the pathogenesis of infection depends on the host's underlying immunosuppression. In the immunocompromised host, IPA typically occurs following inhalation of *Aspergillus* conidia, although hematogenous dissemination from a cutaneous or gastrointestinal source is seen occasionally.[1,2] Damage to respiratory epithelium because of radiation therapy, chemotherapy, GvHD, or prior infection (e.g., RSV, influenza) may facilitate attachment of *Aspergillus* conidia to the respiratory epithelial surface.[5]

Breach of mucosal host defense mechanisms in the setting of underlying immunodeficiency places the host at risk for invasive infection by *Aspergillus* spp. Thus, once *Aspergillus* has invaded the respiratory tract, control of the infection is highly dependent on functional adaptive immune responses. Lymphopenia and local/global dysregulation of the host adaptive Th1/Th2 polarization have been shown to play a key role in the subacute progression of IPA in nonneutropenic hosts.[5–7] Hence, in the late postengraftment period, allogeneic HSCT recipients have a low IFN-γ/IL-4 ratio, which is suggestive of a Th2 response that potentially accounts for their susceptibility to IPA.[3–5,7] In comparison, healthy individuals mount a predominantly Th1-type cellular response to *Aspergillus* infection. In humans, iatrogenic suppression of protective Th1 responses is common, particularly in the setting of chronic GvHD (an excessive Th1 response of allograft T lymphocytes) treated with high-dose corticosteroids and/or other immunosuppressive regimens.[3,5,7] Importantly, *Aspergillus*-mediated suppression of host Th1 responses by production of gliotoxin is also plausible.[2,3] Similarly, recent preclinical data indicate that herpes virus reactivation and bacterial co-infection in the lungs induce profound dysregulation of immune responses, facilitating the development of IPA.[2,3,5–7] For example, CMV infection can result in dysfunction of dendritic cells and phagocytes, which may predispose patients to IPA. Of interest, critically ill patients with prolonged ICU stay develop a systemic deactivation of the immune system following sepsis or any severe insult that has activated a systemic inflammatory response.[3] This sepsis-induced immune paralysis often results in superinfection with opportunistic pathogens, including *Aspergillus*. In agreement, mice recovering from sepsis remain exquisitely susceptible to *Aspergillus* and develop IPA upon pulmonary infection without the need for immunosupression.[3] Although the mechanism of increased susceptibility to *Aspergillus* in sepsis-induced immunosupression remains obscure, there is evidence of predominance of a deregulated myeloid cell response with increased levels of IL-13, IL-4, TGF-β in the lung of mice that develop invasive fungal infection. Importantly, deregulated cytokine release by myeloid cells and associated susceptibility to IPA in septic mice could be restored by adoptive transfer of bone marrow–derived dendritic cells from healthy mice.[3]

Once germination of conidia occurs, *Aspergillus* hyphae invade pulmonary arterioles and lung parenchyma, leading to ischemic necrosis. Hematogenous dissemination with thrombosis, hemorrhagic infarction, and invasion of distant organs may result from invasion of arterioles by *Aspergillus* hyphae and is found in approximately one-third of cases of IPA at autopsy.[2,5–7] Thus, IA, in addition to pneumonia, can present with a clinical picture similar to that of other thrombotic and embolic diseases, such as pulmonary embolism, cerebral vascular accidents, Budd–Chiari syndrome, and renal papillary necrosis. In addition, IA can spread to contiguous structures, across the diaphragm to the stomach, or from the lung to the heart or superior vena cava.

Importantly, it has been recently demonstrated that IPA has different pathophysiological mechanisms depending on the type of immunosuppression. Thus, a low *Aspergillus* tissue burden, extensive inflammatory injury, absence of angioinvasion, and localized infection have been observed in corticosteroid-immunosuppressed mice, whereas minimal inflammation, extensive angioinvasive *Aspergillus* growth, and disseminated infection are characteristic of IPA in cyclophosphamide-treated neutropenic mice.[2,5–7] In corticosteroid-treated mice, host immune effector cells appear to have limited activity against *Aspergillus* hyphae but cause extensive alveolar damage and exudative bronchiolitis, which appears to be more important than the *Aspergillus*-induced injury itself. This nonangioinvasive form of IPA has been increasingly recognized in a wide range of nonneutropenic hosts, including those who received corticosteroids, recipients of solid-organ transplants and allogeneic HSCTs with GvHD, patients with AIDS, and patients with CGD (Fig. 133-6).[2,5,7] Similar to the animal models of IPA, histopathology



A B

Figure 133-6 The characteristic pattern of *Aspergillus* invasion in tissue obtained from (**A**) an HSCT recipient with IPA and severe GvHD and (**B**) a patient with acute leukemia and severe neutropenia in whom IPA developed Extensive inflammation, less *Aspergillus* burden and absence of angioinvasion was observed in the patient with GvHD. In comparison, the histopathology of IPA in the patient with severe neutropenia was characteristic for scant infiltration by phagocytic cells, extensive coagulative tissue necrosis caused by angioinvasion, and a high fungal burden. Gomori methenamine silver stain, ×100. *(Used with permission of Dr. M. Luna.)*

in those nonneutropenic patients is characterized by extensive pyogranulomatous inflammatory reactions, inflammatory necrosis, and extensive cavitation.

Although deficiency of TLR adaptive protein MyD88 and Dectin-1 in humans is not associated with the development of IA, genetic polymorphisms in TLR-1, TLR4, TLR-6, and Dectin-1 predispose to the development of IA in allogenic HSCT recipients.[3] In addition, polymorphisms in IL-10 and plasminogen are associated with increased risk for IA. Thus, better understanding immunogenetics of IA in these high-risk individuals could facilitate risk stratification and design of preventive strategies.[3]

Clinical Features Symptoms of IPA begin with fever (unless the patient is receiving corticosteroids), which may be followed by a mild nonproductive cough suggestive of bronchitis. Pleuritic chest pain and progression to pneumonia occur within 1 to 2 days. Cavitation tends to occur in patients if immunosuppression is decreased, such as in leukemic patients during recovery of bone marrow hematopoiesis or when steroid-based therapy is reduced significantly, and on occasion gives rise to massive hemoptysis (Figs. 133-7 and 133-8).[2,5–7] Pleuritic pain and slight hemoptysis may suggest pulmonary infarction. Patients also may expectorate necrotic tissue filled with hyphae. Cough, sputum production, and pleural effusion are either absent or minimal. IA must be strongly considered when dealing with susceptible patients in whom treatment with broad-spectrum antibiotics fails.

Extrapulmonary sites may be involved including the highly vascular organs such as the kidneys, liver, spleen, and central nervous system. Invasive disease of the nose and paranasal sinuses occurs in immunocompromised patients, and contiguous invasive spread into the orbit or into the cranial vault can result in a syndrome similar to rhinocerebral mucormycosis.

Diagnosis Substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of IPA. Chest radiographs are not sensitive in detecting early forms of bronchopulmonary IPA, and up to 10% of patients with proven IPA have "normal" chest radiographs within a week of death.[2,5–7] High-resolution CT scans of the chest may reveal small wedge-shaped subpleural lesions or nodules typically surrounded by intermediate attenuation. This halo sign correlates with hemorrhage and edema surrounding an infarct caused by thrombosis and is highly suggestive of acute IPA, especially in neutropenic patients with leukemia.[2,5–7] However, the halo sign has been documented only in 33% to 60% of patients and is transient. In fact, to be useful for the diagnosis of IA, CT must be performed within 5 days of the onset of infection, because more than 75% of initial halo signs disappear within a week.[2,5–7] With neutrophil recovery, these lesions coalesce and cavitate, forming the "air crescent" sign, a classic sign of late filamentous invasive mold infection (IMI). However, the air crescent sign does not appear until the third week of the infection, and the appearance may be too delayed to be helpful in the diagnosis of IA. Importantly, lesions frequently increase in size in the first 7 to 10 days following effective antifungal therapy. In view of the angioinvasive nature of IPA, detection of vascular occlusion by CT-based pulmonary angiography was evaluated in a recent study as an early sign of IMI. Importantly, the presence of positive vascular occlusion sign was more sensitive and specific than the halo sign and comparable to serum galactomannan test for diagnosis of IPA. Thus, CT pulmonary angiography could represent a viable diagnostic tool for IPA, especially in patients at low-risk of contrast-induced acute kidney injury.

Persistently febrile neutropenic patients with leukemia would benefit from the use of early high-resolution chest CT to identify early radiologic signs of IPA such as the halo sign. In a recent study of febrile neutropenic patients, early and routine CT scanning coupled with early intensive antifungal-based treatment and surgery resulted in increased survival rates when compared with therapy initiated at the first sign of a pulmonary fungal infection.[2,5] CT also plays a critical role in determining the appropriateness of various downstream diagnostic procedures (bronchoalveolar lavage [BAL], percutaneous needle biopsy, and open lung biopsy) in patients with IPA. Nonetheless, clinical and radiologic presentations of IPA in the

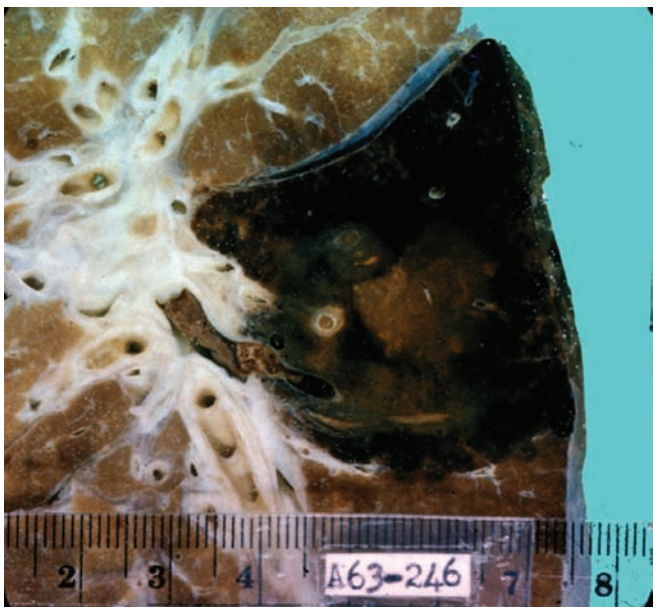


Figure 133-7 A 62-year-old man with acute leukemia in whom IPA developed. The gross appearance of the fungal lesion shows a central necrotic area surrounded by a lining of hemorrhagic infarction. *(Used with permission of Dr. G.P. Bodey.)*

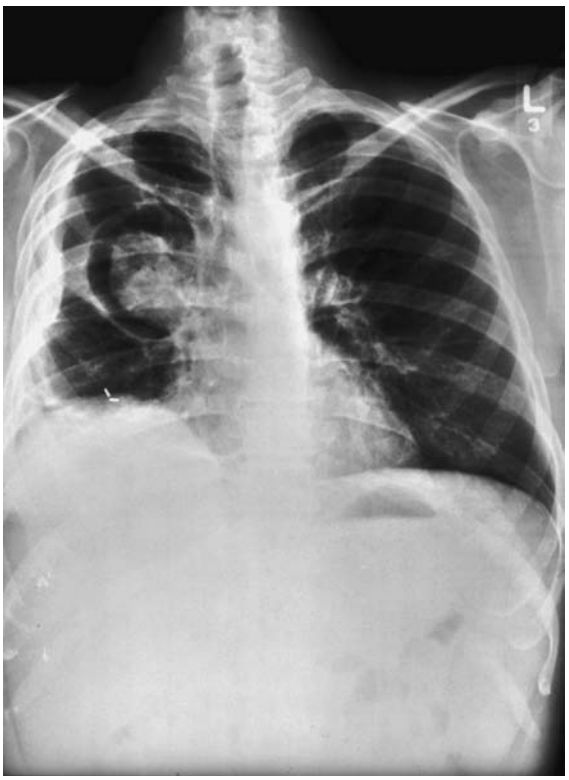


Figure 133-8 The characteristic radiographic features of IPA following neutrophil recovery illustrated in a patient with acute leukemia. A lesion has cavitated, creating the air crescent sign. *(Used with permission of Dr. G.P. Bodey.)*

expanding group of nonneutropenic patients who develop infection is atypical, including cases with tree-in-bud opacities or diffuse ground-glass appearance in CT.[2,5–7]

Respiratory cultures of *Aspergillus* from expectorated sputum, bronchial washings, or BAL specimens have low sensitivity (<30%) for diagnosing IA but a high positive predictive value (>60%) in heavily immunocompromised patients.[5] Early performance of CT-guided fiberoptic bronchoscopy with BAL in immunocompromised patients with pulmonary infiltrates has been shown to improve the diagnostic yield of this procedure. In addition, there is a need for the development of standardized BAL protocols in order to facilitate comparative clinical studies on the diagnosis of IPA. Blood cultures have little diagnostic value for IA but may reflect true disease cases of *A. terreus* infection. Ultimately, open lung biopsy may be required for a definitive diagnosis of IPA and may not be feasible until late in the course of infection or recovery of pancytopenia.

In recent years, efforts have been directed toward identifying non–culture-based markers for rapid, reliable diagnosis of IA.[5–7] Those based on the detection of anti-*Aspergillus* antibodies have very poor sensitivity for IA, especially in patients receiving immunosuppressive agents. Instead, tests based on identifying circulating fungal antigens or metabolites are promising. To date, the two approaches that have demonstrated the greatest promise in early clinical studies are detection of antigens and measurement of *Aspergillus* nucleic acids by using PCR.

Galactomannan is a polysaccharide cell wall component of *Aspergillus* spp. that is released into the circulation during fungal growth in tissues and can be detected in the serum of patients with IA.[5–7] A sandwich enzyme–linked immunosorbent assay (ELISA) capable of detecting galactomannan at concentrations as low as 0.5 ng/mL has been recently developed. Initial studies evaluating the role of galactomannan serum assay in the diagnosis of IA have been predominantly conducted with profoundly neutropenic patients undergoing chemotherapy for cancer or recipients of HSCTs who were on fluconazole prophylaxis. These studies have documented sensitivity rates ranging from 67% to 100% and specificity rates ranging from 86% to 99% in these patients.[5–7] When serially monitored, the galactomannan assay preceded the diagnosis of IA by an average of 6 to 14 days. However, in a recent study that evaluated the value of the galactomannan assay in the detection of early IA, the appearance of major lesions (halo sign, air crescent sign, and cavitation) on high-resolution CT scans almost coincided or even preceded the detection of the galactomannan antigen in serum.[5–7] Furthermore, uncertainties remain regarding the performance of this assay in other settings, such as breakthrough IA to mold-active antifungal prophylaxis, pediatric populations, and solid-organ transplant recipients. Other factors, such as the pretest probability of infection, the patient's immune status (neutropenia vs. GvHD), antifungal therapy, antibacterials, and diet may affect both the performance and interpretation of the galactomannan assay. Hence, sensitivity rates as low as 30% have been reported in nonneutropenic HSCT recipients receiving mold-active antifungal prophylaxis and lung transplant recipients.[5–7] In addition, false-positive results have been described in patients receiving β-lactam antibiotics, particularly piperacillin–tazobactam, as well as in those ingesting certain cereals, pastas, nutritional supplements, and soy sauce produced with fermentation products of *Aspergillus oryzae*, a fungus commonly used in food production.[5,7] In addition, false-positive galactomannan antigenemia has also been reported as a result of transfusion of blood products. Recent studies evaluated the performance of detection of galactomannan in other fluids, particularly BAL and showed that BAL GM has improved sensitivity compared to serum GM in high-risk patients with IPA.[2,5–7] A recent meta-analysis of 30 diagnostic studies with the use of BAL GM, using an otimal cutoff value of 1.0, the BAL-GM assay had 90% sensitivity and performed better compared to PCR and serum GM test although specificity was lower (89%).

A colorimetric assay for the detection of 1,3-β-D-glucan, an integral cell wall component in a number of pathogenic yeasts and filamentous fungi, recently became commercially available.[5,7] The sensitivity and specificity rates for this test in limited studies thus far have ranged from 67% to 100% and from 84 to 100%, respectively. Several false-positive test results have been reported in patients with cirrhosis, in patients undergoing hemodialysis, in patients following abdominal surgery, and in those receiving chemotherapy with particular agents.[5,7] Furthermore, the 1,3-β-D-glucan assay has been reported to be less sensitive and reproducible and become positive later in the course of IA when compared with galactomannan antigen assay.

PCR detection of *Aspergillus* nucleic acids is a promising method for early detection of IA. The sensitivity of PCR is excellent, but its specificity for invasive infections can be problematic, and false-positive results are common.[5,7] Multiple unresolved issues accompany the use of PCR for the diagnosis of IA, including the sample type (serum, BAL fluid), amplification strategy (nested vs. conventional PCR), protocol (real-time quantitative vs. conventional PCR), and primer selection (*Aspergillus*-specific or pan-mold, pan-fungal primers). There have been no good studies examining how PCR performs in comparison with galactomannan detection for the early diagnosis of IA. However, it has been shown that PCR is inferior to serum galactomannan assay in animal models and in some but not all human studies.[5–7] A recent meta-analysis of 19 studies comparing the value of BAL PCR with BAL GM concluded that although sensitivity and specificity of both tests were comparable, combination of both tests increased sensitivity without compromising specificity. Thus, like GM testing, PCR is likely to become an adjunctive diagnostic method alone or in combination with other biomarkers and standard microbiological, histological, and radiographic methods of diagnosing IA.

Novel investigational diagnostic approaches include the development of a breath test to detect volatile *Aspergillus* biomarkers that are not produced by other pathogens, and detection of circulating *Aspergillus* antigens in BAL and serum of patients with IPA by using an immunochromatographic lateral flow device.

Treatment of IPA Although the past two decades have witnessed improved outcomes of patients with IA, the mortality rate of this mycosis in severely immunocompromised patients remains unacceptably high. Several strategies have been applied in an attempt to improve the outcome of IA. These include the introduction of potent antifungal agents such as voriconazole, early onset of treatment triggered by CT and/or galactomannan antigen, use of delivery systems to improve the therapeutic index of currently available antifungals such as lipid formulations of AMB, and possibly combination antifungal therapy, surgical excision of sequestered necrotic lesions, and use of immunomodulating agents in selected patients.[6] There has not been a systemic evaluation of the merit of each of these strategies in the treatment of IA, however. This is not surprising in view of the complexity of IA and the paucity of organized, prospective controlled clinical studies in refractory IA.

Tables 133-5 and 133-6 list the principles of management of IPA. Until early 1990 s, AMB-D was the only drug available for the treatment of aspergillosis, and no prospective evaluations of this drug had been attempted.[5–7] Another major obstacle to evaluating the merit of antifungal therapy for IPA until the early 2000s was difficulty in establishing the diagnosis; hence, most patients received empirical treatment. The introduction of uniform diagnostic criteria for proven, probable, and possible IA by the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) consortium has been an advance.[9] These criteria are standardized and reproducible and consist of

TABLE 133-5 Therapeutic Options for Invasive Fungal Infections

Regimen	Advantages	Disadvantages
Amphotericin B-deoxycholate (AMB-D)	Broad-spectrum activity, lack of frequent resistance, fungicidal activity, lower cost	Acute and chronic toxic effects, minimally effective in patients with neutropenia and with chronic disseminated candidiasis, intravenous preparations only
Lipid formulations of AMB	Broad-spectrum activity, reduced nephrotoxicity, increased doses can be administered	Only prospective randomized trial showed no advantage in efficacy over AMB-D despite higher doses, more expensive, intravenous preparations only
Fluconazole	Oral and intravenous preparation, as effective as AMB in randomized trials of nonneutropenic individuals with candidiasis, minimal toxicity, more effective for chronic disseminated candidiasis, little experience in neutropenic patients but appears to be as effective as AMB	Variable activity against *C. glabrata* and *Candida dubliniensis*, inactive against *C. krusei*, some drug–drug interactions, inactive against molds
Itraconazole	Broad spectrum of activity, lower cost, oral, and intravenous preparations	Drug–drug interactions and poor absorption (capsules) are common causes of clinical resistance, marked interpatient variability in serum levels, expensive
Voriconazole	Oral and intravenous preparations; broad-spectrum activity, including fluconazole- resistant species (e.g., *C. krusei*); fungicidal against *Aspergillus*	Drug–drug interactions, erratic pharmacodynamics, more expensive than fluconazole, inactive against *Zygomycetes*, some cross-resistance with fluconazole, need for drug level monitoring, expensive
Posaconazole	Broadest spectrum of activity among all azoles, including *Candida* spp., *Aspergillus*, *Mucorales* sp. and most other filamentous fungi	Drug–drug interactions, poor absorption, no intravenous formulation available yet (under development, in clinical trials), some cross-resistance with Itraconazole, need for drug level monitoring, expensive
Echinocandins (caspofungin, micafungin, anidulafungin)	Fungicidal activity against most *Candida* spp., minimal toxicity, lack of cross-resistance with azoles, preferred regiment for candidemia, immune modulating properties	No oral preparation, poor central nervous system, and urinary penetration, narrow spectrum of activity (*Candida, Aspergillus*), limited experience in neutropenic patients
Flucytosine	Synergistic with AMB and fluconazole, combination of flucytosine and AMB may be superior to AMB alone for chronic disseminated candidiasis and *C. tropicalis* infection	No IV preparation, causes myelosuppression, often requires monitoring of serum concentrations, emergence of resistance in monotherapy

host-risk, microbiological, clinical/radiological, PCR, and/or galactomannan antigen criteria. Despite the fact that the EORTC/MSG criteria have been updated to incorporate biomarkers for the diagnosis of IMI, their clinical applicability was questioned in real word setting; for example, in an autopsy study more than 60% of proven cases of IA in patients with hematological malignancies were not identified antemortem according standard definitions.[10] In addition, there is lack of a standardized PCR protocol for the detection of *Aspergillus* DNA from clinical specimens with validated, high intralaboratory quality performance.

The introduction of the broad-spectrum triazole voriconazole represents a major therapeutic advance in the management of IA, including IPA.[5–7] Voriconazole is available in both intravenous and oral preparations and is much better tolerated than AMB-D. In a large prospective randomized trial comparing voriconazole with AMB-D in patients with definite or probable aspergillosis, the

TABLE 133-6 Drug Dosages for Serious Invasive Fungal Infections of the Lung

Drug	Loading Dose	Daily Dose	Route
AMB-D	—	1.0–1.5 mg/kg	IV only
Lipid AMB	—	3–5 mg/kg	IV only
Fluconazole	800 mg (12 mg/kg)	400 mg bid (6 mg/kg bid)	IV, PO
IV itraconazole	200 mg bid ×2 d	200 mg	IV
Itraconazole solution	200 mg bid × 2 d	200 mg	PO
Itraconazole caps	200 mg tid × 3 d	200 mg bid	PO
IV voriconazole	6 mg/kg bid × 2 d	4 g/kg q 12 h	IV
Voriconazole tab	—	200 mg q 12 h (≥40/kg) 100 mg q 12 h (<40/kg)	PO
Posaconazole solution	200 mg qid × 7 d	400 mg bid	PO
Caspofungin	70 mg	50–70 mg	IV
Micafungin	150 mg	100–150 mg	IV
Anidulafungin	200 mg	100 mg	IV

bid, twice a day; caps, capsule; d, day; h, hours; IV, intravenous; PO, oral; q, every; sol, solution; tab, tablet; tid, three times a day.

response rate was 53% and 32%, respectively, and the survival rate at 12 weeks was 71% and 58%, respectively.[11] Improved response was seen irrespective of the underlying condition, site of infection, and presence or absence of neutropenia. Patients in whom initial therapy failed received other medications; this occurred more frequently among the AMB-D population primarily because of drug toxicity. The improved survival observed in this comparative study made voriconazole the preferred drug for first-line therapy for IA and this has been endorsed by many guidelines.

Posaconazole is a newer triazole with broad-spectrum activity against most filamentous fungi, which has shown promising activity as salvage therapy in an open-label study for IA with response rates of 42% versus 26% for the control group. Although posaconazole has a better drug interaction profile than voriconazole, it is available only as oral formulation and has to be administered with a high fat meal for optimal absorption, which can be especially problematic in severely immunocompromised and debilitated patients with mucositis or poor oral intake.[5–7] Newer formulations of (IV and oral) posaconazole with improved pharmacokinetic characteristics are currently in phase II and III clinical trials.

Use of lipid formulations of AMB is an attractive alternative to AMB-D because of reduced nephrotoxicity.[5–7] Although no comparative trials between the lipid formulations of AMB have been conducted thus far, they appear to be equally efficacious, although both toxic effects and costs differ. Most of the available data have been derived from indirect comparisons and suggest that all lipid formulations of AMB, when given at the standard dosage of 5 mg/kg, appear to have comparable efficacy to voriconazole.[5–7] That higher dosages of L-AMB are not necessarily equivalent to greater response rate was recently demonstrated in a recent prospective randomized study that compared two different dosages of L-AMB (3 mg/kg/d and 10 mg/kg/d) for the primary treatment of proven and probable IA in 201 patients. Importantly, survival rates and overall response rates were similar among the two different study groups; however higher dosage of L-AMB was associated with greater toxicity.[12] The dose–response relationships for ABLC and ABCD have not been well studied.

The echinocandins, including caspofungin, micafungin, and anidulafungin, belong to a new class of antifungal agents that inhibit the synthesis of 1,3-β-D-glucan, an essential component of the cell wall of many fungi.[5,7] They are all available only in intravenous preparations. In addition, caspofungin and micafungin have been used as primary therapy in noncomparative studies of IA with response rates ranging from 33% to 60% for caspofungin and 50% to 71% for micafungin. In addition, use of caspofungin as salvage therapy has been associated with response rates in 45% (37/83) of patients, including 50% of patients with IPA.[5–7]

Combination Treatment The recent introduction of echinocandins, which have a different mechanism of action than other antifungals, reinforced the concept of combination therapy (e.g., azoles plus echinocandins, AMB plus echinocandins, AMB plus azoles and echinocandins) as a possible means to improve suboptimal long-term survival of high-risk patients with IA treated with monotherapy.[13] Many in vitro studies and animal models suggest that administration of an echinocandin with voriconazole may result in additive or synergistic effects, which can potentially translate into clinical benefits. This hypothesis has been supported by small clinical studies and noncomparative observations. A recently completed double-blind randomized clinical study in 454 patients with IA compared the efficacy of combination of voriconazole and anidulafungin versus voriconazole monotherapy with 6 weeks survival being the primary study endpoint. Importantly, treatment of IA with the combination of voriconazole and anidulafungin was associated with a clinically meaningful survival benefit in patients with hematological malignancies or after HSCT, particularly in patients with a diagnosis of IA based on GM antigen positivity and consistent radiological findings (6 weeks mortality 15.7% for combination and 27.3% for monotherapy, $P = 0.04$). This is the first study to demonstrate a significant impact of combination therapy in the outcome of patients with IA and a positive galactomannan assay.

In another randomized study the efficacy of L-AMB standard dose (3 mg/kg/d) in combination with caspofungin was compared with L-AMB high does (10 mg/kg/d) in 30 patients with hematological malignancies and IPA.[14] The combination of caspofungin plus L-AMB demonstrated higher overall responses rates when compared to L-AMB monotherapy and 100% survival at the end of the study, although differences in responses were not statistically significant, probably because of the small size of the study.

Therapeutic Drug Monitoring A growing body of evidence suggests patient-to-patient variability in the pharmacokinetics of triazoles used for treatment or prophylaxis in IA.[6] Absorption issues (for itraconazole and posaconazole), drug–drug interactions (for all triazoles, especially voriconazole), and pharmacogenetic differences (for voriconazole) may have significant impact in the management and outcome of patients with IA under triazole treatment. Thus, plasma drug level monitoring play an increasingly important role in optimizing the safety (for voriconazole) and efficacy (for itraconazole, posaconazole, and voriconazole) of antifungals with significant interpatient pharmacokinetic variability. The need to perform therapeutic drug monitoring should be individualized as determined by the clinical status of the host (e.g., specific organ function, comorbidities, and receipt of concomitant medications) and the overall treatment plans.[6]

Surgery The role of adjunctive surgery in the management of IPA also has not been demonstrated conclusively. Pulmonary infarcts and tissue sequestration are common causes of antifungal therapy failure and fatal hemorrhage in patients with IPA. Resection of infected pulmonary tissue is beneficial for selected patients.[5–7] Residual cavitary lesions, especially when containing fungus balls, after successful antifungal therapy may cause late exsanguinating hemorrhage or reactivation of infection during subsequent myelosuppressive chemotherapy. Removal of these lesions, if surgically feasible, should be considered and may provide survival benefit. Surgical intervention may be a life-saving procedure for patients with IPA who experience acute pulmonary hemorrhage, when performed early in the disease process. It is less evident whether early removal of well-circumscribed lesions close to pulmonary arteries is beneficial. Likewise, the value of late debulking of a pulmonary mass if the patient has multiple fungal lesions that cannot be completely resected is uncertain. Recent uncontrolled data suggest that resection of the lobe most adversely affected by IA is beneficial in treating pulmonary lesions that worsen despite the use of intense antifungal therapy.[5–7]

Immune Augmentation Treatment Because host immunodeficiency is the critical determinant of the outcome of IA, a large number of studies, mostly preclinical, over the past two decades have focused on strategies to augment cellular immune defenses against IMIs. The available preclinical data suggest that quantitative and qualitative deficiencies in host cellular immune responses can be corrected with adjunctive cytokine therapy, such as the use of myeloid growth factors (e.g., granulocyte colony–stimulating factor [G-CSF], granulocyte macrophage colony–stimulating factor [GM-CSF]), IFN-γ, or a combination of these cytokines plus infusion of host effector cells [e.g., IFN-γ plus granulocyte transfusions]).[5–7] Granulocyte transfusion therapy has become more feasible since the introduction of G-CSF/corticosteroid mobilization into the donor leukocyte collection process.[6] Currently, there are no data from randomized clinical trials examining the efficacy of granulocyte transfusions for

IA or other serious infections during neutropenia. Future studies in this area will likely examine the use of vaccinations and/or cellular transfer with or without adjunctive cytokines to boost adaptive Th1 immunity in immunosuppressed hosts. Importantly, WBC transfusions have been occasionally associated with serious adverse reactions including transfusion-related acute lung injury (TRALI). Clearly, this is a challenging area of investigation. Carefully designed clinical trials will be required to verify results from animal models and other preclinical observations and evaluate both the efficacy and safety of these interventions.

Prophylaxis in High-Risk Patients Reports on nosocomial outbreaks of IPA have linked cases to hospital construction, the absence of appropriate barriers between patients and the environment, and the presence of fungal spores in room air samples. Specialized air-handling systems such as high-efficiency particulate air (HEPA) filtration with or without laminar airflow ventilation have proven to be effective at excluding *Aspergillus* spores.[2,5–7] However, HEPA filters have not been shown to prevent *Aspergillus* infections during building renovation and may not prevent outbreaks of these infections related to building demolition or renovation. A meta-analysis of 16 controlled trials that evaluated the effect of HEPA filtration on neutropenic patients with hematologic malignancies or HSCT found that the placement of patients in protective environments appeared to be beneficial in preventing IFIs, but the data seemed insufficient to support firm conclusions. The Centers for Disease Control and Prevention guidelines for preventing opportunistic IMIs in allogeneic HSCT recipients recommend the use of HEPA filters in patient rooms (http://www.cdc.gov/hicpac/2007ip/2007ip_part4.html). However, highly immunocompromised stem cell transplant recipients are commonly managed as outpatients, where engineering standards of the inpatient protected environment are not feasible. More recently, hospital water systems have been implicated as potential sources of high-level spore bursts of pathogenic fungi. During bathroom activities such as showering and toilet flushing, patients may create aerosolized mists of fungal spores that increase the risk of IPA. In addition, researchers reported an association between molds (*Aspergillus* and *Fusarium* spp.) cultured on hospital sinks and water sources and IMIs in patients with leukemia.[5–7] As a result, some have recommended cleaning of patient showers and bathroom areas with a phenolic cleaning solution prior to use by severely immunocompromised patients. Although these preliminary data are intriguing, establishing a causal link between nosocomial exposure to *Aspergillus* spores and subsequent development of IA remains difficult and requires the demonstration of genetic relatedness of environmental *Aspergillus* strains and clinical isolates. In fact, one of the largest molecular epidemiological studies of IA suggested that any *Aspergillus* strain could be pathogenic in the appropriate host background and that isolates causing invasive disease are not necessarily nosocomially derived.[5]

The new oral, extended-spectrum triazoles such as voriconazole and posaconazole have a satisfactory pharmacokinetic profile and documented efficacy in the treatment of infections, which may make them suitable for prophylaxis in HSCT recipients and neutropenic patients. Posaconazole has been endorsed by several guidelines as the prophylactic azole of choice. Recently, antifungal prophylaxis with the echinocandin micafungin in HSCT recipients was shown to reduce the incidence of IA[5–7]; however, the fact that echinocandins are parenteral drugs limits use in extended antifungal prophylaxis during the postengraftment period, when IA is most likely to occur.

Secondary Prophylaxis Patients with a history of IA are at high risk of reactivation of the infection if they undergo further intensive chemotherapy or HSCT with relapse rates up to 30% to 50%. Patients receiving prophylaxis have fewer relapses than do those who do not.[5–7] In an open-label noncomparative study in 45 high-risk HSCT recipients with a previous history of invasive fungal infection (mostly IA), secondary voriconazole prophylaxis resulted in 6.7% incidence of relapse rate of IFI, which is considered lower than the relapse rate reported in historical control studies. Thus, in the absence of comparative clinical trials, triazoles such as voriconazole seem to be the most appropriate agents for secondary prophylaxis.

PULMONARY CANDIDIASIS

Candida, a commensal fungus of mucosal surfaces, is the predominant fungal pathogen in humans. The spectrum of *Candida*-induced illnesses is broad, ranging from mild, chronic mucocutaneous infections to life-threatening acute invasive infections involving potentially any organ.[15] Pulmonary candidiasis is an infrequent form of invasive *Candida* infection that occurs in cases of aspiration pneumonia in immunocompromised patients who have heavy colonization of *Candida* spp. in the oral cavity (primary *Candida* pneumonia) or as part of disseminated candidiasis.[15–18]

Candida pneumonia is a challenging infection because of a lack of established, reliable clinical criteria for making the diagnosis. *Candida* is frequently an asymptomatic colonizer, particularly among debilitated individuals who are receiving antibacterials.[15–18] Thus, cultures of sputum and/or BAL that are positive for *Candida* in a patient with a pulmonary infiltrate does not establish the diagnosis of *Candida* pneumonia. An autopsy study of patients with cancer demonstrated that whereas many high-risk patients with pneumonia had *Candida* spp. cultured from sputum and BAL specimens, the specificity (57%–60%) and positive predictive value (29%–42%) of cultures of both types of specimens were low.[15] Similarly, quantitative cultures of transbronchial lung biopsy samples in critically ill, mechanically ventilated patients have been of no predictive value for *Candida* pneumonia.[16] Therefore, only histopathological demonstration of yeast cells or pseudohyphae in lung tissue is confirmatory of *Candida* pneumonia, which is often impossible in many patients. Of interest, in a large prospective autopsy study including 233 ICU patients there was no evidence of *Candida* pneumonia despite frequent isolation of *Candida* from the airways. However, *Candida* airway colonization resulted in impaired macrophage effector function in a rat model of *Pseudomonas pneumonia* and has been associated with increased risk for ventilator associated pneumonia by MDR bacteria and overall worse clinical outcome. However, it is still unclear whether *Candida* colonization is causally related to poor outcomes or whether it is a marker of underlying host immunosupression and there are no studies to justify antifungal treatment for this entity.

EPIDEMIOLOGY

The true incidence of *Candida* pneumonia is unknown, and most of the data on this infection are extrapolated from autopsy series. The fact that only 55 patients with unequivocal evidence of primary *Candida* pneumonia had been reported in the literature up to 1993 emphasizes the rarity of this infection.[16] In large autopsy surveys in patients with cancer reported a prevalence of primary *Candida* pneumonia ranging from 0.2% to 0.4%.[17–20] In another autopsy study that included a general population of patients, primary *Candida* pneumonia comprised 17% of all *Candida* infections, with an overall prevalence of 0.3%.[20] On the other hand, primary *Candida* pneumonia has been a relatively frequent finding in autopsy studies of high-risk patients, such as premature neonates (1%) and critically ill, mechanically ventilated patients (8%).[16]

In contrast with primary *Candida* pneumonia, secondary lung involvement by *Candida* spp. is a common finding at autopsy, occurring in 42% to 81% of cases of disseminated candidiasis.[17–20] However, the clinical significance of *Candida* pneumonia identified at autopsy, especially in cases of hematogenous dissemination, has

been questioned. For example, a study demonstrated that almost half of such *Candida* infections were incidental autopsy findings without clinical significance.[20]

Although large surveillance studies to capture the prevalence of *Candida* pneumonia are lacking, *Candida* was the third most common fungal pathogen after *Aspergillus* and *Cryptococcus* in a series of 140 patients with biopsy-proven invasive fungal pneumonia.[19] Interestingly, an increasing number of patients with primary *Candida* pneumonia were reported during the last years of the study. However, whether these latter cases represented a true increase in the incidence of *Candida* pneumonia or simply reflected a bias because of improved diagnosis is not certain.

MYCOLOGY

Similar to the other forms of invasive candidiasis, *Candida albicans* is the predominant species in patients with primary *Candida* pneumonia, accounting for 40% to 70% of all reported cases.[17–20] Until the early 1990s, *Candida tropicalis* and *Candida parapsilosis* were the most common non-*albicans Candida* spp. in patients with primary *Candida* pneumonia. However, the widespread use of broad-spectrum azole antifungals over the past decade has led to the emergence of less susceptible non-*albicans Candida* spp., such as *Candida glabrata* and *Candida krusei*, as important causes of *Candida* pneumonia. Hence, *C. glabrata* is currently considered the second most common *Candida* spp. in cases of primary *Candida* pneumonia in immunocompromised individuals.[17–20] In cases of secondary *Candida* pneumonia caused by hematogenous dissemination, the distribution of the species appears to follow that in bloodstream candidiasis, with *C. albicans* being the predominant species followed by *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*.[17–20]

PATHOGENESIS

Most of the data on the pathogenesis of *Candida* pneumonia have been gained from analysis of histopathological findings at autopsy and studies of animal models of aspiration-induced pneumonia. *Candida* pneumonia develops only rarely in normal hosts, and most of the reported cases of this infection occurred in heavily colonized, immunocompromised individuals. A constellation of factors suggests that primary *Candida* pneumonia has a distinct pathophysiology when compared with other forms of invasive candidiasis and develops in a particular clinical scenario.[16,17] Specifically, the very high percentage of intrabronchial and intra-alveolar fungal involvement without significant vascular invasion, the frequent finding of aspirated material at autopsy, and the concomitant presence of candidal esophagitis at autopsy in most of the patients with primary *Candida* pneumonia demonstrate that the mechanism of entry of *Candida* is aspiration of oropharyngeal contents.[17] In addition, several studies indicated that the typical risk factors for invasive candidiasis, such as chemotherapy-induced neutropenia, prolonged corticosteroid use, immunosuppressive agent use, prior antibiotic use, hyperalimentation, diabetes mellitus, and the presence of vascular devices were not significantly associated with the development of *Candida* pneumonia.[16–20] In contrast, alteration of mental status (with or without subsequent aspiration) was the most important contributing factor in the majority of these patients. Thus, individuals prone to aspiration who have heavy oral colonization with *Candida* spp., such as those with head and neck cancer receiving chemoradiation, premature neonates, and critically ill, mechanically ventilated patients, comprise the population at highest risk for primary *Candida* pneumonia.

However, a distinct type of secondary *Candida* pneumonia caused by hematogenous dissemination has been described occasionally in profoundly neutropenic patients with cancer.[17] The histopathological characteristics of *Candida* lesions reflect pulmonary seeding from systemic bloodstream infections. Specifically, autopsy examination of these patients found evidence of pneumonia with scant inflammation and clumps of *Candida* yeast cells and pseudohyphae present in large portions of the involved lung sections in a pattern that closely resembled *Candida* growth in culture medium. Furthermore, in contrast with primary *Candida* pneumonia, destruction of lung parenchyma is subtle, whereas hemorrhage and angioinvasion by pseudohyphae are prominent. Although speculating that typical risk factors for disseminated candidiasis may apply in cases of secondary *Candida* pneumonia is reasonable, the majority of cases of clinically significant infection have been described in profoundly neutropenic patients with leukemia.[17–21]

Innate immunity is the dominant protective mechanism against all forms of invasive candidiasis, including primary *Candida* pneumonia.[3,22] Different *Candida* morphotypes are sensed by distinct pattern recognition receptors including TLRs and C-type lectins in a collaborative fashion. In contrast, adaptive immunity appears to be dispensable for disseminated candidiasis in humans with innate or acquired T-cell and/or B-cell immunodeficiency and in the relevant mouse models. However adaptive immunity has a critical role in mucosal defense against *Candida* and mediates protective effect of vaccination.[3]

Notably, in murine models of aspiration-induced *Candida* pneumonia, immunocompetent animals were remarkably resistant to intratracheal inoculation of *Candida* whereas they succumbed to infection after intravenous injection of a much lower inoculum.[22] These studies revealed that resident pulmonary macrophages account for much of host resistance against *Candida* infection, with a remarkable ability to engulf and kill yeast cells.[22] The role of resident versus recruited monocytes/macrophages in immunity against systemic *Candida* infection requires further clarification. Of interest, monocytes were recently shown to confer superior protection following systemic *Candida* reinfection via functional reprogramming that involves the dectin-1/Raf-1 noncanonical signaling pathway and results in enhanced cytokine production. Induction of this type of innate immune memory (termed "trained immunity") in monocytes/macrophages appears to involve epigenetic mechanisms. In addition, neutrophils are recruited to the lung within a few hours after initial challenge and have a predominant role in clearing *Candida* infection from the lungs within hours after inoculation. Neutropenic mice are highly susceptible to *Candida* pneumonia. In contrast, although the use of corticosteroids somewhat delays the clearance of *Candida* cells by phagocytic cells, it does not significantly increase the susceptibility of mice to systemic infection.[22] On the other hand, genetically engineered mice deficient in myeloperoxidase and/or other components of respiratory burst are extremely susceptible to *Candida* pneumonia, indicating the importance of mechanisms of oxidative killing of phagocytic cells.[3,19] Blocks in NET release in NADPH- and MPO-defective neutrophils has been associated with defective effector function. Although the role of humoral immunity has not been explored extensively, production of IgA and IgG1 has been shown to be important for protection against *Candida* pneumonia in mice. In contrast with cases of disseminated candidiasis in which Th1 cytokines appears to be critical for outcome, a balanced Th2 anti-*Candida* response at the late phase of infection associated with synthesis of IL-4 and IL-5 is required for optimal resolution of *Candida* pneumonia.[3,19] Of interest, mucosal immunity against *Candida* is predominantly regulated by Th17 cytokines and related antimicrobial peptide induction. Thus, it is plausible that Th17 responses in respiratory epithelia play a critical role in pathogenesis of *Candida* pneumonia. Future studies in genetically engineered mice should allow better characterization of important host determinants for pulmonary host defense against *Candida*.

CLINICAL MANIFESTATIONS

The clinical manifestations of primary *Candida* pneumonia are nonspecific and include persistent fever and tachypnea.[16,17] Chest

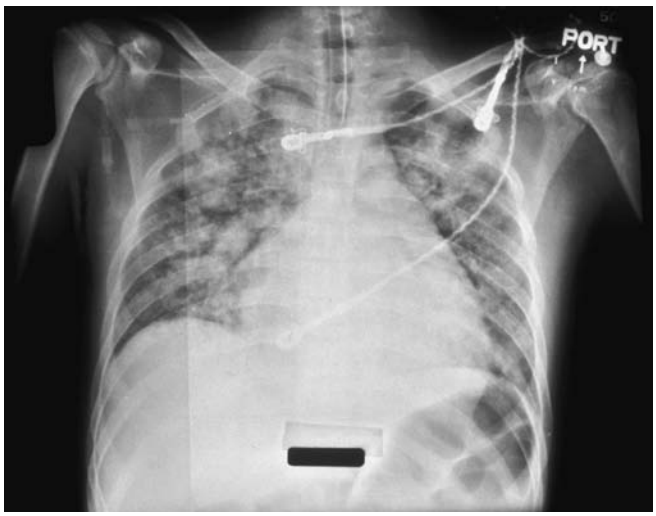


Figure 133-9 The radiographic features of *Candida* pneumonia in a patient with acute leukemia and severe neutropenia in whom disseminated candidiasis developed. Diffuse bilateral infiltrates along with the characteristic macronodular lesions are shown. *(Used with permission of Dr. G.P. Bodey.)*

pain, cough, and sputum production occur occasionally. Also, physical examination and routine laboratory studies are nonspecific. Chest radiographs may demonstrate a local or diffuse infiltrate involving one or both lungs, which is most often associated with infection acquired by the endobronchial route. A miliary-nodular pattern is most often associated with hematogenous seeding of the lung in cases of disseminated candidiasis and often appears late in the clinical course of the disease (Fig. 133-9).[16,17,20]

Extrapulmonary manifestations such as skin lesions, myositis, and endophthalmitis may be the first signs of *Candida* fungemia. Multiple organ involvement prior to or concurrent with pulmonary findings, particularly liver or kidney dysfunction and myocardial failure, may indicate hematogenous seeding that warrants investigation.

Lung transplant recipients occasionally develop an early (within 2 weeks after transplantation) and fulminant *Candida* pneumonia.[16] This association is probably caused by occult aspiration of *Candida* colonizing the donor lung followed by invasive pulmonary *Candida* infection after transplantation when immunosuppression is most intense.

Asthma related to an IgE-mediated allergy to *C. albicans* or allergic bronchopulmonary candidiasis can occur, although this is uncommon. Allergic bronchopulmonary candidiasis should be considered in patients with ABPA with serological and skin tests negative for *Aspergillus*. In addition, cases of chronic eosinophilic pneumonia with peripheral eosinophilia and selective sensitization to *C. albicans* occur rarely in the absence of asthma. Early diagnosis and corticosteroid-based therapy may prevent late fibrosis in those patients. Finally, fatal aspiration pneumonitis characterized by intense inflammatory response and lack of deep tissue invasion has been described in alcoholic patients.

■ DIAGNOSIS

Diagnosis of pulmonary candidiasis is challenging and depends on evidence of tissue invasion.[16–20] Isolation of yeast from sputum does not prove invasive yeast infection of the respiratory tract because of contamination by commensals from the oropharynx. *Candida* is present in the oropharynx of approximately 20% to 40% of all patients, especially those with chronic lung disease and those receiving prolonged antibacterial treatment.[16]

Bronchial washings and BAL specimens provide a more representative picture of the respiratory pathology compared to sputum. However, they can still be contaminated with mouth flora. At least in a selected group of patients with acute leukemia and severe neutropenia, if no other organisms are present and abundant *Candida* yeast cells and pseudohyphae are detected in the cytological examination of BAL specimens clinical suspicion of *Candida* pneumonia should be high.[16] On the other hand, cultures from lung specimens negative for *Candida* spp. have a high negative predictive value and virtually exclude *Candida* pneumonia.[16–18]

Histopathological demonstration of tissue invasion by *Candida* spp. in open lung biopsy or CT-guided fine-needle aspiration of peripheral nodular lesions is definitive, although such biopsies are difficult to perform in pancytopenic patients with pneumonia and are prone to sampling error. Transbronchial biopsy revealing tissue invasion by *Candida* spp. is also diagnostic.

Isolation of *Candida* from the blood may be helpful in the diagnosis of disseminated candidiasis; however, the organism may not be isolated even from multiple blood culture specimens in up to 40% of patients with widespread infection demonstrated at autopsy.[16–20] The use of lysis centrifugation, the BacT-Alert system that monitors CO_2 production, and the high-volume BACTEC system with infrared detection has improved the yield of *Candida*-positive blood cultures. A variety of methodologies have been developed to detect circulating *Candida* antigens, nucleic acids, and metabolites. Among these non–culture-based diagnostic methods PCR and β-D-glucan assays in serum hold most promise for adoption in routine clinical microbiology practice.[15] Of interest, in a recent prospective study of invasive candidiasis both PCR and serum β-D-glucan assays had higher sensitivity than blood cultures among patients with deep-seated candidiasis (88% and 62% vs. 17%, respectively); the combination of both the PCR and β-D-glucan assays resulted in 98% sensitivity. In addition, β-D-glucan levels seem to be a prognostic marker for treatment response in invasive candidiasis.

In cases of disseminated candidiasis, characteristic eye lesions suggestive of *Candida* infection may develop[15]; hence, a careful ophthalmological examination should be performed when this infection is suspected. In addition, typical maculopapular or nodular skin lesions, have been described in up to 10% of patients with hematogenous candidiasis.[15] Some of these patients also have associated myositis, particularly in cases of *C. tropicalis* infection. *Candida* spp. can be identified in the dermis and cultured from about half of all biopsy samples. Finally, CT scans of the abdomen may suggest hepatosplenic candidiasis in compromised hosts with an unrevealing microbiological evaluation.

■ TREATMENT

An unknown number of patients with primary *Candida* pneumonia may have had a response to empirical antifungal therapy but have gone unrecognized because of the difficulty in establishing the diagnosis of this infection. Primary *Candida* pneumonia is considered a life-threatening infection, with mortality rates approaching 70% in severely immunocompromised patients.[16–20] Therefore, rapid clinical diagnosis and prompt initiation of systemic antifungal therapy are important upon suspicion of the infection in the appropriate setting.

Given the rarity of primary *Candida* pneumonia, there are no controlled studies of the treatment of it. Historically, most patients with primary *Candida* pneumonia have received AMB-D (0.7–1.0 mg/kg/d) for a minimum of 2 weeks after all signs and symptoms of infection disappeared and until bone marrow recovery in those with neutropenia.[15–20] In cases of secondary *Candida* pneumonia associated with hematogenously disseminated infection, therapy directed at disseminated candidiasis rather than at *Candida*

pneumonia is indicated.[15] Over the past two decades, several antifungal agents, including fluconazole and the newer triazoles (especially voriconazole), lipid formulations of AMB, and the echinocandins, have become available for the treatment of invasive candidiasis, showing comparable efficacy and significantly less toxicity when compared with AMB-D in several prospective randomized trials.[15]

Although lipid formulations of AMB are less nephrotoxic, there is no convincing evidence that they are more effective than AMB-D. Because most patients with candidiasis do not require prolonged therapy, use of these more expensive preparations is usually not justified.

The introduction of the echinocandins has been a breakthrough in the treatment of invasive candidiasis.[15] All three available echinocandins, including caspofungin, micafungin, and anidulafungin, have shown comparable, broad-spectrum fungicidal activity against *Candida* spp., including azole-resistant non-*albicans Candida* spp.[15] In fact, because of their potency, minimal toxicity, and superior activity when compared to AMB-D and fluconazole in randomized controlled studies in patients with candidemia, the echinocandins have become the drug of choice for candidemia/candidiasis in seriously ill and unstable patients.

The accumulating experience with the treatment of other invasive pulmonary mycoses with echinocandins holds promise for the use of these agents in the treatment of *Candida* pneumonia. However, because of the rarity of *Candida* pneumonia a definite treatment of choice for this entity has not been endorsed in recently published guidelines on treatment of *Candida* infections.[15] Thus, with all of the limitations of the aforementioned studies, and given the fact that fluconazole has been used extensively for prophylaxis in many institutions, initiation of therapy for *Candida* pneumonia with an echinocandin with subsequent switch to an azole may be a reasonable approach in such cases.[15] Also, using higher doses of fluconazole (800 mg/d), at least initially, may be appropriate in neutropenic patients.

PULMONARY MUCORMYCOSIS (FORMERLY ZYGOMYCOSIS)

Mucormycosis (formerly Zygomycosis) has recently emerged as an important opportunistic mycosis in severely immunocompromised patients with hematological malignancies and recipients of stem cell or organ transplantation.[23,24] Zygomycosis, the previous terminology for infections caused by fungi of the order Mucorales, is no longer appropriate due to a recent taxonomic reclassification that abolished Zygomycetes as a class. Necrotizing pneumonia is a predominant feature of mucormycosis, especially in severely immunocompromised patients.[23,24]

Fungi of the order *Mucorales* are distributed in six families, each of which can cause serious invasive infections (Table 133-7). Species of the family *Mucoraceae* are isolated more frequently from patients with mucormycosis than are species of any other family.[23,24] Among the *Mucoraceae*, *Rhizopus oryzae* (*Rhizopus arrhizus*) causes the vast majority (>70%) of *Mucorales* infections. Other less frequently encountered species of the *Mucoraceae* family include *Rhizopus microsporus*, *Lichtheimia* (formerly known as *Absidia* species), *Apophysomyces elegans*, *Mucor* species, and *Rhizomucor pusillus*. *Cunninghamella bertholletiae* is an increasingly reported cause of mucormycosis and appears to be the most virulent *Zygomycetes* species in humans.[24] All of these organisms are indistinguishable by histopathology. Various terms have been used in the past to indicate infections caused by *Mucorales*, such as mucormycosis, phycomycosis, and simply mucor. However, the more accurate term mucormycosis is used throughout this chapter to indicate opportunistic mold infections in humans caused by *Mucorales*, because this is the taxonomically correct description.

TABLE 133-7 Classification of Fungi in the Class Zygomycetes, Order *Mucorales*[a]

1. MUCORACEAE
   - a. *Absidia (Lichtheimiaceae)*
     - i. *A. corymbifera*[b]
   - b. *Apophysomyces*
     - i. *A. elegans*[b]
   - c. Mucor[b]
     - i. *M. circinelloides*
     - ii. *M. hiemalis*
     - iii. *M. racemosus*
     - iv. *M. ramosissimus*
     - v. *M. rouxianus*
   - d. *Rhizomucor*
     - i. *R. pusillus*[b]
   - e. *Rhizopus*
     - i. *R. arrhizus*[b]
     - ii. *R. azygosporus*
     - iii. *R. microsporus var. rhizopodiformis*[b]
     - iv. *R. microsporus var. oliogosporus*
     - v. *R. microsporus var. microsporus*
     - vi. *R. schipperae*
     - vii. *R. stolinfer*
2. *CUNNINGHAMELLACEAE*
   - a. *Cunninghamella*
     - i. *C. bertholletiae*[b]
3. *MORTIERELLACEAE*
   - a. *Mortierella*
     - i. *M. wolfii*
4. SAKSENAEACEAE
   - a. *Saksenaea*
     - i. *S. vasiformis*
5. *SYNCEPHALASTRACEAE*
   - a. *Syncephalastrum*
     - i. *S. racemosum*
6. *THAMNIDACEAE*
   - a. *Cokeromyces*
     - i. *C. recurvatus*

[a]*Based on the classification outlined by Ribes JA, Vanover-Sams CL, Baker DJ: Zygomycetes in human disease. Clin Microbiol Rev. 2000;13:236–301.*
[b]*These species are the more common etiological agents associated with mucormycosis in humans.*

DISEASE MANIFESTATIONS/EPIDEMIOLOGY/ RISK FACTORS

The *Mucorales* are saprophytic fungi ubiquitous in soil and decaying organic material. *Mucorales* species that are pathogenic in humans grow rapidly on any carbohydrate substrate and produce abundant sporangiospores.[24] Spores produced by the fungi become airborne, and inhalation of *Mucorales* conidia into the respiratory tract occurs daily. Even though these fungi grow in many ecological niches, the rarity of mucormycosis reflects the low virulence potential of *Mucorales* in immunocompetent hosts. For reasons that remain unclear, the incidence of *Mucorales* infections, particularly of *Cunninghamella, Absidia,* and *Apophysomyces* spp., is higher in male

patients (65%) than in female patients. The most common forms of mucormycosis based on anatomic localization include (a) rhinocerebral infection (39%), (b) pneumonia (24%), (c) disseminated infection (23%), (d) cutaneous/soft tissue infection (19%), (e) gastrointestinal infection (7%), and (f) uncommon presentations (7%). When compared to other opportunistic molds, *Mucorales* tend to infect a broad, more heterogeneous population of human hosts, including immunocompetent individuals. Specifically, *Mucorales* cause acute angioinvasive infections in patients with a variety of immunosuppressive conditions, including poorly controlled diabetes mellitus (especially with diabetic ketoacidosis), neutropenia, malignancies, burns, chronic renal failure, with iron overload; recipients of transplants, and patients with renal failure receiving the iron (and aluminum)-chelating agent deferoxamine.[24] Although rare, there have been a number of reports of pulmonary mucormycosis in patients with AIDS. It is important to emphasize that dissemination may occur from any of the primary sites of *Mucorales* infection, mainly in patients with profound immunosuppression.

Of note, particular host immune defects predispose to different forms of mucormycosis. For example, patients with diabetic ketoacidosis are prone to the development of the rhinocerebral form of mucormycosis but less often suffer from pulmonary or disseminated infection. In contrast, pulmonary mucormycosis typically affects severely immunocompromised individuals, including patients with high-risk hematological malignancies and recipients of hematopoietic stem cell and organ transplants. The predominance of pulmonary infection in those patients may be a result of chemotherapy-related defects in innate pulmonary host defenses associated with neutropenia and/or chemotherapy-induced mucociliary dysfunction. Prolonged and severe neutropenia is the sole identifying risk factor in approximately 15% of all reported mucormycosis cases. Nonetheless, like aspergillosis, mucormycosis is increasingly reported as a late (1–6 months), or very late (>6 months) community-acquired infection in nonneutropenic, HSCT recipients postengraftment, especially in the setting of multiple, overlapping, and cumulative mechanisms of immunosuppression during GvHD treatment. In these patients, severe immunodeficiency due to high-dose glucocorticosteroid therapy and/or other immunosuppressive therapies frequently coexists with other comorbidities that are interrelated and difficult to quantify, such as hyperglycemia, metabolic acidosis, renal failure, iron overload, malnutrition, advanced age, and CMV infection.

A significant increase in the rates of mucormycosis has been observed recently among severely immunocompromised individuals classically at risk for other opportunistic mold infections, such as patients with acute leukemia, and transplant recipients.[23–25] An autopsy study in hematological malignancy patients from a single cancer institution with high background rates of mucormycosis reported a significant threefold increase in prevalence of autopsy-proven mucormycosis cases from 0.9% to 3% during the study period (1989–2003). Importantly, most of these infections were diagnosed postmortem. Similarly, there was a fourfold increase in the overall incidence of mucormycosis during a period of active surveillance at 25 US transplant centers from 2001 to 2006 whereas the incidence of other opportunistic molds remained constant. In the aforementioned study the overall cumulative annual incidence (CI) of mucormycosis was the highest (0.29%) in HSCT recipients, particularly those receiving transplant from an HLA-unrelated donor (0.85%). Among solid-organ transplant recipients, the overall 12-month CI of mucormycosis was 0.07%, with lung transplants and liver transplants having the highest incidence of mucormycosis, at 0.18% and 0.16%, respectively. Of note, there was a seasonal variation in incidence of mucormycosis with declining rates among the groups transplanted in the first 4 months of each year. Recent national studies in Europe that used administrative data from hospital records to capture cases of mucormycosis, also demonstrated a significant increase in incidence of mucormycosis within a 10-year period.[23–25]

Of concern, a growing proportion of pulmonary mucormycosis cases manifest as breakthrough infections in patients receiving antifungal agents with activity against aspergillosis but not mucormycosis (i.e., voriconazole, echinocandins). Case series in high-risk leukemia and allogeneic HSCT patients suggest that mucormycosis should be considered whenever fungal sinusitis develops while on *Aspergillus*-active antifungal prophylaxis (i.e., voriconazole), especially in patients with prolonged immunosuppression, underlying diabetes or malnutrition, and in the setting of negative *Aspergillus* galactomannan assay and "therapeutic" voriconazole serum levels (e.g., voriconazole levels >2 ng/mL). Animal studies have demonstrated increased virulence of *Mucorales* spp. following voriconazole pre-exposure; previous voriconazole use has been independently associated with the development of mucormycosis in leukemia and transplant patients. Other studies have reported an increase in mucormycosis cases prior to the introduction of voriconazole and a recent randomized trial on voriconazole prophylaxis in low-moderate risk allogenic HSCT recipients with favorable prognostic features did not find a higher incidence of mucormycosis. Hence, it is difficult to establish a causal relationship between voriconazole use and development of mucormycosis as this association may reflect a changing patient risk profile, including hosts at higher risk or increased time at risk, with evolving transplant practices and immunosuppressive strategies that ultimately result in improved posttransplant survival. Very late-onset mucormycosis, occurring 2 years or more after transplantation, has been reported in a significant proportion of HSCT (13.8%) and SOT (33.3%) recipients in a multicenter prospective surveillance study.

There are inherent problems with epidemiological studies on mucormycosis related to challenges in establishing a diagnosis and capturing shifts in prevalence of classic or unknown risk factors of infection in high-risk populations. Furthermore, surveillance strategies to capture the true incidence of mucormycosis are imperfect given that the diagnosis is difficult to achieve antemortem. Instead of registries that create databases based on hospital coding diagnoses, development of active surveillance programs is needed with long-term follow-up in selected high-risk patient groups such as transplant recipients.

MYCOLOGY

Mucorales are molds characterized by growth of hyphae in the environment and in tissue. They grow rapidly – within 2 to 5 days on most culture media – as fluffy gray or brownish colonies, with many of the species demonstrating aggressive vertical growth toward the lid of the Petri dish; these species are referred to as "lid lifters."[24] As the *Mucorales* colony matures, the mycelium may darken and exhibit a black pepper-like effect as large numbers of sporangia are formed. Cycloheximide inhibits the growth of these fungi, and media that contain this compound, such as Mycosel and mycobiotic agar, should not be used. Clinical tissue samples potentially infected with the *Mucorales* should be chopped, not ground, for inoculation into microbiologic cultures. All pathologic species grow well at 37°C.[24]

Microscopic examination for the presence and location of rhizoids and apophyses and to determine the morphology of the columellae differentiates the genera. Isolating and speciating the organism is important for selection of treatment. However, morphological identification of *Mucorales* species is often imprecise.

PATHOGENESIS

Understanding molecular mechanisms of host-fungal interplay is critical in order to develop better therapeutic strategies and

improve mucormycosis outcome. The pathogenesis of pulmonary mucormycosis begins with the inhalation of conidia into the respiratory tract, where infection may remain localized in the lung or disseminate hematogenously. In healthy individuals mononuclear and polymorphonuclear phagocytes efficiently eliminate fungal spores and hyphae by oxidative and nonoxidative killing mechanisms.[3,24] Quantitative (i.e., neutropenia) or qualitative (i.e., associated with glucocorticoids, hyperglycemia and/or acidosis) defects in phagocytic cell activity permit unrestricted growth of the hyphal form and invasive infection. In particular, both hyperglycemia and acidosis are known to impair chemotaxis and the killing activity of phagocytic cells against *Mucorales* by impairing oxidative and nonoxidative mechanisms.[24] Likewise, corticosteroids impair migration, ingestion, and phagolysosome fusion in human macrophages.[3] However, receipt of corticosteroids per se is not the predominant risk factor in the absence of underlying severe immunosuppression. The molecular mechanisms that account for attenuated phagocytic function in patients with hyperglycemia, ketoacidosis, or steroids are only partially characterized. For example, as opposite to *Aspergillus* spp. *Mucorales* spp. rarely infect GGD patients and direct genetic evidence for a role of NADPH-dependent ROS production in ex vivo killing of *Mucorales* by phagocytes is missing. Thus, comparative genetic studies on the mechanisms of phagocytosis, phagosome maturation, and killing of *Aspergillus* vs. Mucorales by phagocytes are required.

Of interest, when compared to *Aspergillus*, *Mucorales* hyphae display inherent resistance to killing by both *Drosophila* and human phagocytes, which might partially account for the increased virulence of these fungi and the ability to infect a broad range of hosts. Whether this resistance to killing by phagocytes is related to the release of virulence factors or is result of a different cell wall composition is currently unknown. Of interest, a recent study found that sporangiospore size dimorphism is linked to virulence of *Mucor* spp. Investigators discovered that asexual reproduction of *Mucor circinelloides* results in formation of larger sporangiospores and increased virulence in vivo when compared to isolates containing a (+) sex allele. In addition, larger sporangiospores germinated inside and lysed a murine macrophages cell line within few hours of uptake, whereas smaller sporangiospores exhibited delayed intracellular growth. Of interest, there was a correlation between spores size and virulence in clinical isolates of *Mucor*. Importantly, when compared to *Aspergillus*, *Mucorales* infection induces macrophage cell death via unknown mechanisms that could be related to the release of virulence factors.

Little is known about the innate sensing of *Mucorales* spp. by immune and/or nonimmune (e.g., endothelial) cells and the role of adaptive immunity in patients with pulmonary mucormycosis. Of interest, similar to *Aspergillus*, β-glucan exposure during germinating growth of *Rhizopus* triggers dectin-1 signaling in human dendritic cells and results in robust induction of the IL-23/Th17 responses. Until recently, the role of adaptive immunity in mucormycosis was underappreciated because acquired T-cell deficiency is not associated with increased susceptibility to infection by the *Mucorales*. However, investigators recently indicated the presence of *Mucorales*-specific T cells in patients and healthy individuals, which enhanced effector function of professional phagocytes and could be harnessed for adoptive immunotherapy strategies.

Iron metabolism has a central role in pathogenesis of mucormycosis.[3,24] Thus, patients with iron overload states, including those undergoing chelation therapy with deferoxamine, are uniquely predisposed to mucormycosis. Deferoxamine abolishes the fungistatic effect of serum and increases in vitro fungal growth by acting as a siderophore for *Mucorales spp*.[24] The key role of iron utilization in pathogenesis of mucormycosis is further illustrated by the fact that conditional inactivation of *R. oryzae* high-affinity iron premease gene, FTR1, renders the fungus nonpathogenic in mice.[24] Similarly, the increased susceptibility to mucormycosis of patients with acidosis, including diabetic acidosis, is attributed to increased availability of serum iron partially due to diminished affinity of transferrin for free iron at a lower pH (<7.4). Unlike deferoxamine, the other iron chelators, such as deferiprone and deferasirox that lack xenosiderophore activity for *Rhizopus*, induce an iron-starvation effect to the fungus and have shown to be protective in animal models of mucormycosis and in anecdotal reports of human infection.

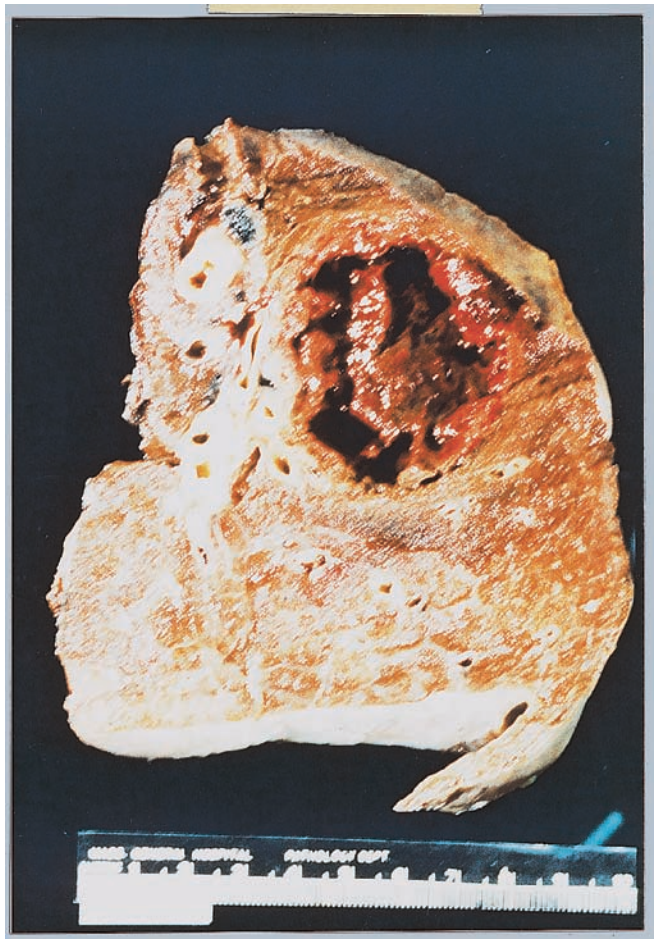


Figure 133-10 Pulmonary mucormycosis in a 63-year-old diabetic kidney transplant recipient with a rapidly expanding pulmonary mass. *(Used with permission of Jay A. Fishman, Massachusetts General Hospital.)*

A hallmark of mucormycosis is extensive angioinvasion with resultant vessel thrombosis and tissue necrosis **(Fig. 133-10)**. Interaction of *Mucorales* spores with endothelial cells appears to play a critical role in angioinvasion. Ibrahim et al. identified glucose-regulated protein-78 (GRP78) as a novel host receptor that selectively and specifically interacts with *Rhizopus* mediating invasion and damage of human endothelial cells by the fungus.[24] Of interest, elevated glucose and iron levels upregulate GRP78 expression and promote endothelial cell invasion and damage by *R. oryzae* in a receptor-dependent manner.

CLINICAL MANIFESTATIONS

Although concomitant sinus infection is suggestive of pulmonary mucormycosis, the clinical manifestations of pulmonary infection are almost indistinguishable from those caused by the more common opportunistic mold *Aspergillus*.[23–25] Therefore, timely diagnosis is critical in the outcome of this infection because first-line

antifungal agents typically used for aspergillosis such as voriconazole, lack activity against *Mucorales*.

Clinical symptoms of pulmonary mucormycosis are subtle and nonspecific even at late stages of infection, especially in neutropenic patients and those receiving immunosuppressive therapies that dampen immune responses. Pulmonary mucormycosis frequently manifests with persistent fever on broad-spectrum antibiotics, nonproductive cough, progressive dyspnea, and pleuritic chest pain.[23–25] Infection has a propensity to traverse tissue planes in the lung, including the bronchi, diaphragm, chest wall, and pleura. Hyphal invasion of blood vessels results in necrosis of the surrounding parenchyma, ultimately leading to cavitation or potentially fatal hemoptysis. In patients with hematological malignancies, clues for distinguishing pulmonary mucormycosis from IPA may include the presence of necrotic lesions in palate, severe sinusitis, rhino-orbital extension, prophylaxis with antifungals that possess activity against aspergillosis but not mucormycosis (i.e., voriconazole and the echinocandins), and possibly the repeated absence of detectable *Aspergillus* galactomannan antigen and/or b-glucan in the serum.[24,25] Unfortunately, the frequent coexistence of bacterial or mixed fungal pneumonia (up to 22% in a single-institution observational study) in high-risk hematological malignancy patients can further complicate early diagnosis and management of pulmonary mucormycosis. Pulmonary mucormycosis rapidly spreads to the contralateral lung and distal organs if not promptly treated. While patients with pulmonary mucormycosis usually die from disseminated disease before respiratory failure occurs, dissemination is rarely detected antemortem. The overall mortality rate of pulmonary mucormycosis ranges from 50% to 70%, but exceeds 90% with extrathoracic dissemination.[23–25]

A multitude of patterns may be present in a regular chest radiograph of patients with pulmonary mucormycosis, including lobar consolidation, nonspecific infiltrates, cavities, masses, and nodules. Similar to IPA, high-resolution chest CT is the best method of determining the extent of pulmonary mucormycosis and typically demonstrates evidence of the infection earlier than standard chest radiographs. While nodular opacities without an air bronchogram indistinguishable from those of aspergillosis are the most common findings on CT scan, the presence of multiple nodules (≥10) and, to a lesser degree, pleural effusions may favor the diagnosis of pulmonary mucormycosis.[24] Halo and air crescent signs are encountered less frequently in leukemic patients with pulmonary mucormycosis compared to pulmonary aspergillosis. However, the presence of air crescent sign in centrally located lesions reflects an increased risk of pulmonary artery erosion and massive hemoptysis. One case series suggested that a reverse-halo sign, a focal round area of ground-glass attenuation surrounded by a ring of consolidation, may be a common early radiographic finding in patients with invasive pulmonary mucormycosis versus aspergillosis.[24,25]

Atypical presentations of pulmonary mucormycosis include chronic infection with constitutional symptoms that last for several months in relatively immunocompetent hosts, multiple mycotic pulmonary artery aneurysms and pseudoaneurysms, bronchial obstruction, asymptomatic solitary nodules, or even normal chest radiographs. Of interest, patients with diabetes mellitus have an apparent predilection for the development of endobronchial lesions, accounting for more than 80% of reported cases in the literature. Furthermore, pulmonary mucormycosis tends to present with a less fulminant, subacute clinical course in these patients. However, endobronchial lesions may occasionally lead to obstruction of major airways or erosion of major pulmonary blood vessels and fatal hemoptysis. In lung transplant recipients, ulcerative tracheobronchitis at the bronchial anastomotic site is rarely caused by *Mucorales* when compared to *Aspergillus*; however, changes in immunosuppressive and antifungal prophylaxis practices could lead to the emergence of this infection in the future.[25]

Similar to *Aspergillus* spp., *Mucorales* spp. rarely produce an asymptomatic mycetoma within a pre-existing lung cavity. Allergic *Rhizomucor* sinusitis has been also reported in immunocompetent individuals. In addition, hypersensitivity pneumonitis caused by *Rhizopus* has been described in farm workers as well as in Scandinavian sawmill workers (wood trimmer's disease).[24]

DIAGNOSIS

Little improvement has been made over the past few decades in the diagnosis of mucormycosis, which still relies on histopathology and traditional culture methods. Timely diagnosis of mucormycosis requires a high index of suspicion and largely depends on histopathological demonstration of tissue invasion by the characteristic hyphae or by isolation of *Mucorales* spp. in cultures of sterile tissue, which necessitates implementation of an invasive procedure. Tissue swabs, sputum, or bronchial alveolar lavage fluid cultures are usually nondiagnostic, but provide an important indication of disease and allow for the establishment of probable infection in immunocompromised patients.[25] Blood cultures rarely, if ever, grow *Mucorales* species despite the angioinvasive nature of these pathogens.

Mucorales stain poorly with the PAS and Gram stains but stain very well with the Grocott–Gomori methenamine-silver. Treatment with fluorescent stains such as **calcofluor-white** or blankofluor may aid in detection of hyphal elements and improve the discrimination between septated and aseptated molds. In tissue specimens *Mucorales* appear as broad (10–20 μm in diameter) nonseptate hyphae with branches occurring at right angles (Fig. 133-11). Differentiation of *Aspergillus*, *Fusarium*, *Scedosporium* spp., or other hyalohyphomycetes from *Mucorales* hyphae in tissue involves visualizing thinner, more regularly shaped fungal elements with more frequent acute angle branching and the presence of septae in the former group.[24]

In the majority of patients with pulmonary mucormycosis, establishment of a definite diagnosis with biopsy is hampered by the presence of comorbidities, such as thrombocytopenia. Furthermore, routine laboratory cultures, even if performed from tissue specimens with abundant *Mucorales* hyphal growth, have a yield of less

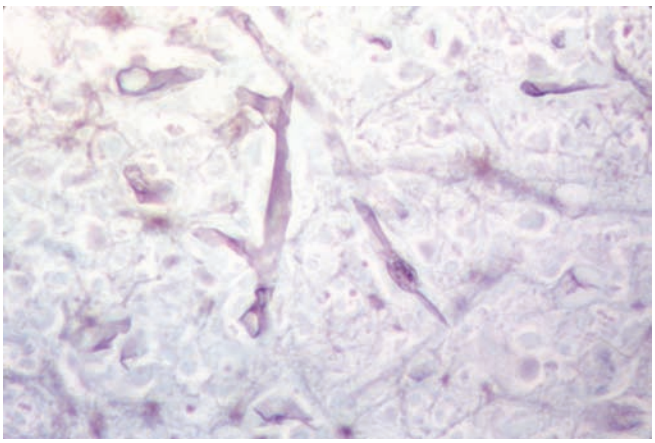


Figure 133-11 Histopathological features of *Zygomycetes* hyphae in a profoundly neutropenic patient with leukemia in whom pulmonary mucormycosis developed. Of note is the characteristic broad nonseptate or rarely septate hyphae with branches at right angles. H&E stain, ×400. *(Used with permission of Dr. G.P. Bodey.)*

than 50%. Recovery from tissue can be improved by mincing (not homogenizing) tissue and use of culture techniques that simulate in vivo growth, including incubation at 35° to 37°C in semi-anaerobic conditions.[24,25]

The importance of early differentiation of pulmonary mucormycosis from other IMIs has generated considerable interest in the development of surrogate diagnostic tests such as detection of specific antigens or nucleic acid by PCR. Unfortunately, serology-based diagnostic assays such as *Aspergillus* galactomannan and b-glucan are not useful for detection of mucormycosis. Other molecular diagnostic techniques using PCR assays in serum samples or paraffin wax embedded tissue or in situ hybridization techniques are promising, but remain investigational. In a prospective study of CT-guided percutaneous lung biopsy samples from high-risk patients with suspected fungal pneumonia, investigators demonstrated that early diagnosis and differentiation of pulmonary mucormycosis from IPA could be improved using a three-step analysis approach of biopsy specimens of lung lesions that included: Calcofluor-white staining to rapidly distinguish septated versus aseptae hyphae, *Aspergillus* galactomannan and PCR testing for rapid identification, and PCR testing of DNA in selected biopsy specimens where aseptate hyphae were observed or *Aspergillus* markers were negative.[24] These promising results require validation in a wider range of patients before PCR becomes a standardized adjunctive diagnostic test for mucormycosis.

TREATMENT

Successful treatment of pulmonary mucormycosis relies on timely diagnosis, reversal of underlying predisposing factors, early and broad surgical debridement of infected tissue (when possible), and rapid administration of effective antifungal therapy in the context of a multidisciplinary approach.[25] Cooperation among the primary care physicians, infectious disease consultants, surgeons, microbiologists, and pathologists is essential in the early stages of infection to avoid unnecessary diagnostic and treatment delays that increase patient mortality. For example, patient outcomes can be improved if initial treatment decisions are based on frozen tissues biopsy rather than from paraffin embedded tissue samples. Similarly, delays in the administration of effective systemic antifungal therapy within the first few days of diagnosis increase the probability of patient death due to progressive and/or disseminated infection. In addition, rapid correction of underlying conditions such hyperglycemia and/or diabetic ketoacidosis, tapering of corticosteroids, and other immunosuppressive drugs is critical to outcome. Notably, there have been rare cases of pulmonary mucormycosis with spontaneous regression of infection after correction of diabetic ketoacidosis.[24]

Antifungal treatment

With the exception of the recently completed DEFEAT *Mucor* study, there are no other prospective studies for the treatment of pulmonary mucormycosis because of the rarity and heterogeneity of the infection. Most evidence on the activity of existing antifungal agents comes from small case series, anecdotal case reports, and animal studies. Based on consensus guidelines,[23] the liposomal formulations of AMB have become the mainstay for treating mucormycosis in view of their favorable toxicity profile and comparable clinical outcomes with those historically reported for conventional AMB-based therapy. Thus, in the largest reported case series of mucormycosis including 24 patients who received a lipid complex of AMB for refractory disease or intolerance of conventional AMB, the overall response rate was 71%, without significant toxic effects even in patients with pre-existing renal disease. Animal models of pulmonary mucormycosis suggest a possible benefit for early administration of higher dosages of lipid AMB, and a phase II clinical study of 10 mg/kg/d liposomal AMB in mucormycosis will address further this question (http://clinicaltrials.gov/ct2/show/NCT00467883).[24]

Alternative routes of administration of amphotericin B as an adjunct to systemic therapy have been reported in pulmonary mucormycosis, although the efficacy of this approach is difficult to discern. For example, case reports describe the successful treatment of cancer patient with pulmonary mucormycosis using systemic therapy and ABLC aerosolized with a Respigard II nebulizer, direct instillation of amphotericin B within pulmonary cavities or into the pleural space.

Posaconazole (800 mg daily in four divided doses), an orally available broad-spectrum triazole, is the only drug of this class that appears to possess potent activity against *Mucorales*. In an open-label salvage trial, the overall success rate of posaconazole was 70% in 24 patients and was associated with minimal toxicity. Similarly, a retrospective review of posaconazole-based salvage therapy in 91 patients who had refractory mucormycosis indicated an overall success rate of 61% including a success rate of 65% in the group of patients with pulmonary mucormycosis.[24] Nonetheless, posaconazole exerts limited activity against *Rhizopus* spp. in neutropenic mouse models and cases of breakthrough mucormycosis in HSCT recipients while on posaconazole prophylaxis have been reported. Therefore, despite encouraging preliminary clinical data, the FDA has not approved posaconazole for primary or salvage therapy of mucormycosis, indicating the need for further studies.

Treatment with oral posaconazole has important pharmacokinetic limitations related to drug interactions and the poor absorption of the drug especially in patients with mucositis and those with poor dietary intake, while steady-state plasma concentrations of posaconazole are not reached until around 1 week of therapy.[25] Drug interactions can be problematic especially in patients receiving drugs that accelerate CYP P450 metabolism (i.e., rifampicin), or acid suppression therapy particularly with proton pump inhibitors. Therefore, it is preferable that patients with mucormycosis should initially receive several days of a lipid AMB formulation before started on posaconazole therapy and plasma drug level monitoring may be necessary in selected patients. Patients with persistently low or undetectable serum drug levels, poor oral intake or GI dysfunction (severe nausea, diarrhea) often must be transitioned back to intravenous liposomal AMB even in the absence of obvious disease if they are receiving additional immunosuppressive therapy. Overall, posaconazole seems to be a favorable option for less severely immunocompromised patients who need to be on continuous long-term antifungal therapy given the high risk for relapse of mucormycosis. The development of new (IV and oral) formulations of posaconazole with improved pharmacokinetics is currently undergoing phase II/III trial testing (www.clinicaltrials.gov/ct2/show/NCT01075984).

Echinocandins lack activity against *Mucorales* in vitro, and clinical experience with caspofungin in the treatment of mucormycosis is extremely limited. Nevertheless, in case reports and a study with a model of disseminated mucormycosis in diabetic mice, echinocandins appear to have some role, especially in combination with a polyene, in serious cases of mucormycosis.[25] A combination ABLC-caspofungin treatment regimen was associated with improved therapeutic success (100% vs. 45%; $P = 0.02$) in 41 diabetic patients with biopsy-proven, mostly rhino-orbital cerebral mucormycosis.[25] Further studies are required to compare this combination regimen to amphotericin B-based monotherapy for mucormycosis.

The duration of treatment required for mucormycosis should be highly individualized. Near normalization of radiographic imaging, negative biopsy specimens, and cultures from the affected site, and

recovery from immunosuppression are indicators that a patient is a candidate for stopping antifungal therapy.

Surgical treatment

Because mucormycosis is a highly angioinvasive infection with resulting extensive thrombosis and tissue necrosis, antifungal agents often display poor penetration at the site of infection. Therefore, even if the causative *Mucorales* strain is susceptible to the antifungal agent in vitro, the agent may be ineffective in vivo. Surgical debridement of infected lung tissue should be performed on an urgent basis. In patients with pulmonary mucormycosis, surgical treatment in conjunction with antifungal therapy has been shown to significantly improve survival when compared with antifungal therapy alone. Hence, a comprehensive review of cases of pulmonary mucormycosis showed that the mortality in patients who received antifungal agents alone was 55% versus 27% in patients who received antifungal agents and surgery.[25] Removal of as much of the infected or devitalized tissue as possible while the infection is localized has the greatest benefit. Lobectomy is often required, and pneumonectomy may be necessary for proximal or extensive involvement. Also, repeated procedures may be needed. The benefit of pulmonary resection diminishes as dissemination occurs.

Other adjunctive therapies

Small case series implicate that treatment with hyperbaric oxygen (HBO) may be a beneficial adjunct to standard therapy for mucormycosis, particularly in patients with diabetes mellitus who have rhinocerebral disease.[25] HBO has pleiotropic properties by promoting wound healing, phagocytic cell function, and oxidative killing mechanisms of *Mucorales* by AMB and also displays direct antifungal activity. However, data on treatment with HBO of pulmonary mucormycosis are scarce, and a role in this setting remains uncertain.

The role of adjunctive cytokine therapy for mucormycosis has not been extensively studied. Cytokines that activate phagocytic activity, such as IFN-γ and GM-CSF, increase the killing efficacy of phagocytic cells against *Mucorales* spp. in vitro. Case reports indicate a favorable outcome in selected patients with rhinocerebral mucormycosis who received IFN-γ and GM-CSF adjunct salvage treatment. In selected neutropenic patients, granulocyte transfusion may be a useful bridge until neutrophil recovery, although the clinical benefit remains unproven and serious adverse effects that resemble immune reconstitution inflammatory syndrome (IRIS), including pulmonary toxicity and accelerated cavitation/bleeding, have been reported in patients with opportunistic lung mycoses.[24,25] Importantly, granulocyte transfusions contain not only neutrophils but also substantial number of lymphocytes and HLA alloimmunization can be a major complication of granulocyte transfusions. Thus, the benefits and risks of granulocyte transfusions should be carefully assessed on an individual basis, particularly for patients who are candidates for HSCT. Adoptive T-cell–based immunotherapeutic strategies are feasible and could represent an attractive future strategy in the management of mucormycosis.

The central role of iron metabolism in the pathogenesis of mucormycosis supports the hypothesis of using iron chelators without xenosiderophore activity, such as deferiprone and deferasirox, as adjunctive antifungal therapy.[25] In contrast with deferoxamine, such iron chelators induce iron starvation in the fungus, thereby inhibiting growth in vitro in the presence of iron and improving survival in a diabetic ketoacidosis animal model of mucormycosis. Case reports imply that deferasirox with antifungals may be less effective in neutropenic patients than in diabetic ketoacidosis patients. Moreover, the bioavailability of oral deferasirox in immunocompromised patients with mucositis due to chemotherapy or GvHD of the gut is unknown. Importantly, a recently completed phase II, double-blind, randomized, placebo-controlled trial of adjunctive deferasirox therapy failed to demonstrate a benefit of the combination regimen in 20 patients with mucormycosis (DEFEAT MUCOR trial, NCT00419770).

EMERGING OPPORTUNISTIC MOLDS

Over the past decade, and with the ever-expanding spectrum of immunocompromised patients, we have witnessed the emergence of less common but medically important opportunistic fungal pathogens, including septate filamentous fungi such as hyalohyphomycetes (e.g., *Fusarium*, *Scedosporium*, and *Trichoderma* species), dematiaceous fungi (e.g., *Phaeohyphomycetes*), endemic dimorphic pathogens (e.g., *Penicillium marneffei*), and rare pathogenic yeasts (e.g., *Trichosporon* species).[26–29] The diagnosis of invasive fungal pneumonia caused by these uncommon filamentous fungi is challenging because of the similarity of the manifestations and histopathological features of these mycoses with those of IA. Given the fact that most of these infections have a poor outcome because of broad-spectrum resistance to conventional antifungal agents, timely diagnosis is critical for outcome. Therefore, pulmonary infections caused by hyalohyphomycetes, including *Fusarium* and *Scedosporium* species, are discussed below.

PULMONARY FUSARIOSIS

Fusarium spp. are ubiquitous filamentous fungi found in soil, water, and decaying material. Although *Fusarium* is a well-known plant pathogen, only a few of the 50 different species have been reported to be pathogenic in humans, including *Fusarium solani, Fusarium oxysporum, Fusarium moniliforme, Fusarium verticilloides, Fusarium dimerum*, and *Fusarium proliferatum.*[28] *Of these species, F. solani* is the most virulent, causing half of all cases of invasive fusariosis reported in humans. Since the description of the first case of disseminated fusariosis in a child with acute leukemia in 1973, invasive fusariosis has emerged in some tertiary care oncology centers as an important IMI in profoundly immunocompromised patients with hematological malignancy.[29]

There seems to be a distinct seasonal peak and geographic distribution of invasive fusariosis. The vast majority of cases have been reported in the United States during the rainy summer season, when the dispersion of fusarial conidia in the air is most pronounced.[29] More than 90% of human invasive fusariosis cases occur in neutropenic patients with hematological malignancies, especially those with acute leukemia. Another risk factor for invasive fusariosis is GvHD treated with high doses of corticosteroids during the postengraftment period in HSCT recipients.[28]

The skin and respiratory tract are the primary portals of entry for *Fusarium* infection. Inhalation of *Fusarium* conidia through the lung and paranasal sinuses by a severely immunocompromised host may lead to sinopulmonary infection characterized by angioinvasion, extensive tissue necrosis, and secondary dissemination. In addition, disruption of skin integrity because of local trauma or placement of a central venous catheter or in the setting of onychomycosis with associated cellulitis appears to be a relatively common portal of entry for disseminated *Fusarium* infection that involves the lung in immunocompromised hosts. The ability of *Fusarium* spp. to undergo adventitious sporulation with formation of microconidia in vivo facilitates dissemination and may account for the high rates of positive blood cultures and associated skin lesions in cases of fusariosis.[28] Neutrophils probably play the most critical role in the control of human *Fusarium* infections. Several studies have demonstrated that the prognosis for patients with fusariosis is associated with the prompt recovery of neutrophil counts. In fact, the mortality rate in patients with fusariosis in the setting of profound, prolonged

TABLE 133-8 Differentiating Features Among the Major Opportunistic Mold Infections of the Lung

Incidence	• *Aspergillus* causes the vast majority of cases of fungal pneumonia, followed by *Zygomycetes*
Predisposing factors	• *Zygomycetes* spp. are associated with the presence of diabetes mellitus, malnutrition, iron overload states, and voriconazole prophylaxis
Clinical features	• Skin lesions are more common in disseminated fusariosis (50–70%) than in disseminated IA (<10%) and disseminated mucormycosis (<10%) • Skin lesions in fusariosis are different from those in IA and mucormycosis (*Aspergillus and Zygomycetes* skin lesions are fewer, less widespread, have a larger diameter, and present with a black eschar with a thinner erythematous halo) • Fungemia is more common in fusariosis (60–70%) than in IA (<5%) and mucormycosis (virtually absent) • Fungemia also often occurs earlier in fusariosis than in IA (shortly before death or after death) • The *Zygomycetes and Fusarium* spp. are highly resistant to antifungal agents and develop as breakthrough infections to antifungals with anti-*Aspergillus activity*
Histopathological features	• Broad-based nonseptate or pauciseptate ribbon-like hyphae are pathognomonic for *Zygomycetes* • The presence of chlamydosporia in histopathology is pathognomonic for *Fusarium* spp.
CT features	• On CT scans, multiple nodules, and pleural effusions favor the diagnosis of pulmonary mucormycosis vs. IPA • Pulmonary mucormycosis has a predilection for the upper lung lobes
Serology	• Positive galactomannan antigen is virtually diagnostic for IPA; cross-reactivity of *Aspergillus* galactomannan antigen with *Fusarium* spp.

neutropenia is essentially 100%, even with aggressive antifungal treatment, compared with a rate of approximately 30% in the setting of neutrophil recovery.[28]

Fusariosis in immunocompromised patients manifests in four major patterns: refractory fever of unknown origin, sinopulmonary infection or pneumonia, disseminated infection, and a variety of focal single-organ infections.[28] Sinopulmonary fusariosis and pneumonia occurs in more than 80% of patients and is most often clinically and radiographically indistinguishable from the much more common IA and other IMIs. Sinus involvement is also frequent, as it has been observed in up to 80% of cases in some reports.[28] One of the diagnostic challenges in immunocompromised patients with fungal pneumonia is differentiating between IA, invasive fusariosis, and mucormycosis. Hence, recovery of *Fusarium* spp. from cultures of appropriate specimens is essential for a definite diagnosis.

The histopathological picture of *Fusarium* is identical to that of *Aspergillus* and other hyalohyphomycetes (e.g., *Scedosporium spp.*) and may lead to misidentification. Even so, there are subtle differences in the histopathological features of *Aspergillus* and *Fusarium* spp. that can facilitate differentiation between the two species based on the histopathology itself, including the presence of *Fusarium* chlamydosporia in tissue (Table 133-8).

Because hyalohyphomycetes (*Aspergillus* vs. *Fusarium* vs. *Scedosporium* spp.) have different levels of susceptibility to antifungal agents, the ability to differentiate between these molds in histopathology positive but culture-negative cases using molecular identification methods could have significant implications on therapeutic decision making. In situ hybridization directed against ribosomal 18 S RNA sequences was recently shown to rapidly and accurately distinguish *Fusarium*, *Aspergillus*, and *Scedosporium* spp. from histopathological specimens.[28] However, further standardization of these promising molecular methods is needed. Proteomic-based approaches with the use of mass spectroscopy (MALTITOF) are capable to provide rapid diagnosis of clinical isolates of *Fusarium*. These techniques are promising in diagnosis of fungal pathogens but require further standardization and are not widely available. Thus, tissue cultures remain the gold standard for differentiation between these fungi.

Despite the clinical similarities between pulmonary fusariosis and IPA, there are some characteristics that favor the diagnosis of invasive fusariosis (Table 133-8). First, *Fusarium* spp. are usually recovered from blood specimens in the setting of disseminated disease. The reported rate of positive blood cultures in patients with disseminated fusariosis ranges from 50% to 70%, and fungemia may be the only manifestation of the infection.[28] *Fusarium* is the most common mold associated with true fungemia in HSCT recipients. This feature contrasts with disseminated IA and mucormycosis cases in which these molds are rarely (<5%) isolated from blood specimens, with the notable exception of *A. terreus*.

Another distinctive feature of invasive fusariosis is the high incidence (50%–70%) of skin lesions in patients with disseminated disease. This contrasts with the low incidence of skin lesions in patients with disseminated aspergillosis (<10%). In fact, skin lesions are frequently the sole diagnostic material for invasive fusariosis in a high-risk patient with presumed fungal pneumonia. Several patterns of skin lesions can be seen: subcutaneous nodules, purpura, red or gray macules and/or papules with or without progressive central necrosis, flaccid pustules, vesicles, and hemorrhagic bullae.[28] The most characteristic skin lesions encountered in cases of disseminated fusariosis are "ecthyma gangrenosum-like" lesions, which are red or gray macules with central ulceration or black eschar. *Fusarium* skin lesions are often tender, especially subcutaneous nodules, and can involve any skin site, although they appear predominantly in the extremities. Most patients have lesions at different stages of evolution. Accompanying myalgias are also common, reflecting concomitant muscle involvement.

Fusarium species are quite resistant to the arsenal of modern antifungal agents, and breakthrough infections to AMB or triazoles are common.[29] In particular, *F. solani* is the most resistant species within the genus. The mainstay in the treatment of fusariosis has traditionally been AMB-D. However, the in vitro susceptibility of *Fusarium* spp. to AMB-D is, at best, mediocre. Whether the in vitro susceptibility of *Fusarium* spp. alone can predict outcome is unclear, because other factors, such as neutrophil recovery, are probably the most critical determinants of the prognosis for fusariosis. There have been reports of improved outcome of fusariosis with the use of high-dose lipid formulations of AMB. Hence, the mortality rate in patients who received high doses of a lipid complex of AMB (>5 mg/kg/d) was significantly lower (<30%) than that observed

in patients who received conventional AMB-D doses (>75%) in a previous study.[28]

Among the antifungal triazoles, fluconazole and itraconazole are not active against *Fusarium* spp. However, the newer broad-spectrum triazoles voriconazole and posaconazole have variable in vitro activity against *Fusarium* spp. and may show promise in the management of fusariosis. A recent retrospective study evaluated the outcome of 73 patients with fusariosis treated with voriconazole either as frontline (22%) or salvage (78%) therapy, with an overall response rate of 47%. Another retrospective study in 21 patients with fusariosis refractory or intolerant to AMB-based therapy reported a 48% response rate in 10 patients receiving salvage posaconazole.[28] Given that AMB and the newer triazoles voriconazole and posaconazole are the most active agents against *Fusarium* spp., a strategy combining a lipid formulation of AMB with one of these triazoles is frequently employed in clinical practice. A retrospective study examined the rationale of combination therapy in 44 hematological malignancy patients with fusariosis. The majority of these patients (73%), received combination therapy, with amphotericin B and a triazole with 41% response at 12 weeks after diagnosis. Overall, the rational of combination therapy for fusariosis is reasonable and merits further investigation.[28]

Because the neutrophil count seems to be the most crucial prognostic determinant in fusariosis cases, a potentially beneficial adjuvant therapeutic strategy is to transfuse granulocytes obtained from G-CSF- and GM-CSF–stimulated donors.[28] Granulocyte transfusion has been suggested to result in more favorable response rates (33%–50%) in profoundly neutropenic patients by shortening the duration of neutropenia.[28]

■ PULMONARY SCEDOSPORIOSIS

The genus *Scedosporium* comprises a group of filamentous fungi found ubiquitously in the environment. The two major human pathogenic species are *Scedosporium apiospermum* – the asexual state of *Pseudallescheria boydii* – and *Scedosporium prolificans*.[26,27] Both of these species histologically resemble *Aspergillus* spp. with hyphae that are septate and branching at acute angles. Although *Scedosporium* infections can occasionally occur in immunocompetent individuals, the overall incidence has increased over the past decade because of improved diagnostic modalities and the expanding population of immunocompromised individuals. These fungi can cause fatal angioinvasive infections in immunocompromised hosts that manifest with sinopulmonary, central nervous system, osteoarticular, ocular, endovascular, and lymphocutaneous involvement.[26,27] Disseminated infection is associated with high (>75%) mortality rates. *Scedosporium* spp. are known to be remarkably resistant to most conventional antifungals, such as AMB; treatment with newer triazoles, such as voriconazole, appears to be more efficacious.[26,27]

Spores of *Scedosporium* spp. enter the respiratory tract by inhalation and the skin by direct inoculation to areas of trauma. Germination of conidia results in hyphal invasion in tissue with the potential to disseminate hematogenously to distant anatomic sites. Similar to *Fusarium* spp., dissemination may be facilitated by the ability of *Scedosporium* spp. to undergo adventitious sporulation in vivo. In general, strains of *S. prolificans* are more virulent than strains of *S. apiospermum*. *S. prolificans* produces melanin, which may be an important virulence factor contributing to in vivo protection against host defense mechanisms.[26,27]

Patients with AIDS, congenital or acquired immunodeficiency, or hematological malignancies as well as recipients of stem cell and solid-organ transplants and those receiving antineoplastic or immunosuppressive medications are especially susceptible to these filamentous molds.[28] In these immunocompromised individuals, sinopulmonary disease with hematogenous dissemination to various organs most often occurs. Of interest, a recent review of 189 cases of pulmonary scedosporiosis reported that 11% of all cases were in immunocompetent patients following near-drowning. This association implies the higher virulence of *Scedosporium* spp compared to other opportunistic molds.[26,27]

The spectrum of pulmonary scedosporiosis largely mimics aspergillosis, ranging from respiratory tract colonization, to allergic bronchopulmonary hypersensitivity, to saprophytic fungus ball formation in pre-existing pulmonary cavities, and finally to invasive pulmonary or disseminated scedosporiosis.[26,27] Invasive disease without pre-existing lung tissue damage caused by *S. apiospermum* generally occurs only in immunocompromised hosts during or immediately after periods of prolonged neutropenia or with intensification of immunosuppression, and fever is the most common clinical presentation. Onset of infection may also be manifested by pulmonary symptoms, maculopapular skin lesions that later may become necrotic, myalgias, and central nervous system and other organ involvement.[26,27] On rare occasions, pulmonary infections that spread to involve the central nervous system are reported in immunocompetent individuals after massive inoculation with *S. apiospermum* by aspiration of polluted water.[26,27] Fungemia is diagnosed in more than two thirds of patients with disseminated *S. prolificans* and *S. apiospermum* infection. The radiographic appearance of pulmonary infections caused by *S. apiospermum* and *S. prolificans* is essentially indistinguishable from that of IPA. Because no radiographic findings are truly pathognomonic for *Scedosporium* infections, diagnosis relies on prompt histopathological and microbiological evaluation.

Histopathological features of *Scedosporium* spp. in tissue sections can be confused with those of other fungi that have acute-angle–branching septate hyphae. The melanin-specific Fontana–Masson stain may be used to confirm the presence of dematiaceous hyphae of *S. prolificans* in tissue.[26,27] Nevertheless, definitive diagnosis requires fungal culture and is crucial for antifungal susceptibility testing.

In general, *S. prolificans* is resistant to all clinically available antifungal agents, whereas *S. apiospermum* may be susceptible to miconazole, voriconazole, and posaconazole.[26,27] Both species are inherently resistant to the polyenes, including AMB. Data from clinical studies are limited. In a multicenter study of voriconazole administered as salvage therapy for scedosporiosis, the overall response rate of voriconazole for scedosporiosis outcomes of voriconazole therapy for *S. apiospermum* (33%) was somewhat better than that for *S. prolificans* (25%).[26,27]

Severe *S. prolificans* infections have been successfully treated with a combination of voriconazole and terbinafine.[26,27] In combination with azoles, terbinafine, an allylamine that blocks squalene epoxidase in the ergosterol synthesis pathway, has demonstrated synergistic interactions in vitro against clinical isolates of *S. prolificans*. Limited experience in patients with disseminated *S. prolificans* suggests that the combination of voriconazole and terbinafine is a legitimate treatment option, although the unfavorable pharmacokinetic characteristics of terbinafine preclude use as monotherapy.

Surgical debridement in cases of pulmonary scedosporiosis should be considered, especially for abscess drainage as well as for localized infections. In general, neutrophil recovery has been associated with an improved prognosis. IFN-g and GM-CSF have been shown to enhance neutrophil oxidative mechanisms of killing against *S. prolificans* hyphae.[26,27] Although clinical data are scarce, in view of the dismal prognosis for patients with *Scedosporium* infections, immunomodulating therapy, including G-CSF, GM-CSF, IFN-γ, and primed white blood cell transfusions, should be considered as an adjunct treatment modality for these infections.[26,27]

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CHAPTER 134

Cryptococcosis and the Endemic Mycoses

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Histoplasmosis and blastomycosis mostly afflict those living in the Mississippi and Ohio River Valleys, while coccidioidomycosis occurs primarily in the Southwestern desert of the United States (Fig. 134-1). Histoplasmosis and coccidioidomycosis also are endemic in parts of Mexico and Central and South America. Infection with *Cryptococcus neoformans* var. *gatti* is endemic to parts of British Columbia, the Pacific Northwest region of the United States and Australia while *C. neoformans* var. *neoformans* exhibits no geographical predilection. These mycoses are often mistakenly diagnosed and incorrectly treated as community-acquired pneumonia or sarcoidosis, resulting in serious morbidity or death in many cases.[1–3]

These organisms are found in the soil, and infection occurs following inhalation of the infectious forms of these fungi when sites containing the organism are disturbed. In some endemic areas over one-half of residents have acquired these mycoses early in life. In healthy individuals the infections are usually asymptomatic or clinically self-limited. In others, especially those who are immunosuppressed, the course of infection may be progressive and fatal without treatment. While these mycoses are less often seen in patients with acquired immunodeficiency syndrome (AIDS) who have access to effective antiretroviral therapy, they are occurring more frequently in those with other immunosuppressive conditions, and continue to be pathogenic for individuals without underlying disease. The majority of those hospitalized due to infection with endemic mycoses in the United States in fact have no identifiable immunologic deficits. In a study of patients hospitalized with histoplasmosis, blastomycosis, or cocciodiodomycosis, only 13% of those infected were immunosuppressed. Hospital costs alone exceeded $250 million,[4] providing an estimate of the impact of the endemic mycoses in the United States. Advances in diagnosis and treatment provide opportunities to improve the outcome of these mycoses.

CRYPTOCOCCAL INFECTIONS

Cryptococcosis is caused by infection with the encapsulated fungus *C. neoformans,* an organism with a worldwide distribution. Inhalation of *C. neoformans* initiates the infection in the lung with hematogenous dissemination most often involving the meninges. Although pulmonary infection may be discovered in the presence or absence of disseminated infection, meningoencephalitis remains the most commonly diagnosed form of cryptococcal infection. The spectrum of disease ranges from asymptomatic pulmonary infection in the immunocompetent host to diffuse pulmonary disease associated with respiratory failure and widespread disseminated disease in the immunocompromised host. It is estimated that nearly 1 million cases of cryptococcal meningitis occur worldwide annually, with the majority of cases occurring in those with HIV infection.[5] The incidence of cryptococcosis in patients with AIDS in the United States has declined since the introduction of potent antiretroviral therapy; most cases now occur in those with limited access to care.[5,6]

MYCOLOGY

C. neoformans is a yeast that is characterized by a thick polysaccharide capsule. The yeast measures 4 to 6 μm in diameter but the capsule thickness varies from 1 to more than 30 μm. Organisms are smaller and less well encapsulated in the environment, explaining the ability to reach the terminal airways following inhalation. *C. neoformans* grows readily in fungal media, allowing isolation in less than 48 hours and identification by biochemical tests or DNA probes. Four serotypes of *C. neoformans* have been described—A, B, C, and D.

EPIDEMIOLOGY

Serotypes A and D predominate in North America and Europe and grow best in composted bird droppings or rotted vegetation. Serotypes B and C are classified as *C. neoformans* var. *gatti* and are more common in tropical and subtropical regions in association with eucalyptus trees rather than avian excreta. Recently outbreaks of infection caused by *C. neoformans* var. *gatti* have been reported in British Columbia and the Pacific Northwest region of the United States (Fig. 134-1). Otherwise outbreaks or clusters of cases are rare in cryptococcosis, and in most cases a history of exposure to birds or dust is lacking. Person-to-person transmission does not occur if cryptococcosis has been transmitted through organ transplantation; cutaneous infection has occurred after direct inoculation.

Patient populations at increased risk for progressive cryptococcosis include those with T-cell–mediated immune defects caused by AIDS, lymphoreticular malignancy (particularly Hodgkin

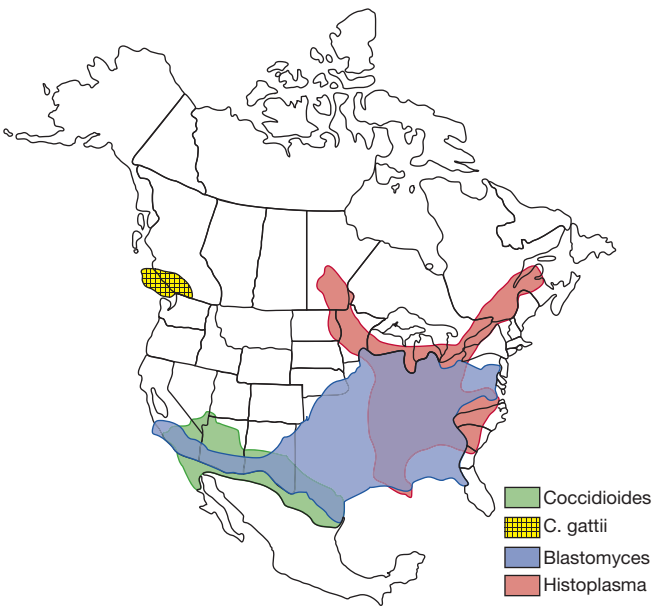


Figure 134-1 Geographical distribution of endemic mycoses in the United States. The area of histoplasmin skin test reactivity in the southwestern US represents cross-reactivity caused by coccidioidomycosis, not endemic histoplasmosis.

disease), or immunosuppressive medications, including tumor necrosis factor (TNF) inhibitors. The disease also appears to be more frequent in diabetics. *While C. neoformans* var. *gatti* infection was initially reported as occurring almost exclusively in immunocompetent hosts, in a recent surveillance study, half of patients infected with this organism had underlying immunosuppression.[7]

■ PATHOGENESIS

Cryptococcosis is acquired by inhaling aerosols containing the yeast but rarely by direct inoculation. Progressive disease often follows exposure in patients with impaired cellular immunity. In tissues, a mixed macrophage, lymphocyte, and plasma-cell response is seen, but inflammation may be minimal in immunodeficient subjects. Granulomas are uncommonly found in the nervous system but may be seen in other tissues.

Macrophages, natural killer cells, and T lymphocytes play the key roles in cellular defense against *C. neoformans*. Inflammatory cytokines (interleukin [IL]-2, IL-12, interferon [IFN]-γ) and macrophage colony-stimulating factor enhance the antifungal activity of these cellular mechanisms. Humoral immunity complements cellular mechanisms in defense against *C. neoformans*.

■ CLINICAL FINDINGS

Cryptococcal infection results in asymptomatic or self-limited pulmonary disease in most healthy individuals. While symptomatic isolated pulmonary cryptococcosis may be diagnosed, meningoencephalitis is the most commonly recognized manifestation of cryptococcosis and the most common cause of death. Hematogenous dissemination to almost any tissue occurs in fewer than 25% of cases.

Pulmonary

Isolated pulmonary infection is not uncommon, and saprophytic colonization has been observed. Pulmonary cryptococcosis often is asymptomatic, discovered when chest radiographs are done for other reasons. Concurrent disseminated disease occurs in about 15% of cases. In symptomatic cases, common complaints include dry cough, dull chest discomfort, and low-grade fever. Less commonly night sweats, fatigue, weight loss, or hemoptysis may occur. Nodular infiltrates are typical of pulmonary cryptococcosis in the normal host (Fig. 134-2). Pulmonary cryptococcosis in nonimmunosuppressed patients usually resolve without therapy. Occasionally pulmonary cryptococcosis progresses slowly or may be accompanied by meningoencephalitis or dissemination to other organs after improvement of the pulmonary process.

In contrast to nonimmunocompromised patients, most immunocompromised patients exhibit fever and cough. Diffuse interstitial infiltrates or widespread alveolar consolidation causing respiratory failure is common in severely immunodeficient hosts. Radiographs in patients with less profound cell–mediated immune defects usually show nodular or patchy alveolar infiltrates (Fig. 134-2). Mortality is high in immunosuppressed patients with diffuse pulmonary involvement. Mass lesions are not uncommon and may resemble malignancy. Cavitation is uncommon and mediastinal adenopathy, pleural effusion, and calcification are rare. A halo sign, usually attributed to aspergillosis, may be observed in cryptococcosis. Empyema, pleural disease suggesting a Pancoast tumor, and pneumothorax have been reported. As immunosuppressed patients with pulmonary cryptococcosis often have meningoencephalitis, a lumbar puncture is recommended in these patients even in the absence of signs or symptoms of central nervous system (CNS) infection.

Meningoencephalitis

Meningoencephalitis is the most common manifestation of cryptococcosis. A gradual onset is typical, but a more rapid presentation may be seen in patients with severe immunodeficiency. Symptoms include fever, headache, nausea, and vomiting, while less than one-third of patients exhibit meningismus, altered mentation, or focal neurological abnormalities. Elevated intracranial pressure is common and may cause brain-stem herniation. Focal brain lesions occur in about 10% of cases, alone or in combination with meningoencephalitis.

Other Sites of Dissemination

Extraneural involvement may be seen in patients with meningoencephalitis or pulmonary cryptococcosis. Hepatosplenomegaly and bone marrow suppression are seen most commonly while lesions involving the skin, eyes, bones, or joints occur in about 5%. Other sites of dissemination include the heart, pericardium, muscle, gastrointestinal tract, peritoneum, thyroid, larynx, breast, placenta, urinary tract, prostate, and organ of Corti.

Immune Reconstitution Syndrome

Up to 30% of patients with AIDS and a recently diagnosed cryptococcal infection may exhibit an immune reconstitution inflammatory syndrome (IRIS) following initiation of highly active antiretroviral therapy (HAART) (see Chapter 123).[8] In AIDS patients, levels of serum cryptococcal antigen titer[9] as well as CSF cryptococcal antigen titers[8] prior to the administration of HAART have been positively correlated with the risk of IRIS. Similar findings have been reported following organ transplantation with reductions in immunosuppression during therapy. Clinical findings have included worsening of meningitis with the development of intracranial hypertension, hypercalcemia, intrathoracic lymphadenopathy, cavitation of pulmonary lesions, and soft tissue abscess. These findings represent inflammation resulting from an enhanced inflammatory response made possible by immune reconstitution. While such changes may resolve spontaneously at times, the inflammatory changes within the CNS have led to death.[10] A recently published study that randomized patients with newly diagnosed AIDS and cryptococcal meningitis to early HAART (approximately 7 days following initiation of antifungals) versus delayed HAART approximately (28 days after initiating antifungals) demonstrated significantly more IRIS events in those treated with early HAART.[11] These findings would support the recommendation by the Infectious Disease Society of America (IDSA) that HAART should be withheld for individuals recently diagnosed with cryptococcal meningitis, for 2 to 10 weeks after initiation of antifungal therapy.[12]

■ DIAGNOSIS

Approaches to the diagnosis of cryptococcal pneumonia and meningoencephalitis are discussed below.

Pneumonia

The diagnosis of pneumonia is usually made by cytology or histopathology of respiratory secretions or lung tissue, and confirmed by culture (Table 134-1).[13–15] Once a diagnosis of pulmonary cryptococcosis is made, an evaluation for extrapulmonary dissemination should be initiated. A serum cryptococcal antigen test should be performed along with fungal blood culture. Cerebrospinal fluid (CSF) examination is recommended if the patient has any symptoms of meningitis or brain involvement, or is immunosuppressed. IDSA guidelines indicate that for immunocompromised patients with pulmonary cryptococcosis, a lumbar puncture to rule out asymptomatic CNS involvement should be considered.[12] However, for normal hosts with an asymptomatic

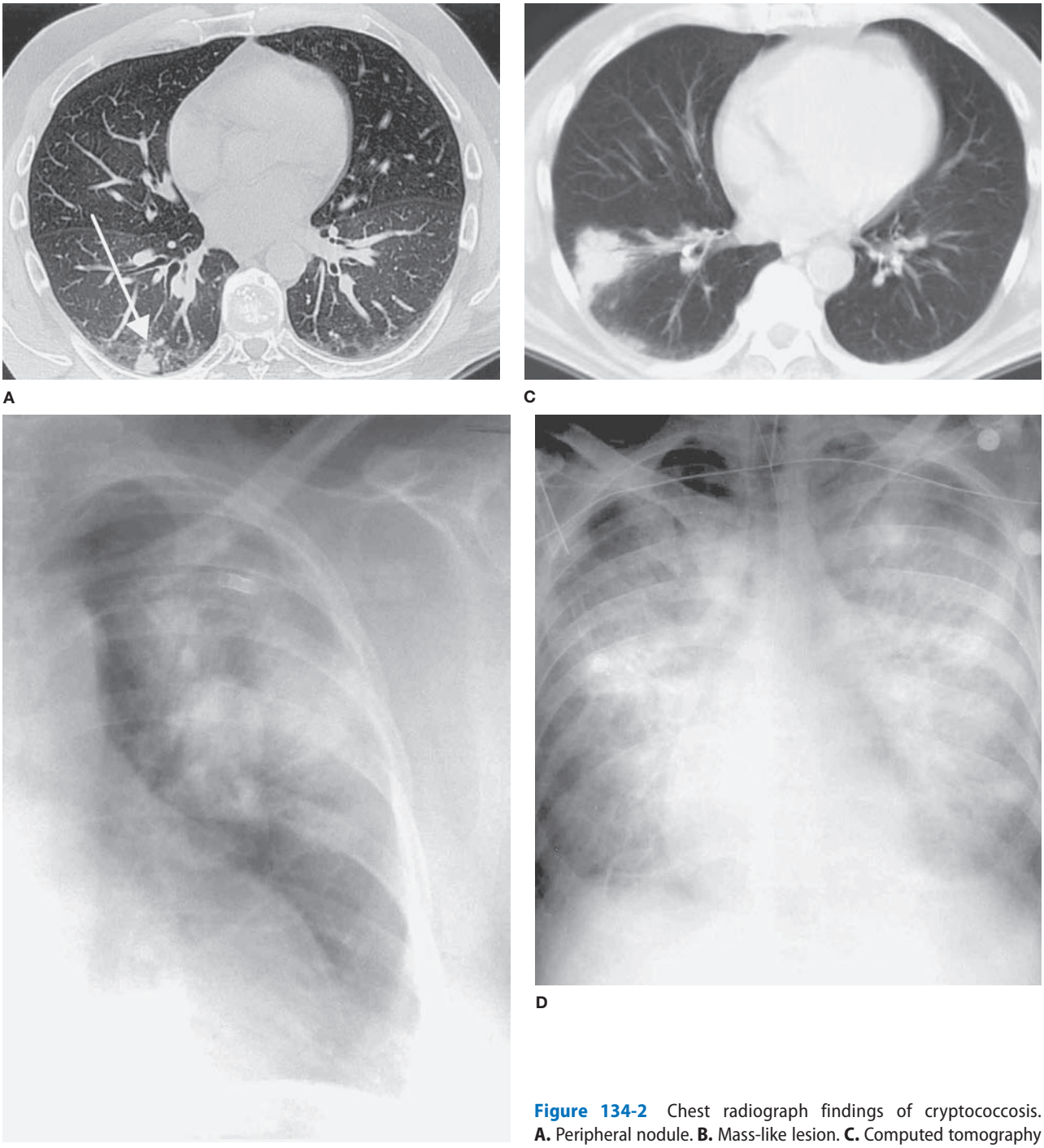


Figure 134-2 Chest radiograph findings of cryptococcosis. **A.** Peripheral nodule. **B.** Mass-like lesion. **C.** Computed tomography of mass lesion. **D.** Chest radiograph showing diffuse infiltrate.

TABLE 134-1 Diagnostic Studies in Cryptococcosis (Percent Positive Assays)

	Pulmonary, Nondisseminated		
	Nonimmunocompromised	Immunocompromised	Meningitis-immunocompromised
India Ink		55[14]	50–80[16–18]
Histopathology	5[15]	66[13]	NA
Antigen, serum	5[15]	89[13]	88–100[16–18]
Antigen, BAL		86[14]	NA
Antigen, CSF	NA	NA	98–100[16–18]
Culture	72[15]	100[13]; 92[14]	90

BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; NA, not applicable.

pulmonary nodule or infiltrate, no CNS symptoms, and a negative or very low serum cryptococcal antigen, a lumbar puncture can be avoided.

Histopathology and Cytology *C. neoformans* can be recognized in tissue as a globose or oval to lemon-shaped yeast with a polysaccharide capsule (Fig. 134-3). Cryptococci are readily identified by the Gomori methenamine silver (GMS) and periodic acid–Schiff (PAS) stains. More specific stains for *C. neoformans* include the Mayer's mucicarmine stain, which stains the fungal capsule and the Masson–Fontana melanin stain, which may detect capsule-deficient cryptococci. Direct microscopic examination of bronchoalveolar lavage (BAL) fluid sediment stained with India ink can identify the organism. The sensitivity of histopathology in patients with AIDS is about 67%. In the nonimmunocompromised host, fungal stains of respiratory specimens are rarely positive (approximately 5%) despite isolation of the fungus in over two-thirds of cases.

Antigen Detection In patients with cryptococcal pneumonia, the serum cryptococcal antigen is usually not detected unless extrapulmonary dissemination has occurred, the pneumonia is extensive, or the patient is immunosuppressed. A negative serum cryptococcal test should not be used to exclude the diagnosis of cryptococcal pneumonia. In patients with AIDS with pulmonary cryptococcosis the serum cryptococcal antigen is positive in most cases. Cryptococcal antigen also may be detected in BAL and pleural fluid. Cryptococcal antigen detection using a lateral flow device simplifies

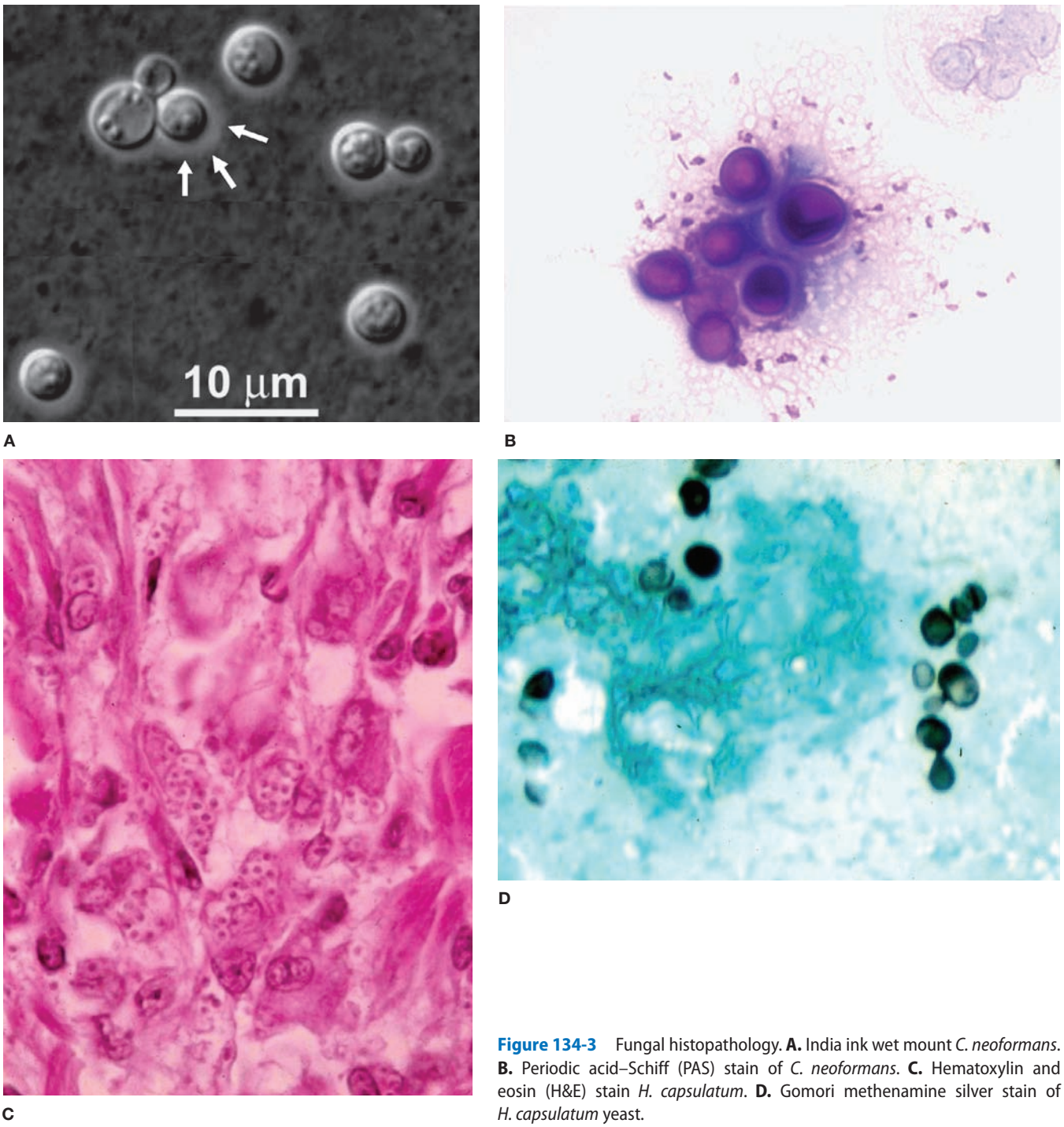
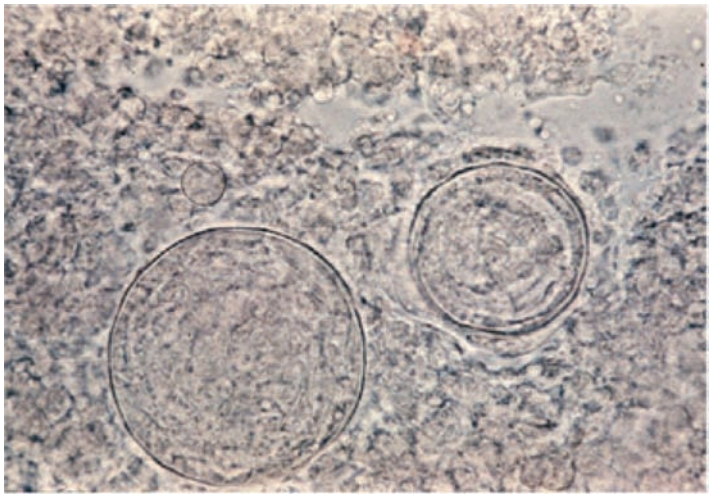


Figure 134-3 Fungal histopathology. **A.** India ink wet mount *C. neoformans*. **B.** Periodic acid–Schiff (PAS) stain of *C. neoformans*. **C.** Hematoxylin and eosin (H&E) stain *H. capsulatum*. **D.** Gomori methenamine silver stain of *H. capsulatum* yeast.



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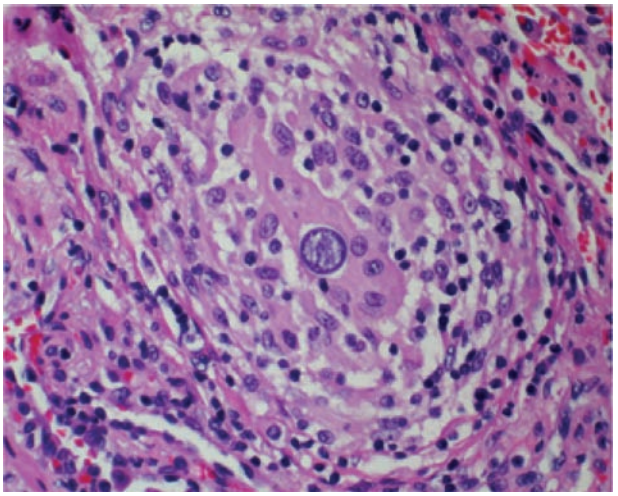

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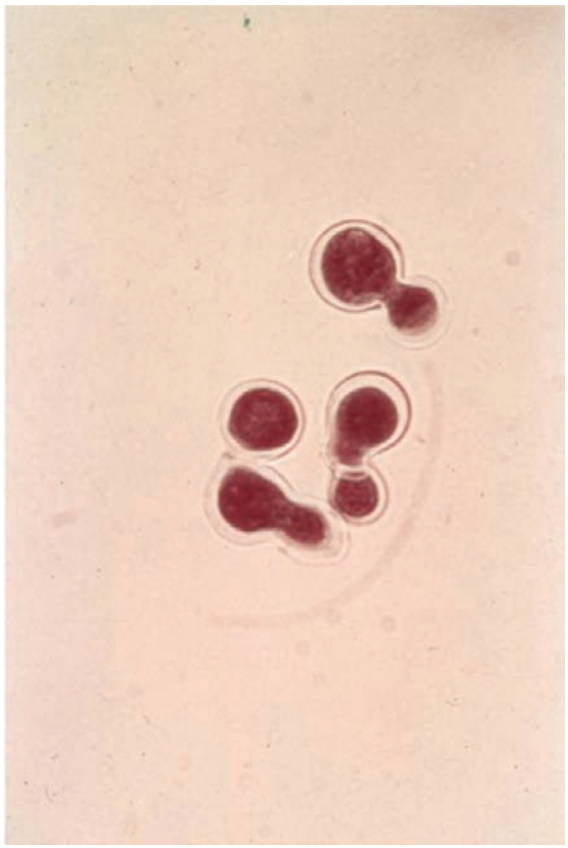

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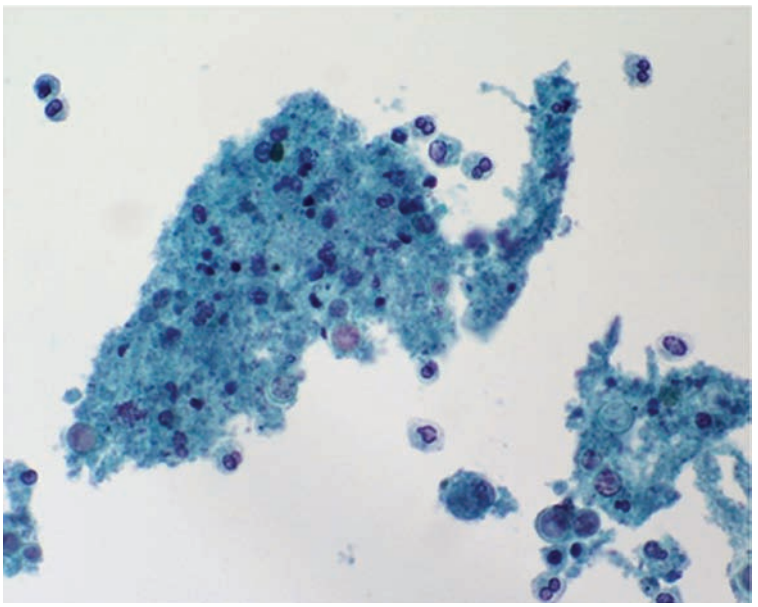


H

Figure 134-3 *(Continued)* **E.** Potassium hydroxide (KOH) wet mount showing *C. immitis* spherule. **F.** H&E stain *C. immitis* spherule in the tissue. **G.** KOH wet mount showing *B. dermatitidis* yeast. **H.** Papanicolaou stain showing *B. dermatitidis* yeast.

point-of-care testing.[19] Cryptococcal serum antigen screening of patients with HIV-infection and a CD4 count <100 cells/mm^3, who reside in an area with a high rate of cryptococcal disease, can identify those at risk to develop cryptococcal meningitis over the subsequent year.[20]

Culture *C. neoformans* often can be isolated from sputum in patients with cryptococcal pneumonia. However, isolation from sputum may represent mere colonization. In patients unable to produce sputum, bronchoscopy may be useful. Cultures of BAL or lung tissue yield the organism in 50% to 90% of cases while fungal stains are positive less often. Needle aspiration of focal lesions also may be useful. Thoracentesis may yield the organism in patients with pleural involvement. Blood cultures may be positive in immunocompromised hosts.

Meningoencephalitis

The diagnosis of meningitis can be made initially by India ink stain or detection of antigen in CSF and confirmed by isolation of the organism from fungal cultures. Antigen also can be detected in serum, providing a clue to the diagnosis before lumbar puncture is performed. Antigen may be detected in the serum in 92% to 100% and the urine in 98% to 100% of immunocompromised patients

TABLE 134-2 Diagnostic Studies in Histoplasmosis (Percent Positive Assays)

Test	Acute Pulmonary	Subacute Pulmonary	Chronic Pulmonary	Mediastinal Granuloma or Fibrosis	Progressive Disseminated
Antigen	80	25–40	20–50	<25	77–95
Fungal stain	20	25–40	40–80	25–50	50–75
Culture	40	25–50	75–80	<25	75–85
Serology	25–75	90–95	80–100	70	75

Source: Data from Swartzentruber S, Rhodes L, Kurkjian K, et al. Diagnosis of acute pulmonary histoplasmosis by antigen detection. Clin Infect Dis. 2009;49(12):1878–1882; Williams B, Fojtasek M, Connolly-Stringfield P, Wheat J. Diagnosis of histoplasmosis by antigen detection during an outbreak in Indianapolis, Ind. Arch Pathol Lab Med. 1994;118(12):1205–1208; Wheat J, French ML, Kohler RB, et al. The diagnostic laboratory tests for histoplasmosis: analysis of experience in a large urban outbreak. Ann Intern Med. 1982;97(5):680–685; Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448–454.

with cryptococcal meningitis,[16–18] but in a lower proportion of nonimmunocompromised patients.[21] Cultures also may be positive from extrapulmonary sites in up to two-thirds of patients.

TREATMENT

Treatment is indicated in patients with symptomatic pulmonary infections, especially if they are immunocompromised and in all patients with meningoencephalitis or disseminated infection (Table 134-2). The rationale and supporting evidence for these recommendations are discussed in an IDSA guideline document published in 2010.[12] Patients with a diagnosis of cryptococcosis at any site should be provided close follow-up for at least 1 year as the majority of relapses occur during this time period.

Indications for Treatment

For asymptomatic and immunologically normal patients without extrapulmonary disease (e.g., pulmonary nodules), antifungal therapy may be withheld for up to a month if patients can be followed closely. Increasing size or numbers of lesions would be indications for the treatment. For symptomatic patients, those who are immunocompromised, and patients showing progression during observation, treatment is advised.

Treatment of meningoencephalitis and and extrapulmonary dissemination (even without meningoencephalitis) is indicated in all cases.

Selection of Antifungal Agent

Selection of an antifungal agent for treatment is considered below for pneumonia, meningoencephalitis, and disseminated disease.

Pneumonia For nonimmunosuppressed patients, fluconazole 400 mg/d for 6 to 12 months is recommended, and itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) may be considered acceptable alternatives only if fluconazole is unavailable or contraindicated.[12] In more severe cases, amphotericin B and flucytosine should be given as recommended for meningitis (see below). Treatment guidelines for meningitis should be followed in immunosuppressed patients.

Meningitis Amphotericin B 0.7 to 1.0 mg/kg/d and 5-flucytosine 100 mg/kg/d are favored and should be given for 2 weeks (induction) followed by fluconazole 400 mg/d for 10 weeks (consolidation). 5-flucytosine accelerates sterilization of the CSF, improves the overall response rates for meningitis and reduces the risk for relapse. Lipid preparations of amphotericin B (3–5 mg/kg/day) are less toxic and may be preferred over the standard formulation, notably in patients with renal impairment or those who are thought to be at increased risk for amphotericin B nephrotoxicity. Amphotericin-containing preparations with or without flucytosine for 4 to 6 weeks without additional therapy can be potentially curative in patients with negative cultures after 2 weeks of therapy who are without any immunosuppression, neurologic complications or meningeal symptoms, though for most some form of antifungal consolidation therapy is recommended. Fluconazole alone is not recommended as induction therapy in immunocompromised hosts when amphotericin and 5-flucytosine are available. Combinations of therapy using amphotericin B and fluconazole at various doses as induction therapy have been studied in cryptococcal meningitis in resource poor settings where 5-flucytosine cannot be administered.[26,27] Compared to amphotericin B alone, combined amphotericin B plus fluconazole was associated with a trend toward improved outcomes.[12] Improved responses using this combination have been associated with a daily dose of fluconazole of 800 mg rather than 400 mg[12,27] and correlated with the ability to achieve higher CSF and serum fluconazole levels.[27] Fluconazole 800 to 1200 mg daily given with 5-flucytosine has been studied as induction therapy and when compared to treatment with fluconazole alone this combination appears to be associated with improved responses though greater toxicities.[28]

Fluconazole alone as induction therapy can be considered when amphotericin and 5-flucytosine are not available as is not uncommon in resource-limited settings. Induction doses of fluconazole of 1200 mg daily are associated with higher response rates than 800 mg fluconazole daily in a recent study.[29] Itraconazole 200 mg twice daily is an alternative in patients unable to take fluconazole for consolidation therapy.

Aggressive management of elevated intracranial pressure through removal of large volumes (about 25 mL) of CSF is essential to achieve the highest survival. Addition of IFN-γ led to clinical improvement in two patients with CD4 lymphopenia unresponsive to amphotericin B.

In patients with active AIDS or other immunosuppressive conditions, so-called maintenance or suppressive treatment with fluconazole 200 mg/d is recommended. Itraconazole is inferior to fluconazole for chronic maintenance therapy and is not advised. If itraconazole is used, 200 mg twice daily is recommended. Amphotericin B at a dose of 1 mg/kg one to three times weekly is another alternative maintenance regimen.

With the use of HAART, studies have indicated that maintenance fluconazole can be safely discontinued in most patients responding to HAART with a CD4 cell count >100 cells/mm^3, an undetectable or low HIV RNA level sustained for 3 months, and at least 1 year of antifungal drug treatment. Patients require careful monitoring for relapse and continued response to HAART. Resumption of antifungal therapy is recommended if the CD4 count falls below 100 cells/mm^3. Monitoring serum cryptococcal antigen should also be performed, as a rising titer would support resumption of antifungal therapy.[12]

For immunosuppressed patients without AIDS, a 6- to 12-month course of fluconazole is recommended. As in patients with AIDS,

careful follow-up is required after antifungal therapy is stopped. In some patients who relapse following such a course of therapy, lifelong maintenance therapy may be appropriate.

Disseminated/Extrapulmonary, without Meningoencephalitis
Trials have not been performed evaluating treatment of non-CNS extrapulmonary disease, and recommendations are based upon experience of the IDSA guideline committee. Recommendations outlined earlier for pneumonia should be followed in nonimmunosuppressed patients and for meningitis in those who are immunosuppressed.

Role of Antifungal Resistance

Resistance may be a cause for fluconazole failure. The minimum inhibitory concentration (MIC) of fluconazole required to inhibit greater than 90% of strains of *C. neoformans* is likely somewhere between 8 and 16 μg/mL, which can be used as a breakpoint for defining resistance.[30] In one study from Spain, patients infected with *C. neoformans* isolates with MICs ≥16 μg/mL failed to respond to fluconazole therapy.[31] In a recent study from Africa evaluating relapses of meningitis in individuals treated with primary fluconazole therapy alone, 76% of relapses associated with positive cultures demonstrated resistance to fluconazole with MICs to fluconazole of ≥64 μg/mL.[32] It is recommended that testing of isolates for fluconazole resistance should be reserved for those who do not respond to therapy, those who relapse and those who develop cryptococcal meningitis after prolonged exposure to azole therapy.[12] As 5-flucytosine susceptibilities have not been demonstrated to be predictive of response, such testing is not routinely recommended. While there are no recommendations to routinely tests isolates for primary amphotericin B resistance, reduced susceptibility of *C. neoformans* isolates to amphotericin B was associated with greater day 14 mortality in one study of meningitis treatment in AIDS patients treated with amphotericin B alone as induction therapy.[33]

Newer Antifungal Agents

Alternatives to itraconazole and fluconazole are needed for patients who fail or do not tolerate those agents. Voriconazole is slightly more active in vitro than posaconazole, with an MIC_{90} levels in the range of 0.12 to 0.25 μg/mL.[34] Voriconazole penetrates CSF, but not as well as fluconazole. Furthermore, strains with high-level resistance to fluconazole may be cross-resistant to voriconazole.[35] Posaconazole was effective in a rabbit model of cryptococcal meningitis.[36] While not studied adequately case reports from salvage studies support the potential effectiveness of voriconazole[37] as well as posaconazole.[38] Neither would appear to offer advantages over fluconazole, however as primary therapy. The echinocandins are not active in vitro,[39] have not been studied in animal models, and are not recommended in patients with cryptococcal infection.

Adjunctive Therapy

Adjunctive IFN-γ immunotherapy has been used in randomized controlled trial in patients with cryptococcal meningitis receiving amphotericin B and 5-flucytosine.[40] While no mortality benefit was seen in those who received IFN-γ in addition to standard antifungal treatment, clearance of *C. neoformans* from the CSF was noted to be significantly faster in those who were treated with adjunctive IFN-γ.[40] Given the expense of this adjunctive therapy and lack of mortality benefit, routine use of IFN-γ for cryptococcal meningitis would appear to be unwarranted. Some however have recommended consideration of this adjunctive therapy or refractory cases.[12]

■ PREVENTION AND SCREENING FOR CRYPTOCOCCOSIS

Although fluconazole and itraconazole reduced the incidence of cryptococcosis in patients with AIDS, prophylaxis is not recommended in resource rich settings, largely because of the low attack rate. In such regions, unlikely cost-effectiveness, limited impact on survival, and potential to induce fluconazole resistance among other fungi are reasons this strategy is not recommended. On the other hand in areas where cryptococcal infections are much more common and associated with high mortality prophylaxis may reduce mortality and represent an effective strategy.[41] Serum cryptococcal antigen screening on all HIV-infected individuals with CD4 counts less than 100 cells/mm^3 living in resource-limited settings characterized by high rates of cryptocccal meningitis, can identify those at high risk for clinical cryptococcal disease.[42] It has been suggested that identifying such individuals who may benefit from antifungal therapy in the absence of clinical disease may represent a cost-effective strategy.[41,42]

HISTOPLASMOSIS

Histoplasmosis is the most common endemic mycosis and a major cause of morbidity in patients who live in endemic areas. Progressive disseminated histoplasmosis (PDH) is an important complication of AIDS, immunosuppression for the prevention of transplant rejection,[43] treatment of inflammatory diseases[44,45] or malignancies, and immunodeficiency disorders.[46] Understanding of the clinical syndromes and untreated course of the infections is essential in the diagnosis and management of patients with histoplasmosis. Improved laboratory tests have made it possible to rapidly diagnose the more severe cases. Expanded treatment options are available using newer triazole antifungal agents and liposomal formulations of amphotericin B.

■ MYCOLOGY

Histoplasma capsulatum grows as a mold in the soil and converts to a yeast in tissues (Fig. 134-3). Microconidia measuring 2 to 4 μm in diameter are the infectious particle in the mold phase of the organism. *H. capsulatum* also grows as a mold on fungal media in the laboratory. Definitive identification of a mold as *H. capsulatum* is made by DNA probe or exoantigen detection. At temperatures above 35°C, *H. capsulatum* grows as a yeast, which is the pathogenic form found in the tissues. The yeast measures about 2 to 5 μm and exhibits narrow-based budding.

■ EPIDEMIOLOGY

H. capsulatum is endemic in areas of North and South America (see Fig. 134-1) but can be found throughout the world. Bird and bat excrement enhance growth of the organism by accelerating sporulation. Cases outside the endemic region may have been acquired by exposure during travel or prior residence in the endemic area, or exposure to microfoci containing the organism within the nonendemic area. In the endemic areas between 10% and 90% of individuals exhibit histoplasmin skin test positivity as evidence of past histoplasmosis.[47]

■ PATHOGENESIS

Infection develops when conidia are inhaled and germinate into yeast. In many cases primary infection is asymptomatic and goes undiagnosed. Clinical illness most often follows exogenous infection or reinfection. With the development of cell-mediated immunity during the first month following initial infection, IFN-γ and IL-12 arm macrophages to kill the fungus and halt progression of the disease.[48] TNF-α also is very important for immune defense against *H. capsulatum*.[49] These defense mechanisms are sufficient to

control the infection in immunocompetent individuals, explaining the subclinical or self-limited course characteristic of acute histoplasmosis.

Reactivation of latent infection may account for some cases occurring in individuals with past histoplasmosis who become immunocompromised. Studies showing a low incidence of histoplasmosis following immunosuppression in children,[50] organ transplantation,[51] or treatment with TNF inhibitors,[44] however, suggest reactivation is rare. Also, latency could not be demonstrated experimentally in calcified lung lesions identified as incidental findings at autopsy.[52]

■ CLINICAL MANIFESTATIONS

Heavy exposure can cause severe illness even in healthy subjects. Low-level exposure is more common, however, and usually causes asymptomatic infection or clinically self-limited infection. The common self-limited presentations include acute and subacute pulmonary histoplasmosis, pericarditis, and rheumatological syndromes.

Asymptomatic Infection

In endemic areas, between 10% and 90% of residents exhibit histoplasmin skin test reactivity by age 20.[47] In most of these cases, infection was presumed to have been asymptomatic. Most asymptomatic cases are identified as an incidental finding on chest radiographs or computed tomography (CT) scans performed for other reasons. The most common findings are enlarged mediastinal or hilar lymph nodes or pulmonary nodules.[1] The main significance of such findings is the need to differentiate them from malignancy or tuberculosis. Asymptomatic infection also may be identified by demonstration of seropositivity during evaluation of another condition.

Pulmonary Syndromes

A variety of pulmonary syndromes may be seen with histoplasmosis. Each is considered below.

Acute Pulmonary Histoplasmosis

Following heavy exposure, patients present with diffuse pulmonary involvement often causing respiratory insufficiency.[1,53] Chest radiographs usually show diffuse interstitial, reticulonodular infiltrates, nodular, or patchy airspace disease, but a miliary pattern suggestive of hematogenous dissemination may be seen (Fig. 134-4). Initial radiographs may appear normal, evolving to show infiltrates over the next few weeks. Mediastinal adenopathy is common. Evidence for extrapulmonary dissemination is present in about 40% of cases.[22] While patients may recover without therapy,[54] recovery may be slow,[55] respiratory failure may develop,[56] and some infections may be fatal.[56,57]

Subacute Pulmonary Histoplasmosis More commonly, the inoculum is small and the presentation is subacute.[1,53] Patients present with fever, cough, and chest pain. Chest radiographs show mediastinal lymphadenopathy with patchy infiltrates. Most patients recover in a few weeks but some experience persistent fatigue.

Chronic Pulmonary Histoplasmosis Chronic pulmonary histoplasmosis occurs in patients with underlying lung disease and is characterized by persistent or recurrent pulmonary symptoms, progressive lung infiltrates, fibrosis, and cavitation.[58,59] Upper lobe infiltrates and cavities are characteristic, resembling the findings in tuberculosis. Progression is manifested by cavity enlargement, formation of new cavities, spread to other areas of the lungs, and bronchopleural fistula. Bacterial pneumonia, *Aspergillus* superinfection, and malignancy also must be considered in evaluation of new masses or infiltrates.

Nodules Nodules need to be differentiated from malignancy.[1,53] Calcification suggests histoplasmosis, but does not exclude malignancy. Conversely, absence of calcification, does not exclude histoplasmosis. Positive positron emission tomography (PET) scan, assumed to support malignancy, is common in histoplasmosis. Rarely, nodules may cavitate, but cavitation of nodules does not represent chronic pulmonary histoplasmosis and does not require therapy. Nodules also may rarely enlarge up to 2 mm/y, but enlargement is not caused by progressive infection and is not a basis for treatment.[60] Calcification occurs in the necrotic central and surrounding fibrous tissue. An approach to the evaluation of pulmonary nodules has been reviewed.

Broncholithiasis Lymph nodes and pulmonary granuloma calcify and may erode into adjacent bronchi causing hemoptysis or obstruction.[1] Patients may expectorate rock-like particles of tissue and experience recurrent and severe hemoptysis, bronchial obstruction, or tracheoesophageal fistula.

Relationship to Sarcoidosis Sarcoidosis and histoplasmosis share several clinical and radiographic findings.[1] Angiotensin-converting enzyme (ACE), sedimentation rate, C-reactive protein, and immunoglobulin elevations occur in both conditions.[61] Noncaseating granulomas are seen with each, and caseation, which is more typical of histoplasmosis, also occurs in sarcoidosis. Histoplasmosis is one of the most common infections that must be excluded before sarcoidosis is diagnosed to prevent mistakes in patient management, most notably administration of immunosuppressive therapy to patients with active histoplasmosis.

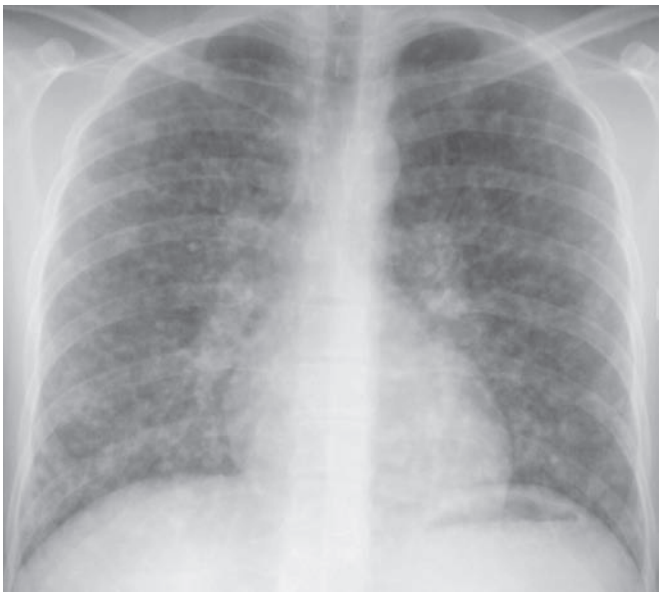
Mediastinal Syndromes

Mediastinal adenitis, mediastinal granuloma, and fibrosing mediastinitis are three mediastinal disorders which may complicate histoplasmosis.

Mediastinal Adenitis Mediastinal lymph node involvement is present in most cases of acute and subacute pulmonary histoplasmosis.[1,53] Although usually asymptomatic, chest pain is the most common manifestation. Rarely, the airways, esophagus, or superior vena cava (SVC) may be impinged, causing obstructive symptoms. Airway obstruction is more likely in children because the airways are less rigid.

Mediastinal Granuloma Histopathology shows a necrotic central core, often containing yeast, surrounding caseating and noncaseating granuloma,[1,53] fibrous tissue, and a thin-walled (less than 5 mm) capsule. The fibrosis is less exuberant than in fibrosing mediastinitis, and does not invade adjacent structures. Symptoms are usually caused by compression of the superior vena cava (SVC) esophagus, or airways, and in some cases the nodes liquefy and drain into adjacent structures.[62,63] Disruption of the capsule, either spontaneous or caused by surgery, may create fistulae to the airways, pericardium, skin, or esophagus. Esophageal involvement may result in diverticulum formation.

Mediastinal Fibrosis Mediastinal fibrosis represents an exuberant scarring reaction to mediastinal histoplasmosis.[1,64] The SVC is most commonly involved, but the fibrosis also may occlude airways, pulmonary arteries or veins, or esophagus, and invade the thoracic duct, recurrent laryngeal nerve, or atrium in rare cases. Chest radiographs show subcarinal or superior mediastinal widening, while CT scans reveal fibrotic restriction and invasion of mediastinal structures and calcification of the lymph nodes. Recurrent and often serious hemoptysis results from lung or airway damage and vascular compromise. Respiratory failure ensues in one-third of cases.



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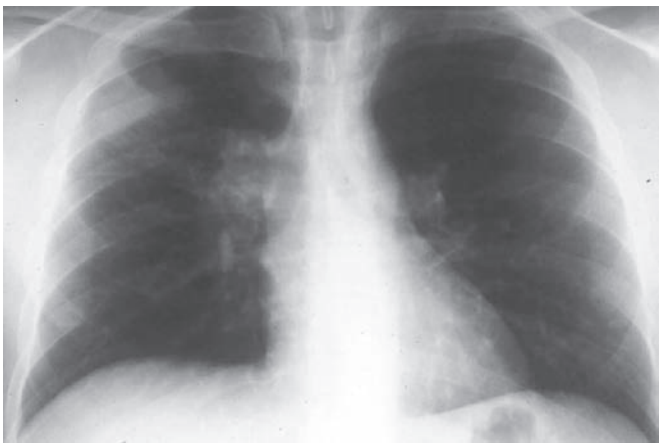

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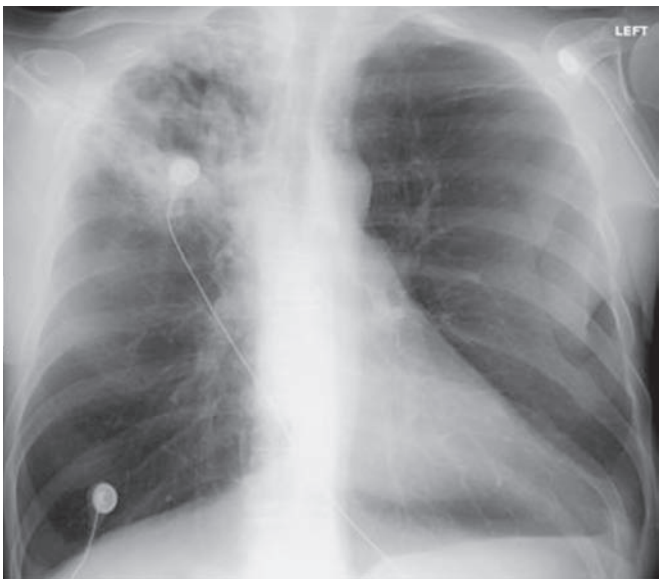

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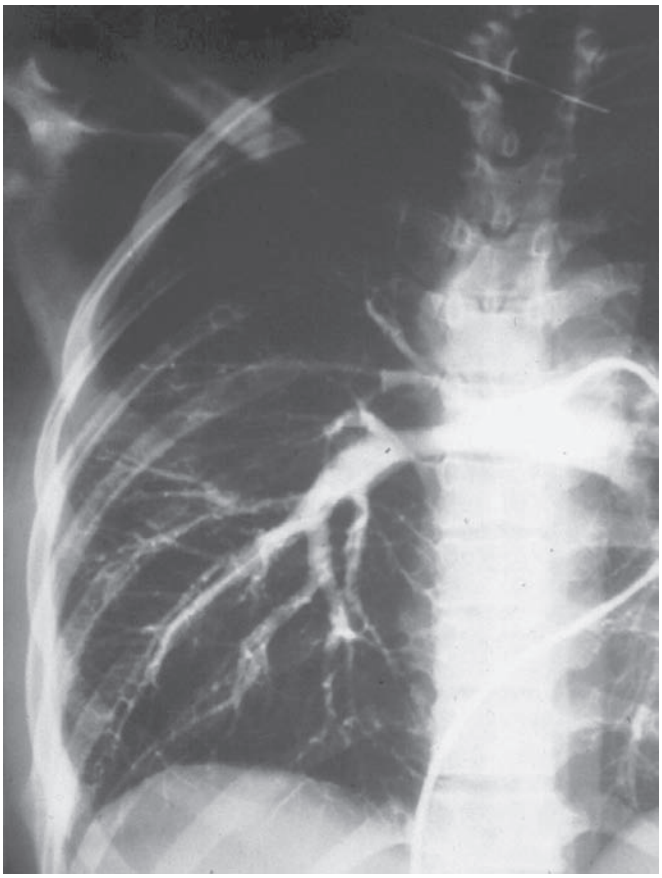

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Figure 134-4 **A.** Chest radiograph of acute diffuse histoplasmosis after large inoculum exposure. **B.** Computed tomography of subacute histoplasmosis with mediastinal adenopathy. **C.** Chest radiograph of cavitary histoplasmosis. **D.** Pulmonary arteriogram showing obstruction of pulmonary artery to right upper lung caused by fibrosing mediastinitis.

Other Inflammatory Syndromes

Inflammatory syndromes complicating histoplasmosis include rheumatologic syndromes and pericarditis.

Rheumatological Syndromes Patients with subacute histoplasmosis may experience arthritis or arthralgia accompanied by erythema nodosum,[65] a manifestation often misdiagnosed as sarcoidosis.[66] Chest radiographs usually show mediastinal lymphadenopathy and focal pulmonary infiltrates, but may be normal. These findings represent a systemic inflammatory response rather than disseminated infection, and are managed by anti-inflammatory treatment, not antifungal therapy. The illness may recur when treatment is stopped.

Pericarditis Pericarditis is another inflammatory complication of primary histoplasmosis, occurring in less than 10% of cases.[67,68] Findings include chest pain, pericardial friction rub, and occasionally signs of pericardial tamponade. Chest radiographs usually show mediastinal lymphadenopathy and increase in the cardiac silhouette, while CT scan and echocardiogram may show pericardial effusion. These patients respond to anti-inflammatory treatment but may require drainage of the

pericardial fluid for the management of tamponade. Late constriction is rare.

Progressive Disseminated Histoplasmosis

PDH occurs in about 1 in 2000 cases, usually in patients who are immunosuppressed or at the extremes of age. AIDS,[69] solid-organ transplantation,[70] and treatment with TNF-α inhibitors[44] are common predisposing conditions. PDH develops during the first year of therapy in nearly half of cases, but may occur more than 10 years after transplantation. Vigilance for dissemination should be maintained throughout the course of immunosuppression.

Fever and weight loss are the most common findings in PDH.[71,72] Examination reveals hepatomegaly or splenomegaly in about one-half of cases and lymphadenopathy in one-third of cases. A syndrome resembling sepsis may be seen in cases with severe immunosuppression, in whom corticosteroids are given for presumed inflammatory or autoimmune disease, or in which diagnosis is delayed. Meningitis or focal brain lesions occur in about 5% to 10% of cases.[72] Other common sites of dissemination include the oral mucosa, gastrointestinal tract, skin, and adrenal glands in 5% to 10% of cases. Chest roentgenograms are abnormal in 70% of patients, usually showing diffuse interstitial or reticulonodular infiltrates, and less often a miliary pattern.[71,73]

In patients who experience improvement in immune function during treatment for histoplasmosis, an immune reconstitution syndrome has been reported.[44,74,75] Manifestations have included respiratory failure, elevation of hepatic enzymes, hepatic or splenic abscesses, lymphadenitis, arthritis, uveitis, and intestinal obstruction.[74]

■ DIAGNOSIS

Histopathology, cytology, and antigen detection are most useful for rapid diagnosis in patients with acute pulmonary and PDH, cases that require therapy (Table 134-3).[22–25] A serological test for antibodies forms the basis for the diagnosis in subacute manifestations in most of the cases.[24,25] Serology or culture of respiratory secretions usually provides the basis for the diagnosis of chronic pulmonary histoplasmosis. Culture results may not be available for up to 1 month, limiting its usefulness for the rapid diagnosis of severe disease.

Antigen Detection

Detection of antigen in the body fluids offers a valuable approach to rapid diagnosis in patients with PDH and acute pulmonary histoplasmosis, providing results within 24 to 48 hours.[25] Antigen is found in urine of over 90% of patients with PDH and 80% with acute diffuse pulmonary disease.[22,25] Sensitivity is improved by testing both serum and urine.[22] Antigen detection is less sensitive in subacute pulmonary histoplasmosis.[25] Detection of antigen in BAL fluid may improve the sensitivity for the diagnosis of pulmonary histoplasmosis.[85] Antigen may be found in CSF in 50% of patients with *Histoplasma* meningitis.[72] Positive results caused by cross-reacting antigens occur in patients with African histoplasmosis, blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection.[25] Antigen levels decline during treatment and increase with relapse, providing a tool for monitoring therapy.[86,87]

Histopathology

Fungal staining permits rapid diagnosis but has a lower sensitivity than antigen detection.[25] The highest yield is from bone marrow. Fungal stain of BAL is positive in 70% of cases of diffuse pulmonary histoplasmosis in patients with AIDS with PDH. The sensitivity of fungal stain of sputum or BAL in patients with other types of pulmonary histoplasmosis has not been reported but appears to be low. Yeast may be seen in peripheral blood smears in patients with severe PDH. *Pneumocystis jirovecii, Candida glabrata*, *Blastomyces dermatitidis, C. neoformans, Toxoplasma gondii,* and *P. marneffei* may be misidentified as *H. capsulatum.*

Serological Tests

Antibodies to *H. capsulatum* measured by immunodiffusion or complement fixation develop in most of the patients.[88] Antibodies require up to 12 weeks to develop following exposure. In acute pulmonary histoplasmosis, antibodies can be detected about 15% of cases during the first 2 weeks of infection, increasing to about 75% by the sixth week.[89] Elevated levels of antibodies persist for several years.[90] The antibody response is greater in patients with heavy exposure and/or more severe clinical disease. Patients with asymptomatic or mild infection[91] and those who are receiving immunosuppressive medications following solid-organ transplantation[25] may not mount an antibody response. Antibody responses do not appear to be impaired by treatment with TNF inhibitors[25,44] and are only slightly impaired in patients with AIDS.[25]

Serology is most useful in patients with subacute manifestations of histoplasmosis (pulmonary, rheumatological, pericarditis, mediastinal syndromes) and chronic pulmonary infection, and is positive in 90% of such cases. Sensitivity is higher while specificity is lower using complement fixation rather than immunodiffusion methods. Complement fixation titers greater than or equal to 1:32 are more suggestive of active infection but titers of 1:8 to 1:16 should not be disregarded. Cross-reactions occur in patients with other fungal diseases. Also, antibodies persisting following prior histoplasmosis may cause confusion in patients with other lung diseases.

Fungal Cultures

Cultures provide the strongest proof for histoplasmosis but are limited by low sensitivity in self-limited infections and delayed growth (2–4 weeks). Cultures are most useful in patients with chronic pulmonary histoplasmosis and PDH. Sputum production is rare in patients with acute pulmonary histoplasmosis, but organisms can be cultured from BAL or other bronchoscopy specimens in some cases. In chronic pulmonary histoplasmosis patients commonly expectorate sputum, and organisms can be found in sputum or bronchoscopy specimens in 60% to 85% of cases.[25,59,85] Multiple specimens must be cultured to achieve the highest yield. In PDH, the highest yield is from bone marrow or blood, positive in over 75% of cases, and in BAL of patients with pulmonary infiltrates.[85] Cultures are usually negative in pulmonary nodules and mediastinal nodes representing subacute or old healed lesions despite demonstration of yeast by histopathology.

Polymerase Chain Reaction

Several studies report diagnosis of histoplasmosis by polymerase chain reaction (PCR) in tissues or body fluids,[92,93] but PCR was less sensitive than fungal stain for the examination of tissue specimens in one report.[92] PCR was positive on only 8% of urine specimens with elevated *Histoplasma* antigen,[94] 22% of BAL specimens[95] but not in CSF or serum.[95] A role of PCR for the diagnosis of histoplasmosis remains to be determined.

■ EXCLUSION OF HISTOPLASMOSIS IN WORKUP OF PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA AND SUSPECTED SARCOIDOSIS

Other conditions to be distinguished from histoplasmosis include community-acquired pneumonia and sarcoidosis.

Community-Acquired Pneumonia

Histoplasmosis is always community acquired and often is initially suspected to be caused by other agents of community-acquired pneumonia.[2] Failure to suspect and correctly diagnose

histoplasmosis may result in mistakes in patient care, which can cause improper therapy, unnecessary morbidity or even death, and higher cost for diagnosis and management. Workup for histoplasmosis should be considered in patients from endemic areas with exposure history, if other causes cannot be established, or if empiric antibiotics do not result in prompt clinical improvement.

Sarcoidosis

Considering the similarity between the two conditions, and the risk for progression of histoplasmosis during immunosuppression for presumed sarcoidosis, active histoplasmosis must be excluded before immunosuppressant therapy is initiated.[1,61] If immunosuppressive therapy was initiated in patients with laboratory findings suggestive of histoplasmosis, the patient should be followed closely for evidence of progression of histoplasmosis. Also, if patients initially respond to immunosuppressive treatment but later relapse, testing for histoplasmosis should be repeated, as immunosuppression may have accelerated the progression of histoplasmosis.

Treatment Most infections are asymptomatic or clinically self-limited, requiring no therapy. Furthermore, treatment has only been studied in PDH and chronic pulmonary histoplasmosis, precluding assessment of effectiveness in the other syndromes. While treatment in cases of acute pulmonary histoplasmosis appears to be effective, studies showing that therapy hastens the response or reduces morbidity have not been conducted. Antifungal therapy for the subacute pulmonary, inflammatory, and mediastinal syndromes is rarely indicated and probably has no effect on the course of the illness, as the pathogenesis appears to involve the inflammatory response and/or mass effects of the enlarged nodes rather than progressive infection.

Treatment guidelines have been published and should serve as reference for indications for the treatment, selection of antifungal agents, duration of therapy, and testing to monitor response.[96,97] An earlier IDSA guideline summarized prior studies evaluating therapy for histoplasmosis.[96]

Indications for Treatment

Treatment of histoplasmosis is considered below according to the type of pulmonary involvement.

Acute Pulmonary Histoplasmosis Patients with symptomatic acute pulmonary histoplasmosis manifested by diffuse infiltrates following heavy exposure appear to benefit from antifungal therapy (Table 134-4).[55,98] Adjunctive therapy with corticosteroids may hasten recovery in such patients. Amphotericin B 0.7 to 1.0 mg/kg/d would be preferred as initial therapy in patients who are more severely ill. Itraconazole, 200 mg once or twice daily, is recommended in patients with milder illnesses, and following response to amphotericin B. A 6- to 12-week course is recommended in the absence of PDH, which should be excluded.

Subacute Pulmonary Histoplasmosis Patients with subacute pulmonary histoplasmosis usually recover without treatment, and there have been no studies to determine if treatment alters the course or prevents complications. Nevertheless, treatment is reasonable in patients who show no improvement of symptoms after a month of observation. Oral therapy with itraconazole would be appropriate, 200 mg once daily for 6 to 12 weeks.

Chronic Pulmonary Histoplasmosis Treatment improves survival, reduces symptoms, promotes radiographic healing, and eradicates *H. capsulatum* from the sputum. Most patients with chronic pulmonary histoplasmosis can be managed without hospitalization and respond well to treatment with itraconazole 200 mg once or twice daily for 12 to 24 months. Amphotericin B (0.7 to 1.0 mg/kg/d) or lipid amphotericin is recommended for initial therapy in patients with more severe respiratory insufficiency to achieve a more rapid response.

Mediastinal Adenitis and Granuloma Patients with obstructive symptoms or fistula caused by mediastinal granuloma should be treated, but whether treatment alters the outcome remains unknown. Itraconazole, 200 mg daily for 6 to 12 weeks, is recommended, after which imaging studies should be repeated to assess response. If the enlarged nodes show reduction in size, therapy might be continued for a total of 3 to 6 months. Surgery should be considered if symptoms persist and are sufficiently bothersome. Antifungal treatment or resection of enlarged mediastinal lymph nodes to prevent fibrosing mediastinitis is not indicated since progression of enlarged mediastinal nodes to fibrosing mediastinitis has not been documented.[64,105]

Mediastinal Fibrosis

Antifungal treatment is not thought to improve the outcome of mediastinal fibrosis, but therapy with itraconazole, 200 mg daily for 6 to 12 weeks, is commonly tried and is not unreasonable considering the seriousness of this complication. Occasionally patients benefit from the placement of stents in pulmonary vessels or the SVC.[106] Stenting of the airways is not recommended because of the risk for growth of inflammatory tissue causing obstruction of the stent. Surgery is associated with a high mortality and limited efficacy, and should be discouraged. In patients with no other options, care should be taken to select a surgeon experienced with this rare manifestation of histoplasmosis.

Broncholithiasis Surgical therapy is required for patients with significant hemoptysis or recurrent pneumonia and for repair of fistulae. Antifungal therapy would not be expected to reduce the symptoms since active infection is uncommon in such cases.

Inflammatory Syndromes Rheumatological syndromes and pericarditis are noninfectious, inflammatory manifestations, and respond to anti-inflammatory therapy. Antifungal therapy is not indicated unless the bone, joint, or pericardium is the site of disseminated infection, or if corticosteroids are used for treatment of the inflammatory syndrome.

Disseminated Treatment is indicated in all patients with PDH. The mortality of untreated disseminated histoplasmosis is 80% but can be reduced to less than 10% with therapy.[44,63,87,107,108] Amphotericin B 0.7 to 1.0 mg/kg/d, liposomal amphotericin B 3 mg/kg/d, and itraconazole 200 mg once or twice daily are highly effective. A total duration of 12 to 24 months is recommended in most of the cases.

Selection of Antifungal Agents

Amphotericin B acts more rapidly than triazole antifungal agents, and is recommended for moderately severe or severe cases, which require hospitalization, and women who are pregnant. While the IDSA guideline recommends use of lipid formulations of amphotericin B,[97] the ATS guidelines recommends the original deoxycholate formulation. Liposomal amphotericin B was superior to the deoxycholate formulation in AIDS patients with histoplasmosis, with improved overall response, reduce mortality, and reduce side effects,[109] forming the basis for the IDSA recommendation.

In patients with AIDS who also have PDH, liposomal amphotericin B is more effective than standard amphotericin B, with more rapid resolution of fever, higher overall response, better survival, and lower toxicity.[109] Liposomal amphotericin B, 3 to 5 mg/kg/d, is preferred for patients with severe or moderately severe PDH. Treatment can be changed to itraconazole after the patient improves, usually in 3 to 14 days.

Itraconazole is highly effective in most mild to moderately severe cases of PDH and in chronic pulmonary histoplasmosis.[96] Itraconazole capsules require an acidic gastric environment for solubilization and should be given with food or cola. Medications that reduce gastric acidity should be avoided. Itraconazole solution is a good alternative in patients who require gastric acid suppression or who have low blood levels while taking the capsule formulation.

Itraconazole blood levels should be measured after 2 to 3 weeks of therapy with a sample obtained just before a dose, striving for a trough concentration between 1 and 10 μg/mL when measured by high pressure liquid chromatography (HPLC).[110] Levels measured by bioassay should generally be about two times higher than HPLC in the target concentration is between 3 and 10 μg/mL. The solution formulation achieves concentrations that are about 30% higher than the capsule formulation.

Hepatic enzyme inducers reduce itraconazole concentrations and should be avoided. Itraconazole also inhibits intestinal and hepatic cytochrome P450 3A4, causing accumulation of several drugs and increasing associated toxicities.[111] As the list of contraindicated medications continues to evolve, physicians should review potential drug interactions before starting itraconazole and when new medications are added to the regimen. Furthermore, itraconazole is eliminated by hepatic metabolism and may be ineffective in patients receiving medications that induce cytochrome P450 enzymes. Itraconazole also may cause congestive heart failure and should be avoided in patients with heart disease unless the benefit outweighs the risk.[112] If itraconazole is used in patients with cardiac disease, careful follow-up for the development of heart failure is essential, and if heart failure develops, itraconazole should be stopped.

Fluconazole is less active in vitro than itraconazole in histoplasmosis. In patients with AIDS and PDH treated with 800 mg/d of fluconazole for 12 weeks followed by 400 mg/d indefinitely, failure occurred in up to one-half of patients within 6 months.[113] Isolates from patients who failed fluconazole exhibited at least a fourfold reduction in susceptibility to fluconazole in over two-thirds of cases.[114]

Newer Antifungal Agents

Posaconazole and voriconazole are active against *H. capsulatum,*[114] and posaconazole was effective in an experimental model of histoplasmosis.[115] However, voriconazole MICs are higher than itraconazole and posaconazole, and fluconazole treatment induced an increase in MIC to voriconazole.[114] A few patients have been treated with voriconazole, with inconsistent results, while posaconazole was highly effective, and appears to be the preferred alternative to itraconazole.[116] Echinocandins are not active in vitro or effective in murine models and have not been studied in patients with histoplasmosis.[117]

Maintenance Therapy

Lifelong maintenance therapy was the standard of care in patients with AIDS complicated by PDH before the advent of HAART. With HAART, maintenance therapy can be discontinued in patients who have received at least 1 year of itraconazole, antigen levels less than 2 ng/mL in urine and serum, and a CD4 count greater than 150 cells/mm^3.[97,118] Unpublished studies suggest that adherence to therapy and absence of CNS involvement should also be considered in decisions to stop treatment. Patients must be carefully monitored for relapse and continued response to HAART. Resumption of antifungal therapy is recommended if the CD4 count falls below 100 cells/mm^3 or if antigen levels in urine or serum increase, providing evidence of relapse.

■ PREVENTION

Patients at high risk for dissemination should avoid activities that expose them to *H. capsulatum*, such as caving or remodeling old buildings inhabited by bats or birds. Hand washing reduces the risk for acute histoplasmosis among persons exposed while crawling in a bat-inhabited cave, while use of loose-fitting paper masks does not. A placebo-controlled study using itraconazole, 200 mg daily, in persons with AIDS demonstrated reduction in the incidence of histoplasmosis.[119] However, since the introduction of HAART, the incidence of these infections has declined, and is too low to justify prophylaxis. Prophylaxis may be reasonable in areas where the combined incidence of systemic fungal infections exceeds 10 cases/100 patient-years.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is the most serious of the endemic mycoses, prone to reactivation and often failing therapy. Furthermore, large outbreaks in Arizona and southern California, increasing population in the southwestern states, and travel have placed large numbers of persons at risk. *Coccidioides immitis* is listed as a "select agent" of bioterrorism, complicating its use in the clinical and research laboratory.

■ MYCOLOGY

Coccidioidomycosis is caused by the pathogenic fungus, *Coccidioides,* which includes two species, *C. immitis* and *C. posadasii.* Except for different geographical locations (*immitis* in California and *posadasii* in Arizona), the laboratory properties, virulence factors, pathogenesis, clinical findings, diagnostic approach, and treatment are the same, hence, *Coccidioides* will be used to refer to both species in this section.

Coccidioides is highly virulent, causing infection upon exposure to only a few conidia and severe disease with larger inoculum. *Coccidioides* has been designated as a select agent by the Centers for Disease Control, requiring that it be destroyed upon identification in the laboratory except at facilities approved for handling select agents. *Coccidioides* grows as a mold with septate hyphae in the soil and on culture media and as an endosporulating spherule in the tissues of patients. Its arrow-shaped arthroconidia are 2.5 to 4 × 3 to 6 μm in size and are the infectious particles found in soil.

Coccidioides converts to an endosporulating spherule at 37° to 40°C. Spherules measure 30 to 60 μm in diameter and contain numerous 2 to 5 μm endospores (Fig. 134-3). Growth on fungal media occurs rapidly, usually within 3 to 5 days.

TABLE 134-3 Diagnostic Studies in Coccidioidomycosis (Percent Positive Assays)

Test	Acute Pneumonia, Focal	Acute Pneumonia, Diffuse[76]	Nodule or Cavity	Chronic Fibrocavitary[77]	Disseminated[78]
Papanicolaou smear or histopathology	<25	64	50[79]	35	>75
Culture	<10[80]	86	10[79]	95	39[80]
Serology	90[81]	54	<50[82]	95	95[80]
Antigen	70[83,84]				

EPIDEMIOLOGY

Coccidioidomycosis, often referred to as Valley Fever (from a San Joaquin Valley outbreak), occurs in a spotty distribution in the southwestern United States, northern Mexico, and Central America (Fig. 134-1). Counties of southern California and southern Arizona are perhaps the most recently well studied and show an increased incidence of disease.[120] Exposure to *Coccidioides* is heaviest in the late summer and fall when the soil is dry and conditions are windy. In Kern County, coccidioidomycosis incidence has a yearly cycle, with the number generally increasing toward the late fall (17 per month per 100,000 population), decreasing in the winter, and reaching a minimum in the spring and summer.[121] Coccidioidomycosis is laboratory-reportable and an abundance of information is available, for example, on the Arizona Department of Health website: (Arizona Department of Health Services 2012); http://www.azdhs.gov/phs/oids/epi/disease/cocci/index.htm.

Coccidioidomycosis is a common cause of community-acquired pneumonia in the southwest endemic areas.[122,123] Cases classically are identified in construction workers, archaeologists, or military personnel. However, dust storms (haboobs) can carry the spores for miles exposing persons with no direct contact with contaminated soil. Cases are identified outside the endemic area in travelers or past residents of the endemic area, often years after exposure. Reports of coccidioidomycosis occurring in otherwise healthy young adults[124] and reports of acquisition of disease outside traditionally defined endemic areas contribute to delays in diagnosis.[125] Coccidioidomycosis also is a threat to laboratory personnel working with the organism outside of biosafety cabinets. African Americans and Hispanics experience a disproportionately higher frequency of disease in some studies. Predictably, coccidioidomycosis is a serious opportunistic infection in immunosuppressed patients, including those with AIDS, transplant recipients, and those receiving immunosuppressive treatment.[126,127]

PATHOGENESIS AND PATHOLOGY

Infection occurs following inhalation of arthroconidia of the mycelial phase of the fungus or reactivation of latent infection during immunosuppression. Person-to-person transmission does not occur and exposure by direct inoculation is rare. Transmission by transplantation of an infected allograft has been reported and causes rapidly progressive disease in the recipient.[128]

In the lungs, the arthroconidia enlarge to form thick-walled spherules, which contain multiple endospores. Spherules rupture releasing endospores, which spread locally and disseminate hematogenously. Cellular immunity and neutrophils both are involved in host defense in coccidioidomycosis.[129] Patients with deficient cellular immunity experience severe progressive forms of coccidioidomycosis.

Coccidioides produces several mixed pyogranulomatous reactions in the tissues. The neutrophil response and caseous necrosis may lead to the development of large abscesses, which often require surgical drainage. Abscesses also may spontaneously rupture or produce fistulas. Tissue and blood eosinophilia can be prominent.[130]

CLINICAL FINDINGS

Coccidioidomycosis is asymptomatic in over one-half of cases, and in the remainder, symptoms appear 1 to 4 weeks following exposure. In symptomatic cases, a pulmonary illness is most common. True coccidioidal infections are difficult to diagnose since the symptoms of early infection overlap substantially with those of other respiratory infections. While most immunocompetent patients recover without treatment over a course of several weeks, many do receive treatment. Nevertheless, serious infections occur and in one outbreak following an earthquake 27% were hospitalized and 1.5% died.[131]

Primary Pulmonary Infection

Symptoms develop within a few weeks following exposure, depending on the intensity of the inoculum and the immune status of the patient. Low inoculum exposure in the nonimmunocompromised host usually results in a localized pneumonia, and can be mistaken for bacterial community-acquired pneumonia. Symptoms include pleuritic or dull chest pain, nonproductive cough, headache, fever, and fatigue.[132] Macular rash, erythema nodosum, and erythema multiforme are common and help to distinguish from bacterial pneumonia. A constellation of fever, arthralgia, and erythema nodosum is referred to as "desert rheumatism." Infection is more severe in older persons, those with diabetes, and smokers. Diffuse bilateral pneumonia suggests dissemination or fungemia, often in an immunosuppressed host.

Although resolution is the norm, acute infection can set the stage for chronic progressive, often apical cavitary pneumonia resembling tuberculosis. In acute disease, chest radiographs show patchy infiltrates, often with mediastinal adenopathy. Pulmonary nodules occur in about 20% of cases and thin-walled cavities in 10%, which are usually asymptomatic and clear without therapy (Fig. 134-5). The main CT finding in acute disease is multiple nodules.[133] When the history of coccidioidomycosis is not secure, residual often asymptomatic nodules may be biopsied or surgically removed as they mimic malignancy.[134] Rarely cavities rupture into the pleural space causing pyopneumothorax, bronchopleural fistula, or empyema.

Disseminated Disease

Approximately 1% of patients will have disseminated infection with the most common extrathoracic sites being skin, soft tissue, bone, and meninges.[135] Progressive disseminated disease is, however, reported in nearly one-half of cases occurring in patients with underlying immunosuppression.[136] Disseminated disease may be first recognized years following exposure. Risk factors for disseminated disease include nonwhite race, extremes of age, and pregnancy.[78,137,138] Pulmonary involvement is common in disseminated disease. Chest radiographs usually show diffuse reticulonodular or miliary infiltrates, but focal pulmonary lesions, nodules, cavities, adenopathy, and pleural effusions also may be seen (see Fig. 134-2).

Meningitis is the most common and severe manifestation of disseminated disease and approximately 300 cases are reported in endemic areas per year.[139,140] Patients complain of headache, nausea, vomiting, and confusion. Meningitis carries a poor prognosis and tendency to relapse, despite long-term maintenance therapy. Abscesses may develop in the brain or spinal cord. Hydrocephalus and vasculitis are dreaded complications of meningitis. Coccidioidomycosis can mimic many diseases. Less frequently involved extrapulmonary sites include liver, peritoneum, kidneys, epididymis, prostate, testes, retina, ears, larynx, heart, thyroid, adrenal, and pituitary glands, esophagus, and pancreas.

DIAGNOSIS

Because the clinical diagnosis of coccidioidomycosis can be difficult, specific radiologic and laboratory testing is usually required to establish a diagnosis. A battery of tests including fungal stain, culture, and serology are useful for the diagnosis of coccidioidomycosis.[76–84,141–143] The sensitivity of these methods is affected by the extent of exposure, immune status of the patient, and the type of infection.

Imaging Studies

The radiologic findings of coccidioidomycosis are diverse (Fig. 134-5).[121,144] Pulmonary infiltrates are identified in the majority of patients. Pleural effusions and adenopathy are commonly identified on chest radiographs. Pulmonary nodules and cavities can be seen. Immunosuppressed patients may manifest a diffuse "miliary" pattern. CT scans of the chest are more sensitive, identifying effusions,

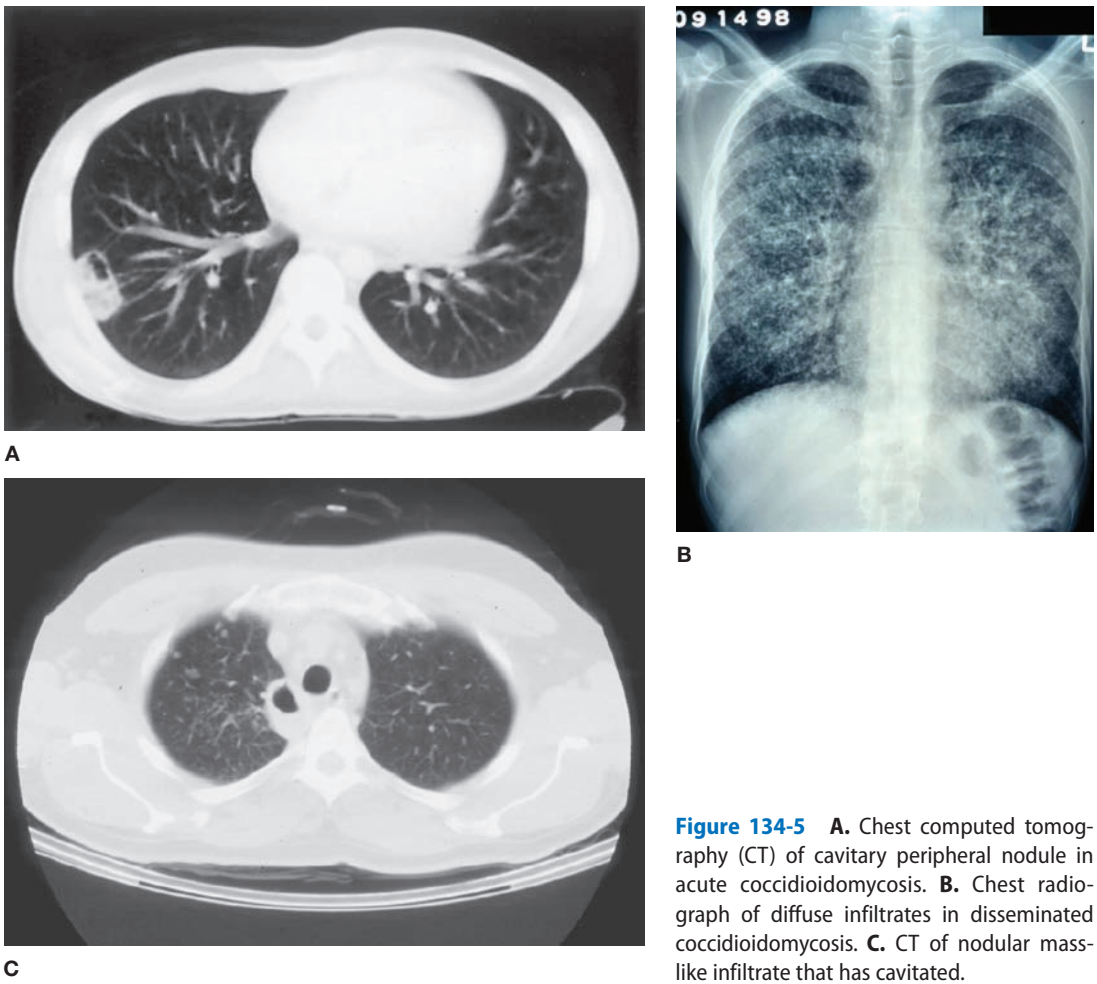


Figure 134-5 **A.** Chest computed tomography (CT) of cavitary peripheral nodule in acute coccidioidomycosis. **B.** Chest radiograph of diffuse infiltrates in disseminated coccidioidomycosis. **C.** CT of nodular mass-like infiltrate that has cavitated.

hilar lymph nodes, micronodular infiltrates, and multifocal ground-glass infiltrates more readily.[133,145] Pulmonary nodules as sequelae of past coccidioidomycosis infection are less than 5 cm in diameter, but can be confused with malignancy. Nodules do not calcify; rather, they may evolve into thin-walled cavities by shelling out the nodule contents. These cavities can predispose to secondary infection, pneumothorax, hemoptysis, and mycetoma. Lymph nodes and nodules exhibit varying degrees of uptake on PET scans.

Serology

Serological tests are useful and the most widely used method of diagnosis.[135] Serology is positive in 90% of clinically recognized cases, and the magnitude of response correlates with the extent of infection. Serology may be negative early in the course of infection, in asymptomatic cases, and those with mild illness, including thin-walled cavities and solitary nodules. Immunocompromised patients may have negative serology due to inefficient antibody production[146] and repeat testing is often performed. Sensitivity may be increased by concentrating the specimen, as is done in some reference laboratories.[81] Detection of antibody in CSF is useful for diagnosing meningitis.[140]

The immunoglobulin M (IgM) response can be measured by enzyme immunoassay (EIA), tube precipitation (TP), or agar gel diffusion (IDTP) and is positive in the majority of cases by the end of the first month of the illness, fading over the next 6 months.[81,147] EIA is emerging as the more commonly utilized initial test. False-positive results are a possibility and an isolated positive EIA IgM warrants further clinical assessment and diagnostic testing.[148,149] Blair et al.[146] found EIA was positive in 87% of healthy patients with coccidioidomycosis compared to 67% of immunosuppressed patients. Sensitivity improved to 95% and 84%, respectively when sequential and confirmatory tests were employed. Serology may be falsely negative in about one-quarter of solid-organ transplant patients with coccidioidomycosis, and two-thirds to three-quarters if positive EIA results alone are not considered diagnostic.[143]

The immunoglobulin G (IgG) response measured by EIA, complement fixation (CF) or immunodiffusion (IDCF) follows the IgM and peaks during the fourth month of illness, and then slowly fades. The commercial IgG EIA tests are commonly used and are generally highly sensitive and specific. Nevertheless, a positive IgG EIA should be sent to specialized reference laboratories for confirmation and quantification. The IgG IDCF quantitative testing or traditional CF testing is often performed as the confirmatory test and provides prognostic information with higher titers (>1:16) suggesting dissemination. However, this finding is neither sensitive nor specific for dissemination, especially in the setting of meningitis.[78] Antibody titers decline with treatment, assisting in monitoring therapy and identifying relapse. Serial testing is also useful in patients who are not receiving therapy, as rising titers suggest progressive infection and support evaluation to exclude dissemination.

Antigen Detection

Two studies highlight the clinical utility of testing *Coccidioides* galactomannan antigenemia and antigenuria in predominantly immunocompromised patients with moderately severe to disseminated disease. In this severely ill patient population, antigenemia can be

detected in up to 71% of urine specimens and 73% of EDTA-treated serum samples.[83,84] Cross-reactivity with other endemic fungi, can occur and clinical context is needed for accurate diagnosis.

Cytology, Histopathology, and Culture

Sputum can be useful in diagnosis when produced. Other respiratory secretions may improve sensitivity. As such, cytology was positive in 35% of culture-positive bronchoscopy specimens from patients with pneumonia, (diffuse infiltrates, 46% and focal infiltrate, 26%).[83,150,151] In a study of severe diffuse pneumonia in patients with AIDS, Papanicolaou smear was positive in 9 or 14 BAL specimens, compared to KOH wet mount in only 3, calcofluor white stain in 2, and culture in 12.[76] Histopathology is positive on needle-biopsy specimens from lung nodules in about one-half of cases. The sensitivity in extrapulmonary lesions has not been reported but presumably is high, except for meningitis.

Interestingly, cultures of respiratory specimens are infrequently positive in patients with acute pneumonia. The sensitivity of culture for diagnosis is uncertain because culture positivity is often a basis for inclusion in the published studies. Nevertheless, culture of lung specimens is more sensitive than cytology but can take weeks to identify and thus cannot be relied upon for a rapid diagnosis.[152] Cultures of skin or bone lesions are positive in the majority of cases of disseminated coccidioidomycosis. However, blood, urine, and CSF cultures are frequently negative, complicating the diagnosis. As such, serology and antigen testing play an important complimentary role in the diagnosis of ill patients.

Polymerase Chain Reaction

Once *Coccidioides* is cultivated in the laboratory, confirmation typically occurs via chemiluminescent DNA probe or by DNA sequencing methods shortening the time to diagnosis. In addition, a few reference laboratories, are applying PCR and real-time PCR methodology to clinical samples.[153] Binnicker et al.[141] applied real-time PCR to 66 fresh tissue specimens that yielded 93% sensitivity and 98% specificity compared to culture. The assay was sensitive enough to be used on paraffin-embedded tissue. Subsequently, clinical sensitivity was shown to be 56% versus 44% for fungal culture, similar to the sensitivity of fungal culture in past studies.[141,142] Molecular methodologies hold great promise for the future of fungal diagnostics.

Skin Test

Skin test reagents are not readily available and have not been used clinically for several years. However, *Coccidioides immitis* Spherule—Derived Skin Test Antigen (Spherusol) is FDA approved (FDA 2012) but not offered for commercial use as of 2013; (http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm266802.htm). Any role for this skin test in clinical practice remains undefined.[154]

■ TREATMENT

Guidelines for treatment are continually being updated.[155,156] Most infections are asymptomatic or self-limited pulmonary infections, and require no treatment in the absence of immunosuppression. Before withholding treatment, however, patients must be evaluated carefully for the extent of disease and evidence for extrapulmonary dissemination. In rare cases, a bone scan to identify skeletal lesions or lumbar puncture to assess CNS symptoms may be indicated. In patients in which treatment is withheld, radiographic and clinical follow-up at 4 to 6 weeks and then at 3- to 6-month intervals for 2 years is recommended to identify evidence for progressive infection.

Indications for Treatment

Treatment of coccidioidomycosis is considered below according to the type of pulmonary involvement.

Acute Uncomplicated Pneumonia Some physicians recommend treatment to prevent long-term complications, but most recommend observation without therapy. Circumstances warranting treatment include symptoms for 4 to 6 weeks, immunosuppression, other chronic diseases or conditions affecting recovery from the acute infection, such as diabetes, COPD, pregnancy, age greater than 55 years, African American or Filipino descent, and severity of illness. Indicators of severe illness include weight loss greater than 10%, intense night sweats for more than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, inability to work, and symptoms persisting for more than 4 to 6 weeks.[156]

Persistent Cavities or Nodules Approximately 10% of patients with acute pulmonary coccidioidomycosis will develop residua of the acute infection (nodules or cavities), which often are asymptomatic, and require no therapy. However, these residua can "reactivate" and symptoms may include pain, cough, hemoptysis, and bacterial superinfection. Antifungal therapy is appropriate in patients with persistent symptoms or rising serologic titer. Treatment also is recommended in those with lesions contiguous with the pleura, or exhibiting progressive enlargement.[156] Biopsy of nodules may be required if a history of infection is not secure to exclude malignancy. For cavities that rupture into the pleural space, drainage is needed. Surgical drainage or in some cases thoracostomy is appropriate. Like chronic pulmonary histoplasmosis, antifungal treatment is recommended in patients with chronic progressive fibrocavitary disease.

Diffuse Pulmonary, Extrapulmonary or Disseminated Treatment is indicated in all patients with diffuse pulmonary or disseminated coccidioidomycosis. More controversial is the role of antifungal therapy in the immunosuppressed host with serological, radiographic, or clinical evidence of prior coccidioidomycosis. Death from coccidioidomycosis was reduced by antifungal therapy used as secondary prophylaxis in solid-organ transplant patients with a history of symptomatic coccidioidomycosis up to 5 years before transplantation, supporting a recommendation for preventive treatment.[157]

Selection of Antifungal Agents

Fluconazole is used in the majority of outpatients treated for pneumonia. Consultation may be warranted for complicated patients. Amphotericin B (0.7 to 1.0 mg/kg/d) is indicated in severe cases, immunosuppressed patients with diffuse pneumonia, and during pregnancy. The lipid formulations are recommended in patients who cannot take the standard formulation because of underlying renal disease or risk for amphotericin-induced nephrotoxicity.[155,156]

Itraconazole and fluconazole are effective in milder nonmeningeal cases. In patients with bone disease, outcome was better with itraconazole.[158,159] Recommended dosages for fluconazole and itraconazole are 400 mg/d for nonmeningeal disease. Drug interactions and inadequate drug exposure occur more often with itraconazole than fluconazole.

Treatment for meningitis is less effective than for other forms of coccidioidomycosis. Fluconazole 400 to 1000 mg per day is recommended because of excellent penetration into CSF.[156,160] Some physicians also administer amphotericin B intrathecally. Consultation with an infectious diseases or pulmonary physician who specializes in coccidioidomycosis treatment is prudent. Treatment for coccidioidal meningitis is lifelong. Response to therapy must be documented.

Newer Antifungal Agents

The newer triazoles exhibit in vitro and in vivo activity against *Coccidioides* and there are a few reports of successful treatment with posaconazole and voriconazole, including cases with meningitis.[161]

Because of poor in vitro activity and inconsistent results caspofungin is not currently recommended.

Duration of Therapy

In patients with acute pulmonary coccidioidomycosis, up to 3 months of therapy may be sufficient. Patients should be re-evaluated before treatment is stopped to identify evidence for chronic infection or extrapulmonary dissemination, in which case treatment should be continued for 12 to 18 months or longer.[156] Treatment should be continued indefinitely for patients with meningitis or those with severe underlying immunodeficiency states.

Adjunctive Surgical Therapy

Surgical debridement or resection of infected tissue often is necessary as an adjunct to antifungal therapy. Chronic foci of pulmonary necrosis or cavitation may require resection to prevent progression or relapse. Hydrocephalus may require surgical or percutaneous intervention. Soft tissue, joint, or bony abscesses may require drainage or debridement.[159]

Adjunctive Steroid Therapy

Although not routinely used, corticosteroid therapy plays a limited role as adjunctive therapy in coccidioidomycosis. In coccidioidomycosis, an intense eosinophilic pneumonia can occur resembling a hypersensitivity reaction and clinical improvement has been noted with concomitant steroid therapy.[130] Steroids may also be of utility as adjunctive therapy in coccidioidal IRIS.

■ PREVENTION

Recommendations exist for the prevention of coccidioidomycosis in high-risk occupations.[162] Patients with diseases that impair cellular immunity probably should avoid activities involving dust or soil, areas experiencing active outbreaks, and the desert during dry and windy periods. Antifungal prophylaxis for high-risk patients is not recommended outside secondary prophylaxis for organ transplant recipients, however, some clinicians have questioned this strategy in the era of biologics. Some clinicians would recommend screening for coccidioidomycosis by chest radiograph and serology before initiating TNF-α inhibitor therapy, and treatment of those with positive results.[127] Efforts to develop a vaccine to prevent coccidioidomycosis in humans have been unsuccessful to date.[163]

BLASTOMYCOSIS

Blastomycosis is the least common of the endemic mycoses.[4] Although recognized in immunocompromised individuals, in whom manifestations are more severe, it is less common than histoplasmosis or coccidioidomycosis in this setting. Unfortunately, the diagnosis is often overlooked until late in the course of the disease[164,165] leading to delayed treatment and potentially poor outcome.

■ MYCOLOGY

B. dermatitidis is a thermally dimorphic fungus–producing mycelia with 2 to 10 μm dumbbell-shaped conidia at 25°C and doubly retractile, broad-based budding yeasts varying in size from 8 to 15 μm at 37°C (Fig. 134-1). While *B. dermatitidis* mycelia may be grown from a primary specimen in less than 2 weeks, final identification may require several weeks including the thermoconversion of the mold form into yeast. Definitive identification is made using DNA probes or exoantigen tests.

■ EPIDEMIOLOGY

B. dermatitidis is found in microfoci, often near waterways, that are enriched with animal excreta. The endemic area for blastomycosis overlaps with that of histoplasmosis for the most part, except that blastomycosis area stretches further north into northern Minnesota, northern Wisconsin, Canadian provinces adjacent to the great lakes and the areas surrounding St. Lawrence Seaway in New York and Canada (Fig. 134-1). Outside North America, blastomycosis is most common in Africa. Fewer cases have been reported from Central and South America and Western Europe. The organism has been isolated from soil in areas inhabited by farm animals and from beaver lodges or dams. Decaying organic matter enhances its growth in the environment. Most cases occur sporadically in endemic areas. Infection usually occurs in the setting of outdoors activity and near waterways.[166] Few point source outbreaks have been reported where most patients present with an acute illness after exposure to contaminated excavation sites and in association with outdoor activities such as hunting, camping, or canoeing in wooded or swampy environments.[167]

■ PATHOGENESIS AND PATHOLOGY

Pulmonary disease follows inhalation of conidia and often is accompanied by hematogenous dissemination. Neutrophils are first recruited to sites of infection, followed by lymphocytes. Cellular immunity plays a lesser role in host defense in blastomycosis than in histoplasmosis, but disease is more severe in immunosuppressed individuals.[108,168]

Pathologically, blastomycosis is characterized by granuloma formation with central microabscesses, so-called pyogranulomas, but not by caseation as seen in histoplasmosis or tuberculosis. Histological changes in the skin may resemble those of squamous-cell carcinoma or keratoacanthoma. Calcification is uncommon.

■ CLINICAL MANIFESTATION

Following exposure, the incubation period ranges from 21 to 106 days with a median of 45 days.[104] As the portal of entry, lungs are the most commonly affected organs in blastomycosis.[169,170] The majority of infected individuals are either asymptomatic or manifest a mild self-limited illness. The typical patient is a middle aged man with history of outdoor activity. The disease is rarely seen in children.

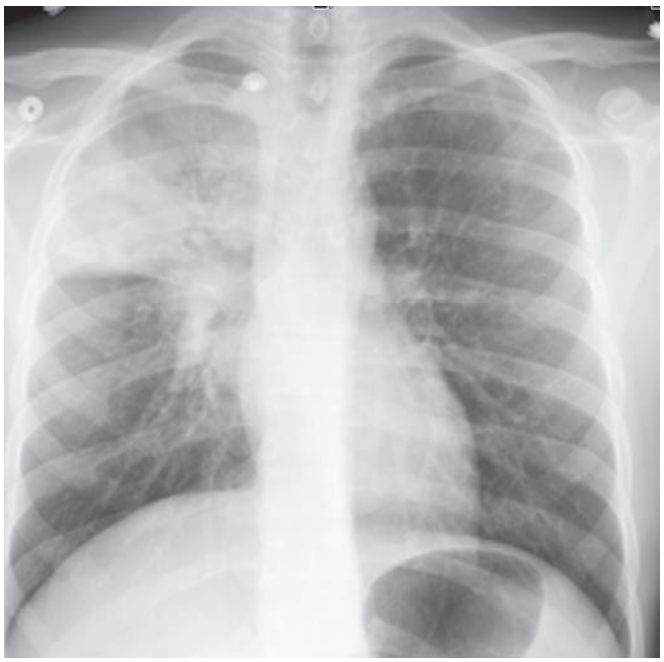
TABLE 134-4 Diagnostic Studies in Blastomycosis

Test	Sensitivity (%)	Author
Antigen	93	Durkin et al., 2004[99,100]
Cytology	50–93	Patel et al., 1999[101]; Martynowicz and Prakash, 2002[102]; Lemos et al., 2000 [103]
KOH	29–83	Patel et al., 1999[101]; Martynowicz and Prakash, 2002[102]; Lemos et al., 2000[103]
Histopathology	85	Lemos et al., 2000[103]
Culture	66–75	Martynowicz and Prakash, 2002[102]; Lemos et al., 2000[103]
Serology	<50	Martynowicz and Prakash, 2002[102]; Klein et al., 1987[104]

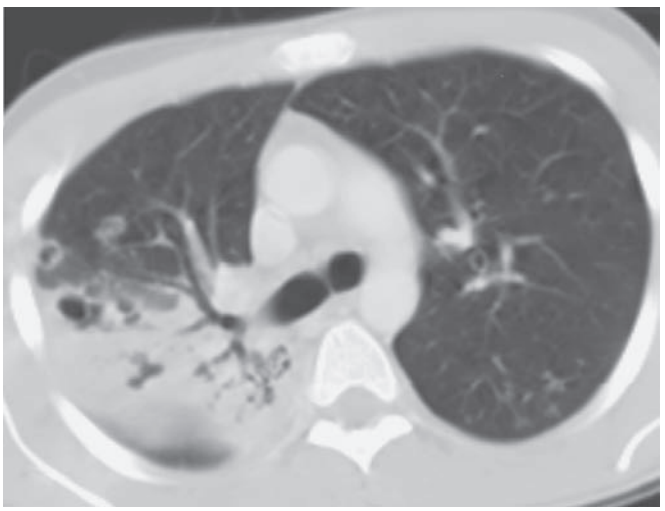
Most patients are otherwise healthy with no underlying systemic or pulmonary illnesses.[164,171]

Pneumonia

Acute pulmonary blastomycosis is commonly seen in the setting of an outbreak. Symptoms are abrupt and most commonly include cough productive of purulent sputum, fever, night sweats, dyspnea, chest pain, weight loss, myalgia and occasionally hemoptysis.[164,165,172] The illness is often confused with bacterial community–acquired pneumonia,[2] and the diagnosis of pulmonary blastomycosis is suspected only after the patient's symptoms fail to respond to antibacterial therapy. As a result the proper diagnosis is usually delayed. In one series it took more than 30 days from presentation to a physician to diagnosis in 43% of the cases. Only a quarter of the patients were diagnosed within a week of their presentation.[164,165] Most common radiographic findings in acute pulmonary blastomycosis include lobar consolidation, air bronchogram, and nodular infiltrates (Fig. 134-6).[101,171,173] Cavities may also be seen within areas of consolidation.[171] In contrast with histoplasmosis, mediastinal and hilar lymphadenopathies seem less prominent in pulmonary blastomycosis.[171] Similarly calcified lymph nodes and pleural effusions are seldom seen on chest imaging of patients with acute blastomycosis.[174] The abnormalities do not seem to follow any particular distribution, involving any lobe on one or both sides of



A



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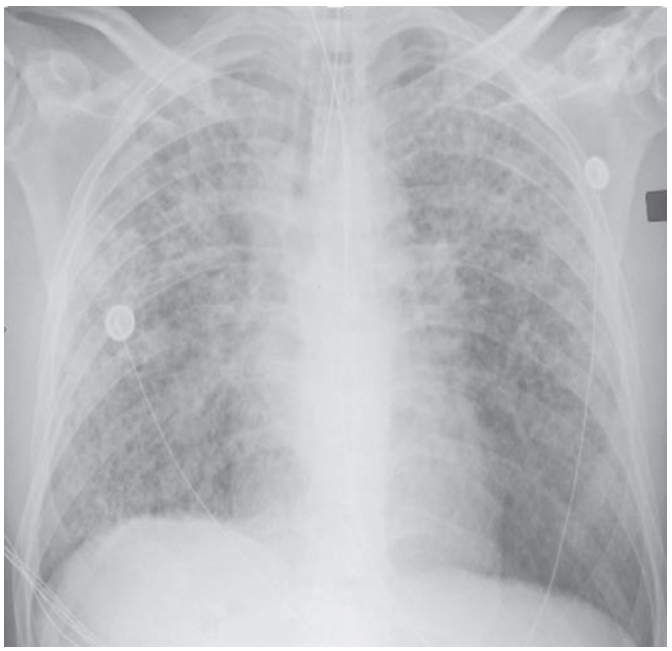
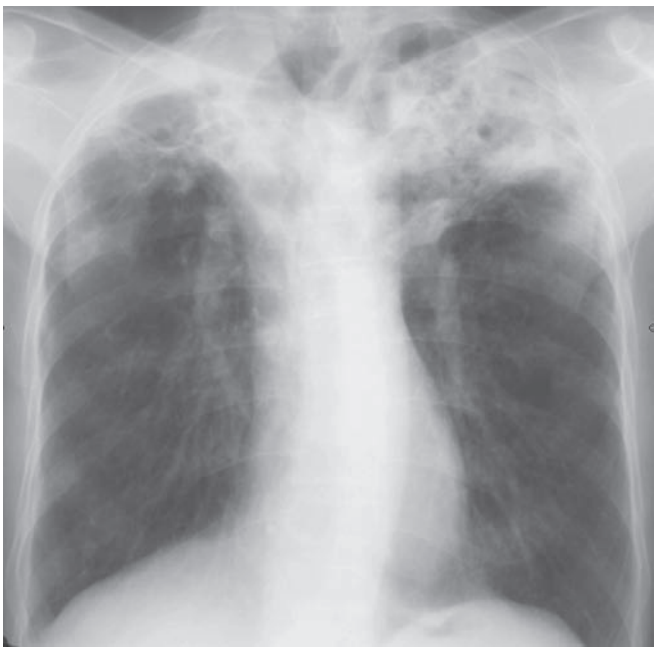


C



D

Figure 134-6 **A.** Chest radiograph of infiltrate resembling bacterial pneumonia in acute blastomycosis. **B.** Computed tomography scan showing lobar infiltrate. **C.** Chest radiograph of diffuse infiltrates associated with acute respiratory distress syndrome. **D.** Chest radiograph of cavitary blastomycosis.

the chest.[173,174] Military nodules and interstitial infiltrates are often in severe blastomycosis with ARDS.[173]

Chronic pulmonary blastomycosis is often seen in sporadic cases. It is clinically similar to reactivation tuberculosis. Fibrocavitary disease, as seen in histoplasmosis and coccidioidomycosis, is uncommon in blastomycosis, occurring in only less than 10% of such cases. The onset of the illness is gradual. Symptoms include cough productive of purulent sputum, fever, night sweats, malaise, and weight loss.[175] Mass-like lesions, nodules, and adjacent adenopathy can be seen with chronic pulmonary blastomycosis.[171] The lesion is often mistaken for lung cancer triggering a needle biopsy especially if the patient smokes cigarette. Depending on the radiographic findings, the illness can be mistaken for tuberculosis (upper lobe cavitary disease) or lung cancer (lung mass). The illness tends to progress if untreated.

Acute Respiratory Distress Syndrome

In up to 10% of the patients with acute pulmonary blastomycosis the illness rapidly progresses leading to acute respiratory distress syndrome with bilateral disease and severe hypoxia requiring mechanical ventilation and sometime vasopressor support for shock.[176] This presentation carries a grim prognosis, with up to 60% mortality rate.[165] The delay in recognition and diagnosis of the illness and consequent delay in proper treatment are often blamed for this poor outcome. Pathology is characterized by dense consolidation, microabscesses, hyaline membranes, and alveoli packed with yeast forms. Severe pulmonary blastomycosis is more often seen in immunocompromised patients,[177] such as those with AIDS,[178] transplant recipients,[108,168] patients receiving treatment with TNF inhibitors.[179] Extrapulmonary dissemination and mortality rates are higher. Diabetes mellitus also seems to be a risk factor for more severe blastomycosis.[165]

Disseminated Blastomycosis

Extrapulmonary dissemination is a hallmark of blastomycosis.[171,180] Dissemination is seen in up to third of cases, more likely with chronic than acute disease. Skin lesions are the most common manifestations, followed by bone, genitourinary, and CNS involvement. Cutaneous or bone lesions in a patient with community-acquired pneumonia who resides in the endemic area, should rise the suspicion for blastomycosis. Dissemination to the CNS occurs in 5% to 10% of cases, more commonly in patients who are immunocompromised, and is associated with a mortality rate approaching 20%.[181] Other sites include the sinuses, ears, eyes, thyroid gland, heart, pericardium, pancreas, spleen, liver, and adrenal glands.

Immunocompromised Host

Blastomycosis is more aggressive in this group, with a mortality of nearly 30%.[177] CNS involvement or ARDS was reported in 5% to 10% of cases. Except for the higher mortality rate and a tendency to relapse, the clinical findings are similar to that in nonimmunocompromised individuals.

■ DIAGNOSIS

The diagnosis of blastomycosis is often delayed.[164] The delays is usually due to the nonspecific nature of the clinical presentation confusing the diagnosis with community-acquired bacterial pneumonia in the case of acute pulmonary blastomycosis[2] and lung cancer or tuberculosis in chronic infection.[182] This is particularly true when the disease is limited to the lungs. The presence of associated extrapulmonary manifestations (skin or bone) usually raises the clinical suspicions.[164] Limitations in the available diagnostic tests also contribute to the difficulties in making a timely and accurate diagnosis of blastomycosis. Until recently the diagnosis of blastomycosis relied heavily on microscopic examination and culture of respiratory specimen. Currently, the detection of *Blastomyces* antigen detection has proven useful for rapid diagnosis of pulmonary and disseminated blastomycosis.[99] Sensitivity may be achieved by use of several diagnostic methods.[85,99–102,104,171,180,183]

Culture

Definitive diagnosis of blastomycosis requires the isolation of the organism by culture. Sputum, tracheal aspirates, and skin lesions exudates are appropriate for fungal culture. BAL fluids or bronchial washings may improve the yield in patients who cannot produce adequate sputum samples and when sputum culture is negative.[102,171] While positive in the vast majority of patients (>85%), culture is time consuming, requiring up to 4 weeks for the final identification of the organism. The organism may grow within one to 2 weeks of inoculation; however, specimen with lower fungal burden may requires up to 4 weeks to grow the fungus. Confirmation of the organism also requires either thermoconversion into the characteristic yeast or the use of DNA hybridization probe. Therefore, one cannot rely on fungal culture to make a timely diagnosis and treatment decisions in symptomatic pulmonary blastomycosis.

Cytology and histopathology

A timely diagnosis of blastomycosis can be made by visualizing the organism in respiratory specimens or sites of extrapulmonary involvement using calcofluor white stain, KOH wet mount cytology or histopathology. The characteristic yeast is a round to oval multinucleated cell, 8 to 15 μm in diameter, with a thick retractile cell wall and single broad–based bud. The yield of cytology is quit variable, ranging from 38%[171] to 97%,[184] depending on the quality of the specimen being examined, the stains used and the experience of the cytopathologist.[102] The yield seems to improve when BAL specimens are used and when culture and cytology are applied to the same specimen.[183] Histopathologic examination of biopsy specimen has been reported to yield the diagnosis in up to 81% of patients.[171,185] Invasive procedure may be required either by performing bronchoscopy or surgical biopsy, or percutaneous needle aspiration to collect the diagnostic specimen used in cytology, potentially adding to the morbidity.

Antigen detection

Blastomyces antigen can be detected in serum, urine, and BAL fluid, providing a noninvasive method for rapid diagnosis. The test is positive in 80% to 93% of patients[85,99,100,171,186] with 98% specificity in patients without endemic mycoses. Nearly complete cross-reactivity occurs in patients with histoplasmosis.[99,100] The sensitivity is highest in patients with acute pulmonary disease and those with severe and disseminated blastomycosis.[99,186] Blastomyces antigen can also be detected in BAL fluid, adding to the diagnostic yield of bronchoscopy in pulmonary blastomycosis.[85,187] Antigen also can be detected in CSF of those with CNS involvement. The current quantitative version may be followed as a mean of assessing the response to treatment similar to the Histoplasma antigen test.[86] A high degree of cross-reactions has been reported with histoplasmosis, paracoccidioidomycosis, and penicilliosis marneffei.[99,100,171,186]

Serology

Unlike histoplasmosis and coccidioidomycosis, currently available tests for blastomyces serology are of little use in the diagnostic workup of blastomycosis because of low sensitivity and specificity. The sensitivity of immunodiffusion ranges between 29% and 64% and that of the complement fixation between 25% and 43%.[88,102,188,189] EIA using the blastomyces A antigen provides better sensitivity (77%–83%) but significant cross-reaction occurs with histoplasmosis.[104,190]

Molecular testing

Molecular assays have been attempted for the detection of *Blastomyces* with limited success. Recently a real-time PCR method

was used on culture isolates as well as primary clinical samples with high sensitivity and specificity; 12 out of 14 (86%) confirmed clinical specimen tested positive in this PCR assay. The test also distinguished between Histoplasma and Blastomyces isolates with no cross-reactivity.[93] This test seems promising and needs to be validated in a larger scale with diverse clinical presentations.

TREATMENT

Although patients with self-limited pulmonary blastomycosis have been reported,[191,192] current guidelines recommend treatment to all patients diagnosed with blastomycosis because of the high likelihood of progression or recurrence of the infection if untreated.[156,193]

Indications for Treatment

Treatment is indicated in all patients with diffuse pneumonia, disseminated disease, underlying immunosuppression, or persistent symptoms more than a month following acute infection. In some cases of acute pneumonia, the course is self-limited and resolves without treatment. Some authorities recommend treatment for all cases, but if observation is under consideration, the following conditions should be met: mild illness and absence of immunosuppression or extrapulmonary dissemination. Furthermore, such patients should be followed carefully for several years for evidence of progression or dissemination.

Whether pregnancy alters the course of infection in the mother is unknown, but there is risk for transplacental transmission to the fetus. Treatment of the mother may reduce the risk for transmission to the fetus. Amphotericin B is recommended as the triazoles are contraindicated because of embryo toxicity and teratogenicity.

Selection of Antifungal Agent

There are no published randomized, blinded studies comparing different regimens for the treatment of blastomycosis. Itraconazole is recommended for most patients with pulmonary blastomycosis with over 90% success rate in mild-to-moderate disease.[194] The recommended dose is 200 mg three times a day for three days followed by 200 mg twice a day for at least 6 months. A longer course is recommended for immunosuppressed patients, those with bone disease, and those who relapse after shorter duration of therapy.

Fluconazole is less effective than itraconazole for blastomycosis[195] and therefore is not recommended. However, fluconazole can be used, at high doses (800 mg/d) in patients who cannot tolerate itraconazole.[196]

Amphotericin B (0.7 to 1.0 mg/kg/d) is recommended for patients with severe pulmonary blastomycosis and those with CNS disease.[193] Response to amphotericin B ranges from 85% to 90%.[197,198] Amphotericin B is usually used until clinical improvement (1–2 weeks) and is followed by itraconazole for the remainder of the treatment course. Lipid formulations of amphotericin B tend to be the first line therapies due to their safety profile.

Despite antifungal therapy, the mortality rate of blastomycosis-associated ARDS is still very high (50%–89%).[176,189,199] Corticosteroids, in addition to amphotericin B, have been used successfully to treat blastomycosis-associated ARDS in few reported cases.[199,200]

Newer Antifungal Agents

Voriconazole and posaconazole are active against *B. dermatitidis* and effective in a murine model of blastomycosis. Neither has been studied in humans, but there are anecdotal reports of successful use of voriconazole for blastomycosis.[181,201] The echinocandins showed variable activity in vitro but have not been studied in animal models or humans, and are not recommended.

Duration of Therapy

Treatment should be continued for at least 6 months[156,193] until clinical and laboratory findings have normalized including antigen levels in urine and serum, and radiographic abnormalities have resolved or at least stabilized to represent residual healed lesions. Some experts recommend chronic maintenance treatment for patients with AIDS or other underlying immunosuppressive conditions. Experience in AIDS is insufficient to assess the safety of discontinuation of maintenance with HAART. If maintenance therapy is stopped, the patient should be followed clinically for relapse, and antigen levels should be monitored. Treatment should be resumed if CD4 counts decline below 100 cells/mm^3 or antigen levels increase.

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CHAPTER 135

Pneumocystis Pneumonia

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Despite widespread use of effective antimicrobial prophylaxis in susceptible immunocompromised patient populations, *Pneumocystis jiroveci* remains an important opportunistic pathogen. The incidence of *Pneumocystis* pneumonia (PCP) has decreased with the appropriate deployment of antimicrobial prophylaxis in susceptible hosts and with the advent of highly effective antiretroviral therapy (HAART) in HIV-infected individuals. PCP remains, however, an important syndrome in HIV infection in the developing world with high mortality. *Pneumocystis* also impacts the growing population of immunocompromised individuals following organ and hematopoietic stem cell and bone marrow transplantation, and with the broader use of immunosuppressive therapies in connective tissue, cancer, and immune disorders. The change in nomenclature this past decade, renaming of *Pneumocystis carinii* as *P. jiroveci*, reflects knowledge about the organisms responsible for this syndrome in different host species. This change has generated significant controversy among scientists, clinicians, and journal editors. Advocates and detractors alike agree that no matter the species name, *Pneumocystis* pneumonia or PCP should continue to be used to describe disease caused by this organism in humans.

HISTORY AND BACKGROUND

The cyst form of *Pneumocystis* was first described in 1909 by the famous parasitologist, Chagas and in 1910 by his colleague Carinii, and was described as a parasite and part of the life cycle of *Trypanosoma cruzi*.[1] The organism was first associated with pulmonary infection in rats by Delanoe and Delanoe but was not recognized in humans until 1942 (Van der Meer and Brug) and was not associated with human disease until 1952 (Vanek and Jírovec) when it was found in association with "plasma cell interstitial pneumonitis" among malnourished children and neonates.[2] Small epidemics of plasma cell interstitial pneumonitis had been noted in children in orphanages in Europe in the 1930s and following World War II and the Vietnam War. In the 1950s, recognition of congenital immune deficiencies and the development of immunosuppressive therapies identified new hosts for PCP. At that time, PCP was recognized in patients receiving corticosteroids and chemotherapeutic drugs and in immunosuppressed rats receiving corticosteroids.

The increasing incidence of PCP led to epidemiologic and therapeutic studies of the disease by the Centers for Disease Control (CDC) in the 1970s, based on the provision of the sole therapeutic agent available at that time (pentamidine). Clusters of *P. carinii* were reported at a variety of clinical oncology and transplant centers. However, the development of pyrimethamine, sulfadoxine, and of trimethoprim (TMP) and sulfamethoxazole (SMX) for the treatment and prevention of *Pneumocystis* infection greatly reduced the occurrence and the morbidity of the infection. These agents are now generally used in a fixed combination (TMP-SMX, or cotrimoxazole). *P. carinii* became known the world over as being the first disease-defining illness associated with AIDS in the 1980s, causing over one-fourth of community-acquired pneumonias in HIV-infected persons and more than 200,000 cases of PCP since 1979. What was once an obscure, poorly understood opportunistic disease, became a common clinical entity in a matter of a decade as a result. By the mid-1990s genetic diversity among isolates of *Pneumocystis* from different host species had been described suggested that the organism was a fungus rather than a parasite and that there was host species specificity. The basis of that specificity (i.e., receptors, nutritional requirements) remains unknown. The organism causing infection in humans was renamed *P. jiroveci* after the Czech parasitologist, Otto Jírovec.[3]

STRUCTURE AND LIFE CYCLE

In humans and animals, three forms of the organism have been identified: trophozoite, cyst, and sporozoite (or intracystic bodies) (Fig. 135-1). The trophozoite, 2 to 5 μ in diameter, is either round or sickle-shaped and contains a nucleus, mitochondria, and vacuoles. It also includes pseudopodia and filopodia, used in limited motility. The cyst usually measures between 3 and 6 μ in diameter. Its cell wall consists of three layers, and its cytoplasm contains eight small pleomorphic intracystic oval bodies called sporozoites.[4] Two other cystic forms have been described, but these are probably intermediates including empty or developing cysts (Fig. 135-1). Many small surface projections, or tubular expansions, form a branching network over the surfaces of the cysts and the trophozoites.

In the alveolus, *Pneumocystis* are covered with a variety of glycoproteins derived from both the organism and the host. Specific and

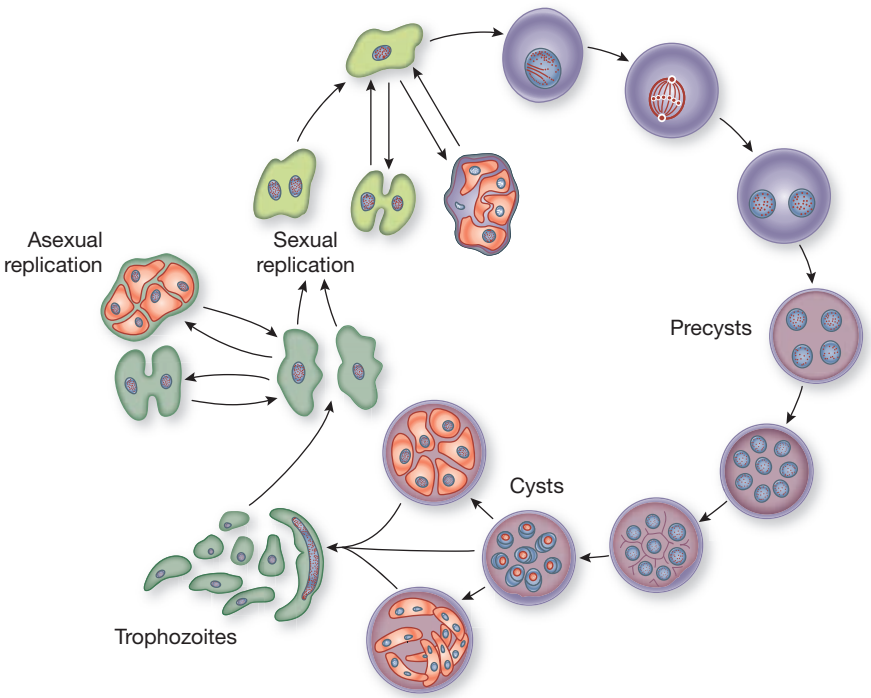


Figure 135-1 The life cycle of *Pneumocystis carinii*.

nonspecific immunoglobulins, albumin, surfactant proteins, laminin, fibronectin, and other serum and lung proteins coat the surface. The organism produces a relatively limited array of surface glycoproteins that share antigenic epitopes. These, and some minor components, are found on both animal- and human-derived organisms. *Pneumocystis* from different species share antigenic epitopes in addition to carrying unique epitopes.[5] The cell wall contains cholesterol but no ergosterol and does not appear to synthesize sterols de novo; this likely accounts for the lack of susceptibility to the azole and polyene antifungal antibiotics.[6] The presence of chitin in the cell wall is controversial. The surface of *P. jiroveci* is carbohydrate-rich with glucose, mannose, and β-1,3-glucan, the latter of which may play a role in phagocytosis of the organism by macrophages and may provide a potential diagnostic and therapeutic target for echinocandin antifungal agents. The surface also contains carbohydrate-binding moieties, which may play a role in attachment to epithelial or surfactant layers.

The life cycle of *Pneumocystis* is incompletely understood (Fig. 135-1). Many of the studies of the life cycle have used organisms derived from infected animals and passaged on a feeder cell layer of epithelial or fibroblastoid cells in tissue culture. Continuous growth has not been achieved in this system, and the human-derived organisms have not been grown consistently in vitro. Success with axenic or cell-free cultivation of *P. jiroveci* has been limited. It is now believed that the sporozoites, or daughter forms, emerge from the cyst to develop into trophozoites. These trophozoites mature to form cysts and then repeat the cycle.[7] This sequence is far from settled, however, and both sexual and asexual intermediate stages have been postulated. It is likely that some differences exist in *Pneumocystis* growth in different hosts and with different immune defects.

Research on *Pneumocystis* has been hampered by the difficulties encountered in propagating the organism in vitro. Studies have been performed on organisms derived from immunosuppressed rodents, which develop PCP in the absence of prophylaxis or respiratory isolation. Researchers have used this model to demonstrate the aerosol transmission of *P. jiroveci*.[8] To this day, unfortunately, cell culture techniques remain useless diagnostically because of the difficulty in culturing the organism from the infected human tissues.

TAXONOMY AND MOLECULAR BIOLOGY

Phylogenetic data support the identification of *P. jiroveci* with the taxonomic kingdom of fungi (*Rhizopoda, Myxomycetes, Zygomycota, Schizosaccharomyces, Neurospora, Candida,* and the red yeasts in various studies), rather than the parasitic kingdom of protozoa. This is based on conserved mRNA sequences and other findings.[9] The presence of separate genes encoding the thymidylate synthase and dihydrofolate reductase of *P. jiroveci*, the presence of a cyst wall rich in β-glucan that stains with periodic acid–Schiff and silver stains, the poorly developed mitochondria, the absence of typical protozoan intracellular organelles, and the airborne spread of infection all support this taxonomic position. The neutral lipid fraction of *P. jiroveci* includes a variety of phytosterols shared by plants and fungi, including *Physarum* species.[10] However, the appearance of the organism with a thick-walled cyst with internal sporozoites and ameboid trophozoites, the absence of ergosterol, susceptibility to antibiotics used in the treatment of protozoan infections (pentamidine, atovaquone, SMX), and the existence of antigenic variation in the major surface glycoprotein (gp120, gpA, MSG) lend credence to the original identification with the protozoa.

Complicating the taxonomy of this organism is the existence of different strains of *Pneumocystis* that have been demonstrated using pulsed-field gel electrophoresis and DNA sequencing.[11] This diversity is greatest between strains infecting different host species, giving rise to the eventual renaming of the organism.[12] It appears that many infections in individuals are often clonal, though multiple strains may coexist in any one single infected person (see below).[11]

P. jiroveci expresses both unique and some common antigens in different host species. Surface antigens have been characterized at the glycoprotein and molecular levels. The MSG represents the main humoral immunogen in the rat model, although other antigens (gp45–55) may have importance in human infection.[13] Several MSG types have been observed simultaneously in single infected humans and animals with monoclonal antibody staining and genetic characterization. The MSG appears to represent a large family of related genes (approximately 50–80), many of which are located in tandem repeated arrays in the subtelomeric regions and may contribute to the generation of the variety of antigenic types. Cross-reactive T cell responses to MSG variants is uncommon and suggests the possibility that *Pneumocystis* utilizes MSG switching to evade human immune responses.[14]

EPIDEMIOLOGY OF INFECTION DUE TO *PNEUMOCYSTIS*

Over the past 60 plus years, PCP has been transformed from a medical curiosity into an important respiratory infection that affects four categories of immunocompromised host: (1) *congenital*, caused by inborn immune defects in antibody-synthesizing capacity and/or the cellular mechanisms responsible for delayed hypersensitivity; (2) *induced*, by immunosuppressive therapy, especially corticosteroids (3) *acquired*, occurring as an identifying opportunistic pathogen in HIV infection or with exogenous immune suppression; and (4) *nutritionally deficient with epidemic infection*, described primarily in susceptible neonates and infants.

P. jiroveci causes pneumonia in persons with a wide variety of underlying immune deficiencies (Table 135-1). Studies performed in immunosuppressed animals and clinical experience indicate that T cell immune defects predominate in individuals with *P. jiroveci* infection. In HIV infection, the progressive depletion of CD4+ T cells heralds the onset of risk for PCP, though CD8+ T cells likely play an important role in responding to *Pneumocystis* infection. Passive transfer of immune CD8+ effector T lymphocytes is protective against PCP in mice.[15] Other immune defects such as neutropenia and hypogammaglobulinemia enhance the risk of PCP by contributing to the overall net state of immunosuppression, and disease may be seen in patients with persistent defects in leukocytes and antibodies, but appears less important for protection than is cellular immunity. Passive immunoglobulin transfer in mice does not have a significant protective effect.[16]

The relative risk of infection with *Pneumocystis* is predictable in most hosts in which infection occurs, including the non-transplant and non-HIV infected populations (Table 135-2). The risk of PCP is greatest in the first 6 months after solid-organ transplantation, after 3 to 6 months of oral corticosteroid therapy (in excess of 15–20 mg prednisone equivalent), and during periods of intensified immune

TABLE 135-1 Conditions Associated with *Pneumocystis* Pneumonia

Acquired immunodeficiency syndrome (AIDS) (without HAART)
Chemotherapy (especially corticosteroids)
Radiation therapy
Organ transplantation
Prematurity
Malnutrition (protein and calorie)
Malignancies (especially hematopoietic)
Congenital immune deficiency diseases (cellular and/or humoral)
Collagen vascular disease
Hematologic disorders
Cushing syndrome
Nephrotic syndrome

TABLE 135-2 Reported Attack Rates for PCP in Non-Transplant Recipients and Non-HIV-Infected Patients Not Receiving Prophylaxis by Underlying Condition

Underlying Disorder	Attack Rate (%)
Acute lymphoblastic leukemia	6.5–42.9
Severe combined immunodeficiency syndrome	27–42
Rhabdomyosarcoma	4–25
Granulomatous polyangiitis (formerly known as Wegener granulomatosis)	3.5–12
Hodgkin's disease	1.3
Collagen vascular disease	<2
Primary or metastatic central nervous system tumor	1.3–1.7

suppression, as with the use of bolus corticosteroids or lymphocyte-depleting antibody therapies for graft rejection.[17] Disease occurring outside this host population or predicted timeframe should suggest an excess epidemiologic hazard or unidentified immune deficiency. PCP has also complicated the syndrome of rapamycin lung, an idiosyncratic syndrome of diffuse pulmonary infiltrates in solid-organ transplant recipients receiving sirolimus-based immune suppression. In untreated AIDS, the risk for PCP increases with the progressive fall of the CD4+ lymphocyte counts to below 200 cells/mm^3 or to less than 20% of the total lymphocyte pool. The correlation with T-lymphocyte numbers is such that the rate of infection nearly doubles with a drop in CD4+ lymphocyte counts from between 100 and 200 to below 100/mm^3.[18] The presence of thrush has also been shown to be an independent predictor of risk for PCP in patients with HIV as has a previous bout of PCP. Rarely, PCP occurs at CD4 counts greater than 200 cells/mm^3 and prophylaxis should be offered to such patients starting around the level at which PCP occurred. The occurrence of PCP infection in persons not in these categories should suggest exposure to infected persons, other immunosuppressive effects (e.g., coinfection with cytomegalovirus (CMV), lymphoma, neutropenia), or in the HIV-infected person, a rapid progression of viral infection with the accompanying decline in systemic immune function.

The spectrum of patients developing PCP has changed with the advent of HAART for HIV infection and the routine use of prophylaxis for most patients with hematologic malignancies and after organ transplantation. Inconsistent use of prophylaxis, however, has been linked to some of the published outbreaks of PCP in solid-organ transplant recipients in recent years.[19] In most HIV-negative, immunocompromised patients, the risk of disease is of the order of 5% to 15%, though the risk following organ transplantation varies with the immunosuppressive regimen and the organ transplanted. The attack rate is highest in the lung and combined lung–heart recipients.[20] The major risk factors for PCP are reflected in a retrospective study of 116 HIV-negative patients with PCP of which 30.2% had hematologic malignancies, 25% were organ transplant recipients, 22.4% had inflammatory disorders, 12.9% had solid tumors, and 9.5% had other conditions. Corticosteroids use was reported in 90.5% of these patients. The median daily dose was 30 mg of prednisone; however, 25% of the patients had received as little as 16 mg/day of prednisone. The median duration of corticosteroid therapy before the diagnosis of PCP was 12 weeks. However, 25% of the patients developed PCP after 8 weeks or less of corticosteroid use.[21] Ultimately, specific immunosuppressive drugs may be less important than the overall net state of immunosuppression that can be engendered by multiple factors (metabolic factors, age, immune cell quantity and quality, viral coinfection, underlying lung disease).

In children, epidemiologic studies suggest that PCP may occur in the setting of concomitant viral infection and may be found in infants who die unexpectedly in the community. Beard et al. demonstrated that different strains of *Pneumocystis* appeared to be present in specimens obtained from infants compared with those from HIV-infected adults. This suggests that different strains circulate among non–HIV-infected infants and in HIV-infected adults.[22] The basis for this difference remains unclear and requires confirmation among larger populations.

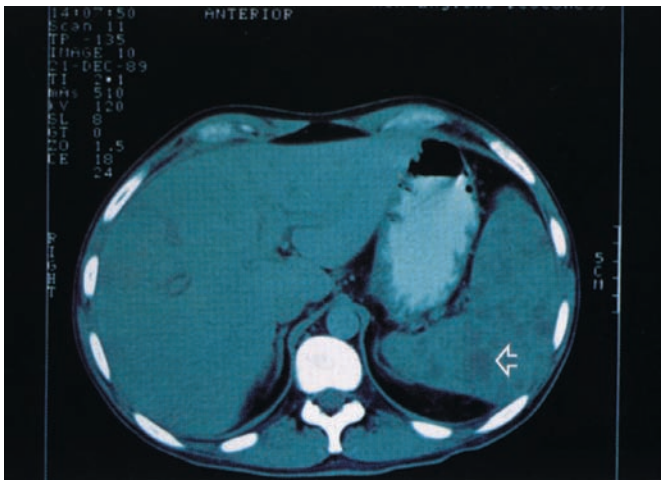
The natural reservoir of infection remains unknown, though *Pneumocystis* species are thought to be fairly ubiquitous in nature. Aerosol transmission of infection has been demonstrated in animal models, and clusters of infection have developed in clinical settings. Outbreaks among solid-organ transplant recipients and among HIV patients have been documented in hospital wards.[19,23–27] Molecular typing studies have implied that some of these outbreaks could be due to person-to-person transmission.[19,23,24] *P. jiroveci* DNA has also been detected by polymerase chain reaction (PCR) in the air of hospital rooms, bronchoscopy suites, and clinics used by infected subjects.[28,29] Whether or not these outbreaks are due to person-to-person transmission or some common environmental source remains unclear. These data have led some experts to recommend strict hospital segregation of immunocompromised hosts with PCP and the use of facemask filtering in the clinical setting, but the efficacy or need for these approaches has not been demonstrated. Prophylaxis remains likely the most effective method at preventing infection in any setting where patients may be at risk of disease.

The prevalence of infection with *P. jiroveci* in patients with AIDS prompted a large effort to study the epidemiology of PCP more closely by developing diagnostic serologic tests that might be applied to the general population. Serologic testing reinforced the view that subclinical infection, exposure, or colonization is common. Most people have serologic evidence of exposure by age 4 years.[30] Other studies have uncovered the presence of *Pneumocystis* in the respiratory tract of asymptomatic nonimmunocompromised hosts. One such study found that as many as one in five people may have *Pneumocystis* DNA in bronchoalveolar lavage (BAL) fluid.[31] These data, along with animal models, have supported the possibility of reactivation of previously established infection as being a potential cause of disease in susceptible hosts. However, data regarding outbreaks, evidence that the infection can be eliminated, subsequent infection with distinct genotypes, and the geographic variability in disease, all combine to suggest that alternative modes of transmission besides reactivation of latent disease is predominant.

In HIV patients, a clear correlation with circulating HIV viral loads is not well established. Historically, the rate of PCP in AIDS was halved by the use of zidovudine for the duration of the effective antiviral effect of this agent.[32] More pronounced effects have been observed in individuals who regain immune function for more than 6 months under HAART therapies; such patients may be able to avoid primary prophylaxis. The rate of infection appears to double in men who have sex with men with AIDS when compared with intravenous drug users. In the absence of effective prophylaxis or HAART, more than 80% of AIDS patients are expected to develop PCP.[18] Clinically symptomatic infection may emerge during the weaning of immunosuppressive agents or as a part of the immune reconstitution syndrome seen with HAART in AIDS. This is consistent with the limited inflammatory response generated by the organism in the susceptible host.

CLINICAL PRESENTATION

The hallmark of infection due to *P. jiroveci* is the presence of marked hypoxemia, dyspnea, and cough out of proportion to physical or radiologic findings. In the transplant recipient or the person undergoing corticosteroid therapy, PCP is generally acute-to-subacute in development and often masked by other processes, including allograft rejection, graft dysfunction or secondary infection. In the AIDS



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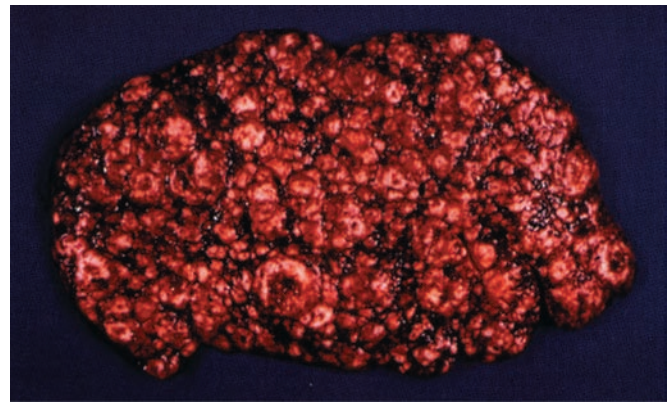

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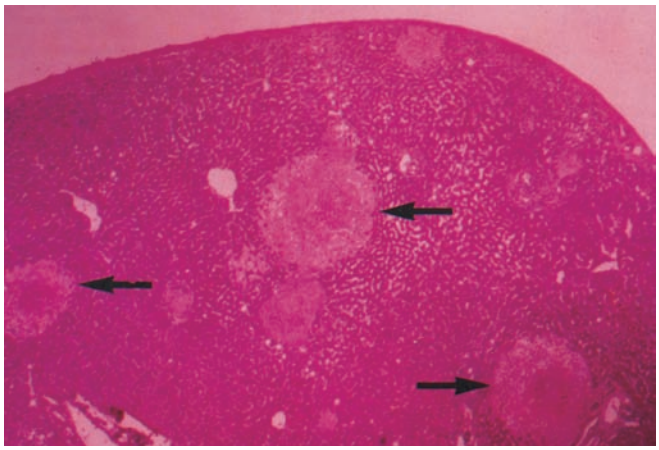

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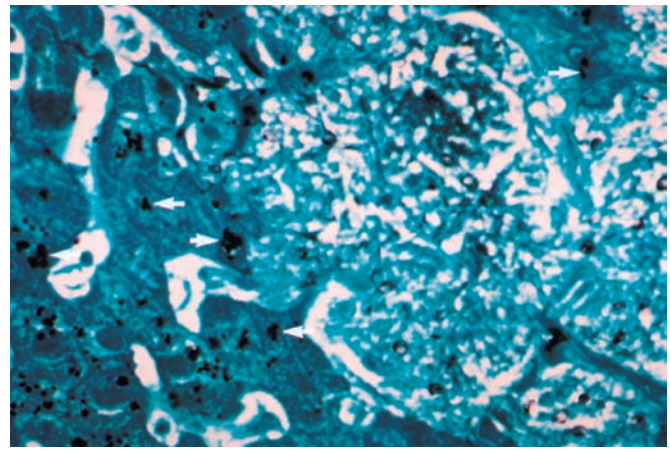

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Figure 135-2 Extrapulmonary pneumocystosis in a patient with AIDS on aerosolized pentamidine prophylaxis presented as a splenic mass lesion with abdominal pain. The computerized body tomographic (CBT) scan reveals a mass lesion (**A**), seen after splenectomy on gross pathology (**B,C**) and on microscopic examination (silver stain, **D**). *(Used with permission of Dr. J. Davis Allen, Jr., New England Deaconess Hospital.)*

patient with a first episode of infection, the evolution is more gradual (often 2–5 weeks) and constitutional symptoms such as weight loss can be prominent. Subsequent infections may evolve more rapidly. In the cancer patient receiving chemotherapy or in the organ or bone marrow–stem cell transplant recipient, the use of corticosteroids, poor lung infection, abnormal pulmonary lymphatics (after heart, lung, or liver transplantation), and neutropenia may contribute to the absence of radiologically apparent disease. The rate of development of clinical infection is exacerbated by the presence of pre-existing lung disease (e.g., cyclophosphamide lung or pulmonary fibrosis) or other infections (e.g., CMV, *Legionella,* mycobacteria) (Fig. 135-2). In the organ transplant recipient, PCP most frequently occurs approximately 2 to 4 months after the initiation of immune suppression or during periods of increased immune suppression (pulsed corticosteroids, antilymphocyte therapies, CMV infection). The incidence and timing of infection vary between institutions, however, and can be dependent on the prophylactic regimens employed. In some series of patients receiving lung or heart–lung transplants the rate of asymptomatic isolation of *P. jiroveci* can be higher than expected, approaching 10% or higher.[33,34]

In AIDS patients without HAART, the presentation of PCP is often complicated by a variety of factors. Prophylaxis with aerosolized pentamidine or subtherapeutic levels of other antibiotics (e.g., dapsone, atovaquone) may delay or alter the presentation of disease and confound diagnostic assays. As in most immunocompromised hosts, coinfection with other organisms may accelerate the progression of disease or alter the radiographic pattern; in particular, CMV, *Histoplasma capsulatum, Legionella* spp., and mycobacterial species may contribute to the constitutional symptoms, hypoxemia, and the localization of pulmonary lesions.

Acute exposure to *Pneumocystis* is rarely documented. In animal models, inoculation of *P. jiroveci* induces a neutrophilic infiltrate that is rapidly (2–3 days) replaced with lymphocytes and macrophages. Similarly, in transplant recipients and despite therapy with cyclosporine, *Pneumocystis* induces lymphocyte- and neutrophil-predominant infiltration into the lungs acutely, followed by macrophage infiltration and clearance of organisms. This contrasts with the macrophage- and neutrophil-predominant infiltrates seen in AIDS patients with acute disease. The lymphocytes are primarily T lymphocytes with normal CD4/8 ratios. Coinfection with CMV and other pathogens will be detected in more than half of *Pneumocystis*-infected patients and likely play a role in the individual immune response of each patient.[21,22] The nature of the immune suppression determines the types of other opportunistic pathogens that coinfect the compromised host and the overall risk of PCP. When cyclosporine began being used widely as an alternative immunosuppressant agent to azathioprine in solid-organ transplantation, the incidence of PCP increased among susceptible transplant recipients.[35] The subsequent development and use of tacrolimus seemed to increase the risk further.[36] The net state of immunosuppression these complex patients experience appears to play a bigger role than any single agent.

EXTRAPULMONARY PNEUMOCYSTOSIS

Pneumocystis was known to cause extrapulmonary disease in the pre-AIDS era, but metastatic infections have been most commonly observed in patients with untreated AIDS. Even in the untreated AIDS population, the incidence of extrapulmonary *Pneumocystis* infection is probably less than 1% of cases.[37] It has been thought that susceptible AIDS patients might be more likely to develop extrapulmonary disease while on inhaled pentamidine prophylaxis since this modality of prevention is largely lung-specific and does not achieve significant systemic drug levels like TMP-SMX. The evidence for this is minimal and difficult to assess with a low incidence of extrapulmonary disease. The diagnosis of extrapulmonary disease is challenging, and clinicians must have a high suspicion to identify infection outside the lungs. Respiratory disease may be minimal or absent in patients with extrapulmonary infection. In addition to the liver and spleen, sites of extrapulmonary disease have included eye, ear, lymph nodes, thymus, skin, mastoids, ascites, gastrointestinal tract and omentum, pleura, kidney, bone marrow, pancreas, and adrenal glands, and it has been reported as a cause of thromboembolic disease. Vasculitis has been reported due to *P. jiroveci* as a cause of ischemic necrosis of the digits and has been associated with granulomatous inflammation on tissue biopsies.[38]

The presentation of extrapulmonary infection is generally a mass lesion with accompanying fever, sweats, and malaise. Visual loss may accompany retinal lesions, hepatitis with liver impairment, and ascites and gastrointestinal tract obstruction with peritoneal and omental lesions. By computed tomographic (CT) scan, many nonenhancing, low-attenuation masses, often with necrosis and/or hemorrhage, may be seen in the liver or spleen (Fig. 135-2). Calcification may occur at the edge of such necrotic lesions during the acute infection, often in the hepatic or renal parenchyma. Histopathology will demonstrate granulomas with giant cells, calcification, or cavities. Distant sites may also contain the same frothy hyaline material seen in the alveoli in pulmonary disease (Fig. 135-3). *P. jiroveci* may be seen adherent to the blood vessel walls with myointimal inflammation and thrombosis. Dual infections at extrapulmonary sites may occur with other opportunistic organisms just like in the lung, including mycobacteria, *Histoplasma*, *Legionella*, other fungi, or common bacteria. Unless superinfection has occurred or splenic rupture or other life-threatening condition is imminent, systemic treatment of multiple small abscesses due to *Pneumocystis* infection should be adequate without surgical intervention.

THORACIC IMAGING

Imaging modalities useful in clinical assessment for PCP include chest radiography, nuclear medicine techniques, and CT scanning.

■ THE CHEST RADIOGRAPH

The chest radiograph plays a central role in the diagnosis of PCP (Figs. 135-4 and 135-5). No radiographic pattern is pathognomonic for *Pneumocystis* infection. PCP presents with hypoxemia and fever without significant sputum production and is more often than not, a diffuse interstitial process on chest radiograph.[39] The radiographic pattern ultimately depends on the patient's underlying or accompanying disease, state of immunosuppression, and duration of infection. Sometimes the chest radiograph is normal despite overt pulmonary disease. More often, the early stage of PCP is manifested by fine, bilateral, perihilar, diffuse infiltrates that progress to an interstitial alveolar butterfly pattern; from the hilar region, the infiltrates often spread to the apices or bases. Despite therapy, this pattern can often be succeeded in 3 to 5 days by progressive consolidation, the appearance of air bronchograms, and complete opacification of the lung fields. Unusual courses and patterns are often observed: nodules, unilateral infiltrates, or even lobar consolidations right from the start (Figs. 135-4 and 135-5). Small pleural effusions may also occur. Distortions in pattern are commonly produced by prior irradiation, drug-induced pulmonary injury, or concurrent infections with other organisms. The patient with recurrent disease may develop chronic interstitial markings, small cysts, or honeycombing on chest radiograph. The distribution of cysts in pneumocystosis, when present at all, is more often diffuse, whereas peripheral or apical bullae are often seen without infection in intravenous drug abusers. Rarely, cavitary disease is seen in the absence of other pathogens; however, *P. jiroveci* can superinfect fungal or mycobacterial cavities.[40]

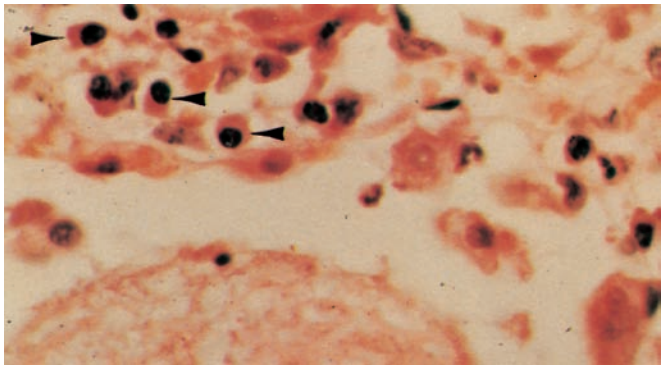
The use of aerosolized pentamidine for the therapy and prophylaxis of PCP in AIDS created some new problems in the diagnosis and treatment of pneumocystosis (Fig. 135-5). Breakthrough disease in patients receiving aerosolized pentamidine classically presents largely or solely in the upper lobes on chest radiograph. Similar presentations may be seen without pentamidine use, suggesting a predilection of infection for the upper lobes. Pneumothorax is another classic finding associated with PCP. Evaluating this particular complication is challenging, but in AIDS patients may be seen in close to 5%. Most pneumothoraces are spontaneous in nature, but roughly half can also be attributed to mechanical ventilation and complications of other procedures. Underlying cystic disease may be a contributing factor to this phenomenon and it may cause significant morbidity and mortality, particularly in patients already requiring mechanical ventilation.[41]

In lung transplant patients, both rejection of the lung allograft and infection often produce similar abnormal chest radiographs. In the first month after transplant, rejection of the allograft lung will cause radiographic changes in up to 75% of patients. These changes include nodular and interstitial infiltrates in the perihilar area and the lower lobes, which may progress to consolidation. These changes may also occur with infection, of which CMV is not uncommon. CMV may be indistinguishable from PCP or organ rejection without biopsy. After the first month, rejection less often yields radiographic changes (about 25%), and the radiographic findings of infection are more often similar to those of other immunocompromised hosts.

■ NUCLEAR IMAGING

Nuclear medicine scans are generally nonspecific and add little to the diagnosis of pulmonary pneumocystosis. However, a normal scan will generally exclude diffuse pulmonary infection due to *Pneumocystis*. Gallium citrate, technetium, indium-immunoglobulin, white blood cell, and diethylenetriamine penta-acetate (DTPA) scans are abnormal in more than 90% of patients with *Pneumocystis* infection. These may be most useful in following the resolution of infection. Gallium scintigraphy can be entirely normal for patients with opportunistic pneumonia with or without AIDS. Conversely, AIDS patients may have abnormal gallium scans in the absence of other infection. Gallium scans often become abnormal before the radiographic appearance of pulmonary disease. Lymph node uptake alone may indicate the condition formerly referred to as AIDS-related complex (ARC), due to HIV infection. The pattern of lymphoid interstitial pneumonitis (LIP) in children with AIDS is indistinguishable from that of PCP as well.[42] Diffuse pulmonary uptake may indicate occult infection in the asymptomatic patient, which would allow early intervention for therapy or prophylaxis, but the cost of routine gallium scanning for AIDS patients outweighs utility when compared with the judicious use of antiviral or anti-*Pneumocystis* antibiotics based on CD4 cell counts, viral load measurements, or other clinical data, and are generally not used for these reasons.

The role of other nuclear medicine–based imaging scans remains unclear. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan imaging has been evaluated in a few small series. Abnormal uptake in the lungs has been seen in confirmed cases of PCP and has even been documented prior to the development of other abnormalities on routine chest radiography.[43] Thus, PET scans may be useful as an early diagnostic tool, although lacking the specificity required for the diagnosis and guidance of specific therapy.



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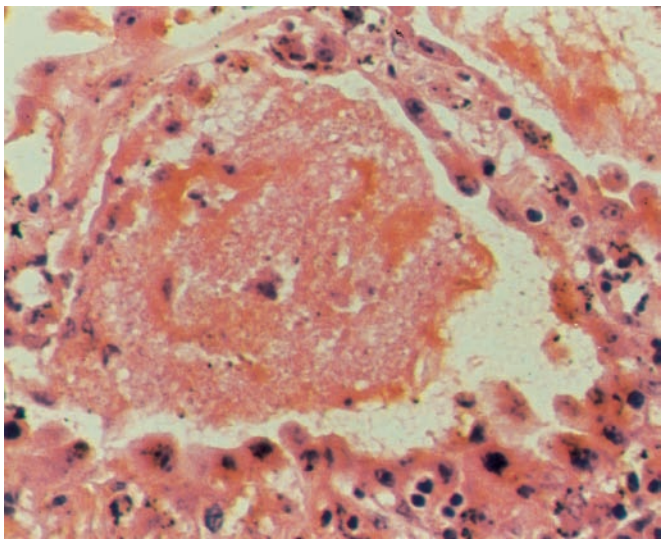

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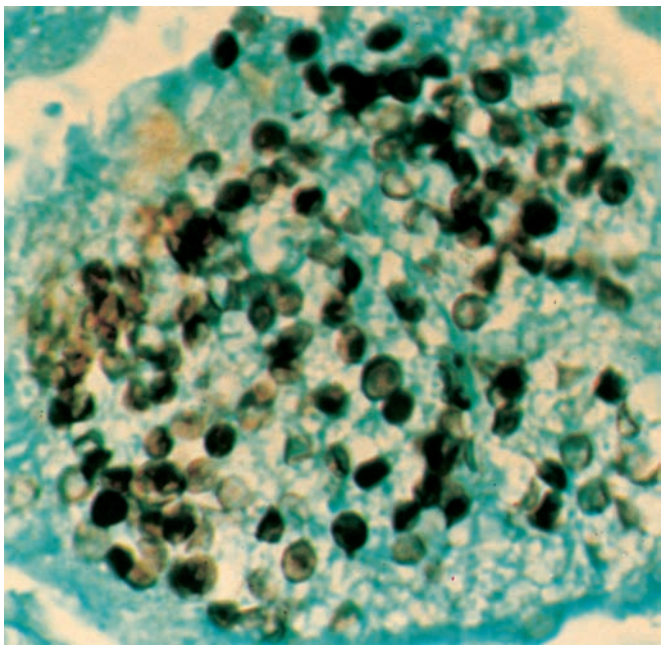

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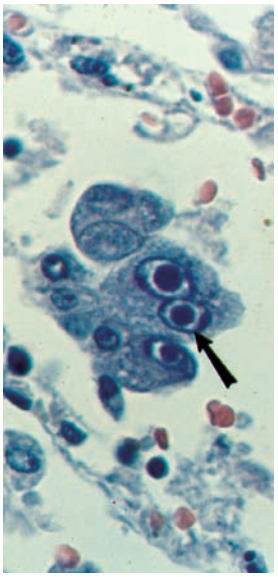

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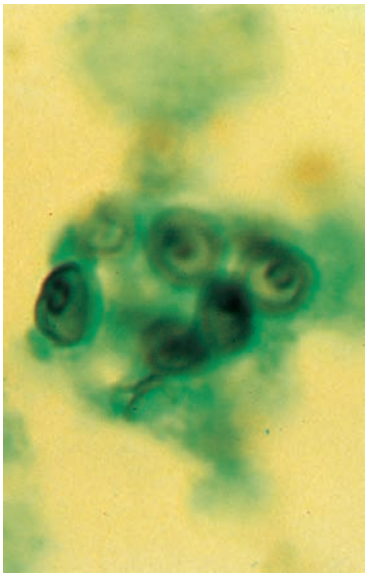

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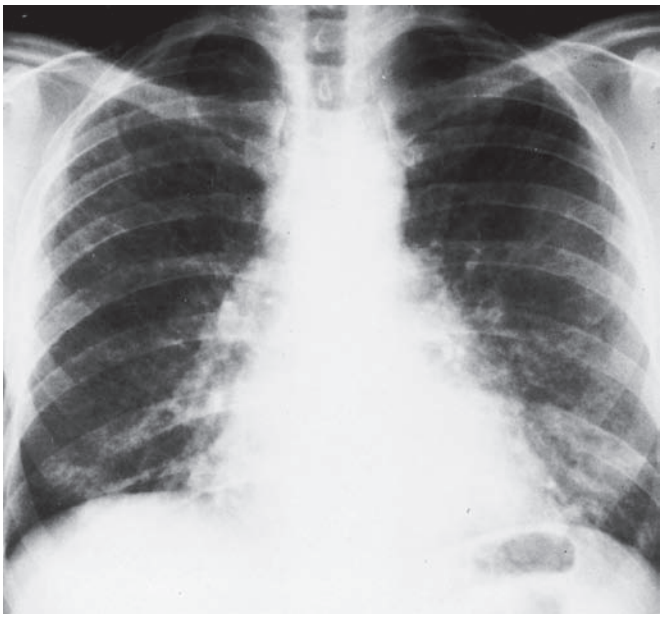

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Figure 135-3 *Pneumocystis jiroveci* pneumonia. **A.** Lung of a malnourished infant showing an intra-alveolar foamy exudate and plasma cells (*arrowheads*) in the interstitium (H&E stain, × 620). **B.** Typical alveolar exudative pattern from the lung of an adult with *Pneumocystis* pneumonia after therapy with corticosteroids. Swelling of the alveolar epithelial cells and interstitial edema are seen. Inflammatory response in interstitium is minimal (H&E stain, × 500). **C.** *Pneumocystis* in the form of thick-walled cysts within the foamy exudate (displayed by Gomori's methenamine-silver nitrate stain and brilliant green counterstain, × 1250). **D.** Cytomegalovirus inclusion bodies in alveolar macrophages in a patient with *Pneumocystis* pneumonia (H&E stain, × 720). **E.** *Pneumocystis* cysts in cytologic preparation of induced sputum from an AIDS patient (silver stain, × 1250). **F.** *Pneumocystis* pneumonitis. Typical chest radiograph showing bilateral, diffuse interstitial infiltrates extending from hilar area.

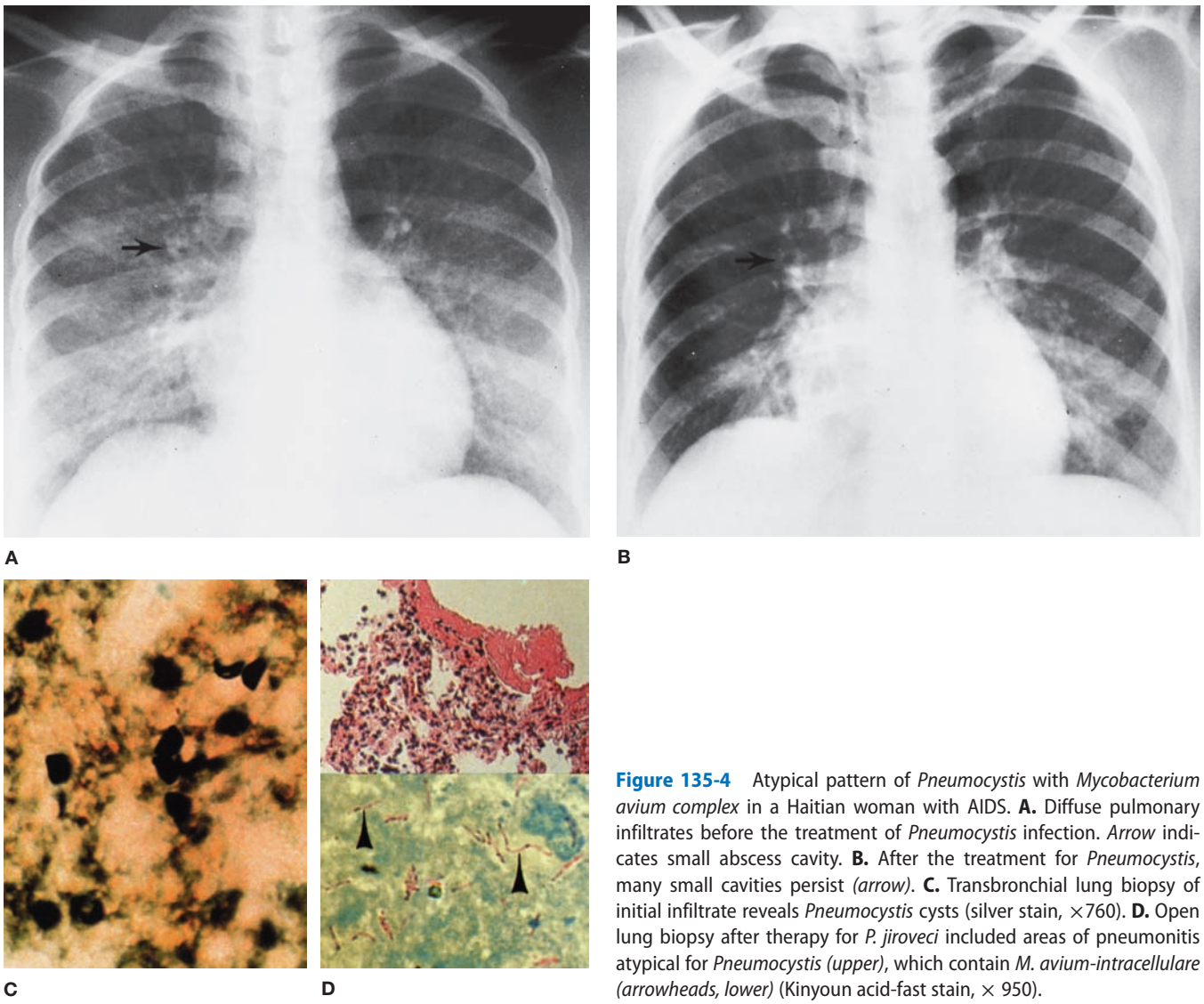


Figure 135-4 Atypical pattern of *Pneumocystis* with *Mycobacterium avium complex* in a Haitian woman with AIDS. **A.** Diffuse pulmonary infiltrates before the treatment of *Pneumocystis* infection. *Arrow* indicates small abscess cavity. **B.** After the treatment for *Pneumocystis*, many small cavities persist *(arrow)*. **C.** Transbronchial lung biopsy of initial infiltrate reveals *Pneumocystis* cysts (silver stain, ×760). **D.** Open lung biopsy after therapy for *P. jiroveci* included areas of pneumonitis atypical for *Pneumocystis (upper)*, which contain *M. avium-intracellulare (arrowheads, lower)* (Kinyoun acid-fast stain, × 950).

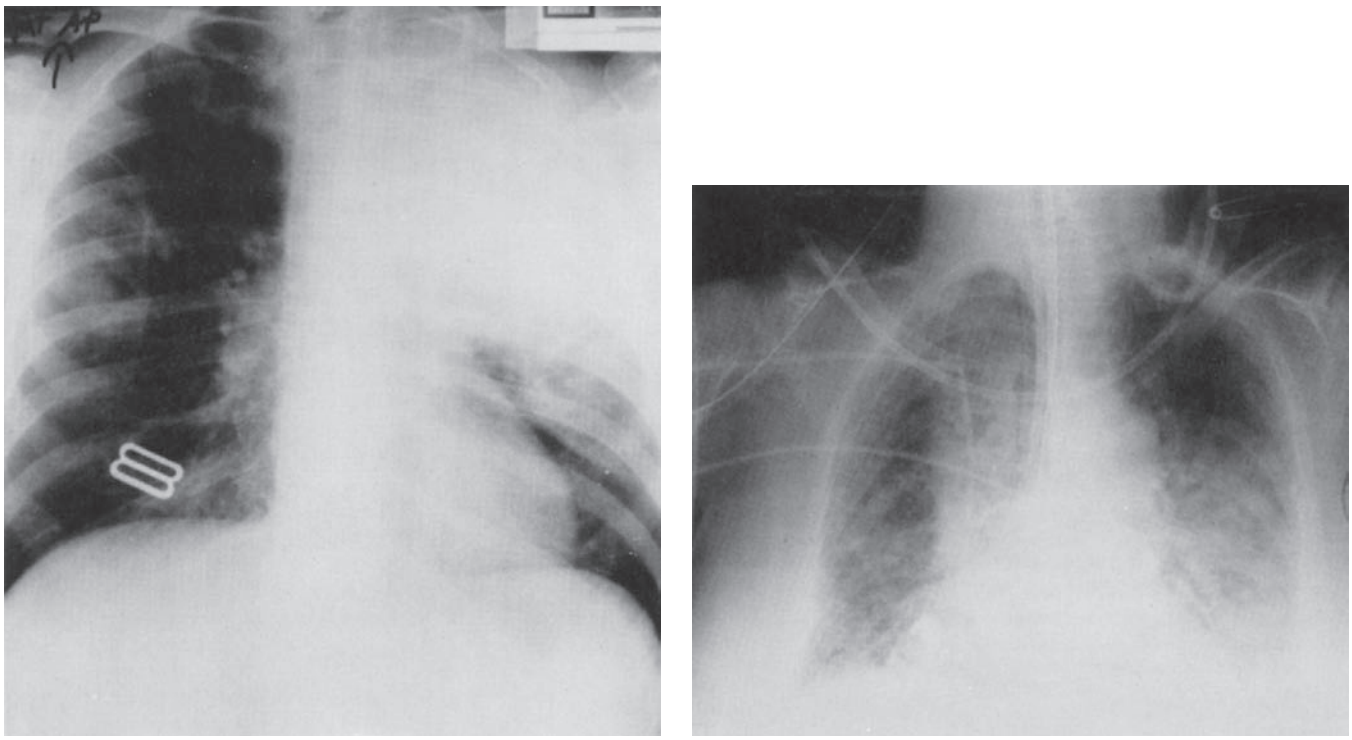
■ COMPUTED TOMOGRAPHY AND OTHER RADIOGRAPHIC DIAGNOSTIC TECHNIQUES

Sometimes, early in the disease process, chest CT may demonstrate abnormalities not appreciated on routine chest radiography. Among HIV patients, the most frequent pattern early in the disease process will be a ground-glass opacification in the central/hilar and apical regions of the lungs bilaterally.[44] In non–HIV-infected immunosuppressed patients, the opacification patterns may be more dense and distorting of the underlying lung architecture.[45] Resolution of abnormalities can be quickly appreciated by CT imaging as well in patients receiving appropriate therapy. Other imaging modalities, such as magnetic resonance imaging (MRI) scans and ultrasound imaging are probably better suited defining extrapulmonary lesions such as pneumocystomas occurring in the soft tissues or intra-abdominal organ systems (discussed above; see Fig. 135-2). Their role in isolated pulmonary disease remains undefined.

LABORATORY FINDINGS

A number of nonspecific indicators of pulmonary processes have been used in the presumptive diagnosis of PCP. In general, the patient will have a P_{O_2} less than 60 mm Hg and a respiratory alkalosis. The serum lactic dehydrogenase (LDH) enzyme will be elevated in almost all cases of PCP (over 300 IU/mL). Because LDH is likely a marker of underlying lung injury in PCP, the degree of elevation correlates with underlying hypoxemia and may have prognostic value.[46] Unfortunately, LDH is nonspecific, and should generally be avoided as a diagnostic tool alone in cases of PCP. Lymphoma, hemolysis, other infections, ischemia, and LIP may also raise the LDH level. Respiratory distress and respiratory failure requiring intubation carry a poor prognosis. The marked hypoxemia of PCP is accompanied by a PA_{O_2}–Pa_{O_2} gradient rise; gradients over 30 mm Hg at the start of therapy are associated with a high mortality (and are an indication for the use of adjunctive corticosteroid therapy—see below). Both LDH and the arterial oxygenation gradient will return to normal with successful therapy. Another nonspecific indicator of lung injury in PCP is the angiotensin-converting enzyme (ACE) level (also nonspecific in that it can be elevated by smoking and sarcoidosis, among other causes). KL-6, a mucin-like glycoprotein expressed on pneumocytes and bronchiolar epithelial cells can also be detected in the serum of patients with PCP, but once again is likely a nonspecific marker of pneumonitis in general.[46] While pulmonary function testing may reveal abnormalities in oxygen exchange and compliance in PCP, they are not useful diagnostically in the acute setting.

Recent interest has been garnered by the plasma-based (1,3) β-D-glucan assay. (1,3) β-D-glucan is a polysaccharide monomer found in a number of fungal cell walls including *Pneumocystis* species. It initially gained use as diagnostic assay in other forms of invasive fungal infections including candidiasis, aspergillosis, and fusariosis.[47] Other



A B

Figure 135-5 Atypical pneumocystosis. **A.** Upper lobe pneumonia in an AIDS patient on prophylactic aerosolized pentamidine therapy for a history of *Pneumocystis* pneumonia. The patient had both *P. jiroveci* and *Legionella pneumophila* infections. **B.** Persistent pulmonary infiltrates in a patient undergoing chemotherapy for non-Hodgkin lymphoma. Despite 21 days of therapy for *P. jiroveci,* oxygenation and pulmonary infiltrates failed to improve. An open lung biopsy revealed cytomegalovirus pneumonitis (which responded to therapy with ganciclovir) and drug-induced interstitial fibrosis.

opportunistic fungi, like *Mucor* species and *Cryptococcus neoformans* have little-to-no (1,3) β-D-glucan in the cell walls and the assay has not been useful for these infections. The presence of (1,3) β-D-glucan in *Pneumocystis* cell walls, however, makes this assay an attractive noninvasive laboratory test for PCP. A number of case series have examined the use of the assay and found a high sensitivity (>90%).[48–54] Because β-D-glucan can be found in other fungal infections, the specificity is lower (less than 80%) in an unselected population. False positive assays occur with immunoglobulin and albumin therapies, and after hemodialysis and exposure to gauze. The assay also has limitations as a marker of response to therapy. Small retrospective evaluations have shown that some patients actually experience serum elevations of (1,3) β-D-glucan while on therapy and showing clinical improvement.[55] The utility of this assay in determining prognosis or in therapeutic monitoring is unclear.

Given the ubiquity of the organism in the environment and the finding that the majority of children have detectable antibodies, use of serologic testing in the diagnosis of PCP is not recommended. Serologic testing may be complicated by inadequate antibody production in many immunosuppressed patients producing a lack of specificity and sensitivity in the diagnosis of acute disease.

SPUTUM EXAMINATION AND HISTOLOGIC DIAGNOSIS

Despite advances in imaging and laboratory testing, the gold standard for the diagnosis of PCP remains the identification of characteristic organisms on examination of pulmonary specimens (Table 135-3). The organism cannot be routinely cultured in the clinical laboratory, and thus direct visualization and correct identification are required.

TABLE 135-3 Diagnostic Techniques for *Pneumocystis jiroveci*

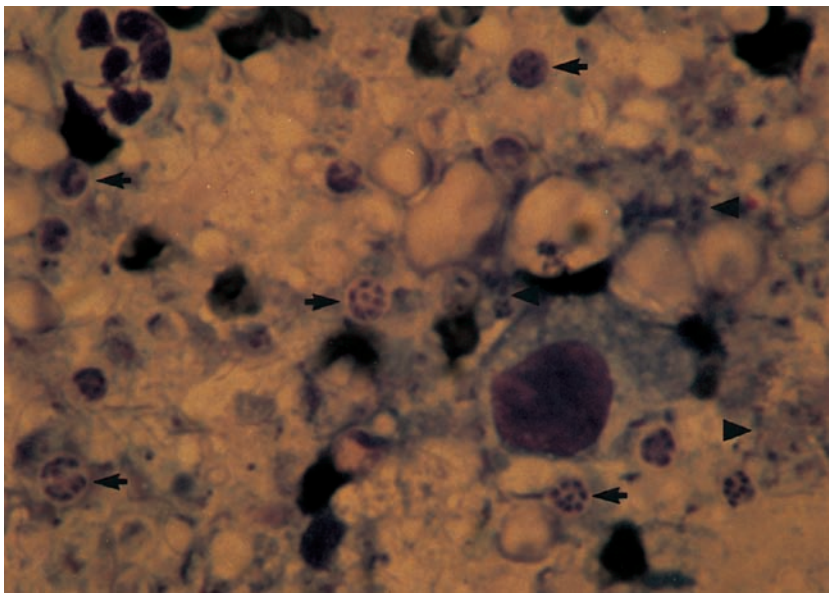
Technique	Yield	Complications	Comments[a]
Routine sputum	Poor	Rare	Routine cultures needed
Induced sputum	30–75%	Rare	First choice; excellent in AIDS
Transtracheal aspiration	Fair (with experience)	Common: bleeding, subcutaneous air	Rarely worthwhile
Bronchoalveolar lavage (BAL)	>50% (>95% in AIDS)	Bleeding, aspiration fever, bronchospasm	Wedged terminal BAL with immunofluorescence
BAL/brushing	As for BAL alone	As for BAL	Not useful for *P. jiroveci*
BAL/transbronchial biopsy	>90% (all patients)	See BAL; pneumothorax	Impression smears; cultures/pathology
Open lung biopsy	>95% (all patients)	Anesthesia, air leakage, altered respiration, wound infection	"Gold standard" noninfectious/infectious processes; large sample
Needle aspirate	≤60%	Pneumothorax, bleeding	Best in localized disease

[a]*All samples should be cultured and stained for bacteria (including mycobacteria), fungi, and viruses, and examined for protozoa. Optimal procedures will depend on the locally available expertise.*

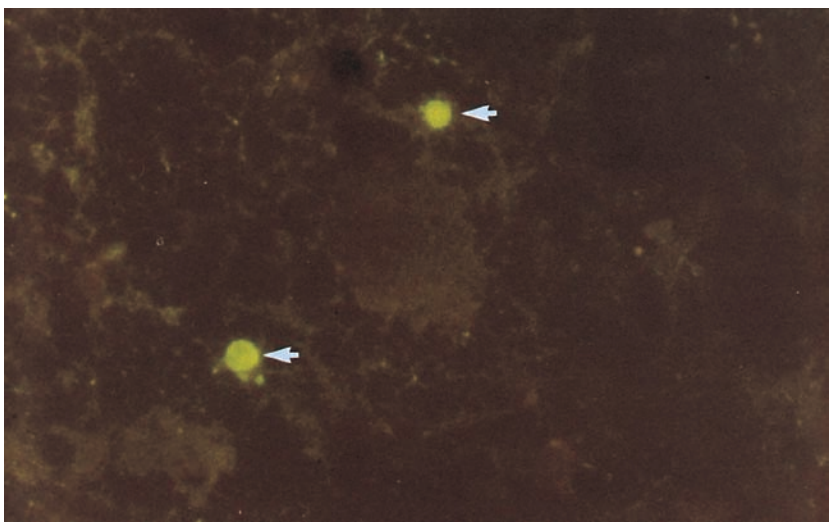
The methods used in making the diagnosis have been changed by the use of the induced sputum examination and bronchoalveolar lavage (BAL) without biopsy, and by immunofluorescent staining using monoclonal antibodies to *P. jiroveci*. As a result, the morbidity associated with diagnostic procedures has been reduced at the same time the diagnosis of coinfecting pathogens has been reduced.

The initial step in the diagnosis of PCP is a realization that the patient is at risk for opportunistic infection. In the appropriately identified patient, the first procedure should be to obtain a sputum sample for bacterial, mycobacterial, and fungal stains and cultures to look for any of the infectious processes consistent with the presentation of pulmonary infection in an immunocompromised host. The selection of diagnostic tests will depend on the status of the patient (ability to cooperate with sputum induction), the distribution of pulmonary disease, and the urgency of diagnosis. Given the opportunity for only a single procedure, or a mixed radiographic appearance, a more invasive test may be preferred. The diagnostic test of choice is the induced sputum examination coupled with direct immunofluorescent staining for *P. jiroveci* along with more routine smears and cultures. Induced sputum may be collected after 20 to 30 minutes of exposure to aerosolized hypertonic saline or water, or after oral hydration. Some bacteria and fungi may not survive the hypertonic saline used for induction, and the yields for these pathogens do not exceed those of routine sputum samples.

Before the availability of immunofluorescent antibody staining techniques, smears were prepared from the mucoid, nonpurulent portion of the specimen and stained with Giemsa or Diff-Quik stain for intracystic bodies, or sporozoites, and trophozoites (see Fig. 135-6). Other usable stains include toluidine blue O or silver, which readily stains only the cyst wall. Because cysts represent only 5% to 10% of the organism burden, this staining procedure may miss the majority of trophozoites in any one sample. Many laboratories prefer the Giemsa to the more complex silver stain, for ease of use and also because the Giemsa, along with the Wright stain, can be used to detect trophozoites, the most common form of the organism in the alveolus. Giemsa-stained smears, unfortunately, are more difficult to read and require expertise to perform and interpret correctly. Overall, Diff-Quick staining (a modified Wright stain) is somewhat less sensitive, while calcofluor white and silver stains may be the most predictive for routine clinical use when monoclonal antibody staining is not available.[56]



A



B

Figure 135-6 Rapid staining of sputum and biopsy specimens for *P. jiroveci*: **A.** Impression smear (touch preparation) from the cut surface of a human lung biopsy stained with Diff-Quik stain reveals the nuclei of clumped trophozoites *(arrowheads)* and of the sporozoites within cysts *(arrows)*. **B.** Human *P. jiroveci* cysts in an induced sputum specimen that has been stained with fluoresceinated monoclonal antibodies raised to the 116-kd surface antigen of human *P. jiroveci*.

The staining method of choice for respiratory secretions from BAL specimens is also direct immunofluorescent staining with monoclonal antibodies (Fig. 135-6). Rapid staining with immunofluorescent monoclonal antibodies directed against surface antigens of *P. jiroveci* has a high degree of specificity and a sensitivity for screening of sputum smears. This method is costly, but significant cost savings can be achieved in terms of the rapidity of specimen preparation and examination. This technique may detect 12% to 16% of *Pneumocystis* beyond standard histologic stains.[57] (Fig. 135-2). Some commercially available antibodies produce high backgrounds and some nonspecific staining; each laboratory must individually optimize the fluorescent staining technique. Smears may be improved through the use of mucolytic agents (Mucomyst, dithiothreitol) in preparation.

The heightened sensitivity of immunofluorescent staining, coupled with the use of either induced sputum or BAL samples, may detect "infections" that are of uncertain clinical significance, particularly when other pathogens are identified. Owing to the broad antibacterial spectrum of TMP-SMX, response to therapy is only a partial confirmation of the existence of PCP. AIDS patients often have residual organisms in their sputum for many weeks after successful treatment, representing dead or nonviable *Pneumocystis*. This makes follow-up testing of sputum in infected patients of little value in tracking response to therapy.[58] However, organisms found in the symptomatic non–AIDS-immunosuppressed patient should suggest disease meriting therapy. This disparity may be exacerbated by the findings that organismal burden tends to be less in the infected transplant

recipient compared to the HIV-infected patient with PCP.[59] Of note, because of the vagaries of sample collection and distribution of infection, a negative smear from any single respiratory specimen cannot be used to exclude PCP.

PCR techniques have been developed to increase the sensitivity of detecting *Pneumocystis* in respiratory specimens. Numerous techniques have been applied, using single-step, nested, and quantitative real-time PCR assays. Most targets for PCR have included areas of ribosomal RNA and the MSG genes. Nested PCR techniques in general may be more sensitive than both routine microscopy and immunofluorescent monoclonal antibody staining, while suffering a loss in specificity in the diagnosis of PCP.[60,61] False-positive results and low positive predictive values limit the ability of molecular assays to distinguish between asymptomatic colonization and infection.[62] Using real-time quantitative PCR may increase the specificity of the approach if clinically relevant cutoff values can be established. A multicenter, prospective study using a commercially available real-time PCR for *Pneumocystis* (targeting mitochondrial ribosomal large subunit genes) showed that the specificity may be increased to >90% while positive predictive values remain limited. This study included primarily non–HIV-infected patients where the organismal burden may be lower, helping to increase the specificity.[63] These assays require further development and validation. The use of such assays in blood samples has not yet been validated.

The histopathology of *Pneumocystis*-infected lung is usually distinctive and diagnostic even when organisms cannot be identified, which is uncommon. In the adult, the disease is predominantly alveolar. The airspaces are filled with a foamy eosinophilic exudate and appear honeycombed. The intra-alveolar exudate consists of organisms, large amounts of surface glycoprotein, proteinaceous exudate from the lungs, and debris of macrophages and inflammatory cells. At the same time, the alveolar interstitium is infiltrated by polymorphonuclear leukocytes and lymphocytes (Fig. 135-3). Patchiness in the distribution of disease within the lungs is common. In contrast to the adult disease, PCP in malnourished infants has a major interstitial component: the interstitium is filled with fluid, plasma cells, and lymphocytes. These formed elements seem to overflow into the airspaces, which are also filled with a frothy eosinophilic exudate. In both forms, the organisms usually appear intermingled with alveolar macrophages in the alveolar exudate (Fig. 135-3). By light microscopy, trophozoites predominate numerically (in more than 90% of the organisms), but cysts are more readily identified.

The earliest indication of disease is the presence of organisms adjacent to the epithelial layer. Cysts or clumps of trophozoites may be seen, with a minimal inflammatory infiltrate. As the number of organisms increases, epithelial injury occurs. The mechanism of alveolar epithelial cell injury is uncertain. The organism preferentially adheres to and injures the surface of type I alveolar epithelial cells, while the adjacent type II cells undergo hyperplasia. Desquamation of alveolar epithelial cells occurs early in the course of disease; denuded basement membrane is occasionally seen. Epithelial injury is followed by mononuclear cell infiltration in the interstitium. Organisms may be seen within vacuolated alveolar macrophages, as well as free in the proteinaceous and cellular debris that fills the airspace (Fig. 135-3).

In AIDS, the interstitial inflammation is less marked than in other adult forms of PCP, and greater numbers of both cysts and trophozoites are seen in the alveoli. While HIV-infected alveolar macrophages appear to bind organisms normally, internalization of *P. jiroveci* may be impaired and clearance of organisms delayed. Many dead macrophages are found in BAL samples from HIV- and *Pneumocystis*-infected lungs. In children with AIDS, the appearance is similar to that of adult AIDS, with the addition of some degree of plasma cell infiltration of the interstitium. Although hyaline membranes may line alveoli, they are not diagnostic of infection with *Pneumocystis*, since oxygen toxicity, alveolar proteinosis, or acute respiratory distress syndrome (ARDS) can evoke similar changes. These may coexist with *Pneumocystis* infection. In pediatric AIDS, LIP, without evidence of an infectious origin, and bacterial pneumonia may mimic or coexist with PCP.

Even when chest radiography indicates that PCP has cleared, interstitial fibrosis is likely to be found at rebiopsy or autopsy. Unfortunately, the contribution of *Pneumocystis* to the residual fibrosis is often obscured by the tendency of superimposed infection, therapeutic agents, or intervening radiation therapy to elicit inflammatory responses in the interstitium. Subsequent infections are likely to present with more rapid progression to hypoxemia due to persistent restrictive lung disease. In AIDS patients, pulmonary interstitial fibrosis has been observed in up to 27% of autopsy and biopsy series, and emphysematous changes are also common. These changes do not appear to be associated with prior *Pneumocystis* infection. A pathogenic role for chronic or recurrent viral (HIV, CMV, etc.) infections or immunologic injury has been postulated.

When looking for common coinfecting agents, it is important to note that demonstration of CMV by culture is not helpful in regard to the presence of CMV disease. Coinfection due to CMV and *P. jiroveci* is common among susceptible hosts and may necessitate treatment for both entities. Diagnosing CMV and other coinfections should always be a priority when managing the patient with PCP.

INVASIVE DIAGNOSIS OF PNEUMOCYSTOSIS

In the immunocompromised patient with significant pulmonary disease, the inability to make a diagnosis of infection on examination of the induced sputum, or the failure to respond to appropriate therapy should lead to a more invasive diagnostic procedure: BAL (with biopsies if possible), radiologically guided needle aspiration (for accessible cystic or mass lesions), or open lung biopsy. The choice of the specific test depends on the clinical condition of the patient and the expertise available at the institution (Table 135-3).

Invasive procedures for the diagnosis of PCP fall into several categories: tracheal aspiration, fiberoptic bronchoscopy, transthoracic aspiration, and open lung biopsy. Attempts to avoid the use of invasive procedures by resorting to empiric therapy run a great risk of inappropriate medications and undesirable side effects, missing coinfecting organisms, as well as delaying effective therapy. Pulmonary specimens obtained by invasive approaches should be processed for bacterial (including mycobacteria, *Nocardia, Actinomyces,* and *Legionella*), fungal, and viral evaluation in addition to making slides for rapid staining with fluorescent antibodies, toluidine blue O, silver, Diff-Quik, Giemsa, or Wright stain. Early diagnosis can be made and therapy initiated on the basis of such smears, especially in cases of AIDS.

■ TRACHEAL ASPIRATION

The yield from transtracheal aspiration is generally low, and the hazards, particularly in inexperienced hands, are high. In intubated patients, respiratory secretions should be carefully smeared on slides, stained, and examined. If the physician or the microbiology technician has had little experience with *Pneumocystis* smears, and direct immunofluorescence techniques are not available, fiberoptic bronchoscopy or open lung biopsy is indicated for the immunocompromised patient with pulmonary disease, followed by methenamine silver staining of the tissue sections.

■ FIBEROPTIC BRONCHOSCOPY

The importance of knowing the success rate of the institution as a basis for selecting the optimal invasive technique is illustrated by published reports of diagnostic yields from fiberoptic bronchoscopy. In patients with AIDS, use of bronchoscopy and BAL for diagnosis can yield positive results in >90% of cases. The yield of BAL versus

induced sputum alone in cases of PCP in AIDS remains unstudied.[64] Because the organismal burden is oftentimes less in the non–HIV-infected host with PCP, sputum may be less revealing and bronchoscopy with BAL may have a higher yield.[65] Sampling from multiple lobes may increase the diagnostic yield even further.[66] As a rule, institutions with a large experience with PCP are more successful in identifying the organism from respiratory samples. Indeed, when BAL and transbronchial lung biopsies are part of the diagnostic procedure, the success rate often exceeds 90% in these settings.[66] To improve yield, lavage specimens must be gathered from a wedged bronchoscope with at least 50 mL of physiologic saline for alveolar washings. Lavage should be performed from the upper lobes if diffuse disease is present. Trophozoites predominate in bronchial washings, so Giemsa or Diff-Quik staining should be performed routinely to back up other staining methods. In general, lung biopsy is not essential for the diagnosis of PCP in AIDS patients. Patients suspected of harboring multiple pathogens may still benefit from any of the more invasive procedures. Although bleeding from the biopsy site is common (in up to 25% of patients), it is rarely life threatening if the coagulation indices are normal.

PERCUTANEOUS NEEDLE ASPIRATION

High success rates when using percutaneous needle aspiration in finding *P. jiroveci* have also been reported in patients with PCP, particularly when aspiration of localized radiologic infiltrates is performed under fluoroscopic or CT guidance. Yield may be similar to other approaches at close to 90%. Needle aspiration is also advantageous when a focal process (e.g., abscess) is peripherally located in the lung parenchyma. Pneumothoraces may occur in up to 20% of patients as a result of the procedure, making this a less ideal first-line diagnostic approach.[67]

LUNG BIOPSY

Thoracotomy or video-assisted thoracoscopic (VATS) procedure followed by open lung biopsy affords the most unequivocal avenue for the diagnosis. Although the patient may be quite ill by the time this step is taken, in the hands of skilled surgeons these procedures are generally safe, even for the patient on mechanical ventilation. Thoracoscopic biopsies can often be performed as minimally invasive procedures. VATS may provide histologic information that allows separation of significant infection of the lower respiratory tract from colonization of the upper respiratory tract by a variety of respiratory pathogens. This information may be critical to therapeutic decision making, as in the use of antiviral agents in the treatment of CMV infection.

Accurate diagnosis in the non-AIDS patient may require invasive procedures (Table 135-3). The choice of the procedure depends on the clinical state of the patient: patients who have an uncorrectable coagulopathy are poor candidates for invasive testing. Patients with atypical presentations or unique epidemiologic exposures have a higher incidence of dual processes or non-*Pneumocystis* infections. Institutions unfamiliar with the proper technique for sampling or handling specimens for the diagnosis of *Pneumocystis* infection should probably use open lung biopsies, which are likely to be more rewarding. Because disease caused by PCP may progress rapidly, the likelihood of success in treatment is greatest at the outset. Therefore, invasive procedures to disclose the organism and any secondary infections should be undertaken early in the course of the disease.

The demonstration of *Pneumocystis* organisms is necessary for the diagnosis in the transplant recipient. The incidence of PCP is affected by the use of prophylaxis, the degree of immunosuppression, and regional and underlying disease-specific variations.[68] Empiric therapy is more reasonable in the untreated AIDS patient not receiving prophylaxis; however, dual infections remain common. Empiric therapy in the transplant recipient may delay specific treatment for other opportunistic pathogens and subject the patient to avoidable toxicities of TMP-SMX or pentamidine. Demonstration of infection due to *P. jiroveci* should lead to successful treatment, barring superinfection, ARDS, or other complications.

PROPHYLAXIS AND PROPHYLACTIC STRATEGIES

In the pre-AIDS era, the prevention of PCP was associated with time-limited antibiotic use in the setting of prolonged neutropenia due to cancer chemotherapy. Because many of the chemotherapeutic regimens included corticosteroids, the incidence of PCP was predictably high. Prophylactic TMP-SMX was pioneered by Walter Hughes and his colleagues at the St. Jude's Children's Research Hospital for use in children with hematopoietic malignancies and severe combined immunodeficiency (SCID) syndrome.[69] This combination agent became the standard for prophylaxis in the AIDS era as well and continues to this day. In pre-HAART AIDS, such prophylaxis was lifelong rather than time-limited in the absence of immune reconstitution. With HAART, prophylaxis can generally be stopped in patients with undetectable viral loads for at least 3 months and CD4 counts that surpass 200 cells/mm^3 for that period.[70] Without HAART, however, more than 60% of those cured of PCP in AIDS will suffer a recurrence within 1 year. Although TMP-SMX is generally well tolerated among non–HIV-infected individuals with side effects reported in <10%, the incidence of side effects among the AIDS population appears to be higher. In at least one study, the incidence of any one side effect was reportedly as high as 80%.[71] The increased incidence of side effects due to TMP-SMX in AIDS patients has led to the development of alternative regimens for prophylaxis against *P. jiroveci*.

The use of appropriate prophylaxis should prevent PCP. In AIDS patients and in transplant recipients, the failure to utilize appropriate prophylaxis is generally a reflection of the toxicities associated with the necessary medications or a failure in compliance due to the large number of medications these patients may be expected to consume. This can be particularly problematic in solid-organ and hematopoietic stem cell transplant recipients. Routine anti-*Pneumocystis* prophylaxis is recommended for any transplant center that otherwise might have an incidence of PCP of at least 3% annually.[72] Widespread use of prophylaxis and the diversity of immunosuppressive regimens among transplant centers obscures the true incidence. The highest risk is generally thought to be within the first 6 months after the transplantation, though numerous factors influence that risk. For that reason, prophylaxis should be maintained in the stable transplant patient for at least 6 months after surgery. In lung transplantation and in stem cell transplant recipients with significant graft-versus-host disease or overall poor recovery, risk for PCP remains high, and prophylaxis may need to be lifelong.[17] Many cardiac and liver transplant programs also advocate lifelong prophylaxis. It should be noted that in transplant centers without a fixed, high incidence of PCP, prophylaxis may be reserved for patients in whom chronic, high-level immune suppression, especially with corticosteroids (now uncommon), is needed to maintain graft function. If immune suppression cannot be reduced after a course of treatment for PCP, prophylaxis should be maintained indefinitely. Recent studies have documented cases of PCP occurring in transplant recipients several years after transplantation in patients not taking effective prophylaxis.[73] In cases where prophylaxis is not deemed necessary or initially withheld, reinstitution should be considered with increases in immune suppression, including those resulting from pulse corticosteroids or antilymphocyte antibody therapies in transplantation, CMV infection in AIDS or transplantation, treatment of graft-versus-host disease following bone marrow transplantation, new-onset neutropenia, or similar conditions.

In untreated HIV infection, adults and adolescents with CD4 counts of fewer than 200 cells/mm^3 (or <15%–20% of the total

lymphocyte number), unexplained fever for more than 2 weeks, a history of oropharyngeal candidiasis, or rapid progression of disease, as measured by rising viral titers or falling CD4 counts, should receive evaluation and prophylaxis. Prophylaxis in HIV-infected children is recommended for CD4 counts of fewer than 1500 cells/mm^3 for less than 11 months of age, fewer than 1000 cells/mm^3 between 1 and 5 years, or fewer than 500 cells/mm^3 after age 5, and in any child in whom the CD4 percentage falls to less than 24%. The greatest risk for children may be in the 3 to 6 months of age range, making the identification of the HIV-infected infant critical to survival.

Resistance of *P. jiroveci* to antibiotics has been proposed based on some clinical failures while receiving prophylaxis. Resistance *may* develop in association with mutations in the dihydropteroate synthase gene of *P. jiroveci,* but is extremely rare. Predictably, the use of prophylaxis both for *P. jiroveci* and for yeasts and the resultant improved survival of HIV-infected persons have increased the relative frequency of other causes of pulmonary disease, including both infectious (e.g., CMV, other invasive mycosis, mycobacteria) and noninfectious processes.

TMP-SMX (cotrimoxazole) is the agent of choice for the prevention of *Pneumocystis* infection in any patient who can tolerate this fixed-combination agent. At a dose of one single-strength tablet per day (80-mg TMP and 160-mg SMX), a wide variety of opportunistic infections are prevented, including *P. jiroveci*, *Toxoplasma gondii, Listeria monocytogenes, Isospora belli*, and susceptible bacteria, including some strains of pneumococci, *Haemophilus influenzae,* community-acquired staphylococci, and some enteric gram-negative rods. Another common opportunistic infection, nocardiosis, which is often sensitive to TMP-SMX, may be incompletely prevented by prophylaxis.[74] While the protection against *T. gondii* is incomplete in AIDS patients (80%–90% effective) at this dosage (generally a double-strength tablet a day might be used in seropositive persons without a history of *T. gondii* infection), breakthrough infection has not been seen in transplant recipients (notably cardiac) or in cancer patients. Studies of low- and high-dose regimens for prophylaxis (single- or double-strength TMP-SMX) in HIV-positive subjects suggest no advantage to the higher dose (no disease in either group when compliant) and earlier occurrence of toxicity in the high-dose group.[75] Administering TMP-SMX three times weekly has also been widely utilized to cut down on potential toxicity but sacrifices other advantages. Randomized studies of HIV-infected patients have shown that using TMP-SMX double-strength tablets three times weekly compared to daily may have a slightly higher risk for PCP, with adverse events more common with the higher strength tablets daily.[76]

Drug toxicity is commonly observed even with low-dose; mild bone marrow suppression occurs, but is generally overestimated. Such bone marrow toxicity is notable in combination with other marrow suppressive agents (e.g., azathioprine, ganciclovir, cyclophosphamide, allopurinol, zidovudine), malnutrition, or infection (HIV, mycobacteria, or CMV). Most toxicity has been related to serum levels of the sulfa component in AIDS. Some patients will not tolerate any dose of sulfa drugs, owing to significant rash (occasional Stevens–Johnson syndrome), hepatitis, eosinophilic nephritis, pancreatitis, aseptic meningitis, or neutropenia. Generally, significant toxicities evolve within the first month of therapy. Hyperkalemia may be observed in the setting of normal renal function as a result of TMP interfering with the secretion of potassium in the renal distal tubule. This is reversible and more common during therapy than with prophylaxis. Patients taking TMP-SMX may benefit from laboratory monitoring of renal function, electrolytes, and cellular blood counts. In general, neutropenia should not be treated with folate as this has been associated with treatment failures. Both oral and intravenous desensitization regimens will allow the use of TMP-SMX in many patients otherwise intolerant of the combination. Reintroduction of TMP-SMX at reduced dose is often tolerated in AIDS patients not severely intolerant of this agent. This is generally preferable to the use of any alternative agent. Non–AIDS-immunocompromised patients appear to be less able to tolerate desensitization.

Alternative regimens are available for the patient intolerant of TMP-SMX. These have historically been primarily dapsone and aerosolized pentamidine. Dapsone (diaminodiphenylsulfone), with or without TMP or pyrimethamine, is in wide use in a variety of combinations. In general, neutropenia (especially in the G6PD-deficient host), hepatitis, and rash can be limiting for each of these regimens, and they offer no benefit over low-dose TMP-SMX. Any patient starting dapsone therapy for prophylaxis should be screened for G6PD deficiency. Because of a long half-life, dapsone may be administered in doses of 50 to 100 mg per day to 100 mg per week. Breakthrough infection has been observed in AIDS patients at 50 mg per day. Therefore, pyrimethamine may be administered weekly (25 or 50 mg) to supplement dapsone in a dose of 50 mg a day. Clinical trials and at least one meta-analysis of dapsone compared to TMP-SMX and aerosolized pentamidine have shown equivalent efficacy at preventing PCP.[77–79] TMP may replace pyrimethamine in this regimen (100–200 mg per day) in patients with creatinine clearances over 15 mL/min. The incidence of intolerance to dapsone varies from study to study. Up to half of the patients who discontinue prophylactic therapy with either of these agents will be able to tolerate the other drug. This strategy is not recommended for any person with severe allergic reactions, however, including desquamation to sulfa drugs, persistent bone marrow suppression, G6PD deficiency, or severe hepatitis. Toxicities observed with dapsone may be even higher than expected in solid-organ transplant recipients.[80] Dapsone alone, like aerosolized pentamidine, does not protect against toxoplasmosis—necessitating dual therapy for prophylaxis in the susceptible host.

The use of prophylaxis with aerosolized pentamidine isethionate (300 mg every 3–4 weeks) was pioneered in AIDS patients and is well tolerated in organ transplant recipients. Clinical trials comparing aerosolized pentamidine to TMP-SMX or dapsone have typically shown there to be a higher incidence of failure with aerosolized pentamidine.[78,81,82] Pentamidine aerosol prophylaxis is generally only effective after the second or third dose administered by experienced personnel with a nebulizer, producing droplets in the range of 1 to 3 μ. The Fisons nebulizer has also been used with an alternative schedule of five 60-mg doses over 2 weeks, followed by 60 mg every 2 weeks. Because the distribution of drug may not reach the upper lobes, or because the growth of *Pneumocystis* may be favored in the upper lobes, adjusting patient positioning during inhalation may be useful. Though generally well tolerated, cough and bronchospasm can occur, as well as pneumothorax in some instances. Prevention of some of these symptoms can be done via preemptive use of albuterol or other beta-agonist therapy. Breakthrough infection has been observed in patients receiving aerosolized pentamidine prophylaxis (particularly in the upper lobes). In single-lung transplant recipients, prophylactic failures have been observed in the residual (native) lung despite successful protection of the allograft. When breakthrough occurs with aerosolized drug, diagnosis by examination of the sputum is often complicated by reduced organism numbers resulting in false negatives and biopsy may be required to confirm the diagnosis.[83] Intravenous pentamidine (4 mg/kg every 2–4 weeks) has also been used, but is less well studied and its use may be complicated by systemic toxicities.

Atovaquone is a structural analog of ubiquinone with potent activity against a number of protozoa as well as *Pneumocystis*. It appears to be active by inhibiting the binding of ubiquinone to the electron transport system of mitochondria. The drug has been approved by the FDA for the treatment of mild-to-moderate *P. jiroveci* infections and may be equally useful for prophylaxis because it is well tolerated, undergoes enterohepatic circulation without metabolism, and has a long half-life. Studies of HIV-infected patients have shown

that in individuals who could not take TMP-SMX, doses of 1500 mg orally once daily was equally efficacious at preventing PCP compared to dapsone or aerosolized pentamidine.[84,85] Atovaquone is only available as a liquid suspension because of bioavailability limitations in tablet form. The high cost of atovaquone can also be a limiting factor in widespread utilization compared to TMP-SMX and dapsone. It otherwise appears to be well-tolerated. Rash, nausea, and elevated liver transaminases have been occasionally documented. Some patients complain about the flavor and color of atovaquone liquid (which stains clothes), but many ultimately find it preferable to aerosolized pentamidine. Prophylactic doses of reformulated liquid drug in the range of 1000 to 1500 mg a day exceed the MIC in serum for *P. jiroveci,* but doses at 1000 mg or less daily have resulted in breakthrough infection.[86] In small numbers of transplant recipients, interactions of atovaquone with cyclosporine and other toxicities have been insignificant.

Less well-studied regimens for prophylaxis might include the combination of clindamycin and pyrimethamine.[87] These two drugs appear to be active against *Pneumocystis* in vitro, and limited data in small numbers of patients suggested efficacy.[88] No prospective trials have been performed with this combination, but retrospective reviews of clindamycin at 300 mg daily with pyrimethamine at 15 mg daily showed it may be of benefit. Analyses suggest, however, that it may not be as efficacious as TMP-SMX or dapsone and breakthrough infections do occur. [87] Gastrointestinal intolerance of clindamycin over an extended period of time may also be a limiting factor for this regimen.

Patients receiving prophylaxis for toxoplasmosis (sulfadiazine, TMP-SMX, clindamycin/primaquine, atovaquone) generally have also been protected against *P. jiroveci.* In patients who are not receiving TMP-SMX or dapsone, who may benefit from antibacterial prophylaxis, an additional agent such a fluoroquinolone may be needed. Transplantation recipients receiving a fluoroquinolone alone for postoperative prophylaxis, however, will be at the same risk for PCP as the general transplant population.

TREATMENT OF PNEUMOCYSTIS PNEUMONIA

The incidence of *Pneumocystis* infection in AIDS patients has led to the development of a number of options for the treatment of this infection in all susceptible hosts (Table 135-4). Because of the severity and rapidity of disease morbidity, which can occur after the infection becomes clinically apparent, treatment should be initiated as soon as the suspicion of PCP is entertained. The short-term use of treatment (48 hours) will not impair the diagnosis of infection if, for example, bronchoscopic or laboratory support services are unavailable. It is likely to be more useful clinically to obtain specimens for *P. jiroveci,* mycobacteria, *Legionella,* other fungi, and routine cultures when these can be properly handled by the clinical laboratory. Further, because the pneumonia can be rapidly progressive, early therapy is essential. Retrospective studies of non–HIV-infected patients with PCP have identified delay in therapy to be a risk factor for death.[89,90] Treatment of *Pneumocystis* should be successful if a 14- to 21-day course of therapy is tolerated.

The incidence of adverse reactions to antibiotics, necessitating switching of agents, is increased in the solid-organ and bone marrow transplant recipient, as it is in AIDS patients. In general, side effects in transplantation are related to synergistic drug toxicities. For example, the bone marrow suppression seen in infection with CMV and treatment of this infection with ganciclovir may be further exacerbated with TMP-SMX. Generally, elevations in liver function tests in the liver transplant recipient or depression in the leukocyte count in the stem cell recipient or chemotherapy patient due to therapy with TMP-SMX is of concern but often tolerable. Nephrotoxicity is common in transplant recipients (both renal and extrarenal) receiving therapy with TMP-SMX, even with adjustment of dosing for renal dysfunction. Thus, while the incidence of intolerance by transplant recipients to one or another agent is somewhat less than the 50% seen in AIDS patients, significant toxicity remains a common feature of therapy. As was noted, resistance to antibiotics by *P. jiroveci* is a rare phenomenon. Thus, changing antibiotics other than for toxicity does not appear to be indicated. While there are patients who appear to do better on one agent than another, it is much more common to recognize a second process (infection, tumor, allergy, ARDS) as complicating PCP than a resistant infection. The chest radiograph is a less reliable indicator of failure than is oxygenation or other clinical parameters. Adding pentamidine to TMP-SMX offers no advantage over simply switching agents. Indeed, animal experiments suggest the possibility of antagonism between these agents when used in combination. As a rule, patients who need to be switched from TMP-SMX to pentamide, or vice versa, do not fare as well as those who can be treated for 14 to 21 days with either agent alone. The prognosis of therapy is most tightly linked with degree of respiratory failure at the time of presentation. Older studies in HIV-infected patients suggested a mortality rate close to 10% in cases of mild-to-moderate disease, but twice that in more severe cases.[91,92] Adjunctive therapies (see below) may provide further benefit.

The proper duration of therapy has not been well studied but is generally 14 to 21 days in all patients.[93] Residual organisms persist after treatment for a number of months, but the role of these organisms in recrudescent or persistent infection is not clear and may just reflect nonviable microbes. Relapse in the non–AIDS-immunocompromised

TABLE 135-4 Treatment of *Pneumocystis jirovecii*[a]

Agent(s)(route)[b]	Dose	Options[b]
Trimethoprim-sulfamethoxazole (TMP-SMX) (IV/PO)	15 mg/kg/d TMP (to 20) 75 mg/kg/d SMX (to 100)	Treat through mild rash: reduce TMP or SMX by one-half; desensitize; first choice
Pentamidine isethionate (IV)	4 mg/kg/d 300 mg/d maximum	IM not advised
Dapsone (PO) with TMP (PO/IV)	100 mg/d 15–20 mg/kg/d (900 mg)	Methemoglobinemia, G6PD; *may* be tolerated in sulfadiazine allergy
Clindamycin (IV/PO) and primaquine	450–600 mg q6h 15–30 mg base qd	Methemoglobinemia, diarrhea (pyrimethamine for primaquine)
Pyrimethamine (PO) with sulfadiazine (PO)	Load 50 mg bid × 2 d, then 25–50 mg qd Load 75 mg/kg, then 100 mg/kg/d	Not studied fully in clinical trials
Atovaquone (PO) suspension	750 mg (PO) tid to 1500 bid	Variable absorbance, improved with fatty food; rash, GI intolerance

IV, intravenous; IM, intramuscular; PO, oral.

[a] *Adjunctive therapies (see text): Corticosteroids (high dose with rapid tapering), possibly γ-interferon, granulocyte-macrophage colony–stimulating factor.*

[b] *Based on clinical judgment of physician; some agents are not FDA-approved for this indication.*

patient should not be expected as long as immunosuppression can be reduced somewhat, notably, with tapering of corticosteroid therapy after disease resolution. Subsequent lifelong prophylaxis may be warranted in these situations.

TMP-SMX is the agent of choice for the treatment of PCP and extrapulmonary disease in all hosts. This combination antibiotic has the advantage of excellent tissue penetration, the most rapid clinical response of anti-*Pneumocystis* agents (3–4 days), and bioavailability from oral therapy comparable with that of parenteral administration. The incidence of some of the side effects is related to serum concentrations. Generally, TMP-SMX should be tolerated when corrected for measured rather than calculated renal function. In part, this is a reflection of dosage schedules derived for children in adults who may not require the same high doses. Therapy is initiated at 15 to 20 mg/kg per day of the TMP component (100–150 mg/kg per day of SMX), divided into three or four doses. Therapy should be initiated intravenously if there is uncertainty about gastrointestinal absorption or marked hypoxemia. For mild-to-moderate PCP, treatment with TMP-SMX can be done using an oral regimen. Two double-strength (160-mg TMP/800-mg SMX) tablets three or four times daily are most often applied depending on overall body mass.

Therapy can be continued (with adjustments) despite mild side effects (rash, transaminase elevations, neutropenia) tolerable to the patient and physician. Dose reduction will often eliminate toxicity in AIDS patients. Desensitization to TMP-SMX may be used in the patient with mild intolerance. With renal dysfunction, dosing must be reduced; daily dosing is sufficient (3–5 mg/kg per day) for a glomerular filtration rate of 10 to 50 mL/min. Renal impairment developing in a patient taking TMP-SMX should prompt a search for urinary eosinophils and an assessment of the need for further therapy with this agent. Nephrotoxicity occurs frequently in the renal transplant recipient on full-dose therapy; this toxicity is both idiosyncratic and dose related. Nephrotoxicity often occurs without demonstrable urinary eosinophils, perhaps as a reflection of the use of corticosteroids for immune suppression. In these patients, interstitial eosinophils may be found on renal biopsy. The transplanted liver is particularly susceptible to TMP-SMX toxicity (eosinophilic infiltrates, hepatocyte necrosis, bilirubinemia) and may be confused with, or complicate treatment for, early graft rejection or systemic infection. The side effects of TMP-SMX are generally those of sulfa allergy: rash (including Stevens–Johnson syndrome), transaminase elevation, neutropenia, thrombocytopenia, erythema multiforme exudativum, and nephrotoxicity. The bone marrow suppression is marked in patients with underlying hematologic disorders; folinic acid supplementation is rarely useful and should be avoided in patients with acute leukemia.

For mild-to-moderate disease, dapsone (100 mg orally per day), in place of SMX and in combination with oral TMP (15 mg/kg per day), is an effective alternative therapeutic regimen. Clinical trials comparing oral TMP-SMX to oral dapsone-TMP and clindamycin-primaquine have shown relatively equivalent efficacy.[92] Many AIDS patients intolerant of SMX will tolerate dapsone, which is metabolized by the liver (half-life at least 30 hours). However, the long half-life and side-effect profile in the non-AIDS patient (hemolysis in G6PD deficiency, methemoglobinemia, rash, hepatitis) may be particularly disadvantageous in the transplant recipient. As noted in the section on prophylaxis, any patient starting dapsone therapy should be screened first for G6PD deficiency. Manifestations of sulfa and TMP toxicity may be masked by corticosteroids. Similarly, side effects of azathioprine (hepatitis, macrocytic anemia, neutropenia, hepatic veno-occlusive disease) or mycophenolate and sirolimus (neutropenia) may be accentuated by TMP-SMX. In AIDS, the toxic side effects of TMP-SMX are generally those of the sulfonamide; however, TMP allergy is not uncommon, and allergies to the "carriers" in the various preparations of TMP-SMX (dyes, coatings, filler) have also been reported. Both components of TMP-SMX interfere with folate metabolism.

Intravenous pentamidine isethionate is the first alternative agent for the treatment of PCP, particularly in severe cases or those with significant hypoxemia. Pentamidine isethionate was first administered intramuscularly during an epidemic of the infantile form of the disease. Small clinical trials of PCP comparing intravenous pentamidine to intravenous TMP-SMX have shown mixed results. Two studies showed pentamidine to be equivalent while one showed improved survival in the TMP-SMX group.[94–96] Clinical responses are generally faster with TMP-SMX. Pentamidine isethionate may be administered intravenously or, if essential, intramuscularly, although only the intravenous route is recommended. Complications with early therapy occurred in up to 50% of patients, notably sterile abscesses at the site of intramuscular injection. Intravenous pentamidine isethionate is given by slow (1—2 hours) infusion in 5% glucose solution as a single dose of 4 mg/kg per day. Pentamidine achieves therapeutic levels in the lungs slowly (in 5–7 days), owing to high levels of extrapulmonary tissue binding. Slow accumulation of pentamidine in pulmonary tissue may account for the delayed onset of activity when compared with TMP-SMX. However, increased serum levels and a long serum half-life and gradual accumulation in the lungs may play a role in the continued therapeutic effect after the cessation of therapy. Because this agent has a long serum half-life (6.4 hours) and delayed excretion due to extensive tissue binding (more than 240 hours), pentamidine tends to accumulate during therapy. The reduction of symptoms by pentamidine may be due, in part, to suppression of the secretion of tumor necrosis factor by alveolar macrophages as well as to treatment of infection. Pentamidine has largely been supplanted by TMP-SMX for therapy of *Pneumocystis* infection in the non-AIDS patient, but pentamidine remains a viable option for treating infection in patients with adverse reactions to TMP or to sulfonamides.

Idiosyncratic side effects of pentamidine include transient hypoglycemia, pancreatitis, diabetes (after prolonged therapy, with or without prior pancreatitis), pancytopenia, hypotension, and renal dysfunction. These side effects are exacerbated by intravenous administration and in the presence of decreased renal function. Pentamidine should be avoided in pancreas transplant recipients, owing to the potential for islet cell necrosis.

Alternative regimens have been developed as a reflection of toxicities observed in AIDS patients treated with either TMP-SMX or pentamidine. Atovaquone (750 mg orally twice daily) has been approved by the FDA for the treatment of mild-to-moderate PCP. Higher doses are commonly used. Preliminary studies showed that the drug resulted in clinical improvement in 85% of those treated. Toxicity was unusual, and was reported in just over 10%. Treatment limiting reactions included fever and rash while elevated hepatic enzymes, though common, were typically not severe enough to warrant discontinuation.[97] When it was prospectively compared to TMP-SMX for the treatment of HIV-infected patients, efficacy was not as good as TMP-SMX, and failure rates were as high as 20%. Diarrhea and low serum levels leading to potential problems with oral absorption contributed to treatment failure with atovaquone. Tolerability of the drug compared to TMP-SMX appeared to be much greater, however.[98] Use of this drug for treating PCP should probably be limited to patients who cannot tolerate TMP-SMX, who lack significant hypoxia and who have functional gastrointestinal tracts where absorption and adequate food intake is not a concern.

The combination of clindamycin (600–900 mg intravenously every 6–8 hours) and primaquine (15–30 mg base per day orally) is effective in mild-to-moderate infection. When compared to TMP-SMX and dapsone–TMP, this regimen appeared to be equivalent, though toxicity was higher.[92] Clindamycin can be limiting due to gastrointestinal intolerance and in today's increased prevalence of *Clostridium difficile* colitis in some inpatient settings, persistent use is a concern. Primaquine can also be associated with rash, hemolytic

anemia, neutropenia, and methemoglobinemia. As with dapsone, any patient to be treated with primaquine should be screened for G6PD deficiency. Studies evaluating this regimen in more severe disease have not been performed in any randomized trial, and thus should probably be avoided in cases of marked hypoxia.

Pyrimethamine (50–100 mg a day by mouth after 100–200 mg load) and sulfadiazine or trisulfapyrimidines (4–8 g a day) are also effective, but require folinic acid (10 mg a day) supplementation. Pyrimethamine will decrease the renal clearance of creatinine without affecting the glomerular filtration rate. The newer macrolides (azithromycin, clarithromycin) have little efficacy alone but appear to enhance the efficacy of SMX. However, this combination provides little benefit over TMP-SMX by itself.

The echinocandin antifungal agents have garnered some interest in recent years as potential therapeutics for PCP infection. These drugs exhibit antifungal activity by inhibiting β-1,3-glucan synthesis, an important component of the *Pneumocystis* cell wall. In vitro studies have suggested that caspofungin may be active against the cyst and trophozoite forms of *Pneumocystis*.[99] Clinical reports have been mixed, however, and no controlled studies have been performed to date on the clinical utility of echinocandins for treating PCP.[100,101] The echinocandins require study before use as a single agents for the treatment of PCP.

Adjunctive therapies in the treatment of PCP include aggressive supportive care, corticosteroids and, potentially, colony-stimulating factors (CSFs). Because the disease can take a severe course, aggressive respiratory management is often necessary and may even lead to intubation and mechanical ventilation. In cases of extreme ventilator and circulatory collapse, temporizing support through use of extracorporeal membrane oxygenation (ECMO) may be of value in institutions where such support can be performed by experienced personnel. Successful cases of ECMO support have been reported in both adults and children with PCP.[102,103] Delayed response to therapy or the inability to reduce immune suppressive therapy may allow progressive disease despite appropriate therapy for PCP in any case, and the time course for improvement in the best of situations can oftentimes be a week or more. In HIV-infected patients, treatment of the underlying PCP should also be accompanied by treatment of the underlying HIV infection with HAART. The AIDS Clinical Trial Group Protocol 5164 was a randomized trial that demonstrated the implementation of antiretroviral therapy within 14 days of the setting of an acute opportunistic infection like PCP reduced AIDS progression and mortality by 50%.[104] Thus, delaying HAART in otherwise untreated AIDS patients presenting with PCP should be avoided.

Given the risks of nosocomial superinfection associated with intubation for assisted ventilation, the use of adjunctive corticosteroids was developed to prevent the early deterioration of AIDS patients with documented PCP. The use of corticosteroids (prednisone, 40–60 mg three or four times a day, orally or equivalent intravenously) in the first 72 hours after admission may reduce pulmonary inflammation to a degree sufficient to avoid intubation. When studied in AIDS patients, the use of corticosteroids in patients with a Pa_{O_2} of 35 to 72 mm Hg or with a hypoxemia ratio of 75 to 350 was of significant benefit in terms of preventing deterioration in oxygenation in the first 7 days of therapy, mortality, and the avoidance of intubation (50% reduction).[105] After such therapy, the exercise tolerance and survival of patients were improved. Steroid tapering is necessary to avert relapse of pulmonary inflammation. Patients may experience an increase in oral thrush and herpes simplex after 2 to 3 weeks of therapy and tapering. The impact of corticosteroids in the non–AIDS-compromised host and in AIDS patients failing initial therapy appears to be similar. However, the utility of additional steroids in the transplant or cancer patient has not been subjected to a controlled clinical trial.

Cytokines, including γ-interferon, have been shown to reduce the amount of *Pneumocystis* found in animal models of disease without greatly increasing the inflammatory response.[106] CSFs including those for the monocyte/macrophage (M-CSF), granulocytes (G-CSF), and granulocyte/macrophage (GM-CSF) lineages, have come into use to supplement immunity in the immunocompromised host. G-CSF has been used successfully in many of our neutropenic cancer and organ transplant recipients without adversely affecting the transplanted organs. GM-CSF has been used with systemic antifungal therapy in patients with acute fungal infections with some success. Preliminary data suggest that M-CSF and GM-CSF may be useful in enhancing the clearance of *P. jiroveci* by resident alveolar macrophages. As of yet, no controlled human data exist and ideal dosing or administration remains unknown. The impact of CSFs on graft rejection has also not been studied.

The response to therapy is generally excellent in patients who receive a diagnosis before respiratory failure. The ability to reduce immune suppression or to supplement the immune response (see above) also improves the rapidity of clearance of infection. Clinical improvement should be seen in most patients being treated with ideal dosing of TMP-SMX in 4 to 5 days. Radiographic improvement may lag behind. The failure to see clinical improvement after a week should suggest the presence of another process such as fibrosis, ARDS, dual infection (especially CMV), abscess, bronchial obstruction, drug allergy, or carcinoma. Bronchoscopic lavage and biopsy for microbiology and pathology, or chest tomography (CT scan), may be revealing in these patients.

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CHAPTER 136

Protozoan Infections of the Thorax

Louise C. Ivers
Edward T. Ryan

AMEBIASIS: *ENTAMOEBA HISTOLYTICA*

Entamoeba histolytica is a protozoan infection of humans that is found worldwide and is globally responsible for up to 100,000 deaths annually. It is endemic in most temperate and tropical areas of the world, particularly in areas with poor socioeconomic development and limited sanitation. Serologic evidence of prior or current infection with *E. histolytica* is present in 5% to 50% of individuals in impoverished populations. *E. histolytica* is infectious in the cyst form. Transmission usually occurs as a result of contamination of food or water, but may also occur by means of oral–anal contact. Infection is common in developing countries. In Europe and the United States, infection is most commonly seen in individuals who have lived in endemic areas of the world. Institutionalized individuals are also at increased risk of infection. Sexually active men who have sex with men are also at increased risk of infection. There does not appear to be an increased risk of invasive disease in persons with HIV infection.

A morphologically identical, but nonpathogenic protozoan, *Entamoeba dispar*, also infects the human gastrointestinal tract. It can be distinguished from *E. histolytica* by antigenic, genetic, and immunologic methods. Infection is 10 times more prevalent with *E. dispar* than with *E. histolytica*; however, the former does not cause invasive disease. Many older epidemiologic studies relied on microscopic diagnosis alone, and inadvertently incorporated both pathogenic and nonpathogenic species in estimates of prevalence of infection.

E. histolytica has a simple life cycle involving an infectious cyst and an ameboid trophozoite phase. Cysts may survive in the external environment for several weeks to months, especially in damp conditions and temperatures between −5°C and 40°C. After ingestion by humans, cysts excyst in the small intestine, each forming eight daughter trophozoites. These motile trophozoites can adhere to the intestinal wall; it is in this form that they may invade the mucosa, causing symptomatic invasive disease. In the colon, trophozoites encyst to complete the life cycle and are excreted. Trophozoites do not survive outside the human host.

CLINICAL MANIFESTATIONS

The incubation period for intestinal amebiasis is usually 1 to 4 weeks, but ranges from a few days to months. Infection with *E. histolytica* is asymptomatic in up to 90% of cases, but may cause a range of gastrointestinal symptoms from mild diarrhea to severe colitis with bloody diarrhea. Symptoms result from penetration of the trophozoites through the mucosal barrier with invasion of the colon wall. In the absence of frank blood, stool is usually positive for occult blood. Fever is present in less than half of cases. Fecal leukocytosis is usually less marked than in bacterial colitis. Rarely, progression of invasive intestinal disease may lead to severe colitis and bowel perforation. On occasion, granulation tissue formation surrounding a localized area of invasive disease may form an inflammatory mass (an "ameboma") and manifest as a tender abdominal mass.

Extraintestinal disease most commonly occurs in the liver, and manifests as a liver "abscess." In this instance, trophozoites migrate to the liver via the portal veins, and infection results in inflammation, necrosis, and ultimately a fluid collection. The collection is often referred to as an abscess; however, it does not contain polymorphonuclear cells like a true abscess, but only cellular debris. Eighty percent of amebic hepatic abscesses are solitary, and 80% occur in the right lobe of the liver. Extraintestinal disease may present years after residence in an endemic area and should be considered in all patients with an appropriate travel history and suggestive symptoms. Liver abscesses occur more frequently in men than women, and usually in the age range of 18 to 50 years.

Thoracic manifestations of *E. histolytica* infection are rare; they have been reported in 2% to 3% of cases of invasive amebiasis. They can be considered chiefly as either pleuropulmonary or pericardial. A case of *E. histolytica* osteomyelitis of the rib has been reported, as has a case of pulmonary amebiasis presenting as superior vena cava syndrome.[1]

PLEUROPULMONARY DISEASE

Amebic pulmonary disease may occur by a number of mechanisms.[1–3] It most often occurs as the result of a concomitant liver abscess. The abscess may result in a sympathetic pleural effusion that does not require specific therapy. A liver abscess may alternatively rupture through the diaphragm into the pleural space, causing respiratory distress, empyema, and subsequent parenchymal lung abscesses (Figs. 136-1 to 136-3). Pulmonary parenchymal disease in the form of lung abscesses and consolidation less often occurs in the absence of hepatic disease, but may occur if there has been hematogenous spread of trophozoites to the lung.

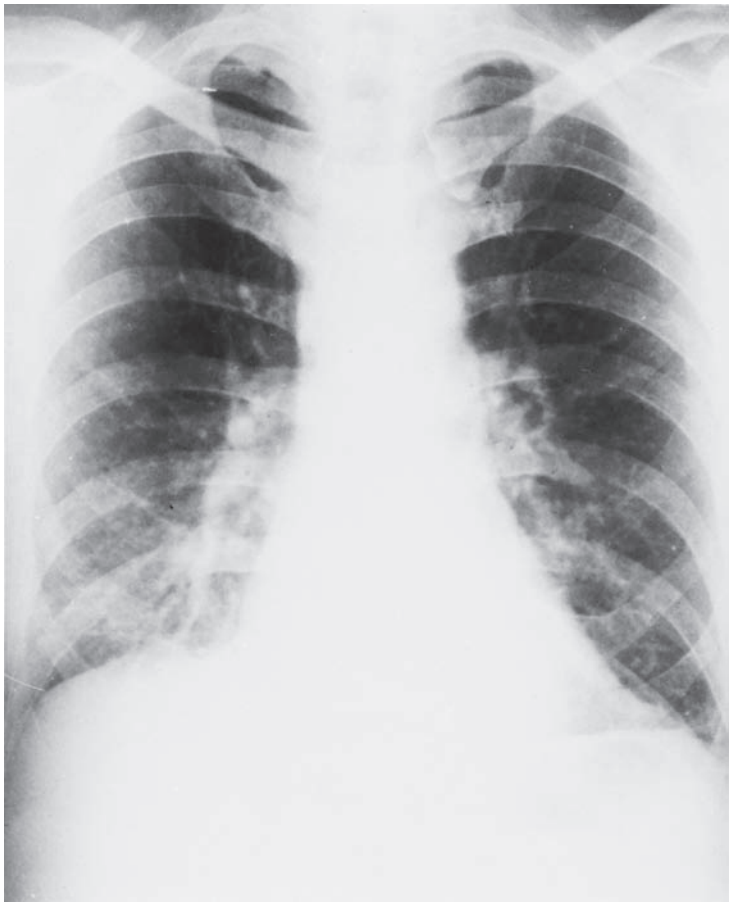
Most patients with extraintestinal amebiasis have not had symptomatic intestinal disease, so the absence of preceding gastrointestinal symptoms does not exclude the diagnosis. Patients with liver abscess often present with insidious onset of fever, right upper quadrant pain, and hepatic tenderness on palpation. Pleuritis, respiratory symptoms such as cough, dyspnea, and/or physical examination consistent with pleural effusion further suggest involvement of the pleuropulmonary system. Sputum production may range from scant to copious, and sputum may contain purulent material, particularly if a hepatobronchial fistula has developed. Classically, the purulent material of amebic abscess is reddish "anchovy paste." Jaundice is uncommon. Leukocytosis may be present, but eosinophilia is not a feature of the disease.

PERICARDIAL DISEASE

Pericardial disease can result from either sterile inflammation of the pericardium as a result of a contiguous liver abscess in the left lobe of the liver, or may be a purulent infection as a result of rupture of a hepatic amebic abscess into the pericardial space (Fig. 136-4). Chest pain, pericardial friction rub, and symptoms and signs of pericarditis may be presenting features. Presentation may be acute and severe, with symptoms and signs of pericardial tamponade.[4]

DIAGNOSIS OF PLEUROPULMONARY AND PERICARDIAL DISEASE

Stool microscopy may reveal the presence of *E. histolytica* trophozoites or cysts, but microscopy is neither a sensitive nor a specific method for the diagnosis of amebiasis. Microscopy is unable to distinguish *E. histolytica* from nonpathogenic *E. dispar*, and extraintestinal disease is associated with presence of the pathogen in stool



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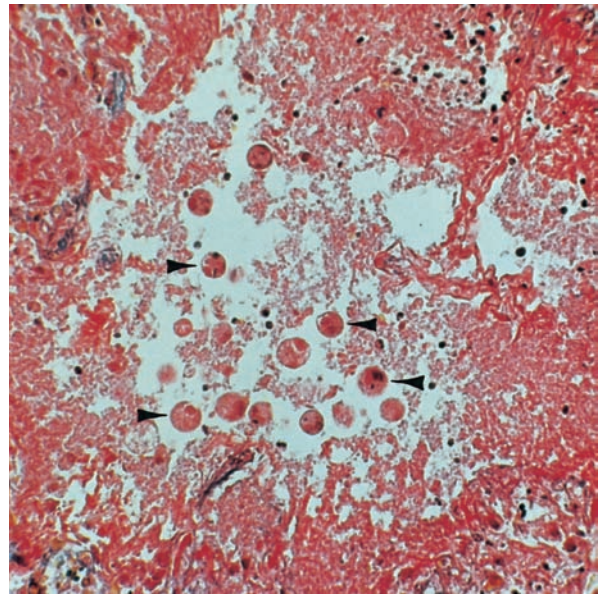

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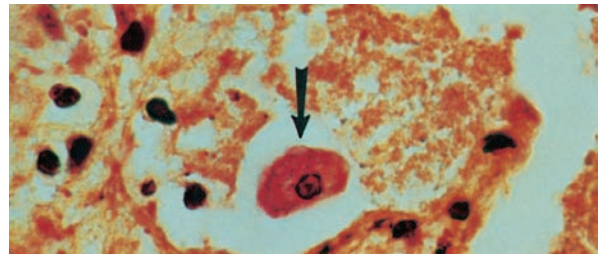
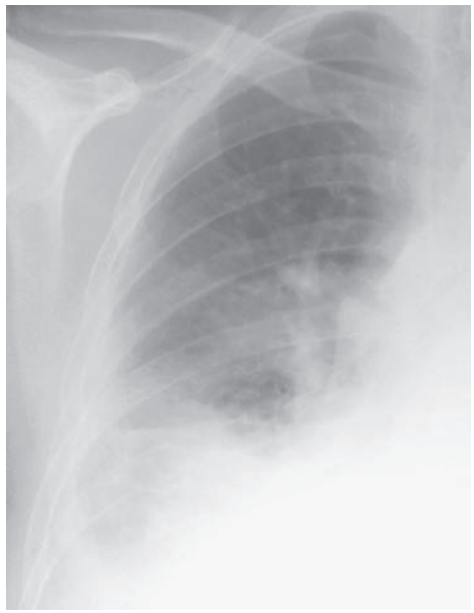


C

Figure 136-1 *Entamoeba histolytica* involving the right lung after rupture of a hepatic abscess through the right hemidiaphragm. **A.** Chest radiograph shows elevated right hemidiaphragm, right lower lobe infiltrate, and effusion. *(Used with permission of Armed Forces Institute of Pathology [AFIP].)* **B.** Alveolar spaces are filled with ameba *(arrowheads)*. (Iron hematoxylin stain, ×300). *(Used with permission of Dr. Y. Gutierrez.)* **C.** Trophozoite *(arrow)* and necrotic debris.



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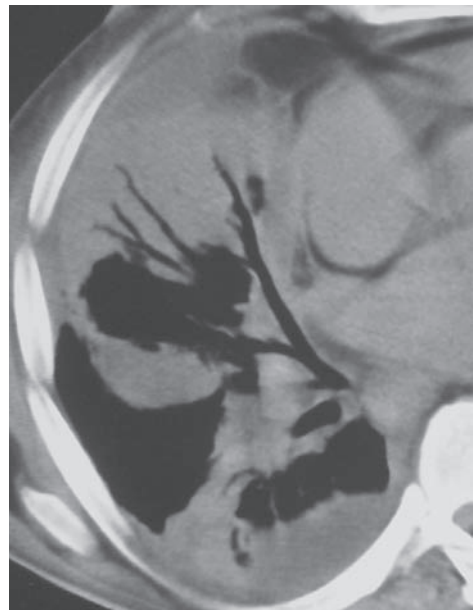
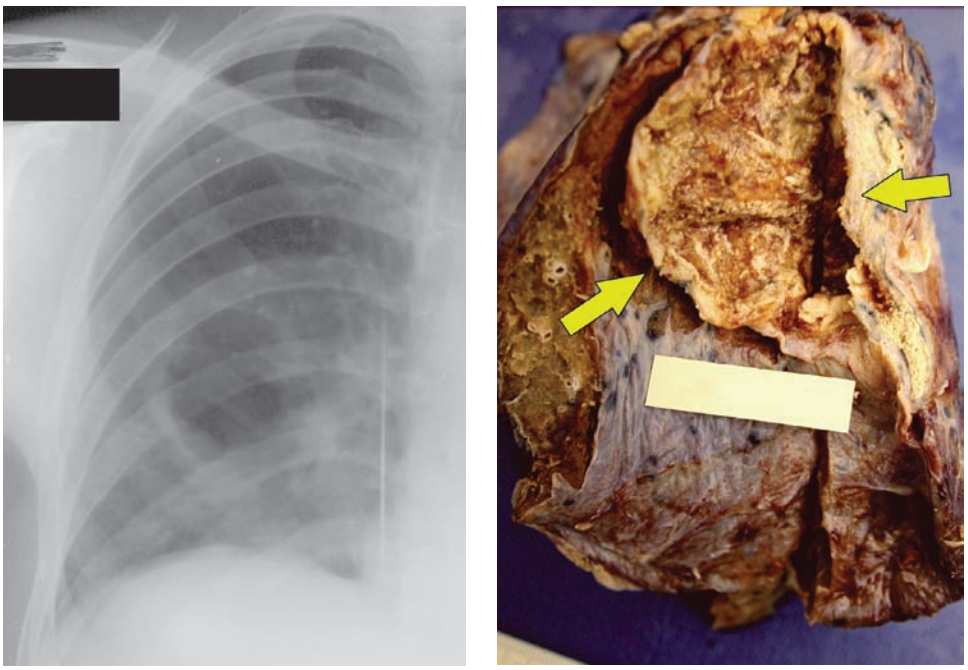


B

Figure 136-2 Right-sided amebic pleural empyema and pneumonia in a 43-year-old man with an abscess of the right hepatic lobe. **A.** Initial chest radiograph shows pleural effusion and right-sided basal consolidation. **B.** Chest CT scan helps confirm pleural involvement and right-sided basal alveolar infiltrates. Trophozoites of *E. histolytica* were obtained at bronchoalveolar lavage. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*



A B

Figure 136-3 Right-sided amebic pneumonia in a 35-year-old man with a hepatic abscess. **A.** Chest radiograph shows elevation of the right hemidiaphragm and right-sided basal consolidation with cavitation. **B.** Photograph of the gross specimen demonstrates an irregular cavitary lesion *(arrows)*. Anchovy sauce content and trophozoites of *E. histolytica* (not shown) were found on the lesion wall. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

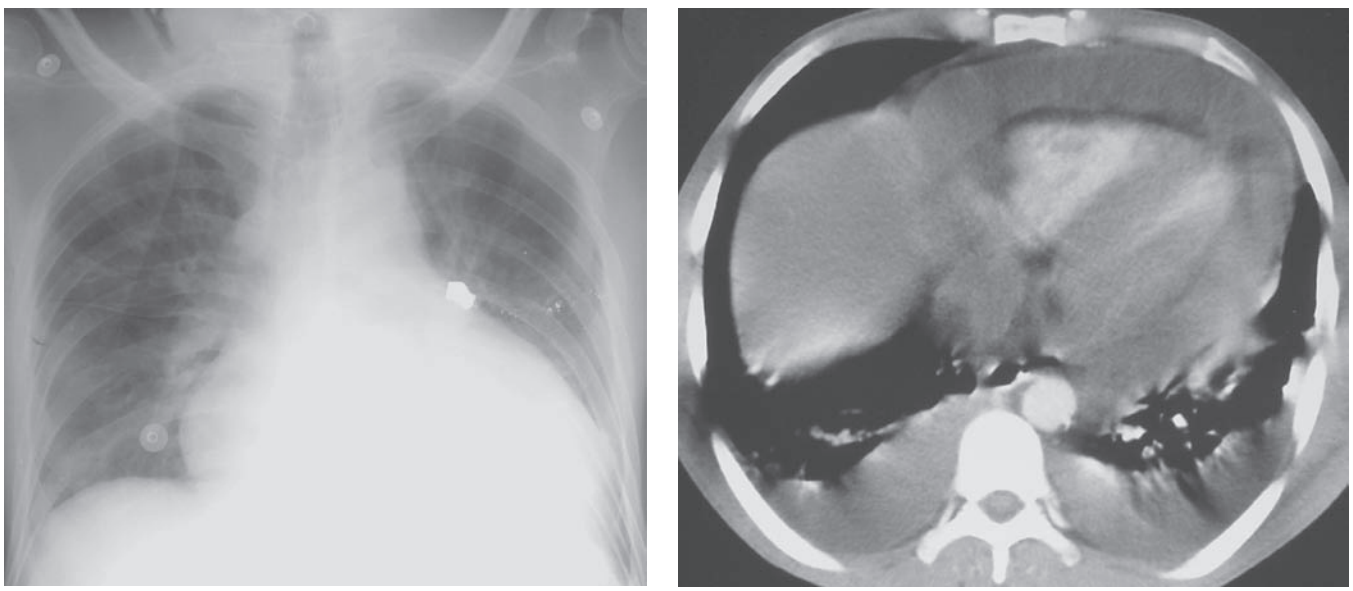
in only a minority of cases. Stool may be concentrated and stained with iodine to evaluate for the presence of cysts. Trophozoites are best seen on a fresh smear with iron hematoxylin and trichome stain. Microscopy of abscess fluid occasionally may reveal presence of trophozoites. Diagnosis of extraintestinal disease is best made by a combination of microscopic examination of samples, antigen detection, and serology tests.

■ ANTIGEN DETECTION

Antigen detection methods detect *E. histolytica*. These tests are able to distinguish *E. dispar* from *E. histolytica*. Stool antigen tests are over 95% sensitive and specific for the diagnosis of intestinal disease. Antigen detection assays are also highly sensitive and specific when applied to abscess fluid.

■ SEROLOGY

Most patients infected with *E. histolytica*, but not *E. dispar*, develop a serum antibody response. Amebic serology is positive in over 90% of patients with extraintestinal disease. Serologic analysis may be negative in early infection. The presence of IgG antibodies does not always indicate active disease; IgG may persist for many years after active infection.



A B

Figure 136-4 Amebic pericardial tamponade in a 27-year-old man with an abscess of the left hepatic lobe. The patient presented with pulsus paradoxus, fever, and chills. **A.** Chest radiograph shows enlargement of the cardiac silhouette. **B.** Chest CT scan shows extensive pericardial effusion that resulted from rupture of a left hepatic lobe abscess (not shown) into the pericardial space. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

TREATMENT

Metronidazole or tinidazole is effective in the treatment of individuals with intestinal and extraintestinal amebiasis. To prevent a relapse, a luminal agent such as iodoquinol or paromomycin also should be administered. Sympathetic pleural effusions do not need specific therapy, other than treatment of the underlying liver abscess. Amebic empyema and amebic pericarditis are best treated with aspiration or percutaneous drainage, in combination with administration of antiamebic microbial therapy.

FREE-LIVING AMEBA: ACANTHAMOEBA

Free-living amebae are rarely associated with human infection; however, when infection does occur, disease tends to be progressive and difficult to treat.

Acanthamoeba spp. are ubiquitous, and have been isolated from a wide variety of locations, including the nasal passages of healthy adults, water sources, soil, and contact lens fluid. Infection in humans usually manifests as either keratitis or systemic disease. Systemic disease usually involves the central nervous system, manifesting as granulomatous amebic encephalitis. Amebic infection of skin also has been reported.

CLINICAL FEATURES

Acanthamoeba sp. keratitis is usually a disease of healthy individuals, often contact lens wearers. Infection is thought to result from direct deposition of ameba into the eye. In contrast, systemic disease results from hematogenous dissemination of ameba, which are thought to first enter the human host via the respiratory tract or skin. Systemic disease is primarily a disease of immunocompromised or debilitated persons, including individuals with acquired immunodeficiency syndrome (AIDS), and those who have undergone bone marrow transplantation, organ transplantation, or are otherwise immunosuppressed. Pulmonary nodular infiltrates and pneumonitis have been reported in cases of systemic disease.[5]

DIAGNOSIS

Diagnosis of systemic acanthamebiasis is usually made late in the clinical course, and unfortunately, very often at autopsy. Evaluation of cerebrospinal fluid from individuals with granulomatous amebic meningoencephalitis may disclose hypoglycorrhachia and elevated protein, but amebae are not usually seen. Evaluation of biopsies of lesions of skin or brain usually provides the definitive diagnosis. *Acanthamoeba* spp. can be identified on histopathology, and may be cultured on nutrient agar overlaid with *Escherichia coli*. Radiographic imaging of the central nervous system is often helpful.

TREATMENT

No single drug is effective against systemic *Acanthamoeba* spp. infection. Combinations of treatment with amphotericin B, azithromycin, voriconazole, fluconazole, 5-fluorocytosine, pentamidine, and sulfadiazine have been attempted, with success in some cases and failure in other cases that used similar regimens. Most individuals with systemic amebiasis do not survive, regardless of therapy. Individuals with acanthamebic keratitis are usually treated topically and may require corneal grafting.

SYSTEMIC COCCIDIOSIS: TOXOPLASMOSIS

Toxoplasmosis is caused by *Toxoplasma gondii*. Asymptomatic disease is common. Symptomatic disease usually occurs in persons with suppressed cell-mediated immunity and infants born with congenital infection.

EPIDEMIOLOGY AND LIFE CYCLE

Understanding the life cycle of *T. gondii* is important in understanding the disease process. The parasite is found worldwide. It has both sexual and asexual stages, the latter being the pathogenic stage in humans and other animals. Cats are the definitive host, and in the feline, oocysts develop after an intestinal intraepithelial sexual cycle. Oocysts are then passed in cat feces, and after 2 to 3 days become infectious. They may persist in soil. If ingested by humans or other animals (sheep, pigs, rodents, or cats), oocysts produce rapidly dividing tachyzoites. Tachyzoites invade varying cell types, and result in cell death and tissue necrosis. Eventually the host immune response curtails this process, and tachyzoites give rise to slowly dividing bradyzoites, which encyst and persist indefinitely in host tissues. Bradyzoites are infectious if ingested, giving rise to tachyzoites in the new host. Bradyzoites may also revert to tachyzoites if a host becomes immunocompromised, leading to "reactivation" of disease. Humans and other animals may be infected, not only by ingestion of oocysts, but also by ingestion of tissue cysts, such as following the consumption of undercooked infected meat. Toxoplasma infection may also be acquired by transplacental passage of tachyzoites, resulting in congenital infection, or by organ transplantation.

Serologic studies demonstrate a wide geographic variation in prevalence of infection between 10% and 90%. In the United States, rates range from 3% in Denver, Colorado, to 17% in Massachusetts, and 30% in Birmingham, Alabama.

CLINICAL FEATURES

Infection may be primary or due to reactivation. After ingestion of infectious oocysts or tissue cysts, tachyzoites disseminate and invade organs, replicating intracellularly. Acute infection may result in tachyzoites being found in all organs, especially muscle, lymphatic tissue, and the central nervous system. Primary infection may be subclinical or asymptomatic. If symptomatic, the most common manifestations of acute disease include fever, painless lymphadenopathy, and a mononucleosis-like syndrome. More rarely pneumonitis, myocarditis, and myositis may occur.

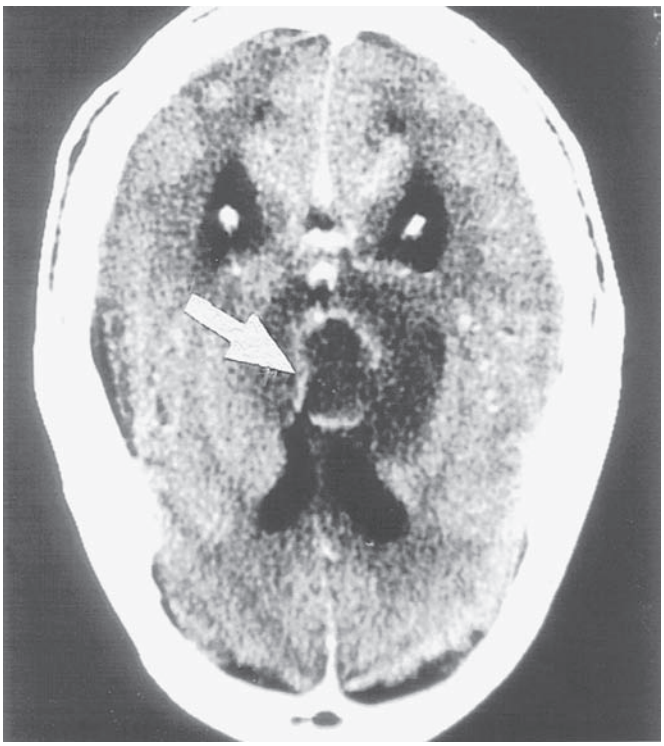
Congenital infection is usually the result of primary infection in the mother, with transplacental passage of tachyzoites resulting in infection of the fetus. Infected infants may be symptomatic at birth, or may have hepatosplenomegaly, pneumonitis, myocarditis, rash, or jaundice. Congenitally infected children may be asymptomatic initially, but may subsequently develop central nervous system or ocular manifestations.

Reactivation disease occurs in persons who are immunocompromised, particularly those with deficiency in cell-mediated immunity. Patients with HIV infection and CD4 cell counts less than 100 cells/mm^3 are at particular risk of life-threatening disease, and although primary infection may occur in these individuals, reactivation disease is most common. Reactivation disease may be prevented in those at particular risk with the prophylactic use of trimethoprim–sulfamethoxazole. Necrotizing central nervous system disease is the most common manifestation of reactivation toxoplasmosis in AIDS patients. Affected individuals usually present with altered mental status, fever, headache, and clinical findings suggestive of focal CNS disease, and neuroimaging often reveals multifocal, ring-enhancing lesions.

PULMONARY DISEASE

Pulmonary involvement in toxoplasmosis is common, and is usually reported in patients with AIDS or in individuals who have undergone bone marrow or solid-organ transplantation (Fig. 136-5).[6,7]

Shortness of breath and cough are the most common presenting symptoms of pulmonary involvement during toxoplasmosis. In one review, immunocompetent patients with toxoplasmic pneumonitis were more likely than immunocompromised individuals to



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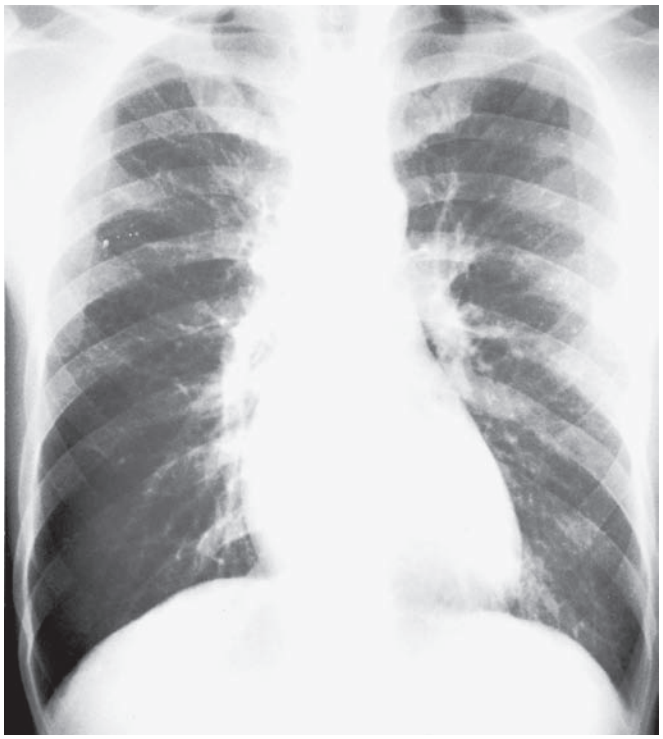

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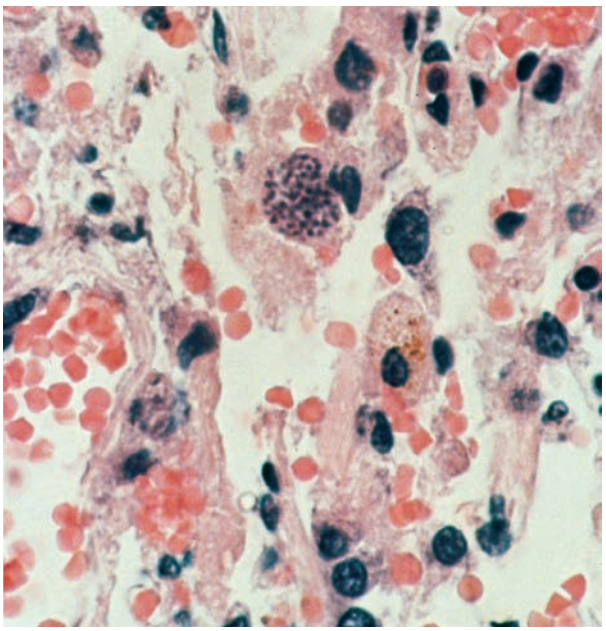

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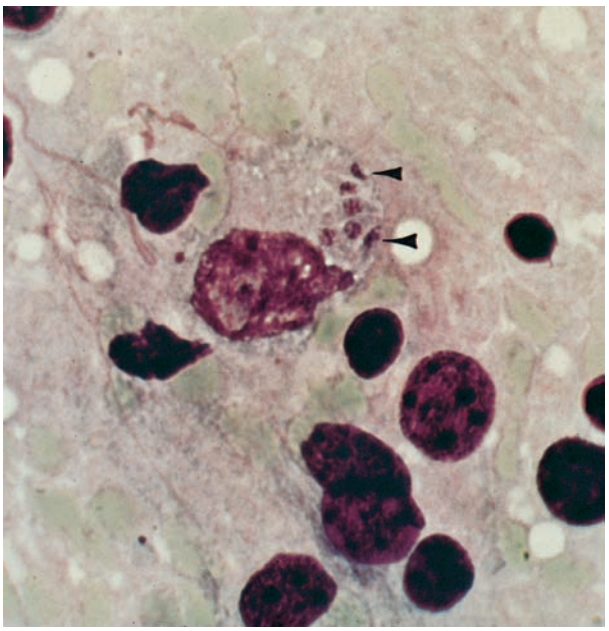


D

Figure 136-5 *Toxoplasma gondii* in the brain and lung of a patient with AIDS. **A.** Brain CT scan shows Toxoplasma abscess as a contrast-enhancing lesion *(arrow)*. **B.** Chest radiography. Diffuse bilateral infiltrates and hilar adenopathy. **C.** Lung biopsy shows Toxoplasma forms (arrow, cyst, hematoxylin & eosin stain, ×100). **D.** Impression smear of brain biopsy shows five intracellular tachyzoite (trophozoite) forms (*arrowheads*; Giemsa stain ×1500). *(C and D are Used with permission of Dr. Y. Gutierrez.)*

have evidence of hepatosplenomegaly at presentation, but clinical findings were otherwise similar. Bilateral interstitial pulmonary infiltrates are most often evident in radiography; however, a variety of other findings, from discrete pulmonary opacities to cavitary disease, also have been described. Severe disease or the acute respiratory distress syndrome (ARDS) may develop. *T. gondii* organisms can invade myocytes, and during acute or reactivation disease, myocarditis may occur and may be severe.

■ DIAGNOSIS

In primary toxoplasmosis, the differential diagnosis is broad, but IgM-specific antibodies will usually be present. During reactivation of toxoplasmosis, IgM and IgG antitoxoplasma antibodies are usually present in serum. Absence of antitoxoplasma IgG antibodies makes the diagnosis of reactivation toxoplasmosis unlikely, but the presence of the antibody itself does not differentiate between latent and active diseases.

Biopsy can confirm the diagnosis. Polymerase chain reaction (PCR) analysis of tissue samples or cerebrospinal fluid is sensitive, and PCR analysis of amniotic fluid is particularly helpful in the antenatal diagnosis of congenital infection. PCR has been used to detect toxoplasma in sputum specimens, but the sensitivity of this method for diagnosing pulmonary toxoplasmosis has not yet been determined. In pulmonary disease, microscopic or molecular analysis of bronchoalveolar lavage fluid or open lung biopsy may be required for confirmation of the diagnosis.[8]

TREATMENT

Except in the case of pregnant women or individuals with severe or persistent symptoms, primary toxoplasmosis in immunocompetent individuals usually does not require treatment. Reactivation disease in immunocompromised individuals is usually treated for the duration of the period of immunosuppression, as therapy does not fully eradicate the parasite. Standard therapy is pyrimethamine and a sulfonamide, usually sulfadiazine. Leucovorin is added to overcome the bone marrow suppressive effects of pyrimethamine. Clindamycin or atovaquone may be used as an alternative in those intolerant of sulfonamides. After acute disease has been controlled, secondary suppressive therapy should be continued for the duration of immunosuppression to prevent relapse. Unfortunately, mortality in immunocompromised patients with *Toxoplasma* pneumonia diagnosed antemortem has been as high as 40%.

INTESTINAL COCCIDIOSIS: CRYPTOSPORIDIOSIS

Cryptosporidium spp. *(C. hominis/parvum* and *C. muris)* are intracellular protozoans that mainly cause intestinal pathology (Fig. 136-6). Disease may occur in immunocompetent hosts, but is more common and severe in immunocompromised individuals, particularly in patients with AIDS, in whom cryptosporidiosis may result in severe and persistent diarrhea. The organism also causes infection in a variety of animals, and fecal contamination of water or food is a common source of infection in humans, although person-to-person transmission also occurs.

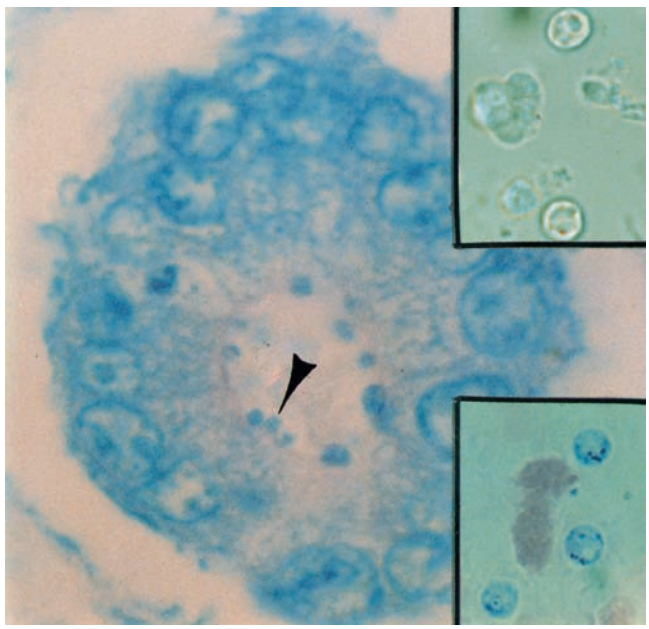


Figure 136-6 *Cryptosporidium parvum* infecting an intestinal crypt *(arrowhead)*. Parasites line the apical surface of the epithelial cells and are covered by host membranes. *Insets*: Oocysts isolated from feces. Upper, organisms isolated after a Sheather's sugar flotation, ×1360. Lower, Giemsa–Jenner stain, ×1360. *(Used with permission of J.A. Fishman, Massachusetts General Hospital.)*

The life cycle of *Cryptosporidium* spp. begins when the infectious oocyst is ingested. These organisms, which are 4 to 5 μm in diameter, may remain viable in the environment for months. After ingestion, they excyst in the small intestine, and release four motile sporozoites, which invade epithelial cells of the intestinal wall. Asexual maturation then results in merozoites being released back into the intestinal lumen. These merozoites either result in reinvasion of epithelial cells, or undergo maturation to become oocysts. The oocysts may then be excreted, or may excyst while still in the lumen to "autoinfect" the host.

CLINICAL FEATURES

Cryptosporidial infection may be asymptomatic, or may be associated with a range of illness from mild diarrhea to severe gastroenteritis. Invasion of the intestinal epithelium results in secretory diarrhea. The biliary tree may be infected, causing cholangitis, and hepatitis and pancreatitis also have been described. Infection may be associated with systemic symptoms such as malaise, nausea, and abdominal cramps. In some patients, diarrhea is voluminous and has been described as "cholera-like." In patients with a normal immune system, cryptosporidial diarrhea usually resolves within 2 weeks. In immunocompromised individuals, especially those with HIV infection and CD4 cell counts less than 100 cells/mm^3, symptoms often continue until the immune status of the individual is restored. In such individuals, cryptosporidiosis may result in a severe wasting syndrome.

PULMONARY CRYPTOSPORIDIOSIS

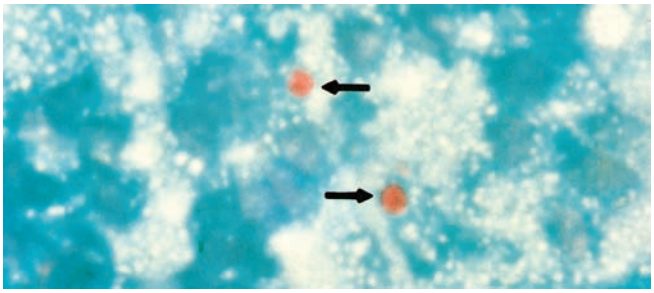
Respiratory infection with *Cryptosporidium* spp. is rare, but has been reported, usually in patients with AIDS (Fig. 136-7).[9] Pulmonary involvement, as with other extraintestinal manifestations of cryptosporidiosis, usually occurs in the setting of intestinal disease. At least one case of pulmonary infection, however, has been reported with no apparent evidence of intestinal infection. Pulmonary involvement may appear as an interstitial infiltrative process or as areas of focal consolidation. Some authors suggest that the prevalence of pulmonary cryptosporidiosis is underestimated, and one study reported a prevalence of 17% in HIV-positive patients with respiratory symptoms.

DIAGNOSIS

Cryptosporidium may not be cultured in vitro, and diagnosis of cryptosporidiosis relies largely on demonstration of pathologic findings in tracheal or bronchial tissues, and visualization of cryptosporidial cysts by microscopy. The cysts may be best seen by acid-fast staining of specimens. Oocysts have been detected in bronchoalveolar lavage, open lung biopsy, and sputum specimens.

TREATMENT

Nitazoxanide decreases diarrhea in immunocompetent individuals with intestinal cryptosporidiosis. However, reliable efficacy has not been demonstrated in individuals with disseminated cryptosporidial disease, or those who are immunocompromised. Thus, in most individuals, treatment is predominantly supportive while attempts are made to restore immune function; in patients with AIDS, this is chiefly through the use of antiretroviral therapy. In addition to nitazoxanide, other agents have been administered to individuals with cryptosporidiosis, although efficacy has not been demonstrated. Administered agents have included paromomycin, trimethoprim–sulfamethoxazole, and metronidazole. Anecdotally, azithromycin has been successfully combined with paromomycin in the therapy of pulmonary infection.



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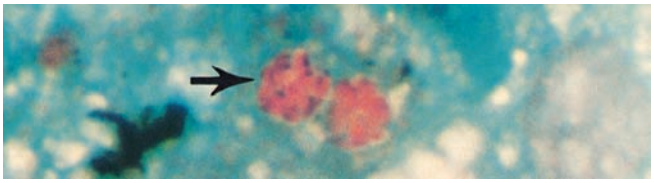

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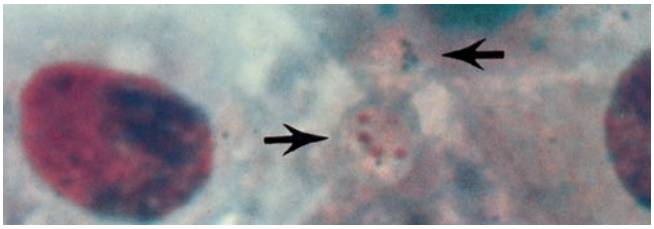

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Figure 136-7 Pulmonary cryptosporidiosis. **A.** Touch preparation from a lung biopsy of a patient with AIDS. *Arrows* show organisms stained with a modified acid-fast stain (modified cold Kinyoun, MCK), which stains the organisms red (×880). **B.** Same preparation and stain as (**A**) showing internal red-black dense granules *(arrow)* characteristic of the organism. **C.** Same preparation as (**A**) showing similar morphology *(arrow)* using a rapid Giemsa hemacolor stain. **D.** Sputum stained with MCK technique reveals organisms *(arrow)*. *(Used with permission of Dr. P. Ma.)*

CYCLOSPORIASIS

Cyclospora cayetanensis is a protozoan organism, usually associated with diarrheal illness in humans. It is ubiquitous, and transmitted usually as a result of contamination of food or water. The protozoan is usually detected as an approximately 10-μm organism on acid-fast stains of specimens. Infection usually responds to trimethoprim–sulfamethoxazole. A single case report of possible pulmonary cyclosporiasis has been reported. A 60-year-old Brazilian man with a history of treated tuberculosis was found to have *C. cayetanensis* organisms in sputum specimens examined for evaluation of respiratory distress and pulmonary infiltrates. No other organisms were detected, and the patient's symptoms resolved following administration of trimethoprim–sulfamethoxazole (and treatment of concomitant intestinal parasitosis).

SARCOCYSTIS

Sarcocystis spp. are intracellular protozoal coccidian two-host parasites. Humans can be a definitive host for *Sarcocystis hominis* and *Sarcocystis suihominis,* and following ingestion of tissue cysts in undercooked beef *(S. hominis)* or pork *(S. suihominis)*, can develop acute gastroenteritis and excrete oocysts. Alternatively, humans can ingest the oocysts of other predator animals and develop a vasculitis that can manifest as myositis, cardiomyositis, or involve the lungs, kidneys, and liver. Eosinophilia is prominent. Eventually the parasites encyst in musculature, including cardiac tissue. Diagnosis is usually based on clinical recognition, myositis associated with eosinophilia and a negative trichinella serology, and/or biopsy of muscle. Treatment is usually supportive, often involving steroids. Cases are usually sporadic, although recurrent outbreaks have been associated with Tioman Island, Malaysia.[10]

MALARIA

Malaria in humans is the result of infection by one of five species of plasmodia: *Plasmodium falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. Human malaria is endemic in parts of sub-Saharan Africa, India, Southeast Asia, the Caribbean, and Central and South America. Approximately 800,000 deaths annually are attributed to malaria, usually among pregnant women and children under the age of 5 years who live in endemic areas. The majority of malaria-related fatalities are a result of infection with *P. falciparum*.

Malaria is acquired by the bite of an infective female *Anopheles* sp. mosquito. In nonendemic areas, malaria cases are found largely in travelers who have returned from malaria-endemic areas, but the parasite also may be transmitted by contaminated blood products, in utero from mother to child, and by organ transplantation. Malaria infection in persons coinfected with HIV is associated with increased HIV viral load, and increased symptoms in the setting of parasitemia.

LIFE CYCLE

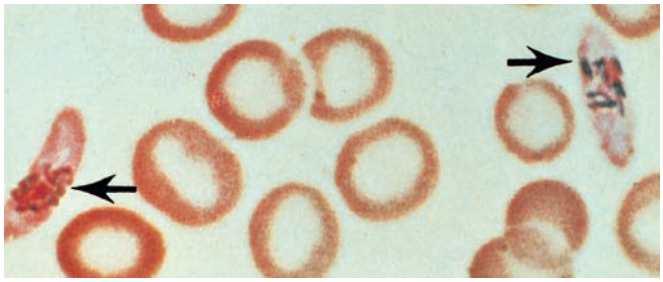
When bitten by an infective mosquito, malarial sporozoites enter the host and travel to the liver, where they invade hepatocytes and divide, forming tissue schizonts in an asymptomatic stage. These schizonts then rupture, releasing thousands of daughter merozoites into the bloodstream. These merozoites invade erythrocytes, and develop to form mature ring forms and ultimately erythrocytic schizonts. A small percentage of merozoites develop into sexual forms called gametocytes. Gametocytes do not cause symptoms, but when another mosquito bites an infected human host, the gametocytes are ingested by the feeding mosquito, permitting the malarial life cycle to continue. *P. falciparum* may infect red blood cells of all ages, resulting in the potential for very high levels of parasitemia.

Infection with *P. vivax* and *P. ovale* may result in a dormant liver phase in which parasites remain in the liver in the form of hypnozoites, potentially causing relapse many months after first infection. *P. falciparum* and *P. malariae* do not have such a dormant stage, and do not cause late relapsing disease. *P. knowlesi* is a simian malarial parasite that has been diagnosed in humans in areas of Asia.

PATHOGENESIS

Malaria-related morbidity and mortality occurs predominantly in children and pregnant women. Most individuals who live in endemic areas develop partial immunity to symptomatic disease as they age. This immunity does not prevent infection, but reduces the frequency of symptoms and severity of disease despite ongoing parasitemia. Infection with any of the five species of malaria causes hemolysis, resulting in anemia that may be severe.

Certain genetic traits associated with hemoglobin structure or erythrocyte surface antigens are associated with decreased infection rates or decreased symptomatic disease. For example, absence of the Duffy antigen on the surface of erythrocytes protects against *P. vivax* infection, and sickle cell trait is protective against severe *P. falciparum* infection. *P. falciparum* also causes the formation of "sticky knobs" on the surface of infected erythrocytes. These knobs comprise host cell and parasite antigens, and mediate binding of infected erythrocytes to endothelial surfaces. This binding results in sequestration of infected erythrocytes, and may result in "sludging"



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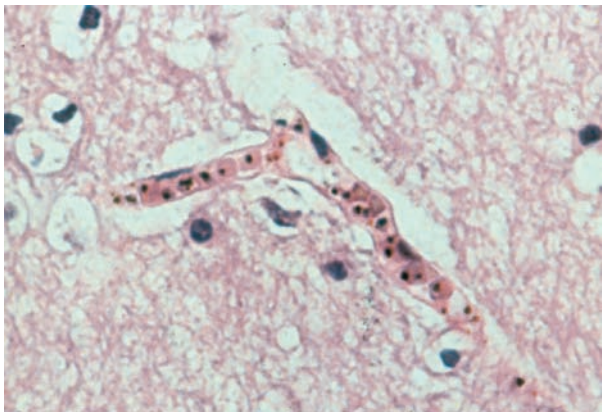

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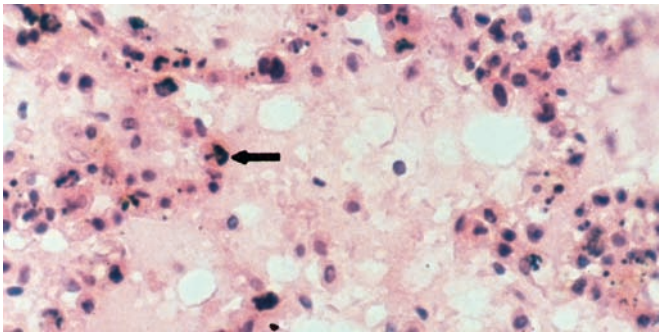

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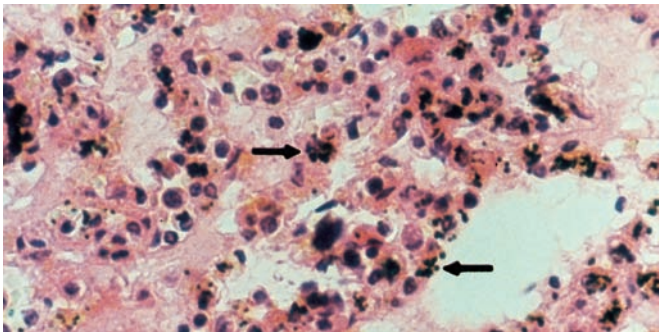

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Figure 136-8 *Plasmodium falciparum*. **A.** Banana-shaped gametocytes on peripheral blood smear *(arrows)*. This form is only seen with falciparum malaria (Wright stain, ×1375). **B.** Cerebral vessels obstructed by parasitized red blood cells *(arrow)* with surrounding edema (hematoxylin and eosin stain, ×1375). **C.** Acute pulmonary edema due to pulmonary venular occlusion (organism at *arrow*; hematoxylin and eosin). **D.** Deposition of malarial pigment *(arrows)* in vicinity of occluded pulmonary vessels.

of blood flow. This sequestration and sludging contributes to microvascular obstruction that can result in organ dysfunction.

CLINICAL FEATURES

Patients with malaria typically present with fever and a constellation of other nonspecific symptoms such as headache, chills, and myalgias. Vomiting, nausea, diarrhea, and cough also may be present. Anemia, thrombocytopenia, and hepatosplenomegaly may be present. Sequestration of infected erythrocytes in the brain may cause cerebral malaria. Individuals with cerebral malaria may present with altered mental status, seizures, focal neurologic findings, or coma. Even with treatment in modern intensive care units, mortality during cerebral malaria is high. Other organ-specific complications of infection are also largely related to microvascular sequestration of parasitized red blood cells in specific tissues, and may manifest as placental, renal, or pulmonary dysfunction (Fig. 136-8).

PULMONARY FEATURES

Pulmonary symptoms such as cough and increased respiratory rate are common during malaria.[11] In African children, malaria frequently presents with symptoms and signs suggestive of pneumonia. Metabolic acidosis is an important cause of respiratory distress in these children, but pneumonitis as a result of sequestered parasitized red blood cells is also responsible. In more severe disease, noncardiogenic pulmonary edema may develop. Initial acute lung injury may progress to ARDS (Fig. 136-9).[12] Tachypnea and dyspnea, followed by hypoxemia and respiratory failure may develop. Studies have confirmed the development of impaired alveolar–capillary membrane function in patients with severe malaria. Lung injury in severe disease is postulated to be not only the result of pulmonary microvascular sequestration, but also a consequence of the inflammatory response to infection.

In a recent study of uncomplicated symptomatic malaria, altered pulmonary physiology, including increased airflow obstruction, decreased gas transfer, impaired ventilation, and increased pulmonary phagocytic activity were found in both *P. vivax*- and *P. falciparum*-associated infections, but were worse in cases of *P. falciparum* malaria.[13] ARDS has also been reported in cases of malaria caused by *P. vivax,* and one case of pulmonary edema has been reported complicating a case of *P. ovale* malaria; however, significant pulmonary morbidity is largely confined to infection by *P. falciparum*, and usually occurs in the context of multisystem involvement.[14] The principal differential diagnosis for pulmonary disease in malaria infection is metabolic acidosis and bacterial pneumonia.

DIAGNOSIS

The diagnosis of malaria should be considered in any symptomatic patient who has had exposure to the parasite in a malaria endemic area. Rare cases of transmission by blood products, organ transplantation, or congenital infection also have occurred. Individuals with malaria caused by *P. falciparum* usually develop symptoms within 3 months of the mosquito bite, and usually within 1 month. Since *P. vivax* and *P. ovale* have potentially dormant liver phases, individuals infected with these parasites may not develop symptoms for many months after exposure (usually within 1 year of the mosquito bite).

Malaria is usually diagnosed through microscopic examination of blood smears, or with antigen-based rapid diagnostic tests (RDTs).

TREATMENT

Appropriate treatment of individuals with malaria depends on the infecting species, severity of disease, age and pregnancy status, and the ability of the patient to take drugs by mouth. Non-falciparum malaria is generally susceptible to chloroquine phosphate, although to date, resistance has been reported in parts of Indonesia, Papua

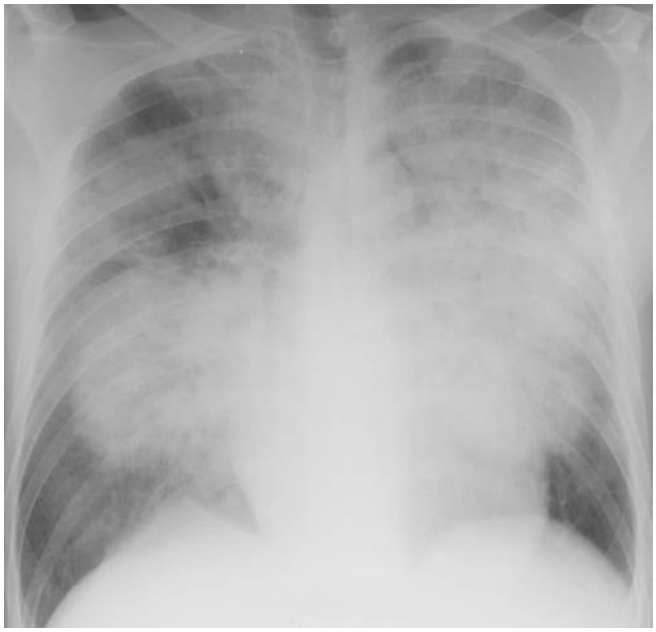

Figure 136-9 ARDS in a 31-year-old man with *P. falciparum* malaria. Chest radiograph demonstrates patchy bilateral areas of increased opacity. *P. falciparum* trophozoites were found in a thick blood smear. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

New Guinea, India, Myanmar, and Brazil. The World Health Organization now recommends that individuals with chloroquine resistant *P. falciparum* malaria be treated with artemisinin-based combination therapies (ACTs) that include an artemisin derivative with a second agent such as lumefantrine, amodiaquine, pyronaridine, piperaquine, or mefloquine. Less optimal alternatives include oral atovaquone–proguanil or mefloquine, or quinine sulfate in combination with either doxycycline or clindamycin. Individuals with severe disease can receive intravenous artesunate in the United States, coadministered with a second agent such as doxycycline or clindamycin. Less optimal alternatives include parenteral quinine dihydrochloride or quinidine gluconate with a second agent.

Individuals with malaria caused by *P. vivax* or *P. ovale* also should be treated with primaquine to treat the hypnozoite form of disease. Primaquine should not be administered to individuals deficient in glucose-6-phosphate dehydrogenase or pregnant women. Pulmonary manifestations and other organ-specific complications of severe infection are treated supportively. Mechanical ventilation may be required. Early institution of renal replacement therapy may prevent subsequent development of ARDS in severe malaria. Exchange transfusion has been recommended for patients with severe falciparum-associated disease with parasitemia levels over 5%, although data on efficacy are controversial.

BABESIOSIS

Babesiosis is a tick-borne infection usually caused by *Babesia microti* in the United States, and *Babesia divergens* in Europe. In the United States, the disease has been reported from Minnesota, Maryland, Virginia, California, Washington State, Georgia, Wisconsin, and Indiana; however, most cases occur in the Northeastern states. Transmission also may occur as the result of infected blood transfusions.

Babesia parasites invade, multiply within, and lyse red blood cells. In immunocompetent hosts, disease is most commonly asymptomatic or relatively mild, and characterized by fever, flu-like illness, myalgias, and nausea. More severe manifestations may include thrombocytopenia, hemolytic anemia, jaundice, meningismus, noncardiogenic pulmonary edema, disseminated intravascular coagulation, hypotension, and shock. Severe disease is most common among the elderly or individuals with compromised immunity. Asplenic individuals are at particular risk of severe disease, and individuals infected with HIV or following organ transplantation are at particular risk of persistent disease. Pulmonary disease in babesiosis occurs in association with multisystem disease, and usually presents as ARDS or noncardiogenic pulmonary edema or ground-glass opacification.[15]

The diagnosis of babesiosis should be considered in any patient with appropriate exposure history who presents with fever or a sepsis syndrome. Diagnosis is usually confirmed by microscopic examination of peripheral blood. Atovaquone, azithromycin, quinine, and clindamycin all have anti-Babesia activity; combination therapy is usually administered.

TRYPANOSOMIASIS

American and African trypanosomiasis are considered below.

AMERICAN TRYPANOSOMIASIS (CHAGAS DISEASE)

Chagas disease is caused by infection with *Trypanosoma cruzi*, a protozoan parasite transmitted to humans most often via the feces of an infected reduviid bug. The disease is endemic in certain South and Central American countries. Clinical manifestations may occur acutely after initial infection. More commonly, clinical manifestations may not become evident until years or decades after initial infection. When acute symptoms do occur, they may include fever, peripheral edema, hepatosplenomegaly, and myocarditis. Chronic sequelae may occur in up to one-third of infected individuals, and usually involves the heart, esophagus, or large bowel (Fig. 136-10).

Cardiac disease usually manifests clinically as congestive-dilatory cardiomyopathy.[16] Chronic dilatation of the esophagus or colon resulting from denervation of the gut may result in Chagasic mega-esophagus or mega-colon. Acute myocarditis may result in pulmonary edema. Pulmonary involvement during Chagas disease is usually secondary to cardiac or intestinal disease, and may include pulmonary edema secondary to congestive heart failure, pulmonary hypertension secondary to right-sided dilatory cardiomyopathy, or aspiration pneumonia secondary to vomiting and regurgitation associated with mega-esophagus or mega-colon. Recurrent aspiration and pneumonitis may lead to lung abscesses, fibrosis, scarring, and bronchiectasis. The debilitation of chronic Chagas disease may lead to cachexia, and may be associated with a higher rate of tuberculosis. In an autopsy review of 69 adult cases of Chagasic mega-esophagus in Brazil, 35% of patients had pneumonia, and 22% had pulmonary tuberculosis—rates that were higher than in a cohort of patients in the same study who had Chagasic cardiac disease, but no mega-esophagus.

Congenital Chagas disease has been associated with pneumonitis; and in an autopsy review of 10 congenital cases, pathologic findings have included diffuse pulmonary interstitial edema and endothelial swelling in lung tissues.

Diagnosis in acute Chagas disease may be made by detecting parasites on blood smear. Culture of parasites from specimens is possible using specialized media, although the usefulness of this method is limited because culture may take several weeks. In chronic disease, parasites are not usually visualized. Diagnosis is usually based on serologic analysis, suggestive radiology, and, more rarely, pathologic examination of tissues. Treatment in acute disease and in patients with immunosuppression is warranted, and nifurtimox and benznidazole are the mainstays of therapy. Posaconazole may also have some activity. The utility of treating individuals with established, chronic disease with antiparasitic agents is currently unclear.

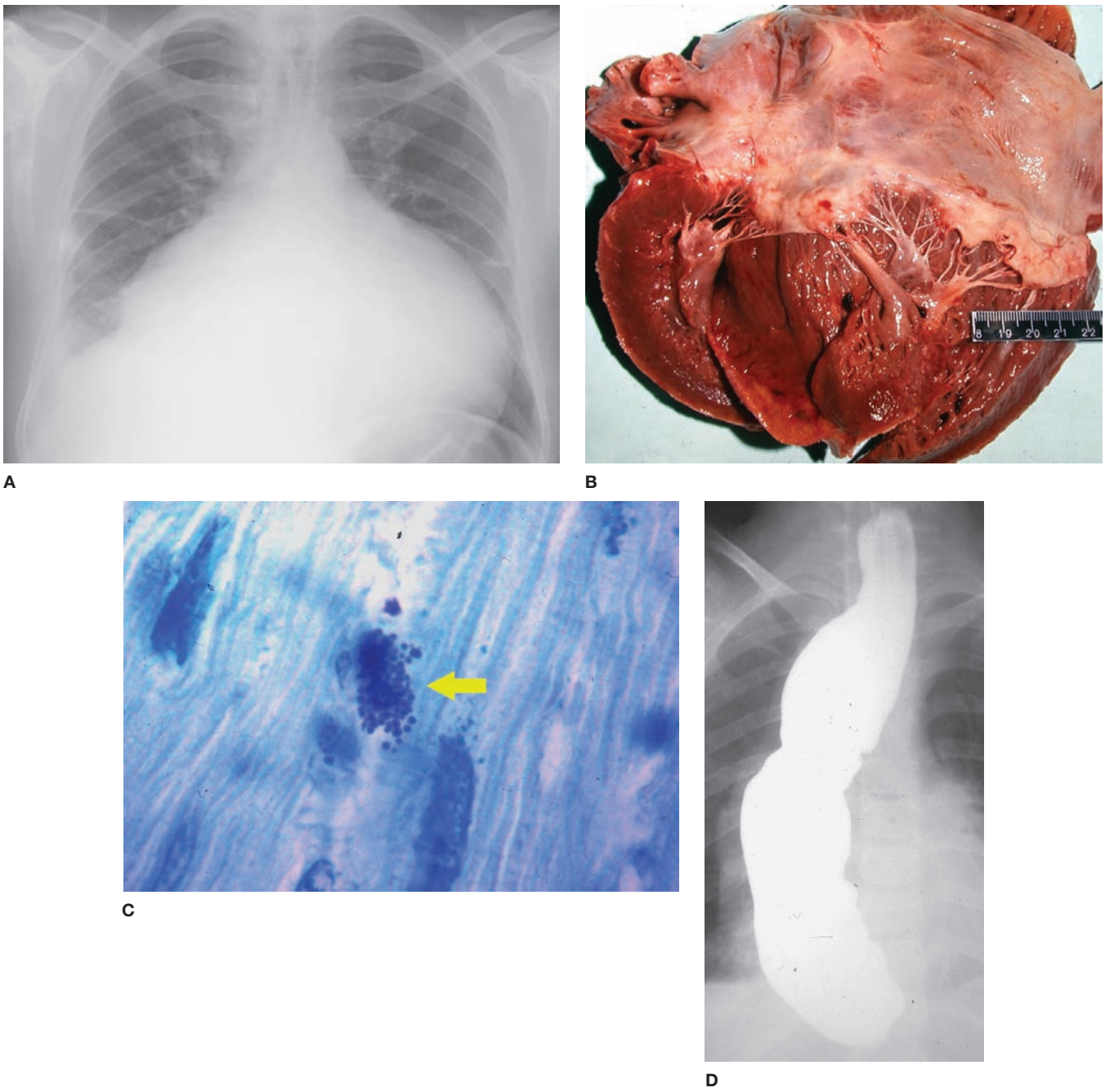

Figure 136-10 Chronic Chagas disease in a 39-year-old man with chronic dilated cardiomyopathy. **A.** Chest radiograph shows global cardiomegaly with pulmonary congestion. **B.** Photograph of the gross specimen demonstrates dilatation of the cardiac chambers with thickening of the ventricular myocardium. Scale is in centimeters. **C.** Low-power photomicrograph (original manifestation, ×10; Giemsa stain) shows *T. cruzi* amastigotes within a myofiber *(arrow)*. **D.** Chagasic achalasia in a 13-year-old girl with Chagas disease. Barium esophagogram shows diffuse and severe dilatation of the esophagus. Histologic analysis demonstrated *T. cruzi* amastigotes within the esophageal wall. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

■ AFRICAN TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS)

Trypanosoma brucei gambiense and *Trypanosoma brucei rhodesiense* are the causative agents of African trypanosomiasis (African sleeping sickness). African sleeping sickness is usually transmitted by the bite of an infective tsetse fly. East African trypanosomiasis is caused by *T.b. rhodesiense*. Individuals with East African trypanosomiasis are often acutely ill with fever, lymphadenopathy, headache, and myalgia. Disease may be fulminant, and individuals may develop disseminated intravascular coagulopathy, ARDS, hypotension, and shock. The most common pulmonary manifestations during acute disease are noncardiogenic pulmonary edema and ARDS. West African trypanosomiasis is caused by *T.b. gambiense*. Individuals with West African trypanosomiasis usually do not develop severe disease during the acute stage. Rather, months or years after initial infection, infected individuals present with mental status changes, personality changes, recurrent fever, lymphadenopathy, weight loss, and disorders of circadian rhythm. QTc prolongation can occur.[17]

The most common pulmonary manifestation during late-stage disease is pneumonitis second to recurrent aspirations associated

with inanition and altered mentation. Direct pulmonary involvement is not common in West African trypanosomiasis. A single case report describes an African child who presented with severe respiratory symptoms, and was later found to have African trypanosomiasis.

LEISHMANIASIS

Leishmaniasis is caused by an intracellular protozoa parasite in the *Leishmania* genus. The Leishmania parasites are widely distributed, and are usually transmitted through the bite of an infective sand fly. Infection of humans may be asymptomatic, or may involve the skin (cutaneous leishmaniasis), the mouth or nose (mucocutaneous leishmaniasis), or be systemic (visceral leishmaniasis). Human infection is most common in South and Central Asia, the Middle East, the Mediterranean, Balkans, North Africa, sub-Saharan Africa, and Central and South America. Specific organisms are often responsible for specific clinical syndromes, although overlap occurs. Disease is often considered as "New World" or "Old World," based on geographic location. The parasite exists as an intracellular organism (amastigote) in host macrophages, and as an extracellular promastigotes in the sandfly gut—being inoculated into the host's skin during the bite of the fly.

CLINICAL FEATURES

Cutaneous syndromes may range from localized disease, usually on exposed areas of skin, to widespread cutaneous involvement. In localized disease, painless ulcers develop and most often resolve spontaneously over months. Classically, "Old World" cutaneous leishmaniasis is caused by *L. major, L. tropica, L. aethiopica,* or *L. infantum*; "New World" cutaneous disease is usually caused by *L. braziliensis* or *L. mexicana* complex organisms. Some New World species are associated with the development of mucocutaneous disease months to years after resolution of the initial skin lesions. Severe destruction and disfiguration of the face with resultant aspiration pneumonitis may occur.

Visceral leishmaniasis is usually caused by *L. donovani, L. infantum,* or *L. chagasi*. Individuals with visceral leishmaniasis usually present with fever, hepatosplenomegaly, weight loss, pancytopenia, and hypergammaglobulinemia. Lymphadenopathy is commonly present. Gastrointestinal symptoms are common in advanced disease, and individuals with untreated visceral leishmaniasis develop a wasting syndrome. Pneumonia and tuberculosis may be the cause of death.

PULMONARY DISEASE

Pulmonary involvement from leishmaniasis in immunocompetent hosts is rare, but interstitial pneumonitis has been reported. However, immunosuppressed patients, particularly those with HIV infection, are at increased risk of atypical disease. In areas surrounding the Mediterranean, where seroprevalence for *L. infantum* in young adults may be as high as 30%, an increase in the incidence of HIV infection has caused an increase in the number of advanced cases of visceral leishmaniasis; a result either of new infections or reactivation of old infections. Patients with leishmaniasis and HIV infection may present with cough, dyspnea, hemoptysis, granulomatous mediastinal lymphadenopathy, solitary pulmonary nodules, or pleural effusions. Advanced visceral leishmaniasis may be complicated by suprainfecting pneumonia even in immunocompetent hosts.[18]

Treatment of leishmaniasis depends on type of disease (cutaneous vs. mucocutaneous vs. visceral), infecting species, parasite resistance patterns, severity of disease, and status of the host. Therapeutic options include liposomal preparations of amphotericin, amphotericin B, pentavalent antimony (sodium antimonylgluconate or N-methylglucamine antimonate), pentamidine, and miltefosine.

CILIATE INFECTIONS: *BALANTIDIUM COLI*

Balantidium coli is the only ciliated protozoa that infects humans. Infection of humans usually occurs in individuals with contact with pigs, and human disease usually manifests as an infectious colitis very similar to amebiasis. Rare cases of pulmonary infection have been reported in humans: in a leukemic patient who presented with pulmonary lesions, in a 71-year-old woman with anal cancer and pneumonia, and a patient with chronic colitis and an intrapulmonary mass.[19,20]

Diagnosis is usually made through histologic examination of tissue samples. Treatment with tetracycline, metronidazole, or iodoquinol is usually effective.

FLAGELLATES

Two flagellates are discussed briefly below: *Trichomonas* species and *Giardia lamblia*.

TRICHOMONAS SP.

Trichomonads are flagellated protozoa. Pulmonary disease has been attributed most commonly to *Trichomonas tenax*, an organism that is most often considered a commensal in the human oropharynx, especially in individuals with poor oral hygiene. In one study of symptomatic patients, prevalence of *T. tenax* by PCR among 100 immunocompromised and 100 patients with chronic pulmonary disease was 10%.[20]

Diagnosis is most often made by examination of a wet mount of sputum or bronchoalveolar lavage specimen. Chronic purulent, necrotic pulmonary disease, or pleural involvement has been described, often thought to be a result of aspiration.[21] Affected individuals have responded to metronidazole therapy.

GIARDIA LAMBLIA

Giardia lamblia is a pathogenic intestinal flagellate of humans. In humans, it usually causes chronic diarrhea and malabsorption. There is one case report of uncertain significance of recovery of *G. lamblia* trophozoites from bronchoalveolar lavage fluid.

MICROSPORIDIOSIS

Microsporidia is the name given to a group of spore-forming obligate intracellular organisms from the phylum *Microsporidia*. These organisms have been variously considered with the protozoa and fungi. Over 1200 microsporidia species occur worldwide, but the most common human pathogens are *Enterocytozoon, Encephalitozoon, Nosema, Pleistophora*, and *Septata* spp.

The microsporidia spore is the infective form of the organism, and when ingested or inhaled, it extends a polar tubule that infects the host cell. Within the host cell, replication occurs and more spores are formed. When spores sufficiently fill the cell, the cell membrane ruptures and spores are released; they may then proceed to infect nearby cells, or be passed into the environment in stool, urine, or respiratory secretions.

Most clinical cases of microsporidiosis in humans occur in immunocompromised hosts. In immunocompetent patients, infection with *Enterocytozoon bieneusi* can be asymptomatic or may cause acute and very rarely chronic diarrhea. In patients with HIV infection, symptomatic microsporidiosis tends to occur in advanced disease, such as when CD4 cell counts are less than 100 cells/mm^3. *E. bieneusi* and some species of Enterocephalitozoon (*E. hellem, E. cuniculi,* and *E. intestinalis*) have come to be recognized as major causes of diarrheal enteritis and disseminated infection in patients with AIDS. Disseminated disease caused by *Trachipleistophora* also has been described. Microsporidial species have been associated with disseminated disease including biliary tract disease, sinusitis, myositis, respiratory infection, and keratoconjunctivitis.

Pulmonary Disease

Microsporidial disease with specific pulmonary involvement has been described in cases of patients with HIV infection, and in individuals who have undergone bone marrow or organ transplantation (Fig. 136-11).[22]

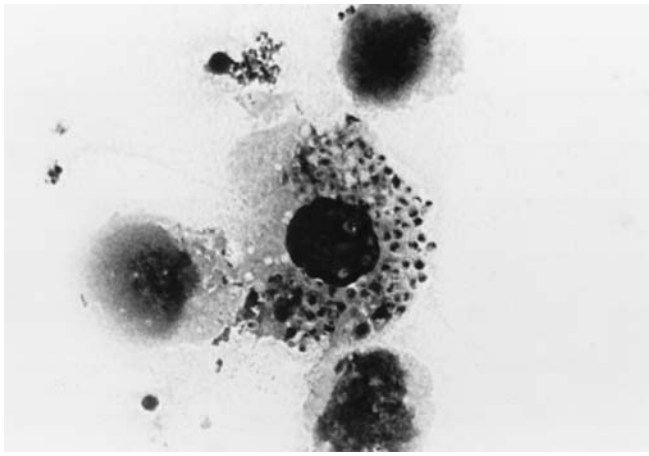

Figure 136-11 Pulmonary microsporidiosis. Tiny organisms (~1 μm) within a pulmonary macrophage obtained via bronchoalveolar lavage (Giemsa–Wright stain, ×1000). *(Used with permission of Dr. C. Wanke.)*

Pulmonary disease usually occurs in the setting of concomitant intestinal infection. In one retrospective review of 42 patients with HIV and microsporidial infection, 24% had respiratory symptoms, and four of six patients who had specimens examined had sputum or bronchoalveolar lavage positive for microsporidia.[23]

Diagnosis

Diagnosis of microsporidiosis is based on identification of organisms in specimens of tissue or stool. Modified trichome staining allows detection of organisms on light microscopy, but electron microscopy is currently the definitive diagnostic method. Tissue culture, serologic assays, and PCR testing are used in research settings, but are not yet commercially available.

Treatment

Albendazole has activity against *Encephalitozoon* species, but is only partly effective against *E. bieneusi*. In immunocompromised individuals, treatment is directed at enhancing the immune status of the patient, that is antiretroviral therapy in patients with HIV infection, and decreased immunosuppression in transplant recipients. Duration of albendazole therapy depends on the severity of illness. *E. bieneusi* infections may be refractory to treatment.

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CHAPTER 137

Helminthic Diseases of the Lungs

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Parasitic helminths are a distinct group of infectious agents that are among the most prevalent causes of morbidity and mortality in humans worldwide. Billions of people harbor parasitic worms. People with helminthic infections of the lungs often seek medical advice because of one or more common chest complaints—cough, pain, or breathlessness. They may also have unexplained laboratory abnormalities, including eosinophilia or pulmonary nodules. They can pose a diagnostic challenge, particularly in areas where helminthic infections are not endemic. More common causes of chest complaints have to be excluded, a history of residence in certain geographic locations or of dietary or other exposures has to be elicited, and the proper procedures for making the diagnosis of helminthiasis selected.

The helminths that parasitize humans include the nematodes (roundworms) and the platyhelminthes (flatworms), with the flatworms divided into the cestodes (tapeworms) and the trematodes (schistosomes and other flukes). The biology of each of these groups is distinct. Ectoparasites (e.g., the Annelida, such as leeches, ragworms, or earthworms) are uncommonly associated with lung disease and are not discussed here.

In humans, worms produce a variety of pulmonary parenchymal and vascular diseases (Table 137-1). Familiarity with the biologic behavior of each organism is essential for proper diagnosis and treatment because several stages in the life cycle of the parasite are typically found in humans, and pulmonary lesions can occur at different stages, depending on the infecting parasite.

BIOLOGY AND IMMUNOLOGY

Worms are multicellular organisms that vary substantially in size—from a few millimeters to several meters. They are covered by a tegument cuticle that protects them from the environment. Reproductive organs – both sexual and hermaphroditic – take up a large portion of the body. They are among the most developed and elaborate of human parasites, and their parasitic capabilities are such that they often inhabit more than one host and survive different hostile environments. Despite their relatively large adult size, the infective stages of the worms invade human tissues by ingestion, penetration of skin, or the bite of insect vectors. Furthermore, parasitic helminths have developed a myriad of mechanisms by which they may evade the defense system of the host.

The life cycle of the helminths includes an egg form, several larval stages, and an adult form. Human infection is by ingestion of the eggs or larvae, penetration of the skin by larvae, or insect transmission of larvae. Humans may be the only host (in whom both development and reproduction of the parasite occur), an accidental host (in whom neither development nor reproduction occur), an intermediate host (in whom only asexual development occurs), or a definitive host (in whom sexual reproduction occurs). A basic biologic generalization about helminthic infections is that the worms, as a rule, cannot multiply within the mammalian host. This phenomenon is important for understanding the dynamics of helminthic infection and the relationship between the intensity of a particular worm load and its pathologic consequences to the host. However, there are exceptions to this rule. For example, *Strongyloides stercoralis* and *Echinococcus granulosus* can increase their numbers within a host, even though the host is not exposed to additional infective forms. This ability of *S. stercoralis* to autoinfect the same subject is of considerable clinical significance, especially in immunosuppressed patients, in whom it can lead to a fatal hyperinfection. A different example is that of echinococcosis, where dissemination is usually a consequence of leakage or rupture of a hydatid cyst, which allows its contents to initiate similar lesions elsewhere.

Another biologic characteristic of worm infections is the association with tissue and peripheral blood eosinophilia and increased levels of immunoglobulin E, similar to that seen with atopic disease.[1] When eosinophilia is marked, this association provides a clinically useful sign of a migratory worm infection. The prominent peripheral blood eosinophilia of tissue migratory worm infections contrasts with the lack of eosinophilia seen in people in whom the worm infection is confined to the gut lumen or in whom the infection is due to another agent (e.g., viruses or bacteria). It should be

TABLE 137-1 Pulmonary Parenchymal and Vascular Diseases Produced by Worms

Major Pulmonary Presentation	Infection	Causative Organism	Infective Stage	Pathogenic Stage
Loeffler-like syndrome	Ascariasis	*Ascaris lumbricoides*	Embryonated eggs in soil	Migrating larvae
	Hookworms	*Ancylostoma duodenale, Necator americanus*	Larvae in soil	Migrating larvae
	Strongyloidiasis rhabditiform	*Strongyloides stercoralis*	Larvae in soil	Migrating larvae
	Hyperinfection with filariform	*S. stercoralis*	Larvae in bowel	Migrating larvae
Pulmonary eosinophilia	Lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi*	Larvae in mosquito	Microfilariae
Eosinophilia, cough	Visceral larva migrans	*Toxocara canis, T. cati*	Egg ingestion	Larvae
Space-occupying lesions	Echinococcosis	*Echinococcus granulosus*	Eggs in soil	Hydatid cysts
	Paragonimiasis	*Paragonimus westermani*	Metacercariae	Adult worms
	Schistosomiasis	*Schistosoma mansoni, S. japonicum, S. haematobium*	Cercariae in fresh water	Eggs

noted that patients who lack *cellular* immune function are often unable to produce this characteristic sign. Corticosteroids may also lyse eosinophils and complicate diagnosis.

Although it has long been thought that eosinophils play a vital role in the host defense against helminths, our understanding of their role has become much more sophisticated in recent years.[1,2] Although eosinophils – along with antibodies or complement – kill the larval forms of several helminths in vitro, not all animal and human studies confirm the importance of eosinophils in host protection.[1,3,4] Moreover, eosinophils may actually contribute to the pathogenesis and tissue destruction seen with certain helminthic infections.[2] Currently, it is thought that immunity to the helminths does not rest on any single cell type, but rather a coordinated effort from multiple immune pathways. Although the adaptive immune system plays a vital role in coordinating this attack via *sensitized* lymphocytes, much of our immunity to parasites rests with innate pathways of host defense.[2,5] It has also become increasingly recognized that sterilizing immunity to helminths is rarely achieved, likely due to their sophisticated mechanisms of immune evasion and the high cost of fully eradicating these large, multicellular organisms Rather, most of the time, humans and helminths exist in a state of evolutionary-derived tolerance.

HOST–PARASITE RELATIONSHIP IN PULMONARY HELMINTHIASES

Human disease caused by pulmonary helminthiases results from various factors. Many helminths can reside in human lungs during one or more of their parasitic stages. However, the stage of the life cycle that causes human pulmonary disease varies—for example, larvae of nematodes, eggs of schistosomes, and adult worms in paragonimiasis or cestode infections. The multiplicity and complex structure of these etiologic agents lead to a heterogeneous set of responses, both immunologic and nonimmunologic. Moreover, disease may result from the mechanical presence of worms (i.e., space-occupying lesions) and the associated inflammatory response, as a byproduct of the host immune response, or both. For example, in echinococcosis, hydatid cysts displace lung tissue, but in pulmonary schistosomiasis, the vascular obstructive lesions are predominantly the outcome of the delayed-hypersensitivity response of the host causing granuloma formation. Therefore, the understanding of the host–parasite relationship in pulmonary helminthiasis is based on an appreciation of the heterogeneity of these etiologic agents and the corresponding host responses.

The immune responses of the host often feature prominently in shaping the pathologic consequences of helminthic infection of the lungs. In experimental animals, the degree of tissue injury and host responsiveness to several helminthiases has been shown to be regulated by modulatory antibody, cellular, and cytokine responses. Whether humans acquire resistance to helminthic infection and whether resistance can be induced has not been fully resolved. Resistance against several helminths occurs in experimental and wild animals after primary infection and can be induced by defined antigens.[6] It can also be seen in individuals who avoid certain parasitic infections, such as lymphatic filariasis, despite living in worm endemic areas.[7]

An additional and biologically relevant factor concerning helminthic infections and their role in the etiology of human disease is the intensity of infection. Since most worms that infect humans cannot increase their population without additional exposure to the infective stages, the worm load largely determines the degree of pathologic sequelae. For example, the number of schistosome eggs reaching the pulmonary circulation is an essential determinant of the severity of the induced disease. Although the number of eggs reaching the lungs may be influenced by several factors, the most important determinant is the number of adult worms in the infected person.

APPROACH TO THE PATIENT WITH HELMINTHIC INFECTION OF THE LUNGS

The major symptoms and signs of pulmonary disease are similar across different etiologic agents—infectious and noninfectious alike. Certain clues in the history are necessary to trigger the consideration of a helminthic infection. The geographic distributions of the major helminthic infections are roughly known. Therefore, a history that the patient has lived overseas or in certain parts of the United States is helpful in alerting the examiner to the possibility of a helminthic infection. Although helminthic infections are generally more common in temperate and hot areas of the world, certain parasites may be acquired in the United States and other colder areas. Other infections are acquired from specific animal exposures or occupations, such as *E. granulosus* and exposure to dogs and sheep. Therefore, infection with *E. granulosus* is more likely in sheep-raising countries and in certain sheep-raising areas in the United States.

Eosinophilia in peripheral blood, sputum, or pulmonary tissue is a helpful clue in directing the diagnostic workup. Although increased eosinophil counts do occur in several other pulmonary diseases, the close association with helminthic infections necessitates appropriate diagnostic procedures to determine whether a worm is implicated. However, eosinophilia may not be present for all individuals. Knowledge of the immunologic status of the patient can be valuable in suggesting helminthic infection in the absence of eosinophilia—for example, the hyperinfection syndrome caused by *S. stercoralis*.

Definitive diagnosis of pulmonary helminthic infections requires isolation and identification of the parasite that routine examination of appropriate specimens may miss. Laboratory personnel should always be alerted when the examiner is considering the possibility of a worm infection so that proper samples can be obtained and preserved for special examinations. Serologic testing for helminths is particularly useful in nonendemic settings. It should be considered an adjunct to isolation of the pathogen and an important diagnostic procedure.

DISEASES DUE TO NEMATODES (ROUNDWORMS)

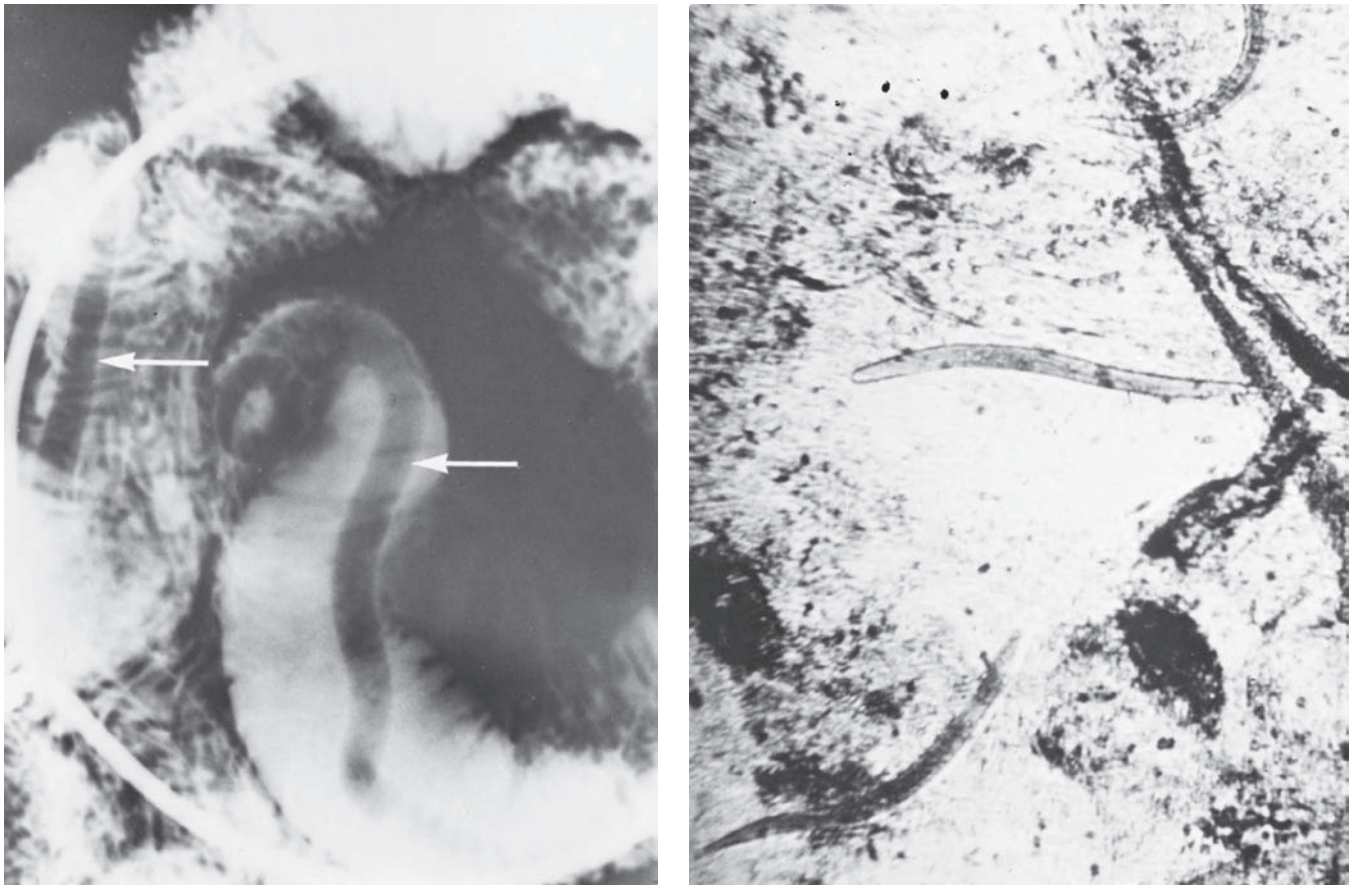
Among the most important helminthic infections of humans are the nematodes. The biology, clinical manifestations, and management of nematode infections are discussed below.

■ ASCARIASIS, HOOKWORMS, AND STRONGYLOIDIASIS

Human infections with *Ascaris lumbricoides,* the hookworms *Ancylostoma duodenale* and *Necator americanus,* and *S. stercoralis* are among the most prevalent helminthiases worldwide. Transmission is seen in the southeastern United States.

Etiology

Human ascariasis (Fig. 137-1) results from ingestion of embryonated *A. lumbricoides* eggs that are contained in feces-contaminated soil. Ingestion of contaminated fruits and vegetables that have not been properly washed is the most frequent transmission vehicle. *Ascaris* eggs hatch in the gastrointestinal tract, producing larvae that penetrate the gut wall and migrate via venous blood and the right side of the heart to the lungs. Hookworms (*A. duodenale* and *N. americanus*) and *S. stercoralis* infect humans when infective larvae in the soil penetrate intact skin. The larvae then travel via the bloodstream to the lungs (Table 137-1). Next, they migrate via the pulmonary capillaries into the alveolar spaces. Once in the alveolar spaces, they ascend in the trachea and, ultimately, are swallowed to begin their final route to habitation in the small intestine. Here, the adults lay eggs that



A B

Figure 137-1 Nematodes. **A.** Ascariasis. Barium in the small intestine outlines two *Ascaris* worms *(arrows)*. **B.** *Strongyloides stercoralis.* Rhabditiform larvae. *(Used with permission of Dr. Stanley H. Abadie.)*

are either directly passed in the stool (*A. lumbricoides, A. duodenale,* and *N. americanus*) or hatch into larvae within the intestinal tract *(S. stercoralis)* and then passed into the stool. Although larvae are sometimes found in the sputum of infected persons, more often examination of the stool yields the diagnosis. Passage to the outside environment, where the noninfectious stool forms develop into forms infective for humans, completes their life cycle.

Pathogenesis and Pathology

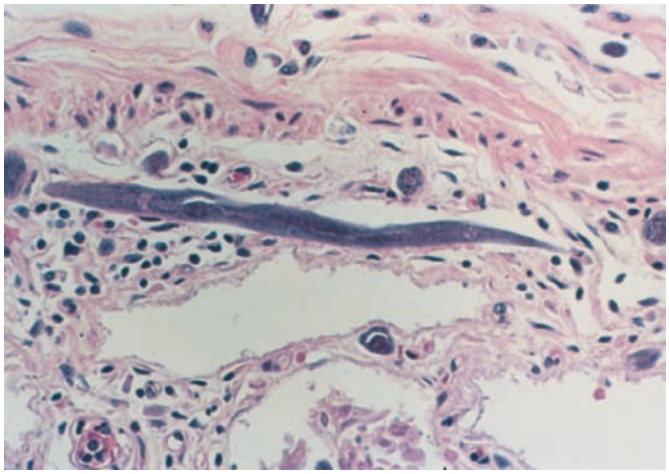
In nematode infections, the most prominent pulmonary pathologic changes occur in persons with ascariasis or the hyperinfection syndrome of strongyloidiasis. Pulmonary symptoms from *Ascaris* may occur 1 to 3 weeks after primary infection. Portions of larvae are seen in the pulmonary parenchyma, surrounded by a patchy infiltrate of neutrophils and eosinophils. The alveoli contain a serous exudate and the production of bronchial mucus is increased. Later, migrating larvae are destroyed within aggregates of eosinophils. The intensity of the reaction depends on the number of parasite larvae and previous sensitization. In areas in which transmission of *Ascaris* eggs occurs seasonally, pulmonary reactions are usually more frequent during these periods.[8]

In *immunocompetent* subjects, pulmonary disease caused by hookworms or *S. stercoralis* is minimal as the worm burden is usually low. It should be noted that infection with *Strongyloides* is lifelong. In nonimmunosuppressed subjects, the majority of the rhabditiform larvae found in the stool have to go to the outside world to transform into the infective filariform larvae. Only a few infective filariform larvae develop in the gut and penetrate the intestinal mucosa to restart the developmental cycle (autoinfection).

The sequence of events in *immunosuppressed* patients indicates that a change has occurred in the reproductive cycle of the parasite. In immunosuppressed patients, adult females may replicate by pathogenesis and the change to infective filariform larvae more frequently occurs within the gut lumen leading to a sharp increase in worm burden.[9] The infective filariform larvae penetrate the intestinal mucosa resulting in massive invasion of almost every organ, including the lungs. Consequently, life-threatening infection with *S. stercoralis* results from the premature development of large numbers of filariform larvae in immunocompromised persons that invade across the gut wall or perianal skin, carrying intestinal bacteria into the peritoneum and bloodstream.[9] Tissue migration of the worms occurs through most body organs, including the lungs. Initially, the pulmonary lesions resemble those of *Ascaris* pneumonia. In some patients, bronchopneumonia and lung abscesses develop while the lungs of fatal cases show intra-alveolar hemorrhages and inflammatory changes.[10]

Clinical Features

The major clinical manifestations caused by infection of the lungs with the larval forms of intestinal nematodes resemble those described by Loeffler;[11] these manifestations occur typically in patients with *Ascaris* pneumonia, but rarely have been reported in patients with hookworm pneumonia.[8,12] Symptoms include persistent, irritating, and nonproductive cough, substernal pain, and – in the severely ill – hemoptysis and dyspnea. Eosinophilia is the most consistent laboratory finding. Radiographic signs – for example, patchy or miliary infiltrate – are sometimes seen. *Ascaris suum* (pig roundworm) may cause a similar pulmonary process, although it



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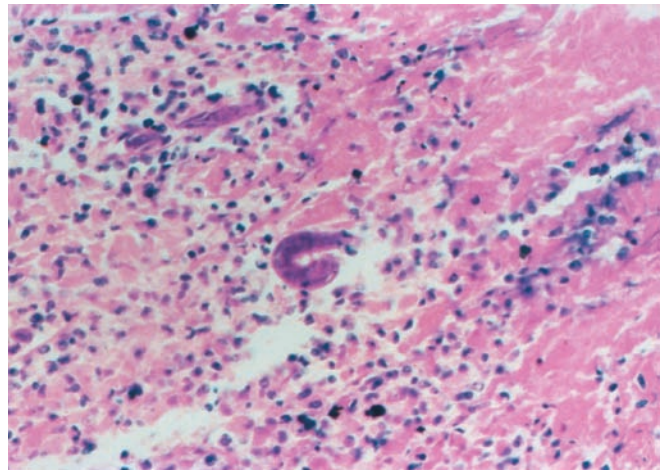


B

Figure 137-2 Strongyloidiasis. **A.** A 55-year-old man with chronic lymphocytic leukemia who presented with abdominal discomfort and weight loss. The patient developed progressive pulmonary congestion and edema with dyspnea, fever to 103°F, and progressive hypotension before death. Blood cultures revealed *Escherichia coli.* Histologic section of colon at autopsy shows adult *S. stercoralis* in wall. **B.** A 24-year-old man with AIDS who developed diarrhea, weight loss, and, finally, shock with *E. coli* bacteremia and strongyloidiasis. The larval form is shown in the jejunum. *(Used with permission of Dr. Jay A. Fishman.)*

does not exhibit all of the same developmental stages as *A. lumbricoides* since humans are only accidental hosts.[13]

The onset of the Loeffler-like syndrome caused by intestinal nematodes usually occurs 1 to 3 weeks after infection, coincident with larval migration from the pulmonary circulation to the alveoli. This timing was illustrated in a report of a group of students exposed to eggs of *A. suum.*[14] Typical pulmonary symptoms occurred 10 to 15 days later, and some of the students developed marked respiratory failure. In locations in which transmission of ascariasis is cyclic because of environmental factors, pneumonitis occurs seasonally.[8] Mild symptoms are occasionally encountered in persons with hookworm infection or in immunocompetent subjects who have strongyloidiasis.

The most clinically significant pulmonary syndrome induced by intestinal nematodes is that caused by hyperinfection with *S. stercoralis* (Fig. 137-2). As a rule, the syndrome occurs in patients with compromised cell-mediated immunity because it is a consequence of a high worm burden. However, it is occasionally encountered in normal persons. Immunosuppression may be the result of neoplastic diseases, including lymphomas and leukemias, or nonmalignant conditions that are being treated with corticosteroids – for example, organ transplantation. However, the autoinfection cycle means that disease due to *S. stercoralis,* including hyperinfection, may develop as late as 75 years after initial exposure.[15]

The major pulmonary clinical features include asthma, pulmonary opacities, which include cavitation, consolidation, and diffuse patchy infiltrates.[10] Usually, widespread dissemination of the nematode is accompanied by secondary infection caused by gram-negative bacteria carried along with *S. stercoralis* from the gut. Consequently, gram-negative meningitis and sepsis may also be prominent features of this syndrome. Eosinophilia is often absent in patients with the *S. stercoralis* hyperinfection syndrome, due to either defective cell-mediated immunity or the use of corticosteroids in many patients. The *S. stercoralis* hyperinfection syndrome is often fatal; mortality occurs in up to 87% of people with disseminated infections.[16]

Management

The diagnosis of infection with intestinal nematodes that causes a Loeffler-like syndrome may be difficult. Only occasionally is the search for parasite larvae in sputum rewarding. Stool examination is negative at this point because the adults have not yet reached the small intestine and begun producing eggs. Not infrequently, definitive diagnosis is delayed for weeks until the adult worms mature in the small intestine. At this stage, fecal examination discloses the characteristic eggs of hookworms or *Ascaris* or the larvae of *S. stercoralis.* The management of patients with the pulmonary manifestations of these parasitic worms is nonspecific and symptomatic. Reduction of exposure in areas in which transmission of ascariasis is seasonal decreases the prevalence and severity of clinical presentations. Specific antihelminthic therapy is ineffective during the pulmonary stage but can cure the infection once the parasites reach maturity in the small intestine.

Albendazole, 400 mg orally once, or mebendazole, 100 mg per day for 2 to 3 days (or 500 mg orally once) are the drugs of choice for treating ascariasis and hookworms (Table 137-2). Ivermectin, 200 μg/kg per day for 2 days (longer for hyperinfection syndrome) is recommended for strongyloidiasis.[17] This treatment may be repeated at 2 weeks (the duration of one autoinfection cycle) to ensure eradication is complete. Albendazole, 400 mg orally daily for 2 days may be used as an alternative, but it is less effective.[17,18]

In patients suspected of having the hyperinfection syndrome, early diagnosis leading to modification of immunosuppressive therapy, prompt anti-*Strongyloides* chemotherapy, and adjunctive antibacterial therapies are important elements in averting a fatal outcome. Thus, a high degree of suspicion for strongyloidiasis is needed in dealing with pulmonary disease associated with bacteremia in immunosuppressed patients. Most instances of strongyloidiasis in these patients are diagnosed only shortly before death or at autopsy. Aggressive efforts at demonstrating *S. stercoralis* larvae entail repeated examination of stools and duodenal aspirates. Sputum and bronchial washings should also be examined for parasite larvae and serology may be of help, particularly in nonendemic areas. In these patients, therapy should be started as early as possible and continued daily for at least 2 weeks after the last positive stool examination (the duration of one autoinfective cycle).[9] Some may require longer or repeat therapy, depending on the cause of their immune suppression and their risk of relapse—for example, HTLV-1 infected individuals.[18] Serologically positive individuals for *Strongyloides* should be treated prior to the start of immunosuppression for organ transplantation or cancer chemotherapy, generally with empiric ivermectin.

TABLE 137-2 Therapies of Pulmonary Diseases Produced by Worms

Organisms	Common Therapies	Comments
Ascaris lumbricoides	Albendazole, mebendazole, pyrantel, ivermectin, piperazine	Infection may persist for 1–2 y
Ancylostoma duodenale		Infection for ~1 y
Necator americanus	Albendazole, mebendazole, levamisole, pyrantel	Infection may persist for 3–5 y
Strongyloides stercoralis	Ivermectin, albendazole, thiabendazole	Hyperinfection with *S. stercoralis* with meningitis or sepsis requires therapy for gram negative or mixed infection; infection may be latent for >30 y (lifetime)
Wuchereria bancrofti, Brugia malayi	None satisfactory; diethylcarbamazine citrate or ivermectin reduces worm burden but no effect on clinical course	Prevention by mosquito control; possible addition of albendazole to other therapies
Echinococcus granulosus	Albendazole, mebendazole	Space-occupying lesion may require surgical resection in toto; may risk dissemination without cysticidal therapy (hypertonic saline, 0.5% cetrimide, 70–95% ethanol, iodine); PAIR procedure—percutaneous aspiration and cysticidal therapy
Paragonimus westermani	Praziquantel (bithionol not always available)	
Schistosoma mansoni, S. japonicum, S. haematobium	Praziquantel (oxamniquine for *S. mansoni* and metrifonate for *S. haematobium* not always available)	
Toxocara canis, T. cati	None proved (albendazole, thiabendazole, mebendazole, diethylcarbamazine citrate, others)	Anti-inflammatories for cough; corticosteroids for symptoms or with therapy

PULMONARY FILARIASIS (TROPICAL PULMONARY EOSINOPHILIA)

Persons living in areas endemic for *Wuchereria bancrofti* and *Brugia malayi* may present with an acute or chronic lung disease, usually referred to as *tropical pulmonary eosinophilia.* This is still a poorly defined clinical entity. Its main features are a history of residence in filaria-endemic areas (particularly India), chronic nocturnal paroxysmal cough, marked eosinophilia, positive serology, and a therapeutic response to the administration of diethylcarbamazine citrate (DEC).

Etiology

Human infection with the tissue nematodes *W. bancrofti* or *B. malayi* can cause several syndromes, including tropical pulmonary eosinophilia.[19] Infection is transmitted by the bite of several mosquito species, thereby introducing the infective third-stage larvae. These organisms undergo ill-defined maturational stages, culminating in the development of adult male and female worms (macrofilaria) that are usually situated in lymphatic vessels and lymph nodes. Mature worms deposit microfilariae that appear in peripheral circulation, often at maximum numbers during specific times of the day (periodicity). However, some filariae show no periodicity with respect to the appearance of their microfilariae in peripheral blood. Microfilariae are taken up by mosquitoes during feeding, thereby completing the life cycle of the parasite.

The life span of adult filariae is not known, but disease is not limited to times when microfilaremia is present. Serologic or histopathologic evidence of infection still can be obtained in *amicrofilaremic* states. For example, in tropical pulmonary eosinophilia, high concentrations of antifilarial IgG and IgE in serum and bronchoalveolar lavage (BAL) fluid have been demonstrated despite invariably negative blood examinations for parasites. Furthermore, microfilariae have been found in lung and lymph node biopsies of patients with tropical pulmonary eosinophilia confirming the filarial origin of this syndrome.

Pathogenesis and Pathology

Only a small number of individuals are susceptible to tropical pulmonary eosinophilia given the lack of pulmonary symptoms in most filarial infections.[7,19] Patients with pulmonary filariasis show evidence of humoral hyperreactivity manifested as increased serum levels of total IgE and antifilarial IgG and IgE. Currently, these antibodies are thought to play a causal role in the disease through either rapid clearance of microfilariae and acute IgE-mediated responses, which manifest as eosinophilic pulmonary infiltrates, or cross-reactivity between specific filarial and human lung proteins and induction of autoimmunity.[20,21] Histopathologically, the earliest lesions are histiocytic infiltrates in the interstitium and alveolar spaces. In established cases, the cell infiltrate consists predominantly of eosinophils, lymphocytes, and histiocytes, and it assumes a nodular configuration. Without therapy, end-stage disease with fibrosing alveolitis and honeycombing occurs.[22]

Clinical Features

For unexplained reasons, young males are predominantly afflicted by tropical pulmonary eosinophilia. The syndrome is characterized by episodes of dry night cough, low-grade fever, and general fatigue. Clinically, it may be mistaken for asthma.[23] Examination of the chest may reveal coarse crackles and rhonchi, along with wheezing. In many patients, pulmonary function tests disclose a restrictive pattern with superimposed obstruction in which vital lung capacity, total lung capacity, and residual volumes are all decreased.[22] Some patients with chronic disease have perfusion impairment. Radiographically, the syndrome may be associated with reticulonodular opacities and increased bronchovascular markings. The sera and BAL fluid of these patients usually demonstrate high IgE levels and specific antibodies to filariae. Eosinophil counts in peripheral blood generally exceed 3000/mm^3.

Management

As the patient is amicrofilaremic in tropical pulmonary eosinophilia, diagnosis is based on the typical clinical, radiographic, and immunologic findings in the setting of an appropriate epidemiology history—that is, previous residence in a filaria-endemic area.[22] Currently, the World Health Organization recommends DEC as the drug of choice for TPE (6 mg per kg daily for 21 days).[24] A favorable

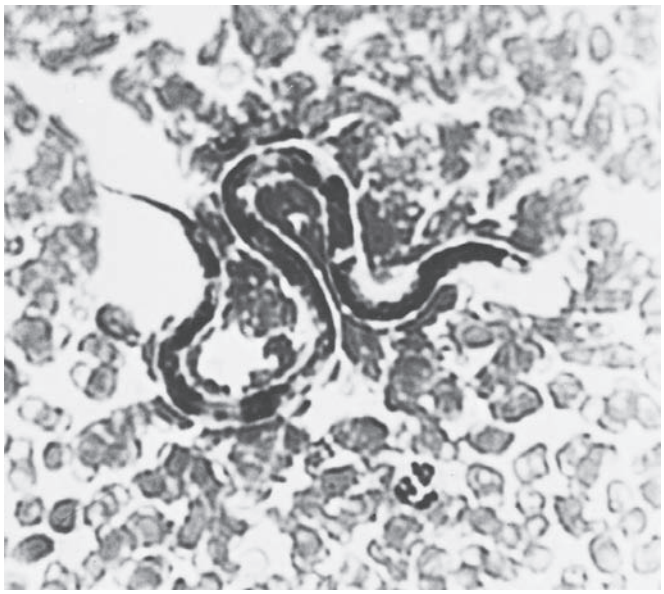
response to doxycycline, 100 mg orally twice daily for 4 to 6 weeks has also been documented—a regimen that works by killing the symbiotic *Wolbachia* bacteria necessary for nutrition and fertility.[25] As adult females are rendered sterile, this agent reduces both microfilaria and the adult macrofilaria populations. Recurrences of tropical pulmonary eosinophilia may occur in 20% of individuals, which would warrant a second course of antihelminthic chemotherapy (WHO suggests DEC 6–12 mg per kg orally daily for 21–30 days).[24] Unfortunately, symptoms may also persist after therapy due to the lung damage incurred prior to treatment.

Dirofilariasis

Another filarial parasite, *Dirofilaria immitis* (dog heartworm), may be transmitted to humans by the bites of the mosquito intermediate vector (Fig. 137-3). Several cases of dirofilariasis have been reported in the United States.[26] In most, the infection was discovered as a pulmonary nodule on the chest radiograph after a worm lodged in the pulmonary arteries. It is often mistaken as cancer. Occasionally, patients have cough, chest pain, hemoptysis, and eosinophilia. Definitive diagnosis is usually obtained from microscopic examination of excised lesions.[27]

■ TOXOCARIASIS (VISCERAL LARVA MIGRANS)

Toxocariasis is due to human infection with animal parasites (dog or cat ascarids). It is most commonly encountered in children. As humans are accidental hosts, the invading larvae migrate in human tissues, but cannot mature to adult worms. *Toxocara canis* and *T. cati* are the two most common etiologic agents of human visceral



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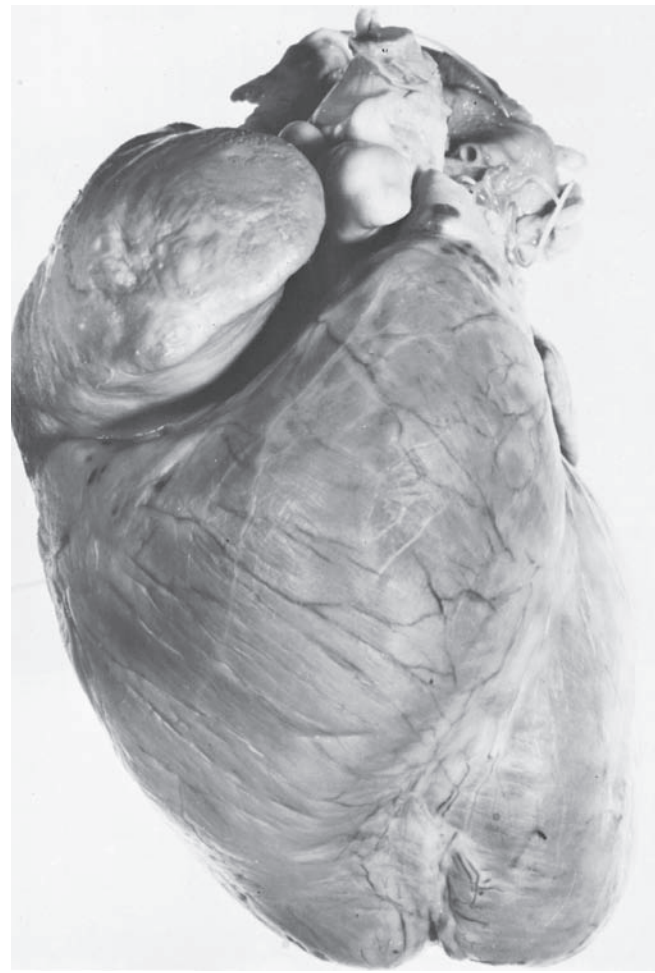

B

Figure 137-3 Pulmonary dirofilariasis in the dog. **A.** Microfilaria *(Dirofilaria immitis)* in blood. **B.** Right ventricular hypertrophy due to dirofilariasis. **C.** Heartworms filling the right atrium and protruding through the pulmonary valve. *(Used with permission of Dr. David H. Knight.)*

larva migrans, although other worms – for example, *A. suum,* the pig roundworm – can cause the same disease. *Toxocara* species are widely distributed, in both developing and developed countries alike.

Etiology

The eggs of *T. canis* and *T. cati* are passed in the stools of dogs and cats, respectively. Transmission to humans occurs by ingestion of embryonated eggs in contaminated food or direct ingestion of contaminated soil.[28] Larvae hatch in the small intestine and penetrate the gut wall. They then migrate to the liver, where they are carried via systemic veins to the systemic arterial circulation for distribution throughout the body. Larval migration through the host tissues and the associated inflammatory responses induced by migration are considered responsible for the manifestations of disease.[29] Most of these features relate to liver pathology, eosinophilia, and pulmonary invasion.

Pathogenesis and Pathology

Tissue injury results from both the invasion of different organs by the parasite larvae and from encapsulation and death of some organisms by the immediate and delayed-hypersensitivity responses of the host.[30] The parasite is capable of evading the immune system for a prolonged period of time due to alterations in the ability of the host to respond to the antigenic challenge and the ability of the parasite to change antigenic identity over time.[31,32] The degree of damage, organ affected, and clinical manifestations varies between individuals. The most commonly affected organ is the liver, where eosinophilic granulomas surround parasite larvae. Similar lesions can be induced in experimental animals (Fig. 137-4). In a few fatal cases of toxocariasis, autopsy revealed that the major pathologic lesions were in the central nervous system.

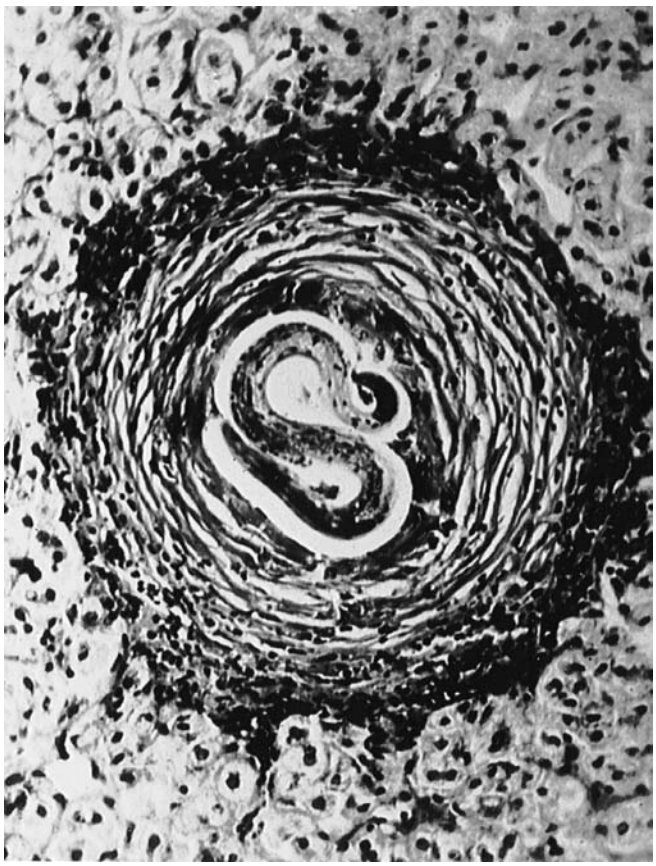

Figure 137-4 *Toxocara canis.* Granulomatous response to larvae in the liver. *(Used with permission of the American Society of Pathologists.)*

Clinical Features

Toxocariasis is generally a disease of children between the ages of 1 and 5 years.[33] It is particularly common in those with a history of pica. However, it may be seen in older individuals, in whom it is often associated with a history of raw meat intake.[34,35] The two main presenting features relate to the chest and abdomen. Pulmonary complaints, such as cough and wheezing, and pulmonary infiltrates occur in more than one-third of symptomatic children.[36] Hepatomegaly, and less commonly splenomegaly, may also be found.[37] Peripheral eosinophilia is usually marked and can persist for years. The concentrations of both total and specific immunoglobulins are also increased in the serum. In recent years, it has become recognized that subtle or covert disease manifestations are also possible, including the suggestion it may trigger asthma or epilepsy in certain afflicted individuals.[30,36]

Management

A diagnosis of toxocariasis is usually made by the clinical presentation and serologic evidence of anti-*Toxocara* antibodies. Imaging of the chest may show transient and migratory infiltrates.[34,35] Since the disease is usually benign and self-limited and the efficacy of most antihelminthics doubtful, no specific therapy is recommended in most cases. In those with severe symptoms, albendazole has been used.[37] Corticosteroids may be necessary to limit the inflammatory response in patients with extensive disease of the lungs or central nervous system.

Rare Nematode Infections

Pulmonary infection from *T. spiralis* is possible. The pulmonary syndrome follows the intestinal phase of infection and is usually associated with other allergic manifestations of trichinosis, including periorbital edema, muscle swelling, and weakness. In severe *T. spiralis* infection, pneumonitis is typically accompanied by eosinophilia.[38]

Anisakiasis in humans results from infection with the larval form of a marine mammal nematode. The disease has been reported in Japan and Western Europe. Although it usually manifests as an intestinal eosinophilic disorder, it has been implicated as the cause of cough, eosinophilia, and pleural effusion as well as anaphylaxis in certain individuals.[39,40]

DISEASES DUE TO CESTODES (SEGMENTED WORMS)

A variety of segmented worms may cause human disease, including Echinococcus.

■ ECHINOCOCCOSIS

Human infection with the larval stage of the canid tapeworm *E. granulosus* is one of the most important helminthic pulmonary diseases. *E. granulosus* is worldwide in distribution, but it occurs most commonly in pastoral communities, such as Australia, South America, the Mediterranean, and some parts of Africa. The infection has also been reported in the United States.

Etiology

There are two unique life cycles for *E. granulosus.* One is the pastoral life cycle, in which the definitive host is the dog and the intermediate hosts are pigs, sheep, and cattle. The other is the sylvatic life cycle, in which the definitive hosts are wolves, foxes, or coyotes, and the intermediate hosts are herbivores, such as moose, deer, elk, and caribou. The pastoral life cycle is generally the more common cause of human disease and results in more severe disease manifestations.[41]

Adult *E. granulosus* worms are found in the intestines of their definitive host. They release eggs from their gravid segments

that are passed in the feces. Humans acquire the infection by ingesting the eggs; embryos are then released and migrate to the liver, where most cysts in humans are found. Embryos may also migrate to the lungs or other tissues. Once the parasite has lodged in human tissues, it develops in a space-occupying hydatid cyst. The inner lining of these cysts is a germinal layer capable of producing daughter cysts that may seed other organs upon spontaneous rupture or surgical manipulation of the original cyst (Fig. 137-5).

Pathogenesis and Pathology

Hydatid cysts are most frequently found in the lungs of children, but can also be seen in older adults.[42] In most instances, the slowly enlarging, space-occupying lesion is well tolerated. Cysts in the lungs are usually discovered early in the course of the disease because radiographic examinations of the chest are now so common. Pulmonary cysts are solitary in 60% of cases and in 50% to 80% of cases affect only one lobe.[10] The cyst is surrounded early in the course of infection by a granulomatous reaction on the part of the host; later, the inflammatory reaction is succeeded by fibrosis leading eventually to a calcified solid mass. Not all cysts are viable—that is, capable of producing new daughter cysts upon rupture. Spontaneous rupture of a viable hydatid cyst can occur through a bronchus, leading to expectoration of scoleces in the sputum while rupture into the mediastinum or pleural cavity can lead to secondary implantations and new daughter cysts. The fluid content of a hydatid cyst is believed to be immunogenic, and leakage of the cyst can evoke an anaphylactic response.[43] Eosinophilia has been

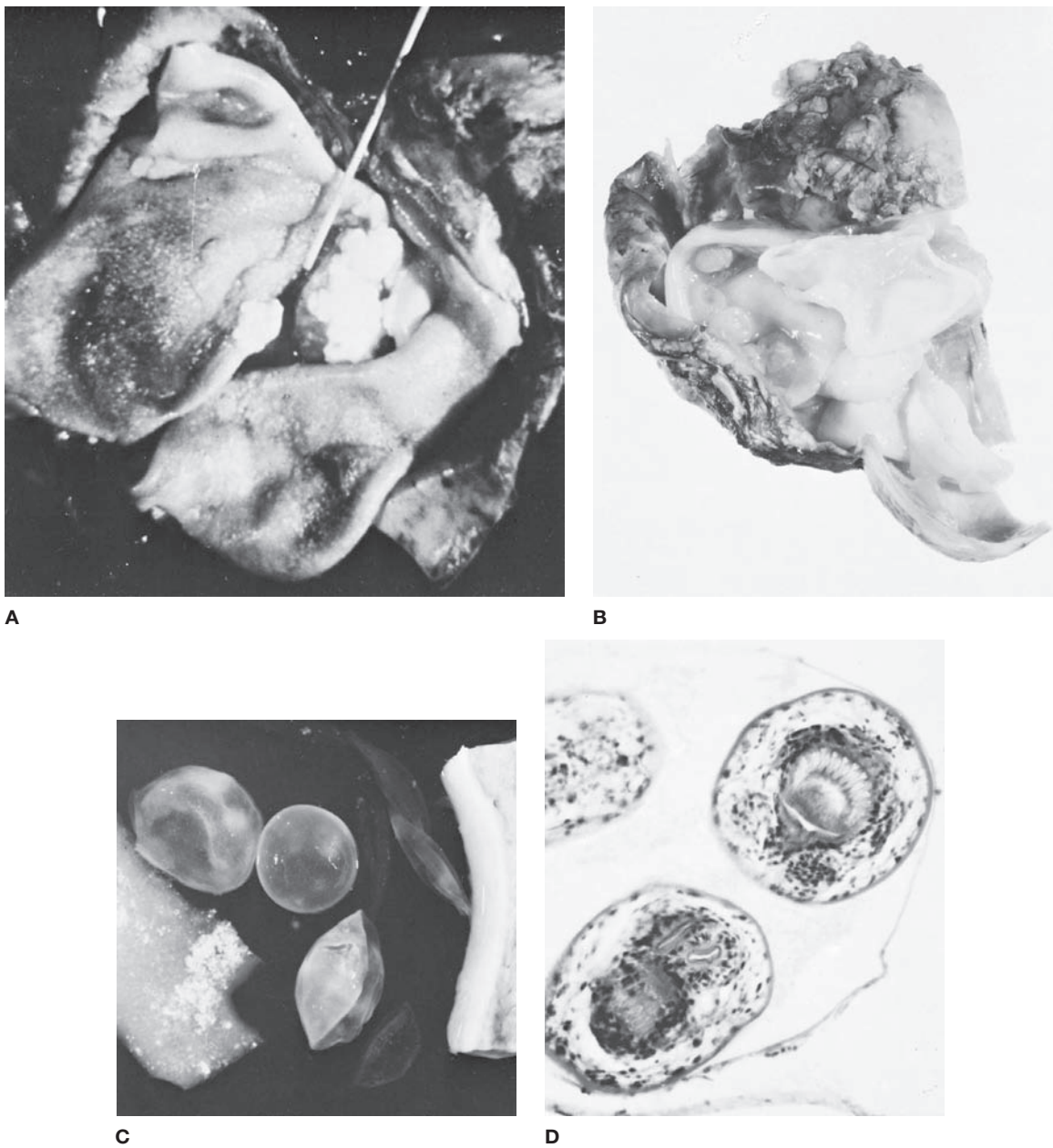

Figure 137-5 Echinococcosis. **A.** Hydatid cyst in the lung. The glistening membrane constitutes the wall of the cyst. **B.** Hydatid cysts in mesentery. Note similarity to appearance in the lung. **C.** Fragment of liver on the right is lined with *Echinococcus* membrane. Brood capsules are on the left. **D.** Three scoleces of *E. granulosus*. The upper right scolex shows the hooklets of the organism. (***A.*** *Used with permission of Dr. Stanley H. Abadie;* ***B–D.*** *Used with permission of Dr. Daniel H. Connor, Armed Forces Institute of Pathology.)*

reported to accompany hydatid disease, but it is not common, with reports ranging from 0% to 25% of cases.[42]

Clinical Features

Hydatid cysts are usually asymptomatic; approximately one-fifth of the clinically diagnosed cysts are in the lungs.[44,45] Most patients with pulmonary hydatid disease are children, while adults usually have cysts confined to the liver. Approximately half of the patients present with cough; smaller fractions present with dyspnea or chest pain. On chest radiography, the lesions vary in diameter from 1 to 20 cm; sometimes the cyst is surrounded by an area of pneumonitis or atelectasis. Less often, a fluid level – the so-called, "water lily sign" (Fig. 137-6) – or calcification is seen. Other diagnostic procedures – for example, serology, computed tomography, and magnetic resonance imaging – may be useful in improving the characterization of the lesions.[10,44]

Management

Diagnosis of a hydatid pulmonary cyst often depends on a combination of epidemiologic, clinical, and laboratory findings—that is, imaging or serology.[44] Surgery is the treatment of choice for hydatid disease of the lungs and it will confirm the diagnosis. Depending on the size and location of the cysts, enucleation of the intact cyst, cystotomy, or removal of the cyst after aspiration may be chosen.[46] If the cyst is large, a drain may need to be left for a period of time in the residual pericystic area. More extensive procedures, such as lobectomy and segmental resection, are usually not necessary.[45] The use of the "PAIR procedure," including *P*ercutaneous *A*spiration,

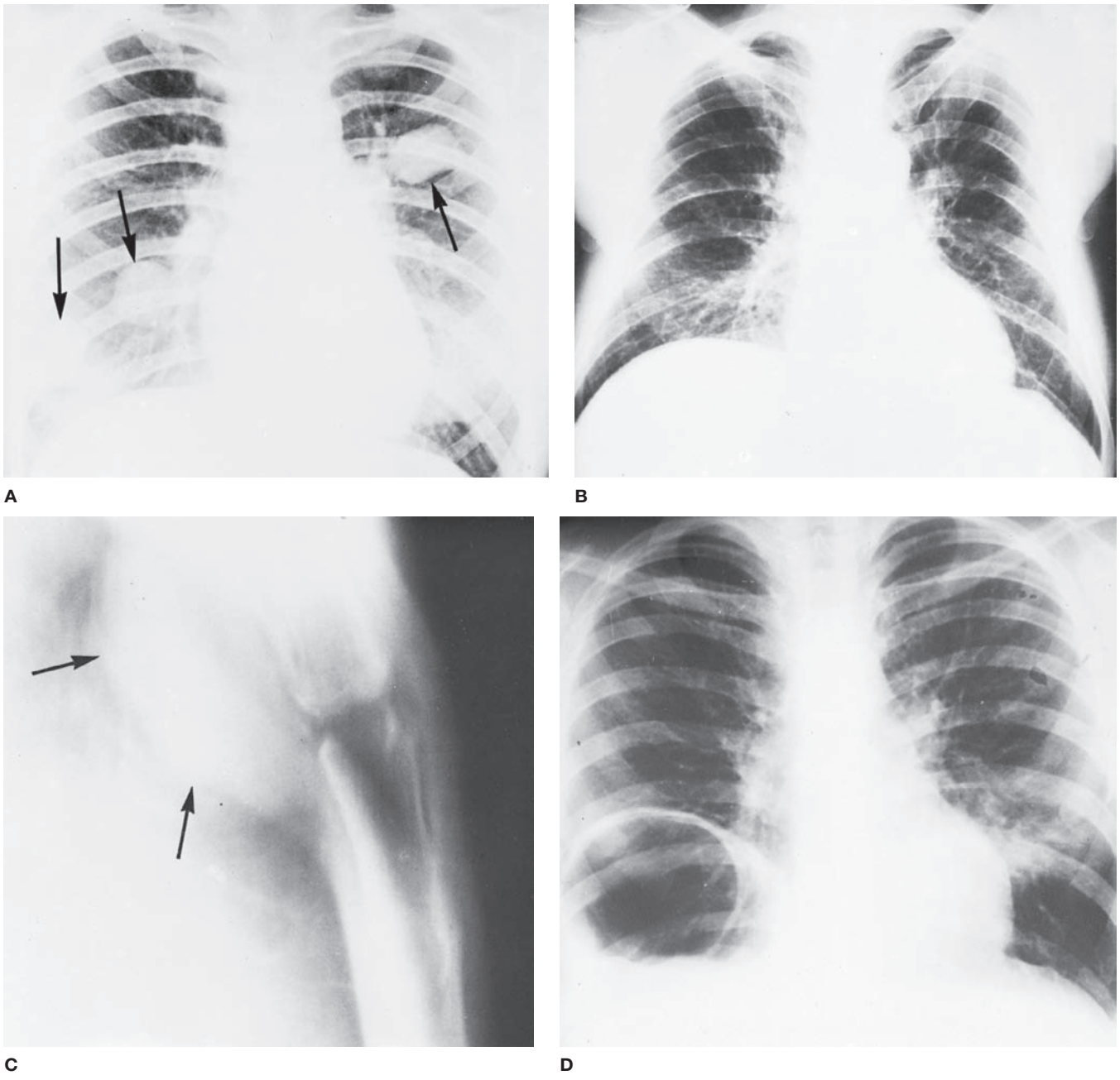

Figure 137-6 Echinococcus. **A.** Multiple pulmonary cysts *(arrows). (Used with permission of Dr. Carl Heitz.)* **B.** Another patient with echinococcus cyst behind the sternum. The retrosternal mass is difficult to discern on the posteroanterior radiograph. **C.** Lateral view. Mass (cyst) is seen *(arrows)*. **D.** Hydatid cyst, right lower lobe. *(Used with permission of Dr. Philip Lerner.)*

*I*njection of cysticidal agent (hypertonic saline, absolute alcohol, or other agents), and *R*e-aspiration using radiographic guidance is well described. Although success has been described in multiple cases, the current recommendation from the World Health Organization is that PAIR should not be used for pulmonary cysts.[44] If PAIR is chosen, it is coupled with administration of albendazole, beginning 4 hours before, and continuing for 28 days after drainage (400 mg orally twice daily for patients >60 kg, and 15 mg/kg divided into two doses for patients <60 kg).

DISEASES DUE TO TREMATODES (FLAT WORMS)

Schistosomiasis and paragonimiasis represent two trematodes that are important in causing human disease. Each is discussed in subsequent sections.

■ SCHISTOSOMIASIS

Schistosomal infections represent one of the major endemic helminthic infections in Southeast Asia, the Middle East, Africa, the Caribbean, and South America. Five species represent the most common and clinically significant infections in humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi,* and *S. intercalatum.*

Etiology

The schistosomes are blood flukes. Human infection is initiated by penetration of intact skin by the free-living cercariae that are shed by specific freshwater snails. The cercariae change within a few hours into schistosomula, which migrate from the subcutaneous tissues to the lungs and then to the liver, where they mature into adult worms. Fecund adult parasites then migrate to their final habitat: the veins around the ureters and urinary bladder *(S. haematobium)* and the mesenteric veins (all other species). Adult worms deposit eggs that pass through the lumen of ureters or gut to the outside environment to complete the life cycle of the parasite. However, some of these ova become trapped in the surrounding host tissues. Other ova may be carried by the venous circulation to the heart and then the lungs.

Pathogenesis and Pathology

Schistosome eggs are the major cause of human pulmonary disease. They reach the pulmonary circulation by routes that depend on the species of the parasite, their final habitat, and the stage of infection. Since *S. haematobium* worms parasitize the vesical venous plexus that connects directly with the inferior vena cava, egg seeding to the lungs may occur at any phase of infection. By contrast, the anatomic location of adult worms of the other species in the mesenteric veins does not allow parasite ova to travel directly through the portal vein to the hepatic and systemic circulations. Eggs of these species typically reach the lungs only in the late stages of infection, after portal hypertension develops and anastomotic channels open between the portal and systemic circulations. Despite this, pulmonary symptoms may still occur early in the infection as a result of immune-complex deposition or because the infection occurs in an individual who has early opening of the portocaval shunts.[47,48]

Upon reaching the pulmonary circulation, schistosome eggs usually gather in small arterioles, where they induce the formation of delayed-hypersensitivity granulomas, made up of eosinophils, lymphocytes, and macrophages (Fig. 137-7), as well as neovascularization and fibrosis. In an autopsy study of 32 cases of *S. mansoni* cor pulmonale, two characteristic histopathologic lesions were identified: (1) focal changes related directly to the presence of schistosome eggs; these were located either within the alveolar tissue or within the pulmonary arteries or arterioles; and (2) plexiform or angiomatoid lesions consisting of thin-walled and dilated vessels.[49] The most prominent vascular lesions were associated with the focal changes surrounding mature schistosome eggs in the lumen of pulmonary arteries or arterioles. The curtailment of the pulmonary vasculature and the decreased distensibility caused by the perivascular fibrosis leads to pulmonary hypertension and cor pulmonale. Pulmonary function testing reveals a predominantly restrictive pattern of disease and is accompanied by a decrease in the diffusing capacity.

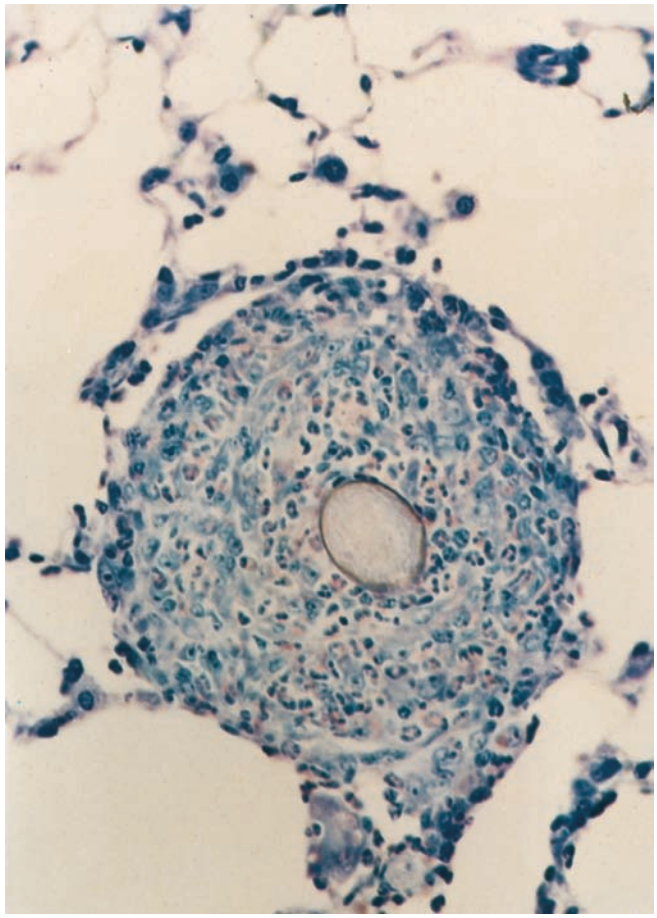

Figure 137-7 Schistosomal granuloma. *(Used with permission of Dr. Jay A. Fishman.)*

Clinical Features

It is not clear whether very early schistosome infection is associated with appreciable pulmonary disease. Migration of schistosomula through human lungs may provoke cough and bronchospasm and may be associated with immune-complex deposition.[47] After the onset of oviposition (approximately 3–6 weeks), some ova may reach the lungs, particularly in *S. haematobium* infection. Immune-complex deposition may also cause symptoms. Patients may present at this point with a myriad of nonspecific symptoms including fever, dyspnea, and a dry cough.[47,50] If chest imaging is obtained, small nodules with or without ground-glass halos may be seen in a hematogenous parenchymal distribution.[10] If the infection is not treated, chronic infection can result in sufficient deposition of eggs in the lungs to cause the development of cor pulmonale. However, the clinical features and radiographic findings in schistosomal pulmonary hypertension and cor pulmonale are not distinctive and the prevalence of the pulmonary hypertensive syndrome in schistosome-infected patients is not fully known.[10,48] In Egypt, 7.5% of patients hospitalized with schistosomal hepatomegaly had cor pulmonale; in another study from Brazil, authors estimated that up to 30% of patients with pulmonary hypertension at the country's reference centers may be due to schistosomiasis.[48]

Management

Diagnosis of pulmonary disease due to schistosomiasis may be achieved by finding the parasite eggs in urine or stools of persons with suggestive clinical manifestations. However, the most severe pulmonary disease typically occurs years after infection, and finding parasite ova in the urine or stool may be difficult. Under these circumstances, demonstrating the characteristic pathologic changes, finding ova directly in the tissue, or positive serology in the nonendemic setting may confirm the diagnosis.

Active schistosome infections are treated with praziquantel, which kills adult worms and stops further destruction of tissue by ova deposition. The drug is administered at a dose of 20 mg/kg body weight twice daily for 1 day (two total doses) for *S. mansoni* and *S. haematobium* infection and three times a day (three total doses) for *S. japonicum* infection. However, reversal of pathologic lesions in the lungs after antischistosomal chemotherapy has not been documented.

■ PARAGONIMIASIS

Human infection with species of the lung fluke *Paragonimus* is prevalent in the Southeast Asia, Africa, and South and Central America. Infection is maintained in endemic areas through contamination of water sources with feces or sputum of infected individuals. Water contamination then results in infection of the intermediate snail and crustacean hosts.

Etiology

Human infection with *Paragonimus* is acquired from food sources. This is classically described in individuals consuming raw or pickled crustacea (freshwater crayfish and crabs) that harbor the infective parasite stage (metacercariae), but infection may occur with the consumption of other foods, such as raw, wild boar.[51] The metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate via the diaphragm and pleural cavity to the lungs, where they mature into adult worms (12 × 6 × 5 mm). Adult *Paragonimus* worms are hermaphroditic; they produce golden-brown eggs, which are then coughed up and excreted through either sputum or feces. The life cycle of the parasite outside the human host goes through a specific snail intermediate host; metacercariae then encyst on freshwater crustacean to start the cycle again.

Pathogenesis and Pathology

The primary site of infection in humans is the lungs. The worm is also found in the brain in 25% of patients, but it is less often seen in other tissues. Three stages of parasite development occur within the lungs—primary infection, encystation, and death. During the initial invasion of the lungs by the maturing adult worms, parasite tunnels in the pulmonary parenchyma may be found, particularly in peripheral areas. The tunnels and parasites are surrounded by a granulocytic reaction made of eosinophils and neutrophils. Charcot–Leyden crystals, which are formed by the enzymes left after eosinophil and basophil degranulation, are often seen. In patients with encysted worms, the parasites are enclosed within cystic lesions that may communicate with each other or with a nearby bronchus. Death of the worms usually leads to collapse of the cyst, disintegration of the parasite, and fibrosis or calcification. The surrounding pulmonary tissue may show evidence of atelectasis, bronchiectasis, or compensatory emphysema. In some patients, secondary infection and lung abscess develop in the cystic lesions.

Clinical Features

The incubation period between infection and the development of maturing adults in the lungs is 2 to 20 days. Few specific symptoms have been described during this stage. In persons with established infection, the worm load seems to determine the extent of clinical features unless secondary infection has occurred. Light worm infection is usually asymptomatic. In moderate to heavy worm loads, complaints of cough, respiratory discomfort (particularly upon rising in the morning), and rusty, blood-tinged sputum containing parasite eggs, necrotic material, and Charcot–Leyden crystals are common.[52] Frank hemoptysis, ranging from mild to severe, may occur. Individuals may be mistaken for having tuberculosis or malignancy. Eosinophilia may be the only clue that the cause is parasitic, as it is found in 80% to 90% of affected individuals.[53]

The chest radiograph is normal in 10% to 20% of infected persons. Radiographic signs in the others include infiltrates, cavitation, fibrosis, pleural effusions, and pulmonary thickening.[10] Findings may be unilateral or bilateral. Radiographic changes over time correspond roughly to the three stages of parasite development within the lungs: (1) on arrival to the lungs, maturing worms are associated with the development of radiographic opacities; (2) these are succeeded by nodules that correspond to the parasite cysts; and (3) eventually, fibrosis or calcification ensues. The characteristic ring shadow with a crescent corona may also be seen in some infected persons.

Management

The diagnosis of paragonimiasis can be made from detection of the characteristic eggs in the sputum or stools of infected persons. Serologic testing is helpful in egg-negative cases. The drug of choice for treating paragonimiasis is praziquantel. It is administered orally, 25 mg/kg three times per day for 2 days, or bithionol 30 to 50 mg/kg orally on alternate days for five doses. Therapy usually leads to cessation of egg passage in sputum and stools, clearing of the chest radiograph in almost two-thirds of treated patients, and a decrease in serum IgG antibodies directed against the parasite.

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CHAPTER 138

Zoonotic and Other Unusual Bacterial Pneumonias

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INTRODUCTION

Many different microorganisms can infect the lung parenchyma; this chapter focuses on zoonoses, human commensals, and other unusual bacterial pathogens. Routes of spread to the lungs are few, clinical presentations overlap, radiologic appearance often is nonspecific, and pathophysiologic mechanisms are limited. Making a clinical diagnosis of pneumonia is relatively easy; defining the causative agent can be difficult. The search for the specific etiologic agent is driven by the desire to administer a specific antimicrobial drug as soon as possible hopefully to avoid progressive functional impairment and to contain spread to other individuals or to a community. Identifying a pathogen may, in turn, expand epidemiologic considerations and public health awareness.

In the almost four decades that have passed since the epidemic of acute respiratory disease due to *Legionella* erupted among delegates to the American Legion Convention in Philadelphia in 1976, physicians, microbiologists, and epidemiologists have become increasingly prepared for the diagnostic challenges of patients with unusual pneumonias. More recent examples of this multidisciplinary approach include the rapid diagnosis of Q fever (due to *Coxiella burnetii*), early identification of cases of *Chlamydia pneumoniae* and *Chlamydia psittaci,* and the etiology of acute respiratory infections due to obscure viral agents like Hantavirus pulmonary syndrome and the newer Coronavirus respiratory illnesses including severe acute respiratory syndrome (SARS). SARS was an excellent example of a zoonotic infection with an initiating event and subsequent person-to-person spread. Similarly, Middle East respiratory syndrome coronavirus (MERS) has been linked to dromedary camel exposure, with subsequent inter-human spread. The complexity of the definition of an etiologic agent in the diagnosis of pneumonia of obscure origin is highlighted in many of the examples mentioned here. Most are discussed in detail elsewhere in this text; the focus will be exclusively on bacterial pathogens most often associated with animals or animal products.

Zoonotic infections can reflect an initial event, followed by person-to-person secondary cases, typical of viral diseases like SARS coronavirus, and occasionally observed with *Yersinia pestis*. While the avian influenza virus (H5N1) has primarily spread to individuals in proximity to chickens, the novel H1N1 influenza in 2009 to 2010 demonstrated an anthropocentric cycle that led to a worldwide pandemic, despite being of zoonotic origin. New zoonoses are continually emerging: A recent outbreak in a monkey colony of deadly titi monkey adenovirus, not known to infect humans, was shown to infect a researcher and a family member, without further spread.[1] Similarly, *Streptococcus equi* subsp. *zooepidemicus (Streptococcus zooepidemicus)*[2] has recently been shown to cause pneumonia in humans after exposure to horses, dogs, and unpasteurized milk.

Companion animals have been the etiology of numerous zoonotic pneumonias, including *Pasteurella multocida,*[3,4] *Chlamydia psittaci,*[5] *Rhodococcus,* and *Bordetella bronchiseptica* (especially in immunocompromised hosts[6–9]). In a study in Spain, contact with pets was associated with an increased risk for community-acquired pneumonia, which tended to be higher as the number of pets increased; the relative risk was similar for birds, cats, and dog exposure.[10] There are multiple examples of animals serving as reservoirs of antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (companion animals,[11,12] pigs[13]), some in association with nosocomial ventilator-associated pneumonia,[11] and highly resistant Enterobacteriaceae.[14] Nonetheless, experts usually permit companion animals even for immunocompromised hosts, balancing the risk of infection with perceived benefit.[6,15] Wild and farm animals may also harbor zoonotic pneumonia pathogens. *P. multocida* has been associated with pneumonia in bighorn sheep,[16] lambs,[17] and pigs.[18] *Y. pestis* has been associated with numerous wild mammals; recent work suggested a correlation between seropositivity in coyotes and human disease.[19]

Many of the zoonotic bacteria discussed in this chapter are recognized as pathogens that can be weaponized for use by terrorist organizations. The global community is developing rapid diagnostics and countermeasures to warn, protect, and treat people exposed to a biologic weapon. Unfortunately, we have the experience of the "mailroom" anthrax event of September 2001 to illustrate the potential of an inhalational disease causing illness, casualties, public panic, diagnostic and therapeutic decisions, as well as the expenses of decontamination and the challenges of criminal investigations.[20] Physicians need to become familiar with the typical and atypical spectrum of disease caused by these pathogens, including the impact and variable expression of a large inoculum aerosol release in a crowded urban area or building.

This chapter focusses on the epidemiologic and clinical features that should be helpful in evaluating typical and atypical features of pneumonia (Table 138-1). The unique properties of these bacteria exemplify how bacteriology, molecular biology, ecology, epidemiology, and pathogenesis serve as clues to earlier etiologic diagnosis and specifically targeted therapies (Table 138-2). The movements of immigrant populations, adventure and other forms of travel, the immune status of individuals, the latency of pathogens, and the legal and illegal transportation of live animals and animal products contribute to the importance of zoonotic pneumonias. Ultimately, the diagnosis is heavily dependent on a detailed history along with appropriate diagnostic studies.

ZOONOTIC BACTERIAL PNEUMONIAS

This section focuses on diseases that are spread to humans predominantly from animal contact, including pasteurellosis, the plague, tularemia, and *Rhodococcus*. The diagnosis usually depends on a careful animal exposure history. Once alerted, the clinician can request appropriate studies, as these diseases may be more elusive to diagnose.

PASTEURELLA MULTOCIDA

P. multocida is a common commensal of the oral cavity of most felines and many dogs and a frequent respiratory pathogen in animals and birds.[3] The respiratory tract is the second most common site of *Pasteurella* infection following skin and supporting tissues. Respiratory infections are probably underreported. Elderly people with structural lung diseases such as emphysema, bronchiectasis, or malignancy are at higher risk for pulmonary infection. Immunocompromised patients, including those with AIDS, may be prone to spontaneous infection without close contact or traumatic dog or cat exposures.

TABLE 138-1 An Overview of Zoonotic and Other Unusual Pneumonias

Environmental Niche	Microorganism	Disease	Epidemiologic Associations	Distribution
Live animal contact or via arthropod	*Francisella tularensis*	Tularemia	Contact with wild and pet animals, birds, or arthropods (ticks, deer fly)	North America, Europe, Asia
	Pasteurella multocida	Pasteurellosis	Feline and dog contact; chronic lung disease	Worldwide
	Rhodococcus equi	Rhodococcus pneumonia	Airborne droplets; contact with soil contaminated with horse, cow, or swine excrement	Worldwide
	Yersinia pestis	Plague	Contact with rodents, fleas; contact with plague pneumonia case	Worldwide, including Asia, southwest US
Soil, stagnant water, and inert animal products	*Bacillus anthracis*	Inhalation anthrax or woolsorter's disease	Industrial; use of or contact with animal products in hobbies	Worldwide in warmer regions inhabited by grazing animals
	Brucella species	Brucellosis	Ingestion or contact with infected animal products, slaughterhouses	Worldwide
	Burkholderia pseudomallei	Melioidosis	Direct penetrating contact of wounds with soil, water	Latitude 20°N to 20°S, especially rural Asia, northern Australia
	Yersinia enterocolitica	Yersiniosis	Ingestion of contaminated foods, water; cirrhosis	Worldwide
Obligate human commensal	*Neisseria meningitidis*	Meningococcal pneumonia	Airborne droplets, human to human; postviral, nosocomial	Humans worldwide
	Moraxella catarrhalis	Moraxella pneumonia	Aspiration, especially individuals with underlying lung disease	Humans worldwide

Bacteriology

P. multocida is a small gram-negative bipolar-staining coccobacillary organism that resembles *Haemophilus* spp. and may form pairs and chains. Rapid growth on blood agar and inhibition by MacConkey medium separate this microorganism from other common components of the respiratory flora, including *Haemophilus* spp. Numerous virulence factors in *P. multocida* have been identified. These include the capsule in serogroups A and B (which interferes with phagocytosis), a toxin in strains causing atrophic rhinitis in pigs, lipopolysaccharide endotoxin, several iron acquisition proteins (e.g., TonB, ExbD, and ExbB), and the putative filamentous hemagglutinins PfhB1 and PfhB2.

Ecology, Epidemiology, and Pathogenesis

In cats and other felines, the organism resides periodontally in the anterior regions of the mouth. Isolates from dogs are characteristically from the posterior pharynx. Many birds and domestic and wild animals worldwide harbor this organism as a commensal in oral or gastrointestinal areas. *P. multocida* is occasionally found in the secretions of persons with chronic lung disease, especially those

TABLE 138-2 Diagnostic Studies and Treatment Recommendations in Zoonotic Pneumonias

Disease	Gram's Stain Morphology	Culture Methods	Identifying Tests
Anthrax	Large gram-positive bacillus (rarely seen)	BAP, blood cultures	FA
Brucellosis	Small gram-negative coccobacillus (rarely seen)	Media enriched with serum, $CO_2 + O_2$; notify laboratory that pathogen may be cultured	Rise in AA, prozone
Melioidosis	Bipolar-staining gram-negative bacillus	BAP, MAC	Morphology, FA, AA
Pasteurellosis	Small bipolar-staining gram-negative bacillus	BAP, CO_2	Inhibited by MAC, biochem. tests
Plague	Enteric bipolar-staining gram-negative bacillus	BAP, MAC, enteric media, blood cultures; notify laboratory that pathogen may be cultured	Biochem. tests, FA, AA
Rhodococcus	Gram-positive coccobacilli (slightly acid-fast positive)	BAP	Biochem. tests
Tularemia	Small gram-negative coccobacillus	Enriched media with cysteine, serum; notify laboratory that pathogen may be cultured	FA, AA, rarely cultured
Yersiniosis	Enteric gram-negative bacillus	BAP, MAC, enteric media, blood cultures	Biochem. tests, motility 25°C

BAP, blood agar plate; FA, fluorescent antibody; AA, agglutinin antibody; MAC, MacConkey agar.

with bronchiectasis and domestic animal contacts. A recent report links the domestic cooking and ingestion of pig trotters (feet) with subsequent pneumonia.[21] Human-to-human transmission has been documented from mother to newborn infant, resulting in neonatal pneumonia. The organism can survive in soil and water for more than 3 weeks and in animal carcasses for approximately 2 months. In about half of the cases of respiratory disease, no clue to airborne spread exists, but there are usually cats in the local environment.

Pathogenic strains have a polysaccharide capsule that inhibits phagocytosis, and they contain endotoxin in the cell envelope. Exotoxins and other pathogenicity-promoting factors have not been specifically identified (see Bacteriology). Almost all patients who develop respiratory infections have underlying chronic pulmonary disease. Aspiration probably initiates active infection. Necrosis and lung abscess, empyema, septicemia, and transbronchial spread to other lung segments have been described.

Clinical and Radiologic Features

The clinical features of *P. multocida* respiratory disease include worsening of the patient's baseline pulmonary function—especially when high fever, tenacious secretions, and pleural effusions develop. Radiologic changes include lobar, multilobar, or diffuse patchy infiltrates, usually sparing the upper lobes, superimposed on underlying chronic lung disease (Fig. 138-1). Effusions, including empyema, have been noted in approximately 20% of cases. Bacteremia has been reported in up to 55% of patients with pneumonia, and endocarditis has occasionally complicated bloodstream invasion.[3]

Diagnosis and Differential Diagnosis

Diagnosis depends on isolation of the organism from sputum, pleural fluid, or blood. Usually the pathogen can be identified with the routine methods of the diagnostic laboratory. The bipolar gram-negative staining bacilli resemble *Brucella* spp., *Y. pestis, Francisella tularensis, Burkholderia* (formerly *Pseudomonas*) *pseudomallei,* and *Haemophilus* spp., but the clinical history of exposure to cats and/or dogs and bacteriologic characteristics can rapidly clarify the identification.

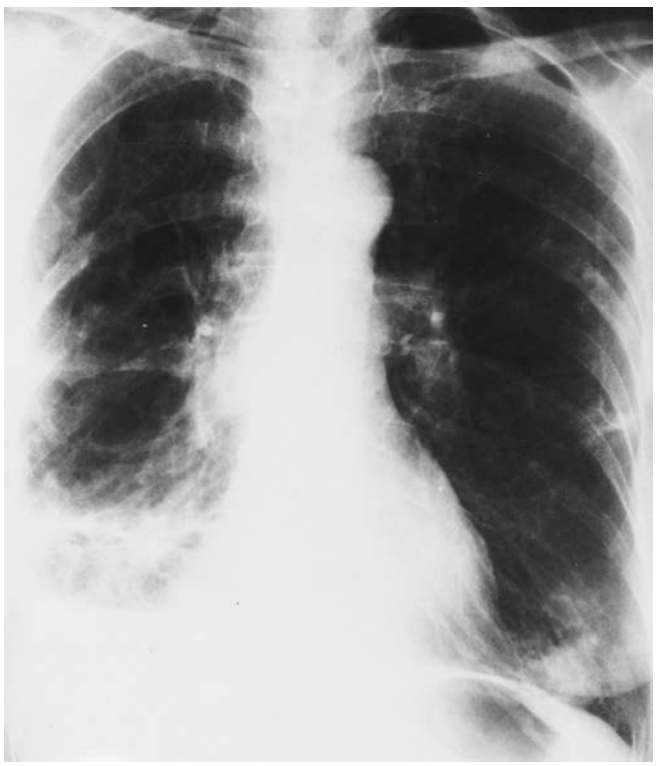

Figure 138-1 Bilateral pneumonia due to *Pasteurella multocida* in a 69-year-old woman suffering from chronic obstructive pulmonary disease and a prior right lower lobectomy for carcinoma. Infiltrates disappeared with penicillin therapy.

Treatment

Most strains are exquisitely susceptible to penicillin or ampicillin. The third-generation cephalosporins, cefotaxime and ceftriaxone, are as active as penicillin and more potent than earlier-generation relatives. Oral preparations of cephalosporins and penicillins are not recommended for treating pneumonias caused by *P. multocida* due to reduced bioavailability. The newer fluoroquinolones, including moxifloxacin and levofloxacin, are very active in vitro against *P. multocida* and other *Pasteurella* spp., although there is limited published experience in humans. Chloramphenicol, with consideration of potential toxicities, and tetracycline are effective alternatives when a history of allergic reactions precludes use of a β-lactam agent.

■ *YERSINIA PESTIS*

This organism left an indelible mark on humanity long before its late 19th-century isolation and characterization. The cause of three major pandemics from the 6th through the 19th centuries, pulmonary disease in a few victims led to aerosol spread to countless others, resulting in acute primary pneumonia and the "black death" of epidemic plague. During the period from 1932 through the end of World War II (1945) the Japanese biologic warfare program included the use of aerosol drops of *Y. pestis* as well as infected flea disseminations in occupied China and at the infamous experimental Unit 731. The effectiveness of the flea drops remains in question to this day but the aerosol dispersal definitely led to clinical pneumonic plague. A contemporary global scare emanated from India's Maharashtra state in 1994, with reports of suspected pneumonic and bubonic plague; interestingly, some suspected cases were subsequently found to be due to *B. pseudomallei*.[22] In the United States, fewer than 20 cases of plague are reported yearly, of which one in five has lung involvement but without any secondary cases. Early recognition and specific therapy, combined with isolation procedures and appropriately directed prophylaxis of contacts should help maintain the record of no human-to-human transmission in the United States since the 1920s. When plague is diagnosed outside an endemic area, bioterrorism should be considered. When *Yersinia* pneumonia occurred in a couple who recently became ill in New York City, the event was originally investigated as a potential bioterrorism event until their travel from an endemic area of plague (Santa Fe County, New Mexico) was discovered.[23] Although the bacteria are difficult to process, handle, and disperse in an aerosol form, person-to-person airborne spread is very efficient and laboratory accidents have occurred.

Bacteriology

Y. pestis is a bipolar-staining, gram-negative bacillus closely related to *Escherichia coli* and other *Enterobacteriaceae*. It grows well on blood or MacConkey agar and is identified definitively with differential biochemical tests, agglutination reactions, and direct fluorescent antibody staining. Concerns for laboratory safety have led to routine of Biosafety level 2 (BSL-2) laboratory procedures as well as better communication between clinicians and microbiology laboratory personnel in suspected cases.

Ecology, Epidemiology, and Pathogenesis

In the United States, *Y. pestis* is endemic in rock squirrels, prairie dogs, rabbits, rats, and other small ground animals primarily in the Southwest. Spread among animals occurs via several species of rodent fleas, especially *Xenopsylla cheopis*. Domestic animals that wander outdoors, like cats, can become infected by direct contact with sick rodents or via rodent flea bites. In addition, cats and dogs can inadvertently

carry fleas to the home. Occasionally rodent die-offs, called epizootics, occur, and many dead animals can be found with viable organisms in carcasses and in the soil surrounding ground dwellings.

In the United States, spread to humans occurs when an infected flea feeds on a susceptible person. Living or working in proximity to local enzootic "hot spots" places certain groups (such as Native Americans, geologists, hikers, veterinarians, and pet owners) at risk. Bubonic and cutaneous plague are usually acquired on exposed areas by contact with infected fleas, but aerosols from ill animals or carcasses can lead to primary pneumonia, pharyngitis, or conjunctivitis. Several cases of cat-to-human aerosol spread have been associated with respiratory infection or submandibular abscesses in pets. A great concern of physicians caring for patients with respiratory infection is the potential for rapid airborne dissemination, especially during coughing and face-to-face contacts, resulting in primary pneumonia and the rapid development of acute respiratory distress syndrome (ARDS).

After the organism gains access to human tissues at 37°C, rapid multiplication occurs. The polysaccharide capsule imparts virulence properties that include resisting phagocytosis and persistence of bacteria within nonsensitized monocytes. Virulence factors include a potent endotoxin and V and W antigens of the cell envelope, which influence intracellular survival. Recent work with a mouse model has demonstrated a biphasic illness with an initial anti-inflammatory phase that rapidly progresses to a highly proinflammatory state by 48 hours and death by 3 days. Microarray analysis demonstrates a change in the expression of about 10% of the bacterium's genes after it infects a host.

Clinical and Radiologic Features

Clinical presentations are highly varied and include subclinical cases (positive serology without evidence of disease), a chancriform skin lesion (pestis minor abortive bubonic plague), pharyngitis, bubonic plague, septicemic plague, pneumonic plague, and meningitis. The clinical presentation of pneumonia depends on the mechanism of spread. In contemporary experience in the United States, cases have all been secondary to bubonic plague, primary septicemia without an overt skin lesion, or inhalation of droplets from an infected pet cat. The onset of respiratory disease follows after days to a week of a febrile illness, and is ushered in by the gradual onset of cough, dyspnea, and increasing toxicity. Pink to hemorrhagic frothy sputum, pleurisy, and respiratory distress are additional symptoms. The unique feature in most cases of pneumonia is the epidemiologic association with classic bubonic plague; that is, in a person in or from an endemic area or who has had contact with a pet cat ill with respiratory symptoms or a facial abscess. From histories of primary inhalation pneumonia described previously, exposure to an index case may be followed by the rapid development of a fulminating respiratory illness, with dyspnea, cyanosis, and thin, watery sputum that rapidly becomes hemorrhagic. The clinical picture is not unlike that of overwhelming pneumococcal pneumonia, with marked toxicity and mental torpor associated with progressive cyanosis.

The radiologic features of secondary pneumonia include basal segment nodular to hazy air space infiltrates, hilar and mediastinal node hypertrophy, and occasionally pleural effusions.[24] In primary pneumonia, infiltrates may be minimal during the first 24 hours, followed by progressive air space disease resembling ARDS or pulmonary edema.

Diagnosis and Differential Diagnosis

The presence of characteristic bipolar-staining gram-negative bacilli in sputum suggests the diagnosis when epidemiologic clues are present. Cultures of blood, sputum, and lymph node aspirates often yield positive results. Direct fluorescent antibody staining can provide immediate etiologic confirmation. A passive hemagglutination test can be performed as a confirmatory study on acute and convalescent sera at selected reference laboratories such as CDC. Rapid assays for diagnosis of plague are under active development, especially given the interest in its potential as a bioterror agent. Other acute respiratory infections caused by microorganisms that appear as gram-negative bacilli with bipolar staining must be considered, including *F. tularensis* and *P. multocida.*

Treatment and Prevention

The combination of streptomycin and tetracycline has been the treatment of choice for serious plague infections. Gentamicin can be substituted for streptomycin if intravenous therapy is necessary or streptomycin is not available. Doxycycline and fluoroquinolones such as ciprofloxacin may also be effective in treating pneumonia; chloramphenicol is a potential option, noting toxicities. Multidrug-resistant plague has been reported and clinicians should be aware of local trends as well as the potential for terrorist-instigated modifications in antibiotic susceptibility.

Persons suspected of having plague pneumonia should be rapidly isolated, and strict contact, respiratory, and conjunctival precautions instituted. Anyone exposed face to face with a coughing patient, including healthcare workers, should be given preventive tetracycline or ciprofloxacin (trimethoprim/sulfamethoxazole is used in pregnant women and children). Isolation procedures are continued until productive cough is no longer present or sputum cultures are negative for *Y. pestis.*

A vaccine is available for laboratory workers and others with frequent exposure to the microorganisms or hyperendemic areas, although it does not appear to protect against pneumonic plague. Careful surveillance of ground rodent populations, posting warnings in endemic regions, watching for die-offs that indicate epizootic spread, and spraying for local flea control may also be effective preventive measures along with public education.

■ *FRANCISELLA TULARENSIS*

Tularemia is a common animal disease in the United States as well as many other regions of the temperate globe. The causative agent, *F. tularensis,* is ubiquitous, distributed among many species of wild and domestic animals and birds. As with plague, the major clinical manifestations include skin lesions and swollen or draining regional lymph nodes. In addition to primary inhalation pneumonia, pulmonary invasion is seen following bacteremia in 10% to 15% of ulceroglandular cases and in more than 50% of patients with the typhoidal syndrome. Approximately 150 human cases are reported in the United States yearly, but this is probably an underestimate; approximately 40% of all tularemia cases each year occur in Arkansas, Oklahoma, and Missouri.[25] In the summer of 2000, an outbreak of pneumonic tularemia occurred on Martha's Vineyard, Massachusetts, and 11 of 15 patients were diagnosed as primary pneumonic tularemia; lawn mowing and brush cutting were found to be risk factors for infection.[26] An epidemic of tularemic pharyngitis from ingestion of contaminated well water and food occurred in war-torn Western Kosovo primarily among young children originally suspected of having group A Streptococcal pharyngitis, with no secondary pneumonias reported.[27]

Bacteriology

F. tularensis is a fragile-appearing gram-negative coccobacillary organism that is quite fastidious and grows poorly on artificial media unless fortified with serum and cysteine (or sulfhydryl compounds). The potential for laboratory-acquired inhalation or ingestion-associated disease is great. Most routine laboratories will not attempt to culture the organism, leaving this to special reference centers. Identification is on the basis of morphologic and biochemical determinants, but direct fluorescent staining or agglutination reactions with specific antisera are also useful.

Ecology, Epidemiology, and Pathogenesis

The organism is associated with more than 100 species of wild and domestic animals and birds, including aquatic mammals, but most clinical cases arise from contact with rabbits, squirrels, or arthropods. Of great concern is the recent fad for exotic pets; tularemia in prairie dogs has led to spread in holding pens and to human transmission. In cold weather the organism can persist in water and mud environments for weeks to months. Bloodsucking arthropods, especially ticks and deerflies, act as reservoirs capable of harboring the pathogen for long periods and are responsible for dissemination among wildlife species as well as infecting people. Domestic cats represent a potentially increasing problem.[28]

Less than half of human cases are acquired from contact with infected animals during hunting, trapping, and other outdoor pursuits, especially during colder months. In southern areas, or in the summer season in northern latitudes, gardening and lawn mowing without animal contact are becoming important methods of dissemination from disturbed soil. Bloodsucking arthropods constitute a significant and increasing mode of spread, especially in warmer seasons. Ingestion of contaminated food or water,[27] animal bites, conjunctival contact, and aerosol dissemination are also important mechanisms for acquiring the pathogen. In recent years, cases secondary to arthropods have been more frequent than those associated with direct animal contact, although domestic cat bites[28] and airborne spread appear to be increasing. Human-to-human transmission is rare, in contrast to the significant theoretical potential for spread of pneumonic plague. If *F. tularensis* were to be used by terrorists, aerosol release would most likely be the mode of spread, with respiratory as well as other locations (skin, conjunctival, pharynx) occurring in the exposed population. Those criminally processing this organism would be at great risk for laboratory infection.

F. tularensis contains a number of protein and polysaccharide antigens in the cell envelope as well as an endotoxin component that is similar to endotoxins of other gram-negative microorganisms. Very little is known about other mechanisms of pathogenesis. The organism is capable of remaining viable within the reticuloendothelial cells of nonimmune subjects and in macrophages that have not been activated by recent exposure to other intracellular pathogens. As few as 10 to 50 organisms can initiate disease following cutaneous penetration or by inhalation, but a significant number are required when the challenge is through ingestion of contaminated water or foods. Local growth usually is followed by regional node suppuration and occasionally bacteremic dissemination to many organs, including the lungs. Primary pneumonia follows inhalation of organisms, resulting in numerous areas of inflammation, necrosis, a tendency to granuloma formation, hilar and mediastinal adenopathy, and pleural inflammation and effusion.

Clinical and Radiologic Features

Respiratory disease is heralded by the onset of a nonproductive cough, usually in a febrile patient ill with the ulceroglandular form of tularemia.[29] In the absence of a local chancriform lesion or a tender swollen lymph node (bubo), the disease may be dominated by constitutional symptoms, with high fever, severe headache, prominent myalgias, and shaking chills (typhoidal tularemia). Pneumonia following an inhalation exposure results in cough, dyspnea, and occasionally pleurisy. Respiratory disease can be subtle, and the diagnosis may be apparent only if a chest radiograph is done. Pleural effusions may be serosanguineous or frankly bloody, an uncommon finding with other pulmonary infections except anthrax.

Radiologic changes include evidence of parenchymal and pleural diseases, which is often out of proportion to the findings on examination. Diffuse areas of bronchopneumonia occur, with hilar node enlargement and occasionally mediastinal widening, similar to radiologic appearance of anthrax. Unilateral or bilateral pleural effusions are often noted (Fig. 138-2).

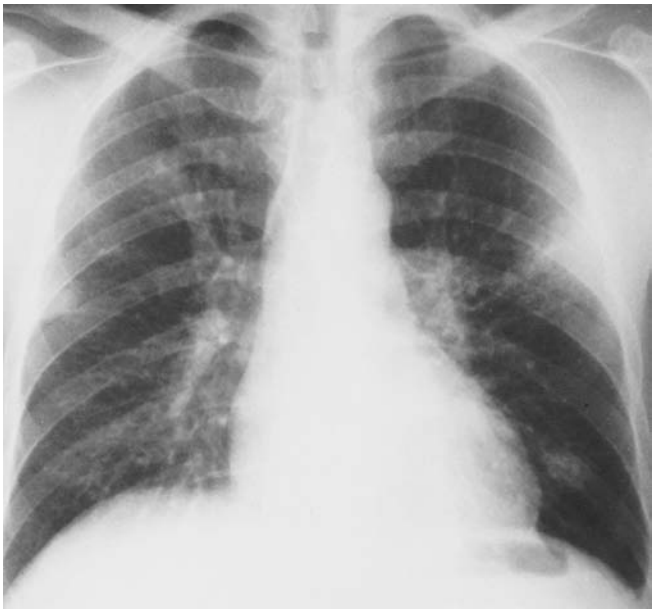

Figure 138-2 Patchy nodular and bronchopneumonia, hilar adenopathy, and left pleural effusion due to *Francisella tularensis* in a 38-year-old veterinarian exposed to a cat dying with a respiratory infection. All the findings resolved with tetracycline therapy.

Diagnosis and Differential Diagnosis

Any febrile patient with animal, arthropod, or landscaping exposure in an endemic region, especially presenting with a chancriforme skin lesion and/or a tender lymph node should be evaluated for tularemia. Cough, when present, is usually nonproductive, and blood cultures are seldom positive. Characteristic organisms are rarely seen in pleural fluid or aspirates of suppurating nodes. Direct fluorescent antibody staining of exudates can confirm the diagnosis, but this method is not widely available. Serologic testing remains the method of choice for confirming a diagnosis. ELISA and microagglutination methods may be more sensitive than tube agglutination testing. A single convalescent titer of 1:160 or greater is considered highly suspect for active disease, but a fourfold rise in titer between acute and convalescent (1–5 weeks) sera is more reliable, since antibodies can persist for many years after infection. Polymerase chain reaction and other molecular biologic techniques have successfully diagnosed tularemia in human specimens. An elevated blood level of creatine phosphokinase may be a clue to tularemia-induced rhabdomyolysis in response to acute infection, especially in highly endemic areas.

Perplexing diseases that are also associated with outdoor and animal exposures, such as psittacosis and Q fever, may be confused with tularemia. Legionnaires' disease and mycoplasma pneumonia can present with similar clinical courses, without diagnostic sputum. Plague, tuberculosis, and systemic fungal infections produce a spectrum of acute to chronic respiratory manifestations that can mimic pulmonary tularemia.

Treatment and Prevention

Streptomycin was the first effective antibiotic for treating all forms of tularemia, and it remains the agent of choice.[29] Gentamicin appears to be equally potent and has the advantage of a broader spectrum of activity if one is initiating treatment when the etiologic diagnosis is less secure.[29] In addition, it can be given intravenously, and blood levels can be monitored. *Tobramycin, however, appears*

to be unreliable and therefore should not be substituted for other aminoglycosides. Recent experience confirms that results of therapy are optimal when an aminoglycoside is chosen early in the clinical illness. Tetracycline/doxycycline, ciprofloxacin, and chloramphenicol may be useful alternatives when an aminoglycoside is contraindicated. Relapse rates are higher with the bacteriostatic agents tetracycline/doxycycline and chloramphenicol, especially when given for less than 2 weeks. β-Lactam antibiotics are not effective. The prognosis is excellent with appropriate antimicrobial therapy.

Cautious practices are required when one is dealing with animals and their carcasses. Using gloves, cooking wild animal meat thoroughly, and wearing protective clothing and repellants to avoid blood-sucking arthropods are helpful measures. An attenuated live vaccine strain (LVS) has been available for over 50 years, although it is not fully licensed (in part due to a lack of knowledge regarding the basis of attenuation), and does not offer a high level of protection against respiratory challenge. With the increase in concern over bioterrorism, numerous groups are working to develop an improved vaccine.

■ *RHODOCOCCUS EQUI*

Rhodococcus equi, formerly known as *Corynebacterium equi,* was first isolated in 1923 by Magnussen when it was identified as a cause of suppurative pneumonia in foals. It was later shown to be a frequent pathogen in horses, cattle, and swine. First described as a pathogen in humans in 1967, the majority of recognized cases in recent years have been in immunocompromised patients, especially individuals receiving corticosteroids, those infected with the human immunodeficiency virus,[30] or those who have undergone solid organ transplantation.[31]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

Rhodococcus is a pleomorphic gram-positive bacillus in the order *Actinomycetales*. It grows well aerobically on most media, at 37°C, as mucoid pale-pink or salmon-pink colonies that are usually observed by 48 hours of incubation. *R. equi* has a high cell wall mycolic acid content and is acid-fast, similar to *Nocardia* spp. and *Mycobacteriaceae*. Some strains ferment glucose, but the majority will not ferment carbohydrates. Most produce catalase and hydrogen sulfide. β-Lactamase is present in some strains.

The majority of reported cases occurring in humans without HIV infection have been in patients who had significant contact either with livestock (including horses) or soil and environments that were heavily contaminated with livestock waste. In contrast, HIV-related *Rhodococcus* disease appears to occur in patients who do not have any particular environmental exposure history—implying a wider distribution of the organism.[30] There is no known geographic endemicity.

R. equi usually is inhaled, although soft tissue infections after cutaneous inoculation can occur. As an intracellular pathogen it causes disease primarily in patients with impaired cell-mediated immunity and defects in phagocytic processing of organisms. Diseased tissues usually show a necrotizing granulomatous reaction, with histiocytes and macrophages frequently containing bacteria. In contrast to lesions associated with *Mycobacterium tuberculosis* and systemic fungi, there is also a prominent infiltration of neutrophils in the affected areas, a characteristic shared with other *Actinomyces* spp.

Clinical and Radiologic Features

Patients frequently complain of indolent symptoms, such as fever, nonproductive cough, and mild dyspnea.[31] Typically there is a paucity of findings on physical examination of the chest, but signs of consolidation and pleural friction rubs may be present. Patients with untreated HIV infection generally present in a manner similar to patients without HIV infection, although pleuritic chest pain may be more common. In untreated HIV-infected patients, *R. equi* disease tends to occur after there has been significant deterioration in the immune system, with CD4 lymphocyte counts less than 200 cells/mm^3.[30] It is often found associated with other pulmonary infections. Extrapulmonary dissemination occurs in HIV-infected and non–HIV-infected patients, but there appears to be a significantly greater rate of recovery of the organism from blood cultures in HIV patients. The central nervous system is a recognized site of metastatic infection, as it is for *Nocardia* spp.

The most common radiographic abnormalities are lobar infiltrates, which usually evolve into nodular or cavitating lesions within weeks or months. There is no predilection for involvement of any particular lobe. Pleural effusions are common, occurring in up to 40% of HIV patients with pulmonary *R. equi* infection. Significant hilar adenopathy is unusual.

Diagnosis and Differential Diagnosis

R. equi can readily be cultured from sputum, bronchial lavage, pleural fluid, or other infected tissue and often from blood. Since the organisms stain as pleomorphic gram-positive bacilli, grow readily on most media, and are usually catalase producers, they can be mistaken for "diphtheroid" or "Coryneform" contaminants unless further testing is done. Therefore it is important for the clinician to alert the microbiology laboratory staff if the possibility of *R. equi* is entertained. *R. equi* is slightly acid fast with modified Ziehl–Neelsen stain.

Rhodococci share many microbiologic features with *Mycobacteria* and *Nocardia,* and this may account for similarities in the subacute to chronic evolution of the disease. The high mycolic acid content of their cell walls results in their acid-fast staining properties and may also play a role in their similar clinical and pathologic manifestations. *Nocardia* spp., *M. tuberculosis,* and nontuberculous mycobacteria also should be considered when acid-fast organisms are found in clinical specimens, especially in immunocompromised patients with nodular or cavitary pneumonia (Table 138-3).

Other considerations in the differential diagnosis of nodular or cavitating pulmonary lesions include malignancy, fungal infection such as *Cryptococcus neoformans,* anaerobic lung abscess, and necrotizing pneumonia caused by facultative bacteria such as *S. aureus* or *Klebsiella pneumoniae.*

Treatment and Prevention

Antibiotic therapy alone is usually adequate to achieve cure.[31] As with mycobacterial infections, multidrug regimens and therapy of at least 2 to 6 months' duration may be needed, especially in immunocompromised patients. Because *R. equi* is an intracellular pathogen that multiplies in phagocytes, antibiotics capable of achieving high intracellular levels, such as rifampin or fluoroquinolones and especially erythromycin and the expanded-spectrum macrolides, clarithromycin or azithromycin, are preferred. Chloramphenicol, sulfonamides, and aminoglycosides are active against most isolates. In some patients, surgical resection of a nodular or cavitating lesion may be necessary to achieve cure. Immunocompromised hosts should avoid contact with horses and their environments.

TABLE 138-3 Diagnosing *Rhodococcus equi* Respiratory Infection

History of exposure to horses, cattle, or their environment
Immunocompromised host: Malignancy, steroids, HIV
Cavitary or nodular infiltrates on radiograph
Gram-positive pleomorphic bacilli
Modified acid fast
Pale-pink or salmon-pink mucoid colonies
Grows rapidly, aerobically on most media
Differential diagnosis includes *Nocardia* species, mycobacteria

ENVIRONMENTAL AND ANIMAL PRODUCT PNEUMONIAS

This section focuses on four diseases that are spread to humans predominantly from contact with contaminated soil, water, foods, or animal structural elements. The diagnosis usually depends on a careful history focused on epidemiologic and ecologic characteristics. Once alerted, the clinician can request studies that may reveal the cause of these often-obscure diseases. It should be apparent that this distinction – an association with environmental contamination and animal products – can be somewhat arbitrary. For example, anthrax bacilli can spread directly from animals to humans, and *R. equi* contamination of soil could place it in this group rather than in the group infected via direct animal exposure.

■ *BACILLUS ANTHRACIS (ANTHRAX)*

Inhalation anthrax was common enough in the 19th and early 20th centuries to be referred to variously as Bradford's disease, after the English town, and woolsorter's disease for the epidemiologic association with the sheep industry. Fortunately, inhalation anthrax has become a rare spontaneously acquired disease.[32] An epidemic of anthrax following an accidental release at a bioweapons facility occurred in the area of Sverdlovsk (now renamed Ekaterinburg) in the former USSR in 1979, resulting in 42 deaths due to inhalational anthrax.[33] In 2001 there were 18 confirmed cases of inhalational and cutaneous anthrax and an additional four suspected cases of cutaneous anthrax in the United States; of the 22 cases, ≥20 were definitively related to mail contaminated with the same strain of *B. anthracis*. The potential zoonotic as well as terrorist-induced exposure of susceptible persons to *B. anthracis* spores argues for including this devastating, often lethal, disease in this chapter.

Bacteriology, Ecology, Epidemiology, and Pathogenesis

B. anthracis is a large (red blood cell diameter), square-ended bacillus that stains gram-positive and has a tendency to form chains. Growth on sheep blood agar results in dull, sticky, irregularly shaped colonies within 24 hours. The organism possesses a polyglutamic acid capsule, produces a complex potent trivalent exotoxin, and, under adverse conditions, forms highly refractile, centrally located spores that are very resistant to temperature and moisture extremes.

Anthrax is primarily a disease of herbivores. The resistant spores present after animals dying of the disease contaminate the soil. Anthrax "hot spots" are found in milder regions in the United States, such as Oklahoma, Texas, and California. Optimal conditions for germination of spores and multiplication of bacilli include alkaline soils containing adequate calcium and low areas that are wet for prolonged periods, termed *incubator areas,* with thick vegetation that produces heat with decay. Periods of extreme drought after a rainy season favor spore formation. Animals grazing in these areas inhale, ingest, or pick up spores on their fur. The cycle is completed when an animal develops the disease, dies, and returns organisms to the soil for eventual sporulation.

Inhalation anthrax rarely occurs from contact with live infected animals, and there is no human-to-human transmission. The animal hide industry, exposure to bone meal fertilizer,[34] and use of imported goat skins and raw wool in home crafts can lead to inhalation of spores and clinical disease in susceptible persons.[35] Inhalation of spores from wind-disturbed soil can also cause infection.

Inhalation results in activation of bronchial clearing mechanisms and entrapment of spores in hilar and mediastinal nodes, where reversion to vegetative bacilli can occur. The polyglutamic acid capsule is antiphagocytic, and the extracellular microorganisms produce a trivalent protein exotoxin that leads acutely to profound local edema, accompanied by hemorrhage in the mediastinal and hilar areas, with compromise of airflow. Studies have clarified the mechanisms involved in the pathogenesis of this tripartite toxin, which consists of a protective antigen, an edema factor, and a lethal factor. The protective antigen fragment of the toxin serves as the binding domain, essential for cell penetration by both the edema factor and the lethal portions of the molecule. Edema factor is a potent adenylate cyclase; activation within mammalian cells stimulates production of cAMP, and the resultant flux of sodium, potassium, and water leads to abundant local edema. When this process takes place in hilar and mediastinal nodes and surrounding tissues, profound airway obstruction ensues, with pooling of secretions and if the patient survives, secondary bacterial pneumonia. Lethal factor is a potent protease that acts primarily in macrophages, activating intracellular mitogen–activated protein kinase, leading to production of proinflammatory cytokines and reactive oxygen intermediates. The pathogen rarely invades lung tissue, as death from asphyxia occurs rapidly, usually associated with pleural effusions (secondary to lymphatic obstruction) and hemorrhagic septicemic lesions in many organs. In a large inoculum exposure, as occurred in the 2001 "mail room" criminal outbreak, patients can develop disease within the pulmonary parenchyma and the gastrointestinal tract.[32]

Clinical and Radiologic Features

In spontaneously occurring disease, the onset is insidious, usually resembling a nonspecific febrile influenza-like illness.[20,32] Malaise and muscle aches, low grade fever, mild headache, coryza, mild and nonproductive cough, pharyngitis, and chest pains have been described as early symptoms. At this stage, it is hardly possible for the physician to entertain a presumptive or possible diagnosis of anthrax unless a history of industrial or craft-related exposure to imported animal hair or hides or to animal products such as bone meal is obtained. Watery nasal discharge can be indicative of nasal or paranasal sinus involvement. Cough may represent hilar and mediastinal node swelling, and careful auscultation may reveal prolonged expiratory wheezes or evidence of a pleural effusion. Chest pain may be the first clue that hilar and mediastinal inflammation is present.

Within hours to a few days, the mild complaints abruptly worsen and acute airway obstructive features dominate the clinical picture. Any activity precipitates severe dyspnea, stridor, and wheezing. Impairment of the nervous system (hemorrhagic meningitis) and hypoxemia result in decreasing levels of consciousness. Edema of the pharynx, neck, and anterior chest may develop. Chest pain, fever, and cyanosis are progressive. Worsening airway obstruction can lead to intercostal space retraction, and pleural effusions are noted on examination. Death usually occurs within hours to a day once acute respiratory symptoms are present. In the 2001 exposure to a significant spore burden, some patients had a biphasic illness with early upper respiratory and gastrointestinal symptoms, followed by respiratory distress days later.

Inhalation anthrax is primarily a mediastinitis, and the radiologic features mostly reflect the pathologic findings.[36] Widening of the mediastinum or prominence of hilar nodes is the earliest radiologic finding, sometimes accompanied by pleural effusion. In advanced cases, the mediastinal shadow is greater than 9 cm in width and sharply demarcated from surrounding lung tissue because of absence of air space consolidation. There may be perihilar and peribronchial streaking associated with edema and hemorrhage.

Diagnosis and Differential Diagnosis

A physician alerted to the possibility of inhalation anthrax has few laboratory studies to rely on. Nasal secretions and sputum rarely reveal the characteristic bulky gram-positive bacilli. Half of the reported cases of inhalation disease are complicated by meningitis, and hemorrhagic cerebrospinal fluid with observable organisms can confirm the diagnosis. There are no available data on examination of buffy-coat smears, and therapy must be instituted before

blood culture results become available. Microscopic examination of pleural fluid may reveal the characteristic organisms. The most commonly recognized form of anthrax, the cutaneous chancriform necrotic lesion, does not usually accompany inhalation cases in naturally occurring disease.

Differential diagnosis includes other causes of acute mediastinitis, such as esophageal perforation. Tuberculosis, histoplasmosis, and tularemia rarely produce acute respiratory failure as part of hilar and mediastinal node involvement. Hantavirus pulmonary syndrome is associated with similar central pulmonary changes, including edema, but should be separable from anthrax by epidemiologic data, the presence of air space disease, and absence of mediastinal involvement. Lymphoproliferative diseases, like nodular sclerosing Hodgkin disease, evolve at a slower pace. Chest wall and neck edema, associated with acute breathing difficulties, can accompany diphtheria or *Streptococcus pyogenes* pneumonia, with bilateral pleural effusions an early manifestation of streptococcal pneumonia. Acute epiglottitis, caused by *Haemophilus influenzae,* was an occasional disease of preteen children prior to vaccine development and can mimic some of the manifestations of inhalation anthrax.

Treatment and Prevention

Combination therapy is currently recommended based upon the "mail room" epidemic of 2001.[20] Regimens with ciprofloxacin or doxycycline, plus clindamycin (to block toxin production) and rifampin (which penetrate CSF and intracellular sites) are favored. Monotherapy with penicillin should not be used in inhalation disease since multiple strains, including the 2001 "mail room" outbreak, produce an inducible β-lactamase. Treatment is recommended for 60 days to avoid activation of persistent spore forms.[20] Corticosteroids should be considered for treatment of significant mediastinal edema or meningitis and early thoracentesis appears to be beneficial. Unfortunately, the airway obstructive manifestations are not reversible once acute respiratory manifestations have progressed. Assisted ventilation and use of diuretics are all reasonable support efforts, but they are generally not successful due to the continued effects of tissue-bound toxin. Before 2001, mortality in inhalation anthrax approached 100% of cases, compared with the rarity of death from cutaneous disease. In the 2001 experience, mortality was 45% (5 of 13 respiratory cases) and knowledge gained from that experience might prove helpful in future cases.

In the animal hide industry, vaccination is the cornerstone of preventing anthrax. Plant workers and others in contact with potentially infected animal products should be immunized with the currently available vaccine. Numerous new vaccines are under development, many based upon the protective antigen segment of the toxin. Animal products imported from endemic regions of the world (e.g., Africa, the Near East, and the Indian subcontinent) are steam sterilized, and there is modern ventilation in the workplace. At-risk subjects, then, are people who service these plants, such as ventilation specialists and other transients who are unlikely to be vaccinated. Bone meal should be treated by heat sterilization before packaging for use by commercial and home gardeners.[34] Those who import yarn from endemic areas are at special risk unless the rules for commercial hide sterilization are also imposed on casual animal hair imports.[35] A recent case of inhalation anthrax in a drum maker who carried goatskins into the United States emphasizes the need for appropriate education and importation controls.[35,37]

■ *BRUCELLA SPP.*

In the approximately 200 cases of brucellosis that are reported yearly in the United States, acute respiratory manifestations are usually insignificant. Lung involvement is an uncommon presentation of brucellosis.[38] Brucellosis is often a prolonged and perplexing illness however, and in chronic cases pleurisy, hilar adenopathy, and nodular lung lesions can be encountered. Exposure to animals, animal-based foods (cheeses or meats), or residence in an endemic region is usually found.

Bacteriology, Ecology, Epidemiology, and Pathogenesis

Brucellae are slow growing, small coccobacillary, gram-negative, nonmotile, aerobic, nonencapsulated organisms that are now classified with the alpha-Proteobacteria, closely related to *Rochalimaea* and *Bartonella* spp. Carbon dioxide is essential for growth of *Brucella abortus,* and all four pathogenic species require growth medium enriched with vitamins and serum. With the aid of a battery of biochemical, metabolic, and immunologic criteria, *Brucellae* pathogenic for humans can be classified as *B. abortus, B. suis, B. melitensis,* and *B. canis.* In general, the species designation corresponds to the animal usually colonized or diseased.

Brucellae spp. are distributed worldwide. Infection and disease occur primarily in domestic animals in geographic regions such as the Mediterranean littoral (*B. melitensis*), worldwide except areas of Europe and Japan (*B. abortus*), the midwestern United States (*B. suis*), and North and Latin America (*B. canis*). Spread from one region to another occurs with live animal movements or when infected animal products are commercially or privately shipped.

The epidemiology of brucellosis is intimately related to the association of susceptible persons with infected animals and animal products. Abattoir workers (especially slaughterers) and others in the meat-processing industry, farmers, dairy workers, veterinarians, and bacteriology laboratory technicians account for most cases in the United States, with a general preponderance of male patients. Fifty percent to 60% of brucellosis infections in the United States now occur in California and Texas, mostly among Hispanics.[39] Also at risk are military personnel and travelers to endemic regions who eat local foods and people who consume imported goat cheese, sausage, and other unpasteurized edibles from endemic areas. The organisms are usually acquired by ingestion, through skin abrasions and lacerations, or via conjunctival inoculation. Aerosol spread can be a route in abattoir workers[40]; inhalation of only 10 to 100 bacteria can cause disease in humans.[41] No human-to-human transmission has been reported.

Organisms invade the local reticuloendothelial system and lymph nodes, followed by bacteremic spread to many organs during the following weeks. There is increasing evidence that the aerosol route may be a rare but especially efficient portal of entry. The distribution of nodular lesions in lung tissue is primarily in basal segments, however, which argues for bacteremia rather than primarily an inhalation mechanism for most cases of pulmonary disease.

A race between bacterial growth and the development of cell-mediated immunity ensues, primarily in lymph nodes and the reticuloendothelial system. As with tuberculosis, the end result is often containment within granulomas that eventually become fibrotic or calcify. Species and strain differences account for the wide variety of tissue reactions encountered, including granulomas, necrosis, and abscess formation. Smooth variants appear to be more virulent than rough forms, and many contain polysaccharide polymers in their superficial envelope that, like true capsules, inhibit phagocytosis and intracellular destruction. Lipopolysaccharide endotoxin is present in the cell envelope and may be responsible for profound metabolic and cardiovascular effects as organisms are killed during therapy, releasing endotoxin. *Brucella* spp. are able to survive within nonstimulated macrophages while escaping host antibodies and antibiotic therapy. As macrophages become activated, they develop the capacity to rapidly kill *Brucella* organisms. Host immunity appears to be primarily cell mediated. Impairment of cell-mediated immunity can lead to reactivation of latent *Brucella* or greater susceptibility and severity with primary infection.

Clinical and Radiologic Features

Clinical brucellosis is dominated by nonspecific flu-like constitutional manifestations, including fever and headache. Nonproductive cough has been described in 10% to 33% of cases, but other indicators of respiratory involvement are rarely or poorly described. In one review of 59 cases, dyspnea and pleuritic chest pain were present in 10% of the patients. Hoarseness, bronchitis, and, rarely, mucopurulent, purulent, or hemorrhagic sputum have been noted. Only one patient with verified pulmonary invasion was described in a review of 160 acute and subacute cases of brucellosis reported in 1974. In a recent description of 37 patients with *Brucella* respiratory disease, 32% had typical lobar pneumonia, 41% had an interstitial pattern on chest x-ray, and a honeycomb pattern was seen in 11%, with pleural effusion(s) in the same number.[42] Extrapulmonary disease was found in 76% of patients, with 22% having greater than one extrapulmonary complication. Unilateral hilar adenopathy and granulomas occur occasionally.

Diagnosis and Differential Diagnosis

During the acute illness or in relapse, blood cultures may be positive. In the presence of an infiltrate or pleural effusion, material for Gram stain and culture should be obtained, although the yield is small. A positive culture may be obtained from a lymph node or pulmonary granuloma biopsy. In most cases the diagnosis is made from a fourfold rise or a single value of at least 1:160 in the agglutination titer. Occasionally "inhibitory" or blocking antibodies are present in the serum, and a positive titer is discovered only if the serum is further diluted (so-called prozone phenomenon). The standard tube agglutination test utilizes *B. abortus* as the antigen and will detect antibodies to *B. suis* and *B. melitensis,* but not to *B. canis.* Diagnostic confusion and numerous alternative diagnoses are the rule in cases of brucellosis. Direct comparison of the clinical manifestations of *B. abortus* with *B. melitensis* reveal that the latter presents more acutely as fevers of unknown origin with statistically significant higher rates of abdominal tenderness, hepatomegaly, splenomegaly, thrombocytopenia, pancytopenia, and hepatic dysfunction. Acute disease can be confused with miliary tuberculosis, endocarditis, tularemia, disseminated histoplasmosis, and lymphoproliferative diseases. Subacute and chronic cases must be differentiated from subacute bacterial endocarditis, tuberculosis, histoplasmosis, other systemic fungal infections and sarcoidosis.

Treatment and Prevention

The combination of doxycycline with rifampin for 4 to 6 weeks is one of the most effective and easiest of the oral antibiotic regimens.[38] Doxycycline combined with streptomycin or gentamicin, or trimethoprim/sulfamethoxazole are also effective alternative regimens. Fluoroquinolones are active in vitro, but they are associated with an unacceptably high relapse rate as monotherapy.

Rigorous control measures such as herd inspections and vaccination procedures have dramatically reduced enzootic and epizootic disease in many regions. Quarantine and inspection activities have diminished the risk of importing infected animals into the United States. The program for *B. suis* eradication has been ineffective, and human cases of *B. suis* now outnumber those due to *B. abortus.* The efficacy of human vaccines is marginal. Education programs for workers in abattoirs have been aimed at protecting and preventing skin lacerations, eye contamination, and aerosol spread.

■ *BURKHOLDERIA (PSEUDOMONAS) PSEUDOMALLEI*

Melioidosis ranges from an acute necrotizing to a chronic fibronodular cavitating process indistinguishable from tuberculosis.[43] It is a disease of tropical latitudes, and most cases have been seen in Southeast Asia, associated with rural settings.[44] A number of cases were noted in survivors of the 2004 tsunami,[44] and after flooding in Puerto Rico.[45] Infection with *B. pseudomallei* has been seen in the United States almost exclusively after a latent period of months to years in military personnel returning from regions such as Vietnam and in refugees from endemic areas, although case reports from areas such as the Caribbean,[45] Africa, the Middle East, and Brazil have also been reported. The mortality rate can reach 40%.[43]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

The organism is an aerobic, bipolar-staining gram-negative bacillus that is motile and lacks a well-defined capsule. Similar to the pseudomonads, *B. pseudomallei* grows well on minimal as well as enriched media, including blood and MacConkey agar, used in most routine laboratories. Typical colonies are distinctive in appearance, rough or wrinkled, and cream to orange in color; they may resemble a flower with folds radiating from a central core. Colonies have the typical musty, fruity odor of the pseudomonads but lack pyocyanin and other pigments that characteristically color the surrounding medium. Identification rests on a battery of biochemical reactions, and confirmation is based on agglutination or fluorescent antibody studies.

B. pseudomallei occupy an environmental niche that includes moist soils, rice paddies, and other stagnant water in tropical and subtropical regions, approximately subtended by latitude 20°N to 20°S. Evidence of subclinical and clinical diseases occurs in wild and domestic animal populations, as well as in humans living permanently or transiently in rural endemic areas, especially in southeast Asia and northeast Australia. As many as 10% to 30% of native populations have evidence of prior infection based on serologic data. Approximately 1% to 2% of healthy American military personnel who served in Southeast Asia have antibodies, and almost 9% of soldiers wounded in Vietnam have titers for *B. pseudomallei.* A significant number of the approximately 3 million U.S. soldiers who fought in the region constitute a reservoir of latent disease that, like tuberculosis, can become active even decades later, far removed from an endemic area. Refugees from Southeast Asia represent another important group of potential carriers.

Transmission is mainly by direct contact with contaminated soil or water through minor abrasions or major wounds. Ingestion and inhalation are probably less frequent modes of spread, but common source outbreaks occur in animals and humans. Animal-to-human disease is very rare, with only three cases reported from Australia. Human-to-human spread has also been exceptional, associated with breastfeeding, urinary catheter contamination, or between siblings with cystic fibrosis. In endemic regions, lack of previous exposure and debilitating circumstances, including malnutrition and uncontrolled diabetes, may increase susceptibility to infection and disease. In a survey of 524 patients with melioidosis in northeast Thailand, coinfection with HIV was detected in only 8 of 524 adults (1.5%); clinical presentation and acute outcome were similar in HIV-positive and -negative patients. Although it is not clear if solid organ transplant alters the risk for melioidosis, pleuropulmonary melioidosis with septicemia has been reported in a renal transplant patient in Australia; although she was not from an endemic region, on revisiting her travel history, it was found that the patient had travelled to the endemic tropical northern Queensland part of Australia during the rainy season.[46]

Pathogenesis and Pathophysiology

The presence of potent endotoxin and the absence of an antiphagocytic capsule have been noted. Acute infections are associated with necrotic lesions containing polymorphonuclear neutrophils (PMNs) in lung and other tissues. Chronic infections, especially in the respiratory tract, resemble tuberculosis with granuloma formation, Langhans or foreign-body giant cells, central caseating necrosis, and occasionally a PMN response in the necrotic area. Activation of latent infection after a period of months to even decades occurs. This "awakening" can be in the wake of influenza and other acute

infections, acute stress (trauma, thermal burn, surgery, etc.), and immunosuppressing illnesses or therapies, but spontaneous activation also occurs. The location of dormant microorganisms and the specific molecular events that stimulate recurrent disease are unknown but remain an area of active investigation.

An antecedent local infection in an area of broken skin can be followed by acute septicemia in nonimmune subjects. Initial pulmonary lesions occur predominantly in the better-vascularized basal segments consistent with bacteremic spread to the lungs. Eventually other areas of the lungs and other tissues are affected. Subacute and chronic disease may result from a subclinical primary focus, often localized in an apical segment, resembling tuberculosis in location and propensity for granuloma formation and cavitation. Subpleural invasion can result in empyema or sympathetic sterile effusions.

Clinical and Radiologic Features

Primary melioidosis occurs within a few days to 3 weeks of exposure, usually via a cutaneous wound in persons from (or with recent exposure to) an endemic area. The portal of entry may be present as a small necrotic skin lesion in an area of known trauma, with accompanying cellulitis or lymphangitis. Although the acute phase of melioidosis is the most common manifestation in endemic areas, it is very rarely seen in the United States. In addition to marked toxicity and high fevers, the respiratory complaints include cough, dyspnea, pleuritic pain, and purulent sputum. Bibasilar rales may be heard, but objective physical findings are often minimal in the face of severe toxicity.

Milder types of subacute and chronic pneumonia are often seen. In addition to fever, productive cough, and pleuritic pain, many patients experience marked weight loss and a clinical picture resembling tuberculosis or fungal disease. Secondary skin manifestations are rarely seen unless bacteremia ensues. Physical changes are often subtle but can include localized rales, a pleural friction rub, signs of an effusion, and manifestations of disease localized to soft tissues, lymph nodes, bones, or joints.

Radiologic findings reflect the stage of disease present. In acute fulminant infections, air space disease can be absent or miliary to larger nodular densities seen in basal segments. In subacute and chronic cases, fibronodular or cavitary apical lesions are found, similar to reactivation tuberculosis.

Diagnostic Features

Melioidosis should be seriously entertained in any febrile patient with a history of residence in a major endemic region such as Southeast Asia or northeast Australia. If sputum is available, the gram-negative bipolar-staining bacilli may be seen, and the organisms can be readily cultured and identified in the routine laboratory. Blood and urine cultures are frequently positive in acute cases. In more indolent infections, biopsy may be necessary. Molecular biology techniques such as polymerase chain reaction are being developed for diagnostic use. Serologic studies can be helpful in active and recrudescent disease, especially in patients residing in nonendemic areas. A specific IgM immunofluorescence test is often positive in recent infections and recrudescent disease. Complement fixation and indirect hemagglutination tests are available and require testing of paired sera over several weeks to confirm active disease.

Differential Diagnosis

In patients from Southeast Asia, acute fulminating infections with pneumonia may be due to traditional bacteria and viruses, but may also be caused by infection with *Y. pestis* (plague) and *F. tularensis* (tularemia) (see Section on *Francisella Tularensis*). Chronic forms of melioidosis resemble tuberculosis and fungal infections such as histoplasmosis and blastomycosis. Occupation, travel, and history of respiratory illness should help to clarify the cause.

Treatment and Prevention

Recommendations for therapy of acute septicemic melioidosis must be couched in cautious statements. During the Vietnam War, mortality greater than 50% occurred, even with use of three-drug regimens in massive doses. In subacute and chronic pneumonias and recrudescent disease cure rates approach 100%. Treatment must be prolonged and surgical intervention for drainage or removal of cavitary lesions is sometimes necessary to prevent relapse.

Imipenem/meropenem or the third-generation cephalosporin ceftazidime in high doses are considered first-line therapy. Some centers add trimethoprim/sulfamethoxazole for better intracellular activity and to potentially decrease the emergence of antimicrobial resistance with combination therapy. Once a good clinical response is seen, usually after at least 14 days, oral therapy may be initiated. Such subsequent oral eradication therapy is considered necessary to prevent recrudescence or later relapse of melioidosis. Eradication regimens are varied and include such agents as doxycycline, chloramphenicol, trimethoprim/sulfamethoxazole, and (less effective) azithromycin and ciprofloxacin. Amoxicillin–clavulanic acid may be used in children. A recent trial in 140 subjects in Thailand showed that trimethoprim/sulfamethoxazole alone is as effective as and better tolerated than cotrimoxazole plus doxycycline for the eradication treatment of melioidosis.[47] With the exception of kanamycin, other aminoglycosides are ineffective.

No prophylactic antimicrobial studies are available, nor has a vaccine been developed. People traveling, living, or working in endemic regions should be advised of this soil- and water-dwelling organism. Traumatic injuries should be avoided, and wounds contaminated with soil or stagnant water should be assiduously cleaned.

■ *COXIELLA BURNETII (Q FEVER)*

Initially described in abattoir workers in Brisbane, Australia in 1935 as Q (for query) fever, Q fever generally causes systemic symptoms, which can progress to atypical pneumonia, occasionally complicated by acute respiratory distress syndrome (ARDS). In temperate-zone countries, the prevalence of acute Q fever in pneumonia patients ranges from 0% to 2.3%: 1.2% in the United Kingdom, 0.9% in the rest of Europe, and 2.3% in the United States.[48] Among endemic regions, rates vary; in the late 1960s in Riyadh, Saudi Arabia, 8.4% of residents >5 years of age were seropositive,[49] while of those with pneumonia, in Greece, the frequency of acute Q fever was 4.7% among 3686 patients with atypical pneumonia.[50] In Israel, a study conducted in 1995 among 346 in patients with pneumonia showed that 20 (5.8%) had Q fever pneumonia,[51] and a study in the Spanish Basque region demonstrated a prevalence of 18.8% in patients with pneumonia.[52] Recent work in French Guiana showed a prevalence of 24%.[48] Although the Middle East is an endemic region, only three soldiers developed Q fever during Desert Storm, probably because most troops had very limited or no contact with herds of animals.[53]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

C. burnetii has traditionally been grouped with the Rickettsiae, which also includes typhus and spotted fevers. Recent phylogenetic studies, based on 16S rRNA sequence analysis, have demonstrated that *C. burnetii* is more closely related to *Legionella*, *Francisella,* and *Rickettsiella.* The organism is now classified in the family Coxiellaceae and order Legionellales in the gamma subdivision of Proteobacteria.[54] *C. burnetii* is an acid-fast, pleomorphic, small coccoid or filamentous organism. It is an obligate intracellular pathogen. Although gram negative, it is often not detected by Gram stains. *C. burnetii* forms spore-like structures that are highly resistant to even severe environmental conditions; it can survive like this for extended periods, especially in very arid soils.

Q fever exists worldwide, except for New Zealand. From 1999 to 2004, there were 18 reported outbreaks of Q fever from 12 different

countries involving 2 to 289 people.[54] The largest outbreak ever described occurred in the Netherlands in 2009. Large outbreaks have been reported in Switzerland, Great Britain, Germany, and in southern France. In North America, Nova Scotia has been the location of a significant number of cases. There are case reports of Q fever in armed forces personnel returning from Iraq.

Transmission occurs via contact with contaminated birthing products, milk, meat, and wool, or inhalation of windblown dust from areas contaminated by placentae and other animal products. Ticks can facilitate transport to other animals. Transfer between humans has been very rarely described, primarily during autopsies or to healthcare workers.[54] Risk factors for spread among animals include relatively closely located bulk milk small ruminant farms, spread from vermin and companion animals, imported straw, and use of artificial insemination.[55] A classic outbreak was described in 12 poker players in Nova Scotia after exposure to a parturient cat, subsequently termed "poker player's pneumonia."[56]

C. burnetti has two distinct antigenic phases. Phase I and II cells are morphologically identical, although differ in certain biochemical characteristics including their lipopolysaccharide composition. Organisms isolated from infected animals or humans express phase I antigens and are very infectious; the ID50 (number of bacilli needed to infect 50% of individuals) is considered to be 1, making it among the most infectious agents known. Organisms expressing phase II antigens are less infectious and are recovered after the bacteria have been repeatedly passaged in cell cultures or eggs. Experimentally infected animals and humans first produce antibodies to phase II antigens and later produce antibodies to phase I antigens, which may be used to distinguish acute from chronic infections.

Monocytes and macrophages are the target cells for *C. burnetti* infection. Phagocytosis of *Coxiella* creates acidic phagolysosomes in which the organisms can persist and multiply. The formation of pseudopodal extensions and transient reorganization of filamentous actin are stimulated by virulent (but not avirulent) bacteria. Cell-mediated immunity and granuloma formation is important for control of primary infection. Chronic Q fever is characterized by defective cellular immunity; lymphocytes from patients with Q fever endocarditis do not proliferate in response to *C. burnetii* antigen, compared to lymphocytes from those with acute Q fever.[54] Severe inflammation is common with Q fever endocarditis, characterized by upregulated levels of TNF and IL-6 (two inflammatory cytokines), type II TNF receptors and IL-1 receptor antagonist.[54]

Clinical and Radiologic Features

The incubation period can be as long as 2 to 3 weeks, stressing the importance of recent travel and exposure history. Acute symptomatic infection develops in 40% of patients, while 60% are asymptomatic.[54] Illness may present acutely, with fever, severe headache, arthralgias, myalgias, cough, and other influenza-like symptoms.[57] Q fever can cause endocarditis, hepatitis, and pneumonia. Unlike the other rickettsial diseases, Q fever primarily affects the lungs, with pneumonia in approximately half of cases. The combination of pneumonia and hepatitis should suggest Q fever. Rashes are rare, unlike in the other rickettsial diseases. There can be variation in the predominant symptoms, with pneumonia more common in some outbreaks, and hepatitis more common in others, perhaps due to strain variation or the method of inoculation (ingestion vs. inhalation).[54]

Chest radiograph findings are nonspecific. Pleural effusion may be present, as may pericardial effusion. In the 1989 West Midlands outbreak, 10% of films were normal, and the features of 62 abnormal films were varied; there were no specific aspects to help distinguish Q fever pneumonia from other pneumonias.[58] Complete radiographic resolution frequently took up to 6 months. In another series in the north of Spain, 87% had a single lobar or segmental alveolar opacity, most commonly in the lower lobes, and chest radiographs returned to normal in 70% of patients within 2 months.[59]

Diagnosis and Differential Diagnosis

Most often normal, the leukocyte count may be elevated in 25% of cases,[57] but is less commonly elevated than with routine community-acquired pneumonia.[48] Elevations in the erythrocyte sedimentation rate, liver enzymes, and creatine phosphokinase as well as thrombocytopenia may be seen.[57] Autoantibodies sometimes develop, including antimitochondrial, antismooth muscle, and antibodies to phospholipids (i.e., anticardiolipin or lupus anticoagulant).

Sputum is infrequent and often nondiagnostic. Diagnosis of Q fever is most commonly made in patients with epidemiologic risk and confirmed by serology using an immunofluorescence assay against phase I (acute infection) and phase II (chronic infection) antigens, comparing acute and convalescent samples. Seroconversion usually occurs by 7 to 15 days after the onset of clinical symptoms, with roughly 90% of patients seropositive by 3 weeks.[57] A significant number of people are exposed and never develop symptoms. In one series, sera of 268 people living or working on 111 dairy goat farms in The Netherlands were tested for *C. burnetii* IgG and IgM antibodies using immunofluorescence assay: The seroprevalence in asymptomatic farmers, spouses, and children (12–17 years) was 73.5%, 66.7%, and 57.1%, respectively.[60] Recent work in French Guiana on development of a predictive score may help accurately identify patients with Q fever pneumonia.[48]

C. burnetii can be cultivated in embryonated eggs, laboratory animals, and *in vitro* cell culture systems; it must be cultured in biosafety level 3 laboratories due to its extreme infectivity. Culture is challenging and is not be readily available. Molecular diagnostics, amplifying bacterial DNA, are increasingly useful, especially for early diagnosis of acute Q fever; *C. burnetii* DNA becomes undetectable in serum as the serologic response develops. With hepatitis, liver biopsy may show the classic granulomas with open space surrounded by a fibrin ring, called "doughnut granulomas." In the placenta, organisms can be identified in exudates or areas of inflammation with a modified Ziehl–Neelsen, Gimenez, Stamp, Giemsa, or modified Koster stain.

Given the relatively nonspecific findings with Q fever, the differential diagnosis is broad, appropriately narrowed at times based on epidemiology. For pneumonia, other diagnoses would include atypical pathogens such as *Chlamydophila pneumoniae, Chlamydia psittaci, F. tularensis, Legionella pneumophila,* and *Mycoplasma pneumoniae.* Viral etiologies may also mimic Q fever. A case report from Turkey describes Q fever mimicking Crimean–Congo hemorrhagic fever.[61]

Treatment and Prevention

Treatment usually involves the use of doxycycline, fluoroquinolones, or rifampin.[54] Trimethoprim/sulfamethoxazole can be used in pregnant woman. In chronic Q fever, recommended treatment in adults is at least 18 months of doxycycline given with an alkalizing agent like hydroxychloroquine (added to neutralize the acid environment of the phagosome). In children, trimethoprim/sulfamethoxazole is the preferred agent.[54]

A whole-cell vaccine for Q fever (Q-Vax), developed in Australia, has effectively protected humans in occupational settings; this vaccine is not commercially available in the United States. An acellular vaccine (CMR) is available in the United States for individuals engaged in research with pregnant sheep or live *C. burnetii*; data is limited on this vaccine. Prior to vaccination, people should have a skin test for previous exposure to *C. burnetii*; those with previous exposure should not receive the vaccination because of severe local reactions. Vaccination of farm animals against Q fever is effective in curtailing spread.

■ YERSINIA ENTEROCOLITICA

Most infections caused by *Y. enterocolitica* are gastrointestinal, resulting in a self-limited gastroenteritis or appendicitis-mimicking mesenteric and terminal ileum adenitis. Septicemias and involvement of the lungs and other viscera are extremely rare, mostly in immunocompromised hosts, alcoholics, and cirrhotics.

Y. enterocolitica is a gram-negative, facultative bacillus that resembles many other enteric microbes. Identification procedures include the ability to grow, exhibit motility on diagnostic media at room temperature, and utilize a battery of biochemical and serologic tests. Most strains are nonlactose or slow-lactose fermenters, causing confusion with *Y. pestis, Salmonella, Shigella,* and several other members of the Enterobacteriaceae family. Cold enrichment techniques and highly selective media, extensively used to identify this organism in feces, are not necessary for other specimens.

Y. enterocolitica has been isolated from a variety of rodents and other wild species, and from cats, dogs, and farm animals. There is little evidence for direct transmission or for spread among people other than by the fecal–oral route. Most cases occur singly, but epidemics involving families and hundreds of people have been described. Disease is initiated by ingestion of contaminated milk or other food. Direct aspiration may be the mechanism for initiation of pulmonary disease, following an initial pharyngitis focus. Bacteremia can complicate pharyngeal disease, although the most likely mechanism entails ulceration of Peyer patches in the terminal ileum, mesenteric adenitis, and portal bacteremia. Systemic shunting to the lungs can follow, especially in cirrhotics, the group that most frequently develops septicemia. Strains virulent for animals and causing human disease have plasmid-mediated V and W envelope antigens, temperature-sensitive calcium dependency (as with *Y. pestis*), a factor that enhances cell penetration, and endotoxin. The development of immune complex manifestations such as erythema nodosum and nonsuppurative polyarthritis may contribute to pathogenicity.

In the past three decades, approximately 15 cases of pneumonia have been described in the literature.[62] Respiratory infections occur in association with an acute febrile septicemic illness or as a primary respiratory process, with cough, dyspnea, and signs of consolidation. The history is usually vague for gastrointestinal symptoms, animal exposure, or unusual food intake. Radiologic findings include nodular basilar densities consistent with septicemic spread, dependent segment infiltrates suggesting an aspiration mechanism, occasional cavitation, and fluffy widespread densities consistent with septic emboli.

The diagnosis often depends on routine blood or sputum cultures. Enteric gram-negative bacilli can be seen in sputum. Pharyngeal cultures should be done if signs of local inflammation are present. Suppurating nodes and peritoneal or joint fluids are other sources of material that may contribute to the diagnosis.

Cases of respiratory infection have responded well to a variety of antibiotics, including ampicillin or second-generation cephalosporins. Third-generation cephalosporins, chloramphenicol, aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole may also be effective. Treatment should be based on antibiotic susceptibility testing. Underlying diseases influence the outcome, but when pneumonia is the major problem, prognosis is excellent. Treatment is usually continued for a total of 3 to 6 weeks.

Preventive measures include avoiding rodent or domestic animal contamination of food and water supplies. Opportunities for susceptible individuals to come in contact with this zoonotic microorganism may be increasing as well, as healthy and immunocompromised people turn to organically grown foods, natural springs, and mountain streams for improved health but with potential contamination with pathogens from animal droppings.[63]

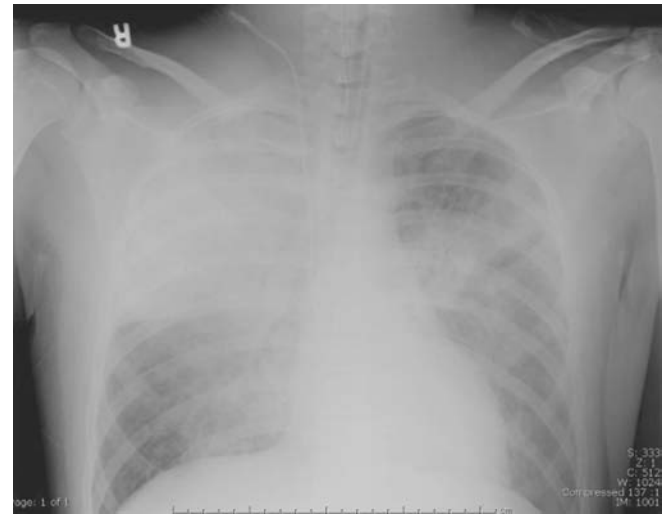

Figure 138-3 Patchy bronchopneumonia, predominantly in the right upper lobe, in a 16-year-old boy with *Neisseria meningitidis* pneumonia and bacteremia. *(Used with permission of Holly Rawizza, MD.)*

PNEUMONIAS CAUSED BY OBLIGATE HUMAN COMMENSALS

Most bacterial pneumonias caused by encapsulated obligate human commensals are easy to isolate, such as *Streptococcus pneumoniae;* among the less common causes, *Neisseria meningitidis* (the meningococcus) and *Moraxella* (formerly *Branhamella*) *catarrhalis* stand out as pathogens or opportunists that may escape routine bacteriologic identification and therefore present problems in diagnosis and therapy.

■ NEISSERIA MENINGITIDES

During the influenza viral pandemic of 1918 to 1919, *N. meningitidis* was an important respiratory pathogen (Fig. 138-3). Afterward, few references to the meningococcus appeared in the medical literature on bacterial pneumonias, as reports of meningococcal disease focused on its role in causing meningitis and septicemia. With the advent of improved bacteriologic techniques, an increasing number of cases of *N. meningitidis* pneumonia have been recognized.[49]

Bacteriology and Immunology

Neisseria are oxygen-requiring, gram-negative cocci recognized by their characteristic paired, kidney-shaped diplococci. They are fastidious, succumbing rapidly to the external environment and extremes of temperature or humidity. Although *Neisseria* can grow on blood agar, optimal conditions include enriched media, such as chocolate agar, and incubation in an atmosphere of 6% CO_2 at 35° to 37°C with 50% humidity. Isolation and identification of *N. meningitidis* in sputum are facilitated by the use of a selective medium, such as modified Thayer–Martin agar (MTM), which contains antibiotics that suppress competing respiratory microorganisms. *N. meningitidis* is distinguishable from other *Neisseria* spp. that are residents of the oral-respiratory region by sugar fermentation reactions and serologic identification (Fig. 138-4).

N. meningitidis is a typical gram-negative organism containing a potent lipopolysaccharide endotoxin in the outer membrane layer of the cell envelope. Exterior to this layer is a polysaccharide capsule, by which *N. meningitidis* can be separated into at least 13 chemically defined serogroups. Groups A, B, C, Y, and W-135 are currently the most important clinically. The less frequently observed serogroup Y meningococci accounted for 44% of isolates in one series of 58 cases of meningococcal pneumonia.

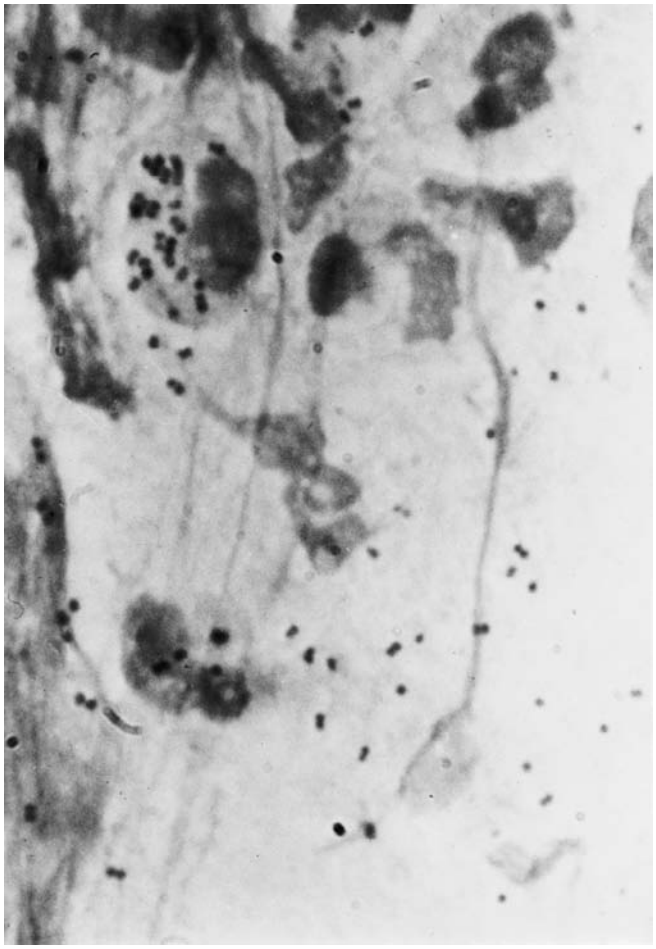

Figure 138-4 Gram stain of expectorated sputum from a patient with proven *Moraxella* pneumonia. In this black-and-white photomicrograph, the distinguishing features include the presence of morphologic kidney-shaped diplococci (gram-negative) associated with polymorphonuclear neutrophils. This appearance suggests *Neisseria* or *Moraxella* infection. Culture confirmed the identity as *Moraxella*.

Ecology, Epidemiology, and Pathogenesis

An obligate human pathogen, there are no records of nonhuman carriage or disease from *N. meningitidis*. Respiratory disease due to meningococci was recognized early in the 20th century, especially during the influenza pandemic of 1918 to 1919. In the mid-1970s, outbreaks of serogroup Y meningococcal pneumonia occurred in military installations.[64] Over the past 25 years, isolated respiratory disease, primarily due to serogroups Y and W-135, has been more frequently detected in civilian populations and nosocomially in persons in contact with an index case.[65] Nosocomial spread of *N. meningitidis* has been recognized in recent decades.[66] Nasopharyngeal carriage of various serogroups of meningococci occurs in approximately 5% to 25% of subjects. Spread is probably by aerosol droplets during close contact, since drying rapidly kills meningococci. A case of meningococcal disease in a family is often associated with an increased prevalence of meningococcal isolation from relatives with symptoms of upper respiratory infection. People ill with influenza or adenoviral respiratory infections appear to be more susceptible to bacterial pneumonias, including meningococcal pneumonia. Stimulation of excessive airway secretions, damage to surface epithelial structures, and interference with clearance of microorganisms all serve to augment the risk of bacterial pneumonia.

Initiation of infection begins when an encapsulated strain colonizes the nasopharynx of a person lacking immunity to that serogroup. Attachment to mucosal cells is facilitated by filamentous pili and outer membrane proteins such as Opa and Opc, and by the action of bacterial IgA1 protease. The capsule helps evade complement fixation and subsequent phagocytosis. Lipopolysaccharide (endotoxin) stimulates release of inflammatory mediators, including TNF-α, IL-1β, IL-6, and IL-8, and thus has a crucial role in the pathogenesis of meningococcal septic shock. Meningitis, petechial eruptions diffuse intravascular coagulation, and ARDS seldom accompany pneumonia, supporting a postulated aspiration rather than hematogenous mechanism.

Clinical and Radiologic Features

The clinical presentation of meningococcal pneumonia ordinarily is a community-acquired pneumonia that resembles pneumococcal infection. Productive cough, pleuritic pain, chills, and fever are associated with rales and consolidation. Unlike pneumococcal disease, pleural rubs and hemoptysis are unusual. The spectrum of respiratory disease includes pharyngitis, common in outbreaks, and purulent tracheobronchitis. Invasive meningococcal respiratory disease carries a mortality rate of 5% to 10%.

Radiologic features are nonspecific and include patchy bronchopneumonia and lobar air space infiltrates. Bilateral involvement occurs in 20% of cases and an effusion is noted in about 13% of cases. Occasionally, the radiologic appearance resembles diffuse pulmonary edema or an antecedent viral infection.

Diagnosis and Differential Diagnosis

Diagnosis depends on isolation of predominantly *N. meningitidis* from a carefully collected sputum specimen that has characteristic gram-negative diplococci and PMNs on the stained smear (Fig. 138-4). Attention to these criteria is essential, since pathogenic and nonpathogenic *Neisseria* and *Moraxella* spp. are part of the normal respiratory flora. Invasive procedures such as bronchoscopy are not necessary if adequate sputum samples are available, and the Gram stain appearance prompts culturing the specimen on MTM media. Alternative methods of identification include the classical capsular swelling technique (to rule out pneumococcal infection), latex bead coagglutination, and fluorescent antibody staining. Recent purification of all of the major group-specific capsular polysaccharides should lead to expansion of these rapid diagnostic methods. Blood cultures were positive in a significant number of recent cases.

Respiratory infections due to other causes, especially when there are clusters of cases, must be considered in the differential diagnosis. Viral agents such as influenza A or B or adenoviruses can cause acute respiratory infections affecting a number of people, especially under institutional or crowded circumstances. Mycoplasmal pneumonia is frequently biphasic, with upper respiratory inflammation and headache prominent early symptoms, and, occasionally, bullous tympanitis producing severe ear pain. The sputum is often purulent, with a mixture of PMNs and mononuclear cells, but no dominant microorganism is observed with Gram stain. Diagnosis is usually confirmed by a cold agglutinin titer of 1:32 or greater, a rising titer of complement-fixing antibody, or PCR of sputum. Other atypical pneumonias to consider include *Legionellae*, *Chlamydia psittaci*,[5] and *Chlamydia pneumoniae*.

In the wake of antecedent viral respiratory infections, *S. pneumonia* and *S. aureus* infections are differentiated with microscopic examination, culture of sputum, and the results of blood cultures. In hospitals, especially among immunocompromised patients or patients on respirators, a variety of gram-negative microorganisms can produce pneumonia, including *H. influenzae* and *M. catarrhalis*.

Treatment and Prevention

Low-dose penicillin is effective for most cases of susceptible *N. meningitides* pneumonia, although those complicated by cavitation

or empyema should be treated with a minimum of 6 million units daily. Cephalosporins (ceftriaxone, cefotaxime) are commonly used. Patients allergic to β-lactam antimicrobials can be given chloramphenicol, although resistance to this agent is increasing worldwide. In contrast to meningitis or meningococcemia, respiratory infections appear to respond uniformly well to treatment.

Meningococci spread via droplet aerosols, so isolation of suspected cases is essential, especially during the first 24 hours of treatment. Chemoprophylaxis is effective in epidemics of meningitis, but no data are available for respiratory disease protection. Penicillin, the drug of choice for treating active disease, does not reliably eradicate the carrier state or protect intimately exposed contacts. Rifampin is an effective prophylactic agent probably due to its transport into oral and respiratory tract secretions in high concentrations. Minocycline diffuses into upper respiratory secretions in high concentrations and is a useful alternative to rifampin. Fluoroquinolones such as ciprofloxacin are also effective. Immunoprophylaxis has been safe and effective when given systematically to large at-risk groups in military installations, schools, day care centers, or defined communities. A protein conjugate quadrivalent vaccine containing serogroups A, C, Y, and W-135 is commercially available and has largely replaced the polysaccharide vaccine. Vaccines for serogroup B are in development or available presently in other countries. There are no contemporary data for efficacy of the vaccine against respiratory infections. Use of influenza viral vaccines should eliminate some cases of secondary bacterial infections, including those caused by *N. meningitidis.*

■ *MORAXELLA (BRANHAMELLA) CATARRHALIS*

Formerly considered a nonpathogenic respiratory commensal, *M. catarrhalis* has aroused renewed interest as an opportunist and primary pathogen.[67] Resemblance to *Neisseria* on Gram stain can be confusing and encourages its inclusion in this section.

Bacteriology

Moraxella are gram-negative cocci that pair as kidney-shaped diplococci, thus indistinguishable morphologically from *Neisseria*. The organisms grow well on nonselective media such as sheep blood agar and enriched chocolate agar, especially with supplemental CO_2. Growth of *Moraxella* is variable on selective media such as MTM, in contrast to pathogenic *Neisseria,* which thrive on that medium. Other biochemical tests and their failure to utilize a variety of sugars help to distinguish them from *Neisseria.*

Epidemiology, Pathogenesis, and Pathophysiology

A member of the resident microflora of the nasopharynx and pharynx, *M. catarrhalis,* can also colonize the mucosa of the genital tract. There is no evidence for human-to-human transmission, although infections in the hospital occur and are probably related to nosocomial spread and the selective pressures from the various antimicrobials used. In normal children and adults, otitis media, sinusitis, and laryngotracheobronchitis probably result from direct invasion from colonized mucosal surfaces.

In contrast to pathogenic *Neisseria, Moraxella* lack antiphagocytic capsules and IgA proteases. Neutrophils as well as humoral immunity have been reported as significant factors in natural host defense of this member of the normal flora. The mechanism of initiation of respiratory disease appears to be primarily related to underlying obstruction and chronic inflammation. Aspiration of nasopharyngeal secretions, stimulated by an acute viral upper respiratory infection, is the most common predisposing pathophysiologic event. Contributing immunocompromising conditions – such as steroid therapy, malignancy, hypogammaglobulinemia, and neutropenia – are present in a large number of patients.[67] Paranasal sinus and ear infections occur predominantly in children, probably because of anatomically crowded drainage ducts. Rarely, *Moraxella* cause primary invasive diseases outside the respiratory tract, including meningitis, endocarditis, septic arthritis, and, in immunocompromised patients, septicemia.

Clinical and Radiologic Features

Respiratory infections from *M. catarrhalis* occur mostly in adults with chronic lung disease from smoking, industrial exposures, or bronchitis and bronchiectasis. Purulent bronchitis or bronchopneumonia can follow an intercurrent viral infection. Signs of consolidation or pleural fluid may be present, along with persistent obstructive changes. Normal adults may develop primary laryngitis and children a nonproductive cough as other manifestations of respiratory tract disease.

The underlying chronic lung disease influences the radiologic appearance. No acute changes may be observed, but increased markings can be seen superimposed on the findings of obstructive lung disease and fibrosis. Patchy consolidation is often noted. Lobar infiltrates, cavitation, and pleural effusions are distinctly unusual findings and suggest mixed infections or other complications of the underlying disease.

Diagnostic Features and Differential Diagnosis

The unique challenge in cases of *M. catarrhalis* respiratory infections is identifying this organism when gram-negative kidney-shaped diplococci associated with a PMN exudate are noted and suggest a meningococcal infection (Fig. 138-4). Diagnosis depends on careful examination of an adequate expectorated sputum sample and culturing the specimen on appropriate media, assuring that these fastidious organisms will be identified even in a crowd of other commensals. Serologic tests are not available.

Diagnostic confusion can result from the presence in sputum of *Neisseria* spp. and other potential pathogens, such as *S. pneumoniae* and *H. influenzae*; such mixed infections make it impossible to ascribe pathogenicity to a specific organism. Coccobacillary microorganisms or gram-negative bacilli that demonstrate bipolar staining (e.g., *Pasteurella, Brucella*) can be mistaken for *M. catarrhalis.*

Treatment

Once the pathogenicity of *M. catarrhalis* was recognized, it became apparent that many isolates produced β-lactamase and were resistant to penicillin and ampicillin. Therapy should be initiated with either a second- or third-generation cephalosporin such as cefuroxime, or trimethoprim/sulfamethoxazole. Alternatives include the expanded-spectrum macrolides clarithromycin or azithromycin, amoxicillin–clavulanic acid (Augmentin), or a fluoroquinolone. In vitro testing may deceptively demonstrate susceptibility to penicillin, amoxicillin–clavulanic acid, or first-generation cephalosporins if β-lactamase production is at a low level; clinical failures may occur if these drugs are used. Supportive therapy with adequate hydration, bronchodilators, and other measures directed at treating the underlying respiratory disease is essential for a favorable outcome.

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CHAPTER 139

Respiratory Failure: An Overview

Michael A. Grippi

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas-exchanging functions; that is, oxygenation of, and carbon dioxide elimination from, mixed venous (pulmonary arterial) blood. Hence, respiratory failure is a syndrome rather than a disease. Many diseases result in respiratory failure, as discussed elsewhere in this volume.

Respiratory failure may be acute or chronic. The clinical presentations of patients with acute and chronic respiratory failure usually are quite different. While acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid–base status, the manifestations of chronic respiratory failure are more indolent and may be clinically inapparent.

Although the causes of respiratory failure are diverse, common underlying pathophysiological mechanisms and management strategies merit a general discussion. This chapter begins with a focus on the definition of respiratory failure and underscores distinctions between acute and chronic varieties. Hypoxemic and hypercapnic respiratory failure are described, and the pathophysiological underpinnings of each type are reviewed. The concepts of ventilatory supply and demand are considered before an overview of the many categories of disease that result in respiratory failure. Finally, an approach to clinical evaluation and management is outlined, followed by a summary of complications, comments on prognosis, and consideration of sites of care for survivors of respiratory failure who remain "chronically critically ill."

CLASSIFICATION OF RESPIRATORY FAILURE

As noted previously, respiratory failure is characterized by inadequate blood oxygenation or carbon dioxide removal. "Adequacy" is defined by tissue requirements for oxygen uptake and carbon dioxide elimination. In the absence of bedside techniques for direct measurement of these metabolic parameters, clinicians must rely on arterial blood gas values.

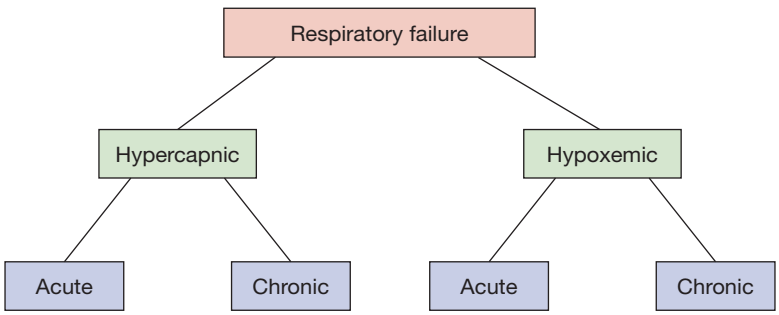

Figure 139-1 Classification of respiratory failure. Although depicted as distinct entities, hypercapnic and hypoxemic respiratory failure frequently coexist. Either may be acute or chronic.

Respiratory failure may be classified as *hypercapnic* or *hypoxemic* (Fig. 139-1). *Hypercapnic respiratory failure* is defined as an arterial P_{CO_2} (Pa_{CO_2}) greater than 45 mm Hg. *Hypoxemic respiratory failure* is defined as an arterial P_{O_2} (Pa_{O_2}) less than 55 mm Hg when the fraction of oxygen in inspired air (FI_{O_2}) is 0.60 or greater. In many cases, hypercapnic and hypoxemic respiratory failure coexist. Disorders that initially cause hypoxemia may be complicated by respiratory pump failure (see below) and hypercapnia. Conversely, diseases that produce respiratory pump failure are frequently complicated by hypoxemia due to secondary pulmonary parenchymal processes (e.g., pneumonia or atelectasis) or vascular disorders (e.g., pulmonary embolism).

Distinctions between *acute* and *chronic* respiratory failure are summarized in Table 139-1. In general, acute hypercapnic respiratory failure is defined as a Pa_{CO_2} greater than 45 mm Hg with accompanying acidemia (pH less than 7.30).[1] The physiological effect of a sudden increment in Pa_{CO_2} depends on the prevailing level of serum bicarbonate anion. In patients with chronic hypercapnic respiratory failure – for example, due to chronic obstructive pulmonary disease (COPD) – a long-standing increase in Pa_{CO_2} results in renal "compensation" and an increased serum bicarbonate concentration. A superimposed acute increase in Pa_{CO_2} has a less dramatic effect than does a comparable increase in a patient with a normal bicarbonate level.

Distinction between acute and chronic hypoxemic respiratory failure may not be readily made on the basis of arterial blood gas values.[1] The presence of markers of chronic hypoxemia (e.g., polycythemia or cor pulmonale) provides clues to a long-standing disorder, whereas abrupt changes in mental status suggest an acute event.

An important fact to bear in mind is that even though the definition of hypoxemic respiratory failure rests on measurement of Pa_{O_2}, the major threat of arterial hypoxemia is inadequate tissue oxygenation, reflected in tissue *oxygen delivery*. Tissue oxygen delivery is determined by the product of cardiac output and blood *oxygen content* (see Chapter 15, Blood-Gas Transport); the latter, in turn, depends on hemoglobin concentration and oxygen saturation. Therefore, factors that lower cardiac output or hemoglobin concentration, or inhibit dissociation of oxygen from hemoglobin at the tissue level, may promote tissue hypoxia without technically producing respiratory failure.

PATHOPHYSIOLOGY

Respiratory failure can arise from an abnormality in any of the "effector" components of the respiratory system—central nervous system, peripheral nervous system, respiratory muscles and chest wall, airways, or alveoli (Fig. 139-2). A defect in any of the first four components, which constitute the "respiratory pump," may cause coexistent hypercapnia and hypoxemia; at least initially, disorders of the alveoli are more apt to result in hypoxemia.[2,3]

HYPOXEMIC RESPIRATORY FAILURE

As described in Chapters 14–16, four pathophysiological mechanisms account for the hypoxemia seen in a wide variety of diseases: alveolar hypoventilation, ventilation–perfusion mismatch, shunt, and diffusion limitation.[2] Alveolar hypoventilation occurs in neuromuscular disorders that affect the respiratory system. In the absence of underlying pulmonary disease, the hypoxemia accompanying alveolar

TABLE 139-1 Distinctions Between Acute and Chronic Respiratory Failure

Category	Characteristic
Hypercapnic respiratory failure	Pa_{CO_2} >45 mm Hg
Acute	Develops in minutes to hours
Chronic	Develops over several days or longer
Hypoxemic respiratory failure	Pa_{O_2} <55 mm Hg when $F_{I_{O_2}} \geq 0.60$
Acute	Develops in minutes to hours
Chronic	Develops over several days or longer

hypoventilation is characterized by a normal alveolar–arterial oxygen gradient,[4] as defined by Equation 1:

$$PA_{O_2} - Pa_{O_2} = [PI_{O_2} - Pa_{CO_2}/R] - Pa_{O_2} \quad (1)$$

where

PA_{O_2} = alveolar P_{O_2}
Pa_{O_2} = arterial P_{O_2}
PI_{O_2} = inspired P_{O_2}
Pa_{CO_2} = arterial P_{CO_2}
R = respiratory exchange ratio

In contradistinction, disorders in which any of the other three mechanisms are operative are characterized by widening of the alveolar–arterial oxygen gradient, which is normally less than 20 mm Hg. With ventilation–perfusion mismatching, areas of low ventilation relative to perfusion contribute to the hypoxemia. Similarly, with shunt, either intrapulmonary or intracardiac, deoxygenated mixed venous blood bypasses ventilated alveoli, resulting in "venous admixture." Finally, diseases that increase the diffusion pathway for oxygen from the alveolar space to pulmonary capillary impair oxygen transport across the alveolar-capillary membrane.

Although changes in minute and alveolar ventilation can change Pa_{CO_2} considerably, this is not so for Pa_{O_2}. Increases in minute ventilation and, secondarily, in alveolar ventilation modestly increase Pa_{O_2}. Indeed, at a Pa_{O_2} above 55 to 60 mm Hg, the effect of increasing ventilation on oxygen content is minimal, since the oxyhemoglobin dissociation curve is flat in this range.

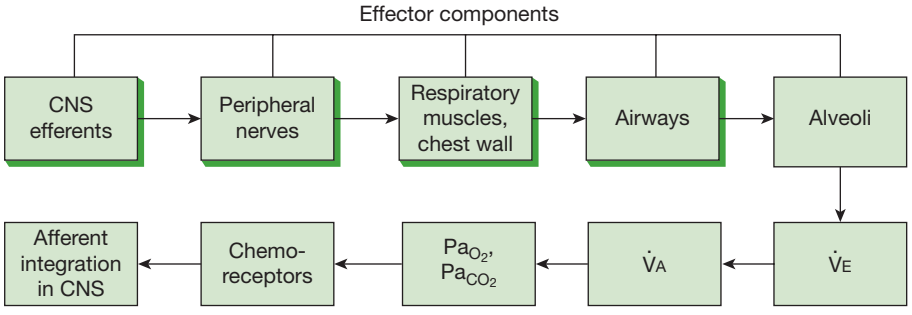

Figure 139-2 Functional components of the respiratory system and its controller. Abnormalities in any of the effector components can result in respiratory failure. The central and peripheral nervous systems, respiratory muscles and chest wall, and airways constitute the "respiratory pump" (*shaded boxes*). Hypercapnia is the hallmark of respiratory pump failure, while hypoxemia constitutes the primary disturbance in alveolar disorders producing respiratory failure. *(Reproduced with permission from Lanken PN. Pathophysiology of respiratory failure. In: Grippi MA, ed. Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.)*

HYPERCAPNIC RESPIRATORY FAILURE

At a constant rate of CO_2 production ($\dot{V}_{CO_2}$), Pa_{CO_2} is determined by the level of alveolar ventilation.[5] The relationship between alveolar ventilation, rate of CO_2 production, and Pa_{CO_2} is described by Equation 2:

$$\dot{V}_A = K \cdot \dot{V}_{CO_2}/Pa_{CO_2} \quad (2)$$

where

$\dot{V}_A$ = minute alveolar ventilation
K = a constant
$\dot{V}_{CO_2}$ = rate of CO_2 production.

When $\dot{V}_{CO_2}$ is constant, Pa_{CO_2} is determined by $\dot{V}_A$, which, in turn, is dictated by two factors: minute ventilation ($\dot{V}_E$) and the relationship between $\dot{V}_E$ and $\dot{V}_A$. The latter is determined by the proportion of $\dot{V}_E$ that constitutes dead space ventilation—that is, the dead space to tidal volume ratio (V_D/V_T):

$$\dot{V}_E = K\,(\dot{V}_{O_2} \cdot RQ)/(Pa_{CO_2}/[1 - V_D/V_T]) \quad (3)$$

where

$\dot{V}_{O_2}$ = rate of O_2 consumption
RQ = respiratory quotient (the respiratory exchange ratio in the steady state)
V_D = dead space volume
V_T = tidal volume.

Inspection of Equation 3 indicates that disorders reducing $\dot{V}_E$ or increasing the proportion of dead space ventilation may result in hypercapnia.

VENTILATORY SUPPLY VERSUS DEMAND

A useful theoretical construct for understanding the pathophysiological basis for hypercapnic respiratory failure is the relationship between ventilatory supply and ventilatory demand (Fig. 139-3).[1]

Ventilatory supply is the maximal spontaneous ventilation that can be maintained without development of respiratory muscle fatigue; ventilatory supply is also known as *maximal sustainable ventilation* (MSV).

Ventilatory demand is the spontaneous minute ventilation, which, when maintained constant, results in a stable Pa_{CO_2} (assuming a fixed rate of CO_2 production).

Normally, ventilatory supply greatly exceeds ventilatory demand. Hence, major changes in minute ventilatory requirements (e.g., during exercise) may occur without hypercapnia. In lung disease, significant abnormalities may be present before ventilatory demand encroaches on MSV. Consequently, hypercapnia is a late finding. When ventilatory demand exceeds MSV, Pa_{CO_2} increases.

As a general rule, MSV is approximated as one-half the *maximal voluntary ventilation,* or MVV (see Chapter 33, Pulmonary Function Testing). A 70-kg adult has an MVV of about 160 L/min, an MSV of 80 L/min, and, under basal conditions, a $\dot{V}_E$ of approximately 6 to 7 liters per minute (90 mL/kg/min). Normally, therefore, there is a 10- to 15-fold difference between resting $\dot{V}_E$ and MSV. In disease states, the $\dot{V}_E$ requirement may approach a markedly reduced MSV. Further reductions in MSV result in ventilatory demand exceeding supply, and hypercapnia occurs.

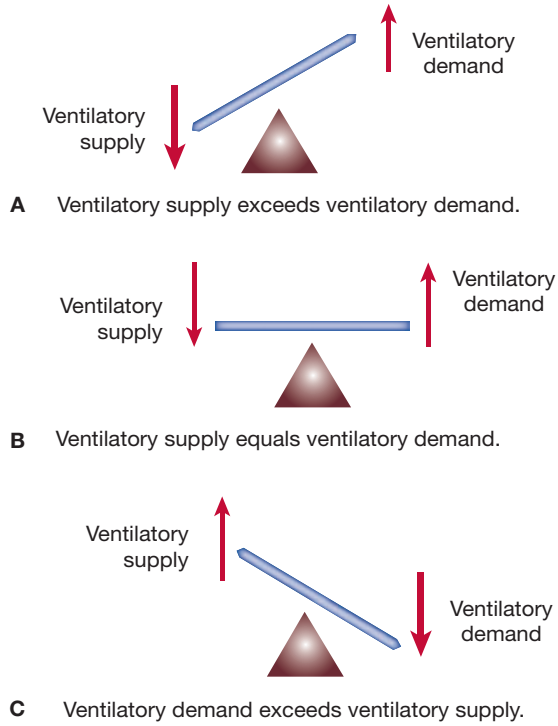

Figure 139-3 Relationship between ventilatory supply (maximal sustainable ventilation) and ventilatory demand (overall level of ventilation specified by the CNS controller). Relative size of the arrows indicates levels of supply and demand in each of the three circumstances illustrated. **A.** Normal. Ventilatory supply greatly exceeds ventilatory demand. Physiological "reserve" is maintained. **B.** Ventilatory supply is decreased and ventilatory demand increased (e.g., acute asthma attack). "Borderline" respiratory failure exists. **C.** Ventilatory demand exceeds ventilatory supply (e.g., sepsis in a patient with COPD). Respiratory muscle fatigue develops, and hypercapnic respiratory failure ensues. See text for details. *(Reproduced with permission from Lanken PN. Pathophysiology of respiratory failure. In: Grippi MA, ed. Pulmonary Pathophysiology. Philadelphia, PA: JB Lippincott; 1995.)*

FACTORS THAT REDUCE VENTILATORY SUPPLY OR INCREASE VENTILATORY DEMAND

Disruption of any component of the efferent arm of the respiratory control system may diminish ventilatory supply (Table 139-2). While a variety of diseases produce specific abnormalities along the efferent pathway (e.g., phrenic nerve and respiratory muscle disorders), some result in respiratory muscle fatigue—the biochemical, cellular, and molecular mechanisms of which remain poorly understood.

As described previously, ventilatory demand can be assessed according to Equation 3:

$$\dot{V}_E = K \cdot (\dot{V}_{O_2} \cdot RQ)/(Pa_{CO_2}/[1 - V_D/V_T])$$

Any factor that affects terms on the right-hand side of the equation may result in ventilatory demand exceeding supply. Selected clinical examples are given in Table 139-3.

CATEGORIES OF RESPIRATORY FAILURE

Although many different diseases cause respiratory failure, they may be grouped conveniently according to primary abnormalities in the individual effector components of the respiratory system.[1,2]

■ ABNORMALITIES OF THE CENTRAL NERVOUS SYSTEM

A variety of pharmacologic, structural, and metabolic disorders of the CNS are characterized by suppression of the neural drive to breathe.[3] The resultant hypoventilation and hypercapnia may be acute or chronic.

An overdose of a narcotic or other drug with sedative properties is a common cause of respiratory failure. While the most striking clinical picture occurs with an acute overdose, long-standing use of some agents (e.g., methadone) may result in chronic hypercapnia.

"Structural" CNS abnormalities producing hypercapnic respiratory failure include meningoencephalitis, localized tumors or vascular abnormalities of the medulla, and strokes affecting medullary control centers. Usually, respiratory failure is observed in the context of other neurologic findings.

A variety of metabolic derangements may produce hypercapnia through depression of respiratory control centers. Examples include severe myxedema, hepatic failure, and advanced uremia. In addition, elevation of P_{CO_2} in the CNS results in neural depression, further enhancing CO_2 retention. A common clinical setting in which

TABLE 139-2 Factors That Diminish Ventilatory Supply

Factor	Clinical Examples
Decreased respiratory muscle strength	
Muscle fatigue	Recovery from acute respiratory failure, high respiratory rates, increased inspiratory time
Disuse atrophy	Prolonged mechanical ventilation, following phrenic nerve injury
Malnutrition	Protein–calorie starvation
Electrolyte abnormalities	Low serum phosphate or potassium concentrations
Arterial blood gas abnormalities	Low pH, low Pa_{O_2}, high Pa_{CO_2}
Fatty infiltration of diaphragm	Obesity
Unfavorable alteration in diaphragm length–tension relationship	Flattened domes of diaphragm caused by hyperinflation
Increased muscle energy requirement or decreased substrate supply	
High elastic work of breathing	Low lung or chest wall compliance, high respiratory rate
High resistive work of breathing	Airway obstruction
Reduced diaphragm perfusion	Shock, anemia
Decreased motor neuron function	
Decreased phrenic nerve output	Polyneuropathy, Guillain–Barré syndrome, phrenic nerve transection or injury, poliomyelitis
Decreased neuromuscular transmission	Myasthenia gravis, use of paralyzing agents
Abnormal respiratory mechanics	
Airflow limitation	Bronchospasm, upper airway obstruction, excessive airway secretions
Loss of lung volume	After lung resection, large pleural effusion
Other restrictive defects	Pain-limited inspiration; tense abdominal distention due to ileus, peritoneal dialysis fluid, or ascites

TABLE 139-3 Factors That Increase Ventilatory Demand

Factor	Clinical Examples
Increased V_D/V_T	Acute asthma, emphysema, late phase of acute respiratory distress syndrome, pulmonary emboli
Increased $\dot{V}_{O_2}$	Fever, sepsis, trauma, shivering, increased work of breathing, massive obesity
Increased RQ	Excessive carbohydrate feeding
Decreased Pa_{CO_2}	Hypoxemia, metabolic acidosis, anxiety, sepsis, renal failure, hepatic failure

Source: Data from Lanken PN. Pathophysiology of respiratory failure. In: Grippi MA, ed. Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.

elevation of Pa_{CO_2} is observed is chronic metabolic alkalosis (e.g., due to diuretic use), as detailed in Chapter 17 (Acid–Base Balance).

Finally, obesity hypoventilation syndrome is characterized by hypercapnia due to hypoventilation on a central basis.[6]

■ ABNORMALITIES OF THE PERIPHERAL NERVOUS SYSTEM OR CHEST WALL

A wide variety of disorders of the peripheral nerves, neuromuscular junction, and chest wall may be associated with hypercapnic and hypoxemic respiratory failure.[3,7–16] While the hallmark is an inability to maintain a level of $\dot{V}_E$ appropriate for the rate of CO_2 production, many of these disorders are complicated by impaired expiratory muscle strength, atelectasis, and aspiration. Through mechanisms outlined previously, hypoxemia develops in conjunction with the hypercapnia.

Among the most common neuromuscular causes of hypercapnic respiratory failure are Guillain–Barré syndrome,[17] myasthenia gravis,[18] polymyositis,[19] the muscular dystrophies, amyotrophic lateral sclerosis (ALS),[20] and a large number of metabolic muscle disorders. In addition, acute poliomyelitis and traumatic spinal cord injury are associated with hypercapnia. Development of respiratory muscle fatigue and atrophy[10,21–23] during prolonged weaning from mechanical ventilation may cause recurrent hypercapnia in the critical care setting.

Pharmacologic causes of hypercapnia in the intensive care unit are frequently encountered. Early reports on use of depolarizing and nondepolarizing paralyzing agents,[24] particularly in conjunction with systemic corticosteroids (e.g., in management of status asthmaticus) have been well documented; cholinergic crisis during therapy of myasthenia gravis, and administration of aminoglycosides to patients with myasthenia gravis are additional examples.

Primary disorders of the chest wall constitute another important category of neuromuscular respiratory failure. The prototype is severe kyphoscoliosis. Additional examples include flail chest (Chapter 106, Thoracic Trauma), extensive thoracoplasty, morbid obesity, and massive abdominal distention due to ascites[25] or distended loops of bowel.

In each of these disorders, a common pathophysiological sequence develops. Because of inadequate activation of inspiratory muscles or limited thoracic excursion, tidal volume falls. While an increase in respiratory rate compensates initially for the fall in $\dot{V}_E$ (and in $\dot{V}_A$), $\dot{V}_E$ eventually declines. In addition, the sigh mechanism is impaired, which, in conjunction with the low tidal volume, results in atelectasis and reduced lung compliance. Reduced lung compliance produces a further fall in tidal volume and an increase in the elastic work of breathing (Chapter 10, Pulmonary Mechanics). Hence, ventilatory supply becomes limited, while ventilatory demand increases due to a rise in V_D/V_T (as a result of atelectasis and other factors noted below). An imbalance between ventilatory supply and demand arises, and hypercapnia ensues. Furthermore, an impaired gag reflex in the setting of bulbar weakness, coupled with impaired cough due to respiratory muscle involvement, may result in aspiration pneumonia and secondary hypoxemia.

In addition to the pathophysiology described, structural abnormalities of the thoracic cage (e.g., severe kyphoscoliosis, ankylosing spondylitis, thoracoplasty, and fibrothorax)[7,26,27] are characterized by an increase in the elastic component of the work of breathing. This results in a higher $\dot{V}_{O_2}$ and a higher proportion of total O_2 consumption by the respiratory muscles (normally, less than 5% of $\dot{V}_{O_2}$).

■ ABNORMALITIES OF THE AIRWAYS

Obstructive diseases of the airways – either upper or lower – are common causes of acute and chronic hypercapnia. Examples in the upper airways include acute epiglottitis, aspirated foreign body, tracheal tumor, and narrowing of the trachea or glottis by fibrotic tissue. Disorders of the lower airways include COPD,[28] asthma, and advanced cystic fibrosis. Increasingly, the development of bronchiolitis obliterans, a manifestation of allograft rejection in patients who have undergone lung transplantation, has been recognized as an important cause of respiratory failure.[29]

The underlying mechanisms in airway abnormalities as causes of respiratory failure are multifaceted and variable. However, several common pathophysiological pathways are operative.

Airway narrowing results in a greater transthoracic pressure gradient requirement for inspiratory airflow. The resistive component of the work of breathing is increased, and the increase is associated with an elevation in $\dot{V}_{O_2}$. In addition, tidal volume falls and dead space ventilation increases. Respiratory muscle fatigue may develop; the consequences of a shallow breathing pattern ensue.

Finally, in some disorders (e.g., acute asthma or an acute exacerbation of COPD), air trapping and lung hyperinflation occur, resulting in diaphragm flattening and worsening diaphragm mechanics (see Chapter 10, Pulmonary Mechanics). The overall effect is a growing imbalance between ventilatory supply and demand.[1]

■ ABNORMALITIES OF THE ALVEOLI

Although diseases characterized by diffuse alveolar filling frequently result in hypoxemic respiratory failure, hypercapnia may complicate the picture. Common clinical examples in this category include cardiogenic and noncardiogenic pulmonary edema,[30] diffuse pneumonia, extensive pulmonary hemorrhage, aspiration of stomach contents, and near drowning.

Diffuse alveolar filling creates a large right-to-left shunt as pulmonary blood flows through nonventilated or poorly ventilated regions of the lung. In addition, coexisting interstitial edema may impair diffusion across the alveolar-capillary membrane, further impairing oxygenation of mixed venous blood.

In extensive, acute pulmonary disease characterized by alveolar filling, ventilatory demand is high because of hypoxemia and increases in V_D/V_T, the elastic work of breathing (due to reduced lung compliance), the resistive work of breathing (due to airway narrowing and increased airway reactivity), and the neural drive to breathe (mediated by pulmonary parenchymal vagal fibers). In conjunction with heightened ventilatory demand, ventilatory supply is reduced because of alveolar flooding, reduced lung elasticity, respiratory muscle fatigue, and, possibly, reduced blood supply to the diaphragm secondary to shock. Once again, the imbalance between ventilatory supply and demand results in hypercapnia.

APPROACH TO THE PATIENT

The diagnosis of acute or chronic respiratory failure begins with clinical suspicion of its presence. Confirmation of the diagnosis is based on arterial blood gas analysis. Evaluation for an underlying cause must be initiated early, frequently in the presence of concurrent treatment for acute respiratory failure. While the diagnosis of chronic respiratory failure is usually easily established with clinical findings of chronic hypoxemia (with or without findings of hypercapnia), the diagnosis of acute respiratory failure requires more careful analysis.

TABLE 139-4 Changes in Arterial Blood Gases, $P_{A_{O_2}}$–Pa_{O_2}, and Ventilation in Acute Respiratory Failure

Failed Respiratory System Component	pH	Pa_{CO_2}	Pa_{O_2}	$P_{A_{O_2}}$–Pa_{O_2}	$\dot{V}_E$	$\dot{V}_A$
Central nervous system	↓	↑	↓[a]	NL or ↑[b]	↓	↓
Peripheral nervous system or chest bellows	↓	↑	↓[a]	NL or ↑[b]	↓	↓
Airways						
In acute asthma						
Early phase (before respiratory failure)	↑	↓	NL	↑	↑	↑
"Crossover point"	NL	NL	NL or ↓	↑	↑	NL
With development of respiratory muscle fatigue	↓	↑	↓	↑	↓[c]	↓
In COPD						
Non–CO_2 retainer	↓	NL or ↑[d]	↓	↑	↑	↓
CO_2 retainer						
Baseline	NL to ↓	↑	↓	↑	NL or ↑	↓
Flare	↓	↑↑	↓↓	↑	NL, ↑or ↓[c]	↓
Alveoli						
Before respiratory muscle fatigue develops	↑	↓	↓↓	↑↑	↑	↑
After respiratory muscle fatigue develops	↓	↑	↓↓	↑↑	↓	↓

↑, increased; ↑↑, very increased; ↓, decreased; ↓↓, very decreased; NL, in normal range.
[a] Pa_{O_2} may decrease when pneumonia or atelectasis occurs as a complication.
[b] ($P_{A_{O_2}}$–Pa_{O_2}) widens when pneumonia or atelectasis occurs as a complication.
[c] $\dot{V}_E$ declines when frank respiratory muscle failure occurs.
[d] Pa_{CO_2} may increase during an exacerbation.
Source: Data from Lanken PN. Pathophysiology of respiratory failure. In: Grippi MA, ed. Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.

Signs and symptoms in acute respiratory failure reflect the underlying disease process and associated hypoxemia or acidemia due to hypercapnia. Localized pulmonary findings reflecting the acute causes of hypoxemia (e.g., pneumonia, pulmonary edema, asthma, or COPD) may be readily apparent. Alternatively, the predominant findings may be systemic (e.g., hypotension due to sepsis). The principal manifestations may even be remote from the thorax – for example, abdominal pain in acute pancreatitis or leg pain due to a long-bone fracture – each associated with acute respiratory distress syndrome (Chapter 140, Acute Respiratory Distress Syndrome: Pathogenesis and Chapter 141, Acute Respiratory Distress Syndrome: Clinical Features, Management, and Outcomes). Frequently, neurologic or cardiovascular symptoms and signs predominate. Neurologic manifestations include restlessness, anxiety, confusion, seizures, or coma. Asterixis may be seen with severe hypercapnia. Common cardiovascular findings include tachycardia and a variety of arrhythmias. Finally, there may be few or no findings other than a complaint of dyspnea, as in some patients with hypoxemia due to pulmonary embolism.

Once respiratory failure is suspected on clinical grounds, arterial blood gas analysis is performed to confirm the diagnosis, to assist in the distinction between acute and chronic forms, to assess the magnitude and metabolic impact, and to help guide management (Table 139-4).

PRINCIPLES OF MANAGEMENT

The principles of management of patients in acute respiratory failure include those that are general[2,3,6–8,20,31–36] and those that are more cause-specific.[28] Triage of the patient to the proper clinical setting, airway maintenance, correction of hypoxemia and hypercapnia, and management of the underlying cause are of paramount importance.

■ TRIAGE DECISIONS

The first step in management is to determine the appropriate setting for care—admission to a standard inpatient medical floor or to an intensive or "intermediate care" unit. Factors that constitute the basis for this decision include the acuity of the respiratory failure; the degree of hypoxemia, hypercapnia, and acidemia; the presence of comorbid conditions (e.g., cardiac disease or renal insufficiency); and the clinical direction that the patient takes over the first few minutes or hours of observation. At one end of the spectrum is the patient with fulminant hypoxemic respiratory failure, metabolic acidosis, and imminent cardiovascular collapse, who needs emergent intubation, mechanical ventilation, and admission to a critical care unit. At the other end of the spectrum is the patient with COPD and chronic, compensated hypercapnic respiratory failure, who requires observation in an intermediate care unit.

■ AIRWAY MANAGEMENT

Assurance of an adequate airway is key in the patient with acute respiratory distress. Whether emergency intubation is required depends on the clinical circumstances described previously. For patients with chronic respiratory insufficiency, the need for intubation also depends on critical arterial blood gas values and the patient's early acute course. When progressive hypoxemia or hypercapnia is observed over the first few minutes or hours of care, intubation and mechanical ventilation are warranted.

In recent years, a number of studies have indicated that, in selected patients, use of noninvasive mechanical ventilation may obviate the need for intubation.[34–39] Such patients include some with hypercapnic, as well as some with acute, hypoxemic respiratory failure (other than ARDS-related). The use of noninvasive mechanical ventilation to facilitate weaning and early extubation[40,41] is controversial. Although studies also point to the use of noninvasive mechanical ventilation for management of recurrent respiratory failure following extubation, a multicenter, randomized trial found no reduction in the need for reintubation or mortality.[42]

Contraindications to a trial of noninvasive ventilation include respiratory arrest, ill-fitting face mask, hemodynamic or cardiac instability, patient agitation, swallowing difficulty, excessive respiratory secretions, inability to protect the airway, and recent upper airway or upper gastrointestinal surgery.[34]

■ CORRECTION OF HYPOXEMIA AND HYPERCAPNIA

Once the airway is secured, the clinician must turn attention to the treatment of hypoxemia—the most life-threatening aspect of acute respiratory insufficiency. The goal is to assure adequate oxygen delivery to tissues, generally achieved with a Pa_{O_2} of about 60 mm Hg (assuming an adequate hematocrit and cardiac output). In patients who have coronary or cerebrovascular disease, a slightly higher level of arterial oxygenation may be desirable in order to provide a "buffer" for any sudden, unpredictable changes in gas exchange.

The means by which supplemental oxygen is administered is determined by the clinical circumstances. While some patients may simply require nasal prongs or a face mask to achieve an adequate Pa_{O_2}, others are best treated with controlled-flow oxygen delivered via a Venturi mask—for example, the patient with COPD and chronic hypercapnia (see Chapter 42, Course and Treatment of Chronic Obstructive Pulmonary Disease). Generally, if an acceptable level of oxygenation, as judged by arterial blood gases, cannot be attained using a face mask, or if administration of supplemental O_2 causes hypercapnia to worsen significantly (e.g., in some patients with COPD), mechanical ventilation (invasive or noninvasive) is required.

While correcting hypoxemia, the clinician must also address any coexisting hypercapnia and respiratory acidosis. Once again, the immediacy of correction depends on the magnitude of the acidosis and its attendant effects (e.g., elevation of serum potassium). A partly compensated respiratory acidosis in a patient with COPD usually constitutes a less urgent clinical circumstance than does profound respiratory acidosis in a patient with a drug overdose.

■ SEARCH FOR AN UNDERLYING CAUSE

Finally, as therapy is initiated to correct the hypoxemia, hypercapnia, and acidosis of respiratory failure, a search for the cause of the problem and its management must be undertaken. In some cases, the cause and management are straightforward (e.g., administration of a narcotic antagonist to the patient with a narcotic overdose). In others, a more protracted course may be in store (e.g., long-term ventilator management of fulminant acute respiratory distress syndrome due to sepsis).

In both brief and prolonged cases of respiratory failure, attention to details of management is important in order to minimize the risks of complications of therapy, as discussed in the following section.

MONITORING PATIENTS WITH ACUTE RESPIRATORY FAILURE

Repeated assessment of the patient with incipient or resolving respiratory failure, as well as the patient with frank hypoxemic or hypercapnic failure, is critical in formulating decisions about therapy. Monitoring methods range from routine bedside observations to use of invasive techniques (see Chapter 147, Hemodynamic and Respiratory Monitoring in Respiratory Failure).

For many patients with acute respiratory failure, simple observation of respiratory rate, tidal volume, use of accessory muscles, and presence of paradoxical breathing movements provides evidence of worsening respiratory failure and the need for intubation and mechanical ventilation. The patient with asthma or an acute exacerbation of COPD will frequently manifest rapid, shallow breathing and paradoxical thoracoabdominal breathing movements as respiratory mechanics deteriorate.[15]

Once placed on mechanical ventilation, the patient must be carefully monitored for ventilator-associated complications (see below). In addition, placement of indwelling arterial and venous catheters, patient immobilization, and use of a broad range of pharmacologic agents present additional potential threats to the acutely ill patient.

While many monitoring techniques are routine and may be universally applicable to patients in a critical care setting (e.g., pulse oximetry), others may be of particular importance in selected clinical circumstances. For example, routine assessment of static respiratory system compliance in a mechanically ventilated patient with acute respiratory distress syndrome or pulmonary fibrosis may provide an early warning of changes in lung edema, atelectasis, or barotrauma.[43] In the patient with status asthmaticus requiring mechanical ventilation, development of hypotension due to intrinsic positive end-expiratory pressure (intrinsic PEEP or "auto-PEEP"),[44] as discussed in Chapter 148, may signal the need to alter ventilator settings or implement sedation or pharmacologic paralysis.

COMPLICATIONS OF ACUTE RESPIRATORY FAILURE

The respiratory patient in a critical care unit must navigate not only the obstacles presented by the underlying pulmonary process, but also the hazards associated with use of mechanical devices and pharmacologic agents. Complications of acute respiratory failure may be broadly categorized as pulmonary, cardiovascular, gastrointestinal, renal, infectious, nutritional, and other (Table 139-5). For details in each of these areas, the reader is referred to chapters elsewhere in this volume.

■ PULMONARY

Common pulmonary complications of acute respiratory failure include ventilator-associated pneumonia ("VAP"),[45–48] ventilator-induced diaphragmatic dysfunction,[49,50,23] critical illness polyneuropathy and myopathy,[51] pulmonary emboli, pulmonary barotrauma, pulmonary fibrosis, and complications directly related to use of mechanical devices.[52]

Pulmonary emboli have been reported in up to one-fourth of patients with respiratory failure in intensive care units. The diagnosis is difficult in this setting, since patients typically have diffuse underlying lung disease, abnormal gas exchange, and many coexisting potential causes for the clinical, radiographic, and physiological consequences of pulmonary emboli.

Pulmonary barotrauma, identified as the presence of extra-alveolar air in structures that do not normally contain air, may occur in patients receiving mechanical ventilation for a variety of indications, including the acute respiratory distress syndrome.[31,53] Manifestations of barotrauma include pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, tension lung cysts, and subpleural air cysts.[54] Pulmonary fibrosis may follow acute lung injury associated with acute respiratory distress syndrome. In addition, use of high inspired concentrations of oxygen may enhance development of fibrosis in the presence of acute lung injury.

A strategy of low-stretch ventilation is currently the standard for managing patients with acute lung injury or ARDS and is aimed at minimizing the risks of ventilator-induced injury.[2,30–32,55–61] Use of such a strategy is outlined in the chapters on ARDS (Chapter 141, Acute Lung Injury and the Acute Respiratory Distress Syndrome: Clinical Features, Management, and Outcomes) and mechanical ventilation (Chapter 148, Principles of Mechanical Ventilation). More limited experience has been described using extracorporeal membrane oxygenation[62,63] and high-frequency oscillation[64] in this setting.

Common device-related complications include those due to pulmonary artery flotation catheters (see Chapter 147, Hemodynamic and Respiratory Monitoring in Respiratory Failure), endotracheal intubation, and tracheostomy (see Chapter 146, Intubation and Upper Airway Management).

New approaches to the use of intravenous sedation, namely, daily interruption of sedative infusions, has been shown to reduce duration of mechanical ventilation and length of stay in the ICU.[65–68]

■ CARDIOVASCULAR

Common cardiovascular complications in patients with acute respiratory failure include hypotension, reduced cardiac output, arrhythmias, pericarditis, and acute myocardial infarction. These complications may be related to the underlying disease process, mechanical ventilation, or use of pulmonary artery flotation catheters.

TABLE 139-5 Complications of Acute Respiratory Failure

Pulmonary
Pulmonary emboli
Pulmonary barotrauma (interstitial emphysema, pneumothorax, subcutaneous emphysema, pneumoperitoneum, tension lung cyst, subpleural air cyst)
Pulmonary fibrosis
Related to Use of Mechanical Devices
Complications of mechanical ventilation (infection, arterial desaturation, hypotension, barotrauma, others)
Complications of insertion and maintenance of pulmonary artery catheter (pneumothorax, air embolism, arrhythmias, infection, thrombosis, pulmonary artery rupture)
Complications of tracheal intubation
Related to prolonged intubation attempt (hypoxemic brain injury, cardiac arrest, seizures, others)
Related to right main bronchus intubation (hypoventilation, pneumothorax, atelectasis)
Self- or inadvertent extubation
Endotracheal tube dislodgment
Endotracheal tube cuff leak
Injury to pharynx, larynx, trachea
Complications of tracheotomy (pneumothorax, bleeding, tube dislodgment, tracheoinnominate fistula, tracheoesophageal fistula, tracheal stenosis)
Gastrointestinal
Hemorrhage (including "stress" ulceration)
Ileus
Diarrhea
Cardiovascular
Hypotension
Arrhythmias
Decreased cardiac output
Myocardial infarction
Pulmonary hypertension
Renal
Acute renal failure
Fluid retention
Infectious
Nosocomial pneumonia
Bacteremia
Sepsis
Paranasal sinusitis
Nutritional
Complications of underlying malnutrition (decreased respiratory muscle strength, immune suppression, others)
Complications of enteral feeding (pneumothorax, pleural effusion, sinusitis, aspiration, diarrhea)
Complications of parenteral feeding (pneumothorax, sepsis, hyperglycemia, hyperosmolar coma, hypophosphatemia, liver function test abnormalities)
Complications of refeeding (hypercapnia)
Other
Psychiatric (anxiety, depression, confusion, sleep dysfunction, psychosis)
Hematologic (anemia, thrombocytopenia)

GASTROINTESTINAL

A variety of gastrointestinal complications of acute respiratory failure, particularly during mechanical ventilation, have been well described.[69] The major ones include hemorrhage, gastric distention, ileus, diarrhea, and pneumoperitoneum. "Stress" ulceration is extremely common in patients with acute respiratory failure. Associated risk factors include trauma, shock due to a variety of causes, sepsis, renal failure, and liver disease.

INFECTIOUS

Nosocomial infections are a frequent complication of acute respiratory failure. Principal among these are pneumonia, sepsis, and urinary tract infections. Each typically occurs with the use of mechanical devices, including endotracheal and tracheotomy tubes, indwelling central venous and pulmonary artery catheters, and urinary bladder catheters.

The incidences of VAP and ventilator-associated tracheobronchitis (VAT)[46,70–73] in the critically ill are significant. The incidence of VAP is estimated to be as high as 5.8 cases per 1000 ventilator days and is particularly prevalent in those with ARDS. The need for prolonged mechanical ventilation is a harbinger for development of VAP. Not unexpectedly, VAP occurring in the medical intensive care unit is associated with a significantly increased length of stay and higher mortality. Guidelines have been developed for treatment of patients with VAP.[74,75]

RENAL

Acute kidney injury, previously referred to as acute renal failure, and abnormalities in electrolyte and water homeostasis are not uncommon in critically ill patients with acute respiratory failure; the former may be seen in up to 60% of patients in intensive care units. Development of acute kidney injury in a patient with acute respiratory failure carries a poor prognosis and a high mortality. The causes of acute kidney injury are numerous and include sepsis or septic shock, cardiogenic shock, hypovolemia, cardiac or extensive gastrointestinal surgery, administration of nephrotoxic drugs, hepatorenal syndrome, and urinary obstruction, among others.[76]

NUTRITIONAL

Nutritional complications of acute respiratory failure include the effects of malnutrition on respiratory performance and complications related to the administration of enteral or parenteral nutrition.[77–79] Complications of enteral nutritional support relate to initial insertion of the catheter (e.g., tracheal or pleural space penetration, pneumomediastinum, pneumothorax, and pleural effusion) and its maintenance (e.g., paranasal sinusitis and aspiration). In addition, vomiting, abdominal distention, and diarrhea are common. Complications of parenteral nutrition are mechanical (e.g., pneumothorax during catheter insertion), infectious (e.g., catheter-related sepsis), or metabolic (e.g., metabolic acidosis, hyperglycemia and hyperosmolar coma, and hypophosphatemia). Hypercapnia, induced by enteral as well as parenteral nutrition, can complicate management of patients who have limited ventilatory reserve.

PROGNOSIS

Interpretation of studies addressing the prognosis of patients with acute respiratory failure is subject to a number of constraints, including marked clinical variability in the patients studied, predominance of studies from intensive care units in large university teaching hospitals, and variability in treatment methods employed over the time span of studies performed. In addition, many studies report only hospital mortality, not long-term survival or quality of life. Finally, findings from large-population studies are difficult to extrapolate to prediction of outcome in a single patient. Nonetheless, several generalizations can be made regarding the prognosis of patients hospitalized with acute respiratory failure.

MORBIDITY AND MORTALITY IN ACUTE HYPOXEMIC RESPIRATORY FAILURE

As expected, mortality in hypoxemic respiratory failure depends on the underlying cause. A number of studies have addressed outcome in patients with ARDS.

Mortality in ARDS appears to have improved in recent years, but it remains high in the elderly; for those 85 years of age or older, mortality is 60%.[80] Patients who develop sepsis after trauma have a lower mortality than do patients with sepsis that complicates medical disorders. Notably, patients with pre-existing lung disease, higher $F_{I_{O_2}}$ or PEEP requirements, or a lower Pa_{O_2} may not necessarily have a poorer chance of survival.

Although earlier studies indicated that many patients who survived an episode of ARDS manifested some impairment of pulmonary function, including obstructive and restrictive defects and reduction in diffusing capacity, one or more years after recovery,[81] more recent data show good preservation of lung function 5 years following survival from ARDS. In fact lung function is usually normal or near normal, especially in young patients.[82]

Despite recovery of pulmonary function, many survivors of ARDS have persistent functional disabilities after discharge, largely related to muscle wasting and weakness.[82] Many survivors of ARDS have neurocognitive findings at hospital discharge, and in a significant number, the deficits persist long term.[82–86]

MORBIDITY AND MORTALITY IN ACUTE HYPERCAPNIC RESPIRATORY FAILURE

In general, several parameters presage a higher mortality in patients admitted with hypercapnic respiratory failure: (1) the patient's "physiological reserve," as determined by concurrent cardiopulmonary, renal, hepatic, or neurologic disease and the patient's age; (2) the underlying cause of the acute deterioration; (3) the severity of the respiratory failure, as defined by arterial pH and P_{CO_2}; and (4) development of complications after onset of acute respiratory failure—for example, sepsis, pneumonia, renal failure, or gastrointestinal bleeding.

For patients hospitalized with an acute exacerbation of COPD, overall mortality is 8% to 12%, but it may be as high as 28% for those with significant comorbidities;[87,88] mortality for this group at 1 year is 43%.[88] For patients with an acute exacerbation of COPD who require mechanical ventilation, in-hospital mortality is high; 1-year mortality approaches 25%, and 5-year mortality 70%.[28,82–86]

POST-ACUTE CARE OPTIONS FOR SURVIVORS WITH CHRONIC CRITICAL ILLNESS

With increasing numbers of patients surviving acute, catastrophic illness or complications of advanced surgical procedures, long-term ventilator dependency and "chronic critical illness" have become challenging clinical issues. This group of patients requires complex medical management and generates considerable debate over medical ethics and healthcare costs. One relatively recent development related to management of chronically critically ill patients is the growth of long-term acute care hospitals—LTACHs (see Chapter 152, Organization of Intensive Care Units and Long-term Acute Care Hospitals).

LTACHs are either free-standing facilities or are based on the concept of a "hospital within a hospital." They focus on management of a wide variety of medically complex patients and typically include a significant cohort of those who are ventilator-dependent. Medicare provides a DRG payment to the LTACH that is separate from that to the acute care facility from which the patient is transferred. Fairly precise rules constitute admission and discharge criteria and, thereby, determine the average length of stay at the LTACH (25 days or greater).[90]

Data on long-term survival and functional status for ventilator-dependent patients discharged from LTACHs are striking. For those who are admitted and subsequently discharged with ventilator dependency (i.e., patients who are not successfully liberated), mean survival post-discharge is 100 days.[91] Furthermore, overall 1-year survival is 56%, with only 9% of patients reporting independent functioning 1 year after discharge.[92]

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CHAPTER 140

Acute Respiratory Distress Syndrome: Pathogenesis

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This chapter focuses on the pathogenesis of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Chapter 141 discusses clinical features and management of these disorders.

A 1994 consensus conference defined the spectrum of ALI/ARDS as follows: (1) ALI, defined as arterial hypoxemia with a Pa_{O_2}/FI_{O_2} <300, and ARDS, defined as a Pa_{O_2}/FI_{O_2} <200, accompanied by (2) bilateral pulmonary infiltrates, and (3) absence of left atrial hypertension.[1] A more recent report, based on the so-called, "Berlin definition," recommends identification of three categories of ARDS, based upon the degree of hypoxemia alone: (1) mild ARDS (200 <Pa_{O_2}/FI_{O_2} ≤300 mm Hg); (2) moderate ARDS (100 <Pa_{O_2}/FI_{O_2} ≤200 mm Hg); or (3) severe ARDS (Pa_{O_2}/FI_{O_2} ≤100 mm Hg).[2] For the purposes of this chapter, both ALI and ARDS will be referred to as ARDS.

PATHOPHYSIOLOGY OF PULMONARY EDEMA IN ACUTE RESPIRATORY DISTRESS SYNDROME

Pulmonary edema occurs when fluid is filtered into the lungs faster than it can be removed. Accumulation of fluid may have major consequences on lung function because efficient gas exchange cannot occur in fluid-filled alveoli. Lung structure relevant to edema formation and the forces governing fluid and protein movement in the lungs have been the subject of classic and more recent reviews.[3]

VASCULAR FLUID AND PROTEIN EXCHANGE

The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier:

$$Jv = LpS[(Pc - Pi) - \sigma d(\pi c - \pi i)]$$

where

- Jv = the net fluid-filtration rate (volume flow) across the microvascular barrier
- Lp = the hydraulic conductivity (permeability) of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier)
- S = the surface area of the barrier
- Pc = the pulmonary capillary (microvascular) hydrostatic pressure
- Pi = the interstitial (perimicrovascular) hydrostatic pressure
- πc = the capillary (microvascular) plasma colloid osmotic (or oncotic) pressure
- πi = the interstitial (perimicrovascular) fluid osmotic pressure
- σd = the average osmotic reflection coefficient of the barrier (a measure of the effectiveness of the barrier in hindering the passage of solutes from one side of the barrier to the other)

The Starling equation predicts the development of two different kinds of pulmonary edema. *Increased pressure pulmonary edema* occurs when the balance of the driving forces increases, forcing fluid across the barrier at a rate that can no longer be accommodated by lymphatic drainage. *Increased permeability pulmonary edema* occurs in the presence of ARDS that damages the normal barriers to fluid filtration and allows increased flux of liquid and protein into the extravascular compartments of the lungs. Congestion, atelectasis, and pulmonary edema were features of the original description of the syndrome.[4]

Thus, pulmonary edema results from increases in either hydrostatic driving pressures (increased pressure edema) or barrier conductance (increased permeability edema), or both. What distinguishes the two types is barrier permeability, which is normal in increased pressure edema, but abnormal in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema by the balance of pressures. ARDS results primarily from an increase in lung vascular permeability, although some cases may be made worse by the presence of elevated lung vascular hydrostatic pressures.

INCREASED PERMEABILITY PULMONARY EDEMA

Increased permeability pulmonary edema is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature is that the integrity of the barrier to fluid and protein flow into the lung interstitium and alveoli is altered. Increased permeability edema is sometimes called *noncardiogenic pulmonary edema*, and the resulting clinical syndromes in humans are commonly lumped together as *ALI* or *ARDS*.

Accumulation of fluid and protein increases when the lung endothelial and epithelial barriers are injured. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased permeability edema occurs. Large animal models employing measurements of hemodynamics and lung lymph flow demonstrate that clinically relevant causes of ARDS, including live bacteria, endotoxin, and microemboli, induce an increase in lung vascular permeability that causes protein-rich lung edema.[5–7] Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by the usual safety factors. Although increases in fluid and protein filtration across the lung endothelium can be removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures, since the barriers to flow are much less restrictive than normal.

Edema formation in injured lungs is sensitive to hydrostatic driving pressures. Driving pressures are often increased when the lungs are injured because of the vasoconstrictive effects of inflammatory mediators, such as thromboxanes. Thromboxanes may shift the main site of vascular resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites, or may exert cardiac effects. For example, elevated left atrial pressure, pulmonary venoconstriction, or an increase in cardiac output in sepsis may increase hydrostatic pressure at the microvascular fluid exchange sites. Although a primary event in ARDS is an increase in lung vascular permeability, the magnitude of lung edema formation in ARDS may be substantially increased when lung vascular pressures and volume are elevated, consistent with the effects of elevated hydrostatic pressure on transvascular flux of fluid and protein.

Because the lung endothelial and epithelial barriers are injured in ARDS, the protective effects of protein osmotic pressure differences across them are lost; driving pressure is unopposed by protein osmotic pressure, and even normal hydrostatic pressure results in significant fluid and protein extravasation into the interstitial and alveolar spaces. The ability of the lymphatics to pump the excess filtrate away is increased when the lungs are injured. If the alveolar epithelial barrier is damaged, edema may accumulate readily in alveoli, since most of the resistance to fluid and protein flow into the alveoli is in the epithelial barrier.

To summarize, the majority of patients with ARDS have normal or low hydrostatic pressures and increased alveolar-capillary permeability. However, up to 30% of patients with ARDS may have an elevated left atrial pressure.[8] Lung fluid balance is a dynamic concept that incorporates both formation and removal of edema fluid in the interstitium and airspaces.

LUNG PHYSIOLOGY

The effects of increased permeability edema on lung mechanics and gas exchange depend, in part, on the magnitude of edema accumulation. As with increased pressure edema, the major effects on pulmonary mechanics occur with alveolar flooding.

About 20% to 30% of the extravascular water of the lungs is in the extravascular interstitial tissue. This volume can more than double before alveolar flooding occurs. In experimental lung injury, functional residual capacity (FRC) is decreased as a consequence of alveolar flooding; the loss of units that can be ventilated accounts for most of the decrease in static lung compliance.[9] Computed tomography has provided new insights into structure–function relationships in human ARDS. In the early stage of lung injury, when alveolar edema predominates, the lungs are characterized by a more homogeneous alteration of vascular permeability, and edema may accumulate evenly in all lung regions, with a nongravitational distribution. Later in the exudative phase of ARDS, the consolidation is more gravity-dependent. In the organizing phase, lung reticulation appears.

Measurements of pulmonary mechanics in mechanically ventilated patients with ARDS show a decrease in static lung compliance as a consequence of loss of ventilated lung units. In addition, airflow resistance is increased as a result of decreased lung volume.[10] Bronchospasm may add to the increase in airflow resistance and may be partially reversed in some patients by administration of inhaled bronchodilators. Chest wall compliance is reduced, probably because of alterations in the intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion. Respiratory mechanics and responses to positive end-expiratory pressure (PEEP) during mechanical ventilation in patients with ARDS originating from pulmonary disease (e.g., pneumonia and associated lung consolidation) and that arising from extrapulmonary disease may differ.[11]

The injured lung in ARDS may release biologically active substances that can interfere with the normal state of low surface tension in the alveoli. In addition, activated neutrophils may reduce surfactant function in vitro and degrade major surfactant apoproteins through a combination of proteolysis and oxidant radical–mediated mechanisms. Human lung surfactant obtained from bronchoalveolar lavage (BAL) fluid in patients at risk for ARDS and from those with established ARDS are abnormal in chemical composition and functional activity.[12] Abnormalities may also be caused by interactions between surfactant and edema proteins, since plasma proteins interfere with surfactant function.

Gas exchange is severely compromised in increased permeability edema, because of both intrapulmonary shunting of blood and ventilation–perfusion inequalities. Clinical evidence indicates that patients with early ARDS have a marked increase in pulmonary dead space fraction.[13] This finding indicates that many ventilated lung units are not well perfused, although intrapulmonary shunting may also contribute to the elevated dead space. Minute ventilation is typically twice normal (approximately 12 L/min) at the onset of ARDS.

PATHOLOGIC FINDINGS

Based on several studies that included a preponderance of postmortem pathology, the light and electron microscopic appearances of human and animal lung tissue in ARDS have been described.[14] The earliest changes are marked by widespread alveolar and interstitial edema, inflammation, and hemorrhage. Hyaline membranes, composed of precipitated plasma proteins, fibrin, and necrotic debris, are frequently found and constitute the footprint of a pathologic finding termed diffuse alveolar damage (DAD), which pathologists use to define ARDS microscopically (Fig. 140-1).[15]

The alveolar epithelium may be more extensively damaged than is the vascular endothelium. Alveoli that demonstrate widespread destruction of type I alveolar epithelial cells may appear adjacent to normal alveoli. The injured alveolar epithelium is swollen, disorganized, and, frequently, detached from basement membranes. The alveolar surface may be covered by hyaline membranes. Type I cells are more severely damaged than type II cells. The thin cytoplasmic extensions of cells far from the nucleus, which cover the thin side of the alveolar-capillary barrier, may be most severely affected. The interstitium is widened by edema (especially in peribronchovascular cuffs) and may be filled with leukocytes, platelets, red blood cells, fibrin, and debris (especially near the alveolar walls). The microvascular endothelium may show cytoplasmic swelling or vacuoles and greater numbers of intraluminal leukocytes.

After about 5 to 10 days, the exudative phase of ARDS is followed by a proliferative phase. The relative contributions of the original insult, repair processes, and effects of therapies on this and subsequent phases are not well known. Some abnormalities occurring after the initial exudative phase are related to effects of traditional modes of mechanical ventilation that used tidal volumes between 12 and 15 mL/kg predicted body weight.

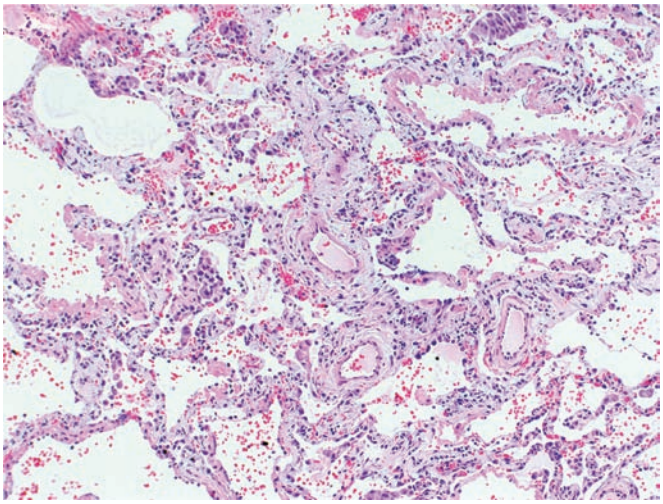
Reabsorption of some of the edema fluid characterizes the proliferative phase. Fibrin may be prominent in alveoli and interstitium, and infiltration with inflammatory cells and fibroblasts, which may have been activated very early in the course of lung injury, may be seen. The alveolar epithelium is often cuboidal and made up largely of proliferating type II cells. The air–blood barrier may be thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may reduce its surface area.

In a study addressing the clinicopathologic correlation of the new Berlin definition of ARDS severity with historical autopsy data, a greater proportion of patients with severe ARDS demonstrated histopathologic findings of DAD compared with those with mild or moderate disease.[16]

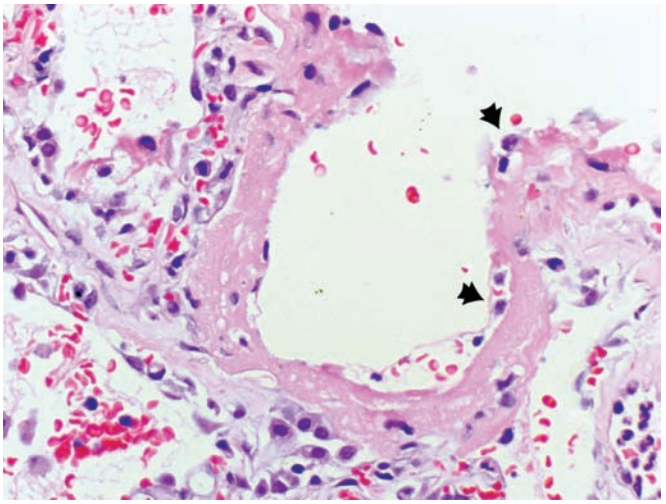
EXPERIMENTAL STUDIES

The most common clinical disorders associated with the development of ARDS are pneumonia, sepsis, gastric aspiration, and major trauma. Other, less common causes include transfusion-associated lung injury, drug overdose, severe acute pancreatitis, and near drowning. The initiating insult to the lungs occurs either via the airways or the bloodstream.

The exact mechanisms by which the lungs are injured have been studied in humans, animals, and cellular systems. Human studies have provided descriptive data regarding the events that occur in the airspaces before and after the onset of lung injury. Studies using BAL or collection of pulmonary edema fluid in patients following the onset of ARDS have demonstrated a major acute inflammatory response, which begins prior to clinical



A



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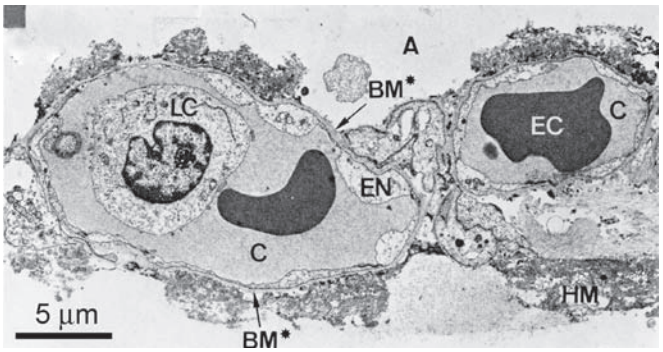

C

Figure 140-1 **A.** A low-power light micrograph of lung biopsy specimen collected 2 days after the onset of ALI/ARDS secondary to gram-negative sepsis demonstrates key features of diffuse alveolar damage, including hyaline membranes, inflammation, intra-alveolar red blood cells and neutrophils, and thickening of the alveolar-capillary membrane. **B.** High-power view of a different field illustrates dense hyaline membrane and diffuse alveolar inflammation. Polymorphonuclear leukocytes are imbedded in the proteinaceous hyaline membrane structure *(black arrows)*. *(Histological sections in A and B used with permission of Dr. K. Jones, University of California, San Francisco).* **C.** Electron micrograph from a classic analysis of ALI/ARDS showing injury to capillary endothelium and alveolar epithelium. LC, leukocyte within the capillary lumen; EC, erythrocytes; EN, blebbing of the capillary endothelium; BM, exposed basement membrane where the epithelium has been denuded; C, capillary; A, alveolar space. *(**C.** Reproduced with permission from Bachofen M, Weibel EAR. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med. 1982;3(1):35–56.)*

recognition of ARDS.[17] The response peaks during the first 1 to 3 days of clinically defined ARDS and resolves slowly over 7 to 14 days in patients who remain intubated. These studies have shown the complexity of the evolving inflammatory responses, characterized by accumulation of acute response cytokines and their naturally occurring inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and the collagen precursors involved in the repair process.

Hypotheses regarding the mechanisms of lung injury have been tested in animal models and in vitro studies, and several reviews have summarized the findings.[3,7] The existing animal models do not completely reproduce all of the aspects of ARDS in humans, in part because human ARDS evolves over a longer period of time than can be studied in the laboratory. In addition, the lungs of humans are exposed not only to the initial injurious insult, but also to the therapies that are used to treat ARDS, such as mechanical ventilation, fluid resuscitation, and antibiotics. Experiments using isolated cells have been helpful in testing specific concepts, but the complexity and redundancy of intact biologic systems is not reproduced in simplified experimental systems. By design, most experimental work limits study to one causative agent, thereby reducing actual clinical complexity to the simplicity of a single experimental pathway. Increased permeability edema in humans is likely to be caused by interactions among a number of different pathways acting in parallel or series, and modulated by process of care variables such as mechanical ventilation, fluid management, vasopressor use, and several comorbidities, including diabetes mellitus, alcohol and cigarette exposure, and renal and liver disease.[7]

Studies in isolated organs and small animals in which hemodynamic variables are not measured can be difficult to evaluate. Indices of lung injury, usually measured by the appearance of markers in lungs, lavage fluid, or perfusate, are not determined solely by the barrier function of the microvasculature. Indeed, when vascular endothelium is injured, fluid and protein movement from the vascular space into the lungs is sensitive to hydrostatic driving pressures and filtration surface area. Hence, the effects of experimental interventions may be caused by changes in these parameters and not by changes in microvascular barrier function.

The effects of microvascular driving pressures and surface area can be difficult to evaluate, even in large, instrumented animals. In

sheep and goats, interpretation of lung lymph fluid and protein flow changes are further complicated by contributions of extrapulmonary lymphatics, physical forces acting on lymphatics, and possible intranodal modification of lymph. Data from experimental animal models suggest that at least two broad categories of mechanisms of ARDS are operative: (1) those that are *indirect* (i.e., require the participation of intermediary mechanisms, e.g., host defenses); and (2) those that are *direct* (i.e., do not require intermediary mechanisms; injury probably occurs as a result of contact between an offending substance and lung tissue). These categories overlap, since once the lungs are injured, inflammatory responses occur, which may compound the primary mechanism of injury.

MECHANISMS OF ACUTE RESPIRATORY DISTRESS SYNDROME

The following themes regarding the mechanisms of ARDS are discussed below: infection, inflammation, and direct toxicity. Although discussed separately, they are all interrelated.

ROLE OF INFECTION

ARDS develops in 20% to 45% of patients with severe sepsis. Increased microvascular permeability to albumin has been shown to accompany human sepsis, and infection and the sepsis syndrome are major causes of ARDS in humans. Patients who develop shock in response to known or suspected infection have a particularly high incidence of ARDS, and the mortality of patients with ARDS associated with infection (i.e., sepsis syndrome) is increased. ARDS also appears to predispose the lungs to infection, and delayed infection is an important cause of morbidity in patients who survive the initial lung insult.

The mechanisms by which infection and sepsis syndrome injure the lungs are only partially understood. The lung injury is likely related to factors other than direct damage by bacteria or other microorganisms, since the prognosis appears unrelated to documented bacteremia or pneumonia. In experimental animals, intravenous infusions of live *Pseudomonas aeruginosa*, or endotoxins from *Escherichia coli*, or surgically induced peritonitis result in increased permeability pulmonary edema.[18] ARDS caused by endotoxin in sheep is thought to be an inflammatory response mediated, at least in part, by neutrophils and tumor necrosis factor (TNF). Endotoxin may also affect the clotting system and metabolic functions of the lungs, as well as predispose the lungs to the development of pulmonary infections by increasing adherence of bacteria to injured endothelium. Exoproducts of bacteria, such as elastase and *Pseudomonas* exoenzyme U, also have been shown to injure the lungs.[7]

Bacterial products may also play a role in pathogenesis of ARDS by sensitizing the lungs to the effects of mechanical stretch. Gram-negative lipopolysaccharide causes an acute inflammatory response in the lungs of humans. Bacterial endotoxin enhances the responses of human alveolar macrophages to positive pressure ventilation; pretreatment of rats with intravenous endotoxin enhances cytokine production in the lungs during mechanical ventilation ex vivo. Furthermore, mechanical ventilation using moderate or large tidal volumes increases the sensitivity of lung macrophages to endotoxin in vitro and the expression of the endotoxin recognition molecule, CD14, on lung cells in vivo. Endotoxin recognition pathways are increased in the lungs of patients with ARDS, and the biologic effects of endotoxin are amplified in the lungs of patients with lung injury. The synergism between bacterial products and mechanical stretch suggests that interrupting these pathways might limit some forms of ARDS in humans.[19]

Increased permeability edema is associated with impaired antibacterial defenses. In animal models, bacterial infections worsen ARDS. The cause of impaired bacterial defenses in ARDS is not known. Genetic polymorphisms that predispose individuals to the injurious effects of specific bacteria or viruses may influence the development of ARDS. Several polymorphisms are associated with more severe pneumococcal, Legionella, and viral lung infections.[20] The genetic factors that regulate the virulence of infecting pathogens also require more research to relate the severity of clinical lung injury to specific microbiologic variables that contribute to severe pneumonia and ARDS.[21]

ROLE OF INFLAMMATION

Substantial evidence implicates host defenses and inflammatory responses in the underlying mechanism of ARDS. The balance between protective and injurious innate and adaptive immune responses and hemostatic pathways may determine whether alveolar injury can be repaired and resolved. For example, in lung infection, acute inflammatory responses to pathogens and their toxins cause ARDS through leukocyte protease release, generation of reactive oxygen species, synthesis of chemokines and cytokines, Toll-like receptor engagement, and actions of lipid mediators. However, these same inflammatory mechanisms, when controlled, rather than excessive, are requisite in pathogen containment and clearance.[22–24]

Normally, the pulmonary circulation contains a large pool of marginated neutrophils that change shape in order to squeeze through the lung capillaries. When neutrophils are activated, they stiffen and become less distensible. These neutrophils are retained for longer periods of time in the pulmonary microcirculation. Endothelial activation leads to increased expression of leukocyte adhesion molecules, providing a second mechanism to slow the transit of neutrophils. Trapped neutrophils respond to chemotactic gradients generated by chemokines produced by alveolar macrophages and mesenchymal cells and migrate into the airspaces. Activated neutrophils generate and release toxic substances (e.g., oxygen metabolites and granular constituents, such as proteases, and cationic lysosomal enzymes) that disrupt the function of the microvascular and epithelial barriers. Normally, these barriers limit liquid and protein flow out of the vascular space and into the alveolar spaces, mitigating the development of permeability edema.[19]

Inflammatory responses also have the potential to induce lung cell injury by activating cell death pathways, leading to apoptosis. Bacterial products, such as *Pseudomonas* Exoenzyme U and mechanical stretch, may lead to direct cellular necrosis. Apoptosis is mediated by a family of death receptors, including TNF and Fas receptors. The Fas ligand (FasL) is a 45-kD peptide that is shed from the cell surface by the action of metalloproteinases.[25] Biologically active soluble FasL (sFasL) accumulates in the lungs of patients with ARDS, inducing apoptotic death of human lung epithelial cells in vitro. Human sFasL induces epithelial cell death in the lungs of rabbits; a monoclonal antibody that activates membrane Fas causes alveolar wall apoptosis and fibrosis in the lungs of mice.[25]

Apoptosis and inflammation pathways intersect, as stimulation of membrane Fas induces cytokine production in human macrophages and inflammation in the lungs of rabbits and mice. In addition, lung injury may be able to trigger apoptosis pathways in distant organs, such as the kidney, perhaps by increasing the concentrations of circulating sFasL. Thus, inflammatory responses may trigger cell death pathways, and cell death pathways triggered by sFasL may induce inflammation in the lung alveolar environment. Recent human studies implicate apoptosis as an important mechanism in human lung injury.[26]

ROLE OF DIRECT TOXICITY

Inflammation is not required for all forms of ARDS. ARDS may develop in neutropenic patients. A clinical trial using granulocyte

colony–stimulating factor to increase the number and activation state of circulating neutrophils in patients with severe pneumonia did not reveal an increased incidence of ARDS.[27] Lung injuries that do not require the participation of neutrophils have been described in animal models.

Direct lung injury is also thought to occur in humans. Putative agents that directly injure the lungs include mechanical forces during mechanical ventilation, toxic and corrosive chemicals and gases (e.g., hydrochloric acid, chlorine gas, phosgene), and aspiration of fresh or salt water (near-drowning). Many of these injuries develop rapidly, supporting the idea that injury is caused directly by contact with the respiratory epithelium in the airways or alveolar walls.

Inflammatory pathways are likely to be rapidly activated following many types of direct lung injury, as probably occurs following aspiration of gastric secretions – one of the most common clinical causes of ARDS. Lung injury occurs rapidly, especially to the epithelium. The injury is probably related, in part, to the low pH of the aspirated stomach contents. Aspirated acid is almost immediately neutralized. However, within hours, proinflammatory mediators are released, the injured lung is infiltrated with neutrophils, fibrin accumulates in the alveolar spaces, and further structural damage is seen on histologic examination. Thus, even direct toxic injuries damage the lung in part through activation of inflammatory pathways.

BIOLOGIC MARKERS

Considerable interest exists in finding a simple test of blood, urine, or BAL fluid that would identify patients at risk for, or in the earliest stages of, ARDS, or that might predict clinical outcome.

Although products of complement activation have been proposed as markers, their serum levels correlate poorly with lung injury. Measurement of circulating endotoxin is not appropriately sensitive or specific for the presence or risk of developing lung injury. The same is true for measurements of release or activity of angiotensin-converting enzyme.[28] Von Willebrand factor (VWF) antigen may be useful as a plasma marker of impending ARDS in patients with nonpulmonary sepsis.[29] VWF levels are elevated in the edema fluid and plasma of patients with ARDS and correlate with poor clinical outcomes.[30] Also, new work indicates that elevated levels of plasma angiopoietin-2 predict the development of ALI in patients with sepsis identified in the emergency department.[31] While increases in other biochemical and inflammatory markers, including surfactant protein D and interleukin-6, correlate somewhat with lung injury and mortality, no simple biologic marker currently serves in the same diagnostic capacity, as do cardiac enzymes in evaluation of suspected acute myocardial infarction.[32]

Other mediators of inflammation in ARDS have been studied. For example, increased levels of TNF are detected in blood and BAL fluid in lung injury, but an association between TNF levels and the development of ARDS has not been found. Furthermore, elevated TNF levels are found in patients with severe congestive heart failure. Lipoxygenase products of arachidonic acid metabolism have been detected in pulmonary edema fluid, BAL fluid, plasma, and urine, and elastase has been detected in BAL fluid in the setting of lung injury.

ARDS follows a wide variety of insults of varying severity. In a study of injured patients with ARDS, investigators found increased levels of IL-6 and thrombomodulin in those who had fewer ventilator-free days.[33] However, since ARDS is such a heterogeneous disorder, with so many possible mechanisms, it is unlikely that any single marker that unequivocally identifies the risk or the presence of ARDS will be found. An investigative focus on particular subgroups of patients with common causes of lung injury, coupled with study of much larger groups of more precisely diagnosed patients, may be a better pathway for future research.

Figure 140-2 depicts multiple pathways involved in the pathogenesis of ARDS in the context of normal and injured alveoli. The depictions place emphasis on potential pathways for injury across the vascular endothelium and alveolar epithelium.

VENTILATOR-INDUCED LUNG INJURY

The most important development of the last 10 years in our understanding of the pathogenesis and treatment of ARDS is recognition that the long-standing practice of mechanically ventilating affected patients using high tidal volumes and airway pressures worsens the injury. Animal studies first suggested the potential contributory role of high tidal volumes and elevated airway pressures in the pathogenesis of lung injury; subsequently, clinical trials confirmed the findings.[3]

ANIMAL STUDIES

Experimental studies have shown that ventilation using high tidal volumes may increase vascular filtration pressures; produce stress fractures of microvascular endothelium, alveolar epithelium, and basement membranes; and cause lung rupture (so-called ventilation-induced lung injury).[34] The injury appears to be due to increased lung excursions at high volumes (volutrauma), rather than the high-airway pressure, per se, since it can be prevented by limiting thoracic motion (e.g., by placing the chest in a cast).

The concept of volutrauma was first established in 1974 when investigators found that modestly elevated tidal volumes, especially in the absence of PEEP, caused lung edema in rats.[35] Several years later, additional animal studies further demonstrated the potential injurious role of high tidal volumes and elevated airway pressures, an effect termed *ventilator-induced lung injury* (VILI).[36] Subsequent experiments demonstrated that VILI could also induce release of several proinflammatory cytokines, injuring the lung and other organs – a process referred to as "biotrauma."[37] These animal studies stimulated clinical investigation that revolutionized the care of patients with ARDS.[36]

CLINICAL STUDIES

The compelling evidence from animal experiments and small clinical trials prompted clinical studies aimed at testing the potential benefit of lower tidal volumes and reduced airway pressures during mechanical ventilation in management of ARDS. In a large, multicenter, National Heart Lung and Blood–sponsored trial of 861 patients, mortality was reduced from 40% to 31% using a tidal volume of 6 mL/kg/ideal body weight and a limited plateau airway pressure of less than 30 cmH_2O.[38] In this trial, use of small tidal volumes was associated with a lower incidence of nonpulmonary organ failure. The protocol for carrying out the lung protective ventilatory strategy is described in detail in Table 140-1. The results of the trial transformed the management of patients with ARDS. Notably, a follow-up clinical trial demonstrated that ventilation using the limited tidal volumes and plateau pressure of the original study is associated with an overall reduction of mortality to 26%. In the follow-up trial, although elevated levels of PEEP did not decrease mortality, the basic lung protective strategy was validated as effective.

The beneficial mechanism underlying the low tidal volume strategy has been well studied. An Italian study reported that use of low tidal volumes in patients with ARDS attenuates the inflammatory response in both lungs and bloodstream, as measured by reductions in neutrophil and cytokine concentrations in BAL and cytokines in circulating blood.[39] Other studies have confirmed a number of these findings. In addition, a reduction in alveolar epithelial injury appears likely, based on a decline in plasma surfactant

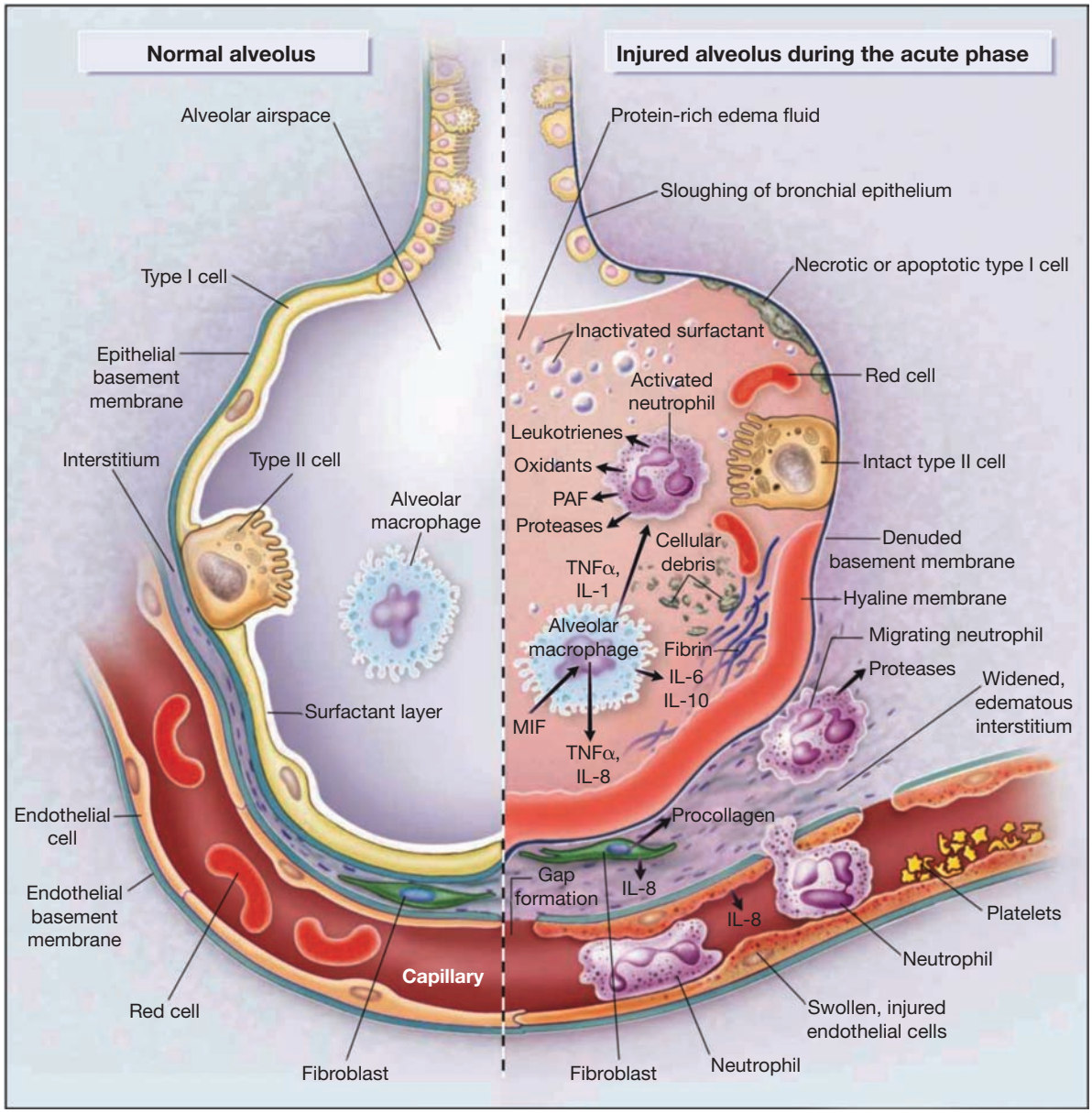

Figure 140-2 Multiple cellular responses and mediators contribute to alveolar-capillary membrane injury *(right-hand side)* and the transition from normal alveolar structure and function *(left-hand side)* in the acute phase of ALI/ARDS. Original investigations of the pathogenesis of ALI/ARDS searched for single mediators that provided final common pathways to inflammation and alveolar edema. Current concepts of pathogenesis involve multiple molecular factors of several classes, a variety of responding cells, and an imbalance between injurious and reparative signals and pathways. See text and Ware & Matthay (2000). *(Reproduced with permission from Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334–1349.)*

protein D levels. Additional clinical and experimental studies are underway. A reduction in lung endothelial and epithelial injury, attenuated inflammatory responses, reduced edema formation, and more rapid resolution of lung edema are likely part of the mechanism(s).[3] Figure 140-3 summarizes current knowledge of the mechanisms of VILI.

■ RESOLUTION OF ACUTE LUNG INJURY

In the last two decades, notable progress has occurred in elucidating the mechanisms responsible for resolution of lung edema. More limited progress characterizes our understanding of the resolution of lung inflammation.

Considerable advances have been made in our understanding of the clearance of fluid and solute from alveoli. Edema can be cleared via five routes: lymphatics, airways, blood vessels, the pleural space, and the mediastinum. Active sodium and chloride transport across the alveolar and distal airway epithelial barriers into the interstitium drives edema fluid removal from the airspaces.[40] The uninjured alveolar epithelium has a remarkable ability to rapidly clear fluid from the airspaces. Even when mild-to-moderate alveolar injury occurs, salt and water transport capacity is often preserved. In severe injury, when the barrier is disrupted, the capacity to clear edema is lost. The vascular endothelium becomes the limiting barrier between the vascular space and airspace. Clinically, the capacity to remove some alveolar edema fluid in the first 4 to 12 hours following ARDS is a favorable prognostic finding; the associated mortality rate is only 20%. In contrast, an inability to resorb alveolar edema fluid early in the course of injury

TABLE 140-1 National Institute of Heart, Lung, and Blood, ARDS Network: Lung Protective Ventilatory Strategy

Ventilator mode	Volume assist-control
Tidal volume	≤6 mL/kg PBW
Plateau pressure	≤30 cmH_2O
Ventilation set rate, pH goal	6–35, adjusted to achieve arterial pH ≥7.30, if possible
Inspiratory flow, I:E	Adjust flow to achieve I:E = 1:1–1:3
Oxygenation goal	$55 \le Pa_{O_2} \le 80$ mm Hg or $88 \le Sp_{O_2} \le 95\%$

$F_{I_{O_2}}$/PEEP Combinations

$F_{I_{O_2}}$	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP, cmH_2O	5	5	8	8	10	10	10	12	14	14	14	16	18	18, 22, 24

(further increases in PEEP to 34 cmH_2O allowed, but not required)

Weaning	Attempts to wean by pressure support required when $F_{I_{O_2}}$/PEEP ≤0.40/8

PBW, predicted body weight

Male PBW = 50 + 2.3 [height (inches) − 60] *or*
50 + 0.91 [height (cm) − 152.4]
Female PBW = 45.5 + 2.3 [height (inches) − 60] *or*
45.5 + 0.91 [height (cm) − 152.4]

I:E, ratio of inspiratory to expiratory duration; Pa_{O_2}, partial pressure of oxygen in arterial blood; Sp_{O_2}, oxyhemoglobin saturation measured by pulse oximetry.
Source: Data from Acute Respiratory Distress Syndrome Network: Ventilation with low tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–1308.

is associated with a mortality of nearly 80%. Thus, the function of the alveolar epithelial barrier early in the course of ARDS may be a useful prognostic index, serving as a marker of the severity and extent of injury.[41]

Resolution of ARDS requires effective: (1) reabsorption of alveolar edema, (2) repair of the epithelial and endothelial barriers, and (3) removal of inflammatory cells and exudates from the distal airspaces. Reabsorption of alveolar edema occurs through vectorial transport of sodium and chloride across alveolar epithelial type I and II cells to create a mini-osmotic gradient to reabsorb water.[42–44] This process is impaired in ARDS, in part because of apoptosis and necrosis of alveolar epithelium and defects in transcellular ion transport induced by proinflammatory cytokines, oxidants, and hypoxia.[26,42,45–48]

In uninjured, ex vivo human lungs, alveolar fluid clearance (AFC) is increased by administration of the beta-2 agonist, salmeterol.[49] However, the beta-adrenergic mediated effect by augmentation of intracellular cAMP works primarily when the alveolar epithelium is not injured, as in hydrostatic edema. Aerosolized or intravenous beta-2 agonist therapy does not appear to improve clinical outcomes.[50,51]

Clearance of protein from flooded alveoli is much slower (1%–2% per hour) than clearance of fluid (10%–20% per hour), resulting in an increased concentration of protein in the airspaces. If alveolar edema formed during increased lung vascular permeability clots, its removal from flooded alveoli may be slowed. Clotting may occur because extravasation of plasma into airspaces may lead to clotting system activation by surfactant or macrophage-derived procoagulants.

Most of the interstitial water in pulmonary edema lies in the peribronchovascular loose connective-tissue spaces, rather than in alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not significant for most interstitial edema. Some fluid from the loose peribronchovascular interstitium may drain directly into the bloodstream by crossing the walls of blood vessels in the lungs. Edema may also drain into the pleural space.

Pleural effusions are more common in increased pressure pulmonary edema (25%–50% of patients; if unilateral, usually on the right). However, pleural effusions occur in ARDS as well (35% of patients). As much as 25% to 30% of edema fluid may leave the lungs through the pleural space. A significant portion of interstitial edema probably follows the prevailing pressure gradient in the lungs to drain into the mediastinum, where it may be picked up by the lymphatics.

Short-term alveolar protein clearance appears to proceed primarily by paracellular diffusion. The process depends on the size of the proteins. Most proteins are cleared intact, rather than as degraded, smaller fragments. However, a few specific proteins (e.g., vasoactive intestinal peptide and gastrin) are degraded before being cleared.

Finally, the general consensus is that transcytosis (transport via vesicles) is not a major mechanism for clearing bulk quantities of albumin or other proteins from the alveolar space. Over the long term, phagocytosis and catabolism by macrophages account for most protein clearance from the alveolar spaces. All insoluble, precipitated proteins are removed in this way. Macrophages are also ultimately responsible for removing senescent and dead neutrophils and other debris. The presence of a small, ciliated surface area of the distal airspaces suggests that the mucociliary route accounts for only a minor fraction of alveolar protein clearance. Complete clearance of alveolar protein from pulmonary edema by any route is slow.

AFC appears to be clinically important. In a study of 116 patients with ARDS, the rate of AFC in patients with shock was significantly slower than in those without shock. AFC also decreased significantly as the number of vasopressors required increased. The findings suggest that vasopressor use may be a marker for impaired alveolar epithelial barrier integrity in patients with ARDS and shock.[52]

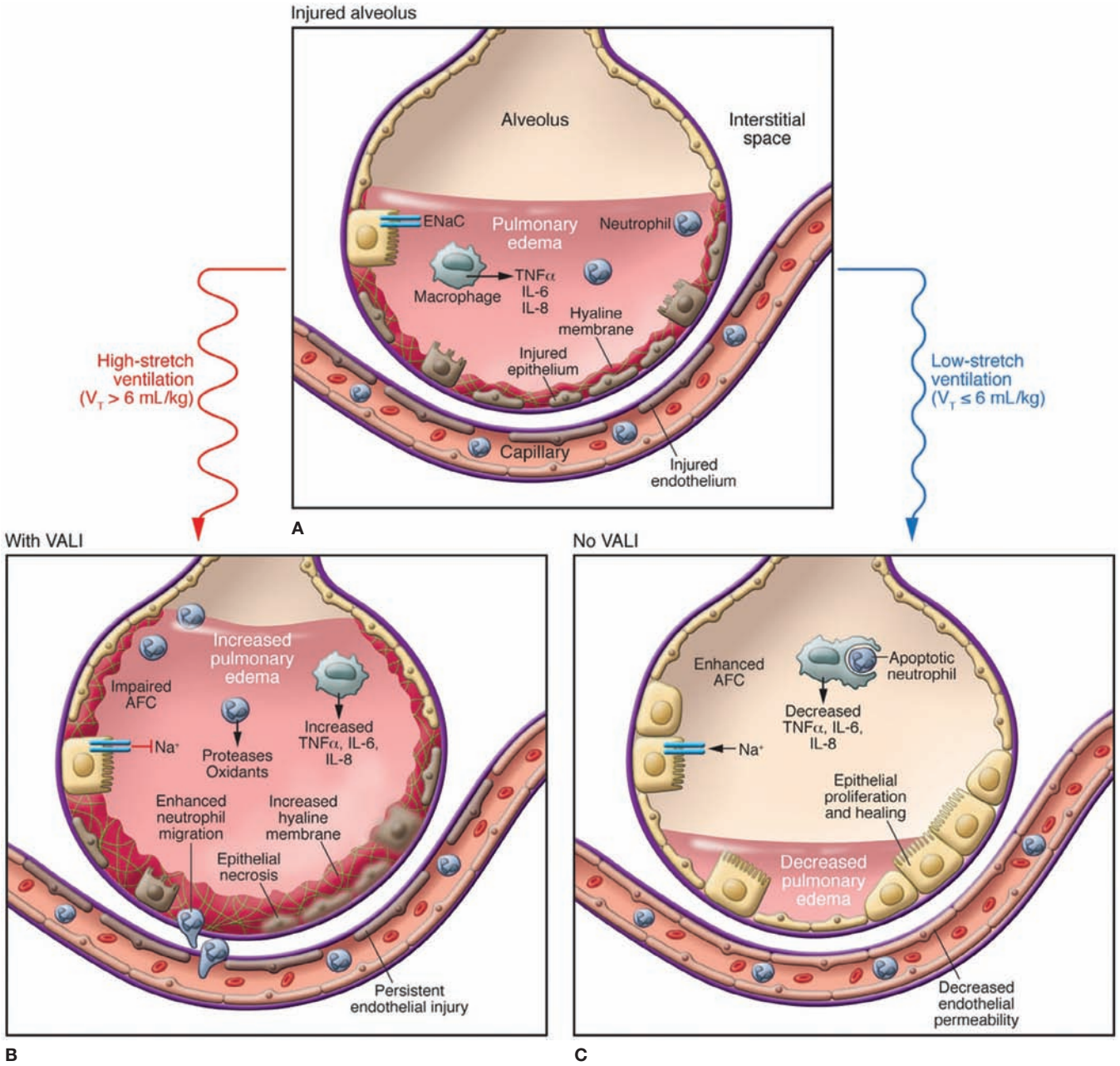

Figure 140-3 Mechanisms of ventilator-associated lung injury (VALI). **A.** Acute lung injury leads to lung endothelial and epithelial injury, increased permeability of the alveolar-capillary barrier, flooding of the airspace with protein-rich pulmonary edema fluid, activation of alveolar macrophages with release of proinflammatory chemokines and cytokines, neutrophil margination and activation, and fibrin deposition (hyaline membranes). **B.** If the injured lung is ventilated with high tidal volumes and high inflation pressures (high-stretch ventilation), then lung injury is exacerbated, with increased lung endothelial and epithelial injury and/or necrosis, enhanced neutrophil margination, release of injurious neutrophil products such as proteases and oxidants, increased release of proinflammatory cytokines from alveolar macrophages and the lung epithelium, increased fibrin deposition, and increased hyaline membrane formation. Injurious mechanical ventilation can also impair alveolar fluid clearance (AFC) mechanisms. **C.** In contrast, a protective ventilatory strategy (low-stretch ventilation) can limit further lung endothelial and epithelial injury, reduce the release of proinflammatory cytokines, and enhance AFC through the active transport of sodium and chloride across the alveolar epithelium, thereby reducing the quantity of pulmonary edema and allowing endothelial and epithelial repair to occur. Epithelial repair occurs through migration, proliferation, and differentiation of alveolar epithelial type II cells to repopulate the denuded basement membrane. *(Reproduced with permission from Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome, J Clin Invest. 2012;122(8):2731–2740.)*

CONCLUSIONS

Among the major advances in respiratory medicine and physiology over the last three decades has been the acquisition of important new knowledge on the physiology of fluid, solute, and protein transport in healthy and diseased lungs. Pulmonary edema, defined as the abnormal accumulation of extravascular lung fluid, is a pathologic state that occurs when fluid is filtered into the lungs faster than it can be removed.

The many causes of pulmonary edema are grouped into two main pathophysiologic categories: (1) increased pressure edema, which results from an increase in hydrostatic or protein osmotic forces (or

both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs; and (2) increased permeability edema, which is seen in ARDS, and in which a breakdown of the normal barrier properties of lung endothelium or epithelium develops. Although these two different types of pulmonary edema share many features, usually they can be distinguished by careful clinical, radiologic, and physiologic evaluation. They also differ in treatment and prognosis.

Major advances in the treatment of ARDS have occurred because of the successful application of lung protective ventilatory strategies early in the course of the illness (Table 140-1). Use of a low tidal volume (6 mL/kg/ideal body weight), coupled with a plateau pressure limit (less than 30 cmH_2O) has resulted in the first therapy demonstrated to reduce mortality in patients with ARDS.[38]

Another major advance in the treatment of ARDS was triggered by findings from the Fluid and Catheter Treatment Trial (FACTT), a large randomized trial comparing liberal and conservative fluid management strategies in affected patients.[8] A marked difference in outcome was reported, with patients in the conservative fluid management arm having 2.5 more ventilator-free days (and improved physiology) than those in the liberal fluid management arm. In addition, although not statistically significant, a 2.9% reduction in the 60-day mortality rate was noted in the conservative fluid management arm. Patients were also randomized to receive either a pulmonary arterial catheter or a central venous catheter for monitoring and fluid management. No differences were noted in clinical outcomes between the two groups.[53]

New insights into the pathogenesis of ARDS suggest that other therapies may also prove efficacious in reducing mortality in this common form of severe acute respiratory failure. A major development has been the ability to conduct large, prospective, randomized, clinical trials (e.g., those sponsored by the National Heart, Lung, and Blood Institute) to test a variety of therapies important in supportive patient care, including use of mechanical ventilation, intravenous fluids, and a variety of pharmacologic agents.

Interest exists in the possibility that cell-based therapy using bone-marrow–derived mesenchymal stem cells may be effective for more severe ARDS.[3] Such trials have led to a better understanding of the pathogenesis of human ARDS and have confirmed the importance of VILI. In addition, ancillary pathogenetic studies carried out on biologic samples from clinical trials have advanced our understanding of underlying mechanisms.

In the future, human studies will be needed to explore new therapeutic strategies suggested by basic investigation conducted in animal models of ALI, including efforts to treat patients at an early phase of acute respiratory failure, prior to the need for positive pressure ventilation.[3]

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CHAPTER 141

Acute Lung Injury and the Acute Respiratory Distress Syndrome: Clinical Features, Management, and Outcomes

John P. Reilly
Jason D. Christie

DESCRIPTION AND DEFINITIONS

In 1967, Ashbaugh et al.[1] described a syndrome characterized by the acute onset of dyspnea, severe hypoxemia, diffuse lung infiltrates, and decreased respiratory system compliance in the absence of evidence for congestive heart failure (CHF). The syndrome, initially called acute respiratory distress in adults (to contrast it with acute respiratory distress in neonates), is now known as the acute respiratory distress syndrome (ARDS). Following the initial report, other authors utilized various definitions that incorporated elements related to time of onset, presence of hypoxemia and radiographic infiltrates, and absence of overt CHF.

In 1988, Murray and others introduced the Lung Injury Score (LIS), an assessment tool for ARDS that reflects the extent of radiographic infiltrates, severity of hypoxemia and reduced respiratory system compliance, and level of positive end expiratory pressure (PEEP) used in mechanically ventilating affected patients.[2] The LIS incorporates four parameters that are graded on a scale of 0 to 4: (1) ratio of Pa_{O_2} to FI_{O_2}(Pa_{O_2}/FI_{O_2}); (2) total respiratory compliance; (3) level of PEEP; and (4) extent of radiographic infiltrates (assessed by noting the number of quadrants in the chest radiograph demonstrating infiltrates). The LIS equals the sum of the scores for the four variables divided by four. In clinical studies, a score of 2.5 or more is generally used as a threshold for severe disease.

CONSENSUS DEFINITIONS OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Prior to 1994, published studies used nonuniform definitions of ARDS, prompting an American European Consensus Conference (AECC) to develop standardized definitions for ARDS and acute lung injury (ALI)—a broader category that encompasses ARDS.[3] The AECC definitions included the acute onset of illness, bilateral chest radiographic infiltrates consistent with pulmonary edema, poor systemic oxygenation, and absence of evidence for left atrial hypertension (Table 141-1A). The syndrome was referred to as ALI when the ratio of Pa_{O_2} to FI_{O_2} (Pa_{O_2}/FI_{O_2}); was ≤300, and ARDS when the ratio was ≤200. The AECC definitions of ALI and ARDS were intentionally broad in order to encompass different types of acute hypoxemic respiratory failure occurring in a wide variety of settings.

DEVELOPMENT OF THE BERLIN DEFINITION OF ARDS

The standardization of definitions of ALI and ARDS lead to significant advances in the understanding of the syndrome and allowed researchers and clinicians to communicate findings using common criteria. The AECC definitions were widely used in clinical trials, including those that demonstrated therapeutic benefit.[4,5] In addition, they added important validity to the definition, allowing clinicians to generalize trial results to clinical decisions involving their own patients. Despite this standardization, little data were available to support the reliability and validity of ARDS definitions. In fact, several components of the AECC definition have been recognized as problematic: (1) Acute onset is not defined within a specific time frame. (2) The chest radiograph is subject to variability in interpretation.[6,7] (3) Pa_{O_2}/FI_{O_2} may vary according to ventilator parameters, for example, PEEP, and at extremes of FI_{O_2}. (4) Accuracy in excluding the presence of heart failure may be influenced by measurement methodology and timing, as discussed below.[8]

Given these limitations, an international expert panel was convened in Berlin in 2012 to revise the definition of ARDS. The resultant "Berlin definition" of ARDS addresses ambiguities in the prior AECC definition. The authors of the Berlin definition also applied proposed criteria for the syndrome to existing databases of patients with ARDS to specifically address the predictive validity of a new ARDS definition.[9] According to the Berlin definition, ARDS is defined as a syndrome characterized by (1) onset within 1 week of a known clinical insult, (2) bilateral radiographic opacities, not fully explained by pleural effusions, atelectasis, or nodules, (3) respiratory failure not fully explained by cardiac failure or fluid overload, and (4) poor systemic oxygenation, with a Pa_{O_2}/FI_{O_2} ≤300 and a PEEP or CPAP ≥5 cm H_2O. The definition also categorizes syndrome severity as mild, moderate, or severe, based on Pa_{O_2}/FI_{O_2}. According to the Berlin definition, patients who previously were diagnosed with ALI, but not ARDS (i.e., Pa_{O_2}/FI_{O_2} ≤300, but >200), are referred to as having mild ARDS, with ALI now an obsolete term. Moderate ARDS is defined as Pa_{O_2}/FI_{O_2} ≤200, but >100, and severe ARDS is defined as Pa_{O_2}/FI_{O_2} ≤100 (Table 141-1B).

While the Berlin definition leaves the AECC definition of ARDS largely unchanged, the new definition addresses several specific ambiguities of the prior diagnostic criteria. First, the definition

TABLE 141-1A American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Acute Lung Injury	Acute Respiratory Distress Syndrome
Onset	Acute	Acute
Hypoxemia	Pa_{O_2}/FI_{O_2} ≤300 mm Hg	Pa_{O_2}/FI_{O_2} ≤200 mm Hg
Chest radiograph	Bilateral infiltrates consistent with pulmonary edema	Bilateral infiltrates consistent with pulmonary edema
Noncardiac etiology	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery wedge pressure ≤18 mm Hg	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery wedge pressure ≤18 mm Hg

Source: Adapted with permission from Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference of ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–824.

TABLE 141-1B Berlin Definition of Mild, Moderate, and Severe Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Mild ARDS	Moderate ARDS	Severe ARDS
Onset	Onset within 1 week of clinical insult known to result in ARDS		
Hypoxemia	Pa_{O_2}/FI_{O_2} ≤300 mm Hg PEEP or CPAP ≥5 cm H_2O	Pa_{O_2}/FI_{O_2} ≤200 mm Hg PEEP ≥5 cm H_2O	Pa_{O_2}/FI_{O_2} ≤100 mm Hg PEEP ≥5 cm H_2O
Chest radiograph	Bilateral opacities, not explained by effusions, atelectasis, or nodules		
Noncardiac etiology	Reparatory failure, not fully explained by cardiogenic pulmonary edema. Exclude hydrostatic edema if no clinical risk factor present.		

Source: Data from ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–2533.

defines "acute onset" and attempts to clarify chest radiograph criteria. In addition, the Pa_{O_2}/FI_{O_2} criterion is influenced by the level of PEEP and other transient factors, including the presence or absence of airway secretions or inadequate sedation. Increasing PEEP generally increases Pa_{O_2} at a given FI_{O_2}. The consequent increase in Pa_{O_2}/FI_{O_2} may result in a value that no longer meets criteria for ARDS. Conversely, without any PEEP, values of Pa_{O_2}/FI_{O_2} <300 may reflect simple atelectasis, rather than ARDS. Adding PEEP may recruit sufficient atelectatic lung to raise Pa_{O_2}/FI_{O_2} >300, thereby excluding such patients from meeting this criterion for ARDS. The Berlin definition addresses this concern directly by requiring a minimum level of PEEP when a determination of Pa_{O_2}/FI_{O_2} ratio is made.

Finally, given the declining use of pulmonary artery catheters (PACs),[10] potential inaccuracies of pulmonary artery occlusion pressure (PAOP) measurements, and the now recognized possibility of concomitant hydrostatic edema and ARDS, the Berlin definition no longer specifies PAOP requirements.[11,12] PAOP in ARDS may be higher than 18 mm Hg due to intravascular volume loading, particularly in the setting of application of goal-directed management paradigms for sepsis. Conversely, some patients with pulmonary edema due to CHF and high left atrial pressures have a normal PAOP by the time the catheter is inserted and PAOP is measured. The Berlin definition specifies that the respiratory failure of ARDS is not fully explained by cardiac failure or fluid overload and requires objective assessment to exclude hydrostatic edema (e.g., an echocardiogram) if no risk factor for ARDS is present.

The predictive validity of the new ARDS definition was assessed in several large cohorts of patients with ALI, as defined by AECC. Compared with the AECC definition, the Berlin definition had marginally better predictive validity for mortality. The identified categories of mild, moderate, and severe ARDS corresponded with progressive increases in mortality. Proposed ancillary variables in the definition of severe ARDS, including a chest radiograph with three or four quadrants demonstrating opacities, PEEP ≥10 cm H_2O, and either a respiratory system static compliance ≤40 mL/cm H_2O or a corrected expired volume per minute of at least 10 L/min did not improve the predictive validity of the definition of severe ARDS. Therefore, the final definition did not include any of these ancillary variables.

While the Berlin definition has been accepted by major professional organizations, it is important to note that the majority of the studies referred to in this chapter were performed prior to its development, and, therefore, utilize the older AECC definition of ALI and ARDS. Further refinements in the reliability and validity of definitions of ARDS constitute important future directions for clinical studies. In addition, attempts at understanding the heterogeneity underlying the syndrome may allow for identification of ARDS subgroups with potential diverse risk factors and pathogenesis. More reliable definitions will not only improve estimates of the public health impact of these syndromes, but also will decrease misclassification errors, which can be especially problematic for research aimed at clarifying underlying mechanisms.

EPIDEMIOLOGY

Over the last several decades, the epidemiology of ARDS has become more clearly delineated.

INCIDENCE AND MORTALITY RATE

A landmark epidemiologic study of the incidence of ARDS in the United States between 1999 and 2000 – the King County Lung Injury Project (conducted in King County, Washington) – represents the first broad, population-based epidemiologic study of ARDS in the United States using the standardized AECC definitions.[13] Study results included an estimated incidence of ARDS based on a Pa_{O_2}/FI_{O_2} ≤300 of 78.9 per 100,000 person-years and an age-adjusted incidence of 86.2 per 100,000 person-years. The incidence of what is now called moderate or severe ARDS was estimated as 58.7 per 100,000 person-years, with an age-adjusted incidence of 64.0 per 100,000 person-years. The incidence of ARDS increased dramatically with age, with an incidence of 306 per 100,000 person-years for ages 75 through 84 years. By extrapolation, an estimated 190,600 cases of ARDS occur each year in the United States (Table 141-2).

TABLE 141-2 Estimated Incidence, Hospital Days and Intensive Care Unit (ICU) Days for Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) in the United States (US) based on American European Consensus Criteria for ALI and ARDS

Variable	ALI	ARDS
Crude incidence, per 100,000 person-years	78.9	58.7
Age-adjusted incidence, per 100,000 person-years	86.2	64.0
Estimated annual Number of cases in US	190,600	141,500
Estimated annual number of hospital days in US	3,622,00	2,746,000
Estimated annual number of days in ICU in US	2,154,000	1,642,000

Source: Adapted with permission from Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–1693.

Although prior estimates of the incidence of ARDS had been lower, the studies were limited by incomplete and nonvalidated data, inaccuracies in the definition of the syndrome, and use of administrative coding.[14–19] Thus, the estimates from King County Lung Injury Project serve as the best indicator of the public health impact of ARDS in the United States. More recently, a retrospective cohort study of all patients admitted to the ICU at the Mayo Clinic from 2001 to 2008 has been reported.[20] Since the Mayo Clinic provides all ICU-level care to the population of Olmsted County, Minnesota, the authors could estimate the incidence trends of ARDS over time. The age and sex adjusted incidence of moderate and severe ARDS ($Pa_{O_2}/FI_{O_2} \leq 200$) declined from 81 cases per 100,000 person-years in 2001 to 38.3 cases per 100,000 person years in 2008. This trend appeared to be driven by declining hospital-acquired ARDS, perhaps the result of improvements is overall ICU care and the increasing use of lower tidal volume ventilation (see Approach to Treatment).

During the time of observation in the King County Lung Injury Project study, the mortality from ARDS was 38.5%, translating into an estimated 74,500 annual deaths from ARDS in the United States.[13] Reported mortality estimates have ranged from 26% to 58% [19–23] To put these figures into perspective, more people die annually with ARDS than from AIDS, asthma, and breast cancer combined.[24] Other than lung cancer, ARDS leads to more annual deaths than any type of cancer, including lymphoma, leukemia, and breast, prostate, colon, ovarian, and pancreatic cancers (Table 141-3). The most common causes of death among patients with ARDS arise from the underlying insult or subsequent nosocomial pneumonia and sepsis.[25,26] Only rarely do patients die from progressive hypoxia and respiratory failure.

Several studies have suggested that ARDS mortality has decreased over time.[26–29] In one hospital using the same definition of ARDS throughout the period analyzed, the mortality rate was 68% in 1982, 29% in 1996, and in the mid-30% range in 1997 and 1998.[26] Obviously, the decrease cannot be ascribed to widespread application of low tidal volume ventilation strategies, since the decline was observed prior to publication of the study reporting the value of using a "low stretch" ventilator protocol in 2000.[4] The improvement is likely attributable to enhancements in general ICU care, including prevention of nosocomial pneumonias and other infections, earlier institution of enteral nutrition, routine use of stress ulcer prophylaxis, and improved teamwork in the ICU.

TABLE 141-3 Estimated Annual Number of Deaths in the United States from Selected Causes

Cause	Number of Deaths
ARDS	59,000
Asthma	3311
HIV/AIDS	7638
Breast cancer	41,271
Leukemia	22,982
Lung cancer	156,614
Lymphoma	21,393
Ovarian cancer	14,312
Pancreatic cancer	37,371
Prostate cancer	27,929

Source: Data for ARDS are from Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685; all other are from CDC National Center for Health Statistics estimated number of deaths in 2011 (http://www.cdc.gov/nchs/).

Interestingly, the case fatality rate for patients with ARDS due to sepsis remained the same over the same time frame noted earlier, while that for patients with ARDS due to trauma or other causes decreased significantly. Mortality rates among subjects enrolled in ARDS Network trials[4,30–33] appear to have decreased from 35% (1996–1997) to 26% (2004–2005).[27,34] These findings were robust in adjusting for covariates, including severity of illness and use of low tidal volume ventilation. However, these rates were obtained from clinical trials in specialized centers, excluding large numbers of patients with high-risk comorbidities. Recent systematic reviews of clinical trials and more inclusive prospective cohort studies have drawn opposing conclusions.[28,35] Also, the previously noted study from the Mayo Clinic demonstrated a reduction in ARDS incidence, but it failed to show a change in mortality.[20] While it is unclear if survival from ARDS is improving, the mortality rate remains unacceptably high and represents a major public health problem. Furthermore, as the population of the United States becomes older, the incidence of those at risk for ARDS and ARDS-related death can be expected to rise.

Precipitating Causes

The severe, extensive lung inflammation characteristic of ARDS represents the common final pathogenic process in response to a large variety of precipitating causes,[36–39] resulting in either direct or indirect (systemic) lung injury.[40,41] In general, *direct* causes of ARDS include those that originate within the lung, such as aspiration of gastric contents or viral pneumonia. Examples of *indirect* causes include sepsis, ingested toxins, hypotension, and ischemia–reperfusion injury. Although some causes of ARDS may fit into either category (e.g., multilobar pneumonia with septic shock), this simple classification scheme is useful both for considering the many predisposing causes of ARDS and their varying mechanisms of lung injury and for future development of therapies aimed at different categories of ARDS. Table 141-4 lists precipitating causes of ARDS according to this construct.

TABLE 141-4 Common Direct and Indirect (Systemic) Precipitating Causes of ARDS

Direct Precipitating Causes	Indirect (Systemic) Precipitating Causes[a]
Aspiration of gastric fluids	Acute pancreatitis
Bacterial pneumonia (diffuse), e.g., Legionnaires' disease	Blood transfusions with transfusion-related acute lung injury (TRALI)
Chest trauma with lung contusion	Postcardiopulmonary bypass
Near drowning	Primary graft failure of lung transplantation
Pneumonia due to *Pneumocystis carinii*	Severe sepsis and septic shock
Toxic inhalations, e.g., smoke inhalation, inhaled crack cocaine	Toxic ingestions, e.g., aspirin, tricyclic antidepressants
Viral pneumonia, e.g., influenza, severe acute respiratory syndrome (SARS)	Trauma with multiple fractures and the fat-emboli syndrome

[a]*In indirect or systemic mechanism of lung injury, the lung injury results from deleterious effects on the alveolar epithelium by inflammatory or other mediators delivered via the pulmonary circulation.*

Source: Reproduced with permission from Christie JC, Lanken PN. Acute lung injury and the acute respiratory distress syndrome. In: Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care, 3d ed. New York, NY: McGraw-Hill; 2005.

FACTORS INFLUENCING RISK OF ARDS

Not all patients with an underlying cause (e.g., sepsis) of ARDS develop the syndrome. In addition to inherent risk differences within at-risk populations, specific clinical variables may be important.

Clinical variables found to be associated with an increased risk of ARDS include chronic alcohol abuse,[42] hypoproteinemia,[43] advanced age,[13] increased severity, and extent of injury or illness as measured by injury severity score (ISS) or APACHE score, hypertransfusion of blood products,[38,44] and possibly, cigarette smoking.[45,46] Diabetes mellitus and prehospitalization antiplatelet therapy appear to decrease the risk of ARDS.[47–49] The role of obesity in modifying ARDS risk is complicated, as excess soft tissue can render chest x-ray interpretation difficult; the potential role of obesity remains the subject of ongoing research. A higher body mass index has been associated with an increased incidence of ARDS; however, obesity has not been associated with a consistent change in mortality.[50–52] Since many studies of risk factors for ARDS are retrospective or based on a single center's experience, the consistency and generalizability of identified risk factors have not been confirmed. Nonetheless, the mechanistic underpinnings and potential therapeutic implications of these probable associations are the subject of ongoing research.

FACTORS INFLUENCING MORTALITY FROM ARDS

Clinical variables at the onset of ARDS that are associated with increased mortality include advanced age, lower Pa_{O_2}/FI_{O_2}, high plateau pressure (i.e., low respiratory system compliance),[53] greater extent of pulmonary infiltrates, sepsis, chronic liver disease, nonpulmonary organ dysfunction, increased global severity of illness, hypoproteinemia, and greater length of hospitalization prior to onset of ARDS.[13,43,53–58] In addition, an increased dead-space fraction has been identified as a risk factor for increased mortality, possibly indicating the importance of early loss of the pulmonary vascular bed as a sign of greater disease severity.[59,60] Although various precipitating causes of ARDS carry somewhat different prognoses, the strategy of low tidal volume ventilation utilized by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI)–sponsored ARDS Clinical Trials Network (ARDSNet) as part of its clinical trials appears to be equally efficacious in all subgroups.[4]

PREDICTING ARDS

Using the identified precipitating causes and modifying risk factors, investigators have recently developed and validated a lung injury prediction score (LIPS) aimed at identifying those at highest risk of developing ARDS early.[61,62] The LIPS was developed in a multicenter cohort of 5,584 hospitalized patients at risk for ARDS, among whom 7% eventually developed the syndrome. The LIPS is generated from the sum of points assigned for each of six predisposing conditions (shock, aspiration, sepsis, pneumonia, high-risk surgery, and high-risk trauma) and nine risk modifiers (alcohol abuse, obesity, hypoalbuminemia, chemotherapy, need for oxygen, tachypnea, hypoxia, academia, and diabetes mellitus). The negative predictive value for a score <4 was 97%, while the sensitivity and specificity for ARDS of a score >4 were 69% and 78%, respectively. While not perfect, the LIPS allows for the identification of a higher-risk population and may prove useful for studies of preventative interventions. The goal of identifying predictive and early indicators of ARDS is to shift the syndrome's treatment paradigm to strategies aimed at prevention and treatment at the earliest phases of development.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation and diagnosis of ARDS are fundamentally related to the syndrome's pathophysiologic changes, regardless of the underlying etiology. A brief description of the pathology and pathophysiology is provided before a detailed discussion of clinical aspects of the disorder. The reader is also referred to Chapter 140 for additional details on disease mechanisms.

PATHOLOGY AND PATHOPHYSIOLOGY

A number of interrelated mechanisms contribute to the development and clinical course of ARDS. Inflammatory cytokines, oxygen radicals, activation of coagulation and complement, platelet and immune cell activation, generation of proteases, and abnormal fluid fluxes resulting in edema fluid generation and defective epithelial alveolar fluid clearance have all been hypothesized to play a role in the early stages.[63–68] In addition, factors specific to apoptosis, edema fluid resolution, and fibrosis and repair, as well as the response to mechanical ventilation are likely to play a role in the pathophysiology of the later phases of ARDS.

Pathologically and clinically, ARDS can be divided into *early* and *late phases* of lung injury (Fig. 141-1).[69–72] In the early phase (first few hours or days), light microscopy shows interstitial and alveolar edema, capillary congestion, and intra-alveolar hemorrhage with minimal evidence of cellular injury. Electron microscopy reveals changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and denudation of the basement membrane. Inflammatory cell infiltration of the lung interstitium may also be seen. Protein-rich pulmonary edema and its clinical effects are most pronounced in the early exudative phase. Hyaline membranes containing condensed fibrin and plasma proteins form over the next several days. Later, in the exudative phase, inflammatory cells become more numerous within the lung interstitium, and extensive necrosis of type I alveolar epithelial cells is present. Pathologists refer to this constellation of findings as *diffuse alveolar damage* (DAD).

Pathophysiologically, in the exudative phase, alveolar edema and alveolar collapse, that is, atelectasis due to loss of normal surfactant-related stabilization of alveoli, interfere with oxygenation.[73,74] Surfactant is washed out of alveoli and inactivated by

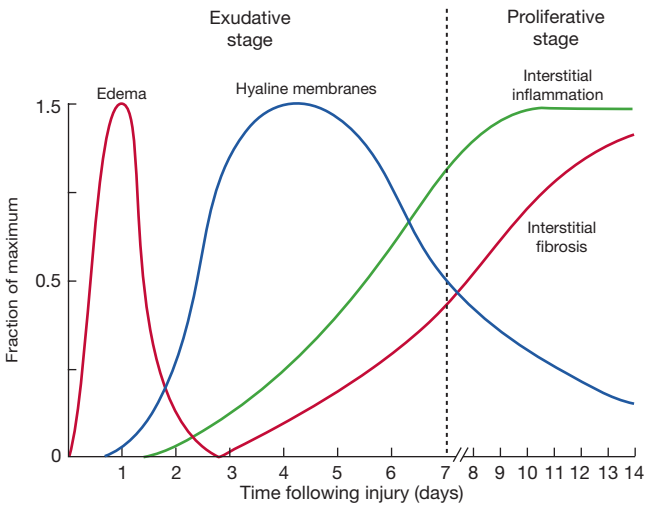


Figure 141-1 Schematic representation showing time course of evolution of the acute respiratory distress syndrome (ARDS). The early or exudative phase is characterized by a pulmonary capillary leak with interstitial and alveolar edema and hemorrhage followed by hyaline membrane formation. Within as short a period of time as 7 to 10 days, a proliferative phase may appear with marked interstitial and alveolar inflammation and cellular proliferation, followed by fibrosis and disordered healing (see text for discussion). *(Reproduced with permission from Katzenstein AA, Askin FB. Surgical Pathology of Non-Neoplastic Lung Diseases. 2nd ed. Philadelphia, PA: Saunders; 1990.)*

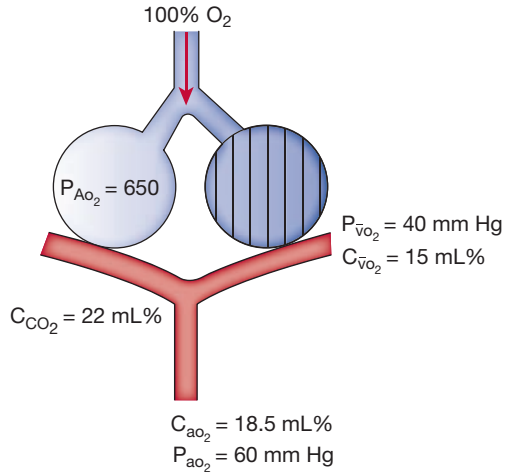


Figure 141-2 Diagram of a two-compartment model of lung perfusion and ventilation demonstrating basis for failure of oxygenation in ARDS. When large portions of the lung are nonventilated due to alveolar collapse or flooding (hatched area), blood flow to these units with mixed venous P_{O_2} ($P\bar{v}_{O_2}$) of 40 mm Hg and content of 15 vol. percent is effectively "shunted" through the lungs without being resaturated. Thus, despite a high concentration of supplemental oxygen (100% in this example) and high alveolar P_{O_2} in ventilated unit, these blood flows mix in accord with their oxygen contents, that is, the resulting left atrial blood has an oxygen content that is the weighted mean of the oxygen content of the shunted and nonshunted blood. In this example of a 50% shunt, the left atrial and systemic arteries have an arterial P_{O_2} of 60 mm Hg. Ca_{O_2}, arterial oxygen content; C_{CO_2}, capillaryoxygen content; $C\bar{v}_{O_2}$, mixed venous oxygen content; P_A, alveolar pressure; Pa_{O_2}, arterial P_{O_2}; $P\bar{v}_{O_2}$, partial pressure of oxygen in the mixed venous blood. *(Reproduced with permission from Christie JD, Lanken PN. Acute lung injury and the acute respiratory distress syndrome. In: Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care. 3rd ed. New York, NY: McGraw-Hill; 2005.)*

the alveolar edema. The hypoxemia in ARDS is typically resistant to supplemental oxygen, reflecting an increased right-to-left shunt (Fig. 141-2). Continued perfusion of alveoli that lack ventilation because of alveolar edema results in ventilation–perfusion ($\dot{V}/\dot{Q}$) ratios of zero, thereby defining physiologic shunt. Furthermore, the effects of this type of shunt are exacerbated by shunt-like contributions from alveoli with very low ventilation–perfusion ratios.

Disordered healing and proliferation of fibrous tissue dominate the late phase of ARDS or persistent ARDS, that is, the *proliferative or fibroproliferative* phase. Type II alveolar cells, fibroblasts, and myofibroblasts proliferate in this phase, which can occur as early as 7 to 10 days after initial injury. The late phase of ARDS is characterized by an increased dead-space fraction, high minute ventilation requirement, pulmonary hypertension, and further reduction in lung compliance.[75,76]

CLINICAL PRESENTATION

The development of ARDS usually follows a rapid course, occurring most often within 12 to 72 hours of the predisposing event.[38] At its onset, patients with ARDS often become anxious, agitated, and dyspneic. Inflammatory changes in the lung decrease lung compliance, which, in turn, leads to an increased work of breathing, small tidal volumes, and tachypnea. If breathing ambient air or low-flow supplementary oxygen, patients with ARDS typically have initial arterial blood gas results showing a Pa_{O_2} less than 50 to 55 mm Hg and pulse oximetry recordings of less than 85% arterial O_2 saturation. The hallmark of ARDS is hypoxemia that is resistant to oxygen therapy because of the large right-to-left shunt (Fig. 141-2). Initially, patients may be able to compensate by hyperventilating, thereby maintaining an acceptable Pa_{O_2} with an acute respiratory alkalosis. Typically, patients deteriorate over several hours, requiring endotracheal intubation and mechanical ventilation.

TABLE 141-5 Differential Diagnosis of Acute Hypoxemic Respiratory Failure (AHRF)

1. ARDS
2. Acute cardiogenic pulmonary edema
3. Bilateral aspiration pneumonia
4. Lobar atelectasis of both lower lobes
5. Severe unilateral lower lobe atelectasis, especially when patient is receiving vasodilators, such as intravenous nitrates, calcium-channel blockers, or sodium nitroprusside, that blunt hypoxic vasoconstriction
6. Acute loss of ventilation to one lung due to complete or near-complete obstruction of its mainstem bronchus, e.g., due to a mucus plug or blood clot
7. Loss of ventilation to one or both lungs due to large pneumothorax/pneumothoraces
8. Loss of ventilation to one or both lungs due to large pleural effusion(s)
9. Diffuse alveolar hemorrhage, especially in patients post–bone marrow transplantation
10. Massive pulmonary embolus
11. Acute opening of a patent foramen ovale in patient with pre-existing pulmonary hypertension

ARDS, acute respiratory distress syndrome.
Source: Reproduced with permission from Christie JD, Schmidt G, Lanken PN. Acute respiratory distress syndrome, ACP Smart Medicine: http://smartmedicine.acponline.org/content.aspx?gbosid=234. Philadelphia: American College of Physicians, 2004.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for acute hypoxemic respiratory failure, in general (Table 141-5), and for ARDS, in particular (Table 141-6), are extensive.[77] Identifying the specific etiology of the diffuse infiltrates in ARDS is important because several causes, for example, acute eosinophilic pneumonia or diffuse alveolar hemorrhage, have specific therapies. Table 141-6 lists the major clinical and diagnostic characteristics of these disorders.

The setting in which respiratory failure occurs usually provides important diagnostic information. ARDS commonly arise following development of a typical predisposing factor (Table 141-4). Sepsis, pneumonia, trauma, transfusion of blood products, and gastric aspiration account for the majority of cases.[38] When an inciting event is obvious and diagnostic criteria (Tables 141-1A and 141-1B) are met, establishment of a clinical diagnosis of ARDS is not difficult. Under such circumstances, management can be instituted immediately. However, in the absence of a clear predisposing event, or when conflicting or ambiguous information exists, the other causes listed in Table 141-6 should be considered, and relevant clues from the history and physical examination sought. For example, cardiogenic edema is most often accompanied by systolic left ventricular or valvular dysfunction, and the appropriate history and physical findings (e.g., a heart murmur or ventricular gallop) are often present. Electrocardiographic and laboratory-based evidence (e.g., serum troponin I levels) of cardiac ischemia suggest cardiogenic edema as

TABLE 141-6 Differential Diagnosis of ARDS

Disorder	Characteristics	Comments
Pulmonary edema due to left heart failure	History of cardiac disease, enlarged heart on chest radiograph, third heart sound.	Rapid improvement with diuresis and/or afterload reduction.
Noncardiogenic pulmonary edema	History of one or more precipitating causes (Table 141-4), crackles absent or not prominent, normal cardiac size on chest radiograph.	Usual etiology for ARDS. Rarely some patients with ARDS have no obvious precipitating cause.
DAH	Often associated with autoimmune diseases (e.g., vasculitis) or following bone marrow transplantation. Often patients do not have bloody sputum. Renal disease or other evidence of systemic vasculitis may be present. Hemosiderin-laden macrophages in bronchoalveolar lavage fluid can confirm diagnosis of DAH. May respond to apheresis, corticosteroids, or cyclophosphamide, depending on etiology.	May meet diagnostic criteria for ARDS (Tables 141-1A and 141-1B), but has different pathophysiology and management.
Acute eosinophilic pneumonia	Cough, fever, pleuritic chest pain, and myalgia are often present. Patients often do not have peripheral blood eosinophilia, but generally have greater than 15% eosinophils in bronchoalveolar lavage fluid. Usually responds rapidly to high-dose corticosteroid therapy.	May meet diagnostic criteria for ARDS (Tables 141-1A and 141-1B), but has different pathophysiology and management.
Lupus pneumonitis	Usually associated with active lupus. May respond to high-dose corticosteroid therapy or cyclophosphamide.	May meet diagnostic criteria for ARDS, but has different pathophysiology and management.
AIP	Slower onset than ARDS (over 4–6 weeks) with progressive course. However it may present in advanced state, mimicking ARDS.	Associated with >90% mortality. AIP includes Hamman–Rich syndrome.
Pulmonary alveolar proteinosis (PAP)	Slower onset than ARDS (over 2–12 months) with progressive course. Can be treated with whole lung lavage.	Characteristic "crazy paving" pattern on high-resolution CT scan of chest.
Bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia	May be precipitated by viral syndrome. Slower onset than ARDS (over >2 weeks) with progressive course. However it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy.	
Hypersensitivity pneumonitis	Typically slower onset than ARDS (over weeks) with progressive course. However, it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy and removal from offending agent.	
Leukemic infiltration	May be rapid in onset during active disease states. Usually leukemia is clinically apparent.	
Drug-induced pulmonary edema and pneumonitis	May follow use of heroin, other opioids, overdose of aspirin, tricyclic antidepressants, or exposure to paraquat.	May progress to overt ARDS.
Acute major pulmonary embolus (PE)	Occurs acutely, occasionally accompanied by severe hypoxemia that may be resistant to O_2 therapy like ARDS, and by hypotension, requiring pressors, mimicking ARDS with sepsis. Patients typically have risk factors for acute PE and may not have common precipitating causes of ARDS.	Chest radiograph in ARDS should have bilateral infiltrates consistent with pulmonary edema. Chest radiograph in acute major PE may have unilateral or no infiltrates. Acute major PE needs a confirmatory study, e.g., CT scan with pulmonary embolism protocol.
Sarcoidosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Historical features and the frequent presence of hilar adenopathy in sarcoidosis usually eliminate confusion with ARDS.
Interstitial pulmonary fibrosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Prior chest radiographs and a history of chronic and progressive dyspnea characterize the collection of diseases causing interstitial pulmonary fibrosis.

AIP, acute interstitial pneumonia; ARDS, acute respiratory distress syndrome; CT, computed tomography; DAH, diffuse alveolar hemorrhage.
Source: Reproduced with permission from Christie JD, Schmidt G, Lanken PN. Acute respiratory distress syndrome, ACP Smart Medicine: http://smartmedicine.acponline.org/content.aspx?gbosid=234. Philadelphia: American College of Physicians, 2004.

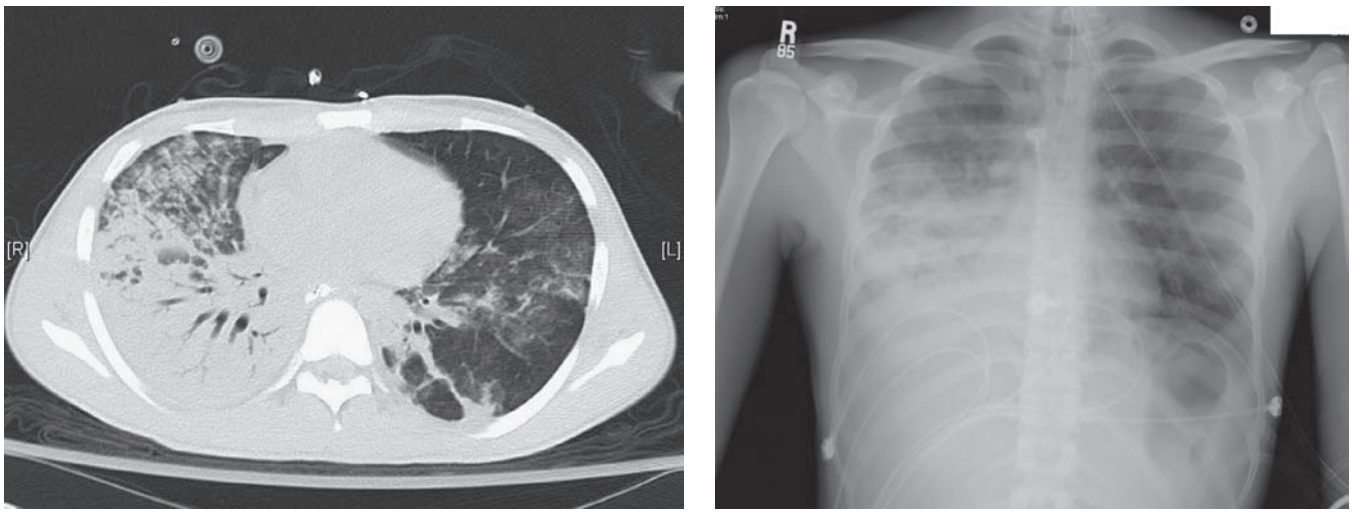
a likely cause. Additional important tests that help to differentiate ARDS from other causes of acute hypoxemic respiratory failure are discussed subsequently.

■ APPROACH TO CLINICAL DIAGNOSIS

A number of diagnostic methods are extremely valuable in evaluating suspected ARDS. Each is briefly described.

Chest Radiograph

The chest radiograph is a simple and widely available test used to assess patients with acute hypoxic respiratory failure. In cases of *established* ARDS, the chest radiograph typically demonstrates findings of diffuse, bilateral alveolar infiltrates consistent with pulmonary edema (Fig. 141-3). However, especially early in the course of the disorder, the infiltrates associated with ARDS may



A B

Figure 141-3 Chest CT and plain radiograph in ARDS. **A.** Chest CT scan reveals asymmetric lung injury, with dense consolidation at the right base, patchy alveolar infiltrates in the right anterior lung field, and patchy ground-glass infiltrates throughout the right lung. **B.** Chest radiograph obtained concurrently with chest CT scan shown in panel (**A**). Dense infiltrates at right base, patchy infiltrates in the right upper lung zone, and more subtle infiltrates in the left lung are demonstrated. The panels illustrate the subtle findings of lung injury that are more apparent on the CT scan than on the chest radiograph.

be variable: mild or dense, interstitial or alveolar, patchy or confluent.[7] In addition, the radiographic infiltrates may not correlate well with the degree of hypoxemia. For example, a patient with early ARDS may have profound hypoxemia in the setting of patchy asymmetrical infiltrates that may be interpreted as pneumonia or segmental atelectasis.

Routine chest radiographs cannot reliably distinguish hydrostatic edema, that is, cardiogenic edema, from ARDS. Nonetheless, several criteria suggest *cardiogenic* edema: increased heart size, increased width of the vascular pedicle, vascular redistribution toward upper lobes, the presence of septal lines, or a perihilar (bat's wing) distribution of the edema.[78] Lack of these findings, in conjunction with patchy peripheral infiltrates that extend to the lateral lung margins, suggests ARDS. In the proper clinical setting, despite a variable radiographic appearance, the presence of bilateral infiltrates and moderate or severe hypoxemia (Pa_{O_2}/FI_{O_2} ≤300 mm Hg) should raise the possibility of ARDS.

Laboratory Studies

Although no laboratory test is specific for the diagnosis of ARDS, arterial blood gas analysis is essential for confirming the diagnosis.[9] Pa_{O_2}/FI_{O_2} is markedly abnormal in patients with ARDS (Tables 141-1A and 141-1B). In addition to the profound oxygen therapy–resistant hypoxemia that is the hallmark of ARDS, acute respiratory alkalosis may also occur in the early stage. If a patient with ARDS then develops respiratory muscle fatigue, hypercapnia results. In late-stage ARDS, patients typically have increased minute ventilation requirements due to an increasing dead-space fraction, despite possible improvement in oxygen exchange.

In addition to arterial blood gas measurements, several other laboratory studies may be helpful in investigating other causes of respiratory failure and evaluating additional aspects of critical illness associated with ARDS. For example, cardiac enzymes (creatine phosphokinase and troponins) are useful for evaluating the presence of myocardial infarction or cardiac ischemia in patients at risk because of increased age or other factors. The results should be interpreted in conjunction with electrocardiographic findings, since elevations in cardiac enzymes, especially troponins, have been reported in patients with sepsis or septic shock in the absence of coronary artery disease.[79,80]

Another cardiac-related laboratory test that may be useful in this clinical context is plasma brain natriuretic peptide (BNP), which is secreted by the cardiac ventricles, and, to a lesser extent, the atria. BNP measurements are often utilized in the evaluation of acute shortness of breath in patients presenting to an emergency department.[81] In this group, a BNP greater than 500 pg/mL indicates that CHF is likely with a positive predictive value greater than 90%. In the same group, a BNP less than 100 pg/mL suggests that congestive heart is unlikely with a negative predictive value greater than 90%. However, interpretation of an elevated BNP in patients who are critically ill is problematic. Reports indicate that BNP increases with renal failure, and that elevations of BNP greater than 500 pg/mL may occur in patients with sepsis and normal left ventricular function.[82] Nonetheless, one can reasonably exclude a cardiac cause for acute pulmonary edema in patients in the intensive care unit if BNP is less than 100 pg/mL.

Echocardiography

Echocardiography is a useful noninvasive method to evaluate potential cardiac causes of acute hypoxemic respiratory failure.[83] Cardiogenic pulmonary edema is suggested by echocardiographic findings of mitral valve stenosis or regurgitation, left ventricular dilatation and systolic dysfunction, or regional left ventricular wall motion abnormalities. Although these findings do not rule out coexisting lung injury, they are helpful in the initial evaluation and management, even in the presence of ARDS.

Invasive Hemodynamic Monitoring

Although pulmonary artery catheterization has been performed often in patients with pulmonary edema, the benefits of the procedure are controversial and the topic of recent investigations (see Chapter 147, Hemodynamic and Respiratory Monitoring in Acute Respiratory Failure).[11,84] Several studies have demonstrated that physician interpretation of data obtained from PACs is inconsistent and often erroneous.[85–87] Previous definitions of ARDS have suggested the measurement of PAOP to distinguish ARDS from cardiogenic

pulmonary edema[3]; however, the recently accepted Berlin definition of ARDS eliminates such suggestions, recognizing the problems inherent in use of PACs.[9] Studies have demonstrated that many patients who originally met AECC criteria for ARDS (i.e., had a PAOP ≤18 mm Hg) often have subsequent measurements with a PAOP >18 mm Hg.[12,88] Furthermore, the Berlin definition recognizes the possibility of concomitant ARDS and cardiogenic edema.

Results of the ARDSNet Fluid and Catheter Treatment Trial (FACCT) support the removal of PAOP criteria from the definition of ARDS, acknowledging that a threshold of 18 mm Hg is arbitrary.[11] FACTT was a large, randomized clinical trial that used a two-by-two factorial design to test a fluid-conservative management strategy against a fluid-liberal management strategy in ARDS. The study also assessed safety and efficacy of a central venous catheter (CVC) or PAC to guide fluid management. In FACTT, 29% of 513 patients enrolled in the PAC arm of the trial were found to have a PAOP greater than 18 mm Hg at the time of initial measurement (following passage of the catheter shortly after enrollment and randomization). Before enrollment, FACTT investigators believed that these patients lacked a primary cardiogenic cause for their pulmonary edema. Approximately one-half of the patients had PAOPs of 19 or 20 mm Hg. Since the vast majority (97%) of this group had a normal cardiac index (≥2.5 L/m^2/min) and a mortality similar to other subjects in FACTT, the elevated PAOP (>18 mm Hg) likely reflected intravascular volume loading, rather than cardiogenic pulmonary edema.

Bronchoalveolar Lavage

Bronchoscopy with bronchoalveolar lavage (BAL) is an important tool in the evaluation of patients who have ARDS of unclear origin. In general, BAL can be performed safely in patients with ARDS, except in those with a very low Pa_{O_2} or those requiring high levels of PEEP. The principal reason for performing bronchoscopy in ARDS is to rule in or rule out acute processes that may have specific therapies.

For example, acute eosinophilic pneumonia is a rare disorder characterized by diffuse eosinophilic infiltrates in the lungs (Table 141-6).[89] When the precipitating cause for ARDS is uncertain, performance of BAL and measurement of the percent of eosinophil count in the lavage fluid is helpful in establishing a diagnosis of this corticosteroid-responsive disorder.

Likewise, BAL may be diagnostic for diffuse alveolar hemorrhage (see Chapter 68, Alveolar Hemorrhage Syndromes).[90] In this case, the bronchoscopy may or may not reveal fresh blood in the trachea and major bronchi. However, BAL generally demonstrates blood-tinged fluid, which contains red blood cells and hemosiderin-laden macrophages. Diffuse alveolar hemorrhage may occur following bone marrow transplantation or as a result of rheumatologic or other immunologic disorders, including Goodpasture syndrome, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), systemic lupus erythematosus, or antiphospholipid antibody syndrome.

Lung Biopsy

Routine lung biopsy is not recommended in ARDS; however, lung biopsy should be considered if alternative etiologies of respiratory failure cannot be adequately excluded. While many patients with ARDS are not sufficiently stable to undergo a lung biopsy, the safety of a surgical lung biopsy has been demonstrated in a highly selective group of patients with hypoxic respiratory failure.[91,92] In general, lung biopsy should be reserved for a highly selective group of patients where alternative diagnoses are possible and would significantly change management and prognosis.

APPROACH TO TREATMENT

The general approach to treatment of ARDS includes addressing precipitating causes and other concurrent clinical issues, ensuring adequate oxygenation, careful implementation of a lung-protective ventilator strategy, prudent fluid and hemodynamic management, special patient positioning coupled with the so-called "lung recruitment" maneuvers, and a multitude of other measures, including pharmacologic considerations. Each is discussed subsequently.

TABLE 141-7 Goals of Management of Patients with ARDS

Treatment of respiratory system abnormalities
Diagnose and treat the precipitating cause of ARDS, if possible (Table 141-8)
Maintain oxygenation, preferably using nontoxic $F_{I_{O_2}}$ (<0.7), PEEP, or mechanical ventilation
Prevent ventilator-induced lung injury (VILI) by using a low tidal volume ventilatory strategy (Table 141-9) with a limit (≤30 cm H_2O) on static end-inspiratory airway pressure (plateau pressure)
Keep pH in normal range without compromising goal to prevent VILI (but reverse a life-threatening acidosis, even if it prevents meeting goal to prevent VILI)
Enhance patient–ventilator synchrony and patient comfort by use of sedation, amnesia, opioid analgesia, and pharmacologic paralysis, if necessary
Liberate or wean from mechanical ventilation when patient can breathe without assisted ventilation
Treatment of nonrespiratory system abnormalities
Support or treat other organ system dysfunction or failure
General critical care (preventive and homeostatic measures)
Adequate early nutritional support

■ GOALS OF MANAGEMENT

Management of patients with ARDS can be complicated and challenging because clinicians are often faced with simultaneous failure of both respiratory and nonrespiratory organ systems (Table 141-7). Unfortunately, only a limited set of controlled clinical trials are available to support an evidence-based approach. For example, even large, multicenter, randomized clinical trials, such as those done by ARDSNet, are limited in the number of variables that can be tested. As a result, patient management rests on a combination of relevant evidence-based medicine, extrapolations from basic and clinical research, and experience-based approaches.

■ DIAGNOSIS AND TREATMENT OF PRECIPITATING CAUSES AND OTHER COMORBIDITIES

The first step in the therapy of ARDS is identification and treatment of the precipitating cause(s) and any other life-threatening medical or surgical issues (Fig. 141-4).

Since ARDS is a *syndrome* based on nonspecific radiographic and physiologic criteria, establishing a diagnosis of ARDS is *not* equivalent to diagnosing the precipitating cause. The fact that early identification and treatment directed at the inciting cause(s) of ARDS are imperative for the resolution of lung injury and respiratory failure cannot be overemphasized. Treatable inciting causes of ARDS include a variety of infectious and noninfectious disorders (Table 141-8).

■ MANAGEMENT OF RESPIRATORY FAILURE

Management of respiratory failure in ARDS rests on assurance of adequate oxygenation and carefully crafted ventilatory strategies, as outlined in the following sections.

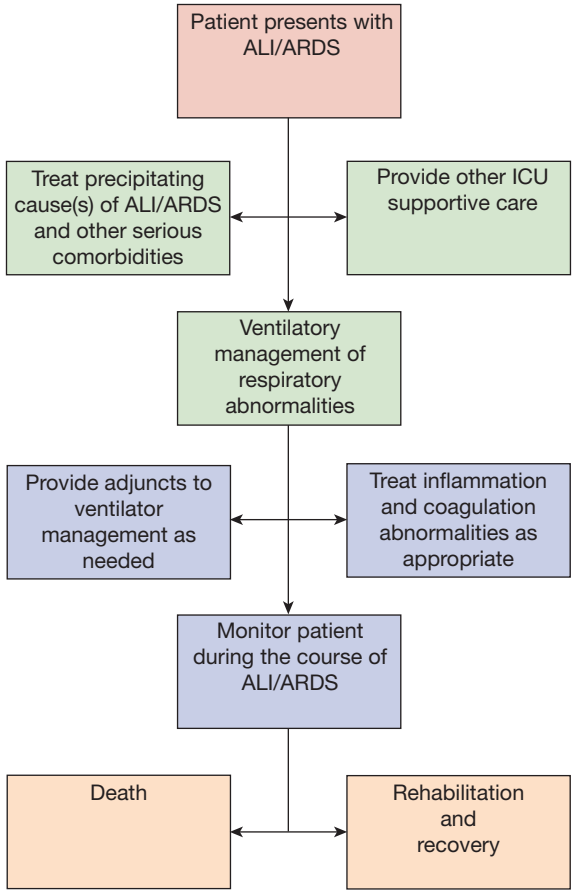


Figure 141-4 Summary of treatment approach to ARDS. Note that, "Treat inflammation and coagulation abnormalities as appropriate," is currently limited. In the ARDSNet "LaSRS" clinical trial, physiologic improvement, but no mortality benefit, was found with high-dose corticosteroid therapy for persistent (late phase) ARDS (see text for details). *(Reproduced with permission from Christie JD, Lanken PN. Acute lung injury and the acute respiratory distress syndrome. In: Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care. 3rd ed. New York, NY: McGraw-Hill; 2004.)*

TABLE 141-8 Treatable Inciting Causes of ARDS

Infectious etiologies
Bacterial or other sepsis, e.g., fungemia, responsive to antimicrobial therapy
Diffuse bacterial pneumonias, e.g., Legionella species
Diffuse viral pneumonias, e.g., cytomegalovirus, influenza A
Diffuse fungal pneumonias, e.g., Candida species, Cryptococcus
Pneumocystis jiroveci pneumonia
Other diffuse lung infections, e.g., military tuberculosis
Noninfectious etiologies
Diffuse alveolar hemorrhage post–bone marrow transplantation
Diffuse alveolar hemorrhage due to vasculitis, e.g., Goodpasture syndrome
Acute eosinophilic pneumonia
Lupus pneumonitis
Toxic drug reactions, e.g., aspirin

Source: Reproduced with permission from Christie JD, Lanken PN. Acute lung injury and the acute respiratory distress syndrome. In: Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care, 3rd ed. New York, NY: McGraw-Hill; 2004.

Maintaining Adequate Oxygenation

As noted, the pathophysiologic hallmark of ARDS is hypoxemia that is resistant to oxygen therapy. Maintaining adequate arterial oxygenation is the primary goal of both traditional and newer ("lung-protective") approaches to assisted ventilation.

As expected with shunt physiology, administration of supplemental oxygen provided by high-flow oxygenation systems, for example, a nonrebreather face mask, is generally ineffective in reversing the oxygenation deficit. Exceptions to this rule are some patients with mild or transient cases of ARDS that are otherwise uncomplicated by other organ system failures.

Upon intubation, most patients with ARDS require high levels of $F_{I_{O_2}}$ to maintain oxygenation; however, high concentrations of oxygen may potentially be toxic. While not studied adequately in patients with ARDS, studies of animals and healthy humans have demonstrated the toxic effects of oxygen therapy within hours of its initiation.[93,94] Given the theoretical concern for oxygen toxicity, PEEP is employed to improve oxygenation by reducing physiologic shunt. When utilized in sufficient amounts, PEEP generally results in some degree of correction of the hypoxemia in patients with ARDS, thereby allowing $F_{I_{O_2}}$ to be lowered from high, potentially toxic concentrations. Although PEEP is usually used in conjunction with mechanical ventilation, in selected cases of mild ARDS it may be effective when applied by means of a continuous positive airway pressure (CPAP) mask or as the lower level of bilevel noninvasive ventilation. The effect of PEEP-induced improvement in arterial oxygenation is attributed predominantly to recruitment of collapsed alveoli. However, application of PEEP may also mediate a redistribution of alveolar fluid into the interstitium and decrease the absolute magnitude of shunt by reducing cardiac output.

Acutely ill patients in intensive care units typically receive assisted ventilation via an endotracheal tube. In selected non-ARDS disorders, for example, COPD or acute cardiogenic pulmonary edema, noninvasive ventilation has been shown to be as effective as invasive ventilation.[95,96] Although the routine use of noninvasive ventilation for patients with ARDS lacks compelling evidence, the data are limited. In a small randomized trial of 40 patients with mild ARDS (formally referred to as ALI), patients receiving noninvasive ventilation were less likely to require intubation than those receiving supplemental oxygen alone; however, the study was small and not fully blinded.[97] One reason for limited study of noninvasive ventilation in ARDS is the high incidence of concomitant, nonrespiratory organ failure (e.g., multisystem organ failure due to septic shock). Except for select subgroups, for example, immunosuppressed patients with hypercapnic respiratory failure who are hemodynamically stable, use of noninvasive ventilation for patients with ARDS generally should be avoided.

Lung-Protective Mechanical Ventilation

As described in Chapter 140, over the past 30 years investigators have convincingly shown that large tidal volumes delivered during mechanical ventilation can injure lungs of normal animals, producing a pathologic pattern resembling ARDS in humans.[98,99]

In animal models of ALI, use of large tidal volume ventilation has been found to augment pre-existing injury. In addition, repetitive opening and closing of alveoli during inspiration and expiration induces ALI in normal animals.[100,101] The injury can be prevented by application of sufficient PEEP. Finally, overexpansion of alveoli in normal lungs of sheep induces multiorgan failure,[102] with studies in other species showing that lung overexpansion results in systemic

release of proinflammatory cytokines—providing a likely mechanism for these remote deleterious effects.[103–105] These observations support the concept that the lung is an "engine of inflammation."

Concurrent with the previously described observations, clinical investigators studying patients with ARDS using computed tomography observed that, in contrast to the typical diffuse-appearing pattern noted on plain chest radiographs, the pattern of consolidation, atelectasis, and normal alveoli is actually heterogeneous (Fig. 141-3).[106] The key physiologic implication of these observations is that a ventilator-delivered tidal volume is preferentially distributed to the open alveoli, which represent only a small fraction of the entire lung.[107] In referring to this lung fraction as "the baby lung" investigators emphasized the potential danger of delivering traditional tidal volumes of 10 to 15 mL/kg actual body weight and the associated risk for alveolar overexpansion and lung injury. Notably, tidal volumes of 10 to 15 mL/kg actual body weight (equivalent to approximately 12 to greater than 15 mL/kg predicted body weight) were used originally in critically ill patients with ARDS as a complementary strategy to PEEP in recruiting atelectatic alveoli.

These productive lines of basic and clinical research strongly support the hypothesis that mechanical ventilation using limited tidal volumes should be less injurious to the lungs of patients with ARDS and should result in better outcomes (i.e., decreased mortality) compared with use of traditional, large tidal volume ventilation. Several randomized controlled trials have been conducted to address the role of low tidal volume ventilation in ARDS, including the landmark ARDSNet trial, ARMA, discussed in detail below.[4,108] Recent meta-analyses of multiple trials support a low tidal volume ventilation approach to reduce mortality in ARDS.[109,110]

In summary, the goals of lung-protective ventilation are to avoid injury due to overexpansion of alveoli during inspiration (so-called "volu-trauma") and injury due to repetitive opening and closing of alveoli during inspiration and expiration (so-called "atelecta-trauma") (Fig. 141-5). The injurious effects of mechanical

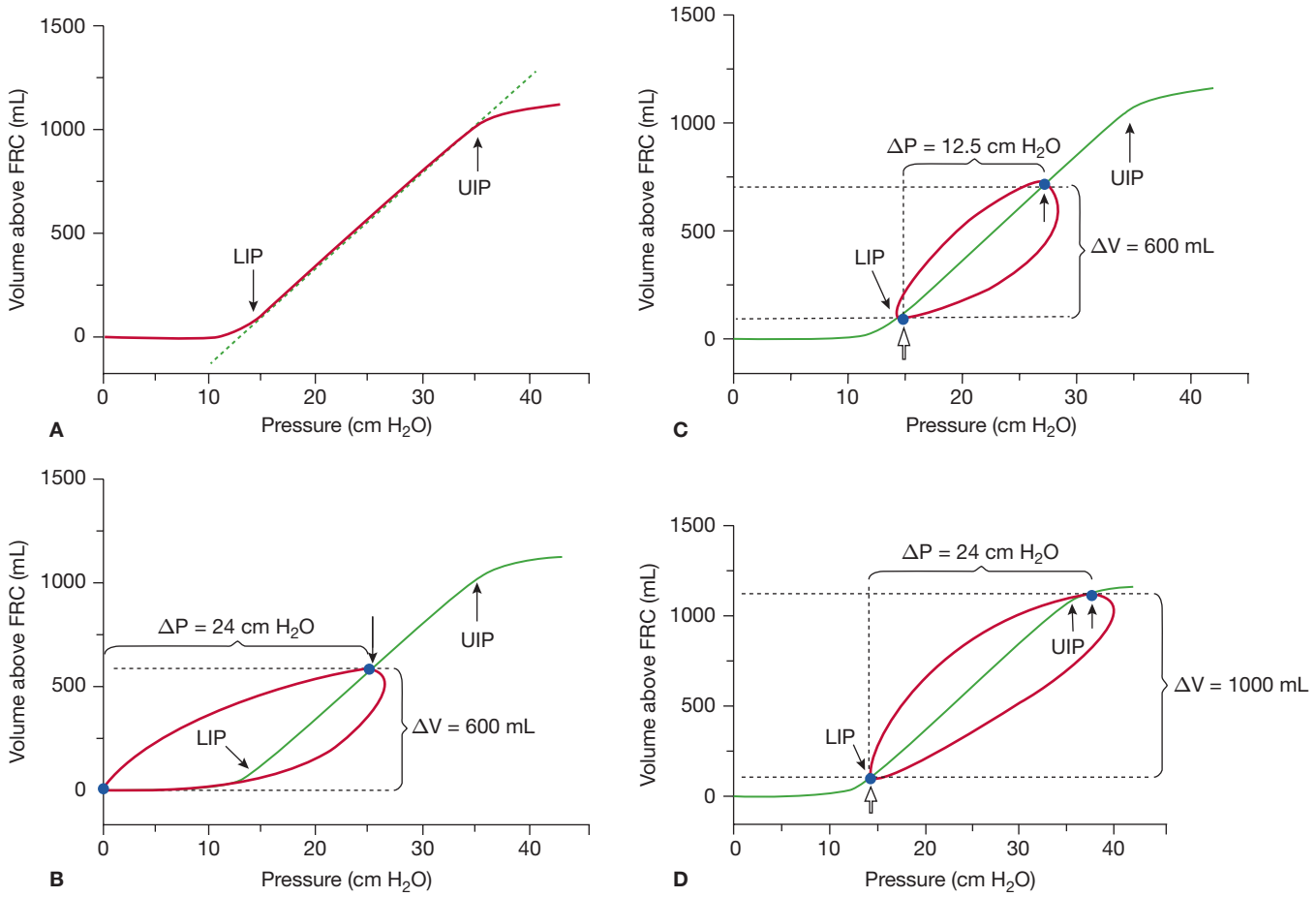


Figure 141-5 **A.** Schematic inspiratory static pressure–volume (P–V) curve of the respiratory system (lung and chest wall combined) in ARDS. Lower inflection point (LIP) is approximately 14 cm H_2O, and upper inflection point (UIP) is approximately 35 cm H_2O. Abscissa is respiratory system recoil pressure; ordinate is lung volume above functional residual capacity (FRC). **B.** Same static P–V curve as (**A**), plus dynamic P–V curve of 600 mL tidal volume starting below the LIP (PEEP = 0). This tidal volume results in a plateau pressure *(closed arrow)* below the UIP (24 cm H_2O). Static compliance (Cstat = $\Delta V/\Delta P$ = 600 mL/24 cm H_2O) is 25 mL/cm H_2O. **C.** PEEP of 15 cm H_2O has moved the starting point for the 600 mL tidal volume up the static P–V curve to a new FRC *(open arrow)*, which is at the LIP. The tidal volume results in a plateau pressure of 27.5 cm H_2O *(closed arrow)*, which is well below the UIP. Cstat ($\Delta V/\Delta P$ = 600 mL/12.5 cm H_2O) is increased to 48 mL/cm H_2O. **D.** Dynamic P–V curve of a 1000 mL tidal volume, starting at 14 cm H_2O PEEP, results in a plateau pressure of 37.5 cm H_2O *(closed arrow)*. Despite an increase in Cstat ($\Delta V/\Delta P$ = 1000 mL/24 cm H_2O = 41.5 mL/cm H_2O), compared with Cstat derived from the 600 mL tidal volume in (**B**), the plateau pressure associated with the 1000 mL tidal volume exceeds the UIP. Delivery of an inflation volume that results in a plateau pressure exceeding the UIP implies alveolar overdistension and is believed to put the lung at risk for ventilator-induced lung injury (see text). *(Reproduced with permission from Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. The Intensive Care Unit Manual. Philadelphia, PA: Saunders; 2001.)*

ventilation on the lung have been referred to as ventilator-induced lung injury or "VILI." The term "bio-trauma" encompasses the direct lung injury and the concomitant release of inflammatory cytokines that produce remote cell death or organ injury.[111] Clinical strategies underlying contemporary applications of mechanical ventilation in treatment of ARDS are described subsequently.

ARDSNet Ventilator Strategies: Low Versus Traditional Tidal Volumes Based on the aforementioned considerations, the ARDSNet conducted a randomized trial (ARMA) in the mid-to-late 1990s to test the hypothesis that low tidal volume ventilation, combined with limited end-inspiratory (plateau) pressure, would lower mortality and ventilator days among survivors of ARDS compared with use of traditional tidal volumes.[4] The trial included 861 subjects. The low tidal volume arm consisted of a tidal volume of 6 mL/kg predicted body weight, as long as the end-inspiratory pressure (Pplat) was ≤30 cm H_2O; if Pplat exceeded 30 cm H_2O, the tidal volume could be decreased to as low as 4 mL/kg. The traditional tidal volume arm used a tidal volume of 12 mL/kg predicted body weight, as long as the Pplat remained <50 cm H_2O. Both arms included explicit goals and protocols as the bases for ventilator adjustments and determination of the time and means of weaning (Table 141-9).

Important results of the ARMA trial are summarized in Table 141-10. The difference in actual tidal volumes resulted from protocol-driven target tidal volumes in each study arm. As expected, the mean plateau pressure for the lower tidal volume group was <30 cm H_2O (25 cm H_2O), since the protocol required decreasing the tidal volume from 6 mL/kg predicted body weight to as low as 4 mL/kg if Pplat exceeded 30 cm H_2O. Of note, the traditional tidal volume group had a mean Pplat of 33 cm H_2O on study day 1 – a value less than the threshold of 35 cm H_2O that some clinicians had believed represented a safe threshold.

Despite the fact that the clinical trial used an arbitrary threshold of 30 cm H_2O for Pplat in the lower tidal volume arm, it should not be assumed that any Pplat ≤30 cm H_2O is safe. If a "safe" upper limit of Pplat exists, its value is unknown. Lack of such a safe threshold is supported by the finding of an absence of any significant interaction between differences in mortality and quartiles of static respiratory compliance or quartiles of plateau pressures (Fig. 141-6). These results suggest that the lower tidal volume ventilatory strategy tends to be effective across a wide range of baseline static compliances and plateau pressures. Likewise, a statistical model of mortality proportion versus day 1 Pplat which combined data from both arms of this clinical trial suggests that, in general, the lower the Pplat, the lower the associated mortality (Fig. 141-7).[112]

These considerations are important, since some clinicians may believe that they can achieve the improved mortality rate simply by lowering tidal volumes to the point where Pplat is at or slightly less than 30 cm H_2O, instead of following the ARDSNet low tidal volume strategy of using a tidal volume of 6 mL/kg predicted body weight. In addition, recognition of the need to use predicted, rather than actual, body weight is important, since the latter has been estimated

TABLE 141-9 NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume Ventilation Strategy

Part I: Ventilator Setup and Adjustment

1. Calculate ideal body weight (IBW)[a] (also known as predicted body weight [PBW])
2. Use Assist/Control mode and set initial TV to 8 mL/kg IBW (if baseline TV >8 mL/kg)
3. Reduce TV by 1 mL/kg at intervals ≤2 h until TV = 6 mL/kg IBW
4. Set initial rate to approximate baseline $\dot{V}_E$ (but not >35 bpm)
5. Adjust TV and RR to achieve pH and plateau pressure (Pplat) goals below.
6. Set inspiratory flow rate above patient demand (usually >80 L/min); adjust flow rate to achieve goal of I:E ratio of 1:1.0–1.3

Part II: Oxygenation Goal: Pa_{O_2} = 55–80 mm Hg or Sp_{O_2} = 88–95%

1. Use these incremental $F_{I_{O_2}}$-PEEP combinations to achieve oxygenation goal:

$F_{I_{O_2}}$	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
$F_{I_{O_2}}$	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

Part III. Plateau Pressure (Pplat) goal: ≤30 cm H_2O

1. Check Pplat (use 0.5-s inspiratory pause), Sp_{O_2}, total RR, TV, and ABG (if available) at least every 4 h and after each change in PEEP or TV.
2. If Pplat >30 cm H_2O, decrease TV by 1 mL/kg steps (minimum 4 mL/kg IBW)
3. If Pplat <25 cm H_2O and TV <6 mL/kg, increase TV by 1 mL/kg until Pplat >25 cm H_2O or TV = 6 mL/kg.
4. If Pplat <20 cm H_2O and breath stacking occurs, one may increase TV in 1 mL/kg increments (to a maximum of 8 mL/kg)

Part IV. pH Goal: 7.30–7.45

Acidosis management: pH <7.30

1. If pH = 7.15–7.30, increase RR until pH >7.30 or Pa_{O_2} <25 mm Hg (maximum RR = 35); if RR = 35 and Pa_{CO_2} <25 mm Hg, may give NaH_{CO_3}
2. If pH <7.15 and NaH_{CO_3} considered or infused, TV may be increased in 1 mL/kg steps until pH >7.15 (Pplat goal may be exceeded)

Alkalosis management: pH >7.45: decrease RR, if possible

ABG, arterial blood gas; RR, respiratory rate on ventilator; Sp_{O_2}, Oxygen saturation by pulse oximetry; TV = tidal volume; $\dot{V}_E$, minute ventilation.

[a]*Male IBW, 50 + 2.3 (height [inches] – 60); female IBW, 45.5 + 2.3 (height [inches] – 60).*

Source: Reproduced with permission from the NIH NHLBI ARDS Clinical Trials Network (Complete protocol is available at www.ardsnet.org) and Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. The Intensive Care Unit Manual. Philadelphia, PA: Saunders Co.; 2001.

TABLE 141-10 Results of NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume Versus Traditional Tidal Volume Clinical Trial ("ARMA")

Variable or Outcome	Units	Low Tidal Volume Ventilatory Strategy Mean ± SD	Traditional Tidal Volume Ventilatory Strategy Mean ± SD	*p* Value
Tidal volume on day 1	mL/kg PBW	6.2 ± 0.9	11.8 ± 0.8	<0.05
Plateau pressure on day 1	cm H_2O	25 ± 7	33 ± 9	<0.05
PEEP on day 1	cm H_2O	9.4 ± 3.6	8.6 ± 3.6	<0.05
Pa_{CO_2}: $F_{I_{O_2}}$ on day 1		158 ± 73	176 ± 76	<0.05
Pa_{CO_2} on day 1	mm Hg	40 ± 10	35 ± 8	<0.05
Death before discharge or 180 days	%	31.0	39.8	0.007
Breathing without assistance at day 28	%	65.7	55.0	<0.001
No. of ventilator-free days by day 28		12 ± 11	10 ± 11	0.007
No. of days without failure of nonpulmonary systems by day 28		15 ± 11	12 ± 11	0.006

PBW, predicted body weight (see footnote of Table 145-9 for details); PEEP, positive end expiratory pressure; SD, standard deviation; ventilator-free days by day 28, number of days alive and not receiving assisted ventilation between days 1 and 28.
Source: Adapted with permission from Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301–1308.

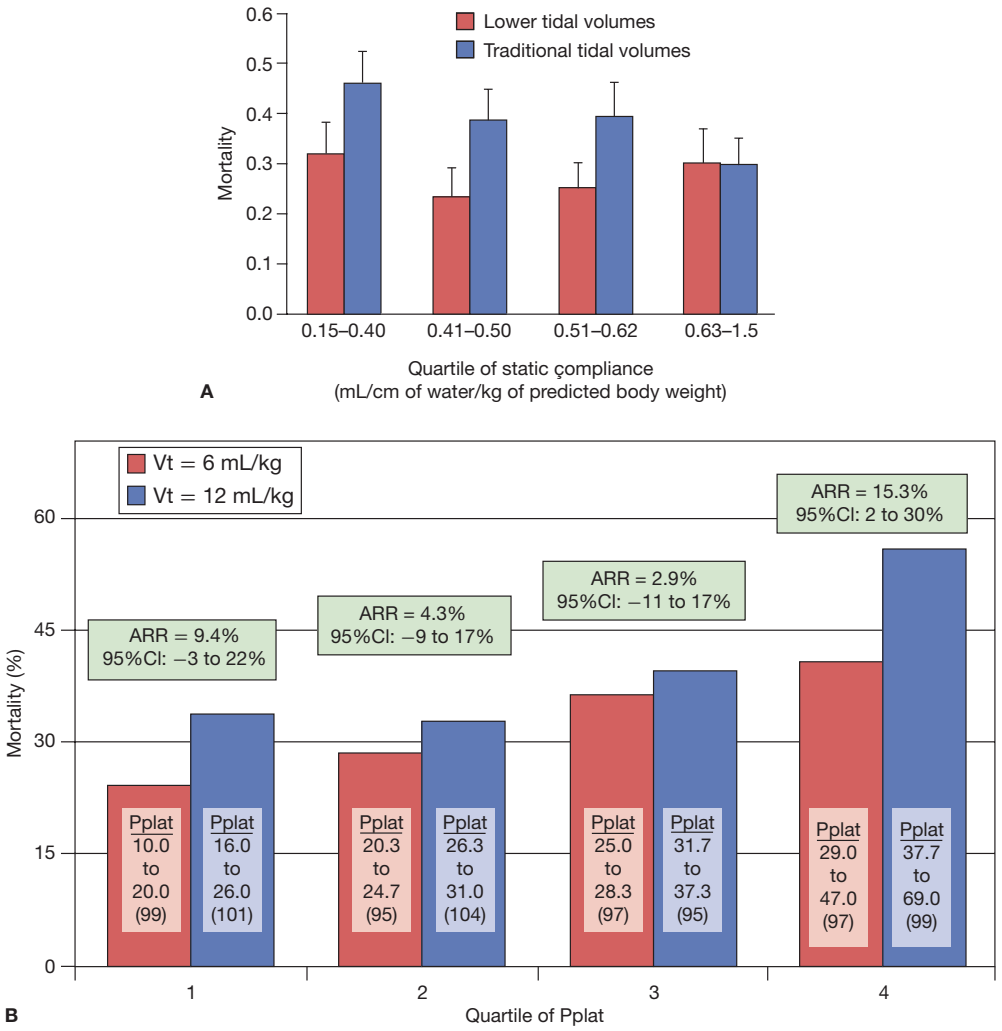


Figure 141-6 ARDSNet ARMA study. Mortality according to quartiles of treatment group (**A**) and end-inspiratory pressure (plateau pressure, Pplat) (**B**) on day 1 in 787 subjects for whom Pplat data are available. Pplat was measured using protocol-dictated tidal volumes. Subjects with the stiffest lungs are likely to have Pplat in the fourth quartile (far right). Range of Pplat (cm H_2O) and number of subjects (parentheses) are shown in each bar of the graph (ARR, (absolute risk reduction; CI, confidence interval). Lower tidal volume ventilation appears to benefit patients with ARDS across a range of Pplat. The hypothesis that a "safe" upper limit exists for Pplat, below which ventilator-induced lung injury does not occur, is *not* supported by the data. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172(10):1241–1245.)*

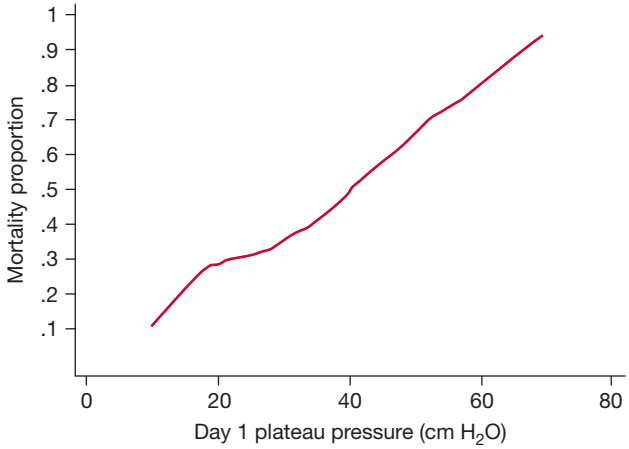


Figure 141-7 Lowess (locally weighted regression and smoothing) plot (bandwidth, 0.4) of mortality proportion and day 1 plateau pressure (Pplat, cm H_2O) for 787 patients enrolled in the ARDSNet ARMA study. Plot includes same subjects and Pplat shown in Figure 141-6. When expressed using this estimating method, the data do not support a safe upper limit for Pplat, the presence of which would be suggested by a leveling in mortality proportion, rather than a further decrease, as the plot demonstrates. The Lowess method is a nonparametric smoother that uses overlapping neighborhoods of data to estimate a local effect. A bandwidth of 0.4 means that 20% of the data on either side of a given Pplat contribute to a local estimate of mortality at that Pplat; data at the high and low ends of the curve represent fewer observations. As data are smoothed using a tricubic weight function, points furthest from the Pplat of interest are assigned the least weight and approach zero. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172(10):1241–1245.)*

to be about 20% greater than the former (due to fat and extravascular fluid). In summary, clinicians should employ the *entire* ARDSNet protocol (Table 141-9), rather than selected parts in attempting to achieve comparably favorable mortality results.

Lung Protection due to Higher PEEP The initial ARDSNet trial (ARMA) described earlier did not address the question of whether application of higher levels of PEEP than used traditionally is beneficial.[4] The possibility of improved outcomes using higher levels of PEEP was suggested by both basic and clinical studies conducted in the early 1990s.[5] To address whether higher levels of PEEP combined with low tidal volumes decrease mortality, the ARDSNet conducted a second ventilator clinical trial (ALVEOLI) in which each of two groups received the same low tidal volume ventilatory strategy, but one group was treated using an additional 4 to 5 cm H_2O of PEEP.[30] Mortality rates at day 60 were below 30% for both groups and were not significantly different, even after adjustment for imbalances in baseline variables. Similarly, ventilator-free days were not significantly different.

Subsequently, two further trials were conducted to address the role of a high PEEP strategy, the Lung Open Ventilation to Decrease Mortality in ARDS (LOVS) trial and the Expiratory Pressure Study (EXPRESS).[113,114] Neither study demonstrated a difference in the primary mortality outcomes between the control and intervention groups. However, the high PEEP strategy improved secondary endpoints, including use of rescue therapies in LOVS and duration of mechanical ventilation and organ failure in EXPRESS. More recently, a meta-analysis combined the data from AVEOLI, LOVS, and EXPRESS.[115] Treatment with higher levels of PEEP was not associated with an in-hospital mortality benefit, but among patients with a Pa_{O_2}/FI_{O_2} <200 there appeared to be a reduction in mortality. In addition, other studies have demonstrated that while some patients with ARDS have little or no alveolar recruitment (i.e., opening previously collapsed or fluid filled airspaces) with increased levels of PEEP, others PEEP show marked recruitment.[116] This suggests that future clinical trials using higher PEEP be restricted to subjects with ARDS in whom PEEP increments can reliably result in recruitment.

Recommended Core Ventilator Management We recommend that as the core ventilator management in ARDS, clinicians follow the ARDSNet low tidal volume ventilatory strategy (Table 141-9).[4] Because higher levels of PEEP have not yet been found to improve outcomes, unless new evidence arises to the contrary, we also recommend that clinicians follow the same combinations of FI_{O_2} and PEEP used in the first ARDSNet trial, ARMA (Table 141-9). Alternatively, clinicians can consider assessing PEEP responsiveness and increasing PEEP in those that demonstrate significant improvements in oxygenation with the addition of higher levels of PEEP.

Because of constraints of sample size, the ARMA trial tested the low-volume strategy only against use of tidal volumes of 12 mL/kg predicted body weight. Notably, a strategy using 6 mL/kg has not been shown to be superior to a strategy using tidal volumes of 8 to 10 mL/kg. However, based on the previous descriptions of ventilator-induced lung injury (VILI) and biotrauma, we believe it is prudent for clinicians to strictly follow the ARDSNet protocol as their core management strategy in ARDS. Modifications should be considered only in special cases, for example, when contraindications for permissive hypercapnia exist (Table 141-11).

Other Approaches to Ventilator Management

In addition to the low-volume protocol described, several additional approaches may be used in the management of ARDS and are discussed briefly subsequently.

Pressure Control Mode The ARDSNet low tidal volume strategy used the volume-assist-control mode – a familiar device setting and the only ventilator intervention that has been shown thus far to improve long-term survival in patients with ARDS.[4] However, other modes of ventilation can also provide low tidal volume ventilation, including pressure control ventilation (PCV).

TABLE 141-11 Contraindications to Permissive Hypercapnia and Acute Respiratory Acidosis

Increased intracranial pressure from any cause (trauma, mass lesion, malignant hypertension)
Acute cerebrovascular disorders, e.g., stroke
Acute or chronic myocardial ischemia
Severe pulmonary hypertension
Right ventricular failure
Uncorrected severe metabolic acidosis
Sickle cell anemia
Tricyclic antidepressant overdose
Patients taking beta-blockers
Pregnancy (due to potential for decreased fetal blood flow from vasodilation-induced steal syndrome; in addition, shift to the right of the O_2 dissociation curve decreases the maternal-fetal gradient for O_2)

PCV can limit maximal peak airway pressure as well as end-inspiratory pressure (Fig. 141-8A) and, hence, is favored by some clinicians. However, the end-inspiratory pressure in PCV can be underestimated. For example, using PCV with an inspiratory pressure of 30 cm H_2O and a PEEP of 10 cm H_2O, the end-inspiratory pressure is 40 cm H_2O (the sum of the two pressures). Some may misinterpret this combination as equivalent to a Pplat of 30 cm H_2O and assume that it is a "safe" value according to interpretation of ARDSNet results. As discussed previously, however, no Pplat is known to be safe, even when end-inspiratory pressure is calculated correctly. Furthermore, use of PCV to mimic both tidal volume and

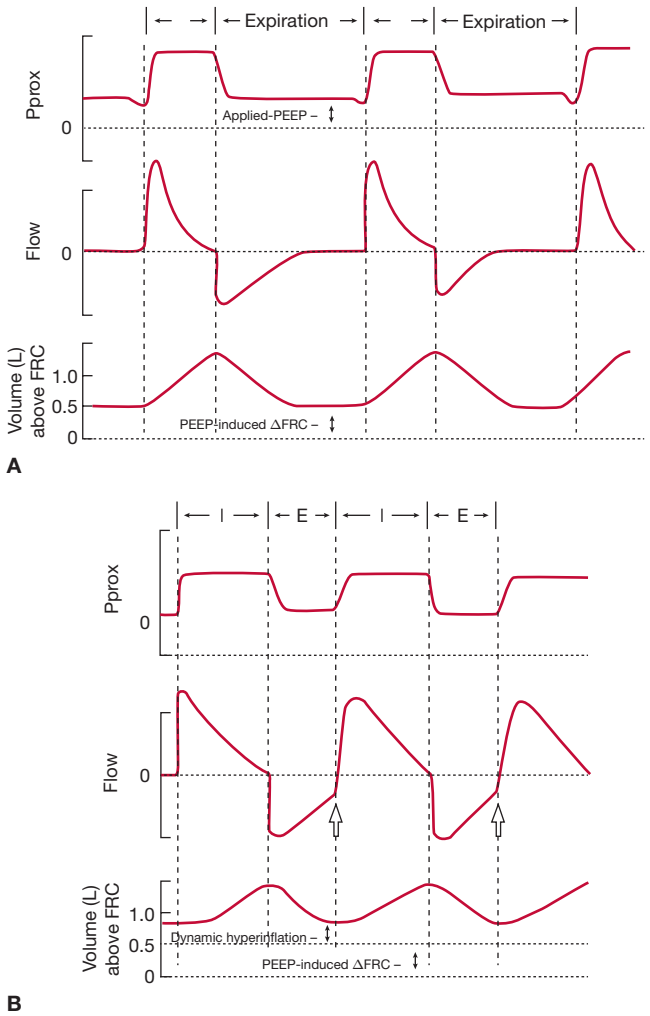


Figure 141-8 Schematic depiction of pressure, flow, and volume waveforms during pressure control ventilation (PCV) with applied PEEP. The x-axis is time and y-axes (from top to bottom) are proximal airway pressure (P_{prose}), inspiratory flow, and volume above functional residual capacity (FRC). Other abbreviations: I, inspiration, ΔFRC, change in FRC. **A.** The inspiratory-to-expiratory (I:E) time is about 1:2. The pressure waveform resembles pressure support ventilation, and the flow pattern is characterized by marked deceleration. Applied PEEP increases FRC (PEEP effect). **B.** I:E time is reversed (I > E), representing pressure-controlled inverse ratio ventilation (PC-IRV). As a result, the next breath starts before expiratory flow has returned to zero (*open arrows*), resulting in auto-PEEP and dynamic hyperinflation. The latter is superimposed on the increased FRC due to the applied PEEP. *(Reproduced with permission from Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. The Intensive Care Unit Manual. Philadelphia, PA: Saunders; 2001.)*

TABLE 141-12 "Rescue" or "Salvage" Interventions Used in Patients with ARDS and Severe Hypoxemia Resistant to Conventional Mechanical Ventilation and PEEP

Corticosteroids
Extracorporeal CO_2 removal ($ECCO_2R$)
Extracorporeal membrane oxygenation (ECMO)
High-frequency oscillatory ventilation (HFOV)
Inhaled nitric oxide (NO) or inhaled prostacyclin (epoprostenol/iloprost)
Pressure-controlled inverse ratio ventilation (PC-IRV)
Prone positioning
Recruitment maneuvers
Tracheal gas insufflation (TGI)

Pplat used in the ARDSNet trial remains problematic. The tidal volume delivered at a set pressure in PCV is dependent on the compliance of the respiratory system and is, therefore, variable, particularly in ARDS. The benefit seen from using the ARDSNet strategy may have been due as much to the use of low tidal volume as to lower Pplat. It may be difficult in PCV to ensure tidal volumes are limited, particularly as compliance improves as ARDS improves, which will result in larger tidal volumes at the same set pressure.

Inverse ratio ventilation (IRV) with PCV is based upon an inspiratory time (I) greater than expiratory time (E), that is, I:E >1 (Fig. 141-8B). Lengthening the inspiratory time increases mean airway pressure because more of the respiratory cycle is spent in inspiration, which may translate into improvements in oxygenation. However, IRV also limits the time for exhalation, potentially resulting in dynamic hyperinflation and auto-PEEP. While increasing auto-PEEP may translate to improved oxygenation, it also results in high pulmonary pressures that may not be lung-protective. IRV with auto-PEEP plus applied PEEP may also compromise cardiac output and increase the risk of nonpulmonary organ dysfunction. Clinicians should consider using PCV–IRV only as a "salvage" mode of ventilation (Table 141-12).

Modes that Allow Spontaneous Breathing During Positive Pressure Ventilation Two ventilatory modes of modern, microprocessor-based devices that permit spontaneous breathing to occur at any phase of the respiratory cycle during assisted ventilation include biphasic airway pressure (BIPAP) and airway pressure release ventilation (APRV). In each, airway pressure cycles between higher and lower levels of PEEP at preset time intervals. APRV represents the extreme of BIPAP whereby patients are given a high level of PEEP to promote alveolar recruitment with a brief release to allow for carbon dioxide removal without allowing alveolar derecruitment. Controlled studies using these ventilator modalities are limited. One report found that the use of APRV in patients with ARDS decreased intrathoracic pressure, improved ventilation–perfusion mismatch and cardiac output, and decreased shunt and dead-space fractions compared with pressure support ventilation (matched for the same airway pressure limits or minute ventilation).[117] However, clinically important outcomes were not compared.

BIPAP and APRV can be expected to decrease the use of neuromuscular blocking agents and possibly sedation in patients with ARDS, since both allow spontaneous breathing and potentially less

patient-ventilator dyssynchrony. However, whether such newer modes of ventilation are better than, equal to, or worse than the ARDSNet lower tidal volume ventilatory strategy remains unknown. Until more clinical evidence supports their superiority or equivalency, their routine use cannot be recommended.

High-Frequency Oscillatory Ventilation High-frequency oscillatory ventilation (HFOV) is a mode of ventilation in which patients are supported with rapid pressure oscillations that generate very small tidal volumes. Theoretically, HFOV may be regarded as the ultimate low-tidal volume ventilator, with a capacity to ventilate a patient using a very small tidal volume, which lies midway between the upper and lower inflection points of the pressure–volume curve (Fig. 141-5). While commonly used in respiratory distress of the newborn, the use of HFOV in ARDS has been limited to centers with necessary ventilatory equipment and technical expertise.

Clinically, use of HFOV has previously been shown to be equivalent to "usual" care.[118] However, previous trials comparing HFOV with usual care were conducted at a time when usual care did *not* include low tidal volume ventilation. Since its application generally requires neuromuscular paralysis, HFOV is unlikely to be utilized in patients with mild ARDS because of the risk of paralytic agent–related quadriparesis.

Two large, multicenter, randomized controlled trials of moderate-to-severe ARDS comparing HFOV and traditional care are noteworthy. The trial conducted by the Oscillation in ARDS (OSCAR) study group demonstrated no significant mortality benefit of HFOV compared with usual care, as determined by local practice of participating ICUs.[119] The Oscillation for ARDS Treated Early (OSCILLATE) Trial was stopped early by the Data Safety and Monitoring Committee, as the HFOV group appeared to have a higher in-hospital mortality compared with a low tidal volume, high PEEP control group.[120] While some clinicians may use high-frequency ventilation as a "salvage" mode (Table 141-12), its use, even in those circumstances, is not supported by controlled clinical trials.

Adjuncts to Lung-Protective Mechanical Ventilation

A number of adjunctive measures to mechanical ventilation have assumed importance in the management of patients with ARDS. In some cases, the physiologic or pharmacologic basis for the measure's beneficial effect is apparent; in others, the mechanism is unknown.

Overview Use of adjuncts to lung-protective ventilation is generally based on extrapolations from animal or basic studies, or from clinical studies using physiologic markers as surrogates for clinically meaningful endpoints, for example, mortality or ICU length of stay or ventilator-free days. However, extrapolation from such studies to clinical practice is problematic. For example, the only intervention that, thus far, has been proved to result in increased survival in ARDS – the ARDSNet low tidal volume ventilatory strategy – also resulted in patients in the low-volume group with significantly lower Pa_{O_2}/FI_{O_2} after enrollment compared with those receiving traditional tidal volume ventilation (Table 141-10).[4] If the trial had used improvement in Pa_{O_2}/FI_{O_2} as a surrogate marker for better survival, the results would have been interpreted as showing that low tidal volume ventilation results in *higher*, rather than *lower*, mortality.

In general, both efficacy and safety data supporting use of the following adjunctive therapies in ARDS are lacking. Thus, these interventions should be used cautiously, if at all.

Permissive Hypercapnia Permissive hypercapnia is defined as clinician-allowed hypercapnia during assisted ventilation, despite an ability to achieve a level of minute ventilation sufficient to maintain a normal Pa_{CO_2} (36–44 mm Hg). Because patients may develop hypercapnia during lower tidal volume ventilation, which is recommended as the core ventilator strategy, permissive hypercapnia should no longer be considered an "adjunct."[4] Although, the ARDSNet lower tidal volume strategy did stipulate maintenance of minute ventilation while decreasing tidal volume in order to decrease the secondary rise in Pa_{CO_2}, permissive hypercapnia was allowed as a consequence of the protocol. The response to the resulting respiratory acidosis was left to the local investigator's discretion.

Fluid Management The ARDSNet Fluid and Catheter Treatment Trial (FACTT), noted previously, used a two-by-two factorial design to test the hypothesis that a management strategy of fluid restriction (conservative fluid management) would improve clinically important outcomes in ARDS compared with more generous fluid management strategy (liberal fluid management).[31] Although the strategy of liberal fluid management was based upon a protocol to determine fluid balance, patients' net fluid balance during the first 7 days of the trial resembled that resulting from the nonprotocol-directed care in the first two ARDSNet clinical trials (ARMA and ALVEOLI).[4,30]

FACTT investigators developed a detailed fluid management protocol that, except for patients in shock (mean arterial pressure [MAP] less than 60 mm Hg or on vasopressors for hypotension), used four basic input variables (assessed every 1–4 hours) to determine the fluid management instructions: (1) MAP; (2) urine output; (3) effectiveness of circulation; and (4) intravascular pressure (central venous pressure [CVP] or PAOP). In both arms of the study, the protocol goals were MAP greater than 60 mm Hg (or vasopressor independence); urine output greater than 0.5 mL/kg predicted body weight/hour; and evidence for effective circulation, including a cardiac index $\geq$2.5 L/min/m^2 in patients with PACs or, in those with CVCs, absence of physical examination findings indicating hypoperfusion of extremities. In the group randomized to conservative fluid strategy, the target intravascular pressure was a CVP less than 4 mm Hg or PAOP less than 8 mm Hg. In contrast, for those randomized to the liberal fluid strategy, targets were a CVP of 4 to 8 mm Hg or PAOP of 8 to 12 mm Hg.

Despite marked differences in cumulative net fluid balance between the conservatively and liberally managed groups, the two showed no statistically significant difference in mortality at 60 days, which was the study's primary outcome (Table 141-13). Nonetheless, compared with the liberal strategy, the conservative strategy resulted in statistically significant improvements in several clinically important outcomes, including decreased duration of assisted ventilation and length of stay in the intensive care unit (Table 141-13). Moreover, the conservative strategy did not worsen the incidence of shock, number of days in shock, frequency or extent of other organ system failures, or rate of use of dialysis. These results support the use of a conservative fluid strategy in managing patients with ARDS who are not in shock.

Hemodynamic Management Using the trial's two-by-two factorial design, the ARDSNet FACTT investigators also compared the safety and efficacy of PACs with CVCs in directing fluid and hemodynamic protocols, as described.[11] Mortality and other important clinical outcomes, such as ventilator-free days, ICU-free days, and organ-failure-free days by study day 28 were no different in patients managed with a PAC versus a CVC (Table 141-14). However, use of a PAC was associated with a significantly higher complication rate during catheter insertion – primarily, cardiac arrhythmias. The excess events were attributed principally to the need for passing both a sheath and catheter; none of the adverse events was fatal.

Based on the results, the FACTT investigators recommend using a CVC to guide a hemodynamic and fluid management. The use of the PAC in the United States had been declining, even prior to the publication of the FACTT trial, as evidence had been accumulating against routine use.[10] However, clinicians may elect to use a PAC in selected circumstances, for example, in addressing the response to volume resuscitation, determining the adequacy of cardiac output,

TABLE 141-13 Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Conservative Fluid Management Strategy Versus Liberal Fluid Management Strategy

Result	Conservative Strategy ($n = 503$)	Liberal Strategy ($n = 497$)	p Value
Cumulative net fluid balance from day 1 to day 7 (mL)			
All patients	−139 ± 491	6992 ± 502	<0.001
Patients in shock at entry	2904 ± 1008	10, 138 ± 922	<0.001
Patients not in shock at entry	−1576 ± 519	5287 ± 576	<0.001
Death at 60 d (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28[a]	14.6 ± 0.5	12.1 ± 0.5	<0.001
ICU-free days from day 1 to day 28[a]	13.4 ± 0.4	11.2 ± 0.4	<0.001
Organ failure-free days from day 1 to day 7[a,b]			
Cardiovascular failure[c]	3.9 ± 0.1	4.2 ± 0.1	0.04
CNS failure[d]	3.4 ± 0.2	2.9 ± 0.2	0.02
Renal failure[c]	5.5 ± 0.1	5.6 ± 0.1	0.45
Hepatic failure[c]	5.7 ± 0.1	5.5 ± 0.1	0.12
Coagulation abnormalities[c]	5.6 ± 0.1	5.37 ± 0.1	0.23
Dialysis to day 60			
Patients (%)	10	14	0.06
Days of dialysis	11.0 ± 1.7	10.9 ± 1.4	0.96

CNS, central nervous system.
Plus–minus values are means ± SE.
[a]This was an a priori secondary outcome. Death at 60 d was the primary outcome.
[b]Cardiovascular failure, systolic blood pressure <90 mm Hg or receiving a vasopressor other than dopamine at 5 μg/kg/min or less; CNS failure, Glasgow Coma Scale of 12 or less; renal failure, serum creatinine ≥ mg/dL (177 μmol/L); hepatic failure, serum bilirubin ≥2 mg/dL (34 μmol/L); coagulation abnormalities, platelet count of 80,000/μL or less. Number of days without organ failure is determined by subtracting the number of days with organ failure from the lesser of 28 or from number of days until death.
[c]This difference was not significant from day 1 to day 28.
[d]This difference was still statistically significant from day 1 to day 28.
Source: Data from National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–2575.

measuring the oxygen saturation of mixed venous blood, calculating the degree of intrapulmonary shunt, or searching for equalization of diastolic pressures during suspected cardiac tamponade.

Prone Positioning About two-thirds of patients with ARDS improve their oxygenation after being placed in a prone position.[121,122] Mechanisms that may explain the improvement include (1) increased functional residual capacity; (2) change in regional diaphragmatic motion; (3) perfusion redistribution; and (4) improved clearance of secretions. Studies of the distribution of ventilation-to-perfusion ratios in animal models suggest that gravity is less influential on the distribution of perfusion in the prone, rather than supine, position.[123] This finding, coupled with the observation that edema fluid migrates to the dependent portions of the lung (as

TABLE 141-14 Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Use of Pulmonary Arterial Catheter (PAC) Versus Use of Central Venous Catheter (CVC) to Direct Fluid and Hemodynamic Management Protocols

Result	Pulmonary Artery Catheter Group ($n = 13$)	Central Venous Catheter Group ($n = 87$)	p Value
Death at 60 d (%)	27.4	26.3	0.69
Ventilator-free days from day 1 to day 28[a]	13.2 ± 0.5	13.5 ± 0.5	0.58
ICU-free days from day 1 to day 28[a]	12.5 ± 0.5	12.0 ± 0.4	0.4
Number of catheters inserted[b]	2.47 ± 0.05	1.64 ± 0.04	<0.001
Number of complications per catheter	0.08 ± 0.01	0.06 ± 0.01	0.35
Total number of catheter-related complications per group[b]	100	41	

Plus–minus values are means ± SE.
[a]This was an a priori secondary outcome. Death at 60 d was the primary outcome.
[b]This includes the sheath for PAC, PAC, and CVC for subjects in the PAC group and sheath (n = 6) and CVC for subjects in the CVC group.
Source: Data from National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med. 2006;354(21):2213–2224.

demonstrated on computed tomography) in patients with ARDS who have been turned prone, suggested that ventilation–perfusion relationships might be favorably altered in the prone position.[124]

Patients managed in the prone position need special attention to prevent pressure necrosis of the nose, face, and ears. Extra care is also needed to ensure security and patency of the endotracheal tube. Pressure on the eye may result in retinal ischemia, especially in hypotensive patients. Others may experience cardiac arrhythmias or hemodynamic instability when turned prone.

In a large clinical trial of prone positioning in patients with ARDS, subjects were randomly placed prone for 6 or more hours daily for 10 days or were left in the supine position.[125] Although the investigators found that oxygenation improved transiently with prone positioning, they demonstrated no survival advantage. More recently, a meta-analysis examined the effects of prone positioning on all patients with ARDS and a prespecified subgroup with severe ARDS (Pa_{O_2}/FI_{O_2} <100 mm Hg).[126] Prone positioning failed to demonstrate a mortality benefit among all patients with ARDS, but findings suggested a mortality benefit among those with severe ARDS. In 2013, a prospective, randomized, controlled trial comparing prone positioning for at least 16 hours a day to supine positioning in 466 patients with ARDS and Pa_{O_2}/FI_{O_2} <150 mm Hg treated with low tidal volume ventilation was published.[127] The primary outcome, 28-day mortality, was 16% in the prone group and 32.8% in the control group. This is the first prospective clinical trial to report a mortality benefit with prone positioning in ARDS.

Placing patients prone carries known risk, even in experienced hands, and cannot be recommended for routine use in all patients with ARDS. However, given the previously noted findings from a meta-analysis and the recently published randomized control trial demonstrating a mortality benefit in the subgroup of patients with severe ARDS, experienced clinicians may opt to use prone positioning as a therapy for severe hypoxemia (Table 141-12).

Recruitment Maneuvers Lung recruitment maneuvers are defined as the application of CPAP aimed at "recruiting" or opening totally or partially collapsed alveoli. The alveoli are then kept inflated during expiration using an appropriately high level of PEEP. In one study of a "lung-protective" strategy utilizing low tidal volume ventilation and extra-high PEEP, recruitment maneuvers were performed by maintaining a CPAP level of 35 to 40 cm H_2O for 30 seconds.[113] Others advocate application of equivalent or higher pressures for longer periods.

No controlled clinical trial supports the efficacy of recruitment maneuvers alone to improve clinically important outcomes, such as mortality or ventilator-free days. Studies of recruitment maneuvers have generally used physiologic end points, for example, improvement in oxygenation.[128,129] In a subset of patients treated with high levels of PEEP in the ARDSNet trial comparing high versus low PEEP in ARDS, no clinically relevant improvements in arterial saturation were noted.[130] However, complications, such as transient hypotension and slight drops in arterial saturation during the maneuver, were reported. On the other hand, other clinical studies have reported that recruitment maneuvers improve oxygenation in patients on relatively low levels of PEEP, receiving large tidal volumes, or maintained on paralytics.

Because no controlled clinical trials demonstrate efficacy in clinically relevant end points, and because there are potentially adverse effects, routine use of recruitment maneuvers is not recommended in ARDS. Likewise, in the absence of data showing efficacy, routine use of ventilator "sighs" exceeding peak pressures of 30 cm H_2O (the threshold used in the ARDSNet clinical trial that showed improved survival) is also not recommended. Some clinicians may use recruitment maneuvers with higher pressures as part of salvage therapy for patients with severe refractory hypoxemia (Table 141-12).

Inhaled Nitric Oxide In 1993, Roissant et al.[131] published a study of inhaled nitric oxide (NO) as a novel therapy for ARDS. Given via inhalation, NO selectively vasodilates pulmonary capillaries and arterioles that serve *ventilated* alveoli, diverting blood flow to these alveoli and away from areas of shunt. Lowering of the pulmonary vascular resistance, accompanied by lowering of the pulmonary artery pressure, appears maximal at very low concentrations (0.1 ppm) in patients with ARDS. Beneficial effects on oxygenation take place at somewhat higher inspired concentrations of NO (1–10 ppm). Rapid inactivation of NO by hemoglobin prevents unwanted systemic hemodynamic side effects, but also requires continuous delivery of gas through the ventilator circuit. Thus, if continuous delivery of NO is interrupted (e.g., during patient transport or due to NO supply exhaustion), precipitous and life-threatening hypoxemia and right-sided heart failure may occur.

Inhaled NO has been studied in several controlled clinical trials in patients with ARDS.[132–134] While demonstrating improvements in oxygenation in some patients, inhaled NO did not improve survival in any of the trials. Based on these trials, the routine use of inhaled NO in ARDS is not recommended. Some clinicians may consider using inhaled NO as a salvage intervention (Table 141-12). However, a much less costly alternative, inhaled prostacyclin (epoprostenol/iloprost), is available. The initial daily cost of inhaled NO is several thousands of dollars, while the daily cost of inhaled prostacyclin is several hundreds of dollars. Although less well studied than inhaled NO, inhaled prostacyclin seems to improve oxygenation to the same degree in a majority of patients with ARDS.[135]

Tracheal Gas Insufflation Tracheal gas insufflation (TGI) consists of delivering fresh gas through a modified endotracheal tube at a point just above the carina. The additional gas flow (i.e., flow provided in addition to the standard tidal volumes delivered by the ventilator) tends to remove CO_2-rich gas from the trachea and smaller airways. It has the effect of reducing anatomic dead space. Although ALI decreases the ability of TGI to reduce Pa_{CO_2}, permissive hypercapnia and higher Pa_{CO_2} values increase its relative effectiveness. For example, in one study of patients with ARDS, TGI using 100% humidified oxygen, delivered throughout the respiratory cycle at a flow of 4 L/min, lowered Pa_{CO_2} from 108 to 84 mm Hg.[136]

Because TGI carries a number of potential risks (e.g., tracheal erosion, oxygen toxicity related to an increased FI_{O_2}, and hemodynamic compromise or barotrauma due to TGI-induced auto-PEEP and a larger tidal volume than the ventilator is set to deliver), its routine use is not recommended. However, once again, some clinicians may employ it as a salvage intervention for patients with high levels of Pa_{CO_2} (e.g., >100 mm Hg).

Extracorporeal Life Support Extracorporeal Life Support (ECLS) is a therapy that utilizes an external artificial membrane and a mechanical pump to provide gas exchange and systemic perfusion in patients with failure of lung and/or heart function. The use of extracorporeal gas exchange, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal ($ECCO_2R$), is based on the hypothesis that more patients will survive if the lung is allowed to recover from its injury by "resting" using extracorporeal gas exchange temporarily. Although this hypothesis was initially stimulated by the desire to decrease the risk of pulmonary oxygen toxicity, its assessment can now be justified in regard to the techniques' potential roles in reducing VILI.

In the 1970s, a large-scale study on use of ECMO in patients with severe ARDS demonstrated that it offered no survival benefit to patients whose mortality was extremely high (approximately 90%).[137] Similarly, a randomized controlled trial in severely ill patients with ARDS reported in 1994 did not find improved survival using $ECCO_2R$.[138] The therapy received renewed attention during the H1N1 influenza pandemic of 2009.[139] Significant technologic advances, along with a population of previously healthy patients

infected with influenza and suffering from severe ARDS, prompted the increased use of ECLS.

Recently, the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) Trial randomized 180 patients with severe, but potentially reversible, respiratory failure to conventional therapy or referral to a single, specialized ECMO center for consideration for ECMO.[140] Death or severe disability, the study's primary outcome, occurred in 53% of the conventional arm versus 37% of those referred to the ECMO center. Among those referred to the ECMO center, 76% received ECMO. While the study demonstrated a statistically significant finding, the study design makes it impossible to distinguish the effects of the ECMO therapy from those of a specialized referral center. Current trials aimed at addressing the use of extracorporeal gas exchange in ARDS, utilizing updated technology, are ongoing. Some specialized centers offer ECLS to a highly selective group of adults with severe ARDS and consider the technique as a safe life-saving salvage intervention (Table 141-12).

Corticosteroids The general consensus among intensivists is that corticosteroids have little or no role to play in treating the acute phase of ARDS. However, the role of corticosteroids in later phases of ARDS has been controversial.

A number of small case series suggest that high-dose corticosteroid therapy may be beneficial during the proliferative phase of ARDS, based on the rationale of preventing lung scarring that occurs during this phase of ARDS as a result of alveolar inflammation.[141–143] Potential risks include immunosuppression of debilitated, instrumented patients managed in environments harboring multiple antibiotic-resistant organisms and potential long-term neuromuscular weakness associated with use of high-dose corticosteroids and paralytic agents.

In 2006, the ARDSNet investigators published results of a double blind, randomized, controlled clinical trial (Late Steroid Rescue Study or LaSRS) designed to evaluate benefits and risks of moderately high doses of corticosteroids in 180 patients with persistent ARDS (ARDS lasting 7–21 days) (Tables 141-15 and 141-16).[144] The study revealed no differences in 60- or 180-day mortality rates. Although parameters of respiratory function, including Pa_{O_2}/FI_{O_2}; plateau pressure; respiratory system compliance; and time to, and rate of, liberation from mechanical ventilation improved after corticosteroid administration; the corticosteroid treated group included more patients who returned to assisted ventilation. Furthermore, no statistically significant differences between treated and untreated groups in ICU or hospital days by 180 days were observed. In addition, more adverse events related to weakness occurred in the treated group than in those receiving placebo. Finally, patients treated with corticosteroids after 14 days of persistent ARDS had a significantly increased mortality (Table 141-16). Hence, the results of this study do not support the routine use of steroids for late-phase ARDS in general, and they argue against their use if ARDS has been present for 14 days or longer.

Neuromuscular Blocking Agents Significant controversy exists regarding the role of neuromuscular blocking agents in ARDS. These agents are frequently used to promote ventilator synchrony and improve oxygenation in severe cases of ARDS; however, they have been associated with prolonged neuromuscular weakness in survivors of ARDS.

In one multicenter study, 340 heavily sedated patients with ARDS and a Pa_{O_2}/FI_{O_2} <150 were randomized to 48 hours of cisatracurium or placebo. The 90-day mortality rate was 31.6% in the cisatracurium group and 40.7% in the placebo group, a finding that was only statistically significant after adjustment for baseline Pa_{O_2}/FI_{O_2}, baseline plateau pressure, and the Simplified Acute Physiology II score. Although not powered for this outcome, ICU-acquired neuromuscular weakness was not different between the groups. While further studies addressing the role of neuromuscular blockade in ARDS are needed, current evidence suggest that they may be useful for short-term use in severe ARDS.

Other Therapies Several other therapies have been the subject of ongoing research in ARDS, including statins, beta agonists, and macrolide antibiotics.

Given their effects on inflammatory cytokines, statins are currently undergoing investigation for their role in ARDS. A small trial of 60 patients failed to demonstrate a mortality benefit.[145] The ARDS Network is conducting a larger randomized controlled trial of rosuvastatin in patients with ARDS.

Beta-agonists stimulate removal of fluid from flooded alveoli by stimulating the epithelial sodium pump and promoting active transport of sodium out of the alveoli (with water following passively according to osmotic gradients) and therefore, were considered as a therapy for ARDS. However, two large, randomized controlled trials failed to demonstrate a mortality benefit from beta agonist.[32,146] One

TABLE 141-15 Results of ARDSNet Late Steroid Rescue Study (LaSRS) in Patients with Persistent ARDS: A Priori Protocol-Defined Outcomes and Adverse Events

Variable or Outcome	Methylprednisolone-Treated Group	Placebo-Treated Group	*p* Value
Mortality at day 60 (%) (95% CI)	28.6 (20.8–38.5)	29.2 (20.8–39.4)	1.0
No. of ventilator-free days at day 28	11.2 ± 9.4	6.8 ± 8.5	<0.001
No. of ICU-free days at day 28	8.9 ± 8.2	6.2 ± 7.8	0.02
No. of serious adverse events associated with myopathy or neuropathy	0	9	0.001
60-day mortality according to time from onset of ARDS (means)			
7–13 d (%)	27	36	0.26
No. of patients	66	66	
>14 d (%)[a]	35	8	0.02
No. of patients	23	25	

SD, standard deviation; ventilator-free days by day 28, number of days alive and not receiving assisted ventilation between days 1 and 28; ICU-free days by day 28, number of days alive and not in ICU between days 1 and 28.
Plus–minus values are means ± SD.
[a]p = 0.02 for the interaction with treatment-group assignment (Wald's test).
Source: Data from Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354(16):1671–1684.

TABLE 141-16 Results of ARDSNet Late Steroid Rescue Study (LaSRS) in Patients with Persistent ARDS: *Post hoc* Analyses of Outcomes and Adverse Events at 180 Days

Variable or Outcome	Methylprednisolone-Treated Group	Placebo-Treated Group	*p* Value
180-Day mortality (%) (mean) (95% CI)	31.5 (22.8–41.7)	31.9 (23.2–42.0)	1.0
No. of days of assisted ventilation in survivors up to 180 d (median)	11	18	0.006
(interquartile range)	(6–22)	(10–33)	
No. of days of ICU stay in survivors up to 180 d (median)	17	20	0.29
(interquartile range)	(10–31)	(11–31)	
No. of days of hospitalization in survivors up to 180 d (median)	26	29	0.73
(interquartile range)	(19–43)	(19–40)	
180-Day mortality according to time from onset of ARDS (means)			
7–13 d (%)	27	39	0.14
No. of patients	66	66	
>14 d (%)[a]	44	12	0.01
No. of patients	23	25	

SD, standard deviation.
[a]p = 0.006 for the interaction with treatment-group assignment (Wald's test).
Source: Data from Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354 (16):1671–1684.

of these trials was actually stopped early for increased mortality among the beta-agonist arm.

Animal studies and an observational cohort study of macrolide antibiotics have suggested they may have a positive effect in ARDS.[147,148] This evidence requires a prospective clinical trial prior to routine use of macrolides in ARDS.

CLINICAL COURSE, OUTCOME, AND LONG-TERM SEQUELAE

The clinical course and outcomes of ARDS have been better delineated in recent years. Both pulmonary and nonpulmonary outcomes have been investigated.

■ CLINICAL COURSE AND DURATION

The course of illness varies considerably in severity and duration among patients. ARDS may last for a few days or even less (e.g., ARDS from opioid exposure, with the patient recovering rapidly after the initial insult). Alternately, ARDS from other causes may last several months and involve a prolonged ICU course. Patients can recover or die at any point in the course of ARDS. Using the new Berlin definition of ARDS, the median duration of mechanical ventilation is approximately 5 days, 7 days, and 9 days for mild, moderate, and severe ARDS, respectively.[9] Up to 25% of patients remain on mechanical ventilation for longer than approximately 2 weeks, many for much longer. Notably, as shown in LaSRS, a longer duration of mechanical ventilation for ARDS does not translate into a higher mortality.[144] Most ARDS-related deaths occur within the first 2 weeks, with one-third occurring by day 7, two-thirds by day 14, and three-fourths to four-fifths by day 28.[26]

The mortality rate of patients on mechanical ventilation after 2 to 4 weeks of persistent ARDS is about 30% over the ensuing 2 to 6 months. These rates are similar to the overall mortality rate (at 180 days) for patients enrolled in ARDSNet clinical trials in which low tidal volume ventilation was used. The findings highlight the importance of continued supportive care in the ICU and vigilance aimed at reducing nosocomial complications.

■ CAUSES OF DEATH

Approximately one-third of ARDS-related deaths occur in the first 7 days.[26] Most are related to the underlying disease or injury, that is, to events occurring before the onset of ARDS. The majority of patients who die succumb after 7 days, with these late deaths also commonly due to the underlying injury or illness. Other causes include complications occurring contemporaneously with, or after the onset of, ARDS. The most common cause of death in this group of patients is sepsis, with associated multiple organ system failure. Of note, only a relatively small fraction of patients – 10% to 20% of all patients with ARDS – die a respiratory death due to irreversible hypoxemia or refractory respiratory acidosis. Therefore, not surprisingly, clinical trials of interventions aimed selectively at improving gas exchange (e.g., use of inhaled nitric oxide or exogenous surfactant) have not demonstrated improved survival.

■ LONG-TERM SEQUELAE

Recent studies indicate that many survivors of ARDS have medical problems and a compromised quality of life, both of which persist well beyond their initial ICU stay.[149–151] Impaired pulmonary, neurologic, musculoskeletal, cognitive, and psychosocial functions have been documented in survivors of ARDS. Furthermore, survivors have a poorer quality-adjusted survival than do critically ill subjects without ARDS.

Research into these disorders is in the early stages; the etiology and pathophysiology of are incompletely understood. Recognition of the problems affecting survivors of ARDS and referral for appropriate evaluation and therapy constitute important components of overall care. With improved therapy of ARDS resulting in greater survival rates, clinicians should anticipate an increase in the prevalence of long-term sequelae.

Health-Related Quality of Life

Health-related quality of life (HRQL) has become increasingly recognized as important in the evaluation of patient-centered outcomes in recovery from a variety of illnesses. A number of studies have evaluated HRQL in ARDS survivors.[149–156] Tools used to assess HRQL include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), St. George's Respiratory Questionnaire, Quality of Well-Being Scale, and Sickness Impact Profile. Each has illustrated impaired quality of life in survivors of ARDS compared with various control populations, including critically ill subjects

without ARDS, and patients with chronic diseases (including cystic fibrosis). In general, impairments in HRQL improve over the first 3 months following discharge from the ICU and appear to plateau by 1 year. Studies of interventions to improve HRQL are under way.

Pulmonary Sequelae

Studies of pulmonary function following ARDS are affected by inconsistent disease definitions, methodologic problems due to lack of patient follow-up, and heterogeneity of pre-existing pulmonary diseases. Consequently, a range of lung function impairments has been reported following recovery.[150,151,154,157,158] Although a proportion of survivors of ARDS may have impaired diffusion capacity or restrictive or obstructive abnormalities, restoration of normal lung function occurs in a substantial proportion. In the Toronto ARDS Outcomes study, spirometry and lung volumes improved rapidly among survivors, reaching normal in most subjects by 6 months.[150] Diffusion capacity is mildly impaired in many patients after ARDS, but it may return to normal by 2 to 5 years among survivors.[150,151] Given the severely impaired physical function domains reported in HRQL surveys and the relatively mild pulmonary impairment, investigation has more recently focused on other limitations and causes of symptoms in survivors of ARDS.

Physical and Neuromuscular Sequelae

In the previously noted Toronto ARDS Outcomes study, persistent physical impairment in survivors of ARDS was assessed.[150,151] Despite improvement in pulmonary function at 1 year following their ICU stay, this cohort had low exercise capacity, weakness, and decreased physical quality of life as far as 5 years after their acute illness. Risk factors for these findings included multiorgan dysfunction in the ICU, prolonged duration of ARDS, treatment with corticosteroids during the ICU stay, and increased comorbid disease burden. Although the basis for many of the abnormalities is not clear, a number of patients demonstrated a range of abnormalities, including critical illness polyneuropathy, ICU-acquired myopathy (critical illness myopathy), entrapment neuropathy, and heterotopic ossification.

Cognitive and Psychological Sequelae

Cognitive impairments can cause major limitations in the ability to return to work, affect mood, and lead to increased healthcare expenditures. Study of long-term cognitive function in survivors of ARDS indicates that many have impaired memory, reduced attention, and decreased concentration and processing speed.[149–151,159,160] The abnormalities appear to be associated with the number and severity of hypoxemic episodes in the ICU. Similar to physical abnormalities, cognitive dysfunction appears to be worse in the first 3 months following hospital discharge; it may improve for up to 1 year and then reach a plateau.

Depression and anxiety are frequent following ARDS. Several studies indicate that the prevalence of depression is over 25% following recovery.[161,162] These emotional problems are likely multifactorial, including prior hypoxic brain injury and delirium and subsequent limitation of physical function. In addition, some authors have suggested the presence of a major component of posttraumatic stress disorder (PTSD) in survivors of ARDS.[163] Because these disorders are potentially treatable using pharmacologic, behavioral, and cognitive therapies, clinicians should ask survivors about possible depression and anxiety, which, in turn, may improve HRQL.

Finally, in accord with the concept that the ICU team treats patients, as well as their families, clinicians need to be aware that familial caregivers of patients who are survivors of ARDS experience long-term health effects.[164] In particular, they are at increased risk for emotional distress (associated with various factors, including patient depression) and a lower HRQL over all domains tested on the Medical Outcomes Short Form 36. Clinicians providing long-term follow-up care for patients with ARDS should aim to ensure adequate social and other support for their familial caregivers.

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CHAPTER 142

Sepsis, Multiple Organ Dysfunction Syndrome, and Chronic Critical Illness

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INTRODUCTION

The past four decades have added greatly to our recognition that *sepsis*, originally defined as a syndrome induced by actively dividing microorganisms in the circulation, is, in fact, a complex and diverse disorder. The term has now come to encompass a constellation of abnormalities that reflect disordered or dysregulated inflammation. As such, sepsis may be initiated by infection; however, it may also occur in the absence of microbial invasion, for example, in response to extensive trauma, uninfected pancreatitis, ruptured aortic aneurysm, or some distinctly unusual entities, such as amniotic fluid embolism. All such patients may develop multiple organ dysfunction syndrome (MODS) and a newly recognized state currently called "chronic critical illness (CCI)." What is now apparent is that our ability to manage shock and to support organ function has unmasked a common family of disorders that have a high mortality and significant morbidity. Familiarity with sepsis is essential for all medical practitioners.

This chapter defines the clinical findings that constitute sepsis, MODS, and CCI. The disorders are described as a function of their position on a continuum of clinical, organ system–specific, cellular, and, indeed, even subcellular, changes that include abnormal biochemistry, metabolism, and energetics. Several pathogenic hypotheses, management strategies, and intriguing new forms of therapy are addressed.

DEFINITIONS, NATURAL HISTORY, AND EPIDEMIOLOGY

The characteristic response to inflammatory stimuli, including surgery and trauma, has been referred to as the *stress response,* the evolutionary importance of which lies in facilitation of survival and tissue repair.[1]

Initially in the stress response, an orchestrated neuro-hormonal-humoral mechanism directs substrate delivery to the most vital organs—the heart and brain. Enabling of the mechanism requires rapid development of vasoconstriction, fluid retention, and translocation of intracellular water into the vasculature. In the absence of exogenous life support, death from shock ensues when these endogenous mechanisms are inadequate.

Resuscitation from the initial phase of shock is followed by a period during which cardiovascular function and global metabolism are markedly enhanced.[2] The driving force behind this second phase is repair of damaged tissue, with white blood cells serving as the primary effectors of the process.[3] To support the increased white blood cell mass, substrate is mobilized from endogenous sources and glucose reserves are rapidly depleted. Because white blood cells are obligate glucose users, muscle (both skeletal and smooth) is broken down to provide precursors for increases in hepatic gluconeogenesis. Nonglucogenic amino acids are used to synthesize structural proteins and enzymes. Energy to support the liver, heart, and other organs is derived from fat and amino acids, since utilization of glucose by tissues other than blood cells and neurons is blocked. Generalized capillary recruitment and leak allow substrate delivery to the avascular area where tissue is damaged. The amount of fluid in the extracellular compartment, particularly in the extracellular, extravascular matrix, increases dramatically. Continued fluid retention and movement of water out of cells fills the dilated, leaky vasculature. Vasodilatation is accompanied by an increase in cardiac output (CO), which further facilitates delivery of substrate. By the fourth day following injury or surgery, neovascularization of damaged tissue results in a sharp increase in substrate delivery to damaged areas. This change is accompanied by a decrease in capillary leak, generalized increase in vascular tone, and mobilization and excretion of fluid in the matrix. Water also returns to cells. In most cases, patients recover uneventfully.

In an unknown fraction of cases, the inflammatory process becomes disordered. Initially the process was defined by the

TABLE 142-1 Diagnostic Criteria for SIRS, Sepsis, Severe Sepsis, Septic Shock, and MODS

SIRS
Temperature >38°C or <36°C
Heart rate >90 beats/min
Respiratory rate >20 breaths/min or P_{CO_2} <32 mm Hg
WBC >12 × 10^9/L or <2 × 10^9/L or >10% immature forms
Sepsis
SIRS + identified or suspected infection
Severe Sepsis
Sepsis + dysfunction of one or more organ systems
Septic Shock
Sepsis + hypotension (BP <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes) despite adequate fluid resuscitation and perfusion abnormalities (e.g., lactic acidosis, oliguria, altered mental status)
MODS
No current definitions

Source: Data from Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250–1256.

presence of two or more of the criteria listed in the original definitions of sepsis (Table 142-1)[4] which indicated enhanced inflammation, a syndrome referred to as the *systemic inflammatory response syndrome* or *SIRS*. Use of SIRS criteria has been very helpful in enabling early recognition of patients for inclusion in epidemiologic and interventional studies on sepsis. However, this approach, even when updated,[5] has been increasingly recognized as problematic because it is too nonspecific and may reflect a view of septic pathophysiology that is too limited. Recent data have shown that disordered inflammation also includes "immunoparalysis," with white blood cell function that is also markedly diminished.[6,7] Thus, virtually all aspects of inflammation are altered in early sepsis.

Previous descriptions of sepsis detailed subsequent development of a state of organ dysfunction or failure.[8–11] This syndrome, MODS, is now considered to begin quite early, perhaps at the very beginning of immune dysregulation. While MODS rarely leads to death, it does progress to a persistent, prolonged, and unchanging state that has come to be known as CCI. Recent studies of CCI indicate that the subset of patients who remain in the ICU for greater than 30 days account for only 8% of total admissions but for 48% of total occupied beds. Six months after hospital discharge, 50% of the cohort is still alive and 80% of the survivors are living in their previous place of residence.[12]

Data on incidence and outcome in sepsis are difficult to determine because the scientific community has used varying definitions of sepsis. In a study published in 2001, sepsis was noted as responsible for 215,000 deaths each year, and overall hospital mortality rate was 28.6%.[13] Expenditures associated with caring for patients with sepsis was estimated at $16.7 billion. More recent work based on examination of the Medicare database from 1996 to 2008 indicated that the number of patients with a diagnosis of sepsis had increased to nearly a million annually.[14] Indeed, the incidence of sepsis in elderly patients has become epidemic: 60% of patients who develop sepsis and 75% of the deaths in sepsis are in patients older than age 65 years. These data are consistent with findings in other industrialized nations.[15–17]

The proportion of patients admitted to ICUs with a diagnosis of sepsis who will progress to developing CCI is difficult to determine. Investigations suggest that, each year, more than 100,000 patients in the United States require prolonged mechanical ventilation.,[18,19] Older studies estimated the annual cost of CCI to exceed $20 billion. This burden has undoubtedly already increased and, in the absence of a change in healthcare policy, will become more pronounced.[20]

Determining the actual mortality from sepsis is equally difficult. Application of evidence-based guidelines for sepsis management indicates a dramatic decline in mortality.[21] Indeed, recent data suggest that mortality may be reduced to <10%.[22] With use of diagnostic and management guidelines for sepsis, patients rarely die of shock. Most develop CCI and expire when exogenous support is discontinued (Deutschman CS, unpublished data). The cause of death in almost all cases is unknown; although patients die *with* CCI, the actual cause of death remains unclear.

PATHOPHYSIOLOGY OF SEPSIS, MODS, AND CHRONIC CRITICAL ILLNESS

As vexing as understanding the pathophysiology of sepsis may be, the mechanisms underlying MODS and CCI are even more problematic.

MODS was once thought to reflect the effects of a sustained activation of the immune system. However, the findings previously cited regarding early immunosuppression cast doubt on this hypothesis.[7] Further, defining "dysfunction" in individual organs is problematic. Although many criteria have been used, none are universally accepted. Some generally used criteria for organ dysfunction are detailed in (Table 142-2).[23] However, these criteria reflect the gaps in our understanding of MODS.

Recent studies suggest that early organ dysfunction differs from the organ failure that becomes evident later in the time course of sepsis. The early changes may represent an adaptive response aimed at preventing further damage from a severe insult.[24–26] The basis for this construct lies in the "mitochondrial hypothesis," which is detailed below. Development of CCI appears to herald the highly lethal state once attributed to MODS. The major factor limiting treatment of MODS is lack of a clear understanding of the underlying pathophysiologic defect. In fact, if not considered carefully, the changes associated with sepsis/MODS may simply resemble an extension of those observed after uncomplicated stress. For example, patients recovering from major surgery undergo increases in metabolic rate, oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production, in addition to glucose intolerance and hyperglycemia. The vasculature is dilated, and CO increases to promote oxygen transport. In addition, lactate production may increase, reflecting the overall increase in metabolism rather than tissue hypoxia.

Typically, the septic patient presents with high fever, shock, and respiratory failure. This clinical picture resulted in the prevailing theory that sepsis reflects uncontrolled inflammation. The hypothesis was consistent with demonstration of increased concentrations of TNF, IL-1, IL-6 and, later in the time course, HMGB1 in sepsis.[27] However, a myriad of trials addressing anti-inflammatory approaches to treatment have not demonstrated reduced survival rates.[28,29] Two observations that may contribute to the negative findings have been offered. First, sepsis is characterized by both proinflammatory *and anti-inflammatory* responses. Second, as previously noted, immunosuppression in sepsis has been reported.[6,7] Indeed, in a study of patients whose deaths were attributed to sepsis,[30] 80% had unresolved foci of infection. Hence, a strategy employing *immune enhancement*, rather than anti-inflammation, may be warranted. Further complicating an understanding of pathogenesis is our inability to define the underlying physiologic basis by which sepsis ultimately leads to organ failure or death. Studies[6] have shown that there is very little cell death in most major organs in sepsis, and that histologic damage does not correlate with the degree of organ dysfunction seen prior to death. The exception to this observation lies in the immune system and in the gastrointestinal tract.[31]

TABLE 142-2 General Criteria for Diagnosis of Organ Dysfunction in Sepsis, MODS, and CCI

System	Mild	Severe
Pulmonary	Hypoxia/hypercarbia requiring assisted ventilation for 3–5 d	ARDS requiring PEEP >10 cm H_2O and F_{IO_2} >0.5
Hepatic	Bilirubin 2–3 mg/dL or other LFTs twice normal, PT elevated to twice normal	Jaundice with bilirubin >8–10 mg/dL
Renal	Oliguria (<500 mL/d) or increasing creatinine (2–3 mg/dL)	Dialysis
Gastrointestinal	Intolerance of GI feeding >5 d	Stress ulceration with need for transfusion, acalculous cholecystitis
Hematologic	PTT >125% of normal, platelets <50,000–80,000 per mm^3	DIC
CNS	Confusion	Coma
PNS	Mild sensory neuropathy	Combined motor and sensory deficit
Cardiovascular	Decreased ejection fraction, persistent capillary leak	Hypodynamic state not responsive to pressors

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; LFTs, liver function tests; PT, prothrombin time; PTT, partial thromboplastin time; DIC, disseminated intravascular coagulation; CNS, central nervous system; PNS, peripheral nervous system.

Source: Data from Fry DE, Pearlstein L, Fulton RL, et al. Multiple system organ failure: the role of uncontrolled infection. Arch Surg. 1980;115:136–140; Faist E, Baue AE, Dittmer H, et al. Multiple organ failure in polytrauma patients. J Trauma. 1983;23:775–787; Henao FR, Daes JE, Dennis RJ. Risk factors for multiorgan failure: a case-control study. J Trauma. 1991;31:74–80; Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg. 1985;202:685–693; Norton LW. Does drainage of intra-abdominal pus reverse multiple organ failure? Am J Surg. 1985;149:347–351; Manship L, McMillian RD, Brown JJ. The influence of sepsis and multisystem and organ failure failure on mortality in the surgical intensive care unit. Am Surg. 1984;50:94–101; Crump JM, Duncan DA, Wears R. Analysis of multiple organ failure in trauma and nontrauma patients. Am Surg. 1988;54:702–708; DeCamp MM, Demling RH. Posttraumatic multisystem organ failure. JAMA. 1988;260:530–534.

Recent studies also suggest that organ dysfunction develops very early after the diagnosis of septic shock or severe sepsis is made. This finding is not surprising, given that both severe sepsis and septic shock are defined in terms of organ dysfunction.

The 2001 SCCM/ESICM definitions of sepsis were explicit in delineating specific clinical criteria for dysfunction in specific organs.[5] In general, these abnormalities are not manifest for several days. However, when biochemical or histologic criteria are applied, organ dysfunction may be noted once the initial resuscitation is complete. The most common clinical abnormality is respiratory failure requiring mechanical ventilation. In some instances, the need for exogenous support of other organ systems (e.g., dialysis) may develop in short order, while in others deterioration may be slower. In either case, the patient progresses to development of CCI. These patients account for 5% to 10% of the ICU population. Most often, affected patients require prolonged mechanical ventilation, but they also may need continuous hemodialysis, cardiovascular support with vasopressors, prolonged exogenous metabolic/nutritional support, or complex wound management. One key characteristic of CCI is evident in ICU survivors[32]: These individuals suffer from prolonged physical symptoms, such as respiratory insufficiency and muscle weakness. Recovering patients are also often left with long-term neuropsychiatric impairment and reduced quality of life. Indeed, data suggest significant cognitive impairment in this cohort.[33,34] Many suffer from posttraumatic stress disorder (PTSD).[35] Perhaps, most alarming, data from the United States, Canada, and Australia demonstrate that ICU survivors are two to five times more likely to die compared with age- and sex-matched population controls.[36–38] Three-year mortality in sepsis survivors is 70%; 5-year survival is 75%.[14]

A better understanding of these issues has emerged from the Surviving Sepsis Campaign (SSC),[39] a program designed to enhance use of evidence-based approaches to sepsis management. Application of some or all of the elements outlined in SSC has dramatically reduced mortality in this early phase of the disorder.[22] Future examination of the effects of the SSC and correlation with an emerging understanding of pathophysiology may help clarify matters.

UNDERLYING MECHANISMS: NEWER HYPOTHESES

As a result of advances in our understanding of the pathophysiology of sepsis, a number of hypotheses have been abandoned. In particular, those that proposed that sepsis reflected only the effects of excessive, uncontrolled inflammation are difficult to reconcile with recent data demonstrating early immunosuppression. Similarly, it has been difficult to demonstrate translocation of bacteria from the gut or the occurrence of "two hits," that is, a scenario in which a second insult precipitates organ dysfunction. Several contemporary alternative hypotheses have emerged.

THE MICROCIRCULATORY HYPOTHESIS

Characteristic features of CCI are a defect in $\dot{V}_{O_2}$ and an increase in the production of lactate. Two theories have been proposed to account for these observations. The first, termed the *microcirculatory hypothesis*, posits that aberrant oxygen extraction results from a failure of cells or organs to receive adequate levels of oxygen or some important nutrient or substrate.[40] Low blood flow, as is likely to occur in hypotension or shock, contributes to cellular dysfunction. The release of vasoactive mediators and vascular congestion secondary to microthrombi and leukocytes are also thought to play important roles.

Reperfusion of ischemic tissue may be as important a determinant of tissue injury as is decreased flow itself.[41,42] In particular, the generation of oxygen-free radicals and peroxidation of membrane lipids following reperfusion may contribute to tissue injury. Sources of free radicals include the conversion of molecular oxygen to superoxide by xanthine oxidase, activated leukocytes, mitochondria, and prostaglandin synthase.

Circulatory shock, microvascular compromise, and free radical generation likely directly affect the endothelium. Endothelial cells actively generate free radicals, provide a point of attachment for leukocytes, and may be exquisitely sensitive to hypoxia. In addition, they produce and respond to vasoactive mediators.[43] As a result of these interactions, the microvascular hypothesis may be viewed as an extension of the *cytokine hypothesis*.[44] Indeed, cytokines activate endothelial cells to elaborate other vasoactive substances and to express surface proteins that promote leukocyte adhesion. Further, endothelial cells are important participants in the formation of microthrombi.

The microvascular hypothesis is supported by autopsy data documenting the presence of microvascular injury and microthrombi containing platelets, neutrophils, and fibrin in patients dying with CCI. The use of side-stream, dark-field videomicroscopy has demonstrated microcirculatory failure in septic patients, while increased microcirculatory flow during resuscitation is associated

with reduced organ failure at 24 hours, even in the absence of substantial changes in hemodynamics.[45] Conversely, antibodies to CD18, which block leukocyte adhesion and are protective in some forms of ischemia–reperfusion injury,[23,46] do not protect against liver injury or leukocyte adherence in experimental sepsis.[46,47]

While microcirculatory failure is present in sepsis and may contribute to the development of MODS and CCI, it cannot explain many of the clinical and pathologic features of these syndromes.

THE MITOCHONDRIAL HYPOTHESIS

An alternative explanation of the sepsis-induced defect in oxygen extraction is based on studies addressing mitochondrial dysfunction. The central tenet of this process, termed "cytopathic hypoxia," is a defect in oxidative phosphorylation. In support of this concept is demonstration of impairment in several of the five complexes that comprise the mitochondrial respiratory chain in humans during experimental sepsis. A decrease in the so-called "Complex I" (NADH: ubiquinone oxidoreductase) activity is observed in skeletal muscle in patients with sepsis and in liver and muscle in septic rats.[48,49] In addition, sepsis decreased Complexes II–III (succinate dehydrogenase and cytochrome bc1, respectively) activity has been reported in the hearts of septic rats,[50] while attenuated Complex IV (cytochrome c oxidase) activity has been reported in cardiac muscle and liver in septic rats.[25,51,52] Others have suggested that Complex IV functions as a sensor of dysoxia.[53–58] Thus, inhibition of this enzyme complex in response to an insult limits oxidative phosphorylation and protects mitochondria.

THE "FAILED COMMUNICATION" HYPOTHESIS

In the 1980s, investigators[59,60] identified the "proinflammatory" cytokines TNFα and IL-1β as primary mediators of septic shock. Other cytokines have since been added to this list, notably IL-6 and HMGB1.[27] For a time, these disorders were believed to reflect "malignant inflammation." However, two important findings have altered perceptions of severe sepsis/septic shock as inflammatory disorders.

First, as mentioned, immunosuppression, in a sense, the antithesis of "malignant inflammation," is an early and important component of severe sepsis.[6,7] To some degree, immunosuppression may be attributed to enhanced production of "anti-inflammatory" cytokines, such as IL-4 and IL-10, and conversion of T-helper (Th) cells from a Th-1 (proinflammatory) to a Th-2 (anti-inflammatory) phenotype. In addition, recent studies suggest impairment of the receptors and intracellular pathways that transduce cytokine-mediated responses in noninflammatory tissues.[61] In response, the production and release of cytokines increases. This finding explains the dramatically increased levels of TNF, IL-1, and, especially, IL-6.[61] Perhaps, more importantly, therapy designed to limit both pro- and anti-inflammatory activities have failed to improve outcomes in sepsis. Thus, the immune dysfunction of sepsis cannot be simply characterized. Some responses are excessive and some inadequate; most defy a simple approach to classification.

The demonstration that white cell activity becomes depressed over time in sepsis, while coupled with the loss of intracellular activity in nonimmune cells, is suggestive immunosuppression.[7] Along this line of thinking, investigators[62] postulated that sepsis represented a disorder where "connectivity" was lost. Under normal conditions, the functions of the heart, lungs, kidneys, and other organs are tightly coupled and exquisitely responsive to local metabolic demand. In sepsis (and, indeed, in other disorders), the tightly orchestrated fluctuations in activity are lost. This hypothesis is consistent with impaired cytokine production and activity. For example, cytokine-mediated effects may alter activity in the same cell that produces the cytokine (autocrine), as well as that in nearby (paracrine) or distant (endocrine) cells. Loss of the endocrine activity of cytokines limits the ability of organ systems to act in concert. However, there are two other mechanisms by which cells and organs interact and by which metabolic interaction between organs may be coupled: the endocrine and central nervous systems.

Sepsis-induced endocrine abnormalities have been studied and abnormalities defined in the activity of a number of hormones that are similar to those described for cytokines.[63,64] In the early stages of sepsis, peripheral effector cells become increasingly unresponsive to endocrine stimulation. These abnormalities reflect changes in the target cells themselves. For example, the conversion of thyroxine (T4) to triiodothyronine (T3) becomes limited. In response, release of T4 by the thyroid and of TSH by the pituitary increases to compensate for decreased peripheral T3 activity. In the later stages of sepsis, the hormonal output of the pituitary and the peripheral glands themselves decrease. Levels of TSH and T4 decline, and both the effects and levels of T3 become even more depressed. Indeed, sepsis-induced dysfunction occurs in the endocrine system.

Abnormalities in the CNS are less well defined. It has long been known that sepsis alters consciousness. More recent data indicate that sepsis may cause cognitive impairment, encephalopathy, delirium, PTSD, and a host of other abnormalities. Until recently, the only pathologic change demonstrated in the CNS was a loss of blood–brain barrier integrity. However, two recent studies have added key information. Animal studies[65] have demonstrated cognitive impairment in mice surviving cecal ligation and puncture (CLP) sepsis. This effect is paralleled by a loss of synaptic plasticity in hippocampal neurons. In the same model, loss of activity in the orexinergic nervous system (ONS) has been demonstrated.[66] The ONS comprises 3000 to 6000 neurons in the lateral hypothalamus that secrete the neurotransmitter orexin (also known as hypocretin). These neurons receive input from throughout the CNS and, in turn, project to multiple different loci. Of key importance, however, is the known ability of the ONS to modulate activity, level of consciousness, hemodynamics, respiration, thermoregulation, and metabolism—all processes that are impaired in sepsis. In addition, the ONS connects with the pituitary and modulates the release of pituitary hormones. Thus, dysfunction in the ONS may explain a number of sepsis-associated abnormalities.

To further elucidate the failed communication hypothesis, two additional pieces of data are required: Demonstration of (1) interactions between the inflammatory system, the endocrine system, and the CNS, and (2) that reversal of the observed abnormalities in the three systems alters septic pathophysiology. Recent studies have demonstrated an interaction between the CNS and inflammatory cells.[67] This "inflammatory reflex" is a nicotinic, vagally mediated reflex that is impaired in sepsis. Vagal stimulation or administration of compounds with nicotinic activity may restore these lost anti-inflammatory effects. In addition, persistently elevated levels of HMGB-1 in animals that survived sepsis have been demonstrated.[65] Neutralization with an anti-HMBG1 antibody reversed the histologic changes in the hippocampus and attenuated cognitive impairment. Similarly, administration of orexin into the cerebrospinal fluid of septic mice reversed sepsis-induced changes in temperature, heart rate, respiratory rate, motor activity, and arousal.[66] Thus, the inflammatory, endocrine, and central nervous systems are linked and impaired in sepsis. Restoration of activity or of interactions improves sepsis-induced pathophysiology.

Hypothyroidism may contribute to excessive fluid retention and edema, relative hypothermia, decreased ventilatory drive, and malabsorption.[68] Attempts at repletion have not proven successful. Cortisol levels are capricious, but they are often elevated. Whether or not cortisol administration is appropriate in septic patients remains controversial.[69,70] Growth hormone (GH) is reported to increase in the acute setting, but in later stages of sepsis, production is suppressed. One trial indicated that supplementing GH in septic patients increased mortality[71]; however, the study has been criticized on methodologic grounds. Finally, although use of intensive insulin therapy in critically ill patients was initially viewed as highly promising,[72] the results could not be duplicated, and a large randomized trial that included 5000 patients suggests that the hypoglycemia accompanying the therapy causes harm.[73]

MANAGEMENT OF SEPSIS, MODS, AND CHRONIC CRITICAL ILLNESS

Management of patients with sepsis is challenging and focuses on support of major end-organ damage. Support modalities have been compiled into treatment "bundles" by the SSC. This group released revised guidelines in 2012.[39] Importantly, the guidelines were evaluated using the "GRADE" (**G**rading of **R**ecommendations **A**ssessment, **D**evelopment, and **E**valuation) system.[74] According to the GRADE system, each guideline is evaluated on the basis of the strength of the supporting evidence (A through D, or UG for ungraded) and on the strength of the recommendation itself (1, strong, with the intervention designated as "recommended"; or 2, weak, with the intervention designated as "suggested"). For additional information, the reader is referred to the GRADE Working Group website (http://www.gradeworkinggroup.org/index.htm).

Key recommendations and suggestions from the SSC are detailed below. For a more complete discussion, the reader is referred to the guidelines themselves.[39] Ungraded recommendations have not been included.

INITIAL RESUSCITATION

Initial resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in the SSC document as hypotension persisting after initial fluid challenge or a blood lactate concentration ≥4 mmol/L) is quantitative and protocol-driven. Goals during the first 6 hours of resuscitation include: (1) central venous pressure of 8 to 12 mm Hg; (2) mean arterial pressure (MAP) ≥65 mm Hg; (3) urine output ≥0.5 mL/kg/h; and (4) central venous (superior vena cava) or mixed venous oxygen saturation of 70% or 65%, respectively (grade 1C).

In patients with elevated lactate levels, resuscitation is targeted to normalize the lactate level (grade for entire recommendation, 2C).

The imperative for early resuscitation aimed at achieving specific goals that are thought to correlate with tissue perfusion arises from the seminal work of Rivers et al.[75] Rivers and colleagues compared standard management to quantitative resuscitation aimed at explicit physiologic endpoints over a 6-hour period immediately following initial suspicion of sepsis. The approach is known as "early goal-directed therapy" or EGDT. This single-center study of 263 patients demonstrated that EGDT led to a 15.9% absolute reduction in 30-day mortality. A second, multicenter trial of 314 patients in eight centers in China confirmed these results.[76] Multicenter trials are underway to further evaluate EGDT, as some of the specific endpoints, especially the CVP, are quite controversial.

EARLY DIAGNOSIS

Cultures should be obtained, as clinically appropriate, before antimicrobial therapy if there is no significant delay (>45 minutes) in the start of antimicrobial(s) (grade 1C). At least two sets of blood cultures (both aerobic and anaerobic) should be obtained before antimicrobial therapy, with at least one set drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hours) inserted (grade 1C).

Perhaps the most important part of this recommendation is that, under no circumstances, should diagnostic testing delay initiation of antimicrobial therapy.

INITIATION OF ANTIMICROBIAL THERAPY

The goal of therapy is administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C).

Initial, empiric, anti-infective therapy is based on use of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

The antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B).

Empiric combination therapy should not be administered for more than 3 to 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

The duration of therapy is typically 7 to 10 days. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, or in some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

Antiviral therapy is initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

The recommendation that antimicrobials be started within 1 hour arises from a study published by Kumar et al.[77] and is substantiated by data in the SSC database (Mitchell M. Levy, personal communication). These data show that, in septic shock, mortality rises measurably with each hour that therapy is delayed. Data supporting a similar approach for severe sepsis are less robust.

SOURCE CONTROL

A specific anatomical diagnosis of infection requiring consideration for emergent source control should be investigated and diagnosed or excluded as rapidly as possible, and intervention should be undertaken for source control within the first 12 hours after the diagnosis is made, if feasible (grade 1C).

Despite a paucity of evidence, early control of anatomically accessible sources is strongly recommended.

HEMODYNAMIC SUPPORT

The important tenets of fluid therapy include: (1) use of crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B); (2) avoiding use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B); (3) administration of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C); and (4) administration of an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion in whom there is suspicion of hypovolemia, aiming to achieve a minimum infusion of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).

The high-grade recommendation to use crystalloid solutions reflects the absence of any demonstrable benefit to use of colloid. While albumin may be administered as an adjunct,[78] three clinical trials indicate that use of hydroxyethyl starch in critically ill patients is associated with enhanced renal impairment and increased requirement for renal replacement therapy.[79–81]

Important to note is that it is nearly impossible to restore the body to preinsult hemodynamic status until the inflammatory response has run its course.

RATIONAL USE OF VASOPRESSORS AND INOTROPES

Animal and human studies indicate that SIRS/MODS renders the cardiovascular system relatively resistant to the effects of native and synthetic catecholamines. Therefore, the choice of vasopressor agent may be of great importance.

Vasopressors

Vasopressor therapy is initially aimed at targeting a MAP of 65 mm Hg (grade 1C).

Norepinephrine (NE) is the first-choice vasopressor (grade 1B).

Epinephrine should be added to and, potentially, substituted for, NE when an additional agent is needed to maintain adequate blood pressure (grade 2B).

Vasopressin, 0.03 units/min, can be added to NE with intent of either raising MAP or decreasing NE dosage (UG).

Dopamine should be considered as an alternative agent to NE only in highly selected patients (e.g., patients with a low risk of tachyarrhythmias or absolute or relative bradycardia) (grade 2C).

Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) CO is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target (grade 1C).

Low-dose dopamine should not be used for renal protection (grade 1A).

The target mean blood pressure of 65 mm Hg, while strongly recommended, is based on grade C data. The primary study supporting this blood pressure goal is based on study of 10 patients with septic shock using indices of perfusion that have since proved to be less than reliable.[82] More importantly, the study assessed mean blood pressures between 65 and 85 mm Hg and demonstrated that perfusion did not change. However, pressures below 65 mm Hg were not evaluated.

A number of studies comparing NE to other agents clearly demonstrate this agent's superiority for septic shock. In particular, NE is a superior vasoconstrictor, primarily because it is a less potent β_2-agonist and has less vasodilatory effects. Importantly, catecholamines exert their major effects on vessels of the somatic circulation (supplying skin and skeletal muscle) and largely spare the visceral beds. Thus, NE, even in high doses, is unlikely to directly alter renal, hepatic, or gut blood flow. In fact, splanchnic flow may be improved when fluid is translocated from the periphery to the central, visceral compartment. Five randomized trials that included nearly 2000 patients have demonstrated that NE is superior to dopamine, at least in the short term.[83–87] A meta-analysis confirms this conclusion.[88]

While epinephrine is recommended as a second-line agent, β_2-stimulation increases lactate production in skeletal muscle and may limit use of lactate clearance as a parameter of perfusion.

Use of vasopressin is not graded. While vasopressin may effectively increase blood pressure, it may also impair splanchnic blood flow, even at low doses. Importantly, doses above 0.03 units/min are suggested only as salvage therapy in truly refractory shock.

Finally, the recommendation against use of low-dose dopamine for renal protection may signal the end of that dubious practice. The recommendation, one of the few given grade 1A status, is based on a large randomized trial and a meta-analysis.[89,90]

Inotropes

A trial of dobutamine infusion, up to 20 μg/kg/min, may be administered or added to a vasopressor (if in use) in the presence of (1) myocardial dysfunction, as suggested by elevated cardiac filling pressures and low CO, or (2) ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate MAP (grade 1C).

A strategy to increase cardiac index to predetermined supranormal levels should not be employed (grade 1B).

The use of inotropes to achieve supranormal levels of CO and $\dot{V}_{O_2}$ is based on a study demonstrating that patients with critical illness who achieve these levels survive, while those failing to do so do not survive.[91] However, intervention to boost CO and $\dot{V}_{O_2}$ does not improve outcomes.[92]

Corticosteroids

Intravenous hydrocortisone should not be used to treat adult septic shock if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability. If fluid and vasopressor therapy fail to restore hemodynamic stability, intravenous hydrocortisone at a dose of 200 mg/d should be given (grade 2C).

The ACTH stimulation test should not be used to identify adults with septic shock with regard to hydrocortisone administration (grade 2B).

In patients given hydrocortisone, the drug should be tapered when vasopressors are no longer required (grade 2D).

Corticosteroids should not be administered for treatment of sepsis in the absence of shock (grade 1D).

When hydrocortisone is given for shock, a continuous infusion, rather than intermittent boluses, should be used (grade 2D).

The value of corticosteroids in sepsis remains controversial primarily because of the contrasting results of the two most definitive studies done to date.[69,70] Even meta-analyses show disparate results.[93,94] It is clear, however, that corticosteroids improve blood pressure and reduce catecholamine doses. These effects are not surprising, given that corticosteroids exert a "permissive" effect on catecholamine activity, making a given dose of catecholamine more potent.

CONCLUSION

Sepsis, MODS, and CCI represent major causes of mortality and morbidity. The nature of the underlying pathologic defect is unknown. Current treatment is supportive and centers on standard critical care management, an intensive search for an excisable or drainable inflammatory site, and avoidance of secondary organ injury.

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CHAPTER 143

Pump Failure: The Pathogenesis of Hypercapnic Respiratory Failure in Patients with Lung and Chest Wall Disease

Steven G. Kelsen

The ventilatory pump accomplishes bulk transfer of air to and from the alveoli. Accordingly, diseases that perturb the mechanical properties of any component of the ventilatory pump (i.e., the bony rib cage, the extra- and intrathoracic conducting airways, and the respiratory muscles) may interfere with CO_2 elimination and O_2 uptake. If disturbances in the function of the ventilatory pump are sufficiently severe, alveolar hypoventilation and respiratory acidosis may ensue. Hypercapnic respiratory failure is defined as a steady-state Pa_{CO_2} while awake at more than 45 mm Hg, the upper limit of normal. This definition is somewhat arbitrary but has proved clinically useful.

Conceptually, diseases that cause hypercapnic respiratory failure do so by deranging respiratory mechanics and lung dead space volume (e.g., chronic obstructive pulmonary disease [COPD], asthma, or kyphoscoliosis) or by impairing the contractile properties of the respiratory muscles (e.g., neuromuscular disease). Diseases that impair respiratory mechanics increase the elastic or resistive load against which the respiratory muscles must contract. On the other hand, neuromuscular diseases impair the strength or endurance properties of the respiratory muscles and impair their ability to generate swings in intrathoracic pressure sufficient to maintain ventilation.

The rhythmic act of breathing results from the activity of a central respiratory pattern generator (CRPG) comprises interacting networks of excitatory and inhibitory neurons in the pons and medulla oblongata.[1,2] In turn, projections from the CRPG to bulbospinal motor neurons activate the respiratory skeletal muscles in the chest wall, abdomen, and upper airway and, hence, shape the neuromuscular drive to breathe. A variety of compensatory neural mechanisms located in the periphery that sense alterations in blood-gas tensions or ventilatory performance which project to the CRPG elicit increases in the neuromuscular drive to breathe and, in turn, help preserve alveolar ventilation.[3–7] In fact, in most patients, rather marked abnormalities in ventilatory pump performance are required before hypercapnic respiratory failure ensues. Conceptually, the susceptibility to develop CO_2 retention in the setting of lung, chest wall, or respiratory muscle dysfunction, therefore, depends on the balance between the severity of the derangement in ventilatory pump function and the intensity of the respiratory neuromuscular drive to breathe.[5]

This chapter deals with the pathogenic mechanisms at work in the development of CO_2 retention in lung and chest wall diseases. The compensatory/adaptive mechanisms that help preserve ventilation (e.g., respiratory chemosensitivity, motor responses to alterations in the mechanics of breathing, and intrinsic changes in respiratory muscle strength and endurance) and the decompensating/maladaptive responses that predispose to CO_2 retention (e.g., respiratory muscle wasting and fatigue and a rapid, shallow pattern of breathing) will be discussed.

COMPENSATORY/ADAPTIVE MECHANISMS

The roles of compensatory or adaptive mechanisms in hypercapnic respiratory failure are considered with respect to respiratory chemosensitivity, blunted chemosensitivity, and alterations in respiratory structure.

RESPIRATORY CHEMOSENSITIVITY

Below is a discussion of normal respiratory chemosensitivity and measures of respiratory motor output.

Overview—Regulation of Ventilation

Hypoxia and hypercapnia stimulate chemoreceptors in the arterial circulation (peripheral chemoreceptors) and ventrolateral medulla (central chemoreceptors) that reflexively increase motor activity to the respiratory skeletal muscles of the chest wall and upper airway.[8] Contraction of the muscles of the chest wall (e.g., diaphragm, intercostals, abdominals, and neck muscles) deforms the ventilatory pump and moves air.[5] Contraction of the muscles of the upper airway (genioglossus, alae nasi, posterior arytenoids, pharyngeal dilators, sternohyoid, etc.) increases the caliber of the upper airway and diminishes its susceptibility to collapse during inspiration.[6]

Chemoreceptor-induced increases in inspiratory and expiratory muscle activity are proportional to the severity of abnormalities in blood-gas tensions and represent a feedback control loop that restores blood-gas tensions toward normal by enhancing alveolar ventilation. The magnitude of the swings in intrathoracic pressure and resistance and compliance of the upper airway are determined by these changes in respiratory motor activity. The maintenance of blood-gas tensions within a relatively narrow, normal range from neonatal life to senescence attests to the power of this homeostatic mechanism.

Hypoxic and hypercapnic chemical drives to breathe exert the following stereotypic effects on the activity of chest wall and upper airway muscles.[6,8,9] Peak respiratory muscle electrical activity and its rate of rise are increased. For the inspiratory muscles, these changes in muscle electrical activity increase the rate of change and peak inspiratory intrathoracic pressure, inspiratory airflow, and tidal volume. For the expiratory muscles, increased electrical activity enhances the rate of expiratory airflow. For the upper airway muscles, the resistance to inspiratory airflow decreases.

Chemosensitivity-induced increases in respiratory activity also affect the timing of respiratory motor activity as reflected in the duration of inspiration (T_I) and expiration (T_E).[10,11] Hypoxia and hypercapnia lead to decreased T_I and T_E, allowing the frequency of breathing to increase. Reductions in T_E are generally out of proportion to T_I, thereby increasing the fraction of the respiratory cycle spent in inspiration. This partitioning of the respiratory cycle is reflected in the T_I/T_T ratio, where T_T is the total breath cycle duration (i.e., the sum of T_I and T_E).

Hypoxia and hypercapnia differ in their effects on the activity of the inspiratory muscles after the cessation of inspiratory airflow, the so-called postinspiratory inspiratory activity (PIIA).[1] Hypoxia increases PIIA in both chest wall inspiratory muscles and muscles that constrict the laryngeal aperture. Accordingly, hypoxia has a

braking effect on the rate of expiratory airflow. As T_E decreases with increasing hypoxic drive, end-expiratory lung volume increases. PIIA-induced increases in lung volume increase the caliber of the intrathoracic airways and the O_2 content of the lung. Hypoxia-induced PIIA affects the load on the respiratory muscles in complex fashion; that is, PIIA reduces inspiratory resistive work of breathing but increases the inspiratory elastic and expiratory resistive work of breathing. It has been suggested, however, that the net effect of hypoxia-induced PIIA is a reduction in overall energy expenditure during breathing. In contrast, hypercapnia diminishes the duration of PIIA.

Indices of Respiratory Motor Output

Ventilation is a well-accepted index of respiratory motor output.[8,10–12] Traditionally, ventilation was viewed as the product of tidal volume (V_T) and respiratory rate (which is equal to $60/T_T$). More recently, ventilation has been viewed as the product of separate "drive" and "timing" components.[10] The average rate of inspiratory airflow, V_T/T_I – which reflects the rate of rise of inspiratory muscle activity and intrathoracic pressure – is increased when blood-gas tensions are deranged. Accordingly, V_T/T_I has been taken as a reflection of the activity of mechanisms that regulate the drive to breathe. Of note, V_T/T_I may also be increased by excitatory inputs arising from respiratory mechanoreceptor afferents (e.g., vagal irritant receptors) and higher central nervous system (CNS) structures engaged in thermoregulation and emotion (i.e., hypothalamic and limbic areas). Conversely, the T_I/T_T ratio has been taken as a reflection of the activity of mechanisms that regulate respiratory timing. The T_I/T_T ratio is strongly affected by afferent input from mechanoreceptors in the lungs, airways, and respiratory muscles, as well as increasing chemical drive. For example, T_I/T_T increases in anesthetized animals when vagal stretch receptors are stimulated by increases in lung volume and is decreased by bronchoconstriction-induced activation of vagal irritant receptors.

In subjects with normal lung function, V_T/T_I and ventilation are accurate reflections of inspiratory muscle electrical activity and the rate of rise of intrathoracic pressure. On the other hand, diseases that adversely affect the mechanical properties of the ventilatory pump (e.g., obstructive lung disease, kyphoscoliosis) interfere with the translation of changes in intrathoracic pressure into ventilation and airflow. Conversely, conditions that impair respiratory muscle contractility (e.g., neuromuscular diseases, respiratory muscle fatigue) interfere with the translation of inspiratory muscle electrical activity into intrathoracic pressure changes. Accordingly, V_T/T_I reflects the intensity of motor outflow to the inspiratory muscles produced by increasing chemical drive only when the mechanical properties of the ventilatory pump and inspiratory muscle strength are normal. When the ventilatory pump function is abnormal, respiratory motor outflow is best assessed from respiratory muscle electrical activity (i.e., diaphragm electromyography [EMG] activity), a complicated measurement largely confined to the research laboratory.

A simpler, clinically useful measurement that reflects the neuromuscular drive to breathe and the driving pressure to inspiratory airflow is the airway occlusion pressure.[10,13–15] The occlusion pressure is the pressure generated at the airway opening 100 ms after the onset of an occluded inspiratory effort (i.e., P_{100} or $P_{0.1}$) initiated at end-expiratory lung volume. Since the airway is occluded, the inspiratory muscles contract quasi-isometrically, a condition in which muscle force correlates closely with muscle electrical activity. Measurements are made early in inspiration (100 ms) to prevent behavioral responses elicited in response to airway occlusion from altering the shape/trajectory of the pressure waveform. The lack of flow or volume change during the measurement means that the occlusion pressure is unaffected by abnormalities in the flow-resistive or compliance properties of the ventilatory pump. The occlusion pressure, therefore, has been used to assess the drive to breathe in patients with lung diseases (e.g., COPD and asthma) and chest wall diseases (e.g., kyphoscoliosis) during resting and chemically stimulated breathing. On the other hand, the occlusion pressure depends on the ability of the inspiratory muscles to convert neural activity into force and pressure. Accordingly, like ventilation, occlusion pressure may not reflect respiratory motor neuron activity when the inspiratory muscles are weak (e.g., neuromuscular disease) or fatigued.

Hypoxic Response Under isocapnic conditions, ventilation (or occlusion pressure) increases in curvilinear fashion as P_{O_2} falls.[8] However, hypoxic responses depend importantly on the prevailing level of Pa_{CO_2} (i.e., the O_2–CO_2 interaction). When Pa_{CO_2} is in the hypocapnic range, arterial P_{O_2} must fall considerably (to approximately 55–60 mm Hg or less) before respiratory activity increases. Hypercapnia profoundly increases the response to hypoxia by shifting the threshold of the response toward higher levels of P_{O_2} and augmenting the change in ventilation elicited for a given reduction in P_{O_2}.

Although the physiological stimulus for the hypoxic response is the Pa_{O_2} of the blood perfusing the peripheral chemoreceptors, for convenience the oxyhemoglobin saturation assessed with a pulse oximeter has been taken as a reflection of the stimulus. Use of the oxyhemoglobin saturation linearizes the relationship between the hypoxic stimulus, ventilation, and occlusion pressure. The intensity of the hypoxic response has been assessed from the slope of the change in ventilation (or occlusion pressure) relative to the change in O_2 saturation (i.e., $\Delta V_E/\Delta\%\ O_2$ sat) and from the intercept of the relationship (e.g., ventilation at O_2 saturation of 85%).

Hypercapnic Response In contrast to the response to hypoxia, the ventilatory and occlusion pressure responses to hypercapnia under iso-oxic conditions are linear over a relatively wide range of Pa_{CO_2} above and below the resting level of 40 mm Hg.[8] The intensity of the ventilatory and occlusion pressure response to CO_2 has been assessed from the slope of the relationship of V_E to Pa_{CO_2} (i.e., $\Delta V_E/\Delta Pa_{CO_2}$) and from the intercept of the relationship (i.e., V_E at Pa_{CO_2} 50 mm Hg).

The ventilatory response to hypercapnia is strongly affected by the prevailing level of Pa_{O_2} and is heightened as Pa_{O_2} decreases. In fact, hypoxemic and hypercapnic stimuli interact multiplicatively to enhance inspiratory and expiratory motor activities. Worsening hypoxemia enhances the ventilatory response to hypercapnia in accordance with the O_2–CO_2 interaction. The strength of a subject's chemosensitivity to O_2 and CO_2 and, in particular, to the O_2–CO_2 interaction is a powerful feedback mechanism opposing the tendency to retain CO_2 in patients with ventilatory pump dysfunction.

Consequently, treatment of the hypercapnic, hypoxemic patient with supplemental O_2 may decrease V_T/T_I and T_I/T_T and, hence, worsen hypercapnia in accordance with O_2–CO_2 interaction. Increases in Pa_{O_2} in hypoxic, hypercapnic subjects move the O_2 response to the right (less stimulus) and decrease the slope and shift the intercept of the ventilatory response to *hypercapnia* to the right (Fig. 143-1). Shifts in the CO_2 response with increases in the prevailing Pa_{O_2} mean that a higher CO_2 stimulus is required to maintain ventilation at the baseline level. Accordingly, ventilation falls and Pa_{CO_2} rises. The magnitude of the rise in Pa_{CO_2} in patients with COPD in acute respiratory failure produced by supplemental O_2 varies widely among subjects as determined by their chemosensitivity.

Of note, hypercapnia induced by supplemental O_2 in patients with COPD is multifactorial and reflects increases in lung dead space volume as well as reductions in alveolar ventilation. Hypoxemia causes bronchoconstriction via increases in parasympathetic outflow to airway smooth muscle. Accordingly, relief of hypoxemia causes bronchodilation and increased dead space volume.

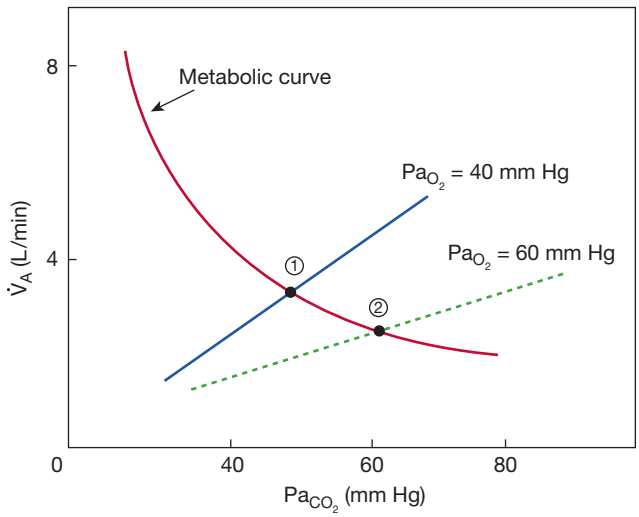

Figure 143-1 Theoretical effects of supplemental O_2 on the ventilatory response to CO_2 and steady-state arterial Pa_{O_2} in subjects with COPD in hypercapnic respiratory failure. Increasing Pa_{O_2} decreases alveolar ventilation and increases Pa_{CO_2} as dictated by effects of O_2 on the CO_2 ventilatory response. The two *straight lines* represent hypercapnic ventilatory response curves at Pa_{O_2} of 40 and 60 mm Hg. As may be seen, increasing Pa_{O_2} produces a downward, rightward shift of the ventilatory response. In contrast, the *hyperbolic line* intersecting the ventilatory response lines is the metabolic CO_2–ventilation curve, which represents the effect of increasing alveolar ventilation (independent variable) on Pa_{CO_2} (the dependent variable) when CO_2 production is normal (~200 mL/min). Steady-state alveolar ventilation and Pa_{CO_2} at rest are dictated by intersection of the ventilatory response curves with the metabolic curve (points 1 and 2). Note the increase in Pa_{CO_2} as the ventilatory response with Pa_{O_2} 60 mm Hg intersects at a lower alveolar ventilation and higher Pa_{CO_2} (point 2) compared to the higher ventilatory response when Pa_{O_2} was 40 mm Hg (point 1).

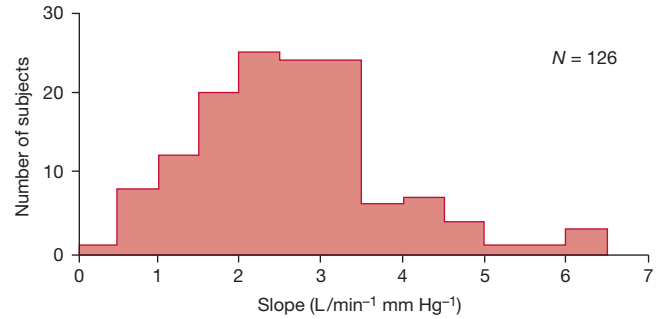

Figure 143-2 Variability of the slopes of the ventilatory responses to progressive hypercapnia (i.e., P_E/P_{CO_2}) in a normal population. Shown is the frequency distribution histogram of the slopes in 126 normal South African medical students. Note the considerable interindividual variation in CO_2 responsiveness. In some healthy subjects, the ventilatory response is blunted to less than 1 L/min/mm Hg P_{CO_2}. *(Data from Irsigler GB. Carbon dioxide response lines in young adults: The limits of the normal response. Am Rev Respir Dis. 1976;114:529–536.)*

ROLE OF BLUNTED CHEMOSENSITIVITY IN DEVELOPMENT OF RESPIRATORY FAILURE

Chemosensitivities to hypoxemia and hypercapnia are heredofamilial and ethnic traits that vary widely interindividually (Fig. 143-2).[16,17] In a given subject, responses to hypoxemia and hypercapnia correlate weakly, so that subjects with strong responses to hypercapnia also tend to have strong responses to hypoxia. Respiratory chemosensitivity to both hypoxemia and hypercapnia declines with age.[18] The decline in chemosensitivity with aging may explain why elderly subjects with lung disease (e.g., COPD) or chest wall disease (e.g., kyphoscoliosis) develop hypercapnic respiratory failure more frequently than young adults. When chemosensitivity is low, subjects with diseases of the ventilatory pump are predisposed to develop hypercapnic respiratory failure.[16,17,19]

In patients with advanced COPD, the severity of airway obstruction required to cause CO_2 retention varies widely from subject to subject (Fig. 143-3).[20,21] Subjects with the greatest respiratory effort responses to changes in Pa_{CO_2} – as measured by diaphragm EMG, respiratory work of breathing, or occlusion pressure – have arterial Pa_{CO_2} values closer to normal than subjects with blunted responses to CO_2 but the same severity of lung dysfunction. Accordingly, when chemosensitivity is low, subjects with diseases of the ventilatory pump are predisposed to develop hypercapnic respiratory failure. However, since CO_2 retention per se may blunt the response to acute hypercapnia, studies in patients in respiratory failure have not been able to determine whether blunted CO_2 responses are a cause or consequence of respiratory failure.[22]

The tendency for chemosensitivity to be inherited has been used in a number of subsequent studies to assess the role of hypoxic and hypercapnic responses in the pathogenesis of CO_2 retention in the setting of obstructive lung disease. Study of relatives with normal lung function and blood gases has been employed to circumvent the effects of CO_2 retention on respiratory chemosensitivity in patients with COPD.

In general, normal relatives of hypercapnic patients with COPD have lower ventilatory responses to hypoxia and hypercapnia than

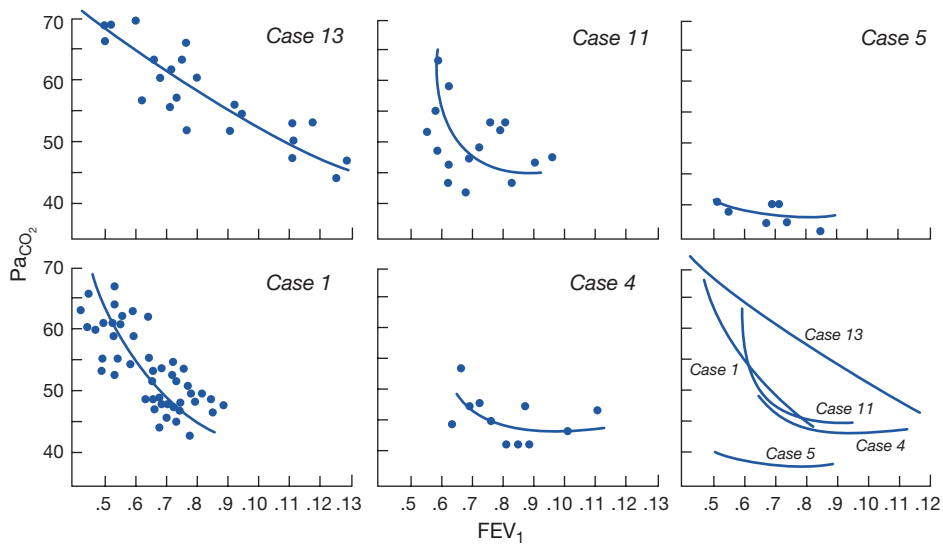

Figure 143-3 Results of repeated measurements of arterial P_{CO_2} and FEV_1 (liters) in five patients with advanced COPD. Free-hand curves of the data are shown plotted together in the lower right graph. Note that cases 1, 11, and 13 show marked increases in P_{CO_2}, with relatively small changes in FEV_1, whereas cases 4 and 5 do not. *(Data from Lane DJ, Howell JBL, Giblin B. Relation between airways obstruction and CO_2 tension in obstructive airways disease. Br Med J. 1968;3:707–709.)*

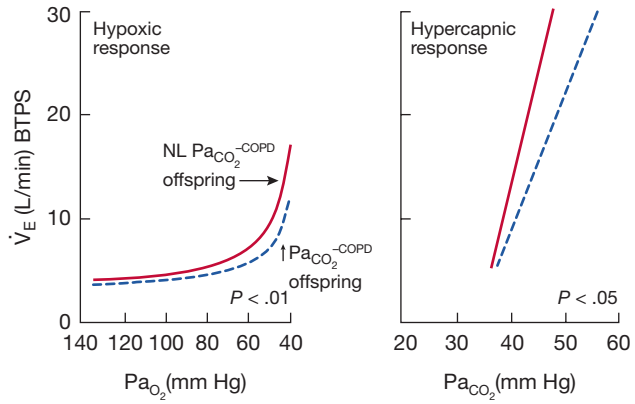

Figure 143-4 Mean isocapnic hypoxia and hyperoxic hypercapnic ventilatory response curves of 12 offspring of hypoventilating patients with COPD *(solid line)* and 10 offspring of eucapnic COPD patients *(dashed line)*. Ventilatory responses to hypoxia and hypercapnia are significantly lower in the offspring of hypercapnic COPD than in the offspring of eucapnic COPD patients. *(Data from Mountain R, Zwillich CW, Weil JV. Hypoventilation in obstructive lung disease: The role of familial factors. N Engl J Med. 1978;297:521–525.)*

relatives of eucapnic patients with COPD (Fig. 143-4).[17] The slopes of the ventilatory responses to isocapnic hypoxemia and hyperoxic hypercapnia are 30% to 40% lower in the offspring of hypercapnic patients than in the offspring of eucapnic patients. Similarly, the slopes of the ventilatory and airway occlusion pressure responses to isocapnic hypoxia are approximately 40% lower in the offspring of hypercapnic patients than in the offspring of normocapnic patients. In one study, the Pa_{O_2} of COPD patients while in a stable state and the Pa_{O_2} and Pa_{CO_2} during COPD exacerbations correlated with the hypoxic ventilatory response of their sons. It appears that blunted chemosensitivities[23] to hypoxia and hypercapnia are likely to be premorbid characteristics of hypercapnic patients with COPD, which contribute to the development of respiratory failure.

A number of reports describe patients with asthma and respiratory failure who had blunted ventilatory responses to hypoxia and hypercapnia and whose healthy immediate family members also showed blunted hypoxic and hypercapnic responses. Respiratory responses to hypoxia and hypercapnia in patients with asthma who have near-fatal attacks differ from those of asthmatics who did not have near-fatal attacks and age-matched, normal subjects.[19] The slopes of the ventilatory and occlusion pressure responses to hypoxia in the patients with a history of near-fatal asthma are approximately 33% similar. Hypercapnic responses tend to be lower in the near-fatal asthmatic groups than in the other two groups, but the differences are smaller in magnitude. Of interest, recent studies indicate that hereditary loss of function mutations in the neuronal transcription factor, paired-like homeobox 2B (Phox2b), which are required for normal development of the retrotrapezoid nucleus, a chemosensitive region, are associated with impaired chemosensitivity to hypercapnia, resting hypercapnia and central hypoventilation in man.[23,24]

Responses to Heightened Respiratory Load

A complex array of mechanoreceptors and proprioceptors whose afferents project to respiratory neurons in the brain stem and higher CNS structures provides the respiratory controller with information about the mechanics of breathing and performance of the ventilatory pump.[6] The sensory receptors providing this afferent feedback and the CNS structures that integrate this feedback into a coordinated respiratory response are not perfectly understood. However, mechanoreceptors in the intercostal muscles that sense muscle tension and length (Golgi tendon receptors and spindle organs, respectively) and pressure and flow sensors in the lower (vagal irritant receptors) and upper airway (larynx and mouth) clearly play a role in shaping the neuromuscular response to alterations in the mechanics of breathing.

Diseases of the airways (COPD and asthma) or chest wall (kyphoscoliosis) change the resistance and compliance properties of the ventilatory pump and, hence, stimulate mechanoreceptors in the ventilatory pump. In normal subjects and those with COPD, mechanoreceptor afferent inputs increase inspiratory neuromuscular output as reflected in airway occlusion pressure in response to bronchoconstriction or external resistances or elastance. Changes in ventilation during acute increases in airway resistance are inversely related to changes in occlusion pressure. Thus, the magnitude of the motor response to increases in respiratory load determines the ventilatory response.

External ventilatory loads that can be consciously detected and alter the intensity of the sensations associated with breathing elicit increases in respiratory effort as reflected by the diaphragm EMG and occlusion pressure.[3,25] Increases in effort occur abruptly within the first loaded breath and in feed-forward fashion; that is, the experience of the previous breath elicits a response in anticipation that the load will still be present. These responses are eliminated by general anesthesia and dulled if not absent in stages III and IV and REM sleep. The afferent input to the CNS elicited by external ventilatory loads probably arises from spindle and tendon organs in the respiratory muscles that project to the sensorimotor cortex and medullary respiratory neurons. The motor response to external ventilatory loads is thought to be behavioral.

The magnitude of the respiratory motor response to external loads varies widely from subject to subject and may be a heredofamilial trait. Of considerable importance, some subjects with COPD demonstrate lesser occlusion pressure responses to acutely applied external resistive loads than age-matched normal subjects.[22] It has been suggested that the blunted respiratory motor response to external loads may be a form of sensory adaptation to chronic increases in respiratory resistance. The fact that occlusion pressure responses of patients with COPD to external elastic loads and patients with asthma to external resistive loads are normal supports this concept. Of interest, the blunted motor response to external loads in some patients with COPD may reflect an increase in endogenous opiates within the CNS, since naloxone administration immediately enhances the response.

In subjects with COPD, bronchoconstriction increases airway occlusion pressure in proportion to increases in airway resistance and to a greater extent than external flow–resistive loads.[26] Bronchoconstriction increases the activity of vagal "irritant" receptors in the airway, which exert an inspiratory augmenting effect on breathing. Irritant receptors may also be excited chemically by inflammatory mediators (e.g., histamine, prostaglandin $F_{2\alpha}$) and, in contrast to external loads, elicit simple monosynaptic reflexes not abolished by sleep or anesthesia.

Mechanoreceptor inputs modify the respiratory motor responses to chemical stimuli to breathing. Increases in the elastic or resistive load to inspiration augment inspiratory muscle electrical activity and the airway occlusion pressures to hypoxia and hypercapnia. Subjects with asthma show heightened occlusion pressure responses to hypoxia and hypercapnia for this reason. Increases in the inspiratory neuromuscular drive to breathe allow ventilation to be maintained in the face of abnormalities in respiratory mechanics. Respiratory motor activity (i.e., occlusion pressure) also tends to be increased when the respiratory muscles are weak. In all likelihood, this reflects the fact that the maintenance of force output by a weakened muscle requires an increase in activation by the CNS.

Increased ventilatory loads also alter the pattern of breathing in load-dependent fashion.[3] Subjects breathing against resistive loads

breathe slowly and deeply, with an increase in tidal volume and prolongation of T_I and T_E. In contrast, subjects breathing against elastic loads tend to breathe with smaller tidal volumes and a reduced T_I and T_E; that is, they demonstrate a rapid and shallow pattern of breathing. Slow, deep breathing during resistive loading and rapid, shallow breathing during elastic loading diminish the resistive and elastic work of breathing, respectively. Alterations in breathing pattern when the mechanics of breathing are deranged are believed to be attempts to minimize the work of breathing, muscle tension, or energy expended.

Integrated Motor Responses

Respiratory motor responses to heightened chemical or mechanoreceptor drives to breathe elicit highly coordinated patterns of muscle activity that optimize the mechanical output of the respiratory musculature contracting in concert.[5,6,27,28] These responses may take the following forms[1]: Simple reflex-mediated recruitment of additional agonists, which exert similar mechanical effects on the chest wall[2]; sequential activation of inspiratory and expiratory muscles, which exert opposing effects on chest wall structures; and[3] complex behavioral acts that use nonrespiratory muscles to effect changes in body posture and expiratory airflow, minimizing dyspnea.

For example, hypercapnia and hypoxia recruit the external intercostal and parasternal muscles during inspiration in a stereotypic rostral-to-caudal direction, and the internal intercostals and triangularis sterni during expiration in the opposite direction. Preferential activation of the inspiratory external intercostal and parasternal muscles in the rostral-most interspaces decreases the impedance of the rib cage to rostral movement and, hence, facilitates thoracic expansion. Conversely, recruitment of the expiratory internal intercostals and triangularis sterni in the most caudal interspaces decreases the impedance to caudal movement and facilitates thoracic deflation. In addition, recruitment of the parasternal intercostal muscles facilitates inspiratory pressure as tidal volume increases. The parasternal intercostal muscle fiber length, which is optimum for tension development, is shorter than that of the diaphragm and occurs at higher lung volume. Accordingly, the parasternal muscles become mechanically more effective than the diaphragm as lung volume increases above functional residual capacity (FRC).

Moreover, hypercapnia and hypoxia increase phasic and tonic inspiratory activities in the dilator muscles of the upper airway (e.g., posterior arytenoid, alae nasi, genioglossus). Increases in activity of the dilator muscles of the upper airway decrease the load on the chest wall pumping muscles by decreasing the resistance to inspiratory airflow through the upper airway. Increased activity of these muscles also diminishes the susceptibility of the upper airway to collapse as inspiratory efforts become greater and subpharyngeal pressure becomes more subatmospheric.

In addition, phasic increases in abdominal expiratory muscle electrical activity during expiratory airflow accelerate lung emptying, thereby allowing the time of expiration to decrease. When sufficiently intense, activation of the abdominal muscles reduces end-expiratory lung volume and improves the ability of the diaphragm to generate pressure by favorably affecting its precontraction length, radius of curvature, and alignment with the rib cage. Reductions in end-expiratory lung volume achieved by the expiratory muscles also allow elastic work to be stored in the passive recoil of the chest wall and released suddenly at the onset of inspiration. Sudden release of the recoil pressure of the chest wall thereby "assists" the inspiratory muscles by contributing to the driving pressure to inspiratory airflow. A portion of the inspiratory load is thus assumed by the expiratory muscles.

Finally, hyperinflated, dyspneic patients with COPD often assume a stereotypic body posture that improves diaphragm, neck accessory, and pectoral girdle muscle mechanical advantage. This posture is forward flexion of the trunk, extension of the head and neck, bracing of the pectoral girdle by rounding of the shoulders, and grasping of the thighs with the arms. The effect of this posture is to increase abdominal pressure (thus increasing diaphragm precontraction length and radius of curvature); provide more favorable alignment of the scalenes and sternomastoid with the upper rib cage; and anchor the pectoral girdle muscles, allowing them to apply an inspiratory action on the rib cage. In this posture, transdiaphragmatic pressure is increased and diaphragm and sternomastoid muscle EMG activity is decreased. Patients with advanced COPD also spontaneously adopt pursed-lip breathing to slow expiratory airflow, thus minimizing dynamic airway compression.

Effects of Sleep

Responses to chemical stimuli to breathing are powerfully influenced by CNS state (e.g., sleep vs. waking).[16,29,30] Slow-wave and REM sleep depress O_2 and CO_2 chemosensitivity, with greatest depression occurring in REM sleep. While the subject is awake, apnea does not occur in the presence of even marked hypocapnia, and ventilation is largely independent of changes in P_{CO_2}. Rather, ventilation persists even when Pa_{CO_2} is less than about 30 to 35 mm Hg. Persistence of ventilation in the setting of hypocapnia (the so-called wakefulness drive to breathe) probably represents the effects on medullary neurons of inputs activated by auditory, visual, and tactile stimuli. In contrast, in the sleeping or anesthetized state, the ventilatory response to CO_2 extrapolates to zero ventilation in the hypocapnic range. In fact, apnea occurs when P_{CO_2} falls only 4 to 6 mm Hg below waking eucapnic levels. Sleep-related changes in chemosensitivity, therefore, underlie the recurrent periods of apnea and hyperpnea and exaggerated hypercapnia that occur in some patients with diseases of the lung and chest wall.

The increase in respiratory motor activity induced by derangements in respiratory mechanics is also state dependent; that is, heightened activity in awake subjects is absent in sleeping or anesthetized subjects. REM sleep, in particular, impairs the "load" response and causes collapse of the upper rib cage during inspiration, which adversely affects the level of ventilation as well as its distribution. Descending inhibitory drives to spinal α– and spindle γ–motor neurons in REM sleep cause atonia of all the respiratory muscles except the diaphragm. Muscle spindle γ–efferent activity determines spindle sensitivity by progressively contracting the intrafusal fiber. Accordingly, reductions in muscle spindle γ–efferent activity diminish spindle organ sensitivity and interfere with a mechanism for augmenting respiratory muscle spinal α–motor neuron activity. The diminished or absent load response during sleep and anesthesia probably explains the exaggerated increases in Pa_{CO_2} that occur during these periods in patients with lung and chest wall disease. In fact, REM sleep is the period in which Pa_{CO_2} is highest and Pa_{O_2} lowest in patients with stable COPD (Fig. 143-5).[31]

■ CHANGES IN RESPIRATORY STRUCTURE

Alterations in respiratory muscles and chest wall anatomy are important to consider in development of hypercapnic respiratory failure.

Respiratory Muscles

The respiratory muscles are highly plastic and undergo changes in structure, biochemistry, and contractile properties in response to chronic increases in load or changes in precontraction length.[32–38] Chronic increases in inspiratory muscle activity enhance their strength and endurance.[37,38] In animal models, chronic increases in inspiratory load produced by emphysema or inspiratory resistive loading increase diaphragm endurance and the content of oxidant enzymes (e.g., succinate dehydrogenase and citrate synthase) essential for high-energy phosphate synthesis. In patients with COPD, the percentage of slow twitch, fatigue-resistant muscle fibers in the diaphragm and parasternal intercostals is increased.[39,40] In chronic asthma, inspiratory and expiratory muscle endurance assessed from the time course of the

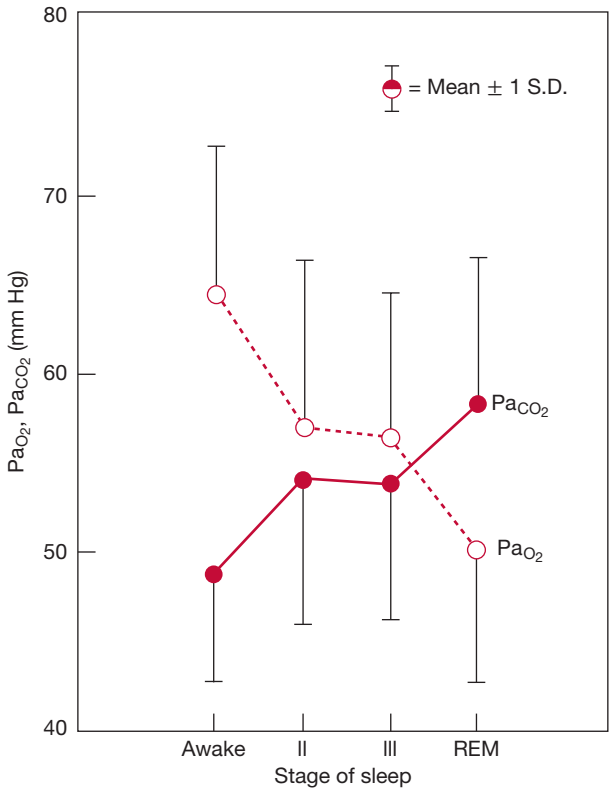

Figure 143-5 Changes in steady-state arterial P_{CO_2} during sleep in eight patients with stable COPD. Note that arterial P_{CO_2} increases and arterial P_{O_2} decreases during sleep. Greatest changes occur during REM sleep. For Pa_{CO_2}, average increase is 10 mm Hg. *(Data from Koo KW, Sax DS, Snider GL. Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. Am J Med. 1975;58:663–670.)*

fall in maximum static pressure is about 40% greater than in normal controls. The effect of COPD per se on inspiratory muscle endurance has not been assessed. In subjects with COPD, however, daily training with inspiratory resistive ventilatory loads increases inspiratory muscle strength by about 40% as reflected by maximum static inspiratory pressure (PI_{max}) over an 8- to 10-week period.

Hyperinflation impairs the force- and pressure-generating ability of the inspiratory muscles by decreasing muscle precontraction length and unfavorably changing muscle alignment with the chest wall.[5,27,41,42] In particular, severe hyperinflation alters diaphragm shape (i.e., flattening) and decreases the zone of apposition with the rib cage. Flattening of the diaphragm displaces the vector of contraction force from a rostral–caudal direction to a medial–lateral direction and diminishes the ability of the diaphragm to increase abdominal pressure. Reductions in the zone of apposition diminish the inflationary effects on the lower rib cage produced by increases in abdominal pressure induced by the diaphragm. In extreme cases of hyperinflation, the diaphragm may exert an expiratory action on the lower rib cage and retract the lower rib cage on inspiration (Hoover sign).

In part, hyperinflation-induced impairment in the action of the diaphragm is compensated for by adaptive changes in the intrinsic muscle length–tension characteristic. In emphysematous animals, the active and passive length–tension curve of the costal diaphragm is displaced toward shorter lengths, thereby allowing maximum tension to be developed at significantly shorter lengths and higher lung volumes (Fig. 143-6). The shift in the length–tension curve appears to be the reverse of normal growth, in which muscle length is increased by addition of sarcomeres in series. A similar adaptation in the diaphragm seems to occur in chronically hyperinflated, stable outpatients with COPD.[43,44]

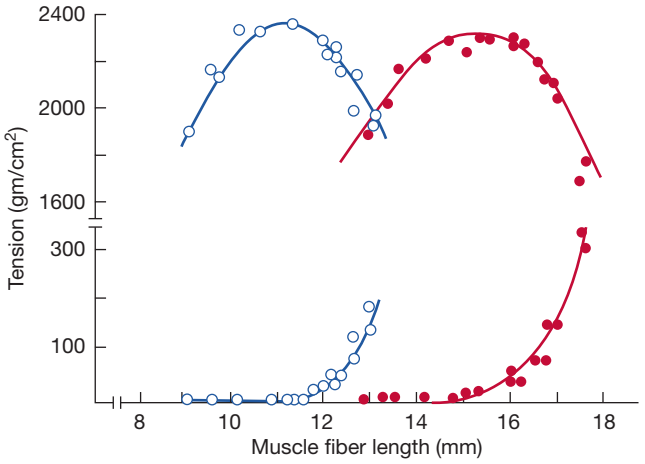

Figure 143-6 Active (upper trace) and passive (lower trace) length–tension (L-T) relationship of costal diaphragm of emphysematous *(open circles)* and normal hamsters *(solid circles)*, assessed in vitro during electrical stimulation. Note that in emphysematous animals, the L-T curve is displaced toward shorter fiber lengths. This adaptive change in emphysematous animals allows the diaphragm to generate maximal tension (force) at shorter fiber lengths and helps preserve diaphragm contractile performance in the face of considerable hyperinflation. *(Reproduced with permission from Supinski GS, Kelsen SG. Effect of elastase-induced emphysema on the force-generating ability of the diaphragm. J Clin Invest. 1982;70(5):978–988.)*

Chest Wall Anatomy

Chronic hyperinflation elicits adaptive changes in the pressure–volume (P-V) characteristic of the passive chest wall.[36] In animal models of emphysema, the static deflation, chest wall P-V curve is shifted up and to the left, so there is a decrease in elastic recoil at any given lung volume. Shifts in the passive P-V curve are accomplished by a structural remodeling of the rigid structures in the chest wall. The length of the sternum and the lengths of the ribs in anteroposterior and transverse dimensions are increased. This displacement of the chest wall P-V curve diminishes the inspiratory elastic work of breathing during hyperinflation and preserves the zone of apposition of the diaphragm. An increase in the zone of apposition of the diaphragm in hyperinflation preserves the appositional force exerted by the diaphragm on the lower rib cage by virtue of changes in abdominal pressure. If present in patients with COPD, the process is reversible, since recent observations of the thorax after volume reduction surgery or lung transplantation for COPD indicate that the shape of the chest wall can quickly revert to normal.

DECOMPENSATING/MALADAPTIVE RESPONSES

Important maladaptive responses must be considered in the setting of hypercapnic respiratory failure.

■ RESPIRATORY MUSCLE FATIGUE

The pathogenesis and clinical manifestations of respiratory muscle fatigue are considered below.

Overview/Definition

Studies in the laboratory and in the clinic indicate that the respiratory skeletal muscles, like muscles in the limbs, fatigue under conditions of intense activity, lead to respiratory failure.[45–50] Conditions that increase the level of phasic inspiratory muscle activity, or the duty cycle of breathing, or that decrease the maximal pressure-generating capacity of the muscle, make fatigue more likely. For example, derangements in the mechanical properties of the lung or chest wall or increases in ventilatory drive increase inspiratory muscle contractile activity. Of

TABLE 143-1 Classification of Respiratory Muscle Fatigue

Central
Refers to decreases in phrenic motor output mediated by spinal or supraspinal mechanisms
Peripheral
Refers to fatigue occurring at the level of the muscle itself
Transmission
Failure of mechanisms operative in muscle excitation ("high-frequency" fatigue)
Contractile
Failure of mechanisms involved in excitation–contraction coupling or contractile protein function ("low-frequency" fatigue)

note, increases in ventilatory drive increase both the peak inspiratory pressure and T_I/T_T ratio, the latter by causing greater reductions in the duration of expiration than in that of inspiration.

Decreases in inspiratory muscle strength caused by aging, protein–calorie malnutrition, or electrolyte imbalances predispose to fatigue at any given level of inspiratory impedance or ventilation by decreasing $P_{I_{max}}$. Finally, on the basis of data from animal models, reductions in diaphragm blood flow are likely to decrease the level of muscle activity that leads to fatigue.[50,51]

Respiratory muscle fatigue has been defined as a loss in muscle capacity to develop force or shorten, resulting from muscle fiber activity under load; which is reversible by rest. In contrast, respiratory muscle weakness has been defined as impairment in the capacity of a fully rested muscle to generate force.

Fatigue is viewed as developing when the muscle is highly active and generating appreciable levels of force. Recovery from fatigue is generally observed over a short time (e.g., minutes to hours). On the other hand, muscle weakness is commonly caused by muscle fiber atrophy, metabolic derangements that impair the ability of actomyosin crossbridges to generate force (e.g., acidosis or electrolyte abnormalities that affect intracellular calcium flux), or chronic reductions in muscle precontraction length that impose a mechanical disadvantage (e.g., hyperinflation of the thorax and its effects on the inspiratory muscles). Implied in the definition of weakness is the idea that alterations in inspiratory muscle function are secondary to alterations in muscle structure or lung volume and hence induce changes in muscle function that are more slowly reversible than fatigue (e.g., days to weeks). In the clinical setting, however, the distinction between muscle weakness and fatigue is difficult and not easily accomplished. Moreover, a close association exists between respiratory muscle weakness and respiratory muscle fatigue. In fact, weak muscles are predisposed to fatigue (see below Pathogenesis of Respiratory Muscle Fatigue).

Fatigue produces complex effects on muscle mechanical output. Fatigue prolongs contraction and relaxation time and depresses the force generated at a given stimulus frequency and fiber length, and reduces the velocity of shortening against a given load.

Depending on the cause of the fatigue, depression of force output can occur at primarily subtetanizing frequencies of muscle stimulation (e.g., <15 to 20 Hz), a condition called low-frequency fatigue, or at frequencies above 50 Hz, a condition called high-frequency fatigue (Table 143-1, Fig. 143-7).[47,52] The biochemical and biophysical processes that underlie low-frequency and high-frequency fatigue differ. Muscle force responses to tetanizing frequencies of stimulation (i.e., >50 Hz) are primarily determined by the processes of neuromuscular transmission and muscle excitation. In contrast, muscle mechanical output at subtetanizing frequencies is determined primarily by the processes of excitation–contraction coupling (e.g., calcium release from the sarcoplasmic reticulum, calcium–troponin interactions), perhaps caused, in part, by O_2 free radical–induced injury.

Of interest, recovery from high-frequency fatigue is more rapid (minutes) than recovery from low-frequency fatigue (hours) (Fig. 143-8). Moreover, the two forms of fatigue have different physiological consequences. High-frequency fatigue impairs muscle force output under conditions in which the muscle is maximally driven by the CNS (i.e., when muscle strength is being evaluated). Low-frequency fatigue, on the other hand, impairs force generation during resting breathing, when phrenic motor unit discharge rates are typically about 15 Hz. Since low- and high-frequency fatigue

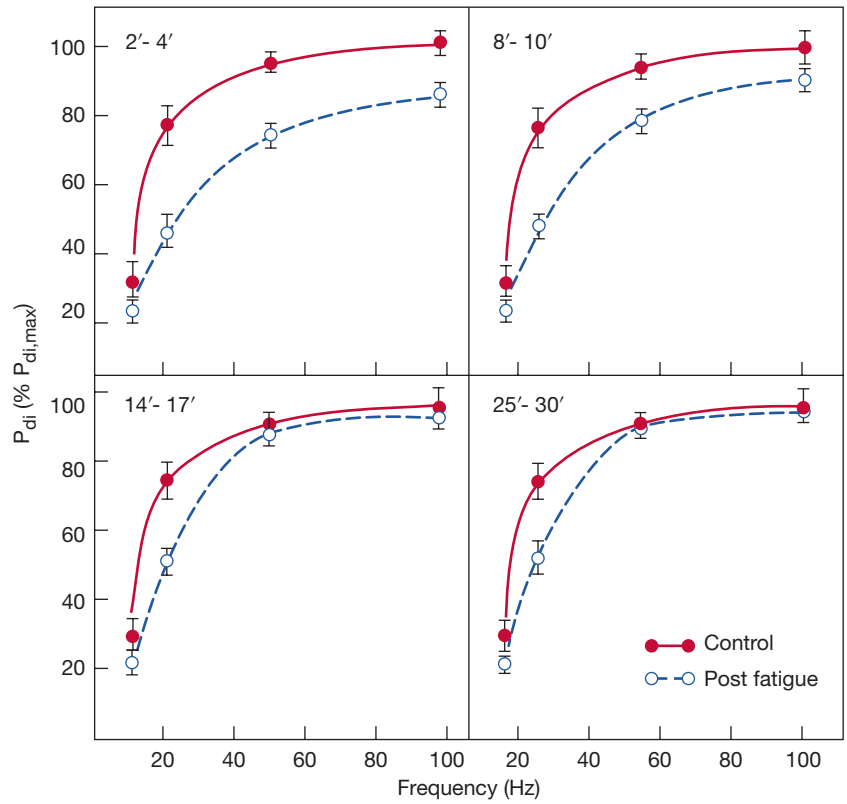

Figure 143-7 Force–frequency relationship of the human diaphragm during electrophrenic stimulation showing rate of recovery from high- and low-frequency fatigue. Data obtained in four subjects before and after a period of inspiratory resistive loading to exhaustion. At the point of exhaustion, the subject was unable to generate targeted values of transdiaphragmatic pressure (P_{di}). Note the decrease in P_{di} in response to low (20 Hz) and high (50 Hz) electrical stimulation immediately after loading, indicating the presence of both high- and low-frequency fatigue. Note also that high-frequency fatigue disappears within 14 to 17 minutes. In contrast, low-frequency fatigue persists beyond the period of observation (>30 minutes). *(Data from Aubier M, Farkas A, De Troyer RT, et al. Detection of diaphragmatic fatigue in man by phrenic stimulation. J Appl Physiol. 1981;50:538–544.)*

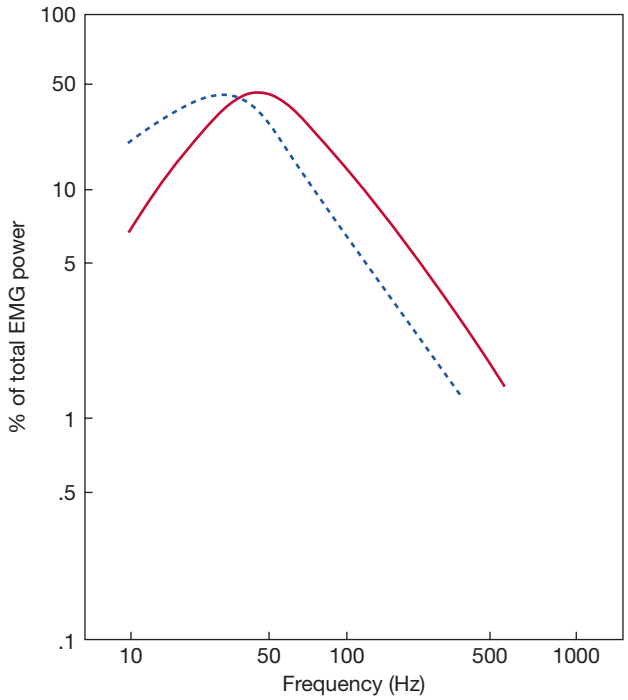

Figure 143-8 Schematic representation of the power spectral density of a respiratory muscle EMG determined by fast Fourier transform. Note the concave appearance of the relationship. Note that fatigue *(dashed line)* decreases and increases power in the high- and low-frequency domains, respectively, thereby shifting the relationship toward the left. *(Data from Moxham J, Edwards RHT, Aubier M, et al. Changes in EMG power spectrum (high-to-low ratio) with force fatigue in humans. J Appl Physiol.1982;53:1094–1099.)*

reflect impairments occurring at the level of the muscle, they have been termed *peripheral fatigue.*

Performance of strenuous ventilatory tasks may also elicit an additional, qualitatively different response—that is, a reduction in central motor output and failure of the CNS to fully activate the respiratory muscles.[47] That is, the diaphragm EMG or phrenic neurogram may decrease late in the performance of strenuous respiratory efforts before the point of exhaustion. This reduction in motor activity may limit task performance. The failure of CNS mechanisms to fully activate the muscle near the point of exhaustion has been termed *central fatigue.* The mechanisms underlying central fatigue are poorly understood. It is not clear whether central fatigue represents a behavioral response elicited by the unpleasant sensations present during ventilatory loading or is mediated reflexively or by changes in brain neurotransmitter levels.

Detection of Respiratory Muscle Fatigue

Diaphragm muscle fatigue has been diagnosed in humans from changes in the response of the muscle to electrical stimulation (i.e., the force–frequency relationship), the power spectral content of the EMG, and $P_{I_{max}}$.[45–47,52,53] As will be seen, the force–frequency relationship and EMG power spectrum analyses are complex and require sophisticated electronics and instrumentation. Consequently, their use has been confined to the research laboratory. On the other hand, $P_{I_{max}}$ is convenient and easily performed at the bedside but suffers from relative nonspecificity.

Electrical Stimulation The force–frequency relationship represents a way of assessing muscle mechanical output over a wide range of stimulus intensities. Since fatigue shifts the force–frequency curve downward (and possibly to the left), the magnitude of the shift in the force–frequency relationship can be used to assess the severity of low- and high-frequency fatigue and the time course of recovery.

Electrical stimulation of the muscle of interest has several advantages. It allows the muscle to be activated in response to a standard stimulus without the cooperation of the subject. Hence, neurological deficits, decreased effort, and central fatigue, which may diminish muscle activation, are circumvented and peripheral fatigue can be detected.

EMG Power Spectrum Fatigue alters the power-EMG spectral content of the raw EMG of the respiratory muscles analyzed by fast Fourier transform (Fig. 143-8). In the fresh diaphragm, the power (or voltage) contained in the EMG waveform reaches a maximum between approximately 85 and 105 Hz, and thereafter declines. (Maximum power in the EMG of the diaphragm, parasternal intercostal, and sternocleidomastoid occurs at somewhat different frequencies, however.) Fatigue-inducing contractions cause a leftward shift of the power spectral density, so that more of the power in the EMG is contained in a lower-frequency domain. The power spectral density of the contracting diaphragm changes almost immediately with fatiguing contractions and considerably before the mechanical output of the muscle fails. The diaphragmatic EMG power spectrum can be obtained from the raw EMG of the muscle, recorded from surface electrodes on the chest wall or within the esophagus. It is, therefore, relatively noninvasive and well tolerated. Moreover, the EMG power spectrum, unlike maximal static pressure, can be measured continuously – that is, breath by breath – and does not require subject cooperation. Accordingly, the EMG power spectrum has proved to be a useful tool to study the pathophysiological mechanisms of human respiratory muscle fatigue. A significant caveat in the use of the power spectrum is the suggestion that it may be unable to detect low-frequency fatigue.

Pathogenesis of Respiratory Muscle Fatigue

Studies designed to examine the pathogenetic mechanisms that led to respiratory muscle fatigue have largely focused on the diaphragm. The diaphragm has been the primary focus of attention for several reasons. First, it is the major respiratory muscle. Second, anatomic considerations allow the mechanical output of the diaphragm (i.e., transdiaphragmatic pressure) and its EMG, an index of phrenic motor outflow and fatigue state, to be assessed relatively easily. Finally, the cervical phrenic nerves can be electrically stimulated, thereby allowing the mechanical output of the muscle to be assessed under standard conditions as well as during volitional contractions.

Muscle Activity In seminal studies, Roussos and Macklem[46] observed that the time of onset of diaphragm fatigue was *not* related to the magnitude of the phasic inspiratory swings in P_{di} during loading alone or to $P_{di,max}$ alone. Rather, the time of onset of mechanical failure of the diaphragm was a unique curvilinear function of the ratio of P_{di} generated on each breath over $P_{di,max}$ ($P_{di}/P_{di,max}$) (Fig. 143-9). Values of $P_{di}/P_{di,max}$ less than 40% to 50% could be maintained indefinitely; values greater than this threshold were associated with progressively more rapid exhaustion. These results made several important points. First, diaphragm fatigue depended on the relative intensity of contraction (i.e., muscle force output as a percentage of its strength). Second, contractions below some critical threshold could be sustained indefinitely and did not lead to fatigue.

Subsequent studies demonstrated that the timing as well as the intensity of diaphragmatic contractions determined the time of onset of mechanical failure of that muscle.[48] Increases in the ratio of the T_I over the T_T increased the rapidity of onset of fatigue at any given $P_{di}/P_{di,max}$ ratio. That is, increasing the duration of diaphragm contraction relative to the period during which the diaphragm is relaxed, the duty cycle of breathing, predisposes to fatigue. In fact, diaphragm fatigue appears to be largely a function of the product of $P_{di}/P_{di,max} \times T_I/T_T$,

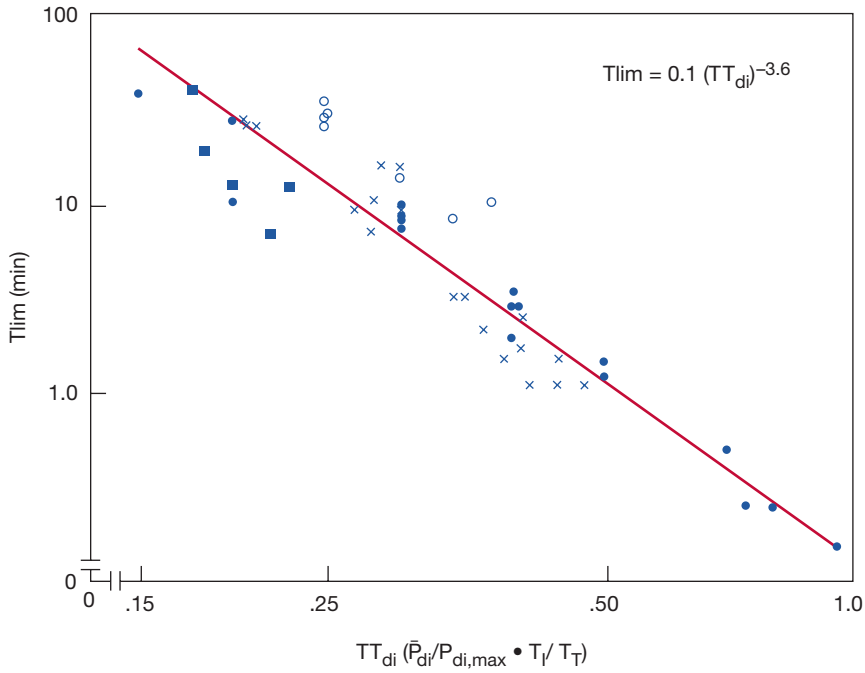

Figure 143-9 Relationship between the intensity of diaphragm contractile activity reflected in the diaphragm tension–time index (TTdi)—that is, the product of $P_{di}/P_{di,max} \times T_I/T_T$ and the time of onset of mechanical failure of the diaphragm, Tlim. The two scales are logarithmic. Data obtained in normal subjects during strenuous volitional contractions during inspiratory resistive ventilatory loading. Note that above approximately 15% TTdi, Tlim decreases progressively with increasing TTdi. These data indicate that a fatigue threshold exists for the human diaphragm above TTdi 15% to 20% and that above this threshold, diaphragm endurance is a unique function of the TTdi. *(Data from Bellemare F, Grassino A. Evaluation of human diaphragm fatigue. J Appl Physiol. 1982;53:1196–1206.)*

which has been termed the *diaphragm tension–time index* (TTI) (Fig. 143-10). The TTI is, in essence, the integrated area under the pressure waveform over time. The TTI is usually expressed not in absolute terms of pressure per unit of time but, rather, in relative terms as a dimensionless value (i.e., as a percentage of the maximum) to reflect the importance of relative changes in pressure and timing of contraction. The TTI determines muscle energy use as reflected in the O_2 consumption.

A threshold for the onset of fatigue occurs at a TTI of approximately 15% to 20% of maximum (Fig. 143-10).[47,48] The greater the TTI above this value, the more rapidly fatigue ensues.

Subsequent studies in normal subjects demonstrated that mechanical failure of the inspiratory muscles as pressure generators can be accelerated at a given TTI by increasing the V_T/T_I. Increases in V_T/T_I reflect an increase in the velocity of inspiratory muscle shortening. Since the greater the velocity of shortening and the more rapid actomyosin crossbridge cycling, the greater the rate of adenosine triphosphate splitting, this is not surprising. Also of interest, respiratory maneuvers associated with high levels of ventilation appear to selectively fatigue the diaphragm, whereas maneuvers that produce high levels of pressure primarily fatigue the intercostal and neck muscles.

Muscle Blood Flow Diaphragm fatigue may relate, in part, to a compromise of muscle blood flow during intense contractions. The relationship of diaphragm blood flow to muscle contractile activity is complex and depends, like fatigue itself, on both the intensity and timing of contractions. The level and pattern of diaphragm activation, therefore, determine not only muscle energy use but also the availability of metabolic fuel (i.e., glucose, free fatty acids, and other nutrients).

Contractions of low intensity increase blood flow.[50,51] In contrast, contractions in excess of 20% to 30% of $P_{di,max}$ mechanically compromise blood flow and cause postcontraction hyperemia. When the diaphragm contracts rhythmically, the T_I/T_T also affects diaphragm blood flow. At $P_{di}/P_{di,max}$ values that compromise blood flow during contraction (i.e., above 20% –30%), blood flow occurs solely during the phase of muscle relaxation. Consequently, increases in the T_I/T_T ratio decrease overall blood flow by encroaching on relaxation time. Diaphragm blood flow is, therefore, a function of the TTI rather than $P_{di}/P_{di,max}$ or the T_I/T_T alone. Blood flow increases up to a TTI of 20% to 30% and thereafter falls progressively with further increases in TTI. Compromise of

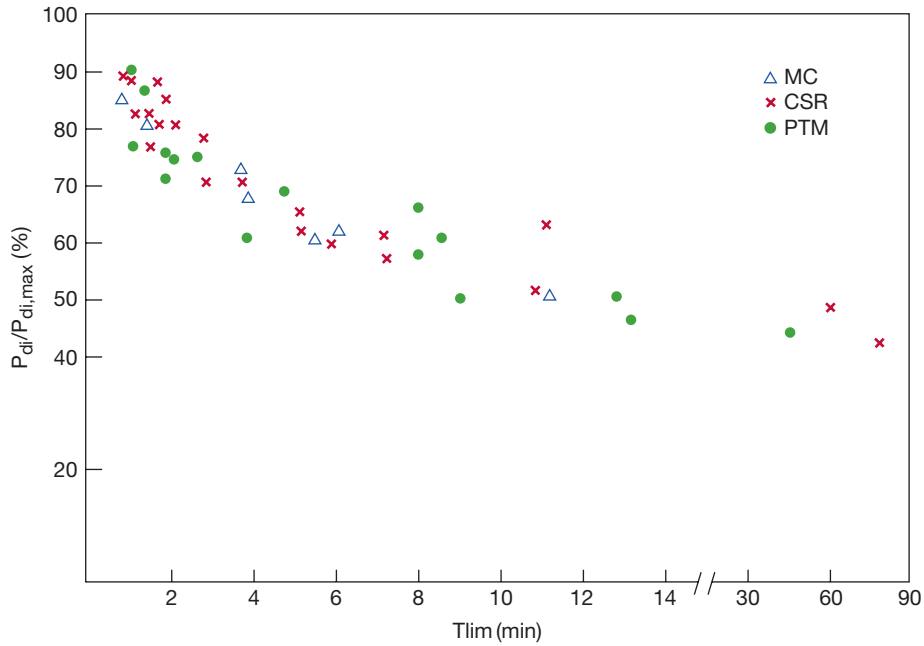

Figure 143-10 Effect of increasing $P_{di}/P_{di,max}$ (i.e., the ratio of peak inspiratory P_{di}) during resistance breathing over maximum static P_{di} (ordinate) at the time of onset of mechanical failure of the diaphragm, Tlim (abscissa). Data from three normal subjects (shown as separate symbols). Note that progressive increases in $P_{di}/P_{di,max}$ are associated with more rapid onset of diaphragm fatigue. Note also the curvilinear nature of the relationship, with apparent asymptote between 40% and 50% $P_{di}/P_{di,max}$, which represents a fatigue threshold. *(Data from Roussos CS, Macklem PT. Inspiratory muscle fatigue, in Macklem PT, Mead J (eds). Handbook of Physiology, section 3: The Respiratory System, vol III: Mechanics of Breathing, part 2. Bethesda, MD, American Physiological Society.1986.)*

diaphragm blood flow when TTI is greater than 20% to 30% of maximum may lead to a condition in which the metabolic needs of the muscle outstrip the availability of energy supply. Alternatively, the importance of blood flow may lie in washing out toxic metabolites (e.g., hydrogen and phosphate ions) from the muscle. The diaphragmatic TTI associated with limitation of blood flow is also a complex function of the level of systemic arterial pressure. Reductions in arterial pressure produced in animal models by bleeding decrease blood flow at any given level of TTI and reduce the P_{di} value at which blood flow is mechanically impeded.

Of considerable importance, diaphragm blood flow may also be a determinant of steady-state diaphragm contractile function in COPD patients in acute respiratory failure.[54] In small numbers of COPD patients, 30% to 50% increases in diaphragm blood flow with intravenous dopamine (8 μg/kg/min) caused rapid, approximately 40% increases in P_{di} during electrophrenic twitch contractions. These findings require confirmation before vasodilator therapy to improve diaphragm function can be advocated. However, they suggest the possibility that diaphragm blood flow may be compromised by intense contractile activity in patients with severe lung disease.

Rapid, Shallow Breathing

Patients with abnormalities in ventilatory pump function breathe rapidly and shallowly in respiratory failure.[55] Respiratory rate is increased and tidal volume is decreased. Reductions in T_I are out of proportion to reductions in T_E, so the duty cycle of breathing (T_I/T_T) is reduced to less than normal values (below 40%). Average inspiratory airflow (V_T/T_I) tends to be normal, despite abnormalities in mechanics, because of increases in the neuromuscular drive to breathe as reflected in the airway occlusion pressure. Reductions in T_I have the effect of increasing the dead space-to-tidal-volume ratio (V_D/V_T) and predisposing to alveolar hypoventilation.

A rapid, shallow pattern of breathing with an abnormally low T_I/T_T ratio and reduced tidal volume is extremely common in patients with COPD during acute exacerbations and tends to get better with improvements in clinical condition.[55] Rapid, shallow breathing appears to cause CO_2 retention rather than result from it. It can be produced in patients with COPD by histamine-induced bronchoconstriction and reversed by topical airway anesthesia. Patients with neuromuscular disease in whom the ability to generate inspiratory pressure is impaired require more intense motor outflow to the respiratory muscles to maintain tidal volume. Patients with respiratory muscle weakness also tend to breathe rapidly and shallowly.

The pattern of breathing has been quantified in adults receiving ventilatory support for acute respiratory failure from the ratio of respiratory rate (breaths per minute) divided by tidal volume (liters). This useful parameter has been termed the *rapid shallow breathing index* (RSBI). It has proved to be an extremely powerful way of assessing weanability in adults with a variety of medical and surgical conditions. The greater the value, the more rapid and shallow is the pattern of breathing. Values for the RSBI exceeding 100 are associated with a high probability of failure to wean from mechanical ventilation. The RSBI lends itself to a more general use in patients with disorders of the ventilatory pump not requiring mechanical ventilation.

Rapid, shallow breathing leading to CO_2 retention exerts a number of deleterious effects. First, CO_2 retention decreases Pa_{O_2} and arterial pH. Decreases in Pa_{O_2} result in accordance with the alveolar air equation. In general, a 1 mm Hg increase in Pa_{O_2} causes a 1.25 mm Hg reduction in Pa_{O_2} (assuming a respiratory quotient of 0.8; larger respiratory quotient values are associated with smaller changes in Pa_{O_2}). Second, renal compensation for hypercapnia-induced respiratory acidosis stimulates bicarbonate resorption. Increases in body fluid bicarbonate restore pH toward normal values but blunt the ventilatory response to further increases in CO_2. Third, hypercapnia depresses diaphragm contractility; that is, P_{di} is decreased at a given level of diaphragm electrical activity in proportion to the increase in P_{CO_2}.

However, rapid, shallow breathing may also confer beneficial effects to subjects with severe ventilatory pump dysfunction. First, CO_2 retention increases the CO_2 partial pressure gradient between the alveolus and atmosphere. Accordingly, during hypercapnia the same volume of metabolically produced CO_2 can be excreted at a lower level of alveolar and minute ventilation and O_2 cost of breathing than during eucapnia. As such, CO_2 retention affords a mechanism to diminish the activity level of the inspiratory muscles and their propensity to fatigue. Normal humans and animal models fatigued by inspiratory resistive loads in the laboratory spontaneously minimize the diaphragm TTI after fatigue by adopting a shallow, rapid pattern of breathing. In fact, a large study of stable outpatients with advanced COPD indicates that the inspiratory muscle TTI is below the fatigue threshold even in markedly hypercapnic (above 60 mm Hg) subjects (see below Pathogenesis of Rapid, Shallow Breathing).[49] Second, rapid, shallow breathing minimizes the magnitude of dynamic hyperinflation in patients with severe COPD who breathe on the envelope of the maximum expiratory flow–volume loop; that is, reductions in tidal volume and decreases in the T_I/T_T ratio diminish the volume to be exhaled and prolong the expiratory time available to reach FRC.

The balance between the beneficial and deleterious effects of CO_2 retention is difficult to define with precision; however, the balance probably is determined by the magnitude and rapidity of the changes in Pa_{CO} and pH and their effect on the cardiovascular and CNSs. Relatively small (5–15 mm Hg) changes in Pa_{CO_2}, produced gradually over days to weeks and leaving pH at levels of 7.25 to 7.30, are likely to be well tolerated and, on balance, beneficial. On the other hand, Pa_{CO_2} changes that occur rapidly and reduce pH to less than 7.25 are likely to exert net negative effects. In fact, respiratory acidosis to pH values under 7.25 is life-threatening and generally considered an indication for intubation and mechanical ventilation. Cardiac function and sympathetic regulation of peripheral vascular resistance are impaired at this level of pH. Patients become encephalopathic (i.e., somnolent and unable to care for themselves and control their airway secretions). Obviously, hypercapnia of such magnitude is to be avoided.

Pathogenesis of Rapid, Shallow Breathing

The neurophysiological mechanisms driving the altered pattern of breathing are obscure. Moreover, whether changes in breathing pattern in animal models and humans are reflexively induced or behaviorally mediated, or reflect changes in brain neurotransmitter levels (e.g., endorphins), are unclear. However, chemosensitivity-induced alterations in respiratory activity do *not* appear to be the explanation. Hypoxia- and hypercapnia-induced reductions in T_E are disproportionately greater than reductions in T_I, so the T_I/T_T ratio increases. Moreover, V_T/T_I and the tidal volume are increasing rather than decreasing.

Reflexes originating from mechanoreceptors in the contracting rib cage muscles and diaphragm (i.e., Golgi tendon organs, spindle organs, and type III and type IV endings) probably play a role in shaping the rapid, shallow pattern of breathing.[7] In deeply anesthetized animals, stretch of the intercostal muscles or an increase in diaphragm tension may abruptly terminate inspiration. Activation of vagal irritant receptors in the airway may also produce rapid, shallow breathing.[4] In animal models, rapid, shallow breathing produced acutely by inhalation of allergen or inflammatory mediators (e.g., histamine, bradykinin) can be prevented by vagal blockade. These observations suggest that rapid, shallow breathing in bronchoconstriction may be mediated by vagal sensory endings in the airways.

Finally, changes in the pattern of breathing may represent a behavioral response to minimize the sense of dyspnea. The sense of dyspnea is a complex perceptual construct that is not fully understood but is probably multifactorial.[56,57] In fact, an important determinant of the sense of dyspnea is the magnitude of the CNS motor command to the inspiratory muscles as reflected in the peak inspiratory intrathoracic pressure. Studies indicate that the sense of breathlessness increases for any set of respiratory mechanical conditions with increases in peak inspiratory pressure, the duration of inspiration, or respiratory rate. In particular, the magnitude of the sense of dyspnea depends on inspiratory pressure (P) swings as a percent of maximum (P/P_{max}), the duration of inspiration relative to the total breath cycle (T_I/T_T), and the respiratory rate (freq). However, the relative importance of these three terms is quite different. The peak inspiratory pressure has a far greater effect than the duration of inspiration, which in turn has a greater effect than breathing frequency. The sensation of dyspnea can be expressed quantitatively by each of these parameters raised to a power:

$$\text{Dyspnea} = P^{1.3} \times T_I / T_T^{1.14} \times \text{freq}^{-0.97}$$

Increases in intrathoracic pressure required to maintain airflow and tidal volume in patients with abnormalities in ventilatory pump function increase the sense of dyspnea. Given the greater exponential value for P than for the timing variables, it can be seen that the magnitude of the swing in inspiratory pressure is the predominant determinant of dyspnea. Thus, at a given level of minute ventilation and set of respiratory mechanics, the pattern of breathing determines the intensity of breathlessness. When the mechanics of breathing are deranged by COPD or kyphoscoliosis, diminishing peak inspiratory intrathoracic pressure (i.e., tidal volume) and increasing respiratory rate (i.e., a rapid, shallow pattern of breathing) tend to minimize the sense of breathlessness.

At equivalent levels of airway resistance and inspiratory effort, the sense of dyspnea is greater during bronchoconstriction than during external resistive loading, probably because of the activation of vagal irritant receptors. Differences in the intensity of dyspnea at any given level of airway obstruction, therefore, may depend on the site of airway obstruction (i.e., intra- vs. extrathoracic). Also, the sense of dyspnea at a given level of peak intrathoracic pressure, T_I/T_T ratio, and frequency of breathing are increased in the setting of inspiratory muscle fatigue, probably because a greater motor command is required to generate a given level of intrathoracic pressure. Finally, it should be apparent from the previous equation that the sense of dyspnea depends on the same variables that determine respiratory muscle fatigability. However, respiratory muscle fatigue, in contrast to dyspnea, does not appear to depend on the pattern in which TTI is developed; that is, whether a given TTI is arrived at by a higher P/P_{max} or a higher T_I/T_T is irrelevant in the development of fatigue, but it *is* important in the generation of respiratory sensations.

Perceptual acuity of the respiratory sensations elicited when the mechanical properties of the ventilatory pump are deranged is a major determinant of the pattern of breathing and tendency to develop CO_2 retention in subjects with COPD.[58,59] For example, when airway resistance is increased experimentally, patients with COPD who retain CO_2 are those with the greatest perceptual acuity for changes in intrathoracic pressure. That is, spontaneous tidal volume and T_I are smallest in patients with COPD who have the highest perceptual acuity for changes in intrathoracic pressure.

On the other hand, when airway resistance was increased experimentally by external resistive loads, asthmatics with near-fatal attacks experienced less dyspnea at any level of resistance than normal subjects (Fig. 143-11).[19] Accordingly, in patients with COPD the acuity of respiratory perception plays an important role in the pathogenesis of respiratory failure. The mechanism by which respiratory perception contributes to respiratory failure awaits clarification.

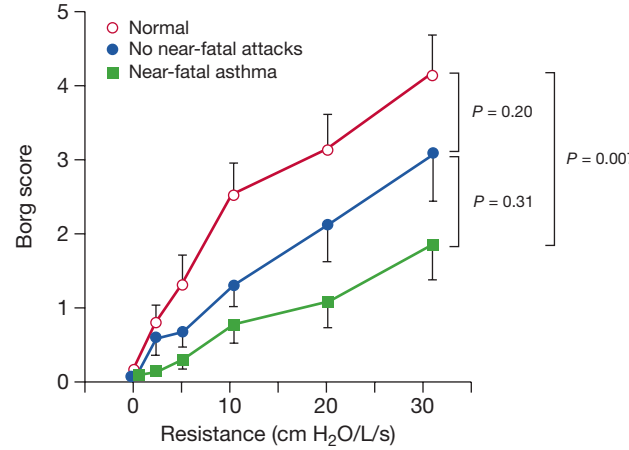

Figure 143-11 Severity of dyspnea experienced during breathing against external resistive ventilatory loads in normal subjects, patients with asthma but no near-fatal attacks, and patients with near-fatal asthma. Y axis indicates the intensity of dyspnea (i.e., Borg score). Increasing numerical values on the Borg score indicate increasing dyspnea. Note that at any given level of external resistance, dyspnea was significantly less in patients with near-fatal asthma than in the normal group. *(Data from Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med.1994;330:1229–1234.)*

UNDERNUTRITION

Undernutrition, defined as a body weight less than 90% of the ideal, is extremely common in patients with COPD, occurring in about 25% of stable outpatients and about 40% of hospitalized patients. Undernutrition is an independent risk factor for mortality. For a given level of lung function, undernourished patients with COPD have a greater 5-year mortality than normally nourished subjects. The respiratory muscles, like skeletal muscles in other parts of the body, atrophy under conditions of chronic protein–calorie deficiency.[60] In patients without lung disease, PI_{max} is significantly smaller in those who are undernourished than in those who are well nourished. In those with COPD at autopsy, the mass (i.e., weight and thickness) of the diaphragm is diminished in undernourished compared to well-nourished subjects. Both slow and fast fibers in respiratory muscles (e.g., the diaphragm and intercostals) atrophy in subjects with advanced COPD. In patients with COPD, resting Pa_{CO_2} is inversely related to PI_{max}. The weaker the subject, the greater the Pa_{CO_2}. Reductions in PI_{max} predispose to inspiratory muscle fatigue by increasing the $P_{di}/P_{di,max}$ ratio and, hence, the TTI during breathing against a given set of lung mechanics. Of practical importance, aggressive nutritional repletion, which increases body weight, augments PI_{max} and $P_{di,max}$. Thus, respiratory muscle wasting and atrophy are reversible in undernourished patients with COPD.

The pathogenesis of body wasting in subjects with chronic diseases like COPD is unclear. However, increases in the work of breathing and respiratory muscle activity increase resting energy expenditure by as much as 50% to 100% above normal. In normal subjects in whom basal energy requirements are similarly increased by heavy physical labor (e.g., lumberjacks), caloric intake is increased appropriately to meet metabolic demands and body weight is preserved. Accordingly, the root of the problem in undernourished patients with COPD may be "relative anorexia," so that increases in basal caloric requirements are not accompanied by adequate caloric intake. Undernourished patients with COPD have higher blood levels of the cachexia factor tumor necrosis factor-α than well-nourished COPD subjects.

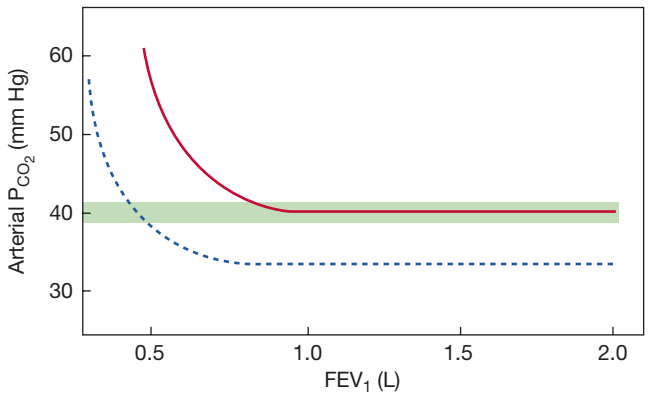

Figure 143-12 Relationship between the severity of airway obstruction reflected in the FEV_1 and steady-state arterial P_{CO_2} in COPD and asthma. *Shaded area* represents normal range of arterial P_{CO_2}. The relationship is curvilinear, so CO_2 retention occurs only after FEV_1 is considerably reduced. The asthmatic curve *(dashed line)* lies below and to the left of the curve for COPD, indicating that much greater levels of obstruction are necessary before arterial P_{CO_2} rises. *(Reproduced with permission from Fishman AP. Pulmonary Diseases and Disorders, vol 1. New York, McGraw-Hill; 1980.)*

SPECIFIC DISEASES

Hypercapnic respiratory failure may complicate a number of specific disorders, as discussed below.

■ CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with advanced COPD develop CO_2 retention because of abnormalities in the gas exchange and mechanical properties of the lung. The relationship between the severity of COPD as reflected by the forced expiratory volume in 1 second (FEV_1) and steady-state resting P_{CO_2} is curvilinear (Fig. 143-12).[61] In general, Pa_{CO_2} does not increase above normal until the FEV_1 decreases to about 20% to 25% of predicted normal values.

The effects of COPD on lung gas exchange are complex. Simply put, increases in lung dead space and abnormalities in ventilation/perfusion relationships impair CO_2 elimination and O_2 uptake. Increases in physiological dead space require greater than normal levels of ventilation and tidal volume to maintain eucapnia. Maintenance of "normal tidal volume" in the setting of increased dead space predisposes to CO_2 retention because of an unfavorable V_D/V_T. Normally, during resting breathing, ventilation is 4 to 5 L/min, of which alveolar ventilation is approximately 70% to 80%. In COPD, abnormalities in lung gas exchange for O_2 and CO_2 (i.e., increased dead space volume and alveolar–arterial O_2 gradient) require greater than normal levels of ventilation to maintain eucapnia and euoxia. Consequently, in subjects with advanced COPD, minute ventilation is typically two to three times the normal value (i.e., 10–15 L/min). Minute ventilation is increased still further in hypoxemia. Increases in ventilation require increases in airflow, tidal volume, and the duty cycle of breathing.

Hyperinflation and heightened airway resistance are common in patients with advanced COPD. Hyperinflation and increases in FRC in patients with COPD are multifactorial. First, emphysema decreases lung (and possibly chest wall) elastic recoil pressure. Second, tonic activation of chest wall inspiratory muscles throughout the respiratory cycle enhances transpulmonary pressure. Third, activation of laryngeal constrictor muscles and pursed-lip breathing during expiration slow the rate of expiratory airflow. Fourth, severely obstructed patients breathing on the envelope of the maximum expiratory flow–volume curve may have insufficient time during expiration to exhale to passively determined FRC.

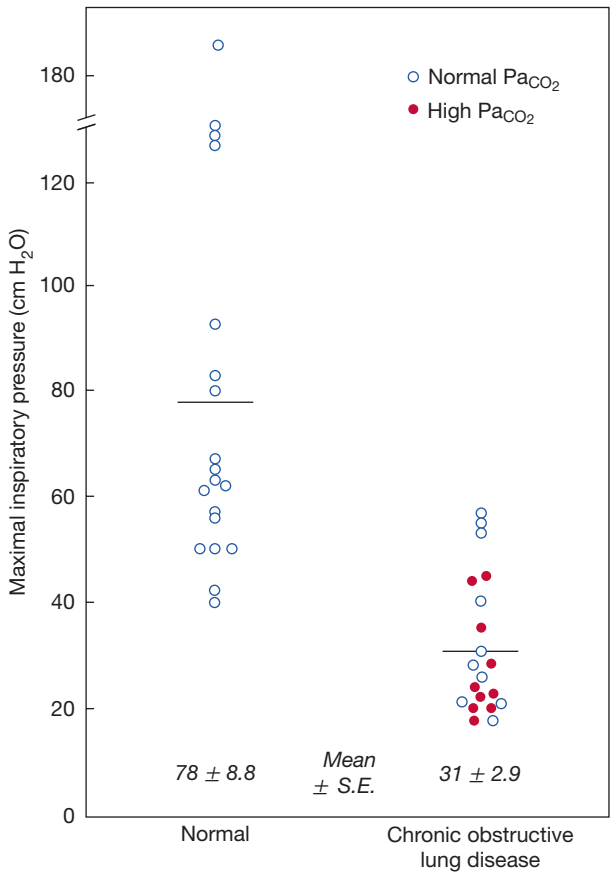

Figure 143-13 Inspiratory muscle strength as reflected in the maximum static inspiratory pressure ($P_{I_{max}}$) at functional residual capacity (FRC) in subjects with advanced COPD and age-matched normal subjects. Each symbol represents a single subject. Note that in COPD subjects, because of hyperinflation and muscle wasting, $P_{I_{max}}$ is reduced to approximately 40% of the value in normal subjects. Note the tendency for hypercapnic subjects to have even lower values of $P_{I_{max}}$ than eucapnic COPD subjects. *(Data from Sharp JT, van Lith P, Nuchprayoon C, et al. The thorax in chronic obstructive lung disease. Am J Med. 1968;44:39–46.)*

In advanced COPD, increases in airway resistance and hyperinflation require greater than normal swings in intrathoracic pressure to generate normal levels of airflow and tidal volume.[38] In consequence, the respiratory neuromuscular drive to breathe, peak inspiratory intrathoracic pressure, and the TTI of the inspiratory muscles are increased considerably.[49,62] Normally, at rest, respiratory muscle O_2 consumption is less than 2% of total body O_2 consumption (i.e., about 5 mL/min or less). In contrast, patients with advanced cardiopulmonary disease may have levels of respiratory muscle O_2 uptake greater than 50% of total body O_2 uptake (i.e., in excess of 125 mL/min).

In subjects with severe COPD, hyperinflation reduces inspiratory muscle mechanical advantage, which decreases the capacity of the inspiratory muscles to generate pressure (P_{max}). P_{max} values in patients with COPD may be as low as one-third to one-half that of age-matched normal subjects (Fig. 143-13). Moreover, aging- and malnutrition-associated changes in the diaphragm may further impair $P_{di,max}$ in subjects with COPD. COPD typically becomes disabling in the sixth and seventh decades of life, a period of life at which P_{di} normally falls. For example, $P_{di,max}$ is about 25% less in healthy men over 65 years of age than in healthy men under 35 years of age.

RESPIRATORY MUSCLE FATIGUE IN COPD

Severe COPD is arguably the clinical condition most likely to cause inspiratory muscle fatigue. The combined effects of increases in

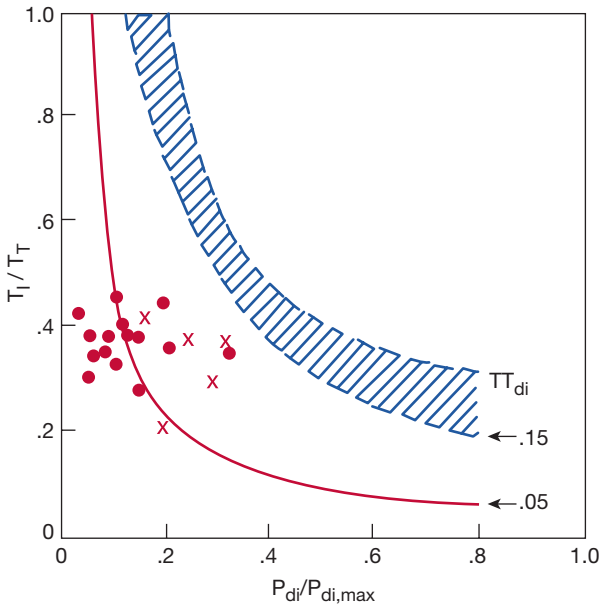

Figure 143-14 Diaphragmatic tension–time index (TTdi) in 20 stable outpatients with COPD breathing room air at rest. Each symbol represents a separate COPD subject. *Shaded area* represents the fatigue threshold in normal subjects. Most COPD subjects breathe well below the fatigue threshold and cluster around 0.05 TTdi. *(Data from Bellemare F, Bigland-Ritchie B. Central components of diaphragmatic fatigue assessed by phrenic nerve stimulation. J Appl Physiol. 1987; 62:1307–1316.)*

inspiratory muscle activity and decreases in muscle strength in severe COPD increase the diaphragm TTI during resting breathing in elderly COPD patients considerably above the normal value of 1% to 2%.[49] The TTI may, in fact, approach the fatigue threshold (i.e., 15%–20%) in patients with COPD (Fig. 143-14). These and similar data indicate that diaphragm activity is increased in patients with advanced COPD, and that the diaphragm is highly susceptible to fatigue when breathing is increased above spontaneous levels by minor increases in tidal volume or T_I/T_T. The diaphragm TTI is higher in hypercapnic than in eucapnic COPD subjects, but even in hypercapnic subjects it does not exceed the fatigue threshold. Mean TTI, even for hypercapnic subjects, is approximately 10%. Therefore, hypercapnia per se does not indicate the presence of diaphragm fatigue even in patients with severe COPD. Rather, hypercapnia may be a manifestation of a breathing strategy (i.e., rapid, shallow breathing) that minimizes inspiratory muscle activity and, hence, prevents fatigue.

On the other hand, inspiratory muscle fatigue may be a relatively common occurrence during the hyperpnea of exercise and could contribute to exercise limitation in COPD subjects. A high percentage (about 50%) of subjects with moderate to severe COPD demonstrate EMG evidence of scalene or diaphragm (or both) fatigue during exercise. Of interest, improvement in exercise performance and elimination of the EMG signs of fatigue can be achieved following inspiratory resistance training.

Subjects with COPD in acute respiratory failure requiring mechanical ventilation are more likely to show evidence of inspiratory muscle fatigue.[53,54] During weaning from mechanical ventilation, diaphragm EMG changes indicative of fatigue precede the increases in Pa_{CO_2}. These findings suggest that diaphragm fatigue contributes to ventilator dependence after the onset of hypercapnic respiratory failure in at least some critically ill subjects.

In COPD patients being weaned from mechanical ventilation during a bout of acute respiratory failure, the tracheal occlusion pressure is usually greater than 6 cm H_2O and EMG evidence of diaphragm fatigue is present during spontaneous breathing.[53] Patients with persistently elevated tracheal occlusion pressure values (>6 cm H_2O) and EMG evidence of diaphragm fatigue generally cannot be successfully weaned from mechanical ventilation. In contrast, sternomastoid muscle fatigue is evident in fewer than 10% of COPD patients hospitalized for worsening respiratory distress.

In summary, most subjects with stable COPD adopt a pattern of breathing that minimizes the diaphragm TTI and prevents inspiratory muscle fatigue. Behavioral mechanisms may be operative in an attempt to minimize the sensation of dyspnea. On the other hand, inspiratory muscle fatigue contributes to the morbidity of a subgroup of patients with COPD by preventing weaning from mechanical ventilation, and possibly by impairing exercise performance. The reported number of COPD subjects with respiratory muscle fatigue is small, however, and may represent a highly select population. Further studies are needed to define the extent of this problem.

■ ASTHMA

The pathophysiology of CO_2 retention appears to be generally similar in patients with asthma and COPD, but the likelihood of developing CO_2 retention is less in asthma than in COPD. That is, the level of expiratory airway obstruction required to produce CO_2 retention in subjects with acute asthma is greater than that required in subjects with COPD (Fig. 143-14).[61] Several possibilities may explain this tendency. First, it appears that inspiratory drive is higher in patients with asthma than in those with COPD. The airway occlusion pressure is considerably higher at any given level of Pa_{CO_2} in patients with asthma than in normal subjects or patients with COPD. The heightened inspiratory drive in patients with asthma may in part arise from irritant receptors within the airway, which have an augmenting effect on inspiratory motor neuron activity. Furthermore, the inspiratory muscles are stronger, and ventilatory responses to CO_2 and hypoxia are greater, in the younger asthmatic than in COPD subjects. These differences are not simply due to age, as the endurance of the inspiratory and expiratory muscles is greater in asthmatic than in age-matched normal subjects. The increased respiratory muscle endurance in subjects with asthma may be a response to chronic increases in inspiratory muscle load. Finally, greater lung elastic recoil in asthma than in COPD tends to preserve maximal expiratory airflow.

■ NEUROMUSCULAR DISEASE

Subjects with neuromuscular disease and weak inspiratory muscles tend to breathe rapidly and shallowly.[63] Despite this breathing pattern, these subjects tend to have hypocapnia at rest, and hyperventilate at any given level of CO_2 during progressive hypercapnia. Increases in ventilation are associated with increases in airway occlusion pressure. Heightened occlusion pressure in the setting of weak inspiratory muscles suggests that the drive to the inspiratory muscles early in inspiration is greater than normal.

The pathogenesis of hypercapnic respiratory failure is very different in patients with neuromuscular disease than in patients with COPD. Patients with neuromuscular disease demonstrate an impaired ability to sigh (i.e., a greater than twofold increase in the tidal volume) because of inspiratory muscle weakness. Inability to sigh decreases lung compliance by interfering with the redistribution of surfactant within the alveolar space. Progressive stiffening of the lung leads to microatelectasis and ultimately lobar atelectasis. Breathing high concentrations of O_2 accelerates this process. In addition, expiratory muscle weakness impairs the cough mechanism and causes retention of secretions.

The best indicators of a tendency to develop CO_2 retention in patients with neuromuscular disease are reductions in inspiratory muscle strength (PI_{max}) and forced vital capacity (FVC). Reductions in PI_{max} and FVC to less than 30% and 25% of predicted, respectively,

are associated with CO_2 retention. Suffice it to say, hypercapnia is a late manifestation of neuromuscular disease and requires marked impairment in inspiratory and expiratory muscle function. With diaphragm dysfunction, hypercapnia may occur during sleep (especially REM sleep) even when the subject is eucapnic while awake.

OBESITY

Obesity imposes a stress on the respiratory system both by altering lung mechanics and the work of breathing (see Chapter 83). The mass loads applied to the thorax and abdomen by excess fatty tissue decrease chest wall compliance and end-expiratory lung volume resulting in increases in the elastic and resistive work of breathing. Furthermore, by diminishing airway caliber, obesity predisposes to premature airway closure and even atelectasis. The resultant low ventilation–perfusion ratios of these lung regions increase alveolar–arterial O_2 gradient and cause arterial hypoxemia. In fact, hypoxemia is the most common respiratory abnormality in the morbidly obese.

In addition, the excessive body mass results in increased CO_2 production and O_2 consumption. Increases in metabolism may be two to three times normal in morbidly obese subjects.[64] These metabolic changes require significant increases in minute and alveolar ventilation to maintain eucapnia and hence, increasing ventilatory demands. For example, a doubling in CO_2 production requires a doubling in alveolar ventilation to maintain eucapnia. Finally, arterial hypoxemia, which is common, induces a further increase in ventilation.

Given these stresses, the maintenance of normal blood-gas tensions requires a considerable increase in respiratory motor output and the work of breathing. Increased work of breathing appears to explain the common occurrence of dyspnea in the morbidly obese person.

Not all morbidly obese subjects develop hypercapnic respiratory failure, however. Although body weight alone does not predict the development of hypercapnia, approximately 30% of severely obese subjects with a body mass index (BMI) of more than 35 kg/m^2 and almost 50% with a BMI of 50 kg/m^2 or greater have unexplained daytime hypercapnia. Observations of eucapnic and hypercapnic obese subjects demonstrate that eucapnic subjects have greater increases in diaphragm electrical activity with increases in CO_2 than hypercapnic subjects. Obese subjects with hypercapnic respiratory failure may have impaired chemosensitivity to hypercapnia and hypoxemia.

A subset of obese subjects with hypercapnia also have daytime hypersomnolence, polycythemia, pulmonary hypertension, and cor pulmonale. This constellation of signs and symptoms has been termed the *obesity hypoventilation syndrome* (see Chapter 92.) Of interest, leptin may be involved in the pathogenesis of hypercapnic respiratory failure in obese individuals. Leptin stimulates ventilation and a deficiency of leptin has been associated with hypoventilation. Clearly excessive body weight is the primary pathogenetic factor, since weight reduction into the normal range, however difficult this may be to accomplish, corrects the problem.

KYPHOSCOLIOSIS

Kyphoscoliosis decreases chest wall and lung compliance, presumably as a result of atelectasis and deformation of the lungs (see Chapter 92). The elastic work of breathing is markedly increased. In addition, the mechanical action of the respiratory muscles may be impaired by changes in configuration of the bony structures on which the respiratory muscles insert. Ventilation–perfusion mismatch and increase in the alveolar–arterial O_2 gradient are common. As expected in patients with diminished respiratory compliance, subjects with kyphoscoliosis breathe rapidly and shallowly. The tendency to develop CO_2 retention is a function of the severity of the restrictive process in kyphoscoliosis, as reflected in the Cobb angles, and is predicted separately for the magnitude of scoliosis and kyphosis.

Hypercapnic respiratory failure tends to develop late in life, even if the severity of the spinal deformity has not changed since childhood; that is, stability of the Cobb angles of kyphosis and scoliosis does not preclude development of hypercapnic respiratory failure. It is not clear why respiratory failure ensues late in life. However, several possibilities exist. Aging adversely affects compliance of the chest wall, leading to an increase in the elastic work of breathing. In addition, aging diminishes respiratory muscle strength. Finally, chemosensitivity to O_2 and CO_2 declines with advancing age, and it seems likely that the subject's ability to compensate for derangements in blood-gas tensions is progressively impaired.

ASSESSMENT OF PATIENTS WITH ABNORMALITIES OF THE VENTILATORY PUMP

Clinical assessment of patients with known or suspected abnormalities of the ventilatory pump is discussed below.

SYMPTOMS

Dyspnea appears to be an early manifestation of respiratory muscle impairment in neuromuscular disease and typically occurs before the development of CO_2 retention. Breathlessness in the supine position is characteristic of isolated diaphragm dysfunction. In the supine position, the increased hydrostatic pressure imposed by the abdominal viscera represents an increased inertial load on the diaphragm.

PHYSICAL FINDINGS

Physical signs of ventilatory pump dysfunction revolve around evidence of accessory respiratory muscle recruitment, abnormal thoracoabdominal movement, and rapid, shallow breathing.[46]

USE OF ACCESSORY MUSCLES

Inspection and palpation demonstrate accessory respiratory muscle use. Intense respiratory efforts are associated with visible activation of the neck accessory muscles, interosseous intercostals, and abdominal expiratory muscles and flaring of the alae nasi.

ABNORMAL THORACOABDOMINAL MOVEMENT

Normally, in the supine position, the anterior abdominal wall displays a prominent outward movement during inspiration. With impaired diaphragm function, as occurs in diaphragm weakness or fatigue, the abdominal wall may move inward on inspiration. This is called *abdominal paradox.* Abdominal paradox reflects cephalad movement of the contracting diaphragm in response to the negative intrathoracic pressure generated by the inspiratory action of the neck and intercostal muscles. Abdominal paradox may also be present in patients with marked derangements in lung mechanics, in whom inspiratory intrathoracic pressure swings exceed 30% of maximum. Abdominal paradox, therefore, is not specific for diaphragm weakness or fatigue.

Abdominal paradox, resulting from ineffectual contractions of the diaphragm, should be distinguished from *pseudoabdominal paradox,* resulting from strong contractions of the expiratory muscles during expiration, with rapid relaxation during early inspiration. For example, intense contraction of the transverse abdominis muscles causes inward movement of the lateral abdominal wall and outward movement of the anterior abdominal wall during expiration. Subsequent relaxation of the abdominal muscles with the onset of inspiration causes outward movement of the lateral abdominal wall and inward movement of the anterior abdominal wall. Tenseness of the lateral abdominal wall during expiration easily distinguishes *pseudo-* from true *abdominal paradox.*

MAXIMUM STATIC INSPIRATORY PRESSURE

Perhaps the most practical method of assessing the function of the inspiratory muscles contracting in aggregate is from the pressure generated during maximal volitional contractions against an

occluded airway at FRC. This parameter is discussed in greater detail in Chapter 84. In brief, however, reductions in $P_{I_{max}}$ indicate inspiratory muscle weakness or high-frequency fatigue. Improvements in $P_{I_{max}}$ occurring over several hours to several days in a patient with COPD suggest that lung volume is improving toward normal and that the mechanical disadvantage imposed on the inspiratory muscles is disappearing. More rapid improvements (occurring over hours) may indicate resolution of high-frequency fatigue or elimination of the metabolic disturbances (e.g., hypercapnia or hypophosphatemia) that depress inspiratory muscle function. Of note, $P_{I_{max}}$ is not affected by low-frequency fatigue.

$P_{I_{max}}$ depends on patient cooperation and motivation. With training, however, patients can provide reproducible values. Performance of the maneuver at FRC, where respiratory system recoil is zero, is preferred; that is, at FRC, changes in airway pressure during inspiratory efforts equal the pressure generated by the inspiratory muscles (P_{mus}).

Maximum static expiratory pressure at FRC ($P_{E_{max}}$) has been used in the laboratory setting to assess the endurance properties of the expiratory muscles. The $P_{E_{max}}$ has not been used extensively in the clinical setting, however, because of the perception that it is more difficult to obtain consistent values than $P_{I_{max}}$ with breathless subjects.

TREATMENT

Abnormalities in respiratory mechanics and gas exchange are the most important pathogenetic factors in the development of respiratory failure. Accordingly, therapy should be directed toward achieving maximum improvement in airway, lung, and respiratory muscle function. For example, in patients with COPD or asthma, an intensive regimen of bronchodilators (e.g., β_2-adrenergic agonists, anticholinergics, and theophylline) and anti-inflammatory therapy (e.g., corticosteroids) can correct respiratory failure by diminishing airway resistance, FRC, lung dead space volume, the alveolar–arterial O_2 partial pressure gradient, and the work of breathing. Improvements in lung function in certain patients with advanced COPD and emphysema may also be accomplished by lung volume reduction surgery (volume reduction pneumectomy) or lung transplantation. Lung volume reduction surgery removes 20% to 30% of the most emphysematous regions of lung and appears to improve FRC, FEV_1, ventilatory capacity, inspiratory muscle function, and elastic recoil pressure of the lung. In patients with myasthenia gravis, cholinesterase inhibitors can improve inspiratory muscle strength and vital capacity and reverse atelectasis, which causes hypercapnia. In addition, noninvasive positive-pressure ventilation (NIPPV) has become one of the most important modalities for treating hypercapnic respiratory failure (see below Chronic Ventilatory Support/Nasal Positive-Pressure Ventilation).

ABNORMALITIES IN CHEMOSENSITIVITY

Respiratory failure caused by impaired chemosensitivity is difficult to treat, since drug treatments to improve chemosensitivity to hypoxia or hypercapnia are not very effective. Since it was observed that women exhibit alveolar hypoventilation during pregnancy and the luteal phase of the menstrual cycle, progestational agents have been used for many years to treat idiopathic hypoventilation syndromes. In some subjects, medroxyprogesterone acetate, given orally in a dose of 20 mg three times a day, acts centrally to augment the ventilatory responses to hypercapnia and hypoxemia and can improve resting arterial blood-gas tensions.[64,65] Medroxyprogesterone is generally well tolerated in women but may produce feminizing side effects in men. The onset of action of the drug is slow. Several weeks may be required before a response is observed. Theophylline, in doses that produce blood levels in the therapeutic range (10–15 μg/mL), also has weak respiratory stimulatory effects, which may contribute to a reduction in Pa_{CO_2} in patients with COPD. Theophylline also produces modest improvements (about 10%–20%) in diaphragm contractile function in this population. Finally, in some patients with hypercapnia, elimination of medications having CNS respiratory depressant effects (e.g., opiate analgesics, benzodiazepine anxiolytics) can lead to improvements in Pa_{CO_2}.

Hypoxemia leading to pulmonary artery hypertension and cor pulmonale may be the most serious complication of chronic hypercapnic respiratory failure. Supplemental O_2 is usually indicated in patients with chronic hypercapnic respiratory failure. Supplemental O_2 may produce exaggerated increases in Pa_{CO_2} in patients with disorders of ventilatory control in whom the ventilatory response to CO_2 is blunted but the O_2 response is preserved. Accordingly, blood-gas tensions should be monitored closely when O_2 is applied initially. During sleep, patients with disorders of the control of breathing typically display exaggerated increases in Pa_{CO_2} (e.g., 15 to >30 mm Hg) with hypoxemia and severe respiratory acidosis. In these subjects, mechanically assisted ventilation (typically with nasal positive-pressure ventilation [NPPV]), with or without O_2, may be required during the sleeping period. NPPV is an effective way of improving blood-gas tensions during sleep. In fact, improvements in blood-gas tensions achieved by nocturnal mechanical ventilation may carry over to the waking period in these patients, perhaps by preventing nocturnal increases in serum bicarbonate or hypoxic depression of CNS function.

RESPIRATORY MUSCLE WEAKNESS OR FATIGUE

The treatment of respiratory muscle weakness depends on pathogenic mechanisms. For example, inspiratory muscle weakness related to the hyperinflation of COPD is best treated by aggressive improvement of airway function. On the other hand, decreases in muscle strength caused by electrolyte abnormalities (e.g., hypophosphatemia) or protein–calorie malnutrition are best dealt with by repletion of the deficits.

The treatment of respiratory muscle fatigue has not been systematically studied. However, several approaches based on theoretical considerations appear to be applicable (Table 143-2). It is clear that diaphragm fatigue is a result of muscle overactivity (i.e., a TTI >20%). Accordingly, attempts should be made to decrease the TTI of the inspiratory muscles to values below the fatigue threshold by improving lung mechanics or reducing ventilatory drive. In

TABLE 143-2 Principles of Therapy for Respiratory Muscle Fatigue

Decrease inspiratory swings in transdiaphragmatic pressure (P_{di})
Improve the mechanics of breathing (i.e., decrease airway resistance, improve thoracic compliance and static lung volume)
Decrease ventilatory drive (i.e., relieve hypoxemia, hypercapnia, metabolic acidosis, fever, pulmonary congestion/inflammation, acute respiratory distress syndrome)
Increase $P_{di,max}$
Correct hyperinflation
Correct muscle atrophy induced by protein–calorie deficiency
Correct electrolyte and blood gas abnormalities (i.e., hypoxemia, hypercapnia, hypophosphatemia, hypokalemia, hypocalcemia, hypomagnesemia)
Optimize muscle blood flow and substrate availability
Correct low cardiac output state (e.g., cardiogenic shock, hypovolemic shock)
Correct hypoxemia, anemia, hypoglycemia

patients with abnormalities in airway resistance and hyperinflation secondary to severe COPD, this can best be accomplished with bronchodilators and corticosteroids. Reductions in ventilatory drive in hypoxic or febrile patients can be accomplished by administration of O_2 or antipyretics.

Unloading the inspiratory muscles by reducing the TTI may be sufficient to prevent or reverse fatigue and allow the muscle to recover. In some cases, however, respiratory muscle fatigue may be sufficiently advanced so that the muscle must be placed at complete rest. Mechanical ventilation and ventilatory muscle rest are certainly indicated when the pH is less than 7.25 or the patient appears unable to maintain ventilation and stable blood-gas tensions. The precise duration of mechanical ventilation to rest the inspiratory muscles in patients with respiratory muscle fatigue is unclear. However, no attempts at weaning should be made until the conditions that initiated fatigue are reversed. Since low-frequency fatigue persists for 24 hours or more, it may not be advisable to wean patients with respiratory muscle fatigue from mechanical ventilation for at least 24 hours, even if the factors that caused fatigue have been corrected.

CHRONIC VENTILATORY SUPPORT/NASAL POSITIVE-PRESSURE VENTILATION

Mechanically assisted ventilation, especially at night, may be helpful in reducing arterial P_{CO_2} and increasing P_{O_2} in the chronically hypercapnic subject.[66] NPPV affords an effective, practical approach to treat selected subjects with chronic hypercapnia secondary to either impaired chemosensitivity or abnormalities in respiratory mechanics. In particular, selected subjects with the obesity hypoventilation syndrome, kyphoscoliosis, or neuromuscular disease have been successfully maintained on NPPV for prolonged periods.[67–70] Its use in neuromuscular disease, particularly for nocturnal hypoventilation or progressive hypercapnic respiratory failure is discussed in Chapter 94.

NPPV obviates the need for airway intubation, provides considerable patient comfort, and is easy to use. The most commonly used masks are oral or oronasal masks with a soft rubber seal. An oronasal mask may be more comfortable for mouth-breathing patients. Small, portable, simple-to-operate bilevel ventilators (BiPAP) that deliver phasic pressure changes are available. Tidal volume is determined by setting the magnitude of the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). Disadvantages of NPPV include aerophagia and air leaks secondary to poorly fitting masks.

The use of NPPV during acute hypercapnic respiratory failure secondary to COPD has been demonstrated repeatedly to reduce mortality, reduce the need for airway intubation, and rapidly improve Pa_{CO_2} and pH.[71]

DEDICATION

This chapter is dedicated to the memory of my mentor and friend, Neil S. Cherniack, M.D. Neil was a world-class respiratory physiologist who made seminal contributions to our understanding of the regulation of respiration and, in particular, the instabilities in breathing which underlie the development of obstructive sleep apnea. His considerable body of work also contributed much to our understanding of the pathogenesis of hypercapnic respiratory failure which is the subject of this chapter.

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CHAPTER 144

Oxygen Therapy and Toxicity

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INTRODUCTION

Oxygen was discovered in the late 18th century simultaneously by several investigators. Joseph Priestley, a minister in England, made his discovery after attempting to melt mercury oxide using a magnifying glass and the sun's rays. The vapor that was produced by this melting allowed a candle to burn brighter, and Priestley later discovered the vapor could be used in place of air to keep a mouse alive. He first published his findings in 1774. At about the same time, and in a similar way (i.e., by burning mercury oxide), Carl Scheele, a pharmacist in Sweden, described a gas he called "fire air." He may have done his experiments before Priestley, but he did not publish his findings until 1777. Finally, after being told about this new vapor during a 1774 visit by Joseph Priestley, the chemist, Antoine Lavoisier, devised quantitative experiments which he used to prove the existence of this element and its role in combustion. He named the element "oxygen" and published his research in 1777.

Soon after its discovery, oxygen was being utilized as a medicine and cure-all for many respiratory diseases, including "consumption" and asthma. However, suspicions about the safety of oxygen therapy were raised almost as soon as it was discovered and even before the element was named. In 1775, Joseph Priestley wrote of oxygen (which, at that time, he called "dephlogisticated air"): "A moralist, at least, may say that the air which nature has provided for us is as good as we deserve."[1]

Rigorous scientific evaluation of the potential toxicities of oxygen did not occur until the work of James Lorrain Smith, an Edinburgh pathologist, who first published the pulmonary pathologic alterations associated with oxygen exposure in 1899. It was also recognized around this time that under ambient air, the arterial blood was already at near-maximal oxygen-carrying capacity, putting into doubt the utility of further increasing the fraction of inspired oxygen.

Following these observations, the use of therapeutic oxygen fell into some disrepute.

In the early 1920s, supplemental oxygen therapy was reevaluated yet again. This was occurring as the detrimental effects of tissue hypoxia were being recognized, along with their reversibility with supplemental oxygen. Since the mid-20th century, especially with the advent of improved oxygen delivery systems, mechanical ventilation, and the modern intensive care unit, the use of oxygen has become a standard prescribed therapy for a multitude of cardiac and respiratory diseases. Oxygen therapy is now common in the outpatient setting. As of 2005 in the United States, approximately 1 million people receive long-term oxygen therapy (LTOT) from the Medicare Program, with total reimbursement costs related to LTOT exceeding 2 billion dollars per year.[2]

In this chapter, the physiology of hypoxia at the tissue level and mechanisms of arterial hypoxemia are discussed. In addition, various clinical assessments of hypoxemia, indications for acute and LTOT, and available methods of noninvasive oxygen administration are considered. Finally, the pathophysiology and clinical manifestations of pulmonary oxygen toxicity are addressed, along with the potential for oxygen toxicity in other organ systems.

TISSUE OXYGENATION

Important to remember is that the primary goal of supplemental oxygen therapy is to ensure appropriate oxygen delivery to vital end-organ tissues. Therefore, one must understand the mechanisms of tissue hypoxia to understand the indications for using supplemental oxygen.

Tissue hypoxia is governed by the balance between oxygen delivery and oxygen utilization. Generally, failures in oxygen delivery lead to most instances of tissue hypoxia. Oxygen delivery is determined by the cardiac output and the oxygen content of arterial blood, as described by the formula:

$$D_{O_2}\ (\text{oxygen delivery}) = CO\ (\text{cardiac output}) \times Ca_{O_2}\ (\text{oxygen content of arterial blood}) \quad (1)$$

where Ca_{O_2} is calculated by the formula:

$$Ca_{O_2}\ (\text{mL } O_2/\text{dL}) = (1.34 \times \text{hemoglobin concentration} \times Sa_{O_2}) + (0.0031 \times Pa_{O_2}) \quad (2)$$

where Sa_{O_2} is the arterial hemoglobin oxygen saturation and Pa_{O_2} is the oxygen tension or partial pressure of arterial blood.

From this formula, the causes of poor oxygen delivery can be narrowed to three categories: Low cardiac output states (i.e., various forms of shock), low hemoglobin concentration states (i.e., anemia), and low Sa_{O_2} states (i.e., arterial hypoxemia or hemoglobinopathies). Note that a low oxygen tension, although often leading to low arterial hemoglobin saturation, does not contribute appreciably to oxygen delivery. This can be seen numerically in the above formula for Ca_{O_2}, where the Pa_{O_2} is multiplied by 0.0031 and, therefore, contributes little to the final product. It is important to point out that supplemental oxygen therapy addresses only arterial hypoxemia. For other causes of tissue hypoxia, more specific therapies are generally required, such as vasoactive agents or intravenous fluid administration to reverse shock, and blood transfusions for anemia.

Along with the primary basis of poor oxygen delivery, tissue hypoxia can also be caused by inappropriate or excessive utilization of oxygen. One cause of inappropriate oxygen utilization is histotoxic hypoxia, which occurs when cells, for a variety of reasons, are unable to utilize oxygen for aerobic metabolic respiration. This is classically seen in cyanide poisoning, where the cyanide molecule inhibits the enzyme cytochrome c oxidase, and the cell is subsequently unable to use oxygen to produce adenosine triphosphate (ATP) via the mitochondrial electron transport chain. This leads to glycolysis, profound lactic acidosis, and cell and tissue death. Administration of oxygen is indicated in this condition, but it will not, by itself, reverse the toxicity of cyanide; other antidotes must be given (generally, sodium nitrite, amyl nitrite, and sodium thiosulfate).[3]

Another cause of decreased oxygen utilization may occur in the setting of sepsis. In this case, oxygen is not utilized by tissues due to both mitochondrial damage and abnormal shunting of blood from a variety of insults at the endothelial and microcirculatory levels. Finally, oxygen may be excessively utilized by tissues relative to oxygen delivery. This may occur in hypermetabolic states, such as thyrotoxicosis[4] and fever.[5]

ARTERIAL HYPOXEMIA

Important is the distinction between the terms *hypoxia* and *hypoxemia*. Hypoxia may be thought of as the functional equivalent of ischemia and refers to a lack or misuse of oxygen at the tissue level. Hypoxemia refers to the blood's oxygen content and can be more formally defined as a validated deficiency of oxygen tension in the blood. In other words, when a patient's Pa_{O_2} and, therefore, Sa_{O_2} are low, the patient is hypoxemic. Since arterial hypoxemia is a major cause of tissue hypoxia, the cause of which is most likely to be reversed or improved with oxygen therapy, its major etiologies are discussed below.

The driving force of oxygen transport across the alveolar barrier into the blood depends on both the partial pressure of oxygen in the alveolus (PA_{O_2}) and overall respiratory function. Thus, arterial hypoxemia results from either reduction of the inspired oxygen tension or dysfunction of the respiratory system. Along with the reduction of inspired oxygen tension (such as at altitude), there are four other pathophysiologic causes of arterial hypoxemia (Table 144-1).

Alveolar hypoventilation leads to a diminished PA_{O_2} and resultant decrease in Pa_{O_2} and Sa_{O_2}. It may constitute the final common pathophysiologic denominator for a variety of pulmonary and nonpulmonary disorders leading to hypercapnia and hypoxemia. Examples of nonpulmonary disorders leading to these derangements include narcotic overdose, which reduces the central drive to breath; abdominal compartment syndrome, which can mechanically reduce ventilation due to abdominal distension; and obstructive sleep apnea, which is the result of transient loss of the upper airway patency.

Another pathophysiologic cause of hypoxemia arises with defects in diffusion of oxygen across the alveolar–capillary membrane, as, for example, in fibrotic lung diseases and interstitial pneumonias. The increased barrier to oxygen diffusion is detected as a reduced diffusion capacity of carbon monoxide (D_{LCO}). Diffusion limitation generally coexists with ventilation–perfusion mismatch. Its effects on oxygenation often become clinically prominent in states of increased cardiac output (such as exercise) in the setting of fibrotic or interstitial lung disease.[6] These higher output states lead to reduced time for diffusion of oxygen across the diseased alveolar–capillary membrane and subsequent hypoxemia.

Clinically, the most frequently observed pathophysiologic mechanisms of hypoxemia are ventilation–perfusion mismatch and shunt.

Ventilation–perfusion mismatch generally results when focal (or sometimes diffuse) areas of diminished ventilation arise relative to persistent pulmonary capillary blood flow. Clinical examples include cardiogenic pulmonary edema, acute lung injury, and pneumonia—all of which are characterized by alveolar filling, reduced ventilation, and continued perfusion. The hypoxemia resulting from lack of ventilation to these areas can generally be overcome simply by increasing the fraction of inspired oxygen (FI_{O_2}), that is, with the use of supplemental oxygen. In the setting of ventilation–perfusion mismatch, without oxygen supplementation, reflex hypoxic pulmonary vasoconstriction occurs, minimizing the impact on Pa_{O_2}. Hypoxic pulmonary vasoconstriction may ultimately lead to increased pulmonary artery pressure and cor pulmonale.

Shunt occurs when a fraction of pulmonary blood flow effectively bypasses the alveolar compartment. Examples include atelectatic lung in which ventilation is absent but perfusion maintained (at least in part). Other examples include atrial septal defect and pulmonary arteriovenous malformations. Increasing the alveolar concentration of oxygen in the setting of shunt has no effect on arterial oxygenation. The hypoxemia from shunt physiology is refractory to the use of supplemental oxygen.

Finally, when tissue hypoxia is severe, or when increased tissue oxygen utilization is present, the oxygen content of venous blood returning to the right heart may be profoundly reduced—detected as a low oxygen saturation of venous blood (Sv_{O_2}). A low Sv_{O_2}, in combination with ventilation–perfusion mismatch or shunt, leads to worsening arterial hypoxemia. This pathophysiologic constellation may be observed when patients with severe lung disease and poor oxygen delivery are physically active or have high metabolic demands due to critical illness. Hemoglobin desaturation can then be seen.

CLINICAL ASSESSMENT OF TISSUE HYPOXIA

To use oxygen therapy correctly, clinicians must recognize the presence of tissue hypoxia and its etiology. With this knowledge, the clinician can determine who may benefit from supplemental oxygen. Furthermore, the degree of hypoxia must be assessed to determine the optimal dosage of oxygen. In this way, one can balance oxygen's benefits and potential toxicities. Unfortunately, tissue hypoxia is not directly measured by any one test. Instead, a combination of clinical and laboratory parameters is used to determine its severity. In the case of tissue hypoxia caused by isolated arterial hypoxemia, measurement of arterial oxygen saturation can be an excellent guide to appropriate oxygen therapy.

■ CLINICAL MANIFESTATIONS

Clinical manifestations of hypoxia are variable and nonspecific. Whether hypoxia develops acutely or is chronic influences patient presentation: Patients with chronic hypoxia often have minimal symptoms. Symptoms and signs of acute hypoxia are outlined in (Table 144-2). The most prominent findings are dyspnea, tachypnea, and respiratory distress. A frequently observed finding is an acute change in mental status, ranging from agitation to delirium to coma. Cardiac arrhythmias are common. Cyanosis is generally a late finding and is often unreliable in diagnosing hypoxia, as it may be absent in the setting of anemia and with poor peripheral perfusion.

■ LABORATORY ASSESSMENT

Distinction between tissue hypoxia and arterial hypoxemia is important in applying various laboratory studies in clinical evaluation. To determine if tissue hypoxia, that is, hypoxia in end-organs, is present, measures such as serum lactate (elevated in ischemia)

TABLE 144-1 Causes of Arterial Hypoxemia and Response to Oxygen Therapy

Cause	Clinical Examples	Response to Oxygen Therapy
Decreased oxygen intake	Altitude (reduced PI_{O_2})	Rapid increase in Pa_{O_2}
Alveolar hypoventilation	COPD, obesity hypoventilation	Increase in Pa_{O_2}, may depress minute ventilation, however
Diffusion defect	Interstitial pneumonitis	Moderately rapid increase in Pa_{O_2}
Ventilation–perfusion mismatch	COPD	Moderately rapid increase in Pa_{O_2}
Shunt	Atrial septal defect, with right-to-left shunting	Variable increase in Pa_{O_2}, depending on size of shunt

TABLE 144-2 Signs and Symptoms of Acute Hypoxia

System	Signs and Symptoms
Respiratory	Tachypnea, breathlessness, dyspnea, cyanosis, pulmonary hypertension
Cardiovascular	Increased cardiac output, palpitations, tachycardia, bradycardia arrhythmias, hypotension, angina, vasodilation, diaphoresis, shock
Central nervous	Headache, impaired judgment, inappropriate behavior, confusion, euphoria, delirium, restlessness, papilledema, seizures, obtundation, coma
Neuromuscular	Weakness, tremor, asterixis, hyperreflexia, incoordination
Metabolic/renal	Sodium and water retention, lactic acidosis, acute tubular necrosis

and Sv_{O_2} (reduced in ischemia) are generally used. Evaluation for anemia by measuring hemoglobin or hematocrit is also important in this context.

When the cause of tissue hypoxia is isolated arterial hypoxemia, measurements of Pa_{O_2} and Sa_{O_2} provide appropriate surrogates of oxygen delivery and, therefore, tissue hypoxia. Values are derived from arterial blood-gas measurements. Since Sa_{O_2} and Pa_{O_2} have a generally predictable relationship according to the oxygen–hemoglobin dissociation curve, measuring only Sa_{O_2} may be sufficient to assess arterial hypoxemia. This is done noninvasively using pulse oximetry; the estimated Sa_{O_2} is designated as Sp_{O_2}. Importantly, various toxins, such as carbon monoxide and those that result in methemoglobinemia will disrupt the predictable relationship between Sa_{O_2} and Pa_{O_2} as measured by pulse oximetry (see next section). Under these circumstances, cooximetry performed on an arterial blood-gas sample is required, and pulse oximetry cannot be relied upon to evaluate arterial hypoxemia.

PULSE OXIMETRY

Pulse oximetry is an important diagnostic tool which is now widely utilized in hospitals, outpatient settings, and at home. The general principles of this technology are useful to understand, as are its limitations.

First proposed conceptually in the 1930s and developed further in the mid-20th century, the underlying principle of oximetry is Beer's law, which states that concentration of an unknown substance dissolved in a solvent can be determined by its light absorption[7]:

$$L_{out} = (L_{in} \times e) - (D \times C \times a) \quad (3)$$

where

L_{out} is the intensity of transmitted light through the substance
L_{in} is the incident light
D is the distance the light travels
C is the concentration of the substance (in this case, oxyhemoglobin or reduced hemoglobin)
a is the absorption coefficient

When light is passed through a finger, ear lobe, or other tissue, the majority of it is absorbed by connective tissue, skin, bone, and venous blood, and the amount absorbed is constant. However, with each heartbeat, pulsatile flow of arterial blood occurs, allowing the pulse oximeter to detect changes in light absorbance at two wavelengths, 660 nm (red) and 940 nm (infrared). Since reduced hemoglobin and oxyhemoglobin have different absorptions at these two wavelengths, the concentration of oxyhemoglobin relative to total hemoglobin can be deduced.

Several limitations to pulse oximetry exist, which can be inferred from its basic principles. Any substance in the blood with similar absorption at the two wavelengths employed will interfere with accuracy. This is clinically important in the evaluation of two acquired hemoglobinopathies—carboxyhemoglobinemia and methemoglobinemia.

Carboxyhemoglobin has a very similar absorption coefficient at 660 nm as oxyhemoglobin; at 940 nm, it has minimal light absorption. Therefore, no matter what the relative concentrations of hemoglobin molecules saturated with CO versus O_2, Sp_{O_2} will be constant (generally about 90%–95%).

In methemoglobinemia, a condition in which the iron moiety of hemoglobin is reduced to the ferric state, the methemoglobin molecule is characterized by equalization of absorption coefficients at 660 nm and 940 nm. Equal absorption at these two wavelengths translates into an Sa_{O_2} of 85%, which is what the pulse oximeter inevitably reads as methemoglobin concentration increases. Furthermore, an antidote for methemoglobinemia, methylene blue, also affects absorption of light at 660 nm and may falsely lower Sp_{O_2}.

Given that pulse oximetry relies upon pulsatile flow, the technology cannot be used in conditions of low flow, such as cardiac arrest or profound shock. Errors also occur when venous pulsatility is prominent, such as in severe tricuspid regurgitation. In this case, the pulsatility of venous blood, with its higher concentration of reduced hemoglobin, may result in artificially low readings of oxygen saturation. When profound arterial hypoxemia exists, for example, Sa_{O_2} <70%, the accuracy of pulse oximetry declines, as the technology has generally not been calibrated at lower saturations.

OTHER ASSESSMENTS OF HYPOXEMIA

Several other calculated assessments of hypoxemia are useful in assessing the degree of respiratory dysfunction.

Pa_{O_2}/Fi_{O_2}

Pa_{O_2}/Fi_{O_2} (P/F ratio) requires an arterial blood-gas specimen. For example, consider a patient breathing gas with an Fi_{O_2} of 0.80, who has a Pa_{O_2} 240 mm Hg. The P/F ratio is 240/0.8 or 300. The ratio, considered to reflect the magnitude of derangement in O_2 transfer across the lung and thought to be relatively unaffected by differences in Fi_{O_2} among measurements, is most useful in mechanical ventilation, when accurate determination of Fi_{O_2} is possible. In the setting of acute hypoxemia, a P/F ratio of <300 indicates abnormal gas exchange, and a P/F ratio <200 indicates severe hypoxemia.

Alveolar–Arterial (A-a) Difference

The A-a difference (also called the A-a gradient) measures the difference in alveolar oxygen tension and arterial oxygen tension. This measurement, which requires an arterial blood gas, is determined as:

$$\text{A-a difference} = P_{A_{O_2}} - Pa_{O_2} \quad (4)$$

$P_{A_{O_2}}$ is calculated using the alveolar air equation:

$$P_{A_{O_2}} = (Fi_{O_2} \times [P_{atm} - P_{H_2O}]) - (Pa_{CO_2}/R) \quad (5)$$

where,

Fi_{O_2} is the fraction of inspired oxygen
P_{atm} is the atmospheric pressure (760 mm Hg at sea level)

P_{H_2O} is the partial pressure of water (47 mm Hg at room temperature)
Pa_{CO_2} is the arterial carbon dioxide tension
R is the respiratory quotient (which, in the steady state, is usually 0.8, depending on the patient's nutritional intake)

A "normal" A-a difference on room air is often considered to be 10 mm Hg. However, two important factors affect the "normal" value. The first is patient's age, the influence of which can be expressed numerically according to the formula:

$$\text{Normal A-a difference on room air} = 2.5 + 0.21 \times \text{age in years} \quad (6)$$

The second is FI_{O_2}: The higher the FI_{O_2}, the larger the A-a difference, since alveolar oxygen tension increases more than does arterial oxygen tension with increasing FI_{O_2}. Note the distinction in this regard with respect to the P/F ratio described previously.

Oxygenation Index

The oxygenation index (OI) is often used in neonates and children with acute hypoxemic respiratory failure to assess the severity of disease and predict outcome.[8] It can be calculated only for mechanically ventilated patients, where mean airway pressures may be measured.

$$OI = [(\text{mean airway pressure} \times FI_{O_2})/Pa_{O_2}] \times 100 \quad (7)$$

A high OI (e.g., >25) indicates severe hypoxemic respiratory failure.

INDICATIONS FOR OXYGEN THERAPY

Supplemental oxygen is a drug with indications, contraindications, and a therapeutic window. Oxygen dosage should be titrated as precisely as possible and oxygen administration monitored closely with respect to clinical benefits and potential toxicities. Indications for oxygen therapy may be considered in both acute and chronic settings. In addition, special circumstances under which oxygen is used therapeutically warrant special discussion, including hyperbaric administration (oxygen delivered at >1 atmosphere) and oxygen therapy during air travel.

■ ACUTE INDICATIONS FOR OXYGEN THERAPY

Indications for acute, short-term supplemental oxygen therapy, listed in Table 144-3, are based upon guidelines established by the American Association of Respiratory Care and other organizations.[9–11]

Usually, when a patient presents with respiratory distress, supplemental oxygen is administered until an assessment of hypoxemia is made. The clearest indication for oxygen therapy is arterial hypoxemia, and supplemental oxygen is generally administered when the Pa_{O_2} is <60 mm Hg, which normally corresponds to an Sa_{O_2} or Sp_{O_2} of 89% to 90%. When the Pa_{O_2} drops below 60 mm Hg, oxygen saturation may drop precipitously, leading to a much lower arterial oxygen content and resultant tissue hypoxia.

As noted previously, the most common pathophysiologic cause of hypoxemia is ventilation–perfusion mismatch, which responds readily to supplemental oxygen. Hypoxemia secondary to right-to-left shunt is less responsive to supplemental oxygen; when the shunt fraction exceeds 20% to 25%, hypoxemia persists, despite administration of inspired gas with an FI_{O_2} of 100%. In the case of hypoxemia due to alveolar hypoventilation, oxygen therapy often improves Sa_{O_2} and oxygen delivery, but it does not correct the underlying cause of respiratory dysfunction; restoration of ventilation must be pursued.

An oxygen saturation target of 94% to 98% is reasonable for patients at sea level who are hypoxemic and who have normal baseline lung function.[10] In certain circumstances, such as shock states characterized by hypoperfusion, the target may be even higher in an attempt to maximize the oxygen content of arterial blood. Conversely, in patients who have abnormal control of respiration, such as those with chronic hypercapnia, a lower Pa_{O_2} goal may be more appropriate (as discussed later in this chapter).

TABLE 144-3 Guidelines for Acute Oxygen Therapy

Accepted Indications
• Documented hypoxemia, defined as Pa_{O_2} below the normal range. Usually Pa_{O_2} <60 mm Hg or Sa_{O_2} <90%.
• Acute care situation in which hypoxemia is suspected, such as respiratory distress. Requires substantiation of hypoxemia (by Sa_{O_2} or Pa_{O_2}) in a reasonable time.
• Severe trauma
• Acute myocardial infarction with hypoxemia
• Low cardiac output with metabolic acidosis
• Hypotension (systolic blood pressure < 100 mm Hg)
Questionable Indications
• Acute myocardial infarction without hypoxemia
• Dyspnea without hypoxemia (palliative)
• Sickle cell pain crisis
• Pneumothorax

Source: Data from Kallstrom TJ; American Association for Respiratory Care (AARC). AARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility–2002 revision & update. Respir Care. 2002;47(6):717–720; O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008;63 Suppl 6:vi1–vi68; Fulmer JD, Snider GL. American College of Chest Physicians (ACCP)–National Heart, Lung, and Blood Institute (NHLBI) Conference on oxygen therapy. Arch Intern Med. 1984;144(8):1645–1655.

Use of supplemental oxygen may be indicated in a few clinical scenarios other than arterial hypoxemia. As discussed earlier, patients in shock states may benefit from enhanced arterial oxygen content and delivery, as may patients in cardiac and respiratory arrest. Similarly, trauma victims and critically ill surgical patients benefit from early oxygen therapy to improve tissue hypoxia. Use of short-term, postoperative supplemental oxygen has also been shown to reduce wound infection in surgical populations.[12] In patients with carbon monoxide poisoning, in whom pulse oximetry readings are unreliable, supplemental oxygen increases Pa_{O_2}. More importantly, it shortens the half-life of carboxyhemoglobin, thereby increasing the percentage of oxyhemoglobin. With administration of pure oxygen, the half-life of carboxyhemoglobin is 70 to 80 minutes,[13] compared with a half-life of 320 minutes when a patient is breathing room air.[14] Under hyperbaric conditions, when pure oxygen is delivered at higher atmospheric pressure, the half-life is shortened even further. Hyperbaric oxygen is generally employed when carboxyhemoglobin levels are high (>25%) and there is an evidence of end-organ damage, such as cardiac ischemia or alterations in sensorium,[15] although use of hyperbaric oxygen in this setting is currently controversial.

Several other disorders may benefit from administration of supplemental oxygen, although supportive data in these settings are lacking or equivocal. Oxygen therapy is often used in cluster headaches,[16] sickle cell pain crises (although this is falling out of favor),[17] palliative relief of dyspnea without hypoxemia,[18] and pneumothorax in patients who do not have a chest tube (in an effort to facilitate resorption of pleural air).[19,20] Administration of supplemental oxygen has also been proposed to reduce postoperative nausea and vomiting and to alleviate nausea associated with medical transport in ambulances.[21] Use of supplemental oxygen in uncomplicated myocardial infarction is common but controversial; the topic is discussed in more detail below. Finally, hyperbaric oxygen is sometimes used in an effort to accelerate healing of complicated, chronic wounds arising in the setting of peripheral or microvascular disease.[22] Hyperbaric oxygen therapy is widely accepted as the therapy of choice in decompression sickness (see Chapter 93).[23]

TABLE 144-4 Physiologic Indications for Long-Term Oxygen Therapy (LTOT) in COPD[a]

Pa_{O_2}	Sa_{O_2}	LTOT Indication	Qualifier
<55 mm Hg	<88%	Absolute	None needed
55–59 mm Hg	88–90%	Relative with qualifier	Presence of any of the following signs of cor pulmonale: • History of dependent edema • Polycythemia (HCT > 55%) • P pulmonale on EKG (P wave > 3 mm in leads II, III, or aVF)
≥60 mm Hg	≥90%	None unless qualifier	At least one of the following: • Exercise desaturation • Sleep desaturation not corrected by CPAP • Lung disease with dyspnea responding to O_2 therapy

[a]*Generally used in other conditions as well.*

Source: Data from Force ATSERST. Standards for the diagnosis and management of patients with COPD [internet]. American Thoracic Society [Guidelines]. 2004; http://www.thoracic.org/go/copd., Version 1.2; Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391–398; Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681–686.

INDICATIONS FOR LONG-TERM OXYGEN THERAPY

The use of LTOT has been growing as our ability to deliver oxygen in outpatient settings has improved. Criteria for administering LTOT have become well established, generally in the context of chronic obstructive pulmonary disease (COPD). Table 144-4 outlines the guidelines of the American Thoracic Society (ATS) for LTOT in COPD.[24] The guidelines are based on the data derived from two major trials.

The first trial, published in 1980, is the Nocturnal Oxygen Therapy Trial (NOTT).[25] In NOTT, 203 hypoxemic patients with COPD were randomized to the treatment with either nocturnal (at least 12 hours) or continuous oxygen. Patients who received nocturnal oxygen therapy alone had a higher mortality at both 12 and 24 months (40.8% at 24 months) compared with those who received continuous oxygen therapy (22.4% at 24 months).

The second trial, published in 1981, is the British Medical Research Council Domiciliary (BMRCD) trial.[26] In this trial, 87 patients with hypoxemia and COPD were randomized to receive either no oxygen therapy or at least 15 h/d of supplemental oxygen. Similar to the NOTT trial, mortality was significantly higher in the no-oxygen group.

From these two trials, in patients with COPD and hypoxemia, we can infer that supplemental oxygen for >15 h/d is better than no oxygen at all, and that continuous supplemental oxygen is better than nocturnal-only therapy. The entry criteria for these trials form the basis of the current Medicare criteria and ATS guidelines for LTOT. Based on the BMRCD trial, most prescriptions for oxygen are written for at least 15 h/d. The data from the two trials have been extrapolated to other conditions complicated by chronic hypoxemia for which data from large trials are lacking, including cystic fibrosis, restrictive lung diseases, and chronic cardiac diseases.

In patients whose hypoxemia does not meet resting criteria for administration of LTOT, evaluation for exercise-related desaturation may be indicated. Some patients may require supplemental oxygen only with exertion; improved exercise performance may be noted,[27] unless cardiac and peripheral circulatory factors are performance-limiting.

Finally, patients with significant desaturation while sleeping may warrant nocturnal supplemental oxygen. Important to note, however, is that in the absence of underlying lung disease, these patients often have obstructive sleep apnea or obesity hypoventilation syndrome, for which noninvasive positive pressure ventilation constitutes primary therapy.[28] Table 144-5 lists the physiologic indications for oxygen therapy during sleep.

INDICATIONS FOR OXYGEN THERAPY IN AIR TRAVEL

An important consideration for clinicians who manage patients with lung disease is determining the need for supplemental oxygen during air travel.

Most commercial aircraft fly at cruising altitudes between 25,000 and 45,000 ft, which would normally result in a very low inspired oxygen tension (PI_{O_2}). Airplane cabins, however, are generally pressurized to an altitude of 8000 ft, which results in an oxygen tension of approximately 108 mm Hg (the PI_{O_2} at sea level is 149 mm Hg). In patients with lung disease, this reduced PI_{O_2} may result in marked reductions in PA_{O_2} and Pa_{O_2}, placing the patient at risk for hypoxemia.

Prior to travel, the patient should have a thorough medical evaluation, with consideration for reevaluating pulmonary function tests, specifically spirometry and D_{LCO}, and obtaining an arterial blood gas. For patients whose Pa_{O_2} ≥70 mm Hg (Sp_{O_2} > 95%) at ground level, their in-flight Pa_{O_2} will likely exceed 50 mm Hg, which is generally considered adequate. For patients with a more marginal Sp_{O_2} or Pa_{O_2} and other risk factors, a 6-minute walk test or other evaluation may be considered.[29]

The 6-minute walk test may be a reliable and practical way of estimating the cardiopulmonary reserve that patients require to deal with the physiologic demands of a reduced PI_{O_2} during flight. Although the entire medical evaluation must be taken into account, if a patient has an abnormally low 6-minute walk distance, has significant dyspnea during the test, or experiences a decline in Sp_{O_2} to

TABLE 144-5 Physiologic Indications for Nocturnal Oxygen Therapy

Pa_{O_2} <55 mm Hg with sleep or Sa_{O_2} <88% with sleep
Or
Pa_{O_2} decreases more than 10 mm Hg with sleep
Or
Sa_{O_2} decreases more than 5% with sleep and signs of nocturnal hypoxemia including: • Pulmonary hypertension • Daytime somnolence • Cardiac arrythmias
Patient should be evaluated for a sleep disorder and need for positive pressure device

<85%, the patient will likely need supplemental oxygen during air travel.

Finally, in anticipation of air travel, a hypoxia altitude simulation test (HAST) may be performed[30] (see Chapter 33). In this test, an arterial blood gas is drawn just prior to administration of a gas mixture with an FI_{O_2} of 15.1%. Another arterial blood gas is drawn 20 minutes later, while the patient breathes the hypoxic gas mixture. If the Pa_{O_2} is <50 mm Hg, administration of supplemental oxygen during flight is recommended. If the Pa_{O_2} is between 50 and 55 mm Hg, further testing should be considered, including a 6-minute walk test. Reviews on oxygen therapy and air travel address the testing options available.[31]

TECHNIQUES OF OXYGEN ADMINISTRATION

When choosing an oxygen delivery device for a given patient, the clinician must consider the degree of hypoxemia, the specificity required with regard to setting the FI_{O_2} (which depends on the patient's respiratory control), and the patient's minute ventilation. The oxygen flow that the device can deliver, the adjustability and precision of that delivery, and the comfort and cost of the device are additional considerations.

Oxygen delivery devices utilized in the acute setting may be divided into low-flow and high-flow delivery systems. The required flow depends on the patient's degree of hypoxemia and minute ventilation. Patients who exhibit a high minute ventilation or are profoundly hypoxemic require high-flow devices (i.e., if they do not require mechanical ventilation). Patients with more moderate degrees of hypoxemia may only need low-flow systems, which are generally more comfortable.

■ LOW-FLOW AND VARIABLE PERFORMANCE OXYGEN DEVICES

Low-flow systems deliver only a fraction of the patient's minute ventilation as pure oxygen. The maximum flow in these systems is 15 L/min. Since a patient's tidal volume usually varies from breath to breath, and the delivered flow of oxygen from the device is constant, the fraction of inspired oxygen for any given breath is impossible to predict. For example, when a patient takes very deep breaths, more room air is entrained, but the flow of pure oxygen is constant, thereby diluting the administered FI_{O_2}. Conversely, when a patient has a reduced minute ventilation or is taking very shallow breaths, the amount of entrained room air is minimal, and the FI_{O_2} inspired is greater than what might be expected. Table 144-6 illustrates this important principle mathematically. The variation in FI_{O_2} with minute ventilation must be considered when administering oxygen to patients with chronic CO_2 retention who are at risk for worsening hypercapnia with excessive oxygen therapy. Because of the uncertainty of the FI_{O_2} delivered by low-flow devices, they are sometimes referred to as "variable performance devices."

Nasal Cannulae

Nasal cannulae allow comfortable delivery of oxygen and unimpeded communication and access to oral intake. The cannula rests just below the nares (Fig. 144-1) and entrains a constant flow of pure oxygen, generally ranging from 2 to 6 L/min. At 6 L/min or higher, the patient may experience discomfort, excessive mucosal dryness, and epistaxis. The continuous flow creates a reservoir of oxygen in the nasopharynx from which the patient draws during inspiration. Contrary to popular belief, even if a patient is a "mouth-breather," the gas inhaled is oxygen enriched because of the effect of the nasopharyngeal reservoir. Although FI_{O_2} varies widely with nasal cannulae (as described above), an approximation of FI_{O_2} based on oxygen flow rate can be derived (Table 144-7). Typically, FI_{O_2} increases by 3% to 4% with each 1 L increment in flow.

Several variations in nasal cannulae design may reduce oxygen waste. The moustache-style reservoir (Fig. 144-1C) contains a soft, inflatable reservoir with a volume of approximately 20 mL. During exhalation, the reservoir fills with oxygen. During inspiration, the patient initially draws from the reservoir and then, when the reservoir is depleted, from the continuous flow of the cannula. This acts to deliver a bolus of oxygen early in the course of the inspiration, while reducing wasted oxygen during expiration. Generally, patients can be maintained at a slightly lower flow rate using the moustache-style cannula compared with a regular nasal cannula.

Another modification is the pendant reservoir cannula (Fig. 144-1B). This device consists of a reservoir worn on the chest like a pendant. The reservoir is attached to a nasal cannula with tubing of slightly greater diameter than normal. The pendant reservoir cannula provides a similar function to the moustache-style cannula.

Simple Oxygen Masks

Oxygen masks can deliver higher oxygen flow rates than nasal cannulae; they entrain less room air and, therefore, can generate a higher FI_{O_2}. In addition, the configuration of simple masks (Fig. 144-2A) enables an enlarged reservoir of oxygen for inhalation. With nasal cannulae, the reservoir comprises anatomic dead space in the airway, such as the nasopharynx. With a well-fitting oxygen mask, the reservoir is expanded to include the volume within the mask. Generally, flow rates for simple masks range from 5 to 12 L/min, which usually requires some room air to be entrained via the side ports of the mask to meet the patient's minute ventilatory needs. Given the higher flow rates delivered using face masks, a humidifier

TABLE 144-6 Effects of Minute Ventilation on FI_{O_2} in Low-Flow Systems

	Respiratory Distress	Relief of Respiratory Distress
Minute ventilation	30 L/min (40 breaths/min × 750 mL/breath)	5 L/min (10 breaths/min × 500 mL/breath)
O_2 flow rate	2 L/min	2 L/min
Calculation of inspired O_2 concentration (FI_{O_2})	2 L/min of 100% oxygen + 28 L/min of 21% oxygen (room air drawn into mask) = 30 L/min minute ventilation Thus, $FI_{O_2} = \frac{(1.0 \times 2) + (0.21 \times 28)}{30} = 0.26$ (**26%** FI_{O2})	2 L/min of 100% oxygen + 3 L/min of 21% oxygen (room air drawn into mask) = 5 L/min minute volume Thus, $FI_{O_2} = \frac{(1.0 \times 2) + (0.21 \times 3)}{5} = 0.53$ (**53%** FI_{O2})

Source: Adapted with permission from Bateman NT, Leach RM. ABC of oxygen: acute oxygen therapy. BMJ. 1998;317(7161):798–801.

Figure 144-1 Nasal oxygen delivery devices. **A.** Nasal cannulae. **B.** Pendant nasal cannulae. **C.** "Moustache" nasal cannulae.

is also often required. The flow rate of a simple mask should never be <5 L/min; below this level, carbon dioxide rebreathing may occur, along with an increased resistance to inspiration.

As is the case with nasal cannulae, predicting the actual $F_{I_{O_2}}$ delivered by simple oxygen masks is difficult, since the $F_{I_{O_2}}$ varies with the size of the patient's tidal volumes and total minute ventilation. Simple masks are also more uncomfortable, making eating and communicating challenging. Because they cover the mouth, aspiration is a risk with any mask.

Reservoir Masks

A reservoir mask is similar to a simple mask but has an attached reservoir of 600 to 800 mL, resting below the patient's chin. Generally, the mask provides flow between 8 and 15 L/min, which keeps the reservoir bag at least half full. Reservoir masks include partial rebreather and nonrebreather types (Fig. 144-3).

When using a partial rebreather mask, the patient exhales approximately the first one-third of the expired tidal volume into the reservoir. That volume is derived predominantly from anatomic

TABLE 144-7 Approximate $F_{I_{O_2}}$ Using Various Oxygen Devices (Assumes Perfect Fit of Mask)

100% O_2 Flow Rate (L/min)	$F_{I_{O_2}}$ (%)
Nasal Cannula	
1	24
2	28
3	32
4	36
5	40
6	44
Oxygen Mask	
5–6	40
6–7	50
7–8	60
Mask with Reservoir Bag	
6	60
7	70
8	80
9	90
10	>99
Nonrebreathing Mask	
4–10	60–100
Venturi Mask[a]	
3 (80)	24
6 (68)	28
9 (50)	35
12 (50)	40
15 (41)	50

[a]*Number in parentheses indicates total flow of entrained room air with Venturi mixture.*

dead space and, consequently, its O_2 content is high and CO_2 content low. The reservoir bag is filled with the exhaled volume and continued oxygen inflow, while the remainder of the patient's tidal volume is exhaled via the mask's side ports and edges. A patient with a high minute ventilation can sometimes deflate the reservoir. As with simple oxygen masks and nasal cannulae, the $F_{I_{O_2}}$ the patient is receiving cannot be determined precisely at any point in time.

The nonrebreathing reservoir mask (Fig. 144-2B) is similar to the partial rebreather, with the exception of a one-way valve at the exit of the reservoir bag. The valve ensures that no exhaled air enters the reservoir (i.e., air can travel only in an inward direction), enabling delivery of 100% oxygen. The mask also incorporates one-way valves on its side ports to minimize the inhalation of room air. When using a nonrebreathing reservoir mask, oxygen flow should be set high enough to prevent deflation of the reservoir bag—usually about 15 L/min. Currently available masks do not fit securely enough to ensure a delivered $F_{I_{O_2}}$ of 100%. Typically, these masks provide a maximum $F_{I_{O_2}}$ of 80% to 90%; the $F_{I_{O_2}}$ may be even lower (60%–80%) in the setting of very high minute ventilation.[32]

■ HIGH-FLOW OR FIXED-PERFORMANCE OXYGEN DEVICES

High-flow oxygen devices deliver a constant $F_{I_{O_2}}$ and are, therefore, sometimes referred to as "fixed performance devices." The devices allow for a fixed $F_{I_{O_2}}$ by providing very high flows of pure oxygen which exceed the patient's minute ventilation, sometimes by a factor of four. Along with very high flow rates, the devices incorporate oxygen reservoirs whose volumes exceed the patient's anatomical dead space. Since the $F_{I_{O_2}}$ is predictable, high-flow devices are ideal for patients who have precise oxygen needs that should be neither exceeded nor unmet. Patients for whom high-flow devices are prescribed may be severely hypoxemic and must be monitored closely for the possible need for noninvasive mechanical ventilation or intubation.

Air-Entrainment Masks (Venturi Masks)

The Venturi mask consists of a mask, a jet nozzle, and entrainment ports (Fig. 144-2D). Oxygen is delivered under pressure via the jet nozzle, which acts to dramatically increase the velocity of the gas. The high-velocity gas entrains ambient air via the entrainment ports. Depending upon the size of entrainment ports, size of the jet nozzle, and flow rate of oxygen, a predictable $F_{I_{O_2}}$ can be delivered.

Typically, the Venturi mask has interchangeable or adjustable valves that enable the clinician or respiratory therapist to better titrate the $F_{I_{O_2}}$ to the patient's needs. Humidification is sometimes difficult to ensure and requires the use of an aerosol-entrainment collar over the jet orifice and entrainment port. Humidification increases the density of the entrained air, slows the speed of entrainment, and thereby reduces the amount of room air entrained, resulting in a higher $F_{I_{O_2}}$. Although described as a high-flow device, air-entrainment masks generally can only ensure a high-flow rate when the $F_{I_{O_2}}$ is <30%.[32] As the $F_{I_{O_2}}$ increases above 30%, the devices are unable to deliver flow rates of 40 L/min (as less room air is entrained) and are considered variable performance devices. However, the ability of these masks to deliver an exact $F_{I_{O_2}}$ at lower levels of $F_{I_{O_2}}$ makes them ideal for patients with chronic lung disease who require a specific $F_{I_{O_2}}$ due to the risk of hypercapnia from hyperoxia. In fact, for treatment of patients with COPD in emergency departments, the British Thoracic Society recommends oxygen administration using a Venturi mask to ensure an appropriate $F_{I_{O_2}}$.[10]

High-Flow Generators

High-flow generators are used to ensure noninvasive delivery of a constant, high concentration of inspired oxygen. High-flow generators are capable of delivering gas in excess of 40 to 60 L/min. From the generator, gas is routed through a heated humidifier, similar to that used for mechanical ventilators. A large reservoir is often placed in line between the humidifier and aerosol face mask. The face mask may incorporate valves which ensure that no rebreathing occurs. Given the high flows delivered, a constant $F_{I_{O_2}}$ is achieved, regardless of the patient's minute ventilation and fit of the mask. When precise oxygen titration is required, air–oxygen blenders are used. The blenders are metering devices which use compressed oxygen and air from a high-pressure wall source (50 psi) to generate a gas mixture which can be delivered at high flow (e.g., 100 L/min) and precise $F_{I_{O_2}}$. The devices are noisy and require specialized personnel to set up and monitor, limiting their usage to intensive care settings.[33]

High-Flow Nasal Cannulae

Recently, nasal cannulae (Fig. 144-2C) that can deliver much higher rates of flow than simple nasal cannulae have been developed (e.g., Vapotherm®) that allow delivery of much higher flows (and therefore, higher $F_{I_{O_2}}$) of humidified oxygen. The devices can deliver between 1 and 60 L/min and may be more comfortable than a facemask.[34] However, particularly in infants, these devices may increase positive end-expiratory pressures (4 cm H_2O or higher). Therefore, the devices' clinical benefits must be weighed against the risk of barotrauma, especially in infants.[35]

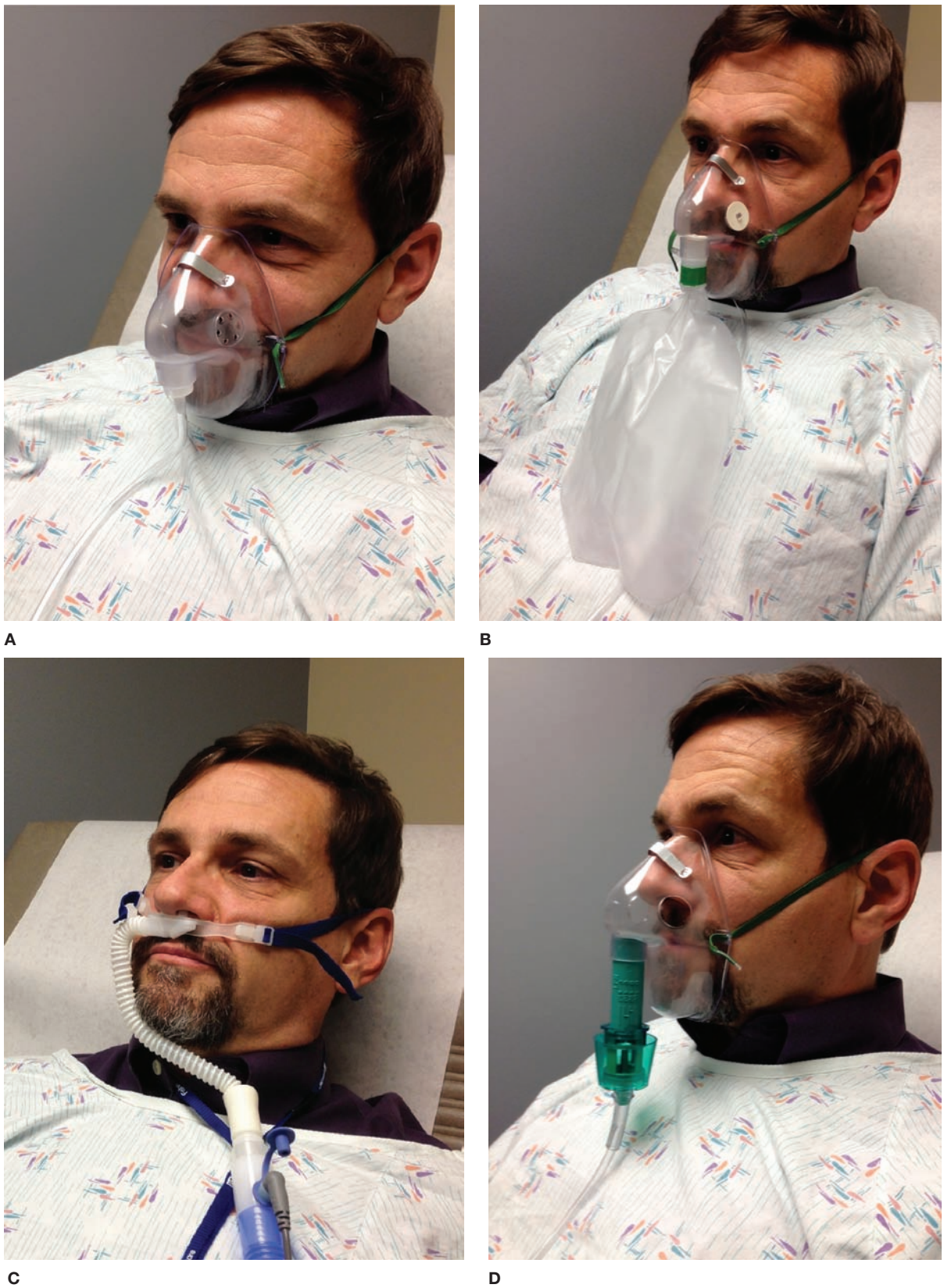

Figure 144-2 Mask oxygen delivery devices. **A.** Simple face mask. **B.** Nonrebreather mask. **C.** High-flow nasal cannulae. **D.** Venturi mask.

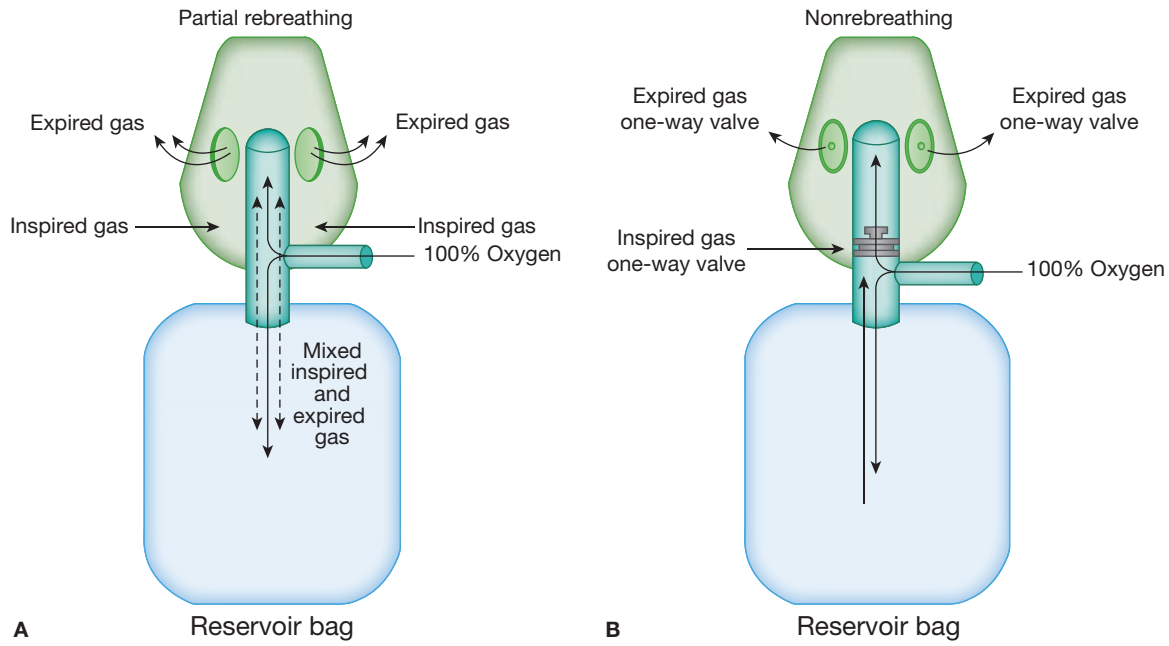

Figure 144-3 Mask reservoir bag systems, illustrating airflows with partial rebreathing (**A**) and nonrebreathing (**B**) masks. *Arrows* indicate direction of airflow.

■ LONG-TERM OXYGEN THERAPY

As noted previously, LTOT has a significant beneficial effect on survival in patients with chronic hypoxemia. However, initiation of chronic home oxygen therapy can be a substantial burden for patients. Like any therapy, LTOT is subject to patient noncompliance. Various studies have noted adherence to LTOT in only 45% to 70% of patients.[36] The barriers to adherence are many and include patient concerns of addiction and dependency, embarrassment from the "stigma" that an oxygen delivery device represents with respect to a smoking-related disease, and the associated limitations on physical activity arising from bulky ambulatory oxygen sources.[36] Therefore, appropriate counseling about the benefits and demands of oxygen therapy is necessary before beginning treatment. Furthermore, the clinician should consider oxygen source portability, social and home support available (e.g., from friends, family, or visiting nurses), and patient attitudes and beliefs when considering LTOT. Finally, the clinical needs to facilitate sufficiently close patient monitoring to ensure long-term benefit from therapy. In the United States, oxygen therapy requires a Certificate of Medical Necessity (CMN). Continued need for LTOT must be recertified annually.

Oxygen Concentrators

Oxygen concentrators use specialized filters to eliminate other gases from room air, thus "concentrating" oxygen for delivery to the patient. Concentrators accomplish this by (1) using a compressor to draw room air into the system, (2) cooling the air (which has been heated up from the compression) using a heat exchanger, and (3) passing the air into molecular sieve beds where oxygen is concentrated. Sieve beds contain granular zeolite crystal composed of an array of small particles which separate gases according to size. Air cycles through two separate sieve beds; the cycling gradually removes nitrogen as waste and isolates oxygen which is diverted to a product tank. The oxygen in the product tank is pressurized at 10 psi and, prior to patient delivery, is passed through a bacteria filter and flow meter. Concentrators usually can produce oxygen concentrations of 95% to 97% at 2 L/min flow; the concentration falls to 86% to 93% at 3 to 5 L/min flow (note that pure oxygen tanks provide 100% oxygen at any flow rate up to 6 L/min).[33] Oxygen concentrators include large devices (weighing about 35 lb) intended for stationary use in the home and smaller portable devices, designed for use outside the home. The larger concentrators can produce high flows (up to 10 L/min) but are often tethered by power cords. High flow rates also demand humidification, which can also be provided by most large concentrators. Portable oxygen concentrators permit patient mobility; their use is increasingly being approved for air travel.[37] They usually weigh between 5 and 10 lb. Battery life is variable, typically of the order of 2.5 hours.

Liquid Oxygen

Although compressed gas oxygen is still utilized, often as an emergency supply in the home environment, liquid oxygen (LOx) has become standard in domiciliary systems. LOx has advantages of being more compact, requiring fewer refills, and operating at lower pressures than gaseous oxygen.

A home system of LOx typically consists of a large stationary reservoir which can hold up to 100 lb of LOx, and a smaller portable system for ambulation. The portable system can be refilled by the patient and may weigh as little as 5 lb. LOx is stored in tanks called dewars, which generally resemble a thermos bottle. The dewar consists of inner and outer containers and interposed insulating material and vacuum to maintain low temperatures.[33] Generally, LOx is more expensive than compressed gas and requires pressure-relief venting. However, LOx delivery systems consume less electricity and enable longer periods of high-flow oxygen administration.

Oxygen-Conserving Devices

LTOT is expensive, and oxygen-conserving devices have been designed to limit oxygen waste. Simple oxygen-conserving devices were discussed earlier. In addition to these simple devices, electronic oxygen-conserving devices are available.

Electronic oxygen-conserving devices are triggered by the onset of inspiration and deliver oxygen in boluses, the volume of which depends on device settings. For *pulse-type devices*, a fixed volume of oxygen is delivered (based on the flow setting) each time a breath is initiated. Some pulse-type devices deliver the volume with alternating breaths, rather than with every breath. For *demand-type devices*, the volume of oxygen is delivered throughout the whole inspiratory cycle; consequently, the volume varies according to the length of the

cycle. For demand-type devices, as respiratory rate decreases, the amount of oxygen conserved also decreases. In fact, demand-type devices commonly deliver an equal or greater volume of oxygen than a continuous-flow device. In the event of an electronic-conserving device malfunction, the delivery system defaults to continuous flow, often without the patient being aware.

Transtracheal Catheters

Transtracheal catheters, also considered oxygen-conserving devices, are considerably more invasive than other forms of LTOT. Transtracheal catheters require insertion directly into the trachea. Usually, this is accomplished percutaneously, using a modified Seldinger technique (similar to that used for placement of a percutaneous tracheostomy), or surgically, using a Lipkin procedure or mini-tracheotomy.[38]

The benefit of a transtracheal catheter is that it delivers oxygen that bypasses much of the anatomical dead space and utilizes the natural oxygen reservoir of the upper airway. Oxygen usage may be reduced by 50% to 75% with the use of a transtracheal catheter. In addition, nasal or facial irritation is minimal. Unfortunately, the catheter can be a nidus for infection and formation of "mucus balls," which rarely are fatal.[39]

PULMONARY OXYGEN TOXICITY

The modern study of pulmonary oxygen toxicity essentially began with J. Lorrain Smith in 1899. Smith described pathologic changes of oxygen toxicity in small animals exposed to the gas at a fractional concentration of 0.4 at 4.5 atmospheres (hyperbaric oxygen).[40] He noted that with high levels of oxygen exposure in mice, "the effect was uniformly fatal, and the immediate cause of death was inflammation of the lungs…and the lungs were found postmortem to be extremely congested…the alveoli were to a great extent filled with an exudate, which was granular and fibrillated in appearance…."

Further studies were conducted in animals to confirm Smith's findings. In the late 1930s, Becker-Freysang et al. studied oxygen exposure in humans and found that with 65 hours of exposure to O_2 at 730 mm Hg, paresthesias, nausea, and significant decreases in vital capacity occurred.[40] In the early 1960s, a healthy volunteer exposed to 110 hours of continuous high oxygen exposure experienced profound alterations in vital capacity, minute ventilation, pH, and Pa_{O_2}.[41] However, in general, the study of oxygen toxicity in humans has proved challenging. Based on animal models, information has been generated on the underlying cellular mechanisms.

■ BIOCHEMICAL BASIS OF PULMONARY OXYGEN TOXICITY

In considering the biochemical basis of pulmonary oxygen toxicity, the roles of free radicals and cellular antioxidant defenses in the production of tissue damage should be noted.

Free Radicals

Descriptions of the mechanisms of oxygen toxicity invariably begin with the concept of highly reactive oxygen-derived free radicals, specifically, superoxide (O_2^-), hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH^-). By definition, free radicals have an unpaired orbital electron which causes either oxidation or reduction of a surrounding molecule. Free radicals are ubiquitously produced during cellular respiration; however, cells normally have the capability of neutralizing them quickly. Invariably, in hyperoxic conditions, generation of free radicals overcomes the cell's natural defenses.[42] Once formed in excess, free radicals are responsible for a cascade of effects, including lipid damage, leading to membrane dysfunction; disruption of enzymatic protein function; and nucleic acids damage.[43] Ultimately, these effects may result in cell death. In the case of nucleic acid damage, mutagenesis may occur.

Cellular Antioxidant Defenses

Various enzymes and cofactors in cells neutralize free radicals produced normally as a by-product of metabolism. These neutralizing enzymes are ubiquitous in eukaryotes.[44] The prototype is the metalloprotein, superoxide dismutase, which converts superoxide to hydrogen peroxide. Hydrogen peroxide so-generated is converted intracellularly to H_2O and O_2 through the actions of catalase (found in peroxisomes) and glutathione peroxidase (found in the cytoplasm). Glutathione peroxidase also repairs damaged lipids. Glutathione reductase and glucose-6-phosphate dehydrogenase regenerate glutathione enabling its recycling as an antioxidant.

Nonenzymatic antioxidants, which are present within cells, include the vitamins, α-tocopherol (vitamin E) and ascorbate (vitamin C). Other antioxidants, such as ceruloplasmin and cysteine, are also normally present in cells and the extracellular fluid. In fact, human lung tissue contains a high concentration of extracellular antioxidants and superoxide dismutase enzymes, which allow exposure to higher-concentration oxygen without development of toxicity.[45–47]

Tissue Damage

The cascade of reactions leading to hyperoxia-induced pulmonary tissue damage can be described in two phases.[48] Three to four days following hyperoxic exposure and generation of free radicals, an *exudative* phase commences, characterized by death of alveolar type 1 and endothelial cells. Interstitial edema is seen along with exudative alveolar filling. Neutrophil recruitment into the capillaries and interstitium is present. Alveolar epithelial damage then occurs, as neutrophils enter the alveoli, as seen in BAL specimens. A second, *proliferative* phase follows, characterized by proliferation of endothelial cells and type 2 pneumocytes. The pneumocytes cover the previously exposed basement membrane. Fibroblast proliferation also occurs in this phase. Recovery from oxygen injury is characterized by interstitial scarring and fairly normal-appearing capillary endothelium and alveolar epithelium.

■ CLINICAL MANIFESTATIONS OF PULMONARY OXYGEN TOXICITY

The exposure level at which oxygen toxicity occurs has not been clearly identified, although a higher $F_{I_{O_2}}$ experienced for a longer period of time is associated with an increased risk.

Clinical oxygen toxicity is manifest in several ways. Normal subjects experience a decrease in vital capacity and fall in $D_{L_{CO}}$.[49] Lung compliance is diminished.[49] Tracheobronchitis, which produces substernal chest pain, may also occur.[50] Clinical toxicity is generally absent when the $F_{I_{O_2}}$ is <50%.

Most clinically relevant concerns over oxygen toxicity center around (1) absorption atelectasis; (2) hypercapnic respiratory failure in at-risk individuals; (3) acute respiratory distress syndrome (ARDS); and (4) hyaline membrane disease, leading to bronchopulmonary dysplasia (BPD) in newborns.[51–53]

Absorption Atelectasis

Absorption atelectasis begins with complete or partial collapse of an alveolar unit's proximal airway. With airway closure, previously inhaled gas is trapped in the distal alveoli. Oxygen passes freely from the alveoli into the capillaries and is bound to hemoglobin or dissolved in plasma. Nitrogen, however, does not diffuse into the blood at nearly the same as oxygen. Hence, alveolar nitrogen "stents" open the alveoli, maintaining patency. For a patient breathing pure oxygen, the absence of nitrogen promotes alveolar collapse.

In a study based on mathematical modeling of alveolar collapse, the time from airway occlusion to alveolar collapse was 37 minutes using 3 minutes of preoxygenation with ambient air, compared with 8.7 minutes using preoxygenation with 100% oxygen (taking into

account hypoxic vasoconstriction).[54] In a clinical context, patients who received 40% oxygen just prior to extubation were shown to have less atelectasis on CT imaging compared with those who received 100% oxygen.[55] Finally, absorption atelectasis is commonly seen with induction of anesthesia. Preoxygenation and resulting nitrogen washout, along with a decrease in FRC from chest wall and diaphragmatic paralysis that occurs with the use of neuromuscular blockade, lead to small airway collapse.[56]

Hypercapnia in the Setting of Chronic CO_2 Retention and Hyperoxia

Patients with chronic CO_2 retention, usually in the setting of COPD, are at risk of worsening hypercapnia when exposed to high levels of oxygen. Classically, this worsening of hypercapnia during excessive supplemental oxygen administration has been attributed to the suppression of hypoxic drive to breathe in the setting of a blunted hypercapnic drive. This formulation was first proposed in a case report published in the middle of the 20th century.[57] However, three other mechanisms have been proposed,[10] as discussed below.

Ventilation–perfusion mismatch is an important cause of hypoxemia in patients with COPD. As discussed previously, hypoxic vasoconstriction (HPV) minimizes the adverse effects of a low $P_{A_{O_2}}$ on Pa_{CO_2}. When $P_{A_{O_2}}$ is increased through administration of supplemental oxygen, HPV is partially reversed, increasing perfusion to alveolar units which are still underventilated and now, oxygen enriched. Alveolar oxygen diffuses across the alveolar–capillary membrane, but because ventilation is still reduced, $P_{A_{CO_2}}$ remains high, reducing the diffusion gradient for CO_2 diffusion out of the blood. As a result, Pa_{CO_2} increases.

An additional consideration is the *Haldane effect*—the increased capacity of deoxygenated blood over oxygenated blood for CO_2 binding. As hemoglobin molecules become deoxygenated (i.e., reduced), they more readily accept protons (H^+). Removal of dissolved protons from plasma drives formation of bicarbonate, which, in turn, is catalyzed by carbonic anhydrase:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \quad (8)$$

Bicarbonate is the primary form in which CO_2 is transported and eliminated from the body. Furthermore, deoxygenated hemoglobin binds CO_2 directly, forming carbaminohemoglobin. As $P_{A_{O_2}}$ and, consequently, Pa_{O_2} increase with oxygen therapy, the concentration of oxyhemoglobin increases while that of deoxyhemoglobin decreases. As a result, buffering capacity is depleted, diminishing venous blood's transport capacity for tissue-generated CO_2; Pa_{CO_2} rises.

Finally, since pure oxygen is of higher viscosity than air, the increased viscosity of oxygen-enriched mixtures may contribute to increased work of breathing in an already compromised patient.[58]

Regardless of the underlying mechanism(s), clinicians must be vigilant when administering supplemental oxygen to those with chronic CO_2 retention. Unfortunately, the worsening of hypercapnia with oxygen administration is unpredictable; some patients with COPD do not develop hypercapnia with hyperoxia, while others may develop frank respiratory failure. Use of a high-performance oxygen delivery device (e.g., Venturi mask), and titration of $F_{I_{O_2}}$ to achieve a goal Sa_{O_2} of 88% to 90% in selected populations is the preferred management strategy.

Acute Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

Oxygen toxicity has been implicated in the pathophysiology of the ARDS, although this subject is controversial. In almost all nonhuman mammals, prolonged exposure to 100% oxygen leads to diffuse alveolar damage and, eventually, death. In humans, replicating these findings has been challenging. Conducting human studies on oxygen toxicity presents ethical considerations of testing healthy human subjects. In addition, when oxygen toxicity is studied in the setting of pulmonary disease, differentiation between damage caused by the underlying lung disease and that caused by excessive oxygen exposure may be impossible. Many human studies have failed to show an association between excessive oxygen exposure and development of acute lung injury or ARDS.

In a study of brain-dead patients whose normal lungs were exposed for 24 hours to 100% oxygen delivered via a mechanical ventilator, only mild increases in alveolar capillary permeability were demonstrated; several more days of oxygen exposure failed to produce pathologic evidence of lung injury.[59] Similarly, another trial in postoperative cardiac patients failed to show any clinical differences between those ventilated with 100% oxygen and those ventilated with the minimal amount of oxygen needed (mean $F_{I_{O_2}}$ of 32%).[60] Notably, an acute lung injury pattern due to oxygen toxicity may be seen in humans with prior drug exposure, as discussed below.

Premature newborns often require high levels of oxygen therapy in the setting of hyaline membrane disease—a disorder caused by surfactant deficiency and characterized by alveolar collapse and inflammation.[61] In survivors, chronic lung disease in the form of BPD is often seen.

Oxygen toxicity is considered a major factor in the pathogenesis of BPD. BPD has been described in infants administered a high concentration of oxygen but not mechanically ventilated.[51] Newborns are particularly prone to damage by hyperoxia, as their cellular antioxidant defenses are not fully developed.

The initial pathologic lesions of BPD resemble diffuse alveolar damage. As BPD evolves, pathologic findings include alternating areas of collapse and emphysema, hyaline eosinophilic material lining distended terminal airways, marked epithelial hyperplasia or metaplasia, peribronchial fibrosis, and elastic fibers around air sacs and lobules. Clinically, the condition presents as a persistent requirement for supplemental oxygen or mechanical ventilation following hyaline membrane disease, along with poor lung compliance and pulmonary hypertension. Most infants gradually improve after 2 to 4 months. In more severe cases, infants require prolonged mechanical ventilation and may develop cor pulmonale from severe pulmonary hypertension.

■ POTENTIATION OF PULMONARY OXYGEN TOXICITY

Several drugs have well-known pulmonary toxicity and may potentiate the pulmonary toxicity of oxygen.

Bleomycin, an antibiotic agent first isolated from the fungus *Streptomyces verticillus* in the late 1960s,[62] has been used as a chemotherapeutic agent in the treatment of lymphomas, germ cell tumors, Kaposi sarcoma, cervical cancer, and squamous cell carcinomas of the head and neck. One mechanism by which bleomycin exerts its antitumor effect is through induction of cytotoxicity via generation of free radicals. Bleomycin forms a complex with Fe^{2+}, which is oxidized to Fe^{3+}, resulting in reduction of oxygen to free radicals. Bleomycin is also thought to exert direct effects on DNA. Along with its elimination by the kidneys, bleomycin can be deactivated by the enzyme bleomycin hydrolase, which is found in most tissues (especially the liver). However, two notable organs lack the enzyme: Lung and skin.

In the lungs, bleomycin toxicity is manifest in three ways: Organizing pneumonia, eosinophilic hypersensitivity, and interstitial pneumonitis, which may progress to fibrosis. An experiment in the hamster demonstrated that high doses of oxygen may work synergistically with bleomycin to cause worsening lung injury.[63] In humans, several case reports describe ARDS in patients previously treated with bleomycin who have exposure to a high $F_{I_{O_2}}$ perioperatively.[64,65] However, one prospective trial failed to show an association between high levels of oxygen exposure, past bleomycin exposure, and significant postoperative pulmonary dysfunction.[66]

Another well-known potentiator of pulmonary oxygen toxicity is paraquat. Paraquat is a commercial herbicide commonly used in the United States. It is associated with considerable toxicity and mortality when ingested orally, often in suicide attempts.[67] Like bleomycin, paraquat-induced pulmonary toxicity is the result of oxidative stress arising from the generation of free radicals, leading to pneumonitis and pulmonary fibrosis. Similar to models of bleomycin toxicity, animal studies suggest worsening toxicity in the setting of higher levels of inspired oxygen.[68,69] Therefore, in managing patients with paraquat poisoning, FI_{O_2} should be minimized as much as clinically possible. Use of paraquat is banned in the European Union and in several other countries, but the herbicide is still available for agricultural use in the United States. Fulminant poisonings carry a mortality that well exceeds 50%.[70]

Other drugs studied with regard to potentiation of oxygen toxicity include disulfiram and nitrofurantoin. Disulfiram is converted in vivo to diethyldithiocarbamate, which inhibits cytosolic superoxide dismutase.[71] Metabolism of nitrofurantoin results in the production of superoxide in a similar way to paraquat. The final pathway in both cases is an accumulation of oxygen-free radicals.[72]

Finally, elements of dietary intake are also associated with potentiation of oxygen toxicity, at least in animal models.[73] Protein deficiency leads to hyperoxic damage, possibly through a lack of sulfur-containing amino acids, which are crucial to glutathione synthesis. Deficiencies in the antioxidants vitamin A and vitamin E have also been implicated in the potentiation of oxygen toxicity.[74,75]

OXYGEN TOXICITY IN OTHER ORGAN SYSTEMS

Hyperoxia has the potential for producing toxicity in other organ systems. For example, an association between increased mortality and hyperoxia in the setting of return of spontaneous circulation (ROSC) following cardiac arrest has been reported.[76] In this large, multicenter, retrospective cohort study, patients who had a Pa_{O_2} >300 mm Hg following ROSC had an odds ratio for in-hospital death of 1.8 (95% CI, 1.8–2.2), based on a model controlling for potential confounders. The increased mortality seen in this study was attributed to hyperoxic reperfusion injury leading to oxidative stress—specifically worsening postarrest functioning of the central nervous system. Based on the results of this study, the American Heart Association has adjusted its postarrest guidelines to emphasize titration of FI_{O_2} to maintain an oxygen saturation ≥94%. Prospective data are not currently available to prove causation.

In a retrospective study conducted at a single trauma center, higher mortality was noted in patients with traumatic brain injuries exposed to hyperoxia (Pa_{O_2} > 200 mm Hg) compared to normoxia.[77] Patients with hyperoxic exposure were more likely to have low Glasgow coma scores (3–8) on discharge than those who were normoxic. In the same study, patients with hypoxemia also had worse outcomes compared to those who were normoxic, emphasizing the importance of close and continued monitoring using pulse oximetry.

Finally, in the case of acute myocardial infarction (AMI), controversy exists regarding oxygen therapy. When treating patients with myocardial ischemia who are hypoxemic, oxygen is absolutely indicated, as it can be life-saving. However, when a patient with AMI is not hypoxemic, whether supplemental oxygen is beneficial is unclear.

A double-blind randomized trial conducted in the late 1970s compared oxygen therapy (6 L/min) with no oxygen therapy in 157 patients with uncomplicated AMI.[78] In patients who received oxygen, higher rates of sinus tachycardia and a greater rise in myocardial enzymes were noted, along with no difference in mortality (actually, a trend toward improved mortality was seen in the no-oxygen arm). Several reasons for the potential deleterious effects of hyperoxia in an AMI have been proposed. In healthy humans, hyperoxia has been shown to induce coronary vasoconstriction. Furthermore, in critically ill patients, high-flow oxygen therapy may lead to maldistribution of microcirculatory blood flow, increased functional O_2 shunting, and a reduction in total body oxygen consumption.[79] Although data supporting the use of supplemental oxygen in uncomplicated AMI remain unclear, the practice remains nearly universal.

CONCLUSION

Since its discovery, oxygen has been successfully utilized in medicine, revolutionizing the field in the early half of the 20th century. Supplemental oxygen remains among the most common therapies provided in the inpatient setting. Oxygen therapy may improve oxygen delivery and reverse tissue ischemia. The role of supplemental oxygen in management of outpatients with chronic, severe, pulmonary and cardiac diseases is broad. In the outpatient setting, supplemental oxygen may considerably improve quality of life in those patients willing to adapt to its use. Despite the widespread availability of supplemental oxygen and its relative ease of use, oxygen must be considered a drug with a therapeutic window, above which the potential for significant toxicity exists.

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CHAPTER 145

Pulmonary Pharmacotherapy

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A wide spectrum of therapeutic agents is currently employed in the treatment of respiratory disorders, including obstructive lung diseases. This chapter reviews the rationale for, and clinical use of, these agents in current clinical practice.

DRUG DELIVERY

Inhaled drug administration is preferred for many medical conditions. Advantages of inhaled drug administration include rapid onset of action and the ability to deliver small drug doses directly to the lungs, minimizing systemic drug exposure. Compressed air nebulizers have been in use for more than 150 years; the first metered-dose inhaler (MDI) became available in the 1950s, followed by the first dry powder inhaler (DPI) in the 1960s.[1] Many new and innovative devices have been marketed as the result of the phase-out of chlorofluorocarbon-containing MDIs.[2]

Device selection depends on drug–device availability, patient characteristics (e.g., age, cognitive function, manual dexterity), and patient preference (Tables 145-1 and 145-2).[3,4] MDIs and nebulizers share universal designs; other drug delivery devices are unique, individually patented devices.

MDIs are small portable devices that protect the medication from contamination; they are difficult to use correctly. Common drug administration errors include improper timing of actuation and inspiration and failure to inspire slowly and deeply. MDI accessory devices (e.g., spacers, valved holding chambers) decrease oropharyngeal drug deposition and reduce the need for precise "press and breathe" timing, but they are bulky, add to the cost of therapy, and must be regularly cleaned to reduce bacterial contamination and electrostatic charges within the chamber. The Respimat device is a unique, multidose liquid inhaler that uses spring-loaded energy to generate a fine aerosol mist.[5]

DPIs are available as premetered devices that contain or accept single doses or as bulk reservoir devices. DPIs are breath actuated, requiring rapid and forcible inhalation to aerosolize and deliver the dose; most require inspiratory flow rates of 30 to 60 L/min. Young children, the elderly, and patients with reduced lung function (e.g., during an acute exacerbation) may be unable to generate adequate inspiratory flow rates.

Nebulizers aerosolize a solution or suspension by one of the three mechanisms: compressed air or oxygen (jet nebulizers), high-frequency ultrasonic energy (ultrasonic nebulizers), and vibrating mesh. Suspensions can only be aerosolized with jet nebulizers. Nebulizers are more expensive, require more dose preparation, and take more time to deliver a dose than other drug delivery devices. However, they require less patient cooperation and may be used by patients of all ages and abilities.

TABLE 145-1 Inhaled Drug–Device Availability

Drug Class	pMDI	BAC MDI	DPI	SMI	Nebulizer
SABA	X	X[a]			X
SAMA	X				X
SABA + SAMA	X[b]			X	X
LABA			X		X
LAMA			X		
ICS	X		X		X
ICS + LABA	X		X		
MCS					X

pMDI, metered-dose inhaler; DPI, dry powder inhaler; SMI, soft-mist inhaler; BAC MDI, breath-actuated metered-dose inhaler; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; MCS, mast cell stabilizer.
[a]December 31, 2013 was the last date for sale for Maxair (pirbuterol) Autohaler, the only marketed chlorofluorocarbon-containing breath-actuated metered-dose inhaler.
[b]December 31, 2013 was the last date for sale for Combivent (albuterol plus ipratropium bromide), the only marketed chlorofluorocarbon-containing combination SABA + SAMA metered-dose inhaler.

BRONCHODILATORS

Bronchodilation produced by β-Adrenergic agonists, muscarinic antagonists, and methylxanthines is a major component of the pharmacologic management of obstructive airway diseases. Other drugs (e.g., magnesium) have been used clinically for bronchodilation.

β-ADRENERGIC AGONISTS

The β-Adrenergic agonists mimic the actions of norepinephrine at neuroeffector and synaptic junctions. Norepinephrine is the major neurotransmitter in the sympathetic nervous system; therefore, this class of drugs is referred to as *adrenergic agonists* or *sympathomimetics.* The two major types of adrenergic receptors are the α and β receptors; at least two α and three β receptor subtypes have been identified.

β-Adrenoceptor stimulation relaxes smooth muscles via cyclic-3′5′-adenosine monophosphate (cAMP)-dependent and cAMP-independent mechanisms. Adrenergic receptor stimulation catalyzes the conversion of adenosine triphosphate (ATP) to cAMP by activating adenyl cyclase, a cofactor in the production of cAMP. The

TABLE 145-2 Age–Device Guidelines

Device	Age
pMDI	≥5 y
	<5 y, use with spacer or VHC and face mask
DPI	≥4 y
Spacer or VHC	≥4 y
	<4 y, use VHC and face mask
Nebulizer	Infants: SVN with face mask or hood
	≤3 y: SVN with face mask
	≥3 y: SVN with mouthpiece
	≥5 y: breath-actuated nebulizer
	All ages unable to use pMDI with VHC and face mask

pMDI, metered-dose inhaler; DPI, dry powder inhaler; VHC, valved holding chamber; SVN, small volume nebulizer.
Source: Data from National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Report No. 07–4051. Bethesda, MD. National Heart, Lung, and Blood Institute (US); 2007. www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

TABLE 145-3 Adrenergic Agonists

Agent	Receptor Activity			Dosage Forms					
	α	β_1	β_2	Duration[a]	pMDI	DPI	Neb	SC	Oral
Albuterol		Slight	+	Short	√		√		√
Arformoterol		Slight	+	Long			√		
Epinephrine	+	+	+	Short				√	
Formoterol		Slight	+	Long		√	√		
Indacaterol		Slight	+	Very long		√			
Levalbuterol		Slight	+	Short	√		√		
Metaproterenol		Slight	+	Short					√
Pirbuterol[b]		Slight	+	Short	√				
Racepinephrine[c]	+	+	+	Short			√		
Salmeterol		Slight	+	Long		√			
Terbutaline		Slight	+	Short				√	√
Vilanterol		Slight	+	Very long		√			

pMDI, metered-dose inhaler; DPI, dry powder inhaler; Neb, nebulizer solution; SC, subcutaneous.
[a]*Duration: short, 1–6 h; long, 8–12 h; very long, 24 h.*
[b]*Breath-activated autohaler; contains chlorofluorocarbons; last date for sale in the United States was December 31, 2012.*
[c]*Nonprescription product.*

increase in cAMP triggers the intracellular events that mediate pulmonary and extrapulmonary responses. β-Adrenoceptor stimulation also activates large-conductance, calcium-activated potassium channels in plasma membranes independent of cAMP.[6]

The β-Adrenergic agonists (Table 145-3) are indicated in the treatment of bronchospasm associated with acute and chronic asthma, bronchitis, emphysema, exercise, and other obstructive pulmonary diseases. Selection of a specific agent and route of administration depends on underlying patient risk factors and the receptor specificity of the drug.

Pharmacology

Adrenergic receptor stimulation produces a wide range of responses, depending on the effector organ and the specific receptor.[7] Although bronchial smooth-muscle relaxation results from β_2-Adrenergic receptor stimulation, none of the currently marketed agonists are completely specific for β_2-Adrenergic receptors. The α-Adrenergic receptor is generally associated with constrictor/contractor responses, including constriction of arteries and veins and contraction of the uterus, radial and sphincter muscles of the iris, urinary bladder, and stomach sphincters. β_1-Adrenergic receptor stimulation increases heart rate, atrial and ventricular contractility, and cardiac conduction velocity. Effects from β_2-Adrenergic receptor stimulation include relaxation of bronchial and uterine smooth muscle, dilatation of arteries and veins, and several metabolic effects, including glycogenolysis, gluconeogenesis, and induction of hepatic pancreatic β-cell secretion.

Structure–Activity Relationships

The parent compound for the adrenergic agonists, phenylethylamine, consists of a benzene ring and an ethylamine side chain. Substituents can be added to the α or β carbons of the ethylamine side chain, the terminal amine group, or one or more of the carbons in the aromatic ring.[8] The addition of hydroxyls at positions 3 and 5 of the aromatic ring (e.g., metaproterenol and terbutaline) promotes oral bioavailability. Large substituents added to the amino group promotes β_2-Adrenergic receptor selectivity and favors a long duration of action (e.g., salmeterol, formoterol, indacaterol, vilanterol).

At least two theories have been proposed to explain the long duration of action of the long-acting and ultra long–acting β_2-Adrenergic agonists (LABAs).[9,10] The *exosite theory* states that a portion of the large side chain on the terminal amine binds to a site separate from, but close to, the β_2-Adrenergic receptor, keeping the active portion of the structure available for binding and rebinding to the β_2-Adrenergic receptor. The *diffusion mucokinetic model* states that the plasma membrane serves as a drug reservoir. However, neither theory fully explains the long duration of action of salmeterol, formoterol, indacaterol, or vilanterol, suggesting additional mechanisms.

Enantiomers

Albuterol and formoterol are 1:1 mixtures of (R)- and (S)-enantiomers. The therapeutic effect of albuterol comes from the (R)-enantiomer; the (R)-enantiomer is marketed separately as levalbuterol. Early in vitro studies suggested that (S)-albuterol might antagonize the effects of (R)-albuterol, but levalbuterol has not been demonstrated to be clinically superior to racemic albuterol.[11] The (R)-formoterol enantiomer, marketed as arformoterol, is 1000-fold more potent in β_2-recetor binding affinity than the (S)-enantiomer.[12] The racemic mixture is marketed as formoterol. Formoterol and arformoterol are equally effective bronchodilators with similar side effect profiles.[13]

Drug Delivery

The β-Adrenergic agonists may be administered systemically or by inhalation; however, not all drugs are marketed in every dosage form (Table 145-1). Systemic dosage forms include oral, subcutaneous, and intravenous preparations. Systemic administration decreases the β_2-Adrenergic receptor selectivity of the drug due to exposure to various metabolic enzymes, including catechol-o-methyl transferase, monoamine oxidase, and sulfatase. These enzymes change the chemical structure of the drug, decreasing the β_2-Adrenergic receptor selectivity.

Inhaled β-Adrenergic agonists are available in several dosage forms, including wet aerosols, aerosols from MDIs, and dry powder forms. Historically, nebulized drug delivery was standard practice for children and for emergency treatment of asthma exacerbations, hospitalized patients, and severely obstructed patients. However, nebulized drug delivery is labor intensive; significant cost savings can be realized, without sacrificing efficacy, by using MDIs coupled with spacer devices.

Clinical Use

The β_2-Adrenergic agonists remain first-line drugs in the treatment of both asthma and chronic obstructive pulmonary disease (COPD).[14,15] In asthma, the short-acting inhaled β_2-Adrenergic agonists are preferred for treating acute symptoms and for preventing exercise-induced bronchospasm. The subcutaneous route of administration is generally reserved for patients unresponsive to frequent, high-dose, inhaled β_2-Adrenergic agonists; uncooperative patients; or patients too severely dyspneic to inhale the dose. Subcutaneous or parenteral administration should not be used in patients with angina or a recent history of myocardial infarction. Oral adrenergic agonists may be appropriate for children too young to cooperate with inhaled drug administration; sustained-release, oral adrenergic agonists decrease nocturnal symptoms, but they are less effective than LABAs.

In COPD, β_2-Adrenergic agonists provide modest symptomatic relief and improvement in pulmonary function. LABAs are standard bronchodilator therapy for patients with moderate and severe COPD. Standard doses of inhaled β_2-Adrenergic agonists appear as effective as inhaled anticholinergic drugs for relief of acute exacerbations of COPD. The value of subcutaneous drugs and high-dose, short-acting bronchodilators in the management of COPD remains indeterminate.

The intensity and duration of response to β_2-Adrenergic agonists is dose and frequency dependent. For patients with asthma, higher doses result in incrementally greater bronchodilation. The dose–response relationships are less well defined for COPD.

The dose–response curve in asthma led to the development of intensive inhaled β_2-Adrenergic agonist drug regimens for the treatment of severe, acute exacerbations. Typically, the nebulized drug is administered every 20 minutes for three to six doses; some patients respond better to continuous nebulized drug delivery. These regimens are generally well tolerated, although cardiac stimulation is common.

The LABAs are add-on agents for patients with moderate or severe asthma when usual doses of inhaled corticosteroids are inadequate and for patients with moderate or severe COPD. The LABAs are also alternate add-on agents for patients with symptoms of nocturnal asthma. The LABAs play no role in the treatment of an acute asthma or COPD exacerbation; all patients should have a short-acting inhaler and should be instructed on how and when to use each type of β_2-Adrenergic agonist.

Tolerance, that is, receptor subsensitivity or tachyphylaxis, is a decreased response to receptor stimulation. Regular use of either short- or long-acting β_2-Adrenergic agonists leads to tolerance of both the nonbronchodilator and bronchodilator effects of the β_2-Adrenergic agonist.[16] Tolerance to the nonbronchodilator effects of the β_2-Adrenergic agonists, including tremor, tachycardia, QT_c prolongation, hypoglycemia, hypokalemia, and vasodilation has been recognized for many years. Tolerance to the bronchodilator effects of the β_2-Adrenergic agonists develop rapidly with quick recovery following discontinuation of the drug.[17] Receptor downregulation likely mediates tolerance to the β_2-Adrenergic agonists.[16]

Safety

The β_2-selective adrenergic agonists produce less cardiovascular toxicity than do the nonselective agents, but β_2-selectivity does not protect from all adverse events. Biochemical abnormalities associated with the β_2-Adrenergic agonists include hyperglycemia, hyperinsulinemia, lipolysis, hypokalemia, hypomagnesemia, and lactic acidosis.[7] These side effects are most pronounced with parenteral and oral drug administration; they are minimal with usual doses of inhaled agents.

β_2-Adrenergic agonists cause dose- and route-dependent hyperglycemia by stimulating glycogenolysis and gluconeogenesis and suppressing glucose clearance.[18] Hyperglycemia may be clinically most important in asthmatic patients with diabetes mellitus or during pregnancy. β_2-Adrenergic agonists increase plasma insulin by directly stimulating pancreatic islet cells; indirect increases occur secondary to the hyperglycemic response. β_2-Adrenergic agonists induce the release of free fatty acids from adipose tissue. Although hyperinsulinemia and high concentrations of free fatty acids have been linked with cardiovascular morbidity and mortality, tolerance minimizes these effects. β_2-Adrenergic receptor stimulation also induces muscle glycogenolysis, increasing lactate production.

The β_2-Adrenergic agonists induce hypokalemia by directly stimulating the uptake of potassium into skeletal muscle cells.[19] β_2-Adrenergic receptor stimulation induces the cellular uptake of magnesium; hypomagnesemia may induce arrhythmias or worsen symptoms of coronary artery disease. Other adverse β_2-Adrenergic agonist effects include (1) an increased baseline tremor by creating an imbalance in fast- and slow-twitch muscle groups; (2) tachycardia by direct chronotropy and through reflex peripheral vasodilatation and decreased venous return; and (3) central nervous symptoms, such as appetite suppression, headache, nausea, and sleep disturbances.[7] The nervousness reported by many patients is probably a response to the peripheral tremors, rather than a result of direct stimulation of the central nervous system.

β-Adrenergic agonist use has increased coincident with the increase in asthma morbidity and mortality in the United States and other countries. The first linkage between β-Adrenergic agonists and asthma mortality was identified during the 1960s when the newly marketed, nonselective β-Adrenergic agonist isoproterenol was associated with an increase in asthma morbidity and mortality in the United Kingdom. More recently, LABA use has been associated with an increased risk of death in patients with asthma.[20,21] The mechanism is unknown, although it may be related to β-receptor downregulation and desensitization. In 2005, the Food and Drug Administration (FDA) began requiring that labeling for all LABAs include a black box warning regarding the increased risk of asthma-related death. In 2010, the FDA released new safe-use requirements for LABAs. The FDA requires that LABAs (1) be used in combination with an asthma controller medication, and only in patients whose asthma is poorly controlled despite controller medications; (2) be used for the shortest duration of time needed to achieve control and then be discontinued, if possible; and (3) that combination inhaled corticosteroid-LABA products be used for children and adolescents.[22] Concurrent corticosteroid use may reduce the risk of death associated with LABAs; FDA-mandated clinical trials designed to answer this question were initiated in 2011.

■ ANTICHOLINERGICS

Atropine, scopolamine, and other naturally occurring antimuscarinic alkaloids from plant extracts have been used for thousands of years to relieve respiratory symptoms in humans with airway diseases. Historically, clinical use of atropine and atropine-like agents has been limited by side effects, including dry mouth and skin, tachycardia, meiosis, and difficulty urinating and mentating. Three synthetic atropine derivatives (ipratropium bromide, tiotropium bromide, and aclidinium bromide), which have more favorable side effect profiles, are available for management of COPD.

Pharmacology

Three of the five known muscarinic receptor subtypes are expressed in the lung (M_1, M_2, and M_3).[23] Activation of airway M_1 and M_3 muscarinic receptors results in bronchial smooth-muscle contraction and mucus secretion. M_2 "autoreceptor" activation decreases acetylcholine (Ach) release; blockade of M_2 receptors increases airway Ach. The ideal anticholinergic drug would selectively block M_1 and M_3 receptors and have no effect on M_2 receptors.

Ipratropium (FDA approved in 1998), tiotropium (FDA approved in 2004), and aclidinium (FDA approved in 2012) are the bromide salts of a different synthetic quaternary ammonium compound. Each does not penetrate the blood–brain barrier, exhibits minimal systemic absorption, and possesses a longer duration of action than atropine; each possesses differing muscarinic receptor binding affinities and receptor–drug complex half-lives.[24]

Ipratropium nonselectively blocks M_1, M_2, and M_3 receptors. Tiotropium has greater muscarinic receptor affinity than ipratropium bromide, but it dissociates rapidly from M_2 receptors, resulting in prolonged M_1- and M_3-drug complex half-lives compared with ipratropium. Aclidinium has a kinetic selectivity for M_3 receptors, with a longer residence time on the receptor than ipratropium or tiotropium.[25]

Ipratropium inhalation produces bronchodilation within 15 minutes, with a peak effect after 1 to 2 hours.[26] Inhalation of tiotropium produces bronchodilation within 30 minutes, with an effect peak after 3 to 4 hours and duration of action for 24 hours.[26] The trough FEV_1 increases after multiple doses, reflecting carryover bronchodilation from the prolonged half-life. Inhalation of aclidinium produces maximal bronchodilation at about 2 hours, with sustained bronchodilation for the 12-hours dosing interval.[27] Tolerance or tachyphylaxis with chronic use has not been reported.

Drug Delivery

Tiotropium bromide and aclidinium bromide are available in the United States as DPIs (HandiHaler™ and Pressair™, respectively). Ipratropium bromide is available in the United States as a HFA MDI, a solution for nebulization, and as a combination product with albuterol in a soft-mist aerosol inhaler (Combivent Respimat™).

Clinical Use

Ipratropium, tiotropium, and aclidinium are most efficacious in patients with COPD, including emphysema and chronic bronchitis, and they are the bronchodilators of choice in the long-term management of moderate-to-severe COPD.[28] In contrast, the role of anticholinergics in the management of asthma has not been established. Compared to the β-Adrenergic agonists, the anticholinergic drugs have a slower onset of action and less effect on lung function.[28] The addition of tiotropium to treatment with inhaled corticosteroids and long-acting β-Adrenergic agonists improves symptoms and lung function and decreases the risk of severe exacerbation in selected patients,[29,30] but these results cannot be generalized to all patients with asthma.

Safety

Consistent with their very low systemic bioavailability, the inhaled anticholinergics are remarkably free of side effects. Transient or mild dry mouth occurs, but it is rarely a reason for halting therapy.[31] Side effects of tiotropium typically appear after 3 to 5 weeks of continued use, reflecting the slow linear tissue accumulation of the drug. Plasma aclidinium is rapidly hydrolyzed to inactive metabolites, reducing systemic exposure to the drug.[32]

The inhaled anticholinergics do not change mucus viscosity or transport, pulmonary hemodynamics, ventilation–perfusion matching, oxyhemoglobin saturation, heart rate, or urinary flow; however, blurred vision and pupillary dilation may occur if any drug inadvertently contacts the eye. All the three drugs should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction. Ipratropium and tiotropium are renally eliminated; patients with moderate or severe renal insufficiency (Cl_{cr} <30–50 mL/min) should be monitored closely for systemic anticholinergic effects.[33] Less than 0.15% of aclidinium bromide is excreted renally.[34]

Increased mortality in patients with COPD has been reported with long-term (≥30 days) use of tiotropium delivered with the fine-mist Respimat™ inhaler.[35] However, a major recent trial directly comparing tiotropium dry powder and fine-mist inhaler safety revealed no significant differences in either safety or efficacy.[36] Until the risks associated with the fine-mist inhaler are fully described, patients with COPD, patients with hypoxia, cardiac arrhythmias, or ischemic heart disease should use the dry powder form of tiotropium.[37]

Concomitant use of other drugs with anticholinergic properties may increase the risk of side effects with either ipratropium or tiotropium.

METHYLXANTHINES

Methylxanthines have been used to treat pulmonary disease for more than 100 years.[38] General use of methylxanthines became widespread in the 1930s; contemporary use is more limited due to the availability of more effective and safer medications.[39] Theophylline and aminophylline, the ethylenediamine salt of theophylline, are used to treat asthma and COPD. Theophylline may also have a role in therapy of obstructive sleep apnea, apnea of prematurity, and airway obstruction secondary to pulmonary edema.

Pharmacology

Potentially beneficial therapeutic effects of theophylline include bronchial smooth-muscle relaxation, enhanced mucociliary transport, inhibition of mediator release, suppression of permeability edema, decreased pulmonary hypertension, increased right ventricular ejection fraction, improved diaphragmatic contractility, and central stimulation of ventilation.

Methylxanthines have direct bronchodilator and immunomodulatory properties; however, despite having been marketed and studied for decades, the precise molecular mechanism of action is not known. Multiple molecular mechanisms have been proposed, including nonselective phosphodiesterase (PDE) inhibition, nonselective adenosine receptor antagonism (A_1, A_{2A}, $A_{2B,}$ and A_3 receptors), promotion of endogenous catecholamine release, agonist activity at ryanodine receptors, activation of histone deacetylase (HDAC), and induction of peroxisome proliferator-activated receptor gamma (PPAR gamma) expression.[39,40] Nonselective PDE inhibition and adenosine receptor antagonism are the most established of the proposed molecular mechanisms of action.[39]

PDEs hydrolyze cAMP and cyclic guanine monophosphate (cGMP) to inactive 5′ monophosphates; inhibition of PDE increases intracellular concentrations and, therefore, the activity of these secondary messengers, resulting in airway smooth-muscle relaxation and bronchodilation. However, methylxanthine PDE inhibition is concentration dependent, with minimum inhibition seen at clinically relevant serum concentrations.[41] Adenosine is a nucleoside signaling molecule. Adenosine receptor antagonism regulates airway smooth muscle, blocks adenosine-induced mast cell degranulation, and activates HDAC enzymatic activity, inhibiting transcription of proinflammatory cytokines. These anti-inflammatory and immunomodulatory effects are observed at clinically achievable serum drug concentrations.

The anti-inflammatory effect of methylxanthines appears to be qualitatively different than that of corticosteroids. Corticosteroids induce HDAC gene transcription; methylxanthines induce HDAC activity. The combination of corticosteroids and methylxanthines may be synergistic.

Structure–Activity Relationships

Theophylline and aminophylline are 1,3-dimethylxanthines. Other methylxanthines, including theobromine (3,7-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine), differ in the positions of the methyl substituents on the xanthine molecule. Dyphylline is 7-(2,3-dihydroxypropyl)-theophylline. N-1 substituents are important for adenosine antagonism, whereas N-3 substituents augment bronchodilator activity. Substituents at N-7 decrease bronchodilator potency; substituents at N-9 decrease the potency of the xanthine.

Drug Delivery

Three methylxanthines are available in the United States: theophylline, aminophylline, and dyphylline. Dosage forms for theophylline include extended-release tablets and capsules, oral solution, oral elixir, and intravenous solution. Aminophylline, the ethylenediamine salt of theophylline, is only available as an intravenous solution. Dyphylline is available as immediate-release tablets.

Clinical Use

Methylxanthines are FDA approved for the treatment of reversible airway obstruction associated with chronic asthma or other chronic lung disease. Concerns regarding the relative efficacy and safety of the methylxanthines in comparison to other bronchodilators and long-term control medications have relegated methylxanthines to alternative therapy status for both asthma and COPD.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend oral theophylline as an alternative maintenance treatment choice for all patients with COPD or as combination therapy with any first- or second-line treatment.[15] Intravenous theophylline or aminophylline are second-line choices for treatment of exacerbations of COPD.[15] The current Global Initiative for Asthma guidelines recommend theophylline as an add-on controller medication for patients inadequately controlled on inhaled glucocorticoids alone.[42] The current National Asthma Education and Prevention Program (NAEPP) guidelines recommend theophylline as an alternate medication for patients with mild persistent asthma, or as an alternate adjunctive therapy in combination with inhaled corticosteroids.[14] The NAEPP guidelines do not recommended theophylline for the treatment of acute asthma exacerbations.[14]

In summary, relatively noncontroversial indications for methylxanthines include severe bronchodilator-dependent COPD; severe, systemic, corticosteroid-dependent asthma; nocturnal asthma uncontrolled with adrenergic agonists; and acute, severe asthma progressing to respiratory failure.

The previously accepted therapeutic range for theophylline (10–20 mg/L) was based on early dose–bronchodilator response studies[43] and is no longer considered state of the art.[44] The current NAEPP asthma guidelines recommend a lower target therapeutic range for theophylline (5–15 mg/L).[14] The rationale for lowering the target serum theophylline range includes improved understanding of the dose–bronchodilator response and recognition of the greater risk of adverse drug reactions at serum theophylline concentrations greater than 15 mg/L.[45] The immunomodulatory effects of theophylline occur at lower serum concentrations (1–5 mg/L).[46,47]

Safety

Adverse effects of methylxanthines are generally attributed to PDE inhibition (nausea, vomiting, diarrhea, headache) and adenosine receptor antagonism (cardiac arrhythmias and seizures).[47] Other adverse effects include irritability and insomnia. The caffeine-like adverse effects (nausea, vomiting, diarrhea, nervousness, insomnia, headache) are generally associated with serum theophylline concentrations greater than 15 mg/L.[45] The more life-threatening adverse effects (ventricular arrhythmias and seizures) are generally associated with serum theophylline concentrations greater than 40 mg/L, although these adverse effects may occur at much lower serum concentrations.[45]

Theophylline is metabolized primarily by cytochrome P450 (CYP1A2) enzymes, making it susceptible to numerous drug–disease and drug–drug interactions. Medical conditions that directly impair hepatic function (e.g., cirrhosis, viral hepatitis), cause passive hepatic congestion (e.g., congestive heart failure, cor pulmonale), or induce interferon (e.g., acute viral illness or pneumonia) increase the serum theophylline concentrations.[45]

Hyperthyroidism and cystic fibrosis decrease serum theophylline concentrations by unknown mechanisms. Polycyclic aromatic hydrocarbons in tobacco smoke, and medications, such as rifampin, phenytoin, antivirals, and barbiturates, induce cytochrome P450 enzymes, reducing serum theophylline concentrations. Macrolide and quinolone antibacterials, fluvoxamine, fluconazole, ketoconazole, and cimetidine inhibit cytochrome P450 enzymes, increasing serum theophylline concentrations. Given the narrow therapeutic window, multitude of drug and disease interactions, and wide interpatient variability, it is important to routinely monitor serum theophylline concentrations. The mid-dosing interval serum concentration should be assessed 3 to 5 days after initiating theophylline or modifying the dose and any time theophylline toxicity is suspected.[14]

■ OTHER BRONCHODILATORS

Ancillary drugs sometimes used as bronchodilators include magnesium sulfate and inhaled diuretics.

Magnesium Sulfate

The bronchodilatory mechanism of action of magnesium has not been definitively identified. Several actions have been proposed, including decreasing smooth-muscle intracellular calcium, T-cell stabilization, inhibition of mast cell degranulation and Ach release, and stimulation of nitric oxide and prostacyclin synthesis.[48]

Several systematic reviews of trials of inhaled and intravenous magnesium sulfate in the management of adults and children presenting to emergency departments with severe acute exacerbations of asthma have been published.[48–50] In general, patients with severe exacerbations demonstrate small improvements in pulmonary function following administration of inhaled or intravenous magnesium sulfate. Potential adverse effects include hypotension with rapid infusion, muscle weakness, respiratory depression, and cardiac conduction abnormalities. Despite these limited clinical data, the Global Initiative for Asthma recommends consideration of intravenous magnesium sulfate therapy for acute severe asthma in selected patients (adults with an FEV_1 25%–30% of predicted at presentation, adults and children who do not respond to initial treatment, and children in whom the FEV_1 remains <60% of predicted after 1 hour of standard treatment).[42]

Inhaled Diuretics

Inhaled diuretics (e.g., furosemide) may act upon the airways through a variety of mechanisms to achieve bronchodilation, reduce mucosal inflammation, or interrupt sensory nerve reflex responses to irritants.[51] Data regarding the clinical efficacy of inhaled diuretics in the treatment of acute and chronic asthma are limited. Additional information from well-designed clinical trials is needed before use of inhaled diuretics can be recommended for the treatment of acute exacerbations or chronic management of asthma.

ANTI-INFLAMMATORY AGENTS

Corticosteroids are the mainstay of current anti-inflammatory regimens; other agents in clinical use include mast cell stabilizers, leukotriene receptor antagonists, and leukotriene formation inhibitors.

■ CORTICOSTEROIDS

Corticosteroids are cortisol-like drugs that influence metabolic pathways and have an anti-inflammatory effect. By reducing airway inflammation, corticosteroids have long been known to be useful in the management of asthma; their role in the management of COPD has been increasingly recognized.

Pharmacology

Cortisol is produced by the adrenal cortex and regulated via the hypothalamic–pituitary axis in response to physical and emotional

distress. Although the usual daily secretion of cortisol is approximately 10 mg/m^2/d,[52] up to 500 mg/d can be secreted during periods of severe stress.[53] Corticosteroids stimulate and inhibit DNA transcription in cells with glucocorticoid receptors, which are widespread throughout the body.

Glucocorticoids diffuse across cellular membranes to bind inactive glucocorticoid cytoplasmic receptors; these activated glucocorticoid-receptor complexes translocate to the nucleus and bind to specific glucocorticoid response elements of the gene, influencing gene transcription. Increased gene transcription increases expression of β_2-Adrenergic receptors, increases the production of anti-inflammatory mediators, and decreases the production of inflammatory mediators.[54] The clinical effects of glucocorticosteroids are delayed for several hours following administration, reflecting the time needed to influence gene transcription. In the airways, glucocorticosteroids increase the number and responsiveness of β_2-Adrenergic receptors, decrease mucus production, decrease bronchial hyperresponsiveness, decrease the number of mucosal mast cells, enhance eosinophil apoptosis, and decrease airway edema.[55] Glucocorticosteroids are inactivated by hepatic metabolism, with a clearance rate approximately the same as liver blood flow; beclomethasone dipropionate and ciclesonide and their metabolites are also inactivated by blood esterases.

The inhaled glucocorticoids (beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, mometasone furoate) have different physicochemical properties (potency, receptor-binding affinity, protein binding, lipophilicity, oral bioavailability, pulmonary bioavailability, systemic clearance, volume of distribution, and half-life).[56,57] Physicochemical properties that enhance inhaled glucocorticosteroid efficacy include high receptor-binding affinity, high pulmonary bioavailability, and long pulmonary retention time. Physicochemical properties that enhance safety include low oropharyngeal deposition, high protein binding, rapid systemic clearance, and conversion of inactive prodrug to active drug in the lungs. Since inhaled glucocorticosteroids are marketed and prescribed in relatively equipotent doses, potency is not an important differentiating characteristic as other physicochemical characteristics.

Data regarding the relative clinical benefits of inhaled corticosteroids with different physicochemical characteristics are limited. However, physicochemical characteristics may influence drug safety. For example, oropharyngeal side effects (dysphonia, oral candidiasis) may be minimized by using drug delivery systems that generate a greater proportion of small particles (<5 μm)[58] and with administration of prodrugs that are converted in the lungs to the active drug. DPI particle size depends on the specific device and the patient-generated inhalation flow rate; hydrofluoroalkane MDIs tend to generate a greater proportion of smaller particles. Beclomethasone 17,21-dipropionate is hydrolyzed in the lungs to the more active drug, beclomethasone 17-monopropionate. Ciclesonide is hydrolyzed in the lungs from the inactive parent drug to the active drug, desiosbutyryl-cilcesonide.

The risk of systemic adverse effects may be minimized by using inhaled corticosteroids with low systemic bioavailability, high protein binding, rapid systemic clearance, and increased pulmonary residence time. Ciclesonide, fluticasone, and mometasone undergo rapid first pass hepatic metabolism, resulting in very low (<1%) oral bioavailability. Ciclesonide and mometasone are highly protein bound (99%). Drugs with a higher lipophilicity and drugs that undergo lipid conjugation have a longer pulmonary residence time. Mometasone furoate and fluticasone propionate, with an esterified lipophilic group at the 17-α position, are the most lipophilic of the marketed inhaled corticosteroids; beclomethasone dipropionate, budesonide, triamcinolone acetonide, and flunisolide follow in descending order of lipophilicity.

Clinical Use

Corticosteroids are the cornerstone of therapy in the treatment of asthma. The role of glucocorticoid therapy in COPD is more limited.

Asthma The role of airway inflammation in asthma is well established, and high-dose systemic (parenteral or oral) corticosteroids are standard therapy for patients experiencing severe acute exacerbations of asthma.[14,42] Parenteral administration of corticosteroids is often used preferentially due to the inability of some patients to swallow medications while in respiratory distress or because of lack of oral access after intubation. The time to initial response, as evidenced by augmentation of FEV_1 with bronchodilator administration, begins as early as 1 hour after corticosteroid administration; maximal response is achieved in 8 to 12 hours. Parenteral methylprednisolone is the corticosteroid of choice, due to its lower mineralocorticoid and greater glucocorticoid effects than hydrocortisone.

The combination of an inhaled corticosteroid and a long-acting bronchodilator is better than either agent alone at improving lung function and preventing asthma exacerbations; in patients with moderate-to-severe asthma, such a combination of low-dose inhaled corticosteroid with a LABA appears equieffective as high-dose inhaled corticosteroid alone.[14] Given the concerns regarding the safety of LABAs (see above) as monotherapy in asthma,[20] the FDA recommends that an inhaled corticosteroid always accompany a LABA in asthma therapy.[22]

Beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, and fluticasone propionate are FDA approved for twice-daily administration; only mometasone furoate is FDA approved for once-daily administration. Poor adherence with inhaled corticosteroid regimens is an ongoing issue. Although data are limited, patients with stable, mild persistent asthma might benefit from once-daily inhaled corticosteroids.[14] Twice-daily dosage regimens are more effective for patients with moderate persistent or severe persistent asthma.[14]

Chronic Obstructive Pulmonary Disease The mechanism underlying the beneficial effects of corticosteroids in COPD is not fully known, but changes in inflammatory gene transcription and modulation of β_2-Adrenergic receptor function appear to play a role. For patients with COPD with an FEV_1 <60% (GOLD grades C and D), treatment with inhaled corticosteroids improves quality of life and lung function, decreases exacerbation frequency, but does not alter long-term FEV_1 decline or improve survival.[15] Short courses (5–15 days) of moderate doses (40 mg/d of prednisone) of systemic corticosteroids in combination with standard bronchodilator therapies are effective for treating acute exacerbations of COPD in outpatients, inpatients, and patients in the emergency room who have moderate or severe COPD.[59] However, the role of systemic corticosteroids in the treatment of patients with COPD who are receiving mechanical ventilation is unknown. Definitive data regarding the clinical usefulness of combining inhaled corticosteroids and long-acting bronchodilators are lacking.[15]

Safety

Short-term use (less than 14 days) of systemic corticosteroids is associated with mild glucose intolerance, fluid retention that may progress to edema and hypertension, proximal muscle weakness (especially with large parenteral doses), and mood alteration. Long-term systemic corticosteroids prolong the short-term effects; in addition, peptic ulcer disease, cataracts, increased risk of infection, and impaired wound healing occur. Truncal obesity, hirsutism, acne, moon-shaped facies, striae, and ecchymoses contribute to a cushingoid appearance. Disruption of bone metabolism predisposes patients to osteoporosis and resultant vertebral and long-bone fractures; inhibition of long-bone growth is the major complication

in children receiving systemic corticosteroids. Suppression of the hypothalamic–pituitary–adrenal axis diminishes body cortisol stores, reducing the response to stresses such as trauma, surgery, or infection.

Inhaled corticosteroids are less systemically bioavailable due to poor absorption from the tracheobronchial tree. The most common adverse effect is local irritation of the oropharynx, cough, and bronchospasm. Dysphonia may arise from vocal cord myopathy induced by the corticosteroid, and oral candidiasis (thrush) may occur secondary to suppression of normal oral flora. The risk of dysphonia and thrush are reduced by rinsing the mouth, gargling, and spitting out the rinse water after each use of a corticosteroid inhaler; using a spacer device to decrease deposition of drug particles in the mouth; and keeping the inhaler mouthpiece clean. Limited data suggest inhaled corticosteroids increase the risk of pneumonia in patients with COPD,[60] but not asthma.[61]

Depending on the bioavailability, dose, and duration of use, inhaled corticosteroids may be associated with the systemic adverse effects typically associated with oral corticosteroids, including adrenal suppression, particularly in children. Inhaled corticosteroids slow bone growth velocity in prepubertal children and reduce ultimate adult height[62]; they also increase the risk of bone fracture, with each 500 μg increase in beclomethasone equivalency yielding a 9% increase in fracture risk.[63]

Steroid Resistance

Patients with asthma unresponsive to usually sufficient doses of corticosteroids are described as *steroid resistant.* Varying definitions of steroid resistance exist, such as a <15% increase in FEV_1 after either oral prednisolone administered for 7 days at a dose of 20 mg daily, or 14 days at a dose of 15 mg daily; or a 2-week trial of 40 mg/d prednisone in bronchodilator-responsive asthmatics.[64,65] Steroid resistance must be distinguished from steroid dependency, which is usually defined as the need for systemic corticosteroids to maintain control of asthma.

Steroid resistance may involve reduced metabolism of oral corticosteroids to the active compound or accelerated drug clearance. An impaired cellular response to corticosteroids has been observed in steroid-resistant asthmatics, and altered receptor binding or the presence of anti-lipocortin antibodies may contribute to the phenomenon.

■ CORTICOSTEROID-SPARING AGENTS

Chronic systemic corticosteroid therapy required for the treatment of severe airflow obstruction often results in numerous side effects. Therefore, many anti-inflammatory agents have been evaluated in an effort to identify alternatives to systemic corticosteroid therapy.[66,67] However, wide variability exists between studies in their assurances of proper inhaler technique, dose and frequency of baseline inhaler regimens, and minimization of exposure to known antigens. In addition, most studies did not systematically evaluate and exclude (or otherwise control for) the concomitant presence of disorders known to mimic or exacerbate asthma, including vocal cord dysfunction, gastroesophageal reflux, and rhinosinusitis. These methodological considerations further restrict the limited conclusions to be drawn from these studies.

Methotrexate

From initial observations in patients with rheumatoid arthritis and coexistent asthma, methotrexate therapy appeared to ameliorate both asthmatic and arthritic symptoms. A small number of older studies offer no clear documentation of the clinical efficacy of methotrexate administration in severe, steroid-dependent asthma. Several more recent meta-analyses suggest a small benefit may exist, but use is associated with a significant risk of toxicity. Due to significant side effects, potentially fatal complications, and long-term toxicity concerns, prudency argues for limiting methotrexate administration in severe, steroid-dependent asthmatics to empiric trials in individual patients or investigations in large-scale, controlled clinical trials.

Cyclosporine

Used widely in organ transplantation, cyclosporine inhibits lymphokine synthesis, thereby blocking the activation of T cells. The absence of significant drug interactions with β-Adrenergic agonists, corticosteroids, or theophylline makes cyclosporine particularly attractive as an anti-inflammatory agent for use in asthma. However, only one of the three small, double-blind, placebo-controlled studies suggested that cyclosporine increased peak expiratory flow and FEV_1, reduced exacerbations of airway obstruction, or reduced oral prednisolone dosage by over 60%. Hypertrichosis, hypertension, reversible nephrotoxicity, and a large number of nonspecific side effects limit widespread use of cyclosporine in the management of asthma.

Other Agents

The search continues for anti-inflammatory agents with potential efficacy in asthma. Historically, a broad spectrum of agents have been touted, including gold salts, pooled immunoglobulins, azathioprine, colchicine, dapsone, hydroxychloroquine, ketotifen, nonsteroidal anti-inflammatory agents, inhaled heparin, and anti-tumor necrosis factor agents (both etanercept and infliximab). The original studies purporting the efficacy of these various agents comprise mainly anecdotal reports, small case series, or early phase studies demonstrating little clinical efficacy. Use of these drugs in obstructive airway disease should be restricted to well-designed, controlled clinical trials.

Antibiotic Macrolides

Recently, the role of macrolide antibiotics as anti-inflammatory agents has been recognized and their potential utility in management of a number of pulmonary disorders examined.

Pharmacology

Erythromycin comprises a 14-membered lactone ring, with two attached sugars (cladinose and desosamine). As the first macrolide antibiotic discovered, erythromycin has served as the base compound for this class of drugs.[68,69] Azithromycin (9-deoxo-9 a-aza-9 a-methyl-9 a-homoerythromycin) is formed by substituting a methyl-substituted nitrogen for the position 9a carbonyl group of the aglycone ring, producing an azalide. Substituting a methoxy group for the C-6 hydroxyl group of erythromycin creates clarithromycin (6-O-methylerythromycin). Compared with erythromycin, both of these macrolide derivatives have superior pharmacokinetic and pharmacodynamic properties, including a longer serum half-life, increased tissue penetration and persistence, oral bioavailability, and greater gram-negative antibacterial activity. Tissue concentrations of clarithromycin and azithromycin can exceed serum concentrations by 100-fold.

In the liver, cytochrome P450 3A4 (CYP3A4) metabolizes clarithromycin to an active 14-hydroxy form and six additional products. Clarithromycin and its metabolites are mostly excreted in the bile. However, since about one-third is excreted in the urine, doses should be reduced in patients with creatinine clearances <30 mL/min. In contrast, with hepatic impairment and normal renal function, the consequent reduced metabolism of clarithromycin to the active 14-hydroxy form allows for increased renal excretion of native clarithromycin and obviates dosing modifications. Since azithromycin elimination occurs primarily in the feces as the unchanged drug, with minimal urinary excretion, dosing modifications are unnecessary in renal or hepatic dysfunction.

Traditionally, antibiotic macrolides are prescribed for infections from a variety of gram-positive bacteria (β-hemolytic streptococci, pneumococci, staphylococci, enterococci), *Haemophilus influenzae*, *Legionella pneumophila*, mycoplasma, mycobacteria, chlamydia and some rickettsias. Macrolides rarely cause allergic reactions, and, therefore, are a common alternative for penicillin-allergic patients.

Macrolides reversibly bind to ribosomes, where they inhibit protein synthesis in several ways.[68,69] They block peptidyl transferase from adding the peptidyl attached to transfer-RNA to the next amino acid, analogous to the activity of chloramphenicol. Macrolides accelerate dissociation of peptidyl-transfer-RNA from ribosomes and also inhibit ribosomal translocation. Since macrolides accumulate within cells, in addition to their antibacterial actions, they can exert numerous anti-inflammatory effects within the respiratory tract, including increasing mucus clearance, inhibiting neutrophil recruitment and activation, promoting neutrophil apoptosis, and decreasing the production of reactive oxygen species and elaboration of cytokines, including interleukins (IL-4, IL-5, IL-8, IL-13) and chemokines (C-X-C motif ligand 2 [CXCL2], and ligand 2 [CCL2], 3 [CCL3] and 4 [CCL4]). These anti-inflammatory actions are believed to mediate the efficacy of macrolides in controlling exacerbations of underlying respiratory diseases.

Clinical Use

Since the first clinical use of erythromycin as an anti-infective agent in the 1950s, over the past decade a new role has emerged for macrolide antibiotics as anti-inflammatory agents, mainly in treatment of chronic suppurative respiratory disorders. In randomized, double-blind, placebo-controlled trials in adults with either noncystic fibrosis bronchiectasis or COPD, azithromycin (250 mg daily) or erythromycin (400 mg twice daily in bronchiectasis, 250 mg twice daily in COPD) reduced clinical exacerbations and yielded modest improvements in FEV_1 and quality of life.[70–72]

Retrospective analysis of the Acute Respiratory Distress Syndrome Network dataset revealed increased survival and decreased time to successful discontinuation of mechanical ventilation associated with use of a macrolide early in the clinical course of respiratory failure.[73] However, no randomized trials have expressly tested the efficacy of macrolides in acute lung injury. Azithromycin effectively reduces exacerbations and improves FEV_1 in children with cystic fibrosis,[74] although this effect is attributed to anti-pseudomonal, rather than anti-inflammatory, effects.[75] Macrolides have not been proved effective in infants with viral bronchiolitis.[76,77]

Safety

Since larger macrolide doses produce higher serum concentrations, the incidence of adverse effects increases with increasing doses. Most common are gastrointestinal side effects, specifically abdominal pain and diarrhea, which are usually tolerable. These side effects appear to represent luminal phenomena, while auditory side effects have been attributed to tissue accumulation. Nonetheless, drug-induced, bilateral, sensorineural hearing loss accentuated at the lower frequencies is usually transient and reverses with discontinuation of the macrolide.

Most clinical trials of chronic macrolide therapy that address resistance demonstrate emergence of macrolide-resistant flora. Hepatotoxicity may occur, as manifested by an increase in liver enzymes or cholestasis—findings that should prompt immediate discontinuation of chronic macrolide therapy.

All macrolides may prolong the QT interval, primarily by blocking the outward delayed rectifier potassium channel encoded by the HERG gene. Indirectly, macrolides may also prolong the QT interval by inhibiting the metabolism of other arrhythmogenic drugs metabolized by CYP3A4. The increase in sudden cardiac death associated with erythromycin administration has led to a marked reduction in use of this drug, particularly in the elderly and patients with heart failure. Electrocardiograms to monitor QT prolongation should be considered during chronic macrolide administration.

Clarithromycin, when oxidized by CYP3A4, forms an inactive metabolite/enzyme complex. Clarithromycin is less potent than erythromycin at inhibiting CYP3A4, and azithromycin minimally inhibits CYP3A4. Therefore, dose reductions, clinical assessments, and therapeutic drug level monitoring (when practicable) are necessary with simultaneous administration of drugs metabolized by the CYP3A4, particularly with clarithromycin or erythromycin therapy. The concurrent use of cisapride, pimozide, terfenadine, and astemizole with clarithromycin or erythromycin is contraindicated because of QT prolongation and reported cases of torsades de pointes. Simultaneous therapy with clarithromycin and ergot compounds risks acute ergot toxicity. Numerous other medications metabolized by CYP3A4 (e.g., benzodiazepines, statins, class 1A antiarrhythmic agents, theophylline, carbamazepine, warfarin, sildenafil, colchicine, and cyclosporine) should be used cautiously when given with clarithromycin. Furthermore, although these drug–drug interactions are less likely to occur with azithromycin because of less efficacious inhibition of CYP3A4, high doses may, nonetheless, produce clinically significant side effects. Similarly, respiratory patients with hepatic dysfunction, concurrent congestive heart failure, or cor pulmonale may require dose adjustments. Finally, combination of macrolides with statins has been linked to rhabdomyolysis.[69]

Troleandomycin

Since the 1960s, anecdotal clinical observations suggested that the macrolide antibiotic, troleandomycin, might reduce corticosteroid requirements in patients with severe asthma by decreasing steroid metabolism. However, results from double-blind, randomized trials were mixed, and the weight of evidence suggests that troleandomycin has no clinical effect at relieving airway obstruction or inflammation independent of its effects on corticosteroid metabolism. Troleandomycin has no role in the current therapy of severe, steroid-dependent asthma.

MAST CELL STABILIZERS

Cromolyn sodium and nedocromil exert anti-inflammatory actions by stabilizing mast cells. This blockade of mast cell degranulation prevents inflammatory mediator release, which is partially responsible for the bronchoconstriction and epithelial injury that are characteristic of asthma. However, these agents remain inferior to inhaled steroids for controlling asthma.[78] In addition, limited commercial availability of these agents hampers current usage, largely supplanted by the oral leukotriene formation inhibitors and receptor antagonists.

Cromolyn Sodium

Cromolyn sodium was the first mast cell stabilizer to be approved for clinical use in asthma and remains in use as a nebulized agent in pediatric asthmatics. MDI formulations are no longer available in the United States and Canada.

Pharmacology Cromolyn sodium potently inhibits inflammatory responses. Cromolyn sodium diminishes early phase reactions in asthma by blocking the release of intracellular calcium and inhibiting enzymes responsible for mast cell degranulation; cromolyn reduces late phase reactions in asthma by inhibiting production of the enzymes necessary for superoxide generation. Cromolyn sodium may also exhibit tachykinin antagonism, accounting for some of its anti-inflammatory properties. In vitro, cromolyn sodium potentially inhibits the activation of inflammatory cells, antibody-induced granulocyte cytotoxicity, IgE production by atopic cells, and monocyte IgG production.

Clinical Use Nebulized cromolyn sodium (20-mg dose) is a second-line agent for the management of asthma in children aged 2 to 5 years of age.[14] Cromolyn sodium, alone, or in combination with β_2-Adrenergic agonists, reportedly improved exercise tolerance, enhanced sleep quality, and reduced asthma exacerbations. Cromolyn sodium prophylaxes against exercise-induced asthma in children, although less efficaciously than β_2-agonists alone.

Safety Cromolyn sodium causes few adverse effects, even after long-term use. Although the efficacy of cromolyn sodium in preventing childhood asthma symptoms remains unclear,[78] its safety record leads to continued use as a second-line agent, in conjunction with β_2-Adrenergic agonists, in management of asthma in children.

Nedocromil

Nedocromil also stabilizes mast cells in the bronchial mucosa, but with a broader anti-inflammatory spectrum than cromolyn sodium. Although useful as prophylaxis against asthma exacerbations, nedocromil is not therapeutically efficacious for acute bronchospasm and is currently available only as a DPI in a small number of countries.

■ ANTILEUKOTRIENE AGENTS

Leukotrienes are synthesized from arachidonic acid, a fatty acid stored in phospholipids of cell walls. Numerous stimuli, including IgE receptor activation, antigen–antibody interactions, and activation of phospholipase A_2 induce release of arachidonic acid from phospholipids. Arachidonic acid is converted to a variety of products via several unrelated pathways; the 5-lipoxygenase (5-LO) pathway is the pathway of importance in asthma. Leukotriene A_4 (LTA_4) is metabolized by two different pathways to either the nonpeptide LTB_4 or the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). LTB_4 recruits and activates inflammatory cells but has no effect on bronchial tone or reactivity. The cysteinyl leukotrienes stimulate smooth-muscle contraction, increase vascular permeability, and enhance bronchial hyperresponsiveness; thus, they have a role in the pathogenesis of asthma.

Leukotriene action may be inhibited by either selective receptor blockade or interference with synthesis. Most clinical experience has been with the LTD_4 receptor antagonists, since LTC_4, LTD_4, and LTE_4 interact with a common LTD_4 receptor. Inhibition of 5-LO reduces the generation of all leukotrienes.

Clinical Use

Two LTD4 receptor antagonists (montelukast and zafirlukast) and one 5-LO inhibitor (zileuton) are FDA approved and marketed in the United States. The receptor antagonist pranlukast is available only in Japan; zafirlukast is unavailable in Europe. The antileukotriene agents are alternate anti-inflammatory medications for long-term use in children and adults with mild or moderate asthma, including aspirin- or exercise-induced asthma and asthma associated with concomitant allergic rhinitis.[14] Montelukast is FDA approved for children beginning at age 2 years; zafirlukast for children beginning at age 6 years; and zileuton for teenagers beginning at age 12 years and adults. Although less effective than inhaled steroids or LABAs at improving asthma control, antileukotriene agents have fewer side effects and can provide incremental clinical benefit through bronchodilation and symptom reduction.[79,80] Acute administration of antileukotriene agents has no role in the management of acute asthma exacerbations.[81] Antileukotriene agents have modest salutary effects on airway obstruction, symptoms, and quality of life in patients with COPD,[82] but administration of zileuton does not reduce length of stay in acute exacerbations of COPD.[83]

Safety

Montelukast and zafirlukast are well tolerated. Montelukast chewable tablets contain phenylalanine and, therefore, are contraindicated in patients with phenylketonuria. The leukotriene receptor antagonists have numerous drug interactions.

Hepatotoxicity has been reported with zileuton, which is contraindicated in patients with active liver disease and in patients with serum transaminase levels exceeding three times the upper limit of normal. Baseline liver function tests should be obtained prior to initiating therapy with zileuton, and patients should be monitored closely for the duration of therapy. Zileuton must be discontinued if serum transaminase levels exceed five times the upper limit of normal.

■ IMMUNOGLOBULIN E ANTIBODY

Administration of antibodies directed against immunoglobulin E (IgE) has a role in management of pulmonary disorders with an allergic basis.

Pharmacology

Omalizumab is a recombinant humanized antibody developed for therapy of allergic diseases that has significant efficacy in severe atopic asthmatics.[84] By specifically binding with high affinity to free IgE, but not to other immunoglobulins, omalizumab does not activate mast cells or basophils. Clinical efficacy depends upon near total elimination of circulating IgE; therefore, the role of omalizumab is limited to those asthmatics with elevated serum IgE levels. Subcutaneous administration of omalizumab produces rapid binding of circulating IgE, with serum levels slowly rebounding over the subsequent 4 to 6 weeks.

Randomized, double-blind, placebo-controlled studies of omalizumab have been completed in patients more than 12 years of age who have moderate or severe atopic asthma refractory to high-dose inhaled corticosteroids alone. Studies have also been conducted in patients with severe asthma ages 6 to 12 years and >12 years who were also receiving inhaled, long-acting β-agonists and oral leukotriene antagonists. Use of omalizumab reproducibly decreased the frequency of asthmatic flares, reduced inhaled and oral steroid dosage, and improved quality of life scores.

Clinical Use

Omalizumab therapy is indicated for moderate or severe asthmatics who have serum IgE levels exceeding 30 IU/mL (75 ng/mL) and an allergic basis for their asthma, as demonstrated by positive skin testing or radioallergosorbent tests (RAST) to common antigens.[84] Although several early trials demonstrated efficacy of omalizumab when added to monotherapy with inhaled corticosteroids alone, current guidelines recommend addition of omalizumab to combined therapy using both inhaled corticosteroids and inhaled, long-acting β-agonists.[14] As a chronic therapy, omalizumab treatment should not be initiated in the setting of an acute asthma flare. Subcutaneous administration of omalizumab every 2 to 4 weeks is required to maintain reductions in circulating IgE, with the required dose and frequency dependent upon body weight and initial serum IgE level. Up to three separate subcutaneous injections, each not exceeding 150 mg at a single site, may be required at each administration. When pretreatment serum IgE levels exceed 300 IU/mL, omalizumab should not be administered to patients whose body weight exceeds 90 kg; with high pretreatment serum IgE levels, for example, levels approaching 700 IU/mL, omalizumab should not be administered, even to individuals of normal weight. Subsequent serum IgE measurements are unnecessary, as levels plummet to negligible levels and slowly rebound after each administration of the drug.

The total duration of necessary therapy is unclear, although a review every 6 to 12 months is commonly employed to assess whether improved asthma control has been achieved (as indicated by reduced inhaled and oral steroid usage, fewer emergency medical

encounters and hospitalizations, and decreased overall medical costs).[85] Because of high acquisition costs, the cost effectiveness of omalizumab remains controversial.[86,87]

Safety

Minor local skin reactions at the injection sites occur in almost one-half of patients. A diffuse urticarial rash has been reported, but it is extremely uncommon. Severe hypersensitivity reactions, including anaphylaxis, are rarely observed (rate of 1–2 per 1000 patients receiving omalizumab). Therefore, close observation, including frequent assessment of vital signs, is recommended for at least 2 hours following initial drug administration; similar monitoring is warranted for at least 1 hour following each subsequent administration.[88] Omalizumab should not be self-administered.

NOVEL ANTI-INTERLEUKIN AGENTS

Recognition of the role of interleukins in mediating inflammation has led to development of a variety of anti-interleukin agents, discussed subsequently.

■ MEPOLIZUMAB

Mepolizumab is a humanized, mouse monoclonal antibody directed against human IL-5. Intermittent intravenous of the agent reduces peripheral blood and sputum eosinophil counts.

Pharmacology

Eosinophils play a role in the development of diverse inflammatory responses and have long been thought to play a pathogenetic role in the inflammation of asthma. Eosinophils migrate from the bloodstream to sites of inflammation, including the tracheobronchial epithelium, where they participate in antigen presentation and release of other inflammatory cytokines, as well as disgorge their own cytotoxic granules. Although IL-3 and GM-CSF have important stimulatory effects upon eosinophils, IL-5 is the most specific stimulant of eosinophil growth and activity, mediated through the IL-5 receptor complex expressed on the surface of eosinophils.

Clinical Use

Monoclonal antibodies directed against IL-5 failed to demonstrate efficacy in three clinical trials performed in patients with asthma, in contrast to their clear effectiveness in patients with hypereosinophilic syndromes.[89] However, in a small, double-blind, placebo-controlled trial in asthmatics with persistent sputum eosinophilia despite oral prednisone therapy, patients receiving monthly infusions of mepolizumab (750 mg) achieved significant reductions in their prednisone dose.[90] In contrast, patients receiving placebo experienced a significant number of asthma exacerbations following prednisone tapering. Accompanying significant reductions in sputum and blood eosinophil counts, as well as maintenance of both asthma control and FEV_1, persisted for 8 weeks following the last infusion of mepolizumab.[90]

Subsequently, in a large, international, multicenter, double-blind, placebo-controlled trial, patients with eosinophilic asthma were randomized to receive monthly intravenous mepolizumab (75 mg, 250 mg, or 750 mg) infusions or placebo for 1 year.[91] In a dose-dependent manner, mepolizumab reduced clinically significant asthma exacerbations, along with both blood and sputum eosinophil counts. The efficacious effects of mepolizumab seem to be limited to patients with severe, eosinophilic asthma that remains refractory to high doses of inhaled corticosteroids and, often, requirements for concurrent oral corticosteroids. This limitation may hinder further development of anti–IL-5 therapies for asthma.

Safety

Mepolizumab appears to be well tolerated, with relatively few significant adverse reactions equally reported in both treatment and placebo groups. The most frequently reported adverse events are headache and nasopharyngitis; no serious life-threatening or anaphylactic reactions have been reported.[89–91]

■ DUPILUMAB

IL-4 and IL-13 have been implicated in the pathogenesis of asthma and atopic diseases, with inflammatory activity from these cytokines present in almost half of the patients with asthma. IL-4 and IL-13 signal inflammatory cells through two distinct receptors, although both receptors contain an α subunit of the IL-4 receptor. Dupilumab, a human monoclonal antibody to the IL-4 receptor α subunit, inhibits both IL-4 and IL-13 signaling.

A recent, double-blind, placebo-controlled trial assessed the efficacy and safety of dupilumab in adults with persistent, moderate-to-severe asthma and elevated blood or sputum eosinophil levels,[92] despite appropriate use of LABAs and inhaled corticosteroids. After initiating administration of dupilumab or placebo subcutaneously once weekly, both LABAs and inhaled corticosteroids were withdrawn. Significant improvements were observed in spirometric values and asthma control, and withdrawal of LABAs and inhaled corticosteroids precipitated fewer asthma exacerbations in patients receiving dupilumab. However, only a minority of asthmatics have blood or sputum eosinophilia, and whether dupilumab will add incremental value to standard therapy with LABAs and inhaled corticosteroids remains to be seen.

■ DACLIZUMAB

Airway inflammation in asthma includes activation of T cells and, consequently, increased levels of IL-2 and soluble IL-2 receptor (IL2R), all of which contribute to airway inflammation. Daclizumab is a humanized, monoclonal murine antibody that specifically binds to the α subunit of the high-affinity IL2R, thereby inhibiting IL-2 binding and subsequent activity.[93] Initially, the agent received FDA approval for induction immunosuppression and rejection prophylaxis of patients receiving renal transplantation. Daclizumab has limited availability due to market competition from basiliximab, used for immunosuppression in the setting of renal transplantation.

In a double-blinded, placebo-controlled study, 116 patients with moderate or severe persistent asthma on stable doses of inhaled triamcinolone were randomized to receive intravenous infusions of daclizumab or placebo every 2 weeks for 5 months. Daclizumab improved FEV_1, reduced asthma symptoms, and delayed exacerbations.[93]

In a study of asthmatic patients,[94] an excess number of serious adverse events occurred in those treated with daclizumab, including an episode of severe anaphylaxis. In contrast, prior to withdrawal from the marketplace, daclizumab appeared to be generally well tolerated, in both renal transplant patients and those with inflammatory diseases receiving the drug off-label.

PHOSPHODIESTERASE 4 INHIBITORS

A new area of interest has evolved in the development of phosphodiesterase 4 (PDE4) inhibitors in the management of airways diseases.

■ PHARMACOLOGY

Roflumilast is the first in-class isozyme-selective PDE4 inhibitor to be marketed in the United States. Although nonselective PDE inhibitors (i.e., theophylline, aminophylline) have been used for decades to treat obstructive lung diseases, roflumilast represents a markedly different type of medication.

PDEs hydrolyze cAMP and cGMP to inactive 5' monophosphates; inhibition of PDE increases intracellular concentrations and, therefore, the activity of these secondary messengers.[94] Intracellular cAMP regulates cytokine and chemokine release from inflammatory cells and cell trafficking.

There are 11 known isoenzymes in the PDE superfamily (PDE 1–11).[95] The PDE 4 isoenzyme is expressed in lung inflammatory (neutrophils, monocytes, macrophages, CD4+ and CD8+ T-lymphocytes) and structural (sensory nerves, smooth muscle cells, fibroblasts, endothelial cells, epithelial cells) cells; PDE 4 inhibition reduces lung inflammation and remodeling.[94,95]

Roflumilast is well absorbed following oral administration and has an absolute bioavailability of about 80%.[96] The drug is rapidly metabolized by cytochrome P450 (CYP450) isoenzymes to roflumilast N-oxide, the major active metabolite that accounts for approximately 90% of the PDE 4 inhibitory activity. Roflumilast N-oxide is metabolized by CYP450 isoenzymes to inactive metabolites. Both roflumilast and its metabolites are excreted in the urine. The long plasma half-lives of roflumilast (approximately 20 hours) and roflumilast N-oxide (30 hours) allow the medication to be administered once daily.

■ DRUG DELIVERY

Roflumilast is marketed as a 500 μg tablet. Food does not affect absorption; patients may take it with or without food, although given the pharmacokinetic and pharmacodynamics profile, patients should take the dose at the same time every day.

Clinical Use

Roflumilast is FDA approved for the treatment of patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The current GOLD guidelines recommend roflumilast as a second choice agent in combination with an inhaled corticosteroid and LABA for patients with Group D COPD, and as an alternative choice in patients with Group C COPD.[15] In preapproval, randomized, controlled clinical trials in patients with moderate-to-severe COPD, roflumilast modestly, though significantly, improved prebronchodilator FEV_1 and reduced exacerbation rates.[97] A recent meta-analysis of 26 clinical trials confirmed that roflumilast reduced exacerbation rates in patients with moderate–to-severe COPD.[98] Very limited data from randomized controlled trials of roflumilast in combination with long-acting bronchodilators indicate that roflumilast modestly improves pre-and postbronchodilator FEV_1 and reduces exacerbations.[99,100]

Safety

Concerns regarding the relative risks and small benefits of roflumilast resulted in the FDA's Pulmonary-Allergy Drugs Advisor Committee's vote against (10 to 5) approval of the drug.[101] Although generally well tolerated, roflumilast has PDE 4 inhibitor class-specific gastrointestinal (diarrhea, nausea, decreased appetite) and neuropsychiatric (insomnia, anxiety, depression, mood changes, suicidality) adverse effects.[52] Unexplained weight loss, typically <3% of baseline body weight, has been reported with roflumilast. Patients should be advised of the possibility of these adverse effects and monitored closely during treatment with roflumilast. Roflumilast is contraindicated in Child–Pugh B or C liver impairment.

Many drugs interact with roflumilast.[102] Strong inducers of CYP450 (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) reduce the effect of roflumilast and should be avoided. CYP3A4 or dual CYP3A4/CYP1A2 inhibitors (e.g., cimetidine, enoxacin, erythromycin, fluvoxamine, ketoconazole) increase the effect of roflumilast and also should be avoided.

Clinical experience with roflumilast in patients with immunological disorders and serious infections is limited. Until more data are available, roflumilast should not be used in patients with severe immunological disorders, severe acute infections, or latent infections (e.g., tuberculosis, herpes viral infections, viral hepatitis).[102] Concurrent use of roflumilast with immunosuppressants, including long-term systemic corticosteroids, is not recommended.[102]

MUCOACTIVE AGENTS

Chronic sputum production or inspissated airway secretions trouble most patients with obstructive lung disease. Mucus, which consists of a tangled network of mucin glycoproteins, oligosaccharide side chains, water, and electrolytes is produced by goblet cells and submucosal glands and is cleared by ciliary action; sputum (expectorated mucus) is cleared by cough. Inflammatory-derived substances (neutrophil-derived DNA, filamentous actin, cells and cellular debris, and bacteria) alter the physical characteristics of mucus.

Mucoactive drugs (expectorants, mucolytics, mucoregulators, mucokinetics) modify mucus viscoelastic properties and enhance mucus clearance.[103] Mucoregulator drugs, such as the anticholinergics and glucocorticoids, decrease mucus secretion and improve mucociliary clearance, respectively. Mucokinetic drugs (e.g., β_2-Adrenergic agonists) enhance ciliary activity.

■ EXPECTORANTS

Expectorants increase mucus secretion or increase airway water to facilitate mucus expulsion from the airways. The mechanism of action of guaifenesin (glyceryl guaiacolate) is thought to be mediated through an increase sputum volume and decrease sputum viscosity. A recent in vitro study demonstrated that guaifenesin decreased mucin release, decreased mucus viscoelasticity, and increased mucociliary transport.[104] Guaifenesin, an FDA-approved expectorant, is not recommended in the current evidence-based guidelines for cough or allergic rhinitis.[105,106] Despite a lack of proven efficacy, guaifenesin, with few adverse effects or drug interactions, is a common component in numerous nonprescription cough medications.

Aerosolized hypertonic saline is used to induce sputum for diagnostic and research purposes. Long-term airway surface hydration with aerosolized hypertonic saline may improve mucus clearance; anti-inflammatory and rheological effects have been proposed.[107] In teens and adults with cystic fibrosis, aerosolized hypertonic saline (7% sodium chloride) enhanced mucus clearance and improved lung function[108,109]; no effect was found in children 4 to 60 months of age.[110]

Potassium iodide is an FDA-approved expectorant. The mechanism of action is not known. Efficacy data are limited; potassium iodide is not recommended in the current American College of Chest Physicians (ACCP) cough guidelines.[105] Potassium iodide may cause significant adverse effects (hypersensitivity, dermatitis, hypothyroidism, chronic iodide poisoning) and must be used with caution in patients with Addison's disease, cardiac disease, and renal impairment. Potassium iodide is contraindicated during pregnancy.

■ MUCOLYTICS

Drugs that directly reduce mucus viscosity are classified as classic (e.g., N-acetylcysteine; NAC) or peptide (e.g., dornase alfa) mucolytics. When administered as an aerosol, the free thiol sulfhydryl group hydrolyzes the disulfide bonds that link mucin strands, resulting in less viscid mucus. Aerosolized NAC is acidic (pH 2.2); pretreatment with inhaled bronchodilators is necessary to reduce NAC-associated cough and bronchospasm. Evidence for the efficacy of aerosolized NAC in cystic fibrosis is limited.[111] High-dose oral NAC is under investigation as an oral antioxidant (mucoregulator) in the treatment of cystic fibrosis,[111] idiopathic pulmonary fibrosis,[112] and COPD.[113]

Dornase alfa, purified recombinant human deoxyribonuclease, depolymerizes DNA and F-actin polymers, reducing sputum

adhesiveness. FDA approved for the management of cystic fibrosis, dornase alfa improves lung function and slows the annual rate of decline in FEV_1.[114] Dornase alfa is administered by nebulizer once daily; some patients benefit from twice-daily administration.[115]

ANTITUSSIVES

Antitussives (cough suppressants) are used for the symptomatic treatment of cough associated with a variety of acute and chronic medical conditions. The number of FDA-approved antitussives is limited; no new antitussives have been approved for decades. Data regarding efficacy and comparative efficacy in specific medical conditions are limited.

PHARMACOLOGY

Cough is a complex coordinated neuromuscular response to mechanical and sensory stimuli in the larynx, trachea, and bronchi.[116] The medullary brainstem cough center controls involuntary cough in response to mechanical and chemical stimulation and is interconnected with suprapontine voluntary control of cough.[117]

Antitussives are classified as centrally acting or peripherally acting, depending on the site of action. Centrally acting opioid (codeine, hydrocodone, and morphine) and nonopioid (dextromethorphan, diphenhydramine, and chlophedianol) antitussives suppress cough by acting on the medullary cough center. Benzonatate, a procaine derivative, inhibits peripheral pulmonary stretch receptors. Levodropropizine and moguisteine (neither available in the United States) may modulate peripheral sensory neuropeptide levels throughout the respiratory tract.[118] Guaifenesin may have antitussive effects in acute viral cough, though the evidence is limited and contradictory.[119]

Drug Delivery

Antitussive medications are available in a variety of product-specific formulations, including solutions (liquids, extended-release liquids, syrups, elixirs, and gels) and solid dosage forms (lozenges, capsules, tablets, chewable tablets, and oral disintegrating strips). Alcohol-, sugar-, dye-, and gluten-free and single-ingredient antitussive products are available, although most products contain multiple additional active ingredients (e.g., expectorants, decongestants, analgesics, antihistamines). The majority of states allow codeine-containing antitussives to be sold as nonprescription medications if the products contain one or more noncodeine active ingredients and a maximum of 200 mg of codeine per 100 mL.[120]

Clinical Use

The 2006 ACCP Evidence-Based Clinical Practice Guidelines recommend codeine or dextromethorphan for short-term symptomatic relief of cough associated with acute and chronic bronchitis and postinfectious cough, and centrally acting antitussives, such as dihydrocodone and hydrocodone, for chronic cough associated with lung tumors. Antitussives are not recommended for any other medical condition, including cough due to viral upper respiratory tract infections.[105,121–123]

Safety

Cough and cold medications have not been shown to be safe or effective in children under 2 years of age.[124] Manufacturers have voluntarily restricted labeling to state, "do not use" in children under 4 years of age.[125]

Common side effects associated with opioid antitussives include sedation, constipation, nausea, and vomiting. At antitussive dosages, dextromethorphan has a wide margin of safety; side effects similar to codeine occur infrequently. Side effects of chlophedianol include excitation, hyperirritability, and hallucinations. Benzonatate may cause drowsiness or dizziness; capsules should be swallowed whole to avoid the local anesthetic effect of the liquid capsule contents.

Codeine and dextromethorphan are abused for the CNS effects associated with high doses. Robotripping, that is, abuse of dextromethorphan-containing cough medications for the dissociative hallucinogenic effects, is well known, especially among adolescents.[126] In 2010, an FDA advisory panel considered, but voted against, recommending that dextromethorphan be scheduled in the Controlled Substance Act.[127]

PHYSIOLOGICAL REPLACEMENTS

Replacement therapy comprises a novel class of agents to replace deficient, or augment existing, endogenous substances. To date, replacement therapy has been employed only in adults with α_1-antitrypsin deficiency or neonates with respiratory distress syndrome. However, clinical studies of replacement therapy are ongoing in patients with a wide spectrum of obstructive and other lung diseases.

α_1-ANTITRYPSIN

α_1-Antitrypsin is a glycoprotein synthesized and secreted largely by hepatocytes. A protease inhibitor, α_1-antitrypsin blocks the actions of neutrophil-derived elastase in the lung. Inherited deficiency of α_1-antitrypsin promotes development of emphysema in adulthood; tobacco smoking rapidly accelerates the clinical presentation and severity of the emphysema. Since 1987, α_1-antitrypsin replacement therapy has been available for intravenous administration as a purified product derived from pooled human plasma.

Clinical Use

Weekly or monthly intravenous infusion of α_1-antitrypsin to deficient patients increases α_1-antitrypsin levels in serum and bronchoalveolar lavage specimens and restores antielastase activity in serum and alveolar lining fluid. Numerous case reports and small series dispute whether α_1-antitrypsin replacement reduces the accelerated rate of decline in pulmonary function, CT-measured lung density, or mortality associated with α_1-antitrypsin deficiency.[128–131] The absence of clear efficacy data and high cost have prevented governmental approval for administration of replacement therapy in many countries. Currently, weekly α_1-antitrypsin replacement infusions of 60 mg/kg are recommended for patients with α_1-antitrypsin deficiency who are older than 18 years of age, maintain complete tobacco abstinence, and have both abnormal pulmonary function tests and a serum α_1-antitrypsin level less than 11 mM.[132] Replacement therapy for α_1-antitrypsin deficient patients is not recommended following lung transplantation.

Side Effects

α_1-Antitrypsin replacement therapy is remarkably nontoxic, and current preparations have few side effects, other than mild fever, headache, dyspnea, or dizziness. Repeated administration of α_1-antitrypsin does not shorten the serum half-life, suggesting that α_1-antitrypsin antibodies do not develop, even in patients with complete deficiency.

PULMONARY SURFACTANT

The administration of pulmonary surfactant to premature infants with, or at risk for, respiratory distress syndrome remains standard of care.[133,134] Surfactant administration decreases mortality from respiratory distress syndrome by 30% to 40% and reduces morbidity due to pneumothoraces, interstitial emphysema, bronchopulmonary dysplasia, and intraventricular hemorrhage. Recent studies suggest administration of nasal CPAP may comprise an equally effective alternative, with no difference in long-term neurodevelopmental outcomes.[135] In addition, surfactant administration has an evolving role in neonates with meconium aspiration syndrome and respiratory failure, reducing the need for extracorporeal membrane oxygenation, but not mortality.[136]

Endogenous pulmonary surfactant is an emulsion of phospholipids, cholesterol, and apoproteins that reduces surface tension within alveoli.[137] Natural surfactant is commercially available and is prepared from lung tissue or lavages from a variety of species. Synthetic surfactant is also available from a number of commercial sources, although the optimal composition of the material remains to be determined.

Pulmonary surfactants reduce oxygen toxicity by scavenging free radicals, and the surfactants may be cytoprotective for alveolar cell surfaces. Pulmonary surfactants suppress mediator release by inflammatory cells and may deactivate inflammatory mediators upon release. In vitro studies indicate that surfactant suppresses lymphocyte mitogenic responses, leading to a decrease in inflammatory cell influx. Pulmonary surfactant has both antibacterial and antiviral properties that are mediated by an increase in alveolar macrophage phagocytosis. Surfactant may promote airway clearance by changing the physical properties of mucus, as well as by increasing ciliary beat frequency. Finally, pulmonary surfactant may directly relax airway smooth muscle. This spectrum of putative biologic activities may directly interrupt the pathogenesis of airway inflammation, chronic infection, and bronchoconstriction seen in most obstructive lung diseases.

In adults with respiratory failure, anecdotal case reports and small patient series suggested that surfactant administration produced occasional increases in Pa_{O_2}, although usually no change in radiographic, physiological, or respiratory findings were reported. However, three large, double-blind, randomized, placebo-controlled trials demonstrated administration of synthetic surfactant yielded no demonstrable physiological benefit and no significant decrease in mortality rate.[137,138]

RESPIRATORY STIMULANTS

Respiratory stimulants are a group of pharmacologically unrelated agents used to treat diverse pathophysiological conditions, including COPD, postanesthesia respiratory depression, apnea of prematurity, acute mountain sickness, and obstructive or central sleep apnea.

■ ACETAZOLAMIDE

Acetazolamide is a noncompetitive inhibitor of carbonic anhydrase that induces a weak diuresis and mild metabolic acidosis. FDA-approved indications include acute mountain sickness (prophylaxis and adjunctive treatment), edema, epilepsy, and glaucoma. Unlabeled uses include chronic hypercapnic COPD[139] and weaning from mechanical ventilation. In one small clinical trial, the combination of acetazolamide and auto-continuous positive airway pressure improved nocturnal oxygen saturation and reduced the apnea/hypopnea index in patients with obstructive sleep apnea at altitude.[140]

Acetazolamide may have both indirect and direct respiratory stimulant properties.[141] The increased hydrogen concentration indirectly stimulates respiration via peripheral and medullary chemoreceptor stimulation. Acetazolamide may also directly stimulate respiration by increasing cerebral blood flow through mechanisms unrelated to the metabolic acidosis.[142] Side effects include drowsiness, numbness or tingling of the face and extremities, tinnitus, hypokalemia, and gastrointestinal upset. Long-term safety and efficacy data for use as a respiratory stimulant are unavailable.

■ ALMITRINE

Almitritine bismesyslate increases alveolar ventilation and improves ventilation–perfusion mismatching by stimulating peripheral aortic and carotid chemoreceptors and enhancing hypoxic pulmonary vasoconstriction.[143,144] Small clinical trials of sequential treatment in patients with moderate or severe COPD and hypoxemia demonstrate a small, dose-dependent improvement in oxygenation.[145,146] Investigational in the United States, but approved as a respiratory stimulant in Europe, side effects, including peripheral neuropathy[147] and weight loss, limit the clinical usefulness of the drug.

■ DOXAPRAM

Doxapram is a short-acting, parenterally administered respiratory stimulant. FDA-approved indications include respiratory depression following anesthesia, acute hypercapnia secondary to COPD, and drug-induced respiratory depression; off-label uses include treatment for apnea in premature infants, weaning from mechanical ventilation, and obstructive sleep apnea.[148,149] Doxapram exhibits dose-dependent peripheral chemoreceptor agonist and central respiratory stimulant properties.[148] Limited case reports and small studies describe use of doxapram as a respiratory stimulant in COPD complicated by acute respiratory failure.[150] Benzyl alcohol-containing solutions may cause significant adverse effects in infants, including metabolic acidosis, hypotension, and the "gasping syndrome."[148] Doxapram-associated side effects include flushing, sweating, elevated blood pressure, and muscle spasticity.

■ MEDROXYPROGESTERONE

Medroxyprogesterone acetate is a synthetic progesterone hormone with central and peripheral respiratory stimulant properties.[151,152] Although the mechanism of action is unclear, medroxyprogesterone increases minute ventilation and produces hypocapnia in normal subjects. However, it does not improve breathing disturbances during sleep in patients with obstructive sleep apnea.[153] Limited data show that medroxyprogesterone improves oxygenation and hypercapnia in patients with hypercapnic obstructive lung disease.[140,155] Medroxyprogesterone side effects include thromboembolic disorders, elevated liver function tests, visual disturbances, breast tenderness, reduced bone mineral density, edema, and gastrointestinal upset.

■ METHYLXANTHINES

Caffeine, theophylline, and aminophylline are structurally related methylxanthines with bronchodilatory and respiratory stimulatory properties. Caffeine is FDA approved for the treatment of apnea of prematurity and respiratory depression in adults. The mechanism of respiratory stimulation is not known, but it may include enhanced medullary respiratory center chemoreceptor responsiveness to carbon dioxide, improved diaphragmatic contractility, and competitive adenosine inhibition.[149,155] Caffeine is the most effective methylxanthine for the treatment of apnea of prematurity, with better long-term outcomes and lower toxicity than theophylline.[149,156] Common side effects include tachycardia, jitteriness, and increased gastric aspiration.[157] Caffeine inhibits adenosine receptors, creating a theoretical risk of cerebral damage and impaired neuronal development.[157] No neurodevelopmental disability was reported 18 to 21 months posttreatment in very low–birth-weight infants.[158]

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CHAPTER 146

Intubation and Upper Airway Management

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The first known use of positive-pressure ventilation (PPV) as a medical intervention dates back to the 16th century, as described in Vesalius' *de Humani Corporis Fabrica*:

> "But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air. Indeed with the slight breath in the case of the living animal, the lung will swell to the full extent of the thoracic cavity, and the heart become strong. . . . for when the lung, long flaccid, has collapsed, the beat of the heart and arteries appears wavy, creepy, twisting; but when the lung is inflated at intervals, the motion of the heart and arteries does not stop."[1]

Vesalius apparently resuscitated a Spanish nobleman by inflating his lungs through the trachea, resulting in resumption of cardiac activity and nearly in Vesalius' death at the hands of the inquisitors. Vesalius, an excellent anatomist who disproved many of the cherished teachings of Galen that had been accepted as absolute truth for 13 centuries, was viewed as a heretic by his peers. In fact, one described him as "an impious madman who is poisoning all of Europe with his vaporings."

Because of the lack of enthusiasm in response to Vesalius' findings and writings, a 100-year hiatus attended the next attempt at endotracheal ventilation. In 1667, Robert Hooke, a prominent mathematician, geologist, and paleontologist kept a dog alive by intermittently insufflating air into its trachea using a set of bellows. One century later, in 1744, John Fothergill, one of the founders of the British Humane Society, described successful mouth-to-mouth resuscitation.

Because of concerns over development of emphysema and tension pneumothorax as complications of PPV (which was recognized as early as 1827), research on artificial ventilation in the nineteenth and early twentieth centuries focused primarily on negative-pressure ventilation (NPV). Iron lungs, tank ventilators, cuirass ventilators, and a variety of strange and remarkable differential pressure chambers and boxes were developed in the United States and Europe. The devices were powered by hand, water, steam, or electricity, and, in some cases, by the patient himself. However, PPV became incorporated into the resuscitation strategy of the Dutch Humane Society, which advocated mouth-to-mouth ventilation in conjunction with external thoracic and abdominal compression. In 1776, John Hunter described an apparatus that blew fresh air into the lungs with one set of bellows and sucked "bad" air out with a second set.

By the end of the nineteenth century, a surge in the evolution of thoracic surgery led to the use of tracheal intubation and PPV through cuffed tubes as acceptable components of medical care. An American surgeon, Joseph O'Dwyer, designed a series of metal tubes that were inserted between the vocal cords of children afflicted with diphtheria. Rudolph Matas referred to O'Dwyer's devices in describing "intralaryngeal intubation" and "insufflation" and noted that, "the procedure that promises the most benefit in preventing pulmonary collapse in operations is . . . the rhythmic maintenance of artificial respiration by a tube in the glottis." In the early part of the twentieth century, Franz Kuhn, a German surgeon, described techniques for oral and nasal intubation using flexible

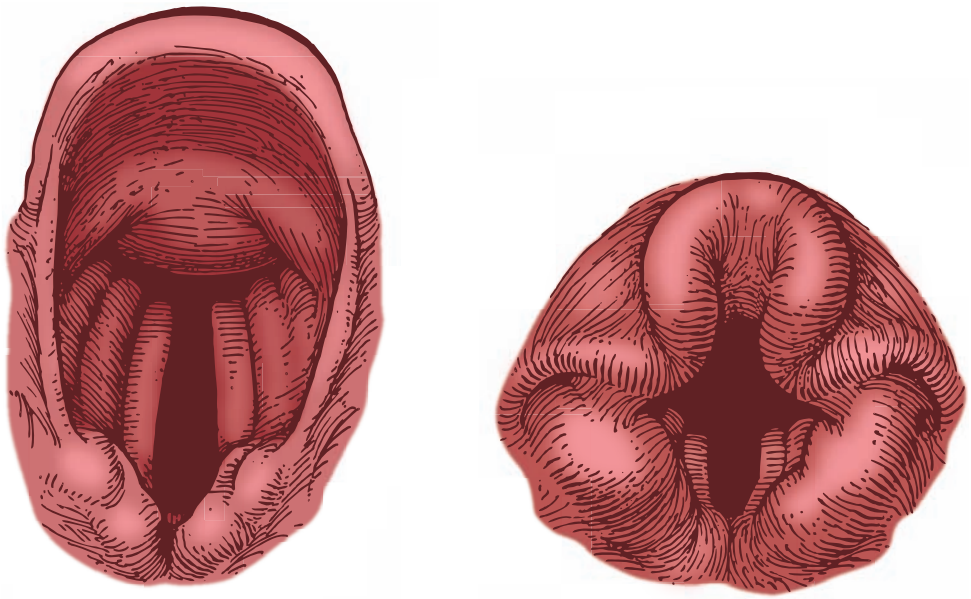

Figure 146-1 Comparative anatomy of adult and infant airways. *(Reproduced with permission from Barash P, et al, eds. Clinical Anesthesia. Philadelphia, PA: Lippincott; 1989:544, D. Factor, illustrator.)*

metal tubes introduced into the trachea with the assistance of the operator's index finger; the procedure was preceded by application of topical anesthesia using cocaine. The airway was then sealed with a supralaryngeal flange and gauze packing.

Among the further advances that followed was the first laryngoscope created by Alfred Kirstein in Berlin. However, his model was never widely accepted. Chevalier Jackson developed a U-shaped laryngoscope that otorhinolaryngologists still use for endoscopy but was never adopted by anesthesiologists. In 1913, Janeway described an endotracheal tube with a removable cuff, an anesthesia ventilator, and a battery-powered laryngoscope. From 1900 to 1920, Dorrance, Elsberg, Löwen, and Sievers published methods for tracheal intubation and PPV.

The most influential figure in the history of endotracheal intubation is Sir Ivan Magill. Along with Stanley Rowbotham, he used anesthetics on Royal Army casualties during World War I (in particular, on patients with disfiguring facial injuries). Their patients were often intubated nasally to allow freer access to the face by the surgeon. Magill's inventions include the Magill forceps, which is still used to facilitate nasal intubation, semirigid endotracheal tubes fashioned from mineralized rubber, and the Magill circuit, an L-shaped laryngoscope. He is also credited with describing the "sniffing position."

Arthur Guedel, an American contemporary of Magill, refined the cuffed endotracheal tube and, by extensive experimentation on animal tracheas, determined that the best position for the cuff was just below the vocal cords. He popularized use of the cuffed endotracheal tube by publicly anesthetizing his pet dog, "Airway," and immersing the animal in a tank of water. Upon awakening, the dog shook itself off and departed the arena.[2]

In current practice, access to the trachea through the nasopharynx or oropharynx takes advantage of laryngoscope blades invented in the 1940s by Robert Miller, a Texas clinician, and Robert Macintosh, an Oxford professor. The Miller blade was an advance over similar straight blades; it was designed to pick up the epiglottis and expose the vocal cords. The curved Macintosh blade differed from previous models and was designed for insertion between the epiglottis and tongue. Although many variants of the two blades are available today, including those with different angulations, prisms, and fiberoptic bundles, the Miller and the Macintosh blades remain the mainstays of the anesthesiologist's armamentarium.

The first departments of anesthesiology were founded in the early 1940s. Thereafter, the skills required for management of the upper airway and endotracheal intubation became widely disseminated in the United States and the United Kingdom.

UPPER AIRWAY ANATOMY AND CLINICAL RELEVANCE

The two functional conduits between the trachea and atmosphere—the oropharynx and the nasopharynx (Fig. 146-1)—join at the level of the base of the skull to form the hypopharynx. The oropharynx includes the base of the tongue, uvula, and tonsils. The nasopharynx is separated from the oropharynx by the mobile soft palate. The hypopharynx includes the vallecula, which is the space posterior to the tongue and anterior to the cervical esophageal inlet. Typically, the adult epiglottis is crescentic, moderately stiff, and thin. Because of its ligamentous attachments, the adult epiglottis can be lifted indirectly using a curved laryngoscope blade applied to the base of the tongue. The U-shaped infant epiglottis is longer and floppier than the epiglottis of the adult. Therefore, a straight blade is typically required to lift the infant epiglottis directly during endotracheal intubation.

The adult and infant airways differ in several other respects. The narrowest portion of the adult airway is the rima glottidis, the area between the vocal cords; in contradistinction, the cricoid is the narrowest portion of the infant's airway. The infant larynx is also situated relatively more cephalad than the larynx of the adult; in addition, the vocal cords of the infant are angled, whereas the vocal cords of the adult are perpendicular to the airway.

In an awake patient, with the head in the neutral position (i.e., neither flexed nor extended), air moves freely through both the oropharynx and nasopharynx. In most normal subjects, the same is true during sleep. Abnormalities of any of the component parts of the upper airway can impede airflow during respiration while awake; alternatively, impeded airflow may only become evident during sleep (e.g., as snoring or obstructive apnea). Consequently, a directed history and physical examination should be performed prior to any procedure on the airway.

A history of nasal polyps or nasal septal deviation mandates caution prior to nasotracheal intubation, transnasal passage of a fiberoptic scope, or insertion of a nasal airway. The patient's sleeping partner is often the best source of information about snoring and apnea, manifestations that may result from a variety of upper airway abnormalities, including soft-tissue redundancy, masses, polyps, stenosis, or lymphoid hypertrophy from the nose to the hypopharynx and larynx. Vocal changes or

abnormalities may suggest abnormalities of the vocal cords and warrant preintubation evaluation.

The physical examination of the airway is preceded by a conversation with the patient. Hoarseness, stridor, tachypnea, and coughing suggest potential upper airway problems. The examination then can be pursued systematically beginning with the nasopharynx. The patient's ability to breathe through a single nostril (when the mouth is closed and the other nostril occluded) indicates that the passage is relatively patent. Asymmetry often exists between the two sides and, whenever possible, instrumentation should be performed on the more patent side.

The ability to open the mouth is limited in patients with temporomandibular joint disease. The temporalis muscle may be scarred or fibrotic (e.g., secondary to prior radiation) resulting in restricted mandibular mobility. Fractures to the mandible produce limited ability to open the mouth that, when the limitation is caused by muscle spasm, disappears with anesthesia. Some fractures functionally affect the mobility of the jaw, irrespective of anesthetic state. Inability to open the mouth more than 40 mm is considered to be clinically significant.

The patient's dentition should also be assessed prior to elective management of the airway. Protruding maxillary incisors ("buck teeth") interfere with direct laryngoscopy by restricting the extent to which the laryngoscope blade can be aligned with the trachea. Dental caps and other prostheses are fragile and easily damaged during laryngoscopy. The laryngoscope may become lodged in gaps between the maxillary teeth during instrumentation and interfere with intubation. Severe dental caries or periodontal diseases make it easier to dislodge teeth during airway instrumentation. The edentulous patient often has an atrophic mandible and large tongue and may be difficult to ventilate by mask because of poor fit of the mask. Intubation of the trachea in such a patient becomes difficult because the tongue, no longer constrained by the teeth, interferes with visualization of the larynx.

Abnormalities of the tongue, hard palate, tonsillar pillars, and hypopharyngeal structures can impede or prevent intubation. Normally the tongue is small and sufficiently flexible to be displaced by a laryngoscope blade during visualization of the vocal cords. However, the tongue is enlarged in obese patients, those with angioedema or impaired lymphatic drainage (e.g., after cervical surgical procedures or trauma), or in the setting of certain neoplasms. Burns, scars, or radiation of the submandibular soft tissue prevent lateral displacement of the tongue into the oropharynx during laryngoscopy. Similarly, in patients with small jaws ("receding chins"), displacement or flattening of the tongue during laryngoscopy is difficult, making intubation a challenge. A hyomental distance (the distance from the hyoid bone to tip of the mandible) of less than 6 cm should raise awareness of potential difficulty with intubation.

A cleft or high, arched palate is seen in a variety of congenital abnormalities of the facial bones, including the Treacher Collins, Pierre Robin, Klippel–Feil, Goldenhar, Beckwith–Wiedemann, and Crouzon syndromes, as well as the mucopolysaccharidosis. Affected patients are difficult or impossible to intubate using standard approaches.[3]

Intraoral, oropharyngeal, hypopharyngeal, and laryngeal lesions, as well as tonsillar hypertrophy, can interfere with both laryngoscopy and ventilation by mask. The epiglottis can be infiltrated, inflamed, floppy, or enlarged by fat. The retropharyngeal and lateral pharyngeal spaces are continuous and therefore subject to expansion by processes that involve the mediastinum (e.g., the presence of edema, blood, pus, or soft-tissue emphysema). Patients with epiglottitis and parapharyngeal swelling often exhibit a characteristic posture, sitting upright in the sniffing position and drooling.

The preferred position for visualization of the vocal cords is the sniffing position (Fig. 146-2). However, this position may be unsuitable in some patients or impossible to achieve in others.

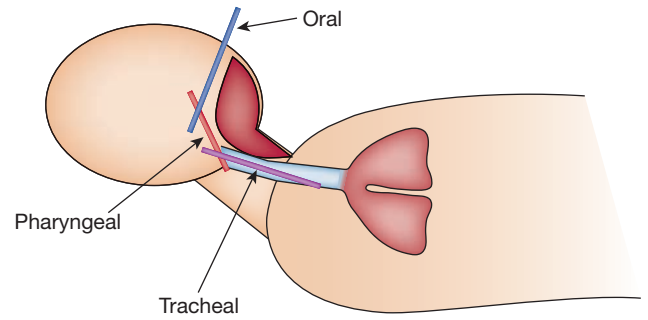

Figure 146-2 The sniffing position with the oral, pharyngeal, and tracheal axes.

The normal range for flexion and extension of the neck ranges from 90 to 165 degrees. A variety of disorders limit this range. Patients with cervical osteophytes or ankylosing spondylitis, who are often fixed in an anteroflexed head position, may be difficult to intubate. Halo fixation imposes similar constraints. Rheumatoid arthritis, which may affect the cervical spine even in asymptomatic patients, may be problematic. By the age of 75 years, the normal aging process results in as much as a 20% reduction in cervical spine mobility. Injury to the cervical spine or the presence of a cervical collar also impairs the ability of the laryngoscopist to position the head. Finally, patients with short, muscular necks have limited neck mobility and redundant soft tissue in the mouth and submandibular space, making airway visualization a challenge.

A variety of other anatomic features, including large breasts or a barrel chest, can complicate airway management by interfering with the excursion of the butt of the laryngoscope blade. During pregnancy, the oral and pharyngeal mucosae are swollen and bleed easily. When associated with a diminished functional residual capacity and increased volume of acidic gastric contents, intubation becomes quite hazardous.

The epidemic of obesity in Western societies has created a new population of patients with airway "abnormalities." Patients with a body mass index greater than 30 may be at increased risk for obstructive sleep apnea and gastroesophageal reflux. On physical examination, these patients often have some combination of macroglossia, a narrower, bulkier oropharynx, decreased neck mobility—all of which can complicate airway management. Some patients have a cervical fat pad, which may prevent optimal head positioning during intubation.[4]

Based upon anatomical considerations, clinicians commonly employ the Mallampati scale (Table 146-1)[5] to evaluate objectively the airway's suitability for placement of the endotracheal tube. The ability to visualize the soft palate, fauces, tonsillar pillars, and uvula is used to predict the degree of difficulty in exposing the larynx. A careful examination of the airway, coupled with attention to difficulties during prior procedures and the physical features described above, permit adequate preparation for instrumentation of the difficult airway.

TABLE 146-1 Mallampati Scale for Characterizing the Airway

Class I
Soft palate, fauces, uvula, and tonsillar pillars visible
Class II
Soft palate, fauces, and uvula visible
Class III
Soft palate and base of uvula visible
Class IV
Soft palate only visible

UPPER AIRWAY MANAGEMENT

Airway management is well suited to the use of algorithms. The American Society of Anesthesiologists has published a "difficult airway" algorithm for use in the operating room.[6] In addition, algorithms for the critical care unit[7] and trauma setting[8] have also been developed. In using an algorithm-based approach, the first decision branch point typically addresses the need for endotracheal intubation, since short-term respiratory insufficiency often can be managed noninvasively.

Factors that must be considered in the care of patients with respiratory compromise include the level of consciousness, clinical context (e.g., the perioperative setting, emergency circumstances, etc.), anticipated duration of respiratory problem, risk of gastric aspiration, airway patency, concurrent medical problems, and anticipated relative ease of noninvasive (i.e., spontaneous or mask ventilation) versus invasive (i.e., endotracheal intubation) management of the airway.

In the patient with neurological depression due to injury of the central nervous system, noninvasive management is usually inappropriate due to the potential for developing hypercarbia or hypoxia and exacerbation of the primary injury. Conversely, in the patient sedated or obtunded by drugs or seizures, the clinical state is often brief in duration, so temporizing measures may be appropriate.

Several factors differentiate elective perioperative airway management from emergency care. During surgery, an anesthesiologist or anesthetist is constantly present; the patient is properly prepared (i.e., the stomach is empty and a drying agent has been administered) and the environment is designed to facilitate airway management (i.e., there is ready access to suction, a ventilator, etc.). Under these circumstances, caregivers may choose to sedate the patient to the point of semi-obtundation. Conversely, in an emergency, the setting is usually less than optimal. Airway management is usually only one component of the care rendered during cardiac or trauma resuscitation, and definitive airway intervention is essential in order to allow care providers to concentrate on other problems.

Potentially quickly reversible processes (e.g., some attacks of asthma or episodes of pulmonary edema) may be appropriately managed without intubation. In other instances (e.g., blunt chest injury), the initial problem can be expected to worsen, and early intubation is warranted.

The volume and acidity of the patient's gastric contents must be factored into any decision about management of the airway. Aspiration of solid food can be catastrophic, as can large volumes of acidic, enzymatically active gastric fluid. Most studies have indicated that aspirated stomach contents with a pH lower than 2.5 or volume greater than 0.5 to 1.0 cc/kg are likely to cause lung damage. The lung damage is manifested by loss of ciliated and nonciliated epithelial cells in the trachea, destruction of type I and II pneumocytes, depletion of surfactant, and increased vascular permeability (see Chapter 141). Pain and narcotics may alter gastric emptying or change gastric pH, as can a number of disease states, such as intestinal obstruction, diabetic gastroparesis, and obesity. Unless the patient has fasted for more than 8 hours and is not subject to the confounding factors noted above, a full stomach should be presumed, and airway management handled accordingly.

The patient's coexisting medical problems and expected course must also be considered in management of the airway. For example, endotracheal intubation can be a dangerous stress to a patient with coronary artery disease and can be performed more safely after suitable preparation than under emergency circumstances. As another example, a patient with Fournier gangrene and normal lungs is appropriately managed by maintaining intubation and sedation between trips to the operating room for debridement, rather than by performing multiple extubations and reintubations. Similarly, elective intubation and mechanical ventilation can prevent aspiration or atelectasis in a patient with hepatic encephalopathy who is awaiting liver transplantation, thereby improving the likelihood of a successful outcome.

TABLE 146-2 Indications for Intubation of the Trachea

Ventilatory failure
Cardiac arrest, primary lung disease, neuromuscular disease or weakness
Airway obstruction
Primary airway process, neurogenic obstruction
Airway protection
Upper airway bleeding or injury (burn), central nervous system depression
Pulmonary toilet
Inability to manage secretions

Some degree of airway obstruction can be managed without intubation by proper positioning of the head, use of an oral or nasal airway, or application of positive airway pressure (PAP) by mask. A rolled towel or small pillow placed behind the neck or occiput reproduces the sniffing position. Oral and nasal airways can alleviate airway obstruction due to redundant airway soft-tissue or muscle relaxation. The application of positive pressure to the mouth and nose (mask continuous positive airway pressure or mask CPAP) distends the soft tissue of the airway. For this reason, nasal mask CPAP is frequently used in the management of obstructive sleep apnea (see Chapter 99). These measures can be used as short-term, temporizing alternatives to intubation in the patient who is ventilating spontaneously in the intensive care unit or operative setting.

Although a growing literature exists on the use of noninvasive ventilation[9–13] in a variety of settings that previously would have mandated endotracheal intubation, anesthesia is frequently administered in the operating room by mask using positive pressure. True mask ventilation is readily accomplished in the anatomically normal patient. However, some anatomic features, such as a beard, flat or sharp nose, or sunken cheeks (in the edentulous patient) can make mask-assisted ventilation difficult or impossible.

Indications for tracheal intubation (Table 146-2) fall broadly under several categories: respiratory failure, airway protection, hemodynamic instability, and perioperative management. If intubation is indicated, the clinician must decide upon the route and technique.

TECHNIQUES AND EQUIPMENT

Although expertise is a function of experience, several principles are generally applicable in any approach to airway management. The first applies to correct head positioning, which facilitates mask management, oral or nasotracheal intubation, and fiberoptic examination of the airway. Incorrect positioning impedes each procedure.

The previously noted sniffing position refers to extension of the head on the neck while the neck is flexed on the thorax (Fig. 146-3). The hypopharynx is at its maximal circumference in this position, and the tongue is farthest from the posterior pharyngeal wall. Anterior displacement of the jaw can be accomplished by pulling it forward or applying pressure on the angle of the mandible (the "jaw thrust" maneuver).

This serves to open further the retrolingual space. Pulling the tongue forward while grasping it with gauze or an instrument accomplishes the same goal. The position is appropriate for spontaneous respiration because it limits soft-tissue obstruction to airflow.

Nasotracheal intubation is easiest in the sniffing position, because the tip of the endotracheal tube is best aligned with the larynx and least likely to be deflected by the walls of the pharynx. Nasal and oral fiberoptic procedures are also easier in this position in which the oral, pharyngeal, and tracheal axes are well aligned. The sniffing

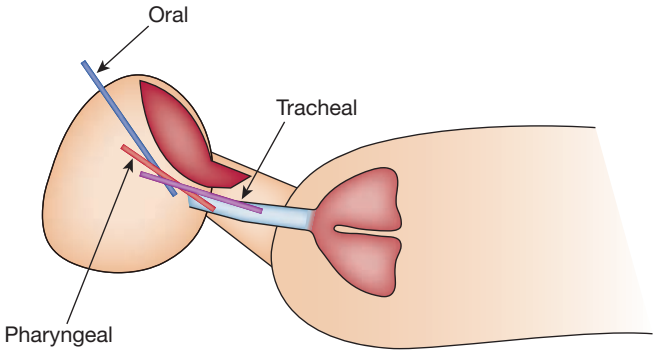

Figure 146-3 The sniffing position modified by additional head extension for oral intubation, with alignment of the oral, pharyngeal, and tracheal axes.

position may be modified by further head extension and flattening of the back of the tongue by the laryngoscope blade during oral intubation (Fig. 146-3).

A second general principle underlining airway management is that saliva and blood interfere with mask ventilation, direct visualization of the airway, and fiberoptic procedures. When circumstances permit, pretreatment with an antisialagogue, such as atropine, glycopyrrolate, or scopolamine, significantly diminishes saliva production. Suction must be available prior to initiation of any elective procedure (as well as on the emergency cart) to clear secretions or deal with regurgitation of gastric contents. A suction tip with a large bore, such as the Yankauer tonsil suction tip, is commonly used; suction should be maximized in order to clear thick, viscous, oral secretions.

A third general principle of airway management refers to preparation of the patient and airway. Small, titrated doses of sedatives, topical anesthesia, and vasoconstrictor agents markedly enhance the ease with which procedures, such as fiberoptic, nasotracheal, or oral intubation, are performed while the patient is awake. Narcotics are more likely to suppress the cough reflex than other agents. Topical cocaine has anesthetic and vasoconstrictor properties, but because of its classification as a controlled agent, the combination of lidocaine and phenylephrine is often used as an alternative. The light source of a laryngoscope or fiberoptic scope should be checked prior to instrumentation, and, with the latter, the focus adjusted. Finally, a backup plan for airway management is essential in case the primary plan should go awry. The American Society of Anesthesiology has published an algorithm, as noted above, with recommended approaches when (1) a difficult airway is identified prior to induction of anesthesia, (2) airway difficulties are encountered after the patient is unconscious, and/or (3) the patient cannot be ventilated nor intubated.[6]

Finally, perhaps the most important principle of airway management is that a source of oxygen and means of ventilation should be available. This implies that the pressure in nearby oxygen tanks should be checked, as should the proximity of a source of wall oxygen. In the absence of an oxygen source, a self-inflating resuscitation bag can provide a method for ventilation, obviously using only room air (see below). Bags used for most anesthesia circuits require a gas source for inflation.

AIRWAYS

A large variety of nasal and oral airways, designed for children and adults of different sizes (Fig. 146-4) are available. Nasal airways are generally made of flexible rubber and have a beveled tip, permitting insertion through narrow nasal passages. Oral airways are curved, designed to lie over and behind the tongue. Some are fashioned with slots for ready passage of a suction catheter, whereas others have a central channel designed to accommodate a fiberoptic scope. Binasal airways are designed to be fitted to a ventilation circuit, permitting ventilation in anesthetized patients without endotracheal intubation.

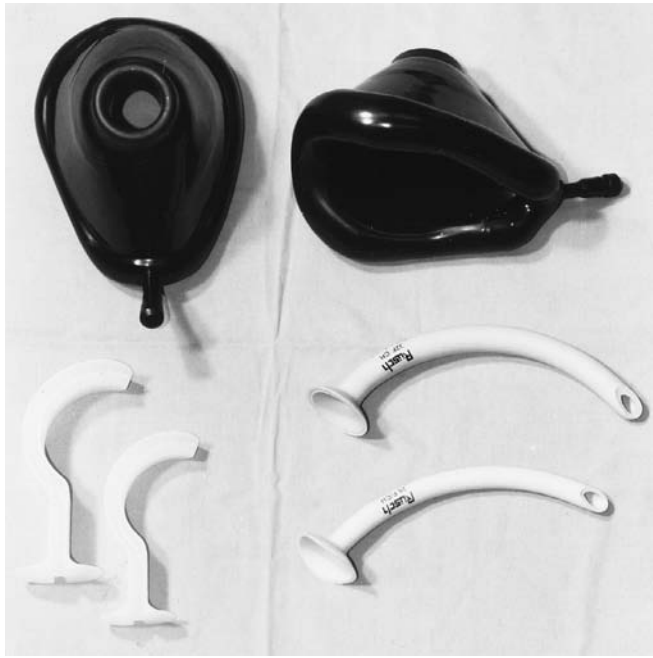

Figure 146-4 Oral and nasal airways and face masks.

RESUSCITATION BAGS

Resuscitation bags are available in many styles (Fig. 146-5) and are designed with several common features. They are self-inflating, and can, therefore, be used in the absence of a gas source. An internal flap valve system directs inflowing gas to the patient or reservoir, permitting application of positive pressure by mask or endotracheal tube

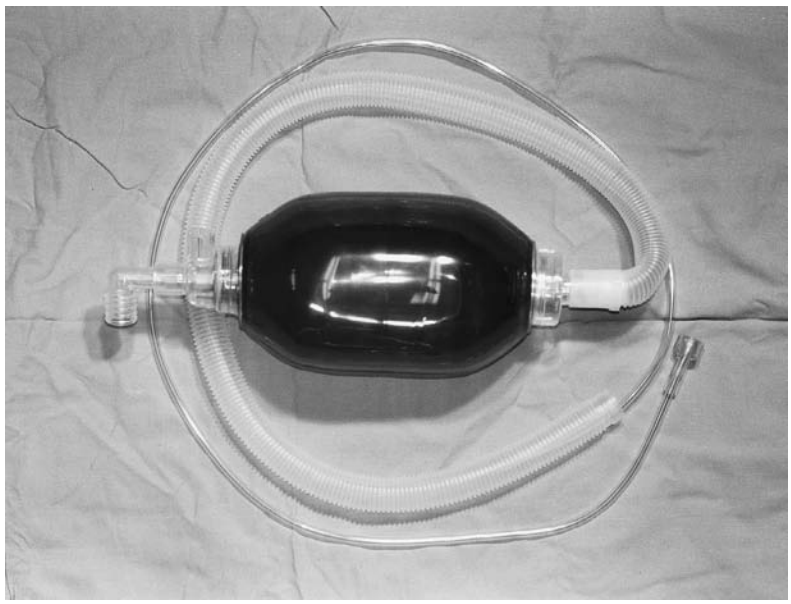

Figure 146-5 Self-inflating resuscitation bag.

and venting exhaled gas to the atmosphere. Inspired oxygen concentration is ordinarily limited to 40% to 60% when oxygen inflow is 10 L/min; bag reinflation is rapid, since room air is entrained with each breath. Addition of an oxygen reservoir, usually in the form of a sleeve or tail at the back of the bag, permits administration of oxygen concentrations of 75% to 90% at 10 to 15 L/min. Some bags are equipped with adjustable valves for application of positive end-expiratory pressure.

MASKS

Although a large variety of masks are available (Fig. 146-4), all have three features in common: the body, seal, and connector. The body is usually made of malleable or moldable material and adjustable to individual facial anatomy. The body of some masks is made of clear plastic to allow diagnosis of regurgitation of gastric contents. The seal is usually a cushioned rim (which can be inflated or deflated) attached to the body, although some are detachable. Some seals are flanged and not cushioned. The connector is designed with a universal fitting (22-mm internal diameter) for attachment to any ventilating circuit. Many are equipped with retaining straps for attachment to mask straps (which pass behind the patient's head, freeing the hand of the operator).

EXTRAGLOTTIC AIRWAY DEVICES

A number of extraglottic or supraglottic airway devices exist,[14,15] and new ones are described every year. Some are cuffed, while others are uncuffed; some are nasally inserted, while others are orally inserted. A few devices are based on cannulation of the esophagus. The most familiar devices are cuffed, orally inserted, hypopharyngeal airways, such as the laryngeal mask airway (LMA)[16,17] and the laryngeal tube airway (LTA).

The LMA (Fig. 146-6) is analogous to the facial mask: It has a compliant cuff that is applied to the dorsal surface of the larynx, isolating the airway from the mouth and esophagus. The LMA came into common intraoperative usage in the early 1990s. While used most extensively in surgical patients, the LMA has also been used for awake, fiberoptic bronchoscopy, in the intensive care unit, and in emergency resuscitation. Variants are specifically designed to be flexible, disposable, or to permit passage of an endotracheal tube through the device's lumen. The LMA is inserted through the mouth into the hypopharynx; its correct positioning is verified by assessment of breath sounds.

The LTA is similar to the LMA. The device has two cuffs, one of which is designed to seal the lower pharynx and esophagus and the other the upper pharynx. A lumen exists between the two.

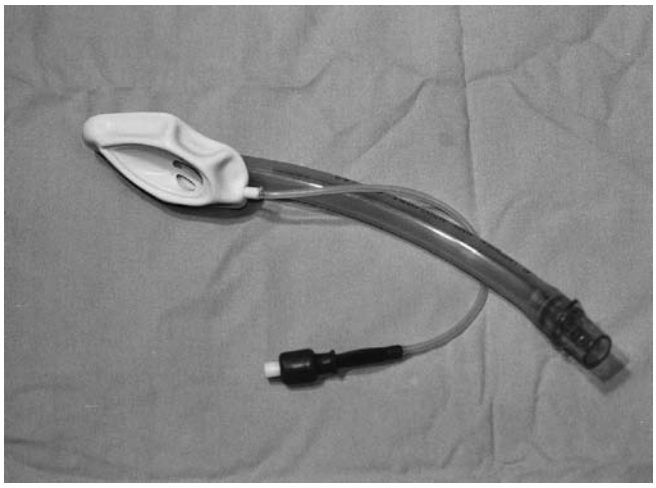

Figure 146-6 The laryngeal mask airway.

The esophageal obturator airway (EOA) is similar to the LTA in that it also has two cuffs and a single lumen. However, the distal end of the device is designed to lie in the esophagus. A newer device, the Combitube (Armstrong Medical Industries), addresses a concern that the tip of the EOA may inadvertently enter the trachea, making ventilation impossible. The Combitube is designed to permit ventilation and airway isolation regardless of whether its tip lies in the esophagus or trachea.

TRACHEAL INTUBATION

Four approaches are commonly employed in tracheal cannulation: nasal, oral, laryngeal, and tracheal. The first two are noninvasive, whereas the latter two require surgical incisions.

Nasotracheal intubation can be done "blindly" (i.e., without tracheal lumen visualization) or using a laryngoscope and forceps. A blind nasotracheal intubation, when performed by a skilled operator, allows rapid control of the airway in an awake patient and minimal suppression of protective airway reflexes. The technique is used widely by paramedics in prehospital patient care, as a component of many difficult airway algorithms, and as an integral part of Advanced Trauma Life Support algorithms.

In performing blind nasotracheal intubation in a nonemergency setting, the operator examines the nasal passages for patency, septal deviation, or the presence of polyps. If the patient is able to cooperate, the larger nasal passage is selected by alternately occluding each nostril and choosing the one with better airflow. A topical anesthetic and vasoconstrictor agent are sprayed in the nostril or applied with cotton pledgets. Anesthetic is also sprayed into the back of the mouth in order to anesthetize the hypopharynx.

An appropriately sized tube (6–7 mm for women, 7–8 mm for men) is selected and lubricated. Lubrication eases passage of the tube and minimizes abrasion of the nasal mucosa, making bleeding less likely. The patient is placed in the sniffing position and the tube inserted and advanced using slow, firm pressure. The natural slope of the tube is oriented so that the tip initially points toward the occiput and curves in a caudad direction as it is advanced.

During the procedure in an awake patient, the operator listens for breath sounds as the tip approaches the vocal cords. A commercially available whistle attachment (Baam, Great Plains Ballistics, Inc., Lubbock, TX) enhances the operator's ability to hear breath sounds (Fig. 146-7). The tube is advanced into the airway during *inspiration*. Slight clockwise or counterclockwise rotation of the tube at the nose can be used to correct for lateral misalignment. A commercially available endotracheal tube (Endotrol, Mallinckrodt, Athlone, Ireland) allows the operator to anteroflex the tip of the tube with a "trigger" at the connector (Fig. 146-8). This is especially effective in patients with anteriorly positioned vocal cords or those who cannot assume the sniffing position (e.g., due to the presence of a cervical collar).

When nasotracheal intubation is performed in an anesthetized patient, the endotracheal tube tip is advanced into the hypopharynx above the vocal cords, laryngoscopy is performed, and the tube is then advanced into the trachea under direct visualization. Magill forceps (Fig. 146-9) are often used to grasp the tube and direct its tip between the vocal cords. Care must be taken to avoid grasping the tube by the cuff, which is easily perforated.

Correct position of the tube can be verified using a number of methods. Audible or palpable air passage (in the spontaneously breathing patient), a visible vapor trail within the tube, or auscultatory evidence of breath sounds over the lung fields are standard approaches. End-tidal capnometry showing phasic variation in carbon dioxide levels is the gold standard and has become more feasible in nonoperative settings because of the development of portable and disposable devices.

Extensive literature exists on the pros and cons of nasal versus oral intubation in the intensive care environment. Nasal intubation

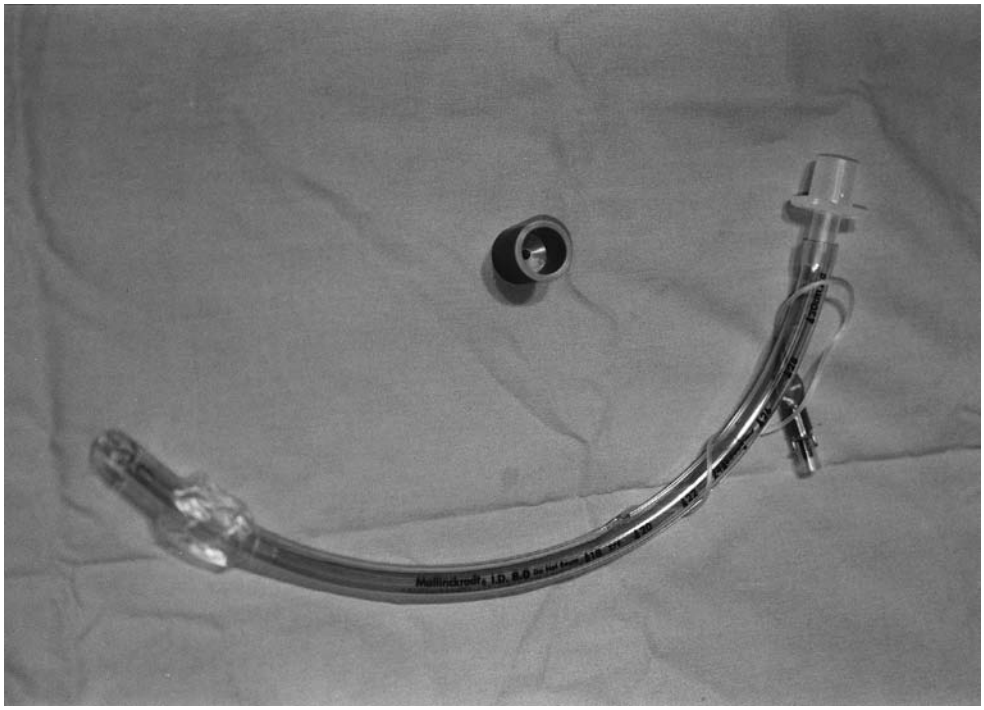

Figure 146-7 Standard endotracheal tube with whistle tip attachment to amplify breath sounds during blind nasal intubation.

is associated with a higher incidence of bleeding, nasal discomfort, and hemodynamic alterations during tube placement. A minimal increase in the dead space of the equipment (less than 10 cc) without significant difference in airflow resistance occurs with nasotracheal intubation compared with the orotracheal route. Literature regarding the incidence of sinusitis and pneumonia as a result of each of the two methods is conflicting; one prospective, randomized trial showed no differences.[18] In general, early tracheostomy is increasingly preferred in critically ill patients who are likely to be intubated for prolonged periods.[19–22]

By far, direct laryngoscopy with orotracheal intubation is the most common approach to secure the airway. With the patient's head in the sniffing position, the operator inserts a Macintosh or Miller blade (Fig. 146-10) into the right side of the mouth using the left hand (regardless of the handedness of the operator). While some anatomic situations make it advantageous to use one blade rather

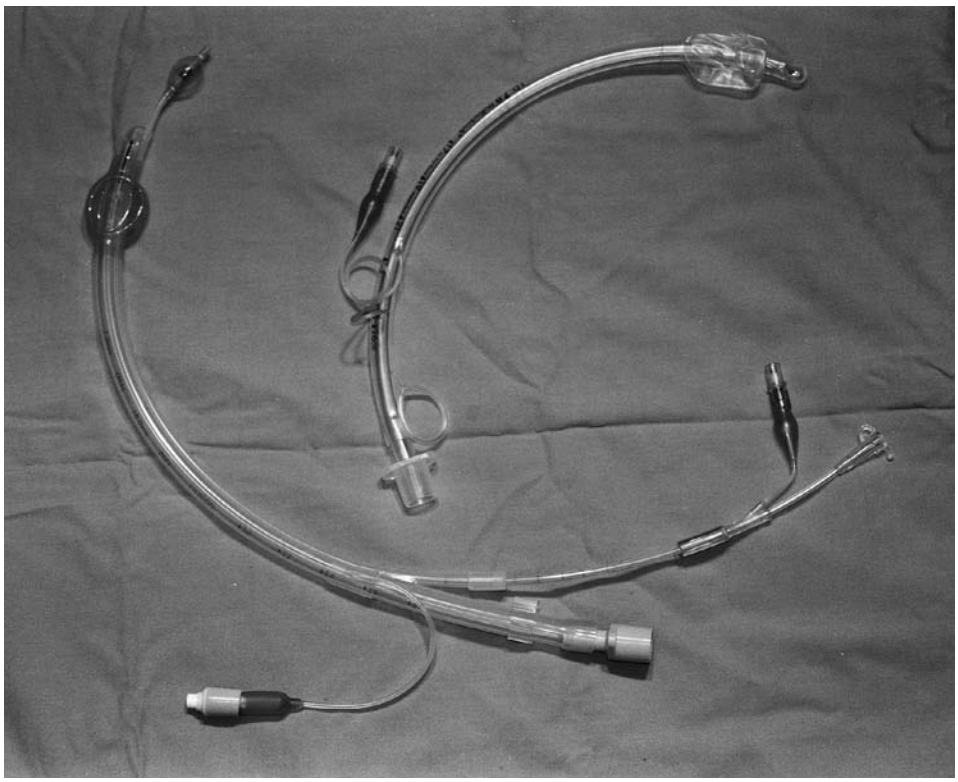

Figure 146-8 Endotracheal tube modified with a "trigger" permitting anteroflexion of the tip of the tube during blind nasal intubation. Univent tube for lung isolation (see text).

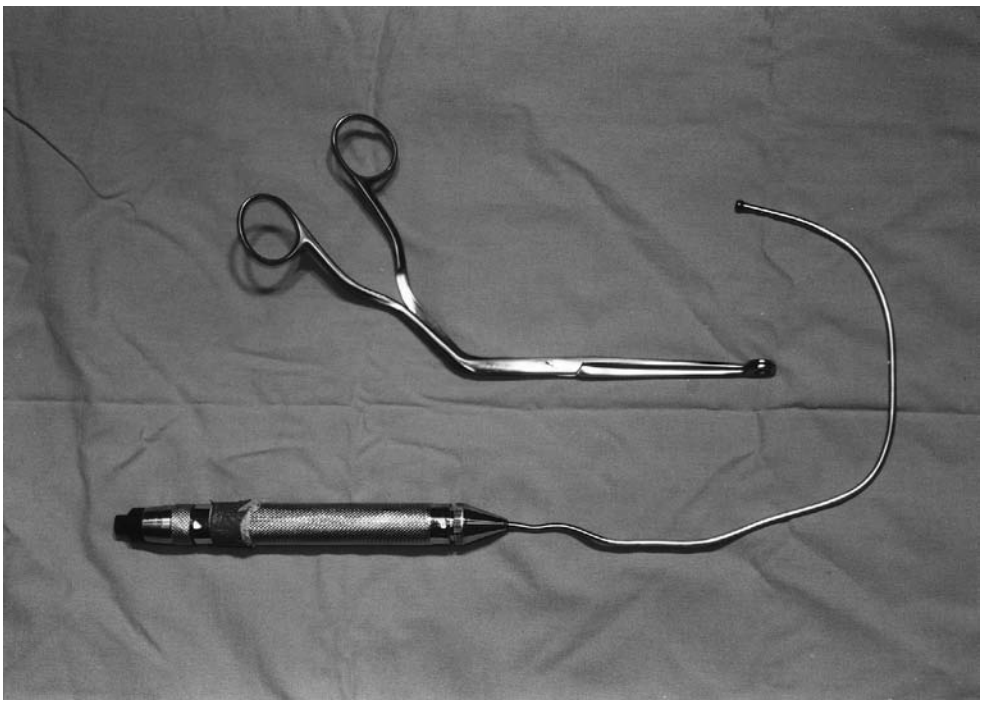

Figure 146-9 Magill forceps (see text) and light wand for transillumination of the trachea during blind oral intubation.

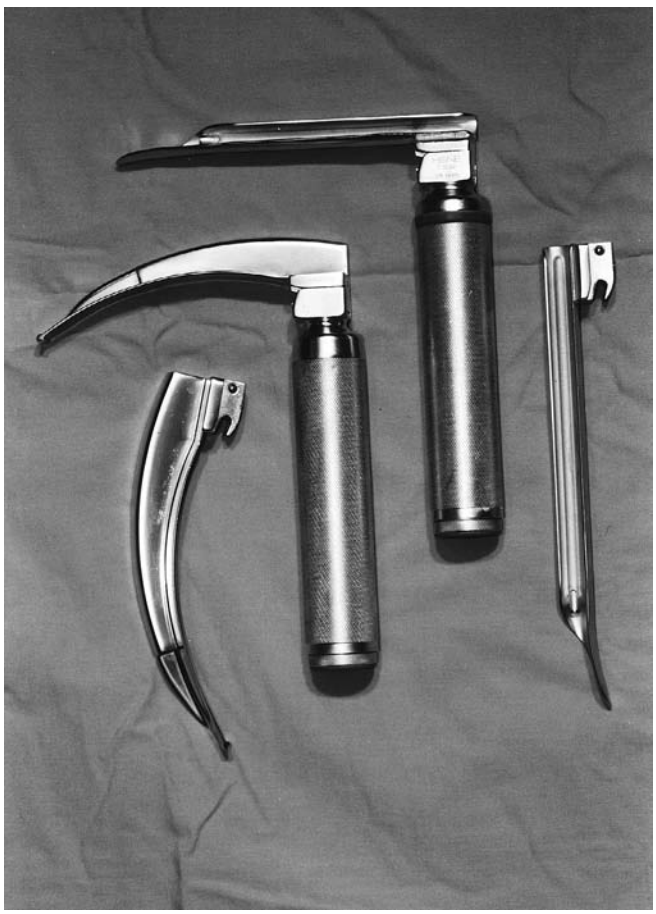

Figure 146-10 Macintosh and Miller blades.

than the other (e.g., the Miller blade in the setting of an anatomically anterior larynx), most operators become familiar with one blade and use it preferentially.

The blades of both instruments are flanged to keep the tongue to the left and out of the visual field. Larger adult blades (Macintosh no. 4 or Miller no. 3) are used for patients with long mandibles, whereas shorter blades (Macintosh no. 3 or Miller no. 2) are used in normal patients. Smaller blades are used for children.

During the procedure, the operator's right hand pulls the upper and lower lips out of the way, so that they are not caught and injured between the blade and teeth. The tip of the laryngoscope blade is advanced along the tongue until the epiglottis is visible. If the Macintosh blade is used, it is advanced between the tongue and epiglottis; when the Miller blade is used, the epiglottis is elevated directly. The cords should be visible immediately below the epiglottis. Most infants are intubated using a Miller blade. The shape, length, and pliancy of the infant epiglottis are such that it must be "picked up" by the tip of the Miller laryngoscope so that the cords can be seen.

Because some patients are difficult to intubate due to anatomic considerations, a number of alternate approaches have evolved. These include fiberoptic laryngoscopy, by which the trachea is entered using a bronchoscope and an endotracheal tube advanced into the airway over the device. A flexible light wand (see Fig. 146-9) can be used to transilluminate and identify the airway; an endotracheal tube is then advanced into the airway using the wand as a stylet. Retrograde techniques involve percutaneous cannulation of the trachea in the neck and retrograde passage of a wire or catheter into the oropharynx. The wire is grasped and secured to an endotracheal tube and used to guide its passage back into the trachea.

A "bougie" tracheal tube introducer has been designed for difficult airways where only the epiglottis or the most posterior portions of the vocal cords are visible on direct laryngoscopy—the bougie is positioned in the airway and the tube threaded over it. The recent development of a "video laryngoscope" has eliminated the need for alternative approaches in many patients with difficult airways,

showing successful intubation rates greater than 90% after failed direct laryngoscopy attempts. Several variants are now available, all of which use a fiberoptic light source and lens connected to a small video display and a dedicated, specially angled laryngoscopic blade.[23–25]

Percutaneous cricothyrotomy kits are available for emergency access to the airway, as are percutaneous tracheostomy kits. Percutaneous ventilation has been taught in airway management portions of Advanced Cardiac Life Support (ACLS), Advanced Trauma Life Support (ATLS), and Pediatric Advanced Life Support (PALS) courses. The technique requires insertion of a needle or intravenous catheter through the cricothyroid membrane in order to insufflate oxygen during emergency airway management.

Anatomic features indicative of the difficult airway are listed in Table 146-3. While a full discussion of the management of the potentially problematic airway is beyond the scope of this chapter, adequate preparation by the operator can prevent a catastrophe.

Early assessment of the anatomy to determine whether difficulty with intubation alone or intubation and ventilation should be anticipated is important. An anteriorly placed larynx is usually associated with difficulty in intubation alone, whereas an obese patient is more likely to present a challenge with regard to both intubation and ventilation.

TABLE 146-3 Indicators of a Potentially Difficult Airway

Poor mouth opening
Temporomandibular joint disease
Mandibular fracture
Dental problems
"Buck" anterior teeth
Caries
Dental hardware (caps, dentures)
Gaps
Abnormalities of the tongue
Large (e.g., in obesity)
Swollen
Edema (surgical)
Angioedema (allergic)
Fixed
Scarring (radiation)
Tumor
Presence of other intraoral structures
Tumors
Enlarged tonsils
Small jaw
"Anterior larynx"
Decreased neck mobility
Cervical disease or injury
Suspected fracture
Rheumatoid arthritis
Ankylosing spondylitis
Increased age (presence of cervical osteophytes)
Congenital syndromes
Cleft palate
Treacher Collins
Pierre Robin
Klippel–Feil

An additional important determination is whether interventional airway management is actually necessary. Can the procedure be performed under regional, rather than general, anesthesia? If regional anesthesia cannot be employed, awake intubation using sedation and topical airway anesthesia may be an excellent alternative. Direct laryngoscopy and fiberoptic bronchoscopy are equally appropriate adjuncts in intubating cooperative patients.

If difficulty in airway management is unexpectedly encountered in an already anesthetized patient, ensuring adequate ventilation and oxygenation is critical. A mask or, if necessary, one of the invasive approaches described above, may be used. Establishment of reliable ventilation allows time for alternate approaches, including abandonment of the procedure (allowing the patient to awaken) or tracheostomy.

A large number of endotracheal tubes are commonly employed in a variety of clinical settings.

Single-lumen, reusable, red rubber tubes with separate cuffs were used as recently as the mid-1970s , and red rubber double-lumen tubes were in common use 5 to 10 years ago. Disposable tubes are now widely available, and a host of different design modifications have been made to make the tubes safer and accommodate different surgical procedures.

The cuff of the adult tube has been changed from a low-volume, noncompliant cuff to a higher volume, very compliant cuff; a corresponding decrease in the incidence of tracheal stenosis has been observed. Pediatric tubes are generally uncuffed because children are more vulnerable to development of subglottic stenosis due to tube contact with the trachea. Uncuffed tubes also maximize the cross-sectional area of the airway. Oral and nasal RAE tubes (Fig. 146-11) are preconfigured to permit facial and oral surgery without interference from the proximal portion of the endotracheal tube.

A variety of special tubes are used for laser surgery. These tubes are less likely to burn when contacted by the laser beam. Reinforced or anode tubes have an embedded wire or nylon filament spiral in the wall of the tube that prevents kinking or collapse due to external pressure (see Fig. 146-11). The Hi-Lo Jet endotracheal tube (Mallinckrodt) has four lumens: one for entrained gas, a second for jet ventilation, a third for cuff inflation, and a fourth for pressure monitoring.

All single-lumen tubes have a 15 mm outer diameter and connect to any standard ventilation device. Most also have a radio-opaque stripe that permits tube localization on chest roentgenograms. The

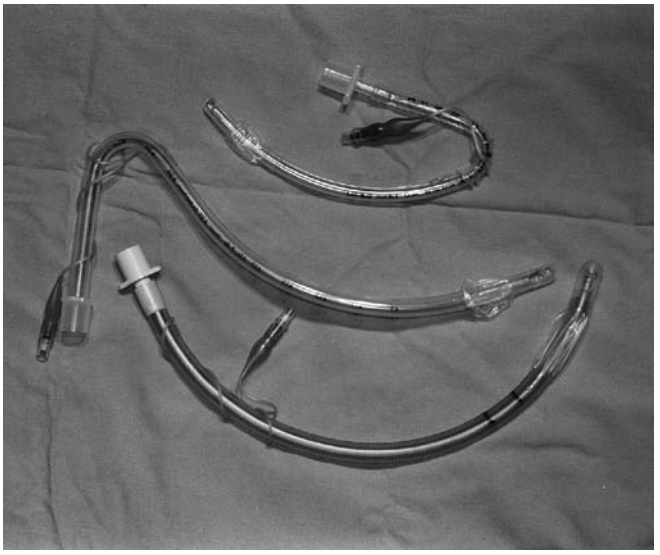

Figure 146-11 Oral and nasal preshaped tubes (RAE tubes). Anode, wire-wrapped tubes to prevent kinking.

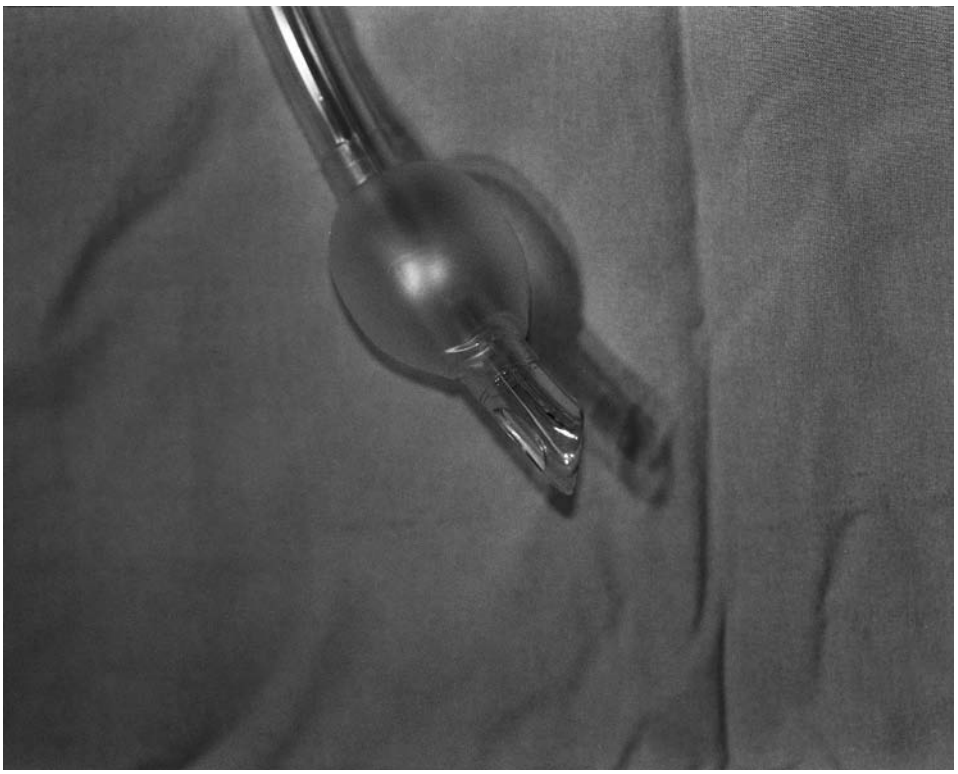

Figure 146-12 Endotracheal tube tip with Murphy eye and bevel (see text).

tip of the tube is beveled (Fig. 146-12); the bevel faces to the left because endotracheal tubes are generally inserted from the right by right-handed operators. An extra hole (Murphy eye) lies opposite to the bevel on many tubes and is designed to permit suctioning or antegrade gas flow if the bevel becomes occluded.

Finally, disposable double-lumen endotracheal tubes are now available. The Carlens and White tubes that were used in the past were equipped with a carinal hook for correct tube placement. These tubes have largely been abandoned in favor of the Robertshaw design, which has tracheal and bronchial cuffs and no hook. The tube is available in four adult sizes (35, 37, 39, and 41 French) in both right- and left-sided designs (Fig. 146-13). The right-sided tube has an oblique bronchial cuff to accommodate the takeoff of the right upper lobe orifice. Correct placement of a double-lumen tube has become easier with development of bronchoscopes small enough to pass through the narrow tube lumens.

An alternative to the double-lumen tube (the Univent tube, introduced in 1982) has a self-contained endobronchial blocker. The tube is inserted in the standard fashion, and the endobronchial blocker is then advanced (blindly or under direct vision) into the right or left main bronchus. A central lumen in the endobronchial blocker allows for inflation or deflation. While the bronchial blocker is integrated into the Univent tube construction, the same functionality can be achieved by using the Arndt wire-guided endobronchial blocker

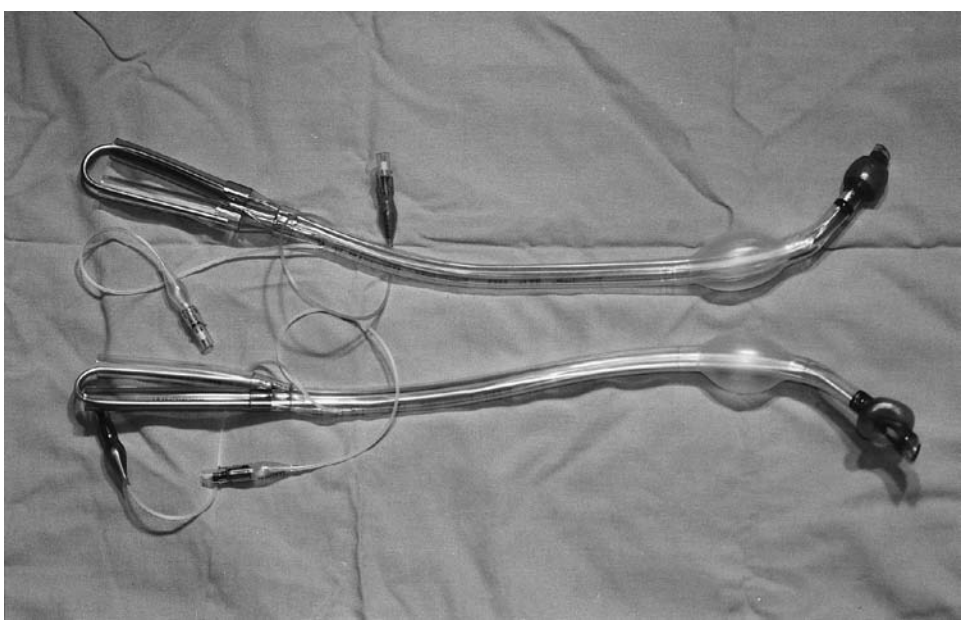

Figure 146-13 Right- and left-sided double-lumen endotracheal tubes. Note oblique bronchial cuff on the right-sided tube to accommodate right upper lobe bronchial orifice.

Figure 146-14 Earlier diagnostic airway intervention. *(Reproduced with permission from Kirstein. Archiv Laryngol Rhinol. 1895;3:156–164. Courtesy of Cushing/Whitney Medical Library.)*

(Cook Critical Care, Bloomington, IN). The device is a multiport airway adapter, which can be used without a tube change (unlike the Univent tube) and can be "swapped" for a standard Y-piece connector, when desired.

CONCLUSION

While some of the skills developed by the early pioneers may be lost to current practitioners (Fig. 146-14), advances in pharmacology, equipment, and equipment manufacturing standards have greatly facilitated airway management and have made new surgical procedures possible.

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CHAPTER 147

Hemodynamic and Respiratory Monitoring in Acute Respiratory Failure

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Barry D. Fuchs

GENERAL PRINCIPLES

Critical illness associated with acute respiratory failure (ARF) results from direct and indirect injuries to the lungs. Patients are admitted to the intensive care unit (ICU) for organ support, principally mechanical ventilation, and invasive monitoring. It is widely believed, based on dramatic improvements in perioperative outcomes since the 1960s, that monitoring the critically ill patient, invasively and noninvasively, leads to clear therapeutic goals, detects early manifestations of disease, and reduces morbidity and mortality.

A number of important goals of ICU monitoring can be identified. One is to ensure adequacy of respiratory and circulatory function in patients who appear clinically stable. Another is to provide close surveillance for early signs of respiratory and circulatory instability, with the presumption that early detection improves outcome. In addition, measurement of the response to therapeutic interventions, including intravenous fluids and the application of supportive devices, such as endotracheal tubes (ETTs) and mechanical ventilators, are routinely performed in the ICU. Although life-saving, these devices, like all therapeutic interventions, are associated with risks that must be considered. Finally, monitoring respiratory and hemodynamic derangements over hours to days provides valuable insight about prognosis, since the trend in physiological derangements over time predicts outcomes far better than does the severity of abnormalities on admission. Consequently, failure to improve over days, despite full support and appropriate treatment, suggests the need for alternative therapeutic strategies, including patient comfort as the primary goal of care.

Physiological parameters normally vary in critically ill patients. The devices used to measure these parameters are often imprecise and, at times, inaccurate. Therefore, clinical assessment and decision making should not be based, in general, on single data points. Rather, trends in data collectively add reliability to interpretation of measurements. This chapter reviews methods currently available for monitoring hemodynamics and respiratory function in patients with ARF.

HEMODYNAMIC MONITORING

Discussed in the following sections are important aspects of hemodynamic monitoring, which in its many forms, is routinely utilized in critical care settings. Respiratory monitoring is considered later in the chapter.

INDICATIONS FOR HEMODYNAMIC MONITORING

Hemodynamic monitoring is used to provide information that is not readily apparent from clinical examination, or when bedside monitoring is unreliable or equivocal.[1] Such circumstances include: (1) for the patient with pulmonary edema, determining whether the edema is cardiogenic or noncardiogenic in origin; (2) assessing whether hypoperfusion is causing, or contributing to, the patient's end-organ dysfunction; (3) deciding whether the patient with ARF who presents with or develops shock be given intravenous fluids, and, if so, how much; (4) deciding for those patients with volume overload, given the risk of causing or exacerbating organ dysfunction, how much fluid should be removed by using diuretics or dialysis to reduce lung water and improve respiratory function.

The first question requires an estimate of ventricular preload, the second an estimate of cardiac output adequacy, and the third and fourth assessment of the interrelationship of both preload and cardiac output. Regrettably, no monitor can provide consistently accurate answers to these questions. Monitors currently available are discussed in subsequent sections.

BLOOD PRESSURE MONITORING

Considered subsequently are general principles of blood pressure monitoring, as well as various noninvasive and invasive techniques employed in the clinical setting.

General Principles

The mean arterial pressure (MAP) is always monitored with the goal of maintaining it at or above 60 to 65 mm Hg, as cardiac and cerebral organ perfusion may be compromised if it falls below this critical threshold. Exceptions include those patients with pre-existing hypertension, where the MAP goal should be raised proportionately to adjust for the compensatory shift upward in their autoregulatory curve. In contrast, if the baseline MAP is low, for example, as in some patients with end-stage liver disease, a lower goal may be tolerated safely. In early circulatory shock, however, perfusion to other, less vital organs falls well before any reduction in MAP. The importance of understanding, recognizing, and intervening during this early period cannot be underscored. Thus, although essential to monitor, MAP is too insensitive a parameter to use for the detection of circulation dysfunction.

In contrast, in circulatory shock, pulse pressure falls much earlier than MAP. Since pulse pressure changes in proportion to stroke volume (SV), as SV (and cardiac output) declines and compensatory tachycardia ensues, pulse pressure will fall. Consequently, if a patient with shock and tachycardia presents with a preserved or increased pulse pressure, this suggests distributive shock as the cause. Pulse pressure may also vary rhythmically with the phases of mechanical ventilation. This pulse pressure variability (PPV) results, in large part, from the effect of respiratory-associated pleural pressure changes on venous return and occurs exclusively in patients who are hypovolemic. Although only applicable in clinical conditions in which it was validated, this observation can help inform decisions about the value of additional fluid resuscitation, as discussed subsequently.

Noninvasive Blood Pressure Monitoring: Auscultatory Technique

Systolic and diastolic arterial pressures have been measured for over a century based on the auscultatory technique, using a sphygmomanometer, cuff, and stethoscope. The cuff is inflated above the anticipated systolic pressure and, as the cuff is gradually deflated, blood flow returns, generating a series of characteristic turbulent noises (Korotkoff sounds) that can be heard over the artery. The pressure at which the first Korotkoff sound is heard is generally accepted as systolic blood pressure (phase I). The sound character progressively changes (phases II and III), becomes muffled (phase IV), and is finally absent (phase V). Diastolic pressure is recorded at phase IV or V. Phase V may never occur in certain pathophysiological states, such as aortic regurgitation. It is used commonly for BP measurement while patients are managed in general care units.

Although widely used in clinical practice, the auscultation technique is inadequate for critical care. There are considerable interobserver differences based on subjective perception, rate of cuff release, and difficulty in hearing the sounds in shock states. In addition, some inexperienced caregivers have a tendency to "disbelieve" abnormal results, resulting in diagnostic delay. Peripheral edema may artificially inflate the blood pressure reading, as will a cuff that is too narrow for the patient; the width of the cuff should be 20% greater than arm diameter. If the cuff is too small, blood pressure will be overestimated. If the cuff is too loose, blood pressure will be underestimated. Finally, in patients with low output shock, the auscultatory method may underestimate intra-arterial measurements by up to 50 mm Hg.[2]

Noninvasive Blood Pressure Monitoring: Oscillometry

Oscillometers are automated, noninvasive blood pressure (NiBP) monitoring devices that are routinely used in operating rooms, recovery rooms, endoscopy suites, high-dependency wards, and ICUs. NiBP devices measure mean arterial pressure and use an algorithm to estimate the systolic and diastolic blood pressures. They offer significant advantages over auscultation in that they are time saving, reliable, reproducible, and have high- and low-pressure alarms built in.

The oscillometer is a single-cuffed device that occludes the artery and senses restoration of blood flow. The cuff is inflated above systolic pressure and then deflates either continuously, at a rate about 4 mm Hg per second, or in a stepwise manner. The sensor detects oscillation as blood flow returns. The pulse pressure wave and the gauge pressure in the occluding cuff are detected and converted into electronic signals by a transducer. The peak amplitude of pulsations corresponds to MAP. The systolic and diastolic components are calculated using proprietary algorithms. Systolic blood pressure is identified as the pressure at which pulsations are increasing and are at 25% to 50% of maximum. Diastolic blood pressure is the most difficult value to determine by oscillometry and is commonly recorded when the pulse amplitude has declined from the peak value by 80%.

Oscillometers are generally safe and reliable, but care must be taken with cuff location, size, and frequency of measurement. Many complications have been reported, including pain, petechiae, bruising, venous stasis, limb edema, thrombophlebitis, and peripheral neuropathy. The likelihood of these complications is proportional to the duration and frequency of cuff inflation; they result from extremity ischemia and local trauma. The events occur more often after prolonged periods of excessively frequent cuff inflation/deflation cycling.

Invasive Blood Pressure Monitoring Techniques

The insertion of an intra-arterial cannula provides the intensive care clinician with continuous, beat-to-beat blood pressure monitoring and arterial blood sampling for pH and blood gas analysis, as well as for the medley of blood tests that may be performed on the critically ill patient. It is widely believed that this form of continuous invasive blood pressure (IBP) monitoring is more reliable than noninvasive approaches and facilitates earlier diagnosis and resulting interventions.[2,3]

Arterial "lines" are constructed of an intra-arterial cannula, fluid-filled tubing, pressure transducer, and microprocessor with display. The pressure transducer is a low-compliance diaphragm that moves in response to pressure changes transmitted through fluid-filled tubing. This movement is converted to an electrical signal using a strain gauge. A pressure waveform is generated, and the mean arterial pressure is calculated by integrating the area under the waveform. The systolic and diastolic pressures are calculated using an algorithm.

Complications of arterial cannulation include infection, air embolism, bleeding, thrombosis, and infarction. The IBP monitor must be zeroed and leveled in the phlebostatic axis (at the level of the right atrium), regardless of the site of the arterial cannula. Inadequate or incorrect zeroing results in incorrect values and inappropriate therapies. The bedside clinician should always check the "zero" before initiating antihypertensive or vasopressor therapy.

Which is more accurate, NiBP or IBP? Mean arterial pressure measurement correlates well between the two techniques.[4] Oscillometry generally underestimates intra-arterial systolic blood pressure,[5,6] as opposed to diastolic blood pressure, which is overestimated, especially in hypertensive patients.[7] IBP is vulnerable to damping. The presence of air bubbles, blood clot, or kinks in the tubing result in a damped signal. Damping decreases the rate of signal change, leading to low pulse pressure, with low systolic and high diastolic pressure readings. Nevertheless, damping will not impact the accuracy of the mean arterial pressure until it is extreme, and only then will it underestimate the true value. Damping is important to recognize, since interventions may be initiated on the basis of reductions in either systolic or pulse pressure; furthermore, pulse pressure is important for estimating cardiac output by several methods (as discussed subsequently). Routine nursing bedside assessments should enable early identification and troubleshooting, including the performance of the "flush test," which measures the arterial pressure recording systems frequency response to a pulse change in pressure.

■ INVASIVE CENTRAL VENOUS PRESSURE MONITORING

Measurement of central venous pressure (CVP) is a critically important component for monitoring many patients in critical care units. Its assessment, as well as parameters derived from venous blood samples obtained from central venous catheters (CVCs), is discussed in the following chapters.

Central Venous Pressure

CVCs are inserted for a variety of reasons, including for administration of vasopressors and hypertonic dextrose solutions (total parenteral nutrition), for long-term venous access, and for measurement of CVP and venous blood gases. CVP is the downstream pressure that governs the rate of venous return to the right heart; it represents a good approximation of mean right atrial (RA) pressure. CVP may be measured accurately through a variety of catheter types, including triple lumen, tunneled, and percutaneously placed catheters. Commonly employed CVP catheter sites include the internal jugular (IJ), subclavian, and femoral veins.

CVP has been used to assess volume status in the diagnosis and management of shock and to infer the etiology of pulmonary edema. There is no "normal" CVP, and small changes in its magnitude may accompany large changes in circulating blood volume.[2] Although, in some cases, a very low (<5 mm Hg) or a very high (>20 mm Hg) CVP may be helpful in guiding decisions about circulating blood volume, in most patients, a single CVP value is rarely helpful.[8] Numerous studies have failed to show that the CVP value has utility in predicting fluid responsiveness. Nevertheless, the CVP may help in categorizing the pathophysiology of shock and may be a useful parameter to guide protocol-driven resuscitation in an ICU staffed by inexperienced practitioners or trainees. In summary, although CVP has limited utility in volume status assessments, it remains a complementary assessment tool.

One of the most important problems confounding CVP interpretation, which is pertinent to all intravascular pressure measurements taken from within the thorax, is the impact of respiratory-induced intrapleural pressure changes on the interpretation of intravascular pressure. Intravascular pressure is measured relative to atmospheric pressure, providing a zero reference for the transducer. Unless the magnitude of the intrapleural pressure swings are considered, (i.e., referencing intravascular pressure to intrapleural,

rather than atmospheric, pressure) intravascular pressures fluctuate despite constancy in the transmural pressure; if the impact of these intrapleural pressure swings are not considered, spurious readings will arise. Consequently, pressures are recorded at end expiration to minimize this potential error. End expiration is easy to determine in spontaneously breathing patients; in patients on mechanical ventilation who are actively breathing, recording and displaying intraairway pressure and intravascular pressure simultaneously enables accurate timing.

Important clinical questions are whether the CVP or RA pressure is useful in estimating right and left ventricular preload or in determining if pulmonary edema is cardiogenic in origin. Preload is best defined as end-diastolic volume (EDV), which requires an estimate of both the transmural filling pressure (CVP–pericardial pressure) and ventricular compliance, neither of which can be determined reliably at the bedside. Even if CVP correlated with RVEDV, the latter correlates poorly with LVEDV in patients with ARF because of discordance in ventricular afterload and contractility. Indeed, lung disease and the positive end-expiratory pressure (PEEP) used to treat it increase pulmonary vascular resistance and may precipitate right ventricular failure. Furthermore, since the pericardium limits ventricular dilatation, ventricular interdependence further increases the disparity in LVEDV and RVEDV when differential contractility or loading conditions are present. This occurs because ventricular dilatation displaces the septum laterally and compresses the adjacent ventricle. Thus, the CVP is of little or no value in determining ventricular preload or in determining whether pulmonary edema is of cardiogenic or noncardiogenic origin.

The CVP waveform, however, may provide evidence to suggest the presence of specific cardiac or pericardial disorders (Fig. 147-1).

Characteristic findings on the CVP waveform may suggest certain cardiac disorders. For example, a prominent Y descent suggests myocardial restriction; pericardial constriction; or right ventricular ischemia, infarction, or overload. In contrast, the Y descent is greatly attenuated in cardiac tamponade. A large V wave suggests tricuspid regurgitation (TR), which is associated with RV failure. In atrial fibrillation, the A wave disappears. A tall A wave (so-called, "canon A wave") may be seen in atrioventricular dissociation or a junctional rhythm, due to atrial contraction occurs against a closed tricuspid valve. In patients with diastolic dysfunction, these arrhythmias may cause sudden hypotension, and CVP waveform analysis may be diagnostic.

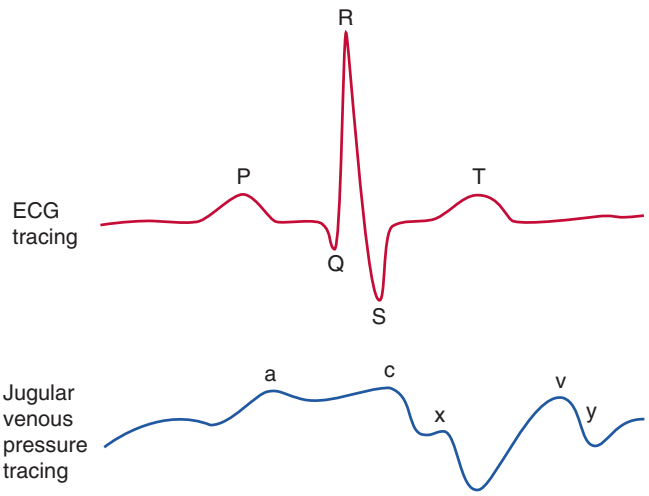

Figure 147-1 **CVP waveforms:** Since there are no valves between the vena cava and the right atrium, central venous pressure waveform reflects the events of cardiac contraction. Simultaneous display of the ECG allows one to identify and time the CVP waveform. **a wave:** Increased atrial pressure during right atrial contraction. It occurs following the P wave on an ECG. **c wave:** During early ventricular contraction the tricuspid valve bulges into the right atrium. It occurs at the end of the QRS segment on an ECG. **x descent:** Atrial relaxation. It occurs before the T wave on an EKG. **v wave:** Atrial filling—the right atrium progressively fills while the tricuspid valve is closed. It occurs at the end of the T wave on an EKG. **y descent:** Following opening of the tricuspid valve in diastole, the atrium empties as blood flows into the right ventricle. It occurs before the P wave on an EKG.

Mixed Venous Oxygen Saturation

Normally, the circulation delivers oxygen to the tissues at a rate sufficient to maintain an intracellular (mitochondrial) oxygen tension above a critical threshold. If oxygen delivery (D_{O_2}) fails to meet tissue oxygen requirements ($\dot{V}_{O_2}$), shock occurs and anaerobic metabolism ensues. If prolonged, cell death may occur.

If D_{O_2} decreases and tissue $\dot{V}_{O_2}$ remains constant, a reduction in the oxygen content is seen. This increase in oxygen extraction results from both an increased capillary transit time and increased gradient for oxygen diffusion, as mitochondrial and tissue P_{O_2} fall. As most of the oxygen in venous blood is attached to hemoglobin, the mixed venous oxygen saturation (Sv_{O_2}), as measured in the pulmonary artery, has traditionally been used as a surrogate for oxygen content.

Since blood flow and metabolic rate vary among organs, so does the venous oxygen content draining from different organs. However, when well mixed in the pulmonary artery, the Sv_{O_2} represents a weighted average of the product of blood flow and oxygen content from every organ and reflects the adequacy of "global" oxygen delivery. Thus, Sv_{O_2} is insensitive to localized tissue ischemia (e.g., bowel ischemia), reflecting an important limitation in its clinical use.

Based on an understanding of the determinants of Sv_{O_2}, the clinician can use the Fick equation (Equation 1) to elucidate the mechanism of shock and to select the most appropriate therapy:

$$\dot{V}_{O_2} = CO \times (\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}) \quad (1)$$

where CO is cardiac output. Recalling that O_2 content of either arterial or venous blood is the sum of hemoglobin (Hgb)-bound oxygen (1.34 mL O_2/g Hgb × [Hgb]/100 mL blood × % hemoglobin saturation) and dissolved oxygen (0.003 mL O_2/mm Hg), the following expression (Equation 2) for mixed venous O_2 is derived:

$$Sv_{O_2} = (\text{arterial } O_2 \text{ content} \times [\text{Hgb}] \times CO)/\dot{V}_{O_2} \quad (2)$$

Thus, if Sa_{O_2} is stable, Sv_{O_2} will decrease if either CO or [Hgb] decreases or $\dot{V}_{O_2}$ increases. Since Sa_{O_2} and [Hgb] are readily measured and changes in $\dot{V}_{O_2}$ can be grossly estimated, the cause of a decrease in Sv_{O_2} can usually be determined quickly. Compared with alternative methods of monitoring CO, Sv_{O_2} reflects the adequacy of CO relative to oxygen requirements. This is more valuable than the absolute CO, since reference values for CO or body surface area–normalized cardiac indices assume that $\dot{V}_{O_2}$ is normal, which is often not the case in critical illness.

Since Sv_{O_2} is measured from the pulmonary artery, it requires placement of a pulmonary artery catheter (PAC), which is now rarely performed, because randomized control trials have failed to show a benefit on patient outcome. Consequently, since 2001 there has been considerable interest in using the venous oxygen saturation measured from the superior vena cava (SVC) (Scv_{O_2}) as a surrogate for Sv_{O_2}.[9] Since many critically ill patients already have a CVC in place for vasoactive medications, this measurement requires no additional procedures and, therefore, carries no additional risk. To minimize measurement errors, blood should be sampled from the proximal SVC or from within the right atrium via any CVC or device. Importantly, since many hospitalized patients not in critical care units have a CVC or long-term CV access port, Scv_{O_2} may

be used for both diagnostic and therapeutic purposes well before transfer to an ICU.[10,11]

Pulmonary Artery Occlusion (Capillary Wedge) Pressure

The PAC was first introduced into clinical practice in 1970. For many years, the PAC was used widely for hemodynamic measurements in the ICU, particularly in North America. However, more recently, usage has fallen dramatically with the lack of any evidence of meaningful benefit and known complications.[12–14]

The PAC is used to measure CVP and pulmonary artery occlusion or "wedge" pressure (PAOP) for the estimation of right and left ventricular filling pressures and to determine cardiac output. PAOP closely approximates the left ventricular end-diastolic pressure (LVEDP). If "a" and "v" waves are visible in the transduced pressure recording, the mean value of the "a" wave (halfway between the top of the "a" wave and the bottom of x descent) is used to indicate the PAOP. PAOP is also used to estimate pulmonary capillary pressure to determine whether pulmonary edema is due to increased capillary permeability or hydrostatic pressure. In contrast to when the PAOP is used to estimate LVEDP, the mean of the end-expiratory tracing is always used, even if large "v" waves are present, since the systolic pressure spike ('v" wave) is transmitted with an equal contribution to the capillary hydrostatic pressure. If the PAOP never exceeds 18 mm Hg, hydrostatic pulmonary edema can be excluded; however, transient spikes in left atrial pressure that can cause pulmonary edema, may occur between normal PAOP measurements, and may be missed. A PAOP >18 mm Hg is consistent with a hydrostatic cause of pulmonary edema, but high-permeability edema cannot be excluded.

The correct interpretation of PAC-derived hemodynamic data remains a major challenge and may be an important reason for studies having failed to show a benefit on patient outcomes.[15,16]

Does the PAOP provide an estimate of LV preload? Regrettably, this is an equally tenuous proposition, fraught with all the same limitations of those discussed previously regarding CVP as a poor reflection of RV preload.[8,17,18] But even if PAOP provided an accurate estimate of ventricular volume (preload), it should not be used to guide volume resuscitation. EDV does not correlate with fluid responsiveness, the important issue when resuscitating a patient. Fluid responsiveness can only be determined from dynamic indices, which are discussed subsequently. Nevertheless the measurement of pulmonary arterial pressure from the PAC is useful. Right ventricular dysfunction not uncommonly complicates acute respiratory distress syndrome (ARDS) and thromboembolic disease.[19] The presence of high PA pressures should alert the clinician to these diagnoses. Pulmonary artery pressure is also important to follow when titrating pulmonary vasodilators, diuretics, hemofiltration, inotropes, or other therapies.

■ CARDIAC OUTPUT MONITORING

Monitoring cardiac output in critically ill patients has been a central element in clinical management for decades. Underlying principles and techniques are discussed in the following paragraphs.

General Principles

Shock or frank hypotension commonly complicates critical illness and may result from absolute or relative hypovolemia, vasoplegia, or cardiac failure. The ability to measure cardiac output and titrate inotropes, vasopressors, and fluids remains a cornerstone of 21st-century critical care.

In critically ill patients, the history, physical examination, and laboratory testing can help to estimate absolute and relative changes in cardiac output and organ perfusion. In addition, Scv_{O_2} monitoring has become a routine component of hemodynamic monitoring. Although more outcome studies are needed, these routine assessments often provide all the information necessary to categorize the nature of shock and assess the response to early resuscitative interventions. However, in the population of patients who fail to recover fully from shock, these assessments alone may not provide the information necessary for optimal patient management. For instance, additional decisions may need to be made on whether to proceed with more fluid challenges, deciding whether there has been a favorable response to a fluid challenge, or determining when to stop diuresis or ultrafiltration to avoid a reduction in cardiac output. These questions are best addressed by measuring the change in cardiac output in response to an intervention. From a practical standpoint then, accurate determination of *trends* in cardiac output is more important than absolute values.

Traditionally, thermodilution (TD) using a PAC has used to measure cardiac output. Due to the inherent issues with the use of PACs, a variety of less invasive SV/cardiac output monitors have been developed for this purpose.

Thermodilution and Indicator Dilution Techniques

Measurement of CO with a PAC using a TD-based technique is considered the gold standard to which other CO-measuring technologies are compared. CO can also be measured indirectly with the PAC using the Fick method, based on the principle that CO is equal to oxygen consumption ($\dot{V}_{O_2}$) divided by the difference in O_2 content across the circulation (i.e., the arteriovenous O_2 difference). Since $\dot{V}_{O_2}$ is not usually measured directly and may vary considerably in critically ill patients, inaccuracies may result. Hence, in patients with ARF who have a PAC, CO should be measured using TD, unless significant TR is present. If the values obtained by TD are unexpected, then the Fick method should be used for corroboration.

Even if we accept that the CO measurement is accurate, more information is needed to make clinical decisions. Oxygen consumption varies significantly within and between patients with ARF. Since CO usually increases in proportion to $\dot{V}_{O_2}$ and inversely with hemoglobin concentration and O_2 saturation, there is no normal or range of normal values for CO in patients with ARF. Similarly, normalizing CO to body surface area for comparison to reference values is unhelpful. In managing a critically ill patient, the relevant questions are whether the measured CO is adequate for the patient's needs, and if not, whether CO can be improved with intravenous fluids. Alternatively, for the volume-overloaded patient, an important question is how much fluid can be removed by diuresis or dialysis without reducing CO.

Lithium Dilution Technique

Lithium, in low doses, is a nontoxic substance that is not metabolized. When injected, its concentration is easily measured using an ion-selective electrode. Lithium dilution cardiac output (LiDCO) is calculated from the area under the concentration–time curve when lithium is injected into a CVC and measured peripherally in arterial blood. Injection into the antecubital vein appears to be as accurate as injection through a CVC. LiDCO is also used to intermittently calibrate the PulseCO cardiac output monitor.

Dynamic Preload Indices and Pulse Contour Analysis

Positive intrathoracic pressure increases right ventricular (RV) afterload and reduces RV preload. On inspiration, RV stroke volume falls and LV stroke volume increases as a consequence of increased LV filling from enhanced pulmonary venous return, increased LV compliance because of decreased RV dimensions, decreased LV afterload, and external pressure on the LV. The subsequent LV stroke volume is lower, due to the reduction in RV stroke volume. Consequently, blood pressure falls slightly during inspiration and returns to normal during expiration. These cyclic variations are quite sensitive to volume status, such that when the patient is

TABLE 147-1 Devices Used to Measure Cardiac Output

Device	Advantages	Disadvantages
Pulmonary artery catheter	Can be used in extubated patients Accurate cardiac output Can measure pulmonary artery pressures and mixed venous oxygen saturation Continuous monitoring provides core temperature	Inaccurate with tricuspid regurgitation Complications, including arrhythmias, pulmonary artery rupture, infarct Misinterpretation of data
PiCCO	Simple Calibrated cardiac output Can be used to assess fluid responsiveness and extravascular lung water Continuous monitoring	Additional arterial line required
Flotrac-Vigileo	Simple—connected to arterial line Predicts fluid responsiveness Continuous	Patient ideally should be mechanically ventilated Not useful for titrating vasopressors Not responsive to changes in vascular tone
LiDCO	Simple Accurate cardiac output	Requires frequent recalibration Intermittent Not useful for titrating vasopressors Not dynamic enough to titrate fluid responsiveness
Esophageal Doppler	Relatively simple Predicts fluid responsiveness	Patient must be intubated and sedated Intermittent Interuser variability
Echocardiography	Accurate measurement of cardiac output, stroke volume, filling volumes and pressures	Complex High level of skill required Intermittent Requires technician to be present while titrating pressors and fluid
Thoracic bioreactance	Accurate measurement of stroke volume Completely noninvasive Mechanical ventilation, sedation, and regular cardiac rhythm are not required Ease of use	Electrocautery causes interference

relatively hypovolemic and on the steep part of the Frank–Starling curve, SV and, hence, pulse pressure variation (PPV) are greater.[20] Patients on the flat portion of the Frank–Starling curve are insensitive to these cyclic respiratory-related changes in preload.[21]

A PPV >13% appears to be a sensitive indicator of fluid responsiveness.[22] PPV and stroke volume variability (SVV) have become the major focus of current generation cardiac output monitors (Table 147-1).[23] However, these two measurements of fluid responsiveness are only valid under the ideal conditions in which they were validated. These include passive mechanical ventilation with a tidal volume of at least 8 mL/kg IBW, a regular cardiac rhythm, a closed chest, and no evidence of intra-abdominal hypertension or right ventricular failure. Unfortunately, these conditions are met in only a small proportion of patients in ICUs, given their reductions in tidal volume and use of sedation. Thus, for the majority of critically ill patients, alternative approaches to assess fluid responsiveness are required. Most commonly, this involves measuring the change in cardiac output in response to a fluid challenge (bolus) of 250 to 500 cc given rapidly (over 5–10 minutes).

If there is a concern about the safety of giving an additional fluid challenge, measuring the cardiac output response to a passive leg raise (PLR) maneuver should be used. Repositioning from the semirecumbent position (45 degrees) to supine, with the legs raised 45 degrees, provides a rapid endogenous shift of blood volume of approximately 300 cc, mirroring the effect on venous return produced by an exogenous fluid bolus. The technique has been validated under a variety of clinical conditions, albeit in small studies, including those that render other invalid functional hemodynamic assessments, that is, PPV, SVV, and IVC collapsibility.[24] This technique is promising, but large validation and outcome studies are needed.

The Flotrac-Vigileo (F/V) device (Edwards Lifesciences, Irvine, CA) calculates SV and cardiac output, using proprietary algorithms, from a single sensor attached to an arterial line at any site. It does not require external calibration or the presence of a CVC or specialized catheter.

F/V combines rapid analysis in real time of the arterial pressure waveform with demographic data (e.g., gender, age, weight, and height) applied to a continuously evolving algorithm to calculate cardiac output. Arterial pulsatility is directly proportional to SV. As changes in vascular tone and compliance occur dynamically, the device appears capable of correcting the changes by analyzing skewness and kurtosis of the arterial waveform. These correction variables are updated every 60 seconds, and the arterial waveform is analyzed and averaged over 20 seconds, thus eliminating artifacts, jitter, and premature contractions. Cardiac output is calculated utilizing the arterial waveform and the heart rate. F/V also calculates accurately SVV and, hence, provides an assessment of fluid responsiveness.[25]

An increasing number of studies and a meta-analysis[26] on performance of this system have been published. While early studies

demonstrated poor correlation between F/V and TD methods, with application of newer software the correlation has improved.[27] Of note, although TD methods are considered the gold standard for CO measurement, comparison with the F/V device is not ideal, since measurement intervals and averaging times are substantially longer with all TD methods. Hence, F/V may be more sensitive to dynamic changes in cardiovascular function. Obviously, F/V requires an uninterrupted arterial waveform. Thus, in the presence of arterial obstruction, for example, aortic valve disease, aortic coarctation, or use of balloon counterpulsation, the data will be inaccurate and misleading. Care should also be taken in scenarios in which patients are being rewarmed from induced hypothermia (e.g., after cardiac surgery or cardiac arrest) or when intracardiac shunts are present.

Data to date have suggested that F/V is quite accurate at measuring changes in cardiac output associated with volume expansion (i.e., in which there is preload sensitivity),[28] but not changes associated with vasopressor use.[29–31] Accuracy is also likely dependent on the patient having a regular cardiac rhythm and a consistent tidal volume.[25,32]

Pulse Contour Cardiac Output

Systolic ejection results in distension of the arterial tree; if the distension pressure is transduced by an arterial line, a characteristic waveform is observed. This waveform reflects the SV and elastic properties of the arterial wall. The shape of the pulse waveform and the area under the curve (AUC) is proportional to the cardiac output. Measurement of the AOC and pulse contour provides clinicians with a bedside cardiac output. However, arterial compliance is not constant or consistent; there is tremendous inter- and intrapatient variability. Since compliance is mathematically defined as the change in volume divided by the change in pressure, external calibration of the pressure signal with an alternative cardiac output technique is required. Pulse contour devices, for example, Pulse CO, LiDCO (LiDCO plus, LiDCO LTD, Cambridge, UK), and PiCCO (Pulsion, Germany), combine pulse contour analysis to calculate SV, and indicator dilution or TD cardiac output measurements to calibrate the system.

In addition to calculating cardiac output, devices that analyze pulse waveforms also analyze and display PPV that can be used for dynamic preload assessment and fluid responsiveness in mechanically ventilated patients.

PiCCO-plus (Pulsion Medical, Munich, Germany) calculates cardiac output continuously from pulse contour analysis of the aortic waveform via an arterial cannula. The cannula can be placed in the femoral (preferably), brachial, or axillary arteries. The system requires the concurrent placement of a CVC, which is required to perform transpulmonary TD cardiac output measurements, and a thermistor in the arterial catheter to calibrate the system. The major advantage of the system over a PAC is that there is no requirement to cannulate the right heart. Conversely, two separate lines are required, and often this involves the placement of a second arterial line.

The PiCCO device measures the area under the aortic waveform; the systolic area is identified as that part of the waveform proximal to the dicrotic notch, which is proportional to the SV. Although beat-to-beat volumes are measured, they are averaged over 30 seconds to avoid inaccuracy associated with anomalous waveforms, interference, and extrasystoles. The continued accuracy of PiCCO depends on the frequency of calibration using TD. The manufacturer recommends recalibration every 8 hours, but this interval may be insufficient in unstable patients.[33]

In the PiCCO system the temperature differential detected using the arterial thermistor is composed of a series of exponential decay curves as the cold injectate passes through the various compartments of the circulatory system. Unlike the PAC, the receiver is located at a significant distance from the injector. Consequently, a series of exponential decay curves is constructed as the injectate passes along the circulation. Since the injectate is administered centrally and the temperature difference is measured in a proximal artery, the majority of the temperature change occurs in the intrathoracic compartment. As a consequence, it is possible to measure intrathoracic blood volume and extravascular lung water. This provides an advantage of the PiCCO device over the PAC, as the volume of extravascular lung water in patients with ARDS predicts adverse outcomes.[34] Finally, the device also purports to measure global EDV, permitting the construction of Frank–Starling curves and volume titration. To date, the PiCCO system appears to correlate very well with TD techniques.[35–38]

Pulse CO LiDCO (LiDCO plus) combines pulse contour analysis with lithium dilution calibration. The major advantage of LiDCO plus is that no specialized central or arterial catheter is required. The major disadvantage of LiDCO plus is the requirement for lithium injection for the calibration of CO at least every 8 hours. Of note, in patients that are hyponatremic or have recently received neuromuscular blocking agents, the calibration may be inaccurate. As with all of these devices, data are unreliable in the setting of aortic valve disease or balloon counterpulsation therapy. Furthermore, as noted previously, other requirements must be met to mimic the conditions used for validation of the technique.

Esophageal Doppler

While application of esophageal Doppler technology has been widely used in perioperative medicine, it has made little inroads into ICUs.

Given the proximity of the thoracic aorta and esophagus, insertion of an esophageal probe using Doppler ultrasound permits measurement of aortic blood flow parameters that, when entered into an algorithm, allow derivation of SV and cardiac output. There are significant limitations with this technique, particularly in nonoperative venues. Patients must be sedated deeply to tolerate probe positioning, and there is a steep user learning curve and significant interobserver variability. In addition, the technique is contraindicated in the presence of esophageal disease, and it does not provide continuous monitoring, since the probe needs to be refocused for each measurement. Nonetheless, substantial data have been published to support use of the device in the perioperative setting as a component of goal-directed therapy.[39] In the appropriate setting, device insertion is rapid and data can be derived that are clinically useful within seconds.

Other Devices

Noninvasive cardiac output (NiCO, Novametrix, Connecticut, USA), a device that uses partial rebreathing of CO_2 to derive cardiac output using the Fick principle in mechanically ventilated patients, provides data on both respiratory mechanics and cardiac output. However, the device has not found widespread use in intensive care.

Pulse dye densitometry (Nihon, Kohden, Japan) is a technique that uses transpulmonary dye dilution and transcutaneous signal detection to measure cardiac output. The dye is injected intravenously and, although the system is relatively noninvasive, data to date are limited; the approach cannot be currently recommended.

Thoracic electrical bioimpedance is a noninvasive technique that relies on the electrical conductivity of the chest to measure cardiac output. Each cardiac contraction causes a change in transthoracic impedance that is in direct proportion to the additional volume of blood ejected (SV) and its velocity.[40] By placing multiple current-transmitting and voltage-sensing electrodes on the chest, SV can be calculated based on dynamic changes in chest impedance from baseline. The technique has not been shown to be sufficiently accurate in patients in an ICU, in large part due to electrical interference

from other equipment and body motion. Inaccuracy also results from variations in electrode placement and conductivity, operator performance, patient body habitus, and variability in electrode conductivity of skin among patients.[41]

Bioreactance, using the NICOM device (Cheetah Medical, Portland, OR), is a related methodology that has overcome many of the limitations of bioimpedance by processing the data differently. This technique measures the phase shift in voltage across the thorax. The methodology has several advantages over the others, including its noninvasive basis, lack of need for sedation or mechanical ventilation, and applicability in the setting of cardiac arrhythmias; hence, the technique is a promising one for the ICU. Studies performed in the OR, ICU, and ED have shown the technique to be accurate for measuring cardiac output and volume responsiveness, although it cannot be used in the OR while doing electrocautery.[42] Confirmatory studies, as well as outcome studies, are needed.

Echocardiography in the ICU Echocardiography in critically ill patients expands the capabilities of intensivists to more accurately and rapidly diagnose hemodynamic instability. Although expertise in echocardiography requires significant training, commitment, and experience, even basic knowledge may provide life-saving bedside diagnoses in certain conditions, such as profound hypovolemia, systolic heart failure, right heart syndromes, or pericardial tamponade.[43]

Echocardiography plays a key role in the assessment of left and right ventricular function, chamber size, and valvular dysfunction. It may be helpful in preload assessment when intravascular volume determination is difficult. Echocardiography may also be helpful in distinguishing intracardiac from intrapulmonary shunt and for diagnosing cardiac tamponade and aortic dissection.

Transthoracic Versus Transesophageal Echocardiography For the majority of critically ill patients who are hemodynamically unstable, transthoracic echocardiography (TTE) is safe, reliable, and rapidly available.[44] Image quality, due to poor or limited acoustic windows, may be an issue, but new technology, harmonic imaging, and new echo-contrast products, have significantly improved echo signal acquisition.[45] Transesophageal echocardiography (TEE) is used when views on TTE are inadequate or when clear views of the left atrium and aorta are required—such as evaluation for intra-atrial thrombus (prior to cardioversion), aortic dissection, or evaluation of prosthetic valves for evidence of endocarditis. TEE is relatively easy to perform in the ICU, as patients are usually intubated and often sedated.[46] The presence of esophageal varices, recent esophageal or gastric surgery, or an unstable cervical spine are contraindications to TEE.

Uses of Echocardiography in the ICU Application of echocardiography to the ICU setting encompasses a broad array of clinical issues, the most important of which are highlighted below.

Assessment of Ventricular Function Left ventricle (LV) dysfunction in critically ill patients is common and may be caused by ischemia, sepsis, or hyperadrenergic states (i.e., "neurogenic shock"). When the LV becomes dysfunctional, its diameter progressively increases, as does the diastolic volume-to-stroke volume ratio. As the volume of end-diastolic blood that is ejected per cycle is reduced, the "ejection fraction (EF)," expressed as a percentage, falls. EF can be reliably measured by echocardiography. MAP may appear normal despite a severe reduction in ventricular function, which may be impaired further by the use of vasopressors used to restore MAP in septic shock. The size of the ventricle is measured using either M-mode or two-dimensional (2D) techniques. Echocardiography provides an accurate description of global ventricular function and may reveal regional wall motion abnormalities, which are usually associated with myocardial ischemia.

Right ventricle (RV) dysfunction is also very common in critically ill patients. Pulmonary embolism (PE) and ARDS are main causes[47]; however, excessive mean airway pressure, fat embolism, and elevated pulmonary vascular resistance also cause increase RV afterload and RV strain. In patients presenting in shock, identifying this pathophysiology early is very important. Unlike other shock states in which excessive volume resuscitation may result in volume overload and pulmonary edema, neither of which may be life-threatening, inappropriate fluid administration in right heart failure may worsen shock and potentially lead to cardiovascular collapse. This relates directly to ventricular interdependence, wherein RV distension causes a bowing of the interventricular septum into the LV, resulting in LV systolic and diastolic dysfunction. Additional fluid boluses only exacerbate the condition; expeditious volume removal can be life-saving. These pathophysiological circumstances are relatively easy to diagnose with echocardiography and very difficult to diagnose using hemodynamic monitors. The integral parts of complete evaluation of the RV include 2D-echocardiography evaluation of RV size, shape, kinetics of the septum and RV free wall, along with assessment of severity of TR by color Doppler.

RV size is generally compared to LV size. In the four-chamber view, the ratio of RV to LV end-diastolic area is measured. A diastolic ventricular ratio >0.6 suggests moderate dilation and a ratio >1.0 severe dilatation.[48]

Evaluation of Refractory Hypoxemia and Right-to-Left Shunt Commonly seen are patients with hypoxemia despite a clear CXR, or who have pulmonary edema who fail to respond to increasing FI_{O_2} or increases in airway pressure, raising the possibility of a right-to-left shunt. Notably, the incidence of patent foramen ovale is about 30%.

In the setting of right ventricle dysfunction, RA pressure may exceed left atrial pressure, leading to opening of the foramen ovale and significant intracardiac shunt. This can be detected by intravenous injection of agitated saline as a contrast medium during echocardiography. After the injection through a peripheral or central vein, the appearance of microbubbles in the left atrium within three cardiac cycles is diagnostic of a right-to-left shunt. If microbubbles appear in the left atrium after six cardiac cycles, an intrapulmonary right-to-left shunt is suggested, for example, pulmonary AVM or hepatopulmonary syndrome.

Assessment of Cardiac Output (CO) Echocardiography may provide a relatively reliable measure of SV and, hence, CO.[49] The most common technique for measuring CO using echocardiography is Doppler-derived instantaneous blood flow measurement through a conduit (LV outflow tract or pulmonic or mitral valve). SV is equal to the product of cross-sectional area (CSA) of the conduit, determined by 2D echo, and the integral of instantaneous blood flow or velocity–time integral (VTI) through the conduit:

$$\text{CSA} = \text{diameter of conduit (D)}^2 \times (\pi/4)$$
$$\text{SV} = \text{CSA} \times \text{VTI}$$
$$\text{SV} \times \text{HR} = \text{CO}$$
$$\text{CO} = \text{CSA} \times \text{VTI} \times \text{HR}$$

Evaluation of Volume Status Echocardiography may be helpful in estimating volume status or fluid responsiveness. If there is inadequate preload, the left ventricle may appear to collapse during systole ("obliteration"). Echo may also help demonstrate whether inadequate LV filling results from RV dysfunction. Conversely, the finding of acute or chronic ventricular dilatation, defined by LV end-diastolic diameter, does not rule out volume responsiveness.[50] Thus, there are two other echocardiographic techniques that have been used to evaluate fluid responsiveness in mechanically ventilated patients: The *collapsibility index* of the SVC, and respiratory variation in inferior vena cava diameter (i.e., the *distensibility index*).[51–53] Measurement of IVC diameter can be challenging in obese patients,

and its utility is limited in the setting of intra-abdominal hypertension. Accurate SVC measurements require a TEE. In addition neither measurement can be performed continuously.

RESPIRATORY MONITORING

A variety of methods may be employed in monitoring ventilatory and gas exchange functions of the lung, respiratory mechanics, and respiratory muscle strength. Each is described below.

METHODS FOR MONITORING RESPIRATORY FUNCTION

A number of respiratory parameters are routinely monitored in patients with ARF and are discussed subsequently.

Oxygenation

In the ICU, oxygenation is generally monitored using pulse oximetry, arterial blood gas analysis, and, occasionally, transcutaneous methods.

Pulse Oximetry Pulse oximeters are universally deployed in the monitoring of perioperative and critically ill patients. Unique as monitoring devices, they provide useful data regarding oxyhemoglobin saturation (Sp_{O_2}), heart rate, pulse volume, and tissue perfusion.

Pulse oximeters use the spectrophotometric characteristics of pulsatile arterial blood to determine oxygen saturation and heart rate. Oxygenated blood absorbs light at 660 nm (red light), while deoxygenated blood absorbs light preferentially at 940 nm (infrared light). The oximeter consists of two light-emitting diodes (wavelengths, 600 nm and 940 nm) and two light-collecting sensors that measure the amount of red and infrared light emerging from tissues traversed by the light rays. The relative light absorption by oxyhemoglobin and deoxyhemoglobin is analyzed by the device and an oxygen saturation is calculated. The sensing function of the device is directed at pulsatile arterial blood, while local "noise" arising from the tissues is ignored. The result is a continuous qualitative measurement of oxyhemoglobin saturation.

The use of pulse oximetry has not been shown to improve clinical outcomes, but epidemiological data have demonstrated a significant reduction in anesthesia-related morbidity. Although the technique accurately predicts arterial oxygen tension, the relationship between Pa_{O_2} and Sp_{O_2} is nonlinear, as dictated by the oxyhemoglobin dissociation curve. Accuracy falls off substantially at low-oxygen tensions, and saturation readings of less than 80% cannot be used reliably to guide oxygen therapy.

A new generation of rapid oximeters has promised more accurate breath-to-breath analysis of oxygenation and the potential for using the pulse waveform to measure PPV. To date, no positive outcome data have been published.[54]

The use of pulse oximeters is limited by a number of factors. The devices are designed to measure levels of oxygenated and deoxygenated hemoglobin, but no provision is made for measurement error in the presence of dyshemoglobinemias, including carboxyhemoglobinemia and methemoglobinemia. Since carboxyhemoglobin absorbs red light, conventional oximeters cannot distinguish oxy- from carboxyhemoglobin. In clinical situations in which carbon monoxide poisoning is suspected, co-oximetry is essential. Co-oximeters measure reduced hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin.

An additional source of error in using oximeters is abnormal patient movement (e.g., due to agitation). Low blood flow, hypotension, vasoconstriction, or hypothermia reduce pulsatility of capillary blood, resulting in underreading or no reading of oxygen saturation. Conversely, increased venous pulsation, such as occurs with TR, may result in an erroneously low reading by the device. Finally, oximetry-determined saturation is inaccurate on the steep part of the oxyhemoglobin dissociation curve. While the *trend* between directly measured arterial saturation and Sp_{O_2} appears accurate, the correlation between the two is not; a drop in Sp_{O_2} below 90% must be considered a potentially significant clinical event.

Arterial Blood Gases Blood gas analyzers have been available for 45 years and provide accurate measurement of Pa_{O_2}, Pa_{CO_2}, and pH. From these primary determinations, a number of parameters are calculated, including serum bicarbonate, base deficit or base excess, and oxyhemoglobin saturation.

Through application of the alveolar gas equation (see Chapters 14 and 33), arterial blood-gas analysis is used commonly in calculating the alveolar–arterial oxygen gradient, a number that reflects the severity of ventilation–perfusion abnormalities. A significant limitation of the alveolar–arterial oxygen gradient is that it varies directly with FI_{O_2}; consequently, changes in the value may not reflect changes in the underlying disease process. An alternative calculation – the ratio of Pa_{O_2} to FI_{O_2}, ("PF ratio"), which does not vary with FI_{O_2} – has been used as a measure permitting comparisons of gas exchange at differing levels of FI_{O_2}.

The PF ratio has been incorporated into consensus definitions of ARDS. A PF ratio ≤200 defines ARDS.[55] Neither the alveolar–arterial oxygen gradient nor the PF ratio takes into account differences in mean airway pressure. Although comparisons using the PF ratio would be more accurate if arterial blood was sampled uniformly at end expiration and in the absence of PEEP, clinical constraints may preclude such sampling conditions.

Ventilation

Clinical assessment of CO_2 metabolism is usually considered with regard to the amount of gas that is dissolved in plasma (Pa_{CO_2}), the amount present in the exhaled tidal volume, and the total extracellular content (total CO_2 or bicarbonate concentration). In the setting of respiratory failure, these measurements provide information on adequacy of ventilation, percentage of physiological dead space, acid–base balance, and nutritional status.

In progressive chronic respiratory failure, as the ability to eliminate CO_2 declines, total body CO_2 stores (bicarbonate) increase. The ratio of total CO_2 to bicarbonate concentration provides an indication of the acuity of the respiratory failure (Table 147-2).

Changes in Pa_{CO_2} may also be related to changes in base deficit or excess[56]:

$$SBEc = (HCO_3^- - 24.4) + ([8.3 \times \text{albumin g/dL} \times 0.15] + [0.29 \times PO_4^{2-}\ \text{mg/dL} \times 0.32]) \times [\text{pH} - 7.4])$$

where SBEc = standardized base excess corrected for weak acids (albumin and phosphate)

Assessment of CO_2 elimination forms the basis of calculating the ratio of dead space to tidal volume—a useful physiological construct in gauging the severity of underlying lung disease in respiratory failure. Through application of the modified Bohr equation (see Chapter 14), the ratio of dead space to tidal volume (V_D/V_T) is calculated in Equation 3 as follows:

$$V_D/V_T = (Pa_{CO_2} - PE_{CO_2})/Pa_{CO_2} \quad (3)$$

Where PE_{CO_2} is mean expired CO_2. PE_{CO_2} can be measured using a metabolic monitor that collects expired gas over 5 minutes. Alternatively, main stream or side stream capnometry can be used to measure PE_{CO_2}.

TABLE 147-2 Changes in Pa_{CO_2} and $[HCO_3^-]$ in Response to Acute and Chronic Acid–Base Disturbances

Disturbance	$[HCO_3^-]$ versus Pa_{CO_2}
Acute respiratory acidosis	$\Delta HCO3^- = 0.2\ \Delta\ Pa_{CO_2}$
Chronic respiratory acidosis	$\Delta HCO3^- = 0.5\ \Delta\ Pa_{CO_2}$

$[HCO_3^-]$, concentration of bicarbonate ion; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Δ, change in value.

In the normal lung, alveolar P_{CO_2} is equivalent to Pa_{CO_2} and can be estimated by sampling expired end-tidal gas. However, in the presence of significant physiological dead space (as in ARF), end-tidal CO_2 ($P_{ET}CO_2$) grossly underestimates Pa_{CO_2}. However, $P_{ET}CO_2$ remains useful in monitoring the adequacy of ventilation, particularly in "spontaneously breathing patients" who are receiving conscious sedation. There is renewed interest in using $P_{ET}CO_2$ as a measure of the adequacy of the circulation during CPR. In addition, recent data suggest that $P_{ET}CO_2$ can be used to assess fluid responsiveness, as indicated by an increase in $P_{ET}CO_2$ following a fluid bolus or straight leg raise.[57]

Endotracheal Tube Placement

For the intubated patient it is important to monitor the position of the ETT. An extremely common complication of intubation is misplacement of the ETT, with passage into the right main bronchus. Ideally, the ETT tip should be located between 2 and 5 cm above the carina. In the case of a tracheostomy, the tube tip should be located about halfway between the tracheotomy stoma and carina.

ETT placement may be confirmed in several ways: (1) By assessing for the presence of bilateral breath sounds during breath delivery, (2) by palpation of the ETT cuff in the jugular notch, (3) using chest radiography, (4) using fiberoptic bronchoscopy, or (5) determining the presence of $P_{ET}CO_2$ using either capnometry or capnography.

The pressure within the ETT cuff should also be measured regularly. The cuff is inflated to create a seal between the side wall of the ETT and the tracheal wall. Since capillary perfusion pressure of the tracheal mucosa is approximately 25 cm H_2O, cuff pressure should be kept below this level to prevent mucosal ischemia, which may lead to ulceration, inflammation, and, if severe, tracheal dilatation. In addition, the injured tracheal segment may develop fibrosis and, ultimately, stenosis. On the other hand, evidence exists that low cuff pressures may increase the risk of pneumonia, presumably by promoting microaspiration. Thus, the current recommendation for optimal tracheal cuff pressure is 20 to 25 cm H_2O.[58]

Following intubation and ETT positioning, the tube cuff should be slowly and progressively inflated just to the point of loss of gas leak occurring with ventilation—the so-called "minimal occluding pressure" technique (some experts advocate use of the "minimal leak" technique). To measure cuff pressure, an aneroid manometer is connected to the cuff's pilot tube (the tube from which the balloon is inflated). If excessive cuff pressure is required to maintain an adequate tracheal seal, the ETT is likely too narrow for the patient's trachea. If cuff pressure increases over time, tracheomalacia should be suspected and the tube changed to a longer one or one with a foam cuff, to alleviate the pressure on the malacic segment.

The presence of a cuff leak may be problematic, particularly in patients who are critically ill. Signs of leak include an audible noise during inspiration, audible patient phonation, frothy mouth secretions with each breath, a difference between set and exhaled tidal volumes, inadequate ventilatory volumes, hypoxemia, and the presence of a thrill over the trachea. Cuff leaks may be caused by rupture or herniation of the cuff, proximal displacement of the ETT, pilot tube valve malfunction, or inadvertent cuff deflation.[59]

■ RESPIRATORY SYSTEM MECHANICS

Assessment of respiratory system mechanics is useful in differentiating the etiology of ARF (e.g., restrictive vs. obstructive disease or upper vs. lower airway obstruction), troubleshooting the cause of new episodes of clinical instability, assessing the effectiveness of therapeutic interventions (e.g., use of bronchodilators or application of PEEP), or minimizing the risk of ventilator-induced lung injury. These measurements are most reliable when patients are being ventilated passively, which is now much less common, as current best practice has shifted to providing the least sedation necessary for comfort and ventilator synchrony. Thus, in addition to their routine and as-needed measurement, mechanics should always be assessed immediately following intubation, while patients are unconscious or paralyzed, to help clarify the underlying initial pathophysiology. If subsequent measurements are thwarted by patient efforts, ventilator adjustments to minimize ventilator drive should be attempted. In addition, in extreme cases in which diagnosis is essential, transient high-dose sedation and even paralysis may be necessary.

Airway Pressure

Airway pressure is an important variable monitored routinely during mechanical ventilation. Respiratory pressures are usually referenced to atmospheric pressure ("single-ended" pressures). Electromechanical transducers (or aneroid manometers), that convert pressure to electrical current, may be located in the patient's ventilator circuit or esophagus. The most common site of pressure transduction is the wye connector (the connector that joins the inspiratory and expiratory limbs of the ventilator circuit), although the distal ETT can also be used. Pressure measured within the ventilator or ventilator circuit is referred to as "airway pressure," P_{AW} (or, more correctly, airway opening pressure, P_{AO}), while that measured at the tip of the ETT is referred to as "tracheal pressure," P_{TR}. Pressure measured within the esophagus is referred to as "esophageal pressure," P_{ES}.

Five different pressure measurements are commonly made during the respiratory cycle: (1) Peak airway pressure (P_{PEAK}), (2) plateau pressure (P_{PLAT}), (3) mean airway pressure (P_{MEAN}), (4) PEEP, and (5) auto-PEEP (also called intrinsic PEEP). Measurement of tracheal pressure at the tip of the distal ETT provides an assessment of pressure in the native airway, as the effect of flow through the ETT is eliminated. Esophageal pressure provides an estimate of pleural pressure. Although not used routinely in clinical practice, esophageal pressure can be used to estimate transpulmonary pressure, which is a more accurate measure of alveolar distending pressure than is plateau pressure.

Accurate measurement of airway resistance requires that airway pressures be determined using constant flow conditions (i.e., a square flow–wave profile) (Fig. 147-2). Most modern ventilators make the flow–wave profile adjustment automatically when the "mechanics function" of the device is selected. In addition, since airway pressures are altered by respiratory muscle contraction, patients must be fully relaxed and exert minimal breathing effort. These conditions may be accomplished by using ventilator settings designed to fully support the patient (e.g., by providing a level of ventilatory support that

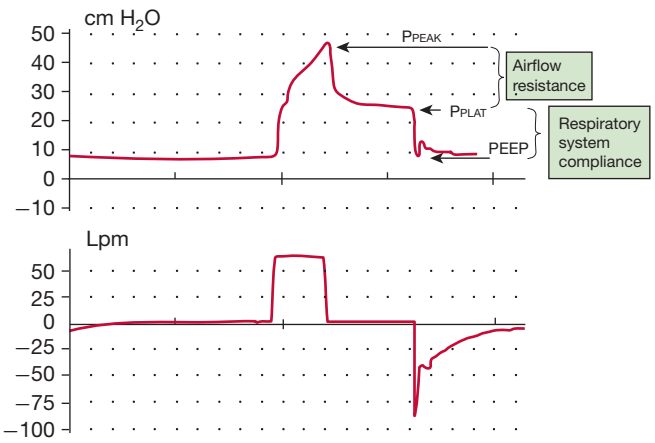

Figure 147-2 Inspiratory hold maneuver during constant flow in a volume-controlled breath. Note the significant difference between the patient's peak airway pressure (48 cm H_2O) and plateau pressure (26 cm H_2O), indicative of increased airway resistance.

exceeds patient demand, or administration of sedation). For quality control, ventilator waveforms should be assessed during the mechanics maneuver to ensure the conditions have been met.

P_{PEAK} represents the total pressure the ventilator must generate to overcome the impedance of the respiratory system, including airflow resistance, elastic load (lung and chest wall distention), and any threshold load due to dynamic hyperinflation (DHI; from auto-PEEP). When interpreting P_{PEAK}, in addition to impedance, several other factors must be considered, including peak flow rate, waveform profile (square or decelerating), and tidal volume. This is a very important point in clinical practice, since P_{PEAK} may erroneously be considered as the primary determinant of barotrauma. When a high P_{PEAK} is observed (as commonly seen in obstructive lung diseases), an attempt to lower P_{PEAK} by reducing inspiratory flow rate may achieve the opposite effect. The risk of barotrauma may be increased by the resulting increment in plateau pressure that occurs as a consequence of reduced expiratory time and increased auto-PEEP.

P_{PLAT} reflects the pressure within the alveoli at end inhalation and is the most important pressure to monitor in preventing barotrauma. The goal P_{PLAT} is ≤30 mm Hg in all cases of ARF, including those due to obstructive airway disease.[60] P_{PLAT} is measured at end inspiration during a period of zero flow, which is achieved by applying an inspiratory "hold" during volume-controlled ventilation (Fig. 147-5). P_{PLAT} is always lower than P_{PEAK} by an amount equal to the pressure required to drive inspiratory flow through the ventilator circuit, ETT, and airways.

For the patient with a high P_{AW}, clinician can determine rapidly whether the problem is resistive (airway) or elastic (lung or chest wall) in nature by assessing the pressure gradient between P_{PEAK} and P_{PLAT} and between P_{PLAT} and total PEEP (set PEEP plus auto-PEEP) (Fig. 147-2). For instance, if the differential between P_{PEAK} and P_{PLAT} increases, airflow resistance must have increased; potential causes include bronchospasm, a kink in the ETT, and increased airway secretions. In contrast, if the rise in P_{AW} is unaccompanied by an increase in the $P_{PEAK} - P_{PLAT}$ pressure gradient (i.e., both P_{PEAK} and P_{PLAT} increase relative to total PEEP), the elastic load must have increased; causes include loss of lung volume (e.g., right main bronchus intubation; lobar atelectasis; or an alveolar filling process, such as pneumonia or CHF) or a stiffer chest wall apparatus (e.g., pleural effusion or intra-abdominal hypertension).[61]

These routinely measured airway pressures are also used to calculate additional important measures of respiratory mechanics, including airway resistance and respiratory compliance. Dividing the $P_{PEAK} - P_{PLAT}$ pressure gradient by inspiratory flow rate yields *airway resistance*. The normal value depends on the size of the ETT, but it is typically about 5 to 15 cm H_2O/L/s.

Respiratory system compliance, expressed as mL/cm H_2O, is calculated as tidal volume divided by the difference between P_{PLAT} and total PEEP. Failure to consider auto-PEEP in the calculation results in overestimation of compliance. Normal respiratory system compliance is >60 mL/cm H_2O.

Auto-PEEP

Auto-PEEP (also known as "intrinsic" PEEP) refers to the positive pressure within alveoli at end expiration that has not been generated by a ventilator.[62] A form of naturally occurring auto-PEEP may be observed with forced exhalation that occurs during heavy exercise. This is also commonly observed in mechanically ventilated patients (Fig. 147-3) with increased respiratory drive. In this case, lung mechanics may be normal, and expiratory muscle force maintains positive intrathoracic and airway pressures throughout expiration; functional residual capacity (FRC) may be normal or decreased.

In contrast, two other types of auto-PEEP are associated with DHI. In one, auto-PEEP results from a high minute ventilatory requirement, as occurs in ARDS, where insufficient expiratory time

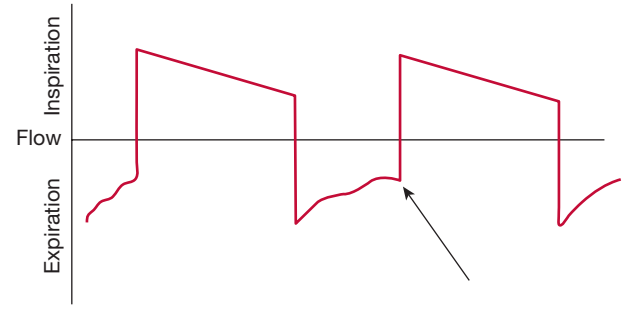

Figure 147-3 The presence of auto-PEEP is identified from the flow waveform. The next breath commences before expiratory flow returns to zero.

promotes incomplete expiration before delivery of the next breath. In the other, more common variety, auto-PEEP results primarily from delayed emptying of alveoli due to expiratory airflow obstruction, as most commonly seen in status asthmaticus or chronic obstructive pulmonary disease (COPD). These two obstructive syndromes have different pathophysiological mechanisms, which impact potential therapeutic interventions. In COPD due to emphysema, DHI results from flow limitation, which is not generally a feature of asthma or other obstructive states.

The development of auto-PEEP is determined by three factors: Tidal volume, expiratory time, and the respiratory system expiratory time constant (the product of resistance and compliance). Auto-PEEP poses significant problems in pressure-targeted mechanical ventilation, where the additional PEEP reduces ventilator-driving pressure, and consequently, tidal volume. In contrast, in volume-targeted ventilation, auto-PEEP causes P_{AW} and P_{PLAT} to increase, which, in turn, increase end-inspiratory lung volumes and alveolar "stretch."

In a mechanically ventilated patient, auto-PEEP is most easily identified by examining the expiratory flow waveform to see if flow fails to return to zero before initiation of the next breath (Fig. 147-3). It is important, however, to first rule out active expiratory effort as the cause (no DHI) as that is treated differently from the other causes of auto-PEEP. Visual inspection or palpation of the abdominal muscles is usually diagnostic. Quantification of the magnitude of auto-PEEP is achieved by implementing an "expiratory hold" maneuver, during which equilibration of pressure is achieved throughout the ventilator circuit (Fig. 147-4). A mechanically

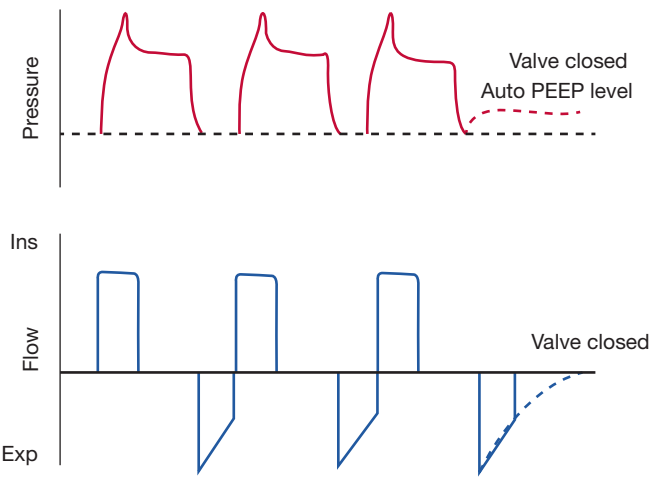

Figure 147-4 Expiratory hold technique to quantify auto-PEEP. The expiratory valve is closed during an expiratory "hold" at the end of a set expiratory time. When flow equals zero, airway pressure rises to the auto-PEEP level.

ventilated patient who is generating spontaneous breaths presents a challenge for measurement of auto-PEEP, as airway occlusion usually incites increased respiratory drive. Under these circumstances, heavy sedation and/or paralysis may be required to obtain accurate recordings.

Esophageal Pressure

Measurement of respiratory system compliance includes the mechanical properties of the lung *and* chest wall. By measuring pleural pressure, the transmural distending pressure of the lung can be calculated. Although regional variation in pleural pressure exists, measurement of lung compliance is based on the *change* in pleural pressure, rather than its absolute value.

Pleural pressure is usually estimated from esophageal pressure, which is recorded using an esophageal catheter. The typical device consists of a latex balloon which is 10 cm long and has several holes. The catheter is inserted into the lower esophagus (usually to a depth of about 40 cm). At this level, artifact from the beating heart is minimized. The adequacy of esophageal balloon positioning is confirmed by having the patient perform inspiratory attempts against an occluded airway. The esophageal pressure changes should be equal (±10%) to airway pressure changes. In the paralyzed patient, external chest compressions are used to create pressure fluctuations. Esophageal pressure has been validated in a small trial of patients with ARDS as a means of determining optimal transpulmonary pressure.[63] Given the complexities involved in employing these catheters, they will likely remain a research tool until more studies show that their use can impact favorably on patient outcomes.

Ventilator Waveforms

Mechanical ventilators all have a spirometer or flow monitor to measure the volume and flow of gas passing through the ventilator circuit with each breath. Data are analyzed by a microprocessor in the ventilator and are graphically represented as waveforms. The most commonly displayed waveforms include pressure, flow, and volume versus time. Plots of flow versus volume (flow–volume loops) and pressure versus volume can be constructed electronically from the measurements, although they do not provide unique information. Monitoring of ventilator waveforms provides useful information about patient–ventilator synchrony, (Fig. 147-5) circuit leaks, patient–ventilator disconnection, development of auto-PEEP, (Fig. 147-3) and airway obstruction.[64]

Pressure versus Time This waveform is usually evaluated first and is most useful in volume-cycled modes, where pressure is the dependent variable. This waveform provides information about whether the patient is initiating breaths (negative deflection prior to inhalation), how much work is required to trigger the ventilator (how negative the trigger deflection is), whether there is sufficient flow during inhalation to meet patient demand (degree of scooping or downward deflection from the usual waveform contour expected during inhalation of a passively breathing patient), and how the prescribed duration of inhalation compares to the patient's neural inspiratory time (airway pressure rise at end exhalation suggests it is too long and "double triggering" suggests it is too short). The inspiratory and expiratory hold maneuvers are evaluated on this waveform to determine resistance and compliance and to quantitate auto-PEEP. Finally, in volume-cycled ventilation, the shape of this curve during inhalation – using a constant flow waveform – may reveal whether the prescribed tidal volume is causing overdistension (concave up), tidal recruitment (concave down), or neither (linear).[65]

Flow versus Time Since flow rate and pattern are set by the clinician in volume-cycled modes, this waveform is most useful in pressure preset modes, for example, pressure control and pressure support, where flow is the dependent variable. In these modes, flow at end inspiration

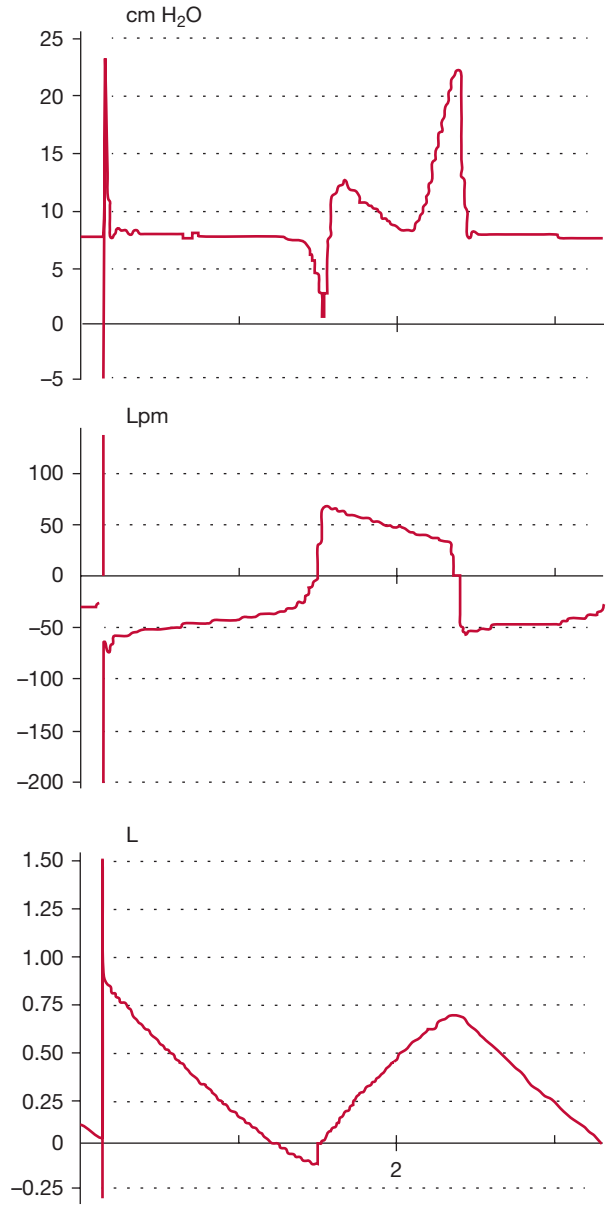

Figure 147-5 Patient-ventilator dyssynchrony during volume-controlled ventilation, secondary to inadequate flow.

helps in determining the most appropriate inspiratory time. In pressure control, where inspiratory time is set, flow should cease immediately prior to exhalation. If not, this can guide subsequent adjustments in inspiratory time. In pressure support, where inspiratory time is variable, flow may fail to fall sufficiently to trigger exhalation, which is typically set at 25% of the peak flow. This is not uncommon in COPD, where inspiratory flow fails to fall sufficiently as alveolar pressure remains low throughout inhalation due to the high lung compliance. To troubleshoot, the expiratory sensitivity setting can be increased to trigger expiration at a much higher end inspiratory flow rate.

For the expiratory limb of the flow versus time waveform, it is important to evaluate whether flow ceases prior to the next inhalation; and if not, auto-PEEP is present. The expiratory hold maneuver will allow quantitation of the auto-PEEP, but it is imperative to first rule out active expiratory effort as the cause.

RESPIRATORY MUSCLE STRENGTH

Respiratory muscle strength may be assessed by measuring maximum inspiratory and expiratory pressures generated against an

occluded airway. This is most easily measured using an aneroid manometer.

Inspiratory strength is measured at FRC, where the length–tension relationship of the inspiratory muscles is optimal. The pressure determined by this maneuver is known as the negative inspiratory force (NIF) or maximal inspiratory pressure (MIP). Clearly, the measurement is dependent on the intensity of the inspiratory effort, which may be suboptimal in uncooperative or unconscious patients. This problem can be circumvented by performing the maneuver off the ventilator, using a one-way valve; the NIF is measured over 10 sequential breaths or 30 seconds. With recurrent efforts over time using the one-way valve, progressively lower lung volumes are reached and the inspiratory drive increases progressively, promoting a maximal effort.[66] Although the utility of the NIF as a predictor of weaning outcome has fallen out of favor, it remains a useful measurement in troubleshooting reasons for ventilator dependence.

Maximal expiratory pressure (MEP) is measured at total lung capacity, where the expiratory muscle length–tension relationship is optimal. Although not routinely employed in clinical practice, MEP may be useful in predicting extubation outcome in selected patient populations.

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CHAPTER 148

Principles of Mechanical Ventilation

Martin J. Tobin

The historical evolution of mechanical ventilation is rich and built on advances in many fields, including endeavors by anatomists, chemists, explorers, physiologists, and clinicians.[1] In 1543, Vesalius demonstrated that positive-pressure ventilation could be used to resuscitate a dying animal. Bellows ventilation was advocated by various lay bodies in the resuscitation of near-drowning victims late in the 18th century. In 1827, however, Leroy demonstrated that overzealous bellows inflation could result in pneumothoraces. Official bodies condemned the technique, and, thus, early in its infancy, positive-pressure ventilation was banned from use. Around this time, negative-pressure ventilators were developed and later popularized as a panacea for a wide variety of ailments.

The modern era of mechanical ventilation was ushered in by Bjorn Ibsen in response to epidemic of bulbar poliomyelitis in Copenhagen in 1952. In the first 3 weeks of the epidemic, 31 patients had been treated with negative-pressure respirators, and 27 had died. Ibsen advised immediate tracheostomy and the use of positive-pressure ventilation with manual positive pressure from a rubber bag, as was then customary in the operating room. Hundreds of medical students worked in relays, delivering bag ventilation during the epidemic; shortly thereafter, machines were introduced to deliver positive-pressure ventilation. Over the following 40 years, ventilators changed enormously in appearance, becoming more sophisticated and versatile and having enhanced capabilities for monitoring and alarming.

OBJECTIVES AND INDICATIONS FOR MECHANICAL VENTILATION

The objectives of mechanical ventilation are listed in Table 148-1.[2] In isolation, hypoxemia of mild-to-moderate severity can be managed by administration of oxygen (O_2) through a face mask. With more severe hypoxemia secondary to shunt or ventilation–perfusion $\dot{V}_A/\dot{Q}$ mismatching, it is difficult to guarantee the delivery of a high fractional inspired oxygen concentration ($F_{I_{O_2}}$) through a face mask. Moreover, these patients are commonly in considerable distress. Thus, intubation helps by ensuring delivery of the required $F_{I_{O_2}}$, and positive-pressure ventilation helps by recruiting collapsed lung units, leading to improved matching of ventilation and perfusion.

TABLE 148-1 Objectives of Mechanical Ventilation

Improve pulmonary gas exchange
Reverse hypoxemia
Relieve acute respiratory acidosis
Relieve respiratory distress
Decrease oxygen cost of breathing
Reverse respiratory muscle fatigue
Alter pressure–volume relationships
Prevent or reverse atelectasis
Improve lung compliance
Prevent further lung injury
Permit lung and airway healing
Avoid complications

Source: Reproduced with permission from Tobin MJ. Mechanical ventilation. N Engl J Med. 1994;330(15):1056–1061.

Acute progressive respiratory acidosis is a major indication for mechanical ventilation, although simpler measures can sometimes reverse the process.[3] For example, among patients with acute severe asthma and hypercapnia, hypercapnia resolves with standard bronchodilator therapy, without the need for mechanical ventilation, in more than 90% of patients.[4] If a patient has severe respiratory depression that is expected to be slow in resolving (e.g., certain drug overdoses), intubation and mechanical ventilation should be instituted without delay.

A substantial proportion of patients who require (and benefit from) mechanical ventilation have relatively normal arterial blood gases but have clinical signs of increased work of breathing: nasal flaring; vigorous activity of the sternomastoid muscles; tracheal tug; recession of the suprasternal, supraclavicular, and intercostal spaces; paradoxical motion of the abdomen; and pulsus paradoxus. This picture of a patient "tiring out" is the most common reason for instituting mechanical ventilation. The increase in work of breathing may be the result of increased airway resistance, increased stiffness of the lungs or chest wall, or the presence of a threshold inspiratory load secondary to auto- or intrinsic positive end-expiratory pressure ($PEEP_i$).

Increased respiratory work increases the O_2 cost of breathing to as much as 50% of total O_2 consumption.[5] By decreasing respiratory work, mechanical ventilation allows precious O_2 stores to be rerouted to other vulnerable tissue beds. To substantially reduce patient effort, the ventilator must cycle in unison with the patient's central respiratory rhythm (Fig. 148-1). For perfect synchronization, the period of mechanical inflation must match the period of neural inspiratory time (the duration of inspiratory effort), and the period of mechanical inactivity must match the neural expiratory time.[6] Work of breathing is increased in patients with atelectasis or acute lung injury because breathing occurs on the low, flat portion of the pressure–volume curve. By shifting tidal ventilation to the steep, compliant portion of the curve, mechanical ventilation can decrease respiratory work.

Commonly listed indications for mechanical ventilation include acute respiratory failure, exacerbation of chronic respiratory failure (e.g., secondary to infection, bronchoconstriction, or heart failure), coma, and neuromuscular disease. Many patients with these same conditions, however, do not require ventilator assistance. Indeed, the most common, and honest, reason that mechanical ventilation is instituted is a tautology: A physician thinks that "the patient looks like he (or she) needs to be placed on the ventilator."[7] Mechanical ventilation is most commonly instituted based on a physician's clinical gestalt, formed through assessing a patient's signs and symptoms, rather than because a patient satisfies a certain set of criteria on a checklist. It is important to ground this decision on solid knowledge of pulmonary pathophysiology.

MODES OF MECHANICAL VENTILATION

The term *mode* refers to the relationship among various breath types (mandatory, assisted, supported, and spontaneous), as well as inspiratory phase variables.

CONTROLLED MECHANICAL VENTILATION

In controlled mechanical ventilation, the ventilator delivers all breaths at a preset rate, and the patient cannot trigger the machine.

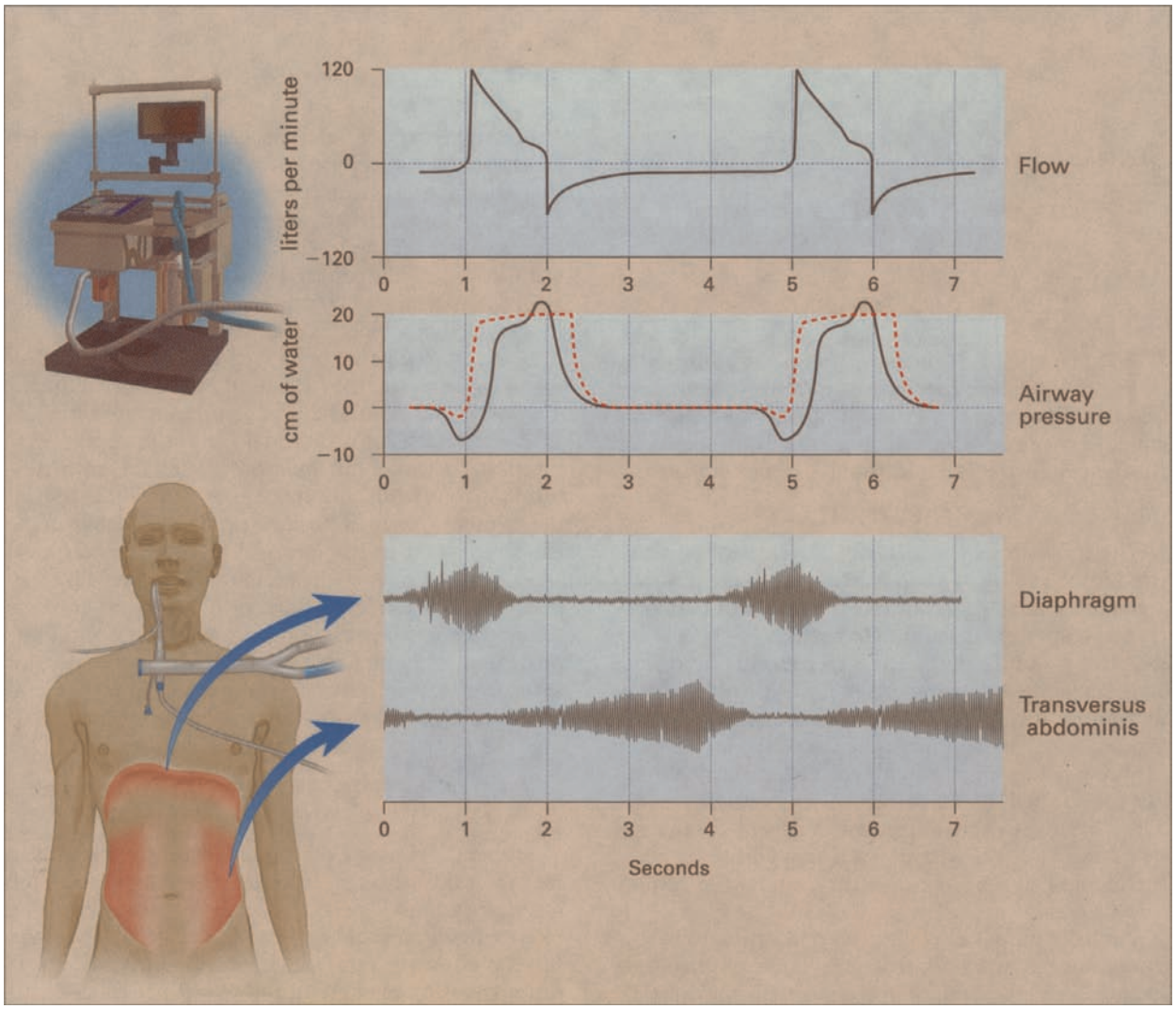

Figure 148-1 Flow, airway pressure, and inspiratory and expiratory muscle activity in a patient with chronic obstructive pulmonary disease who received pressure-support ventilation at an airway pressure of 20 cm H_2O. The electromyograms in the lower portion of the figure show inspiratory muscle activity in the patient's diaphragm and expiratory muscle activity in the transversus abdominis. The patient's increased inspiratory effort caused the airway pressure to fall below the set sensitivity (−2 cm H_2O), and inadequate delivery of flow by the ventilator resulted in a scooped contour on the airway–pressure curve during inspiration. While the ventilator was still pumping gas into the patient, his expiratory muscles were recruited, causing a bump in the airway–pressure curve. That the flow never returned to zero throughout expiration reflected the presence of $PEEP_i$. The broken red line shows airway pressure in another patient, who generated just enough effort to trigger the ventilator and in whom there was adequate delivery of gas by the ventilator. *(Data are from Jubran A, Van de Graaff WB, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1995;152:129–136; Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. Am J Respir Crit Care Med. 1998;158:1471–1478. Reproduced with permission from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344:1986–1996.)*

In the volume-targeted mode, the breaths have a preset volume—the so-called volume-controlled ventilation. When the breaths are pressure limited and time cycled, the mode is termed *pressure-controlled* ventilation. Use of volume-controlled ventilation is largely restricted to patients who are apneic as a result of brain damage, sedation, or paralysis.

■ ASSIST–CONTROL VENTILATION

In the assist–control mode, the ventilator delivers a breath either when triggered by the patient's inspiratory effort (pressure or flow triggered) or, independently, if such an effort does not occur within a preselected time period.[8] All breaths are delivered under positive pressure by the machine, but unlike controlled mechanical ventilation, the patient's triggering effort can exceed the preset rate. If the patient's spontaneous rate drops below the preset back-up rate, controlled ventilation is provided. The breath delivered by the ventilator may have a predetermined volume (volume-cycled form of assist–control ventilation) or a predetermined inflation pressure that is applied for a predetermined inflation time (pressure control form of assist–control ventilation). By design, delivered tidal volume is not influenced by patient effort. The greater the inspiratory effort made by the patient, the lower will be the airway pressure during the volume-cycled form of assist–control ventilation, such that the overall airway pressure on the ventilator monitor bears an inverse relationship to patient-generated pressure.

The ventilator cycles off when the preset tidal volume is reached, and machine inspiratory time may be shorter or longer than the patient's intrinsic (neural) inspiratory time.[6] If the set tidal volume

is reached before the end of neural inspiratory time, the machine cycles off while the patient's inspiratory effort continues. If the patient's inspiratory effort ceases before the set tidal volume is reached, the machine increases pressure to provide continued inspiratory flow. The amount of active work performed by a patient ventilated in the assist–control mode is critically dependent on the trigger sensitivity and inspiratory flow settings. Even when these settings are selected appropriately, patients actively perform about one-third of the work performed by the ventilator during passive conditions.[9]

INTERMITTENT MANDATORY VENTILATION

With intermittent mandatory ventilation (IMV), the patient receives periodic positive-pressure breaths from the ventilator at a preset volume and rate, but the patient can also breathe spontaneously between these mandatory breaths.[10] A problem unforeseen at the time IMV was introduced is the difficulty that patients encounter in trying to adapt to the intermittent nature of ventilator assistance. It had been assumed that the degree of respiratory muscle rest achieved by IMV would be proportional to the number of mandatory breaths delivered. Studies, however, have demonstrated that inspiratory effort is equivalent for spontaneous and assisted breaths during IMV (Fig. 148-2).[11,12] Indeed, the tension-time index for both spontaneous and assisted breaths is above the threshold associated with respiratory muscle fatigue at IMV rates of 14 breaths/min or less.[11] At a moderate level of machine assistance (at which the ventilator accounts for 20% to 50% of total ventilation), electromyographic activity of the diaphragm and sternocleidomastoid muscles is equivalent for assisted and spontaneous breaths.[12] These findings suggest that respiratory center output is preprogrammed and does not adjust to breath-to-breath changes in load, as occurs during IMV. As a result, IMV may contribute to development of respiratory muscle fatigue or prevent its recovery.

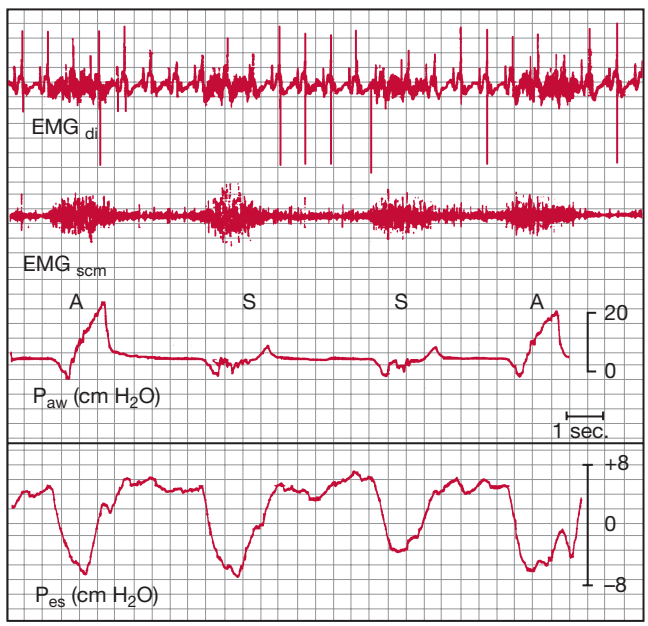

Figure 148-2 Electromyograms of the diaphragm (EMGdi) and sternocleidomastoid muscles (EMGscm) in a patient receiving synchronized intermittent mandatory ventilation. Similar intensity and duration of electrical activity during assisted (A) and spontaneous (S) cycles are demonstrated. P_{aw}, airway pressure; P_{es}, esophageal pressure. *(Reproduced with permission from Imsand C, Feihl F, Perret C, et al. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. Anesthesiology. 1994;80(1):13–22.)*

PRESSURE-SUPPORT VENTILATION

Pressure-support ventilation is patient triggered, like assist–control ventilation and IMV, but it differs in that it is pressure targeted and flow cycled.[13] The physician sets a level of pressure that augments every spontaneous effort, and the patient may alter respiratory frequency, inspiratory time, and tidal volume. Tidal volume is determined by the pressure setting, the patient's effort, and pulmonary mechanics, in contrast to assist–control ventilation and IMV, in which a guaranteed volume is delivered. With volume-targeted ventilation, the inspiratory flow setting is a crucial determinant of patient work. There is no flow setting with pressure-support ventilation, although the initial peak flow determines the speed of pressurization and the initial pressure ramp profile.

Pressure support can be very effective in decreasing the work of inspiration. The degree of inspiratory muscle unloading, however, is variable, with a coefficient of variation of up to 96% among patients.[14] The level of pressure delivered by the ventilator is usually adjusted in accordance with changes in the patient's respiratory frequency. The frequency, however, which signals a satisfactory level of respiratory muscle rest has never been well defined, and recommendations range from 16 to 30 breaths/min.[14]

Cycling to exhalation is triggered by a decrease in inspiratory flow to a preset level, such as 5 L/min or 25% of peak inspiratory flow, depending on the manufacturer's algorithm (Fig. 148-3). The algorithm for "cycling-off" of mechanical inflation causes problems in patients with COPD, because increases in resistance and compliance produce a slow time constant (of the respiratory system). The longer time needed for flow to fall to the threshold value may cause mechanical inflation to persist into neural expiration. In 12 patients with COPD receiving pressure support of 20 cm H_2O, Jubran et al.[14] found that 5 recruited their expiratory muscles while the machine was still inflating the thorax. The patients who recruited their expiratory muscles during mechanical inflation had an average time constant of 0.54 seconds, as compared with an average of 0.38 seconds in patients who did not exhibit expiratory muscle activity.

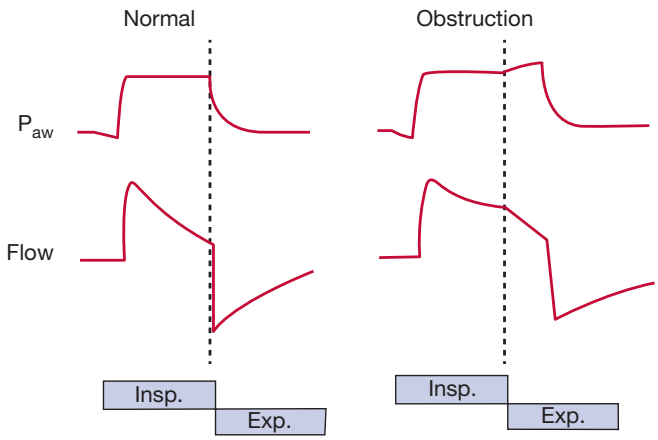

Figure 148-3 Airway pressure (P_{aw}) and inspiratory (Insp) and expiratory (Exp) flow during pressure-support ventilation in patients with normal and obstructed airways. Patient effort triggers the ventilator to deliver a preset pressure, and inspiratory assistance continues until the flow rate falls to 25% of the peak inspiratory flow. In patients with airway obstruction, who have a prolonged time constant, more time is required for flow to decrease to this threshold value, so that neural expiration commences before the termination of mechanical inflation. The resulting activation of the expiratory muscles hastens the fall in flow, but it also results in dyssynchrony between the patient's neuromuscular activity and the mechanical phase of the ventilator—so-called "fighting the ventilator."

The persistence of mechanical inflation into neural expiration is very uncomfortable, as well recognized with use of inverse-ratio ventilation (where, contrary to the normal pattern, inflation lasts longer than exhalation).

■ NEW MODES

New modes of mechanical ventilation are frequently introduced. Each has an acronym, and the jargon is inhibiting to those unfamiliar with it. Yet each new mode involves nothing more than a modification of the manner in which positive pressure is delivered to the airway and of the interplay between mechanical assistance and the patient's respiratory effort.[15] The purpose of a new mode may be to enhance respiratory muscle rest, prevent deconditioning, improve gas exchange, prevent lung damage, enhance coordination between ventilator assistance and patient respiratory effort, and foster lung healing; the priority given to each goal varies.

VENTILATOR SETTINGS

Ventilator settings are based on the patient's size and clinical condition. Determination of the settings is a dynamic process, based on a patient's physiologic response, rather than on a fixed set of numbers.[16] The settings require repeated readjustment over the period of ventilator dependency. Such an iterative process requires careful respiratory monitoring.

■ TRIGGERING

Many ventilators employ pressure triggering, whereby a decrease in circuit pressure is required to initiate ventilator assistance. Patients reach the set sensitivity by activating their inspiratory muscles. When the threshold is reached, however, inspiratory neurons do not simply switch off.[6] Consequently, the patient may expend considerable inspiratory effort throughout a machine-cycled inflation. The level of patient effort during this post-trigger phase is closely related to a patient's respiratory motor output at the point of triggering.[17] As such, measures that decrease respiratory drive may enhance respiratory muscle rest during mechanical ventilation.

If respiratory motor output at the point of triggering is important, one might expect that effort during the time of triggering would determine patient effort during the remainder of inspiration. To elucidate this issue, Leung et al.[17] applied graded levels of pressure support in 11 critically ill patients. They achieved a fourfold reduction in overall patient effort. Yet patient effort during the time of triggering did not change. The constancy of effort during the trigger phase was probably secondary to different factors becoming operational as the level of ventilator assistance was varied (Fig. 148-4). Thus, increases in the level of ventilator assistance do not substantially decrease patient effort during the time of triggering.

The display of airway pressure and flow tracings on ventilator screens has increased awareness that inspiratory effort is frequently insufficient to trigger the ventilator.[6,15] At high levels of mechanical assistance, up to one-third of a patient's inspiratory efforts may fail to trigger the machine (Fig. 148-5). The number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance. Surprisingly, unsuccessful triggering is not the result of poor inspiratory effort. In a study of factors contributing to ineffective triggering, effort was noted to be more than one-third greater when the threshold for triggering the ventilator was not reached than when it was.[17] Breaths that do not reach the threshold for triggering the ventilator have higher tidal volumes and shorter expiratory times than do breaths that do trigger the ventilator. Consequently, elastic recoil pressure builds up within the thorax in the form of $PEEP_i$. To trigger the ventilator, the patient's inspiratory effort has to first generate a negative intrathoracic pressure in order to counterbalance the elastic recoil; it then must reach the set sensitivity.

The time at which a patient initiates an expiratory effort (in relation to the cycling of the ventilator) partly determines the success of the ensuing inspiratory effort in triggering the machine. The relationship between the onset of expiratory muscle activity and termination of mechanical inflation by the ventilator has been quantified.[18] At a pressure support of 20 cm H_2O, mechanical inflation continues for a longer time into neural expiration in the

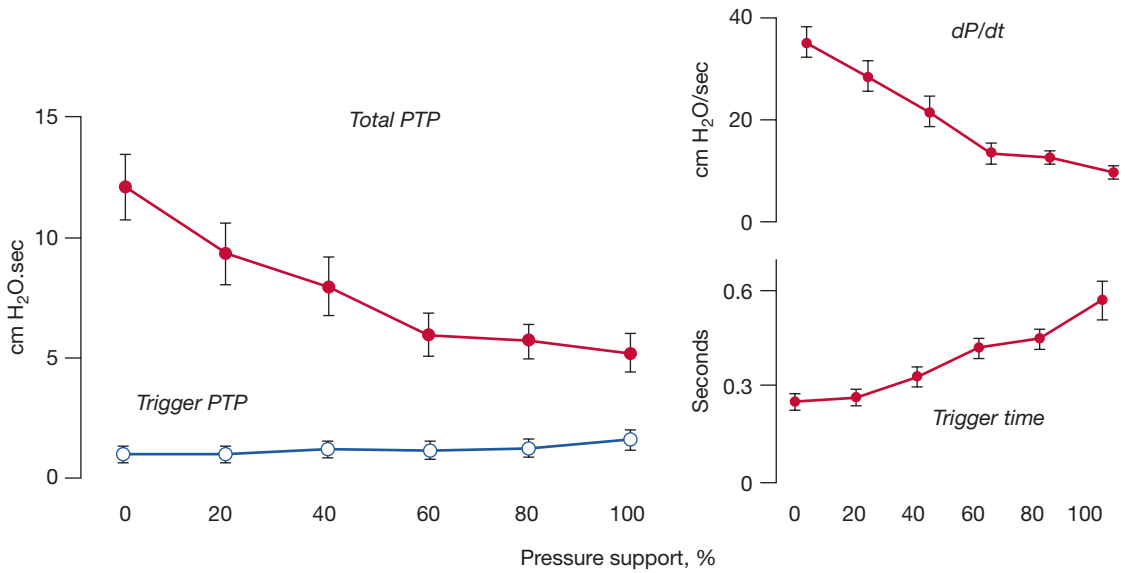

Figure 148-4 Graded increases in pressure support produced a decrease in total pressure–time product (PTP) per breath (*closed symbols*), although PTP during the trigger phase (*open symbols*) did not change (*left panel*). The constancy of PTP during triggering probably resulted from different factors becoming operational at different levels of assistance (*right panel*). At low levels of pressure support, respiratory drive (dP/dt) and $PEEP_i$ were high, but triggering time was short, resulting in a large change in pleural pressure over a brief interval. At high levels of pressure support, dP/dt and $PEEP_i$ were low, but triggering time was long, resulting in a smaller change in pleural pressure over a longer time. *(Data from Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med. 1997;155:1940–1948; Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. Am J Respir Crit Care Med. 2001;163:1059–1063.)*

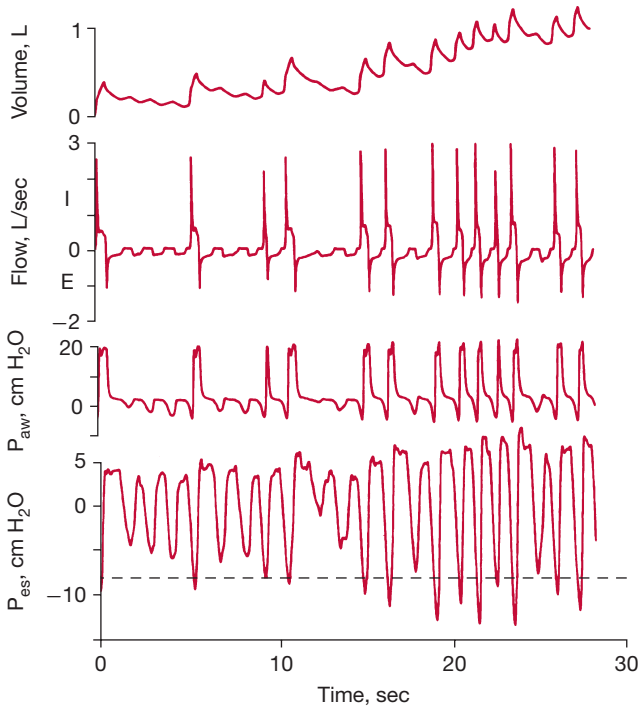

Figure 148-5 Recordings of tidal volume, inspiratory (I) and expiratory (E) flow, airway pressure (P_{aw}), and esophageal pressure (P_{es}) in a patient with COPD receiving pressure-support ventilation. Approximately half of the patient's inspiratory efforts do not succeed in triggering the ventilator. Triggering occurs only when the patient generates P_{es} more negative than −8 cm H_2O (indicated by the interrupted horizontal line), a pressure equal in magnitude to the opposing elastic recoil pressure. Expiratory flow exhibits a biphasic pattern, with momentary braking signaling ineffective inspiratory effort. Thus, monitoring of expiratory flow provides a more accurate measurement of the patient's intrinsic respiratory rate than does the number of machine cycles displayed on the bedside monitor. *(Reproduced with permission from Tobin MJ, Jubran A. Pathophysiology of failure to wean from mechanical ventilation. Schweiz Med Wochenschr. 1994;124:2138–2145.)*

breaths preceding nontriggering attempts. Continuation of mechanical inflation into neural expiration counters expiratory flow, and also decreases the time available for unopposed exhalation. Consequently, elastic recoil increases. In turn, a greater inspiratory effort will be needed to achieve effective triggering. In this way, the time at which a patient commences an expiratory effort (in relation to cycling-off of mechanical inflation) partly determines the success of the ensuing inspiratory effort in triggering the ventilator.

TIDAL VOLUME

In the past, the standard setting for tidal volume was 10 to 15 mL/kg; moreover, every effort was made to ensure that Pa_{CO_2} did not rise above the normal range. This thinking was overturned by a revolutionary study published in 1984 by Darioli and Perret.[19] Analyzing a retrospective dataset collected in patients with status asthmaticus receiving mechanical ventilation, they found that use of lower tidal volumes, with inevitable increase in Pa_{CO_2}, resulted in better survival. A few years later, Hickling et al.[20] applied a similar approach in patients with the acute respiratory distress syndrome (ARDS). A retrospective dataset again revealed better survival with use of permissive hypercapnia. A randomized controlled trial, undertaken by Amato et al.[21] corroborated the Perret–Hickling hypothesis; additional support subsequently came from a randomized trial conducted by the ARDS Network.[22] Three other groups of investigators, however, found that lowering tidal volume tended to increase mortality.[23–25] The only variable that discriminated between the positive and negative studies was the average airway plateau pressure: patients with significantly increased mortality had plateau pressures above 32 cm H_2O. Accordingly, tidal volume should be reduced in patients with ARDS in order to maintain a plateau pressure of no more than 32 cm H_2O.[26,27]

In patients without ARDS, it is usual to use higher tidal volumes, approximately 8 mL/kg, as lower tidal volumes may give rise to considerable dyspnea.[3]

RESPIRATORY RATE

Correct setting of the ventilator rate depends on the mode of ventilation employed.[16] With assist–control ventilation, the ventilator supplies a breath in response to each patient effort. With this mode, physicians commonly pay little attention to the machine rate, which may be set much lower than the patient's spontaneous rate. This gap results in two problems: (1) If the patient has a sudden decrease in respiratory center output, a low machine rate results in serious hypoventilation.[3] (2) A large discrepancy between the patient's spontaneous rate and the machine's back-up rate results in a respiratory cycle with an inverse inspiratory-to-expiratory time (I:E) ratio.

Development of an inverse I:E ratio arises because inspiratory time (T_I) on the machine remains fixed at the initial setting and does not change in response to increases in the patient's spontaneous rate (Fig. 148-6).[16] For example, if the machine rate is initially set at 12 breaths/min (T_{TOT} of 5 seconds) and T_I set at 1.65 seconds (either set directly or indirectly as a consequence of the volume and flow settings), then T_E will be 3.35 seconds. The I:E ratio will be 1:2. If the patient's spontaneous respiratory rate is increased to 25 breaths/min, T_{TOT} will be 2.4 seconds. Because T_I remains fixed at 1.65 seconds, T_E will be 0.75 s, and the I:E ratio will be 2:1. Such inverse-ratio ventilation is very uncomfortable and may lead to increased sedative use, or even to use of neuromuscular blockade, simply because of inappropriate setting of the back-up rate. Based on these considerations, the back-up rate during assist–control ventilation should be set at approximately four breaths less than the patient's spontaneous rate.[2]

With IMV, the ventilator (or mandatory) rate is initially set high and then gradually reduced according to patient tolerance.[10] Unfortunately, titration is often based on data from arterial blood gases, and even a small number of ventilator breaths can result in acceptable values for Pa_{O_2} and Pa_{CO_2} but achieve little or no respiratory muscle rest in patients with increased work of breathing. In

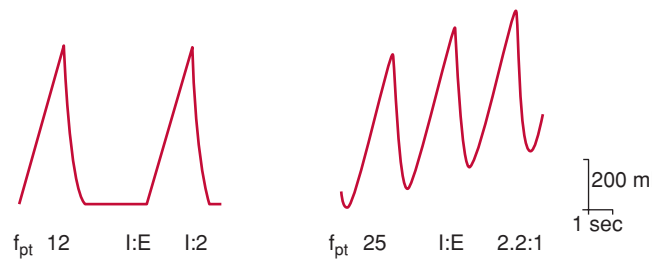

Figure 148-6 Effect of interaction between a patient's respiratory rate and the ventilator back-up rate on inspiratory time—expiratory time ratio (I:E) during assist–control ventilation. Ventilator back-up rate is 12 breaths/min and inspiratory time (T_I) 1.65 seconds. *Left panel.* If the patient's intrinsic respiratory (f_{pt}) rate is also 12 breaths/min, the total respiratory cycle time (T_{TOT}) is 5.0 seconds, the expiratory time (T_E) is 3.35 seconds, and the I:E ratio is 1:2. *Right panel.* If the patient's respiratory rate increases to 25 breaths per minute, the new T_{TOT} is 2.4 seconds, T_E is 0.75 seconds, and I:E is 1:0.45 (or, as more conventionally noted, 2.2:1).

ventilator-dependent patients, work of breathing at IMV rates of 14 breaths/min or less may be sufficient to induce respiratory muscle fatigue.[11,12] With PS ventilation, the ventilator rate is not set.[13]

INSPIRATORY FLOW RATE

Clinicians initially set the inspiratory flow rate at a default value, such as 60 L/min. Many critically ill patients, however, have an elevated respiratory motor output, and the initial flow setting may be insufficient to meet flow demands.[3] As a result, patients will struggle against their own respiratory impedance and that of the ventilator.[9,28] Consequently, work of breathing increases. Clinicians sometimes increase flow in order to shorten the inspiratory time and increase the expiratory time. An increase in flow, however, causes immediate and persistent tachypnea; as a result, expiratory time may be shortened.[29] In a study of healthy subjects, Laghi et al.[30] found that increases in inspiratory flow from 30 L/min to 60 and 90 L/min caused increases in respiratory rate of 20% and 41%, respectively.

One of the main reasons that clinicians increase inspiratory flow is to decrease inspiratory time, in the hope of allowing more time for expiration and, thereby, decreasing $PEEP_i$, especially in patients with COPD. Because increased flow usually leads to an increase in respiratory rate, the expected shortening of expiratory time might actually increase $PEEP_i$.

Laghi et al.[31] investigated this phenomenon in 10 patients with COPD (Fig. 148-7). As with healthy subjects, an increase in flow from 30 to 90 L/min caused respiratory rate to increase from 16 to 21 breaths/min. Despite the increase in rate, $PEEP_i$ fell from 7.0 to 6.4 cm H_2O. The decrease in $PEEP_i$ arose because of an increase in expiratory time (from 2.1 to 2.3 seconds), which allowed more time for lung deflation. Why did expiratory time increase? An increase in inspiratory flow is usually achieved by shortening of mechanical inspiratory time. The shortened inspiratory time, combined with time-constant inhomogeneity of COPD, causes overinflation of some lung units to persist into neural expiration. Continued inflation during neural expiration causes stimulation of the vagus nerve, which prolongs expiratory time.

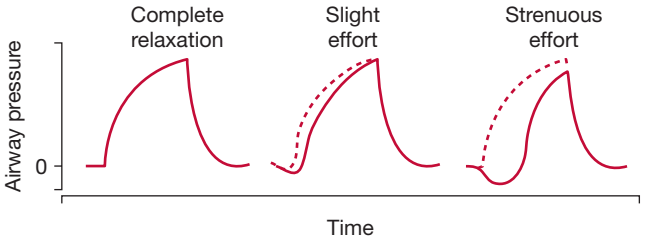

Figure 148-8 Airway-pressure waveforms recorded during assist–control ventilation. The tracings represent changes in airway pressure during inspiration in a completely relaxed patient, and in patients making slight (center tracing) and strenuous efforts (tracing on right) to breathe. The distance between the dashed line (representing controlled ventilation) and the solid line (representing spontaneous breathing) is proportional to the patient's work of breathing. *(Reproduced with permission from Tobin MJ. Mechanical ventilation. N Engl J Med. 1994;330(15):1056–1061.)*

When adjusting the flow rate and trigger sensitivity, examination of the contour of the airway pressure waveform is helpful (Figs. 148-8 and 148-9).[2] Ideally, the waveform should show a smooth rise and convex appearance during inspiration. In contrast, a prolonged negative phase, with excessive scalloping of the tracing, indicates unsatisfactory settings of sensitivity or flow.

FRACTIONAL INSPIRED OXYGEN CONCENTRATION

Correction of hypoxemia and its prevention are major goals in mechanically ventilated patients. Many predictive equations have been published to aid in selecting an appropriate $F_{I_{O_2}}$, but none is

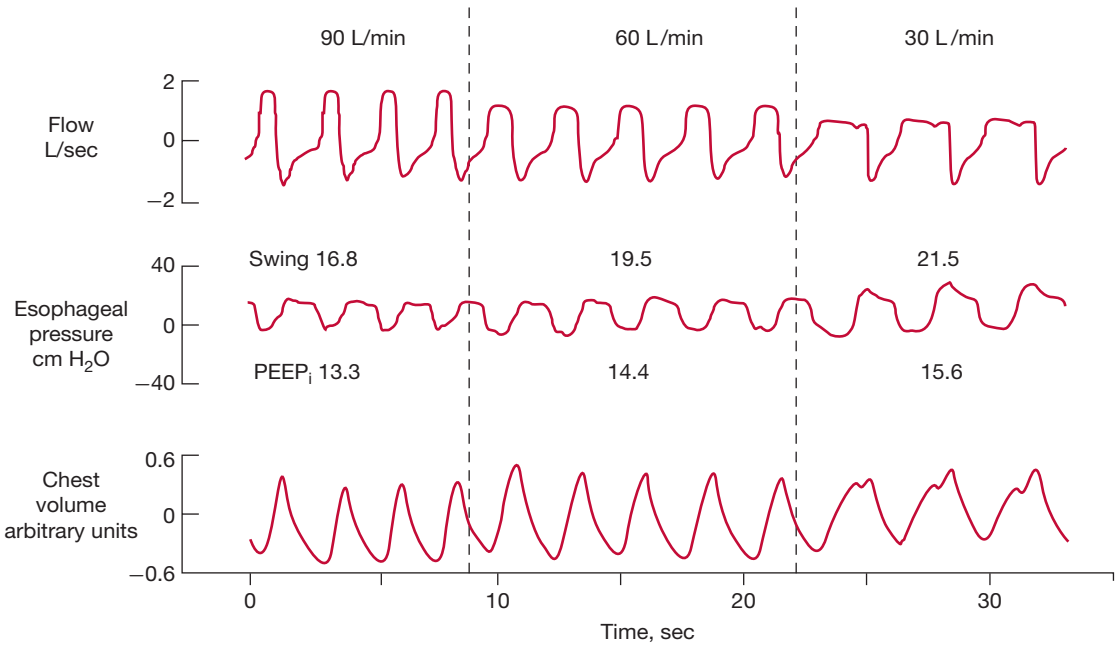

Figure 148-7 Continuous recordings of flow, esophageal pressure (Pes), and the sum of rib cage and abdominal motion, in a patient with chronic obstructive pulmonary disease receiving assist–control ventilation at a constant tidal volume. As flow increased from 30 to 60 and 90 L/min (from right to left), frequency increased (from 18 to 23 and 26 breaths/min, respectively), $PEEP_i$ decreased (from 15.6 to 14.4 and 13.3 cm H_2O, respectively), and end-expiratory lung volume also fell. Increases in flow from 30 L/min to 60 and 90 L/min also led to decreases in the swings in Pes from 21.5 to 19.5 and 16.8 cm H_2O, respectively. *(Reproduced with permission from Laghi F, Segal J, Choe WK, et al. Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(6):1365–1370.)*

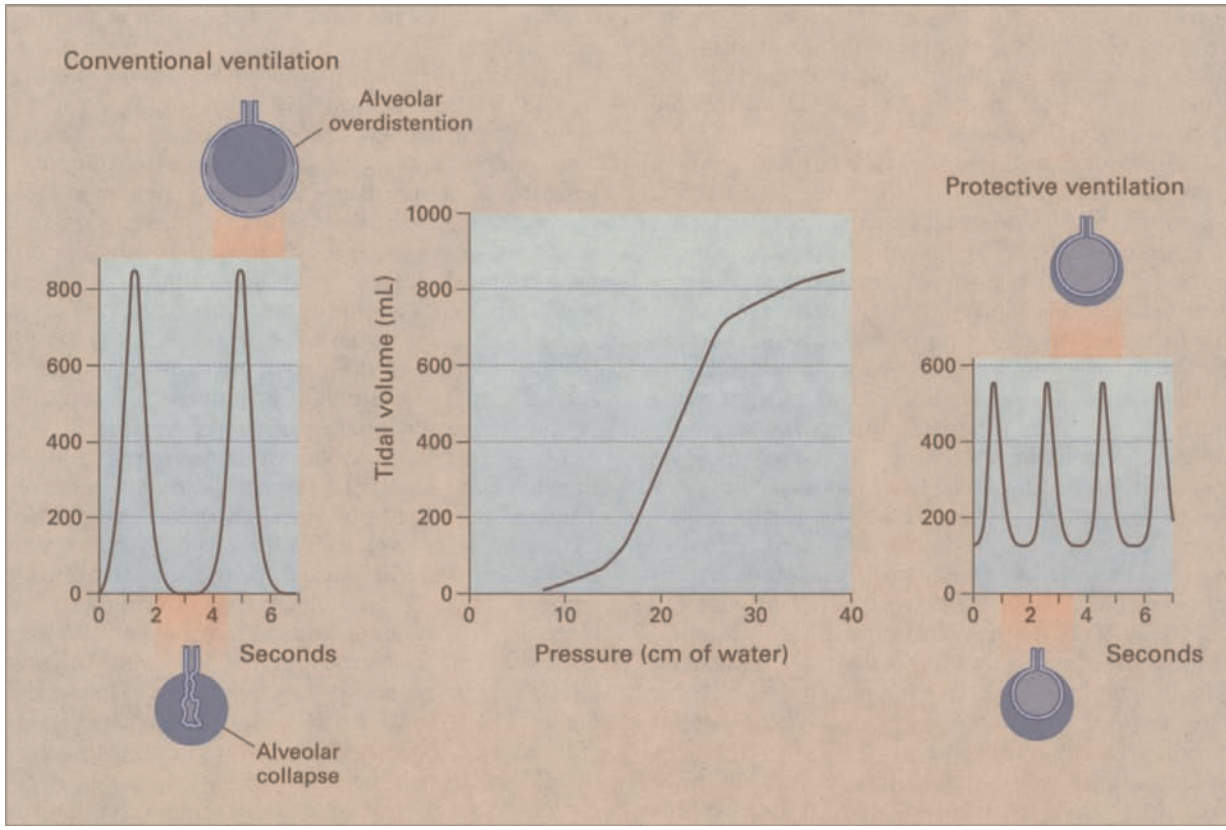

Figure 148-9 Respiratory pressure–volume curve and the effects of traditional versus protective ventilation in a 70-kg patient with acute respiratory distress syndrome. The lower and upper inflection points of the inspiratory pressure–volume curve (center panel) are at 14 and 26 cm H_2O, respectively. With conventional ventilation at a tidal volume of 12 mL/kg and zero end-expiratory pressure (*left panel*), alveoli collapse at the end of expiration. The generation of shear forces during the subsequent mechanical inflation may tear the alveolar lining, and attaining an end-inspiratory volume higher than the upper inflection point causes alveolar overdistention. With protective ventilation at a tidal volume of 6 mL/kg (*right panel*), the end-inspiratory volume remains below the upper inflection point; the addition of PEEP at 2 cm H_2O above the lower inflection point may prevent alveolar collapse at the end of expiration and provide protection against the development of shear forces during mechanical inflation. *(Reproduced with permission from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344(26):1986–1996.)*

sufficiently accurate to substitute for a trial-and-error approach.[32] Initially, $F_{I_{O_2}}$ is set at a high value (often 1.0) to ensure adequate oxygenation. Thereafter, the lowest $F_{I_{O_2}}$ that achieves satisfactory arterial oxygenation should be selected. The usual target is a Pa_{O_2} of 60 mm Hg or an arterial saturation (Sa_{O_2}) of 90%; higher values do not substantially enhance tissue oxygenation. Although it is customary to wait 30 minutes to assess the response to a change in $F_{I_{O_2}}$, the effect is usually well defined within 10 minutes. When using arterial blood samples to assess oxygenation, a target of 90% for Sa_{O_2} is appropriate. If pulse oximetry is employed, a Sp_{O_2} target may result in values for Pa_{O_2} as low as 41 mm Hg. In white patients, a target of 92% for Sp_{O_2} indicates satisfactory oxygenation. In black patients, however, this target may still result in significant hypoxemia.[33]

In experimental animals, hyperoxia produces diffuse alveolar damage, with histologic changes that are indistinguishable from ARDS resulting from any other cause. No diagnostic tests distinguish O_2-induced injury from progression of the underlying disease. Thus, the possibility of O_2 toxicity should be considered in any patient receiving an $F_{I_{O_2}}$ of more than 0.50 to 0.60 for 24 to 48 hours or longer. Healthy human subjects who inhale 100% O_2 develop acute tracheobronchitis, manifested as substernal discomfort, cough, sore throat, nasal congestion, eye and ear discomfort, paresthesias, and fatigue. Symptoms begin within 4 hours; bronchoscopic features of tracheal inflammation are evident after 6 hours.[34] Retrosternal discomfort also occurs with an $F_{I_{O_2}}$ of 0.75, but not with an $F_{I_{O_2}}$ of 0.50. Hyperoxia causes absorption atelectasis in lung units with low $\dot{V}_A/\dot{Q}$ ratios, because the rate of absorption of O_2 from the alveoli into the bloodstream is faster than the rate of replenishment from inspired gas. Such atelectasis results in a small shunt (approximately 3%) in healthy elderly subjects and requires only about 6 minutes to develop.

In the face of potential O_2 toxicity, the only possible strategy is to reduce the $F_{I_{O_2}}$ to the lowest level compatible with adequate systemic oxygenation. Thus, excess O_2 demand should be minimized, and measures to enhance systemic oxygenation optimized. Although excessive O_2 administration should be avoided, there is more to fear from severe hypoxemia than from the potential damage that might result from hyperoxia.

■ POSITIVE END-EXPIRATORY PRESSURE

The beneficial effects of positive end-expiratory pressure (PEEP) include improvement in arterial oxygenation, improvement in lung compliance, alleviation of excessive respiratory work secondary to $PEEP_i$ in patients with airflow limitation, and, possibly, a decrease in lung injury resulting from repeated alveolar collapse and reopening.[15] The principal beneficial effect of PEEP is an increase in Pa_{O_2}, which permits a decrease in $F_{I_{O_2}}$ and a reduction in the risk of O_2 toxicity. The major mechanism for the increase in Pa_{O_2} with PEEP is an increase in end-expiratory lung volume (Table 148-2).

Patients with ARDS develop alveolar instability and collapse (see Chapters 140 and 141). Consequently, functional residual capacity falls below closing volume, and small airways close during tidal

TABLE 148-2 Mechanisms of Increased Pa_{CO_2} with PEEP

Increase in end-expiratory lung volume
Distention of patent lung units
Recruitment of collapsed lung units
Redistribution of fluid within the lung
Decrease in shunt
Increase in end-expiratory lung volume
Decrease in cardiac output

breathing, leading to intrapulmonary shunt and hypoxemia. PEEP increases end-inspiratory lung volume by distending lung units that are already open, preventing collapse of unstable alveoli at end expiration, recruiting collapsed lung units, and redistributing liquid within the lung.[35–37] The decrease in venous admixture with PEEP is proportional to alveolar recruitment. It had been thought that the decrease in venous admixture with PEEP resulted largely from a decrease in cardiac output. This view has been shown to be erroneous.[38]

At one time PEEP was thought to decrease extravascular lung water by "pushing" alveolar fluid back into the circulation. On the contrary, PEEP can actually increase lung water.[39] As alveoli expand with application of PEEP, interstitial pressure in the extra-alveolar space decreases, leading to an increase in transmural pressure across the vessel wall. If intravascular pressures remain the same or increase, the filtration of fluid across the vessel wall increases, causing an increase in pulmonary edema; if PEEP causes a decrease in cardiac output and vascular pressures, lung water does not change. The beneficial action of PEEP in pulmonary edema is produced by redistribution of edema fluid from the alveolar space into the perivascular cuffs. This redistribution of lung water, in association with an increase in end-expiratory lung volume, is the major mechanism underlying the increase in Pa_{O_2} with PEEP.

In patients with ARDS, PEEP is often used for the purpose of recruiting previously nonfunctioning lung tissue (see Chapter 141). Selecting the right level of PEEP for a given patient is difficult, however, because the severity of injury varies throughout the lungs. PEEP can recruit atelectatic areas, but it may also overdistend normally aerated areas.[37]

The addition of PEEP also influences lung mechanics. Patients with acute lung injury commonly have a decreased end-expiratory lung volume and, thus, tidal breathing occurs on the low, flat portion of the pressure–volume curve. By shifting tidal breathing to a more compliant portion of the curve, PEEP may reduce the work of breathing.[40] In patients with an airflow limitation and auto-PEEP who have difficulty triggering the ventilator, the addition of external PEEP (to a level not exceeding the level of auto-PEEP) can help to counteract this problem, because to trigger the ventilator the alveolar pressure needs to be decreased only below the level of external PEEP, rather than below zero.[41,42] In addition to the injury induced by high inflation pressures, mechanical ventilation at a low end-expiratory lung volume aggravates lung injury in laboratory animals, possibly because of shear stresses associated with the repeated closing and opening of alveolar units.[43,44]

Overall, about 30% of patients with acute lung injury either do not benefit from PEEP or experience a fall in Pa_{O_2}.[45–47] With the patient in the supine posture, PEEP generally recruits the regions of the lung closest to the apex and sternum. Conversely, PEEP can increase the amount of nonaerated tissue in the regions close to the spine and diaphragm.[47] Among patients in the early stages of ARDS, those with pulmonary causes, such as pneumonia, are less likely to benefit from PEEP than patients with nonpulmonary causes, such as intra-abdominal sepsis or extrathoracic trauma.[48] This distinction may be related to the type of morphologic involvement: Pulmonary causes of ARDS are characterized by alveolar filling, whereas nonpulmonary causes are characterized by interstitial edema and alveolar collapse. In the later stages of ARDS, remodeling and fibrosis may eliminate this distinction between pulmonary and nonpulmonary causes.

Three randomized trials on the effect of PEEP on survival in patients with ARDS have been undertaken: the ALVEOLI trial, the LOV trial, and the Express trial.[49–51] The results of all three trials revealed no improvement in patient survival. Although the subsequent two trials differed in some details from the ALVEOLI trial, the overall design followed the same general principles. The ALVEOLI investigators employed a complex sliding scale for adjusting PEEP and FI_{O_2}.[49] When patients were receiving an FI_{O_2} of 0.60, the design mandated that patients receive either a PEEP of 10 or 20 cm H_2O, with no other options. At an FI_{O_2} of 0.80, patients were mandated to receive either a PEEP of 14 or 22 cm H_2O, with no other options. Of course, physicians do not set PEEP in this manner; hence, this trial design bears no relationship to everyday clinical practice. The investigators of the LOV trial employed the exact same fatal flaw in their study design.[50] The Express investigators adjusted PEEP to achieve a plateau pressure of 28 cm H_2O—a compromise between achieving recruitment and avoiding overdistention.[51] It is well recognized, however, that the response to PEEP is very variable in ARDS. Some patients develop overdistention with PEEP of 10 cm H_2O, whereas other patients show little aeration despite an airway pressure of 45 cm H_2O.[37] The investigators, however, made no attempt to determine the individual characteristics of patients; instead, every patient was treated the same in each arm of the trial.[51]

Rather than setting PEEP on the basis of airway pressure recordings, Talmor et al.[52] investigated whether the selection of PEEP based on transpulmonary pressure might achieve a better physiologic result. They randomized 61 patients with acute lung injury or ARDS to two study arms. In the intervention arm, transpulmonary pressure was measured with an esophageal catheter and PEEP was adjusted to maintain a transpulmonary pressure between 0 and 10 cm H_2O at end expiration. In the control arm, patients were managed according to the protocol employed in the ALVEOLI trial of the ARDS Network.[49] The primary end point was improvement in oxygenation; after 61 patients were enrolled, the stopping criterion was reached. At 72 hours after study entry, Pa_{O_2}:FI_{O_2} ratio was higher in the esophageal-catheter group than in the control group: 280 + 126 versus 191 + 71. A strong, but not statistically significant, trend toward lower mortality at 28 days was observed in the esophageal-catheter group than in the control group: 5/30 (17%) versus 12/31 (39%). A major reservation with this study is that the strategy employed by Talmor et al. depended on making an estimate of absolute pleural pressure; for this step, the investigators employed a correction factor of 5 cm H_2O in all patients. This correction constitutes a major assumption, and it is not clear whether this will prove a stumbling block when investigators attempt to replicate the results of the study.

BRONCHODILATOR THERAPY

Several obstacles are encountered when inhaled drugs are administered to ventilated patients. As a result, drug deposition to the lower respiratory tract is less than that in ambulatory patients. Determinants of aerosol deposition include the configuration of the endotracheal tube and ventilator circuit, ventilator mode and settings, and patient-related factors.[53]

Nebulizers have been used traditionally for the delivery of bronchodilators, but they have a number of disadvantages.[53] Nebulizer

contamination causes aerosolization of bacteria, and lack of attention to this matter by health-care providers has led to epidemics of nosocomial pneumonia. Tidal volume and inspiratory flow must be adjusted to compensate for nebulizer flow. This factor is inconsequential in most adults, but instances of hypoventilation have occurred in patients who are unable to trigger the ventilator. Another shortcoming of nebulizers is the considerable variation in efficiency of different commercial brands, as well as among various batches of the same brand.

In contrast, metered-dose inhalers (MDIs) are easy to administer, involve less personnel time, and provide reliable dosing. Moreover, when MDIs are used with a collapsible cylindrical spacer, it is not necessary to disconnect the ventilator circuit for each treatment. Thus, risk of ventilator-associated pneumonia is decreased. Using MDIs instead of nebulizers results in substantial cost savings. The combination of an MDI and a chamber device achieves a four- to sixfold greater delivery of aerosol than MDI actuation into a connector attached directly to the endotracheal tube or into an in-line device that lacks a chamber.[53] Aerosol delivery is increased with use of a higher tidal volume and longer fractional inspiratory time (T_I/T_{TOT}). Aerosol delivery is decreased by a high inspiratory flow rate; heating and humidification of inhaled gas reduce aerosol deposition by about 40%. When an aerosol is carried by a low-density gas, such as an 80:20 helium–oxygen mixture, aerosol delivery from an MDI is increased by more than 50%.

A dose–response study of 4, 8, and 16 puffs of albuterol (administered with an MDI and cylindrical spacer) conducted in ventilated patients with COPD (Fig. 148-10) demonstrated a decrease in airway resistance after 4 puffs of albuterol; no additional effects were noted after cumulative doses of 12 and 28 puffs.[54] In another study in ventilated patients with COPD, the bronchodilator effect of a single dose of four puffs of albuterol was sustained for at least 60 minutes. The bronchodilator effect obtained with 4 puffs of albuterol from an MDI was comparable to that obtained with 6 to 12 times the same dose given by a nebulizer.

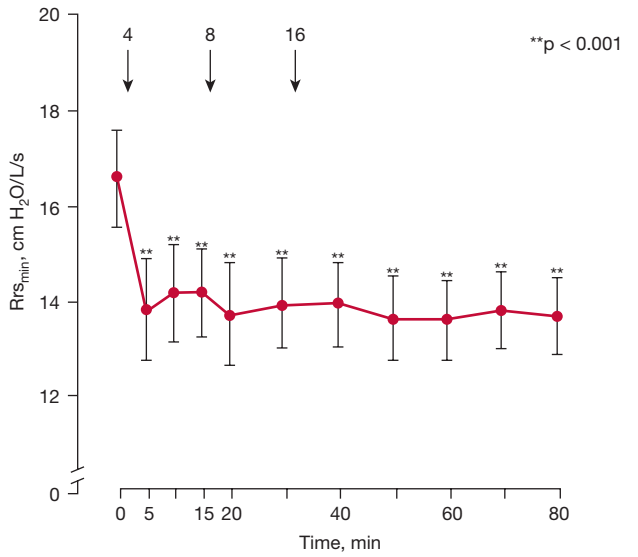

Figure 148-10 Effect of albuterol on minimal inspiratory resistance (Rrs_{min}) in 12 stable mechanically ventilated patients with chronic obstructive pulmonary disease. Significant decreases in resistance occurred within 5 minutes of administration of four puffs of albuterol. The addition of 8 and 16 puffs (cumulative doses of 12 and 28 puffs, respectively) did not achieve a significantly greater effect than that with 4 puffs ($p > 0.05$). Bars represent SE. $^{**}p < 0.001$. *(Modified with permission from Dhand R, Duarte AG, Jubran A, et al. Dose–response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med. 1996;154(2 Pt 1):388–393.)*

TABLE 148-3 Technique for Using Metered-Dose Inhalers in Mechanically Ventilated Patients

1. Assure $V_T > 500$ mL (in adults) during assisted ventilation
2. Aim for an inspiratory time (excluding the inspiratory pause) >0.30 of total breath duration
3. Ensure that the ventilator breath is synchronized with the patient's inspiration
4. Shake the metered-dose inhalers vigorously
5. Place canister in actuator of a cylindrical spacer situated in inspiratory limb of ventilator circuit[a]
6. Actuate metered-dose inhalers to synchronize with precise onset of inspiration by the ventilator[b]
7. Allow a breath hold at end-inspiration for 3–5 s
8. Allow passive exhalation
9. Repeat actuations after 20–30 s until total dose is delivered[c]

[a]With metered-dose inhalers, it is preferable to use a spacer that remains in the ventilator circuit to avoid disconnecting the ventilator circuit for each bronchodilator treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs each treatment and requires disconnecting the ventilator circuit.
[b]In ambulatory patients with metered-dose inhalers placed inside the mouth, actuation is recommended briefly after initiation of inspiratory airflow. In mechanically ventilated patients using a metered-dose inhaler and spacer combination, actuation should be synchronized with onset of inspiration.
[c]The manufacturer recommends repeating the dose after 1 min.
Metered-dose inhalers' actuation within 20–30 s after the previous dose does not compromise drug delivery.
Source: Modified with permission from Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med. 1997;156(1):3–10.

Based on recent research conducted, it is possible to formulate specific steps to achieve maximum bronchodilator effect with use of MDIs in ventilated patients (Table 148-3).[53] Therapy may be given in combination with either controlled or assisted ventilation, provided aerosol administration is synchronized with inspiratory flow. Based on the recommended technique for use of an MDI in ambulatory patients, some authors recommend use of a postinspiratory breath hold; with optimal technique, however, this maneuver does not influence bronchodilator response in ventilated patients. Although humidification of the circuit reduces aerosol deposition, it is advisable not to bypass the humidifier. Even with a humidified circuit, significant bronchodilation can be achieved with as few as four puffs of a bronchodilator aerosol when the MDI technique is carefully executed.

MONITORING AND COMPLICATIONS

Several devices can be used to monitor pulmonary gas exchange, respiratory neuromuscular function, respiratory mechanics, and patient–ventilator interaction. Use of the derived information permits the physician to better tailor ventilator settings to an individual patient's requirements, with the promise of enhancing patient comfort.[55] Monitoring of key variables helps to minimize the risk of iatrogenic complications and alerts the physician to the likelihood of an impending catastrophe, allowing sufficient time for the institution of lifesaving measures. A detailed discussion of techniques used for monitoring of ventilator-supported patients can be found in Chapter 147 and in other textbooks.

Patients receiving mechanical ventilation are at risk for numerous complications, including O_2 toxicity, volutrauma and air leaks,

decreased cardiac output, and endotracheal tube–related issues. These problems are discussed elsewhere in this volume.

WEANING

The term *weaning* literally means a slow, gradual decrease in the amount of ventilator support. The term, however, is used more commonly to refer to all methods of discontinuing mechanical ventilation.[56]

■ CAUSES OF WEANING FAILURE

After discontinuation of mechanical ventilation, up to 25% of patients experience respiratory distress severe enough to necessitate the reinstitution of ventilator support. Our understanding of the basis for weaning failure in patients has advanced considerably in recent years. Among patients who cannot be weaned, disconnection from the ventilator is followed almost immediately by an increase in respiratory frequency and fall in tidal volume, that is, rapid, shallow breathing (Fig. 148-11).[57] As a trial of spontaneous breathing is continued over the next 30 to 60 minutes, respiratory effort increases considerably, reaching more than four times the normal value at the end of this period (Fig. 148-12).[58] The increased effort is caused mainly by worsening respiratory mechanics.[59] Respiratory resistance increases progressively, reaching about seven times the normal value at the end of a failed weaning trial; lung stiffness also increases, reaching five times the normal value; and gas trapping, measured as $PEEP_i$, more than doubles over the course of the trial.[58] Before weaning is started, however, respiratory mechanics in such patients are similar to patients in whom subsequent weaning is successful. Thus, unknown mechanisms associated with the act of spontaneous breathing cause the worsening of respiratory mechanics in patients who are weaning failures.

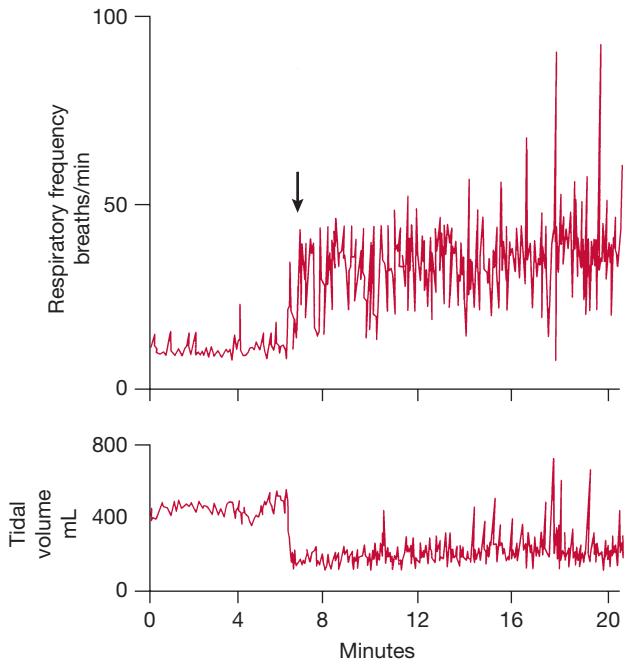

Figure 148-11 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The arrow indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator. *(Reproduced with permission from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis. 1986;134(6):1111–1118.)*

In addition to the increase in respiratory effort, an unsuccessful attempt at spontaneous breathing causes considerable cardiovascular stress. Patients may experience substantial increases in right- and left-ventricular afterload during a trial of spontaneous breathing, with increases of 39% and 27% in pulmonary and systemic arterial pressures, respectively.[60] The changes are most likely attributable to the extreme negative swings in intrathoracic pressure. At the completion of a weaning trial, the level of O_2 consumption is equivalent in patients who can be weaned and in those who cannot. How the cardiovascular system meets the O_2 demand differs in the two groups of patients.

In patients who are successfully weaned, O_2 demand is met through an increase in O_2 delivery, mediated by the expected increase in cardiac output on discontinuation of positive-pressure ventilation. In patients who cannot be weaned, O_2 demand is met through an increase in O_2 extraction; these patients have a relative decrease in O_2 delivery. The greater O_2 extraction causes a substantial decrease in mixed venous O_2 saturation, contributing to the arterial hypoxemia that occurs in some patients.[60]

Over the course of a trial of spontaneous breathing, about half of the patients in whom the trial fails have an increase in Pa_{CO_2} of 10 mm Hg or more. The hypercapnia is not usually a consequence of a decrease in minute ventilation. Instead, hypercapnia results from rapid, shallow breathing, which causes an increase in dead-space ventilation.[57] In a small proportion of patients who cannot be weaned, primary depression of respiratory drive may be responsible for the hypercapnia.

■ TIMING OF THE WEANING PROCESS

One of the major challenges in the management of ventilator-supported patients is deciding on the right time to discontinue mechanical ventilation. If the physician is too conservative and postpones weaning onset, the patient is placed at an increased risk of life-threatening, ventilator-induced complications. Conversely, if weaning is begun prematurely, the patient may suffer cardiopulmonary or psychological decompensation of sufficient severity to set back a patient's clinical course.[56]

In randomized trials of different weaning techniques, most patients who had received mechanical ventilation for a week or longer were able to tolerate ventilator discontinuation on the first day that weaning-predictor tests were measured.[61,62] Many of these patients would have tolerated extubation a day or so earlier. As such, one of the main sources of weaning delay is the failure of the physician to *think* that the patient *just might* come off the ventilator. Psychological research suggests that much of this delay in ventilator weaning results from clinicians being overconfident in their intuition that a patient is not ready for a weaning trial.[56] Another source of error is the failure of clinicians to pay close attention to pretest probability—they fail to recognize the importance of Bayesian principles in clinical decision-making. When taking care of a ventilator-supported patient, physicians should be mindful of these cognitive processes and employ compensatory tactics, specifically the use of screening tests, to spot a patient's readiness for weaning. By alerting an unsuspecting physician to a patient's readiness to tolerate unassisted ventilation—hours or days before he or she would otherwise order a spontaneous breathing trial—weaning-predictor tests circumvent the cognitive errors inherent in clinical decision-making.[56]

Physicians commonly view diagnostic testing in monolithic terms: a test is a test is a test. In reality, diagnostic testing has to satisfy two very different tasks: one is screening, the other is confirmation.[63] The characteristics of these test types differ, and a single diagnostic test rarely fulfills both functions.[63]

The fundamental job of a weaning-predictor test is screening. Because the goal is to not miss anyone with the condition under consideration, a good screening test has a very low rate of

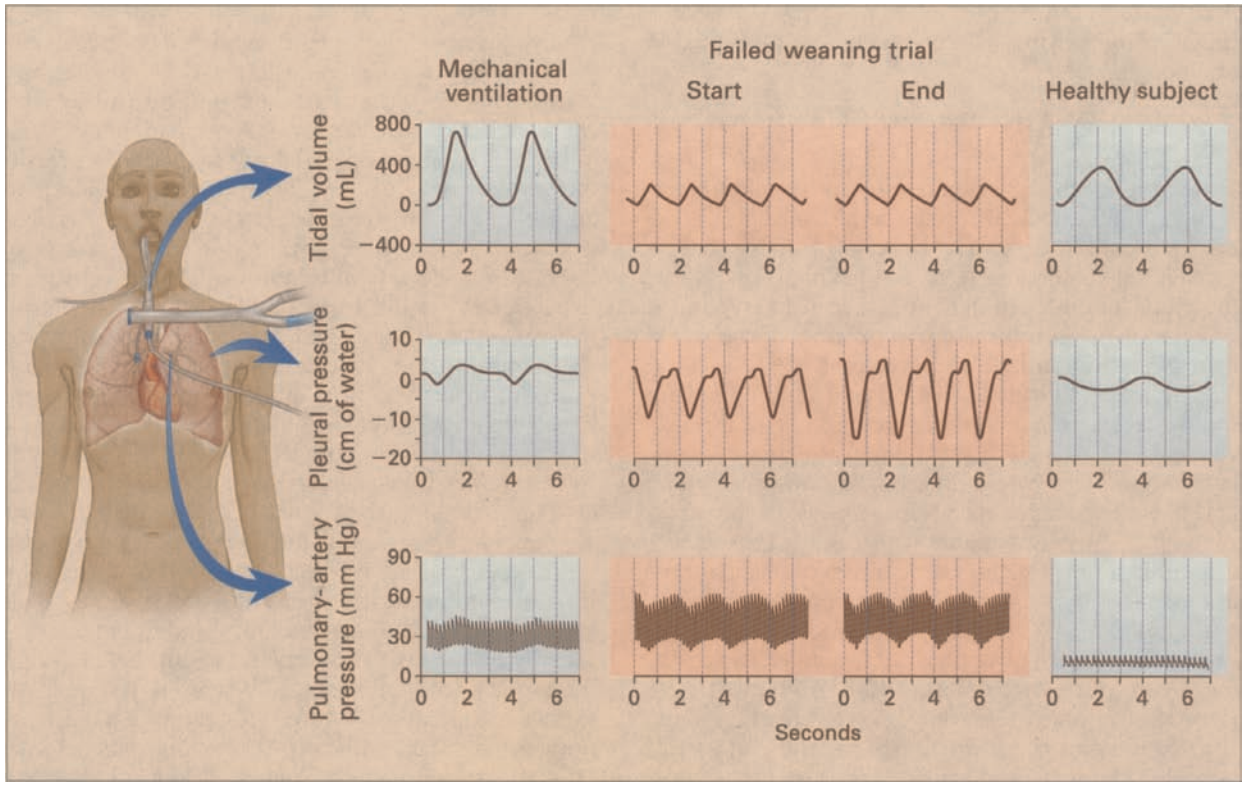

Figure 148-12 Tidal volume, pleural pressure, and pulmonary-artery pressure during assist-control ventilation and at the start and end of a failed weaning trial. During mechanical ventilation, the patient's inspiratory effort is in the normal range, and the pulmonary-artery pressure is 45/22 mm Hg. At the start of the weaning trial, tidal volume falls to 200 mL, respiratory frequency increases to 33 breaths per minute, and a swing of 11 cm H_2O in pleural pressure is noted; the pulmonary-artery pressure at the end of expiration is 60/28 mm Hg. At the end of the trial, 45 minutes later, the tidal volume and respiratory frequency are unchanged, a swing in pleural pressure of 19 cm H_2O is evident, and $PEEP_i$ is 4 cm H_2O; pulmonary artery pressure is 60/31 mm Hg. The values in a healthy subject are tidal volume, 380 mL; respiratory frequency, 17 breaths per minute; pleural-pressure swing, 3 cm H_2O; and pulmonary artery pressure, 18/8 mm Hg. *(Data are from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis. 1986;134:1111–1118; Jubran A, Mathru M, Dries D, et al. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med. 1998;158:1763–1769; Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med. 1997;155:906–915. Reproduced from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344:1986–1996.)*

false-negative results; to achieve this goal, a higher false-positive rate is acceptable. Thus, an ideal screening test has a very high sensitivity. The ratio of respiratory frequency to tidal volume (f/V_T) meets this requirement; numerous studies have documented that its sensitivity is 0.90 or higher.[64,65]

The f/V_T ratio must be calculated during spontaneous breathing. Measurements of f/V_T in the presence of pressure support or CPAP will result in inaccurate predictions of weaning outcome.[56] The higher the f/V_T ratio, the more rapid and shallow the breathing and the greater the likelihood of unsuccessful weaning. A ratio of 100 discriminates between successful (less than 100) and unsuccessful (greater than 100) attempts at weaning.[64]

Because the results of screening tests are often negative, an ideal screening test should be simple, expeditious, and safe.[63] Measurement of f/V_T takes a minute or so to perform. In contrast, a trial of spontaneous breathing takes one-half to two hours to perform, during which time attendants commonly leave the patient's room. Accordingly, a spontaneous breathing trial does not satisfy the criteria for a desirable screening test, and commencing weaning with such a trial is likely to prolong the weaning process.[56]

If clinicians obtain weaning-predictor tests at the earliest point that a patient might tolerate extubation, the results will be negative at least half the time. In studies of weaning-predictor tests, however, positive results have been obtained at least 75% of time.[65] Such a high rate of positive test results indicates that clinicians were being too slow in initiating the weaning process.

When a screening test is positive, the diagnostician proceeds to a confirmatory test.[63] A positive confirmatory test result essentially rules in a condition: The likelihood of a patient tolerating a trial of extubation is very high. An ideal confirmatory test has a very low rate of false-positive results, that is, a high specificity. The specificity of a weaning trial is not known and will never be known, since its determination would require an unethical experiment—extubating all patients who fail a weaning trial and noting how many require reintubation.[56]

■ WEANING TRIALS

Four methods can be used for conducting a weaning trial. The oldest is to perform trials of spontaneous breathing several times a day, using a T-tube circuit that contains an enriched supply of O_2.[56] Initially 5 to 10 minutes in duration, T-tube trials are extended and repeated several times a day until the patient can sustain spontaneous ventilation for several hours. This approach has become unpopular because it requires considerable time on the part of ICU staff.

For many years, IMV was the most popular methods of weaning.[56] With IMV, the mandatory rate from the ventilator is reduced in steps of 1 to 2 breaths/min, and an arterial blood gas is obtained about 30 minutes after each rate change.[10] Unfortunately, titrating the number of breaths from the ventilator in accordance with the results of arterial blood gases can produce a false sense of security. As few as two to three positive-pressure breaths per minute can achieve acceptable blood gases, but these values provide no information regarding the patient's work of breathing (which may be excessive). At IMV rates of 14 breaths/min or less, patient inspiratory efforts are increased to a level likely to cause respiratory muscle fatigue.[11,12] Moreover, this occurs not only with the intervening spontaneous breaths, but also with ventilator-assisted breaths. Consequently, use of IMV may actually contribute to the development of respiratory muscle fatigue or prevent its recovery.

When pressure support is used for weaning, the level of pressure is reduced gradually (decrements of 3 to 6 cm H_2O) and titrated on the basis of the patient's respiratory frequency.[13,61] When the patient tolerates a minimal level of pressure support, he or she is extubated. What exactly constitutes a "minimal level of pressure support" has never been defined.[14]

The fourth method of weaning is to perform a single daily T-tube trial, lasting for 30 to 120 minutes.[56,62] If this trial is successful, the patient is extubated. If the trial is unsuccessful, the patient is given at least 24 hours of respiratory muscle rest with full ventilator support before another trial is performed.[59]

Two randomized trials have revealed that weaning time was three times longer with IMV than it was with the use of T-tube trials.[61,62] In a study involving patients with respiratory difficulties on attempted weaning, T-tube trials halved the weaning time as compared with pressure support[62]; in another study, the weaning time was similar with the two methods.[61] Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day, but much simpler.[62] In patients not expecting to pose any particular difficulty with weaning, a half-hour trial of spontaneous breathing is as effective as a 2-hour trial.[66] In a recent study of patients requiring prolonged mechanical ventilation at a long-term acute care hospital, the rate of successful weaning was more than 40% higher with trials involving unassisted breathing through a tracheostomy than with use of pressure support.[67]

In conclusion, to minimize the likelihood of either delayed weaning or premature extubation, a two-step diagnostic strategy is recommended: measurement of weaning predictors followed by a weaning trial. The critical step is for the physician to contemplate the possibility that a patient *just might* be able to tolerate weaning. Such diagnostic triggering is facilitated through use of a screening test, which is the rationale for measurement of weaning-predictor tests. It is important not to postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial.

EXTUBATION

Decisions about weaning and extubation are commonly conflated. When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. Before removing the endotracheal tube, however, the clinician also has to judge whether or not the patient will be able to maintain a patent upper airway after extubation.[68]

Of patients who are expected to tolerate extubation without difficulty, about 10% to 20% fail and require reintubation.[61] Mortality among patients who require reintubation is more than six times as high as mortality among patients who can tolerate extubation.[66] The reason for the higher mortality is unknown. It might be related to the development of new problems after extubation or complications associated with reinsertion of a new tube. A more likely explanation is that the need for reintubation reflects greater severity of the underlying illness.[68]

Because of the high mortality associated with reintubation, clinicians are eager to avoid this problem. The major diagnostic test used to predict the success of an extubation attempt is a weaning trial. In contrast to the many studies that have evaluated the reliability of diagnostic tests that predict the outcome of a trial of weaning, the diagnostic accuracy of weaning trials in predicting the outcome of a trial of extubation is unknown. Moreover, the accuracy is impossible to determine, because the experiments necessary to measure the sensitivity and specificity of a weaning trial (for predicting extubation outcome) are unethical.

Many physicians find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cm H_2O and PEEP 5 cm H_2O based on the belief that such "minimal ventilator settings" are simply overcoming the resistance engendered by an endotracheal tube.[69] This claim ignores the inflammation and edema that develops in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance. Straus et al.[70] demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus, applying any level of pressure support causes physicians to underestimate the respiratory resistance a patient will encounter after extubation. The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cm H_2O decreases inspiratory work by 31% to 38%, and 10 cm H_2O decreases work by 46% to 60%.[14,71] Independently, addition of 5 cm H_2O of PEEP can decrease work of breathing by as much as 40% in ventilated patients.[71] In the case of a patient who might experience cardiorespiratory difficulties after extubation, it is incumbent on a physician to ensure that the patient is able to breathe comfortably for about 30 minutes in the complete absence of pressure support or PEEP before removal of the endotracheal tube.[69]

CONCLUSION

Since the previous edition of this textbook, we have gained a better understanding of the pathophysiology associated with unsuccessful weaning and have learned how to wean patients more efficiently. We have also learned how ventilator settings influence survival in patients with ARDS. Less progress has been made in determining how the ventilator can best be used to achieve maximal respiratory muscle rest, which is the most common reason for providing mechanical ventilation.

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CHAPTER 149

Nutrition in Pulmonary Disease

David S. Seres

INTRODUCTION

Clinical nutrition is somewhat complex. Much of clinical practice is based on observation or on flawed, biased, or severely underpowered studies. Furthermore, terminology related to malnutrition is extremely confusing; incorporating terms referring to problems attributable to alterations in nutritional intake intermixed with those secondary to inflammatory illness, which are not responsive to changes in nutrition intake.

Many excellent clinical publications[1,2] review general and specific nutritional concepts. This chapter focuses on newly proposed definitions for malnutrition and on the clinical challenges specific to selected pulmonary diseases and acute respiratory failure and the critical care setting. Chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) serve as the prototypes for nutrition-related issues encountered in chronic pulmonary disease.

MALNUTRITION REDEFINED

Malnutrition has long been known to be associated with poor outcomes in medical and surgical patients.[3] However, for decades the terminology describing malnutrition has created great confusion. While new efforts focus on defining malnutrition based on etiology,[4] clinical parameters unrelated and unresponsive to nutrient intake[5,6] remain entrenched.

The new definition of malnutrition (Table 149-1) describes two forms: malnutrition due to nutrient imbalance or malnourishment (e.g., starvation, marasmus, obesity), and that which occurs due to systemic illness (e.g., catabolism, cachexia).[4] Only malnutrition due to nutrient imbalance resulting from alterations in intake or uptake can be treated by alterations in nourishment.

The belief that most traditional markers of malnutrition (e.g., albumin, prealbumin [transthyretin], measures of immune function) reflect adequacy of nourishment has been disproved,[5,6] and some of these elements have been removed from the new definition.[4]

Confusion will likely continue, however, because remaining in the definition are clinical findings, such as loss of lean body mass, which may be caused by starvation, systemic inflammation, or both. The etiology of these signs may be difficult, if not impossible, to distinguish clinically; furthermore, lean body mass loss due to inflammation, for example, does not respond to stand-alone nourishment strategies when inflammation is present. Patients with "malnutrition" may or may not be "malnourished." Well-nourished patients (e.g. receiving tube feeding or eating well) with disease-related muscle wasting are "cachectic."

While it still comes as a "surprise" to many clinicians that so-called nutritional markers are, in truth, markers of systemic inflammation, this is far from a new finding.[7,8] Discussion of alterations in serum albumin and other parameters as arising from systemic inflammation has appeared in physiology and biology texts for decades.[9] By the same token, these "nutritional" markers have long been known to identify patients at high risk for untoward outcomes and to reflect severity of illness.[8] Moreover, nutritional assessments that incorporate the markers, such as the Prognostic Inflammatory and Nutritional Index (PINI),[10] are highly validated to predict poor outcomes. Consequently, the work of nutrition practitioners conducting clinical assessments is very important in identifying high-risk patients.

Insurers have recognized that patients with "malnutrition" are more complex than those who are not and have increased their reimbursement to hospitals for these patients. The author contends that dietitians should be renamed, "riskologists" to acknowledge this added value, and that patients identified as, "at risk for nutritional complications" be relabeled, "very sick and at risk for morbidity and mortality." In addition, patients so identified should receive intensive oversight by a multidisciplinary team of highly qualified clinicians.

Finally, inflammatory markers, such as C-reactive protein, and serum albumin and prealbumin, do not necessarily correlate linearly with the patient's clinical status. New indices that utilize multiple markers, such as the ratio of C-reactive protein to albumin,[11] have shown promise as sensitive outcome predictors.

While weight gain, especially due to increase in lean mass, is considered desirable because of the association between low weight, morbidity, and mortality, weight gain is not, by itself, a nutritional outcome in sick patients. Rather, it is more likely an epiphenomenon and a marker of disease severity.[6] Meaningful outcomes resulting from nutrition support include morbidity, cost of care, and mortality.[5] Moreover, defining ideal nourishment for an individual patient is extraordinarily difficult. Most feeding recommendations arise from studies of surrogate markers, rather than outcomes. In general, meaningful investigations in nutrition require extremely large cohorts and are expensive; few have between conducted in patients with acute or chronic illnesses.

TABLE 149-1 Findings in the New Definition of Malnutrition

	Starvation-Related Malnutrition (Malnourishment)	Disease-Related Malnutrition
Starvation	X	X
Fat wasting	X	+/–
Muscle wasting	X	X
Hypoproteinemia		X
Elevated inflammatory markers		X

ETIOLOGY AND MECHANISMS

Imbalance-related malnutrition is a result of inadequate nutrition; it is treatable by refeeding or nutrition supplementation. On the other hand, disease-related malnutrition is neither due to, nor responsive to, changes in calorie or protein intake.[5] Muscle wasting, decrements in serum proteins, insulin resistance, and immunosuppression are associated with disease-related malnutrition. All of these findings are due to systemic inflammation and, based on our current knowledge, are not due to inadequate nutritional intake.

For example, until systemic inflammation is resolved, serum albumin levels and muscle mass will not normalize, despite protein supplementation. Conversely, normalization of serum albumin may occur despite starvation, once systemic inflammation has resolved.[6] Prealbumin, properly referred to as transthyretin, normalizes more quickly than albumin with resolution of systemic inflammation,

but it is no more reflective of adequacy of nutritional intake than is albumin. Moreover, nutritional supplementation has not proved to slow the decrements seen in these markers.

Traditional nutritional markers, such as serum proteins and muscle mass, should be considered surrogates for systemic inflammation and not markers for adequacy of nourishment. Nor should they be seen as an indication for nutrition support. For example, administration of parenteral nutrition in response to finding a low serum albumin in a patient who is eating and absorbing nutrients normally exposes the patient to potential harm without potential benefit.

The mechanism for inflammation-related muscle wasting that occurs despite adequate or supplemental nutrition is poorly understood, but it is clearly related to production of inflammatory cytokines.[12] One proposed mechanism is that muscle breakdown supports uncontrolled hepatic gluconeogenesis resulting from the insulin resistance observed in this setting. The decrement in serum albumin, as well as in other carrier proteins, is likely due to its extravasation from capillaries, along with other macromolecules, due to increases in capillary permeability arising with inflammation. With maintenance of vascular volume, plasma protein concentrations are diluted. In addition, plasma protein oncotic pressure falls, or becomes nonexistent, once normally semipermeable capillary membranes become permeable, and plays a diminished role in minimizing fluid flux across capillary membranes into soft tissues.

TERMINOLOGY

The two previously noted forms of malnutrition often coexist. Sick patients often exhibit anorexia and decreased nutritional intake. In this instance, loss of muscle mass is due to both systemic inflammation and lack of nutritional intake. Distinguishing between the two forms is difficult. Recognizing a component of caloric deficit provides an opportunity to intervene.

Identifying ongoing inflammation by "nutritional" assessment, may lead to recognition of a medical or surgical condition that may require medical or surgical treatment or help to guide ethical decision-making. Prolonged, untreatable catabolism may predict incurable or fatal illness. Low muscle mass may be hidden in an obese patient with preserved adiposity, but it can be discerned with careful physical examination and may help explain a delay in physical recovery. Muscle mass is an important determinate of serum creatinine concentrations. Physical assessment of muscle mass may also be important in explaining whether a widening of the ratio of blood urea nitrogen (BUN) to creatinine represents hypoperfusion or hypovolemia on the one hand, or severe muscle loss with renal impairment on the other.

Albumin levels require approximately 6 weeks to normalize once inflammation resolves. Consequently, direct markers of inflammation (e.g., C-reactive protein and cytokines) may provide a more accurate measure of inflammation in the presence of persistent hypoalbuminemia. Reversal of hypoalbuminemia is a helpful sign in tracking resolution of inflammation and may indicate a better prognosis; however, trending in albumin levels over weeks is required for the measurements to be useful in this regard.

In distinguishing between the two types of malnutrition, the terminology employed should be very specific. Undernourishment, starvation, nutritional deficiency, nutritional imbalance, obesity, and nutritional excess may be used to describe imbalance-related malnutrition. Conversely, catabolism and disease-related malnutrition are used synonymously with malnutrition due to inflammation. *Marasmus* is an older term that refers to pure starvation. *Kwashiorkor*, an endemic disease in children, is likely due to systemic inflammatory response, but the term is no longer applied to hospitalized patients, especially adults, in nonendemic areas.[13]

Cachexia is the syndrome resulting from severe chronic malnutrition, which contains a component of inflammation-related malnutrition. It results, at least in part, from catabolism. Cachexia may be predominantly due to inflammation, with a smaller component of starvation, or alternatively, from starvation with a smaller component of inflammation.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is an extremely common form of chronic lung disease. Management of COPD is challenging and frequently entails consideration of both starvation and disease-related malnutrition.

MALNUTRITION IN COPD

COPD encompasses a number of systemic manifestations, including malnutrition; hence, it should not be considered solely a pulmonary disease. Cachexia is common in COPD. The underlying mechanisms are difficult to ascertain from existing epidemiological and observational studies. Muscle dysfunction and wasting are common. Fat-free mass predicts mortality.[14] However, muscle wasting and dysfunction may, in part, be related to systemic inflammation or increased oxidative stress.[15] In addition, it has long been known that weight loss in COPD is associated with an increase in inflammatory markers, such as TNFα.[16]

Given the systemic nature of cachexia and muscle dysfunction in COPD, purely nutritional strategies would be expected to have little impact on outcomes. In fact, until recently, whether nutrition support had any clinical outcome benefits was unclear, even though patients given such support gained weight.[17] Notably, however, as discussed previously, weight gain is solely a surrogate marker and not a meaningful clinical outcome. While weight gain may be desirable, it may not be associated with improvement in quality or quantity of life or a decrease in the cost of care.

Recent studies, reassessing data in patients with COPD who received nutrition support compared versus those who did not, demonstrated weight gain in the treated group, as well as improvements in both skeletal and pulmonary muscle function. In addition, improvement in health-related quality of life (HRQoL) was observed when data using the St. George's Respiratory Questionnaire (SGRQ) were analyzed, although not when data from SGRQ were pooled with data from the Chronic Respiratory Questionnaire (CRQ).[18] It is reasonable to continue to recommend that patients with COPD who are undernourished receive nutrition support.

Macronutrient mix in COPD may be far less important than previously thought (see below), but total calories may play an important role. In a nutritional supplementation study, provision of excess calories to subjects with COPD was shown to cause a decrease in exercise performance. This was most profound in patients with more advanced disease and cachexia.[19]

The author's opinion is that as an initial goal, it is reasonable to choose a nutritional prescription based either on an estimate of basal requirements at ideal weight, or calorimetric measurement of basal metabolic rate, and increases aimed at slow (1–2 lb per week or 3600 –7200 kcal excess per week) weight gain. Consultation with a nutrition clinician is recommended, and care should be taken to avoid overfeeding.

MACRONUTRIENTS IN COPD

A great deal of attention has been paid to concerns over the impact of macronutrients in COPD. In particular, because carbohydrates are metabolized to CO_2 and water, concern exists that a diet or tube feeding high in carbohydrate content may result in increases in $PaCO_2$ and adverse outcomes. While initial studies seemed to support this concern, recent investigations suggest the opposite. In one study, nutritional supplementation using a high-fat product resulted in more dyspnea with exercise than did

a high-carbohydrate product.[20] While the respiratory quotient (RQ)—the ratio of carbon dioxide produced to oxygen consumed per minute ($\dot{V}_{CO_2}/\dot{V}_{O_2}$)—increases more with a high-carbohydrate supplement, oxygen consumption is lower than that seen using a high-fat supplement.

These clinical findings are consistent with studies of skeletal muscle in patients with COPD, which suggest impaired fat metabolism and an increase in carbohydrate metabolism. In these patients, studies have shown a decrease in oxidative function[21] and expression of peroxisome proliferator-activated receptors (PPAR),[22] which have an extremely important role in up-regulating lipid uptake and metabolism in cells. In addition, in COPD, a shift from oxidative to glycolytic muscle fibers occurs in skeletal muscle, the degree to which is directly correlated with disease severity.[23]

OTHER NUTRITION-RELATED CONSIDERATIONS IN COPD

Anabolic steroids have been demonstrated to increase fat-free mass in patients with COPD, but have been proved to have minimal benefit in clinical outcomes. In a study of patients with COPD enrolled in a pulmonary rehabilitation program, those who received an anabolic steroid had a higher fat-free mass than those who did not, but improvements in muscle function, exercise capacity, and health status were not different between the two groups. Patients who received corticosteroids demonstrated less response to the rehabilitation. Maximal inspiratory mouth pressure and peak workload were improved in patients receiving both chronic corticosteroids and anabolic steroids compared with those given placebo; this was the only positive outcome.[24]

Appetite stimulants have not proved effective in improving outcomes in COPD. In a study of patients receiving megestrol acetate versus those receiving placebo, the treated group demonstrated a lower 6-minute walk distance, despite having a decreased Pa_{CO_2} and increased Pa_{O_2}. Megestrol increased weight, but it did so by increasing fat mass.[25] No studies on use of cannabinoid appetite stimulants in COPD are available.

RECOMMENDATIONS

Patients with COPD should be screened for malnutrition and referred to a nutrition practitioner when any sign of diminished nutritional intake or weight loss is found. Similarly, obesity or excess weight gain in an individual previously of normal weight should serve as indications for nutritional intervention.

Because of difficulties in distinguishing malnourishment from disease-related changes, along with the inability of nutrition support to impact the latter, failure of nutritional interventions should be viewed as evidence of disease progression and factored into prognostic assessments. Strategies such as appetite stimulation and use of anabolic steroids may impact selected metrics, but they have not been demonstrated to impact outcomes. Measuring and monitoring markers, such as serum albumin, should be considered, but the results should be viewed as reflective of an underlying inflammatory state. In this regard, they may be prognostic, but not reflective of nutritional adequacy.[5,6]

CYSTIC FIBROSIS

Cystic fibrosis (CF) is associated with nutritional issues that are far more complex than in most other pulmonary diseases. Patients with CF are prone to significant chronic inflammation, with acute worsening in the presence of infection. As in other inflammatory disorders, disease-related muscle wasting may be noted, which although not necessarily obvious, may be evident even at an early age.[26]

Patients with CF are at high risk for malnutrition arising from a variety of issues: (1) Inflammation may result in anorexia. (2) Malabsorption may occur due to exocrine pancreatic insufficiency. (3) Patients with longstanding disease may develop gastroparesis severe enough to warrant jejunal tube feeding, which may, itself, be a challenge, given increasing evidence for slowing of small bowel transit in affected patients.[27]

MACRONUTRIENTS AND MICRONUTRIENTS IN CYSTIC FIBROSIS

No properly designed prospective, randomized controlled trials comparing enteral feeding to no intervention have been conducted in CF to determine whether enteral feeding improves outcomes.[28] Such studies are nearly impossible to perform because of the ethical dilemmas posed by not providing supplemental or artificial feeding to patients who are, as best as we can determine, chronically starved.

Multiple approaches have been employed to overcome the complex feeding issues encountered in CF, including use of special, predigested tube feeding mixes and supplementation of nutrients thought to be supportive of immune function. Given difficulties with maldigestion due to pancreatic insufficiency and resulting malabsorption in patients with CF, the concept has arisen that providing partially predigested feedings may enhance absorption. However, in small studies, provision of predigested feedings appears not to improve absorption over use of enzyme replacement therapy.[29] Our approach is to feed patients concentrated, high-fat tube feed products (Altman K. Personal communication. 2013), enabling provision of goal calories in the face of small bowel dysmotility.

Among the micronutrient issues considered in CF—a disorder characterized by immune dysfunction—zinc has long been of interest. Zinc deficiency may cause untoward immunological changes, but zinc supplementation in the setting of normal levels generally has no beneficial effect and may be harmful. Zinc supplementation lowers copper levels,[30] and copper deficiency caused by excessive zinc ingestion may result in mortality.[31,32] Only a few trials, with small number of subjects, have assessed the efficacy of wholesale zinc supplementation for CF. Not surprisingly, zinc supplementation in patients with CF who have normal zinc levels has demonstrated no significant benefit, while supplementation in those with low zinc levels results in fewer days on antibiotics.[33]

STRATEGIES AND RECOMMENDATIONS

In an effort to improve patient education and clinical outcomes, multidisciplinary care, including early involvement by nutrition practitioners, is recommended for all patients with CF.[34]

Nutrition practitioners should have specialized knowledge of CF, as the feeding and nutritional problems can be quite complex.

Malabsorption may be particularly challenging when patients require tube feeding, especially jejunal tube feeding. In recent years, the production of powdered pancreatic enzyme replacements has ceased. Currently, the only available form of pancreatic enzyme replacement is an enteric-coated product. Administration of the product through a gastric tube requires that the outer capsule be opened, exposing coated spherules that require suspension prior to administration. However, the spherules tend to coalesce and may clog the tube. One proposed method to avoid this problem is to mix the spherules into a viscous solution prior to administration,[35] thereby keeping them suspended and preventing settling and coalescence. Others recommend dissolution of the spherules in an alkaline solution, which is then added to the feed product and allowed to sit prior to administration, resulting in feed predigestion. While addition of enzymes to the feed may facilitate predigestion, concern exists that any manipulation of feed products prior to feeding tube installation may increase the risk of bacterial contamination.[36] The data supporting this

concern, however, relate primarily to bacterial counts, rather than clinical outcomes.

ACUTE RESPIRATORY FAILURE

The importance of adequate nutrition in patients with acute respiratory failure who are admitted to critical care units has been recognized for some time. Several practical considerations in administration of nutrition in this setting are outlined subsequently.

SPECIFIC NUTRIENTS

Much has been written about the role of specific macro- and micronutrients in patients with acute respiratory failure. As discussed previously, attempts at manipulating the composition of the feedings administered, for example, the ratio of carbohydrate to fat, have been shown to be without benefit. Use of specific fats, especially oils containing omega-3 fats or their precursors, has been studied in the acute respiratory distress syndrome (ARDS), but the results are still debated.

Three prospective randomized trials were performed comparing a feeding product high in omega-3 fats and supplemented with antioxidant vitamins against a formula similarly high in fat, but with omega-6 fats. Use of the omega-3 formula resulted in decreases in the development of new organ failure, time on mechanical ventilation, and time in the ICU.[37–39] However, in the more recent ARDSNet study, patients were randomized to receive a supplement containing omega-3 fats and antioxidants. The study was terminated early due to no effect, which creates a high risk for inducing bias. Nevertheless, enthusiasm for this nutritional approach has been challenged.

TIMING AND ROUTE OF ADMINISTRATION OF ARTIFICIAL NUTRITION IN ACUTE RESPIRATORY FAILURE

The timing of initiation of enteral or parenteral feeding in critically ill patients appears to be clinically important.[40] Early enteral feeding has become standard of care in the critically ill.[41] However, studies[42] and reviews[43] of this practice have limitations and risks for bias. While early enteral feeding does not stand up to the strictest requirements for evidence-based practice and garners a C grade in evidence-based guidelines,[41] a large body of evidence exists that food in the gut may play an important role in modulating systemic inflammatory response,[44] which theoretically may lead to preservation of immune function, less catabolism, and fewer complications. Indeed, in many cases the physiologic basis for septic shock may be related to interactions between gut pathogens and mucosal cells, with or without actual septicemia.[44]

Enteral nutrition (Tables 149-2–149-4), except in the face of severe prolonged gut failure, is almost always preferred over parenteral nutrition.[45] Early parenteral nutrition, whether the sole source of calories,[46] or as a means of augmenting enteral nutrition,[47] has not proved beneficial in critically ill patients, and may, in fact, be harmful (Table 149-5). The time point at which the risks of starvation exceed the risks of parenteral nutrition is unknown, since most studies have excluded patients already suffering from malnutrition.[48] American guidelines recommend withholding parenteral nutrition during the first week of critical illness when enteral feeding is not possible.[41] Subsequent to publication of the most recent critical care nutrition guidelines, a large randomized trial showed an increase in morbidity when parenteral nutrition was added to early enteral feeding.[47]

TOTAL CALORIES PROVIDED

Whether critically ill patients should receive 100% of estimated or measured calorie needs, especially early in the course of their critical illness, is the subject of great debate. Failure of current practice to deliver "adequate" calories to critically ill patients has also received a great deal of attention. Recent surveys suggest that patients admitted to ICUs receive only about 50% of prescribed calories during their stay.[49] As a consequence, significant efforts have been made to increase calorie delivery through protocol development and quality improvement initiatives,[50] as well as through immediate initiation of parenteral nutrition to "top-off" the calories that early enteral nutrition cannot provide.[51] However, the outcome benefits of these approaches have not been proven.

In the absence of high-quality, prospective, randomized studies, we do not know how to determine the individual caloric needs of critically ill patients. Indirect calorimetry has the potential to lead us completely astray. No currently available marker, assessment tool, or nutritional score can help discern what calorie and protein prescriptions will result in the best clinical outcomes.[5] In addition, high-quality studies in which calorie top-off was achieved enterally[52] or parenterally[47] have showed no benefit. Indeed, a significant increase in gastrointestinal intolerance with early full enteral feeding,[53] and in complications and prolonged length of stay with a parenteral top-off approach have been reported.[47] The findings, from the studies using parenteral nutrition have been criticized by proponents of early achievement of calorie goals on the basis that the investigators used a parenteral nutrition practice different from that employed in North America; in fact, two small studies suggest a benefit.[51,54] However,

TABLE 149-2 Choice of Route for Administration of Enteral Nutrition

Large-bore nasogastric sump tube
Short-term (several days) feeding
Transition from gastric drainage to gastric feeding
Small-bore nasogastric feeding tube
Primary choice for nasal tubes
Short-term (up to 30–90 d)
Small-bore Nasoenteric (nasoduodenal, nasojejunal)[a]
Gastric dysmotility[b]
Very high aspiration risk[c]
Gastrostomy (percutaneous endoscopic, surgical)
Long-term (greater than 30–90 d)
Technical issues with nasal tube[d]
Jejunostomy (percutaneous endoscopic, surgical)
Gastric dysfunction[a]
Long-term access when gastric surgery anticipated[e]
Long-term access when gastric tube not possible[e]

[a]Usually 6–10 French in adults.
[b]Concomitant gastric drainage is likely to be required or vomiting can occur. Short term, a second (nasogastric sump) draining tube or use of a combined dual lumen nasogastrojejunal (draining nasogastric, feeding nasojejunal) tube may be useful. Combined dual tube draining gastrostomy-feeding jejunostomy may be useful longer term.
[c]This recommendation appears in guidelines but is not supported by prospective randomized data. While jejunal placement may result in better calorie delivery, there are no outcome data to support routine choice of jejunal, over gastric, placement of feeding tubes.
[d]With the availability of techniques, such as the nasal bridle for securing nasal tubes, security of the tube is less commonly an indication for percutaneous feeding tubes.
[e]For example, patients with gastric cancer, or esophageal cancer and planned esophagectomy and gastric pull-up.

TABLE 149-3 Usual Characteristics and Indications for Enteral Feeding Formulas

	Standard	Standard Concentrated	Standard High Protein	Renal	Diabetic	Predigested[a]	Pulmonary[b]	Immune/ Inflammation Modulating
Use	First choice[c]	Fluid restriction/ bolus feeding[d]	Highly catabolic/ Wound healing	Fluid and electrolyte restriction[e]	Bolus feeding diabetics[f]	Maldigestion or severe tube-feed intolerance[a]	See footnote[b]	See footnote[g]
Calories per mL	1–1.25	1.5–2.0	1.0–1.5	1.8–2.0	1.0–1.5	1.0–1.5	2.0	1.0–2.0
Protein g/ 1000 kcal	40–44	40–44	62.5	40–44	40–44	40–62.5	40–44	40–62.5
Electrolytes	Standard	Standard	Standard	Restricted[e]	Standard	Standard or restricted	Standard	Standard or restricted
Fiber[h]	+/–	+/–	+/–	+/–	+	+/–	–	+/–
Fat		High			Somewhat increased	See footnote[i]	High	See footnote[j]
Osmolarity[k]	Iso	Up to ~700 mOsm/L	Iso or slightly increased	~700 mOsm/L	Iso or slightly increased	Iso up to ~700 mOsm/L	Increased	Iso or slightly increased

[a]Predigested feeding products may be made up of simple sugars and individual amino acids (e.g., Vivonex™) or of oligosaccharides and oligopeptides (e.g., Vital™, Peptamen™). These are marketed as providing superior tolerance, and better absorption in states such as maldigestion, hypoproteinemia. Most of the data on these is preclinical, and there is no outcome data supporting their superiority. Very low fat feeding has been promoted as an alternative to parenteral nutrition in patients with chyle leakage. Randomized studies are lacking.

[b]These products have not been shown to have any benefit in randomized trials. The principle on which they were created is that dietary fat produces less CO_2 than does carbohydrate. While this effect can be measured on calorimetry, patients are not extubated sooner. Certainly, these products are not indicated for patients on long-term ventilatory support.

[c]Most patients can be fed with a standard feeding product. The cost differential between a standard product and the disease-specific feeds can be as much as 15 fold.

[d]An increase in calorie density, from 1.0 to 1.5 kcal/mL will not substantially increase viscosity and decreases the volume of tube feeding product required to meet calorie goals. The remainder of the volume requirements may be given as water boluses. This decreases overall feeding time and increases convenience for ambulatory patients.

[e]Patients with renal insufficiency and/or on hemodialysis, but not continuous renal replacement, require restriction of dietary sodium, potassium, and phosphorus. In addition, these products are fluid restricted.

[f]Glycemic index is the area under the curve of the rise in blood glucose after a bolus or meal, compared to a standard. This concept does not apply to patients receiving continuous feeding as rate of appearance of glucose will be equal to rate of delivery plus rate of gluconeogenesis in these patients. Glycemic control formulas only improve glycemic control in patients fed intermittently.

[g]Because of the biochemical derangements that occur in critical illness, nutrient levels and consumption are altered. These alterations have led to a great interest in supplementation of specific nutrients to reverse these derangements. There is no strong evidence that these approaches result in improved outcomes. The author believes this may be due to these derangements being adaptive, or epiphenomena.

[h]Insoluble fiber, while favored in long-term tube feeding, should be avoided in critically ill patients, especially while on pressor agents. Bezoar may form when peristalsis is diminished.

[i]Fat content in these products varies. In some, it is highly restricted to 10% of calories (long-chain fat, Vivonex™). In others, fat has been engineered to provide theoretical improvements in absorption and may contain mixtures of medium-chain, long-chain omega-3, and long-chain omega-6 fats.

[j]Fat content in these products varies widely. Products focused on inflammation may have a large amount of omega-3 and other putatively anti-inflammatory fats. Other products provide engineered triglycerides, with a mixture of long-chain omega-3 and omega-6 plus medium-chain fats. Discussed more fully in Acute Respiratory Failure/ Specific Nutrients section in text.

[k]Osmolarity of tube feeds ranges from isotonic to approximately two times isotonic. The osmolarity of many medications and electrolytes is orders of magnitude higher. The latter is a far more important concern when evaluation patients with diarrhea. It is unlikely the osmolarity of current tube feeding products will be the cause.

these smaller studies have significant flaws, and given the rigor of the larger parenteral study, its findings cannot be dismissed.

POSITION AND TIMING OF FEEDING TUBE PLACEMENT

The choice of enteral feeding tube location has been a focus of discussion in the critical care setting: gastric versus duodenal or jejunal. A related center of debate is the incidence of pneumonia with each choice. Overall, studies have shown an increase in calorie delivery using nasoenteric tubes compared with nasogastric tubes.[55] However, current investigations using more stringent feeding protocols do not demonstrate a benefit with nasoenteric tube placement. Neither mortality nor the incidence of pneumonia is affected by tube placement.[55,56] Regardless, postpyloric tube placement is advantageous over gastric placement in the setting of severe gastroparesis or severe pancreatitis, especially when the inflammatory pancreatic phlegmon causes compression of the duodenum.

When artificial feeding is desired, enteral feeding is the standard of care in pancreatitis.[57] Whether the tube should be placed in the stomach or jejunum is still a subject of debate; comparative studies have failed to show any differences in outcomes between these methods.[58]

In recent times, the practice of simultaneous insertion of tracheostomy and PEG tubes (PEG-TRACH) has gained some traction.[59] In certain institutions, interventional pulmonologists or surgeons perform both procedures in the same setting, alone or in collaboration with a gastroenterologist.

Tracheostomy is an important and beneficial adjunct in the management of the critically ill. It is used when clinicians predict that a patient will need a prolonged period of mechanical ventilation. The procedure is well tolerated and may be performed at the bedside. Tracheostomy insertion has been associated with a faster wean from mechanical ventilation, reduced incidence of pneumonia, and ultimately, shorter hospital stay.[60] Timing of tracheostomy insertion

TABLE 149-4 Challenges and Complications of Enteral Nourishment[a]

Gastrointestinal intolerance
Abdominal distension
Nausea and vomiting
Diarrhea
Maldigestion/malabsorption
Contamination of enteral feeding solution
Infusion of hypertonic medications and solutions
Medication side effects
Gastrointestinal diseases
Constipation
Intestinal ischemia
Gastroparesis and ileus
Metabolic derangements
Hyperglycemia
Refeeding syndrome
Hypokalemia
Hypophosphatemia
Hypomagnesemia
Wernicke encephalopathy
Dehydration
Complications of tube access

[a]Note that while aspiration and pneumonia are associated with use of enteral nutrition, recent studies have demonstrated a lack of relationship between even vomiting and pneumonia in patients receiving enteral nutrition.[76] Furthermore, the incidence of pneumonia does not appear to be decreased by positioning tubes in the jejunum.[57]

has been debated; a move toward earlier performance has been observed because of a suggestion of improved outcomes reported in meta-analysis.[61] However, recent trials have suggested lack of real benefit from early tracheostomy. Consequently, this practice is liable to change.[62,63] Nevertheless, at present, the combination procedure of PEG-TRACH has been advocated by some and has resulted in simultaneous, early PEG insertions (in some cases within 4 days of admission to ICU).[59] Historic observational data on the feasibility of this approach are available, although the effectiveness and safety of this approach have not been studied.[64,65]

TABLE 149-5 Complications of Parenteral Nutrition

Complications of access
Bleeding
Infections
Venous thrombosis
Metabolic complications
Refeeding syndrome
Hyperglycemia
Vitamin and mineral deficiencies due to shortages
Systemic complications
Bacteremia/central-line associated blood stream infections (CLABSI)
Overall increased incidence of infections
Hepatic dysfunction
Prolonged ICU and hospital stays

We postulate, based on discussions with critical care colleagues throughout the country, that a large portion of the drive for simultaneous PEG-TRACH is based on refusal by nursing homes in some parts of the United States to accept patients with nasal feeding tubes, coupled with the push for shorter lengths of stay. In a phone survey of the 127 nursing homes (participation rate, 85%) in New York City, 88 (81.5% of respondents) indicated that they have policies prohibiting nasal feeding tubes. Twenty nursing homes (18.5% of respondents) indicated they would accept nasal tubes, but most had not in the past 6 to 12 months.

Gastroenterologists and interventional radiologists at our institution have estimated that a large percentage of the gastrostomies placed were done solely because of anticipated discharge of the patient to a nursing home. Most nursing homes reported that their refusal of nasal feeding tubes is based on the perception of high risk of aspiration and tube dislodgement.[66] This concern is unsubstantiated in the literature. Indeed, only a total of 686 patients have been randomized in 9 trials comparing nasogastric feeding tube to PEG. PEG has been associated with fewer episodes of feeding interruption, tube blockage, tube leakage, or lack of adherence to treatment in a subset of 7 of these studies, which included only 314 patients. In aggregate, no differences were observed in the incidence of pneumonia or complication rates between the two feeding methods.[67]

Consensus guidelines suggest that PEG should be considered for patients likely to require enteral nutrition >30 days.[68] New York State Department of Health policy allows for nasal feeding tubes for up to 96 days.[69] PEG, while safe and reasonably well tolerated, is not a frivolous procedure. Mortality post-PEG insertion has been reported to be 26% at 30 days,[70] and as high as 43% at *1 week*.[71] These high rates are likely largely driven by poor patient selection. Based on these data, selection of critically ill patients undergoing tracheostomy for concurrent PEG insertion needs to be questioned. By virtue of their complex critical illness, patients undergoing tracheostomy are not at low risk for the procedure. The 30-day mortality posttracheostomy has been variously reported at approximately 30%.[60,62] By extension, one may conclude that selection criteria for combined PEG-TRACH in these series resulted in an excess PEG insertion rate of at least 30%, without demonstrable outcome benefit.

In one series of patients undergoing simultaneous PEG-TRACH, the mortality at 30 days was 11%.[59] In the surviving patients, PEG tubes were removed in 73%, with a median of 76 days (range, 24–611 days). Thus, it seems likely that PEG insertion may have been avoided in many of these patients by deferring simultaneous insertion until the prognosis for resumption of oral diet and prognosis overall were clearer and the patient more medically stable.

In summary, nasogastric feeding tubes are widely regarded as safe and are the preferred option for short-term (30–90 days) delivery of nutrition. While the risks of simultaneous PEG-TRACH insertion appears to be tolerable, based mostly on anecdotal evidence, the procedure has not been proven to be superior to a "watch and wait" approach of continuing with nasogastric feeding. Patients undergoing simultaneous PEG-TRACH should be carefully chosen for procedural risk and likelihood of long-term requirement for a tube feeding.

■ ASPIRATION AND GASTRIC RESIDUAL VOLUMES

Aspiration of gastric contents is a serious concern in the critically ill. But aspiration, by itself, should not be considered an adverse outcome unless it leads to a clinically significant event, such as ventilator-associated pneumonia. Aspiration is common in a variety of settings, such as intubation for routine surgery[72] and during sleep.[73,74] In a study published over 40 years ago, aspiration was

demonstrated in 50% of normal volunteers and in 75% of subjects with depressed consciousness.[74]

Based on the belief that the risk of aspiration is related to the volume of gastric contents, measurement of gastric residual volumes has become common practice in patients receiving enteral feeding. Many protocols and guidelines have been developed for managing tube feedings based on gastric residual volumes. Increasingly, however, this practice has been challenged. High gastric residual volumes are not associated with increases in ventilator-associated pneumonia. In fact, recent studies have questioned the value of checking gastric residuals at all. In a before–after study[75] and in a prospective randomized study,[76] checking gastric residual volumes had no impact on the incidence of pneumonia. In fact, in the randomized trial, vomiting was increased in the group of patients in whom gastric residual volumes were not assessed, but this did not result in an increase in the incidence of pneumonia.[76]

STRATEGIES AND RECOMMENDATIONS

Critically ill patients, whose prognosis warrants the intervention, should receive enteral nutrition early in their course if they are malnourished and are expected to be without nourishment for some time. Parenteral nutrition should only be used for patients with chronic gut failure, and it should not be used early. Our practice is to wait for up to 2 weeks to start parenteral nutrition in patients without preexistent malnourishment who do not respond to efforts at enteral feeding. The practice of routinely measuring gastric residual volumes has been shown to have no clinical benefit and may decrease calorie delivery.

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CHAPTER 150

Diagnosis and Treatment of Pain, Agitation, and Delirium in the Intensive Care Unit

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INTRODUCTION

The large majority of patients in intensive care units (ICUs) experience pain, agitation, or delirium at some point during their critical illness. During the last two decades, tremendous growth in knowledge regarding the assessment and management of these syndromes in the ICU has prompted important changes in the practice of intensive care medicine. Validated tools now exist that allow clinicians to quickly and reliably evaluate patients for pain, assess their level of consciousness, and detect delirium. These assessments, in turn, guide clinicians as they choose and titrate therapies targeted to best manage a patient's symptoms. Novel strategies to address pain, agitation, and delirium have also recently been investigated. The use of validated tools to diagnose these important clinical issues using evidence-based management strategies has been shown to improve both short- and long-term outcomes in numerous studies. This chapter reviews these assessment tools and presents best practices for management in critically ill patients.

PAIN IN THE CRITICALLY ILL

Critically ill patients frequently suffer from pain.[1,2] Whereas effective treatments for pain are widely available, detecting pain in those critically ill patients who are unable to report it is challenging. Prolonged pain in the critically ill is associated with adverse physiologic effects.[3] Because analgesia is most effective when pain is identified and treated early, clinicians should frequently assess patients for pain and treat it when identified.[4]

■ ASSESSING PAIN IN THE CRITICALLY ILL

Pain is subjective in nature; therefore, a patient's self-report (using numeric scale or visual analog scale) is an easy and reliable method to determine its presence. In fact, the 2013 Society of Critical Care Medicine (SCCM) clinical practice guidelines on the management of pain, agitation, and delirium in the ICU suggest that the numeric rating scale be used to assess pain when patients are able to self-report.[5] Among the critically ill, however, self-reporting is not always possible due to the presence of endotracheal tubes, sedation, or delirium. Therefore, several instruments have been developed and validated to aid clinicians in identifying the presence of pain in critically ill patients.

The two most widely studied pain assessment tools for use in patients in the ICU who are unable to report pain are the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT).[6,7] Both the BPS and CPOT utilize nonverbal cues and patient behaviors commonly indicative of the presence of pain; these include facial expressions, body movements, and compliance with mechanical ventilation to establish the presence of pain (Table 150-1A,B). Alternatively, a patient's surrogate may be able to provide description of behaviors indicative of pain in a particular patient, based on the surrogate's prior knowledge of the patient.[8] Finally, in the case where the clinician is unsure if a patient is having pain, a trial of an analgesic medication can be used to assess for a decrease in the suspected pain-related behaviors.[8] Regardless of the assessment method used, it is important to note that assessing for pain among the critically ill is associated with improved clinical outcomes, including optimized analgesic and sedative administration and reduced duration of mechanical ventilation and ICU stay.[9–11]

■ TREATING PAIN IN THE CRITICALLY ILL

Comprehensive pain management in the critically ill consists of pharmacologic therapies (e.g., opioid medications and nonopioid

TABLE 150-1A Critical Illness Pain Observation Tool (CPOT)

Clinical Indicator	Description	Score
Facial expression	Relaxed; no muscular tension observed	0
	Tense; frowning, brow lowering, eye tightening, neck contraction	1
	Grimacing; all previous facial movements plus eye lids tightly closed	2
Body movements	Absence of movements or normal position	0
	Protection; cautious movements, touching/rubbing site of pain, seeking attention through movements	1
	Restlessness/agitation; pulling tube, attempting to sit up, thrashing, not following commands, striking at staff, trying to climb out of bed	2
Muscle tension	Relaxed; no resistance to passive movements	0
	Tense/rigid; resistance to passive movements	1
	Very tense/rigid; strong resistance to passive movements	2
Intubated patients: Compliance with the ventilator	Tolerating vent/movement; alarms not activated, easy ventilation	0
	Cough but tolerating; alarms stop spontaneously	1
	Fighting ventilator; blocking ventilation, alarms frequently activated	2
Nonintubated patients: Verbalization	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2

Higher scores indicate greater pain.
Source: Data from Gélinas C1, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–427 and Payen JF1, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–2263.

TABLE 150-1B Behavioral Pain Scale (BPS)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Higher scores indicate greater pain.
Source: Data from Gélinas C1, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–427 and Payen JF1, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–2263.

medications) in combination with nonpharmacologic approaches to ensure adequate analgesia.[4]

First-line treatment for acute, nonneuropathic pain among the critically ill is intravenous opioid analgesics, such as fentanyl, morphine, hydromorphone, methadone, and remifentanil. The specific drug choice and dose are determined by the severity of the pain, patient characteristics (e.g., age, renal, and hepatic function), the patient's clinical status, and the properties of the drug (e.g., pharmacokinetics and pharmacodynamics) (Table 150-2).

Nonopioid analgesics (e.g., acetaminophen, ibuprofen, ketamine) may be administered as adjuvant therapies to reduce the overall dose of opioids. Nonpharmacologic interventions such as massage, relaxation techniques, heat or ice application, and music therapy may provide additional analgesic effect.[4] For patients experiencing neuropathic pain, use of gabapentin or carbamazepine may be added to opioid and nonopioid analgesics.[5]

AGITATION IN THE CRITICALLY ILL

Agitation in critically ill patients is associated with adverse outcomes, such as the removal of life-support devices and danger to the patient or beside staff. Commonly, agitated patients are given sedatives to reduce agitation and prevent harm.[12] Nevertheless, it is important to remember that agitation does not equate to "sedation deficiency." Rather, the presence of agitation should prompt the clinician to search for and treat an underlying cause, such as pain, hypoxemia, metabolic derangements, developing sepsis, delirium, or withdrawal from alcohol or other drugs. Agitation exists at one extreme of the continuum of consciousness that also includes calm states and states of decreased arousal, such as stupor and coma. This section reviews methods to assess level of consciousness, as well as best practices for the treatment of agitation, primarily through the judicious use of sedative medications.

TABLE 150-2 Pharmacology of Selected Opioid Analgesics

Drug	Equianalgesic Dose	Half-life	Intermittent Dose	Infusion Dose	Adverse Effects/Other Information
Morphine	10 mg	2–3 h	0.01–0.15 mg/kg every 1–2 h	0.07–0.5 mg/kg/h	Accumulates in renal and hepatic failure; hypotension (due to histamine release)
Fentanyl	100 μg	1.5–6 h	0.35–1.5 μg/kg every 0.5–1 h	0.7–10 μg/kg/h	Less hypotension than morphine; accumulates in hepatic failure
Hydromorphone	1.5 mg	3–7 h	10–30 μg/kg every 1–2 h	7–15 μg/kg/h	Accumulates in renal and hepatic failure; use in patients intolerant of morphine or fentanyl
Remifentanil	—	3–10 min	—	Loading dose: 1.5 μg/kg Maintenance dose: 0.6–15 μg/kg/h	No accumulation in hepatic or renal failure

TABLE 150-3 Level of Consciousness Scales: Richmond Agitation–Sedation Scale (RASS) and Riker Sedation–Agitation Scale (SAS)

RASS Level	Label	Description	Label	SAS Score
+4	Combative	Combative, violent, immediate danger to staff, climbing over bedrail, thrashing side to side	Dangerous agitation	7
+3	Very agitated	Pulls to remove tubes or catheters, aggressive, requiring restraint and frequent reminder of limits	Very agitated	6
+2	Agitated	Frequent nonpurposeful movement; fights ventilator	Agitated	5
+1	Restless	Anxious, apprehensive, movements not aggressive; follows commands		
0	Alert and calm	Spontaneously pays attention to caregiver; follows commands	Calm and cooperative	4
−1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact for more than 10 s)	Sedated	3
−2	Light sedation	Briefly awakens to voice (eyes open and contact for less than 10 s)		
−3	Moderate sedation	Movement or eye opening to voice (no eye contact)		
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimuli	Very sedated	2
−5	Unarousable	No response to voice, physical or noxious stimulation	Unarousable	1

Higher (more positive) scores indicate greater agitation.
RASS, Richmond Agitation–Sedation Scale; SAS, Riker Sedation–Agitation Scale.
Source: Data from Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–1344; Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983–2991; Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med. 1999;27(7):1325–1329.

■ ASSESSING AGITATION AND LEVEL OF CONSCIOUSNESS IN THE CRITICALLY ILL

A number of standardized measures can be used to determine level of consciousness in the critically ill. Although these tools are commonly referred to as "sedation-agitation scales," they can be used to evaluate all patients in the ICU, regardless of whether they are receiving sedatives, as they assess patient behaviors and response to verbal or physical stimuli to determine the patient's level of consciousness. The current SCCM guidelines recommend the Richmond Agitation–Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS), noting that these scales are the most valid and reliable for determining level of consciousness during critical illness (Table 150-3). Unlike the Glasgow Coma Scale (GCS), the RASS and SAS have been validated for use in the setting of ongoing critical illness, even when patients are sedated or nonverbal due to placement of an endotracheal tube. Regular assessments of level of consciousness can improve detection of changes in neurologic status, as well as facilitate and guide delivery of sedatives and other psychoactive medications.

■ TREATING AGITATION IN THE CRITICALLY ILL

The first step in treating agitation should be to seek out the underlying (and potentially reversible) cause(s). Providing adequate analgesia, treating hypoxemia with supplemental oxygen, correcting electrolyte abnormalities, treating infection, providing reorientation, ensuring an environment conducive to sleep, and treating alcohol and drug withdrawal may eliminate agitation in the appropriate situation. If agitation persists despite measures aimed at addressing the underlying cause, consideration should be given to administration of sedatives.

The past decade has seen a dramatic shift in the strategies used to sedate patients in the ICU. As a result of numerous trials reporting better outcomes among patients managed using protocol-based administration of sedation compared with those managed without the guidance of a protocol,[13–16] an increasing number of ICUs are adopting algorithmic approaches to the delivery of sedatives to critically ill patients. While a multitude of protocols exists, common threads are present in each, including objective assessment of level of consciousness; prioritization of analgesia over administration of sedatives; targeting lighter, rather than moderate or heavy sedation, using intermittent dosing of medications or daily interruption of medications; and relying on benzodiazepine-sparing regimens.

■ PRIORITIZING ANALGESIA

As discussed earlier in this chapter, pain is pervasive among critically ill patients and is a frequent reason for agitation. Thus, evaluation and treatment of pain using the techniques described earlier may be sufficient to restore a patient to a calm and alert state. Several studies of sedation protocols that preferentially treated pain before administering sedatives have demonstrated improved patient outcomes,[13,17,18] and current guidelines recommend treatment of pain prior to administration of sedatives.[5]

A dramatic example of the value of pain management prior to administration of sedatives was provided in a randomized trial comparing a control group (sedated primarily with propofol) with patients managed using a strategy of "no sedation."[19] Patients received morphine for pain first, then haloperidol for agitation, then, if needed, intermittent short-course (i.e., 6-hour) administration of propofol. Only after failing this regimen (as indicated by ongoing agitation) did patients in the intervention group receive sedation using a more conventional propofol- and midazolam-based sedation strategy. Patients managed with the "no sedation" strategy had significantly better outcomes than those in the control group, spending more time off mechanical ventilation and experiencing earlier discharge from the ICU and hospital. Only 18% of patients managed using the "no sedation" strategy required continuous propofol >6 hours, a result that calls into question the still common assumption that endotracheal intubation and mechanical ventilation cannot be tolerated without the use of moderate or heavy sedation.

■ INTERMITTENT VERSUS CONTINUOUS DOSING OF SEDATIVES

As demonstrated in the aforementioned "no sedation" trial, which prioritized use of intermittent morphine and haloperidol, many analgesic and sedative medications can be delivered via intermittent

(bolus), rather than continuous, dosing. The latter has been the most common method used in ICUs,[9] with routine use of continuous infusions reflecting the fact that the majority of early studies of sedation in the ICU utilized continuous infusion strategies. Nevertheless, continuous infusion of analgesics and sedatives can lead to accumulation of the infused drug, resulting in delayed clearance and prolonged effects. Moreover, continuously infused medications are readily titrated to higher doses to treat agitation, but often the infusion may not be rapidly titrated to lower doses once the acute agitation has been controlled. These factors may combine to lead to adverse outcomes, including prolongation of mechanical ventilation and ICU and hospital stays.

One study addressed the association between continuous infusions and outcomes among 242 mechanically ventilated patients in the ICU.[20] Patients who were managed using intermittent doses of benzodiazepines were extubated sooner, were discharged from the ICU and hospital earlier, and had lower rates of reintubation compared with those who received continuous sedation. Based on these findings, the same group developed a sedation protocol that prioritized analgesia first, then intermittent bolus sedatives, before allowing continuous infusions of sedatives. In a randomized controlled trial, this sedation protocol resulted in earlier extubation and discharge from the ICU and hospital compared with management without a sedation protocol.[13] As previously described, the study comparing "no sedation" versus propofol-employed bolus doses of morphine to control pain, and even extended the preference for intermittent treatments to the use of propofol, which was limited, when possible, to only short 6-hour treatment periods—an approach that significantly improved outcomes.[19]

AVOIDING BENZODIAZEPINES

Although early trials of sedation protocols[13] utilized benzodiazepines as the sedative of choice (when an analgesia-only approach did not adequately treat agitation), more recent trials have consistently shown that benzodiazepines lead to worse outcomes than alternative sedative agents. These findings led to the SCCM guidelines suggesting that nonbenzodiazepine sedatives are preferred over sedation using benzodiazepines.

In the late 1980s and 1990s, more than a dozen randomized trials found sedation with propofol led to better outcomes than sedation with benzodiazepines.[21] However, the results did not lead to changes in standard of care, in part because control groups used continuously infused midazolam rather than intermittent boluses. In fact, clinical guidelines published in 2002 recommended lorazepam as the drug of choice for sedating patients in the ICU.[22] Therefore, a randomized trial was conducted to compare intermittent lorazepam with continuous propofol for the sedation of mechanically ventilated patients in the ICU.[23]

Patients in both groups were managed using daily interruption of sedatives. Despite the avoidance of continuous infusions in only the lorazepam group (since propofol generally requires delivery by continuous infusion when used in the ICU), patients sedated with propofol spent fewer days on mechanical ventilation. These findings were consistent with nearly every other trial comparing propofol with benzodiazepines, suggesting that continuous sedation with shorter-acting agents, such as propofol, when interrupted daily, improve outcomes compared with intermittent doses of benzodiazepines.

More recently, benzodiazepine-based sedation has been compared with other sedative agents; the alternatives to benzodiazepines have been found superior. Seven randomized trials compared sedation with benzodiazepines with dexmedetomidine among mechanically ventilated patients in the ICU; all seven found that patients randomized to sedation with dexmedetomidine had better outcomes, for example, less delirium and earlier extubation, than those sedated with benzodiazepines.[24–30] Similarly, in three trials randomizing mechanically ventilated patients to remifentanil-based sedation versus benzodiazepine-based sedation, those sedated with benzodiazepines had worse outcomes.[31–33] The pharmacologic properties of these and other agents commonly used for sedation in the ICU are presented in Table 150-4.

TARGETING LIGHT SEDATION AND DAILY INTERRUPTION OF SEDATIVES

Regardless of which medications are used to provide analgesia and sedation, it should be given in the smallest doses necessary to treat pain and agitation while allowing patients to maintain wakefulness, that is, light, rather than heavy, sedation should be the goal. Sedation protocols not only prioritize analgesics and intermittent sedatives over continuous infusions, they may also target light sedation (measured using a sedation scale) over moderate or heavy sedation.[13] Other studies[34] that randomized mechanically ventilated patients to targeted light versus moderate or heavy sedation also found that those managed with light sedation had shorter periods of ventilator dependency and ICU stays, as well as fewer disturbing memories of the ICU, compared with those managed with heavier sedation.

Whenever given, sedatives should be held each day that basic safety criteria are met, so that the clinician may assess the need for, and optimal dose of, analgesic and sedative medication required to maintain patient comfort and alert mental status. This period of daily interruption of sedatives, also referred to as a daily "wake-up," "sedation holiday," or "spontaneous awakening trial," led to

TABLE 150-4 Selected Sedative Agents

Drug	Mechanism of Action	Half-life	Intermittent Dose	Infusion Dose	Adverse Effects
Propofol	$GABA_a$ agonist	40 min	0.2–0.6 mg/kg	5–80 μg/kg/min	Hypotension, respiratory depression, pancreatitis, hypertriglyceridemia, PRIS
Dexmedetomidine	CNS α-2 agonist	$T_{1/2}$ a = 6 min $T_{1/2}$ b = 2 h	—	0.2–1.5 μg/kg/h	Hypotension and bradycardia (with loading dose); loss of airway reflexes
Haloperidol	CNS D_1 & D_2	18 h	2–10 mg	0.04–0.15 mg/kg/h	QTc prolongation; extrapyramidal symptoms; dystonia
Midazolam	$GABA_a$ agonist	3 h	0.02–0.08 mg/kg	0.04–0.2 mg/kg/h	Respiratory depression; hypotension; accumulates in renal and hepatic failure
Lorazepam	$GABA_a$ agonist	8 h	0.02–0.04 mg/kg	0.01–0.1 mg/kg/h	Respiratory depression; hypotension; propylene glycol–related acidosis; nephrotoxicity

PRIS, propofol-related infusion syndrome; $T_{1/2}$ a, distribution half-life; $T_{1/2}$ b, elimination half-life; QTc, corrected QT interval.

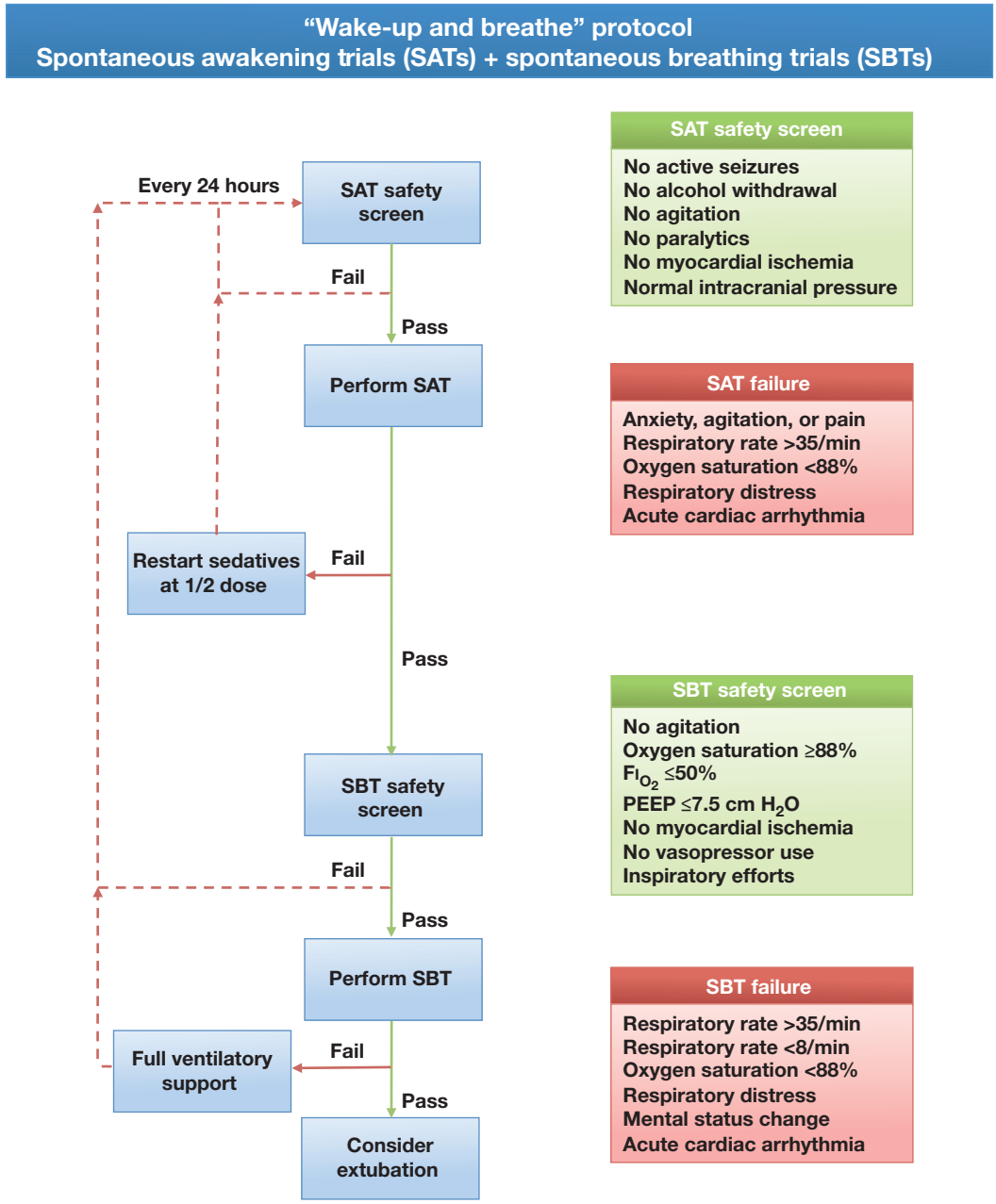

Figure 150-1 Wake-up and breathe flowchart. Each day patients should be assessed for safety criteria to perform a spontaneous awakening trial (SAT), if the safety screen is passed, all sedating medications are held until the patient is RASS-3/SAS 3 or more alert. The patient is then screened for the presence of safety criteria to undergo a spontaneous breathing trial (SBT). As with the SAT, if the SBT safety screen is passed, the patient should undergo an SBT. If the patient meets any of the failure criteria, either sedation or ventilatory support is resumed and the trial begins anew the next day. Combining daily SATs with daily SBTs is associated with shorter duration of mechanical ventilation, ICU length of stay, and a 14% improvement in mortality 1 year following critical illness. *(Reproduced with permission from copyright © icudelirium.org and Vanderbilt University, all rights reserved.)*

significantly better outcomes in two randomized trials. In one,[14] patients managed with daily interruption of sedatives had shorter durations of mechanical ventilation and shorter stays in the ICU, and in another,[15] those managed using this strategy were not only extubated earlier than those in the control group, they also were discharged earlier from the ICU and hospital; furthermore, their 1-year mortality was 14% lower than that observed in the control group. The latter trial paired daily interruption of sedatives or daily spontaneous awakening trials with daily spontaneous breathing trials as part of a strategy referred to as "Wake-up and Breathe" (Fig. 150-1).

Although most sedation trials have examined either targeted light sedation or daily interruption of sedatives, one recent randomized trial attempted to determine whether combining the two strategies yielded improved outcomes over using only targeted light sedation.[35] Patients randomized to targeted light sedation with daily interruption had similar outcomes to those managed without targeted light sedation alone; however, it is unclear whether daily interruption of sedatives was successfully carried out in this trial. Unlike prior studies in which daily interruption of sedatives significantly reduced overall exposure to sedating medications, this approach actually

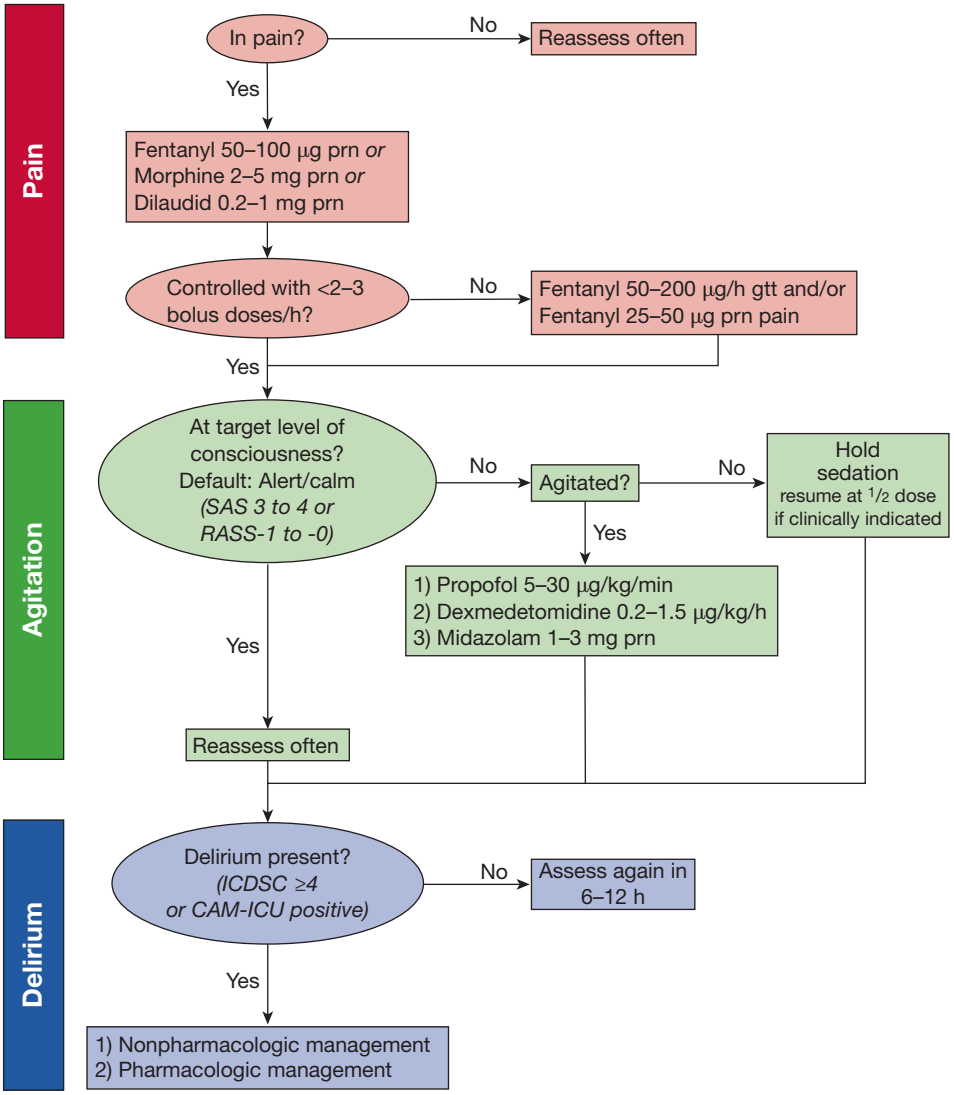

Figure 150-2 Example pain, agitation, and delirium protocol. In this example protocol, pain is first assessed and, if present, IV analgesia is given first with intermittent dosing. If more than three boluses are needed in an hour, an infusion of fentanyl is started. The patient's level of consciousness is monitored using the Richmond Agitation–Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS), with a default of alert/calm or drowsy (RASS-0 to -1 or a SAS 4). If the patient is agitated despite adequate pain control, an infusion of either propofol or dexmedetomidine is preferentially used. Midazolam is begun only if the patient is withdrawing from alcohol, has a propofol intolerance or has received propofol for >96 hours. If the patient is more deeply sedated than RASS-1 or SAS 3, sedatives and analgesics are held until the patient is again alert and calm. If needed, analgesics and sedatives are resumed at half (or less) of the previous infusing dose. Each day patients undergo coordinated spontaneous awakening and breathing trials (SAT+SBT). Finally, patients are screened for delirium using either the Intensive Care Delirium Screening Checklist (ICDSC) or the Confusion Assessment Method for the ICU (CAM-ICU) and if delirium is present a cause is first sought with nonpharmacologic and pharmacologic interventions begun if no reversible cause is identified. *(Reproduced with permission from copyright © icudelirium.org and Vanderbilt University, all rights reserved.)*

increased the doses of benzodiazepines given to patients. Although this trial does not rule out the possibility that daily interruption of sedatives is beneficial when added to targeted light sedation in a way that lowers sedative doses, the study did strongly suggest that the benefit of daily interruption of sedatives is mediated through a reduction in sedative exposure. If overall exposure is not reduced, patients are less likely to benefit.

In summary, modern sedation practices (1) place an emphasis on targeted light sedation, as assessed using a validated tool for determining level of consciousness; (2) prioritize treating pain first using intravenous opiates and then, if the patient requires additional sedation, intermittent and sometimes continuous doses of a nonbenzodiazepine sedative; and (3) routinely incorporate daily interruption of drugs, maintaining a "light" level of sedation (Fig. 150-2).

DELIRIUM IN THE CRITICALLY ILL

Delirium during critical illness represents an acute form of brain dysfunction. Because it is frequently observed in the ICU, this syndrome was previously considered by many to be an expected, inconsequential complication of critical illness, often referred to as "ICU syndrome."[36] Multiple studies have shown, however, that delirium is associated with numerous adverse short- and long-term outcomes. Yet, it often goes unrecognized, in part because the most common presentation is that of hypoactive (quiet) delirium. This section reviews the definition of delirium, key features and differences from other forms of altered mental status, the current understanding of delirium's pathophysiologic basis, risk factors for development, bedside tools specifically designed to assess delirium

in the ICU, the short- and long-term consequences associated with delirium, and methods for preventing and treating delirium.

DEFINITION OF DELIRIUM

The American Psychiatric Association (APA) recently updated their Diagnostic and Statistical Manual of Mental Disorders (DSM).[37] The fifth edition (DSM-5) retained the core diagnostic criteria for delirium while making some changes: What was previously described as a "disturbance of consciousness" is now a "disturbance in attention," and the manual now explicitly states that delirium cannot be diagnosed in the setting of a "severely reduced level of arousal, such as coma." The diagnostic criteria[37] for delirium are (1) a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment); (2) development of the disturbance over a short period of time (usually hours to a few days), in which the development represents a change from baseline in attention and awareness and which tends to fluctuate in severity during the course of a day; (3) an additional disturbance in cognition (e.g., memory deficit, disorientation, language, visual–spatial ability, or perception); (4) the disturbances in criteria (1) and (2) are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma; (5) there is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), exposure to a toxin, or is due to multiple etiologies.

Many signs and symptoms commonly observed in delirium, such as disturbance in the sleep–wake cycle, psychomotor agitation or decreased psychomotor activity, hallucinations, delusions and perceptual disturbances, support the diagnosis, but they are neither sufficient nor required to make the diagnosis. Because these symptoms may be caused by other neurocognitive disorders, delirium is sometimes mistaken for other disorders, particularly dementia. Table 150-5 summarizes differences between delirium and dementia.

Historically, a large number of terms have been used to describe delirium in ICU patients, including encephalopathy, ICU psychosis, ICU syndrome, toxic confusional state, brain failure, subacute befuddlement, postoperative psychosis, and septic encephalopathy.[38] Use of these terms can lead to misunderstanding by practitioners, and certain terms, including ICU syndrome and ICU psychosis, can imply that the syndrome is an expected part of an ICU stay.[36,38] Therefore, regardless of the underlying etiology, the standardized term *delirium* should be used to describe a patient who meets the DSM criteria for delirium, with that underlying etiology then used to describe the delirium (e.g., use the term "delirium due to sepsis" rather than, "septic encephalopathy").[36,38]

PREVALENCE AND SUBTYPES OF DELIRIUM

Delirium is highly prevalent among mechanically ventilated patients in ICUs (60%–80% develop delirium at some point during the ICU stay)[15,24,25,39–41] and also commonly affects nonventilated patients in the ICU setting (20%–40%).[42–45] Delirium is often classified into subtypes according to the motor activity of the patient; these subtypes include *hyperactive, hypoactive*, and *mixed delirium*. Patients with hyperactive delirium are agitated, restless, and may show signs of hallucinations or delusions. Those with the hypoactive subtype are calm, lethargic, and may have decreased spontaneous movements. Finally, the mixed delirium subtype presents with features of both hyperactive and hypoactive delirium. The most common subtypes observed in the ICU are mixed and hypoactive, with purely hyperactive delirium comprising only about 1% of cases of delirium.[46–48] Research is needed to determine the clinical outcomes, especially long-term, associated with specific subtypes of delirium in the critically ill. Nonetheless, as data continue to accumulate that the length of time a patient is delirious is associated with worse clinical outcomes, the fact that a majority of delirious patients in the ICU have mixed or hypoactive subtypes is an important point for clinicians, as the presence of delirium is frequently overlooked.[49]

RISK FACTORS FOR DELIRIUM

Delirium during critical illness is typically a multifactorial syndrome that develops when a vulnerable patient encounters a sufficiently strong insult or insults to precipitate onset of the syndrome.[50] Whereas a patient with high baseline vulnerability, such as an elderly patient with underlying dementia, may require only a mild insult, such as pneumonia, a younger patient without pre-existing cognitive impairment, that is, low baseline vulnerability, may require multiple strong insults, such as severe sepsis, sedation with

TABLE 150-5 Distinguishing Delirium From Dementia

Syndrome	Onset	Course	Diagnostic Features	Associated Features	Common Causes
Delirium	Acute (hours to days)	Fluctuating	Disturbance in attention and awareness Memory impairment, disorientation, or language impairment	Sleep/wake disturbances Extremes in psychomotor activity Emotional disturbances (e.g., fear, anxiety, depression, irritability, euphoria, apathy)	Acute medical illnesses Medications Substance intoxication or withdrawal Multifactorial
Dementia	Insidious (months to years)	Progressive	Memory impairment, plus one of the following: – Aphasia – Apraxia – Agnosia – Impaired executive functioning Impairments must be severe enough to cause impairments in social or occupational functioning and represent a decline from baseline	Visuospatial impairment Little/no awareness of memory impairment Gait disturbance Anxiety/mood/sleep disturbances	Dementia of Alzheimer type Vascular dementia Chronic medical conditions (Pick disease, HIV, stroke, head injury)

Source: Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC: American Psychiatric Association; 2013.

benzodiazepines, and immobilization. This scenario is not uncommon, given that critically ill patients are exposed on average to 11 risk factors for delirium.[51]

Risk factors for delirium can be thought of as predisposing factors and include baseline patient characteristics and premorbid conditions, as well as precipitating factors, such as those related to critical illness and treatment in an ICU. Baseline risk factors include older age, baseline cognitive impairment or dementia, use of alcohol or tobacco, hypertension, visual or hearing impairment, and APOE4 genotype.[40,52–56] A number of precipitating factors are linked to development of delirium during critical illness, including high severity of illness, admission to an ICU for a medical illness, need for mechanical ventilation, high number of infusing medications, hypotension, acidosis, fevers, sepsis, electrolyte abnormalities, liver function test abnormalities, and anemia.[41,52–55,57,58] Whereas each of these risk factors results from a patient's critical illness, factors associated with treatment may also increase risk. Precipitating risk factors associated with treatment in an ICU include immobility, presence of gastric tubes, bladder catheters, arterial lines, sedative and analgesic medications, particularly benzodiazepines, and those factors related to the overall ICU environment, including lack of daylight, isolation, lack of visitors, and sleep disturbances.[57,59]

PATHOPHYSIOLOGY OF DELIRIUM

Delirium pathophysiology, although incompletely understood, likely represents a final common pathway from many different and, perhaps, interrelated pathophysiologic mechanisms, including neurotransmitter imbalances, inflammatory responses, aberrant stress responses, and impaired cerebral perfusion. It is thought that imbalances in the neurotransmitters that maintain arousal and sleep–wake cycles – acetylcholine and dopamine – are primary drivers of delirium.[60,61] Impaired central cholinergic functioning can result from derangements occurring anywhere along the pathway from acetylcholine production to its release and action of postsynaptic receptors. Acetylcholine deficiency or blockade has been associated with delirium, as has dopamine excess, likely through dopamine receptor regulation of acetylcholine activity.[61–63] Other neurotransmitters, such as gamma-aminobutyric acid (GABA), norepinephrine, serotonin, glutamate, and melatonin have also been hypothesized to play a role in delirium, although the contribution of these neurotransmitters in the development of delirium is less well understood.[60–65]

Alterations in precursor molecules to neurotransmitters, such as dopamine, norepinephrine, serotonin, and melatonin – in particular, the large neutral amino acids (LNAAs) – have also been hypothesized to be involved in the pathogenesis of delirium.[65] LNAAs, which include leucine, valine, tryptophan, tyrosine, and phenylalanine, compete for transfer across the blood–brain barrier via a single transport receptor, such that increased transport of one LNAA results in decreased transport of others. Thus, the concentration of neurotransmitters in the CNS is related to changes in serum concentrations of LNAAs, and changes in these concentrations have been associated with delirium during critical illness.[66–68]

Systemic inflammation, which is very common during critical illness, is also thought to play a role in development of delirium. Inflammatory molecules, such as interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor-α, prostaglandins, and blood-borne molecules, such as lipopolysaccharide, are released in response to infection, tissue damage, and surgery. These molecules interact with the brain via direct autonomic neural pathways, second-messenger systems, active transport across the blood–brain barrier, and through disruptions in the blood–brain barrier, resulting in neuroinflammation.[69–71] Neuroinflammation triggers CNS production of additional inflammatory cytokines and metalloproteinases, release of reactive oxygen species, and expansion and activation of microglia, resulting in alterations in CNS perfusion, impaired neurotransmitter production, and derangements in oxidative metabolism, ultimately leading to neuronal damage and cell death.[69,71] Neuronal death results in a functional disconnect between neuroanatomical structures, culminating in the neurobehavioral changes observed in delirium.[69]

SCREENING TOOLS FOR DELIRIUM

Since many delirious patients are lethargic or calm, rather than agitated, delirium in the ICU is overlooked nearly 70% of the time.[49] Thus, current expert guidelines recommend that all patients in an ICU be routinely monitored using a well-validated delirium-screening tool.[5] Two screening tools that were developed specifically for assessment of critically ill adult patients, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), have been the most rigorously validated and widely implemented and, thus, are recommended in expert guidelines.[5] Validated before the recent release of DSM-5[37] criteria, both the CAM-ICU and the ICDSC were compared in validation studies with expert psychiatric examinations applying the DSM-IV[72] criteria for delirium and were found to have high sensitivity and specificity, as well as excellent interrater reliability when performed by ICU physicians and nurses.[39,44,73–77] Both screening tools identify features of delirium that remain part of the DSM-5 definition, such that the tools are considered current and valid in the DSM-5 era.

When using either the CAM-ICU or the ICDSC, the first step in assessing for delirium is to assess the patient's level of arousal/consciousness (see Assessing Agitation and Level of Consciousness in the Critically Ill); as stated in the DSM-5, delirium cannot be assessed in the setting of coma. In validation studies of the CAM-ICU, this was operationalized by determining that patients were arousable to voice (e.g., RASS-3 or more awake) before proceeding with the CAM-ICU assessment. Similarly, the ICDSC excludes patients in coma or stupor from delirium assessment. Once level of consciousness is assessed, the second step in the delirium screen is to assess the content of consciousness using either the ICDSC or the CAM-ICU.

The CAM-ICU was developed based on the full Confusion Assessment Method[78] but tailored to the specific needs of patients in the ICU (e.g., it can be performed in both nonintubated and intubated patients, even in the setting of sedation [as long as the patient is not comatose]). During what is typically a 1- to 2-minute evaluation, the CAM-ICU assesses four key features of delirium: (1) Acute change or fluctuation in mental status, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking.[39,74] The CAM-ICU is positive, that is, the patient is considered to have delirium, if features 1 and 2 are present and *at least* feature 3 or 4 is present. See Figure 150-3 for instructions on how to assess each feature in the CAM-ICU. This tool has been translated into over 20 different languages, and many of these translated versions have been validated.

The ICDSC is an 8-item checklist of delirium symptoms assessed over an 8- to 24-hour period. Providers monitor patients for the symptoms on the checklist during that period of time (e.g., during a nursing shift) and mark items on the checklist as they are observed. The symptoms include altered level of consciousness, inattention, disorientation, hallucinations/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake disturbances, and fluctuation of symptoms. One point is given for each symptom observed; a score of four or greater indicates delirium (Table 150-6).

OUTCOMES ASSOCIATED WITH DELIRIUM

In both the short- and long-term, patients who suffer from delirium are at risk for a number of adverse outcomes. Within the context of the acute critical illness, patients who are delirious are more likely to remove catheters and endotracheal tubes, require physical restraints, and have prolonged mechanical ventilation.[52,79,80] In

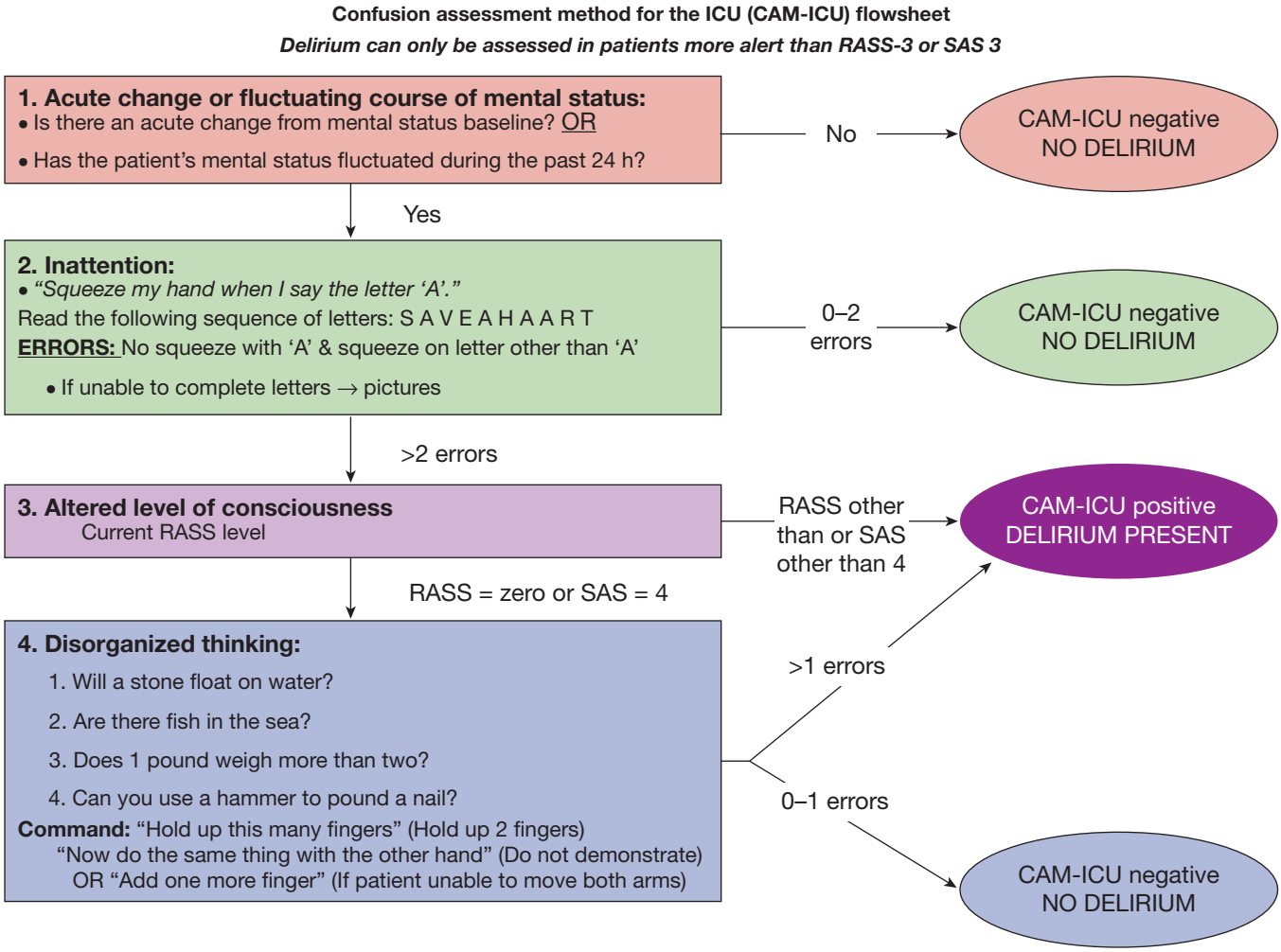

Figure 150-3 The Confusion Assessment Method for the ICU (CAM-ICU). The CAM-ICU assesses for the four features of delirium. Feature 1 is an acute change in mental status or a fluctuating mental status *(orange box)*, feature 2, is inattention, *(green box)*, feature 3, is altered level of consciousness *(purple box)*, and feature 4, is disorganized thinking *(blue box)*. A patient screens positive for delirium if features 1 and 2 and either feature 3 or feature 4 are present. *(Reproduced with permission from copyright © 2002, E. Wesley Ely, MD and Vanderbilt University.)*

addition, compared with those who do not become delirious, these patients are at higher risk for prolonged stays in the ICU and hospital, higher healthcare costs, and discharge to a location other than home.[39,55,80–83]

The adverse outcomes associated with delirium do not end at the time of hospital discharge. In two separate prospective cohort studies, each additional day a patient was delirious in the ICU was associated with a 10% increase in the hazard of death in the 6 to 12 months following hospital discharge.[84,85] In addition, two separate cohort studies have identified duration of delirium as a strong independent predictor of long-term cognitive impairment, with longer delirium durations in the ICU associated with poorer cognitive performance a full year after discharge.[86,87] Finally, one additional study noted that duration of delirium during critical illness was also associated with activities of daily living among survivors of critical illness, with prolonged delirium predicting disability during long-term follow-up.[88]

■ PREVENTING DELIRIUM

Preventing delirium from developing during a patient's ICU stay can be difficult because at the time of the patient's ICU admission, acute organ failures (often including delirium) are already present. Nevertheless, preventative measures may be beneficial, since some patients do not develop delirium until several days into their ICU stay. Additionally, because the duration of delirium is also associated with adverse outcomes, including cognitive impairment, physical disability, and death, measures that may shorten the duration of delirium should be implemented. Although not all risk factors for delirium can be avoided, three risk factors common in the ICU – exposure to sedative and analgesic medications, immobility, and sleep deprivation – have been targeted by interventions designed to prevent delirium; a number of studies have shown that these interventions are associated with reductions in delirium.

Benzodiazepines are consistently associated with the development of delirium in patients in the ICU and, therefore, serve as an easily modifiable risk factor. In studies of medical, surgical, cardiac, trauma, and burn patients, higher doses of benzodiazepines have been independently associated with higher risk for delirium.[41,53,89,90] Based on these data, a number of interventions intended to reduce exposure to benzodiazepines have been investigated. Sedation of mechanically ventilated patients using dexmedetomidine, for example, rather than benzodiazepines, reduced daily risk of delirium in two randomized trials.[24,25] In addition, in one study addressing avoidance of benzodiazepines as one part of a multicomponent quality improvement program designed to reduce delirium risk, a significant increase in days patients spent without delirium was noted.[91]

TABLE 150-6 The Intensive Care Unit Delirium Screening Checklist (ICDSC)

1. **Altered level of consciousness** Choose **ONE** from A–E
Note: May need to reassess patient if recent administration of sedation therapy
A. Exaggerated response to normal stimulation SAS = 5, 6, or 7 Score 1 point
B. Normal wakefulness SAS = 4 Score 0 points
C. Response to mild or moderate stimulation SAS = 3 Score 1 point
(follows commands) **Score 0 if LOC related to recent sedation/analgesia**
D. Response only to intense and repeated stimulation (e.g., loud voice and pain) SAS = 2 **Stop assessment**
E. No response SAS = 1 **Stop assessment**
2. **Inattention** Score 1 point for any of the following abnormalities:
A. Difficulty in following commands OR
B. Easily distracted by external stimuli OR
C. Difficulty in shifting focus
Does the patient follow you with their eyes?
3. **Disorientation** Score 1 point for any one obvious abnormality:
A. Mistake in either time, place, or person
Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in? (list examples)
4. **Hallucinations or delusions** Score 1 point for either:
A. Equivocal evidence of hallucinations or a behavior due to hallucinations (Hallucination = perception of something that is not there with NO stimulus) OR
B. Delusions or gross impairment of reality testing (Delusion = false belief that is fixed/unchanging)
Any hallucinations now or over past 24 h? Are you afraid of the people or things around you?
(fear that is inappropriate to clinical situation)
5. **Psychomotor agitation or retardation** Score 1 point for either:
A. Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger (e.g., pulling IV lines out or hitting staff) OR
B. Hypoactive or clinically noticeable psychomotor slowing or retardation
Based on documentation and observation over shift by primary caregiver
6. **Inappropriate speech or mood Score 1 point for either:**
A. Inappropriate, disorganized, or incoherent speech OR
B. Inappropriate mood related to events or situation
Is the patient apathetic to current clinical situation (i.e., lack of emotion)?
Any gross abnormalities in speech or mood? Is patient inappropriately demanding?
7. **Sleep/wake cycle disturbance Score 1 point for:**
A. Sleeping less than 4 h at night OR
B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) OR
C. Sleep ≥4 h during day based on primary caregiver assessment
8. **Symptom fluctuation Score 1 point for:**
Fluctuation of any of the above items (i.e., 1–7) over 24 h (e.g., from one shift to another) **based on primary caregiver assessment**
TOTAL ICSDC SCORE (Add 1–8)

This 8-item checklist should be completed using clinical information gathered over the last 8 or 24 h. First assess level of consciousness. If level of consciousness is C, D, or E proceed with the remaining items. Patients are given 1 point for having an obvious manifestation of the item. A score of 4 or greater is considered a positive delirium screen.

SAS, Riker Sedation–Agitation Scale; LOC, level of consciousness.

Source: Adapted with permission from Morris PE1, Goad A, Thompson C et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238–2243.

Opioid analgesic medications have also been associated with development of delirium in some studies, but the relationship between opioids and delirium is not as straightforward as the one between benzodiazepines and delirium. This difference likely relates to the dual effects of opioids. For example, when opioids are used to heavily sedate patients (particularly when used to induce coma), the risk of delirium is dramatically increased.[54,55,58] Alternatively, when opioids are used primarily to relieve pain, such as in patients with trauma or burns, the risk of delirium is actually reduced.[41,92,93] Although no delirium prevention trial to date has focused on the role of opioids, treating pain while taking care to not oversedate patients (through use of the principles described earlier in this chapter) may protect patients from developing delirium.

Immobility, particularly due to the use of physical restraints, is a strong risk factor for the development of delirium among both non–ICU-hospitalized and critically ill patients.[50,57,94] Studies in which early mobilization is promoted among critically ill patients have found that it reduced delirium.[95–98] For example, in one study,[95] mechanically ventilated patients in the ICU who were randomized to early physical and occupational therapy, rather than usual care (i.e., delayed physical therapy), on average, spent 2 fewer days in delirium than those in the control group. Similarly, another study noted that a quality improvement program focused on reducing sedation and implementing physical therapy early during the ICU stay resulted in fewer days in delirium.[99]

Critically ill patients frequently suffer sleep deprivation. In fact, studies suggest that normal sleep rarely, if ever, occurs during acute respiratory failure requiring mechanical ventilation in the ICU; in one study, only a small percentage of the sleep observed was restorative (REM) sleep, and nearly half occurred during daytime hours.[100] In light of these data and the known association between sleep deprivation and delirium outside the ICU, investigators studied the effect of earplugs in a randomized trial of patients in ICUs and found significant reductions in incidence of delirium.[101] Using a multicomponent intervention that reduced nocturnal lights and noises and provided eye masks, earplugs, and pharmacologic sleep aids, others were able to increase the number of days that patients were not delirious.[102]

TREATING DELIRIUM

After implementing the preventative measures, practitioners will likely continue to observe delirium in the ICU. Because delirium often serves as the "canary in the coal mine," heralding the onset of a new or exacerbated underlying pathology (e.g., infection, shock, or metabolic abnormality) or a response to a deliriogenic medication, a positive screen for delirium should prompt an immediate search for, and correction of, an underlying etiology and any modifiable risk factors. After addressing potentially modifiable causes of delirium, pharmacologic therapies can be considered. Although antipsychotics are frequently used to treat delirium in the ICU,[103] they are primarily used to treat hyperactive delirium[104]; this practice is primarily supported by results from studies conducted outside the ICU.

Haloperidol, the drug most commonly prescribed for delirium in the ICU,[103] is a "typical" antipsychotic that works primarily as a dopamine receptor antagonist by blocking the D2 receptor, which is believed to treat the "positive" symptoms of delirium (e.g., hallucinations, unstructured thought patterns, etc.). It also may have some sedative effect that does not result in respiratory depression. Outside the ICU, the recommended starting dose of haloperidol is 0.5 to 1.0 mg orally or parenterally, repeated every 20 to 30 minutes until the desired effect is achieved, which is usually resolution of agitation, rather than complete resolution of delirium. In the ICU, higher doses are often used, for example, 2 to 10 mg intravenously, with doses repeated every 20 to 30 minutes until the desired effect is attained. Some practitioners use scheduled haloperidol every 6 to 12 hours (intravenously or orally). Neither of these approaches, however, has been proved to be beneficial to patients in ICUs. Typical antipsychotics, in general, have not yet been extensively studied in the ICU setting. The only randomized trial to compare haloperidol with placebo for the prevention and treatment of delirium during critical illness found no significant improvement among patients treated with an antipsychotic.[105] This pilot study was small, however, and it cannot be interpreted as ruling out a beneficial effect of haloperidol in delirium.

Atypical antipsychotics (e.g., risperidone, ziprasidone, quetiapine, and olanzapine) are also used to treat delirium in the ICU.[105–107] The rationale supporting their use over haloperidol is theoretical and arises from the atypical antipsychotics' effect not only on dopamine, but also on other potentially key neurotransmitters, such as serotonin, acetylcholine, and norepinephrine.[108] Results of prospective studies comparing atypical antipsychotics with placebo or typical antipsychotics in the treatment of delirium have been mixed.[105,107] Although one very small randomized trial found that quetiapine was effective in treating delirium compared with placebo,[106] another small randomized trial found no differences in neurologic outcomes among patients treated with ziprasidone, haloperidol, or placebo.[105] In aggregate, these trials do not provide strong evidence for use of atypical antipsychotics over typical antipsychotics; thus, recent guidelines review the evidence but do not explicitly recommend antipsychotics for the treatment of delirium.

When antipsychotics are used to treat delirium in the ICU, clinicians should monitor for adverse effects, which may include hypotension, acute dystonia, extrapyramidal effects, thrombotic complications, oversedation, laryngeal spasm, neuroleptic malignant syndrome, glucose and lipid dysregulation, and anticholinergic effects, such as dry mouth, constipation, and urinary retention. One of the most immediate life-threatening adverse effects of antipsychotics is torsades de pointes,[109–111] so these agents should be given to patients with prolonged QTc intervals with caution.

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CHAPTER 151

Early Mobilization of Patients in the ICU

William D. Schweickert

INTRODUCTION

Improvements in diagnosis and resuscitation of critically ill patients have prompted investigation into the burden of "survivorship."[1–5] Observational research has described substantial morbidity in survivors of critical illness, including general deconditioning, muscle weakness, dyspnea, depression, anxiety, and reduced health-related quality of life.[6] A major catalyst for widespread attention was the comprehensive observations on a cohort of survivors of acute respiratory distress syndrome (ARDS).[7] In this case series, patients were young and generally healthy prior to ARDS, and they experienced severe illness with prolonged critical care. Despite severe acute lung injury, serial follow-up examinations demonstrated that lung function generally normalized during the first year after ICU discharge. In contrast, all patients reported poor function attributed to the loss of muscle bulk, proximal limb weakness, and fatigue. Patients exhibited impaired endurance, and only 49% of patients had returned to work. At 5 years after ICU discharge, subjective weakness and decreased exercise capacity continued.[8] Although 77% of patients were working by the fifth year, patients often required a modified work schedule, gradual transition back to work, or job retraining. In addition, patients were plagued with psychological illness. More than half of survivors experienced at least one episode of depression or anxiety.

Other investigations have reported similar findings of post-ARDS debilitation.[9,10] An observational trial measured a 66% cumulative incidence of physical impairment during 2-year follow-up.[9] The impairment, defined as the acquisition of two or more dependencies in instrumental activities of daily living, had greatest incidence by 3 months after discharge and was associated with longer ICU stay and prior depressive symptoms.

Acquired neuromuscular weaknesses, loss of function, and cognitive impairment have been measured in other critical care settings, such as in severe sepsis and during mechanical ventilation in the elderly. For example, the morbidity of a hospitalization for severe sepsis was evaluated utilizing a registry of Americans over age 50 years who underwent biennial evaluations of cognitive and physical function.[11] Among patients with no functional limitations at baseline, hospitalization for severe sepsis was associated with the development of 1.57 new limitations, as well as a more rapid rate of development of functional limitations after hospitalization. In addition, the incidence of severe sepsis was highly associated with progression to moderate-to-severe cognitive impairment. Similar acquired disability has been observed in a longitudinal study of elderly patients undergoing hospitalizations that included need for mechanical ventilation.[12] In adjusted analyses, mechanical ventilation was associated with a 30% greater disability in activities of daily living and a 14% greater disability in mobility.

These studies show that decrements in physical function occur across the spectrum of critical illness. Although outcomes may be influenced by other factors, such as age, pre-existing comorbidities, acquired psychological and cognitive dysfunction, and social support, it is clear that weakness needs to be recognized early to enable preventive interventions.

ICU-ACQUIRED WEAKNESS

Many patients admitted to the ICU develop a syndrome of neuromuscular dysfunction characterized by generalized muscle weakness and an inability to be liberated from mechanical ventilation. Since this syndrome occurs in the absence of preexisting neuromuscular disease, it is believed to reflect illnesses or treatments occurring in the ICU. Early reports described two categories of acute, acquired neuromuscular dysfunction: polyneuropathy and myopathy.[13–15] Decades of research on this acquired nerve and muscle injury has characterized specific phenotypes with respect to comprehensive physical examination findings, electrophysiologic testing results, and muscle and nerve histopathology. Overall, the spectrum of neuromuscular disorders acquired in the ICU is now collectively referred to as "ICU-acquired weakness" (ICUAW).[16]

Several studies have attempted to establish the prevalence of ICUAW and its associated risk factors. To date, the best summary data are outlined in a systematic review of 24 published studies that included both clinical and electrophysiologic characterizations of the weakness.[17] Of 1421 total patients with sepsis, multiorgan failure, or prolonged mechanical ventilation, 46% had ICUAW. The risk of ICUAW was associated with hyperglycemia (and inversely associated with tight glycemic control), the systemic inflammatory response syndrome (SIRS), sepsis, multiple organ dysfunction, renal replacement therapy, and catecholamine administration. Across studies, there was no consistent relationship between ICUAW and patient age, gender, severity of illness, or medication exposure. Similar findings have been found in a seminal observational study describing ICUAW.[18] In this study of patients undergoing seven or more days of mechanical ventilation, 25% experienced ICUAW. Independent predictors of ICUAW included the number of days with multiple organ dysfunction and the duration of mechanical ventilation. In contrast to the systematic review, female sex and administration of corticosteroids were strong predictors of ICUAW.

Unfortunately, few modifiable risk factors for ICUAW have generated opportunities to improve outcomes. Prospective, randomized trials focusing on exposure to corticosteroids and neuromuscular blocking agents have demonstrated neither consistent nor conclusive results for an association with weakness.[19–21] A Cochrane review identified only one successful preventive intervention for ICUAW: insulin therapy with strict glycemic control.[22] This finding, based on two, single-center, randomized trials, has been challenged by results from subsequent multicenter trials. Specifically, recent trials of intensive insulin therapy have been associated with an increased risk of severe hypoglycemia and either increased or unchanged mortality rates when compared to more permissive blood glucose ranges.[23,24] Accordingly, this treatment option has not been embraced.

For all forms of ICUAW, care is supportive and includes aggressive management of sepsis and underlying medical conditions. Because prolonged immobilization and bed rest have been shown to accelerate muscle loss, early mobilization has emerged as a potential preventive measure. Although no one has systematically measured immobility during ICU care, clinicians acknowledge its occurrence during the earliest days of critical illness, particularly during deep sedation or neuromuscular blockade, specific mechanical ventilation strategies (e.g., prone ventilation), and other advanced support (e.g., continuous hemodialysis).

THE CONSEQUENCES OF BED REST AND INACTIVITY

Rest is necessary for the repair of weak or damaged tissue and muscle remodeling. Prolonging rest has potential benefit, such as avoiding pain in the injured body part and permitting maximal

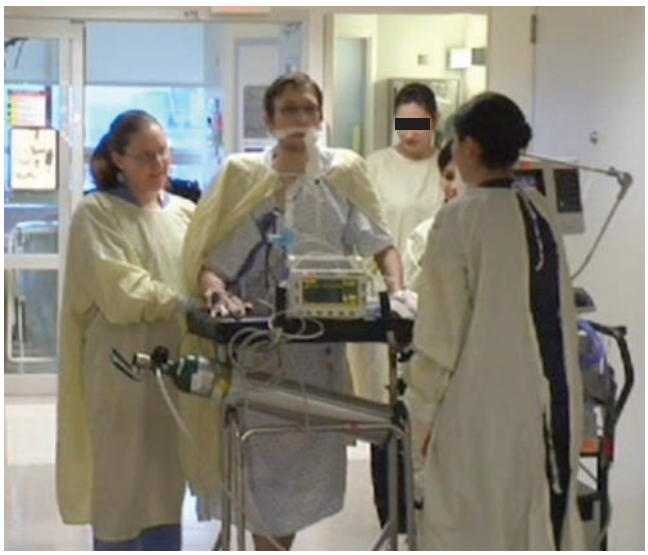

Figure 151-1 **A.** A patient with cystic fibrosis, pneumonia, and respiratory failure ambulating in ICU on day 5 while receiving invasive mechanical ventilation via an oral endotracheal tube. He is accompanied by his nurse, respiratory therapist, physical therapist, and wife. **B.** Patient with exacerbation of chronic obstructive pulmonary disease and pneumonia marching in place while undergoing noninvasive ventilation under the direction of a physical therapist.

utilization of metabolic resources for healing.[25] Reducing oxygen consumption, minute ventilation needs, and cardiac demand via rest during critical illness may be logical. However, investigations have found few studies that demonstrate even modest benefits from extending bed rest. In contrast, trials of rheumatoid arthritis, low back pain, uncomplicated myocardial infarction, pulmonary tuberculosis, and deep venous thrombosis have demonstrated improved outcomes when bed rest was limited or avoided.[26]

Prolonged physical inactivity has been modeled through investigations of space flight, immobilization of a limb, lower limb suspension, and bed rest.[25,27] Each of these modalities demonstrate that muscle mass, as assessed using computed tomography or magnetic resonance imaging, decreases by approximately 1.5% to 2.0% per day during the first 2 to 3 weeks of enforced rest. Measures of muscle strength demonstrate weakness that parallels the changes in muscle size. For example, individual studies have shown knee extensor strength declined by 22% after 14 days and by 53% after 28 days of limb immobilization.[28,29] Limb casting models of immobilization demonstrate declines in strength as high as 5% to 6% per day.[30,31] The antigravity muscle groups – located in the legs, trunk, and neck – experience the most pronounced muscle atrophy.

Limb injuries of prolonged inactivity also include loss of joint range of motion and muscle contractures. One study of survivors of a 2-week or longer critical illness found that joint contractures occurred in 39% of patients.[32] At the time of discharge from intensive care, 34% of patients had at least one functionally significant contracture, and 23% of patients had functionally significant contractures persisting at the time of discharge. The most commonly affected joints at the time of discharge were the elbow (34%) and ankle (33%).

Other injuries associated with prolonged bed rest and inactivity include pressure ulcers, atelectasis, and thromboembolic disease.[25] Indolent effects, such as endocrinopathy and cardiovascular function, have also been described. For example, healthy volunteers undergoing bed rest demonstrate insulin resistance and increases in total cholesterol and triglycerides.[33] Orthostatic intolerance from baroreceptor dysfunction is commonplace; studies demonstrate increases in systemic vascular resistance following bed rest. For the patient in the ICU, superimposing these developments on existing critical illness may be costly with respect to both survival and survivorship.

MOBILIZATION OF THE CRITICALLY ILL PATIENT

Mobility has long been recognized as a measure to hasten recovery. Given the commonality of ICUAW and the potential for immobility in routine critical care, particularly during mechanical ventilation, investigators have targeted early mobilization as a potential opportunity to improve strength and functional outcomes in survivors (Fig. 151-1). In summary, recent trials highlight that early exercise and mobilization are safe to conduct despite ongoing critical illness, improve patient functional outcomes, and shorten ICU and hospital lengths of stay.[34] Although most investigations have focused selectively on patients undergoing mechanical ventilation, the results are likely generalizable to broader populations of critically ill patients.

PASSIVE RANGE OF MOTION

Passive range of motion exercise is conducted to preserve the range of the joint. Passive range of motion exercise is an expectation of routine care, yet often overlooked. However, evidence to support the isolated use of passive movement is weak. Limited evidence suggests that it may prevent protein degradation, maintain muscle mass, and alter the inflammatory profile in humans. For example, in 20 subjects with severe sepsis or septic shock randomized to 30 minutes of predominantly passive exercise or no intervention, the group receiving passive exercise demonstrated preserved fat-free mass, decreased IL-6 and increased IL-10 levels compared with control patients, who lost 7% of fat-free mass in the first 7 days following admission to the ICU.[35]

One study examined whether muscle wasting in critically ill patients could be prevented with stretching alone.[36] Continuous passive motion was administered by a machine over 7 days to one leg of five separate critically ill adults. In the muscles that received continuous passive stretch, smaller reductions in muscle fiber cross-sectional area and protein per gram of wet muscle weight were noted. However, clinical observation suggests that more than simple passive movement is necessary to help preserve muscle strength.

■ ACTIVE RANGE OF MOTION

"Early mobilization" is defined as the intensification and early application of physical and occupational therapy administered to critically ill patients. The safety and feasibility for early mobilization during mechanical ventilation was first captured in a descriptive cohort study published in 2007.[37] This single-center study in a respiratory ICU tracked the activity levels of 103 patients over an average of 10 days following inception of critical illness. The exercise program began once patients responded to verbal stimulation and exhibited stable respiratory and cardiovascular function (defined as $F_{I_{O_2}} \leq 0.6$, PEEP ≤ 10 cm H_2O, and absence of orthostatic hypotension and catecholamine drips). The exercise team, including physical therapist, respiratory therapist, nurse, and critical care technician, focused training on three activities: sitting on the edge of the bed, sitting in a chair after bed transfer, and ambulation. Maximal activity level was tracked. For this cohort, ICU measurements at discharge showed that 77% of patients were able to ambulate (including 69% able to ambulate >100 ft), 15% of patients were able to sit in a chair, and 5% of patients were only able to sit at the edge of the bed. Most importantly, only 14 of the 1449 activity events resulted in predefined adverse events. Specifically, there were five falls to the knees without injury, four drops in systolic blood pressures to <90 mm Hg, one systolic blood pressure rise to >200 mm Hg, three oxygen desaturations to <80% saturation, and one nasal feeding tube dislodgement.

To emphasize the differences in their practice of early mobilization compared to other ICUs, the same investigators studied the performance levels of mechanically ventilated patients within a 2-day window before and after transfer to the ICU.[38] Within 24 hours of arrival, patients successfully underwent more intense physical activities. For example, ambulation increased from 11% pretransfer to 41% within 48 hours. Multivariable logistic regression demonstrated that transfer to the therapy-dominant ICU was independently associated with the likelihood of ambulation. This study was the first to demonstrate that a unit-based culture of early mobilization could significantly influence patient functional performance.

The first prospective trial comparing early exercise and mobilization with usual care was published in 2008.[39] In this study, a mobility team, including a physical therapist, nurse, and nurse assistant, implemented stepwise increases in therapy based on patient participation and tolerance. Therapy spanned passive range of motion (ROM) to active ROM exercise, sitting, transfers, and ambulation. Therapy practices between groups were strikingly different: 80% of intervention patients underwent at least one therapy session compared with only 47% of patients in the usual care group. Intervention patients were bedridden for a shorter period (8.5 vs. 13.7 days) and had a reduced hospital length of stay (14.9 vs. 17.2 days). Recently, longer-term outcomes of the initial 330 patient cohort were reported.[40] In multivariate analysis, the lack of early ICU mobility was independently associated with readmission(s) or death during the first year. Although the etiology for readmission and death was not specified, these findings suggest early ICU mobility may have a sustained effect.

In 2009, a prospective, dual-center, randomized, clinical trial of very early mobilization was published.[41] One hundred and four patients in medical ICUs were enrolled within 72 hours of the onset of respiratory failure requiring mechanical ventilation. Patients were randomized to an intervention group that received mandated, progressive physical and occupational therapy, or a control group with therapy services ordered by the primary team. The dual therapist team treated patients daily with progressive mobilization, including bed exercises, sitting at the edge of the bed, simulation of activities of daily living, transfer training, and ambulation. In the intervention group, patients underwent therapy on 87% of days, beginning 1.5 days after intubation, compared to 7 days in the control group. Within 4 days, 76% of intervention group were sitting at the edge of the bed, 33% were standing and transferring to a chair, and 15% were ambulating. At hospital discharge, patients in the intervention group had a higher rate of return to independent functional status (59% vs. 35%), greater independent walk distance, and were more likely to be discharged to home (43% vs. 24%). In addition, patients in the intervention group experienced a reduced duration of delirium (2 vs. 4 days) and more ventilator-free days (23.5 vs. 21.1 days), but no significant difference in ICU or hospital length of stay.

Finally, combining the interventions of sedation minimization and early mobilization may yield the most pronounced benefit for patients with respiratory failure. This was demonstrated by a quality improvement project conducted in 2010 in a tertiary academic center.[42] In the preintervention phase, mechanically ventilated patients were deeply sedated during 58% of all patient-days and were either deeply sedated or delirious on more than 85% of all patient-days. Only 24% of patients had consultations for PT or OT while in the medical ICU. Early mobilization stakeholders implemented the following changes: education on sedation and mobilization practices, augmentation of therapist staffing, promotion of physiatry and neurology consultation, and provision of regular feedback to clinicians on these practices. In the postintervention period, patients were more likely to be awake without delirium, receive more therapy services, and exhibit improved functional mobility. In addition, administrative data on all patients in the medical ICU demonstrated reductions in lengths of stay in the ICU (2.1 days) and hospital (3.1 days).

■ USE OF ASSISTIVE TECHNOLOGIES

Assistive technologies offer the opportunity to begin physical activity at the earliest phases in critical illness. So far, two techniques have been studied most extensively: cycle ergometry and neuromuscular electrical stimulation. Both interventions offer the promise of muscle engagement in the noninteractive patient.

The cycle ergometer is a stationary cycle that can be positioned above the foot of the bed (Fig. 151-2). The device can alter the

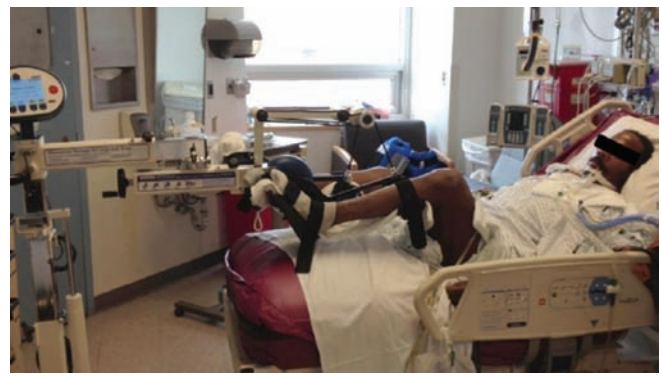

Figure 151-2 A 58-year-old man with chronic hemiparesis undergoing passive cycling on a cycle ergometer while undergoing invasive mechanical ventilation for acute respiratory distress syndrome complicated by severe sepsis and hypoactive delirium.

amount of work performed by the patient, including passive cycling for the comatose patient. Engaged patients can actively pedal with varying resistance. In healthy subjects undergoing prolonged immobilization, this cycling has been shown to preserve thigh muscle thickness.[43] In addition, the technique has been proved to be both feasible and safe during hemodialysis and for patients with chronic obstructive pulmonary disease.[44,45]

Multimodality mobilization, combining cycle ergometry and standard physical therapy, has been tested in a single-center randomized trial.[46] Ninety patients with ICU stays greater than 5 days were randomized to either multimodality therapy or standard physical therapy alone. Patients receiving the intervention underwent cycling sessions conducted 5 days per week, lasting approximately 30 minutes per session. The study demonstrated safety, feasibility, and efficacy. Of the 425 cycling sessions, no serious adverse events were noted. Only 4% of sessions resulted in early termination due to oxygen desaturation or significant changes in blood pressure. At hospital discharge, patients in the intervention group exhibited a longer 6-minute walk distance, higher survey scores on physical function, and greater increases in quadriceps force.

The second technique, neuromuscular electrical stimulation (NMES), creates nonvolitional contraction of skeletal muscles. Skin surface electrodes deliver low-voltage electrical impulses to underlying muscle. NMES has been studied in outpatients with chronic heart failure and chronic obstructive lung disease to preserve or improve muscle mass, exercise capacity, and function.[47] Despite the promise of the technique, randomized trials in critical illness have reported conflicting results. Six unique ICU trials in patients with acute respiratory failure and sepsis and a trial in patients receiving chronic mechanical ventilation demonstrated mixed, but promising results for potential efficacy.[48] For example, the largest study of critically ill patients randomized 140 patients to NMES versus standard care. Sessions of transcutaneous lower extremity muscle stimulation were conducted daily for 1 hour.[49] Patients in the intervention arm exhibited higher static muscle strength sum scores compared with controls. However, concerns over endpoint selection, measurement

TABLE 151-1 Criteria to Guide Physical Therapy Consultation based on Prior Clinical Trials of Exercise and Mobilization

Neurologic	Patient responsive to voice (e.g., RASS ≥ -3)[40]
Respiratory	PEEP ≤ 10 cm H_2O
	F_{IO_2} ≤ 0.6
Circulation	Minimal vasopressor(s)
	No increase in dose of any vasopressor for ≥ 2 h
	No evidence of active myocardial ischemia
	Stable heart rate and cardiac rhythm

F_{IO_2}, Fraction of inspired oxygen; PEEP, Positive end-expiratory pressure; RASS, Richmond Agitation-Sedation Scale.

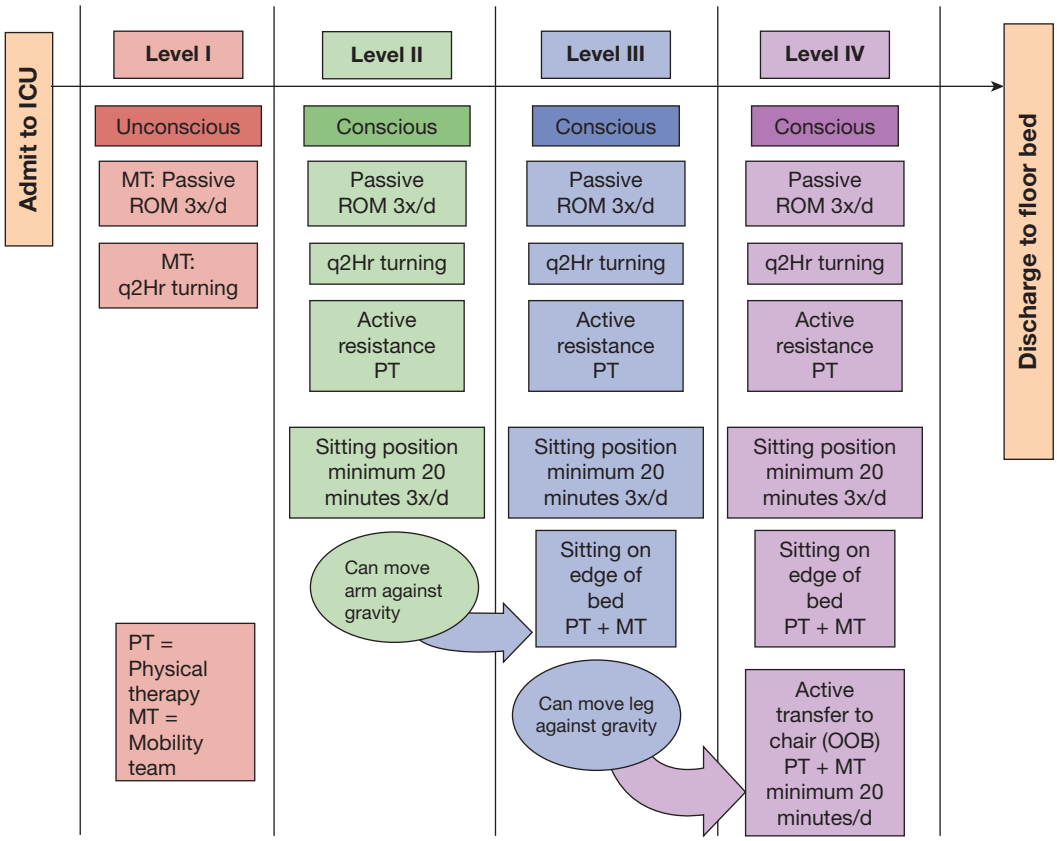

Figure 151-3 Passive range of motion therapy started on day 1 of protocol (level I). As patients demonstrated consciousness and increased strength, they were moved to the next higher level. Physical therapy would first be attempted at level II. The protocol's intervention ceased as a patient was transferred to a floor bed and the patient within both "protocol" and "usual care" groups would receive usual care mobility therapy as dictated by the floor physician teams. *(Reproduced with permission from Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238–2243.)*

bias, and the need to assess patient tolerance have generated a call for further investigation prior to widespread implementation.

PRACTICAL IMPLEMENTATION OF AN EXERCISE AND MOBILIZATION PROGRAM IN AN ICU

To translate early exercise and mobilization to the acute care ICU, programs must adapt to balancing unpredictable acute care management with the desire to keep rehabilitation a priority. Competing challenges include patient factors (such as delirium and pain), critical care procedures (such as dialysis and bedside procedures like vascular catheter insertion), and clinician factors (such as biases about safety and rehabilitation).

Maximal patient engagement requires optimal management of pain, agitation, and delirium. Protocols to guide drug sedative and analgesic administration may be a necessary prerequisite. In accordance with guidelines, hallmarks of such programs include the utilization of a reproducible, validated scale (e.g., Richmond Agitation and Sedation Scale), an established sedation target prescribed daily, and nurse-led titration of drug administration.[50] Although recent research has questioned the necessity of daily interruption of continuous sedative and analgesic infusions, all experts agree that methods to aggressively minimize drug administration to a "least necessary" model are optimal.[51]

For the mechanically ventilated patients, some experts have advocated the bundling of early mobilization with programs that include spontaneous awakening trials, spontaneous breathing trials, and delirium screening. This bundle, termed "ABCDE," stands for Awake and Breathing Coordination, Delirium screening, and Early mobility.[52] The individual components are based upon clinical trials of benefit (excluding delirium screening) with improved outcomes, such as reductions in ICU and hospital lengths of stay and duration of mechanical ventilation, as well as an association with improved mortality at 1 year.[41,53,54] Clinical researchers are now assessing the feasibility of broad implementation of the initiative.[55]

Criteria to guide initiation of therapy are similarly important. Observational and interventional trials to date have used criteria focusing on the cardiovascular, pulmonary, and neurologic systems to identify candidate ICU patients (Table 151-1).[37,39,42] However, these criteria have been developed for patients undergoing mechanical ventilation and may need further additions as broader patient populations are engaged (e.g., patients with recent gastrointestinal bleeding or surgery). In contrast, veteran critical care therapists may find these criteria too conservative. Data has shown that mobilization may occur in contexts of greater ventilator or oxygen dependence, and patients with advanced delirium or coma may engage in exercise through the use of assistive devices.[56]

Finally, therapy should proceed in a logical, stepwise fashion. Activity and exercise should be targeted for the appropriate intensity and modality. Investigators have proposed detailed approaches for the progression of activities, based on levels of patient consciousness, cooperation, and functional status.[39] Figure 151-3 is a general guide for emerging programs. Acutely ill, comatose patients receive passive ROM, muscle stretching, splinting as needed, and body positioning. Once interactive, patients can increase their level of activity, progressing from active ROM to sitting at the edge of the bed, transfers to chair, marching in place, and then ambulation. Standing and walking frames enable the patient to mobilize safely with attachments for bags, lines, and leads that cannot be disconnected. For the patient with advanced weakness, standing aids and tilt tables enhance physiologic responses as a modality to promote early mobilization of those who are critically ill.

CONCLUSIONS

Although early mobilization may be undertaken by physical and occupational therapists, the feasibility of the intervention rests firmly upon the entire ICU team. Clinicians must balance the desire for rest and recovery from the acute illness with the recognition that maintaining some degree of activity will improve patient outcome. Standardized approaches to pain, agitation, mechanical ventilation, and device management may help to safely conduct mobilization during the earliest days of critical illness. This multidisciplinary teamwork – involving physicians, nurses, and respiratory, physical, and occupational therapists – is necessary to maximize both survival and quality of life for survivors.

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CHAPTER 152

Organization of Intensive Care Units and Long-Term Acute Care Hospitals

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INTRODUCTION

The birth of modern day critical care is traditionally ascribed to Bjorn Ibsen, a Harvard-trained Danish anesthesiologist, who led the efforts to combat the poliomyelitis epidemic in Copenhagen in 1952.[1] By relying on the manual power of volunteers to ventilate the critically ill for extended periods of time, respiratory failure-related mortality declined precipitously. From these humble beginnings, the growth of critical care medicine over the ensuing years has been exponential.

The tenets of 21st century critical care include the provision of care by professionals with diverse yet complementary experience and expertise that is delivered across the continuum of care. The nexus of critical care is the Intensive Care Unit (ICU), where critically ill patients are brought to be resuscitated and managed. It is estimated that there are in excess of 5.7 million annual ICU admissions in the United States, and the numbers continue to increase.[2,3] The costs attributed to the care of the critically ill continue to increase dramatically and currently exceed $80 billion, 13% of hospital costs, 4% of the United States healthcare expenditures, and approximately 1% of the gross domestic product.[4] Approximately 500,000 patients admitted to an ICU die.[2] However, as a result of advances in the field, mortality is decreasing and the vast majority of critically ill patients survive. The direct result is that coordinated care is required following discharge from the ICU for these complex patients who have often sustained significant morbidity (e.g., postintensive care syndrome).[5,6]

STRUCTURAL ORGANIZATION

The administrative and functional organization of critical care has evolved over decades. Selected aspects of this organization are discussed in the following sections.

THE CONTINUUM OF CRITICAL CARE

The care of the critically ill patient begins at first recognition of physiologic derangement. The opportunity to alter the patient's course begins with the initial encounter with the healthcare system. Across the continuum of care (Fig. 152-1), this encounter may occur in the prehospital environment, outpatient clinic, or emergency department (ED). For the hospitalized patient, deterioration may occur on the medical or surgical inpatient unit. Evidence suggests that outcomes are significantly worse in patients admitted to the ICU from the general inpatient unit, in comparison to patients admitted through the ED or postoperatively.[7] Once critical illness has been recognized, the tenets of care include resuscitation and stabilization and efficient and safe transport to the ICU. Traditionally, efforts to optimize care of the critically ill patient were focused on management provided in the ICU. One of the greatest advances in critical care medicine has been the recognition that the structure and processes of care in locations outside of the ICU (prehospital environment, ED, inpatient unit) are of paramount importance in optimizing care for these vulnerable patients.

THE RAPID RESPONSE TEAM

Over the last 15 years, driven by the observation that many transfers to the ICU were either avoidable or characterized by delayed or

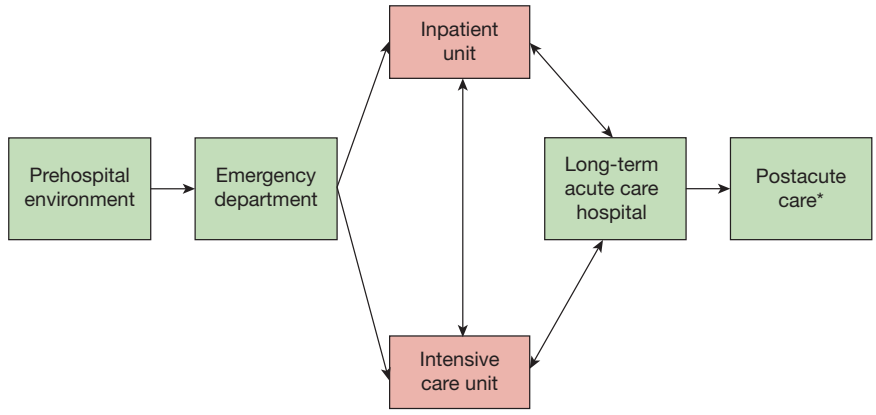

Figure 152-1 The continuum of critical care. *Postacute care includes skilled nursing facility, acute rehabilitation, and home.

suboptimal care,[8,9] substantial growth in the use of rapid response teams (RRTs) has been observed. RRTs, also known as emergency medical teams, serve as the efferent arm of the critical care response in the hospital. Traditionally, primary care providers, including trainees inexperienced in the management of the critically ill, led the resuscitation. However, primary care providers often have competing responsibilities that may impede their ability to assess and manage the deteriorating patient in a timely fashion. Further, based on the concept that a team of experienced critical care providers tasked to respond immediately to the bedside of a deteriorating patient would result in improved outcomes, hospitals have widely adopted the RRT model as a means to improve patient safety.

The success of the RRT is dependent on the ability of the screening method to detect the deteriorating patient ("afferent" limb), as well as the staffing and experience of the efferent arm. Several strategies exist to recognize the deteriorating patient in a timely fashion. The most commonly applied strategy is the modified early warning score (MEWS), a simple and effective tool that trends vital signs and consciousness to identify patients at risk of adverse outcomes, including ICU admission and death.[10] The MEWS has been validated in medical and surgical patients; an important characteristic is that it relies on *serial* measurements, since admission of vital signs is an insensitive marker of subsequent deterioration.[11,12] Future directions aimed at optimizing the strategy include incorporation of clinical data focusing on at-risk patient populations;[13] use of laboratory data and computer programming to incorporate trends in laboratory values, as well as threshold values; and use of automated information technology to improve the efficiency of the system.

Traditionally, the efferent limb or first responders were clinically available staff, who often included inexperienced trainees. The evolution in patient safety has prioritized, appropriately, that the resuscitation efforts for such vulnerable patients are led by practitioners with expertise in managing critically ill patients. It remains unclear whether outcomes differ when the team is led by a critical care certified nurse, advanced practitioner, or intensivist. Further investigation is required to address this important question, given limited resources across the continuum of care. In addition, ancillary personnel (e.g., respiratory therapists, pharmacists) are critical in facilitating delivery of time-sensitive interventions in the deteriorating patient.

Despite a sound rationale, it remains unclear whether an RRT improves patient outcomes.[14] In a large multicenter trial, while more deteriorating patients were managed following implementation of an RRT, no significant decreases in the incidence of cardiac arrest, ICU admissions, or mortality were noted.[15] However, in a more recent meta-analysis, the introduction of an RRT appeared to reduce the rate of non-ICU cardiac arrests.[16] Furthermore, an additional potential benefit of an RRT is that its introduction may facilitate timely end-of-life discussions, preempting ICU admission when such an admission would not align with the patient's preferences and values.[17]

THE INTENSIVE CARE UNIT

Internationally, the availability of resources to care for the critically ill varies significantly, even in developed countries.[3,18] Importantly, evidence suggests that lack of ICU bed availability is associated with increased mortality.[19] In the United States, there has been a rapid increase in the number of ICU beds per capita, with an estimated 5.7 million annual ICU admissions (Table 152-1).[20] The growth in ICU bed availability in the United States is driven by several pressures, including the need to meet the expected demand of critical care services required to care for an aging population, and the demand resulting from high-intensity care elsewhere in the healthcare system (e.g., solid-organ transplantation, intensive chemotherapy, and high-risk surgery).[18,20]

In 2007, 67,357 critical care beds were encompassed in approximately 6000 ICUs.[3,20–22] This equates to 2.80 critical care beds per 10,000 persons,[21,22] an increase from 2.00 beds per 10,000 persons less than a decade earlier.[3] The growth in ICU beds across the United States has been transformative, as ICUs were uncommon prior to the 1970s. At the same time, the growth in ICU beds has been disproportionate at a regional level. As a result of this regional variability, the potential exists that areas with less ICU bed availability may be unable to respond to a disaster or epidemic.[21]

TABLE 152-1 Characteristics of Intensive Care Units in the United States[a]

Variable	Count
Number of ICUs	5980
ICU size (beds)	12 (range, 1–55)
ICU bed to acute care bed ratio	1:9.0
Estimated annual ICU admissions	5,700,000
Type of ICU	(%)
General (mixed medical/surgical)	65
Surgical	12
Medical	12
Other	11

[a]*Data exclude noncoronary ICUs.*

Source: Data from Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. Crit Care Med. 2008;36:2787–2793; Angus DC, Shorr AF, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. Crit Care Med. 2006;34:1016–1024.

Drawn from a representative sample of hospitals across the nation, the median number of ICUs per hospital is 2, with an interquartile range of 1 to 3 and range of 1 to 8.[22] In general, the number of ICUs per hospital increases in proportion to hospital size, with the smallest hospitals using a single ICU, and the largest hospitals using 3 or more ICUs.[20,23] It has been estimated that approximately half of ICU beds are located in small-to-moderate size hospitals (<300 beds).[20] Importantly, the optimal ratio of ICU beds to hospital beds to ensure safe, efficient, high-quality care remains unclear; furthermore, the ratio is variable from institution to institution and, within institution, from service to service (e.g., medical vs. surgical). Since 1992, the average ICU size (12 beds per ICU) has remained relatively stable, as has the proportion of hospital beds apportioned as ICU beds (8%–9%).[20,23] In general, given evidence that patient admissions to an ICU, when delayed or denied due to bed availability, are at increased risk of adverse outcomes,[22,24,25] a general principle is to apportion 10% to 20% of total beds as ICU beds. Institutions that provide high-intensity care (e.g., intensive chemotherapy) should allot a greater proportion of beds as ICU beds to enable provision of necessary care.

ICU ADMISSION DIAGNOSES AND USE OF LIFE SUPPORT

In general, patients perceived to be at high risk for an adverse outcome are admitted to an ICU; the indication for ICU admission depends largely on the type of ICU. The ED serves as the admitting source for approximately 50% of ICU admissions. Postoperative patients account for an additional 25%, while the remaining patients are admitted from inpatient units or another hospital.[20]

The most common indications for ICU admission include respiratory failure, postoperative care, acute coronary syndrome and congestive heart failure, and severe sepsis.[20–22] On average, the mean length of stay in the ICU is approximately 4 days, with significant variability from hospital to hospital and among ICU types (e.g., length of stay is significantly greater in burn and trauma ICUs than in general medical or surgical ICUs).[20] An additional explanation

for these observed differences is the considerable variation in use of intensive care, as evidenced by the variable rates of ICU admission for a resource-intensive condition associated with a very low rate of mortality—diabetic ketoacidosis.[26] Further investigation is required to better understand the "appropriateness" of ICU admissions and ICU care delivery, given that an increasing proportion of our gross domestic product is allocated to such care.

Life support, including use of noninvasive and invasive mechanical ventilation for respiratory failure, vasoactive agents for cardiovascular failure, and hemodialysis for renal replacement therapy is commonly indicated. These examples of life support highlight the sophisticated technology required to guide resuscitation and support organ failure. Experience with such technology in caring for critically ill patients may explain the observed relationship between patient volume and outcomes.[27,28]

GENERAL VERSUS SPECIALITY ICUS

Two types of ICUs within hospitals in the United States may be generally identified: general and specialty. The general ICU, or mixed medical/surgical ICU, is the care site for patients with diverse diagnoses and is the most common type of ICU (Table 152-1). Usually, these ICUs are located within smaller, community-based hospitals. In contrast, specialty ICUs are located predominantly within larger, urban hospitals. The specialty ICU (e.g., coronary care unit, dedicated medical unit, neurologic unit, cardiothoracic surgery unit) centralizes nursing and physician expertise in a single location to enable efficient, diagnosis-specific care. Interestingly, despite the rationale for specialization, the evidence does not support adopting such an organizational model in efforts to improve outcomes (e.g., mortality, length of stay).[22] However, admission to a specialty ICU of a patient with a diagnosis not typically cared for by that ICU (in which the patient is considered a "boarder") appears to be associated with increased mortality.[22] Consequently, hospitals may elect specialization for a number of reasons distinct from mortality and length of stay (e.g., cost, convenience, staff and family satisfaction). However, these same hospitals should incorporate provisions for optimizing care for "boarders."

ORGANIZATIONAL FACTORS ASSOCIATED WITH PATIENT OUTCOMES

A number of organizational factors have been identified, which, when implemented, are associated with improved outcomes. Broadly, these factors can be categorized as (1) personnel and staffing-related, and (2) processes of care (e.g., multidisciplinary patient and family-centered rounds) that streamline delivery of high-quality critical care. High-quality critical care is delivered by a dedicated critical care team,[29,30] incorporating strong, collaborative physician and nursing leadership,[31] operating within a "closed" unit.[32–34] In an "open" model, care is provided by physicians who have competing responsibilities outside of the ICU (e.g., operating room activities or outpatient practices). In open models, critical care consultation is an option (e.g., consultation for mechanically ventilated patients). In a "closed" model, care is provided exclusively by critical care specialists.

PERSONNEL

Multidisciplinary critical care harnesses the expertise of the entire critical care team. The personnel required to provide critical care include physicians, nurses, respiratory therapists, critical care pharmacists, nutritionists, physical and occupational therapists, speech therapists, social workers, and palliative care experts. The integrated care provided by each of these professionals is essential for optimizing care delivery.[35,36] Given the ever-increasing complexity of critical care,[37] each team member must contribute the necessary expertise to reduce errors, improve communication, and facilitate delivery of safe, efficient, cost-effective care.[38,39] Because of the complexity of the administrative duties required to co-manage an ICU, ensuring that the medical and nursing directors are provided sufficient time to manage and lead effectively is critical.

STAFFING

Physician and nursing staffing models vary across the United States; the optimal approach is unknown. Traditional physician staffing models include coverage by general practitioners (medical and surgical), elective consultation from board-certified critical care physicians (intensivists), or mandatory management by intensivists. The general practitioner model may include physicians trained in Internal Medicine (in the case of medical critical care) or hospitalists. Traditionally, ICU physician staffing is categorized as either low-intensity (staffing by general, nonintensivist practitioners with intensivist consultation) or high-intensity (mandatory intensivist consultation or primary care delivery by an intensivist).[40]

With few exceptions,[41] a high-intensity physician staffing model, which is synonymous with a "closed" ICU is associated with improved outcomes.[40] A systematic review found that high-intensity physician staffing results in lower in-hospital mortality, reduced ICU length of stay, and to a lesser degree, reduced hospital length of stay.[40] While the potential benefits of high-intensity staffing are likely multifactorial, one clear benefit appears to be in use of evidence-based processes of care when care is delivered by practitioners with expertise in critical care. For example, the mortality benefit achieved when intensivists care for patients with ARDS is, in part, mediated by intensivists' increased use of lung protective ventilation.[34] Use of evidence-based protocols (see Process of Care), is one strategy to ensure delivery of evidence-based care that is applicable to ICUs, regardless of their structure and staffing.

In response to the growing costs and use of critical care, and in light of evidence that high-intensity physician staffing is associated with improved outcomes, the Leapfrog Group, a US-based alliance of employers dedicated to improving the safety and quality of healthcare and optimizing purchasing power, identified critical care staffing as one of the principal opportunities to save lives. The Group recommended provision of critical care in metropolitan areas by intensivists on-site during daytime hours and their availability to return in a time-sensitive manner during off-hours. The Group estimated that adoption of these recommendations could save >50,000 lives each year.[42]

A recent analysis of critical care delivery in the United States conducted by the Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS) estimated that approximately 25% of ICUs provide high-intensity physician staffing.[20] In addition, the majority of ICUs in the United States, in contrast to those in Western Europe, remain "open" units in which patients are managed by nonintensivists who have the option to consult intensivists.[3,41,43]

A legitimate threat to high-intensity staffing is the anticipated intensivist shortage, which will be exacerbated by the anticipated national nursing shortage. Preservation of a limited patient-to-nurse ratio (2:1 or less) and ICU bed-to-intensivist ratio (less than 15:1) is vital to the optimal delivery of critical care.[29,43–45] Until and unless healthcare is able to avoid the pending shortage of intensivists, given the present environment, novel strategies will be necessary for optimizing critical care delivery.

Based on the relationship between volume and outcomes observed across medical and surgical critical care,[27,28,46–48] one potential strategy to improve outcomes is regionalization of critical care.[49] Regionalization has proven beneficial in traumatology and in neonatology, but its effectiveness when applied to adult critical care remains largely speculative. Furthermore, significant barriers to its implementation would exist.[18] Despite these barriers, recent analyses reveal that informal networks already are in place to enable transfer of patients who require a higher level of care.[50]

Given the national shortage of intensivists and expectation of a widening gap between available and necessary critical care providers

over the next several decades as the population ages,[20] it is anticipated that a greater burden of care will be delivered by general practitioners or physician extenders (i.e., nurse practitioners and physician assistants). The optimal approach to meet this growing need is an area of active investigation and inquiry. Potential solutions, beyond regionalization of care[49,50] and use of physician extenders, include expanded use of telemedicine[51] and embracement of the concept of co-management, in which only the most severely ill patients are managed by intensivists.[52]

STAFFING SCHEDULES

The optimal schedule for nursing and physician coverage remains unclear. For attending physicians, models vary from extended rotations (1-, 2-, or 4-week rotations) to traditional shift-work coverage employing a varying mix of day and night schedules, consistent with the model used by most EDs. Whether outcomes or patient or staff satisfaction differ in the different models remain unknown. Of interest, a cluster-randomized trial comparing the effects of 2- and 4-week inpatient attending physician rotations on a general medicine service found that 2-week rotations were not associated with improved outcomes (as measured by readmission rate and length of stay). The shorter rotation was accompanied by less attending physician burnout, a benefit that appeared to be counterbalanced by trainees' perceptions of an inability to be adequately evaluated.[53] Schedules that incorporate a weekend respite appear to result in less burnout, lower job distress, and improved work-life balance.[54] Of import, although continuity of care was disrupted in the model of weekend cross-coverage, outcomes did not appear to differ.[54]

NIGHTTIME COVERAGE

To optimize ICU outcomes, many have advocated for expanding high-intensity staffing to 24 hours per day. The potential benefits of nighttime intensivist coverage are many: improved outcomes; improved efficiency of care delivery; increased adherence to evidence-based care; improved end-of-life care; improved staff, patient, and family satisfaction; and improved trainee satisfaction, given the additional support and educational opportunities afforded by this approach.[55] The potential risks include erosion of trainee autonomy, physician burnout, and incremental cost, although arguments to the contrary have been made for the latter two points.[55,56] Without evidence to guide institutional decisions regarding adoption of nighttime intensivist coverage, as many as one-third of academic ICUs already provide nighttime intensivist staffing,[57] compared with only 6% 20 years ago.[23]

To date, the evidence suggests that the incremental benefit on patient outcomes of nighttime intensivist staffing may be dependent on the daytime staffing model employed. Specifically, nighttime coverage only appears to improve patient outcomes when layered on top of low-intensity physician staffing.[58,59] In observational studies, the theoretical incremental benefit has not been demonstrated in units with high-intensity staffing models,[58–60] an observation confirmed in a recent randomized trial.[61] Distinct from patient-centered outcomes, evidence suggests that intensivists experience less burnout, while trainee autonomy is impacted.[58]

PROCESS OF CARE

The principles of high-quality critical care related to process of care delivery include multidisciplinary rounds, use of evidence-based protocols and guidelines, and use of checklists to ensure that evidence-based care is provided. These principles should be applied to care delivery across the healthcare continuum, as the benefits are not specific to the ICU.

MULTIDISCIPLINARY ROUNDS

The first tenet, multidisciplinary rounds, has been demonstrated to reduce ICU length of stay and ICU mortality.[62,63] In a large population-based cohort study, the highest odds of survival were observed in patients managed in ICUs with high-intensity physician staffing and multidisciplinary rounds.[63] Multidisciplinary care harnesses the expertise of the entire critical care team, including physicians, nurses, and others, in optimizing care delivery and reducing errors.[35,36] Recognizing the importance of effective and timely communication among team members and with patients and their families, multidisciplinary rounds are the forum in which multidisciplinary care takes place. In ICUs that are unable to provide high-intensity physician staffing,[64] (estimated at approximately 50% of ICUs as recently as 2006[63]) implementation of multidisciplinary rounds is one strategy to optimize care delivery.

EVIDENCE-BASED PROTOCOLS

The primary aim of protocols and guidelines is to standardize evidence-based critical care medicine. Protocol adoption is more likely in units that incorporate high-intensity staffing and use multidisciplinary rounds,[65] factors that may account for improved patient outcomes.[63] Importantly, management protocols have been at the core of landmark studies demonstrating benefit in caring for mechanically ventilated patients,[66,67] severe sepsis,[68,69] and following cardiac arrest.[70,71] In addition, protocols are often created to standardize management of complicated, common clinical scenarios (e.g., diabetic ketoacidosis, alcohol withdrawal syndromes) with the goal of improving outcomes and reducing errors in management. Protocols are also a useful means of ensuring that knowledge is effectively translated to patient care. Despite the theoretical threat that use of protocols might erode the education of trainees, evidence does not support the concern.[72]

The science of implementation of evidence-based care is complex and challenging. The initial step required for effective implementation is engaging relevant stakeholders and local experts. This can be accomplished through stand-alone committees or by incorporating the assignment into pre-existing quality committees at the unit or hospital level. After the protocol development phase has been completed, implementation and efforts to ensure compliance are necessary. This iterative process requires a multifaceted approach incorporating academic detailing (e.g., educational efforts by local opinion leaders), reminders (e.g., checklists), prompts (including electronic prompts), and periodic auditing and feedback to ensure compliance. Effective implementation is predicated on a culture of safety, transparency, mutual respect among care providers, and a willingness to learn from one another.

THE CHECKLIST

One of the transformative events in modern day critical care is the incorporation of checklists into multidisciplinary rounds to help ensure that evidence-based care is provided. The checklist has proved to be a simple, effective tool to combat effects of stress and fatigue on memory and provider performance. The benefits, in part, are achieved by reducing errors of omission, reducing unintended complications, and standardizing practice. The benefits derived from checklists have been observed in both surgical and medical critical care settings.[51,73–75] The checklist results in a safer environment by ensuring that important details are not overlooked (e.g., time-out to ensure the correct procedure is being performed on the correct patient, use of deep venous thrombosis and stress ulcer prophylaxis, physical therapy consultation).[73,76] At the conclusion of rounds, a daily goals checklist can be incorporated to ensure that all team members are aware of the plan and goals for the day; "read-back" verification may help facilitate an understanding of the plan.[77] The manner in which a checklist is implemented is not trivial; a strategy employing prompting as a means of ensuring that the checklist is not overlooked improves care delivery and outcomes.[74]

TEAM DYNAMICS

An often overlooked, but vital component of high-quality critical care medicine is effective team dynamics. Effective team dynamics rely on strong team leadership, effective communication among providers, and team composition.[78] Attributes that define positive team dynamics include (1) creating a safe work environment where questions and concerns are encouraged and errors are reported, and (2) recognizing team member skills and attributes, thereby fostering a team-oriented approach to patient care in which "the sum is greater than the parts."[79] Positive team dynamics have been associated with decreased errors and improved patient safety,[80] enhanced staff satisfaction,[81] lower frequency of perceived inappropriateness of care,[82] reduced rates of provider burnout,[83] and improved patient outcomes.[84]

THE LONG-TERM ACUTE CARE HOSPITAL

Advances in critical care over the last several decades have resulted in an expanding population of patients who survive critical illness. These patients, the *chronically critically ill*, remain dependent on higher levels of support than can be provided elsewhere in the healthcare system (i.e., medical or surgical floor, skilled nursing facility, acute rehabilitation). In response to the growth of the chronically critically ill patient population, and as a means to combat the costs associated with extended acute care hospitalization, long-term acute care hospitals (LTACHs) have emerged as a viable option for care delivery.

The origins of the modern day LTACH can be traced to facilities that tended to the chronically ill (e.g., those with tuberculosis) nearly a century ago. The recent growth in the number of LTACHs is attributable to two federal reimbursement decisions in the 1980s. First, the Health Care Financing Administration (HCFA) established that certain facilities, including LTACHs, would be exempted from the traditional, prospective, diagnostic-related group (DRG)-driven reimbursement system used in acute care hospitals. Second, in 1982, the Tax Equitable Fiscal Responsibility Act (TEFRA) created an alternative, cost-based system that incentivized transfer of the chronically critically ill patients from the intermediate care unit or ICU within the acute care hospital to LTACHs.

Over the ensuing 30 years, the LTACH industry has grown exponentially, both in its ability to care for the chronically critically ill and in sheer numbers. In the 1980s, fewer than 100 LTACHs existed. In contrast, by the late 2000s, approximately 400 LTACHs were in operation (representing an annual growth rate approaching 9%), and annual LTACH admissions exceeded 40,000.[85,86] The majority of LTACHs are operated by for-profit companies, are concentrated in the Northeast and Southern United States, and are integrated into the physical structure of an acute care hospital ("hospital within a hospital").

LTACH admissions are more likely to be male and nonwhite. One-year mortality is uniformly poor, remaining at about 50% from 1997 to 2006.[85] Although the setting in which the needs of chronically critically ill patients are met in regions with limited LTACH penetration is not well defined, use of "intermediate care units" is one potential option. Despite introduction in 2003 of a prospective payment system specific for LTACHs (long-term care-diagnosis-related groups [LTC-DRG]) – a system designed to curb costs – Medicare reimbursement for LTACH care approaches $5 billion annually.[87]

The average length of stay for patients in an LTACH approaches 1 month. In fact, as one of the several means to ensure that patients transferred to an LTACH are appropriate admissions, the facility must demonstrate an average length of stay of 25 days or more for Medicare patients during the 6-month demonstration period—a requirement for Medicare certification of the facility. On average, two-thirds of LTACH admissions are Medicare patients. The most common LTC-DRG is respiratory-related (accounting for approximately one-quarter of Medicare-specific discharges), followed by care for complex illness associated with prior intensive care (including postsurgical care, critical illness–associated neuromuscular weakness, infectious disease management, and recovery from multisystem organ failure), chronic neurologic disorders, complicated infectious diseases, and general wound care. As a destination for ICU survivors, LTACHs may provide the necessary care and support, over an extended period of time, to combat the long-term effects of postintensive care syndrome, described as new or worsening impairment in physical function, cognition, or mood.[6]

Evidence to support the LTACH model as an efficient, cost-effective approach for managing the chronically critically ill, as compared with traditional care in an acute care hospital, is lacking. To date, the majority of investigative effort has focused on ventilator liberation rates (estimated at 50%–70%), given the proportion of LTACH admissions requiring prolonged mechanical ventilation.[88] Systematic study reveals that outcomes, in general, do not appear to differ, although a potential benefit may be observed when analyses are extended to include chronically critically ill patients with shorter lengths of stay in the ICU (perhaps, by including patients with overall better outcomes).[89,90] This observation raises the question of whether some patients (e.g., the chronically critically ill patient with reversible disease) may benefit from an LTACH admission, while others (e.g., the moribund, chronically critically ill patient with irreversible organ failure) may not.

When examining management for prolonged mechanical ventilation, care in an LTACH may provide cost savings compared with care provided in traditional acute care hospitals.[89,90] The cost savings, in part, appear to be due to a reduction in subsequent admissions to skilled nursing facilities following the phase of acute care. Yet, from the payer perspective, these apparent cost-savings appear to be counterbalanced by increased overall Medicare payments, equating to increased cost to the public at large.[90]

The potential benefits and costs of LTACH care should be viewed in light of the long-term outcomes of the largest subgroup of patients admitted—those undergoing prolonged mechanical ventilation. In general, outcomes remain poor for this group.[91] At 1 year, approximately 50% of patients who are mechanically ventilated in an LTACH and subsequently discharged are alive; fewer than 10% are living independently at home.[91,92] The clinical trajectory for such patients is often a chaotic one, with a median of four transitions of care postdischarge, including readmission to acute care for the majority.[91] In addition, expectations of patients and their family members often are not congruent with clinical reality, as most surrogates are unrealistically optimistic regarding survival, functional status, and quality of life.[92] Consequently, while outcomes achieved may be optimized through the expertise and experience afforded at an LTACH, studies highlight the importance of identifying patients with the greatest potential for benefit, as well as the importance of educating patients and surrogate decision-makers about the prognosis of the chronically critically ill patient.[92]

CONCLUSION

Modern day, high-quality, critical care medicine requires complex coordination across disciplines and across the continuum of care. Strong leadership and careful planning are required to ensure that the inpatient unit structure and processes of care enable recognition of impending critical illness and facilitate efficient and expert patient management. The ICU remains the hub of critical care, yet coordination between the pre-ICU environment (e.g., ED, general medical or surgical floor) and post-ICU environment (e.g., LTACH) is critical in bridging the continuum from acute injury and illness to rehabilitation and recovery.

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CHAPTER 153

Ethics and Palliative Care in Critical Care Units

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Death is common in the intensive care unit (ICU), with approximately 20% of deaths in the United States occurring during or shortly after a stay in an ICU.[1] The majority of these deaths involve the withholding or withdrawal of life-sustaining therapy.[2] Therefore, the ICU represents a particularly distinct clinical setting where the thoughtful and considered application of ethical concepts is required. A proper understanding of the basic principles of bioethics as well as the principles of providing comfort-focused, end-of-life care are essential elements in the competent practice of intensive care medicine.

A number of common ethical themes arise in the ICU. Technological advancements have allowed healthcare providers to keep patients alive for prolonged periods in the context of diseases that, in the past, would have resulted in death. However, the capacity for delivering life-sustaining care has not been matched by efforts to align treatments with the care individual patients wish to receive at end of life, resulting in a discordance between care wanted and care received.[3–5] Compounding this problem is the reality that many patients dying in the ICU, prior to death, lack the capacity to make decisions regarding end-of-life care[6] and have not completed an advance directive that might aid surrogates and physicians in the decision-making process.[7] Many decisions about end-of-life care in the ICU are, therefore, made without the involvement or input of the patient.[6] The resulting uncertainty means that many patients frequently receive far more aggressive interventions than they would have otherwise chosen for themselves, or they receive care that has a low likelihood of restoring health, enabling discharge from the ICU, and having the potential for providing a meaningful quality of life.[5]

Ethical dilemmas that characterize critical care medicine often arise from this interface between the ability to prolong life by expensive and sometimes scarce technology and an inability to cure patients or restore them to their baseline. The relevant ethical question often is whether technology is being used wisely, that is, should the patient's life be prolonged? The question becomes even more complex for practitioners and patients' families when different ethical principles suggest conflicting answers.

Although the practice of critical care medicine encompasses a broad range of bioethical issues, several are particularly common, including palliative and end-of-life care, surrogate decision making, medical futility, communication, and professionalism. These issues are among the most challenging for critical care practitioners and constitute the focus of this chapter.

FUNDAMENTAL PRINCIPLES OF BIOETHICS

Several fundamental principles of bioethics are at the core of the practice of critical care medicine: respect for patient autonomy, beneficence, nonmaleficence, and distributive justice.[8] Ethical dilemmas in the ICU arise when two or more of the principles are in conflict. An understanding of these areas provides a basis for addressing conflict and is imperative in providing high-quality palliative care at the end-of-life.

RESPECT FOR PATIENT AUTONOMY

The principle of patient *autonomy* refers to the concept of self-determination, which asserts that a competent and informed adult patient possessing adequate decision-making capacity has the right to determine what will be done to his or her body.[8] According to this principle, the patient has the ethical right to accept or refuse medical interventions, including those that might sustain life. In addition, the principle of autonomy encompasses the right to privacy and the requirement for informed consent. As such, except in an emergency, a competent adult must give informed consent before receiving medical care, especially interventions that have the potential to cause further harm or death. Under emergency conditions, consent is presumed. Respect for patient autonomy is applicable with respect not only to patients, but also their families and surrogate decision makers or proxies—that is, individuals who speak on behalf of patients who lack the capacity to make medical care decisions.

In the United States, societal and professional consensus, as well as statutory law and judicial precedents, support the principle of patient autonomy. Absent countervailing obligations, healthcare providers are required to respect a competent and informed patient's decision to forgo life-sustaining care. Important to note, however, is that autonomy does not provide patients or their surrogates with the right to demand and receive any desired treatment. Rather, patients or their surrogates are permitted to accept or forgo medical interventions that fall within the standard of medical care.

BENEFICENCE AND NONMALEFICENCE

The principle of *beneficence* obligates healthcare providers to promote the well-being of their patient and provide services that benefit the patient.[8] *Nonmaleficence* is the duty to minimize pain and suffering.[8] The Hippocratic maxim, *primum non nocere,* which can be translated as "First, do no harm," reflects the fundamental importance of this principle for physicians. Both principles relate to the provision of care that maximizes each individual's dignity and worth as a human being. However, a constant tension exists between these two principles: Efforts to cure medical illness often come with substantial suffering. Provided the benefits outweigh the harms, administration of life-sustaining therapies is appropriate. However, once the physician believes the attendant harms may be greater than the foreseen benefits, the physician is obligated to communicate his or her concerns to patients and/or their families. A common example of this tension is provision of cardiopulmonary resuscitation (CPR) to patients who have refractory sepsis despite aggressive medical intervention. The medical literature indicates that offering CPR in this setting is unlikely to restore spontaneous circulation, or at the very best, delay the dying process.[9] Consequently, offering CPR in this context could constitute a harm that outweighs the benefits. Despite this ethical construct, the proportion of patients receiving CPR prior to death continues to rise, particularly among minority groups.[9]

DISTRIBUTIVE JUSTICE

Justice refers to fairness in the distribution of limited resources, that is, *distributive justice*.[8] Ethically, this principle holds that equals should be treated equally and unequals treated unequally. In practice, the principle of distributive justice pertains to defining fairness in allocating resources among individuals when not all can receive the resources. The principle is applicable on two levels in health care: macroallocation and microallocation of resources.

Macroallocation entails the distribution of resources among various goods and services at a governmental or institutional level. In contrast, *microallocation* refers to decision making about an individual patient or small group of patients within, for example, an individual ICU or hospital. A single formulation for the application of this principle in patient care is not available because widely accepted criteria are lacking. Various ethical theories (e.g., deontology, utilitarianism, egalitarianism, among others) define different values as the most relevant criteria for making such judgments. In general, determinations of how to allocate resources and treat patients are best left to institutional or governmental authorities, while physicians provide reasonable and appropriate care on an individual patient basis.

CONSIDERATIONS IN END-OF-LIFE CARE IN THE ICU

A number of considerations comprise the core practice of bioethics in the ICU. Included are the withdrawal and withholding of life-sustaining therapies, surrogate decision making, trust and communication, provision of good palliative care, and medical futility. In this regard, bioethics in the ICU should not be viewed as a fixed body of knowledge, but rather as a continually evolving field, similar to the rest of clinical medicine.

WITHDRAWAL AND WITHHOLDING OF LIFE-SUSTAINING THERAPY

Over the last several decades, a broad societal consensus has developed in addressing the ethics of withholding or withdrawing life-sustaining therapies or "life support." Landmark judicial cases, such as the 1976 New Jersey Supreme Court decision regarding Karen Ann Quinlan[10] and the 1990 US Supreme Court decision regarding Nancy Cruzan,[11] played substantial roles in defining both ethical and legal standards. Based on the principle of autonomy, the current societal and legal standard is that adequately informed adults possessing decision-making capacity have the right to refuse any life-sustaining medical therapy, even if the decision results in death. *Capacity* requires that the patient have the ability to comprehend relevant information, understand their condition, compare and contrast treatment options, and communicate wishes consistently.[12]

In practice, no meaningful legal or ethical difference exists between withdrawing and withholding life-sustaining therapy. In addition, legal precedent has established that artificial nutrition and hydration are considered medical interventions that are no different than CPR or mechanical ventilation. The legal issue of whether artificial nutrition and hydration provided by a feeding tube constitutes medical care was decided when the US Supreme Court deemed it so in its 1990 decision on Nancy Cruzan.[11] This decision established a constitutionally protected legal right to refuse any medical care by a competent adult or appropriate surrogate decision maker acting in accord with the patient's previously expressed preferences or values, including artificial nutrition and hydration. Of note, despite the legal and moral equivalence between withdrawal and withholding of life-sustaining therapy, many patients, families, and healthcare providers often perceive differences between the two.

Morally, controversy continues to exist over the distinction between actions and omissions leading to a patient's death.[13,14] Although the debate is ongoing in the United States, currently, withdrawal and withholding of life-sustaining therapies (sometimes referred to as passive euthanasia) are permissible. In contrast, active euthanasia, where a physician administers an intervention with the intent of hastening death, is neither morally nor legally permissible. This is in direct contradiction to attitudes in many other countries, including parts of Western Europe, where active euthanasia is currently practiced.[15]

RELIEF OF PAIN AND SUFFERING

A key ethical principle in end-of-life care is that physicians are obligated, whenever possible, to provide relief of pain and suffering and ensure a dignified death for the dying patient. *Dignity* can be defined in various ways, but at its core is the idea that patients should be treated respectfully and humanely. This includes efforts to keep the patient clean and comfortable, with as little distress as possible. Control of pain is particularly important in the ICU, where significant doses of sedatives may be required to relieve suffering. For some healthcare providers, fear exists that administration of high doses of sedating medications could suppress respiration or cause hemodynamic instability, thus accelerating the dying process. Consequently, they may underdose patients to prevent potential side effects. Unfortunately, this approach carries the unintended consequence of incompletely or ineffectively controlling pain and suffering, thereby diminishing the quality of the dying experience for both the patient and their loved ones.

The *Doctrine of Double Effect* is a key ethical principle that guides the practice of end-of-life care and informs our understanding of how we can effectively relieve pain and suffering. It holds that if, in the process of treating pain or distress of a dying patient, an intervention has the unintended consequence of hastening death, it is ethically and morally permissible.[8] In other words, as long as the intent is not to hasten death, aggressive treatment of symptoms to achieve comfort for the dying patient is acceptable and encouraged and is consistent with the ethical principle of beneficence. This should not be confused with active euthanasia or assisted suicide. The intention of active euthanasia or physician-assisted suicide is specifically to *cause* the patient's death. Based on current societal norms and judicial precedent, active euthanasia is ethically and legally distinct from withdrawal and withholding of life-sustaining therapies, which are intended to allow patients to die from their underlying disease.

SURROGATE DECISION MAKING

As noted previously, a majority of patients in the ICU lack the capacity to provide either informed consent for, or refusal of, a medical intervention.[6] Many factors may compromise decision-making capacity, including pain, anxiety, disorientation, fear, sleep deprivation, effects of the underlying disease, and the use of sedatives and narcotics. Unfortunately, most patients have not previously discussed their wishes with family and friends or outpatient medical providers, and they often have not completed an advance directive to articulate their wishes.[7]

When patients lack adequate decision-making capacity, surrogate decision makers are often involved in decisions to limit life-sustaining therapy. The current approach for decision making in the ICU is a shared decision-making model, in which providers offer information about medical issues, anticipated benefits, and the patient's prognosis, while families provide an understanding of the patient's values and preferences.[16–18] Some patients may have previously explicitly identified a surrogate decision maker. In the absence of an identified individual, standards for identifying someone to fill that role vary from state to state.

Under ideal circumstances, the surrogate is an individual who knows the patient well and has a good understanding of the patient's values and preferences, allowing them to advocate for the patient based on the *substituted judgment standard*. This standard holds that the surrogate must have knowledge about the patient's wishes, as expressed orally or in writing, or about the patient's values and life goals, from which valid inferences can be made. In situations in which the patient's explicit wishes are unknown, the healthcare team and the patient's loved ones should work collaboratively to make decisions based on the *best interest standard*, taking into consideration the patient's values, preferences, life goals, prior medical decisions, current condition, and prognosis. Under this standard, the surrogate, along with the caregivers, must base their decision on a weighing of the benefits and burdens of life-sustaining therapy—for example, the benefits of life, chance of survival, and chance of full recovery with a high quality of life, compared with the burdens of pain, additional suffering, and poor quality of life.

For a small subset of patients, a surrogate decision maker cannot be identified.[19] Uniform standards for managing patients in this situation are lacking. In general, the manner in which this circumstance is handled varies by institution and may include multiple physician opinions, chief medical officer concurrence, and/or hospital ethics committee review. Institutions are encouraged to establish a written policy for this practice.

MEDICAL FUTILITY

An example of when ethical principles may conflict is in the ongoing debate over the use of medical futility to guide care of critically ill patients. While there are various conceptions of futility in health care, broadly, an intervention may be considered *futile* when it is incapable of accomplishing the result for which it is intended.[20] In the ICU, this goal is typically understood to be meaningful recovery from critical illness, where *meaningful* refers to a survival that the patient can value and appreciate.

An important distinction exists between *physiological futility* and *medical futility.* An intervention that is judged to be *physiologically futile* is one that is not expected to, or does not achieve, the relevant physiological function as an end point. There is both an ethical and professional consensus that healthcare providers are not required to provide such interventions.[21] As described previously, CPR may be judged to be physiologically futile in a patient with refractory septic shock complicated by cardiac arrest after progressively worsening hypotension, despite maximal therapy. Under these circumstances, the conclusion that CPR would have extremely little or no chance of success (beyond, possibly, a brief time period) is well supported by published literature and clinical experience. Further, an attempt at CPR would not only prolong the patient's dying, but could also do physical harm by fracturing ribs and burning the skin. Prolonging dying is not one of the goals of medicine and, under these circumstances, CPR would violate the principle of nonmaleficence. Moreover, an argument has been made that forcing healthcare providers to perform CPR when there is virtually no prospect of success undermines the ethical integrity of the medical profession.[21]

Medical futility is more difficult to define than physiological futility and is, therefore, less well supported in its application. Some of the older literature describes qualitative approaches, in which experience suggests an intervention will not result in a meaningful survival,[22] as well as quantitative approaches, in which the success of interventions is measured in a more standardized way.[23] However, it is important to recognize that physicians may be limited in their ability to accurately determine the prognosis of a patient.[24] Furthermore, what constitutes meaningful survival or good quality of life is inherently unique to a particular individual and, therefore, is difficult to measure. Consequently, employing a medical futility standard, rather than a physiological standard, is more challenging.

Not uncommonly, patients or their families request continuation of treatments that physicians believe are incapable of producing meaningful survival, based on the principle of autonomy. This tension between the rights of patients as autonomous beings and the obligation of physicians to honor the principles of beneficence and nonmaleficence may result in conflict between the parties. In this setting, the current ethical norm is that medical futility should not be used as a means to circumvent patient or surrogate wishes when conflict exists with regard to the value of an intervention. Specifically, in the absence of predetermined, institutionally based criteria, individual physicians should not attempt to unilaterally withhold or withdraw life-sustaining therapies against the wishes of patients and surrogates based on medical futility. Instead, if medical futility is to be invoked, it should be applied based on an explicitly defined institutional policy that is transparent, inclusive of patients and their families, ensures effective communication, and incorporates an appeal process. Ultimately, conflict that is mediated by parties to achieve a mutually agreeable solution is preferable to invoking "futility."

COMMUNICATION AND PROFESSIONALISM

As noted previously, disagreements regarding the plans and goals of care arise at times between medical providers and patients or their surrogates. Frequently, disagreements are a consequence of a breakdown in communication or a loss of trust by the patient or the patient's surrogate for the medical team.

Recognizing the value of good communication and trust in the ICU serves to enhance the quality of care, promote the autonomy of the patient, and increase the likelihood of a patient-centered outcome. Rather than being assumed, trust should be viewed as something that must be earned from each patient and their family. Trust can be earned by providing compassionate care, communicating with patients and their families on a regular basis, encouraging dialogue, and listening empathically.

Good communication starts with a determination to uniquely understand each patient and to engage patients and families in a culturally sensitive and transparent manner. Information should be presented in a language, and at a level of detail, such that patients and their surrogates feel well informed. This is particularly important in light of studies that have found that half of patients and their families are unable to clearly express an understanding of medical facts, diagnoses, and prognosis after meeting with physicians.[25] In addition, the proportion of time families are allowed to speak during family meetings correlates with the degree of their satisfaction with the care.[26] Despite these data, studies have shown that physicians typically do the majority of the talking and rarely initiate discussions about values and goals.[27,28]

The timing and manner of discussions with patients and families may vary, ranging from informal discussions on daily rounds to more formal family meetings to discuss changes in the goals of care. Efforts should be made to engage families initially at the time of admission, followed by a more formal discussion after 24 to 48 hours to review events related to ICU care. This meeting should be less about goals of care or prognosis, and more about providing support for the family, while describing expectations for recovery and establishing benchmarks for recovery or decline. Following the meeting, short daily debriefings should occur to provide updates on the clinical status of the patient and the care being provided. If the patient declines clinically and it becomes clear that chances of recovery are limited, honest and open discussions should occur to provide truthful assessments of the patient's prognosis. Transparent communication enhances patient autonomy and allows families to make more informed decisions about the care of their loved one. This does not mean that all medically available options can, or even should, be discussed with each patient and family. The decision to offer specific treatments should be based on the medical judgment that the treatments in question are beneficial to the patient; they should be informed by a clear understanding of the patient's values and known wishes—what some have referred to as *authentic decisions*.[29]

Each family will vary in its comfort with the responsibilities of being surrogate decision makers and the amount of information needed to make decisions.[30–32] While some families may prefer greater detail and more autonomy to make care decisions, others may lack the ability to process significant amounts of medical information, or they might prefer to take a lesser role in decision making, deferring to the medical judgment of the physician. Evidence suggests that discordance in decision-making roles may substantially increase the incidence of anxiety and posttraumatic stress disorder (PTSD) among surrogates.[33] Consequently, identifying the category into which each family or members of families fit into is essential for successful engagement and provision of adequate support.

Finally, the ICU and critical illness can be potentially overwhelming to patients and families. The ICU experience can evoke powerful emotions, including fear, anger, frustration, guilt, and intense grief—emotions that are as important as physical symptoms and which need to be addressed by clinicians with empathy, patience, and understanding. At times, physicians may need to take time out from direct patient care to actively listen and allow patients and families to express their concerns and discuss the emotional burden of having a loved one in an ICU. These opportunities for empathic discussion provide for not only a catharsis for the patient or family but also a chance for the physician to obtain further insight into the patient's life, goals and wishes, further enhancing trust.

DISCUSSING GOALS OF CARE FOR THE DYING PATIENT

Many patients fail to improve and will die in the ICU. As such, end-of-life discussions have a prominent role in the management of critically ill patients. One of the most difficult and important roles of the ICU physician is to engage in end-of-life discussions with patients and surrogates when it becomes evident the patient will not survive. Included in these discussions are efforts to reach consensus regarding the goals, and the subsequent plan, of care. Agreement is most likely to be reached when trust has been established through good communication. Although each circumstance is unique, basic communication skills and techniques can enhance the quality and success of these meetings.

Critical to the success of these discussions is advance preparation by the medical team, development of a clear understanding of the facts at hand, and establishment of a consensus regarding the best course of action before meeting with the family. Consideration of which team members should be present at the meeting is necessary to facilitate a patient-centered discussion and to reduce the likelihood of overwhelming the family. Ideally, the medical team members should not outnumber the family. At a minimum, the primary ICU physician and bedside nurse should be present. Other participants might include staff from pastoral care, social work, palliative care services, and, when appropriate, the patient's outpatient primary provider. Family members should be made aware of the purpose of the meeting in advance and should be offered the opportunity to meet at a time and place that allows for as many members as appropriate to participate. Determining the size or number of family members should be based on each unique case, but the meeting should incorporate essential members, including those directly involved in decision making. Table 153-1 outlines recommendations for facilitating the goals of care meeting. While these recommendations are not proscriptive, they summarize the current published literature on the best practice for approaching these discussions.[16,29,30,34,35]

The goals of care meeting can be divided into four phases: Preparation, discussion, negotiation, and debriefing. The preparation phase is a premeeting opportunity for the medical team to

TABLE 153-1 A Recommended Approach for Facilitating the Goals of Care Meeting

I. Preparation phase
- (i) Notify family and friends of the time and location of the meeting
- (ii) Hold a premeeting huddle
  - a) Confirm understanding of medical facts, prognosis, and direction of care and ensure team agreement about proposed changes to the goals and plan
  - b) Consider who should be present at the meeting and how to approach potential issues that may arise during conversation
- (iii) Establish conditions for a productive conversation
  - a) Designate a quiet space for the meeting
  - b) Silence pagers and phones
  - c) Provide boxes of tissue
  - d) Disperse team members throughout the room

II. Discussion phase
- (i) Describe the purpose and goal of the meeting
- (ii) Have everyone introduce themselves and state their relationship to the patient
- (iii) Express appreciation for everyone's willingness to participate in the meeting
- (iv) Determine and clarify the family's understanding of medical facts
- (v) Provide additional information about anticipated prognosis and trajectory
- (vi) Elicit fears, concerns, expectations, hopes, etc. from family and friends
- (vii) Ask about the patient's life, values, and goals

III. Negotiation phase
- (i) Recommend treatments and options consistent with the patient's goals
- (ii) Develop explicit consensus about the plan of care
- (iii) Ensure all voices have been heard

IV. Debriefing phase
- (i) Summarize agreed upon plan of care
- (ii) Describe next steps for patient care
- (iii) Respond to unanswered questions
- (iv) Attend to emotions
- (v) Invite the family to share personal stories or experiences about the patient
- (vi) If appropriate, invite prayer by a family member, their clergy, or a hospital chaplain
- (vii) Acknowledge the difficulty of the conversation and decisions made
- (viii) Assure ongoing care for the patient
- (ix) Thank the family for their involvement

assemble and agree on what will be discussed, as described previously. The discussion phase is the early portion of the meeting, during which the medical team has an opportunity to describe current medical facts and prognosis, and the family has an opportunity to express fears, concerns, and expectations. The negotiation phase is an opportunity for the entire group to develop a mutually agreeable plan of care and to establish boundaries and limitations on care based on the patient's values, the family's individual hopes and wishes, and the medical realities of the patient's condition. Finally, the debriefing phase allows the medical team to provide emotional support to the family and to come together after the meeting to prepare to implement the agreed upon plan of care.

PROVIDING PALLIATIVE AND END-OF-LIFE CARE IN THE ICU

Palliative care is an essential component of good patient care in the ICU and has been strongly advocated as a core competency at an international level.[36] Good palliative care matches the care patients desire at end of life with that which they receive and can increase quality of life for patients prior to death. In addition, palliative care can enhance the perception of quality of death among family members and reduce instances of complicated bereavement, including caregiver depression, anxiety, and PTSD.[5] The vast majority of deaths in the ICU are preceded by a change in goals of care toward an approach that emphasizes comfort over cure. As such, a strong foundation and comfort with principles of hospice and palliative medicine is essential to the comprehensive care of critically ill patients. In addition, standardized policies are critical to ensuring effective and efficient relief of pain and suffering in the terminally ill.

The fundamental goal of palliative care is to restore or maintain quality of life and prevent needless physical or emotional suffering for patients and their loved ones. This includes not only administering analgesics and other medications to relieve symptoms of the dying process, but also providing other compassionate care. In fact, it is important to explicitly state that while palliative care encompasses limiting or discontinuing various life-sustaining interventions, it does not mean we are limiting "care" for our patients and their loved ones. In addition to symptom control, "care" also means providing general patient hygiene and attending to the spiritual, emotional, and psychological distress of the patient and the family of a dying patient. As an example of a simple, yet successful, intervention, use of empathic statements about the difficulty of making decisions to withhold or withdraw life-sustaining therapy and losing a loved one have been associated with increased ratings of family satisfaction and bereavement among surrogates.[37]

Once the decision is made to focus exclusively on care that promotes comfort, only treatments and interventions that achieve this goal should be employed. As appropriate, opiates and sedatives should be titrated to prevent pain, dyspnea, or anxiety before withdrawing life-sustaining therapies. When the patient is perceived to be comfortable by the medical staff and family, all life-sustaining interventions should be withdrawn or withheld so as to not prolong the dying process. While care should be tailored to the wishes and values of each family, some basic guidelines should be followed.

First, a clear explanation should be provided to the patient's loved ones before initiating comfort care interventions. Families should understand that comfort care will be provided throughout the dying process, and that time to death is variable. In addition, family should be offered the opportunity to be present at the time of death, understanding that for some, presence is associated with increased incidence of PTSD.[38] Second, withdrawal of all agreed upon life-sustaining therapies should occur at one time, rather than in a sequential fashion, to minimize discomfort to the patient and disruption to the family. Third, any evidence of recurring pain, anxiety, or discomfort, as witnessed by a team member or family, should be aggressively treated. This includes any spiritual or existential suffering, which should be addressed with the support of palliative and pastoral care services. Fourth, when possible, in-room physiological monitoring should be discontinued, as well as unnecessary medications, tests, devices, vascular access, and catheters. Finally, members of the medical team should be in close proximity and readily available to quickly address any issues that arise.

As a general rule, actively dying patients should not be transferred out of the ICU unless the bed is needed for a new critically ill patient. These patients often require high levels of nursing and physician support and typically die relatively quickly after life-sustaining therapies are withdrawn. In addition, leaving the patient in the ICU allows for continuity of care, which can be immensely helpful to grieving families. However, for patients whose needs for palliative care can be met by a less intense level of nursing and medical care, or for patients whose death may not be imminent, consideration should be given to transferring that patient to another room outside of the ICU, where there is more privacy and quiet during the dying process. Some hospitals have hospice units with specially trained nursing and medical staff and pleasant, private surroundings for patients and families. It is customary for hospital visiting hours to be suspended for dying patients.

CONFLICT RESOLUTION IN THE ICU

As a rule, good communication and sustaining of trust in the ICU significantly lessen the likelihood of conflict between healthcare staff and patients and their families. Unfortunately, conflict does arise at times. Although some disagreements may be based on ethical issues (e.g., autonomy vs. beneficence), in most instances conflict occurs due to breakdowns in communication, a loss of trust, or both. At these moments of conflict, it is important to recognize that individuals each have their own sets of values and beliefs that may inform their opinion about a plan of care. This applies not only to patients and their families, but also to medical staff as well. In addition, the ICU is a challenging environment. ICU staff are busy, patient conditions rapidly change, and families suffer from varying degrees of emotional distress. Recognizing and acknowledging these challenges is important in achieving resolution of conflict.

Conflict resolution begins with open communication among all parties. Usually, patient and honest negotiation between parties will result in resolution. In particular, attempting to understand the values and perspective of patients and their families can improve the communication process and diffuse difficult situations. However, at times further discussion may not resolve the dispute. At that point, a number of additional strategies may be considered.

PALLIATIVE CARE CONSULTATION

Palliative care services are an excellent resource for providing additional support in the end-of-life process. In addition to expertise in symptom control, palliative care teams can provide supportive counseling to patients and families, improve communication with the medical team, and aid in conflict resolution. Various studies of the effectiveness of palliative care consultation in the ICU have demonstrated improved quality of death and dying, better family bereavement scores, increased advance directive completion rates and hospice discharge rates, reductions in utilization of nonbeneficial life-sustaining therapies, and reductions in hospital and ICU length of stay.[39,40] In the absence of dedicated palliative care consultative services, social work and pastoral care (two common members of the palliative care multidisciplinary team) may be able to provide support.

ETHICS CONSULTATION AND BIOETHICS MEDIATION

Another potential option for dealing with conflict resolution is the hospital ethics committee. Ethics consultants are excellent resources for clarifying ethical uncertainty when it arises. However, much of the conflict occurring in the ICU is not truly of an ethical nature. In this context, ethics consultation may not necessarily be helpful. In general, use of ethics consultation has produced similar outcomes as the palliative care interventions described earlier.[41]

When not employed appropriately, ethics consults may be viewed as arbitrary and biased in favor of the hospital and medical team. Rendering a decision runs the risk of not meeting the needs of the patient and family and increasing conflict. Given these reservations, it is imperative that hospital ethics committees have sufficient community representation and seek out the involved patients and their families directly to enable a complete understanding of their values, perceptions, and goals when conflict exists.

More recently, bioethics mediation has emerged as another potential approach for resolving conflicts in the ICU. Mediation has been practiced in legal and business settings for decades. Although new to health care, mediation offers an alternative means of handling disputes by focusing on a shared decision-making model, rather than the win–lose scenario of the healthcare team versus the patient and family.

Mediation operates under the premise that mutually agreeable solutions can be negotiated when conflict arises between multiple parties involved in the care of a patient. Unlike legal and business settings, healthcare mediation is nonbinding and, therefore, might be more akin to marriage counseling than true legal mediation. In this sense, it is perhaps better termed "facilitation." The goal of mediation is to create a neutral environment for all parties to come together and share perspectives and concerns. Although promising, bioethics mediation in the healthcare setting remains untested. Furthermore, there are few individuals currently trained in bioethics mediation to make its practice widely applicable at this time. There is, however, a growing sentiment that ICU clinicians should have some knowledge or training in principles of mediation to effectively negotiate conflict.

STRATEGIES FOR WHEN CONFLICTS PERSIST

Even with the previously noted resources, times will arise when the relationship between providers and patient or family is irrevocably damaged, and further communication and negotiation will not successfully resolve the conflict. In these settings, healthcare providers may find themselves providing care they believe to be ineffective or even harmful. This can have unfortunate consequences of burnout and cynicism, both of which can result in erosion of professionalism and poor quality of care for current and future patients.[42] If a provider feels strongly that he or she cannot, in good conscience, offer the care that the patient or family is requesting, the provider may transfer the care to another provider within the same institution or offer to transfer to another hospital. However, if another provider or hospital cannot be identified, it is vital that the medical staff support each other while continuing to provide good care to their patients. One effective approach that is being adopted in many ICUs to minimize emotional and moral distress is "death" or "grief" rounds, during which ICU staff come together to debrief and discuss difficult cases. Grief rounds allow staff to decompress and avoid burnout that could otherwise negatively impact job satisfaction and patient interaction.[43]

CONCLUSION

In today's critical care environment, death in the ICU is common and usually occurs after life-sustaining therapy is withheld or withdrawn. Many ethical considerations arise from the frequency and complexity of this process. Consequently, healthcare providers face challenging ethical dilemmas in weighing these considerations while providing care for their patients.

There is broad legal, ethical, societal, and professional support for limiting life-sustaining therapy at the end of life. As a general rule, the overriding principle is respect for patient autonomy. However, physicians must engage patients and their families to create a shared decision-making environment in which medical facts are matched by a desire to understand the values and wishes of patients with critical illness and terminal disease. Ultimately, effective communication enhances the quality of patient care and family satisfaction and is likely to result in patients getting the care they wish to receive.

Conflicts occur, although they can usually be resolved by good communication and honest, respectful engagement. In situations in which communication strategies fail, additional resources (e.g., palliative care, ethics committees, or bioethics mediation) may prove helpful to resolve conflict. Only in very rare cases should providers find themselves in situations where they are morally distressed by the care they are required to provide. In these situations, the conflict can be resolved by transferring the patient to another provider or hospital and by supporting each other while continuing to provide high-quality critical care.

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APPENDIXES

Appendix A Terms and Symbols in Respiratory Physiology A-2

Appendix B Normal Values for a Healthy 20-Year Old Seated Man A-5

APPENDIX A

Terms and Symbols in Respiratory Physiology

GENERAL SYMBOLS

P	Partial pressure in blood or gas P_{O_2} = partial pressure of O_2
$\bar{X}$	A bar over the symbol indicates a mean value. $\bar{P}$ = mean pressure, as distinct from instantaneous pressure
$\dot{X}$	A time derivative (rate) is indicated by a dot above the symbol $\dot{V}_{O_2}$ = oxygen consumption per minute, mL $\dot{V}_{CO_2}$ = CO_2 production per minute, mL
% X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign following a symbol indicates a ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated $FEV_1/FVC, \% = 100 \times FEV_1/FVC$
XA, Xa	A small capital letter or a lower-case letter on the same line following a primary symbol is a qualifier to further define the primary symbol. Alternatively, subscript letters may be used $X_A = X_A$, $Xa = X_a$ Additional qualifiers of the primary symbol may be identified as shown $P_{E_{O_2}}$ = Pressure of CO_2 in the expired air, mm Hg

GAS PHASE SYMBOLS

PRIMARY SYMBOLS

V	Volume of gas
$\dot{V}$	Flow of gas
F	Fractional concentration of a gas

QUALIFYING SYMBOLS

I	Inspired V_I = inspired volume
E	Expired V_E = expired volume $\dot{V}_E$ = expired volume per minute
A	Alveolar V_A = alveolar volume $\dot{V}$ = alveolar ventilation per minute
T	Tidal V_T = tidal volume
D	Dead space V_D = volume of dead space $\dot{V}_D$ = dead-space ventilation per minute
B	Barometric P_B = barometric pressure
STPD	Standard conditions: temperature 0°C, pressure 760 mm Hg, and dry (0 mm Hg water vapor)
BTPS	Body conditions: body temperature and ambient pressure, saturated with water vapor at these conditions
ATPD	Ambient temperature and pressure, dry
ATPS	Ambient temperature and pressure, saturated with water vapor at these conditions
an	Anatomic
p	Physiological
f	Respiratory frequency, per minute
max	Maximum
t	Time

BLOOD PHASE SYMBOLS

PRIMARY SYMBOLS

Q	Volume of blood
$\dot{Q}$	Blood flow $\dot{Q}$ = cardiac output, L/min
C	Concentration in the blood phase C_{O_2} = concentration of oxygen in blood, mL of O_2 per 100 mL of blood
S	Saturation in the blood phase S_{O_2} = Saturation of hemoglobin with O_2, percent

QUALIFYING SYMBOLS

a	Arterial Ca_{O_2} = concentration of O_2 in arterial blood, mL of O_2 per 100 mL of blood
c	Capillary Cc_{O_2} = concentration of O_2 in capillary blood, mL of O_2 per 100 mL of blood
C′	Pulmonary end-capillary Pc'_{O_2} = partial pressure of O_2 in end-capillary blood, mm Hg
v	Venous Cv_{O_2} = concentration of O_2 in venous blood, mL of O_2 per 100 mL of blood
$\bar{v}$	Mixed venous $C\bar{v}_{O_2}$ = concentration of O_2 in mixed venous blood, mL of O_2 per 100 mL of blood

VENTILATION AND LUNG MECHANICS TESTS AND SYMBOLS

■ STATIC LUNG VOLUMES*

RV	Residual volume. Volume of air remaining in the lungs after maximum expiration.
CV	Closing volume. Volume of air expired from the onset of airways closure to residual volume. May be expressed as a fraction of VC: CV/VC,%.
ERV	Expiratory reserve volume. Maximum volume of air expired from the resting end-expiratory level.
V_T	Tidal volume. Volume of air inspired or expired with each breath during quiet breathing. When tidal volume is used in gas-exchange formulations, this symbol is used.
IRV	Inspiratory reserve volume. Maximum volume of air inspired from the end-tidal inspiratory level.

■ LUNG CAPACITIES**

IC	Inspiratory capacity. The sum of IRV and TV.
IVC	Inspiratory vital capacity. Maximum volume of air inspired from the point of maximum expiration, i.e., from RV.
VC	Vital capacity. Maximum volume of air expired from the point of maximum inspiration, i.e., from TLC.
FRC	Functional residual capacity. Sum of RV and ERV. FRC is the volume of air remaining in the lungs at the resting end-expiratory position.
TLC	Total lung capacity. Volume of air in the lungs after maximum inspiration. Also, the sum of all volume compartments of the lungs.
RV/TLC,%	Residual volume to total lung capacity ratio, expressed as a percentage.
CC	Closing capacity. Closing volume plus residual volume, may be expressed as a percentage of TLC: CC/TLC, %.

■ FORCED RESPIRATORY MANEUVERS DURING SPIROMETRY†

FVC	Forced vital capacity. The maximum volume of air forcibly expired from total lung capacity
FIVC	Forced inspiratory vital capacity. Maximum volume of air forcibly inspired starting from residual volume.
FEV*t*	Timed forced expiratory volume. Volume of air expired in a specified time in the course of the forced vital capacity maneuver. FEV_1 = volume of air expired during the first second of the FVC.
FEV*t*/FVC,%	Ratio of timed forced expiratory volume to forced vital capacity, expressed in percentage.
FEF*x*	Forced expiratory flow, related to some portion of the FVC curve. Modifiers refer to the amount of the FVC that has been expired at the time of measurement.
$FEF_{200-1200}$	Forced expiratory flow between 200 and 1200 mL of the FVC (formerly called the maximum expiratory flow rate).
FEF_{25-75}	Forced expiratory flow during middle half of the FVC (formerly called the maximum midexpiratory flow rate or MMEF)
PEF	Peak expiratory flow. Highest value for expiratory flow.
$\dot{V}_{max_x}$	Maximum flow when *x* percent of the FVC has been expired. $\dot{V}_{max\,75}$ = flow (instantaneous) when 75% of the FVC has been expired.
FIF*x*	Forced inspiratory flow. As in the case of the FEF, appropriate modifiers designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of measurement. FIF_{25-75} = forced inspiratory flow during the middle half of the FIVC.
MVV	Maximum voluntary ventilation. Volume of air exhaled during maximum breathing efforts within a specified time period. Formerly called the maximum breathing capacity (MBC) MVV_{60} = MVV at a breathing frequency of 60 per minute.
PImax	Maximum inspiratory pressure. The maximum pressure generated during a maximal inspiratory effort made at RV.
PEmax	Maximum expiratory pressure. The maximum pressure generated during a maximal expiratory effort made at TLC.

*Expressed as BTPS.

**Combinations of volumes for practical purposes.

†All values at BTPS.

■ MEASUREMENTS RELATED TO VENTILATION

$\dot{V}_E$	Expired volume per minute (BTPS)
$\dot{V}_I$	Inspired volume per minute (BTPS)
$\dot{V}_{CO_2}$	Carbon dioxide production per minute (STPD)
$\dot{V}_{O_2}$	Oxygen consumption per minute (STPD)
R	Respiratory exchange ratio, the ratio of CO_2 output to O_2 intake in the lungs
$\dot{V}A$	Alveolar ventilation per minute (BTPS)
$\dot{V}_D$	Ventilation per minute of the physiological dead space (BTPS) defined by the equation $\dot{V} = \dot{V}_E \frac{Pa_{CO_2} - PA_{CO_2}}{Pa_{CO_2} - PI_{CO_2}}$
V_D	Volume of the physiological dead space, calculated as $\dot{V}_D/f$.
V_D/V_T	Ratio of dead space to tidal volume. The fraction, usually expressed as a percentage, of each breath that does not contribute to CO_2 elimination.

■ MECHANICS OF BREATHING*

Pressure Terms

Paw	Pressure at any point along the airways
Pao	Pressure at the airway opening
Ppl	Pleural pressure
P_A	Alveolar pressure

*All pressures expressed relative to ambient pressure unless otherwise specified.

Pbs	Pressure at the body surface
Pes	Esophageal pressure: used to estimate Ppl
P_A–Pbs	Transthoracic pressure
P_A–Ppl	Transpulmonary pressure
Ppl–Pbs	Pressure difference across the chest wall
Paw–Ppl	Transbronchial pressure, estimated as difference between airway and pleural pressures.

Flow–Pressure Relationships†

R	General symbol for frictional resistance, defined as the ratio of pressure difference to flow.
Raw	Airway resistance, calculated from pressure difference between airway opening (Pa_o) and alveoli (Pa) divided by the airflow, cm H_2O/L/s.
Rl	Total pulmonary resistance, measured by relating flow-dependent transpulmonary pressure to airflow at the mouth.
Rti	Tissue resistance (viscous resistance of lung tissue), calculated as difference between Rl and Raw.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Gaw	Airway conductance, reciprocal of Raw.
Gaw/Vl	Specific conductance, airway conductance, expressed per liter of lung volume at which Gaw is measured.

Volume–Pressure Relationships

C	General symbol for compliance of the lungs, chest wall, or total respiratory system. Volume change per unit change in applied pressure. For the lungs, the applied pressure is the pressure difference across the lungs, or transpulmonary pressure, Pao–Ppl; for the chest wall, the applied pressure is the transthoracic pressure, Ppl–Pbs; for the entire respiratory system, the applied pressure is Pao–Pbs.
Cl	Lung compliance. Value for the volume change divided by the transpulmonary pressure.
Cw	Chest wall compliance. Value for the volume change divided by the transthoracic pressure.
Cdyn	Dynamic compliance. Value for compliance determined at time of zero gas flow at the mouth during uninterrupted breathing. The respiratory frequency appears as a qualifier. $Cdyn_{40}$ = dynamic compliance at a respiratory frequency of 40 per minute.
Cst	Static compliance, value for compliance determined on the basis of measurements made during a period of zero airflow.
C/Vl	Specific compliance. Compliance divided by the lung volume at which it is determined, usually FRC.

†Unless otherwise specified, resistance measurements are assumed to be made at FRC.

Pst	Static pulmonary pressure at a specified lung volume. Pst_{TLC} = static recoil pressure of the lung measured at TLC (maximum recoil pressure)

■ DIFFUSING CAPACITY TESTS AND SYMBOLS

D_Lx	Diffusing capacity of the lung expressed as volume (STPD) of gas (x) uptake per minute per unit alveolar-capillary pressure difference for the gas used. A modifier can be used to designate the technique: D_{LCO}/sb = Single-breath CO diffusing capacity; D_{LCO}/ss = Steady-state CO diffusing capacity
D_M	Diffusing capacity of the alveolar-capillary membrane (STPD).
θ	Reaction rate coefficient for red blood cells. Determined as the volume of gas (STPD) that will combine per minute with 1 unit volume of blood per unit of gas tension. If the specific gas is not stated, θ is assumed to refer to CO and is a function of existing O_2 tension.
Vc	Pulmonary capillary blood volume. This should be Qc for consistency with other symbols, but Vc is entrenched in the literature. In the equation that follows for 1/D_L, Vc represents the effective pulmonary capillary blood volume, i.e., capillary blood volume in intimate association with alveolar gas.
1/D_L	Total resistance to diffusion, including resistance to diffusion of test gas across the alveolar-capillary membrane, through plasma in the capillary, and across the red blood cell membrane (1/Dm), with the resistance to diffusion within the red blood cell arising from the chemical reaction of the test gas and hemoglobin (1/θVc), according to the formulation $\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta Vc}$
D_L/V_A	Diffusing capacity per unit of alveolar volume. D_L is expressed STPD, and V_A is expressed in liters, BTPS.

BLOOD GAS SYMBOLS

Symbols for these values are readily composed by combining general symbols. Some examples include the following:

Pa_{CO_2}	Arterial CO_2 tension, mm Hg
Sa_{O_2}	Arterial O_2 saturation, percent
CcO_2	Oxygen content of pulmonary end-capillary blood, mL of O_2 per 100 mL of blood
$(A\text{-}a)Po_2$	Alveolar–arterial difference in the partial pressure of O_2, mm Hg
$Ca_{O_2} - C\bar{v}_{O_2}$	O_2 content difference between arterial and mixed venous blood (arteriovenous O_2 difference), mL of O_2 per 100 mL of blood

PULMONARY SHUNT SYMBOLS

$\dot{Q}s$	Flow of blood via shunts. This is usually determined as percent of cardiac output ($\dot{Q}$) while breathing 100% O_2, according to the equation $\frac{\dot{Q}s}{\dot{Q}} = \frac{CcO_2 - Ca_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}} \times 100$ Where CcO_2 = O_2 content of end-capillary blood; CaO_2 = O_2 content of arterial blood; $C\bar{v}_{O_2}$ = O_2 content of mixed venous blood

APPENDIX B

Normal Values for a Healthy 20-Year Old Seated Man

Ventilation (BTPS)	
Tidal volume (V_T), L	0.6
Frequency (f), breaths/min	12
Minute ventilation (V_E), L/min	7.2
Respiratory dead space (V_D), mL	150
Alveolar ventilation, V_A, L/min	5.4
Lung Volumes and Capacities (BTPS)	
Inspiratory capacity (IC), L	3.0
Expiratory reserve volume (ERV), L	1.9
Vital capacity (VC), L	4.9
Residual volume (RV), L	1.4
Functional residual capacity (FRC), L	3.2
Total lung capacity (TLC), L	6.3
Residual volume/total lung capacity × 100 (RV/TLC), %	22
Mechanics of Breathing	
Forced vital capacity (FVC), L	4.9
Forced expiratory volume, first second (FEV_1), L	4.0
Maximum voluntary ventilation (MVV), L/min	170
Forced expiratory volume in 1 s/forced vital capacity × 100 (FEV_1/FVC), %	83
Forced expiratory volume in 3 s/forced vital capacity × 100 (FEV_3/FVC), %	97
Forced expiratory flow during middle half of FVC ($FEF_{25–75}$), L/s	4.7
Forced inspiratory flow at the middle of forced inspiratory capacity (FIF_{50}), L/s	5.0
Static compliance of the lungs (Cst, l), L/cm H_2O	0.2
Compliance of lungs and thoracic cage (CRS, respiratory system compliance) L/cm H_2O	0.1
Airway resistance at FRC (Raw), cm H_2O/L/s	1.5
Pulmonary resistance at FRC, cm H_2O/L/s	2.0
Airway conductance at FRC (G_{aw}), L/s/cm H_2O	0.66
Specific conductance (G_{aw}/V_1)	0.22
Maximum inspiratory pressure, mm Hg	– 75
Maximum expiratory pressure, mm Hg	120
Distribution of Inspired Gas	
Single-breath N_2 test (ΔN_2 from 750 to 1250 mL in expired gas), % N_2	<1.5
Alveolar N_2 after 7 min of breathing O_2, % N_2	<2.5
Closing volume (CV), mL	400
CV/VC × 100, %	8
Closing capacity (CC), mL	1900
CC/TLC × 100,%	30
Slope of phase III in single-breath N_2 test, % N_2/L	<2
Gas Exchange	
O_2 consumption at rest (STPD), mL/min	240
CO_2 output at rest (STPD), mL/min	192
Respiratory exchange ratio (R), CO_2 output/O_2 uptake	0.8
ALVEOLAR GAS	
$P_{A_{O_2}}$, mm Hg	105
$P_{A_{CO_2}}$, mm Hg	40
ARTERIAL BLOOD	
Pa_{O_2}, mm Hg	95
Sa_{O_2}, %	98
pH	7.40
Pa_{CO_2}, mm Hg	40
Pa_{O_2}, while breathing 100% O_2, mm Hg	640
Alveolar Ventilation and Gas Exchange	
Alveolar ventilation, L/min	4.2
Physiological dead space/tidal volume × 100 (V_D/V_T), %	<30
Alveolar–arterial oxygen-gradient, (A-a) P_{O_2}, mm Hg	10
Diffusing Capacity	
Diffusing capacity at rest for CO, single-breath (DL_{COsb}), mL CO/min/mm Hg	29
Diffusing capacity per unit alveolar volume (D_L/V_A)	4.8
Control of Ventilation	
Ventilatory response to hypercapnia, L/min/per ΔPa_{CO_2} mm Hg	>1.5
Pulmonary Hemodynamics	
Pulmonary blood flow (cardiac output), L/min	5.4
Pulmonary artery systolic/diastolic pressure, mm Hg	25/8
Pulmonary capillary blood volume, mL	100
Pulmonary "capillary" (wedge) blood pressure, mm Hg	<10

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